



# Disease Team Workshop: Information Gathering Session

Workshop Report  
July 25-26, 2007

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## EXECUTIVE SUMMARY

The California Institute of Regenerative Medicine (CIRM) is charged with furthering the development of therapies, cures and diagnostics based on human stem cell research in California. To fulfill this ambitious mission, CIRM developed a Scientific Strategic Plan in 2006 that defined the specific goals of the Institute and established a detailed blueprint for achieving these goals. Several funding programs targeting different aspects of biomedical research were proposed, among them the Disease Team Initiative that would support teams composed of basic, translational and clinical scientists working together to develop therapies and diagnostics for specific diseases. This initiative aims to “organize funding in new and unconventional ways in order to promote progress,” and allows the use of innovative research models such as requiring active team management and emphasizing defined milestones to better support and to accelerate research that is poised for the development of stem cell based treatments. The Disease Team Initiative is meant to complement other CIRM programs that are already in place (e.g. Comprehensive Research and SEED grants, the Training Program, New Faculty Awards) or that are planned to focus on specific stages in the pathway to stem cell based therapies and diagnostics, such as the initiatives for Translational Research, Preclinical Product Development, and Clinical Investigation. Given the novelty of this particular funding model, two workshops were planned to explore different types of Disease Team projects and ways of implementing and managing them.

The first workshop, which took place in July of 2007, brought together scientists from industry and academia, patient advocates, and representatives from federal funding and regulatory agencies as well as from foundations that fund disease-targeted research. Participants considered how to best support teams of researchers translating human stem cell therapies and diagnostics to the clinic. The interim Chief Scientific Officer of CIRM, Dr. Arlene Chiu, defined the goals of the workshop as “gathering information to help CIRM understand how best to support and fund targeted team efforts in translational research” involving stem cells. She asked that participants discuss how functional teams are built, funded and managed, and that they present models for team-based development of therapies and diagnostics.

The workshop began with a series of presentations highlighting successful models of team-based research. Speakers introduced a particular model, discussed its functions, and highlighted aspects that contributed to the team’s success. Following these presentations, participants were invited to participate in seven independent discussions focusing on particular areas related to funding team-based research. Three overarching themes specific to team-based translational projects emerged from these discussions, and are presented in more detail below:

- I. Translational research benefits from team-based research, which encourages early consultation and cooperation with researchers of diverse skills and expertise.
- II. Strong scientific leadership and project management are essential for team recruitment, motivation, and success.
- III. Active management and oversight provided by the funding organization can increase the rate of successful translation to the clinic. Active oversight is resource-intensive and can be achieved in different ways.

Participants were asked to consider at what stage of development team-based research could operate most effectively. The overwhelming consensus was that the Disease Team Research Award Request for Applications (RFA) should invite team-based proposals that intend to address a disease-related issue, but that CIRM should not limit the RFA to specific diseases. Most felt that funding multidisciplinary teams would have a positive impact on therapy development, especially if stable funding for long-term projects were available. Opinions differed as to what stage of research warranted a team approach, but most favored funding preclinical research “within shouting range” of a development candidate, or at most 4-5 years from clinical testing.

Leadership and management were very quickly identified as essential for the success of team-based research. An ideal scientific leader would function as “a leader among equals”, and would be responsible for motivating the team, establishing clear project ownership, and recognizing individual contributions to team goals. The scientific research plan would be a collaborative effort developed by the team members in a process orchestrated by the leader. Therefore, the leader would need to be a practicing scientist of good stature whose laboratory is involved in the project. Advisory committees could be assembled by the team to further assist with scientific direction. Stable funding was identified as critical to attract the top scientific leaders to team-based research, given institutional pressures on investigators to perform and to be competitive as individuals.

Most workshop participants agreed that active management would facilitate the rate of successful translation of scientific ideas into the clinic. A role for a project manager during preclinical research was recognized as important, although the description of potential roles, responsibilities and qualifications required of a project manager varied greatly among the participants. Most felt that active oversight provided by an expert committee is needed to advise on team progress, to provide executive oversight, and to make decisions at critical points in the projects. They suggested that oversight committees should consist of third party members who are willing to commit time to the project, and that these committees might be assembled by the funding organization with input from the team. Participants envisioned periodic evaluation against defined milestones or checkpoints resulting in three possible outcomes: 1) moving successful projects toward the clinic 2) re-orienting of projects if milestones are missed, and finally 3) terminating projects that fail to meet critical milestones. Progress can be

evaluated formally, either via teleconference or biannual or annual review, and informally, via regular verbal communication with the project manager or project leader. The group favored having the Disease Team Research Award RFA require that applicants describe project management and oversight mechanisms (including project management plans) in their applications.

In addition to these three central themes, workshop participants identified resources that may be needed to support the complex endeavor of therapy discovery and development. Most workshop participants cited access to core services and regulatory expertise (beyond the scope of the core team) as helpful in streamlining the process of translation to the clinic. Suggestions that would help teams meet key regulatory requirements included: establishing a broad range of core services within California, increasing access to regulatory expertise, and encouraging the development of standard tools and techniques for stem cell research. Institutional Review Boards (IRBs) could benefit from education to overcome uncertainties in approving human stem cell protocols for use in patients, and participants noted that CIRM could assemble a few expert opinions on how best to support the education of local IRBs.

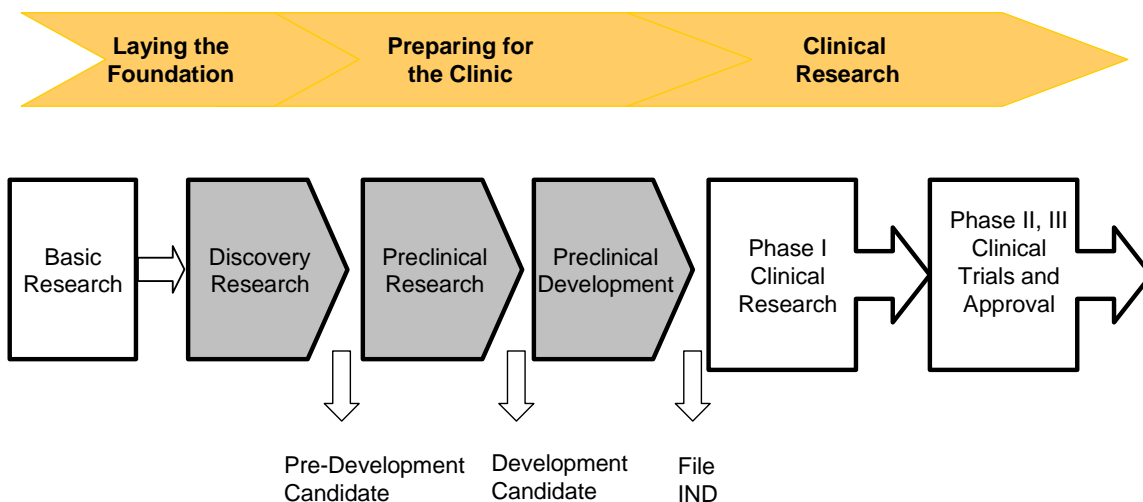
The workshop satisfied two distinct goals (1) it contextualized the process of therapy and diagnostic development, highlighting issues specific to the use of human stem cells, and (2) it presented CIRM staff with a number of current working models of team research aimed at developing therapies or diagnostics, and different funding mechanisms created to support these teams. Consideration of the strengths and challenges of these concepts will assist CIRM in developing a successful Disease Team Initiative. Since the workshop's intent was to gather information, this report documents the full range of ideas expressed during the discussions.

## INTRODUCTION

The intent of this initiative is to explore a new method of integrating and organizing the highest quality basic, translational and clinical research with the specific aim of producing a therapy for a particular disease or group of diseases whose research is poised for the development of therapies. *-CIRM Scientific Strategic Plan*

The Disease Team Initiative will support teams of researchers developing therapies, diagnostics or cures based on human stem cell research. The novel program elements proposed for this initiative include comprehensive project plans, the coordination of multidisciplinary researchers into teams that are developing a specific product, and active oversight and management of team projects. This workshop was conducted to solicit input on topics relevant to the successful design and implementation of a CIRM program for funding Disease Team research.

The figure below describes the typical progression of potential therapies from basic discovery into the clinic. The research activities required to take a basic scientific discovery through preclinical development (Figure 1, shaded pentagons) are often referred to as the “valley of death,” reflecting the lack of adequate funding and the low rates of project success. In the past, there has been limited government funding available for preclinical research, since it was perceived to be the responsibility of industry to finance the development of commercial products



**Figure 1. Typical progression of therapies from basic discovery into clinical use.**

from basic findings. However, developing a therapy or diagnostic from a basic finding can take several years of expensive research and optimization. Since industry is moderately risk-averse and most projects do not result in commercially

viable applications, typically only projects at the later phases of preclinical development are currently picked up by industry researchers. Research that translates basic scientific discoveries into projects appropriate for clinical testing is currently funded by foundations targeting specific diseases, by a handful of academic researchers interested in commercializing their findings, and by a few entrepreneurial biotechnology companies. Given that therapies and diagnostics derived from human stem cell research are in their infancy, innovative models to increase the rates of translation are needed.

Several CIRM Initiatives target different aspects of the pathway from basic science to the clinic. Some of them, such as the Preclinical Product Development Initiative or the Clinical Investigation Initiative, target specific stages of therapy development. Others, such as the Annual Innovation Grants, were designed to be broader in their scientific scope. The Disease Team Initiative is unique in that it will fund the development of therapies and diagnostics from stem cells using an innovative team-based funding model.

### ***The Workshop***

The Disease Team Workshop comprised one day of presentations on topics related to team-based research and challenges unique to stem cell-based therapy development, followed by a second day of short, focused discussions on issues relating specifically to the Disease Team Initiative.

*Day 1:* The first group of presentations, entitled *Disease Team Models*, focused on specific examples of team-based research projects. Scientists and foundation representatives presented different models for achieving targeted research goals through collaborative research, discussed the strengths and weaknesses of each model, and emphasized features that, in their opinion, contributed to the success of a team research effort. This was followed by a presentation on *Stem Cell Unique Requirements: Technology and Approach Considerations* that highlighted some of the specific technical and regulatory challenges faced by researchers engaged in cell-based therapies. Participants discussed the length of time that it would take for stem cell-based therapies and diagnostics to move from concept to clinical application. The session concluded with a detailed overview of the regulatory issues that exist and are being developed by the Food and Drug Administration for the approval of therapies based on stem cells.

*Day 2:* Participants discussed seven topics related to the Disease Team Research Awards. The primary focus of the Proposition 71 is the development of therapies and diagnostics based on human stem cell research. The goals and scope of Disease Team Research Awards were considered in the first session, *Scientific Scope and Stages*. In this session, participants discussed the types of research projects that might benefit from a team approach, highlighted different stages of research that the Disease Team Initiative might support, discussed management strategies and evaluation methods that are used by teams engaged in translational research, and identified project characteristics that might hasten the progress of different types of therapy-driven projects into the clinic. They also

highlighted factors that might be considered by CIRM when preparing and reviewing Disease Team Research Awards, such as providing applicants with time and resources to build their teams or requiring that applicants describe plans to integrate projects into clinical use if they are successful.

Stem cell therapies pose unique regulatory challenges, such as the need to develop ways of establishing cell identity and “substantial equivalence” of different cell preparations. Regulatory issues that could impact the research activities of teams working on stem cell therapies were discussed in the second session, *Regulatory Considerations*. Areas where CIRM could assist teams in the regulatory process were identified.

The Disease Team Initiative intends to support a broad diversity of team-based research that will be carried out over relatively long terms of 6-8 years (pending project success). The complexity of these research activities and the ultimate goal of therapy development require more active models of management both within a research team and by the funding agencies. On the other hand, management must respect team members’ independence in order to ensure their commitment to the project. In *Project Management and Oversight*, participants considered different models of project management. Among issues discussed were the roles of team leaders, project managers, steering committees and advisory boards, and the possible involvement of the funding agency in overseeing each of these levels of management.

Funding can be structured to give varying levels of project control to researchers, managers and funding agencies. In areas of scarce funding, such as translational research for stem cell therapies, the characteristics of the few existing funding models can affect the success of the projects. CIRM is considering several funding models in addition to traditional grants. In *Funding Considerations*, participants discussed the impact of different funding mechanisms on project progress, options to ensure that successful projects can move to the next level of implementation after completion of a Disease Team Research Award, and ways of leveraging CIRM funding by partnering with foundations or industry partners interested in particular aspects of stem cell research.

