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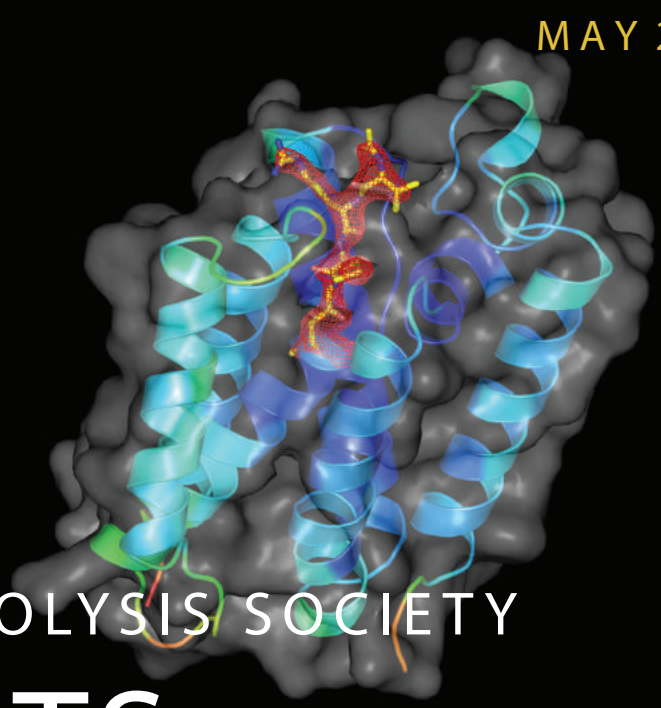
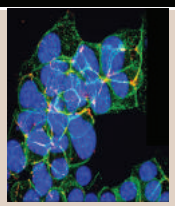
MAY 2018

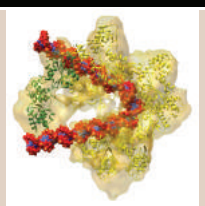


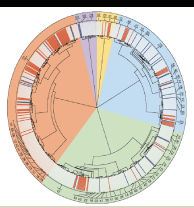
INTERNATIONAL PROTEOLYSIS SOCIETY

QUICKCUTS

Editors:
Leila Akkari (Netherlands Cancer Institute)
Margarete Heck (University of Edinburgh)







THE PREMIER RESOURCE FOR ALL YOUR IMPORTANT PROTEASE QUESTIONS

A Message From the President:

First of all, the warmest welcome to all new IPS members into the Society! I was thrilled to see that we have increased our memberships by more than twenty percent, and we look forward to you being engaged in the future success of the IPS. I also very much welcome all our new Council members and send a big thanks to our outgoing members of council for all their efforts towards the success of the society.

It has been a while, since we concluded our 10th General Meeting in beautiful Banff, Canada. Still, it feels as it was yesterday that we left this stunning place and a fantastic conference with exciting science and fabulous networking. Congratulations and thank you so much for making this possible to the organizers Joanne Lemieux, Jean-Bernard Denault and Chris Overall! Sessions of the meeting are covered in this issue.

With Michael James and Motoharu Seiki, we have added two more heroes of protease research to our stellar list of Lifetime Members. Both outstandingly contributed to the field and will ever inspire the next generation. Sadly, we also lost a longtime member with passing of Hiroyuki Sorimachi in January who shaped the Calpain field and served on the IPS council from 2011 to 2015. We will never forget Hiroyuki and remember him here.

I already look very much forward to the 11th General Meeting of the Society that will be organized by Jan Kovalinka and Kvido Strisovsky and held in historic Marianske Lazne in the Czech Republic from September 29 to October 4, 2019 with IPS workshops in magnificent Prague. Till then, there will be many more exciting conferences of interest to IPS members. These are highlighted in this issue and constantly updated on our website www.protease.org.

I am very honored to serve as the president of IPS, and on behalf of the IPS Council I look forward to receiving your suggestions for improvements that can always be directed either to me or to any member of council. This is your society – we value all input to make it even better! Last but not least, I want to thank Leila Akkari and Margarete Heck for all the work to compile this issue of QuickCuts to the enjoyment of all our members.

Ulrich auf dem Keller, IPS President

COUNCIL OF THE INTERNATIONAL PROTEOLYSIS SOCIETY

Meeting Report

Tenth General Meeting of the International Proteolysis Society Banff, Canada 28 Oct-2 Nov, 2017

The Canadian Rockies formed the stunning backdrop to the 10th General Meeting of the International Proteolysis Society. Held every two years – rotating between The Americas, Europe/Africa, and Asia Pacific – it was time for the Canadians to showcase this event. And that they did – with aplomb! Jean-Bernard Denault (Sherbrooke), Joanne Lemieux (Edmonton) and Chris Overall (Vancouver) comprised a terrific team, organising an outstanding scientific agenda, along with extracurricular activities reminding everyone why actually attending these conferences is so much better than reading about them after the fact in the IPS newsletter! A country Barbeque, along with line dancing, a Halloween costumed poster session, a disco, and a session swap allowing nearly everyone to take advantage of a clear afternoon to travel to Lake Louise all made for a truly memorable event. Even the snow was appreciated – resulting in a snowball fight between the proteases and inhibitors! On top of all this, the organisers even generated a significant profit for the IPS.

