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ProteoCure: A European network to fine-tune the proteome

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ABSTRACT

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

Proteostasis is a key process allowing cells or organisms to maintain an appropriate but dynamic equilibrium of their proteome (the ensemble of all their proteins). It relies on multiple mechanisms that together control the level, fate and function of individual proteins, and ensure elimination of abnormal ones. The proteostasis network is essential for development and adaptation to environmental changes or challenges. Its dysfunctions can lead to accumulation of deleterious proteins or, conversely, to excessive degradation of beneficial ones, and are implicated in many diseases such as cancers, neurodegeneration, or developmental and aging disorders. Manipulating this network to control abundance of selected target proteins is therefore a strategy with enormous therapeutic or biotechnological potential.

The ProteoCure COST Action gathers more than 350 researchers and their teams (31 countries represented) from the academic, clinical, and industrial sectors, who share the conviction that our understanding of proteostasis is mature enough to develop novel and highly specific therapies based on selective tuning of protein levels. Towards this objective, the Action organizes community-building activities to foster synergies among its participants and reinforce training of the next generation of European researchers. Its ambition is to function as a knowledge-based network and a creative exchange hub on normal and pathologic proteostasis, focusing on developing innovative tools modulating the level of specific protein(s).

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1. Introduction

Life requires tight **quality control** mechanisms to carry out the extremely complex and intricate processes that allow a cell or an organism to exist. As critical effector molecules in biology, proteins are under intense scrutiny, from their synthesis to their degradation, to ensure that they can appropriately perform their function at the right cellular location and during the proper time window. The **proteome** is thus continuously surveyed by an elaborate network

of mechanisms that allows it to answer and to adapt to cellular needs [1].

Among the mechanisms that control proteostasis, proteolysis plays key roles as it allows to (i) eliminate faulty proteins damaged during their synthesis or later, (ii) regulate through partial or total degradation the levels and the expression windows of individual proteins, and (iii) modify the properties of some proteins by cleaving them into smaller products that have different functions than their precursors [2]. With its myriad of targets and its multiple roles, proteolysis engages hundreds of components that together regulate proteostasis and therefore all cellular processes, including protein turnover, responses to various stresses, transcriptional regulation, DNA replication/repair, cell-cycle, signal transduction, endocytosis, cellular organization, or immunity (Fig. 1).

Next to specialized proteins called proteases capable of cleaving other proteins, often with high specificity, two tightly regulated and complex pathways play a central role in intracellular proteolysis in eukaryotes. **Autophagy** uses specialized organelles called

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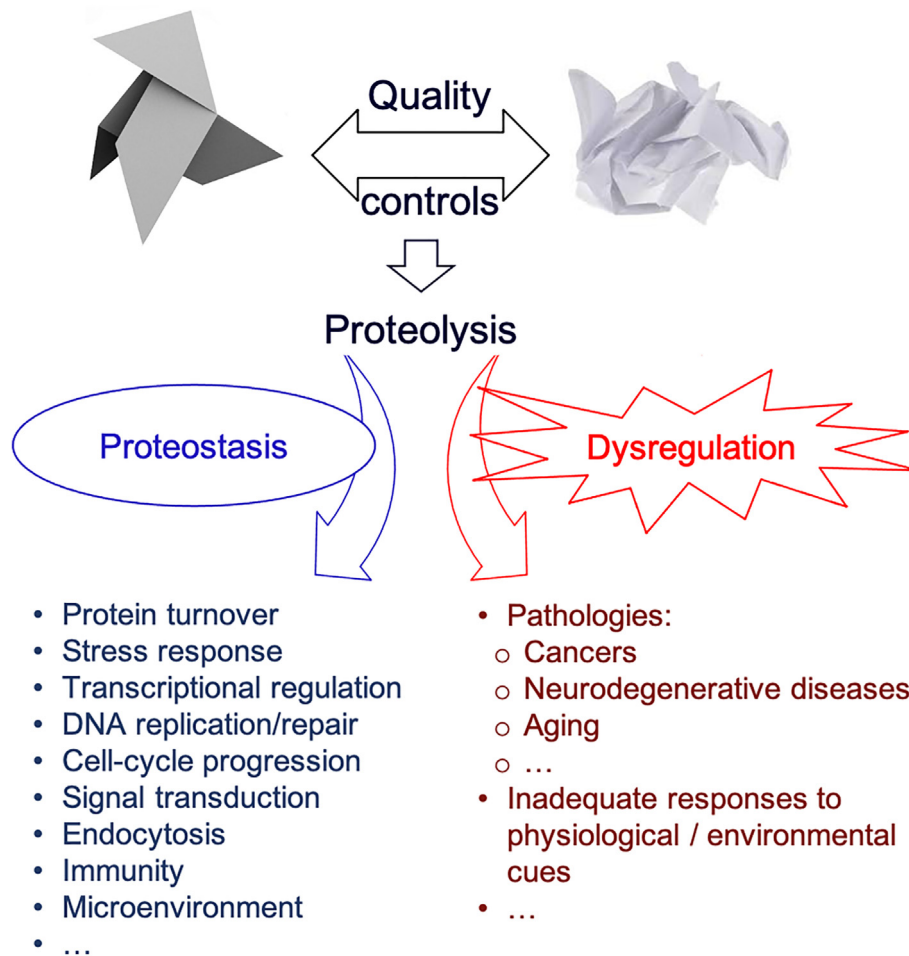


