PROTEOCURE Newsletter 10

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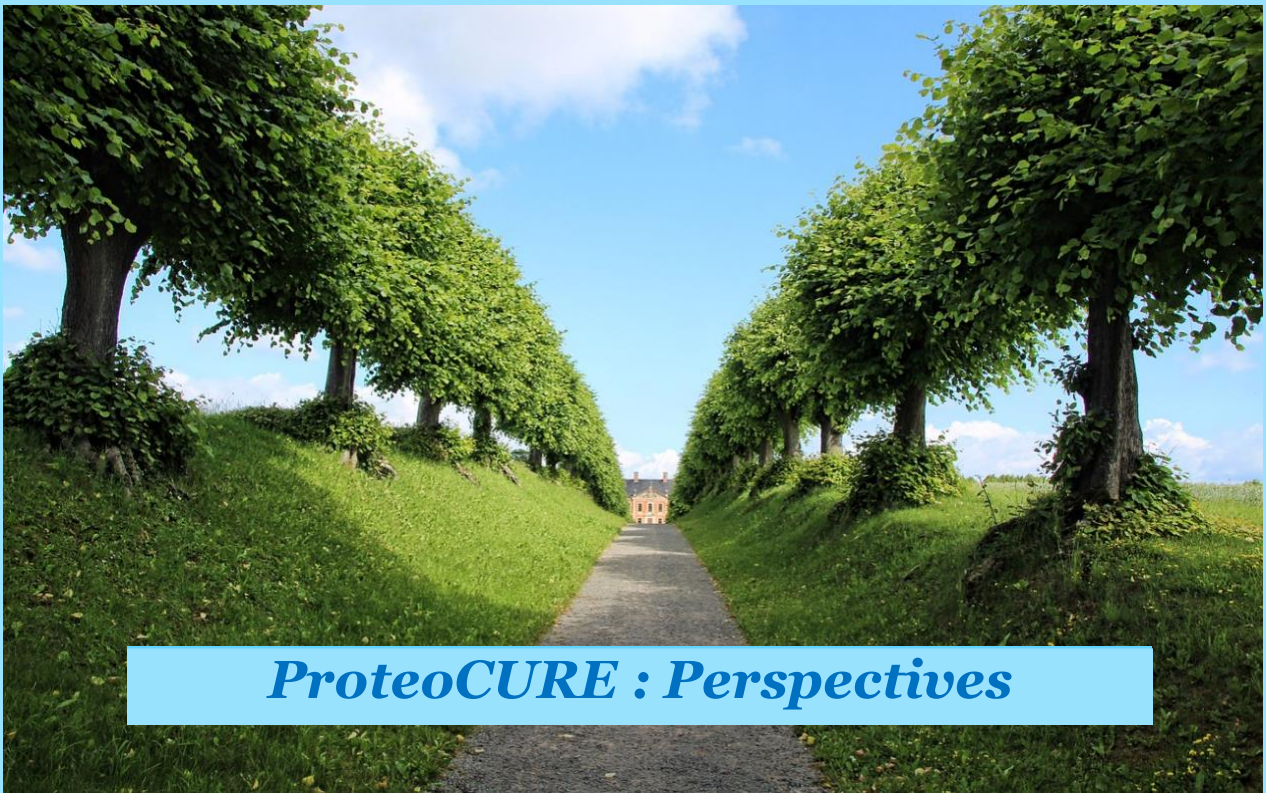
A SOUND PROTEOME FOR A SOUND BODY:
TARGETING PROTEOLYSIS FOR PROTEOME REMODELING



ProteoCURE : Perspectives

ACTIVITIES & HIGHLIGHTS

by the ProteoCURE dissemination committee

In this official last year of ProteoCURE existence as COST action network we have to consider the way we would like to finish our activities but also the way we want to continue with a long-term perspective. As you all know, we will have our annual meeting 2025 in Crete which will give us the opportunity to share our science but also to discuss on the way we want to continue collaborating. We are aware that some initiatives have been developed including grant applications such as several Marie Curie doctoral networks but also a couple of new COST initiatives. COST initiatives have the intention to be inclusive allowing the integration of many of the actual laboratories integrated in ProteoCURE. If you have not joint at the stage of application, we hope you will be able to do it later if these grants are successful. We all hope for the best results to help us to continue collaborating. In this last newsletter of the year, we are also highlighting the new ProteoCURE calls that are open with a deadline in January 2025. These calls are a new opportunity to consolidate or create new interactions between our members. We have also interviewed some ProteoCURE members to know about their work and how our action has impacted their professional life. Finally, we invited Shigeo Murata to write some words on the memory of Keiji Tanaka that passed away last summer.
Whatever the perspective at short or long-term we hope we can continue working together within this enthusiastic community.

