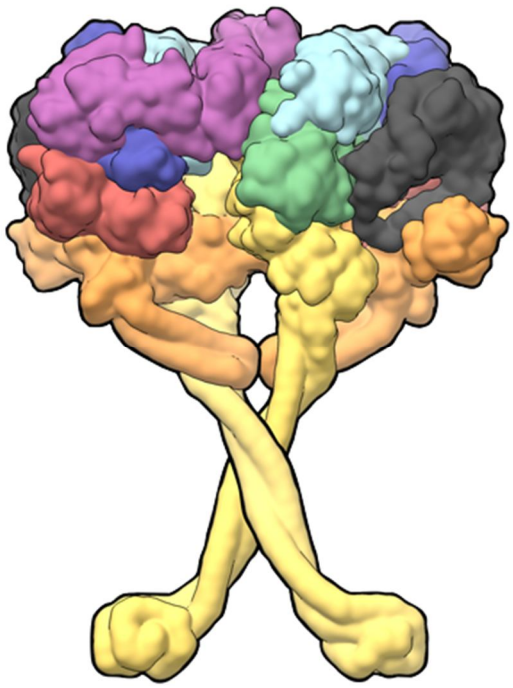
ISMB NEWS

Issue 13, Summer 2017

ISMB NEWS is a news bulletin published 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



Crossed Legs Shut Down Molecular Motor Dynein (see ISMB commentary at http://www.ismb.lon.ac.uk/news.html). Reference: Katerina Toropova, Miroslav Mladenov, Anthony J Roberts (2017) *Intraflagellar transport dynein is autoinhibited by trapping of its mechanical and track-binding elements*. Nature Structural & Molecular Biology doi:10.1038/nsmb.3391

WELCOME TO... FAREWELL TO...

We welcome **Dr Shu Chen**, incoming Electron Microscopy lab manager at Birkbeck – see page 2 for Shu's featured ISMB profile.

Welcome to the following Post-Doctoral Research Associates who have recently joined ISMB lab groups: **Dr Neela Rambaruth** (Prof Snezana Djordjevic's group), **Dr Charlotte Ford** (Dr Richard Hayward's group), **Dr Jesus Gomez** and **Dr Marina Ivanova** (Prof Helen Saibil's group), **Dr Nicole Hartig** (Prof Matilda Katan's group), **Dr Kwasi Kwakwa** (Prof Bart Hoogenboom's group, co-supervised by Dr Alan Lowe and Prof Helen Saibil), **Dr Somnath Mondal** (Dr Flemming Hansen's group), **Dr Ed Parsons** (Prof Bart Hoogenboom's group), **Dr Alejandro Pena** (Prof Carolyn Moores' group), **Dr Chris Penny** (Dr Matthew Gold's group) and **Dr Daniel Richards** (Dr Vijay Chudasama's group).

Farewell to **Dr Maud Dumoux**, microbiology lab manager and previously senior post-doc in Dr Richard Hayward's group, and to the following post-docs: **Dr Adam Cryar** (Prof Gabriel Waksman's group), **Dr Robert Dagil** (Prof Andres Ramos' group), **Dr Natalya Dudkina** (Prof Helen Saibil's group), **Dr Vicky Hale** (Prof Helen Saibil's group), **Dr Ksenia Rhyzenkova** (Prof Elena Orlova's group), **Dr Katherine Smollett** (Prof Finn Werner's group) and **Dr Wenjuan Zhang** (Dr Cara Vaughan's group).

Dr Shu Chen

I joined Birkbeck as the ISMB Electron Microscopy Laboratory Manager in November 2016. I have extensive experience on the development and application of high resolution analytical electron microscopy techniques for the study of interfaces at biology, chemistry and physics.

