MEMORANDUM

Date: August 24, 2012

From: Alan Trounson, PhD
CIRM President

To: Independent Citizen's Oversight Committee

Subject: Extraordinary Petition for Application DR2-05410

Enclosed is a letter from Dr. Roberta Brinton of the University of Southern California, an applicant for funding under RFA 10-05, CIRM Disease Team Therapy Development Research Awards. This letter was received at CIRM on August 23, 2012. As the Extraordinary Petition Policy normally refers such petitions to the ICOC meeting that first considers the application, we are forwarding the letter as correspondence to the board rather than a petition that was pursuant to the policy.

Dr. Roberta Brinton
R. Pete Vanderveen Chair in Therapeutic Discovery and Development
Professor Pharmacology and Pharmaceutical Sciences, Biomedical, Engineering & Neurology
Norris Foundation Laboratory for Neuroscience Research
Director of the USC STAR Program for Science Education
Director SC CTSI Preclinical Translation and Regulatory Support

Jonathan Thomas, Ph.D., J.D. Chair Independent Citizens' Oversight Committee
Alan Trounson, Ph.D. CIRM President and Chief Scientific Officer,

August 22, 2012

Dear Dr. Thomas and Dr. Trounson:

We respectfully submit an Extraordinary Petition to the CIRM Governing Board in consideration of our grant application DR2-05410 "Allopregnanolone as a Regenerative Therapeutic for Prevention and Treatment of Alzheimer's Disease." We are submitting the petition at this time as we are new to the CIRM ICOC process and after listening to the July 26 ICOC meeting deliberations now understand that the petition process allows the ICOC to further consider our proposal. We noted that the proposal scored one point above ours and another two points below ours, each utilized the extraordinary petition strategy to gain ICOC review which resulted in funding approval in the former, and reconsideration in the latter instance.

We appreciated the reviewers' very favorable overall evaluation of our proposal. The goal of our project is to determine the safety and efficacy of **allopregnanolone (APα)** as a regenerative therapy for the treatment of **Alzheimer's disease (AD)** through a dose-finding and tolerability study, followed by a proof of concept phase 2a. The reviewers recognized that we achieved therapeutic development readiness based on APα IND-enabling preclinical efficacy and pre-IND meeting with that FDA that resulted in: 1) inclusion of two preclinical safety studies to address FDA's specific requirements for AD therapeutics; 2) FDA permission to cross-reference the Rogawski APα IND 111085 and 3) FDA acceptance of current human safety data for APα.

Reviewers acknowledged our well-qualified and experienced team; our excellent track record to support the studies and the clinical development program; our strong collaborators and scientific advisory board which include Dr. Weiner, PI of the NIA Alzheimer's Disease Neuroimaging Initiative, Dr. Reiman an internationally recognized imager, geneticist and clinical trialist in AD, Drs. Steven Paul and William Potter, both former VPs of research at Lilly and Merck respectively, with extensive pharmaceutical experience in Alzheimer's therapeutics; and a CA contract research organization that has conducted Alzheimer's clinical trials since 1986.

Very importantly, the reviewers agreed that we met CIRM's condition of the planning grant award. Below we address the three issues of particular concern to reviewers: 1) responsiveness to RFA; 2) sedation and memory impairment and 3) commercialization potential. In addition, we provide an update on FDA approval and stability of our proposed Allopregnanolone / Captisol formulation. We believe that the information provided below addresses reviewers concerns and demonstrates that we continue to be therapeutic development ready.

