NHLBI PACT Workshop

Cell Therapy for Pediatric Diseases: A Growing Frontier

September 14 – 15, 2011

National Library of Medicine
Lister Hill Center Auditorium
National Institutes of Health
Bethesda, Maryland
September 14, 2011

Dear Workshop Attendees:

Welcome to the “Cell Therapy for Pediatric Diseases: A Growing Frontier” workshop. This is the first PACT meeting focusing on the special needs of pediatric populations. Cellular therapies are among the few areas in which the opportunities for therapeutics for children may be significantly greater than those for adults. The smaller size of the recipients is an advantage here; in contrast, it is a disadvantage in developing left ventricular assist devices. The patients heal in spite of us, and may be able to tolerate the imperfections of our therapies. They don’t feel sorry for themselves. And if we are successful, they reclaim the healthy lives we and their parents so desperately want for them.

The unique needs of pediatric patients also offer real challenges. Kids are more likely to need allogeneic transplants than autologous ones, so the source of stem cells is problematic. The diseases are different - rare inherited metabolic diseases are just not the same as multiple myeloma – but if they are monogenic, repairing a gene instead of replacing an entire organ system makes sense. In some cases, such as many of the bone marrow failure syndromes, kids may not tolerate the treatments we have to give them to enable gene repaired cells to dominate, or allogeneic cells to engraft. Kids have a long time to manifest the impact of their diseases and our therapies on all their organs, not just hematopoietic and immunologic.

Recent clinical successes in gene therapy and technologic advances which address persistent problems have renewed our optimism that we may finally be able to realize the elusive promise of these modalities. Recent data on the impact of sickle cell disease on the brains of clinically well adults raise the question of whether we should be transplanting more of these patients in childhood; less toxic modalities and better cellular products would open up new opportunities. And in the next decade or so, the potential for better engineering of cellular products may provide many patients with options they don’t have now. We have many opportunities, and owe it to our patients to identify and pursue them.

The National Heart, Lung, and Blood Institute (NHLBI) is pleased to sponsor this workshop through the Production Assistance for Cellular Therapies (PACT) program. The workshop consists of three scientific sessions. Each session will focus on a defined group of diseases and disorders affecting the pediatric population. The clinical applications of cell and gene-based therapies and regenerative medicine, including the ethical considerations and clinical trial design, will be examined. In addition to the speakers, a panel composed of ethicists, statisticians, regulatory experts, and parent/patient advocates, will participate in the sessions to provide their respective perspectives.

Our common goal is not only to cure diseases in children but also to ensure the best possible outcomes. This workshop is designed to identify the unique opportunities and challenges of developing cellular therapies in the pediatric population in this emerging and somewhat controversial field.

Sincerely,

Susan B. Shurin, MD
Acting Director
National Heart, Lung, and Blood Institute
National Institutes of Health
Rosa Sanchez Rosen, MD received her BS in Biology from Stanford University in Stanford, California and her MD from the University of Southern California in Los Angeles, California. She completed her pediatric internship and residency at the University of Texas Medical Branch at Galveston, Texas. Dr. Sanchez completed pediatric hematology-oncology and transfusion medicine fellowships at the University of California San Francisco (UCSF) and Blood Centers of the Pacific (BCP) in San Francisco, California. After completing her fellowship training in 2007, Dr. Sanchez was one of four recipients of a Pediatric Transfusion Medicine Academic Career Award (K07), sponsored by the National Heart, Lung, and Blood Institute of the NIH, for the development, implementation, and dissemination of a pediatric transfusion medicine curriculum for medical trainees. Currently, she is an Assistant Clinical Investigator at the Blood Systems Research Institute and Assistant Clinical Professor in the Department of Laboratory Medicine at UCSF. Dr. Sanchez has conducted the following research studies 1) transfusion-related acute lung injury (TRALI): pilot case-control study to evaluate risk factors, 2) cost analysis of hemochromatosis patients as blood donors at BCP, and 3) evaluation of longitudinal platelet counts of frequent plateletpheresis donors at BCP. Most recently, she investigated the incidence and persistence of transfusion-associated microchimerism in medical and surgical pediatric and adult female recipients of leukoreduced and mostly gamma irradiated male donor derived blood components. Her research interests include transfusion medicine education, long-term consequences of blood transfusion in children, and non-malignant pediatric hematology. Dr. Sanchez teaches and supervises laboratory medicine residents on the hospital transfusion medicine service at UCSF. Currently, she is developing pediatric transfusion medicine computer-based teaching modules for laboratory medicine trainees. Dr. Sanchez is a member of the American Association of Blood Banks, the American Society of Hematology, and Committee on Human Research at UCSF.
Workshop Description

This workshop will address strategies to overcome the barriers to advancing the development and delivery of cell-based therapies for pediatric patients, in particular those with rare and life-threatening diseases. The clinical applications of cellular therapies and regenerative medicine, including the ethical considerations and models of clinical trial design, will be examined with intent to optimize overall processes for the future.

Workshop Objectives

- Evaluate the risks, problems with trial enrollment and conduct, and ethical considerations of novel cell-based therapies for patients with life-threatening diseases.
- Review and formulate new directions for upcoming projects and foster expansion of cell therapies and regenerative medicine to encompass a wider range of pediatric patients and diseases.
- Determine appropriate clinical trial design(s) for studies with a small number of patients and identify relevant measurable clinical endpoints to monitor for long-term consequences of cell-based therapies in pediatric patients.
- Identify strategies to bridge gaps and overcome barriers in development, production, delivery, and long-term monitoring of cell therapies for pediatric diseases.

Day 1 – Wednesday, September 14, 2011

Morning Session

7:30 – 8:30 am  Check-in/Continental Breakfast

8:30 – 8:45 am  Meeting Introduction & Objectives – NHLBI

8:45 – 9:15 am  Opening Remarks: “Opportunities and Challenges of Cellular and Gene Therapies for Pediatric Patients”
Rosa Sanchez Rosen, MD

9:15 – 10:30 am  Session 1: “Congenital Blood Disorders” – Part 1
Moderator: John E. Wagner, MD

Hematopoietic Stem Cell Transplantation for Hemoglobinopathies
Mark Walters, MD (Children’s Hospital & Research Center Oakland)

Gene Therapy for Thalassemia
John F. Tisdale, MD (National Heart, Lung and Blood Institute)

Stem Cell Gene Therapy for Immunodeficiency
Sung-Yun Pai, MD (Children’s Hospital Boston)

Thymus Transplantation for Complete DiGeorge Anomaly
M. Louise Markert, MD, PhD (Duke University Medical Center)

10:30 – 10:45 am  Break

10:45 – 11:30 am  Session 1: “Congenital Blood Disorders” – Part 2
Moderator: John E. Wagner, MD

Stem Cell Gene Therapy for Fanconi Anemia
Hans-Peter Kiem, MD, FACP (Fred Hutchinson Cancer Research Center)

Hematopoietic Stem Cell Transplantation for Fanconi Anemia
John E. Wagner, MD (University of Minnesota)

Please turn off all mobile devices while you are in the auditorium.
Day 1 – Wednesday, September 14, 2011

Morning Session Continued

11:30 – 12:30 pm  Panel Q & A
Ethicist – Seema K. Shah, JD (National Institutes of Health)
Ethicist – Lainie Friedman Ross, MD, PhD (University of Chicago)
Statistician – John Scott, PhD (FDA/CBER/OBE/DB)
Patient advocate – Amy Frohnmayer
Regulatory – John Hyde, MD, PhD (FDA)

12:30 – 1:30 pm  Lunch Break

Afternoon Session

1:30 – 3:00 pm  Session 2: “Neurodegenerative Diseases and Brain Injury”
Moderator: Leslie Silberstein, MD

Hematopoietic Stem Cell Transplantation for Adrenoleukodystrophy
Paul J. Orchard, MD (University of Minnesota)

Stem Cell Gene Therapy in Childhood Cerebral Adrenoleukodystrophy
David A. Williams, MD (Children’s Hospital Boston)

