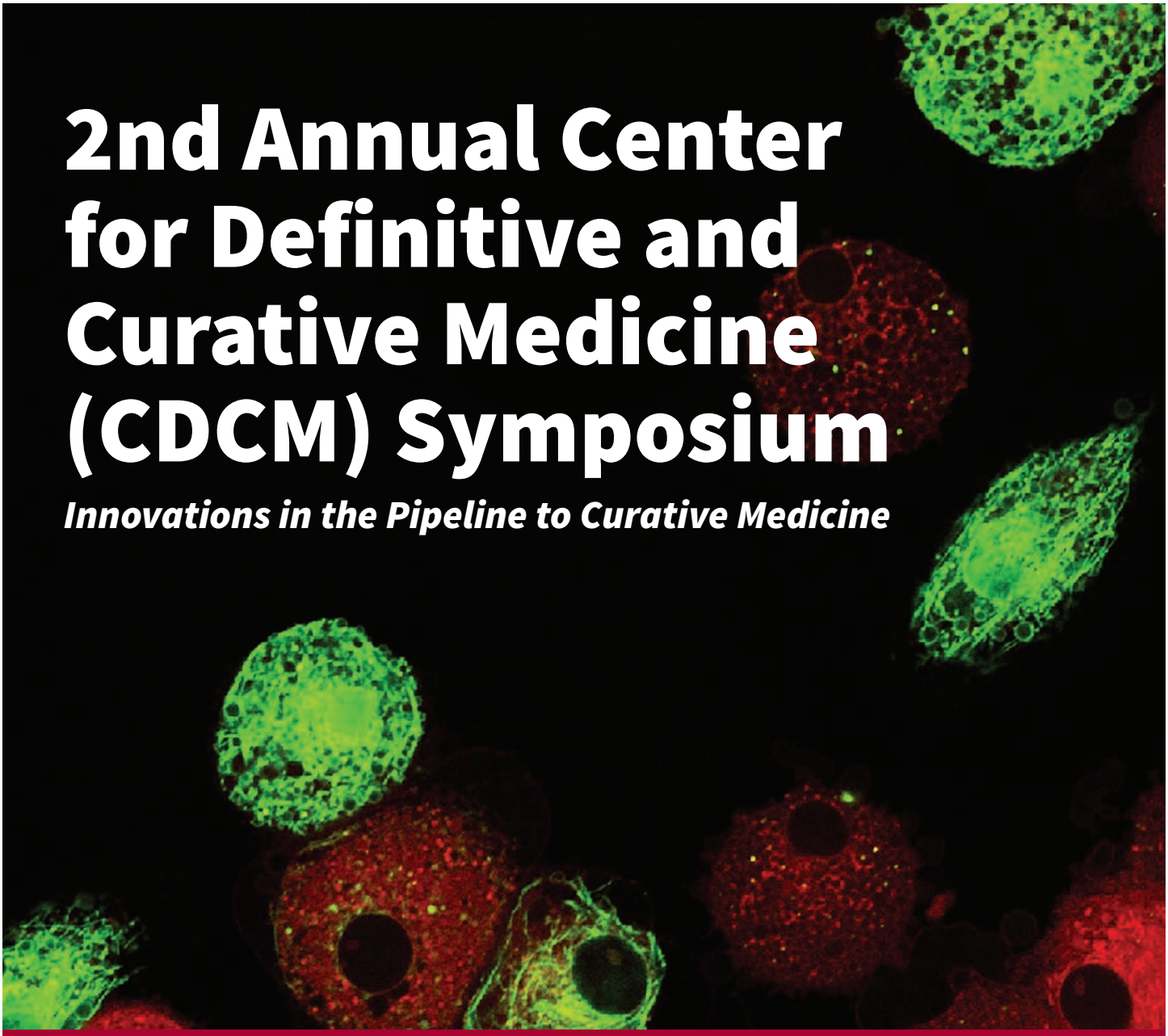
2nd Annual Center for Definitive and Curative Medicine (CDCM) Symposium

Innovations in the Pipeline to Curative Medicine



TUESDAY, FEBRUARY 27, 2018

Paul Berg Hall, Li Ka Shing Learning and Knowledge Center (LKSC), Stanford, California

Stanford MEDICINE | Center for Definitive and Curative Medicine

CHILD HEALTH RESEARCH INSTITUTE

Stanford Children's Health | Lucile Packard Children's Hospital Stanford

Welcome

The 2nd Annual Center for Definitive and Curative Medicine (CDCM) Symposium is titled "Innovations in the Pipeline to Curative Medicine" as we grapple with the many roadblocks that slow or prevent developing novel cell and gene therapies for clinical use. The Symposium consists of four sessions, each of which represent an important area of clinical development and featuring innovative speakers that have made contributions to that area in the past year. Our keynote speakers, Drs. Katherine High and Michel Sadelain, have brought cell and gene therapies into clinics and will discuss their own challenges and successes. It is our hope that this Symposium will stimulate the community to contribute to one or more of the four areas of clinical development to accelerate the delivery of these novel medicines to our patients.

Please contact us with any questions, inquiries, or project ideas.

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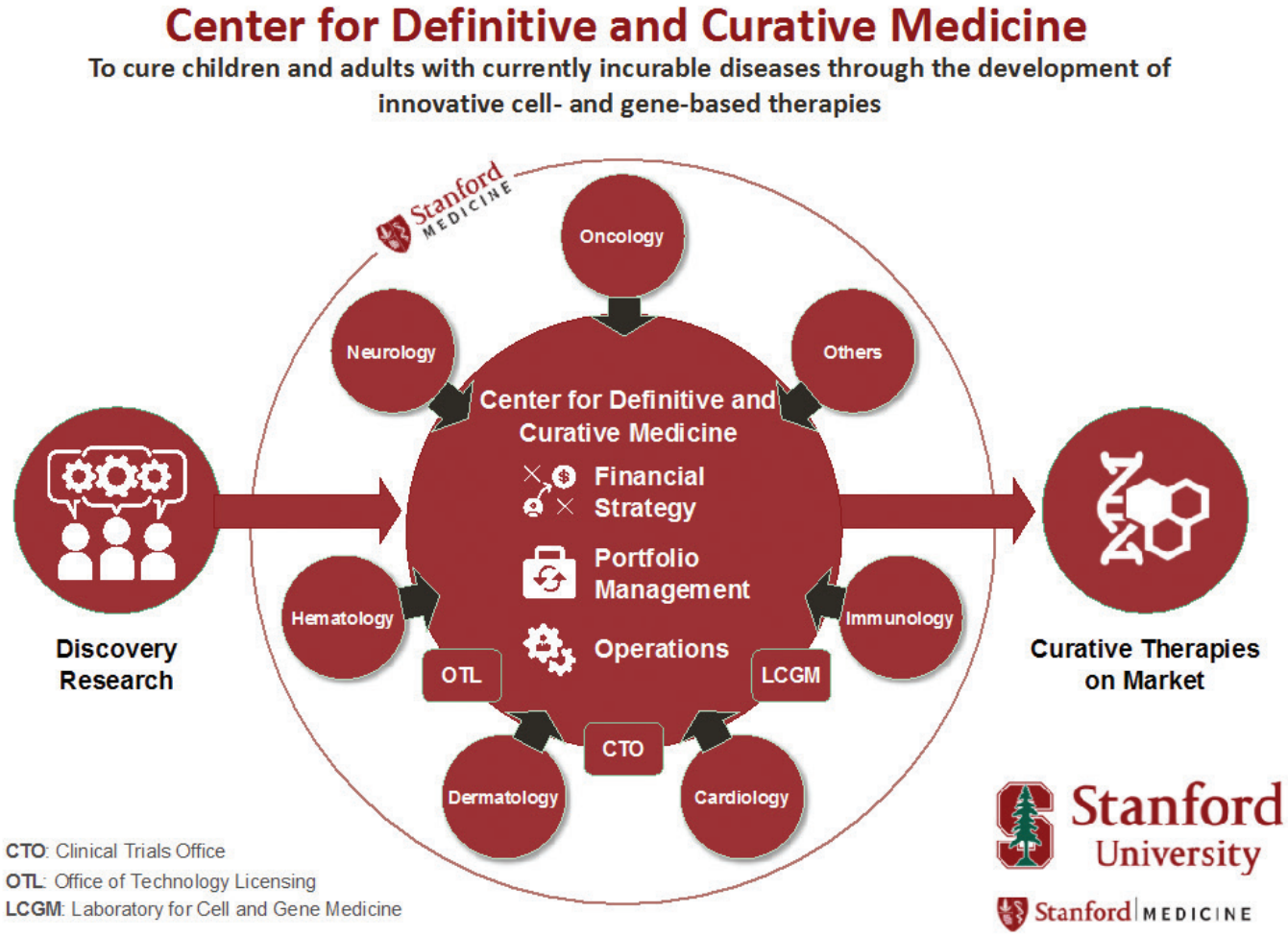


