CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

March 11, 2012

From: Ellen G. Feigal, M.D., Senior Vice President, Research and Development

To: Independent Citizens Oversight Committee (ICOC)

Re: Pre-read for the Disease Teams 1 Update at ICOC on March 21, 2012

This document, provided as a pre-read to the ICOC, is a work in progress, and summarizes the current status of CIRM's 14 Disease Teams as of March 2012, including a brief outline of each Disease Team project, key progress and accomplishments to date, status of their progress towards filing a successful IND within 4 years, and budget allocated.

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Disease Teams 1 Status Updates – Executive Summary

CIRM's mission is to advance stem cell research for the discovery and development of cures, therapies, diagnostics and research technologies to relieve human suffering from chronic disease and injury. As a key strategy to progress stem cell science into clinical trials, CIRM funded 14 multidisciplinary Disease Teams in 2010 to initiate the IND-enabling studies that could lead to successful filing of an Investigational New Drug (IND) application with the US Food and Drug Administration (FDA) for these stem cell based therapies to enter human clinical trials over the next 4 years.

CIRM convened 3 clinical development advisor panels between July and November 2011 to meet with CIRM and the funded Disease Teams at their 12 to 18 month milestones, for the purpose of providing a venue for interactive discussions that could lead to better positioning of the Disease Teams' advance on the regulatory pathway into patients. The convening of clinical development advisors to provide external input into the milestone process was approved in the concept plan for the Disease Team solicitation, was identified in the Disease Team request for applications, and subsequently communicated to all of the Disease Teams.

The panels of clinical development advisors, composed of experts in product development, including preclinical and clinical research, process development and manufacturing, regulatory standards, stem cell/disease-specific biology, disease-specific clinical expertise, and commercial relevance, provided advice and recommendations on project strategy, progress in meeting goals and go/no-go decision points, and approaches to meeting challenges in their product development plans to the Senior Vice President of Research and Development.[1] CIRM considered this advice in subsequent internal deliberations about the merit of continued support, and under the guidance of the President, made the final decisions and followed-up with the 14 Disease Teams on these issues.

CIRM is exploring strategies to drive success in the coming years. One of the key challenges will be to connect and transition the activities and investments in research and discovery of the first stage of CIRM's development to a new stage characterized by a proactive strategy, leadership, industry engagement, product development, portfolio prioritization and outreach while continuing to nurture the people and science that will drive the initiative forward. CIRM's initial focus has been to support research at the highest level of scientific excellence. Our challenge now is to continue to support the most promising research while placing increased emphasis on clinical translation and product development. We established the panels of clinical development advisors to help our investigators and CIRM build on the success of the first stage to drive further growth towards CIRM's long-term mission of providing significant health and economic benefits to the people of California.

[1] To prevent even the appearance of a conflict of interest, CIRM applied the Grants Working Group conflict of interest rules. Clinical development advisors who had a financial, professional or personal conflict of interest with respect to one of the awards were disqualified from participating in the panel's consideration of that award.

Disease Team 1 Overview

Grant/PI	Project Start	Total Award	Current Status
DR1-01421 Aboody	3/2010	18,015,429	Continue
DR1-01426 Berger	4/2010	19,162,435	Terminating 3/31/2012 did not meet Go/No-Go milestone
DR1-01430 Carson	3/2010	19,999,826	Continue with revisions
DR1-01444 Humayun	4/2010	15,904,916	Continue
DR1-01477 Slamon	5/2010	19,979,660	Continue
DR1-01485 Weissman	3/2010	19,317,614	Continue
DR1-01471 Goldstein	6/2010	11,500,429	Continue
DR1-01461 Marban	3/2010	5,560,232	Continue
DR1-01431 Chen	6/2010	19,999,580	Continue
DR1-01452 Kohn	3/2010	9,212,365	Continue
DR1-01454 Lane	5/2010	11,709,574	Continue
DR1-01423 Robins	2/2010	19,999,937	Continue
DR1-01480 Steinberg	2/2010	20,000,000	Continue
DR1-01490 Zaia	5/2010	14,583,187	Continue

