

Alpha Stem Cell Clinics: Delivering a New Kind of Medicine

Natalie D. DeWitt, Geoffrey Lomax, Maria Millan, Ellen Feigal, and Alan Trounson

California Institute for Regenerative Medicine
210 King Street
San Francisco, CA 94107

I. CIRM Alpha Stem Cell Clinics Network

Introduction

CIRM convened a workshop of stakeholders in stem cell therapeutics on November 14 and 15, 2012, in Palo Alto, California, to discuss the creation of a sustainable footprint of excellence in clinical research for advancing the testing and delivery of effective and safe stem cell-based therapies. The group comprised ~70 scientists, clinicians, cell manufacturers, clinical trial and regulatory experts, members of biotechnology and pharmaceutical industries, investors and funding agencies, patient advocates, and experts on health care economics and insurance. They were asked to consider how the existing California clinical infrastructure could be enhanced to accelerate the implementation of well-designed and safe clinical trials for experimental stem cell therapies, with the long-term goal of improving healthcare.

Key Outcomes

CIRM's therapeutic pipeline is focused on stem cell-based therapies. A majority of candidates entering the CIRM therapeutic pipeline during the next five years will come from academic investigators, some with little or no experience in running clinical trials. Accordingly, workshop participants emphasized infrastructure needs commensurate with CIRM's anticipated therapeutic pipeline. Establishing an Alpha Clinics Network was proposed in response to these many academic-initiated trials, but not to the exclusion of industry. Attracting industry investments, where possible, is also an important goal.

Major themes include:

- Development of resources designed to support the effective design and execution of clinical trials. A special emphasis should be given to forecasting and addressing regulatory considerations.
- Compilation of information about related clinical efforts both positive and negative. A robust system for sharing "lessons learned" should be developed to ensure best use of limited resources.

- Dissemination of information about therapeutic options and clinical trials involving stem cells. Systems should be comprehensive with a special emphasis towards the need of potential trial participants.

These capacities should be built into a network that is scalable, and which leverages existing strengths in academic and other clinical centers. Capacity enhancements should be targeted towards new resources, expertise, and efficiencies specifically designed to accelerate implementation of clinical trials and delivery of stem cell therapies. This focus should ensure data, information, and protocols are continuously maintained as community resources, far beyond the longevity of individual trials.

To develop this infrastructure, workshop participants recommended organizing a network as depicted in Figure 1, with the following elements:

- 1) A robust network of clinical sites located in or affiliated with existing academic centers of excellence, with internal expertise in targeted disease areas. These sites would have a track record of successful execution of clinical trials and would provide experienced investigators; clinical staff; imaging, surgical and diagnostic technologies; and high patient volumes for given disease indications which could be accessed for recruitment into stem cell-based clinical trials.
- 2) A coordinating center to facilitate the network of sites and possible trials, and offer clinical trial and regulatory expertise. It would also have an information management component that would be HIPAA compliant and ensure maintenance and accessibility of valuable data and information about clinical trials to the public, patients and the research community, as appropriate.

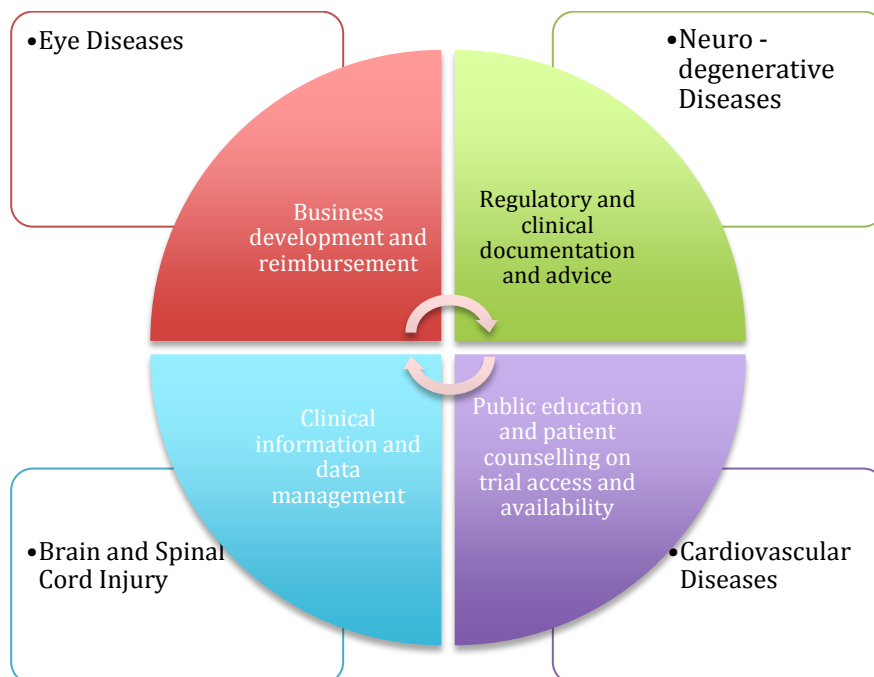


Figure 1. Organization Structure of Alpha Stem Cell Clinic Network, consisting of clinical sites (some examples of potential clinical areas represented in squares) and a Coordinating and Information Management Center (circle).

II. Background

A. Scope, Focus and Goals of Alpha Clinics Network

The development of therapies has so-far comprised three components: small molecules, biologics, and medical devices (Figure 2). Genetically modified cell-therapies and stem cell-based therapies represent a nascent technology platform still very much under development, but with the promise of treating many incurable diseases and injuries. Whereas currently there are few cell therapies in routine medical practice (with the exception of bone marrow/HSC transplantation), a concentration of R&D funding and innovations in this area in the past decade has stimulated translational and pre-clinical stem cell research with the potential to deliver many more new therapies for testing in humans in the coming decade. CIRM alone has funded over 77 translational programs headed to the clinic.

