Cell Stem Cell
Forum

Developing a Case Study Model for Successful Translation of Stem Cell Therapies

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Cell therapies derived from pluripotent stem cells are entering the preclinical and early clinical development phase, but eventual translation faces many challenges. We describe a new approach by California to form global public-private "disease team" partnerships to enable new clinical opportunities to be evaluated in the complex regulatory environment.

There are three key elements that must be present to ensure the clinical translation of candidate stem cell therapies. The first two are obvious. There needs to be adequate funding, and the therapies need to be shown to be safe and efficacious in accordance with regulatory requirements. Third, and perhaps less obvious, is in order to accelerate and perhaps even succeed in demonstrating safety and efficacy of these novel therapies, researchers need to work in multidisciplinary, collaborative teams (U.S. Department of Health and Human Services, 2005).

The opportunity for stem cell science to lead to therapeutic benefit is increasing as evidenced by rapid advances and reproducible results in so many parts of the field from self-renewal and differentiation to reprogramming pluripotentiality. There are also challenges to realizing this opportunity. The business climate is presently difficult, but it seems to be particularly challenging for therapies originating from pluripotent stem cells or genetically manipulated adult stem cells. Venture capital is increasingly risk-averse and intolerant of waiting for long-term payouts. Product regulatory bodies are acting with caution, and insurers and healthcare payers have yet to determine whether health-care reform will allow them to benefit from regenerative therapies that are likely to require many years to accrue sufficient savings to cover upfront costs.

Sustained funding will be critical because the complex nature of the delivery and monitoring of stem cell treatments will result in an extended time frame for development of many therapies. Candidate small molecule and protein therapeutics arising from stem cell research would be expected to reach the clinic more quickly than pluripotential stem cell treatments or even genetically modified adult cells. Yet, with the field promising to significantly alter healthcare by delivering not just incremental improvements but potentially cures, this is an area that warrants investment and, even in these difficult economic times, public financial support.

With most funding sources pressuring research to increase speed to the market at the same time the Food and Drug Administration (FDA) and other regulators are showing caution with some new avenues to therapy, industry publications and conferences have started to discuss the theory that the best way to increase speed to market without increasing risk is via industry-industry collaboration and cooperation to solve the common preclinical chalenges in the precompetitive space (Brainloop, Inc., 2010; Cambridge Health Institute, 2010). We postulate that while this aspect of collaboration can help, a broader, more effective way to accelerate the path from research bench to clinic is to foster academic-industry collaborations that are structured in a manner that is more focused than these relationships have been in the past. Academic stem cell biologists and those clinicians who will be responsible for testing these treatments can answer questions that are blocking a particular path to the clinic and may be able to take advantage of more favorable licensing and Material Transfer Agreements (MTAs) offered to academia. A discussion on risk involving regulators, industry and academic team members, patient advocates, and clinicians who will be involved in delivery of the candidate therapy may be more productive in looking at new measures of risk. Also, since existing cell-based therapies, largely from bone marrow, have generally relied on academic-based clinical trials and early roll-out, creating those partnerships that include clinical staff at the beginning can cut steps and time to a marketable product.

A test case of this hypothesis is now underway. In October 2009, the California Institute for Regenerative Medicine (CIRM) awarded 14 Disease Team Awards (CIRM, 2009), averaging over U.S. $16 million each, and involved some level of academic-industry partnerships to achieve the team goal of filing an Investigational New Drug (IND) application within 4 years to begin a clinical trial. Four of the five awards for pluripotent-derived therapies have industry participation, as do three of the five genetically manipulated adult stem cell therapies. Two of the three targeting cancer stem cells have industry participants. In these first awards, the grants were awarded based on scientific merit and the potential to achieve an IND filing. Hence, several grants targeted the same disease. Given the probability of success for any of the awards is far from assured, CIRM decided not to restrict the awards programmatically on this occasion.

Incentives for Translational Research

As Dr. Susan Desmond-Hellmann, Chancellor of UCSF and former President of Product Development at Genentech, stated at CIRM's recent grantee conference, "what matters to patients is not that these therapies get into a clinic, but rather that they ultimately get approved

for wide use in patients.'' It is not getting into clinical trials that matters; it's getting commercial approval for use in all patients that could benefit. This requires funding of the complete program from preclinical translational studies to the safety and proof of concept of benefit to patients, commonly referred to as Phase I and IIA/B clinical trials. There is very little funding available from investment financing or pharmaceutical company support for this component of the development chain.

