Stem Cells Translational Medicine

Perspectives

The Alpha Stem Cell Clinic: A Model for Evaluating and Delivering Stem Cell-Based Therapies

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Summary

Cellular therapies require the careful preparation, expansion, characterization, and delivery of cells in a clinical environment. There are major challenges associated with the delivery of cell therapies and high costs that will limit the companies available to fully evaluate their merit in clinical trials, and will handicap their application at the present financial environment. Cells will be manufactured in good manufacturing practice or near-equivalent facilities with prerequisite safety practices in place, and cell delivery systems will be specialized and require well-trained medical and nursing staff, technicians or nurses trained to handle cells once delivered, patient counselors, as well as statisticians and database managers who will oversee the monitoring of patients in relatively long-term follow-up studies. The model proposed for Alpha Stem Cell Clinics will initially use the capacities and infrastructure that exist in the most advanced tertiary medical clinics for delivery of established bone marrow stem cell therapies. As the research evolves, they will incorporate improved procedures and cell preparations. This model enables commercialization of medical devices, reagents, and other products required for cell therapies. A carefully constructed cell therapy clinical infrastructure with the requisite scientific, technical, and medical expertise and operational efficiencies will have the capabilities to address three fundamental and critical functions: 1) fostering clinical trials; 2) evaluating and establishing safe and effective therapies, and 3) developing and maintaining the delivery of therapies approved by the Food and Drug Administration, or other regulatory agencies.

Introduction

The average cost of delivery of a new biopharmaceutical drug into medical practice has been estimated to be $1.2-3.9 billion, including capital costs and the costs of failed drugs [1-3]. It will be difficult for the new generation of cell therapies to generate sufficient revenues to offset this present well-defined, but very expensive, drug regulatory development pathway to the clinic. It is of interest that more than 20% of all new drugs registered between 1990 and 2007 came from public research institutes, with a disproportionate number having important clinical effects [4]. This trend could be expected to continue and accentuates the importance of government funded efforts in linking basic research to therapeutic outcomes, one that can be emulated in injecting government funding to cell therapeutics.

In the private sector, there are currently too few investors and pharmaceutical or biotechnology companies with sufficient resources and interest in cell therapies to enable the full opportunity for clinical trials to occur. Cell therapies are likely to be very disease-, injury-, and even patient-specific for many autologous applications. They may require genetic modification and be given as progenitor or stem cells that can renew as part of their curative properties and persist in the body for long periods of time. Unlike a drug or biological, donor cells may proliferate, which will entail long-term follow-up for safety and efficacy. This model is not a typical model for the pharmaceutical industry and requires that an alternative logistic and financial model be put in place to achieve widespread clinical application. In doing so, we envision partnerships between academic scientists, medical clinics, biotechnology companies, and government funding agencies who can together build a sustainable model for cell therapy, ensuring that only the most efficacious and safe therapies become available, in the shortest timeframe possible, to the people who need them.

Role of Industry in Delivery of Stem Cell Applications

Industry will and should have a central role in providing stem cell therapies. Whereas the return on investment for companies implicit in such a long and uncertain process continues to handicap company involvement in the provision of cell therapies, it is clear that significant opportunities exist for industry involvement. Industry partners are ideal for academic and medical center researchers and clinicians. They provide the focus, manufacturing, quality control programs, pharmacokinetic data, and substantive capacity in preclinical investigational new drug (IND) -enabling research. Companies, logically, are providers of products, reagents, and devices necessary for clinical cell-based therapies. Examples abound of these critical contributions to in vitro fertilization (IVF) clinics, bone marrow transplant units, and cancer centers. For example, going forward, new methods of tissue engineering will provide ample opportunities for companies to provide scaffolds and tissue and organ culture services. Companies that develop specialized instruments for standardized delivery and monitoring of cells will also create profitable businesses from widespread implementation of cell therapies. Successful clinical applications of cell therapies will then depend on the availability of these service-based resources, medical

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devices, and in vivo cell monitoring technologies from the private sector. Biotechnology companies may also evolve into the clinical providers of cell therapeutics, but it appears this route is presently severely limited by lack of venture capital, although views of this may vary within the biotechnology and pharmaceutical sectors [5].