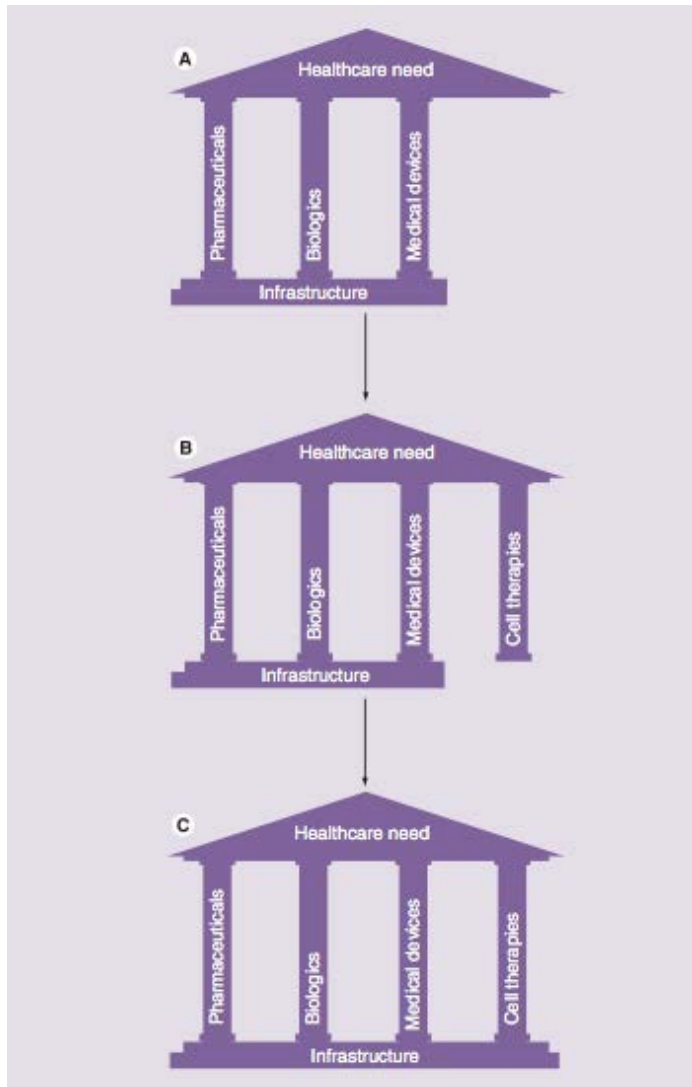


Figure 2. Four pillars of healthcare technologies (A) Currently, healthcare needs are supported by three platform technologies (represented by pillars), which is supported by the existing medical infrastructure. (B) Genetically modifying-cell therapies and stem cell therapies represent a new platform technology currently under development, with a relatively small number of approved products. (C) An expanding infrastructure will be necessary to broadly implement these technologies so as to support healthcare needs not addressed by pharmaceuticals, biologics, and medical devices. (From Mason *et al*) [1].

Once a new investigational therapy is shown to have merit through pre-clinical testing in animal models, it must then be tested for safety and efficacy in humans. To provide infrastructure for such testing to proceed in a safe, efficient, and scientifically sound manner, CIRM is proposing to establish a network of Alpha Stem Cell Clinics in California. In 2012, Trounson *et al.* defined the Alpha Stem Cell Clinics as a “carefully constructed clinical infrastructure with the requisite

scientific, technical and medical expertise and operational efficiencies” to--in the area of stem cell-based therapies--foster clinical trials and implement FDA-approved therapies into clinical practice[2].

As represented in CIRM’s current portfolio, “stem-cell based therapies” are defined quite broadly, and can be permanent or transient, employ gene modification and scaffolds, as well as a variety of different stem cell types from a range of tissue of origin. The Alpha Stem Cell Clinics would address areas of the greatest need and would enable the creation of a statewide clinical infrastructure. The Alpha Stem Cell Clinics will focus on facilitating:

- 1) Investigative therapies that are conceptually novel as opposed to modifications of therapies in current medical practice, and
- 2) Procedures that require transplantation or infusion of cells, as opposed to small molecules or biologics.

In addition, the focused activities of this initiative would create an Education, Outreach, and Training (OET) component, which would develop educational resources, including mechanisms to educate clinical staff and the public. The Alpha Stem Cell Clinics could provide medical consulting services that would inform patients on the full range of potential stem cell-based approaches for their disease, informing them of scientifically sound, regulated trials and potentially dangerous, unproven procedures. Furthermore, by establishing or leveraging existing accreditation programs for all participating clinics, similar to those existing for blood banks, the Alpha Stem Cell Clinics would help ensure safety and quality of trials and treatments, and define and promote international standards of excellence in cell therapies.

CIRM would fund the Alpha Stem Cell Clinics Network start up phase with five years of support on the order of \$70M. Network members would be expected to provide substantial facilities and other infrastructure support. The Network will have immediate and longer-term goals.

The major immediate goal of the Alpha Stem Cell Clinics Network is to address the needs of the scientific community and the unmet medical needs of patients by advancing cell therapies into the arena of first in human phase 1 and 2 clinical trials on a timeframe of less than five years in the future. Simultaneously, the Network should anticipate later stage clinical testing on larger patient populations.