The composition of Disease Teams and the role that funding organizations play in helping to create and support these teams were discussed in *Organization of Disease Teams*. Disease Teams will encompass clinical and basic researchers, regulatory and compliance experts, and a variety of supportive services and technologies. The precise composition of a Disease Team will be influenced by the techniques being applied, the developmental state of the project, and the specific disease being addressed.

Team research is relatively novel in academic biomedical research settings, and may involve inter-institutional collaborations. Operational issues such as how team members are rewarded, how data is shared and reported, and how intellectual property is captured and protected will need to be developed as this model of research evolves. In *Operational Issues*, participants discussed the need



for teams to address some of these issues before embarking on a collaborative project, and the role of CIRM in this process.

The Disease Team Initiative will provide funds for large, multi-year, multi-disciplinary projects. Many of the research activities, particularly those involving human subjects or requiring clinical-grade reagents, are resource intensive and expensive. The purpose of the *Resources and Budgetary Considerations* session was to identify the major budgetary needs of targeted translational projects in stem cell research. In addition, issues surrounding intellectual property and revenue sharing were highlighted and discussed.

## DAY 1: PRESENTATIONS

### DISEASE TEAMS AND STEM CELL ISSUES

#### Key Points of Presentations

- Translational research is not monolithic. Early phase, discovery research is unpredictable and requires frequent reassessment. Later phases of preclinical research are often driven by regulatory requirements and benefit from developing a project plan with clear milestones and deliverables.
- Targeted translational projects benefit from early consultation and co-operation with researchers of diverse skills and expertise. For this reason, a team approach is often productive even for early stages of translational research.
- Although teams can be formed early in the process of translation, they must be flexible and dynamic in order to expand in unpredictable directions (or eliminate counterproductive members, if necessary).
- An engaged and energetic leader is essential for team recruitment, motivation, and success. The leader may change naturally as the project progresses.
- A project manager is highly desirable to help coordinate large teams of multidisciplinary investigators, particularly during the later stages of preclinical research.
- Active management and periodic reassessment and re-orienting of team-based projects increase the rate of successful translation of scientific ideas into the clinic.
- Active oversight of projects could help CIRM more adequately support team-based research. This can be achieved through direct staff oversight, through close communication with project managers, and through the appointment of independent scientific advisory boards for each project. Active oversight is therefore resource intensive.
- Services provided by effective, stable core centers are essential for many aspects of translational research, including research involving human stem cells. At times, translational research might involve innovative use of services provided by core centers, and therefore flexibility is essential. Other projects might require a high level of reproducibility or high throughput potential over an extended period of time, meaning that capacity and stability are important.
- Core service centers can exist within a laboratory, or they can be professionally managed. Although there is a high level of variability among core centers, laboratory-based service centers are normally more flexible and can accommodate novel uses, whereas professionally managed service centers are more stable and can handle higher volumes of samples.

- Academia and industry have different rewards and incentive systems, but neither provides an ideal environment to support long-term, risky, team-based research involving human stem cells. CIRM must be aware of the limitations imposed by investigators' environments. Supporting successful team-based research may encourage different research entities to evaluate and change their reward systems, but this is an extensive process outside of CIRM's circle of influence.
- Teams involved in translating human embryonic stem cell research to the clinic would benefit from training and support in appropriate regulatory procedures. Stem cell-based therapies are novel, and the regulatory mechanisms that will be used to determine the safety and efficacy of these therapies are not universally understood and have not been fully established.
- The development of standard tools and techniques for the isolation, handling/storing, and characterization of stem cells would help streamline the process of meeting key regulatory requirements.

This section of the report attempts to capture the main points raised during the focused presentations.

### ***Disease Team Models***

The intent of the Disease Team Initiative is to support new ways of integrating basic and clinical research in order to promote the development of new therapies and diagnostics based on human stem cell research. The goal of the presentations in the *Disease Team Models* session of this workshop was to identify characteristics of successful teams, and to understand the role of management, oversight, and funding strategies in successfully moving research projects into the clinic. Speakers analyzed the structure of teams from several different perspectives: the point of view of academic scientists engaged in targeted, team-based research; the efforts of foundations encouraging research collaborations aimed at developing therapies for specific diseases; and the experience of a targeted research project at a government organization. These examples raised issues that CIRM will likely encounter when implementing the Disease Team Initiative.

#### Academic Medical Center Models: Targeted research programs in an academic medical center (AMC)

The first presentation discussed the experience of university researchers engaged in collaborative projects related to the development and regeneration of the hearing system. This example was provided as a model of how a team developed and evolved in a university setting. As is typical in many AMCs, research was conducted independently in different laboratories and the team had shared ideas but no defined goals.

Initially, these collaborations were supported by traditional program project grants funded by the National Institutes of Health (NIH). The discovery in 1988 that hair

cells regenerated in the inner ear of birds led to the exciting hypothesis that regeneration could provide a mechanism for curing hearing loss in humans. This idea created much enthusiasm: financing flowed to newly-generated companies and new team-based research projects were established. The system turned out to be more complex than early excitement would have predicted, and it became clear that developing cures for hearing loss based on the regeneration of hair cells would require a long-term team effort involving researchers with very diverse skills. Ultimately in this example, seven laboratories began to collaborate in a drug discovery project funded by a program project grant, under the direction of two team leaders.

In discussing the teams formed during 22 years of translational research in hearing loss, the speaker raised the following issues as being particularly relevant to successful targeted projects in an academic setting:

- Targeted research requires such a diversity of skills and approaches that it must be done in teams. The hearing loss translational project, for instance, benefits from the rich academic environment at a university with a strong biomedical community. This allows for the recruitment of researchers with varied expertise.
- Teams are dynamic, and therefore must be flexible enough to survive the entry and exit of team members at different stages of project development. Not all of the changes in membership can be predicted at the outset of a project, especially since not all scientists make good team members.
- Teams benefit from guarantees of sustainability, such as guaranteed funding for a certain period of time. Team members can then focus on working together toward a common goal, making their individual success secondary to the success of the team.
- Real progress needs to be made in order to sustain team enthusiasm. In the case of hearing loss, progress meant getting hair cells in the inner ear to proliferate in significant numbers.
- Talented leadership is essential for the success of a research team. The speaker felt that good leaders should establish clear project ownership and recognition guidelines, should empower others to “own” and take responsibility for their research, and should display fallibility.
- The most significant challenge facing team research in an academic setting is the existing reward system, which judges researchers on their individual accomplishments. Industry, on the other hand, rewards team research but focuses mostly on short-term goals. A mix of these qualities might be achieved by the creation of diverse teams with long-term goals and guaranteed funding.

### Disease-Focused Foundation Models: Approaches to funding and managing targeted research

Much of the impetus for targeted, collaborative approaches to therapy development comes from foundations that make funds available for particular diseases. These foundations are typically very interested in ensuring that their money is invested in projects that are consistent with the foundation's mission, and that projects do not stray from that mission throughout the lifetime of the grant.

Two speakers in the Disease Team Model session described the efforts of foundations to promote collaborative, translational research and to be actively involved in the evaluation and management of this research.

Over time, both of these foundations developed separate funding models to support the different needs of early and late phase translational research. Both foundations now offer individual research grants to support the early stages of basic research, and more substantial collaborative funding mechanisms designed to move projects through preclinical and clinical testing. Collaborative or team grants are, in each case, more actively managed, although the mechanisms for oversight differed substantially between the two granting agencies. These different oversight strategies, which reflect the type of translational research that is supported by each foundation, are discussed below.

*a. Supportive management.* In the management model developed by one foundation, a consortium of researcher-initiated collaborations is extensively supported financially, operationally and administratively by the foundation. The consortium is a network of laboratories engaged in collaborative translational research projects at every stage of development, including the more exploratory stages of "discovery" research (such as developing cell-based assays or animal models in areas of research that are in their infancy). Principal investigators within the consortium network assign trainees in their laboratory to specific projects, and these post-doctoral fellows or students are responsible for reporting their progress directly to other consortium members and to an advisory panel. Foundation oversight is achieved through rigorous biannual advisory panel meetings, during which the collaborating team presents its data, discusses the project's direction, and receives advice from the panel and foundation staff. In addition, an independent group of ad hoc reviewers periodically evaluates each project, and an independent leadership advisor meets with the team to reassess the project's mission and overall goals. Finally, the foundation provides access to core services, either by supporting facilities that can be used by all consortium members, or by providing funds for outsourcing of services. Most workshop participants acknowledged that the support of core services was essential to the success of all translational projects.

The speaker suggested that the factors that contribute to the success of team-based research in this funding model are:

- a highly qualified foundation administrator who supports the project and brings out the best from each investigator.

- the dynamic nature of the consortium network and the freedom of members to select projects and collaborators within this network.
- trust and respect among the principal investigators.
- a good mix of established investigators and researchers new to the field.
- palpable energy and excitement about the projects among participants.
- strong cores that support researchers within the consortium. These cores might also provide services to the wider research community.
- a leader who is motivated by the mission rather than by personal advancement.

This foundation's management style is "supportive" because the researchers are the driving force for each project/collaboration, and the foundation provides active management and support services without always relying on milestones. Project teams are expected to develop concrete plans and detailed milestones to be met in order to translate their ideas to the clinic, but less developed projects do not always have fixed milestones and pre-established deliverables. Therapy development must be every team's long-term mission, but teams engaged in more exploratory translational research can be more flexible in their composition and goals in order to incorporate unexpected findings.

The strength of this management model is that it achieves excellent buy-in, since investigators retain significant control over their projects and membership in the consortium confers benefits such as access to core resources. Furthermore, centrally involving trainees in all team decisions creates a new generation of scientists with the skills required to work in groups, and who are accustomed to reporting progress to other consortium members and to an advisory panel. The flexibility of this approach has allowed the foundation to successfully support team-based projects in the earlier phases of therapy development – in other words, discovery research that is geared towards facilitating translation. A potential disadvantage of this funding model is that the foundation does not fully control the direction of research collaborations within its network.

*b. Directed management.* A more active model for funding and administering targeted translational projects was developed by a second foundation represented at the workshop. This model was designed to accelerate the translation of well-developed therapeutic targets into the clinic, at a stage when research teams are large and diverse, regulation and compliance issues become more complex, and milestones become more standardized and enforceable.

This foundation has a four-stage approach to funding:

- **Charting the Course.** Top scientists provide the foundation with strategic advice and grant assessment expertise, which helps the foundation identify the areas of research that specific grants will fund. Over 350 scientists participate in this process throughout the year.

- **Honing in on Translational Science.** A two-stage grant assessment strategy (pre-application and application) allows for the formulation and selection of projects that, if successful, will translate into treatments. The foundation staff advises applicants on their pre-application and can provide guidance to more closely align proposals with the scientific mission. Foundation staff is ultimately responsible for project selection, although it takes the recommendation of a scientific advisory board that reviews most grant applications. Over 800 grant applications were received by the foundation in the previous year.
- **Speed and Accountability.** Resources are made available to researchers as quickly as possible. Foundation representatives are actively involved in each project and work with investigators in order to meet milestones, establish future directions, and translate ideas into therapies. Milestones are set in advance, progress is assessed periodically, and the foundation staff is available for support, troubleshooting, and mid-term project evaluations.
- **Capitalization of Results.** The foundation constantly seeks partnering opportunities for its research projects.

Multi-year, multi-million-dollar grants are available for teams of researchers engaged in preclinical experiments that intend to progress to clinical trials. Research can be in the early phases of translation, but proposals must contain concrete milestones and a blueprint of the project's anticipated path into clinical testing in humans. Focused Requests for Proposals are established to address particularly promising hypotheses identified by the foundation. Grants are open to teams from academic institutions and from industry, and are often set up as contracts with clear deliverables. Contracts with industry can include payback clauses that come into effect when projects become commercially successful. To date, four grants have been awarded, and 2-3 more will be funded in 2007.

This "directed" management model requires considerable oversight by foundation staff, which is typically comprised of a PhD scientist in the field and a business professional skilled in project management. The foundation staff actively manages and oversees these team-based projects at every stage of development. In the pre-application phase, the staff advises applicants on scientific and project endpoints, team composition and management, and expected milestones. During the project, the staff continuously monitors progress and can be involved in scientific decisions, such as helping select the compounds that will be tested in an animal model. Progress is assessed periodically by the staff and by a scientific advisory board, who are encouraged to take into account success metrics other than publications. Award money is disbursed as project milestones are achieved, and awards can be terminated if the foundation determines that a project is not successfully meeting its milestones.

