Nov 2022

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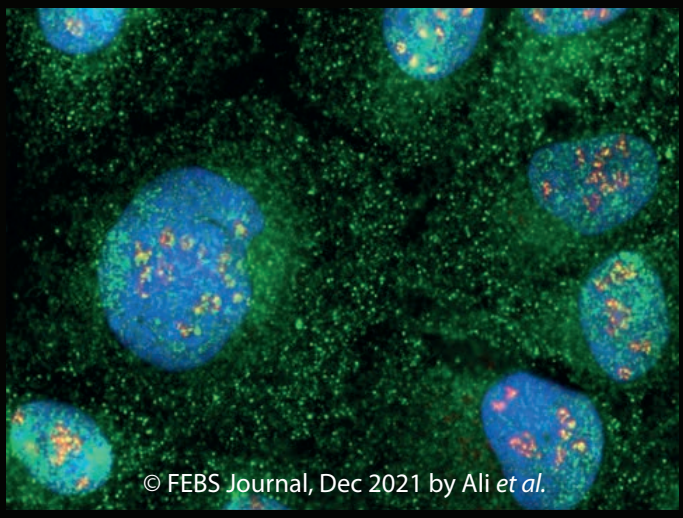

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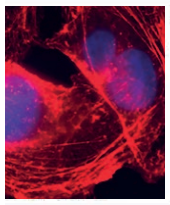
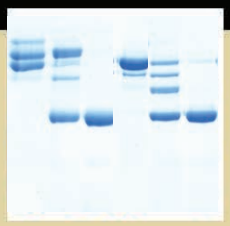
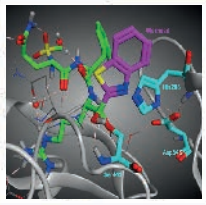
INTERNATIONAL PROTEOLYSIS SOCIETY

QUICKCUTS

Editor : Catherine Moali
(CNRS, University of Lyon)







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COUNCIL OF THE INTERNATIONAL PROTEOLYSIS SOCIETY

A Message From the President:

Dear IPS community,

I hope you are all doing well, and that life has returned to normal for you. The 12th General Meeting of the International Proteolysis Society will take place on the campus of the National University of Singapore from June 24th to 29th 2023. The nearby Park Avenue Rochester hotel has been booked for our accommodation. We are very excited to finally get a chance to see you in person after the 2021 meeting was postponed due to COVID-19. We hope that you will enjoy this wonderful meeting that has been organized by Henry Mok Yu-Keung, Jayaraman Sivaraman and Manjunatha Kini and that you will get an opportunity to experience all that Singapore has to offer. Registration for this meeting will open very soon (end of November). In addition, the training workshop for Ph.D students and postdocs will take place on June 23th and 24th. We will have training sessions on structural biology, enzyme kinetics, imaging and substrate discovery, so please encourage your students and postdocs to register.

As four years is a long time between our general meetings, we decided to launch a series of IPS webinars in 2022. The first webinar took place in January and was focused on Proteases in Viral Infections with Rolf Hilgenfeld giving the keynote talk. The second webinar in April was focused on imaging in Cancer and Inflammation and the keynote speakers were Irit Sagi and Matt Bogyo. Between these two webinars, we had ~300 participants and it was a great opportunity to hear about the protease research being done by several early career and accomplished scientists.

In this edition of Quickcuts, we have highlighted research from the laboratories of François-Xavier Gomis-Rüth, Kohei Oda, Ben Dunn, Alexander Wlodawer, Ruth Geiss-Friedlander, Vivian Hook, Emmanuelle Liaudet-Coopman, François Jean, Malte Gersch, Stefan Lichtenthaler and Chris Overall. In addition, we have highlighted several job openings, upcoming meetings and awards.

I would like to sincerely thank Catherine Moali for putting this newsletter together as it keeps us all informed about the exciting research activities of our members.
Stay safe and I hope to see you soon in Singapore.

Best wishes,

Anthony O'Donoghue, IPS President

IPS webinars report

IPS Webinars - A wind of change
by Ruth Geiss-Friedlander, IPS vice-president

The IPS launched Webinars to bridge the time gaps between meetings that were enforced on the scientific community due to the international Corona lock-downs.

The first IPS webinar focused on the SARS-CoV2 Proteases. The Key note talk was held by Rolf Hilgenfeld from the University of Lübeck, Germany, who gave an exciting overview on his work on the SARS COV-2 main protease - inhibitors, structures and mutations. Additional speakers were Wioletta Rut (the Wrocław University of Technology, Poland), Joanne Lemieux (University of Alberta, Canada), Isabel Pablos (University of British Columbia, Canada), James W. Janetka (Washington University, Medical Campus, USA), and Georg Jocher from the German Center for Neurodegenerative Diseases (DZNE) in Munich, Germany. This webinar was organized by Ruth Geiss-Friedlander (Albert-Ludwigs-University Freiburg, Freiburg) and Anthony O'Donoghue (University of California, San Diego, USA) in cooperation with the DFG Research Training Group ProtPath in Freiburg. The webinar was fully booked, with more than 200 participants.

The second Webinar was on Imaging in Cancer and Inflammation. In this exciting session the two key note speakers were Irit Sagi (Weizmann Institute, Israel) who talked about "Tumor-reactive natural antibodies targeting matrix enzymes evolve from non-binding and autoreactive precursors"and Matt Bogyo (Stanford University, USA) who shared his research on "Protease probes for imaging cancer, inflammation and infectious diseases". Additional speakers included Maren Stillger (University of Freiburg, Germany), Craig Jenne (University of Calgary, Canada) and Hartland Jackson from the University of Toronto, Canada. Thanks to Barbara Grunwald (University of Toronto, Canada) and Antoine Dufour (University of Calgary, Canada) for organizing this webinar.

We acknowledge the difficulties due to the different time zones, thus the sessions were recorded and can be sent out upon request to ips@protease.org. We thank all speakers for their great contributions and participants for the lively discussions ! We also encourage members of the IPS to contact us if they are interested in organizing a specialized webinar.

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Congratulations

Professor Christopher M. Overall (University of British Columbia, Canada) was awarded the 2022 Helmut Holzer Award

The Helmut Holzer Award is an honour recognizing outstanding contributions to the advancement of the field of proteolysis.

The Award, sponsored by The International Union of Biochemistry and Molecular Biology, was presented September 18 at the opening plenary lecture of the September 19 – 22, 2022 Federation of European Biochemical Societies conference "Proteolysis at the Interface between Health and Disease," in Bled, Slovenia. Dr. Overall's lecture was entitled. "Pathobiology of COVID-19 Deciphered by TAILS Analysis of SARS CoV-2 3CLpro Substrates."

Dr. Helmut Holzer (1921-1997) served as chairman of the Scientific Society of Freiburg for 25 years. The award in his honour was established after his death in 1997.

Dr. Overall reports that in a happy coincidence, he was an external senior fellow at the Freiburg Institute of Advanced Studies (FRIAS), School of Life Sciences – LifeNet, Albert-Ludwigs Universität Freiburg, Freiburg, Germany, where he is now an honorary professor. At UBC, Dr. Overall is a professor in the Faculty of Dentistry, Department of Oral Biological and Medical Sciences, and is also affiliated with the Departments of Biochemistry and Molecular Biology, Obstetrics and Gynecology, and is a member of the Centre for Blood Research, where he has his research team and laboratory.

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News from IPS members

From Judith Clements (Queensland University of Technology, Australia)

We held a small **DAAD Collaboration Protease Symposium** in Brisbane, Australia, October 13, 2022 in honour of Viktor Magdolen and our protease collaborations over the years. Speakers included Viktor Magdolen (TUM), Ashley Buckle (Replay, San Diego), Jonathan Harris (QUT), Alex Duff (QUT), Achala Vitharanage (QUT) and Chamikara Liyanage (QUT). The attached photo shows some attendees along with speakers - Achala Vitharanage (left, front row), Jonathan Harris, Viktor Magdolen and Judith Clements (middle of photo), and Alex Duff and Ashley Buckle, right hand side of photo.

From Thomas Reinheckel (University of Freiburg, Germany)

Black Forest Retreat of the DFG Research Training Group 2606 – ProtPath

Webpage: https://www.protpath.uni-freiburg.de/

On October 4th and 5th, 2022, the Freiburg doctoral program on proteolysis research "ProtPath", went on its annual retreat in St. Peter, which is located in the midst of black forest. This year, the scientific focus was on structural biology of proteases. In preparation of the retreat, doctoral researchers received an introduction to structural biology by Prof Oliver Einsle, and were hence primed for the excellent guest lectures on structural biology approaches in proteolysis research given by Prof Hans Brandstetter, Dr Yogesh Kulatu and Dr Eva-Maria Huber.

