CIRM CALIFORNIA'S STEM CELL AGENCY
California Institute for Regenerative Medicine

Creating a Cell Therapy Manufacturing Center of Excellence

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In a 2013 roundtable co-sponsored by the California Institute for Regenerative Medicine (CIRM), stakeholders from across the field of regenerative medicine identified a set of manufacturing challenges that are impeding the translation of emerging cell therapies to patients. In 2014, CIRM convened a follow-up workshop to discuss how best to overcome these bottlenecks and spur the development of innovative technologies for cell manufacture. Participants evaluated the idea of establishing a Cell Therapy Manufacturing Center of Excellence (CoE) to be supported by CIRM and partners from industry and academia. Because the process for manufacturing a cell product is inseparably linked to the therapy's safety and efficacy, improvements in manufacturing processes would increase the chances that cell therapies will reach clinical trials and that clinical trials will have successful outcomes. This report summarizes the opinions presented at the workshop verbally and in a written questionnaire. As is to be expected from such a diverse group, different stakeholders had varying perspectives and expressed different levels of support for a CoE, with some strongly supporting it and others favoring alternative solutions focused on leveraging existing resources in California.

I. Introduction

Moving a stem cell–based therapy that shows promise in preclinical studies to human trials and commercial manufacture is a complex endeavor with many technological and

regulatory challenges. There is an enormous gap between showing therapeutic proof-of-principle in animal models and industrial manufacture of clinical-grade, affordable cell products that could be used to treat thousands or millions of patients. The challenges of translation exist across drug development in general, but they are especially onerous in the cell therapy industry because manufacturing a product consisting of sensitive, living cells that change in response to their environment is far more complex than manufacturing small-molecule or protein drugs. Unlike the latter, manufacture of cell therapies requires a seamless connection between research and development (R&D) and the manufacturing process, between knowledge of the underlying biology of the cell product and the ability to manufacture it consistently from lot to lot. A close interaction between R&D and manufacturing is essential to establishing a robust, scalable, and cost-effective manufacturing process that will enable the development of new generations of products over the long-term.

CIRM has an overriding interest in ensuring that the research programs it has funded have the best chance of reaching patients. In June 2013, CIRM co-sponsored a roundtable that sought to identify the key technology hurdles that are delaying clinical translation of stem cell–based therapies. Eighteen specific challenges related to manufacturing and product characterization were defined (ref. 1). Although some of the challenges are being tackled by various groups in industry and academia, these efforts may not be adequate to resolve them in a timely and coordinated fashion. No systematic, comprehensive initiative to overcome the major barriers to manufacturing cell therapies currently exists in the US.

To address this problem, on June 12, 2014 CIRM brought together stakeholders from across the field of regenerative medicine—cell therapy/pharmaceutical companies, tools and

technology companies, contract manufacturing organizations (CMOs), and academic researchers. As a starting point for discussion, CIRM provided a strawman proposal for a cell therapy manufacturing CoE. Participants were tasked with assessing the need for a CoE, evaluating the feasibility of such a center, and determining the benefits that it would provide to CIRM, California, and the industry as whole.

Workshop presenters emphasized that the challenges of cell therapy manufacturing occur at every stage of the process, beginning with the development and characterization of robust master cell banks that comply with the Food and Drug Administration's (FDA) Good Manufacturing Practices (GMPs) and continuing through to cell expansion and differentiation; potency testing; safety testing; and shipping and chain of custody. Design of a manufacturing process must take into account anticipated clinical trial size, anticipated dosing (lot size requirements), anticipated demand, anticipated pace of clinical development, potential cost efficiencies that could be achieved by scale up, likelihood of therapeutic success, and anticipated funding levels. To expand on just one of the many challenges, manufacturing capacity is currently constrained not only by the numbers of cells that can be produced but also by the numbers of cells that are lost, which can reach 50% or more. Substantial cell losses occur at all stages of manufacture (e.g., volume reduction), during storage and distribution through the supply chain, and after implantation in patients. However, the mechanisms underlying cell loss and strategies to avoid it are poorly understood.

