Days of Molecular Medicine 2012

Science Translational Medicine AAAS

Days of Molecular Medicine 2012

The Translational Science of Rare Diseases: From Rare to Care

October 8 - 10, 2012

Program Guide

Organized by:

Days of Molecular Medicine Global Foundation

Science Translational Medicine AAAS

FONDATION IPSEN

Karolinska Institutet

IMBA

LMU

Organizers & Sponsors

Organizers:

Days of Molecular Medicine Global Foundation

Science Translational Medicine AAAS

IMBA Institute of Molecular Biotechnology of the Austrian Academy of Sciences

LMU

Karolinska Institutet

Fondation IPSEN

Platinum Sponsor:

Boehringer Ingelheim

Sponsors:

Fondation IPSEN

LGT Private Banking

AMGEN

Hotel Sacher

Table of Contents

Welcome

Dear Participant,

On behalf of the DMM Global Foundation, AAAS/*Science Translational Medicine*, The Institute of Molecular Biotechnology of the Austrian Academy of Sciences, Ludwig-Maximilians-University, Karolinska Institutet and Fondation IPSEN, welcome to the 2012 Days of Molecular Medicine (DMM) meeting in Vienna, Austria.

This year's meeting *"The Translational Science of Rare Diseases: From Rare to Care"* will explore how new technologies are providing fresh insights into the causes of rare diseases and ways forward for developing new treatments.

This interdisciplinary conference will cover a broad range of topics including a new targeted therapy for cystic fibrosis, exon skipping for treating muscular dystrophy, gene therapy for immunodeficiencies and hemophilia, tailoring treatments with genomics, and stem cells for treating blindness.

One of the goals of DMM has been to foster the career pathways for young scientists and physician scientists working in translational medicine. We are pleased to say that this year we will again sponsor a select number of trainees from around the world to receive travel scholarships to attend the meeting.

We would like to take this opportunity to thank you all for being an important part of DMM 2012 and we hope you enjoy the meeting.

The Organizers

Kenneth Chien
DMM Global Foundation
Harvard University

Orla Smith and Katrina Kelner
AAAS/*Science Translational Medicine*

Josef Penninger
The Institute of Molecular Biotechnology of the Austrian Academy of Sciences

Christoph Klein
Ludwig-Maximilians-University

Urban Lendahl
Karolinska Institutet

Yves Christen
Jacqueline Mervaillie
Fondation IPSEN

Palais Liechtenstein

Days of Molecular Medicine 2012 is being held at the magnificent Palais Liechtenstein in Vienna, Austria.

Built in the early 18th century, the structure originally served as a summer palace for the Liechtenstein family. Today it is home to the Liechtenstein Museum, which displays a private collection of paintings and sculptures in a sumptuous Baroque setting.

The DMM 2012 conference will be held in the impressive Hercules Hall, which features ornate decoration and the colorful frescoes of Andrea Pozzo.

About

DMM Global Foundation

The DMM Global Foundation is a non-profit organization dedicated to forming a bridge between advances in molecular medicine and global cardiovascular health, through educational programs and research collaborations. Our primary focus is to promote global collaboration in the field of molecular medicine through the organization of conferences with other leading international institutions. A key to the success of these conferences is our dedication to support young physician-scientists, from all parts of the world, to participate in these conferences and to expand the international biomedical network to further advance global health issues. In addition we are developing a Global Health initiative designed to identify, design, and catalyze promising research collaborations that may uncover new scientific approaches to global cardiovascular health, particularly but not limited to the regions of Africa and Asia.

AAAS/*Science Translational Medicine*

The American Association for the Advancement of Science (AAAS), the world's largest general scientific society, is the publisher of the journal *Science* (www.sciencemag.org) and the sister journals *Science Translational Medicine* (www.sciencetranslationalmedicine.org) and *Science Signaling* (www.sciencesignaling.org). The goal of *Science Translational Medicine*, launched in October 2009, is to promote human health by providing a forum for communicating the latest biomedical research findings from all established and emerging disciplines relevant to medicine. Despite 50 years of advances in our fundamental understanding of human biology and the emergence of powerful new technologies, the translation of this knowledge into effective new treatments and health measures has been slow. *Science Translational Medicine* seeks to publish articles that identify and fill the scientific knowledge gaps at the junction of basic research and medical application in order to accelerate the translation of this knowledge into new ways to prevent, diagnose and treat human disease.

Institute of Molecular Biotechnology of the Austrian Academy of Sciences (IMBA)

The Institute of Molecular Biotechnology is a subsidiary of the Austrian Academy of Sciences, the leading organization promoting non-university academic basic research in Austria. IMBA, located at the Campus Vienna Biocenter, a cluster of research institutes and companies dedicated to excellence of research (http://www.imba.oeaw.ac.at), has become the largest institute of the Austrian Academy of Sciences in both personnel and budget. In order to develop a strong and recognizable research profile, IMBA focuses on the following three topics: Disease Modeling and Mouse Genetics, Cell and Stem Cell Biology, and RNA Biology and Epigenetics. IMBA closely cooperates with the Research Institute of Molecular Pathology (IMP), a research institute financed by Boehringer Ingelheim (BI). IMBA and IMP share all infrastructures which

allow IMBA to have immediate access to technology platforms, scientific services and an international PhD Programme, key prerequisites for the rapid and successful implementation of the newly established institute. The philosophy and business model of IMBA is always to hire the best young scientists in the world and to provide them with academic freedom and free access to the best possible infrastructure. IMBA is also recognized as an excellent place for the training of students and provides multidisciplinary training opportunities for students and post-doctoral fellows and was voted in 2012 by *The Scientist* as the second best place for Postdoctoral training internationally (i.e., outside the USA).

Ludwig-Maximilians-University (LMU)

The Ludwig-Maximilians-University in Munich is one of the leading research universities in Europe. It has a more than 500-year long tradition as a top-level European research university, clearly demonstrated in its international character and its areas of academic cooperation from research to teaching and student exchange. The university is divided into 18 faculties which group together major areas of teaching and research. It has a classical academic profile ranging from the humanities and cultural sciences, law, economics, and social sciences to medicine and natural sciences. Numerous research centers specializing either in one subject area or crossing the borders of individual disciplines as well as one of Germany's finest library systems complete the well-differentiated research infrastructure at LMU. The Medical Center of the University of Munich provides the maximum level of care and the highest standard of treatment and nursing. With 2,300 beds, it is, next to the Charité in Berlin, the largest institution of this kind in Germany. The diversity of research at LMU Munich depends on close collaborations with research centers far beyond the confines of the university. As a leading German university, it enjoys excellent relationships with renowned partner research institutes.

Karolinska Institutet

Karolinska Institutet (KI) is a renowned medical university, and one of the largest in Europe (http://ki.se). It is the only university in Sweden to specialize in medicine and is the main center for medical education and research. KI was founded in 1810 by Jöns Jacob Berzelius amongst others. His many successors have continued the university's research tradition, firmly establishing KI on the world medical map. In 1895, Alfred Nobel selected KI as the organization that would select the laureates of the Nobel Prize in Physiology or Medicine. KI offers specialized academic education and research for the health sector. Our primary mission is to improve people's health through research and education. Science for Life Laboratory (SciLifeLab) is a national resource center dedicated to large-scale research in molecular biosciences and medicine. SciLifeLab Stockholm is a joint collaboration between three universities, The Royal Institute of Technology (KTH), Karolinska Institutet (KI) and Stockholm University (SU). The

vision of SciLifeLab Stockholm is to create a center for large-scale life sciences by co-localization of technological platforms and research groups. The main activities focus on genomics and proteomics, with protein profiling, bioimaging, bioinformatics and systems biology. SciLifeLab will enable research using extensive and comprehensive analysis of genes, transcripts and proteins in humans and relevant organisms. The aim is to cast light on the complex interplay between different molecular components in living cells, tissues and organs related to human diseases.

Fondation IPSEN

Created in 1983 under the auspices of the Fondation de France, the Fondation IPSEN tracks progress in biomedical research with the continuing aim of highlighting major advances. The ambition of the foundation is to identify emerging research areas and new scientific paradigms and to foster strong interdisciplinary connections among researchers and clinical practitioners. Fondation IPSEN seeks to facilitate the cross-fertilization of ideas in an atmosphere of excellence and openess.

Over the past 30 years, Fondation IPSEN has organized more than 200 meetings and produced several hundred publications, and almost 300 scientists and biomedical researchers have been awarded prizes (and grants until 2000). Fondation IPSEN has concentrated its efforts on select scientific topics that reflect some of the most important challenges: the aging of populations, the spectacular development of neuroscience and its contribution to the understanding of cognitive mechanisms; the interactions between different tissues such as the nervous and endocrine systems; and the medical challenges posed by the biomedical revolution in our understanding of diseases such as cancer. Many of these activities have been carried out in collaboration with outstanding institutions and partners to whom we are immensely grateful.

Monday, October 8th, 2012

TIME	TOPIC	SPEAKER	PLACE
11:00 am	Registration Opens		Sala Terrena/ Foyer of the LM Palace
11:45 to 12:45 pm	***Special Session: Career Paths in Translational Medicine*** For MD/PhD, MD and PhD trainees working in translational medicine.		Sala Terrena Gallery Room
1:00 to 1:30 pm	***Opening Remarks*** **H.S.H. Prince Max von und zu Liechtenstein**, CEO LGT Group **Helmut Denk**, President of the Austrian Academy of Sciences **Josef Penninger**, Director, IMBA **Kenneth Chien**, DMM Global Foundation and Harvard University **Orla Smith**, AAAS/*Science Translational Medicine*		Hercules Hall
1:30 to 2:30 pm	***Keynote Lecture*** ***Mice, Men and Mental Illness: Animal Models of Mental Disorders*** SPEAKER: **Eric Kandel**, Columbia University, New York, NY, USA CHAIR: **Helmut Denk**, President of the Austrian Academy of Sciences		
SESSION I: DRUGS AND TARGETS FOR RARE DISEASES (2:30 - 5:30 PM) CHAIR: **Kaan Boztug**, CeMM, Vienna, Austria			
2:30 pm	***Kalydeco: Targeting the G551D Mutation in Cystic Fibrosis***	**Peter Mueller** Vertex, Cambridge, MA, USA	
3:00 pm	***Synuclein Pathology: A Unifying Factor In Rare and Common Diseases***	**Susan Lindquist** Whitehead Institute, Cambridge, MA, USA	
3:30 pm	Coffee Break		Sala Terrena/ Gardens
4:00 pm	***A New Angle on Angelman Syndrome***	**Ben Philpot** University of North Carolina, Chapel Hill, NC, USA	Hercules Hall
4:30 pm	***From Mutations in the Few to Drugs for the Many***	**Michael Hayden** University of British Columbia, Vancouver, Canada	
5:00 pm	***From iPS Cells to Drug Discovery in Familial Dysautonomia***	**Lorenz Studer** Memorial Sloan Kettering Cancer Center, New York, NY, USA	
5:30 pm	Opening Reception		Sala Terrena/ Garderns and 3 Galleries
	Tour of Palace Art Gallery		

