Program & Abstracts

The 12th International Collaborative Forum of Human Gene Therapy for Genetic Disease

Expanding clinical application of gene therapy for genetic diseases

President　Takanori Yamagata (Jichi Medical University))

Date　Jan. 20 (Thu.), 2022　*Hybrid Meeting

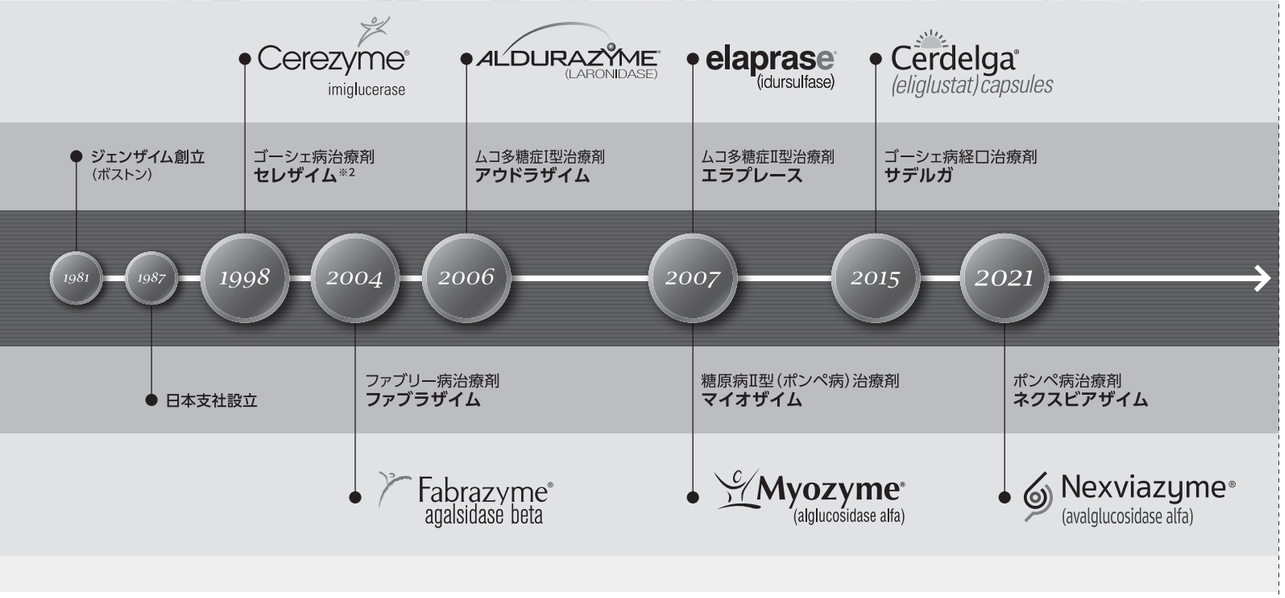
Venue　The Jikei University School of Medicine, Building 1 Hall

サノフィジェンザイムは、今後も

スペシャルティケアのリーダーとして、

患者さんとそのご家族に

希望をお届けしていきます。



ジェンザイム※1として始まり30余年、

希少疾患の患者さんと共に これからも。

※1：現・サノフィジェンザイムビジネスユニット
※2：セレザイム静注用400単位は2011年販売開始

2021年11月作成
MAT-JP-2110484-1.0

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The 12th International Collaborative Forum of Human Gene Therapy for Genetic Disease

第12回 国際協力遺伝病遺伝子治療フォーラム

Expanding clinical application of gene therapy for genetic diseases

飛躍する、遺伝病に対する遺伝子治療の臨床応用

Program & Abstracts

President
当番幹事

Takanori Yamagata (Department of Pediatrics, Jichi Medical University)
山形 崇倫（自治医科大学小児科学 主任教授）

Date

January 20 (Thu.), 2022 *Hybrid Meeting

Venue

The Jikei University School of Medicine, Building 1 Hall

Welcome Greetings

The 12th International Collaborative Forum of Human Gene Therapy for Genetic Disease.

It is our honor to organize the 12th International Collaborative Forum of Human Gene Therapy for Genetic Disease.

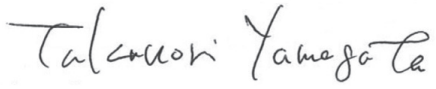
The development of gene therapy for a wide range of genetic diseases has been on the rise worldwide. The main procedures available at present are in vivo gene therapy using an adeno-associated viral (AAV) vector and *ex vivo* gene therapy using a lentiviral vector. Intravenous Onasemnogene abeparvovec (zolgensma) treatment using an AAV9 vector for spinal muscular atrophy was approved in Japan last year and has since shown marked efficacy for patients treated early. In addition, the advent of this treatment has helped familiarize many physicians with gene therapy as a whole. Following the development of Onasemnogene abeparvovec, progress in AAV gene therapies for several diseases, including neurological diseases, such as AADC deficiency, congenital metabolic diseases (mainly lysosomal diseases), and hemophilia has been achieved, and clinical trials are underway. *Ex vivo* gene therapies using lentiviral vector have been developed for immune deficiency as well as for neuronal and metabolic diseases, including adrenoleukodystrophy, metachromatic leukodystrophy and Hurler disease.

We invited global front-runners in the clinical application of gene therapy to participate in this forum. It is our great pleasure to have them here to inform us about the progress and benefits of gene therapy. Gene therapy is a promising therapy, but some issues remain to be addressed. Massive intravenous AAV gene therapy induced liver dysfunction and thrombocytopenia in some patients, albeit transiently. Myelodysplastic syndrome was observed in some patients in lentiviral gene therapy. We have also invited prominent researchers to tell us more about gene therapy, including its mechanism of action, expression control, and associated adverse events. We also hope to learn more about the available support from the government for gene therapy.

We would enjoy hearing lectures directly from researchers and discussing their work in a face-to-face manner, but we understand that is difficult in the current global situation. Therefore, we plan to hold this forum in a hybrid system. Please join the forum either in person or attend via the web. We hope this forum will be a good chance to learn about the worldwide progress of gene therapy, improving international/academic and pharmaceutical cooperation and stimulating further research in this field in Japan.

We thank the participants as well as the individuals and companies who have supported this forum.

Sincerely yours,



Takanori Yamagata

President of the 12th International Collaborative Forum of Human Gene Therapy for Genetic Disease
Professor,
Department of Pediatrics, Jichi Medical University

Program (プログラム)

9:00~9:15 **Opening Remarks (開会挨拶)**

Takanori Yamagata (President of the 12th GT Forum)
山形　崇倫 (第 12 回国際協力遺伝病遺伝子治療フォーラム 当番幹事)

Yoshikatsu Eto (Executive Chairperson of the Committee)
衛藤　義勝 (国際協力遺伝病遺伝子治療フォーラム 代表幹事)

9:15~10:15 **Clinical experience of AAV-based gene therapy (AAV を用いた遺伝子治療の臨床)**

Chairs: Torayuki Okuyama (National Center for Child Health and Development) /
奥山　虎之 (国立成育医療研究センター ライソゾーム病センター)
Kazuhiro Muramatsu (Jichi Medical University) /
村松　一洋 (自治医科大学 小児科学)

10:15~10:55 **Special lecture (特別講演)**

Chair: Keiya Ozawa (Jichi Medical University) /
小澤　敬也 (自治医科大学 免疫遺伝子細胞治療学 (タカラバイオ) 講座)

11:00~11:40 **Special lecture (特別講演)**

Chair: Yoshikatsu Eto (Institute of Neurological Disorders) /
衛藤　義勝 (脳神経疾患研究所附属先端医療センター&遺伝病治療研究所)

11:40~12:40 **Gene therapy for Haemophilia (血友病の遺伝子治療)**

Chairs: Toya Ohashi (The Jikei University School of Medicine) /
大橋　十也 (東京慈恵会医科大学医学部看護学科)
Toshinao Kawai (National Center for Child Health and Development) /
河合　利尚 (国立成育医療研究センター 小児内科系専門診療部 免疫科)

12:45~13:45 **Luncheon Seminar (ランチョンセミナー)**

Chair: Takanori Yamagata (Jichi Medical University) /
山形　崇倫 (自治医科大学 小児科学)

Takara Bio's efforts to address gene therapy vectors
(遺伝子治療用ベクターに対するタカラバイオの取り組み) 24
Tatsuji Enoki (Takara Bio Inc., Japan)
榎　竜嗣

13:55~14:25 **Special lecture (特別講演)**

Chair: Takashi Shimada (AMED/PMDA) /
島田　隆 (AMED プログラムオフィサー、PMDA 専門委員)

Efforts on Gene and Cell Therapy Projects at AMED 28
Michiko Takakura (AMED, Japan)
高倉 美智子 (国立研究開発法人 日本医療研究開発機構)

14:25~15:25 **Gene therapy for AADC deficiency (AADC 欠損症の遺伝子治療)**

Chairs: Shinichi Muramatsu (Jichi Medical University) /
村松　慎一 (自治医科大学 神経遺伝子治療部)
Hitoshi Osaka (Jichi Medical University) /
小坂　仁 (自治医科大学 小児科学)

1) Gene therapy for aromatic L-amino acid decarboxylase deficiency in Japan improved the motor and mental function of patients with various phenotypes 32
Karin Kojima (Jichi Medical University, Japan)
小島　華林 (自治医科大学 小児科学)

2) Gene therapy with rAAV2-hAADC for patients with aromatic L-amino acid decarboxylase deficiency 34
Wuh-Liang Hwu (National Taiwan University Hospital, Taiwan)

