

Editorial

# To Go Where Nature Leads: Focus on Palmitoylethanolamide and Related ALIAmides as Innovative Approach to Neuroinflammatory and Pain-Related Disease States in Honor of Doctor Francesco Della Valle

Salvatore Cuzzocrea <sup>1,\*</sup>  and Rosalia Crupi <sup>2,\*</sup> 

<sup>1</sup> Department of Chemical, Biological, Pharmaceutical and Environmental Sciences, University of Messina, 98166 Messina, Italy

<sup>2</sup> Department of Veterinary Science, University of Messina, 98166 Messina, Italy

\* Correspondence: salvatore.cuzzocrea@unime.it (S.C.); rosalia.crupi@unime.it (R.C.)

Dr. Francesco Della Valle made a significant impact in both the business and scientific domains. Reading for a degree in chemistry, with an emphasis on organic and biological disciplines, he quickly distinguished himself in the pharmaceutical industry. This distinction was largely due to the industrial ventures he passionately and adeptly led. His fervor for science resulted in him receiving three honorary degrees and co-inventing numerous pharmaceutical patents, including more than 100 in Europe, with broad recognition in major countries, and as many active patents in the United States.

A quintessential man of science, Dr. Della Valle was simultaneously a visionary entrepreneur always in search of innovation and a thorough, meticulous manager who steered his company with determination. Recognizing the importance of open innovation, he valued the synergistic relationships between academia and industry [1].

A devoted scholar of neuroscience, Dr. Della Valle collaborated with Nobel laureate Rita Levi Montalcini for many years. He deeply grasped the significance of biological breakthroughs like the nerve growth factor (NGF), drawing him closer to Professor Montalcini [2]. “Try to understand the strategy that Nature would use to protect itself from harm”, was the counsel given to him by the Nobel laureate in 1991 [3]. Inspired by this advice, Della Valle pursued the discovery and development of substances that could emulate nature’s protective strategies through the ALIA mechanism [4]. He was profoundly invested in studying neuroinflammation as the foundation for various ailments, ranging from neuropathic pain to neurological diseases [5]. His scientific journey was marked by a relentless “quest for life”, gleaned insights and motivation from nature.

Dr. Francesco Della Valle leaves behind a legacy of pharmaceutical patents, scientific publications, pharmacological innovations, and concepts of neuroinflammation and neuropathic pain. Yet, his most invaluable legacy is his passion for science, truth, dialogue, and life itself.

The research presented in this Issue underscores the importance of continuing studies on PEA and related ALIAmides, using insights from nature to tackle new and increasingly complex challenges. We would like to express a heartfelt thank you to all the authors, reviewers, and contributors who have made the publication of this Special Issue possible. Our hope is that the information shared will inspire further research and exploration.

Here is a List of contributions contained in the Special Issue.

**Conflicts of Interest:** The authors declare no conflict of interest.



**Citation:** Cuzzocrea, S.; Crupi, R. To Go Where Nature Leads: Focus on Palmitoylethanolamide and Related ALIAmides as Innovative Approach to Neuroinflammatory and Pain-Related Disease States in Honor of Doctor Francesco Della Valle.

