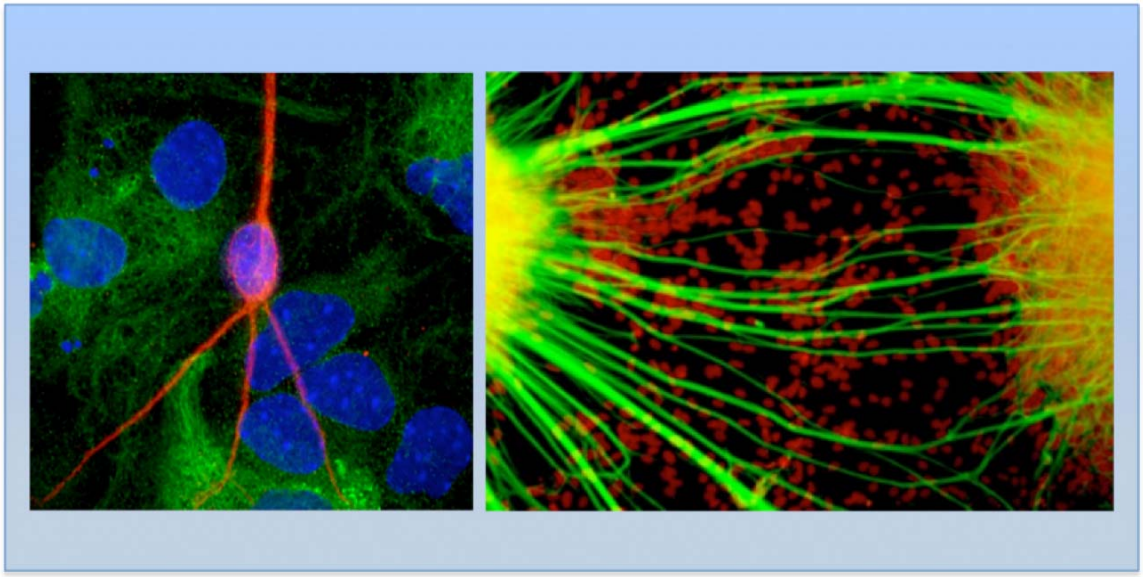
CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Preparing for the Clinic: Policy Considerations for the Use of Cell Based Therapies



Summary of the Clinical Trials Workshop

Presented at the 2009 Annual Meeting of the

Medical Accountability Standards Working Group to
The California Institute for Regenerative Medicine

February 17-18, 2009
Los Angeles, California

Contents

Photo Credits:

Left cover image of functional neuron (red) growing above cells nucleus, courtesy Paul Knoepfler PhD UC Davis

Right cover image of two neurospheres, courtesy of Fred Gage PhD and Carol Marchetto PhD the Salk Institute

Summary of the Clinical Trials Workshop

Introduction

CIRM's mission is to support and advance stem cell research and regenerative medicine under the highest ethical and medical standard for the discovery and development of therapies and cures for chronic disease and injury A major operational goal for the Institute is to accelerate progress towards translational research, including pre-clinical and clinical research.

The Institute's Medical Accountability Standards Working Group charge includes recommending to the ICOC safe and ethical procedures for clinical research. Commensurate with this charge, the Working Group convened a public Clinical Trials Workshop for its 2009 annual meeting. The workshop was designed to provide participants with an understanding of:

- The current regulatory and policy environment for developing human cell therapies;
- The role of clinical trials for the development of new therapies;
- How ethical concerns are addressed in the oversight of clinical trials and consider emerging issues specific to stem-cell-based therapies;
- How institutions involved in clinical trials address regulatory policy issues.

In addition, the Working Group and workshop participants considered issues CIRM should consider in the context of translational and clinical research. This report summarizes information related to the goals above, describes issues that emerged from the workshop deliberations, and provides supplementary analysis of specific issues identified by the Working Group.

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

ANNUAL MEETING OF
THE SCIENTIFIC AND MEDICAL ACCOUNTABILITY STANDARDS WORKING GROUP (SWG) OF THE CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

AGENDA ITEM #4
SWG CLINICAL TRIALS WORKSHOP

DATE: Tuesday, February 17, 2009 – 1:00pm to 6:00pm (Estimated)
Wednesday, February 18, 2009 – 9:00am to 3:00pm (Estimated)

LOCATION: Luxe Hotel, 11461 W Sunset Blvd., Los Angeles, CA 90049

This workshop is presented as part of the CIRM Medical and Ethical Standards Working Group Annual Meeting for 2009. The workshop is incorporated into the full meeting agenda, which is posted at http://www.cirm.ca.gov/workgroups/stds.asp. The workshop goals and program are identified below.

WORKSHOP GOALS:

- Describe the regulatory policy context for developing human cell therapies;
- Understand the role of clinical trials in the context of developing new therapies;
- Understand how ethical considerations are addressed in the oversight of clinical trials and consider stem-cell specific issues;
- Understand how institutions involved in clinical trials address regulatory policy issues;
- Describe guidance and regulatory activities related to stem cell clinical trials; and
- Consider issues for further consideration by CIRM or the SWG.

PROGRAM SEGMENTS:

Segment 1: Introductions and statement of the scientific need for clinical trials.

Segment 2: The process of developing cell-based therapies: An overview regulatory policy context.

Segment 3: The role of clinical trials and fundamental design issues.

Segment 4: Issues for developing cell therapies and implementing cell-based clinical trials.

Segment 5: Ethical considerations in clinical trials generally.

Segment 6: *ISSCR Guidelines for Clinical Trials*.

Segment 7: Institutional approach to implementing trials in the current regulatory/policy environment.

Segment 1: The Need for Clinical Trials

Marie Csete MD

Summary:

We are continuing to see rapid progression in the field. 2008 marked the tenth anniversary of human embryonic stem cells (hESC) and in 2009 the FDA approved the first Investigational New Drug Application for clinical testing of cells derived from hESCs, it is useful to consider our experience from bone marrow transplantation. It has been applied to a wide variety of disease in some cases with good forethought and preliminary research and in some cases there was no theoretical basis for transplantation. A similar pattern is occurring with adult stem cell transplantation. A major concern for CIRM and the research community should be the use of seemingly safe autologous cell therapies for disease where there is limited hope of benefit and potential for harm. Similarly, the transplantation of non-autologuous adult stem cells for conditions where there is no strong experimental basis for efficacy is a source of risk and cause for concern.

CIRM has a unique opportunity and responsibility through its Disease Team program to advance the safe and effective application of novel cell therapies. CIRM anticipates that both cells and products derived from hESCs and iPS cells will be potential candidates for clinical application. The progress towards the clinic raises many questions and creates challenges. Many of these questions have not been resolved for cell therapies in general and especially for pluripotent-derived stem cells. The challenge for CIRM and the field in general will be to determine the degree of completeness of data required to determine the risk verses benefits of cell therapies.

Segment 2: Regulatory & Policy Framework for Cell-based Therapies

R. Alta Charo JD Link to Full Presentation
Elizabeth Read, MD Link to Full Presentation

Summary:

Cell-based therapies are generally regulated under the Food Drug and Cosmetic Act law as "biologics." They may be regulated as devices or drugs depending upon their primary mode of action. Biologics are also regulated under the Public Health Service Act primarily for control of disease transmission. To develop a cell-based therapy the following steps would be required:

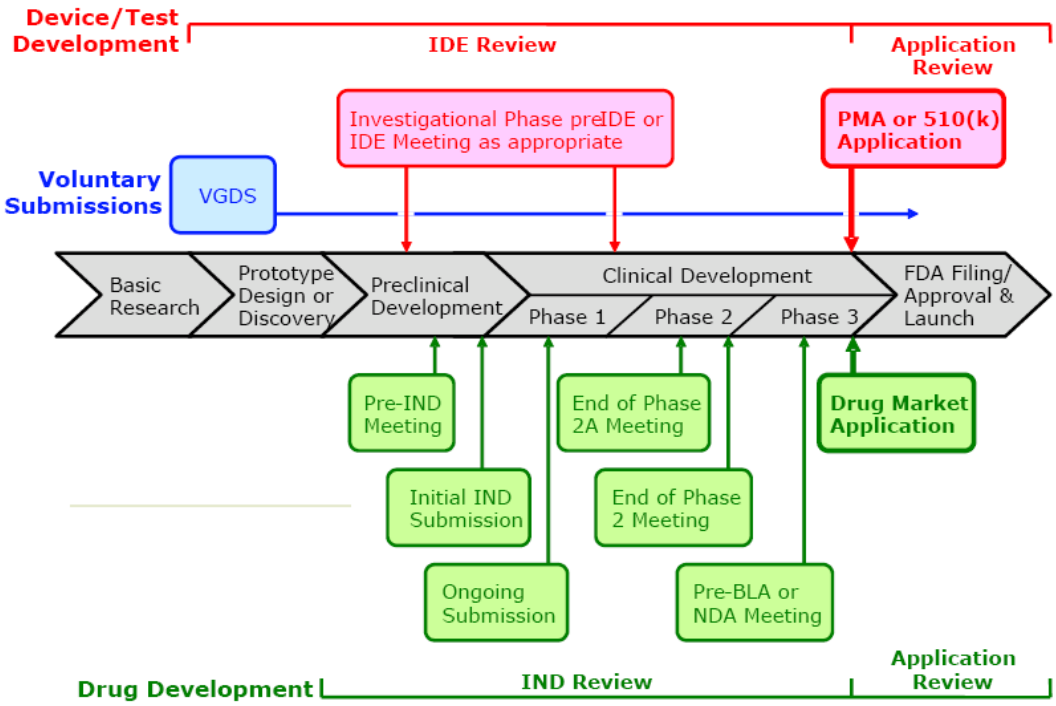
- Derive or import a clinical grade line consistent with FDA good laboratory practice rules
- Preclinical laboratory work
- Preclinical animal work
- Obtain Investigational New Drug Application (IND) or Investigational Device Exemption (IDE) from FDA
- Obtain institutional review board (IRB) approval to recruit subjects
- Recruit subjects into Phase 1,2 and 3 trials
- Submit a Biologics Licensing Application (BLA), for a cell therapy, or a 510(k) pre-marketing notification for devices (PMN) and received approval to market from FDA
- Implement risk management plan for post-market surveillance

All clinical research involving drugs, devices and biological products is subject to FDA regulations. FDA has developed draft guidance(s) for safely obtaining and processing tissue. The practice includes a system to permit tracking from cell lines or tissue back to the donor(s). There is guidance under the FDA's Good Clinical Practice Program to coordinate policies on human subjects research. The FDA's Center for Biologics Evaluation and Research (CBER) is the lead center for regulation of cell therapies.

For clinical trials, steps must be taken under HIPAA and the Common Rule to ensure the donor identities cannot be readily ascertained. Institutional Animal Care and Use Committees review animal work to ensure proper care. The Common Rule, incorporated into the CIRM regulations, requires an IRB to consider risk/possible benefit of a proposed protocol. The IRB must also approve the consent process and recruitment plan. Phase 1 studies are primarily safety studies with small numbers of subjects. The FDA does have compassionate use rules for access to drugs and devices as early as Phase 2, which test for preliminary signs of efficacy. Phase 3 trials expand to test benefits and recruit larger numbers of patients. "Parallel track" was developed

to offer investigational interventions to those not able to enroll in Phase 3. Approval to market may be conditioned on additional trials or enhanced surveillance post marketing.

Figure1: General Pathway for Drug/Device Development



Source: FDA http://www.fda.gov/Cder/genomics/pharmacoconceptfn.pdf

Issues for Consideration

- With the exception of bone marrow and cord blood transplantations, there is limited experience about the risks and benefits of cell-based interventions. It may be helpful to explore with data repositories the possibility of aggregating outcome data related to cell-based interventions from existing health registries.
- Participant literacy and comprehension can present challenges to truly informed consent (see segment 7). Consider supporting the understanding and dissemination of best practices for developing easily understood explanatory (audio and visual included) materials for recruitment and consent.
- Compassionate use and parallel track protocols may present challenges for cell-based therapies that cannot be easily “scaled-up.” CIRM should monitor FDA and manufactures efforts to manage patient expectations and organizing compassionate use protocols.
- More generally CIRM should serve as a “broker” to support exchange of information between regulatory authorities and grantees. The

objective should be to support regulatory compliance without compromising propriety information.

