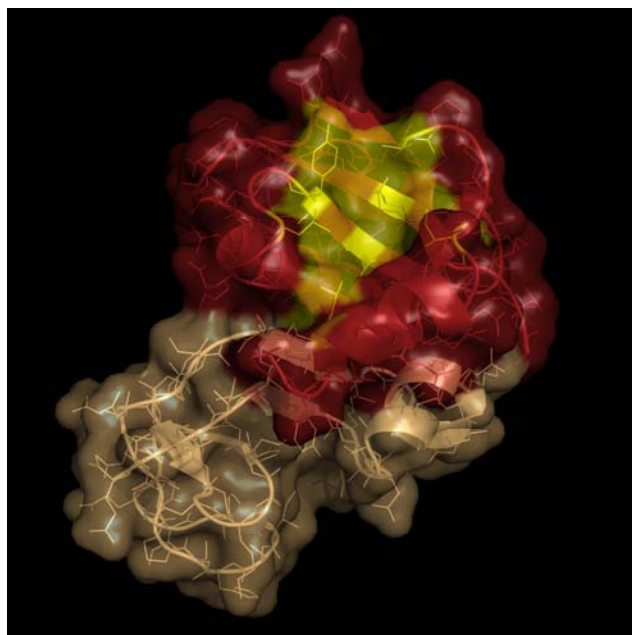


ISMB NEWS is a news bulletin published twice a year in order to share information between the various departments involved in the Institute of Structural and Molecular Biology. This includes information such as events, research highlights, new staff appointments, awards and grants.

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.

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X-ray structure of the *M. jannaschii* transcription elongation factor Spt4/5 core complex. The hydrophobic cavity that facilitates binding to the archaeal RNAP is highlighted in yellow.

Angela Hirtreiter, Dina Grohmann and Finn Werner (Research Department of Structural & Molecular Biology, ISMB) in a collaborative effort with the Cramer laboratory at the Gene Centre, LMU Munich.

BIRKBECK RESTRUCTURING

Birkbeck has recently undertaken a complete restructuring, which led to the merging of the former Schools of Biological and Chemical Sciences and Crystallography in August 2009. The newly created *Department of Biological Sciences* builds on the many existing strengths of these schools in research, teaching and administration so as to allow sustained future growth in all areas. The head of the Department is Prof Gabriel Waksman.

The department is included in the School of Sciences, alongside with the Department of Earth and Planetary Sciences, and the department of Psychological Sciences. Prof Nick Keep has been appointed as the Executive Dean of the School of Sciences.

The former School of Computer Science and Information Systems is now the Department of the same name, integrated in the School of Business, Economics & Informatics.



Dr Erik Årstad, Senior Lecturer in Radiochemistry



"After completing my Ph.D. in radiochemistry at the University of Oslo, Norway, in 2001, I moved to Imperial College to work with Prof. Anthony Barrett on polymer supported reagents. I subsequently joined the Institute of Nuclear Medicine at UCL/UCLH as a research assistant and became involved in nuclear imaging with positron emission tomography (PET) and single photon emission computed tomography (SPECT). PET and SPECT are by far the most sensitive techniques for whole body human imaging and enables studies of biomolecules such as receptors and enzymes in vivo. I was intrigued by the possibility of designing new biomarkers to study human physiology and molecular pathways of disease, particularly related to the function of the brain but also in other areas, such as oncology and cardiology. In 2004 I was recruited by GE Healthcare to lead the radiochemistry research group at the PET centre at Hammersmith Hospital. In 2006 I became leader for the Tracer Discovery team, overseeing radiochemistry research as well as the biological evaluation of new tracer candidates. My work at GEHC focused on the development of diagnostic tracers for imaging with PET and new methods for labelling with fluorine-18 (half-life 110 min). In 2008 I returned to UCL as part of a new collaborative initiative between the Department of Chemistry and the Division of Medicine to establish radiochemistry for translational research. Since my return to UCL I have overseen construction of a state-of-the-art radiochemistry facility designed for work with short-lived radionuclides for nuclear imaging. My current research is focused on development of tracers for imaging of neurotransmission, labelling groups with dual reporters for multi-scale imaging with optical and nuclear techniques, and tracers for imaging of stem cells in vivo."