Tuesday, October 9th, 2012

TIME	TOPIC	SPEAKER	PLACE
8:30 to 9:30 am	Coffee/Registration		Sala Terrena/ Foyer of the LM Palace
SESSION II: MOLECULAR INSIGHTS INTO RARE DISEASES OF MUSCLE AND BONE (9:30 - 12:00 PM) **CHAIR: Till Voigtländer**, Medical University, Vienna, Austria			Hercules Hall
9:30 am	***RANKL/RANK, a Therapeutic Target for Bone Disease***	**Josef Penninger** IMBA, Vienna, Austria	
10:00 am	Short Talk – ***Sclerosteosis: New Treatment Opportunities for Bone Diseases***	**Michaela Kneissel** Novartis, Basel, Switzerland	
10:20 am	Coffee Break		Sala Terrena/ Gardens
10:50 am	***Genetic Analyses of Inherited Cardiomyopathies***	**Jon Seidman** Harvard Medical School, Boston, MA, USA	Hercules Hall
11:20 am	Short Talk – ***Back to the Future: The Evolution of Targeted Therapies for Canavan Disease***	**Paola Leone** University of Medicine and Dentistry of New Jersey, Stratford, NJ, USA	
11:40 am	***DMM Global Foundation Fellows Award:*** Short Talk – ***Harlequin Ichthyosis Mouse Skin Synthesizes Missing Ceramide When Treated Topically With Precursor***	**Jorge Haller** Massachusetts General Hospital, Cambridge, MA, USA	
12:00 to 2:00 pm	Lunch and Poster Session I		Sala Terrena/ 3 Galleries
SESSION III: RARE DISEASES OF BLOOD (2:00 TO 5:00 PM) **CHAIR: Kenneth Chien**, Harvard University, Cambridge, MA, USA			Hercules Hall
2:00 pm	***Primary Immunodeficiencies, From Genes and Pathophysiology to Therapy***	**Alain Fischer** Necker Hospital, Paris, France	
2:30 pm	***Preclinical Development of Gene Therapeutics***	**Christopher Baum** Hannover Medical School, Hannover, Germany	

Tuesday, October 9th, 2012 (continued)

TIME	TOPIC	SPEAKER	PLACE
3:00 pm	***From Rare to Common: What We Can Learn about IBD from Rare Monogenic Forms of Pediatric Colitis***	**Christoph Klein** Ludwig-Maximilians-University, Munich, Germany	Hercules Hall
3:30 pm	Coffee Break		Sala Terrena/ Gardens
4:00 pm	***Adventures in the Genomics of Inflammation***	**Dan Kastner** National Institutes of Health, Rockville, MD, USA	Hercules Hall
4:30 pm	***Gene Therapy for Haemophilia B, From Bench to Bedside***	**Amit Nathwani** University College London, London, UK	
5:00 pm	Tour of Palace Art Gallery		Sala Terrena/ 3 Galleries
8:00 pm	Speakers Dinner		Hotel Sacher

Wednesday, October 10th, 2012

TIME	TOPIC	SPEAKER	PLACE
8:30 to 9:00 am	Coffee		Sala Terrena/ Foyer of the LM Palace
SESSION IV: GENOMICS AND STEM CELL TECHNOLOGY FOR RARE DISEASES (9:00 - 10:20 AM) **CHAIR: Christoph Klein**, Ludwig-Maximilians-University, Munich, Germany			Hercules Hall
9:00 am	***The Building Blocks of Human Genetics***	**Richard Gibbs** Baylor College of Medicine, Houston, TX, USA	
9:30 am	***Stem Cell Derived Retinal Transplantation: The First Human Experience***	**Steven Schwartz** University of California Los Angeles, Los Angeles, CA, USA	
10:00 am	Short Talk – ***High Throughput Forward and Reverse Genetics By Deriving Haploid Mouse ES Cells***	**Ulrich Elling** IMBA, Vienna, Austria	
10:20 am	Coffee Break		Sala Terrena/ Gardens
WORKSHOP: STATE OF THE ART TECHNOLOGIES FOR DECIPHERING RARE DISEASES (10:45 - 12:45 pm) **CHAIR: Josef Penninger,** IMBA, Vienna, Austria			Hercules Hall
10:45 am	***Genome Editing to Generate Human Isogenic Models of Metabolic Disease***	**Kiran Musunuru** Harvard University, Cambridge, MA, USA	
11:10 am	***Molecular Networks in Innate Immunity and Leukemias***	**Giulio Superti-Furga** CeMM, Vienna, Austria	
11:35 am	***A New Technology Platform for Paracrine Factor Therapeutics***	**Kenneth Chien** Harvard University, Cambridge, MA, USA	
12:00 pm	Panel Discussion		

Wednesday, October 10th, 2012 (continued)

TIME	TOPIC	SPEAKER	PLACE
12:45 to 2:00 pm	Lunch and Poster Session I (continued)		Sala Terrena/ Garderns and 3 Galleries
SESSION V: RARE DISEASES OF EPITHELIA (2:00 - 4:30 PM) **CHAIR: John Dart,** COO, DEBRA International, Deputy General Secretary, EURORDIS			Hercules Hall
2:00 pm	***Hirschsprung Disease: From Genes and Cells to Patients***	**Paul Tam** The University of Hong Kong, Hong Kong, China	
2:30 pm	***Inborn Errors of Metabolism: From Genes to Treatment in Biochemical Genetics***	**Anna Wedell** Karolinska Institutet, Stockholm, Sweden	
3:00 pm	***DMM Global Foundation Fellows Award: Short Talk – Hyper-resection of Telomeres in a Mouse Model of Dyskeratosis Congenita***	**Peng Wu** Rockefeller University, New York, NY, USA	
3:20 pm	***DMM Global Foundation Fellows Award: Short Talk – Apo-Skip, A Treatment For Familial Hyper-cholesterolemia***	**Petra Disterer** University College London, London, UK	
3:40 pm	***Medical Mysteries and Rare Diseases: NIH's Undiagnosed Diseases Program***	**William Gahl** National Institutes of Health, Rockville, MD, USA	
4:10 pm	Closing Remarks		
6:30 pm	Gala Dinner		Viennese wine tavern "Heuriger" (see Page 40 for details)

Keynote Speaker Bio

Eric R. Kandel

Eric Kandel, MD, is University Professor at Columbia, Fred Kavli Professor and Director, Kavli Institute for Brain Science and a Senior Investigator at the Howard Hughes Medical Institute. A graduate of Harvard College and N.Y.U. School of Medicine, Kandel trained in Neurobiology at the NIH and in Psychiatry at Harvard Medical School. He joined the faculty of the College of Physicians and Surgeons at Columbia University in 1974 as the founding director of the Center for Neurobiology and Behavior. At Columbia Kandel organized the neuroscience curriculum. He is an editor of *Principles of Neural Science*, the standard textbook in the field. Prior to writing *The Age of Insight*, Eric Kandel wrote a book on the brain for the general public entitled *In Search of Memory: The Emergence of a New Science of Mind*, which won both the L.A. Times and U.S. National Academy of Science Awards for best book in Science and Technology in 2008. A documentary film based on that book is also entitled *In Search of Memory*. Kandel's recent book, *The Age of Insight: The Quest to Understand the Unconscious in Art, Mind, and Brain, from Vienna 1900 to the Present*, just appeared this spring. Eric Kandel's research has been concerned with the molecular mechanisms of memory storage in *Aplysia* and mice. More recently, he has studied animal models in mice of memory disorders and mental illness. Kandel has received twenty honorary degrees, is a member of the U.S. National Academy of Sciences as well as the National Science Academies of Austria, France, Germany and Greece. He has been recognized with the Albert Lasker Award, the Heineken Award of the Netherlands, the Gairdner Award of Canada, the Harvey Prize and the Wolf Prize of Israel, the National Medal of Science USA and the Nobel Prize for Physiology or Medicine in 2000.

Christopher Baum

After studying medicine in Essen, Freiburg and Hamburg (Germany), Christopher Baum started his scientific career with projects in developmental biology, retrovirology and hematology. Since 2006, he is full professor and head of the Institute of Experimental Hematology at Hannover Medical School, a major center for transplantation medicine, where he also serves as Dean of Research. He also worked several years as adjunct faculty member of Cincinnati Children's Hospital Medical Center, one of the largest pediatric hospitals in the USA. His research focuses on genetically-modified cell therapy in the hematopoietic system, with the goal to increase efficiency and safety for the treatment of various genetic or acquired disorders. Scientific achievements and ongoing developments of his team cover four complementary fields: (1) developing retrovirus-based vectors and gene expression systems for stable and reversible cell modification; (2) establishing novel preclinical assays to evaluate gene vector potency and biosafety; (3) understanding and preventing clonal imbalance related to random transgene insertion; and (4) using insertional mutagenesis by gene vectors and other molecular tools to discover gene networks that regulate stem cell fitness and transformation.

Kenneth R. Chien

Dr. Kenneth R. Chien is a world-recognized leader in cardiovascular science and medicine and currently is a Professor in the Department of Stem Cell and Regenerative Biology at Harvard University in Cambridge and at the Massachusetts General Hospital. Recently, he has also been appointed by the Karolinska Institute to lead a new international Cardiovascular Science Initiative, which is based on his long-standing interest in physician-scientist training.

Dr. Chien's laboratory has reported the discovery of a "master" heart progenitor cell, marked by the expression of Islet-1, in the mammalian heart, which play a critical role in generating diverse cardiovascular lineages during cardiogenesis. Recent studies have now led to the identification and purification of a primordial human islet-1 progenitor from human ES cells, which give rise to a family of downstream intermediate multipotent heart progenitors that have been implicated in human congenital heart disease. In addition, his lab has generated, for the first time, a fully mature strip of ventricular muscle from ES cells, via combining tissue engineering and stem cell technology together. This approach opens the path towards the generation of heart parts for end stage cardiovascular diseases via controlling the cell fate of pluripotent human ES and iPS cells.

Dr. Chien has served as an advisor and/or board member to several scientific institutions in the public and private sector, including the Karolinska Institute, Doris Duke Charitable Foundation, The Wellcome Trust, The Institute of Molecular Biotechnology of Austria, Genentech, Hoffman La-Roche, Pfizer, GlaxoSmithKline, AstraZeneca, Wyeth, University of Edinburgh, CNIC in Madrid, and Oxford University. Dr. Chien also has strong interests in biotechnology and biomedical science in China, and is the founder of the Institute of Molecular Medicine at Peking University. For his training efforts and his work, he has received several awards, including the Pasarow Foundation Award, an honorary Doctorate of Science from the University of Edinburgh, and recent election as a foreign member of the Austrian Academy of Sciences, and the Norwegian Academy of Sciences.