Segment 3: The Role of Clinical Trails and Design Issues

Bruce Dobkin, MD

Link to Full Presentation
Link to Tutorial

Summary:

Randomized clinical trials are needed for the development of interventions involving stem cell or differentiated cells. Animal models are limited in their predictive value for humans.

Trials serve to address scientific questions regarding the safety and efficacy of an intervention. There are a number of reasons, unrelated to the specific therapy that may explain improvement in a patient, including:

- Post-intervention physical therapy and training;
- Spontaneous regeneration processes and expression of residual pathways (can be a problem in protocols where treatment is immediately proximate to injury);
- Psychological responses to treatment (our minds are wired to hope and believe).

People with disease fluctuate with regard to strength, mobility and cognitive function. This variance creates a wide range of "noise." Requires that we develop test systems that can overcome this noise to determine the efficacy of the intervention. Generally the design of a trial requires:

- Multiple sites doing the same intervention;
- Patients matched with controls (currently with disease) for the state of their disease; may need to "equalize" patients with therapy to utilize latent capacity so it does not appear future improvement is the result of intervention;
- Therapy supported with rehabilitation with trained personnel;
- Control group where patient and caregivers believe the intervention has been administered (may require "sham" surgery);
- Outcome measures that are specific to the therapy.

Issues for Consideration

- Randomized trials present ethical challenges with regard to control groups, placebo and sham surgery. CIRM should support public education on the conduct of such trails.

- ▷ CIRM should consider how collaborative funding of clinical initiatives can create shared objectives, reduce IP barriers and align institutional goals.

Summary of the Clinical Trials Workshop

Segment 4: Issues and Experience From Cell-Based Trials

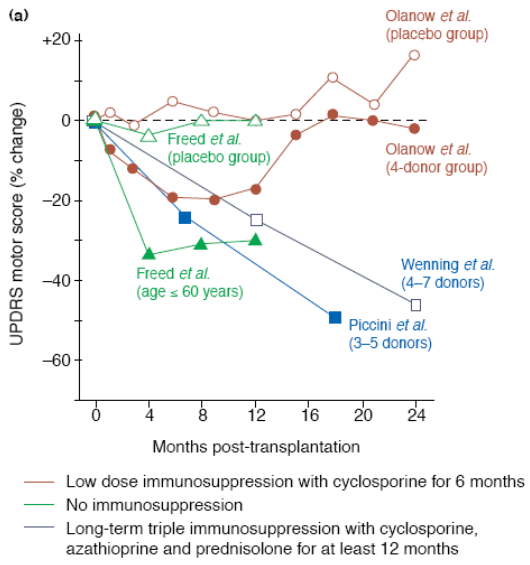
Marie Csete, MD Link to Full Presentation

Summary:

Parkinson's disease (PD) is one example where NIH funded cell based trials. This session describes experience with well-designed historic trials. One study was a randomized double blind control trial involved 40 patients receiving cultured fetal cells or sham surgery. The trial showed mixed results; some treated patients under 60 reported benefit at one year whereas treated patients over 60 indicated that they did not get better. Subsequently, several years out, 5 transplant patients developed dyskinesias. A second trial demonstrated no long-term difference between groups.

A major challenge in PD trials is trying to determine if patients are getting better. Timing is a critical issue. This point is illustrated in the diagram below where improvement is reported 4-12 months after treatment, but this difference is no longer observed after about one year.

Figure2: Functional recovery after neural transplantation in Parkinson's disease (PD), source Winkler et. al.



This research suggests a number of variables that need to be optimized including:

- Cell source (fetal, embryonic, whole tissue)
- Cell numbers
- Cell preparation and storage
- Cell potency assays
- Effect in multiple animal models (2 species)
- Disease state of patients, other patient factors
- Immunosupression, other drugs
- Surgical site, technique, placement

Longer-term autopsy results have emerged from these trials suggesting that the grafts did survive but disease pathology was present in these cells. Other

findings from autopsy indicated that graft neurons were not only dopaminergic and grafting in one location doesn't improve disease in other brain areas

Issues for Consideration

CIRM will be embarking on a new era with a new cell type. There will need to be considerable pre-clinical research to evaluate safety, function and potency. PD has specific challenges because there is not a good animal model for the disease in humans. There are general lessons we can take from the PD experience, including:

- There are increasing demands from patient advocates and patients with end-stage disease. There are diseases that are fatal in the short term, and they may be candidates for trials without controls where historical data are utilized to evaluate efficacy. One example is ALS.

- Require maximum transparency and results dissemination with for CIRM-supported trials. This effort should include pursuing opportunities for long-term follow up with patients and incorporation of historic data.

- Initial studies will likely involve small numbers of patients and they will not provide definitive efficacy but they should provide "clues" for addressing variables and issues that need to be optimized. Capturing these clues will be critical for further development.

- Trials should consider narrowly defined patient populations to enable "like-like" comparisons and make results more analyzable. Comparison of intervention and control patients matched for a "healthier" disease state may be particularly helpful for detecting modest effects that are not completely curative but improve patient health. In general, trials should be designed to detect clinically relevant improvement in endpoint(s).

Segment 5: Ethical Considerations in Clinical Trials

Michael Kalichman, MD Link to Full Presentation

Summary:

The use of cell-based therapies is distinct from drugs because the intervention may not be readily terminated or reversed. For cell-based interventions for the central nervous system, some have argued for an extensive battery of tests for any possible problem Kalichman and Schwartz suggest data from pre-clinical work or clinical trials should serve as the basis for considering whether such testing is likely to be useful or yield results.[1] However, there should be a number of approaches at the pre-clinical and trial design stage to advance the safety of subsequent trials.

Issues for Consideration

1. Pre-clinical animal research: given the intervention may not be readily terminated or reversed, consider how we can go beyond existing standards for safety and efficacy in animal research;
2. Mechanistic explanations: develop a better sense of the mechanisms regarding the plausible mode of therapeutic actions and / or toxicity before initiating a trial;
3. Disease candidates: restricting initial trials to diseases and disorders with high levels of mortality and morbidity could help balance the unknown risks against the known harms of the particular illness;
4. Robust consent extended to all parties: Prospective research subjects, prospective patients, the families of patients and subjects, treating physicians, *and the researchers conducting the clinical trials* should all be alerted to the fact that this is uncharted territory and that significant anomalies of any kind (not just those we consider likely) should be reported.
5. Anecdotal information: Observations of events of concern should be accumulated during clinical trials and subsequently in clinical practice and evidence-based testing.
6. The "meta" challenge of balancing risk and benefits: *Ignorance of special risks* of these interventions risks serious setbacks to the field of research. *Placing excessive hurdles* in front of such research risks impeding progress.

[1] This commentary will appear in a forthcoming edition of the American Journal of Bioethics http://www.bioethics.net/journal/.

In moving forward, CIRM should recognize that existing institutional review committees have structure, expertise, and authority to address many of the proposed recommendations above. However, there may need for a specific charge in research applications or by regulations to ensure extra steps are taken on the recommendations above.

Segment 6: ISSCR Guidelines for Clinical Trials

Insoo Hyun, Ph.D.

Summary:

Drafting the *ISSCR Guidelines* was a 13-month process with 30 committee members from 13 different countries. There is a difficult balance between focusing on key issues specific to stem cell science while avoiding "stem cell exceptionalism." There are clearly issues in clinical translation that apply to trials broadly not just those involving cell therapy. The group focused on agreeing on a general set of principals for addressing stem cell specific issues in translational and clinical research. The document contains 40 recommendations.

A major topic for the committee was the application of cell treatments outside the context of a clinical trail. The committee did acknowledge there might be opportunities for use of cell treatments outside the clinical trial context ("medical innovation") and information gained could be valuable to the field. Members of the Standards Working Group expressed general discomfort with such application, and there was a suggestion that CIRM take a position on the issue.

In the context of human subjects / oversight committee review, the committee felt there should be a explicit mandate for stem cell specific expertise in the review process.

Issues for Consideration

- For pre-clinical studies there may not be animal models for the disease in humans, in such cases it may be acceptable to proceed without an animal model;
- There should be testing for interactions with drugs that the patient may be expected to take during a trial;
- Informed consent considerations:
  - Who gets to perform the consent (e.g. someone outside the research team)
  - What are the requirements for surrogates consenting
- Clear timely plan for adverse event reporting
- Plan for treating adverse events
- Reporting could emerge from an treatment team that is not part of the research team
- How long should the individual be followed and how do you attribute outcomes to the cell based therapy;

- Encouraged the development of policies mechanisms to support availability of cell-based therapies to public.
- There are federal funds available to expand research comparing the effectiveness of medical treatments. This may be an opportunity to evaluate cell-based therapies.
- CIRM is subject to FDA rules and laws, so it may be legally impossible to utilize cell therapies in the same manner that is being used internationally.

Summary of the Clinical Trials Workshop

Segment 7: Institutional Approach to Implementing Trials

Steven Peckman, Ph.D. Link to Full Presentation

Summary:

Federal regulations DHHS-OHRP, FDA and California law CA Medical Experimentation Act provide a very comprehensive framework for protecting participants in clinical trials. Specifically, IRB and other committees provide review and oversight that addresses many of the issues that have been discussed in the workshop. With regard to issues that have already been raised, consider the following points:

- Subject selection: IRBs are required to assess the appropriate selection of subjects including but not limited to the following issues:
  - Patients v. non-patients
  - Patient v. patient (getting a similar disease baseline)
  - Older patients v. younger patients
  - Adults v. minors
  - Earlier v. later disease
  - Received standard of care v. treatment naive
- Risk benefit calculation: IRBs are required to find that risks are reasonable in relation to anticipated benefits. The IRB "lifts the cloak of secrecy" and the investigator must disclose data to enable risk/benefit.
- Informed consent process: Consent is a process starting with recruitment. There is a need to adapt a communication process suited to the participant population. It may be particularly difficult to communicate risks. Novel approaches to disseminating information – audio, video, graphs and charts – are required.
- Right to be included: AIDS crisis resulted in research being the only mode of treatment creating a right to be included. This circumstance is one extreme and may not apply in to less sever conditions.
- Therapeutic misconception: Therapeutic misconceptions, which are well documented for oncology trials, may be particularly prevalent in trials of novel biotechnologies such as gene transfer, recombinant drugs, or stem cells. This misconception is brought by the subject and investigator research suggests.
- Injury: There is a requirement for the IRB to describe to how medical treatment will be provided but there is no requirement to pay for treatment.
- Potential conflict of interest: How should CIRM or IRBs address the situation where the researcher is the inventor of a therapeutic? What if the researcher is the only one who has performed the procedure or used the product?
- Data Safety Monitoring Boards: DSMBs provide monitoring of the trial.

- Monitor and make recommendations for, study procedures, data quality, adherence to protocol and toxicity
- DSMBs can stop or suspend the trial.

▷ DSMBs opportunities for improvement: There are ways to improve DSMB function:

- DSMBs rarely meet in real time relationship to the research and AERs. Therefore may take months to uncover and understand a trend that may pose immediate harm to subjects. Consider requiring plans for interaction during a trail.
- DSMBs are unlikely to account for multiple uses of a product across various experiments. Coinsider mechanisms for accounting for multiple uses.
- DSMBs commonly report minimal information to IRBs, such as "things are going well." Encourage more robust interaction, possible through more formal reports, with IRB.

▷ Role of SCRO: SCRO primary role is to oversee basic research where IRB is not involved and provide scientific expertise. There is overlap between SCRO / IRB / Scientific Review (see table below). Minimize redundancy in the review / oversight process.

