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ABSTRACT BOOK

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CELL & GENE THERAPY SUMMIT-2024

The Global Cell & Gene Therapy Summit 2024

July 08-10, 2024 (Hybrid) | Boston, MA

Monday, July 08, 2024

SESSION: GENOME ENGINEERING, GENE REGULATION, GENE EDITING BREAK THROUGHS & THERAPEUTIC APPROACHES

Group II Intron Reverse Transcriptases: Drivers of Genome Evolution and Toolboxes for Genome Engineering

Alan M. Lambowitz

Departments of Molecular Biosciences and Oncology, The University of Texas at Austin, TX, USA

Abstract:

Reverse transcriptase (RTs) are ancient enzymes that evolved from an RNA-dependent RNA polymerase, likely during the transition from an RNA to DNA world. They are prevalent in bacteria, both as RTs encoded by RNA-guided retrotransposons called mobile group II introns and as "domesticated" chromosomally encoded RTs that evolved from group II intron RTs to carry out diverse cellular functions. Mobile group II introns are thought to have entered ancestral eukaryotes with bacterial endosymbionts that gave rise to mitochondria and chloroplasts and proliferated in what became the nuclear genome, a key event in evolution of higher organisms. In eukaryotes, group II intron RNA domains evolved into spliceosomal snRNAs and group II intron RTs evolved into the core spliceosomal protein Prp8, as well as non-LTR-retrotransposon RTs, an enzyme family that includes human LINE-1 element RTs. This was followed by the evolution or more divergent telomerase and retroviral RTs. Reflecting their evolutionary history, all RTs share a common structural framework comprised of finger, palm, and thumb regions that fold into a hand-like structure, forming a cleft that contains the RT ac-tive site. The RT fingers and palm contain 7 conserved sequence blocks (RT1-7) positioned around the RT active site in a manner that contributes to RT activity. Bacterial and eukaryotic non-LTR-retrotransposons RTs contain three additional regions that have been lost by retroviral RTs: an N-terminal extension (NTE) with an RT0 loop and two extended regions (RT2a and RT3a) between conserved RT sequence blocks. These additional regions contribute to tighter substrate binding pockets that enable high fidelity, processivity, and strand displacement activity of group II intron RTs, as well as an efficient, highly accurate end-to-end template-switching activity that has been used for RNA-seq adapter addition and enables accurate synthesis of fused cDNAs. Domesticated bacterial RTs have evolved to perform a variety of different bio-logical functions, including by using novel mechanisms that could not have been envisioned or rationally designed by human beings. In addition to a variety phage defence mechanism, these biological functions include site-specific integration of RNA into DNA genomes by RT-Cas1 proteins comprised of an RT domain fused directly to a DNA integrase, and double-strand break repair via microhomology-mediated end-joining, dependent upon conserved structural features of non-LTR-retroelement RTs but optimized for use as a cellular function in class of domesticated bacterial group II intron-like RTs. These novel biochemical mechanisms have potential to be used in different ways for genome engineering applications.

Biography:

Prof. Alan M. Lambowitz is Mr. and Mrs. A. Frank Smith, Jr. Regents Chair in Molecular Biology, Professor of Molecular Biosciences and Oncology, College of Natural Sciences and Dell Medical School at University of Texas at Austin, TX. He is Member National Academy of Sciences and American Academy of Arts and Sciences.

Prof. Alan known for his pioneering research in molecular biology, particularly in intron splicing and mitochondrial ribosomal assembly. His career spans significant contributions at Rockefeller University, St. Louis University School of Medicine, and Ohio State University, where he explored mitochondrial DNA and plasmids in fungal strains. Since 1997, Prof. Lambowitz has led The Institute for Cellular and Molecular Biology at UT Austin, garnering recognition such as Fellowships in the American Academy of Arts and Sciences, the American Association for the Advancement of Science, and the American Academy for Microbiology. His research, often centered on Neurospora Crassa, has reshaped understanding of bacterial splicing mechanisms, particularly group 2 introns, challenging and advancing scientific knowledge in the field.

SESSION: GENOME ENGINEERING, GENE REGULATION, GENE EDITING BREAK THROUGHS & THERAPEUTIC APPROACHES

Epigenetic Editing with CRISPR-GNDM: Novel Muscle-tropic AAV Vectors Deliver Promising Single-dose Treatment for LAMA2-CMD

T. Yamagata*, Y. Qin, T. Akbulut, and Y. Nakashima
Modalis Therapeutics Inc., MA, USA

Abstract:

Modalis Therapeutics, founded in 2016, is a pioneer in the development of CRISPR-based epigenetic editing technology. Epigenetic editing holds great promise as a next-generation therapy platform. Our proprietary CRISPR-GNDM® epigenetic editors are precisely engineered to target genes and modify local nucleosomes without DNA cleavage, achieved through coupling an engineered Cas9 variant with potent epigenetic modifiers.

