CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

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To: ICOC

From: CIRM Management

RE: Plan to Implement the Recommendations of the External Review Panel

Context— As mandated in its Scientific Strategic Plan, CIRM Management organized a review of the agency's performance to assess its progress against its goals. This thorough effort culminated in December, when the report of the External Review Panel (Panel) was presented to the Governing Board.

The review was conducted by a panel of 8 experts who came from different domains that intersect with CIRM's mission. This group included stem cell scientists, leaders of private and public research funding organizations, an ethicist and representatives from the biotech industry and venture capital. To help prepare the Panel for its task CIRM Management and the Office of the Chair sent the Panel members, in advance, two documents ("A Brief History, Current Status Report and Options for Next Steps" and "Report of the Office of the Chairman to External Reviewers") designed to provide comprehensive background on CIRM's history, organization, funding programs, and accomplishments to date. Both documents are available here: http://www.cirm.ca.gov/Announcement_112410

The Panel convened in San Francisco for three days in October (13-15). During that site visit the Panel met with CIRM Management, Board members and various stakeholder groups – members of the Grants Working Group, stem cell researchers, representatives of the stem cell industry, patient advocates, trainees and members of the public. Subsequently, the Panel drafted a report of its findings and recommendations and submitted it to CIRM at the end of November. The report was discussed in public at the Governing Board's meeting on December 8, 2010. Since then there have been several meetings with groups within CIRM, including one with the entire staff, to solicit input regarding the recommendations of the Panel.

In January, groups made up of members of CIRM Management and staff undertook the task of developing plans for incorporating the recommendations and spirit of the Report of the External

Review Panel into CIRM's day-to-day operations. The reports from those groups were completed in early February and incorporated into this document. It is intended to stimulate strategic discussions with the Governing Board as a "next step" in defining how CIRM will reach its goals and meet its mission.

Panel Recommendations— One of the recurring messages from the Panel was to move away from traditional funding agency models. They emphasized that CIRM should adopt a "more aggressively proactive approach." CIRM should be selective; limit its portfolio; and seek out promising projects to fund. Within that general message the Report of the Panel listed 10 specific recommendations:

1. *Maintain focus on meaningful, targeted scientific excellence*
2. *Sustain fundamental discovery*
3. *Pave a path from fundamental to translational research, translational medicine, product development and healthcare delivery*
4. *Conduct a critical assessment and prioritization of the current portfolio with input from CIRM's diverse stakeholders*
5. *Develop an open innovation-focused, porous pipeline strategy*
6. *Assume a leadership role in the critical social, ethical, regulatory and health care delivery issues*
7. *Develop strategies to improve/expand engagement with industry*
8. *Broaden international partnerships to leverage expertise and resources*
9. *Expand breadth of outreach and education to ensure state-wide visibility and awareness*
10. *Clarify the roles and responsibilities of the Governing Board Chair and the President as it pertains to CIRM's strategic directions*

Several of these recommendations have overlapping themes. Most notably, sections 3-5 all describe approaches aimed at maximizing the impact of CIRM's research investments to ensure that it reaches its scientific goals. Similarly parts of sections 3 and 7 deal with ways to better engage industry as CIRM's partner. In developing an operational plan for incorporating these recommendations, it made sense to combine some of the individual recommendations of the Panel. Thus, this document is organized into 8 sections. Some address specific recommendations of the Panel while others describe processes that are more broadly applicable and have an impact on more than one Panel recommendation.

1. Keep CIRM on the leading edge of Stem Cell Science (Panel recommendations 1, 2)

The Panel emphasized the need for CIRM to continue funding only the best research proposals and not to lose sight of the fact that basic research will always be the engine that drives innovation. To maintain the momentum that has been created over the past four years Management believes that CIRM should:

- Develop innovative prescreening methods, such as Pre-application review, for consideration of a large number of proposals to enable selection of the most promising applications for full review;
- Continually strive to recruit world-class scientists from both academia and industry to its Grants Working Group;
- Emphasize that funding decisions should be driven by the scientific merit (score) except when there are compelling, mission-critical programmatic and portfolio reasons;
- Maintain regular, repeating funding opportunities for basic research on stem cells.

