



Engineering Strategies, Opportunities, and Challenges for Tissue Repair and Regeneration: CIRM Workshop Summary and Recommendations

San Francisco, CA; January 12-13, 2012

EXECUTIVE SUMMARY

CIRM organized a workshop in January 2012 to explore the role of tissue engineering and biomaterials development in regenerative medicine, and to determine whether areas of opportunity exist for CIRM to help further support and advance the field. This report summarizes the workshop proceedings and the recommendations made by the participants.

Tissue engineering (TE) refers to combining biological approaches to regenerative medicine with engineering and materials science. A consortium of federal agencies defined TE as “the use of physical, chemical, biological and engineering processes to control and direct the aggregate behavior of cells” (Multi-Agency Tissue Engineering Sciences Interagency Working Group, 2007). By this definition, TE encompasses a variety of tools and approaches for tissue growth, repair and/or regeneration, which enable treatment of diseases and injuries for which cell therapy alone may be inadequate.

Workshop participants identified a number of areas where CIRM could help advance tissue engineering. Those recommendations could be grouped into two general categories: 1) those that address communication and/or collaborative opportunities to advance the field more broadly and 2) those that target specific technical hurdles in the field.

The workshop participants recommended:

1. Support research using scaffolds pre-seeded with cells for transplantation as well as cell-free scaffold approaches.
2. Support the development of hydrogels that mimic natural tissue properties.
3. Develop biomaterials-based methods to model the niche in which stem cells reside *in vivo* to enhance and direct stem cell expansion *in vitro*.
4. Develop better quantitative tools for testing tissue engineered products.
5. Develop materials that mitigate immune response and enhance engraftment.
6. Help educate researchers about the translational considerations of cell-scaffold combination products.
7. Promote interaction between the stem cell and biomaterials communities
8. Facilitate dialogue with the FDA regarding regulation of tissue engineered products.

Recommendation #1: Support research using scaffolds pre-seeded with cells for transplantation as well as cell-free scaffold approaches (**see full report Page 12**). Cell-seeded scaffolds offer technology that protects and delivers cells to a target tissue and provides three-dimensional architecture to facilitate regeneration and/or repair. However, these scaffolds can present challenges to developing an off-the-shelf product. Acellular scaffolds, which can recruit the appropriate endogenous stem cells and their associated support cells, are an encouraging development in the tissue engineering field. The

success of these scaffolds relies on understanding and subsequently providing the proper matrix molecules, mechanical cues, and/or chemical cues.

Recommendation #2: Support the development of hydrogels that mimic natural tissue properties (see full report Page 15). Hydrogels are aqueous networks of chain-like molecules and are a promising technological approach both for cell delivery and to enable endogenous repair processes. Their properties can be modulated to mimic and integrate with a range of tissue types. Hydrogels are likely to play an increasingly significant role in regenerative medicine applications.

Recommendation #3: Develop biomaterials-based methods to model stem cell niches *in vivo* to enhance and direct stem cell expansion *in vitro* (see full report Page 18). A synthetic niche refers to the 2D or 3D microenvironment created by the integration of extracellular matrix molecules and/or growth factors and engineering technologies. These synthetic niches are needed to direct stem cell differentiation and expansion *in vitro* and in certain cases *in vivo*.

Recommendation #4: Develop better quantitative tools for testing tissue engineered products (see full report Page 19). Characterization methods are essential to understanding a product and are particularly important in the FDA's regulatory review process to enable clinical trials. This is especially the case for combination products, such as cells on a scaffolding material, which can be difficult to analyze and may behave differently than the individual components. Possible methods may include polarized light microscopy to determine tissue/fiber orientation and 3D imaging for evaluating repair processes.

Recommendation #5: Develop materials that mitigate immune response and enhance engraftment (see full report Page 22). Tissue engineering and the foreign body response are intricately linked. Almost all implants trigger a foreign body response, which leads to fibrotic capsule formation and/or phagocytic toxic byproduct accumulation at the implant site. Developing materials and devices that minimize this process is critical to successful implant engraftment.

Recommendation #6: Help educate researchers about the translational considerations of cell-scaffold combination products (see full report Page 24). Combination products can be particularly challenging to navigate through the regulatory process and advance to human clinical trials. Informing researchers regarding early considerations to avoid potential pitfalls can enable translation of tissue engineered products. CIRM has numerous programs designed to help educate researchers on aspects of facilitating research translation, ranging from webinars and other active educational outreach efforts to embedding translational considerations into CIRM's processes such as by mandating the development of a Target Product Profile with certain research award applications. These and other efforts with particular emphasis on combination products will be continued and, where possible, expanded.

Recommendation #7: Promote interaction between the stem cell and biomaterials communities (see full report Page 25). Participants discussed the importance of fostering collaboration between these disciplines to help develop innovative tissue engineered products that are aligned with biological systems applications and clinical needs. The materials science field has unique tools and technologies that can benefit stem cell research and other biological applications. Attendees saw opportunities for CIRM to help promote interaction and foster collaborations between these complementary fields. CIRM has encouraged collaborative work in its Requests for Application (RFAs) to include engineering based strategies on a project-by-project basis and sends representatives to attend conferences with both biomaterials and stem cell science emphases. Recent RFAs, such as Tools and Technologies III (RFA 13-05), have identified tissue engineering and biomaterials-based approaches as priority areas and the new External Innovation Pilot Program (RFA 13-04) includes the ability to help bring transformative research, which might include tissue engineering technologies, into California from outside the state. However, significant opportunities to promote further interaction between these vital communities still exist.

Recommendation #8: Facilitate dialogue with the FDA regarding regulation of tissue engineered products (see full report Page 29). Products utilizing tissue engineering strategies continue to move towards clinical application with some products already in trials and/or on the market. Many of these products have multiple components, which can complicate the regulatory pathway. It is important for the field to maintain an understanding of the current regulatory process and a dialogue with the FDA. Attendees felt that CIRM could play a valuable role in facilitating these discussions. In fact, CIRM is already serving in such capacity and regularly hosts webinars (available at: <http://www.cirm.ca.gov/our-funding/regenerative-medicine-consortium>) and participates in roundtables with the FDA on topics which have included some that are important for tissue engineering research and development. CIRM will continue to seek opportunities to further implement this recommendation.

While some of the workshop's recommendations are already represented within CIRM's portfolio, the agency will seek opportunities to expand on our support of these identified needs. These research topics may be considered as areas of particular interest in forthcoming Requests for Applications (RFAs).