Fig. 1. Proteolysis in health and disease.

lysosomes to degrade proteins or protein aggregates after their engulfment into autophagosomes [3]. The ubiquitin-proteasome system (UPS) uses a tag (**ubiquitin**, Ub) to mark proteins and thereby trigger their degradation by a giant protease called the **proteasome** [2]. However, as several **Ub-like proteins** (Ubl) that can also be conjugated to protein substrates to tune their function(s) [4], Ub can serve functions other than degradation, such as enzyme activation, endocytosis, creation of new interactions, DNA repair and regulation of transcription [5].

It is important to emphasize that proteostasis goes beyond just protein breakdown (proteolysis), and encompasses all intricately regulated proteome-shaping processes, including among others protein translation, protein folding, protein trafficking, protein compartmentalization, and formation of molecular condensates through phase transition. Proteostasis regulation therefore results from the action of a profusion of highly specific proteome tuners that altogether control the interactions, the functions and the fate of their targets and thereby cell homeostasis, proliferation and rapid adaptation to changing conditions. Due to this central position in cell and organismal homeostasis, dysfunction of these processes can lead to numerous pathologies, including **cancers**, **neurodegenerative diseases** such as **Parkinson's**, **Alzheimer's**, and **Huntington's Diseases**, as well as many other disorders linked to misexpression of specific protein(s) (Fig. 1). Consequently, directed modulation of proteostatic pathways by targeting specific proteome tuners opens up highly promising, yet under-exploited therapeutic avenues to restore dysfunctional processes in a highly

specific manner.

The COST Action ProteoCure, whose slogan is “A sound proteome for a sound body: targeting proteolysis for proteome remodeling” is committed to driving innovation in European medicinal strategies and treatments by focusing on targeted proteome remodeling. Its ambition is to harness European expertise in the field, whether in basic research, the clinic or industry, to train young researchers in proteostasis and drug design and encourage the development of powerful and selective new medicines.

2. ProteoCure: the network

The European Cooperation in Science and Technology (COST, www.cost.eu) is an EU-funded, intergovernmental framework with currently 41 members and 1 cooperating member countries. Its mission is to fund research networks that foster collaboration among European scientists. The Action ProteoCure was approved by COST in 2021 and started on November of the same year. It will end in October 2025.

The ProteoCure COST Action was successful, with ≈ 180 teams registered during the first weeks. Since then, the number of participants has been growing continuously, to reach at present more than 350. Taking into account that one of the early decisions of the network was to accept only one person per research team (usually the principal investigator, PI) and that all the members of the team are eligible to participate in the Action initiatives, the number of scientists effectively concerned by ProteoCure activity is in fact

much higher.

As shown in Fig. 2, in May 2024 a large number of COST-countries are ProteoCure participants. Among them, 5 (Spain, France, Germany, Turkey, Great Britain) have more than 30 teams involved in the Action. Importantly, many COST Inclusiveness Target Countries (countries considered to be the less research-intensive, which are a priority regarding the COST mission to support development of research) are represented in ProteoCure.