2. Optimize CIRM's portfolio (Panel recommendation 4)

The Panel encouraged CIRM to prioritize its portfolio and make difficult decisions about which programs to move forward. For programs near the translational/clinical end of the development pipeline, only those with significant promise for success in clinic trials and that have a genuine opportunity to become broadly available patient therapies should be supported. Plans for this type of prioritization review are already underway for the Disease Team projects. A Clinical Advisory Panel is being established that will include individuals with appropriate skill sets related to the delivery of preclinical and clinical research, process development and manufacturing, regulatory standards, stem cell/disease-specific biology, disease-specific clinical expertise and commercial relevance[1]. The VP, R&D will consult with these experts on project strategy, progress against milestones, and success at go-no-go decision points, and advise the President about the merit of continued support.

However, Management recommends that portfolio prioritization be examined more globally. This would require periodic surveys of the stem cell field by a group of experts to identify the most promising developments arising in stem cell science.

To perform this task, CIRM's management team and Science Office will consult with internationally recognized experts, including scientists, clinicians, regulatory experts, industry representatives, venture capitalists, and disease advocacy organizations in order to:

- Develop criteria that define projects most likely to succeed;
- Incorporate "Commercial Relevance" as a consideration in evaluating projects;
- Identify key gaps in CIRM's portfolio;
- Determine which diseases are most amenable to stem cell therapies.

These discussions will include the Chair and Vice Chairs of the Governing Board, where appropriate.

[1] Members of this advisory panel will be subject to the same rigorous conflict of interest standards as scientific members of the Grants Working Group.

These results could then be used by CIRM Management and the Board to:

- Develop targeted translational and clinical RFAs;
- Identify specific approaches to specific diseases;
- Proactively seek to attract priority projects, research groups and companies to California.

3. Develop a proactive strategy that enables porosity of access and targets for the most promising research (Panel recommendations 3, 5, 7)

The thrust of these recommendations is that CIRM must be more aggressive and proactive in seeking out the best research, if it hopes to meet its mission. It cannot exclusively follow the traditional funding model of issuing a call for applications and then waiting to see who applies. In particular they recommended that CIRM:

- Bring promising projects into the development pipeline at all stages;
- Efficiently push forward only the most promising projects, whether or not they have been initially developed with CIRM funds;
- Find ways to better engage with industry in order to:
    - Capture industry's special capabilities (e.g. toxicity testing, manufacturing and scale-up);
    - Better meet industry timeline requirements;
    - Ensure the development projects have the best chance to attract outside investment;
    - Provide some direction to academia and industry on critical needs in specific areas based on portfolio analysis, internal assessment and external advice.

To be clear, CIRM's RFAs cover the full spectrum of the portfolio, from basic biology, to early translational to clinical development. This program encourages promising projects to enter the portfolio at any stage of development, and many have done so. However, there has been no route for scientists or companies to obtain research funds other than through the traditional RFA mechanism and there has been no concerted effort to solicit applications to support selected projects. When entities with promising new developments outside California are identified, CIRM will encourage them to partner with California institutions and apply to general or specific RFAs. The challenge is to find ways to pull projects under CIRM's umbrella while staying within the spirit and regulations that govern the Institute. Management suggests CIRM use the new advisory groups to identify the most promising stem cell research programs within and outside California.

For programs already funded by CIRM and approaching the clinical stage of the development pipeline:

- The Governing Board could create an "Opportunity Fund" to be used by the President to rapidly provide continuation funds for projects identified by VP, R&D and members of the Clinical Advisory Panel as having been highly successful and their plan to move forward is compelling and competitive as assessed against defined criteria. This process would accelerate existing promising and competitive CIRM projects and reduce the amount of time spent writing proposals and in review. CIRM already has mechanisms to discontinue or cut back projects that are not making progress. This additional tool would allow CIRM to accelerate projects that are beating expectations.

- Repeat core RFAs (Basic Biology, Early Translation, Disease Teams, and Therapy Development) on a regular basis so that new projects can enter the pipeline at the appropriate stage and those projects within the pipeline can plan for progression in the context of a competitive renewal, if they do not receive Opportunity Funds.

For Programs singled out by the priority review process but not currently funded by CIRM:

- For research groups within California, contact them and make them aware of up-coming competitions that could fund their research. Encourage collaborations among researchers with complementary expertise and invite them to apply.
- For research groups outside California, invite them to networking meetings/workshops with California researchers &/or companies that have overlapping interests. The goals would be to establish collaborations and encourage their development in California.