Agenda

7:30 - 8:00 A.M BREAKFAST

8:00 - 8:15 A.M. OPENING
DEAN LLOYD MINOR, DAVID ENTWISTLE AND CHRISTOPHER DAWES

8:15 - 8:20 A.M. WELCOME
ANTHONY ORO

8:20 - 9:00 A.M. OPENING KEYNOTE
MICHEL SADELAIN – CAR THERAPY: THE CD19 PARADIGM AND BEYOND

SESSION ONE:
NEW CELL-BASED MEDICINE DISCOVERIES
MODERATOR: RAVI MAJETI

9:00 - 9:30 A.M. **AGNIESZKA CZECHOWICZ**
Discovery of Non-toxic Conditioning Regimens for Stem Cell Therapies

9:30 - 10:00 A.M. **SERGIU PASCA**
Building Functional Human Brain Models in a Dish

10:00 - 10:30 A.M. **ROELAND NUSSE**
Wnt Signaling in Cancer and Stem Cells

10:30 - 10:45 A.M. BREAK

SESSION TWO:
PRE-CLINICAL DEVELOPMENT OF CURATIVE MEDICINES
MODERATOR: MARY LEONARD

10:45 - 11:15 A.M. **SARAH HEILSHORN**
Hydrogels for Stem Cell Expansion, 3D Printing, and Transplantation

11:15 - 11:45 A.M. **MICHAEL LONGAKER**
Skeletal Stem Cells: Repair and Disease

11:45 A.M. - 12:15 P.M. **MATTHEW PORTEUS**
Genome Editing of HSCs: A Platform for Curing Genetic Diseases of the Blood and Immune System

12:15 - 1:30 P.M. LUNCH

SESSION THREE:
CLINICAL TRIALS IN CURATIVE MEDICINES
MODERATOR: JOHN DAY

1:30 - 2:00 P.M. **JUDITH SHIZURU**
Antibody Based Conditioning Regimens for Stem Cell Therapy

2:00 - 2:30 P.M. **JEAN TANG**
Gene Therapy Skin Grafts for RDEB Chronic Wounds

2:30 - 3:00 P.M. **SAMUEL STROBER**
Mixed Chimerism and Tolerance to Organ Transplants

3:00 - 3:15 P.M. BREAK

SESSION FOUR:
CHALLENGES IN DEVELOPMENT AND COMMERCIALIZATION OF CURATIVE MEDICINES
MODERATOR: IRVING WEISSMAN

3:15 - 3:45 P.M. **DAVID DIGIUSTO**
Academic Perspective on Cell and Gene Therapy Development and Manufacturing

3:45 - 4:15 P.M. **MATT WILSEY**
2,978 Days & the Race to Cure NGLY1

4:15 - 4:20 P.M. CLOSING THOUGHTS
MARIA GRAZIA RONCAROLO

4:20 - 5:00 P.M. CLOSING KEYNOTE
KATHERINE HIGH – DISCOVERING, DEVELOPING, AND DELIVERING GENE THERAPIES FOR GENETIC DISEASE

5:00 - 5:05 P.M. CLOSING
PRESIDENT MARC TESSIER-LAVIGNE

5:05 - 6:00 P.M. WINE AND CHEESE RECEPTION

Special Remarks

LLOYD B. MINOR, MD
CARL AND ELIZABETH NAUMANN DEAN OF STANFORD SCHOOL OF MEDICINE

PROFESSOR, OTOLARYNGOLOGY (HEAD AND NECK SURGERY) AND, BY COURTESY, NEUROBIOLOGY AND, BY COURTESY, OF BIOENGINEERING

STANFORD UNIVERSITY SCHOOL OF MEDICINE AND, BY COURTESY, OF ENGINEERING

DAVID ENTWISTLE, MHSA
PRESIDENT AND CHIEF EXECUTIVE OFFICER

STANFORD HEALTH CARE

CHRISTOPHER DAWES, MBA
PRESIDENT AND CHIEF EXECUTIVE OFFICER

LUCILE PACKARD CHILDREN'S HOSPITAL

ANTHONY ORO, MD, PHD
ASSOCIATE DIRECTOR, CENTER FOR DEFINITIVE AND CURATIVE MEDICINE

CO-DIRECTOR, CHILD HEALTH RESEARCH INSTITUTE

EUGENE AND GLORIA BAUER PROFESSOR OF DERMATOLOGY

STANFORD UNIVERSITY SCHOOL OF MEDICINE

MARIA GRAZIA RONCAROLO, MD
CHIEF, PEDIATRIC DIVISION OF STEM CELL TRANSPLANTATION AND REGENERATIVE MEDICINE

DIRECTOR, CENTER FOR DEFINITIVE AND CURATIVE MEDICINE

CO-DIRECTOR, INSTITUTE FOR STEM CELL BIOLOGY AND REGENERATIVE MEDICINE

CO-DIRECTOR, BASS CENTER FOR CHILDHOOD CANCER AND BLOOD DISEASES

GEORGE D. SMITH ENDOWED PROFESSOR OF PEDIATRICS (STEM CELL TRANSPLANTATION AND REGENERATIVE MEDICINE) AND OF MEDICINE (BLOOD AND MARROW TRANSPLANTATION)

STANFORD UNIVERSITY SCHOOL OF MEDICINE

MARC TESSIER-LAVIGNE, PHD, FRS, FRSC, FMEDSCI
PRESIDENT

BING PRESIDENTIAL PROFESSORSHIP

STANFORD UNIVERSITY

Biographies

Biographies

KEYNOTE SPEAKERS

MICHEL SADELAIN, MD, PHD

FOUNDING DIRECTOR, CENTER FOR CELL ENGINEERING

HEAD, GENE TRANSFER AND GENE EXPRESSION LABORATORY

STEPHEN AND BARBARA FRIEDMAN CHAIR
MEMORIAL SLOAN KETTERING CANCER CENTER

Dr. Sadelain is the Director of the Center for Cell Engineering and the incumbent of the Stephen and Barbara Friedman Chair at Memorial Sloan Kettering Cancer Center. Dr. Sadelain's research focuses on human cell engineering and cell therapy to treat cancer and hereditary blood disorders. His laboratory has made several seminal contributions to the field of chimeric antigen receptors (CARs), from design to clinical translation. His group was the first to publish dramatic molecular remissions in patients with chemorefractory acute lymphoblastic leukemia following treatment with CD19 CAR T cells.

