Getting to Know Your 2019 PMDF Grant Winners

By April Ingram, Apr, 2019

Repositioning a Traditional Therapy - Taking Aim at a New Target

Principal Investigator - Giuseppe Esposito, PhD

Collaborators: Maria Carafa, PhD, Dr. Carlotta Marianecci, PhD, Stefano Gigli and Luisa Seguella

Research Title: **Innovative Parkinson's disease modifying strategy: preclinical evaluation of intranasal delivery of pentamidine (IN-pentasome) in MPTP-intoxicated mice.**

Dr. Guiseppe Esposito and colleagues at his laboratory in the Department of Physiology and Pharmacology 'Vittorio Erspamer' at the **University SAPIENZA in Rome Italy**, are focussed on new ways to reduce the neuroinflammation that can be an underlying cause of neurodegeneration in disorders like Parkinsons' Disease (PD).

The term neuroinflammation is used to describe an inflammatory response within the brain or spinal cord. This inflammatory process is controlled by the production of cytokines, a large group of proteins and other neurochemicals that are secreted by specific cells of immune system. These cytokines are powerful regulators of glial cells—the cells responsible for supporting neurons in the brain. When glial cells are not performing normally, they can become activated in a process called gliosis, and produce inflammatory and toxic chemicals that can damage or kill neurons. Gliosis is a key step in the progression of PD, so it would make sense that blocking gliosis from occurring might delay or stop PD from progressing.

A protein called S100B is produced by normally reacting glial cells and it regulates normal neuron development, but there can be too much of a good thing. Secretion of too much S100B can be toxic and cause destruction of dopamine-producing neurons in areas of the brain responsible for movement control.

Dr. Esposito is excited to share an important part of his research, linked to the possibility of targeting the glial cells to act on gliosis and protect the dopaminergic neurons indirectly. It is important to protect the dopaminergic neurons because they are the main source of dopamine in the central nervous system and their loss underlies the motor symptoms of PD. Dr. Esposito explains that there are nine glia for every neuron, so glia are not bystanders in neurodegeneration, but actively participate in cell death.

Animal research has shown that when too much S100B is expressed, animals are predisposed to develop severe PD. Dr. Esposito shares the potential in this research, “The possibility of pharmacologically blocking the S100B protein can represent an interesting strategy in limiting the progression of Parkinson's disease and favoring a sensible improvement, which is key. Our research project is based on the study of an antiprotozoal drug, pentamidine, which has shown the ability to block the activity of S100B in different pathological conditions in which this protein is overexpressed, such as in cancer, colitis and experimental Alzheimer’s disease.” Studies have shown that pentamidine, historically used to prevent the growth of harmful or infectious microorganisms, effectively blocks S100B, so it has been repositioned as anti-tumor treatment and is in phase III studies on melanoma. Research is being conducted to determine if it can be successfully repurposed to treat other conditions.

Pentamidine is usually administered by aerosol or intravenously, and Dr. Esposito is looking to produce a form that can be administered as a nasal spray. This is a novel way to deliver the drug, allowing for microscopic particles of pentamidine to be easily absorbed. The Esposito lab will conduct a study of the new pentamidine formulation, niosome (IN-pentasome), in Parkinsonian mice and verify improvements in movement and neuropathology (study of the actions of the drug on the nervous system) in the animals. Dr. Esposito explains, “This work will lead to more in-depth studies in the future to determine if repositioning pentamidine treatment in Parkinson's disease may represent an important innovation to improve the conditions of people living with PD.”

Dr. Esposito recognizes the challenges of conducting movement disorder research, he explains, “I believe that one of the most important challenges in the field of movement disorder research, particularly in PD, is early diagnosis and the possibility to optimize the individual therapeutic approach for the patient. Early diagnosis implies a wide range of therapeutic options for the subjects, minimization of side-effects and huge achievement of therapeutic success. Today we are experiencing a total renewal of anti-PD drugs, beyond Levodopa, there is a new exciting world of molecules to be tested, that can be developed in the attempt to delay the disease progression and, at the same time, obtain a significant reduction of on-off phases that strongly limit in the time the patient’s life quality. Pentamidine is one of them. It has the advantage to be quickly repositioned from laboratory research to being used in the clinics since it has been largely known as an antiprotozoal drug. We already know its potential toxic profile, and that it can be strongly limited by its intranasal administration.”

Grant funding is essential to new discoveries and advancements. Dr. Esposito is grateful for the support of the PMDF and shares how this grant is fundamental to move their work toward future treatments, “This grant will help my group to determine if IN-pentasome works the way we expect it to, leading to clinical improvements in

experimental PD in mice. We will also be able to determine if administering it as a nasal spray is as safe as we expect it will be."

Dr. Esposito strongly believes that new therapies for PD are right around the corner, "A more detailed understanding of neurological triggering factors, and early diagnosis are fundamental to achieve a new perspective of care. New approaches have to be developed, but also need to be looked at in a 360 degree view. Drugs capable of acting earlier, more effectively, and most importantly with fewer side effects, require a better knowledge of the mechanisms that predispose someone to PD."