第６回国際協力遺伝病遺伝子治療フォーラム

The 6th International Collaboration Forum of Human Gene Therapy for Genetic Disease

-Open New Era of Human Gene Therapy-

開催日：２０１６年1月２１日（木）午前１０時―午後７時

会　場：東京慈恵会医科大学 大学１号館３階講堂

〒 105-8461 東京都港区新橋 3-25-8

大会長：衞藤　義勝（一般財団法人　脳神経疾患研究所

先端医療研究センター＆遺伝病治療研究所）

第６回国際協力遺伝病遺伝子治療フォーラム　プログラム

The 6th International Collaboration Forum of Human Gene Therapy for Genetic Disease (ICFHGTGD)-

日付：２０１６年１月２１日（木）午前１０時～午後７時
会場： 東京慈恵会医科大学大学１号館３階講堂

総合司会　小林 博司（東京慈恵会医科大学）

9:00- 9:50 Business meeting

10:00-10:30

Greeting　Yoshikatsu Eto (6th Meeting Chair)
Greeting; Officer from a Ministry of Welfare and Labor
Norikazu Matsubara
Government Cabinet-　Kato Katsunobu (a Ministry of National Project)

10:30-11:00

President Lecture：New Opening Era of Gene Therapy for Genetic Diseases
Chair：Fumio Endo(Department of Pediatrics Kumamoto University School of Medicine)

Yoshikatsu Eto, M.D. PhD
Advanced Clinical Research Center Institute of Neurological Diseases, Kanagawa, Japan

11:00-11:30

Special Lecture：Editing Gene Therapy―最近の進歩
Chair：Toya Ohashi
(Division of Gene Therapy, Research Center for Medical Sciences, The Jikei University School of Medicine)

Ko Mitani, Ph.D.
Gene Therapy Division, Research Center for Genomic Medicine, Saitama Medical University

11:30-12:10

Invited Lecture 1: AAV-mediated gene therapy for genetic disease
Chair：Keiya Ozawa(The Institute of Medical Science The University of Tokyo)

Katherine A. High, M.D.
Co-Founder, President and Chief Scientific Officer, Spark Therapeutics, Inc.

12:20-13:00

Education Seminar (Lunch)
(Takara Bio CO.)

遺伝病遺伝子治療の最前線―日本並びに欧米の臨床試験

13:10-14:20

(I) Retina & Muscle & CNS Gene Therapy

Chair : Takashi Shimada

(Nippon Medical School, Department of Biochemistry and Molecular Biology, Division of Clinical Genetics)

Shoji Tsuji(Department of Neurology and Medical Genome Center, The University of Tokyo Hospital)

1. Neuroprotective gene therapy for patients with retinitis pigmentosa: interim report of low-titer group
   Yasuhiro Ikeda
   Department of Ophthalmology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
2. Exon Skipping Therapy for Muscular Dystrophy
   Shin'ichi TAKEDA
   National Institute of Neuroscience, National Center of Neurology and Psychiatry
3. Translational Fidelity of Adeno-associated Virus-mediated RNA Interference for Huntington's Disease.
   Seng H. Cheng, PhD
   Sanofi Genzyme, Framingham, MA, USA

14:20-15:30

(II) Immune disease and Hemophilia

Chair : Makoto Otsu
(Center for Stem Cell Biology and Regenerative Medicine Institute of Medical Science, University of Tokyo)

Hiroaki MIZUKAMI (Div. of Genetic Therapeutics, Center for Molecular Medicine, Jichi Medical Univ.)

1. Gene therapy for chronic granulomatous disease
   Toshinao Kawai
   Department of Human Genetics National Center for Child Health and Development
2. Gene Therapy for Hemophilia
   Barrie Carter
   BioMarin Pharmaceutical Inc, Novato, CA, USA
3. "Gene therapy for inherited retinal dystrophies due to RPE65 mutations"
   Daniel C. Chung DO
   Spark, USA

15:30-16:40

(III) Inborn Error of Metabolism

Chair : Torayuki Okuyama(Director of Center for Lysosomal Storage Diseases Director of Clinical Laboratory Medicine National Center for Child Health and Development)

Takashi Okada(Department of Biochemistry and Molecular Biology, Nippon Medical School)

1. Gene therapy for AADC deficiency.
   Takanori Yamagata
   Department of Pediatrics, Jichi Medical University

2. AAVrh10 SGSH Intracerebral Gene Therapy in Mucopolysaccharidosis Type IIIA
   Micha l Hocquemiller, PhD
   Lysogene, France

3. Phase I/II results at 12 months of intra-cerebral administration of AAV vector containing human alpha-N-acetylglucosaminidase (NAGLU) in children with Mucopolysaccharidosis Type IIIB (Sanfilippo B Syndrome).
   Charles W Richard III* (uniQure USA), Marc Tardieu#, Michel Zerah, Marie-Lise Gougeon, Jerome Ausseil, and Jean-Michel Heard (France)
   *Senior Vice President, Neuroscience Research and Development, uniQure, Lexington, MA, USA
   # Principal Investigator, Paris Hospital Sud, France

17:00-17:10 Coffee Break

17:10-17:55

Invited Lecture 2:

Gene therapy for inherited disorders of the hematopoietic system

Chair : Masafumi Onodera
(Head. Department of Human Genetics (Research Institute) National Center for Child Health and Development)

Prof. Alessandro Aiuti M.D. PhD*
San Raffaele Telethon Institute for Gene Therapy (TIGET) and Vita Salute San Raffaele University, Milan, Italy

18:00-18:20
加藤勝信特命大臣　ご挨拶

18:20-19:05
Invited Lecture 3:

Gene therapy for genetic blood diseases: from viral vectors to genome editing

Chair Yoshikatsu Eto(Advanced Clinical Research Center Institute of Neurological Diseases, Kanagawa, Japan)

Fulvio Mavilio,
Genethon, Evry, France

19:05-19:20

Greeting from President, Japan Gene Therapy Society- Kaneda Yasufumi

Closing- Next 7th Meeting Chair- Onodera Masashi

19:30-21:00　Banquet

Chair : Fumio Endo(Department of Pediatrics Kumamoto University School of Medicine)

New Opening Era of Gene Therapy for Genetic Diseases

Yoshikatsu Eto, M.D. PhD

Advanced Clinical Research Center Institute of Neurological Diseases, Kanagawa, Japan

Recently, many genetic diseases have been treated by various technologies such as organ transplantation, enzyme replacement therapy (ERT), bone marrow transplantation (BMT), and small molecules (chaperon, substrate reduction therapy). However, these therapies are not curable therapy for such genetic diseases.

Now, ERT is golden standard for lysosomal storage diseases, but patients must have weekly or biweekly intravenous administration of enzymes and need life long therapy. The cost for ERT is also too expensive to carry out in many different genetic diseases.

