SN43  
TCR/CD3, CD28 AND CTLA-4 RECEPTOR SIGNALLING IN T-CELLS  
Christopher E. Rudd  
Division of Tumor Immunology, Dana-Farber Cancer Institute and Harvard Medical School, Boston MA 02115  
T-cell activation is regulated by a complex interplay of positive and negative signals mediated by TCR-CD3, CD4/CD8, CD28 and CTLA-4. TCR/CD3 and CD3/CD8 signalling involves kinases p65k, PI 3-kinase, ZAP-70 and downstream substrates such as vav and SLP-76. PI 3-kinase is recruited via p65k and p59k SH3 domain binding to proline residues within the p85 subunit of the enzyme. Within this signalling matrix is a recently cloned downstream component termed FYB (FN Binding Domain). This structure is restricted to T and myeloid cells and up-regulates intercellulin 2 (IL-2) production. Despite the intricacies of TCR/CD3/CD24 signalling, optimal T-cell stimulation requires co-stimulation mediated by CD28 and other receptors. Proximal events of CD28 signalling are initiated by the phosphorylation of CD28 at the cytoplasmic YMMN motif, followed by the recruitment of PI 3-kinase, GRB-2 and T-cell specific protein tyrosine kinase (ITK). Among the CTLA-4 family members, CD80 binds to PI 3-kinase, and negatively regulates the response via engagement of a tyrosine phosphatase, mediating an effect on CD28. Distal events of CD28 signalling include the activation of the serine kinase modules (MAPK, SAPK/JNK, p38), Jan phosphorylation and ultimately the initiation of IL-2 transcription. PI 3-kinase may bridge these proximal and distal events. Lastly, binding to PI 3-kinase implicates CD28 and CTLA-4 in functions that have not previously been attributed to these regulators.

SN44  
SIGNAL TRANSDUCTION EVENTS ASSOCIATED SURVIVAL AND DIFFERENTIATION IN PRIMITIVE HAEOMPOIETIC CELLS  
A.D. Whetton  
Leukaemia Research Fund Cellular Development Unit, UMIST, Manchester M1 7DN  
Haematopoietic stem and progenitor cells require cytokines for their survival, proliferation and development. In the absence of these cytokines they undergo apoptosis. Molecular mechanisms suppressing apoptosis and their regulation and role in leukaemogenesis have been used to identify a haematopoietic stem cell line, FDC-Mix. Cellular signalling events, including the ras/MAP kinase pathway, JAK/STAT pathway and also lipid hydrolysis and protein kinase C activation have been assessed for their contribution to apoptotic suppression. Furthermore the relevance of these pathways to the oncoembryonic activity of the BCR/ABL tyrosine kinase in Chronic Myeloid Leukemia will be discussed. Another aspect of leukaemogenesis in the myeloid sistema is a blockade or disruption of development. For this reason we have studied the specific signalling events associated with lineage commitment in bipotential haematopoietic progenitor cells and present evidence that a specific cytokine-stimulated signalling pathway which leads to nuclear translocation of a Protein Kinase C isoform activates lineage commitment.

SN45  
REGULATION OF SIGNALING THROUGH THE B LYMPHOCYTE ANTIGEN RECEPTOR COMPLEX  
Edward A. Clark, University of Washington Med. Cir., Box 357242, Seattle, WA 98195, USA  
B lymphocytes recognize antigen through surface B cell receptor (BCR) complexes. The consequences of ligating the BCR vary depending on the B cell developmental stage: ligation BCRs on immature B cells can lead to activation-induced cell death while ligation BCRs on mature peripheral B cells can promote B cells undergoing apoptosis. In this talk I will describe our current thinking about how crosslinking the BCR leads to cell death. This process appears to require the protein tyrosine kinase Syk and phospholipase C y1/2 which are activated by Syk and downstream members of the MAPK activated family of ser/thr kinases such as p38 kinase. A novel member of the protein kinase C (PKC) family, PKCz, appears to regulate this pathway. Much as adverbs can modify transitive verbs, the actions induced via the BCR can be modified by B cell-associated surface molecules such as CD19, CD22 and CD40, CD45. In particular, our studies with CD22-deficient mice suggest that CD22 acts as an 'adverb' to slow down the BCR-mediated 'action'. It may do so via a protein tyrosine phosphatase, SHP-1, which is recruited into and activated within a CD22 complex after BCR ligation. By contrast, the CD40 'modifier' appears to act as a 'preliminary' to modifying BCR-induced MAPK-related and c-Myc-related signalling pathways. Insights into how the BCR 'sentences' are constructed may lead to new ways to modify defective messages in lymphomas and autoeractive B cells.

SN46  
MECHANISMS OF LYMPHOCYTE HOMING IN CHRONIC INFLAMMATION  
Costantino Pitrakis, Rheumatology Unit, UMDS Guy's and St Thomas Hospitals, St. Thomas Street, London SE1 9RT, UK  
Several chronic systemic diseases are characterised by inflammation which can affect different tissue organs simultaneously. Phenotypic analysis of the lymphocytic infiltrate, typically found at sites of chronic inflammation, indicates that distinct subsets of lymphocytes accumulate in different tissues such as lung, gut, skin and joint. The reason for this is not completely understood but it is thought that regulatory mechanisms intervene at least at three different levels. The first level of control relates to specific lymphocyte-endothelial recognition systems operating in the microvascular beds of various tissues. These include the interaction of lymphocyte "homing" receptors such as L-selectin, CLA and e47 with the respective endothelial "address" ligands PNA, E-selectin and MAACAM-1. A second level of regulation may involve the local production of specific chemokine cytokines capable of recruiting lymphocytes programmed to recirculate to a given tissue. Although further work is needed in this area it appears that some β chemokines can act on distinct subpopulations of lymphocytes. Finally, once in the tissues, specific lymphocytes can be preferentially retained locally by binding to specific tissue ligands. An example of this is represented by e47 positive lymphocytes which bind gut epithelia E-cadherin. Such complex regulation of lymphocyte migration will allow specific homing to exist along side universal migration. This will facilitate the development of immune responses in specialized compartments while permitting their integration throughout the body.