Nov 2021

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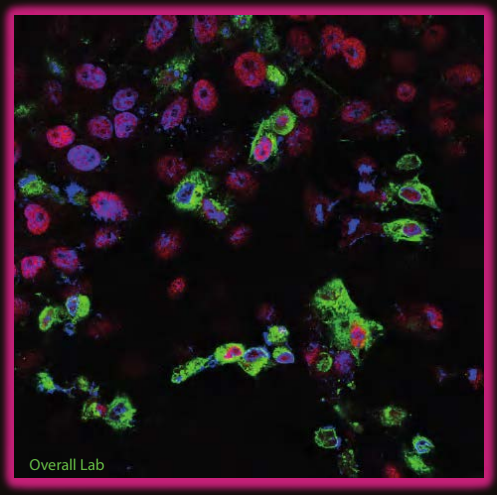
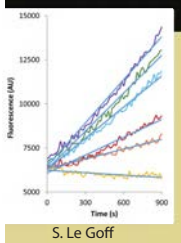
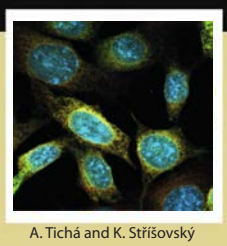


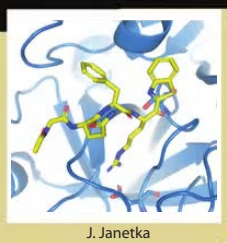
INTERNATIONAL PROTEOLYSIS SOCIETY

QUICKCUTS

Editors :
Catherine Moali (CNRS, University of Lyon)
Leila Akkari (NKI, Amsterdam)


S. Le Goff


A. Tichá and K. Střížovský


J. Janetka

THE PREMIER RESOURCE
FOR ALL YOUR IMPORTANT PROTEASE QUESTIONS

A Message From the President:

Dear IPS community,

I hope you are all doing well, and that normal life has begun to return for you. As you will already know, the 12th General Meeting of IPS was due to take place in Singapore in September 2021 but has been postponed. It was subsequently scheduled for December 2021 so that everyone would have sufficient time to get vaccinated. However, due to travel restrictions and rising numbers of variant strains, the organizers Henry Mok Yu-Keung, Jayaraman Sivaraman and Manjunatha Kini decided to postpone again until June 2023. Hopefully, by this date, worldwide travel will have returned to normal, and we can see each other in-person. Personally, I am looking forward to visiting Singapore and to enjoy all that it has to offer. I would like to thank the meeting organizers for their flexibility and smart decision making. In normal times, hosting an international meeting is a big task. In these abnormal times, it has been even more complicated. However, the Singapore team have been able to work well with their sponsors, with the National University of Singapore and the Hotel to ensure that the meeting can take place in 2023.

Since IPS was founded in 1999, we have had a general meeting every two years and voting for new officers takes place on the last day of the meeting. Each of the 12 officers serves a 4-year term. As we will not have a meeting in 2021, there will not be an opportunity for members to vote for new officers, and therefore I have asked the current officers to extend their terms by 2 years. All have agreed and I would like to thank them for their continued service to IPS.

As 4 years is a long time to be without a meeting, we have decided to launch a series of IPS Webinars. The first Webinar will take place on January 20th, 2022 and will focus on Proteases in SARS-CoV2 infection. The webinar will be hosted by Ruth Geiss-Friedlander and the University of Freiburg and you will find full details in this edition of Quickcuts and on the IPS website.

In this edition of Quickcuts, we have highlighted much of the great work that has been performed by the IPS community members in the area of COVID-19. Thank you to all Quickcuts contributors and to Catherine Moali and Leila Akkari for putting together this newsletter.

Stay safe and I hope to see you soon at the webinar.

Anthony O'Donoghue (IPS President)

COUNCIL OF THE INTERNATIONAL PROTEOLYSIS SOCIETY

IPS members in the fight against COVID19

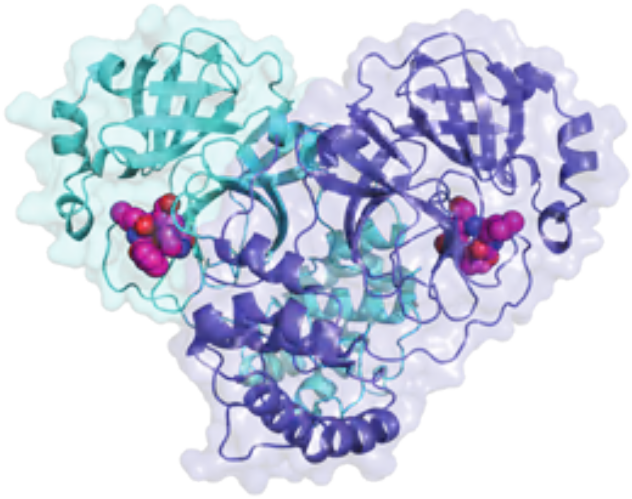
The next articles give examples of how IPS members became actively involved in COVID19 research and made remarkable contributions to the elucidation of infection mechanisms and to the search of new treatments.

Joanne Lemieux in her lab at the University of Alberta (August 2021).

Lab website: https://lemieuxlab.biochem.ualberta.ca/

Joanne Lemieux is a crystallographer in the Biochemistry Department at the University of Alberta, and has led a team with Medicinal Chemistry (James Nieman and John Vederas labs) and Virology (Lorne Tyrrell, Distinguished University Professor) and Biochemistry (Howard Young lab), all at the University of Alberta, to develop antiviral inhibitors that target the main protease of SARS-CoV-2.

First, we demonstrated that a feline Mpro inhibitor, GC376, was effective at inhibiting the protease both in vitro and in cell culture (Vuong et al, 2020 Nat Comm). Next crystallographic studies demonstrated the importance of dimerization in organizing the substrate binding pocket (Arutyunova et al, 2021 J Mol Biol).