My post-doctoral work at Imperial College London with Dr Alexandra Porter, Professor Mary Ryan and Professor Milo Shaffer focused on using a combination of state-of-the-art analytical electron microscopy and sample preparation techniques to study the interactions of silver and carbon nanomaterials with pulmonary cells and tissues. The ability to visualize the physicochemical properties change of nanomaterials in cellular environment, using analytic electron microscope at the atomic scale, presents exciting opportunities for understanding nanotoxicity mechanisms and design of effective nano-therapeutics. These projects were highly multidisciplinary and involved close collaborations between international teams of chemists, physicists, biologists and clinicians.

I also have a strong background in carbon, metallic and silica nanomaterials synthesis, modification, characterisation, and bioapplication. I obtained my PhD in Physics and Chemistry from the University of St Andrews with Dr Pascal André and Professor David Cole-Hamilton working on the synthesis, functionalisation and characterisation of magnetic iron platinum alloy nanoparticles for magnetic resonance imaging (MRI) application. At Imperial, I also developed silica based bioactive nanomaterials for selective cancer treatment with Professor Julian Jones.

At the ISMB, I am part of the ISMB Electron Microscopy Laboratory team together with Dr Natasha Lukoyanova, providing research support to users and staff, assisting in facility and safety operations management, as well as conducting research projects. Please get in touch if you want to be part of the "resolution revolution"!

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Dr Shu Chen

Prof Frances Brodsky

My lab group investigates the biochemistry, cell biology and physiological functions of clathrin proteins. In particular, we focus on the molecular basis for clathrin function; clathrin proteins' roles in physiology, including lymphocyte function, glucose metabolism and oncogenesis and potential therapeutic value; the genetic diversity and evolutionary origins of clathrin proteins, and the functional consequences of clathrin subunit diversity. Towards these goals, we employ a range of scientific techniques, including biochemical analysis, protein production and purification, proteomics, tissue culture and cellular assays, electron and confocal light microscopy, physiological models and human and evolutionary genetics.

Clathrin is a self-assembling protein that controls the formation of intracellular transport vesicles required for several key membrane traffic pathways. These include receptor-mediated endocytosis and biogenesis of lysosomes and secretory granules. Thus clathrin plays a critical role in cell growth control, antigen presentation, neuronal function and hormone secretion. Malfunction of clathrin pathways is associated with development of cancer, heart disease and neuronal defects. Clathrin-mediated pathways are also subverted by certain viruses and intracellular bacteria to facilitate their infection. A novel isoform of clathrin (CHC22) that is primarily expressed in skeletal muscle, cardiac muscle and fat was recently characterized by my laboratory. Its tissue-specific function is to package the GLUT4 glucose transporter into intracellular vesicles that are released in response to insulin stimulation, leading to clearance of glucose from the bloodstream. This CHC22 clathrin isoform is therefore associated with pathways that are defective in type 2 diabetes.

I graduated from Harvard University with a degree in Biochemical Sciences in 1976, and received my doctorate from Oxford University under a Marshall Scholarship in 1979. My graduate work with immunologist Sir Walter Bodmer applied the then-novel technology of monoclonal antibodies to study human histocompatability molecules (HLA). I worked as a post-doctoral researcher first with Jack Strominger at Harvard, then with Peter Parham at Stanford University, making the discovery that the clathrin protein controls intracellular transport important for HLA stimulation of immune responses. Joining Becton Dickinson Immunocytometry Systems as a Programme Manager, I ran my own lab for four years and then became an Assistant Professor at University of California, San Francisco (UCSF). I was awarded tenure at UCSF in 1994 and was a full professor until 2014, when I became Professor of Cell Biology and Director of the Division of Biosciences at University College London (UCL). The lab group previously based at UCSF has since fully relocated to London with me.

Studying the remarkable self-assembling clathrin proteins has led us in diverse research directions, crossing interfaces between biochemistry, cell biology, immunology and metabolism. It is exciting and gratifying that our basic molecular studies are now revealing intracellular mechanisms and pathways that are directly relevant to several human diseases including infection, Type 2 Diabetes and cancer.