15:40~16:40 **Ex vivo Gene therapy (Ex vivo 遺伝子治療)**

Chairs: Hiroshi Kobayashi (The Jikei University School of Medicine) /
小林　博司 (東京慈恵会医科大学 遺伝子治療研究部)
Toru Uchiyama (National Center for Child Health and Development) /
内山　徹 (国立成育医療研究センター 成育遺伝研究部)

1) Hematopoietic stem cell gene therapy with a lentiviral gene delivery 38
Naoya Uchida (The Institute of Medical Science, The University of Tokyo, Japan)
内田　直也 (東京大学医科学研究所 遺伝子・細胞治療センター)

2) Orchard Therapeutics and its Gene Therapy Programs 40
Christopher Dott (Orchard Therapeutics Ltd., UK)

16:40~17:20 **Special lecture (特別講演)**

Chair: Masafumi Onodera (National Center for Child Health and Development) /
小野寺　雅史 (国立成育医療研究センター 遺伝子細胞治療推進センター)

Hematopoietic stem cell gene therapy for inborn errors of immunity and metabolism 44

Aiuti Alessandro (San Raffaele Telethon Institute for Gene Therapy, Italy)

17:20~17:40 **Closing Remarks (閉会挨拶)**

Ryuichi Morishita (President of the JSGCT, Osaka University)
森下　竜一 (一般社団法人日本遺伝子細胞治療学会 理事長、大阪大学 大学院医学系研究科臨床遺伝子治療学)

Clinical experience of AAV-based gene therapy

-Abstracts & Curriculum Vitae-

Sandra P. Reyna

Address (Affiliation) Novartis Gene Therapies
Field of Research Child Neurology, Neurology, Genetics

Education

Dr. Sandra P. Reyna received her M.D. degree from San Carlos University Medical School in Guatemala and subsequently pursued a career as a research physician in cardiovascular clinical genetics. She then trained in pediatrics at Primary Children's Hospital, Salt Lake City, Utah, and there continued her medical training in Neurology and Genetics.

Professional Experience

As an Assistant Professor of Neurology at the University of Utah, she led the Neurology Clinical Trials Unit as Director whilst keeping her appointment as Co-Director of the Pediatric Motor Disorders Research Program; and as Project Director of NeuroNEXT and StrokeNet, for the National Institute of Health awards.
Since 2005, Dr Reyna's academic career and research focus has been in neuromuscular disorders, with much of her time spent on Spinal Muscular Atrophy. Dr. Reyna led the SMA clinical trial network through Project Cure SMA, funded by CureSMA, which led to the CARNI-VAL trials and publications.
After working at Massachusetts General Hospital from 2015 to 2016, she transitioned to her first industry position at Biogen. There she participated in the physician development program, gaining experience in Pharmacovigilance, Clinical Pharmacology and Clinical Development. She joined the SMA Clinical Research Development team and ultimately led all Nusinersen global trials with symptomatic and pre-symptomatic SMA affected children. She managed all medical aspects of the study, including medical monitoring, investigator interactions, subject recruitment and retention, event adjudication, data presentations, Global Steering Committee interactions and study data interpretation. She participated in the filing for Nusinersen and supported the launch of SPINRAZA. In February 2019, she transitioned to Bluebird Bio to work on gene therapy clinical trials for adrenoleukodystrophy. Throughout her time in industry, Sandy has stayed involved in multiple SMA and other movement disorders, initiatives and interest groups.
Currently she is Vice President of Medical Affairs, Global Therapeutic Area Head, where she is responsible for the Global Medical Affairs plan for SMA aligned with Novartis Gene Therapies' corporate strategy and tracking the execution of each tactic and in support of country launch teams.

Recent Related Publications (5 Papers)

1. Day JW, Mendell JR, **Reyna PS**, et al.: Clinical Trial and Postmarketing Safety of Onasemnogene Abeparvovec Therapy. ***Drug Saf***. 2021 Oct;44(10):1109-1119.
2. Chand DH, Zaidman C, **Reyna SP**, et al..: Thrombotic Microangiopathy Following Onasemnogene Abeparvovec for Spinal Muscular Atrophy: ***A Case Series***. J Pediatr. 2021 Apr 231:265-268
3. Elsheikh B, King W, Peng J, **Reyna SP**, et al.: Outcome measures in a cohort of ambulatory adults with spinal muscular atrophy. ***Muscle Nerve***. 2020 Feb;61(2):187-191.
4. Jones CC, Cook SF, **Reyna SP**, et al..:Spinal Muscular Atrophy (SMA) Subtype Concordance in Siblings:Findings From the Cure SMA Cohort.***J Neuromuscul Dis***. 2020;7(1):33-40.
5. De Vivo DC, Bertini E, **Reyna SP**,et al. ; NURTURE Study Group.: Nusinersen initiated in infants during the presymptomatic stage of spinal muscular atrophy: Interim efficacy and safety results from the Phase 2 NURTURE study. ***Neuromuscul Disord***. 2019 Nov;29(11):842-856.

Onasemnogene abeparvovec (Zolgensma®) for Spinal Muscular Atrophy: Clinical and Real World Experience

Sandra P. Reyna

Novartis Gene Therapies

Spinal muscular atrophy (SMA) is a rare neurodegenerative disorder caused by the bi-allelic deletion or mutation of the essential survival motor neuron 1 (*SMN1*) gene. Early intervention is critical to halt irreversible loss of motor neurons and progressive muscle weakness for SMA patients these individuals. Onasemnogene abeparvovec (ZOLGENSMA®) is a novel gene therapy designed to target the genetic root cause of SMA and consists of an adeno-associated virus serotype 9 vector containing a recombinant, self-complementary genome, a transgene encoding the human SMN protein, under the control of a continuous cytomegalovirus enhancer / chicken-β--actin hybrid promoter. Over 1600 patients have been treated with intravenous (IV) onasemnogene abeparvovec in 41 countries across clinical trials, managed access programs, and commercially.

Findings from the START, STR1VE-US, and STR1VE-EU trials, indicate that onasemnogene abeparvovec significantly increases event-free survival in symptomatic patients with SMA type 1 compared with natural history. As of June 2020, all pre-symptomatic SMA patients with two or three copies of *SMN2* gene in the SPR1NT trial were alive and free of permanent ventilation. No patient required feeding tube support, and the majority of patients achieved age-appropriate milestones, such as sitting, standing, and walking.

The RESTORE registry provides real-world data for effectiveness of onasemnogene abeparvovec patients beyond those studied in clinical trials, specifically patients who are 6 months of age or older, and patients who weigh at least 8.5 kg. As of June 2021, the database comprised information from 274 patients and 77 active sites.

The phase 3b SMART study aims to evaluate safety and efficacy of a one-time IV onasemnogene abeparvovec dose in children with SMA weighing ≥8.5 kg and ≤21 kg. Enrollment is ongoing. The intrathecal (IT) formulation is under investigation as a one-time, treatment option for older patients with SMA. The phase 3 STEER study is estimated to start enrollment in December 2021 and aims to evaluate the efficacy and safety of IT onasemnogene abeparvovec in patients with type 2 SMA aged ≥2 to <18 years of age.

Across clinical studies and post-marketing surveillance, adverse events associated with IV administration of onasemnogene abeparvovec are consistent and manageable. As of November 12, 2020, 101 of 102 (99%) patients experienced an adverse event, with 56.9% of patients experiencing a serious adverse event (SAE), 10.8% considered related to treatment. The most frequently reported treatment-related SAEs were pyrexia and increased liver function tests, which resolved with systemic corticosteroids. Transient platelet count decreases and cases of thrombotic microangiopathy have also been identified from post-marketing experience.

Onasemnogene abeparvovec is an effective treatment for SMA with a safety profile that can be anticipated, monitored, and managed. Durable efficacy and safety following a single IV dose have been demonstrated for more than 5.6 years. For maximal clinical outcomes following early intervention, carrier and newborn screening for SMA are being implemented in several countries around the world. Further collection of IV and IT treatment efficacy and safety in a broad SMA patient population continues to be supported by ongoing clinical studies and emerging real-world data.

Marie-Laure Névoret

Address (Affiliation) REGENXBIO Inc.
9804 Medical Center Drive
Rockville, Maryland 20850
United States

Field of Research AAV Gene Therapy

Education

Duke University	B.A. Chemistry with Biology concentration and German Language
Loyola University Stritch School of Medicine	M.D.
Loyola University Medical Center	General Surgery Residency

Professional Experience

Executive Director, Clinical Development Lead, Rare Diseases
Senior Clinical Development Lead, Rare Diseases
REGENXBIO, Inc.

Director, Global Clinical Development
Clinical Director
Global Medical/Clinical Trial Manager
Helixmith Co., Ltd (formerly ViroMed Co., Ltd)

Associate Director, Pharmacovigilance
PPD, LLC

Medical Director, North America
Impeto Medical, Inc.

Recent Related Publications (5 Papers)

1. Khalfallah K, Calvet JH, Brunswick P, **Névoret M-L**, Ayoub H, Cassir M. A Simple and Accurate Method to Assess Autonomic Nervous System through Sudomotor Function. ***Advances in Biosensors: Reviews***. Volume 3, Chapter 6. Sep 2020.
2. **Névoret M-L**. Electrochemical skin conductance is sensitive and has clinical utility in patients with untreated or poorly controlled diabetes. Letter to the editor. ***Biomedical Engineering Letters***. 2019;9:507-509.
3. **Névoret M-L**., Vinik AI. What Can Sudorimetry Tell us about Somatic and Autonomic Function. ***J Cardiol & Cardiovasc Ther***. 2018:11: JOCCT.MS.ID.555822.
4. Vinik AI, **Névoret M-L**. Diagnostic accuracy of neuropathy tests in obese population remains elusive. ***Clin Neurophysiology***. 2018;129:1502–1503.
5. Vinik AI, Casellini CM, Parson H, Colberg-Ochs SR, **Nevoret ML**. Cardiac Autonomic Neuropathy in Diabetes: A Predictor of Cardiometabolic Events. ***Front. Neurosci***. 2018;12:591.

