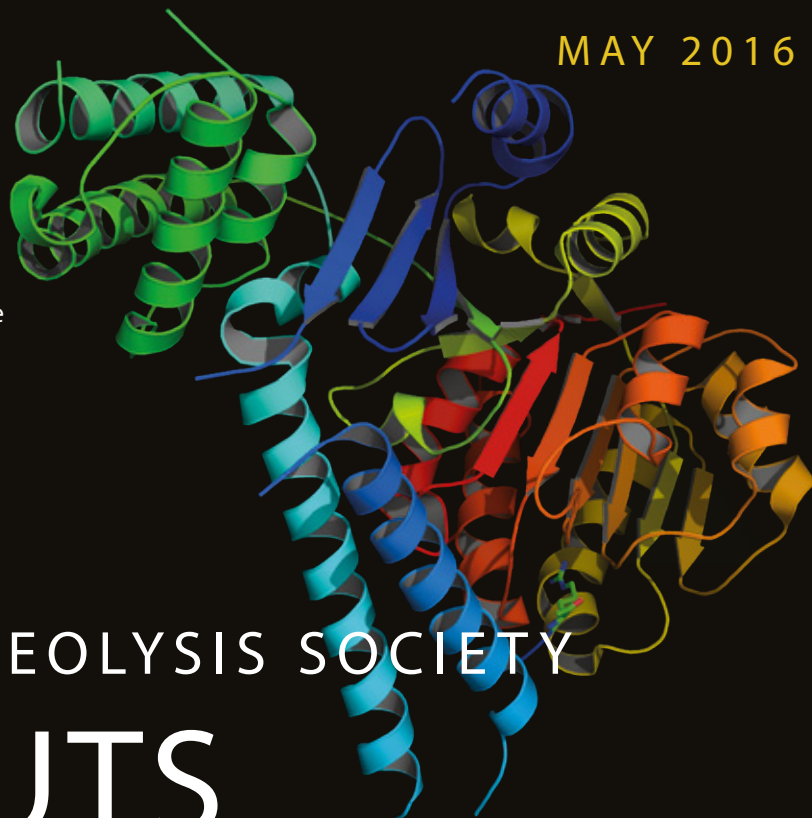


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- Membership Renewal Reminder
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- IPS Lifetime Achievement - Hideaki Nagase
- Meet your new IPS council
- Meeting announcements and Job Listings

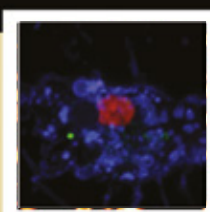


INTERNATIONAL PROTEOLYSIS SOCIETY

QUICKCUTS

Editors:

Sheena McGowan (Monash University)
Margarete Heck (University of Edinburgh)



THE PREMIER RESOURCE
FOR ALL YOUR IMPORTANT PROTEASE QUESTIONS

A Message From the President:

I would like to welcome all new IPS members into the Society! We look forward to your participation and engagement in years to come. I also formally welcome all our new Council members and thank our outgoing council members for their service.

Currently we are still in the aftermath of our 9th General Meeting held at the island of Penang, Malaysia. This issue of QuickCuts will provide various impressions of that meeting. The post conference survey among the participants gave very positive / excellent ratings of the conference in terms of organization, science, and personal interactions. I should also point out that the financial conclusion of the Penang meeting turned out to be safely in the "black". Thus all that is left to me is to congratulate and to thank Judith Clements and her team for organizing this outstanding science event!

Another highlight of the past 6 months was the acquisition of the company Dyax as IPS Gold Sponsor. The credit for bringing in this sponsorship should be given to our former president Bob Lazarus. Thanks Bob! Along this line - IPS needs sponsors! Therefore ideas of whom to contact for possible sponsorships are welcome at ipssecretary@gmail.com. However, besides the sponsors, having active members is equally or even more important for a prosperous scientific society. Please encourage early and late career scientists, which are likely to agree with the mission of IPS, to join our society. All officers are certainly happy to answer any questions.