The speaker stated that the main advantage of this model is that the granting agency can affect the direction of research being done in order to encourage translation of basic discoveries into the clinic. A disadvantage is that researchers can resent this top-down approach and opt out of a project, particularly when their

view of the translation pathway differs from that of the foundation. In addition, the model relies on highly specialized foundation staff that directly oversees each project, which can be a burden for a small funding agency interested in supporting therapy development for a potentially large number of diseases.

#### Government Agency Models: Targeted research

A recurring issue in translating discoveries from the basic laboratory to the clinic is recruiting the appropriate team of investigators to execute these long-term projects. Academic researchers are motivated by basic questions that will lead to innovative scientific insights, and are often not interested in long-term commitments to directed, preclinical research. On the other hand, industry will not tolerate the heavy failure rate inherent in the early phases of translational research. Government agencies have the funding capacity, the motivation, and the incentives to withstand failures that are necessary to translate discoveries to the clinic. The final disease team model discussed in this workshop involved an experimental government research program aimed at optimizing and moving a chemical compound from candidate therapy into clinical trials. The government agency provides funding, scientific vision, and program oversight, but most research and project management is conducted through contracts. In addition to developing a cure for the disease in question, the granting agency is using this project as a model to help support team-based translational projects through its Translational Grant Program.

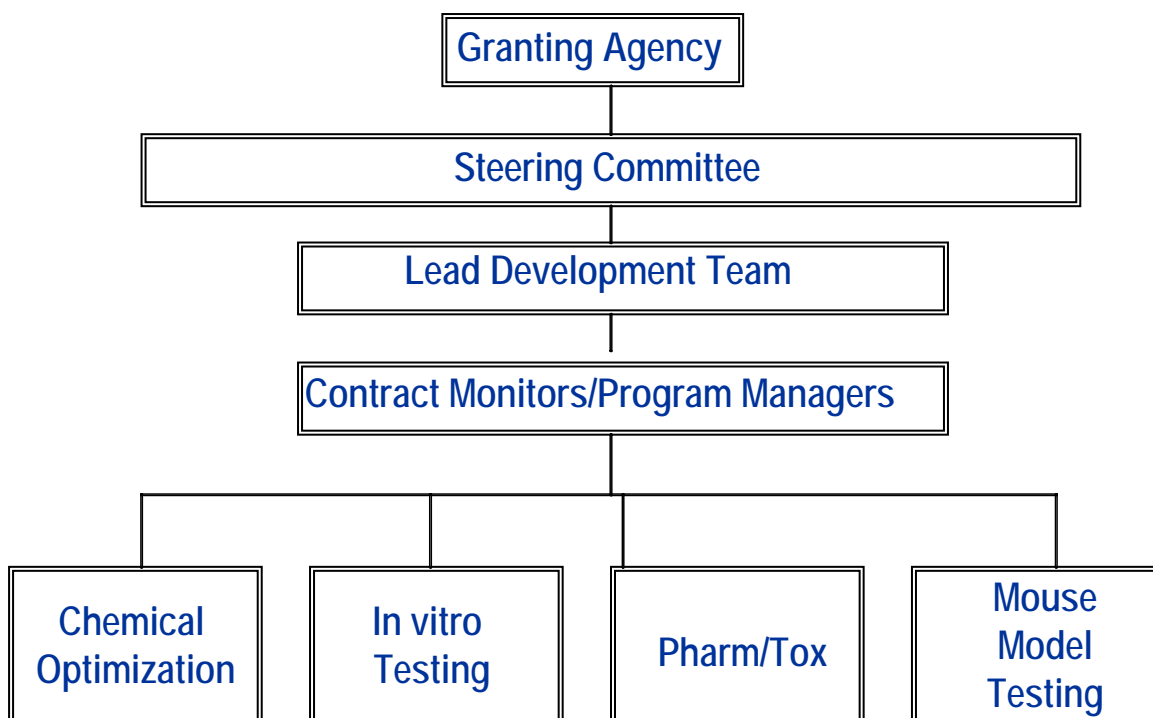
a. *Contracted research.* The disease selected for this experiment, Spinal Muscular Atrophy (SMA), presented a unique opportunity for translation: the cause for the disease in question was known to be a mutation in the SMN1 gene, a good target for therapy; the field was in a relatively advanced state; proof-of-principle experiments had identified a potential therapeutic candidate, indoprofen; and the critical path for therapy development was clear. Although SMA is one of the most common genetic causes of infant death, industry was not interested in therapeutic development because of the low number of clinical cases involved. In 2004, the agency set up a research program and a management structure to oversee development of this project.

Indoprofen had been identified as a potential therapy for SMA because it increased expression of SMN genes *in vitro*, although the mechanism of action was not known. The drug had significant liabilities that prevented its immediate testing in clinical trials: its activity was low, it exhibited some toxicity in mice, and it was unable to cross the blood-brain barrier. This final liability would inhibit oral administration, a particularly important feature for a pediatric therapy. The program goals were to optimize the chemical compound through medicinal chemistry, select candidates with high efficacy and low toxicity in defined assays, and complete all experiments necessary to file an Investigational New Drug (IND) application with the FDA. In 2005, the team established a weekly cycle of producing and testing new compounds, resulting in the identification two years later of a few candidates that displayed increased efficacy and decreased toxicity. In mice, the candidates are orally bio-available, well-tolerated, display a good half-



life, and are chemically stable. They are also less toxic than indoprofen, the original compound. In the process of testing candidate drugs, research contractors discovered that the drug being investigated promotes translational read-through by overcoming premature stop codons. The elucidation of the drug's mechanism of action resulted in a scientific publication and raised the possibility that it could be used to treat diseases other than SMA. The agency expects to file an IND with the FDA in 2008 to assess the possible use of indoprofen-derived candidates for the treatment of SMA. Since it owns all intellectual property derived from this program, the agency will begin to consider licensing options.

The funding and management model for this program is quite novel. A defining feature of the program is the Steering Committee, which includes translational scientists from industry and academia, and *ex officio* members of the FDA and NIH. All research is sub-contracted out to industry and to contracting and academic laboratories (Figure 2). An independent contracting agency monitors the progress of each subcontractor through individual project managers, who report weekly to the program's Lead Development Team. The Lead Development



**Figure 2. Management of a translational project within a government funding agency.**

Team includes members with extensive experience in industry drug discovery, who are contracted by the granting agency. The Lead Development Team acts as a hub that coordinates all program activities and ensures that all projects stay on track and achieve pre-established milestones. The Steering Committee and the Lead Development Team establish the workflow for the research program and determine the timeline and milestones for each project based on a drug discovery

and development testing funnel model. Progress of the project is assessed biannually by a Steering Committee.

The speaker identified both the concept of a Steering Committee and the idea that a funding agency can be represented on it as potential oversight mechanisms for Disease Team Research Awards.

*b. Cooperative Translational Research Program.* Based in part on the experience derived from its experimental contracted research model (described above), this government agency has developed a Translational Research Program that supports projects moving from discovery research into preclinical development. This relatively new program funds milestone-driven cooperative agreements rather than grants. A cooperative agreement combines features of a grant and a contract: it uses the administratively simple grant mechanism to allocate resources, and yet gives the funding agency significant input and control over the work being done (for instance, milestones can be used to decide whether funding will be continued). The project's review committee includes representatives from both industry and academia, and reviewers receive instructions on the agency's expectations for these projects before each review session. The agency staff is significantly involved in each project, monitoring progress, establishing collaborations with other organizations, and coordinating the overall program. Staff can withhold funding from projects that have not met their identified milestones.

Critical success factors for the Translational Research Program agreements identified by the speaker were:

- the commitment of the principal investigator/leader
- the team's experience with therapeutic discovery and development
- involvement of the agency and staff commitment to the project

The speaker indicated that investigator commitment is critical to success but is not generally evaluated in most grant review procedures. Key factors to evaluate would be leadership potential and the potential for a team's success based on the leader's experience.

### ***Stem Cell Unique Requirements: Technology and Approach Considerations***

Stem cell approaches to treating disease might involve using stem cells to produce a therapeutic factor or as a diagnostic tool; targeting stem cells for patient-specific treatments; or introducing stem cells expanded from a stem cell line into patients in order to correct a disease. This presentation highlighted some of the technical and regulatory issues specific to stem cells that must be considered when proposing to use these cells for therapeutic purposes, and described predicted timelines for turning human stem cell research into clinically-useful applications. The speaker described two examples that have been achieved for introducing stem cells into patients; 1) isolating, manipulating and reintroducing a patient's own stem cells and 2) introducing stem cells expanded from a stem cell line. These examples were used to provide a perspective on requirements and

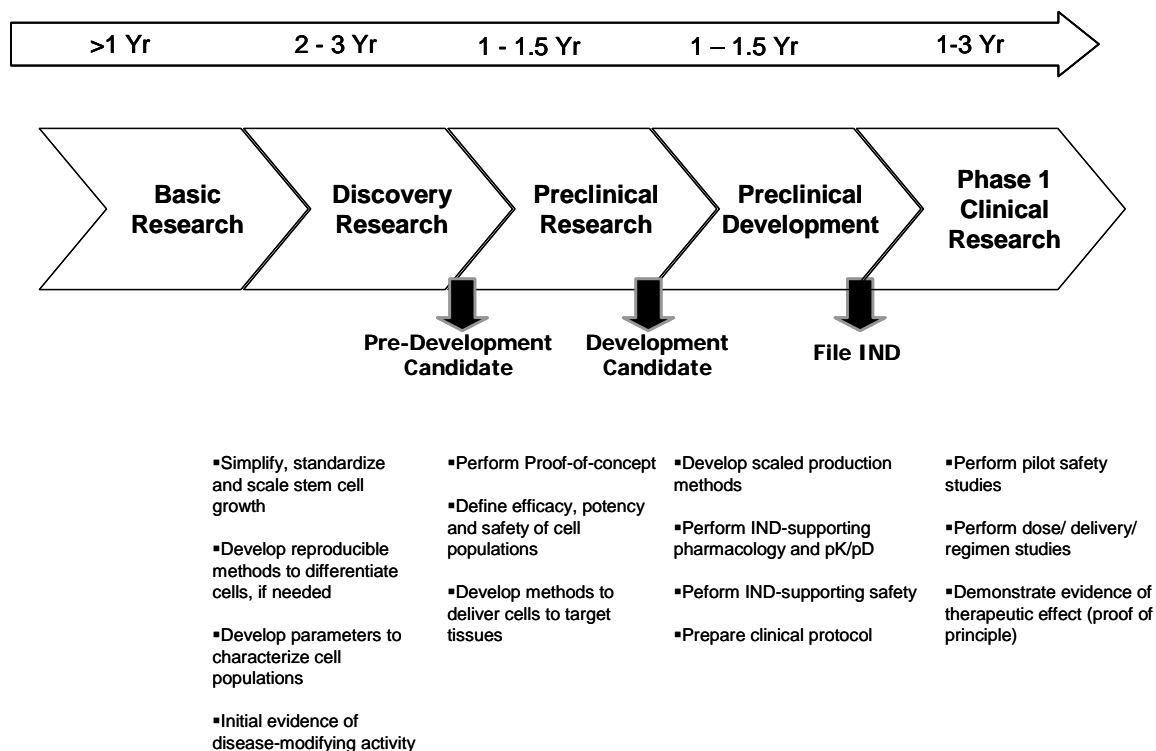
timelines for translating a discovery to clinical testing. Evaluating the possible therapeutic use of stem cells for treating a disease involves a series of diverse but interconnected steps:

- Understanding the disease physiology.
- Identifying the advantages and challenges of cellular intervention over more traditional small molecule therapies.
- Identifying the best cell for a particular therapeutic model. How much characterization and what level of purity are required? How reproducible are results? Bear in mind that stem cells are self-renewing and may represent a lifelong treatment.
- Developing appropriate regulatory and compliance protocols early in the planning process. The Center for Biologics Evaluation and Research (CBER) should be consulted throughout project development in order to avoid expensive mistakes. The clinical planning process involves sketching out a pre-clinical path, defining the first patient population, and determining when and how to move on to a more significant patient population.
- Translating the potential therapy to the clinic with *in vitro* and *in vivo* proof of principle.

