Proceedings: The SEED Grant Program: A Brief Synopsis of the Outcomes and Impact of CIRM’s First Research Initiative

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SUMMARY

In late 2006, the California Institute for Regenerative Medicine (CIRM) launched its first major research initiative to catalyze the nascent field of human embryonic stem cell (hESC) research at a time when federal funding of such studies was severely restricted. This Scientific Excellence through Exploration and Development (SEED) grant program supported a portfolio of scientific endeavors ranging from the most fundamental studies of hESC biology and behavior to exploring the therapeutic potential and value of these cells as tools of biomedical innovation. The SEED program attracted new investigators from all stages of their career into the field of hESC research, many of whom continue to pursue related studies through CIRM’s ongoing research and development programs or with the support of other funding organizations. The scientific impact of the SEED grant program can be measured in the scientific publications, disclosures of inventions, and measurable progress toward advancing CIRM’s mission and strategic objectives. In addition, CIRM has obtained valuable insights on how grant administration and policy considerations can affect the progress and conduct of scientific programs in a challenging period of both limits and opportunity.

INTRODUCTION

On August 2, 2006, the governing board of the California Institute for Regenerative Medicine (CIRM) approved a concept for its first research grant initiative, Innovation in Human Embryonic Stem Cell Research, to “jump-start” the field of human embryonic stem cell (hESC) research in California. This initiative, through a series of three sequential Requests for Applications (RFAs), sought to address the immediate needs of the scientific community by providing near-term support for pressing research opportunities and creating a shared infrastructure to enable such studies to be pursued free from the federal restrictions on funding (Table 1). The first of these RFAs, the Scientific Excellence through Exploration and Development (SEED) grant program, was designed to attract new investigators to the field of hES research and to support preliminary studies in the biology, derivation, and application of hESCs, including groundbreaking and exploratory new concepts in the field. These 2-year awards were not targeted to any specific aspect of hES or disease research, but rather to projects with the potential to add substantially to the existing body of knowledge on hESCs or to enable a useful research tool or therapy to be developed. In response to this solicitation, CIRM received 231 SEED grant applications, which were reviewed in November 2006 by members of CIRM’s Scientific and Medical Research Funding Working Group (SMRFWG), comprising 15 scientists from outside of California, 7 patient advocates, who are members of CIRM’s governing board, and CIRM’s Chair. The proposals were given scores of 1–100 by scientist members according to review criteria, which included significance and impact, innovation, research design and feasibility, collaboration, eligibility for federal funding, and responsiveness to RFA objectives. After the scientific evaluation, the SMRFWG engaged in a “programmatic review” to arrive at a series of funding recommendations according to scientific merit and portfolio considerations, such as the balance between innovation and feasibility, the balance between basic and translational research; the range of diseases addressed; and additional considerations from the perspective of the patient advocates. Because CIRM’s governing board had initially allocated up to $24 million to support as many as 30 SEED grants, the SMRFWG recommended the top 38 proposals for funding (tier 1, scores 84–96), representing a total investment of ~$22 million. A second set of applications, receiving scores from 71 to 83 (tier 2) were provisionally recommended for funding,
should funds become available. Impressed with the overall merit of these proposals, CIRM’s governing board ultimately voted to extend funding to an additional 36 applications from this group, bringing the total number of awards to 73 (1 was subsequently disqualified). Representing a $45-million investment, this resulting “SEED Portfolio” was rechristened the Leon J. Thal SEED Grants to honor the memory of Dr. Thal, a leading expert on Alzheimer’s disease and late member of CIRM’s governing board.

**Program Outcomes**

Creating and Maintaining an hESC Community in California

The SEED program largely met its goal of attracting many new investigators to direct their focus to hESC research, from young scientists early in their careers to established scientists who had built their careers in other fields. In a survey completed by 45 principal investigators (PIs) on grant completion (“Close-out Survey”), 18 had self-identified as junior investigators on receiving their SEED grants, 11 had considered themselves to be mid-career, and 16 had considered themselves to be senior investigators. Of all the respondents, 69% were new to the field of hESC research and 82% planned to seek additional funding to continue their hESC studies, whether as a direct extension of their SEED project (87%) or by pursuing an indirect offshoot of that research (88%). In addition to the principal investigators, many SEED projects supported the training of graduate students and postdoctoral fellows in hESC science. Although it would not be possible to precisely calculate the total number of trainees supported through this program, data from CIRM’s internal grants management system indicate that more than 100 graduate students and

