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Palmitoylethanolamide: Research Synergy between Academia and Industry, Based on Insights and Work of Nobel Laureate Rita Levi-Montalcini

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Abstract

The development story of the autacoid palmitoylethanolamide is a classical example of an optimal cooperation between academia and pharmaceutical industry. Based on the work of the Nobel laureate Rita Levi-Montalcini a small Italian pharmaceutical company, LifeGroup Spa, could start in the 90s the research and development phase of this remarkable lipid signaling molecule. Their joint efforts led to new insights in mast-cell related disorders, and a series of patents. This example supports the case that we need to rethink our stringent policies on 'conflict of interest'. It is due to the mutual interest in innovative biological principles of autacoid medicine that the work of Levi-Montalcini and LifeGroup Spa led to a new treatment paradigm for chronic pain and inflammations.

Introduction

The current trend is to frown on virtually all interactions between academic key opinion leaders and colleagues from the pharmaceutical industry. To avoid 'conflicts of interest' modern opinion leaders are externally motivated to shy away from collaboration with 'big pharma' or other commercial companies and parties. Such concerns however restrain innovation and delay translation of basic discoveries to clinical benefit [1]. This is quite unfortunate and we will demonstrate how synergies between academia and industry can lead to important paradigm-shifting innovations, by focussing on the case of palmitoylethanolamide (N-(2-Hydroxyethyl)hexadecanamide; Palmidrol; PEA). PEA is a lipid autacoid and one of the main fundaments for the emergence of a new treatment paradigm for chronic pain and (neuro-) inflammation [2]. The illustrious Nobel laureate professor Rita Levi-Montalcini, together with colleagues from a small Italian pharmaceutical company, in the period 1991-1996 discovered an entirely new treatment principle, and currently literature referring to this principle is expanding rapidly with more than 500 PubMed indexed papers on PEA [3].

The evolution of insights around the endogenous lipid mediator and autacoid palmitoylethanolamide.

The evolution of the PEA treatment concept and insight in PEA's many mechanisms of action is very relevant to review in detail for our case and we will start defining a number of discrete periods of this evolution based on research findings and patents.

Phase 1 (1957-1980): The discovery and the chemical characterization of PEA as an anti-inflammatory agent by Merck researchers in 1957 and subsequent development of PEA from 1969 onwards by the Czech SPOFA United Pharmaceutical Works as Impulsin for flu and common cold [4]. It was highly remarkable that Merck did not file a patent before the publication in 1957 on the molecule as a New Chemical Entity, and this was especially strange as the Merck researchers did not only identify PEA's molecular structure, but they also described its biological action as an inflammatory agent [5]. It is unknown when exactly SPOFA took up the production of matrix tablets containing 300 mg PEA, but a clinical trial in children was already reported in 1969 [6]. In 1976 a new PEA formulation became available, a suspension, developed by the Spanish company Almirall for the indication prophylaxis of respiratory disorders, under the branded name 'Palmidrol'. It still seems to be available in certain South American countries. In this period many thousands of patients were treated and PEA was found to be quite effective and very safe, with good tolerability. Doses up to 100 mg/kg Body Weight (BW) were tested and found to be safe and in children doses were explored up to 50 mg/kg BW.

Phase 2 (1980-1991): A silent period with very few activities in the field, most probably because the mechanism of PEA remained obscure and its first selected indication seemed not to be a commercial success.

Phase 3 (1991-1996): Clinical research and development phase in Italy for developing PEA as a drug in neuropathic pain (sciatic pain) and multiple sclerosis by LifeGroup Spa.

Around 1990 PEA was recognized as endogenous molecule (an autacoid) acting as a mast cell modulator by Prof. Levi-Montalcini in close cooperation with scientists from LifeGroup Spa [7]. This first mechanistic explanation of PEA's mode of action was presented by Prof. Levi-Montalcini, and it paved the way for the clinical development of PEA in mast-cell related indications. The development code for PEA used by LifeGroup was LG 2110/1. During this period a first patent was filed by LifeGroup and a prototype tablet consisting of 300 mg PEA in a matrix tablet was developed and tested in patients and described as an example in the first patent

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[8]. A great number of potential mast-cell related indications were summarized in this patent, such as various allergic and inflammatory conditions, colitis, keratoconjunctivitis sicca, rheumatic disorders en neurological disorders such as multiple sclerosis and Alzheimer. A series of patents around this molecule and its derivatives were filed in this period [9-13].

