MS05 O2

Protein-protein interaction: from mechanism to protein design Gideon Schreiber[a], Dana Reichmann[a], Mati Cohen[a], Yael Pillip[a], Ofer Rahat[a], Orly Dym[b], Vladimir Potapov[c], Vladimir Sobolev[c], Marvin Edelman[c]. [a]*Department of Biological Chemistry,* [b]*ISPC,* [c]Department of Plant Science, *Weizmann Institute of Science, Israel.*
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Keywords: protein-protein interactions, mutagenesis, structure-function

The formations of specific protein interactions play a crucial role in most, if not all biological processes, including signal transduction, cell regulation, the immune response and others. In this talk I will highlight recent advances in understanding the molecular architecture of protein-protein binding sites that allow for such diversity in binding affinity and specificity as dictated by the biological requirements. What is the amino-acid composition of binding sites, what are interface hotspots, how are binding sites organized, what are the differences between tight and weak interacting complexes, how does water contribute to binding and how can the gained knowledge be translated into protein design. If time permits, I will also stress kinetic aspects of binding, and how this may work in the dense cellular environment. The work presented is based on observations done though detailed mutagenesis and structural analysis on the interaction between TEM1-β-lactamase and its protein inhibitor BLIP, as well as on bioinformatic studies.

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MS05 O3

HIV-1 Reverse Transcriptase Structure-Based Drug Design: Crystals to Clinic Chris Phillips, Steve Irving, Heather Ringrose, Romu Corbau, Charles Mowbray. *Pfizer Research and Development, Sandwich laboratories, Ramsgate Road, Sandwich, Kent. UK. CT13 9NJ.*
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Keywords: HIV reverse transcriptase, drug design, inhibitor binding.

HIV-1 reverse transcriptase (RT), a major target for anti-HIV drugs, has been extensively studied crystallographically. The overall heterodimeric structure has been defined and numerous inhibitor complex structures described [1-4]. Three non-nucleoside RT inhibitors (NNRTIs), namely efavirenz, nevirapine and

delavirdine, are approved as key components of Highly Active Antireteroviral Therapy (HAART) combinations. However each of these inhibitors are susceptible to mutations in RT leading to drug resistance. The novel NNRTi UK-453061 is active against a broad range of drug-resistant viral strains. We report findings from some 50 plus crystal structures of different NNRTi enzyme complexes determined as part of a structure based design program. The complexes with UK-453061 itself, close analogues and representatives of several more diverse chemical series including both novel 'in-house' and literature compounds are described. Structural determinates of broad mutant profile, series SAR, and examples of structure based design approaches used are discussed.

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Structural studies of verified virulence factors from *S. pneumoniae* Heinz Gut[a], Mario Bumann[a], Alan Riboldi-Tunnicliffe[b], Tim Mitchell[b], Neil Isaacs[b] & Martin A. Walsh[a] [a]*BM14 CRG, MRC France, Grenoble, France.* [b]*University of Glasgow, Glasgow, Scotland.*
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Keywords: Infectious Diseases, Virulence Factors, Drug Design

Streptococcus pneumoniae is a human pathogen present in the nasopharynx of many healthy individuals. Upon gene regulatory mechanisms, it can spread to other host tissues and cause severe disease like pneumonia, bacteraemia, otitis media and meningitis [1]. The bacterium is estimated to cause 3 million deaths in children every year [2] accounting for 9 % of deaths in underdeveloped countries. Colonization of such diverse host niches (nasopharynx, lung, blood, brain) implies modulation of a wide range of bacterial virulence factors such as surface adherence proteins, toxins or lytic enzymes. Like for many bacterial pathogens, *S. pneumoniae* strains resistant to multiple antibiotics are emerging [3]. Research is focused on the structural and functional characterization of verified pneumococcal virulence factors for the development of new classes of antiobiotics. We have chosen to target three functions critical to *S. pneumoniae* virulence and survival, namely bacterial adhesion, transcriptional regulation and adaptive response. X-ray structures of native and drug-inhibited key virulence factors will be presented. In particular, investigations into the use of commercial antiviral drugs as lead compounds for structure-based drug design will be presented.

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