In time, examples of profitable cell therapeutic applications may evolve through new start-up companies that will attract the interest of major investors or mergers and acquisitions. In the absence of significant venture capital and major pharmaceutical company interest, an alternative system is needed for academic stem cell scientists to partner with industry biotechnology expertise. These partnerships that are forming, for example, under the guidance of California Institute for Regenerative Medicine (CIRM), and will lead to creation of an alternative system to enable the clinical trials necessary for clinical acceptance of cell therapies [6]. In many respects, this has already happened with bone marrow and, to a lesser extent, for umbilical cord blood transplants. The major cancer centers and hospitals with substantial hematology services provide these treatment options for patients. The very successful fertility or assisted conception clinics that provide IVF services also evolved through major clinics attached to universities and primary clinical research organizations [7, 8], with biotechnology companies emerging to provide equipment and reagents to service the clinics. The role of biotechnology in cell therapies is likely to be broader, with the possibility of providing a wide range of hardware, services, and manufactured cells and materials, suggesting much greater commercial opportunities will be supported in the clinical application of cell therapies.

The Alpha Stem Cell Clinic

The Alpha Stem Cell Clinics will have the capability to address the three fundamental functions critical for advancing stem cell-based science into safe, effective, and accessible therapies for patients by: 1) fostering clinical trials; 2) evaluating investigational cell therapies through carefully controlled clinical studies to obtain the evidence needed for establishing safe and effective therapies, and 3) providing access and delivery of proven therapies to patients (Table 1). Patients accessing Alpha Stem Cells Clinics will comprise three categories, according to the maturity of the cell therapy they seek (Fig. 1), ranging from patients with no therapeutic options seeking experimental treatment to patients seeking standard of care treatment that will be paid for by their insurance. Clinical trials will require a source of funding, and effective access and delivery will require that the therapy is valued by physicians, patients, and those who pay the bill. In many circumstances, this will, by necessity, require that the therapy have a market advantage over other available therapeutic options and require the appropriate levels of coverage and reimbursement.

The Alpha Stem Cell Clinic may be seen as another form of the networked clinical research centers (CRCs) that have evolved with National Institutes of Health support. Their role is to provide clinical trials capacity for those studies evolving with IND registration, establishing proven therapies with benefits exceeding the alternative treatments presently available and enabling patients to access proven therapies. Clearly, the clinical trials will continue to demonstrate new benefits and curative opportunities that can be evaluated in such clinical environments, whereas maintaining the long-term patient records necessary for vigilance of safety for these new cell therapies.

The financing of the "Alpha Clinic" will require public support in the beginning, and CIRM sees this as a potential role for this agency in California, which has, through a public initiative, Proposition 71, committed substantial resources toward the goal of advancing stem cell basic research and emerging therapies towards the clinics. Through providing funding, CIRM and analogous funding bodies can also provide a review structure, whereby clinics applying for Alpha Clinic funding and designation would be vetted by clinicians and scientists engaged in translational research, clinical trials, cell therapies, and cell manufacturing (when appropriate). In parallel, the business model will have to develop as the cell therapies move through clinical trials to proven patient availability. Insurance reimbursements will need to accompany these developments to constrain the costs to individual patients. The business model developed for IVF clinics may be useful in this regard. This is a mixture of patient fees and reimbursement in the U.S., but, in other countries, a variety of public and private funding is used successfully. It is hoped that, as treatments with proven efficacy and improvements over current standard of care emerge through clinical trials, they will be accepted by insurance companies as reimbursable to patients. Those treatments that alleviate the need for more expensive, long-term, alternative care should provide substantial savings to medical insurers, and, thus, it is imperative that efficacy and safety studies are well-designed and swiftly implemented for the most promising therapeutic candidates.