KATHERINE A. HIGH, MD

CO-FOUNDER, PRESIDENT AND CHIEF SCIENTIFIC OFFICER
SPARK THERAPEUTICS

Dr. High is a hematologist and was a Professor at the Perelman School of Medicine at the University of Pennsylvania for 22 years. During that time, she was also an Investigator for the Howard Hughes Medical Institute and the Founding Director of the Center for Cellular and Molecular Therapeutics at the Children's Hospital of Philadelphia. Dr. High has a long-standing interest in gene therapy for genetic diseases and has pioneered the safe and effective translation to clinical studies. In 2014 she helped co-found a gene therapy company, Spark Therapeutics, where she currently serves as President and Chief Science Officer. Dr. High is an elected member of the National Academy of Medicine and the American Academy of Arts and Sciences. She has published over 200 scientific papers and holds a number of patents related to gene therapy.

Biographies

SPEAKERS

AGNIESZKA CZECHOWICZ, MD, PHD

ASSISTANT PROFESSOR OF PEDIATRICS
(STEM CELL TRANSPLANTATION AND REGENERATIVE MEDICINE)
STANFORD UNIVERSITY SCHOOL OF MEDICINE

Dr. Czechowicz is the newest recruit to the Stanford University School of Medicine faculty and is an Assistant Professor of Pediatrics in the Division of Stem Cell Transplantation and Regenerative Medicine. Dr. Czechowicz completed her undergraduate and medical school training at Stanford University and was a doctoral scholar under the direction of Prof. Irving Weissman obtaining a PhD in Developmental Biology from Stanford in 2010. Subsequently she completed further clinical training in Pediatrics at Boston Children's Hospital and was a clinical fellow in Pediatric Hematology/Oncology at the Dana Farber Cancer Institute, while she simultaneously pursued postdoctoral research with Prof. Derrick Rossi at Boston Children's Hospital/Harvard Medical School/Harvard Stem Cell Institute. She recently returned to Stanford to establish her own laboratory and to contribute to the translational efforts of the Center for Definitive and Curative Medicine. The Czechowicz lab is focused on understanding how hematopoietic stem cells interact with their microenvironment and the principles guiding hematopoietic stem cell engraftment in bone marrow transplantation, with the aim to exploit these discoveries for the advancement of stem cell therapies. In particular, Dr. Czechowicz has done pioneering research over the last decade highlighting that host hematopoietic stem cells limit donor stem cell engraftment, and already several novel antibody-based conditioning clinical regimens are in development based upon from her work. Clinically, Dr. Czechowicz attends on the pediatric stem cell transplantation service and is currently building a new clinic for patients with bone marrow failure.

SERGIU P. PASCA, MD

NYSCF ROBERTSON STEM CELL INVESTIGATOR

FELLOW, STANFORD CHEMISTRY, ENGINEERING & MEDICINE FOR HUMAN HEALTH INSTITUTE

ASSISTANT PROFESSOR OF PSYCHIATRY AND BEHAVIORAL SCIENCES
(STANFORD CENTER FOR SLEEP SCIENCES AND MEDICINE)
STANFORD UNIVERSITY SCHOOL OF MEDICINE

Dr. Pasca is an Assistant Professor of Psychiatry and Behavioral Sciences at Stanford University. During his clinical training, he used biochemistry and genetics to explore gene-environment interactions in autism and schizophrenia. He continued his neuroscience training at the Max Planck Institute for Brain Research in Frankfurt where he investigated the role of gamma oscillations in visual processing. During his postdoctoral studies in Dr. Ricardo Dolmetsch's laboratory, he developed some of the first cellular models with induced pluripotent stem cells to study neuropsychiatric disorders. Dr. Pasca's lab has pioneered novel approaches for deriving 3D human brain tissue and to assemble region-specific spheroids/organoids to study in vitro circuits. Dr. Pasca is a a NYSCF Robertson Investigator, the recipient of the NARSAD Young and the Independent Investigator Award, the Sammy Kuo Award for Neurosciences, MQ Fellow Award for Transforming Mental Health, the Baxter Faculty Scholar Award, the NIMH Director's BRAINS Award and the Folch-Pi Award for Neurochemistry. The interest of the Pasca lab at Stanford University is to decipher the molecular and cellular mechanisms of mental disorders employing a multidisciplinary approach with the ultimate objective of identifying novel and reliable drug targets.

Biographies

ROELAND NUSSE, PHD

HOWARD HUGHES MEDICAL INSTITUTE INVESTIGATOR

VIRGINIA AND DANIEL K. LUDWIG PROFESSOR OF DEVELOPMENTAL BIOLOGY

STANFORD UNIVERSITY SCHOOL OF MEDICINE

Dr. Nusse is a professor in the Department of Developmental Biology at Stanford University School of Medicine, the Virginia and Daniel K. Ludwig Professor of Cancer Research and a Howard Hughes Medical Institute Investigator. He is a member of the Institute for Stem Cell Biology and Regenerative Medicine at Stanford and the Stanford Ludwig Center for Cancer Stem Cell Research and Medicine.

Dr. Nusse received his PhD from the Netherlands Cancer Institute at the University of Amsterdam in 1980. He completed postdoctoral studies at the University of California, San Francisco in 1982 working with Dr. Harold Varmus. After several years as head of the Molecular Biology Department at the Netherlands Cancer Institute, he returned to the Bay Area and joined the Stanford medical faculty in 1990 as an Associate Professor of Developmental Biology. In 1994 he was promoted to Professor. In 1999 he was appointed as Chair of the Department of Developmental Biology at Stanford. In 2010, he was elected as a member of the National Academy of Sciences. Roel Nusse is also a fellow of the American Academy of Arts and Sciences and a member of the Royal Dutch Academy of Sciences. In 2017, he received the Breakthrough Prize in Life Sciences.

SARAH HEILSHORN, MS, PHD

LEE OTTERSON FACULTY SCHOLAR

WILLIAM R. AND GRETCHEN B. KIMBALL UNIVERSITY FELLOW IN UNDERGRADUATE EDUCATION

ASSOCIATE PROFESSOR OF MATERIALS SCIENCE AND ENGINEERING AND, BY COURTESY, CHEMICAL ENGINEERING AND, BY COURTESY, BIOENGINEERING

STANFORD UNIVERSITY SCHOOL OF ENGINEERING AND, BY COURTESY, OF MEDICINE

Dr. Heilshorn is Associate Professor and Otterson Faculty Scholar in the Materials Science & Engineering Department at Stanford University. Her laboratory integrates concepts from materials engineering and protein science to design new, bioinspired materials. These materials are being explored for applications in regenerative medicine, 3D bio-printing, and ex vivo human tissue mimics. She completed her PhD in Chemical Engineering at Caltech and was a postdoctoral scholar in Molecular and Cell Biology at the University of California, Berkeley. Dr. Heilshorn is a fervent supporter of diversifying the engineering community and serves in multiple leadership roles to help achieve this goal. She is a Fellow of the American Institute for Medical and Biological Engineering and serves as an Associate Editor for Science Advances.

