

Editorial for the Special Collection “Women in Peptide Science”

Dear Colleagues,

Did you know that amelogenin-derived peptides play a role for sex determination and that samples from even poorly preserved human skeletons are used for this purpose? One prominent example is tooth enamel that is utilized in gender archaeology to study prehistoric social organization.^{1,2} Remarkably, a recent analysis of the peptide composition of the aforementioned enamel-forming protein by nanoLC-coupled tandem mass spectrometry revealed female leadership in Iberian Copper Age (c. 3200–2200 BC).² As a consequence, the so-called “Ivory Man” actually had to be reassigned to be “The Ivory Lady”! We are confident that it will not take so long before women of our (scientific) community become visible and recognized.

It is the year 2024 and, certainly, no efforts are spared out for making women more visible in terms of their work and the perception of their achievements. However, despite enormous progress, women are still underrepresented in university and non-university research worldwide. In the past, we have often come across headlines like these: “science must become more open to everyone,” “science must change,” and “we need all the bright minds,” always referring to the proportion of women in the population, which is not reflected everywhere in science.^{3,4} These are just a few examples that we have encountered lately, and we are all familiar with many examples of activities aimed at making the successes of women more visible in different disciplines, including medicine, biology, chemistry, and engineering.

To expand on this, the present compilation is meant to highlight the broad and excellent contributions of female scientists to the fascinating world of peptides. Their research presented herein ranges from peptide synthesis approaches to produce natural peptides and to provide more sustainable and eco-friendly protocols for automated peptide synthesis, to the application of peptides as tools to either investigate enzyme mechanisms and intracellular signaling molecules or develop potential new drugs for specific target proteins, and finally to the broad field of peptide applications in biomedicine and material sciences.

Let's give you a flavor to the exciting research outlined within this special issue by highlighting some of the contributions. One topic of continuous interest is to investigate and improve peptides derived from natural sources. Indeed, there is a plethora of natural molecules, including peptides, possessing interesting bioactivities; however, for

many of them, their biological relevance is still unknown. The contribution by M. Rubini and coworkers (University College Dublin, Ireland) concerning the total synthesis of analogs of the antifungal lipopeptide iturin A goes in this direction. It shows how modifications of the native precursor by, for example, introducing alkylated cysteines and D-amino acids to generate monocyclic iturin A analogs influence their bioactivity. In general, combating antimicrobial resistance is considered one of the most important tasks nowadays. The groups of S. Gazzola (Universite degli Studi dell'Insubria, Como, Italy) and G. Bertoni (Universite degli Studi Milano, Italy) investigated how the protein-protein interaction (PPI) sites of the YeaZ protein from *Pseudomonas aeruginosa* could be used to prevent, for example, dimerization of the protein or the formation of higher oligomers. To implement their strategy, the authors used a tetradecapeptide sequence derived from the surface of YeaZ as lead structure and designed peptides with the intention to inhibit bacterial PPIs.

Thus, addressing such PPIs by using peptides has attracted great interest in basic research, not least owing to the high success in drug development, particularly in the areas of oncology, immune checkpoints in cancer immunotherapy, infectious diseases, or neurological disorders. Similarly to the aforementioned article, the work provided by E.J. Kennedy et al. (University of Georgia, Athens, USA) deals with the development of peptide mimetics that interfere with the interaction of the small GTPase Rab8a and the effector RILP-like protein 2 (RILPL2, Rab-interacting lysosomal protein-like protein 2) that regulates protein localization in the primary cilium. Thereby, Rab8a is a substrate of leucine-rich repeat serine/threonine kinase 2 (LRRK2) that is linked to Parkinson's disease. The article reports on the synthesis of constrained Rab-derived phospho-mimics that are intended to downregulate LRRK2 signaling.

In the past, great efforts have been made also to study enzymes and their catalytic mechanisms with the help of peptides and peptide analogs. This field opened even more over recent years by including the strategies applied in the context of artificial protein design. The review contribution to this special issue by the group of A. Lombardi (University of Naples, Italy) highlights how peptides can be used to mimic the metal-binding sites in metalloproteins and how such mimics and models support the study of the electron transfer reactions in the respective native enzymes.

Furthermore, this special issue showcases interesting work focusing on the targeted application of peptides or peptide analogs

for various biomedical applications. The article contributed by the group of B. Kocsch (Free University Berlin, Germany) and colleagues is on investigating and influencing the properties of hydrogel-forming glycopeptides for the development of mucus mimetics, in particular the impact on structural and conformational behavior and how it affects material properties such as viscosity and nature of the gels.

Two further studies deal with the use and potential of siRNA in different therapeutic approaches. Thereby, the need for efficient and specific cellular uptake and sufficient stability in complex biological systems is highlighted and discussed to be overcome by, for example, peptide conjugation. In the example provided by the group of A. Beck-Sickingher (University of Leipzig, Germany), the produced receptor-specific NPY-peptide-based siRNA shuttle system is internalized as a stable complex into cells, where it efficiently decreased mRNA expression. On the contrary, a liposomal delivery system called lipoproteoplex for siRNA transfer is within the focus of another article by J.K. Montclare et al. (New York University, USA) that investigates supercharged coiled-coil protein components for constructing the nucleic acid vehicle. Thus, the size of the molecules is significantly larger in the latter approach, and consequently, recombinant expression plays an essential role in producing the proteins. Also, the introduction of specific point mutations and tags and their impact on the siRNA delivery was studied and indeed revealed promising candidates that increased the overall cellular uptake.

This special issue is enriched by contributions from women working in the field of peptide science all over the world. Many of them have been working in this area for years and, as such, function as role models, while others have only recently joined the field. In any case, the changes that are already visible in our field can mean that even more young female scientists will live out their passion for peptide chemistry in the future or to use the words of Marie S. Curie: "Life is not easy for any of us. But what of that? We must have perseverance and above all confidence in ourselves. We must believe that we are gifted for something and that this thing must be attained."⁵

With this in mind, we are pleased to present this compilation to the community of peptide chemists and give a great thank you to all our contributors. Enjoy reading and let us all look forward to what the future will bring!

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