FONDATION LOUIS-JEANTET

2018 LOUIS-JEANTET SYMPOSIUM

09 October 2018
Centre Medical Universitaire (CMU), Geneva
Auditorium 250

Richard Henderson

MRC Laboratory of Molecular Biology, Cambridge

Tuesday, 09 October 2018, 09:00 – 09:30

Electron cryomicroscopy: theory and practice

In the last few years, single particle electron cryomicroscopy (cryoEM) has experienced a quantum leap in its capability, due to improved electron microscopes, better detectors and better software, and this is revolutionising structural biology. Using the technique invented by Jacques Dubochet and his colleagues, a thin film containing a suspension of the macromolecules of interest is plunge-frozen into liquid ethane at liquid nitrogen temperature, creating a frozen sample in which individual images of the structures can be seen in many different orientations. Subsequent computer-based image analysis is then used to determine the three-dimensional structure, frequently at near-atomic resolution. I will describe some recent results and discuss remaining barriers to progress. CryoEM is already a very powerful method, but there are still many improvements that can be made before the approach reaches its theoretical limits. There is always a gap between theory and practice, but this is getting narrower.

Biography

Richard Henderson is a structural biologist, with a background in physics. His research trajectory began with protein crystallography using X-ray diffraction, then electron crystallography especially on bacteriorhodopsin, and most recently single particle electron cryomicroscopy (cryoEM). CryoEM has now reached the stage where it is possible to obtain atomic structures of a wide variety of macromolecular complexes routinely without crystals. He is now focused on understanding the remaining problems in cryoEM that need to be solved to make the method reach its theoretical potential.

http://www2.mrc-lmb.cam.ac.uk/groups/rh15/

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09 October 2018
Centre Medical Universitaire (CMU), Geneva
Auditorium 250

Nenad Ban

Institute of Molecular Biology and Biophysics, ETH, Zürich

Tuesday, 09 October 2018, 09:30 – 10:00

Protein synthesis: from ribosome assembly to targeting of membrane proteins

We are investigating bacterial and eukaryotic ribosomes and their functional complexes to obtain insights into the process of protein synthesis. Building on our studies of bacterial ribosomes we have increasingly shifted our attention to studying eukaryotic cytosolic and mitochondrial translation and were successful in obtaining first insights into the atomic structures of eukaryotic and mammalian mitochondrial ribosomes (1-3), which pose a significant challenge for structural studies as they are more complex and heterogeneous than their bacterial counterparts. The focus of our research has been to understand eukaryotic translation initiation, targeting of proteins to membranes, regulation of protein synthesis, and the assembly of eukaryotic ribosomes (4-6). The complete molecular structure of the unusual mammalian mitochondrial ribosome specialized for synthesis of membrane proteins was one of the first examples of electron microscopic structure determinations that allowed de-novo building, refinement and validation of the structure. These results revealed the interactions between tRNA and mRNA in the decoding centre, the peptidyl transferase center, and the path of the nascent polypeptide through the idiosyncratic tunnel of the mammalian mitochondrial ribosome. Furthermore, the structure suggests a mechanism of how mitochondrial ribosomes, specialized for the synthesis of membrane proteins, are attached to membranes (3).

1. Rabl J, Leibundgut M, Sandro F. Ataide SF, Haag A and Ban N. (2010) Nature 331(6018):730-6.
2. Klinge S, Voigts-Hoffmann F, Leibundgut M, Arpagaus S, Ban N. (2011) Science, 334, 941-8.
3. Greber BJ, Bieri P, et al. (2015) Science. 348(6232):303-8.
4. Erzberger JP et al. (2014) Cell 158(5):1123-35.
5. Greber BJ, et al. (2016) Cell 164(1-2):91-102.
6. Kobayashi K, Jomaa A, et al. (2018) Science. 360(6386):323-327.

