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Biotech Pioneers
A philosophical inquiry concerning the genetically engineered mouse

Ellen ter Gast
Biotech Pioneers
A philosophical inquiry concerning
the genetically engineered mouse

Een wetenschappelijke proeve op het gebied van de
Natuurwetenschappen, Wiskunde en Informatica

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Ellen ter Gast
geboren op 8 februari 1971
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Promotor: Prof. dr H.A.E. Zwart
Manuscriptcommissie: Prof. dr R. ten Bos
                      Prof. dr Tj. de Cock Buning
                      Dr C.N. van der Weele

To Anne and Else, the greatest joy in my life.
Acknowledgements

As long as I can remember, I have been fascinated by the nature of living organisms, the mysteries of life, and the way we humans make sense of it. This is why I decided to study both Biology and Philosophy. Entering University in the late 1980s as a student of Biology I soon learned about the revolutionary possibilities of biotechnology. I was absolutely stunned when I found out that human genes could be transferred successfully to a mouse (see below for the drawing I made during class expressing how I imagined such a mouse would look).

The question: ‘What impact will biotechnology have on life and nature itself and on our understanding of life and nature?’ has captured me ever since. Therefore, I am very grateful for having had the opportunity to do this philosophical inquiry into the remarkable ‘biotech mouse’, who, as I will argue throughout this book, is the protagonist in the biotech revolution that is taking place right now.

My gratitude first and above all is addressed to my professor and supervisor Hub Zwart who 5 years ago offered me a research position at the...
Department of Philosophy at the Faculty of Science of the Radboud University in Nijmegen. When I accepted this offer I basically followed my intuition. My intuition proved to be right. Hub has always been supportive and enthusiastic about my ideas and plans and gave me the freedom to follow my own philosophical path. But perhaps, even more important, he always showed confidence in my work and future results. I am also grateful for his close reading of the manuscript; it always led to improvement. To put it simply: I cannot imagine having had a better academic supervisor.

Of course, I am also indebted to my other colleagues at the department of philosophy, the Centre for Society of Genomics, and ISIS for the friendly atmosphere and lively discussions at department meetings, lunches and coffee breaks. I would like to thank in particular Pieter Lemmens, Frans van Dam, Peter Stegmeier and Martijntje Smits for their supportive and helpful comments on parts of the manuscript. I would also like to thank the members of the task force Science and Society for their financial and academic support, the supervisory committee, in particular Tjard de Cock Buning, for input during the start up phase, and Saskia Segers and Marieke van Oostveen for their ‘non-academic’ support and assistance with administrative paperwork.

Although my office was at Nijmegen, my base has always been at home in Amsterdam. This is one of the many reasons I enjoy being a member of the workgroup New Representational Forms of The Arts and Genomics Centre (TAGC). The final manuscript has greatly benefited from the monthly discussions in Amsterdam about Art and the Life Sciences with Rob Zwijnenberg, Miriam van Rijssingen, Daniëlle Hofmans, Jenny Boulboulé, Helen Chandler, Cor van der Weele and Anne Kienhuis. In particular, I am much indebted to them for their input to the final versions of the Chapters 3 and 5.

A crucial stage in the explorative phase of my research has been the fieldwork I did at the Dutch Cancer Institute. Being able to meet the mice in real flesh and blood (in the literal sense) inspired me to write the book as it now. I wish to thank Marco Breurer and Evert van Garderen for their openness to this ‘ethical experiment’, and Richard van de Berg, Ton Schrauwers, Yvonne van der Peijl-Kempen, Johan Jongsm, Arnoud Lagro, Esmeralda de Jong and Paul Krimpenfort for the ‘guided tours’ in their laboratories and conversations about their work and animals. It is here that my ‘research object’ became real and alive.

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Thanks also to my two paranimfen Marjolijn Voogel en Susanne van de Wateringen who have already shown to understand the importance of their role by asking me that vital question: ‘What do we wear at the public defense?’

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Introduction

“Well it is scary, isn’t it, all this genetic engineering?”

“Is it?”

“Yeah, you know, messing about with the body. They reckon there’s a gene for intelligence, sexuality—practically everything, you know? Recombinant DNA technology” said the girl using the term cautiously as if testing the water to see how much Marcus really knew. Seeing no recognition in his face she continued with more confidence. “Once you know the restriction enzyme for a particular, like, bit of DNA, you can switch anything on or off, like a bloody stereo. That’s what they are doing to those poor mice. It is pretty fucking scary”.

Zadie Smith

Why a book about mice?

What made me, a philosopher and a biologist, decide to write a book on mice? The answer to this question can be found in the quotation cited above, taken from Zadie Smith’s novel *White Teeth*. In this book one of the characters, Marcus, a scientist, has created FutureMouse©. In this animal he implanted custom-designed genes that can be ‘turned on’ and ‘off’. This gives Marcus the absolute control over its life and death. In collaboration with a novelist, he has written a pop science book called *Time Bombs and Body Clocks: Adventures in Our Genetic Future* that also includes a chapter on this mouse. The girl who is quoted above is reading this book, unaware that the person she is addressing is one of the authors. While the girl is lecturing him about the scary aspects of recombinant DNA technology, Marcus is wondering why it is that people fail to see his mouse as a laboratory entity that is determining the future of cancer, of reproductive life cycles, of the human life-span and ageing, but rather continue to see it merely as a mouse, an animal. They focus on the mouse ‘as mouse’, in a manner that never failed to surprise him: ‘They seemed unable to think of the animal as a site for experimentation into heredity, into disease, into mortality. The mouseness of the mouse seemed inescapable’ (Smith 2000: 345).

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This fictitious scene taken from a popular novel illustrates a number of interesting aspects of the laboratory mouse.

First of all, it illustrates the different perspectives from which different individuals can perceive the genetically engineered mouse. On the one hand, we see a girl who is definitely not as hysterical as Marcus takes her to be. On the contrary, she is amazingly well informed, and expresses genuine feelings of moral concern. According to her views, a genetically engineered mouse is unnatural and the idea that you can program the mouse...is experienced as ‘pretty fucking scary’. On the other hand, we have Marcus who represents the rather stereotypical image of a scientist, seemingly unable to understand the feelings and reactions of lay people. He has a very instrumental view on laboratory mice connected with a deep faith in scientific progress. There is no such thing as mutual understanding between Marcus and the girl. Secondly, when we listen carefully to what the girl says, and consider what Marcus thinks, a whole variety of moral values emerges: a fuzzy set of morally relevant notions that are somehow involved in mouse biotechnology. The genetically engineered mouse is a complex phenomenon, from a moral point of view. Yet, in the end, although they seem to disagree considerably over the value and moral status of the mouse, both Marcus and the girl seem to agree about one thing: namely, the fact that a biotechnological revolution is taking place, here and now, at this very moment, and that FutureMouse© is one of the main characters in this revolution. To Marcus this is progress; to the girl there is ‘something a little fascist about the whole deal’ (Smith 2000: 346).

Today, in laboratories all over the world, genetically engineered mice like Future/Mouse are being produced and used for biomedical research. These mice are determining the future of medicine. Mouse geneticists have sequenced (‘cracked’) the mouse genome and added genes coding for fluorescent proteins to it. In addition to the thousands of mouse models that mimic human diseases they have created mice that are smarter, stronger and live longer than ordinary mice. In the biotech revolution that is taking place, the mouse plays a central role. The biotech revolution is a radical change in terms of the way ‘we’ are taking control over living entities. Biotechnologists are challenging nature. Or, to put it more precisely, the biotech revolution challenges traditional beliefs about nature. These gentech mice are not simply unnatural, they force us to reconsider long-held beliefs about natural species, about life and death, disease and health. In other words, these mice raise, and force us to reframe, a series of profound philosophical questions. By way of the mouse, biotechnology affects what lies at the core of humanity, of what it is to be human. For biologists these mouse technologies offer great possibilities to study the mysteries of life. For philosophers, they are a source of confusion. How does mouse biotechnology affect the way we make sense of life? Are we seizing the position of Dawkins’s blind watchmaker? The mice also raise many ethical questions: ‘Are we doing the right thing?’ ‘Where will all this tinkering with genes’ lead to?’

The key message I want to put forward in this book is that, if we want to understand the impact of the biotech revolution, we have to look at the mouse. The mouse is the key actor in this radical series of events that is taking place in the life sciences right now. To understand the meaning of biotechnology both from a biological perspective and a philosophical perspective, we have to take a closer look at this animal’s unique history and its presence in biomedical laboratories. I will do so by focussing on three central questions: an ontological, an epistemological, and an ethical one:

1. What is the genetically engineered laboratory mouse?
2. How is the mouse currently used, and what is its role and function in the pursuit of knowledge and power?
3. What are the moral implications of mouse biotechnology, or, how must we deal with the issues raised by the genetically engineered mouse?

As the fictitious dialogue between Marcus and the girl from White Teeth illustrates, there are many perspectives from which we can look at the genetically engineered mouse. All of these perspectives will produce different answers to these questions. Each perspective produces a different image of the mouse. We cannot say that one of them is more ‘real’, more ‘adequate’ more ‘truthful’ than the others. Rather they reveal complementary dimensions. One cannot be replaced by any of the others: they emerge on different levels. Every perspective has its own revelatory power, its own truth, its own value. At the same time every perspective on the mouse also entails a certain blindness to the aspects of the mouse that are brought to the fore by the other perspectives. A typical mouse image coming from a biologists’ perspective is that of an animal which provides ‘inside’ information concerning the in vivo behaviour of our DNA. This raises a number of philosophical (notably epistemological) questions concerning the role of the mouse in the process of knowledge production in
the field of mammalian or human genetics. What is the value of the mouse as a model organism?

Philosophical questions can also be asked about ‘boundary conflicts’. What exactly is an animal that carries genes from both mice and humans? Such an animal not only transgresses the species boundary between mouse and man, it also transgresses the boundary between nature and culture, what is given by nature and what is man-made. This results in the ethical question whether the mouse also signifies the crossing of a moral boundary. And, if so, why? Other ethical questions are related to animal welfare issues raised by contemporary mouse biotechnology. Do these animals suffer from the instrumental use we make of them?

By far the most intriguing questions about the mouse are those about its future. What will be the implications of these technologies, tested in and developed with the help of mice? Will they eventually be applied to humans? What can we learn about biotechnology in general by looking at the mice? What can we learn about our own future? What does the (hi) story of the mouse tell us about possible future scenarios? What can we learn from the mouse about ourselves, our genes and the role we play in the ‘natural’ process of evolution? I believe these are questions of vital importance precisely because a revolution is taking place right here and now that will have a radical impact on the way we view and – perhaps – reshape ourselves, in a distant future that begins today.

A short note on methodology

In order to address these questions, a variety of sources will be consulted. Being a philosopher, my main tool, my main method of investigation, is of course reading. Most of the sources I will use are written documents. In order to understand what the genetically engineered mouse is, I will study what is written and said about these mice and about animal biotechnology more general. This discourse on mice emerges at various levels. In the first place, there is a scientific discourse on mice that materialises in the form of research articles in scientific journals such as Science, Nature and the Proceedings of the National Academy of Science where major breakthroughs in mouse biotechnology are eagerly reported. But also important are the writings of philosophers, reflecting on the moral aspects of animal biotechnology, or of social scientists, studying the role of the mouse in the scientific practice. Besides research papers and scientific articles, I also consulted (auto) biographical reflections of scientists involved in mouse biotechnology. This latter type of written information can be found not only in scientific journals but also in the popular press such as newspapers and magazines. In addition to the reflections and reports on the mouse that originate from academic circles, there are highly relevant forms of ‘mouse discourse’, emerging in more popular environments. This may involve written materials, such as (science) fiction stories and articles in the media, but also works of art produced by contemporary artists.

The discourse (scientific, philosophical and otherwise) on genetically engineered mice amounts to an archive of incredible proportions. Therefore, one has to be selective. Insofar as the scientific literature is taken into account, I will focus on the highlights, the breakthroughs, such as the ‘birth’ of the first inbred strains, the birth of the first transgenic mouse, the first human gene inserted in the mouse genome, the emergence of the first knock-out mouse, etc. To this I added a number of biographical or autobiographical publications, focussing on authors who themselves had played a major role in the mouse biotech revolution.

Insofar as the philosophical and ethical literature is concerned, it was not at all that easy to steer my own course in an ocean of writings. First of all, I was primarily interested in publications on animal biotechnology that evoke a living or ‘tangible’ image of the mouse. In other words, I was interested in publications that really speak about mice, rather than about philosophical concepts. Therefore, I more or less ignored philosophical writings in which, because of their level of abstraction, the mouse is lost in a jungle of words. This book is about real, living mice, the myths they evoke, their images, and their meanings.

Moreover, this book is neither about animal ethics (or animal ethics committees), nor about policy making and legislation on animal biotechnology. Again, the focus is on the meaning of the genetically modified mouse. Therefore, I hardly discuss the writings of the various Dutch bioethicists who have tried to analyse and clarify notions such as integrity and intrinsic value in order to make them suitable for use in animal ethics committees or bioethics committees. Moreover, the focus is on the international literature, rather than on sources written in Dutch that focus on national policy development.

While reading these diverse sources of information I ask myself a number of questions: What language is used in these different sources? What do they reveal about mice? What metaphors are used? What myths are referred
to? What kind of images of the mouse emerge in these writings or in these works of art? For this ‘reading method’, the writings of a number of philosophers and social scientists have served as a source of inspiration. They have provided me with basic concepts and methodological tools. Mary Midgley, for instance, has inspired me to take a closer look at metaphors and myths at work in scientific practice. Karen Rader inspired me to take a historical perspective on mouse biotechnology, and Jon Turney taught me how to connect scientific reports with public perceptions articulated in the media. These and other sources have allowed me to see the mouse as the ‘right organism’ for the job. They taught me that mouse images evolve along ‘never-converging tracks’, and that a philosophical understanding of the mouse calls for a ‘palaeontology of the present’. Finally, powerful images such as Bryan Crockett’s Ecce Homo have been of major importance for the development of my view on the genetically engineered mouse.

But there is more to philosophy than reading. An important, perhaps even decisive, source of information is personal experience. Trained as a medical biologist, I have worked with laboratory animals and, as a result, even decisive, source of information is personal experience. Trained as a medical biologist, I have worked with laboratory animals and, as a result, a ‘scientific gaze’ on the laboratory animal (Nuijtinck et al. 1997). I know, from ‘inside’ so to speak, what a scientist means when he or she says ‘we study these complex phenomena in the mouse model because …’. I understand what is to be deeply fascinated by small and inconspicuous processes such as cell-cell interactions or the function of a single gene in the complex process called DNA regulation that can only be made visible by technological devices such as microscopes, amplifiers, oscilloscopes and micro-arrays. On the other hand, as a philosopher I am trained to ‘read’ what lies behind these sentences: the so-called ‘self-evident’ and ‘obvious’ conventions of these research practices. How can an animal be a model? What is a model, and what kind of knowledge does it produce? The distance between various mouse perspectives becomes visible as soon as they come into contact, or even conflict with one another. The use of animals in experimental research is an issue of public moral debate of long-standing. Many philosophical questions about the use of mice in research are translated sooner or later into ethical questions. Can an animal be regarded as an instrument? Does it have intrinsic value, besides instrumental value? And, if it has intrinsic value, what does this imply for the scientific practice concerned? Some of the ethical questions are related to the practice of biotechnology. Does the genetic engineering of the mouse amount to a violation of the animal’s integrity?

In my experience the different vocabularies used in experimental biology and philosophy do not mix very well. This has been my experience as a member of an Animal Ethics Committee (In Dutch: Dier Experimenteren Commissie or DEC). On countless occasions, I had to explain the difference between ‘intrinsic value’ and ‘integrity’ at a DEC meeting or answer questions such as: ‘Is the integrity of the offspring of transgenic mice violated at birth?’ or ‘Can the integrity of mice be violated in different degrees and, if so, how can you measure this objectively?’ Between the two cultures of experimental biology and philosophy a gap seems to exist that is both epistemological and ethical. In order to deepen my understanding of this gap, I decided to do fieldwork in the mouse facility at the same institute where I was a DEC member, the Netherlands Cancer Institute (NKI). This institute plays a leading role in the Dutch mouse biotechnology. Much of the research conducted at the NKI involves transgenic mice. Mice are also created for scientists who work in laboratories outside the institute. The mice travel all over the world. At the NKI I visited the mice in the transgenic mouse facilities and talked to the biotechnicians who perform many of the surgical operations and actually do the genetic modifications, the animal caretakers who feed the mice and clean their cages, the researchers who plan the genetic modifications and use the mice for their research, and the mouse pathologists who search for the cause of death. I did this when they were all at work. I witnessed the routine procedures for breeding mice, transplantations of genetically modified embryos into foster mothers, the checking of the health and fitness status of the mice, the removal of organs as part of an experiment, and post-mortem autopsies of mice. As a result, I learned about the day-to-day ‘facts of life’ of these mice and the motives and visions of the people who work with them.

These experiences, together with the written sources studied, have shaped the outline of my research. It is not at all my intention to give a ‘correct’ or ‘objective’ image of the mouse. Such an image does not exist. Instead, I will present a broad variety of images in the form of photographs, quotes, artworks, visions, etc. The resulting image of the mouse is highly complex and ambiguous. Nonetheless, there is a certain amount of structure that can be discovered in this bewildering variety. Three basic (irreducible) mouse images will be identified.

2. Albert Wistar rats and goldfish, rather than mice.
**Rough outline of the book**

In Chapter 1, I focus on biological science. I introduce the mouse, so to speak, by entering its ‘natural’ habitat, the scientific laboratory. In order to answer the questions how it got there and how it evolved towards its present form, I go back to the early 1900s when the mouse made its entrance into biomedical science. From thereon I follow its ‘career’ as ‘the right tool for the job’ in genetics research. I describe three crucial steps in the ‘genealogy’ of the lab mouse: 1) the transformation of the mouse from an object of study as an *animal* into a homogeneous laboratory tool that could be used for studying of the laws of genetics; 2) its becoming the pioneering species in transgenic technology; and 3) its transformation into a mouse *model* used for the study of human diseases. It is here, I argue, that the mouse, as a result of a long process of human interference in its genetic make-up, has become a living artefact.

In Chapter 2, I focus on the moral and social debate about mouse biotechnology. What are the moral implications of the genetic engineering of research animals, and how should we deal with the genetically engineered mouse? How are these questions addressed and answered by philosophers? In the moral debate about animal biotechnology, I see three never-converging tracks. On the first, there is a discussion about the promise of biotechnology to cure us from life-threatening diseases; on the second, a discussion about animal suffering; and, on the third, a discussion whether we humans have any right at all to tamper with genes or to ‘play God’. On these three tracks, three different images of mice appear: (1) mice as high-tech laboratory tools; (2) mice as animals of flesh and blood and as victims of science; and (3) mice as monsters that resemble the one that Frankenstein created. These images do not easily converge into an unequivocal moral verdict on mouse biotechnology, since they refer to different and perhaps even incommensurable moral values, such as progress in biomedicine, animal welfare, and respect for nature. According to Bernard Rollin, one of the most influential philosophers writing about animal biotechnology, only welfare issues are morally relevant. Other objections are, as he argues, ‘merely’ aesthetic. Many philosophers (including me) and members of lay audiences have strong objections to this line of reasoning. There clearly seems to be more at stake in animal biotechnology than animal welfare: namely, our vision of nature, or what we take as being natural. However, in day-to-day research practice, a utilitarian balance between human benefits and animal welfare seems to be the dominant ethical framework, for biomedical scientists, as well as for members of animal experimentation committees. Why this is the case I will explain by building on Martijn Smits’s monster theory. This theory discusses public responses to the products of new technologies that at first sight challenge the nature-culture dichotomy. The genetically engineered mouse is such a ‘product’. I will argue that the mouse, despite its general use in the biomedical laboratory and its apparent domestication, is still a monster for many. Its monster character is, amongst other things, revealed by the myths, metaphors and vocabularies that dominate the biotechnology debate. I will highlight the three most important ones: Playing God; the Frankenstein thing; and the yuk!-factor. What ‘truths’ lie behind these metaphors and myths? In order to answer these questions, I analyse these metaphors and/or myths in Chapters 3, 4 and 5 in more depth.

In Chapter 3, I take the artwork *Ecce Homo* by Crockett as a starting point to discuss the playing God metaphor, or God talk, in biotechnology. In this sculpture, the genetically engineered oncomouse is represented as Jesus Christ. It is a very powerful visual image of the playing God metaphor. It suggests not only that scientists who are involved in mouse biotechnology play God but also that this type of science leads to salvation. Exploring this myth of science as salvation, I will argue that, regardless of whether we take the science-as-salvation idea literally or metaphorically, it reveals that biotechnology has the character of a promise. And the genetically engineered mouse represents the promise of biotechnology in flesh and blood. Biotechnology is a future-oriented technology, a technology whose hopes and promises are more or less science fiction. But who is promising, and what is being promised? Who is playing God? What is their ultimate plan? What are the implications of mouse biotechnology for ordinary people?

This takes me to the fear of monsters coming out of laboratories, to be discussed in Chapter 4. This fear is often formulated by referring to Mary Shelley’s *Frankenstein*. Frankenstein’s monster is more or less the archetype of popular ‘biotech monster phobia’. In this chapter, I will address the question what it is that people find fearsome about biotechnology when they refer to Frankenstein. How does the myth of Frankenstein relate to new developments in biotechnology? What is the actuality of the myth? In order to answer this question I will tell the stories of four super mice and their creators and illustrate some of the (future) possibilities of genetic human enhancement. I will argue that, in the days of the super mice,
rereading Shelley’s novel is of great importance because biotechnologists did indeed discover a monster: namely, the fact that our own DNA, our essence, is malleable. How do we distinguish between good and bad ‘genetic re-creations’? Is this purely a matter of taste?

Finally, in Chapter 5, I will explore more extensively the relationship between judgments of taste, aesthetic judgments and moral judgments about animal (or human) biotechnology. To do this, first, I will return to Rollin’s argumentation, as it was discussed in Chapter 2. Rollin believes that moral concerns based on ‘aesthetic judgements’ are not genuine moral concerns. In opposition to Rollin, I will argue that we have to take aesthetic judgements very seriously. Moral convictions are always based on a mixture of both reason and feeling. People who say ‘yuk!’ when being confronted with animal biotechnology are expressing genuine feelings of moral concern but apparently lack the vocabulary to do so in a philosophically articulate way. What is expressed when people say ‘yuk!’? I will argue that two things are involved in the yuk-response to animal biotechnology: namely, a feeling of confusion, or even disgust, that is the result of our vision of nature losing its status of being given, unquestioned and self-evident ‘objectivity’, and the threat that animal biotechnology imposes on what we perceive as good life, or a life worth living. The second question I address in this chapter is what the role of art could be in the age of the biotech revolution. How can contemporary art assist in the moral and social assessment of animal biotechnology, in particular where questions about visions of nature, quality of life, identity, the normal and the abnormal are concerned? To illustrate my argument, I will introduce three art projects: the GFP Bunny project by Eduardo Kac (2000); the Transgenic Mice series by Catherine Chalmers (2000); and Genpets™ by Adam Brandejs (2005). I will argue that the most important value of bioart lies in making visible the invisible.

Chapter 1
The birth of the transgenic laboratory mouse

Over time, one invariable lesson of biological research has been the difficulty, virtual impossibility, of reliably predicting the properties of intact organisms from the properties of their constituent tissues, cells and molecules. Philosophers have argued the reasons, but empirically we know that accurate prediction is not possible now, or in the foreseeable future. For the genetics revolution to provide the insights we hope to gain into the human condition, we must have adequate experimental animals.3

Kenneth Paigen

The human code was just the top layer of Celera’s information lode. Most valuable of all – even more important, perhaps, than the human code – would be the mouse genome… on the genomic level people and mice are amazingly similar… This is what makes mice such superb lab models for cancer and other human diseases: genetically, they are essentially little hairy human beings that can be manipulated in the lab in ways that people obviously cannot.4

James Shreeve

Animals are born, are sentient and are mortal. In these things they resemble man. In their superficial anatomy – less in their deep anatomy – in their habits, in their time, in their physical capacities, they differ from man. They are both like and unlike.5

John Berger

Introduction
Meet them in the lab

They are mice like any other. As a rule, there is no way you can tell from the outside whether a mouse is genetically modified or not. If you want to know, you have to look at its genes. This is not to say that transgenic mice

are ordinary mice. On the contrary, whoever visits the transgenic unit of a research laboratory for the first time will be surprised by the large variety of specific mouse strains that are involved in mouse biotechnology. Every mouse strain has its unique properties. They differ in coat colour, the typical behaviour they display, and the distinct physical properties they have. The OLA, for example, also known as the 129, is very cute; it has a beautiful silver grey coat. It is a mouse of great value because it has good embryonic stem (ES) cells. At this moment there is no other mouse with ES that can so easily be cultured in vitro. Apart from that, however, it is a remarkably stupid animal, according to some researchers at least. Moreover, the 129 mice have a bizarre pathology. Over time they all develop an infection of the eye. The FVB, a traditional white mouse, is a neurotic creature. You can easily recognize this animal when it is running in circles. But according to the molecular biologists who work with such mice, it is a 'supermouse' because of its embryonic properties. The FVB embryo is very easy to manipulate, but only by means of micro-injection. You cannot place cells of another mouse into a FVB blastocyst. In contrast to the FVB the blastocysts, those of the ‘black six’, also known as B6, are easy to manipulate. This is one of the reasons why it has become such a popular mouse. The B6 is also an excellent foster mother. Because of its character and good looks, it is the favourite animal of many who work with mice. The B6 is a beautiful, dark-coated, small mouse, originally bred by Chinese breeders of fancy mice. Quite striking to see are the patched chimeras, which are a mixture of two mouse strains. The cells of these mice, including the cells that make up the coat, originate from the embryo cells of two different mice and therefore have a different genetic make-up.

The transgenic mice live in animal quarters referred to as mouse facilities. A tag is attached to their cage that provides information about the specific mouse strain: the genetic modification it carries; whether it is a homozygote or a heterozygote for this modification; its date of birth; and other specific information relevant to the animal caretakers and researchers. Before entering the mouse facilities one has to change clothing and shoes and wash hands thoroughly for a minute. This is merely one of the measures that have been taken to avoid the contamination of these precious animals. Bred only to live in laboratories, these mice are very susceptible to infections. For example, mice with severe immune deficiencies need to be kept pathogen free⁶. Outside the safe walls of the laboratory, many of these inbred mice, transgenic or not, would probably not survive very long.

The secret of the mouse’s scientific career

The ‘natural’ habitat of these laboratory mice is the laboratory. Nobody who is at home in contemporary bio-medical science will be surprised to see transgenic mice in a research facility. But how did they get there, and, why were these mice introduced into the laboratory? Since the first transgenic mice were born in the early 1980s, transgenic mice have had an impressive career within the life sciences. The vast majority of transgenic animals that can be found in a contemporary laboratory are mice. But, why was it the mouse, and not another animal, that became the most popular animal in transgenic technology? And, last but not least, how has the mouse evolved during the past 100 years as a laboratory animal? Not only in a literal sense: How did scientists influence the evolution of the lab mouse as a species, how did they influence its genetic make up, its genome? But also in a ‘conceptual’ sense: How did the mouse change from the perspective of the researchers?

This chapter is meant to be an introduction to the main protagonist of this book: the genetically modified mouse. It is not a creature ‘ex nihilo’, but the outcome of a long and unique history, an important chapter of the history of the life sciences. To understand the transgenic mouse of today, we have to look at its genealogy. For the reconstruction of the ‘birth and rise’ of the genetically engineered laboratory mouse, I use four types of written sources: 1) publications in the major scientific journals such as Science, Nature and Proceedings of the National Academy of Science. It is here that scientific breakthroughs are first presented to the scientific community and the public, and the scientists discuss the new mouse technologies in scientific reviews; 2) responses to these publications in the popular media such as national newspapers. These are a useful source of information because they reflect the spirit of the times and give a good impression of how developments in biotechnology are perceived by the public, and in the interviews with the responsible scientists important personal statements can be found that are illustrative of the scientific expectations of biotechnology at a particular time (e.g. Schmeck 1983; Saltus 1990; 6. This introduction is based on exploratory ‘fieldwork’ carried out at the NKI in the Spring of 2003.
Rensberger 1992b; Schrage 1993); 3) retrospectives by scientists who, for different reasons, look back on their own field of research and the animal with which they are so familiar, by highlighting either the pioneering role of great scientists (e.g. Paigen 2003a,b; Crow 2002; Klein 2001; Arechaga 1998; Papaioannou 1998; Russel 1978) or their own role in the development of the new revolutionary technology (e.g. Snell 1978; Strong 1978; Smithies 2001; Evans 2001; Capechi 2001; Tarkowski 1998; Palmitier 1998; Bradley et al. 1998), or in order to praise the mouse after the cracking of its genetic code for its contribution to biomedicine (Clarke 2002; Travis 2003); and, 4) last but not least, the work of social scientists who study the emergence of typical research models, laboratory animals, and research materials and give answers to the question how and why the mice became ‘the right organism for the job’ (Rader 1999, 2001). From these sources it can be concluded that the mouse was introduced into the biomedical laboratory a century ago. Since then, it has experienced a number of dramatic transformations. These transformations reflect important shifts and changes in biomedical power. For many years, before the emergence of transgenic technology, mice had been present in biomedical laboratories all over the world. Their specific evolution is highly influenced by science, but at the same time the laboratory mouse (its strengths and weaknesses as a model) has influenced the evolution of science as well. Ever since mice were introduced into laboratories, their genome has been influenced by the research agendas of science, but the opposite is also true: research agendas have been adapted to the mouse genome. The laboratory mice that have been used to create transgenic mice were by no means ‘normal’ mice. They were the result of a long process of inbreeding. But, probably even more important, as a result of the inbreeding, inbred mice have developed some unique properties that make them very suitable for transgenic technology.

Three crucial steps can be discerned in the ‘scientific career’ or ‘genealogy’ of the lab mouse. The first step was the transformation of the mouse from an object of study as an animal into a homogeneous laboratory tool that could be used for studying the laws of genetics. A second important step in the career of the mouse came about when the mouse became the pioneering species of transgenic technology. The third and final step can be described as the transformation of the mouse into a model. The mouse has become a mouse model, a transgenic stand-in for human beings in biomedical research.

This chapter takes a more or less chronological approach, and is structured around these three steps. In Part One, I describe the birth of the laboratory mouse. Its history begins in the early years of the 20th century when researchers in biology began to inbreed mice for scientific purposes. Once this first step was taken, the inbred mouse became an important instrument in genetics. With this practice of inbreeding a new ‘phenomenon’ was born, the mouse became a laboratory mouse. In Part Two, I describe the transgenic revolution. When two critical threshold conditions were met in the 1970s: namely, the possibility to culture embryos in vitro, and the availability of DNA recombination technologies, a second step was taken: the creation of the transgenic mouse. I will refer to the development of the first transgenic mice and the technological improvements that led to the increasing control over gene expression as the ‘transgenic revolution’. In Part Three, I describe the development of the mouse as a model. During the transgenic revolution, research was primarily focused on gene regulation. When the possibility arose to knocked out genes in a more direct and controlled manner, the mimicking of human gene defects in mice became the next challenge. With the ‘discovery’ of the knock-out technology the ‘career’ of the transgenic mice received a real boost. The mouse then evolved into the animal model for human diseases. This evolution, from laboratory tool into stand-in, is one that is still taking place today. Every week, it seems, new mouse models are reported that mimic human genetic diseases.

Part One: The ‘birth’ of the laboratory mouse

Clarence Cook Little’s inbred mice

All the sources I consulted concerning the history of the laboratory mouse point to Clarence Cook Little as the first and most important scientist responsible for the ‘creation’ of the inbred mouse, the predecessor of the

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7. The three steps are defined on basis of content not chronology: the different steps run parallel in time.
8. Rader (1997, 1999); Mobraaten and Sharp (1999); Russell (1978); Paigen (2003a); Strong (1978); Hogan et al. (1986).
9. Three inbred strains in particular play a role in the transgenic revolution: the FVB, because of the large nucleus of its embryos; the B6, because of its easy to manipulate blastocysts; and the 129, the only
transgenic mouse. In retrospect, his work can be seen as the beginning, the first milestone in controlling the genetic nature of mice for research purposes (Mobraaten and Sharp, 1999). Little studied biology at the beginning of the 20th century at Harvard University. There he followed genetics classes with W.E. Castle, Professor of Zoology, who invited him to work at his lab at the Bussey Institute. In November 1907, Little took over the work of maintaining Castle’s mouse stock. Castle believed that practical experience with real organisms was the best way to learn about genetics (Rader 1999). At the Bussey Institute, Little studied the inheritance of coat colour in mice. Most mice came from Granby Mouse Farm, managed by Abbie Lathrop. In those days, fancy and exotic mice were a much sought after curiosity. The mice that came from Lathrop’s farm were selected on the basis of physical features such as: friendly character, coat colour, or curious kinds of behaviour (for example: the Japanese waltzing mice). These animals – by no means wild mice – were Castle’s and Little’s experimental raw materials. Before entering Little’s scientific breeding programme, these mice were already the result of many years of selective breeding.

In the early days of the Bussey Institute, shortly after the rediscovery of Mendel’s work10, there was much discussion about whether the laws of genetics could be studied through inbreeding. Little was convinced that, for research on the Mendelian inheritance of specific characteristics in mice, pure strains (that is, strains with a homogeneous genetic background) were needed. This was the reason why in 1909 he began to inbreed mice for his research in genetics. He bred mice that were recessive for specific coat colour genes by mating brother and sister in each generation in order to maintain the recessive genes. In those days, inbreeding of mammals was a controversial practice. For example, Castle, his own professor, who saw himself as an ‘experimental evolutionist’, did not believe that inbreeding alone could ever produce artificial yet stable genetic forms of truly stable strains (Rader 1999). An inbred variety tends to be delicate and sickly, and to be therefore rather susceptible to disease. Animals that do survive often become infertile. Few scientists believed that viable strains of inbreds could be maintained in the long run (Strong 1978). Notwithstanding the overall scepticism that his work provoked, in 1911 Little was able to report his first successful inbred strain, the DBA strain, named after its coat colour, diluted, brown, non-agouti.

It was not only his breeding skills that made Little the ‘father’ of the laboratory mouse. According to ‘laboratory mouse historian’ Karen Rader, Little was ‘not the first person to think of inbreeding mice or mammals, he was not the only researcher working with mice and not the only scientist to see the methodological potential of homogeneous mammalian animals for freeing genetic research from the local limits of time and space. [...] however, he stabilized inbred mouse material at the time that he effectively connected this material to well understood sets of research questions and approaches in the rapidly expanding discipline of Mendelian genetics.’ (Rader 1999: 328).

Of mice, Mendel and cancer research

Researchers soon discovered that an important property of inbred mice was the relatively high incidence of spontaneous tumours. Some strains possessed unique susceptibility characteristics to various types of cancer (Mobraaten and Sharp 1999). Little’s DBA mouse for example displayed a hereditary susceptibility to mamma tumours (Rader 2001). It was not surprising, therefore, that the focus of Little’s research changed from coat colour to cancer research (Russel 1978). He was convinced that cancer was genetically determined and followed a Mendelian pattern of inheritance12. In order to study his hypothesis, he moved to Tyzzer’s lab in 1913. Tyzzer, a researcher on tumour resistance, had recently discovered that tumours derived from the Japanese Waltzing mouse (also an inbred strain) could be transported to mice of the same strain, but not to mice of other strains. Wild mice did not ‘accept’ the tumour transplants. In addition he saw that when he crossed the Japanese mice with wild type mice the resulting offspring F1 generation accepted the tumour but mice of the F2 generation did not. From these data he concluded that tumour susceptibility was not an inherited Mendelian trait. These confusing research data were the reason for a strong debate within the scientific community about the

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10. In 1900, three botanists – Hugo de Vries, Carl Correns, and Erich von Tschermak – independently rediscovered Mendel’s work.


12. Mice breeder Lathrop also reports in 1908 the occurrence of spontaneous tumours in some of her mouse strains. Lathrop and researcher Loeb started a study on the inheritance of cancer in mice. But unlike Little they did not link their cancer data to the Mendelian laws of inheritance. (Rader 1999)
validity of the Mendelian postulates. Arguing in favour of Mendel, Little postulated that multiple Mendelian factors could explain the observation of the different tumour susceptibility in the F1 and F2 crosses. In other words, Little suspected that the effect observed could be explained by the involvement of more than one gene in tumour resistance. He suggested that a large number of genes were involved in determining whether a mouse would reject or accept a transplanted tumour, and that for each of these genes there were two alleles, one dominant and one recessive (Paigen 2003a). In order to prove his theory, Little compared two different homogeneous strains: the Japanese Waltzing mouse and his own DBA. His hypothesis was confirmed (Paigen 2003a; Rader 1999). It is important to note that, because of the mathematical precision of Little’s Mendelian based theory predictions, the multi-factorial hypothesis of cancer transmission could, by definition, only be probed with inbred mice (Rader 1999). In heterogeneous mice one has no control over the interference of other ‘background’ genes in the resulting phenotype. Research data obtained from heterogeneous mice would simply be too complex to interpret.

With the linking of mouse genetics to cancer research the inbred mouse became the model animal for this type of research, simply because it was the best available candidate. Amongst mammals the mouse is second only to man in frequency and variety of spontaneous cancers. ‘Regrettably the frequency of occurrence was still all too rare’, noted Strong in a reflection on Little’s work. ‘A single mouse with a spontaneous tumour was selling for $300 in laboratories on the eastern seaboard. The use of mice in the number for quantitative research necessitated a ready supply at minimal cost’ (Strong 1978) 13. During the first half of the 20th century, cancer was the driving force behind mouse genetics. It greatly influenced the development of the mouse as a genetic system (Paigen 2003a). However, the career of the inbred mouse as model animal for cancer research did not proceed without dispute. Little became involved in a controversy with another prominent researcher in cancer genetics, Maud Slye, that lasted for years (Russel 1978; Rader 1999). Slye was of the opinion that research on inbred animals could never lead to reliable research data. Little had to convince other scientists of the usefulness of his inbred mice. Not only did the mice themselves have to be changed – into homogeneous lab animals – but the dominant mind-set in the scientific community had to change as well. Little invested 40 years of work in his own laboratory, now known as the Jackson Laboratory, to get his inbred mice accepted.

The rise of mouse genetics

Of course, Little was not the only researcher involved in the early history of the inbred mouse. In 1918 he moved to the Cold Spring Harbor laboratory on Long Island (New York) where, at the station for experimental evolution, a small but robust research group was formed, focussing on mouse genetics. They called themselves the ‘Mouse Club of America’. It was here that the research on tumour genetics using inbred mice started to get serious. (Russel 1978; Pennisi 2000; Rader 1997). Well-known researchers from the Mouse Club, besides Little, were Halsey Bagg, Leonard C. Strong, George Snell and Leslie C. Dunn. A number of inbred mouse strains in common use today were developed during that period by these researchers. These mouse strains were created either as strains exhibiting a very high incidence of spontaneous neoplasia or as strains that proved to be useful as the necessary low-incidence controls (Paigen 2003a). The BALB/c for example, the first albino mouse, now one of the best known inbred mice, was bred by Halsey Bagg (Pennisi 2000). Strong, one of Little’s co-workers, crossed this BALB/c with an albino produced by Little into what they called the ‘A-strain’ (Strong 1978). This mouse had a very high predisposition for lung and mamma tumours and was therefore very suitable for cancer research. Subsequently, Strong kept inbreeding this A-strain resulting into the C3H high tumour incidence sub-strain. With the aid of these mice he was able to show that cancer is indeed inherited (usually in a dominant way) (Strong 1978). In 1921 Little bred the C57BL line. This is the inbred mouse line from which the sub-variety C57BL/6 originates. C57BL/6 also referred to as

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13. The origin of inbred mice by Morse III (1978) is accessed via the digital version on the internet. Therefore, the page numbers of quotations from this book are not available.
B6 or ‘black six’, is one of the most popular mice today. It is also the mouse whose genome was ‘cracked’ in 2002 (Waterston et al. 2002). The name ‘B6’ originates from the number of the ‘mother’ or founding female of this strain; she was female number 6 of the C57BL strain (Russell 1978). In 1928 Dunn bred the 129, a mouse with a high incidence of testicular carcinoma. This mouse was the predecessor of the 129/Sv, a mouse variety of great importance for transgenic technology because of its ES cells.

In 1929, Little founded the Roscoe B. Jackson Memorial Laboratory, now known as the Jackson Laboratory, in Bar Harbor. Other prominent members of the Mouse Club soon followed him. It is from here that the inbred mice started to conquer the world, notably when in 1933 the laboratory began to sell inbred mice to other laboratories. The selling of mice soon became an important activity of the Jackson Lab, as it still is today. In 1941 the laboratory shipped 2500 mice a week, and in 2002 the number of mice shipped per week was 44,000 (Crow 2002). Thus was established the international fame that the Jackson Lab and the ‘Jax™’ mice have today.

Although cancer research was a dominant stream, not all members of the Mouse Club were into it. Dunn for example, also a pupil of Castle, used inbred mice to study genetic mapping, the localisation of genes on the chromosomes (Lyon 1990). In 1920, he published the first paper on the systematic search for linkage amongst coat colour varieties. This pioneer work on the genetic mapping of the mouse genome would later become of great importance to genomics and the human genome project. Another big name in mouse genetics was George Snell, who joined the Jackson Lab in 1935. He too was a pupil of Castle, and was mainly interested in the genetics of tumour rejection, rather than in the genetic mechanisms underlying cancer as such. Snell was interested in the genetics behind the immune system. In 1936, the major immune histocompatibility complex, at that time referred to as H2, had been discovered by immunologist Peter Gorer. In order to eliminate complexity introduced by the presence of different interacting H loci, Snell set up an ingenious strategy of cross-intercrossing and cross-backcrossing and started with the breeding of congenic strains14 (Klein, 2001). With these mice, Snell discovered in 1951 that one of these H loci was more important than the others, and he also found a visible genetic marker with which he could follow the segregation of the H locus. Later, Snell discovered that the H locus was in fact a complex. Today we know this H2 locus as the major histocompatibility locus, one of the most important elements of the immune system. In 1980 he received the Nobel Prize for this boundary-breaking work (Paigen 2003a).