I have served as a member and chair of numerous boards, study sections, and advisory committees for organisations such as the U.S. National Institutes of Health and the Pew Scholars Program. In 2000, I co-founded the scientific journal Traffic, which specialises in intracellular transport.

[Details of work and papers at https://www.ucl.ac.uk/brodsky-lab]
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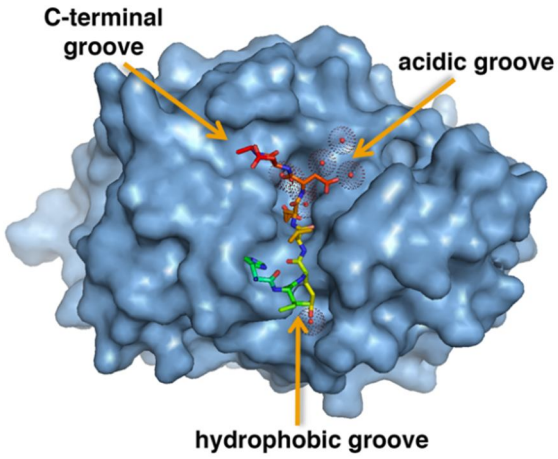
Prof Frances Brodsky

RESEARCH HIGHLIGHTS

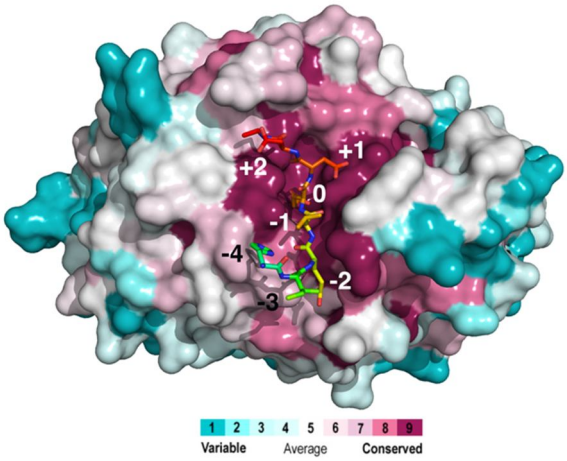
The structure of Protein Phosphatase 5 bound to a substrate reveals determinants of phosphatase specificity

The phospho-protein phosphatase (PPP) family of phosphatases play a central role in cellular signalling, removing the phosphate moiety covalently attached to serine and threonine residues by kinases. Working together with kinases in a tightly regulated and highly specific manner, these enzymes are the molecular switches that turn many signalling pathways in the cell on and off. While specificity of kinases is achieved primarily through numbers (there are more than 500 kinases in the human kinome), serine-threonine phosphatases are an order of magnitude fewer in number, and the PPP family is the largest of these. Their catalytic domains are highly conserved in structure, especially around the catalytic site, and all display high non-specific phosphatase activity. Substrate specificity comes from a large cohort of regulatory proteins that associate with the PPP family members, thereby stringently regulating their function.

The PP5 phosphatase is unique amongst the PPP family because it is auto-inhibited. This auto-inhibition is relieved on association with the molecular chaperone Hsp90. Our previous research showed that Hsp90 targets PP5 phosphatase activity to the Hsp90 cochaperone Cdc37 and that this step is essential for the activation of Hsp90-dependent kinases, which account for ~60% of the kinome. Many of these kinases are central players in the dysregulated signalling that occurs in tumour cells therefore we wanted to elucidate the molecular determinants of Cdc37 dephosphorylation by PP5. To this end we determined the crystal structure of a phosphomimetic peptide of Cdc37 trapped in the catalytic site of PP5. This shows that Cdc37 occupies two of the three arms of a "Y" whose central point lies at the active site. The phosphomimetic residue is deeply buried at this point, coordinating residues and metal ions that are known to be essential for phosphatase activity. The majority of the interactions made between the substrate and the PP5 catalytic domain are with residues of the phosphatase that are conserved, not only within PP5 homologues but also between PPP family members.