DR1-01421 Aboody

PI: Karen Aboody, City of Hope
Co-PIs: Larry Couture, City of Hope
Jana Portnow, City of Hope

Disease Target: Recurrent Glioblastoma

Cell Therapy or Therapeutic Candidate: Allogeneic, established hNSC line to target tumors, engineered ex vivo to deliver carboxylesterase (CE) to locally convert prodrug CPT-11 to the more cytotoxic SN-38 metabolite.

The goal of this project is to develop a hNSC-based treatment strategy that produces potent localized anti-tumor effects while minimizing toxic side effects. NSCs hold the promise of improved treatment for brain cancers because they have an innate ability to distribute within and around a tumor mass and to seek out tumor cells that have invaded further into surrounding brain tissue. By homing to cancer cells, NSCs offer a way to selectively deliver concentrated chemotherapy to brain tumor sites. The team is modifying NSCs to make the protein carboxylesterase (CE), which will convert a systemically administered prodrug, CPT-11 (irinotecan) to an active, potent anti-cancer drug, SN38 at the tumor sites.

Project Start date: 3/1/2010

Key Accomplishments

The team has made progress toward selecting their final therapeutic candidate, consisting of the hNSC line (in a first-in-human trial since 2010), a transduction protocol, and an enzyme variant of human carboxylesterase (CE) which activates the prodrug CPT-11 (irinotecan) to a very potent anti-cancer agent, SN-38. This selected CE is being developed under GMP conditions for clinical grade use.

The team has also investigated the optimal route and dose of NSC administration to achieve the maximum percentage of tumor coverage. They determined the greatest tumor distribution followed direct injection of the NSCs into the brain, and will focus on developing this approach for the initial NSC.CE + CPT-11 clinical trials. However, following intravenous injections the team found the NSCs localize prominently at the invasive tumor edges, which may prove therapeutically efficacious as well. Due to the significant clinical and commercial advantages that intravenous administration presents, this approach will also be developed toward patient trials.

Toward preclinical efficacy, the team has shown that CPT-11 + CE is 1,000 fold more toxic to glioma cells than CPT-11 alone. In vivo microdialysis studies in preclinical

models have confirmed the conversion of CPT-11 to SN-38 by CE-secreting NSCs in the brain.

Under this disease team award, CIRM funded preclinical development and safety/toxicity studies on a novel iron nanoparticle (ferumoxytol) stem cell-labeling technique that allows tracking of the stem cells by MR imaging in vivo. The team was able to leverage the CIRM-funded work to submit an amendment to the IND under which a current NSC-mediated brain tumor clinical trial is being conducted. If the amendment is accepted by the FDA, this will be the first use in patients of ferumoxytol as a stem cell tracker, allowing the investigators to monitor the migration and tumor distribution over time by non-invasive imaging techniques.

The team has one CIRM-funded publication recently accepted for publication; Gutova M, Shackleford GM, Khandaldyyan V, Herrmann KA, Shi XH, Mittelholtz K, Abramyants Y, Blanchard MS, Kim SU, Annala AJ, Najbauer J, Synold TW, D'Apuzzo M, Barish ME, Moats RA, and Aboody KS **Neural Stem Cell-mediated CE/CPT-11 Enzyme/prodrug Therapy in Transgenic mouse model of Intracerebellar Medulloblastoma.** Gene Therapy March 8 2012; doi: 10.1038/gt.2012.12. This paper demonstrates that the Disease Team funded therapeutic strategy significantly reduces the tumor growth rate in a preclinical model of medulloblastoma, the most common malignant childhood brain tumor.