It is necessary for private foundations and public funding initiatives, such as NIH's expenditures on Clinical and Translation Science Centers, to fill the void left by the virtual exit of angel funders (investors interested for simply programmatic reasons) and venture capital from the translational phases of stem cell research. In the present difficult economic environment, it is challenging to persuade government to contribute to funding medical research despite the acknowledged economic return of such investments because the benefits are long term and budget shortfalls are acute (Murphy and Topel, 2003; Health Economics Research Group, 2008). The long-term benefits for the economy and for health require funding that is reliably sustained for decades. This enables the discovery process to mature and the translational phase to support proof of concept. Few public agencies adequately support the translation phase, and even those that do require multiple grant application rounds to enable a new product, such as stem cells, to reach a mature stage attractive for private investment.

CIRM has decided to invest significantly in preclinical and clinical research with grants of up to U.S. $25 million for pluripotent-derived stem cell candidate clinical trials, up to U.S. $20 million for each ''Disease Team'' research award and up to U.S. $6 million each for ''Early Translational'' research awards. These awards are large enough to support multiple phases of preclinical-clinical development through a single grant application and have been supplemented with additional funding by collaborative funding partners in other nations and, in some instances, further leveraged by funds from the grantee.

The size of the grants available and the potential to collaborate within California and with overseas and interstate researchers has dramatically incentivized the research community. There are a very large number of applications submitted to CIRM in response to calls for applications, many with merit for support.

Global Collaborations Accelerate Research Benefits

Team research is effective in achieving high impact developments because of its speed of producing innovative high quality data. This is true on a national scale and an international scale, but there are relatively few funding bodies that support international collaborations between multiple public and private teams. The European Framework Programme and NIH have such collaborative initiatives, but they are limited in number and in the level of funding available for translational research. While some countries have some private-public funding mechanisms, they are still relatively rare and don't provide comprehensive funding for the full translational process, particularly for stem cell research. One partial exception is seen in Spain, in the form of the Andalusian Initiative for Advanced Therapies (Cuende and Izeta, 2010, this issue). Klein and Trounson have argued that state or international bond funded initiatives for such purposes can be a very effective approach to stimulate these arrangements with little direct influence on public debt repayments before substantial economic returns are generated (Klein and Trounson, 2010). They argue returns to California on the bond sales are likely to be substantial as debt repayments are offset for 5 years in the capital raising, and taxation benefits accrue as buildings are erected and academic and biotechnology components expand. Clinical trials have already been initiated with potentially large savings on the state's healthcare budget expected.

CIRM has taken a very proactive role in creating international collaborative agreements to cofund stem cell research. These agreements enable scientists to jointly submit research team applications for review by CIRM's international review panels (excludes Californian reviewers) and the collaborating national or state review panels if necessary. The agreements include the State of Victoria, Australia, the Canadian Cancer Stem Cell Consortium, the UK Medical Research Council, the Japanese Science and Technology (JST) organization, the Chinese Ministry of Science and Technology, Spanish Ministry of Science and Innovation, German Ministry of Education and Research, and the U.S. State of Maryland and the New York Stem Cell Foundation.

Globalizing collaborations provides opportunities for different communities to participate in the development of a new area of research and to ensure that the priorities of these communities are included in determining the direction of the research. Consequently the emphasis on cancer stem cells is driven by both Californian and Canadian researchers as a priority for their communities. Certain diseases that may dominate in one community may be less frequent in another but collaborative research tends to be inclusive of these needs. For example, the need for affordable cures for diseases such as HIV/AIDS and malaria becomes evident when global health priorities are considered.

Regulatory Approval: Drugs and Biologics versus Cell Therapies

While CIRM's funding of the translational phases of the research pipeline will provide the critical financial support needed to meet the first condition laid out above for success in this field, the second element, proving safety and efficacy, will be more challenging. Unlike for biologics and small molecules, the regulatory pathway for stem cell-derived therapeutics is not well defined and, hence, not well understood. While the biologic and small molecule industries benefit from a well-defined regulatory pathway and commonly accepted best practices for preclinical safety testing, product characterization, and measures of purity and potency, the same cannot be said for product development for the stem cell industry. Certainly, there are a number of autologous stem cell therapies in clinical trial as well as some allogenic adult cell therapies, but pluripotent and genetically manipulated stem cell therapies are experiencing significant delays in entering into the clinic (Plagnol et al., 2009). While it may be argued that companies need to address significant concerns of the regulators, the

burn rate of capital while waiting for additional data and approval to proceed makes survival particularly difficult for any corporate entity with limited financial flexibility (McKernan et al., 2010, this issue). While the FDA is not insensitive to the situation, many unknowns remain in this new field that can delay approvals, despite the best intentions of all parties.

