MEMORANDUM

Date: July 20, 2012

From: Alan Trounson, PhD
CIRM President

To: Independent Citizen's Oversight Committee

Subject: Extraordinary Petition for Application DR2-05426 (**LATE**)

Enclosed is a petition letter from Dr. Stanley F. Nelson and Dr. M. Carrie Miceli of University of California Los Angeles, an applicant for funding under RFA 10-05, CIRM Disease Team Therapy Development Research Awards. This letter was received at CIRM on July 19, 2012 and we are forwarding it pursuant to the ICOC Policy Governing Extraordinary Petitions for ICOC Consideration of Applications for Funding.

We thank the ICOC for the opportunity to provide this Extraordinary Petition for DR2A-05426 "Combination Therapy to Enhance Antisense Mediated Exon Skipping for Duchenne Muscular Dystrophy (DMD)". A single effective therapy for DMD, an otherwise fatal and relatively common childhood onset genetic muscular disease, would transform the field and bolster the CIRM portfolio in an area of large unmet medical need. As noted by the scientific reviewers, we have assembled an outstanding team including scientists, physicians, clinical trialists, preclinical toxicologists and regulatory experts [UCLA, Sarepta Therapeutics (formerly AVI) and SRI and collaborators], with the necessary regulatory knowledge concerning the requirements for an IND application and conduct of a clinical trial.

It is important to note that the PI and co-PI of this proposal, Drs. Nelson and Miceli, write not only as a physician scientist and scientists running laboratories dedicated to finding treatments for DMD, but also as parents of a young boy affected by DMD. This unusual situation enables our unique perspective of the state of the field, the realistic pace of science, the urgency of the unmet need, and a clear understanding of the impact of DMD on families and the costs to the state of California in the absence of a transformative treatment. Our experience provides extra incentive that the studies be performed safely in an efficient and rapid time frame.

The review committee recognized the responsiveness of this proposal to the RFA, the importance of effective therapies for DMD, the viability of the proposed strategy, and the therapeutic development readiness, yet a motion to elevate it to tier 1 did not carry. We clarify information regarding the five key issues that were articulated as critical for the motion to carry.

We are in a highly advantageous position to directly address reviewer concerns because AVI has already addressed similar issues with the FDA during the course of successfully obtaining IND approval to take the single AO agent through phase I-IIb clinical trials for exon skipping in DMD. We focus on these key criticisms and highlight the tremendous opportunity this project provides to the CIRM for leading the nation in defining a pathway for personalized genetic medicine that takes full advantage of and requires the use of patient derived stem cells for drug discovery, preclinical assessment and clinical trial design.

[1]. ***Absence of clinical benefit for the single agent*** *- "One reviewer cited the Phase 2b results and recommended against funding this program until the absence of functional effect with the single AO agent is delineated."* The rationale for moving the combination therapy forward now, based on available clinical trial data, is described in our application on pages 6-8 (citing refs 6, 7, 16, 17, 20, 27, and 36) and is restated here. Most boys with DMD have 0% of normal dystrophin, while boys/men who are very mildly affected with Becker muscular dystrophy (BMD) express in-frame *DMD* mutations similar to those achieved by exon skipping, and have at least 40% of normal dystrophin expression levels. In BMD, there is a strong correlation between higher dystrophin expression and milder disease progression. The published data indicate that a minimum of 10% of normal levels of dystrophin are needed for any observed benefit and 30-40% of normal dystrophin levels are necessary to fully protect skeletal muscles. All of the single agent AO data from AVI/Sarepta and from GSK/Prosensa in human DMD trials to date indicate that the dystrophin restoration by AO alone is on average 8% of normal, with a range from 0-17%. Available clinical trial data strongly argue that optimal dystrophin levels and functionality will not be achieved in all patients.