The Panel emphasized that industry brings special skills and abilities to the stem cell field that are not easily handled in an academic setting or at a research institute. These include toxicity testing, product development and regulatory know-how, and the ability to develop, scale-up and optimize production for clinical use. However, many companies lack experience and expertise in grant writing, a skill perfected by academics, and their timelines are often short, especially when trying to satisfy and attract private funders.

Over the past 3-4 years CIRM has undertaken several initiatives in an effort to address concerns raised by companies interested in receiving research support. CIRM has held numerous public meetings to solicit input on intellectual property issues and on policies related to its loan program. In addition, CIRM organized a webinar on grant writing that included successful applicants from biotech companies, and it has steadily increased the number of Grants Working Group reviewers with industry experience. However, additional steps could be taken to better accommodate the private sector.

- CIRM could fund grant writing expertise for some companies that meet qualifications (e.g. at least 20 employees or $5 million in cash liquidity).
- For some RFAs in the translational arena, CIRM could require partnerships between academia and industry as a mechanism to meld the strengths from both domains.
- CIRM could create a rolling RFA that would target industry and accommodate the need for shorter timelines. The RFA would have to be specific in its focus so that only a limited number of applications would arrive at any time (for example development stage projects based on pluripotent cell-derived cell therapies). There could be 2 submission deadlines per year and review could be telephonic (as for the Research Leadership Awards) to minimize the turnaround time between submission and Governing Board decision.

4. Engage with Industry to encourage and enable commercialization of the most promising stem cell research (Panel recommendations 3, 7)

The Panel emphasized that the private sector will have to participate, if stem cell based therapies are to be readily available to doctors and patients in California. CIRM does not have adequate resources to fund Phase 3 clinical trials, and academic institutions do not have the capacity for large-scale manufacturing. If CIRM can encourage and foster stem cell related, industrial expansion in California, it will produce economic benefits to the State and health-related benefits to its citizens. In this regard, Management is proposing the following initiatives:

- Promote California-based stem cell related companies to the broader stem cell research community
    - Invite California-based research support companies to the CIRM Grantee Meeting to exhibit their stem cell related products and services;
    - Feature companies in a searchable resource portal on the CIRM website.
- Develop a process to create and recruit an Industry Advisory Board with 8-10 internationally recognized expert members representing biotech, pharma, venture capital and disease foundations. This group would be subject to the same rigorous Conflict of Interest standards followed by the scientific members of the Grants Working Group. CIRM would seek ideas from members to:
    - Make its programs attractive to industry;
    - Identify research areas most appropriate for industry;
    - Identify CIRM-funded inventions that should be patented;
    - Create opportunities for follow-on funding for CIRM-funded research programs especially those approaching clinical trail;
    - Identify and assist CIRM in fostering industry-academic partnering opportunities;
    - Identify and advance business models for regenerative medicine;
- Provide supplemental funding to grants that have already been approved by the Governing Board to help fund the costs of patent filing for the most promising stem cell technologies;
- Help broker research collaborations between academic institutions in California and pharmaceutical and large biotech companies in order to leverage CIRM's research investments, and increase the commercial appeal of candidate therapeutics;
- Create a forum for researchers to present their findings to industry and venture representatives.

5. Take a leadership role in developing national and international standards related to regulatory issues, policy and ethics (Panel recommendation 6)

The Panel recognized that CIRM's mandate, the breadth and depth of its experience and its budget give it great convening capabilities, enabling CIRM to take a leadership role on issues central to the success of the field, such as creation of regulatory pathways and standards, and

social, ethical and economic issues. The Panel encouraged CIRM to take leadership roles on these matters both nationally and internationally.

In many areas this is already happening. CIRM representatives sit on the key national panels and committees that are developing these standards, and the Institute is taking the initiative to help advance the process. On-going efforts that are already in place include:

- CIRM is organizing regulatory webinars and roundtables with FDA participation.
    - CIRM has sponsored webinars focused on specific regulatory issues relevant to the stem cell field and each has included participation by FDA representatives. These will continue.
    - CIRM sponsored two roundtables that brought key thought leaders to Washington, DC, to discuss issues related to regulatory oversight of stem cell research. Members of the FDA attended both. The objectives of these roundtables have included the education of researchers, CIRM and the FDA about approaches being established to ensure that breakthrough therapies will be safe and effective. CIRM plans to hold these roundtable meetings annually.
    - CIRM has conceptually approved the sponsoring of a Regenerative Medicine Translational Journal to assist information sharing in translational, preclinical and clinical research in cell therapies, including the publication of negative results.
- Members of CIRM's senior management team hold leadership positions on a number of national and international committees including:
    - International Society for Stem Cell Research (ISSCR) – the world's largest organization devoted to stem cell research;
    - Alliance for Regenerative Medicine (ARM) – a group of (mostly) industry representatives that promotes stem cell research and regenerative medicine with the federal government;
    - Interstate Alliance for Stem Cell Research (IASCR) – a national organization that promotes regulatory and ethical standards for the use of stem cells.
- CIRM must and will remain vigilant and responsive to legislative and judicial efforts to restrict stem cell research.
    - When the NIH issued new guidelines, allowing broader funding for hESC research, the NIH was sued by stem cell research opponents. While that lawsuit, Sherley v. Sebelius, was pending in the federal courts in Washington, DC, the NIH approved grant applications under the new guidelines, and research proceeded. In August 2010, the judge granted the plaintiffs' request for an order that immediately terminated all NIH funding for human embryonic stem cell research. Following this adverse ruling the ICOC issued a resolution supporting legislation, which would permit the continued funding of stem cell research.
    - As other legislative issues arise, CIRM personnel will coordinate with the Office of the Chair to advance positions adopted by the Board.

As stem cell research advances and potential therapies move closer to the clinic, CIRM must monitor and, when possible, help resolve issues that present regulatory and ethical challenges. CIRM will need to partner with its grantees to understand these issues.

The potential challenges include:

- Donor consent – especially related to cell banking as it becomes more prevalent.
    - CIRM should consider building an educational module about consent issues for donors to banks.
    - CIRM should plan a workshop and/or develop a white paper to explore ethical issues that will arise as research with banked cells reveals health risks to the donors.
- Offshore Clinical Research – CIRM will consider decisions about overseas research where CIRM may be a collaborator– through clinical trials or co-funding partnerships on a case by case basis.

On a parallel track CIRM should develop tools on its website to educate the public on the ethics of stem cell research.

6. Expand CIRM's international partnerships and collaborations (Panel recommendation 8)

The Panel was very supportive of CIRM's network of international Collaborative Funding Partners (Collaborating Network). Not only have these collaborations leveraged funding and talent to advance CIRM's mission but they have also educated scientists around the world about the commitment to supporting stem cell research in California. The Panel recommends that this program be expanded internationally and broadened to encompass more US entities, while keeping within our legal parameters. Under Prop 71, CIRM can only fund California research.

Currently CIRM has Memoranda of Understanding ("MOU") with funding agencies in 9 countries, one state and one region within other countries, one U.S. state (Maryland), the New York Stem Cell Foundation and 1 disease foundation (JDRF). The funding partners have made financial commitments totaling $116 million overall to these projects. The MOUs, which articulate a high level commitment to searching for opportunities to jointly support stem cell research, have led CIRM's partners to fund 15 collaborative projects through 8 RFAs. These 15 projects have leveraged $53 million in research funds from the Collaborating Networks. The main shortcomings of this program have been two-fold. First, the funding partners must work within CIRM's RFA schedule as well as its procedures, regulations and timelines. Second, collaborative projects are substantially more complex to manage and administer.

To incorporate the Panel's recommendations that these programs be expanded and that CIRM be more proactive and selective in what it funds, management recommends that CIRM, with assistance from the outside experts it consults regarding prioritization, do the following:

- Identify areas where the California stem cell research community needs support from or lacks expertise that exists in other jurisdictions.
- Identify and approach additional participants for the Collaborating Network program (international and national) based upon:
    - The identified areas of California need; and
    - The strength of California's existing work and emerging programs.
- Adopt a "rolling RFA" program modeled on the CIRM Leadership Awards, which would fast-track clinical and advanced translational projects involving members of the Collaborating Network. Regular communications would allow CIRM and its partners to identify collaborative projects that satisfy the articulated criteria. Identified projects would be peer reviewed on a rolling basis.
- Develop regular communications with select disease foundations active in supporting stem cell research. Provide them opportunities to partner with CIRM in moving late stage projects into clinical development. CIRM could also include disease foundations in efforts to develop and support regulatory pathways.