Moving a cell therapy product from concept into practice thus requires a team with a diverse set of skills. Most organizations will not have all of the necessary components to take a therapy to the clinic, so collaborations between different fields and organizations are essential. These collaborators should be identified and consulted as early as possible. For instance, both clinical and basic science advice should be sought when establishing basic cellular or animal models, since clinicians may have the best understanding of achievable routes of therapy and basic scientists might understand the scientific limitations of a particular cellular or animal model. Likewise, though a small team or young organization may not have in-house regulatory staff, contract services are available, even at early stages of preclinical research. Alternatively, the FDA can be consulted to provide regulatory guidance. Such early consultation helps develop engaged collaborators, and can avoid lengthy and expensive replication of experiments later on in the process.

Three factors unique to stem cell-based therapy development can greatly impact project progress and success. First, what is required of the cells in order for the proposed therapy to be successful? Are the cells capable of doing what is required? Appropriate animal models might need to be developed to provide proof-of-concept studies. Second, how will the therapy be assessed? Since stem cell-based therapeutics are so novel, new methods may be required to demonstrate that the stem cell has migrated to the appropriate site, differentiated into the required cell type, and integrated into the tissue as required. These studies will be necessary to evaluate therapeutic effectiveness. Third, what are the specific safety issues that will arise from the use of a specific human stem cell? For instance, purification and *ex vivo* expansion of cells could alter their karyotype,

whereas injection of an incompletely differentiated precursor cell into humans might cause teratoma formation. At this early stage in the development of therapies based on stem cells or stem cell research, these practical issues might significantly slow the progress of potential therapies through the translational pipeline.



**Figure 3. Timeline expected for stem cell therapies moving from the bench to the clinic.**

There are no public industry benchmarks that can be used to predict the timeline required to develop stem cell based diagnostics and therapies. However, predictions can be made based on existing models for drug development (Figure 3). For therapies involving transplantation of stem cells into patients, the following scientific criteria must be met in order to move the product into clinical application:

- Stem cells must be identifiable and isolatable
- In order for stem cells to be used as a general therapeutic for a disease, rather than for patient-specific therapies, it should be possible to expand the cells *ex vivo*
- Stem cells should be stable and bankable if they are to be used as a general therapeutic
- Stem cells must survive transplantation
- Transplantation should be safe and effective and should yield a predictable outcome (as established in preclinical tests)

- A disease model must be available or developed
- A toxicology model must be available or developed

The time required to translate a stem cell therapy or diagnostic will obviously vary depending on the project's stage of development. For therapies involving transplantation of stem cells into patients, the more of the criteria listed above that have been met the faster a potential therapy can move through the translation pipeline (Figure 3). The speaker reviewed the examples of two stem cell-based therapy products moving towards clinical application. The average time from isolation of the appropriate human stem cell to the initiation of phase I/II trials in these two cases was 5-7 years. The speaker indicated that data from disease and toxicology models could be developed for good therapeutic candidates within 2-4 years, provided that appropriate models exist, and that Phase I/II clinical testing could be completed within 1-3 years, depending on many factors. These are some of the earliest industry data on the time required to develop therapies from stem cells.

### ***Regulatory Considerations***

Development of a stem cell based product requires clinical testing regulated by the Food and Drug Administration (FDA), but the biological characteristics of stem cells pose significant regulatory challenges. Stem cells display a robust proliferative potential and are capable of differentiating into a diversity of cell types. The developmental stage of a cell, exogenous influences such as growth factors and cell-cell interactions, and manufacturing manipulations such as cell isolation, expansion and banking can all affect the behavior of a stem cell intended for therapeutic use. The FDA is collaborating with all stem cell therapy stakeholders to develop guidelines that will establish the identity, sterility, purity, potency, stability, safety and efficacy of therapeutic stem cells. Many of these guidelines are discussed in a CIRM conference report from 2005, *Stem Cell Research: Charting New Directions for California*, and are available on the Internet at: <http://www.fda.gov/cber/guidelines.htm>. Speakers strongly recommended that researchers thinking of developing therapies based on stem cells contact the FDA well before their pre-IND meeting.

In determining stem cell safety, factors to be considered are the *source* from which the stem cells were derived, the *process* used to isolate cells and prepare them for therapeutic use, and the *preclinical evaluation* used to establish cell identity and genetic stability. Preclinical efficacy assessment of a stem cell therapy will involve proof-of-concept experiments in animal models and toxicology studies in healthy animals (these experiments can be combined in well-designed studies). To facilitate FDA review, analytical tools and experimental techniques should be developed to test the "degree of equivalence between stem-cell based products derived from different starting materials." It is recommended that researchers determine the impact of genetic instability of cultured stem cells on biological properties pertinent to their use as cellular therapies. Animal-based and *in vitro* models to assess feasibility, determine toxicity, conduct dose exploration, and

monitor cellular parameters are also needed. Non-invasive imaging technologies to monitor the fate of stem cell products following administration would also be useful. Finally, the research community should evaluate different approaches for the delivery of stem cell based products. All stem cell based therapies will be evaluated under these general guidelines, so speakers indicated that it would be efficient for the research community to begin developing standard operating procedures and assessment tools to facilitate this evaluation.

## DAY 2: WORKSHOPS

The rationale for the initiative is the idea that development can proceed faster, more efficiently and more effectively when:

- a) there is a comprehensive plan for development leading from the laboratory to the clinic;
- b) the multidisciplinary members of the team necessary to implement the plan participate in all of its phases; and
- c) there is active team management.

- *CIRM Scientific Strategic Plan*

On the second day of the workshop, Dr. Bettina Steffen introduced the intent of the Disease Team Initiative with this quote. Referring to a thread that had run through the presentations of the day before, Dr. Steffen proposed a fourth factor that appears to be essential for successful team-based research: an engaged and motivated team leader. Dr. Steffen then asked participants to consider the aims of the workshop:

- 1) to explore the scope, resources, program management and funding of effective disease teams;
- 2) to explore the strengths and weaknesses of various research team approaches;
- 3) to identify requirements for disease teams that are unique to therapies and diagnostics developed using stem cells.

For each of the seven sessions that followed, participants were led in moderated discussion. Discussion questions were distributed and are available for review in Appendix A. The exception was the Regulatory Considerations Section (pages 30-31), which was conducted as an informal Question and Answer Session. This section of the report attempts to represent the spectrum of opinions expressed by participants during the discussions; it is not intended to develop consensus or to make conclusions based on individual opinions.

### ***Scientific Scope and Stages***

#### *Key Points of the Discussion*

- Encouraging team-based proposals that address a therapy, but not limiting the program to any single specific disease or condition, will capture the highest quality research ideas.
- Funding multidisciplinary teams will have a positive impact on therapy development.
- Stable funding of long-term projects will encourage researchers to invest in the success of their team, freeing them of institutional pressures that can undermine lengthy projects or team-based research.

- Research at early phases of the translation pipeline requires more flexible evaluation criteria, whereas later phase research can be held accountable to defined milestones.
- A two-tiered funding program, or two separate funding opportunities, would accommodate disease-focused projects that may be in very different states of “readiness” for the clinic.
- The Disease Team concept might be effective for relatively early phases of translational research, and is a clear asset throughout preclinical testing, development, and clinical trials.
- Disease Teams are useful models for organizing projects that are focused on entry into the clinic, and including Phase I/II clinical trials.
- Building effective teams and establishing appropriate management procedures for translational projects is a complex and lengthy procedure that would benefit from CIRM support.

#### *a. Goals and Focus*

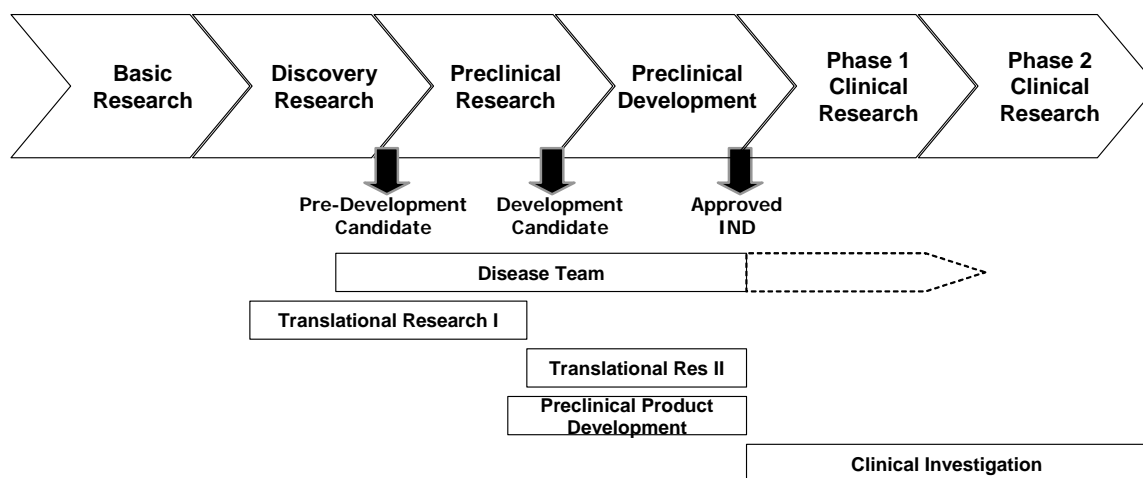
The first issue discussed in this session was whether to focus the scope of Disease Team grants on specific diseases, technologies, or uses of stem cells. Participants observed that it would be difficult to decide *a priori* whether to focus on high-incidence diseases such as Alzheimer’s, fatal diseases such as ALS, diseases with well-known etiologies, or “safe” diseases such as male pattern baldness and long bone fracture. The overwhelming consensus was that the Request for Applications (RFA) should invite team-based proposals that intend to address a disease-related issue, but that it should not limit the focus to specific diseases or conditions. Participants voiced strong encouragement to open the RFA to all potential roles of stem cells in developing therapies, not limited to but including: cells as a delivery vehicle, cells to mobilize endogenous cells, cells to modify the immune system, cells for transplantation and integration, and cells as disease models for small molecule screening and toxicity evaluations. This strategy would capture as many good research ideas as possible. On the other hand, most discussants felt that it was reasonable to request that applications define a clear pathway to clinical application, even if the pathway extended beyond the funding period of the grant.

The dual Initiative goals of team- and disease-oriented research were each considered important. Most discussants felt that supporting strong multi-disciplinary teams will have a positive impact on targeted projects. They commented that team research will create more integrated knowledge and will lead to a more efficient translation pipeline. They also commented on the value of supporting a culture of “resilient teams,” that could combine positive features of both academic and industry-based research and overcome institutional challenges to targeted, translational research. Researchers in academic settings are willing to



take scientific risks and are adept at changing course in response to project results, but they are vulnerable to institutional expectations of individual achievement, which can lead to reluctance to participate in team research projects that do not acknowledge traditional individual accomplishments. Industry partners on the other hand are motivated to work in teams and to align themselves with the mission of their project, but they are encouraged to seek rapid, commercially-viable results and might therefore shy away from more risky long-term projects. Multi-year, well-funded project grants that provide a guarantee of stability can encourage all team members to invest in the long-term success of the team’s mission in spite of conflicting institutional pressures. One participant pointed out that team building was the distinctive feature of the Disease Team Initiative, and that the intent of the initiative would be satisfied by supporting any high quality *team-based* effort aimed at furthering research poised for the development of a therapy (or a diagnostic tool).

*b. Stages*



**Figure 4. CIRM anticipated preclinical and clinical research initiatives.**

Opinions differed regarding what types of projects would benefit from a Disease Team approach. Many participants expected that the Disease Team Initiative would focus on projects intending to enter the clinic within the term of the grant, since this focus offers teams a concrete mission with the possibility of clear project milestones and outputs. On the other hand, some participants noted that stem cell research and therapy development is still in its infancy and not many diseases would qualify as being “ready for the clinic”. They indicated that a targeted, team-based approach to relieving preclinical bottlenecks relevant to the development of therapies for several diseases (for instance, developing new delivery methodologies or new animal models) would significantly enhance the rate of development of multiple stem cell-based therapies, and would be an effective immediate funding priority for CIRM’s Disease Team Initiative. This issue arose repeatedly throughout the workshop and was clearly a concern for many

participants, even though CIRM staff noted that other CIRM initiatives (such as the Initiatives for Translational Research and for Preclinical Product Development, Figure 4) were intended to address bottlenecks to therapy development and other aspects of translational research.