Biography

Nenad Ban was educated at the University of Zagreb. He continued with his studies at the University of California at Riverside and at Yale where his research in the laboratory of Thomas Steitz demonstrated that the ribosome is a ribozyme. Since 2000, Nenad Ban is a professor of Structural Molecular Biology at the ETH Zurich. His group provided fundamental insights into the process of protein synthesis in all kingdoms of life through their studies of ribosomes and their functional complexes. Nenad Ban is a member of EMBO, the German Academy of Sciences and the recipient of several prizes.

http://www.bangroup.ethz.ch/

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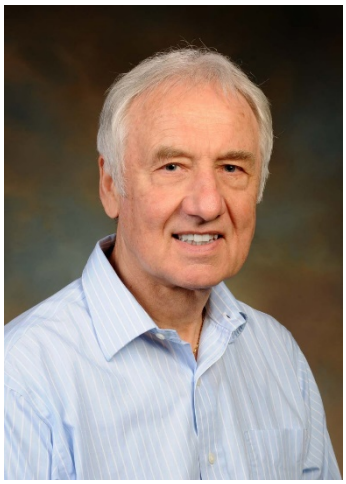

Ian Wilson

The Scripps Research Institute, La Jolla

Tuesday, 09 October 2018, 10:00 – 10:30

Structure-assisted Design of Universal Vaccines and Therapeutics against Influenza Virus

Influenza virus remains a constant threat to global health. The 1918 H1N1 pandemic caused around 50 million deaths worldwide and up to 30-50% mortality in those hospitalized has been reported for recent emerging viruses, such as H5N1 and H7N9. Therefore, there is an urgent need to design much more effective vaccines and therapies to protect against the multiple subtypes and types of influenza virus. It was previously thought that antibodies to influenza virus were strain-specific and could protect only against highly related strains within the same subtype. However, since 2008, many potent human antibodies have been isolated that target the hemagglutinin glycoprotein (HA) and are much broader in their neutralization of influenza virus. We have determined crystal structures of a number of these broadly neutralizing human antibodies (bnAbs) and shown that they target the highly conserved functional sites on the HA: fusion domain (stem) and receptor binding site (head). These structures have revealed common motifs for HA recognition despite different antibody origins and germlines. This information has been utilized in design of vaccine immunogens as well as small proteins, peptides and small molecules as potential therapeutics that target these functional sites. This structural and functional information of human bnAbs against the HA is now providing exciting new opportunities for design of novel vaccines and therapeutics that afford greater protection against influenza virus.

Biography

Prof. Wilson received a B.Sc. from Edinburgh University, D. Phil. from Oxford University, and a D.Sc. from Oxford University. He has been on the faculty at The Scripps Research Institute since 1982 and is Hansen Professor of Structural Biology and Chair of the Department of Integrative Structural and Computational Biology. His laboratory studies the structural basis of immune recognition of microbial pathogens by the adaptive and innate immune systems. His current focus is on broadly neutralizing antibodies to HIV-1, influenza virus, HCV, and P. falciparum, to inform on design of novel vaccines and therapeutics.

https://wilson.scripps.edu/

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Auditorium 250

Matthias Mann

Max-Planck Institute of Biochemistry, Munich and Novo Nordisk Foundation Center for Protein Research, Copenhagen

