**MEMORANDUM**

**Date:** July 18, 2012

**From:** Alan Trounson, PhD
CIRM President

**To:** Independent Citizen's Oversight Committee

**Subject:** Extraordinary Petition for Application DR2-05288

Enclosed is a petition letter from Dr. Dan Gazit of Cedaers Sinai Medical Center, an applicant for funding under RFA 10-05, CIRM Disease Team Therapy Development Research Awards. This letter was received at CIRM on July 17, 2012 and we are forwarding it pursuant to the ICOC Policy Governing Extraordinary Petitions for ICOC Consideration of Applications for Funding.

**Extraordinary Petition DR2A- 05288**
**July 17, 2012**

To: Dr. Thomas, Dr. Trounson and Distinguished Members of the Governing Board:

We would like to highlight the following key points of our proposal that may shed some light on several of the concerns raised by the reviewers:

**Significance of the Clinical Problem:**

**The concept that osteoporotic vertebral compression fractures (VCFs) are mostly asymptomatic or result in symptoms that improve over time is a common misperception.** Suzuki et al., (*Eur. Spine J.,* 2008) followed patients with acute VCFs for twelve months and determined: "*Instead of the generally believed good prognosis for the greater majority of those fractured, the acute vertebral body fracture was the beginning of a long-lasting severe deterioration of the patient's health*". It is important to note that:

- **Approximately 150,000 VCFs are refractory to conservative treatment** and require hospitalization, which usually involves intravenous narcotics and prolonged bed rest that can weaken the patient and exacerbate the problem (*Riggs & Melton, NEJM, 1986)*.
- There is a clear correlation between VCFs and enhanced mortality rate. **Multiple publications have shown that mortality risk is increased up to nine-fold following vertebral fractures** *(e.g., Rao & Singrakhia, JBJS, 2010).*
- The economic burden of VCFs is enormous and keeps growing. VCFs in patients over 45 account for 150,000 hospital admissions, 161,000 physician office visits and 5 million restricted activity days per year. **Direct medical costs are estimated to be around $1.1 billion** *(Kondo, Semin. Intervent. Radiol., 2008).*

**Therefore, osteoporotic VCFs are a clinical problem of immense magnitude.**

- Non-operative management of symptomatic VCFs is very limited and ineffective. The American Academy of Orthopaedic Surgeons (AAOS) was unable to recommend non-operative treatments for symptomatic VCFs (AAOS, 2010). In fact, standard treatments such as bed rest even worsen bone loss leading to an increased risk for additional VCFs (*Krolner and Toft, Clinical Science, 1983*).
- Based on the limited and ineffective treatment options for these patients, minimally invasive surgical techniques like vertebroplasty with plastic filler (PMMA) were developed. **In 2010 in the U.S. alone, it was estimated that up to 180,000 patients underwent PMMA vertebroplasty annually** *(Baerlocher et al., Radiology, 2010).*
- Yet, in two prospective studies reported in the *New England Journal of Medicine*, treatment with PMMA vertebroplasty was no more effective than sham surgery *(Buchbinder et al., 2009; Kallmes et al., 2009).* Following these studies, **the American Academy of Orthopaedic Surgeons recommended against vertebroplasty for patients with symptomatic VCFs** *(AAOS, 2010).*

**Thus, there is a significant unmet medical need for novel therapies to treat VCFs.**

**Project Rationale:**

Over the last twenty years my group has shown in 16 publications that mesenchymal stem cells (MSCs), genetically engineered to overexpress a BMP gene, are extremely efficient in bone regeneration and fracture repair. Specifically related to this proposal, **we have shown that BMP6 engineered MSCs accelerated bone regeneration and induced complete bone defect repair in rat and pig models.** Our rat study was published in the journal of *Molecular Pharmaceutics (Sheyn et al., 2011)* and the results of the pig study were included in the grant proposal. From **Figure 1** it is quite clear that **restoration of normal vertebral architecture** was indeed achieved by implanting BMP6-MSCs in the fracture site.

The reviewers acknowledged that "**the rationale that MSCs modified to overexpress BMP6 will induce bone formation is valid***"* and "**that utilizing MSCs to produce BMP6 is a good approach and could overcome the manufacturing challenges of producing recombinant**

**BMPs as a therapeutic***"*. Yet they indicated that: "The therapeutic candidate would better address bone healing in non-union fracture or other bony defects". We would like to note that if successful in the treatment of VCF, **the use of BMP6 engineered MSCs could be further developed for use in other bone loss condition,** as proposed by the reviewers. We believe that the unmet medical need is greatest for patients with symptomatic osteoporotic VCFs.

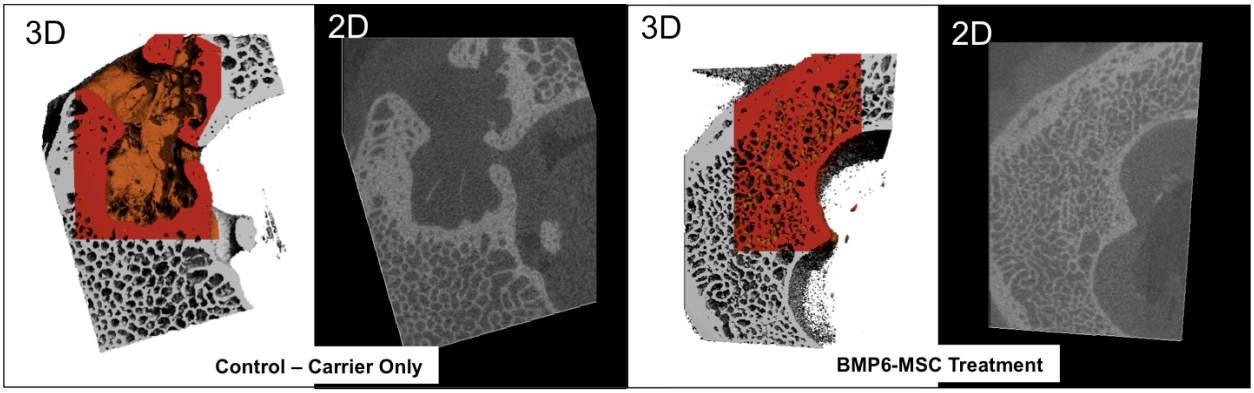


**Figure 1: BMP6-MSC treatment restores the normal architecture of pig-fractured vertebra.** CT scans of BMP6-MSC treated vertebra (left) compared to a vertebra treated with carrier (Fibrin gel) only (right). Region of bone fracture is highlighted in red.

