SALK INSTITUTE
FOR BIOLOGICAL STUDIES

David Schubert, Professor
Cellular Neurobiology Laboratory –CNB-S
Tel 858-453-4100 Ext. 1528
e-mail: schubert@salk.edu

March 16, 2015

Dear ICOC Committee,

There are over 600,000 Alzheimer's disease (AD) patients in California, and AD is the third leading cause of death. The social and economic cost is enormous, there is no effective treatment that halts disease progression, and the number of patients is expected to double in the next twenty years. With the intent of developing a small molecule drug for the treatment of AD, I am currently completing a CIRM Early Translational Research Grant.

The goal of the Early Translational project was to create a drug candidate that prevents and perhaps reverses the progress of AD. Development of this drug candidate was based upon its ability to stimulate the production of new nerve cells from human stem cells and, at the same time, protect the new cells from the toxic environment of AD brain tissue that results in the death of the existing nerve cells.

It should be pointed out that this is a very novel approach to AD drug discovery and, as far as I know, we are the only laboratory that is taking this approach. Simply replacing dying or dead nerve cells is not going to work for AD treatment unless the new nerve cells are protected from the harmful AD environment. In addition, because our drug candidate is a small molecule, the FDA review process is very straightforward. Moreover, once our drug candidate passes the initial FDA phase 1 clinical trial, new FDA rules will allow for the fast tracking of this drug candidate into large numbers of patients

As outlined in a series of Progress Reports, this project has been extremely successful. We have synthesized and screened over three hundred new compounds. Of these, one new AD drug candidate is neurogenic for human cells, is very neuroprotective, and has much better pharmacological properties than any of its precursors. The drug candidate, called CAD-031, was recently tested in two mouse AD models, one for preventing the disease and another for reversing the AD pathology in old AD mice. CAD-031 was exceptionally effective in both models. It is the only AD drug candidate that is neurogenic for human cells, very neuroprotective, and is able to reverse AD symptoms in old mice. CAD-031 is, as far as I know, the only viable AD drug candidate that was developed on the basis of human ES stem cell technology, and we believe it to be the best candidate in the AD drug 'pipeline'.

Based upon these results I applied for a CIRM Preclinical Development Award which I believed was a logical extension of our previous grant and would allow for the completion of the necessary experiments to move our drug candidate into the FDA-required toxicity program that must be done in FDA-approved facilities. However, the score of the application was 71, below the stated funding level of 75 but hardly a statistically significant difference. This was a major setback for our lab and, I believe, the AD field as well because it is our only source of funding for the development of a novel and very promising AD drug candidate. The only viable

alternative for labs at Salk is NIH that is funding only an extremely small percentage of its AD applications and is very biased against innovative drug discovery such as the work supported by the CIRM Early Translational Research program.

Importantly, the overall enthusiasm for our CIRM Preclinical Development Award grant proposal was excellent and, in addition, we have exciting, new information that was not available when the application was submitted. First, we have now shown that CAD-031 is highly effective at reversing the memory deficits in a reversal model of AD. In this experiment, AD transgenic mice were allowed to age until they developed AD symptoms and then were left untreated or treated for three months with CAD-031. The untreated mice showed significant memory deficits whereas the mice treated with CAD-031 performed as well as control, non-AD mice in the memory tests. This is very important because AD patients will be treated after they develop disease symptoms but most AD drug discovery has been based on testing in animal models of AD symptom prevention not symptom reversal. Second, we have determined the likely molecular basis underlying the ability of CAD-031 to stimulate the production of new nerve cells.

We believe that the very substantial data outlined in our CIRM Progress Reports strongly argue that CAD-031 is a strong and viable candidate for the treatment of AD and that our CIRM Preclinical Development Award application should be funded. The experiments outlined in this application are absolutely necessary in order to move CAD-031 into patients. As noted above, there are currently no drugs that halt AD progression so the potential benefits of moving CAD-031 into human trials are enormous. Furthermore, since CAD-031 was developed on the basis of human stem cell technology, it would be one of the early CIRM projects to make it into the clinic. However, to accomplish this goal we need continued CIRM funding for our laboratory. Given the prior investment of CIRM in this research program, and the significant burden of billions of dollars that will be spent on AD care absent an effective therapy, we ask that the ICOC fund this CIRM Preclinical Development Award application thereby allowing the advancement of the highly promising AD drug candidate CAD-031 through the final stages of pre-clinical development.

Respectfully,

David Schubert

10010 North Torrey Pines Road, La Jolla, CA 92037-1099
Tel 858.453.4100 x1528
www.salk.edu