April 2025

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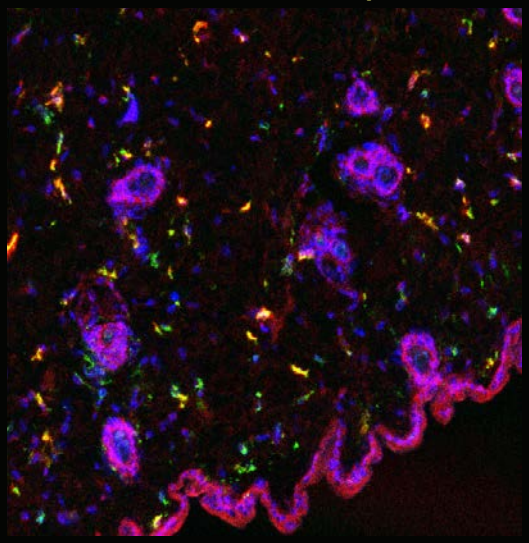
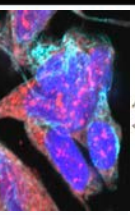
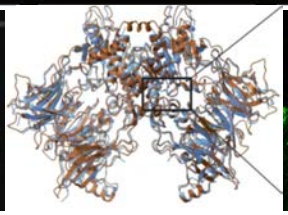
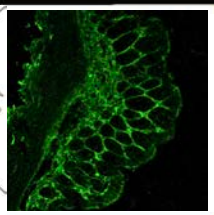


INTERNATIONAL PROTEOLYSIS SOCIETY

# QUICKCUTS

Edited by:
Laura Edgington-Mitchell

THE PREMIER RESOURCE
FOR ALL YOUR IMPORTANT PROTEASE NEWS

## A Message From the President:

Dear IPS community, dear friends,

It is a great pleasure to announce that registration for the upcoming General IPS meeting is now open. This meeting, which will celebrate 25 years of IPS, will take place in Brazil, Buzios. We anticipate a strong turnout from the international protease community. The scientific program will highlight the most cutting-edge research across a broad spectrum of protease-related fields, including blood disorders, cancer, immunity, aging, drug development, proteolysis-related tools, structure-function relationship and much more. We anticipate an exciting and inspiring meeting, with a great scientific exchange that will reflect the vibrant state of the field. A heartful thank you goes to the meeting organisers: Chair: Ana Paula Lima – Universidade Federal do Rio de Janeiro and Co-Chair: Maria Luiza Oliva – Universidade Federal de São Paulo.

I strongly encourage you to register for the meeting as soon as possible. Additionally, I would like to highlight the Early Career Training Workshops, which offer a unique opportunity for professional development and networking. As space is limited, we urge early registration for these Workshops. In this context, I thank the many excellent colleagues that will hold the workshops prior to the meeting

Guy Salvesen (Sanford-Burnham Medical Research Institute), Christian Sommerhoff (University of Munich), Scott Snipas (Sanford Burnham Prebys Medical Discovery Institute), Fernanda dos Reis Rocho (USP), Anthony D'Donoghue (UCSD), Antoine Dufour (University of Calgary), Galia Blum (The Hebrew University), Olivier Julien (University of Alberta), Konstantinos Kalogeropoulos (Technical University of Denmark), Peter Bell (University of British Columbia). Thank you for your time and commitment!
We are also pleased to open nominations for the Young Investigator Award Ulrich auf dem Keller. This award which was initiated by the late Ulrich auf dem Keller, recognizes outstanding contributions by early-career researchers in the protease field. Full eligibility criteria are available in this QuickCuts edition.
It is also with deep sadness that we dedicate this QuickCuts to Prof. Dr. Wolfram Bode, who passed away in January 2025. Wolfram was a life-time scientist, who mentored generations of scientists, with an impressive repertoire of publications. It is thus not surprising that he was awarded the IPS life-time achievement award. Beyond a great scientist, Wolfram will also be remembered as a true gentleman, as a mentor, as a friend. I send my deepest condolences to his many past colleagues, friends and especially to his family. Wolfram will be greatly missed.

Finally, I urge all members to renew their IPS membership. Your continued support ensures the sustainability of our society and its mission: to promote scientific excellence, collaborations, and the development of early-career scientists through travel awards, webinars, and training workshops.

My big thanks is extended to Laura Edgington-Mitchell for putting together this QuickCuts edition.

Best wishes

Ruth Geiss-Friedlander
Email: ruth.geiss-friedlander@mol-med.uni-freiburg.de

# Announcing IPS 2025


**Register now!**
**https://ipsbrazil.com.br/**

**Submit abstracts by 31 Aug**

**Register for Early Career Training Workshops by 23 May**

**Travel Awards will be available**

**Don't forget to renew your IPS membership!**


# Ulrich auf dem Keller Young Investigator Award

The International Proteolysis Society (IPS) recognizes excellence across disciplines that advance our understanding of proteases, their inhibitors and their uses. The Ulrich auf dem Keller Young Investigator Award honors researchers within 6 years* of obtaining their first independent research position, who have distinguished themselves with significant achievements in protease research. Awardees are selected by The International Proteolysis Society Executive Council. Recipients are honored at the biannual meeting of the International Proteolysis Society. Nominations are due by or on June 30, 2025.

## ELIGIBILITY

**Nominator:**

1. Nominators may be IPS members. (www.protease.org)
2. International Proteolysis Society Executive Council Members may submit nominations, but may not provide letters of support.

**Nominee:**

1. Nominees must be IPS members. (www.protease.org)
2. For the Ulrich auf dem Keller Young Investigator Award, there are no age or gender requirements. IPS encourages nominations of individuals from diverse backgrounds.
3. The Young Investigator Award nominations are accepted only for nominees within 5 years* of starting an independent career (Assistant Professor or equivalent).*With allowances for familial leave or other exigent circumstance.

**Multiple nominations:**

1. Nominators can nominate more than one individual.
2. If two independent nominators nominate the same person for the same award, the nominations will be combined into one.

## COMPLETED NOMINATIONS PACKAGES MUST INCLUDE:

1. Nominee's name, professional title, affiliation, e-mail address and phone number.
2. Nominee's Curriculum Vitae (limited to five pages) to include achievements on which the nomination is based.
3. Nominating statement (limit 500 words). Short summary of the nominee's achievements on which the nomination is based. The statement should clearly summarize how the nominee is deserving of the award.
4. One letter of support. The nominator should arrange for at least one, or up to three letters supporting the nomination. Supporting letters should be no more than two pages each. Letters of support contributors do not need to be IPS members.
5. Compiled nomination packages should be submitted as a single pdf to ipssecretary@gmail.com no later than midnight GMT June 30, 2025.

# In Memoriam: *Dr. Wolfram Bode*

It was with great sadness that we received the news of the passing of Prof. Dr. Wolfram Bode in January of this year, two months short of his 83rd birthday. We mourn the loss of a uniquely kind and spirited mentor, colleague and friend. As a scientist, Wolfram is best known for his many ground-breaking discoveries of protease biochemistry, especially atomic level descriptions of function and regulation through crystal structure analysis. Among his many accolades, he chaired the Gordon Research Conference "Proteolytic Enzymes and Their Inhibitors" in 2000, was co-organizer of the second "International Conference on Protease Inhibitors" in Freising in 2001, and was recipient of the International Proteolysis Society (IPS) Lifetime Award in 2005.