The team has two other CIRM-funded publication under review: Gutova M, Frank JA, Annala AJ, D'Apuzzo M, Khankaldyyan V, Metz MZ, Abramyant Y, Herrmann KA, Ghoda LY, Najbauer J, Brown CE, Barish ME, Aboody KS and Moats R: MRI Tracking of Ferumoxytol-labeled Human Neural Stem Cells: Implications for Clinical Use. Stem Cells, Mar 2012 (*under review*). This paper describes the preclinical development of ferumoxytol labeling for *in vivo* stem cell tracking. This work supports the IND amendment to the current clinical trial, described above.

Nousha Khosh, Christine E. Brown, Karen S. Aboody and Michael E. Barish: Human neural stem cell contact and encirclement of glioma cells is a cell autonomous behavior, PLoS ONE Feb 2012 (under review). This paper characterizes the interactions of NSCs with target cells in a 3-dimensional culture system. The purpose of this paper is to better understand the signals and conditions involved in NSC migration to glioma.

Dr. Aboody has given 11 invited presentations in which she has discussed and acknowledged her Disease Team CIRM funded work. The team has submitted two abstracts for the upcoming ISSCR 2012 meeting in Japan: "MRI Tracking of Ferumoxytol-labeled Human Neural Stem Cells: Implications for Clinical Use" and "Neural Stem Cell Delivery of Carboxylesterases + CPT-11 for Cancer Treatment: Implications for Clinical Use".

In June 2011, Dr. Aboody founded a company, TheraBiologics Inc., of which she is CSO and Director. TheraBiologics is a clinical stage biopharmaceutical company

supporting clinical development of a proprietary human neural stem cell (NSC) platform for targeted therapeutic delivery to malignant tumors. The company holds IP for NSC-mediated brain tumor and metastatic cancer treatment, and is looking to raise funds to cover upcoming Phase I-II trials.

Impact

There is no financial or timeline impact to the project at this time. The team is on target to complete proof-of-concept efficacy studies in fall 2012 and conduct a pre-IND discussion with the FDA.

DR1-01426 Berger

PI: Mitch Berger, UC San Francisco
Co-PIs: Webster Cavanee, Ludwig Cancer Institute
Evan Snyder, Sanford-Burnham

Disease target: Recurrent Glioblastoma

Cell Therapy or Therapeutic Candidate: Allogeneic hNSC or MSC (from best of 3 sources) to target tumors and engineered ex vivo to deliver a tumoricidal gene product (TRAIL or cytosine deaminase and a suicide gene)

The project was initiated to compare:

- Three types of stem cells
- Two distinct therapeutic gene modifications of stem cells, and
- Intravascular administration vs direct tumor injection of stem cells

The purpose was to identify the most efficacious stem cell + therapeutic gene + route of administration, in developing a stem cell therapy approach for treating patients with recurrent glioblastoma (GBM), a brain tumor that has a dismal prognosis needing innovative treatments for improving patient outcomes.

Project start date: 4/1/2010

Key Accomplishments

The team summarized the results and associated decisions that led to the selection of one route of delivery for one type of therapeutic stem cell:

- Stem cells administered by the vascular route do not reach brain tumors established in preclinical models, to an extent and/or a consistency in which

demonstrable therapeutic stem cell anti-tumor activity should be anticipated;

- Neural stem cells and mesenchymal stem cells delivered directly into the intracranial tumor in preclinical models display similar extents of dispersion in tumor, as well as similar duration of presence within tumor, indicating these stem cell types should perform comparably as concerns their ability to disseminate within, and sustain delivery of therapy to tumor;

- Unmodified (non-immortalized) neural stem cells, derived from single adult or young sources, were determined to have insufficient proliferative capacity for production as therapeutic stem cells to be used in clinical trials that enroll multiple patients;

- Studies conducted in vitro, with therapeutic stem cell + tumor cell mixtures, indicated superior anti-tumor activity of stem cells modified with a cytosine deaminase (CD), in the presence of 5-fluorocytosine (5FC) pro-drug, as compared with stem cells modified to express secretable TRAIL, and

- Relevant to point immediately above, the team compared the in vitro anti-tumor activity of CD only vs CD fused to uracil phosphoribosyltransferase (CD-UPRT) with UPRT providing an enzymatic activity that rapidly produces toxic metabolities from the 5-FU produced by CD.