It will be relatively straightforward to seed primary Alpha Stem Cell Clinics within major medical centers that have the clinical infrastructure and are presently involved in clinical phase 1-3 studies for cell therapeutics, particularly those with established clinical translation research centers in place. These clinics already possess the critical human resources and infrastructure needed for cell therapies, including key clinicians and nursing staff. Moreover, they should have access to molecular and cell biologists and good manufacturing practice (GMP) facilities within their network

Table 1. Attributes of the Alpha Stem Cell Clinic

- Links with translational researchers
- Highly qualified clinicians with disease expertise
- Expertise in handling, delivery, and monitoring of cell therapies
- Clinical trial expertise
- Patient safeguards of medical standards, ethical oversight, IRBs, and ESCROs
- Data and safety monitoring
- Laboratory and personnel with key technical expertise
- Informatics infrastructure for long-term storage of confidential data
- Capacity to collect long term, longitudinal data on safety and efficacy of the cell therapy
- Educational outreach to patients and their caregivers
- Appropriate licensing of cell therapies
- Sustainable business model capable of generating subsidiary Beta clinics

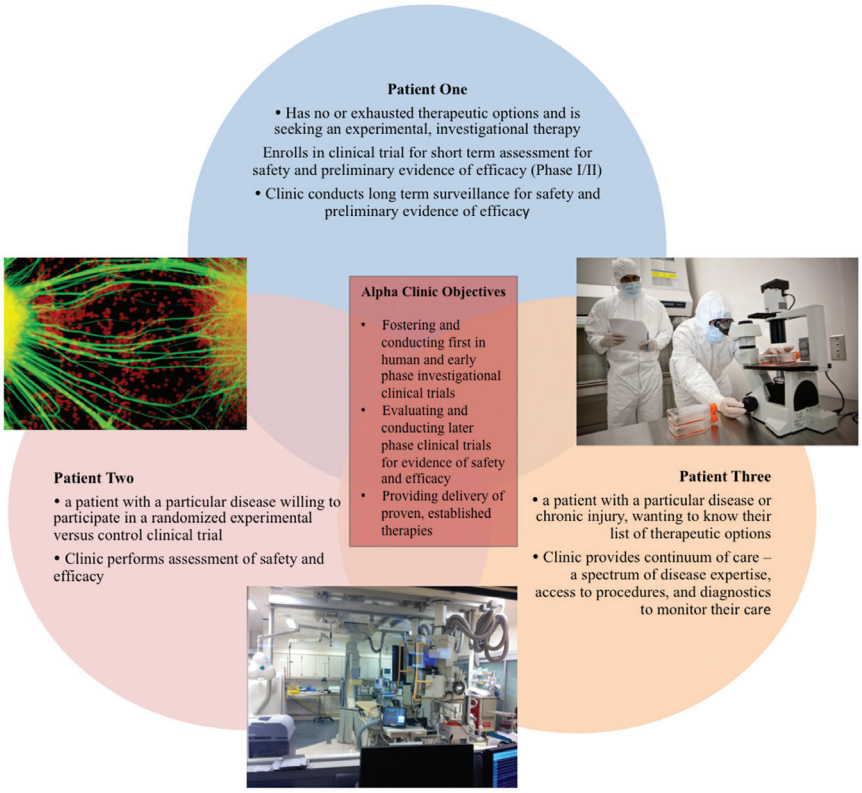

Figure 1. The Alpha Clinic will possess the infrastructure to treat patients who are participating in experimental cell therapies as well as deliver proven cell therapies. Images, from left going clockwise: neurospheres derived from human embryonic stem cells, as captured by a fluorescent microscope (photo: Carol Marchetto, Salk Institute); worker in California Institute for Regenerative Medicine-funded good manufacturing practice facility at University of California (UC) Davis (photo: Gerhard Bauer, UC Davis); a catheter-based delivery room where two stem cell trials have been performed at UC Davis for heart and vascular disease (photo: Natalie DeWitt, CIRM).

to handle and manipulate cells. In addition, we anticipate the need for staff able to explain the associated risks and benefits of cell therapies to prospective clinical trial subjects and patients. These staff can be counselors or specially trained nurses who can objectively counsel patients on the merit and risks of the evolving cell therapies and costs for their individual indication (including gene therapy issues, where appropriate). As a model, such counselors have proven invaluable in IVF clinics [9].

