

PROJECT SUMMARY (See instructions):

Alzheimer's disease (AD) is a devastating neurodegenerative disorder for which there is not cure or efficient treatment. Although much research has been done over the past decades to understand the pathogenesis of AD, we still are not certain about the specific role of the various abnormalities detected in the brain of patients. Furthermore, many of recent clinical trials with drugs that showed beneficial effects in animal models have failed to demonstrate improvements in patients. Numerous in vitro and in vivo models have been created to attempt understanding the molecular bases and mechanisms of AD pathology. Perhaps, the most useful models are genetically modified mice over-expressing the human version of proteins harboring mutations associated to familial AD. Despite these models have been very useful to understand different aspects of AD, they are rodents modeling a human disease, and there are several important features that they cannot mimic. The main goal of this project is to develop new animal models of AD by grafting into the mouse brain, human derived cells from healthy individuals, as well as from AD patients affected by inherited and sporadic forms of the disease. Our working hypothesis is that chimeric mice harboring human nerve cells will reproduce the complete cerebral abnormalities observed in AD patients. Thus, chimeric mice may be more relevant and predictable models of AD and may become great tools to investigate the molecular bases of neurodegenerative processes, discover new pharmaceutical targets and biomarkers, and the development of new drugs to treat or even prevent the onset of the disease.

To reach this goal and test the hypothesis, we will perform the following specific studies: 1. Generation, optimization and characterization of mouse chimeras harboring human nerve cells. For this purpose, mouse embryos will be injected with GFP-labeled human induced pluripotent stem cells (iPSCs) or neural precursors. A detailed characterization of human cells' survival, integration, differentiation and functional activity will be done using histological, biochemical and electrophysiological techniques. 2. Generation and characterization of chimeric mice harboring nerve cells from patients affected by sporadic and inherited AD. The plan for this aim will be producing a model that recapitulates many of the pathological abnormalities associated to AD in the context of a wild type mouse. For this purpose, we will introduce human nerve cells derived from patients affected by sporadic and inherited forms of AD into wild type mouse embryos. The development of AD brain abnormalities without the need for artificial overexpression of human transgenes, but purely originating from human nerve cells may provide a more complete and relevant animal model for AD.

The findings generated in this project may lead to the production of more complete, relevant and predictable animal models of AD. These animals may represent an excellent tool to investigate the molecular bases of the disease and play a key role in the development of much needed efficient treatments. The data generated in this project may have a profound impact to understand the specific biology of human neurons and may be useful to develop new and improved models for various brain diseases.

RELEVANCE (See instructions):

In this project we propose to develop chimeric mice harboring human nerve cells derived from either control individuals or patients affected by sporadic or inherited forms of AD as a more relevant and predictable model for this disease. This project emerges from the collaboration between two researchers hosted at UT Health Science Center in Houston: Dr Brian Davis, an expert on stem cells technologies who has available all the facilities, resources and expertise to work with stem cells and Dr Claudio Soto, an expert in neurodegenerative diseases associated to the cerebral accumulation of misfolded protein aggregates, who has been working for the past two decades on the molecular basis of Alzheimer's disease and related brain disorders. Although Dr Davis does not currently work in brain diseases, he has a long-term experience working with stem cell technologies and has recently implemented in his lab the generation of induced pluripotent stem cells (iPSCs) from adult somatic cells. The combination of the expertise from these two investigators to attempt the generation of new animal models that may reproduce the human brain biology and disease in a more accurate manner, fits very well with the intent of the UT Brain program. The findings generated in these studies may serve as a tool for research in many different areas of brain physiology and pathology.