Personally, I am looking very much forward to meet all IPS members at the 10th General Meeting of the Society held in beautiful Banff, Canada, from Oct. 28th- Nov. 2nd, 2017. Seeing plans for "Frontiers in Proteolysis" emerging, I am sure that Joanne Lemieux and her co-organizers Jean-Bernard Denault and Cristopher Overall will provide us with the right frontier spirit.

In the meantime there will be many more conferences of interest to IPS members. We always try to highlight these in Quick Cuts and on our website (www.protease.org). Please check it out! Please send suggestions or feedback to any of the IPS officers or councilors, especially as we update the website.

Finally I thank Sheena McGowan and Margarete Heck for this issue of Quick Cuts. Enjoy!

Thomas Reinheckel, IPS President Email: thomas.reinheckel@uniklinik-freiburg.de

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Meeting Report

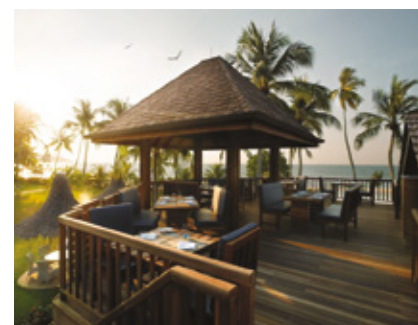
9TH GENERAL MEETING OF THE INTERNATIONAL PROTEOLYSIS SOCIETY

PROTEOLYSIS CONFERENCE IPS 2015



October 4 - 8, 2015 | Golden Sands Hotel Conference Centre, Penang, Malaysia

During the period of 4 – 8 October 2015, delegates from 25 countries travelled to Penang, Malaysia for the 9th General Meeting of the International Proteolysis Society. An early career forum preceded the meeting and provided 37 members-in-training with protease specific training. The Meeting was organised by [Judith Clements \(Translational Research Institute, Queensland University of Technology, Australia\)](#) and included excellent scientific talks, stimulating posters sessions and discussions, and many networking opportunities (over a cocktail by the pool!). Delegates were treated to a South East Asian island paradise (albeit slightly hazy due to smoke pollution) with an abundance of tropical treats!



The 9th General Meeting of the International Proteolysis Society, 3-8 October 2015

The 9th General Meeting of the IPS started on Sunday evening with an outstanding overview by the keynote speaker [Chris Overall \(University of British Columbia, Canada\)](#) on the complexity of proteolysis within both extra-cellular and intracellular environments. The ‘protease web’ became a overarching theme for the meeting with sessions encompassing the study of proteolytic networks both inside and outside the cell. See *selected session highlights in this issue of QuickCuts*. As per one of the IPS missions, the meeting also encouraged collaboration between both academic and industry research. Delegates heard about the latest research from [Genentech](#), [Novo Nordisk](#) and [Novartis](#).

CONTINUED NEXT PAGE ►

Session Highlights

Drug Design and Therapeutic Approaches II

The session started with a tour de force talk by **Holger Sellner (Novartis)** on the production of inhibitors to target two unusual proteases from the alternative pathway of complement in order to provide treatments for age related macular degeneration in particular.

Holger described the efforts of a large team over multiple years to produce effective inhibitors that successfully targeted Factors D and B and thus have strong potential as therapeutic treatments. **Lakshmi Wijeyewickrema (La Trobe University, Australia)** then showed how polyphosphate could act as a novel cofactor for C1-inhibitor-mediated inhibition of the C1s enzyme from the classical pathway of complement and provided new insights into the mechanism whereby



