CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE
"INDUSTRY & STEM CELLS IN CALIFORNIA: FOSTERING R&D"
TUESDAY, JULY 25, 2006
1:00 PM TO 6:00 PM
ROBERTSON AUDITORIUM, MISSION BAY CONFERENCE CENTER AT UCSF

On July 25, 2006, the California Institute for Regenerative Medicine (CIRM) held a conference with representatives from the private sector to discuss how CIRM might help foster R&D within industry in California. This meeting was structured around a series of presentations by these representatives, followed by a question and answer period, then a roundtable discussion, and a final question and answer session with the public. This summary is not intended to be comprehensive with respect to reporting on this conference, but presents the discussion to the best of our understanding. This summary reflects the comments and opinions of the speakers; inclusion in this summary does not imply agreement, endorsement, or verification by CIRM.

Zach Hall, PhD; President, California Institute for Regenerative Medicine
Welcome and Introduction

- This is one in a series of meetings that we are holding as part of the scientific strategic planning exercise. As all of you know, we are entrusted with a major scientific task, which is to invest $3 B over 10 years in stem cell research for the benefit of patients and those suffering from chronic disease and injury. This is on the frontier of biomedical science. It is a wonderful and daunting challenge that we have to try to put together a plan for how we are going to go about awarding this money in such a way as to return the highest possible scientific benefit and also be true to our charge as an agency of the state of California.

- We have had two similar meetings in the past: one on funding structures and one on scientific strategies. We are devoting parts of ICOC meetings to the scientific strategic plan and are engaging in focus group meetings and are conducting extensive interviews. The meeting today focuses on fostering R&D in the stem cell industry in California.

- The four meetings involving the ICOC that will contribute to the development of the plan are:
  - Slide 1 - ICOC Meetings
    - June 1/2, 2006: Mission Statement and Long-term Objectives
    - August 1/2, 2006: Values
  - Slide 2 - CIRM Scientific Meetings for ICOC Members and the Public
    - May 25, 2006: Funding Structures
    - July 13, 2006: Scientific Strategies

- It is essential to the success of our mission to partner with the private sector. Ed Penhoet has been an early and eloquent advocate for the position that if we are to take scientific progress out of the laboratory for the benefit of the patients in the clinic, it is absolutely necessary for us to do this in partnership with the private sector.
  - There is a second aspect of the work in the private sector that should not go unnoticed. In addition to late stage work, much of the early stage work in the field is funded by and has been performed in, and in some cases been sponsored by, the private sector.
  - We see engaging the private sector as an important part of our overall plan. It is a particularly challenging mission to make that engagement in the best possible way. We have many good examples of how granting agencies should interact with non-profit universities and research institutions but its seems to me that there are some opportunities and also some challenges as to how we best structure our relationship with the private sector to push forward our mission in stem cell research.

- We have an extraordinary qualified and distinguished group of speakers this afternoon.
  - The format of the meeting is that we will ask each speaker to speak for 10 minutes. Then we will have a Q&A session on all the talks. Ed Penhoet will then lead a panel discussion on some of the issues that have been raised.

Sumit K. Chanda, Ph.D., Group Leader, Division of Cellular Genomics, Genomics Institute of the Novartis Research Foundation (GNF)

- Slide 1 - Title Slide
  - We are a research foundation located on the Torrey Pines mesa in San Diego, next to the Burnham Institute. Our range of activities at GNF starts from basic research and goes all the way to drug discovery. Today, I will talk to you about our efforts in cell-based screening and try to plant some seeds in your head on how some of this technology can be applied to stem cell research.

- Slide 2 - Target Identification & Validation
  - I want to start off with a large scale overview of how we go about target identification in the drug discovery process. Target identification and target validation is either done *de novo* by starting projects from scratch or mining the literature for interesting targets.
    - When we start *de novo*, what we do is we exploit the different genomics tools available to us, starting from bioinformatics on sequences, continuing to RNA dynamics and expression, then to cell-based screening, and finally to *in vivo* validation in mice and whatever other *in vivo* models are most applicable.
    - As you go from left to right [from bioinformatics to *in vivo* models], your throughput goes down, your cost goes up, and your validation goes up.
  - The work we have done has been around siRNA [small interfering RNA] and cDNA [complimentary DNA] screening and small molecule screening in cells to facilitate the opening of this bottleneck and transitioning from RNA dynamics to cell-based screening and to get into *in vivo* models more quickly.
  - Target identification and target validation is really the first step in the drug discovery campaign. The technology we developed mainly facilitates these 2 steps, although we have developed technology at GNF which aids in target screening and medicinal chemistry. Of course, the most expensive parts of the effort are the preclinical studies and clinical trials.

- Slide 3
  - Our genetics screening platform is established to continue studies people have been doing in model organisms such as yeast and d*rosophila*. These types of genetic analyses are done on a genome scale to, first, let us understand how genes function across the genome and a particular phenotype, and second, to discover new targets which perturb various phenotypes or pathways.
  - What we did was build an automated robot which enables us to screen approximately 150,000 wells of siRNA or cDNA [for a measurable effect on the cells]. This allows us to perform gain of function or loss of function screens to identify novel targets.
  - We are also able to package these siRNAs and cDNAs into lentiviruses so this enables us to get these siRNAs and cDNAs into cells that are hard to get into with normal transfection methodology, such as embryonic stem cells. So we can package lentiviruses [with siRNA or cDNA] targeting every gene in the genome and ask the question about which genes are essential for particular differentiation processes.
  - These capabilities are coupled with high-throughput image analysis, high-content imaging, or high-throughput microscopy which lets you visualize phenotypes (effect on the cells of test siRNA or cDNA) by antibody staining or morphological staining or high-throughput FACS based assays.
  - Today we run about 150 unbiased functional genome-wide screens. The figures on this slide visualize for you the output of one of the stem cell assays that we ran looking at adipocyte differentiation. These [fluorescent cells] contain siRNAs which promote mesenchymal stem cells to become adipocytes as evidenced by staining.

- Slide 4
  - Of course chemical space is more complex than genomic space. There are only so many genes in our genome but with chemistry you can generate millions of small molecules.
  - We also built an automated system which enables us to screen 2 million compounds. We've moved this system into a 1536 well format; this miniaturization enabled us cut the costs of our assays. Now we are down to 1.5 cents a well or $15,000 an assay to interrogate about 2 million compounds, which is about 1/20th of the cost of conventional assays.
    - This also enables us to store information about our compounds online and deliver sub-microliter quantities of compounds and also allows us to do HCPCS [Healthcare Common Procedure Coding System] online. It's amenable to both cell-based assays and biochemical stains. We run about 200 different screens and we are doing about 80 screens a year.
    - This is the same technology that the NIH, Scripps Florida, and Merck has adopted to address their chemical screening needs.
  - The combination of these two automated platforms has really enabled screening to be a low cost, high-throughput robust tool for chemical and functional genomics efforts. These platforms are independent of the type of cells you add, so you can conceivably develop any sort of phenotypic assay you are interested in and (particularly in stem cells) probe differentiation pathways and understand both genetically and chemically what are the components that perturb those pathways.

- Slide 5
  - From our perspective, we have started to get into a little bit of stem cell screening. These are the major challenges and possibilities that we have seen using high-throughput screens using stem cells:
    - **Costs.** Setting up this kind of automation at various institutes in California would be redundant. One of the possible solutions that I am proposing is a core facility for screening where everyone in California who is interested in running high-throughput stem cell screens can go. This would be parallel to the NIH roadmap project where they had the MLSCN [Molecular Libraries Screening Centers Network] centers located in different areas in the States.
      - The only exception I would make to this is that the NIH had the centers run by academic groups. It is really the private sector that has been making advances in screening in the last 20 years or so, so it might make more sense to have the private sector spearhead a screening facility.
    - **Technical Roadblocks (high-throughput manipulation of hESCs, assay detection, etc).** Miniaturization of assays is where the most significant cost savings comes in, but that also brings up a number of technical roadblocks that we have encountered and I'm sure that most people will encounter when working with stem cells. There are challenges associated with being able to manipulate stem cells in a high-throughput fashion, to screen a million or two million wells per day, to use different assay detection methodologies that are amenable to high-throughput.
      - Some potential solutions I came up with to address these challenges would be to promote the development of ESC lines that are particularly suited to high-

throughput biology. Most of the cells lines we now work with, in aggregate, are difficult to work with. It has really been a major limitation for us to run a number of screens. Perhaps we can develop a defined chemical condition for stem cells so that they don't spontaneously differentiate based on the serum batch, etc.

    - We also need to transfer ESC know-how to people who actually run the screens. The people who run the screens are not usually the ones who work on the stem cells, so we have had a lot of difficulty in moving stem cell technology into the screening center.
    - One thing I think the NIH has done very successfully is supporting assay development, such as the miniaturization of assays for the MLSCN. You can imagine that various groups could miniaturize assays and send them to the screening centers to run chemical or genetic screens.

- **Cultural Roadblocks (translation research between academic and biotech sectors).** We have found that there are culture roadblocks between the academic and biotech sectors, even though we have pretty good relationships with various academic groups. We find that the collaborations are very fruitful, but most of our knowledge of what is going on from academic groups comes from publications, which usually do not give you enough information and often occur a couple of years later than the initial discovery.
- **Target Deconvolution (small molecule screening).** This is a problem endemic to cell-based screening. It refers to trying to figure out the mechanism of action of a small molecule, that when added to a cell, has an effect on the desired phenotype. It is a major challenge for medicinal chemistry and trying to figure out the potential side effects a small molecule would have.
    - A potential solution is to promote genetic-based screening to identify the target in the cell first and then do biochemical screens and further target identification.
- **Validation of Results from Cellular Assays.** One of the things we see coming up on the horizon is model systems that can validate our high-throughput screens in a rapid fashion. The big challenge is to figure out what to do with the results. We see a lack of *in vivo* models and transplantation methodologies where we can move our results from cell-based screening to *in vivo* evaluation.
- **Exploratory Chemistry.** This is where we do small molecule screening and where most of our projects are killed because we cannot get chemistry support.
- **Large Scale (GMP) Production.** This is way down the line, but we see the need for standard operating procedures around manufacturing. Novel automation and non-invasive monitoring of cell line cultures needs to be promoted before this can become a reality.

- High-throughput, cell-based screening can be applicable to stem cells. There is an enormous opportunity to be able to interrogate genomic and chemical space, but a number of things need to happen before this can become a reality.

Bruce Cohen, President and Chief Executive Officer, Cellerant Therapeutics

- Slide 1 - Title Slide
  - I want to talk to you about Cellerant Therapeutics and what we do in adult stem cell research.
    - Cellerant is a San Carlos based company and we've been in California for about 4 years. We have about 35 employees and have gone through 2 rounds of VC financing, as is customary in our field.