We present our lead molecule MDL101, a GNDM construct packaged in an innovative muscle-tropic AAV capsid, designed for treating the severe, early-onset congenital muscular dystrophy known as LAMA2-CMD. In the DyW mouse disease model, MDL101 demonstrated robust distribution of the vector to muscle tissue, coupled with strong expression of GNDM and the target gene mRNA induction, and notable long-term functional improvement of the disease phenotype. In NHPs, MDL101 displayed up to a 60-fold increase in GNDM expression in muscle tissue compared to AAV9, with a comprehensive safety profile devoid of obvious toxicity. Taken together, MDL101 showcases compelling preclinical proof of concept with a favorable safety profile, underscoring the promise of epigenetic medicine for future therapeutics.

Keywords: CRISPR-Cas; Epigenetic Editing; Muscular dystrophy; Muscle tropic AAV

Biography:

Dr. Yamagata serves as the Chief Scientific Officer at Modalis Therapeutics, advancing the development of a novel therapeutic platform using epigenetic editing technology since 2016. Under his leadership, Modalis's lead program has emerged as one of the frontrunners among pipelines in burgeoning peer companies.

With over 15 years of experience in biotechnology, Dr. Yamagata possesses specialized expertise in immunology, molecular biology, and genetics. His extensive medical background includes dedicated years treating cancer patients with haematological disorders. Leveraging his profound knowledge of biomedical science, Dr. Yamagata aims to address unmet medical needs through tackling the most promising indications for epigenetic medicine.

SESSION: GENOME ENGINEERING, GENE REGULATION, GENE EDITING BREAK THROUGHS & THERAPEUTIC APPROACHES

Cis-regulatory Networks of key Methylation Sites Describe Inter-patients Transcriptional Variation

A. Hellman*, Y. Edrei, R. Levy, D. Kaye, A. Marom, and B. Radlwimmer

Department of Developmental Biology and Cancer Research, The Institute for Medical Research Israel-Canada (IMRIC), The Hebrew University-Hadassah Medical School, Israel

Abstract:

Common diseases manifest differentially between patients, but the genetic origin of this variation remains unclear. To explore possible involvement of gene transcriptional-variation, we produce a DNA methylation-oriented, driver-gene-wide dataset of regulatory elements in human glioblastomas and study their effect on inter-patient gene expression variation. In 175 of 177 analyzed gene regulatory domains, transcriptional enhancers and silencers were intermixed. Under experimental conditions, DNA methylation induces enhancers to alter their enhancing effects or convert into silencers, while silencers are affected inversely. High-resolution mapping of the association between DNA methylation and gene expression in intact genomes reveals methylation-related regulatory units (average size = 915.1 base-pairs). Upon increased methylation of these units, their target-genes either increased or decreased in expression. Gene-enhancing and silencing units constitute cis-regulatory networks of genes. Mathematical modeling of the networks highlights indicative methylation sites, which signified the effect of key regulatory units, and add up to make the overall transcriptional effect of the network. Methylation variation in these sites effectively describe inter-patient expression variation and, compared with DNA sequence-alterations, appears as a major contributor of gene-expression variation among glioblastoma patients. We describe complex cis-regulatory networks, which determine gene expression by summing the effects of positive and negative transcriptional inputs. In these networks, DNA methylation induces both enhancing and silencing effects, depending on the context. The revealed mechanism sheds light on the regulatory role of DNA methylation, explains inter-individual gene-expression variation, and opens the way for monitoring the driving forces behind deferential courses of cancer and other diseases.

Keywords: Cancer driver genes; Cis-regulatory elements; DNA methylations; Expression variation

Biography:

Professor Hellman received his education at the Hebrew University of Jerusalem, The Whitehead Institute at Massachusetts Institute of Technology, and Harvard Medical School. Since 2007, he has led a dedicated research team investigating the epigenetic origins of phenotypic diversity. Additionally, Professor Hellman serves as the chair of the Program for Computational Medicine at the Hebrew University-Hadassah Medical School.