After an interactive social evening with pub quiz and games, the doctoral researchers presented their research in a poster session with lively discussions with the guests and investigators of the research training group on the second day. The "ProtPath Annual Doctoral Researcher Achievement Award" for the best scientific poster was awarded to Saskia Barz (Institute of Biochemistry and Molecular Biology, Freiburg) for her work on autophagy regulation. The concluding highlight of two wonderful autumn days was an archery workshop and competition before heading back to Freiburg.

During the retreat, current IPS vice president Ruth Geiss-Friedlander highlighted goals and mission of IPS, while Hans Brandstetter advertised the upcoming Winter School in Tiers (Italy), which will take place March 1-5, 2023.

Susanne Elfert (Scientific coordinator RTG 2606)
Thomas Reinheckel (Director RTG 2606)

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Important protease papers

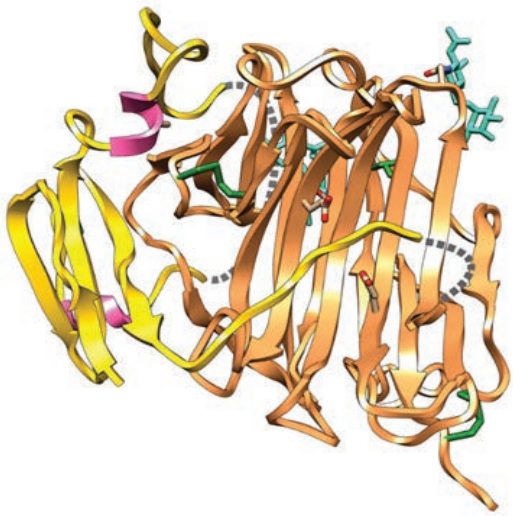
"NEW" PROTEASES : Paper highlight # 1

From François-Xavier Gomis-Rüth (Molecular Biology Institute of Barcelona, Spain)

Neprosin is a proline-specific glutamate peptidase with therapeutic potential against coeliac disease

The digestion of gluten generates highly immunogenic proline-rich toxic peptides, among which a 33-mer, which trigger coeliac disease. Neprosin from the digestive fluid of the carnivorous pitcher plant Nepenthes × ventrata is a prolyl endopeptidase (PEP), which in combination with other peptidases from the digestive fluid has been identified as part of a potential glutenase preparation (1-4). Purified neprosin has also been considered a useful reagent for proteomics (3, 4). Further studies were hampered by the absence of an efficient production and purification protocol.

Here, we produced recombinant neprosin and found that the full-length protein is a zymogen, which is self-activated at gastric pH by the release of an all-β pro domain via a pH-switch mechanism featuring a lysine plug (5). The catalytic domain is an atypical 7+8-stranded β-sandwich with an extended active-site cleft containing an unprecedented pair of catalytic glutamates, which ascribes the enzyme to the poorly-studied glutamate peptidases (6, 7). Neprosin efficiently degraded both gliadin and the 33-mer in vitro under gastric conditions and was reversibly inactivated at pH>5. Moreover, co-administration of gliadin and the neprosin zymogen at the ratio 500:1 reduced the abundance of toxic peptides in the small intestine of mice by up to 90% as determined by ELISA. Neprosin therefore founds a family of eukaryotic glutamate endopeptidases that fulfils requisites for a therapeutic glutenase.



Ribbon-type plot of pro-neprosin in frontal perspective. The pro-domain is gold with magenta helices. The mature enzyme is shown in salmon. The two glycosylation sites, the seven cysteines and the two catalytic glutamates are shown with their side chains.

1. Lee *et al.* J. Proteome Res., 15(9), 3108-3117 (2016) doi:10.1021/acs.jproteome.6b00224
2. Rey *et al.* Sci. Rep., 6, 30980 (2016) doi:10.1038/srep30980
3. Schräder *et al.* Mol. Cell. Proteomics, 16(6), 1162-1171 (2017) doi:10.1074/mcp.M116.066803
4. Schräder *et al.* Anal. Chem., 90(5), 3083-3090 (2018) doi:10.1021/acs.analchem.7b03948

5. Molecular and in vivo studies of a glutamate-class prolyl-endopeptidase for coeliac disease therapy.
L. Del Amo-Maestro, S. R. Mendes, A. Rodriguez-Banqueri, L. Garzon-Flores, M. Girbal, M. J. Rodriguez-Lagunas, T. Guevara, A. Franch, F. J. Perez-Cano, U. Eckhard, F. X. Gomis-Ruth (2022).
Nat Commun. 13, 4446. https://doi.org/10.1038/s41467-022-32215-1.

6. Fujinaga *et al.* Proc. Natl. Acad. Sci. USA, 101(10), 3364-3369 (2004) doi:10.1073/pnas.0400246101
7. Kondo *et al.* J. Biol. Chem., 285(28), 21437-45 (2010) doi:10.1074/jbc.M110.122432

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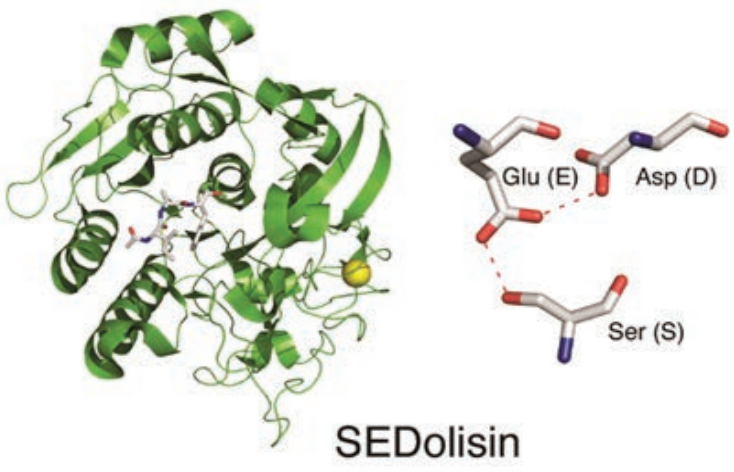
Important protease papers

"NEW" PROTEASES : Paper highlight # 2

From Kohei Oda (Kyoto Institute of Technology, Japan), Ben M. Dunn (University of Florida College of Medicine, USA) and Alexander Wlodawer (National Cancer Institute, Frederick, USA)

Review of the sedolisin family of peptidases

A perspective entitled "Serine-carboxyl peptidases, sedolisins: from discovery to evolution" was published this August in Biochemistry. In terms of their optimum pH at the catalytic action, proteolytic enzymes (peptidases or proteinases) could be divided into two groups, neutral or alkaline peptidases and acid peptidases. The former group consists of serine, cysteine, and metallopeptidases, whereas the latter includes aspartic and glutamic peptidases. In this perspective is described an additional acid peptidase that nominally is a serine peptidase, but belongs to a subfamily of serine-carboxyl peptidases. The representative enzymes of this subfamily are sedolisin, kumamolisin, and tripeptidyl peptidase (TPP-1). Both glutamic peptidases and serine-carboxyl peptidases are pepstatin-insensitive carboxyl peptidases that are distributed broadly in nature, from prokaryotes to eukaryotes, including humans. Their unique features are: (1) The fold of the molecule is similar to that of subtilisin, but the catalytic residues consist of a triad Ser/Glu/Asp, that is unlike the Ser/His/Asp triad of subtilisin. This property led to assigning the name SEDolisin to founding member of the family, and naming the family itself SEDolisins. (2) A sedolisin molecule is expressed as a pro-form composed of the amino-terminal prosegment and the active domain. (3) Distribution of sedolisins in nature is very broad across the three kingdoms of life. (4) Some of these enzymes from fungi and bacteria are pathogens to plants. (5) Some of them have significant potential applications for industry. (6) The lack of a TPP-1 gene in human brain is the cause of incurable juvenile neuronal ceroid lipofuscinosis (Batten's disease). (6) It is supposed that sedolisins might have evolved from serine peptidases in order to change their properties such that they would become more active in an acidic environment rather than at neutral pH.



Crystal structure of sedolisin and its catalytic residues (PDB entry 1GA1). From Oda *et al.* Biochemistry, 2022. (Copyright: American Chemical Society, 1 Aug 2022. Copyright permission: 4 Nov 2022).

Serine-Carboxyl Peptidases, Sedolisins: From Discovery to Evolution.
K. Oda, B. M. Dunn, A. Wlodawer (2022).
Biochemistry. 61, 1643-1664. https://doi.org/10.1021/acs.biochem.2c00239.

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Important protease papers

NEW PROTEASES ACTIVITIES : Paper highlight

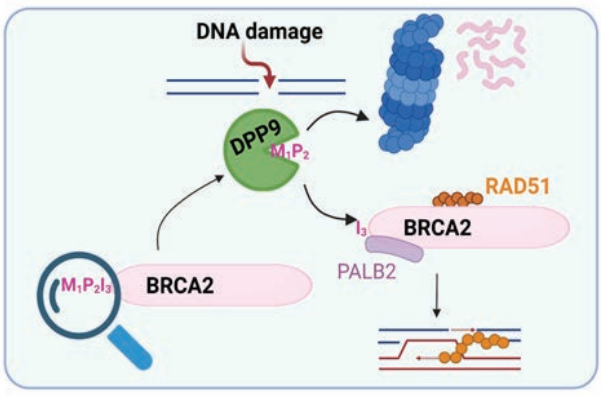
From Oguz Bolgi and Ruth Geiss-Friedlander (University of Freiburg, Germany)

Dipeptidyl peptidase 9 triggers BRCA2 degradation and promotes DNA damage repair.