To reduce some of the shortcomings of the current Collaborating Network system, CIRM should encourage selective use of a supplemental funding ("bolt-on") model as used in CIRM's agreement with JDRF and Maryland. In this model:

- Collaborating Network members would be invited to fund supplemental work by foreign scientists on projects after the California projects have been approved by the Governing Board.
- Under this mechanism the CIRM Science Office need not seek consensus with every Funding Partner during RFA development, grant review, and pre-funding administrative review. Collaborative grant performance monitoring could be streamlined.
- The Collaborating Network members would have more autonomy. CIRM would not set financial thresholds, timing, criteria for participation by foreign scientists, etc. In addition, Collaborating Network members would have assurance, up front, that CIRM will pay for the California portion of the projects.

7. Communicating with the public (Panel recommendation 9)

The Panel stated that CIRM has a responsibility to report to the citizens of California about the activities and successes of the Institute. It encouraged CIRM to ensure statewide visibility and awareness of the contributions that California is making to this global research effort and to provide realistic assessments of the potential benefits to the State and its citizens.

Other than funding decisions related to its largest grant programs, CIRM does not generate many hard news "pegs." Instead it needs to work with other organizations, such as its grantee institutions and patient advocate organizations to generate feature stories not pegged to specific news events.

Most scientific news related to CIRM's research investments is owned first by the scientists and institutions that CIRM funds. Thus CIRM must partner with these organizations to individually package features for broadcast and print outlets. To accomplish this CIRM should:

- Hire a Public Communications Officer who will report into the Office of the Chair – Meeting this goal will take a labor intensive process that will require fulltime attention;
- Further develop processes for interactions with the public and patient advocates;
- Develop regional strategies that pair local researchers with local patient advocates and disease organizations.

To augment this new effort on feature placements, CIRM will need to continue its efforts to place opinion pieces in key papers and to renew its efforts to reach out to editorial boards.

CIRM has now begun a concerted effort to engage with patients and disease-related organizations and has hired a consultant team to help advance this effort. CIRM will continue to expand this engagement.

CIRM will also need to continue and increase its efforts to take information directly to the public, bypassing the old media. Over the past 3 years CIRM has made great strides in its public education efforts, most notably through a new website, fostering relationships through social media, and the development of a high school curriculum. The new website contains a robust body of information, both in written and video formats. However, early on it was of limited value to patients and disease organizations because CIRM's focus was on training, facilities and early stage research. That changed in 2010 with the first Disease Team awards. More recently, in August 2010, modifications were made to the website so that CIRM's funding portfolio can be searched in many different ways, including by disease, making it much more attractive and useful for members of the public seeking information about specific diseases. The high school curriculum will not only educate young students about stem cells, but that knowledge should also spread to family members and friends.

To expand CIRM's outreach, the Office of Science Education and Communications will:

- Summarize scientific developments associated with CIRM advances;
- Arrange webinars for direct interactions with CIRM-funded researchers;
- Create web-based interactive tools explaining how CIRM's stem cell grants are accelerating cures;
- Identify "CIRM Heroes" – Grantees who are willing and able to effectively communicate with the public about their research and other advances in the stem cell field.

For all these efforts, CIRM's Office of Science Education and Communication would need to continually provide new content for the various on-line venues to keep members of the public returning to our materials and sharing them with others. This content development effort would provide fodder for the media outreach efforts as well. The amount of effort required to produce continually renewed content cannot be under estimated.

8. Improving CIRM's governance (Panel recommendation 10)

The Panel recognized that the Governing Board had taken a very hands-on approach while CIRM was in its start-up phase, but stated, "This is an appropriate time for the Governing Board to examine its role and composition, mindful of the legal reporting, fiduciary and accountability requirements of the state of California." The Report stated that the roles and responsibilities of the Board Chair and the President need to be clearly defined, distinct and complementary. CIRM Management agrees with that assessment.

The Governance Subcommittee and the full Governing Board have recently undertaken a survey of the Board members to assess their current views about the role of the Board Chair and the overall performance of the board as a whole. As the reviewers noted, the Board's role would be expected to evolve as CIRM's workload has grown exponentially and as CIRM has recruited a full complement of professional staff. Management looks forward to the results of that exercise and to working with the Board to implement any policy changes that are recommended.

Proposition 71 designates the President as CIRM's chief executive, while reserving several executive functions for the Board Chair. Within that legal framework, there is a need to identify the official with primary authority and accountability for each area of the agency's work. These roles will necessarily evolve as the agency matures. To succeed, the President and Chair will benefit from a cooperative working relationship and regular communication, and the flexibility to adapt as new challenges emerge.