Intracisternal AAV9-based Gene Therapy for Neuronopathic Lysosomal Storage Diseases: Experience from a Clinical Trial Program

Marie-Laure Névoret
REGENXBIO, Rockville, MD, United States

MPS II is an x-linked lysosomal storage disease caused by deficiency of iduronate-2-sulfatase (I2S) leading to accumulation of glycosaminoglycans in tissues. Neuronopathic MPS II results in irreversible neurodevelopmental decline not addressed by intravenously administered enzyme replacement therapy; gene therapy may offer a one-time treatment for genetic disorders with central nervous system (CNS) involvement such as MPS II. RGX-121, a recombinant adeno-associated virus serotype 9 capsid containing a human iduronate-2-sulfatase expression cassette (AAV9.CB7.hIDS), when administered to the CNS, may provide a permanent source of secreted I2S, potentially correcting neurologic and systemic disease manifestations.

The route of administration used to optimize CNS biodistribution of the therapeutic transgene while maintaining safety is critical. Early pre-clinical work demonstrated that intracisternal (IC) administration (suboccipital puncture) of AAV9 vectors expressing missing lysosomal enzymes may have advantages over intracerebroventricular (ICV), intraparenchymal, or intrathecal (IT) lumbar puncture. Positron emission tomography biodistribution studies using [89ZR]-AAV9-GFP in non-human primates showed that IC administration resulted in greater uptake in the brain (grey matter) compared to IT administration which shows greater uptake in the spinal cord. IC administration has been adopted as the primary route for dosing RGX-121 in clinical trials, with image-assisted ICV administration considered when IC may not be anatomically feasible. Prior to vector administration, magnetic resonance imaging of the brain and C1-C2 intrathecal space is reviewed by a team of neuroradiologists and neurosurgeons to confirm patient suitability for IC administration. Computed tomography-guided IC delivery is performed under anesthesia by a trained neuroradiologist or neurosurgeon.

In a phase 1/2, first-in-human, multicenter, open-label, dose escalation trial (NCT03566043), participants with neuronopathic MPS II ages 4 months to 5 years receive one image-guided RGX-121 injection to the CNS with follow-up for safety, tolerability, and efficacy for 104 weeks. Assessments include cerebrospinal fluid, plasma and urine biomarkers; cognition, language, and motor neurodevelopmental scales; and imaging. Nine participants have been enrolled in 3 dose cohorts (1.3x1010, 6.5x1010, and 2.0x1011 genome copies/gram brain mass) as of April 25, 2021. Following RGX-121 administration, there were consistent reductions of CSF heparan sulfate levels, a biomarker of neuronopathic MPS II disease. In addition, interim neurodevelopmental testing demonstrated ongoing skill acquisition in multiple domains after RGX-121 administration. Plasma I2S enzyme expression, total urine GAGs, and abdominal ultrasound imaging suggested emerging evidence of systemic RGX-121 efficacy. Updated interim results from this clinical trial will be presented.

RGX-121 gene therapy has the potential to provide sustained CNS clinical outcomes and additional systemic effects in MPS II patients.

Memo

Special lectures

-Abstracts & Curriculum Vitae-

James M. Willson

Address (Affiliation) Rose H. Weiss Professor and Director, Orphan Disease Center
Professor of Medicine and Pediatrics
Director, Gene Therapy Program
Perelman School of Medicine
University of Pennsylvania

Education

Albion College, Albion, MI	BA	Chemistry
University of Michigan, Ann Arbor, MI	PhD	Biological Chemistry
University of Michigan School of Medicine, Ann Arbor, MI	MD	

Professional Experience

1988-1993	Assistant Professor to Associate Professor, Internal Medicine and Biological Chemistry, University of Michigan
1988-1993	Assistant Investigator, Howard Hughes Medical Institute Medical School, University of Michigan
1991-1993	Chief, Division of Molecular Medicine and Genetics, University of Michigan
1993-2000	Chief, Division of Medical Genetics, Department of Medicine, University of Pennsylvania
1993-2001	Professor and Chair, Department of Molecular and Cellular Engineering, University of Pennsylvania
1993-2002	Director, Institute for Human Gene Therapy, University of Pennsylvania
1994-2006	Professor of Pediatrics, University of Pennsylvania
1993-2005	Professor, The Wistar Institute
1993-2009	John Herr Musser Professor of Research Medicine, University of Pennsylvania
2010	Visiting Professor, Dept. of Biochemistry and Molecular Biology, University of Florida
2006-2015	Professor of Pathology and Laboratory Medicine, Division of Transfusion Medicine, University of Pennsylvania
2014-present	Director, Orphan Disease Center, University of Pennsylvania
2006-present	Director, Gene Therapy Program, University of Pennsylvania
2015-present	Professor of Medicine, Division of Translational Medicine and Human Genetics University of Pennsylvania

Recent Related Publications (5 Papers)

1. Martino RA, Fluck EC III, Murphy J, Wang Q, Hoff H, Pumroy RA, Lee CY, Sims JJ, Roy S, Moiseenkova-Bell VY, **Wilson JM**. Context-Specific Function of the Engineered Peptide Domain of PHP. B. ***J Virol***, Aug 4;JVI0116421, 2021.
2. Greig JA, Jennis M, Dandekar A, Chorazeczewski JK, Smith MK, Ashley SN, Yan H, **Wilson JM**. Muscle-directed AAV gene therapy rescues the maple syrup urine disease phenotype in a mouse model. ***Mol Genet Metab*** Aug 17;S1096-7192(21)00767-8, 2021. PMID: 34454844.
3. Tycko J, Adam VS, Crosariol M, Ohlstein J, Sanmiguel J, Tretiakova AP, Roy S, Worgall S, **Wilson JM**, Limberis MP. Adeno-associated virus vector-mediated expression of anti-respiratory syncytial virus antibody prevents infection in mouse airways. ***Hum Gene Ther***, Aug 20, 2021. PMID: 34415793.
4. Wang Q, Nambiar K, **Wilson JM**. Isolating Natural Adeno-Associated Viruses from Primate Tissues with a High-Fidelity Polymerase. ***Hum Gene Ther***, Aug 26, 2021. PMID: 34448594.
5. Greig JA, Smith MK, Nordin JML, Goode T, Chroscinski EA, Buza EL, Schmidt N, Kattenhorn LM, Wadsworth S, **Wilson JM**. Determining the Minimally Effective Dose of a Clinical Candidate AAV Vector in a Mouse Model of Hemophilia A. ***Hum Gene Ther***, Oct 15, 2021. PMID: 34652966.

Gene Therapy and Genome Editing for Human Genetic Diseases

James M. Willson

Perelman School of Medicine at the University of Pennsylvania

Gene Therapy and Gene Editing offer solutions to a wide array of rare monogenic diseases. I will discuss our work using AAV vectors for neurologic diseases. I will also present studies in which we use gene editing for the treatment of neonatal onset liver metabolic diseases.

Beverly L. Davidson

Address (Affiliation) Pathology and Laboratory Medicine
Perelman School of Medicine
University of Pennsylvania

Education

Nebraska Wesleyan University	B.S.	Biology
University of Michigan	Ph.D.	Biological Chemistry
	Postdoctoral	Molecular Genetics

Professional Experience

1990-92	Research Investigator, Department of Internal Medicine, University of Michigan
1992-94	Assistant Research Scientist, Department of Internal Medicine, University of Michigan
1993-94	Director, Vector Core, Department of Internal Medicine, University of Michigan
1994	Assistant Professor, Department of Internal Medicine, University of Michigan
1994-98	Assistant Professor, Department of Internal Medicine, University of Iowa
1994-2013	Director, Gene Transfer Vector Core, University of Iowa
1998-2001	Associate Professor, Department of Internal Medicine, University of Iowa
2001-04	Co-Director, Iowa Biosciences Advantage Program for Gifted Minorities
2001-14	Professor, Departments of Internal Medicine, Neurology, Physiology & Biophysics
2005-14	Vice Chair for Research, Department of Internal Medicine, University of Iowa
2014-	Professor of Pathology and Laboratory Medicine, Perelman School of Medicine at the University of Pennsylvania
2014-	Director, Raymond G. Perelman Center for Cellular and Molecular Therapy, The Children's Hospital of Philadelphia
2014-	Arthur V. Meigs Chair in Pediatrics, The Children's Hospital of Philadelphia
2014-	Director, Research Vector Core, The Children's Hospital of Philadelphia
2016-	Chief Scientific Strategy Officer, The Children's Hospital of Philadelphia Research Institute
2016-	Committee on Appointments and Promotion, Perelman School of Medicine, UPENN
2016-	Dean's Advisory Council, Perelman School of Medicine, UPENN
2017-	Translational Neuroscience Center Scientific Advisory Board, UPENN
2017-	Neuroscience Advisory Committee, Mahoney Institute for Neuroscience (MINS), UPENN

