

SPEAKERS

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University of Sheffield

ROBERT N. GOLDEN, M.D.
Dean, School of Medicine & Public Health,
University of Wisconsin – Madison

CARL E. GULBRANDSEN, PH.D., J.D.
Director, Wisconsin Alumni Research Foundation

DEREK HEI, PH.D.
Technical Director, Waisman Clinical Biomanufacturing
Facility and Principal Investigator, National Stem Cell Bank,
University of Wisconsin – Madison

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CEO and President, Stratatech Corporation and Professor,
Department of Pathology and Laboratory Medicine,
University of Wisconsin – Madison

LINDA F. HOGLE, PH.D.
Associate Professor, Medical History & Bioethics,
University of Wisconsin – Madison

TIM KAMP, M.D., PH.D.
Director, Stem Cell & Regenerative Medicine Center,
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RAYMOND LUND, PH.D.
Professor, Casey Eye Institute, Oregon Health
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Research Biologist, Center for Biologics Evaluation
and Research, U.S. Food and Drug Administration

THOMAS B. OKARMA, PH.D., M.D.
President, Chief Executive Officer, Genon

AMISH RAVAL, M.D.
Assistant Professor, School of Medicine & Public Health,
University of Wisconsin – Madison

PETER ZANDSTRA, PH.D.
Professor and Canada Research Chair of Stem Cell
Biotechnology, University of Toronto

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18272-BR-BT



5th Annual Wisconsin Stem Cell Symposium

The Road to Stem Cell Applications

Bioprocessing, Safety & Preclinical Evaluation

April 21, 2010
BioPharmaceutical Technology Center
Madison, Wisconsin

KEY TOPICS

This symposium brings together world leaders in multidisciplinary areas that are actively working to address key hurdles that we face in advancing stem cell therapeutics into clinical and commercial applications.

- What role does cell line characterization and banking play in supporting the transition of stem cell research into clinical and commercial applications?
- What will the FDA focus on reviewing applications to move a cell therapeutic into early-stage human clinical trials?
- What key safety issues need to be addressed when moving a stem cell therapy into human clinical trials and how can *in vitro* and *in vivo* studies be used to assess risk?
- What lessons have we learned from completed and on-going cell therapeutic clinical trials?
- What challenges will we face in delivering cell therapeutics to patients and how can these challenges be addressed?
- What manufacturing challenges remain for commercial applications involving stem cells?

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SCHEDULE OF EVENTS

8:00am	REGISTRATION & CONTINENTAL BREAKFAST
8:30am	Welcome Robert N. Golden, Carl E. Gulbrandsen
8:40am	Human embryonic stem cells: commitment, adaptation and cancer Peter Andrews
9:20am	Integrating cell banking, characterization, and cGMP production efforts to support the efficient translation of stem cell therapeutics into clinical trials Derek Hei
10:00am	BREAK & POSTER VIEWING
10:20am	Bioprocessing for growth and differentiation of stem cells Peter Zandstra
11:00am	Pre-clinical animal studies: a view from the retina Raymond Lund
11:40am	LUNCH AND POSTER VIEWING
1:00pm	FDA requirements for products derived from stem cells Brent McCright
1:40pm	Clinical trials for cell therapies: cell delivery and <i>in vivo</i> imaging technologies Amish Raval
2:20pm	BREAK AND POSTER VIEWING
2:40pm	Development of human embryonic stem cells for therapeutic applications Thomas Okarma
3:20pm	Bench to bedside: Stratatech's path to clinical evaluation Lynn Allen-Hoffmann
4:00pm	PANEL: What are the Next Steps? Challenges and Innovations on the Road to Stem Cell Applications PANEL: Linda F. Hogle (Moderator) and Invited Speakers
4:40pm	Concluding Comments Tim Kamp
5:00pm	RECEPTION Sponsored by: Michael Best & Friedrich LLP

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ABSTRACTS IN ORDER OF PRESENTATION