Biographies

MICHAEL T. LONGAKER, MD, MBA, FACS

VICE CHAIR, DEPARTMENT OF SURGERY

CO-DIRECTOR, STANFORD INSTITUTE FOR STEM CELL BIOLOGY AND REGENERATIVE MEDICINE

DIRECTOR, CHILDREN'S SURGICAL RESEARCH

DIRECTOR, PROGRAM IN REGENERATIVE MEDICINE

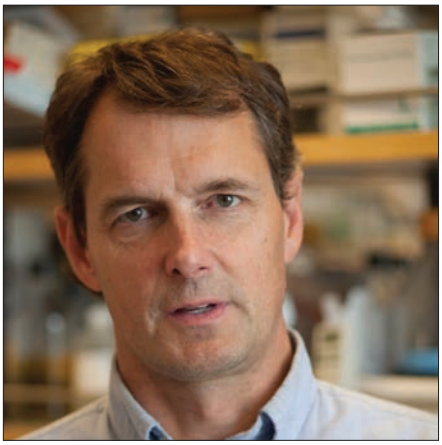
DEANE P. AND LOUISE MITCHELL PROFESSOR OF SURGERY (PLASTIC AND RECONSTRUCTIVE SURGERY) AND, BY COURTESY, MATERIALS SCIENCE AND ENGINEERING AND, BY COURTESY, BIOENGINEERING

STANFORD UNIVERSITY SCHOOL OF MEDICINE AND, BY COURTESY, OF ENGINEERING

Dr. Longaker's research experience focuses on wound repair and fibrosis, with specific applications to the differences between fetal and post-natal wound healing, the biology of keloids and hypertrophic scars. Another area of his research focuses on skeletal development and repair. Most recently, his research has focused on skeletal stem cells and mesenchymal cells from adipose tissue and their applications for tissue repair, replacement, and regeneration. Dr. Longaker has published over 1200 papers. He is a member of the American Society for Clinical Investigation, Association of American Physicians and the National Academy of Medicine.

He is an inventor on over 40 issued patents and patent applications. Dr. Longaker has also funded several venture-backed start-up companies, including Neodyne Biosciences (www.neodynebio.com) and Arresto Biosciences, which was acquired by Gilead (NASDAQ:GILD) in January 2011. Dr. Longaker is also a founding partner of Tautona Group (www.tautonagroup.com), an early-stage life science fund that has created novel biomedical technologies that have been sold to industry leading companies, such as Allergan (NYSE:AGN), Novadaq (NASDAQ:NVDQ), and Acelity/KCI (San Antonio, TX).

Biographies



MATTHEW PORTEUS, MD, PHD

ASSOCIATE DIRECTOR, CENTER FOR DEFINITIVE AND CURATIVE MEDICINE

ASSOCIATE PROFESSOR OF PEDIATRICS (STEM CELL TRANSPLANTATION AND REGENERATIVE MEDICINE)
STANFORD UNIVERSITY SCHOOL OF MEDICINE

Dr. Porteus is an Associate Professor in the Department of Pediatrics and Institute of Stem Cell Biology and Regenerative Medicine at Stanford. His primary research focus is on developing genome editing as an approach to cure disease, particularly those of the blood but also of other organ systems as well. His research program has made important discoveries in advancing the field of genome editing including the first use of genome editing using engineered nucleases in human cells and optimizing the use of the CRISPR/Cas9 system in primary human stem cells. He also works as an attending physician on the Pediatric Hematopoietic Stem Cell Transplant service at Lucile Packard Children's Hospital where he cares for children undergoing bone marrow transplantation for both malignant and non-malignant diseases. His goal is to combine his research and clinical interests to bring innovative curative therapies to patients. He served on the National Academy Study Committee of Human Genome Editing and as a History and Science major at Harvard he wrote his undergraduate thesis on the social interpretation of the recombinant DNA controversy in the early 1970s.

JUDITH SHIZURU, MD, PHD

PROFESSOR OF MEDICINE (BLOOD AND MARROW TRANSPLANTATION) AND OF PEDIATRICS (STEM CELL TRANSPLANTATION AND REGENERATIVE MEDICINE)
STANFORD UNIVERSITY SCHOOL OF MEDICINE

Dr. Shizuru is a Professor of Medicine and Pediatrics and a member of the Stanford Immunology Program and the Institute of Stem Cell Biology and Regenerative Medicine. Dr. Shizuru received her MD and PhD from Stanford University studying the immunology of childhood (Type 1) diabetes. She completed medical residency training at the University of California, San Francisco and a fellowship in Hematology at Stanford. Dr. Shizuru oversees a research laboratory and carries out clinical duties as an attending on the adult BMT service. Dr. Shizuru pursued BMT as a clinical subspecialty because of its potential to cure many life-threatening disorders including various cancers; non-cancerous conditions resulting from defects in blood formation, such as sickle cell anemia and severe combined immune deficiency (i.e., bubble boy disease or SCID); and autoimmune diseases like Type 1 diabetes, systemic lupus erythematosus, and multiple sclerosis. Her research focuses on making BMT safer and more effective. She was awarded a multi-million dollar grant that permitted her team to translate from bench-to-bedside a monoclonal antibody that targets blood stem cells with the purpose of allowing donor blood stem cells to engraft. This antibody may replace toxic radiation and chemotherapy, which are currently a necessary part of BMT treatment.

Biographies

JEAN Y. TANG, MD, PHD

ASSOCIATE PROFESSOR OF DERMATOLOGY

STANFORD UNIVERSITY SCHOOL OF MEDICINE

Dr. Tang is an Associate Professor at Stanford University School of Medicine in the Department of Dermatology. She received her MD and PhD (Biophysics) from Stanford in 2003. Dr. Tang's research focuses on the clinical development of novel therapeutics for rare monogenetic skin diseases such as Basal Cell Nevus (Gorlin) Syndrome and Epidermolysis Bullosa. Dr. Tang was the co-PI on the Phase 1/2A clinical trial that treated the first 7 adult patients with Recessive Dystrophic Epidermolysis Bullosa (RDEB) using autologous keratinocyte skin grafts transduced with Collagen 7 (LEAES grafts). These gene-corrected grafts healed RDEB chronic wounds, and were granted FDA's Breakthrough Therapy Designation and Regenerative Medicine Advanced Therapy Designation.

SAMUEL STROBER, MD

PROFESSOR OF MEDICINE (IMMUNOLOGY AND RHEUMATOLOGY)

STANFORD UNIVERSITY SCHOOL OF MEDICINE

Dr. Strober is Professor of Medicine and was previously the Chief of the Division of Immunology and Rheumatology in the Department of Medicine at Stanford Medical School, President of the Clinical Immunology Society, and Chairman of the Board of Directors of the La Jolla Institute for Immunology. He is the Director of a multi-disciplinary NIH Program Project Grant and California Institute of Regenerative Medicine Grant involving faculty from multiple Stanford departments, which is focused on the goal of achieving complete immunosuppressive drug withdrawal from kidney transplant recipients based on the establishment of immune tolerance. Key faculty include members of the Division of Nephrology and members of the Division of Multi-Organ Transplant Surgery. The basis of the clinical trial is the longstanding pre-clinical research in Dr. Strober's laboratory on the establishment of immune tolerance in laboratory animals.