In terms of specialized infrastructure, autologous and allogeneic cell therapies will require access to on- or off-site GMP facilities to enable the preparation of cell products and, where appropriate, their purification, cryo-storage, genetic modification, expansion, and characterization. In California, GMP facilities have been established in a number of venues; these include academic research centers, such as University of California (UC) Davis, UC San Francisco, and UCLA, clinical centers, such as the City of Hope, and biotechnology companies, such as Progenitor Cell Therapy and Pacific GMP. From a practical standpoint, the cost for cell biologists to properly manage the cell products during the manufacturing of the cells is not unlike the necessity for experienced cell biologists in blood banks and embryologists at IVF clinics. Depending on the complexity of the therapy, there may be a need for cell and molecular biologists at the point of care to modify the cells prior to delivery to the patient. However, in another and likely parallel model, companies will function as service providers; clinicians will send cell therapy companies patient cells for modification, expansion, purification, characterization, and/or seeding scaffolds, and the company will perform the required service and deliver an implantable or perfusable product to the clinic for delivery to the patient.

The "Alpha Clinics" could each have a particular expertise, such as neurodegenerative disease, cardiac repair, eye disease, bone and cartilage repair, or diabetes. However, some or all may be capable of providing treatments across a broad spectrum of stem cell applications and be networked to enable the capture of the best expertise and capacity of the clinical specialists involved, as have academic cancer centers. In time, subsidiary beta clinics will evolve as the expertise and demand for cell therapies increases; again, this capacity may mirror what has been achieved in community cancer centers. It is possible that specific cell therapies could be handed on to clinics within the community, as have the IVF centers devolved as time and transfer of medical expertise occurs. It would be important to ensure that the entire community has access to these clinics and proven therapeutics. Looking forward, we predict that advances in "telemedicine", whereby surgeons employ telecommunication of images and magnetically controlled delivery devices, will enable cell therapy procedures on patients from a distance. It is hoped that, in the future, such innovations will further extend the reach of cell therapies to patients in remote communities.

Stem Cell Therapies and Tissue Products Evolving for Clinical Application

There are many new cell therapies progressing through clinical trials for a wide variety of applications [10] , and there will be

an increasing availability of these for patient utilization in the near future. Whereas it has been difficult to expand hematopoietic stem cells, mesenchymal, neural, and adipose stem cells are more readily expandable, as are cardiomyocytes, which might be applied to autologous transplants for cardiomyopathy [11].

Many of these applications pose additional logistical challenges. For instance, the possibility of genetically modifying autologous hematopoietic stem cells to correct genetic disease, such as targeting sickle cell anemia or β-thalessemia [12] presents an additional technical complexity; specifically, the need to isolate and prepare hematopoietic stem cells from mobilized marrow cells induced by specific growth factors to purify those cells and, often, to genetically modify them will require cell and molecular biology expertise that will be very specialized and demanding. As an example, the gene therapy associated with targeted interruption of genes that could be a cure for human immunodeficiency virus (HIV)/AIDS relies on the isolation of T-cells or hematopoietic stem cells and the disruption or interference in the CCR5 gene—a critical coreceptor for HIV binding to blood cells [12, 13].

Tissue engineering presents a separate set of specialized conditions and expertise. This field has progressed rapidly, with tracheal transplants using stem cells bioprocessed with decellularized and manufactured scaffolds [14] and construction and transplantation in bladder repair [15] attracting considerable interest. Implementation of such transplants will require one procedure to harvest patients' cells, then many weeks of ex vivo culture under carefully controlled aseptic conditions to produce the functional transplant-ready organ or tissue, and then surgical delivery to the patient. Long-term monitoring of organ function and overall outcomes must be built into the Alpha Clinic model.