Human embryonic stem cells: commitment, adaptation and cancer

Peter W. Andrews – When pluripotent stem cells divide, they must choose between self renewal, commitment to differentiation, or apoptosis. Further, if they commit to differentiate they must choose between different lineages. Some degree of spontaneous differentiation is common in cultures of human ES cells and this propensity for differentiation provides a basis for selective pressures that may lead to the appearance of variant ES cells that exhibit an increased probability of self renewal over differentiation, or cell death through apoptosis. Indeed human ES cell lines do accumulate non-random genetic changes on prolonged culture. These genetic changes include amplifications of chromosomes 12, 17 and X similar to those seen in embryonal carcinoma (EC) cells, the stem cells of teratocarcinomas and the malignant counterparts of ES cells. Thus the progressive culture adaptation of human ES cells in culture provides a unique model that may be pertinent to the progression of stem cell based cancers. Accumulating evidence suggests that the ‘stem cell compartment’ in both ES and other stem cells, including cancer stem cells, may be composed of distinct substrates. Another aspect of culture adaptation of human ES cells is that it alters the population dynamics of ES cultures, particularly affecting the behavior of substrates within the stem cell compartment. Understanding the nature of these substrates and their interactions may provide insights into the mechanisms that control self renewal, commitment to differentiation and lineage selection of ES and, ultimately iPS cells. Inevitably these same mechanisms may also play a role in cancer progression.

Integrating cell banking, characterization, and cGMP production efforts to support the efficient translation of stem cell therapeutics into clinical trials

Derek Hei – The successful translation of pluripotent stem cells into human therapeutics will require the development of manufacturing processes capable of producing consistent batches of cells that meet strict Quality Control testing requirements. Pluripotent stem cells pose several unique and significant manufacturing challenges including control of differentiation, genetic stability, and potential tumorigenicity, properties that may be significantly influenced by cell line characteristics. Efficient and successful translation of pluripotent stem cell research into clinical trials will therefore require high quality, well characterized cell banks capable of supporting therapeutic development from research through to human clinical trials. In order to support the growing field of human ES cell research, NIH provided funding to WfCell Research Institute to establish the National Stem Cell Bank (NSCB). Over the past four and a half years, the NSCB has supported human embryonic stem cell (hESC) researchers by banking and distributing NIH-approved hESC lines and developing standardized methods for cell culture, cryopreservation and characterization. Cells distributed by the NSCB underwent extensive testing including characterization studies that provided detailed information on genetic stability, gene expression, and differentiation potential. Efforts from the NSCB program have established a foundation for transition of banking efforts into clinical applications. To support translational research, the Waisman Clinical Biomanufacturing Facility has partnered with WfCell Research Institute to provide hESC Master and Working Cell Banks (M/WCBs) produced under current Good Manufacturing Practice

(cGMP) guidelines. We are currently producing MCBs of the two most widely distributed hESC lines (WA01 and WA09) under cGMPs in the WCBF cleanroom using feeder-independent, defined conditions for cell culture and cryopreservation. Full cGMP documentation was developed for the process and extensive quality control testing was performed on the MCBs. In addition to standard testing for identity, genetic stability, purity, and hESC marker expression, comprehensive testing for potential adventitious agents, including murine adventitious agents, was performed in compliance with FDA and ICH guidelines. We plan to produce additional MCBs for clinical applications as part of the Process Assistance for Cell Therapeutics (PACT) contract that was recently awarded to WCBF/UIW by NHLBI. This program will provide broad support for translation investigators with the potential to support an efficient and economical transition of promising research into human clinical trials.

Bioprocessing for growth and differentiation of stem cells

Peter Zandstra – Local micro-environmental cues consisting of soluble factors, extra-cellular matrix, and cell-cell contacts are determining factors in stem cell fate. These extrinsic cues form a complex niche that governs a stem cell's decision to self-renew (generate equivalent daughter cells) or differentiate (generate functional cells necessary to treat degenerative disease). This presentation will overview my lab's strategies for controlling endogenous and exogenous protein signaling in stem cell cultures, for developing experimental and mathematical descriptions of stem cell niche dynamics, and for designing bioprocesses for the targeted and clinically relevant generation of stem cells or their derivatives. Examples of our work in blood stem cell expansion and embryonic stem cell differentiation will be provided.