Table 1: Comparison of Membership and Duties of Oversight Committees

	SCRO	**IRB**	**Scientific Peer Review**
MEMBERSHIP			
Scientific expertise	Yes	Yes	Yes
Medical clinical trial expertise	No	Yes	Yes
Ethics expertise	Yes	Implied	No
Community (non-scientist)	Yes	Yes	No
Diversity of membership (race, gender, culture)	Not required	Yes	No
Biostatistics	No	Often but not required	Yes
Pharmacist	No	Often but not required	Yes

RN	No	Often but not required	Yes
DUTIES			
	SCRO	**IRB**	**Scientific Peer Review**
Scientific evaluation	Yes	Yes	Yes
Ethics	Yes	Yes	No
Risk:Benefit analysis	Yes	Yes	Yes
Informed consent	Yes	Yes	No
Accrual	No	Yes	Yes
Education	Yes	Yes	Yes

Issues for Consideration

- CIRM is in a position to provide a framework for addressing key issues identified throughout the workshop. The RfA process should include key issues / element to be addressed in advance so the they do not arise in an IRB context first. For example, have the applicant discuss:
  - How will participants be recruited to obtain suitable matching for disease state
  - What is the plan for providing treatment for injured patients
  - How will data safety monitoring and adverse event responses data feed back into the protocol to for safety and risk reduction
- The University of California requires industry sponsors to pay for any research related injury.
- CIRM should be sensitive to issues that are unique to stem cell research that have solutions that are not more bureaucratic. For example, technical options to manage risk (e.g. methods modulate cell activity).
- CIRM can support the “transmission” of relevant information among grantees.
- NAS survey suggest the SCRO committees have utility but there is general concern nationally over redundancy.

Ideas to Pursue for Future SWG Deliberation

The following issues were identified by the SWG as priorities for further analysis by CIRM. The SWG requested that the following questions addressed by staff for future consideration by the working group.

1. What is the need, if any, for a consensus meeting to develop standards on preclinical testing? Is it feasible to think that such a meeting could serve to provide clearer direction to pre-clinical research?
2. What steps can CIRM reasonably take to ensure timely dissemination of findings, including negative results? Are new rules required or does CIRM have sufficient authority to require this reporting?
3. What opportunities exist to support effective informed consent? Is there value in CIRM supporting research or the development of educational tools? Are there opportunities to evaluate comprehension of consent to support good practices?
4. How will health care for complications in trials be provided and funded?
5. What is the role of sham surgery in trials?
6. How can CIRM work with grantees to ensure existing rules and regulations designed to protect research subjects are effectively implemented. Is there a need to have grantees address specific safety and compliance consideration in the application process.

Moving Into Clinical Trials

R. Alta Charo
University of Wisconsin
February 2009

Cell-based therapies

- Cell-based therapies are generally regulated as biologics.
- Biologics can be regulated as devices or drugs (with the relevant pre-clearance or pre-market approvals based on safety and efficacy data) depending upon their primary mode of action, as per the FDCA and its subsequent amendments.
- In addition, biologics are subject to additional precautions based on the PHS Act, primarily aimed at control of transmission of infectious disease.

Basic Steps

- Derive or Import a Clinical-Grade Cell Line
- Preclinical Laboratory Work
- Preclinical Animal Work
- Obtain IND/IDE from FDA
- Obtain IRB approval
- Recruit subjects into Phase 1,2 and 3 trials
- Get NDA from FDA
- Implement risk management plan for post-market surveillance

Derive a Clinical-Grade Cell Line

- Be sure the work is done in a manner consistent with FDA good laboratory practice rules
- Ensure that donor suitability screening is performed, and medical information preserved
- If donor information is preserved with identifiers, ensure compliance with HIPAA and human subjects rules.
- For consent to donate, ensure compliance with local rules, especially with regard to conflict of interest, adventitious findings, and unanticipated future avenues of research with the lines.

Import a Clinical-Grade Cell Line

- Ensure the line was originally derived in a manner deemed acceptable by your own jurisdiction.
- If imported from outside the U.S., check to see if it meets FDA regulations to prevent the transmission of communicable diseases.

Components of the Tissue Action Plan for Manufacturers of Human Cell Therapy Products

- Establishment Registration and Listing – applies to recovery, screening, testing, processing, storage, or distribution of human cells, tissues, and cellular and tissue-based products
- Donor Suitability Determination
- Good Tissue Practices – to prevent the introduction, transmission, or spread of communicable diseases; governs the methods used in, and the facilities and controls used for, the manufacture of HCT/Ps.
- Labeling
- Enforcement

Donor Suitability and Tracking

- The good tissue practices include screening of donors to prevent the spread of communicable diseases, and a tracking system that will permit tracking from each human cell line or tissue back to the original donor(s).
- Note the interplay between the tracking rules and the question of whether the donors are identifiable to those working on the cell lines – this affects the human subjects research status of the lab

Preclinical Laboratory Work: Cell lines with Identifiers

- Even lab work may be "human subjects research" if the donor(s) may be identified, by name or by links (such as a code) to identifying information. **IRB review and approval is required for such research.**

Exception to Rule Concerning Cell Lines with Identifiers:

- Research on cell line that retains a link to identifying information will not be considered human subjects research if the identity of the donor(s) cannot be "readily ascertained" by the investigator or associated with the cell line because:
- (1) the investigator and research institution do not have access to identifiable private information related to the cell line; and
- (2) **a written agreement is obtained from the holder of the identifiable private information related to the cell line providing that such information will not be released to the investigator under any circumstances.**
- In this case, an institution or an IRB could determine that **IRB review of the research using the cell line was not needed.**

Preclinical Animal Work: creating transgenic or chimeric animals using ES cells

- ES cell research that involves the creation of transgenic or chimeric live-born animals is subject to animal welfare protections
- The Animal Welfare Act ensures the most humane use of animals in research.
- Animals covered include dogs, cats, nonhuman primate mammals, guinea pigs, hamsters, and rabbits.
- Animals not covered include birds, rats, and mice bred for use in research.
- Institutional Animal Care and Use Committees (IACUC) review this work.

Obtain IND/IDE from FDA

- Requires submission of all preclinical data and a plan for the clinical trials.
- In most cases, researchers have worked with FDA already as they move through the preclinical phases

Obtain IRB approval

- IRB must approve protocol based on risk/ possible benefit ratio.
- IRB must approve consent process and documents
- IRB must approve recruitment plan

Phase 1 and 2 studies

- Phase 1 and 2 studies are primarily safety studies with small numbers of subjects
- Pent-up demand for access to ES cell therapies may lead to significant pressure to hurry these trials or open them to larger numbers of participants

"Compassionate Use"

- FDA does have compassionate use rules for access to investigational drugs and devices, even as early as Phase 2; these rules include compensation to the manufacturers for the cost of production.
- With biologics, however, there may be limits on the ability to scale up to meet production demands for compassionate use.

Phase 3 Trials

- Phase 3 trials expand to test benefits, and recruit larger numbers of patients
- In 1980s AIDS research, "parallel track" was developed to offer investigational interventions to those not able to enroll in Phase 3
- At some point, compassionate use may interfere with the ability to get properly randomized trials and gold standard data on risks and benefits

NDA/device approval order

- Following submission of all clinical trial data, and performance of additional trials as requested by FDA, application can be made for an NDA or device approval order
- Approval may be conditioned upon development of various post-market protections, e.g. Phase 4 trials; enhanced surveillance; limitations on advertising; patient screening tools.

Areas for CIRM/SWG activity?

- Assist IRBs in collecting and analyzing most up-to-date information about risks and benefits of various types of stem cell interventions.
- Work with IRBs to develop easily understood explanatory materials for recruitment and consenting process
- Work with IRBs and (if welcomed) with FDA and manufacturers on managing patient expectations and organizing compassionate use protocols.

Standards and Regulations for Cellular Therapy Products

Elizabeth Read, MD

Regulatory Knowledge & Services Program
UCSF Clinical & Translational Science Institute

Department of Laboratory Medicine, UCSF

Blood Systems Research Institute

February 17, 2009

Part 1

How does FDA regulate the bench-to-bedside translation of cellular therapies?

FDA & Clinical Research

- Regardless of funding source, ALL clinical research that involves drugs, devices, and biological products-- including cells or test articles regulated as drugs, devices, and biological products-- is subject to
  - FDA regulations for investigational new drugs (INDs) or devices (IDEs) (21 CFR 312 or 812)
  - FDA regulations for IRBs and informed consent (21 CFR 50 & 56)

FDA's Good Clinical Practice Program

http://www.fda.gov/oc/gcp/default.htm

- Coordinates FDA policies on human research
- Leads FDA's Human Subject Protection/ Bioresearch Monitoring Council
- Coordinates FDA's Bioresearch Monitoring program, with FDA's Office of Regulatory Affairs (ORA)
- Promotes harmonization with ICH GCP activities
- Serves as liaison with OHRP and other federal agencies and external stakeholders

FDA Centers

CDER Drugs (+ some biologics)

CBER Biologics (+ some devices & diagnostics)

CDRH Devices & Radiologic Products

CFSAN Foods

CVM Veterinary drugs, food additives, devices

FDA/CBER has been thinking about cellular therapies for 20 years

1989 PTC for ex vivo activated mononuclear cells

1993 Announced intent to regulate human somatic cell and gene therapies

1997 Guidance for submission of CMC & establishment description for somatic cell therapy products

1997 Proposed approach to regulation of cellular and tissue-based products (tiered, risk-based)

FDA/CBER has been thinking about cellular therapies for 20 years

1998-2008 Proposed & final Tissue Rules

Draft & final guidances (donor eligibility, CGTP, CMC for somatic cell therapy, CMC for gene therapy, etc)

Interactions with public, professional organizations, and sponsors

- Advisory committee meetings
- Public workshops
- Cell therapy liaison meetings with OCTGT
- Interactions with sponsors – currently over 1200 active files in OCTGT

CBER regulates…

- Blood, blood products, and plasma derivatives
- Human cells, tissues, and cellular and tissue-based products (HCT/Ps)
- Other biological products (allergenics, vaccines, antitoxins/antivenins/venoms, gene therapy products, xenotransplantation products)
- Devices (assoc w/ processing, testing, manufacture, and administration of licensed blood & cellular products; HIV test kits)
- Some combination products

FDA Definition of HCT/Ps

Articles containing human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient

HCT/Ps include

- Musculoskeletal tissue and skin
- Ocular tissue
- Cellular therapies
- Hematopoietic stem/progenitor cells
- Therapeutic cells (DLI)
- Somatic cells
- Reproductive tissue
- Combination tissue/device, tissue/drug
- Human heart valve allografts
- Human dura mater

HCT/Ps do NOT include

Vascularized whole organs	HRSA regulates
Bone marrow, **minimally manipulated, homologous use - AUTO or FAMILY DONOR**	Practice of medicine (not regulated by FDA)
Bone marrow, **minimally manipulated, homologous use – UNRELATED DONOR**	HRSA regulates
Xenografts	FDA separate regs
Blood & blood products	FDA separate regs
Secreted or extracted products (e.g., human milk, collagen, cell factors)	FDA separate regs
In vitro diagnostic products	FDA separate regs

HCT/P Regulatory Tiers

Both tiers subject to new "Tissue Rules"

- "361" = Less complex products, regulated solely under section 361 of the PHS Act ("361")
  - Tissues of the body, if minimally manipulated
  - Reproductive tissues
  - PBSC or cord blood, if autologous or family-related
- "351" = More complex products with "kick up" factors, regulated under section 351 of the PHS Act
  - More than minimally manipulated
  - Non-homologous use
  - PBSC and cord blood from UNRELATED donors

What are the Tissue Rules?
21 CFR 1271

Establishment registration

Donor eligibility

CGTP manufacturing requirements

FDA Regulations for HCT/Ps

	361 HCT/Ps	351 HCT/Ps
(Tissue) Establishment registration	√	√
(Tissue) Donor eligibility	√	√
(Tissue) CGTP manufacturing	√	√
CGMP regulations		√
IND / IDE regulations		√
Premarket approval (BLA)		√

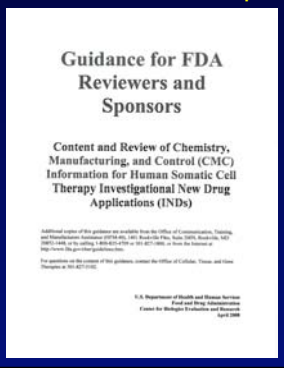
Where do stem cell products fit?