Therefore, more effective and cost beneficial therapies are essentially necessary. Gene therapy just fits to these purposes.

We, now, face to new era to open the door for gene therapy of genetic diseases. More than hundreds patients in different genetic diseases have been treated using by retrovirus, lentivirsus or AAV vectors. Many inherited immune disorders such as SCID, ADA deficiency and etc have been successfully treated by retrovirus vector. Metachromatic leukodystrophy, Sanfilippo A and other LSD have, now, treated by lentivirus or AAV gene therapy. Leber congenital amaurosis, Parkinson disease, and other neurological disorders have also treated by various viral vector. Editing gene therapy could also realize to treat various genetic disorders. We will discuss these novel therapies in this exciting forum for gene therapy of various genetic diseases.

- Biography of Prof. Yoshikatsu Eto-

Prof. Eto is currently a Director of Advanced Clinical Research Center, Institute of Neurological Diseases and Professor Emeritus , Jikei University School of Medicine. He served as a Professor and chairman, Department of Pediatrics, Director of DNA Institute for Medical Science and also Vice President, University Hospital, the Jikei University School of Medicine. Prof. Eto studied for more than 40 years in the field of lysosomal storage diseases and has left many achievements. He also served as a President of Japan Pediatric Society for four years and also as a President of Japan Society of Inherited Metabolic Disorders for 7 years. He has been leading the research in Pediatrics in Japan. Internationally, he also serves as a Standing Committee Member of International Pediatric Association for 6 years and as a President of the 10th International Congress of Inborn Error of Metabolism, 2006, Tokyo. He contributed to the establishments of Asian Society of Pediatric Research and also Japan Society of Gene Therapy, and is also a founder of Japan Society of LSD. He published more than 350 English written papers. Currently, he has studying about clinical and basic research in LSD, particularly, Fabry disease, Pompe disease and genetic leukodystrophy, and also iPS research in LSD, as well.

Special Lecture 11:00~11:30

Chair： Toya Ohashi (Division of Gene Therapy, Research Center for Medical Sciences, The Jikei University School of Medicine)

“Clinical gene editing: How close are we?”

Ko Mitani, Ph.D.

Gene Therapy Division, Research Center for Genomic Medicine,
Saitama Medical University

Gene repair by genome editing would be an ideal strategy for gene therapy of inherited disorders. Recently developed artificial nucleases, such as ZFNs, TALENs, and CRISPR-Cas9, overcame low efficiencies of homology-directed repair in human cells. Currently, the CCR5-targeting ZFNs are clinically applied to disrupt the gene and block the spread of HIV in AIDS patients. In addition, a B-ALL patent was infused with universal CD19 CAT-T cells, which are manipulated by TALENs to knock-out CD52 and TCRa genes, resulting in enhanced therapeutic effects. Data obtained from these somatic gene knockout applications would allow us to evaluate the risks the technologies, eventually leading to clinical gene repair therapy targeting somatic cells, which requires higher standards for efficiency and safety. Human germline gene editing would obviously raise ethical and societal issues, and more intensive discussion by various stakeholders will be required.

Curriculum vitae

1984　B.S.　Health Science, the University of Tokyo

1986　Ph.D.　Health Science, the University of Tokyo

1989　Research Resident. AIDS Research Center, N.I.H. Japan

1990　Research Associate. Howard Hughes Medical Institute, Baylor College of Medicine, USA

1994　Assistant Professor. Department of Disease-related Gene Regulation Research (Sandoz), Faculty of Medicine, the University of Tokyo, Japan

1996　Assistant Professor. Department of Microbiology, Immunology and Molecular Genetics, UCLA School of Medicine, USA

2003　Division Head / Associate Professor. Gene Therapy Division, Research Center for Genomic Medicine, Saitama Medical University

2007　Division Head / Professor. Gene Therapy Division, Research Center for Genomic Medicine, Saitama Medical University

Chair：Keiya Ozawa (Director, IMSUT Hospital Director, Center for Gene & Cell Therapy (CGCT)
Professor, Division of Genetic Therapeutics The Advanced Clinical Research Center The Institute of Medical Science The University of Tokyo)

AAV-mediated gene therapy for genetic disease

Katherine A. High, M.D

Co-founder, President and Chief Scientific Officer, Spark Therapeutics

Clinical gene therapy began in 1990, with infusion of autologous gene-modified T cells in two children with severe combined immunodeficiency disease at the NIH. Work through the ensuing decade demonstrated safety of the approach, but compelling data in support of efficacy were lacking. The close of the first decade was tumultuous; clear efficacy was demonstrated in a trial of gene therapy for X-linked SCID, but high profile adverse events that occurred in the same time frame raised questions about the safety of gene therapy. Despite these reverses, the second decade of clinical gene therapy was characterized by steady accumulation of evidence for efficacy in a number of clinical trials, and capped by the first licensing of a gene therapy product for genetic disease, alipogene tiparvovec, an AAV vector for a rare genetic lipid disorder, by the EMA. As the onset of the third decade of clinical development of gene therapy, the field is moving from primarily academic-based to biotech and pharmaceutical-based settings, and is poised to tackle the problems that will need to be addressed for more extensive development of therapeutics, including the need for natural history data for many orphan diseases, and the need to develop and validate clinical endpoints for rare diseases for which there are currently no treatments. Other challenges include meeting commercial standards for manufacture of these complex biologics, establishing consensus on critical quality attributes of products, developing pricing models, and achieving harmonization of product registration standards at the international level. There may be a need for post-marketing safety studies for many of the first approved gene therapy products, given regulatory requirements for up to 15 years follow-up. Previous experience in development of other novel classes of therapeutics, and in development of therapies for rare and ultra-rare diseases, hold lessons for the field.

Our work has focused primarily on the use of adeno-associated viral vectors (AAV) for the treatment of genetic disease. Attractive features of these vectors include their low immunogenicity, lack of pathogenicity of the parent virus, the fact that they are stabilized in a non-integrated form, and their ability to direct long-term expression of the transgene. Wild-type AAV is naturally replication-defective, providing an additional safety feature. Nonetheless the final investigational agent is a recombinant vision, and it has been critical to optimal clinical application to understand the human immune response to recombinant AAV, which is administered in the background of a pre-existing human exposure to the wild-type virus from which the vector is engineered. Reflecting the fact that many aspects of the human immune response are tissue-specific, clinical investigation of AAV vectors has progressed most rapidly in target tissues where the immune response is less robust, for example in the subretinal space. However, ongoing studies in other target tissues, including the liver and skeletal muscle, have helped to delineate the nature of the response and how

it can be managed to achieve long-term expression from AAV vectors. This presentation will cover progress in clinical studies in inherited retinal dystrophies, clinical and pre-clinical studies in hemophilia B and A, and strong proof-of-concept studies in a large animal model of Batten's disease, using AAV vectors.

