Cell Stem Cell
Forum

CIRM Alpha Stem Cell Clinics: Collaboratively Addressing Regenerative Medicine Challenges

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The California Institute for Regenerative Medicine (CIRM) Alpha Stem Cell Clinic (ASCC) Network was launched in 2015 to address a compelling unmet medical need for rigorous, FDA-regulated, stem cell-related clinical trials for patients with challenging, incurable diseases. Here, we describe our multi-center experiences addressing current and future challenges.

Regenerative Medicine Challenges and Opportunities

The goal of regenerative medicine is to regenerate diseased or damaged patient tissues with stem cells or related products. Until recently, the evolving clinical regenerative medicine field was plagued by a dearth of (1) systematic review of supporting pre-clinical evidence, (2) independent review of safety and efficacy by appropriate regulatory bodies, (3) trial-specific patient education, and (4) collaborative management of clinical trials to accelerate study activation and access for a broad array of patients. Other clinical trial challenges include cellular therapy product-specific manufacturing, delivery, and administration requirements and the need for long-term follow up of patients. Numerous correlative study biospecimens are also required to satisfy rigorous regulatory requirements (Kimmelman et al., 2016). The operational complexity of and training required for administering stem cell protocols has also slowed study implementation. To address these challenges and future hurdles, the California Institute for Regenerative Medicine (CIRM) Alpha Stem Cell Clinic (ASCC) Network was established and recently expanded as described below.

Meeting the Challenges through Network Cooperation

The major challenges toward streamlined, safe, and effective implementation of regenerative medicine clinical trials can be considered from the patient standpoint, which include access, education, and rapid inclusion in effective, regulated, and rigorous trials. From the medical personnel and regulatory perspective, it includes having the requisite stem cell trial training and rigorous adverse event reporting, biospecimen handling, and prospective patient identification through registries. From a scientific perspective, it involves developing novel targeted therapies that reproducibly enhance tissue regeneration and repair. In general, a major hurdle in clinical medicine is the rapid dispatch of scientific discoveries from the laboratory bench to the patient bedside; this obstacle is amplified by unique challenges in the emerging regenerative medicine field. While there is a robust national Blood and Marrow Transplant Clinical Research Network for administration of hematopoietic cell products and a national marrow donor program that provides a patient match registry (Blood and Marrow Transplant Clinical Research Network, NCT00023530) (Walker et al., 2011), the networked implementation of other stem cell and regenerative medicine trials has not been addressed. In 2015, the first integrated stem clinical network tasked with developing and implementing a panoply of regenerative medicine trials was formed by four leading California Medical Centers (UC San Diego, City of Hope, UC Los Angeles, and UC Irvine) in partnership with CIRM. In 2017, this network expanded to include UC San Francisco/Benioff Children's Hospital and UC Davis. This Network was funded by CIRM and institutional commitments to accelerate delivery of a diverse portfolio of stem cell therapies (https://www.cirm.ca.gov/patients/alpha-clinics-network) (Figure 1A). These clinics operate independently while concomitantly leveraging their respective institutional assets and the collective power of the network. Network priorities and joint activities are determined by a steering committee with oversight from CIRM.

Organizational Challenges and Opportunities

A delay in clinical trial activation resulting from unique stem cell regulatory, contracting, and coverage analysis requirements provided part of the impetus in developing the ASCC Network (Table 1). The clinics are only as good as the ability of the parts to create an integrated network. This is particularly challenging across institutions because of the heterogeneity in type and breadth of clinical trials being supported (Figure 1B). These trials involve autologous and allogeneic stem cell treatments as well as cancer stem cell-targeting small molecules and biologic therapeutic strategies alone or

