

ISMB NEWS is a news bulletin published twice a year in order to share information between the various departments involved in the Institute of Structural and Molecular Biology. This includes information such as events, research highlights, new staff appointments, awards and grants.

Your comments, suggestions and contributions are welcome and will help us put together a newsletter which meets your expectations. Please email the ISMB administrator at ismb-admin@ismb.lon.ac.uk.

In this issue

IN FOCUS: ISMB PROFILES

Prof Jim Anderson

RESEARCH HIGHLIGHTS

ISMB Researcher involved in CRT-Cephalon partnership to co-develop a new class of anti-cancer drugs

ISMB Researchers identify a crucial underlying mechanism for Hirschsprung's disease development

AWARDS, PRIZES & GRANTS

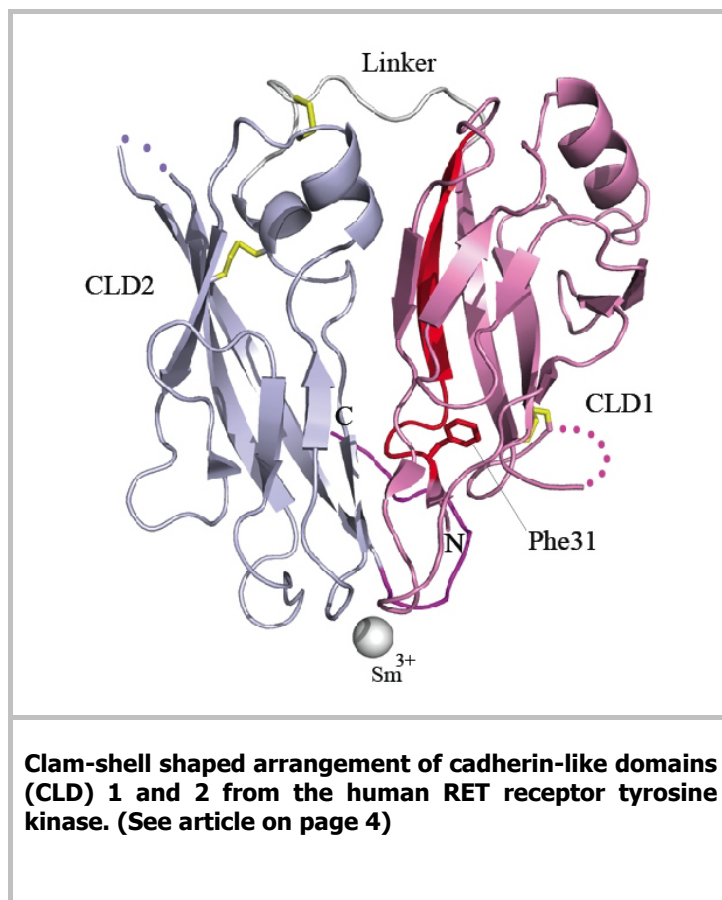
Grants applications - Deadlines

Rita and John Cornforth Award

ISMB EVENTS

ISMB Graduate Symposium

The ISMB holds its fourth symposium



WELCOME TO...

Dr Konstantinos Thalassinos will join the ISMB in September 2010 as a lecturer in Biophysical Mass Spectrometry. Flemming Hansen was awarded a David Phillips BBSRC fellowship. Andrew Osborne, who will arrive in September 2010, was awarded a Wellcome Trust grant.