Cdc37 occupies two arms of the Y-shaped groove that forms the catalytic cleft in PP5



The exception to this is found at the -2 position in the substrate i.e. 2 residues upstream of the phosphomimetic. This sidechain makes a unique interaction to a PP5 residue that is not conserved in other PPP family members, suggesting that a degree of substrate-specificity is contributed by this interaction. We tested this hypothesis *in vivo* by comparing the affinity of variants of PP5, mutated at this site, for Cdc37 and an unrelated PP5 substrate, glucocorticoid receptor (GR). These results showed that specificity is contributed by this interaction, since mutations that affect the interaction of PP5 with Cdc37 do not alter PP5's interaction with GR.

Taken together this work reveals that PP5 can dephosphorylate a large number of unrelated substrates through an association that predominantly relies on interaction with the substrate backbone, and that while the major part of substrate specificity is provided by the regulatory partner – in this case Hsp90 - the catalytic domain does nevertheless contribute towards substrate specificity. In addition, the fact that the PPP family members have very highly conserved catalytic grooves suggests the tantalising prospect that the PP5-Cdc37 structure is a general template for substrate interactions of the PPP family as a whole, and that other family members might also be able to contribute to their substrate specificity in a similar manner. This in turn may provide clues to help in the design of inhibitors that more efficiently recognise individual PPP family members, something that has been extremely challenging to date.

The surface of the PP5 catalytic domain coloured by conservation amongst PPP family members reveals a poorly conserved pocket in which the -2 sidechain of the substrate is tightly nestled.

Oberoi J, Dunn DM, Woodford MR, Mariotti L, Schulman J, Bourboulia D, Mollapour M, Vaughan CK. (2016) *Structural and functional basis of Protein Phosphatase-5 susbtrate specificity*. PNAS 113(32): p.9009-9014

ISMB Featured Articles and Commentaries

Commentaries on the following articles are available at http://www.ismb.lon.ac.uk/news.html

Sheppard C, Blombach F, Belsom A, Schulz S, Daviter T, Smollett K, Mahieu E, Erdman S, Tinnefeld P, Garrett R, Grohmann D, Rappsilber J, Werner F. (2016) *Repression of RNA polymerase by the archaeo-viral regulator ORF145/RIP*. Nature Communications Nov 24; 7.

Toropova K, Mladenov M, Roberts AJ. (2017) *Intraflagellar transport dynein is autoinhibited by trapping of its mechanical and track-binding elements*. Nature Structural & Molecular Biology May; 24(5): 461-468.

Leung C, Hodel AW, Brennan AJ, Lukoyanova N, Tran S, House CM, Kondos SC, Whisstock JC, Dunstone MA, Trapani JA, Voskoboinik I, Saibil HR, Hoogenboom BW. (2017) *Real-time visualization of perforin nanopore assembly*. Nature Nanotechnology 12: 467-472.

Selected other recent publications

Scott TA, Quintaneiro LM, Norvaisas P, Prudence PL, Wilson MP, Leung KY, Herrera-Dominguez L, Sudiwala S, Pessia A, Clayton PT, Bryson K, Velagapudi V, Mills PB, Typas A, Greene NDE, Cabreiro F.(2017) *Host-Microbe Co-metabolism Dictates Cancer Drug Efficacy in C. elegans*. Cell 169(3): 442-456.