Technology developed as a result of the CIRM funded research includes:

- Development of approaches for delivering stem cells through distinct routes of administration in preclinical model: Serwer L, Hashizume R, Ozawa T, James CD. Systemic and local drug delivery for treating diseases of the central nervous system in rodent models. J Vis Exp. 2010 Aug 16;(42). pii: 1992. doi: 10.3791/1992. **CIRM support acknowledged**.

- Development of a cell labeling approach that enables tracking of stem cell migration in preclinical model: Chaumeil MM, Gini B, Yang B, Iwanami A, Subramanian S, Ozawa T, Pieper RO, Mischel PSb, James CD, Berger MS, and Ronen SM. Longitudinal evaluation of MPIO-labeled stem cell biodistribution in glioblastoma using high resolution and contrast enhanced MR imaging at 14.1Tesla. Submitted: Neuro-Oncology. **CIRM support acknowledged**.

- The team developed methods (one histochemical and one PCR-based) for detecting human cells in preclinical models, and multiple tumorigenic human glioblastoma xenograft models were developed and characterized for use in therapeutic testing. One of these, SF7796, was established from a therapy resistant tumor obtained from a recurrent GBM patient, and is especially appropriate for use in association with any project involving the development of a therapeutic for treating recurrent GBM.

Impact

Research did not meet criteria for Go/No-Go milestone; wind-down of financing and research by 3/31/2012, with potential estimated savings of approximately $13 million.

DR-01430 Carson

PI: Dennis Carson – UCSD
Co-PI: Catriona Jamieson, UCSD
Canada PI: John Dick University Health Network, Toronto

Disease Target: Cancer Stem Cells in CML, AML, T-ALL, B-ALL and CLL

Cell Therapy or Therapeutic Candidate(s): 3 small molecules (JAK, SMO and SYK inhibitors) and 3 monoclonal antibodies (anti-CD44, CD-123 and ROR1)

Project Start date: 3/1/2010

Key Accomplishments

This team in collaboration with Dr. John Dick (University Health Network,Toronto) is developing therapies that target specific survival and self-renewal pathways in leukemic stem cells. The Carson team is focusing on the novel monoclonal antibody (anti-ROR1) that blocks Wnt5 signaling in Chronic Lymphocytic Leukemia stem cells. The Dick team (Canada) is focusing on a small molecule that inhibits JAK2 kinase in Acute Myeloid Leukemia. They have shown efficacy with both these therapies using the rigorous serial transplant models in preclinical models using patient leukemic cells. In addition, the Carson and Dick teams are doing extensive genomics to develop a leukemic stem cell biomarker signature of response/resistance. Ultimately, this signature could be used to individualize therapies and improve response. Progress toward IND-enabling studies is moving well.

Impact

CIRM recommended the Disease Team focus their work on the anti-

ROR1(California) in CLL and AML (Canada) program and reduce the number of potential therapeutics to a total of 2. Budgets and timelines are being assessed and realigned accordingly.

DR1-01444 Humayun

PI: Mark Humayun, USC
Co-PIs: David Hinton, USC
Dennis Clegg, UCSB
CFP PI: Peter Coffey, University College, London (Funding Partner: MRC)

Disease Target: Age-Related Macular Degeneration AMD

Cell Therapy or Therapeutic Candidate: HESC-derived RPE cells on a synthetic matrix

To develop a cellular therapy for dry Age Related Macular Degeneration (AMD) using retinal pigment epithelium (RPE) derived from human embryonic stem cells (hESC). An important component of this approach is the use of hESC-derived RPE plated as a polarized monolayer on a synthetic substrate (rather than as a cell suspension). The substrate mimics the natural Bruch's membrane, which is important for the attachment, survival and differentiation of RPE.

