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Education

Ph.D. Utrecht University
Biochemistry

B.Sc. Basque Country University
Chemistry

Biography

Originally a chemist Dr. Ubarretxena obtained his PhD in Biochemistry in the center for Biomembranes and Lipid Enzymology (CBLE) at Utrecht University in The Netherlands. His PhD work centered on the biochemical and structural characterization of outer membrane phospholipase A. He went on as a postdoctoral fellow to Yale University to study the biophysics of biological membranes in the laboratory of Don Engelman. Thereafter he moved to the MRC-LMB in Cambridge as an EMBO postdoctoral fellow to work on the structure determination of multidrug transporters using high-resolution electron microscopy in the laboratory of Richard Henderson. He is currently an assistant professor at Mount Sinai School of Medicine working on the molecular mechanisms leading to neurodegenerative diseases, with a focus on Alzheimer and Parkinson disease. He is an expert in the study of membrane proteins and in the application of electron microscopy to protein structure determination. He is a member of several scientific societies and recipient of a National Science Foundation CAREER award.

Research

Our research focuses on unraveling the molecular etiology of neurodegenerative disorders. We employ high-resolution electron cryomicroscopy to determine the structure of proteins and then integrate this structural information with mechanistic and functional studies. Our long-term aim is to learn how to modulate protein function and open new therapeutic avenues in neurodegeneration. A main focus of our research is Alzheimer disease (AD). Amyloid β-peptides (Aβs), which are components of the senile plaques involved in AD, are produced from amyloid precursor proteins (APP) by an intramembrane cleavage catalyzed by the membrane protein γ-secretase. The precise sites of intramembrane cleavage are key for the pathogenicity of Aβs, as the longer peptide Aβ42 - relative to the Aβ40 species - is prone to aggregation. Our goal is to gain functional, mechanistic and structural insights into the production of Aβs by γ-secretase. To this end we are using single-particle 3D reconstruction techniques and crystallographic approaches in combination with biochemical assays.

Our expertise in high-resolution electron cryomicroscopy has allowed us to establish collaborations with investigators at Mount Sinai School of Medicine. For example we have been collaborating with the laboratory of Dr. Zhenyu Yue (Dept. of Neurology and Neuroscience) on the structural characterization of leucine reach repeat kinase 2 (LRRK2). The *LRRK2* gene has attracted intense attention, due to the fact that point mutations in *LRRK2* constitute the most common cause for autosomal-dominant PD. The *LRRK2* gene encodes a 286 kDa multi-domain protein characterized by an unique

modular architecture, with a GTPase a kinase located in the same molecule. We are using single-particle 3D reconstruction techniques to gain structural insight on full-length and catalytically active LRRK2 purified from recombinant mouse brain.

Our laboratory has also a strong commitment to the development of electron crystallography of membrane proteins. In collaboration with Dr. Stokes at NYU we have recently developed a pipeline for screening of 2D membrane protein crystallization trials, including a 96-well dialysis block for comprehensive screening of crystallization conditions, a 96-grid negative staining platform for preparing electron microscopy samples, and a robot for automated insertion and imaging of specimens. We are using these innovative tools to discover crystallization conditions for a variety of targets. Using this pipeline, we hope to obtain 2D membrane protein crystals suitable for atomic resolution structure determination by electron cryomicroscopy.

Publications

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