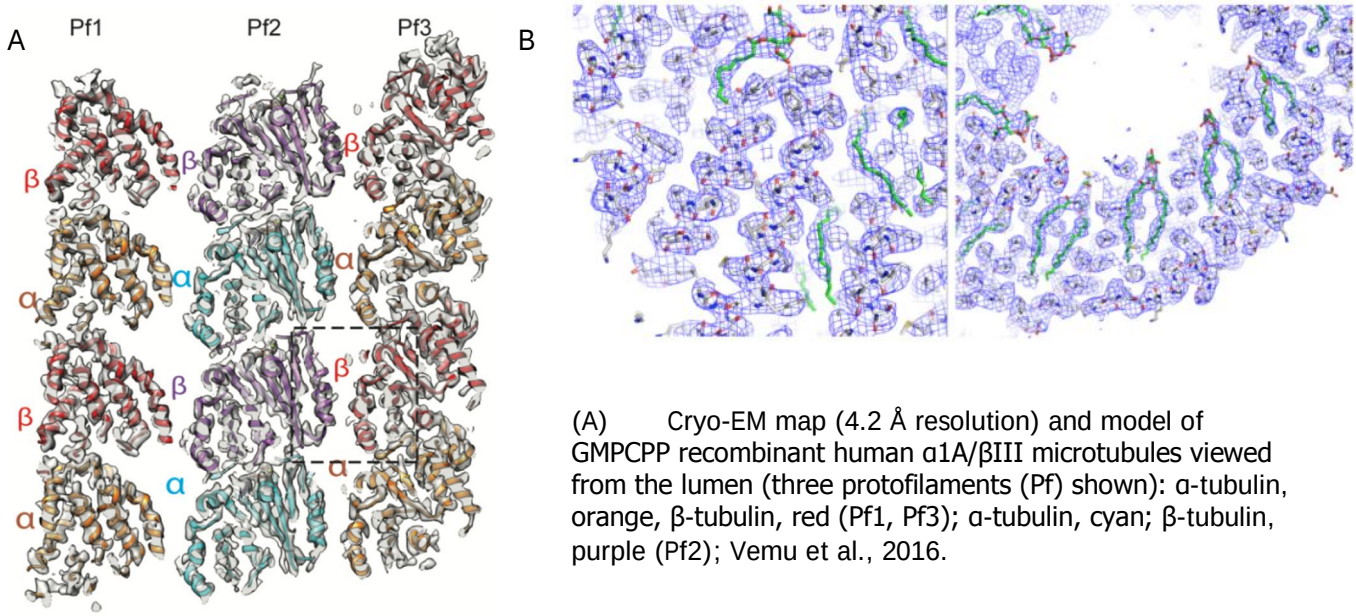
Ilangovan A, Kay CWM, Roier S, El Mkami H, Salvadori E, Zechner EL, Zanetti G, Waksman G. (2017) *Cryo-EM Structure of a Relaxase Reveals the Molecular Basis of DNA Unwinding during Bacterial Conjugation*. Cell 169(4): 708-721.

UPDATE ON CENTRES & LABORATORIES

New cryo-electron microscope in the ISMB

The ISMB has been awarded major funding for a state-of-the-art, 300 kV cryo-electron microscope. The grant, co-funded by the Wellcome Trust was awarded to Prof Helen Saibil, Prof Maya Topf, Dr Giulia Zanetti, Prof Elena Orlova, Prof Carolyn Moores, Prof Mark Marsh, Prof Gregory Towers, Dr Anthony Roberts, Dr Alan Cheung and Prof Gabriel Waksman. This acquisition has also been made possible by a significant investment from Birkbeck and UCL towards the purchase cost of the equipment and for room refurbishment to accommodate the new microscope.

The recent explosion of interest in cryo-electron microscopy (cryo-EM) among structural biologists was triggered by technical advances that have moved it into the front rank of structural and cellular biology methods. Cryo-EM enables imaging of frozen–hydrated specimens in their native state without the need for dyes or fixatives, allowing the study of fine cellular structures, viruses and macromolecular complexes. The hardware and software advances have supported spectacular progress, so that the method is often sufficient to determine structures to atomic resolution, and to sort out conformational variations.
This is therefore a very exciting (and busy) time for the ISMB EM lab. The facility, which was established at Birkbeck by Professor Saibil, is now headed by Professor Moores and incorporates an expanding number of ISMB groups. With our four microscopes, we provide training and expertise for EM sample preparation and visualization. ISMB researchers have recently solved a number of cryo-EM structures to near-atomic resolution (published examples include Costa *et al*., 2016; Vemu *et al.*, 2016).



