CALIFORNIA'S STEM CELL AGENCY

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Scientific Advisory Board Recommendations and Preliminary Management Response

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Purpose of SAB review

- SAB was established in response to 2012 recommendation of IOM panel charged by CIRM with reviewing the Institute's operations.
- 13-member IOM panel, made up of experts in stem cell research, business and finance, law and bioethics, and research administration produced a set of recommendations aimed at ensuring that "all aspects of CIRM's operations are functioning at peak performance".
- One recommendation was for CIRM to establish an external SAB, made up of experts in the "scientific, clinical ethical, industry, and regulatory aspects of stem cell biology" to be appointed by and report to the president. The IOM panel believed that a single SAB as opposed to multiple advisory boards would be best positioned to provide integrated advice to the president on strategic priorities for future RFAs, innovation projects, and the research portfolio.

SAB members – see appendix for details

- **Sir John Bell**, Oxford University, UK (Chair for August 2013 meeting)
- **Dr. Corey Goodman**, VenBio Corp. USA
- **Dr. Maria Grazia Roncarolo** Hospital San Raffaele, Italy (not attending)
- **Dr. Sean Morrison**, Children's Research Institute at UTSW, USA
- **Dr. Christine Mummery**, Leiden University Medical Center, The Netherlands
- **Dr. Stuart Orkin**, Harvard Medical School, Dana Farber Cancer Institute, USA
- **Dr. Fiona Watt**, *Centre for Stem Cells and Regenerative Medicine*, King's College, UK
- **Dr. John Wagner**, University of Minnesota Stem Cell Institute, USA

Plan is to conduct 3 to 4 SAB sessions per year, with at least one session in person

Meeting Agenda and Process

CIRM president convened the SAB on August 23rd , and asked them to consider the following high-level questions relating to CIRM's strategy during its next cycles of funding:

- CIRM is completing the allocation of funds provided by the California bond initiative and seeks advice on the best use of the remaining funds from this cycle of funding. How can we best maximize the impact of CIRM in regenerative medicine with the remaining funds, which at this time is approximately $600 million dollars, to be allocated in projects to be completed by approximately 2021?
- What unique priorities does the SAB recommend for CIRM for the next four years, consistent with the goals and objectives of the 2012 Strategic Plan?

Meeting Agenda and Process

On August 23, the SAB convened one-day meeting with CIRM staff and a closed session of the SAB to draw up a set of recommendations. The SAB also requested a closed-session, one-hour teleconference with several CIRM grantees (Irv Weissman, Rusty Gage, Owen Witte, and Larry Goldstein).

- Prior to the meeting, the SAB was provided with a document summarizing the following: 2012 Strategic Plan Update, Scientific Programs, Collaborative Funding Program, Industry Engagement, and other ancillary information.

Recommendations - overview

- SAB advises CIRM to identify, through a prioritization process, the top 6 to 8 projects, with clear relevance to the remit of CIRM's stem cell mission, and to setaside the funding to ensure the projects can proceed to phase 1 and 2a clinical trials as rapidly as possible, without financial impediments
  - Achieving clinical proof of concept is a key goal to achieve, to attract future potential investors and supporters of stem cell research, and has a strong chance of success, as long as CIRM advances the most promising clinical candidates "at speed"; this will require careful assessment / prioritization of portfolio

Recommendations - overview

Preliminary management response: Management accepts this recommendation and will need to identify a process for selection of these projects that would include representatives from GWG, CDAP, and other external expertise as needed, and the amount of funding that would need to be set aside by the ICOC. Recommendations will be developed for this priority group of projects as to where expertise and approach need to be modified to maximize the potential and to ensure rapid and effective progress. Management will provide separately a process to select these priority projects.

Recommendations - specific

CIRM Question : Training grants and shared laboratory funding build infrastructure and future capacity. Current training grants and shared laboratories will end in the next few years. However, there is strong support for these from California institutions and advice is sought on whether to continue or cease this program. Please advise whether there are particular opportunities or areas of unmet need in training that could be accomplished in the next 4 yrs

Recommendations - specific

- SAB recommends continued funding of training programs at all levels to develop a work force of trained individuals, which will be valuable as cell therapies burgeon; the SAB does not recommend continued funding of the 17 shared labs; these should operate on a revenue-neutral basis; although essential as a safe haven during NIH funding ban, the importance of these resources to CIRM's mission and achieving sustainability of earlier investments is not as compelling.