Neural Stem Cell Transplantation for Neuronal Ceroid Lipofuscinosis
(Batten Disease): Successes and Challenges
Robert D. Steiner, MD (Oregon Health & Science University)

Progenitor Cell Therapies for Pediatric Traumatic Brain Injury
Charles S. Cox, Jr., MD (University of Texas – Houston)

Can Autologous Cord Blood Correct Acquired Brain Injury in Pediatric Patients?
Joanne Kurtzberg, MD (Duke University Medical Center)

3:00 – 3:15 pm  Break

3:15 – 4:15 pm  Panel Q & A
Ethicist – Seema K. Shah, JD (National Institutes of Health)
Ethicist – Lainie Friedman Ross, MD, PhD (University of Chicago)
Statistician – John Scott, PhD (FDA/CBER/OBE/DB)
Parent advocate – Tracy VanHoutan
Regulatory – David Maybee, MD (FDA/CBER/OCTGT/DCEPT/CEB)
Day 2 – Thursday, September 15, 2011

Morning Session

7:30 – 8:30 am  Check-in/Continental Breakfast

8:30 – 10:00 am  Session 3: “Regenerative Medicine”
Moderator: David Maybee, MD

Clinical Application of ESC derived Motor Neuron Progenitors (MotorGraft™) in the Treatment of Infantile Spinal Muscular Atrophy (SMA) Type I
Kenneth L. Berger, PhD (CA Stem Cell, Inc.)

Human Embryonic Stem Cell Therapy for Spinal Cord Injury
Jane S. Lebkowski, PhD (Geron Corporation)

Transplantation for Extracellular Matrix Disorder: Problems, Premises, and Promises
Jakub Tolar, MD, PhD (University of Minnesota)

The Translation of Tissue Engineered Vascular Grafts for Use in Congenital Heart Surgery
Christopher Breuer, MD (Yale University)

10:00 – 10:15 am  Break

10:15 – 11:15 am  Panel Q & A
Ethicist – Seema K. Shah, JD (National Institutes of Health)
Ethicist – Lainie Friedman Ross, MD, PhD (University of Chicago)
Statistician – John Scott, PhD (FDA/CBER/OBE/DB)
Patient advocate – Amy Frohnmayer
Parent advocate – Tim Ringgold
Regulatory – Keith Wonnacott, PhD (FDA)

11:15 – 11:45 am  Open Mike

11:45 – 12:00 pm  Wrap Up

Please turn off all mobile devices while you are in the auditorium.
Kenneth L. Berger, PhD  
California Stem Cell, Inc.

Kenneth L. Berger, PhD is currently Director of Regulatory Affairs at California Stem Cell, Inc. (CSC, Irvine, California). CSC is developing stem cell-based therapies for spinal muscular atrophy (SMA), amyotrophic lateral sclerosis (ALS, or Lou Gehrig’s Disease), and spinal cord injury (SCI). Dr. Berger has 36 years of experience in the pharmaceutical, biologics, and medical device industries, with 17 years of regulatory and quality management experience. Prior to joining CSC, Dr. Berger held numerous senior QA/RA positions in FDA regulated industries including Irvine Pharmaceutical Services (Irvine, CA), cGMP Validation (West Coast), LifePoint (Ontario, CA), Techniclone (Irvine, CA), and Synbiotics, (San Diego, CA), and also held key R&D positions at VLI (Irvine, CA), American McGaw (Irvine, CA), and Syntex Research (Palo Alto, Ca). He has a comprehensive understanding of new product development and product efficacy evaluations, cGMP regulation and global cGMP harmonized guidance, and is trained in Quality System compliance. Dr. Berger has a PhD in Biochemistry from the University of Southern California, Los Angeles.

Christopher Breuer, MD  
Yale University – New Haven Children's Hospital

Christopher Breuer, MD is an Associate Professor of Surgery at the Yale University School of Medicine. He is a board certified pediatric surgeon and directs the cardiovascular tissue-engineering laboratory at Yale. His clinical work focuses on the surgical management of children born with congenital birth defects. For the past 17 years he has focused his research efforts in the field of cardiovascular tissue-engineering. Tissue engineering is a multidisciplinary science whose goal is to create tissue from its cellular components. He developed the first tissue engineered heart valve and one of the early tissue engineered vascular grafts. His laboratory is the first to receive FDA approval for investigating the use of tissue engineered vascular grafts in humans. He is currently enrolling patients in a study evaluating the safety and growth potential of tissue engineered vascular grafts used in congenital heart surgery.

Charles S. Cox, Jr., MD  
University of Texas Medical School at Houston

Charles S. Cox, Jr., MD is the Children's Fund, Inc. Distinguished Professor of Pediatric Surgery and directs the Pediatric Surgical Translational Laboratories and Pediatric Program in Regenerative Medicine at the University of Texas Medical School at Houston. He directs the Pediatric Trauma Program at the University of Texas-Houston/Children’s Memorial Hermann Hospital in the Texas Medical Center. A Texas native, Dr. Cox received his undergraduate degree from the University of Texas at Austin in the Plan II Liberal Arts Honors Program. Upon graduating from the University of Texas Medical Branch, he completed his Surgery residency at the University of Texas Medical School at Houston. Further post-graduate fellowships were completed in Pediatric Surgery at the University of Michigan, an NIH T32 sponsored clinical and research fellowship in cardiopulmonary support/circulatory support devices/bio-hybrid organs at the Shriner’s Burns Institute, and Surgical Critical Care/Trauma at the University of Texas Medical School at Houston. He is certified by the American Board of Surgery in Surgery, with added qualifications in Pediatric Surgery and Surgical Critical Care.

The Pediatric Translational Laboratories and Pediatric Program in Regenerative Medicine is a multidisciplinary effort that addresses problems that originate with traumatic injury and the consequences of resuscitation and critical care. The Program focuses on progenitor cell-based therapy (stem cells) for traumatic brain injury, and related neurological injuries (hypoxic-ischemic encephalopathy, stroke, spinal cord injury), recently completing the first acute, autologous cell therapy treatment Phase I study for traumatic brain injury in children (Neurosurgery, 2011). Three subsequent INDs have been approved for cell-based therapies for neurological injury.
The program also develops novel bio-hybrid organs using cell-based and tissue engineering approaches to trauma and injury related problems. These efforts have recently resulted in two IND based cell therapeutic studies and three patents in the past two years. The program is funded through the National Institutes of Health, Texas Higher Education Coordinating Board/ Emerging Technology Funds, Industry Collaboration, and philanthropic contributions. The Program is housed in state-of-the-art laboratory facilities (4500 sf), and includes two cGMP facilities for the production of clinical grade cell and tissue products: Hoffberger Cellular Therapeutics Laboratory and the Griffin Stem Cell Therapeutics Research Laboratory.

Dr. Cox has served on scientific study sections/review groups for the National Institutes of Health, American Heart Association, Veterans Affairs MERIT Awards, Department of Defense, Congressionally Directed Medical Research Programs, as well as National Research Programs in Canada, Singapore, Spain, and the Czech Republic. He is the author of over 120 scientific publications, 20 book chapters, and is the editor of a text entitled, Progenitor Cell Therapy for Neurological Injury.

Hans-Peter Kiem, MD, FACP
Fred Hutchinson Cancer Research Center

Hans-Peter Kiem, MD, FACP received his Medical Degree in 1987 and Doctorate in Medicine in 1988 at the University of Ulm, Germany. Dr. Kiem is the José Carreras/E. Donnall Thomas Endowed Chair for Cancer Research; full Member, Clinical Research Division, Fred Hutchinson Cancer Research Center and a Professor of Medicine and Adjunct Professor of Pathology at the University of Washington School of Medicine. Dr. Kiem has extensive experience in stem cell biology and stem cell gene transfer studies including stem cell transplantation and stem cell gene therapy studies in preclinical and clinical studies.

