



BURNHAM INSTITUTE
for MEDICAL RESEARCH

From Research, the Power to Cure

JOHN C. REED, M.D., PH.D.
President & Chief Executive Officer

August 2, 2007

Ms. Arlene Chiu
California Institute for Regenerative Medicine (CIRM)
210 King Street
San Francisco, CA 94107

Dear Arlene:

It has been brought to my attention that CIRM staff has questioned the eligibility of Dr. David Smotrich to serve as Principal Investigator of the SEED grant that the Grants Review Working Group and ICOC highly recommended for funding. Having conferred with our Stem Cell Research Center director, Dr. Evan Snyder, and others, I am hereby submitting a letter of appeal, asking CIRM to recognize the validity of Dr. Smotrich as a faculty member of the Burnham Institute for Medical Research, and to award the SEED grant that he rightfully deserves. I also wish to emphasize the potentially damaging consequences that a decision not to recognize Dr. Smotrich's legitimacy as a faculty member may have on clinician investigators, as it will surely discourage clinical researchers from participating in the CIRM mission to advance stem cell therapies. Finally, the particular grant recommended for funding is of great strategic importance to the entire CIRM effort, and therefore we urge CIRM staff to take this into consideration.

First, before reaching a final conclusion, CIRM staff should be aware of several historical factors concerning Dr. Smotrich and his position and activities as a member of our faculty. The Burnham created a faculty-track for Clinicians a few years ago, with Dr. Smotrich receiving his appointment in 2006. The impetus to create a clinical investigator category of faculty came with the arrival of Evan Y. Snyder, M.D., Ph.D. in 2003 from Harvard Medical School to Burnham to direct and build the Stem Cell & Regenerative Biology Program. With Dr. Snyder's arrival, a commitment was made by our Institution to enhance the translational aspects of the Program by creating close ties between our basic science faculty and clinician investigators. Therefore, we began to recruit clinicians to join our laboratories and our faculty from fields relevant to stem cell

biology and regenerative medicine. These initial fields included reproductive medicine (a subspecialty within obstetrics/gynecology), perinatal/neonatal medicine and pediatrics, neurosurgery and neurology, endocrinology, oncology. Those clinicians that displayed the strongest commitments to collaborative research were offered faculty appointments as Clinical Associates, and Dr. Smotrich and his associate Dr. Ari Mackler were the first to be offered these new clinical-track positions with our research organization. In connection with these faculty appointments, our institution provided funds from discretionary sources to support research in Dr. Smotrich's laboratory for 2 years, including purchasing equipment and subsidizing personnel in their research endeavors.

We should emphasize that during our search for in vitro fertilization (IVF) clinic partners, we screened and rejected other clinicians who would not accept the stipulations of an academic appointment – i.e., no fee for service arrangement; an “always-ready” commitment to teaching and research supported by grants and acceptance of a salary cap for academic activities.

Second, Dr. Smotrich is treated by our organization as a full member of the faculty in every way. He has a primary appointment in the Stem Cell and Regenerative Biology Program. He has full access to our internal website and all the functionalities available to other employees. He is invited to all faculty meetings and retreats. He participates in monthly meetings of the Stem Cell Program at Burnham, which is limited to faculty with appointments in that Program (Department) at our organization. He is represented on our external website, along with the other faculty.

Third, Dr. Smotrich is amply qualified for faculty status. Dr. Smotrich is a practicing reproductive gynecologist and clinical embryologist who trained in reproductive endocrinology at an academic medical center, George Washington University Medical Center (Washington, DC). A Fellow of the American College of Obstetrics and Gynecology (ACOG), Dr. Smotrich became one of earliest practitioners of and leading lecturers in assisted reproduction and vitro fertilization (IVF) in the early 90's when it was still a relatively new discipline. He is an expert in the clinical skill of pre-implantation genetic diagnosis (PGD), the necessary prior step to generating human embryonic stem cells (hESCs) that model human disease. Dr. Smotrich's team, for example, is proficient in (and has established novel technology for) dissecting single cells from human embryos, extracting DNA from the isolated cells to identify genetic defects, and then implanting non-defective embryos into recipient donors, while providing the genetically defective embryos for our research. This is a rare talent of strategic importance for CIRM. Dr.

Smotrich's research activities, in addition to hESC research, have included a clinical egg donor study on endometrial receptivity (2004-2006) and immunocytochemical investigations of growth factors in early human embryo development, with an emphasis on the role of trophinin and tastin in embryo implantation. Other skills in which he has made technological and research advances include oocyte freezing (he is one of a handful of practitioners to take IVF frozen oocytes to term), embryo implantation, micromanipulation of human oocytes and embryos, surrogacy, and techniques for IVF and inner cell mass (ICM) isolation.