- Slide 2 - Private Company Perspective on Proposition 71
  - I'm going to give you a little bit of the private company perspective on Proposition 71 and tell you about what we do as a company and our perspective of how Proposition 71 and industry can best interact.
    - It is our view, as is obvious to most people, there is enthusiasm around Proposition 71. That is undermined by the uncertainty of the court challenge, the emergence of IP [intellectual property] policy, and the discussion of how the state intends to recover its investment. One would not want all this to be on the table but it does create uncertainty in the community which continues to be a problem.
    - In our view, because we are an adult stem cell company, we like to distinguish between adult [stem cell] based therapies that could have an impact on patient lives in the near term. In the longer term, work in the embryonic [stem cell] space has terrific promise and somewhat unknown economics.
    - In my view, as someone who spends most of his time raising money for novel scientific endeavors, I would like to see the Proposition 71 discussion framed by our ability to have the state's investment prime the pump for private equity.
      - The big question from us as a private company when we think of Proposition 71 is: can we find an effective way to use public money to help facilitate the inflow of private capital in this space? Even $3B is not enough to get all these programs into the clinic and into patients. We need to think creatively about how to do that. Public money has been used efficiently to create private investments.

- Slide 3 - Investor Reluctance to Fund Cell-based Therapies
  - Investors have been reluctant to fund cell-based therapies. I will focus exclusively on the adult stem cell side.
    - When we talk about regenerative medicine, we are talking about one-time, expensive, curative therapies. That is not a business model that is well established in the pharma industry.
    - Because we don't have a recurring revenue model, we have to be careful how we recover an enormous investment on what may be a relatively small number of patients. We do a lot of manipulation of cells, so unlike the majority of the pharmaceutical industry, one of our primary costs is in labor (versus in capital).
    - On the macro level, we have to start thinking about patients in terms of whether or not they will be interested in the risk / benefit ratio of a potentially heroic procedure versus a benign drug that one may take chronically.

        - For example, we are moving cancer from a disease that has been treated heroically to one that is treated more chronically. It is changing the way we are thinking about the economics of cancer.
    - We have argued that cell-based medicines have lower risks because we understand how the cell works as opposed to small molecules which can surprise you at the very end of the drug discovery process. The question is can we translate that risk profile into what investors can understand?

- Slide 4 - Core Hematopoetic Stem Cell Platform
    - Our business is about adult blood-forming stem cells. These are the cells that populate the blood to form red blood cells and the immune system. Scientists around the world have articulated the whole ontogeny of how a blood-forming (hematopoietic, HSC) stem cell becomes all the mature components of the blood and immune system.
        - Our intent is to use HSC and its derivatives to treat a wide variety of diseases like cancer and autoimmune disease and various disorders like sickle cell disease.

- Slide 5 - Stem Cell Therapy for Genetic Diseases
    - I want to talk about one case of stem cell therapy actually being curative. The stem cells given through bone marrow transplants have been shown to be curative of very severe disease like sickle cell disease
    - Most of this work was done by Mark Walters at Children's Hospital Oakland. He showed that you can cure sickle cell disease with bone marrow transplant.
    - The active ingredient in a bone marrow transplant that is curative in this setting is the blood-forming stem cell. The reason this is not more widely used is because the current method of using bone marrow transplant has an unacceptable side effect, which is the risk of graft versus host disease, which is potentially fatal. But it is important to understand that we have good examples of stem cell and stem cell-based therapies that are curative today with real patients.
    - Our mission is to make those therapies more widely available, in our case by purifying the stem cells to eliminate the side effects.

- Slide 6 - Tomorrow: Stem Cell Oriented Drug Targets
    - In the future, through the use of stem cells, we will be able to understand complicated diseases like cancer. We now think about cancer as a stem cell disease. It is pretty clearly understood that when you have a disease like leukemia, what you really have is a disease that is carried through the stem cell and carried though a defect in the stem cell multiplied many times.
    - It is therefore important to have the ability to use stems cells regeneratively based on our understanding of how stem cells evolve to understand what caused the disease and also to find drug therapies and targets we can treat conventionally.

- Slide 7 - How Proposition 71 Can Make a Difference?
  - In my view, it is to structure the grant process to encourage, but not replace, private investment. Proposition 71 can make the hugest difference in the world if it is seen as a way to leverage private capital.
  - We need to support clinical development and enabling technology. When you do drug development, the riskiest part is in the clinic. This is a place where public dollars can make a big difference.
  - You don't get something for nothing in terms of IP; all companies in my space pay license fees that are reasonable. We ought to be cautious about having something that would approach a punitive recovery on IP.
  - I think we have to start thinking downstream about how we might incentivize the state and payors who operate in the state to think about curative approaches versus chronic treatment and incentivize innovation as opposed to a "me too" approach.

Ann F. Hanham, Ph.D., Managing Director and General Partner, Burrill & Company

- Slide 1 - Title Slide
  - Burrill & Company is a life science merchant based in SF. We have a little over $600M in investments and invest exclusively in the life sciences.

- Slide 2 - Venture Capital (VC) Requirements
  - What does a VC look for when we make a decision whether or not to invest in a technology?
    - Patent protection is at the top of the list. This is where we dig in first and make a decision on whether or not we go forward.
    - We also look at the regulatory and clinical considerations. The regulatory steps or hurdles you go through to generate a product are benchmarks for how we value the technology and on how we can get return on investment.
    - Good markets are attractive for VC. If the economics are appropriate (i.e. if the cost of getting approval is low enough) we may go into smaller markets. It's all how you manage your capital.
    - We look for an experienced management team. The company will ultimately be successful if it has good management.
    - We look at the capital requirements to get a clinical proof of concept (POC) and approval; the stem cell question here is a new territory.
    - We need our exit in 5-7 years. We are not long-term grant holders. We have to get a return to our investors. Typically our funds are 10-year funds. Through the cycle, we have to make that investment and get our exit through the sale of the company to large pharma or through an IPO. We need to get our cash back in that period of time.

- Slide 3 - Stem Cell Technology
  - Strengths
    - The technology is maturing. I took the first stem cell device to the FDA 20 years ago (a hematopoetic device) and a lot of progress have been made since then. It always takes longer than you expect, so I have to look to see if that product is mature enough that I can get my exit in that 5-7 year time frame.
    - We like the wide applications from basic research. You are able to put money into a basic platform or technology and it can have wide applications. That is an attractive investment for a VC.
    - We would like to get a cure. If we can get a cure, that is the best outcome.
  - Concerns
    - How much more basic research is going to need to be done? Many of the companies that pitch to our firm are not ready for VC funding yet. They have not worked up their business metrics or their technology or their idea or how much time / resources they need to get to a final product.
    - Patents are a huge issue for VCs. We need to protect our investment. If we are going to put capital in, we need to ensure protection of that asset. The University of Wisconsin patents have raised issues about whether we can invest in this field.
    - We also need to see a commercialization strategy. Right now, stem cell science is much more on the research side than the development side of the R&D process.
      - There are issues to be addressed around manufacturing and the scalability and reproducibility of manufacturing.
      - There are questions to be answered such as: Can you pool stem cells? What is the right commercialization strategy? Wow do you become a company and earn back that money that was put in?

- Slide 4 - Regulatory and Clinical Considerations
  - **FDA and EMEA review is in development.** The two largest regulatory review bodies are the FDA and EMEA [European Agency for the Evaluation of Medicinal Products]. The specifics of how their criteria will be applied and how they will regulate stem cells are still in development and VCs hate uncertainty in that respect. CIRM could do a lot to provide leadership there.
  - **Informed consent.** The stem cells companies we are working with do not have robust informed consent procedures. It is tough to move forward here.
  - **Clinical endpoints and follow up.** The clinical endpoints and follow up procedures still need to be ironed out. Leadership can be provided to researchers in this area.
  - **"Dose" of stem cells.** We don't know how many stem cells to give for treatment or what "dose" to use. You have to think through your strategy because most pharma and biotech companies are very traditionally oriented.
  - **Poolability of data.** If you are using different stem cells for different cancer patients, can I pool that data and show that all that data can be evaluated and put forward in the submission?

- **Long-term follow up**. How long will we need to follow these patients? When do we expect to see adverse events? Could a patient develop a tumor related to that stem cell 10-15 years down the line?
- **Manufacturing consideration.** Including scalability and reproducibility, among others.
- **QA and QC requirements for small labs.** These are onerous and very expensive.

- Slide 5 - Stem Cell Markets
  - Everyone here is aware of how important stem cells may be in cancer, diabetes, etc. There is strong interest and the markets are attractive. But there are some problems:
    - Is this a one time administration and how do you charge for that?
    - What is your reimbursement strategy and pricing going to be for a one-time therapy?
    - With respect to distribution and wholesalers, how are these cells going to hold up? How long are these cells viable? Most distributors require 24 hours stability. How do we put stem cells in that commercial frame?
    - How do we handle long-term follow up and serious adverse event (SAE) tracking?

- Slide 6 - Who is Financing PRIVATE Stem Cell Companies?
  - I have provided a list of different VC firms and the companies who have received funding (in parentheses). We have Cellerant and Geron here today. It looks like a long list but you have to put it in a context of biotech companies that are getting financing.
  - There are roughly 5,000 biotech companies in the US, 500 of which are public. This is just a small handful in comparison. VCs are not picking up the whole aspect of commercially viable biotech companies in the stem cell arena.

- Slide 7 - Who will finance stem companies?
  - Federal Government
    - Specific stem cell types (Bush administration)
    - Switch to all stem types? (The 2008 administration?)
  - State Governments
    - California (CIRM), Mass, NJ, Wisconsin, others
  - Philanthropists
    - Bloomberg donation to John Hopkins
    - Gates Foundation
    - Others
  - Celebrity Charitable Organizations
    - Michael J. Fox Foundation
    - Reeve Foundation
  - Private Equity Investors
    - Principally VCs
  - Public Equity Investors
  - Foreign Governments
    - BRIC, (Brazil, Russia, India & China) UK, Singapore, Korea, Sweden

Martin McGlynn, President and Chief Executive Officer, StemCells, Inc.

- Slide 1 - Title Slide
  - Thank you to CIRM for inviting us to participate in this discussion.
  - I would like to echo some of the ideas, comments, and ideas brought up by my colleagues.
  - We have to grapple with really high-class problems. At this stage of the game we are focused on getting great science translated and into the clinic.

- Slide 2 - Who Are We?
  - I will explain who we are at Stem Cells Inc. and what we do.
    - We are a public company and we have a small cap valuation of $185 M.
    - We operate in a leased facility in Palo Alto and have 50 employees but are slowing building up. Our annual payroll is $6 M.
    - We were founded in 1995 by 3 icons in academic stem cell research - Irv Weissman, Rusty Gage, and David Anderson.
    - Their company was a virtual endeavor for 3 years due to the lack of cash. In 1997, we merged with CytoTherapeutics and became Stem Cells Inc. in 2000.
    - Since then, we have burned ~$66.5 M and raised ~$115 M. Our cash balance $60 M and we are burning $1.5 M per month.