Joanne Kurtzberg, MD
Duke University Medical Center

Joanne Kurtzberg, MD is an internationally renowned expert in pediatric hematology/oncology, pediatric blood and marrow transplantation and umbilical cord blood banking. She is Director of the Pediatric Blood and Marrow Transplant Program at Duke University Medical Center in Durham, North Carolina. Dr. Kurtzberg is also the Director of the Carolinas Cord Blood Bank at Duke, Co-Director of the Stem Cell Laboratory, and Chief Scientific Officer of the Robertson Clinical and Translational Cell Therapy Program. Dr. Kurtzberg earned her medical degree from New York Medical College, internship at Dartmouth Medical Center, and residency at Upstate Medical Center. Dr. Kurtzberg then completed her fellowship at Duke University Medical Center in Pediatric Hematology-Oncology. She joined faculty at Duke in 1983 and is currently the Jerome Harris Distinguished Professor of Pediatrics and a Professor of Pathology at Duke. Dr. Kurtzberg has earned renown in the field of basic research due to her role in the development of several anti-leukemia drugs and for her pioneering work in umbilical cord blood banking and transplantation. Her other work includes the study of actions of recombinant hematopoietic growth factors, the use of umbilical cord blood in human blood stem cell transplantation, the ex vivo expansion of stem cells derived from umbilical cord blood, and the use of cord blood to correct genetic and acquired brain injuries. Dr. Kurtzberg has published almost 400 manuscripts in peer-reviewed journals and 30 chapters for textbooks. Since 1988, Dr. Kurtzberg has mentored 29 post-doctoral fellows in her research laboratory and has served as preceptor to 69 medical students in laboratory and clinical environments. Dr. Kurtzberg holds positions on a number of scientific advisory boards, including the US Department of Health and Human Services Advisory Council on Blood Stem Cell Transplantation. Dr. Kurtzberg is a member of several national and international committees, and currently co-chairs the National Marrow Donor Program Cord Blood Committee and is a member of the Foundation for the Accreditation of Cellular Therapy Board of Directors. Her current research focuses on the uses of cord blood treatment of children with malignant and genetic diseases.
Jane S. Lebkowski, PhD
Geron Corporation

Jane Lebkowski, PhD joined Geron Corporation in 1998 and is currently Senior Vice President and Chief Scientific Officer of the Regenerative Medicine Division. Dr. Lebkowski heads Geron’s human embryonic stem cell program, and is responsible for all research, preclinical development, product development, manufacturing, and clinical development activities. Prior to Geron, Dr. Lebkowski was Vice President of Research and Development at Applied Immune Sciences. Following the acquisition of Applied Immune Sciences by Rhone Poulenc Rorer (RPR, currently Sanofi-Aventis), Dr. Lebkowski remained at RPR as Vice President of Discovery Research. During Dr. Lebkowski’s tenure at RPR, she coordinated preclinical investigations of gene therapy approaches for treatment of cancer, cardiovascular disease and nervous system disorders, and directed vector formulations and delivery development. Dr. Lebkowski received a BS in chemistry and biology from Syracuse University. She received her PhD in Biochemistry from Princeton University in 1982, and completed a postdoctoral fellowship at the Department of Genetics, Stanford University in 1986. Dr. Lebkowski has published over 70 peer reviewed papers and has 12 issued US patents. Dr. Lebkowski serves as the co-chair of the Industrial Committee of the International Society for Stem Cell Research and serves on the editorial boards of several scientific publications.

M. Louise Markert, MD, PhD
Duke University Medical Center

M. Louise Markert, MD, PhD is Associate Professor of Pediatrics and Immunology at Duke University in North Carolina. She graduated summa cum laude from Smith College majoring in biochemistry. She obtained the MD and PhD in the Medical Scientist Training Program at Duke University Medical Center. Her PhD training was in immunology with Dr. Peter Cresswell. She trained in Pediatrics at Duke under Dr. Samuel Katz and then in Pediatric Allergy and Immunology under Dr. Rebecca Buckley. Dr. Markert joined the Duke faculty in 1987. She was Program Director of the Duke NIH-funded General Clinical Research Center from 1993 – 2004. Dr. Markert served on the American Board of Allergy and Immunology from 1996 – 2004 and was Chair of the Board in 2002. She served on the Recombinant DNA Advisory Committee from 1997 to 2001. She currently is serving on the Institute of Medicine Committee to Review Adverse Effects of Vaccines. Dr. Markert has pioneered the development of thymus transplantation for infants born with the fatal primary immunodeficiency complete DiGeorge anomaly. She is internationally known for her work in this area and currently the only investigator in the United States performing this transplantation. She has published 46 research articles plus invited chapters and reviews.

David Maybee, MD
US Food and Drug Administration

David Maybee, MD is a graduate of Swarthmore College and the University of Pittsburgh School of Medicine and is board certified in Pediatric Hematology-Oncology. His internship, pediatric residency and subsequent Pediatric Hematology-Oncology (PHO) Fellowship training all were at Walter Reed Army Medical Center in Washington, DC. He graduated from the fellowship in 1974, and remained on active duty in the Army Medical Corps until 1997, for the last 14 years as director of the Walter Reed PHO fellowship training program, consultant to the Army Surgeon General in his subspecialty, and Associate Professor of Clinical Pediatrics at the Uniformed Services University of the Health Sciences in Bethesda. Since retiring from the military he has been a Medical Reviewer at the FDA for CBER, originally assigned to the CBER Office of Therapeutics Research and Review, and, since 2003, assigned to the CBER Office of Cellular, Tissue and Gene Therapies (OCTGT), Oncology Branch.
Speaker Biosketches

Paul J. Orchard, MD
University of Minnesota

Paul J. Orchard, MD is an Associate Professor of Pediatrics in the Division of Hematology-Oncology and Blood and Marrow Transplantation at the University of Minnesota. He is the Medical Director of the Inherited Metabolic and Storage Disease Bone Marrow Transplantation Program. Dr. Orchard received his MD degree from the Brown University Program in Medicine in 1984, and completed his training in Pediatrics at the University of Wisconsin in Madison in 1987. He did his fellowship training in Hematology-Oncology and Bone Marrow Transplantation in Minnesota, and joined the faculty at the University of Minnesota in 1990. He is board certified in Pediatric Hematology/Oncology.

Dr. Orchard’s focus has been in the use of hematopoietic stem cell transplantation for genetic, metabolic and storage diseases. This includes lysosomal storage diseases such as Hurler syndrome, as well as inherited leukodystrophies including metachromatic and globoid cell leukodystrophy and adrenoleukodystrophy. He also has a long standing interest in osteopetrosis. An important area of study includes the integration of cellular therapy, such as transplantation, with other modalities to optimize outcomes. This includes modifications within the transplant process and the use of enzyme replacement in association with transplant. Dr. Orchard is also studying long-term functional outcomes of transplanted patients with these disorders, and how modification of the transplant process and the addition of other agents can affect these parameters.

Sung-Yun Pai, MD
Dana-Farber Cancer Institute/Children’s Hospital Boston

Sung-Yun Pai, MD received her MD degree with honors from Harvard Medical School in 1994. She trained in pediatrics at Children’s Hospital in Boston from 1994 to 1997 and in Pediatric Hematology-Oncology at Dana-Farber Cancer Institute/Children’s Hospital Boston from 1998 to 2001. She has been on staff at Children’s Hospital and Dana-Farber Cancer Institute since 2001. She evaluates patients with primary immunodeficiency for curative hematopoietic stem cell transplantation.