(A) Cryo-EM map (4.2 Å resolution) and model of GMPCPP recombinant human α1A/βIII microtubules viewed from the lumen (three protofilaments (Pf) shown): α-tubulin, orange, β-tubulin, red (Pf1, Pf3); α-tubulin, cyan; β-tubulin, purple (Pf2); Vemu et al., 2016.

(B) Cryo-EM structure of the bacterial pED208 pilus (3.6 Å resolution): the electron density map is shown in wire representation colored in blue, the pED208 TraA model is in stick representation, the lipid model is PG in stick representation. For clarity, two views are provided: one in which the protein structure is clearly apparent (left) and the other where the lipid structure is clearly apparent (right); Costa et al., 2016

The increased interest and dramatic progress in the field have highlighted the need for a substantial upgrade of ISMB EM facilities in parallel with the expansion of the national facility at Diamond. The new microscope will provide cutting-edge, high throughput performance for analysis of single particles and cellular assemblies. We anticipate it will have a transformative impact on the ISMB EM lab – building on our accumulated expertise, the facility will enhance our support to scientists in ISMB who seeking to address important research questions using cryo-EM.

Dr Natalya Lukoyanova

STUDENT NEWS

Dr Victoria Hale, former PhD student and ISSF Fellow with Prof Helen Saibil and now post-doc at the MRC laboratory of Molecular Biology, recently published the following paper on Malaria-infected blood cells: Hale VL, Watermeyer JM, Hackett F, Vizcay-Barrena G, van Ooij, Thomas JA, Spink MC, Harkiolaki M, Duke E, Fleck RA, Blackman MJ, Saibil HR. (2017) *Parasitophorous vacuole poration precedes its rupture and rapid host erythrocyte cytoskeleton collapse in Plasmodium falciparum egress*. PNAS: 114 (13), 3439–3444.

Vicky is also a keen cake baker – one of her creations is pictured below.

Prizes Awarded

Congratulations to Max Lee and Joao Noguiera from Dr Vijay Chudasama's group for winning 1st prizes for their poster presentations at the RSC Organic Division Poster Symposium and EPSRC i-sense conference, respectively.

Congratulations to Monisha Shaik (an MRes Microbiology student at the ISMB-Mycobacteria Research Laboratory) on winning best poster presentation award on Day 3 of the international TB Summit 2016 organised by EuroSciCon. A report for the meeting has been published (open public access) in *Virulence* 2016; 4:1-20 where Monisha is an author.

Congratulations to Claudia Hinze, Fiona Shilliday and Jennifer Booker and who won prizes for Best 3rd Year Talk, Best 1st Year Talk and Best Poster presentation respectively at the 2017 ISMB Postgraduate Symposium that took place on 13th and 14th June.

Cake representing a Malaria-infected red blood cell, by Vicky Hale

AWARDS, PRIZES & GRANTS

Congratulations to Professor Bart Hoogenboom on being awarded a Royal Microscopial Society (RMS) Medal for outstanding progress in the field of scanning probe microscopy.
Professor Hoogenboom is recognised for the development and application of scanning probe microscopy to a wide range of scientific areas throughout his research career, for his group's development of AFM methodology and data analysis to probe inside the channel of nuclear pore complexes and its starting of a programme of real time imaging of membrane degradation of antimicrobial peptides and pore forming proteins, and for his pivotal role in setting up the LCN.
Professor Hoogenboom will be presented with the medal and will give a talk at mmc2017, the Microscience Microscopy Congress which takes place in Manchester from 3-6 July 2017.

Congratulations to Dr Andrew Martin on his appointment to the WHO INN committee. The World Health Organization (WHO) International Nonproprietary Names (INN) committee provides unique generic names for drugs that are globally recognized and are public property. Dr Martin has been appointed to the INN expert committee to advise on the naming of antibody-based drugs and on the documentation of the structure of the drugs.

