CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

MEMORANDUM

Date: March 11, 2013

From: Alan Trounson, PhD
CIRM President

To: Independent Citizen's Oversight Committee

Subject: Extraordinary Petition for Application IR1-06564

Enclosed is a petition letter from Dr. Sascha Hasan of Sanguine Biosciences, an applicant for funding under RFA 12-04, CIRM hiPSC Repository Awards. This letter was received at CIRM on March 11, 2013 and we are forwarding it pursuant to the ICOC Policy Governing Extraordinary Petitions for ICOC Consideration of Applications for Funding.

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IR1-06564 - Development of a biorepository to provide the research community with patient-derived, high-quality pluripotent stem cells and associated clinical information

PD: Sascha Hasan, Ph.D., MBA - Sanguine Biosciences

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

Thank you for the opportunity to present this petition for our application in response to RFA 12-04: CIRM hPSC Repository Award. We sincerely thank the reviewers for their consideration and feedback. However, we believe that certain concerns and inaccuracies need to be pointed out and addressed with regards to the initial, as well as the programmatic, review.

While evaluating the reviews of applications for RFA 12-03 and RFA 12-04, the Grant Working Group (GWG) chose to make their recommendations based on "pair combinations" that they deemed feasible without any prior instructions. Since, none of the applicants were provided with clear guidelines regarding how a feasible partnership should be formed between a Deriver and Repository applicants, we strongly believe that evaluating proposals based on arbitrary pair combinations that were decided by the members of GWG alter the outcome of funding recommendations if each entity would be evaluated and recommended for funding separately.

For, example, pairing a potential Deriver based on unknown criteria with a potential Repository and evaluating the pair "as a team" creates enormous disadvantage for each applicant. Sanguine Biosciences (IR1-06564) was paired with a Deriver (ID1-06576) without clear definition of which criteria was used for this selection, and ultimately was not recommended for funding based on the following criticism: "*Geographically, this Deriver/Repository combination would be challenging to coordinate*". Since our application was never paired with other potential Derivers that might be geographically closer to us, picking only one of the 6 potential Derivers and pairing it with Sanguine Biosciences appears highly inappropriate. In addition, the GWG also states "*Reviewers felt that this Repository should only be considered for funding if a unique synergy could be identified between it and a specific Deriver.*"

Fortunately, we are able to address this concern and are proposing to form a coordinated effort with one of the Derivers, the Sanford-Burnham Medical Research Institute (SBMRI). The PD of SBMRI application (ID1-06560), Dr. Evan Snyder, shares similar concerns with regards to how initial, as well as the programmatic, review was performed. Similar to Sanguine's case, even though SBMRI scored second highest in the Deriver rankings, it was arbitrarily paired with Repository IR1-06600, and the particular pairing was not recommended for funding with the statement of "*the Deriver and Repository would be located relatively far apart in California, adding logistic hurdles to the execution of this combination*". As also mentioned in Dr. Snyder's letter, we are proposing to establish a unique synergy within Southern California by coordinating our efforts. In reality, transporting frozen cells within the State, is not a significant limitation, and CIRM was correct in *not* requiring such a partnership in the original RFA. A similar requirement could just as well be imposed on the "Collectors", probably with greater justification since those starting cells are optimally *not* frozen and should be transported with little delay. To reward adequately meritorious proposals, to preserve the appearance of fairness, and to insure that hiPSC derivation be quite near the multiple cell "Collectors" statewide, I, like Dr. Snyder, would propose, counter to CIRM's initial plans, that the ICOC eventually endorses the creation of a *Northern* California Deriver and Repository and a *Southern* California Deriver and Repository, perhaps splitting equally the task of generating hiPSC from 3000 samples as well as the ear-marked funds.

CIRM promotes state-funded research with the aim of advancing stem cell research and therapy in the state of California. We are a company based in Southern California with strong connections to regional hospitals and patient advocacy groups as well as business operations in San Francisco and San Diego. We find it extremely puzzling that GWG recommended number of applications from out of state entities (e.g., New York Stem Cell Foundation) over number of qualified applications from California for both Deriver and Repository positions.