Born in Berlin during the Second World War, his earliest years were characterized by displacement and deprivation. Wolfram studied chemistry and biochemistry at the Universities of Göttingen, Tübingen and finally Munich, where he obtained his PhD studying bacterial flagella and the flagellar protein flagellin.[1] In 1972, Wolfram joined Robert Huber's laboratory at the newly established Max-Planck-Institut für Biochemie in Martinsried. Here he began a scientific life devoted almost exclusively to the study of the structure and function of proteases and their inhibitors. This he did with such enormous energy and productivity that we can cover only a few selected aspects of his work here.

Wolfram and Robert proved to be a formidable team, establishing Martinsried as a powerhouse for protein X-ray crystallography, which in those days required painstakingly detailed and careful experimentation and computation. Their earliest work revealed structures of bovine trypsin[2] and its complex with basic pancreatic trypsin inhibitor.[3] The prevailing view of enzyme catalysis at the time was based on Emil Fischer's "lock and key" model,[4] with the substrate as key and the enzyme as a rigid "lock", and the structures of trypsin were consistent with this model. Key features were in agreement with the catalytic elements identified previously in chymotrypsin by David Blow:[5,6] a catalytic triad of Ser195, His57 and Asp102, and a positively charged cavity (the "oxyanion hole") that stabilizes the negatively charged oxygen in the tetrahedral intermediate of the scissile peptide bond. The only substantial differences were in the substrate recognition pocket, reflecting their specificities for cleavage after basic / hydrophobic residues.

The "lock and key" model did not obviously apply to inactive enzymes, however. Solving the crystal structure of the inactive zymogen trypsinogen at high resolution[7] produced a perplexing result: many amino acid residues near the active site were not visible in the experimental electron density distribution. At the time, disorder in crystal structures was generally considered to be due to crystal defects or technical errors during structure determination rather than an intrinsic property of proteins. By applying rigorous crystallographic refinement techniques developed in Robert's lab by Hans Deisenhofer and Wolfgang Steigemann,[8] Wolfram and Robert concluded that the missing density was due to conformational disorder and proposed that trypsin activation involves an extensive disorder-to-order transition initiated by the cleavage of the trypsinogen activation peptide. The specific activation mechanism was revealed to be the formation

of a buried salt bridge between the positively charged-N-terminus created by the cleavage (at Ile16) and the negatively charged side chain Asp194, rearranging the enzyme to form the substrate recognition pocket and the oxyanion hole of the active proteinase. In a series of seminal publications,[9,10] they demonstrated that this disorder-to-order transition was in fact the activation mechanism, and not an artifact of poor crystal quality. One of the most convincing demonstrations was the addition of dipeptides that mimicked the N-terminus formed after cleavage of trypsinogen (e.g. $NH_3^+$-Ile-Val) to uncleaved trypsinogen. The dipeptide indeed inserted into the cavity that otherwise accommodated the N-terminus, activating the enzyme. Knowing the importance of communicating their findings in a memorable fashion, Wolfram and Robert used the phrase "molecular sexuality" to describe the process. This activation mechanism proved to apply in variations across all serine proteinases, explaining e.g. the low intrinsic activity of coagulation factor IXa,[11] the inhibition of tissue kallikrein 4 by zinc,[12] the high intrinsic activity of the zymogen of tissue plasminogen activator,[13] and the ability of staphylocoagulase to activate prothrombin.[14] Wolfram had the perseverance and meticulous care that were needed to solve crystal structures in the early days of protein crystallography. But even more essentially, he had a deep fascination with interpreting those structures scientifically, to answer the question of "how does the structure explain the biochemical function?". His curiosity and excitement were infectious to all around him, including non-crystallographers. Recognizing the need to study and become intimately familiar with the structure and its variations, Wolfram emphasised the importance of presenting protease structures and their active sites in standard orientation[15] and, of course, in stereo! Now, the stereo view seems almost forgotten, and the increasing barriers to acquiring a solid intuitive understanding of structure are driving a risky and almost blind deference to computational analysis.

Wolfram's work on serine proteases progressed to thrombin[16] and its complexes with inhibitors and co-factors,[17] including the ground-breaking thrombin-hirudin complex.[18] These studies were not only of great importance for the fundamental understanding of coagulation but also of enormous pharmaceutical relevance. Wolfram proceeded to solve structures of many more clotting and fibrinolytic proteases, shedding light on the molecular basis of haemostasis and revealing the enormous diversity of pro- and anticoagulant strategies developed by haematophagous organisms.

Other proteinase classes drew his attention; Wolfram once said that he was interested in "anything with a cleft". A highly productive cooperation with Vito Turk yielded structures of the lysosomal cysteine proteinase cathepsin B[19] and its inhibitors cystatin[20] and stefin B,[21] culminating in the elephant trunk model of inhibition. Solution of the structure of the crayfish metalloproteinase astacin[22] (in collaboration with Walter Stöcker) identified a structurally conserved methionine C-terminal to the zinc-binding consensus motif. Wolfram coined the term metzincin for this metalloprotease superfamily,[23] which was subsequently demonstrated to encompass MMPs, collagenases, ADAMs and meprins.

The career statistics of 349 publications (h-index of 120)[24] testify to Wolfram's remarkable productivity. Even more meaningful testimonials come from his colleagues and students from all over the world. After hearing of his passing, Guy Salvesen spoke for many when he said that Wolfram was "one of the most decent individuals that it was my privilege to know". Wolfram's genuine interest in the science and in his collaborators and students was at the core of his ability to inspire hard work and extensive cooperation on

important projects. He was always happy to demonstrate crucial techniques such as crystal mounting to new investigators, or show his newest structures. He had a store of "sure fire" projects in reserve that "rescued" a number of doctoral candidates. His energy was always evident, whistling classical music while working, lecturing at blistering speeds, cursing when losing a freshly harvested crystal, and so on.

Dissemination of insights from his work was very important to Wolfram, and he liked good use of humour and catchy titles ("The Clot Thickens",[25] suggested by Edgar Meyer, was one of his favourites). A favourite phrase in publications was "in a something-like manner (insert the most appropriate metaphor). He was for many years active at the Winter School on Proteinases and Their Inhibitors (since decades at the Rosengarten in Tiers, South Tirol) organized by Hans Fritz and Vito Turk, where he took a sporting approach to the "Awards" ceremonies. In his presentations, a lack of stereo – or even slides – was no hindrance to Wolfram's knowledge of proteinase structure; many conference attendees can attest to his ability to discuss structural details with only his bare hands!

In private, Wolfram was devoted to his family and to musicianship, playing the viola in a string quartet founded in his student days, and to charity work. Just as he helped and supported students and colleagues in science, he later became involved in helping refugees, and maintained his interest in open-minded politics. We were extremely fortunate to have had our lives shaped by work with Wolfram, both professionally and personally, and we cherish the memories. He leaves behind his two sons Achim and Jan and five grandchildren as he joins his beloved wife Antje and daughter Julia.

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**Acknowledgements**
We thank Robert Huber and Guy Salvesen for their helpful comments on the manuscript.