Moderators asked participants to identify what phases of the translation pipeline would benefit from the Disease Team Initiative – that is, whether to favor low-hanging fruit (“late” projects very close to therapy) or projects that are at an earlier development phase (“early” projects).

Each phase has its own characteristics, detailed in Table 1 . Focusing on projects at later phases of development is less risky and more likely to yield successful therapies in the short term, an important CIRM goal. However, many participants felt that the field of stem cell research is so new that bringing therapies at any stage of development closer to the clinic is a more realistic priority. Broadening the capture radius of the Initiative would have a very large impact on the diseases addressed in the long run. Opening up the Disease Team Initiative to diseases at earlier phases of preclinical development would also allow CIRM to bolster this novel, team-based funding model throughout the stem cell research community. On the other hand, one discussant commented that CIRM should, in thinking about this RFA, “avoid the fear that someone will be left out. This (disease team initiative) is not for everyone.” It was noted by CIRM staff that the Disease Team Research Awards will be offered in multiple rounds.

**Table 1. Characteristics of early and late phase translational research.**

<b>Characteristic</b>	<b>Targeted Discovery (Early Phase)</b>	<b>Preclinical-to-Patients (Late Phase)</b>
Time to Clinical Studies	4-8 years	1-3 years
Likelihood to Progress to Clinic	Lower	Higher
Milestones	*Fluid tasks *Discovery-driven	*Standardized tasks *Regulatory-driven
Interim Evaluation Decisions	Frequent re-direction	Go/no go decisions at defined points
Current State of Stem Cell Research	Many projects	Few projects

There was no group consensus on the stage of translational research that should be targeted by Disease Team Research Awards. Some participants felt that the focus should be on programs in late phase preclinical development and Phase I/II clinical trials. Some felt that the RFA should encourage any project that directly targeted a disease, and that reviewers should compare applications based on merit regardless of whether entry into the clinic of a therapy would be achieved within the term of the award. Many participants favored the idea of a two-tiered RFA (or two RFAs), reviewed separately, that would fund two distinct types of team-based projects:

i) **Preclinical-to-Patients.** These teams would target therapies in the later phases of preclinical research, where a candidate therapy is proceeding on a path to regulatory filing. Projects would have clear, FDA-driven milestones or other natural go/no go decision points that could be used to evaluate progress or success. Projects would end in Phase I/II clinical trials, and could then feed into other CIRM initiatives or could be handed off to industry for further development. Projects would be actively managed.

The Preclinical-to-Patients tier would fund projects with a clear potential of introducing a therapy or diagnostic into the clinic within the term of the Disease Team Research Award, and would therefore help meet the first of CIRM's ten-year goals:

Goal I: CIRM grantees will have clinical proof-of-principle that transplanted cells derived from pluripotent cells can be used to restore function for at least one disease.  
*-From CIRM's ten-year goals*

ii) **Targeted Discovery.** These teams would target earlier phases of translational research, including research that could more broadly benefit the translation of stem cell based therapies and research that could populate the translation pipeline. Projects would have more flexible tasks in order to encourage the exploration of serendipitous observations that could lead to medical breakthroughs, but project leadership would still be accountable for achieving milestones and deliverables. Successful projects would have the opportunity to feed into the second (or potentially third) round of the Disease Team Research Awards, making this initiative more successful. They could also seek funding from CIRM's Translational Research or Preclinical Product Development Initiatives. Projects may or may not require active management.

### *c. Achievable Objectives, Milestones and Deliverables*

There was general agreement that a Disease Team project should have "a comprehensive plan for development leading from the laboratory to the clinic," and that this would involve developing project workflows with clear accountability. Participants commented that research at different phases of the translation pipeline requires different management strategies and evaluation criteria. Teams focusing on early preclinical or discovery research have more fluid tasks, and

require more flexible workflows that might need frequent re-charting. Teams focusing on later preclinical research can develop comprehensive milestones driven by FDA requirements and other natural decision points.

In support of this division, academic researchers expressed their discomfort with the concept of “milestone-driven research,” as they felt that it did not reflect the fluidity of the process and threatened to repress the ability to pursue serendipitous observations – an aspect considered central to the creative process. Task-driven research, with opportunities for course correction in response to research results, seemed more attractive. Researchers engaged in studies closer to a clinical application, on the other hand, commented that milestones made their research progress rapidly and predictably, helped integrate diverse and complex activities, and naturally fit with the FDA regulatory requirements. Reaching go/no-go decision points for a project was seen as important, regardless of their outcome.

There was some discussion about whether CIRM should be involved in establishing project milestones and evaluations, and whether it should have the power to terminate projects if milestones are not achieved. This was discussed more thoroughly in the *Project Management and Oversight* session. Important issues to consider were:

- a. Establishing a critical path and critical path tasks are essential for team work.
- b. Key time points and checkpoints should be included in a project plan.
- c. Consequences for not meeting established goals should be clarified. The consequences for terminating funding for academic and industry labs should also be considered.
- d. Consequences for superseding established goals should be clarified.
- e. Each project plan must contain a mix of flexibility and accountability.

#### *d. Project Endpoints*

The endpoint and hand-off potential of projects in the Disease Team Initiative were also discussed. Projects would ideally be developed with an end goal in mind: a candidate therapy to be used in the treatment of a specific disease or chronic injury. Hand-off to industry, which routinely occurs in small-molecule drug development, would be greatly facilitated if CIRM grants could include industry partners. Most large pharmaceutical companies are observing rather than participating in the nascent development of human stem cell based therapies, because the potential is not yet fully known. Since smaller biotechnology companies often do not have the resources to pick up projects in the preclinical development phase, they are more likely to seek partnering opportunities with academia and CIRM.

In order to increase the probability of hand-off of successful projects to industry for further development, it was proposed that CIRM support research through a combined Phase I (testing for safety) and Phase II (testing for efficacy) clinical

trial. Efficacy for human stem cell therapies may be difficult to assess because this is a new treatment modality; studies will likely be done in patients with life-threatening conditions, so the FDA is encouraging stem cell therapy trials to assess safety and at least a measure of biological efficacy in parallel. Interim Chief Scientific Officer Dr. Arlene Chiu commented that other CIRM funding mechanisms exist for Phase I and II clinical trials (for instance, the Clinical Investigation Initiative, see Figure 4, page 27), which would be another mechanism to fund clinical research for these types of projects. One representative from a funding agency cautioned against defining the project endpoint in terms of filing an IND, but rather as “entry into a trial”.

This discussion led to a loose consensus that Disease Team grants could include mechanisms that would allow teams to obtain funding through Phase I/II clinical trials, and that partnering with biotechnology companies will facilitate hand-off of successful projects.

#### *e. Planning Grants*

The usefulness of planning grants to help teams prepare for the Disease Team Initiative RFA was debated throughout the workshop. Initially, participants did not support the concept of planning grants, as they feared that they would enforce a long waiting period between the conceptualization of a Disease Team project and its implementation, thus diffusing the team effort and losing the enthusiasm and commitment of a PI. However, in discussing management and oversight issues relating to teams, it became clear that teams would benefit from a focused time to build their teams, and that some projects would benefit from support in identifying appropriate resources and recruiting appropriate collaborators. For example, participants were confident about investigators’ ability to identify and engage scientific collaborators, but recruiting and integrating a project management professional would be a new task for most teams.

In considering how to streamline the planning grant application and review process while allowing CIRM to support team building, Dr. Bettina Steffen presented a model utilized by one private foundation that included additional time, after grants are awarded, to build a management team. In this private foundation’s model, a project management position is identified and accounted for in the application budget, but is filled post-award by the team in conjunction with the foundation. This would encourage projects to be assessed in terms of project merit and core team strength during the application process, while allowing CIRM to provide management and structural input to strengthen each team. In addition, Disease Teams could be required to engage in a team-building process in partnership with CIRM once grants are awarded, which would include establishing Steering or Advisory Committees in charge of project oversight and milestone development.

**Regulatory Considerations: Question and Answer Session***Key Points of the Discussion*

- Regulatory requirements for stem cell based therapies are in place, but given the paucity of experience with these therapies the regulatory requirements may continue to evolve.
- Disease Teams focused on stem cell-related therapies would benefit from regulatory support and increased cell therapy-specific regulatory knowledge, particularly within Institutional Review Boards (IRBs).
- The FDA will require a demonstration of “substantial equivalence” for cells when derived from different sources for the same use. There is no consensus on the specific tests that will be used to establish “substantial equivalence” of stem cell-related candidate therapies, but they will likely reflect the tools available and the tests used to determine identity and potency.

This session was structured as an informal Question and Answer session, and participants were invited to ask questions of FDA representatives. No formal discussion questions were prepared in advance of the workshop. The panel focused mostly on practical issues such as the requirements of Good Manufacturing Practice (GMP), including traceability and shipping issues and establishing cell identity. It was suggested that plans for handling of stem cells should be in place when submitting an IND; guidance is provided in relevant FDA guidance documents, and early consultation with the FDA is strongly encouraged.

In establishing cell identity, the FDA’s Center for Biologics Evaluation and Research (CBER) is focusing on analytical measures that can be used to differentiate similar products and to establish that products are what they are claimed to be, rather than on labeling strategies. The Code of Federal Regulations (CFR) has tried to keep identification criteria broad (it can include profiling, use of cell surface molecules, assessment of biological activity, and donor-specific tests). This issue needs to be addressed in the IND.

It was noted that all reagents used in the production of a product submitted for an IND must be cited, and the manufacturers identified. Not all reagents need to be GMP quality, and not all instruments used for research purposes need to be approved by the FDA for clinical use. However, for reagents that are not clinical grade, the FDA will need sufficient information to judge the quality of such reagents. A certificate of analysis from the manufacturer and additional testing by the applicant will likely be required to qualify for acceptance. Similarly, antibodies to be used for the purification of a stem cell to be tested in people do not need to be produced under GMP, but again if they are not, the testing required to establish that they are clinical grade reagents means that in the end they will be “GMP-like” in quality. It was pointed out that a GMP antibody currently costs around \$1 million to produce.

Since the FDA prefers that the material used in a clinical trial be the same as the test material used in animal safety studies, some discussants cautioned that it might make sense to plan on following GMP guidelines to produce stem cells intended for therapy even at this early stage of testing. If a cell bank is not made from cells derived under GMP conditions, the FDA might not allow it to be used in clinical studies. It might not be practical to re-derive cells once the project is ready for clinical use given the time it takes to derive and test cell lines and the likely requirement for a repetition of animal safety studies.

In discussing stem cells as a source material, it became clear that protocols for establishing “substantial equivalence” of different cell lines will be essential when stem cells obtained from an original source are exhausted. For an evaluation of “substantial equivalence”, the FDA is interested in cell characterization and function, so developing assays to establish these parameters will be key.

The FDA clarified that it can evaluate proposals for clinical use of non-federally funded cell lines. However, the FDA itself cannot conduct any research on these cells.

### ***Project Management and Oversight***

#### *Key Points of the Discussion*

- A team leader, responsible for scientific vision and team motivation, is key to project success.
- A project manager (PM), distinct from the leader, is also essential for team success. The description of the PM roles, responsibilities and qualifications varied greatly among the participants.
- The effectiveness of this project management structure will be determined by the relationship of the PM to the leader, and of the leader and the PM to the rest of the team. Selection of the PM should therefore come from the team itself.
- The group favored having the Disease Team RFA list a project management plan (including the PM) as a requirement.
- Lead-time between submitting the grant and identifying the PM was desirable.
- Recruiting, developing, and retaining creative staff with excellent scientific and programmatic skills requires commitment on the part of the funding agency.
- Advisory and steering committees were identified as effective team management and oversight tools. Advisory teams might provide scientific direction and advice.
- External steering committees were suggested as one mechanism by which CIRM could evaluate and assess a Disease Team’s progress.
- Steering committee membership, degree of oversight, and operational involvement varies among funding organizations.

- Management and oversight mechanisms should be listed as requirements in any RFA.

In this section, discussants were asked to consider how Disease Team Research Awards might be managed and evaluated.

*a. Project Management*

There was overwhelming support for both a project manager and a team leader for each Disease Team. These two individuals would be responsible for maintaining team energy and keeping a team focused and moving forward.

