

Chemistry & Biology of Peptides 2006

Thursday 30 March 2006, University of Nottingham, Nottingham, UK

A mini-symposium sponsored by the Royal Society of Chemistry Protein & Peptide Science Group and Novabiochem Merck Biosciences Ltd.

The one day meeting was organized by Drs Weng Chan (Sch Pharmacy, University of Nottingham) and Peter White (Novabiochem Merck Biosciences), which brought together over 80 chemists and biologists from academia and industry. The symposium had two main themes: the morning session was focused on recent developments in new chemical methodologies for the preparation of peptides, proteins and peptidic toolkits, and the afternoon session was primarily focused on the use of peptides to probe biological systems. The three keynote presentations were given by Professors Albericio (Univ Barcelona) Ramage (Almac Sciences Ltd.) and Flitsch (Univ Manchester).

Details of the meeting can be found at <http://www.merckbiosciences.co.uk/g.asp?f=NBC/chembiolpept.htm>

The first presentation entitled '**Synergy between methodology and protein synthesis/semi-synthesis**' was delivered by Professor Bob Ramage, FRS (Emeritus Professor, Univ Edinburgh, and CSS-Albachelor, Almac Sciences, Craigavon, Scotland). The presentation highlighted a number of synthetic strategies that will enable the chemical synthesis of proteins, e.g. the use of ethyl 1-hydroxy-1H-1,2,3-triazole-4-carboxylate (HOCT) as an auxiliary reagent for peptide coupling reactions. Professor Ramage also discussed a number of orthogonal protecting groups for Lys and Cys, including the 1,5-dioxaspiro[5.5]undecane-3-nitro-3-methoxycarbonyl (Tmn) group for lysine side-chain protection, and the picolyl group for cysteine S-protection. Elements of native chemical ligation that are appropriate for the preparation of c-Myc tagged peptides were also discussed.

Professor Fernando Albericio (Barcelona Biomedical Research Institute and Dept of Organic Chemistry, Univ Barcelona) in his presentation entitled '**Peptides in therapeutics**' gave an account on the pros and cons of peptide based drugs compared with more traditional small molecules including the problems of drug delivery. He reviewed the structures and activities of several recently introduced peptidic drugs, including Eptifibatid (Integrilin[®], Millennium-Schering/Plough), Ziconotide (Prialt[®], Elan Pharmaceuticals) and Pramlintid (Symlin[®], Amylin Pharmaceuticals). He then described synthetic strategies that can facilitate the discovery of peptide-based drugs, including the use of ChemMatrix resin and pseudoproline dipeptides. Professor Albericio completed his talk by describing the synthesis of a variety of γ -peptide foldamers based on the γ -aminoproline monomer in which the α -nitrogen was modified with a variety of alkyl groups.

The presentation entitled '**Novel strategies for the synthesis of labelled peptides**' was given by Dr Peter White, which described the use of commercially available Nova-tag[®] resins for the robust preparation of FRET enzyme substrates. The influence of the position of fluorophores or biotin installed into peptides on a variety of *in vitro* assays (kinase, calpain and alpha-screen) was also discussed. Dr Neil Thomas (Sch Chemistry, Univ Nottingham), in his talk '**Development of internally quenched peptide substrates for lysostaphin an anti-microbial protease**' described the elucidation of the structure and catalytic activity of the staphylococcal protease lysostaphin. He outlined the preparation of a range of FRET substrates that are based on the peptidoglycan of *S. aureus*, which were used to quantitatively determine the catalytic activity of lysostaphin and its mutants. The presentation '**Chimeric cell penetrating peptides as signal transduction modulators**' by Dr John Howl (Sch Applied Sciences, Univ Wolverhampton) focused on the internalization of TP-10 peptides conjugated to a variety of peptidic 'cargoes'. In a further study, the TAT sequence was synthesized in line with the P10 antigen of proliferating cell nuclear antigen (PCNA). This Tat-TP10 construct was shown to display moderate levels of cytotoxicity in several mammalian cell lines.

The afternoon session started by the presentation '**Biocatalysis of substrates linked to solid surfaces**' by Professor Sabine Flitsch. She discussed fundamental studies into the accessibility of substrates immobilized on the surface and internally within PEGA and Tentagel[®] beads. Reactions involving penicillin acylase (M.W. 35KDa) and thermolysin (78 KDa) were monitored using two-photon microscopy, and it was found that only PEGA-1900 allowed the proteases access to the internally tethered substrates. From a study of the kinetics of the system, it was concluded that the diffusion of thermolysin into the interior of the bead was rate limiting.

Dr Weng Chan presented a paper on '**Competitive modulators of staphylococcal AgrC: synthesis and biological evaluation of thiolactone peptides**'. The preparation of analogues of the thiolactone hexapeptide AIP1 by solid-phase chemistry was described. These analogues were then biologically evaluated, and the Ala-5 analogue was discovered to be a potent antagonist. SAR studies around the Phe-6 residue were also described. In the presentation '**Discovering antagonist peptides against bacterial helicase-primase interaction by yeast three hybrid**' by Dr Panos Soultanas (Sch Chemistry, Univ Nottingham) a novel 'reversed yeast three-hybrid system' which has the capacity to bio-screen ca. 10⁶ peptides was described. As a proof-of-concept, by exploiting the bacterial helicase (DnaB)-bacterial primase (DnaG) interaction, the approach identified several novel antagonist peptides. Details of the work were reported in *Chem. & Biol.* **12**: 595-604. In the final talk of the symposium, Dr Barbara Dörner (Merck Biosciences AG, Switzerland) discussed '**Innovative tools for enhancing the efficiency of peptide synthesis**', focusing on the use of pseudoproline dipeptides for the solid-phase peptide synthesis of 'difficult' peptides and mini-proteins.