3. ProteoCure: the action

3.1. The structure

One of the key objectives of ProteoCure is to help defragment proteostasis science in Europe. Despite the strong expertise of Europe in this field, as well as in healthcare and in industrial drug development and production, Europe still lacks appropriate links between these different specialists. Furthermore, thematic or technical specialization tends to confine each actor in their domain of expertise, limiting opportunities to address the proteostasis issue as a continuum of highly complex and intricate processes.

Reducing fragmentation to nourish a fertile ecosystem efficient for the transfer of information, knowledge and ideas between different groups requires easy connections based on personal contacts, mutual knowledge and respect, and frequent discussions. To foster this spirit of collaboration, the overall goal of the ProteoCure COST Action is to actively help building effective and active bridges between interested groups. This approach is reflected by the structuring of the Action into four complementary Working Groups (WGs), each tailored to address specific scientific and technical needs (Fig. 3).

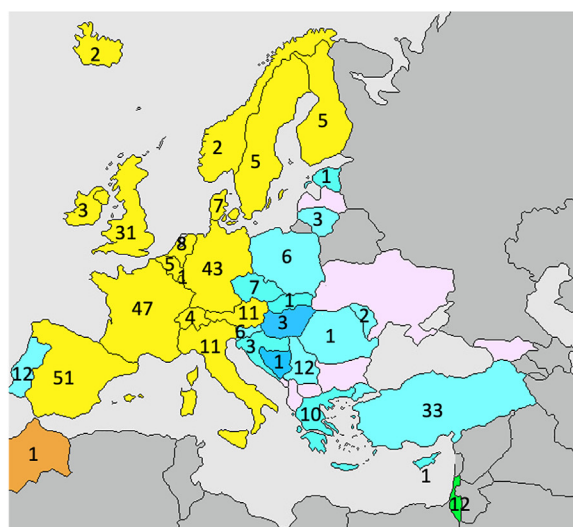
These WGs act as focal points and bring together participants with diverse expertise around specific topics, thus fostering multidisciplinary and multi-approach exchanges essential for innovative discoveries and developments. To broaden cross-pollination of ideas and concepts, each member is encouraged to participate in at least two working groups.

WG1 is dedicated to exploring proteostasis and its intricate

interplay with pathology. Its *raison d'être* is to foster synergies between ProteoCure members who wish to join forces to study common or connected issues. Typically, researchers studying processes that are *a priori* distinct but involved in the same pathology, or the same pathway, can constitute a 'task force' to explore the possible connections between the processes, share experimental or animal models, apply for common grants, or simply share knowledge. From the very beginning, WG1 has been the group with the largest number of ProteoCure members. To help initiate the first connections, four online meetings were organized, each centered around broad keywords: Cancer/Repair; Ageing/Autophagy; Neurodegenerative diseases/Stresses; Inflammation/Hypoxia. After this first contact, the initiative was to let members create thematic subgroups of their choice, without any constraint in terms of size or scientific axis, the overall goal being to improve our understanding of normal and pathological proteostasis and promote innovative therapeutic interventions. One important initiative of WG1 was to co-organize in May 2023 a meeting in Paris with the 'Cellular proteolysis' group of the French Society of Biochemistry and Molecular Biology (<https://proteolysis2023.sciencesconf.org/>).

The goal of WG2 is to support identification and translational maturation of bioactive molecules targeting proteostasis. Its overall function in the Action is to build a stimulating environment in which available expertise and tools can be shared to foster development of active molecules at each stage of their maturation process. Accordingly, this WG comprises members with expertise in and/or access to a wide range of technologies and resources critical for drug discovery, screening and early-stage development. This includes, for example, proteomics for target identification, high- or medium throughput *in vitro* or *in cellulo* drug screening, artificial intelligence-assisted drug pre-selection, drug optimization using computational chemistry and biophysical approaches, etc.

WG3 focuses on targeted proteolysis, a rapidly growing field with enormous transformative potential to combat proteotoxic stress and mitigate disease progression. Targeted proteolysis approaches [6], well exemplified by the PROTACs (PROteolysis TArgeting Chimeras), take advantage of the exquisite specificity and efficiency of the proteolytic machinery to specifically eliminate in a



• 355 members (102 from ITC)

• 33 COST countries

• 31 COST countries represented in the MC

- COST member (Non ITC)
- COST member (Inclusiveness Target Country, ITC)
- COST member, ITC -- no MC representative --
- Cooperating member
- + Morocco (1)
(Non COST member, Near Neighbour Country, NNC)
- + Canada (1) China (2) Mexico (1) USA (2)

Fig. 2. Number of ProteoCure participants per country. Yellow and blue, COST full member countries; blue: Inclusiveness Target Countries (ITC) dark blue: ITC countries with ProteoCure participants but no MC representative in the Action; green: COST cooperating member country; light brown: Near Neighbour Country (can participate in a COST Action but not organize it); pink: ITC countries with no ProteoCure participants.