Crystal structure of SARS-CoV-2 Mpro in complex with CG376

Since the feline drug would require a large dosage in human, more effective antivirals were needed, and therefore derivatives were optimised with higher selectivity (Vuong et al, Eur J Med Chem).

Working with the Nieman team, peptidomimetic based on early Pfizer compounds were optimised (Bai et al, 2021 J Med Chem). In this paper, an irreversible acyloxymethylketone (AMK) warhead was used, which showed a selective index well above the feline drug. In more recent work, we demonstrated the use of a nitrile warhead in enhancing specificity over other cellular cysteine proteases (Bai et al, 2021 RSC Med Chem). All work was conducted at the University of Alberta, except for remote data collection at CLS and SSRL, which led to a productive 1.5 years, especially during the challenging times of the pandemic !

- Arutyunova, Khan, Fischer, Lu, Lamer et al. (2021). N-Terminal Finger Stabilizes the S1 Pocket for the Reversible Feline Drug GC376 in the SARS-CoV-2 M(pro) Dimer. J Mol Biol. 433, 167003. DOI: 10.1016/j.jmb.2021.167003.

- Bai, Belovodskiy, Hena, Kandadai, Joyce et al. (2021). Peptidomimetic alpha-Acyloxymethylketone Warheads with Six-Membered Lactam P1 Glutamine Mimic: SARS-CoV-2 3CL Protease Inhibition, Coronavirus Antiviral Activity, and in Vitro Biological Stability. J Med Chem. DOI: 10.1021/acs.jmedchem.1c00616.

- Bai, Arutyunova, Khan, Lu, Joyce et al. (2021). Peptidomimetic nitrile warheads as SARS-CoV-2 3 CL protease inhibtors. RSC Med Chem. DOI: 10.1039/D1MD00247C

- Vuong, Fischer, Khan, van Belkum, Lamer et al. (2021). Improved SARS-CoV-2 M(pro) inhibitors based on feline antiviral drug GC376: Structural enhancements, increased solubility, and micellar studies. Eur J Med Chem. 222, 113584. DOI: 10.1016/j.ejmech.2021.113584.

- Vuong, Khan, Fischer, Arutyunova, Lamer et al. (2020). Feline coronavirus drug inhibits the main protease of SARS-CoV-2 and blocks virus replication. Nat Commun. 11, 4282. DOI: 10.1038/s41467-020-18096-2.

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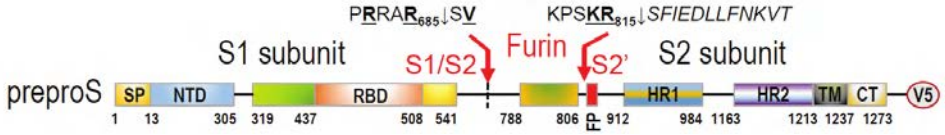
IPS members in the fight against COVID19

From Nabil G. Seidah
Montreal Clinical Research Institute (IRCM, affiliated to the University of Montreal), Canada

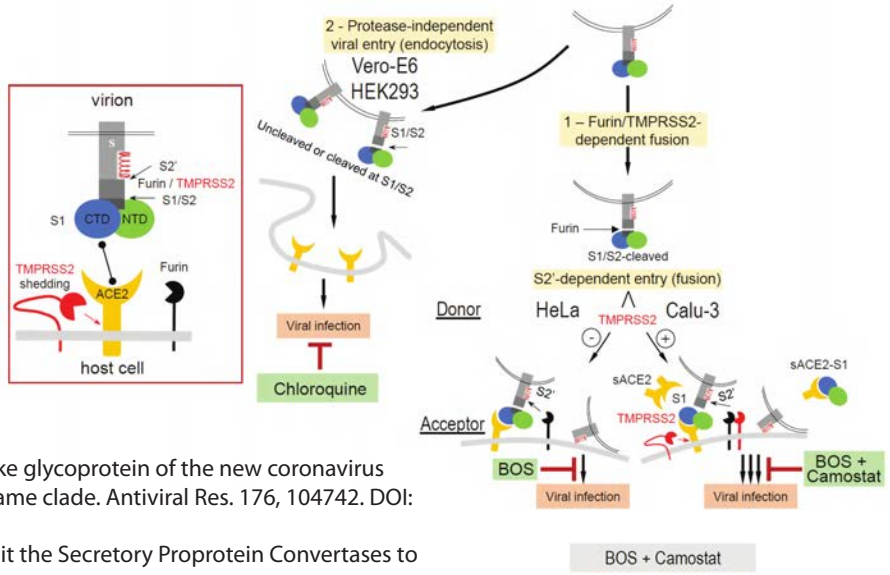
SARS-CoV-2 spike-glycoprotein processing at S1/S2 and S2′ and shedding of the ACE2 viral receptor: role of Furin and TMPRSS2 and implications for viral infectivity and cell-to-cell fusion

SARS-CoV-2 is the etiological agent of the COVID-19 pandemic that spread around the world in 2020 resulting in ~5 million deaths. The surface spike protein (S) of the virus directs infection of the lungs and other tissues by binding the host-cell receptor: angiotensin-converting enzyme 2 (ACE2). The S-protein requires proteolytic "priming" at P**R**RA**R**685↓into S1 and S2 (cleavage at S1/S2), and "fusion-activation" at a S2′ site for viral entry. Cleavage at S1/S2 induces a conformational change in the spike protein favouring the recognition of the ACE2 receptor. The S2′ cleavage is critical for the exposure of the fusion domain of the S-protein needed for virus entry into host cells. Both cleavages occur at Furin-like motifs suggesting that proprotein convertases might promote virus entry (Coutard et al, 2020 Antiviral Res; Seidah et al, 2021 Viruses).