There should also be consideration of financial models for sustainability, and for implementing clinical delivery of approved products. Applicants who want to be part of the Alpha Clinics Network should develop a sustainability plan to create a lasting footprint for patients in California. The plan should encompass commercial products as well as therapies for which there is not likely to be commercialization, for instance those that will follow a model like HSC

transplantation: treatment is paid for by insurers and pharmaceutical companies are not engaged. The Network would also facilitate collaborations with other centers of excellence and expertise outside the state and internationally.

B. Stem cell clinical trials in California: charting the landscape

California is a rich environment for launching Alpha Stem Cell Clinics: to date, CIRM alone has funded over 77 translational programs worth \$632 M for 38 diseases, all with the goal of finding a new candidate cell type or drug, or reaching the stage of filing for investigational new drug (IND) status with the FDA, or of completing a clinical trial ([Table 1\[pdf\]](#)) These translational awards include 50 Early Translation; 25 Disease Teams, and 2 Strategic Partnerships, and are focused on a range of medical needs, including type 1 diabetes, Alzheimer's, heart failure, HIV/AIDS, macular degeneration, and cancer. In addition, ClinicalTrials.gov lists many other clinical trials conducted in California, employing a range of autologous and allogeneic strategies, including cells derived from fetal and embryonic stem cells, cord blood, and various "adult" stem cell types.

Given this diverse landscape, a major challenge in defining the Alpha Clinic Network concept is to identify the particular niches where CIRM support can accelerate the implementation of well-designed and safe clinical trials for stem cell therapies that would be unlikely to take place absent CIRM support. A review of CIRM's existing portfolio suggests the required expertise and infrastructure for testing therapeutic candidates will vary depending on the source and preparation of cells; whether gene modification is used; urgency and duration of the intervention; modes of delivery; and follow up care needed for the trial subjects. Thus CIRM foresees the need for a scalable infrastructure with the capacity to adapt to a diverse set of therapeutic candidates.

III. Workshop Gap Analysis

A. Strengths of California Cell Therapy Infrastructure

During the CIRM Alpha Stem Cell Clinics workshop, stakeholders were asked to perform a "gap analysis" to 1) identify strengths and weaknesses in the current infrastructure for testing and delivery of stem cell-based therapies and 2) brainstorm about possible attributes and organizational models for an Alpha Stem Cell Clinics Network that would fulfill the most important unmet needs with funds available of \$70M over five years. Among the strengths identified were the following:

- CIRM-funded disease teams
- existing academic clinical centers of excellence and clinical networks
- adequate cell manufacturing capacity for pre-clinical work and early phase clinical trials
- a growing knowledge base among CIRM staff and grantees for taking experimental stem cell based approaches through to IND registration
- CIRM staff's substantive engagement with the FDA, through meetings, webinars, and roundtables, which is helping CIRM grantees' to more effectively navigate regulatory pathways

In particular, workshop participants identified as a key strength the 26 CIRM-supported “disease teams”. CIRM has been funding a diverse portfolio of innovative approaches in a broad spectrum of therapeutic areas, trying to balance near term opportunities with higher risk but potentially impactful approaches. CIRM is utilizing mutually agreed upon (between CIRM and funded investigators) “go, no-go” decisions, and progress milestones with predefined criteria for success. The evaluation process involves consultation with an external panel of experts with expertise including preclinical pharmacology/toxicology, manufacturing, clinical, regulatory, and commercial viability so that CIRM and its grantees have the ability to terminate, refine the approach, or move forward with projects based upon whether the data supports moving forward and milestones are being met. Overall, the strategy is aimed at advancing our knowledge so that within the next 5 years clinical proof of concept is established with one or more approaches. Another element of CIRM’s strategy is funding the early stages of clinical trials – ones that are typically higher scientific, technical and regulatory risk and otherwise harder to fund– to obtain the evidence to attract later stage funding from industry, and other external sources of funding.

In addition to the CIRM Disease Teams, California is home to a large number of academic clinical centers of excellence, as well as numerous biotechnology companies in the cell therapy space, and networks for clinical trials in areas such as oncology, neurology, and HIV. To maximize efficiencies, the Alpha Clinics Network should “plug into” this existing infrastructure to the greatest extent possible. For example, locating Alpha Clinics at sites with large numbers of excellent, highly trained clinicians, that are already part of existing clinical trial networks, will facilitate participation in later stage clinical trials of experimental therapies enrolling a large number of subjects.

By virtue of initial investments from CIRM in establishing GMP facilities at City of Hope and UC Davis, the current capacity within the state is considered adequate for pre-clinical work and early stage clinical trials. Moreover, training programs at City of Hope and UC Davis have made significant inroads to generating a trained workforce.

B. Gaps in California Cell Therapy Clinical Infrastructure

1. Cell Manufacturing

Cell manufacturing was considered a strength by workshop participants, in the near term. CIRM has funded Good Manufacturing Practice (GMP) facilities at City of Hope and UC Davis that are currently preparing cGMP cells for IND-enabling studies and clinical trials, both within and outside of the state of California, and are working closely with the FDA to ensure adherence to regulatory guidelines. Both facilities have also established training programs for undergraduates through the CIRM Bridges program, which at this point have enrolled 54 students, making some inroads to the need for an adequately trained workforce in this crucial area.

According to 2009 CIRM GMP Workshop Report, Geron estimated that a single ES cell-based development project would “require 40 people with 12 involved in manufacturing and 3 senior experts in GMP”. Looking ahead to phase 3 clinical trials, some participants foresaw a looming and worrisome gap in capacity, whereas others felt that industry would step in to fill any manufacturing gap when it becomes profitable to do so. Indeed, companies such as Neostem’s Progenitor Cell Therapy have already been successful in securing cell-manufacturing contracts for phase 3 clinical trials sponsored by Baxter, SOTIO, Dendreon, and others.