IPS 2017 Delegates, Banff Centre, Canada

Not only did the scenery inspire the nearly 200 delegates from 27 countries, it also distracted the speakers who had the good fortune to speak not only to an engaged audience, but also to the panorama of amazing mountain beauty. The meeting motto being "Frontiers in proteolysis" sessions focused on Intramembrane Proteolytic Systems, Proteolysis in Protein Quality Control and Proteostasis, Protease Structure, Protease Mechanisms Intracellular Proteases, Cancer and Metastasis, Protease Systems Biology, Therapeutic Intervention, Proteases in Diseases and Development, Proteases in Extracellular Space, and New Technologies in Protease Inhibitor Development. More than 60 talks from invited speakers and those selected from abstracts were complemented by 5 minute 'lightning' talks and vibrant poster sessions – one taking place on Halloween (including some creative costumes!). Notably, an even gender split amongst invited speakers was achieved!

Bookending the conference were two sessions by luminaries of the protease world. Jim Wells kicked off the meeting with a Keynote Address entitled "Engineered Proteases for Signaling in Cells and Animals." A huge thank you to Jim for a passionate overview of a fascinating career filled with exciting biology, and important technological development. Finishing the conference were two Lifetime Lectures by Dr. Michael James (University of Alberta, Edmonton, Canada) "A Proposal for a Substrate-Assisted Catalytic Mechanism for SerinePeptidas", and Dr. Motoharu Seiki (Kanazawa University, Japan) "Playing with MT1-MMP/MMP-14 for 25 years." I believe all present were suitably inspired by these captivating addresses.

The baton now transfers to Kvido Strisovsky and Jan Konvalinka, both from Prague, as they organise the 11th General Meeting to be held in 2019 in Marienbad, Czech Republic (29 Sept-4 Oct). Good (and inexpensive!) beer and stimulating science await the lucky community that call themselves the International Proteolysis Society.

CONTINUED NEXT PAGE

Meeting Report

The Sunday morning session on "Proteolysis in protein quality control and proteostasis" was chaired by Bob Lazarus and James Whisstock. Kvido Strisovsky from the Institute of Organic Chemistry and Biochemistry (Prague), discussed targeting rhomboids by engineering reversible electrophilic warheads onto peptides that had been optimized from P5 to P1 to design initial inhibitors. Using structural and functional studies, he was able to generate peptidyl ketoamides incorporating additional residues binding at the P2′ site that were nanomolar inhibitors. These reversible noncompetitive inhibitors also selectively inhibited activity in the membranes of living cells and thus represent potential starting points to develop drugs for malaria, Parkinson's Disease, cancer and others where rhomboids have been implicated. The second part of his talk explored the B. subtilis rhomboid protease YqgP, and one of its substrates MgtE, an ATP-dependent Mg2+ transporter important in membrane homeostasis. Kvido presented possible regulatory roles as well as Mg2+, Mn2+ and Zn2+ dependence and effects. In addition, there was evidence for association with FtsH, an AAA+ membrane bound protease that can also cleave MgtE, albeit in a different place.

Tim Clausen from the Institute of Molecular Pathology in Vienna, Austria presented a fascinating talk looking into new pathways of protein turnover in B. subtilis, which is also present in other gram-positive bacteria. Tim made the key discovery that phosphoarginine is a novel tag for proteins to be targeted for degradation by the ClpC–ClpP proteolytic complex. Arginine phosphorylation (Pargylation) is mediated by McsB, an arginine kinase that is required and sufficient for targeted degradation. Complex structures revealed that phospoarginine binds to the N-terminal region of ClpC. There is an intriguing functional similarity of the phosphoarginine/ClpC–ClpP system with the ubiquitin/proteasome system in eukaryotic biology, both serving to incorporate their respective tags for protein degradation. This novel area stimulated a lot of lively discussion.