### Box 2

**Decoding a mouse name**

The rules for coding a (transgenic) mouse strain are described by the International Committee on Standardized Genetic Nomenclature for Mice (see: http://www.informatics.jax.org/mgihome/nomen/gene.shtml)

A name code informs about the strain of the mouse, its origin (the lab where it was bred), the name(s) of the researcher(s) responsible, and its mutation.

<table>
<thead>
<tr>
<th>Origin</th>
<th>Strain</th>
<th>Researcher</th>
<th>Gene (mutation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cr</td>
<td>129</td>
<td>Stevens</td>
<td>b-m2</td>
</tr>
<tr>
<td>J</td>
<td>A</td>
<td>Evans</td>
<td></td>
</tr>
<tr>
<td>Tac</td>
<td>B6=57/b6</td>
<td>Bradley</td>
<td></td>
</tr>
<tr>
<td>HSD</td>
<td>D1=DBA1</td>
<td>Balb/c</td>
<td></td>
</tr>
</tbody>
</table>

This mouse is the 7th sub-strain (steel-colour coat) of the 129 that it was bred in Stevens, Evans and Bradley’s laboratory, and that carries a mutation for the b allele of the Hprt gene. The coding ‘m2’ indicates that the gene has been mutated for the second time (Malakoff 2000).

In 1939, the inbreeding of mice had reached such proportions that a reliable and extensive overview of the inbred strains was needed. For that purpose The International Committee on Standardized Nomenclature for Mice was founded. All mice strains were given names and codes on the basis of a standardised system. Later the term ‘genetic’ was added to the nomenclature. The committee was charged with the task of establishing and updating rules and guidelines for genetic nomenclature (Silver 1995). Mouse genetics is by its very nature a collaborative field of scientific investigations. It is therefore of key importance that researchers speak the same language and use the same coding system. Now, with the explosive growth of transgenic mouse strains this nomenclature, has become indispensable.

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14. Congenic strains were created by repeated back-crossing of the F1 to one of the parents and selecting those individuals from the F2 that carried the H2 type coming from the other parent (Paigen 2003a).
Another sign of how the mouse research became more strongly organised was the *Mouse News Letter* that started to circulate in 1949. This newsletter was renamed *Mouse Genome* in 1990 and *Mammalian Genome* in 1997.

**The mouse and the Wistar rat**

An interesting comparison can be made with the rat, another commonly used laboratory animal. The tale of the Wistar rat also starts at the beginning of the 20th century, when Helen Dean King at the Wistar Institute worked on an inbred rat strain. It was her explicit goal to develop a standard lab animal, an animal that would generate the same research data at different laboratories (Tocher Clause 1993), an animal one could make atlases of. This albino rat, also known as the Wistar rat, can still be found in large numbers in laboratories all over the world. It has become the standard lab rat. In modern laboratories, the name ‘Wistar’ stands for reliability and quality. As Little and Dean had already shown, inbreeding does not necessarily lead to inferiority and infertility. On the contrary, with her Wistar rat, Dean proved that by inbreeding it is possible to produce useful qualities such as mild character, fertility, etc. Notwithstanding these similarities, the *inbred* mouse and the *inbred* rat have had totally different careers in science. Whereas the rat is a popular animal in physiology and behaviour studies, the mouse is the animal associated with genetics and cancer research. After the discovery of the MHC, mice also became associated with immunology.

**‘The right tool for the job’**

One of the most important transformations that the mouse underwent at the beginning of the 20th century was from animal research object into a ‘laboratory tool’. Little was not interested in mice as animals, but in what he could learn from them about genetics. He used his inbred mice to study Mendelian genetics in a living species. As a result of his scientific approach, a combination of inbreeding and mathematics, the mouse became an instrument rather than an animal. Mice became part of the standard equipment of the modern genetics laboratory. For Little, the mouse probably had the same meaning as the pea had for Mendel. 15.

Little and his contemporaries were trying, so to speak, to look *through* the animals towards the laws of genetics. They were not interested in the mouse per se, but in his mysterious genes. They developed a *genetic gaze* on the animal. The laboratory mouse as a *phenomenon* was born.

The scientific rationale behind the mouse strains is well illustrated by the words of Mobraaten and Sharp: ‘High quality research depends on the purity and consistency of reagents, including experimental animals, for efficient reproducibility of results. It is readily recognized that the purity and consistency in experimental animals depends on both genetic homogeneity and controlled environments that avoid variation caused by nutritional, pathogenic or other environmental effects’ (Mobraaten and Sharp 1999: 129). To serve science best, the mouse not only had to be transformed into a tool or instrument, it had to become the ideal tool for studying genetics, that is, it had to be as reliable and predictable as possible. In order to achieve this goal, Little and his colleagues had to eliminate as much variation as possible within their mouse strains. The interchangeability of individual mice within a strain guaranteed scientific objectivity and efficient reproducibility of results. The quality of the mice depended on their purity and consistency. In the hands of the geneticists, the population of laboratory mice evolved into a collection of homogeneous strains. Mice of a congenic mouse strain are more or less genetically identical and therefore exchangeable. The variety *between* mouse strains, on the other hand, is quite significant. A specific inbred strain stands for specific behavioural and physical properties. This genetic variation between, but not within, different mouse strains, has made it possible to study genetics on the smallest level: the single gene. In the process of becoming the *right tool* for genetics research, the individual mouse lost its former identity as an animal. The individual mouse became the equivalent of the mouse strain it represented. This is also reflected in the language of researchers, who refer to their mice as to ‘BALB/c’, 129 or ‘black six’. In a unique process of selection, an artificial *subspecies*; namely, that of *inbred* strains, was created.

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15. Mendel himself started his research on the genetic inheritance of coat-colour traits by breeding mice he kept in his two-room living quarters. But, according to the Austrian Bishop Anton Schaffgots, it was inappropriate for a monk to share his living quarters with creatures that had sex and copulated.

The transformation into a ‘standard’ or model animal was not unique for the mouse. But its role in genetics was. For research in genetics, mice were, at that time (as they are today) simply the right organism for the job. The mouse was cheap, easy to keep, and eager to multiply and reproduce itself. Newborn pups take about ten weeks to mature, so scientists could breed several generations in a short period. Moreover, mice are small, relatively tame, and require less space, food and attention than, for instance, dogs, rabbits, or other animals. But most importantly, fancy mice, available from breeders and collectors of pet mice, were a physically diverse lot (Stroh 2002). They were a pool of interesting mutations in terms of coat colour and behaviour. All these characteristics made the mouse of key importance to genetics research. And when it turned out those mice, partly as an effect of their inbreeding, displayed a high incidence of tumours, the career of the mouse became a fact. Genetics determined the (genetic) fate (evolution) of the research mouse. As the dominant mammal in genetic cancer research, the mouse, in turn, influenced the course of mammalian genetics. The fact that researchers knew so much about its genes, their familiarity with the animal in the lab, and some typical properties of some inbred strains, all made the inbred mouse the ideal candidate for a pioneering role in the transgenic revolution that started in the late 1970s.

Part Two: The transgenic revolution

‘Those were heady days’ wrote Virginia Papaioannou in 1998, in a reflection on the ‘coming of age of the transgenic era’. ‘For those of us entering the field of genetics and mammalian embryology in the 60s and 70s, the excitement was palpable. As graduate students and post-docs, we saw that long-standing barriers were tumbling down before an onslaught of technological advances. And not only that the scientists breaking those barriers were all around us as mentors and colleagues. The rapid pace of progress and the seemingly boundless possibilities hooked us into the field, and we gradually became aware that we, too, were part of a revolution that was the way to opening the mammalian genome to experimental alteration’ (Papaioannou 1998: 841).

Manipulating the genome: recombinant DNA technology

In the early 1970s, two necessary conditions for the making of transgenic mice were met: recombinant DNA technology, and in vitro culture of mouse embryos. In 1972, Paul Berg, a pioneer in the field of biotechnology, created the first recombinant DNA molecule. With his pioneering work, Berg showed that DNA can be manipulated and, even more, that DNA from one organism could be transported to another organism. In 1972 he used a plasmid, a bacteriophage, and E. coli DNA for his recombination. In 1980 he received the Nobel Prize for this boundary-breaking work (Anonymous 1980). The big question was, of course, whether DNA recombination would also be possible in mammalian cells, or even whole organisms. The genetic modification of a mammal is for several reasons more complicated than a single mammalian cell or single cell organism. In order to create a genetically modified mammal, one needs to manipulate its embryonic cells. This is only possible in vitro. The next step is to place the manipulated embryo into a pseudo-pregnant foster mother in order to let it develop into a normal whole organism. This asked for completely different skills, knowledge and technologies than those which the geneticists had been acquainted with so far.

Manipulating the embryo: the search for the ES cell line

In the late 1960s and early 1970s, besides genetics, another field within biology: namely, developmental biology, started to play an important role in the history of the lab mouse. Scientists such as Andrzej Tarkowski, Beatrice Mintz, Ralph Brinster and Richard Gardner started to experiment with the in vitro culture and manipulation of embryonic cells. They did so because they were fascinated by the processes that led to the development of a complex organism out of one single embryo cell. In the early 1960s, Tarkowski and Mintz independently demonstrated that fusing two 8-cell mouse embryos (3-day old) would produce chimeric adults containing cells from each original embryo (Arechaga 1998). The mouse embryos they used originated from mice with different coat colours. The resulting chimeras had a patterned coloured coat. ‘The composite animals that developed from such combinations of genetically different cells were dramatic to look at, but were even more impressive considering the potential they held for tracing cell lines, testing cell potential, and eventually (as we shall see later) as vehicles for gene manipulation’ (Papaioannou 1998: 841).
that these were remarkable experiments can also be concluded from the words of Tarkowski, who reflected upon his own work in 1998: ‘At that time the idea of making one mammalian individual by aggregating two cleaving embryos must have looked rather preposterous and later I wondered why Professor Rogers F.W. Brambell, under whose supervision I worked […], had accepted this […] crazy project which I proposed to carry out in his laboratory’. But the fact that somebody else, namely Beatrice Mintz, was involved in exactly the same experiments surprised him even more (Tarkowski 1998: 903).

Soon, others started to experiment with embryos. In 1968, Richard Gardner also successfully ‘created’ mouse chimeras. Unlike Mintz and Tarkowski, he did not fuse whole embryos. He injected embryo cells from one mouse into 4-day old blastocysts of another mouse (Arechaga 1998; Tarkowski 1998). Ralph Brinster, who was inspired by Gardner’s work, saw great potential in this blastocyst injection technique: ‘I believed that there were multipotent cells in older postimplantation embryos (e.g. 6-8 days old) as well as cells from teratocarcinomas that would colonize a blastocyst, thereby influencing differentiation of an embryo in a predictable way, and perhaps enter the germ line’ (Arechaga 1998: 866). In 1972 Brinster and his co-worker Moustafa were able to report another success when they succeeded in the creation of chimeras out of embryo cells of different ages, even up to 7-8 days (Moustafa and Brinster 1972). These studies supported the idea that mouse blastocysts could be colonised by nonsynchronous cells (cells of different age).

Encouraged by these results, Brinster searched for a pluripotent cell line that could be manipulated in vitro and subsequently replaced in a mouse blastocyst. Today we know this pluripotent cell line as the ES cell line. The history of the ES cell line dates back to 1967. In that year, Leroy Stevens bred a mouse strain with a high incidence of spontaneous testicular teratomas. This mouse, still widely used today, is the 129/Sv. In 1972 Stevens cultured the OTT6050 cell line. These stem cells and also of multipotent (non-differentiated) stem cells known as embryonal carcinoma (EC) cells or teratocarcinoma. From these 129/Sv teratocarcinoma, Stevens cultured the OTT6050 cell line. These stem cells, or EC cells, resemble early embryos qua morphology, biochemistry and cell surface (Papaioannou et al., 1975). After his success with the chimeras in 1972, Brinster was able to lay his hands on this OTT6050 teratocarcinoma cell line. The cells he obtained had to be cultured as an ascites17 tumour (in the abdomen of a host mouse). Brinster injected these embryonic cells, once obtained from an agouti-pigmented mouse, into the blastocyst from a random bred albino mouse. According to his own reports these experiments were very successful18. In 1974 the chimera mouse with agouti stripes on an albino background was born (Arechaga 1998). In 1975 Mintz, working at the Institute for Cancer Research in Fox Chase, Philadelphia, reported about the genetically mosaic mice. Like Brinster, she used Stevens’s 129/Sv teratocarcinoma. Mintz was surprised about the potential of malignant cells to develop after 200 transplant generations (8 years in culture as an ascites tumour) into normal functional cells in the chimeric mice. ‘The tumor itself generally kills its host by 3-4 weeks after transplantation. Yet our oldest mosaic animal […] is now 11 weeks old and appears to be healthy and vigorous’, she wrote in a Proceedings of the National Academy of Science article in 1975 (Mintz and Illmensee 1975: 3588). On the basis of these experiments, Mintz drew important conclusions about the development of malignancies. The origin of this tumour from a disorganized embryo suggests that malignancies of some other, more specialized, stem cells might arise from comparably thorough tissue disorganization, leading to developmental aberrations of gene expression rather than changes in gene structure’ (Mintz and Illmensee 1975: 3585).

Gardner’s team from Oxford and Evans from London together confirmed in 1975 that these teratocarcinoma in vivo could add to normal morphogenesis and differentiation (Papaioannou et al. 1975).

The results were impressive and hopeful but, nevertheless, the researchers did not succeed in the transmission of the teratocarcinoma cell line into the germ line of the mouse (Papaioannou 1998; Bradley et al. 1998). An additional complication was the method of culture. The teratocarcinoma had to be cultured in vitro as an ascites tumour, which made it hard to manipulate the cells prior to injection into the blastocyst. This problem was solved when Evans and Kaufman in 1981 reported about a pluripotent ES cell line that could be kept in an in vitro culture. These ES cells had, in contrast to cells derived from the embryonic carcinoma, a normal karyotype (Evans and Kaufman 1981). Another great advantage of the ES cells was that they could be cultured directly from the embryo. The

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17. An ascites tumour is a tumour that is kept alive in the abdomen of the mouse. As a result the mouse develops a painful ascites.

18. Beatrice Mintz is, however, more sceptical about his results (Mintz and Illmensee 1975).
technique to culture ES cells from embryonic cells was of great importance to the later gene transfer technology. Evans and Kaufman initially named their cell line the EK cell line, an acronym of their own names. But Gail Martin, who conducted similar experiments a year later, introduced the term ‘Embryonic Stem cell’, ES cell, a term that is still in use. (Evans 2001). In 1984, Alan Bradley and his co-workers Evans, Roberston and Kaufman succeeded in the transmission of these ES cells into the germ line of chimeric mice (Bradley et al. 1984). The appearance of a pup with dark eyes in a litter caused great excitement in the Evans’ laboratory. This pup was fathered by a male chimera generated from cultured embryonic stem (ES) cells. [...] Unbeknownst to us at that time, this germ line transmission event signalled the emergence of a new age in mouse genetics’ (Bradley et al. 1998: 943).19

However, it was not via the ES cell-chimeric mice route that the first transgenic mice were created. The first transgenic mice were created in the early 1980s by the micro-injection of foreign DNA fragments into the pronucleus of a fertilized mouse egg cell20. In the period between December 1980 and November 1981, six groups reported independently about the birth of the transgenic mice (Constantini and Lacy 1981; Brinster et al. 1981; Wagner (E.F.) 1981; Wagner (T.E.) 1981; Harbers 1981; Gordon et al. 1980). The first group that was successful in the creation of transgenic mice was Frank Ruddle’s team from Yale University (Gordon et al. 1980). They injected a recombinant bacterial plasmid into the pro-nucleus of a fertilized egg cell of a mouse. The plasmid they used contained DNA segments (thymidylate kinase) of the human herpes simplex virus (HSVtk) and the monkey SV40 virus. The foreign DNA fragment they injected seemed to have integrated in the genome of their mice, but since the plasmid only contained a DNA, the DNA fragment could not be expressed (Palmiter 1998). The news was covered by two New York Times reporters who envisioned the ‘creation of animals with new traits and, ultimately, of cures for hereditary diseases amongst humans’ (Ferrel and Slade 1980: 7). Six months later, Mintz’s group reported the successful introduction of the human Beta-globulin and the HSVtk gene into the genome of mice foetuses (Wagner (EF) et al. 1981). They also use a plasmid as vector. Unlike Ruddle, they did observe the expression of the HSVtk gene in one of their (late foetal) animals, although it was barely detectable. The researchers were clear about the implications of these results for medical research: ‘These experiments provide a practical basis for novel investigations of the developmental control of normal gene expression in vivo of the cause and possible cures of genetic diseases’ they wrote in their article (Wagner (EF) et al. 1981: 5016). Jaenisch (at that time located in Hamburg) also successfully created transgenic mice (Harbers et al. 1981). The cloned viral DNA (M-MulV) that he injected was integrated and expressed at different levels in different mouse tissues. To Jaenisch and colleagues it was the greatest challenge to predict the expression of genes in different tissues (Harbers et al. 1981). Thomas Wagner (from Ohio) and co-workers (of the Jackson Laboratory) and (independently) Franklin Constantini and Elizabeth Lacy (working at Oxford) showed that the rabbit beta globulin gene could not only be expressed21 (at low levels) but also transmitted to the offspring (Wagner (TE) et al. 1981; Constantini and Lacy 1981).

Although these researchers were very successful in the integration of foreign DNA into the mouse genome, little or no gene expression was observed. (Palmiter 1998). The first experiment that delivered convincing evidence of gene expression was conducted by Richard Palmiter and

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19. In response to this achievement Ralph Brinster sent a letter to Bradley with the simple message: ‘Congratulations’. Bradley felt honoured that an individual of Brinster’s stature had taken the trouble to send a letter to a graduate student ‘Clearly Dr. Brinster recognized the breakthrough’ (Bradley et al. 1998).

20. The ‘true’ birth date of the first transgenic mouse can be debated. Already in 1976, Rudolph Jaenisch at the Salk Institute in San Diego, had injected pre-implantation embryos with the M-MulV virus. He observed that viral DNA could also be transmitted to the germ line of the mouse (Jaenisch 1976). But Jaenisch was at that time not thinking about the creation of transgenic mice by means of viral transfection. He was interested in the infection of mammalian cells by DNA tumour viruses such as the M-MulV virus. He studied the activity and integration site of the virus in the different organs and the Mendelian inheritance of the viral DNA by the offspring of infected individuals. Whether he – unintentionally – created the first transgenic mice in 1976 is a matter of dispute. It was the first time a researcher had introduced exogenous DNA into a mouse embryo and observed the integration of foreign (viral) DNA. But the virus was not used intentionally as a vector to integrate a specific DNA fragment into the mouse genome.

21. It is interesting to note that, according to Palmiter, in both cases there was no expression of the B-globulin gene (Palmiter 1998).
Ralph Brinster (Brinster et al. 1981). In the fall of 1979, Brinster, who was originally trained as a veterinarian, contacted geneticist Palmiter and asked him for chicken ovalbumin messenger RNA. Palmiter, in turn, supplied him (by mail) with the requested RNA constructs for Brinster’s micro-injection experiments. After a series of experiments with ovalbumin mRNA, Palmiter decided to create a gene construct of the thymidine kinase TK gene and the metallothioneine (MT) promoter. Because of the specific properties of the MT promoter, the expression of the MT-MK fusion gene could be induced or increased by exposure to heavy metals. In the hope of potentially increasing the expression of the MT-TK gene, Brinster injected the mice with Cadmium (Arechaga 1998). This turned out to be a good set-up. Some of the mice thus born showed ‘phenomenally’ high thymidine kinase activity in the liver. In 1981, these mice appeared on the front page of the journal *Nature* and Brinster introduced the term ‘transgenic’ for mice that carried foreign DNA in their genome (Palmiter 1998).

**Giant mice**

In November 1981 Palmiter and Brinster heard about dwarf mice, mice with a genetical growth deficiency, also known as *little*. They decided to try to correct this growth defect by providing these mice with an exogenous growth hormone (GH) gene. Their plan was to create a fusion gene similar to the MT-TK gene construct used in their previous experiments. They would fuse the MT-promotor gene with the gene that codes for rat growth hormone. They contacted Ron Evans, who had just given a lecture on the cloning and characterisation of the rat growth hormone. Together with Evans, they designed a suitable gene construct for their transgenic experiments (Palmiter 1998). In 1982 the metalloine rat growth hormone (MT-rGH) fusion gene was ready for injection. The birth of giant mice in that same year meant a real breakthrough. In December 1982, the results were published in *Nature* (Palmiter et al. 1982). The dramatic image on the cover of *Nature* of a dwarf and a giant mouse (see Figure 1) received considerable attention both from the scientific community and the media. The news about the giant mice was widely covered. ‘When these experiments were published, scientists, cartoonists, comedians and animal rights activists were aroused to the potential of transgenic technology. The ability to change the phenotype of the animal was so dramatic that everyone took notice, even though the experiments we published a year earlier clearly demonstrated the potential of the technique’, recalls Palmiter 16 years later (Arechaga 1998: 871). The image of the giant mouse soon took on a life of its own. The technology behind the size of the mice was not always well understood. In retrospect, Palmiter said he wished they ‘had used a GH from an animal smaller than the mouse, because many people mistakenly thought that the transgenic mice grew larger than normal because we used a GH gene from rat. Thus, some people missed the salient point that directing the expression of a gene to a more abundant cell type (such as hepatocytes) enhances the accumulation of protein in the blood and prevented normal feedback regulation’ (Palmiter 1998: 849).

The event was covered by Harold Schmeck from *The New York Times*, who wrote about ‘a new era in genetic engineering, from which important practical as well as scientific effects could be expected’ (Schmeck 1982: 1). Two and a half weeks after Harold Schmeck covered the scientific breakthrough in *The New York Times*, an anonymous reporter published a much more critical piece on the giant mice in the same newspaper. This reporter was surprised that so little attention was paid to the ethical implications of this new technology (Anonymous 1982). ‘Though it is just a matter of time before such interventions become technically feasible in humans, the issue has received remarkably little public discussion from the biologists who are fast developing the tools for reshaping the handiwork of evolution … This asks for a critical review of the conclusions of the report of the President’s Bioethics Committee about the subject’, he wrote. ‘There are no ethical or religious reasons to stop the research […]. The only restriction the committee proposes is against human-animal hybrids.’ According to this *New York Times* reporter, these restrictions were ‘both too late and too soon’, too late because the first steps had already been taken with the introduction of the human insulin gene into bacteria, and too early because nobody thinks of creating mermaids or centaurs (Anonymous 1982: 18). A year later, on the 18 November 1983, his words were already

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22. These early experiments conducted by Brinster with Palmiter’s DNA constructs were the beginning of a very productive collaboration. The combination of genetics and embryology proved to be a fruitful one. Together they published over 120 articles in a 10-year period (Arechaga 1998).

23. In the following, I will use both ‘transgenic’ and ‘genetically modified’ or ‘genetically engineered’ to refer to these mice, with a preference for the last. In the strict sense, ‘transgenic’ indicates the introduction of foreign genes to its genome. In this book I also discuss knock-out technology. Knock-out mice are not transgenic but are genetically engineered or modified.
outdated. That day, Palmiter and Brinster again reported about their giant mice (Palmiter et al. 1983). This time the giant mice carried the human growth factor. Some of them grew twice as large as their normal littermates. ‘Scientists are setting out to grow breeds of giant mice that are genetically a little bit human’, wrote Harold Schmeck in a response to this news in The New York Times (Schmeck 1983: 1). The species barrier between mouse and man was crumbling.

Transgenic farm animals

In the early 1980s, the public and in particular scientists were impressed by the mouse experiments, but probably nobody would have guessed that 25 years later the mouse would still be the leading character in the world of animal biotechnology. Palmiter and Brinster clearly saw a great future for this new technology, both medical and non-medical, but they had other, bigger, animals in mind. They talked about the ability to mimic or correct genetic disorders with this technology (Palmiter et al. 1982). They were very much interested in the processes of gene regulation. But, from their statements in their research papers and to the press, one can conclude that they were primarily interested in applying this technology to farm animals. ‘Practically nobody’s interested in big mice, but there are obvious applications to agriculture’ Palmiter acknowledged to a reporter of United Press International (Khalsa 1983). They were particularly interested in the effect of increased growth hormone expression on animal size: ‘The implicit possibility is to use this technology to stimulate rapid growth of commercially valuable animals’ (Palmiter et al. 1982: 614). Another interesting application of gene technology on farm animals that they mentioned was farming24. ‘The exceptionally high levels of GH found in the sera of some of these mice, raises the possibility of extending this technology to the production of other important polypeptides in farm animals’ (Palmiter et al. 1982: 614). But, before applying the technology to larger animals, the technique needed to be improved. This was at that time the biggest challenge. Optimising the conditions for integration and expression of foreign genes in mice should facilitate the eventual application of these techniques to other animals.

As a result of this future perspective, the transgenic experiments that followed often involved other animals than mice. In the early 1980s, Palmiter announced in several interviews that they would proceed with gene transfer experiments in sheep, rabbits and goats ‘to document the principle’ (Anonymous, 1983). In response to initial successes, Thomas Wagner from Ohio likewise changed the focus of his research to farm animals (Schmeck 1983). He announced that he had extended his research to sheep. He expected to create animals that would grow faster with the same amount of food, a commercially attractive efficient form of meat production. He saw no ethical objections to this kind of research since ‘people have been manipulating the evolution of farm animals for thousands of years’ (Schmeck 1983: 1). A year later, he rejected ethical objections in a similar vein. He saw no threat from genetic manipulation of farm animals because ‘animals cannot infect the environment and they cannot escape from human control, in contrast to the image people have by watching horror movies’ (Anonymous 1984). In 1985, the birth of the first transgenic pigs and rabbits was reported by Palmiter and Brinster in Nature (Hammer et al. 1985). In spite of the optimistic tone of both Hammer’s article and the News and Views commentary, the results failed to be as impressive as the results achieved earlier in mice. The dramatic effect on growth in the mice could not be repeated in pigs and rabbits (Hammer et al. 1985; Lovell-Badge 1985).

In the years that followed, the experiments with farm animals continued to disappoint. The injection of human growth hormone into pigs had disastrous effects. The Belstville pigs (named after the laboratory where the pigs were ‘created’) suffered from arthritis, impotence, and weak muscles. Sheep with added human growth hormone, that were bred in Australia, developed diabetes, abnormal kidneys, and malformed bones, and survived less than a year (Kohn 1994). Because of the technical difficulties and lack of public acceptance of transgenic meat, there was never a market for this form animal biotechnology. In 1993, the creation of transgenic farm animals for meat production was simply put off the agenda. ‘The science wasn’t ready yet to make it economically feasible’, explained James Sherblum, President of a biotech company, to the reporter from The New York Times (Andrews 1993). But though the experiments with the farm animals were disappointing, those with the transgenic mouse continued to be successful.

24 Later, the term for this practice was changed into pharming.
Gene targeting and controlled gene expression

The results of the early 1980s microinjection experiments were impressive, but the approach had some major disadvantages. If a DNA fragment was injected into the pro-nucleus of an implantation embryo, there was no control over the site where the foreign DNA has inserted. Furthermore there was no control over the activity of the DNA and the number of copies that could be integrated. These problems could be circumvented by the more complicated ES technology discussed earlier. The great advantage of the use of ES cells for the creation of transgenic mice was that a large number of techniques could be applied to manipulate the genome. For example, foreign DNA could be introduced in the ES cells by mutagenesis or with the aid of retroviral vectors. But, even more important, was that it gave the researchers the opportunity to select or screen for a clone with a rare genetic change from millions of cells in culture before constructing a mouse chimera (Robertson et al. 1986; Gossler et al. 1986; Bradley et al. 1998). In 1987, the first successes were reported of experiments in which ES cells that were manipulated in vitro were transmitted in the germ line of chimera. The offspring of these chimeras were the first mice with a modification of a specific endogenous gene through the modification of a cell line in vitro (Hooper et al. 1987; and see also Kuehn et al. 1987 in the same edition of Nature). Both the group from Cambridge UK (Evans, Bradley, Robertson and Kuehn) and the group led by Hooper made an animal model for the Lesch-Nyhan syndrome with this technology. This rare disease, that only affects male individuals, is the result of heritable genetic mutation in the HPRT gene. The male mutant mice made by the researchers of this strain had similar biochemical defects as Lesch-Nyhan patients (Hooper et al. 1987; Kuehn et al. 1987).

‘They are knock-outs’

Halfway through the 1980s, a number of important discoveries and inventions were made that would be of major importance for the further development of transgenic technology. In 1983, Kary Mullis invented the polymerase chain reaction (PCR), for which he received the Nobel Prize in 1993. The PCR technique made it possible to make several copies of DNA sequences in a short time. A second development that was of great importance to mouse gene technology was the discovery by Oliver Smithies and Mario Capecchi (who worked independently of each other) of homologous recombination technology. Homologous recombination made it possible to turn specific genes off in a directed way (Smithies et al. 1985, 2001; Capecchi 1989, 2001). In 1985, Smithies and his team published an article in which they discussed how they could modify a specific human gene (in bone marrow cells) by means of homologous recombination (Smithies et al. 1985), a breakthrough because at that time the prevailing view was that the mammalian genome was much too complex for incoming vector DNA to search, find, and recombine with a homologous target before the efficient non-homologous recombination pathway effectively inserted the vector into a random location in the genome. ‘How wrong this view was!’, remarks Bradley 13 years later (Bradley et al. 1998: 946). In 1987, both Capecchi’s group and Smithies’s group applied this technology (also called gene targeting) successfully to embryonic stem cells (Thomas and Capecchi 1987; Doetschman et al. 1987). Like Evans and Hooper, Capecchi and Smithies chose the HPRT gene for their gene targeting experiments. With these ES experiments, they laid the foundation for the possibility to correct gene defects or to eliminate, or to ‘knock out’, genes in mice (Koller et al. 1989; Thompson et al. 1989). In 1989, Capecchi wrote a review about the ‘new mouse genetics’, in which he claimed that through gene targeting, the potential existed to generate mice of any desired genotype (Capecchi 1989). Soon afterwards, the first knock-out mice, mice whose β2-m gene was disrupted by targeted mutation, were born in Jaenisch’s lab at MIT (Zijlstra et al. 1990).

The new technologies used by these pioneers in mouse genetics did not only receive attention from the media. They also attracted researchers from other laboratories. ‘Now that scientists can create desired mutations in mouse genes almost at will, instead of working with mice that turn up occasionally with accidental mutations, they are excitedly planning systematic experiments to resolve longstanding questions in biology’, wrote Richard Saltus in 1990 in The Boston Globe (Saltus 1990: 29). But the method was at that time extremely complicated. In 1990 there were only a few laboratories that had mastered the techniques for making knock-out mice. These laboratories received a considerable number of requests from scientists who wanted to come and visit for week and learn the technique (Saltus 1990). Within a few years the ‘knock-out mouse’ became a familiar phenomenon, both within the scientific community and the public.
Gene Control Switches

With the introduction of knock-out technology, the foundation was laid for an explosive increase of transgenic mouse models. In November 1992 The Washington Post communicated that researchers estimated the number of genes that had been examined with the knock-out mice to be 100 (Rensberger 1992b). In that same article, Capecchi explained to Rensberger that ‘the he next challenge was likely to be in making mice whose genes are not knocked out from the start but with engineered “switches” – regulatory sequences spliced onto the end of a replacement gene – that can be thrown to knock them out at later stages of life, or even toggle them on and off’ (Rensberger 1992b: A3). The most important technological breakthroughs that followed were indeed refinements of this type of the existing method. In 1992, two groups published on the application of the Cre-Lox system in transgenic mice (Lakso et al. 1992; Orban et al. 1992). Using the Cre-Lox system, which originally stems from bacteria, it is possible to modulate genes in vivo in a controlled and site-directed approach. With the Cre-Lox system, genes can be knocked out in a specific cell type. The Cre-Lox system was already known, but only received particular attention when it was patented by DuPont in 1992.25 When in 1995, Rajewski’s team placed an interferon dependent promoter in front of the Cre-recombinase gene, the ‘genetic on and off switch’ was literally ‘found’ (Kuhn et al. 1995). By using this promoter, the activity of a specific gene could be induced by administering interferon26. ‘This is real genetic engineering,’ said Ronald Evans from the Salk Institute when talking to a reporter from Science about these kinds of knock-out technologies. ‘As soon as you get to a certain state of technology, you can think of nice tricks and questions you wouldn’t normally think about, and that is fun’ (Barinaga 1994: 28).

‘They glow in the dark’

Another important breakthrough in mouse gene technology has been the development of bioluminescent and fluorescent genetic markers such as the green fluorescent protein (GFP) and luciferase. GFP, originally found in jelly fish, was discovered in 1962 by Osamu Shimomura and rediscovered in the 1990s when scientists decided to use it as a marker for gene expression. In 1997, a Japanese research team led by Masaru Okabe used an enhanced version of this bioluminescent protein to produce transgenic mouse lines (Okabe et al. 1997). The spectacular photographs made by Okabe and his team showed green fluorescent mice. These mice produced by Okabe were used as a source of green cells in the context of cell transplantation experiments. These and other experiments indicated that GFP could be a powerful in vivo tool for non-invasive real-time visualisation of gene expression in living animals (Yang et al. 2000, 2004, see Figure 2). Another bioluminescent marker is luciferase, the protein responsible for bioluminescence in the firefly. The gene coding for this protein was also first transferred into mice in the late 1990s (Contag et al. 1998). The difference between luciferase and GFP is basically the type of emission (light versus fluorescent) and the need for a substrate. Only in the case of luciferase is a substrate needed. Before GFP and other bioluminescent markers became available, the measurement of gene expression in response to physiological signals was extremely difficult. Every data point required killing and dissecting experimental animals and measuring the distribution of a reporter gene (Yang et al. 2000). The different types of visible light imaging are developed, patented and marketed by biotech companies. For example, Xenogen, one of the industry leaders in the usage of bioluminescent markers, develops light-producing animal models. These LPTA® animal models are transgenic mice with a luciferase reporter driven by a specific promoter27. AntiCancer incorporated, based in San Diego, has pioneered the use of fluorescent markers such as green fluorescence protein. AntiCancer offers products such as oncobrite® and genebrite®, gene constructs that can produce fluorescent tumour cell lines28. Using imaging systems like these, researchers can observe tumour cells emitting light, they can keep track of their growth and calculate their growth rate. Subsequently, they can administer drugs and determine whether the light goes away. Since it is non-destructive, you can use the animal for an extended period of time. If the tumour cells develop resistance to the drug, this is indicated by the light coming back. The technique essentially records a glow from the inside of the animal (Stokstad 1999). The next
step is to use different markers with different colours at the same time so gene interaction or even protein-protein interactions or nerve cell activity can be observed *in vivo* (Ray et al. 2002). A spectacular example of this is ‘Brainbow mouse’ developed and patented by Jeff W. Lichtman, Jean Livet and Joshua Sanes working at Harvard University. In the brain of this mouse each nerve cell glows with a different colour. Brainbow mouse is genetically engineered so its neurons produce fluorescent proteins in a random combination of colours. As a result, the colours mix and give each cell a different colour (Cook 2006).

**The year of the mouse**

If 2000 was the year of the human genome, 2002 was the year of the mouse. In August 2002, a physical map of the mouse genome was published, followed four months later by the initial sequence and comparative analysis of the mouse genome, both in *Nature* (Gregory et al. 2002; Waterston et al. 2002). Using the C57BL inbred mouse strain, an international consortium of researchers had deciphered nearly the entire DNA sequence of the mouse (Travis 2003). According to 86 authors who did the job: ‘The sequence of the mouse genome is a key informational tool for understanding the contents of the human genome and a key experimental tool for biomedical research’ (Waterston et al. 2002: 520). It is clear that this breakthrough has to be valued in relation to the sequencing of the human genome two years before, as a prelude to studying the genomics of human disease. Nicholas Wade from *The New York Times* has an interesting perspective on the relatedness of man and mouse: ‘Now that the mouse’s genome has been decoded, revealing just as many genes as its host, the 25 million mice that work in the laboratories throughout the world may be demanding a lot more respect. It is the close cousinship that makes this vast labour force of furry little human surrogates so useful for exploring the human genome’ [italics mine]. The mouse genome-sequencing consortium wrote in similar vein: ‘The sequence of the mouse genome will have a huge impact on biological research and human health. It will provide critical information and reagents for use in mouse experimental models. It will become possible to unravel the mechanisms of complex mammalian biological processes and human disease’ (Gregory et al. 2002: 743). The mouse genome offers additional information and tools when compared with the human genome. The most important difference between the humane genome and the mouse genome is that ‘the mouse genome encodes an experimentally tractable organism’ (Bradley 2002: 512). By this, Bradley means to say that because the mouse, unlike man, is a *laboratory* animal, it is now ‘truly possible to determine the function of each and every component gene by experimental manipulation and evaluation, in the context of a whole organism’ (Bradley 2002: 512). The mouse has become the Rosetta stone for understanding human biology (Travis, 2003). One of the outcomes of a comparative genomic analysis was the enumeration of the total number of genes shared by man and mouse. The consortium estimated that the mouse has 27,000–30,000 protein-coding genes of which 99 percent have a sequence match in the human genome (Boguski 2002). It is this ‘conservation of synteny’ between mouse and man that constitutes the value of the mouse. It is also the source of imaginings of the future. Mark Boguski predicts that ‘the comprehensiveness and precision afforded by the genome sequences will allow effective cross-reference of locations of any genetically mapped traits in the mouse with genes in the orthologous regions of the human genome (and vice versa). This will greatly accelerate the isolation of disease genes. It will also be important for precise deletion (knock-out) of mouse genes to study their functions and for targeting human sequences to their syntenic locations in the mouse genome, allowing the mice to be ‘humanized’ for various traits’ (Boguski 2002: 515).

**‘A fuzzy furry test tube’**

During the transgenic revolution the traditional research methods in the study of genetics changed radically. The traditional approach, where the study of genes was based on whole organisms, implying the crossing of endless numbers of animals and mathematical calculation, was replaced by a molecular approach. Researchers were no longer limited to studies in patterns of inheritance based on phenotypes. The molecular technology allowed detailed studies of gene regulation in both *in vivo* and *in vitro* models. A specific change in the *genotype* made *in vitro* could now be observed *in vivo*. The gaze on the mouse turned from the outside of the mouse to the inside of mouse, and even entered the nucleus of its cells, in search of the animal’s genetic core, the heart of the matter. Researchers no

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29. In comparative genomics, **synteny** (a neologism meaning ‘on the same ribbon’; Greek: σύν, *syn* = along with + ταινία, *tainía* = band) describes the preserved order of genes between related species. During evolution, chromosomal rearrangement occurs and hence even closely-related species have different patterns of synteny (Wikipedia).
longer had to look ‘look through’ the animal towards its invisible genes: now, they could ‘really’ gaze at its genes resulting in a true molecular gaze on the mice.

At the beginning of the previous century, the mouse transformed from a research object into a tool. During the transgenic revolution, the mouse further developed into a high-bio-tech tool, a sophisticated or fuzzy test tube, a living laboratory. The animal as a furry envelope of genes became a litmus-paper that allows us to see whether genes are successfully expressed. They became tailor-made animals; canvases upon which researchers do genetic transplantations. Or, as one reporter put it, ‘molecular biologists now struggle to genetically manipulate their mammals into research masterpieces’ (Schrage, 1993). But, as the control over its genes increased, the ‘animal’ behind the genes gradually disappeared.

As the disappointing experiments with farm animals have shown, from a biotechnological perspective the mouse is a very special animal. No other mammal can be genetically manipulated so easily as the mouse. In the 25 years since its genome has been altered for scientific purposes, the mouse thus proved to be the perfect candidate for the development of animal biotechnology. One of the reasons why this is the case has to do with the inbreeding of mice. The inbreeding resulted in a unique population of animals with unique genetic and embryonic characteristics, some of them highly convenient for animal biotechnologists (Beck et al. 2000). Earlier, the unique characteristics of the 129/Ev strain were discussed. Even today, the ES cells of these inbred mice are used for the production of transgenic mice. But also, the B6 and the FVB deserve particular attention. The FVB is well known for its large embryos. The large pronuclei of these embryos makes them very suitable for micro-injection. The B6 has the unique property that its blastocysts are very easy to manipulate. These mice are therefore very important for the production of transgenic mice with the ES cell-mouse chimera route. The blastocysts of most of the other mice do not develop into healthy mice if cells of other mice are placed in them. Moreover, the female B6 mice have proved to be very good foster mothers. As Rader remarks: ‘The suitability of these animals for research was not determined, but engineered. These rodents’ physical bodies, as well as their representations, were not static. They were adapted and constructed for a scientific culture that valued genetically controlled answers to biological and medical questions’ (Rader 2001).

Selection of the fittest in the lab means selection of those mice best adapted to living in a lab and most suitable for transgenic technology. It means selecting the most bizarre, easiest to manipulate, most extraordinary mice. In retrospect, it is probably legitimate to say that the mouse could never have been that successful in transgenic technology had it not been for the extended process of inbreeding it had already undergone over the years.

**Part Three: Transgenic mouse models**

**Animal models and human diseases**

In the history of medicine, animals have always played an important role, but animals suffering from genetic diseases that paralleled human conditions have been of special value. Some well-known examples of animal models are: dogs with haemophilia caused by a defect in factor IX; hypercholesterolemia that is found in rabbits as a consequence of a defect in the low-density lipoprotein receptor; and pigs with arteriosclerosis as a result of genetic variations in apolipoproteins (Smithies 1993). A number of inbred mice strains are also well known as animal models for human diseases: for example the oncomice of the CH3 strain described earlier. But other mice that have emerged in the hundred years that they have been at home in the laboratory have also played important roles in the development of medicine. For example, the obese mice that were discovered in 1962, have been used in the study of the role of lipoproteins in obesity. The naked mouse and the SCID mouse have been of great value to both cancer research and the studies in immunology. The naked mouse has no thymus and cannot develop T cells for this reason. The SCID mouse does not have T and B cells. Because the naked mouse and the SCID mouse do not develop an adequate immune response to human cells, these mice can well be used for studying human tumours in vivo. This explains their unique value to research. However, useful animal models do not occur spontaneously that often. And, if it happens, their specific gene defects may be as difficult to identify and to characterise as their human counterparts. Another problem that arises with naturally-occurring animal models is that the affected animals often differ from unaffected control animals in other genetic factors besides the gene in question. These problems do not arise in the highly controlled transgenic mouse models. In
addition, mice are easier and less expensive to raise than many other species (Smithies 1993).