both polyphosphate and heparin could have this cofactor effect for this serpin-enzyme reaction. **Paul Conroy (Monash University, Australia)** then presented on an antibody selected from a library of chicken antibodies to target the prostate-specific antigen (Klk3), a well known marker for prostate cancer. The crystal structures of the complex between the antibody and PSA revealed a novel binding mode and demonstrated that this antibody might have potential as a diagnostic for prostate cancer. **Ashley Buckle (Monash University, Australia)** then presented the structure and functional features of sunflower trypsin analogues that potently inhibited kallikrein-4 and thus might have potential as anticancer compounds. He also showed how metal ions might have strong allosteric effects in this enzyme. **Shahriar Mobashery (Notre Dame University, USA)** showed his work on novel endopeptidases from *Pseudomonas aeruginosa* that cleaved the cell wall of the bacterium to liberate a particular mureopeptide, which stimulates the antibiotic resistance in this bacterium. **Nyssa Drinkwater (Monash University, Australia)** then presented the novel structure of the unusual aminopeptidase from *Plasmodium falciparum* that cleaves before proline residues to liberate amino acids from hemoglobin that are required for the nutrition of the parasite. Due to its vital role for the parasite, these structural data may provide important information that will aid the development of inhibitors of this enzyme to provide new drugs to fight this important parasite. Finally, **Daniel Kirchhofer (Genentech, USA)** showed their data on the selection of a small peptide that bound to the proprotein convertase PCSK9 and prevented its interaction with the LDL receptor. The peptide thereby prevents the PCSK9-mediated internalization of the receptor and thus, retains its presence on cell surfaces to ensure continued clearance of LDL and associated cholesterol. This molecule therefore has the potential to aid in lowering LDL and cholesterol levels in patients at risk of developing heart disease.

Proteolytic networks outside the cell

The Monday morning session on “Proteolytic networks outside the cell”, chaired by **Christian Sommerhoff & Ed Sturrock**, began with **David Granville (Univ. British Columbia, Canada)** who reviewed

recent studies on granzyme B, a protease well known from cytotoxic lymphocyte-induced apoptosis. More recent studies have shown that this protease is also expressed in various other immune and non-immune cells and has extracellular roles, such as contributing to matrix remodeling, impaired wound healing and UV-induced skin aging. To analyze the allosteric regulation of tryptase, a mast cell protease thought to be involved in allergic inflammation, **Henry Maun (Genentech Inc., USA)** used engineered variants to demonstrate that in the enzymatically active tetramer each monomer functions as a cofactor for its neighbours. **Mayland Chang**

(**Univ. Notre Dame, USA**) presented preclinical data showing that the topical application of a small molecule MMP-9 inhibitor and of active recombinant MMP-8 synergistically accelerated wound healing, a novel approach that bears promise as therapeutic strategy for diabetic wounds. **Ruby Law (Monash Univ., Australia)** combined X-ray crystallography and functional studies to analyze the two glycoforms of plasminogen and the interaction of plasmin with small-molecule inhibitors. Finally, **Margarete Heck (Univ. of Edinburgh, UK)** reviewed invadolysin, a zinc-metalloprotease first linked to cell division and migration in *D. melanogaster*, later localized to lipid droplets, and currently studied as a biomarker present in both *Drosophila* hemolymph and vertebrate serum.

“Omics” Systems Biology Approaches to Understanding Protease Function

Kicking off the session, **Christoph Becker-Pauly (Kiel University, Germany)**, demonstrated how Terminal Amine Isotopic Labeling of Substrates (TAILS) helped to identify more than 100 substrates of the metalloprotease meprin β . Based on these degradomics data biochemical analyses, cell based assays, and mouse models validated a fascinating regulatory interaction of meprin β and ADAM10, important for ectodomain shedding and subsequent activation in the small intestine. Here, the activity of soluble meprin β is required for mucus detachment and proper barrier function. **Ulrich auf dem Keller (ETH Zurich, Switzerland)**, introduced a next-generation degradomics workflow that exploits the power of data-independent acquisition mass spectrometry to comprehensively assess proteolytic cleavage events by concomitantly monitoring neo-N, neo-C and cleavage site spanning peptides. The approach was validated with help of canonical cleavage events exerted by GluC, whereby the rich dataset also allowed assessing degrees of substrate processing through

Session Highlights

quantitative analysis of neo-termini and spanning peptides of the same cleavage site. Moreover, the approaches flexible experimental design was demonstrated by analyzing multiple samples from a time course study of kallikrein-5 (KLK5) activity on keratinocyte secretomes that revealed cleavages of known substrates and of novel targets, such as other proteases and growth factor binding proteins with new implications for KLK5 function in the epidermis.