Tuesday, 09 October 2018, 11:00 – 11:30

Proteomics for biological mechanisms and translational research

Mass spectrometry (MS)-based proteomics has become a standard and essential method in nearly every branch of biology. It offers an increasingly sophisticated toolbox of approaches and technologies for a wide variety of biological questions. Our group is particularly interested in the large scale characterization of cell signaling events, such as phosphorylation, ubiquitilyation and many other post-translational modifications. We have developed and applied the 'EasyPhos' to study complex signaling events in vivo and we have used it to uncover the long sought substrates of the Parkinson's kinase LRRK2. It has also revealed that a large percentage of the phospho-proteome is coordinately regulated during the day and night cycle, and that many of the target sites appear to fine tune the metabolic machinery. Recently, we have used EasyPhos to unravel signaling events downstream of opioid receptors in the brain in the context of analgesia and addiction. This knowledge can be used to selectively ablate the undesired signaling effects. I will also describe a multi-layered proteomics approach to discover a new biomarker in ovarian cancer that correlates with long term survival after chemotherapy. We use proteomics together with cell biological follow-up – especially DNA damage assays – to reveal the mechanism of action of this novel protein.
The plasma proteome can potentially be used to directly measure 'phenotype' of individuals with minimally invasive procedures. However, the high dynamic range – along with other challenges – have long stymied this otherwise attractive approach. We have recently revisited this area using the latest technological advances. Plasma proteome profiling approach allows us to study the plasma proteome rapidly in a wide range of conditions. We have now increased the protein coverage several-fold using a novel scan mode termed BoxCar and applied our workflow to a number of clinical studies. These will be described in the talk together with a perspective of how plasma proteome profiling could be implemented in the clinic.

Biography

Matthias Mann studied physics and mathematics at Göttingen University in Germany and obtained his Ph.D. in chemical engineering at Yale University. He was professor for bioinformatics at the University of Southern Denmark in Odense before taking up, in 2005, a director position at the Max-Planck Institute of Biochemistry in Munich. In 2009 he was additionally appointed director of the proteomics program of the Novo Nordisk Foundation Center for Protein Research in Copenhagen.

http://www.biochem.mpg.de/en/rd/mann
https://www.cpr.ku.dk/research/proteomics/mann-group

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09 October 2018
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Paola Picotti

Institute of Molecular Systems Biology, ETH, Zürich

Tuesday, 09 October 2018, 11:30 – 12:00

Probing protein structural changes on a proteome-wide scale

Protein structural changes induced by external perturbations or internal cues can profoundly influence protein activity and thus modulate cellular physiology. Mass spectrometry (MS)-based proteomic techniques are routinely used to measure changes in protein abundance, post-translational modification and protein interactors, but much less is known about protein structural changes. In my talk, I will present a recently developed structural proteomics method that enables analysis of protein structural changes on a proteome-wide scale and directly in complex biological extracts. The approach relies on the coupling of limited proteolysis (LiP) tools and MS. LiP-MS can detect subtle alterations in secondary structure content, larger scale movements such as domain motions, and more pronounced transitions such as the switch between folded and unfolded states. I will describe how we are applying this approach to study the molecular bases of protein aggregation diseases. I will also describe other applications of the technique such as the identification of protein-small molecule interactions (e.g. drug targets) and the analysis of proteome thermostability. Last, I will discuss the power and limitations of the new approach.

Biography

After her PhD at the University of Padua (Italy), Paola Picotti joined as a postdoc the group of Ruedi Aebersold at ETH Zurich, where she developed targeted proteomic technologies based on mass spectrometry. In 2011, she was appointed Assistant Professor at the Institute of Biochemistry of ETHZ and in 2017 tenured Professor at the Institute of Molecular Systems Biology at ETHZ. Major contributions of the Picotti group include the development of structural proteomics technologies to probe in situ protein structural changes. Dr. Picotti was awarded the Latsis Prize, the Cotter Award of the US HUPO, the SGMS award, the EMBO Young Investigator Award, the Friedrich Miescher Award, the Juan-Pablo Albar award of the European Proteome Association and an ERC Starting Grant.

http://www.imsb.ethz.ch/research/picotti.html

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Carol Robinson

University of Oxford

Tuesday, 09 October 2018, 12:00 – 12:30

Membrane proteins - the lipid connection

The realisation that the lipid environment is crucial for maintaining the structure and function of membrane proteins prompts new methods to understand lipid interactions. One such method, mass spectrometry, is emerging with the potential to monitor different modes of lipid binding to membrane protein complexes. Initial studies monitored the addition of lipids and deduced the kinetic and thermodynamic effects of lipid binding to proteins. Recently however, we have focused on identifying lipids already present, explicitly in plugs, annular rings or cavities. Lipids that bind within these orifices to membrane proteins will have higher residence times than those in the bulk lipid bilayer and consequently can be quantified and characterized by mass spectrometry. In special cases, lipids identified within cavities have been proposed as substrates following activity assays. Alternatively, a gas phase unfolding protocol can be used to distinguish lipids that are important for stability. In this lecture I will provide an overview of recent advances in mass spectrometry, with a particular focus on the distinction of the various modes of lipid binding, their implications for structure and function, as well as new directions that lie ahead.