### Table 1. CIRM’s first research initiative: Innovation in Human Embryonic Stem Cell Research

| Program | Objectives |
|---------|------------|
| RFA 06-01: SEED grants (Fall, 2006) | To fund preliminary research in the biology, derivation, and application of hESCs and their derivatives<br>To fund groundbreaking, exploratory new concepts and approaches in the field<br>To attract new investigators, young, as well as established, scientists in other fields, to direct their focus to hESC research |
| RFA 06-02: Comprehensive grants (Winter, 2007) | To support mature, ongoing studies on hESCs by scientists with a record of accomplishment in this field |
| RFA 07-01: Shared research laboratories and stem cell techniques courses (Spring, 2007) | To create dedicated laboratory space for the culture and maintenance of hESCs, in particular, the hESC lines that fall outside the federal guidelines, by supporting the creation of core laboratories to be used by multiple investigators<br>To provide space and equipment for hESC research without regard to federal limits<br>To train scientists and technical staff in hESC laboratory techniques through development of hands-on courses for California investigators |

Dates listed with the RFA titles indicate the time frame in which the proposals received in response to these solicitations were reviewed for scientific merit; only the SEED grants, RFA 06-01, were analyzed in the present report.

Abbreviations: CIRM, California Institute for Regenerative Medicine; hESC, human embryonic stem cell; RFA, Requests for Applications; SEED, Scientific Excellence through Exploration and Development.

**Project Features and Areas of Investigation**

Approximately two thirds of the SEED Portfolio comprised studies defined by CIRM as “basic research” (i.e., focused on exploration of molecular or cellular pathways that underpin fundamental hESC properties and behaviors, such as self-renewal, pluripotency, or differentiation into a given lineage or cell type). The remaining one third, categorized as “applied research,” included projects focused on developing tools, testing the therapeutic potential of hESC derivatives, or creating better protocols for hESC derivation, maintenance, and/or differentiation (Fig. 1A, 1B).

Although some SEED grants focused primarily on the biology of undifferentiated hESCs, most exploited differentiation strategies to derive specific lineages or tissue types from hESCs, either to elucidate the molecular determinants of cell fate decisions or to explore their potential for developing therapeutic applications. By far, most of the grants with a lineage focus were concentrated on derivatives of the nervous system, followed distantly by those exploring pathways relevant to cardiac and hematopoietic differentiation and early developmental fates (Fig. 1C). A few projects explored hESC derivatives of other specialized cell types and tissues, including germ cells, intestine, pancreas, skeletal muscle, cartilage, vascular cells, thymus, and retinal pigmented epithelium, as indicated by the “other” category (Fig. 1C).

Rather than investigating the intrinsic biology of hESCs per se, some SEED grants focused on using hESCs and their derivatives as a novel method to elucidate the molecular basis of pathology for diseases such as cancer, muscular dystrophy, and Alzheimer’s disease. These early “disease-in-a-dish” projects, which were conceived before the first published description of human induced pluripotent stem cells [1], sought to generate disease models using hESC lines derived from embryos harboring mutations or by engineering specific disease mutations into existing hESC lines, a significant technical challenge at the time. Other grants recipients sought to address recognized hurdles in the eventual translation of stem cell-based therapies to the clinic (e.g., the need to overcome immune rejection of transplanted tissues; the need to track and monitor the fate of transplanted cells; the desire to accurately and efficiently modify the genome of hESCs; and a need for clinically compatible, efficient protocols to grow, maintain, and differentiate hESCs to specific fates). Finally, a handful of SEED grants aimed to establish therapeutic proof of principle for use of unmodified or gene-modified hESC derivatives to treat disorders such as multiple sclerosis, damage to the central nervous system, and HIV/AIDS. Although the original SEED funding for these projects has concluded, several of these programs have progressed, either directly or indirectly, into related projects within CIRM’s translational and development portfolios, including a program that is poised to launch a phase I clinical trial in 2015 for the treatment of age-related macular degeneration [2].
postdoctoral and clinical fellows were supported as key personnel by SEED grants, an average of 1–2 trainees per project. These numbers are likely to be underestimates, because several trainees associated with SEED grants might not have been named specifically as key personnel or were supported by alternative sources of funding in the investigators’ laboratories. To date, more than 20 SEED PIs have notified CIRM of former SEED-supported graduate students who have continued to pursue hESC and stem cell–related studies in academia or who have sought and obtained faculty positions within and outside California. Several trainees have also found positions in the biotechnology/pharmaceutical or government sectors, and a few have remained in their PI’s laboratories.