Project Start date: 4/1/2010

Key Accomplishments

- The Humayun team is using hESC-derived retinal pigment epithelial cells (RPE) to replace the endogenous RPE that degenerate in dry AMD. An important component of this team's approach is the use of hESC-derived RPE plated as a monolayer on a ***synthetic substrate*** (rather than as a cell suspension). The substrate mimics the natural Bruch's membrane which is defective in diseased eyes, and which is important for the attachment, survival and differentiation of RPE.

- The team has put much time and effort into perfecting the design of the synthetic substrate and has developed an ultra-thin substrate that not only has sufficient mechanical strength for culturing and surgical handling, but at the same time has permeability characteristics that mimic Bruch's membrane (allowing for passage of most proteins but preventing migration of cells).

- The CIRM-funded project has led to ***7 patent filings*** (4 from USC, 2 from UCSB and 1 from Caltech) covering the synthetic substrate, the placement of cells on the substrate, methods for producing the RPE, a method for tracking cells after implantation and specialized instrumentation for surgical delivery of the

implant.

- The team has obtained convincing preclinical proof-of-concept results using hESC-derived RPE seeded on the synthetic substrate. Following implantation into a preclinical model of retinal degeneration, histology shows successful interdigitation of the transplanted RPE with host photoreceptors, leading to both morphological and functional rescue of the photoreceptors. Consistent with these finding, the implants also rescue vision in this model.

- The team has created a **spin-off company** called Regenerative Patch Technologies (RPT) in order to further develop and commercialize their product.

Impact

Continue according to original plan, with goal of filing IND within the 4-year award period. Financials remain unchanged.

DR-01477 Slamon

PI: Dennis Slamon, UCLA
Co-PI: Garry Nolan, Stanford
Canada PI: Tak Mak, University Health Network, Toronto

Disease target: Cancer Stem Cells in solid malignancies: glioma, colon carcinoma and ovarian cancer

Cell Therapy or Therapeutic Candidate: novel small molecule inhibitors of 2 kinases

Project start date: 5/1/2010

Key Accomplishments

This team in collaboration with Dr. Tak Mak (University Health Network,Toronto) is developing small molecule inhibitors that target solid tumors cancer stem cells (CSC) in colon, ovarian and brain cancers. The first lead candidate molecule has shown efficacy in preclinical models using human tumors and specifically targeting cancer stem cells. This candidate molecule is now ready to move into IND-enabling studies. The team is working on a second molecule targeting a different novel pathway in CSC.

Impact

This team is on track with 1st kinase inhibitor and is starting IND-enabling studies now. At this time no change in financials.

DR1-01485 Weissman

PI: Irv Weissman, Stanford;
Co-PI: Ravi Majeti, Stanford;
CFP PI: Paresh Vyas, Univ Oxford, UK

Disease Target: AML- Cancer Stem Cells

Cell Therapy or Therapeutic Candidate: Humanized anti-CD47 MAb

To develop a therapeutic antibody directed against CD47, a cell surface target preferentially expressed on acute myeloid leukemia (AML) and other cancer stem cells. CD47 functions as a "don't eat me" signal by binding to SIRPα on phagocytic macrophages and delivering a dominant inhibitory signal.

Project Start date: 3/1/2010

Key Accomplishments

- The team successfully humanized and evaluated a number of candidate anti-CD47 antibodies aimed at targeting cancer stem cells in AML
- The team has filed a patent covering the sequence and uses thereof for the novel anti-CD47 antibody that is their lead therapeutic candidate.
- The team has obtained preclinical proof-of-concept efficacy data with this antibody; they have shown that they can completely eradicate the cancer from tumor-bearing xenograft model in which recipients of preclinical model have been injected with primary cancer cells from AML patients.
- The team is currently conducting preclinical dose exploration and pilot safety studies.