Dr. Pai has a longstanding interest in the cellular and molecular mechanisms of lymphocyte development and function, as evidenced by published work in the mechanism of action of immunosuppressive medications (calcineurin, tacrolimus and rapamycin) and in the transcriptional regulation of T cell development by GATA-3. Her laboratory investigates the cellular and molecular mechanisms of human immunodeficiency and reconstitution post-transplant. She has clinical expertise in the treatment of severe combined immunodeficiency (SCID) and Wiskott-Aldrich syndrome (WAS) and is part of several research efforts in the diagnosis and treatment of SCID, including a workgroup for universal newborn screening for SCID in Massachusetts, a multicenter trial of gene therapy for X-linked SCID using a self-inactivating gammaretrovirus, and a collaborative trial of gene therapy for WAS using a self-inactivating lentivirus.
Leslie Silberstein, MD
Center for Human Cell Therapy
Boston

Leslie Silberstein, MD received his baccalaureate and MD degrees from the University of Leiden, the Netherlands, and had postgraduate training in Hematology/Oncology and Transfusion Medicine at Tufts-New England Medical Center in Boston, MA. He then joined the staff at The University of Pennsylvania, where he worked from 1983-2000. During this time Dr. Silberstein established an academic transfusion medicine division with the Department of Pathology and Laboratory Medicine. He also served as Director of the Blood Bank and Transfusion Medicine Section, and Associate Director, Bone Marrow Transplant Program.

Dr. Silberstein was then recruited to Harvard, where he is a Professor of Pathology at Harvard Medical School and Director of the Joint Program in Transfusion Medicine at Children's Hospital Boston, Brigham and Women's Hospital, and the Dana-Farber Cancer Institute. The Joint Program has three interrelated components: research, clinical and educational. An increasingly prominent activity within the Joint Program is the development of cell-based therapies. Dr. Silberstein is the Director of the Center for Human Cell Therapy (CHCT) at the Immune Disease Institute. In addition, Dr. Silberstein is a Senior Investigator at the Immune Disease Institute and Head of the Harvard Stem Cell Institute’s Translational Research Program.

Robert D. Steiner, MD
Doernbecher Children’s Hospital at Oregon Health & Science University

Robert D. Steiner, MD is Credit Unions for Kids Professor of Pediatric Research, Professor of Pediatrics and Molecular & Medical Genetics, and Vice Chair for Research in Pediatrics at Doernbecher Children’s Hospital at Oregon Health & Science University (OHSU) in Portland, Oregon, USA. He earned his MD from the University of Wisconsin in Madison, and completed a residency in pediatrics at Cincinnati Children’s Hospital Medical Center in Ohio and a fellowship in medical genetics at the University of Washington and Seattle Children’s Hospital. Dr. Steiner is board certified in pediatrics, clinical genetics, and clinical biochemical genetics.

Dr. Steiner is the Principal Investigator or Co-Investigator of more than a dozen ongoing clinical trials and clinical research studies on Smith-Lemli-Opitz Syndrome (SLOS), Osteogenesis Imperfecta, Autism, and lysosomal storage diseases including Fabry Disease, Gaucher disease, and Neuronal Ceroid Lipofuscinosis. His research on SLOS and related disorders is funded by the National Institutes of Health, in part by an NIH Rare Disease Clinical Research Network (RDCRN) grant (Steiner PI).

Dr. Steiner is a member of several medical societies, including the American Society of Human Genetics, Society for the Study of Inborn Errors of Metabolism, and the American Society for Biochemistry and Molecular Biology.

John F. Tisdale, MD
NIH, National Heart, Lung, and Blood Institute

John F. Tisdale, MD received his MD degree from the Medical University of South Carolina in Charleston in 1990. He completed an internal medicine and chief residency at Vanderbilt University Medical Center in Nashville and then trained in hematology in the Hematology Branch, National Heart, Lung and Blood Institute (NHLBI), where he served as a postdoctoral fellow. He joined the Molecular and Clinical Hematology Branch of NHLBI in 1998 and is currently a senior investigator in that lab. His group focuses on bone marrow stem cell-based approaches to treat sickle cell disease. The work focuses on the development of methods for transplantation of either normal donor-derived or genetically modified patient-derived bone marrow stem cells.
Jakub Tolar, MD, PhD
University of Minnesota

Jakub Tolar, MD, PhD is originally from the Czech Republic and received his medical education in Prague at the Charles University. In 1992, he came to the University of Minnesota, where he completed his PhD in Molecular, Cellular & Developmental Biology and Genetics. He is currently an Associate Professor in the Department of Pediatrics, Blood and Marrow Transplantation, the Albert D. and Eva J. Corniea Chair, and the Director of Stem Cell/Gene Therapies. He is a member of the graduate faculty of the Microbiology, Immunology and Cancer Biology (MICaB) Program, the Molecular, Cellular, and Developmental Biology and Genetics (MCDB&G) Program, and the Stem Cell Biology (SCB) Program. Dr. Tolar’s research interests include: integrating clinical observation, molecular biology, immunology, and laboratory research in studying and treating children with lethal diseases—cancer, inborn errors of metabolism, and other devastating genetic disorders; developing cellular therapies (including mesenchymal stromal cells and cellular reprogramming; improving the safety of existing therapies (hematopoietic cell transplantation and its conditioning regimens); and investigating mechanisms by which stem cell transplantation is effective in repair of damaged tissues (e.g., heart, skin and brain).

Clinically, Dr. Tolar is currently working on protocols using hematopoietic stem cell transplant as a treatment for Hurler syndrome, Fanconi anemia, recessive dystrophic epidermolysis bullosa, dyskeratosis congenita, and severe aplastic anemia.

John E. Wagner, MD
University of Minnesota

John Wagner, MD is Professor of Pediatrics; Director of the Division of Blood and Marrow Transplantation at the University of Minnesota Amplatz Children’s Hospital and Co-Director of the Center for Translational Medicine at the University of Minnesota. He currently holds two endowed chairs: the Children’s Cancer Research Fund/Hageboeck Family Chair in Pediatric Cancer Research and the University of Minnesota McKnight Presidential Chair in Hematology and Oncology.

Dr. Wagner’s research has focused on the development of new treatment approaches for malignant and non-malignant diseases, including skin diseases, cardiovascular diseases, diabetes, and various neurological diseases. Specific projects include investigation of hematopoietic recovery and engraftment after umbilical cord blood transplantation; prevention of graft-versus-host disease after blood and marrow transplantation; development of novel conditioning regimens; disease specific studies on Fanconi anemia and severe epidermolysis bullosa; and development of novel cellular therapies involving cardiac stem cells, regulatory T cells, dendritic cell based vaccines for brain tumors, NK cells for anticancer therapy, and tissue repair.

Dr. Wagner has served on numerous national and international scientific advisory committees including the National Institutes of Health (NIH) - National Heart, Lung, and Blood Institute (NHLBI), National Marrow Donor Program; Food and Drug Administration (FDA) Biological Response Modifiers Advisory Committee; and the American Association of Blood Banks. He has also made significant contributions as a member of the CIRM’s Standards Working Group, has served as a committee member for the Institute of Medicine’s ‘Establishing a National Cord Blood Stem Cell Banking Program’ and as a member of the National Academies of Science ‘Human Embryonic Stem Cell Research Advisory Committee’.
Speaker Biosketches

Mark C. Walters, MD
Children’s Hospital & Research Center, Oakland

Mark C. Walters, MD is the Jordan Family Director of the Blood and Marrow Transplantation Program at Children’s Hospital & Research Center, Oakland and Associate Adjunct Professor in the Department of Pediatrics at the University of California, San Francisco School of Medicine. Dr. Walters received his AB with honors in Genetics from the University of California, Berkeley and his MD from the University of California, San Diego. He has been active in cooperative clinical transplantation trials and has led several NIH-supported investigations of hematopoietic cell transplantation for sickle cell anemia and thalassemia. He has authored or co-authored many publications with a focus on hematopoietic cell transplantation for hemoglobin disorders, and he has a research interest in the application of umbilical cord blood transplantation for hereditary hematological disorders.

