AUG 2020

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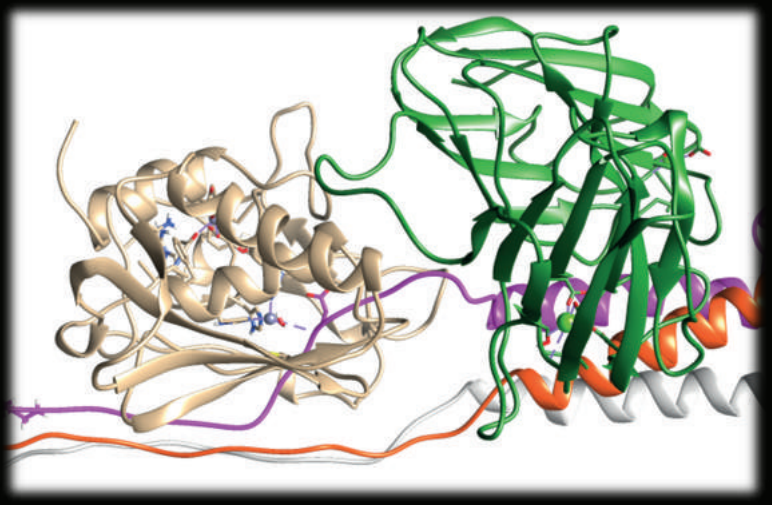
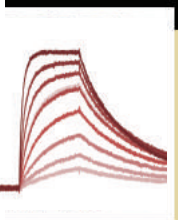
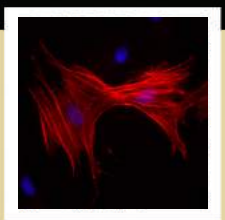


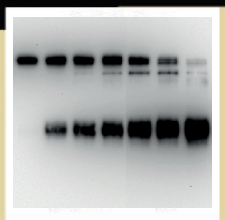
INTERNATIONAL PROTEOLYSIS SOCIETY

QUICKCUTS

Editors :
Leila Akkari (Netherlands Cancer Institute)
Catherine Moali (CNRS, University of Lyon)







THE PREMIER RESOURCE
FOR ALL YOUR IMPORTANT PROTEASE QUESTIONS

A Message From the President:

Dear IPS community,

I hope you are all doing well during these crazy times. Many of us were fortunate enough to visit Mariánské Lázně (Marienbad) in Czech Republic before worldwide travel came to a standstill. The 11th General Meeting of IPS was a great success and I would like to sincerely thank Kvido Stříšovský and Jan Konvalinka for organizing the meeting in such a historic and beautiful location. In addition, I want to congratulate Judith Clements for receiving the IPS Lifetime achievement award and Lucía Chávez Gutiérrez for receiving the inaugural IPS Young Investigator Award.

I would like to welcome all of our new IPS members and hope that our society can provide you with mentoring and networking opportunities to allow you to thrive in your scientific career. In addition, I would like to welcome our new officers and to thank our departing officers for their service to IPS. In particular, I am very grateful to Ulrich auf den Keller, for all his hard work over the past 4 years serving as IPS secretary and then president; and to Catherine Moali and Leila Akkari for putting together this QuickCuts newsletter.

Sadly, we have lost two members of the protease community, Professor Zena Werb and Professor Kanti Daya Bhoola, who have each made major contributions to MMP and peptide hormones research, respectively. I hope that the scientific knowledge that they have uncovered during their lives will be a platform for the next generation of young scientists to advance their research.

While the COVID-19 pandemic has brought nothing but bad news to our lives, I want to mention two small silver linings that we should focus on during these trying times. Firstly, the pandemic has highlighted the importance of protease inhibitors in the treatment of disease and it would be great for our community, if one or more inhibitors become key drugs for the treatment of coronavirus infections. Secondly, I have been delighted to hear that many members of our community have been willing to share data and reagents such as plasmids, substrates, inhibitors, in order to speed up the discovery of a protease inhibitor to treat coronavirus. I believe that much of this camaraderie and teamwork has been fostered by the positive one-on-one interactions that we have all had at past IPS meetings.

Looking to the future, I hope to see you at the 12th General Meeting of IPS that will take place in Singapore from September 19th to 24th, 2021. This meeting is being organized by Henry Mok Yu-Keung, Jayaraman Sivaraman and Manjunatha Kini. I truly hope that worldwide travel will return to normal so that we can see each other in-person and enjoy the beauty that Singapore and the surrounding area has to offer. The future is also bright for young scientists in the protease field with the recent announcement of a German Research Foundation-funded doctoral program that is focused exclusively on protease research. I hope that this is a sign that governments and other funding agencies appreciate the importance of our research and will continue to support our scientific endeavors. Stay safe,

Anthony O'Donoghue, IPS President

COUNCIL OF THE INTERNATIONAL PROTEOLYSIS SOCIETY

Meeting report

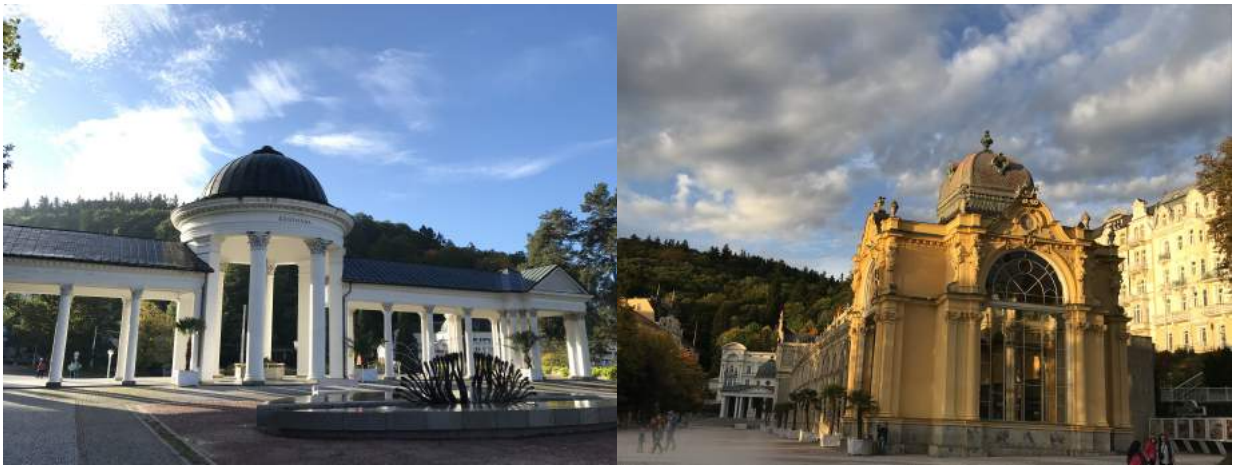
11th General Meeting of the International Proteolysis Society *´Interfaces in Proteolysis´* 29 Sep - 4 Oct 2019, Mariánské Lázně, Czech Republic

(photo credit : IPS organizers and Sandrine Vadon-Le Goff)

Close your eyes and imagine a time when travelling around the world was still possible… It was before the rapid spread of a small virus eradicated one of the most enjoyable habits of scientists consisting in having regular meetings to discuss recent progress in their research field. The 207 delegates from 28 countries of 6 continents who attended the IPS 2019 conference last October must retrospectively appreciate their good fortune! This meeting was made possible thanks to the great work of the organizers, Kvido Stříšovský and Jan Konvalinka from IOCB, Prague. After the very successful IPS 2017 meeting in Banff, they had courageously taken up the challenge of organizing another stunning meeting and they actually did it very well.