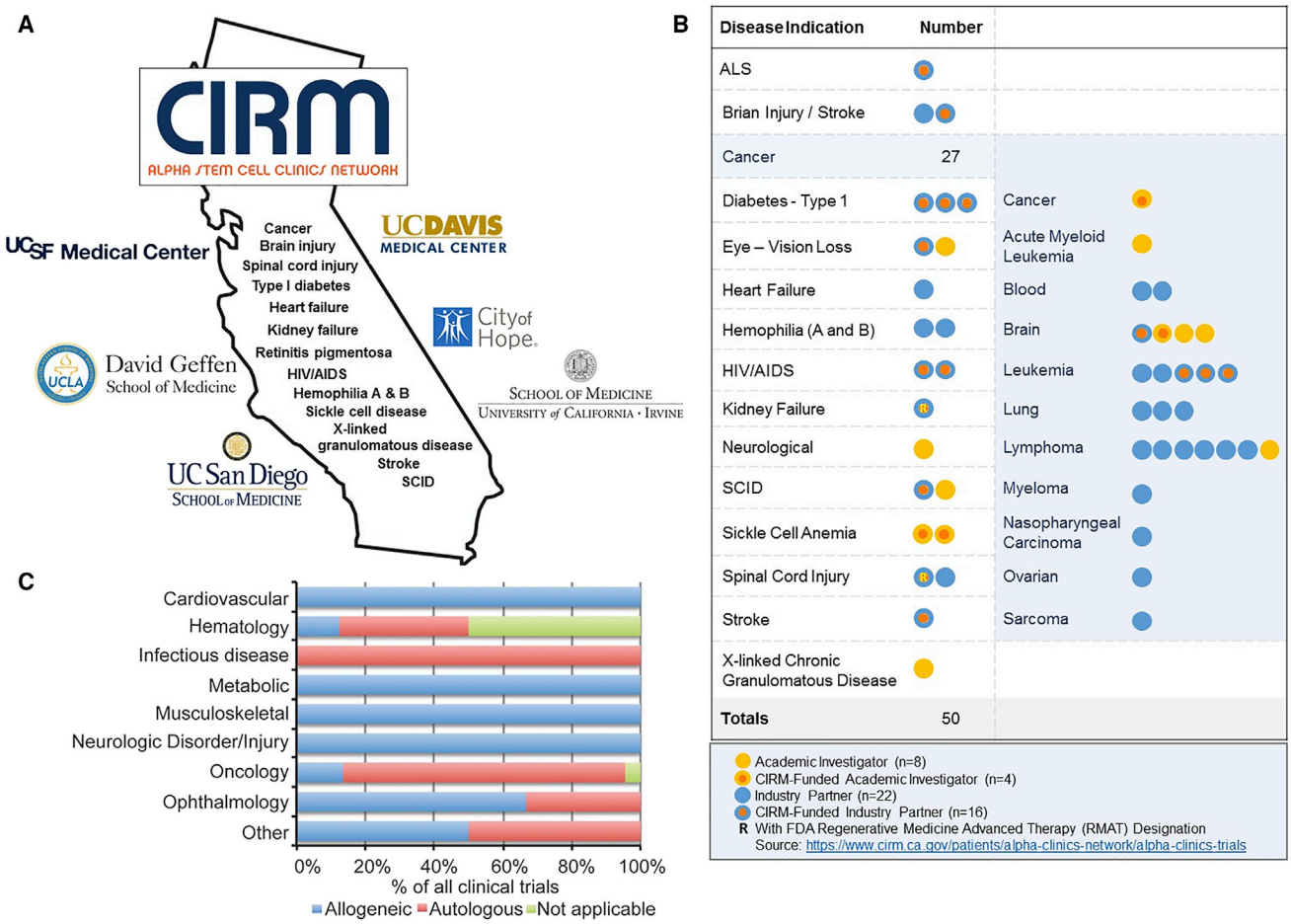

Figure 1. The CIRM Alpha Stem Cell Clinic (ASCC) Network and Clinical Trials
(A) CIRM ASCC Network and the disease indications.
(B) ASCC trials (n = 50) by disease indication.
(C) ASCC trials (n = 50) by cell type and indication. "Not applicable" indicates small-molecule, biologic, or non-cellular therapy.