David A. Williams, MD
Children’s Hospital Boston

David A. Williams, MD is the Chief of Hematology/Oncology and Director of Translational Research at Children’s Hospital Boston and Associate Chair of Pediatric Oncology at Dana-Farber Cancer Institute. He was a Howard Hughes Medical Institute Investigator for 16 years and his laboratory has been continuously NIH funded since 1986. Dr. Williams has trained over 45 fellows and post-doctoral fellows and numerous residents and medical students in his laboratory, the majority of which are still in academic medicine. He is a member of the Institute of Medicine of the National Academy of Sciences. He has published over 250 peer-reviewed manuscripts and textbook chapters. Dr. Williams formerly served on the NIH Recombinant DNA Advisory Committee and Gene Therapy Safety Assessment Board. He has been the Principle Investigator, Co-Investigator and/or sponsor of multiple human gene therapy trials. Dr. Williams is actively involved in gene therapy trials for immunodeficiency and neurological genetic diseases. Currently he is serving on the Damon Runyon Cancer Research Foundation Translational Investigator Review Panel and is a councilor for the American Society of Hematology (ASH) and serves on the Joint Oversight Committee of ASH/European Hematology Association Translational Research Training in Hematology. He has served as the Editor-In-Chief of Molecular Therapy from 2004-2009. His basic research has focused on hematopoietic stem cell biology, including genetic diseases of the blood and specifically molecular and biochemical analysis of the interaction between hematopoietic stem cells and the bone marrow supporting environment.
Session 1: Congenital Blood Disorders
Part 1 and Part 2

Session Moderator: John E. Wagner, MD

Session Summary: There is an urgent need for safer effective therapies in the treatment of congenital disorders of the lymphohematopoietic compartment. For these diseases, allogeneic hematopoietic stem cell transplantation is the standard treatment approach with a long track record that clearly demonstrates its curative potential. However, transplantation is associated with substantial risks of treatment-related morbidity and mortality. For this reason, newer transplant and non-transplant cellular approaches are being considered. In this session, the speakers will highlight promising treatment strategies for selected congenital blood disorders and describe the barriers to the translational development and clinical implementation of the particular cellular therapy (e.g., access to preclinical material, regulatory requirements, clinical trial development with appropriate patient eligibility and meaningful endpoints). While scientifically promising, it is often difficult, if not impossible, to quantify the risks associated with the newer cellular therapy. Therefore, the speakers will also discuss obstacles in obtaining access to comparable early and late outcome data between studies in similar populations.

Mark C. Walters, MD
Children’s Hospital & Research Center, Oakland
Title: Hematopoietic Stem Cell Transplantation for Hemoglobinopathies

Sickle cell anemia and thalassemia major together comprise the most common genetic diseases in humans, thus representing a significant world health challenge with regard to health care costs and quality of life. While hematopoietic cell transplantation is curative, it is applied sparingly in the US, in part due to concerns of toxicity and difficulties in identifying suitable donors. Thus, clinical trials have suffered from poor accrual and there are no randomized, prospective comparisons of transplantation and supportive care. However, excellent outcomes after transplantation and a better understanding about the severity of these disorders together have sparked interest in developing transplantation as a broader therapeutic option.

Clinical trials in hemoglobin disorders illustrate: 1) the importance of developing broad consensus among hematology and transplant investigators about study design and multicenter participation to ensure timely trial completion, 2) how education and inclusion of patients and their families in developing a better understanding of long-term disease severity and novel therapeutic options might promote clinical trial participation, 3) a need for short-term clinical endpoints that would enable randomized clinical trial development with cellular therapy as a treatment arm, and 4) how the evolution of these disorders into chronic illnesses has amplified the importance of conducting long-term follow-up studies.
Session 1: Congenital Blood Disorders
Part 1 and Part 2 continued

John F. Tisdale, MD
NIH, National Heart, Lung, and Blood Institute

Title: Gene Therapy for Thalassemia

Globin disorders, such as sickle cell disease (SCD) and ß-thalassemias, represent ideal targets for genetically-based therapeutic approaches. Allogeneic hematopoietic stem cell (HSC) transplantation has demonstrated the proof of concept that even with partial engraftment the disease corrected. For those lacking a suitable allogeneic HSC donor, autologous HSC gene transfer is a promising alternative. Application of HSC gene correction for globin disorders requires high efficiency gene transfer conferring regulated, lineage specific, and high-level globin expression.

The path to clinical trials using HSC gene therapy for hemoglobinopathies illustrates: 1) the difficulty in achieving high gene transfer rates and expression levels while minimizing the risk of insertional mutagenesis, 2) need for tissue specific globin lentiviral vectors, 3) poor predictive value of rodent models for human HSC behavior and need for a suitable large animal disease model, 4) need for clinical phenotype which reliably predicts poor short term outcome and a patient subpopulation appropriate for consideration on experimental therapeutic trials, 5) lack of infrastructure required to perform clinical gene transfer trials at most medical centers, and 6) difficulty in securing funding for incremental work required to move from murine to human studies.

Sung-Yun Pai, MD
Dana-Farber Cancer Institute/Children’s Hospital Boston

Title: Stem Cell Gene Therapy for Immunodeficiency

Severe combined immunodeficiency (SCID) is caused by defects in at least 14 different genes and is fatal without definitive treatment due to death from infection. Standard treatment with allogeneic hematopoietic cell transplantation can be performed successfully with a variety of donor sources, either with or without prior conditioning, but survival remains low in certain high risk categories of patients. The X-linked form of SCID caused by mutations in the IL-2 receptor gamma gene (IL2RG) has been successfully treated with gene therapy, using retroviral vectors to introduce the gene into hematopoietic precursor cells. Unfortunately, 5 of 20 patients treated for X-linked SCID developed leukemia caused by retroviral insertion near oncogenes. Other immunodeficiencies treated with gene therapy include ADA-SCID, chronic granulomatous disease and Wiskott-Aldrich syndrome.

Clinical trials in immunodeficiency illustrate: 1) the need for robust collaborative studies of outcome after standard treatment(s) and risk stratify, 2) unique challenges presented by treatment of rare diseases in a vulnerable population, 3) hurdles that particularly impact implementation and accrual to small trials, and 4) the need for systems that support and foster international collaboration for rare diseases.
DiGeorge anomaly is a congenital disorder characterized by hypoparathyroidism, congenital heart disease and thymic hypoplasia. This is a heterogeneous condition with approximately 50% due to 22q11 hemizygosity. Infants with complete DiGeorge anomaly are athymic and represent approximately 1% of all DiGeorge infants. Lacking thymus, infants with complete DiGeorge anomaly cannot make T cells and usually die from infection by 2 years of age. Treatment of these infants with thymus transplantation using unmatched allogeneic thymus tissue has led to survival of 70% of infants. Host T cells develop in 97% of surviving infants. Despite developing in an unmatched thymus, the host T cells are able to protect the recipient and prevent development of serious disease such as EBV-associated lymphoproliferative disease.

Clinical trials in complete DiGeorge anomaly illustrate: 1) the challenges of funding for regulatory requirements and attracting industry sponsors for a very small patient population, and 2) the need for a registry that collects outcome data on all complete DiGeorge anomaly patients in order to assess efficacy and safety of therapies being used.

As a monogenic inherited disorder with hematological manifestations, Fanconi anemia (FA) is an attractive candidate disease for gene therapy of autologous hematopoietic stem/progenitor cells. For the past fifteen years, various groups have attempted gene therapy in this disease setting; however, these studies have been hindered in their success, first by poor gene transfer efficiencies and then low isolation and recovery of HSCs from FA patients. Advances in gene transfer technology, including improved retrovirus vectors and protocols for gene delivery have greatly facilitated efficiency and safety of gene transfer to hematopoietic stem/progenitor cells. Using these improved approaches, we have shown that hematopoietic stem/progenitor cells from FA patients can be efficiently corrected. In animal studies we have shown that the proposed vector is safe and allows for the selection of corrected cells. Based on these discoveries, we will initiate a clinical trial in patients with FA. The initial trial will utilize a safety-improved lentiviral vector in patients with FANCA, older than > 6 years and without an HLA-matched sibling donor.