**References and notes**

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# Meeting Report: Winter School

**The 42nd Protease Winter School in Tiers took place from 12 to 16 March 2025.**

As every year, protease scientists from leading laboratories in Europe and all continents gathered in the beautiful setting of the Rosengarten in the Dolomites in Tiers, Italy. The Winter School was co-organised by ProteoCure (https://proteocure.eu). This year's Winter School was truly unique as it even provided the answer to the ultimate question of life, the universe, and everything. In addition, we discussed other important questions in major disease areas such as cancer, neurodegeneration, cardiovascular diseases, and pathogens & viral infections. We also had technology-focused sessions on microscopy, spatial biology and computational methods. Rupert Ecker gave a fascinating presentation and demonstration of the capabilities of TissueFAXS.

In keeping with the Winter School tradition, senior scientists introduced each of the seven session topics, but it is the young scientists who present their research, with ample time for discussion. Among these sessions with many excellent presentations, Naiá Santos (Paris Lodron University of Salzburg), Samuel Zolg (University of Freiburg) and Peter Grin (University of British Columbia & University of Bern) stood out and were honoured with Young Investigator Awards from the Henner-Graeff-Foundation (https://www.henner-graeff-stiftung.de). Another USP of the Winter School is the legendary Fritzi Awards, feared (when red) and coveted (when green), but always received with awe and pride. The Fritzis recognise unique achievements, including the Dancing Queen Award, given for best practice in the Acoustics and Kinetics workshop, featuring the InhibiTIERS AllStar Band. This year it was an extremely tough decision and in the end groups from Freiburg and Munich were awarded a Green Dancing Queen Fritzi!

We are already looking forward to next year's meeting, which will take place in Tiers from 11 to 15 March 2026. Check the website https://plus.ac.at/tiers to stay tuned.

Wolfram Bode (middle) together with Hans Brandstetter and Walter Stöcker in Tiers 2020.

Enzyme acoustics and kinetics night session featuring The InhibiTiers AllStar Band.

Extreme(ly nice) hiking tour guided by Thomas Reinheckel.

# International Society for Protein Termini (ISPT)

We are reaching out to invite you to join the new mailing list of the International Society for Protein Termini (ISPT). In 2018, a group of scientists interested in the molecular meaning of exposure and modifications of protein neo-termini came up with the idea to establish a Society to combine interests, communication, and initiatives. In the meanwhile, we had some Society meetings in Halle (Saale), Seoul, Bergen, and Oxford, the next one is planned to take place 2026 in Palermo.

After our last Society meeting, that was held as a FEBS workshop in Oxford last September, we decided to compile a unique list of individuals who share common interests in areas such as proteostasis across the kingdoms of life, proteases, co- and post-translational protein modifications (N- and C- termini), protein quality control, biocondensates, proteasomes, autophagy, physiological roles of these complex systems and more. Our goal is to use this list to keep you informed about the activities of the ISPT.


**Website: https://ispt-cdbc.snu.ac.kr/about/ispt**

If you are interested in being included, please sign up. We would be delighted to have your participation!

We will keep you updated about our activities, including upcoming congresses, invitations to meetings, grant opportunities, and other relevant news. We'd love to have you on board, so far, we have about 500 subscribers.

We are looking forward to receiving your positive responses. Stay tuned and all the best,

**Carmela Giglione & Nico Dissmeyer**
On behalf of the ISPT Management Board

# Meeting Announcement


## Fourth Annual Meeting of the ProteoCure COST Action

Atlantis Aquila Hotel, Heraklion, Crete, Greece

May 20-23, 2025.

The COST action ProteoCure is happy to invite you at its fourth annual meeting. In line with the 3 previous meetings (Ljubljana, Slovenia, May 2022; Zagreb, Croatia, June 2023; Warsaw, Poland, May 2024), this conference aims at gathering European research teams and companies sharing the objective to develop new approaches and strategies to selectively manipulate protein fate for therapeutic or biotechnological purposes.

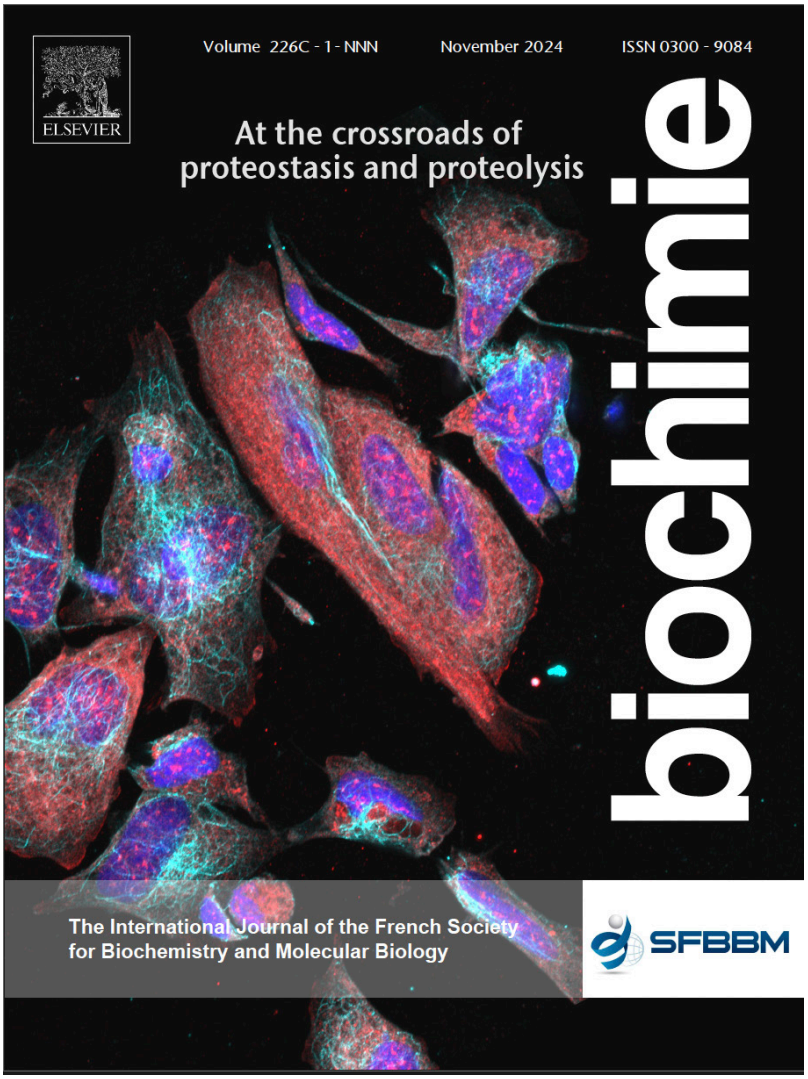
Indeed, ProteoCure's goal is to help uniting individuals from academia, clinical sector and industry studying proteostasis, i.e. the mutiple and intricate processes regulating protein expression and function, as well as its manipulation for therapeutic or biotechnologic needs.