[Details of work and papers at <http://www.chem.ucl.ac.uk/people/arstad/index.htm>]
[e.arstad@ucl.ac.uk]

Erik Årstad

Dr Richard Hayward, Royal Society University Research Fellow



"I have a longstanding interest in the molecular cell biology of pathogen-host interactions. I began my scientific career at the Universities of York and Bayreuth (Germany), studying the transforming proteins of human papillomavirus and molecular chaperones in *Bacillus subtilis*. In 1996 I joined the laboratory of Vassilis Koronakis at the University of Cambridge. It was emerging that many bacterial pathogens possess a conserved macromolecular machine, which 'injects' virulence 'effector' protein directly into eukaryotic cells. These effectors, which promote bacterial entry and replication by mimicking eukaryotic functions, are potential targets for novel diagnostics, therapeutics and vaccines, and can be exploited as reagents to study cellular processes of broader relevance to physiology and disease. As a graduate student and postdoctoral researcher, I applied biochemical, cell biology and imaging approaches to investigate *Salmonella* and enteropathogenic *Escherichia coli* effectors, in particular their coordinated subversion of host cytoskeletal dynamics at the plasma membrane. Although a clearer view of this sophisticated interplay is now emerging, little is known about how effectors promote intracellular replication at the vacuolar interface. My group at the ISMB is investigating the effectors of the obligate intracellular pathogen *Chlamydia trachomatis*, which remains a significant public health threat worldwide. Its unusual hydrophobic effectors, which share little obvious homology to prokaryotic or eukaryotic proteins, likely interfere with host intracellular trafficking, apoptotic and cytokinesis pathways from the membrane of the pathogen-containing vacuole."

[Details of work and papers at <http://www.smb.ucl.ac.uk/molecular-cell-biology/dr-richard-hayward.html>]
[richard.hayward@ucl.ac.uk]

Richard Hayward



Complement Factor H binds at two independent sites to C-reactive protein in acute-phase concentrations

Paper of the Week in the Journal of Biological Chemistry

Poster Prize at the 18th International Analytical Ultracentrifugation Conference, Uppsala, Sweden

Factor H (FH) regulates C3b in the alternative pathway of complement activation, both in plasma and at host cell surfaces. FH is composed of 20 short complement regulator (SCR) domains. Analytical ultracentrifugation (AUC) and small-angle X-ray scattering (SAXS) show that this protein forms a series of oligomers in solution. The Tyr402His polymorphism in FH is a risk factor for age-related macular degeneration (AMD). C-reactive protein (CRP) is an acute-phase protein in plasma that binds Ca^{2+} . AUC, SAXS and surface plasmon resonance (SPR) showed that CRP exists as a pentamer-decamer equilibrium in physiological buffer.

We established the native FH-CRP interaction using a multidisciplinary application of AUC, SPR and SAXS. It proved crucial to work with physiological FH and CRP concentrations in 137 mM NaCl and 2 mM Ca^{2+} in which the occurrence of denatured CRP is avoided. In solution, AUC revealed FH-CRP binding because the FH-CRP interaction inhibited the formation of both higher FH oligomers and CRP decamers. This indicated that CRP blocks the FH dimerisation sites at each of SCR-6/8 and SCR-16/20. In confirmation of this, SPR showed that the SCR-1/5 fragment of FH does not bind to CRP, while in order of increasing affinity the SCR-16/20, SCR-6/8 (His402) and SCR-6/8 (Tyr402) fragments bind to CRP. Binding only takes place at elevated acute phase plasma concentrations of CRP in physiological buffer, which occurs under inflammatory conditions. These findings provided intriguing insights into the beneficial role of the CRP and FH interaction for ordinarily preventing AMD, and the adverse effect of the His402 polymorphism in failing to regulate C3b properly. In addition, the CRP binding site at SCR-16/20 is novel and indicates the importance of the FH-CRP interaction for atypical haemolytic uraemic syndrome, a cause of renal failure.