IPS 2018 Hands-on workshop- Practical Enzyme Kinetics with Guy Salvesen and students. University of Calgary

IPS 2018 Opening Dinner with Line Dancing

The following session on "Protease Structure" was chaired by Xavier Gomis-Rüth and Jim Huntington. Michael Wiener (University of Virginia, Charlottesville, USA) is a relative newcomer to proteases following on the discovery of Ste24p structure in 2013.Ste24p was discovered via yeast genetics, and is a zinc metalloprotease with a novel fold and diverse functions, including isoprenylation, proteolytic processing and methylation. The second invited speaker, Catherine Moali (University of Lyon, France), presented her new structure on the CUB domain of PCPE-1 with the C-propeptide of collagen III. Procollagen C-proteinase enhancers (PCPEs) bind to both the collagenase (BMP-1/tolloid-like protease, or BTP) and to the substrate procollagen, cleavage of which produces insoluble collagen fibrils. Xavier Gomis-Rüth (Molecular Biology Institute of Barcelona, Spain) presented structures of the serpin Miropin, named after its discoverer, Miroslaw Ksiazek, derived from T. forsythia. Miropin appears to use several residues for P1 and inhibit across classes (serine and cysteine). Ed Sturrock (University of Cape Town, SA) gave the last presentation on his long-standing work on angiotensinogen-converting enzyme (ACE), the zinc metalloprotease responsible for processing of angiotensin I to II. Although ACE is known to be a master regulator of blood pressure, the cardioprotective effects of ACE inhibitors suggests interactions between ACE and RAS receptors, AT2R and MAS. These potential interactions were investigated by FRET and revealed that dimers of somatic and testes ACE do exist and interact with AT2R, but not with MAS.

The final two 5 minutes speed talks were on the potential targets of a Kazal type protease inhibitor, including proteases involved in blood coagulation, and on Pro-Pro endopeptidease-2 from P. alvei which was shown by various structural and biochemical experiments to differ from type-1.

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Meeting Report

The Monday morning session on "Intracellular Proteases" was chaired by Catherine Moali and Galia Blum.
Where in the world can a protease take you? The title from Margarete Heck's opening talk was actually an excellent title for the entire session on intracellular proteases. The first answer was "to Banff"! The second answer was from the interior of the cell to the circulation as exemplified by Margarete with invadolysin which was initially identified to play a role in chromosome condensation but recently found to also be present as a secreted protein in Drosophila and vertebrates. Other possible answers include the numerous proteolytic battlefields where, on one side, pathogens can display exquisite inventiveness to survive antibiotic treatment (e.g. the Lon protease targeted by Brett Babin) and, on the other side, inflammatory cells develop equally smart mechanisms to efficiently fight microbes and cancer cells.
Cornelius Taabazuing and Sabrina Sofia Burgener illustrated the great diversity of pathways which lead to cell death and their control by caspases and cathepsin G. Additionally, Paulina Kaspierkiewicz described how selective activity based probes to neutrophil proteases show strict specialization within granules. Lastly, Maria Alejandra Parigiani depicted the role of Cathepsin L in immune and tumor epithelial cells. During these talks, several highly sophisticated peptide libraries and colorful activity-based probes were presented.

Dr. Motoharu Seiki receiving his award

Lifetime lecture by Dr. Michael James

The follwing session on "Proteases in Cancer and Metastasis" was chaired by Christoph Peters and Bonnie Sloane.
Barbara Fingleton, Associate Professor at Vanderbilt University, Nashville presented the work of her lab on the role of the metalloprotease MMP10 (stromelysin 2) in colon cancer. Repair from epithelial injury induced by administration of dextran sodium sulfate (DSS) in the large intestine of the mouse is greatly impaired in the absence of MMP10.
The mechanism appears due to a function of MMP10 in macrophages, regulating their wound healing properties.
Leila Akkari, junior group leader at the Netherlands Cancer Institute, Amsterdam presented latest results on the role of cysteine cathepsins in pancreatic neuroendocrine tumors (PanNET) and aggressive brain cancers (glioblastoma). These results have potential implications for the clinical consideration of selective versus pan-family cathepsin inhibitors for treatment of specific cancers.
Barbara Grünwald, postdoctoral fellow in the group of Dr. Rama Khokha, Toronto, showed that the MMP/TIMP-system is not only involved in the tumor - stroma interaction at the primary tumor site but also in metastasis. TIMP-1 secreted from pancreas tumors activates hepatic stellate cells (HSCs) to prime the liver microenvironment for accepting disseminated tumor cells from the pancreas. Both pre-cancerous and cancerous pancreatic lesions produce TIMP-1 in human patients and mice. Development of this liver-specific metastatic niche is initiated already at premalignant stages. The presentation shed light on the roles of the protease inhibitor TIMP-1 on local as well as distant tissue microenvironments in cancer.
Lena Hölzen, PhD student in the Reinheckel/Peters groups in Freiburg, presented a high-throughput degradome-wide knock down screen for identification of additional proteases implicated in breast cancer progression. A competitive screen to analyze the effect of protease knock down on cancer cell proliferation and survival was presented and identified 24 hits. A kinase and protease co-inhibition screen is also being performed. These screens are suited to identify novel proteases involved – also in combination with kinases – in the progression and invasion of breast cancer.