Founded by the European Union

COST (European Cooperation in Science and Technology) is a funding agency for research and innovation networks. Our Actions help connect research initiatives across Europe and enable scientists to grow their ideas by sharing them with their peers. This boosts their research, career and innovation.

ANNOUNCEMENTS-CALLS

PROTEOCURE CALLS 2025

Our new grant period has started. This year we have a new call to support the participation of Young Researchers and Innovators (YRI) in high level conferences. All the information required to apply is included in our web page: https://proteocure.eu/category/calls/

Applications to get support for:

- STSM
- YRI Conference Grants
- ITC Conference Grants
- Training School organisation

Key dates for all Calls:

- Application deadline: 24 January 2025
- Approval of applications: Mid-February 2025

Special issue on TPD

Dear ProteoCUREr, Elah Pick will be editing a special number on Targeted Protein Degradation (TPD). The aim is to advance our understanding of TPD and its role in managing proteotoxic stress and disease progression.

About the collection: TPD has rapidly gained attention for its potential to target undruggable proteins involved in various diseases. At the forefront are Proteolysis-Targeting Chimeras (PROTACs), which harness the ubiquitin-proteasome system to selectively degrade harmful proteins. Since their introduction, additional TPD methods have been developed, expanding the scope to novel targets such as membrane proteins, protein aggregates, and organelles.

This collection is designed to foster the exchange of knowledge and accelerate progress in this field(s). Which journals participate? The collection will be featured across several high- impact journals, including Nature Communications, Communications Biology, Communications Chemistry, and Scientific Reports. This provides flexibility in choosing the most suitable journal for your work and simplifies the process of finding reviewers, making submission easier and more efficient. More details about the participating journals can be found here: https://www.nature.com/collections/chbcfafjfc.

FUTURE SCIENTIFIC EVENTS

SAVE THE DATES:
4th Annual meeting of ProteoCure May 20, 2025 - May 23, 2025
Venue Heraklion, Greece. Organizer Makis Skoulakis.
For more information visit our Web page

COMING ProteoCURE WEBINARS

December 12 , 2024: Prof. Devrim Gözüaçık, Koç University, Turkey
Title: The role of autophagy in cancer biology and implications for cancer treatment

INTERVIEWS WITH ProteoCURE SCIENTST

Dear Colleagues, we have interviewed some of our members to know about their activities and how our action has impacted their work. We have addressed 3 questions:

Q1. Can you briefly describe your current research focus?

Q2. What's a fun fact or unique aspect about your lab or research environment?

Q3. How has being part of the ProteoCure network impacted your work or collaborations?

Prof. Chahrazade El Amri
Sorbonne University, Paris France.

Q1. Our team "Integrated Cellular Ageing and Inflammation (ICAI)" has specific skills in cellular senescence, pathological proteolysis and proteostasis, the development of pharmacological agents, and proteomic and metabolic studies. The research project aims to dissect out cellular aging processes, focusing in particular on the proteolytic machinery (extracellular serine proteases such as kallikrein-related peptidases: KLKs and proteasomes) and redox systems (thioredoxins), in the context of age-related diseases (neurodegenerative diseases, cancer and inflammation).

The two main lines of research are: (i) loss of proteostasis and pathological proteolysis: molecular and cellular impact on markers and pathways of aging; (ii) cellular senescence: identification of new pathways and therapeutical targets. The expected outcome is the translation into the development of innovative therapeutic agents.

Q2. One of the main features of the ICAI team is its multi-disciplinarity, members are indeed from different disciplines, including biochemistry, biophysics, medicinal chemistry, cell biology and physiology. This multidisciplinarity enables the emergence of innovative and disruptive projects aimed at designing new therapeutics and molecular tools targeting deregulated proteolysis in age-related diseases.

Q3. Above all, participation to ProteoCure network has enabled us to become aware of the diversity and impressive size of the Proteostasis and Proteolysis community, opening up new inspirations and collaboration's opportunities. It has also given us a better visibility and a real sense of belonging to a structured community.