Katherine High is a physician and hematologist with a longstanding interest in the development of gene therapy for the treatment of genetic disease. Dr. High graduated from Harvard with a degree in Chemistry, and from the University of North Carolina (UNC) School of Medicine. After completing training in internal medicine, she trained as a Fellow in the Hematology Section at Yale University School of Medicine. She returned to the University of North Carolina as an Assistant Professor of Medicine, where she began her independent research career characterizing mutations that caused hemophilia. In 1992 she accepted a position as a tenured professor at the University Of Pennsylvania School Of Medicine and the Children's Hospital of Philadelphia. At Penn she was the holder of an endowed chair and in 2002 was named an Investigator of the Howard Hughes Medical Institute, based on her work establishing proof of concept in animal models and in human subjects for gene therapy for genetic disease. In 2004, Dr. High was named the Founding Director of the Center for Cellular and Molecular Therapeutics at The Children's Hospital of Philadelphia, a Center focused on developing novel cell and gene-based therapies for genetic disease. Dr. High led the Center in the conduct of successful clinical studies of AAV-mediated gene therapy for a rare blinding condition and for hemophilia B. These clinical trials and the manufacturing capabilities of the Center formed the nidus of Spark Therapeutics, a fully integrated gene therapy company that was spun out of CHOP in March 2013. In September 2014, Dr. High assumed the role of President and Chief Scientific Officer at Spark, and helped to lead the company through a successful IPO in January 2015. In a novel model, the initial capitalization of the company came from Children's Hospital of Philadelphia, which is still a substantial stockholder in the Company.

Dr. High has been elected to the Institute of Medicine (IOM) and the American Academy of Arts & Sciences (AAAS). She is a past president of the American Society of Gene and Cell Therapy, served a 5-year term on the FDA Advisory Committee on Cell, Gene, and Tissue Therapies, and a 4-year term on the Advisory Council of the NIH National Heart, Lung and Blood Institute. She is a past recipient of the E. Donnall Thomas Award of the American Society of Hematology, the Distinguished Achievement Award of the American Society of Gene and Cell Therapy, and the Directors' Award of the Foundation Fighting Blindness. Dr. High previously served on the Scientific Advisory Boards of Genzyme, a Sanofi company; of bluebirdbio; and of Alnylam. She consulted for, and subsequently collaborated with, Amsterdam Molecular Therapeutics (now Uniqure) in the clinical trials of Glybera, the first licensed AAV gene therapy product.

Dr. High has pioneered safe and effective clinical translation of genetic therapies for inherited disorders. These clinical trials have led to long-term correction of disease in hemophilia B and in Leber's congenital amaurosis, a hereditary cause of blindness.

Chair : Takashi Shimada(Nippon Medical School, Department of Biochemistry and Molecular Biology, Division of Clinical Genetics)
Shoji Tsuji(Department of Neurology and Medical Genome Center, The University of Tokyo Hospital)

Neuroprotective gene therapy for patients with retinitis pigmentosa: interim report of low-titer group

Yasuhiro Ikeda

Department of Ophthalmology, Graduate School of Medical Sciences,
Kyushu University, Fukuoka, Japan

Retinitis pigmentosa (RP) is a major cause of blindness, affecting approximately 1 in 3,500 people pan-ethnically. Patients typically report impaired night vision and a gradual loss of visual fields. RP is caused by mutations in various genes (more than 50 responsible genes). However, the biological processes by which these mutations lead to progressive photoreceptor death are still unclear and no effective treatment exists for RP.

We have attempted the neuroprotective gene therapy for patients with RP, via subretinal administration of a non-pathogenic simian immunodeficiency virus (SIV) vector derived from the non-pathogenic simian immunodeficiency virus (SIV) carrying human pigment epithelium-derived factor (hPEDF) gene (SIV-hPEDF). To assess the safety of subretinal administration of SIV-hPEDF, we will enroll 20 RP patients in this open-label, dose-escalation study. In this interim report, we demonstrated the results of the initial 5 subjects in the low titer group (2.5 x 107 transducing units/mL).

First trial subject was registered on March 2013, and 5th subject was entered on January 2014. No severe adverse effects were observed at this moment, however, subretinal fluid was not completely absorbed and the additional treatment was performed two week after treatment in third subject. To assess the therapeutic protein (hPEDF) expression in the eye, we measured the hPEDF protein concentration in the aqueous humor samples (second, 4th and 5th subjects) before and after treatment. We detected the increase of hPEDF protein concentration in all samples. Subretinal administration of SIV-hPEDF was safe and well tolerated in the initial 5 subjects in the low titer group. We will enroll the high titer group subjects in the near future.

Yasuhiro Ikeda, M.D., Ph.D.

1995 Faculty of Medicine, Kyushu University, M.D. graduation
1995 Department of Ophthalmology, Graduate School of Medical Sciences, Kyushu University, Resident
2003 Graduate School of Medical Sciences, Kyushu University, Ph.D. graduation
2003 Department of Ophthalmology, Kyushu University Hospital, Medical staff
2004 Department of Ophthalmology, Kyushu University Hospital, Assistant Professor

Chair : Takashi Shimada(Nippon Medical School, Department of Biochemistry and Molecular Biology, Division of Clinical Genetics)
Shoji Tsuji(Department of Neurology and Medical Genome Center, The University of Tokyo Hospital)

Exon Skipping Therapy for Muscular Dystrophy

Shin'ichi TAKEDA

National Institute of Neuroscience, National Center of Neurology and Psychiatry

Duchenne muscular dystrophy (DMD) is the most common childhood genetic disease, affecting one among 3,500 newborn boys, causing progressive muscle weakness, heart and respiratory failure and premature death. This disease is caused by the mutations of the DMD gene, and there is no cure exists for this disease, but a number of promising new molecular therapies are being intensively studied. Exon skipping by antisense oligonucleotides (AOs) is a novel method to restore the reading frame of the mutated DMD gene, and rescue dystrophin expression. We reported that systemic delivery of AOs targeting exon 6 and 8 of the canine DMD gene to CXMDJ, a dystrophin-deficient animal model, efficiently restored functional dystrophin proteins at the sarcolemma of these dogs, and improved phenotypes of affected dogs without serious adverse effects (Ann Neurol. 2009;65:667-76). We then optimized AO sequences, which allow exon 53 skipping of the human DMD gene together with Nippon Shinyaku Co. Ltd. After numbers of toxicology study of the AOs, NS-065/NCNP-01, we proposed an early phase clinical trial of exon 53 skipping of DMD patients, which was approved by Pharmaceutical and Medical Devices Agency (PMDA) and the trial has been successfully carried as investigator-initiated trial in NCNP hospital. We would report the results of this first-in-human early phase trial of the drug.