An analysis of the potential manufacturing needs of CIRM grantees for Phase 3 trials (carried out by workshop presenter Anthony Davies, formerly Chief Technology Officer at Capricor and VP, Product Development at Geron) found that the number of cells that would be

required for different therapies varies widely (by 400-fold) and, more importantly, that the total number of cells that would be needed to supply Phase 3 clinical trials for all CIRM-funded therapies under development outstrips currently available manufacturing capacity. If manufactured using existing technologies (whether planar culture methods or suspension bioreactors), the square footage of space required for manufacturing facilities would be inordinately high. Workshop presenter David Smith (Head of Cell and Viral Therapy, Lonza) calculated that supplying cells for cell therapies that require high numbers of cells (e.g., gastrointestinal therapies, which may require doses of up to one billion cells per patient) and that would be used in large numbers of patients would require facilities on "the order of the size of the island of Manhattan and armies of technicians if we do not move to large-scale culture technologies like bioreactors."

Many participants agreed that market-based incentives to develop innovative cell-manufacturing technologies are inadequate given the longer time lines and greater risks in this industry compared with the pharmaceutical industry. Process development and small-scale cell production for Phase 1 and Phase 2 clinical trials are generally not financially attractive to CMOs, which are focused on manufacture for Phase 3 clinical trials and post-approval marketing, or to investors, who generally expect to see at least Phase 2 clinical trial results before considering investment. Autologous therapies (which use a patient's own cells and must be manufactured separately for each patient) can be especially prohibitive financially. Given this situation, a strong argument can be made that improving cell therapy manufacturing deserves public investment through public-private partnerships. Participants emphasized that such investments would have an impact well beyond the sphere of manufacturing. Because manufacturing

processes determine the very identity of cells, improving these processes may lead to improvements in therapeutic efficacy and safety. In addition, improved manufacturing would reduce the costs of therapies, making them available to more patients, and would provide a substantial competitive advantage to developers, establishing the foundation of a sustainable cell therapy industry.

Initiatives similar in concept to the proposed CoE have already been established in Canada and the United Kingdom (UK). Canada's Centre for the Commercialization of Regenerative Medicine (CCRM) is a "federally incorporated, not-for-profit organization supporting the development of foundational technologies that accelerate the commercialization of stem cell- and biomaterials-based products and therapies." CCRM actively promotes collaboration among companies in the regenerative medicine space, including large multinational companies, small-to-medium enterprises, and startup companies (http://ccrm.ca/industry-consortium). Companies that join CCRM's "industry consortium" have privileged access to the laboratories, technologies, and knowledge developed within CCRM. Industry members collaborate with CCRM on specific projects, which allows them to embark on riskier endeavors with a reduced investment. CCRM also partners with scientists and academic institutes (http://ccrm.ca/partners), including the Stem Cell Network and the McEwen Centre for Regenerative Medicine, to promote technology transfer and commercialization of scientific advances. CCRM is collaborating with the University Health Network to jointly construct and operate a new GMP-compliant cell manufacturing facility with the goal of accelerating the clinical validation and commercialization of cell therapies.

Like CCRM, the UK's Cell Therapy Catapult aims to promote the clinical translation and commercialization of cell therapies. Its remit includes 'de-risking' emerging cell therapies to make them attractive to investors; providing clinical, regulatory, and technical expertise; promoting national and global collaborations; and increasing access to financial support such as grants and investments (https://www.catapult.org.uk/cell-therapy-catapult). Cell Therapy Catapult maintains laboratories and staff who help companies to improve, standardize, and scale up their cell manufacturing processes. Currently, the UK has a network of approximately 20 small, mainly academic GMP-level cell manufacturing facilities attached to hospitals, supporting early-stage development. To address Phase 3 and commercialization manufacturing requirements, Cell Therapy Catapult will manage a new UK Cell Therapy Manufacturing Center. The Center, scheduled to open in 2017, will provide vital large-scale manufacturing facilities specifically aimed at enabling the UK to retain manufacturing activity, attract investment and boost exports. The Center is receiving $93M of funding from the UK government in addition to the existing $116M of government funding for Cell Therapy Catapult for 2012 -2017. The Center will be a large-scale facility designed to accommodate allogeneic and autologous GMP manufacturing. Part of the facility will operate as a dedicated CMO, while another part will operate as a 'hotel facility' in which third parties can rent space to manufacture their products. The hotel facility concept leverages the equipment and resources, such as quality management systems, of the facility while allowing third parties to provide their own expertise without having to share their intellectual property with a CMO. It also provides for significantly lower upfront costs and major savings in time compared with building the infrastructure de novo.