Biographies

DAVID DIGIUSTO, PHD

EXECUTIVE DIRECTOR, STEM CELLS AND CELLULAR THERAPEUTICS OPERATIONS

FOUNDING DIRECTOR, STANFORD LABORATORY FOR CELL AND GENE MEDICINE

SENIOR RESEARCH SCIENTIST OF PEDIATRICS (STEM CELL TRANSPLANTATION AND REGENERATIVE MEDICINE)
STANFORD HEALTH CARE

STANFORD UNIVERSITY SCHOOL OF MEDICINE

Dr. DiGiusto is currently the Executive Director of Stem Cell and Cellular Therapeutic Operations for Stanford Hospital and Clinics and a Senior Academic Researcher in the Pediatric Division of Stem Cell Transplantation and Regenerative Medicine at Stanford University. He has over 25 years of experience in the scientific, clinical, and regulatory aspects of cells as therapeutic agents including the isolation, characterization and genetic modification of hematopoietic stem cells and T-cells for clinical applications. He has been instrumental in the creation of six GMP-compliant biologics manufacturing facilities and associated quality systems, production and QC testing programs. Under his direction, plasmid DNA, CAR-T cells, regulatory T-cells, engineered stem cell grafts and gene modified hematopoietic stem cell products have been manufactured and released for use in Phase I/II clinical trials. Dr. DiGiusto is a major contributor to first-in-human (and other ongoing) studies for cancer and HIV gene therapy and has developed methods for assessing ex-vivo stem cell manipulations using in vitro and in vivo models. His laboratory (the Laboratory for Cell and Gene Medicine) specializes in the development of manufacturing processes and QC assays and provides cGMP compliant clinical materials production and regulatory support activities for investigational cell products. Dr. DiGiusto is the North American Vice President of the International Society for Cell Therapy, a member of the NIH recombinant DNA advisory committee (RAC) and also serves as an independent consultant to the biotech industry.

MATT WILSEY, MBA

CHAIRMAN, PRESIDENT & CO-FOUNDER

GRACE SCIENCE FOUNDATION

Mr. Wilsey is a Silicon Valley entrepreneur, angel investor, and start-up advisor. In addition to consumer products and services, Mr. Wilsey invests in and advocates for biomedical research, drug development, and genetic sequencing technologies.

Before moving to the investment side, he spent many years as a front-line operator. Most recently, Mr. Wilsey was Co-founder and Chief Revenue Officer of CardSpring, a payment infrastructure company that was acquired by Twitter. Previously, Mr. Wilsey ran West coast sales and business development for Howcast.com. Before Howcast, he worked for Kohlberg Kravis Roberts (KKR) on the Capital Markets team focused on new product development, capital raising, and investor relations. Prior to that, he spent five years as Co-founder and Vice President of Business Development at Zazzle.com. He started his career serving in various roles at the White House and the Department of Defense.

Mr. Wilsey became a “rare disease hunter” and advocate after his daughter, Grace, was born with NGLY1 Deficiency. He has since funded over 150 scientists at 20 medical centers in 6 countries with the sole purpose of treating the disease.

Mr. Wilsey holds a BA from Stanford University and a MBA from Stanford’s Graduate School of Business. In addition to the Grace Science Foundation, he is also a Board member at the Charles and Helen Schwab Foundation, Stanford School of Medicine Board of Fellows, and Perlara PBC.

Biographies

MODERATORS

RAVI MAJETI, MD, PHD

CHIEF, MEDICAL DIVISION OF HEMATOLOGY

ASSOCIATE PROFESSOR OF MEDICINE (HEMATOLOGY)
STANFORD UNIVERSITY SCHOOL OF MEDICINE

Dr. Majeti is an Associate Professor in the Department of Medicine, Chief of the Division of Hematology, and Member of the Institute for Stem Cell Biology and Regenerative Medicine at Stanford University. He was an undergraduate at Harvard, earned his MD and PhD from UCSF, and trained in Internal Medicine at Brigham and Women's Hospital in Boston. Dr. Majeti completed his Hematology Fellowship at Stanford and is a board-certified hematologist. While at Stanford, he completed post-doctoral training in the laboratory of Irving Weissman where he investigated acute myeloid leukemia (AML) stem cells and therapeutic targeting with anti-CD47 antibodies. With Dr. Weissman, he developed a humanized anti-CD47 antibody, initiated first-in-human clinical trials, and in 2015, co-founded Forty Seven Inc. Dr. Majeti established his independent laboratory in 2009 with research focused on the molecular/genomic characterization and therapeutic targeting of leukemia stem cells in human hematologic malignancies, particularly AML. Dr. Majeti is a recipient of the Burroughs Wellcome Fund Career Award for Medical Scientists, the New York Stem Cell Foundation Robertson Investigator Award, and the Leukemia and Lymphoma Society Scholar Award.

Biographies

MODERATORS

MARY LEONARD, MD, MSCE

CHAIR, DEPARTMENT OF PEDIATRICS

ADALYN JAY PHYSICIAN-IN-CHIEF, LUCILE PACKARD CHILDREN'S HOSPITAL

DIRECTOR, CHILD HEALTH RESEARCH INSTITUTE

CO-LEADER, SPECTRUM CHILD HEALTH

ARLINE AND PETE HARMAN PROFESSOR OF PEDIATRICS (NEPHROLOGY) AND OF MEDICINE (NEPHROLOGY) AND, BY COURTESY, OF HEALTH RESEARCH AND POLICY (EPIDEMIOLOGY)
STANFORD UNIVERSITY SCHOOL OF MEDICINE

Dr. Leonard is chair of the Department of Pediatrics at Stanford University School of Medicine and the Adalyn Jay Physician-in-Chief at Lucile Packard Children's Hospital. She assumed these positions on July 1, 2016.

Energetic and collaborative, Dr. Leonard is a compassionate clinician and researcher who cares deeply about improving the health and well-being of children everywhere. A graduate of the Stanford University School of Medicine, Dr. Leonard returned to Stanford Medicine in 2014 after spending 25 years at the Children's Hospital of Philadelphia and the University of Pennsylvania. At Stanford, her multi-disciplinary research program is focused on the impact of chronic diseases on bone metabolism and nutrition across the life span. Dr. Leonard directs the innovative and trans-disciplinary child and maternal health research and training initiatives of the Stanford Child Health Research Institute.

Dr. Leonard is a distinguished investigator, an expert clinician, and a respected mentor who embodies the academic and integrated mission of Stanford Medicine. A member of the Precision Health Committee, she is committed to Stanford Medicine's vision of proactive and personalized health care and has been at the forefront of efforts to integrate Precision Health approaches and skills into our training programs.

Biographies

MODERATORS

JOHN W. DAY, MD, PHD

DIRECTOR, NEUROMUSCULAR DIVISION AND CLINICS

PROFESSOR OF NEUROLOGY (NEUROMUSCULAR DISORDERS) AND OF PEDIATRICS (GENETICS) AND, BY COURTESY, OF PATHOLOGY

STANFORD UNIVERSITY SCHOOL OF MEDICINE

Dr. Day is Professor of Neurology and Pediatrics, and Director of the Division of Neuromuscular Medicine at Stanford University. Prior to moving to Stanford in 2011, Dr. Day was Professor of Neurology and Pediatrics, and Founding Director of the Paul and Sheila Wellstone Muscular Dystrophy Center at the University of Minnesota. Dr. Day's research has identified the genetic cause of several neurodegenerative and neuromuscular disorders and helped develop treatments for neurodegenerative diseases. At Stanford, Dr. Day has spearheaded clinical trials of antisense oligonucleotides for myotonic dystrophy, spinal muscular atrophy and C9Orf72 ALS, as well as AAV gene replacement trials for SMA.

Biographies

MODERATORS

IRVING WEISSMAN, MD

DIRECTOR, INSTITUTE OF STEM CELL BIOLOGY AND REGENERATIVE MEDICINE

VIRGINIA AND D.K. LUDWIG PROFESSOR OF PATHOLOGY (PATHOLOGY STEM CELL INSTITUTE), DEVELOPMENTAL BIOLOGY AND, BY COURTESY, OF BIOLOGY
STANFORD UNIVERSITY SCHOOL OF MEDICINE AND, BY COURTESY, OF HUMANITIES & SCIENCES

Dr. Weissman is the Founder and Director of the Stanford Institute for Stem Cell Biology and Regenerative Medicine (SCBRM) since 2002, the former director of the Stanford Cancer Center and the Founder and Director of several companies that were established to develop new therapies based on scientific discoveries from his group including Systemix, Stem Cells Inc, Cellerant, and Forty Seven Sciences.