Biography

Professor Dame Carol Robinson holds the Chair of Dr. Lee's Professor of Chemistry at the University of Oxford. She is recognised for using mass spectrometry to further her research into the 3D structure of proteins and their complexes. Recent highlights from her work include the discovery that membrane protein complexes can be liberated from micelles in the gas phase while retaining their subunits interactions, lipid binding properties and overall topology. Carol is a Fellow of the Royal Society, President Elect of the Royal Society of Chemistry and a foreign associate of the National Academy of Sciences USA.

http://robinsonweb.chem.ox.ac.uk/Default.aspx

2018 LOUIS-JEANTET SYMPOSIUM

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Centre Medical Universitaire (CMU), Geneva
Auditorium 250

Chuna Choudhary

Novo Nordisk Foundation Center for Protein Research, Copenhagen

Tuesday, 09 October 2018, 13:45 – 14:15

Mass spectrometry for cell signaling: from global maps to new biological insights

The eukaryotic cell signaling system is shaped by two major mechanisms: protein-protein interactions (PPIs) and posttranslational modifications (PTMs). Indeed, these mechanisms provide the 'first line response' to virtually all environmental and internal signals in a cell and form the heart of eukaryotic cellular communication system. The dynamic PPIs and PTMs vastly expand the functional complexity of the proteome. Because these mechanisms impact all proteins and processes in cell, a systematic analysis of PPIs and PTMs is fundamental for understanding the regulatory principles in biology. We use quantitative mass spectrometry to reveal the global scope, mechanisms and dynamics of lysine acetylation. Our latest findings reveal that metazoan-specific acetyltransferase CBP/p300-catalyzed rapid acetylation is an essential regulator of cell-type-specific gene transcription. In another work, we combined quantitative mass spectrometry with proximity biotinylation to obtain a detailed protein-protein interaction map of endogenous DNA repair networks. These analyses discovered the novel protein complex shieldin that protects DNA double-strand breaks and promotes DNA repair by non-homologous end joining. Higher-vertebrate-specific shieldin is required for antibody diversification as well as for clinical sensitivity of BRCA1-deficient tumors to PARP inhibitor therapy. I will discuss these recent findings to highlight the usefulness of quantitative mass spectrometry for a systematic understanding of signaling networks and for revealing new biological insights.

Biography

Dr. Chuna Choudhary is a professor at the NNF Center for Protein Research, University of Copenhagen, Denmark. He carried out his doctoral studies at the University of Muenster and his postdoctoral training at the Max Planck Institute for Biochemistry, Germany. His group combines quantitative proteomics with cell and molecular biology approaches to investigate the dynamics and functions of lysine acetylation and ubiquitylation in cellular signaling networks. Dr. Choudhary has widely published in high-ranked journals and received several honors and awards, including the EMBO Young Investigator award, the Danish Cancer Society Junior Researcher award, and the ERC Consolidator grant.

https://www.cpr.ku.dk/research/proteomics/choudhary/

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Martin Beck

EMBL, Heidelberg

Tuesday, 09 October 2018, 14:15 – 14:45

Structural proteomics of the nuclear transport system

I will present our work on the nucleocytoplasmic transport system. I will discuss how proteomic approaches add an additional dimension to structural biology and are suitable to provide functional context to often static snapshots of protein complexes.