Congratulations to Professor Helen Saibil, who has been conferred an honorary doctorate from the Faculty of Philosphy of the University of Helsinki.
The doctorate is in recognition of Professor Saibil's research having focused on "three major areas relevant to Helsinki University: the mechanisms of protein folding, unfolding and aggregation, host-parasite interactions in malaria and chlamydia, and the formation of membrane attack complexes". Professor Saibil received the doctorate at a Conferment Ceremony in May 2017.

Congratulations to Professor Bonnie Wallace on joining the Biotechnology and Biological Sciences Research Council (BBSRC) Pool of Experts. Members of the pool help to assess research grant proposals and identify the highest quality research for investment.

Recently awarded grants

Funding Body	Awardee/s	Details
BBSRC	Prof Christine Orengo	Awarded £104,715 from September 2017 for 12 months for the research project *FunPDBe - Community driven enrichment of PDB data with structural and functional annotations*.
BBSRC	Dr Anthony Roberts	New Investigator award of £433,701 over 3 years with one PDRA for the research project *Dissecting the Molecular Mechanism of Intraflagellar Transport Motors*.
BBSRC	Prof Bonnie Wallace	Awarded £920,070 over 5 years with funding for 2 PDRAs.
ERC	Prof David Jones	Advanced Grant of €2,433,679 over 5 years for the project *ProCovar: Exploring new applications of amino acid covariation analysis in modelling proteins and their complexes*
MRC	Prof Helen Saibil	Awarded £552,077 over 3 years with one PDRA.
Wellcome Trust	Prof Helen Saibil et al	Awarded two grants totalling £3,340,000 over 5 years for the acquisition of a new cryo electron microscope for high-resolution single particle analysis (see *New cryo-electron microscope in the ISMB,* page 6).

Grants applications – upcoming deadlines

Funding body	Funding opportunities	Deadlines
BBSRC	Responsive Mode Research Grants	Call open - next deadline: 4pm, 4th October 2017 through Je-S.
EPSRC	Fellowships	Applications can be submitted at any time through Je-S.
EPSRC	*Manufacturing the future: Call for investigator-led research projects*	Invitation for proposals. Deadline for 2017 consideration: 4pm, 31st July 2017 through Je-S.
EPSRC	*Very- and Ultra-High Field NMR for the physical and life sciences*	Invitation for proposals. Deadline for expression of intention to apply: 11th August 2017, deadline for proposals: 19th September 2017 through Je-S.
Wellcome Trust	Investigator Awards	July 2017 round deadline 27th July, through Wellcome Trust Grant Tracker (WTGT).
Wellcome Trust	Seed Awards	July 2017 round deadline 3rd July, through WTGT.

UPCOMING EVENTS

2017 ISMB Retreat	The ISMB's 7th Biennial Retreat will take place on **Thursday 29th and Friday 30th June 2017** at Robinson College, Cambridge. The confirmed programme of speakers is available at http://www.ismb.lon.ac.uk/retreat.html.
Autumn 2017 ISMB Seminars and Friday Wraps	A new series of ISMB seminars and a new programme of ISMB Friday Wraps will begin in **October 2017**, taking place on Wednesdays and Fridays respectively. Full details will be announced on the following pages of the ISMB website: ISMB Seminars: http://www.ismb.lon.ac.uk/seminar.html ISMB Friday Wraps: http://www.ismb.lon.ac.uk/fridaywrap.html
2017/18 London Structural Biology Club (LSBC) meetings	The 2017/18 meeting dates of the LSBC have been announced: Autumn: **Tuesday, 21st November 2017**, 3-6pm Spring: **Tuesday, 6th March 2018**, 3-6pm Summer: **Tuesday, 19th June 2018**, 3-6pm All will take place in Room B62/3, Birkbeck. Further details will be announced nearer to the time of each meeting.

News items are added monthly to the ISMB news page: www.ismb.lon.ac.uk/news
Please email items of news to the ISMB Administrator (Andrew Service): ismb-admin@ismb.lon.ac.uk.