In vitro, the proprotein convertase Furin cleaved peptides mimicking the S1/S2 site more efficiently than at the putative S2′, whereas TMPRSS2 cleaved at both sites. Endogenous Furin-like enzymes cleave mainly at S1/S2 during intracellular protein trafficking in HeLa cells, as confirmed by mutagenesis. We also mapped the S2′ cleavage site by proteomics at KPS**KR**815↓ and further showed that S2′-processing by Furin, while limited, was strongly enhanced in the presence of ACE2. In contrast, the furin-optimized S2′ KRRKR815↓ mutant (μS2′) was considerably better cleaved by Furin. Pharmacological inhibitors of convertases (Boston Pharmaceuticals - BOS-inhibitors) effectively blocked endogenous S-protein processing in HeLa cells. Quantitative analysis of cell-to-cell fusion and spike processing using Hela cells revealed the key importance of the Furin sites for syncytia formation and unveiled the enhanced fusogenic potential of the α- and δ-variants of the S-protein of SARS-CoV-2. Our fusion assay indicated that TMPRSS2 enhances S2′ formation, especially in the absence of Furin cleavage, and promotes ACE2 shedding to generate a secreted ACE2 (sACE2). Furthermore, we provide evidence using pseudoparticles that while entry by a "pH-dependent" endocytosis pathway in HEK293 cells did not require Furin processing at S1/S2, a "pH-independent" viral entry in lung-derived Calu-3 cells was sensitive to inhibitors of Furin (BOS-inhibitors) and TMPRSS2 (Camostat). Consistently, in Calu-3 cells these inhibitors potently reduce infectious viral titer and cytopathic effects and this outcome was enhanced when both compounds were combined. Overall, our results show that Furin and TMPRSS2 play synergistic roles in generating fusion-competent S-protein and promote viral entry.

Our study (Essalmani et al, 2021 BioRxiv) contributes to a better understanding of the dynamics of interaction between Furin and TMPRSS2 in SARS-CoV-2 entry and suggests that the combination of a non-toxic Furin inhibitor with that of TMPRSS2 could significantly reduce viral entry in lung cells, as evidenced by our results showing an average synergistic ~95% reduction of viral infection. This represents a powerful novel antiviral approach to reduce viral spread in individuals infected by SARS-CoV-2 or future related coronaviruses.



- Coutard, Valle, de Lamballerie, Canard, Seidah et al. (2020). The spike glycoprotein of the new coronavirus 2019-nCoV contains a furin-like cleavage site absent in CoV of the same clade. Antiviral Res. 176, 104742. DOI: 10.1016/j.antiviral.2020.104742.
- Seidah, Pasquato, Andreo (2021). How Do Enveloped Viruses Exploit the Secretory Proprotein Convertases to Regulate Infectivity and Spread? Viruses. 13. DOI: 10.3390/v13071229.
- Essalmani, Jain, Susan-Resiga, Andréo, Evagelidis et al. (2021). Implications of Spike-glycoprotein processing at S1/S2 by Furin, at S2′ by Furin and/or TMPRSS2 and shedding of ACE2: cell-to-cell fusion, cell entry and infectivity of SARS-CoV-2. BioRxiv. https://www.biorxiv.org/content/10.1101/2020.12.18.423106v2

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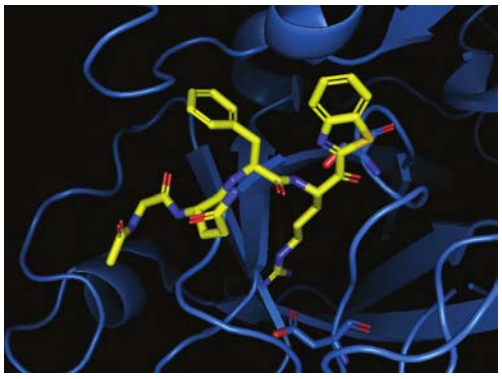
IPS members in the fight against COVID19

From James W. Janetka
School of medicine, Washington University in St Louis, USA

A new disease that is uncovered, while disturbing in one sense for human health, often brings with it much allure and excitement to scientists eager to undertake studies to not only understand it but ultimately to develop a cure. This was the case with COVID-19, the ongoing pandemic that started in late 2019 and continues to this day still with no approved drugs to treat it and only recently vaccines have been developed for prevention. The disease emanates from severe lung infection and associated complications caused by the newly emerged RNA coronavirus, named SARS-CoV-2, related to the previous coronaviruses SARS-CoV and MERS.

While my lab was not currently working on antivirals, I have past experience in antiviral drug discovery as my PhD thesis was focused on the rational design of first-generation HIV-protease (an aspartic protease) inhibitors and my initial work at Vertex Pharmaceuticals focused on HCV, targeting both the DNA helicase and main serine protease. However, during the last 10+ years my lab has been dedicated to developing covalent peptidomimetic serine protease inhibitors called ketobenzothiazoles (kbts), specifically targeting HGF-Activator (HGFA) and the transmembrane proteases matriptase and hepsin for cancer. In early 2020, a paper appeared showing that another transmembrane serine protease, TMPRSS2 was essential for the viral entry of SARS-CoV-2. Ironically, we had been discussing for several years inclusion of TMPRSS2 into our desired target proteases due to its importance in prostate cancer, and in particular since it shares one of the same substrates, pro-HGF with HGFA, matriptase and hepsin.



Model of MM3122 in the active site of TMPRSS2 (PDB code 7MEQ ; https://doi.org/10.1101/2021.06.23.449282)

This latter observation convinced us that our kbt inhibitors would likely be effective at inhibiting TMPRSS2, so we entered into a key collaboration with Dr. Stefan Pöhlmann in Germany, whose lab published the paper mentioned above which identified TMPRSS2 as the major host cell protease which cleaves the outer Spike protein of the virus, allowing it to bind the ACE2 receptor and subsequently enter and infect lung epithelial cells. To our delight, we found that a selected set of our current inhibitors did indeed block VSV SARS-CoV-2 pseudotype viral entry into human Calu-3 lung cells.