The path to initiate a gene therapy trial in FA illustrates: 1) difficulties in obtaining patient cells, 2) difficulties in finding a suitable patient population when there are competing treatment strategies, 3) difficulties when ideal animal models are not available, 4) intense regulatory burden for gene therapy trials, and 5) high cost of studies requiring large animal models.
Session 1: Congenital Blood Disorders
Part 1 and Part 2 continued

John E. Wagner, MD
University of Minnesota

Title: Hematopoietic Stem Cell Transplantation for Fanconia Anemia

Fanconianemia (FA) is a genetically and phenotypically heterogeneous autosomal and X-linked recessive disorder characterized by congenital malformations, progressive marrow failure, and marked predisposition to malignancy. As of 9/2011, allogeneic hematopoietic cell transplantation (HCT) remains the only treatment with the potential of correcting the hematological manifestations of FA. While poor outcomes after allogeneic HCT before 2000 were primarily the result of excessive regimen-related toxicity, graft failure and complications of acute graft-versus-host disease, the expectation today is survival >80% for those with an unrelated donor and >95% for those with an HLA matched sibling donor with excellent quality of life. However, new challenges, namely high risk of endocrinopathies, infertility and cancer remain particularly as HCT survivors age.

Clinical trials in FA illustrate: 1) the need for novel statistical methods for small sample sizes, 2) importance of the family support group in design and accrual to clinical trials, and 3) importance of focused research efforts for a specific rare disease at a single center.

Session 2: Neurodegenerative Diseases and Brain Injury

Session Moderator: Leslie Silberstein, MD

Session Summary: Allogeneic hematopoietic stem cell transplantation (HSCT) is a possible treatment for selected peroxisomal and lysosomal storage diseases. While HSCT may ameliorate or prevent further neurodegeneration in this setting, it has recently been considered in the treatment of acquired head injury, a leading cause of trauma-death among children. Novel cell-based therapies with various stem cell populations, such as neural stem cells and genetically-modified HSCs, are being considered in the treatment of lysosomal storage diseases in an attempt to augment or replace deficient enzyme activity or repair damaged neural tissue. Similarly, novel cell-based therapies, such as with umbilical cord blood, are being considered for the treatment of acquired brain injury in an attempt to replace or repair the damaged brain. In this session, the speakers will highlight the challenges (e.g., short- and long-term costs, small sample sizes, cell processing, and identification of biomarkers to predict severity of disease) of pre-clinical and clinical trial development in the context of cell-based therapies to treat children with inherited neurodegenerative diseases and acquired brain injury.

Paul J. Orchard, MD
University of Minnesota

Title: Hematopoietic Stem Cell Transplantation for Adrenoleukodystrophy

Adrenoleukodystrophy (ALD) is an X-linked peroxisomal disease that can result in a diffuse central nervous system inflammatory process ultimately resulting in progressive demyelinating process associated with neurological deterioration and early death. Over four decades ago the pioneering studies of Neufeld et al provided the proof of concept that normal cells producing enzyme could “cross-correct” cells derived from patients with lysosomal storage diseases (LSD). Based on these findings, allogeneic hematopoietic stem cell transplantation (HSCT) was utilized as therapy for LSD. Over the past 3 decades, it has been established that HSCT can result in disease stabilization for selected LSDs, including Hurler syndrome, metachromatic leukodystrophy and globoid cell leukodystrophy. Recent availability of recombinant enzyme presents new opportunities for evaluating the potential impact of enzyme on HSCT outcomes, combining enzyme and HSCT.

Clinical trials in ALD illustrate: 1) hurdles in identifying a) genetic and clinical parameters for predicting the cerebral form of the disease before its onset and b) sensitive neuropsychological test parameters for predicting response to therapy, 2) need for non-neurotoxic immunosuppressive agents, and 3) need for a registry to systematically collect data on all ALD patients regardless of therapy long term.
David A. Williams, MD
Children's Hospital Boston

Title: Stem Cell Gene Therapy in Childhood Cerebral Adrenoleukodystrophy

Childhood cerebral adrenoleukodystrophy (CCALD) has been treated with allogeneic hematopoietic stem cell transplantation (HSCT). Although it has been shown to ameliorate disease progress, allogeneic HSCT is limited by donor availability and high risk of morbidity and mortality. As an alternate strategy, gene correction has been considered. The use of viral vectors today allows high efficiency transfer of genetic sequences into rare disease populations, including HSCs. HSCs are advantageous targets of gene transfer for therapeutic purposes because they are long-lived, have self-renewal capacity and are able to differentiate into all blood lineages. Using advanced gene transfer methods, gene therapy has now proven efficacious in several immunodeficiency diseases, although serious side effects have been encountered in some trials. This approach has now been applied in CCALD. This talk will focus on the basic technology of stem cell gene transfer for therapy of human diseases, the results of first in human trials for CCALD and the planned multi-institutional trial for this disease currently undergoing regulatory review.

HSC gene therapy for ALD illustrates: 1) need for multi institutional collaborations for rare diseases, 2) high cost for establishing validated, highly technical clinical cell processing methodology, and 3) hurdles in applying a novel treatment approach to diseases with effective established therapies.

Robert D. Steiner, MD
Oregon Health & Science University

Title: Neural Stem Cell Transplantation for Neuronal Ceroid Lipofuscinosis (Batten Disease): Successes and Challenges

Infantile and late-infantile neuronal ceroid lipofuscinosis (NCL) are lysosomal storage diseases which are uniformly fatal and for which no treatments are available. Fetal neural stem cells may be a promising approach based on preclinical work in a relevant murine model. In 2006, a Phase I clinical trial of fetal neural stem cell transplantation for NCL was initiated, representing the first use of purified neural stem cells in humans. Results of the clinical trial will be presented.

Neural stem cell transplantation for NCL illustrates: 1) difficulty in sustained recruitment in rare diseases especially those for which there are multiple early phase clinical trials, 2) challenges with identifying appropriate outcome measures for neurodegenerative disorders in children, and 3) obstacles in moving past successful Phase I clinical trials in rare diseases.
Session 2: Neurodegenerative Diseases and Brain Injury continued

Charles S. Cox, Jr., MD
University of Texas Medical School at Houston
Title: Progenitor Cell Therapies for Pediatric Traumatic Brain Injury

Traumatic brain injury (TBI) is a common cause of death and disability in children. There are currently no effective reparative treatments for TBI. Progenitor cell therapy has shown promise in pre-clinical and Phase 1 clinical trials for severe TBI in children. A Phase 2 clinical trial is proposed (submitted to NINDS). Many barriers to the execution of pediatric cell-based therapies exist. The trials are very expensive and often require specific pre-clinical, IND enabling studies related directly to the disease/injury type. There is not a central federal funding home that cuts across institutes at the NIH, and this impedes the movement forward outside of industry sponsors (who are often reluctant to pursue pediatric trials). Although the NINDS has moved to the Common Data Elements and new consensus outcomes measures, the FDA has continued to request studies powered toward a dichotomized Glasgow Outcome Scale (GOS). Finally, there has not been uniform enforcement of FDA based regulations, undermining the legitimate trials. Solutions include a trans-NIH initiative (and study sections) focusing on cellular therapies for children within certain disease “silos”, novel statistical design to reduce sample size requirements such as Bayesian approaches, and robust enforcement of non-approved approaches.

Cell therapy for traumatic brain injury illustrates: 1) requirement of expensive specific pre-clinical, IND enabling studies related directly to the disease/injury type, 2) need for central federal funding home that cuts across NIH institutes without which forward movement through the translational pipeline is impeded, 3) need for consensus on outcome measures, and 4) need for novel statistical designs to reduce sample size requirements.

Joanne Kurtzberg, MD
Duke University Medical Center
Title: Can Autologous Cord Blood Correct Acquired Brain Injury in Pediatric Patients?