1) "The responsiveness of this proposal to the RFA is marginal." Reviewers affirmed that we provided compelling preclinical evidence for APα's induction of neurogenesis and its association with restoration of learning and memory function to normal in preclinical models of both genetically determined Alzheimer's disease and aging (the greatest risk factor for Alzheimer's). Reviewers were concerned, however, that in humans, therapeutic efficacy of APα could not be *solely attributed to neurogenesis*. In part, we agree with the reviewers as we posit that APα is inducing three regenerative responses in brain including 1) regeneration of neurons; 2) regeneration of white matter and 3) regeneration of synaptic circuitry. In brains of Alzheimer's mouse model, regeneration of neurons was evidenced by neurogenesis, regeneration of white matter was evidenced by increased markers of white matter and increased white matter volume and regeneration of synaptic circuitry was evidenced by restoration of both learning and memory function. To address the issue of whether APα promotes regenerative responses in the human Alzheimer's brain, we specifically included three indicators of regenerative efficacy in our clinical trial design (p10 Rationale, p33-34 Clinical Protocol Synopsis Study Objectives & Endpoints, p242-244 MRI procedures).

1. Hippocampal (segmented) volume as indicator of regeneration and survival of neurons.
2. White matter volume as an indicator of regeneration of white matter which must occur via oligodendrocyte progenitors, i.e., the cells that regenerate myelin in brain.
3. Resting default mode network as an indicator of regeneration of synaptic connectivity.

Collectively, our preclinical data indicate that APα functions as a regenerative small molecule that promotes the generation and survival of newly generated neurons in the hippocampus, induces markers of white matter generation, restores both learning and memory function indicative of regeneration of synaptic connectivity required for these cognitive functions. Thus, under our established optimal regenerative treatment regimen of once per week exposure, APα meets the criteria for a small molecule brain penetrant regenerative therapeutic that promotes the endogenous regenerative responses in brain.

2) Concerns regarding sedation: For therapeutic development of APα, we definitively established and published in highly rated peer-reviewed journals the APα doses and treatment regimens that promote neural regeneration and restore cognitive function. Further, we also determined and published or referenced doses and treatment regimens that inhibit neurogenesis and cognitive function. ***APα is regenerative at doses that are non-sedative and administered once per week.*** We and others have shown that, APα administered in regimens typical for non-regenerative drug therapies, constant infusion for 1-2 months or daily injection for 3 months *inhibit regeneration and cognitive function*. Thus, we have established the parameters of and conditions for APα-induced regenerative responses.

We repeatedly stated throughout the proposal (34 relevant entries) that ***our clinical studies would only use non-sedative doses of APα***. Further, our PK/PD modeling, preclinical bridging and toxicity studies are designed to ensure non-sedative dosing. To safeguard study participants and to optimize the potential neurogenic effect, our team specifically designed a multiple ascending dose study in an MCI aged target population to establish a dose range of APα from non-sedative to mildly sedative ***with declared use of non-sedative dose in our proof of concept efficacy trial***. Throughout our proposal 1) we defined the non-sedative dose of APα as determined by preclinical analyses, PK/PD modeling and previous human exposure, 2) stated that ***we would only use a non-sedative dose of APα in our clinical trials***; 3) emphasized that we would actively monitor patients for sedation and 4) included sedation in our Go/No Go decision matrix for advancing to phase 2b clinical proof of efficacy trial.

Given the concern of reviewers regarding sedation-induced memory impairment, it is important to note, as we did in the proposal, that the single report of "memory impairment" in humans occurred 10 minutes following injection of a *sedative dose* of APα and on *only one* of three tests of memory, word list recall / episodic memory. The magnitude of the "memory impairment" was less than 1 word, 10 minutes following infusion of placebo or APα: placebo = 0.4 word decrement vs APα 0.6 word decrement. *No effect of a sedative dose of APα occurred on either semantic or working memory tests* (Kask et al., 2008; Table 3). Based on current clinical standards, a difference of less than one word 10 minutes following a sedative dose of APα is not considered clinically meaningful particularly since there was *no effect of APα on either semantic or working memory tests at the same time point.*

3) Commercialization Potential: Commercial and IP protection assessment conducted by Sage Therapeutics indicate that APα can be a viable commercial product for the prevention and treatment of Alzheimer's Disease based on layers of several patents that cover: method of use, specific dosage regiment(s), method of delivery, and composition of formulation. The commercial viability of an APα product for AD has been evaluated by a leading CNS biotech company – SAGE Therapeutics, Inc. – and based upon a favorable evaluation by SAGE the company is now actively working with the CIRM Disease Team on the APα product.