- Therapeutic cellular products derived from embryonic, fetal, or adult stem cell sources are regulated and reviewed under FDA's existing framework for HCT/Ps
- Almost all new products will have "kick up" factors, and therefore be subject to requirements for 351 HCT/Ps

Key Elements of IND

- Proposed clinical trial & informed consent
  - IRB approval required
- Product description = Chemistry, manufacturing, and control (CMC)
- Preclinical data, pharmacology & toxicology
- Previous human experience
- Responsibilities & assurances
  - Form 1571 (sponsor, investigational drug, phase of investigation, parties responsible for monitoring conduct of clinical trial)
  - Form 1572 (signed statement by each investigator containing contact & IRB information; agreement to follow regulations

CMC Guidance for Somatic Cell Therapies

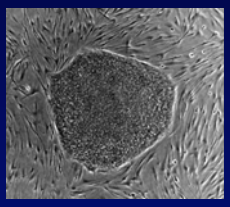


Guidance for FDA Reviewers and Sponsors

Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs)

Source cells, tissue, and cell lines used to develop HCT/Ps

- Not by themselves considered HCT/Ps
- Require detailed qualification
- CMC guidance for somatic cell therapies outlines requirements and references other guidances on
  - Donor screening & testing
  - Manufacturing, banking, and testing of cell lines
  - Use of xenogeneic materials in cell banking



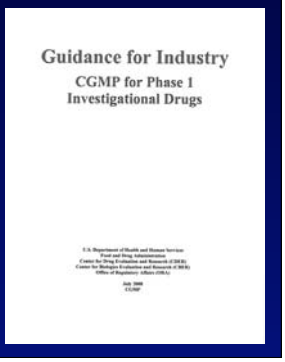
CGMP
Current Good Manufacturing Practice

- Represents the minimum standards for methods used to manufacture a drug (or biologic) to assure its safety, identity, purity, and potency
- Not just about the facility, which is only one element of quality manufacturing and regulatory compliance

CGMP in Phase 1

"Manufacturers should establish manufacturing controls, based on identified hazards for the manufacturing setting, that follow good scientific and QC principles."

A. Personnel
B. QC Function
C. Facility and Equipment
D. Control of Components, and Containers & Closures
E. Manufacturing & Records
F. Laboratory Controls
H. Packaging, Labeling, Distribution
I. Recordkeeping

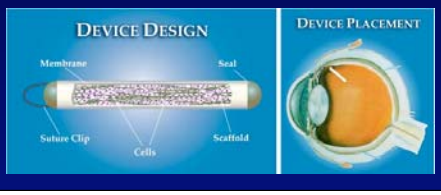


Guidance for Industry

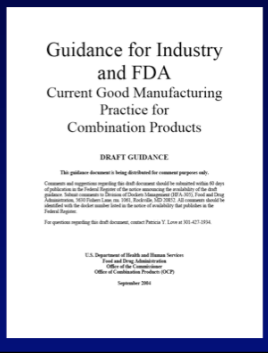
CGMP for Phase 1 Investigational Drugs

HCT/P Combination Products

Neurotech-USA



Combination Product Guidance



Guidance for Industry and FDA

Current Good Manufacturing Practice for Combination Products

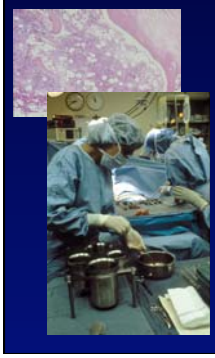
DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

U.S. Department of Health and Human Services
Food and Drug Administration
Office of the Commissioner
Office of Combination Products (OCP)

September 2004

How did standards & accreditation for cellular therapies begin?



Bone Marrow Transplantation
"Practice of Medicine"

1970s – 1980s

- BM harvested, filtered, and transferred to blood bags in operating room, sent to patient unit for infusion
- Minimal donor & product testing, graft manipulation, quality systems

Late 1980s – early 1990s

- Increasing use of PB as source

1991 – 1992

- Quality & standardization concerns led to AABB and FACT standards & accreditation programs for BM, PB, and later to CB sources

Standards & Regulations for Hematopoietic Stem Cell Products

	Standards & Accreditation	FDA	California
Blood products	AABB	21 CFR 606 21 CFR 210,211	AABB Stds in CA code
Bone marrow Auto/Family	AABB or FACT		CDPH TB license?
PBSCs Auto/Family	AABB or FACT	361 HCT/P	CDPH BBB license
Cord blood Auto/Family	AABB or FACT	361 HCT/P	CDPH BBB license
Bone marrow Allo URD	AABB or FACT + NMDP	351 HCT/P	CDPH TB license?
PBSC Allo URD	AABB or FACT + NMDP	351 HCT/P	CDPH BBB license
Cord blood Allo URD	AABB or FACT + NMDP	351 HCT/P	CDPH BBB license

CA Department of Public Health Role in Cell & Tissue Therapies

Licensure of

- Clinical labs
  - Clinical lab personnel
  - Clinical lab facilities (moderate & high complexity testing)
  - Blood bank and biologics facilities (blood banks & blood collection centers, HPC collection (apheresis) centers, cord blood facilities, plasma collection facilities)
  - Tissue banking facilities
    - Cadaveric tissue collection, processing, storage, distribution
    - Assisted reproductive technologies
    - Stem cell processing from sources other than cord blood & circulating blood
    - Donor milk collection, processing, storage, distribution
    - Autologous tissue stored overnight or longer
- Drug manufacturers
- Medical device manufacturers

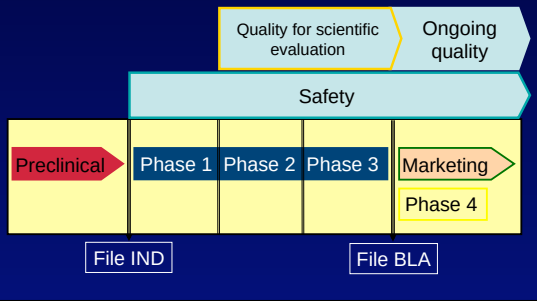
CBER Regs/Guidance on the Web

- Proposed and Final Rules
  http://www.fda.gov/cber/rules.htm
- Draft and Final Guidances
  http://www.fda.gov/cber/guidelines.htm
- Email notification for CBER documents, advisory meetings, workshops, etc.
  http://www.fda.gov/cber/whatsnew.htm

Part 2

Regulatory considerations for stem cell therapies

What is FDA focused on during product development?



Key Elements of IND

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- Responsibilities & assurances
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Interactions between Sponsor & CBER

- Pre-Pre-IND meeting/conf call: informal, general, no minutes
- Pre-IND meeting/conf call: Responds to specific questions raised by sponsor, minutes taken
- Review of IND submission: Formal, team includes reviewers for
  - Preclinical
  - Clinical
  - Product
  - Statistics
- Ongoing interactions w/ sponsors, from IND to BLA

Interactions between Sponsor & CBER

- Communications are considered proprietary to sponsor, and not accessible by public or other sponsors
- Sponsors may discuss in public their interactions with FDA, if they so choose – but most commercial sponsors do not

CBER Guidance on Development of Stem Cell Products

- General guidance comes from HCT/P documents
- Public comments and guidance specific to stem cell therapies have been minimal, but are likely to increase over next few years, as science matures
- Best way to prompt guidance from FDA is to engage with them, propose approaches, and present scientific data

What's Unique for Stem Cell Products?

- Product issues
  - Cell sources
  - Characterization – assays
  - What attributes are desirable or undesirable?
- Preclinical animal studies
  - Efficacy (proof of principle)
  - Pharmacology
  - Toxicology
- Clinical issues
  - Choice of population, screening of subjects
  - Trial design
  - Monitoring of subjects

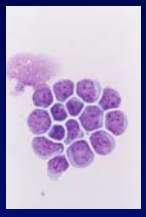
Translation of Stem Cell Therapies: Best Practices and Regulatory Considerations

- A one-day symposium to be held May 2, 2009, in San Diego, CA
- Intended to
  - Provide attendees with an understanding of clinical product development for stem cell therapies
  - Identify and discuss critical issues/challenges for early, mid, and late-stage product development
  - Provide a forum for developing best practices in stem cell product development, where "lessons learned" and interactions with FDA are openly shared

Part 3

Banking & transplantation of unrelated donor cord blood

Hematopoietic Progenitor Cells (HPCs)



- Multipotent stem cells responsible for continuous production of normal blood cells
- Transplanted to patients with variety of blood diseases and cancers since 1960s
- Most important factors predicting favorable outcome of HPC transplantation are
  - degree of match between donor & recipient
  - cell dose

Sources of HPCs

Bone marrow

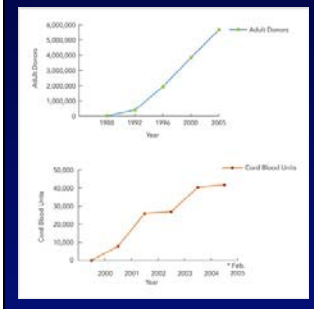
Mobilized peripheral blood stem cells collected by apheresis

Umbilical cord blood

Matching on the HLA (Human Leukocyte Antigen) System

- Critical for all allogeneic HPC transplants
- Of approx 12,000 HPC transplant candidates in a given year
  - only 30% have an HLA-matched sibling donor
  - 70% need to search for an unrelated donor
    - living donor registries (BM, PBSC)
    - frozen cord blood registries

National Marrow Donor Program (NMDP) Registries



- Probability of 6/6 match using NMDP donor registry
  - 85% (all patients averaged)
  - Lower for certain minority groups, e.g. 65% for African Americans
- Current usable CB unit inventory in USA is approx 50,000 (NMDP and others). Increasing from 50,000 to 300,000 units would increase likelihood of
  - 6/6 match from 7 to 17%
  - 5/6 match from 40 to 65%
  - 4/6 match from 84 to 96%

Federal Support of BM, PBSC, CB from Unrelated Donors

2004
- Congress authorized $10 million to establish National Cord Blood Stem Cell Bank, and
- Asked IOM to review options, make recommendations

April 2005 – IOM report published

Dec 2005 - Stem Cell Therapeutic and Research Act
- C.W. Bill Young Transplantation Program to replace and expand NMDP registry functions
- National Cord Blood Inventory (NCBI) to collect and store 150,000 high quality cord blood units
- Formation of Advisory Council

HRSA Contracting Structure for

CW Bill Young Transplantation Program

CONTRACTS	AWARDED TO
NCBI Cord Blood Banks	Established CB banks
Cord Blood Coordinating Center	NMDP
Outcomes Database	CIBMTR
BM Coordinating Center	NMDP
Single Point of Access - Patient Advocacy Services	NMDP

What regulations, standards, and accreditation requirements apply to public cord blood banks?

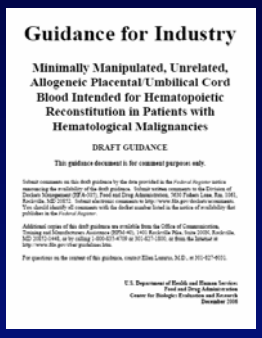
(a story of many moving parts)

FDA Regulations: Cord blood from unrelated donor is a "351" HCT/P

	361 HCT/Ps	351 HCT/ Ps
Tissue - Establishment registration	√	√
Tissue - Donor eligibility	√	√
Tissue - CGTP manufacturing	√	√
CGMP regulations		√
IND / IDE regulations		√
Premarket approval		√

FDA Cord Blood Guidance

- CBER draft guidance
  - published January 2007
  - to be finalized soon
  - will require public banks to have Biologics License (BLA)
- Challenges
  - Use of CB for other indications
  - Comparability of historical inventory to licensed inventory
  - Differences between US and non-US donor screening & other requirements



Guidance for Industry

Minimally Manipulated, Unrelated, Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution in Patients with Hematological Malignancies

DRAFT GUIDANCE

This guidance document is for comment purposes only.