in combination (Figure 1C). In 2015, CIRM ASCC grants were awarded to institutions in Southern California, including City of Hope, UCLA/UC Irvine, and UC San Diego. To enhance patient access throughout California to stem cell-related clinical trials, the ASCC Network was expanded in 2017 to include UC San Francisco/Benioff Children's Hospital and UC Davis. These areas were added to enhance clinical trial accrual and adherence by providing geographically proximate treatment and/or follow-up for patients in the San Francisco and Sacramento metropolitan areas, where ~30% of the California population resides. In addition, these sites maintain substantial telemedicine infrastructure. Moreover, some ASCC trials are expanding to sites outside of the network and outside of California together with specific industry sponsors. CIRM funding supports dedicated teams within each center to coordinate organizational resources in support of specific stem cell trials' needs . These teams and the Network as a whole have gained operational insights into effective processing, testing, and multi-site delivery of novel investigational stem cell treatments to patients.

The benefit of the Network and the CIRM ASCC partnership is the ability to rapidly implement and conduct more robust clinical trials collectively rather than independently. The number and diversity of trials create loop learning opportunities, which in turn drive innovation across the Network. These innovations combined with CIRM's continuous funding pathways and pre-existing ASCC Network capacities have resulted in coordinated organizational synergy to accelerate the development of stem cell treatments.

The efficacy of this network approach and organizational synergy is reflected in direct feedback from commercial sponsors, who experienced product evaluation at a faster than usual rate. For example, CIRM partnered with Oncternal, Inc. to support a Phase 1b/2 trial of Cirmtuzumab combined with Ibrutinib (Burger et al., 2016, Rigolin et al., 2016) for refractory B cell malignancies and has applied all aspects of the CIRM ASCC partnership to this trial including a network-generated IRB reliance agreement, accelerated confidentiality agreement (CDA), and accelerated clinical trial agreement (CTA). Moreover, the first ASCC trial to lead to an FDA-approved product is Yescarta (axicabtagene ciloleucel) (Neelapu et al., 2017), an immunotherapeutic agent

Table 1. Clinical Trial Hurdles and Opportunities

Emerging Issue or Need	Solution	Status
Delays in initiating new sites due to IRB review schedule	IRB Reliance Agreement	Implemented for both clinical trial and compassionate use protocols
Patient cohort identification and recruitment	Using cohort finding and recruitment tools UCRex and LADR	Cohort identification tool routinely used to evaluate trial feasibility
Regulatory strategy and IND filings	Develop teams with content area experts to advise sponsors	ASCC sites and CIRM maintain internal systems to conserve knowledge gained from regulatory filing and processes
Appropriate facilities for product manufacturing and/or processing for both cell and/or gene therapy products	Leverage existing CIRM-supported services and upgrade existing facilities	Three sites have GMP facilities; City of Hope provides and UC Davis will expand cell manufacturing services
Patient education and comprehensive informed consent	Enhanced informed consent using tablet devices where patients and families can obtain information about their disease, treatment, and other support services	Enhanced consent utilized in three ASCC sites
Biospecimen handling and management	Developed new standard operating procedures for biospecimens	Capacity in place to manage all ASCC patient visits monthly
Increasing access for patients	Funding to support ASCCs at UC Davis and UCSF/Oakland Children's Hospital	Initial startup phase

for treatment of lymphoma. Other trials, such as those for severe combined immunodeficiency (SCID) (Schiroli et al., 2017), spinal cord injury (Takahashi, 2018), and hematologic malignancies (Abou-El-Enein et al., 2017, Sessa et al., 2016) have also experienced accelerated product evaluation with CIRM ASCC assistance.

