MEMORANDUM

Date: August 17, 2011

From: Alan Trounson, PhD
CIRM President

To: Independent Citizen's Oversight Committee

Subject: Extraordinary Petition for Application DR2-05346

Enclosed is a petition letter from Dr. John S. Adams of the University of California Los Angeles, an applicant for funding under RFA 10-05, CIRM Disease Team Therapy Development Planning Awards. This letter was received at CIRM on August 17, 2011 and we are forwarding it pursuant to the ICOC Policy Governing Extraordinary Petitions for ICOC Consideration of Applications for Funding.

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August 17, 2011

DEPARTMENT OF ORTHOPAEDIC SURGERY
DAVID GEFFEN SCHOOL OF MEDICINE AT UCLA
ORTHOPAEDIC HOSPITAL RESEARCH CENTER
BOX 957358
LOS ANGELES, CALIFORNIA 90095-7358

Jonathan Thomas, Ph.D., J.D., CIRM Chairman
Alan Trounson, Ph.D., CIRM President and Chief Scientific Officer

RE: **Extraordinary Petition for DR2-05346**: Regenerating Bone in Patients with Osteoporosis
Principal Investigator: John S. Adams, M.D. & Planning Leader: Chia Soo, M.D.

Dear Chairman Thomas, President Trounson and members of the ICOC:

Thank you for the opportunity to present this petition requesting ICOC support our CIRM Planning Award application. We also sincerely thank the reviewers for their useful feedback regarding our application. We carefully considered the reviewers' comments and feel compelled to clarify some misconceptions regarding our project. Our program involves development of a combination device, not a drug. Therefore, what follows is i) a brief overview of the crucial elements of our product, ii) a clarifying, point-by-point response to each of the comments rendered by the reviewers, iii) an explanation of the differences in FDA requirements for device versus drug approval and iv) the current status on our combination device pathway to approval.

Overview. Our product has three components as noted in the application: 1) a mesh sack made out of suture material (already FDA-approved for human use) that will hold the allograft bone particles in place when deployed to the interior of a crushed vertebral body; 2) an allograft of devitalized human bone chips (also already FDA-approved for human use); and 3) the NELL-1 protein bound to already FDA-approved ß-tricalcium phosphate carrier particles (ß-TCP). Combination of these three, FDA-approved elements in combination with the stem cell-directing NELL-1 protein into a device safe and suitable for use in humans is the focus of our disease team investigational device exemption (IDE) and premarket approval (PMA) efforts.

Responses to Reviewer Comments. Comment 1. *Compare biologic device against device material alone in the proposed clinical trial to show benefit of the protein biologic component*. The combination of the mesh (OptiMesh) and allograft is submitted but not yet approved by the FDA for the indication of vertebral compression fractures [see **page 10**]. As such, it would not be ethically permissible to test the mesh+allograft against our mesh+allograft+NELL-1 product in an FDA-approved clinical trial for vertebral compression fracture as any control (gold standard) used in such a head-to-head clinical trial has to be an already FDA-approved therapy for the tested indication. Furthermore, **Figure 4** on **page 13** of our application clearly shows that when implanted into the vertebral defect of osteoporotic sheep, the mesh+allograft+Nell-1 regenerates significantly more bone than does the mesh+allograft alone. Demonstration of device efficacy in a large animal model that closely simulates human vertebrae is an FDA requirement and a significant milestone that will accelerate our IDE-enabling studies.