Biography

Martin Beck studied Biochemistry at the Martin Luther University Halle/Wittenberg and has been further trained in the laboratories of Wolfgang Baumeister in Martinsried and Ruedi Aebersold in Zurich. Martin is a group leader and senior scientist at EMBL in Heidelberg. Research in his laboratory combines cryo electron microscopy with quantitative mass spectrometry to study the structure and assembly of protein complexes, with a particular focus on the human nuclear pore complex.

http://www.embl.de/research/units/scb/beck/

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Emma Lundberg

KTH Royal Institute of Technology, Stockholm

Tuesday, 09 October 2018, 14:45 – 15:15

Dissecting the spatiotemporal subcellular distribution of the human proteome

Compartmentalization of biological reactions is an important mechanism to allow multiple cellular reactions to occur in parallel. Resolving the spatial distribution of the human proteome at a subcellular level increases our understanding of human biology and disease. We have generated a high-resolution map of the subcellular distribution of the human proteome as part of the open access Human Protein Atlas database. We have shown that as much as half of all proteins localize to multiple compartments. Such proteins may have context specific functions and 'moonlight' in different parts of the cell, thus increasing the functionality of the proteome and the complexity of the cell from a systems perspective. I will present how this spatial data can complement quantitative omics data for improved functional read-out. Furthermore, I will present unpublished data on the extent of single cell variations of the human proteome, in correlation to cell cycle progression and other deterministic factors, as well as the overlap with observed variations at the RNA level. In summary, I will demonstrate the importance of spatial proteomics data for improved single cell biology.

Biography

Dr. Lundberg is Associate Professor in cell biology proteomics at KTH Royal Institute of Technology, Sweden, and Director of the Cell Atlas, part of the Swedish Human Protein Atlas program. Currently spending a sabbatical year as visiting Associate Professor at Stanford and the Chan-Zuckerberg Biohub. In the interface between bioimaging, proteomics and artificial intelligence my research aims to define the spatiotemporal organization of the human proteome at a subcellular level, with the goal to understand how variations and deviations in protein expression patterns can contribute to cellular function and disease.

https://www.scilifelab.se/researchers/emma-lundberg/

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Auditorium 250

Frederic Allain

Institute of Molecular Biology and Biophysics, ETH, Zürich

Tuesday, 09 October 2018, 15:45 – 16:15

Hybrid structural approaches to solve structures of protein-nucleic acid complexes

Protein-RNA-complexes are central for the regulation of gene expression and thus crucial for cellular function. While solving structures of protein-RNA complex with NMR has been very successful owing to the low affinity of many RNA-protein interactions, the size limitation of the complexes that could be tackled structurally solely by NMR has remained an issue. Using EPR in collaboration with Gunnar Jeschke (ETH Zurich), Mass-spectrometry in collaboration of Ruedi Aebersold (ETH Zurich) and more recently solid-state NMR in collaboration with Beat Meier (ETH Zurich), all in combination with liquid-state NMR, we could investigate the structures of several protein-nucleic acid complexes of size and complexity that we could not be tackled solely with solution-state NMR.

Biography

Prof. Frédéric Allain obtained his doctorate with Dr.G.Varani at the MRC-LMB of Cambridge (1993-1997). Between 1997 and 2000, he was a Postdoctoral Fellow at UCLA with Prof. J.Feigon, followed by one year as Research associate with Prof.D.Black (HHMI). In 2001, Frédéric Allain joined the department of Biology of the ETH in Zürich initially as an assistant Professor and since 2010, he is a full Professor. Prof. Allain's research interest is primarily to determine structures of protein-RNA complexes in order to understand mechanisms of post-transcriptional gene regulation like alternative-splicing, RNA editing and translation regulation. Prof. Allain was elected EMBO member in 2009. Prof. Allain is the co-director of the SNF-NCCR RNA and Disease since 2014.