Recent Related Publications

1. Monteys AM, Hundley AA, Ranum PT, Tecedor L, Muehlmatt A, Lim E, Lukashev D, Sivasankaran R, **Davidson BL**. Regulated control of gene therapies by drug-induced splicing. ***Nature***. 2021;596:291-295.
2. Tecedor L, Muehlmatt A, **Davidson BL**. Regulated control of gene therapies with a drug induced switch. ***bioRxiv*** 2020.02.21.956664
3. Lang JF, Toulmin SA, Brida KL, Eisenlohr LC, **Davidson BL**. Standard screening methods underreport AAV-mediated transduction and gene editing. ***Nat Commun***. 2019;1:3415.
4. Victor MB, Richner M, Olsen HE, Lee SW, Monteys AM, Ma C, Huh CJ, Zhang B, **Davidson BL**, Yang XW, Yoo AS. Striatal neurons directly converted from Huntington's disease patient fibroblasts recapitulate age-associated disease phenotypes. ***Nat Neurosci***. 2018;21:341-352.
5. Yrigollen, CM, **Davidson BL**. CRISPR to the Rescue: Advances in Gene Editing for the FMRI Gene. ***Brain Sci***, 9(1):piiE17, 2019. PMC6357057

Advancing gene therapies for the brain

Beverly L. Davidson

Pathology and Laboratory Medicine, Perelman School of Medicine of the University of Pennsylvania

Memo

Gene therapy for Haemophilia

-Abstracts & Curriculum Vitae-

Gregory Di Russo

Address (Affiliation) Pfizer Inc., USA

Field of Research Clinical development of gene therapies
Biologics and small molecules in rare disease
Bleeding disorders
Transplantation
Cardiovascular diseases and pediatrics

Education

Johns Hopkins University	Business of Medicine Certificate	2004
Jefferson Medical College	MD	1991
Princeton University	AB: Romance Languages	1987

Professional Experience

Pfizer, Inc., Collegeville, PA
Vice President, Medicine Team Lead, Hemophilia, GPD Rare Disease 2016-present
Asset Team Leader/Global Clinical Leader, Eliquis 2015-2016
CytoSorbents, Inc., Monmouth Junction, NJ. Senior Vice President, Clinical Development 2015
CSL Behring, King of Prussia, PA
Therapeutic Area Head - Acquired Bleeding and Head of Specialized Sciences 2014
Therapeutic Area Head - Acquired Bleeding 2013-2014
Senior Global Clinical Program Director - Acquired Bleeding/Critical Care 2011-2013
Program Director – Acquired Bleeding/Critical Care 2011
Bristol-Myers Squibb, Princeton, NJ - Global Clinical Development
Director – CV/Metabolics 2010-2011
Director – Immunology 2007-2010
Children's National Medical Center/George Washington University, Washington, DC
Vice Chairman of Cardiovascular Surgery 2001-2005
Director of Cardiac Transplantation, Assistant Professor of Surgery
Primary Children's Medical Center/University of Utah School of Medicine, Salt Lake City, Utah
Assistant Professor of Surgery 1999-2001

Recent Related Publications

1. Byon W, Cirincione B, **Di Russo G**, et al. The renal elimination of apixaban: the totality of data relating to the renal clearance of apixaban in patients with impaired renal function: response to Hellfritzsch et al. ***Pharmacoepidemiol Drug Saf***. 2017;26:603-605.
2. Larsen CP, Grinyó J, **Di Russo GB**, et al. Belatacept-Based Regimens Versus a Cyclosporine A-Based Regimen in Kidney Transplant Recipients: 2-Year Results From the BENEFIT and BENEFIT-EXT Studies. ***Transplantation*** 2010;90:1528-35.
3. Durrbach A, Pestana JM, **Di Russo GB**, et al. A Phase III Study of Belatacept Versus Cyclosporine in Kidney Transplants From Extended Criteria Donors (BENEFIT-EXT Study). ***Am J Transplantation*** 2010;10:547-57.
4. Vincenti F, Charpentier B, **Di Russo GB**, et al. A phase III study of belatacept-based immunosuppression regimens versus cyclosporine in renal transplant recipients (BENEFIT study). ***Am J Transplant***. 2010;10:535-46.
5. Benjamin LC, Nahar J, Sable C, Midgley FM, **Di Russo GB**. Separation of thoracopagus-cardiopagus twins joined by a myocardial bridge. ***J Thorac Cardiovasc Surg***. 2005;130:1212-3.

Clinical Application of Gene Therapy for Hemophilia: Experience with fidanacogene elaparvovec and giroctocogene fitelparvovec

Gregory Di Russo
Pfizer Inc., USA

Hemophilia A/B is a rare bleeding disorder caused by pathogenic variants in the F8/F9 gene. Adeno-associated virus (AAV)–mediated gene transfer enables the delivery of a modified functional F8/F9 coding sequence to hepatocytes that subsequently synthesize FVIII/FIX at levels that may prevent bleeding events. We present updated results with nearly 2-year follow-up from an ongoing gene therapy study in patients with hemophilia A (NCT03061201), and more than 5-year follow-up in a cohort of patients with hemophilia B (NCT02484092). Hemophilia A Eleven patients with hemophilia A (FVIII activity <1%) were treated with giroctocogene fitelparvovec in 4 dose cohorts (9e11, 2e12, 1e13, and 3e13 vg/kg) in the phase 1/2 study. As of the cutoff date, patients had been followed for 95 to 195 weeks overall. Treatment-related serious AEs were reported in 1 patient who experienced hypotension and fever. ALT elevations requiring >7 days of corticosteroid treatment were observed in 4 of the 5 patients in the 3e13-vg/kg cohort. For the 4 patients in the 3e13-vg/kg cohort, patients had mean FVIII activity maintained in the mild to normal range through week 104. The annualized bleeding rate was 0 for the first year postinfusion and 0.9 throughout the total duration of follow-up. 2 patients experienced a total of 3 bleeding events necessitating treatment with exogenous FVIII. No patients in have resumed prophylaxis. Hemophilia B Fifteen patients with hemophilia BFifteen patients with hemophilia B (FIX(FIX activity ≤activity ≤2%)2%) were treated with fidanacogene were treated with fidanacogene elaparvovec at a dose of 5e11 vg/kg. All 15 patients completed the phase 1/2a studyelaparvovec at a dose of 5e11 vg/kg. All 15 patients completed the phase 1/2a study ((52 52 weeksweeks)), and 14 patients were subsequently enrolled in the , and 14 patients were subsequently enrolled in the longlong--term followterm follow--up (LTFU)up (LTFU) studystudy ((5 years5 years)). . As of the cutoff date, 13 patients were enrolled in the LTFU study, with follow, 13 patients were enrolled in the LTFU study, with follow--up ranging up ranging from >2.5 years to >5 years following vector administration. 3 patients were treated with from >2.5 years to >5 years following vector administration. 3 patients were treated with corticosteroids within the first 6 months of the phase 1/2a study. There were no serious corticosteroids within the first 6 months of the phase 1/2a study. There were no serious adverseadverse events (SAEs) in the phase 1/2a study, and 3 patients reported SAEs in the LTFU events (SAEs) in the phase 1/2a study, and 3 patients reported SAEs in the LTFU study, none of which were considered treatment related. study, none of which were considered treatment related. Mean FIX activity levels by year remain in the mild hemophilia severity rangeMean FIX activity levels by year remain in the mild hemophilia severity range,, associated with associated with mean annualized bleedinmean annualized bleeding rates ranging from 0g rates ranging from 0––0.9 over the course of follow0.9 over the course of follow--up, and no up, and no patients have resumed FIX prophylaxis. Four patients have undergone 6 surgical procedures patients have resumed FIX prophylaxis. Four patients have undergone 6 surgical procedures during the LTFU study. There were no bleeding complications with these procedures, and the during the LTFU study. There were no bleeding complications with these procedures, and the 2 emergent 2 emergent procedures (appendectomy and lumbar discectomy) were performed without the procedures (appendectomy and lumbar discectomy) were performed without the need of additional FIX. need of additional FIX.

Overall, both a single infusion of giroctocogene fitelparvovec in patients with hemophilia A and fidanacogene elaparvovec in patients with hemophilia B were generally well tolerated with associated increases in FVIII/FIX levels in the mild to normal range, without sustained AEs, and with minimal bleeding. Phase 3 studies of giroctocogene fitelparvovec in patients with hemophilia A (NCT04370054) and fidanacogene elaparvovec in patients with hemophilia B (NCT03861273) are ongoing.

Kevin Eggan

Address (Affiliation) BioMarin Pharmaceutical Inc.
Field of Research Genetic Disease

Education

University of Illinois	B.S.	Microbiology
MIT	Ph.D.	Biology

Professional Experience

Kevin Eggan, Ph.D., joined BioMarin as Group Vice President, Head of Research and Early Development in 2020. He is responsible for the execution of BioMarin's discovery research programs, playing a critical role in shaping the vision of the company's future research pipeline. He heads BioMarin's Research organization, providing scientific leadership throughout the drug discovery process. Dr. Eggan is charged with further building BioMarin's leadership position in genetic medicines in support of people affected by rare genetic diseases and contributing to the long-term growth of BioMarin through the oversight of an exceptional pipeline of first- or best-in-class therapies. Dr. Eggan has served as a tenured Professor in the Department of Stem Cell and Regenerative Biology at Harvard University, Director of Stem Cell Biology for the Stanley Center for Psychiatric Research at the Broad Institute, and as an Institute Member of the Broad Institute of MIT and Harvard. In addition, Dr. Eggan has published approximately 130 scientific articles and holds 13 patents. He has served on the Scientific Advisory Boards of Ipierian, Roche, and Angelini Pharma among others. He has co-founded three biotechs, Q-State Bioscience, Quralis, and Enclear Therapies which have raised more than $85 million of investment. He has also collaborated with Ipierian on establishing human neuronal models that were later used to discover and characterize an anti-Tau antibody that is currently part of Biogen's portfolio for a potential treatment of Alzheimer's disease.