武田　伸一（たけだ　しんいち）
国立研究開発法人　国立精神・神経医療研究センター
神経研究所 所長

1977 年	秋田大学医学部医学科卒業
1981 年	信州大学大学院博士課程修了（医学博士）
1984 年	信州大学第三内科（助手）　勤務
1987 年	フランス・パリ・パストゥール研究所　博士研究員
1992 年	国立精神・神経センター神経研究所　室長
2000 年	同研究所　遺伝子疾患治療研究部長
2008 年	トランスレーショナル・メディカルセンター長併任
2010 年	独立行政法人国立精神・神経医療研究センターに名称変更 トランスレーショナル・メディカルセンター長 神経研究所　遺伝子疾患治療研究部長（併任）
2015 年	国立研究開発法人　国立精神・神経医療研究センターに名称変更 神経研究所 所長 神経研究所　遺伝子疾患治療研究部長（併任） 現在に至る

【研究分野】
骨格筋と筋疾患の分子生物学、分子治療学

【所属学会、研究会】
日本筋学会（理事長）、日本神経学会（代議員）、日本炎症・再生医学会（評議員）、日本遺伝子治療学会（評議員）、日本再生医療学会（代議員）、日本分子生物学会、American Society of Gene and Cell Therapy (Muscle subcommittee member)、Asian Oceanian Myology Center (Treasurer)、World Muscle Society、J Neuromuscular Diseases (Associate editor)、Am J Pathology (Associate editor)、宇宙航空研究開発機構 (JAXA) 国際宇宙ステーション・「きぼう」利用　生命科学分野重点課題テーマ　領域アドバイザ、AMED － CREST アドバイザ他。

【その他の所属等】
徳島大学大学院　医学部・栄養生命科学教育部　客員教授、東北大学医学部　非常勤講師。1998 年から、厚労省　精神・神経疾患研究委託費（現、精神・神経疾患研究開発費）による筋ジストロフィーに対して治療を開発するための研究班の主任研究者（班長）を 5 期 15 年に渡って勤め、2013 年 4 月から、6 期目に就任している。

Chair : Takashi Shimada(Nippon Medical School, Department of Biochemistry and Molecular Biology, Division of Clinical Genetics)
Shoji Tsuji(Department of Neurology and Medical Genome Center, The University of Tokyo Hospital)

Translational Fidelity of Adeno-associated Virus-mediated RNA Interference for Huntington's Disease.

Seng H. Cheng, PhD

Sanofi Genzyme, Framingham, MA, USA

Huntington's disease (HD) is a fatal autosomal dominant neurodegenerative disease caused by an increase in the number of polyglutamine residues in the huntingtin (Htt) protein. With the identification of the underlying basis of HD, therapies are being developed that reduce the expression of the causative mutant Htt. RNA interference (RNAi) that seeks to selectively reduce the expression of such disease-causing agents is emerging as a potential therapeutic strategy for this and similar disorders. We examined the merits of administering a recombinant adeno-associated viral (AAV) vector designed to deliver small interfering RNA (siRNA) that targeted the degradation of the Htt transcript. The aim was to lower Htt levels and to correct the behavioral, biochemical, and neuropathological deficits shown to be associated with the YAC128 mouse model of HD. We showed that AAV-mediated RNAi was effective at transducing greater than 80% of the cells in the mouse striatum and partially reducing the levels (*40%) of both wild-type and mutant Htt in this region. Concomitant with these reductions were significant improvements in behavioral deficits, reduction of striatal Htt aggregates, and partial correction of the aberrant striatal transcriptional profile observed in YAC128 mice. Importantly, a partial reduction of both the mutant and wild-type Htt levels was not associated with any notable overt neurotoxicity. However, despite these promising data, global delivery of AAV, particularly to a large adult brain remains an elusive goal. Furthermore, the appropriate brain areas to target for achieving a transformative therapeutic benefit in HD patients remain to be defined. Postmortem analyses of HD patient brains revealed extensive medium spiny neuronal loss in the striatum, in addition to loss of pyramidal neurons in the cerebral cortex and hippocampus. Recent studies in rodent models also suggested that simultaneous targeting of striatum and cortex was more efficacious than targeting either individually. Thus, available evidence suggests that delivery of Htt-lowering therapeutics to both striatal and cortical regions may be needed to confer an optimal therapeutic outcome. To address this, the potential of two recombinant adeno-associated viral vectors (AAV1 and AAV2) to transduce the cortico-striatal tissues that are predominantly affected in HD was explored. Green fluorescent protein was used as a reporter in each vector to show that both serotypes were broadly distributed in medium spiny neurons in the striatum and cortico-striatal neurons after infusion into the putamen and caudate nucleus of nonhuman primates, with AAV1-directed expression being slightly more robust than AAV2-driven expression. This study suggested that both serotypes were capable of targeting neurons that degenerate in HD, and it sets the stage for the advanced preclinical evaluation of an RNAi-based therapy for this disease.

Seng Cheng is Head of Research and Early Development of the Rare Diseases Division at Sanofi Genzyme. He received his BSc and PhD degrees in Biochemistry from the University of London, UK and trained as a postdoctoral fellow at the National Institute for Medical Research in London in the field of tumour biology. He worked as a Staff Scientist at Integrated Genetics Inc., and later joined Genzyme Corporation to work on several discovery projects including the structure and function of the cystic fibrosis transmembrane conductance regulator. As Group Vice President of Genetic Diseases Science at Genzyme, he also managed the development of novel gene delivery systems as well as translational research in genetic diseases, a number of which transitioned to clinical testing. Dr Cheng's current areas of focus include inherited metabolic, muscle, lung, kidney and neurodegenerative diseases. He has co-authored 254 research articles and reviews, and is a named co-inventor on 63 issued patents in the area of biotechnology. In his current position, he is responsible for directing the translational research and early clinical development activities in rare genetic diseases.

Chair: Makoto Otsu (Center for Stem Cell Biology and Regenerative Medicine Institute of Medical Science, University of Tokyo)
Hiroaki MIZUKAMI (Div. of Genetic Therapeutics, Center for Molecular Medicine, Jichi Medical Univ.)