Following these initial exciting results, my labs' efforts shifted to protein expression for assay development and X-ray crystallography as well as lead compound optimization to rationally design more selective inhibitors of TMPRSS2 with good pharmacokinetic drug-like properties that also could be used in animal studies although none were available at the time. The research blossomed into a multi-lab collaboration involving several groups at Washington University, University of California San Francisco and San Diego, and the University of Cincinnati in addition to Georg-August University Göttingen in Germany.

Ultimately, we discovered the lead compound called MM3122 which has sub-nM potency against TMPRSS2 enzyme activity and blocking SARS-CoV-2 viral entry, and an amazing 8 h half-life when dosed IP in mice. While this compound has excellent selectivity over undesired proteases such as factor Xa and thrombin, it still potently inhibits HGFA, matriptase and hepsin making it a great drug candidate not only for COVID-19 but also cancer. A manuscript was submitted earlier this summer which has been accepted to the Proceedings of the National Academy of Sciences (Mohoney et al, 2021 PNAS) and will be published very soon. We have since demonstrated good efficacy in both the prevention and treatment of COVID-19 in mice and are following up with advanced studies in hamsters, both contracted by and funded generously by the National Institute of Allergy and Infectious Disease (NIAID) of the National Institutes of Health (NIH). MM3122 has potential to be a new broad-spectrum antiviral specifically against all coronaviruses and influenza viruses since TMPRSS2 plays a role in all known coronaviruses and matriptase in the proteolytic processing of the influenza hemagglutinin (HA) protein which is akin to the Spike protein. The compounds have been covered in a patent application by Washington University and licensed to my start-up company ProteXase Therapeutics, Inc. in Saint Louis, MO who plans to commercialize MM3122 and this class of protease inhibitors for treatment of COVID-19 and cancer.

Mahoney, Damalanka, Tartell, Chung, Lourenco et al. (2021). A novel class of TMPRSS2 inhibitors potently block SARS-CoV-2 and MERS-CoV viral entry and protect human epithelial lung cells. Proc Natl Acad Sci U S A. 118. DOI: 10.1073/pnas.2108728118.

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IPS members in the fight against COVID19

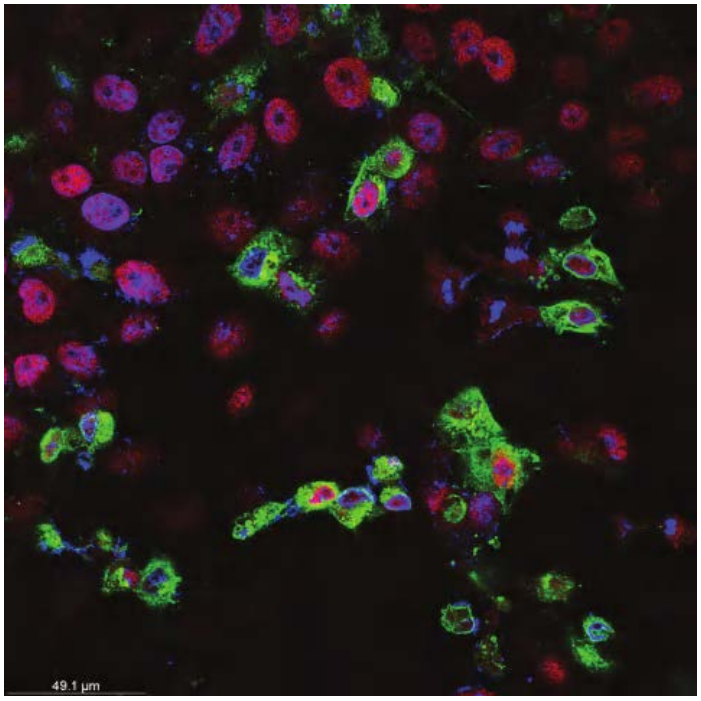
From Christopher M. Overall
University of British Columbia, Vancouver, Canada

Pablos *et al* report diverse SARS-CoV-2 3CLpro host substrates and interactors, so identifying subversive pathways in the COVID-19 cellular coup d'état.

To maximize the processes facilitated by a small genome, viral proteins are pleiotropic and multi-functional. As such, understanding the roles of each viral protein is crucial for the development of antiviral therapies. Proteases are vital components of viral protein repertoires, and antiviral inhibitor drugs have been game-changers, e.g., HIV AIDS and hepatitis C. Hence, it is incredibly important to predict the outcome of therapeutic inhibition of the SARS CoV-2 main protease, 3CLpro. This can only come from understanding the full extent of proteolysis of host cellular substrates by 3CLpro, yet most studies cherry-pick targets to screen, and few employs highly validated proteomics analyses targeted to substrate discovery.

The Overall Lab has reported on October 9, in CELL REPORTS (Pablos et al, 2021) , a proteomic analysis of the 3CLpro degradome. Using TAILS, Pablos et al, discovered >100 3CLpro substrates in ≥7/9 independent human lung cell and/or ≥ 2/3 HEK-293 cell TAILS analyses and 68 high confidence candidate substrates. With MALDI-TOF-MS cleavage site validation and Edman sequencing confirming the proteomic data, an Atlas of substrates is presented. Kinetic validation of 43 3CLpro substrates and molecular simulation modelling of 7 peptide/3CLpro interactions reveal noncanonical P1 residues (methionine and histidine) and dynamic occupancy of S3' that inform drug development.