IPS 2019 delegates in the magnificent lecture hall of the Casino Cultural and Conference center, Marienbad, Czech Republic

The location (Marienbad or Mariánské Lázně in Czech) and the meeting venue (the Casino Cultural and Conference Center built around 1900) were totally amazing in terms of history and culture and were largely commented by the speakers. Singing fountains, nice walking trails, colored poisonous mushrooms, relaxing (post-session) spa meetings and passionate debates on gender issues in science also contributed to create a very special atmosphere. The only thing the organizers did not manage to keep at the top was the weather… but this was largely compensated by abundant food with some very typical Czech dishes, good beer and wine!



Colonnade, singing fountain and springs in Marienbad under two different weather conditions

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Meeting report

Beside offering the romance of a 19th century spa town with all the modern comfort, Marienbad was also the perfect place to organize a protease meeting because, as all brochures will tell you, springs and protease targets have similar recognized benefits to treat a number of disorders such as "disorders of the kidneys and of the urinary tract, respiratory disorders, locomotive system disorders, metabolic disorders, gynaecological disorders including sterility and oncological disorders".

From the organizers themselves, the motto of the meeting 'Interfaces in proteolysis' denoted their aim to assemble a program exploring "the roles of proteolysis across biology at the interfaces between health and disease, aqueous and lipidic, ordered and disordered, academic and industrial, or even between the enzymatic and non-enzymatic".

This motto was beautifully exemplified by Matthew Freeman who kicked off the meeting with an impressive Keynote Lecture entitled "Rhomboids and proteolysis at membrane interfaces". Also very inspiring for the community was the Lifetime Lecture by Judith Clements "From mice to me" who talked about her fascinating work on kallikreins in hormone-dependent cancers, after a vibrant introduction by Klaudia Brix. The meeting was concluded by the Keynote Lecture given by Seamus Martin who told us about "Proteases at the nexus between cell death and inflammation" and gave a brilliant lesson of how to catch audience attention after 5 days of meeting.

Opening and closing Keynote Lectures by Matthew Freeman and Seamus Martin

Lifetime Lecture by Judith Clements

We are not forgetting the more than 50 excellent talks from invited speakers or selected from abstracts, the flash talks and the posters which all contributed to make this conference another memorable IPS meeting. A glimpse of the session content is given below (special thanks to the session chairs who took the time to write summaries!).

The next meeting, planned in Singapour in 2021, will be organized by Henry Mok Yu-Keung, Jayaraman Sivaraman and Manjunatha Kini and also show great promise in terms of scientific, culinary and cultural experience! Let's now continue to work actively to find treatments for COVID19 and make sure that the meeting can be held in safe conditions!

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Meeting report

The Monday morning session was all about the bigger picture of **proteostasis in health and disease** in cellular damage, rescue and repair and was chaired by Klaudia Brix and Jan Konvalinka. Michael Groll gave an insightful presentation focusing on the assembly of proteasomes, the versatile macromolecular complexes constituting the constitutive, immuno- or thymo-proteasomes. Eventually, a molecular mechanism is emerging and the solutions to many open questions uncovered by integrating a wealth of structural data with the effects of specific mutations of proteasomal subunits on the survival of e.g. yeast cells. Another group of essential proteolytic enzymes, cathepsins, was then introduced by Galia Blum, who focused on their roles in atherosclerosis. Being one of the pioneers generating activity-based probes to spot cysteine cathepsin activities, she showed promising results of using the probes as more than diagnostic tools, namely, as future therapeutic agents in treatment of cardiovascular diseases.

Charles Craik inspired the audience by linking proteolysis with protein homeostasis in more general terms. He elegantly revisited the connections of caspase-mediated unmasking of substrate C-termini with their binding to co-chaperones. Thereby, a re-wiring of protein degradation emerges that regulates protein fates from degradation to persistence. Clearly, a pathway of protease-governed signaling was brought in the spotlight to be important for proteostasis in cellular survival strategies. Proteases are essential in all circumstances, and so is their involvement in DNA damage and repair functions. Klara Grantz Saskova spoke about a specific protease that engages in resolving the cross-links between DNA and proteins. Yet, another promising theme was discussed, namely, how proteases involve in connecting the DNA damage response with cellular rescue mechanisms.

New collaborations discussed at coffee break

Former IPS presidents Ulrich auf dem Keller and Thomas Reinheckel

The afternoon session, focused on **technological platforms and tools**, was chaired by Manu Platt and Steven Verhelst. The first speaker was Yifat Merbl of the Weizmann Institute in Israel. Yifat presented work on the isolation and mass spectrometry analysis of proteolytic peptides (MAPP) generated by the proteasome. A nice analogy to this work is to analyze what is in cellular garbage cans (the proteasome) to distinguish cell behaviour and functions. Interestingly, applying this analytical technique to clinical samples revealed proteasomal regulatory mechanisms in cancer and degradome profiles that were distinguishably different between cell types in proteasomal degradation, but not in total degradome, thus corroborating the additional power of this method. Next, Alessio Ciulli from the University of Dundee explained the concept of PROTACs, proteolysis targeting chimeras. PROTACs are small molecules that have a dual binding mode: they can be designed to target and bind proteins on one hand, and recruit E3 ubiquitin ligases on the other hand. As a result, this leads to degradation of the targeted protein. It was demonstrated during the talk how it is now possible to change the different parts of the PROTAC molecules to induce degradation of specific proteins.

Third speaker in the session was Oded Kleifeld from the Technion (Israel Institute of Technology), who presented new work on the enrichment of carboxy-terminal substrates of proteases. Most techniques have focused on the isolation of newly formed N-termini after proteolytic cleavage, but he presented CarboxyterminAl Peptide Enrichment (CAPE) as a method that takes advantage of C-terminal labeling and identification.

The last talk of the session was presented by Olga Vasiljeva of CytomX Therapeutics describing Probody technology. Probodies are antibody prodrugs that are inactive until they encounter a specific protease at which point the proteolytic cleavage event activates, binds, and labels targets. Here, these probodies were used to image target engagement of disease-associated proteases in preclinical models and patient samples demonstrating their utility.

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Meeting report

During Tuesday morning session on **proteases in cancer**, chaired by Bonnie Sloane and Aleksi Sedo, recent studies on two types of metalloproteases (MMPs and ADAMs) and two families of cathepsins (the aspartic protease cathepsin D and the cysteine protease cathepsin L) were presented. Dr. Irit Sagi, Mauizio Pontecorvo Professorial Chair in the Department of Biological Regulation and Dean of the Feinberg Graduate School of the Weizmann Institute of Science, Rehovot, Israel, spoke with passion on the efforts of her group to translate their basic biochemical and biophysical studies on MMPs to clinical use. The emphasis of this talk was pancreatic cancer. She described her group's success in integrating real-time spectroscopic and molecular imaging approaches to uncover complex and dynamic molecular interactions among MMPs, proteases that remodel the extracellular matrix, and lysyl oxidase (LOX), an enzyme that catalyzes collagen cross-linking and thus regulates ordered collagen architecture. Those studies led to drug design efforts and the development of a new class of inhibitory antibodies against MMPs and LOX. These antibodies are currently being optimized for clinical use in cancers as well as inflammatory diseases. Of note for the protease community is that Dr. Sagi indicated that the experimental tools that her group has developed are available on request.