HRSA-Funded Cord Blood Banks

- Before award (per RFP SOW):
  - Must comply with state and federal regulations
  - Must be accredited by recognized organization
- After award (per RFP SOW):
  - Above, and must also comply with HRSA-specific requirements that exceed the standards and regulatory requirements

U.S. Statutory Mandate for Cord Blood Bank Accreditation

PL 109-129 (Stem Cell Therapeutic & Research Act)

- "The Secretary shall, through a public process, recognize one or more accreditation entities for the accreditation of cord blood banks"
- NCBI banks must be accredited by the organization(s) so recognized

Senate and IOM Reports mention importance of CBB accreditation to ensure quality of cord blood units

Senate Report notes accreditation seen as vital for ensuring quality, along with:

- FDA requirements for licensure of cord blood
- Continued regulation by FDA and States

Before Advisory Council formed…

- HRSA staff, after internal research, drafted accreditation specifications
- HRSA noted that nearly all public cord blood banks were accredited by AABB or FACT-Netcord, or both
- HRSA gave interim recognition to AABB and FACT-Netcord as accreditation organizations for banks competing for contract awards
- Interim decision was to be followed by a recognition process that allowed for input by the Advisory Council and the public

HRSA's Advisory Council = ACBSCT Started Jan 2008

- Accreditation Work Group formed Jan 2008

Jan – Dec 2008

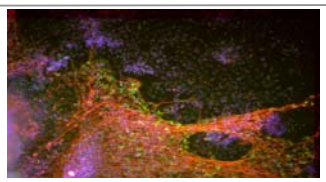
- Reviewed, reworked, and finalized HRSA's Draft Specifications for Accreditation Organizations
- Assessed ability of AABB and FACT-Netcord to meet specifications
- Reviewed AABB and FACT-Netcord standards & accreditation practices for comparability, deficiencies, incompatibilities
- Outlined recognition process

ACBSCT Accreditation WG

- Currently assessing HRSA-specific requirements, and how they will be handled
- Plan to have full Council vote on recommendations for recognition - May 2009
- Prospective activities
  - HRSA staff to receive inspection reports
  - Generic inspection issues to be referred to Council (or WG?), for development of improved practices and standard-setting

Issues

- Will use of existing accreditation organization(s) meet the goal of ensuring highest quality products?
- If both organizations are recognized, will they work together to improve standard-setting and accreditation activities?
- What will happen when FDA finalizes guidance, and public banks start submitting BLAs?
- What should ongoing relationship be between Council and accreditation organizations?
- Will HRSA-specific requirements and mechanism for feedback to Advisory Council improve practices for HRSA-funded banks?
- Will these activities improve quality in ALL public cord blood banking?



Case study: The long road to stem cell transplantation for PD

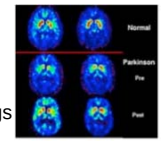
Marie Csete MD, PhD
CIRM CSO

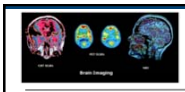
Parkinson's disease

-Progressive movement disorder
  -tremor, muscle rigidity, hypokinesia, postural instability
  -pain, sleep disturbances, GI problems
-Neurons in substantia nigra are lost (dopamine lost in striatum)
-Age is the major risk factor
-Dopamine replacement: Mainstay of rx

History: Cell transplants

- 1980's: Open label fetal cell transplants
- Showed long-term graft survival and some improvement in a few patients
- 2000: Isacson et al: 10 patients receive pig embryonic transplants
  - 12,000,000 cells on one side (striatum)
  - Safe, immunosuppression used
  - 3/10 improved at 1 yr (still on PD drugs)
  - PET did not correlate with clinical findings
  - Recommend larger, controlled studies

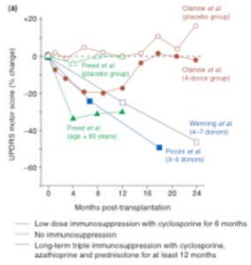




Randomized trials (NIH funded)

-NEJM, 2000: 40 patients
Cultured fetal cells vs. Sham surgery
-4 embryos/graft in putamen (double-blind), no immunosuppression
-Transient significant improvement in some (younger) patients
-Overall, patient evaluation of their own progress showed no benefit to transplants
-Several years out, 5 transplant patients developed severe symptoms (dyskinesias)
-Second trial (solid pieces of fetal mesencephalon: 1 vs. 4 donors vs sham surgery) had similar results.
  -At six months, larger dose better
  -Long-term no difference between groups

Lessons from trials



Long-term higher dose immunosuppression (Lund) associated with better function

How much work should precede a trial like this?

- VARIABLES NEEDED FOR OPTIMIZATION
  - Cell source (age of embryo, part of brain)
  - Cell number
  - Cell preparation and storage
  - Cell potency assays (GDNF?)
  - Effect in multiple animal models (2 species)
  - Disease state of patient, other patient factors
  - Immunosuppression, other drugs
  - Surgical site, technique, placement

Long-term

•Nat Med, 2008
•3 groups reported autopsy findings of patients long after fetal grafts (9-16 yr)
•3/6 in one group: PD pathology in grafts
•In Mendez patients: Graft neurons were not only dopaminergic (serotonin)
•Grafting in one location doesn't improve disease in other important brain areas

Why ES cells?

- Fetal sources problematic, variable
- Could have master banks of defined cell populations (less variability)
- Define differentiation in animals first
  - Can animal models really predict human results?
  - Balance proliferation/differentiation/survival
  - New risks
  - Is it ethical to compare fetal vs. ES-derived grafts?

Duty to interrogate all previous studies carefully;
Need for trials that are transparent

Fundamental problems

- Why do some grafts get recurrent disease?
  - Does it really matter?
- Successful grafts may not have remaining healthy places to make synapses as the disease progresses—But early disease patients have potential for more risk
- Influence of immunosuppression on graft function still not clear

How much do we need to know?

- When is the right time to start again?
- New and improved cells? Is this enough?
  - Safety
  - Function, potency
- End-stage patient demands to be in trials?
- Transparency is key, extensive data dissemination

Inconvenient Truths About Stem Cell Clinical Trials

Hope and Complex Biological Interventions

Bruce Dobkin, MD
Professor of Neurology, UCLA
Director, UCLA Neurologic Rehabilitation Program
Scientific officer, Adelson Program in Neural Repair and Rehabilitation

"Doc, I need those stem cells"

The Patient:

I am disabled or dying; my hope is waning. You gotta give me what the media and stem sellers say is ready for prime time. Deliver me past the conspiracy within the medical establishment that withholds stem cell transplants.

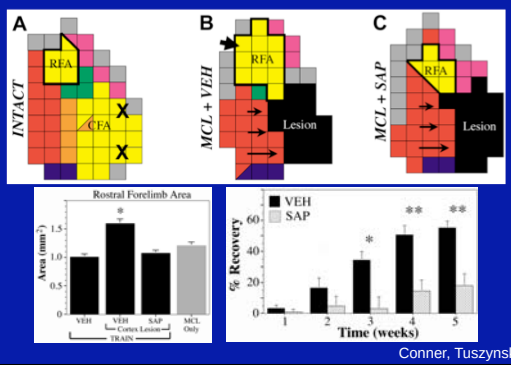
The Medical Establishment:

* Stem cells and precursors may have niche uses in the near future. We need multicenter RCTs first.
* Are stem cells the answer and the only option?
* Is our research process maximizing in an ethical, transparent, and productive way the paths to stem cell interventions for neurological diseases?

THREE R's OF NEURAL REPAIR TO PROMOTE FUNCTIONAL REWIRING

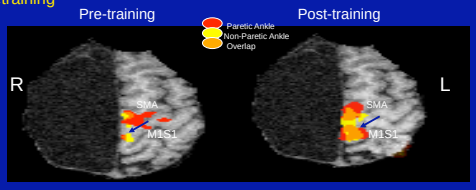
- REPLACE cells; messengers (via cells or drugs)
- REGROW connecting axons, dendrites
- RETRAIN circuits, networks, behaviors

Cortical Reorganization Map Following Focal Brain Injury and Training - Impact of Loss of Cholinergic Input on Functional Recovery



Conner, Tuszynski

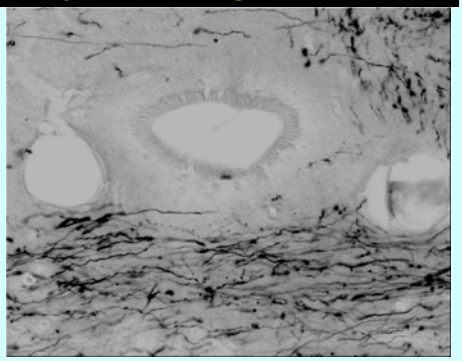
Increased cortical overlap in M1/S1 and in SMA with voluntary ankle dorsiflexion of paretic and nonparetic foot following locomotor retraining



Child with right hemispherectomy for intractable sz at age 6, now 10

DeBode, Dobkin, Neurorehabil Neural Repair, 2007

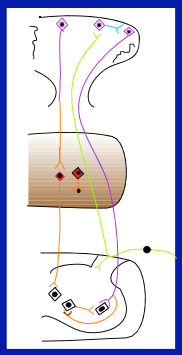
Crossing CST axons under spinal cord's central canal



Tuszynski, Havton, 2009

Strategies For SCI Repair

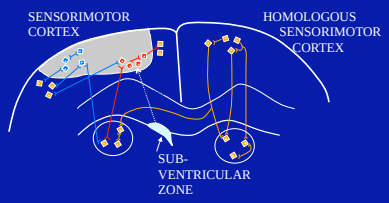
- Optimize use of residual pathways, e.g. task-oriented training
- Cortex to muscle-interface neuroprosthesis
- Bridge injury site, e.g., nerve grafts, biopolymer, Schwann cells, olfactory ensheathing glia, or embryonic tissue
- Modulate inflammation - implant stimulated macro-phages to clear myelin
- Implant neuron or oligodr precursors
- Incorporate axonal sprouts and spared pathways via activity-dependent plasticity
- Stimulate spinal movement network



- Training-induced representational plasticity for practiced movements
- Neuromodulating drugs to enhance relearning
- Growth cone signaling, e.g., cAMP (rolipram); induce or implant neurotrophins, e.g., BDNF or NT3 secreting fibroblasts
- Block axonal growth cone inhibitors, e.g., NgR or Rho
- Degrade glial scar products, e.g., chondroitinase
- Guide regenerating axons to targets, e.g. adhesion molecules, netrins
- Manipulate neurogenesis
- Promote sprouting and functional connections

B. Dobkin, The Clinical Science of Neurologic Rehabilitation, Oxford U. Press, 2003

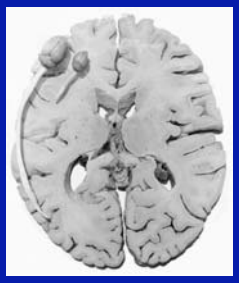
Stroke Model for Neural Repair
New Cells and Wiring



What can be expected of endogenous or exogenously implanted stem, precursor or support cells?

Replace lost or poorly functioning neurons within a confined region:
e.g., dopaminergic neurons for Parkinson's, motor neurons for ALS, SCI
Replace a neurotransmitter locally:
e.g., fibroblasts reconstructed to secrete acetylcholine for Alzheimer's
Recreate or strengthen a neural network:
e.g., cells that produce trophic factors to promote dendritic sprouts
Protect and augment molecules for plasticity:
e.g., bone marrow stromal cells that migrate to peri-infarct tissue
Alter signals in the milieu to promote regeneration:
e.g., stem or progenitor cells altered to make high levels of cAMP
Bridge a gap induced by an injury and provide growth promoting molecules:
e.g., cortical stroke; spinal cord injury
More globally replace a missing gene/protein or a special cell type:
e.g., replace oligodendrocytes in Pelizeus-Merzbacher disease

Mouse and rat brain on a gyrus of a horizontal section of the human brain



The Clinical Science of Neurologic Rehabilitation, B.H. Dobkin, Oxford U. Press, 2003

Potential for misappropriation of experimental models in their translation to clinical interventions

1. Is the brain and spinal cord of a rat or mouse simply a thimble-sized version of the human brain? Are caged, inbred rodents enough like us for results to be translated in human trials?
2. What is the study population - differences among species and strains of rodents, transgenic mice, pigs, non-human primates?
3. Is the model of injury and repair in rodents similar enough to what happens in human disease?
4. Is the timing, dose and location of the intervention the same in the model of disease as it will be for patients?
5. Were the rodents randomly assigned to an intervention and were outcome measures blinded? Animal RCTs must be unbiased.
6. How were the animals of each group trained?
7. What were the measures of efficacy (biomarkers, behavior, anatomy, physiology)? Are the changes relevant to outcomes in patients?
8. Were the published results replicated by another lab/model?
9. Were the outcomes both statistically and clinically significant?
10. How might results of animal studies be (mis)interpreted by layman and clinicians? Are they reliable as a path to RCTs?

