A CIRM Disease Team to Develop Allopregnanolone for Prevention and Treatment of Alzheimer's Disease

Grant Award Details

A CIRM Disease Team to Develop Allopregnanolone for Prevention and Treatment of Alzheimer's Disease

Grant Type: Disease Team Therapy Planning I

Grant Number: DR2-05410

Investigator:

Name:	Roberta Brinton
Institution:	University of Southern California
Type:	PI

Disease Focus: Alzheimer's Disease, Neurological Disorders

Award Value: $107,961

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Progress Reports

Reporting Period:	Year 1
View Report	

Grant Application Details

Application Title: A CIRM Disease Team to Develop Allopregnanolone for Prevention and Treatment of Alzheimer's Disease

Public Abstract: Alzheimer's disease (AD) is now a nation-wide epidemic and California is at the epicenter of the epidemic. One-tenth of all people in the United States diagnosed with AD live in California. In the US, 5.4 million people have AD and another American develops AD every 69 seconds. No therapeutic strategies exist to prevent or treat AD. And the situation is worse than expected. Results of a recent two year clinical study show that the currently available medications for managing AD symptoms are ineffective in patients with mild cognitive impairment or mild AD.

We seek to develop a small molecule therapeutic, allopregnanolone (APα) to prevent and treat AD. APα promotes the ability of brain to regenerate itself by increasing the number and survival of newly generated neurons. The APα-induced increase in newly generated neurons was associated with a reversal of cognitive deficits and restored learning and memory function to normal in a preclinical mouse model of AD. Further, APα reduced the amount of AD pathology in the brain. Importantly, when given peripherally either by injection under the skin or applied topically to the skin, APα was able to enter the brain to increase the generation of new neurons. The unique mechanism of APα action reduces the risk that APα would cause proliferation of other cells in the body. Because APα was efficacious in both pre-pathology and post-pathology stages of AD progression, APα has the potential to be effective for both the prevention of and early stage treatment of Alzheimer's disease. Further, APα induced neurogenesis and restoration of cognitive function in normal aged mice suggesting that APα could be efficacious to sustain cognitive function and prevent development of AD in a normal aged population. In other clinical studies, APα has been proven safe in animals and humans and in both men and women. Together, these findings provide a strong foundation on which to plan a clinical trial of APα in persons with prodromal and diagnosed Alzheimer's disease.

To plan for a Phase I-IIa clinical trial to determine safety, dosing and clinical efficacy, we have assembled an interdisciplinary team of clinicians, scientists, therapeutic development, regulatory, data management and statistical analysis experts. The objectives of this proposal are to: a) develop allopregnanolone as a therapeutic for Alzheimer's disease; to plan an early clinical development program for its use as a neurogenesis agent; b) file a complete and well-supported IND with the Food and Drug Administration (FDA); c) complete phase I/IIa clinical studies to evaluate safety, biological activity, and early efficacy in humans; and (d) complete a phase II clinical trial that will evaluate efficacy and lead to larger multisite clinical studies of efficacy.

Statement of Benefit to California:	California is at the epicenter of the epidemic of Alzheimer's disease (AD). Nationwide there are 5.4 million persons living with AD. Ten percent or over half a million Californians have AD. Among California's baby boomers aged 55 and over, one in eight will develop AD. It is estimated that one in six Californians will develop a form of dementia. By 2030 the number of Californians living with AD will double to over 1.1 million. While all races and ethnic groups and regions of the state will be affected, not all regions within California will be equally affected. Los Angeles County has the greatest population in the state and thus will be the true epicenter of the Alzheimer's epidemic in California.

Alzheimer's is a disease that affects an entire family, community and health care system. Nation-wide there are nearly 15 million Alzheimer and dementia care givers providing 17 billion hours of unpaid care per year. Total costs for caring for people with AD, totals $183 billion per year. California shouldered $18.3 billion of those costs and most of those costs were born by persons and health care services in Los Angeles County. Because of the psychological and physical toll of caring for people with Alzheimer's, caregivers had $7.9 billion in additional health care costs. Proportionally that translates into $790 million of health care costs for Californians. In total, California spent over $19 billion per year for costs associated with Alzheimer's disease. Multiple analyses indicate that a delay of just 5 years can reduce the number of persons diagnosed with Alzheimer's by 50% and dramatically reduce the associated costs.

We seek to develop a small molecule therapeutic, allopregnanolone (APα) to prevent and treat AD. APα promotes the innate regenerative capacity of the brain to increase the pool of neural progenitor cells. The APα-induced increase in neurogenesis was associated with a reversal of cognitive deficits and restored learning and memory function to normal in a preclinical mouse model of AD. Further, APα reduced the development of AD pathology. APα crosses the blood brain barrier and acts through a mechanism unique to neural progenitor cells and thus is unlikely to exert proliferative effects in other organs. Because APα was efficacious in both pre-pathology and post-pathology stages of AD progression, APα has the potential to be effective for both the prevention of and early stage treatment .

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