Prof. Gilles Lalmanach, Research Center for Respiratory Diseases (CEPR), University of Tours, France.

Q1. CEPR is an academic laboratory comprising 4 teams located within the shared campus of the Faculty of Medicine and the University Hospital of Tours (CHRU, Bretonneau site). CEPR focuses on elucidating the molecular and cellular mechanisms underlying inflammatory and infectious respiratory diseases. The main research themes include proteolytic mechanisms in inflammation, antimicrobial immunity, medicinal chemistry and inhaled therapies for respiratory diseases. More specifically, our team (team 2: Proteolytic enzymes and their pharmacological targeting in lung diseases) is a basic research team oriented to a multidisciplinary and translational research investigating proteolytic

mechanisms associated with two chronic pulmonary diseases (chronic obstructive pulmonary disease (COPD) and fibrosis) and more recently lung cancer. Our primary purpose is to decipher signaling pathways

and proteolytic mechanisms involving serine proteases (from neutrophils and epithelial cells) and cysteine cathepsins (from fibroblasts and macrophages). Our group also participates in the design of selective FRET substrates, pseudo peptidyl inhibitors and activity-based probes to monitor proteolytic activities and investigates interventional strategies for targeting lung proteases in the inflammatory microenvironment. Likewise, we develop new small chemical (heterocyclic) inhibitors, innovative bio analogs directed towards binding sites (exosites) of selected proteases and antibody-drug conjugates (ADCs) allowing selective delivery of cytotoxic agents. Reestablishing the homeostasis of the proteolytic balance (proteases/antiproteases) is both a perspective and a goal to develop therapeutic approaches (of weaker systemic toxicity) for inflammatory lung diseases. The Team gathered biochemists, enzymologists, organic and medicinal chemists, cell biologists and physicians.

Q2. Our INSERM research structure offers a very rare and stimulating environment. Indeed, people often insist on developing research that prioritizes translational exchanges as much as possible (from “the bench to the patient's bedside”). In our case, this is a daily reality. We cover the entire spectrum of scientific approaches. We go from the fundamental side (design and synthesis of innovative molecules, through microbiological, immunological and enzymatic/biochemical analyses, i.e. cellular and molecular studies) to pharmacological and clinical approaches (pharmacokinetics and pharmacodynamics of inhaled drugs, participation in various clinical trials). This was made possible by the winning association of academic scientists with many hospital clinicians who joined our research structure. This allows our INSERM unit to rely on the departments of parasitology/mycology, medical intensive care and pneumology of the University Hospital of Tours (CHRU Tours).

Q3. ProteoCure has made it possible to strengthen existing collaborations and initiate new links and opportunities for collaboration on a European scale. In close collaboration with my colleague Dr. Carmela Giglione at the head of WG1, we were able to set up several scientific events that had an extremely unifying effect. We were thus able to organize a congress in Paris in May 2023 in close collaboration with the French Society of Biochemistry and Molecular Biology (SFBBM) (co-organizers: Prof. Chahrazade El Amri and Prof. Bertrand Friguet). We also launch several webinars. Thanks to ProteoCure, the links between two scientific publics (i.e.,” proteostasis” and “proteolysis” communities) that usually have little contact have been noticeably strengthened, especially via the establishment of a new and fruitful training school dedicated to mass spectrometry as well as unwavering support for a winter school dedicated to proteases and their inhibitors. A concrete consequence of these increased connections is the release in November 2024 of a thematic issue of Biochimie (Elsevier) entitled: “At the crossroads of proteostasis and proteolysis” (Editor-in-Chief of Biochimie and handling editor: B. Friguet; Guest editors: C. El Amri, C. Giglione, G. Lalmanach) which provides an outline of some foremost players and cutting-edge progress in the field of proteostasis, including proteolysis.

On a more personal level, the numerous meetings including the annual ProteoCure meetings have permitted to discover many scientific aspects of which I knew nothing or almost nothing. Therefore, such events have enriched me intellectually and opened up new perspectives for my future personal work and allowed me to connect with several colleagues.