His research on hematopoiesis, hematologic malignancies and solid tumors has led to several discoveries and the development of new therapies. These include the isolation and transplantation of pure hematopoietic stem cells (HSCs) and the demonstration that, upon transplantation, pure HSCs can regenerate the entire blood and immune system in a host without causing graft vs. host disease.

He also led clinical trials in the 1990s that demonstrated the therapeutic potential and superior outcomes of transplanted purified, cancer-free HSC for women with metastatic breast cancer who received high dose chemotherapy.

The earlier studies on HSCs and hematopoiesis served as a foundation for the biological definition and prospective isolation of human leukemia stem cells (LSC). Next, by comparing LSC to HSC, Dr. Weissman discovered CD47 as a 'don't eat me' signal used by leukemias and all other human cancers to evade innate immunity. Binding of CD47 to SIRP, its receptor on macrophages, inhibits phagocytosis, and blocking this interaction with anti CD47 antibodies unleashes phagocytosis of cancer cells by macrophages. Dr. Weissman then led the clinical development of CD47 blockade as a new cancer immunotherapy and to the establishment of forty seven inc.

Abstracts

Abstracts

OPENING KEYNOTE

MICHEL SADELAIN

CAR therapy: the CD19 paradigm and beyond

Chimeric antigen receptors (CARs) are synthetic receptors that redirect and reprogram T cells to mediate tumor rejection. The most successful CARs used to date are those targeting CD19, which offer the prospect of complete remissions in patients with chemorefractory/relapsed B cell malignancies, especially acute lymphoblastic leukemia (ALL). To broaden the applicability of CAR therapy, we are investigating novel CAR designs, novel CAR targets and alternative T cell engineering modalities. To enhance the intrinsic (function, persistence) and extrinsic (action on the tumor microenvironment) potency of adoptively transferred T cells, we are studying the impact of constitutive T cell-encoded 4-1BBL expression on therapeutic efficacy. To identify new CAR targets, we rely on integrated proteomics and transcriptomics to address the challenges of tumor heterogeneity and on-target/off-tumor toxicity based on combinatorial targeting. Using CRISPR/Cas9, we found that directing a CAR to the T cell receptor alpha chain (TRAC) locus not only results in uniform CAR expression in human peripheral blood T cells, but enhances T cell potency by greatly attenuating T cell exhaustion, vastly outperforming conventionally transduced CAR T cells.

NOTES

NOTES

Abstracts

SESSION 1: NEW CELL-BASED MEDICINE DISCOVERIES

AGNIESZKA CZECHOWICZ

Discovery of Non-toxic Conditioning Regimens for Stem Cell Therapies

Bone marrow/hematopoietic stem cell transplantation (BMT/HSCT) can be used to cure many blood or immune diseases. However, despite its potential, it is used in less than <25% of patients that could benefit. This is primarily due to the high morbidity/mortality that is associated with graft versus host disease and the irradiation/chemotherapy conditioning currently needed to enable donor engraftment. Classic conditioning can lead to multi-organ damage, mucositis, infertility, secondary malignancies, and cytopenias which can also lead to deadly infections, unfortunately limiting use of this curative procedure. Eliminating genotoxic conditioning regimens would dramatically improve outcomes for the many patients already undergoing transplants today and open BMT/HSCT to many other patients that could benefit. We have found that competition with host HSCs limits donor HSC engraftment, and that eliminating host HSCs can be accomplished using a variety of more targeted means. Specifically, we and colleagues have shown that using various antibodies that target and deplete HSCs, we can safely and efficiently eliminate host HSCs and enable high donor HSC engraftment enabling restoration of new blood and immune systems. Our most recent approach utilizes a CD117-antibody-drug conjugate that also spares the immune system, and may be particularly useful for gene-therapy/gene-editing applications. These approaches are now being rapidly translated to patients, and we anticipate them being used in the treatment of a wide array of blood and immune diseases, ranging from genetic diseases, cancers, autoimmune diseases and even infectious diseases such as HIV.

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Abstracts

SESSION 1: NEW CELL-BASED MEDICINE DISCOVERIES

SERGIU PASCA

Building Functional Human Brain Models in a Dish

Progress in dissecting the molecular programs underlying human brain development and in understanding neuropsychiatric disorders has been remarkably slow. This is partly due to lack of access to functioning human brain tissue, translating findings in rodent models and unavailability of functionally relevant in vitro models. In my talk, I will describe efforts in my laboratory to derive three-dimensional (3D) brain region-specific cultures starting from human pluripotent stem cells. Specifically, I will show how to derive functional 3D organoids resembling either the dorsal forebrain (hCS) and containing cortical glutamatergic neurons, or ventral forebrain (hSS) and containing GABAergic neurons. These subdomain-specific forebrain organoids can be assembled in vitro to recapitulate the saltatory migration of interneurons similar to migration in fetal forebrain and to generate functional circuits of the human cerebral cortex. Lastly, I will demonstrate how this novel modular 3D platform can be used to model neuropsychiatric disorders.

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Abstracts

SESSION 1: NEW CELL-BASED MEDICINE DISCOVERIES

ROEL NUSSE

Building Functional Human Brain Models in a Dish

Wnt signaling is widely implicated in stem cell control, as a mechanism to regulate the number of stem cells in tissues. Using various cell labeling and lineage tracing methods, we have described novel populations of stem cells in various tissues, including in the liver. In that tissue, we found that hepatocytes that reside in the pericentral domain of the liver demonstrate stem cell behavior. Although these cells are functional hepatocytes, they are diploid and thus differ from the mostly polyploid mature hepatocyte population. They are active in homeostatic cell replacement and therefore distinct from oval cells, which require injury for their induction. We have found a molecular mechanism that maintains the stem cells in a diploid state, involving a transcriptional repressor, Tbx3. Human liver cancer cells (HCC) often express Tbx3 as well. It is noteworthy that liver cancer is often characterized by loss of function mutations in negative components of the Wnt pathway, including Axin and APC. We suggest that peri-central hepatocyte stem cells, normally controlled by a paracrine Wnt signal, are precursors to liver cancer. Ongoing research includes developing methods to expand mouse and human hepatocytes in culture, based on hepatocyte growth promoting factors we have identified in vivo.

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Abstracts

SESSION 2: PRE-CLINICAL DEVELOPMENT OF CURATIVE MEDICINES

SARAH HEILSHORN

Hydrogels for Stem Cell Expansion, 3D Printing, and Transplantation

Stem cell transplantation is a promising therapy for a myriad of debilitating diseases and injuries; however, current expansion and delivery protocols are inadequate. Transplantation by direct injection, which is clinically preferred for its minimal invasiveness, commonly results in less than 5% cell viability, greatly inhibiting clinical outcomes. As a strategy to protect cells from these detrimental forces, we show that cell encapsulation within hydrogels can significantly improve transplanted cell viability. Building on these fundamental studies, we have designed a family of injectable, bioresorbable, customizable hydrogels using protein-engineering technology. Through a series of in vitro and in vivo studies, we demonstrate that protein-engineered hydrogels may significantly improve transplanted stem cell retention and regenerative function. Furthermore, many of the lessons learned about designing injectable biomaterials can be extended to design new bio-inks for 3D printing applications. While 3D printing has enormous potential for tissue engineering, few bio-inks are currently available to facilitate the printing of complex, cell-laden constructs. We demonstrate the design of a new, customizable bio-ink that enables the printing of multiple cell types into distinct geometric forms.