- Slide 3 - What Do We Do?
  - We are in the regenerative medicine field and we are using cell-based therapeutics.
  - We search for rare cells in donated human organ tissue.
  - To date, we have identified 3 human cell types
    - A human neural stem cell which is currently in phase I clinical trials.
    - A liver engrafting cell, for which we have demonstrated long-term survival *in vivo*.
    - Candidate insulin producing cell.
  - Our human CNS neural stem cell (HuCNS) is interesting in that we are able to grow billions of these cells *ex vivo*. Consequently, that allows us to develop a product based business model. These can be characterized as stem cells and have potential uses in treating CNS disorders.

- Slide 4 - Initial Clinical Applications: Neuroprotection.
  - Our initial focus for clinical application of neural stem cell is in the field of neural protection. I am reluctant to refer to neuroprotection as low hanging fruit. In the context of neurogenesis, it is not such a lofty goal.

- Our focus is to provide neuroprotection in the host. We have confirmed that our cells produce 5 of the enzymes that can be missing in different lysosomal storage diseases affecting the CNS and have demonstrated a preclinical POC in the Batten mouse model.
- Remylelination continues to be the focus. We have data that suggests that we might be able to restore motor function in a model of spinal cord injury.

➢ Slide 5 - Batten Disease
- Batten disease is a group of fatal genetic disorders affecting infants and children. Children present with cognitive and motor degeneration.

➢ Slide 6 - MRI of End-stage Batten Brain
- This is an MRI of the brain of a 7 year-old child with end-stage Batten disease in contrast with the normal brain. The dark spaces in the Batten brain is where the neural tissue has been lost and the space created has been filled with CSF [cerebrospinal fluid].

➢ Slide 7 - Phase I Clinical Study: Batten Disease
- Our protocol involves 6 patients and is an open label study with cells injected directly into the brain. We administer one year of immunosuppression and we follow the patients for an additional year thereafter. It is primarily a safety study. We expect that it should take about 2 years before we have data.

➢ Slide 8 - Challenges: Organ Derived Stem/Progenitor Cell Approach
- The challenges that we face with our approach to deriving stem cells is that there may not be a stem cell in every organ. To date, approximately 9 adult stem cells have been identified but only 3 have demonstrated long-term engraftment.
- This is a slow and tedious process. When you find the cells, it is an expensive exercise to characterize them. We isolated a neural stem cell in 1999 and our first IND was approved in 2005.
- The mesenchymal stem cell (MSC) and neural stem cell (NSC) are both expandable *ex vivo*. Hematopoetic stem cells (HSC) are not.
- Tissues must be sourced to meet good tissue practices (cGTP).
- One of the major problems we have is the absence of well-characterized, predictive animal models.

Thomas B. Okarma, Ph.D., M.D., President & Chief Executive Officer, Geron Corporation

- Slide 1 - Title Slide
  - It's a pleasure to spend some time with you today. My message is going to be straight forward. Because of the depths of your pockets and lack of competition at the state and federal level, we have an opportunity to shape the way the field is developed.
  - My take home message to you today is the "D" word - development. My advice to you is to subordinate research to support development. Don't eliminate the research in R&D, but do the research as necessary to support the "D".

- Slide 2 - Human Embryonic Stem Cells
  - Starting 11 years ago in 1995, Geron first began funding labs in this country. We were in on this story at the beginning.
    - We funded the labs that took the human blastocyst and turned it into long-term surviving, genomically stable, human ESC lines. We used lines that were derived before and after Bush's decree from 2001. These lines are from Wisconsin and Bush-approved and two of them are approved for human uses.
    - Our first program in spinal cord injury uses the H-1, Bush-approved line
    - What we have learned to do from 1998 when we received these cells from Wisconsin is to produce the cell types you see here: neural cells for spinal cord injury and Parkinson's disease, cardiomyocytes for heart muscle, insulin producing islet cells for diabetes, hematopoetic cells for bone marrow, osteoblasts for bone, cartilage forming cells for arthritis, and liver cells for drug discovery and liver failure. This composite picture illustrates one of the things we accomplished in 10 years, that is, to illustrate the promise of this technology as a self renewing source for the scalable manufacturing of replacement cells for every tissue in the body.

- Slide 3 - Human Embryonic Stem Cells, cont.
  - How do we do this? This is the roadmap. This is published in our annual report from last year and is readily available. This is to provide some guidance in what it takes to enable discovery research.
    - We did the first genomics database with Celera.
    - We established lots of important infrastructure along the way, such as a GMP master cell bank. We have taken all these technologies through to 2 IND meetings with the FDA. This led up to our spinal cord injury program.
    - We've been in front of the agency twice with a formal, recognized meeting. They understand the benefits of scalability and tight product release specs and GMP processes and procedures and master batch records.
  - In terms of advice to CIRM, I would say that to ignore this type of experience will be a fatal flaw for you.
    - Zach pointed out that one of the unique features of this field is that its early development is not exclusively the purview of academia.
    - If you go back to the history of pharmaceutical companies putting monoclonal antibodies into clinical development and commercialization, that took 25 years.

- This is about what academia can and cannot do in terms of taking a new breakthrough technology through development. That is your opportunity here. Take advantage of this roadmap that we are willingly offering to move the ball faster. This is an opportunity to create cures, not just treatments.

- Slide 4 - Spinal Cord Injury Phase 1-2 Study Design
  - We have interviewed over a dozen clinical trial sites in North America. We have a focused group of neurosurgeons who are helping us write a protocol. This will be the world's first.
  - The IND enabling studies are extraordinarily extensive for the world's first embryonic stem cell trial. These studies will need to be completed before we move to the clinical environment. The bar is both appropriately high for the FDA and for us.
  - We will start with patients with complete thoracic lesions. We will inject these cells between a week and two weeks after their injury, when they would usually go to spinal stabilization surgery. We have developed an injection device that works to fill a cavity in the spinal cord with cells that we have shown (in animal models) are able to remyelinate and secrete neurotrophic factors to allow axons to grow and survive the injury. We will follow patients for over a year.
  - The glial cells, the product in this trial, are not recognized in the immune system *in vivo*. We are looking for improvement even in patients with complete lesions.
  - We have invested over $100 M to achieve this - this did not come cheap. What we can provide CIRM as a result is help on how to reduce science to product development formats that have survived the rigors of FDA challenge.

Alan K. Smith, Ph.D., President & Chief Operating Officer, Cognate BioServices

- Slide 1 through 3 - What is Cognate BioServices?
  - I would like to thank the organizers for allowing us an opportunity to share a little bit about Cognate BioServices and to also share some areas as food for thought as to where we could help CIRM in the development of their programs.
  - We provide contract/consultation services including direct manufacturing services related to the development of cell-based therapeutics but not exclusively stem cell therapeutics.
  - Our range of contract services covers:
    - Preclinical services to help position stem cells from a safety or efficacy perspective in the appropriate animal model.
    - cGMP manufacturing of cells for preclinical work in animal models, safety studies, and human clinical trials. We have the ability to produce cells of sufficient quality to meet the requirements for human clinical trials.
    - Quality control and quality assurance services, in conjunction with the manufacturing, to clients who have these needs.

- Process development and scale-up services:
  - We have an operating manufacturing facility in Sunnyvale, California including ~10,000 square feet dedicated to cGMP manufacturing.
  - We have been issued a California Department of Health Services Food and Drug Branch manufacturing license.
  - We have been approved by the U.S. FDA as a clinical manufacturing facility for a number of therapeutics in human clinical trials.
- Consulting services on preclinical research, process scale-up, GMP manufacturing, QA and QC, and regulatory issues.

- Our list of accomplishments includes:
  - We have been material contributors to 16 IND applications that have been approved for human clinical trials, some with stem cell products and others with cell-based therapeutic products.
  - We also have a number of years of translational "productization" and we specialize in successfully translated things from the bench to the bedside.

➢ Slide 4 through 6- Stem Cell Development Challenges

- CIRM should consider some funding or opportunities to establish programs for cell sourcing, banking and characterization. There are opportunities for CIRM to provide:
  - A means for consistent characterization and quality control of cells that are advancing toward use in the clinic.
  - Help with documentation and traceability of those cells, and
  - Help in developing appropriate protocols to document storage conditions and stability of banked cells.
- A lot of researchers may benefit from an arm-in-arm relationship and an opportunity to collaborate with folks who have some experience and the ability to help scale up a process and incorporate elements of cGMP into those processes, such that these result in reliable, reproducible, robust processes that will ultimately be amenable to clinical and commercial-scale stem cell products being generated.
- I think there are challenges in terms of availability of suitable cGMP manufacturing. These facilities, in order to be of maximum use, likely need to be for multiple use and flexible in their capabilities.
- Something that should not be understated is the availability of trained manufacturing, QC, and QA staff for these endeavors.
  - The use of suitable materials, documentation methods, etc. has already been mentioned by the previous speakers.
  - Hand in hand with the manufacturing, there needs to be suitable quality control and quality assurance. How does one demonstrate the safety of a cell product to be tested clinically?
  - Consistency of the product is also important. How can one appropriately characterize that product for consistency, potency, purity, etc.?
- I don't think it is too early to start thinking about storage and distribution. This is often an overlooked but critical aspect to wide spread application for therapeutics that require specialized handling such as refrigeration or freezing.

- There are also opportunities for CIRM to participate in the development of resource bases that can be generally used by researchers developing these therapies. This allows them to get an early grasp on cGXP (where "X" equals laboratory, tissue, manufacturing and clinical).
  - It is critical to encourage scientists and clinicians to draw on theses resources early and often.
  - An ounce of prevention may be worth millions in savings on misdirected projects in this light.

➢ Slide 7 - Other Considerations
- Guidelines and resources for standardization are needed. This is an area where hematopoetic stem cells struggled for years before some specific guidelines were established to allow apples to apples comparison of doses of hematopoetic stem cells in clinical trials.
- There are also some areas where new tools may be required which will be beneficial to this endeavor, including ways to track the trafficking cells in preclinical models.
- The bottom line is that we will succeed or fail as a community and to the extent we can share and deploy resources that will be to the benefit of the community in total.

➢ Slide 8 - Stem Cell-based Therapeutics and Regenerative Medicine
- So how do we work together to expedite translational research and help patients? I think that is what this meeting is all about.

Michael D. West, Ph.D., Chairman of the Board, President and Chief Scientific Officer, Advanced Cell Technology, Inc.

➢ Introduction
- Advanced Cell Technology recently moved its headquarters to California in part due to all the activity here.
- We focus on ESC based cell therapy and have 3 products for which we recently announced plans to file an IND within the next two years:
  - Retinal pigment epithelium (for macular degeneration), which is hESC-derived
  - Hemangioblasts, which are precursors to blood circulating vascular precursor cells
  - Early dermal progenitor cells, which allow the dermis to regenerate without scar formation and which we plan to use to promote wound repair.
- I feel we are at an important point in history here with the people of California making such an important vote to fund this field of regenerative medicine. It is important for us to realize the historic opportunity and to do everything we possibly can to make sure the money is wisely spent to advance human healthcare.