Antoine Dufour (University of British Columbia, Canada), revealed novel intracellular roles of matrix metalloproteinase-12 in breast cancer. 4T1 shMMP12 and 4T1 shControl cell lines were implanted in BALB/c. No differences in tumor growth were observed, but the 4T1 shMMP12 tumors resulted in a lower incidence of lung metastasis, lower angiogenesis and an increased survival post-primary tumor



resection at 21 days. Novel *in vivo* substrates of MMP12 were identified by TAILS and biochemically validated *in vitro* including tumor suppressors involved in dampening the migration and the metastatic potential of breast cancer cells. Treatment of the MMP12 knockdown cells with an inhibitor of the suppressor or rescue experiments by addition of recombinant MMP12, both enhanced cell migration to the same extent. Thus, tumor cell derived MMP12 enhances the cell migration and metastatic potential of breast cancer cells *in vivo* and *in vitro* through the intracellular processing and inactivation of two tumor suppressors, thus decreasing the survival of mice post-tumor resection.

Ruth Fuhrman-Luck (Queensland University of Technology, Australia) combined TAILS with the PROtein TOpography and Migration Analysis Platform (PROTOMAP) to identify 57 novel substrates of the prostate cancer-enriched protease, kallikrein-related peptidase 4 (KLK4), within secretions from prostate cancer and stromal cells. By integrating degradomics analyses with data generated by microarray profiling of KLK4-regulated genes, KLK4 appeared to activate stromal transforming growth factor β (TGF β) signaling and promote fibroblast activation, a process integral for tumor progression. Findings were validated in biochemical and cell-based assays, with potential proteolytic substrate intermediates underway. This study demonstrates the power of combined degradomic and transcriptomic analyses in generating novel data-driven hypotheses regarding protease function, and highlights KLK4 as a promising therapeutic target for prostate cancer. As a first step towards clinical and translational degradomic approaches, **Oliver**

Schilling (University of Freiburg, Germany), investigated proteolytic processing in the progression of Glioblastoma multiforme. Thereby, TAILS identified 100s of affected sites of proteolytic processing, including zymogen activation and ectodomain shedding. To further expand the ability for disease-centric degradomics based on pathological specimens, N-terminomic profiling of formalin-fixed, paraffin-embedded specimens was developed. Lastly, he showed a simplified version of the proteomic identification of protease cleavage sites (PICS) workflow by introducing a straightforward protocol that alleviates the need for affinity enrichment of cleavage precepts.

Why was Penang so hazy?

Unfortunately, the air quality in Malaysia was very poor throughout the meeting. The haze or smoke pollution is a result of annual “burning off” to clear land for palm oil plantations.

Palm oil is a key export for the region and is a source of income and jobs. However, as the delegates of IPS2015 became aware, its impact on air quality is severe and poses serious health problems for plantation works and people throughout Southeast Asia! Officially, the practise has been banned in both Malaysia and Indonesia but this has not practically stopped the problem. The production of palm oil is an environmental disaster not only for air quality but also for the tropical forests and biodiversity that is lost when the land is cleared for these plantations. If you want to help Southeast Asia, then only buy products that use sustainable palm oil! For more information, check out http://wwf.panda.org/what_we_do/footprint/agriculture/palm_oil/.