SESSION: CELL AND GENE THERAPIES FOR OCULAR DISORDERS

The Future of Stem Cell Therapy in Ocular Disorders

Ula V. Jurkunas

Cornea Center of Excellence, Harvard University, MA, USA

Abstract:

There have been a lot of advances in treatment of ocular disorders with ocular and nonocular stem cells, including generation of retinal and corneal cells from embryonic and iPSC cells. To tackle corneal diseases, we developed a two-stage manufacturing process utilizing cultivated autologous limbal epithelial cells (CALEC) to treat blindness caused by unilateral limbal stem cell deficiency (LSCD) and conducted a phase I/II clinical trial to evaluate its feasibility, safety, and preliminary efficacy. Participants with unilateral LSCD were enrolled at a single clinical center. Cellular grafts were produced in a two-stage manufacturing process following a GMP-compliant protocol with strict quality measures for product release. Efficacy outcomes were based on improvement in corneal epithelial surface integrity (complete success) or improvement in extent of corneal vascularization and/or participant symptomatology (partial success). CALEC grafts met release criteria in 14 (93%) of 15 participants and 86%, 93%, and 92% of grafts resulted in complete or partial success at 3, 12, and 18 months, respectively. After first stage manufacturing, intracellular adenosine triphosphate levels correlated with colony forming efficiency (r=0.65, 95% CI [0.04, 0.89]), identifying novel product release criteria. Our feasibility, safety, and efficacy results provide strong support for establishing cellular therapy products as a viable option for patients with LSCD.

Biography:

Dr. Ula Jurkunas is a leading corneal and refractive surgeon at Mass Eye and Ear, where she also researches Fuchs Endothelial Corneal Dystrophy and stem cell transplantation. She trains residents and fellows and serves as Associate Director of the Cornea Service and Co-Director of the Harvard Ophthalmology Cornea Center of Excellence. Dr. Jurkunas received the prestigious K12-Harvard-Vision Clinical Scientist Development Program Award in 2006 and the PACT grant from the National Heart, Lung, and Blood Program. Her research, funded by major grants, has led to numerous publications and global presentations.

SESSION: CELL AND GENE THERAPIES FOR OCULAR DISORDERS

'Mass-Scale' Cell Therapy for Corneal Endothelial Disease

Greg Kunst

Aurion Biotech, WA, USA

Abstract:

Corneal endothelial diseases (CED) affect 4% of eyes over the age of 40, or tens of millions of people globally. CED is caused by inherited disease (Fuchs Endothelial Corneal Dystrophy), aging and/or surgical trauma. If left untreated, the cornea will swell and become cloudy, causing loss of vision. Due to a chronic shortage of transplant tissue, most people with CED will face the inevitable onset of blindness. Aurion Biotech's AURN001 cell therapy has the potential to eradicate this disease. From a single donor, the company can manufacture more than 1,000 doses of fully differentiated, allogeneic corneal endothelial cells. The company has received approval from Japan's PMDA and is currently enrolling patients in a Phase 1 / 2 Trial in the U.S. Aurion Biotech CEO Greg Kunst will describe the company's recent milestones and discuss clinical outcomes from the 130 subjects that have been treated successfully with the company's cell therapy.

Biography:

Greg Kunst is the CEO of Aurion Biotech, bringing a wealth of experience from his six years at Glaukos Corporation, where he was promoted to vice president of global marketing, a role in which he managed market access, reimbursement, health economics and outcomes research, government affairs, and business development. Greg was also the global franchise director for Alcon's glaucoma surgery and retina pharmaceutical divisions and led global market access at Kinetic Concepts, Inc. (Acelity Inc.). He also serves as a board member of Pr3vent. Greg holds an MBA from Vanderbilt University and a BS in Economics from Brigham Young University.

SESSION: CELL AND GENE THERAPIES FOR OCULAR DISORDERS

AXV-101, a New Codon-optimised *BBS1* AAV9 Vector Halts Photoreceptor and Outer Nuclear Retinal Layer Organisation Degeneration in a Dose-dependent Manner

V. Hernandez*, Guillermin, J. Grey, G. Carreno, N. Elangkovan, N. Jeffrey, M. Freitas-Martins, C. Sidoli, A. Crespo, E. Mustafa, P. Beales, and E. Cuevas

Axovia Therapeutics Ltd, United Kingdom

Abstract:

Bardet-Biedl syndrome (BBS) is an autosomal recessive disorder associated with primary cilia dysfunction, presenting with retinal dystrophy and progressive visual loss. BBS1 is the most common mutated gene found in BBS, with the missense BBS1 M390R mutation being the most common allele. We have previously demonstrated that different AAV vectors, expressing the wild-type BBS1 cDNA are safe and able to halt the retinal degeneration in the Bbs1M390R/M390R (M390R) mouse. In this study we have improved the efficacy and safety profiles with AXV-101, an AAV9 capsid vector expressing a human codon-optimised BBS1 cDNA sequence (hCOBBS1) under the regulation of the CAG promoter (AAV9-CAG-hCOBB1). To test safety, efficacy, and potency of AXV-101, 1.5µl of three doses of vector were administered subretinally and unilaterally at p7-9: low dose (6.67x1011vg/ml), medium dose (3.33x1012vg/ml) and high dose (6.67x1012vg/ml). M390R and Wild-type (WT) groups were dosed, including untreated (contralateral eyes) and subretinal injected retinae with phosphate-buffered saline (PBS) and AXV-101 formulation buffer. Functional and structural readouts were captured at 2.5-, 4- and 6-months of age and included electroretinogram (ERG) and retinal Optical Coherence Tomography (OCT). The ONL thickness of WT retinae treated with either low, medium or high doses maintain a normal structure with a stable ONL thickness at 6 months. At 2.5 months, M390R treated eyes display a dose response in ONL thickness, where PBS and buffer averages are 18 mm and 23 mm respectively, low dose at 25 mm, medium at 28 mm and high dose at 31mm. At 6 months medium and high doses treated M390R retinae have a 99.3% and 98% chance of retaining the ONL. These results were corroborated with the histological analysis 6-month after treatment. Buffer-treated eyes displayed an ONL throughout the entire retina about 2 nuclei thick, However, four out of five M390R eyes treated with medium dose exhibit rescue with an ONL thickness between 9 and 10 nuclei observed, compared with the 11 to 12 nuclei of WT controls. ERG responses show a high variability. Notably, rod photoreceptor activity measured by scotopic a and b wave amplitude, is significantly improved in both medium and high dose treatment groups when compared to buffer treated at 4 months. At 6 months, the rescue is maintained for medium and high dose treated eyes for scotopic b wave measurements. In summary, these results indicate that AXV-101 can halt retinal degeneration in the M390R retinae in a dose dependent manner.

Keywords: Bardet-Biedl syndrome; AAV9; Retinal degeneration; Gene therapy; Ciliopathies

Biography:

Victor Hernandez completed his BSc in Biology at Barcelona University and his PhD in the Genetic Department on the development of the hindbrain. In 2008 he joined Prof. Beales lab at the Institute of Child Health, UCL where he started working on the animal modelling the new genes that were discovered to be causative of the ciliopathies. He studied Bardet-Biedl Syndrome (BBS) genes, a multi-syndromic disorder with characteristic truncal severe obesity, brain anomalies and retinal degeneration but also other linked human disorders like craniofacial anomalies. In 2013 he started leading the research on gene therapy for Bardet-Biedl Syndrome using multiple Adeno-associated virus approaches and routes of administration. His research was boosted when the lab received the support of Apollo Therapeutics to quickly advance these transformative therapies. Victor joined Brunel University London in January 2019, where he is a Senior Lecturer in Biomedical Sciences. In July 2020 he cofounded Axovia Therapeutics, a new biotech with the mission to develop clinical gene therapy solutions for multisyndromic ciliopathies where he is the Chief Scientific Officer (CSO)

SESSION: ADVANCEMENTS IN CELL AND STEM CELL-BASED THERAPIES

An Overview of Stem Cell Transplant: Current Scenario in Tissue Regeneration

Anand Srivastava

Global Institute of Stem Cell Therapy and Research, CA, USA

Abstract:

The experimental evidence strongly suggest that embryonic stem (ES) cell lines can be created from human blastocyst-stage embryos and stimulated to develop into practically all types of cells found in the body. Cellular treatments produced from ES cells have attracted fresh interest. The potential utility of ES cells for gene therapy, tissue engineering, and the treatment of a wide spectrum of currently untreatable diseases is simply too vital to ignore; however, further improvements in our understanding of the basic biology of ES cells are required to deliver these forms of therapy in a safe and efficient manner. In this meeting, I'll share my research using ES cells and how they can be used to treat hematopoietic and neurodegenerative disorders.

Biography:

Dr. Anand Srivastava is a Chairman and Co-founder of California based Global Institute of Stem Cell Therapy and Research (GIOSTAR) headquartered in San Diego, California, (U.S.A.). The company was formed with the vision to provide stem cell-based therapy to aid those suffering from degenerative or genetic diseases around the world such as Parkinson's, Alzheimer's, Autism, Diabetes, Heart Disease, Stroke, Spinal Cord Injuries, Paralysis, Blood Related Diseases, Cancer and Burns. Dr. Srivastava has been associated with leading universities and research institutions of USA. In affiliation with University of California San Diego Medical College (UCSD), University of California Irvine Medical College (UCI), Salk Research Institute, San Diego, Burnham Institute For Medical Research, San Diego, University of California Los Angeles Medical College (UCLA), USA has developed several research collaborations and has an extensive research experience in the field of Embryonic Stem cell which is documented by several publications in revered scientific journals. Furthermore, Dr. Srivastava's expertise and scientific achievements were recognized by many scientific fellowships and by two consecutive award of highly prestigious and internationally recognized, JISTEC award from Science and Technology Agency, Government of Japan. Also, his research presentation was awarded with the excellent presentation award in the "Meeting of Clinical Chemistry and Medicine, Kyoto, Japan. Based on his extraordinary scientific achievements his biography has been included in "WHO IS WHO IN AMERICA" data bank two times, first in 2005 and second in 2010.