Pre-clinical animal studies: a view from the retina

Ray Lund – Determined vision due to photoreceptor degeneration affects up to 10 million people in the US alone. This is due to defects intrinsic to the photoreceptors themselves, or to deficiencies in the environment in which they exist, including dysfunction of the lining cells of the eye, the retinal pigment epithelium (RPE). Cell-based therapies have explored replacing the RPE, improving the ‘chemical environment’ surrounding the photoreceptors or replacing the photoreceptors themselves. Of the human stem cells that have been explored, es-derived RPE for RPE replacement, and somatic neural stem cells have proven particularly effective in rescuing vision and both are moving towards clinical application.

Testing efficacy in rodent models of human diseases represents a major step in this progression and tests relevant to human clinical assessment are critical. Morphological studies show the disposition of the donor cells, allow molecular characterization, and show any indication of atypical transformations or uncontrolled growth. Histological studies also examine survival patterns of host photoreceptors over many months post-transplantation and host responses to the continued presence of the donor cells. Both cell types highlighted have resulted in maintenance of vision and good photoreceptor rescue: neither has elicited untoward reactions. The indication for immune suppression, given that the eye is deemed an immune-privileged site, is still under refinement for the clinical setting.

Further attention has been given to the question of administration of cells to a larger eye, more closely comparable to the human eye, and preliminary studies in non-human primates are encouraging.

In summary, rescue of vision and of photoreceptors has been documented in animal models. Cell transplantation does not elicit adverse reactions and clinical application is already being explored

with the goal of protecting retinal structure and function. For the many patients with slow progressing loss of vision, early intervention with an appropriate cell and safe cell would be ideal. The more complex question of replacing photoreceptors once lost is a topic of growing activity, but presently is still some way from clinic.

Supported by grants from Advanced Cell Technology, Stem Cell Inc, Limby Foundation and Foundation Fighting Blindness.

FDA requirements for products derived from stem cells

Brent McCright – This talk will focus on the preclinical and product characterization information that should be submitted to FDA for review before a stem cell derived product is used in clinical studies. FDA reviews and regulates stem cell derived therapies with the same evaluation criteria used for other cellular therapies. Pre-clinical proof of concept studies should be performed in animal models that reflect the proposed clinical indication as closely as possible. The goals of these studies should be to provide bioactivity and safety information, determine feasibility, identity, route of administration, and to establish a safe and effective dose. Chemistry, Manufacturing and Control (CMC) regulatory concerns that are common to all Biologic Drugs include their safety, identity, purity, and potency. Quality control of the final product and manufacturing intermediates is also important in ensuring product consistency, safety, and efficacy. One of the major concerns associated with the use of stem cell therapeutics is the presence of undifferentiated cells in the final product. Manufacturing methods, in-process assays, and lot release specifications should be developed to minimize the presence of cells with undesired characteristics, including undifferentiated cells.

Clinical trials for cell therapies: cell delivery and in vivo imaging technologies

Amish Ravel – Translating cell-based therapies into humans requires a careful understanding of the therapeutic potential of the cells themselves, but also of how and where the cells are delivered and what happens to their fate. Among the variety of cell delivery methods proposed, those considered “minimally invasive” are most appealing. Investigational targeted delivery and enhanced homing methods may help to exceed a therapeutic threshold dose sufficient to enable tissue repair. Labeling techniques for *in vivo* tracking may permit observations on acute cell retention and chronic cell engraftment, as a step to completely understanding transplanted cell fate in humans.