The authors report a wide array of new mechanistic insights into crucial cell processes that are hijacked by SARS-CoV-2, driven by 3CLpro-cleavage of host cell proteins. Pablos et al show cleavage of endogenous RPAP1 and PTBP1 by 3CLpro in primary human bronchial epithelium lysates from five donors, and SARS-CoV-2–infected human lung cells. This confirms protein cleavage assays and Edman validation of every TAILS site in these proteins. Loss of the nuclear localization sequence mobilized PTBP1 from the nucleus to the cytosol in SARS-CoV-2 infected Vero E6 cells.



Redistribution of polypyrimidine tract binding protein (PTBP1) to the cytosol from the nucleus upon SARS-CoV-2 infection. PTBP1 binding mRNA downregulates viral transcription in other infections. Pablos et al. reveal that PTBP1 is one of 101 host cell substrates of SARS-CoV-2 3CLpro (main protease). Confocal imaging confirms nuclear (blue) localization of PTBP1 (red) in uninfected Vero-E6 cells, which translocates to the cytosol of Spike-positive (green) infected cells following cleavage removal of the nuclear localization sequence.

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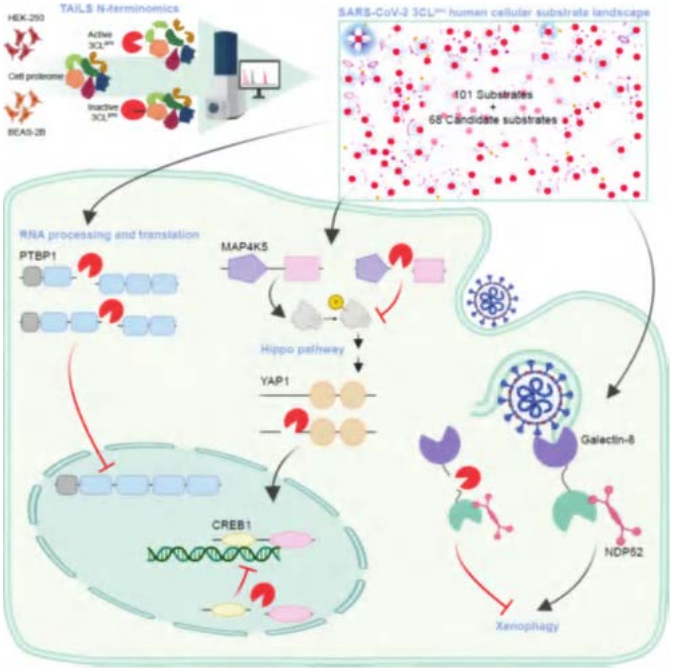
IPS members in the fight against COVID19

The Hippo signalling pathway, which regulates cell morphology, mechanotransduction, tissue growth and regeneration, is not a generally recognized target of viral proteolytic attack. Nevertheless, TAILS identified four substrates integral to Hippo signalling. The redundant inactivation of YAP1 by removal of the YAP1 Ser127 kinase-activation sequence/14-3-3 binding site, the inactivation of an upstream regulator kinase, MAP4K5, together with two downstream transcription factor targets, CREB1 and ATF1, strongly implicate the importance of repressing Hippo-regulated gene transcription and TBK1 activity for optimal SARS-CoV-2 infection.

The authors show that Galectin-8 functions as an intracellular sensor for SARS-CoV-2. By direct binding to Spike protein galectin-8 nucleates autophagy foci via binding the autophagy adapter NDP52 but autophagy is abolished by 3CLpro cleavage of Galectin-8. In post-mortem human lung samples of COVID-19 patients (N = 4), just 5% of galectin-8 colocalized with NDP52, but > 95% colocalized in healthy lung tissue samples from noninfected subjects (N = 3). Thus, 3CLpro decouples antiviral autophagy.



The interactome of 3CLpro human substrates is a highly interconnected network where 94 substrates interact directly or via third-party interactors. This connectivity suggests that proteolytic processing of the cellular proteome by 3CLpro sculpts SARS-CoV-2/host interactions by disrupting cellular processes in a concerted and redundant manner, as seen for the transcription, Hippo and xenophagy pathways. Notably, the interactome reveals several hub proteins left "stranded" by 3CLpro cleavage after losing two or more interactors. Without a scissile bond, the authors hypothesize that these numerous stranded proteins are opportunistically targeted by cleavage of essential interactors, thereby directly impacting their function to favor viral replication.

The cleaved substrate neo-N-termini will help assess on-target drug efficacy in vivo. Moreover, clinical translation to detect cleaved substrate neo-N-termini, which more precisely reflect disease stage than the levels of the protein or transcript alone, is a precise diagnostic strategy for infection surveillance of SARS-CoV-2 and future coronavirus outbreaks that infect humans—which is just a matter of time.

Pablos, I.M., Machado, Y., Cesar, H.C.d.J., Mohamud, Y., Kappelhoff, R., Lindskog, C., Vlok, M., Bell, P.A, Butler, G.S., Grin, P.M., Cao, Q.T., Nguyen, J.P., Solis, N., Abbina, S., Rut, W., Vederas, J.C., Szekely, L., Szakos, A., Drag, M., Kizhakkedathu, J., Mossman, K., Hirota, J., Jan, E., Lou, H., Banerjee, A., and Overall, C.M. 2021. Mechanistic Insights into COVID-19 from Global Analysis of the SARS-CoV-2 3CLpro Substrate Degradome. Cell Reports, DOI: 10.1016/j.celrep.2021.109892.

