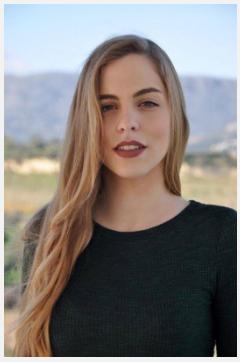
ImmunoTools *special* Award 2018



Evangelia Thanou, Master's -student

Supervisor: Dr. Hardy J. Rideout

Basic Neuroscience Division, Biomedical Research Foundation of the Academy of Athens, 4 Soranou Efesiou St 11527, Athens, Greece

The role of LRRK2 signaling in resident and infiltrating immune cells in different models of familial and sporadic Parkinson's disease

Parkinson's disease (PD) is the second most common neurodegenerative disorder, with the biggest risk factor being age. The majority of cases are sporadic in nature, however approximately 10% of cases are linked to both autosomal dominant as well as recessive inherited mutations in several genes. Our work is focused on the mechanisms of neurodegeneration associated with the most commonly mutated gene: leucine-rich repeat kinase 2 (LRRK2). LRRK2 is widely expressed in most tissue of the body, with highest expression in the lung and kidney, as well as in the brain and immune cells (e.g. monocytes, myeloid cells, macrophages and microglia, etc). In addition to PD, mutations in LRRK2 have also been linked to Crohn's disease, and altered signaling in other forms of inflammatory bowel diseases.

Previous studies have identified multiple mechanisms by which mutant forms of LRRK2 can lead to neurodegeneration typical of PD; however, there is evidence that normal, wild type, LRRK2 also plays a role in PD pathogenesis linked to other forms of the disease, as well as idiopathic PD. Through its action in regulating inflammation and immune system signaling, LRRK2 may play a vital role in PD in general, including rare cases associated with mutations in the alpha-synuclein gene (which are more common in Greece). LRRK2 inhibition, either genetically or by pharmacological inhibition of its kinase activity, suppresses microglial activation following exposure to TLR4-pathway agonists such as LPS and fibrillar alpha-synuclein. Moreover, deletion of the LRRK2 gene in rats is protective against viral alpha-synuclein over-expression models, via a suppression of infiltrating myeloid cells in the striatum and ventral midbrain.

Our studies will focus on identifying the precise signaling pathways triggered by LRRK2, in particular its kinase activity, in various cellular and animal models of PD. Specifically, my thesis project is focused on several specific questions, for which the reagents provided by the ImmunoTools award will be used. First, we will examine the activation of microglial and macrophage cell lines in which LRRK2 is stably down-regulated, or pharmacologically inhibited, in relation to specific known phospho-substrates of LRRK2, following exposure to different species of alpha-synuclein.

Secondly, as part of an ongoing project using a novel transgenic mouse model, we will examine the role of a known binding partner of LRRK2 in microglial activation in vivo, following stereotactic injections of fibrillar alpha-synuclein into the striatum or viral over-expression of alpha-synuclein. Finally, we will measure cytokine/inflammatory mediators in clinical samples of PD patients correlated with measures of LRRK2 activity within the same samples.

The reagents provided by the ImmunoTools award will provide us with the opportunity to address several critical outstanding questions regarding the role of LRRK2 and its partners in immune cell signaling in multiple models of PD. This will improve our understanding of LRRK2 biology, and can provide the rationale for targeting LRRK2 as a potential therapeutic strategy in PD.

ImmunoTools *special* AWARD for **Evangelia Thanou** includes 23 reagents

FITC - conjugated anti-human CD14, CD19

PE - conjugated anti-human CD16, CD19

FITC - conjugated anti-mouse CD45

PE - conjugated anti-mouse CD11b, CD40

human ELISA set (for one 96 plate): human IL1b, human TNF-a

mouse ELISA set (for one 96 plate): mouse IL6, mouse TNF-a

DETAILS more AWARDS