The MRC-funded UK component of the project involves the collection and analysis of samples from patients enrolled in AML trials being conducted by the UK AML working group. The objective is to evaluate the diagnostic and prognostic value of CD47 and other markers of interest and to test the hypothesis that $CD47^+$ leukemia stem cells are involved in driving relapse. Thus far, CD47 analysis has been done on 132 patients. Further analysis of data will be possible in March 2012 when outcome data on the last 12 months are analysed.

Impact

The team is pursuing preclinical safety and efficacy studies. No financial impact at this time.

DR1-01471 Goldstein

PI: Larry Goldstein, UCSD
Co-PIs: Martin Marsala UCSD
Sam Pfaff Salk

Disease Target: Amyotrophic Lateral Sclerosis (ALS)

Cell Therapy or Therapeutic Candidate: hESC-derived Astrocyte Precursor Cells

Project Start date: 6/1/2010

Key Accomplishments

Using hESCs to differentiate to astrocytes for subsequent development of a product to inject into ALS patient's spinal cord.

- The team has generated cells from different sources of hESCs and are in the process of identifying the cell lines with the best characteristics of minimal toxicity and efficient production of the final cell type. They have preclinical proof of concept studies demonstrating hESC-derived neural stem cells can protect motor neuron viability in the SOD preclinical model. They are on track for selecting a single cell line in mid-2012.

Impact

Continue with the project, and financials remain unchanged.

DR1-01461 Marban

PI: Eduardo Marban, Cedars-Sinai Medical Center

Disease Target: Advanced ischemic cardiomyopathy (heart failure)

Cell Therapy or Therapeutic Candidate: Autologous cardiac-derived cardiospheres (CSps) or c**a**rdiosphere-derived cells (CDCs)
To develop a therapy for advanced ischemic cadiomyopathy using autologous cardiac-derived cells.

Project Start date: 3/1/2010

Key Accomplishments

This team started out with the goal of developing an ***autologous*** cardiac-derived cell product for the treatment of advanced ischemic cardiomyopathy. The choice of autologous cells was based on the belief that *allogeneic* cells were likely to be immunogenic and that their efficacy might thus be compromised. The team has since discovered that ***allogeneic*** cells appear to be as effective as autologous cells in improving cardiac function in a preclinical model, and the immune consequences of injecting allogeneic cells appear to be negligible. With CIRM support, the team has recently extended that discovery to another preclinical model. Allogeneic cells can be obtained in very large numbers from a donor heart, which greatly facilitates scale up and manufacture, and enables the generation of a highly-standardized "off the shelf" product. Because of these advantages, the Disease Team, with recommendations from the clinical development advisors and approval from CIRM, has switched focus towards an allogeneic product and is now working towards an IND filing for an ***allogeneic*** cardiac-derived cell product.

There are 2 major differences between the CIRM-funded Disease Team project and the approach used in the CADUCEUS trial (Dec 2011 Spotlight and February Lancet), which was not CIRM-funded. The CIRM Disease Team is using ***cardiospheres (CSps)*** as the therapeutic candidate and will deliver them via direct injection into the heart (***intramyocardial injection***) using a special magnetically-guided catheter; In contrast, CADUCEUS used ***cardiosphere-derived cells (CDC)*** (obtained by dissociating cardiospheres) and delivered them via ***intracoronary injection.*** Based on their preclinical data, the team believes that CSps are a superior product, likely to prove more efficacious than CDCs in advanced heart disease, although they noted CDCs work well in patients with recent heart attacks.

Impact

CIRM approved switch from autologous product to allogeneic product. The team will continue with original goal of filing an IND within the award period, however, for an allo- , not auto- product. IND filing is anticipated in mid-2012. No impact to timeline or financials.