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Important protease papers

COVID-19 PROTEOLYTIC REGULATION

'A Clinical-Stage Cysteine Protease Inhibitor blocks SARS-CoV-2 Infection of Human and Monkey Cells'. Mellott, D. M., C. T. Tseng, A. Drelich, P. Fajtova, B. C. Chenna, D. H. Kostomiris, J. Hsu, J. Zhu, Z. W. Taylor, K. I. Kocurek, V. Tat, A. Katzfuss, L. Li, M. A. Giardini, D. Skinner, K. Hirata, M. C. Yoon, S. Beck, A. F. Carlin, A. E. Clark, L. Beretta, D. Maneval, V. Hook, F. Frueh, B. L. Hurst, H. Wang, F. M. Raushel, A. J. O'Donoghue, J. L. de Siqueira-Neto, T. D. Meek, and J. H. McKerrow. 2021. ACS Chem Biol, 16: 642-50. doi: 10.1021/acschembio.0c00875

'Challenges for Targeting SARS-CoV-2 Proteases as a Therapeutic Strategy for COVID-19'. Steuten, K., H. Kim, J. C. Widen, B. M. Babin, O. Onguka, S. Lovell, O. Bolgi, B. Cerikan, C. J. Neufeldt, M. Cortese, R. K. Muir, J. M. Bennett, R. Geiss-Friedlander, C. Peters, R. Bartenschlager, and M. Bogyo. 2021. ACS Infect Dis, 7: 1457-68. doi: 10.1021/acsinfecdis.0c00815

PROTEASES IN CANCER

'Significance of nuclear cathepsin V in normal thyroid epithelial and carcinoma cells'. Al-Hashimi, A., V. Venugopalan, N. Sereesongsaeng, S. Tedelind, A. M. Pinzaru, Z. Hein, S. Springer, E. Weber, D. Fuhrer, C. J. Scott, R. E. Burden, and K. Brix. 2020. Biochim Biophys Acta Mol Cell Res, 1867: 118846. doi: 10.1016/j.bbamcr.2020.118846

'A 9-kDa matricellular SPARC fragment released by cathepsin D exhibits pro-tumor activity in the triple-negative breast cancer microenvironment'. Alcaraz, L. B., A. Mallavialle, T. David, D. Derocq, F. Delolme, C. Dieryckx, C. Mollevi, F. Boissiere-Michot, J. Simony-Lafontaine, S. Du Manoir, P. F. Huesgen, C. M. Overall, S. Tartare-Deckert, W. Jacot, T. Chardes, S. Guiu, P. Roger, T. Reinheckel, C. Moali, and E. Liaudet-Coopman. 2021. Theranostics, 11: 6173-92. doi: 10.7150/thno.58254

'The molecular function of kallikrein-related peptidase 14 demonstrates a key modulatory role in advanced prostate cancer'. Kryza, T., N. Bock, S. Lovell, A. Rockstroh, M. L. Lehman, A. Lesner, J. Panchadsaram, L. M. Silva, S. Srinivasan, C. E. Snell, E. D. Williams, L. Fazli, M. Gleave, J. Batra, C. Nelson, E. W. Tate, J. Harris, J. D. Hooper, and J. A. Clements. 2020. Mol Oncol, 14: 105-28. doi: 10.1002/1878-0261.12587

'Cystatin M/E (Cystatin 6): A Janus-Faced Cysteine Protease Inhibitor with Both Tumor-Suppressing and Tumor-Promoting Functions'. Lalmanach, G., M. Kasabova-Arjomand, F. Lecaille, and A. Saidi. 2021. Cancers (Basel), 13. doi: 10.3390/-cancers13081877

'A Suite of Activity-Based Probes To Dissect the KLK Activome in Drug-Resistant Prostate Cancer'. Lovell, S., L. Zhang, T. Kryza, A. Neodo, N. Bock, E. De Vita, E. D. Williams, E. Engelsberger, C. Xu, A. T. Bakker, M. Maneiro, R. J. Tanaka, C. L. Bevan, J. A. Clements, and E. W. Tate. 2021. J Am Chem Soc, 143: 8911-24. doi: 10.1021/jacs.1c03950

'Beyond the biomarker role: prostate-specific antigen (PSA) in the prostate cancer microenvironment'. Moradi, A., S. Srinivasan, J. Clements, and J. Batra. 2019. Cancer Metastasis Rev, 38: 333-46. doi: 10.1007/s10555-019-09815-3

'KLK4 Induces Anti-Tumor Effects in Human Xenograft Mouse Models of Orthotopic and Metastatic Prostate Cancer'. Tse, B. W., T. Kryza, M. C. Yeh, Y. Dong, K. A. Sokolowski, C. Walpole, T. Dreyer, J. Felber, J. Harris, V. Magdolen, P. J. Russell, and J. A. Clements. 2020. Cancers (Basel), 12. doi: 10.3390/cancers12123501

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Important protease papers

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CATHEPSINS IN PHYSIO-PATHOLOGY

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Coming soon... a webinar series!

We are proud to launch a series of IPS Webinars!

The first Webinar will take place on Thursday January 20, 2022 at 17:00 CET, 8:00 am PDT.

This webinar will focus on *Proteases in SARS-CoV2 infection*.

The goal of these Webinars is to transfer the lively scientific environment that we know from the International Protease Society meetings to an online platform.

Confirmed speakers:
Rolf Hilgenfeld
Joanne Lemieux
Wioletta Rut
James W. Janetka
Isabel Pablos

This is a partnership project with
GRK 2606 - the Doctoral Research Training Group on proteases in Freiburg.

Please look into the IPS website for registration.

We are looking forwards to an exciting session.

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News from IPS members

From Olivier Coux, Chair of the Action, CRBM-CNRS, Montpellier, France
and Rosa Farràs, Vice-chair of the Action, CIPF, Valencia, Spain

contact@proteocure.eu

European researchers: join the ProteoCure COST Action !

November 2021 – October 2025
Register at proteocure.eu

The ProteoCure COST Action aims at fostering research and innovation in the field of proteolysis in Europe with the goal of manipulating the proteolysis machinery for the development of novel, specific and efficient therapies.