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Meeting Report

The Tuesday morning session on "Therapeutic Intervention" was chaired by Ed Sturrock and Grant E. Blouse. David C. Schriemer (University of Alberta, Calgary) in their search for proteases that thrive in harsh environments, tapped into the transcriptome and proteome of the carnivorous pitcher plant Nepenthes x ventrata secreted fluid. Here in this complex digestive mixture they discovered a novel prolyl endoprotease, neprosin-1 that shares no homology with other prolyl endopeptidases and lacks a standard catalytic triad. Two applications were highlighted: (1) as an additional enzyme in the proteomic toolbox to yield improved peptide signatures, and (2) as a potential enzyme for digesting gluten in celiac disease. Nabil Seidah (Montreal Clinical Research Institute, Canada) described a new sorting motif, (E)LEXXPL, in the cytosolic tail of PC7 that regulates trafficking to the late endosome for activation. This motif further mediates shedding of TFR1 as well as newly identified substrates CASC4 and GPP130 where shedding may prove t o be protective in cancer. Single domain nanobodies directed against the C-terminal domain (CHRD) of PCSK9, which drives lysosomal targeting and prevention of LDLR recycling, were characterized. They showed that the targeted nanobodies prevented degradation of the PCSK9-LDLR complex thereby preserving LDLR for cholesterol clearance. Next, Daniel Kirchhofer (Genentech, USA) described the discovery of a cryptic binding site of PCSK9 and the structure-based design of peptides that bind to the N-terminal groove of PCSK9. These were engineered into antagonists using a minimized groove-binding peptide as a new anchor to extend towards the EGF(A) binding site. The crystal structure of one of the identified peptides revealed that the N-terminally appended residues encroached on the EGF(A) binding site, consistent with their antagonistic activity in LDL receptor binding assays and HepG2 cell assays. These findings herald the development of a new class of small molecule inhibitors of PCSK9. Tamara Lah Turnsek (National Institute of Biology, Slovenia) explored the expression of invasion-associated proteases, such as cathepsin B, calpain1, MMP-9 and -14, and showed that an increase in their expression enhanced an aggressive phenotype of a subtype of glioblastoma (GBM) cells on interaction with mesenchymal stromal cells (MSC). Their results suggest that the response of GBM cells to MSCs depends on the cancer cells' genetic subtype and possibly is driven by a single promoter enhancement of certain protease genes. Lisa Douglas (Queen's University Belfast, Ireland) showed novel inhibitors of channel-activating proteases caused a reduction of IL-8 expression in CuFi cells. In addition, the inhibitors decreased TNFα and LPS-stimulated IL-6 and IL-8 secretion, and reduced PAR-2 activation. These inhibitors present an exciting option for therapeutic intervention i n cystic fibrosis lung disease via the inactivation of epithelial sodium channels. Simon Law (University of British Columbia, Canada) presented the crystal structure of Cathepsin K with the LMW allosteric inhibitor NSC-13345 and identified three distinct binding sites located in the S2' pocket, the chondroitin-sulfate binding site an additional site of unknown function. Their findings suggest a multi-modal inhibition mechanism for NSC-13345 blocking both the active site as well as the substrate recognition exosite.

Social gathering at the IPS worshop

Poster session and Halloween costumes

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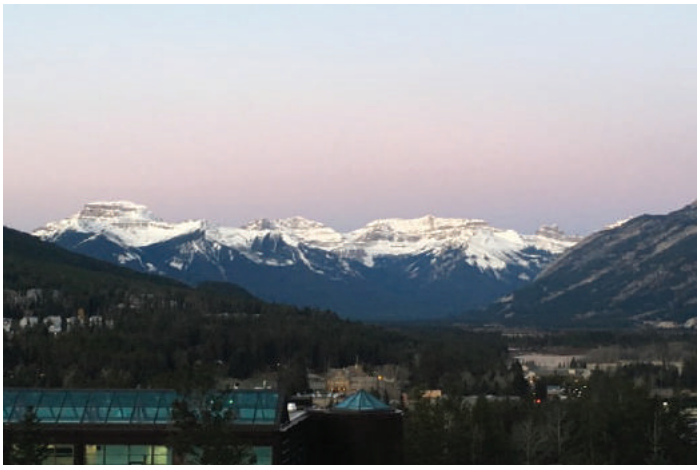
Meeting Report

The session on "Proteolysis in Diseases and Development" was chaired by Laura Edgington-Mitchell and Nabil Seidah. Christopher Heise (Genentech, USA) kicked off this diverse session by describing new strategies to combat multidrug resistant bacteria using protease-targeted antibiotics. Using a medicinal chemistry approach, his team modified the natural antibiotic arylomycin, an inhibitor of the essential bacterial signal peptidase lepB, to generate promising new compounds with potent and broad-spectrum activity against gram negative bacteria. James Whisstock (Monash University, Australia) then changed gears to discuss his recent insights into the functions of Torso (a receptor tyrosine kinase), its ligand, Trunk, which is proteolytically activated by Furin proteases and Torso-like (a perforin-like protein) during embryonic patterning of Drosophila. These findings may be translated to further our understanding of brain disorders like schizophrenia. Next, Antoine Dufour (University of Calgary, Canada) described his recent discovery that MMP-12 cleaves interferon gamma at two sites. This cleavage functions to dampen pro-inflammatory immune responses, which may be an important regulatory mechanism that is lost in diseases like arthritis, lupus, and glomerular nephritis. Tatjana Bosjnak (University of Oslo, Norway) rounded out the session by presenting recent data showing that proton pump inhibitors (PPIs) like Lansoprazole can inhibit the asparaginyl endopeptidase legumain. Given the role of legumain in osteoblasts and osteoclasts, this observation may explain some of the off-target effects of PPIs on bone health.