DR1-01431 Chen

PI: Irvin S Y Chen, UCLA
Co-PI: Geoff Symonds, Calimmune

Disease Target: HIV Disease patients failing HAART, naïve to HAART, AIDS/lymphoma

Cell Therapy or Therapeutic Candidate: HSC (CD34+) genetically modified ex vivo with lentiviral vector encoding sh RNAs against CCR5 and encoding a C46 HIV fusion inhibitor

Project Start date: 6/1/2010

Key Accomplishments

- Identification of unique anti-HIV small RNA to prevent HIV infection – Dr. Chen's team over the course of this award has identified several unique short hairpin RNAs, which in combination, prevent HIV entry into cells by targeting CCR5 as well as HIV replication through inhibiting different steps of the HIV replication cycle. Ongoing studies demonstrate HIV inhibition both *in vitro* as well as *in vivo* preclinical model for HSPC transplant and HIV pathogenesis.

Impact

Continuing with planned studies, no impact on financials at this time.

DR1-1452 Kohn

PI : Don Kohn – UCLA
Co-PI: Thomas Coates – UCLA
Co-PI: Victor Marder-UCLA

Disease Target: Sickle Cell Diseases

Cell Therapy or Therapeutic Candidate: Autologous human bone marrow hematopoietic stem cells (HSC) genetically modified by ex-vivo transduction using lentiviral vector encoding anti-sickling human b-globin

Project Start Date: 3/1/10

Key Accomplishments

- The Disease Team has successfully selected the single therapeutic candidate with disease modifying activity demonstrated *in vitro* and *in vivo* preclinical model, has had their pre-IND meeting with the FDA, and are planning preclinical toxicological studies.

- The Disease Team presented results of ongoing studies at the American Society for Hematology (ASH) Annual Meeting in San Diego in December 2012.

Impact

At this time no impact on the timeline or the budget. If the team is able to demonstrate the feasibility of obtaining sufficient numbers of CD34 cells by dual bone marrow harvest then impact on the time line and the budget may not be significant. The team has already done preclinical proof of concept studies with bone marrow derived CD34 cells. Other activities will continue as planned.

DR1-01454 Lane

PI: Alfred Lane, Stanford
Co-PIs: Marius Wernig, Stanford
Anthony Oro, Stanford

Disease Target: Dystrophic Epidermolysis Bullosa (DEB)

Cell Therapy or Therapeutic Candidate: Autologous iPSC-derived, gene-corrected keratinocytes

Dystrophic Epidermolysis Bullosa (DEB) is caused by mutations in the COL7A1 gene that encodes Type VII collagen. The Team is targeting 2 forms of DEB, the recessive form (RDEB) and the dominant form (DDEB). The Type VII collagen gene locus, COL7A1, is extremely large (~31,000 base pairs), and is remarkable for the extreme fragmentation of its coding sequence into 118 exons. More than 400 mutations have been identified in DEB patients.

Project Start date: 5/1/2010

Key Accomplishments

- Team has successfully generated iPSC lines from several RDEB patients.

Impact

No immediate impact on time lines or financials.

DR1-01423 Robins

PI: Allan Robins, ViaCyte
Co-PI: Peter Stock, UCSF
Project Manager: Eugene Brandon, ViaCyte

Disease target: Type I Diabetes

Cell Therapy or Therapeutic Candidate: Allogeneic human ESC-derived pancreatic progenitors that mature in vivo to beta cells that secrete insulin in response to glucose (GSIS, glucose sensing, insulin secreting), delivered in a retrievable immunoisolation device implanted subcutaneously.

Project start date: Feb 1, 2010

Key Accomplishments

- Prototypes of the product have been repeatedly tested in preclinical model, and in preclinical proof-of-concept studies, this cell-device combination has cured drug-induced diabetes.
- ViaCyte has established cell manufacturing and device manufacturing that can proceed at a scale and level of quality that will enable pre-clinical and clinical testing of the combination product.
- Specifically, ViaCyte has
    - Made and qualified a cGMP hESC Master Cell Bank that met defined criteria. Also made a cGMP Working Cell bank.
    - Finalized the progenitor cell manufacturing process.
    - Determined final device configuration for clinical testing. A device manufacturing facility was designed and built.
    - Has established preclinical models in collaboration with world-renowned immunologists and are testing ability of device to protect cells from allo and auto immunity.
    - Are preparing for pivotal IND enabling studies.
    - Are developing the clinical plan for the first-in-human testing.
- Two invention disclosures.