**The promise of transgenic mouse models**

Soon after the birth of the first knock-out mice, the value of the transgenic mice became clear, both within and outside the scientific community. With the transgenic knock-out technology, a technique became available that made it possible to selectively eliminate genes in order to mimic human diseases. From that moment onwards, the career of the transgenic mice was predominantly determined by the demand for reliable mouse models for human diseases. The knock-out technology spread rapidly through laboratories all over the world. In 1993, the Chicago Sun-Times was already talking about a routine: ‘Scientists now almost routinely knock-out animal genes in an embryo and plunk in human ones, including mutations that mimic human traits or maladies. In effect, the scientists are creating miniature patients to examine some of the world’s deadliest and most baffling diseases. The creatures provide living laboratories in which scientists can study diseases that ethically cannot be inflicted on human subject’ [italics mine] (Cone 1993: 28). There has certainly been an explosion in transgenic mouse models for disease, as remarked in 1993 by Caltech’s Daniel Kevles, co-author of the book *The Code of Codes* (Schrage 1993). It is clear that in the early 1990s the great potential of the mouse as a model was recognised. The expectations were high. ‘From the California Institute of Technology to the Pasteur Institute of Health, these four-legged “biomedia” will ultimately determine which human diseases get cured and when. The better engineered the mammal, the better – and possibly, more cost effective – the medical options for humans’, wrote Michael Schrage in *The Washington Post*, after talking to researchers from GenPharm and Caltech (Schrage 1993: F3). To Kenneth Paigen, at that time the Director of the Jackson Lab, it meant a scientific revolution: ‘We suddenly have the ability to create tailor-made mammalian models of human disease which offers the opportunity to study complex physiological phenomena, such as the nervous system, cancer and aids, as never before’ (Connor 1993: 4) 30.

One of the first mouse models that was created was the mouse model for sickle cell disease. Sickle cell anaemia was one of the first diseases demonstrated to be a molecular disease (Bedell et al. 1997). The cause of the disease was found to be an alteration of the B-globuline gene. Since the gene was already known, sickle cell anaemia was an obvious candidate for a mouse model. In 1990, two groups reported about the sickle cell mouse model, one in *Science* the other in *Nature*. However these animals mimicked the sickle trait rather than the sickle cell disease 31 (Ryan et al. 1997). Subsequently, several other groups worked on the sickle cell mouse model. Several times it was claimed that the model was created, but none of these models modelled the severe haemolytic anaemia observed in human sickle cell disease. It was only in 1997 that, for the first time, a mouse was created that developed a severe haemolytic anaemia and extensive organ pathology similar to that observed in human patients (Ryan et al. 1997). Nevertheless, in spite of the mouse model, to this day no cure for sickle cell disease has been found.

Another high-potential mouse model was the mouse model for cystic fibrosis. Cystic fibrosis is the most common lethal disorder of Caucasian populations. It is a recessive disease that is carried by 1 out of 22 individuals of European descent. One out of 3,600 (Dutch population) newborn babies is affected with the disease. It is caused by defective chlorine transport and excess mucus production by epithelial cells. In animals the disease does not occur, and therefore a naturally-occurring animal model is not available. In 1989, the gene coding for the protein responsible for this disorder (*cystic fibrosis transmembrane conductance regulator* – *Cftr*) was isolated. Since that time, several mouse models for CF have been constructed through gene targeting in ES cells (Bedell et al. 1997). The first mouse models were created within three years after the discovery of the *Cftr* gene. In August 1992, the group of Oliver Smithies and Beverly Koller was the first to report about the animal model for cystic fibrosis. In the scientific journal *Science* they described how they had created *Cftr/-* mice with gene targeting. The animals displayed many features common to young human cystic fibrosis patients, but they usually died before 40 days of life as a result of severe intestinal obstruction (Snouwaert et al. 1992). Because of the early death of the animals, the mouse model was not very useful for studying the disease. A month later a Scottish group led by David Porteus reported about their animal model in *Nature* (Dorin at...
al. 1992). They used an alternative splicing allowing a low level of residual 
Cftr expression. As a result, their mice suffered from a less severe form of cystic fibrosis and mimicked the pulmonary disease found in CF patients more closely (Bedell et al. 1997). In the years that followed, several approaches were used to successfully correct the intestinal and pulmonary defects in mice carrying the severe and leaky Cftr mutations described above. However, the majority of CF patients carry much more subtle Cftr mutations, and strategies that interfere with such mutant proteins may have to be different from those required to correct defects resulting from the absence of normal protein (Bedell 1997). The search for a reliable CF mouse continued. As a result, a number of different mouse models of CF exist today. In 2001, researchers Davidson and Dorin wrote about 12 mouse models in their extensive review of CF. In their conclusion, they stated that: ‘Despite some tantalizing similarities between CF lung disease in humans and mouse models of CF, under the experimental conditions described, the suitability of these models remains controversial and significant differences are evident’ (Davidson and Dorin 2001:15). This did not imply that the mouse models were worthless. As Davidson and Dorin wrote: ‘By recognizing the key similarities and differences, mouse models of CF might provide useful in vivo systems for the analysis of specific aspects of CF lung disease and for testing the validity of specific hypotheses’ (Davidson and Dorin 2001: 15-16). Studies with the different Cftr knock-outs have shown that the disease results from a failure to clear certain bacteria from the lungs, which leads to mucus retention and subsequent lung disease. But, so far, the mouse models have not yet led to a breakthrough in the treatment of cystic fibrosis in human patients.

That the creation of a reliable mouse model is not as easy as was initially expected was also illustrated by the Alzheimer mouse model. The first animal model for Alzheimer’s disease (AD) was presented in 1991, but later it turned out that this model did not develop Alzheimer’s at all (Cone 1993). And the mouse model presented in 1993 also did not develop AD. Since then it seems as if every year the new model for AD is being presented. In 2001, researchers concluded that because of phylogenetic differences, as well as fundamental differences in behavioural ecology, exact replication of AD in mice may not be attainable (Janus and Westaway 2001). But ‘rigorous comparative analysis of cognitive behavior observed in various mouse models of AD should provide a framework for better understanding of molecular mechanisms underlying cognitive impairment observed in AD patients’ (Janus and Westaway 2001: 882). Today the number of transgenic research models for AD at JAX is 4132. A cure for AD has not yet been found.

What the stories of the sickle cell mouse model, the cystic fibrosis mouse model, and the Alzheimer’s mouse model demonstrate is that it is not that easy to make a reliable mouse model, as was initially expected. In spite of the high expectations, scientists already had to admit in 1993 that the use of transgenic animals had not led to substantial medical breakthroughs (Cone 1993). ‘In an embarrassing public failure, scientists who initially reported that they had created mice with Alzheimer’s disease had to retract their findings, and other researchers remain slightly off the mark in mimicking various diseases’, wrote Marla Cone in a critical article in the Chicago Sun-Times (Cone 1993: 28). The first scientific review article about animal models by Oliver Smithies that appeared in 1993 in Recent Developments in Genetics was also very modest about the scientific achievements so far. As Smithies wrote: ‘One of the biggest uncertainties when modelling human genetic diseases in mice is whether the resulting phenotype will be equivalent to that observed in humans’ (Smithies 1993: 113). Mice are not humans. Still, scientists maintain that these gene-altered rodents are the best hope they have (Cone, 1993). On the basis of that hope, the number of mouse models has increased exponentially.

The Knock-Out Mouse Project

A project that will most likely boost the growth in the number of mouse models is the Knock-Out Mouse Project (KOMP) (Austin et al. 2004; Collins et al. 2007). After the sequencing of the human and the mouse genome, the focus of attention of the genetics research community turned to elucidating gene function and identifying gene products that might have therapeutic value. An effective approach to study gene function in vivo is through knock-out technology. But, despite public and private sector initiatives to produce mouse mutants on a large scale, the total number of knock-out mice described in the literature in 2004 is still modest, corresponding only to about 10% of the about 25,000 mouse genes (Austin et al. 2004). In October 2003, a large gathering of members of the genomic community met at the Banbury Conference Centre to discuss the advisability and feasibility of a dedicated project to knock out alleles for all

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mouse genes and place them into the public domain’ (Austin et al. 2004: 921). Ambitious targets were set at that meeting by the mouse geneticists – 500 new mouse lines per year – in order to create a publicly available resource of knock-out mice and phenotypic data ‘that will knock down barriers for biologists to use mouse genetics in their research’ (Austin et al. 2004). Recently, Francis Collins reported that the first steps had been taken (Collins et al. 2007). The first step was the acquisition of 251 knock-out strains (mutant mice and frozen embryos) from two private collections of knock-out mice created and ‘owned’ by Deltagen Incorporated and Lexicon Genetics Incorporated. The second step was the supporting of Mutant Mouse Regional Resource Centres to repatriate and archive their 320 mouse strains for broad distribution. The centrepiece of the KOMP effort, however, consists of two programmes that aim to create 8500 targeted mutations in ES cells in genes that have not yet been knocked out. To achieve this goal, two groups have developed high-throughput pipelines to target genes in mouse ES cell lines (Collins et al. 2007).

From model mouse to mouse model

If one listens carefully to researchers talking about their mice, one easily gets the impression that the mouse has really become the equivalent to the disease or gene defect it stands for. The mouse is always a mouse model, so it seems. In the early 1980s, the mouse was a model animal, an animal to practice on, in order to try out new techniques or ideas; an animal that could be replaced in principle by other species. Today the mouse is no longer an animal model; it has become more or less the disease itself. As a mouse model, the mouse serves two distinctive goals in biomedical research. First of all, it serves as a stand-in for us humans in clinical tests. For example, new therapies to treat human cancer can be tested in mice especially designed to develop spontaneous human tumours. Moreover, the mouse models are also used to study the development of genetic diseases. In mouse models, researchers seek to understand the complex mechanisms that, for example, lead to cystic fibrosis or Alzheimer’s. The first type of mouse models have proven to be very useful. Many anti-cancer drugs are tested in such mouse models before going into the clinic. The value of the second type of mouse models is more difficult to assess. So far, these mouse models have not led to a cure for Alzheimer’s disease, sickle cell anaemia or cystic fibrosis. There is considerable uncertainty in predicting the phenotypes that will be displayed by the mutant mice. As Bradley wrote in 2002: ‘A knock-out mouse phenotype often shamelessly displays our collective ignorance about gene function’ (Bradley, 2002: 514). However, the transgenic mouse models are presented by researchers as the promise to finding the cure for life-threatening diseases. In their battle against genetic human diseases, the genetically altered mouse is the best hope they have.

Although its gene pool has been enriched with (defective) human genes, the mouse itself remained a mouse. The disadvantage of the mouse model is that the human genes have to interact with mouse genes in the complex in vivo system the mouse is. In the mouse model, human genes will never behave exactly as similar genes would do in a human. No matter how many human genes are added to the mouse, the mouse is still a mouse and not a human. In fact, scientists who use mouse models do not study human diseases, they study the behaviour of (defective) human genes in transgenic mouse models. A mouse model can never be the biological equivalent of a human being. The question is whether problems related to the mousehood of the mouse models can be overcome by making the mouse more human. How many human genes do we have to add to the mouse genome in order to make it anthropomorphenic enough?

Apparently this is a serious question for researchers. As an eye-catcher for job advertisement of the Amsterdam Medical Centre (AMC) in the NRC handelsblad of 18 November 2006, a photograph was presented of a young negro boy playing with an albino mouse (see Figure 3). The accompanying text boldly stated: ‘If we have to change a mouse into a human in order to cure AIDS we will do so’. The story behind this advertisement was a donation of 900,000 dollars from the Bill and Melinda Gates Foundation to a research group at the AMC. The mission of the Bill and Melinda Gates Foundation Global Health Program is to encourage the development of life-saving medical advances and to help ensure they reach the people who are disproportionately affected. Funding research devoted to find a cure for AIDS is in line with this mission. For several biological reasons, the animal models now available are not suitable for HIV research. Although the available mice have a transplanted human immune system, part of their own immune system is still intact. The money donated by the Bill and Melinda Gates foundation will be used to develop a transgenic mouse model that will be more suitable for HIV research.

I find the advertisement highly provocative for several reasons, but what strikes me most is this: apparently, the advertisement suggests that...
scientists in Amsterdam are claiming that they can change the mouse into a human being. This advertisement does not only illustrate the need for more humanlike mouse models, it also illustrates the strong motivation of researchers to continue on the path of changing the mouse into a human.

**New frontiers: ES cells and human-mouse hybrids**

The history of the laboratory mouse is far from completed. For the pioneer species in the new era of biotechnology now entering the 21st century, the story has only just begun. After the knock-out mouse project, the next technological frontier is already awaiting us: the growing possibilities of ES cells. Scientists are rapidly discovering the potential of ES cells. Pioneers in embryonic stem cell research Andras Nagy and Janet Rossant reported in 1993 about the production of completely ES cell-derived mice (Nagy et al. 1993). In 1999, *Science* reporter Gretchen Vogel discussed the results of experiments performed in Hawaii by reproductive biologist Teruhiko Wakayama, who cloned mice out of ES cell lines that had gone through more than 30 cell divisions (Vogel 1999). What will be the next step in ES cell technology? In his book *Challenging Nature*, Lee Silver discusses experiments with ES cells that can grow into egg and sperm cells. The implication of such experiments is in theory that (human) ES cells could almost certainly engage in sexual reproduction with others (in a petri dish) to produce (human) embryos with unique genomes. A child born from the development of such an embryo would not have parents who had ever been born themselves (Silver 2006a: 143)! Another thought provoking possibility of ES cell technology is the creation of human-mouse chimeras. Mice are not only used as models to study the expression of human genes, but also the behaviour of whole human cells are studied within the mouse. The genealogy of the laboratory mouse started with the transplantation of human tumour cells into mice. I want to complete this retrospective with another form of human-mouse hybrids, the fusion of our brains and reproductive systems. The whole idea of making human-mouse hybrids stems from the recent interest in stem cell therapy. Stem cells, ‘a kind of universal clay’, have high promise as an all-purpose material for repairing many degenerative diseases of ‘old age’, such as Parkinson’s, cancer, and heart disease (Wade 2002a). Stem cells, like other biomedical materials, have to be studied in laboratory animals before they can be applied to human patients in the context of therapy.

The potential for good of ES cells seems unlimited, but when brain or reproductive cells are used to create human-mouse hybrids one might feel less optimistic. What if a human being is born from an ES cell that originates from a mouse, or what if a man-mouse hybrid with human brain cells starts thinking? These questions are not ‘far out’ questions based on science fantasies. They are legitimate questions in response to scientific experiments. In 2002, researchers transplanted neural stem cells derived from human foetal brains into neonatal NOD-SCID mice, in order to see whether human nerve cells could develop into functional cells in a ‘mouse transplantation model’ (Tamaki et al. 2002). The resulting animals had man-mouse hybrid brains. The human neural cells were distributed and showed neural differentiation in NOD-SCID neonatal recipients. This result supports the potential usability of neural ES cells in human brain transplantation therapy. A therapy that, of course, needs to be tested in other man-mouse hybrids before being applied to humans. Will these mice develop something similar to human cognitive functions? In December 2006, Fred Gage from the Salk Institute injected human embryonic cells into the brains of developing mouse foetuses still inside their mother’s uterus. The human cells became active human neurons that successfully integrated into the mouse forebrain, the place where higher brain function is localised (Silver 2006b). Another useful application of human-mouse hybrid is a mouse that can produce human oocytes (unfertilised eggs). Tissues made from ES cells are likely to be rejected by the patient’s immune system. One way to avoid this problem is to create ES cells from a patient’s own tissue, by transferring the nucleus from the patient’s skin cell into a human oocyte whose own nucleus has been removed. However, these nuclear transfers are highly inefficient and require some 200 oocytes for each successful cloning (Wade 2005). Where do we get so many human oocytes from? Chimeric mice that make human oocytes could be the answer (Wade 2005). Imagine a mouse making human eggs cells mating with a mouse making human sperm cells. Would their baby be a human being?

**Concluding remarks**

What can we conclude from the history of the transgenic mouse? The most important conclusion is that this mouse is as much a man-made artefact as a biological species. The transgenic mouse is a living artefact. But, when saying this, it is important to note that the transgenic mouse was not
The birth of the transgenic laboratory mouse

created *ex nihilo*. The history of the ‘man-made’ mouse did not begin with the birth of the first transgenic mice in the early 1980s. It was in the course of a long process of development that the laboratory mouse became increasingly artificial, starting with the fancy mice that were brought into the laboratory at the beginning of the 20th century, and eventually giving rise to today’s mouse models. A crucial moment in the evolution of the laboratory mouse was, of course, the start of the intensive inbreeding programme. But the selection for distinct genetic properties, such as the high incidence of spontaneous tumours and the culture of teratocarcinoma and ES cells by the early embryologists, has also been of key importance to the mouse’s fate. Together all these human interventions in the mouse as a biological species have paved the way for the introduction of foreign DNA.

Another conclusion to be drawn from the mouse story is that the mouse is a unique animal. Its susceptibility to genetic modification seems without precedent among mammalian species. As a result of the unique genetic and embryological characteristics of the inbred mice, the mouse became the pioneer species in mammalian biotechnology. Biomedical science has had an enormous impact on the mouse genome. The mouse, in turn, has been the animal that has altered our scientific and medical landscape (Clarke 2002). Transgenic mice can be found all over the world, and they have become part of the standard equipment of the modern biomedical laboratory. The genetically altered mouse models are the best tools scientists involved in these areas have. In the process of becoming a mouse model the mouse has lost much of its identity as a mouse. To some researchers, the mouse is basically a fuzzy furry *in vivo* test tube, to others it is a surrogate for exploring human biology. Maybe it is both. After the transgenic revolution the mouse evolved more and more into a living test tube. As a result of the introduction of various human genes the laboratory mouse also evolved into a more humanlike species. This evolution has by no means reached its end. As long as scientists proclaim that, if they have to turn the mouse into a human in order to banish a life-threatening disease, they will do so, then mice will continue to become increasingly human.

The mouse story is not only a unique story about the scientific career of a particular animal species; it is also a story that mirrors the development of the life sciences. Being the pioneer species in biotechnology their history reflects how, at what pace, and in what directions, the life sciences are evolving. Mice that are born out of the ‘mating’ of two ES cell lines instead of real living mice, an experiment that, according to Lee Silver is theoretically possible, have a devastating impact on our perception of the mysteries of life. Moreover, biotechnologically or genetically engineered mice are living proof of the fact that scientists are gaining control over life. The successful experiments with transgenic mice have illustrated how easy it is to modify mammalian DNA. In addition, transgenic mice have showed that DNA is universal; all living species share the same DNA. DNA can be placed from any organism into another. Whether they derive from a human being, a jellyfish or a fly, the mice express these genes as if they were their own. This not only questions our perception of species barriers, in particular the one between mouse and man, but also what it means to be ‘human’. If the mouse genome is malleable, and if DNA is universal, then the human genome is also malleable.

The history of the transgenic mouse also renders a number of bio-ethical concepts problematic, such as the concept of animal integrity in the context of genetic modification. The artificialisation of the laboratory mouse is an ongoing process, and the introduction of techniques to add or delete genes is simply one step in a broader development. At what point in this history does its integrity become affected? That question becomes rather difficult to answer. What is the use of a concept such as ‘integrity’ when looking at Brainbow mouse’s neurons illuminating in the dark? Other bio-ethical concepts that are becoming more and more problematic are related to our understanding of nature and what is natural. How should we understand the notion of a ‘natural species barrier’, as it appears that such barriers can so easily be transgressed? What is the status of ‘unique life forms’ created out of genetically modified ES cell lines? But perhaps one of the most burning ethical questions about the mouse gene technology is whether these technologies can, will, and should be applied to man. Therefore, the history of the laboratory mouse may actually be a prelude to, or anticipation of, posthumanism. We may use the history of the mouse in order to reflect on our own approaching future in an anticipatory manner. As the laboratory mouse is already a stand-in for future patients, it may also become a stand-in for future human (or post-human) individuals.
Chapter 2
Mouse ethics, the taming of a monster

Dualism, or dilemma thinking, is the enemy of compromise and the archenemy of the middle way. As long as people schematize the issue of genetic engineering of animals as ‘all is permitted’ versus ‘nothing is permitted’, rational social progress on the issue is impossible. What is demanded therefore is a fair description of the issues, one that separates genuine moral questions from spurious ones, dissects out real concerns from obfuscatory rhetoric, and lays bare truly fundamental areas of concern.

Bernard E. Rollin

There invariably are moral claims of welfare, respect, justice and the human and natural good at play in particular situations of animal biotechnological practice, but the fabric or constellation of these claims may significantly shift from context to context. What might be ethically permissible in the biomedical laboratory might be prohibited on farms, in the market place, or in the wild. But in each context all things morally relevant need explicitly to be considered and given their due.

Strachan Donelly

Introduction
The social and moral debate on mouse biotechnology

Just a few years after the first transgenic mice were born (1980-1981), the debate over the moral and social issues of animal biotechnology gained momentum. When Bernard Rollin published the paper he had presented at the First International Conference on Genetic Engineering of Animals, he was surprised to discover that this was actually the first publication on the social and moral issues of animal biotechnology (Rollin 1995). With the publishing of this paper (entitled The Frankenstein thing) in 1986, the

transgenic mouse ‘entered’ bioethical discourse. In his paper, Rollin argues that both scientists and the general public are usually unable to sort out the genuine moral issues emerging from the practice of animal biotechnology. Concerns that have nothing to do with animal suffering, in Rollin’s view the only genuine moral issue at stake, he refers to as ‘the Frankenstein thing’: the intuitive belief that animal biotechnology is one of those things ‘man is not meant to do’. Nine years later, Rollin published The Frankenstein Syndrome, ethical and social issues in the genetic engineering of animals, the book in which he further developed his ideas (Rollin 1995). Rollin was not only the first to write about animal biotechnology, he also became one of the most influential writers on the topic. His highly provocative ideas, notably about the creation of chickens that would be happy to live in battery cages because their nesting instincts had been eliminated by means of genetic modification, evoked many responses from the bioethics community.

In addition to Rollin’s The Frankenstein Syndrome, three other influential academic books on the social and moral aspects of animal biotechnology were published in the 1990s: The Bio-revolution: Cornucopia or Pandora’s box (Wheale and McNally 1990); Animal genetic engineering, of pigs, oncomice and men (Wheale and McNally 1995); and Animal Biotechnology and Ethics (Holland and Johnson 1998). Together, these books give a good impression of how the debate on the social and moral aspects of animal biotechnology took shape. As the title of the first volume (The Bio-revolution, etc.) reveals, mixed feelings about animal biotechnology abounded in the 1990s. In the late 1980s and early 1990s, scientists and experts from the food industry had high expectations about the genetic engineering of farm animals used for consumption. But, as the BST affair showed, public acceptance of farm animal biotechnology was very low (Rollin 1995). The contents of The Bio-revolution reflect these concerns about the genetic engineering of farm animals. Animal genetic engineering, of pigs, oncomice and men also includes a section on the genetic engineering of laboratory animals and a section on the patenting of transgenic animals. In this book various bio-ethical notions that have become central to the debate on animal biotechnology are already discussed: the telos concept, the notion of intrinsic value, quality of life and animal integrity. These notions are also central in the overview of the ethical debate presented in Animal Biotechnology and Ethics in 1998.

In short, the ethical debate about animal biotechnology focuses on animal welfare and the supposed unnaturalness of animal biotechnology. Roughly, it comes down to two major questions: (1) Do the benefits of animal biotechnology outweigh the harm done to the animals?; and (2) Is animal biotechnology unnatural and therefore immoral? The benefits of the animal experiments are put forward by the proponents of animal biotechnology, usually the scientists themselves (e.g. Dzierzak 1995). Animal welfare issues, on the other hand, are raised by animal ethicists who strive for the protection of (laboratory) animals (e.g. Ryder 1990; Fox 1990). Finally, worries about the unnaturalness are expressed by authors who question the rights of humans to alter the blueprint of life, either because they feel creation or nature is sacred; or because they think that the genome of a species should be left in peace for holistic reasons (Verhoog 1992; Fox 1990); or because they fear that in the long run humans will be incapable of controlling the outcome of biotechnology (Mayer 1995).

Three never-converging tracks

In an article about the invisibility of animals in animal experimentation, Jacky Turner speaks about ‘three never-converging tracks’. On the first of these tracks, animals are seen as ‘disposable mechanisms and materials for research’. On the second track, concern for animals as the ‘cute, the wild or the furry’ is the key issue, while on the third and final track a ‘muted discussion about whether we should be doing all this anyway’ is taking place (Turner, 1998). In the debate about animal biotechnology, three similar tracks emerge. On the first track, there is a discussion about the promises of biotechnology to cure us from life-threatening diseases; on the second track a discussion about animal suffering and animal welfare; and, finally, on the third track a discussion on whether we humans have any right at all to tamper with genes or to ‘play God’. Along these three ‘never-converging tracks’ of animal biotechnology, different and even incompatible images of mice seem to appear. On the first track, the mouse appears as a high-tech laboratory tool, the best scientific model to study human diseases imaginable. On the second track, concern for animals is the ‘cute, the wild or the furry’ and animal experiments are put forward by the proponents of animal biotechnology, usually the scientists themselves (e.g. Dzierzak 1995). Finally, worries about the unnaturalness are expressed by authors who question the rights of humans to alter the blueprint of life, either because they feel creation or nature is sacred; or because they think that the genome of a species should be left in peace for holistic reasons (Verhoog 1992; Fox 1990); or because they fear that in the long run humans will be incapable of controlling the outcome of biotechnology (Mayer 1995).
If there are so many different and apparently incompatible mouse images, then is it possible at all to find an unequivocal answer to the question; What exactly is the genetically engineered mouse? And, if not, can at least some consensus about the moral meaning of the genetic engineering of mice be reached? How should we deal with the genetically engineered mouse? What are the key issues that lie at the heart of the moral and social debate about animal biotechnology? How do researchers, in particular those who are members of animal ethics committees, deal with these issues?

In order to answer these questions, I will reconstruct the moral debate about animal biotechnology along the three different tracks mentioned above. In the following sections I describe the different mouse images that appear along these tracks in more detail. I base my reconstruction on two types of documents, two sources. On the one hand, I will focus on the writings of philosophers who participate in the debate, but I will also rely on publications by biomedical scientists. In this latter discourse, much emphasis is placed on animals as research tools, but also on animal welfare issues. I will flesh out how the articulation of the moral and social aspects of animal biotechnology differs on each track.

The first track is dominated by the scientific perspective. Here the genetic engineering of mice is seen as a more or less standard laboratory technology that plays an important role in a scientific understanding of genetics and genetic diseases in particular. The animal suffering involved is taken as a necessary evil, to be mitigated no doubt (by technological means: that is, by ‘refinement’, see below), but in a manner comparable to the way scientists treat other instruments, that is with care. The moral significance of these mice is that they help scientists to unravel the genetics of human diseases.

On the second track, we have the individual animal's interests in mind, and welfare aspects become relevant. Genetically modified or not, these mice have the same needs and interests as ordinary mice. They feel and behave like ordinary laboratory mice. In discussing the mouse images on these two tracks, I will argue that the technology as such, that is, the modification of the mouse’s genome, does not seem to be of decisive moral relevance. It is the effect on the individual animal’s welfare that is morally problematic.

This takes me to the central point in my argumentation, a point that is put forward by Bernard Rollin. Why not, as he invites us to do, solve this problem with biotechnology and ‘genetically turn off’ the animal’s ability to suffer? It is here that moral objections that stem from the third track emerge. In discussing the ‘Rollin chicken debate’ (focusing on key authors such as Fox, Verhoog, Bovenkerk et al., and Rutgers and Heeger), I will argue that the current bioethical debate is stuck somewhere at the crossroads between the second and third track, unable to bring about any convergence between the two perspectives. According to Rollin, only welfare issues are morally relevant. Other objections are, as he argues, merely aesthetic. Many other philosophers have strong objections to this way of reasoning, since there is clearly more at stake in animal biotechnology than animal welfare: issues such as ‘integrity’ or ‘naturalness’. But these ideas are intimately connected with our vision of nature. Therefore, they are difficult to explain and to discuss. In day-to-day practice, a utilitarian balance between human benefits and animal welfare seems to be the dominant ethical framework, for both biomedical scientists and members of animal experimentation committees. Yet, sooner or later, discontent with such an approach stimulates authors to open up alternative perspectives: a third track. Why this is the case can be explained using Martijn Smits’s monster theory. I will argue that, to many people, the genetically modified mouse, despite its general use in the biomedical laboratory and its apparent domestication, is still a ‘monster’.

**Part One: Images of the mouse and their moral meaning**

**First track: The invisible mouse**

As we saw in the previous chapter, scientists like to present the genetically engineered mouse as the best laboratory animal available (Clarke 2002). It is the top dog of the biomedical laboratory, an indispensable tool for investigators in many areas of biomedical research (Boguski 2002). With the help of transgenic mice, scientists can study human diseases in animal models that mimic these diseases more closely than any other scientific model imaginable, except Homo sapiens himself. In the words of Kenneth Paigan, former Director of the Jackson laboratories: ‘The mouse has become our surrogate. It is the creature we turn to do experiments, so important in reaching an understanding of ourselves, that are either technically impossible or morally inconceivable in human subjects’ (Paigen 1995: 215). The genetically engineered mice embody promises of new therapies
and medicines that may cure us from life-threatening diseases. These mice, as the living promise of modern biotechnology, give hope to patients. According to some researchers, genetically engineered mice are our only hope to find a cure for cancer. That the mouse represents a promise is also noticed by philosophers. They promise to transform scientific and biomedical research, medical therapies and health care, economic markets [...] if not the rest of our lives. They augur a new era of human existence and well-being’ (Donnelly 1994: S14). From this perspective, these mice represent the faith we have in the progress in biomedical science and salvation from human physical suffering. The mice are sacrificed in order to improve our lives. In that sense, the genetically engineered mouse is a potential hero, an animal that (figuratively speaking) puts its life at risk and suffers for the benefit of all. If we find a cure for cancer, we owe it to the mouse. The mouse is one of scientist’s greatest allies (Clarke 2002). It is a brave soldier that helps scientists in their search to find cures for life-threatening diseases.

In contrast with the image of the mouse as a brave soldier, but using the same metaphor of the battlefield, the mouse also appears as ‘the unknown soldier’. Seen this way, the mouse is an animal without a name, without an identity, merely a means to an end. Turner speaks about laboratory animals as the disposable mechanisms and materials for research (Turner 1998). This description is justified by the sheer number of mice involved in medical research and the scientific, statistical, and molecular gaze that so detachedly studies these animals. Researchers usually have no interest for the animal as such. They are only interested in specific parts, the expression of specific genes in particular organs. After the removal of these parts of interest, cells are examined in test tubes or Petri dishes, and gazed upon with the aid of microscopes. In the laboratory, the researchers study microscopic cells that, once outside the body, no longer refer to the mouse from which these cells were taken. The remainder (the dead mouse) is disposed of as mere waste material.

On the first track, that of the disposable mechanisms and mechanisms for research, a complex image of the genetically engineered mouse appears. On the one hand, the mouse is presented as disposable material, while, on the other, the genetically engineered mouse is praised as a hero, a brave soldier, the living promise of biotechnology. Both are extreme images of the genetically engineered mice and only show a part of the total picture. They reveal a great deal about the practice of biomedical science, but very little about the living animals that are used. In this process of technification and glorification, the living animals that are the central source of information and research data in the biomedical laboratory become invisible. This process can be observed by examining the language used in scientific reports. As Turner states, ‘animals used in experiments are conventionally referred to in scientific reports with no more recognition of their sentient existence than if they were inanimate items of laboratory equipment’ (Turner 1998: 29). Maybe this is even more the case for the creation of high-tech genetically engineered mice. When Paul Orban and his group reported about the Cre-Lox technology, they explained that they ‘sought to generate a transgenic mouse system that would establish whether Cre could effectively mediate chromosomal DNA recombination’ [italics mine] (Orban et al. 1992: 6681). Masaru Okabe who created the first ‘green mice’ refers to his experiments as ‘the production of mouse lines’ [italics mine] (Okabe et al. 1997).

This is not to say that scientists do not see the mice they use, but rather that, from a strictly scientific perspective, the mice themselves are irrelevant. Palmiter and Brinster, after creating the giant mice, promise that ‘optimizing the condition for integration and gene expression of foreign genes in mice should facilitate the [...] application in other animals’ (Palmiter et al. 1982: 614). The scientific value of the genetically engineered mouse is that of a system, a model, a mouse line, or, in brief, a tool. The challenge of the scientist is to make the mouse into the best molecular model or system of (human) genetics imaginable. Of course, this may imply that this system is to be handled with care, but basically for technical reasons. The genetically engineered mouse itself has disappeared under this ‘molecular gaze’. In the scientific journals, the mouse is referred to by a number, the code name that reveals its genetic modification. The genetically engineered mouse has become an artifact, a man-made laboratory tool.

Another aspect of the invisibility of the animals, that Turner observes in scientific writing is the assumption of the unavoidable necessity of animal experiments (Turner 1998). ‘Nearly every paper or research news article involving animal experiments makes a ritual bow in the first paragraph or the abstract to a human disease or health problem’, she writes. However, a surprisingly common ending to these articles is of the form: ‘The question remains, how relevant are these findings to human beings?’ (Turner 1998: 33). In this respect, experiments with genetically engineered mice do not differ from other animal experiments. On the one hand, this has to do with
stereotypical forms of legitimating animal experiments; on the other hand, this uncertainty about clinical applications is an inherent part of science in general and of animal experiments in particular. Animal experiments always precede clinical studies. The results of clinical tests on real patients cannot be built into reports of animal studies simply because they have not yet been conducted. After the conclusions are drawn, based on the animal trials, relevance of the research still remains an open question.

Most researchers involved in the genetic engineering of mice will no doubt have sincere motives. They will genuinely believe that one way or another their research efforts will help biomedicine to effectively address health problems such as AIDS or cancer. At the same time, they have to be realistic, in the sense that the creation of the ultimate research model that might lead to a cure for cancer or AIDS is still a long way off. A good example of an over-optimistic view on the progress of science as a result of mouse research is *Mice make medical history*, a response to the breaking news of the cracking of the mouse genome, published by Tom Clarke in *Nature*’s Internet news service: ‘An army of mice, perhaps 25 million strong, each day helps researchers worldwide to study and devise treatments for human ailments such as cancer, heart disease, AIDS and malaria. Mice are helping to unravel mysteries of biology, such as why we grow old. Discoveries made using mice have netted 17 Nobel Prizes, and more will undoubtedly follow’ (Clarke 2002).

**Second track: The mouse that suffers**

On the second track, that of the wild, the cute and the furry, the genetically engineered mouse appears primarily as a victim of science, an animal that suffers from being subjected to biotechnology and deserves some form of protection against this practice. It is the image of the mouse made of flesh and blood, the effort to make visible again the animal that became invisible in the scientific representation of the mouse. On this track, what we see is the phenotype of the mouse; its genetic code no longer matters. We look at the consequences of the genetic modification, so to speak, from ‘the animal’s point of view’. One of the most important arguments against animal biotechnology is that the animals might suffer from it, that their welfare is at stake.

According to the members of the **Joint Working Group on Refinement**, the use of genetically modified mice is of serious concern from an animal welfare standpoint (Joint Working Group on Refinement 2003). This is not just because of the numbers of animals involved (current transgenic technologies are inherently inefficient in terms of the numbers of mice used in relation to the number of founder genetically modified mice ultimately obtained, prior to these animals being conventionally bred). It is also because of the surgery and other invasive techniques associated with it and the deleterious effect that genetic modification can have on animal welfare. In particular, female mice used as providers of fertilized eggs or as embryo recipients undergo procedures, such as surgery, that can cause pain, suffering, distress and lasting harm (ibid.). In the case of donor mothers, (by egg donation), discomfort is caused by superovulation and the subsequent killing to collect the eggs. In the case of the foster-mothers, discomfort is caused by laparotomy after mating with sterile males. Discomfort also occurs when females that in nature are too young are forced to mate with often much bigger and aggressive males. The sterile males used to cause a ‘pseudopregnancy’ with the foster mothers, have in many cases undergone vasectomy.

In addition, genetic modification *as such* can also compromise animal welfare by exposing animals to pain, suffering, distress or lasting harm. This may be intentional (as a result of the genetic modification introduced) or unintentional (through the disruption of gene function by random integration of the transgene into the genome, ibid.). Perhaps the animal will suffer pain as a consequence of the modification of its genome, or perhaps it will be seriously deformed. Transgenic mice are usually designed as animal models for a human disease. This means that the animals are genetically programmed to become ill. Doing harm to the animal’s welfare is not only inevitable; it is the very aim of these interventions. As a result some mice will suffer from being genetically engineered. However, for the individual laboratory mouse, it will not make much difference whether it suffers as a result of a genetic modification or as a result of another type of animal experiment. The same rules of animal care apply to genetically modified and otherwise modified mice. From a ‘second track perspective’,

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36. In the context of the first track, where the mouse as a living being is invisible, killing animals is not regarded as harm or discomfort.
the intrinsic value\footnote{The notion of intrinsic value is used to indicate that mice, both genetically engineered and the ‘wild type’ (laboratory) mouse. To the individual mouse it is irrelevant whether it is transgenic or genetically modified: it ‘feels’ and behaves like a mouse and has mouse needs and interests.} of a genetically engineered mouse is equal to that of an ordinary or ‘wild type’ (laboratory) mouse. To the individual mouse it is irrelevant whether it is transgenic or genetically modified: it ‘feels’ and behaves like a mouse and has mouse needs and interests.

Within scientific practice, there is a long tradition of discussing and developing ethical guidelines and codes of practice for the use of laboratory animals. This discussion is influenced by the works of animal ethicists, in particular by the works of Peter Singer and Tom Regan. To Peter Singer the most important reason to respect the rights of animals is that they have feelings and can suffer pain. Singer speaks about sentience in this respect: ‘The capacity for suffering and enjoying things is a prerequisite for having interests at all’ (Singer 1989: 78-79). If a being is not capable of suffering, or of experiencing enjoyment or happiness, there is nothing to be taken into account. Tom Regan argues for animal rights on the basis of the principle that an animal is an ‘experiencing subject of life’. According to Regan, those who are the experiencing subjects of life have inherent moral value (Regan 1989: 112). And, according to the definition of Regan, all mammals fall into the category of being a subject of life. Because the animal is aware of the fact that it lives, it has a moral status. In their writings, Singer and Regan have pointed out that animals have characteristics that justify us to consider animals as being morally respectable.

Long before Peter Singer published his Animal Liberation (1975), Russell and Burch formulated the most influential guiding principles for the use of laboratory animals. In order to ‘remove inhumanity’ from the laboratory, they introduced the three R’s: replacement, reduction, and refinement. ‘Replacement means the substitution for conscious living higher animals by insentient material. Reduction means reduction in the numbers of animals used to obtain information of a given amount and precision. Refinement means any decrease in the incidence or severity of inhumane procedures applied to those animals which still have to be used’ (Russell and Burch 1959: Chapter 4\textsuperscript{37}). These key principles in laboratory animal ethics also apply to the genetic engineering of mice. When planning an animal experiment with genetically engineered mice, scientists should always first

investigate seriously whether it is possible to conduct an alternative experiment that does not require the use of animals. Secondly, they should always try use the smallest number of mice that is statistically possible. And, last but not least, if no alternative is available, they should always seek to design the experiment in the most mouse-friendly way.

Some animal experiments involving biotechnology will, according to the three R’s, be more ‘mouse-friendly’ than others. If one compares the genetically modified mouse to the ‘wild type’ inbred mouse, the former is not always worse off. The new technologies are in many cases more mouse-friendly. Take, for example, clinical test where genetically modified mouse models are used with inducible promoters. These mouse models are more refined than the classical mouse models. They mimic human diseases better and are therefore more reliable. The onset of a disease can be studied in a controlled manner. An example of an improvement of technology that led to reduction of animal numbers is the use of fluorescence gene markers. This technique means that a visible marker is added to the gene of interest. The gene expression can be followed in such a mouse in real time over a longer period. Because the development of the illness can be followed in the same mouse over an extended period of time, researchers need smaller numbers of mice than before to answer the same question in a statistically reliable way. This is why Jeffery Burkhardt can argue that ‘biotechnology is perhaps the best for animals’ (Burkhardt 1998: 117).

In spite of the positive effect on the number of mice needed for a single experiment, the estimate is that the number of mice used in biomedical research will nevertheless increase as a result of the genetic engineering technologies. Some predict that the new possibilities of gene technology will result in an explosion in the number of laboratory mice. For each gene there will be a scientist who wants to study its function in a knock-out or otherwise genetically modified mouse. In his commentary in Nature, on the publication of mouse genome sequence, Bradley predicts that ‘the avalanche of the (mouse) genome sequence will be followed by an explosion of mutant mice’ (Bradley 2002: 514). That the genetically engineered mice will never offer an alternative to (replacement) animal experiments needs no further explanation. The genetically engineered mouse models are perhaps more refined and will result in the use of a lower number animals than the classical research models, but they are still based on using living laboratory animals.
At the crossroads: ‘The Rollin chicken’ debate

The image of the living mouse, with mouse needs and interests and the ability to suffer from biotechnology, is hard to reconcile with the image of the laboratory mouse as a disposable mechanism or material for research. It is as if we are standing on two different tracks simultaneously, or at a crossroads. On the one track, we see an animal we have to take good care of as we keep it in captivity. On the other track, we see a valuable laboratory tool that helps us in our investigations into the mysteries of genetic diseases. The genetically engineered mouse is a living artifact. Between the ‘cute and the furry’ living animal and the ‘man-made’ laboratory tool there seems to be an unbridgeable gap. However, it is the responsibility of the researchers and the animal ethics committees to somehow make a trade-off between the two. The benefits of the experiments, the promise of the mouse experiments, have to be weighed against the animal suffering involved. The key question in laboratory animal ethics is: ‘Does the benefit of the animal experiment outweigh the harm done to animal?’ In order to cope with the tension between doing harm to the animal (wrongdoing) and the benefits of science (utility), the mouse is reduced to an abstract or idealized life form, or, as Turner argues, made invisible. Another solution to the necessary animal suffering can perhaps be found in biotechnology itself. If, for the individual animal, only welfare issues are morally relevant, then why not, genetically turn off its capability to suffer? This would be a first-track solution to the second track-problem. This question lies at the heart of the ‘Rollin chicken debate’.