- I'm going to tell you from a biotech / development prospective (as I see it) the opportunities and challenges of human embryonic stem cells based therapies.

- Slide 1
  - The Opportunities with hES cells
    - ESCs can differentiate into every cell in the human body. These cells are so early in their development, they have not made the fundamental decision to go germ line and make sperm and egg or become somatic and make any of the cells in the human body.
      - As a result, they maintain the option of immortality. They keep the telomere clock "wound up" so to speak, such that cells made from them are "born young". This is a unique aspect; we don't know any other cell types that have those properties.
    - We have ease of gene targeting. We now have an immortal substrate here of human cells cultured in the lab dish which are amenable to homologous recombination. We can target specific gene sequences and alter them.
      - We can target genetic modifications in hESC and then turn them into any type of cell in the body, all of which can be genetically engineered through gene targeting. This has profound implications in the long-term to the power of these cells and their use in medicine.
    - The third point is that because human ESC cells stand at the very beginnings of human cellular differentiation, when cells differentiate from them *in vitro*, they display a pattern of gene expression that is different than the adult. The embryonic stem cell in the normal embryo would give rise *de novo* to all the human tissues.
      - As a result, when we do gene expression studies of ES derived cells, we see patterns of gene expression that are different between the fetal and adult stages of development. These cells are actively genetically programmed to build *de novo* tissues. I call that pattern of gene expression 'regenerative gene expression'.

- Slides 2 and 3
  - It would be wise for CIRM to focus on the development side of the equation. There are some challenges here.
    - **Scalability.** If we are going to deliver these therapies, we will need to be able to manufacture them in large quantities.
      - Human embryonic stem cells have the unique property of immortality. They propagate *in vitro*. That aspect of these cells makes people think the initial point of scalability should be in embryonic stem cells themselves, so we should be building big bioreactors and scaling up human ES cells and then purifying whatever type of cells from them.
      - I don't disagree with that, but I would like to challenge it in one respect. Down stream cells are also scaleable (i.e. skin cells, retinal pigment epithelial cells). I think research in the basic scalability of cells that have been propagated in bioreactors as compared to the scale up of down stream cells is an important investment. It could be that the down stream cells are more genetically stable than human ES cells.

- **Purification protocols.** We need to develop purification protocols specific to whatever the cell type it is.
  - For many cells types, we know almost nothing on how to purify these cells.
  - Another challenge is that we make these cells from human ES cells and it is frustrating to those in development to find that the patterns of gene expression displayed in these early embryonic cells are highly unexpected.
  - If we are tying to make a precursor to a beta cells or lung epithelium, we know almost nothing about what transcription factors should be expressed, what genes to expect, and what the molecular markers of these early lineages are. An intensive effort to understand the gene expression profiles these of early embryonic lineages would be invaluable in the development of the products.
- **Cryopreservation.** This was touched upon. In our experiences, the standard cryopreservation techniques often disturb the growth of ES derived cells and need to be improved upon.
- **Transplantation Studies.** We need to undertake transplantation studies. What would be beneficial here, which privately funded companies often cannot do, is long-term transplantation studies.
  - I mentioned transplant rejection studies and long-term engraftment studies which could be expensive but helpful to the field. You will need to understand how transplanted cells migrate and try to differentiate and we need to image them better.
- **Histocompatibility.** We need to solve the problem of transplant rejection because of histocompatibility.
  - One of the benefits is the courage and willingness of the people of California to tackle this problem.
  - Somatic cell nuclear transfer is one of the controversial aspects of regenerative medicine, but the long-term benefits to the patient would be greatly served by being able to transplant autologous cells. I think this is an important area to fund.
  - There are important strategies to address histocompatibility I would like to touch upon. One is the generation of a bank of cells that has homozygosity / hemizygosity in their HLA Class I genes.

- Thinking of this in terms of a development priority, we need to be able to meet the needs of the patients.
  - It would be a benefit to the field for the CIRM or other funding agencies to help the researchers learn the basic molecular biology of nuclear programming as it occurs in SCNT, and reduce that to what we call a "cloning machine", which is a machine that does not use nuclear transfer but can reprogram cells using cellular extracts and molecules. By understanding the basic biology of reprogramming, we would have a technology that would be widely applicable and with a lower cost.
- The generation of data on the scalability of cells other than human ES cells, the generation of histocompatibility strategies, an understanding of how the gene expression profiles of cells derived from human ES cells differ from mouse cells, and strategies to help us to purify cells are the issues I would like to emphasize today.

E. Edward Baetge, Ph.D., Chief Scientific Officer Novocell, Inc.

- Slide 1 - Title Slide
  - We now come under the banner of Novocell, which is a combination of three companies that existed in three various regions: Georgia, San Diego, and Irvine.
  - Two of these three companies were stem cell-based companies, with one focused on the nervous system and one on diabetes, and the third was developing encapsulation technology that allows you to take human primary islets, encapsulate them, and put them into patients with diabetes. We are in clinical trials with that right now.

- Slide 2 - Mission
  - Novocell is a stem cell engineering company that is dedicated to creating, delivering and commercializing cell and drug therapies for diabetes primarily and other chronic diseases.

- Slide 3 - Stem Cell Engineering: A Transforming and Disruptive Technology
  - Stem cell engineering is comprised of a lot of things. This is the century of the cell. We are going to need to understand how to engineer stem cells to produce the products we need to make.
  - The areas we will have to focus on are:
    - First, the stem cells. How do you produce these cells and isolate them? How do we make banks? Where do you get the embryos to do this?
    - Then you need to understand how to expand the cells and grow them in a way they can be used, not only on a small scale, but also in a large scale. You need to keep them in a normal fashion to eventually use them as a product in humans.
    - Once you have these cells and expand them, you will need to differentiate them into the cell type you are interested in using either as a cell therapy or as a drug screening tool. We are focused in the area of endoderm, which is one of the three lineages that give rise to all somatic cells in the human body.
    - In terms of scale-up issues, it depends on what type of product you are interested in making. You are going to have a bigger issue with regard to scale-up for instance, with diabetes than for a neurological disease such as Parkinson's in terms of the number of cells needed to treat the patient.
  - Not only can you use stem cells for the traditional approach of cell therapy, but also as screening tools for small molecules, peptides, and antibodies. It is a broad platform that stem cells represent. They go across all these disciplines.

- Slide 4 - Stem Cell Engineering: A Transforming Technology with Challenges
  - Stem cell engineering is a really a transforming technology, but it has major challenges.
    - The dollars that need to go into this expensive research and development to produce products is a challenge. There are also political and ethical issues that have to be

overcome. Venture capitalists (VCs) are sitting on the sidelines in terms of putting enough money into this. The state (like CIRM) and private institutions are really the sources we are finding for financial support.

- Intellectual property (IP) is also something you are quite familiar with. I refer to this as ROW versus WARF, or in other words, the Rest of the World versus Wisconsin Alumni Research Foundation. If WARF can be brought into this equation and be a collaborator / partner, this is where we will really gain.
- If you actually want to produce these cell therapies one of the biggest hurdles will be after you scale them up and want to put in humans, to show to the FDA that they are safe in order to get these approved as products.

- How could CIRM help?
  - As a state organization CIRM is helping to fund this type of research. This will be critical in going forward.
  - CIRM could help broker a solution between the rest of the world and WARF.
  - CIRM could help educate the FDA on the issues and the needs of stem cell companies as they develop these products.
- In addition there are other areas we think CIRM can put resources toward to facilitate the development of this technology. CIRM might also consider:
  - Supporting a large number of core facilities with the help of the commercial and research entities.
  - Supporting consented embryo banks that can be accessed
  - Supporting core facilities for doing karyotypic and gene fingerprint analysis of the cell lines that are produced.
  - Supporting core facilities for training personnel in how to grow, culture, and isolate stem cells and eventually how to differentiate them.
  - Supporting core facilities for doing gene expression, proteomics, and signaling studies.
  - Addressing scale-up issues for particular applications of these cells. For example, it is going to take ~1 billion cells to treat one diabetic patient.
  - Addressing safety and regulatory issues are paramount; a CRO dedicated to stem cell-based research in California can be useful here.

➢ Slide 5 - CIRM & Stem Cell Companies: Creating Global Leadership in Regenerative Medicine

- How can the CIRM and stem cell companies create global leadership in regenerative medicine?
  - Grant support. How are we going to pay CIRM back? Either through royalties, milestones, and / or IP. Our preference as a commercial concern is to pay back according to milestones in the form of cash instead of in the form of royalties or IP.
  - Freedom to operate. We believe that CIRM can help in bringing in WARF into the equation and making this work properly in terms of critical IP which is blocking the free development of this technology.
  - Research and Development. We need to recruit and train new talent. California can be a magnet for training.

- Creating core facilities including manufacturing facilities.
- Supporting CRO focused on stem cell product development
- Supporting FDA education.

Question & Answer

- **Q (Jim Kovach, The Buck Institute):** In terms of core facilitates, if you take scale-up for example, all the experience is in the business sector right now. Do you envision the potential for corporate scientists interacting in a more direct way, perhaps in a pre-consortia / consortia model as other industries have done? Do you envision allowing the scientists in your company to interact with academics directly?
  - **A (Edward Baetge):** There are different ways to scale these cells up, such as roller bottles and flasks or using fermentation systems and hollow fiber cultures. We envision having a facility that has small scale and commercial-scale applications of these technologies within one house where commercial companies can come out and try these various technologies to see what works best for them and then potentially move into larger scale operations in such a facility. These sorts of technologies can be developed for use with various products that are being developed by each of these commercial concerns.

- **Q (John Simpson, Foundation for Consumer and Taxpayer Rights):** Do you see a patent pool that would have some of the key patents that were developed with CIRM funded research as a possible way around the WARF issue?
  - **A (Edward Baetge):** It's a complex question and answer. It is most likely that the way you would deal with technology that overrides an entire field is to make it available on a non-exclusive basis to all comers. For instance, the technology of recombinant DNA is an example of where these kinds of overreaching patents can be placed out so that all people can get a nonexclusive license and then push the field forward.

- **Q (Jim Kovach, The Buck Institute):** One of the things that has always interested me is the use of stem cells for small molecule screening. Do you see this as something that is limiting in that it is outside of the business that you have in doing this kind of activity or is this something you view as less valuable than the cell as a therapy itself?
  - **A (Thomas Okarma):** It is certainly subordinate to the medical utility and economic reward of a therapeutic application, but we are actively engaged in using our cells for screening. The three cells most often asked for are cardiomyocytes, neural cells, and hepatocytes.
    - We have a major program with a partner in the UK on the latter cell type. We have learned how to make true liver cells with inducible drug metabolizing enzyme which are currently being formatted for medium and high-throughput screens not so much

for identifying a drug to a target, but for defining the Phase I / Phase II drug metabolizing enzyme patterns for a new drug *in vitro* long before it goes into human testing.

- You can do that *in vitro* analysis in combination with other agents that you pre-added to the culture so that you are mimicking the kind of poly-pharmacy that patients often have on board when they take a new drug for the first time.
- I don't think the screening opportunity is lost on any of us in the field. It is certainly 10% effort on our plate.