Participants from non-COST countries (USA, Mexico and Canada in ProteoCure) can participate in the Action activities but at their own expense. The Management Committee (MC) is the decision-making committee of the Action, in which COST-member countries can be represented by up to 2 representatives. See COST website for more details (<https://www.cost.eu/>).

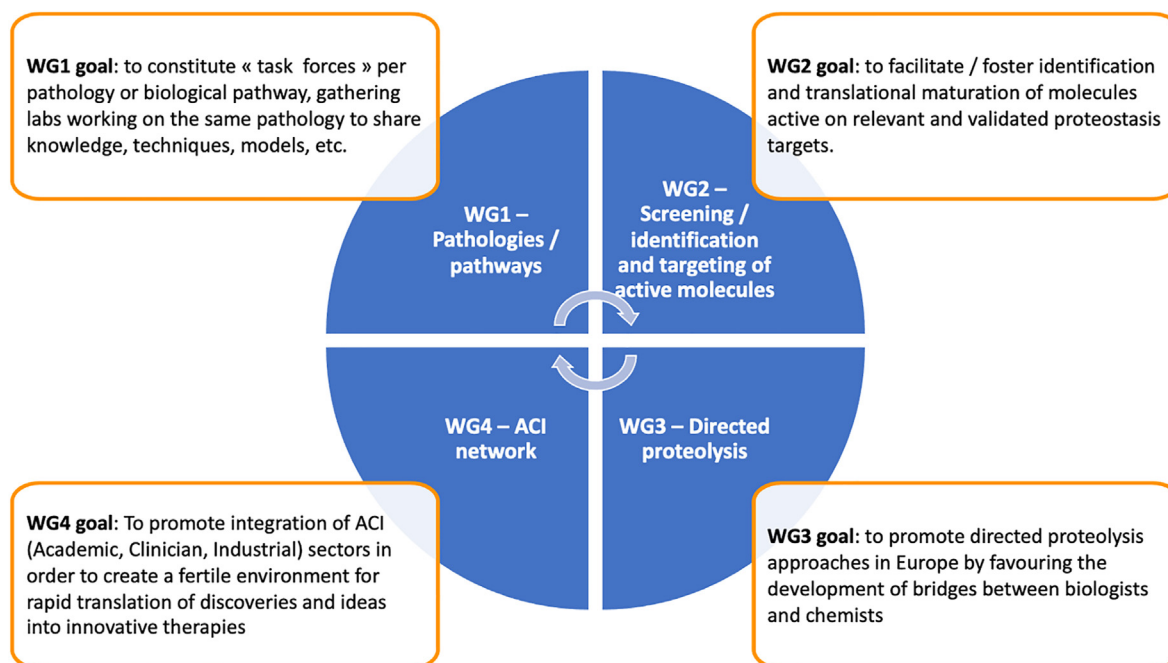


Fig. 3. ProteoCure working groups (WGs).

controlled manner harmful proteins involved in various pathologies. Although these approaches are highly promising, they are in fact still in their infancy, and a lot of technical issues need to be addressed on a case-by-case basis to develop efficient drug candidates. WG3 acts as a hub to collect and share expertise on these issues, by promoting interdisciplinary collaborations and knowledge-sharing initiatives.

Finally, WG4 has the critical role of bridging academia, clinicians and industry to facilitate the translation of scientific discoveries into clinical applications. Indeed, one of the weaknesses in Europe regarding drug development is the lack of scientific porosity and communication between these three sectors, which maintains dividing walls whereas easy contacts and transfer of knowledge and expertise should be the rule. WG4's aim is to help in decreasing the energy barrier between the three sectors, by taking various initiatives to promote reciprocal appreciation of the strengths and potential complementarities of each sector. The ultimate goal is to foster sustained partnerships to accelerate bench-to-bedside innovations.