Speaker Bios

Ulrich Elling

Ulrich Elling was born in 1975 in Freising, Germany. He studied biology at the University of Regensburg, Germany, and also at the University of Boulder in Colorado. His PhD at EMBL in Heidelberg involved dissecting the role of SALL transcription factors in development and embryonic stem cells using mouse models. During his postdoctoral work in the laboratory of Josef Penninger at the IMBA in Vienna, Austria he studied hematopoiesis using a genomewide *Drosophila* screen. His current work focuses on haploid murine embryonic stem cells and a screening technology that he developed in order to do saturated genetic screens in embryonic stem cells.

Alain Fischer

Alain Fischer is professor of paediatrics since 1986, Director of the Department of Paediatric Immunology and Hematology at Hospital Necker-Enfants Malades, University Paris Descartes. He is the Head of an INSERM research laboratory and Director of the Institut des Maladies génétiques (Imagine). He studied Medicine in Paris, received an MD in 1979 and a PhD in Immulology in 1979. He had a post doctoral training in Immunology at University College London in 1980-1981. His main research interests are the development of the immune system, genetic diseases of the immune system and gene therapy. He is or has been the author or co-author of 550 publications in peer-reviewed journals. He is a member of the board of reviewing editors of *Science* magazine and is or has been in the editorial committees of *Plos Medicine*, *Embo Molecular Medicine*, *European Journal of Immunology* and *Immunological Reviews*.

William A. Gahl

Dr. William A. Gahl, MD, PhD, received his undergraduate degree from MIT in 1972 and his MD and PhD from the University of Wisconsin. He completed a residency in pediatrics at the University of Wisconsin and a postdoctoral fellowship in genetics at the National Institutes of Health. Dr. Gahl is certified in Pediatrics, Clinical Genetics, and Clinical Biochemical Genetics. He is a past member of the Board of Directors of the American Board of Medical Genetics, past president of the Society for Inherited Metabolic Disorders, and a member of the American Society for Clinical Investigation and the Association of American Physicians. Dr. Gahl is an international expert in cystinosis, Hermansky-Pudlak syndrome, alkaptonuria, and disorders of free sialic acid metabolism. He is currently Clinical Director of the National Human Genome Research Institute, director of the intramural program of the Office of Rare Diseases, and Director of the NIH Undiagnosed Diseases Program. Dr. Gahl is a recipient of the 2011 Service to America Medal in Science and the Environment.

Richard Gibbs

Richard A. Gibbs, PhD was born in Australia and moved to the USA in 1986 where he performed key work on the molecular characterization of human genetic disease and the development of methods for mutation

detection. He provided an early leadership role for the Human Genome Project (HGP) and in 1997 founded the Baylor College of Medicine Human Genome Sequencing Center (HGSC) in Houston, Texas. Under his leadership the HGSC was one of five main groups to complete the HGP, and since has completed the genomes of many other species. Subsequently the group has both contributed to major international large scale genetics projects and focused upon the analysis of individual personal human genomes, including the Watson, Tutu and Lupski genome projects. His group has been a major force in developing the entire field of genomics and has led efforts to use genomics in medicine. He was elected to the Institute of Medicine of the National Academy of Sciences in 2011. Gibbs currently holds the rank and title of the Wofford Cain Distinguished Professor of Molecular and Human Genetics and Director of the HGSC.

Michael Hayden

Dr. Michael Hayden is the Killam Professor of Medical Genetics at the UBC and Canada Research Chair in Human Genetics and Molecular Medicine. He is the Director of the Center for Molecular Medicine and Therapeutics (CMMT) and founder of three biotechnology companies: NeuroVir Therapeutics Inc., Xenon Pharmaceuticals Inc., and Aspreva Pharmaceuticals Corp.

Author of over 700 peer-reviewed publications and invited submissions, Michael focuses his research primarily on genetic diseases, including genetics of lipoprotein disorders, Huntington disease, predictive and personalized medicine. Michael and his research group have identified 10 disease-causing genes which includes the identification of the major gene underlying high-density lipoprotein (HDL) in humans. Michael also identified the first mutations underlying Lipoprotein Lipase (LPL) Deficiency and developed gene therapy approaches to treat this condition. Michael is also the most cited author in the world for ABCA1 and Huntington Disease.

Michael is the recipient of numerous recent prestigious honours and awards, including the Margolese National Brain Disorder Prize (2011), awarded to Canadians who have made outstanding contributions to the treatment, amelioration, or cure of brain diseases; the Killam Prize by the Canada Council of the Arts (2011), in recognition of his outstanding career achievements; and the Canada Gairdner Wightman award (2011), recognizing him as a physician-scientist who has demonstrated outstanding leadership in medicine and medical science. Michael has also been awarded the Order of Canada (2011), and the Order of British Columbia (2010). He was named Canada's Health Researcher of the Year by CIHR in 2008, and he received the Prix Galien in 2007, which recognizes the outstanding contribution of a researcher to Canadian pharmaceutical research.

Dan Kastner

Dan Kastner is currently the Scientific Director of the Intramural Research Program of the National Human Genome Research Institute. His group has played a major role in elucidating the molecular basis, pathophysiology, and treatment of several human disorders of inflammation. This has included the identification of the gene causing familial Mediterrranean fever, discovery of the TNF receptor-associated periodic syndrome (TRAPS),

and work that has established three other distinct illnesses as disorders of the IL-1 pathway, thus helping to define the role of IL-1 in human biology and establishing IL-1 inhibitors as effective therapy. More recently his laboratory described PLAID, a disorder of immune regulation caused by mutations in phospholipase Cγ2, and has identified several genetic loci predisposing to Behçet's disease. Dan's group also proposed the now widely accepted concept of autoinflammatory disease to denote disorders of innate immunity. Over the course of his career Dan has won a number of awards and honors, including the Lee C. Howley, Sr. Prize for Arthritis Research from the Arthritis Foundation, the American College of Rheumatology Distinguished Investigator Award, and numerous named lectureships. In 2010 he was elected to the National Academy of Sciences.

Christoph Klein

Dr. Christoph Klein is Director of the Department of Pediatrics at the Dr. von Hauner Children's Hospital, Ludwig-Maximilians-University Munich. He trained in pediatric immunology/hematology/oncology and has a specific focus on rare disorders of the blood and immune system. His group has discovered numerous monogenetic disorders of the immune system and has set up a clinical gene therapy study for children with Wiskott-Aldrich Syndrome.

Michaela Kneissel

Michaela Kneissel is Director of Connective Tissue and Mineral Disorder Research in the Musculoskeletal Disease Area, Novartis Institutes for BioMedical Research (NIBR), Novartis Pharma AG, Basel, Switzerland. Michaela Kneissel leads a group of scientists who work together to develop novel agents that will improve patients' bone and mineral metabolism and tendon health. Michaela Kneissel received her PhD from the University of Vienna, Austria. She performed part of her PhD work at the Hard Tissue Research Unit, University College London, UK and was postdoctoral fellow at the Radiobiology Division, University of Utah, Salt Lake City, USA before joining Novartis. In recent years her research interest was centered on the bone formation inhibitor sclerostin and osteocyte biology. She currently serves on the board of directors of the International Society for Bone Morphometry and on the editorial boards of Calcified Tissue International and BONE.

Paola Leone

Paola Leone earned her doctorate in Neuroscience in 1987 at the University of Padua, Italy. Upon completing a postdoctoral research fellowship at Concordia University in Montreal, Canada, she began her career as a research scientist at Yale University and the University of Auckland, New Zealand. In 1998, she returned to the U.S. to accept a position as Assistant Professor at Thomas Jefferson University in Philadelphia, PA. Then in 2002, Dr. Leone founded the Cell & Gene Therapy Center (CGTC) at UMDNJ-RWJMS. Since 2007, Dr. Leone has been based at UMDNJ School of Medicine in Stratford, NJ. In 2007, Dr. Leone and her team completed a NIH-sponsored Phase I/II study on Gene Therapy for Canavan Disease in collaboration with Children's Hospital of Philadelphia and several other major medical centers in the USA. The author of over 63 scientific papers, she

has emerged as an international leader in Canavan disease research. Her laboratory is currently investigating treatments for brain diseases using gene transfer, stem cells, and pharmacological technologies. Her research interests encompass the study of fundamental neurochemical processes underlying cerebral metabolic deficits associated with neurodegenerative diseases. In terms of volunteer work, Dr. Leone has served as a conference organizer and chair of several rare disease conferences. She is a distinguished member of numerous Scientific Advisory Boards and has been honored with several distinguished awards, including a UNESCO Award in 1999 and a MD Advantage Outstanding Medical Research Scientist Award in 2012.

Susan Lindquist

Susan Lindquist is a pioneer in protein folding. She has demonstrated that alternative protein conformations have profound effects in human disease, evolution, and biomaterials. Her work on yeast prions established the basis of protein-only inheritance, creating a new understanding of amyloids. She showed that molecular chaperones pervasively influence evolution by chaperoning the folding of signal transduction proteins. Her seminal work on the role of protein homeostasis in cancer lead to the development of Hsp90-based therapeutics. Her group is developing new platforms for deciphering the protein-folding problems that drive neurodegenerative diseases to discover potential therapeutic strategies based on stopping the precipitating causes.

Susan Lindquist is a Member of the Whitehead Institute, National Academy of Sciences, American Academy of Arts and Science, American Philosophical Society, and the Institute of Medicine. Her honors include the Dickson Prize in Medicine, Otto-Warburg Prize, Genetics Society of America Medal, FASEB Excellence in Science Award, Max Delbrück and Mendel Medals, and the National Medal of Science.

Susan Lindquist is on the Johnson & Johnson Board of Directors and co-founded FoldRx, a company (recently acquired by Pfizer) that develops therapies for diseases of protein misfolding and amyloidosis. She was the Director (2001-2004) of the Whitehead Institute and became an Investigator of the Howard Hughes Medical Institute in 2006. Previously she was the Albert D. Lasker Professor of Medical Science at the University of Chicago. She received her PhD in Biology from Harvard University, and was a postdoctoral fellow of the American Cancer Society at the University of Chicago.