SESSION: ADVANCEMENTS IN CELL AND STEM CELL-BASED THERAPIES

Innovative Approaches for Developing Pluripotent Stem Cell-based Therapies

Erin A. Kimbrel

Astellas Institute for Regenerative Medicine, MA, USA

Abstract:

Keywords: Preclinical models; AI; Automation; Engineering

Biography:

Erin Kimbrel, PhD is the newly appointed Head of Astellas Institute for Regenerative Medicine (AIRM). With previous roles at AIRM, Ocata Therapeutics, and Advanced Cell Technologies, she has extensive experience developing PSC-based therapies across a broad range of therapeutic areas including ophthalmology, immune-related indications, vascular and liver disease. Dr. Kimbrel is a former Fulbright Scholar and holds a Ph.D. in Cancer Biology from Duke University. She completed post-doctoral training at the Dana-Farber Cancer Institute and is a co-author on numerous publications and patents.

SESSION: ADVANCEMENTS IN CELL AND STEM CELL-BASED THERAPIES

Pioneering Macrophage Cell Therapy in End Stage Liver Disease

Amir Hefni

Resolution Therapeutics, United Kingdom

Abstract:

Resolution Therapeutics is a clinical-stage biopharmaceutical company pioneering macrophage cell therapy for transformative outcomes in inflammatory organ diseases. The Company leverages its proprietary platform to engineer autologous macrophages with distinct pro-regenerative properties as cell therapy medicines capable of delivering superior patient outcomes across the spectrum of inflammatory organ disease. Resolution's initial focus is on developing RTX001, its lead product candidate with first-in-class potential supported by preclinical data demonstrating anti-fibrotic and anti-inflammatory advantages relative to non-engineered macrophages, for patients diagnosed with end-stage liver disease. The Company is also advancing efforts to expand the potential of its platform beyond the liver into indications where engineered macrophages have therapeutic potential. Resolution Therapeutics is based in Edinburgh and London.

Biography:

Amir is the CEO of Resolution Therapeutics. Prior to joining Resolution, he was the Global Head of Cell and Gene Therapy at Novartis where he was responsible for the company's global product development, manufacturing, supply chain and commercialisation of innovative cell therapies. Previously, he was a Global Asset Lead in Oncology at Ipsen and was Executive Director US Oncology at Bristol-Myers Squibb. Amir holds a BSc and PhD in Pharmacology from King's College London and an MBA from Warwick Business School.

SESSION: ADVANCEMENTS IN CELL AND STEM CELL-BASED THERAPIES

ProtoNK™ Cells from Pluripotent Stem Cells: Therapeutics for All Patients

Shi-Jiang (John) Lu

HebeCell Corporation, MA, USA

Abstract:

NK cells recognize and kill targets without HLA restriction and do not cause GvHD, representing an ideal off-the-shelf cellular immunotherapy product. Next generation designer NK cells can be manufactured from donors and pluripotent stem cells (PSC) which can be easily genetically engineered with CARs or desired gene edits. The establishment of permanent CAR/gene edited-PSC lines allows manufacturing of unlimited as well as more efficacious NK cells and will provide inexhaustible cell therapeutics readily available for all patients. However, the major challenge facing NK cells as therapeutics is how to produce industrial scale of healthy and efficacious NK cells. HebeCell has developed a robust proprietary 3D- ProtoNK™ platform technology for industrial scale PSC expansion and NK cell differentiation with superior scalability and consistency compared to traditional approaches. Our platform first exponentially expands PSCs, then differentiates into NK cells with industrial scale, which is a defined, serum- and feeder-free system. A majority of ProtoNK™ cells are CD8+, which are substantially more potent than current sources of NK cells. ProtoNK™ cells efficiently killed multiple blood and solid cancer cells *in vitro* and significantly increased the survival of mice inoculated with AML or osteosarcoma with pulmonary metastasis. Furthermore ProtoNK™ cells also significantly inhibited/prevented Ewing sarcoma lung metastasis, paving the way for metastatic cancer treatment. With the development of next generation bioreactors and logistics our 3D-ProtoNK™ platform will ultimately make ProtoNK™ products affordable and available for ordinary patients worldwide.