Compared with Canada and the UK, the US has far more investment and research activity devoted to cell therapy, and therefore a much greater need to solve the challenges of cell therapy manufacturing. As one of the largest and leading institutions devoted specifically to regenerative medicine in the US, CIRM is well-positioned to fill this gap.

II. Proposal for a manufacturing CoE

Based on a strawman proposal provided by CIRM to stimulate discussion, workshop participants discussed the scope and feasibility of a cell therapy manufacturing CoE initiated by CIRM. The center would be structured as a consortium of private and public member organizations (including cell therapy/pharmaceutical companies, tools and technology companies, CMOs, academic researchers, and patient advocacy groups) dedicated to the mission of accelerating clinical translation of cell therapies. Specific objectives would include identifying key technology gaps in a subset of CIRM projects, optimizing the manufacturing processes of these projects to speed their paths to the clinic, developing innovative technologies for more-scalable, cost-effective manufacturing, and promoting the regenerative medicine industry in California by establishing a cluster of economic activity around the CoE. Another important function of the proposed center would be development of manufacturing standards and best practices in collaboration with partners such as the National Institute for Standards and Technology (NIST), the Alliance for Regenerative Medicine (ARM), the International Society for Stem Cell Research, the International Society for Cell Therapy, the FDA, and the US Pharmacopeial Convention for the benefit of the cell therapy industry as a whole. If successful in facilitating groundbreaking advances in technology, the CoE would be at the forefront of

supporting the transformation of the nascent cell therapy sector into a multibillion-dollar global industry, while providing a competitive advantage for California over a period of decades and ensuring an enduring legacy for CIRM. The ultimate goal of the CoE would be helping to accelerate the delivery of cell therapies into routine clinical practice by streamlining process development and manufacturing and avoiding potential bridging studies (i.e., comparability studies) and clinical stoppages due to manufacturing challenges.

During discussion, participants emphasized that, given the close connection between product manufacturing and cell therapy R&D, improvements in manufacturing may increase the chances of successful outcomes in Phase 1/2 clinical trials. The CoE would focus its efforts on a critical stage in the translation process: process development and manufacturing for Phase 1/2 trials. It would not address larger-scale manufacturing (for Phase 3 trials and commercial production), but it would collaborate with larger-scale manufacturers (CMOs and cell therapy/pharmaceutical companies) as member partners and would indirectly support such manufacturers based in California.

The CoE would have one or two entities as lead sponsors together with sub-contracts focused on specific challenges. Consortium members would be drawn from the full spectrum of stakeholders in the regenerative medicine field, including patient advocates, who would be instrumental in educating patients about the benefits of the CoE, the new technologies being developed and any new clinical trials. The center would be supervised by a representative governance board or steering committee. Staff would have experience in industry; their expertise would cover the areas of preclinical and clinical therapy development, manufacturing and engineering, regulatory affairs, and technology transfer. A team of five or six 'cell therapy

manufacturing envoys' would be responsible for promoting best practices, information sharing, and comparability testing across the industry. Their remit would include establishing operating protocols between the CoE and third parties, resolving disputes, creating a repository of best practices, and providing leadership in standards creation by leading and hosting workshops. The envoys would work with customers to identify key processes to enhance the robustness, scalability, and cost-effectiveness of manufacturing. They would also be responsible for ensuring that the CoE has a robust pipeline of projects across various stages of development and cell types, including projects that may be underserved elsewhere and would benefit from expertise within the CoE. Finally, they would educate the community about the benefits and resources available through the CoE as well as educate the CoE about the latest knowledge and technology from industry.