Gene therapy for chronic granulomatous disease

Toshinao Kawai

Department of Human Genetics
National Center for Child Health and Development

A genetic disorder is a disease that is caused by a mutation in an individual's DNA, which affects more than one million patients worldwide. X-linked chronic granulomatous disease (X-CGD) is an inherited primary immunodeficiency disease characterized by failure of the nicotinamide adenine dinucleotide phosphate enzyme system in phagocytes to produce reactive oxygen species (ROS). The X-CGD patients suffer from recurrent infection and hyper-inflammation, occasionally represented by CGD-associated colitis (CGD colitis). Hematopoietic stem cell transplantation (HST) is the only curative therapy for X-CGD, and in Europe and America, the clinical trials of gene therapy have been performed to the patients who have no HLA-matched donor. To assess the safety and efficacy of hematopoietic stem cell gene therapy, we collaborated with Dr. Harry Malech, National Institutes of Health in United States and commenced a retroviral gene therapy clinical study for the X-CGD patient.

The patient was a 27-year-old man, who was complicated by refractory subcutaneous abscess, fungal lung disease, lymphadenitis and CGD colitis. He had been treated with antibacterial and antifungal drugs over two years. He did not have an appropriate HLA-matched donor for HST, and received the hematopoietic stem cell gene therapy using a busulfan-based preconditioning treatment regimen. At two weeks of the gene therapy, the gene-modified phagocytes appeared in peripheral blood produced ROS and his clinical symptoms of subcutaneous abscess and CGD colitis improved until day +95. Vector integration site analysis performed with next-generation sequencing revealed that the vector was not located approximately 10 kb upstream and downstream from the MDS1/EVI1 locus in neutrophil at two months of gene therapy.

Unlike the gene therapy for severe combined immunodeficiency and Wiskott–Aldrich syndrome, the therapeutic gene itself does not confer a growth advantage on the transduced cells in CGD. Since previous studies indicated that a susceptibility to infection improved in CGD even if the phagocytes producing ROS were a few in peripheral blood, the gene therapy may be alternatives to HST in the CGD patients who have no HLA-matched donor for HST.

河合利尚（かわい としなお、Kawai, Toshinao）

【略歴】

1998年　東京慈恵会医科大学医学部卒業

2000年　東京慈恵会医科大学附属病院小児科助手

2002年　埼玉県立小児医療センター感染免疫科医員

2003年　米国National Institutes of Health　postdoctoral fellow

2006年　東京慈恵会医科大学附属病院小児科助教

2008年　国立成育医療センター膠原病感染症科専門修練医

2009年　国立成育医療センター成育遺伝研究部遺伝子診断治療研究室長（現職）

2010年　国立成育医療研究センター 生体防御系内科部免疫科医員（併任）

【専門】

感染免疫、遺伝子治療、小児リウマチ

【所属学会】

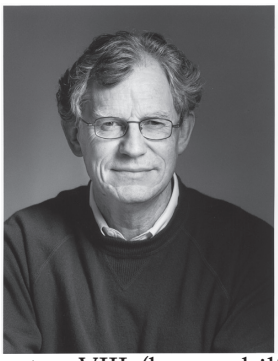
日本小児科学会、日本感染症学会、日本リウマチ学会、日本小児感染症学会、日本小児リウマチ学会、日本遺伝子治療学会、American Society of Gene & Cell Therapy

【免許・資格】

医学博士、小児科専門医、リウマチ専門医、日本感染症学会ICD認定医

Chair: Makoto Otsu (Center for Stem Cell Biology and Regenerative Medicine Institute of Medical Science, University of Tokyo)
Hiroaki MIZUKAMI (Div. of Genetic Therapeutics, Center for Molecular Medicine, Jichi Medical Univ.)

Gene Therapy for Hemophilia



Barrie J. Carter, Ph D

BioMarin Pharmaceutical Inc, Novato, CA, USA

Deficiencies of either of the X-linked coagulation factors, Factor VIII (hemophilia A) or Factor IX (hemophilia B), lead to clinically similar bleeding disorders. In each case the severe phenotype, manifested in subjects who have less than 1% of normal levels, leads to frequent unprovoked bleeding episodes in joints as soft tissues causing permanent disability and sometimes death. Treatment generally comprises intravenous injection of the protein (plasma-derived or recombinant) either prophylactically or at the time of a bleed. These proteins have relatively short half-lives and for prophylactic use must be administered frequently up to several times per week.

Gene therapy offers the potential of a long term treatment by creating continuous endogenous production of the absent factor after a single administration. Recombinant adeno-associated virus vectors (rAAV) provide a suitable gene delivery system that can persist in non-dividing cells primarily as un-integrated circular episomes. Furthermore, in over 100 clinical trials for multiple clinical indications rAAV administered by multiple routes have exhibited strong safety profiles. Recently, in subjects with hemophilia B, a single administration of a rAAV8-FIX vector, provided clinical proof of concept for hemophilia gene therapy. In subjects treated with the vector, continuous expression of FIX was maintained at levels of 5 to 7% for several years and both spontaneous bleeding episodes and need for protein prophylaxis were greatly reduced or eliminated.

We are developing a rAAV based gene therapy approach for hemophilia A. The cDNA for Factor VIII is much larger that that for FIX and exceeds the maximum size of genome that can be packaged into AAV capsids. However, smaller FVIII coding cassettes can be designed that are more conducive to being packaged into rAAV.

We evaluated a rAAV-huFVIII vector in mice by administration via the tail vein. At 5 to 13 weeks after a single administration of vector, normal levels of huFVIII antigen and huFVIII activity could be detected in the plasma of the mice. Western blot analysis showed that the huFVIII in the plasma was appropriately processed to heavy and light chains. Furthermore, in preclinical mouse models of hemophilia bleeding time correction, the coagulation defect in FVIII-/- mice could be fully corrected.

Barrie Carter has 23 years experience in the biotechnology industry and joined BioMarin Pharmaceutical, Inc. in 2013. He was chief scientific officer of Targeted Genetics Corporation from 1992-2008. Prior to that time, he conducted research at the US National Institutes of Health (NIH) in Bethesda, Maryland for 22 years, where he was Chief of the Laboratory of Molecular and Cellular Biology in the National Institute for Diabetes and Digestive and Kidney Diseases.

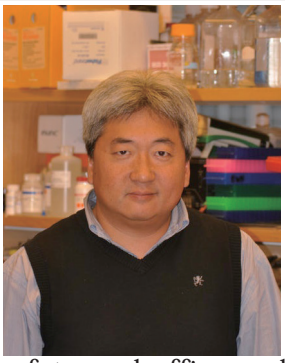
His long-term research interests are in biology of viruses, development of gene delivery vectors and clinical development of gene therapy. While at NIH he was a pioneer in early studies of adeno-associated virus (AAV) biology and development of the first AAV vectors. In the biotechnology industry he led the clinical development of AAV vectors, as well as being involved in clinical development of non-viral vectors and cell therapies.