Peter Mueller

Dr. Peter Mueller joined Vertex in July 2003. As Executive Vice President Global Research and Development & Chief Scientific Officer, he provides strategic oversight for Vertex's worldwide drug discovery research programs, Pharmaceutical Development, Quality Assurance and Control, Pharmaceutical Operations as well as Clinical and Non-Clinical Development, Regulatory and Medical Affairs. Key areas of Vertex' R&D are Hepatitis C, Cystic Fibrosis, IMID, Cancer, and Neurological Diseases which led in 2011 to the successful approval and launch of INCIVEK (HepC), a NDA/MAA submission for KALYDECO (CF) with the first approval in the US on January 31, 2012 and several proof of clinical concept candidates in various disease areas. Prior to coming

to Vertex, Dr. Mueller served as Senior Vice President, Research and Development, for Boehringer Ingelheim Pharmaceuticals, Inc. where he was responsible for the development of all drug candidates of the company's worldwide portfolio in North and South America, Canada and Japan, beginning in 1997. He also led research programs in the areas of immunology, inflammation, cardiovascular disease and gene therapy on a global basis. During his time with Boehringer Ingelheim, Dr. Mueller oversaw the discovery of numerous development candidates, held several positions in basic research, medicinal chemistry and management in different centers of BI worldwide. Dr. Mueller received both an undergraduate degree and a PhD in Chemistry at the Albert Einstein University of Ulm, Germany, where he also holds a Professorship in Theoretical Organic Chemistry. He completed fellowships in Quantum Pharmacology at Oxford University and in Biophysics at Rochester University. He is a (Board) member of various scientific and political societies, such as the Gesellschaft Deutscher Chemiker (GDCh) and Verband Chemische Industrie (Germany), Royal Society of Chemistry (UK); US-India Chamber of Commerce Biotech, Pharma & Medical Devices Council, IRI, RNA-Society, ASAP, AAAS (USA), Harvard Accelerator Fund. Before he left Connecticut to join Vertex, Dr. Mueller was also a member of Govenor Roland's Council on Economic Competitiveness and Technology for the State of Connecticut (USA).

Kiran Musunuru

Dr. Kiran Musunuru is Assistant Professor of Stem Cell and Regenerative Biology at Harvard University and Associate Physician at Brigham and Women's Hospital. Dr. Musunuru received his MD degree from Weill Cornell Medical College, his PhD degree from The Rockefeller University, and his MPH degree from Johns Hopkins Bloomberg School of Public Health. He trained in Internal Medicine at Brigham and Women's Hospital and Cardiovascular Medicine at Johns Hopkins Hospital, followed by postdoctoral work at Massachusetts General Hospital and the Broad Institute of MIT and Harvard. Dr. Musunuru's research focuses on the genetics of cardiovascular and metabolic diseases.

Amit C. Nathwani

Professor Amit C. Nathwani is the Director of the Katharine Dormandy Haemophilia Centre at the Royal Free Hospital. He is also the North London Cancer Network lead for Chronic Lymphocytic Leukaemia. He graduated in Medicine from the University of Aberdeen in 1984. His PhD was on the regulation of the tissue factor gene. In 1997 he moved briefly to St Jude Children's Research Hospital, Memphis, Tennessee, USA to work with Dr. Arthur Nienhuis on adeno-associated virus mediated gene transfer, which is where he started his pioneering work on gene therapy for haemophilia B. In 2001 he returned to University College London as a Senior Lecturer in Haematology and a Consultant to the National Blood Services in the U.K. He was the first to show successful correction of bleeding diathesis in patients with severe haemophilia B using a distinct approach developed in collaboration with Drs. Davidoff and Nienhuis at St Jude Children's Research Hospital. Professor Nathwani's team of clinical and non-clinical scientists and students are currently engaged in a diverse range of translational research including gene therapy for haemophilia A, congenital bleeding disorder, chronic lymphocytic leukaemia, age related macular degeneration and hepatocellular carcinoma. Professor Nathwani is on the advisory

boards of various medical charities and biotech companies. He is also a frequent reviewer for a wide range of scientific journals and granting bodies.

Josef Penninger

Josef Penninger was born in 1964 in Gurten, Austria. He received a High School education in classical humanities and studied Medicine, Immunology, and History of Arts in Innsbruck, Austria. After his graduation in 1990 he left Austria to pursue postgraduate studies at the Ontario Cancer Institute in Toronto. From 1994 to 2002, Josef Penninger worked as a lead researcher at the Amgen Research Institute in Toronto affiliated with the University of Toronto and the Ontario Cancer Institute. In 2002, he accepted the appointment as director of the newly established Institute of Molecular Biotechnology of the Austrian Academy of Sciences, IMBA, and moved back to Vienna. Currently, Josef Penninger is Full Professor at the Departments of Immunology and Medical Biophysics at the University of Toronto, Professor of Genetics at the University of Vienna, Austria, and Honorary Professor of the Chinese Academy of Sciences/Peking Union Medical College.

Scientifically, his basic approach is to genetically manipulate and change genes in mice and to determine the effects of these mutations in the development of the whole organism and in diseases. Through these mutations, he tries to establish basic principles of development and basic mechanisms of disease pathogenesis. The main focus of his laboratory lies on heart and lung diseases, autoimmune diseases and cancer as well as bone metabolism disorders.

Josef Penninger has received various prizes and honors, such as the EU Excellence Award (2004), Elected Young Global Leader by the World Economic Forum (2005), Ernst Jung Prize for Medicine (highest endowed medicine prize in Europe, 2007), Descartes Prize (highest EU research prize, 2007), Carus Medal (2008), ESCI Award for Excellence in Biomedical Investigation, ASMR-Medal of the Australian Society for Medical Research (2009) and the Award as Elected Fellow of the American Association for the Advancement of Science (2011).

Ben Philpot

Ben Philpot is an Associate Professor at the University of North Carolina, Chapel Hill, and is co-Director of the Carolina Institute for Developmental Disabilities postdoctoral training program. Dr. Philpot earned his PhD in psychobiology from the University of Virginia in 1997, where he examined the role of sensory experience in shaping the anatomy and function of the olfactory system. He performed a postdoctoral fellowship in the laboratory of Dr. Mark Bear at Brown University and MIT, where he pioneered studies on how experience-driven changes in glutamate receptors can adjust the properties of synaptic plasticity in the neocortex. Dr. Philpot's current research focuses on developing therapeutic strategies to treat neurodevelopmental disorders, and he has helped develop the first-ever screen to activate disease-relevant genes in neurons. Dr. Philpot joined the Department of Cell Biology and Physiology at UNC in 2004, and he is also a member of the Neuroscience Center, the Neurobiology Curriculum, and the Carolina Institute for Developmental Disabilities. He has authored over

40 scientific publications, served on review boards for the National Institutes of Health, and is on the Scientific Advisory Committee for the Angelman Syndrome Foundation. He has received a number of research awards, including awards from the NIH, Angelman Syndrome Foundation, Rett Syndrome Research Trust, NARSAD, Whitehall Foundation, and Simons Foundation.

Steven D. Schwartz

Dr. Schwartz is leading two new clinical trials testing the use of stem cell-derived retinal pigment epithelial cells to address vision loss in people suffering from Stargardt's macular dystrophy and dry age-related macular degeneration. Dr. Schwartz' primary areas of research include early diagnosis and treatment of diseases such as retinopathy of prematurity (ROP), diabetic eye disease, and macular degeneration. Additionally, his focus includes development and evaluation of novel medical device technologies, imaging technologies, surgical equipment (including surgical robots), and drug delivery systems, with particular emphasis on diagnostic and treatment applications. Dr. Schwartz' clinical research focuses on trials of novel pharmacotherapeutic agents to discover treatments for both wet and dry age-related macular degeneration, ROP, and diabetic retinopathy. Through innovative teleophthalmological approaches to screen for eye diseases (such as diabetic retinopathy and ROP), Dr. Schwartz is dedicated to improving both the quality of and access to specialized ophthalmology care. Currently, a collaborative program with UCLA's Gonda Diabetes Center and Venice Family Clinic is underway, in which screening for diabetic retinopathy is conducted with a nonmydriatic camera (a camera that does not require dilation of the eyes) as part of each patient's regular diabetes treatment. Results are telecommunicated to specialists at the Jules Stein Eye Institute for interpretation and follow up.

Jonathan Seidman

Dr. Jonathan Seidman is the Henrietta B. and Frederick H. Bugher Foundation Professor of Genetics at Harvard Medical School. He received his undergraduate degree from Harvard University ('72) and his PhD degree from the University of Wisconsin-Madison. His postdoctoral studies were carried out in Dr. Philip Leder's laboratory at the National Institute of Child Health and Human Development. He has been a member of the Genetics Department, Harvard Medical School since 1981. Over the past ten years his research has been directed towards understanding the molecular basis and epidemiology of hypertrophic cardiomyopathy, dilated cardiomyopathy and congenital heart disease.

Lorenz Studer

Lorenz Studer, MD, is a native of Switzerland. He graduated from medical school in 1991 and received his doctoral degree in neuroscience at the University of Bern in 1994. While there, he initiated studies with Christian Spenger, leading to the first clinical trial of fetal tissue transplantation for Parkinson's disease in Switzerland. Studer next pursued his research interests at the National Institutes of Health (NIH) in Bethesda, Maryland, where he worked in the laboratory of Ron McKay. At the NIH, he pioneered the derivation of dopamine cells

from dividing precursor cells. In 1998, he was first to demonstrate that the transplantation of dopamine cells generated in culture improved clinical symptoms in Parkinsonian rats.

In 2000, he moved to New York City where he started his research program at the Memorial Sloan-Kettering Cancer Center (MSKCC). Early contributions of his lab include the in vitro derivation of midbrain dopamine neurons from ES, nuclear transfer ES cells and parthenogenetic stem cells. His laboratory was also first to demonstrate "therapeutic cloning" in a mouse model of a CNS disorder, and he has pioneered studies on the directed differentiation, high-throughput screening and genetic modification of human ES cells. His most recent work increasingly focuses on the translational application of human pluripotent stem cells in disease modeling, drug discovery and cell therapy.

Studer is the Director of the Sloan-Kettering Center for Stem Cell Biology. He is a Member of the Developmental Biology Program and the Department of Neurosurgery at MSKCC and a Professor in Neuroscience at Weill-Cornell.

Giulio Superti-Furga

Giulio Superti-Furga has performed studies in molecular biology at the University Zurich, Genentech, and IMP/Vienna. Post-doctoral fellow and Team Leader at EMBL. Co-founded biotech company Cellzome and became Scientific Director until 2005. Member of: Austrian Academy of Sciences, German Academy of Sciences, EMBO, European Academy of Cancer Sciences. Chair of the EMBL Alumni Association. 2009 Advanced Investigator ERC Grant and Knight Officer Order of Merit of the Republic of Italy. 2011, Prize of the City of Vienna for Natural Sciences, and 2011 "Austria´s scientist of the Year". Since 2005 he directs the new Center for Molecular Medicine for the Austrian Academy of Sciences (CeMM) in the middle of the large general hospital campus in Vienna, where, together with some 120 scientists and medical doctors, he is trying to bring the genomic and systems-views close to the clinical world to improve medical practice. Among his major achievements to date are the elucidation of basic regulatory mechanisms of tyrosine kinases in human cancers, the discovery of fundamental organization principles of the proteome of higher organisms, and the characterization of the molecular machinery involved in innate immunity. His work on the organization of the eukaryotic proteome is among most highly cited in the field.

