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Special Issue: Emerging Peptide Science in Italy

Guest Editors: Dr Giancarlo Morelli (Università di Napoli "Federico II"), Prof. Paolo Rovero (Università di Firenze) and Prof. Claudio Toniolo (Università di Padova)

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Emerging peptide science in Italy

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Bruno Casciaro, Debarun Dutta, Maria Rosa Loffredo, Stefania Marcheggiani, Alison M McDermott, Mark DP Willcox and Maria Luisa Mangoni, *Peptide Science* 2018, doi: [10.1002/bip.23074](https://doi.org/10.1002/bip.23074)

Effect of targeted minimal sequence variations on the structure and biological activities of the human cathelicidin LL-37

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Peptide modulators of Rac1/Tiam1 protein-protein interaction: An alternative approach for cardiovascular diseases

Alessandro Contini, Nicola Ferri, Raffaella Bucci, Maria Giovanna Lupo, Emanuela Erba, Maria Luisa Gelmi and Sara Pellegrino, *Peptide Science* 2018, doi: [10.1002/bip.23089](https://doi.org/10.1002/bip.23089)



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Selective detection of $\alpha 4\beta 1$ integrin (VLA-4)-expressing cells using peptide-functionalized nanostructured materials mimicking endothelial surfaces adjacent to inflammatory sites

Rossella De Marco, Arianna Greco, Natalia Calonghi, Samantha D. Dattoli, Monica Baiula, Santi Spampinato, Pierre Picchetti, Luisa De Cola, Michele Anselmi, Francesca Cipriani and Luca Gentilucci, *Peptide Science* 2018, doi: [10.1002/bip.23081](https://doi.org/10.1002/bip.23081)

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Luigi Russo, Biancamaria Farina, Annarita Del Gatto, Daniela Comegna, Sonia Di Gaetano, Domenica Capasso, Annamaria Liguoro, Gaetano Malgieri, Michele Saviano, Roberto Fattorusso and Laura Zaccaro, *Peptide Science* 2018, doi: [10.1002/pep2.24065](https://doi.org/10.1002/pep2.24065)

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Giuseppe Di Natale, Stefania Zimbone, Francesco Bellia, Marianna F. Tomasello, Maria L. Giuffrida, Giuseppe Pappalardo and Enrico Rizzarelli, *Peptide Science* 2018, doi: [10.1002/pep2.24083](https://doi.org/10.1002/pep2.24083)

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Chiara Testa, Debora D'Addona, Mario Scrima, Anna Maria Tedeschi, Anna Maria D'Ursi, Claire Bernhard, Franck Denat, Claudia Bello, Paolo Rovero, Michael Chorev and Anna Maria Papini, *Peptide Science* 2018, doi: [10.1002/pep2.24071](https://doi.org/10.1002/pep2.24071)

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Emanuela Gatto, Maria Elena Palleschi, Beatrice Zangrilli, Marta De Zotti, Benedetta Di Napoli, Antonio Palleschi, Claudia Mazzuca, Fernando Formaggio, Claudio Toniolo and Mariano Venanzi, *Peptide Science* 2018, doi: [10.1002/pep2.24081](https://doi.org/10.1002/pep2.24081)

Synthesis and biological activity of an Anderson polyoxometalate bis-functionalized with a Bombesin-analog peptide

Daniele Ventura, Andrea Calderan, Claudia Honisch, Silke Krol, Simona Serrati, Marcella Bonchio, Mauro Carraro and Paolo Ruzza, *Peptide Science* 2018, doi: [10.1002/pep2.24047](https://doi.org/10.1002/pep2.24047)



EDITORIAL

Emerging Peptide Science in Italy

Welcome to the third special issue of *Peptide Science* dedicated to highlighting research taking place in a country with a well-established peptide science community of long-standing tradition, and/or recent and rapidly growing scientific activity in the area. Two special issues in this series—from Japan and Australia—have already appeared [106(4), 2016 and 110(3), 2018, respectively]. This issue presents a collection of papers submitted by members of the Italian peptide science community who enthusiastically responded to this timely initiative. It includes 7 review articles and 17 original articles.