The work at NIH lead to the first published in vivo animal study of any AAV vector (Flotte et al 1993, PNAS 93:10163) and at Targeted Genetics the first clinical trials of an AAV vector, initiated in 1994 (Flotte et al Hum Gene Ther 7:1145).

Dr. Carter is a Past-President of the American Society for Gene and Cell Therapy. He has served on the Advisory Committee to the Director, NIH, and on many other advisory and review committees for NIH, FDA, Cystic Fibrosis Foundation, The New Zealand Medical Research Council and the School of Public Health, University of Washington.

Chair: Makoto Otsu (Center for Stem Cell Biology and Regenerative Medicine Institute of Medical Science, University of Tokyo)
Hiroaki MIZUKAMI (Div. of Genetic Therapeutics, Center for Molecular Medicine, Jichi Medical Univ.)

Gene therapy for inherited retinal dystrophies due to RPE65 mutations



Daniel C. Chung DO

BioMarin Pharmaceutical Inc, Novato, CA, USA

Purpose: Several early-phase human trials provided preliminary safety and efficacy data for adeno-associated viral vector-mediated human RPE65 augmentation for RPE65 mutation-associated inherited retinal dystrophies. We report the results from a Phase 3, open-label, randomized, controlled trial that reached its primary completion date in 2015 at The Children's Hospital of Philadelphia and the University of Iowa evaluating the safety and efficacy of AAV2-hRPE65v2 (SPK-RPE65) to treat RPE65-mediated inherited retinal dystrophies (NCT00999609).

Methods: Thirty-one subjects with disease-causing biallelic RPE65 mutations were randomized 2:1 to intervention or control groups. Eligibility criteria included age ≥ 3 years old; bilateral visual acuity worse than 20/60 and/or visual field less than 20 degrees in any meridian; evidence of sufficient viable retinal cells by fundus photography and optical coherence tomography; ability to be evaluated on mobility testing; and willingness to provide consent or parental permission and assent, where appropriate. Subjects in the intervention group received subretinal injections of AAV2-hRPE65v2 sequentially to each eye within an 18-day window. Control subjects did not receive AAV2-hRPE65v2 for at least 1 year from baseline, but completed the same testing regiment as those in the intervention arm. Using a standardized subretinal delivery procedure, under general anesthesia, 1.5E11 vector genomes/eye were delivered in a total volume of 300 µL. Standardized mobility testing under different luminance conditions was the primary efficacy endpoint, with secondary endpoints full-field light sensitivity threshold testing, assigned first eye mobility test change score, and visual acuity tested hierarchically.

Results: All subjects who continued beyond randomization completed Year 1 follow-up testing. Phase 3 study results include demographics, safety information, mobility test change score (performance at 1 year compared with baseline), and secondary endpoints of full-field light sensitivity threshold testing, assigned first eye mobility test change score, and visual acuity. A separate study analyzing mobility test data in untreated control and inherited retinal dystrophy cohorts was used to validate the mobility test's ability to distinguish low vision from normal-sighted populations, differentiate a range of performance in low vision subjects, and confirm changes in functional vision over time. The Phase 3 trial of 31 subjects met with statistical significance its primary endpoint, the bilateral mobility test change score ($p = 0.001$), as well

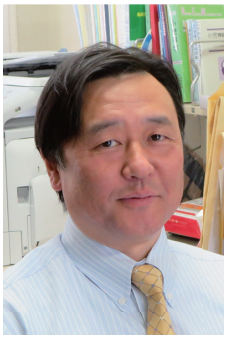
as the first two of three secondary endpoints, specifically full-field light sensitivity threshold testing, or FST ($p < 0.001$), and the assigned first eye mobility test change score ($p = 0.001$). Statistical significance was not achieved for the third secondary endpoint, visual acuity ($p = 0.17$).

Conclusions: Results of this study, the first Phase 3 gene therapy study completed for a retinal dystrophy, provide additional efficacy and safety data related to gene therapy intervention by surgical subretinal administration of AAV2-hRPE65v2 (SPK-RPE65) as measured by the primary endpoint of mobility testing, and 2 of the 3 secondary endpoints.

Dr. Chung is the Ophthalmic Lead for Spark Therapeutics. Prior to joining Spark Therapeutics, he was a senior investigator at the FM Kirby Center for Molecular Ophthalmology at the Scheie Eye Institute at the Perelman School of Medicine of the University of Pennsylvania, working in retinal gene therapy and transfer. Concurrently, he served as the scientific advisor on the RPE65 gene therapy study team at the Children's Hospital of Philadelphia (CHOP). Dr. Chung earned his medical degree from the New York Institute of Technology College of Osteopathic Medicine and completed his residency in Akron, Ohio. He then completed fellowships in pediatric ophthalmology and ocular genetics research at the Cole Eye Institute at the Cleveland Clinic, with additional training in retinal gene therapy at the National Eye Institute in Bethesda, MD. While at the University of Pennsylvania, Dr. Chung concentrated on pre-clinical and translational research for inherited retinal degenerative diseases. Additionally, in his duties on the RPE65 gene therapy team at CHOP, he concentrated on the development, standardization and implementation of the primary outcome measure for the study. In his current duties, he continues to be connected to the RPE65 gene therapy trial, as Spark Therapeutics is now the sponsor. As the global ophthalmic lead, he works in the areas of medical affairs, clinical development and operations, research and development and commercial operations.

Chair : Torayuki Okuyama(Director of Center for Lysosomal Storage Diseases Director of Clinical Laboratory Medicine National Center for Child Health and Development)
Takashi Okada(Department of Biochemistry and Molecular Biology, Nippon Medical School)

Gene therapy for AADC deficiency.



Takanori Yamagata

Department of Pediatrics, Jichi Medical University

Aromatic L-amino acid decarboxylase (AADC) deficiency is an autosomal recessive disorder caused by the AADC gene mutation. AADC is responsible for the generation of dopamine and serotonin from L-dopa and 5-hydroxytryprophane, respectively. As results, dopamine, catecholamine and serotonin were deficient, and patients exhibit movement disorders including intermittent oculogyric crisis, dystonic attacks, and loss of voluntary movement. Most of the patients were bed ridden for whole life. We performed gene therapy for three Japanese patients with AADC deficiency, thus far.

As a treatment vector, human AADC gene with CMV promoter was inserted into type 2 AAV vector (AAV-hAADC-2). AAV-hAADC-2 was injected into two points each in the bilateral putamen by stereotaxic operation; 50 μ l each and total 200 μ l, 2 $\times$ 1011 vector genome.