Financial support for the CoE would be split between CIRM and member organizations. Potential sources of revenue include corporate sponsors, royalties and licenses, fee-for-service contracts, and government funding. Financial support by CoE members could include in-kind contributions and employee full-time equivalents (FTEs).

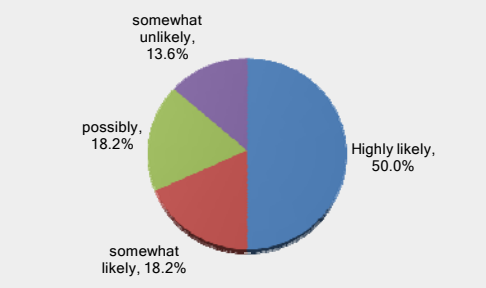
III. Questionnaire

In advance of the workshop, participants filled out a questionnaire regarding the proposed CoE (**Fig. 1**). Many were highly supportive of such an initiative and appreciated its potential synergies. The strongest support was for collaborative efforts focused on hardware, reagents, and downstream processing steps (everything subsequent to cell production). The questionnaire results indicated that 50% of workshop participants were 'highly likely' to join the

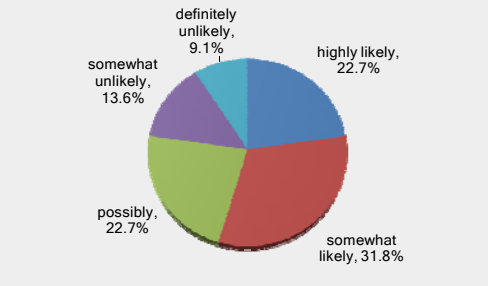
CoE, and 18% were 'somewhat likely' to want to join the CoE. 55% were 'highly likely' or 'somewhat likely' to contribute funding or employee FTEs to the CoE. A full 41% of respondents were "highly likely" or "somewhat likely" to assume the role of leading the CoE.

Figure 1
Summary of Survey Results

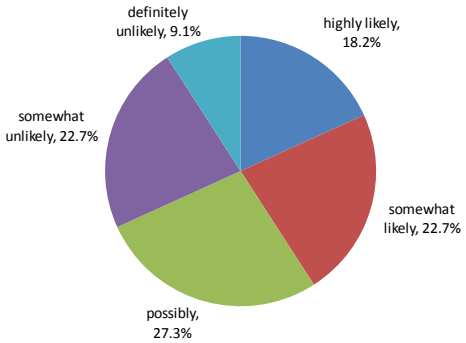
Would you be interested in joining a consortium of entities that apply for a CIRM award?



Would you be interested in joining a consortium of entities that apply for a CIRM award if it required you to commit to contributing FTEs and or some level of funding?



Would you be interested in leading a consortium of entities that apply for a CIRM award and applying as the grantee organization if it required you to commit to contributing FTEs and or some level of funding?



IV. Summary of ideas presented at break-out tables

Four break-out tables, each comprising representatives of the different stakeholders in the regenerative medicine field, discussed the following questions:

1. *Is a CoE a worthwhile endeavor for CIRM to undertake? What is the interest in, need for, and feasibility of such an initiative?*
2. *What is the optimal structure of a CoE and projected operating costs (equipment, staffing, facility leasing)?*
3. *How would a CoE prioritize projects?*

Is a CoE a worthwhile endeavor for CIRM to undertake?

As is to be expected from such a diverse group, different stakeholders had varying perspectives and expressed different levels of support for a CoE.

Tools and technology companies (i.e., companies that supply equipment and reagents) were strongly supportive. A CoE would give them an opportunity to test and compare existing equipment as well as to design new equipment to address manufacturing challenges; several tools and technology companies were willing to act as the lead sponsor of a CoE. They appreciated that a CoE would allow them to showcase their latest product offerings, involve their own experts in collaborative process development, and potentially acquire new clients.

Large CMOs were supportive. The CoE could optimize the processes that come from academic laboratories and small biotechnology companies, which typically must be reworked. Improved early processes would benefit large CMOs as they would receive more robust technology transfer packages from clients and could focus on the more profitable parts of their business (i.e., Phase 3 manufacturing). In addition, participation of CMOs in the CoE could lead to contracts at a later stage of commercialization.

