PROFILE

Pharmamel SL is a biotechnological company devoted to the I+D+I in the field of melatonin and its applications. From several years ago, prof. Darío Acuña and Germaine Escames obtained outstanding findings in its mechanisms of action and its clinical applications. To date, 5 patents, 3 of them licensed to Pharmamel, and four clinical trials have been developed. The research lines include: 1) Regulation of mitochondrial bioenergetics by melatonin; 2) study of the clock genes on the cellular and mitochondrial damage in experimental models of Parkinson and sepsis and aging, and 3) melatonin and its metabolites as new pharmacological tools against cancer and chemo- and radio-resistance.

SPEAKER

Darío Acuña is a Professor of Physiology at the Universidad de Granada and a medical specialist in clinical analysis. His line of investigation the past 40 years has been the mechanism of action of melatonin and its application in aging, neurodegeneration and sepsis. As a result, several patents has been developed, included those licensed to Pharmamel, S.L., an *spin-off* what he is a co-founder.

dacuna@ugr.es

PRODUCT

A new formulation of an injectable of melatonin for the treatment of sepsis

MECHANISM OF ACTION

Melatonin is a unique anti-inflammatory drug because it block the two main pathways of the innate immunity, i.e., the NF-kB pathway and the NLRP3-inflammasome pathway, both activated in sepsis. Whereas the NF-kB transcription factor induced many inflammatory mediators and pro-inflammatory cytokines such as pro-IL-1β, pro-IL-18 and pro-IL-33, and produced mitochondrial damage and oxidative damage that activates the NLRP3 inflammasome that, in turn, activates a caspase 1 that maturates these pro-cytokines to their active form, IL-1β. This cytokine positively feed-back the activation of NF-kB, potentiating the inflammatory response.

Melatonin is an endogenous product from all living being in the world; it ids produced from plants to humans and it acts mainly as a cell protector preventing cell damage. The melatonin injectable is a result of several years of research to obtain a stable formulation of this molecule. As a result, we invented a stable formulation of liquid melatonin, which is stable for a long time and even at high concentrations at room temperature, at -4 degrees and at -20 degrees Celsius. Moreover, animal and human studies reported the low toxicity of the product and high effectiveness in controlling the inflammations associated to sepsis.

TARGET INDICATIONS

Mainly in sepsis, but it can be used in other diseases coursing with inflammation, oxidative stress and mitochondrial impairment.

CURRENT STATUS

- In experimental animals of severe sepsis, Parkinson's disease, and aging, melatonin was able to counteract the inflammation, preventing the death of animals, recovering the neurodegenerative process, and increasing live span, respectively, at the time that restored mitochondrial bioenergetics in all of them.

- Analysis of the cardiovascular, hepatic, renal, and metabolic markers supported melatonin administration at high doses as a secure drug.
- From these data, we apply for a phase II clinical trial in sepsis to the AEMPS (EudraCT 2008-006782-8), to evaluate its toxicity and effectiveness; the results showed absence of toxicity and benefits in terms of reduction of hospital stay and mortality.
- Recently, and in view that covid-19 patients die in the ICUs by multiorgan failure and sepsis, we apply to the AEMPS a phase II clinical trial in these patients (EudraCT 2020-001808-2), to evaluate its toxicity and effectiveness. The results also support the effectiveness of melatonin in covid-19 patients.

INNOVATIVE ASPECTS

- The action mechanism, acting on both NF-kB and NLRP3 inflammasome made melatonin a unique anti-inflammatory drug; other anti-inflammatory compounds such as corticoids only act at the NF-kB level, having low efficiency in sepsis.
- Moreover, melatonin lacks of side effects even at high doses, an effect reported in animal studies and in humans, both in healthy subjects and in patients with sepsis, COVID-19, and mucositis, among others.
- Melatonin is highly effective against inflammation, oxidative stress and mitochondrial impairment, because besides its anti-inflammatory actions, is an outstanding antioxidant and protects mitochondria from oxidative damage, boosting their production of ATP.
- Thus, melatonin is the unique drug able to counteract inflammation, oxidative damage and mitochondrial defunction at time.

IPR

Injectable of melatonin is currently patented (PCT/ES2015/070236) in the EU, USA, Brazil, and China.

PARTNERING OPPORTUNITIES

We want to start with a phase III clinical trial to analyze the benefit of the melatonin injectable in sepsis. Our interest is to perform this clinical trial in the EU and in the USA, to extend as much as possible the results and further put in the market this formulation.