An important objective of ProteoCure is also to contribute to the training of the next generation of scientists. To favor participation and visibility of our young colleagues, travel grants will be offered and the scientific program will be organized in order to permit as many short talks as possible.

https://proteocure2025.sciencesconf.org/

# Biochimie Special Issue

## "At the crossroads of proteostasis and proteolysis"




Since 2008, Biochimie (Elsevier), the official journal of French Society of Biochemistry and Molecular Biology (SFBBM), has published four thematic issues (Guest editor: Prof. Gilles Lalmanach) devoted to the field of proteolytic enzymes: "Cellular proteolysis" (Vol. 90(2), February 2008), "Protease inhibitors and biological control" (Vol. 92(11), November 2010), "A potpourri of proteases and inhibitors: from molecular toolboxes to signaling scissors" (Vol. 122(C), March 2016) and "Proteases: goldies enzymes always on the agenda" (Vol. 166, November 2019).

Following the successful organization of a scientific joint conference (https://proteolysis2023.sciences-conf.org/, held in the beautiful and historical Campus Les Cordeliers-Sorbonne Université, May 22-24th, 2023, Paris, France) between the "cellular proteolysis" thematic group of the SFBBM and one of the four working groups of the COST European network "ProteoCure" (so called "a sound proteome for a sound body: targeting proteolysis for proteome remodeling"), a fifth thematic issue of Biochimie dedicated to proteolysis has been recently released (November 2024). This special issue is entitled "At the crossroads of proteostasis and proteolysis" (Handling Editor: Prof. Bertrand Friguet - Guest editors: Prof. Chahrazade El Amri, Dr. Carmela Giglione and Prof. Gilles Lalmanach). It is a fair combination of sixteen articles (assembled in five chapters blending bibliographic reviews and original research contributions) authored by distinguished colleagues. The detailed list of articles and authors is directly accessible via the following link: https://www.sciencedirect.com/journal/biochimie/vol/226/suppl/C.

The cover of this issue was kindly provided by **Prof. Klaudia Brix** and colleagues.

**Prof. Gilles Lalmanach**
University of Tours & INSERM UMR1100, Research Center for Respiratory Diseases (CEPR), Team "Proteolytic enzymes and their pharmacological targeting in lung diseases", Tours, France.
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# Recent Protease Papers

Rotenberg N, Feldman M, Shirian J, Hockla A, **Radisky ES,** Shifman JM. **Engineered TIMP2 with narrow MMP-9 specificity is an effective inhibitor of invasion and proliferation of triple-negative breast cancer cells.** (2024) J Biol Chem. 300(11):107867. doi: 10.1016/j.jbc.2024.107867. PMID: 39419285; PMCID: PMC11609464.

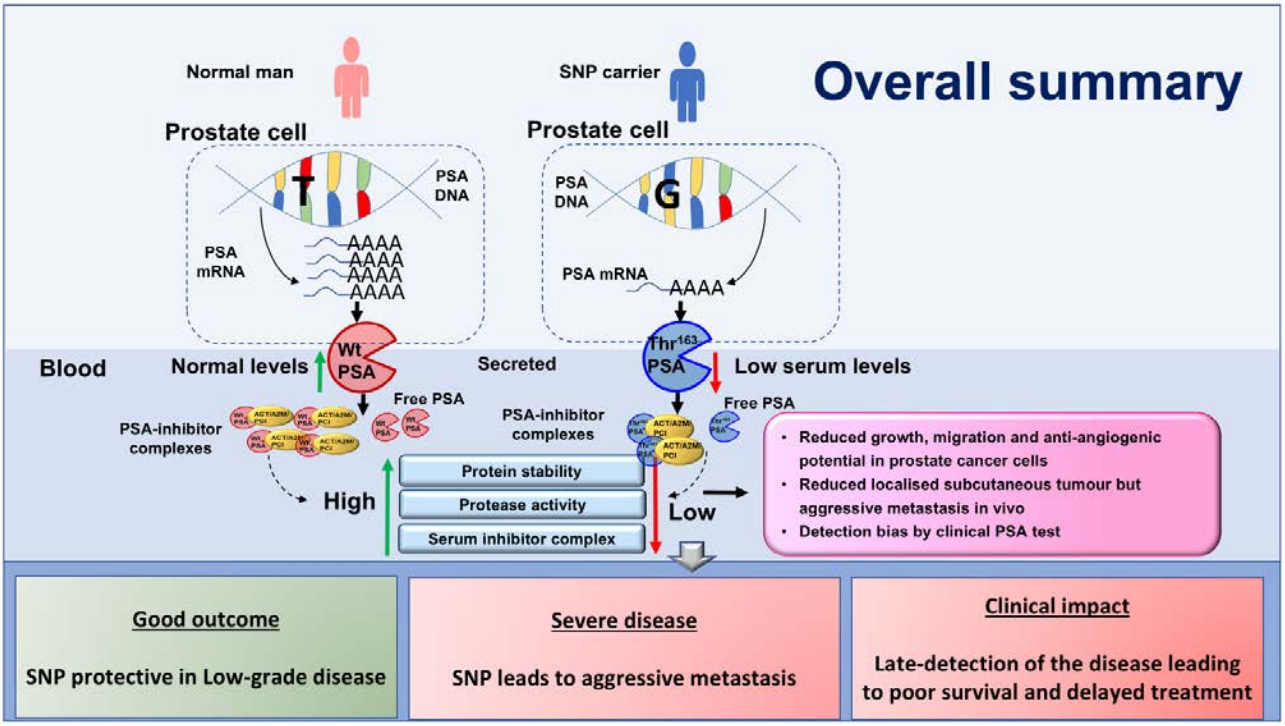
Shirian J, Hockla A, Gleba JJ, Coban M, Rotenberg N, Strik LM, Alasonyalilar Demirer A, Pawlush ML, Copland JA, **Radisky ES**, Shifman JM. (2024) **Improving Circulation Half-Life of Therapeutic Candidate N-TIMP2 by Unfolded Peptide Extension.** Biomolecules. 14(9):1187. doi: 10.3390/biom14091187. PMID: 39334953; PMCID: PMC11429640.

**Lalmanach G**, Rigoux B, David A, Tahri-Joutey M, Lecaille F, Marchand-Adam S, Saidi A. (2024) **Human cystatin C in fibrotic diseases.** Clin Chim Acta. 565:120016. doi: 10.1016/j.cca.2024.120016.

Ghodge, SV. and **Lazarus, RA.** (2024) **Analysis of kallikrein-related peptidase 7 (KLK7) autolysis reveals novel protease and cytokine substrates.** Biological Chemistry. https://doi.org/10.1515/hsz-2024-0127.

Srinivathan S...**Clements J**, & Batra J. (2024) **A PSA SNP associates with cellular function and clinical outcome in men with prostate cancer.** Nat Comms. 5(1):9587. doi: 10.1038/s41467-024-52472-6.

