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**Trends in Biochemical Sciences**  
**Protein termini 2022 Central roles of protein ends**  
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| <b>Corresponding Author:</b> | Carmela Giglione, Ph.D<br>Paris-Saclay University<br>Gif-sur-Yvette, FRANCE  |
| <b>First Author:</b>         | Thomas Arnesen, PhD  |
| <b>Order of Authors:</b>     | Thomas Arnesen, PhD  |
|                              | Henriette Aksnes, PhD  |
|                              | Carmela Giglione, Ph.D   |

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## ***Protein termini 2022: Central roles of protein ends***

Thomas Arnesen<sup>1,2,3\*</sup>, Henriette Aksnes<sup>1\*</sup>, Carmela Giglione<sup>4\*</sup>

<sup>1</sup>Department of Biomedicine, University of Bergen, Norway

<sup>2</sup>Department of Biological Sciences, University of Bergen, Norway

<sup>3</sup>Department of Surgery, Haukeland University Hospital, Norway

<sup>4</sup>Université Paris Saclay, CEA, CNRS, Institute for Integrative Biology of the Cell (I2BC), France

\*Correspondence: [thomas.arnesen@uib.no](mailto:thomas.arnesen@uib.no) (Arnesen, T.), [henriette.aksnes@uib.no](mailto:henriette.aksnes@uib.no) (Aksnes, H.) and [carmela.giglione@i2bc.paris-saclay.fr](mailto:carmela.giglione@i2bc.paris-saclay.fr) (Giglione, C.)

ORCID: 0000-0002-3005-147X (Arnesen, T.); 0000-0003-4968-2324 (Aksnes, H.); 0000-0002-7475-1558 (Giglione, C.)

Twitter: @NAT\_machinery (Arnesen, T.); @HenrietteAksnes (Aksnes, H.); @Giglionelab (Giglione, C.); @proteintermini (the International Society of Protein Termini, ISPT)

### **Abstract**

Although locating at the protein ends, N- and C-termini are at the center of numerous cellular functions. This topic engages an increasing number of scientists, recently forming the International Society of Protein Termini (ISPT). *Protein termini 2022* gathered this interdisciplinary community to discuss how protein ends may steer protein functionality.

### **Keywords**

N- and C- protein modifications, Proteoforms; N-degron pathway; acetylation; myristoylation; oxidation; proteostasis

## **A community is formed**

Protein termini are hotspots for a number of protein modifications thereby steering a broad spectrum of cellular functions. Scientists have for a long time studied protein ends from different perspectives, but such interests have been pursued in separate communities. For example, focusing on specific organisms, or a specific protein modification, or on different stages of protein lifetime such as protein translation or degradation.

Over the past decade, a growing community interested in protein termini has inexorably established itself. In 2012, a Jacques Monod conference in Roscoff, *The translating ribosome: towards mature proteins*, gathered many scientists with an interest in protein N-termini and how these were modified whilst emerging from the ribosome. In 2015, the Society of Experimental Biology's meeting in Prague included a small plant-specific workshop focused on N-terminal protein modifications. A step up towards a larger community was made in 2017, when the *N-term 2017: Proteostasis via the N-terminus* attracted 100 scientists to Halle for a cross-kingdom meeting, with intentions to establish a meeting series on a regular basis. After a 2018 intermezzo with a session on *Control of fundamental biological processes by N-terminal protein modifications* at the FEBS Congress in Prague, the *Protein Termini 2019* was arranged in Seoul. This was the first meeting of the International Society of Protein Termini (ISPT), which was established on this occasion. Professor Yong Tae Kwon, Seoul National University, was appointed president and scientists from Europe, USA and Asia formed the scientific council.