Biography:

Shi-Jiang (John) Lu, PhD, MPH, is currently the President and CEO of HebeCell Corporation, focusing on the development and clinical translation of regenerative medicine and cell therapy technologies, especially PCS-CAR-NK cells for the treatment of cancer, autoimmune and viral infectious diseases. Before establishing HebeCell, he was the Senior Director of Research at Advanced Cell Technology/Ocata Therapeutics, which was acquired by Astellas Pharma in 2016. John is an expert in stem cell biology and regenerative medicine with 20 years of experiences. He has been conducting translational research and discovery of novel therapeutic strategies utilizing human pluripotent stem cells (PSC) and their derivatives. The goal of his research is to generate human PSC-derived products for the treatment of human diseases. He also has extensive experience in process development and large-scale production of human PSC derivatives under defined conditions for clinical trials. John is the inventor of more than 20 patents in stem cell field: in an analysis of global stem cell patent landscape by Nature Biotechnology in 2014, John's patent application and citation ranked No. 7 and No. 5, respectively. In addition to stem cell research, Dr. Lu also has more than 10 years of experiences in cancer research. John received his BS degree in Biochemistry from Wuhan University, MSc degree in Oncology/Pathophysiology from Peking Union Medical College, MPH degree in Molecular Toxicology/Environmental Sciences from Columbia University and PhD degree in Molecular Cancer Biology from University of Toronto.

SESSION: ADVANCEMENTS IN CELL AND STEM CELL-BASED THERAPIES

Jump Start Allogenic Cell Therapies using cGMP-Grade TARGATT Master iPSCs

Ruby Tsai*, Alfonso Farruggio, Simon Wu, and Lin Jiang
Applied StemCell, Inc., CA, USA

Abstract:
Induced pluripotent cells (iPSCs) for site-specific DNA-fragment knock-in are essential for developing and manufacturing the next generation of cell therapeutic products. Traditional genome editing technologies, such as CRISPR/Cas9 systems, can be used to establish stable knock-in cell lines; however, transgene size is limited with low knock-in efficiency. Furthermore, substantial licensing fees or inaccessible to CRISPR/Cas9 license prohibit moving the engineered cell line into product development and manufacturing. To generate a ready-to-use cGMP grade iPSC line for site-specific therapeutic gene knock-in, we adapted the TARGATT system by integrating a landing pad into our proprietary Hipp11 locus (H11) using MAD7 in a cGMP-grade iPSC line, and isolated desired clones harbouring the landing pad. With an established cGMP-grade TARGATT iPSC line, we have inserted a single copy of RFP construct at the H11 locus to verify efficiency of knock-in (insertion) as well as expression robustness and the ability of engineered iPSCs to be differentiated into natural killer (NK) cells (iPSC-derived NK cells). Our data demonstrates that the TARGATT system is highly efficient and safe in many applications that require site-specific gene insertion. For example, unique therapeutic genes (such as CAR constructs) can be inserted in the cGMP TARGATT Master iPSC line and CAR-iPSC can be differentiated into NK cells or T cells for allogeneic cell therapeutics.
Keywords: Immunotherapy; Cancer - cell therapy; Stem cells; Gene editing; iPSC manufacturing

Biography:
Dr. Ruby Tsai received her PhD from Cornell University and did her post-doc research at Stanford University. She has been doing research in genome editing and stem cells over 20 years. Prior to joining ASC, Dr. Chen-Tsai worked at Stanford University for 16 years as the Director of Transgenic Research Center and Associate Director of the Stanford Cancer Institute, overseeing nine research technology labs. Her research at Stanford focused on using Parkinson patient-specific iPS cell lines and their differentiation to dopaminergic neurons as a disease model-in-a-dish. She is a co-inventor of the TARGATT™ integrase technology for site-specific gene insertion. Dr. Chen-Tsai is an author of many scientific papers and holder of over fifteen patents. Prior to becoming the CEO of Applied StemCell, Dr. Chen-Tsai led the ASC Therapeutics' gene/cell therapeutic pipeline in the past 5 years. She also led the successful filing of three pre-IND (one stem cell therapy, one gene therapy and one gene editing therapy) with the FDA.

SESSION: ADVANCEMENTS IN CELL AND STEM CELL-BASED THERAPIES

Regenerative Medicine Using Conserved Mechanisms for Women's Health

Demet (Dee) Sag
Genome2Life, MA, USA

Biography:

Dr. Sag is a renowned expert in translating science into medicine, specializing in drug and device development from bench to clinic. Known as the "Pollinator" for her thought leadership in life sciences, she has earned eight international awards and funded her own research by age 23. She established an independent lab focused on embryonic stem cell development and diseases at age 29. Dr. Sag is a pioneer in using B cells as biosensors and vaccines and contributed to the founding of the Society of Gene Therapy. She also led the creation of the first Women in Bio Chapter at RTP and initiated programs to empower young women in science. Currently, she leads Functional Trans genomics, providing consulting for translational medicine and global regulatory strategy for drug and device development.