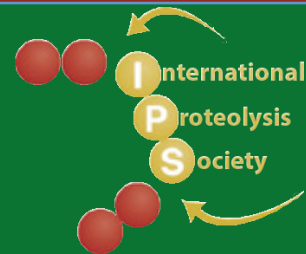


Meeting Report

Ninth General Meeting of the International Proteolysis Society

EARLY CAREER FORUM

3-4 October, 2015



The Oceania meeting location presented a conundrum for the much loved training workshops of the General Meeting. There just wasn't a university on the island that could be used for the 'hands on' workshops! Therefore, the 9th General Meeting had a non-traditional 'Early Career Forum' that incorporated 'dry' training workshops, professional development sessions and a chance for our younger researchers and members-in-training to present their research. Starting one day before the General Meeting, the Early Career Forum had 35 attendees from 15 countries who selected relevant training workshops to attend, who heard from Bob Lazarus (Genentech Inc, USA) on his journey through an industry-based career and attended two scientific sessions. The IPS2015 committee gratefully acknowledge our expert tutors who generously contributed to the forum.



Above (left to right): Paul Conroy (Monash, Australia), Laura Sanman (Stanford, USA), Laura Edgington-Mitchell (Monash, Australia) & Nyssa Drinkwater (Monash, Australia).



Left: Science sessions gave delegates an opportunity to present their latest research.

Far left: Practical protease kinetics workshop led by Christian Sommerhoff (standing) and Maresa Grundhuber.

Below: Networking in the breaks and the Batu Ferringhi Long Beach cafe where the delegates had dinner together.



A big thank you to our expert tutors!

- Phil Bird (Monash, Australia)
- Maresa Grundhuber (Uni Munich, Germany)
- Bob Lazarus (Genentech, USA)
- Georg Ramm (Monash, Australia)
- Thomas Reinheckel (Uni Freiburg, Germany)
- Oliver Schilling (Uni Freiburg, Germany)
- Bonnie Sloane (Wayne State, USA)
- Christian Sommerhoff (Uni Munich, Germany)



CONTINUED NEXT PAGE

Meeting Report

IPS 2015 Trainee Awards

Alexandre Desroches	Université de Sherbrooke, Canada
Laura Edgington-Mitchell	Monash University, Australia
Stephen Fienberg	University of Cape Town, South Africa
Nikolaus Fortelny	UBC Vancouver, Canada
Ruth Fuhrman-Luck	Queensland Uni of Technology, Australia
Maresa Grundhuber	LMU, Germany
Jennifer Guerrero	University of California, Santa Barbara, USA
David Hartmann	BC ASCR, v.v.i., Czech Republic
James Henderson	The Centenary Institute, Australia
Lilian Hor	La Trobe University, Australia
Ippei Iizuka	Iwate Medical University, Japan
Magdalena Kalinska	Jagiellonian University, Poland
Tomas Knedlik	Academy of Sciences of the Czech Republic
Thomaskryza	Australian Prostate Cancer Research Centre
Lizelle Lubbe	University of Cape Town, South Africa
Ngoc Lunde	University of Oslo, Norway
Shishir Pant	University of Helsinki, Finland
Marcin Poreba	Wroclaw University of Technology, Poland
Johannes Prox	University of Kiel, Germany
Juinn Quek	Monash University, Australia
Pedro Quimbar	LIMS, Australia
Vinasha Ramasamy	University of Cape Town, South Africa
Wioletta Rut	Wroclaw University of Technology, Poland
Laura Sanman	Stanford School of Medicine, USA
Chris Schulze	Stanford University, USA
Valeriia Tereshchenkova	Lomonosov Moscow State University, Russia
Guojie Wu	Monash University, Australia
Konstanze Zieger	Institute for Biochemistry, Leipzig, Germany

Company of Biologist Awards

Best presentation by an early career researcher

Ruth Fuhrman-Luck (QUT, Australia)

Best poster prize(s)

Ben Buckley (University of Wollongong, Australia)

Larissa Hillebrand (University of Freiburg, Germany)

Laura Sanman (Stanford School of Medicine, USA)

What did our awardees have to say?