Potential Complications of Cellular Interventions

- Maladaptive plasticity : pain, seizures, movement disorders, hypertonicity and spasms, autonomic dysreflexia.
- Worsening of impairments and disability.
- Risks include rejection of the cells with meningoencephalitis, immune response, local infection, growth of tumors, introduction of potent viruses. Genetically modified cells and epigenetics pose uncertain consequences when cells are placed in a new environment. Lengthy followup necessary.
- Limitations of animal models to provide insight about safety and efficacy.

Why do RCTs?

Patients fluctuate for the better or worse, day to day; appreciation of change is a source of bias. No two therapy sites get the same results. Our minds are wired to hope and to believe.

False alternatives:
- Hope and desperation - something is better than nothing.
- Excuses - placebos are not ethical, possible, fundable …
- Hubris - I know it works.
- Historical controls for comparison.
- Enter chronically impaired subjects.
- Exceed the *Minimal Detectable Difference* or *Minimal Clinically Important Difference* for the outcome measure.

Consequences of failure to design a rigorous RCT:
- No knowledge generated for the risks taken.
- Does it really work or not? Compared to what? For whom & what?
- No way to weigh risks and benefits of interventions.
- No way to improve upon an intervention.
- Slippery slope of sloppy science and sales.

Some Guiding Principles for Cellular RCTs

RCTs are arduous, expensive and delay gratification. Investigators, subjects, peer basic and clinical experts, IRBs and FDA should be convinced that the RCT is likely to provide important knowledge and improve health outcomes.

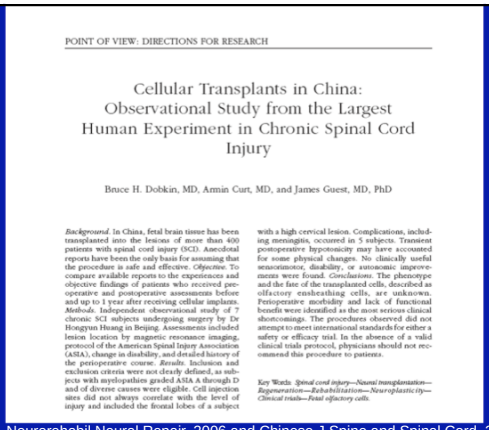
Phase-in the focus of the outcome for both arms with 12-18 hours of task-related therapy prior to randomization, until no further gains can be measured.

Combine the cellular intervention and placebo with task-related practice that is relevant to the outcome sought. Practice Itself may induce plasticity and 'train' a circuit-related behavior. Do not compare something to usual care or nothing.

Outcome measures must be relevant to the intervention, valued by patients, and reduce impairment or disability or mollify a neurodegenerative disease.

Sample size - aim for an effect size of 0.4 - 0.6 (25-50 subjects per arm).

Train personnel in every aspect of the trial - identifying and keeping subjects; data acquisition, entry and management. Maintain masking. Keep the statisticians and safety committee highly involved. Never lose follow-up.



POINT OF VIEW: DIRECTIONS FOR RESEARCH

Cellular Transplants in China: Observational Study from the Largest Human Experiment in Chronic Spinal Cord Injury

Bruce H. Dobkin, MD, Armin Curt, MD, and James Guest, MD, PhD

Background. In China, fetal brain tissue has been transplanted into the lesions of more than 400 patients with spinal cord injury (SCI). Anecdotal reports have been the only basis for assuming that the procedure is safe and effective. *Objective.* To compare available reports to the experiences and objective findings of patients who received pre-operative and postoperative assessments before and up to 1 year after receiving cellular implants. *Methods.* Independent observational study of 7 chronic SCI subjects undergoing surgery by Dr Hongyun Huang in Beijing. Assessments included lesion location by magnetic resonance imaging, protocol of the American Spinal Injury Association (ASIA), change in disability, and detailed history of the perioperative course. *Results.* Inclusion and exclusion criteria were not clearly defined, as subjects with myelopathies graded ASIA A through D and of diverse causes were eligible. Cell injection sites did not always correlate with the level of injury and included the frontal lobes of a subject with a high cervical lesion. Complications, including meningitis, occurred in 5 subjects. Transient postoperative hypotonicity may have accounted for some physical changes. No clinically useful sensorimotor, disability, or autonomic improvements were found. *Conclusions.* The phenotype and the fate of the transplanted cells, described as olfactory ensheathing cells, are unknown. Perioperative morbidity and lack of functional benefit were identified as the most serious clinical shortcomings. The procedures observed did not attempt to meet international standards for either a safety or efficacy trial. In the absence of a valid clinical trials protocol, physicians should not recommend this procedure to patients.

Key Words: Spinal cord injury—Neural transplantation—Regeneration—Rehabilitation—Neuroplasticity—Clinical trials—Fetal olfactory cells.

Neurorehabil Neural Repair, 2006 and Chinese J Spine and Spinal Cord, 2006

Dr. Huang's response:

"If you were honest and fair, in face of the fact that the patient obtained improvements both according to ASIA standard and his quality of life, you should not continue denying the positive results. But what makes one regrets is that no matter what recovered the patient痴 neurological function and what happened improving his quality of life, you keep denying it. Facing the fact, and insisting on absolutely denying it, I wonder if you hate to see the patients with this disease improving their quality of life or your personality and credits have some problems except unfair and dishonest. I believe that no one in the world has the right to deprive the patients privilege to know the truth and get the effective treatment; especially when the scientists and doctors currently tell the patients with complete chronic spinal cord injury that there were no any effective methods which can be available for improving their neurological functions and their quality of life. So the best way is that all people should tell the patients the truth and let them decide whether they will want to get this treatment. So, as a trained observer to be concerned, the liar should be excluded firstly."

Beike Biotech's Treatable Conditions
http://www.beikebiotech.com

Alzheimer's
Arteriosclerosis and Atherosclerosis
Ataxia, Friedrich's
Autism
Brain Injury
Cerebral palsy
Diseases of blood vessels
Epilepsy
Heart failure
Huntington's
Multiple sclerosis
Muscular dystrophy
Optic neuropathy
Peripheral arterial disease
Spinal muscular atrophy
Vasculitis

Web site for Bieke Biotech in China

Karim, 36, is sitting in a wheelchair, paralysed from the chest down and praying that kind-hearted people will help him financially to afford surgery that could help him walk again. Karim contacted doctors at the Shenyang Hospital in China and forwarded his medical history to them. After studying the case, Dr Christine Taylor responded to Karim, stating that they could help him walk again. The problem is that Karim now has to raise $50,000 to have the stem cell treatment. Karim hopes to go to China in August. "Any help will go a long way in helping me heal," he said.

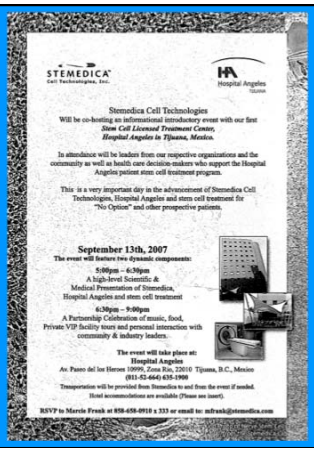
Beike Biotech Web Site

"Of the over 2,000 patients we have treated, about 70 to 80% of patients are satisfied with the improvements they have depending on the ailment. This percentage is increasing as we become more intelligent in our patient selection. If our medical department does not believe you will benefit from the treatment, we will tell you and suggest you seek treatment elsewhere. We by no means guarantee improvement but our treatment consists of multiple injections of stem cells accompanied by daily rehabilitation to ensure that if umbilical cord stem cells can help your condition, you will get some improvement."

After an NPR quotation on stem cell sellers, Beike Biotech added:

"This doctor (Dobkin), who is focused on stem cell research for optic disorders in the US and has a lot to lose if the treatment is accepted elsewhere, could have read the front page of the Beike web site to see that Beike is not talking nonsense, but that there is much evidence to back up our theory."

American venture capital for Russian cells


STEMEDICA
Cell Technologies, Inc.

Hospital Angeles

Stemedica Cell Technologies
Will be co-hosting an informational introductory event with our first
Stem Cell Licensed Treatment Center,
Hospital Angeles in Tijuana, Mexico.

In attendance will be leaders from our respective organizations and the community as well as health care decision-makers who support the Hospital Angeles patient stem cell treatment program.

This is a very important day in the advancement of Stemedica Cell Technologies, Hospital Angeles and stem cell treatment for "No Option" and other prospective patients.

September 13th, 2007
The event will feature two dynamic components:

5:00pm – 6:30pm
A high-level Scientific &
Medical Presentation of Stemedica,
Hospital Angeles and stem cell treatment

6:30pm – 9:00pm
A Partnership Celebration of music, food,
Private VIP facility tours and personal interaction with
community & industry leaders.

The event will take place at:
Hospital Angeles
Av. Paseo del los Heroes 10999, Zona Rio, 22010 Tijuana, B.C., Mexico
(011-52-664) 635-1900

Transportation will be provided from Stemedica to and from the event if needed.
Hotel accommodations are available (Please see insert).

RSVP to Marcia Frank at 858-658-0910 x 333 or email to: mfrank@stemedica.com

Ethical Issues Raised by Single Lab or Biopharma Intervention

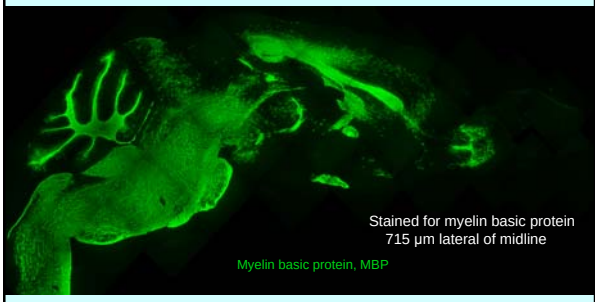
Secrecy about the intervention:

Geron, e.g., develops its hESC for SCI myelination from one lab's published rodent model study and then performs its own safety studies in 2000 rodents without further peer review. The limited behavioral and anatomical effects have not been reproduced by other investigators or in other models.

Tie up eligible subjects:

StemCells, Inc, e.g., purified human neural stem cells to target rare cases of Pelizaeus-Merzbacher disease. But could glial progenitors that others are working be better for remyelination?

Will decisions about RCTs that use vulnerable patients be made in isolation by mom-and-pop shops and by biopharma because the FDA agrees that the study is safe? How can we increase the likelihood of a robust effect for the fellow who wants those stem cells?



Human fetal glial progenitor cells engrafted at birth into shiverer x rag2 null mice

Survived 35 weeks

Windrem & Goldman, 2007

How to meet this ethical challenge?

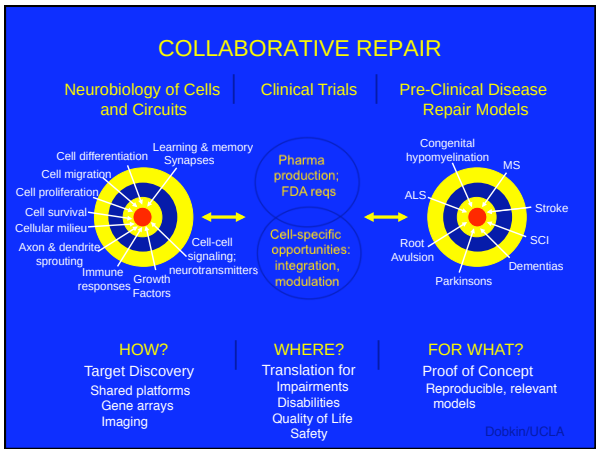
Collaborators could use their expertise to choose the most appropriate lines of research by sharing experiments, data and seeking consensus. They could establish the proof-of-principle intervention for the most appropriate group of subjects.