Fourth, Dr. Smotrich's academic accomplishments and academic activities since establishing his association with Burnham clearly demonstrate his commitment to stem cell research. In the past 2 years, for example, he has delivered multiple lectures at scientific meetings, participated as a coauthor for many posters presented at international meetings, and co-published multiple papers, always citing his affiliation with Burnham. (See attached for a complete listing)

In addition, Dr. Smotrich routinely lectures at the Burnham's NIH-sponsored human embryonic stem cell courses. These lectures will increase in frequency given (a) funding from CIRM to serve as the formal training site in San Diego for hESCs (the result of Burnham's recent well-received Facilities grant application, which scored second in the State for scientific merit) and (b) a recent contract with Millipore/Chemicon to hold monthly short-courses on hESC techniques for a national audience. Furthermore, as is typical in all scientific training, Dr. Smotrich and his laboratory staff have trained, and continue to train, graduate students (at least 3 to date), post-doctoral fellows (at least 5 to date), and faculty (at least 4 to date) in human embryology, as well as inner cell mass (ICM) isolation, propagation, and characterization. He routinely assists these individuals with their own scholarly work in a terrifically collaborative manner. He diagnoses the abnormal blastocysts based on PGD technique, the basis for generating and studying hESCs that model disease processes. He also teaches bedside infertility treatment, PGD technique, the endocrinology of pregnancy and embryogenesis, prenatal ultrasonography, etc. to both basic science (including graduate students from UCSD and Burnham) and clinical trainees at the Burnham (e.g., perinatologists, endocrinologists) who do their scientific work here. He is always "on-call" and available for research and teaching activities in addition to his regularly scheduled teaching and research activities. Dr. Smotrich participated in generating and drafting the Burnham's clinical and informed consent protocols for our internal review board (IRB) as well as for UCSD's IRB on obtaining embryo and oocyte donations. He contributes to our ESCRO as well as formal conferences on ethics. He also

represents the Burnham as our reproductive biologist in a number of academic collaborations, e.g., with UCSD, Cedars-Sinai, University of Southern California, Children's Hospital of Orange County, etc. Thus, Dr. Smotrich is heavily engaged in the sorts of scholar activities commonly associated with faculty-level appointments.

Fifth, we take issue with the apparent CIRM staff interpretation that full time faculty must have laboratory space on the campus of the organizations applying for CIRM funds. As a clinical embryologist and reproductive endocrinologist, Dr. Smotrich's physical laboratory space *must* be adjacent to a Joint Commission on Accreditation of Healthcare Organizations (JCAHO)-approved clinical center and patient care-appropriate space for both regulatory and safety reasons. His impressive laboratory, which the Burnham helped to equip and fund, is located 3 miles from our campus, adjacent to Dr. Smotrich's clinic. This arrangement is not in anyway different from what exists at other academic entities in the State. For example, the UCSD Medical School Basic Science campus is located ~15 miles from its adult hospital in Hillcrest and ~15 miles from its pediatric facility (Rady Children's Hospital).

Also, the unique logistics of producing and working with newly created human embryos demand close proximity of the laboratory to the clinic. In this regard, Drs. Smotrich and Snyder, with funding from Burnham, created an academic entity called the *Stem Cell Resource* (SCR) to serve as a human embryology lab, including the provision of material for generating new hESC lines, fulfilling needs that could not be met directly in basic research laboratories on our campus. It was recognized, for example, that pre-implantation embryos must be frozen, thawed, and cultured directly adjacent to the patients donating eggs or being implanted (typically under general or local anesthesia). JCAHO as well as the State places restrictions on where such activities might take place and specifies the demands for such a clinical facility. Similarly, it was recognized by Burnham investigators (including Dr. Smotrich) that, after thawing and isolation of the ICM to make hESC lines, early transport of the cells was inimical to their health. Therefore, the initial stages (essentially the first 7-10 days) of hESC derivation needed to be done at the SCR. Furthermore, generating hESC lines that model human disease from abnormal blastocysts diagnosed by PGD needed to be done shortly after culturing at SCR. Similarly, all judgments regarding health of the fresh zygotes and thawed morulae and blastocysts needed to be done on-site and made by a clinical embryologist. Further, nuclear transfer (NT) needed to be done following egg retrieval without transport. For all of these reasons, it became clear that Dr. Smotrich's laboratory space by necessity needed to be near a clinical entity, and Burnham

supported his research activities by funding supplies, equipment, and researchers and providing administrative and regulatory support.

For training, our Burnham graduate students, post-doctoral fellows, and junior and senior faculty go to the SCR to learn and perform ICM dissection, hESC line generation, and pluripotent cell characterization and become trained in hands-on human clinical embryology. Indeed, the first stages of all of Burnham's new hESC line research and studies on early human development are performed at SCR.