Case 1 and 2 were sibling of 15 year-old boy and 12 year-old girl. Both patients were bedridden with little voluntary movement, and had dystonia attacks and oculogyric crisis (OGC). Two months after the gene transfer, Case 1 has started to move voluntary, and Case 2 could sit with a little support and started the training to walk with a walker. Dystonia was disappeared in both. FMT-PET showed no signal before the treatment, but showed signals on the putamen after two months. Case 3 was a 5 year-old girl with milder phenotype that she can walk with support. She had OGC, but no dystonia. After one month, OGC was disappeared. All three patients showed choreic movement, but did not have severe adverse events such as dyskinesia and apnea observed in the patients treated in Taiwan.

We set up the system to diagnose the patients earlier to treat earlier. Gene transfer into the brain using AAV vector was shown to be effective and safe. Development of gene therapy using AAV vector for other child neurological diseases were underway.

1986 年 3 月　　岐阜大学医学部卒業
1986 年 5 月　　自治医科大学附属病院研修医（小児科）
1991 年 10 月　　国立精神神経センター流動研究員（1992 年 3 月まで）
1996 年 4 月　　自治医科大学小児科学　講師
1997 年 11 月　　米国ベイラー医科大学 分子遺伝学教室留学（2000 年 3 月）
2002 年 9 月　　自治医科大学遺伝カウンセリング室室長補佐併任
2004 年 8 月　　自治医科大学小児科学　准教授
2010 年 5 月　　自治医科大学小児科学発達医学部門　教授
2013 年 12 月　　自治医科大学小児科学主任教授
2014 年 4 月　　自治医科大学とちぎ子ども医療センター　センター長併任

Chair : Torayuki Okuyama(Director of Center for Lysosomal Storage Diseases Director of Clinical Laboratory Medicine National Center for Child Health and Development)
Takashi Okada(Department of Biochemistry and Molecular Biology, Nippon Medical School)

AAVrh10–SGSH Intracerebral Gene Therapy in Mucopolysaccharidosis Type IIIA

Michaël Hocquemiller

Lysogene, France

Mucopolysaccharidosis type IIIA (MPSIIIA) is a lysosomal storage disorder caused by mutations in N-sulfoglucosamine sulfohydrolase (SGSH), resulting in heparan sulfate (HS) accumulation and progressive neurodegeneration. There is currently no treatment. Our approach is intracerebral gene therapy. The efficacy of AAV serotype rh.10 carrying the human SGSH cDNA has been demonstrated in the MPSIIIA mouse model. Toxicity has been examined in rats and juvenile dogs. A Phase I/II clinical non-comparative, open-label study in 4 children with MPSIIIA has been completed with the primary objective of assessing the tolerance and safety. A secondary objective was the collection of data to determine potential future efficacy endpoints. The study showed that the treatment was safe and well-tolerated after one year in the four children. All patients showed improvement in behavioral disorders, hyperactivity and sleep disorders. Furthermore a cognitive enhancement was suggested by neurocognitive evaluation in the youngest child at one year but not sustained at two years. A phase II/III multi-centric clinical study in Europe and the USA is planned to start in 2016. The trial will be an open-label, single arm intracerebral administration of an AAV serotype rh.10 carrying the human SGSH cDNA. Our clinical development plan also includes a multi-center natural history study in untreated patients to function as a non-concurrent control. This talk will focus on pre-clinical studies and elaborate on current clinical development.

Michaël Hocquemiller, PhD, is Head of Lysogene's Scientific Research Unit since 2010. Dr. Hocquemiller is responsible for Lysogene's scientific intelligence and clinical biobanking research program, coordination of vector production and pre-clinical studies. He also takes part in the scientific evaluation of new research areas and products. Prior to joining Lysogene, Dr. Hocquemiller worked as a research scientist at the Pasteur Institute (INSERM U622) on the Sanfilippo syndrome neurophysiopathology and gene therapy correction in animal models. Dr. Hocquemiller obtained his PhD in Neuroscience from the Pasteur Institute and the University Paris Descartes (Paris V) in 2009 and his Master in Genetics from the Pierre and Marie Curie (Paris VI) University in 2005. He was certified as a Clinical Research Associate in 2010.

Chair : Torayuki Okuyama(Director of Center for Lysosomal Storage Diseases Director of Clinical Laboratory Medicine National Center for Child Health and Development)
Takashi Okada(Department of Biochemistry and Molecular Biology, Nippon Medical School)

Phase I/II results at 12 months of intra-cerebral administration of AAV vector containing human alpha-N-acetylglucosaminidase (NAGLU) in children with Mucopolysaccharidosis Type IIIB (Sanfilippo B Syndrome).

Charles W Richard III* (uniQure USA), Marc Tardieu#, Michel Zerah, Marie-Lise Gougeon, Jerome Ausseil, and Jean-Michel Heard (France)

*Senior Vice President, Neuroscience Research and Development, uniQure, Lexington, MA, USA
Principal Investigator, Paris Hospital Sud, France

Sanfilippo B (MPS IIIB) is a devastating, autosomal recessive, neurodegenerative lysosomal storage disease of children caused by missing enzyme alpha-N-acetylglucosaminidase (NAGLU) .

Four children with no detectable NAGLU activity in peripheral cells received intracerebral deposits of highly purified rAAV2/5-hNAGLU vector particles produced by Sf9 insect cells engineered with baculovirus vectors (manufactured by Uniqure, NL). At the time of treatment, the youngest patient (20 months) had normal cognitive evaluation, two patients (26 and 30 months) were slightly below normal, and the oldest patient (53 months) was in the mild delay range.

The AAV vector dose of 4x1012 viral genomes/subject in 60 ul injections was delivered over 2 hours at 16 sites in the cerebral cortical and cerebellum white matter. Gene therapy was combined with immunosuppression (mycophenolate mofetil X 8 weeks, tacrolimus, long-term) to prevent immune rejection. Low titer vector was detected in blood and urine for 48 hours post-deposition. Safety data collected over the one-year follow-up showed good safety and tolerability. We observed no reactive inflammation on brain MRI images, no adverse events related to product or procedure, no increase in number of infectious events, no sign of toxicity related to immunosuppressive drugs (except a short period of high transaminases in one child). Available preliminary results indicate durable expression of catalytically-active NAGLU in CSF at 1, 3, and 12 month time points (14-17% of normal), appearance of NAGLU-responsive T-lymphocytes in blood, normal brain development without evidence of atrophy in sequential brain MRIs, and cognitive progression after one year, as measured through a battery of complementary neuropsychological testing.

