

Overview.

My research program will center on elucidating the impact of comorbid-risk factors on the development and progression of Alzheimer's disease (AD). In particular, I am interested in determining how stress and diabetes affect synaptic function, which is one of the main features that better correlates with cognitive status in AD cases. Specifically, I am interested in studying how stress and diabetes affects the actin cytoskeleton, which plays a pivotal role in modulating synaptic function.

As an undergraduate, I decided to join Dr. Antonia Gutierrez Perez's laboratory at the University of Malaga (Spain), where I was introduced to the field of Neuroscience and the broader Biological Sciences. Under her expert supervision, I lead a project to study the role of the Glutamatergic and GABAergic system in the regulation of insulin and glucagon expression in the Langerhans's islets¹. During this time, I gained important experience in biochemical and cellular techniques to discover the role of these neurotransmitter systems to regulate the synthesis and release of two of the most important hormones, involved in glucose regulation, in our body. The project was supported by the Spanish-Government Program Project for Undergraduate students. The undergraduate research experience inspired me to pursue a doctoral degree oriented in the Neuroscience field. In particular, I focused my studies on the cellular and molecular mechanism involved in the neurodegenerative processes underlying AD. Under Dr. Antonia Gutierrez Perez expert supervision, I investigated the cellular and molecular mechanisms involved in the neurodegenerative processes found in the diseased hippocampus of AD, using the PS1(M146L)xAPP(751SL) transgenic mouse model. My studies demonstrated for the first time that the inhibitory GABAergic system is significantly affected early in the hippocampus of this transgenic AD mouse model²⁻⁴. These findings represent a significant breakthrough in determining the vulnerability of different neuronal populations within the hippocampus, at an early stage of Alzheimer's pathogenesis, and allowed me to identify several potential biomarkers of disease progression to be used in preclinical studies and drug screening²⁻⁴. Furthermore, two of the biomarkers our group identified are currently being used by Sanofi, one of the world's leading Pharmaceutical companies, in its screening program for novel Alzheimer's drugs. Following my initial work, additional studies were conducted to identify possible pathological pathways that mediated the early neurodegeneration of the GABAergic cells in the hippocampus of PS1(M146L)xAPP(751SL) mice. My contribution focused on the molecular and cellular characterization of the neuroinflammatory processes that could lead to the observed early neuronal loss. My results strongly suggested that changes in neuroinflammation might be a potential factor involved in the degenerative process of the GABAergic cells^{3,5}.

In order to extend my training in the derivation and characterization of novel genetically-modified mice for AD research, I was pleased to be accepted a postdoctoral fellow position in the laboratory of Dr. LaFerla at UC Irvine, which houses an internationally renowned group of Alzheimer's researchers. During my postdoctoral studies, I have been specifically interested in determining how co-morbidities can modulate the onset and progression of AD. My initial studies focused on the impact of psychological stress on AD, and I investigated the effects of anti-glucocorticoid drugs as potential treatments for AD^{6,7}. Interestingly, I found that blocking the effects of elevated circulating glucocorticoids in transgenic mice, which display Alzheimer's disease pathologies, leads to an amelioration of A β and tau pathologies, as well as restores cognition to wild-type levels. My findings highlighted the significant role that the glucocorticoid stress hormones play in exacerbating AD-related cognitive decline and pathology, and demonstrate that compounds targeting the glucocorticoid system could be useful for the treatment of AD, in part through novel disease-modifying effects on A β generation. (Please, see the following comment: [http://www.biologicalpsychiatryjournal.com/article/S0006-3223\(13\)00623-9/abstract](http://www.biologicalpsychiatryjournal.com/article/S0006-3223(13)00623-9/abstract)). Moreover, I investigated the effects of short, multi-modal "modern-life-like" stress on AD pathogenesis, and its implications to synaptic plasticity and cognitive function. These studies are pioneering as I have provided, in great detail, the molecular determinants by which stressful events that we suffer during our daily lives likely affect AD pathogenesis and cognition. Overall, my study suggests that multi-modal stress, recapitulating salient features of modern-life conditions, promotes synaptic and memory loss and accelerates AD pathogenesis (Please, see the following comment:

<https://vpn.nacs.uci.edu/+CSCO+1h756767633A2F2F62617976617279766F656E656C2E6A7679726C2E70627A++/doi/10.1111/jnc.13210/abstract>).

Most recently, I have turned my attention to another prominent Alzheimer's co-morbidity, diabetes mellitus. Patients with diabetes have a significantly higher risk of developing Alzheimer's disease. As such, I have sought to study the molecular relationship between these disorders. Because most work on the relationship between Alzheimer's and diabetes has focused on the role of amyloid, I decided to study the under explored role that tau plays as a mediator induced by diabetes. This project has enabled me to generate several novel transgenic models, including studying the role of type 1 diabetes in tau null mice, where I made the critical discovery that the cognitive deficits associated with diabetes are critically dependent on tau⁸. The current proposal enables me to build upon this exciting preliminary data and investigate whether type 2 diabetes induces cognitive dysfunction also requires tau. With the newly developed animal models, I will elucidate the underlying molecular mechanisms by which type 1 and 2 diabetes impacts cognition and impairs synaptic plasticity. Currently, I am collaborating with Dr. LaFerla at UCI to develop this project.

Bibliography.

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