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In its active form p53 exists as a tetramer and is known to be a tumor suppressor protein with cell cycle checkpoint control function [1]. The adapter protein 14-3-3σ binds to p53 and stabilizes the functional tetramer and thereby enhances anti-tumor activity. Several binding sites for 14-3-3 proteins have been identified in the C-terminus of p53 [2]. We could solve the crystal structure of the C-terminus of p53 (residues 385-393) in complex with 14-3-3σ at a resolution of 1.2Å. The accommodation of the peptide in the 14-3-3 binding pocket implies a starting point for discussion of binding of 14-3-3σ to the active p53 tetramer and its stabilization. Furthermore the structure reveals the existence of a pocket for small molecules which could be used to stabilize the 14-3-3/p53 interaction and which could be used as a possible starting point for therapeutic intervention.

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Recognition of the CD1d-Alpha-GalactosylCeramide analogues by the NKT T Cell Receptor.

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Unlike the Major Histocompatibility molecules (MHC), CD1d molecule is suited to capture and present lipid-based antigen for T cell recognition [1]. One of the diverse range of lipids that CD1d can present includes the potent immune stimulator glycolipid: α-galactosylceramide (α-GalCer) consisting of a galactose sugar head group connected by two lipid tails. This CD1d-α-GalCer molecule can be recognised by a unique class of T cells, termed Type I NKT cells that expresses T cell receptor (TCR) encoding an invariant α chain and a restricted β chain repertoire. Through the crystal structure of the NKT TCR-CD1d-α-GalCer complex, it can be observed that the NKT TCR recognises CD1d-α-GalCer in a very distinct manner when compared to any other TCR-peptide-MHC (TCR-pMHC) complexes [2]. More specifically, the NKT TCR docks the CD1d-α-GalCer molecule in a parallel conformation with its Vα domain contacting both the α1 and α2 helices of CD1d, a phenomenon that is not observed in any TCR-pMHC complexes. Using the crystal structure as a guide, an alanine scanning mutagenesis of the residues on the NKT TCR and CD1d molecule as well as the use of different α-GalCer analogues enabled the minimal binding requirement of CD1d-α-GalCer restriction to be defined [3]. Collectively, these results highlight the fundamental differences of the way the immune system recognises peptide and lipid-based antigens. The current focus of the project involves the use of different α-GalCer analogues that the NKT cells can recognise. Importantly, these analogues have been tested in vivo to be shown to induce bias cytokine responses, thus, illustrating the potential of using these analogues for future immuno-drug therapy. Here I shall present recent findings pertaining to the recognition of these α-GalCer analogues.

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