Recommendations - specific

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Preliminary management response: Management supports the continued support of training programs; in addition, management supports the recommendation of not extending support for the shared labs, recognizing that some institutions may have problems in maintaining these facilities; need for these facilities has declined with political changes and time, and where possible, these facilities could be absorbed into general institutional facilities

Recommendations - specific

CIRM Question: The 2012 Strategic Plan Update emphasizes movement from the bench to bedside, which, in fact, is how CIRM's scientific programs have evolved, with increased emphasis on funding research in the clinic as opposed to basic and early translational research. Nonetheless, CIRM is still strongly supporting the engine of discovery, so please discuss whether there are particularly important areas of opportunity in the next four years for a) basic discovery and b) early translational research.

Recommendations - specific

- Basic: SAB recommends continued support for basic research, but felt restriction of CIRM funding in some RFAs to projects using only human cells was too prescriptive, and doesn't take into account the benefits that model organism research can offer.

Recommendations - specific

- Translation: SAB noted clinical projects should be carefully selected so they are strong in terms of their mechanistic basis, and have a strong chance of success. There was no consensus on particular areas of research - some felt a focus on ES cells, where California has already shown leadership and accumulated expertise, one suggested CIRM not focus on iPSCs given Japan's strong push in this area , whereas others thought a broader approach would be most effective in terms of maximizing successes and taking advantage of the broad range of projects and expertise in the state.
- Grant reviewers: SAB noted CIRM should continue to obtain the very best external reviewers, and could consider enhancing funding for its chairs, and schedule review mtgs 1-2 yrs ahead, if there are difficulties in recruitment.

Recommendations - specific

Preliminary management response

- Basic: Management supports continued funding of basic science. Priority of supporting “transforming” basic research is a feature of more recent RFAs. Human cells rather than cells of model systems have been a CIRM priority from the beginning. Innovative ideas that could be demonstrated with research on model systems has been included in Basic Science RFAs in recent years. Management believes we should continue to emphasize study of human cell systems, but will ensure any likely transforming work in other organisms be supported in selection of grants for review.

Recommendations - specific

Preliminary management response

- Translational Research: Management agrees that translational studies should have a strong mechanistic basis. There was no SAB consensus on particular cell types to pursue, and management thinks it is in the best interest of CIRM to pursue broad range of scientifically compelling stem cell platforms.
- Grant Reviewers: Management agrees that the best available reviewers should continue to be chosen for assessing grants, and CIRM's remuneration to reviewers already compares favorably to NIH and other foundations. It is available time, not dollars, that is a rate limiting step for reviewers.

Recommendations - specific

CIRM Question: What is your advice on how to better engage the private sector to partner with CIRM, to enable the translational and clinical development programs further opportunities to continue towards clinical proof of concept, and if successful, towards FDA approval and commercialization? Should CIRM funding support California cell manufacturing capacity for large-scale phase 3 studies to begin in 2-5 years? What types of costs and facilities would be necessary and is it reasonable to fund these without private-public partnerships?

Recommendations - specific

- SAB had a very positive view of interactions between CIRM and the commercial sector. They noted an advantage of leveraged funding from the commercial sector of externally validating the quality of science and the likelihood of success. They also recommended for the top prioritized set of projects, that it is important to ensure they can be funded without requiring matched leverage funding until after phase 2a when successful programs should readily obtain external support.

Recommendations - specific

Preliminary management response: Management agrees that where appropriate, translational and development studies can be driven inside academia. Management believes that preclinical and early clinical trials need expertise that generally resides in industry and that consultants and partnerships should be integrated into academic teams. Industry needs to be encouraged to participate in clinical trials with teams working across the portfolio and particularly for studies involving small molecules and biologics. However, it is important not to adversely penalize teams with sound competitive projects where industry does not buy in.