Paul K.H. Tam

Professor Tam Kwong Hang, Paul, *MBBS(HK); ChM(Liv); FRCS(Eng, Edin, Glas, and Ire); FRCPCH; FHKAM (Surgery)* has been Chair of Paediatric Surgery at The University of Hong Kong since 1996. He is also the Pro-Vice-Chancellor & Vice-President for Research and Dean of the Graduate School in The University of Hong Kong. Professor Tam graduated from The University of Hong Kong in 1976, and received his training and worked in the Department of Surgery until 1986. He was Senior Lecturer at the University of Liverpool in 1986-90, and Reader and Director of Paediatric Surgery at the University of Oxford in 1990-96. Professor Tam is a

dedicated clinician, researcher, teacher and university administrator. He specializes in the surgery, genetics and regenerative medicine of birth defects such as Hirschsprung's disease. He steers research strategies and development of the University and has served in numerous administrative positions. He also serves on various local and international associations of the medical profession and was a member of the Biology and Medicine Panel of the Research Grants Council in 2000-2005, and President of the Pacific Association of Paediatric Surgeons in 2008-09. He is Associate Editor of Journal of Pediatric Surgery and serves on editorial boards of several international journals. He has given keynote lectures including *Journal of Pediatric Surgery* Lecture and the Suruga Lecture at international conferences. He is the recipient of numerous awards including the British Association of Pediatric Surgery Prize, and the "International Outstanding Leadership Award in Endoscopy" from the National Office for Science and Technology, PRC

Anna Wedell

Anna Wedell, MD, PhD, is Professor of Medical Genetics at Karolinska Institutet and Senior Consultant in Clinical Genetics at the Centre for Inherited Metabolic Diseases, Karolinska University Hospital. This centre is a specialized laboratory for diagnostics of Inborn Errors of Metabolism (IEM), serving more than half of the Swedish population with expert advice and laboratory investigations. The centre also runs the nation-wide Swedish neonatal screening program, currently comprising 24 different rare, treatable disorders. Anna Wedell is also Clinical Director of the Science for Life Laboratory, a national infrastructure for large-scale molecular biosciences in Stockholm.

Mice, Men and Mental Illness: Animal Models of Mental Disorders

Eric Kandel, Columbia University, New York, NY, USA

In the last two decades molecular genetics has transformed neurology. Diagnoses of neurological disorders are no longer based only on signs and symptoms, but also on tests for the dysfunction of specific genes, proteins, and nerve cell components as well as brain scans for disturbances of neural systems. Molecular genetics also has led to the discovery of 1) several newly defined molecular diseases caused by mutations in specific genes, such as the channelopathies and 2) new mechanisms of pathogensis such as the trinucleotide-repeat and the prion folding disorders. To date, however, molecular biology has had only a modest impact on psychiatry. I propose to address this issue by illustrating that whereas neurology has long been based on the location of disease in the brain, there is not a comparable strong neuropathology of mental illness. In addition, tracing the genetic causes of mental illness is a much more difficult task than finding the gene for Huntington's disease. There is no single gene for schizophrenia, or most other mental illnesses. Most psychiatric disorders have a combined multigenic and environmental basis. As a result of these limitations, psychiatry has not been able to benefit from animal models of mental illness. I will suggest that during the next few years things may change. We also are beginning to know something about the neural circuits affected by these diseases. As a result, we can now begin to develop satisfactory animal models of components of these disorders. I will devote most of the lecture to describe attempts of my laboratory to develop mouse models schizophrenia, focusing on the cognitive symptoms reflected in working memory deficit and the negative symptoms reflected in motivation.

Kalydeco: Targeting the G551D Mutation in Cystic Fibrosis

Peter Mueller, Vertex, Cambridge, MA, USA

Cystic Fibrosis (CF), a multi factorial, autosomal recessive hereditary disorder, occurring mainly in Caucasians, affects about 70000 people globally. To date, more than 1900 different genetic mutations are known in the gene encoding the Cystic Fibrosis Transmembrane Regulator (CFTR) protein resulting in different CF phenotypes, that, fundamentally, drive reduction or loss of chloride transport across the epithelia of multiple organs due to impaired protein synthesis, trafficking or gating of CFTR. In CF, the loss of chloride transport in multiple organs results in a range of clinical manifestations, including high sweat chloride concentrations, pancreatic and intestinal disorders resulting in malnutrition and failure to gain or maintain weight, reproductive disorders, and lung disease. Of these, CF lung disease is the most life threatening manifestation. It is characterized by the build up of a thick sticky mucus resulting in chronic infection and inflammation that leads to airway plugging and bronchiectasis.

Approximately ~ 4 – 5% of the total CF population carries at least one copy of the G551D CFTR mutation. The G551D CFTR mutation results in normal quantities of CFTR protein at the cell surface, but prevents the CFTR channel from opening and closing properly (defective channel gating), resulting in the loss of chloride transport.

In vivo, the loss of chloride transport is reflected by a high sweat chloride concentration (mean ~108mmol/l) and a severe CF phenotype, as characterized by a high incidence (>90 %) of pancreatic insufficiency, early age of diagnosis, and a more rapid decline in lung function as determined by FEV_1.

A breakthrough therapeutic approach to treat the underlying root cause of CF in patients with the G551D mutation is to enhance chloride transport using a CFTR potentiator. CFTR potentiators act allosterically on the CFTR protein located on the surface of epithelial cells, increase the channel gating activity, resulting in enhanced chloride transport. One such CFTR potentiator, recently approved by the FDA and EMA, is known as KALYDECO™ (ivacaftor, VX-770). In patients with the G551D mutation, KALYDECO™ significantly increases the function of G551D-CFTR, as measured by a decrease in the sweat chloride concentration, resulting in improved lung function, a decrease in the exacerbation rate, as well as an improvement in patient reported outcomes and a gain in weight.

Relevant biological concepts and clinical development strategies addressing different aspects of the complex interplay between genotype and phenotype in patients with Cystic Fibrosis will be discussed.

Synuclein Pathology: A Unifying Factor in Rare and Common Diseases

Susan Lindquist, Whitehead Institute for Biomedical Research, Howard Hughes Medical Institute, Cambridge, MA, USA

Many human diseases result from basic problems in protein folding and homeostasis. These disorders may appear to have little in common with each other besides their devastating clinical effects. Yet one feature neurodegenerative diseases share is the occurrence of misfolded, aggregated proteins in affected neurons. Strong evidence links the misfolding and mis-functioning of one such protein, alpha-synuclein (α-syn), to Parkinson's disease (PD), Dementia with Lewy Bodies (DLB), and Multiple System Atrophy (MSA). We have developed yeast models over-expressing human disease-associated proteins. Yeast offers opportunities for systems-level analysis to investigate combinations of causative factors in a high-throughput manner. Yeast cell expressing human α-syn recapitulates the cellular pathology and toxicity seen in PD and other synucleinopathies. Screening the entire yeast genome, we found dozens of genes that either enhance or suppress α-syn toxicity. We also screened 550,000 compounds and identified those that rescue yeast cells from α-syn. Importantly, both the genes and compounds rescued dopaminergic neurons in nematode and rat primary culture models of α-syn toxicity. The small molecules also rescued cultured rat dopaminergic neurons from toxicity induced by rotenone, validating the yeast screening approach. In a published genetic screen, we uncovered a PARK9, a gene that is mutated in some forms of early-onset PD, connected it to α-syn toxicity, and discovered its function in Mn detoxification. In unpublished work we are elucidating the function of several other disease alleles. Yeast studies have allowed us to directly link α-syn pathology, environmental toxins, and highly diverse proteins whose mutations cause PD, DLB, MSA and to now include a number of rarer, related neurodegenerative disesases in this analysis.

A New Angle on Angelman Syndrome

Ben Philpot, Department of Cell Biology and Physiology, University of North Carolina, Chapel HIll, NC, USA

Angelman syndrome (AS) is a debilitating autism spectrum disorder for which no effective treatment or cure currently exists. AS is caused by maternal deletions or mutations of a single gene, the E3 ubiquitin ligase UBE3A. The UBE3A gene is expressed monoallelically in neurons due to epigenetic silencing of the paternal allele, so losing function of the maternal allele eliminates UBE3A protein. Motivated by this biology, we hypothesized that neural and behavioral dysfunctions associated with AS could be treated by unsilencing the intact paternal UBE3A. Towards this goal, we developed the first-ever screen to identify small molecule compounds that can unsilence an imprinted gene. This seminar will discuss the assay development, drug screen, target identification, and pre-clinical testing of potential AS therapeutics that arose through our novel drug discovery approach.

From Mutations in the Few to Drugs for the Many

Michael Hayden, Centre for Molecular Medicine and Therapeutics, University of British Columbia, Vancouver, BC, Canada

Black swans have existed in the imaginations of philosophers for thousands of years as a metaphor of extreme outliers and unexpected rare events of large magnitude and consequence. Philosophers argued that even though black swans were extremely rare, collectively they had a vastly larger impact than common, regular occurrences. In genetics and drug discovery, the exceptional black swans of rare genetic illnesses can lead to high-impact discoveries beyond the realm of normal expectations. Following "extreme genetics" and "opposite phenotype" strategies, we have made inroads in studying many devastating rare genetic illnesses in order to decipher the basis for common diseases. Studying the very rare Tangier's Disease, we unravelled the genetic underpinnings of coronary disease and are developing a therapy that could benefit millions of coronary patients. Investigating the "Opposite Phenotype" of pain in rare patients who are unable to perceive or understand pain, we have developed new drugs that may be able to treat pain in a profound way for the general population. The importance of the rare patient and clinical genetics is crucial in the identification and validation of novel drug targets.

From iPS Cells to Drug Discovery in Familial Dysautonomia

Lorenz Studer, Developmental Biology Program and the Department of Neurosurgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Patient-specific induced pluripotent stem cells (iPSCs) represent a novel system for modeling human genetic disease and could develop into a key drug discovery platform. We have recently demonstrated the modeling of Familial Dysautonomia (FD) in iPSCs. FD is a rare but fatal genetic disorder affecting neural crest lineages. We reported several disease-related phenotypes at the molecular, developmental and cell biological level. In addition to modeling human disease we also developed the FD-iPSC model into a tool for drug discovery. We have completed a screen of 6,912 compounds, and characterized 8 hits that rescue expression of *IKBKAP*, the gene responsible for FD. Data will be presented on the potential mechanism of action of some of those compounds capable of rescuing *IKBKAP* expression and autonomic neurogenesis in FD-iPSC derived neural crest precursors. The FD study is a first example of using an iPSC based disease modeling for the discovery of novel therapeutic compounds, and it has resulted in the identification of several promising compounds for potential future translation. Another interesting example of human disease modeling using iPSC technology is the study of primary immune deficiencies such as Herpes Simplex Encephalitis (HSE). We will present some new results that illustrate the power of the iPSC approach for gaining novel insights into the disease mechanisms underlying the CNS specific manifestation of HSE.