Cerebral palsy (CP) can be a devastating disease resulting from hypoxic ischemic encephalopathy (HIE) at birth or in utero stroke. CP affects 1 in 500 children and is a major life-long health issue. Based on preclinical and clinical data with umbilical cord blood (UCB), it is possible that infusion(s) of autologous UCB may ameliorate the severity of the disease. Thus far, ~300 children have been treated with UCB. While early, these studies demonstrate that autologous cord blood can be infused safely with anecdotes of response. However, to objectively determine whether cord blood infusion(s) favorably alter the course of the disease, a randomized, placebo-controlled trial is underway.

Clinical studies of umbilical cord blood cell therapy for acquired brain injury illustrate: 1) difficulty in identifying objective clinical measures of response in a disease where improvements are seen over the early years of life, 2) difficulty in separating placebo from true biological effects, 3) a need for preclinical models closely aligned with human clinical disease to understand potential mechanisms of action and fate of cell therapy in acute brain injury, 4) difficulties in doing research in vulnerable patient populations, 5) management of short term and long term costs of research, and 6) a need for improved and more sensitive biomarkers to predict severity of disease and response to various interventions.

Session 3: Regenerative Medicine

Session Moderator: David Maybee, MD

Session Summary: Regenerative Medicine encompasses an ever-increasing number of complex and evolving cell-based therapies and broad clinical applications, not only limited to congenital disorders, but potentially therapeutic applications for acquired pediatric conditions (e.g., lung, kidney, and traumatic injuries). This session will review the obstacles in the development and implementation of three cellular therapeutic applications for congenital conditions involving the skin, muscle, and heart, and one potential application for pediatric spinal cord injury. In this session, sponsor-investigator and industry speakers will identify possible strategies to minimize or eliminate the roadblocks to product evaluation for safety and efficacy, including preclinical development studies and inclusion of patient populations which are most likely to benefit from such therapies. In addition, the ethical considerations of these novel cell-based therapies for acquired debilitating conditions will be highlighted as these may be different than in patients with congenital life-threatening diseases for which there are no or minimum therapeutic interventions available.
Kenneth L. Berger, PhD
California Stem Cell, Inc.

Title: Clinical Application of ESC derived Motor Neuron Progenitors (MotorGraft™) in the Treatment of Infantile Spinal Muscular Atrophy (SMA) Type I

SMA Type I is characterized by severe, generalized muscle weakness within the first sixth months. Infants are never able to sit. The diagnosis of SMA Type I is usually made before 3 months of age and >95 percent die or require full-time respiratory support in infancy. Type I SMA is the most common form, representing 60 to 70% of newly diagnosed cases. To date, there are no existing treatments that can reverse or delay disease progression from motor neuron death.

MotorGraft™ is a highly purified allogeneic motor neuron progenitor cell population derived from human embryonic stem cells from a single donor embryo. MotorGraft™ was manufactured by California Stem Cell Inc. (CSC) as a cellular therapy for diseases characterized by motor neuron loss, such as SMA Type I, Amyotrophic Lateral Sclerosis (ALS), and spinal cord injury (SCI). Transplantation of MotorGraft™ into the diseased or damaged spinal cord may: 1) secrete motor neuron specific factors that delay the loss of host motor neurons, and 2) replace dying or dead motor neurons. In the latter instance, axonal growth from transplanted cells to the periphery would ultimately restore muscle function.

This proposed ESC derived therapy for SMA Type I illustrates: 1) the difficulties in meeting the regulatory requirements for high-risk ‘first-in-human’ treatments, such finding a similar adult patient population, interpreting the safety and efficacy measures observed in that population where absence of evident benefit might stall product development in the ‘target’ pediatric population or an observed benefit could change an investigational direction away from children, 2) the need for an appropriate animal model for pre-clinical safety and efficacy evaluations, 3) the need for a pre-determined investigational strategy approved by the regulatory bodies, and 4) high cost of translational and clinical research.

Jane S. Lebkowski, PhD
Geron Corporation

Title: Human Embryonic Stem Cell Therapy for Spinal Cord Injury

Spinal cord injuries affect approximately 12,000 individuals annually in the US and include increasing numbers of children and seniors. Human embryonic stem cell-derived oligodendrocyte progenitor cells have the potential to improve the outcome of such injuries as these cells produce neurotrophic factors, stimulate vascularization and induce remyelination of axons, all features important for tissue repair.

The path to and through Phase 1 clinical testing of ES cell derived cellular therapy for spinal cord injury illustrates a number of significant challenges, including: 1) development of robust, scalable manufacturing procedures to produce the therapeutic cell candidate, 2) development of quantitative assays to assess the composition, function, and potency of the product, 3) long, large preclinical development studies to assess the biodistribution, potential toxicity and efficacy of the candidate therapeutic cell type, 4) achieving long-term survival of human cells as a xenograft in preclinical animal models, 5) long start-up phases for clinical studies due to numerous committee reviews, 6) requirements for numerous clinical trial sites due to narrow inclusion/exclusion criteria for first-in-human studies, 7) long-term, rigorous follow-up of patients in the trial, 8) selection of outcome measures for the first-in-human clinical trial, and 9) the need for a staged approach to expand the inclusion criteria in the trials to test the cells in patient populations which are most likely to benefit from such a therapy.
Session 3: Regenerative Medicine continued

Jakub Tolar, MD, PhD
University of Minnesota

Title: Transplantation for Extracellular Matrix Disorder: Problems, Premises, and Promises

Epidermolysis bullosa (EB) is a severe congenital mechanobullous disorder that results in severe scarring and contractures, ultimately leading to shortened survival most often due to infections and an aggressive squamous cell carcinoma. While there are multiple forms of EB, among the severest is recessive dystrophic EB caused by mutations in collagen type VII and junctional EB caused by mutations in laminin 332. Based on proof of concept studies in a murine model demonstrating replacement of missing collagen VII and skin repair, a first in human study was initiated in 2007. To date, 17 patients have been treated (15 recessive dystrophic EB; 2 junctional EB) with survival in 13 and amelioration of the disease clinically in 11. The results of these trials demonstrate that the infusion of allogeneic hematopoietic cells can result in substantial clinical benefit.

These studies illustrate: 1) the importance of proof of concept studies in appropriate animal models for providing the rationale for a novel treatment and future modifications, 2) the difficulty in obtaining early phase financial support especially when the disease is outside your historical area of research focus, 3) need for objective oversight from external experts in the field to insure subject eligibility and evaluate response to treatment, particularly when the treatment is high risk and the population is especially vulnerable, and 4) need for a national registry to collect clinical and biological data from patients treated in various ways (e.g., supportive care, local cellular therapy, local gene or protein injections, application of epidermal grafts, allogeneic cell infusions).

Christopher Breuer, MD
Yale University – New Haven Children’s Hospital

Title: The Translation of Tissue Engineered Vascular Grafts for Use in Congenital Heart Surgery

Congenital cardiac anomalies are the most common birth defect, and despite significant advances in the surgical and medical management of congenital heart disease, it remains a leading cause of death in the newborn period. Complications arising from the use of synthetic vascular grafts include increased risks of thrombo-embolic and infectious complications and are a major source of post operative morbidity and mortality. In addition, such grafts to date have lacked growth potential, which can be quite problematic in the pediatric population. We developed the first vascular graft designed specifically for use in congenital heart surgery, called the tissue engineered vascular graft. This vascular conduit is created by seeding autologous cells onto a biodegradable tubular scaffold. Over time the scaffold degrades as neotissue forms ultimately creating a living vascular graft with growth potential. We have performed an initial pilot study in Japan evaluating the feasibility of using this technology in humans and are currently performing the first clinical trial in the United States.