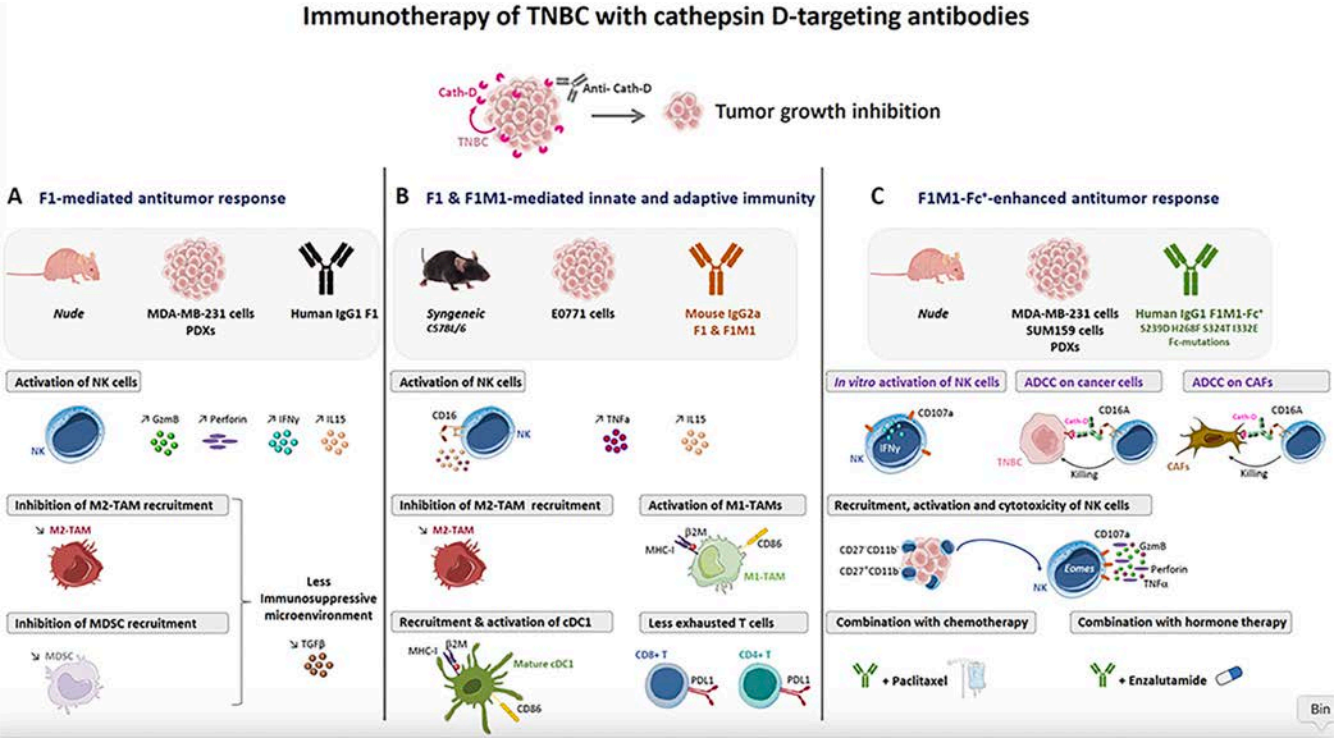
A single nucleotide polymorphism leading to an (Ile163Thr-substitution) in the PSA serine protease encoding KLK3 gene is associated with reduced prostate cancer risk in genetic studies. Herein, we show that this 'Thr' PSA variant leads to small subcutaneous tumours, supporting reduced prostate cancer risk. However, paradoxically, 'Thr' PSA also displays higher metastatic potential with pronounced osteolytic activity in an experimental metastasis in-vivo model. Biochemical characterisation of this PSA variant demonstrates markedly reduced proteolytic activity that correlates with differences in in-vivo tumour burden. Carriers of this SNP allele have reduced serum total PSA and a higher free/total PSA ratio (due to an inability of 'Thr' PSA to bind to circulating binding proteins) that could contribute to late biopsy decisions and delay in diagnosis. Our results provide a molecular explanation for the prominent 19q13.3 KLK locus, rs17632542 SNP, association with a spectrum of prostate cancer clinical outcomes.



# Recent Protease Papers

David T, du Roure PD, Mallavialle A, Laurent-Matha V, Roger P, Guiu S, Chardès T, **Liaudet-Coopman E.** (2025) **Cathepsins: Novel opportunities for antibody therapeutics in cancer.** Br J Pharmacol. doi: 10.1111/bph.17437. Online ahead of print. PMID: 39834229 Review.

Desroys du Roure P, David T, Mallavialle A, Laurent-Matha V, Roger P, Guiu S, Chardès T, **Liaudet-Coopman E.** (2025) **Antibodies against the multifaceted cathepsin D protein open new avenues for TNBC immunotherapy.** J Immunother Cancer. 13(1):e009548. doi: 10.1136/jitc-2024-009548. PMID: 39800383




Desroys du Roure P, Lajoie L, Mallavialle A, Alcaraz LB, Mansouri H, Fenou L, Garambois V, Rubio L, David T, Coenon L, Boissière-Michot F, Chateau MC, Ngo G, Jarlier M, Villalba M, Martineau P, Laurent-Matha V, Roger P, Guiu S, Chardès T, Gros L, **Liaudet-Coopman E.** (2024) **A novel Fc-engineered cathepsin D-targeting antibody enhances ADCC, triggers tumor-infiltrating NK cell recruitment, and improves treatment with paclitaxel and enzalutamide in triple-negative breast cancer.** J Immunother Cancer. 12(1):e007135. doi: 10.1136/jitc-2023-007135. PMID: 38290768