Dr. Marie Kveiborg, Associate Professor in the Biotech Research and Innovation Centre at the University of Copenhagen, Denmark, discussed the role of ADAMs in cancer progression. She presented data on both proteolytic and non-proteolytic roles for these transmembrane proteases. Examples of proteolytic roles are ectodomain shedding of basigin, a transmembrane glycoprotein, by ADAM12 in a variety of cancers and of EGFR ligands by ADAM17 in colorectal cancer. An example of a non-proteolytic role is an increase in β1 integrin levels on the surface of prostate cancer cells that is mediated by ADAM9 regulation of endocytosis. Dr. Kveiborg also discussed how the subcellular localization and trafficking of ADAMs affects function and how protein kinases, adaptor and transport proteins contribute to spatiotemporal control of the ADAMs.

Threat or treat? Amanitas along Marienbad trails…

Dr. Thomas Reinheckel, Professor of Molecular Medicine in the Institute of Molecular Medicine and Cell Research at the University of Freiburg, Germany, spoke on their studies using the MMTV-PyMT breast cancer transgenic mouse model to characterize the lysosomal aspartic protease cathepsin D. Although this aspartic protease is elevated and is a prognostic marker in breast cancer, its function has remained unclear. By crossing a conditional cathepsin D knockout mice with MMTV-PyMT mice, Reinheckel and colleagues revealed that the absence of cathepsin D in mammary epithelial cells leads to a delay in tumor development. This is mediated by a reduction in mTORC1 signaling and an induction of cellular senescence. Although mTORC1 signaling remains disrupted in cathepsin D deficient mammary epithelial cells, senescence is eventually overridden in these cells by switching to alternative oncogenic signaling pathways.

Maria Alejandra Parigiani, MSc, a graduate student in the Institute of Molecular Medicine and Cell Research, University of Freiburg, Germany (Reinheckel/Peters lab), also presented data on use of the MMTV-PyMT transgenic mouse model of breast cancer to define protease involvement in malignant progression. Her studies however focused on another lysosomal cathepsin, the cysteine protease cathepsin L, which as seen for cathepsin D, is upregulated in breast cancer. Parigiani and colleagues deleted cathepsin L specifically in epithelial or myeloid cells to study its role in those two cell types. They reported that absence of cathepsin L in mammary epithelial cells significantly delays the onset of tumors. The cells themselves acquire mesenchymal features, including a migratory phenotype, and the tumors become high grade and primarily dedifferentiated.

Excursion to Chateau Becov nad Teplou

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Meeting report

The topic for session 6 was focused on **intramembrane proteases**. The session was chaired by Joanne Lemieux and Harald Steiner and started with a talk from Marius Lemberg (ZMBH Research Group Leader, Heidelberg, Germany) on the role of signal peptide peptidase in the control of cellular protein homeostasis and the regulation of cholesterol levels. This talk was followed by Lucia Chavez Gutierrez (VIB-KU Leuven, Belgium) on the mechanisms securing γ-Secretase APP interactions and regulating Aβ length, where thermoactivity assays were used to explore the stepwise cleavage of amyloid precursor protein/Aβ substrates. Short talks were delivered by Guanghui Yang (Tsinghua University in Beijing) who discussed the structural basis of substrates recognition by human γ-secretase. Insights into the binding of amyloid precursor protein were revealed. The last talk of the session was given by Bernd Schroeder (TU Dresden, Germany) on the role of intramembrane proteases SPPL2a/b in metabolic regulation and the identification of SNARE proteins as substrates of these proteases.

Session 7 was chaired by Kvido Strisovsky and titled **protease/pseudoprotease interfaces**. It was started by Colin Adrain (IGC Lisbon, PT) who reported on the unexpected role of rhomboid-like pseudoprotease iRhom2 and its client ADAM17 in energy metabolism in the mouse adipose tissue. Loss of iRhom2 protects mice from weight gain, and metabolic syndrome symptoms when on high-fat diet, and promotes thermogenesis in brown adipose tissue, enabling iRhom2 deficient mice to dissipate excess energy more efficiently than wild type animals. These findings indicate that iRhom2 is a central orchestrator of adipose tissue homeostasis during metabolic disease. Second speaker was Sonya Neal (USCD) who reported on the unexpected finding that the rhomboid pseudoprotease derlin (Dfm1) in yeast is key for retrotranslocation by both Hrd1 and Doa10 E3 ligase complexes (Neal et al. Mol Cell 2018) and discussed its implications.

Session continued by the talk of Jakub Began (IOCB Prague, CZ) on the dual role of rhomboid protease YqgP in Bacillus subtilis in membrane protein quality control. YqgP licenses degradation of magnesium transporter MgtE under metal cation stress conditions by catalyzing intramembrane cleavage of MgtE and by acting as a pseudoprotease recruiter/adaptor of substrates for the membrane bound degradative ATP-dependent metalloprotease/unfoldase FtsH. This process is conceptually strikingly analogous to a primitive form of the eukaryotic ER associated degradation, and this study is now published (Began et al. EMBO J 2020).

Private concert for IPS delegates !

Session was concluded by Regina Fluhrer (University of Augsburg, DE) who reported on the aspartyl intramembrane protease SPPL2c in the regulation of vesicular transport during spermatogenesis in mice. SPPL2c was until recently thought to be an orphan protease, but it was now shown to catalyze cleavage of SNARE proteins, which impairs vesicular transport and leads to cargo retention in the ER. This causes disturbances of intracellular compartments, mainly Golgi, which manifests as altered glycan patterns in mouse spermatids and impaired acrosome functions in SPPL2c knock-out mice. This session prominently demonstrated the regulatory importance of rhomboid pseudoproteases, and illustrated that proteases can cave pseudoprotease roles. Overall, speakers of this session presented exciting and largely unpublished data, instigating lively discussions.

Close interactions during poster sessions

Meeting report

On the morning of the fourth day of the conference, discussion leaders Jeanne Hardy and Jan Dvořák chaired a session entitled **proteases in parasite biology**. Prof. Jim McKerrow (Univ. California San Diego) led off the session elucidating roles of cysteine proteases in the evolution of parasitic organisms. He explained how oxygen rich environments contributed to evolutional switch from cysteine to serine proteases because they are less susceptible to oxidation. Later, he presented detailed studies on a cathepsin L-like cysteine protease called cruzain from T*rypanosoma cruzii* causing Chagas Disease. He described the herculean efforts he has directed over the past decade to bring an effective treatment for Chagas Disease based on cruzain inhibitors using academic resources. He described how this intracellular parasite (parasite being named for Greek priests who ate at the public expenses) evolved a cysteine protease for successful intracellular parasitism. McKerrow's group focused on a covalent inhibitor K11777, which was originally developed as a 5 nM Cathepsin L inhibitor but failed clinical development as it also inhibits Cat B and S. Cathepsins are in the lysozymes of the host but the *T. cruzii* protease is secreted to the cytosol. This provided the inhibitor an excellent safety profile. This subcellular localization also provides a novel mechanism for inhibition of cruzain impacting parasite viability. Because cruzain is inactive, it leads to substrate build up in the Golgi apparatus, which causes swelling and ultimately parasitic death. McKerrow continues his pursuit of development of another unique class of Gallinamide A based inhibitors of cysteine proteases.