Please find our point-to-point response to GWG comments below:

Reviewer Comment #1: The reviewers expressed concerns regarding the location/proximity of the dedicated vivarium space as a future risk for contamination.
Response #1: The vivarium is equipped with state of the art barrier facility to prevent any contamination with outside and had been used by a pharmaceutical company to test preclinical R&D compounds. Besides, the vivarium has not been in use for the last year and does not provide any risk to the proposed repository.

Reviewer Comment #2: Reviewers considered the plans to perform karyotyping only after expansion into larger cell banks to be somewhat risky, as the patient-derived cells may harbor genetic abnormalities that could affect their stability or behavior in response to standard procedures.
Response #2: To address the reviewers concerns, we propose karyotyping the initial starting cells to document any pre-existing karyotypic abnormalities emanating from the patient. If the hiPSCs harbor different genomic changes, then that would be an indication that they were introduced during the hiPSC generation process and would suggest that that hiPSC clone/line should be abandoned. In addition, we propose karyotyping the hiPSC lines in phases to ensure cell lines are subject to a full panel of quality control testing.

Reviewer Comment #3: The applicant's software platform integration and dedicated personnel to this aspect of the project are major assets. Significant thought has been given to the breadth and depth of the information management program.
Response #3: We appreciate the feedback from the members of the GWG.

Reviewer Comment #4: While the management plan appeared reasonable, a reviewer suggested that all quality control operations should report directly to the Program Director rather than through the Laboratory Director.
Response #4: We agree that QC operations should report directly to the PD, while the Lab Director is informed regularly about the outcomes.

Reviewer Comment #5: The sustainability plan lacked details on required budget and revenues from orders, leaving reviewers uncertain of the extent to which the repository could become self-sustaining.
Response #5: To continue smooth operations after the 4-years funding period, a minimum annual revenue stream of $1.7M would be required. Given the fact Sanguine counts already >150 customers worldwide, including all major pharmaceutical/biotechnology companies as well as academic research institutes, the company expects the following revenue streams: $0.3M (year 2), $1.2M (year 3), $2.8M (year 4), $4M+ afterwards. Currently, with a 7-digit annual revenue (8-digit revenue income expected in 2014), the company is cash-flow positive.

Reviewer Comment #6: The applicant's heavy reliance on off site collaborators for operational planning, hiPSC expertise, and major staff hiring /training poses a significant risk to overall program.
Response #6: We respectfully disagree. Sanguine has extensive expertise in biobanking, and our excellent collaborations at UCLA and USC would ensure smooth operation of the proposed Repository procedures. The precise contribution of each collaborator is listed in the application, as well as in the support letters and there's no indication that any part of this operation would be problematic and/or risky. Furthermore, once the Repository is setup and the personnel (e.g., junior technicians) are trained, the role of collaborators would change to advisory positions. In addition, please note that the highest scored Repository by GWG was criticized for outsourcing hiPSC expansion, and this significant shortfall didn't warrant a "major risk" to the overall program.

Reviewer Comment #7: While the collaborations are admirable, the large number of moving parts within this proposal may prove challenging to coordinate, especially as information management will rely on combining existing systems with newly developed ones.
Response #7: We would like to learn how our solution has more moving parts than the competition's. Unless we are proposing to perform more services for the users, how can this be? Are competitors being credited with fewer moving parts whenever two adjacent tasks are performed in the same room? We also wonder if the greater detail we provided about the error reduction features of our proposed system gave the impression of additional complexity. Assigning barcodes at the time of data entry, and within the same system, is a requirement for reducing errors created among these moving parts. In contrast to our competitors' software, ours is adaptable to new protocols through configuration, rather than programming. It is always lower risk to configure and integrate battle tested tools like Magento (e-commerce/inventory platform) and Salesforce (customer relationship platform), than to write and use custom software. This principle is universally accepted in the software industry.