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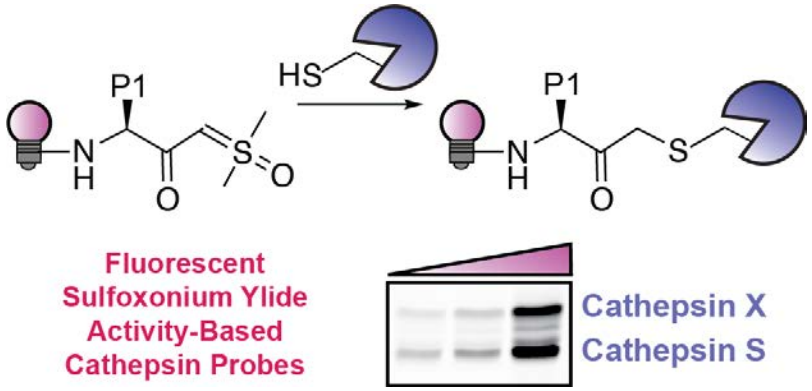
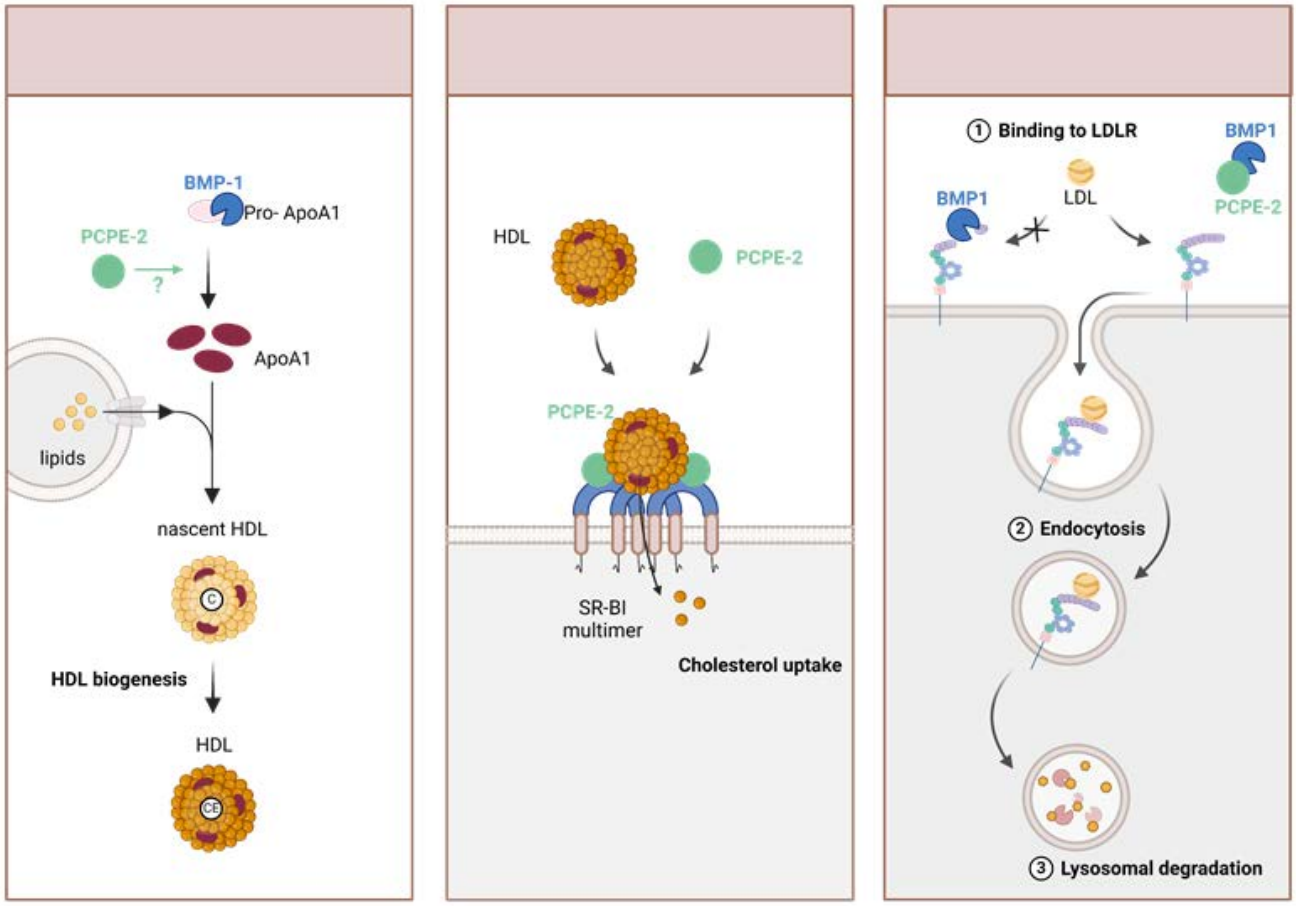
# Recent Protease Papers

Ziegler, A.R., Anderson, B.M., Latorre, R., McQuade, R.M., Dufour, A., Schmidt, B.L., Bunnett, N.W., Scott, N.E. **Edgington-Mitchell, L.E.** (2024) **N-terminomics profiling of naïve and inflamed murine colon reveals proteolytic signatures of legumain.** J Cell Physiol e31466.

Xu, B.,* Mountford, S.J.,* Thompson, P.E., **Edgington-Mitchell, L.E.** (2024) **Expanding the library of covalent cysteine cathepsin probes featuring sulfoxonium ylide electrophiles.** ACS Omega 9:43940-43947.



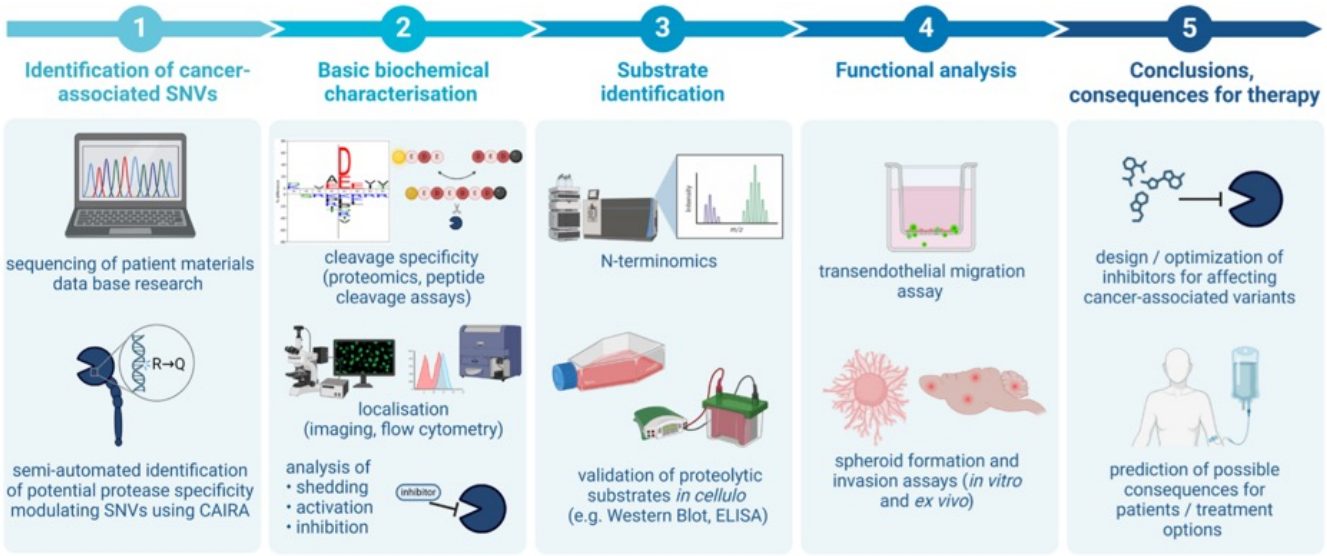

Napoli M, Bauer J, Bonod C, Vadon-Le Goff S, **Moali C.** (2024) **PCPE-2 (procollagen C-proteinase enhancer-2): The non-identical twin of PCPE-1.** Matrix Biol. 134:59-78. doi: 10.1016/j.matbio.2024.09.001



# Recent Protease Papers

Bickenbach K, David N, Koudelka T, Joos C, Scharfenberg F, Rüffer M, Armbrust F, Georgiadis D, Beau F, Stahmer L, Rahn S, Tholey A, Pietrzik C, **Becker-Pauly C.** (2025) **Targeted approach to determine the impact of cancer-associated protease variants.** Sci Adv. 11(7):eadp5958. doi: 10.1126/sciadv.adp5958.PMID: 39937919

Several steps of cancer progression, from tumor onset to metastasis, critically involve proteolytic activity. To elucidate the role of proteases in cancer, it is particularly important to consider single-nucleotide variants (SNVs) that affect the active site of proteases, thereby influencing cleavage specificity, substrate processing, and thus cancer cell behavior. To facilitate systematic studies, we here present a targeted approach to determine the impact of cancer-associated protease variants (TACAP). Starting with the semiautomated identification of potential specificity-modulating SNVs, our workflow comprises mass spectrometry–based cleavage specificity profiling and substrate identification, localization, and inhibitor studies, followed by functional analyses investigating cancer cell properties. To demonstrate the feasibility of TACAP, we analyzed the meprin β R238Q variant. This amino acid exchange R238Q leads to a loss of meprin β's characteristic cleavage preference for acidic amino acids at P1' position, accompanied with changes in substrate pool and inhibitor affinity compared to meprin β wild type.