In December 2006, CIRM published its first formal Scientific Strategic Plan, describing a series of 5- and 10-year goals toward advancing its mission and a planned set of research initiatives to address them [3]. Many SEED investigators applied for subsequent rounds of funding under these new initiatives. As of early 2015, 36 had become PIs or co-PIs on subsequent CIRM awards spanning the entire research spectrum from basic biology to planned clinical trials. Another dozen remained involved as key personnel or subcontractors on subsequent awards or acting as mentors to graduate students or postdoctoral fellows supported through one of CIRM’s training grant programs. In addition to CIRM funding opportunities, 90% of survey respondents were actively seeking new funding opportunities through the National Institutes of Health and other agencies or foundations. In a 5-year follow-up survey in the fall of 2014 (“2014 Survey”), 14 of 28 former SEED grantees indicated they had received new, non-CIRM sources of funding to support projects related to their SEED grants. In this more recent questionnaire, 18 respondents reported continued pursuit of hESC research in their laboratory either as a major focus (n = 9) or as part of their ongoing research program (n = 9). Seven respondents indicated that they were not actively using hESCs but might do so in the future, and two indicated a departure from hESC research to focus more on the biology of endogenous stem cells. Although the overall response to this follow-up survey was low (n = 28 or ~40%), CIRM is aware through subsequent CIRM awards that at least 15 additional SEED grantees continue to use hESCs and other types of human stem cells in their active research programs. Thus, more than one half continue to participate in research directed toward advancing CIRM’s mission.

### Scientific Impact

The SEED Program targeted and funded multiple projects that were considered exploratory or high risk in nature at a time when hESC biology was being little studied in the greater scientific community. In addition, many SEED investigators were new to the field of hESC research and encountered significant technical challenges in adapting this new platform to their laboratories and becoming proficient in the culture and manipulation of these cells. Despite these initial difficulties, the first scientific findings for which SEED funding directly contributed began to appear in the published literature in 2008 and increased during the next few years, peaking in 2009 through 2011 and then decreasing steadily from 2012 to the present. At the end of 2014, SEED funding had been acknowledged in a total of 205 scientific publications, including 149 research studies, 21 methods articles, and 35 reviews. Thirty-three of the research articles had been published in high impact factor journals, many describing novel characterization of pathways involved in key hESC behaviors, such as self-renewal, oncogenic potential, and differentiation to specific lineages. Of particular impact were some of the earliest descriptions

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**Figure 1.** Research captured within the Scientific Excellence through Exploration and Development (SEED) portfolio. (A) Approximately 60% of SEED projects were categorized as “basic research” or those investigating the underlying biology of hESC properties and behavior. The remaining projects were considered “applied research” (i.e., those developing tools, protocols, or exploring therapeutic potential). (B) The number of individual SEED projects categorized broadly by research area of focus. (C) SEED grants grouped by the types of hESC derivatives studied or used. “Stem” indicates the focus was on the biology of the undifferentiated hESC instead of a differentiated derivative. “Early” indicates cell types of early development, such as those of the primary germ layers or trophectoderm. The “other” category includes specialized tissue derivatives of various organs, such as the intestine, liver, or skin. Abbreviation: hESC, human embryonic stem cell.
of epigenetic regulation in hESCs and the discovery of hESC-specific micro-RNAs involved in pluripotency [4–7]. Other highlights included the development of a bioluminescent imaging platform for noninvasive detection of teratomas in transplanted hESC-derived populations [8] and the discovery of small molecules that influence hESC differentiation [9, 10]. More information on the published findings associated with individual SEED grants can be found on CIRM’s website using the “Search CIRM Grants” tool and selecting “Seed Grant” as the funding type [11].