The US federal government has taken steps to address the issue. The FDA is in active discussion with industry, in part through the Regenerative Medicine Consortium, which was convened by CIRM and has a mix of industry and academic participants. FDA Commissioner Margaret Hamburg's emphasis in regulatory science may ultimately provide more tools and regulatory certainty to the field. Likewise, NIH has declared its intention to work with the FDA as well.

There are concerns that the relative ease of obtaining regulatory approval for clinical studies for transient cell therapies, such as those based on autologous bone marrow implantations for a wide variety of disorders without solid scientific rationale, may be counterproductive for regulatory support of regenerative therapies involving pluripotent stem cell derivatives. Others see these as a logical order for the relative risk versus benefit.

Developing a Symbiotic Team Approach

In the absence of well-defined regulatory requirements for the development and approval of pluripotential and genetically manipulated stem cell therapeutics, it is necessary to have sufficient innovative expertise on the team to address the concerns of regulators. The knowledge base for new developments in stem cell biology generally resides in the academic research community and in biotechnology companies with a substantial research capacity or those well connected to academic research groups. The academic community is, however, generally less well prepared for the highly regulated aspects of product development, particularly those relating to toxicological testing, consistency, and source of product as required for cGMP (current Good Manufacturing Practices) manufacturing, etc. Academic scientists are, in many instances, less familiar with the timeline and milestone demands of industry, where delays in product development are very costly, not only to the funder but potentially to the patient. There is clearly a potential symbiotic relationship between academic research talent and the know-how of the biotechnology industry. In fact, it is difficult for one to make major advances without the other in the present relative absence of significant venture capital.

The depth of research resources in the university sector and the considerable infrastructure there is of immense value to biotechnology companies that have limited capital. The companies, in turn, can keep academic scientists focused on the critical developments needed for regulatory filing. Hence, merging the resources provided by companies and academic research institutions can create the ideal team.

CIRM has implemented an active team management approach for its multidisciplinary Disease Teams. The approach is based on best practices following discussion with individuals whose expertise and relevant experience derives from academia, the biotechnology and pharmaceutical industries, and from private foundations (CIRM, 2007).

Challenges to translational research teams include maintaining focus, ensuring that the scope of the research conducted best addresses the project goal, and maintaining good communication among team members and with funders. For Disease Team projects, each team is required to have a project team leader(s) and a project manager with development experience to ensure team direction, focus, energy, and communication. Prior to the start of funding, to further facilitate successful project outcomes, each team, together with CIRM, develops mutually agreed upon timelines for key project activities and determines milestones that reflect critical measures of project progress and go/no go decision points. These, in conjunction with an activity based budget, help teams to refine project plans to ensure that all necessary research is conducted, and that the time and funding allowed for the conduct of the research activities are sufficient and reasonable.

The response of the Disease Team investigators to the new funding format opportunity has been exceptional, given that academics are rarely organized in such a targeted and highly focused manner. These academic-industry partnerships could provide ongoing benefit in future steps as well. It is anticipated that, like bone marrow and organ transplantation, many new cell therapies are likely to be delivered in tertiary clinical settings that will involve academic and community clinicians and networked stem cell clinics that may be partnered with companies supplying specific reagents and cell products.

Public-Private Partnerships for Translation Established by CIRM Funding

In the area of human embryonic stem cells (hESCs), the studies on dry macular degeneration at the University of Southern California, University of California (UC) Santa Barbara, and University College London are further enhanced through collaboration with the company Geron and the Center for Applied Technology Development (CATD) at City of Hope, which serves as a national academic biologics manufacturing resource. Geron and CATD provide cell banks, cGMP manufacturing, and expertise for regulatory requirements. A study on ESCs derivatives for treatment of stroke at Stanford University has a collaboration with Progenitor Cell Therapy, a company that provides the expertise in product and assay development and cGMP manufacturing for the therapeutic candidate. This team is also working with SRI whose expertise in toxicological testing and their successful record in medical product development are major assets. Progenitor Cell Therapy will also be participating in the development and manufacture of neural stem cells on behalf of a team at UC San Francisco in support of their efforts to leverage the homing ability of these cells to deliver drugs to treat glioblastoma. The team from UC San Diego and the Salk Institute are working with Life Technologies Inc. for the scale-up, differentiation, and purification of ESCs to astrocyte precursors and cGMP manufacturing for treatment of Amyotrophic Lateral Sclerosis (ALS). For diabetes, the company ViaCyte Inc. has several associations with academia, including a critical collaboration on immune modulation with UC San Francisco.