- a. Team Leader: The leader provides vision and overall project direction. Participants stressed that an engaged, charismatic, and motivated leader was essential for team success. The leader would need to be a practicing scientist of good stature whose laboratory is involved in the project.
- b. Project Manager/Scientific Coordinator (PM): The project manager would oversee project operations and ensure that team activities progress smoothly. The tasks identified for the PM were varied, but included the following:
  - Administrative oversight: ensuring that all protocols and approvals are up-to-date (animal protocols, internal review board protocols, regulatory and compliance issues). For large projects, the PM may need an administrative assistant to coordinate these activities.
  - Logistic support: coordinating multidisciplinary team meetings and supporting communication between different members.
  - Project support: helping the team develop a timeline, and keeping the project on time. Managing the project budget developed in concert with the team and project leader.
  - Scientific coordination: collect and summarize data, maintain a project webpage, encourage collaborative problem solving between team members from different labs, identify areas of need. In coordination with each of the principal investigators (PI's) in the project, the PM could oversee all individuals engaged in work and provide support.
  - Project oversight: deliver progress reports to funding agencies and the scientific advisory board, assist in evaluating team progress, report project needs to leadership.

A PM would be the one person who would know all of the mechanistic details of a project. By analogy to the Nurse Administrator of a clinical trial, the PM should be a scientific coordinator. The PM should have enough technical knowledge to understand the preclinical process, enough scientific stature and authority to command respect from project PI's, and the ability to communicate across all aspects of the program. Ideally, the PM should be competent and non-threatening in order to encourage access from all team members.



The effectiveness of this management structure will be determined by the relationship of the PM to the leader, and of the leader and PM to the rest of the team. It was suggested that each team should have the authority to choose their own PM in order to optimize the working relationships and avoid the problem of PMs reporting to two bosses. However, PMs must have some formal authority in order to be effective and take corrective action if projects are off schedule or task, since academic scientists are accustomed to a high level of control over their projects and may resist even competent forms of active management.

PMs might be members of the research team or employees of the funding agency, but in either case they are key contact points for the funding organization. One foundation representative commented that "...the desire for a skilled program/project staff requires a real commitment on the part of the funding organization to recruit, develop, and retain creative staff with excellent scientific and programmatic skills." At one translational research organization, program managers are part of the organization's staff and report to the organization's management on a weekly basis. They therefore have funding authority and the ability to request additional resources for their projects. Although this model works for this example, it would be a difficult model for CIRM because of its FTE cap. Creative solutions, such as contracting of PMs, would need to be developed for CIRM to utilize this management model.

In an alternative model developed at one foundation, PMs who are members of the research team hold regular meetings to share regulatory knowledge and techniques, get training, and further develop their profession. Funding agencies can thus affect project management by encouraging such meetings and training opportunities.

One mechanism for ensuring that teams develop appropriate project management is to list a project management plan (that includes a PM) as a grant requirement in the Disease Team RFA, indicating that some form of management authority is to be built into each project. Most participants favored this approach.

#### *b. Project Oversight*

Several types of project oversight were discussed in the Disease Team Models on Day 1. Advisory committees, funding agency staff, project oversight teams, and project managers/coordinators offer several layers of checkpoints that can be used to evaluate a project's progress and to ensure that appropriate course corrections occur. It was recommended that CIRM ensure that each team develops internal and external oversight mechanisms that work for each project, possibly by helping teams set up their management and oversight systems once grants have been awarded (see "Planning Grants").

CIRM will also need to have effective procedures for evaluating and assessing a Disease Team's progress. An active steering committee would be an effective tool for evaluation and ongoing course correction, and CIRM representative(s) could sit on this committee. It was also proposed that program managers within CIRM

could oversee Disease Team projects, interacting with the project's PM and reporting project progress to CIRM's Disease Team advisory board or steering committee. Discussants informed CIRM that written reports are not the best method to stay abreast of true progress and issues with a particular grant.

Active oversight is resource-intensive. In addition to the management costs for each project (PMs and administrative support), projects must contain budgets to pay a steering committee or advisory board. The NIH project discussed above has a Steering Committee that holds monthly calls and meets twice a year. Committee members are paid \$100/hour as consultants. As another example, the Executive Committee of a translational research organization holds weekly conference calls, and some members are paid a 20% salary (10 hours/week) to compensate them for their time-intensive oversight responsibilities. Many discussants recommended that CIRM consider sharing the cost of oversight with the applicant organization, or partnering with other funding organizations.

In terms of consequences of evaluation, a clear plan with defined tasks or milestones was considered essential for active management. Positive outcomes and rapid progress could be rewarded with additional resources to continue to a new phase of development toward the clinic, if a project team exceeded defined goals. Both course corrections and project termination were discussed as potential consequences of a project not meeting agreed-to milestones, or when the data indicate that the proposed direction is not viable.

### ***Funding Considerations***

#### *Key Points of the Discussion*

- Various funding mechanisms were discussed, each with varying levels of funding agency control and staffing levels needed to administer the programs.
- Contingency funding must be retained by CIRM to address: 1) successful projects that have high priority; 2) clinical project cost carry-over.
- CIRM should have a plan for funding projects that involve collaborations, including out-of-state collaborations. Suggestions from the NIH and other funding agencies were “not to mix money”, and it was also discussed that Proposition 71 may not permit the funding of some out-of-state aspects of the project.
- Matching funds were presented by several participants as a way to “de-risk” projects. Participation via matching funds can be taken as a sign of commitment from the funded university or company.

In this session, moderators presented several different funding mechanisms and asked discussants to consider the possible impact of each on the project lifecycle. In considering the advantages and disadvantages of different funding mechanisms, participants pointed out that funding mechanisms in part may determine the level of control that the funding agency has over a research project.

Different funding mechanisms also require different levels of agency staff involvement. The features of funding models discussed are listed below:

- Traditional grant. Funding agency reviews progress, but traditionally does not interfere with the project once a grant is awarded. Low agency staff requirement.
- Cooperative agreement. Some involvement of granting agency in assessing achievement of milestones. Agency is engaged in project, and is often represented on the advisory committee. Medium staff requirement.
- Contract. Funding agency is buying a product or service; therefore, control of the project and intellectual property rests with the agency, who dictates the work and schedule. High staff requirement.
- Loans. Like a grant, funding agency is minimally involved in the project, and does not share intellectual property. Payback is generally required once a product becomes commercially successful. Low staff requirement.

Proposition 71 established a cap of 50 employees for CIRM's staff. This limits CIRM's options for active management to those with lower staff requirements.

Disease Team Research Awards are meant to move projects down the translation pipeline. However, projects might not be ready for hand-off to industry for further clinical development at the end of their funding term. CIRM staff asked discussants to present funding options that ensure continued financial support of successful projects. Options raised included funneling projects into other competitive initiatives, setting aside a contingency fund that CIRM could access in order to help bridge a successful project into the next stage, and leveraging CIRM funding by establishing matching grants and cost-sharing partnerships with industry and other granting agencies.

Cost-sharing mechanisms have been used in the University of California Discovery Grants, and are effective means of increasing the possibility that industry partners will support the commercialization of successful projects. Partnering with foundations is an additional way of ensuring continuation of successful projects, but might impose constraints. Grants would need to be co-reviewed prior to funding, and determined to be in compliance with each agency's policies. Partnering with foundations may make sense for more costly, later-stage clinical projects; since appropriate patient study populations may be limited, collaborative efforts would not need to "compete" for patients. Furthermore, funding partners that can support out-of-state work might help CIRM-funded researchers gain access to out-of-state collaborations and resources. Each potential partnership would need to be evaluated on an individual basis.

### ***Organization of Disease Teams***

#### *Key Points of the Discussion*

- A diverse set of skills is needed to develop stem cell therapies. Personnel with these skills may not all be available within one organization at any one time.

- Individuals with regulatory affairs or clinical expertise should become involved early in the development process.
- CIRM could assist in building successful disease teams by providing access to the appropriate expertise or laboratory core services.

In this session, discussants considered the diverse skills required for an effective Disease Team project, and where to find people with those skills. Everyone recognized the need for team flexibility and the concept of a dynamic team (that team members will change as projects progress), and most agreed that the multidisciplinary members of the team necessary to implement the plan should become involved early in a project's development. The model that emerged from these discussions was a core team of researchers (physicians or Ph.D.s) conceiving of a disease-targeted project, consulting from the onset with a wide net of advisors and core facilities that could be brought in as the project evolved. As the project becomes less discovery-research-driven and more targeted to the clinic, the basic scientists might decrease their involvement and advisors might become more active members. Group composition will change naturally over the course of a project, and the profile of each group will be unique and should not be regulated by CIRM.

In order to understand the diversity of input required at the onset, it is sometimes useful to move backwards through a clinically-oriented project, beginning with the endpoint of (for example) initiating a Phase I clinical trial. With a careful plan each of the stages of a project can be roughly accounted for and budgeted. When viewed from this vantage point, team members with the following expertise might be required for a stem cell project:

- stem cell biology
- animal models
- immunology
- specialization in treatment of a particular disease
- transplantation
- project management
- pharmacology
- toxicology
- process development
- quality control and assurance
- biostatistics
- regulation of biomedical products
- conduct of clinical trials

Many of these specialists will be used only sporadically on any particular project, but their advice is useful for planning purposes even in the early stages of a project.

In considering the role of CIRM in supporting Disease Teams, participants considered ways of providing infrastructure and networking support to help investigators or teams identify and recruit appropriate consultants or facilities. Recommendations included helping Disease Teams identify core services and facilities with expertise in stem cell research that could be available to all grantees. CIRM staff cautioned that this would have to be done without the perception of endorsements. Alternatively, for high demand services with a limited supply of expertise, such as regulatory expertise for cellular therapy products, it was suggested that CIRM could provide a contracting service such as the National Cancer Institute's Rapid Access to Interventional Development (NCI-RAID). It is difficult for any team to recruit all of the skills and services required for a long-term preclinical project, and providing this sort of customizable support could compensate for team weaknesses and make each team more effective.

### ***Operational Issues***

#### *Key Points of the Discussion*

- The metrics for success are important motivators for individuals and teams, yet the reward systems for individuals and teams are very different. Teams of individuals can be successful if members identify strongly with their teams, and if the leader functions as “a leader among equals”.
- Opportunities to demonstrate leadership and success should be identified in advance of the project, and assignments of “ownership” should be made in the planning phase of the project. This will help motivate team members, particularly young faculty at Academic Medical Centers (AMCs).
- Well-defined rules governing data sharing and publication guidelines facilitate interactions between academic and corporate partners.
- In collaborative situations, academia and industry need to recognize that each may have different incentives to publish quickly (academia) vs. retain data until patent applications are filed and milestones are achieved (industry). These issues should be discussed up front.

Moderators introduced this session by asking the group to consider how team projects can be most successful in environments where individual performance is traditionally emphasized. The discussion that followed identified motivating factors required for successful team science. Participants highlighted the types of rewards available to individuals within a team (publications, intellectual property, compensation, support for other areas of a team member's research), intangibles relating to the group (a powerful mission, an energetic team, a feeling of success), and institutional issues (promotion issues, institutional recognition). It was

determined that successful teams are composed of a self-selected group of scientists who create their own internal reward structure.

Some of these reward structures, such as institutional guidelines for promotion, cannot be influenced directly by CIRM. However, rewarding successful models of team-based research may encourage institutions to develop innovative strategies to support these teams. For instance, in one academic-industry collaboration, a separate promotion and pay structure was developed for lab technicians, post-doctoral fellows and scientists working on translational projects, to be more aligned with industry. This incentive structure successfully motivates the team to produce the project-oriented goals, rather than individual research goals.

Team incentive and reward structures can be negotiated and specified by each team before the start of the project, and the Disease Team Research Award RFA could include language to encourage teams to develop their own rewards. Guidelines can be developed for issues such as publication, distribution of intellectual property (IP), and compensation. Different models for negotiating publications and managing intellectual property were discussed as examples: 1) For some large consortiums, all authors in the consortium are listed as authors on publications, often in alphabetical order to increase group identity. If group identity is strong, all members feel equal recognition. 2) Unfortunately, large team publications will hurt junior faculty, who often rely on publications for promotion. For certain projects, it may be possible to assign defined areas of research to particular investigators, allowing them to “own” that aspect of the project. 3) Data should be accessible to all team members, yet Memoranda of Understanding (MOU) or other contracts between academic and industry partners should be put in place to govern data sharing and publication, at the project outset. 4) Organizations differ in their attitudes about intellectual property. Some may wish to establish consortia or non-profit organizations to own any resulting IP, but this is likely to vary.