Lucia Chavez-Gutierrez receiving the first Young Investigator Award of the IPS

Prof. Mike Blackman of the Francis Crick Institute provided a captivating talk entitled "Breaking out: proteases in egress of the malaria parasite from its host red blood cell". Like Prof. McKerrow, Prof. Blackman's talk also focused on repurposing the drug E64d, which is a natural product from *Aspergillus japonicus* and an inhibitor of cysteine proteases. It was originally developed as a treatment for muscular dystrophy, but stopped for lack of efficacy. Prof. Blackman's team is currently pursuing this inhibitor for the treatment of malaria by blocking egress of merozoites from red blood cells.

Prof. Jeremy Mottram from Univ. of York presented his work on the *Leishmania* cysteine proteases. The talk described their systematic approach to identify the optimal protease drug target for treatment of leishmaniasis. They undertook a CRISPR-based screen and found 16 essential and 3 non-essential proteases, 18 essential and 4 non-essential deubiquitinases (DUBs), as well as a number of essential E1, E2 and E3 ligases in the ubiquitin-proteasome pathways. They also screened 161 kinases. At this stage, DUBs 1,2,13 and 16 are some of the most fascinating proteases under investigation.

The final speaker of the session was Dr. Daniel Sojka of Biology Centre CAS described his fascinating work on protease network from ticks. Using the European Lyme disease vector *Ixodes ricinus*, their past research has revealed that the catabolic part of this process in females, prior rapid engorgement, occurs intracellularly in tick female gut cells via a multienzyme network of cysteine and aspartic peptidases comprising cathepsins L (IrCL), B (IrCB), D (IrCD) and legumain (IrAE). However, omics and experimental data clearly display differences in tick intracellular digestion after rapid engorgement and post tick detachment from hosts. In addition to their role in blood-to-eggs metabolic protein turnover, IrCL3 and IrCD2 seem to contribute to the production of hemoglobin-derived antimicrobial peptides, which helps to conserve the large amount of blood meal "stored" inside the tick gut lumen of detached fully-fed tick females preparing for oviposition. The long-term goal of this project is to target the tick proteolytic digestion as a strategy against ticks and the diseases they transmit.

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The Thursday morning session on **chemical biology approaches to proteases** was chaired by Julia Mitschke and Oliver Schilling. It was opened by an exciting talk of Edward Tate from the Imperial College London on highly efficient and selective chemical probes for secreted and intracellular proteases. He presented data from his collaboration with Mission therapeutics on a potent activity probe targeting the deubiquitinase Ubiquitin carboxy-terminal hydrolase L1 (UCHL1). UCHL1 is proposed as a potential therapeutic target in neurodegeneration, cancer as well as liver and lung fibrosis. Ed further reported on his collaboration with Judith Clements' lab (Queensland University of Technology). In this project they gained new insights into the kallikrein "activome", a network of 15 secreted serine proteases.

Edgar Deu (Francis Crick Institute London) gave an intriguing talk on *Plasmodium* proteases, namely dipeptidyl aminopeptidases DPAP1 & 3 and Ddi1, which play a role in erythrocyte invasion. He demonstrated that DPAP1 and 3 are primarily involved in red blood cell (RBC) invasion of the parasite with relevance for RBC surface receptor recognition. They identified different subsets of substrates for the two proteases by N-TAILS, which suggested complementary roles of DPAP1 and 3 in RBC invasion as well as a DPAP-independent invasion pathway. Edgar's second topic covered new insights into the function of DNA-damage inducible protein 1 (Ddi1). Ddi1 is implicated in protein secretion, sorting, proteasome regulation, cell cycle progression and stress response. However, the role of its retropepsin-like domain is yet unknown. Edgar demonstrated that conditional knockout of *Plasmodium* Ddi1 (PfDdi1) completely blocks RBC invasion. The same phenotype was achieved by switching the catalytic Asp to Asn suggesting a critical role for PfDdi1 catalytic activity. Interacting proteins identified by pull down experiments included proteins involved in protein quality control, proteasome regulatory particle and ERAD pathway. As PfDdi1 deficient parasites are more sensitive to heat shock, Edgar suggested that loss of PfDdi1 function in the ubiquitin-proteasome system increases cellular stress resulting in RBC invasion defects.

Marcin Drag from Wroclaw University of Technology, Poland, reported on a new technology for incorporating unnatural amino acids into ubiquitin sequences. This groundbreaking technology allows to create unnatural ubiquitin with high activity and selectivity thereby facilitating the design of ubiquitin substrates and activity-based probes optimal for individual deubiquitinating enzymes (DUBs) which are otherwise difficult to target due to overlapping substrate specificity, similar activity and location.

Anthony O'Donoghue, the IPS president for the 2019-2021 period, acknowledging IPS 2019 organizing team (from left to right : hotel event manager Veronika Smutná, Kvido Strisovsky and Jan Konvalinka)

The final talk of this session was held by Andrew Griswold (Memorial Sloan Kettering Cancer Center, New York). He is a very talented graduate student from Daniel Bachovchin's lab and introduced CHOPS (Chemical enrichment Of Protease Substrates) as a novel tool to identify protease substrates. CHOPS exploits a 2-pyridinecarboxaldehyde (2PCA)-biotin probe, which selectively biotinylates protein N-termini except those with proline in the second position. CHOPS is suitable to unravel substrates for any protease and it is particularly well suited to discover canonical DPP substrates. Using CHOPS, he showed that DPP8 and DPP9, enzymes that control the Nlrp1 inflammasome through an unknown mechanism, do not directly cleave Nlrp1 but rather process short peptides. More generally, this work highlights a novel technology for identifying protease substrates, which Andrew anticipates will complement available "N-terminomic" approaches.

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Meeting report

The final session of the meeting was chaired by Manjunatha Kini and Ulrich auf dem Keller and featured four presentations on **emerging topics** in proteolysis research. Matt Bogyo from Stanford University gave an impressive and inspiring talk about newest technologies in functional protease imaging in disease. By designing novel imaging probes with multiple integrated functionalities, his research team devised new chemical tools that reach unprecedented sensitivity and specificity in tumor tissue imaging and will pave the way for automated image-guided surgeries.

Next, Jan Potempa (University of Louisville and Jagiellonian University Krakow, Poland) presented a fascinating body of work on *P. gingivalis* as an unexpected pathogen in Alzheimer's disease. Following Koch's molecular criteria of bacterial infections, he showed clear evidence of colonization and infective behavior in patients' brains and concluded with promising strategies for therapeutic intervention based on targeting of gingipain proteases as critical virulence factors.

Anthony O'Donoghue continued this highly translational session by introducing a novel concept and first implementation of a device for wound diagnostics. He teamed up with a collaborating engineer and combined knowledge about disease-related protease activities with microfluidics to produce a versatile sensor for point-of-care quantitation of protease activity in body fluids. The session was concluded by Hans-Ulrich Demuth from the Fraunhofer Institute for Cell Therapy and Immunology in Halle, Germany who followed up on *P. gingivalis* as an important pathogen in periodontitis and presented a translational study unraveling glutaminyl cyclase (GC) as a critical upstream regulator of gingipains. On this basis, he demonstrated that targeting GC with potent and specific inhibitors has a high potential to specifically interfere with detrimental pathogen activities while keeping side effects at a minimum.