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SESSION: ADVANCEMENTS IN CELL AND STEM CELL-BASED THERAPIES

Advancing Liver Disease Therapies: A Perfusable Vascularized Liver Organoid-on-a-chip Model

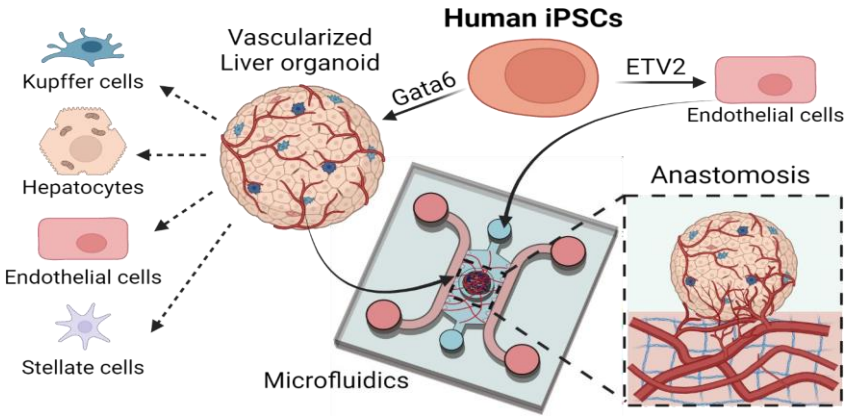
Z. Wan (Jason), R. Weiss*, and R Kamm*

Massachusetts Institute of Technology, Cambridge, MA, USA

Abstract:

Liver disease presents a significant global health challenge, necessitating innovative treatment approaches. While liver cell and stem cell transplantation, alongside hepatic microenvironment remodeling, have shown promise, there remains a pressing need for more effective cell and gene therapies. Recently, liver organoid and Liver-on-a-chip models have been used as supplement or replacement of traditional 2D cell culture and animal models, facilitating the study and optimization of liver disease therapies. However, a critical obstacle in these models is the establishment of perfusable vasculature within engineered liver tissues, crucial for the delivery of gene and cell therapies, and the faithful replication of *in vivo* disease conditions.

Figure/Scheme:



Our research is centered on the development of a vascularized liver organoid and a perfusable liver organoid-on-a-chip platform to address this challenge. Our approach focuses on enhancing vascularization within liver organoids through the orthogonal co-differentiation of induced pluripotent stem cells (iPSCs) using Gata6 and ETV2 transcription factors. Through modulation of Gata6 expression levels, we have successfully generated highly vascularized liver organoids. Furthermore, by incorporating ETV2-iPSCs and employing various strategies, we have augmented vascularization in these organoids. Subsequently, highly vascularized liver organoids are co-cultured with a microvascular bed in a novel microfluidic device. Through the induction of anastomosis between the liver organoid vasculature and microvascular bed, the liver organoids seamlessly integrate with the perfusable vasculature, culminating in a functional perfusable liver organoid model.

This platform represents a significant advancement in the study of liver regeneration, inflammation, infection, cancer, and injury. It also facilitates investigations into cell and drug transport into liver tissue, the development of cell and gene therapies-such as adeno-associated virus (AAV)-based therapies-and the preclinical toxicology evaluation of novel therapies.

Keywords: Liver Organoid; Vascularization; Microfluidic; Anastomosis; Isogenic model

Biography:

Zhengpeng Wan (Jason) is a research scientist from Prof. Roger D. Kamm's lab at the Massachusetts Institute of Technology (MIT). He obtained his Ph.D. from the Tsinghua University. His current research focuses on engineering functional microvasculature using microfluidic systems, developing vascularized tumor-on-a-chip models, and creating vascularized organoid models. Dr. Wan has received several awards, including the Ludwig Postdoc Fellowship, as well as several travel awards in conferences like Keystone, MPS, CMBE. Notably, he has been honored with the Student and Young Investigator Sections (SYIS) Scientific Excellence Award from TERMIS-AM.