A final discussion point regarding the mechanics of collaborations involved the management of finances between institutions. It was recommended that CIRM look carefully at how overhead is collected in cross-institutional collaborations. Often the managing institution disburses money and collects overhead for the project, but collaborating institutions also collect overhead. Since the Disease Team Research Awards are large, overhead will constitute a large sum of money. Some funding organizations set caps as to how much overhead can be charged for a project.

### ***Resources and Budgetary Considerations***

#### ***Key Points of the Discussion***

- Disease Teams will require human stem-cell specific resources, such as core facility development and regulatory support, and team-specific resources, such as communication and data sharing technologies.

- CIRM could support Disease Teams by increasing access to regulatory expertise.
- Research grants of \$20 million would adequately support the progression of therapies and diagnostics to the clinic.
- CIRM could fund a small number of well-developed projects per round, or a larger number of more diverse projects that would be evaluated regularly and could be terminated if projects fail to reach their identified milestones.

The goals of the final session were to identify resources not already discussed that may be needed for Disease Teams to operate effectively, and to assess budgetary needs specific to teams engaged in human stem cell research.

The list of potential resources presented for discussion included:

- Communication technologies
- Data sharing support
- Documentation and communication assistance: for instance, a template material transfer agreement (MTA) or a memorandum of understanding (MOU) on data sharing might be useful.
- Capturing, documenting and protecting intellectual property
- Core services
- IRB facilitation
- Data and safety monitoring
- Biostatistics
- Regulatory assistance
- Legal assistance: for instance, insuring that all agreements are set up appropriately.

Data sharing support was considered particularly important, given CIRM's policy requirements. Since requests for materials could be very costly for a laboratory or a company, especially if amounts requested are high, CIRM should consider mechanisms to facilitate the production and distribution of tools and reagents. Data sharing resources that would help the entire field of stem cell research included developing reference standards for human stem cells, in collaboration with the FDA, and establishing human stem cell banking agencies similar to the American Type Culture Collection (ATCC).

Regarding intellectual property (IP), many participants indicated the need for establishing a clear IP pathway for CIRM-funded projects.

Assistance in navigating Institutional Review Boards (IRBs) was identified as an important potential resource for Disease Team grants moving towards clinical trials. Each institution has unique policies and IRBs vary in their knowledge

regarding FDA guidelines, particularly in regard to stem cells. The discussants indicated that senior team leaders would understand how to work within their system or could work with the Western Institutional Review Board (WIRB), but CIRM might consider resources to increase regulatory knowledge – “a huge task because the rules are so complicated.” One favored suggestion was that CIRM approach the Office for Human Research Protections (OHRP) in order to provide workshops to help California IRBs develop more standard guidelines for trials involving human stem cell therapies. Education is one of the central missions of the OHRP:

OHRP provides clarification and guidance to research institutions, develops educational programs and materials, and promotes innovative approaches to enhancing human subject protections. - *OHRP website.*

Other agencies that could provide guidelines on regulations regarding stem cells are the Drug Information Agency ([www.diahome.org](http://www.diahome.org)) and the International Society for Cellular Therapy ([www.celltherapysociety.org](http://www.celltherapysociety.org)).

To assist CIRM determine what the budget for a Disease Team Research Award might include, the overall costs of preclinical development and clinical safety studies were estimated. Although each Disease Team project would involve different components, a budget of up to \$20 million for Disease Team Research Awards seemed to be appropriate for Disease Team projects, given the costs of specific elements of the process (e.g. safety studies in two species, efficacy studies, GMP and regulatory requirements). Since \$120 million was budgeted for this Initiative, around 6-8 projects could be fully funded in two or three Disease Team Research Award rounds. Two funding models were discussed. In one, 3-4 awards would be granted per round. Lessons learned in the first round could be used to inform the second round. In another, around twenty awards would be granted in the first round of funding and continued funding would be contingent on achieving specific milestones. Since most of these will not reach their early benchmarks, and since the larger costs are incurred only as projects reach the clinic, most of the funds would be available for a second round of funding. The advantage of the second model is that it increases the chances of getting a successful therapy, and it allows for multiple diseases to be addressed.



## WRAP-UP

The goal of the Disease Team Research Awards is to develop new methods of integrating basic, translational and clinical research involving stem cells in order to develop therapies for specific diseases. Dr. Patricia Olson from CIRM summarized the recommendations of the first Disease Team Workshop, stating that it was a “challenging task because we’ve had lengthy and good discussions” on several topics related to the initiative.

- The Disease Team Research Awards should focus on therapies, as mandated in Proposition 71, but should not be limited to specific strategies or diseases.
- Funding should favor preclinical research “within shouting range” of a development candidate, or at most 4-5 years from clinical testing, assuming complexities associated with a stem cell derived cell therapy. Many people were interested in funding earlier stages of translation in order to develop candidates for subsequent Disease Team Research Award rounds.
- There was support for release of two types of RFAs, one that would allow funding of the earlier stage of translational research as well as one for later preclinical research. Conversely, additional programs in the Scientific Strategic Plan were mentioned as appropriate funding mechanisms for more focused basic, translational, and clinical projects.
- Academic researchers do not like the term “milestones”, but all agreed that there must be checkpoints along the way for early-stage research. At later stages of a therapy development project, defined milestones including those to meet FDA requirements will be more important.
- There is a role for a project manager during preclinical research, but more so once a candidate therapeutic has been identified. This person could be identified by the research team or by CIRM.
- Advisory committee(s) will be important. An advisory committee could provide expert advice to a team in the specific areas required for complex multidisciplinary projects. An expert committee is needed to advise on team progress, to provide executive oversight, and to make decisions at critical points in the projects. The advisory committee should consist of external (mainly third party) members that are willing to commit their time.
- In tracking progress, do not ask for too much paperwork too often. CIRM does need to track progress, but this could be done formally by teleconference or biannual or annual professional review; informally, progress evaluation could be done verbally through communication with the project manager or the project leader. Finally, an agency representative could sit on the advisory or steering committee, which would meet periodically to assess progress.
- Evaluations must be data-driven. Consequences of an evaluation could include course correction or project termination if a project is not working, or people

can be asked to leave a team if they are not contributing to progress or their contribution is negative.

- The workshop participants recognized that there were different mechanisms for Disease Team funding and did not indicate a preference for any one mechanism. Different kinds of funding might impact who owns IP. Also, CIRM must recognize that if a Disease Team has been successful at moving forward a candidate therapy (or diagnostic), there has to be a way to fund the next step in its progression to the clinic. A non-competitive mechanism for renewing funding might make sense.
- A large diversity of skills and expertise will be required for these projects. Earlier stage discovery teams could consist of mostly basic scientists, consulting with specific experts early on in the process (regulatory experts, clinical trial experts, medical practitioners). Such experts can provide advice that could minimize later hurdles. At later stages in the project, basic scientists might want to naturally decrease their involvement. We should expect that teams will be dynamic.
- The role of a team leader is crucial. Ideally he/she should function as “a leader among equals.” The panel talked about the best characteristics of team leaders, and how leadership comes down to: motivating people, ensuring that each team member has work that he/she can own, and recognizing individual contributions to team goals.
- Operational issues such as intellectual property and publication guidelines will be different in different team settings. Teams should set rules for ownership of intellectual property up front.
- Publishable findings and data should be reported. Publication protocols (authorship, timing, etc.) and collaboration rules should be clarified at the onset, and all team members should have access to all data. CIRM should consider providing funding to facilitate team communication.
- Therapy discovery and development is a complex endeavor. There was discussion regarding other ways in which CIRM could facilitate this endeavor. Suggestions included establishing cores, developing a “toolbox” of resources, and providing assistance with outsourcing and training for groups with good ideas but little experience at moving their ideas forward. Discussants proposed other ways that CIRM could promote stem cell based therapies, including providing training in therapy development and developing a list of existing resources and funding use of these resources.

Dr. Arlene Chiu ended the meeting by providing a possible funding model for Disease Team Research Awards, based in part on input from the workshop: each funding cycle would start with a large number of projects that would be winnowed down as some projects are dropped. Successful Disease Team projects can feed into other CIRM initiatives, which would continue funding the clinical research

phase. This could be a winning strategy for developing new therapies and diagnostics based on human stem cell research.

## REPORT TO THE GRANTS WORKING GROUP

A synopsis of the Workshop findings was presented to the Grants Working Group on September 19, 2007, in a session which included interested members of the public. The presentation focused on key findings from the workshop, and invited members of the Grants Working Group and the public to comment. Materials presented are available in Appendix B.

### Summary of Discussion

#### ***Facilitating Institutional Review Board and Institutional Animal Care and Use Committee Approvals***

- Institutional Review Boards (IRBs) are not yet set up to deal with human ES cell-based therapy trials. Education may be important in helping IRBs overcome uncertainties in approving hESC protocols and use in patients.
- CIRM could help applicants by providing education to IRBs at the local level. Issues to overcome are: “nothing except autologous cells in a do-no-harm situation” mentality, fear of being in violation of federal regulations, and lack of knowledge of particular cell types, and the potential of therapies.
- CIRM could gather a few expert opinions in how to best support the education of local IRBs. Appropriate timing might be two years before the first Disease Team project is expected to be ready for clinical trials.
- CIRM should also consider working with Compliance Offices in medical schools, as they share responsibilities with the IRBs.
- Institutional Animal Care and Use Committees (IACUC) may have similar challenges in not yet being ready to evaluate the *in vivo* experiments required for this type of research.
- Examples were cited from within the UC system that provide for shared protocols and forms, to help facilitate the process and to avoid “reinventing the wheel” for IRB, IACUC, and other required approval processes.
- A team approach may help address one of the major challenges in going from bench→animal→human study subjects. By bringing together the preclinical and clinical trial researchers, animal studies may become more representative of the clinical conditions in patients, in which they will eventually be tested. For example, many animal study protocols use veterinary anesthetic medications which are not approved for use in humans, and therefore do not reflect a viable treatment protocol in humans. CIRM has the opportunity to emphasize the need for appropriate preclinical animal models in this RFA.

### ***Supporting Regulatory Procedures***

- One model for regulatory support was described at a major university. A “Clinical Trials Office” supports development and submission of INDs. An 8 FTE office supports basic scientists that have not previously worked with clinical trials. Expertise in the office includes: regulatory, medical writing, research nurses and coordinators, and biostatisticians.
- The Immune Tolerance Network was also cited as providing regulatory support with an in-house office. The office supports any trial which is funded through the ITN.
- CIRM could issue a contract for a core regulatory team, or even multiple teams, to provide a centralized group for regulatory expertise and support. One example of this model is the clinical trial support core in Cincinnati, competed for and awarded through the NIH’s rare lung disease consortium.

### ***Team Leadership and Composition***

- The technology for cell-based therapy is so complicated that one observer suggested that dual leadership by a disease-specific scientist and a “technology expert” at the basic research level would be appropriate.
- CIRM should also consider adding a modeling/simulation expert who specializes in systems biology mathematics.

### ***Evaluating Proposals***

- Feasibility and “scientific maturity” should be weighed considerably in comparing these proposals. This may increase the probability of seeing stem cell based therapies entering the clinic.
- Judging the quality of identification of the bottlenecks in a particular area of research and plans to overcome the bottlenecks could be evaluated as a component of feasibility.
- The integration of the team should carefully be assessed and high ratings given to teams that demonstrate a unified goal, versus those applications that appear to be a collection of individual projects and people “thrown together” simply to respond to the RFA.
- Subject experts may be required for review of specific diseases in which the GWG does not have internal expertise.

***Additional Requirements***

- CIRM might need to consider site visits as part of the on-going evaluation of these grants.

***Length of Funding***

- To accomplish the suggested scope from initial evidence of disease modifying activity through IND and enrollment in Phase I trials, 7 years would be necessary. CIRM could consider a 5 year grant period, with an administrative review at the end of that period prior to release of additional funding.
- CIRM should keep the program flexible enough to fund projects that come in at different times during the development continuum.
- Discontinuity at the NIH in review of the discovery, preclinical, and clinical programs within a single project can really slow down the translation of basic discoveries to the clinic. CIRM could overcome this roadblock by having stable, continuous funding.