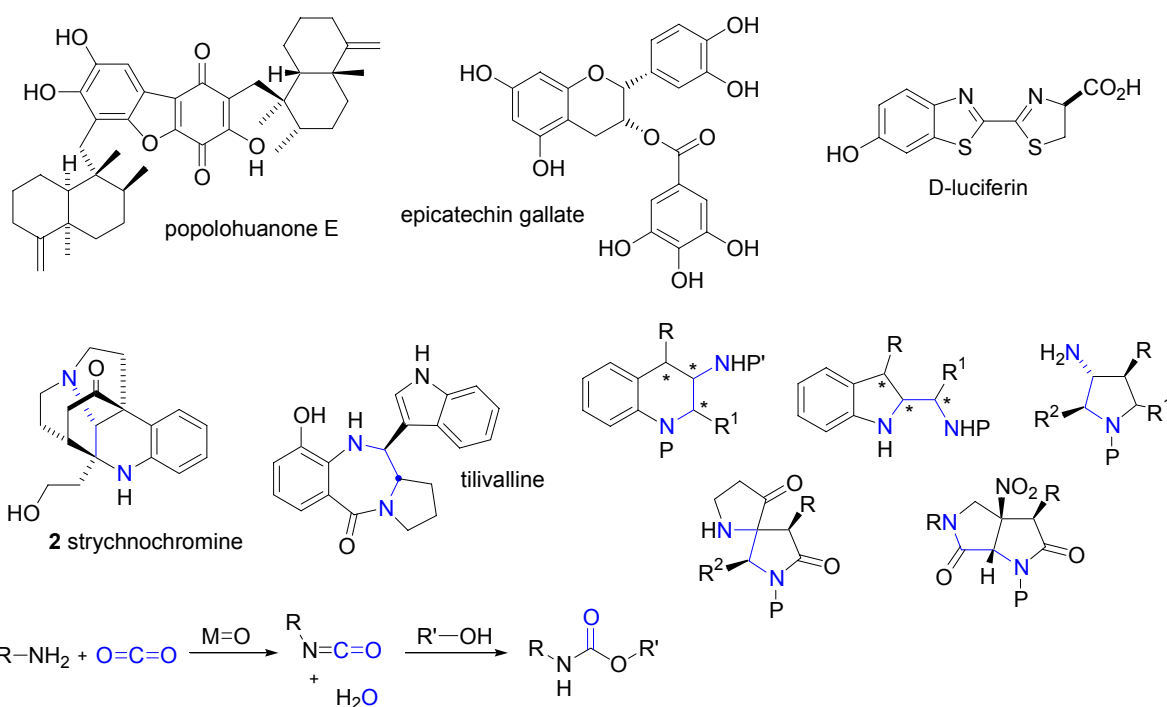


Prof Jim Anderson, Head of Organic and Biological Chemistry



I recently joined UCL in April last year. I have been an independent academic since 1993 and have built a broad portfolio of projects combining contemporary synthetic organic chemistry methodology with highly adventurous, blue sky research. One impetus for our work is the synthesis of complex biologically active molecules and we are always looking for opportunities to collaborate on new molecules of medicinal interest.

We are currently working on a number of synthesis projects such as the anti cancer molecule popolohuanone E via a proposed biomimetic synthesis, *de novo* epicatechingallate analogues to investigate the resensitisation of MRSA toward common beta-lactam antibiotics (in collaboration with Prof P. Taylor, London School of Pharmacy), analogues of D-luciferin to extend their chemiluminescence into the infra red region (in collaboration with Dr M. Pule, UCL Cancer Institute), the alkaloids tilivalline and strychnochromine using our method for the synthesis of 1,2-diaimines, and many methods to make heterocyclic structures which may be important building blocks for other small molecules. We are also interested in enabling fundamental reactions of CO₂.



Details of other work and papers at <http://www.chem.ucl.ac.uk/people/janderson/index.html>

RESEARCH HIGHLIGHTS

ISMB Researcher involved in CRT-Cephalon partnership to co-develop a new class of anti-cancer drugs