Product Manufacturing and Delivery

The ability to manufacture, process, and deliver cells in a timely manner is a vital feature of deploying effective stem cell therapies. This aspect is thus a strong focus of the Network, which supports a variety of technology platforms ranging across stem cell-expanded hematopoietic cell transplantation; brain or spinal cord delivery of neural stem cells; retinal, liver, lung, or cardiac delivery of stem cells; infusion of chimeric antigen receptor T cells; gene-modified progenitor cells; and small molecules and biologics that target stem cells. For example, one protocol requires patient screening and enrollment at the UCLA clinic followed by stem cell collection, genetic editing, and infusion at the City of Hope site, and then long-term follow-up at the referring clinic.

Manufacturing capacity is bolstered further by the IQVia Stem Cell Center, which is a CIRM infrastructure-funded entity to accelerate stem cell projects in the pre-IND (investigational new drug) and post-IND phases of cell product development. The Center is an ASCC Network partner and provides cell manufacturing, clinical operations, regulatory, and pharmaco-economic capabilities to the sponsors. This CIRM IQVia Stem Cell Center-ASCC partnership can also enable sponsors to scale their manufacturing needs to support the entire product development life cycle.

Unique Patient Care Requirements

Pressing challenges for patients are access to and adequate education about appropriate regenerative medicine clinical trials. Patient-focused teams at each clinic disperse patient information about trial education, trial enrollment, informed consent, procedures, and follow-up visits. Rapid patient education is required to keep up with the substantial recent increase in the number of clinical trials in the Network; as of March 2018, 50 trials in the key therapeutic areas of oncology, hematology, ophthalmology, neurology, cardiovascular disease, metabolic disorders, and musculoskeletal disorders are recruiting (Figure 1B), with many other trials in the near-term clinical pipeline.

A particular challenge is the training of nursing staff in the rapidly evolving stem cell therapy field. This nursing expertise is a critical aspect of successful stem cell trial implementation and completion. The CIRM ASCC Network sites have been placed in existing clinical research units or in separate nursing units; integration of research nurses with clinical nurses is often necessary depending on the nature of the stem cell therapy. The Network has developed core competencies as well as validation and inventory processes that allow assessment of staff as needed. Personnel dedicated to biospecimen management work alongside nurses and study coordinators to ensure that product administration, clinical correlative studies, and research procedures are performed correctly and efficiently (Perrin et al., 2018). To coordinate nurse activity, the CIRM ASCC Network developed a nursing role entitled "patient care coordinator." The patient care coordinator oversees the portfolio of stem cell therapies and is responsible for ensuring that nursing staff is adequately trained for treatment and patient care management. Simultaneously, the education of the research subject and family is among the nursing roles; the Network has developed stem cell-specific educational materials that serve to educate the study participant and their caregivers and to prevent non-compliance with study-associated medications. The ability of nurses to coordinate specialized, complex outpatient activities is paramount to safe and efficient conduct of clinical trials.

Biospecimen Handling and Data Science

The large number of biospecimens that need to be collected for stem cell-related trials to ensure both safety and long-tern

efficacy has posed an enormous challenge to clinical trial coordinators, as has data entry and tracking of these specimens.

ASCC trials represent a broad array of cell therapies that often include specialized infusion or surgical procedures. To support this, the ASCC has a Network-wide patient registry and database. These trials also require a large number of biospecimens, and autologous treatments are particularly demanding. For example, the clinic at the City of Hope averaged 66 patient visits and the handling of 344 biospecimens per month in the first quarter of 2017. To support effective management, processing, and mailing/delivery of biospecimens, standard operating procedures and biospecimen coordinators have been employed rather than relying on clinical trial coordinators alone for biospecimen handling and data entry. Thus, the ASCC is well positioned to contribute to the data science initiatives that are being launched on a national level (https://grants.nih.gov/grants/rfi/NIH-Strategic-Plan-for-Data-Science.pdf).