The happy laureates of the best poster awards by the FEBS Journal and the Czech Society for Biochemistry and Molecular Biology. Left to right:
- Alexandre Desroches
- Lauren Eyssen
- Tess Malcolm
- Pavla Fajtová
- John Widen
- Kristýna Blažková

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Meeting report

IPS 2019 Travel Awards

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Ahmed Muhammad, Nouman
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Hölzen, Lena
Madzharova, Elizabeta
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Sabino, Fabio
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Anderson, Bethany
Marijanovic, Emilia
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Distribution of travel awards by IPS vice-president Manjunatha Kini, assisted by stage director Ulrich auf dem Keller

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Congratulations

Professor Marcin Drag (Wrocław University of Science and Technology, Poland) has been awarded the so-called Polish Nobel Prize by the Foundation for Polish Science.

On the 4th of December 2019, at the Royal Castle in Warsaw, Marcin Drag was awarded the Foundation for Polish Science (FNP) Prize. This prize is the most important and prestigious scientific award in Poland. It is awarded in four fields by the FNP council for "significant advancements and scientific discoveries which shift cognitive boundaries and open new perspectives for research". Marcin Drag received the prize in the field of chemical and material sciences "for developing a new technological platform for obtaining biologically active compounds, in particular proteolytic enzymes inhibitors".

Most of us have already heard (or used) the smart HyCoSuL (Hybrid Combinatorial Substrate Library) approach that he established for several enzymes but it is only one example of the developments made in the field by Marcin. His contribution to protease research is outstanding with more than 100 scientific papers published in top-class journals and quoted over 2 thousand times and 9 patents. Congratulations to him!

From Paulina Kasperkiewicz who attended the ceremony :
"It was the second time in my life when I saw Marcin in a suit and a tie.
And I have met him for the first time
when I was a 3rd year student (11 years ago)!"

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In memorium - Prof. Zena Werb

In the next two articles, Chris Overall and Charles S. Craik celebrate the extraordinary life of Professor Zena Werb.

We have lived through the years in an amazing field, watching it grow from three MMPs to more, drugs coming and going, companies rising and falling, and now dear colleagues, Zena Werb's passing.

Zena played a major part in understanding the perplexing mysteries of MMPs: from co-eluting MMPs confounding interpretation, from collagenase, gelatinase and proteoglycanase to stromelysin (renamed by Zena); from zymogen and molecular weight mysteries; trypsin versus APMA activation; from Collagenase Activator Protein to stromelysin-1, and ConA to MT1-MMP (s); from integrin binding or not; from one TIMP to four; from classic protein purification to cloning, transgenic and KO mice, from matrix to more. Zena had a major part in all of these advances, and she certainly told us about them! We all have our Zena stories, what a character, what a force, what a reviewer, difficult at times, mellow and supportive at others, she had opinions and strengths and relentlessly nurtured female scientists, with a fierce scientific brain to relentless promoting MMPs to the broader field.

Chris Overall (Chair) and Zena Werb (Vice-Chair) at the 2003 Gordon Research Conference in Matrix Metalloproteinases, Big Sky Resort, Montana

Chris Overall,
University of British Columbia,
July 22, 2020

Charles Craik with Zena Werb after she had received the 2015 Lifetime Achievement in Mentoring award from UCSF

Zena died unexpectedly on June 16th, 2020, 75 years after being been born in the German Bergen-Belsen concentration camp in March of 1945. A week before her passing, she attended a UCSF Cancer Center leadership meeting on Zoom and was in good spirits because she had some unspent funds and wanted to use them for a few students who needed funding in the Fall of 2020. We connected afterwards and talked about mutual interests and in particular her thinking regarding immune effector monocyte-neutrophil cooperation and its role in preventing metastatic progression of breast cancer.

The topic was an example of what often impressed me about her approach to science and reminded me of what she told me early on in our 30-some year relationship; namely, that if you are going to spend 80 plus hours a week thinking about something, why not have it be something important and worthwhile. This particular question involved a long-standing interest of hers which was the mechanisms behind the findings that many breast cancer patients do not develop metastatic outgrowths. She wanted to see if her latest results could provide novel immunotherapeutic target molecules and was asking my opinion. After agreeing to start looking into it together with some recombinant antibody campaigns in my lab using some of her targets, I brought the discussion back to proteases and the extracellular matrix, her first love, and the flip side of the question. In particular, we went through the data from her recent collaborative paper showing that MMP9 modulated the metastatic cascade and immune landscape for breast cancer in a metastatic lung cancer model.

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In memorium - Prof. Zena Werb

We finished the lengthy discussion reminiscing about a previous happy time we were together to celebrate her receiving the highest award that UCSF gives to mentors, the Lifetime Achievement in Mentoring award. She was always passionate about helping younger generations succeed and would spend countless hours helping them think about and how to accomplish the science they wanted to do. We agreed to get together to visit the upcoming Frida Kahlo exhibit, "Looks Can be Deceiving" at the San Francisco De Young museum. Zena was a fan of Frida Kahlo and especially her 1937 painting "My Nurse and I" since it depicted the ducts and glands of the lactating breast with remarkable accuracy. Zena often used the picture in the introduction to her talks on mammary gland development and breast cancer.

Zena was a truly independent thinker. This type of thinking, coupled with her penchant for asking big questions and providing insight and answers provided her with a strikingly high H factor over 150 and a listing in the top 100,000 referenced scientists at position 459. We have much to be thankful for and have lost a great leader in our field.
Her independence was sometimes viewed as contrarian. For example, when the opportunity to expand beyond the seriously overcrowded Parnassus Heights campus, she was very supportive of my being the first to move to the Mission Bay campus even though it would make it much more difficult for us to meet face to face on a regular basis. Our labs had been in close proximity at the former campus and we shared a grant with one another. She felt that we could stay in touch by phone and that she would move once the Cancer Center was established at Mission Bay. But as time progressed, she decided to stay where she was despite multiple attempts encouraging her to move to the new Cancer Center. I mentioned that she may be contrarian and she said, no, I genuinely believe that I can make a greater impact where I am and indeed she did. To name a few of her more notable awards, she was elected fellow of the American Academy of Arts and Sciences and the American Association for the Advancement of Science and member of the National Academy of Medicine and the National Academy of Sciences.

Like so many of her collaborators, colleagues, students and friends, I will miss Zena's penetrating insight, encyclopedic information about biology, annual holiday letters, rugalach care packages and genuine interest in what I was doing both in and out of the lab. We often laughed about our first encounter when I showed her the structure of a site directed variant protease I had been working on and I was beyond excited about. She told me then that "it looks like a wall paper pattern to me" and "I am not sure how that will help me understand what the enzyme really does". We spent the next 30 years helping one another see what the other saw and I was ready for many more years of learning from her.

Charles S. Craik, PhD
with input from Allan Basbaum PhD,
Robert Fletterick PhD
& Michael Marletta PhD
University of California, San Francisco
July 19, 2020

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In memorium - Prof. Kanti Daya Bhoola

On December 18, 2019, our colleague and friend Professor Kanti Daya Bhoola, a world leader in the field of peptide hormones, passed away at the age of 89 in Alice Springs, Australia.

Kanti was born in South Africa and, after completing his grade-school education, enrolled at the University of Witwatersrand, Johannesburg, where, despite not being a musician, he received a first class pass in History and Theory of Music. However, Kanti wanted to be a doctor. Under apartheid, however, that was all but impossible; fortunately, a family friend happened to be Eamon de Valera, then the Taoiseach of the Republic of Ireland. Thus, in 1948 Kanti was able to enroll at the National University of Ireland where he graduated as Medical Doctor in 1957. Fifty years later, University College of Dublin honored him with its Distinguished Medical Graduate Medal.