RANKL/RANK, a Therapeutic Target for Bone Disease

Josef Penninger, IMBA, Vienna, Austria

Rare disorders of bone have markedly contributed to the molecular dissection of bone development and the regulation of the key cell types that control bone homeostasis. Bone-related diseases, such as osteoporosis or rheumatoid arthritis, affect hundreds of millions of people worldwide and pose a tremendous burden to health care. By deepening our understanding of the molecular mechanisms of bone metabolism and bone turnover, it became possible over the past years to devise new and promising strategies for treating such diseases. In particular, three tumor necrosis factor (TNF) family molecules, the receptor activator of NF-kB (RANK), its ligand RANKL, and the decoy receptor of RANKL, osteoprotegerin (OPG), have attracted the attention of scientists and pharmaceutical companies alike. Genetic experiments evolving around these molecules established their pivotal role as central regulators of osteoclast development and osteoclast function, leading to entirely novel medicines to treat bone loss. RANK-RANKL signaling not only activates a variety of downstream signaling pathways required for osteoclast development, but crosstalk to other signaling pathways and organ systems in normal physiology and disease. In particular, RANKL-RANK control thermoregulation in the central nervous system and are essential for the development of a lactating mammary gland during pregnancy with direct implications on hormonal driven-breast cancer.

Sclerosteosis: New Treatment Opportunities for Bone Diseases

M.K. Chang, I. Kramer, D. Jenkins, S. Ettenberg, Leupin O., Halleux C., F. Cong, M. Kneissel,
Novartis Institutes for BioMedical Research, Basel, Switzerland

Sclerostin, encoded by *SOST*, is an osteocyte secreted negative regulator of bone formation. Its absence is the cause of bone overgrowth in sclerosteosis (MIM269500). Sclerostin is thought to exert its action on cells of the osteoblastic lineage, which includes osteocytes, by binding to the WNT co-receptor LRP5 thereby blocking WNT/beta-catenin signaling. However, this hypothesis has not been proven *in vivo*. Hence we tested it using mouse genetic approaches. First we crossed *Sost* knockout (KO) mice, which recapitulate the sclerosteosis phenotype, with mice lacking beta-catenin in osteocytes (*Ctnnb1*$^{loxP/loxP}$*;Dmp1-cre*), which are osteoporotic. Absence of sclerostin did not rescue the osteoporotic phenotype suggesting that sclerostin targets Wnt/beta-catenin signaling in those cells. Next, we generated *Sost;Lrp5* double knockout (dKO) mice. Compared to *Sost* single mutants dKO mice presented with reduced yet not abolished bone overgrowth. To determine whether the remaining bone overgrowth was induced by aberrant Wnt signaling mediated by the second Wnt-coreceptor Lrp6, we utilized Lrp6 targeting antibodies with distinct modes of action. We treated *Sost* KO and wildtype mice with antibodies either (1) blocking Wnt1 class ligand mediated signaling, but potentiating Wnt3a class mediated signaling, or (2) displaying the reverse pattern, or (3) blocking both types of signaling. Blocking Wnt1 class mediated signaling reduced abnormal bone gain in *Sost* KO mice and to a lesser extent also bone growth in wild-type mice. This effect was irrespective of enhancement or blockage of Wnt3a class mediated signaling. Reversely and consistently, promotion of Wnt1 class mediated signaling further enhanced abnormal bone accumulation in *Sost* KO mice and induced bone gain in wild-type mice. These data indicate that sclerostin interferes with Lrp6 mediated signaling induced by Wnt1 class ligands. Importantly, administration of antibodies blocking Wnt1 class mediated signaling to *Sost;Lrp5* dKO mice completely abolished their remaining bone overgrowth. Together, we conclude that sclerostin exerts its action by targeting osteocyte Wnt/beta-catenin signaling. Mechanistically, sclerostin targets both Lrp5 and Lrp6 to block Wnt1 type ligand mediated signaling. Our findings not only support the concept to treat osteoporotic conditions by enhancing WNT/beta-catenin signaling in bone, but also suggest that reduction of signaling may decrease bone overgrowth in sclerosteosis patients.

Genetic Analyses of Inherited Cardiomyopathies

Jon Seidman, Department of Genetics, Harvard Medical School, Boston, MA, USA

Dilated cardiomyopathy (DCM) is an important cause of heart failure, a devastating condition affecting millions world-wide. DCM can arise from an underlying cardiovascular disease or as a primary genetic disorder of the myocardium. More than 40 DCM genes have been identified, most of which encode components of the sarcomere, the cytoskeleton, or the nuclear lamina. Despite this robust repertoire and clinical evidence for a genetic etiology in 30 to 50% of DCM cases, pathogenic mutations are found in only 20 to 30% of cases. To understand

this dichotomy, we undertook analyses of a previously identified DCM gene, TTN, which encodes the sarcomere protein titin. TTN mutations have been shown to cause DCM in 3 kindreds and are hypothesized to also cause HCM. However, definitive assessment of the role of TTN mutations in DCM or HCM has been hindered due to its enormous size. Using next-generation or dideoxy sequencing we analyzed over coding 145 kb of sequence that encode 33,000 amino acids in titin in cohorts of DCM, HCM, and controls samples from adults and children. After excluding TTN variants with frequencies ≥0.01 in the 1000 Genomes Project or among over 800 study subjects we identified rare nonsynonymous (missense, nonsense, frameshift, splicing or copy number variants) TTN variants. Due to the large numbers of rare missense variants in TTN, further analyses was restricted to variants that encoded a premature truncation of titin protein. All of these TTN truncating variants were independently validated. We identified few TTN truncating variants among HCM or control subjects. In contrast TTN truncating variants were strongly enriched in DCM subjects and segregated with affection status in families, defining these are DCM mutations. TTN truncating mutations are the most common cause of DCM, occurring in approximately 25% of familial and 18% of sporadic idiopathic DCM. Defining the functional impact of TTN truncating mutations on myocyte biology should improve understanding of DCM pathophysiology and may provide new opportunities to attenuate heart failure.

Back to the Future: The Evolution of Targeted Therapies for Canavan Disease

Paola Leone, Department of Cell Biology UMDNJ/SOM, Stratford, NJ, USA

Canavan Disease (CD) is a rare leukodystrophy for which no effective treatment has been available. This monogeneic, autosomal recessive disease is caused by mutations in the aspartylacylase gene (ASPA). The lack of functional enzyme leads to an increase in the substrate molecule, N-acetyl aspartate (NAA), which results in spongiform degeneration of the brain. Our group has built expertise in the clinical application of novel therapeutics to CD. We implemented brain gene transfer to patients affected by CD with the first clinical application of adeno-associated viral vectors in the human brain, as part of an international Phase I/II clinical trial. Gene therapy resulted in a decrease in pathologically elevated brain NAA levels and rate of change of brain atrophy, with improvements in seizure frequency and various quality of life measures. In addition, we previously reported the beneficial effects of lithium citrate in CD vis-à-vis intracerebral NAA levels, which has changed the current clinical management of newly diagnosed patients with CD. In the process, we have contributed to the characterization of the natural history of CD, have identified rare mutations associated with a mild phenotype, and have ascertained a novel role of aspartocylase in oligodendrogenesis. We have generated a significant body of data which suggests an abnormally low number of oligodendrocytes and an associated metabolic deficit as a central feature of the hypomyelinated phenotype presented by the Nur7 model of Canavan Disease. This presentation will summarize developments in the understanding of the pathology of CD and describe current therapeutic interventions.

Primary Immunodeficiencies, From Genes and Pathophysiology to Therapy

Alain Fischer, INSERM U768 & Unité d'Immunologie Hématologie Pédiatrique, Hôpital Necker-Enfants Malades, Université Paris Descartes, Paris, France

Primary immunodeficiencies (PID) consist in a group of rare diseases mostly with mendelian inheritance that impair capacity of fighting infections and/or controlling self reactivity and inflammation. Their studies have been instrumental to decipher the role of key molecules in both differentiation and effector functions of innate and adaptive immune cells. Examples will be presented to illustrate such findings and how they may lead to therapeutic development. Among them, is the observation that spontaneously occurring mutations can partially revert the consequences of key gene germ line mutations that result in a complete block in T cell development causing severe combined immunodeficiency (SCID). This was notably noticed for the common gc cytokine receptor deficiency leading to the concept that a few functioning T cell precursors can be sufficient to reconstitute a functional T cell immune system. On this ground were initiated a gene therapy trial for γc deficiency and then for other forms of SCID (and PID) that indeed validated this concept based on more than 13 years of observation.

Preclinical Development of Gene Therapeutics

Christopher Baum, Institute of Experimental Hematology, Hannover Medical School, Hannover, Germany

Gene therapy opens new treatment options for patients suffering from serious diseases, including rare monogenetic syndromes. Proof of concept is available for an increasing number of clinical entities, but insights into the pharmadynamic mechanisms and pharmakokinetic profiles are still limited. As a direct consequence of the novelty of the effective principles, gene therapeutic interventions may also trigger new forms of adverse reactions. Typical safety concerns address the risk of transmission of gene vectors to secondary tissues or individuals; immune responses to the gene vector or the encoded transgene product; off-target effects of the encoded transgene product ("phenotoxicity"); and mutagenic effects of the gene transfer procedure ("genotoxicity"). As most clinical trials in this field are initiated by academic investigators, many preclinical assays do not yet follow the standards of quality control established for industry-driven pharmaceutical developments. To share resources, drive innovation and improve quality control at all levels, large international academic consortia have been formed. Focusing on the genetic modification of hematopoietic cells for the treatment of congenital disorders of blood formation, I will describe recent developments of assays for preclinical safety and potency determination of gene therapeutics, and compare "conventional" strategies using retrovirus-based vectors to modify postnatal stem cells with new avenues involving cellular reprogramming.

Speaker Abstracts

From Rare to Common: What We Can Learn About IBD from Rare Monogenic Forms of Pediatric Colitis

Christoph Klein MD PhD, Director, Dr. von Hauner Children's Hospital, Ludwig-Maximilians-University, Munich, Germany

Inflammatory bowel diseases (IBD) comprise a wide spectrum of complex disorders. We have identified rare monogenetic variants in children with very early onset IBD. Mutations in genes encoding IL10R and IL10 lead to severe and refractory gut inflammation and account for approximately 15-20% of all very early onset cases. Defects in the IL10R dependent pathways lead to uncontrolled inflammatory reactions upon colonization with commensal bacteria. The discovery of the molecular etiology has allowed us to develop an innovative therapeutic strategy based on allogeneic hematopoietic stem cell transplantation.