Sewald L, Tabak WWA, Fehr L, Zolg S, Najdzion M, Verhoef CJA, Podlesainski D, **Geiss-Friedlander R**, Lammens A, Kaschani F, Hellerschmied D, Huber R & Kaiser M. (2025) **Sulphostin-inspired N-phosphonopiperidones as selective covalent DPP8 and DPP9 inhibitors.** Nat Commun 16, 3208 (2025). https://doi.org/10.1038/s41467-025-58493-z

Lakemeyer M, Latorre R, Blazkova K, Jensen D, Wood HM, Shakil N, Thomas SC, Saxena D, Mulpuri Y, Poolman D, de Haro P, Keller LJ, Reed DE, Schmidt BL, Lomax AE, Bunnett NW, **Bogyo M.** (2025) **Identification of a secreted protease from Bacteroides fragilis that induces intestinal pain and inflammation by cleavage of PAR2.** BioRxiv https://doi.org/10.1101/2025.01.15.633241

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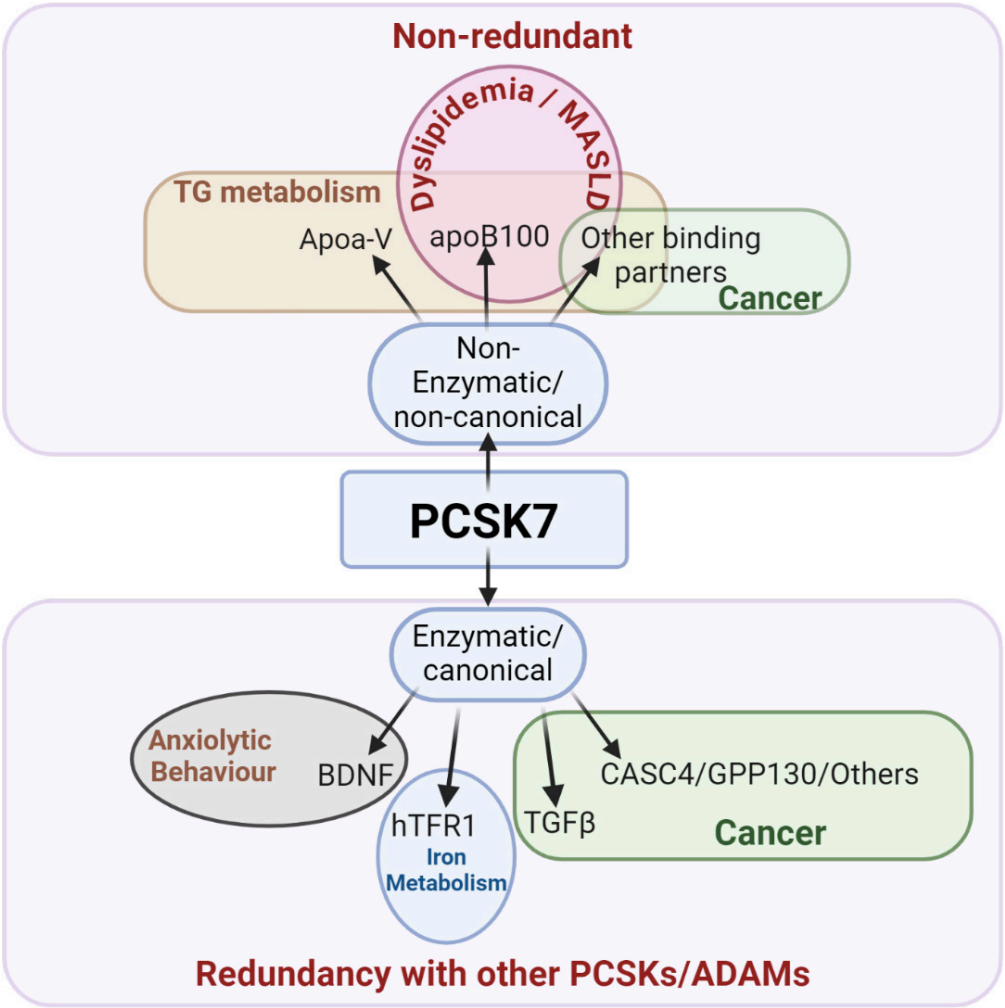
Mikaeeli S, Ouadda ABD, Evagelidis A, Salmani R, Ramos OHP, Fruchart-Gaillard C, **Seidah NG.** (2024) **Insights into PCSK9-LDLR Regulation and Trafficking via the Differential Functions of MHC-I Proteins HFE and HLA-C.** Cells. 13(10):857. doi: 10.3390/cells13100857.

Moon SH, Chung I, Yoon NH, Jin J, Kweon HY, Yoon WK, **Seidah NG**, Oh GT. (2024) **Targeting proprotein convertase subtilisin/kexin type 7 in macrophages as a therapeutic strategy to mitigate myocardial infarction-induced inflammation.** BMB Rep. 57(12):553-558. doi: 10.5483/BMBRep.2024-0162.

Sachan V, Susan-Resiga D, Lam K, **Seidah NG**. (2025) **The Biology and Clinical Implications of PCSK7**. Endocrine Rev 46(2):281-299. doi: 10.1210/endrev/bnae031.

**By modulating the trafficking of key secretory proteins, PCSK7 is implicated in the regulation of major diseases. The graphical abstract depicts the canonical and non-canonical substrates/targets of PCSK7, as well as the intersection between the substrates/targets and pathophysiology.**



# Recent Protease Papers

Grin, P. M., Baid, K., de Jesus, H. C., Kozarac, N., Bell, P. A., Jiang, S. Z., Kappelhoff, R., Butler, G.S., Leborgne, N.G.F., Pan, C., Pablos, I., Machado, Y., Vederas, J.C., Kim, H., Benarafa, C., Banerjee, A., & **Overall, C. M.** (2024). **SARS-CoV-2 3CLpro (main protease) regulates caspase activation of gasdermin-D/E pores leading to secretion and extracellular activity of 3CLpro.** Cell Reports, 43(12).

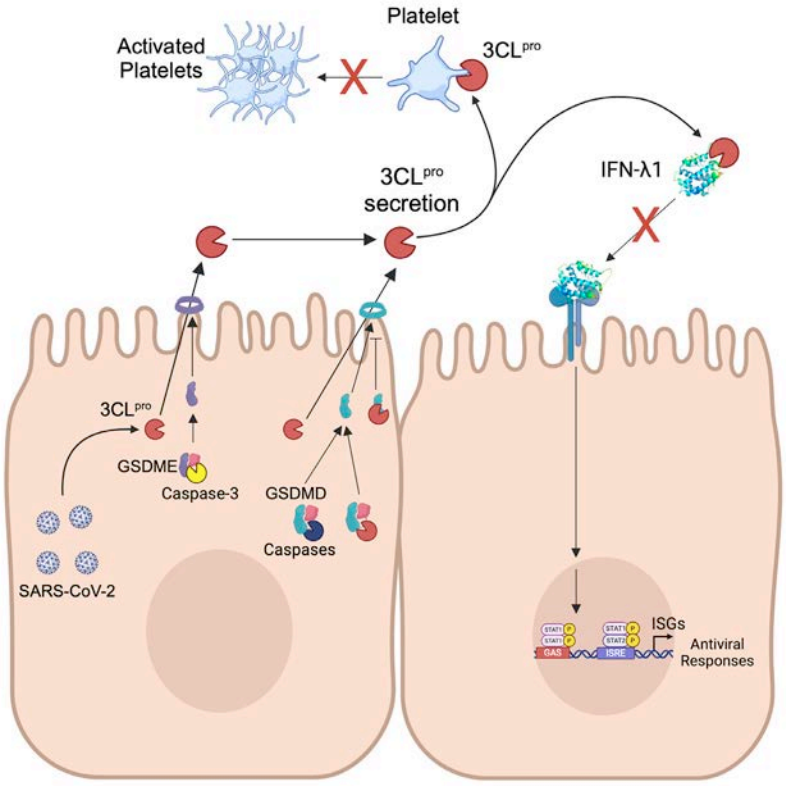
Grin et al report the first known secretion of a viral protease in infection. 3C-like viral proteases (3CL) are utilized by coronaviruses, including severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), to cleave the viral polyprotein into individual functional proteins necessary for viral replication. In addition, to these essential intracellular cleavage events, over 160 intracellular host substrates by the SARS-CoV-2 3CLpro (also known as main protease $M^{pro}$) have been characterised and identified (Pablos et al. 2021, Cell Reports).