Comment 2. *Control treatment ineffective in New England Journal of Medicine (NEJM) studies.* The two NEJM studies[1, 2] cited by the reviewer are not applicable to our present proposal as both studies describe vertebroplasty, injection of cement directly into the crushed vertebral body space, and use only pain relief as a primary outcome criteria. In contrast, our proposed control treatment is kyphoplasty, injection of cement after internal balloon inflation of the crushed vertebral body space; this is a distinctly different procedure than vertebroplasty in terms of both

indication and efficacy endpoints. Kyphoplasty is indicated for fracture reduction with vertebral height retention and pain relief as endpoints. Overall, fracture reduction and vertebral height maintenance by kyphoplasty better preserves spinal alignment to decrease overall back strain and provide better long term pain relief than vertebroplasty[3] and kyphoplasty efficacy has been demonstrated in randomized studies[4]. As a consequence, we have specifically designed our device to reduce fracture and restore vertebral height. It is also worth noting that the design of both NEJM studies generated significant controversy (see Letters to the Editor, NEJM 2009; 361:2097-2100) and that the NEJM findings were refuted in a later Lancet study with more robust experimental design with respect to inclusion criteria and patient numbers[5].

1. Kallmes, D.F., et al., The New England Journal of Medicine, 2009. **361**(6): p. 569-79.
2. Buchbinder, R., et al., The New England Journal of Medicine, 2009. **361**(6): p. 557-68.
3. Kumar, K., et al., Neurosurgery, 2010. **67**(3 Suppl Operative): p. ons171-88.
4. Wardlaw, D. and J. Van Meirhaeghe, Lancet, 2010. **376**(9746): p. 1031-3.
5. Klazen, C.A., et al., Lancet, 2010. **376**(9746): p. 1085-92.

Comment 3. *More detail needed on the novel biologic component of the device (production, attachment, incorporation)*. We appreciate this opportunity to clarify the details provided in the application. On **page 2** the proposal states *"rhNELL-1 is produced by a cGMP compliant Chinese Hamster Ovary (CHO) Research Cell Bank and lyophilized onto FDA-approved ß-tricalcium phosphate carrier particles (ß-TCP) to enhance biochemical stability and biological efficiency*." In addition, at the end of the quoted sentence, we also cited our previous publication [Li, W. *et al.* Delivery of lyophilized Nell-1 in a rat spinal fusion model. Tissue Eng Part A 16:2861-70, 2010] that describes in more detail how the cGMP-grade NELL-1-ß-TCP particles are produced, the release profile of NELL-1 from those particles and the cGMP-capable company already producing the NELL-1 protein for us (Aragen Bioscience, Morgan Hill, CA). With respect to NELL-1, the biologic component, the NELL-1 ß-TCP particles are simply mixed in with the allograft bone particles prior to installation as described in Li *et al.,* above; there is no need for "attachment" or "incorporation" of NELL-1 into the allograft.

Comment 4. *Direct contribution of the biologic component.* As noted in response to Comment 1, our NELL-1 biologic was significantly effective in a robust large animal model of established osteoporosis; before implantation of the device the sheep underwent not only ovariectomy but regular glucocorticoid injections and diet depletion of calcium and vitamin D accounting for an average 16% decrease in bone mineral density by dual-emission X-ray absorptiometry (DXA) scan. It should be noted that animal models of established osteoporosis are more rigorous than osteoporosis prevention models, as the biologic has to demonstrate bone anabolic (bone-building) effects. Using this rigorous model, we have since shown that a single application of the biologic component alone (NELL-1+ß-TCP) to the osteoporotic sheep vertebral bodies i) significantly increased bone mineral density ($p<0.001$) and ii) increased trabecular volume by 17.8% at 1 month ($p=0.021$) and by 31.9% at 2 months ($p=0.0001$). Lastly, on **page 13** we have reproducibly documented a potent effect of the NELL-1 biologic on bone formation in both sheep (**Figure 1**) and non-human primate (**Figure 2**) spine fusion models.

Comment 5. *Better define types and rates of adverse events observed with the combination of surgical mesh and the allograft.* It goes without saying that we will carefully document all adverse events that may arise. We should also reiterate another significant strength of our proposal (see Response to Programmatic Review below) that may have been underappreciated in review. We have already met with the FDA, and they have determined that our therapeutic is a combination device that will undergo the IDE and PMA process. This is because two of the major components of our biologic device (mesh and allograft) are already 510(k)-cleared by the FDA for use in humans. The fact that the surgical mesh and allograft components are based on predicate devices already in use in millions of patients is a major strength and safety feature of our proposal.