Anticipating and planning for manufacturing needs during the next decade should be a goal of CIRM, and one that is developed in parallel with establishment of the Alpha Clinics Networks. Whereas there are insufficient CIRM facilities’ funds for CIRM to invest in new “bricks and mortar” GMP facilities as was done in the past, workshop participants recommended that CIRM investigate ways to efficiently and cost-effectively increase capacity.

Regarding manufacturing, the workshop participants made the following recommendations to CIRM:

Further support for workforce training in cell manufacturing is needed (hands on experience through longer internship-type programs).

Investigators need help in understanding how to integrate their research with FDA guidelines early in the product development process, since it might be too late at the stage of IND-enabling studies.

Automation, new GMP facility development and expanding existing capacity represent business opportunities for the biotech industry in California.

Existing academic GMP facilities are small and not scalable for commercialization, however they can support the transition from small scale manufacturing to commercial scale GMP by helping to optimize processes.

A continuous knowledge-base with specialization in stem cell therapies

Workshop participants recommended that CIRM establish a “brain-trust” whereby experienced individuals could provide consulting services as a continuous resource for information on stem cell- therapy clinical trials as the field matures, and share their knowledge with investigators needing assistance. Actively gathering and disseminating new information would be an important function of such a resource, as workshop participants pointed out that in the past, the proprietary nature of industry product development has deterred the sharing of critical information necessary for advancing the field.

Because stem cell-based therapies are a nascent technology, it is not surprising that, as depicted in Figure 2, key foundational elements of the infrastructure are lacking, in California and elsewhere. An Alpha Clinics Network should establish a coordinating center staffed by experts who could provide consultations on important aspects of clinical trial design and implementation, regulatory and compliance issues, and information management.

Academic investigators sponsoring clinical trials pointed to having to “reinvent the wheel” in learning about the transition from pre-clinical to clinical research. They also emphasized the need for continuity in the growing knowledge base for cell therapies-- a

view held both by seasoned veterans in clinical trials, and others who have only had experience in pre-clinical animal models, but are eager to see their research have a positive impact on human health

In recent years, translational research has increasingly shifted from the private sector to universities, and many stem cell-based clinical trials are now originating in academia, making this gap in faculty experience and training a serious institutional problem. The workshop participants identified many key areas where academic investigators would benefit from having access to a repository of knowledge and information designed to hasten the transition from pre-clinical to clinical studies, build in efficiencies, and improve the quality of clinical research for cell therapies. That process is already occurring with the CIRM Disease Teams, who are monitored on a quarterly basis in the context of milestones and go-no go decisions—standards more characteristic of industry than academia.

The Alpha Clinic Coordinating Center would therefore serve as the central repository for valuable information, data and networks, incorporating valuable translational “lessons” of CIRM, its grantees, and future Alpha Clinic projects. This evolving “brain trust” would then provide valuable support and guidance for investigators as they bring product candidates to first-in-human clinical testing.

Workshop participants also pointed to inefficiencies in processes surrounding IRBs and SCROs, especially where approval is required from multiple committees in multiple institutions. CIRM has already supported efforts to streamline the system to address such regulatory inefficiencies (see for example, Henry Greely’s commentary recommending combined IRB and SCRO reviews[5]). Workshop participant Clay Johnston from the UCSF Clinical and Translational Science Institute described University of California’s Biomedical Research Integration, Acceleration and Development (BRAID) program, which has developed a central IRB for stem cell research across the UC system. An Alpha Clinics Network coordinating center should be charged with developing policies and resources to continue streamlining and improving institutional regulatory processes for stem cell research and clinical trials.

Another key concern of workshop participants was their ability to productively and appropriately engage with the FDA. The regulatory pathway for stem cell therapies, particularly those using

pluripotent stem cells, is famously difficult to navigate, due to the paucity of clinical safety data. CIRM already supports its grantees by providing guidance on regulatory interactions and facilitating community engagement with the FDA. An Alpha Clinic Coordinating Center could build on these efforts by employing experts with combined knowledge of regulatory issues and stem cell therapies to serve as consultants for investigators seeking regulatory guidance.

This type of consultation could include clinical trial design, such as outcome measurements, secondary endpoints, surrogate markers, and so on. In some cases, consortiums such as the International Collaboration on Repair Discoveries (ICORD) have been active for many years in setting guidelines for conduct of clinical trials (in ICORD's case, for spinal cord injury) [6]. An Alpha Clinics Coordinating and Information Management Center should actively seek to engage with such consortiums and clinical trial networks, to exchange information that would accelerate stem cell therapy clinical trials, as well as approval and delivery of products.

Workshop participants also emphasized the need for engaged experts who can consider and implement strategies for reimbursement for stem cell therapies, and to gather evidence for their value and effectiveness that will be important for coverage by payers. Having clear pathways in place will help in building financially sustainable clinics as stem cell therapies gain approval and are implemented as standard medical practice. The Alpha Coordinating Center would work with Accountable Care Organizations and multi-stakeholder collaborations to generate evidence for informing coverage and payment policies.

2. Integrated Information Management Resources

Workshop participants proposed establishing a resource to support the coordinated collection, storage, integration, analysis and dissemination of information for the Alpha Stem Cell Clinics Network. An important aim of such an Information Management Resource would be to ensure collection and analysis of patient data over the long-term. The FDA may in some cases require long-term follow-up studies requiring data collection over many decades. A HIPAA-compliant data management system is needed, which would assist investigators and sponsors in collecting and warehousing this data over the long term and to advocate for mechanisms to ensure that data on safety and efficacy is available to inform development of new cell-based products.