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Send us an email to: dissemination@proteocure.eu

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On the Memory of Keiji Tanaka

by Shigeo Murata from the University of Tokyo

On July 23, 2024, the scientific community lost a true pioneer with the passing of Dr. Keiji Tanaka. At the age of 75, he left us unexpectedly due to ischemic heart disease. Keiji's groundbreaking work in intracellular protein degradation profoundly shaped the field. His influence will be felt for generations, and his absence is deeply mourned by colleagues, collaborators, and friends worldwide.

Born and raised in Tokushima, Japan, Keiji's journey into science began at Tokushima University, where he studied amino acid metabolism under the mentorship of Professor Akira Ichihara. His transition into protein degradation research began in 1980 when he joined Dr. Alfred (Fred) Goldberg's laboratory at Harvard University. At the time, Fred was exploring ATP-dependent protein degradation using reticulocyte lysates, a novel system for studying cellular proteolysis. Shortly before Keiji's arrival, Avram Hershko and Aaron Ciechanover had made a breakthrough, demonstrating that ubiquitin tagging required energy for protein degradation. Despite this, Keiji's arrival revitalized Fred lab's efforts. With his expertise in enzymology, Keiji uncovered that energy was essential not just for ubiquitination but also for the degradation process itself. This finding established the two-step ATP-dependent proteolysis model, which became a cornerstone of proteasome research and laid the groundwork for the discovery of the proteasome.

Keiji's resourcefulness stood out during his time in Fred's lab. Reticulocyte lysates, essential for their experiments, quickly lost activity within a day, forcing the lab to maintain hundreds of rabbits and inject them daily with phenylhydrazine to stimulate reticulocyte production—a demanding and labor-intensive task. Drawing on knowledge from his time at Tokushima University, Keiji added glycerol to the lysates, successfully stabilizing enzyme activity for several months. This simple yet brilliant solution greatly reduced the number of rabbits needed and earned him the admiration of his lab mates.

Returning to Japan, Keiji advanced his research with remarkable speed. Around the same time as Martin Rechsteiner in Utah, he identified a large protease complex responsible for degrading ubiquitinated proteins. This complex, later named the proteasome, initially faced skepticism due to its multi-subunit structure. When Keiji presented a two-dimensional electrophoresis image of the purified proteasome showing multiple spots, critics doubted his findings, arguing that only one spot should represent the protease. Undeterred, Keiji shifted his focus to identifying the proteasome's subunits and elucidating its structure.

Despite the technical challenges of the time, Keiji embarked on gene cloning to determine the proteasome's primary structure. He succeeded in cloning over 70% of the mammalian proteasome subunit genes, an extraordinary achievement that laid the foundation for decades of proteasome research and enabled subsequent discoveries.

Among his many accomplishments, Keiji's identification of specialized proteasome isoforms remains one of the most impactful. He discovered the immunoproteasome, which plays a critical role in adaptive immunity by generating peptides suited for presentation on MHC class I molecules. Later, he identified the thymoproteasome, which is essential for the positive selection of $CD8^+$ T cells in the thymus. These discoveries expanded the understanding of protein degradation from a basic cellular maintenance process to a key player in immune regulation.

Keiji's contributions weren't confined to the proteasome. He also made major advances in ubiquitin and autophagy research. Notably, he helped identify the role of Parkin, a gene associated with familial Parkinson's disease, as a ubiquitin ligase involved in mitochondrial quality control. His work on autophagy revealed its physiological roles and the mechanisms of selective autophagy, opening new frontiers in cell biology.

Beyond his scientific achievements, Keiji was deeply committed to nurturing young researchers. He frequently brought early-career scientists to international conferences, providing them with valuable opportunities to engage with the global scientific community. Known for his humility, he once joked during an award ceremony, "I'll spend all the prize money on drinks with young researchers," sparking laughter and admiration from the audience. His warmth and generosity were hallmarks of his character, earning him the affection of colleagues and students alike.

In his later years, as Director and Chairman of the Board at the Tokyo Metropolitan Institute of Medical Science, Keiji skillfully balanced leadership responsibilities with active research. It's clear he had many unfulfilled dreams, as his curiosity and drive never waned. Those who knew him can imagine him now, reunited with his mentor Fred, sharing a drink and engaging in spirited discussions, just as they did during their time together.

Dr. Keiji Tanaka's legacy is not just in the discoveries he made but in the countless lives he touched. His work has transformed our understanding of cellular processes, and his influence will continue to inspire researchers around the world.

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