Comment 6. *Role of PI.* The PI, Dr. Adams, fills much more than just an administrative role in this program. His extensive experience in both the conduct and supervision of investigator-initiated experiments involving human subjects will be crucial to the conduct of the clinical studies proposed. In addition to his other delineated responsibilities, as a practicing member of the UCLA Osteoporosis Center and leading expert on human osteoporosis, the bone disease under study in this proposal, he will serve as the principal resource for identification, screening, recruitment and care of subjects in our Pilot/Phase 1 study.

Programmatic Review. *No programmatic reason to fund the application was proposed.* This proposal fills an important programmatic need for diversity in the CIRM Translational Portfolio. The goal of Proposition 71 is "the rapid advancement of research that could benefit millions of Californians." However, to reach the greatest number of people, the product has to be FDA-approved. Currently, all programs in the CIRM Translational Portfolio are either biologic license applications (BLAs) or new drug applications (NDAs); there are no PMAs.

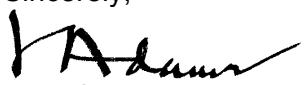
From concept to market, the typical BLA takes 7-10 years at a cost of $80-400 million; the typical NDA takes 12 to 15 years at a cost of $800 million to $1.7 billion. In contrast, the costs for a PMA approval are generally half that of a BLA and the time to market approval also shorter. This is because PMAs typically require only two phases of human clinical testing (Pilot and Pivotal studies) with significantly fewer total patient numbers (e.g., <500 patients) before product approval. In contrast, BLA/NDAs require three phases of clinical study (Phase 1, 2, and 3 studies) with significantly higher total patient numbers (e.g., 1000-35,000 patients) before product approval, especially if the product is intended for systemic administration. Thus, since our proposal is a PMA, it would add significant diversification to the CIRM portfolio and may accelerate general, widespread public access to a CIRM-funded product.

In addition, from a disease diversification standpoint, although there are osteoporosis-related applications in the CIRM Portfolio, there are no applications that address vertebral fracture reduction or vertebral height restoration to compressed vertebral fractures. Restoration of normal spinal alignment is critical to preventing progressive and debilitating spinal hyperkyphosis that can lead to decreased lung function, gastric distress, impaired gait, increased vertebral fractures, increased back pain and degenerative joint disease, poor quality of life, and increased death risk. Overall, our device provides a simple, efficacious, and safer solution to vertebral compression fractures than the current toxic, cement-based kyphoplasty or the less effective non-surgical therapy of bed rest, analgesia, and bracing. Moreover, long-term use of narcotic analgesics or anti-inflammatory drugs is poorly tolerated in the elderly. Narcotics may increase the risk of falls, while prolonged bed rest may lead to rapid deconditioning, as well as further bone loss.

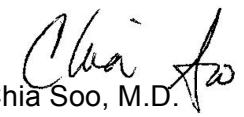
Where do we stand on the pathway to FDA approval? We already have i) a NELL-1 Research Cell Bank in a cGMP cell line ready for scale up to Master and Working Cell Banks, ii) established FDA-required large animal efficacy models, and iii) a defined two-phased IDE/PMA pathway that will be significantly shorter and less costly to implement than three-phased BLA/NDA products.

In conclusion, our device combines a novel biologic (NELL-1) with FDA approved products of known safety and efficacy (mesh and allograft) so that we may more rapidly address the unmet needs of over 700,000 Americans per year suffering vertebral compression fractures.

Sincerely,



John S. Adams, M.D.
Professor
UCLA Department of Orthopaedic Surgery



Chia Soo, M.D.
Associate Professor
UCLA Department of Orthopaedic Surgery