Impact

Continue program with goal of filing an IND within the 4-year period. The team recently received supplemental financial support from the Juvenile Diabetes Research Foundation, and is in discussion with a potential partner. CIRM will need to continue to monitor whether adequate resources are available and to consider providing bridging funds to support all activities needed to file the IND.

DR1-01480 Steinberg

PI: Gary Steinberg, Stanford
Co-PI: Stanley Carmichael, UCLA
Project Manager: Martha Reitman

Disease Target: Stroke

Cell Therapy or Therapeutic Candidate: Allogeneic hESC-derived NSC line transplanted alone or in combination with matrix material into infarcted area of brain, with concomitant immunosuppression

Project Start date: 2/1/2010

Key Accomplishments

Summarizing progress of the project:

- Utilizing a research bank of candidate cells, functional recovery has been demonstrated in three preclinical models of stroke in three independent labs;
- The team continues to establish cell manufacturing and testing processes that will enable preclinical and clinical testing. The team has produced two qualification lots that can be elected as the Master Cell Bank and Working Cell bank, based on extensive characterization, functional and safety testing;
- The team has conducted a pre-pre IND meeting with the FDA.

As an example of how the team is working under multiple CIRM awards to move therapy development in stroke forward:

This is an example of a Development Team that made a good decision to pursue a less complex manufacturing process in order to bring the candidate to IND and first-in-human testing expeditiously. The project team explored the use of a hydrogel formulation versus cells alone, and demonstrated an increase in cell survival and function. However, this increase did not meet a pre-determined threshold for success, which was necessary to meet in order to justify the more complex product development and regulatory pathway that a combination product would warrant. Although hydrogel will not be part of the initial therapeutic candidate, the Co-PI is funded under a CIRM Tools and Technology award and the optimization of the hydrogel continues.

Impact

There is no impact to the original timeline and budget at this time.

DR-01490 Zaia

PI : John Zaia, City of Hope
Co-PIs: Paula Cannon, USC
Dave DiGiusto, COH
Michael Holmes, Sangamo

Disease Target: AIDS-related lymphoma patients infected with CCR5-tropic HIV and undergoing autologous hematopoietic stem cell transplantation (HSCT). Ultimately as method is improved using non-ablative HSCT, this indication would expand to include AIDS patients with retroviral drug failure

Cell Therapy or Therapeutic Candidate: Adenovirus modified HSC (CD34+ cells) expressing zinc finger nuclease targeting CCR5.

Project Start Date: 5/1/2010

Key Accomplishments

- Optimization of methods for adenoviral vector mediated transduction of hematopoietic stem cells and CCR5 disruption. During the course of this award the team has optimized methods for the expression of zinc finger nuclease in the hematopoietic cells to target CCR5;

- Development of preclinical model to test stem cell therapy for HIV – Dr. David DiGiusto from Dr. Zaia's team used zinc-finger nucleases to alter the CCR5 gene in human blood-forming stem cells, and Dr. Paula Cannon demonstrated that these cells can be transplanted into a preclinical model. The CCR5 gene encodes the cell surface receptor used by HIV to enter into the cells. When those altered blood forming stem cells were administered in a preclinical model that lacked an effective immune system, the cells colonized the bone marrow in the preclinical model and created a new blood system replete with the mutated CCR5. As previously shown by Dr. Cannon, that mutation closed the door on HIV. Exposed to HIV, the preclinical model recipients of the modified human stem cells beat it back. This model provides the means to test the efficacy of the therapeutic candidate that this disease team is developing;

- Progress towards IND-enabling studies for scale-up of cell processing is moving well.

Impact

No impact on time lines or budget. A clinical development advisor panel meeting is planned for winter 2012.