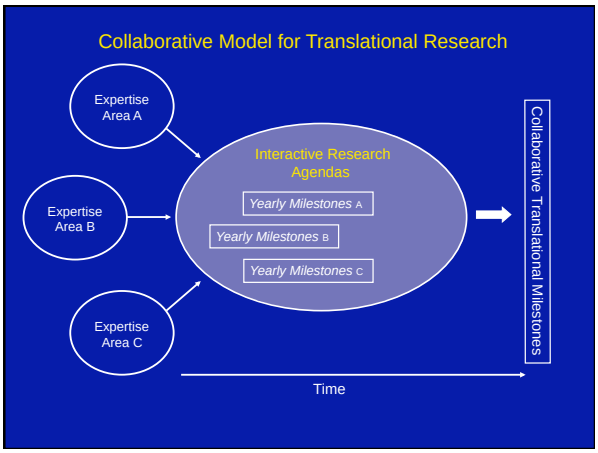
H Varmus: "The pleasure of science lies in the balance between the imagination of the individual and the conviction of the community." (in The Art and Politics of Science)

E Zerhouni: "Effective scientific teams of the future will require closer working relationships among basic, translational, and clinical scientists. Traditional disciplinary, departmental, and other artificial or organizational barriers will have to be breeched in an era of scientific convergence in which basic life processes have been shown to be common across disease conditions, chronic multisystemic diseases are the norm rather than the exception, and research tactics and strategies have become very similar across diseases." (JAMA)

The production process for research matters, but almost no research has been carried out on how to find solutions to medical research problems or to optimize translational research.

We need research on research.





Summation

Cellular neural repair interventions for SCI, stroke, TBI, MS, and ALS and other degenerative diseases may augment neuro-rehabilitation efforts.

The goals for repair strategies must be clearly drawn, not given to patients to decide. The specific effects of the cellular strategy and of task-related practice to lessen impairments and disability will determine the primary outcome measures.

Anecdotes, historical controls, quasi-experimental trials, and faith are misleading ways to develop evidence-based practices. Cellular interventions must be proven to benefit patients by prospective, blinded RCTs in well-defined subjects with a tally of adverse reactions and functionally important outcomes, and follow up for at least 1 year. Clever enrichment strategies for RCTs will be needed to obtain a reasonable effect size.

Funded collaborations among basic and clinical scientists, clinicians, and other experts with proper infrastructure for communication and flexible shared research objectives, as well as relief from perceived barriers such as IP and cross-institutional interactions, is a model for ethical and productive basic and translational stem cell research.

Westwood and the UCLA medical campus

Ethical Considerations in Clinical Trials

Michael Kalichman

CIRM Clinical Trials Workshop
Los Angeles, CA
February 18, 2009

PH Schwartz, MW Kalichman

Ethical Challenges to Cell-Based Interventions for the Central Nervous System: Some Recommendations for Clinical Trials and Practice

Open Peer Commentary,
American Journal of Bioethics

The American Journal of BIOETHICS

UCSD

Irreversibility

- Unlike many other interventions, consequences likely to be irreversible.
- However, obligations similar to other clinical trials:
  1. ***Choose standards to proceed*** in absence of certainty that intervention will be effective or safe
  2. ***Sufficiently inform*** prospective research subjects

UCSD

Are the risks too great?

- Should we stop the research? No
- Standards of medical research:
  - shouldn't intentionally do harm
  - but shouldn't avoid chance of doing good solely because of possibility of harm

UCSD

Should we test for everything?

- Rigorous battery of tests: Costly
  - Research Subjects
  - Money and Effort
  - Time
- Begin such testing only when data from preclinical studies or other clinical trials provide reason to predict particular, measurable outcomes of concern.

What should we do?

1. **Animal studies**

For any interventions likely to be irreversible, the standard for preclinical data should be higher than for other interventions.

What should we do?

A → B
B → C
Therefore
A → C

2. **Mechanisms**

For any interventions likely to be irreversible, the standard for mechanistic explanations of disease and treatment should be higher than for other interventions.

What should we do?

3. **Untreatable and severely debilitating disease**

Restricting initial trials to diseases and disorders with high levels of mortality and morbidity could help balance the unknown risks against the known harms of the particular illness.

What should we do?

4. Robust informed consent process

Prospective research subjects, prospective patients, the families of patients and subjects, treating physicians, *and the researchers conducting the clinical trials* should all be alerted to the fact that this is uncharted territory and that significant anomalies of any kind (not just those we consider likely) should be reported.

What should we do?

5. Anecdotal information

Observations of events of concern should be accumulated during clinical trials and subsequently in clinical practice.

What should we do?

6. Prospective studies to test for plausible risks

The decision to conduct studies of potential adverse events should be based evidence: animal studies, mechanistic explanations, or anecdotal observations during previous clinical trials or applications.

What should we do?

7. Balance risks

Ignorance of special risks of these interventions risks serious setbacks to the field of research.
Placing excessive hurdles in front of such research risks impeding progress.

Either error risks slowing promising new technology, restricting opportunities for clinical studies, and denying patients new therapeutic options.

Summary of Recommendations

Raise standard for evidence before first trials in humans:

1. Animal studies
2. Mechanistic explanations

3. Conduct initial Phase I trials for severe untreatable conditions
4. Enhance informed consent process
5. Anecdotal information
6. Evidence-based testing for adverse events
7. Balance risks

How do we do this?

- Public outreach is essential
- Existing institutional review committees have structure and expertise to address proposed recommendations
- But likely to happen only if specifically charged by regulations that highlight the differences inherent to irreversible interventions

Segment VII: Institutional Implementation of Clinical Research Regulations

Steven Peckman
Eli & Edythe Broad Center of Regenerative Medicine
and Stem Cell Research at UCLA

Outline

- Re-Invent the Wheel?
  - Well-established & effective clinical research review requirements and oversight
    - DHHS-OHRP
    - FDA
    - California (CA Medical Experimentation Act)
    - Academic Medical Centers: Comprehensive Cancer Centers Scientific Review & Monitoring Committees
- IRB review
  - IRB membership/expertise
  - Risk/Benefit calculation
  - Subject selection
  - Informed consent
  - Investigator Conflict of Interest
  - Injury
  - Continuing review, Monitoring & DSMB
- Navigating the old and new compliance committees: SCRO

Institutional Compliance Committees

- Institutional Review Board (IRB)
- Institutional Animal Care & Use Committee (IACUC)
- Institutional Biosafety Committee (IBC)
- Medical Radiation Safety Committee (MRSC)
- Scientific Peer Review Committee (SPRC)
- Gene Medicine Committee
- Conflict of Interest (COI)
- Stem Cell Research Oversight Committee (SCRO)

IRB: Ethical Principles

- Beneficence
- Justice
- Respect for Persons

IRB Review: Membership & Expertise

- Sufficiently qualified through the experience, expertise, and diversity of its members to promote respect for its advice and counsel and safeguard the rights and welfare of human subjects
- Professional competence to review and assess the research in terms of institutional commitments, regulations, applicable law, and standards of professional conduct and practice.

45 CFR 46.107 & 21 CFR 56.107

Selection of Subjects

IRBs are required to assess the appropriate selection of subjects

- Patients v. non-patients
- Patient v. patient
  - Older patients v. younger patients
  - Adults v. minors
  - Earlier v. later disease
  - Received standard of care v. treatment naive

Risk -Benefit

- Nuremberg Code:
  - Avoid all unnecessary physical and mental suffering and injury
  - No experiments where there is an *a priori* reason to believe that death or disabling injury will occur
  - Ensure adequate facilities & preparations to protect the subject against "even remote possibilities of injury, disability, or death"
  - Degree of risk should never exceed the humanitarian importance of the problem to be solved by the experiment
- The Belmont Report
  - Beneficence: maximize benefit and minimize harm
  - Risk / Benefit Assessment = the probability and magnitude of harm and anticipated benefits
  - Harm = Psychological, Physical, Social, Legal, Economic
  - Risks should be reduced to those necessary to achieve the research objective
  - Should determine whether the research justifies the participation of human subjects
  - Significant potential risks requires IRBs to insist on justification of the risk and possible benefits to subjects through a valid research question
- Declaration of Helsinki
  - Should cease research if risks are found to outweigh potential benefits or conclusive proof of a positive or negative result

Risk -Benefit

- Federal Regulations *(45 CFR 46.111(a)(2) & 21 CFR 56.111)*
  - Research may be justified if the risks are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge reasonably expected to result
  - Evaluation:
    - Only those risks/benefits that may result from the research
    - Not include standard therapies that subjects would otherwise receive
  - Tools of the review
    - Scientific protocol
    - Investigator's Brochure or Manufacturer's Device Manual
      - Sufficient pre-clinical studies in relevant animal models
      - Manufacture and potency of cell products
- Continuing Review
- Federal Guidelines: Data & Safety Monitoring Plans

Managing Expectations

August 7, 2006

February 9, 2009

Informed Consent: Respect for Persons, Dignity & Autonomy

- The Nuremberg Code
  - "The voluntary consent of the human subject is absolutely essential."
- The Belmont Report
  - Individuals should be treated as autonomous agents
  - Persons with diminished autonomy are entitled to extra protection
- Federal Regulations *45 CFR 46.116*
  - "No investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative.
  - "The information that is given to the subject or the representative shall be in a language understandable to the subject."

What is legally effective informed consent? The Basic Elements

1. Research
2. Voluntary
3. Purpose
4. Procedures, including duration
5. Risks
6. Benefits
7. Alternatives
8. Confidentiality
9. Costs
10. No penalties or loss of benefits
11. Withdrawal
12. Waiver of rights
13. Contact the PI
14. Contact the OPRS
15. Signature (when documented consent is required)
16. When appropriate:
    - Injury
    - Unforeseeable risks
    - Circumstances that might warrant termination
    - Significant new findings

Informed Consent & Assent

- Informed consent is more than a document
  - Process of communication
    - Begins at identification of potential subjects
    - Create an environment for dialogue
  - Comprehension
    - Empower subjects' knowledgeable decision making
    - Various tools to accomplish the goal of comprehension
  - Voluntariness

Context of Consent

"Language and culture have subtle implications for disclosure and consent."

- C. Cox McPherson and R. L. Connolly, Enough is Enough? Disclosure in Cross-Cultural Research, IRB: May – June 2002.

"Because the subject's ability to understand is a function of intelligence, rationality, maturity and language, it is necessary to adapt the presentation of the information to the subject's capacities."

- *The Belmont Report*

World and Worlds Apart: LA Times

- *Jane E. Allen, L.A. Times, November 6, 2000.*

224 languages spoken in California

40% of Los Angeles County residents born in another country

Those on the front lines of patient care do not doubt a communication gap exists.

Medical access for foreign speakers doesn't simply involve hiring people who speak other languages; it means having interpreters who can deftly convey doctors' and patients' points of view while protecting confidentiality.

Who are the Subjects? Basic Demographic Assumptions

Majority v. Minority

California in the 1940s:
89.9 percent European American

David Hayes-Bautista, "Formulating Health Policy in a Multicultural Society," Health Policy and the Hispanic, ed. Antonio Furino, (Boulder: Westview Press, 1992)

Who are the Subjects? Challenge Assumptions….

California of the 1990s:

Rapid and unprecedented demographic changes challenge our assumptions

- Population changes reversed the traditional demographic structure and CA now has a minority Euro-American population
- Changing demographic trends challenge us to "question assumptions" of minority versus majority as well as homogenous Euro-American value systems that may not be applicable to communities of color

L.A. Workers Held Back by Low Education Rate

"One in 10 adults in the Los Angeles region has six years of education or less. The rate is the worst of all U.S. metropolitan areas, including the immigrant magnets of New York, Chicago, and Miami, and is more than double that of San Francisco and Sacramento…."

Nancy Cleeland, L.A. Times, February 5, 2002.

"53% of working age LA County residents have trouble reading street signs or bus schedules, filling out job applications or understanding a utility bill. The national average is 48% according to the 1992 National Adult Literacy Survey."

Jean Merl, LA Times, September 9, 2004.

What we understand…

- 1992-2003, the percentage of adults with graduate school experience who were rated proficient in prose reading dropped by 10 points = 20% rate of decline.
  USDoEd, NCES, National Assessment of Adult Literacy, 2007
- The number of adults w/BA, BS, etc., and "proficient in reading prose" dropped from 40% in 1992 to 31% in 2003.
  National Endowment of the Arts, To Read or Not Read, 2008.
- On average, Americans ages 15-24 spend almost 2 hours a day watching TV and only 7 minutes of their leisure time on reading.
  USDoLabor, Bureau of Statistics, American Time Use Survey, 2006

Changing vision of research

- 1970s: *The Belmont Report*
  - Research ≠ Treatment
  - Research is a burden
  - Protectionist
  - Exclusionary
- 1980s: AIDS crisis
  - Research = Treatment
  - Research is a benefit
  - Inclusion
  - Right

Research ≠ Treatment

Therapeutic Misconception

"Research itself is not therapeutic; for ill patients, research interventions may or may not be beneficial. Indeed the purpose of evaluative research is to determine whether the test intervention is in fact therapeutic." *- OHRP IRB Guidebook*

"It is ethically problematic if both investigators and patient volunteers see research from an exclusively therapeutic perspective… In the face of this potential divergence between pursuing patient-centered beneficence and scientific knowledge, the orientation of investigators as clinicians can promote a form of 'cognitive dissonance.'"