After appointment as physician at the National Health Service, Kanti started work on his Ph.D. at University College London in 1958. As doctoral student, he discovered a new kinin in hornet venom, research that formed the basis of his thesis, 'Properties of kallikrein and kallidin and related substances'.

He subsequently published four papers in Journal of Physiology and British Journal of Pharmacology based on that work. In 1962, Kanti became Lecturer in Physiology at the University of Singapore, and, in 1963, returned to England where he was appointed Registrar in Cardiothoracic Medicine and Lecturer in Clinical Pharmacology at Central Middlesex Hospital. Here, Kanti's enthusiasm for and competence in basic medical research led to widely respected papers in The Lancet and the New England Journal of Medicine.

In 1967, following his appointment as Lecturer in Pharmacology at the University of Bristol, he delineated in submaxillary glands the cellular localization of tissue kallikrein (KLK1), i.e. the major kinin-releasing enzyme, showing that kallikrein is sequestered in secretory granules. Working on exocrine pancreas, he reported the role of cGMP as second messenger for peptide hormone action (Nature 262: 404-406, 1976). Mechanisms of proteases secretion occupied his attention the next 10 years. In the eighties, Kanti and his group discovered that KLK1 is expressed in human neutrophils. In 1992, he published a comprehensive review on kallikreins and kinins, a seminal contribution still cited by many authors (Pharmacological Reviews 44:1-80,1992).

Four universities on three continents appointed Kanti as Professor, five times over. However, the one he was most proud of was conferred by the University of Natal in his native South Africa, which had refused to admit him as medical student. In 1992, he was appointed as Founding Head of the Department of Clinical and Experimental Pharmacology at the university's Nelson Mandela School of Medicine. In 1996, he was bestowed with the Frey-Werle Gold Medal for his outstanding scientific achievements. The same year he was elected Fellow of the Royal Society of South Africa. In 2000, he received the Gold Medal by the Southern African Association for the Advancement of Science, and in 2009, the South African Medical Association conferred him the Art and Science of Medicine Award for his eminent contributions to clinical medicine. At the age of 76, Kanti was appointed Honorary Professor at the Lung Institute of Western Australia in Perth. After his retirement, he continued working and publishing; his last paper was published this year (Yale Journal of Biology & Medicine 93:175-185, 2020).

Kanti was a true cosmopolitan and warm-hearted philanthropist who loved science and possessed a remarkable combination of curiosity, creativity, and endless energy. As a brilliant teacher and dedicated mentor, he passed on his enthusiasm and passion to staff and students, many of whom went on to become leading scientists with international reputation. Kanti is survived by his daughters Ishani and Harshini and his granddaughters Zareena, Varsha, Monique and Natasha. He will be sorely missed.

Carlos Figueroa, Universidad Austral de Chile, Valdivia, Chile
Hans Fritz, Ludwig Maximilians Universität, Munich, Germany
Werner Müller-Esterl, Goethe Universität, Frankfurt, Germany

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News from IPS members

From Brice KORKMAZ
INSERM UMR-1100,
Centre d'Etude des Pathologies Respiratoires (CEPR)
Université de Tours, Tours, France

Good news for all of us working on proteases

Pharmacological targeting of cathepsin C: a key therapeutic target in chronic inflammatory and auto-immune diseases

Cathepsin C also called dipeptidyl peptidase 1, attracts more and more attention from both scientists and clinicians because of its role in the activation of pro-inflammatory neutrophil serine proteases implicated in diverse chronic inflammatory/auto-immune disorders. Promising preclinical and clinical data suggest that pharmacological inhibition of neutrophilic serine proteases might ameliorate these conditions. Patients with Papillon-Lefèvre syndrome (PLS) have a genetically determined deficiency in cathepsin C but, reassuringly, do not exhibit marked immunodeficiency despite the absence of neutrophil serine proteases in immune defense cells. Hence, the pharmacological control of cathepsin C activity in bone marrow precursor cells represents an attractive therapeutic strategy for neutrophil serine protease-mediated disorders including chronic obstructive pulmonary disease (COPD), cystic fibrosis, bronchiectasis, ANCA-associated vasculitis and rheumatoid arthritis. Chronic inflammatory respiratory diseases affect over 1 billion people worldwide, and cause the death of 4 million people every year. More specifically, COPD will be the 3rd leading cause of death in the world in 2030. A variety of cathepsin C inhibitors, developed by pharmaceutical companies and academic investigators, are currently evaluated in preclinical/clinical trials as anti-inflammatory drugs. A review of the therapeutic targeting of cathepsin C resulted from the first International Symposium on Cathepsin C (**IsyCatC**, Tours/France, April 2017) and was published in the journal *Pharmacology and Therapeutics* (1). This symposium launched the **International Cathepsin C Consortium (IcatCC)** that we recently set up.

Positive and promising results (Phase 2 study) were also recently reported for treatment of patients with non-cystic fibrosis bronchiectasis with a cathepsin C inhibitor (2). Such news is very inspiring for biochemists and cell biologists studying functionality, maturation or tissue localization of cathepsin C, as well for chemists developing specific cathepsin C inhibitors and clinicians managing patients with neutrophil serine proteases-mediated disorders. Lowering the constitutively produced neutrophil serine by pharmacological inhibition of cathepsin C holds great promise for future therapies.

It is gratifying to see that the hard work of all colleagues from academic labs and industry as well as advocacy in the cathepsin C field may have a clinical payoff.

1. Korkmaz, B.; Caughey, G. H.; Chapple, I.; Gauthier, F.; Hirschfeld, J.; Jenne, D. E.; Kettritz, R.; Lalmanach, G.; Lamort, A. S.; Lauritzen, C.; Legowska, M.; Lesner, A.; Marchand-Adam, S.; McKaig, S. J.; Moss, C.; Pedersen, J.; Roberts, H.; Schreiber, A.; Seren, S.; Thakker, N. S., Therapeutic targeting of cathepsin C: from pathophysiology to treatment. Pharmacol Ther 2018, 190, 202-236.

2. https://www.prnewswire.com/news-releases/insmed-announces-positive-top-line-results-from-phase-2-willow-study-of-ins1007-in-patients-with-non-cystic-fibrosis-bronchiectasis-300997568.html

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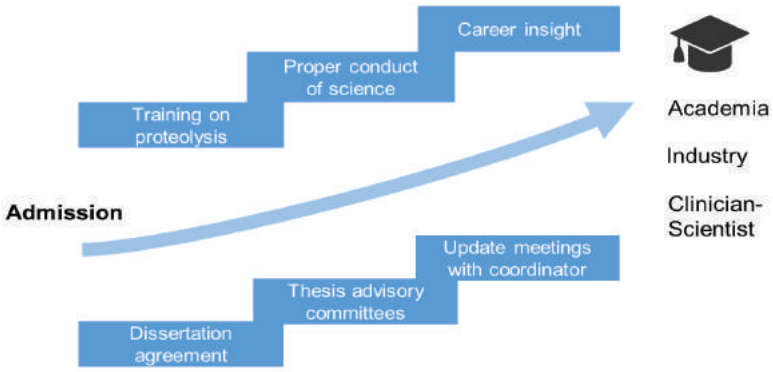
News from IPS members

An exciting new PhD training school in Freiburg, Germany

From Dr. Ruth Geiss-Friedlander
Institut für Molekulare Medizin und Zellforschung
Zentrum für Biochemie und Molekulare Zellforschung (ZBMZ)
Albert-Ludwigs-Universität Freiburg, Freiburg, Germany



A new PhD training program on proteases has been approved by the German Research Foundation (DFG):
Understanding Protease Functions in Cellular Pathways through Discovery and Analysis of Protease Substrates (ProtPath).
Speaker: Prof. Thomas Reinheckel.