Pluripotent stem cell derivatives have entered phase 1 clinical trials for spinal cord repair and retinal regeneration, and neural stem cells are under clinical trial evaluation for a number of conditions [16]. There will be a progressive expansion of the cell and tissue transplant strategies evolving for clinical evaluation and comparison with currently available treatments, if they exist. There will also be newer cell types and approaches evolving that will need very careful evaluation. Even if cell products were available commercially, there is a need to have the clinical and associated infrastructure to utilize and deliver these therapies and to monitor long-term outcomes. It is likely that reagents for cell therapies will become commercial products, and this is the opportunity that major pharmaceutical companies will adopt, as they did with IVF reagents (including hormones and drugs).

For a full range of applications, clinics or the GMP facilities that service them will also need advanced fluorescent activated cell separation equipment, cell culture facilities, molecular biology technology, cell monitoring equipment, and access to appropriate cell handing and manipulation facilities (e.g., GMP laboratory). In some cases, cell manufacturing will be performed by companies and the product shipped to the clinics. However, in some advanced medical facilities, all these capacities are already integrated on one campus. With consolidation and network building to streamline these facilities for optimum clinical efficiency and patient access to cell therapies, they may well evolve to become the Alpha Stem Cell Clinics. There are good reasons to encourage them to be recognized as CIRM Alpha Stem Cell Clinics in California, especially those that are dedicated to providing cutting edge stem cell therapies for conditions where there is evidence of safety and efficacy from already completed clinical trials. This model would strongly attract patients who are seeking therapeutic intervention for otherwise intractable disease and serious injury as an alternative to seeking treatment in places that do not have the proper regulatory endorsement and scientific basis for their advertised treatments [17].

The cell therapeutics model deviates from the drug model of small molecules and biologics that the pharmaceutical industry is required to follow and creates a paradigm that would place responsibility for treatment quality assurance and patient long-term follow-up with clinicians and the major tertiary clinics and their research and ethics oversight committees, partnering with companies providing services and products, where appropriate. Possibly significant savings could accrue for the stem cell therapies, when compared with the cost of new drug candidates, if they follow the standards set by the bone marrow transplant service centers.

In addition, there is a need to expand the number and expertise of sites for early clinical trials to enable the wave of new potential opportunities in stem cell clinical trials to progress in a financially viable manner. There are currently relatively few clinical trials centers with the full scientific and clinical expertise necessary to provide cell therapies in California, and this is probably the case elsewhere. A more targeted and integrated infrastructure across the state, nationally, and internationally to conduct the cell therapy clinical trials would be of immense value, particularly if it is scalable and opportunistic.

Allogeneic cell therapies will probably require the use of immune modulation to prevent rejection and enable long-term survival and renewal of the regenerative cells. Long-term immune suppression is undesirable, as it poses extreme risks for infection, development of malignancies, and patient well-being. CIRM has funded a program of new studies to develop immune tolerance strategies [18]. Increasing interest in immune modulation for transplant tolerance and correction of autoimmunity should enable more effective and efficient utilization of allogeneic stem cell therapies, but will necessitate careful monitoring of patients, which would be an important role for Alpha Stem Cell Clinics. Recently, it was shown that, when purified hematopoietic stem cells were expanded in culture, they were effective in establishing allogeneic chimerism when transplanted across major histocompatibility complex barriers [19]. In addition, it is possible to expand regulatory natural T-cells (CD4+, CD25+) for transplantation tolerance and the treatment of autoimmunity [20]. These developments could lead to effective tolerance strategies based on T-cell tolerance [21, 22]. The Alpha Stem Cell Clinic model should incorporate these new developments, where appropriate.

CIRMs Translational Portfolio

Since 2009, CIRM has substantively increased its focus and funding on translational programs with 44 projects, including a first-in-human clinical trial with the first Food and Drug Administration (FDA)-approved clinical trial using human embryonic stem cell derived oligodendrocyte progenitors in patients with sub-acute spinal cord injury. There are 14 multidisciplinary "disease teams" aimed at completing the studies required on the regulatory pathway to file an IND application for entry into human clinical trials over the next 4 years and 29 early translational programs aimed at target identification and selection of a development candidate. CIRM has invested approximately $361 million in translational

projects, leveraging an additional $50 million from collaborative funding partners across the globe.