O. Bolgi, M. Silva-Garcia, B. Ross, E. Pilla, V. Kari, M. Killisch, M. Spitzner, N. Stark, C. Lenz, K. Weiss, L. Donzelli, M. D. Gorrell, M. Grade, J. Riemer, H. Urlaub, M. Dobbelstein, R. Huber, R. Geiss-Friedlander (2022).
EMBO Rep. 23, e54136. https://doi.org/10.15252/embr.202154136.
Preprint in BioRxiv: doi.org/10.1101/2020.08.24.265033

Proteases of the DPPIV family are serine aminopeptidases with the rare ability to cleave off N-terminal dipeptides with the imino-acid proline in second position. Four members of this family are known, with DPP8 and DPP9 as intracellular members. Of the two, DPP9 is more abundant and is rate limiting for cleavage of proline-containing peptides in the cytosol. Furthermore, low DPP9 mRNA expression correlates with poor overall survival for patients with breast cancer.

Here, we identify the tumour-suppressor BRCA2 as a DPP9 substrate and show an interaction between DPP9 and BRCA2 that is induced by DNA damage. We present crystallographic structures documenting intra-crystalline enzymatic activity of DPP9, with the N-terminal Met1-Pro2 of a BRCA2$_{1\text{-}40}$ peptide captured in its active-site. Intriguingly, DPP9-depleted cells are hypersensitive to genotoxic agents, including Olaparib, and impaired in repair of DNA double-strand breaks by Homologous-Recombination. Mechanistically, DPP9 targets BRCA2 for degradation by the N-degron pathway. We show that DPP9 regulates the interaction between BRCA2 and its partner PALB2, and promotes the formation of RAD51 foci, the downstream function of BRCA2. These effects are phenocopied by N-terminal truncation mutants of BRCA2 that mimic DPP9 products, and rescued by over-expression of active DPP9. Taken together, we present DPP9 as a regulator of BRCA2 stability, and propose that by fine-tuning BRCA2 levels, DPP9 alters BRCA2 interactome, providing a possible explanation to the involvement of DPP9 in cancer.



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Important protease papers

NEW PROTEASE ACTIVITIES : Other important papers

Matrix metalloproteinase-2 mediates ribosomal RNA transcription by cleaving nucleolar histones.
M. A. M. Ali, J. A. Garcia-Vilas, C. R. Cromwell, B. P. Hubbard, M. J. Hendzel, R. Schulz (2021).
FEBS J. 288, 6736-6751. https://doi.org/10.1111/febs.16061.

Multifunctional intracellular matrix metalloproteinases: implications in disease.
W. Bassiouni, M. A. M. Ali, R. Schulz (2021).
FEBS J. 288, 7162-7182. https://doi.org/10.1111/febs.15701.

Genetic and chemical validation of Plasmodium falciparum aminopeptidase PfA-M17 as a drug target in the hemoglobin digestion pathway.
R. C. S. Edgar, G. Siddiqui, K. Hjerrild, T. R. Malcolm, N. B. Vinh, C. T. Webb, C. Holmes, C. A. MacRaild, H. C. Chernih, W. W. Suen, N. A. Counihan, D. J. Creek, P. J. Scammells, S. McGowan, T. F. de Koning-Ward (2022).
Elife. 11. https://doi.org/10.7554/eLife.80813.

Identification of novel ADAMTS1, ADAMTS4 and ADAMTS5 cleavage sites in versican using a label-free quantitative proteomics approach.
D. R. Martin, S. Santamaria, C. D. Koch, J. Ahnstrom, S. S. Apte (2021).
J Proteomics. 249, 104358. https://doi.org/10.1016/j.jprot.2021.104358.

Proteolysis of fibrillin-2 microfibrils is essential for normal skeletal development.
T. J. Mead, D. R. Martin, L. W. Wang, S. A. Cain, C. Gulec, E. Cahill, J. Mauch, D. Reinhardt, C. Lo, C. Baldock, S. S. Apte (2022).
Elife. 11. https://doi.org/10.7554/eLife.71142.

Proteolysis: a key post-translational modification regulating proteoglycans.
T. J. Mead, S. Bhutada, D. R. Martin, S. S. Apte (2022).
Am J Physiol Cell Physiol. 323, C651-C665. https://doi.org/10.1152/ajpcell.00215.2022.

MT1-MMP and ADAM10/17 exhibit a remarkable overlap of shedding properties.
L. Werny, A. Grogro, K. Bickenbach, C. Bulck, F. Armbrust, T. Koudelka, K. Pathak, F. Scharfenberg, M. Sammel, F. Sheikhouny, A. Tholey, S. Linder, C. Becker-Pauly (2022).
FEBS J. https://doi.org/10.1111/febs.16586.

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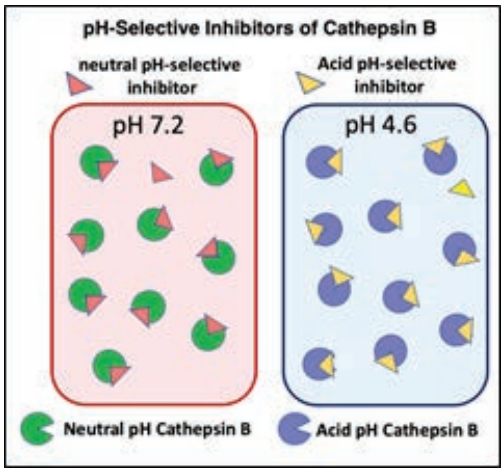
Important protease papers

REGULATION OF PROTEASE ACTIVITIES : Paper highlight

From Vivian Hook and Anthony O'Donoghue (University of California San Diego, USA)

- Distinct pH Selective Inhibitors of Cathepsin B



Cathepsin B functions in both acidic lysosomes and in neutral pH biological locations of the cytosol, nuclei, and extracellular sites. The neutral pH locations are prevalent in human diseases including neurodegenerative Alzheimer's disease and injury as well as in cancer.
The hypothesis that distinct cleavage properties of cathepsin B occur at acidic and neutral pH conditions was demonstrated by mass spectrometry analysis using a peptide library digestion assay. The distinct cleavage preferences allowed design of the neutral pH selective inhibitor of cathepsin B (Z-Arg-Lys-AOMK), having 100-fold greater potency at pH 7.2 compared to pH 4.6 (Yoon et al., 2021). Furthermore, recent studies with the cathepsin B inhibitor, CA-074, revealed that it inhibits at acidic pH with 100-fold more potency than at pH 7.2 (Yoon et al., 2022). The development of two important tools consisting of the neutral pH selective Z-Arg-Lys-AOMK inhibitor and the acid pH selective CA-074 inhibitor provides the field with tools to assess the lysosomal acidic function compared to extra-lysosomal functions of cathepsin B.

Selective Neutral pH Inhibitor of Cathepsin B Designed Based on Cleavage Preferences at Cytosolic and Lysosomal pH Conditions.
M. C. Yoon, A. Solania, Z. Jiang, M. P. Christy, S. Podvin, C. Mosier, C. B. Lietz, G. Ito, W. H. Gerwick, D. W. Wolan, G. Hook, A. J. O'Donoghue, V. Hook (2021).
ACS Chem Biol. 16, 1628-1643. https://doi.org/10.1021/acschembio.1c00138.

Molecular Features of CA-074 pH-Dependent Inhibition of Cathepsin B.
M. C. Yoon, M. P. Christy, V. V. Phan, W. H. Gerwick, G. Hook, A. J. O'Donoghue, V. Hook (2022).
Biochemistry. 61, 228-238. https://doi.org/10.1021/acs.biochem.1c00684.

- The Carboxypeptidase and Endopeptidase Activities of Cathepsin B Occur Over a Broad pH Range

The protease field has viewed cathepsin B as a carboxypeptidase at acidic pH and as an endopeptidase at neutral pH. But our recent findings have changed that concept. We show that carboxypeptidase and endopeptidase activities of cathepsin B occur over a broad pH range from acidic to neutral pH conditions. Notably, pH selective substrates can possess selectivity for acidic or neutral pH detection of carboxypeptidase and endopeptidase activities. Also, pH-independent substrates exist for cathepsin B. The specific amino acids of the substrate defines effective cleavages at each of the pH conditions assessed. This finding is important with respect to the in vivo substrates cleaved by cathepsin B in acidic lysosomes compared to neutral extra-lysosomal biological locations.