This doctoral Graduate Program will be situated in Freiburg, and is a great opportunity for scientists interested in learning more about proteases, their substrates, and their functions in biology and medicine.
Biochemistry, cell biology, genetics, and proteomics are the key methodologies of our research endeavour.
In total, we offer 11 PhD positions which will be fully funded by the DFG.

Please note:
The call will close September 20th.
The project start will be between January 1st and April 1st, 2021.

For more information, please visit us on https://www.protpath.uni-freiburg.de/
https://academicpositions.de/employer/grk-2606-research-training-group-protpath

See you in Freiburg!

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TopFIND 4.0: The protease web, substrate and cleavage site termini database updated

From Simran Rai, Paul Pavlidis, Christopher M. Overall,
University of British Columbia, Vancouver, BC Canada
chris.overall(at)ubc.ca

A new version of TopFIND 4.0 with an improved user interface and functionality is now online with a new URL: https://topfind-.clip.msl.ubc.ca. TopFIND now has 331,278 natural and neo N- and C- termini from 35,044 protease cleavage sites listed. TopFIND species coverage has increased and covers additional species: H. sapiens, M. musculus, R. norvegicus, S. cerevisiae, A. thaliana, E. coli, C. elegans and D. rerio. Literature describing TopFIND, the protease web and the protease expression analysis are listed at the end.

In order to strengthen grants to support the continued operation of TopFIND, users of TopFIND agree to cite the following two papers when reporting data:
1) Lange, P. and Overall, C.M. 2011. TopFIND, a Knowledgebase Linking Protein Termini with Function. Nature Methods 8, 703-704;
2) Fortelny, N., Yang, S., Pavlidis, P., Lange, P.F., and Overall, C.M. 2015. Proteome TopFIND 3.0 with TopFINDer and PathFINDer: Database and Analysis Tools for the Association of Protein Termini to Pre- and Post-Translational Events. Nucleic Acids Research 43 (Database Issue), D290-D297.

Features have also been added or improved, in order to increase the abilities of the knowledgebase and ameliorate the user experience. The protein searching and listing functionality, as well as the same functionality for N-termini and C-termini, have all been improved to make it easier for users to easily find particular proteins or termini. The terminus modification listing and searching has also been updated. Exporting of lists of N-termini and C-termini has been added to the knowledgebase. For proteins in TopFIND, the pages associated with each individual protein, as well as the similar pages for termini, have been updated to provide more information about each protein or terminus in a clearer fashion. Additionally, the documentation for TopFIND has been updated in order to provide users with information pertinent to this iteration. The application's underlying implementation has been updated to the most current versions of Ruby (2.5.6) and Rails (6.0). Under the user interface, this iteration has a restructured Model-View-Controller (MVC) design. Several models, database tables, and controllers were removed in order to clean up the design. Overall, the knowledgebase has overhauled the user interface, both functionally and aesthetically.

One key additional change made to the TopFIND v 4.0, which may seem minor, is the method of data submission from users. Rather than submitting through an embedded form, users are instructed to send their data directly to the TopFIND-associated email address, which is indicated on the site. This has been implemented to encourage faster approval of data that meets quality standards, as screening this data will prevent any issues that would potentially occur later due to invalid data. As always, users are strongly encouraged to share their data with the community, as it allows us to improve our knowledgebase and the available tools are able to draw upon a larger pool of data and produce more accurate results.

The following two tools, PathFINDer and TopFINDer are particularly useful and are described below so new users can explore their features and knowledge readouts.

PathFINDer
Pathfinding in the protease web allows for the identification of known direct and indirect explanations of observed cleavage. This is particularly important in interpretations of in vivo terminomics data, where proteins act as players in large interconnected networks. Proteases can cleave cognate substrates (direct effect) and these substrates can further cleave or inhibit downstream substrates (indirect effect). PathFINDer can facilitate differentiation of direct and indirect effects and help explain counterintuitive experimental results.

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PathFINDer accepts a list of identified human or mouse in vivo substrate candidates with their cleavage sites, along with a candidate protease, to find known direct and indirect "paths" (connections) from protease to identified. Creating this protease web is based on cleavage and inhibition data found in TopFIND. Cross-species mapping can also be accomplished between human and mouse orthologous proteins, as data for each species on its own can be sparse, particularly mouse. This allows for the formulation of a reasonable prediction to test even if data is absent. Identified paths are visualized into a network, and also listed tabularly. PathFINDer can be used on its own, or in tandem with a TopFINDer analysis.

TopFINDer, or the TopFIND ExploreR, is an analysis software allowing for the statistical evaluation and annotation of large-scale proteomics data available in TopFIND. Using a list of protein identifiers and N-/C-terminal peptide sequences as input, users are now able to obtain protein and terminus related (position-specific) information produced from TopFIND. A typical output consists of a table with general protein annotation and position-specific information for each inputted protein/-peptide sequence, including position of the terminus relative to its genome encoded sequence, the sequence context surrounding the terminus and evidences from TopFIND for the terminus.

New information provided includes evidence for five types of classification by origin: (i) termini inferred from alternative splicing derived protein isoforms in Ensembl or UniProt, (ii) N-termini inferred from alternative translation, (iii) termini inferred from cleavage together with the associated proteases, (iv) status as UniProt annotated canonical protein termini and (v) termini observed experimentally by without a known protease responsible for the cleavage. TopFINDer enables comparative analyses of observed termini in the input list to evidences for the termini in TopFIND, thus allowing assessment of biological relevance and inference on how protein termini might have biologically originated. The user will also be shown features and domains that are N- and C-terminal to the inputted terminus, and features located at the specific point of the inputted terminus, which can help with inference of the terminus' impact on protein function.

TopFINDer allows users to retrieve information in the proximity of termini of interest using a self-defined N- and/or C-terminal extension that can extend up to 10 amino acids either way from the terminus. This feature permits users to account for biological processes such as ragging, which leads to the existence of termini that are nearby but are distinct from the termini of interest. A new ragging interpreter program is under development and will be introduced by early 2021.

Not restricted solely to annotation, TopFINDer will classify by origin type and also calculate enrichment and summary statistics for submitted termini, visualized as a Venn diagram showing overlap and relative distributions of origin types. An IceLogo summarizing the amino acid sequence of submitted termini, excluding termini originating from translational events, is generated as well. The IceLogo can be used with protease specificity logos that TopFIND provides in order to identify one or more dominant protease activities. With the ability to statistically classify submitted terminal sequences by the aforementioned five distinct origin types, generation of Venn diagrams, analysis of ragged peptides, and automatic annotation of functional domains, TopFINDer is an invaluable tool in TopFIND.