CIRM is substantively increasing its interactions and encouraging collaborations with industry through this increase and expansion of its translational programs, with over 16 awards totaling approximately $76 million to over 10 different companies. CIRM is providing additional opportunities to increase industry's awareness and exposure to CIRM-funded academic investigators and opportunities to collaborate. In addition, CIRM is making its award programs (grants and loans) in timetables and terms attractive to industry engagement.

In addition to funding and actively managing programs with mutually defined GO/NO-GO milestones, predefined criteria, and progress milestones, CIRM is also trying to help clarify the regulatory pathway for innovative therapies through collaborative interactions with the FDA. CIRM provides educational webinars and roundtables that focus on challenges and bottlenecks in development and potential approaches to address them and is actively engaged with industry in the Alliance for Regenerative Medicine. In addition, CIRM is actively working with patient organizations to help understand their needs and perspectives and trying to provide them with tools and information that would be helpful in better understanding the disease. CIRM brings strategic stakeholders together at conferences for interactive dialogue on ways to enhance and leverage expertise and resources to work together on translational programs. A strategic collaborative funding partnerships (CFPs) program enables CIRM to extend its leadership and influence in translation of cell therapies nationally and internationally, with the CFPs including 13 international agreements to collaborate, 3 U.S. states, the Junior Diabetes Research Foundation, and the U.S. National Institutes of Health.

There are many new translational research projects progressing worldwide in stem cell medicine. CIRM has a vibrant and growing portfolio of translation projects, and many may evolve to early clinical trials. However, it is difficult to see how all these opportunities can be financed through all phases of clinical trials without a new model to assist their progress to clinical application. As examples of what may be expected to develop under CIRMs guidance, the following areas are in translational study.

CIRM has a rapidly expanding translational portfolio primarily based on cell therapies (Fig. 1). The largest disease program is neurological disease and injuries. However, much of this work is in early translation, with studies focused on proving up a disease candidate (Parkinson's, Huntington's and Alzheimer's diseases, and spinal muscular atrophy). There are also earlier stage studies looking at disease candidate feasibility, including molecules targeting neuroinflammation in Parkinson's disease, Canavan disease, autism, epilepsy, and traumatic brain injury and the use of motor and autonomic precursor neurons for spinal cord repair. The leading edge of the CIRM portfolio is the Geron Inc. clinical trial using embryonic stem cell (ESC)-derived oligodendrocytes for spinal cord injury. We are also backing research on the use of ESC derivatives for stroke and amyotrophic lateral sclerosis that are presently in preclinical study for clinical registration.

Eye diseases are also well represented in the portfolio, with disease candidate studies well advanced on induced pluripotent stem (iPS) cell derivatives for dry macular degeneration and retinitis pigmentosa. Candidate feasibility studies are progressing on limbal cell deficiency. The front running project is focused on the use of ESCs for dry macular degeneration, using scaffolding to control the migration of the retinal monolayer. This should be ready for clinical trials in the next few years.

We are funding studies for how to eliminate cancer and cancer stem cells by a variety of mechanisms. Hematological malignancies are being targeted by small molecule inhibitors of B-cell lymphoma 2 and 6 in disease candidate studies. There is also a study on destroying glioblastoma using an engineered cell vehicle with a replicating retrovirus encoding a suicide gene. We have five cancer strategies in preclinical evaluation. Two target glioblastoma using cells that home to tumors and deliver a cytotoxic drug at high levels in the localized tumor or convert one to a much more toxic molecule to wipe out these dangerous tumors. Two studies are targeted to hematological cancers using small molecule and monoclonal antibodies to eradicate the cancer stem cell population. Another study focuses on the attack of cancer stem cells in solid tumors. We expect some of these projects to reach clinical trial in the next 2-3 years.

There are four projects moving forward on gene therapy using cells as vehicles for delivery of the missing protein. One is proving up genetically modified iPS cells for correcting Fanconi anemia. There is also a Duchenne muscular dystrophy study as a candidate feasibility project involving genetically corrected iPS cells. The other two are in preclinical evaluation for correcting sickle cell disease by modifying the patient's own hematopoietic stem cells and the other addresses the dreadful skin disease known as dystrophic epidermolysis bullosa using genetically corrected iPS cells. Whereas these projects are technically challenging, they are making very good progress towards clinical registration.