Cathepsin B Dipeptidyl Carboxypeptidase and Endopeptidase Activities Demonstrated across a Broad pH Range.
M. C. Yoon, V. Hook, A. J. O'Donoghue (2022).
Biochemistry. 61, 1904-1914. https://doi.org/10.1021/acs.biochem.2c00358.

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Important protease papers

REGULATION OF PROTEASE ACTIVITIES : Other important papers

In silico and in vitro mapping of specificity patterns of glycosaminoglycans towards cysteine cathepsins B, L, K, S and V.
K. K. Bojarski, J. Sage, G. Lalmanach, F. Lecaille, S. A. Samsonov (2022).
J Mol Graph Model. 113, 108153. https://doi.org/10.1016/j.jmgm.2022.108153.

Binding of heparan sulfate to human cystatin C modulates inhibition of cathepsin L: Putative consequences in mucopolysaccharidosis.
S. Denamur, T. Chazeirat, M. Maszota-Zieleniak, R. R. Vivès, A. Saidi, F. Zhang, R. J. Linhardt, F. Labarthe, S. A. Samsonov, G. Lalmanach, F. Lecaille (2022).
Carbohydrate Polymers. 293, 119734. https://doi.org/https://doi.org/10.1016/j.carbpol.2022.119734.

Zymogenic latency in an approximately 250-million-year-old astacin metallopeptidase.
T. Guevara, A. Rodriguez-Banqueri, W. Stocker, C. Becker-Pauly, F. X. Gomis-Ruth (2022).
Acta Crystallogr D Struct Biol. 78, 1347-1357. https://doi.org/10.1107/S2059798322009688.

Exosite binding modulates the specificity of the immunomodulatory enzyme ScpA, a C5a inactivating bacterial protease.
M. Jain, M. Tecza, T. F. Kagawa, J. C. Cooney (2022).
Comput Struct Biotechnol J. 20, 4860-4869. https://doi.org/10.1016/j.csbj.2022.08.018.

Low-level lysosomal membrane permeabilization for limited release and sublethal functions of cathepsin proteases in the cytosol and nucleus.
T. Reinheckel, M. Tholen (2022).
FEBS Open Bio. 12, 694-707. https://doi.org/10.1002/2211-5463.13385.

Post-translational regulation and proteolytic activity of the metalloproteinase ADAMTS8.
S. Santamaria, D. R. Martin, X. Dong, K. Yamamoto, S. S. Apte, J. Ahnstrom (2021).
J Biol Chem. 297, 101323. https://doi.org/10.1016/j.jbc.2021.101323.

Dynamics of the secreted frizzled related protein Sizzled and potential implications for binding to bone morphogenetic protein-1 (BMP-1).
U. Sharma, S. Vadon-Le Goff, K. Harlos, Y. Zhao, N. Mariano, C. Bijakowski, J. M. Bourhis, C. Moali, D. J. S. Hulmes, N. Aghajari (2022).
Sci Rep. 12, 14850. https://doi.org/10.1038/s41598-022-18795-4.

Trafficking of Full-Length and N-Terminally Truncated Cathepsin B in Human Colorectal Carcinoma Cells.
T. Tamhane, R. W. Njenga, R. E. Burden, H. Büth, G. M. Maelandsmo, M. H. Haugen, C. J. Scott, K. Brix (2021).
Appl Sci. 11, 11936. https://doi.org/10.3390/app112411936.

A metal ion-dependent conformational switch modulates activity of the Plasmodium M17 aminopeptidase.
C. T. Webb, W. Yang, B. T. Riley, B. K. Hayes, K. K. Sivaraman, T. R. Malcolm, S. Harrop, S. C. Atkinson, I. Kass, A. M. Buckle, N. Drinkwater, S. McGowan (2022).
J Biol Chem. 298, 102119. https://doi.org/10.1016/j.jbc.2022.102119.

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Important protease papers

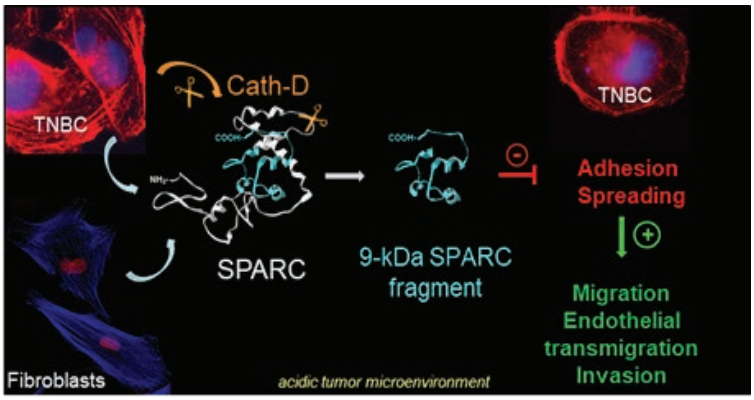
PROTEASES IN CANCER : Paper highlight

From Emmanuelle Liaudet-Coopman, Institut de Recherche en Cancérologie de Montpellier (IRCM), France

A 9-kDa matricellular SPARC fragment released by cathepsin D exhibits pro-tumor activity in the triple-negative breast cancer microenvironment.

L. B. Alcaraz, 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, E. Liaudet-Coopman (2021).
Theranostics. 11, 6173-6192. https://doi.org/10.7150/thno.58254.

The protease cathepsin D (cath-D) is a marker of poor prognosis in TNBC and a tumor-specific extracellular target for antibody-based therapy. The identification of cath-D substrates is crucial for the mechanistic understanding of its role in the TNBC microenvironment and future therapeutic developments. The cath-D substrate repertoire was investigated by N-Terminal Amine Isotopic Labeling of Substrates (TAILS)-based degradome analysis in a co-culture assay of TNBC cells and breast fibroblasts. TAILS analysis showed that the matricellular protein SPARC is a substrate of extracellular cath-D. Our study establishes a novel crosstalk between proteases and matricellular proteins in the tumor microenvironment through limited SPARC proteolysis, revealing a novel targetable 9-kDa bioactive SPARC fragment for new TNBC treatments.



Cath-D secreted by TNBC cells triggers limited proteolysis of SPARC at the tumor acidic pH, releasing a 9-kDa SPARC fragment that inhibits adhesion and spreading, and stimulates migration, endothelial transmigration, and invasion of TNBC cells.

PROTEASES IN CANCER : Other important papers

RNA interference screens discover proteases as synthetic lethal partners of PI3K inhibition in breast cancer cells.
L. Holzen, J. Mitschke, C. Schonichen, M. E. Hess, S. Ehrenfeld, M. Boerries, C. Miething, T. Brummer, T. Reinheckel (2022).
Theranostics. 12, 4348-4373. https://doi.org/10.7150/thno.68299.

Activity-based protein profiling reveals active serine proteases that drive malignancy of human ovarian clear cell carcinoma.
C. Mehner, A. Hockla, M. Coban, B. Madden, R. Estrada, D. C. Radisky, E. S. Radisky (2022).
J Biol Chem. 298, 102146. https://doi.org/10.1016/j.jbc.2022.102146.

Trafficking of Full-Length and N-Terminally Truncated Cathepsin B in Human Colorectal Carcinoma Cells.
T. Tamhane, R. W. Njenga, R. E. Burden, H. Büth, G. M. Maelandsmo, M. H. Haugen, C. J. Scott, K. Brix (2021).
Appl Sci. 11, 11936. https://doi.org/10.3390/app112411936.

Remodelling of the tumour microenvironment by the kallikrein-related peptidases.
S. Srinivasan, T. Kryza, J. Batra, J. Clements (2022).
Nat Rev Cancer. 22, 223-238. https://doi.org/10.1038/s41568-021-00436-z.

CONTINUED NEXT PAGE

Important protease papers

PROTEASES IN OTHER DISEASES : important papers

Forward and reverse degradomics defines the proteolytic landscape of human knee osteoarthritic cartilage and the role of the serine protease HtrA1.
S. Bhutada, L. Li, B. Willard, G. Muschler, N. Piuzzi, S. S. Apte (2022).
Osteoarthritis Cartilage. 30, 1091-1102. https://doi.org/10.1016/j.joca.2022.02.622.

DPP9 deficiency: An inflammasomopathy that can be rescued by lowering NLRP1/IL-1 signaling.
C. R. Harapas, K. S. Robinson, K. Lay, J. Wong, R. Moreno Traspas, N. Nabavizadeh, A. Rass-Rothschild, B. Boisson, S. B. Drutman, P. Laohamonthonkul, D. Bonner, J. R. Xiong, M. D. Gorrell, S. Davidson, C. H. Yu, M. D. Fleming, J. Gudera, J. Stein, M. Ben-Harosh, E. Groopman, A. Shimamura, H. Tamary, H. Kayserili, N. Hatipoglu, J. L. Casanova, J. A. Bernstein, F. L. Zhong, S. L. Masters, B. Reversade (2022).
Sci Immunol. 7, eabi4611. https://doi.org/10.1126/sciimmunol.abi4611.