**APPENDIX A:****Disease Team Workshop Session Questions****Session I: Scientific Scope and Stages of Disease Teams**

- *To illustrate the scope and stage of possible Disease Team scientific projects*
- *To explore how Disease Teams can be effective in the continuum of discovery → development → clinical research projects*

## Discussion Questions - Scientific Scope of Disease Teams

- *How are goals and focus for a disease team determined?*
  - Therapy, vaccine, diagnostic?
  - Possible uses of stem cells
    - Includes: modify the immune system, delivery vehicle, mobilize endogenous cells, transplantation and integration, disease model/small molecule screen/tox
- *What types of projects warrant a Disease Team approach and funding?*
  - How are the critical needs defined for Disease Team projects?
  - What are the bottlenecks and key gaps in the discovery → development → clinical research process? (specific to stage, disease, approach, etc.)

## Discussion Questions - Stages of Effective Disease Team Projects

- *At what point in the discovery → development → clinical research process are disease teams effective? (in contrast to individual PI projects)*
  - To what extent should a Disease Teams address 'translational' activities including but not limited to source of cell/manufacturing process/preclinical study?
  - Should a pre-clinical component be required? (Define pre-clinical)
- *What would define achievable objectives, milestones, and deliverables for Disease Teams?*
  - Stage-specific objectives and deliverables?
  - Goal-specific deliverables?
  - Schedule feasibility?
- *How could Disease Teams enable clinical trials?*
  - Cell Therapy Development
  - Therapy Development

**Session II: Regulatory Q&A**

### **Session III: Project Management and Oversight**

- *To explore Project Management models for Disease Teams, and issues relevant to “active management”*

#### Discussion Questions – Project Management and Oversight

- *How can a project plan be developed to achieve the Disease Team objectives:*
  - How to coordinate inter-disciplinary members?
  - How to coordinate inter-institutional members?
  - Is a project manager needed?
- *What are the roles and responsibilities of the internal project manager?*
- *Is there a role for an advisory committee and/or a steering committee?*
  - What authority does the committee have (steering committee)?
  - What is the composition of the committee?
  - What is CIRM’s role?
  - Is there a role for independent 3<sup>rd</sup> parties?
  - What are the roles and responsibilities of the advisory team with respect to the research progress?
- *How can research progress be tracked against the plan?*
  - What are possible models for progress reporting and evaluation?
  - Pros and cons of various models for progress reporting and evaluation?
- *What are the possible consequences of the evaluation?*
  - Changes in planned funding?
  - Changes in scope or focus?

### **Session IV: Funding Considerations**

- *To explore funding models for Disease Teams and possible impact on the project lifecycle*

#### Discussion Questions – Funding Considerations

- *What are advantages and disadvantages of different funding mechanisms?*
  - Possible funding mechanisms include:
    - Grant
    - Cooperative Agreement
    - Contract (Firm Fixed Price, Time & Materials)
    - Loans
    - Others



- *How might funds be made available for continuation of successful Disease Team projects?*
  - Non-competitive mechanisms?
  - Competitive mechanisms?
  - Other?
- *What are the advantages of offering a Planning Grant for Disease Teams?*

### **Session V: Organization of Disease Teams**

- *To identify what key skills and expertise should be represented on the Disease Team (and timing of each)*

#### Discussion Questions – Organization of Disease Teams

- *What critical skills and expertise are needed to address a defined research problem for a disease?*
  - What are the qualifications and characteristics of individual team members?
- *How might the roles and responsibilities of team members be defined?*
  - Are team composition and leadership dynamic?
  - How might Disease Teams differ in composition depending on the research objective?
  - How might team members and roles change over time as the research progresses closer to the clinical stages?
- *What team member roles are needed, should be required, or are recommended?*

### **Session VI: Operational Issues**

- *To discuss conditions that promote effectiveness of Disease Teams, including practical, philosophical, legal and other issues that support inter-disciplinary and inter-institutional efforts*

#### Discussion Questions – Operational Issues

- *How can team projects be most successful in environments where individual performance is traditionally emphasized?*
  - How is team behavior rewarded?
- *What are the strengths and weaknesses of various decision-making models for Disease Team-based research?*

- *When (and how) should teams report findings?*
  - What is the publication process?
- *Do all team members have access to the data?*
- *What types of collaborations and consortia are likely to be formed for Disease Teams?*
  - What are operational concerns about collaborations and consortia?
- *What are the intellectual property (IP) concerns?*
  - How is IP captured and protected?
  - Who “owns” the IP?

### **Session VII: Resources and Budgetary Considerations**

- *To identify additional resources needed for Disease Teams to operate effectively*
- *To assess budgetary needs of Disease Teams*

#### Discussion Questions – Resources for Disease Teams

- *What additional resources are necessary for Disease Teams to operate effectively?*
  - Communication technologies?
  - Support sharing of data?
  - Documentation and communication assistance?
  - Capturing, documenting and protecting intellectual property?
  - Core services?
  - IRB facilitation?
  - Data and safety monitoring?
  - Biostatistics?
  - Regulatory assistance?

#### Discussion Questions – Budgetary Considerations

- *What elements might the budget for a Disease Team grant include?*
- *What level of funding is needed to conduct various Disease Team projects as envisioned by this group?*

### **Final Thoughts**

- *What are possible review criteria by which different Disease Team proposals can be compared?*

- How can CIRM establish review criteria for proposals that may be very different in scope, duration and stage of research
- *What are the advantages of offering a Planning Grant for Disease Teams?*

**APPENDIX B:****Presentation to the Grants Working Group on September 19, 2007****4. Report from: Disease Team  
Workshop****Agenda**

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- Overview of the Disease Team Initiative
  - Presentation of Workshop Findings
  - Discussion



## Disease Teams - Intent

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The intent of the Disease Team Initiative is:

“...to explore a new method of integrating and organizing the highest quality basic, translational and clinical research with the specific aim of producing a therapy for a particular disease or group of diseases whose research is poised for the development of therapies.”

– CIRM Scientific Strategic Plan



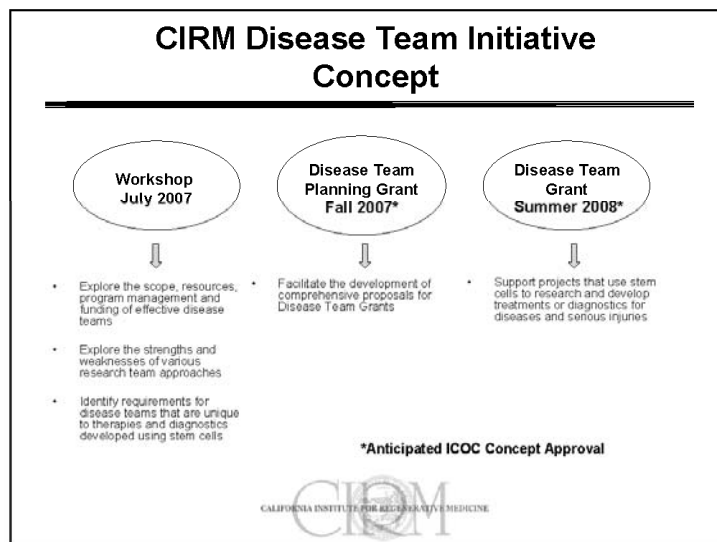
## Disease Teams - Rationale

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- Development of therapies and diagnostics can proceed faster and more effectively if:
  - The multidisciplinary members of the team participate in all phases
  - There is a comprehensive plan for development
  - There is active team management

- CIRM Scientific Strategic Plan





- ### Disease Team Workshop July 25-26, 2007
- 
- **Participants included:**
    - **Scientists from academia and industry**
    - **Patient advocates**
    - **Representatives from Federal funding and regulatory agencies**
    - **Private foundations (which fund disease-targeted research)**
    - **CIRM staff**
-   
CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

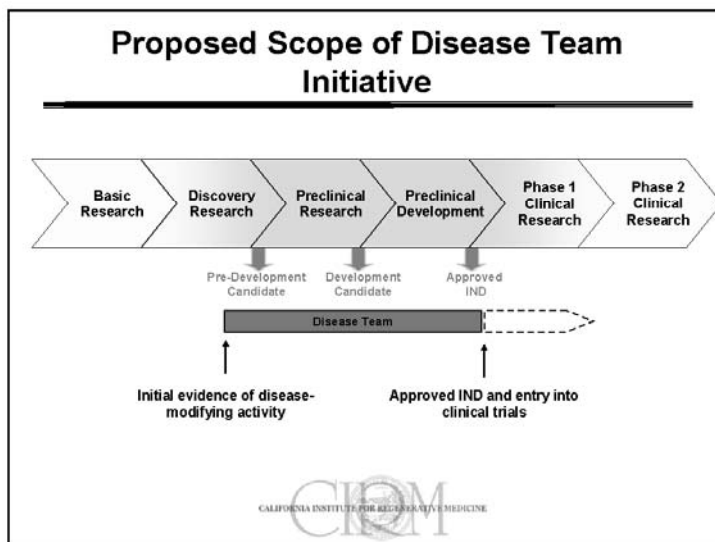
### Workshop Participants

<p>Jeffrey Bluestone, PhD <i>University of California, San Francisco</i></p> <p>Fred Gage, PhD <i>Salk Institute for Biological Studies</i></p> <p>Jan Nolte, PhD <i>University of California, Davis</i></p> <p>Edwin Rubel, PhD <i>University of Washington</i></p> <p>John Sladek, PhD <i>University of Colorado</i></p> <p>Deepak Srivastava, MD <i>Gladstone Institute</i></p>	<p>Melissa Carpenter, PhD <i>Novocell, Inc.</i></p> <p>Jane S. Lebkowski, PhD <i>Geron Corporation</i></p> <p>Mahendra Rao, MD, PhD <i>Invitrogen Corporation</i></p> <p>Alan K. Smith, PhD <i>Cognate BioServices, Inc.</i></p> <p>Ann Tsukamoto, PhD <i>StemCells, Inc.</i></p>
<p>Joan Samuelson, JD <i>Independent Citizens Oversight Committee</i></p> <p>Jeff Sheehy <i>Independent Citizens Oversight Committee</i></p>	<p>Donald Fink, PhD (via telephone) <i>Food and Drug Administration</i></p> <p>Mercedes Serbian, MS (via telephone) <i>Food and Drug Administration</i></p>
<p>Jamshid Arjomand, PhD <i>High Q Foundation</i></p> <p>Brian Fiske, PhD <i>Michael J. Fox Foundation</i></p> <p>Adrienne Wong, PhD <i>Juvenile Diabetes Research Foundation</i></p>	<p>Jill Heemsker, PhD <i>NIH / NINDS</i></p>

### Discussion Sessions Presented at the Workshop

- Scope of Disease Teams
- Organization of Disease Teams
  - Team Composition
  - Leadership
- Active Management and Oversight
- Resources for Disease Teams
- Operational Challenges





- ### Team Composition
- **A diverse set of skills is needed to develop stem cell-based therapies**
    - Personnel may not all be available within a single organization at any one time
  - **An engaged and energetic leader is essential for team recruitment, motivation, and success**
  - **A project manager is highly desirable to help coordinate large teams of multidisciplinary investigators**
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## Team Expertise

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- Stem cell biologist
- Animal model expert
- Immunologist
- Disease specialist
- Transplant experience
- Project management
- Pharmacologist
- Toxicologist
- Process development
- Quality control and assurance
- Biostatistician
- Regulatory specialist
- Clinical trial expertise



## Team Leadership

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- Success of translational projects is dependent on commitment of the team leader(s)
- Stable funding is critical to attract the top scientific leaders to team projects
- The team leader
  - Is a practicing scientist whose lab is involved in the project
  - Orchestrates the development of the scientific research plan
  - Ideally functions as “a leader among equals”



## Active Management and Oversight

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- **Executive committees**
  - Advisory committees
  - Oversight committees
- **Project leadership communication with funding agency**
- **Periodic evaluations against a project plan and milestones**
  - Potential to move successful projects to the clinic
  - Re-orienting of projects if feasible
  - Failure to meet critical milestones could result in project termination



## Resources

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- **Team-specific resources might include**
  - Communication technologies
  - Data sharing technologies
- **Stem-cell specific resources might include**
  - Core services
  - Regulatory expertise
- **Regulatory requirements drive many preclinical development project needs**



## **Operational Challenges**

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- **Metrics for success and reward systems are different for team projects (compared to individual scientist projects)**
- **Guidelines governing data sharing and publication should be defined up front**
- **Teams need to establish well-defined rules regarding intellectual property ownership up front**



## **Discussion**



### Questions for Discussion

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- How would one assess a Disease Team proposal?
- How would one compare different Disease Team proposals?
- What expertise do we need to evaluate team-based proposals?