Thomas Reinheckel and Christoph Peters-Lake Louise



View of the Canadian Rockies

The session on "Protease Systems Biology" was chaired by Oliver Schilling and Chris Overall. Stefan Lichtenthaler (Center for Neurodegenerative Diseases, Munich) reported on new proteomic methods to study function, substrates, and therapeutic potential of cell surface proteases. The methods were then applied to the protease BACE1 (also known as beta-secretase), which is a major drug target in Alzheimer's disease. The lab developed click chemistry-based methods for substrate identification (SPECS) and for capturing cell surface proteins (SUSPECS) and demonstrated that BACE1 has by now over 40 substrates and selectively remodels the surface proteome of neurons. Benedikt Kessler (University of Oxford, UK) presented ubiquitin specific protease (USP)-7 inhibition as a strategy to selectively control the abundance of oncoproteins, which are typically deubiquitinated by USP-7, hence leading to their accumulation. In a team effort, a specific USP-7 inhibitor was developed. Target selectivity was validated in vitro and in vivo, including a tumor growth retarding effect in murine systems. Structural analysis showed that the inhibitor binds to the apo-form state of USP-7. Since the apo-form of USP-7 differs from other USPs, this finding explains the exquisite selectivity of the inhibitor. Boris Turk (Jozef Stefan Institute, Slovenia) presented on the determination of protease specificity, which is of crucial importance for understanding protease function. We have developed the first gel-based label-free proteomic approach (DIPPS- Direct In-gel Profilling of Protease Specificity) that enables quick and reliable determination of protease cleavage specificities under large variety of experimental conditions. Ulrich auf dem Keller (Technical University of Denmark) presented novel targeted degradomics technologies allowing to study interconnected protease activation networks in complex biological systems. First, he introduced parallel reaction monitoring as a powerful and highly sensitive method to identify and quantify proteases in complex samples. Next, he elucidated the principle of targeted degradomics by designing and applying assays to monitor zymogen removal in MMP activation in cell free systems.

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Meeting Report

The concluding session "New Technologies in Protease Inhibitor Development" at this year's IPS meeting in Banff dealt with the latest technologies and forthcomings in protease inhibitor development and was chaired by Klaudia Brix and Matt Bogyo.

Grant Blouse presented in a snappy and highly informative talk on engineering factor IXa variants. He described the variant design learning tool used at Novo Nordisk which allows refinements within few days only, thus, really establishing a high-throughput screening library that allow sensitive quantification based on assays employing sensitive biotin-streptavidin technologies in a BIAcore setting. To identify hot spots to target, a loop swap strategy was used, such that exosite and allosteric effectors for improved protease activity targeting were determined. Anthony O'Donoghue further impressed the audience by his talk about proteasome inhibitors that are specifically targeting the malaria parasite Plasmodium falciparum while leaving mammalian host cell's proteasomes mainly unaffected. This is achieved by chemically modifying and thereby improving natural antimalarials. Again, a very sophisticated approach was used, namely multiplex substrate profiling by mass spectrometry (MSP-MS). He described how to distinguish somewhat exotic proteases even in "nasty" fluids like pancreatic cyst fluids in benign versus malignant conditions. We learned about immunoproteasome substrates and that it is possible for the O'Donoghue group to profile approx. 12 proteases as fast as within one month.

Jan Konvalinka must still be sorting out the many emails in his inbox-email folder as he inspired us by his DIANA approach which is based upon the previous generation of iBodies. These combine inhibitory functions with the features of highly specific antibodies, such that the avidity effects of this modular LEGO-like system allow achieving inhibitors with Ki values of 3 pM. Another highly sophisticated approach was then introduced that uses a reporter DNA linked to an inhibitor which targets an antibody-captured protease. The approach is referred to as DIANA, which stands for DNA-(linked to)-inhibitor antibody assay. With DIANA, approx. 4500 different compounds can be tested in a weekend while being ultrasensitive, namely picking up proteases in zeptomolar amounts with an R2 of 0.999, which is due to the power of PCR technology that comes into effect here. That was an amazing presentation by Jan Konvalinka and starting a collaboration with this group might yet serve as another reason to travel to Prague besides the obvious plan to attend the IPS meeting 2019 in the Czech Republic, which Jan together with his colleagues will organize. Finally, Olivier Julien kept up with the dynamics of this session and reported on quantitative N-terminomics approaches to identify protein substrates of caspases 2 and 6, however in a manner that takes subcellular localization into account. His biological system addresses necroptosis which in itself is an already very interesting type of cell death that combines apoptotic with necrotic features. He can distinguish between actual substrates of the caspases and bystanders.