Genome-wide association study identifies kallikrein 5 in type 2 inflammation-low asthma.
J. K. Jackman, A. Stockwell, D. F. Choy, M. M. Xie, P. Lu, G. Jia, H. Li, A. R. Abbas, P. G. Bronson, W. Y. Lin, C. P. C. Chiu, H. R. Maun, M. Roose-Girma, L. Tam, J. Zhang, Z. Modrusan, R. R. Graham, T. W. Behrens, S. R. White, T. Naureckas, C. Ober, M. Ferreira, R. Sedlacek, J. Wu, W. P. Lee, R. A. Lazarus, J. T. Koerber, J. R. Arron, B. L. Yaspan, T. Yi (2022).
J Allergy Clin Immunol. 150, 972-978 e977. https://doi.org/10.1016/j.jaci.2022.03.033.

Circulating Dipeptidyl Peptidase Activity Is a Potential Biomarker for Inflammatory Bowel Disease.
S. E. Jaenisch, C. A. Abbott, M. D. Gorrell, P. Bampton, R. N. Butler, R. Yazbeck (2022).
Clin Transl Gastroenterol. 13, e00452. https://doi.org/10.14309/ctg.0000000000000452.

Meprin and ADAM proteases as triggers of systemic inflammation in sepsis.
S. Rahn, C. Becker-Pauly (2022).
FEBS Lett. 596, 534-556. https://doi.org/10.1002/1873-3468.14225.

Deletion of fibroblast activation protein provides atheroprotection.
S. Stein, J. Weber, S. Nusser-Stein, J. Pahla, H. E. Zhang, S. A. Mohammed, S. Oppi, D. S. Gaul, F. Paneni, A. Tailleux, B. Staels, F. von Meyenn, F. Ruschitzka, M. D. Gorrell, T. F. Luscher, C. M. Matter (2021).
Cardiovasc Res. 117, 1060-1069. https://doi.org/10.1093/cvr/cvaa142.

Cathepsin V: Molecular characteristics and significance in health and disease.
F. Lecaille, T. Chazeirat, A. Saidi, G. Lalmanach (2022).
Mol Aspects Med. 88, 101086. https://doi.org/10.1016/j.mam.2022.101086.

Meprin β knockout reduces brain Aβ levels and rescues learning and memory impairments in the APP/lon mouse model for Alzheimer's disease.
L. Marengo, F. Armbrust, C. Schoenherr, S. E. Storck, U. Schmitt, S. Zampar, O. Wirths, H. Altmeppen, M. Glatzel, C. Kaether, S. Weggen, C. Becker-Pauly, C. U. Pietrzik (2022).
Cell Mol Life Sci. 79, 168. https://doi.org/10.1007/s00018-022-04205-5.

PCSK9 acts as a key regulator of Aβ clearance across the blood-brain barrier.
A. D. Mazura, A. Ohler, S. E. Storck, M. Kurtyka, F. Scharfenberg, S. Weggen, C. Becker-Pauly, C. U. Pietrzik (2022).
Cell Mol Life Sci. 79, 212. https://doi.org/10.1007/s00018-022-04237-x.

Characterization of Cysteine Cathepsin Expression in the Central Nervous System of Aged Wild-Type and Cathepsin-Deficient Mice.
D. M. T. Yu, S. Dauth, M. B. Margineanu, V. Snetkova, M. Rehders, S. Jordans, K. Brix (2022).
Appl Sci. 12, 2608. https://doi.org/10.3390/app12052608.

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Important protease papers

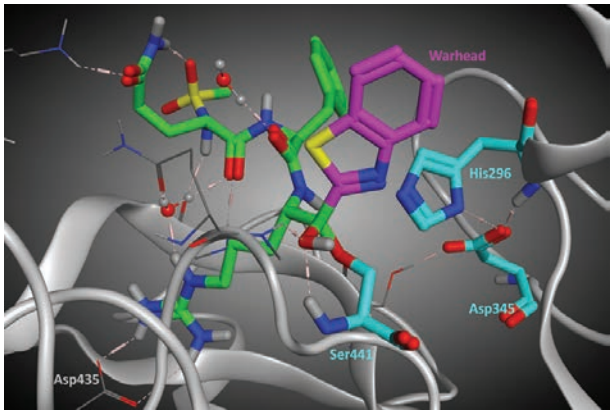
INIHIBITOR DEVELOPMENT : Paper highlight # 1

From Pierre-Luc Boudreault (Université de Sherbrooke, Canada), Richard Leduc (Université de Sherbrooke, Canada), Hector C. Aguilar (Cornell University College of Veterinary Medicine, USA) & François Jean (University of British Columbia, Canada)

A TMPRSS2 inhibitor acts as a pan-SARS-CoV-2 prophylactic and therapeutic.

T. Shapira, I. A. Monreal, S. P. Dion, D. W. Buchholz, B. Imbiakha, A. D. Olmstead, M. Jager, A. Desilets, G. Gao, M. Martins, T. Vandal, C. A. H. Thompson, A. Chin, W. D. Rees, T. Steiner, I. R. Nabi, E. Marsault, J. Sahler, D. G. Diel, G. R. Van de Walle, A. August, G. R. Whittaker, P. L. Boudreault, R. Leduc, H. C. Aguilar, F. Jean (2022).
Nature. 605, 340-348. https://doi.org/10.1038/s41586-022-04661-w.

The antiviral is a protease inhibitor of TMPRSS2, a member of the type-II transmembrane serine proteases, which helps cleave the viral spike protein needed to help the virus enter the cell. The specially designed antiviral, named N-0385, blocks TMPRSS2's activity, used by the virus to infect a host cell. The small molecule was developed by Drs. Richard Leduc, Éric Marsault, Pierre-Luc Boudreault and their team at Université de Sherbrooke. Dr. François Jean's team at University of British Columbia tested four SARS-CoV-2 variants of concern, including Delta, in human lung cells and organoids, tissue cultures that can mimic the organ they're taken from, and found that N-0385 inhibits infection, with no evidence of toxicity. At Cornell, N-0385 was shown by Dr. Aguilar's team to protect mice from infection prior to exposure, while also providing effective treatment when administered up to 12 hours after exposure. Published in Nature, the research opens the door to developing a therapeutic spray for humans. This work was funded by the Coronavirus Variants Rapid Response Network (Dr. Jean), and CIHR COVID-Rapid Research Fundings (Drs. Leduc, Jean, and Boudreault).



Molecular docking of the peptidomimetic N-0385 to TMPRRS2 showed a covalent bond between Ser441 of the catalytic triad (His296 and Asp345) and the warhead. The binding of N-0385/TMPRSS2 indicated that the small molecule interacts by an electrostatic interaction with Asp435, several hydrogen bonds, and a hydrophobic interaction with the warhead (not shown).

INHIBITOR DEVELOPMENT : Other important papers

GNS561, a clinical-stage PPT1 inhibitor, is efficient against hepatocellular carcinoma via modulation of lysosomal functions.

S. Brun, E. Bestion, E. Raymond, F. Bassissi, Z. M. Jilkova, S. Mezouar, M. Rachid, M. Novello, J. Tracz, A. Hamai, G. Lalmanach, L. Vanderlynden, R. Legouffe, J. Stauber, T. Schubert, M. G. Plach, J. Courcambeck, C. Drouot, G. Jacquemot, C. Serdjebi, G. Roth, J. P. Baudoin, C. Ansaldi, T. Decaens, P. Halfon (2022).
Autophagy. 18, 678-694. https://doi.org/10.1080/15548627.2021.1988357.

Sitagliptin Is More Effective Than Gliclazide in Preventing Pro-Fibrotic and Pro-Inflammatory Changes in a Rodent Model of Diet-Induced Non-Alcoholic Fatty Liver Disease.

J. Ren, X. Wang, C. Yee, M. D. Gorrell, S. V. McLennan, S. M. Twigg (2022).
Molecules. 27. https://doi.org/10.3390/molecules27030727.

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Important protease papers

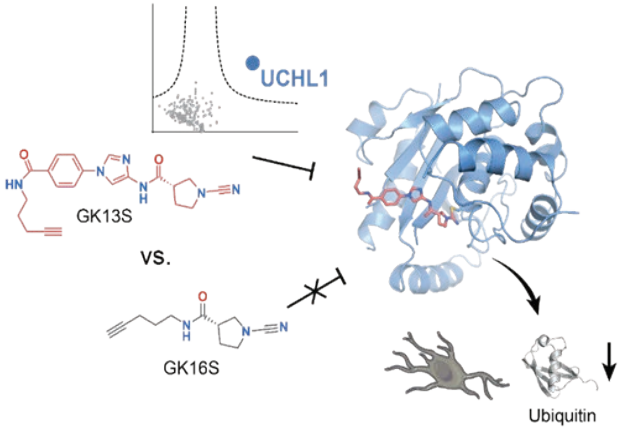
INIHIBITOR DEVELOPMENT : Paper highlight # 2

From Dr. Malte Gersch (Max Planck Institute of Molecular Physiology / Technische Universität Dortmund, Germany)

Structural basis for specific inhibition of the deubiquitinase UCHL1

C. Grethe, M. Schmidt, G. M. Kipka, R. O'Dea, K. Gallant, P. Janning, M. Gersch (2022).
Nat Commun. 13, 5950. https://doi.org/10.1038/s41467-022-33559-4.