Reviewer Comment #8: Reviewers appreciated the innovative plan to take small banks forward initially with subsequent expansion of popular lines on demand, a method that should drive down initial costs and labor requirements.

Response #8: We appreciate the feedback from the members of the GWG.

Reviewer Comment #9: The Program Director is an established scientist entrepreneur with general experience in biobanking, but limited experience with iPSCs or running larger scale banking operations.
Response #9: Dr. Hasan has extensive experience with the business aspect of biobanking. Although, Sanguine Biosciences hasn't worked with hiPSC material, it possesses the necessary infrastructure and the capability. A coordinated effort of Dr. Hasan with our consultants (e.g., Drs. Plath, Lowry and Zack at UCLA), with our collaborators (e.g., Drs. Fox, McMahon and Triche at USC), and with exceptionally talented personnel, who is performing day-to-day Repository tasks, will ensure problem-free operation of the hiPSC bank. Geographically USC and UCLA are located within a short drive to Sanguine's base of operations in Valencia.

Reviewer Comment #10: Collaborators at the subcontracted organizations provide a useful set of talents that are well suited to the tasks proposed.
Response #10: We appreciate the feedback from the members of the GWG.

Reviewer Comment #11: The majority of laboratory expertise relating to hiPSC resides with a key collaborator who is located off site from the main laboratory. Given this crucial role, reviewers recommended that this individual's percent effort for Years 1 and 2 be increased.
Response #11: We agree with the GWG recommendation and will increase the percent effort accordingly.

Reviewer Comment #12: The positions of Laboratory Director and Quality Control Manager are key to the success of this project, but are yet to be named.
Response #12: We are proposing Dr. Bruno Blanchi from UCLA as a Quality Control Manager. He has extensive experience (8 years) on working with hESCs and hiPSCs at UCLA. In addition to maintaining numerous hESC lines (e.g., H1, H9, and UCLA lines), Dr. Blanchi has created an in vitro model of Rett Syndrome using hESCs (in combination with shRNA knockdown approach), as well as patient-specific hiPSCs. A potential Laboratory Director, however, is still to be determined.

Reviewer Comment #13: The proposed budgets for personnel, equipment and supplies are generally reasonable, but some reviewers felt the costs related whole-genome/epigenetic data acquisition were significantly underestimated.
Response #13: Only the "highest-demand" hiPSC lines will be analyzed for their genomic integrity. Based on customer demand, 10-15% of total hiPSC lines are expected to be sequenced. With a total cost of about $1000 per genome (an agreement that Sanguine has in place with Dr. Timothy Triche, USC/CHLA) and an allocated amount of $500,000 for this purpose, we expect to be able to sequence 10-15% of hiPSC cell lines (triplicates not considered). Nevertheless, it is the allocated dollar amount that will dictate the number of genomes to be sequenced, and not vice versa. If, however, a certain hiPSC line does not reach the threshold of heavy demand, but a user requests full genomic profiling, a modest fee would simply be added to the cost of the line. Furthermore, SBMRI, the Deriver, can also provide services such as profiling, differentiation and gene editing to users of the Repository.

Reviewer Comment #14: Reviewers considered the budget for mycoplasma testing to be excessive and suggested that alternative testing methods be explored.
Response #14: We would initially conduct mycoplasma testing in house using the MycoAlert™ testing kit from Lonza. This would reduce the budget for testing to 1/3 the original cost. We would then contract outside testing laboratories such as RADILL to perform more in depth testing of lines that are frequently requested to ensure cell quality. This dual approach to mycoplasma testing has been utilized by the USC Stem Cell Core for 6 years and during this time we have found it to be extremely reliable. That is to say the results of the MycoAlert™ kit have always directly correlated with those obtained from RADILL.

We thank the CIRM Independent Citizens' Oversight Committee for their consideration of our petition and express our gratitude for their consideration.

Sincerely,

Sascha Hasan, Ph.D., MBA