SAGE Therapeutics who has obtained an exclusive license for arguably the most effective formulation of APα called Captisol. The formulation challenge of APα provides a significant barrier to entry against generic forms of APα, as the two other potential formulations of APα (Trappsol and Intralipid) are significantly inferior to Captisol due to safety issues. The Captisol formulation has a family of patents that cover its composition *that cover the formulation into 2030*, and SAGE has obtained an exclusive license for Captisol to formulate APα (see Sage Therapeutics letter and patent list).

While APα's structure has been known, as well as its ability to modulate $GABA_A$ channels, what was not known is the potential for APα to induce proliferation of neural progenitor cells and improve cognition in preclinical Alzheimer's model making it first in its class as a regenerative therapeutic for AD. Brinton and USC have filed a method of use patent (US patent application # 0105646) to cover a method of reversing learning and memory deficits from a neurodegenerative disorder using APα. In addition to a method of use patent, Brinton and USC have also filed a patent that covers the appropriate regenerative treatment regimen for APα to treat neurodegenerative diseases including Alzheimer's (US patent application # 0204192). There are numerous examples of successful commercial products in which composition of matter intellectual property has not existed, but alternative method of use, dosage, and formulation intellectual property has enabled appropriate protection. For example, in the Alzheimer's disease marketplace one of the most successful drugs – Namenda (Memantine) which sold over $1B in 2010 – had its structure disclosed in 1968, but Forest Labs was able to obtain method of use intellectual property that precluded generic companies from entering into the market. Another example is progesterone that is being developed for treatment of Traumatic Brain Injury (TBI). While there is no composition of matter intellectual property for progesterone, Emory was able to obtain patents that cover the use, specific dosages and specific formulations of progesterone for TBI. This patent protection led to licensing to BHR Pharma after a phase 2 clinical trial showed efficacy in TBI, and now BHR Pharma has funded and is in the midst of performing a 1,000 patient phase 3 clinical trial (SYNAPSE).

To summarize, APα can be a viable commercial product for the treatment of Alzheimer's Disease based on an intellectual property strategy that will include layers of several patents that cover: method of use, specific dosage regimen(s), method of delivery, and composition of formulation. SAGE Therapeutics, a leading CNS biotech company is working with the CIRM team to advance this program.

Update: Through our collaboration with Dr. Michael Rogawski and Dr. Gerhard Bauer of the CIRM GMP UC Davis facility, the APα / Captisol formulation for the proposed CIRM clinical trial will be the same as that used for the Department of Defense FDA approved trial of APα for traumatic brain injury. This formulation that meets USP 388 has been approved for use under the Rogawski FDA IND 111085 and is in production at the CIRM UC Davis GMP Facility.

Fiscal Consideration: While we have requested sufficient funds to 1) conduct FDA mandated Alzheimer's disease specific preclinical analyses, 2) a Phase 2a multiple ascending dose finding study and 3) a Phase 2b therapeutic efficacy study, it is important to note that we have very clearly specified Go / No Go criteria for advancement to each therapeutic development phase. As per CIRM practice, investment in the project will be milestone and Go / No Go criteria driven. Thus, investment in this project will be sequential and if all milestones are met will consume the requested budget whereas if Go criteria are not met, the least costly aspects of the project (preclinical and Phase 2a study) will be conducted *but not the most costly*, Phase 2b study.

We thank the CIRM Independent Citizens' Oversight Committee for their consideration of our petition and express our gratitude for their consideration to fund CIRM DR2-05410 that addresses an urgent health and financial issue for California. Alzheimer's remains a devastating illness without therapeutics to prevent, delay or cure the disease. The latest in a long list of failed AD clinical trials against a single target, β–amyloid, attests to the ***critical and urgent need for a novel innovative regenerative therapeutic to cure Alzheimer's disease.***

Sincerely,

Roberta Diaz Brinton, Ph.D.

Lon S. Schneider, M.D.