Each WG is supervised by two Working Group Leaders (WGLs), who coordinate the activities and the interactions with the other WGs. In addition, specialized *ad hoc* committees support the Working Group Leaders (WGLs) by providing strategic guidance on issues such as target demographics, stakeholder engagement and network development. ProteoCure is committed to the principles of equity and inclusion, and to this end the Target Groups Committee supervises and monitors gender balance and participation of Young Researchers and Innovators (YRIs) and Inclusiveness Target Countries (ITCs). The Stakeholders Committee is dedicated to promoting the integration of industry and clinicians at all levels in ProteoCure's activities. Finally, the Networking Committee coordinates the dissemination of the objectives, activities and achievements of the Action, both internally (among Action members) and externally (to the non-academic world, patient associations, the general public ...). This dissemination takes place through many channels, including a quarterly newsletter (<https://proteocure.eu/category/newsletters/>) and social media such as X and YouTube

(@proteocure).

Together with the WGLs, the Chairs of the Action, the Grant Awarding and Scientific Communication Coordinators and the committee members form the Action Core Group. The Core Group ensures the execution of the overall objectives and organizes the various initiatives taken by the Action. However, as for all COST Actions, the effective decision-making structure is its Management Committee, to which each participating country can nominate two representatives.

3.2. The activities

The ProteoCure Action coordinates numerous initiatives aimed at facilitating the dissemination of pertinent scientific information, training the next generation of researchers and fostering collaborative interactions within and between academic, clinical, and industrial sectors. All activities prioritize equitable representation across gender, age and geographic regions. Additionally, a key objective of the Action is to elevate the visibility of researchers from countries with less developed research infrastructure and facilitate their collaboration with colleagues from other countries.

Major activities such as meetings, training schools, grants for lab exchange or participation to meetings are initiated through regular calls, which are published on the website of the Action (www.proteocure.eu) and sent by email to all ProteoCure participants. Applications sent by members in response to these calls are evaluated and ranked by appropriate committees, based on their scientific soundness relative to ProteoCure objectives and equitable age, gender and country representation.

To date (May 2024), the Action has successfully organized three annual meetings, held in 2022 (Ljubljana, Slovenia), 2023 (Zagreb, Croatia) and 2024 (Warsaw, Poland), along with co-hosting eight meetings focused on advancements in proteolysis research. Furthermore, through its support in the organization of three training schools since 2022 (Winter School on Proteinases and Their Inhibitors, Tiers), ProteoCure is actively enhancing the expertise and knowledge of young scientists in the field of

proteolysis. These training sessions encompass various facets of proteostasis research, including mechanistic studies conducted at the molecular, cellular and organismic levels. It is worth noting that a training school on proteomics, organized by ProteoCure, will be held in September 2024 in Freiburg, Germany (<https://proteocure.eu/proteocure-training-school-on-basics-and-perspectives-of-mass-spectrometry-based-proteomics/>). Facilitating the mobility of young researchers and fostering collaboration among European laboratories, the Action has awarded to date (May 2024) 33 Short Term Scientific Missions (Fig. 4), enabling young researchers to spend several weeks in other labs for skills acquisition, knowledge exchange and best practice sharing across different institutions and countries. Such exchanges are pivotal for strengthening cooperation and enhancing the quality of research undertaken within ProteoCure labs, making STSMs a highly appreciated tool of the Action. ProteoCure has also awarded thus far (May 2024) 7 ITC conference grants and 8 dissemination grants, enabling participations at international meetings and representations of ProteoCure's

initiatives.

Finally, the Action is organizing a variety of other activities, such as an online training on European funding (<https://proteocure.eu/event/proteocure-cost-action-event-on-network-opportunities-for-funding-and-collaboration/>) and many webinars (<https://proteocure.eu/category/webinars/>). ProteoCure membership is free of charge. To gain further insight into the ProteoCure network, we invite you to visit our website (<https://proteocure.eu>).