"IPS was a great opportunity to share my research with a friendly and knowledgeable community and to hear about all of the exciting and diverse happenings in the protease field." - anonymous

"Attending IPS2015 and the associated early career forum was a fantastic experience. I thoroughly enjoyed hearing about different research in the protease field and meeting people from around the world. The location was also really lovely!" - anonymous

"IPS2015 was an amazing conference in a fantastic location with ample networking opportunities. As an emerging graduate student I found the exposure to the vast range of protease research being conducted globally highly stimulating. Presentation of my own research to this audience was a definite highlight and the perfect way to establish future collaborations." - anonymous

"Attending the IPS meeting in Penang, Malaysia was a great opportunity for me to connect with experts in the field of proteolysis and get a strong sense of the important questions being asked and solved in the field. I thoroughly enjoyed being able to give an oral presentation of my graduate work and received invaluable feedback on my talk. Meeting graduate students and professionals from across the world was an incredible experience and I hope to foster the new relationships I made over the years despite the distance." - Jennifer Guerrero

"IPS was a unique opportunity to obtain guidance and detailed technical advice from experts during the workshops. That alone was already a valuable experience. On top of that the oral presentations were great and the conference as whole served as a fantastic platform for collaborative work. I look forward to remain an active member of the society and attend following IPS meetings." - anonymous

"I am a second-year PhD student and benefit a lot from attending my first IPS conference by knowing the talented scientists, great research ideas and a wide range of topics in the field of proteolysis. This really make me realize that how our current work can relate to other potential future work, rather than just restricting in my own field. This is really important for me as a quite fresh PhD student. Hopefully, my personal is valuable to you and I look forward to the next IPS." - Guojie Wu



IPS 2015 Trainee Travel Awardees

CONTINUED NEXT PAGE ►

Meeting Report



CONTINUED NEXT PAGE ►

IPS Lifetime Achievement Award 2015

Hideaki Nagase

A Journey with Matrix Metalloproteinases

In 1973 I went to the USA to pursue my PhD in Biochemistry in Fred Woessner's laboratory at the University of Miami. The project was to purify a protease in bovine nasal cartilage that digests aggrecan. The enzyme was characterized a zinc metalloproteinase. Since then I have been attracted by extracellular matrix (ECM)-degrading metalloproteinases, as they were thought to play key roles in both biology and pathology. Only a handful mammalian metalloendopeptidases were known then.

From mid 1980's cDNA cloning techniques advanced the field rapidly and identified 23 MMPs and 4 tissue inhibitors of metalloproteinases (TIMPs) in humans. I was fortunate to be involved in discovery of a collagenase activator (MMP-3) in Ted Harris' lab in Dartmouth in early 1980's. From 1986 to 1999 I was in Kansas City, where I continued to study activation mechanisms of proMMPs and demonstrated the stepwise activation mechanism. Structural functional studies with Keth Brew in Florida and Wolfram Bode in Munich let us elucidate how TIMPs inhibit MMPs. We also obtained biochemical evidence that collagenase (MMP-1) unfolds triple helical collagen before it cuts peptide bonds. After moving to London in 1999, a success in getting crystal structure of the MMP-1-collagen peptide with Erhard Hohenester (Imperial College) and Richard Farndale (Cambridge) let us propose how collagenase may unwinds collagen.

In London I started a project on osteoarthritis, the most prevalent age-related arthritis. We recently found that ADAMTS-4 and ADAMTS-5, two major aggrecanases, and MMP-13 (collagenase 3) and their inhibitor TIMP-3 are rapidly endocytosed via low-density lipoprotein receptor-related protein 1 (LRP1) in healthy cartilage. This endocytic pathway is impaired in osteoarthritic cartilage due to an increased shedding of LRP1. LRP1 is expressed in many cell types. We propose that the control of extracellular trafficking of matrix-degrading systems is an important component in ECM turnover in health and disease.