Cancer Research Technology (CRT) has announced an exclusive agreement with Cephalon Inc., an international biotechnology company, to collaborate on the development of small molecule inhibitors. These molecules will target specific members of the 'protein kinase C' superfamily of cell signalling proteins - which have been shown to be associated with the development of cancer. The collaborative development programme will progress CRT's promising lead compounds through to the selection of pre-clinical candidate molecules. Under the terms of the agreement CRT will be entitled to significant upfront and milestone payments, and upon achievement of specific product sales targets, a double-digit royalty rate. These small molecule inhibitors will target specific variants – called isoforms – of the protein kinase C family. The isoforms at the centre of the collaboration have been strongly implicated in the development of cancer. Cancer Research UK-funded researchers Professors Peter Parker and Neil McDonald, working within its world class London Research Institute significantly contributed to the structural biology of these targets and their validation as important players in cancer cell growth and spread. New chemical compounds have been rapidly progressed towards lead candidates using CRT Discovery Laboratories drug screening, specialist cancer biology and medicinal chemistry expertise. The aim of this cross-discipline, two-centre collaboration, is to generate pre-clinical candidate molecules for development by Cephalon into new drug therapies for cancer patients.

Cephalon will contribute substantial resources which will boost existing investment by Cancer Research UK, and allow quicker translation of potential drugs that may benefit cancer patients. The work will take place at CRT's Discovery Laboratories in London and Cephalon's research and development facility in West Chester, Pennsylvania.

Dr Keith Blundy, chief executive of Cancer Research Technology, said: "The agreement with Cephalon is a major milestone for CRT's Discovery Laboratories being the first of its small molecule discovery programmes to partner with an international biopharmaceutical company. This unique collaboration will enable us to drive forward the development of potential innovative cancer medicines."

Dr. John Mallamo, Vice President of Worldwide Chemical R&D at Cephalon said: "This collaboration between Cephalon and CRT creates a critical mass of biology and chemistry expertise, capable of quickly advancing the high quality lead series CRT has identified, and provides Cephalon with an expanded oncology discovery portfolio. Cephalon is very pleased to be able to join forces with CRT to discover and develop first-in-class therapies in our fight against cancer. "

About Protein Kinase C (PKC)

PKC is a superfamily of proteins that play a pivotal role in cell signalling – and control of the cells most important processes including growth and division. PKC controls the activity of other important proteins by switching them on or off – they do this by adding phosphate groups at strategic points on target proteins. There are a number of variations between this family of proteins – called isoforms.

About the Principal Scientists

Peter Parker is a Principal Scientist at Cancer Research UK's London Research Institute, and also Professor of Cancer Studies at King's College London. Neil McDonald is a Principal Scientist at the London Research Institute and also Professor of Crystallography at Birkbeck College and a member of the ISMB.

See <http://info.cancerresearchuk.org/news/archive/pressrelease/2010-03-19-CRT-Cephalon-deal-to-develop-PKC-inhibs>

Neil McDonald



ISMB Researchers identify a crucial underlying mechanism for Hirschsprung's disease development

Cancer Research UK-funded researchers, working in the Structural Biology Laboratory at the London Research Institute, have determined the first atomic description of a crucial part of a medically important cell surface protein called RET (Figure 1). RET is a receptor tyrosine kinase that plays a pivotal role in cell signalling and survival. It is mutated in at least five human diseases including multiple endocrine cancers and developmental disorders. Determining the RET structure is a tour-de-force technical achievement that has taken almost 5 years to determine and provides unexpected insights into the molecular background for the development of Hirschsprung's disease (HSCR), a rare congenital disease found in newly born children, originally described the Danish Paediatrician Harald Hirschsprung in 1887. Mutations in the *RET* gene are directly responsible for HSCR disease in the majority of patients but with different degrees of severity depending on the nature of the mutation. Until now there has been no way of correlating the genotype of the patient with the severity of the disease. Researchers Dr. Svend Kjær (Danish post-doctoral fellow) and Dr. Neil McDonald (Head of Structural Biology Laboratory and Professor of Crystallography at Birkbeck College), who made the discovery, have established a simple biochemical assay for HSCR disease-causing RET mutations that allows researchers and clinicians to predict the severity of the disease in individual cases. They also identify a folding bottleneck for the RET protein which, if overcome by pharmacological chaperones, could help alleviate sufferers of the disease with less severe RET mutations. The results from this work are published in the prestigious scientific journal *Nature Structure and Molecular Biology* Volume: 17, Pages: 726-731 (2010) (Epub on May 16th , doi:10.1038/nsmb.1808).