- **Q (Unidentified Audience Member):** Toxicology screening is one of the areas I thought would be a fantastic use of liver cells. What I'm trying to do is get an impression of the margin. Because there are so many things to invest in, it must be difficult to make these decisions in terms of where to put those marginal dollars.
  - **A (Martin McGlynn):** We focus exclusively on therapeutics for a number of reasons, number one being expertise and know-how.
    - Discovery and development in therapeutics requires a different set of expertise and know-how than for the development of cell-based assays as well as validation and their transport to high-throughput screening capabilities.
    - We are aware of the potential value. Quite frankly, no one has made a lot of money supplying tools to the pharmaceutical industry. It really has not gained our attention at this stage other than the fact that once we are satisfied that we have well-characterized cells that have potential utility, for example, in evaluating toxicity, we would be interested in engaging other parties to take the baton and move the technology forward.
    - Do we view it as a major source of revenue for the company and shareholders? No, we do not.
  - **A (Michael West):** I agree with previous speakers. In the classic view of a biotech company, it would not be money well spent pursuing those applications. I would suggest that the opposite would be true for agencies like the CIRM.
    - What if, for instance, the CIRM decided to launch a large scale effort to gene trap in human ESCs?
      - What this would entail would be funding a network of labs in California to transfer into hESC markers like florescent genes, such that when they land within a gene frame, and that gene is turned on, the florescent marker beacons indicating that gene is on. Making that library of cells would require a lot of time.
      - If the state of California funded such an effort, in my mind, it would be as important as the genome project was for molecular biology.
      - Imagine bank of [these marked] cells that researchers around the world would have access to. There would be reduction of all these redundancies of researchers engineering all these constructs on their own. It would be a central source of cells for researchers around the world to use for basic research. There would be direct applicability for cell-based screening.

        - This type of strategic way to invest capital at this point in history helps to reduce redundancy which would be a benefit to biotech and basic research for many years.
    - **A (Sumit Chanda):** We do a lot of cell-based screening also around stem cells, mainly to study pathways, but we don't see immediate commercial potential for them. We are in a bit of a privileged position in that we don't necessarily need to look at our bottom line since we have funding from Novartis to do this type of exploratory work. If something comes out it, these are the kinds of things that would eventually perk big pharma's interest. We would try to get additional traction from the initial projects in those areas.

- **Q (Don Reed, for Ann Hanham):** Did I understand correctly that you were involved in early stem cell research 20 years ago? I wonder if you have any memories on the political difficulties that you have faced and if you have any thoughts and guidance for us in that matter?
    - **A (Ann Hanham):** It was a different time. It was a time when biotechnology was going to solve all of our medical problems. It was an easier time when we were going through the regulatory aspects in bringing stem cells forward.
        - The questions were mainly scientific and less political. We were in this unknown. Everything up to that point has been mostly small molecule pharmaceutical development and the FDA and most of the regulatory agencies around the world were set in their ways.
            - We actually had to do primate studies. We knew we were facing problems in immunogenicity, but the "box-checkers" demanded it. But to satisfy them, we did 3 years of primate studies even though they showed nothing.
            - The center for biologics at the FDA was recognizing that the old standards for regulatory approvals did not apply for these biological therapies, particularly for cellular therapies. When I walked into my first meeting with the FDA, we had 500 attend from the NIH and all the different research groups. There was such interest in the research we were doing and a lot of friendly input.
            - It is almost the same kind of feeling here in terms of the strong public interest in how new technology can provide better medicine. We were really in the dark. We had no idea at that time. We spent weeks on the dose and what we needed to do for safety testing, QA, and QC.
        - All of the issues we face here are ones we struggled with years ago. It will be slow but we will learn a lot.

- **Q (John Simpson, for Bruce Cohen):** You said that we should avoid "punitive IP recovery". Can you give us a sense of what punitive IP recovery would entail?
    - **A (Bruce Cohen):** The industry tends to be comfortable with low single digits percentages on sales for royalties. This is what we typically pay universities and other companies when we license discoveries. What that digit is varies by the size of the program and how many other people we have to pay, so there is no single number.
        - All of us here have gotten used to the idea that venture capitalists don't go crazy if the royalty rates are modest. If the royalty rates are excessive and there are too many

people on the trail, then you cannot raise capital. There would not be enough left over for a return.

- One of the problems is that the federal government never really asked for a percentage back. They allowed universities to capture that. The risk is that we have the state and the university both with their hand out looking for recovery. This is what we call "stacking royalties". When the stack gets too high, then you walk away from the deal. That number has to be reasonable and not punitive.

- **Q (John Simpson, for Ann Hanham):** You touched on the WARF patents. As you may know, the Foundation for Consumer and Taxpayer Rights has filed for a request for re-examination along with a public patent foundation. I would be interested in what the VC community views of the WARF patents and some of the views in industry as well.
  - **A (Ann Hanham):** I don't have a specific view on those particular patents.
    - Where it gets complicated are those stacked royalties. The IP around stem cells can get very complicated very fast. If each institution claims 6% or 10% and this starts getting added up, and you factor in the uncertainty of thinking you've captured all the IP and wanting to go forward but learning of another institute that claims they had a percentage as well, the economics soon become nonviable.
    - That's where the Wisconsin patents are. Because they are so layered into so many others, they have precluded a number of companies from going forward. The question is, "Could they be done in a way to still allow these commercial opportunities to go move forward and still provide benefit to the University?" I don't have a quick answer to that. It is an interesting question. We do need patent protection. We won't do a deal if there is not good IP there.

- **Q (Jim Kovach):** Bruce is being diplomatic in saying that the system is working well. The panel has talked about deals that have fallen through. To me, the empirical evidence is that it is not working as well as it could. I think it is because of the uncertainties faced by the companies. It seems to me that one of the things that could help everyone is to generate more certainly going into relationships between institutions that will get funding from CIRM and the businesses.
  - To the royalty issue, because you cannot control all the IP that is being generated, one idea is to have stacking provisions. I hear companies say that they are amenable to low single digit royalties. It seems to me that if we could come up with something more, that the more certainty we have going in, the more productive we can be. I would like to ask the panel members for the kinds of things / tools you use in dealing with IP and getting what you need and dealing with uncertainty.
    - **A (Martin McGlynn):** That is part of the risk decision that describes the private sector. If you are going to invest in technology from academic institutions, you want to do it with a lot of diligence. You want to understand it and understand how it might fit in your overall objectives. This is a risk decision you take. The academic center is taking a risk decision, particularly for the exclusive license to one particular company. They [the company] may fumble; they may not have the financial resources, technology, or other resources to work the technology. It's a risk decision on both parties. It's part of the game. You have to take into consideration all those

factors. The academic institutions and the tech transfer offices have to do the same. At the end of the day, there needs to be compromises where the deal complies with institutional policies.

- At the end of the day, unless the technology is actually applied, the royalty will be moot. I can point to one case, in our own company, where we have licensed IP from a major institution in California. To date, we have not had the financial sources necessary to work that technology.
- At the end of the day, it's going to be a negotiated agreement where both parties feel that they are getting a reasonable deal.

- **Q (Don Reed):** What kind of public outreach programs do you have? It's in the papers that big pharma and big biotech are controlling, greedy people. I think you have a friendly product and when you succeed, people's suffering will diminish, and paralyzed people like my son will have a chance to walk again. Do you do public outreach so that people can hear what your overall goals are?
  - **A (Thomas Okarma):** I am on the board of BIO so I have an unusual view of big versus little biotech. Speaking for Geron, we don't get ahead of the value of our products in terms of marketing or advertising. We were in support of Proposition 71 for obvious reason.
    - We try to contact patient groups to correctly frame their expectations. That does change as biotech grows up. Some of the larger players (i.e. the Amgens) are no different from the Mercks and Pfizers in terms of advertising of their products.
  - **A (Bruce Cohen):** You raise an important point: we get lost in the shuffle of public perceptions of the industry. We lose that nationally and even through BIO, our own industry group that represents large and small companies.
    - We need to do a better job in letting people understand that these are not a group of people developing conventional medicines. We have lost that. The public perception is that this is an undistinguishable bunch of greedy companies that gets tainted by everything the drug industry does wrong.
    - My sense is that this is something CIRM can help us with. I don't think the Mercks and Pfizers are going to be in line to get a lot of support from Proposition 71 but there is perception that this taxpayer money will find its way into the hands of highly profitable drug companies. That is something we have to communicate through CIRM; this is not a give away to the drug business.
  - **A (Sumit Chanda):** We are studying what Novartis is doing to change public perception. Our institute does basic research really with no commercial gain. They try to develop scientific outreach more than public outreach. It is really to contribute to basic understandings that don't present immediate profit potentials.

Roundtable Discussion
Moderator: Edward Penhoet, Vice-Chair, Independent Citizens Oversight Committee

- **Q:** In the presentations, there was somewhat of a disconnect about the importance of immune tolerance as an area we need to get involved in.
  - Michael indicated that SCNT was an important issue and immune tolerance was important area for anyone to invest in who is interested in this field.
  - Tom, you indicated that at least for the clinical trial you are planning, the cells you are using seem to be immuno-transparent. You mentioned your work in cell-based screening but you didn't mention prospects for patient-specific cell lines that you might use.
  - So, I am going to ask this group here to see if you can cast a little more light on the issue of the importance of immune tolerance.
    - **A (Tom Okarma):** We take stem cell clinical trials, their limits, and potential seriously and we think we know a lot. We decided early on that because of the complexity of SCNT, that the notion of what patient specific ESC lines achieve in this way would abrogate their main advantage: scalability.
      - You can't trade a convenient potential of idiosyncrasy in the immune response for losing the foundational characteristic of ESCs which we think will guarantee their commercialization.
      - But the problem has to be solved. We discovered that the undifferentiated ESC are different from all other stem cells in the way they are recognized by T-cells. They express Class I and a little of Class 2 HLA antigens but they change the way T-cells react to them when they are recognized. There is precedent in biology for the immune privileged nature of the undifferentiated stem cell. This means that the bar for immune suppression, the degree of difficulty of achieving tolerance is much lower than what we experience every day in whole organ transplants.
      - We are not resting on the immune privileged nature of these cells to solve the problem. We've worked with collaborators in the UK on how to derive a special cell that could be used to generate complete tolerance to transplantation itself - an immature dendritic cell. We have the worldwide license from a group at Oxford to produce this cell. This cell, when transplanted, will produce complete tolerance to a transplant antigen shared by that cell. Because ESC lines are pluripotent, if you make the immature dendritic cell from cell line A, that tolerizes a patient to any cell made later from that same line.
      - This is a scaleable way to create immune recognition to the transplanted cell given after that dendritic cell creates tolerance. We will accomplish the same result as patient specific lines with less cost and not sacrificing scalability. Our cell bank will let us provide glial cells for everyone in North America for the next 22 years. Don't sacrifice the element that will lead to commercialization when there is a more efficient method.
    - **A (Sumit Chanda):** Scalability is important. Perhaps more important are the needs of the patient. I would urge a strategy to deal robustly with the problem of histocompatibility. For acute medical indications, like a body burn or heart attack, any kind of technology to reprogram a cell is not feasible if immediate therapy is needed. The issue is one of transplant rejection. In chronic diseases, where people

have time, if those patient's cells can me made autologous, the benefit to the patient would trickle down to profitability for companies.