http://www.allainlab.ethz.ch/

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Auditorium 250

Ichio Shimada

University of Tokyo, Tokyo

Tuesday, 09 October 2018, 16:15 – 16:45

Function-related Dynamics of Membrane Proteins

Membrane proteins play fundamental roles in many physiological processes and are target proteins for drug development. For better understanding of the functions of the membrane proteins, not only precise static three-dimensional structures determined by X-ray crystallography and cryo-electron microscopy methodologies, but also dynamical nature are required. NMR (nuclear magnetic resonance spectroscopy) provides us information about membrane proteins dynamics, including conformation equilibrium related to functions. However, it is frequently difficult to obtain information about the membrane protein dynamics related to the functions, due to the molecular weight limitation in NMR. We have recently developed novel NMR methods for characterizing protein dynamics utilizing multiple quantum relaxation rates of side-chain methyl groups, which can be sensitively observed in high molecular weight proteins. In this paper, we will show our recent results of function-related dynamics of membrane proteins.

Biography

Ichio Shimada is the professor of the University of Tokyo. His research interests are the development of NMR methodologies for larger protein complexes and functional analyses of membrane proteins. He has served as Dean of the Graduate School of Pharmaceutical Sciences, the University of Tokyo. He is currently a council member of The International Council on Magnetic Resonance in Biological Systems (ICMRBS) and The International Society of Magnetic Resonance (ISMAR) and he was elected an ISMAR fellow in 2017, for his contributions to the field of magnetic resonance.

http://ishimada.f.u-tokyo.ac.jp/public_html/

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2018 LOUIS-JEANTET SYMPOSIUM

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Kurt Wüthrich

The Scripps Research Institute, La Jolla
Institute of Molecular Biology and Biophysics, ETH, Zürich

Tuesday, 09 October 2018, 16:45 – 17:15

NMR, Structural Dynamics and Signal Transfer of G protein-coupled Receptors (GPCRs)

There are 826 G protein-coupled receptors (GPCR) in the human proteome, which regulate key physiological processes and have therefore long been attractive as drug targets. With crystal structure determinations of more than 50 different human GPCRs during the last decade, an initial platform for structure-based rational design was established for drugs that target GPCRs. The principal method used for our own research is nuclear magnetic resonance (NMR) spectroscopy in solution, which is one of the key approaches for expanding the crystal structure platform with dynamics features of GPCRs at near-physiological conditions. In this context, it is of special interest that NMR measurements can be performed without modification of the GPCRs by amino acid replacements and/or fusion with other proteins, which is routinely used to facilitate crystallization. In my lecture I describe strategies for the use of NMR techniques with GPCRs, which will be illustrated with projects where results obtained with X-ray crystallography or cryo-electron microscopy (cryo-EM) have been complemented with NMR investigations in solution, and discuss the impact of this integrative approach on GPCR biology and drug discovery.

References

Liu, J.J., Horst, R., Katritch, V., Stevens, R.C. and Wüthrich, K. (2012) Science 335, 1106-1110. Biased signaling pathways in β2-adrenergic receptor characterized by 19F-NMR.

Eddy, M., Lee, M.-Y., Gao, Z.-G., White, K.L., Didenko, T., Horst, R., Audet, M., Stanczak, P., McClary, K.M., Han, G.W., Jacobson, K.A., Stevens, R. and Wüthrich, K. (2018) Cell 172, 68–80. Allosteric coupling of drug binding and intracellular signaling in the A2A adenosine receptor.

Biography

Kurt Wüthrich is the Cecil H. and Ida M. Green Professor of Structural Biology at The Scripps Research Institute, La Jolla, CA, USA, and a Professor of Biophysics at the ETH Zürich, Zürich, Switzerland. His research interests are in structural biology and structural genomics. His specialty is nuclear magnetic resonance (NMR) spectroscopy with biological macromolecules, where he contributed the NMR method of three-dimensional structure determination of proteins and nucleic acids in solution. Kurt Wüthrich's achievements have been recognized by the Prix Louis-Jeantet de Médecine, the Kyoto Prize in Advanced Technology, the Nobel Prize in Chemistry, and by a number of other awards and honorary degrees.

https://www.scripps.edu/wuthrich/
http://www.wuthrich-group.ethz.ch/