Long-term follow-up data can also be important for demonstrating efficacy of stem cell therapies that may not be apparent during the study period. One workshop participant, Irving Weissman, recounted his experience with a clinical trial for breast cancer, where patients were treated with chemotherapy and then infused with autologous highly purified hematopoietic stem cells (HSCs). The company sponsor, Novartis, terminated the trial in a short timeframe, at which point the therapy did not appear to improve patient outcomes. However, long term monitoring of the cohort indicated that the therapy resulted in better than expected patient survival [7]. In another recent CIRM-sponsored workshop on stem cell-based therapies for Parkinson's Disease, Curt Freed presented long-term follow up data on patients who had received fetal cell transplants. Freed said that although the trial was technically "a failure" because of flawed design and adverse effects in some patients in a short time frame, long term monitoring of the cohort revealed lasting survival of transplanted cells and neurologic improvement for several of the treated patients. Thus such long term monitoring is valuable for supporting and informing further highly powered studies to test and refine experimental therapies going forward.

Incentivizing company sponsors of clinical trials to participate in data sharing will be challenging, and it will be important to protect their interests as appropriate, by respecting confidentiality of proprietary information, while at the same time requiring an appropriate degree of data sharing to advance the mission of the Alpha Stem Cell Clinics Network. It is interesting to note that at this time, the landscape of disclosing clinical trial results is in flux, and there is increasing international pressure for companies to disclose information on safety and efficacy to the research and medical communities [8]. Some developments in this area are that the European Medicines Agency (EMA) has promised to establish a policy to improve clinical trial data transparency by January 2014; and clinical data-sharing consortiums for cancer and Alzheimer's Disease have been established (Datasphere and CAMD, respectively). Interestingly, all these efforts include pharmaceutical companies. The Alpha Clinics Network should emulate such consortiums and implement progressive policies on data transparency.

Establishing an expert information management resource for the Alpha Stem Cell Clinics Network will also promote data quality assurance, provide assistance to investigators for statistical design and analysis of clinical trials, managing and harmonizing electronic records, clinical trial registries, and establishing

searchable databases of SOPs, forms, and data, which could include de-identified patient data, when appropriate. The information management system should implement different levels of access depending on the confidentiality, and a public resource should also be established.

In nationally funded clinical networks, information management resources often function as a distinct component, separate from a coordinating center (eg the NIH's Neuronext Data Coordination Center). However workshop participants with experience in managing an information infrastructure noted that integrating information management into the network coordinating center provides more efficient management and operations. They recommended adopting such an organizational structure for the Alpha Clinics Network.

3. Adequate counseling and educational tools for patients, potential clinical trial subjects, and their families

The Alpha Stem Cell Clinics workshop participants pointed out a serious gap in navigational resources available to patients seeking stem cell based-treatments, or enrollment in clinical trials. The web is challenging to navigate, and is a mix of information coming from credible sources, with information from dubious clinics offering treatments that charge patients for untested, unregulated products that are not being evaluated as part of an investigational clinical trial.

The Alpha Stem Cell Clinics should provide counseling and education about cell therapies from knowledgeable staff, who have studied what treatments are safe and effective, and what clinical trials are available for individuals interested in enrolling. Generally, physicians perform this role as part of their discussions with patients; however, in some circumstances, having someone removed from the process was seen as desirable, as physicians directly involved in a clinical trial might find themselves in a conflicted position. Therefore stem cell therapy consultants analogous to genetic counselors were seen as providing an important service. California universities and colleges would need to establish training programs that would gradually create a cadre of experts in public education and patient counseling for stem cell therapies.

Educational resources for the public were also seen as lacking, and important for offsetting the flood of misinformation found on the internet. Currently there are websites such as the ISSCR's that

provide information to prospective patients seeking stem cell therapies. However, workshop participants suggested that through an EOT program operated through the Coordinating and Information Management Site, in conjunction with the Sites, extending such information by creating visual aids such as apps, animations, and videos that would address cultural differences and simplify the information. Such tools would be valuable for informed consent as well as general educational tools.

Facilitating the establishment of “support groups” was also recommended as a part of Alpha Stem Cell Clinics remit. Workshop participants noted that interactions between individuals enrolled or considering enrollment in clinical trials can provide a powerful educational tool. Finding ways to link together such individuals and their families, while ensuring privacy would be a valuable resource. At the workshop, Katy Sharify, a patient advocate and one of five subjects in the discontinued Geron clinical trial, suggested that individuals such as herself who have “gone public” about their participation in a clinical trial can promote understanding of clinical trials and how they help advance the development of more effective therapies. The Alpha Stem Cell Clinics Network should support patient advocates in these efforts, by helping to organize forums, educational resources, and support groups through a strong EOT function.

C. Overview of Recommendations

Mission:

A CIRM Alpha Stem Cell Clinics Network will aim to establish a robust pipeline of the highest quality stem cell therapy clinical trials, and to establish financially sustainable clinics for delivery of stem cell therapies into medical practice.

D. Recommended organization of Alpha Stem Cell Clinics Network

Based on the outcome of the workshop, CIRM proposes to establish several clinical sites (Alpha Stem Cell Clinics) as well as Coordinating and Information Management Center. Their activities may include but are not necessarily limited to those listed below.