Dr. Eggan resolved early in his academic career to raising support for the stem cell research community at large. While he has been involved in a variety of efforts outside of Harvard, Dr. Eggan worked from 2005 until 2015 with The New York Stem Cell Foundation (NYSCF) and their CEO Susan Solomon to raise more than $200 million for stem cell research. Amongst the most impactful of these efforts has been the ability to raise more than $100 million for young investigator programs in stem cell biology and neuroscience that have supported more than 70 five-year awards to junior faculty and fellowships for 75 postdoctoral trainees.

Dr. Eggan received his B.S. in microbiology at the University of Illinois and his Ph.D. in biology from M.I.T. where he focused on cloning, stem cells, and reprogramming after nuclear transfer under the guidance of Rudolph Jaenisch, Ph.D. a scientific pioneer in genetics. Dr. Eggan remained in the lab of Dr. Jaenisch for a one-year post-doctoral position at the Whitehead Institute for Biomedical Research where he conducted a study with Nobel laureate Richard Axel, M.D. Dr. Eggan has received international recognition for his work including receiving the MacArthur Foundation's "Genius Grant." He has also been named one of 50 Howard Hughes Medical Institute Early Career Scientists, one of the 50 Most Influential People in Science by Scientific American two years in a row, Innovator of the Year by Technology Review Magazine, a Top Innovator under 35 by Technology Review Magazine, and a "Brilliant 10" by Popular Science Magazine.

Recent Related Publications

1. Burberry A, Wells M, **Eggan K**, et al. *C9orf72* suppresses systemic and neural inflammation induced by gut bacteria. ***Nature***. 2020;582:89-94.
2. Hazelbaker DZ, Beccard A, **Eggan K**, et al.. A multiplexed gRNA piggyBac transposon system facilitates efficientinduction of CRISPRi and CRISPRa in human pluripotent stem cells. ***Sci Rep***. 2020;10:635.
3. Oh HS, Neuhausser WM, **Eggan KC**, et al. Herpesviral lytic gene functions render the viral genome susceptible to novelediting by CRISPR/Cas9. ***Elife***. 2019;8:e51662.
4. Farhan SMK, Howrigan DP, **Eggan K**, et al. Exome sequencing in amyotrophic lateral sclerosis implicates a novel gene, DNAJC7, encoding a heat-shock protein. ***Nat Neurosci***. 2019;22:1966-1974.

Gene therapy of hemophilia A

Kevin Eggan

BioMarin Pharmaceutical Inc.

BACKGROUND

A single infusion of valoctocogene roxaparvovec (AAV5-hFVIII-SQ) resulted in clinically significant Factor VIII (FVIII) activity levels and reduced annualized bleeding and FVIII utilization over 5 years of follow-up. Previous studies showed durable expression is associated with presence of circularized episomal DNA in target tissues. AAV5-hFVIII-SQ, an oversized vector, drives FVIII expression using a liver specific promoter, but vector DNA presence in hepatocytes has not been confirmed through liver biopsy.

AIMS

To evaluate histopathology and vector genome forms and distribution in human liver biopsies following AAV5-hFVIII-SQ administration.

METHODS

Liver biopsies were obtained from five participants receiving $6x10^{12}$, $4x10^{13}$ or $6x10^{13}$ vg/kg doses of AAV5-hFVIII-SQ. Biopsy samples collected 2.6-4.1 years following dosing underwent histopathological examination, and in situ hybridization to detect vector genomes.

RESULTS

Histopathological examination revealed normal liver architecture, no evidence of dysplasia, architectural distortion, fibrosis, or chronic inflammation, and no endoplasmic reticulum stress was detected in hepatocytes expressing hFVIII-SQ protein. Mild steatosis was detected in four out of five participants. Hepatocytes stained positive for vector genome dose-dependently and molecular analysis demonstrated the presence of full-length, ITR-fused, circular episomal genomes, which are associated with long-term expression.

Memo

Luncheon Seminar

-Abstract & Curriculum Vitae-

Tatsuji Enoki

Address (Affiliation) Takara Bio Inc., Japan
Field of Research Gene therapy, Immunology and Stem cell research

Education

Osaka Prefecture University	B.A.	1993	Agricultural Chemistry
Osaka Prefecture University	M.A.	1995	Agricultural Chemistry
Kagoshima University	Ph,D.	2012	Agriculture

Professional Experience

1995 – 2002 Takara Shuzo Co. Ltd.
2002 – 2004 Takara Bio Inc.*
2004 – 2016 Takara Bio Inc., Senior Scientist,
(Oct. 2010 – Jul. 2011 Dr. Nakai Lab., University of Pittsburgh)
2016 – 2017 Takara Bio Inc., Deputy General Manager,
2017 – present Takara Bio Inc., General Manager
*(successor-in-interest of Takara Shuzo Co., Ltd. Biomedical Group)

Recent Related Publications

1. Okamoto S, Amaishi Y, Maki I, **Enoki T,** Mineno J. Highly efficient genome editing for single-base substitutions using optimized ssODNs with Cas9-RNPs. ***Sci Rep***., 9(1):4811. doi: 10.1038/s41598-019-41121-4, 2019.
2. Ishikawa T, Okayama T, Sakamoto N, Ideno M, Oka K, **Enoki T**, Mineno J, Yoshida N, Katada K, Kamada K, Uchiyama K, Handa O, Takagi T, Konishi H, Kokura S, Uno K, Naito Y, Itoh Y. Phase I clinical trial of adoptive transfer of expanded natural killer cells in combination with IgG1 antibody in patients with gastric or colorectal cancer. ***Int J Cance***r, doi: 10.1002/ijc.31285, 2018.
3. Hosoi H, Ikeda H, Imai N, Amaike C, Wang L, Orito Y, Yamane M, Ueno H, Ideno M, Nukaya I, **Enoki T**, Mineno J, Takesako K, Hirano S, Shiku H. Stimulation through very late antigen-4 and -5 improves the multifunctionality and memory formation of $CD8^+$ T cells. ***Eur J Immunol***., 44(6): 1747-1758, 2014.
4. Ishikawa T, Kokura S, **Enoki T**, Sakamoto N, Okayama T, Ideno M, Mineno J, Uno K, Yoshida N, Kamada K, Katada K, Uchiyama K, Handa O, Takagi T, Konishi H, Yagi N, Naito Y, Itoh Y, Yoshikawa T. Phase I clinical trial of fibronectin CH296-stimulated T cell therapy in patients with advanced cancer. ***PLoS One***, 9(1): e83786, 2014.
5. Adachi K, **Enoki T**, Kawano Y, Veraz M, Nakai H. Drawing a high-resolution functional map of adeno-associated virus capsid by massively parallel sequencing. ***Nat Commun***., 5: 3075, doi:10.1038/ncomms4075, 2014.

Takara Bio's efforts to address gene therapy vectors

Tatsuji Enoki

Takara Bio Inc., Japan

遺伝子治療用製剤の開発においては、in vivo、ex vivo のいずれにおいてもウイルスベクターが広く利用されている。ウイルスベクターの開発過程では、ベースとなるベクターの選定及び設計、ベクターの調製、タイターの測定等、多くの研究用ツールが利用される。

当社においては、レトロネクチン ® による造血幹細胞や T 細胞への遺伝子導入法の開発を契機に、遺伝子治療用ウイルスベクターに対する検討を継続して行っており、最近では、アデノ随伴ウイルス（AAV）ベクターに関してセロタイプを問わず培養上清と細胞内からまとめて精製できる手法や、臨床応用を想定して HIV-1 由来配列を極力削減したレンチウイルス（LV）ベクターを開発し、研究用ツールとして提供している。また、ウイルスベクターの GMP 受託製造サービスにおいて、AAV ベクター等の臨床応用のためには大量のベクター量が必要となることがあるため、その GMP 製造に対応するための設備の拡充を進めている。

今回、これら LV ベクター及び AAV ベクターを中心に、遺伝子治療用ウイルスベクターに対する当社の取り組みについて紹介する。

Memo

Special lecture

-Abstract & Curriculum Vitae-

Michiko Takakura

Address (Affiliation) Deputy Manager,
Division of Gene Therapy
Department of Regenerative Medicine and Cell and Gene Therapies
Japan Agency for Medical Research and Development (AMED)
21F Yomiuri Shimbun Bldg. 1-7-1 Otemachi, Chiyoda-ku, Tokyo 100-0004 Japan

Field of Research Biochemistry, Molecular biology, Cell and Gene Therapies

Education

Graduate School of Environmental Health, Azabu University -Doctor of Science and Culture (Ph.D.)

Professional Experience

2020-present AMED-Division of Gene Therapy Department of Regenerative Medicine and Cell and Gene Therapies

2018-2020 AMED-Division of Drug Research Department of Innovative Drug Discovery and Development, Responsible for Project Management of Research and development of core technologies for gene and cell therapy

2017-2018 AMED-Division of Rare/Intractable Disease Research Department of Research Promotion, Member of the AMED-Task Force of the IRUD (Initiative on Rare and Undiagnosed Diseases) and IRDiRC (International rare disease research consortium)

2015-2017 Division of Biological Chemistry and Biologicals, National Institute of Health Sciences, Project Member of Evaluating and predicting the activation of human immune cells by novel Fc-engineered mAbs

Recent Related Publications (5 Papers)

1. Michiko Takakura, et.al. ***Biochem Biophys Res Commun***. 2017 Mar 25;485(1):189-194
2. Michiko Takakura, et.al. ***ISRN Oncology***. Vol. 19, 1-10, 2012,
3. Michiko Takakura, et.al. ***Cancer Biomarkers***. Vol.10 (3-4), 175-183, 2011/2012.