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Abstracts

SESSION 2: PRE-CLINICAL DEVELOPMENT OF CURATIVE MEDICINES

MICHAEL LONGAKER

Skeletal Stem Cells: Repair and Disease

Stem cell regulation in the skeletal system remains relatively unexplored. While contemporary efforts have begun to identify bone, cartilage, and stromal progenitors for rigorous functional characterization, little is known about how individual progenitors relate to one another from a stem cell lineage perspective. We have mapped bone and cartilage development from a population of highly pure, post-natal skeletal stem cells (mouse Skeletal Stem Cell, mSSC) and its downstream distinct progenitors of bone, cartilage and stromal tissue. We then determined the mSSC lineage relationships to its progeny. By conducting single cell transcriptomic comparison of purified mSSC and downstream lineage-restricted progenitors of bone and cartilage, we have identified unique genetic regulatory mechanisms guiding mSSC expansion and lineage commitment. We also identified specific mSSC niche factors upstream of mSSC regulatory pathways that are potent inducers of skeletal regeneration. Specific combinations of recombinant mSSC niche factors can even activate mSSC genetic programs in situ, even in non-skeletal tissues, resulting in de-novo formation of cartilage or bone and bone marrow stroma.

Skeletal stem cells are also critically important to regeneration of damaged skeletal tissues. To determine if skeletal disorders could arise from defects in the activity of skeletal stem cells or its downstream lineages, we have examined poor fracture healing associated with Diabetes Mellitus. Through the stem cells lens, we identified specific SSC niche-related abnormalities that could impair skeletal repair in diabetic rodent models including repressed expression of IHH. These deficiencies also correspond to molecular changes observed in skeletal progenitors isolated from diabetic human patients undergoing joint replacement procedures. We further show that these deficiencies could be reversed, however, by precise delivery of purified IHH to the fracture site using a specially formulated slow-release hydrogel. We anticipate that further refinement of the skeletal stem cell lineage map in mice and humans will facilitate exploration of new areas of inquiry on the basic mechanism of skeletogenesis during embryonic development and into the maintenance of skeletal structures in adulthood.

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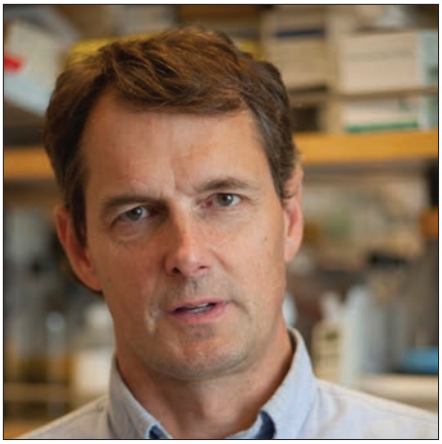
SESSION 2: PRE-CLINICAL DEVELOPMENT OF CURATIVE MEDICINES



MATTHEW PORTEUS

Genome Editing of HSCs: A Platform for Curing Genetic Diseases of the Blood and Immune System

Genome editing provides a method to precisely change the DNA sequence of a cell with single nucleotide precision. In theory this precision should permit the correction of pathologic nucleotide variants to non-pathologic variants in order to cure genetic diseases, especially those of the blood and immune system. The most efficient process works by using an engineered nuclease to create a DNA double-stranded break near to the desired change. We have used zinc finger nucleases, TAL effector nucleases, and CRISPR/Cas9 nucleases and found that the CRISPR/Cas9 system gives the highest activity and greatest specificity. When we deliver the CRISPR/Cas9 nuclease as ribonucleoprotein (RNP) complex via electroporation and then deliver a recombination template using AAV6 delivery, we can achieve gene targeting frequencies of 40-80% in a wide variety of stem cells, including hematopoietic stem cells. In this talk, I will review our iterative approach to making the process both more efficient and more specific and discuss our progress towards completing the IND enabling experiments to initiate first in human clinical trials using gene correction to cure patients with genetic diseases of the blood and immune system, including sickle cell disease and x-linked severe combined immunodeficiency (SCID-X1).

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SESSION 3: CLINICAL TRIALS IN CURATIVE MEDICINES

JUDITH SHIZURU

Antibody Based Conditioning Regimens for Stem Cell Therapy

Hematopoietic stem cell (HSC) therapies rely on chemotherapy and/or radiation to overcome host barriers to permit cell engraftment and provide life-long donor derived hematopoiesis. In conventional allogeneic transplantation these modalities function to both suppress immune rejection and create sufficient niche space to allow HSC to engraft. For gene-corrected or gene-modified cells that are derived from autologous patient sources, access to the HSC niche constitutes the primary barrier. Non-genotoxic approaches are being developed with the goal to target molecules expressed on hematopoietic stem and progenitors. We have studied the use of monoclonal antibodies (mAbs) that target the molecule CD117, also known as cKit, to deplete endogenous stem cells and safely allow engraftment of purified HSC. CD117 is a cell surface molecule expressed at high levels on HSC and early myeloid progenitors as well as other non-hematopoietic cell types. It is a receptor tyrosine kinase that upon binding to its ligand, stem cell factor (SCF), propagates intracellular signaling pathways that regulate activities including cell survival, proliferation and differentiation. Studies in immune deficient mice showed that a single dose of anti-CD117 mAb transiently depletes HSC, creating a therapeutic window for donor HSC to engraft. We have developed for use in clinical transplantation an anti-human CD117 (anti-hCD117) mAb. This antibody significantly inhibits in vitro proliferation of human HSC and effectively depletes human HSC in mice xenografted with human cord blood cells, and is effective in depleting HSC and progenitors from the bone marrow of non-human primates (NHP). Although CD117 is expressed on non-hematopoietic cells including mast cells, melanocytes, and cells in the gastrointestinal tract, antibody administration in animals and in healthy human volunteers, show little to no off-target toxicity. We are currently testing in a Phase I clinical trial the anti-hCD117 mAb as the sole conditioning agent for the transplantation of children with severe combined immunodeficiency (SCID). Early results from this study appear very promising.

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SESSION 3: CLINICAL TRIALS IN CURATIVE MEDICINES

JEAN TANG

Gene Therapy Skin Grafts for RDEB Chronic Wounds

This presentation will review the 15 years of pre-clinical, regulatory and clinical development of LEAES/EB-101 keratinocyte skin grafts for chronic wounds in patients with Recessive Dystrophic Epidermolysis Bullosa (RDEB). Autologous keratinocyte skin sheets are transduced with a retrovirus to express Collagen 7, the defective protein in RDEB. Six gene corrected skin grafts are generated from two small biopsies, and are currently being manufactured at the LCGM/GMP facility for a Phase 3 clinical trial in adults and children with RDEB.

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Abstracts

SESSION 3: CLINICAL TRIALS IN CURATIVE MEDICINES

SAMUEL STROBER

Mixed Chimerism and Tolerance to Organ Transplants

Classical preclinical studies showed that establishment of mixed chimerism of hematopoietic cells in fetal cattle and neonatal rodents is permanent, and linked to acceptance of organ allografts without immunosuppressive (IS) drugs. The goal of our clinical study was to determine whether recipients of combined kidney and hematopoietic cell transplants followed the preclinical paradigm. Persistent mixed chimerism was established in 24 HLA matched and 9 mismatched kidney transplant recipients for at least 1 year after conditioning with lymphoid tissue irradiation. Thirty were withdrawn from IS drugs, and 10 matched patients maintained chimerism and kidney graft acceptance thereafter in a manner consistent with the paradigm. In contrast with the paradigm, the remaining 20 lost chimerism during the second year, and 14 of the latter patients maintained matched kidney graft acceptance without IS drugs despite the loss of chimerism. Maintenance of chimerism and kidney graft acceptance was dependent on tacrolimus monotherapy in mismatched patients. No evidence of rejection was observed in all surveillance graft biopsies obtained from chimeric patients, and none developed graft versus host disease. In conclusion, persistent mixed chimerism can be established in both HLA matched and mismatched patients, and is beneficial regardless of independence or dependence on IS drugs.