Key concepts and discussion points in this presentation are as follows:

- Invasive and minimally invasive methods of cell delivery: advantages and disadvantages
- Systemic versus targeted delivery
- Imaging tools available for targeted cell delivery
- Imaging tools available for tracking cells *in vivo*
- Integrating cell delivery and imaging tools into clinical trial design

Discussion points will concentrate on technologies that are under use or are being developed for use in humans, with examples from cardiovascular disease studies.

Development of human embryonic stem cells for therapeutic applications

Thomas Okarma – hESC-based regenerative cell therapies require 1) evidence for reliable production and quality control of product manufacturing, 2) rigorous safety testing in preclinical models, and 3) the design of clinical trial protocols that assess the safety and benefit of the therapy in appropriate patient populations. GRNOPC is a population of allogeneic cells containing oligodendrocyte progenitors derived from

characterized, dedicated, human embryonic stem cell banks. GRNOPC induces myelination of axons in rats with spinal cord injuries and in Shiverer mice, which lack compact myelin, and also produces numerous neurotrophic factors such as midline, BDNF, and activin. Extensive preclinical studies were performed to determine the distribution of GRNOPC as well as any potential toxicities after injection near the thoracic injury epicenter. Pending clearance from the FDA, a Phase I clinical trial to assess the safety of GRNOPC in patients with subacute, complete ASIA A, thoracic injuries whose last fully preserved neurological level is T₃ to T₁₀ will be conducted.

Bench to bedside: Stratatech's path to clinical evolution

Lynn Allen-Hoffman – Major trauma to the skin and chronic, non-healing wounds are life-threatening injuries that often require immediate surgical intervention. Typically, this involves temporary coverage of the wound site with cadaver skin or synthetic dressings to prevent infection and dehydration. Permanent closure of the wound is generally accomplished through subsequent split-thickness skin autografting. Although this regimen is the standard of care, safe and effective alternatives are needed to improve care for patients with these life-threatening wounds. Stratatech Corporation has developed StrataGraft[®], a novel living human skin substitute with the biological structure and function of natural human skin, for the treatment of burns and other skin trauma. A clinical trial evaluating the safety and initial effectiveness of the StrataGraft[®] skin substitute was completed in 2008. In patients with major skin trauma that required temporary skin replacement before autografting, StrataGraft[®] skin substitute was well tolerated and equivalent to cadaver allograft, the standard of care, with respect to antigenicity of the allograft as well as to subsequent autograft take. Notably, there were no adverse or serious adverse events associated with exposure to StrataGraft[®] skin substitute. In addition to StrataGraft[®], Stratatech is developing the ExpressGraft[®] line of enhanced skin substitute tissues. These next generation cell-based therapies are engineered to express factors known to enhance wound healing and combat infection. Following public review and commentary from the NIH Recombinant DNA Advisory Committee, Stratatech recently received a unanimous vote in favor of a proposed clinical trial for an ExpressGraft[®] product. This review confirmed the strategic approach taken for development of ExpressGraft[®] therapeutic products.

PANEL: What are the Next Steps? Challenges and Innovations on The Road to Stem Cell Applications

Linda E. Hogle (Moderator) – In their individual presentations, speakers in this symposium will discuss the complexity of issues facing stem cell research on the road to therapeutic and other commercial applications. Much work remains in the areas of standardized methods for culture and characterization, the choice of preclinical models, identifying appropriate evidence of safety and efficacy, and managing manufacturing and scale-up. Add to this picture the new landscape of changes in oversight, funding and distribution policies plus an uncertain economic climate, and it is clear that the field needs concentrated effort beyond issues related to specific cell lines or applications. Rather, broader thinking is needed about best research practices, most appropriate regulatory pathways, and supportive organizational strategies that will sustain the field as a whole. Symposium speakers will join together in this panel to discuss the challenges ahead as well as opportunities to innovate new ways of thinking about problems in bioprocessing and evaluation of stem cell products.

Coordinated by the University of Wisconsin Stem Cell & Regenerative Medicine Center, the Waisman Clinical Biomanufacturing Facility and the BioPharmaceutical Technology Center Institute. For more information & to register, please visit www.bpci.org.