### ***Protein Termini 2022***

The COVID-19 pandemic affected us all, including most ISPT plans, but in June 2022 the community could finally meet in Bergen Norway for the EMBO Workshop on *Protein termini: From mechanisms to biological impact*. This in-person meeting hosted 115 scientists at all career stages from Europe, America and Asia (Figure 1). Covering animal, plant and bacterial sciences, as well as medicine and biotechnology, there were overall 50 regular plenary talks, held by recognized keynote lecturers and seniors or early-stage researchers. In addition to the classic poster sessions welcoming posters from all participants, the meeting also included two poster slam sessions allowing further 20 young scientists to briefly present their research and pitch their poster in plenum. *Protein termini 2022* also included a "meet the speaker"-session in the format of scientific speed dating, where 15 invited speakers each met six participants for five minutes according to topical preferences.

The workshop opened with the birth of a protein, a keynote lecture by Bernd Bukau, Heidelberg University, on the mechanisms of folding and assembly of nascent chains. The nascent chain is exposed to a number of modifying enzymes and chaperones that steer its fate. Prof. Bukau has pioneered this field and recently also

established the mechanisms of co-translational assembly of protein complexes [1]. The second keynote lecture was held by Alexander Varshavsky, Caltech. He outlined 36 years of work defining the designs and functions of N-degron pathways including an overview of the currently known N-degron branches [2].

The workshop additionally covered ribosome heterogeneity and relevant mechanisms from protein birth to destruction and defined the broader implications of protein terminal regulation.

The many enzymes modifying protein termini were extensively presented. The most frequent N-terminal (Nt) modifications and the respective modifiers include methionine excision (methionine aminopeptidases, MetAPs), acetylation (N-terminal acetyltransferases, NATs), myristoylation (N-terminal myristoyltransferases, NMTs), methylation (N-terminal methyltransferases, NTMTs), oxygenation (cysteine dioxygenases, ADO/PCO), and arginylation (arginyltransferases, ATE1) (Figure 2). Structural, biochemical and large-scale proteomics studies have uncovered how these enzymes may target specific terminal sequences, or sometimes a bulk of the proteome [3]. For those enzymes acting co-translationally, recent structures of enzymes bound to ribosomes were released, thus aiding our understanding of how nascent chains may undergo several modification steps.

An emerging topic was the interplay and competition between different types of enzymes modifying the same type of N-terminal sequence. A focus on the generation of differentially Nt-modified proteins is likely to uncover a deeper biological understanding of why proteins carry Nt-modifications and how this process is regulated.

Protein fate dependence on N- and C-termini was extensively discussed. In particular, the N-degron and C-degron pathways in bacteria, plants and animal cells received much focus [2-4]. Although internal protein residues are major mediators of protein degradation, the terminal amino acid sequences and their modification status may be significant determinants for protein stability. In both plants and human cells, Nt-acetylation was presented as a stabilizing factor for cellular proteins. Unacetylated N-termini of different categories are recognized by specific E3 ligases and targeted for degradation [5-7]. N-terminal cysteine and the Cys-branch of the N-degron pathway was at the heart of many presentations and discussions. After N-terminal Met excision by MetAPs, oxidation of the N-terminal Cys by PCO/ADO or non-enzymatically, the Cys is arginylated by ATE1 and the protein is finally degraded. This oxygen sensing plays a key role in plants and animals [8]. Recently, this N-degron branch was revealed to steer altitude adaptation in flowering plants [9], as well as autophagy in mammalian cells [10]. The presentation of a large number of substrates and signaling pathways controlled by the different N-degron pathways suggests that its full impact has not yet revealed itself.