Furthermore, the review stated that "very limited data in application support that BMP6 is superior to BMP2". However, we provided substantial experimental data showing that that **the overexpression of BMP6 in MSCs yielded significantly more bone in vivo and in a shorter time frame as compared to BMP2.** Since the submission of the grant application, these data have been published in the journal of *Gene Therapy (Mizrahi et al., 2012).*

**Feasibility of Project Plan:**

The reviewers indicated, "**The plan is straightforward, and … could achieve an IND within the four-year timeframe"**, which is the stated objective of the Disease Team Award program. However, the following concerns were identified:

- **The choice of animal model relevant to the disease being studied**:

The only animal model reported in the literature for evaluating potential bone regeneration in VCF involves the generation of a bone defect in the vertebral body of animals *(Phillips et al., Spine J., 2006; Liang et al., Bone, 2010).* Similar models were included in our supporting studies and in the proposed project. Therefore, as the reviewers recommended, we have selected the most appropriate disease model for our program.

- **The risk of bony overgrowth:**

The Co-PI, Dr. Bae, is the PI in **five different human clinical trials conducted under INDs, which involve injection of BMP 7 and 14 or stem cells directly into the spinal column of patients** and where the FDA approved human treatment following demonstration of safety in similar animal models. The indications were for normal degenerative conditions of the spine that cause moderate low back pain and disability, which is less than that observed in our target population. Although we understand the potential of bony overgrowth, we feel that osteoporotic VCF is a more disabling condition where the risk:benefit ratio is more compelling than in these previously FDA-approved studies. To date in these ongoing trials of BMP and stem cells, **none of the studies have had to be stopped due to bony overgrowth**.

We have included dose escalation studies in animal models that are designed to characterize and measure bone growth, and identify a safe starting clinical dose range that will be carefully characterized in the clinical development program that also includes an initial dose escalation

study with extensive safety monitoring and follow-up. Importantly, **we did not observe any bony overgrowth in our published rat study and in our pilot pig study.**

**Therapeutic Development Readiness:**

- The review report noted, "The program does not yet appear ready to begin preclinical development".

We have developed a very focused development strategy. We will use a clinically-approved source of MSCs (by Osiris Therapeutics, Inc.), a clinically approved transfection system (by Maxcyte, Inc.) and have selected well-established CROs and CMOs for development and manufacturing, in addition to having assembled a project team with product development, manufacturing and regulatory experience.

The reviewers agreed and commended us on: our "**good strategy**", a "**team that is supported by good product development, manufacturing and regulatory experience**", selection of "**solid CMOs and qualified CROs**", and that the "**plan is straightforward and in the right indication could achieve an IND in four years**". Therefore, we are convinced that our proposed strategy has a high likelihood of success to achieve an IND in the four-year timeframe.

- An additional concern was the **immunogenicity of differentiated MSCs:**

Here as well we agree with the reviewers regarding the risk of an immune response and therefore included tests throughout the studies to exclude this unwanted result. Nevertheless, we would like to indicate that Djouad et al., in a 2003 *Blood* paper demonstrated that: "*MSCs expressing the human bone morphogenetic protein 2 (hBMP-2) differentiation factor were not rejected when implanted in various allogeneic immunocompetent mice and were still able to differentiate into bone".* We further corroborated these results in our pilot pig study in which we did not detect any inflammatory reaction using **allogeneic, BMP6-transfected MSCs.**

**Impact:**

Several comments were related to the Target Product Profile (TPP):

In the TPP, we identified patients with chronic osteoporotic VCFs that have been refractory to conservative treatment and pain management as our minimally acceptable target population and where our treatment goal was considered clinically meaningful by **five leading spine surgeons in California**. The team plans to demonstrate safety and efficacy within this subpopulation first since they have no available recommended treatment alternatives, and then expand into subjects with acute and chronic osteoporotic VCFs if the risk:benefit ratio supports this approach. As orthopedic surgeons are currently debating the standard of care in VCFs, the selection of the most appropriate clinical comparator for our initial trials would be formalized during discussions with a spine surgeon advisory panel and subsequently with the FDA during a pre-IND meeting. As with many cell therapy development programs, the initial therapeutic approach proposed is to evaluate the safety and efficacy of a single treatment. Once it has been adequately evaluated in the clinic and approved by the FDA, the development program can be expanded to multiple treatments. With this approach the team will initially conduct a preclinical safety program focusing on single doses of our product and as the clinical program progresses and demonstrates safety and utility, additional preclinical safety studies of multiple doses can be designed and conducted that will support multiple treatments in patients. This step-wise approach the TPP is commonly used and supported by the FDA. Finally, we wish to state that **the proposed treatment has the advantage of being a targeted therapy to a specific fracture**, without the potential risk of side effects that could arise from systemic therapies using hormones or other small molecules, which are currently being investigated.

Respectfully,

Dan Gazit

Dan Gazit, PhD, DMD