Proteins are essential molecular actors in every cellular process. From their synthesis to their degradation, they are subject to continuous and precise quality control mechanisms to ensure that they properly and timely take on their functions to fulfil cellular needs.

Proteolysis (i.e. degradation of proteins) is a key biological process that directly controls individual protein levels. It also ensures the degradation of abnormal proteins. Malfunctions of the proteolysis machinery leading to accumulation of deleterious proteins or in the opposite to excessive degradation of beneficial ones are implicated in multiple human diseases such as cancers, neurodegeneration, developmental and aging disorders, as well as in infectious diseases. Therefore, manipulating the proteolytic machinery to control abundance of specific proteins is a strategy of enormous potential for therapeutic intervention.

ProteoCure will gather European researchers from the academic, clinical, and industry sectors, interested to develop a knowledge-based network fostering research on this issue. By organizing community-building activities, fostering synergies among European scientists and reinforcing the training of the next generation of European researchers, the Action will allow creation of a large and creative exchange hub focusing on normal and pathologic proteolysis, and on the development of innovative tools modulating the level of specific protein(s). The final aim is to facilitate the translation of novel discoveries into products of clinical and/or economical value.

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Job position

PhD fellowship in parasitology and molecular biology at the Institute of Parasitology, Biology Centre of Czech Academy of Sciences, Czech Republic

Laboratory of Fish Protistology,
Institute of Parasitology,
Biology Centre of CAS (PAU BC CAS),
České Budějovice, Czech Republic

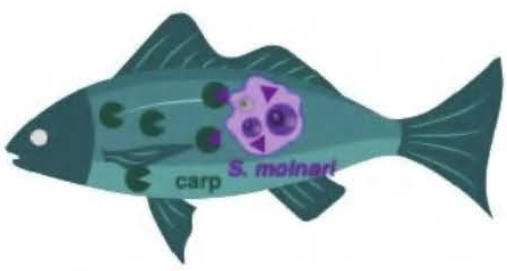
We are offering a PhD fellowship in parasitology and molecular biology commencing 1 January 2022 or as soon as possible hereafter.

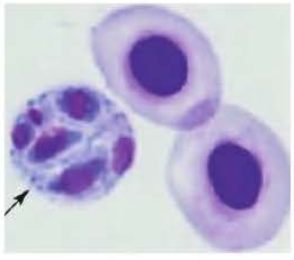
Our group and research

The main interest of our group is the Myxozoa, an ancient lineage of cnidarian parasites that have conquered a range of different aquatic habitats. They have a complex life cycle and have largely diversified mostly in their fish hosts in which some of them cause serious diseases. Efficient strategies against these parasites in fish destined for human consumption are still lacking. We study all aspects of their structure, biology, physiology, life cycles, host-parasite interactions, ecology, and evolution. We also carry out research into a range of parasite problems which create economic and health consequences for the aquaculture industry, in collaboration with various academic and professional institutions worldwide.

Project description

The fellow will join the research team at PAU BC CAS elucidating the interactions between the myxozoan parasite *Sphaerospora molnari* and its fish host, the common carp *Cyprinus carpio*. *S. molnari* represents the main research model of our group which we maintain in a continuous intrapiscine model system. In the project, the PhD fellow will explore *S. molnari* and carp proteases and protease inhibitors as important molecules for the crosstalk during the fish infection. This will include identification of target proteins and monitoring of gene expression by quantitative PCR in various fish tissues and throughout parasite life cycle; biochemical characterization of target proteins by evaluation of their enzymatic properties and inhibitory specificity; characterization of biological function of target proteins by localization within the cells and tissues, fish challenge experiments, RNAi; bioinformatic analyses to explore the cross genome comparison of the gene repertoire of proteases and protease inhibitors across myxozoan lineages. In *S. molnari*, candidate proteins will be explored as vaccine targets.



Start: 1 January 2022

Duration: 4 years as a PhD fellow at PAU BC CAS and as a PhD student at the Faculty of Science, University of South Bohemia, Ceske Budejovice, Czech Republic.

Job description

Your key tasks as a PhD fellow at PAU BC CAS will be:

- Carry out an independent research project under supervision
- Participate in active research environments including a stay at another institution

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Job position

- Present the results at international conferences
- Write a PhD thesis on the grounds of your project

Key criteria for the assessment of applicants
Applicants must have qualifications corresponding to a master's degree in biology, veterinary medicine, or a relevant biological/biochemical discipline. The program supports exclusively European students or foreigners with a valid EU visa at time of application.

Other important criteria are:

- Good lab technical skills
- Good English language skills
- Curious mind-set with a strong interest in developing strategies for parasite control
- No allergy for handling of fish
- Previous publications within the field of parasitology, bioinformatics, or biochemistry
- Experience with bioinformatics, quantitative PCR, immunolabeling methods, biochemical assays, RNAi

Place of employment
The place of employment is the Laboratory of Fish Protistology at PAU BC CAS. We offer creative and stimulating working conditions in dynamic and international research environment. PAU BC CAS is one of the largest European centers of parasitological research and provides all state-of-the-art facilities required to undertake a multi-disciplinary repertoire of methods, enabling studies on host-parasite interactions at the organismal, cellular, and molecular level. The institute is located in České Budějovice (Budweis), the capital city of South Bohemia known for its original Budweiser Budvar beer. The city is surrounded by the UNESCO heritage sites of Hluboká nad Vltavou and Český Krumlov, and the pristine nature of the Bohemian Forest National Park.

Terms of employment
The employment as PhD fellow is full time and for 4 years. It is conditioned upon the applicant's successful enrolment as a PhD student at the Faculty of Science, University of South Bohemia, České Budějovice, Czech Republic. This requires submission and acceptance of an application for the specific project realized at PAU BC CAS. The student will have an opportunity to select a wide variety courses in the fields of parasitology and molecular biology. The PhD fellow will receive funding from the resources of PAU BC CAS, grants of our laboratory (Grant Agency of the Czech Republic) as well as the stipend from the Faculty of Science. Depending on seniority, the monthly salary from all sources will be around 1500 EUR. Negotiation for salary supplement is possible.