IPS 2017 organizers Joanne Lemieux, Jean Bernard Denault (left) and Chris Overall (right)

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Meeting Report

IPS 2017 Trainee Awards

Gopal Periyannan
Crowley E
Xin Ge
Brian L. Mark
Brandon Goblirsch
mohd faizan siddiqui
François Béliveau
Gaurav Sinsinbar
Amy M. Weeks
Janice H. Xu
Angelo Solania
Maureen E. Hill
Vatsal Sachan
Duval Stéphanie
Sébastien Dion
Seiya Kitamura

Loreleï Durand
Adrian Leontovyc
Radka Hobizalova
Alkmini Papadopoulou
Charlotte Spitz
Simonas Savickas
Tim Van Kersavond
Katia Celina Santos Correa
Ngoc Nguyen Lunde
Minh T. N. Nguyen
Tetsuo Cai
Ariela Liven
Jessica R Maye
Lisa E.J. Douglas
Kazunori Kikuchi
Lena Hölzen
Tatjana Bosnjak

Sabrina Sofia Burgener
Yusuke Hatakawa
P. Schulz
Gal Itzhak
Tommy Weiss Sadan1
Stephen Lu
Paulina Kasperkiewicz
Drishtant Singh
Emilia Marijanovic
Tess Malcolm
Blake Riley
Lauren B. Arendse
Maria Alejandra Parigiani
Pierre-Marie Andrault
Shishir Pant
Yesid A. Ramirez

Rhiannon Campden
Ouma Onguka
Sandra Paschkowsky
Agne Tubeleviciute-Aydin
Euna Yoo
Alexander J. Baker-Williams
Javier Sánchez-Pozo
Monica L. Gonzalez
Cyrielle Martini
Alexandre Desroches
Miroslaw Ksiazek
Mansi Manchanda
Gaurav Sinsinbar
Simon Law
Megan Garlan
Brett M. Babin
Preety Panward

"IPS2017 provided a unique opportunity to engage with colleagues in the protease field in an intimate and immersive environment. I'm grateful for the opportunities that I had to build my network, to learn about important emerging areas of research, to get feedback on the direction of my work, to establish new collaborations, and to forge lasting scientific relationships. I'm already looking forward to the next IPS meeting!" *Amy Weeks, UCSF, USA.*

"I participated to the IPS general meeting for the first time and had an excellent and valuable experience. These experiences were made possible by receiving a Travel Award, which encouraged me so much". *Yusuke Hatakawa, Setsunan University, Japan.*

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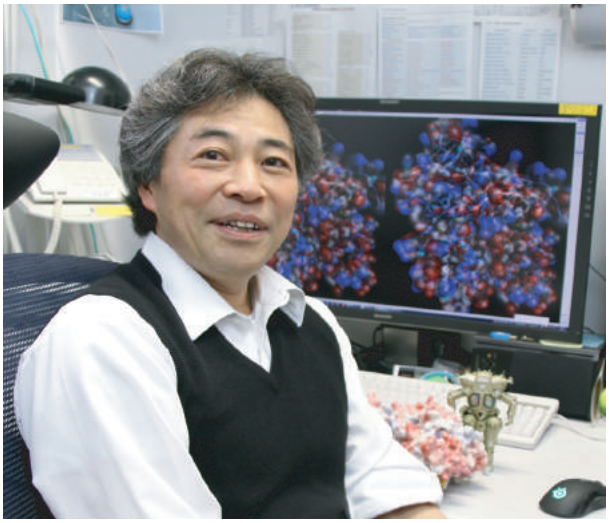
In Memorium- Prof. Hiroyuki Sorimachi

This article celebrates the life of Professor Hiroyuki Sorimachi a pioneer in the field who contributed tremendously to the understanding of intracellular proteolysis.
With Hiro's passing, proteolysis in general and calpains in particular has lost a great scientist, pioneer and a visionary, leader and friend.