Mutations in the deubiquitinase UCHL1 lead to neurodegeneration, yet its dysregulation promotes cancer metastasis and invasiveness. While no truly UCHL1-specific inhibitor exists to date, we introduce a pair of probes with which UCHL1-dependent effects can be studied in cells. The probes indeed confirm the phenotype of mutant mice in a cellular setting. By solving the crystal structure of the probe in complex with UCHL1, we show the enzyme locked in a hybrid conformation of apo and Ubiquitin-bound states, which underlies its UCHL1-specificity within the UCH deubiquitinase family. The structure further suggests a general hotspot for ligandability across DUB families.



INHIBITOR DEVELOPMENT : Other important papers

Chemoproteomics-Enabled Identification of 4-Oxo-beta-Lactams as Inhibitors of Dipeptidyl Peptidases 8 and 9.

L. A. R. Carvalho, B. Ross, L. Fehr, O. Bolgi, S. Wohrle, K. M. Lum, D. Podlesainski, A. C. Vieira, R. Kiefersauer, R. Felix, T. Rodrigues, S. D. Lucas, O. Gross, R. Geiss-Friedlander, B. F. Cravatt, R. Huber, M. Kaiser, R. Moreira (2022).
Angew Chem Int Ed Engl. 61, e202210498. https://doi.org/10.1002/anie.202210498.

Potent Inhibitor of Human Trypsins from the Aeruginosin Family of Natural Products.

M. N. Ahmed, M. Wahlsten, J. Jokela, M. Nees, U. H. Stenman, D. O. Alvarenga, T. Strandin, K. Sivonen, A. Poso, P. Permi, M. Metsa-Ketela, H. Koistinen, D. P. Fewer (2021).
ACS Chem Biol. 16, 2537-2546. https://doi.org/10.1021/acschembio.1c00611.

Discovery of varlaxins, new aeruginosin-type inhibitors of human trypsins.

L. M. P. Heinila, J. Jokela, M. N. Ahmed, M. Wahlsten, S. Kumar, P. Hrouzek, P. Permi, H. Koistinen, D. P. Fewer, K. Sivonen (2022).
Org Biomol Chem. 20, 2681-2692. https://doi.org/10.1039/d1ob02454j.

Modulation of the expression and activity of cathepsin S in reconstructed human skin by neohesperidin dihydrochalcone.

J. Sage, J. Renault, R. Domain, K. K. Bojarski, T. Chazeirat, A. Saidi, E. Leblanc, C. Nizard, S. A. Samsonov, R. Kurfurst, G. Lalmanach, F. Lecaille (2022).
Matrix Biol. 107, 97-112. https://doi.org/10.1016/j.matbio.2022.02.003.

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Important protease papers

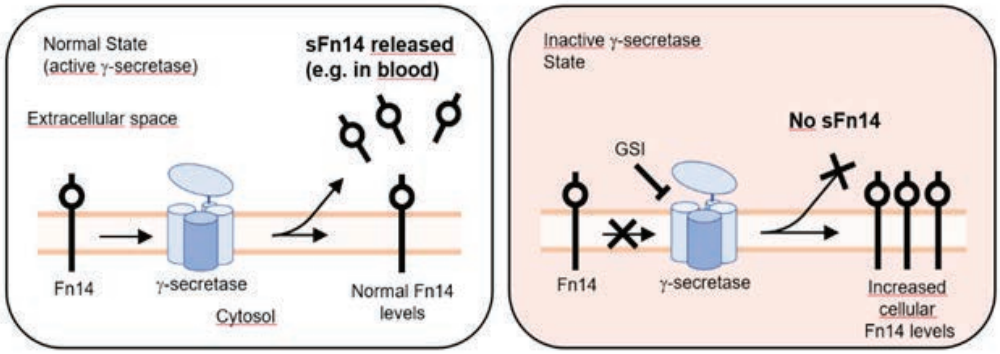
NEW METHODOLOGIES TO ANALYZE PROTEASE ACTIVITIES : Paper highlight # 1

From Marlene Aßfalg (German Center for Neurodegenerative Diseases (DZNE), Munich, Germany)

Proteolytically generated soluble Tweak Receptor Fn14 is a blood biomarker for gamma-secretase activity.

G. Guner, M. Assfalg, K. Zhao, T. Dreyer, S. Lahiri, Y. Lo, B. I. Slivinschi, A. Imhof, G. Jocher, L. Strohm, C. Behrends, D. Langosch, H. Bronger, C. Nimsky, J. W. Bartsch, S. R. Riddell, H. Steiner, S. F. Lichtenthaler (2022).
EMBO Mol Med. 14, e16084. https://doi.org/10.15252/emmm.202216084.

The protease γ-secretase is a major drug target for Alzheimer's disease and Notch-dependent tumors, but therapeutic γ-secretase inhibition is associated with mechanism-based side effects. A major challenge for monitoring and adjusting γ-secretase inhibition is the lack of a suitable, easily measurable in vivo pharmacodynamic marker for γ-secretase activity.
We identified the cell surface TWEAK receptor Fn14 as a novel substrate that is directly cleaved by γ-secretase within its transmembrane domain resulting in the secretion of the soluble ectodomain (sFn14), as seen in cell lines, primary cells, mice and humans.
Our study also demonstrates a novel function for γ-secretase in attenuating TWEAK/Fn14 signaling and suggests the use of sFn14 as an easily measurable pharmacodynamic biomarker in mice and humans to monitor γ-secretase activity in vivo. This may be instrumental for developing a new generation of γ-secretase-targeted drugs with enhanced specificity and a better safety profile.
Given the major role of Fn14 in tissue homeostasis, injury, and chronic diseases, the newly discovered proteolytic cleavage of Fn14 by γ-secretase may also offer new therapeutic options for modulating Fn14 function in disease.



NEW METHODOLOGIES TO ANALYZE PROTEASE ACTIVITIES : Other important papers

Immunoassay for trypsinogen-4.

H. Koistinen, R. Koistinen, K. Hotakainen, A. Lempiainen, K. Jokelainen, M. Farkkila, U. H. Stenman (2022).
Anal Biochem. 648, 114681. https://doi.org/10.1016/j.ab.2022.114681.

Engineering of tissue inhibitor of metalloproteinases TIMP-1 for fine discrimination between closely related stromelysins MMP-3 and MMP-10.

M. Raeeszadeh-Sarmazdeh, M. Coban, S. Mahajan, A. Hockla, B. Sankaran, G. P. Downey, D. C. Radisky, E. S. Radisky (2022).
J Biol Chem. 298, 101654. https://doi.org/10.1016/j.jbc.2022.101654.

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Important protease papers

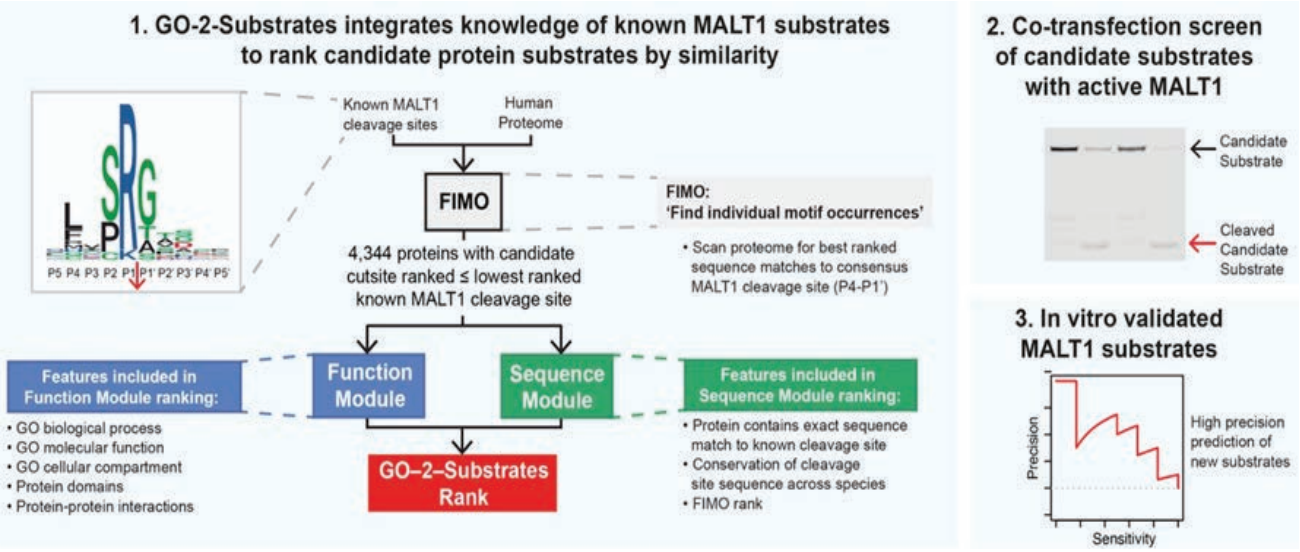
NEW METHODOLOGIES TO ANALYZE PROTEASE ACTIVITIES : Paper highlight # 2

From Peter Bell and Christopher Overall (University of British Columbia, Canada)

Integrating knowledge of protein sequence with protein function for the prediction and validation of new MALT1 substrates.