Adventures in the Genomics of Inflammation

Dan Kastner, MD, PhD, Scientific Director, National Human Genome Research Institute, NIH, Rockville, MD, USA

The genetic and genomic analysis of inherited disorders of inflammation has had a major impact on our understanding of innate immunity in man. In this lecture I will focus on three topics. The first involves the study of a number of Mendelian disorders that we now know are caused by mutations in genes involved in IL-1β activation. These illnesses include familial Mediterranean fever (FMF), the cryopyrin-associated periodic syndromes (CAPS, which include familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and neonatal-onset multisystem inflammatory disease), the deficiency of the IL-1 receptor antagonist (DIRA), and the syndrome of pyogenic arthritis with pyodermagangrenosum and acne (PAPA). Although they are phenotypically distinct, excessive IL-1β signaling plays an important role in the pathogenesis of each of these illnesses, as evidenced by the effectiveness of therapies targeting this cytokine, and there is an emerging body of data implicating IL-1β in the pathogenesis of other more common, genetically complex illnesses. Recent work from our laboratory implicates intracellular Ca^{2+} and cAMP in the regulation of IL-1β activation. The second topic that I will discuss concerns the investigation of two related phenotypes, each of which is caused by mutations in *PLCG2*. One of these illnesses, now denoted PLAID (phospholipase $C\gamma_2$-associated antibody deficiency and immune dysregulation), was discovered through classical genetic analysis, and is characterized by cold-induced urticaria, with varying degrees of both autoimmunity and immunodeficiency. It is caused by dominantly inherited genomic deletions in the autoinhibitory domain of *PLCG2*, leading to constitutive enzyme activation but paradoxically reduced signaling in leukocyte subsets. The related phenotype, APLAID (autoinflammatory PLAID), was discovered by whole-exome sequencing, and is caused by the S707Y missense change in the same autoinhibitory domain disrupted in PLAID. Finally, I will review recent genome-wide association studies our laboratory has performed in Behçet's disease. In addition to confirming the long-recognized association with *HLA-B*51*, GWAS establishes an association of Behçet's disease with common variants in several other non-MHC loci, including *IL10*, *IL23R*, *CCR1*, *KLRC4*, *ERAP1*, and *STAT4*, while deep resequencing indicates a role for rare variants in some of these loci, and in others regulating the innate immune system.

Gene Therapy for Haemophilia B, From Bench to Bedside

Amit C. Nathwani[1,2,3], Edward G.D. Tuddenham, Cecilia Rosales, Jenny Macintosh, Pratima Chowdary, Anne Riddell, Saman Aghighi, Anja Griffioen, Jun Pie, Chris Harrington, Bert Glader, Catherine Y.C. Ng, Mark Kay, Junfang Zhou, James Allay, John Coleman, Susan Sleep, Katherine High, Federico Mingozzi, John T. Gray, Ulrike M. Reiss, Arthur W. Nienhuis, and Andrew M. Davidoff

1. Department of Haematology, University College London, London, UK
2. KD Haemophilia Centre and Thrombosis Unit, Royal Free NHS Trust, London, UK
3. NHS Blood and Transplant, UK

Haemophilia B, an X-linked bleeding condition, is an important target for proof-of-concept gene therapy trials. This is primarily because a small increase in the levels of FIX protein would have significant clinical impact. We have recently reported preliminary results of our distinct gene therapy approach for haemophilia B. This entailed a single peripheral vein administration of our novel self-complementary adeno-associated virus (AAV) vector encoding human FIX (scAAV2/8-LP1-hFIXco) at three different dose levels in subjects with severe haemophilia B. Our results showed a dose dependent increase in plasma FIX levels from less than 1% to peak levels of between 2-12% of normal in the 6 severe haemophilia B subjects enrolled in the study (Nathwani et al, NEJM 365:2357-65, 2011). This level of FIX expression following gene transfer was sufficient to convert the severe bleeding phenotype into a moderate or mild form of the disease. Four of the six patients have discontinued prophylaxis and remain free of spontaneous haemorrhage, despite engaging in activities previously associated with bleeding. Longer follow-up of these participants, as well as data from two additional participants recently enrolled at the high dose level will now be reported. This study continues to show promise and raises hope for patients with severe haemophilia B as well as those with other inherited disorders in which long term protein delivery could be curative.

The Building Blocks of Human Genetics

Richard Gibbs, Director, Baylor College of Medicine Human Genome Sequencing Center, Houston, Texas, USA

In 2007 we described the first 'personal genome' generated by a next-generation sequencer (NGS) - the sequence of James Watson. Subsequently we described methods for multiplex capture of human exons, via synthethic oligonucleotide arrays. Now, the combination of NGS and whole exome capture sequencing (WECS) has transformed our ability to characterize genetic variation within a given individual. The methods are being used to build a complete catalog of all the loci that can lead to Mendelian diseases aiming to increase the current count of 'known disease genes' (~2,600 disease associated loci) to more than 5,000 in the next few years. As each association between a disease and a specific gene/locus is made, there are increments in the understanding of the functional role of the affected genes. The analysis of allelic and locus heterogeneity in related phenotypes further increases our basic knowledge of gene interactions and complex biological processes. This increase in

knowledge is leveraged through lessons learned from historical strengths in comparative biology and genomics. The gains in the area of Mendelian disease, offer the prospects of unraveling the 'genetic architecture' of risk to common human diseases and provide a plethora of information and heuristic models relevant to human biology and medicine.

Stem Cell Derived Retinal Transplantation: The First Human Experience

Steven D. Schwartz, Jules Stein Eye Institute Retina Division, Department of Ophthalmology, David Geffen School of Medicine, University of California, Los Angeles, CA, USA

We started two prospective clinical studies (NCT01345006, NCT01344993) to establish the safety and tolerability of subretinal transplantation of hESC-derived retinal pigment epithelium (RPE) in patients with Stargardt's macular dystrophy and dry age-related macular degeneration—the leading cause of blindness in the developed world. Preoperative and postoperative ophthalmic examinations included visual acuity, fluorescein angiography, optical coherence tomography, and visual field testing.

Controlled hESC differentiation resulted in greater than 99% pure RPE. The cells displayed typical RPE behaviour and integrated into the host RPE layer forming mature quiescent monolayers after transplantation in animals. The stage of differentiation substantially affected attachment and survival of the cells in vitro after clinical formulation. Lightly pigmented cells attached and spread in a substantially greater proportion (>90%) than more darkly pigmented cells after culture. After surgery, structural evidence confirmed cells had attached and continued to persist during our study. We did not identify signs of hyperproliferation, abnormal growth, or immune mediated transplant rejection in either patient during the first 4 months. Although there is little agreement between investigators on visual endpoints in patients with low vision, it is encouraging that during the observation period neither patient lost vision. Best corrected visual acuity improved from hand motions to 20/800 (and improved from 0 to 5 letters on the Early Treatment Diabetic Retinopathy Study [ETDRS] visual acuity chart) in the study eye of the patient with Stargardt's macular dystrophy, and vision also seemed to improve in the patient with dry age-related macular degeneration (from 21 ETDRS letters to 28).

The hESC-derived RPE cells showed no signs of hyperproliferation, tumorigenicity, ectopic tissue formation, or apparent rejection after 4 months. The future therapeutic goal will be to treat patients earlier in the disease processes, potentially increasing the likelihood of photoreceptor and central visual rescue.

High Throughput Forward and Reverse Genetics By Deriving Haploid Mouse ES Cells

Ulrich Elling[1], Jasmin Taubenschmid, Gerald Wirnsberger, Ronan O'Malley, Simon-Pierre Demers, Quentin Vanhaelen, Andrey I. Shukalyuk, Gerald Schmauss, Daniel Schramek, Frank Schnuetgen, Harald von Melchner, Joseph R. Ecker, William L. Stanford, Johannes Zuber, Alexander Stark, and Josef M. Penninger

1. Institute of Molecular Biotechnology of the Austrian Academy of Sciences, Vienna, Austria

All somatic mammalian cells carry two copies of chromosomes (diploidy) which obscure mutational screens, whereas organism with a single copy of their genome such as yeast provide a basis for genetic analyses where any recessive mutation of essential genes will show a dominant phenotype due to the absence of a second gene copy. Haploidy has been achieved in fish embryonic stem cells, human KBM-7 leukemia cells, or partially by electrofusion to generate hybrid cells. However, since haploidy is thought to be incompatible with mammalian development, with the exception of KBM-7 cells, no somatic haploid cell has ever been reported in mammals. We report the generation of haploid mouse ES cell lines from parthenogenetic embryos. These cells carry 20 chromosomes, express bona fide stem cell markers, and can develop into multiple cell types of all germ-layers in vitro and in vivo. Such cells show stable growth over multiple passages, can be efficiently subcloned, differentiate at similar kinetics as diploid ES cells and can maintain haploidy even upon initiation of differentiation. We also developed insertional mutagenesis protocols that allow for saturated recessive genetic screens and results in homozygous alleles that can be reverted for immediate functional analysis of target genes. This system allowed us to generate the first knock-out cell line for Drosha and to confirm that Drosha is essential for microRNA processing in mammals. In a forward genetic screen, we identified the orphan GPCR Gpr107 as a novel molecule essential for killing by ricin, a toxin being used as bioweapon for which no antitoxins are available. In addition, fucosylation in the target cell was identified and confirmed as prerequisite for ricin toxicity. Our results open the possibility to combine the power of a haploid genome with pluripotency of embryonic stem cells to uncover fundamental developmental and biological processes in defined cell types at the genomic level.

Genome Editing to Generate Human Isogenic Models of Metabolic Disease

Kiran Musunuru, Department of Stem Cell and Regenerative Biology, Harvard University Division of Cardiovascular Medicine, Brigham and Women's Hospital, Cambridge, MA, USA

Transcription activator-like effector nucleases (TALENs) are a new class of engineered nucleases that have proven to be easier to design to bind and cleave at desired sites in the genome than previous types of nucleases. We report the use of TALENs to rapidly and efficiently generate knockout or mutant alleles of more than a dozen genes in either cultured somatic cells or human pluripotent stem cells, the latter of which we differentiated both the targeted lines and isogenic control lines into various cell types relevant to metabolic disorders.

We demonstrate cellautonomous phenotypes that are directly linked to disease—dyslipidemia, insulin resistance, hypoglycemia, lipodystrophy, motor neuron death, and hepatitis C infection—and yield new biological insights. Given the speed and ease with which we were able to derive and characterize these cell lines, especially in comparison to transgenic animals, we anticipate that TALEN-mediated genome editing of human cells will become a mainstay for the investigation of human biology and disease.