For genetically modified adult stem cells, the team at the City of Hope that

is devising permanent resistance to HIV/AIDS is using Sangamo Biosciences' novel zinc-finger nuclease (ZFN) technology to disrupt the gene CCR5 in hematopoietic stem cells (HSCs), which encodes a critical HIV coreceptor in blood cells. The team at UC Los Angeles is mimicking a naturally occurring mutation in CCR5 by transducing the patient's HSCs using a shRNA . They are partnered with City of Hope's CATD and with Calimmune Inc., who provide expertise in preclinical development and product commercialization. According to the Principal investigator Dr. Chen, "traditionally, research, drug development, and clinical medicine were three virtually separate endeavors…CIRM created a funding mechanism that breaks down the barriers to this critical interaction." (Atchison, 2010).

Connecting to the End User

While organizations like CIRM are unable to maintain financial support beyond Phase II studies of proof of concept for human efficacy, it can provide the data that make the project more attractive for Phase III partnerships involving venture funding and major pharmaceutical company support. However, with the costs of clinical trials spiraling out of control with estimates now approaching U.S. $4 billion per drug (Munos, 2009), it seems unlikely that the present model is sustainable, particularly for smaller market diseases. It is apparent that government may need to coinvest and to persuade the health insurance companies to also join in supporting biotech and pharma in the clinical trials. Government and health insurance companies are beneficiaries of cures and improvement in the quality of life of patients with serious diseases. With the increasing number of clinical trials proposed for cell therapies, there is an urgent need to address this issue.

WEB RESOURCES

Atchison K.A. (2010). Inventor Spotlight: Professor Irvin Chen and Calimmune, Inc. The Inventor (http://oip.ucla.edu/publications/Newsletter_Winter_Quarter_09_10.pdf).

CIRM (California Institute for Regenerative Medicine) (2007). The California Institute for Regenerative Medicine Disease Team Workshop Report. (http://www.cirm.ca.gov/pub/pdf/DTW_Report.pdf).

CIRM (California Institute for Regenerative Medicine) (2009). CIRM, the UK and Canada Award more than $250 Million to Accelerate the Pace of Bringing Stem Cell Therapies to the Clinic. (http://www.cirm.ca.gov/PressRelease_102809).

U.S. Department of Health and Human Services (2005). 2020: A New Vision: A Future for Regenerative Medicine. (http://www.hhs.gov/reference/newfuture.shtml).

REFERENCES

Brainloop, Inc.. (2010). White Paper: Seamless life sciences collaboration (Boston, MA: Brainloop, Inc.).

Cambridge Health Institute. (2010). Conference: Second Annual Collaborative Innovation in Biomedicine, Strategies and Best Practices for Pre-Competitive Sharing of Data, Results and Costs.

Cuende, N., and Izeta, A. (2010). Cell Stem Cell *6*, this issue, 508–512.

Health Economics Research Group. (2008). Medical Research: What's it worth? Estimating the economic benefits from medical research in the UK (London: UK Evaluation Forum).

Klein, R.N., and Trounson, A. (2010). A New Political-Financial Paradigm for Medical Research: The California Model. In The Delivery of Regenerative Medicines and Their Impact on Healthcare, C. Prescott and J. Polak, eds. (Boca Raton: Taylor & Francis), in press. 978-1-4398360-6-4.

McKernan, R., McNeish, J., and Smith, D. (2010). Cell Stem Cell *6*, this issue, 517–520.

Munos, B. (2009). Nat. Rev. Drug Discov. *8*, 959–968.

Murphy, K.M., and Topel, R.H. (2003). The Economic Value of Medical Research. In Measuring the Gains from Medical Research: An Economic Approach, K.M. Murphy and R.H. Topel, eds. (Chicago: University of Chicago Press), pp. 41–73.

Plagnol, A.C., Rowley, E., Martin, P., and Livesey, F. (2009). Regen. Med. *4*, 549–559.