*Biomolecules* **2023**, *13*, 1583. <https://doi.org/10.3390/biom13111583>

Received: 23 October 2023

Accepted: 24 October 2023

Published: 26 October 2023



**Copyright:** © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

**List of Contributions:**

1. Palenca, I.; Seguella, L.; Del Re, A.; Franzin, S.B.; Corpetti, C.; Pesce, M.; Rurgo, S.; Steardo, L.; Sarnelli, G.; Esposito, G. N-Palmitoyl-D-Glucosamine Inhibits TLR-4/NLRP3 and Improves DNBS-Induced Colon Inflammation through a PPAR- $\alpha$ -Dependent Mechanism. *Biomolecules* **2022**, *12*, 1163. <https://doi.org/10.3390/biom12081163>.
2. Cristiano, C.; Avagliano, C.; Cuzzo, M.; Liguori, F.M.; Calignano, A.; Russo, R. The Beneficial Effects of Ultramicronized Palmitoylethanolamide in the Management of Neuropathic Pain and Associated Mood Disorders Induced by Paclitaxel in Mice. *Biomolecules* **2022**, *12*, 1155. <https://doi.org/10.3390/biom12081155>.
3. Guida, F.; Rocco, M.; Luongo, L.; Persiani, P.; Vulpiani, M.C.; Nusca, S.M.; Maione, S.; Coluzzi, F. Targeting Neuroinflammation in Osteoarthritis with Intra-Articular Adelmidrol. *Biomolecules* **2022**, *12*, 1453. <https://doi.org/10.3390/biom12101453>.
4. Valenza, M.; Facchinetti, R.; Steardo, L.; Scuderi, C. Palmitoylethanolamide and White Matter Lesions: Evidence for Therapeutic Implications. *Biomolecules* **2022**, *12*, 1191. <https://doi.org/10.3390/biom12091191>.
5. della Rocca, G.; Re, G. Palmitoylethanolamide and Related ALIAMides for Small Animal Health: State of the Art. *Biomolecules* **2022**, *12*, 1186. <https://doi.org/10.3390/biom12091186>.
6. Assogna, M.; Di Lorenzo, F.; Martorana, A.; Koch, G. Synaptic Effects of Palmitoylethanolamide in Neurodegenerative Disorders. *Biomolecules* **2022**, *12*, 1161. <https://doi.org/10.3390/biom12081161>.
7. Cifelli, P.; Ruffolo, G.; Ceccanti, M.; Cambieri, C.; Libonati, L.; Palma, E.; Inghilleri, M. Classical and Unexpected Effects of Ultra-Micronized PEA in Neuromuscular Function. *Biomolecules* **2022**, *12*, 758. <https://doi.org/10.3390/biom12060758>.
8. Landolfo, E.; Cutuli, D.; Petrosini, L.; Caltagirone, C. Effects of Palmitoylethanolamide on Neurodegenerative Diseases: A Review from Rodents to Humans. *Biomolecules* **2022**, *12*, 667. <https://doi.org/10.3390/biom12050667>.
9. Crupi, R.; Cuzzocrea, S. Role of EPA in Inflammation: Mechanisms, Effects, and Clinical Relevance. *Biomolecules* **2022**, *12*, 242. <https://doi.org/10.3390/biom12020242>.
10. Toti, A.; Micheli, L.; Lucarini, E.; Ferrara, V.; Ciampi, C.; Margiotta, F.; Failli, P.; Gomiero, C.; Pallecchi, M.; Bartolucci, G.; et al. Ultramicronized N-Palmitoylethanolamine Regulates Mast Cell-Astrocyte Crosstalk: A New Potential Mechanism Underlying the Inhibition of Morphine Tolerance. *Biomolecules* **2023**, *13*, 233. <https://doi.org/10.3390/biom13020233>.
11. Schiano Moriello, A.; Roviezzo, F.; Iannotti, F.A.; Rea, G.; Allarà, M.; Camerlingo, R.; Verde, R.; Di Marzo, V.; Petrosino, S. First Evidence of the Protective Effects of 2-Pentadecyl-2-Oxazoline (PEA-OXA) in In Vitro Models of Acute Lung Injury. *Biomolecules* **2023**, *13*, 33. <https://doi.org/10.3390/biom13010033>.
12. Elfarnawany, A.; Dehghani, F. Palmitoylethanolamide Mitigates Paclitaxel Toxicity in Primary Dorsal Root Ganglion Neurons. *Biomolecules* **2022**, *12*, 1873. <https://doi.org/10.3390/biom12121873>.
13. Interdonato, L.; D'amico, R.; Cordaro, M.; Siracusa, R.; Fusco, R.; Peritore, A.F.; Gugliandolo, E.; Crupi, R.; Coaccioli, S.; Genovese, T.; et al. Aerosol-Administered Adelmidrol Attenuates Lung Inflammation in a Murine Model of Acute Lung Injury. *Biomolecules* **2022**, *12*, 1308. <https://doi.org/10.3390/biom12091308>.

**References**

1. Della Valle, F.; Gambardella, A. 'Biological' Revolution and Strategies for Innovation in Pharmaceutical Companies. *R&D Manag.* **1993**, *23*, 287–302.
2. Aloe, L. Rita Levi-Montalcini: The Discovery of Nerve Growth Factor and Modern Neurobiology. *Trends Cell Biol.* **2004**, *14*, 395–399. [[CrossRef](#)] [[PubMed](#)]
3. Aloe, L.; Leon, A.; Levi-Montalcini, R. A Proposed Autacoid Mechanism Controlling Mastocyte Behaviour. *Agents Actions* **1993**, *39*, C145–C147. [[CrossRef](#)] [[PubMed](#)]
4. Levi-Montalcini, R.; Skaper, S.D.; Dal Toso, R.; Petrelli, L.; Leon, A. Nerve Growth Factor: From Neurotrophin to Neurokinine. *Trends Neurosci.* **1996**, *19*, 514–520. [[CrossRef](#)] [[PubMed](#)]
5. Petrosino, S.; Schiano Moriello, A. Palmitoylethanolamide: A Nutritional Approach to Keep Neuroinflammation within Physiological Boundaries—A Systematic Review. *Int. J. Mol. Sci.* **2020**, *21*, 9526. [[CrossRef](#)] [[PubMed](#)]

**Disclaimer/Publisher's Note:** The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.