Hideaki Nagase, 2015

2 Substrate Specificity of MMPs

Hideaki Nagase, PhD

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INTRODUCTION
ACTIONS ON PROTEIN SUBSTRATES
PEPTIDE SUBSTRATE SPECIFICITY
CONCLUSIONS



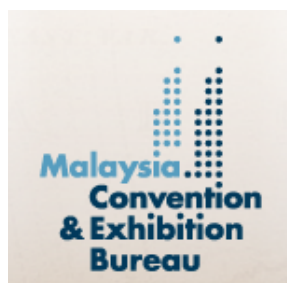
Hideaki Nagase is Honorary Emeritus Fellow of Nuffield Department of Orthopaedics, Rheumatology, and Musculoskeletal Sciences, University of Oxford, and Adjunct Professor in the School of Biotechnology, Amrita University, Kollam, India. He was Professor and Head of Matrix Biology at the Kennedy Institute of Rheumatology of University of Oxford from 2011 till 2014. Prior appointments include Professor of Matrix Biology at Imperial College London, UK, Professor of Biochemistry at the University of Kansas Medical Center, USA and Assistant Professor of Medicine and Biochemistry at University of Medicine and Dentistry of New Jersey, USA. He holds a B.Sc. in Pharmacy from Tokyo College of Pharmacy, a M.Sc. degree in Physiological Chemistry from Science University of Tokyo in Japan and a Ph.D. degree in Biochemistry from the University of Miami, USA. He received his postdoctoral training at Strangeways Research Laboratory, Cambridge, UK and Dartmouth Medical School, USA. He was elected as an Honorary Fellow of The Royal College of Physicians in 2004. He investigates the structure and function of matrix metalloproteinases and tissue inhibitors of metalloproteinases (TIMPs) and their roles in cartilage matrix destruction during the progression of arthritis.



IPS2015 gratefully acknowledges its sponsors and supporters.



Institute of Health and Biomedical Innovation



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We have exciting ongoing projects to further develop new methods and approaches to unravel the mysteries of proteolysis and in their application to deciphering pathology. No training in proteomics required and post-Docs will receive intensive and high level training in advanced mass spectrometry.

Apply to chris.overall@ubc.ca, www.clip.ubc.ca

Who is on the cover?

The structure on the cover of this issue of QuickCuts is separase protease domain (5FC3.pdb) from the thermophilic fungus *Chaetomium thermophilum* (Lin, Luo and Yu, *Nature*, 2016). The structure revealed how separase recognises cohesin and how cohesin phosphorylation enhances cleavage.

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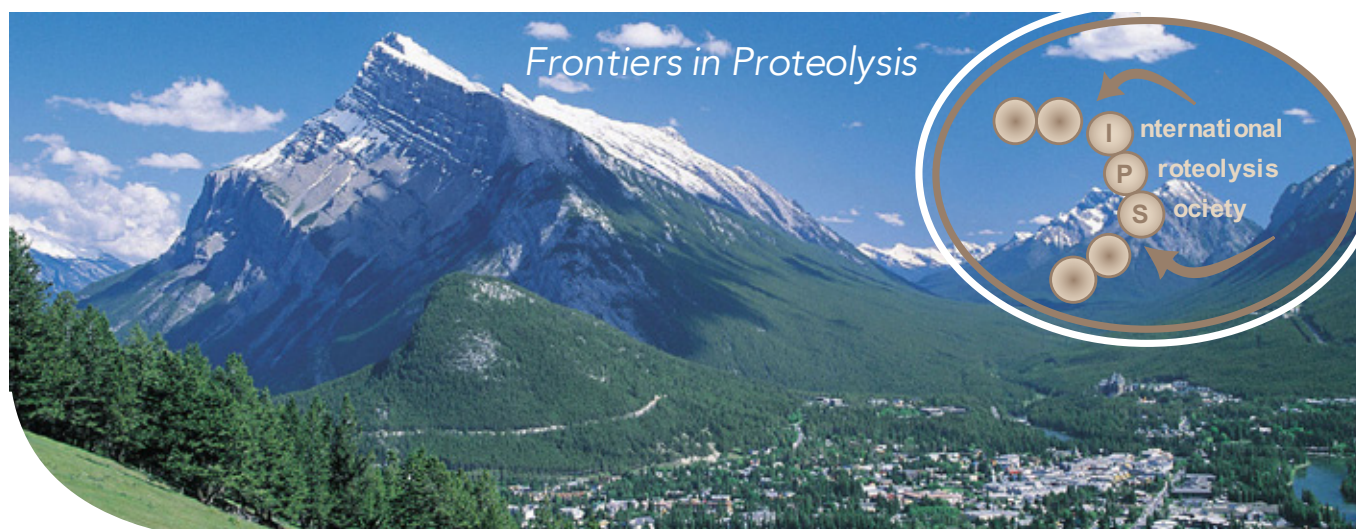
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The International Proteolysis society is always keen to keep in touch! Email us today or find us on