- **A (Alan Smith):** There are two scenarios, the application of stem cells in an acute setting, which has different requirements and logistics that for their use in a chronic setting. In an acute setting, there are still some challenges before that's practical.
- **A (Edward Baetge):** We're focused on diabetes and our approach initially will be to take the cells that have properties of pancreatic islets and encapsulate them in a polyethylene glycol coating to prevent immune attack. There are steps you can take early on that will allow you to use some of these cells in a number of different products were the cells serve as an individual component of all the substances you need and in that case you can encapsulate.

- **Q:** I've heard the primary reason for the failure of a number of companies in this business is cost or producing the therapy. Is that true?
  - **A (Tom Okarma):** It's 100% true. Terry Sorsac (sp?) and I ran GenCell, Rhone-Poulenc Rorer's division of cell and gene and cell therapy. We were trying to develop a product-based business model for about two dozen products, cells and genes, and we failed not because of toxicity or lack of efficacy, but because of cost of good sold.
    - When you go to an individualized therapy, that individual cell has to be recovered, purified, and quality controlled before it can be re-administered to the patient. That cost structure is prohibitive. Things need to enter a cost-effective space. Until cells enter that space, they won't succeed. ESCs are the only cells that can enter that space.
    - The minute we can demonstrate that, pharma will be all over it. That's an important milestone. We've got to get the big guys engaged to maximize and utilize the potential of scalability to get these therapies into the hands of patients.
  - **A (Bruce Cohen):** At Systemics, the company failed for a number of reasons, but they never got far enough to know if it was the economics. In hindsight, they were developing a product for a disease where the economics didn't work in that disease. If you're developing a cell-based therapy that will have the same impact as a pill, you will lose. If you will fundamentally change a patient's life, you will win.
    - We're working on a cure for sickle cell disease and we feel we can charge a price that will work for us. It's a very disease-specific approach and the first generation of companies made a lot of mistakes in trying to get drug-like results with cells.
    - You can scale individual cell therapies at a level comparable to other sources of therapy. A year's course of Herceptin® and Avastin® is $100-150K. They're being developed as chronic therapies, but they make a huge difference in people's lives. These are very expensive therapies that offer a big change in patients' lives. Whether we get to scale is a bonus. If you have curative intent you can justify [cell] processing for individual patients.
    - The FDA has a new review process for this that is less drug-like. The government understands cell-based therapies need a new set of regulations, particularly when it is personalized.

- **Q (Ed Penhoet):** We've had a number of discussions today on a variety of views on where funding would best be utilized in the private sector. Some of what we have heard is for CIRM to support clinical trials or the other strengths of the private sector. We also heard that some very good research gets done in the private sector so we shouldn't ignore the private sector when it comes to basic research. So I'd like to open the discussion: In the spectrum of activities CIRM will fund, where are the places where industry can most productively use the money and where we should think about putting it?
- **A (Ann Hanham):** We need to ask where the VCs will start funding and where CIRM will be of assistance in getting them to that point.
  - Typically, VCs will invest when you get close to the clinic. When I listen to companies that come in and present and look at why they're not ready, the big issues around manufacturing raise their head. Those services are really needed. We often see great academic researchers with great ideas who don't know how to take those ideas to the commercial side. VCs will pick it up when you take it to clinical trials, so maybe CIRM doesn't need to invest there, but to get things to an IND stage is tough for companies.
    - If you look at how the NIH and NCI treated this issue, they created a manufacturing facility in Fredericksburg. If there was a centralized manufacturing facility in California where academic researchers could get into production so they can do earlier feasibility studies that would be huge because that's beyond what most small biotechs have access to funding for.
    - The academics have also characterized what they have and they have interesting early animal data but can't get over the hump of getting it into clinical trials and there's a big expenditure there. The pooled experience of the group here could be valuable.
- **Q (Ed Penhoet):** So should CIRM go into competition with Alan's company, or fund organizations that want to work with Alan's company or do we fund Alan's company?
  - **A (Alan Smith):** I think that certainly we are willing and anxious if opportunities came our way to help folks who are trying to make this transition or translation from the bench to the appropriate scale to allow them to get final data preparatory to clinical trials or manufacturing for clinical trials.
    - In the absence of some outlet for that type of activity, it will be a significant limitation on the activities in the state to make the jump from applied research and the pre-clinical model stage to the point where a suitable cell product is available in sufficient quality and quantity to be used in the clinic.
  - **A (Ann Hanham):** I think most small biotechs don't have the money to pay Alan. Maybe we could cost out the three models. CIRM can either provide grants to do a contract, or it might be more economical to have that capacity in California that would be jointly used. It may be a blend - until you can get a facility up and running perhaps you can provide grants for manufacturing. Manufacturing is a big hurdle for many companies and I would tackle that.
  - **Q (Ed Penhoet, for Alan Smith):** Are you a sole source for California?
  - **A (Alan Smith):** No, there are others.
  - **Q (Martin McGlynn):** What kind of approach are we discussing?
  - **A (Ed Penhoet):** I posed three models. I don't have a bias.
  - **A (Martin McGlynn):** My answer would be driven by what we've actually done. I would strongly favor that you fund a company that is trying to develop the technology for

production. It's not just about dollars and cents, which is a major factor; it also comes down to know-how. In our case as it relates to manufacturing capacity for early clinical trials, initially we were using our own space, and then we engaged in a contract arrangement with an independent third party.

- Our preference was to lease an "envelop" and put in our own equipment, people, procedures, know-how, and overall management because of the nature and complexity of the operation and the very "tweaky" nature of the things we learned over many years of experimentation and the evolution of our learning.
- I would be concerned you would have so many requirements and nuances for the different-cells based on where they were derived and their stage of differentiation. I would be concerned that you couldn't have a one stop shopping "Wal-Mart" where you could get your choice. I'm not sure it's possible,

- **A (Bruce Cohen):** It's an attractive idea and people all over the world are talking about these centralized resources. The idea is common, but the problem is if you really think you know what you're doing you wouldn't expose proprietary knowledge to someone else.
  - In the cell-based business, the processing is quite proprietary. We wouldn't take the risk of doing our research in a state funded institution where we couldn't be absolutely sure we were protected. Our processes tend to be proprietary and the incremental value of sharing doesn't add up for us.
  - I do think there is gap between animal proof of concept work and scale-up. That would be a very effective use of state resources to get into the clinical arena. I also think there's room for clinical development funding, which offsets the investor risk.

- **Q (Ed Penhoet):** What application of funds would accelerate things into the clinic if it's not manufacturing because it's too proprietary?
  - **A (Bruce Cohen):** Start-up money to do FDA qualification and your own scale-up to get into the clinic would be helpful. Investors want to see these results before they put their money in. That money is hard to come by through the conventional NIH routes. It's not a huge amount of money in the context of $3B, but for a company it can be significant.
    - The best use of CIRM money is to leverage other investments, not replace them. Modest grants from the state should allow us to raise public and private equity capital.
  - **A (Tom Okarma):** I agree from that perspective, but I thought you were asking a more fundamental question.
    - The bulk of your grantees will be academics. I can tell you after working under a cancer IND that was very successful that the barriers at the FDA for cell-based products will be equally high for an investigator sponsored IND or a corporate one. You may fund the scientist who derives and characterizes a new cell, but the real value added for the VC community is clinical data. How can you do that if you can't produce the cell?
    - Rent the space, get those with experience, and offer that as a service to grantees who want to take things to the next level. You eliminated some of the risks of failure and created some of the ability for a university to license that out.
  - **A (Ed Penhoet):** There's a general perception that CIRM is here to fund academic research. I don't believe that's a conclusion we've come to. Many of us believe the

money should be spent where it's most effective in moving therapies forward. We don't have a built in bias.

- **A (Ann Hanham):** I want to emphasize that translational medicine where the funding doesn't happen is where you need to focus; VC, large pharma, and biotech will pick it up when you get close to the clinic. I need clinical data to get me to my 5-year timeframe.
  - I also remember the early days of monoclonal antibodies where the production was propriety. Now everybody contracts it out because it's faster and cheaper. You could keep everything propriety, but you could learn a lot from the documentation from a manufacturing facility. If you can keep it proprietary, you can really speed it up.
- **A (Alan Smith):** I won't disagree with Martin and Bruce, but I would point out that in our Sunnyvale facility, we have about 325 SOPs, and probably 250 are either quality, system, or facilities related, which has no relationship to a specific process. To ask an academician or young company to bite that off is a very expensive proposition, especially for the capital required to lease a clean room or start from a shell and build a facility. Those are very capital intensive endeavors.
  - One of the other value added propositions is there are often times when people have spent a lot of time and energy in developing a process, that may be good in a lab scale, but there's a lot they can learn from those who have done it at a clinical and commercial-scale .
- **A (Bruce Cohen):** I have no problem with contract manufacturers; I just don't want to be mandated into state facility. Contracting is efficient and a good use of resources. I'm leery about the state building a facility or building infrastructure that exists in the private sector. I would feel less safe in a large public institution.
- **A (Martin McGlynn):** We're using a quote-unquote "contract manufacturer" right now, but because of the complexity of the process we used, we decided to take advantage of the SOPs, because we could not afford to do that. We in effect rented space to get the best of both worlds, to get the best people to produce and manipulate the cells in the best possible setting in a cost efficient way.
  - I think it would be a mistake for CIRM to invest money in bricks and mortar - there are already infrastructures at various forms of development in place. If CIRM is looking for points on the board, it should start looking first at product candidates that have been identified (instead of looking for new ones) and look at pre-clinical, toxicology, process cGLP and cGMP, and the funding of first into man clinical trials.
  - Once that's done Ann and her colleagues will be knocking at the door. If you have clinical proof of principle in a significant disease, you need not worry about the dollars after that.

- **Q (Ed Penhoet):** So clinical proof of principle means post Phase II then?
  - **A (Martin McGlynn):** It means that your have established a *prima facie* case that your therapeutic agent seems to have the desired effect in the patient population. As to when the VCs and big pharma might come in, big pharma and big biotech is not coming into cell therapy until someone demonstrates clinical success. This is probably true of VC as well. There are exceptions, but the big, sustainable dollars are all standing back on the sidelines until such time as someone demonstrates in the clinic that this stuff works
- **Q (Ed Penhoet):** And that means a successful Phase III clinical trial in your view?
  - **A (Martin McGlynn):** No. There are a lot of failures in Phase III.