An Evolving Regulatory Paradigm

The recent passage of the 21st Century Cures Act and creation of the Regenerative Medicine and Advanced Therapy (RMAT) designation have established an expedited pathway for stem cell and regenerative medicine products (U.S. Public Lab #114-255; 12/13/2016). Three of the first 12 projects to obtain the RMAT designation from the FDA were CIRM programs. With regard to relevance outside of California, the NIH has launched the Regenerative Medicine Initiative project as part of the 21st Century Cures Act to accelerate, implement, and develop regenerative medicine clinical trials. CIRM and the ASCC Network have developed mechanisms to exchange experiences that provide guidance and can engage with content area experts to advise on regulatory strategies. For example, the ASCC provides support to investigators on the regulatory issues governing both pre-clinical and clinical trial projects. Furthermore, CIRM maintains a clinical advisory panel (CAP) for its clinical programs. Each CAP includes CIRM scientific staff and external experts in (1) the field research program, (2) cell manufacturing, (3) regulatory sciences, and (4) clinical operations. Importantly, each CAP has a patient representative. The CAP is designed to facilitate the accelerated development of these programs, overcome obstacles, and provide continuous consultation to the teams for this innovative and relatively new product development area. CIRM-funded trials in the ASCC Network have utilized these CAPs for extensive consultation on regulatory considerations specific to cell-based treatments.

Operational Opportunities

Another key challenge is to accelerate clinical research while supporting high-quality and safe clinical trials particularly for difficult-to-treat and/or rare diseases. The Network has met this challenge by instituting operational efficiencies and acceleration tools as described below. Once a project has IND approval and a protocol has been submitted for review and approval by the directors of each of the ASCCs in the Network, the clinic sites aspire to achieve first patient enrollment in 90 days. An early priority has been the development of tools to accelerate trial initiation. These tools include (1) shared non-disclosure agreements (NDAs) and model CTAs, (2) an IRB reliance mechanism whereby IRB approval by a single institution in the ASCC is sufficient for IRB approval at other Network sites that would like to participate in the trial, (3) large-scale (>25 million patient lives) electronic medical records-based cohort-finding and patient-recruitment registries (e.g., University of California Research eXchange, UCReX, and the Los Angeles Data Resource, LADR), and (4) enhanced (electronic) informed consent (eConsent) tools. A collective marketing tool kit has been developed whereby sponsors are introduced to the Network and provided with a preliminary feasibility assessment in addition to a review of the availability of manufacturing and/or processing facilities. This feasibility assessment is facilitated by availability of a common Network NDA.

The capacity to share clinical data and documents in real time between the ASCCs has proven pivotal for overcoming hurdles blocking study initiation and conduct. UCLA took the lead in building an IRB reliance agreement between ASCC sites. Currently, all stem cell trials conducted at the ASCCs have been reviewed and authorized by the FDA and are approved and monitored by the clinic's research ethics committee. All sites have entered into a reliance agreement whereby IRB review (including RMAT designation with FDA guidance) can be delegated to a lead site. Other Network sites can then rely on the lead IRB review to initiate trials more quickly. For example, one gene-transfer therapy protocol requires 9 weeks of monitoring from screening to infusion, with continual patient follow-up over a 48-week period. Patients are typically not familiar with the clinical workup, apheresis, and processing procedures or concomitant risks; therefore, informed consent must be dynamic and robust. To support robust consent, the Network developed enhanced electronic consent utilizing electronic tablet devices. Such enhanced consent has been utilized in three ASCC trials; patients and families find them easy to access and simple to use.