1. Alpha Stem Cell Clinics Sites

Alpha Stem Cell Clinics sites would be integrated into academic clinical centers, where there is a combination of pre-clinical research, clinical staff, specialized imaging and other technologies for implementing cell delivery, and ample patient populations. The sites would create a positive “brand” that would attract clinical trials by ensuring the prestige and excellence of the individual investigators and managers associated with the clinics, the ability to enroll patients, and for their access to the Coordinating and Information Management Center, which would streamline administrative requirements, and provide efficiencies, clinical trial information, and quality control. As emphasized below, information would flow bi-directionally between the Coordinating and Information Management Center, and the Alpha Stem Cell Clinics Sites to add efficiencies and strengthen the enterprise as a whole.

The Alpha Stem Cell Clinics sites would also serve as portals to members of the public seeking information about stem cell therapies and clinical trials.

1) Patient portals for screening for trials and education, that will

- a) provide on-site health education services (HES) and participate with EOT activities through the Coordinating and Information Management Center
- b) advise patients about ongoing clinical trials
- c) provide resources for patient recruitment and informed consent

2) State-of-the-art clinical facilities and staff for conducting clinical trials, with initial priority for first in human clinical trials phase 1 and 2 studies; capacity to scale to phase 3, and for delivery of registered treatments as they become available.

Active participation in the bidirectional flow of information and feedback to Coordinating and Information Management Center, with the aim of improving efficiencies to the benefit of the Alpha Stem Cell Clinics Network and for advancing stem cell therapies worldwide

- a) Established excellence in translational research
- b) On site core facilities for imaging, diagnostics, and biomarkers
- c) In-patient and out-patient resources, as appropriate (eg outpatient infusion units, inpatient beds, interventional radiology, operating rooms, clinical laboratory, pharmacy, wide array of medical services, expertise and personnel, e.g. critical care, infectious disease)

- d) Capacity for patient management including social services and the necessary resources for coordinating insurance, long term medication, rehabilitation
- e) Resources for coordinating with patients' general long-term medical care, including appropriate return to primary care physicians, new physician and specialist referrals as needed and rehabilitative care.

2. Alpha Stem Cell Clinics Coordinating and Information Management Center

As envisioned by workshop participants, the Alpha Stem Cell Clinics Coordinating and Information Management Center would share many attributes of contract research organizations that provide consultation services, or coordination centers for clinical trial consortiums. One example is the Production Assistance for Cellular Therapies (PACT), which is funded by the National Heart, Lung and Blood Institute (NHLBI). The goal of the program is to provide aid to researchers engaged in the development of novel cell therapies by providing clinical grade products compliant with regulatory guidelines and with data that can support IND applications. PACT comprises a coordinating site (the CRO EMMES) and five cell processing facilities throughout the US (one at City of Hope in California).

A number of clinical trial networks such as NINDS's NeuroNext also employ multiple clinical sites along with a Clinical Coordinating Center, and a separate Data Coordinating Center. Whereas the goals for PACT and NeuroNext differ from the Alpha Stem Cell Clinic Network, with the former focusing on cell manufacturing and the latter on later stage multi-site clinical trials, the idea of having centralized resources that can aid a large number of researchers at distinct sites would serve the Alpha Stem Cell Clinics Network model well.

In the case of the Alpha Stem Cell Clinics Coordinating and Information Management Center, the focus will be on helping to streamline clinical trial design and execution, regulatory processes, and to provide high quality educational materials and develop online resources to educate the public, patients, and clinicians about cell therapies.

An Information Management Center would be integrated with the Coordinating Center, and would provide a variety of services to aid the efficient, secure, and appropriate management of clinical trial information for investigators, clinicians, patients, and the public.

The main activities of the Alpha Stem Cell Clinics Coordinating and Information Management Center would be:

1) Services for clinical trial design and execution

Active participation in the bidirectional flow of information and feedback to Alpha Stem Cell Clinics sites, with the aim of improving efficiencies to the benefit of the networks and advancing stem cell therapies worldwide

- a) Form steering committee to establish criteria, standards, and appropriate accreditation for Alpha Stem Cell Clinics
- b) Advise investigators on regulatory issues, statistics, project management, and other cross-cutting needs common to clinical trial development and execution
- c) Resources for creation of high quality reports and presentations for Data and Safety Monitoring Board (DSMB) and other purposes
- d) Establish expertise to provide IRB and SCRO consultation and work to improve efficiency of regulatory matters
- e) Establish standing master trial agreements with “pre-negotiation of recurring issues”
- f) Compile information on quality systems and Standard Operating Procedures (SOPs)
- g) Establish and maintain links with existing infrastructure such as specialized clinical networks, academic translational centers, NCATS and CTSA
- h) Provide training to clinical staff on Good Clinical Practices in cell therapies
- i) Build expertise in healthcare economics, partnerships with Accountable Care Organizations, and participate in initiatives for gathering evidence for informing coverage and payment decisions
- j) Patient referrals and recruitment for clinical trials at other sites

2) Outreach, Education, and Training (OET)

- a) Create uniform “branded” information for people interested in a variety of treatments and clinical trials, encompassing a wide range of diseases and injuries
- b) Create community-based advocacy platforms to address range of issues including information about clinical trials, consent, payment policy and other infrastructure needs

- c) Create CME programs to educate physicians about stem cell treatments and what is available for their patients
- d) Create templates for informed consent to improve consistency, efficiency, and compliance
- e) Organize workshops and teleconferences for Alpha Stem Cell Clinic Network Participants, including patient/trial subject support groups, as well as with non-CIRM sponsored participants and investigators

3) Information Management Center

- a) Support for OET and clinical trial registries
- b) HIPAA compliant data and Clinical Report Form (CRF) collection, long-term warehousing and management of data from clinical trials and long-term follow-up studies
- c) Harmonization of data platforms and data collection protocols
- d) Statistical design and analysis on consultation basis
- e) Searchable database of standard operating procedures, forms and de-identified data
- f) Integration of electronic medical records and clinical trial data

4) Business development

- a) Build expertise in healthcare economics, partnerships with Accountable Care Organizations, and participate in initiatives for informing coverage and payment decisions
- b) Design strategies to attract investors and philanthropists

E. Economic models for Alpha Stem Cell Clinics Network

Alpha Stem Cell Clinics will create unique models for assessing the financial viability of stem cell therapies in a clinical setting. Cost and revenue data may serve as the basis for developing reimbursement options among the public and private sector as therapies accumulate. Identification of reimbursement options can reduce investor uncertainties and encourage further investment by pharmaceutical companies, investors, funding agencies and philanthropists.