- **Q (Ed Penhoet):** How big is that barrier? What will constitute enough proof?
  - **A (Martin McGlynn):** Let's call it a Phase IIa - a demonstration that you can safely intervene in a patient population and that the agent is doing what it's intended in that population. If you want to go off and do dose ranging studies or do multi-center global trials that not the place for CIRM. That's the place for VC, big biotech, and big pharma.
- **A (Ed Penhoet, for Tom Okarma):** You made the strongest argument for funding clinical trials. Would you agree with that?
  - **A (Tom Okarma):** I hesitate to advise how far along the clinical continuum you should put your money. Our business is to design good Phase I and Phase II studies. For mainline diseases where there are clear outcomes, a well designed Phase I/II is as far as you need to go.
  - **A (Sumit Chanda):** I want to comment on the rush to clinical trials. A negative outcome on clinical trials could have a detrimental effect on the field; I bring in the parallel of gene therapy. People put the cart before the horse and that had a chilling effect on the field and set it back. It's important to realize that an unfavorable outcome could set the field back. It might be worth considering figuring out the biology before getting things into the clinic.
  - **A (Martin McGlynn):** Clinical experimentation is by nature high-risk and the prospect for failure is higher than for success. I fully identify with the concern that a rush into the clinic and an early disaster could have a chilling effect, so I endorse the sentiment. But one has to balance the appetite of patients for risk, the money available, and ability to get job done in a period acceptable to the investors. It is a balancing act.
    - We have the FDA and we go through tough reviews and also go through reviews at the hands of IRB. There are checks and balances, but pioneering new technology and a new field are endeavors that are inherently risky, and more so than developing a small molecule and even proteins.

- **Q (Zach Hall, for Tom Okarma):** Could you share with us what you had to do to prove the safety of your cells?
  - **A (Tom Okarma):** Upon our first interaction with FDA, we were surprised about its level of knowledge of the field. The integration between FDA and NIH is seamless. They have a high-level understanding of the field. They have a lot of experience with different types of cells, so there is a track record and they understand what is a flag and what is not.
    - The bar is very high - they recognize that first [embryonic stem cell derived therapy] in man has baggage and they are adamant to keep the bar as high as it needs to be to satisfy all questions and we came in with the same attitude. But they blessed the breadth of our preclinical plan, which reduces our risk of failure {not getting an approval to go into people] when we file the IND.
    - We came away with a great deal of respect for the agency. They appreciate what scalability means. When we enter the clinic, neither the agency nor we will feel we failed to uncover any stone that had toxicology under it. The issue is safety and reliable production and they will not and should not compromise on that.

- Much of the talk about rushing into the clinic comes from people not experienced in clinical trials design or whose cells have not held up under FDA scrutiny. They want to help you and want this to work.

- **A (Ed Penhoet, for Ed Baetge):** One of your slides mentioned the FDA as an issue to deal with. Have they been cooperative? What would be a potential role for CIRM in helping deal with FDA issues?
  - **A (Edward Baetge):** I don't have a different view. They want safe ways to develop cell therapies and they want to work with us. We have to continue to educate them. It's one thing to have stem cell themselves. It's another to make a difficult product, so there needs to be various safety steps run and you have to work with and have a dialogue with the FDA along the process.
    - If the CIRM can bring together a consortium of experts to educate the FDA on various aspects of stem cell technology, to bring to light assay systems for quality control, and to further educate them as to the benefits of these assays and the safety studies that have resulted, this would help the FDA be a better sounding board and be able to bring us along in a more rapid way.
  - **A (Ann Hanham):** We talked about giving grants and there are different ways to do this.
    - When I was with a small biotech, we received an orphan grant. When we went to the FDA, we had two representatives from the granting body with us. Their money was in play, and the Office of Orphan Grants facilitated the process and gained a lot of insight. They were at the table and were useful advocates because when we hit a "hiccup" in the clinical trials, since they were part of the FDA, they gave us more insight. They acted as a sounding board and another independent group that could talk to the FDA.
    - I would suggest that CIRM might want to create some regulatory expertise to help new companies going forward to guide them. It's also a way for you to make sure your money is well spent because you're sitting at the table, hearing the questions, and understanding what the companies are trying to do. You can pass that to other companies you are trying to facilitate. You will gain experience.

- **Q (Ed Penhoet):** There is a question of dialogue with industry. If CIRM were going to set up an industry advisory board would you be willing to serve? Do you have other suggestions about how you might add input? How can you help us sort through the reality of the number of issues we will have to deal with? Would you find this useful or interesting? How will we get meaningful input from industry into our grant process?
  - **A (Martin McGlynn):** The difficulty there is conflict of interest.
  - **A (Tom Okarma):** Get the very best people on the planet you can find and if they live in California, too bad. Having people who don't have experience in growing these cells simply because they come from outside California isn't the way to go. Identify the people and if they have a conflict of interest, send your lawyers on a mission to insulate that. Pick the very best people and create a vehicle to allow them to contribute openly and transparently.

- **A (Bruce Cohen):** It may be useful to follow NIH practice and make awarding of grants to private companies separate. What the NIH does through SBIR is separate and you don't compete with academia.

- **Q (Zach Hall):** Why not compete?
  - **A (Bruce Cohen):** You would probably be looking for different things. Plus the peer review system is biased toward the CVs of investigators. When an NIH scores a grant based on the quality of the investigators, companies always lose because they don't have Nobel Prize winners sitting around doing research.
    - So the NIH decided to score them separately and they have specific rules they apply to private enterprise they wouldn't apply to an institution. It works well because you have a study section deciding how to allocate among private companies rather than between Stanford and Geron. I know we don't want CIRM to follow all the vagaries of NIH, but that system seems to be working fairly well.
    - One of the other issues when you look at private companies is you have to distinguish between small grants and big grants. Companies on this panel wouldn't be interested in small grants because the overhead makes it uneconomical. A small start up coming out of academia won't have this problem. You have to be careful of that, which is different from how you deal with academia.
- **Q (Ed Penhoet):** Have grants you have received from the public been helpful?
  - **A (Tom Okarma):** With few expectations, most of what we've done was on our own nickel. On the cancer side of the company, we have had NCI funding for eight years, and that gave a different imprimatur on the work. We would love you guys to fund a bunch of academic collaborators.
  - **A (Sumit Chanda):** We've been applying for RO1 money and the combination we've found successful is paring our technical know-how with academics. These have been fairly well received by the review committee because you have the Burnham name for example and our technical expertise. CIRM might want to consider joint applications with milestones built in.
  - **A (Edward Baetge):** We've gotten a number of grants from the JDRF and NIH, and all have been very useful. You might be able to break up the types of grants you give and allow companies and academics to compete with one another. You can also have development grants where you develop a process leading into the clinic and you might have clinical grants; everybody should be allowed to apply for any of those grants. There's a bit of basic science going on in for-profits. Most of the expertise working with ESCs resides in companies. There should be an opportunity to apply for development and clinical grants.
- **Q (Ed Penhoet):** So the idea is not to have a special category for industry grants but to compete on the basis of the science?
  - **A (Alan Smith):** The NIH SBIR program still has some issues. If you look at a typical study section reviewing grants related to business proposals it's still 90% academicians in its composition. The NIH begs industrial people to participate in the review process and is unable to get sufficient participants. It's a bit of an imperfect system. There's also the STTR program, which requires coallaboration between academia and industry which is another mechanism that might be considered.

- **A (Edward Baetge):** We were interested in government grants because we were working on privately derived lines so we weren't able to get funding. If we could get funding from the government for privately derived lines we would pursue such funding, because those are the lines we want to work with. You can get surrogates but it makes more sense to work with the actual cells.

- **Q (Sumit Chanda):** Is it within CIRM's purview to address IP issues?
  - **A (Ed Penhoet):** Probably not. We are a granting agency. Public opinion has a strong role to play in what people do with licensing their patents. At Chiron we were criticized for not providing licensing broadly for people to do drug development. We decided it wasn't responsible for us to retain all those licenses so we licensed them out to many companies, in part due to public pressure. It was the right thing to do and we were happy to do it. This is by definition a messy business, and we don't have the funds to take on this issue. We're interested observers and will discuss this issue but it's not within our mandate to weigh into the patent area. We're not infringing on anyone's patents.
  - **A (Martin McGlynn):** If you step back and question what it is CIRM is trying to accomplish, if when it's done and there's no more money to come from CIRM, what is it you're looking to have accomplished. You have to be like Solomon as it relates to IP.
    - On the one hand, the academic centers need to have a dog in the fight and have a return on their successes. That's part of building sustainable centers of excellence and the revenue that come out of that will help.
    - By the same token, when you come from the for profit sector, you don't want to kill the goose that lays the golden egg. CIRM should also strive for a sustainable, vibrant for-profit sector. They're not going to be able to attract private money if there isn't a strong IP component.
    - At the end of the day, everyone has to get their pound of flesh and you have to be like Solomon. IP and patents only become relevant if what you're trying to protect has value. We have to give this technology a chance and provide the money in this "funding valley of death" where the money isn't available now. It only becomes valuable if translators find a way to extract value and bring therapies to the marketplace.

- **Q (Ed Penhoet):** You're here because you have successfully raised money and many of you have said if you get thorough a successful Phase II you can get big pharma money. What kinds of rejection do you run into in your financing and are we being over optimistic about the VC community?
    - **A (Bruce Cohen):** The financial community is waiting for one success and that hasn't yet happened. We are relatively close to success as an industry and that's a big difference. In our case, we're in the clinic in Phase I and II, so we and others are pretty close to having gone reasonably close to near end of line.
    - CIRM has a lot to do with whether VC and big pharma come into this space. When we were raising money, there was excitement when Proposition 71 passed. There was a presumption among some investors that the availability of public money would let us be more efficient with the use or private money. That evaporated with the lawsuits.

- There is still excitement that someone will share the risk. That's one of the answers CIRM can offer. I was with another company that raised $55M on the basis of a $6M DARPA grant. That leverage is real.
- My own view is that the private equity and some public equity markets are more interested in this space than private VC. The existence of even modest public support has a huge impact there.

- **Q (Ed Penhoet):** One specific aim of Proposition 71 was to grow biotech in California. Some have brought up the issue of whether we should fund start-ups. We do have the capability under Proposition 71 to make loans. Does it make sense to think about a program to assist in company formation via loans that match the VC portion or loans for companies that are somewhat further along? It is a messy area to delve into?
  - **A (Martin McGlynn):** I think of leveragability.
    - To the extent the money can be directed to an existing entity where other dollars have gone in, I think that make business sense. Focus in on what you can leverage and what's already there. When you do make the grant, will the receiving party have not just the expertise to deliver but do they also have the critical mass and financial muscle to see the job through. No one in the for-profit sector expects CIRM to pick up the entire tab.
    - Secondly, when it comes to spinning out companies from academia, you have to be careful because there is not a lot of leveragability in the first dollars.
  - **A (Alan Smith):** We had a company tell us we're afraid to do this, but we're afraid not to do this. There is enormous investor interest in leveraging resources and CIRM can play a role. There's an assumption this will be a profitable business that will benefit humanity but it's a psychological war. It's that fear factor. This political football stem cell research has become has scared some investors. Clarifying the atmosphere and talking about the role of industry can help free up a lot of this investment capital.
  - **A (Edward Baetge):** The CSCN [Canadian Stem Cell Network] brought in people with experience in industry to look at the technology that came out of the Universities and make recommendations about which technologies might have promise to start a commercial operation around. Maybe CIRM can use a model such as that. They brought together a panel of experts to examine the technologies coming out of the academic world or that industry couldn't develop.