Sixth, we disagree with the apparent condition by CIRM that all faculty derive the majority of their salary support from the host institution. For example, at Harvard Medical School (HMS), from where Dr. Snyder was recruited, *all* medical school-affiliated hospitals are actually financially and administratively independent of HMS. Each Harvard investigator, despite having a full-time academic affiliation with HMS, receives a check from their respective clinical entity based on contributions from their clinical activity plus grant support plus administrative, supervisory, and teaching activities (paid by HMS to the hospital). Moreover, as a soft money institution, even our basic science faculty who perform traditional laboratory research are not guaranteed a salary, and some of them, from time to time due to lapses in grant funding, continue their appointment without receiving a pay-check from the Institute. While this arrangement differs from state-funded medical schools, we argue that faculty who do not derived the bulk of their salary from the hosting institutions should not be disqualified from participation in CIRM grant programs assuming their academic appointment and their scholarly activities remain uninterrupted. Surely, this would preclude some of California's most talented and dedicated clinician scientists and basic scientists from contributing.

Dr. Smotrich became a full-time *clinical* faculty member of Burnham, but, by definition, did not give up his clinical practice, a condition true of any surgeon or physician who would spearhead CIRM-funded research. In his role as a full-time member of our clinical faculty, Dr. Smotrich performs a function similar to many clinician-scientists at many other private medical schools in the country – he lectures, provides direct one-on-one mentorship both at the bench and bedside to trainees at all levels, co-authors scholarly papers and reviews, and he presents papers and posters at scholarly meetings, all while still maintaining a robust clinical practice.

Seventh, before CIRM staff irrevocably rejects our appeal to have Dr. Smotrich's legitimate faculty appointment recognized, it bears noting that the particular SEED grant that he authored is of strategic importance for the success of the CIRM initiative. The grant in question is solely to fund the SRC that makes it possible to collect thousands of unwanted human embryos under strict IRB-approved, informed consent procedures and to derive new hESC lines. Already, Dr. Smotrich has received and banked over 1,000 frozen embryos from IVF clinics across the country, rescuing normal embryos that would otherwise be discarded. Burnham's affiliated SCR has been recognized by academic and private-practice entities around the country as one of the few places to transfer such embryos for non-profit scholarly pursuits and has been profiled in such professional journals as *Nature* and *Science*. It has also received wide exposure in the lay community through the national broadcast (NPR Public Radio) and print media. The embryo rescue program occurs in parallel with Dr. Smotrich's production of fresh embryos from his current clinical practice, from whence we obtain embryos harboring specific genetic mutations for use as novel disease models. This is a unique resource not found anywhere else in the entire state and the only source currently available in California for deriving new hESC lines with the goal to share these freely with the entire CIRM research community to advance the fundamental goals of CIRM. Thus, to abandon the grant on perceived technical grounds flies in the face of the mission of CIRM.

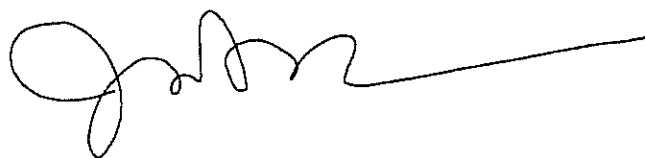
Dr. Smotrich's SEED grant proposal received the second highest score in the State of all submitted applications (only 1 point below California's highest SEED grant score). The Study Section remarked about the strength of the preliminary data, as well as the appeal of Dr. Smotrich's having knitted together a strong collaborative effort between reproductive clinicians, stem cells biologists, clinical embryologists, and molecular biologists from the Burnham community. It also bears mentioning that this grant was vetted not only scientifically by the Study Section and the ICOC but also administratively and recommended each time for funding. In addition, prior to submission of the application, Dr. Smotrich's relationship as a member of the newly-established clinical faculty of Burnham was given the "green light" for submission over the phone by CIRM administrators. We took that "go-ahead" – and the subsequent multiple positive reviews – in good faith.

In denying peer-reviewed funding to a clinical faculty member such as Dr. Smotrich, the ICOC, the patient advocates, and the Study Section members should all be made aware that it sets a dangerous precedent that adversely affects *all* clinician-scientists, most of whom will have a

significant component of their time devoted to clinical activity and whom will often be supported by non-academic sources.

For all these reasons, we urge CIRM staff to reconsider their ruling, and to award the SEED grant that Dr. Smotrich has earned. If CIRM staff cannot see the merits of the logic in funding this grant, then I respectfully request that the matter be reviewed by the Standard Committee of the ICOC.

Thank you for your consideration.

A handwritten signature in black ink, appearing to read 'John C. Reed', with a long horizontal line extending to the right.

John C. Reed, MD, Ph.D.
President & CEO
Professor, and Donald Bren Presidential Chair