In a recent Cell Reports paper from the Overall Lab, Grin et al. reveal the unconventional secretion of the SARS-CoV-2 main protease, $3CL^{pro}$, from infected cells into the extracellular milieu through gasdermin (GSDM)-D and GSDME pores activated by caspases. These pores are the terminal effectors of pyroptosis - a form of cell death that is activated during infection. Grin et al show that while the pores form conduits for $3CL^{pro}$ and also viral nucleocapsid protein release from infected cells, excessive pore formation kills the host cell by pyroptosis, thus inhibiting $3CL^{pro}$ expression and secretion. To this end, $3CL^{pro}$ performs a delicate balance: it regulates its own secretion through GSDMD pores by cleaving at $LH^{270}\downarrow N$ to activate pore formation, but later also cuts at $LQ^{29}\downarrow S$ and $LQ^{193}\downarrow G$ to inhibit pore formation. By balancing the levels of pore formation to release 3CLpro but still maintain cell function by preventing pyroptosis, selected host and viral proteins are secreted by GSDMD and also GSDME pores.

What functions does $3CL^{pro}$ exert extracellularly? Through hypothesis-driven investigations, the authors identified and characterized two inactivating cleavages in IFN-λ1 by $3CL^{pro}$ using amino terminal-oriented mass spectrometry. Such inactivation of IFN-λ1 is hypothesized to be an immune escape mechanism for SARS-CoV-2.

The authors further show that $3CL^{pro}$ retained ~70% of its activity when incubated in human serum that contains high levels of endogenous protease inhibitors. $3CL^{pro}$ also inhibited platelet activation and aggregation in response to the platelet agonist thrombin. These newly described extracellular functions of $3CL^{pro}$ may promote the spread of SARS-CoV-2 infection to distal tissues, such as the brain, liver, kidneys, and heart.

This discovery of the regulated secretion of a viral protease with extracellular activity opens the door for future studies to investigate whether release of viral proteases from infected cells occurs with other coronaviruses or diverse virus families.



# Position Advertisements

**Dr Rachael Barry's** research group at Imperial College London is seeking a Postdoctoral Researcher/Research Associate to investigate proteases that are active in an inflamed and cancerous gut. The Barry Lab employs interdisciplinary approaches—including chemical proteomics, gut culture models (e.g., organoids, gut-on-chip), and clinical samples—to explore protease activities as potential biomarkers and therapeutic targets.

We are looking for a highly motivated candidate with expertise in chemical biology and/or cell and molecular biology, along with experience in proteomics. A strong interest in cancer biology and gut health is essential. This position offers the opportunity to work at the interface of fundamental and translational research in a dynamic and collaborative environment.

Please contact Dr Rachael Barry for more information: r.barry@imperial.ac.uk

**9 PhD positions within the DFG-funded Research Training Group 'Regulation of Membrane Proteins' (RTG-ReMPro) at Kiel University, Germany.**

Within the RTG-ReMPro, we aim to understand how posttranslational modifications (PTMs) influence the plasticity of membrane proteins for the regulation of cells, specialized tissues and body homeostasis. Dysregulation of membrane proteins can lead to pathological conditions. Our vision is that the RTG-ReMPro will lead to a better understanding of the diverse modifications of membrane proteins, by analyzing posttranslational events such as ectodomain shedding that regulate the function of receptors, proteases, channels, transporters, and adhesion molecules.

The most important tasks of the RTG-ReMPro training program are the support and promotion of doctoral researchers and early career scientists in a stimulating scientific environment of different disciplines from basic research with clinical application potential.

**For more information and contact details visit :** www.rtg-rempro.de

# Position Advertisements

## Post-Doctoral Researcher and Ph.D. Student Positions at the Institute of Molecular Biology and Biotechnology in Heraklion Crete, Greece

The Laboratory of Disease Vector Biology at the Institute of Molecular Biology and Biotechnology (IMBB), located in Heraklion, Crete, Greece, is seeking passionate and talented individuals to join our dynamic research team.

**About the Lab**
Our laboratory is dedicated to understanding the molecular interactions between ticks, their hosts, and the pathogens they transmit with emphasis on the role of tick salivary serine and cysteine protease inhibitors in tick blood feeding success. By combining molecular biology, bioinformatics, and immunology, we aim to uncover novel insights into vector-host-pathogen dynamics and drive the development of innovative strategies for disease prevention and control.

**For more information, visit our website:** https://www.imbb.forth.gr/imbb-people/en/kotsyfakis-research

### Post-Doctoral Researcher Position

**Duration:** Two years, with the possibility of a one-year extension based on performance.
**Responsibilities:** Conduct high-quality research in alignment with the lab's objectives. Design, execute, and analyze experiments. Prepare manuscripts for publication in peer-reviewed journals. Collaborate with team members and contribute to ongoing projects.
**Requirements:** Ph.D. in Molecular Biology, Biochemistry, Immunology, Epidemiology, Molecular Ecology, or a related field. Strong publication record, including impact factor (IF) metrics. Experience in molecular biology techniques, bioinformatics, or immunology is highly desirable.

### Ph.D. Student Position

**Eligibility:** Applicants must secure acceptance into a graduate program at one of the following:
- The University of Crete Graduate Programs.
- The Hellenic Mediterranean University Postgraduate Programs.
- Another relevant graduate program.

**Responsibilities:** Engage in cutting-edge research under the guidance of Dr. Michail Kotsyfakis. Contribute to collaborative projects and lab publications.
**Requirements:** A strong background in biology, molecular biology, or a related field. Motivation and dedication to pursuing innovative research.

### Application Process

**Interested candidates are encouraged to submit the following:**
1. A CV, including a detailed list of publications with impact factors (IF).
2. A brief statement of research interests (required for Post-Doctoral applicants).
3. Contact information for at least two referees.

**Submit applications and inquiries to:** Dr. Michail Kotsyfakis
**Email:** mich_kotsyfakis@yahoo.com

**Review Process:** Applications will be reviewed on a rolling basis until the positions are filled. Early submissions are strongly encouraged.