Several robust and global approaches are used to define the modification status of protein termini and N-terminal proteoforms [11]. Optimized methods are constantly developed, and these were received with great interest. N-terminal and C-terminal degrons were recently mapped by large scale screening approaches [12, 13]. Further explorations are underway and are likely to define novel sets of targeted substrates (N- or C-degrons) and Ubiquitin ligases (recognins). Data suggest that terminal parts of the proteome have to some extent evolved to be protected from targeted degradation, and only during stress, disease, or other abnormal conditions such degrons are activated. Impaired or overexpressed Nt-modifying enzymes are associated with human diseases such as cancers and neurodegenerative disease, and specific Nt-modifications such as Nt-myristoylation mediated by the host cell are essential for virus infection. Thus, Nt-modifying enzymes and Nt-recognins may be attractive targets for drug treatment. A variety of inhibitors were presented, including such targeting NTMTs, NMTs and NATs [14, 15]. In addition to their potential development for drug purposes, such compounds are also attractive for probing global substrate profiles and cellular impact of specific Nt-modifying enzymes.

Four poster prizes were awarded to Early Career Researchers and these reflected the wide-spanning themes of this conference (Figure 1). Hannes Vanhaeren, Ghent University (The dark side of protein stability in plants: protein C-degrons) received the EMBO Reports poster award presented by Bernd Pulverer, Editor in Chief. Three presenters were selected by the conference delegates for ISPT poster awards based on their presentation and the significance of their work: Nikola Winter, University of Vienna (N-degron pathways in plants), Bong Heon Kim, Korea University (Structure of Ate1, arginyl-tRNA-protein transferase 1 in the Arg/N-degron pathway) and Alessia Caiella, University of Bergen ( $\alpha$ -Synuclein N-terminal acetylation affects aggregation and membrane binding properties in cell models).

The meeting ended with the encouraging announcement of the *Protein Termini 2024* meeting in Oxford which will be organized by Francesco Licausi and Emily Flashman, University of Oxford.

## Resources

International Society of Protein Termini (ISPT) website: <http://ispt.zenda.co.kr>

EMBO Protein termini 2022 website: <https://meetings.embo.org/event/21-protein-termini>

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## Figure captions

### Figure 1. Official EMBO poster and some glimpses from the *Protein termini 2022* meeting.

*Top*: Poster session. *Left*: Official EMBO Workshop advertisement poster. *Protein termini 2022* was supported by and advertised under the EMBO umbrella. *Bottom*: Group photo from the official opening at mount Fløyen, by the Bergen municipality. *Right, from top*: Poster award winners together with organizers and Poster award committee members. Names, from left: Hannes Vanhaeren, VIB-Ugent (awardee EMBO poster prize), Bernd Pulverer (Chief Editor of EMBO Reports) Nikola Winter, University of Vienna (awardee), Bong Heon Kim, Korea University (awardee), Alessia Caiella, University of Bergen (awardee), and organizers Michael Knop, Henriette Aksnes, Carmela Giglione and Thomas Arnesen. *Below*: Glimpse from the conference lecture room. *Below*: Presentation of keynote lectures by Bernd Bukau, ZMBH (*left*) and Alexander Varshavsky, Caltech (*right*). Photos: Laura Kind and Monica Hellesvik.

**Figure 2. The central roles of protein ends.** *Center*: Protein N- and C-termini were at the center attention of this meeting. Abbreviations: MetAP, methionine aminopeptidase; AP, aminopeptidase; CP, carboxypeptidase; NAT, N-terminal acetyltransferase; NTMT, N-terminal methyltransferase; NMT, N-terminal myristoyltransferase; PAT, palmitoyltransferase; ATE1, arginyltransferase 1; Ub-Ligase, ubiquitin ligase; PCO, plant cysteine oxidase; ADO, cysteamine dioxygenase. *Next layer*: Protein termini may be subjected to many modifications, here depicted with some of the key modifiers. *Next layer*: These modifications of protein termini impact various aspects of protein functionality and consequently affect (*outer layer*) a broad spectrum of biological processes in cells and organisms. Some elements of the figure were created with BioRender.





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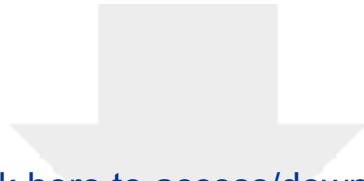
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