The first peptide synthesis carried out in Italy was performed on a sequence of the so-called S-peptide of the enzyme RNase A. The results were submitted to the Proceedings of the 6th European Peptide Society (EPS) meeting, held in Athens (Greece) in 1963, by Scoffone and coworkers.^[1] (Ernesto Scoffone [University of Padua, Italy] became interested in this fascinating topic in the late 1950s, when he was Visiting Scientist at the Rockefeller Institute [New York, U.S.A.] in the laboratory of Prof. Stanford Moore [1972 Nobel Laureate in Chemistry for his studies on RNase A].) The importance of peptide science research in Italy has subsequently been recognized by the EPS, inviting our country to organize its 10th meeting in Abano Terme (1969), the 27th meeting in Sorrento (2002) and the 37th meeting, which will take place in Florence in 2022. Activity in the area has been solidified further by the founding of the Italian Peptide Society (ItPS) in 2015.

The initial part of this issue contains the review articles, covering a broad variety of topics. In the first two, peptide–bio- and model-membrane interactions, an emerging area of research, are discussed from different perspectives. Savini *et al.* compare activity and selectivity data from physicochemical and microbiological studies on membranes and cells of host defense peptides, whereas Falanga *et al.* summarize recent findings on cell membrane-disrupting peptides and delivery of the viral genome into the host. Novelli *et al.* then provide an overview of the intriguing conformational properties, and recent applications in nanotechnology and biomedicine, of linear and cyclic regularly alternating $-(L-D)_n-$ peptide sequences that self-assemble into tubular architectures. In their contribution, De Filippis *et al.* show that enzyme-catalyzed semi-synthesis and solid-phase peptide synthesis methodologies allow convenient incorporation of noncoded amino acids with appropriately tailored side chains into small proteins by outlining relevant examples, principally from their own laboratory. Brunetti *et al.* focus their review on the increasingly investigated branched peptides, considering in particular the stability, half-life, toxicity, and efficacy, compared to those of their linear counterparts, and current attempts to improve these properties for clinical applications. Biscaglia *et al.* present a summary of the photophysical

properties of recently developed porphyrin-peptide hybrids, exploited to detect and fight a variety of diseases. Much of the piece focuses on photodynamic therapy. In the final review of the issue, Tedeschi *et al.* from the University of Parma, where the European Food Safety Authority (EFSA) is based, provide an overview of the innovative analytical techniques (e.g., advances in mass spectrometry) used to identify peptide markers for food authenticity and to quantify protein fragments in complex mixtures.

The second part of this issue comprises the primary research articles reflecting the large number of exciting fields currently being investigated by our colleagues. Using combined results from X-ray diffraction studies on peptides, bioinformatics analysis on proteins, and DFT conformational energy computations on homo peptides, Crisma *et al.* (including teams of experts from India and Spain), provide a detailed update of the still neglected fully extended, or 2.0(5)-helical secondary structure. Biondi *et al.*, in collaboration with Russian co-workers, present the results of their investigations into the preferred conformation of the 14-mer peptaibiotic chalciporin A (predominantly α -helix despite the relatively low content of Aib residues) by a large set of spectroscopic techniques. Cell membrane permeability and antibacterial activity are also discussed. Pizzi *et al.* in their crystallographic analysis of A β pentapeptides mono-halogenated at a Phe residue, reveal the absence of halogen-bond formation if the Phe residue is located at the C-terminus, meaning that the halogen atom does not help stabilize β -sheet formation. Marafon *et al.* describe the polymerization reaction of peptide-acetylene organogelator hybrids to produce poly-acetylenes and poly-diacetylenes characterized by intermolecularly H-bonded β -sheet networks. Angelici *et al.* report the synthesis and conformational analysis, in solution and in crystals, of short heterochiral peptide sequences, marked at the N-terminus by a ferrocene (Fc) moiety and characterized in the backbone by a five-membered lactam moiety. Intramolecularly H-bonded peptide turns and strong Fc–phenyl (Phe) π interactions are unveiled. Lima de Oliveira *et al.* discuss the orientation in SDS micelles of two synthetic N-terminal peptide sequences of different length from the pore-forming toxin actinoporin stycholysin. Their findings account for the different mechanism of action of these peptides, thus offering new information on stycholysin lytic activity at the molecular level. La Manna *et al.* describe the design and preparation of PS5 peptidomimetics with appropriate structural constraints (and extracted their conformational features) for the production of SOCS1-related, potentially anti-inflammatory compounds. Casciaro *et al.* report antibacterial activity of the frog skin-derived 1-21 sequence of esculentin-1a and one of its diastereomers against biofilms formed on contact lenses. These