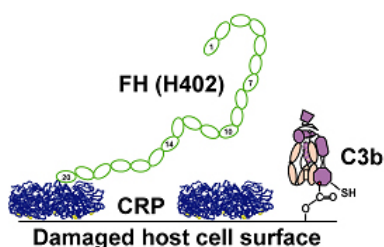
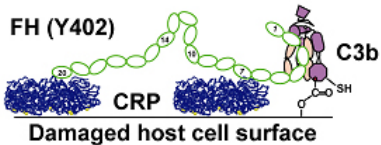
This FH-CRP study was published in J. Biol. Chem. back-to-back with a sister study dealing with CRP alone. Zuby Okemefuna was awarded a poster prize for the two studies at the 18th International AUC conference in Uppsala, at the former laboratory of The Svedberg, Nobel Laureate. Subsequently the FH-CRP study was picked as a "Paper of the Week" at J. Biol. Chem. This status is awarded to about 50-100 papers that are selected from over 6600 published every year in J. Biol. Chem.

Okemefuna, A. I., Stach, L., Rana, S., Ziai Buetas, A. J., Gor, J. & Perkins, S. J. (2010). C-reactive protein exists in an NaCl concentration dependent pentamer-decamer equilibrium in physiological buffer. J. Biol. Chem. **285**, 1041-1052.

Okemefuna, A. I., Nan, R., Miller, A. Gor, J. & Perkins, S. J. (2010) Complement Factor H binds at two independent sites to C-reactive protein in acute-phase concentrations. J. Biol. Chem. **285**, 1053-1065. **"Paper of the Week"**

Steve Perkins

FH + CRP + C3b



Up left: Cover page of the Journal of Biological Chemistry (8 January 2010)

Up right: Zuby Okemefuna receives the poster prize from Helmut Coelfen (Potsdam, Germany: meeting organiser) at the AUC meeting dinner.

Right: Schematic cartoon of a proposed mechanism of action of wild type Tyr402 FH (green) binding to CRP (blue) on damaged host cell surfaces. The double CRP binding site is postulated to position FH appropriately on host cell surfaces for regulatory activity against complement C3b. The His402 polymorphic form (which is a risk factor for AMD) binds less well to CRP and FH is less able to regulate C3b. Taken from the "Paper of the Week".



Key Research Paper Selected

Finn Werner and his research group have recently published a paper which has been selected by the 'Faculty of 1000 Biology' for its originality and important contribution to the field. The paper by Dina Grohmann, Angela Hirtreiter and Finn is entitled 'RNAP subunits F/E (RPB4/7) are stably associated with archaeal RNA polymerase: using fluorescence anisotropy to monitor RNAP assembly in vitro'. (see Grohmann D, Hirtreiter A, Werner F, *Biochem J* 2009 Aug 1 421(3):339-43)

ISMB Featured articles and commentaries

Commentary available for reading at www.ismb.lon.ac.uk/commentary.html

Chandran V, Fronzes R, Duquerroy S, Cronin N, Navaza J and Waksman, G. Structure of the outer membrane complex of a type IV secretion system. *Nature* (2009). 462:1011-1015. Doi 10.1038/nature08588

UPDATE ON CENTRES & LABORATORIES

UCL ChemiBank

Paul Gane, Steve Caddick, James Baker, David Selwood

UCL ChemiBank is a new resource for identifying small molecule ligands for proteins. The facility stores complete chemical libraries and compound collections in a controlled environment. A range of chemoinformatic and biological assay services is provided for early drug discovery projects and to further existing projects in lead selection and library design. Chemibank's main aim is to enable small molecule ligand discovery for UCL's research community.

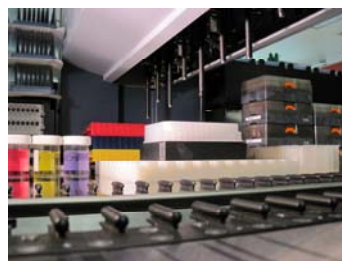


Our chemical libraries include:

- 30,000 ASINEX compounds
 - 500 Maybridge fragments
 - 300 channel selective compounds
 - more than 2,000 specialist compounds
- from the UCL Department of Chemistry

UCL ChemiBank's main focus is the early discovery of hits using the tools of virtual screening such as docking, pharmacophore filtering and *de novo* fragment building. To accompany the chemoinformatics, UCL ChemiBank can provide a number of other services such as:

- Biological assay development and screening
- sequence searching, alignments, binding site analysis
- G-protein coupled receptor modelling
- Electrostatics, molecular dynamics
- property profiling, quantitative structure-activity relationships



From virtual to real discovery, the UCL ChemiBank facility will prepare chemical libraries and develop the biological assays for compound screening. UCL Chemibank, which is located in the Wolfson Institute for Biomedical Research, is available as a resource for UCL and affiliated institutes.