P. A. Bell, S. Scheuermann, F. Renner, C. L. Pan, H. Y. Lu, S. E. Turvey, F. Bornancin, C. H. Regnier, C. M. Overall (2022). Comput Struct Biotechnol J. 20, 4717-4732. https://doi.org/10.1016/j.csbj.2022.08.021.

We developed a bioinformatics-led substrate discovery workflow to expand the known substrate repertoire of MALT1. Our approach, termed GO-2-Substrates, integrates protein function information, including GO terms from known substrates, with protein sequences to rank substrate candidates by similarity. We applied GO-2-Substrates to MALT1, a paracaspase and master regulator of NF-κB signalling in adaptive immune responses. With only 12 known substrates, the evolutionarily conserved paracaspase functions and phenotypes of Malt1 –/– mice strongly implicate the existence of undiscovered substrates. We tested the ranked predictions from GO-2-Substrates of new MALT1 human substrates by co-expression of candidates transfected with the oncogenic constitutively active cIAP2-MALT1 fusion protein or CARD11/BCL10/MALT1 active signalosome. We identified seven new MALT1 substrates by the co-transfection screen: TANK, TAB3, CASP10, ZC3H12D, ZC3H12B, CILK1 and ILDR2. Using catalytically inactive cIAP2-MALT1 (Cys464Ala), a MALT1 inhibitor, MLT-748, and noncleavable P1-Arg to Ala mutant versions of each substrate in dual transfections, we validated the seven new substrates in vitro. By mining our TAILS N-terminomics datasets and Western blotting of B lymphocyte lysates, we confirmed the cleavage of endogenous TANK and the RNase ZC3H12D by endogenous B cell MALT1. Thus, protein function information improves substrate predictions. The new substrates and other high-ranked MALT1 candidate substrates should open new biological frontiers for validation and exploration of the function of MALT1 within and beyond NF-κB regulation.



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Job positions

From Charaf Benarafa (University of Bern, Switzerland)

Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra

Date	25.10.2022
Workplace	Institute of Virology and Immunology (IVI), Mittelhäusern, Switzerland The IVI is Switzerland's reference laboratory for the diagnosis and monitoring of highly contagious animal diseases, including zoonoses. The IVI reports to the Swiss Federal Food Safety and Veterinary Office (FSVO) and, in cooperation with the Vetsuisse faculty of the University of Bern, the IVI contributes to teaching and research in the fields of virology and immunology. The IVI provides a collaborative environment with experienced immunologists, virologists, veterinarians, and support teams within a unique high biosafety level containment laboratory.
Project Title	**PhD Studentship in immunology**
Description	A PhD student position is available in the laboratory of Prof. Charaf Benarafa to work on a project building on previous work on leukocyte proteases and their inhibitors of the serpin family (*1-3*). Using an unbiased proteomics approach (TAILS degradomics), we aim to identify key proteolytic targets of neutrophil serine proteases involved in cell death, inflammation, and emerging infectious diseases such as SARS-CoV-2 (*4-7*). To reach the research objectives, the successful candidate will use a broad range of techniques in immunology, virology, and biochemistry, and will characterize newly generated genetically-modified mouse models. The project is funded by Swiss National Science Foundation for 4 years. The successful applicant will be enrolled in the interfaculty PhD Program in Cellular and Biomedical Sciences of the University of Bern (www.gcb.unibe.ch). 1. S. S. Burgener *et al.*, Granule Leakage Induces Cell-Intrinsic, Granzyme B-Mediated Apoptosis in Mast Cells. *Front Cell Dev Biol* 9, 630166 (2021). 2. N. G. F. Leborgne, A. Taddeo, S. Freigang, C. Benarafa, Serpinb1a Is Dispensable for the Development and Cytokine Response of Invariant Natural Killer T Cell Subsets. *Front Immunol* 11, 562587 (2020). 3. S. S. Burgener *et al.*, Cathepsin G Inhibition by Serpinb1 and Serpinb6 Prevents Programmed Necrosis in Neutrophils and Monocytes and Reduces GSDMD-Driven Inflammation. *Cell Rep* 27, 3646-3656 e3645 (2019). 4. L. Ulrich *et al.*, Enhanced fitness of SARS-CoV-2 variant of concern Alpha but not Beta. *Nature* 602, 307-313 (2022). 5. A. Taddeo *et al.*, Optimized intramuscular immunization with VSV-vectored spike protein triggers a superior immune response to SARS-CoV-2. *NPJ Vaccines* 7, 82 (2022). 6. B. Zhou *et al.*, SARS-CoV-2 spike D614G change enhances replication and transmission. *Nature* 592, 122-127 (2021). 7. G. T. Barut *et al.*, The spike gene is a major determinant for the SARS-CoV-2 Omicron-BA.1 phenotype. *Nat Commun* 13, 5929 (2022).
Requirements	We are seeking a highly motivated candidate with a MSc degree in life sciences or a similar discipline with a solid background and interest in immunology, virology, proteomics, or cellular biology. Interest in working with mouse models is required but previous experience is not a prerequisite. The candidate should be proactive, have a highly collaborative spirit, and be able to work independently. Very good communication skills in English are essential. Basic knowledge of a Swiss national language would be helpful but not essential. Only outstanding applicants will be considered.
Entrance upon	01.01.2023
Application	To apply, please send a single PDF file including: - a short cover letter stating your qualifications and specific interest for this position - a curriculum vitae including name and email of 2 references - copy of MSc diploma including transcripts Review of applications will start immediately.
Contact **Email**	Prof. Charaf Benarafa, https://orcid.org/0000-0002-2049-7769 charaf.benarafa@unibe.ch
Link to the institution	http://www.ivi.unibe.ch/research/immunology/group_benarafa/projects/index_eng.html

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Job positions

From Charaf Benarafa (University of Bern, Switzerland)

Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra

Date	25.10.2022
Workplace	Institute of Virology and Immunology (IVI), Mittelhäusern, Switzerland The IVI is Switzerland's reference laboratory for the diagnosis and monitoring of highly contagious animal diseases, including zoonoses. The IVI reports to the Swiss Federal Food Safety and Veterinary Office (FSVO) and, in cooperation with the Vetsuisse faculty of the University of Bern, the IVI contributes to teaching and research in the fields of virology and immunology. The IVI provides a collaborative environment with experienced immunologists, virologists, veterinarians, and support teams within a unique high biosafety level containment laboratory.
Project Title	**Post-doctoral fellowship in immunology and proteomics**
Description	A post-doctoral position is available in the laboratory of Prof. Charaf Benarafa to work on a project building on previous work on leukocyte proteases and their inhibitors of the serpin family (*1-3*). The project will explore proteolytic pathways in immune cells and emerging infectious diseases such as COVID-19 and African swine fever (*4-8*). In this project, we aim to identify key proteolytic targets of proteases involved in cell death, inflammation, and antiviral responses. To reach the research objectives, the successful candidate will use unbiased proteomics approaches (such as TAILS degradomics) in collaboration the laboratory of Prof. Ulrich auf dem Keller (DTU, Denmark). The project is funded by Swiss National Science Foundation. 1. S. S. Burgener *et al.*, Granule Leakage Induces Cell-Intrinsic, Granzyme B-Mediated Apoptosis in Mast Cells. *Front Cell Dev Biol* **9**, 630166 (2021). 2. N. G. F. Leborgne, A. Taddeo, S. Freigang, C. Benarafa, Serpinb1a Is Dispensable for the Development and Cytokine Response of Invariant Natural Killer T Cell Subsets. *Front Immunol* **11**, 562587 (2020). 3. S. S. Burgener *et al.*, Cathepsin G Inhibition by Serpinb1 and Serpinb6 Prevents Programmed Necrosis in Neutrophils and Monocytes and Reduces GSDMD-Driven Inflammation. *Cell Rep* **27**, 3646-3656 e3645 (2019). 4. L. Ulrich *et al.*, Enhanced fitness of SARS-CoV-2 variant of concern Alpha but not Beta. *Nature* **602**, 307-313 (2022). 5. A. Taddeo *et al.*, Optimized intramuscular immunization with VSV-vectored spike protein triggers a superior immune response to SARS-CoV-2. *NPJ Vaccines* **7**, 82 (2022). 6. B. Zhou *et al.*, SARS-CoV-2 spike D614G change enhances replication and transmission. *Nature* **592**, 122-127 (2021). 7. G. T. Barut *et al.*, The spike gene is a major determinant for the SARS-CoV-2 Omicron-BA.1 phenotype. *Nat Commun* **13**, 5929 (2022). 8. E. Radulovic *et al.*, The baseline immunological and hygienic status of pigs impact disease severity of African swine fever. *PLoS Pathog* **18**, e1010522 (2022).
Requirements	We are looking for a highly motivated candidate with a PhD degree in biochemistry, cell biology, or immunology with a special interest in proteomics or bioinformatics. Experience or interest with working with mouse models is an advantage. The candidate should be self-motivated, able to work independently, and help supervise junior team members. Very good oral and writing skills in English are essential. Basic knowledge of a Swiss national language is helpful but not essential. Only outstanding applicants will be considered.
Entrance upon	01.01.2023
Application	To apply, please send a single PDF file including: - a short cover letter stating your qualifications and specific interest for this position - a curriculum vitae including name and email of 2 references - copy of PhD diploma and PhD thesis summary Review of applications will start immediately.
Contact **Email**	Prof. Charaf Benarafa, https://orcid.org/0000-0002-2049-7769 charaf.benarafa@unibe.ch
Link to the institution	http://www.ivi.unibe.ch/research/immunology/group_benarafa/projects/index_eng.html