Molecular Networks in Innate Immunity and Leukemias

Giulio Superti-Furga[1], Georg Winter, Uwe Rix, Tilmann Bürckstümmer, Florian Grebien, Karoline V. Gleixner, Peter Valent, Martin Bilban, Scott M. Carlson, Forest M. White, Vincent Blomen, Kumaran Kandasamy, Alexey Stukalov, Andre' Müller, Keiryn L Bennett, Stefan Kubicek, Thijn Brummelkamp and Jacques Colinge

1. CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, Vienna, Austria

Despite tremendous progress in targeted therapy, numerous hematological malignancies are still treated in a way that does not consider the underlying molecular lesions. On the other hand, even in the exemplar case of Chronic Myelogenous Leukemia (CML), where the lesion is mostly known, resistance to single-agent therapy prevents a lasting cure. To contribute to a more comprehensive understanding of drug action on biological systems and hopefully identify ways to overcome resistance, employ combination interventions and re-use existing agents for ill-treated diseases, we have, over the years, assembled a multi-pronged approach. It consists of affinity proteomics with drugs and proteins, genomic profiling, phosphoproteomics, combination drug screens and the use of human near-haploid cells to screen for drug effectors. We find that 1) pharmacological targets are typically multidomain proteins undergoing complex intra and inter-molecular interactions within protein complexes, 2) these proteins are embedded in large protein-interaction networks that can be characterized in a quantitative and dynamic way and that include effectors and modulators of drug action 3) chemical agents, including approved therapeutics almost invariably target multiple proteins, often belonging to diverse biochemical classes. We report on a new allosteric intervention strategy for BCR-ABL, the identification of a combination of approved drugs that may be effective against the main CML drug-resistant BCR-ABLT315I gatekeeper mutation along with the deconvolution of the underlying mechanism of synergy and, lastly, the identification of an approach to predict the action of tyrosine kinase inhibitors against distinct BCR-ABL+ Acute Lymphoblastic Leukemia (ALL).

A New Technology Platform for Paracrine Factor Therapeutics

Kenneth R. Chien, Department of Stem Cell and Regenerative Biology, Harvard University, Cambridge, MA, USA

A number of multipotent heart progenitors are responsible for the diversification and expansion of cardiac myocyte, smooth muscle, and endothelial cell lineages during cardiogenesis. These progenitors persist after birth and may represent an opportunity for cell-based regenerative therapeutics. However, efforts towards unlocking their therapeutic potential have met with limited success. The localized, transient and efficient delivery to the heart of paracrine factors which control the expansion and differentiation of resident heart progenitors might represent a viable alternative therapeutic strategy, akin to the known clinical utility of cytokines to selectively augment specific blood cell lineages. Herein, we establish chemically modified mRNA (m*RNA) as a platform for localized, transient and highly efficient expression of paracrine factors in the murine heart in vivo and cardiomyocytes in vitro. We show that human vascular endothelial growth factor-A (hVEGF-A) that previously administrated to hearts mostly in the form of DNA plasmids or viral vectors can be delivered into the heart as m*RNA. This m*RNA delivery system allows better yet more transient protein expression (pulse-like behavior) compared to the DNA plasmid delivery system. hVEGF-A m*RNA administered in the setting of myocardial infarction (MI) markedly improved heart functionality and promoted long-term survival of recipients over one year after MI. Such an improvement is largely due to attenuated fibrosis and increased capillary density that allow successful heart remodeling following injury. In addition, we show that hVEGF-A is one of the ligands that expanded the pool of Wilm's tumor 1 (Wt1)-expressing epicardial heart progenitors (EPDCs). This six-fold increase of EPDCs diminished upon treatment with Flk-1 inhibitors, indicating the involvement of hVEGF-A in expansion of the pre-existing EPDCs. Moreover, hVEGF-A induced a cell-fate shift, driving rare pre-existing EPDCs away from a previously described interstitial fibroblast vimentin-like state and towards a vascular or cardiac fate following MI. To better understand the role of the EPDCs in heart remodeling after MI, we have also generated a m*RNA gel which has been applied on the heart surface, allowing us to label only the epicardium. We employed this system for cre activation of epicardial cells in the R26mTmG mice in the presence and absence of hVEGF-A m*RNA. Our result indicates that EPDCs are truly multipotent cardiac cells and under appropriate condition (e.g. hVEGF-A administration), these cells could differentiate into several cell types including cardiomyocytes. Altogether, these results show that hVEGF-A is responsible for promoting proliferation of heart progenitors and facilitating cell fate shift following injury. Therefore, m*RNA could provide a new cell-free therapeutic paradigm for promoting in vivo recruitment and differentiation of endogenous heart progenitors for therapeutic regeneration. Additional utility for this therapeutic platform of chemically modified mRNA for rare diseases will also be discussed.

Hirschsprung Disease: From Genes and Cells to Patients

Paul KH Tam, The University of Hong Kong, Hong Kong, China

Hirschsprung disease (HSCR) is a developmental disorder characterized by the absence of ganglion cells along variable portions of the distal intestine. HSCR is a complex rare disease with significant clinical and genetic heterogeneity and gender bias. The complexity observed in HSCR can be understood in the light of the molecular and cellular events that take place during the development of the enteric nervous system. The success of the colonization of the gut by neural crest cells (NCCs) depends on the synchronization and balance of the signaling network implicated. DNA alterations in the genes codifying for the signaling molecules may represent a primary etiology for HSCR. Severe mutations in a major gene encoding a crucial molecule or accumulation of less severe mutations in several genes may account for the variable phenotypes of HSCR. Recently, through a genome-wide association study, we have not only identified new genes implicated in the disease, but also highlighted the importance of functional crosstalk between the main signaling pathways for enteric ganglion formation. As early stages of human gestation are virtually inaccessible for experimental research, making human induced pluriopotent stem cell (iPSC) cultures provides a unique model for studying human NC development and the associated diseases. To date, we have successfully established various iPSC lines from syndromic and non-syndromic HSCR patients, and our preliminary data demonstrated that these patient lines exhibit severe diffentiation defects which may lead to diseases. As these lines carry exactly the same genetic make-up as the patients, they will provide powerful tools to unravel the complexity and to identify the missing heritability of the disease. High-throughput technologies, such as exome or RNA sequencing, applied to the genome of patients or to individual cell types are providing major breakthrough in the molecular studies of the HSCR pathogenesis and importantly, also in novel therapeutic intervention.

Inborn Errors of Metabolism: From Genes to Treatment in Biochemical Genetics

Anna Wedell, MD, PhD, Department of Molecular Medicine & Surgery, Karolinska Institutet, Centre for Inherited Metabolic Diseases, Karolinska University Hospital, Stockholm, Sweden

Inborn Errors of Metabolism (IEM) comprise many hundred different monogenic diseases disrupting metabolic pathways. Most are autosomal recessive due to mutations in genes encoding enzymes or transporter proteins. IEM can affect any organ and present at any age in life. Patients are therefore found across all clinical disciplines. The brain is particularly sensitive to metabolic disturbances, and most IEM lead to mental retardation unless treatment is started in time. For many traditionally untreatable diseases novel therapies are currently being developed.

Next generation DNA sequencing (NGS) is revolutionizing diagnostics in medical genetics. IEM are ideal targets, as their biochemical nature provides a functional context facilitating validation of encountered genetic variants. The Centre for Inherited Metabolic Diseases at the Karolinska University Hospital in Stockholm, Sweden, is a

specialized laboratory for investigation of IEM using a range of biochemical methods, serving more than half of the population. The centre also runs the national Swedish neonatal screening program, currently comprising 24 different rare, treatable conditions. We use NGS to identify disease-causing mutations in families with suspected IEM. Two novel disorders, AGC1 and ADK deficiencies, have recently been discovered, shedding light on novel pathogenetic mechanisms operating in the CNS. AGC1 deficiency has shown a dramatic response to dietary treatment, which could be designed based on the underlying biochemical defect. The identification of novel disease genes causing IEM can thus both shed light on normal brain metabolism and reveal novel pathogenetic mechanisms that can be exploited for treatment. Work is in progress to establish reprogramming of patient fibroblasts into relevant cell types, for detailed investigation of pathogenetic mechanisms as well as for drug screening.

Medical Mysteries and Rare Diseases: NIH's Undiagnosed Diseases Program

William A. Gahl, MD, PhD, Director, UDP; Clinical Director, NHGRI, NIH

The NIH Undiagnosed Diseases Program (UDP), supported by the Office of Rare Disease Research, the NHGRI, and the NIH Clinical Center, was established to diagnose patients who have long sought a diagnosis, and to discover new diseases and insights into their physiology, cell biology, and biochemistry. Since its inception in May of 2008, the highly selective UDP has reviewed more than 2400 medical records and admitted over 500 patients to the NIH Clinical Center. More than half of the cases involve neurological disease. The UDP has made approximately 100 diagnoses (mostly extremely rare diseases), documented several new genetic diseases (Arterial Calcification due to Deficiency of CD73, HINT3 Deficiency, SPAX5 due to biallelic mutations in AFG3L2) and identified extremely credible candidate genes for a score of other disorders. The UDP's greatest expertise involves genetic analysis, largely using probands and family members. SNP and whole exome sequencing analyses provide lists of candidate genes to pursue. Examples of successful diagnoses and of enigmatic disorders will be shown. The UDP provides hope to a desperate population by offering access to comprehensive and coordinated specialty examinations and state-of-the-art genetic evaluations. It also identifies new diseases for the field of medicine and novel pathways for the research community.

Gala Dinner

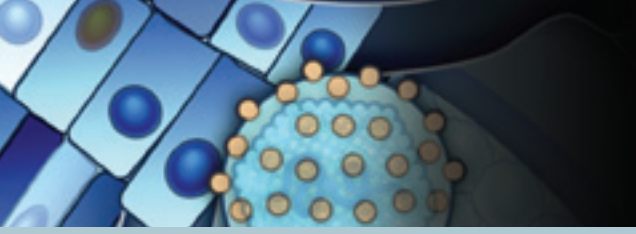
The Days of Molecular Medicine 2012 Gala Dinner will be held on Wednesday October 10th at 6.30 pm:

Heuriger Zimmermann
Armbrustergasse 5
A1190 Wien

http://www.zimmermanns.at/

Cost is US$ 50

Buses will transport guests from the Palais de Liechtenstein and Hotel de France to Heuriger Zimmerman and return.



Notes

Notes

Call for Papers

Science Translational Medicine

Integrating Medicine and Science

The peer-reviewed research journal publishes papers that identify and fill the scientific knowledge gaps at the junction of basic research and medical application in order to accelerate the translation of scientific knowledge into new ways of preventing, diagnosing, and treating human disease.

Our broad scope includes:

- Cardiovascular Disease
- Neuroscience/ Neurology/Psychiatry
- Infectious Diseases
- Cancer
- Health Policy
- Bioengineering
- Chemical Genomics/ Drug Discovery
- Phase I/II Clinical Trials
- Applied Physical Sciences
- Drug Delivery
- Gene Therapy/ Regenerative Medicine
- Cell Culture, Animal, and Human Studies
- Other Interdisciplinary Approaches to Medicine

Submit your research at www.submit2scitranslmed.org

Subscribing to ***Science Translational Medicine*** ensures that you and your colleagues have access to the latest studies and breakthroughs in the field of translational medicine.

To recommend a subscription, visit **ScienceOnline.org/recommend**

Science Translational Medicine
AAAS

For more information, contact scitranslmededitors@aaas.org

ScienceTranslationalMedicine.org

Days of Molecular Medicine 2012

Science Translational Medicine
AAAS

http://stm.sciencemag.org/