Our second generation combined therapeutic promises to lower the extremely high projected cost of treatment and/or enhance the levels of dystrophin expression achieved (and thus the degree of functional enhancement). This is worth pursuing regardless of whether the AO single agent trials show a degree of functional improvement or not. Should single agent AO therapies prove more beneficial and cost effective than anticipated, obviating the proposed value of combination therapy, this program could be halted. Given the large unmet need in this population and the dire consequences of delaying the development of effective treatment by 2-3 years (to wait for definitive phase 3 studies), the "wait and see" attitude is not justified. Of note, the reviews already highlight that "At a minimum, a benefit would be a decrease in cost to treat with the single agent AO." Thus, even if the combination therapy is no more effective than

single agent therapy, it may result in significantly reduced costs to CCS/Medi-Cal and California.

[2]. ***The unknowns of the proposed combination product regarding immunogenicity.*** *- "The safety data for the single AO was judged incomplete for the proposed combination. Several examples were discussed: off-target effects of the AO should be evaluated in combination with the proposed drug; immunogenicity should be evaluated with repeat administration of the AO."* First, we included novel experiments in year 2 to assess 'off target' effects of AO with drug which rely on deep RNA sequencing of potential splice variants expressed in treated patient stem cell derived myotubes and other lineage cells, and indicated that these results will be used to guide additional off target assessment in animal models and human trials if indicated (on p 20 of application).

Second, since both the single agent AO and our combination therapy have the ability to produce novel dystrophin in boys who currently do not express dystrophin, a concern is whether an immune response will form to newly produced dystrophin (p 29). We explicitly highlight on page 20 the substantial immunogenicity data (including repeat administration) already performed by AVI/Sarepta in animal models using AO. Data from ongoing phase 1-2b exon skipping trials from AVI/Sarepta (including data from 1 year weekly dosing) and GSK/Prosensa (including 96 week extension study with repeat AO administration) already demonstrate persistent dystrophin expression in responders, and no induction of an immune response to AO or to dystrophin and actually a reduction in muscle inflammatory infiltrate. Thus, there is already ample evidence that AO as a single agent is not immunogenic. However, because there are additional immunogenicity concerns in the context of the combination therapy, especially in light of the possible increased efficacy, we agree with the reviewers that it would be prudent to add immunogenicity assays to assess antibody responses to AO and dystrophin and note that this can be readily done within the already proposed mouse and primate repeat-dose toxicology studies with minor rebudgeting. Immunogenicity assays are routinely performed by SRI and this addition will also address the reviewer requested pK/pD assessment.

We note that Myozyme, a recombinant protein used to replace the genetic deficiency that causes Pompe disease, leads to antibody production, which is manageable, and was not predicted in preclinical animal studies. Nonetheless, Myozyme has been a very successful product, receiving regulatory approval worldwide. Of note, project collaborator, Dr. Kaye (Sarepta), played a key role in gaining Myozyme approval while at Genzyme and is thus well experienced in such matters. Similarly, the immune response to dystrophin is not adequately modeled in non-human models. Thus, an important time to evaluate immunogenicity of novel dystrophin protein is during early human clinical trials, which is included as an explicit aspect of the Clinical Protocol Synopsis (p 29).

[3]. ***Relevance of the proposed model****: - "Several reviewers identified an excellent preclinical model that is often used for DMD, and noted that it is not introduced into this program. This is important because structural and physiologic endpoints should be assessed in a relevant weight-bearing model."* We are well aware of other mouse and other larger 'weight-bearing' animal DMD models, such as the Golden Retriever model, which more closely mimic the human physiologic defects of DMD. However, these are not relevant here for AO or combination therapy pre-IND studies for which dystrophin expression functions as a biomarker. The dog model is especially complicated in the context of our proposed studies, given that two exons must be skipped in order to restore the *DMD* reading frame, thus requiring a combination of two AOs (non-equivalent to the AOs in the combination therapy). Therefore, the dog model will not accurately model efficacy, dosing or toxicity of the combined therapeutic for eventual clinical trials. Moreover, the dog model would incur substantial expense and actually slow the program due to the extraordinary cost of breeding and caring for such ill dogs, and genetic variability of the offspring that influences severity. While the proof of principle that exon skipping in the dog model can restore dystrophin (and possibly function) is published, this model is underpowered to detect changes in efficacy. AVI/Sarepta took the AO single agent through DMD phase 1 to 2b studies using the mdx mouse model and did not use the dog model, nor did the FDA request

it or other alternate disease models for their program (see table page 15-16 of application). We project that the FDA will not require an alternate disease model for IND approval of the combination therapeutic; however, we will gladly raise this issue with FDA in a pre-IND meeting.