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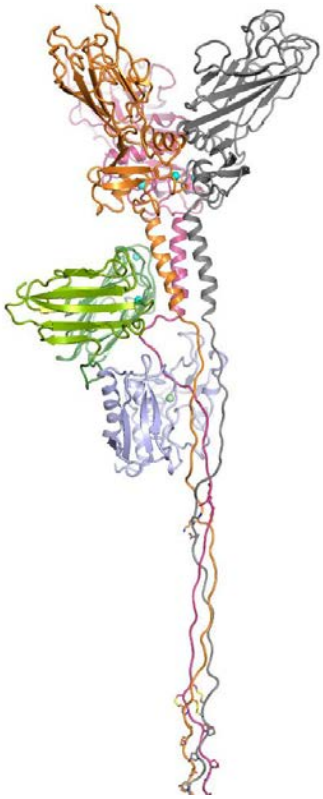
Job positions

From Catherine Moali (CNRS / University of Lyon, France)

Post-doc position LBTI, Lyon
Group Metalloproteinases and Tissue Remodeling (C. Moali)

Structure-function analysis of a prominent target in fibrosis: the proteolytic maturation complex of fibrillar collagens



The biosynthesis of fibrillar collagens is severely deregulated in fibrosis, the common and deleterious outcome of a great diversity of tissue injuries. A better understanding of the various steps leading from the synthesis of individual procollagen chains to collagen fibrils would greatly benefit the development of new therapeutic tools. In the *P^3-complex* project, we focus on the C-terminal proteolytic maturation of fibrillar procollagens in order to :

- better understand, at the molecular level, how the various components of the maturation complex (substrate, protease, regulatory proteins) associate and work together. This is done mainly by cryo-electron microscopy and through a combination of biochemical/biophysical approaches.

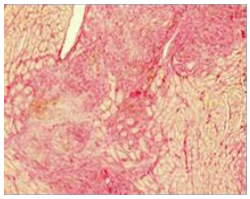
- learn more about how this complex affects tissue biology and extracellular matrix remodelling using transcriptomics, targeted mass spectrometry and biochemical assays.

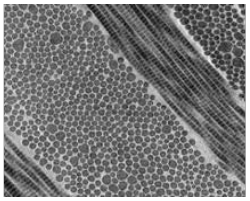
This project is funded by the French Research Agency (ANR) and is performed in collaboration with the OPIC (Oxford Particle Imaging Center) facility in Oxford for cryo-EM and with the University Hospital of Dijon for fibrosis samples. It will contribute to optimize innovative tools, currently under development in the group, to diagnose and treat fibrosis.

Skills :
- Excellent theoritical and practical knowledge of molecular biology and protein biochemistry
- Experience in running protein-protein interaction analyses (ideally SPR) and biochemical assays to measure protein concentrations (ELISA, mass spectrometry)
- Knowledge in structural biology; previous experience in cryo-EM would be an advantage
- Knowledge in extracellular matrix biology

More information and applications here :
https://emploi.cnrs.fr/Offres/CDD/UMR5305-CATMOA-007/Default.aspx?lang=EN

We invite highly motivated candidates to apply directly on the above website (detailed CV with publication list and names of 2 references, cover letter) or by sending their documents to catherine.moali@ibcp.fr before **December 13, 2022**. The position is already open and can start immediately.





***L**aboratoire de **B**iologie **T**issulaire et **I**ngénierie thérapeutique*
***I**nstitut de **B**iologie et **C**himie des **P**rotéines*
Unité Mixte de Recherche 5305 - CNRS / Université Lyon 1
https://lbti.ibcp.fr/

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Meeting announcements

12th General Meeting of the International Proteolysis Society

Mark your dates for 24 – 29 June 2023.
We will open for registration soon!
https://www.dbs.nus.edu.sg/ips2023/

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.

NUS National University of Singapore

International Proteolysis Society

Training workshops : 23 – 24 June 2023
Workshop topics : structural biology, enzyme kinetics, imaging and substrate discovery

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Meeting announcements

Crosstalk between the ECM and Proteases from destruction to regeneration

Proteolysis is a critical post-translational modification as every protein encounters a protease in its lifetime, be it signal peptide removal, activation, processing, or degradation. Proteases act in concerted networks to amplify signals, regulate biology, and are hypothesized molecular switches and effectors involved in tissue remodeling. The extracellular matrix (ECM) regulates key functions such as cell movement, shape, growth and survival via cell adhesion, cell-ECM, and cell-cell interactions. The ECM is a non-cellular structure that is highly dynamic and remains in close contact with cells either throughout their entire life or at important phases of their development. For this reason, the ECM is present in all tissues and organs of the body, providing structural support as one of its main functions. However, the ECM plays additional biological functions that are still uncharacterized. We are only beginning to understand the intriguing regulatory aspects of proteases that modulate the ECM dynamic remodeling; but many questions remain. Specifically, 1- How universal are the auto-feedback mechanisms driven by ECM proteolysis? 2- How does cleaved ECM regulate the initiation and resolution of inflammation and cancer progression? 3- Does aberrant proteolysis dysregulate the resolution of inflammation or it is the ECM that regulate proteolysis?

Our meeting will directly address these questions by inviting several experts from the ECM and proteases and give them an opportunity to discuss where the next decade will take us. We will also discuss advanced system-biology experimental and computational tools designed to characterise ECM-protease multi-factorial proteolytic cascades and networks in health and disease.

Topics related to proteases and extracellular matrix organization, cell adhesion, cell migration, matrix-mediated cell signaling and new technologies including single cell RNA-sequencing, proteomics, N-terminomics and bioinformatics, will be the target of this 1st FEBS-ALC. These topics are of great importance to understand the maintenance of normal tissue homeostasis and disease initiation, signaling elicited by interactions of cell surface receptors with matrix components and growth factors and rapid and sensitive structure analysis, proteolysis, and novel drug development.

People can register on tinyurl.com/53y34em5 and check the activity as it will be posted on https://www.febs.org/our-activities/advanced-courses/

Antoine Dufour (University of Calgary, Canada) and Irit Sagi (Weizmann Institute of Science, Israel)

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Meeting announcements

WELCOME to the 40th Winter School on Proteinases and Inhibitors in Tiers (Wednesday, March 1 – Sunday, March 5, 2023)!

Deadline for registration : January 31, 2023
Deadline for abstract submission : January 15, 2023

Founded by Hans Fritz and Vito Turk more than three decades ago, the Winter School continues to provide a scientifically stimulating and personally outstandingly open atmosphere to researchers on proteolytic enzymes.
By its tradition, the Winter School provides a forum primarily to young scientists allowing them to present their exciting and /or intriguing results for discussion with leading experts.
The exceptional success story of the Winter School also relates to the beautiful scenery of the Tiers valley which serves as an ideal incubator for scientific exchange.
The splendid spirit of the Winter School in Tiers attracts scientists from Europe and worldwide, covering diverse and vibrant fields of protease research, such as mechanistic studies on proteases in their molecular, cellular and organismic context. Participate and enjoy this unique event !

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Meeting announcements

ProteCURE ANNUAL MEETING 2023: FIRST ANNOUNCEMENT
Zagreb, Croatia. 12-15/06/2023
SAVE THE DATE

PROTEOCURE

cost
EUROPEAN COOPERATION IN SCIENCE & TECHNOLOGY

Funded by the European Union

EMBO Workshop: THE 20S PROTEASOME DEGRADATION PATHWAY

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