Although peer-reviewed research findings might provide an objective measure of scientific productivity, publications alone cannot fully capture the broader impact of the SEED program on stem cell science. Many SEED grants centered on very early-stage research, whose fruits might not be realized for many years to come or whose outcomes might have evolved considerably from what was proposed in 2006. Perhaps not surprisingly, the SEED grants that led to the greatest number of research articles per project were largely focused on investigating the processes and behaviors of the hESCs themselves, for which the methodology was less dependent on developing new tools or using differentiation protocols that, at the time, were based on a relatively limited understanding of hESC fate decisions. This trend can be visualized in Figure 2, which categorized two groups of SEED grants with the most or least publications to date by their area of focus. The “most published” group consisted of 16 SEED grants that each contributed to 4–14 original research articles and/or methods publications per grant. The “least published group” included 14 SEED grants that have thus far generated no publications, excluding reviews. It is important to note that despite a dearth of published results, many SEED grants were considered productive by other measures, in that they had partially or fully realized their specific aims, addressed CIRM’s strategic goals (discussed below), enabled successful acquisition of other grant funds, or generated negative data that would be unlikely to be published. In any case, ~60% of the grants in the “least published” group focused on cell type derivation compared with ~25% of those in the “most published” group. The cell derivation grants for the most published group (n = 4) were evenly split between a cardiac and an early neurological focus. In contrast, those from the least published group (n = 8) included efforts to derive more specific neuronal and cardiac subtypes and other specialized cell types, such as germ cells, hematopoietic stem cells, and endodermal lineages (data not shown), perhaps indicative of the riskier or more preliminary nature of those studies, as differentiation of hESCs to mature, specialized cell types remains a significant challenge to this day. Publishing frequency did not strongly correlate with whether an investigator had previously worked with hESCs, although the median number of research/methods publications was twice as high for grants recommended for funding as part of tier 1 compared with tier 2, as defined in the Introduction. Finally, it is possible that the relative inexperience of many SEED investigators with hESCs, combined with the riskier, more preliminary nature of their projects, could have contributed to an overall lower number of publications than might have been expected otherwise. As a point of comparison, CIRM’s Comprehensive grants (see Table 1), which targeted mature, ongoing hESC studies from scientists with a record of accomplishment in that field, had a median number of research/methods publications that was 3 times greater than that of the SEED grants in a contemporaneous time period (2008–2010). In the first 2 years of each program, the Comprehensive grants averaged ~1.9 publications per grant compared with 1 per grant for the SEED program (excluding reviews).

In addition to the findings reported in the scientific literature, investigators have disclosed 23 inventions that were developed wholly or in part using funds from 16 different SEED grants, several of which are currently being marketed. Examples of the disclosed inventions include a new disease model for heart arrhythmia; small molecules for manipulating hESC fate and/or promoting differentiation to specific lineages; various improvements of hESC culture methods; and new technological platforms for cellular imaging and other forms of analysis.

In 2009 and, again in 2012, CIRM’s science office assessed the impact of funded research on its 5- and 10-year strategic goals outlined in the CIRM 2006 Strategic Plan, taking into consideration unpublished and published results. The results of this assessment are listed in Table 2, indicating the number of SEED grants that were considered to have made tangible progress in advancing one of these scientific objectives. In addition, several examples of specific SEED grant outcomes that affected individual goals are highlighted in the 2009 and 2012 Strategic Plan Updates [12, 13]. The goals that were most significantly affected by the SEED grants were those targeting the identification and
characterization of factors underpinning key aspects of hESC biology, including their ability to self-renew and differentiate into multiple lineages and a better understanding of their oncogenic potential. (The Strategic Plan defined additional goals that pertain to CIRM activities and were therefore not listed in Table 2; e.g., efforts to develop partnerships between private companies and nonprofit institutions.)

Finally, in a study previously reported [14], the SEED grants provided a wealth of information on the use and derivation of existing and new hESC lines in California, before the 2009 Executive Order that restored federal funding for research involving hESCs and the accompanying National Institutes of Health guidelines that were established in response.