Smaller CMOs were less supportive, perceiving the CoE as a potential competitor that may overlap with a portion of their core business of early-stage process development and Phase 1/2 manufacturing. A smaller CMO located at an academic center indicated that they did not have the capacity or resources to focus on process development and that a CoE would complement their work, although they felt that a targeted funding initiative, such as a Request for Application (RFA) by CIRM for which they could apply, would be a preferable approach.

Cell therapy developers supported the CoE, with the strongest support coming from academic researchers. Both small biotechnology companies and academic researchers would greatly benefit from a CoE that provided support services for process development and manufacturing as these are critical bottlenecks in the translation of therapies from bench to bedside.

Participants noted that the incentives to participate in a CoE would differ among members. For some members, 'added value' for their contributions could mean evidence that the CoE was accelerating pathways to the clinic, as measured by the number of key milestones reached (Investigational New Drug applications, Phase 3 clinical trials, Biologics License Applications (BLAs), and FDA approvals). However, the CoE would have to be financially self-sustaining in a four-year time frame, once the original CIRM funding ran out, and this time frame would be too short for many clinical milestones to be reached. The success of the CoE may be difficult to measure over the short term. For other potential members, however, evidence that the CoE was accelerating pathways to the clinic may not be enough incentive to participate.

Participants expressed opposing views as to whether a physical facility (to be leased rather than constructed) would be the most cost-effective use of funds. Those opposed noted

that given the high projected operating costs of a CoE (~$15 million/year), it would be preferable to leverage existing facilities and staff in California (although one participant questioned whether there is enough existing infrastructure in California to leverage, given the time frame). One strategy for leveraging existing California resources would be for CIRM to issue RFAs targeted to specific manufacturing challenges (tools, validated cell lines, etc.); the successful applicant would receive funding but provide their own staff and equipment. The focus would be on empowering experts in existing organizations to solve specific problems; several participants felt that the private sector currently has sufficient expertise and resources to carry out the activities of the proposed CoE. An advantage of the targeted RFA approach for companies is that they could participate without worrying about risks to their business model, whereas a CoE facility could raise issues related to competition between companies and intellectual property. However, this approach may lack other critical components, such as a centralized knowledge base, data sharing, and education and outreach to the community.

Many participants supported establishment of a physical facility (to be leased rather than constructed). They argued that a centralized space is necessary to assemble a critical mass of experts, technologies, and knowledge and to conduct direct comparisons between competing technologies. Moreover, a facility would be more capital- and resource-efficient than administering a virtual network of pre-existing expertise scattered in different locations. In the UK it was recognized that the existing virtual network of hospital-affiliated facilities, focused on early-stage processes, was not sufficient to build an internationally competitive cell manufacturing base and that a centralized facility, the UK Cell Therapy Manufacturing Center, was necessary to support cell therapy development all the way through late clinical trials and

commercial supply. In this model, each client will have separate laboratory bays and all the equipment is on wheels, facilitating sharing and collaboration.

A minority view was that the technologies required to mass-produce cell therapies already exist and that what is needed now is not to develop new technologies but to understand how to use existing technologies effectively.

Whether the CoE is creating new technologies or determining how to best implement existing technologies, its ultimate goal would be to accelerate the development of cellular therapies for routine clinical practice. This would be achieved for CIRM programs and other projects by enabling direct connections between laboratory research and the manufacturing process to develop substantial improvements in manufacturing processes and lower manufacturing costs.

What is the optimal structure of a CoE and projected operating costs?

Participants supporting the CoE emphasized that it must have a clear business model and a seasoned management team. It would need to use quality management systems, billing systems, and milestones and metrics for deliverables. Costs were estimated to be on the order of $10-15 million for upfront costs, which include leasing an existing facility and installing quality management and other QA tracking systems; $10-15 million for the purchase and installation of equipment that is not supplied by CoE participants (e.g., tools and technology companies) such as HVAC systems; and $15 million annually for fixed operational expenses.

How best to assign intellectual property rights to inventions developed in the CoE would be worked out at a later stage.

How would a CoE prioritize projects?