4. Conclusion

Through its structured network, ProteoCure is dedicated to advancing proteostasis research in Europe, enhancing basic science, drug discovery and translational applications. By facilitating collaboration between the academic, clinical and industrial sectors, and by supporting young researchers and under-represented countries, ProteoCure's aim is to nurture a fertile ecosystem for significant contributions to biomedical science and therapeutic

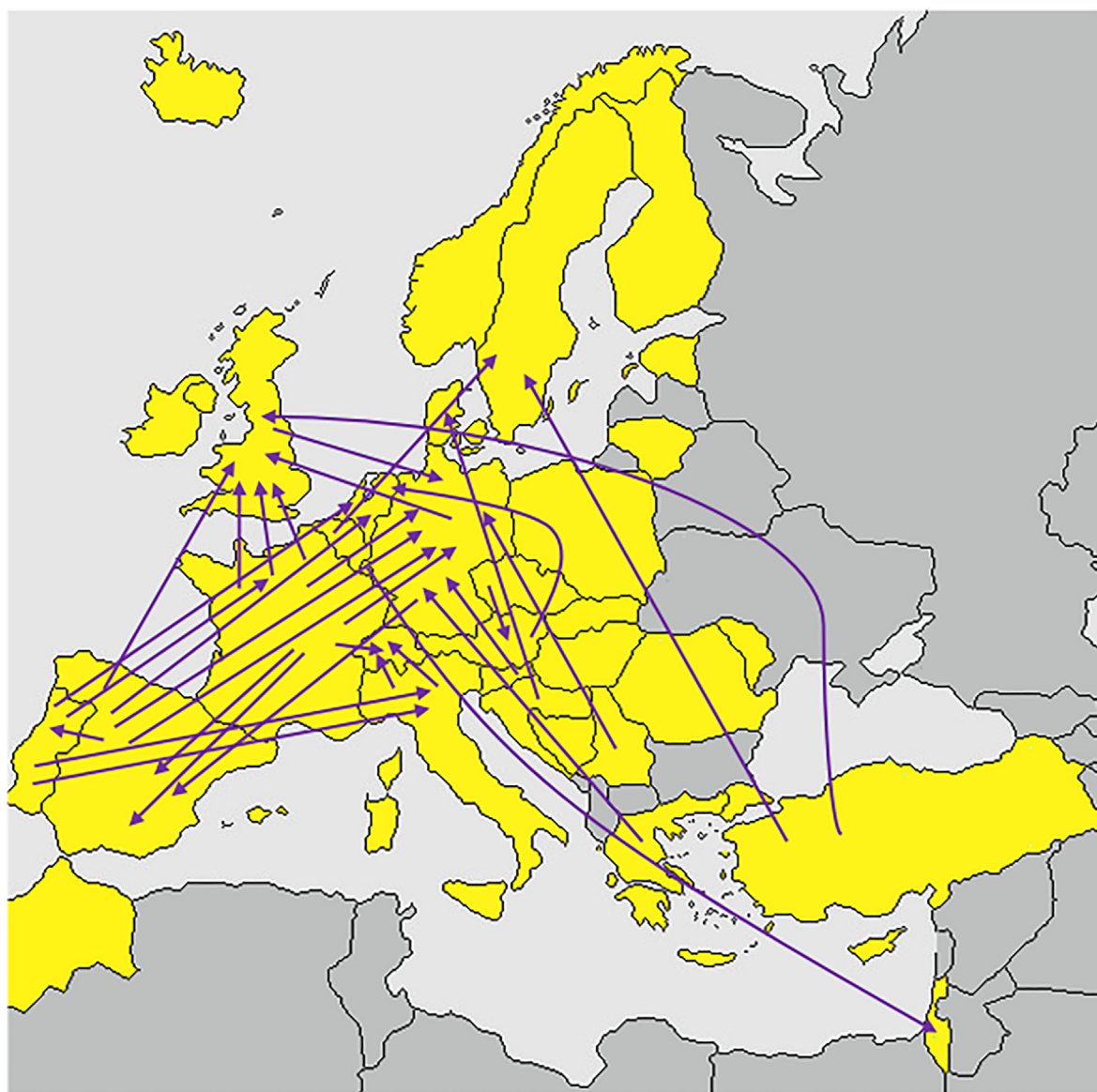


Fig. 4. Summary of the STSMs granted by ProteoCure (up to May 2024). The arrows indicate the origin and the hosting lab countries.

innovations in the field of proteostasis.

CRediT authorship contribution statement

Olivier Coux: Writing – review & editing, Writing – original draft, Project administration, Conceptualization. **Rosa Farràs:** Writing – review & editing, Writing – original draft, Project administration, Conceptualization.

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