Neil McDonald

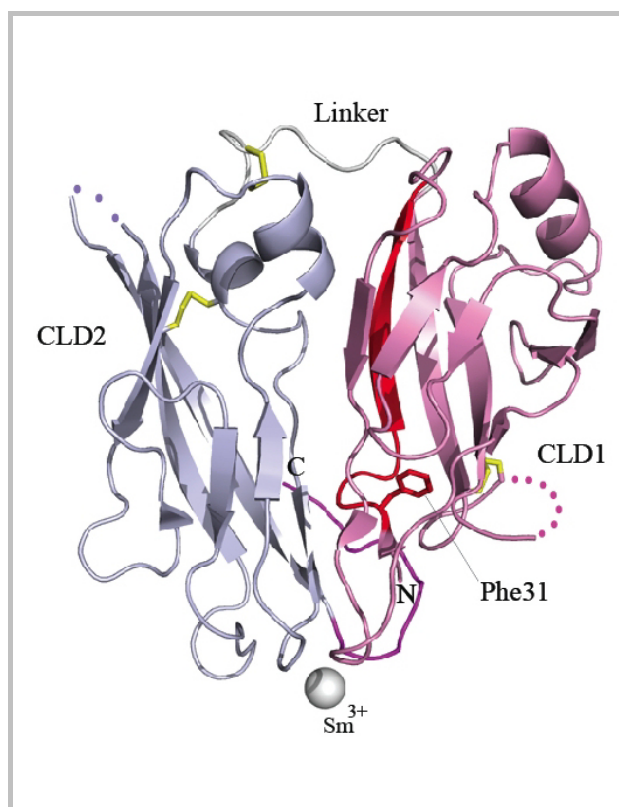


Figure 1: Clam-shell shaped arrangement of cadherin-like domains (CLD) 1 and 2 from the human RET receptor tyrosine kinase. CLD1 contains the highly conserved strand A (shown in red) and the aromatic residue (Phe31) used by classical cadherins in forming *trans* adhesive dimers. Three disulphide bridges within RET CLD1-2 are also indicated and a bound samarium site used for structure determination. Two missing loops are indicated by small spheres.

AWARDS, PRIZES & GRANTS

Grants applications - Deadlines

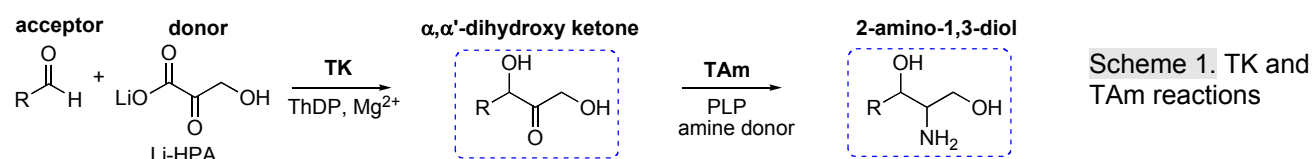
Funding body	Funding opportunities	Deadlines
BBSRC	Responsive Research Grants	6 October 2010
Wellcome Trust		Applications invited at any time
MRC Research board	Molecular and Cellular Medicine	4 pm on 1st September 2010
	Infections and Immunity	4 pm on 8 September 2010
	Programme Grants; Molecular & Cellular or Infections & Immunity.	21 July 2010
EPSRC	Responsive Research grants	Applications invited at any time
	Leadership Fellowships 2011	4 pm on 11 August 2010
	Career Acceleration Fellowships 2011	4 pm on 11 August 2010
British Council	UK Netherlands Partnership Programme in Science	20 August 2010