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2. Fortelny, N., Butler, G.S., Overall, C.M., and Pavlidis, P. 2017. Protease-Inhibitor Interaction Predictions: Lessons on the Complexity of Protein-Protein Interactions. Molecular & Cellular Proteomics 16, 1,038 – 1,051. Featured Editors Pick.
3. Scott, N.E., Rogers, L.D., Prudova, A., Brown, N.F., Fortelny, N., Overall, C.M., and Foster, L.J. 2017 Interactome Disassembly During Apoptosis Occurs Independent of Caspase Cleavage. Molecular Systems Biology 13: 906, 1 – 22, doi: 10.15252/msb.20167067.
4. Fortelny, N., Yang, S., Pavlidis, P., Lange, P.F., and Overall, C.M. 2015. Proteome TopFIND 3.0 with TopFINDer and PathFINDer: Database and Analysis Tools for the Association of Protein Termini to Pre- and Post-Translational Events. Nucleic Acids Research 43 (Database Issue), D290-D297.
5. Fortelny, N., Pavlidis, P., and Overall, C.M. 2015. The Path of No Return—Truncated Protein N-Termini and Current Ignorance of their Genesis. Proteomics 15, 2547-2552.
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8. Lange, P., Huesgen, P., and Overall, C.M. 2012. TopFIND 2.0—Linking Protein Termini with Proteolytic Processing and Modifications Altering Protein Function. Nucleic Acids Research 40 (Database Issue), D351-361.
9. Lange, P. and Overall, C.M. 2011. TopFIND, a Knowledgebase Linking Protein Termini with Function. Nature Methods 8, 703-704.

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Welcome to new IPS members !

Amiram	Sananes	Ben-Gurion University	Israel
Andrew	Bayne	McGill University	Canada
Andreja	Bratovš	Jozef Stefan Institute	Slovenia
Anthonia	Anowai	University of Calgary	Canada
Yu Keung	Mok	National University of Singapore	Singapore
Jakub	Began	Institute of organic chemistry and biochemistry	Czechia
Jakub	Benysek	IOCB	Czech Republic
Betsaida	Bibo Verdugo	Sanford Burnham Prebys Medical Discovery Institute	US
Bethany	Anderson	University of Melbourne	Australia
Michal	Busa	Czech Academy of Sciences	Czech Republic
Catharina	Conrad	University of California	United States
Christine	Schlosser	DZNE/LMU	Germany
Daniel	Young	University of Calgary	Canada
Dieter	Petit	University of Leuven (KUL)	Belgium
Jan	Dvorak	Czech University of Life Sciences Prague	Czech Republic
Elizabeta	Madzharova	Technical University of Denmark	Denmark
Elisabeth	Nyström	Gothenburg University	Sweden
Eva	Riedlinger	Ludwig-Maximilians-Universität München	Germany
Fabian Thomas Hermann	Ullrich	Ludwig-Maximilians-University Munich	Germany
Fernanda	dos Reis Rocho	University of Sao Paulo	Brazil
Regina	Fluhrer	University of Augsburg	Germany
Idan	Adir	The Weizmann Institute	Israel
Isabel Maria	Pablos Ocampo	University of British Columbia	Canada
Marie	Jalovecka	Biology Centre CAS	Czech Republic
Jennifer	Vandooren	KU Leuven	Belgium
Jayaraman	Sivaraman	National University of Singapore	Singapore
Johannes	Trambauer	Ludwig-Maximilians-University	Germany
John	Widen	Stanford University	United States
Katherine	Falkowski	Jagiellonian University	Poland
Konstantinos	Kalogeropoulos	Technical University of Denmark	Denmark
Krzysztof	Piotrowski	University of Copenhagen	Denmark
Kyoko	Shirakabe	Ritsumeikan University	Japan
Lauren	Eyssen	University of KwaZulu-Natal	South Africa
Lorenzo	Cianni	University of Sao Paulo	Brazil
Lucia	Chavez-Gutierrez	VIB VZW	Leuven
Bermudez Diaz	Ludisleydis	IPDIE	Peru
Luise	Robbertse	Biology Centre CAS	Czech Republic
Lukas	Feilen	German Center for Neurodegenerative Diseases	Germany
Magali	Pederzoli-ribeil	Akrevia Therapeutics	USA
Masaya	Matsuzaki	University of Tokyo	Japan
Michelle	De bruyn	University of Antwerp	Belgium
Muhammad Nouman	Ahmed	University of Helsinki	Finland
Nicholas	Johnson	IOCB	Czechia
Nabangshu	Das	University of Calgary	Canada
Eiichiro	Nishi	Shiga University of Medical Science	Japan
Oguz	Bolgi	Universitätsmedizin Göttingen	Germany
Kleifeld	Oded	Technion - Israel Institute of Technology	Israel
Peter	Bell	UBC	Canada
Pavla	Sojkova	Biology Centre of the CAS	Czech Republic
Pavla	Fajtova	Institute of Organic Chemistry and Biochemistry	Czech Republic
Petra	Rubešová	Institute of Organic Chemistry and Biochemistry of the CAS	Czech republic
Raelynn	Brassard	University of Alberta	Canada
Rhogerry	Deshycka	University of California San Francisco	United States
Rama	Khokha	University Health Network	Canada
Rui	Moreira	Faculty of Pharmacy, University	Portugal
Robrecht	Thoonen	Kalvista Pharmaceuticals Inc	United States
Roger	Yazbek	Flinders University	Australia
Simone	Douglas	Georgia Institute of Technology	United States
Stepanka	Nedvedova	Czech University of Life Sciences Prague	Czech Republic
Yuki	Sudo	The University of Tokyo	Japan
Sandrine	Le Goff	CNRS	France
Tatiana	Shamorkina	Leiden	Netherlands
Aneka	Ticha	IOCB of the CAS	Czech Republic
Venkat Raghavan	Krishnaswamy	Weizmann Institute of Science	Israel

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Meeting announcements

Meetings planned in 2020 have been rescheduled in 2022

Proteolytic Enzymes and Their Inhibitors (GRS)
Gordon Research Seminar

The Regulation of Proteolysis in Health, Disease and Treatment

May 23 - 24, 2020 **New dates : June 4 - 5, 2022**

Chairs
Paulina Kasperkiewicz and Amy Weeks

Contact Chairs

Renaissance Tuscany Il Ciocco
Via Giovanni Pascoli
Lucca (Barga), IT

Venue and Travel Information

Proteolytic Enzymes and Their Inhibitors
Gordon Research Conference

The Regulation of Proteolysis in Health, Disease and Treatment

May 24 - 29, 2020 **New dates : June 5 - 10, 2022**

Chair
James A. Huntington

Vice Chair
Jeanne A. Hardy

Contact Chairs

Renaissance Tuscany Il Ciocco
Via Giovanni Pascoli
Lucca (Barga), IT

Venue and Travel Information

Protein Processing, Trafficking and Secretion (GRS)
Gordon Research Seminar

Insights into the Molecular Mechanisms of Protein Trafficking

July 18 - 19, 2020 **New dates : July 16 - 17, 2022**

Chairs
James W. Checco and Julie Cruanes

Contact Chairs

Colby-Sawyer College
541 Main Street
New London, NH, US

Venue and Travel Information

Protein Processing, Trafficking and Secretion
Gordon Research Conference

Tracking the Fate of Proteins and Lipids in the Secretory Pathway: From Cell Biology to Human Disease

July 19 - 24, 2020 **New dates : July 17 - 22, 2022**

Chair
Alan D. Attie

Vice Chair
Julia von Blume

Contact Chairs

Colby-Sawyer College
541 Main Street
New London, NH, US

Venue and Travel Information

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