Clinical trials evaluating tissue engineered vascular grafts in congenital heart surgery illustrate: 1) there is a disconnect between the NIH and FDA that is both an asset and an obstacle. Continued efforts to address this issue could pay great dividends, 2) The significant financial barriers to performing pediatric research can in some cases be greatly reduced using the FDA’s orphan pathway, and 3) while time constraints are a significant barrier to translating research initially they tend to improve with time and experience.
Special Recognition

The NHLBI and PACT group would like to extend our gratitude to the following individuals and the organizations they represent for their dedication, leadership and guidance in organizing this workshop:

**Workshop Chair – Rosa Sanchez Rosen, MD**
(Blood Systems Research Institute)

Robert Lindblad, MD (PACT)
David Maybee, MD (FDA)
Traci Heath Mondoro, PhD (NHLBI)
Leslie Silberstein, MD (PACT)
John E. Wagner, MD (PACT)
Lisbeth A. Welniak, PhD (NHLBI)

**Special Thanks**

To our distinguished speakers and panelists for taking the time to be here and making this event possible.

Kenneth L. Berger, PhD
*California Stem Cell, Inc.*

Christopher Breuer, MD
*Yale University*
*New Haven Children’s Hospital*

Charles S. Cox, Jr., MD
*University of Texas Medical School at Houston*

Hans-Peter Kiem, MD, FACP
*Fred Hutchinson Cancer Research Center*

Joanne Kurtzberg, MD
*Duke University Medical Center*

Jane S. Lebkowski, PhD
*Geron Corporation*

M. Louise Markert, MD, PhD
*Duke University Medical Center*

David Maybee, MD
*US Food and Drug Administration*

Paul J. Orchard, MD
*University of Minnesota*

Amy Frohnmayer
*Patient Advocate*

John E. Hyde, MD, PhD
*US Food and Drug Administration*

Tim Ringgold
*Parent Advocate*

Lainie Friedman Ross, MD, PhD
*University of Chicago*

Sung-Yun Pai, MD
*Dana-Farber Cancer Institute*
*Children’s Hospital Boston*

Rosa Sanchez Rosen, MD
*Blood Systems Research Institute*

Leslie Silberstein, MD
*Center for Human Cell Therapy Boston*

Robert D. Steiner, MD
*Dornerbecher Children’s Hospital at Oregon Health & Science University*

John F. Tisdale, MD
*NICH, National Heart, Lung, and Blood Institute*

Jakub Tolar, MD, PhD
*University of Minnesota*

John E. Wagner, MD
*University of Minnesota*

Mark C. Walters, MD
*Children’s Hospital & Research Center, Oakland*

David A. Williams, MD
*Children’s Hospital Boston*

John Scott, PhD
*US Food and Drug Administration*

Seema K. Shah, JD
*National Institutes of Health*

Tracy VanHoutan
*Parent Advocate*

Keith Wonacott, PhD
*US Food and Drug Administration*
Sponsors and Collaborating Organizations

This workshop is being sponsored by NIH, NHLBI and PACT

PACT Centers

Baylor College of Medicine
Center for Cell and Gene Therapy
Contract Number: HHSN268201000007C

Center for Human Cell Therapy Boston
Contract Number: HHSN268201000009C

City of Hope
Center for Applied Technology Development
Contract Number: HHSN268201000011C

University of Minnesota
Molecular and Cellular Therapeutics
Contract Number: HHSN268201000008C

University of Wisconsin – Madison
Waisman Biomanufacturing
Contract Number: HHSN268201000010C

Coordinating Center
The EMMES Corporation
Contract Number: HHSN268201000006C

This project has been funded in whole or in part with Federal funds from the National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services, under Contract No. HHSN268201000006C.

In collaboration with the following organizations:
Faculty Disclosure Information

The Accreditation Council for Continuing Medical Education (ACCME) is the governing body that accredits AABB to provide continuing medical education credits for physicians. In accordance with the ACCME Standards for Commercial Support, all faculty for this event have signed a conflict of interest form in which they have disclosed any significant financial interests or other relationships with the industry relative to the topics they will discuss during this program. Such disclosure allows you to better evaluate the objectivity of the information presented in the lectures. Please report any undisclosed conflict of interest you may perceive on the evaluation form. Thank You.

<table>
<thead>
<tr>
<th>Faculty Name</th>
<th>Disclosure</th>
<th>Nature of relationship</th>
<th>Manufacturer/Provider</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kenneth L. Berger, PhD - Speaker</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Christopher Breuer, MD - Speaker</td>
<td>Yes</td>
<td>Grants/Research Patent</td>
<td>Pall Corporation, Gunze Limited</td>
</tr>
<tr>
<td>Charles S. Cox, Jr., MD - Speaker</td>
<td>Yes</td>
<td>Grants/Research Ownership/Partnership</td>
<td>Athersys/Celgene Emit Corp</td>
</tr>
<tr>
<td>Amy Frohmayer - Panelist</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>John Hyde, MD, PhD - Panelist</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hans-Peter Kiem, MD, FACP - Speaker</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joanne Kurtzberg, MD - Speaker</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jane S. Lebkowski, PhD - Speaker</td>
<td>Yes</td>
<td>Stocks/Bonds, Other</td>
<td>Geron Corp.</td>
</tr>
<tr>
<td>Robert Lindblad, MD*</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M. Louise Markert, MD, PhD - Speaker</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>David Maybee, MD*</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Traci Heath Mondoro, PhD*</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paul J. Orchard, MD - Speaker</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sung-Yun Pai, MD - Speaker</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Karin Quinnan*</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tim Ringgold - Panelist</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosa Sanchez Rosen, MD* - Speaker</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lainie Friedman Ross, MD, PhD - Panelist</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>John Scott, PhD - Panelist</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seema K. Shah, JD - Panelist</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leslie Silberstein, MD*</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Robert D. Steiner, MD - Speaker</td>
<td>Yes</td>
<td>Consulting/Travel</td>
<td>Actelion, Biomarin, Shire, Genzyme, Amicus</td>
</tr>
<tr>
<td>John F. Tisdale, MD - Speaker</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jakub Tolar, MD, PhD - Speaker</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tracy VanHoutan - Panelist</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>John E. Wagner, MD* - Speaker</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mark Walters, MD - Speaker</td>
<td>Yes</td>
<td>Medical Director</td>
<td>ViaCord Processing Lab</td>
</tr>
<tr>
<td>Lisbeth A. Welniaik, PhD*</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>David A. Williams, MD - Speaker</td>
<td>Yes</td>
<td>Consulting/Travel</td>
<td>Bluebird Bio</td>
</tr>
<tr>
<td>Jamie Winestone*</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Keith Wonnacott, PhD - Panelist</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Debbie Wood*</td>
<td>No</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Indicates members of the planning committee
CME Accreditation Statement

Cell Therapy for Pediatric Diseases: *A Growing Frontier*

September 14-15, 2011

Physicians

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of AABB and PACT. AABB is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians (Provider number 0000381). AABB designates this educational activity for a maximum of 9 hours of Category 1 credit toward the AMA Physicians Recognition Award. Each physician should claim those credits that he/she actually spent in the activity.

California Clinical Laboratory Personnel

AABB is approved by the California Board of Clinical Laboratory Personnel to provide continuing education for California-licensed clinical laboratory personnel (Provider number 0011). AABB designates this education activity for a maximum of 9 credits. California clinical laboratory personnel must provide a personal signature and other required information on the attendance log.

Florida Clinical Laboratory Personnel

AABB is approved by the Florida Board of Clinical Laboratory Personnel to provide continuing education for Florida-licensed clinical laboratory personnel (Provider number 50-4261). AABB designates this education activity for a maximum of 10.8 credits.

Faculty Disclosure

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of AABB and PACT. AABB is accredited by the ACCME to provide continuing medical education for physicians. In accordance with the ACCME Standards for Commercial Supportsm, all faculty for this event have signed a conflict of interest form in which they have disclosed any significant financial interests or other relationships with the industry relative to the topics they will discuss during this program.

Live Learning Center

After the workshop, you will receive an email from AABB with instructions on how to print your CME/CE certificates for the workshop. To access the Live Learning Center, visit [www.aabb.org](http://www.aabb.org).

Please call 301-215-6482 or email professionaldevelopment@aabb.org for questions regarding CME.
Cell Therapy for Pediatric Diseases: A Growing Frontier