Final Comments

- **A (Ann Hanham):** I think VC will pick up these programs when you're near the clinic. We'll invest before proof of concept.
  - The concerns are what is your commercialization strategy and how will you charge, manufacture, distribute - those sorts of questions are fundamental. Once we have one

success, it will carve the road for us. The VC is a lot more reluctant to invest in early stages. VC's can no longer make money by doing that.

- I would counsel CIRM to focus on that translational step. Put the money where it's most needed. You might want to create grants for development in the pre-clinical stages and not weight as much money in the clinical stage. The capital will be there if the data are good.

- **A (Edward Baetge):** I agree with Ann. CIRM needs to be supportive along all stages of development. In a company where you have a focus toward making a product, especially a complex cell product like stem cells, you need to understand that complexity through all stages leading into the clinic and development and scale-up. You can't get to the translational part unless you understand the fundamentals of what you're trying to translate.

- **A (Michael West):** There is an opportunity for CIRM to fund basic fundamental tools that will be used in industry. Funding those at the beginning would prevent a lot of redundancy. Second, with the collaborations CIRM is trying to aid, not just with academic researchers, these funds would not just go into obscure scientific studies that would not be translated into therapies. With help of industry, signals like that would trigger a Niagara Falls of investment to help us change the field.

- **A (Alan Smith):** If I could add one or two suggestions - it's critically important for CIRM to build a resource base for people who are grant applicants or recipients that allows them to tap into expertise that already exists rather than putting them into position of having to find their own way or recreate things from scratch. That may be related to regulations, personnel, manufacturing, or preclinical work. That would be money well spent if those resources could be empanelled with the state for all you have an investment to draw upon.
- **A (Tom Okarma):** I really think the honeymoon is over and you should start planning for succession when the NIH gets back on the ball field. The worst part of the Bush decree is the invisible stranglehold it has placed on NIH dollars. I would urge you to make your planning for a short term splash and then have a contingency plan for when the NIH comes back on the field.

- **A (Martin McGlynn):** I would ask CIRM to clearly define success. Publish a road map to achieve those successes. I would offer two thoughts as to what you might deem success. I look to the notion of what happens when the party is over. I would look for two things at the end of the day:
  - There would be Centers of Excellence in the state with a critical mass of world-class talent and a proven track record or diversity at each center in its chosen field of endeavor
  - You would have created a vibrant, sustainable for-profit sector that focuses on applied research and the translation of discoveries into use for the benefit of mankind. Those entities by then should be fundable by more traditional sources of funds.
  - The cycle time for the work that needs to be done is twice what VCs wants to see, so get out of blocks quickly, leverage your dollars, and make sure you are the first money to accomplish your mission.

- **A (Bruce Cohen):** Think about stakeholders.
  - First, the taxpayer needs to see a return on this investment you need to find a way for them to see company and job creation, which will come sooner than cures for some of the debilitating disease we are trying to address. So we need to encourage capital to come in to cerate new businesses and let exiting businesses get bigger.
  - Second, you also need to get therapies into the clinic so voters will see a potential change in their lives. You need to accelerate the process by which adult and embryonic stem cells therapies find their way to people. Even if it's an inconclusive Phase I trial, you'll be happy someone with state funding is trying to accelerate the process.
  - It's those two things that will make people who voted for this appreciate what's been done on their behalf.

- **A (Sumit Chanda):** I would echo most of the sentiments but I would add in addition to promoting an environment where investors are willing to invest and bring new science in the field, CIRM should lay a foundation where both academia and companies can benefit. Ideas have been presented to build core facilities, but it doesn't make sense to me to have redundant infrastructure between San Diego and Los Angeles and so on. If these core facilities can come on line a lot of biotechs that wouldn't otherwise have access can have access and that would facilitate research in the area.

Open Discussion

- **Q (Jeff Sheehy):** I had two questions.
  - Does it make sense to put an overlay of what the mix should be for funding of for profit and non-profits? There was strong assumption that most funding would go to non-for profit industries. Does it make sense to set a target mix so we really make it our goal to fund the for-profit sector? Will that help us get to the clinic faster?
  - What would an RFA for looking at those viable drug candidates we discussed look like and what would be the cost? Does it make sense to try and move these product candidates and have an RFA out within the year?
    - **A (Michael West):** An additional reason for us to consider that CIRM fund company-based clinical trails is the risk factors we identified with the case of gene therapy. This hurt the field. Given the nature of the ESC field, a major failure in clinical trials could have a worse impact. So an additional reason for CIRM to fund such trials is to have an additional oversight mechanism. There is always a risk that biotech, in the race to the clinic could miss some important safety standard so an additional reason to fund the field would be to help prevent that.
    - **A (Sumit Chanda):** Funding should be activity based - what can you do and how well can you do it. Put out the RFA and if people can do the work and have the resources and expertise let them all compete for the same money.
    - **A (Bruce Cohen):** It depends on the disease, but from my experience we have convincing data in mouse models that we can essentially cure a handful of

autoimmune diseases. We don't have the resources. To treat 10 patients on an exploratory trial would cost $2M. We're in the adult stem cell business so we have less complicated drug restrictions. If you're spending $2M a month as your burn, that's a lot of money to you but not to the state. We all have things in our portfolio that could be in the clinic faster for a small amount of money. The state can have a say in what diseases it wants to treat. We're not talking about significant amounts of money.

- **A (Ann Hanham):** This goes back to CIRM's mission. If it's to fund academia, that wasn't my sense when Proposition 71 came out - it was to find cures and create jobs and find a financially responsible way to return funds to the state. If your money is just going into academia, you're missing part of the goal. You don't just fund academia, you fund cures. You need to fund some research to bolster your understanding. If you want to push cures out there's a whole other science you need to push out.
- **A (Martin McGlynn):** I would go back to your success criteria and what your map looks like. Money should be directed to pursue those activities. As to the second question, the grant applications from my company would be disease, target, and activity specific and milestone measured. As for the amount, it's in the $3-5M range.

- **Q (Bob Klein):** Bruce and Martin mentioned leveraging our dollars. In doing that it's important that the structure for our funds not create a transaction burden. We don't want to add to the complexity. What are your thoughts about moving into a model where we're using participating debt? It could be simple, definable, straightforward, and at a low transaction cost.
  - **A (Martin McGlynn):** At face value, that sounds attractive but the question we would have is how the debt is repaid or forgiven and would we lose our company if we failed to measure up to those requirements. Milestone driven forgiveness could be one way, but anything that stays away from punitive royalty rates and doesn't keep other investors out of the game I would favor.
  - **A (Tom Okarma):** Debt financing is available and it's generally advised to stay away from it. I'd be wary about the impact that might have on companies to be rather than companies that are.
  - **A (Bruce Cohen):** Debt would accelerate some of our development and would not attract equity. It might not have the affect you want.
  - **A (Bob Klien):** Investor might see it as validation
  - **A (Martin McGlynn):** Equity participation would be number one on our list but there are restrictions on CIRM. Debt has always come up in our financing discussion but it's not terribly toxic. I wouldn't rule that possibility out and would welcome knowing more about terms and conditions.

- **Q (Don Reed):** Would a stem cell repository be valuable to you?
  - **A (Tom Okarma):** No. We have about 17 lines of our own and I would offer us as a state of the art comparative, evaluative facility for looking at the pros and cons of those lines. The notion of a central repository, of putting all the lines there and having SOPs to characterize them, and making them freely available is one that is being underused in the

UK. They have their own lines and are not using them. It wouldn't be useful to us but possibly to others in the field.

- **A (Michael West):** One way it makes sense is in the concept of engineering the histocompatibility genes. Because hESCs will replicate without limit, one can imagine taking the HLA types and knocking out the Class I antigens and dropping in by gene targeting the common alleles that cause the most rigorous rejection. Making a bank of cells that are manufactured under GMP that have the common antigens of the people of California could make sense. That's a large scale project to capture the common antigens and the rare HLA types. A commercial entity would not fill out that list for most of the population.
- **A (Edward Baetge):** It would be useful to companies just entering the field if they were made according to GMP standards so that they were almost clinically ready. That would save a start up company a lot of money and time.

➢ **Q (Ed Penhoet):** Do we have access to the UK lines?

- **A (Martin McGlynn):** In theory, you have to get them out of the UK, you have to get in line for them, and there aren't that many. The greatest advantage to ESC banks would be to the academic community and rather than creating banks for GMP I would see far better leverage and use in the academic setting for non-GMP cell lines that carry the disease traits that can be studied in the academic setting

➢ **Q (John Simpson):** The IP task force is close to completing standard not-for-profit IP rules. Do you think IP regulations for grants, loans, and so on to commercial entities can be established as one across the broad policy or do we need to do separate deals with each grant or loan and make the IP rules subject to negotiation?

- **A (Martin McGlynn):** You will have to operate within CIRM policy but allow sufficient room for customization on a case by case basis.
- **A (Bruce Cohen):** The state of California has a lot of experience through the University of California, which has a general policy that is administered on a case by case basis. Technology is licensed and the state gets a royalty but there's not a hard and fast rule. You negotiate based on who is at the table. We can learn a lot there and UC is reputed to be one of the toughest licensing offices in the world.

➢ **Q (Janet Wright, for Martin McGlynn):** One thing I've learned is that getting to cures and therapies, reducing healthcare costs, and creating jobs is a collaborative effort. Please give us some more thoughts on Centers of Excellence?

- **A (Martin McGlynn):** What I was referring to was the notion that you don't want to build in redundancy throughout the state. Once you've made the determination as to the critical areas of interest (and a relatively quick evaluation will reveal existing centers where the infrastructure, personnel, labs, and track records exist) and build on those. To the extent there are holes by all means, on a *de novo* basis, on adjunct basis or as a stand alone, create what missing, but leverage what's there.
  - For example, there's a significant presence at Stanford with regard to neuroscience and cancer biology. I would suggest there are a couple of other places that have demonstrated credentials and have critical mass. It good to have completion provided you have critical mass. So avoid redundancy, put money into assets that will have a

dynamic effect of having scientists in close proximity. Allow for competition but not redundancy.

- **A (Ann Hanham):** At the end of the ten years you want to know if the experiment was a success and having Centers of Excellence is important. It's important to set out goals and have something in hand that's tangible and turn back to taxpayers and say through this initiative we created these centers, we had trials in these areas, we created these jobs, and IP was created in these areas. You will have tangible assets to say this is what we accomplished. Leverage what you have and add to it and you'll have something very tangible to show to taxpayers.