Efforts on Gene and Cell Therapy Projects at AMED

Michiko Takakura
AMED, Japan

Since its establishment as a national research and development (R&D) agency in 2015, the Japan Agency for Medical Research and Development (AMED) has worked to promote seamless R&D in medicine and related areas, extending from basic research to practical application, and to apply the outcomes of such research in practice.

In 2020, AMED's Second Medium- to Long-Term Plan was launched. During the second plan period, we will further advance and consolidate the results we achieved during the five years of the first plan, thoroughly verifying the issues that remain, as we seek to forge a smoother path toward a strong structure and operations. The key concern among issues that have been raised relates to the integrated projects under the first plan, comprising five cross-sectional projects and four disease area-specific projects. It allocates funding to six projects according to therapeutic approaches and modalities, one of which is the "Project for Regenerative / Cellular Medicine and Gene Therapies".

The project supports basic, non-clinical and clinical research on regenerative and cellular medicine to promote studies of fundamental technologies and to develop regenerative medical products. In addition, it covers research on gene therapies to put in practice or to contribute the advancement of this area of therapeutics. Research includes therapies by *in vivo*, ex vivo delivery, oncolytic virus, and gene editing, to develop novel treatment for incurable diseases, especially cancers and rare disorders.

Today, I will introduce our efforts and activities for R&D on gene therapies, financial supports for non-clinical and clinical research on gene therapies for cancers and rare disorders, and the project to support practical application of gene therapies. For those of cancers, we are supporting 14 programs this fiscal year. Nine are for CAR T-cell therapies and three are therapies that utilize oncolytic virus. For rare and intractable diseases, we support ten programs. Of which eight are for *in vivo* gene therapies, and one program each for ex vivo gene therapies and gene editing.
The project designed to contribute to the advancement of gene therapy will integrate advanced key technologies scattered in Japan into core centers to develop new large-scale vector production methods, create a network of research centers with these large-scale production technologies, and establish a basis for research on novel gene/cell therapy with the overarching goal of its eventual clinical application. Another goal is the acceleration of R&D on advanced gene/cell therapy by creating new technologies for high-quality production and improved safety required to reach clinical use. Taken together, we work with the aim to develop and implement gene therapies for incurable diseases, to give patients a way to novel treatment in the near future.

Memo

Gene therapy for AADC deficiency

-Abstracts & Curriculum Vitae-

Karin Kojima

Address (Affiliation) Department of Pediatrics, Jichi Medical University
Field of Research Child neurology, gene therapy

Education

2001 Graduated from Faculty of Medicine, Jichi Medical University, Japan
2014 Graduated from Graduate School, Jichi Medical University, Japan

Professional Experience

2001 Junior resident of internal medicine, Aomori Prefectural Central Hospital, Japan
2003 Medical director of internal medicine. National Health Insurance Hospital in Aomori
2007 Senior resident of pediatrics, Jichi Children's Medical Center Tochigi, Japan
2008 Medical director of Pediatric, Public health hospital in Nagasaki, Japan
2014 Research associate, Department of Pediatrics, Jichi Medical University
2017 Assistant Professor, Department of Pediatrics, Jichi Medical University
2019 Postdoctoral associate, Dr. Parchem lab, Center for Gene Therapy, Baylor College of Medicine, TX, US
2021 Manager in Pediatrics, Tochigi rehabilitation center hospital, Japan

Recent Related Publications (5 Papers)

1. **Kojima K**, Nakajima T, Taga N, Miyauchi A, Kato M, Matsumoto A, et al. Gene therapy improves motor and mental function of aromatic l-amino acid decarboxylase deficiency. ***Brain***. 2019;142(2):322-33.
2. Keuls R, **Kojima K**, Lozzi B, Steele J, Chen Q, Gross S, et al. Mir-302 Regulates Glycolysis to Control Cell-Cycle during Neural Tube Closure. ***Int J Mol Sci***. 2020;21(20):7534. soi: 10.3390/ijms21207534.
3. Onuki Y, Ono S, Nakajima T, **Kojima K**, Taga N, et al. Dopaminergic restoration of prefrontal cortico-putaminal network in gene therapy for aromatic l-amino acid decarboxylase deficiency. ***Brain Commun***. 2021:3(3):fcab078.doi: 10.1093/braincomms/fcab078.
4. Kuwajima M, **Kojima K**, Osaka H, Hamada Y, Jimbo E, et al. Valine metabolites analysis in ECHS1 deficiency. ***Mol Genet Metab Rep***. 2021;(29):100809. doi: 10.1016/j.ymgmr.2021.100809.
5. **Kojima K**, Anzai R, Ohba C, Goto T, Miyauchi A, Thony B, et al. A female case of aromatic l-amino acid decarboxylase deficiency responsive to MAO-B inhibition. ***Brain Dev***. 2016;38(10):959-63

Gene therapy for aromatic L-amino acid decarboxylase deficiency in Japan improved the motor and mental function of patients with various phenotypes

Karin Kojima
Jichi Medical University, Japan

Aromatic L-amino acid decarboxylase (AADC) deficiency (OMIM #608643) is an autosomal recessive neurotransmitter disorder caused by defects in the DDC gene, which encodes AADC. AADC catalyzes the formation of neurotransmitters from L-DOPA and 5-hydroxytryptophan to dopamine and serotonin, respectively. The main phonotype of AADC deficiency is movement disorder, including loss of voluntary movements, hypotonia, intermittent oculogyric crisis (OGC) and trunk dystonia. Patients also present with autonomic dysfunction, intellectual disability and emotional instability. Patients with AADC deficiency are classified as severe type (80%: bedridden and fully dependent), mild (5%: ambulatory without assistance, intellectual disability) or moderate (15%: between severe and mild). Since 2015, we have been performing gene therapy for AADC deficiency as a clinical study using the AAV2 vector carrying the DDC gene (AAV2-AADC), which expresses AADC. Eight patients with AADC deficiency (seven severe type and one moderate type) were subjected to gene therapy via the injection of AAV2-AADC into both sides of the putamen during stereotactic brain surgery.

We herein report the long-term course after gene therapy. Over a maximum of six and a half years after gene therapy, improvement of symptoms has continued in all cases, albeit to varying degrees. Before treatment, the seven severe-type patients had no head control even with full assistance and frequent dystonia attacks. However, all of these severe patients are now able to control their heads, and six are able to use walkers. Dystonia attacks disappeared in all patients. And their autonomic dysfunction also improved. The moderate-type patient was able to walk with assistance before gene therapy but could walk independently after gene therapy and is now able to go to school on her own. She also showed intellectual development and has now reached a normal level.

Positron emission tomography (PET) using FMT, an AADC tracer, showed that the FMT accumulation in the putamen after five years was at the same level as at six months after treatment, and the effect of gene therapy was sustained for a long period of time. The resting functional MRI activity was compared before and after surgery, and the functional connectivity of the basal ganglia centered on the putamen was improved after treatment.

In a series of eye-tracking assessments, we conducted three types of tests: gap-overlap, word comprehension, and perspective-taking tasks. We explored the developmental trajectories of these tasks in patients with AADC. Although there was a difference in efficacy depending on the severity of the gene mutation site and the age at the time of treatment, gene therapy improved clinical symptoms in all cases, and the effect of gene therapy was maintained even after six years. The recovery of dopamine in the putamen by this treatment is believed to have promoted the functional recovery of the basal ganglia network.

We are currently preparing for a clinical trial.

Wuh-Liang Hwu

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National Taiwan University Hospital (NTUH)
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Field of Research Pediatrics, Genetics, Gene therapy

Education

College of Medicine, National Taiwan University	M.D.
Institute of Molecular Medicine, National Taiwan University	Ph.D.

Professional Experience

Director, Department of Medical Genetics, National Taiwan University Hospital	2006-2012
Deputy Director, Department of Pediatrics, National Taiwan University Hospital	2018-2021
Professor, Department of Pediatrics, National Taiwan University Hospital	2010-now

Recent Related Publications

1. Tai CH, Lee NC, Chien YH, Byrne BJ, Muramatsu SI, Tseng SH, **Hwu WL**. Long-Term Efficacy and Safety of Eladocagene Exuparvovec in Patients with AADC Deficiency. ***Mol Ther***.2021:S1525-0016(21)00576-1
2. H**wu PW**, Kiening K, Anselm I, Compton DR, Nakajima T, Opladen T, Pearl PL, Roubertie A, Roujeau T, Muramatsu SI. Gene therapy in the putamen for curing AADC deficiency and Parkinson's disease. ***EMBO Mol Med***. 2021;13:e14712.
3. Tseng CH, Chien YH, Lee NC, Hsu YC, Peng SF, Tseng WI, **Hwu WL**. Gene therapy improves brain white matter in aromatic l-amino acid decarboxylase deficiency. ***Ann Neurol***. 2019 May;85:644-652.
4. Chien YH, Lee NC, Tseng SH, Tai CH, Muramatsu S, Byrne BJ, **Hwu WL**. Efficacy and safety of AAV2 gene therapy in children with aromatic L-amino acid decarboxylase deficiency: an open-label, phase 1/2 trial. ***Lancet Child Adolesc Health***. 2017;1:265–73
5. Lee NC, Lee YM, Chen PW, Byrne BJ, **Hwu WL**. Mutation-adapted U1 snRNA corrects asplicing error of the dopa decarboxylase gene. ***Hum Mol Genet***. 2016;25:5142-5147

Gene therapy with rAAV2-hAADC for patients with aromatic L-amino acid decarboxylase deficiency

Wuh-Liang Hwu

Department of Pediatrics, National Taiwan University Hospital, Taipei, Taiwan

Aromatic L-amino acid decarboxylase (AADC) deficiency is a rare autosomal recessive disorder resulting in congenital deficiency of dopamine, serotonin, and downstream monoamine neurotransmitters. Patients with severe AADC deficiency present hypokinesia and dystonic since early infancy, followed by a characteristic movement disorder, oculogyric crisis (OGC). In a natural history study in Taiwan, patients usually stopped growing after one year of age, and most of patient didn't develop any meaningful motor milestone, including head control.