Recommendations - specific

CIRM Question: Should we engage our collaborating partners in a major project as a flagship to set the field in motion as we wind down?

Recommendations - specific

- SAB considered this option around a “straw man” in one therapeutic area, but felt the uncertainty of science in any one therapeutic area would make this a very high risk strategy and the SAB was against consolidating programs in this way. If an opportunity arose to participate in a major project in a single therapeutic area in a partnership that provided significant financial leverage to CIRM, it might be an effective use of resources provided it did not constrain progression of the prioritized portfolio.

Recommendations - specific

Preliminary management response: Management agrees that a major flagship project that would commit a large quantum of CIRM funds is not appropriate at this stage of CIRM's life. However, if significant national or international projects evolve in time, it may be appropriate for the ICOC to consider some involvement together with other relevant agencies.

Recommendations - specific

CIRM Question: Looking to the future, how would you best make the case that CIRM was a great innovation in public funding of cutting edge science and whether it has delivered, and could continue to deliver in the future, value to the citizens of California and to the field of regenerative medicine?

Recommendations - specific

- Advancing a project to the stage of clinical proof of concept will be important to making this case to the public. Care must be taken to ensure that the most promising projects are supported through to this stage by CIRM funding.

- The case that CIRM has been transformative in this exciting emerging field of biomedical science seems self-evident to the SAB. The level of activity in this field in California is extraordinarily high and there are many excellent programs being supported by the CIRM that would have failed to be supported given the limited amounts of funding available for this field when CIRM was established. The program has yielded a large number of extremely well trained students and investigators supported directly or indirectly by the CIRM, there is a critical mass in a number of the major academic centers around California that has allowed it to compete internationally in this field, and the commercial environment for regenerative medicine in California has thrived as a result of CIRM intervention.

Recommendations - other

SAB noted that CIRM, despite its considerable achievements, had not received the attention and attribution that many equivalent funding bodies would have had for their contribution to successful science. SAB strongly suggests that CIRM ramps up its outreach activities, both to improve the California public's awareness of CIRM's uniqueness in the world, its successes so far, and the potential of stem cell research to advance treatment of diseases and injuries. Its brand recognition internationally and even nationally is limited and this should be corrected.

Recommendations - other

Preliminary management response: Management recognizes that CIRM should continue to elevate recognition in leading global developments in stem cell research and medical applications, and will work on ways to more effectively ensure that advances and developments arising from CIRM supported activities are effectively transmitted to scientific community and the public. Management will work with CIRM communications particularly relating to communication to the public.

CIRM staff attending SAB review

- **Ms. Elona Baum**, General Counsel & Vice President for Business Development
- **Dr. Natalie DeWitt**, Special Projects Officer to President
- **Dr. Ellen Feigal**, Senior Vice President of Research and Development
- **Dr. Patricia Olson**, Executive Director of Scientific Activities
- **Dr. Bettina Steffen**, Associate Director of Development Activities
- **Mr. Ian Sweedler**, Senior Counsel for International Programs
- **Dr. Jonathan Thomas**, Chair, ICOC
- **Dr. Alan Trounson**, President
- **Dr Michael Yaffe**, Associate Director, Research Activities

Meeting agenda

August 22, 2013	
6:00-9:00	Dinner and Discussion
August 23, 2013	
8:30-9:00	Breakfast: election of meeting Chair
9:00-Noon	CIRM staff presentations and discussion (15 min presentations)
Alan Trounson	CIRM
Pat Olson	Funding: awarded, approved and allocated
Michael Yaffe	Basic Science, shared facilities, and training programs
Ellen Feigal	Translation/Development and Clinical Programs
Elona Baum	Business development programs
Natalie DeWitt	Innovation programs
Jonathan Thomas	New financing opportunities
Noon-1:00	Lunch and Discussion with Californian Stem Cell Leaders (Irv Weissman, Owen Witte, Rusty Gage and Larry Goldstein)
1:00-5:00	SAB closed session
5:00-5:30	SAB and Alan Trounson