peptides exhibit a chirality-dependent ability to disrupt the bacterial biofilms and are not toxic to mammalian cells.

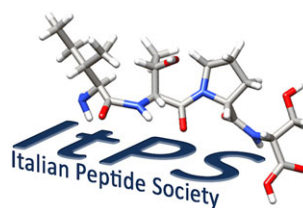
Pacor *et al.* discuss their findings on the structure and interaction of the LL-37 peptide derived from human cathelicidin with model biological membranes after incorporating minimal targeted residue variations to alter its pattern of intramolecular salt bridges. The subtle effects on helical structuring indicate that the particular properties of this innate immunity peptide likely depend on a complex pattern of intramolecular interactions. Contini *et al.* outline the conformational and biological effects of side-chain stapling and insertion of helicogenic residues in peptide inhibitors of protein–protein interactions responsible for several cardiovascular diseases and various types of cancer.

The following three articles all relate to research on the extensively investigated field of integrin receptors. The contribution of De Marco *et al.* describes the production of self-assembled monolayers based on dye-loaded zeolite L crystals coated with integrin peptide ligands and the results of subsequent cell adhesion studies. Russo *et al.* report on the ability of a chimeric bifunctional peptide to bind integrin, documenting experimentally and computationally the molecular determinants governing the interaction. In the last of the three, Di Gaetano *et al.* identify a 16-mer peptide encompassing the N-terminal segment of a potent salivary thrombin inhibitor containing the RGD motif as a compound with excellent adhesion inhibitory properties and the capacity to inhibit the invasiveness of malignant cell lines.

Di Natale *et al.* describe their work on the pentapeptide LPFFD β -sheet breaker of A β amyloid covalently conjugated to trehalose. This new class of peptidomimetics shows high affinity for A β , high stability in biological fluids, and an inhibitory effect on fibril formation. Testa *et al.* tackle the current need for the development of more stable and selective octreotide-derived somatostatin therapeutics by designing, synthesizing, and investigating by NMR the conformational propensities of a series of analogues characterized by a cyclic side-chain and chemically stable mimetic of the disulfide moiety of this cyclic 14-mer peptide. Intriguingly, the luminescence of Tb(III) ions in the visible region greatly increases after chelation. In their contribution, Gatto *et al.* report on the use of this property to study the binding of an N^α-Fmoc-functionalized analogue of the 10-mer peptaibiotic trichogin GA IV with Tb(III) ions. The final article of this issue, by Ventura *et al.*,

deals with the functionalization of a polyoxometalate with two copies of a bombesin antagonist peptide, showing specifically the interplay between these domains in terms of 3D structural changes and assembly, and exploring the impact of this hybrid conjugate on antitumor activity.

We would like to extend our special thanks to our colleagues from all over Italy for their active participation in this delightful editorial adventure that coincidentally and successfully marks the first few years of the ItPS. Finally, we are grateful to our colleague Lorenzo Stella (University of Rome, Tor Vergata) whose brilliant imagination produced an excellent cover that combines a wonderful piece of Italian Renaissance art with the scientifically fundamental and aesthetically beautiful peptide helix and sheet secondary structure representations developed in U.S.A. in the early 1950s.



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