Bone and cartilage repair projects are all in early translation, with small molecule and chondrocyte products in two studies focused on osteoarthritis (focal cartilage defect) and a spinal fusion study using perivascular cells, an osteoinductive protein, and a scaffold. An earlier feasibility award addresses cell therapy for osteoporosis (vertebral compression fractures).

CIRM is also funding three studies on HIV/AIDS in translation. One is an early disease candidate study addressing hematopoietic stem cells genetically engineered with multiple anti-HIV resistance genes and a drug resistance gene. The other two are preclinical studies that target the CCR5 gene that is a coreceptor for the virus on blood cells. One uses the zinc finger nuclease technology for gene disruption and the other uses a small hairpin RNA approach against CCR5. Both involve manipulation of the patient's own hematopoietic stem cells. There is high expectation that these studies may evolve into clinical trials that may cure HIV/AIDS.

Diabetes is being addressed by wound healing studies in early disease candidate studies and by ESC-derived insulin producing cells protected by encapsulation in a preclinical study that is progressing very well.

In addition, CIRM is supporting studies on liver failure using ESC-derived hepatocytes and multiple endogenous cell repair using a recombinant Wnt molecule delivered by sustained release methods in disease candidate studies. There is also a preclinical study on advanced ischemic cardiomyopathy using autologous, expanded cardiospheres formed from cardiac biopsies from the patient.

It is possible that many of these clinical trials could progress in CIRM Alpha Stem Cell Clinics, should they be established in the next few years, giving the work already underway the opportunity to progress in a very supportive environment.

Conclusion

Stem cell tourism is a recent and disturbing trend, where people suffering diseases or injuries, who have little hope from conventional medicine and with little assurance from the mainstream scientific community that help will arrive in time to help them, travel to clinics promising therapies and cures without proven efficacy and where little if no long-term follow-up is performed. This trend is not only costly to the individuals seeking out such therapies, but threatens to cast a pall on the promising areas of cell therapies that are showing tangible signs of progress. It is understandable that people in such situations are attracted—the claims that many of these clinics make are spectacular, albeit, usually unproven, individuals seeking treatment usually have few if any options, and their window of time to benefit from therapies is tragically short. Unfortunately, this impasse is unlikely to resolve soon. However, given that hundreds of clinical trials for cell therapies are now underway [16], we owe it to these people and their families to rapidly implement the best and safest practices for cell therapy clinical trials and move toward fast-tracking in therapies where safety and efficacy has been proven, so that more of them have evidence-based alternatives to these last ditch resorts.

As a first goal, the Alpha Clinic model can immediately target therapies toward those patients who can be helped, based on proven clinical evidence of efficacy and safety, such as for limbal cell treatments for people suffering from corneal burn injuries. Simultaneously, investment in Alpha Clinics will accelerate ongoing clinical trials for a wide spectrum of diseases and injuries and, by applying rigorous and efficient practices of clinical research to cell therapies, ensure that the best treatments possible will be available. This will be done by investing in and, where possible, leveraging existing infrastructure for standardized methods of cell manufacturing, delivery, outcome assessment, patient care, and long-term monitoring.

Moving cell therapies towards and into clinical trials will pose a series of scientific, clinical, and operational challenges over the coming decade. If we are to successfully accelerate the translation of promising stem cell discoveries into clinical trials and eventually into the marketplace, it is clear that we need to have an efficient, high-quality network of clinical centers with the appropriate disease and regulatory expertise in conjunction with on-site technology capabilities to handle some of the unique complexities of stem cell therapies or off-site capacities to provide these services. Providing evidence of safety and efficacy will be a mandatory step to advance this field, and efforts to help chart clearer, more predictable regulatory and reimbursement pathways should help steer industry into more active engagement in stem cell technologies for potential treatments and cures.

Disclosure of Potential Conflicts of Interest

The authors indicate no potential conflicts of interest.

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