Join the 'International Proteolysis Society' Group within your preferred media

Save the date for the IPS 2017 General Meeting



10th GENERAL MEETING OF THE INTERNATIONAL PROTEOLYSIS SOCIETY
Banff Conference Centre, CANADA 28 Oct.-1 Nov. 2017

Training workshops and seminars

27-28 Oct. 2017

It is be our pleasure to invite you to the 10th General Meeting of the International Proteolysis Society from 28 October to 1 November 2017, and early career seminars and training workshops on the 27-28 October. The meeting will be held at the Kinnear Centre in Banff, in the middle of the Canadian Rockies. It is a splendid venue to be inspired, discuss with colleagues, forge new collaborations and see the best science from the proteolysis field.

Of course we will mark the 10th anniversary of our meeting in a special way! We look forward to seeing you in Banff, Alberta. Cowgirl or cowboy boots, belt buckle and bolo tie optional but highly recommended! We'll provide the hat!



Joanne, Jean-Bernard and Chris

www.IPS2017.org

Meeting topics (preliminary)

- Proteases in Immunity
- Protease Systems Biology
- Biologicals for Therapeutic Intervention
- Proprotein convertases and Metabolism
- Cancer and Metastasis
- Proteasome and ubiquitination systems
- Intracellular Proteolytic Systems
- Proteases in Developmental Biology
- Viral Proteases
- Membrane-Associated Proteolysis
- Proteases in bacteria, fungi and elsewhere

Save the date for the IPS 2017 General Meeting



Gordon Research Conferences

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Protein Processing, Trafficking & Secretion

Secretory and Endocytic Pathways in Health and Disease

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New London, NH USA

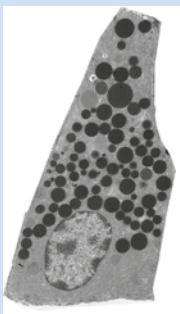
Organizers

Chair: Paul Taghert (Washington Univ. Med Sch.)
Vice Chair: Klaudia Brix (Jacobs Univ.)

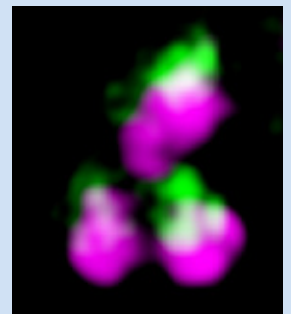
Meeting Description

The cell biology of endocytosis and protein secretion presents many fascinating problems in normal and pathophysiological states. This GRC hosts cutting-edge presentations on the latest research using diverse approaches.

Topics



- Keynote: The Steiner Session - NextGen Protein Processing
- Regulated Intramembrane Proteolysis
- Processing Enzymes of the Endocytic and Secretory Pathways
- New Views on Peptide Processing and Release
- Generation of the Endolysosomal Pathway
- Inter-Organelle Communication
- Molecular Takes on Dense Core Vesicles
- Feeding into Autophagosomes and Lysosomes
- To Image Trafficking and Exocytosis



Gordon Research Seminar (GRS)

Co-Chairs: Anna Mai Jansen (Univ. Copenhagen) & Frederic Couture (Univ. Sherbrooke)

Keynote: Klaudia Brix (Jacobs Univ.)

<http://www.arc.org/programs.aspx?id=15416>



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