The success of the Network relies on obtaining sustainable funding and clinical expertise as well as enhancing data and operational systems developed through the ASCC Network that will contribute to therapeutic practice standards and help to guide future regenerative medicine efforts. Clinical trials in the network are increasingly industry sponsored: leveraging of ASCC resources promotes efficiency and increases the chance of industry-sponsored clinical trial success. The ASCC Network has gained key operational insights and developed strategies to overcome roadblocks that hinder processing, testing, and delivery of investigational stem cell therapies. Future opportunities for the ASCC Network are in broadening the pipeline of regenerative medicine therapies and enhancing its geographic reach via telemedicine to reduce the cost associated with patient screening, follow-up, and adherence. Another future goal is a centralized patient registry. By connecting to and leveraging emerging data science efforts, there is great potential to enable stem cell clinical research on a more global scale and to provide healthcare economics data that would support payment models and enable access to these treatments. Going forward, it is anticipated that challenges posed in the arena of stem cell therapeutics will be met in creative partnership with CIRM, its ASCC Network, industry partners, and the Regenerative Medicine Innovation Project at the NIH. While unique regulatory requirements and availability of

academic, philanthropic, and industry sponsorship may limit access to stem cell-related clinical trials in other areas, the ASCC Network provides a pivotal paradigm for establishing rigorously regulated stem cell clinical trials in a large geographic area. This paradigm could be implemented outside of the state of California as well as in other countries.

DECLARATION OF INTERESTS

All authors have CIRM funding to declare. M.C.W. is a Consultant for Bioverativ, Inc., Bluebird Bio, Inc., and Sangamo Biotherapeutics and a Medical Director for AllCells, Inc. and ViaCord Processing Lab.

REFERENCES

Abou-El-Enein, M., Cathomen, T., Ivics, Z., June, C.H., Renner, M., Schneider, C.K., and Bauer, G. (2017). Human Genome Editing in the Clinic: New Challenges in Regulatory Benefit-Risk Assessment. Cell Stem Cell *21*, 427–430.

Burger, J.A., Styles, L., and Kipps, T.J. (2016). Ibrutinib for Chronic Lymphocytic Leukemia. N. Engl. J. Med. *374*, 1594–1595.

Kimmelman, J., Heslop, H.E., Sugarman, J., Studer, L., Benvenisty, N., Caulfield, T., Hyun, I., Murry, C.E., Sipp, D., and Daley, G.Q. (2016). New ISSCR guidelines: clinical translation of stem cell research. Lancet *387*, 1979–1981.

Neelapu, S.S., Locke, F.L., Bartlett, N.L., Lekakis, L.J., Miklos, D.B., Jacobson, C.A., Braunschweig, I., Oluwole, O.O., Siddiqi, T., Lin, Y., et al. (2017). Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. N. Engl. J. Med. *377*, 2531–2544.

Perrin, M., Kim, T., Stan, R., Giesie, P., Tabor, J., Le Verche, V., Johnson, S., Lomax, G.P., and Zaia, J.A. (2018). Role of Nursing Competencies for Accelerating Clinical Trials in Stem Cell Clinics. Stem Cells Transl. Med. *7*, 6–10.

Rigolin, G.M., Cavazzini, F., and Cuneo, A. (2016). Ibrutinib for Chronic Lymphocytic Leukemia. N. Engl. J. Med. *374*, 1593.

Schiroli, G., Ferrari, S., Conway, A., Jacob, A., Capo, V., Albano, L., Plati, T., Castiello, M.C., Sanvito, F., Gennery, A.R., et al. (2017). Preclinical modeling highlights the therapeutic potential of hematopoietic stem cell gene editing for correction of SCID-X1. Sci. Transl. Med. *9*, eaan0820.

Sessa, M., Lorioli, L., Fumagalli, F., Acquati, S., Redaelli, D., Baldoli, C., Canale, S., Lopez, I.D., Morena, F., Calabria, A., et al. (2016). Lentiviral haemopoietic stem-cell gene therapy in early-onset metachromatic leukodystrophy: an ad-hoc analysis of a non-randomised, open-label, phase 1/2 trial. Lancet *388*, 476–487.

Takahashi, J. (2018). Stem cells and regenerative medicine for neural repair. Curr. Opin. Biotechnol. *52*, 102–108.

Walker, T., Milford, E., Chell, J., Maiers, M., and Confer, D. (2011). The National Marrow Donor Program: improving access to hematopoietic cell transplantation. Clin. Transpl., 55–62.