Rita and John Cornforth Award

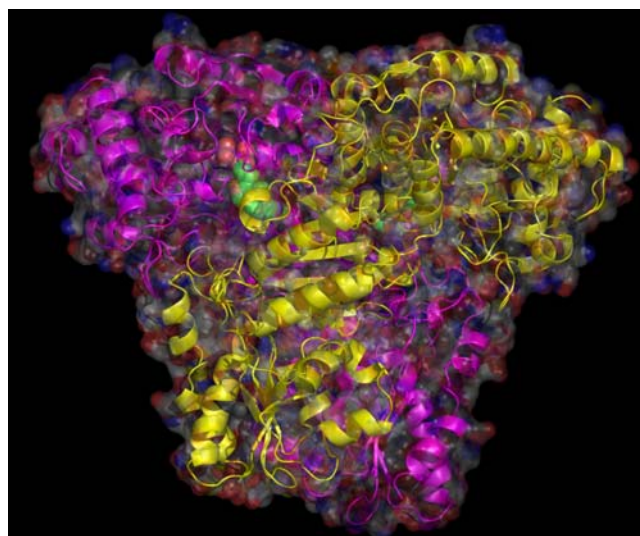
BiCE Team UCL

The Royal Society of Chemistry's Chemical Biology Interface Forum has awarded the 2010 Rita & John Cornforth Award¹ to **BiCE² Team UCL**, with Helen Hailes in Chemistry as the Team Leader, together with John Ward in SMB, Gary Lye, Nicolas Szita, Paul Dalby, Frank Baganz and Martina Micheletti in Biochemical Engineering and John Woodley now at the DTU. The award is for the use of key chemical biology and synthetic skills, interfaced with molecular biology and process engineering to achieve stereoselective enzymatic synthesis with potential for industrial scale-up. The award consists of £2000 and a medal, which will be presented to the team at a symposium arranged by the Chemical Biology Interface Forum.

The BiCE research programme is an internationally recognised multidisciplinary research team that was established in 2004 with the overall aim to develop a framework and tools for constructing multi-step enzymatic processes rapidly and efficiently, ultimately for industrial synthesis. Comparison to available chemical routes and chemo-enzymatic integration where appropriate is also important. The team is comprised of a core of multidisciplinary academics at UCL, with a long history of working together towards common goals that contribute to the delivery of the BiCE aims. Collaborative doctoral and post-doctoral projects have been established, funded by a combination of BBSRC, EPSRC, Technology Strategy Board and CIF awards and industry. The team operates via a close collaboration with significant cross talk and PDRAs and students work in more than one laboratory and gain interdisciplinary research skills. The impact of the BiCE research is evidenced by the take up of BiCE enzymes and engineering approaches for industrial use. The use of biocatalysts for the synthesis of biologically active compounds is of increasing interest to the chemical, pharmaceutical and industrial biotechnology sectors in the search for sustainable, cost effective, synthetic strategies. We are now using synthetic biology approaches to building new biosynthetic pathways and integrating these with the hosts metabolism.



One key focus has been the enzymatic preparation of 2-amino-1,3-diols, a motif found in a range of biologically active compounds such as sugars, sphingosines, antibiotics and antivirals. Our integrated approach has delivered a highly effective route to the aminodiol diastereoisomers and ketodiol intermediates using available biocatalysts, transketolase (TK) and transaminase (TAm) that operate in mild aqueous conditions. Furthermore, chemical synthesis and assay development, pathway engineering, enzyme evolution and process development within an interdisciplinary team enabled this to be delivered from a starting point without available assays, mutant TKs or suitable TAm enzymes.



E. coli Transketolase

The UCL BiCE team fits well within the ethos at UCL of encouraging interdisciplinary research to address challenges that individuals cannot otherwise pursue.

¹<http://www.rsc.org/ScienceAndTechnology/Awards/Winners/2010.asp>

² BiCE = Biocatalysis integrated with Chemistry and Engineering (<http://www.ucl.ac.uk/biochemeng/industry/bice>).