In order to ‘pass between the horns of the dilemma regarding chronically defective, suffering, genetically engineered animals’ and ‘the principle of conservation of welfare’ in the case of creating genetically engineered mouse models, Rollin suggests that it is necessary ‘to obliterate all subjective experience’, that is, ‘to totally eliminate consciousness’ in the mouse. One possible way of achieving such a mouse model could be by genetically engineering ‘these animals both to be a research model and to be born decerebrate’ (Rollin 1995: 205). With this ‘solution’ Rollin follows the same line of reasoning as he did in his ‘chicken’ example. In his 1986 paper, he first suggested creating a chicken deprived of its nesting instinct by turning off of the gene that codes for the drive to nest. This gene can be substituted by a gene that will allow the chicken to be satisfied with merely laying her eggs in a cage. Such a chicken, Rollin argued, would not need a nest when laying eggs. Being happy to lay eggs in a cage, this chicken would not suffer from being a battery cage chicken (Rollin 1995: 172).

To Michael Fox, however, the creation of such animals amounts to a highly disputable proposition.39 Expressing his disgust, he refers to Rollin’s chicken experiment as ‘a potentially misleading eugenic idealism’ (Fox 1990: 34). In reply to Rollin, he introduces the telos concept. The telos or ‘beingness’ of an animal is ‘its intrinsic nature coupled with the environment in which it is able to develop and experience life’ (Fox 1990: 32). What Rollin is suggesting to do with the chicken is telos-violating and therefore immoral. Interestingly, telos is also one of the key concepts for Rollin when discussing animal biotechnology. At first sight, he seems to have a similar definition of telos: ‘the set of needs and interest, physical and psychological, genetically encoded and environmentally expressed which make up the animal’s nature’ (Rollin 1989: 295). In 1995 Rollin more or less gives the same definition. ‘As ordinary people know well, animals too have natures, genetically based, physically and psychologically expressed which determine how they live in their environments. Following Aristotle, I call this the telos of an animal, the pigness of a pig, the dogness of a dog – “fish gotta swim, birds gotta fly”’ (Rollin 1995: 159). How is it possible that two philosophers using the same notion come to such different conclusions about the moral acceptability of animal biotechnology?

The reason why these two authors articulate such diverging moral reasonings concerning the chicken experiment is because they stand on two separate tracks. Rollin discusses the fate of the chicken while focusing on the interests of the individual animal. He is standing, so to say, on the track of the cute, the furry and the feathery in this respect. On this track, only animal welfare is relevant. Rollin’s chicken is, according to its re-engineered telos, no longer able to suffer. It is exactly for this reason that Rollin sees no moral objections to the genetic engineering of the chicken. ‘If genetic engineering is used to genuinely suit the animal to its stipulated environment, and therefore eliminate the friction between telos and the environment which clearly results in suffering, boredom, pain, stress and disease, and this conduces to the animal’s happiness, it does not appear morally problematic’ (Rollin 1986: 296). In 1995, he adds

39. Fox notably refers to ‘the chicken thought experiment’, as the decerebrated mice were not mentioned by Rollin before 1990.
that: ‘If the animal could be made happier by changing their natures, I see no problem in doing so […]. Telos is not sacred; what is sacred are the interests that follow from it’ (Rollin 1995: 171-2).

Fox, however, who refers to harmony and the unity between the animal and its environment, is standing on a third track, where the effects of animal biotechnology on the animal’s ‘nature’ are emphasised. The kind of animal proposed by Rollin is, in important respects, no longer a chicken. To Fox it is not only relevant that the animal is not suffering; it is also relevant that Rollin’s artifact no longer functions like a ‘normal’ animal in a ‘natural’ environment. ‘The organism and its environment are one, and we recognize that unity and harmony as health and the full expression of the animal’s telos. The telos is in part preconditioned for and dependent upon a particular environmental niche and optimal conditions for its normal development and expression, which in turn means health and fulfillment for the animal’ (Fox 1990: 34). The debate between Fox and Rollin is not really a debate in the sense of ‘exchange or arguments’. Rather, they are arguing along the lines of two completely different, never converging tracks. We might consider this an example of what Lyotard (1983) has called a ‘différend’. On the one track, the focus is on the suffering and well-being of the individual animal, while, on the other, the focus is on the significance of the animal as part a larger whole, a natural world where different species have their unique place. A trade-off between the second and third track seems hardly possible.

The problematic position of Rollin at this bifurcation is well expressed by Henk Verhoog who asks: ‘How can we get to know that transgenic animals show abnormal behavior, or that they suffer, when the animal’s “telos” is changed through genetic engineering?’ (Verhoog 1992: 272). What is happening in Rollin’s example of the chicken without the urge to nest, is that the telos is replaced by a new telos which is intentionally designed by humans. But what is the meaning of telos if it does not refer to anything outside human action? Something that belongs to the animal as such, something that is given? According to Verhoog this is where Rollin goes wrong. Taking the concept of telos seriously means that we have to refer to the idea of species-specific behaviour in a particular habitat. ‘To have a nature of its own is unthinkable without taking into account the species to which the animal belongs’ (Verhoog 1992: 272). Accepting that the animal’s species-specific nature may be changed by genetic engineering will in the long run undermine the very foundation of Rollin’s theory.

Verhoog argues. If telos is simply the equivalent of the genetic program, it has no value in the moral assessment of animal biotechnology. Telos can only be of moral relevance if it refers to something outside the individual animal, something that is given by nature.

Precisely at this point something interesting occurs in Rollin’s line of reasoning. Somewhere between 1995 and 1998, he realises that the reference to nature (a notion that clearly has a normative dimension according to some philosophers) in his telos definition is problematic. In his 1998 definition he therefore replaces ‘nature’ with ‘genetic program’. ‘The telos of an animal means the set of needs and interests, which are genetically based and environmentally expressed, and which collectively constitute or divine the form of life or way or living exhibited by that animal and whose fulfillment or thwarting matter to the animal’. In order to emphasise that only welfare is relevant he adds that ‘the fulfillment matters positively to the animal and brings happiness’ and that the ‘thwarting matters in a negative way and brings suffering’ (Rollin 1998:162). Nature is irrelevant, because, as he explains, ‘strictly speaking, as Aristotle points out, individuals do not have natures’. According to Rollin, we may see telos ‘neither as eternally fixed’ as did Aristotle, ‘nor as a stop action snapshot of a permanently dynamic process as did Darwin, but rather as something infinitely malleable by human hands’ (Rollin 1998:157). For Rollin there are no fundamental moral objections against the genetic engineering of animals.

The only relevant question is whether or not animals will suffer from the genetic modification. No wonder that Rollin speaks about win-win situations when discussing the creation of animals that have no consciousness (Rollin 1995: 183). To Rollin the third track is simply morally irrelevant. It is based on misguided emotions; it is ‘the Frankenstein thing’. This does not mean that Rollin sees no objections to this type of experiments. Only they are not moral objections, they are aesthetic objections (Rollin 1995: 175; Rollin 1998: 168). People simply prefer to see chickens brooding on a nest.

Animal integrity and the species concept

With his ‘chicken experiment’ and his suggestion of creating a decerebrate mouse model for biomedical studies Rollin has challenged many philosophers to point out what it is other than animal welfare that is at stake in animal biotechnology. Most people seem to reject this type of experiments and do not believe that their objections are merely aesthetic. As
The third and most dominant species concept is what is called \textit{interbreeding population}, defined by Mayr as 'groups of interbreeding populations that are reproductively isolated from other such groups' (Mayr, 2002). In addition to the species concepts that stem from the natural sciences, there is a variety of species concepts that are not based on biology, such as the biblical notion of a species. In contrast to the Darwinian dynamic vision of a species, the biblical species concept is rather static.

Whether or not the violation of a species is regarded as problematic depends (amongst other things) on the choice of a particular definition of a species. When Rutgers and Heeger speak about species-specific behaviour, they refer to a concept of a species that belongs to Mayr's second type. Verhoog proposes to view species as natural kinds. They all refer to species as a particular way of being and appearing, which animals of the same type share on the basis of their nature. If we perceive this nature as morally relevant, then the violation of a species is morally relevant. But, if we view the species as 'a momentary organization of a certain chunk of information' (Verhoog 1992: 273, quoting Shapiro), the genetic engineering of animals, in terms of violating species, cannot be regarded as morally problematic. When the definition 'interbreeding population' is used, as Rollin does, most forms of genetic modification do not violate the nature or integrity of a species. A genetically modified mouse with human genes inserted in its genome can still reproduce itself by mating with a wild type mouse. Therefore, to Rollin the violation of species is not an object for moral concern. But why should Rollin's definition be more adequate and of greater moral relevance than the phylogenetic definitions, or other definitions, based on other theoretical frameworks? (Verhoog 1992: 276). To non-biologists, the species concept is not a biological concept, but rather a cultural concept, it refers to a particular recognisable entity that forms a meaningful whole that we can observe and recognise immediately for what it is, we simply see which individuals belong to a specific species. This assumes a totally different perspective on nature and on species than the 'objective' species concept of the natural scientist.

\section*{Part Two: The ‘thing’ about animal biotechnology}

\subsection*{The mouse that challenges ‘nature’}

If animal welfare were the only relevant aspect of animal biotechnology it would be difficult to object to a genetic modification if that modification had a beneficial impact on the animal’s well-being, or if the capacity to feel pain were to be eliminated, as in the extreme case of Rollin's decerebrate...
mouse. Yet, most people intuitively seem to have strong moral objections to this type of biotechnology. To most people the image of the Rollin chicken, or a decerebrate laboratory animal, is an abject image. That is not to say that they reject such an image merely for aesthetic reasons, as Rollin suggests. With his thought experiment about the chicken, Rollin did not offer convincing arguments in favour of his opinion that only animal welfare is relevant in the ethical assessment of animal biotechnology. On the contrary, the responses to his thought experiment have clearly illustrated that something else, less easy to define, is at stake in the genetic engineering of animals. Apparently, for Rollin, ‘hard to define’ equals ‘irrational’. What is hard to define is discarded as morally irrelevant. Moral intuitions that lack ‘good reason’, that do not refer to objective values such as animal well-being, are simply delisted as subjective, as merely aesthetic judgments. But is it acceptable to disqualify moral assessments based on aesthetic judgments for this reason? Should we not rather say that many moral intuitions are to a certain extent aesthetically grounded? Another way to interpret these ‘subjective’ moral intuitions is to say that they clearly indicate that animal biotechnology still offers some ‘food for thought’.

What troubles participants in the debate about the Rollin chicken and the genetically engineered decerebrate mouse is that these animals are to a certain extent ‘unnatural’. They may argue that the integrity of such animals is violated, or that they no longer display species-specific behaviour, but these and similar articulations seem to express the basic sense that these animals (in our perception at least) are somehow ‘abnormal’ or ‘unnatural’. But what it is that people exactly mean by these and similar phrases is often difficult to explain. Terms such as ‘nature’ and ‘the natural’ may refer to many different things. Nature, in the broadest sense, is equivalent to the natural or physical world, and also to life in general.

The word ‘nature’ is derived from the Latin word natura, which means something like ‘the course of things’ or ‘natural character.’ In various contexts, notably in environmental philosophy, nature may mean something like the ‘natural environment’ or ‘wilderness’. But it may also refer to an essential quality of something, notably of living things. Many philosophers have written about nature. They agree on one issue: that ‘nature’ is a very complicated concept and may be used to highlight very different aspects of our complex relationship with nature. In medical ethics, ‘naturalness’ is usually discarded as being outdated. In environmental ethics, it is still in use, notably in order to refer to situations that are more or less unspoiled by human influence. In animal ethics, naturalness is usually replaced by concepts such as ‘integrity’. To discuss all these possible meanings here in detail would be quite outside the scope of my inquiry. What these writings have in common is that central to notions such as nature and the natural they refer to is that they are used to refer to something that is untouched by humans, something non-artificial, something given, not man-made, something that displays a life and an identity of its own. Nature and the natural are usually opposed to the artificial world, the world produced and reproduced by humans. The term ‘nature’ is used in contrast to notions such as ‘culture’ and ‘technology’ that put humans in opposition to nature. ‘Natural’ is also used to indicate a moral quality. ‘Natural’ is usually regarded as better than ‘artificial’ (for instance in traditional aesthetics) or even ‘perverse’ (for instance, in traditional sexual morality). But there are probably no terms in general currency in debates in applied ethics that are as intricately, subtly and bewildering ambiguous as the terms “natural” and “unnatural” (Burgess and Walsh 1998: 396).

For scientists involved in animal biotechnology, the concepts of nature or natural in relation to DNA are highly problematic. Humans have always influenced the living world and the natural order. Ever since the dawn of humanity, we have left our mark on the living world. This applies in particular to the laboratory mouse. The history of genetics is characterised by the manipulation of the mouse genome: in the first place, by the selective breeding of mice and, later, by the technologies of molecular biology. When the first transgenic mice were born in 1980, true ‘wild type’ laboratory mice had already ceased to exist. When talking about nature, I would like to argue that genetically engineered mice are as much man-made living artifacts as they are natural living beings. In fact, they are the result both of natural processes and of human technological culture, they are living artifacts. This, precisely, seems to be the paradox: How can a living animal be fundamentally unnatural?

The mouse as a monster
An interesting study of how society deals with these types of technologies that challenge the nature-culture dichotomy is Martijntje Smits’s Monster-bezweringen (Taming Monsters, the English version, is forthcoming). In this book, Smits introduces the notion of a monster to refer to the products of technologies that make us feel uncomfortable. She gives the following description of a monster: ‘A monster is an ambiguous creature combining...
seemingly incompatible elements. Due to its indefinite nature it evokes fear and uncertainty (Smits 2002: 2840). Techno-monsters challenge cultural categories that shape and give meaning to our world. Cultural categories are at the same time moral categories (Smits 2006). They are real to the extent that they are shared by members of a cultural group. They are the result of social learning processes. When new phenomena emerge that do not fit into one of the existing cultural categories, or rather that seem to fit into two categories that are mutually exclusive, we speak of a category error. A monster is such a category error. It displays characteristics of different cultural categories. According to Smits, the monster is at a stage of semi-identity. Monsters generally evoke strong responses of rejection, followed by attempts to restore the order and correct the category error. This is not to say that only negative responses occur. In the positive sense such errors in classification can also be perceived as miracles or moments of transgression. Two cultural categories that as a result of technology are often the subject of category errors are culture and nature. In modern Western thinking, nature and culture form a central dichotomy: they are twin notions that, on the one hand, exclude and, on the other, presuppose one another. Modern monsters always entail confusions in terms of the culture/nature dichotomy (Smits 2002: 138).

The genetically engineered mice seem to correspond to Smits’s definition of a monster. As living artefacts they transgress the borders between nature and culture. As carriers of both human and mouse genes, they transgress the species barrier between mouse and man, a barrier that until recently was regarded as fixed and unchangeable. In which category do we want to place these mice? As we have seen, they are laboratory animals, that we have to take good care of, but also high-tech and highly valuable laboratory tools. They are victims of science but also potential heroes of biomedical salvation. And, last but not least, as pioneers in biotechnology, the mice represent a model for future human beings. Just like Smits’s monsters, the genetically engineered mice do not fit into any unequivocal cultural or moral category. The genetically engineered mice are what we, in the words of Smits, perceive as products of an uncomfortable technology. As monsters the genetically engineered mice ask for

 monster ethics, an ethics of ‘domestication’. How do we have to handle these monster mice?

The taming of monsters

According to Smits, monsters can be tamed, or domesticated, by accommodating categories, or by gradually recognising that monsters (perhaps after some slight adaptations) can, in fact, be placed in an existing unequivocal category, or by adapting the monster itself to the existing categories. She describes four different styles of ‘monster treatment’: a dogmatic style of monster exorcism; a ritualistic style where the monster is adapted; a romantic style of monster embracing; and, finally, a pragmatist style in which the monster is forced to assimilate. The dogmatic style has the character of monster exorcism, because those who adhere to this style want to expel the monster. In the dogmatic style, cultural categories are taken to be strict and inflexible dichotomies. Cultural borders as well as current knowledge and morality are experienced as firmly established, as real. For monster exorcists, the categories form an unchangeable and objective order. As a consequence, in the perception of monster exorcists, there is no place for monsters. For this reason monsters must be eliminated. The exorcism of the genetically engineered mouse as a monster would be the total banishment of animal biotechnology. In this way, the transgression of the border between nature and culture is effectively prevented.

The second option, ‘monster adaptation, aims at transforming the monster into a phenomenon that will better fit into categories’ (Smits 2006: 501). This is the ritualistic style. Again in this approach cultural borders are not really questioned. Borders are not conceived as pliable, human constructions, but as a reflection of reality. The category classification is, however, less rigid, less inflexible and therefore more refined compared with the dogmatic style. As a result, in this style, slight inconsistencies can be fitted in more easily within the system. Strange new phenomena are not considered directly as undermining and threatening, but rather as not yet fully identified. When the ritualistic style is applied to the case of the genetically engineered mouse, the mouse will be adapted to existing categories. This can be done, for example, by denying that there is something really new or revolutionary in these mice; for example, by stating that genetic engineering is not an unnatural procedure, or that genetic engineering is nothing but a high-speed version of more traditional processes of animal breeding or even of evolution as it occurs in nature. Another

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40. Quote translated from: Monsterbezweringen: ‘Een monster is [...] dubbelzinnig wezen, dat elementen in zich verenigt die niet te verenigen lijken. En daardoor, door zijn onbepaaldheid, vaak angst en onzekerheid oproept.’
approach would be the denial of one of the categories. This is what Rollin
does when he claims nature to be an irrelevant notion in the discussion of
animal biotechnology. When nature ceases to exist as a category there is
no such thing as border-crossing behaviour of the genetically engineered
mouse. It is highly questionable, however, whether something like ‘nature’
will go away simply by no longer mentioning it.

The third style of monster taming that Smits discusses is the pragmatist
style. In this approach monsters are assimilated. Both monsters and cat-
gegories can be mutually adapted to one another. Cultural borders are taken
to be human conventions, flexible descriptions of reality. Categories are
regarded as descriptive tools. They are much more flexible than in the first
two models. Monsters are assimilated in a way that drastically reconsider-
s both the character of the monster and the conception of what it was a
repetition of. Pragmatic monster tamers have a clear, opportunistic willing-
ness to reposition established borders, if that would be advantageous. A
form of assimilation of the monster genetically engineered mouse would
be the introduction of a new ethical or cultural category, that of the living
artefacts. This implies that the well-established culture/nature dichotomy
must be amended.

Finally, Smits discusses the romantic style. She describes this style as
a form of monster embracement. Embracing of monsters is romantic, ac-
cording to Smits, because this style clearly distinguishes itself from the
striving towards unequivocality and control that is so typical of the first
two styles, and to a lesser degree of the third. In her discussion of the
different styles of monster taming, Smits shows how fear gradually gives
way to fascination. Monster embracers are fascinated by monsters. In their
effort to understand the monster, they rely on intuition and spirituality
rather than on the logic of classification. This style of monster taming is
the least unequivocal style. Fascination for ‘living on the edge’, for catas-
trophes, and for the category of the obscene, can be mixed with feelings
of abomination. Yet, although this style certainly has some sympathetic
elements, the unconditional acceptance or even admiration of the mon-
ster is not very suitable for dealing with monsters on a societal level. An
unrestricted acceptance of the monster would disrupt cultural and societal
life and could lead to total madness. The dogmatic style is also rejected by
Smits as an unsuitable way of dealing with monsters. It lacks openness for
new phenomena that seems indispensable in a quickly evolving technol-
culture, and is therefore not realistic. With the current developments in
biotechnology new phenomena will emerge almost continuously. The
ritualistic style can also have possible violent consequences. The monster
can be pressed into a category where it does not belong. That could be
the cause of many problems. Important aspects of the monster can be
overlooked by ritualistic denial.

**The taming of the genetically engineered mouse**

On the basis of Smits’s monster theory we can conclude that the way in
which scientists and animal ethicists deal with the genetically engineered
mice reveals a ritualistic style of monster taming. Genetically engineered
mice are adapted to existing categories. They are reduced to the cultural
category of laboratory animals. To the scientists, the genetic engineering
of mice is nothing new. It is a continuation of a practice of selective
cross-breeding of mice for medical science that has been done for quite a
long time. Ever since the beginning of the previous century, scientists have
used the mouse to unravel the mysteries of genetics. From the perspective
of science, the genetically engineered mouse is a logical consequence of
developments within molecular biological sciences. Today it is hard to
imagine a biomedical laboratory without them. As a result, the average
scientist will not question genetic modifications as such. In his or her
perception, the genetically engineered mouse will simply be a laboratory
mouse. For the use of genetically engineered mice in biomedical science
the same ethical rules apply as to ordinary laboratory animals. These rules
are described within laboratory animal ethics. The animal suffering has to
be justified with good reasons. Between ethics committees and scientists
there seems to be more or less agreement that animal biotechnology has
to be reviewed and how this has to be done. In animal ethics committees,
the fact that the mouse is genetically engineered usually will not play a
significant role. In practice, they are treated the same way as ordinary
lab mice. For each animal experiment a convincing justification has to be
given. That every individual researcher literally has to justify his experi-
ments before an ethics commission might lead to bureaucracy and delay,
but it is in general not perceived as unreasonable. A review by an animal
experimentation committee has become a routine element within standard
scientific practice. Most leading scientific journals demand a notification of
ethical approval when animals are used. An ethical review by an animal
experimentation committee provides the scientists working with these
animals with an index of legitimisation.
The focus of the ethical assessment is on the human intentions behind the genetic modification. What is the goal of the intervention? Does this outweigh the potential animal suffering involved? In practice, only by reducing the genetically engineered mouse to an ordinary laboratory animal, is an ethical assessment of animal biotechnology possible. For questions concerning laboratory animal ethics, such as how to balance animal suffering against future human benefits and how to achieve minimal animal suffering, several reliable ethical frameworks and a number of specific codes of conduct for the genetic modification of animals are available (de Cock Buning and Theune 1994; Joint Working Group on Refinement 2003). To assess ethical questions about the unnaturalness of the mice, is, however, far more difficult. To some animal ethics committees, the fact that the genome is altered does not play a role. For example in the Dutch National Committee on Animal Biotechnology (in Dutch: CBD), questions about animal integrity are opened up for discussion. But in other countries this is not taken to be relevant. For example, in the UK, animal welfare legislation no distinction is made between genetically modified mice and non-genetically modified laboratory mice. But, even if taken into ethical consideration, in practice, notions like ‘integrity’ and ‘unnaturalness’ are not easily captured by ethical frameworks and balances. So questions about the so-called unnaturalness are usually avoided. They do not fit within the moral framework used by the ethics committees that have to make an assessment of animal experiments in a case-by-case approach. On the other hand, there seems to be general agreement on the fact that the genetic engineering of animals is problematic and therefore ought to be restricted to research that serves biomedical purposes only.

So, in addition to the ritualistic style, a dogmatic style of monster taming can be observed. Outside the biomedical realm, genetically engineered ‘monsters’ are banned. The presence of genetically engineered mice outside the scientific laboratory, where the category of laboratory animal does not exist, has been prohibited. This prohibition, a form of monster exorcism, is typical of the dogmatic attitude.

I will refer to this combination of attitudes as ‘the strategy of containment’. We have locked away the genetically engineered mice inside laboratories, both in the literal sense and the figurative sense: they are simply seen as part of the ‘laboratory animal’ category. In the most literal sense, mice are locked away by strictly prohibiting their presence outside the laboratory. Laboratories where genetically engineered mice are produced and kept are working on the basis of very strict guidelines for genetically modified animal husbandry. In the figurative sense the genetically engineered mice are locked away by refusing to consider their introduction in other domains such as pet keeping or wildlife preservation. As a result we can not speak of the domestication of the genetically engineered mouse monster. Outside the laboratory the genetically engineered animals are still not welcome (as yet).

Concluding remarks

Genetically engineered mice are highly ambiguous animals. This makes it hard to reach consensus about the ethical and societal aspects of their existence and use in bio-medical research. As I have argued, there are three different tracks in the debate about animal biotechnology. On each track, different mouse images appear, and all these images evoke different moral responses. On the first track, the genetically engineered mice can be seen as the ‘right tool for the job’ that will enable us to find a cure for life-threatening genetic diseases. From that perspective, these mice are presented to the public as potential heroes. For the scientists who work with them, these mice are very sophisticated models compared with traditional mouse models. They are ‘high-bio-tech fuzzy test tubes’ that allow us to gaze at human genes in an \textit{in vivo} model. They are treated with care, but mostly because they are valuable laboratory equipment.

On the second track the mice appear as the victims of biomedical science. They are often programmed to become ill and suffer from human illnesses. Their welfare is clearly at stake. In this respect, they are mice like other mice, ordinary living animals, with ordinary mouse needs and interests that ought to be respected and protected. Their suffering is an issue of concern.

On the third track the genetically engineered mouse emerges as a monster that challenges the nature-technology dichotomy. This mouse monster is a living boundary object, a boundary being. As a man-made living animal, the genetically engineered mouse belongs both to the world of artifacts and to the world of the living creatures that are part of nature. The genetically engineered mouse is a living artifact that can have a radical impact on our (genetic) self-understanding. Such mice embody future biomedical strategies and applications.
However, the dominant view on the ethical aspects animal biotechnology seems to be a utilitarian (or consequentialist) trade-off between animal welfare and human benefits. Why this is the case can be explained with the help of Smits’s monster theory. The genetically engineered mouse does not belong to one unequivocal cultural category. For scientists it is simply a lab animal. For outsiders it has aspects of monsterhood, as undisputed cultural categories do not yet exist to capture it. But, being there and being real, the genetically engineered mice ask for an immediate response. There is not enough time to develop new rules that may be seen as appropriate by all for the new phenomenon. The ‘birth’ of this monster was not accompanied with clear-cut instructions for its use. The formulation of instructions for use calls for a time-consuming social learning process, which in the case of animal biotechnology still has a long way to go. For the time being, we have to rely on the limited sets of instructions that are available. In the case of the genetically engineered mouse, the rules that apply to the ‘wild type’ (inbred) laboratory animal are the best candidates. The use and treatment of these animals within science are regulated by laboratory animal ethical principles, such as the three R’s formulated by Russell and Burch. This ritualistic style of monster taming seems adequate as a temporary response from a practical point of view. We need a solution right now. Ethical assessment of animal biotechnology in a case-by-case approach by an ethics committee would otherwise be impossible. Scientific practices need clear and workable solutions right now.

But the genetically engineered mice also engender difficult questions concerning, for example naturalness, for which no straightforward answers are available. By reducing these mice to the status of ordinary lab mice these difficult issues are simply avoided. As a result, not all the concerns that are raised by the introduction of these ‘monsters’ are addressed in the animal ethics committees. What we see is that, in addition to the reduction of the mouse to an ordinary lab mouse, the strategy of containment is applied to meet these concerns. Containment is an approach we apply to animals which we find both fascinating or useful and fearsome. The combination of reduction and containment is therefore a fairly understandable monster strategy. It is a reasonably adequate solution for today, but highly unsatisfactory from a philosophical point of view that takes a broader perspective, placing current biotechnology in the context of its past and possible futures. This (temporary) approach only covers the moral questions that emerge on the first and second track. Issues arising on the third track, concerning our vision of nature, remain inarticulate. I believe this is a matter of great concern.

Of all the different tracks, the third track is by far the most problematic one. Mouse biotechnology confronts us with the fact that nature, animal nature and, by implication, human nature, is malleable. What is most troublesome about the genetic modification of mice is that a genetically engineered mouse is unnatural and that by changing its genetic make-up we change something unique that has been the result of the long ‘natural’ process called evolution. We do thing with genes that would never have happened in ‘nature’. We are messing with ‘nature’. But how can a living being be unnatural? How can a living being be an artifact? It is not only nature but also our conception of nature and the natural that is under attack, or at least under pressure. Our vision of nature seems adrift as a consequence of biotechnology. But the difficulty we have in defining nature does not mean that we, like Rollin, should simply disqualify the concept of nature as a meaningless phrase when it comes to morally assessing biotechnology. I rather believe it is the other way around. Biotechnology (and the biotech-evolution of the lab mouse) entails important lessons about nature that need to be further explored by philosophy. Biotechnology challenges us to redefine what nature is, what species are, and even what human nature is. We have to redefine what it is to be human. What is the status of our traditional understanding of our own species when DNA can so easily be transferred from one species to the other? But the impact of animal biotechnology as a technology, with considerable implications for our understanding of nature in general and our own (malleable) nature in particular, has remained more or less out of focus in the animal biotechnology debate. The technology as such, the impact of the knowledge of genes on our self-understanding, is not really debated by animal ethicists.

In short I wish to argue that the difficulties in addressing the question about the unnaturalness of genetically engineered mice reveal that the mouse is still considered to be a monster. Dealing with new phenomena such as genetically engineered mice calls for a social learning process. We need time to get used to monsters. Monsters need time to feel ‘at home’ with us. If one wants to follow a monster strategy that in the ideal situation leads to domestication, Smits recommends the pragmatist attitude. Instant improvisation and creativity are important characteristics of this style of monster taming. The pragmatist has an open mind to the constructed character of borders and different rationalities of the various parties involved.
Because of its ontological scepticism, the pragmatist approach displays openness to different perspectives. In the case of the genetically modified mouse, pragmatists have an open mind towards the promises the mouse holds for correcting debilitating genetic diseases. But the pragmatist is also aware that, as our understanding of the interaction of genetics and human personality increases, the technology also has the potential to radically alter human nature. As I discussed in the previous chapter, I believe the most important mouse image that may help us to address the complex issues arising on the third track is that of the mouse as the pioneer species guiding us and leading the way into the new world of biotechnology. In my view, seeing the mouse as a pioneer in the biotechnology revolution involves critical analysis of the future potential or the promise of animal biotechnology and the dynamics of power behind animal biotechnology, in combination with a critical analysis of what we mean by (human) nature. We can do this by paying careful attention to imagination, and to the myths, metaphors, images and other half-conscious apparatus of thought that surround the moral and social debate on animal biotechnology (Midgley 1992). What do people express when they say biotechnologists are ‘playing God’? What is it people fear when they refer to ‘Frankenstein’s monster’. What monsters do they fear? And what can we learn by investigating our ‘aesthetic’ objections to animal biotechnology? All this is to be explored further in the following chapters.

Chapter 3
Playing God or the promise of mouse biotechnology

And Pilate saith unto them, Behold the man!\(^{41}\)

John 19:5

In Simone de Beauvoir’s existentialist novel All Men Are Mortal, two creatures attain immortality: a man who intends to be an enlightened ruler and a circling mouse. Clearly, this was a mutant mouse — perhaps a descendant of the Chinese waltzing mice that were first described several thousand years ago. De Beauvoir’s would-be king chose the mouse as his companion for eternity for the same reason that we are pursuing mouse mutants today: the mouse provides us with an effective model of ourselves, be it for testing potions of immortality or for understanding human disease and development\(^{42}\).

Introduction

Ecce homo: the Passion of the Oncomouse

In 2000, a photograph of Ecce Homo, a sculpture by Bryan Crockett of a giant oncomouse, appeared in the New York Times (see Figure 4). Two years later, another photograph of Ecce Homo appeared in Nature Genetics as an illustration to an article by Dorothy Nelkin and Susanne Anker about the influence of genetics on art (Nelkin and Anker 2002). Ecce Homo is a dramatic interpretation of the transgenic oncomouse. Standing on its hind legs, the mouse is portrayed as a humanlike animal on a human scale. But perhaps the most shocking part of the sculpture is the title, Ecce Homo (Behold the Man!) (John 19:5). Bryan Crockett portrays the mouse as Jesus Christ. Crockett deliberately chose a realistic style for representing his oncomouse in order to evoke a sense of living. ‘Almost six feet tall

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\(^{41}\) The Holy Bible: King James Version (2000).

he is nude (as is the Oncomouse⁴³) and his flesh is a very convincing pale skin tone. Upon further inspection, however, one realizes the mouse/man is actually sculpted in flesh-colored marble. The lifelike sculpture and skin texture makes the sculpture oscillate between a living creature and a strong likeness, evoking the Pygmalion myth’ (Crockett 2001a).

In the catalogue of Paradise Now, the exhibition where Ecce Homo was first presented, Crockett explains his motivations for presenting a laboratory mouse as a religious icon. He is rather explicit about his understanding of the God-playing activities of scientists. ‘Science has taken over the authority that religion once held. In this body of work, I am exploring the sacredness of the flesh and soul in a time when we have acquired the knowledge and tools to play God’ (Crockett 2001b). Crockett sees the practice of genetics as an analogy to the worlds of allegory and mythology: ‘Like the Satyr or Minotaur, the Oncomouse is the literalisation of a cliché man/mouse’. But more striking is the explicit reference he makes to the Christ figure. ‘That is why I have chosen to reinterpret the ultimate figure of salvation, Christ, through the ultimate actor of contemporary science, the Oncomouse. This sculpture is intended to be a monument to the test object of modern science, human kind’s symbolic and literal stand-in personified. This human-scale, fleshy mouse, sculpted with the pathos of classical sculpture, stands in a gesture reminiscent of Christ revealing his wounds’ (Crockett 2001a/b).

Now what is it that Bryan Crockett wishes to say with this sculpture? There is long tradition of presenting Ecce Homo in Christian iconography. But a comparison with other traditional Ecce Homos shows that Crockett’s Ecce Homo, apart from being a mouse and not a human figure, is not an Ecce Homo in the traditional sense. Crockett’s mouse is not sacrificing itself. The mouse has neither choice nor inner calling, and no free will is involved. The mouse is not willingly taking the burden of sin on his shoulders; it is playing the burden of sin back to his audience, so to say. There is a new iconography involved. It seems we have to conclude that Crockett is presenting us a new – modern secular version – of Jesus Christ! By presenting the mouse as a Jesus figure Crockett is not only suggesting that scientists are playing God, he is also suggesting (or at least invoking the suggestion) that mouse biotechnology leads to salvation. Where does such an idea come from?

The meaning of the playing God metaphor

‘Playing God’ is a phrase often heard in the biotechnology debate. Also the salvation to be expected from science is a familiar theme. In this chapter I want to go into two sets of questions. First, in what way is biotechnology related to religion? How can the variety of references to God and religion in the debate about biotechnology (‘playing God’, ‘salvation’, etc.) and particularly about mouse biotechnology be explained? Second, what feelings and concerns are expressed by the playing God metaphor? Are these primarily moral concerns about messing with His creation, or does ‘God talk’ also reveal other more complex issues of moral concern?

In the following, I address these questions by examining the playing God metaphor and other forms of God talk in relation to the genetic engineering of mice. In my inquiry into the ‘religious aspects’ of the genetically engineered mice I will use a variety of sources: research papers by scientists and philosophical discussions, but also art works by visual artists and their own comments on these works. I will begin with a number of observations made by Dorothy Nelkin, who did extensive research on gene metaphors in science and popular culture, including that of the ‘sacred gene’. After discussing some of her examples of God talk in the life sciences, I will briefly reflect on the complex relationship between religion and science. To some, the two are in a state of war; to others, science can be understood as a religious pursuit, with the salvation of mankind as its ultimate goal. In order to illustrate how these different perceptions of science and religion influence the moral attitudes towards animal biotechnology, I will subsequently discuss three philosophical positions that can be found in the playing God debate. Two extreme positions are taken by David Noble (who argues that we have to take science as salvation literally) and Ronald Dworkin (who takes the playing God metaphor to be nothing but the expression of a distinction we make between what is made by us and what is given by nature). An intermediate position is taken by Mary Midgley (who challenges us to take the myths we live by seriously and to search for the meaning that lies behind them). I will argue that, regardless of whether we take science as salvation literally or metaphorically, in both cases it reveals that biotechnology has a character.

⁴³ Harvard/OncoMouse™ is not a nude mouse. The original Harvard/OncoMouse™ was a furry albino mouse (see Figure 6). Nude mice do exist in laboratories. They lack hair and an effective immune system. This last property makes nude mice, discovered in 1962, a very good candidate for cancer research because they do not reject human tumour transplants. However, this nude mouse is not genetically engineered.
of promise. Biotechnology is a technology of hope. It is here that another dimension of God talk emerges. This dimension is a bio-political one. In order to explain the bio-political dimension of mouse biotechnology, I introduce the work of Nikolas Rose and Eugene Thacker, who both write about bio-politics. Using their theories on the futurist dimension, that is the future-orientedness of biotechnology, I discuss the role of the mouse in what Rose refers to as a ‘political economy of hope’. Subsequently, by presenting another work of art representing a transgenic mouse that has also been published in *Nature* namely, *Mann und Maus* by Katerina Fritsch, I will introduce the genetically engineered mouse as the flesh and blood promise of biotechnology. I will use both *Ecce Homo* and *Mann und Maus* to illustrate how scientists like to present our dependence on the mouse in our current quest to find cures for life-threatening diseases. Although the messages conveyed by these works of art differ, they are both powerful visualisations of the promise of the biotechnologically engineered mouse. And both invite us to look upon the moral and social aspects of mouse technology in a critical way.

**Part One: Biotech and religion**

**God talk in the life sciences**

‘God talk is in vogue’, writes Dorothy Nelkin in her posthumous essay on the confusion between science and religion. In this paper Nelkin discusses the motives of scientists engaged in biotechnology for using religious metaphors. ‘Geneticists call the genome the Bible, the book of life, or the Holy Grail. DNA is not just a biological entity in the rhetoric of science; it is a so-called sacred text, the core of essential humanity or the master code’ (Nelkin 2004:140). In this respect, according to Bill Clinton: ‘Today we are learning the language in which God created life. We are gaining ever more awe for the complexity, the beauty, and the wonder of God’s most divine and sacred gift.’ These words, spoken during the famous White House press conference announcing the completion of the first draft version of the sequence of the human genome, have since become famous (Collins 2006). Similar examples of God talk can be found in various publications by Francis Collins, Director of the Human Genome Project44. ‘When you have for the first time in front of you this 3.1 billion-letter instruction book [the sequence of the humane genome] that conveys all kinds of information and all kinds of mystery about humankind, you can’t survey that going through page after page without a certain sense of awe. I can’t help but look at those pages and have a vague sense that this is giving me a glimpse of God’s mind’ (Swinford 2006). How sincere these feelings are can be concluded from the title of his autobiographical book about the cracking of the human genome, *The language of God* (Collins 2006).

One possible answer to the question why God talk is in vogue might be that both biology and religion address issues involved in the origin and future of (human) life. Thus, scientists involved in the life sciences may see themselves as engaged in a pursuit that is similar (to some extent) to religious enterprises of the past. Nelkin also gives another explanation. She takes it to be the response of scientists to tensions between science and religion. ‘By drawing on powerful images of Christianity, scientists are seeking to attract converts – to convince the public and many sceptics of the power of their ideas’ (Nelkin 2004: 150). This is an interesting hypothesis, because usually it is the critics of modern biotechnology who refer to God and the Bible, expressing moral doubts about ‘tinkering’ with genes, rather than the scientists themselves. Experiments in genetic engineering such as the creation of transgenic organisms have evoked objections from people who are convinced that scientists are *playing God* and are ‘tampering’ with God’s creation (Nelkin 2004: 142). In other words, we are faced with the interesting situation that both advocates and opponents of biotechnology have recourse to God talk or religious language, either to stress the importance and legitimacy of their scientific work, or to articulate moral arguments against scientific practices such as genetic engineering. There appears to be a thin line between ‘doing God’s work’ and ‘playing God’. Regardless of whether we value this as positive or negative, God talk conveys the general feeling that something important – boundary breaking – is happening within the life sciences.

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44. Francis Collins claims to be the ghost writer of Bill Clinton. He writes about this in his book: ‘Was I, a rigorously trained scientist, taken aback at such a blatantly religious reference by the leader of the free world at a moment such as this? Was I tempted to scowl or look at the floor in embarrassment? No, not at all. In fact I had worked closely with the president’s speechwriter in the frantic days just prior to this announcement, and had strongly endorsed the inclusion of this paragraph. When it came time for me to add a few words of my own, I echoed this sentiment: “It’s a happy day for the world. It is humbling for me, and awe-inspiring, to realize that we have caught the first glimpse of our own instruction book, previously known only to God” (Collins 2006).
Science as salvation

There is an ambiguous relationship between religion and science. Paul Fayter of the Canadian Council of Churches (CCC) explains this in the CCC booklet on the OncoMouse patent case as follows: ‘The most common view held of how “Science” relates to “Religion” can be called the conflict thesis or the warfare model. In this view – an ideological invention of late nineteenth century anticlerical scientists – religion and science represent two independent autonomous and inevitably opposing domains: ‘Science stands for the progressive light of reason; religion, for the dark ignorance of superstition. The church [...] has done little more than to oppress and persecute scientists throughout history’ (Fayter 2003: 10). This model of conflict is also described by Mary Midgley. According to her, the idea of a conflict arose at the end of the 19th century when science was regarded, not merely as a repository of scientific facts, but rather as a kind of world-view, ‘a philosophical conception of the world and the forces within it, directly related to the meaning of human life’ [...] ‘People like T.H. Huxley meant by science a vast interpretative scheme which could shape the spiritual life, a faith by which people might live’, she explains. ‘This [scientific] faith was a competitor with existing religious faiths, not a way of having no faith at all’ (Midgley 1992: 52). But the idea that the battle between science and religion is won by science – that science in some sense has disproven religion and reigns instead of it – Midgley finds extremely odd. It would suggest that the two are competing for the same job. When discussing the spiritual and intellectual ambitions of modern scientists, Midgley deliberately talks about salvation and not about the value of science. The point of using the dramatic word, ‘salvation’ is ‘to show how much the whole thing matters and especially to draw attention to the high ambitions underlying the strong claims about the value of science’ (Midgley 1992: 51). It is to bring out the vital importance to all scientists, Midgley deliberately talks about salvation. The cry for salvation is a response to confusion, confusion about the fact why we are here and how to make sense of it all (Midgley 1992). To Midgley the faith in, and the very idea of, salvation through science is about myths and metaphors, visions or categories that help us to understand the physical world. So when ‘scientific facts clash with beliefs formerly held significant it is not to declare war, nor to bend the facts. It is to rethink the significance, to look much deeper into what underlies the symbols’ (Midgley 1992: 54).

Another critique on the warfare interpretation is that it ignores the fact the modern sciences are deeply rooted in Christian belief. According to Midgley, the idea that we can reach salvation through science is ancient and powerful (1992:1). In the 17th century, when modern science first arose, it was an entirely natural thought. The great thinkers of that time took it for granted, it was central to their endeavour. Nature was God’s creation, and to study it was simply one of the many ways to celebrate His glory (Midgley 1992:1). This point is also made by Fayter who claims that ‘foundational for the new views of nature in the seventeenth century were theistic assumptions. [...] These assumptions included the intelligibility of the physical world; the reliability of human reason; the orderliness of nature; and the universal uniformity of natural law’ (Fayter 2003: 1).