Biosketch

Dr. Charles W. (Charlie) Richard III MD, PhD is Senior Vice President of Neuroscience Research and Development at uniQure with 30 years of industry, academic and medical practice experience with a focus on rare and orphan diseases and the translation of emerging genetic and genomic technologies into drug development. Dr Richard most recently served as Chief Medical Officer of Oxyrane, a biotechnology company focused on developing second-generation enzyme replacement therapies for rare lysosomal storage diseases, where he remains a member of the Board of Directors. Previously, Dr. Richard led the Translational Medicine group at Shire Human Genetic Therapies, in the role of Principal Medical Director and Head of Translational Medicine, Clinical R&D. There he was responsible for the clinical development of novel enzyme replacement therapies for rare and orphan diseases including Sanfilippo A syndrome and Hunter Syndrome, among others. Prior to Shire, Dr. Richard held multiple roles at Wyeth, including Vice President and Head of the Department of Genomics at Wyeth Discovery Research where he established and led a team of 135 scientists providing core functions in bioinformatics, genetically-modified animal models, gene expression profiling, molecular medicine and pharmacogenomics, functional genomics and genomics core sciences. Before moving into industry, Dr. Richard was an Assistant Professor of Psychiatry and Human Genetics at the University of Pittsburgh Medical Center and before that position had completed nearly 10 years of medical practice and academic research. He received a Ph.D. in Pharmacology and an M.D., both from the Ohio State University School of Medicine, and a B.S. in Biology from Stanford University.

Chair : Masafumi Onodera(Head. Department of Human Genetics (Research Institute) National Center for Child Health and Development)

Gene therapy for inherited disorders of the hematopoietic system

Prof. Alessandro Aiuti M.D. PhD*

San Raffaele Telethon Institute for Gene Therapy (TIGET) and
Vita Salute San Raffaele University, Milan, Italy

Gene therapy with hematopoietic stem cells (HSC) is an attractive therapeutic strategy for inherited genetic disorders. In the past 15 years we have pioneered clinical application of HSC gene therapy for two primary immunodeficiency disorders (ADA-SCID and Wiskott-Aldrich Syndrome, WAS) and Metachromatic Leukodystropy (MLD), a severe lysosomal storage disorder. Collectively, more than 40 patients have received autologous CD34+ cells transduced with a gammaretroviral vector (ADA-SCID) or lentiviral vector (LV) (WAS and MLD) encoding the therapeutic gene. Prior to gene therapy patients received a chemotherapy conditioning to favour HSC engraftment. The intensity and type of conditioning were adapted to take in account the disease biology (i.e. selective advantage for immunodeficiencies and the need to replace microglia in MLD) as well as the degree of chimerism needed. Sustained HSC engraftment was observed in all trials, with higher levels (20-80%) achieved in the LV-based studies. The efficiency of gene transfer in CD34+ cells, the dose of cells, and the intensity of conditioning were key parameters in determining the level of in vivo HSC engraftment. Genetically modified cells expressed the therapeutic gene to levels that were sufficient to achieve biological activity and clinical benefit. No insertional mutagenesis or leukemic events have been observed, indicating that GT has a favourable safety profile. The clinical development is continuing in the context of an established alliance with GSK, which has in-licensed GT for the three diseases. These results have opened the way for the application of HSC GT in other blood borne disorders. A phase I/II clinical trial for beta thalassemia has been recently started at TIGET, aimed at assessing safety and efficacy of gene therapy in adult and pediatric patients. Preclinical studies for mucopolysaccharidosis (MPS) I and chronic granulomatous disease (CGD) have showed promising results.

In summary, the success of the clinical studies based on integrating vectors and the progress in the use of new technologies, such as gene editing, indicates that gene therapy could become a more generally applied treatment for a wider spectrum of genetic disorders of the hematopoietic system.

Gene therapy for genetic blood diseases: from viral vectors to genome editing

Fulvio Mavilio, PhD

Genethon, Evry, France

Twenty-four years ago, genetically modified bone marrow cells were administered for the first time to a child suffering from adenosine deaminase (ADA) deficiency, a rare disorder of the immune system. Since then, gene therapy has struggled to find its place in clinical medicine, amid a rollercoaster of successes and setbacks and hype and skepticism with little precedent in modern times. Recently, a series of authoritative clinical studies proved that transplantation of genetically modified hematopoietic stem cells can cure severe diseases like immunodeficiencies, hemoglobinopathies and metabolic diseases, contributing to transforming gene therapy into one of the hottest area of investment for the biotechnology and the pharma industry. The basic technology for the genetic modification of stem cells relies on retroviral vectors, and particularly on those derived from oncoretroviruses or lentiviruses, such as HIV-1. Integration of these vectors in the genome may, however, have undesired effects caused by insertional deregulation of gene expression at the transcriptional or post-transcriptional level. The occurrence of severe adverse events in several clinical trials involving the transplantation of stem cells genetically corrected with retroviral vectors showed that insertional mutagenesis is not just a theoretical event, and that retroviral transgenesis is associated with a finite risk of genotoxicity. Addressing these issues brought new basic knowledge on virus-host interactions and on the biology and dynamics of human somatic stem cells. More recently, a new generation of technology emerged, aimed at correcting the genome rather than replacing defective gene function. This technology relies on designer nucleases capable of generating double- or single-stranded breaks in genomic DNA, which are then repaired either by error-prone non homologous end-joining or by the more precise homologous recombination. This allows generating knock-out mutations or repairing genes with remarkable precision and efficiency in many cell types. At Genethon, we are using lentiviral vector technology to correct Wiskott-Aldrich syndrome, X-linked SCID, chronic granulomatous disease and sickle-cell disease, while developing CRISPR/Cas9-based genome editing for a number of applications.

Fulvio Mavilio, Ph.D., is Scientific Director of Genethon (Evry, France), and Professor of Molecular Biology and University of Modena and Reggio Emilia (Modena, Italy). He was Director of Discovery of Molmed S.p.A. (2002-2005) and founder and Chief Scientific Officer of Genera S.p.A. (1999-2002), two biotechnology companies in Milan. He had previously served as co-Director of the San Raffaele-Telethon Institute of Gene Therapy in Milan (1995 to 2002), as director of the Molecular Hematology unit of the San Raffaele Institute (1989 to 1995), as Visiting Scientist at the Wistar Institute, Philadelphia, (1986 to 1988), as group leader in the Department of Hematology-Oncology of an the Istituto Superiore di Sanità, Rome (1984 to 1988), and as staff scientist of the Institute of Experimental Medicine of the Italian National Research Council in Rome (1982 to 1984). Prof. Mavilio is graduated in Biology at the University of Rome in 1976, obtained a Ph.D. in Medical Genetics at the same University in 1979 and was awarded a U.S. Public Health Service International Research Fellowship by the Fogarty International Center, NIH, Bethesda in 1986. Prof. Mavilio is an expert and a pioneer in the fields of gene therapy and stem cell research, and author of over 180 articles in major international journals. He is a member of the European Molecular Biology Organization, member of the Board of the American Society of Gene and Cell Therapy, and member of the Editorial Board of several international journals in the field of gene therapy and molecular genetics. He was born in Naples in 1953.

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