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Abstracts

SESSION 4: CHALLENGES IN DEVELOPMENT AND COMMERCIALIZATION OF CURATIVE MEDICINES

DAVID DIGIUSTO

Academic Perspective on Cell and Gene Therapy Development and Manufacturing

The translation of cell and gene therapy products from the research laboratory to the clinic requires careful assessment and development of individual candidate products (assets). Among the activities for creating assets with commercial feasibility are process development, raw materials sourcing, assay development and regulatory path determination. The Center for Definitive and Curative Medicine (in conjunction with Stanford Medicine) has developed the Laboratory for Cell and Gene Medicine (LCGM) to facilitate these activities. The laboratory contains facilities for product development, testing and clinical materials production according to cGMP (current good manufacturing practices) requirements and is staffed by industry professionals in process development, manufacturing, quality systems and regulatory affairs. We are currently manufacturing cells for 4 open clinical trials, managing regulatory filings for 2 more trials and performing process development for a first in human phase I trial and comparability studies for a Phase III registration trial. A description of LCGM operations and examples of product development and manufacturing results will be presented.

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Abstracts

SESSION 4: CHALLENGES IN DEVELOPMENT AND COMMERCIALIZATION OF CURATIVE MEDICINES

MATT WILSEY

2,978 Days & the Race to Cure NGLY1

Like many stories of hope, ours begins with struggle. In 2013, Grace Wilsey was diagnosed with a rare genetic disorder called NGLY1 Deficiency. Her parents, Matt and Kristen, quickly discovered the incredible challenges they faced. At the time, Grace was one of only six known patients worldwide. Diseases that rare weren't on the radars of big labs or pharmaceutical companies. Funding for research was virtually nonexistent. The world wasn't set up to save Grace. So Matt and Kristen did what any good parents would do — they set out to change the world. And so, Grace Science Foundation was born. The Foundation is dedicated to pioneering approaches to scientific exploration that are faster, less expensive and more collaborative. Their advances aren't just bringing the world closer to a cure for NGLY1 Deficiency, they are being used to discover and treat countless other diseases. In this way, their work doesn't just help the few — it impacts the lives of billions.

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Abstracts

CLOSING KEYNOTE

KATHY HIGH

Discovering, Developing, and Delivering Gene Therapies for Genetic Disease

In December 2017, the US FDA approved voretigene neparvovec, an AAV gene therapy for a rare form of congenital blindness due to autosomal recessive mutations in the RPE65 gene. Voretigene is the first gene therapy for a genetic disease, and the first AAV vector, to be approved in the US. At the FDA press conference held on the day of the approval, the FDA Commissioner Dr. Scott Gottlieb stated, "I believe that gene therapy will become a mainstay in treating, and maybe curing, many of our most devastating and intractable illnesses". This presentation will review the clinical development program for voretigene, with an emphasis on hurdles presented by classes of diseases such as inherited retinal dystrophies that have previously lacked pharmacologic treatments. Considerations in clinical trial design for small populations and rare diseases will also be discussed, and issues discussed at the FDA Advisory Committee meeting will be reviewed. In the second part of the talk, progress in development of an AAV gene therapy for hemophilia will be reviewed. Differences in the clinical development programs for hemophilia, where endpoints are well understood and a treatment already exists, and inherited retinal dystrophies, which have lacked treatment and have a less extensive natural history database, will be discussed.

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ADDITIONAL NOTES

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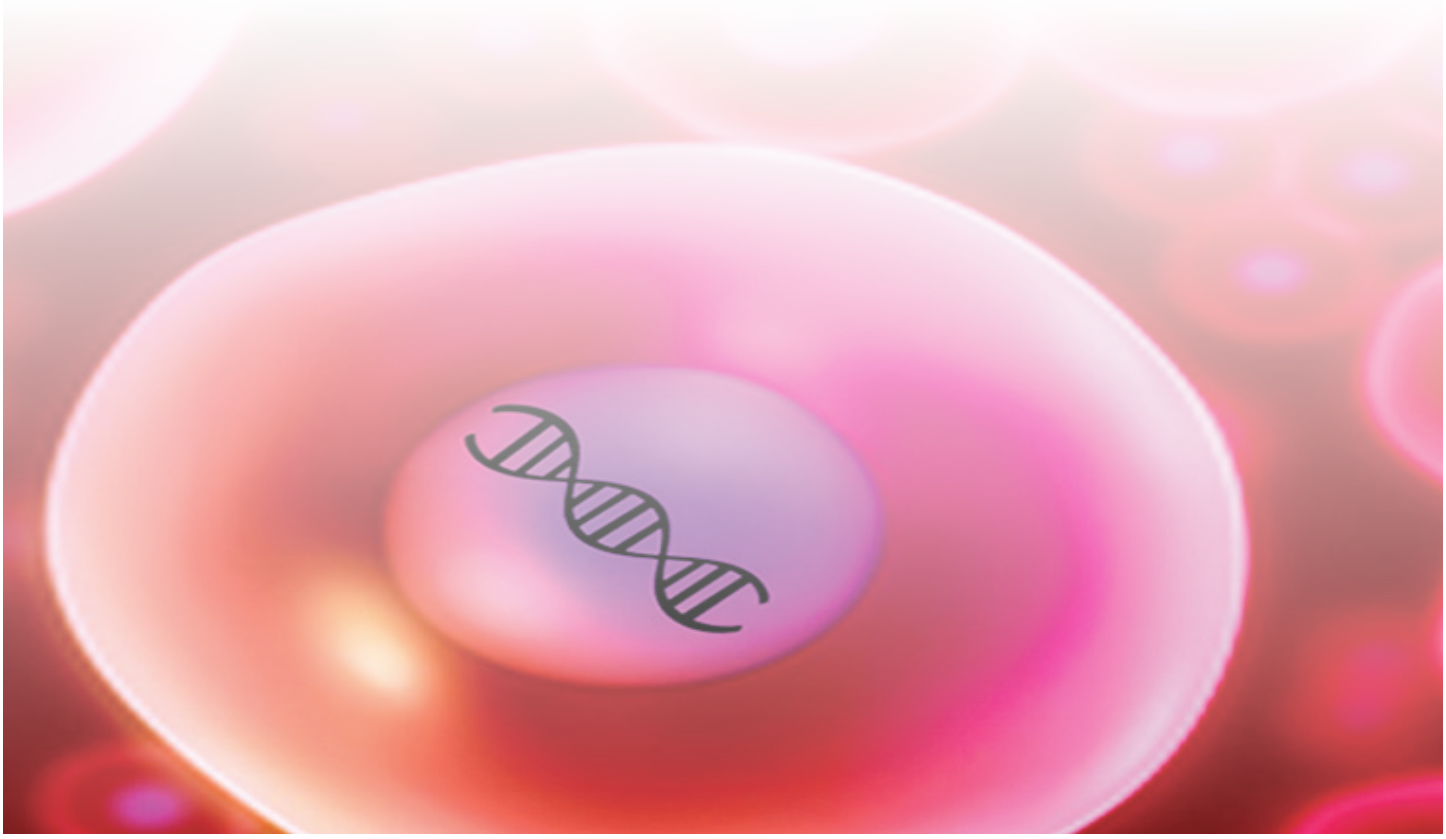

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