A rather radical elaboration of this latter point of view can be found in The Religion of technology: The divinity of man and the spirit of invention by the historian David Noble (Noble 1997). Noble does not regard the cry for salvation as a metaphor or myth as Midgley does, he takes it literally. In the first half of his book, Noble describes how the roots of modern technology reach back to the 9th century when the useful arts first became implicated in the Christian project of redemption. Going through history he illustrates his arguments with examples of influential Millenarian thinkers. The book starts with the, in those days radical, thoughts of the 9th century Carolingian philosopher John Scottus Eriugena, who was the first to identify the arts as vehicles of redemption (Noble 1997: 17) Subsequently, in the mechanics-minded world of the 12th century, the spiritualisation of the arts was undertaken by Benedictine monks (Noble 1997: 18) It was at this time that the ‘development of technology gave some assurance that mankind was on the road to recovery [from the Fall]’ (Noble 1997:21). The Franciscans carried the Millenarian message though the 13th and 14th century into the modern age, where it is reflected in the mentality of, for example, Columbus (Noble 1997: 31-34). According to Noble the discovery of the New World brought new life into the promise of mankind’s redemption through science: ‘After Columbus, paradise became more than just a vision, it became a place’ (Noble 1997: 38). In the chapter Heavenly virtuosi, Noble describes how 17th century scientists like Boyle and Newton were also deeply inspired by Millenarian prophecies.

45. Millenarism is, according to Noble, in essence the expectation that the end of the world is near, and that, accordingly, a new earthly paradise is at hand (Noble 1997: 23).
The notion of a ‘heavenly virtuosi’ refers to scientists who were involved in projects aimed at the recovery of prelapsarian Adamic perfection: a return to the state of innocence before the Fall. To illustrate his point, Noble quotes Boyle, who believed that scientists had a privileged relationship with God and that the scientific virtuosi (in the new Millennium) will have a greater knowledge of God’s wonderful universe than Adam ever had (Noble 1997: pp. 62-67). By studying nature, these modern scientists would come closer to God.

The eighth day of creation

In the second half of his book Noble focuses on contemporary technologies. Biotechnology is one of these technologies. In the chapter Powers of perfection; genetic engineering, Noble discusses the development of molecular biology, referred to by Horace Judson (and many others inspired by him) as the ‘the eighth day of creation’, and the Human Genome Project (HGP). In brief, Noble argues that genetic engineering allows us to become a co-creator and to free humans from the deficiencies of the human condition after the Fall. As such the HGP and the development of mammalian genetic engineering technologies (now predominately developed in mice but, in theory, also applicable in man) can be seen as radical attempts to transcend the limitations of fallen creation. In the words of Noble: ‘If the new technology endowed bioengineers with Adamic dominion and God-like powers over nature, enabling them to ‘improve’ upon presumably lesser living organisms according to their own lights, and interests, it also, and perhaps most important, enlarged the prospect for their own, human perfection. (Noble 1997: 184) According to Noble, the HGP is not about humble science devoted to incrementally advancing knowledge of human genetics or to incrementally improving the human condition. Rather, it has a profile reminiscent of Millenarian prophecies. In the eyes of its director, Francis Collins, it is nothing less than ‘the most important and the most significant project that humankind has ever mounted’. Other prominent scientists involved in the HGP are also openly religious and do not hesitate to reveal their Millenarian motives. Noble quotes, for example, Warren Weaver and Arthur Paecocke, who write and speak about their divine mandates, but also Robert Sinsheimer who in 1994, years before the completion of the sequence of the human genome, had already written that: ‘Today we might say that we have discovered the language in which God created life…. After three billion years, in our time we have come to this understanding, and all the future will be different (Noble 1997: 190 quoting Sinsheimer 1994). As Noble summarises, ‘most genetic engineers […] act as if their physical enterprise was indeed a project of perfection, as if their accumulated knowledge and techniques might ultimately restore mankind to its pristine condition, freed from its myriad deliberating defects inherited from the Fall’ (Noble 1997: 200).

It is unlikely, however, that those participants in the biotechnology debate that adhere to religious convictions will share these grand schemes. They will rather feel uneasy about such a project, whose scientific results may entail profound social problems and threaten cherished values and beliefs, in particular those about God the creator and His sacred creation: Nature. On various occasions (Galileo, Darwin, etc.), science has challenged Christian views on creation and the nature of God. But in response to scientific progress, our understanding of God and His relationship with creation has also changed. In his Religion in the age of science, Ian Barbour describes eight different models of God’s role in Nature, ranging from the omnipotent classical ruler to an interpretation of God as a process leader, a wise teacher who desires his students to choose for themselves and interact harmoniously (Barbour 1990). Two of these models are of particular importance to the understanding of the relationship between science and religion; the classical model and the mechanical model. The classical model describes God as divine omnipotence, a God who governs and rules the world, who is himself eternal, unchanging and impassible, unaffected by the world. This monarchical model is challenged by the scientific evidence of evolution and the discovery of continuous change in nature. In addition, there is no place for human freedom in this model. The growth of science in the 17th century led to a mechanical model of God as a clockmaker, the designer of a mechanical nature. But this view of God as the inactive God of deism who started the mechanism and then let it run leaves little place for continuous creation, personal encounters, or the biblical view of God as acting in history. Other models of God can be understood as intermediary positions between these two extremes.

These models do not only reflect the different ways we can view God in his relationship with nature, they also reflect different visions of nature as such. James Procter distinguishes five different visions of nature: evolutionary nature; emergent nature; nature as sacred; malleable nature; and nature as culture (Procter 2004). Is nature sacred and therefore not to be disrupted by men? Do we have to interpret nature as finished, or do we
have to view nature as the result of an ongoing evolutionary process? If nature is changing, is it also malleable by us? These questions lie at the heart of the biotechnology debate. In contrast to classical biology, biotechnology is not about simply understanding the secret (or sacred) laws governing the living world. By changing the genetic code biotechnologists can change the essence of living beings. Biotechnology almost by definition presupposes a vision of nature as malleable, malleable by man. When we change ‘nature’s essence’, DNA, we become co-creator.

Playing God versus doing God’s work

The vision of malleable nature implies that we distance ourselves from the view that creation is in principle finished, as well as from the idea that God bypasses human beings in arranging everything. In this view, the history of God’s creation is one in which humans have co-responsibility (Drees 2004). Concerns about human interference in life or nature are often articulated in terms of ‘playing God’. These concerns are not always religious in a strict sense. They can often be understood as metaphorical ways of expressing moral concerns for which a proper (secular) ethical vocabulary does not readily exist. It is not necessary to be a religious person to understand the symbolic or moral meaning of the statement that scientists involved in genetic engineering are playing God. In her book about the myths we live by, Midgley illustrates how the language in which some scientists express themselves seems to reveal that: ‘The mystics of the genetic revolution see themselves as experts engaged in completing nature’s work and especially in the business of ultimately perfecting humanity’ (Midgley 2003: 110). Furthermore, she points out that a powerful image lurks behind the use of the verb ‘engineering’: the simple analogy with machines. ‘Those who use the analogy [of engineering] seem to be claiming that we have a similar understanding of plants and animals as we have of machines and industrial plants into which we might put new components. But we did not design these plants and animals. This is perhaps an importance difference’ (Midgley 2003: 114).

Ronald Dworkin takes a different position in the playing God debate. He explains the use of the playing God metaphor as the expression of a distinction we make between that which is given and that which lies within our hands (Dworkin 2000). Everybody intuitively feels there is a dividing line between, on the one hand, what we are or nature is (regardless of whether this is the work of God or a blind process) and, on the other hand, what we create when we change what is given by nature. This distinction, argues Dworkin, is the backbone of our morality. Biotechnology, like no other technology, challenges this distinction. The biotechnologists who ‘play God’ are involved in matters that go beyond the way we traditionally understand concepts like nature, the unity of life, or species boundaries. To play God is to play with fire. But is this a reason to put a hold on biotechnology? According to Dworkin, the answer should be No. To play with fire is what we mortals have done ever since Prometheus. We play with fire and accept the consequences, because the alternative is an irresponsible cowardice in the face of the unknown (Dworkin 2000).

This provides me with an answer to the first set of questions about the way biotechnology is related to religion and how the variety of references to God and religion in the debate about biotechnology can be explained. In summary, I believe God talk reveals that there is an important relationship between religion and biotechnology, either in a metaphorical sense or in a literal sense. This explains why moral or social concerns about biotechnology are often expressed in religious language. Biotechnology is about changing creation, changing the essential code of life, the sacred script. These terms already convey a more or less religious world-view, even if they are used metaphorically. With biotechnology we cross the Rubicon, so to speak. Yet, instead of simply accepting what is given, by God, nature or life itself, we may also see ourselves as co-creators of life or nature. Behind the playing God metaphor (or the playing God accusation) lies a complex history of interaction between science and religion and the quest for salvation, either literally in the sense of returning to a state of original perfection, or metaphorically in the sense of leading towards a better life. With respect to the point I wish to make, it does not matter whether biotechnologist are metaphorically speaking about doing God’s work (the positive interpretation) or playing God (a phrase that usually carries a negative connotation). What does matter to my argument is the assumption that seems to underlie all biotechnology: the promise that man can in fact improve life, the work of God or Nature. In the following, I will elaborate the argument that scientists claim to do so, in the first place, by manipulating the mouse genome.

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46. A Dutch translation of the original paper that appeared in Prospectus Magazine is used.
Part Two: The healing powers of genetically engineered mice

The promise of mouse biotechnology

Improving the conditions of human life is the driving force behind medicine and biomedical research. All over the world, scientists are studying human biology and diseases in biomedical laboratories. In their search for ‘salvation’ – knowledge of the genome that will lead to longer, healthier and happier lives – scientists are ‘assisted’ by an army of perhaps 25 million mice (Clarke 2002). Many of these lab mice are genetically modified. Transgenic mice, also known as ‘mouse models’, are created in order to study human diseases. Mouse genes analogous to human genes are knocked out, and certain genes that possibly predispose for human diseases are knocked in. And, according to Kenneth Paigan, who was the Director of Jackson Laboratories in 1995: ‘There is every reason to believe that these efforts will have great impact; that over time they will lead to new strategies, new therapies, new means of alleviating ills, and new methods of preventing disease’ (Paigen 1995: 215). Also some patients’ groups praise the healing powers of genetically engineered mice. For example, the Patients’ Voice for Medical Advance, the national voluntary patients’ group that supports the humane use of animals and the ethical use of biotechnology in medical research in the UK, explicitly promotes mouse biotechnology on their website, in the first place as a response to animal activism47. ‘Transgenic mouse models enable researchers to study the complex interactions, at every stage of life, within a whole living environment. It is remarkable that, during the last 20 years or so, the genes responsible for nearly all the relatively common inherited diseases have been located and isolated. For example, Duchenne muscular dystrophy, cystic fibrosis, haemophilia, neurofibromatosis, Huntington’s disease, infantile spinal muscular atrophy, and many others. Genetic research, using mostly mice, is set to revolutionise our medical understanding and give hope of finding cures where previously hope could hardly be offered’ (Patients’ Voice website accessed on 1 May 2007). For many diseases these mice are the only hope patients have.

A beautiful visual image of the promise and hope for the genetically engineered mouse can be found in Joseph L. Goldstein’s ‘reading’ of Mann und Maus [Man and Mouse], a sculpture by Katerina Frisch: ‘The rise of the mouse to such exalted status in biomedical research is symbolized aptly by Katharina Fritsch in her large polyester sculpture Mann und Maus. Here, a gigantic mouse (in black) sits enthroned on top of a male figure in bed [see cover image]. The rigid division of the sculpture into black and white emphasises the obvious importance of the dominant animal model for human biology. Despite being dominated by the gigantic mouse, the man seems completely relaxed as he dreams of the many new advances in basic research and clinical medicine that will emerge from the new mouse technology. Curling its long tail like a question mark over the end of the duvet, the mouse wonders how long it will take for these new basic advances to be translated into clinical practice’ (Goldstein 2001: 1079)48.

What is striking about this interpretation of Fritsch’s mouse sculpture is the complete confidence Goldstein seems to have in the fact that the promise of mouse biotechnology will become true. Sooner or later, basic advances in mouse biotechnology will be translated into clinical practice. It is a clear example of Eugene Thacker’s statement that ‘a certain type of futurological, forward thinking is a key component to the continued development of the biotech industry and its future applications in medicine and health care’ (Thacker 2001: 156). Thacker predicts a ‘future biotechnology in which medicine is both curative and preventive, in large part due to advances in both molecular sciences and information technology’ (Thacker 2001: 155). Nikolas Rose also speaks of a future-oriented technology when discussing biotechnology. ‘The key feature of [the] new technologies of life is their forward vision: they seek to optimize the vital future by action in the vital presence’ (Rose 2007: 8). Rose discusses two of these future-oriented technologies: those of (genetic) susceptibility and those of (genetic) enhancement. ‘Technologies of susceptibility aim to identify and treat persons in the present for ills from which they are predicted to suffer in the future’ (Rose 2007: 8). Technologies of enhancement, Rose argues, are likewise future-oriented: ‘Almost any capacity of human beings

47. See <http://www.simr.org.uk/pages/research.11.html>. However, a quick search on the Internet reveals that most patients’ groups remain silent about the use of mouse biotechnology.

48. Please note that this is Goldstein’s interpretation of the sculpture and not Katerina Fritsch’s. According to the artist, the sculpture is about the relation between men and women: ‘Insofern hat das ganze Bild natürlich mit den Beziehungen zwischen Mann uns Frau zu tun, mit gescheiterten Liebesbeziehungen’ (Blazwick 2002).
strength, endurance, attention, intelligence and lifespan itself – seems potentially open to improvement by technological intervention’ (Rose 2007: 9-10)49. Both Thacker and Rose present a vision of biotechnology that is in line with the idea of salvation through science. Biotechnology is about faith and hope. A key characteristic of biotechnology, in particular mouse biotechnology, is its high degree of science fiction. It is a science of promises and hope, a science well visualised by Mann und Maus, but also one that deserves some critical evaluation. ‘The “science fiction” in technoscience does strategically utilise extrapolation and speculation. It does create visions of future worlds in which advanced science and medicine have developed new relations to diseases and to the body, and in doing so it does make a comment on the ways in which future biotechnology is largely dependent upon technological development to achieve this future vision’ (Thacker 2001:157).

Bio-economy or the ‘other’ promise of the genetically engineered mouse

The genetically engineered mice do not only promise better health, they also promise profit. That there are commercial interests involved in transgenic mice became clear on 12 April 1988 when, after a four-year process, for the first time in history a patent was granted on a higher form of life. In the years that followed, Harvard/OncoMouse™, the mouse involved, has beyond doubt become the best-known (see Figure 6). transgenic mouse. This mouse, expressing the MMTV myc oncogene, was developed in the laboratory of Harvard professor and geneticist Phil Leder in the early 1980s. The patent for the transgenic Harvard mouse was granted to Phil Leder and the company DuPont that donated 6 million dollars to the research (Blaugh et al. 2004). It concerned all transgenic mice carrying a gene construct for the development of spontaneous mamma tumours. The patent was related not only to the use of the mouse created by Leder but to all mammals (with the exception of human beings) that carry foreign tumour genes. DuPont’s commercial idea was to sell these mice for $50 each (Andrews 1989). Harvard researchers would be exempted from these costs (Schneider 1988a, 1988b). The patent created a stir in academia and industry. To the scientific community, it meant a threat to research because the patent included all non-human transgenic organisms that express a cancer-causing transgene. With this patent, DuPont got a tight grip on all research involving oncomice, including the mice that were created by the researchers themselves. It took more than ten years to come to a workable agreement between DuPont and academia on the free use of oncomice (Marshall 2000, 2002; Smaglik 2000; Blaugh et al. 2004). To the industry it indicated that the transgenic mouse technologies can offer interesting business opportunities.

OncoMouse™ also created a stir in society. The public was more upset about the fact that this mouse was supposedly a human invention than about DuPont’s aggressive licensing policies. The trade mark was taken to be the ultimate sign of human arrogance towards the creation of God or Nature. This was even more upsetting than the fact that species barriers had been crossed or humans had interfered in the mouse genome. In 1995, representatives from virtually every major religion in the US started a campaign against the patenting practices of genetic engineering (Andrews 1995; Stone 1995). In interviews they claimed not to be opposed to the practice of biotechnology as such. It was the patenting of human genes or organisms to which they were opposed. Their major criticism on patenting was that it would reduce the ‘blueprint of evolution’ to a marketable commodity (Andrews 1995). OncoMouse™ became the topic of wide public moral and religious debate, but also a source of inspiration for artists and philosophers. In the process, OncoMouse™ became the cultural icon of the transgenic lab mouse. Interestingly, playing God as such was not necessarily the problem but the doing it for profit was.

At the very moment Harvard and DuPont were granted their oncomouse patent, 21 patents filed for other animal biotechnology applications were pending. A year later in April 1989, the number was already up to 65 patents pending. They were filed by hospitals, universities and commercial companies (Andrews 1989). It took the Patent Office five years before they granted another patent on a transgenic mouse (Anonymous 1992; Andrews 1993). In December 1992, three patents were granted on transgenic mice intended for biomedical research. At that time, more than 180 applications were awaiting Government action for animal patents (Andrews 1993). While the research community and biotech entrepreneurs were anxiously awaiting the next patents on genetically modified animals, Harvard/OncoMouse™ turned out to be a commercial failure for DuPont (Marshall 2000). Cancer researchers preferred to develop their own cancer mice and mutually exchange them rather than pay for the expensive licences. But the

49. In the next chapter, I will discuss the scientific arguments for these statements in more detail.
creation of new oncomice is also protected by the DuPont patent. Initially this caused no problems. But, in the mid-1990s, DuPont started to claim its rights and requested researchers to put a halt to their oncomice activities. Harold Varmus, Director of the NIH, negotiated with DuPont about this restrictive patent. And in 2000, they came to an agreement concerning the use of oncomice in non-profit institutions (Marshall 2000)50.

Transgenic mice did not only give rise to a battle over legal rights on technologies and animals between commercial companies and academic researchers, they also gave rise to legal battles between companies. As Marla Cone writes in the Chicago Sun-Times ‘by blurring the lines between people and animals, this latest explosion in genetic engineering is not only transforming medical and developmental biology, it is raising disturbing legal economic and moral quandaries. Everyone, it seems, is clamoring to transform medical and developmental biology, it is raising disturbing people and animals, this latest explosion in genetic engineering is not only...’

A big industry that, according to The Observer’s Mike Bygrave, is based on hope and promise, very powerful driving forces (Bygrave 2002). In 2006, more than 6000 patents had been granted on transgenic animals, mostly mice (Silver 2006a). The knock-out mouse project, a coordinated project to systematically knock out all mouse genes, launched after a meeting of the world’s key mouse geneticists in 2003, can be seen as a response from the scientific community to the growing influence (or obstruction) of privately-owned commercial companies in mouse biotechnology. One of the aims of this project now in progress is to create a publicly-available databank resource for genetic and phenotypic data derived from knock-out mice (Austin et al. 2004). The first effort involved the acquisition of 251 knock-out strains, the most relevant mouse models, and the extensive phenotypic data from Deltagen and Lexicon Genetics, two commercial companies (Collins et al. 2007).

As this strategic activity around the mouse illustrates, in the past 20 years the promise of mouse biotechnology has become a complex dynamic network linking together many different actors. These can be ‘actual or potential sufferers [from disease hoping] for a cure, scientists and researchers seeking a breakthrough that will [allow them to] make their name and advance their career, doctors and health care professionals wanting a therapy that will help treat their patients, biotech companies aiming for products that generate profit, governments looking for industrial and commercial developments that will generate employment and stimulate economic activity and international competitiveness’ (Rose 2007: 14). In short, this is a network that exemplifies what Rose refers to as a ‘political economy of hope’.

A critical perspective on the political economy of hope

It is in the light of this political economy of hope that I wish to reinterpret Crockett’s Ecce Homo. His sculpture presents the genetically engineered mouse as a quasi-religious icon of hope. Crockett is suggesting that biotechnologists, by giving us OncoMouse, are promising some sort of salvation, just like God the Father did when he granted us Jesus, His Son. Crockett is not the first visual artist to compare OncoMouse with the Christ figure. As a response to the first draft of ‘Mice into Wormholes’ by Donna Haraway52 in 1994, the artist Lynn Randolph painted a transspecific human mouse hybrid ‘The Laboratory, or the Passion of Oncomouse’. In this picture OncoMouse is portrayed as half-human half-mouse with clearly recognizable human breasts. In contrast to Crockett’s Ecce Homo this mouse is definitely a ‘she’. The reference to Christ is made by the crown of thorns she is carrying. In contrast to Crockett’s Ecce Homo this female/man/mouse is not visibly suffering. She seems to be obedient and awaiting her destiny in peace. Haraway describes Randolph’s picture as follows: ‘She is a Christ figure, and her story is that of the Passion. She is a figure in the sacred-secular dramas of technoscientific salvation history, with all

50. Similar problems arose with a patent for Cre-Lox the system owned by DuPont, granted to DuPont in 1992. This patent was the beginning of another battle of many years fought between the research community led by Harold Varmus and DuPont (Marshall 1998). Problems started in 1995, when DuPont started to approach researchers who were using the Cre-Lox system to sign a contract that limited their activities. Jackson Lab negotiated this for about 2 years with DuPont, but was not able to reach an agreement. Varmus, however, succeeded after a year of negotiation. Since 19 August 1998, researchers who work for non-profit institutions are allowed to use the Cre-Lox system, but DuPont preserves the commercial rights (Marshall 1998).

51. One of the three patents the US patent office granted in 1993 was related to a transgenic mouse designed with a human immune system. The patent was granted to Genpharm international, but the company Cell Gensys claimed that technology had been stolen from them (Coghlan 1994).

of the disavowed links to Christian narrative that pervade US scientific discourse. The laboratory animal is sacrificed; her suffering promises to relieve our own; she is a scapegoat and a surrogate’ (Haraway 1997:47). Elsewhere, Haraway points out that ‘although her promise is decidedly secular, she is a figure in the sense developed within Christian realism; S/ he is our scapegoat; s/he bears our suffering; s/he signifies and enacts our mortality in a powerful historically specific way that promises a culturally privileged kind of salvation – a ‘cure for cancer’ (Haraway 1997: 79). Haraway chooses to interpret her oncomouse within a feminist technoscience discourse. Her OncoMouse is a model for breast cancer that may in principle affect all women. ‘If not in my own body, then surely in those of my friends, I will some day owe to OncoMouse’ or her subsequently designed rodent kin a large debt. […] Whether I agree to her existence and use or not, s/he suffers, physically, repeatedly and profoundly that I and my sisters may live’ (Haraway 1997: 79). Crockett chooses a similar perspective on the transgenic oncomouse. ‘Because the lab mouse has been used to test almost every product, disease and other facet of human life, I have chosen to interpret this ultimate actor of modern science through the ultimate figure of salvation, Jesus Christ’ (Crockett 2001). To Crockett the transgenic laboratory mice as scientific models represent modern science. These mice represent mankind in a deeply symbolic way. But, according to Crockett: ‘This all happens out of the public eye, invisible yet also somehow present’ (Rapaport 2006).

In addition to Ecce Homo Crockett made Pinkie, a marble sculpture of a baby mouse representing the Christ-child. The scale of Pinkie is that of a fleshy human baby, sculpted with the pathos of classical sculpture. Pinkie/Christ’s hand reaches upward in a gesture of blessing. What does Crockett want to tell/show us with these monstrous mice? According to himself, he is not opposed to ‘genetic tampering’, but he believes that it will force us to come to terms with the metaphysical meaning of science’ (Crockett 2001b).

In 2001 Crockett takes a step further in his artistic exploration of the man/mouse metaphor in his project Cultured. This group of marble sculptures, in the same style as Pinkie, represents seven newborn mice personifying the Seven Deadly Sins: lust, anger (wrath), gluttony, pride, sloth, greed and envy (see Figure 5 a-g). The figures are representatives of actual mice that are engineered to study human diseases. Gluttony was based on the ob-mouse, that is: the obese mouse engineered by Jackson Laboratory in Maine to study obesity and diabetes. Anger is pumped up on testosterone, and Lust is a mouse genetically altered to have an extremely sensitive skin. Pride refers to the vanity of cloning. Greed manifests the extra chromosome that predisposes to Down’s syndrome. Sloth has malformed legs as a result of arthritis and the effect of thalidomide. Envy, with its tiny human shaped ears, refers to the human ear that was grown on a laboratory mouse, as well as to the replication of a human immune system in mice (Johnson 2002; Rapaport 2006; Leffingwell 2002). With Cultured, Crockett sets a double agenda. He wants to make ‘these invisible little workers/prisoners more anthropomorphic or human’. But, by choosing the theme of the seven sins he also merges religious ideas with scientific ones (Rapaport 2006). Ecce Homo, Pinkie and Cultured refer to both technoscientific practices and to religion. Therefore, the work of Crockett can be placed in the tradition of Christian iconography, as well as in the public debate on biotechnology. It is an explicit religious interpretation of the scientific practice of biotechnology.

The message of Ecce Homo the OncoMouse

Someone who gets to meet real oncomice in a laboratory after having seen Crockett’s mice, may well be disappointed. Compared with the grotesque and monstrous Ecce Homo, real oncomice are sweet little mice. There is nothing special about them. They are neither huge nor nude. They do not stand on their hind legs. They develop tumours and become visibly ill. But you cannot tell by simply looking at them that these mice carry human genes so that they may mimic human cancer. The trade mark is not imprinted on their fur. They look like normal lab mice and they behave like normal lab mice. The technology behind these mice is invisible to the naked eye. Not only are their genetic mutations invisible, the mice themselves, who live in laboratories specialised in the containment of hazardous material, remain (as Crockett also pointed out) invisible to the public eye.

When Ecce Homo and, subsequently, Pinkie and Cultured entered the public arena through their exhibition in art galleries and reviews in art magazines, newspapers and even Nature (Nelkin and Anker 2002), the transgenic mice on which they were modelled also became visible to broader audiences. But Crockett dramatically added meaning to the original oncomice. He gave his OncoMouse a human size and a human posture. Standing on its hind legs Ecce Homo, the mouse/man mouse
model, literally resembles Man. Being at eye level, Ecce Homo can interact with his audience in a way that would not be possible for a mouse on a mouse-scale. The pathos of the sculpture reveals how transgenic mice like Ecce Homo are used by us humans; they are similar to us, but also victims of science.

How does Crockett help us to understand the moral meaning of animal biotechnology? Notwithstanding his pathos, Crockett refuses to take a position on animal biotechnology from a bioethics or animal rights point of view. In my opinion, this explains why his work is so powerful in pointing out the important issues at stake. Rather than entering the debate over the use of animals in laboratory experiments with a clear-cut moral message, Crockett’s sculptures visualise the time-old conflict between religious doctrine and scientific rationality. By explicitly referring to the Christ figure, Crockett seems to indicate we have chosen science as a substitute for faith in an era of dwindling spirituality, and he seems to be questioning this choice (Gladman 2002). This observation takes us to Crockett’s statement that man has to come to terms with the ‘metaphysical meaning of science’. Ecce Homo the OncoMouse can be interpreted as an icon of our overall optimistic faith in salvation by technoscience. But it also echoes the rhetoric of saving lives that is so stereotypically conveyed by moral justifications of (animal) biotechnology. Animal biotechnology is only permitted when experiments are useful and necessary. Whether an experiment is useful and necessary usually depends on how much it is expected to contribute in finding a cure for a life-threatening disease. It is about what we want to believe and what we are told.

If a secular equivalent of redemption can be found in the promise of biotechnology to save us from life-threatening diseases, what would be the equivalent of the Fall from Eden? By portraying his cultured transgenic mice as the Seven Deadly Sins, Crockett seems to explicitly reflect upon this question. The sculptures are not about sick mice, they are about us, humans. They urge us to have a closer look at the relationship between his transgenic mice and the human individuals they are actually modelling. These mice are mouse copies of obese people, people who want to regenerate some of their degenerating tissues, or children of mothers who took thalidomide while pregnant. Thalidomide was a widely used sedative to prevent morning sickness in pregnant women in the early 1960s. By the time it became clear what the effect of thalidomide actually had on embryonic development, more than ten thousand thalidomide-induced teratologies (short limbs) had been found (Leroi 2003: 118-121). The medical examples that the mice represent are carefully chosen by Crockett. These illnesses are the result either of ‘bad’ or ‘immoral’ (unhealthy or risky) human behaviour or of scientific mistakes. Also many forms of cancer, the raison d’être of OncoMouse™, are related to (unhealthy) lifestyles. There is a general consensus on the existence of a relationship between smoking and lung cancer, sunbathing and skin cancer, unhealthy diet and colon cancer. They all represent diseases that are caused by morally-questionable lifestyles. It seems that Crockett wants to argue that these mice designed to model these forms of cancer are literally sacrificed for our sins. With Cultured, in my opinion, Crockett adds a very critical note to the heroic statement that with transgenic mice scientists are finding cures to life-threatening diseases. Genetic diseases are the result of genes and behaviour. Transgenic mice will not change our behaviour.

But Ecce Homo the OncoMouse™ and Cultured are not only about human sins and faith in redemption by science and technology. They are also critical reflections on the commodification of life and the trade marks that the transgenic mice are carrying. OncoMouse™ is not just a transgenic mouse; it is the first patented animal. The sculpture of Ecce Homo does not only comment on the promises made by the scientists, it also comments upon the promises made by DuPont and all the other commercial companies involved in the worldwide transgenic mouse business. In advertising their commercially available OncoMouse™, DuPont promised ‘better things for better life’. It is hard to believe in the sincerity of this promise, given the problems that the patenting of OncoMouse™ and other biotechnologies entailed for the non-profit-scientific community.

Concluding remarks

Ecce Homo the OncoMouse can be interpreted as a modern icon of our optimistic faith in salvation through technoscience. To many people, religious or not, the idea that science can and will bring about a form of salvation, a longer, healthier and even happier life, is a tempting one. The whole biotech industry is based on this hope and promise. Nevertheless, I do not think I can subscribe to Nelkin’s statement that ‘by drawing on powerful images of Christianity, scientists are seeking to attract converts – to convince the public and many sceptics of the power of their ideas’. I do not see God talk simply as a matter of strategic rhetorics. Rather I am
convinced that God talk illustrates how biotechnology itself has become a belief system, albeit a belief system that includes a number of varieties. To some, biotechnology means hope to find a cure for life-threatening diseases. To others, breakthroughs in mouse biotechnologies represent the promise that a healthy biotech industry will provide jobs for the people who work there and revenues for the shareholders. Lessons learned about the malleability of nature challenge long-held beliefs about creation. So, in this sense too, biotechnology is becoming a belief system, one that replaces traditional beliefs in God. To the extent that God has left the scene, he left behind a rather unsettling imaginative vacuum that is now being occupied by biotechnologists (Midgley 2004). According to Midgley, this has to do with the persistence of the idea of the world as machinery, but now in the absence of a designer. Where there is no designer the whole idea of a mechanism begins to grow incoherent. Natural selection is supposed to fill the gap, but it is a thin idea, not very satisfying to the imagination’ (Midgley 2003: 118). We need something to believe in, something that will help us to coherently frame our imagination, something that entails a vision of nature.

This takes me to the answer to the second set of questions about the feelings and concerns that are expressed by the playing God metaphor. Are these primarily moral concerns about messing with His creation or Nature, or does ‘God talk’ also reveal other more complex issues of moral concern? In summary, I believe God talk reveals much more than moral concerns about messing with His creation. It also expresses concerns about power, or to put it more specifically, about the distribution of power. Who is promising salvation through biotechnology? If this is really the first time ‘a living creature understands its origin and can undertake to design its future’, it is an important question which living creature it is that understands itself. Who is playing God? As Midgley points out, it cannot be human beings in general. Most people have no idea how to do it. This means that the biotech revolution is creating a new type of elite. These are the biotechnologists, the only people who are able to make the changes in the DNA of living organisms (Midgley 2004). This elite, with unprecedented knowledge concerning matters of life and death, can play a dominant role in a political economy of hope.

The danger of biotechnology turned into a belief system is that, by doing so, it may become less susceptible to critique. If one sincerely believes that mouse biotechnology will lead to some sort of salvation: for example, by saving lives that would otherwise be lost, every mouse and every amount of funding invested in mouse research becomes important and necessary – a belief which is almost impossible to question. Such a belief may stand in the way of a sound moral and political debate on what animal biotechnology is really about, the animal suffering involved, and the implications of biotechnology for our own human future and other bio-political issues. What is it exactly that mouse biotechnology is promising? For example, one of the critical points Crockett seems to be making is that biotechnology will encourage a hedonistic lifestyle. What effect will the genetically engineered mice have on our lifestyle if ‘sins’ related to the western way of living, such as the consumption of unhealthy food, smoking, stress and pollution, can be compensated with research on genetically engineered mice? If research on the mouse and the human genome is directed towards correcting or overcoming genetic errors, what will be the future standards of health and quality of life? Will ‘health’ simply mean to be free of life-threatening diseases such as cancer, or will it also come to imply freedom from ‘genetic errors’ involved in obesity or colour blindness? This is an important question because, as Rose observes, biotechnology implies a shift from technologies of health to technologies of life. ‘Contemporary medical technologies do not merely seek to cure diseases, but to control and manage vital processes of the body and mind’ (Rose 2007: 8). How will our perceptions of genetic diseases evolve when our understanding of the genome and of the complex interactions between genes (of both mouse and man) increases? What will we look like in the future when: ‘Interventions are demanded by customers making choices on the basis of desires shaped not by medical necessity but by the market and consumer culture’ (Rose 2007: 10). If scientists are playing God, what is their (or the market’s) Divine plan? Are genetically modified mice to be seen as monstrous anticipations of what we will become ourselves?
Figure 1 A giant mouse (left) grown from an egg injected with rat growth-hormone genes weighs nearly twice as much as its normal sibling. Photo: Ralph Brinster, University of Pennsylvania School of Veterinary Medicine, taken from Palmiter, R.D, Brinster R.L et al. 'Dramatic growth of mice that develop from eggs microinjected with metallothionein-growth hormone fusion genes,' Nature, Vol. 300, pp. 611-615, 16 December 1982. Courtesy of Ralph Brinster.

Als we een muis in een mens moeten veranderen om aids te genezen, doen we dat.

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Figure 3 “If we have to change a mouse into a human to cure aids we will do so.” From the recruitment campaign ‘It is your world’ (Het is jouw wereld) of the Academic Medical Centre (AMC), Amsterdam.

Figure 4 Ecce Homo by Bryan Crockett. Courtesy of Bryan Crockett.
Figure 5 Cultured by Bryan Crockett, The Seven Deadly Sins, clockwise: a Lust, b Anger (Wrath), c Gluttony, d Pride, e Sloth, f Greed, and g Envy. Courtesy of Bryan Crockett.

Figure 6 Harvard/OncoMouse created by Phil Leder at Harvard. Courtesy of Phil Leder.

Figure 7 Doogie the smart mouse created by Joe Tsien at Princeton. Courtesy of Joe Tsien.
Figure 8 the GFP Bunny project: a Alba, and b Eduardo Kac holding Alba in his arms.

Figure 9 From the Transgenic Mice Series by Catherine Chalmers: a Rhino, and b Obese. Courtesy of Catherine Chalmers.
Chapter 4
The ‘Frankenstein thing’ or the monsters we fear

We have a choice of what myths, what visions we will use to help us understand the physical world. We do not have a choice of understanding it without using myths or visions at all. Again we have a real choice between becoming aware of these myths and ignoring them. If we ignore them, we travel blindly inside myths and visions which are largely provided by other people. This makes it much harder to know where we are going.\footnote{Mary Midgley (1992) Science as salvation. A modern myth and its meaning, London and New York: Routledge, p. 13.}

Mary Midgley

Introduction

Of Monsters and Mutants

In their book *The Molecular Gaze*, Suzanne Anker and Dorothy Nelkin discuss monsters in relation to bioart, a new form of contemporary art involving techniques borrowed from biology. In the chapter *mutation, manipulation and monsters: the new grotesque in arts*, they describe how research in genetics and, especially, the possibilities of genetic manipulation have resurrected a long-standing interest in monsters and mutants in popular culture and the visual arts. ‘The monsters and mutations of contemporary culture and visual art are expressing the ethical dilemmas and the ambiguities that are inherent in science and technology – activities that can cure or kill, create or destroy, provide benefits or cause harm’ (Anker and Nelkin 2004: 76). In their discussion of the (artistic) imagination and biological science underlying popular visions of the monstrous, they not only show how the definition of the monster is time-dependent, but also how closely it is related to developments in (molecular) biology. ‘Once called “freaks”, today’s “monsters” are construed as beings with mutations that are expressed as bodily aberrations. As genetics guides one’s vision of the normal, anomalies have turned into congenital deformities, oddities into specimens and monsters into mutations’ (Anker and Nelkin 2004: 47).

In the 16th and 17th centuries, monsters were virtually everywhere. Princes collected them; naturalists catalogued them; theologians used them for religious propaganda; scholars charted their occurrence and their significance in exquisitely illustrated books (Leroi 2003). In those days, monsters were human beings with developmental deformities like those associated with Siamese twins and Cyclops – physical deformities which were taken to be a punishment by God. The ontogenesis of monsters was taken to lie in unnatural acts that offended the Divine laws. Thus, despite the monster’s bodily malformation, the issue at stake in the phenomena of monstrosity was not physical, but moral (Graham 2002).

The etymological roots of the term ‘monster’, derived from the Latin monere (to warn) suggest that abnormalities of this kind were taken to be dangerous (Anker and Nelkin 2004). Associated with grotesque deformity, gross incongruity, and inhumane cruelty, monsters represent a threatening force, a terrifying and convincing deviation from the natural, as well as something that draws public attention and must be exposed to the public gaze. An alternative etymological reading starts from the French montrer, or the Latin monstrare, to point out, or show forth, as the origin of the term ‘monster’54. A monster is something to be shown, to be displayed, precisely because it is so different and frightening. Following this etymology, the purpose of a monster is to reveal the Divine Will (Graham 2002). Although those who warn us about Divine Will evoke fear, they also attract curiosity. The fear of monsters is often accompanied with fascination. Freak shows, the public exhibition of human oddities such as dwarfs, giants and Siamese twins, were a popular form of entertainment from the late 17th century onward to the early 20th century. At the start of the 17th century, natural philosophers like Francis Bacon began to take a more scientific perspective on monsters. Teratology, ‘monster studies’, replaced the old medieval wonder books. Scholars no longer explained abnormalities in terms of Divine punishment, but in terms of natural causation (Leroi 2003).

Monsters have always been, and still are, of great value to biology. Monster research is of particular importance for developmental biology. By studying anatomical abnormalities, developmental biologists gain insight into the complex mechanisms underlying normal development. Since the discovery of the homeobox genes in 1984, molecular biology has become a dominant discipline within the field of developmental biology. Today, most developmental disorders that lead to phenotypic abnormalities can be explained on the basis of genetic defects or mutations (Leroi 2003). This process the ‘geneticisation’ of developmental biology entailed a ‘demystification’ of the monster. Freaks that were traditionally seen as monstrosities lost their mystical character. They are no longer monsters, they have become genetic mutants.

But, as Anker and Nelkin point out, in spite of these new insights from modern biology, the term ‘monster’ did not loose its archetypical significance. With the aid of modern biotechnology, humans are capable of altering the ‘blueprint’ of life and recreating living organisms. During the molecular revolution, the life sciences reduced the naturally occurring (mystic) monsters to genetic mutants. At the same time, with the art of genetic engineering, scientists are creating a new class of potential monsters. Therefore, classical definitions of the monster are no longer adequate. Monsters are no longer the effect of Divine interventions or nature’s contingencies. Today’s monsters are human creations. That is why Anker and Nelkin argue that the monster metaphor is more relevant than ever. ‘The growing possibilities of altering the body, tampering with nature, and manipulating reproductive processes are clinically and philosophically seductive, yet troublesome as well. They promise control and even perfection, but they do also evoke fundamental questions of authenticity, identity and bodily integrity – the same questions that, two centuries ago, inspired Mary Shelley to create Frankenstein (Anker and Nelkin 2004: 3). If the questions are the same as two centuries ago, what has changed since 1818?

Is Frankenstein no longer a myth?

If we have to believe Anker and Nelkin, the life sciences have changed in such way that ‘Mary Shelley’s novel is no longer a myth’ because biotechnology has given all the resources we need ‘to engineer the human body for cosmetic as well as therapeutic purposes’ (ibid.: 71). And, as they write in the closing paragraph of their chapter on monsters, the continuing tampering with genes might lead to ‘a gruesome parade of horribles’. How can we interpret this horrific vision of biotechnology? This is an important question, because Anker and Nelkin do not stand alone with their reference to Frankenstein. Frankenstein’s monster is more or less...
the archetype of popular ‘biotech-monsterphobia’. What is it exactly that people like Anker and Nelkin fear about biotechnology when they refer to Frankenstein? This question implies three sub-questions. First of all, what is it exactly that is ‘no longer a myth’? Secondly, do scientists really possess the resources necessary for re-engineering the human body? And thirdly, if this proves to be the case, are contemporary biotechnologists indeed examples of scientists who are following in the footsteps of Victor Frankenstein? In other words, how does the myth of Frankenstein relate to new developments in biotechnology, now and in the near future?

In order to answer these questions, I will first of all subject the Frankenstein myth to a close rereading. What are the essential ingredients/characteristics of the Frankenstein myth? Why did the story become a myth? And why do people feel that the Frankenstein story is relevant for understanding the implications of biotechnology today? Subsequently, I will turn my attention to the contemporary monsters of modern biotechnology: genetically engineered and mutant mice. I will tell the story of four supermice and their creators in order to illustrate the (future) possibilities of genetic human enhancement. I will argue that, in the days of the supermice, rereading Shelley’s novel is of great importance. Myths play an important role in our perception of the world. In our understanding of modern biotechnology, the Frankenstein myth is beyond doubt the most influential myth. It has helped us to frame the issue. But exactly how does the Frankenstein myth influence our ‘spontaneous’ (that is: culturally and socially constructed) responses to biotechnology? Shelley’s was the first effort to flesh out the intuitive reception of what was just beginning to take shape. Now that the project of redesigning life seems to becoming reality, I believe it is important to return to this first original effort and see what we, who live at the beginnings of a biotech revolution, may learn from it.