John Ward and Helen Hailes



The ISMB holds its fourth symposium

The Institute of Structural and Molecular Biology (ISMB), based in University College and Birkbeck, University of London, held its fourth biennial symposium at University College on June 17 and 18, 2010. The symposium was well attended with almost a full turn-out from the constituent departments and many visitors from further afield. During the two days, delegates were treated to a feast of molecular science with twelve excellent talks covering four of the Institute's constituent disciplines: structural biology, chemical biology, biophysics and bioinformatics. The distinguished speakers were drawn equally from the Institute itself, from elsewhere in the UK and from abroad; several external speakers were alumni of the Institute's departments and others collaborate closely with Institute researchers.

The symposium was supported by both colleges at the highest levels, and addressed by the Executive Deans of the relevant Faculties of both colleges, respectively, Mary Collins from Life Sciences at UCL and Nicholas Keep of the Faculty of Science at Birkbeck. In her introductory remarks, Collins congratulated the ISMB's director, Gabriel Waksman, for putting together "one of the highest quality structural biology meetings" that she had been to in a long time. Waksman, in turn, paid tribute to the quality of the research presented and stressed the theme of protein-protein complexes and "molecular machines" that ran through all four disciplines.

Wolfgang Baumeister of the Max-Planck Institute of Biochemistry, Martinsried, Germany presented a structure of the nuclear pore complex, through which molecules pass into and out of the cell nucleus, obtained using electron tomography. Later, Andrej Sali of the University of California, San Francisco, and an alumnus of Birkbeck College, described his use of a bioinformatics approach to synthesise information from several sources and obtain a model of this complex that fits as much known data as possible. Former UCL professor Laurence Pearl, now at the University of Sussex, described using X-ray crystallography to study the structure of a molecular chaperone, heat shock protein 90, which helps other proteins to maintain their folds. Another highlight was the presentation by Steve Block of Stanford University, California, of an elegant technique known as the "double optical trap", which is sensitive enough to record the process of RNA synthesis, literally, one base at a time.



Speakers at the Symposium included (from left to right): Wolfgang Baumeister, Andrej Sali, Sheena Radford, Steve Block and Ben Davies

Several speakers described studies of proteins and their complexes with clear medical applications. Among these, Sheena Radford of the Astbury Centre for Structural Molecular Biology at Leeds University described the structures and physical properties of protein amyloid fibres, which can cause disease when they aggregate, and Mark Sansom of the University of Oxford described molecular dynamics simulations of the M2 proton channel from the influenza virus, which is a good target for antiviral drug design.

A full report of the event is available at <http://www.ismb.lon.ac.uk/symposium2010.html>

Clare Sansom

ISMB Graduate Symposium

ISMB staff and graduate students recently enjoyed an excellent programme of talks and posters at the 2010 ISMB Graduate Symposium. Day one featured a fascinating schedule of talks from our first year students and concluded with a talk from guest speaker Prof Ken Smith of Cambridge University on "Fc receptors, malaria and CD8 T cells". On day two the audience heard more exciting talks from our third year students and later viewed posters published by the second years. The Symposium ended with a drinks reception at which student prizes were awarded by the Head of the ISMB, Prof Gabriel Waksman.

Congratulations go to Mr Vishal Sanchania who was awarded the prize for best first year talk for his presentation on 'Spintronic Biosensors'; Ms Pascale Monteil who received a prize for best poster 'Investigating the Role of CoA in Regulating the Function of Cellular proteins and Signalling Pathways'; and Ms Sandra Gonzalez-Malagon for the best third year talk, 'Studies on the phenotype of the Flavin containing monooxygenase 5 (Fmo5) knockout mouse'.

Michael Wright

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To contribute to the next newsletter, please email Anne-Cécile Maffat at ismb-admin@ismb.lon.ac.uk.

Previous issues are available at <http://www.ismb.lon.ac.uk/newsletter.html>