More information
More information about BC CAS, PAU BC CAS and Faculty of Science can be found at www.bc.cas.cz/en/homepage/, www.paru.cas.cz/en/ and www.prf.jcu.cz/en. For further information about the position, applicants may contact Dr. Pavla Sojková, PAU BC CAS (email: bartoska81@gmail.com, phone: +420-387775450) or Dr. Astrid S. Holzer, PAU BC CAS, email: astrid.holzer@paru.cas.cz, phone: +420-387775424).

Application
The application must include a cover letter, a curriculum vitae (including the publication list if applicable), Master diploma, 1-3 reference letters and contact information for possible reference persons, as well as any other relevant material as a single .pdf file.

The closing date for applications is 15 November 2021. Candidates must submit their application electronically by email. Interviews are expected to be held in November/December 2021.

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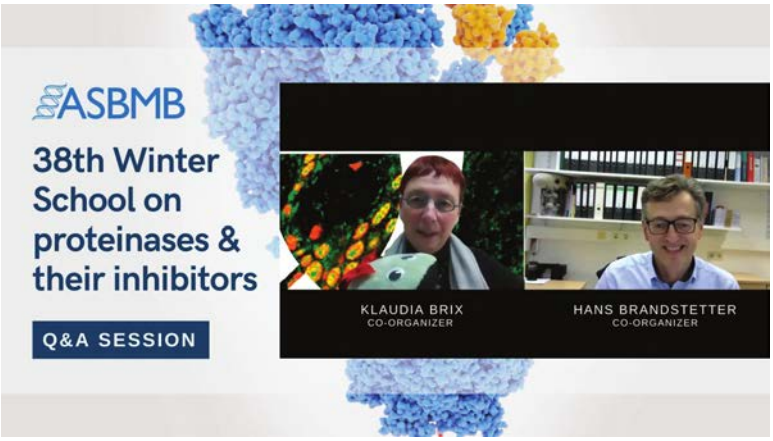
Meeting announcements

From Hans Brandstetter
University of Salzburg, Austria

Winterschool on Proteinases and Their Inhibitors: A review on 2021 and an outlook to 2022

Challenged by the Corona pandemics we decided to run the traditional Winterschool on Proteases and Their Inhibitors in 2021 in a virtual format. We were excited that the American Society for Biochemistry and Molecular Biology (ASBMB) agreed to co-organize the Protease meeting. More than 200 participants made the 38th Winterschool a great success. In attractive plenary and poster sessions, young scientists reported about their latest results in diverse areas like physiology & homeostasis, neurodegeneration, cancer, and virology, including SARS-CoV-2. Defying the organizers' concerns, the virtual setting did not hamper discussion, quite the contrary. The multiple scientific and social interaction channels in the virtual platform sparked a vivid scientific exchange and networking, in particular by the next generation of scientists.



From Klaudia Brix (Jacobs University Bremen, Germany) who was co-organizer of the 38th Winter School : "The chat groups and video conferences with friends from this fantastic protease field cheered me up – I am so happy and grateful being part of our IPS community. And, believe it or not, I became a YouTube star – perhaps not quite, but video "productions" are definitely high up on the agenda."

With this positive experience, we take pleasure to invite you to join the 39th Winterschool on Proteinases and Their Inhibitors, which will take place 16 – 20 February 2022 as a hybrid event. We will be able to meet in person in Tiers / Italy (complete and approved vaccination or recovery required). With the lessons learnt from last Winterschool and still prevailing uncertainties about the Corona pandemics, we don't want to miss out on scientists who cannot attend the Winterschool in presence. Virtual Winterschool attendants will be able to present and discuss their latest protease research and network online efficiently. Finally, we are glad to announce that the Henner Graeff Foundation continues to support the Winterschool with generous Young Investigator Awards. Please check out https://plus.ac.at/tiers for further details.

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Meeting announcements

For important information regarding GRC's vaccination policy and on-site COVID-19 protocols : https://www.grc.org/_resources/common/userfiles/-file/10.7%20Revised%20Alert.pdf

Proteolytic Enzymes and Their Inhibitors
Gordon Research Conference

The Regulation of Proteolysis in Health, Disease and Treatment

June 5 - 10, 2022

Apply Now

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James A. Huntington

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Jeanne A. Hardy

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Via Giovanni Pascoli
Lucca (Barga), IT

Proteolytic Enzymes and Their Inhibitors (GRS)
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June 4 - 5, 2022

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Protein Processing, Trafficking and Secretion
Gordon Research Conference

From Cell Biology to Human Disease

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

July 16 - 17, 2022

Apply Now

Chairs
James W. Checco and Julie Cruanes

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Meeting announcements

Protein Recognition and Processing in the Membrane

2nd International Meeting 2022

of the DFG research unit FOR2290
'Understanding Intramembrane Proteolysis'
May 4-6, 2022, Munich, Germany

Registration start: September 2021

3rd International Symposium
of the Collaborative Research Centre 877

PROTEIN CLEAVAGE FOR REGULATION

'Protease World in Health & Disease'

11-14 September 2022

Keep the date

University of Kiel, Germany

www.uni-kiel.de/Biochemie/sfb877/

Program and registration details
will be announced in Jan 2022

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Meeting announcements

ORGANIZING COMMITTEE


MOK YU-KEUNG HENRY


KINI R MANJUNATHA


J SIVARAMAN

VENUE

Shaw Foundation Alumni House

Directions to the venue | LINK

Shaw Foundation Alumni House is located within the campus of the National University of Singapore.