Other Outcomes and Lessons

The SEED grants represented CIRM’s first independent research initiative as a new funding agency, and many lessons were learned through their administration, beyond scientific discovery. As alluded to, the transition from other fields into hESC science, even from related disciplines such as developmental biology, was more challenging than many investigators had anticipated, which, in some cases, led to delays of up to 1 year in getting productive new studies off the ground. From an internal assessment of scientific progress reported by grantees after the first year of SEED funding, CIRM estimated that approximately one third of the projects were somewhat behind in terms of their project goals, including 9 grants (~13%) that had yet to generate any data using hESCs. Some of these delays had resulted from difficulties in generating tools or reagents needed for study or difficulty in acquiring the needed hESC lines. In other cases, grantees had diverted their attention away from hESC studies to pursue activities other than those described in their grant proposals. CIRM administrators made efforts to resolve such issues by communicating the expectations, requiring prior approval for changes in scope, and, occasionally, by stating that future grant payments were contingent on demonstrable progress toward addressing the grant objectives. However, a small minority of grantees were unable or reluctant to maintain their focus on hESCs, resulting in the early termination of some awards. Although the SEED program was designed to support research projects for 24 months, nearly one half of the programs (n = 33) were granted no-cost extensions ranging from 3 to 12 months to allow additional time to complete project goals.

CIRM’s experience with administering SEED grants has illustrated the importance of proactive and flexible oversight and a need for appropriate incentive structures to ensure that focus on the RFA objectives remained a joint priority between CIRM and the investigator. These lessons were carried forward into other CIRM initiatives, some of which (e.g., the Basic Biology Awards) have continued to attract new investigators to the hESC field. Subsequent grant solicitations included language that more precisely defined the scope and research priorities and placed increased emphasis on preliminary data that could support the applicant’s ability and commitment to working with hESCs or other human stem cells. For several initiatives, CIRM implemented the practice of milestone negotiation before the launch of new awards and more frequent progress reporting to ensure more timely opportunities for advice and assistance. CIRM continues to seek improved methods advance its mission. On January 1, 2015, CIRM launched “CIRM 2.0,” a radical overhaul of how it does business. CIRM 2.0 includes efficient new systems and programs to emphasize speed, partnerships, and patients and will provide new opportunities for SEED grantees and others to accelerate the development of successful treatments for people in need.

CONCLUSION

The SEED Grant Initiative provided a unique opportunity for many Californian scientists to explore the biology of hESCs and become familiar with the challenges and rewards of this pursuit. Most SEED investigators have remained engaged in stem cell science and, in some cases, have built on CIRM’s early investment in their research program and successfully competed for subsequent awards. Moreover, some have become increasingly engaged in the translation of stem cell discoveries toward the clinic. A great amount has been learned about the biology of pluripotent stem cells in the 8 years since this program was launched; however, the field is still young, and we have much more to learn. Although we

Table 2. Impact of SEED grants on CIRM’s strategic goals, as defined in the 2006 Strategic Plan

| Strategic goal | Grants* (n) |
|----------------|------------|
| Five-year goals | |
| I: 6 Stem cell-based therapies in preclinical development | 2 |
| II: New methods for making stem cell lines | 7 |
| III: Disease-specific cell lines for at least 4 diseases | 5 |
| IV: Methods for growing stem cells in defined media | 9 |
| VI: Methods for inducing immune tolerance in animal models | 2 |
| VIII: Stem cell-based tools for toxicity testing | 2 |
| Ten-year goals | |
| 1: Clinical proof of concept for a pluripotent stem cell-therapy | 0 |
| 2: Clinical trials for stem cell-based trials 2–4 more diseases | 1 |
| 4: New approaches for immune tolerance in preclinical development | 2 |
| 5: Preclinical proof of concept for stem cell therapies for 6–8 diseases | 7 |
| 6: Disease-specific cell lines for ≥20 diseases and new insights | 5 |
| 7: GMP-compatible procedures for stem cell-based products | 1 |
| 8: Describing differentiation steps to various lineages | 49 |
| 9: Understanding self-renewal and oncogenic potential of hESC | 29 |
| 10: New methods for tissue replacement | 3 |

*The number of SEED grants that made measurable progress toward that goal, as assessed internally through unpublished and published data. (Several goals, such as 10-year goal 3, are not listed because they are not applicable to the present report.)

**Five-year goals III and VI are intermediate steps toward 10-year goals 6 and 4, respectively.

Abbreviations: CIRM, California Institute for Regenerative Medicine; GMP, Good Manufacturing Practice; hESC, human embryonic stem cell; RFA, Requests for Applications; SEED, Scientific Excellence through Exploration and Development.
cannot always predict the future course of discovery, we can be confident that many former SEED grantees will be charting it.

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Disclosure of Potential Conflicts of Interest

The author indicated no potential conflicts of interest.

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