**Part One: The Frankenstein myth**

**The story of Victor Frankenstein**

*Frankenstein* is the story of a young and ambitious scientist, seeking dangerous knowledge, and his hideous creation. Victor Frankenstein is haunted by the ambition to unravel the secrets of life. He wants to control life and to learn how to put life into lifeless matter. ‘With the greatest diligence’ he wants to become involved in ‘the search of the philosopher’s stone and the elixir of life’ (Shelley 2002: 42). He is very clear about what it is he is after. He dreams about the glory awaiting him if he ‘could banish disease from the human frame and render man invulnerable to any but a violent death’ (ibid.: 42). Victor is soon captured by the spirit of scientific discovery. He describes enthusiastically how ‘in other studies you go as far as others have gone before you, and there is nothing more to know; but in scientific pursuit there is continual food for discovery and wonder’ (ibid.: 52). What exactly he is doing in his laboratory and elsewhere remains somewhat unclear, but it involves ‘collecting bones from charnel-houses’ and disturbing ‘the tremendous secrets of the human frame’ with ‘profane fingers’ (ibid.: 55). One dreary night in November, he finally succeeds with his experiments. He puts life into a humanlike creature he has made himself from various materials, including human remains. Initially he is excited when he sees ‘the dull yellow eye of the creature open’ (ibid.: 58). But only a moment later, he finds himself filled with horror and disgust. The experiment turns out to be a catastrophe. The creature he made looks like a wretch. He abandons it and flees from his laboratory, in order to return to the beautiful places where he spent his innocent, dreamy youth. But the traumatic event will not leave him in peace. When his younger brother is viciously murdered, it is clear to him that his hideous creation is responsible for this violent death. Unable to work things out with the monster he himself created, Victor must then witness how his best friend and wife also fall victim to ‘the fiend’. Sorrow and regret are the results of Victor’s irresponsible behaviour. At the end of the story, he sets out to reunite with the monster he himself created, Victor must then witness how his best friend and wife also fall victim to ‘the fiend’. Sorrow and regret are the results of Victor’s irresponsible behaviour. At the end of the story, he sets out to reunite with the monster who has decided to retreat from the civilized world. When his life is coming to an end, Victor Frankenstein confesses the story of his life to Captain Walton, who finds him almost frozen, wandering in an Arctic waste. When Victor recognises the ambition of the young adventurer, he warns him about the possible consequences of scientific aspirations. ‘You seek for knowledge and wisdom as I once did; and I ardently hope that the gratification of your wishes may not be a serpent to you, as mine has been’ (ibid.: 31).

**The birth of a myth**

In the two centuries that have passed since it was first published, the story of Frankenstein has truly become a modern myth (Turney 1998; Haynes 1995). In his book *Frankenstein’s footsteps, science, genetics and popular culture*, Jon Turney explores the birth of the Frankenstein myth. As he
explains, whether a story becomes a myth depends on the number of times it is retold. The vitality of myths lies in their capacity to change, their adaptability and openness to new combinations of meaning (Turney 1998). In other words, a myth is a story that takes on a life of its own. A myth is a narrative that, through many retellings, becomes part of our collective memory, our reservoir of shared references. In the process of becoming a myth, the author more or less loses control over his or her own story. What is thought, felt and said about the story by countless others takes on progressively greater significance while the details and nuances of the original story are more or less erased. By the time a story approaches mythical status, the original version has become almost irrelevant. In that respect Mary Shelley’s novel is remarkable. It is a modern example of a myth: an almost ‘anonymous’ story that became firmly embedded in our culture (Turney 1998). Since its first appearance, the story has more or less emancipated itself from the original book. *Frankenstein* has been continually retold in various media (novels, plays, films, newspaper articles, etc.). Two years after its publication, the first stage version based on the novel was performed. And within three years, 14 other dramatisations appeared on English and French stages (Lederer 2002). The story is still being retold in comic magazines, horror movies, and motion pictures. Although only a few people have actually read the original book, everybody has heard of Frankenstein.

The rough outline of the Frankenstein myth (in all its adaptations and retellings) is the story of the mad scientist. These stories display a typical structure or script: a scientist makes a discovery that poses a significant threat to society, to the everyday world, either deliberately or by accident. Like the traditional monsters, these man-made monsters serve as a warning to those who intend to transgress natural or Divine laws. But this does not imply that the Frankenstein myth is a straightforward anti-science story (Turney 1998). Very often, the mad scientist is simply naïve. He failed to really consider possible consequences, but acts with good intentions. It is too easy to read the Frankenstein story simply as a warning about the dangers of scientific ambitions, as some readers (both in Shelley’s own time and today) have done. The subtitle of her novel, *the new Prometheus*, suggests that the novel displays a number of layers, and that its message concerning the potential dangers and benefits involved in penetrating the secrets of nature is more ambiguous. By introducing Frankenstein as the new Prometheus, Shelley is intentionally creating a character of mythical proportions. Frankenstein, with his scientific mindset, serves as a model for the new scientific ideal. Like Prometheus, Frankenstein could be considered a benefactor of humankind. His desire to renew life where death had apparently condemned the body to corruption, was a vision he shared with other medical ‘Prometheans’ of the early 19th century (Lederer 2002). But Victor Frankenstein was more successful with his experiments. He truly succeeded in finding the elixir of life. The creature he made was really alive. But, at the same time, the experiment was a dramatic failure, notably because the creature he made was hideous rather than perfect.

What is it that distinguishes the myth from other fictional narratives such as legends or fables that are also continuously being retold? Part of the answer is that myths seem to have a predictive power. Myths are stories intended to explain apparently inexplicable events, such as the creation of the world or the introduction of important technical devices (such as fire) or cultural conventions (such as marriage). In that sense, they have both explicative and normative meaning. They reveal fundamental truths about the human condition, often through the use of archetypes, and serve as moral guides. This should also apply to the Frankenstein tale if it is to be truly a myth. It should have a mythical aura and should convey an important moral message about modern technology. The truth of the Frankenstein myth is that those who go beyond nature, by artificially reshaping life, are playing with ‘fire’ and will be punished for this. Containment will prove impossible. Their artifacts will get out of control.

According to Jon Turney (1998), the Frankenstein story became a myth because Shelley’s novel was the first secular narrative about a scientist involved in the artificial creation of life. As Turney explains: ‘Frankenstein marks a transition in stories of men creating life because Victor does not invoke the aid of a Deity or any other supernatural agency. He achieves his goal by dint of his own (scientific) efforts’ (Turney 1998: 14). He has good intentions, but is blind to the consequences. ‘Natural philosophy is the genius that regulated my fate’, Victor Frankenstein confesses when he explains his deeds (Shelley 2002: 40). Herein lies the crucial difference between the Frankenstein story and other classical narratives like the Faust story, the Golem legend, and the Prometheus myth: it offers the first truly secular treatment of the great aspirations and fears of humanity, replacing eschatological punishment with scientific determinism (Haynes 1995).

Frankenstein-the-monster myth continues to allow individuals to articulate uneasiness about the natural sciences, in particular biology. Of all
the sciences, biology is the discipline that touches on the most powerful desires of human life. Biological research is about life itself: birth, sex, suffering, disease, disability, and death. We have always been prisoners of the body, victims of morbidity and mortality, and we desire that the power that biology might give us will relieve us from these burdens. The realisation that biology offers the prospect of ultimate control over the living realm evokes deep-rooted ambivalent feelings. The ambiguity in the story of Victor Frankenstein articulates a deeply-felt cultural neurosis about modern science (Turney 1998). This neurosis evolves out of a conflict between apparently incompatible basic attitudes towards science: (manifest) enthusiasm and (latent) fear. Enthusiasm, because of the progress it will entail in the medical sciences; fear because of the potential monstrous artifacts that are made in laboratories (see Zwart 2004). Frankenstein himself is the classical example of a person suffering from this neurosis. He is both extremely enthusiastic and extremely traumatised. After fleeing from his laboratory and abandoning his creature, he suffers from a severe nervous breakdown. Unable to act in a responsible way, he does not act at all. He is has paralyses of will and suffers from depression. The Frankenstein story is an archetypical myth that expresses deep concerns that trouble the modern mind. The many interpretations of the Frankenstein story offer a powerful illustration of the ways in which society responds to discoveries in biology and other sciences. Frankenstein is part of our cultural vocabulary and can readily be used to express fears and anxieties about the implications of new developments in science and medicine55. It differs from other classical myths like the Prometheus myth because it is neither a Divine power, nor a troubled conscience, but the artifact itself that turns against us. This is what the artist Adam Zaretsky refers to as Boomerangaphobia. If a biotechnological artifact gets out of control and turns against us, there is nobody to blame but ourselves. The myth offers a vehicle for packaging and personifying fears and doubts about science and technology. This form of personalisation helps us to deal with these fears. The myth also contains an element of catharsis: namely, by punishing those who intend to go beyond nature. The fact that Frankenstein is punished offers a certain amount of comfort. In the end, cultural stability is more or less regained. Yet, the fact that he managed to achieve his goals remains a source of uneasiness.

**Mad science**

The ‘birth’ of the Frankenstein myth took place at a time when the method of experimental investigation was rapidly gaining prominence in the life sciences. The new scientists no longer studied the secrets of nature by relying only on books or observation (‘natural history’); they subjected nature to experimental procedures. The shift from natural philosophy and natural history to experimental life science is an important element in the Frankenstein story. The new powers over life and death are associated with the new, experimental approach, the new inheritor of time-old mythical aspiration. In the final decades of the 18th and in the early decades of the 19th century, a new practice of science evolved that we nowadays call ‘experimental biology’. Biology increasingly came to rely on experiments on living animals: vivisection. Biologists began to have dirty hands57. In the story, Victor testifies to Walton how he ‘tortured the living animal to animate the lifeless clay’ (Turney 1998; Shelley 2002: 55). Vivisection was not completely new at the time when Shelley wrote her novel (Harvey, Von Haller, etc.), but it was now done on a much larger scale than before, and it started to become ‘normal practice’.

The ‘torturing of animals’, for several reasons, takes place behind closed doors, invisible to the public eye. First of all, in order to create a secluded space where specialists can freely work in a scientific atmosphere. But perhaps even more important, secrecy prevents exposure to, the ‘emotional responses’ of the public that would probably make this type of scientific work impossible. In Shelley’s novel, there is a clear tension between the importance attributed to this type of work by the scientists involved (i.e. Victor) and the moral sensitivities of his cultural environment. This renders the moral profile of this practice (the animal cruelty it involves, the use of human corpses, etc.) highly problematic. Somehow, the public needs to come to terms with this ambiguous image of the sciences. Turney describes how, in response to this ‘dirty work’, at the turn of the 18th century a paradoxical public image of the scientist develops. On the one hand,

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55. e.g. Greenpeace’s anti-biotech slogan: ‘Say no to Frankenfood’.
56. Personal communication.
57. In the early 19th century, anatomical studies like those conducted by Victor Frankenstein also generated public hostility. Before the revised version of the novel in 1831, the only bodies legally available to physicians and surgeons for study were those of executed criminals (Lederer 2002).
scientists are celebrated as heroes because of their achievements in the medical sciences. On the other, the image of the scientists in popular fiction begins to resemble that of the mad scientist. Whereas newspapers frequently report on medical breakthroughs as the result of scientific research, ‘The image of the fictional biologist, at the turn of the nineteenth century, is one of an unfeeling and obsessive scientist’ (Turney 1998: 54). Another famous fictional (late) nineteenth century scientist is Wells’s Dr Moreau58. While Frankenstein more or less represents the beginning of the 19th century, Moreau emerges when the century approaches its final years. His experiments on beast people – he tries to turn animals into humans by means of surgical operations – are of such an evil nature that he can only perform his ‘research’ far away from the civilised world on a secret island. This paradoxical image of the (biomedical) scientist, being, on the one hand, benevolent and, on the other involved in dirty business, is still persistent today.

A life of its own
Frankenstein, however, seems to have been deprived more or less of his original ambiguity. In the two centuries that have passed since Mary Shelley published her novel, Victor Frankenstein became the stereotype of the mad bio-scientist, his hideous creation the archetype of science out of control. He is no longer a potential benefactor. He is simply portrayed as a mad scientist. His monster is no longer a pitiful creature seeking for acceptance and understanding. In the popular myth it has become a plainly evil monster. In the process of turning Frankenstein into a myth, the movie industry played an important role. Shelley’s story has been used as a source of inspiration for an impressive number of horror movies. The first motion picture of Frankenstein was made in 1931 by James Whale. It was the actor Boris Karloff who defined the popular image of the monster: a flat forehead of massive size, lots of highly visible stitches in the facial area and two metal studs protruding from the neck. In this movie and the countless Hollywood remakes that followed, the fate of Frankenstein and his monster became a clear-cut moral lesson illustrating the punishment that awaits ambitious scientists who play God by creating life. Much emphasis it put on the bloody revenge and horrible features of the monster and the evil or mad character of the scientist. As a result, in popular

perceptions, the creature and its maker lost much of the complexity, that Mary Shelley had given them59.

Whoever takes the trouble to read Shelley’s original novel will, however, understand that the monster is not born as a vicious and murderous creature, but is driven to his horrible deeds after years of sadness, loneliness and deprivation. It is the negligence of his creator Victor Frankenstein, who failed to take responsibility for his creation, that resulted in the traumatic failure of the monster’s efforts to become civilised. And this (abandonment and rejection by society) was what made the creature become a monster. Victor Frankenstein’s struggle with his own responsibilities – Should he kill the creature? Make him a female counterpart, in order to free him from his loneliness? Who is to blame for the terrible death of his young brother, maid, wife, and friend, he or his creature? – indicates that the novel is not at all a simple horror story. Rather, it is a story about science ethics and bioethics.

Frankensteinian ethics and contemporary biotechnology
To warn about the consequences of the search for dangerous knowledge is a key theme in the story. It is the reason why Victor confesses to Walton: ‘Learn from me’, he begs him, ‘if not by my precepts, at least by my example, how dangerous is the acquirement of knowledge and much happier that man is who believes his native town to be the world, than he who aspires to become greater than his nature will allow’ (Shelley 2002: 54). Nevertheless, the ethical lessons to be learned from Shelley’s novel are more than simple warnings about the catastrophic consequences of playing God. It is not an anti-science novel. In the words of Stephen Jay Gould: ‘Victor Frankenstein is guilty of a great moral failing, but his crime is not technological transgression against natural or divine order’ (Gould 1996: 54). Had Shelley believed that scientists should not explore the ‘cause of generation and life’, she would surely have chosen to portray him as a genuine moral monster (Segal 2001). The story tells us about the scientists’ responsibility for their work. It urges us to take good care of our creations. Indeed, it is a story about care rather than a story about control.

Another important theme in the novel is the way Frankenstein communicates about his experiments to the people that surround him (Zwart

58. H.G. Wells, The Island of Doctor Moreau was first published in 1896.
59. An exception to this is the 1994 movie Mary Shelley’s Frankenstein by Kenneth Branagh, starring Robert de Niro as the monster.
2004). He is working night and day on his scientific project. Obsessed with his work, he becomes estranged from the research community to which he belongs. He does not communicate about his work: neither to his professional colleagues nor to the people who love and care about him. He does not even inform his own professor. He keeps the doors to his laboratory closed to the outside world. In a solitary chamber, or rather a cell, at the top of the house he keeps his ‘workshop of filthy creation’. Even when it becomes clear that his monster is on the rampage; hurting and killing his loved ones, he still does not confide in anyone. Rather than revealing what he knows about the murder of his young brother William, he prefers to say nothing. By remaining silent he lets the tragedy continue and more violent deaths follow. Only at the end of his life, when the monster has decided to withdraw from the hard and unwelcome world he was forced to live in, does Frankenstein confess his deeds to a stranger.

So the moral of the story is not to place a moratorium on all research involving matters of life and death. Rather, its moral is a much more modern one. It is about careful scientists’ communication with others. According to Gould, Frankenstein should have taken time to educate the monster in order to make him fit for our society and at the same time educate society in acceptance and tolerance (Zwart 2004)60. ‘Frankenstein’s monster was a good man in an appallingly ugly body. His countrymen could have been educated to accept him, but the person responsible for that instruction – his creator Victor Frankenstein – ran away from his foremost duty and abandoned him at first sight’ (Gould 1996: 61). In 1818, Mary Shelley identified a feature of scientific research that people find disturbing today: the idea that scientists do not share their information and the results of their experiments, but keep silent about their research and its possible implications (Lederer 2002).

How does modern biotechnology relate to the obscure activities of Victor Frankenstein? In contrast to Frankenstein’s fictional scientific environment, today’s life sciences are controlled by strong internal and external monitoring practices and guided by strict safety procedures. Unlike the situation in Mary Shelley’s days, where access to medical and scientific knowledge was limited to the wealthy and educated elite, today we have unparalleled access to information about scientific developments through the popular media, including television, film, radio, magazines and newspapers and, most recently, through the Internet. But, it is only on rare occasions that these sources of information confront us with real monsters, resembling Frankenstein’s. They hardly exist in laboratories. They are the product of imagination, produced by authors of fiction and Hollywood film directors. At the same time, biotechnology is progressing at an unprecedented pace, and it is not at all easy for the public to keep track of what the scientists are doing. In the field of animal biotechnology, breakthrough after breakthrough is being reported. Transgenic pigs are supposed to become donors of human organs; a cloned sheep demonstrates \textit{in vivo} the extent to which we have become masters in mammalian reproduction, and the OncoMouse™ is expected to free us from cancer. Does this also imply that we truly have all the resources we need ‘to engineer the human body’? What monsters are hidden away in secret laboratories? And what monsters are bound to emerge in the near future if things continue to evolve in this manner?

\textbf{Part Two: Transgenic mice and the longing for perfection}

\textbf{Human health and genetically engineered model mice}

If there were a suitable candidate for monster status in today’s laboratories, it would probably be the transgenic mouse. Transgenic mice are the pioneers in tomorrow’s world of biotechnology. Virtually everything in biomedicine that will be applied to humans will first be tested on a mouse. So, if we think we have all the resources needed ‘to engineer the human body for cosmetic as well as therapeutic purposes’ as Anker and Nelkin argue, mice will tell us whether this really is the case (Anker and Nelkin 2004: 71). The techniques of genetic engineering are not new. The first transgenic mice were born at the beginning of the 1980s, when a molecular bio-revolution took place as five different laboratories independently reported the successful transduction of foreign genes into a mouse embryo. In the 25 years that followed the revolutionary events of the early 1980s, transgenic mice have successfully invaded biomedicine. They have become part of the standard equipment of an average biomedical laboratory. In 2002, the year in which the mouse genome was ‘cracked’, Tom Clarke whom I quoted before in Chapter 2, estimated ‘the army of mice helping researchers each day all over the world’ to be 25 million strong (Clarke 2002).

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60. Zwart is referring to Gould (1996).
The widespread use of the mouse as a research animal is based on the homology between the mouse and the human genome. Genomics research reveals that the mouse genome and the human genome are closely related. Transgenic mice, also known as ‘mouse models’, are created in order to study human genetic diseases. Mouse genes analogous to human genes are knocked out, while genes that code for human diseases are knocked in. Since the first knock-out mouse was made in 1990, the ‘knock-out mouse’ has become the most important model organism for biomedical research. The reason for the existence of these mice is their role in the battle against life-threatening diseases. It is here that I see a resemblance with Frankenstein’s creature. These mice are created on the basis of the same desire that drove Frankenstein to conduct his experiments. Both Frankenstein and contemporary biotechnologists acted, and continue to act, in order ‘to banish disease from the human frame’. Their ‘working materials’ also have certain features in common. Like the monster, transgenic mice are man-made living creatures, living artifacts. Because some of them carry human genes, they are also to a certain extent human. If not literally, they are quasi-human in the figurative sense. In scientific practice, mice serve as models for human diseases. In laboratory research, mice are stand-ins for human beings. In other words, transgenic mice are designed to be like us, humans. With their humanised genomes, they inform us about life-threatening human diseases. Transgenic mouse genetics is never an end in itself, it is always about human genetics. Being a mixture of, or intermediate form between, mouse and human, these mice are contemporary monsters that perhaps rightfully evoke associations with mythical monsters such as Frankenstein’s. But what is it we have to fear? These mice are neither out of control, nor hurting the innocent. They are safely hidden away in scientific laboratories specialised in the containment of hazardous materials. No human body parts are stitched on their backs. There is no physical resemblance with Frankenstein’s monster.

Is there any other reason to associate the genetic engineering (of animals) with the activities of Frankenstein? What horror scenarios may be awaiting us? Of course it is not the monstrous mouse, as such, that people fear when they refer to Frankenstein. What they fear are monsters that visibly resemble humans, monsters that are human. The ‘gruesome parade of horribles’ that Anker and Nelkin have in mind will be the horrifying result of engineering applied to human bodies, but made possible by the OncoMouse™. People who refer to Frankenstein, tend to express the fear that the human abnormalities that will be shown on tomorrow’s mass media freak shows are being created in today’s laboratories. Does the mouse research as it actually evolves justify this fear? Genetically engineered humans do not exist yet. Since mice are the practice material, so to speak, for human enhancement studies, mouse genetics is the place to look for (future) monster anthropotechnologies.

Supermice

Although usually presented as laboratory animals necessary in our fight to conquer life-threatening diseases, not all transgenic mice represent the ill and the weak. On the contrary, serious research is undertaken on mice that can be referred to as genetic enhancement studies to further improve the normal and healthy. For example, biologists are studying the process of ageing by producing mutant mice that live longer. Others study decay of the physical body (muscles) in genetically engineered super-muscle-mice in order to learn how to stop or deter the process of physical ageing in humans. And, last but not least, there are biologists who study genes that are regarded as coding for intelligence in the smart mutant mouse. Unlike the majority of genetically modified mice that are only identifiable by the codes that describe their genetic mutations, mice that participate in such enhancement studies are given a name. These mice are supermice. They are part of research projects aiming at mouse improvement and, as a future implication, the enhancement of the human body. Therefore, they carry the names of superheroes. Yoda is famous for his longevity; Doogie is the smart one; and He-Man and Marathon Mouse are the ones with the superior muscles, useful for strength and endurance.

Yoda

In 2001, Richard Miller and his group reported about lifespan extension in (naturally occurring) mutant dwarf mice in the scientific journal Proceeding of the National Academy of science. In this paper, they stated that ‘These observations show that a single genetic difference can retard multiple indices of senescence as well as an increasing longevity in mammals’ (Flurkey et al. 2001: 6736). When one of these dwarf mice reached 61. Usually not as individuals, but as a strain.
62. These mice are not transgenic. The genetic mutations occurred spontaneously. The mice are inbred by researchers.
its 4th birthday in 2004, it was nicknamed Yoda. The mouse was named after the 900-year-old yedi Yoda, known from the popular SF movie series Star Wars. After celebrating his 4th birthday, Yoda’s picture appeared in several newspapers and on Internet websites (Ayres 2004; O’Connor 2004). 4 years is a rather exceptional age for a mouse that has not been on a special restrictive diet. The average lifespan of an ordinary laboratory mouse is 2 years. Mice in Miller’s stock usually grow to an average of 3½ years. According to Miller, Yoda did reach a milestone. When asked about the future applications of his research results to human health, Miller responded to a NY Times reporter ‘that it was not a lead in for gene therapy’. His idea was to find out what the key controlling chemicals are, so that the problems people now are facing in their 60s or 70s can be postponed for another 20 or 30 years’ (O’Connor 2004: A2). Miller’s mice do not only get very old, they also remain in a strikingly good physical condition. Probably the most important reason for being able to grow that old is their enhanced resistance to a number of lethal and chronic diseases. They do not develop arthritis for many years, they are resistant to cataracts and they are resistant to cancers. Their immune system stays healthy for a very long time. Interesting lessons could be learned from these mice. As Miller explained on the Australian ABC radio programme The Science Show, he would like to ‘be able to translate the mouse findings to figure out ways to produce medicines basically so that people in their 80s 90s, up to the age of 100, 110 perhaps, are also active and viable and have good cognitive powers and retain most of the functions they had when they were middle-aged.

**He-Man and Marathon Mouse**

A tempting thought. Imagine that with the aid of biotechnology we can really live longer, retaining a mid-life condition. The next step would, of course, be the wish for a younger and stronger body. If we are able to ‘live forever’, we also want to feel ‘forever young’. We need a healthy and strong body that keeps in shape despite old age. This might not just be a fantastic dream. Like old age, a young and healthy body is one of the promises made by today’s biotechnology. At the end of the 1990s, a group led by H. Lee Sweeney at the University of Pennsylvania reported results on mice injected with synthetic genes that indicated that stronger muscles are in fact technologically possible by means of genetic therapy. The results of their experiments with mice that were injected with a virus carrying the IGF-I gene suggested ‘that gene transfer of IGF-I into muscle could form the basis of a human gene therapy for preventing the loss of muscle function associated with ageing’ (Barton-Davis et al. 1998: 15603).

It was in 2001 that the IGF mouse started to receive wide public attention (Hruby 2002; Swift and Yeager 2001; Fitzpatrick 2002; Purgavie 2002; Brownlee 2004; Henderson 2004; Sokolove 2004; DeFrancesco 2004; Garreau 2005; Naam 2006). By then, it turned out that these mice, two years after injection, developed 60 percent more muscle mass than an average mouse. Two years after the initial experimental treatment with the gene transfer, these mice’s strength remained intact. This is, of course, very interesting, not only for people with particular forms of muscular dystrophy, but also for example for the (professional) sports community. ‘Are the mice representatives of a future generation of athletes?’, as E.M. Swift and Don Yeager write in The Observer. Because of their massive muscles the mice were named after He-Man (‘the most powerful man in the universe’), the popular muscular superhero from the toy series the Masters of the Universe. The He-Man mice received massive attention from the sports and fitness community. In September 2001, an article about these mice was published in Sports Illustrated. The ramifications for sports are obvious: to enhance the gene is to enhance the performance. Not to mention the potential. ‘If researchers are developing genetic therapies to treat broken bones, muscle tears and ligament damage, performance enhancing sports applications aren’t far behind’, remarks Patrick Hruby in The Washington Post (Hruby 2002: C01).

How great the potential for sports could be, is easy to illustrate. ‘Even if you train you lose speed’, explains Sweeney in the interview with Swift and Yeager. ‘It happened to Carl Lewis, Linford Christie, Jeremy Guscott, among others. But it hasn’t happened to He-Man [the mouse]. Because of the gene that was injected two years ago, the mouse grew exceptionally large muscles, and those muscles keep producing IGF-I. He-Man in the

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64. Complementary to Miller’s research is the work of Makoto Kuro-o. This scientist from Dallas has found that mice engineered with overactive Klotho genes live, on average, 20 to 30 percent longer than normal mice (Kuro-o et al. 1997; Stein 2004).
66. They are also referred to as Schwarzenegger mice (see Brownlee 2004).
Sweeney to treat his whole team (ibid.; Brownlee 2004). On whom he might test the IGF-1 gene. A high school football coach asked about his research and wonder if he is looking for human volunteers by several athletes, most of them weightlifters and sprinters who have received emails and calls from sports people with requests to perform this gene treatment on them. He has been contacted several times by his work. ‘Even in its infancy, this technology clearly has tremendous potential to change both sports and society. The ethical issues surrounding genetic enhancement are many and complex’. But, nevertheless, he does not feel uncomfortable about future consequences because ‘for once we have time to discuss and debate them before the ability to use this power is upon us’ (Sweeney 2004: 44). This remark seems reassuring. But it is questionable whether this is a realistic view of the situation. It is perhaps too optimistic a view on the level and impact of the ethical debate on biotechnology and genetic enhancement, and perhaps too modest a view with regard to the state of the art in biotechnology. The biotech future could be closer to us than he realises. In the words of WADA’s Friedman: ‘It is not rocket science. If you ask a molecular biologist, or even his students, how he would implant genes to change muscle function within half an hour he could write down three or four ways to do it’ (Swift and Yeager 2001: 44).

Three years after He-Man hit the newspapers, the marathon mice from San Diego excited the sports community. Researchers from the Salk Institute injected a human version of the PPARδ gene into the mouse DNA (Salk Institute 2004). The genetically engineered mice which were the result of this treatment could run twice as far as their unaltered buddies (Anonymous 2004). In contrast to He-Man, these ‘marathon mice’ are transgenic. This means they will pass on their athletic talents to their offspring. In the laboratory of Ron Evans of the Salk Institute, the transgenic mice were run on oxygen-infused enclosed treadmills until exhaustion. The running time these transgenic mice were able to sustain increased by 6 percent compared with normal mice, and the distance they were able to travel by 92 percent (Wang et al. 2004). Compare these results with the breaking of a record in sports. ‘Records are broken on a fraction of a percent, a few percentage points is like a minute or two in a race. This was a big change: 100 percent’, explains Evans to a reporter from Wired (Philipkoski 2004). This work demonstrates that complex physiological properties such as fatigue, endurance, and running capacity can relatively easily be genetically manipulated (Wang et al. 2004). ‘They are like Lance Armstrong without getting on a bike’ Evans told the reporter of The Guardian (Pearson 2005: 28).

Doogie

We not only want to live longer and feel forever young. We also want to be super-intelligent. People have always been fascinated with the genetic basis of intelligence, and this also goes for biotechnologists. Only two years 67. I have accessed the Scientific American via the Internet; therefore, a page number is not available.
Biotech Pioneers

The ‘Frankenstein thing’ or the monsters we fear

Young? The transgenic supermice represent the promise of biotechnology. They are the pioneer species entering the future world of biotech. And, as these mice show, reshaping the living body into something more perfect, healthier, stronger and even more intelligent is no longer science fiction. If it is possible in mice, then why not try it on humans? After supermice, the next frontier will be our own body. The scientists involved in research with these supermice all sincerely believe that biotechnology someday in some form or other will be applied to humans. This is simply because we have the choice and nobody wants to end his life in a wheelchair.

Part Three: Rereading Shelley and the Frankensteinian nature of biotechnology

Remaking Eden

In the two centuries that have passed since the Frankenstein story was first published, the meaning of the monster and the state of the art in the life sciences has changed dramatically. As I pointed out above, in the course of its development into a myth, the Frankenstein story lost much of its ambiguity. Victor Frankenstein was transformed from a student lost in his groundbreaking quest to make man more invulnerable into a mad scientist. As the story evolved into a myth, Frankenstein seems to have lost his good intentions. No positive reading about scientists involved in matters of life and death seems possible. His hideous creation likewise transformed from a sensitive, intelligent, self-educated, potential role model into a plainly evil and revengeful monster. But perhaps the most radical change that has taken place in the process of becoming a myth has been that the creature lost its human character.

The life sciences, however, and biotechnology in particular, have moved forward in directions that allow scientists to perform experiments that Shelley in her day could only dream of. The most powerful image of the Frankenstein story is that of a human being created in the laboratory by a scientist. Today, two centuries after Shelley’s fantasy, laboratory mice show that it is theoretically possible to create ‘superior’ human beings in the laboratory. If people are willing to donate their own offspring, embryos, to scientific procedures involving human germ line enhancement, and scientists can be found who are willing to assist people in their wish for the

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68. In 2004, Joe Tsien moved to Boston University and, as a result, Doogie’s website at Princeton was reduced to one page: <http://www.princeton.edu/pr/pictures/other/smartmouse/index.html>.

69. I have accessed the *Scientific American* via the Internet; therefore, a page number is not available.
genetic enhancement of their embryos, then the genetic enhancement of humans suddenly becomes a very realistic story. Lee Silver, a well-known mouse geneticist and author of the book *Remaking Eden, how genetic engineering and cloning will transform the American family,* has no doubt that this will happen: ‘I am absolutely convinced that we will have […]’ expansion of the enhancement of embryos. The reason I’m sure this is going to happen is because we have already perfected this in animals. It is something we do with mice […] everyday.’ According to Silver, people who are denied the technology will say: ‘Why can’t I give this to my child when others get it naturally?’ (PBS date unknown). For most people today, changing man’s genetic code – our blueprint, human nature, our essence – is morally out of the question. The vast majority of experimental scientists who perform research involving genetic engineering of animals also tend to oppose genetic engineering of human beings. But, Silver adds, almost always they state their objections in terms of safety and efficiency rather than ethics (Silver 2006a), thereby suggesting that the genetic engineering of the first human being is simply a matter of time, until the technologies involved have become more reliable. As soon as mouse studies prove that genetic engineering has become safe and efficient enough, what further objections will there be for the scientists to proceed with the genetic enhancement of human embryos? The first candidates will be couples who are both carriers of recessive genes for life-threatening diseases and who nevertheless wish to have a healthy child. And then, in time, the fulfillment of other, more trivial and bizarre gene-based wishes will follow.

Does this imply that the Frankenstein myth is about to become reality and is therefore no longer a myth? As I have argued, the Frankenstein story gained popularity because it appeals to a widespread public fear of monsters coming out of laboratories. I cited Turney who described this fear as a deeply-felt cultural ambivalence about modern science, a conflict in our basic attitudes towards science: (manifest) enthusiasm and (latent) fear. In that respect, the transgenic supermice are good examples of the ambiguities evoked by modern science. The attention they have received from popular media suggests that the public is fascinated by transgenic supermice. The press certainly do like to give the impression that human enhancement is a realistic future scenario. For example, after hearing the news about the smart mouse, TIME magazine did not show Doogie on its front page (13 September issue), but a human baby with a double helix representing its umbilical cord suggesting that the creation of the super-intelligent baby is on its way. However, the mice are indeed awesome examples of progress made in biotechnology. In the popular media, the positive impact that mouse biotechnology research might have on human medicine is often highlighted. At the same time, the possibility that these technologies could also be applied to humans is a genuine issue of concern.

Taking as my point of departure a number of recent mouse stories, I have argued that the genetic enhancement of man is indeed theoretically possible. Does this mean that contemporary biotechnologists are producing (or about to produce) monsters? Are the supermice I presented monsters? Is Doogie a monster? Is Yoda horrible? Is He-Man mouse gruesome? When I take a look at their pictures my answer cannot be affirmative. Although these mice are living artifacts, ‘man-made’ laboratory creatures, they seem to have nothing in common with traditional monsters discussed in the beginning of this chapter. They are incredible; they are extraordinary, but above all they are cute and funny. The mice are fascinating and thought-provoking because they challenge our ideas about the ‘given nature’ of mice. Even more disturbing, these mice show that capacities such as intelligence, muscular strength, and resistance to the physical process of ageing have a genetic basis that can, in principle, be manipulated. Beyond doubt they are monsters of the type discussed in Chapter 2. They are man-made living beings. But given their beauty and superpowers, in what sense do these products of biotechnology resemble the monster Frankenstein created?

Who or what is the monster?

The question whether these genetically modified mice are monsters of the type Frankenstein created can also be phrased differently: Are the scientists involved in this type of research actually following in the footsteps of Frankenstein? In my view, the analogy between current genetic enhancement research and the Frankenstein story is very problematic; in particular with regard to the way the research is embedded in our society. One of the most important ethical lessons to be drawn from Shelley’s original story is the importance of communication about, and the visibility of, the scientific practice. Well, Sweeney, Tsien, Evans, Miller and Silver, all scientists who work at the frontiers of biotechnology, have a remarkably open attitude...
towards the public. In that sense, Sweeney, Tsien, Miller and Evans, who not only publicly discuss their work but also openly express their fantasies about the application of genetic technology for the benefit of humans, in no way resemble the neurotic and obscure Victor Frankenstein. They are highly visible geneticists. They write papers for popular science magazines, accessible to the general public, they appear on radio and television and they willingly discuss their scientific work and the implications for society with the members of the \textit{President's Council on Bioethics}\footnote{Miller was represented by his colleague Steve Austad, and Sweeney addressed the committee in person. See: <http://www.bioethics.gov/transcripts/sep02/session7.html> and <http://www.bioethics.gov/transcripts/decoz/session1.html>}. They do their very best to ‘educate’ the public about the future of biotechnology.

So, if the mice are not monsters in the literal sense and the scientists who create them do not resemble Victor Frankenstein, then how can the ‘monster phobia’ evoked by contemporary biotechnology be explained? If the mice are not the monsters, who or what is the monster of modern biotechnology? My answer to this question is that the monstrosity of the mice is that they show us what the future possibilities for genetic enhancement could be. They tell us something about the malleability of human nature. And, according to Gregory Stock, ‘the next frontier might be ourselves’ (Garreau 2005). They are not gruesome and horrible, they are animals that transgress a border between what is given by nature and made by man. They show us what is given by nature can and probably will be perfected by man. This makes them monsters of the type defined by Smits, but not monstrosities of the Frankenstein type. So strictly speaking these mice represent fear. The present ‘Frankenstein thing’ is not that scientists will create monstrosities. On the contrary, we should rather fear (or at least expect) that scientists will succeed where Victor Frankenstein failed, and that scientists like Lee Silver will actually do a good job in the genetic enhancement of human embryos and will successfully create strong, healthy and good-looking human beings. The supermice do indeed indicate that scientists have a good chance to achieve their goals. What the stories of the supermice also show is that it is very likely that people will make use of new technologies. Stories about Yoda and He-Man mouse were widely covered in sports journals, as well as in magazines with a focus on geriatrics. Overall, the reviews were optimistic and very positive.

Although I do take Silver’s future scenario seriously, I do not believe that the first biotech supermen will be created in Petri dishes. To me, the most likely future scenario based on the supermouse story seems to be one where individuals (most likely weightlifters and top athletes) will start applying biotechnology to their own body, in other words: genetic doping. In this future scenario, human enhancement is achieved by introducing genetically modified materials into our own bodies. Like the IGF 1 mouse, people will be injected with genes – contained in non-germ-line cells – in order to enhance, so they believe, their sportive, intellectual, or seductive (sexual) capabilities. It is only the individual himself or herself that is affected. In contrast to the genetic engineering of the embryo, the genetic changes will not be transmitted to the offspring. So, whatever the consequences, the effect will only be noticeable on the individual level. Gene doping will not really influence human evolution. Genetic engineering of embryos would, of course, do so, but such a scenario seems, for the time being at least, less plausible. Moreover, both in the case of genetic enhancement and in the case of genetic doping I find it hard to imagine how human enhancement will lead to ‘a gruesome parade of horribles’.

On the contrary, I believe what worries people the most is the possibility that these ‘enhanced’ people – either resulting from embryo enhancement or gene doping – will not essentially differ from us. These superpeople will still be human beings, and they will have a human ‘nature’. Silver’s genetically enhanced babies will be born the same way as other human babies. Their parents will not look that different in comparison with their children. These children will look like ‘normal’ ones. A genetically enhanced athlete who uses gene doping to boost his sportive achievements, is no less a human being than he was before the gene treatment. This is why I argue that perhaps ‘the monstrous’ that people fear is not so much ‘the parade of gruesome horribles’ but rather that idea that humans are, by their nature, malleable. Genetic ‘supermen’ and ‘supermice’ challenge our vision of human nature. It is the very fact that biotechnologists have discovered that humans, like mice, have a malleable genetic make-up, which makes these scientists the contemporary equivalents of Frankenstein.

\textbf{A different reading}

This puts the questions how the Frankenstein myth helps us to deal with our fear of monsters (and how the Frankenstein story can be meaningful in an ethical assessment of biotechnology) in a new perspective. As I
have already indicated, there are two different readings of the Frankenstein myth. The ‘popular’ reading of the myth is a rather straightforward anti-science interpretation of the tale. It carries the unambiguous moral lesson that those who transgress Divine will or natural law will be punished. In this reading, the Frankenstein myth offers a good metaphor for science out of control. Like no other story, it shows how tampering with the essence of life (genes) will inevitably lead to catastrophe. The second, more ‘academic’, reading is more optimistic about biotechnology. In this reading, Frankenstein is not a mad scientist who transgresses natural or Divine orders. If one reads the original story about Frankenstein, one will understand that it is about a scientist who acts irresponsibly, both towards society and towards his creation. In this reading, as put forward by, amongst others, the biologist Stephen Jay Gould, the Frankenstein story is not an anti-science story but rather a story about the importance of communication in science. If only scientists would better inform and educate the public about science and technology, the public would be more likely to accept or even embrace the monsters that scientists create.

Both readings have their attractions and their shortcomings. The first reading is very powerful in the sense that it invokes a strong sense of the potential danger involved in biotechnologies. But it remains unsatisfying since it fails to explain why or how this is so dangerous. For example, the apocalyptic scenario is not shared by the experts involved in genetic engineering, the biotechnologists themselves. However lacking a sound ‘evidence-based’ underpinning, biotechnology leads to a horror scenario which often fails to rise above the level of stereotypical, indeed ‘Pavlovian’ responses. Another objection that can be made is that it is a too simplistic or even ‘reductionist’ reading of the original story. There is no place for the ambiguity that is so characteristic of both Shelley’s novel and the currently evolving practice of biotechnology. Authors like Anker and Nelkin, so it seems, are somewhat too eager to join the chorus, so to speak. They do not really want to consider the original story that lies at the basis of the popular myth, they do not really take it seriously. It is their – no doubt sincere – intention to warn people about the future risks of biotechnology, but in doing so they seem to neglect other dimensions of the original story, other levels of meaning, notably the original ‘good intentions’ of both Victor Frankenstein and contemporary biotechnologists.

In my reading, biotechnologists are not creating monsters. However, they did discover one: namely, the more or less ‘monstrous’ idea that we are potentially malleable entities. This idea is monstrous because it forces us to reconsider our views about ourselves. The monster we fear is the idea that we humans are malleable. The discovery of the malleable genome does not imply that biotechnologists will inevitably create gruesome and horrible creatures, resembling Frankenstein’s monster in their physical appearance. I can find no convincing argument that biotechnologists would have the creation of this type of monsters in mind. This is simply an evocation of the monster image. The monster we are confronted with is rather a symbolic monster, something like a boundary we have crossed. We thought we were in control, but in reality we are becoming the object, the ultimate target of future biotechnology. The popular reading of the myth somehow suggests that contemporary scientists have a hidden agenda: that biotechnologists are ‘mad scientists’ who use their dangerous knowledge only to feed their curiosity or ambition, regardless of the outcome. Therefore, the public needs to be protected against science. Without proper warning the public is defenseless against what science brings. It will be forced to eat the bitter fruits of biotechnology.