Chemibank was established with funding from MRC and UCL business. Support services are provided by The Wolfson Institute for Biomedical Research, scientific support.

Contact: Dr Paul Gane, UCL Chemibank, p.gane@ucl.ac.uk



The X-ray Facility, Birkbeck, ISMB

The ethos of the X-ray Facility is to provide end-users with a complete service commencing with a purified macromolecular sample and completing with an X-ray structure.

We provide a robotic platform currently comprising a PE MultiProbe II liquid-handler and a Mosquito nanodispenser to enable efficient screening of several hundred crystallization conditions with a minimum of initial sample. Initial screening is carried using our central repository of 96 well 2ml deepwell blocks comprising screens suitable for soluble proteins, membrane proteins, multi-protein complexes, nucleic acid and protein/nucleic acid complexes. Optimization of initial crystal conditions can be carried out by setting up screens around initial conditions with the MultiProbe II liquid handler. We also provide several optimization screens and the facility to use seeding techniques in conjunction with the Mosquito robot.

Once good quality crystals are obtained we are equipped with a completely integrated X-ray diffraction system for optimal performance including generator, optic, detector, software and crystal cryo-cooling. Our system is the Rigaku RA-Micro7 HFM tabletop rotating anode X-ray generator with uses a Cu rotating anode to provide an X-ray beam with an effective focal spot size of 0.07 mm in diameter achieving ultrahigh power (1.2 kW output) and 31 kW/mm² brilliance.

Once initial screening of diffraction quality is carried out in-house we provide the option of collecting in-

house where suitable or booking synchrotron beamtime.

We are currently members of BAG proposals for Diamond, ESRF and Soleil synchrotron sources.



Figure 1: Microfocus source in-house diffraction system comprising 007 rotating anode generator, Confocal Max-Flux variable dispersive optic, CCD detector mounted on quarter chi goniometer with cryo-cooling device.

The X-ray Facility is actively undergoing a complete refurbishment to relocate all services to a single location and upgrade equipment

All enquires about the service provide by the X-ray Facility should be made to the Facility Manager, Dr Nora Cronin (n.cronin@bbk.ac.uk)

Nora Cronin

FAREWELL TO...

Retirement of Professor David Saggerson



David Saggerson, Professor of Biochemistry in the Research Department of Structural and Molecular Biology, announced his retirement from UCL after 47 years of distinguished service with the college.

David joined UCL as an undergraduate in 1962 and has continued his academic career here ever since. David was awarded a first class degree in Biochemistry in 1965 and went on to complete his PhD in 1969. He was later awarded a DSc in recognition of his extensive contribution to UCL in 1980. Professor Saggerson served as Vice-Dean in the Faculty of Life Sciences from 1990 to 1994, Deputy Head of Department of the former Biochemistry and Molecular Biology Department from 1995 to 2001, and Head of Department from 2001 until 2006.

David has authored over 160 refereed publications, supervised 30 PhD students and served on numerous committees and exam boards at UCL. He has also served as a member of many significant groups outside of UCL including the University of London Senate and the University of London Medical Studies Committee. He is currently a member of the Medical Research Council's Panel of Experts.

A very well-attended reception was held in the Wilkins Old Refectory at UCL on 6th November 2009 to mark David's retirement. Gabriel Waksman thanked David for his tremendous contributions to UCL, and David responded in his usual humour with a remarkable list of reminiscences of life in the Darwin Building.



AWARDS, PRIZES & GRANTS

'Stress Busters' win Silver Medal at 2009 iGEM competition

This year the first UCL team ever to participate in the International Genetically Engineered Machine Competition (iGEM) have won a Silver Medal. The team of three students from UCL was composed of one final year biochemists, Xiang Chen, from Structural and Molecular Biology and two Biochemical Engineering students, Anike Akinrinlade and Axel Nystrom. They competed with 110 other teams from all over the world and their success is even more stunning when one considers that the majority of teams often have 10-40 students.