A strength of our proposal is the development of human DMD preclinical models that better model outcome than animal models in the context of personalized genetic therapeutics; where particular AO sequences (and combination therapy) can be assessed against a variety of clinically relevant patient mutations for efficacy of RNA skipping and rescue of BMD-like dystrophin proteins, and their capacity to restore the muscle membrane dystrophin glycoprotein complex (DGC). Restoration of dystrophin and the DGC are the only known biomarkers that strongly correlate with disease severity. Loss of dystrophin is both the proximate genetic cause of the disease and also the direct therapeutic target here (p 23). Patient stem cell derived muscle cultures will directly inform dosing and efficacy studies; whereas xenografts will enable DGC biomarker development and inform trial design to guide patient inclusion parameters.

[4]. ***Whether the proposed therapeutic would target critical cardiac pathology*** *- "A major flaw in the application was the absence of any data or discussion addressing whether this potential therapy would impact cardiac muscle, since most patients ultimately succumb to heart failure."* While cardiomyopathy is desirable to effectively treat, this statement is incorrect as only 20% of DMD patients succumb to heart failure; most patients die from complications of respiratory failure due to skeletal muscle and diaphragm weakness. The proposal does explicitly mention the potential impact of treatment on cardiomyopathy in the TPP (p 2-3). Preclinical data suggest that the combined therapeutic will not induce dystrophin expression in the heart, although this still needs to be proven. Nonetheless, the rationale for developing treatments that may only treat skeletal muscle is sound. In the DMD mouse model, restoration of dystrophin to diaphragm normalizes cardiac function in the absence of cardiac dystrophin restoration (Ref 26, p7). Preventative medications have proven to slow the onset of heart disease leading to recent inclusion of these medications within the current standards of care for DMD, and predicting that cardiomyopathy will be less of an issue in the future. Further, transplantation and cardiac assist devices provide additional routes to treat heart failure.

As parents, physicians and scientists, we reject the concept that a therapy must be able to directly influence the heart (or otherwise address all aspects of a disease process) to be worthwhile. Slowing the profound progressive skeletal muscle disease would greatly improve quality of life, potentially enabling self-feeding, toileting, ambulation, access to education, participation in the workforce, and reduce the enormous impact on family members who bear financial, physical and emotional burden of caring for affected loved ones. Because of skeletal muscle defects, most teens and adults affected by DMD need 24 hour care, often requiring parents to forgo participation in the workforce, driving many families into poverty and greatly increasing costs to the state (indicated in Statement of Benefit to California in our application). To stop the project based on the concern that heart failure may not be effectively treated by this combination therapy is wrong.

[5]. ***Timing*** *-"Several reviewers commented that progression to IND submission is slow, and were unclear on the rationale for the full four years required to file an IND."* Since the therapy is intended to be life long, the FDA will likely request longer-term evaluations, and since the therapy involves a combination, the necessary IND enabling experiments require consideration of a larger number of combined parameters. Here we have modeled the pre-IND studies after AVI's experience, where 12 weekly doses plus 4 weeks post therapy evaluation were requested for the single agent AO to gain approval for an IND. CIRM reviewers are most likely familiar with the shorter 4 week repeat dose studies typically needed for a single small molecule therapeutic. Additionally, we consider the combination product and indication qualifies it as a candidate for Fast Track designation by the FDA.

Our team is prepared to address any remaining ICOC concerns and are confident that there is a high likelihood that the proposed IND-enabling studies will result in a successful IND application and complete clinical trial readiness.