Three clinical trials have been conducted in Taiwan, employing a recombinant adeno-associated virus serotype 2 containing the human cDNA encoding the AADC enzyme (rAAV2-hAADC). Viral vector was administered bilaterally in the putamen with a total of 1.8×10^{11} vg or 2.4×10^{11} vg. Patients were assessed using the Peabody Developmental Motor Scales, 2nd Edition (PDMS-2) and ^{18}F-DOPA-PET. We recently published the treatment outcomes of 26 patients. Increase in PDMS-2 score and PET signal were seen in all patients. Improvements in non-motor symptoms, including emotion instability, OGC, excessive sweating, and temperature instability, were also seen. Younger age at the time of treatment was a significant prognostic factor.

The most commonly reported TEAEs across all three studies were pyrexia and dyskinesia. Post-gene transduction dyskinesia was transient and may be related to receptor hypersensitivity. In conclusion, this gene therapy is safe and highly effective. It is currently under commercialization by PTC therapeutics as a brand name of Eladocagene exuparvovec.

Memo

Ex vivo Gene therapy

-Abstracts & Curriculum Vitae-

Naoya Uchida

Address (Affiliation) Division of Molecular and Medical Genetics,
Center for Gene and Cell Therapy,
The Institute of Medical Science, The University of Tokyo

Field of Research Hematopoietic stem cell transplantation, Gene therapy, Genome editing, Lentiviral vector

Education

Nippon Medical School Ph.D.
Nippon Medical School M.D.

Professional Experience

2020-present Associate Professor in Division of Molecular and Medical Genetics, Center for Gene and Cell Therapy, The Institute of Medical Science, The University of Tokyo, Japan
2009-present Staff Scientist in Cellular and Molecular Therapeutics Branch
NHLBI, NIH, Bethesda, MD, USA

Recent Related Publications (5 Papers)

1. Uchida N*, Li L, Nassehi T, Drysdale CM, Yapundich M, Gamer J, Haro-Mora JJ, Demirci S, Leonard A, Bonifacino AC, Krouse AE, Linde NS, Allen C, Peshwa MV, De Ravin SS, Donahue RE, Malech HL, Tisdale JF. Preclinical evaluation for engraftment of $CD34^+$ cells gene-edited at the sickle cell disease locus in xenograft mouse and non-human primate models. ***Cell Rep Med***. 2021 Apr 20;2(4):100247.
2. Uchida N*, Ferrara F, Drysdale CM, Yapundich M, Gamer J, Nassehi T, DiNicola J, Shibata Y, Wielgosz M, Kim YS, Bauler M, Throm RE, Haro-Mora JJ, Demirci S, Bonifacino AC, Krouse AE, Linde NS, Donahue RE, Ryu BY, Tisdale JF. Sustained fetal hemoglobin induction in vivo is achieved by BCL11A interference and coexpressed truncated erythropoietin receptor. ***Sci Transl Med***. 2021 Apr 28;13(591):eabb0411.
3. Drysdale CM, Nassehi T, Gamer J, Yapundich M, Tisdale JF*, Uchida N*. Hematopoietic-Stem-Cell-Targeted Gene-Addition and Gene-Editing Strategies for β-hemoglobinopathies. ***Cell Stem Cell***. 2021 Feb 4;28(2):191-208.
4. Hsieh MM, Bonner M, Pierciey FJ, **Uchida N**, Rottman J, Demopoulos L, Schmidt M, Kanter J, Walters MC, Thompson A, Asmal M, Tisdale JF*. Myelodysplastic syndrome unrelated to lentiviral vector in a patient treated with gene therapy for sickle cell disease. ***Blood Adv***. 2020 May 12;4(9):2058-2063.
5. **Uchida N***, Hsieh MM, Raines L, Haro-Mora JJ, Demirci S, Bonifacino AC, Krouse AE, Metzger ME, Donahue RE, Tisdale JF. Development of a forward-oriented therapeutic lentiviral vector for hemoglobin disorders. ***Nat Commun***. 2019 Oct 2;10(1):4479.

Hematopoietic stem cell gene therapy with a lentiviral gene delivery

Naoya Uchida

The Institute of Medical Science, The University of Tokyo, Japan

Hematopoietic stem cell (HSC)-targeted gene therapy is curative for various hereditary diseases, including immunodeficiencies, hemoglobinopathies, congenital cytopenia, and metabolic diseases. HSCs reconstitute peripheral blood for life due to their self-renewal and multipotency specific for hematopoietic lineages; therefore, a replacement or repair of pathogenic mutations/deletions in HSCs allows for one-time cure of genetic diseases. A human immunodeficiency virus type-1 (HIV-1)-based lentiviral vector system has been developed to deliver a normal or therapeutic gene to the target cell genome, and lentiviral integration can allow for long-term therapeutic gene expression in HSCs. In preliminary HSC gene therapy trials in immunodeficiencies, a γ-retroviral vector system was used for a therapeutic gene delivery; however, hematological malignancies were developed due to insertional mutagenesis (Howe SJ. J Clin Invest. 2008). The γ -retroviral vector system is generated from murine 'leukemia' virus (likely enhancing cell expansion), which favor integration into transcription start sites (near to a promoter) in activated genes, and if the γ -retroviral vector is integrated into an oncogene, the oncogene expression can increase by the viral enhancer in the long terminal repeat (LTR), thereby inducing leukemia (Wu X. Science. 2003). In contrast, a new generation of lentiviral vector system has a minimal risk of leukemia development, since this vector was generated from human 'immunodeficiency' virus (likely reducing cell expansion), which are more equally integrated into a coding region in activated genes, and the viral enhancer is removed from the LTR to produce self-inactivation. The HSC gene therapy trials with lentiviral transduction result in phenotypic correction in 80-90% patients with various diseases, and no insertional mutagenesis was observed for more than 200 patients (Eichler F. N Engl J Med. 2017, Cavazzana M. Nat Rev Drug Discov. 2019, Kohn DB. Nat Med. 2020, Kohn DB. N Engl J Med. 2021). Recently, 2 cases of acute myeloid leukemia were reported following an HSC gene therapy in sickle cell disease (SCD) (Leonard A. Mol Ther. 2021). The lentiviral vector was not integrated into leukemia cells in the first patient; however, in the second patient, the lentiviral integration was detected within the *VAMP4* gene in leukemia cells. The *VAMP4* is not related to oncogenes, and it was not overexpressed in leukemia cells. In addition, patients with SCD have a risk of myeloid malignancies in their natural history as well as post-transplantation. Therefore, this leukemia development is thought to be caused by disease status and/or conditioning instead of lentiviral integration. In conclusion, HSC gene therapies should improve the outlook for patients with genetic diseases.

Christopher Dott

Address (Affiliation) Vice President Clinical Development, Orchard Therapeutics Ltd.

Field of Research Gene Therapy

Education

1974-1977	Queen Mary College, London University	BSc.	Biology
1980-1984	Royal Free Hospital, School of Medicine, University of London	Ph. D.	Biochemistry

Professional Experience

1985-1988	Senior Clinical Research Associate G D Searle Ltd , UK
1988-1993	Clinical Research Manager, SmithKline Beecham, UK
1993-1999	Director Medical and Regulatory Affairs, Speywood Pharmaceuticals, UK
1999-2005	International Project Director, Ipsen Ltd, UK
2005-2006	Senior Director Clinical Affairs, Inamed, UK
2006-2018	Principle Consultant, CSD Pharma Consulting Ltd UK
2018 -present	Vice President Clinical Development, Orchard Therapeutics Ltd. UK

Recent Related Publications (5 Papers)

1. Ferrua F, Cicalese MP, Galimberti S, Scaramuzza S, Giannelli S, Pajno R, Dionisio F, Biasco L, Castiello MC, Casiraghi M, Facchini M, Finocchi A, Metin A, Orange JS, Albert MH, Petrescu C, Bosticardo M, Villa A, **Dott C**, vanRossem K, Valsecchi MG, Ciceri F, Roncarolo MG, Naldini L, Aiuti A. Safety and clinical benefit of lentiviral hematopoietic stem cell gene therapy for Wiskott-Aldrich syndrome. ***Blood*** 2015; 126;259 [ASH 2015]
2. Ferrua F, Cicalese MP, Galimberti S, Giannelli S, Dionisio F, Bernardo ME, Migliavacca M, Barzaghi F, Assanelli A, Scaramuzza S, Brigida I, Salerio F, Pajno R, Castiello MC, Casiraghi M, Facchini M, Fossati C, Finocchi A, Metin A, Orange JS, Albert MH, Petrescu C, Xhafa M, Pesce F, Bosticardo M, Villa A, **Dott C**, van Rossem K, Valsecchi MG, Ciceri F, Roncarolo MG, Naldini L, Aiuti A : Safety and clinical benefit of lentiviral hematopoietic stem cell gene therapy for Wiskott-Aldrich syndrome: the TIGET-WAS clinical trial. ***ESID*** 2016
3. Ferrua F, Cicalese MP, Galimberti S, Giannelli S, Dionisio F, Bernardo ME, Migliavacca M, Barzaghi F, Assanelli A, Scaramuzza S, Brigida I, Salerio F, Pajno R, Castiello MC, Casiraghi M, Facchini M, Fossati C, Finocchi A, Metin A, Orange JS, Albert MH, Petrescu C, Xhafa M, Pesce F, Bosticardo M, Villa A, **Dott C**, van Rossem K, Valsecchi MG, Ciceri F, Roncarolo MG, Naldini L, Aiuti A. TIGET-WAS Phase I/II Clinical Trial: Safety and Clinical Benefit of Lentiviral Hematopoietic Stem Cell Gene Therapy for Wiskott-Aldrich Syndrome. XLP-WAS 2016 Symposium London 26-27 September 2016

Orchard Therapeutics and its Gene Therapy Programs

Christopher Dott
Orchard Therapeutics Ltd.