The elements of the Alpha Stem Cell Clinics Network, namely the clinical sites and central coordinating center, will interact with external entities to generate revenue streams that would ultimately ensure financial sustainability independent of CIRM funding (Figure 3). Here we discuss

some models for financial sustainability, from the start-up phase to maturity and sustainability.

CIRM support for the entire Network would be on the order of \$70M for five years. Initially, the Alpha Stem Cell Clinics Network would be funded by CIRM through a process whereby applicants would compete to become the Coordinating and Information Management Center. To reduce costs and capitalize on existing infrastructure, the designated Coordinating and Information Management Center would likely be an existing profit or non-profit entity with appropriate organization, management, and general expertise in clinical trials, which could then employ staff with specific expertise in the area of cell therapies.

Similarly, Alpha Stem Cell Clinics would be hosted within existing academic clinical centers to minimize start-up and infrastructure costs. The early goal of the Alpha Stem Cell Clinics will be to attract high quality clinical trials to the clinics, therefore criteria for their inclusion into the network will include their demonstrated ability to conduct clinical trials, to recruit participants, and to have relationships in place with companies and academic sponsors preparing to launch stem cell therapy clinical trials.

These sponsors, both academic and commercial, will be able to utilize the menu of consulting services available through the Coordinating and Information Management Center, and will engage with the Alpha Stem Cell Clinics sites to access clinical staff and services, technologies, and patient pools (Figure 3).

The Coordinating and Information Management Center could develop a fee for service model for its consulting services, and operate like a CRO. Sponsors could choose whether to use the consulting services and whether to use the Alpha Stem Cell Clinics Sites. The Alpha Stem Cell Clinics Sites would generate operating revenue by running the clinical trials and could perhaps support the Center with revenues, as the volume of trials grows and the Network builds steam.

In a second model, clinical trial sponsors would all contract with the Coordinating and Information Management Center, which would then set prices according to services needed. From this revenue, the Center would pay the Alpha Stem Cell Clinics Sites for costs associated with the clinical trials.

By the time the CIRM seed money is depleted, the clinics should have established a strong track record and brand for excellence in conducting clinical trials in stem cell therapies, which would attract more clinical trial sponsors, including companies. To have the largest possible impact on

healthcare, it will be desirable to increase industry involvement for cell therapies. However engaging corporate involvement could be challenging, given that many cell therapies are not considered patentable, and many of the ongoing trials are conducted in academic settings. It was suggested that the Alpha Stem Cell Clinics Network align as much as possible with corporate “mentality” to maximize corporate participation.

Overall, the Alpha Stem Cell Clinics Network will help companies increase their “bandwidth” and run stem cell therapy clinical trials more effectively and successfully. Many companies will already have sufficient in-house expertise for administration and regulatory guidance, and may not need to engage the Center’s consulting services. They would be attracted to the Alpha Stem Cell Clinics Network because of advantages for clinical trials such as benefiting from the collective databases, know-how and experience of the “brain trust,” positive interactions and lines of communication with the FDA and regulatory experts, positive branding, quality control, accreditation for their trials, access to patient registries for outreach and patient recruitment and, through its clinical trial management resources, help with enrollment.

Workshop participants also emphasized that attaining reimbursement for stem cell therapies will be necessary for delivering approved therapies into medical practice. It is likely that the business models for at least some of the clinics will resemble bone marrow/HSC transplant clinics, where for stem cell therapies that are proven superior to the standard of care, the clinic will directly receive reimbursement from insurers for the procedure and follow-up care.

Reaching this point will require advance advocacy and preparation, and the engagement with the CMS at an early stage of product development. It was recommended that the Alpha Stem Cell Clinics Coordinating and Information Management Center should employ experts in reimbursement methodologies to facilitate entry of approved products into healthcare delivery. One workshop participant, Jeff Sheehy, suggested that early engagement with Accountable Care Organizations (ACOs) could be helpful, given that stem cell therapies offer the promise of cures, which in the long run will offer high value and effectiveness, albeit with “ high front end costs and the necessity of developing the appropriate infrastructure for delivering complex cell based procedures.” Consortia such as the Green Park Collaborative are being established to develop methodological standards to demonstrate the effectiveness and value of new technologies. These data could be used to inform healthcare payers of the overall benefits of cell therapies and their long-term value, as compared with existing therapies.