Phase 4 (1996-2005): In this period no overt activity due to bankruptcy of LifeGroup.

Apparently the process of registration of PEA as a drug in Italy did not go as expected and it appears complications arose with the competent authorities, which created much delay in the expected marketing authorization. The burn rate of the company however, with no assets on the market, was high and sadly enough led to a premature bankruptcy and a stagnation of PEA's further development. There was however some covert action, as a new company prepared a new patent on formulation, filed in 1999 [14].

Phase 5 (2005-) Introduction of PEA as a nutraceutical in Italy, Spain and Germany of palmitoylethanolamide in a special newly developed formulation (micro-PEA) in 300 mg and 600 mg matrix tablets by Epitech Srl. Due to the documented safety, and due to the fact PEA was widely present in food, and in nearly all living animals, PEA became notified in a new class, food for special medical purposes [15]. PEA was subsequently introduced as a nutraceutical in various formulations, including a PEA formulation containing micro-PEA without excipients by JP Russell Science Ltd in 2012 (400 mg capsules). Micro-PEA is a general term for PEA containing fine and ultrafine particles and such formulations are protected by a number of formulation patents of the above mentioned two companies. Formulations containing micro-PEA are designed to improve PEA's bioavailability.

First patent on PEA and the PEA project of LifeGroup and Professor Levi-Montalcini

Professor Levi-Montalcini disclosed for the first time the indication neuro-inflammation for PEA in her seminal paper of 1993 [7]. She introduced the Autacoid Local Inflammation Antagonism (ALIA) principle and presented PEA as a novel mast cell modulator. The mast cell has been promoted by her work from a Cinderella cell to a Primadona cell, as she used to say. Her explanation of the importance of the mast cell and of autacoids such as PEA as mast cell modulators can be seen on a video on Youtube: https://www.youtube.com/watch?v=VndV_NO-mAU. From 1991 to 1996 various patents were filed by Lifegroup Spa, on the use of PEA and derivatives in auto-immune processes and (neuro-) inflammatory disorders.

The invention described in the first 1991 patent related to: "the use of N-acyl derivatives of aminoalcohols with polycarboxylic acids for the preparation of pharmaceutical compositions for the therapeutic treatment of pathologies undergoing mast cells degranulation, consequent to a neuroimmunogenic and/or immunogenic hyperstimulation [8]".This invention was supported by a series of experiments, some of which were published by Rita Levi-Montalcini and one of her pupils, together with a researcher from LifeGroup, Dr Leon in 1993 [7]. In the first experiment described in the patent two weeks old rats, were first locally treated by intradermal injection on the auricular pinna with PEA and smaller C chain PEA derivatives (0.5 mg/kg BW). After 10 minutes a local administration of the mast cell stimulator substance P (10^{-4} M), was applied to trigger a mast cells degranulation response. After 30 minutes the animals were sacrificed and the degree of inhibition of mast cell degranulation in the tissues of the animals treated with PEA and derivates were compared with controls. PEA could significantly reduce the biological read-out related to mast-cell degranulation. This was one of the first experiments supporting the promising therapeutic activity of the lipid autacoid PEA, designed by a Nobel Prize laureate and members of a small Italian pharmaceutical company.

Conclusion

The current dominant thinking around the interface academia-pharmaceutical industry is centered on avoiding all 'conflicts of interest'. The case we presented above invites the reader to rethink this position, as it is due to the mutual interest in innovative treatment principles that the work of Rita Levi-Montalcini and LifeGroup Spa led to a new treatment paradigm for chronic pain and inflammations as well as to a series patents.

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