By Vito Turk



Dr. Hiroyuki Sorimachi, an internationally renowned biochemist in the proteolysis field, passed away on January 6, 2018 in Tokyo, at the age of 54, after two years of courageous battle with fatal disease. Hiro, as he was known to his friends and colleagues, was a scientific leader of calpain research at the national and international levels.
Although relatively young, he made an extraordinary career in short time. Hiro was a remarkable scientist, remembered in the scientific community as skilled, creative and extremely modest personality. His pleasant and friendly character motivated his students, and colleagues to pursue research they were interested in. Hiro is survived by his wife and scientist Noriko, and daughter.
Hiro was born in Kawasaki City near Tokyo on April 24, 1963. After high school he enrolled to Faculty/Graduate School of Science, The University of Tokyo and completed his undergraduate education in 1988. The same year he joined already internationally recognized Professor Koichi Suzuki's laboratory at Tokyo Metropolitan Institute of Medical Science (Rinshoken/Igakuken), thus entering the field of calpains. As a talented and hard working young researcher Hiro was an indispensable member of Dr. Suzuki's group, as Koichi mentioned to me. Hiro earned a PhD in 1992 from Tokyo University. In the same year he was appointed Assistant Professor, and in 1997 he became an Associate Professor at the Graduate School of Agricultural and Life Sciences at the same University. In 2004, he returned to Rinshoken/Igakuken and became the project leader of the "Calpain Project", and in 2008 he became Head of the Department of Advanced Science for Biomolecules, until his premature death.
Dr. Sorimachi's career was almost entirely connected to calpains, one of the superfamily of cysteine proteases (peptidases), which participate in many physiological and pathological events by "limited proteolysis" processes, thus modulating the substrate's function and structure. Progress in structure determination, discoveries of new human calpain genes, pathology of calpain-related diseases resulted in the establishment of the CALPAIN project led by Dr. Sorimachi. Hiro's talent and knowledge enabled him to continue successfully Dr. Koichi Suzuki's scientific legacy. The project was oriented to further the understanding of the physiological functions and molecular mechanisms of calpains as well as calpainopathies, and to develop effective drugs and therapies for calpain-related diseases. The recent excellent review article "Calpain research for drug discovery: challenges and potential" (authors Y. Ono, T. C. Saido and H. Sorimachi) published in Nature Reviews Drug Discovery in 2016 sumarizes present knowledge in the field and challenges in targeting calpains by inhibition of their harmful activities.

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In Memorium- Prof. Hiroyuki Sorimachi

Dr. Sorimachi successfully continued the calpain research of his predecessors such as Darrel E. Goll, Kazutomo Imahori, Takashi Murachi and his great teacher Koichi Suzuki. They were all my friends, Darrel and Koichi in particular. Interestingly, they did not study cathepsins, and I not calpains. However, we were all interested in cysteine proteases as structurally and functionally related enzymes actively participating in proteolysis. Unfortunately, they all passed away.

I first met Hiro as a graduate student during my visit to Dr. Suzuki's laboratory after delivering a lecture. I had the chance to discuss with him. Hiro impressed me by his knowlwdge and his personality. Then we met several times during my frequent visits to Japan. For the first time he visited Slovenia in 2005 attending IX. International Symposium on Proteinase Inhibitors and Biological Control organized by our group in Brdo, where he presented an excellent invited lecture "Physiological roles of intracellular modulator protease calpain". Already the next year he delivered a lecture in the coastal city Portoroz, which participants, particularly scientists from Japan, preferred (above, last row). This place became the traditional place for all symposia in the future. The last lecture "Muscle homeostasis controlled by two calpains" Dr. Sorimachi presented in Portoroz 2014. Unfortunately I did not expect that this was our last meeting.
Dr. Sorimachi received several awards including Young Investigator Award from the Japanese Biochemical Society (1999) and Lifetime Achievement Award from FASEB SRC Calpain meeting (2016). He served many other duties in Japanese scientific community, however, he resigned when he found out his illness. He was often an invited speaker at the congresses, symposia, different universities and research institutions at home and abroad. In his free time he enjoyed the famous novels of Haruki Murakami. When visiting Slovenia he enjoyed savoring good wines and frequently carried bottles back to Japan.
With Hiro's passing, proteolysis in general and calpains in particular has lost a great scientist, pioneer and a visionary, leader and friend.
I am very grateful to Dr. Yasuko Ono and Dr. Shoji Hata, close collaborators of Dr. Sorimachi, for helping me with some data from his career.

Dear Hiro,

Last greetings from Tokushima Cherry blossoms –

Sakura, growing in my Japanese garden in Ljubljana

May your soul rest in peace.