The UCL iGEM team named themselves the 'Stress Busters' (http://2009.igem.org/Team:UCL_London) and they designed *in vivo* detectors of stress for *E. coli* that could monitor and report on shear stress and pH stress in real time for cells growing in fermenters. They have submitted several new BioBricks to the BioBrick registry. They divided their time between John Wards lab on the ground floor in SMB for their molecular biology work and the Advanced Centre for Biochemical Engineering for their fermentations. Dr Darren Nesbeth helped them in the lab and Darren has recently given up his position as a postdoc supervised by John Ward and Eli Keshavarz-Moore (Biochemical Engineering) to become the first Lecturer in Synthetic Biology in the Biochemical Engineering Department, UCL.



Xiang Chen, Anike Akinrinlade and Axel Nystrom

What is iGEM?

iGEM stands for International Genetically Engineered Machines and is an undergraduate Synthetic Biology competition that has now been running since 2003. Students have access to the toolkit of biological parts at the Registry of Standard Biological Parts (http://partsregistry.org/Main_Page) and are encouraged to construct new parts, called BioBricks, to add to the repository. The iGEM teams have from January till September to plan, design and implement their project. All the teams from around the world then present their projects at the iGEM Jamboree in MIT, USA in November (http://2009.igem.org/Main_Page)

Well Done 'Stress Busters' and all who helped aided and assisted.

John Ward

Grants applications - Deadlines

Funding body	Funding opportunities	Deadlines
BBSRC	Responsive Research Grants	14 April 2010
Wellcome Trust		Applications invited at any time
MRC Research board	Molecular and Cellular Medicine	4 pm on 20 January 2010
	Infections and Immunity	4 pm on 27 January 2010
MRC	Career development award	29 January 2010
EPSRC	Responsive Research grants	Applications invited at any time
Royal Society	Dorothy Hodgkin Fellowships	20 January 2010
	International Travel Grants	1 February 2010
	Newton International Fellowships	08 February 2010
Royal Society of Chemistry	Small Awards and prizes	31 January 2010
Leverhulme Trust	Emeritus Fellowships	2 February 2010



UPCOMING EVENTS

ISMB Seminar Hartmut Oschkinat, University of Berlin 'Structural Investigations on AlphaB Crystallin Oligomers by Solid-State NMR and SAXS'	2nd February 2010
ISMB Seminar Bernd Bukau, ZMBH, University of Heidelberg 'Action of molecular chaperones in protein quality control'	10 February 2010
ISMB Seminar Judith Frydman, Stanford University 'Molecular Origami: protein folding and misfolding in the eukaryotic cytosol'	17 February 2010
ISMB Seminar Johannes Buchner, TU Munich, Germany 'The dynamics and regulation of molecular chaperones'	24 February 2010
ISMB Seminar Roland Beckman, Gene Centre, University of Munich, Germany 'Cryo-EM studies of ribosome nascent chain complexes'	3rd March 2010
ISMB Seminar Ineke Braakman, Utrecht University Title to be confirmed	10 March 2010
LSBC meeting	23 March 2010
ISMB Symposium *** Registration open! *** Venue: Christopher Ingold Auditorium , Christopher Ingold Building, UCL Chemistry The symposium is free to attend and all are welcome but places are limited. To register please send an email to Andrew Service at a.service@mail.cryst.bbk.ac.uk , mentioning your name, institution and department. Please see the programme on page 8 of this newsletter. It is also available at http://www.ismb.lon.ac.uk/symposium.html	17 & 18 June 2010

More ISMB news on <http://www.ismb.lon.ac.uk/news.html>

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>





ISMB Symposium 2010

17-18 June 2010 - Final programme

Structural biology programme

Wolfgang Baumeister (Max-Planck-Institute of Biochemistry, Germany)

John Christodoulou (ISMB)

Laurence Pearl (University of Sussex, UK)

Chemical biology programme

Gregory Verdine (Harvard University, USA)

Derek Macmillan (ISMB)

Ben Davis (Oxford University, UK)

Biophysics programme

Steve Block (Stanford University, USA)

Mark Williams (ISMB)

Sheena Radford (Leeds University, UK)

Computational Biology programme

Andrej Sali (UCSF, USA)

Andrew Martin (ISMB)

Mark Sansom (Oxford University, UK)