At Orchard Therapeutics, our vision is to end the devastation caused by genetic and other severe diseases. We aim to do this by discovering, developing and commercializing new treatments that tap into the curative potential of hematopoietic stem cell (HSC) gene therapy. In this approach, a patient's own blood stem cells are genetically modified outside of the body and then reinserted, with the goal of correcting the underlying cause of disease in a single treatment.

In 2018, the company acquired GSK's rare disease gene therapy portfolio, which originated from a pioneering collaboration between GSK and the San Raffaele Telethon Institute for Gene Therapy in Milan, Italy. Today, Orchard has a deep pipeline spanning pre-clinical, clinical and commercial stage HSC gene therapies designed to address serious diseases where the burden is immense for patients, families and society and current treatment options are limited or do not exist.

Orchard are active in the primary immunodeficiencies and inherited neurometabolic disorders fields. The primary immunodeficiency disorders (PIDs) cover adenosine deaminase severe combined immunodeficiency (ADA-SCID) and Wiskott-Aldrich Syndrome (WAS). Within the ADA-SCID area Orchard have the first ex-vivo commercial product, Strimvelis®. As this product does not have a cryopreserved formulation patients can only be treated in Milan, Italy where the product was developed. WAS will be the second PID to be submitted for registration in the EU in early 2022. The results from the WAS program show pronounced reductions in the clinical symptoms of the disease such as severe infections and bleeds and restoration of the defective protein in the haemopoietic cells. Orchard also had its first inherited neurometabolic product approved in the EU in December 2020 for the treatment of metachromatic leukodystrophy disease (MLD) which is called Libmeldy®. Libmeldy is used in children with MLD who have mutations in the arylsulfatase A gene. It is given to those with late infantile or early juvenile forms of the disease who have not yet developed symptoms and those with early juvenile MLD who have initial symptoms but can still walk independently and have not yet developed mental deterioration. Subjects have been followed up for up to 11years in this program with no serious adverse events related to the product. The pipeline of products at Orchard is currently focused on a number of other rare diseases such as Mucopolysaccharidosis type I (Hurlers) and Mucopolysaccharidosis type IIIa also known as Sanfilippo syndrome. Preclinical development work is ongoing is other larger indications such as Crohn's Diseases and Frontotemporal dementia.

Memo

Special lecture

-Abstract & Curriculum Vitae-

Aiuti Alessandro

Address (Affiliation) Full professor of Pediatrics, "Vita-Salute San Raffaele" University School of Medicine, Milan, Italy
Deputy Director Clinical Research and Head of Unit, San Raffaele Telethon Institute for Gene Therapy, Milan, Italy
Chief of Clinic, Pediatric Immunohematology Unit, San Raffaele Hospital, Milan, Italy

Field of Research

-Gene transfer into human hematopoietic stem/progenitor cells using retroviral and lentiviral vectors.
-Safety and efficacy of hematopoietic stem cell gene therapy for inherited disorders (ADA, WAS, MLD, MPSI, CGD).
-Study of dynamics and fate of human hematopoietic stem cells after gene therapy.
-Genetic and immunological characterization of primary immunodeficiencies due to unknown genetic defect.

Education

School of Medicine, University of Rome "La Sapienza"	MD 1990, PhD 1996
School of Medicine, University of Milan	National Board (Hematology) 1998

Professional Experience

1997-2000	Research Scientist, Telethon Foundation, Rome, Italy
2000-2007	MD Research Scientist, Scientific Institute H.S. Raffaele, Milan, Italy
2000-2007	Haematologist, Pediatric Clinical Research Unit, SR-TIGET, Scientific Institute H.S. Raffaele, Milan, Italy
2003-2007	Head of Research Unit, SR-TIGET, Scientific Institute H.S. Raffaele, Milan, Italy
2004-2007	Member of the Committee for the Appointment and Promotions, Scientific Institute H.S. Raffaele, Milan, Italy
2004-2010	Temporary assignment of Professorship, Course of "Molecular Pediatrics", School of Medicine, "Vita-Salute" San Raffaele University, Milan, Italy
2007-present	Head of Unit. Pathogenesis and therapy of primary immunodeficiencies, SR-TIGET, Scientific Institute H.S. Raffaele, Milan, Italy
2007-2014	Haematologist, Pediatric Immunohematology Unit, San Raffaele Hospital, Milan, Italy
2007-10/2014	Associate Professor of Pediatrics, University of Roma Tor Vergata, Rome, Italy
2009-present	Coordinator of Clinical Research, SR-TIGET, Scientific Institute H.S. Raffaele, Milan, Italy
2010-2013	Head, Gene Therapy Unit, Department of Pediatrics, University of Rome "Tor Vergata", Bambino Gesù Pediatric Hospital, Rome, Italy
2011-2014	Head, Primary Immunodeficiencies (PID) outpatients' clinic, Department of Pediatrics, University of Rome "Tor Vergata", Bambino Gesù Pediatric Hospital, Rome, Italy
05/2011-present	Head, Clinical Research Unit, SR-TIGET, Scientific Institute H.S. Raffaele, Milan, Italy
11/2014-present	Director, Pediatric Immunohematology Unit, San Raffaele Hospital, Milan, Italy
01/2016-present	Full Professor of Pediatrics, "Vita-Salute" San Raffaele University, Milan, Italy
11/2016-present	Director, Pediatrics Residency Program, "Vita-Salute" San Raffaele University, Milan, Italy
04/2017-present	Deputy Director Clinical Research, SR-TIGET, Scientific Institute H.S. Raffaele, Milan, Italy

Recent Related Publications (5 Papers)

1. Ferrua F, Cicalese MP, **Aiuti A**, et al. (2019) . Lentiviral haematopoietic stem/progenitor cell gene therapy for the treatment of Wiskott-Aldrich syndrome: interim results of a non-randomized, open-label, phase 1/2 clinical study. ***Lancet Hematology***. 6: e239-e253. Epub 2019 April 10
2. Scala S, Basso-Ricci L, **Aiuti A**, et al. (2018). Dynamics of hematopoietic stem/progenitor cells after autologous transplantation in humans. ***Nat Med***. 24:1683-1690. Epub 2018 Oct 1.
3. Ferrari G, Thrasher AJ, **Aiuti A**. (2021). Gene therapy using haematopoietic stem and progenitor cells. ***Nat Rev Genet***. 22: 216-234. Epub 2020 Dec 10.
4. Gentner B, Tucci F, **Aiuti A**, et al.; MPSI Study Group.(2021). Hematopoietic Stem- and Progenitor-Cell Gene Therapy for Hurler Syndrome. ***N Engl J Med***. 385:1929-1940.
5. Fumagalli F, Calbi V, **Aiuti A**, et al. (2021). Lentiviral haematopoietic stem-cell gene therapy for early-onset metachromatic leukodystrophy: long-term results from a non-randomised, open-label, phase 1/2 trial and expanded access. ***The Lancet***. In press.

Hematopoietic stem cell gene therapy for inborn errors of immunity and metabolism

Aiuti Alessandro

San Raffaele Telethon Institute for Gene Therapy, Milan, Italy

Gene therapy using haematopoietic stem and progenitor cell (HSPC) has been shown an effective treatment for inborn errors of immunity, such as ADA-SCID, SCID-X1, chronic granulomatous disease. Several studies have shown engineered HSPCs can also be used to cross-correct non-haematopoietic cells in neurodegenerative metabolic diseases such as metachromatic leukodystrophy and mucopolysaccharidosis type I. In Europe, medicinal products based on autologous HSPCs have been approved for clinical use and others are under clinical development. I will discuss the most recent advances and challenges in HSPC gene therapy.

Memo

Acknowledgments

後援　一般社団法人日本遺伝子細胞治療学会

共催　NPO 法人日本ライソゾーム病研究センター

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当番幹事　山形　崇倫

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ー主なパイプラインー
・孤発性筋萎縮性側索硬化症(ALS)、AADC欠損症、パーキンソン病、脊髄小脳失調症(1型)、テイ-サックス病、GLUT1 欠損症、アルツハイマー病、OTC欠損症、ニーマンピック病C型

ー当社の特徴ー
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- ◆ カルタヘナ二種申請業務
- ◆ 治療申請資料作成　など

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・pipetty独自のハンドウォーミング抑制機能搭載

新しい生きるを、創る。

独自技術で難病に挑み、ひとりの「生きる」に希望をとどける。
ユニークな機能性食品で、みんなの「生きる」を健やかにする。
新しい時代の、新しい生きるを、わたしたちは、創っていく。

健康未来、創ります
日本新薬

まだないくすりを
創るしごと。

世界には、まだ治せない病気があります。

世界には、まだ治せない病気とたたかう人たちがいます。

明日を変える一錠を創る。

アステラスの、しごとです。

明日は変えられる。

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