It would be important to apply due diligence in selecting projects. Some participants argued that the focus should be on 'moon shot' projects unlikely to be attempted elsewhere (e.g. pluripotent stem cell lines engineered to be suitable for allogeneic transplantation; very large suspension bioreactors for pluripotent stem cells). One model for project selection is competitions; winners would collaborate on the project in the CoE facility.

Participants expressed different views as to whether the CoE should be GMP compliant. Some believed that it was important to have GMP experts and GMP processes in house for their educational value to the regenerative-medicine community, whereas others thought that a requirement for GMP processes would be too costly and that the better route would be rigorous, 'controlled' processes that are not fully GMP compliant. An argument in favor of GMP compliance comes from the experience of the UK, where it was determined that the UK Cell Therapy Manufacturing Center should be GMP compliant in order to attract potential clients. Having a facility that is fully GMP compliant ensures that there are no delays between process development and transfer of the technology to a CMO for larger-scale manufacturing.

V. Future considerations

The workshop provided CIRM with valuable insights into the different perspectives of stakeholders on how to overcome the manufacturing hurdles that are slowing clinical translation of cell therapies. While no consensus was reached, two potential strategies emerged: (i) establishment of a jointly funded (public/private) CoE in California, and (ii) use of

CIRM's existing RFA process to target specific technological gaps through a new, targeted RFA; or include a specific process development module within an existing RFA structure. The pros and cons of these strategies are summarized in **Tables 1** and **2**. Participants provided specific recommendations regarding some of the major technological gaps that could be addressed through either strategy; these are summarized in **Table 3**.

Table 1: Benefits of Establishing a Center of Excellence	
1.	Accelerates the delivery of therapies to patients by integrating R&D and process development, thereby potentially streamlining the development timeline and avoiding manufacturing-related delays
2.	Integration of R&D, process development, and manufacturing may lead to improved therapies and more successful clinical trial outcomes
3.	Promotes the development of standards in conjunction with other organizations such as ARM and NIST
4.	Positions CA at the forefront of cell therapy and promotes the establishment of a sustainable cell therapy industry in CA
5.	Facilitates comparisons of existing technologies and development of new technologies
6.	Creates a multidisciplinary consortium of stakeholders and a centralized knowledge base
7.	Provides industry envoys to promote best practices, information sharing, and comparability testing across the industry
8.	Establishes an education and training resource for cell therapy manufacturing and bioprocessing
9.	Provides a robust quality management system that is adequate for BLA filings

Table 2: Benefits of Targeted RFAs	
1.	Leverages existing facilities, infrastructure, and FTEs in CA
2.	Complementary to private-sector business models
3.	Encourages companies to collaborate and share knowledge across their organizations
4.	Saves on operating costs of a CoE

Table 3: Addressable Hurdles That a CoE or Targeted RFA Approach May Address
General Goals: Facilitate interactions of industry and research; enable scalable manufacturing; reduce cost of goods to support universal and widespread access to novel cell therapies **Process Development Goals:** Tumorgenicity assays, validation assays, potency assays

Major Step-Changes Goals: Single use-disposables, closed system processing, suspension culture systems, adherent culture systems, automation

VI. Conclusion

The workshop hosted by CIRM on June 12, 2014 to discuss the potential benefits of creating a Cell Therapy Manufacturing CoE elicited differing viewpoints owing to the diversity of participating stakeholders. However, the majority of participants agreed that such a center would be beneficial not only for CIRM's programs but for the industry as a whole. They agreed that significant translational challenges currently exist and that a CoE would be useful in developing processes that could be used for larger-scale manufacture of cell therapies. The challenges stemmed from questions about how efficiently such a CoE could operate and sustain itself after the term of CIRM funding ends and how establishment of a CoE compares to issuing targeted RFAs directed at specific technology hurdles, which would allow grant recipients to carry out projects in their own laboratories with their own staff. Overall, there was substantial support for establishing a CoE in California, with the majority of stakeholders recognizing the benefits of creating a centralized facility in which to compare existing technologies, develop new technologies, share knowledge, and establish standards and best practices that could be used across the cell therapy industry.

References

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