As I said, I believe this diagnosis of biotechnology to be one-sided and misleading. I do not think that an informed public will automatically accept biotechnology. On the contrary, this would come down to suggesting that biotechnology is unproblematic and people’s fears about this technology are irrational, emotional or based on ignorance. Both these assumptions are too simplistic. Many people feel deeply that there is something wrong with the manipulation of genes even if or, as I have argued, particularly if scientists prove to be successful with human genetic-enhancement technologies. The monstrous facts that our genetic make-up is malleable, and that some traits can ‘simply’ be improved by means of genetic engineering, are disturbing in themselves. Biotechnology does have a radical impact on our self-understanding. This is both fascinating and frightening. Are we wise enough to use this new knowledge of our genes in a responsible way? What effect will biotechnology have on future society? At what point does benevolence turn into monstrosity? What does it mean for our understanding of human nature? These are serious questions. In answering these questions we have to take the Frankenstein myth seriously because it plays such an important role in the public understanding of biotechnology.
Concluding remarks

I do not believe that the genetic engineering of mice is a practice that can or should be put on hold. Nor do I believe that human beings will never become subject to genetic engineering because it is in itself an ‘unethical’ thing to do. One important implication of the discovery of the malleable human genome is that this awareness, once gained, is not something that can simply be reversed. We simply have to face the monster. Neurosis, a paralysed state of not being able to cope with the consequences of recently discovered knowledge, is not a very responsive way of facing the monster. Therefore, I propose a different reading of the story, one that asks for a different use of our imagination. In contrast to the popular myth – predicting that hubris inevitably leads to nemesis – the original story leaves open other possibilities than catastrophe and punishment. What would have happened if Victor had openly discussed his experiments with colleagues, and the people would have been better prepared and ‘educated’ to accept his creature? Would it have meant that his experiment would not have turned into a catastrophe? Imagine that Victor had truly succeeded in his ambitions, and that the creature would have been perfect and beautiful. In other words, what would happen if biotechnologists were to truly succeed in relieving us from the burden of ageing? That we would really live to become 130 years old in bodies that look like 35? Would that be gruesome, would that be horrible? This is an important and intriguing – and no doubt even troubling – question, but not one that can be answered by referring to ‘the Frankenstein myth becoming true’ or by simply reducing it to a story of communication and education.

‘Metaphors’, as Nelkin explains in her Nature article in 2001, ‘are a prevalent and important form of public communication, and they are especially important in conveying scientific information. [...] By connecting different orders of reality, metaphors enable the translation of very complex scientific information in culturally meaningful ways. But metaphors are more than an aid to explanation: repeated metaphors affect the way we perceive, think and act, for they shape our understanding of events’ (Nelkin 2001: 556). I believe this is exactly what the Frankenstein myth does. It keeps the cultural neurosis alive. And this is worrisome, because I do believe that scientific progress is inevitable and the public ought to be educated about the futures of biotechnology. Not in the sense that we should be lured towards a more science-positive attitude, but rather because we really need to face the monster. We have to develop the conceptual and ethical tools to do so. And this cannot be done by telling horror stories. We need to re-consider and redefine who and what we are, and can become. But this is only possible when biotechnology, as well as the society in which it is embedded, has – finally! – come to terms with the Frankenstein myth.
Chapter 5
‘Yuk!’ and the aesthetics of mouse biotechnology

By stripping bio-science of its pragmatic function and recontextualizing it as aesthetics, gene artists reanimate issues Duchamp would have appreciated, especially those about authorship and originality and the nature and purpose of art.72

Steve Tomasula

That artists are now showing living organisms as art is an incredible step in the aesthetic sense of human culture.73

Dave Powell

Introduction

Gut feelings and moral judgements

In the previous chapters, I have argued that the genetically modified mouse, despite its general use in the biomedical laboratory and its apparent domestication, still has for many people the appearance of a technomonster. Its monstrous character is underscored by the myths, metaphors and vocabularies that mark the biotechnology debate. I have examined the two most dominant ones: the playing God metaphor and the Frankenstein myth. In this chapter, I want to examine the role of the yuk!-factor in the debate on animal biotechnology. What is it in biotechnology that is evoking a gut response? Of all the metaphors, myths and words that are used to express feelings of moral concern, the yuk!-factor is the one that most closely resembles Bernard Rollin’s definition of ‘aesthetic judgement’ in animal biotechnology. Rollin believes that moral concerns based on ‘aesthetic judgements’ are not genuine moral concerns. In his argumentation, Rollin makes a distinction between rational moral judgments based on objective measurable factors (such as animal suffering) and subjective

aesthetic judgments based on feelings and emotionally-laden notions such as ‘nature’, ‘harmony’ or ‘quality of life’. In his perception of the animal biotechnology debate, the moral concerns based on objective reasoning and subjective feeling (also referred to as the ‘Frankenstein thing’) tend to get confused, and Rollin wants to see the two separated. For example, we have to understand that any appeal to ‘nature’ entails, in fact, aesthetic judgments and is therefore morally irrelevant (Rollin 1995, 1998).

However, there are two elements in Rollin’s vision that I find difficult to accept. My first difficulty with Rollin’s distinction of aesthetic judgments and ethical reasoning is that, as Mary Midgley argues: ‘In real life we tend not to find that reason and feeling are separate items. They are interdependent aspects of a person, divisible only for thought’ (Midgley 2003: 102). Moral convictions are always partly non-rational. This is not to say that moral convictions are contrary to reason. They are non-rational in the sense of being ultimately not based on, or guided by, any process of rational decision making (Hauskeller 2005). Moral convictions are always based on a mixture of both reason and feeling. Secondly, I do not see why aesthetic judgments should not be morally relevant. People who say ‘yuk!’ at being confronted with animal biotechnology are not, as is sometimes suggested, merely expressing an inarticulate disgust with the unfamiliar. As Midgley explains it: ‘Their further conversation shows that they are saying something intelligible, something that needs to be answered’ (Midgley 2003: 105). In opposition to what Rollin believes, I will argue that we have to take aesthetic judgements and yuk!-responses very seriously. Moral convictions are always based on a mixture of both reason and (gut) feeling. Exploring the roots of what we perceive as ‘yuk!’ is what ethics is about. People who say ‘yuk!’ at being confronted with animal biotechnology are expressing genuine feelings of moral concern, but apparently lack the vocabulary to do so in an articulate way. The question remains: What is expressed when people say ‘yuk!’?

I believe the yuk!-response in the animal biotechnology debate involves a number of things. First of all, there is a feeling of confusion that results from the fact that apparently self-evident notions such as ‘natural’ and ‘unnatural’ are challenged and undermined. Secondly, it refers to the threat that animal biotechnology imposes on what we perceive as ‘a good life’, or a life worth living. This is what Robin Attfield refers to as the ‘quality of life’ (Attfield 1995, 1998); And, thirdly, there is the awareness that animals are acquiring more and more the status of ‘instruments’ or commodities, instruments with primarily economic value. What we perceive as a good life for a genetically engineered animal that is deprived of feeling (so as not to experience suffering from being subjected to animal experimentation) is basically a ‘matter of taste’. What we perceive as ‘natural’ is probably also based on aesthetic deliberations (at least in part). We tend to have a (more or less idealistic) vision of nature, but in fact an unequivocal and robust definition of ‘nature’ or ‘natural’ is not available. When people express their moral intuition about animal biotechnology and say that it is ‘unnatural’, they seem to appeal to a visual image, to an aesthetic norm that informs their vision of nature or what they believe to be natural. This also goes for the species concept. There is a strong concern that, at a certain point, genetically modified mice will no longer look like mice, will no longer look like natural animals at all. When Susanne Anker and Dorothy Nelkin, whom I quoted before, state that (human) biotechnology will lead to a ‘gruesome parade of horribles’, they make a moral judgment by appealing to an aesthetic norm (Anker and Nelkin 2004). Others, who believe that biotechnological enhancement of the human race will lead to ‘perfect’ people, fear a world where there will no longer be room for (natural) imperfection. Perfection and imperfection in this much feared future of biotechnology can both be regarded as aesthetic notions. In these scenarios, biotechnology leads either to monstrosities or to beauty in its most extreme form. Both outcomes are apparently regarded as undesirable, both evoke a gut response. Finally, these ‘distasteful’ practices are only possible when commercial biotech companies are willing to invest in them. And these companies usually do so merely for the sake of profit-making.

Given the important role that ‘aesthetic’ notions play in the genesis of moral judgments on animal biotechnology, I do not find it very helpful to see the debate on animal biotechnology as a conflict between thought and feeling like Rollin does. Both are involved, both are intimately connected. As Midgley claims, to oppose feeling and thought has been especially unfortunate in the case of animal biotechnology. ‘People often have the impression that reason quite simply favours the new developments although feeling is against them. This stereotyping paralyses them because they cannot see how to arbitrate between these different litigants’ (Midgley 2003: 103). Therefore, a more fruitful approach than simply rejecting aesthetically-informed moral judgments as irrational, would be to study how moral and aesthetic judgments are connected in people’s appreciation of animal biotechnology, and
to find out what people mean or fear when they express the feeling that some forms of bio-engineering are monstrous or unnatural. That is what ethics, the critical assessment of morality, is about.

Works of art as a source of moral inspiration

But, as I have shown, the vocabulary and approaches developed in the field of bioethics have serious shortcomings when it comes to addressing issues that are related to the way biotechnology challenges our vision of nature. The ethical framework developed for bioethical committees dealing with animal biotechnology roughly comes down to a trade-off between animal suffering and human benefits. From a practical point of view, this is an adequate approach, but philosophically speaking it is highly unsatisfying. I believe one of the reasons why the bioethical vocabulary is unsatisfactory is because, as a reflective discipline, bioethics is not as dynamic and lively as its object of reflection. It does not share the explosive creativity of biotechnology. In short, I believe the bioethical vocabulary suffers from an imagination deficit. Biotechnology is simply evolving at too high a pace for bioethics to keep up with it. Or, as Joe Tsien (the creator of Doogie the smart mouse) puts it: ‘We are in an era when breakthroughs in biology and intelligence are outpacing the culture’s capacity to deal with the ethics’ (Weiss 1999: A01). For most people, it is hard to imagine what it is really about. Although transgenic mice have become a commodity within the biomedical industry, to audiences outside the scientific and biotech community they are still highly invisible animals. The most important reason for this is that the mice in question spend their entire lives in laboratories and, as such, seldom enter the public arena. Not surprisingly, most people are unaware of the large number of transgenic mice (millions worldwide) that are used in medical research and (as a consequence of this) are also unaware of the state of the art in mammalian biotechnology. Another reason for the invisibility of transgenic mice has to do with the microscopic size of DNA. Genetic technologies are technologies of the invisible. Even if the mouse as such is visible, the genetic modifications of its genome remain invisible from the outside, to the untrained eye. So, even if we had the opportunity to see ‘real’ transgenic mice, we would probably see nothing peculiar or special. Usually one cannot tell from the outside whether or not a laboratory mouse is a genetically engineered laboratory mouse. Most transgenic mice simply look like ordinary laboratory mice. And, because most people are unable to ‘physically experience’ the genetic modifiedness of these mice, they remain abstract animals. As a result, the moral assessment of animal biotechnology remains an abstract activity. This abstractness is reflected in the bioethical vocabulary, which consists of rather abstract notions such as ‘animal integrity’, ‘intrinsic value’, ‘telos’, etc. The contrast between the very real and lively mice and the abstract and inflexible ethical vocabulary calls for a less abstract and a more creative style of ethical assessment. How can this be achieved?

In my discussion of the playing God metaphor, the sculptures Ecce Homo by Bryan Crockett and Mann und Maus by Katharina Fritsch were essential to my argumentation. These sculptures tell us something about mouse biotechnology that written discourses of bioethics can not: not simply as visual images, but by suggesting a ‘physical’ presence of the genetically engineered mice. These sculptures are ‘real’. Ecce Homo evokes mixed responses that include both aesthetic and moral judgments on the oncomouse. So does Mann und Maus. This sculpture is both comforting and disturbing: it is ‘unheimlich’74. I believe these works of art are morally effective – by this I mean that they make a moral appeal to us – because the responses they evoke are as ambiguous as the technology to which they refer (or seem75 to refer). The yuk!-factor is essential to the understanding of both Ecce Homo and my interpretation of Mann und Maus. Mann und Maus and Ecce Homo illustrate how, in discussing the meaning of a work of art, the aesthetic and the ethical cannot be separated. It is here that I see the great potential that art can have in the moral and social assessment of animal biotechnology, in particular where issues such as visions of nature, quality of life, identity, the normal and the abnormal are concerned. This leads me to the central question of this chapter: How can works of art assist us in exploring the yuk!-factor of animal biotechnology and our moral understanding and evaluation of animal biotechnology?

74. According to Freud ‘unheimlich’, as an aesthetic category, refers to something that used to be familiar but from which we have suddenly become estranged (such as a corpse). Certain locations are definitely unheimlich, such as graveyards or – laboratories, really a ‘locus suspectus’. ’Very unheimlich’ are loose body parts (such as head, hands, eyes). According to Freud, this category used to be associated with mechanisms (with automatons), but has moved to the life sciences where the new homunculus is now produced. Sigmund Freud (1919/1947) ‘Das Unheimliche’, in: Gesammelte Werke XII. London: Imago; Frankfurt am Main, Fischer.

75. One can doubt whether it really was Katharina Frisch’s intention to express something about the mouse as it is used in biomedical research (see also Chapter 3).
In the first part of this chapter, I will address this question by discussing the possible roles of the work of art in the age of biotechnology, building on an article by W.T.J. Mitchell about the work of art in the age of biocybernetic reproduction (Mitchell 2003). As an example of an art form that meets Mitchell’s criteria, I will discuss a ‘new’ form of contemporary art: namely, bioart. By bioart, I mean artistic reflections on the life sciences, either by representing and visualising biotechnological developments or by using biotechnologies as artistic tools. In the second part, I introduce the work of three artists whose artworks explicitly reflect upon the present and future practice of animal biotechnology: the *GFP Bunny project* by Eduardo Kac (2000), the *Transgenic Mice Series* by Catherine Chalmers (2000), and *Genpets™* by Adam Brandejs (2005). These works are selected because they seem to convey something about the genetic engineering of mice, either directly or indirectly, that is important for our question. But as works of art they differ significantly from one another. They involve different media and seem to entail different forms of ‘intentionality’ as it were. By ‘works of art’ I do not only mean the physical objects that form the artwork. In my view, it also includes the processes of producing art, the responses to these works, and the role of the artist in the ensuing debates. In these three works of art I see the ambiguities of the genetically modified mice represented: their monstrosity, their unnaturalness, their promise, and even their innocence. All these artworks, – the *GFP Bunny* project, Chalmers’s *Transgenic Mice Series* and Brandejs’s *Genpets™* –, evoke yuk!-responses. What do these yuk!-responses I am after. Is something expressed in these yuk!-responses that can help us to understand yuk!-responses to animal or mouse biotechnology in general? What do these works of art express or reveal about animal biotechnology that is so difficult to articulate when we solely rely on current bioethical vocabularies?

**Part One: Art, ethics and animal biotechnology**

**The work of art in the age of biotechnology**

In ‘The work of art in the age of cybernetic reproduction’, W.J.T. Mitchell explores the possible new roles of artworks in the age of the contemporary technosciences. As ‘a target of inquiry’, Mitchell offers the concept of ‘biocybernetic reproduction’. Mitchell tends to use this concept in a rather strict sense: ‘the combination of computer technology and biological science that makes cloning and genetic engineering possible’. In a somewhat broader sense, the concept refers to ‘the new technical media and structures of political economy that are transforming the conditions of all living organisms on this planet’ (Mitchell 2003: 483). According to Mitchell, bio(techn)ology has replaced physics at the frontiers of science and has become the dominant technical and scientific discipline of our age. Mitchell, who is obviously referring to Walter Benjamin’s classic text *The work of art in the age of mechanical reproduction* (1936), explains how, during the biocybernetic revolution, the status of the original artwork and its copy have changed radically. First, ‘the copy is no longer inferior to the original, but is in principal an improvement of the original; secondly, the relation between the artist and the work, the work and the model, is both more distant and more intimate than anything that had been possible in the realm of mechanical reproduction; and, thirdly, a new temporality, characterized by an erosion of the event, and a vertiginous deepening of the relevant past, produces a peculiar sense of “accelerated stasis” in our sense of history’ (Mitchell 2003:487). We live in a time that is at best described as ‘a limbo of continually deferred expectations and anxieties. Everything is about to happen or has already happened without our noticing it’ (Mitchell 2003: 489). As an example he discusses the cracking of the human genome. This is what he calls a ‘non-event’. ‘The very “secret of life itself” is decoded, and yet everything remains the same’ (Mitchell 2001: 490).

Now, this type of confusion is of course typical of revolutions. When a revolution is actually taking place, no one knows where it is heading. Initially, bystanders tend to underestimate the dramatic consequences for the future. They tend to think that, after some turbulence, their lives can be resumed as usual. It is only with hindsight that we are really forced to ask ourselves how life has changed as a result of the revolution. But the biotech revolution involves something that has never happened before, something that is radical and really new, something that calls for a critical mode of questioning the present. DNA technologies enable us, for the first time in history, to change the mouse’s and our own evolution in a controlled and directed way. It is a revolution that will allow us to ‘control’ ourselves. What could or should be the role of art in this age of revolutionary biotechnology? Mitchell discusses four tasks of art in the age of biocybernetic reproduction: 1) to ‘reveal the codes and expose the illusion of the ultimate mastery of life’; 2) to re-articulate what we mean
by the human, by humanism and the humanities; 3) to elaborate a ‘paleo-
tonology of the present’, a discipline that should begin by acknowledging
that the contemporary world is perhaps even more mysterious to us than
the recent or distant past, challenging our insistence on the connectedness
of all forms of life; and, 4) ‘to unleash the images, in order to see where
they lead us, how they go before us’ (Mitchell 2003: 498). How can these
four tasks be translated into something that is applicable to the biotech
revolution, something that can be useful in exploring the yuk-factor of
animal biotechnology? The first task, ‘to reveal the codes’ implies a read-
ing of the biotechnology language. Mitchell seems to imply that it is the
task of artists to critically assess and inform their audiences about what
the state of the art in technology is. The second task, ‘to re-articulate
what it means to be human’, seems to suggest that biotechnology has an
impact on our self-understanding. Artists, according to Mitchell, have to
take a lead in reflecting on the impact that biotechnology has on what it
means to be human. The third task, to elaborate ‘a palaeontology of the
present’ seems to refer to a level of complexity and confusion that is typi-
cal for the biotech revolution of the present. Whereas previous revolutions
were guided by future objectives, this seems to be a revolution without
a goal, driven simply by the dynamics of science. A palaeontology of the
present would be the reconstruction of what is going on today in the age
of biotechnology by putting together pieces of information that, seen in
isolation, do not make much sense: pieces of information, for instance,
that inform us about the state of the art in DNA technology and embryo
and stem cell research, but that are so technical, leading to applications
that are so difficult to imagine, that as such they hardly seem to make
any sense. Too many things are happening at the same time that seem
unrelated, but taken together certain constellations may emerge that may
help us determine what the biotech revolution means. Mitchell seems to
imply that by building these pieces of information into a coherent image
(a reconstruction), artists can help us make sense of this revolution that is
taking place right now. And last but not least, he believes that artists have
the freedom to do this in a more or less ‘irresponsible’ way. They have to
unleash the images and see where they go.

Bioart

In the last two decades, a new art form has emerged that seems to
correspond quite well with this idea of the work of art in the age of bio-
cybernetic reproduction: namely, bioart. It is a general term used to refer
to works of art that in some way relate to biology, biotechnology and life.77
Preferably, these works are created with new visualisation techniques and
tools borrowed from the life sciences, such as MRI, DNA gels, fluorescent
bacteria, etc., as ways of representing bodies, identities. Contemporary
bioart portraits are good examples of art that reflects (on) biotechnology.
A well-known example of such an artwork is Marc Quinn’s portrait of Sir
John Sulston. This portrait, Sir John Sulston: a genomic portrait, was made
out of colonies grown from bacterial cells taken from Sulston’s sperm
(Ibid.). But also the works of artists like Alexis Roxygen, Catherine Chalm-
mers and Bryan Crockett who use ‘traditional’ materials and processes of
representation like paint, photography and marble to comment upon the
biotech revolution are relevant to my question (Anker and Nelkin 2004).
In addition to these ‘dead’ or rather ‘non-living’ artworks, a new phenom-
enon within the biological arts can be observed: one that is very different
from the traditional artistic engagement with science because, ‘with it,
biological materials/life and scientific tools and protocols have become an
integral part of the artistic process as well as the artwork itself’ (Zurr and
Catts 2003, 2004). Bioartists who are involved in this latest type of bioart
create living and/or semi-living beings. Life itself, the living organism, is
the medium with which they work.

The discussion about bioart and the growing number of art exhibitions
on themes, materials, technologies, etc. borrowed from the life sciences,
such as the DNA code, genes, life and the post-human, indicate that the
arts ‘have discovered’ biotechnology. ‘A molecular gaze’ has emerged in
the world of contemporary art (Anker and Nelkin 2004). There are many
different reasons for artist to engage with the (life) sciences. Art critic Sian
Ede gives four: first, because artists are challenged by the new ‘materials’

76. In 1982, artist Joe Davis walked uninvited into the MIT Center for Advanced Visual Studies and walked
out 45 minutes later with an appointment as a research fellow (Gibbs 2001). So, in fact, it is three decades,
but Davis was ahead of his time.
77. The definition of bioart is a topic of debate. Since I am primarily interested in the role bioart can play
in the ethical and social debate and not in demarcating bioart from other forms of art, this dispute about
the definition of bioart is irrelevant to me. I am interested in how contemporary art (or bioart) reflects
upon current developments in biotechnology.
provided by the life sciences; secondly, because they are fascinated with scientific paradigms that help us to view the world differently; thirdly, (in a few rare cases) because artists can assist with scientific investigation; and, finally, because they feel they need to engage in a complex, non-simplistic way with the political and ethical consequences of science (Ede 2002: 67). Working with new, sometimes living materials, and participating in ethical or political debates, bioart elicits two main types of discourse. One is technical: an assessment and categorisation of artworks according to the process of their production. The other one focuses on content. It is about bioart as a social, political and ethical commentary. It is this latter discourse that interests me.

**The morality of bioart**

The writings of art critics, or art historians and bioartists on bioart reveal both fascination for the new technologies offered by the life sciences and worries about the impacts of biotechnology on (our understanding of) life. In the light of the biotech revolution, some authors see it explicitly as the task of art to address the big questions concerning life. The gaze of artists often dwells on the values challenged by a rapidly growing science that frequently seems to defy natural categories, common morality, and traditional understandings of human nature. Touching on the moral and ethical dilemmas of manipulating nature, the patenting of genes, and the consequences brought about by the changing status of humans in the post-genomic world, visual artists portray the expectations and salient anxieties of our genetic age, write Anker and Nelkin in their book on bioart (Anker and Nelkin 2004: 4). Stephen Tomasula has a similar view on the task of gene artists: ‘By collapsing the metaphor of art as a mirror of life with life itself, by making art that mirrors biological processes and the network of commercial concerns that configure our dawning biological age, gene artists engage in questions raised by their scientific/corporate/government counterparts: What does it mean to alter a natural evolutionary process millions years old? How will people think of themselves and their relationships to others once boundaries such as ‘plant’ and ‘animal’ have eroded?’ (Tomasula 2002: 138). In a similar vein, art critic and artist Dave Powell sees a specific task for artists in addressing these questions in the public forum. ‘In this age of ecological awareness and animal rights it is we, the artistic community, who should consciously and wholeheartedly embrace the asking of these vital questions as part of the greater art discourse. I would think that artists can be yet another powerful force ensuring that these matters are addressed in the public forum and not merely in closely guarded laboratories and behind closed doors of corporate boardrooms’ (Powell 2004, 340).

When discussing bioart as a social, political and ethical activity it is important to acknowledge that bioart is a heterogeneous practice, with various artists occupying a broad variety of (sometimes rather fluid) ethical positions. Bioartists may have many different (ethical) agendas. As a consequence, there cannot be such a thing as a ‘general theory of the morality of bioart’. And it is definitely not my intention to make any general statements concerning the role that bioart ‘should’ play in the ethical debate on animal biotechnology. Nonetheless, some artists involved in bioart do explicitly take an ethical position when talking or writing about their artwork. For instance, in their paper *The ethical claims of Bio Art: killing the other or self-cannibalism*, Ionat Zurr and Oron Catts of the Tissue Culture and Art project (TC&A) describe how some of the outcomes of biotechnologies bring into question ‘deep-rooted perceptions of life and identity, concept of self, and the position of the human in regard to other living beings and the environment’ (Zurr and Catts 2003/2004)78. As artists, they believe that it is their role to ‘reveal inconsistencies with regard to our current attitudes to life and to focus attention on the discrepancies between our western cultural perceptions and the new techno-scientific understandings about life’. Moreover, they also intend to ‘further problematise ethical frameworks and shift the goalposts of contemporary ethics’ (Ibid.). Transgenic artist Eduardo Kac has similar ideas about the critical task of art. He sees it as ‘the urgent task of art’ to unpack the implicit meanings of the biotechnology revolution by revealing the cultural implications of the revolution underway and by offering ‘different ways of thinking about and with biotechnology’ (Kac 2000)79.

Kac and TC&A do not attempt to give answers or find solutions to the ethical dilemmas raised by biotechnology. Rather they attempt ‘to generate further debate and expose our social inconsistencies towards the living’ (Zurr and Catts 2003, 2004) or to offer ‘new perspectives that offer further debate and expose our social inconsistencies towards the living’ (Zurr and Catts 2003/2004)78. As artists, they believe that it is their role to ‘reveal inconsistencies with regard to our current attitudes to life and to focus attention on the discrepancies between our western cultural perceptions and the new techno-scientific understandings about life’. Moreover, they also intend to ‘further problematise ethical frameworks and shift the goalposts of contemporary ethics’ (Ibid.).

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78. The article by Zurr and Catts is accessed via the web, and therefore the page number is not available.

79. The references Kac (1998, 2000, 2001) are all accessed via the Eduardo Kac website, and therefore page numbers are not available.
ambiguity and subtlety where we usually only find affirmative (‘in favor’) and negative (‘against’) polarity’ (Kac 2000). Kac who sees transgenic art as a firm rejection of the reductionist view that life is purely and simply a matter of genetics emphasizes our communication with transgenic life. According to Kac transgenic art can ‘help science to recognize the role of relational and communicational issues in the development of organisms’ (Kac 2000). The questions remain: What is it exactly that bioartists have to offer to the social and moral debate on animal biotechnology? How does bioart in practice address these bio-philosophical questions? And, finally, how does this affect the aesthetic and ethical quality of their work?

**Part Two: Bioart on animal biotechnology: Yuk!**

Bioartists are inspired in numerous ways by a wide range of biotechnologies. I am interested in artworks that reflect upon, are inspired by, or involve animal biotechnology. In particular, artworks that evoke yuk!-responses. These are the artworks that make a moral appeal to us, that challenge us to think (more deeply) about animal biotechnology. I have chosen three art projects that meet my criteria for further investigation: Kac’s ‘GFP Bunny’ project™, Catherine Chalmers’s Transgenic Mice Series, and Adam Brandejs’s Genpets™. I have chosen these three art projects because they show the (future) potential of animal biotechnology and play a prominent role in social and moral debate, either by accident or on purpose. The artists who created these artworks are all visible artists, their work is discussed by academic writers and exhibited in galleries, travelling exhibitions, on websites, in newspapers and magazines.

In the following, I will analyse the aesthetic and moral quality of these artworks more or less along the lines of the four questions that I have ‘distilled’ from Mitchell’s four tasks of the work of art in the age of biocybernetic reproduction: First, what does this particular work of art tell/imply about the state of the art in animal biotechnology; what does it reveal about the technologies of manipulation; and what does it say about biology as the science that seeks knowledge about life and death? Secondly, what does it tell us about the implications of biotechnology for us humans? Thirdly, how does it make sense of biotechnology? In what sense does the artwork contribute to an elaboration of a paleontology of the present? And, finally, what kind of images are unleashed and where do they go? For each individual art project, I will discuss the moral appeal it makes, the yuk!-factor it entails (in particular the messages it seems to convey with regard to issues such as naturalness, quality of life and the commodification of life). By discussing these works of art, I want to demonstrate that, when discussing animal biotechnology, it is impossible to separate aesthetics from ethics.

**The ‘GFP Bunny’ project**

In 2000, Eduardo Kac surprised and shocked the (art) world by claiming to have created a green fluorescent rabbit for merely artistic reasons. Alba was the first living transgenic rabbit made for non-scientific purposes. Two years before, Kac introduced/defined the notion of transgenic art as a ‘new art form based on the use of genetic-engineering techniques to transfer synthetic genes to an organism or to transfer natural genetic material from one species into another, to create unique living beings’ (Kac 1998). But the transgenic artwork ‘GFP Bunny’ was not simply about the creation of the green fluorescent rabbit Alba. Of much more importance to Kac was the public dialogue generated by the project and the social integration and cultural adoption of the rabbit (Kac 2000).

On his website, Kac keeps a record of the public debate on Alba. All kinds of publications about his rabbit can be found. However, as the webmaster, he decides what to put on his website and what not to include. For example, an article in Wired that is rather critical about the reality of Alba’s green fluorescence and the relationship between the artist and the scientist responsible for her creation, cannot be found on this website (Philipkoski 2002). This indicates the dubious extent to which Kac is not only inciting a public debate on Alba but also trying to control and direct it. Apart from this website, two images from the GFP Bunny project are very important. One is a photograph of a green (albeit compared with the green fluorescent OncoBrite mice (see Figure 2) rather unrealistically green) fluorescent rabbit (Figure 8a), and the other is a photograph of the artist holding a white rabbit in his arms in front of a wall, – or is it a studio? It is definitely not in a laboratory – as it is decorated with a somewhat oddly designed, 1970s style wallpaper (Figure 8b).

What was new and radical about Alba the GFP bunny was not the technology involved, but rather the fact that she was supposed to be a work of art. At the time Alba was ‘created’, the use of green fluorescent...
protein as a marker was an established and well-known tool in the field of molecular biology (Okabe et al. 1997; Yang et al. 2000). The ‘GFP Bunny’ project was not a genetic experiment but an artistic experiment. Kac’s fluorescent rabbit Alba was in a sense ‘ready-made’. The birth of Alba has always been surrounded by a cloud of vagueness. The one story about Alba I find most convincing is that she was created in a laboratory in the context of a routine process and picked up by Kac who took her in his arms and must have said something like ‘I name you Alba and from now on you are a work of art’ (Philipkoski 2002). Whether Alba was really created on behalf of Kac – on special demand as it were – or was in fact an ordinary (even non–transgenic?) laboratory rabbit that had her 15 minutes of fame simply because she was picked out for a photo session with an artist, remains unclear. But, even if Alba is a hoax, the fact remains that, by staging Alba, Kac introduced the concept of the GFP Bunny as a genetic animal ‘biopaint’ to a wider audience.

By choosing the GFP gene as the gene to be added to Alba’s genome, Kac made gene technology visible. Whether the green fluorescent colour was really the effect of a GFP gene added to Alba’s genome, or rather the result of photoshopping is in fact irrelevant. On the image of Alba that was sent into the world, you could really see that her genome was altered. By taking her out of the laboratory and showing Alba to the public, Kac pointed both to the state of the art in gene technology (a technology easily applied to mammals like us), and to our responsibility for, and moral connectedness with, these animals that are created with the aid of new genetic technologies.

The staging of Alba involves more that just presenting a green fluorescent rabbit to the world. With the GFP Bunny project, Kac was actually initiating a social debate on Alba and the social integration of transgenic animals. Kac is not only the initiator of the debate – his involvement goes much further than that. After unleashing the image of Alba, he continued to play a rather important role in this debate. He was, and still is, more or less its ‘conductor’. Raising our level of awareness is what he seems to be after. ‘More than making visible the invisible, art needs to raise our awareness of what firmly remains beyond our visual reach but which, nonetheless, affects us directly’, he writes (Kac 1998). There is something taking place behind closed doors that ‘in the safe harbour of scientific rationalism, nourished by global capital […] unfortunately remains partially sheltered from larger social issues’ (Kac 1998). Kac is particularly concerned about the ‘domestic and social integration of transgenic animals’. As a transgenic artist, Kac claims not to be interested in ‘the creation of genetic objects, but in the invention of transgenic social subjects’ (Kac 2000). In his article on the GFP Bunny, he explains that the project is about ‘the completely integrated process of creating the bunny, bringing her to society at large, and providing her with a loving, caring, and nurturing environment in which she can grow safe and healthy’ (Kac 2000). The most radical moment of the GFP Bunny project is the moment Kac takes Alba out of her cage and holds her in his arms for a photo opportunity. This is how Kac describes this moment: ‘She immediately awoke in me a strong and urgent sense of responsibility for her well-being’ (Kac 2000).

What do people find disturbing about Alba? Why does she evoke a yuk!-response? As Kac himself has noted, he did not break any social rule with the ‘GFP Bunny project’. Neither did the rabbit suffer from being fluorescent. Humans have determined the evolution of rabbits for at least 1400 years, and there were no mutagenic effects resulting from transgene integration into the host genome (Kac 2000). In other words, Kac did not do anything unethical to the rabbit. The procedure used in order to create Alba was fairly standard within accepted scientific practice. This is basically the most important information Kac gives about the state of the art in animal biotechnology. Nonetheless, Alba was the subject of a public debate, a public debate initiated by Kac himself. What was so ‘yukky’ about Alba, was the fact as such that Kac had created her as a work of art. In doing so, he bypassed a dominant ethical rule: that there should be a clear human benefit that outweighs the use of transgenic animals. Alba was not meant to be used as a laboratory animal to help a scientist find a cure for a genetic disease.

More or less in response to this type of criticism, Kac put emphasis on the responsibility one has as an artist vis-a-vis transgenic artworks. He states that we have to love and nurture these new forms of life we have created just like any other animal (Kac 1998). Is he suggesting that scientists do not love and nurture their animals? What does Alba tell us about what goes on with animals inside the laboratory? Kac is suggesting that dramatic events are taking place behind closed doors, but he remains rather silent about what exactly those might be. He does not say anything about the millions of transgenic creatures like Alba that are living in today’s modern biomedical laboratories, nor does he say anything about her countless invisible transgenic brothers and sisters who live identity-less lives in laboratories.
that are closed to the public. By focussing on the social integration of Alba, rather than her monstrosity, Kac is in a sense elaborating a palaeontology of the present. He is making sense of something that usually remains out of focus, but is highly relevant. We are in many ways connected to these transgenic animals.

This takes me to Mitchell’s final point. How does Kac unleash his image, and where does the work lead to? Is the fact that Alba is art and not science relevant at all? Is there really a difference? And, if so, what exactly is the difference, from a moral point of view? Alba differs from her transgenic kin because she is a work of art. But in fact she is not really different at all. Yet, at the same time, she is different from all other laboratory rabbits because an artist claimed her to be a work of art and promised to take her home and care for her as if she were his pet. By displaying her as a work of art because an artist claimed her to be a work of art and promised to take her all. Yet, at the same time, she is different from all other laboratory rabbits because an artist claimed her to be a work of art and promised to take her home and care for her as if she were his pet. By displaying her as a work of art and potential pet, Kac changed her fate. Alba was set free from the laboratory premises?

**Catherine Chalmers’ transgenic mice series**

In 2000, six highly artistic photographs of transgenic mice, taken by nature photographer Catherine Chalmers, appeared in The New York Times as illustrations to the article *Fuzzy Little Test Tubes* by Lawrence Osborne. The photographs, taken at the Jackson Laboratories, showed not only exemplary genetically engineered mice as they are used in biomedical science but also the price tag attached to them. The most expensive mouse Chalmers portrayed is *Blind Sterile*, a mouse that is used for research into genetically-related reproductive disorders and eye disorders. At that time, such mice made a fair price: $231.70 per breeding pair. The photographs that Chalmers took of these mice are not mere illustrations, they are portraits of these mice. The focus is on their face and its expression. As a result the photographs show something of these mice that might be called their ‘personality’. *Pigmented Nude* seems highly vulnerable, it is nude and seems to be shivering all over, it is a pitiful animal. *Down’s Syndrome* simply looks severely ill. It seems smaller than the other mice, and its body seems cramped and in a curved position. *Blind Sterile* seems more lively and normal, except for its creepy eyes. They are white/blueish. The animal is blind but still seems rather attentive. *Obese* is strikingly fat. It seems highly dubious whether he is still able to stand on his own feet. This gives us the impression that he is a lazy mouse (see Figure 9a). *Curly Tail* does not show his face. In this portrait, it is the curly tail that is pointing at the lens. The tail is its most dominant feature. Except for this strange tail, the mouse looks normal and healthy. The most active one seems to be *Rhino*, a pink nude with a spectacular wrinkled skin. He is standing high on his feet, and points his nose squarely at the camera. He is both monstrous and cute (see Figure 9b).

This publication of mouse portraits was not an isolated event. Rather, it was part of a series of events. In April 2002, Chalmers’s *Transgenic Mice series* were presented at *Genes(sis): Contemporary Art Explores Human Genomics*, a national touring exhibition in the USA that explored the implications of human genome research on human life and understanding (Stern 2003). The artworks presented at this exhibition were artistic explorations and imaginings of the social and economic ramifications of genetic and genome research. The idea behind the exhibition was to stimulate public dialogue about contemporary genetics. Especially for this occasion, the size of the photographs, originally taken as illustrations to a critical journalistic article about the mouse business and the Jackson Lab, were increased to a scale enormously larger than the original prints. Exhibited in a gallery, these photographs became impressive works of art. In order to explore the experience and response of the audience to the artworks presented, the Henry Art Gallery (where the opening of the travelling exhibition took place) developed a *visual thinking strategy adapted for dialogue* (VTS). Described by the staff as an ‘interactive looking experience’, VTS had to ‘initiate dialogue by posing questions that encourage viewers to bring their own personal associations and interpretations to the work’ (Stern 2003). In order to set up a dialogue about ethics, questions were asked about the abnormality of Chalmers’s mice, the right we have to use transgenic mice for research, and the financial benefits Chalmers might enjoy from the artworks that exploit these mice.

Chalmers’s work was much praised for the feelings of ambivalence it evoked. ‘Enlarged in huge, full-colour prints to hundreds of times their actual size, it is impossible to ignore their disfigurement, and yet we can’t help guiltily thinking that many of them are still cute. The mice are both horrible and darling; they represent both a massively profitable industry and little bits of intelligent, furry life with whom we are fully capable of empathizing’, writes one art critic (Westbrook 2003). ‘Catherine Chalmers’ large-scale portraits of mice bred for specific diseases give a heightened
sense of obligation to the control of actual lives, without resorting to easy emotions. These mice have a larger-than-life dignity; they very nearly dare you to feel sorry for them’ wrote another (Hall 2002).

Unlike Kac, Chalmers did not write about her ‘yukky’ mice. She probably did not intend at all to participate in a moral and social debate on mouse biotechnology with her photographs. As a photographer, she documented what she saw in the laboratory. Not by taking snapshots of these transgenic mice, but by carefully picking some striking examples and putting them in the spotlight, she made portraits of these mice emphasising certain features. The photographs do not reveal the endless rows of (dirty) cages or other typical laboratory surroundings of laboratory mice. Neither do the photographs reveal the countless numbers of animals that are ‘genetically speaking’ interchangeable. The photographs show unique animals, individuals with their specific ugliness or beauty. These photographs show the mice in all their ambiguity. Some are cute, some are weird, and others are monstrous. ‘Make up your mind’, they seem to say. To somebody who is confronted with these to animals for the first time, they raise questions. What are these mice, and why do they exist? In what way are these bizarre creatures connected to our health?

Chalmers’s photographs of transgenic mice that appeared in The New York Times were probably an eye opener to the public. Gazing into the camera’s lens the mice confronted their audience with the bare fact of their existence. Animals that are normally invisible, abstract and anonymous suddenly look us straight in the face. They become real. These mice, in particular Rhino and Pigmented Nude, the two nude mice, have something uncanny about them, something yukky. Being confronted with these transgenic mice, the viewers are forced out of their comfort zone. The mice are both real and bizarre; they have something monstrous about them, they look emphatically unnatural. Chalmers shows them the way they are, ambiguous animals. On the one hand, these mice are mice like any other mice. On the other, they are grotesque, – technological artefacts. They are high-tech fuzzy in vivo test tubes. By adding to the mouse images the price tags and their specific use in biomedicine, these works of art inform the public about the animals behind biomedicine and biomedical industry in a disturbing way. The work reveals an uncomfortable relationship between human health, science and the biotech industry. A relationship that makes many people feel yukky. They seem to suggest there is not only a trade-off between animal suffering and human health, but also between animal welfare and profit-making. Chalmers took the pictures in 2000. At that time, the US law on animal welfare, the Department of Agriculture’s 1966 Animal Welfare Act (AWA) was highly debated. The definition on ‘an animal’ of the AWA excludes birds, rats and mice bred for use in research. As a result, laboratory mice are unprotected and their standards of care unmonitored81. A change in the status of the mouse could have an effect on profits. By exposing these mice in The New York Times, Chalmers made visible the ‘fuzzy little test tubes’ that Osborne wrote about. Behind the production and use of genetically engineered mice for medical research a ‘bioindustrial complex’ exists that is as much driven by economic interests as by scientific or medical ones. In his article mentioned above, Osborne estimated that the profit of private ‘mouse ranches’ nationwide amounts to $200 million per year (Osborne 2000). Chalmers’s Transgenic Mice Series ‘highlights this industry that has until recently escaped public scrutiny or calls for accountability’ as curator Robin Held wrote on the genesis website82.

Adam Brandejs’s Genpets™

The work Genpets™ by the artist Adam Brandejs is presented on his personal website and was exhibited in several art galleries. The work represents both the virtual biotech company Bio-Genica and its products, – the Genpets. Bio-Genica is presented on a website (www.genpet.com) that gives information about the mission of the company and its products, and it contains a service and support page that gives online assistance, as well as ‘tech support’ for dealing with ‘your Genpet’. Genpets™ are mass-produced Bio-engineered pets made by Bio-Genica (see Figure 10). Genpets™ are actually ‘bizarre, altered, bipedal mammals sealed in a plastic bubble where they uneasily rest in some kind of induced hibernation. They are there, ready to take home and add to your life as the next entertainment gadget; bioengineered creatures, mass-produced, and pre-packaged.