INTERNATIONAL PROTEOLYSIS SOCIETY

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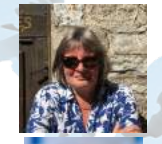

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The International Proteolysis society is always keen to keep in touch! Email us today or find us on

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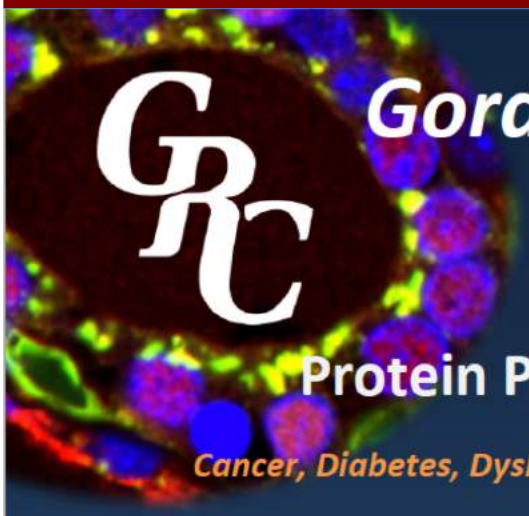
Meeting Announcements



Gordon Research Conferences

frontiers of science

Announcing the 2018 Gordon Research Conference on:

Protein Processing, Trafficking and Secretion

Molecular Mechanisms and Translational Approaches to Cancer, Diabetes, Dyslipidemia, Cardiovascular and Neurodegenerative Disorders

Date and Location: **July 15 - 20, 2018, Colby-Sawyer College, New London, NH, USA**

Organizers:
Chair: **Klaudia Brix**, Jacobs University Bremen
Vice Chair: **Alan D. Attie**, UW-Madison, University of Wisconsin

Meeting Description: *Join us for cutting-edge presentations on the cell biology of the secretory and endocytic pathways, including proteolytic processing.*

Topics:

- New Takes on Transport along the Secretory Pathway
- Endocytic Pathway Trafficking and Connections to the Secretory Pathway
- Updates on Processing (and Beyond) in the Secretory and Endocytic Pathways
- Novel Treatment Mechanisms Targeting Diabetes, Obesity, Metabolic Syndrome *et al.*
- Significance of Intra-Membrane Proteolysis
- Protein Processing in Development, Reproduction, and Ageing
- Secretory Proteases and Inhibitors in Health and Disease
- Challenges in Defining Therapeutic Approaches Targeting Protein Processing
- Systems Biology Approaches in Protein Processing and Signaling

SUBMIT ABSTRACTS for SHORT TALKS

POSTER PITCHES Monday – Thursday 12:00 – 12:30 pm

Confirmed Speakers:

Alan D. Attie	Carl Blobel		Juan Bonifacino
Ashley Buckle	Jan Christian		Judith Clements
Melanie Cobb	Spencer Freeman		Benjamin S. Glick
Daniel Kirchhofer	Judith Klumperman		Iris Lindberg
Timo D. Müller	Christopher Overall		Eleanor Raffan
Nabil Seidah	Bonnie F. Sloane		Paul H. Taghert
Amantha Thathiah	Gary Thomas	Sinisa Urban	James Whisstock

July 14 – 15, 2018 **Associated Gordon Research Seminar (GRS)**

Novel Techniques to Identify Molecular Mechanisms of Protein Processing and Trafficking

Co-Chairs: **Stephanie Duval, IRCM Montreal, Canada, and Stephen C. Ireland, University of Michigan**

Confirmed Speakers: Erik Jorgensen Jonathan Sweedler

More details and online application are available at:

http://www.grc.org/protein-processing-trafficking-and-secretion-conference/2018/

Meeting Announcements

Proteolytic Enzymes and Their Inhibitors (GRS)

Gordon Research Seminar

Exploring the Opportunities and Confronting the Challenges Surrounding Protease-Targeted Therapies

June 2 - 3, 2018

Apply Now

Chairs

Laura E. Edgington-Mitchell and
Jaideep S. Dudani

Contact Chairs

Renaissance Tuscany Il Ciocco

Via Giovanni Pascoli
Lucca (Barga), IT

Venue and Travel Information

Proteolytic Enzymes and Their Inhibitors

Gordon Research Conference

Understanding Proteases and Their Roles as Regulators of Health and Disease

June 3 - 8, 2018

Apply Now

Chair

Matthew Bogyo

Vice Chair

James A. Huntington

Contact Chairs

Renaissance Tuscany Il Ciocco

Via Giovanni Pascoli
Lucca (Barga), IT

Venue and Travel Information

International Proteolysis Society

Meeting Announcements

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  - Programme
  - Abstract Submission
  - About the Conference
  - Registration
  - About Edinburgh

The 2nd Joint Meeting of the International Society of Fibrinolysis and Proteolysis and the Plasminogen Activation Workshop

Edinburgh, UK

September 3-7th 2018

Dear Colleagues,

It is with great pleasure that we invite you to participate in the second joint meeting between the 24th International Congress on Fibrinolysis and Proteolysis and 17th International Workshop on Molecular and Cellular Biology of Plasminogen Activation. The congress will take place in the beautiful and historic city of Edinburgh, UK. The first joint meeting of these societies was held in 2016 Shizouka, Japan and was an incredible success. We hope to emulate this accomplishment in Edinburgh where we strive to host an exciting and stimulating conference with a mixture of invited state of the art speakers and presentations from the top selected abstracts.

We hope you will join us in Edinburgh to experience some Scottish hospitality.

Want to know more? Check
http://www.protease.org/meetings.html !

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