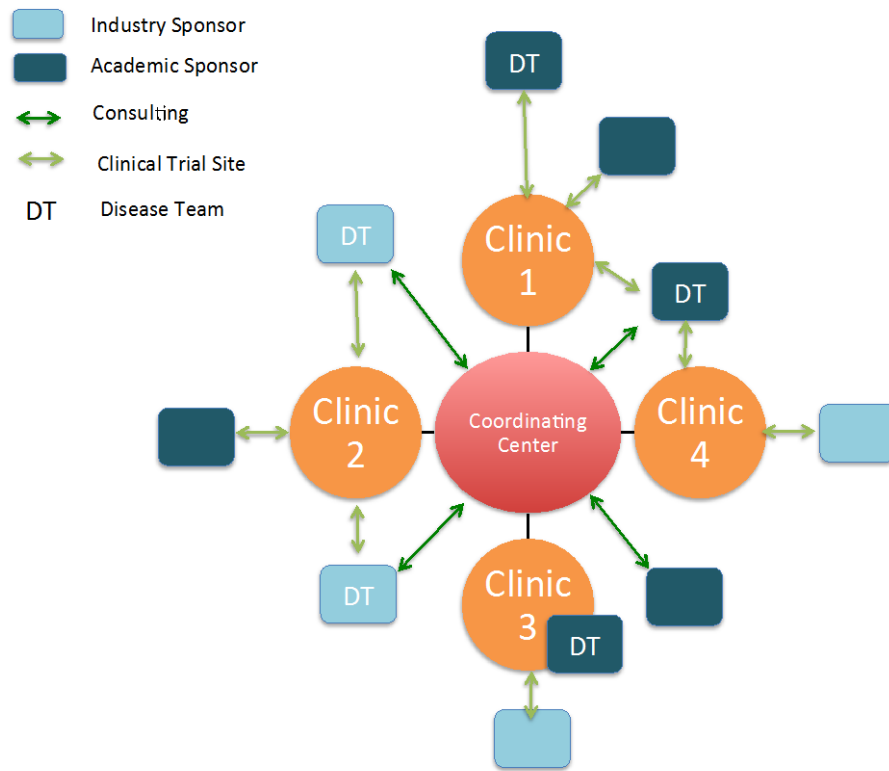


Figure 3. An organizational model for the Alpha Stem Cell Clinics Network. The Alpha Stem Cell Clinics Network would consist of Alpha Stem Cell Clinics Sites (orange circles), and a Coordinating and Information Management Center (red circle). They would work together to bidirectionally share information and expertise to enhance efficiencies and accelerate clinical trials for stem cell therapies and their delivery into medical practice; and to improve public understanding of stem cell therapies and their potential. Academic and corporate sponsors of stem cell therapy clinical trials (blue squares) would contract with the Coordinating and Information Management Center, and choose from a menu of consulting services that would streamline and provide economies of scale for clinical, data management, and regulatory processes. The Alpha Stem Cell Clinics Network would also be charged with developing standards, accreditation, and high quality educational resources for patients and the public.

IV. Summary

Establishing an Alpha Stem Cell Clinics Network in California will accelerate current and projected strategic goals for the CIRM, which comprises three phases: Exploratory, Focus and Delivery (see [Scientific Strategic Plan, 2012](#)). Currently, CIRM is currently engaged in “Focus” stage, which has as one of its aims to “drive clinical trials for patients

to generate preliminary evidence of therapeutic benefit”. In 2016 and beyond, CIRM will initiate the “Delivery” phase, in which priorities will be “facilitating commercialization (and non-commercial adoption, where appropriate) of therapies, advancing therapies to patients, and enabling business models for stem cell-based therapies”. Connecting this network to other networks and centers with a similar mission outside of California will further accelerate the development and delivery of stem cell therapies, through the global exchange of information and expertise. International testing of experimental therapies developed in California will be essential for ensuring their sustainability, as regulatory approval and widespread delivery of these products in major markets throughout the world will ensure commercial viability and sustainability of companies and universities that produce them, which will in turn help deliver returns to investors. Ultimately, establishing a solid foundation for investor engagement will ensure the viability of stem cell therapies as they move into clinical practice.

V. REFERENCES

1. Mason C, Brindley DA, Culme-Seymour EJ, Davie NL: **Cell therapy industry: Billion dollar global business with unlimited potential.** *Regenerative medicine* (2011) **6**(3):265-272.
2. Trounson A, DeWitt ND, Feigal EG: **The alpha stem cell clinic: A model for evaluating and delivering stem cell-based therapies.** *Stem cells translational medicine* (2012) **1**(1):9-14.
3. Werner M, Mayleben T, Van Bokkelen G: **Autologous cell therapies: The importance of regulatory oversight.** *Regenerative medicine* (2012) **7**(6 Suppl):100-103.
4. McAllister TN, Audley D, L'Heureux N: **Autologous cell therapies: Challenges in us fda regulation.** *Regenerative medicine* (2012) **7**(6 Suppl):94-97.
5. Greely HT: **Assessing escros: Yesterday and tomorrow.** *The American journal of bioethics : AJOB* (2013) **13**(1):44-52.
6. Steeves JD, Lammertse D, Curt A, Fawcett JW, Tuszynski MH, Ditunno JF, Ellaway PH, Fehlings MG, Guest JD, Kleitman N, Bartlett PF *et al*: **Guidelines for the conduct of clinical trials for spinal cord injury (sci) as developed by the iccp panel: Clinical trial outcome measures.** *Spinal cord* (2007) **45**(3):206-221.
7. Muller AM, Kohrt HE, Cha S, Laport G, Klein J, Guardino AE, Johnston LJ, Stockerl-Goldstein KE, Hanania E, Juttner C, Blume KG *et al*: **Long-term**

outcome of patients with metastatic breast cancer treated with high-dose chemotherapy and transplantation of purified autologous hematopoietic stem cells. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation* (2012) **18**(1):125-133.

8. Cressey D: **Drug-company data vaults to be opened.** *Nature* (2013) **495**(7442):419-420.