81. Today, the Animal Welfare Act in the USA still does not include laboratory mice. Researchers claim that the welfare of mice is adequately regulated by the Environmental Protection Agency (EPA)/Food & Drug Administration (FDA) Good Laboratory Practice Standards (GLP), the US Public Health Service (PHS) Policy on Humane Care and Use of Laboratory Animals, and the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC).
83. At www.biogenica.com the website of a real biotech company can be found.
as a fully self-contained unit for your convenience’ (Brandejs 2005b). On the website the catalogue of Bio-Gencia can also be found with interesting details about the company profile and the market potential of Genpets™.

The Genpets™ are made of plastics and electronics. They are not real living creatures but Brandejs does everything to give the spectator the feeling that these genetically engineered pets are really alive. As he argues, it is ‘easier to dismiss Genpets as a hoax or exaggeration when you’re not faced with a wall of them. The experience of a grainy photo is different than standing face to face with a breathing, sleeping creature’. The whole set-up of the Genpets™ artwork is designed to give the audience the impression that they are alive. The packages contain a series of glowing and beeping heart monitors, the chests of the pets rise and fall as if they are breathing and they occasionally twitch, shake and claw. Their movements are limited by tie-wraps, which keep them in place. All of this seems to confirm that these creatures are alive, that they are real, like biotech foetuses. But the sculpture is not about whether the Genpets are real or not. To Brandejs, the sculpture is ‘the physical representation of a question.’ And this question about bioengineering is not about its positive or negative ramifications, or where it can take us. To Brandejs, the question is ‘whether or not we are ready to go there’ (Brandejs 2005b). It shows us the future of biotechnologies that, at present, are in their foetal stage. Are we ready for the adult version?

Brandejs’s work differs from Chalmers’s and Kac’s in the sense that it is not about ‘the real thing’ and not about today’s scientific practice. Brandejs reflects upon the future of animal biotechnology. His work is a kind of science fiction. To Brandejs: ‘Art is something that pushes boundaries and stirs thought and debate as well as something that reflects the times it was created in’ (Brandejs 2005b). So, reflecting upon today, Brandejs is stretching reality and creating an image of the world of tomorrow. He is using mixed media: (imaginary) biological sciences and computer technology. In doing so, he is reflecting upon his world. When he looks around he does not see bronze or wood, he sees ‘plastic, cement, steel, flashing lights, electronics, and LCD displays’. He sees ‘a mass media machine telling us to “buy, buy, buy”, so these are the elements he uses to accomplish his artworks (Brandejs 2005b). Brandejs is showing us where biotechnology might lead.

Brandejs has a clear message built into his artwork. ‘Re-think nature’, he writes in Bio-Genica’s catalogue. ‘Nature has never been a closed system, nor has it ever been balanced – we as a species have been affecting it for thousands of years. It has been our inspiration, and by choosing the best it has to offer we have been able to create absolute perfection. Patenting of living systems has become slowly accepted as our outlook on life has changed. As it is obvious that Genpets™ have never, and would never exist in nature, it seems silly to even question them as patented technology. Unlike other domesticated pets, Genpets™ have not been torn out of their natural environment and forced to quickly adapt to a foreign habitat; instead they are fulfilling a pre-designed destiny. Now doesn’t bioengineering nature make far more sense?’ (Brandejs 2005a: 8)

The Genpets™ are explicitly presented as pets and not as laboratory animals. They are apparently made by a biotech company, but clearly in order to be useful at home in a pet-like fashion; they are high-tech living gadgets for personal use. With this artwork, Brandejs is implying that biotechnology will lead us, or has already begun to lead us, into a world where there is a growing (mis)use of animals by humans, even for purposes that many will consider as frivolous. But most striking are the responses of the public to his Genpets™. In his afterthought about the Genpets artwork, Brandejs writes how the piece was meant to illicit a reaction and how surprised or even shocked he was by the many positive responses, the eager acceptance of his Genpets™, eager to an uncanny extent. This notably applied to the responses he received from teens. ‘When I designed Genpets, I had no clue how people would react. It disturbed me to see such a positive acceptance of Genpets by people who wanted to buy a genetic pet’ (Brandejs 2005b). There are, of course, people that understand very well what the Genpets as an art project are about. And there were also people that ‘cried upon seeing them’. Overall though, Genpets.com was swamped with emails from people wanting to buy a pre-packaged pet. To Brandejs, this proves the importance and relevance of Genpets™ as an art piece. ‘It baffles me how one generation can be banging at a store window in absolute protest and outrage, while the younger is crying out and demanding I sell them’ (Brandejs 2005b). It is here I believe the artwork of Brandejs is a good example of ‘a palaeontology of the present’. The artwork gives a hint about the future, but by provoking a series of comments it opens up future scenarios that could not be predicted beforehand. The response to Genpets seems to suggest that future generations (Brandejs was born in the 1980s (1982), but a significant part of his

84. The reference Brandejs 2005b is a website, and therefore a page number is not available.
audience in the 1990s) are likely to have less problems with using these kinds of biotechnologies in such a way. To them, Genpets™ are cool.

In fact, the artwork Genpets™ has two layers. The work has an upper layer that consists of the Genpets and the website. This is the layer of artistic fantasy, Brandejs’s vision of how a biotech company in future might look. But the artwork also has a second layer: the layer of physical reality. Some people take the website seriously, and really believe that they can order Genpets at Bio-Genica. To them, the Genpets are not simply images; Genpets are real. These people send in serious requests to Genpets.com. As a result, a true conversation about gen-tech animals takes place between the artist and his audience.

What is yukky about the Genpets is that the genetically engineered animals are presented as commodities, packed for retail. This is what the work is about. ‘Life itself is quickly becoming a processed commodity in the privatization of nature. Biological engineering by large companies, outside of nature has become a terrifying reality for my generation to contend with’, Brandejs writes in his artist statement about the Genpets series 01 (Brandejs 2005b). ‘Today, we are well within the process of desensitizing an upcoming generation towards accepting bioengineering as “natural”’ (Brandejs 2005b). By presenting Genpets as commodities, he is highlighting the commercial interests that companies have (and will have even more in the future) in genetic engineering. When making profit is the number one incentive of the biotech industry, claiming to do animal biotechnology in order to save lives and to feed the world does not sound very sincere. It is marketing rhetoric: it is what people wish to hear. According to Brandejs, the work Genpets™ deals with three, related but different themes: fear, ignorance, and consumerism. ‘Bioengineering’, he explains ‘like any new technology promises a great deal of positive effects. We as a race, however, tend to put a great deal more faith into technology as a savior than it necessarily has earned. Through Genpets I question the negative effect that bioengineering can have, for we all know that when it all comes down to it, profit is the bottom line’ (Brandejs 2005b).

What is equally disturbing, or yukky, is the unnaturalness of the Genpets. BioGenica’s vision of nature is a vision of nature as malleable, a nature that in and of itself has no value. What has economic value is not given by nature, but rather determined by man. This vision of nature resembles Rollin’s vision when discussing animal biotechnology. But unlike Rollin, who prefers to avoid the issue of nature (by claiming that nature is irrelevant because strictly speaking individuals do not have natures), Bio-Genica has a rather radical vision of nature: a vision of nature that is by essence malleable. ‘Nature to us is nothing more than inspiration for rough parts. We have picked out the best of everything to create absolute perfection’ (Brandejs 2005a).

What strikes me most about Brandejs’s writing on biotechnology is that he seems surprised by the fact that the actual biotechnological developments (the ‘real thing’) are progressing much faster and further (are more ‘far out’) than he had imagined. In a ‘quick note’ about the packaging of the Genpets, Brandejs writes: ‘I don’t believe the pets in packages to be a far stretch. Take a look at any farm or pet store; we already package our animals. The idea behind the Genpet packages is that Bio-Genica places the animals into an artificial hibernation. Again, when I read in a newspaper that scientists have just combined sheep + spider to make stronger thread, is it far out to assume we could add a gene for hibernation from another animal? I think not. I think many of the concepts behind Genpets are far less “out there” than the majority of what is happening behind closed doors’ (Brandejs 2005b).

Part three: Making the invisible visible

Presenting the invisible

This chapter began with the hypothesis that bioart, sharing some of its ambiguities with the technologies upon which it is reflecting, but at the same time apparently being driven by a strong ethical agenda (the morality of bio-art), could offer something useful to the debate on the social and moral aspects of animal biotechnology. By making animal biotechnology visible in a way that confronts, disturbs and/or challenges our imagination, bioart can make an appeal to a variety of aesthetically-based moral judgments on animal biotechnology.

In the first place, I have described how bioartists make animal biotechnology visible and even tangible (both the animals themselves and the technology), not by merely ‘informing’ the public about mouse biotechnology, but also by merely presenting them with images of the mice, but by presenting mouse biotechnology in its full and often ambiguous meaning. By this, I mean presenting transgenic mice as monsters (Chalmers), as commodities (Brandejs), as innocent

‘Yuk!’ and the aesthetics of mouse biotechnology
creatures (Kac, Chalmers), as individual personalities of unique animals (Chalmers), etc. When presenting the transgenic mice (or other genetically engineered animals), the bio-artists I discussed also present the myths and metaphors that give meaning to these mice.

Presenting the monster
Both scientist and ethicist – the former with their day-to-day experience and the latter with their focus on animal welfare –, have reduced the genetically engineered mouse to an ordinary laboratory mouse. In everyday laboratory practice, genetically engineered mice do not differ from non-genetically altered mice. Therefore, I see it as one of the merits of bioart to put emphasis on the fact that these animals are genetically engineered animals, and that there is something about biotechnology that deserves our attention. The genetically modified mouse is not simply a pitiful animal that is being used in science, it is the pioneer species of biotechnology. It is that latter role that is still in need of thorough investigation. What will biotechnology bring to the mouse, and, by implication, to us? What will FutureMouse look like? What will FutureMan look like?

I argued that ethicist and scientist when dealing with the transgenic mouse monster usually apply a strategy of containment. Genetically engineered animals are carefully locked away in laboratories. The outside world is a no-go-area for these gen-tech animals. By ‘creating’ transgenic pet animals and bringing them out in the open, both Kac and Brandjes have broken this rule. They have set the monster free. Kac set the monster free by literally embracing his monster and asking for her domestication. He asked us to welcome transgenic organisms like Alba in our homes. He did exactly what Frankenstein failed to do. Brandejs did a similar thing by offering Genpets for sale on his website. He introduced them to the world outside the laboratory, to the marketplace, to be more specific. When referring to animal biotechnology, both Kac and Brandjes speak about what goes on ‘behind closed doors’. But they keep the mystery alive. They do not reveal anything about what happens behind these closed doors of the laboratories. They only present what comes out.

Chalmers did go behind these closed doors, where she was able to take a closer look at these mice. But she focused on the mice as such. We do not see laboratory equipment on her mouse portraits; we do not see scientists wearing white coats. Yet, in her work the products of these laboratories are presented. And these products – monsters – are very real.

The work of Brandejs, in particular the public response to it, suggests that when the biotechnology is ready for it, transgenic animals might very well become part of our lives\(^85\). This is also what Kac believes: ‘As we try to negotiate current disputes, it is clear that transgenics will be an integral part of our existence in the future. It will be possible, for example, to harness the glow of the jellyfish protein for optical data storage devices. Transgenic crops will be a predominant part of the landscape, transgenic organisms will populate the farm, and transgenic animals will become part of our expanded family’ (Kac 1998).

The message of these works of bioart seems to be that we already seem to have accepted that, sooner or later, these monstrous products will enter the public sphere. Therefore, we can no longer (mentally) hide these animals in laboratories. The question how we relate to transgenic or genetically modified animals suddenly becomes highly relevant. Because at the moment, so it seems, we do not relate to them at all, they are invisible. By presenting them as ‘real’ (Chalmers and Kac) or as a future possibility (Brandejs), these bioartists have made the genetically modified animals visible and by doing so they are questioning our confused (reluctant) moral position towards these creatures. They present us with the state of the art; this is what animal biotechnology (potentially) is about. There are monsters hidden in laboratories, and it is our moral duty, not only to take good care of them, but also to be prepared to welcome them into our world.

The economy of hope
Another issue that is addressed in a provocative way by these bioartists concerns the supposed benefits of biotechnology. When discussing the blessings of biotechnology, Catts frequently refers to the ‘rhetoric of saving lives and feeding the world’\(^86\). By scientists, both from academic circles and from biotech companies, animal biotechnology is often presented as a necessary evil: ‘Only with the use of genetically engineered mice will we have a chance of finding a cure for cancer’, or, ‘We can only win the battle against AIDS if we have a reliable transgenic mouse model’. Presented like this, transgenic mice are the only hope we have. Bioartists seem to be more critical about this hope and the promise of biotechnology than

\(^{85}\) Transgenic glowing fish are already available. You can order at Glofish.com.

\(^{86}\) Personal communication.
bioethicists. They seem more willing to question what exactly is promised, and how this promise relates to the millions of mice used, or sacrificed, in biomedical science. Chalmers’s transgenic mice, like Bryan Crockett’s Ecce Homo and his Cultured (the mice representing the Seven Deadly Sins) pose a difficult question: How is the fate of these individual mice connected to human interests, both financial and medical?

On nature
Biotechnology is changing our vision of nature: ‘nature’ and ‘the natural’ seem rather vague notions referring to a world ‘out there’ not yet influenced by us humans, something that is quickly becoming marginal or even non-existent. The invention of recombinant DNA technology revealed, as no other technology had done before, that the raw materials of nature and life are by nature malleable. ‘Do not fight this idea’, ‘do not deny the power of biotechnology’ is what bioartists seem to say, ‘but learn to live with it and put it to use in a responsible way’. To Kac the image of a world that is visibly influenced by biotechnology is a highly realistic future scenario. ‘In the future we will have foreign genetic material in us as today we have mechanical and electronic implants. In other words, we will be transgenic. As the concept of species based on breeding barriers is undone through genetic engineering, the very notion of what it means to be human is at stake. However, this does not constitute an ontological crisis. To be human will mean that the human genome is not a limitation, but our starting point’ (Kac 1998). When we accept biotechnology as a fact, the question surrounding bioengineering is not whether it’s good or bad, or where it can take us; it is whether or not we are ready to go there.

The works of Kac, Chalmers and Brandejs, each in their own way, pose questions that are relevant to the social and moral assessment of the genetic engineering of animals, in particular where questions concerning our vision of nature, the normal and the abnormal are at stake. Like Alba, the fluorescent mice that inhabit the laboratories look very unnatural. But what is natural or unnatural when thinking about laboratory inbred mice? Any attempt to introduce an objective unequivocal notion of nature or the natural fails in the light of scientific progress. Biotechnologists have shown that nature is more malleable than we believed, and that we are more connected through our DNA with other species than we expected. In short, our (scientific) notion of nature is adrift as a result of the insights of biotechnology. Fluorescent rabbits and mice are the living proof of ‘shifting boundaries’. They are unnatural, but are in the process of becoming accepted as ‘normal’, at least by the scientific community. In his art project, Brandejs presents the question about nature as totally irrelevant in the light of future applications. The practice of patenting genes by biotech companies is illustrative of this changing attitude towards nature. Only what is created or adopted by the biotech companies has economic value to the biotech industry, not what is created by nature. Moreover, to care about the quality of life of individuals seems out of place in the light of the future commodification of genetically engineered animals. To most people today, Brandejs’s Genpets™ are both unnatural and do not have lives worth living. But as the public response to Brandejs’s artwork is pointing out, the attitude towards the genetic engineering of animals might be changing more rapidly than we can at present imagine. What is perceived today as totally unthinkable in terms of ethical acceptability, within a decade or two might be the coolest thing.

Concluding remarks: towards a more creative style of ethical inquiry
In answer to the question how works of art can be of assistance to our moral understanding and evaluation of animal biotechnology, we may conclude that art has something valuable to offer to the ethical debate on animal biotechnology, first of all by placing concrete applications in a broader, future-oriented perspective. Artistic visualisations are of vital importance when it comes to the moral assessment of a technology that not only takes place behind the closed doors of the laboratory and on the level of the invisible, the DNA molecule, but is bound to become visible outside the laboratory in the future. DNA technology is in a sense science fiction, a science of future promises. In order to understand the meaning and future implications of biotechnology, we have to rely on (artistic) imagination. This is what bioart in a broad sense – meaning art inspired by, reflecting upon, commenting upon, or involving bio(techn)ology – can offer. Artists have a long tradition of visualising the present and the future, the fantastic and the real, the good and the bad, using various media, varying from traditional materials to multi-media and biotechnology. They can visualise the effects of biotechnology by representing or applying it.

But there is another reason why bioart can play a valuable role in the social and ethical debate on animal biotechnology. Art can have a
refreshing impact on the debate because artists open up a different perspective on biotechnology than scientists and philosophers or bioethicists usually do. Artists can reflect on science by ‘doing science’ and/or ‘ethics’ outside the existing scientific or ethical frameworks such as laboratories, ethics committees or philosophical discourses. Artists can create ‘truth’ by manipulating or disturbing facts. This artistic truth can be of great value to the moral debate. An artwork like Alba forces us to step outside the dominant ethical discourse and take another (second) look at the monsters we are creating. It is because Alba is art and not science that she forces us to look at animal biotechnology from a different, not necessarily ‘scientific’ perspective.

These works of art enable us to physically experience what usually remains unsaid and out of sight: the mice as monsters, but not perhaps monsters that we have to fear. On the contrary, these are monsters we have to take good care of. These monsters promise many good things. But it is our task to remain critical about these promises.

Chapter 6
Conclusions: of FutureMice and FutureMen

The FutureMouse© experiment offers the public a unique opportunity to see life and death in a “close-up.” The opportunity to witness for themselves a technology that might yet slow the progress of disease, control the process of aging, and eliminate genetic defect. The FutureMouse© holds out the tantalizing promise of a new phase in human history, where we are not victims of the random but instead the director and arbitrators of our own fate.”

Zadie Smith

In this final chapter, I wish to go back to the beginning and refer once again to a passage from Zadie Smith’s White Teeth. This time the quotation is taken from a press release about Marcus’s FutureMouse©. Stressing the importance of FutureMouse© the author of this press release presents the mouse as ‘the promise of a new phase in human history’. The quote illustrates very well how the fate of the mouse, the future of the FutureMouse© is related to the future of humans, a future where we, with the help of biotechnology are said to become ‘directors and arbitrators of our own fate’. This is more or less the key message I have put forward in this philosophical inquiry into the genetically engineered mouse: if we want to understand the biotech revolution, and see what future lies ahead for us, we have to look at the mouse. Since in biotechnology research, the mouse is often used as a stand-in for us humans, FutureMouse© might very well be a stand-in for FutureMan.

But, before jumping to conclusions, I wish to reflect briefly on the previous chapters and give answers to the questions raised in the Introduction. One of the central questions of this book was: What is the genetically engineered laboratory mouse? On the basis of the many mouse images I came across in my philosophical inquiry, I have come to the conclusion that the genetically engineered mouse is much more than merely a laboratory animal whose genome is modified by humans. The genetically engineered mouse is a much more ambiguous animal.

It is the ‘right tool for the job’ that will enable us to find a cure for life-threatening genetic diseases, as well as a victim of biomedical science, programmed to become ill and to suffer from human illnesses. It is ‘a high-bio-tech fuzzy test tube’, but also a mouse like any other mouse, with ordinary mouse needs and interests. On the one hand, it is looked upon (by the scientists who work with it) as a piece of standard equipment of the modern biomedical laboratory, or even a commodity while, on the other hand, it is praised as a potential hero by these same researchers. From an animal ethics perspective, the genetically engineered mouse models can be seen as a ‘refinement’ of the ‘conventional’ mouse experiments. For example, the fluorescent oncomice discussed in Chapter 1 are highly sophisticated research models compared with traditional cancer mouse models. So in that respect, biotechnology can be seen as an improvement for the animals involved. But, in the near future, it will definitely not lead to replacement or reduction, as is sometimes suggested. On the contrary, animal biotechnology is the major driving force behind the breeding of a growing number of laboratory animals. If we take the ambitions of the mouse knock-out project seriously, then eventually every single gene will be knocked out in the mouse. Mouse biotechnology is Big Science, a practice that involves millions of mice. They are of great scientific value because they can serve as a stand-in for us humans in medical research. But their intrinsic value is similar to that of other animals. We use them because, biologically speaking, they resemble us so much. And yet we believe we are allowed to use them because, morally speaking, they are different, not human. The genetically engineered mouse is perceived both as a promise and as a threat. It is compared to Jesus, but also regarded as a monster. Being at the frontiers of science, they are a source of inspiration for artists and writers.

From this broad variety of mouse images, or perceptions of the mouse, I believe the image of the mouse as the pioneer species in biotechnology is the most powerful. It is the most complete image. It is an image that can incorporate the others. It is an image that allows me to answer the other two questions that lie at the heart of this book: What can we learn from the mouse, about life, the life sciences, and about ourselves? And, what are the moral consequences of the genetic engineering of mice: that is, how should we deal with the mouse?

A pioneer is defined by the Oxford Dictionary as ‘1) a person who explores or settles in a new region; 2) a developer of new ideas or techniques; and, 3) a member of an infantry group preparing roads or terrain for the main body of troops’. Wikipedia gives the following definition: ‘One who goes before, as into the wilderness, preparing the way for others to follow’. These two definitions point out that being a pioneer is about being the first one to enter a new territory, about going to a place where no one has gone before. A pioneer is an innovator. But, also essential to the definition is that pioneers pave the way for others soon to follow.

When I refer to the mouse as a ‘pioneer’ I do not mean, of course, that mice themselves must be seen as developers of new ideas or techniques. Rather, the mouse is a ‘pioneer species’ that has already entered a future into which we will sooner or later follow him. Because of its unique genetic properties the mouse enables us to learn things about genetics and biotechnology that would have been unimaginable without its existence. Whether the laws of Mendelian genetic inheritance also apply to complex organisms such as mammals was tested and proved in the mouse. Because of the mouse, biologists were able to unravel mysteries about DNA regulation and transcription. The mouse enabled scientists to discover that DNA is universal. But perhaps even more important, through the mouse we learned about our own genetic development and genetic diseases. This knowledge about genetics is both comforting and disturbing. We are no longer prisoners of our own DNA. We can liberate ourselves from our genetic fate. This makes the mouse – apart from the animal welfare issues animal biotechnology raises – an animal of great moral importance.

As I have shown in Chapter 1, the mouse became the pioneer in the biotech revolution sometime in the late 1970s, early 1980s, when scientists ‘discovered’ recombinant DNA technology, and developed techniques to culture embryos and ES cells in vitro, and the first transgenic mice were born. As I have argued, the mouse did not become a pioneer ‘out of the blue’, the first transgenic mouse was not created ex nihilo. The history of these biotech pioneers began over a hundred years ago when Clarence Cook Little started inbreeding mice for scientific purposes. As a result of these inbreeding practices, some of the inbred strains developed unique genetic and embryological characteristics that made the introduction of foreign DNA in the early 1980s possible. Like no other mammal the inbred mouse can be genetically modified. So it was in the course of a long process of inbreeding and other forms of biological interference with the mouse genome that the genetically engineered laboratory mouse became a living artefact, a creature that could never have been the result of a
‘natural process’. This made me conclude that the transgenic mouse is as much a man-made species as a biological species. As a man-made living animal it belongs to both the world of artifacts that can be patented and to the world of the living creatures that are part of nature.

As I have explained in Chapter 2, the fact that these animals are both natural and unnatural is what, apart from the animal suffering involved, people find most disturbing about mouse biotechnology. By changing the mouse’s genetic make-up, we change something unique that has been the result of a long ‘natural’ process called evolution. We do things with genes that would never have happened in ‘nature’. Through our ‘messing with nature’ we have created living artefacts. But how can a living being be unnatural? How can a living being be an artifact? What does being ‘natural’ or ‘unnatural’ mean in the case of laboratory animals? Humans have interfered with the mouse’s genome for more than a century. What makes biotechnology more unnatural than traditional cross-breeding or Little’s inbreeding? The moral debate on the genetic engineering of mice illustrates that ‘nature’ or, more precisely, our vision of nature is adrift as a consequence of biotechnology. The difficulty of defining ‘nature’ and ‘natural’ in a way that is both satisfactory both to the high-tech rapidly changing life sciences and to our common sense makes it hard to make a moral assessment of mouse biotechnology. Being a product of both nature and techno-science, these mice challenge the nature/culture dichotomy and, by doing so, they make us feel uncomfortable. According to Smits’s monster theory these mice are ‘monsters’, since they belong to two categories that are mutually exclusive. An effective strategy to deal with monsters of this kind is to reduce them to a less problematic category. In the case of the genetically engineered mouse, this is the category of the ordinary laboratory mouse. But as I have argued in Chapter 2, this monster strategy does not lead to the domestication of the mouse monster. Its most monstrous aspect is simply ignored. The mouse remains a monster.

Subsequently, I investigated the two most dominant myths and metaphors to which people refer when they express their moral feelings about these monster mice: the playing God metaphor, and the Frankenstein myth. When people refer to God or Frankenstein in order to express their moral doubts, or their anxieties, I argued, they are not simply being emotional or irrational. On the contrary, by referring to these myths and by using these metaphors they reveal something important about how we are struggling to make sense of what we know about mouse biotechnology. This is what myths do; they help us shape the meaning of the world as we perceive it. By paying close attention to the myth and metaphors that give shape to the mouse debate, we can learn something about the complex meaning that the genetically engineered mouse has for us humans.

A superficial reading of ‘God talk’ indicates that people feel there is a dividing line between what is man-made and what is given. Apparently, they worry about what happens when we cross this line. Crossing that line is a gesture that evokes fear, fear of the unknown consequences, or, in a religious vocabulary, fear of God’s punishment. But as I have shown in Chapter 3, the ‘playing God’ metaphor involves much more than simply a fear of God’s punishment. It also reveals that the genetically engineered mouse, as the pioneer species in biotechnology, has the character of a promise. If we see the mouse as a promise, as many people whom I have quoted throughout this book tend to do, we may begin to understand the political and economic driving forces behind biotechnology. We begin to acknowledge that the mouse is one of the key actors in a political economy of hope. This is, in fact, a network that involves various kinds of people, and various kinds of hope, such as: carriers of or sufferers from a genetic disease hoping for a cure; scientists and researchers seeking a breakthrough; doctors and health care professionals in search of a successful therapy; biotech companies aiming for products that generate profit; and governments looking for industrial and commercial developments that will generate employment and stimulate economic activity and international competitiveness. A whole industry is based on this hope and promise.

A point of moral concern is the position of the mouse in the trade-off between the potential harm done to the animal and the potential human benefits. In this trade-off, the mouse does not really stand a chance. In the light of the element of promise, every mouse that is ‘sacrificed’ is worth the try. As I argued before, there are not many members of animal ethics committees who dare to say ‘no’ to an experiment that potentially could lead to a significant breakthrough in cancer research. It is my own experience that most people on such committees feel very reluctant to reject an experiment and prefer to reason on the basis of the benefit of the doubt. In this trade-off, the mouse does not really stand a chance. In the light of the element of promise, every mouse that is ‘sacrificed’ is worth the try. As I argued before, there are not many members of animal ethics committees who dare to say ‘no’ to an experiment that potentially could lead to a significant breakthrough in cancer research. It is my own experience that most people on such committees feel very reluctant to reject an experiment and prefer to reason on the basis of the benefit of the doubt. They take the promise of biotechnology seriously, they simply have to.

Another point of moral concern has to do with the division of power in the new bio-politics in the age of biotechnology. Who is promising all these ‘good things’ about biotechnology? Who is playing God? Of course,
it is not the mice themselves who are promising this type of ‘salvation’ through biotech, they merely represent this promise. They are the living flesh, the physical ‘proof’ of this promise. The biotechnologists, the universities that employ them, and the biotech and pharmaceutical companies who pay for the research are the ones who are making these claims. And whom do they address? Is it a new emerging elite class of those who will have access to the benefits of our biotech future?

What seems to worry people most is probably the promise itself. What is exactly promised, what is the master plan of the creative biotechnologists? Experiments with transgenic mice have illustrated how easy it is to modify mammalian DNA. They have shown that DNA is universal; that all living species share the same DNA and that DNA can easily be transported from any organism to another. The mouse genome is malleable, and, if DNA is universal, by implication the human genome is also malleable. What we can do with the mouse today, we can do with humans tomorrow. The mouse is after all a stand-in for us humans. This means that through biotechnology we will someday be able to cure people who suffer from life-threatening or degenerative diseases. We can correct genes in humans that cause illness just like we can correct genes in mice. If scientists can cure mice through biotechnology, they can cure humans through biotechnology. But, as I have shown in Chapter 4, if we resemble mice that much in terms of ‘genetic correctability’, this implies, in theory at least, that we also can enhance ourselves: that we can become more intelligent, stronger and live longer. If scientists can create ‘supermice’, they can also create ‘supermen’. Now this is a thought that really seems to disturb most people. When giving their opinion about the creation of ‘supermen’ through biotechnology, people often refer to Frankenstein. The reference to Frankenstein is an expression of a feeling of disgust. It is the expression of the fear that (human) biotechnology will lead to ‘a gruesome parade of horribles’. This is what a superficial reading of the Frankenstein myth is about. But after looking more closely at the Frankenstein myth, I have suggested a different reading. I came to the conclusion that biotechnologists have not created a monster, but discovered one. This is the main conclusion of my chapter on the ‘Frankenstein thing’. Supermice Doogie, He-Man-mouse, Yoda and Marathon-mouse show what is possible; they show what biotech can do. The monster the biotechnologists discovered is the idea that mice, and by implication also humans, are potentially malleable entities. In answer to the second question of this book: What can we learn from the mouse?, I believe this is the most important lesson the mouse teaches us. The mice have taught us about the potential of genetics. They made it possible to develop the techniques to modify genes, to turn them ‘off’ and ‘on’ on command, and to make genes visible. Over a period of 25 years the mice have ‘taught us’ to control fate – theirs and ours. We have also learned that DNA is universal and can be exchanged between animals of different species, including man. Taken together, this suggests that we can also control the fate of man; and that FutureMouse© is indeed holding out the tantalising promise of a new phase in human history, where we are not victims of random variation but rather the directors and arbitrators of our own fate. This is the ‘monster’ we fear. But, as I put forward in Chapter 4, I do not believe the genetic engineering of mice is a practice that can, or should be, put on hold. Nor, do I believe that human beings will never be subject to genetic engineering because it is an ‘unethical’ thing to do. The discovery of the malleable human genome is not one that can be turned back. We simply have to face the monster.

This takes me to the third and final question of this book: How should we face this monster? How can we make a moral assessment of mouse biotechnology? One of the reasons why I find the image of the mouse as a biotech pioneer appealing is that presenting the mouse as a pioneer is a way of facing the monster. A pioneer is facing the future. A pioneer is discovering new territories that have future potential. The main purpose of the pioneer’s travels is that sooner or later others will follow. This is what the genetically engineered mice are doing, they are test animals, they are stand-ins, and this is why Marcus (or Zadie Smith as his inventor) calls his mouse FutureMouse. As the pioneer species par excellence, the mouse provides us with important information about the biotech future. But, how can we make sense of this biotech revolution? How do we know where we are heading? How can we make a moral assessment of something that lies ahead of us?

One way to address these questions is by using our imagination: think of what might be possible, let your guts speak (figuratively speaking of course). Yuk!, the outcry of disgust, can be a very good starting point for a moral assessment. This is not to say that what evokes a yuk!-response is by definition wrong. On the contrary, disgust is a rather primal emotion that probably evolved in order to protect us from eating contaminated food (Jones 2007). But in a moral context disgust is a response in need of further investigation. There is a difference in moral and visceral disgust.
An outcry of disgust in response to an image of a genetically engineered mouse or any other animal is a first verbalization of a moral intuition. The next step is to ask ourselves why we feel that a fluorescent rabbit, for instance, is yukky, or a nude pink mouse with a wrinkled skin? On what convictions is this moral intuition based? The conviction that rabbits ought not to fluorescent? The conviction that humans ought not to engineer themselves into genetically stronger, more intelligent and more healthy human beings? Why not embrace biotechnology? These are important questions that lie ahead of us when facing the biotech future.

In Chapter 5, I used artworks to explore the yuk-factor of animal biotechnology. I carefully selected artworks that convey a moral message about animal biotechnology. These moral messages are often far from clear. But this is exactly why these artworks can be so valuable in a moral assessment. The messages of the artworks I discussed are as ambiguous as the mixed feelings animal biotechnology raises. Works of (bio)art and moral intuitions have something in common: in order to make sense of them, we need interpret them. And in the process of interpretation we will find that a straightforward unequivocal judgement is probably not possible. Discussing these artworks (aesthetics) can be a useful step in a morale debate (ethics). But there is another reason why I believe that in the case of animal biotechnology aesthetics can contribute to ethics. Genetically engineered animals are artificial animals. These are animals created by humans, so in a sense they are works of art. This is why in the moral assessment of animal biotechnology aesthetic judgements play an important role. Why do we find genetically engineered mice cute or disgusting? What we perceive as tasteful or disgusting is dependent on many factors. In the case of animal biotechnology I have argued that one of these is our perception of nature and another that of a good life. Both these notions are as aesthetic as they are ethical. Dealing with animal biotechnology implies dealing with these notions.

Meanwhile, we have to make sense of a future that is not yet here and a technology that is not fully understood by many. In Chapter 5, I used the concept of ‘a palaeontology of the present’ to address this issue. The concept was introduced by Mitchell as one of the tasks of the work of art in the age of biocybernetic reproduction. I would like to see a ‘palaeontology of the present’ as a collective and interdisciplinary effort. Therefore I would like to expand the group of people responsible for its elaboration far beyond the usual candidates. As I have argued in Chapter 5, contributions by artists can be of great value to the moral debate on animal biotechnology, but so are those of scientists, philosophers, journalists, literary authors, and various other parties involved in the creation of the image of the mouse. I see it as the task of this heterogeneous group of scientists, philosophers, artists, journalists, writers, etc to elaborate a palaeontology of the present, trying to discover patterns of meaning in series of apparently fragmented and unrelated events. This will help us to face the monster, to make our moral assessments, and to prepare us for the future.

This takes me to my final question about the moral consequences. Indeed, as Adam Brandejs puts it: the basic issue raised by mouse biotechnology is not an ethical ‘No, unless’. Rather, the questions are: Where will biotechnology take us? And are we ready now to go there?

Therefore, we should keep a close eye on the biotech mouse. We should put it in the spotlight. Not only because it is the pioneer species, but because as a visible living being it deserves good care and attention and forces us to think more critically about the promises of biotechnology. With the mouse in mind we can ask ourselves:

So, are we ready to go there?
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Nederlandse samenvatting

Vandaag de dag is het genetisch modificeren van muizen ten behoeve van biomedische onderzoek een gangbare wetenschappelijke praktijk. Miljoenen transgene muizen bevolken laboratoria over de gehele wereld. De meeste van deze transgene muizen zijn door biotechnologen ontwikkeld als diermodel voor studie naar humane genetische ziekten. Maar daarnaast hebben biotechnologen muizen gecreëerd die slimmer zijn, langer leven en sterker zijn dan gewone muizen. De vraag hierbij is niet zozeer of deze technologieën ooit op de mens zullen worden toegepast. De vraag is eerder wanneer dat zal gebeuren. Elke vorm van biotechnologie die ooit op de mens zal worden toegepast, zoals gentherapie of genetic enhancement, zal hoogstwaarschijnlijk in de muis worden ontwikkeld en eerst op de muis worden getest. De muis is dus, zo luidt de hoofdstelling van mijn proefschrift, de pionier in de nieuwe wereld van de biotechnologie.

In dit proefschrift onderzoek ik de verwachtingen en angsten die ten grondslag liggen aan de biotechnologie revolutie door haar hoofdrolspeler, de genetisch gemodificeerde muis, te presenteren als afwisselend een monster, een held, een Messias, een levend artefact en een deerniswekkend proefdier. Wijsgerig gezien is de muis een uitermate dubbelzinnig wezen dat vanwege zijn unieke genetische eigenschappen carrière wist te maken binnen de biomedische wetenschappen.

In het eerste hoofdstuk, The birth of the transgenic laboratory mouse (De geboorte van de transgene labmuis), richt ik mijn aandacht primair op de biomedische wetenschappen. In dit hoofdstuk introduceer ik de transgene muis door hem op te zoeken in zijn ‘natuurlijke’ habitat: het laboratorium. Ten einde het antwoord te geven op de vragen hoe de muis daar terecht is gekomen en hoe hij zich heeft kunnen ontwikkelen tot meest gebruikte proefdier, ga ik terug naar het begin van de vorige eeuw toen de muis zijn intrede deed in het wetenschappelijke laboratorium. Vanaf dat moment volg ik zijn ‘carrière’ tot standaard proefdier voor studies in de genetica. Ik onderscheid drie cruciale stappen in de ‘genealogie’ van laboratorium muis.1) De transformatie van de muis van een studieobject als dier naar een homogeen laboratorium instrument of het modeldier
dat geschikt is voor onderzoek naar de genetica; 2) de ontwikkeling tot pionier in de transgene technologie; en 3) zijn transformatie van modeldier tot muismodel geschikt voor onderzoek naar menselijke ziekten. Dit hoofdstuk sluit ik af met de conclusie dat de muis als gevolg van een lang proces van menselijke interventie in zijn genetische opmaak een ‘levend artefact’ is geworden.


Volgens Bernard Rollin, een van de meest invloedrijke filosofen op het gebied van biotechnologie bij dieren, zijn alleen bezwaren die te maken hebben met dierenwelzijnmoreel relevant. De overige bezwaren die worden geuit tegen biotechnologie bij dieren zijn, volgens hem, esthetische bezwaren. Veel filosofen, (mijzelf inclus) en leken hebben moeite met deze lijn van redeneren. Er staat zonder twijfel meer op het spel dan alleen dierenwelzijn; namelijk ons natuurbeeld of onze definitie van wat we als natuurlijk beschouwen. Echter, in de dagelijkse onderzoekspraktijk lijkt een utilistische afweging tussen dierenwelzijn en maatschappelijk nut het dominante ethische toetskader te zijn. Dit geldt zowel voor de betrokken biomedisch onderzoekers als voor leden van Dier Experimenten Commissies. Hoe dit is te verklaren leg ik uit aan de hand van Martijn Smits’s monstertheorie. Deze theorie biedt een verklaring voor publieke reacties op producten van nieuwe technologieën die zich niet laten herleiden tot de natuur-cultuur dichotomie. De genetisch gemodificeerde muis is zo’n ‘product’. In dit hoofdstuk beargumenteer ik, tot slot, dat de muis ondanks zijn wijdverbreide gebruik in biomedische laboratoria en de schijn van domesticatie, voor velen nog steeds het karakter van monster heeft. Het monsterkarakter van de muis blijkt onder andere uit de mythen en metaforen die het vocabulaire van het debat over biotechnologie bij dieren domineren. In de hoofdstukken 3, 4 en 5 bespreek ik achtereenvolgens de ‘waarheden’ die schuil gaan achter de drie belangrijkste metaforen en domein van biotechnologie bij dieren: 1) zijn transformatie van model-
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Biotech Pioneers

zijn. Hoe verhoudt de Frankenstein mythe zich tot de ontwikkelingen in de hedendaagse biotechnologie? Om deze vraag te beantwoorden vertel ik het verhaal van vier supermuizen en illustreer daarmee de toekomstige mogelijkheden van human enhancement. Ik beargumenteer dat in deze dagen van supermuizen het kritisch lezen van Shelley’s roman van groot belang is en dat biotechnologen inderdaad een monster hebben ontdekt. Immers, DNA, onze essentie, is van nature manipuleerbaar en daarmee is de mens net als de muis ‘maakbaar’. De cruciale vraag is dan hoe we geslaagde ‘re-creaties’ kunnen onderscheiden van monsterlijke. Is het mogelijk hier een objectief moreel oordeel over te vellen of is dit slechts een kwestie van smaak?

Om deze vraag te beantwoorden bespreek ik het vijfde hoofdstuk, ‘Yuk’ and the aesthetics of mouse biotechnology (Yuk! en de esthetica van muis-biotechnologie), de relatie tussen smaakoordelen en ethische oordelen over biotechnologie bij dieren (en mensen) in meer detail. Daartoe keer ik eerst terug naar het argument van Rollin dat ik al eerder heb besproken in hoofdstuk 2 (Ik doel hier op het argument dat morele zorgen die hun basis vinden in een esthetisch oordeel, geen serieus te nemen, want emotionele of subjectieve, morele oordelen zijn.) In tegenstelling tot Rollin beargumenteer ik dat we in het debat over biotechnologie bij dieren esthetische oordelen juist zeer serieus moeten nemen. Morele overtuigingen hebben altijd rationele en emotionele elementen in zich. Mensen die ‘yuk!’ roepen in confrontatie met concrete voorbeelden van biotechnologie bij dieren geven uiting aan diepe gevoelens van morele zorg, maar beschikken blijkbaar nog niet over het vocabulaire om dat op filosofisch gearticuleerde wijze te doen. Wat drukken mensen uit wanneer zij yuk! zeggen? In het vijfde hoofdstuk beargumenteer ik dat yuk!-responsen over het algemeen uiting geven aan twee elementen van zorg: ten eerste, het gevoel van verwarring dat ontstaat wanneer schijnbaar evidente en objectieve noties als ‘natuurlijk’ dat opeens niet meer blijken te zijn. En, ten tweede, de zorg over de dreiging die biotechnologie vormt voor de kwaliteit van het leven, dat wat een leven de moeite waard maakt om te worden geleefd.

De tweede vraag die ik in dit hoofdstuk centraal stel is de wat de rol van kunst kan zijn in de ‘biotech eeuw’. Hoe kan hedendaagse kunst van dienst zijn bij het vellen van een moreel oordeel over biotechnologie bij dieren, in het bijzonder als het gaat om vragen over natuur en natuurlijkheid, kwaliteit van het leven, identiteit, het normale en het abnormale? Om mijn argumenten te illustreren bespreek ik drie kunstprojecten: het GFP Bunny project van Eduardo Kac (2000); de Transgenic Mice series van Catherine Chalmers (2000); en Genpets™ van Adam Brandejs (2005). Aan de hand van deze kunstwerken laat ik zien dat kunst een belangrijke bijdrage kan spelen in onze morele oordeelsvorming, omdat kunstenaars het onzichtbare zichtbaar maken en omdat beelden soms kunnen overbrengen wat taal (nog) niet kan uitdrukken.