- Franklin Miller, et.al., Professional Integrity in Clinical Research, JAMA, Vol 280, No 16, October, 18, 1998

Phase I Research

- What is the purpose of a Phase I Clinical trial?
  - Treatment
  - Study
  - Research
  - Experiment
- Test safety and define appropriate dose (maximum tolerated dose). How is this done?

Phase I Oncology Trials

- Consent forms for phase 1 oncology studies:
  - almost never promise direct benefit to subjects,
  - rarely mention cure, and
  - usually communicate the seriousness and unpredictability of risk
- Although there is room for improvement, the substance of these forms is unlikely to be the primary source of misunderstanding by subjects in phase 1 oncology trials.

Horng, et.al., NEJM 2002;347:2134-40.

Phase I Human Gene Transfer

- "Therapeutic misconceptions, which are well documented for oncology trials, may be particularly prevalent in trials of novel biotechnologies such as gene transfer, recombinant drugs, or stem cells."
  - Greater uncertainty and hazard, therefore, enroll people with advanced disease who are more susceptible to therapeutic misconception
  - Biotechnologies regarded by clinicians and public as heralding revolutionary advances [new is better]
  - Clinicians who develop novel approaches often conduct their own clinical trials

Kimmelman & Levenstadt, *Elements of Style: Consent Form Language in Phase 1 Gene Transfer Trials*, Human Gene Therapy 16:502-508 (April 2005)

Testimonials: RCTs

-Paul Applebaum, et.al.,Therapeutic Misconception in Clinical Research, IRB: Ethics & Human Research, v26, n2: March-April 2004

- Subject #345

  (Interviewer): [clarifying previous response] So [the choice of treatment] does depend on what each individual needs?

  (Subject): I think so, yes. I think they do take into account what each person needs.

Testimonials: RCTs

-Paul Applebaum, et.al.,Therapeutic Misconception in Clinical Research, IRB: Ethics & Human Research, v26, n2: March-April 2004

- *Subject #112:* I think it's a win-win for anybody. I don't think they would ask you to do this or present this to you if they didn't think it was going to help you.

Interviewer: So do you think that they are giving everyone the best treatment?

- *Subject #318:* I don't think they'd be in this if they didn't. You know it's just like being a doctor with a sign on the door. You know, they're healers.

Testimonials: RCTs

-Paul Applebaum, et.al.,Therapeutic Misconception in Clinical Research, IRB: Ethics & Human Research, v26, n2: March-April 2004

- 31% (n=70) expressed inaccurate beliefs regarding the degree of individualization treatment
- 51.1% (n=115) manifested unreasonable belief in the nature of the likelihood of benefit, given the methods of the study
- 61.8% (n=139) of subjects were judged to have a therapeutic misconception on one (n=93) or both (n=46) of these bases.

Testimonials: RCTs

Who were the subjects?

- 225 subjects from 44 clinical trials
  - 99 subjects from 26 studies at center One
  - 126 subjects from 18 studies at center Two
- 18 – 82 years of age
- 68 male (30.2%)
- 157 females (69.8%)

- 91% non-Hispanic white
- 5.4% African American
- 1.3% Hispanic
- 2.7% other
- 14.2 years of schooling (mean)

-Paul Applebaum, et.al.,Therapeutic Misconception in Clinical Research, IRB: Ethics & Human Research, v26, n2: March-April 2004

Research Acronyms

- Clinical research meets Marketing Strategies
- Therapeutic Misconception
  - CURE: Clopidogrel in Unstanble Angina to Prevent Recurrent Events
  - SURVIVE: Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support
  - AWESOME, BRILLIANT, CASH, COURAGE, PROTECT, PROSPER, VIGOR, BIGMAC, HERO, CABG PATCH, ALIVE
- Is marketing taking over appropriate decision making?

Explaining the Risks/Benefits in Phase I

- Benefits
  - There is no intent to prove effectiveness
  - There is no direct benefit intended
  - Subjects may experience a psychological benefit from the altruistic participation on behalf of others
- Risks:
  - Potential risks
    - Unknown toxicities
    - Known toxicities from similar research or relevant animal models
    - Inability to control proliferation of cells
    - Worsening condition or disability
  - ISSCR Guidelines
    - Acknowledges the novelty and unpredictability of early stem cell based research
    - Differentiation potential (unipotent v. multipotent)
    - Integration of cells into tissue
    - Pre-clinical animal findings
      - May not accurately reflect human disease or predict toxicities
      - May not provide full prediction of immune or other biologic responses in humans
    - Stem cells may
      - Act on several different targets with both detrimental and beneficial effects
      - Risk of ectopic tissue and tumor formation
      - Transplants persisting for many years with actions that are irreversible necessitating careful subject monitoring and long-term follow-up

Alternatives to Research

- Standard care
- If the potential subjects are suffering from a terminal illness, and there are no alternative treatments available:
  - Palliative care
  - Treatment of symptoms and pain control are available through supportive care such as, hospice, home health care, clinics, private physicians, etc. e.g., supportive care
  - Avoid suggesting that participation in the research is the only way to obtain medical care and attention
- Rehabilitation

Injury from the Research

- Federal Regulations *(45 CFR 46.116 & 21 CFR 50.25)*
  - No requirement to pay for research related injuries
  - Must indicate:
    - whether any compensation for injury is available
    - whether any medical treatments are available if injury occurs and if so, what they consist of
  - Any additional costs to the subject that may result from the research
- CIRM
  - No specific regulations about injury to subjects receiving a test article in CIRM funded research
  - References obligations consistent with 45 CFR 46 for institutions that hold DHHS Assurance of Compliance *(100100(a))*

Investigator Conflict of Interest (COI)

- **How should IRBs and institutions hosting research manage investigator conflicts of interest when the investigator is also the inventor?**
- CIRM and Federal Regulations
  - No specific human research regulations regarding an investigator who is also an inventor
- ISSCR
  - Acknowledges that the novel research may require investigators to assist in the design and development of the manufacturing process and assays

Post-Approval Monitoring

- Continuing Review: "An IRB shall conduct continuing review of research covered by this policy at intervals appropriate to the degree of risk, but not less than once per year" *45 CFR 46.109(e)*
  - IRB continuing review responsibilities include reviewing reports of adverse reactions and unexpected events involving risks to subjects
  - Information that may impact on risk/benefit ratio should be promptly reported to, and reviewed by, the IRB to ensure adequate protection of the subjects. Based on such information, the IRB may need to reconsider its approval of the study, require modifications to the study, or revise the continuing review timetable.

David Lepay, MD FDA: 2001

Post-Approval Monitoring: Informed Consent

- Federal Regulations *(45 CFR 46.109(e) & 21 CFR 56.109(f))*
  - An IRB shall have authority to observe or have a third party observe the consent process and the research.
  - Empower and facilitate decisionmaking (helping subjects help themselves)
    - As risk-benefit ratio changes
    - As competency changes
- Designated by the IRB to advocate on behalf of research subjects
- Monitors the informed consent process & advocates for the subject
  - Active or passive interaction
  - Singular event (signing) or
  - On-going process
  - Post signing

Duties of the Monitor-Advocate

- Listen & Observe
  - Listen and observe the consent process and communication between the investigator and the subject and the subject's family.
- Ask Questions
  - Be prepared to ask questions in order to facilitate comprehension of the subject.
  - Questions should elicit a response from the subject that requires some deliberation and thought about the research rather than yes/no responses.

Duties of the Monitor-Advocate

- Determination
  - Determine understanding
  - If necessary, request that the investigator re-review the materials with the subject
  - If the monitor does not think the subject understands the research or all items of the consent document, then the subject should not be enrolled in the research.
- **Report to the IRB**

Is it Worth It?

- Change of behavior
  - Anecdotal: Yes
- Helps PI
- Assures the IRB
- May address some ethical issues
- Facilitate or impede autonomy?

Post-Approval Monitoring

- On-going monitoring: "When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects." *45 CFR 46.111(a)(6)*
  - Data and Safety Monitoring Plans
  - Real Time Monitoring
  - Long Term Follow-up

DSMP & DSMB: What does it do?

- Plays an essential role in protecting subjects and assuring integrity of the research
- In existence at least 30 years
- Operated by sponsors, investigators, and IRBs
- COI procedures to minimize evaluation bias
- Develop protocol specific monitoring guidelines
- Provides interim evaluation of accumulating trial data to the sponsor
  - The interim analyses assess safety, efficacy, and data integrity

DSMB: What does it do?

- Conducts
  - Appropriate analysis of the progress of the research and adverse event reports
  - Monitor and make recommendations
    - Enrollment
    - Study procedures
    - Data quality
    - Adherence to protocol
    - Toxicity
- May suspend or recommend early termination of the research
  - Due to safety concerns
  - Inadequate performance or accrual
  - Research objectives attained or unattainable

DSMB Communication

- Should inform IRB of operating procedures
- Do IRBs request DSMB reports?
- Are the reports valuable in informing IRB monitoring & continuing review activities?
- What information do IRBs receive from DSMBs?

Maximizing the Usefulness of DSMBs

- DSMBs rarely meet in real time relationship to the research and AERs.
  - Therefore may take months to uncover and understand a trend that may pose immediate harm to subjects.
- DSMBs are unlikely to account for multiple uses of a product across various experiments
- DSMBs commonly report minimal information to IRBs, such as "things are going well."
  - Never received a DSMB report that indicates which arm of the study has more AER or
  - the DSMB biostatistician resigned because the sponsor was uncooperative as described by an FDA representative during a national meeting.

IRBs, DSMBs, SAEs

- IRBs may need complete information regarding subjects' assignment to study arms in order to maximize the protection of the subjects,
  - Regardless of the scientific impact of unblinding the data.
- The investigator or the research team need not have such information but certainly the IRB should have the information necessary to effectively deliberate and determine appropriate mechanisms for minimizing risks.

Long Term Follow-up

- Cell based research may need long term follow-up of subjects to ensure safety of current and future recipients of the product and maximize generalizable knowledge:
  - Quality of life
  - Life time follow-up in gene transfer research
  - ISSCR: Transplants persisting for many years with actions that are irreversible necessitating careful subject monitoring and long-term follow-up

Comparison of SCRO and IRB Membership and Duties as Defined by CIRM and Federal Regulations

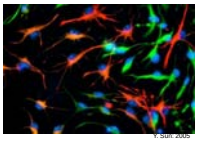
	SCRO	IRB	Scientific Peer Review
MEMBERSHIP			
Scientific expertise	Yes	Yes	Yes
Medical clinical trial expertise	No	Yes	Yes
Ethics expertise	Yes	Implied	No
Community (non-scientist)	Yes	Yes	No
Diversity of membership (race, gender, culture)	Not required	Yes	No
Biostatistics	No	Often but not required	Yes
Pharmacist	No	Often but not required	Yes
RN	No	Often but not required	Yes
DUTIES			
Scientific evaluation	Yes	Yes	Yes
Ethics	Yes	Yes	No
Risk:Benefit analysis	Yes	Yes	Yes
Informed consent	Yes	Yes	No
Accrual	No	Yes	Yes
Education	Yes	Yes	Yes

Summary

- Well-established clinical research review requirements and oversight
  - Includes various compliance committees, including IRBs, DSMBs, RSC, IBC, IACUC, Scientific Review Committees, etc.
  - Governed by Federal and State regulations as well as institutional policies
- IRBs
  - required to have sufficient scientific expertise to evaluate the research and protect human subjects
  - Minimize risks and maximize benefits
  - Ensure respect for the dignity and autonomy of subjects and fair subject selection
  - On-going monitoring of research, including informed consent
- Room for improvement: DSMBs
- Evaluate and minimize redundancy of SCROs in the review of clinical research in order to remove unnecessary roadblocks that provide additional value

What is now proved was once, only imagin'd.

- William Blake, 1790



Y. Sun. 2005