SESSION: ADVANCEMENTS IN CELL AND STEM CELL-BASED THERAPIES

Augmented Anti-tumour Potency via Functionalised Mesenchymal Stem Cells for Treatment of Peritoneal Carcinomatosis

J.Y. Woo*, Y.K. Ho*, K.M. Loke, L.W. Deng, and H.P. Too*

Department of Biochemistry, National University of Singapore, Singapore

Abstract:

Mesenchymal stem cells (MSCs) have gained significant attention due to their tumor-tropic properties, making them promising vehicles for delivering cancer therapies. In previous studies, our group has shown non-virally engineered MSCs expressing a therapeutic transgene encoding cytosine deaminase and uracil phosphoribosyl transferase (CDUPRT) along with green fluorescent protein (GFP) demonstrated substantial anti-tumor activity in mice models and in companion animals with naturally occurring cancers. Clinical investigations have also shown improved response rates when combining 5-fluorouracil and Interferon-beta (IFNb) for treating peritoneal carcinomatosis (PC). However, systemic toxicities have limited the clinical use of this approach.

In this study, we investigated the feasibility of intraperitoneal administration of non-virally engineered MSCs to co-deliver the CDUPRT/5-Flucytosine prodrug system and Interferon-beta (IFNb). MSCs were genetically modified to express either CDUPRT or CDUPRT-IFNb and Flow cytometry and ELISA confirmed the expression of the transgene. We evaluated the anti-cancer efficacy of the engineered MSCs using both *in-vitro* and *in-vivo* models. *In-vitro* co-culture with of relevant PC cell lines (ES2, HT-29, and Colo-205) with engineered MSCs allowed us to assess preliminary proof-of-concept of this approach. Additionally, we established a peritoneal carcinomatosis mouse model by intraperitoneal injection of luciferase-expressing ES2 stable cells, to enable the tracking tumor burden through bioluminescence measurements.

Our results show that despite high expression of the transgene encoding CDUPRT and IFNb (CDUPRT-IFNb), there were no changes in the phenotypes of the MSCs. Transwell migration assays and *in-vivo* tracking indicated that co-expression of multiple transgenes did not impact the migratory capability of MSCs. *In-vitro* experiments demonstrated the superiority of CDUPRT-IFNb over CDUPRT-expressing MSCs in PC cell lines. Similar observations were made in an intraperitoneal ES2 ovarian cancer xenograft model, where tumor growth was inhibited by approximately 90% and 46% in mice treated with MSCs expressing CDUPRT-IFNb or CDUPRT, respectively.

Biography:

Dr. Jun Yung Woo is currently serving as a research fellow at the Department of Biochemistry, National University of Singapore. His work focuses on the clinical translation of gene-modified Mesenchymal Stem Cells (MSCs) for cancer treatment. Dr Woo developed several inventions to enhance the scale up and storage of therapeutically modified cells. These inventions are currently actively applied to the clinical manufacturing of MSC-based therapy. Dr Woo holds a PhD from the National University of Singapore. He is also a co-founder of AGEM Bio – a startup company that focuses on the development of early-stage clinical assets for oncology and regenerative medicine.

SESSION: ADVANCEMENTS IN CELL AND STEM CELL-BASED THERAPIES

Fine-tuning Immunity – *ex vivo* siRNA Treatment to Enhance Efficiency of Cell Therapies

A. Kremer*, T. Ryaykenen, R.A. Haraszti
University Hospital Tuebingen, Germany

Abstract:
Allogeneic cell therapy stands out as a potent strategy for leukemia treatment. However, allogeneic T cells can trigger the desired Graft-versus-Leukemia (GvL) effect and the unwanted Graft-versus-Host (GvH) Disease. Conventional GvHD drugs are non-selective, simultaneously inhibiting both GvH and GvL effects, resulting in widespread toxicities and complications in patients. This study explores the potential of sequence-specific siRNAs to temporarily modify the phenotype of allogeneic T cells, thereby enhancing the efficacy of cell-based therapies. Here, we designed siRNAs targeting four genes (AURKA, WAPAL, KIF15, RAN) that were shown to be upregulated during GvHD. Through screening, we identified best performing siRNAs and subjected them to functional GvH and GvL assays to assess their ability to inhibit allogeneic T cell proliferation. Treatment with siRNA targeting RAN demonstrated dose-dependent inhibition of T cell proliferation in response to both allogeneic (activated by major-mismatched dendritic cells, up to 80%, $p=0.01$, $N=5$) and non-specific (activated by CD2/CD3/CD28 beads, 60%, $p<0.0001$, $N=3$) stimuli.Yet, precision treatments preserving non-specific activation of T cells are needed in the clinic. Therefore, we aimed to further optimize the siRNA treatment in order to make it more specific to the GvH situation. First, we formulated siRNA in mesenchymal stem cell (MSC) derived extracellular vesicles (EV), which have been shown to improve GvHD and facilitate siRNA delivery to difficult-to-transfect cell types. Inhibitory effect of siRNA could be enhanced up to 50% ($p= 0.006$, $N=4$) upon allogeneic stimulus through formulation into EVs, while not affecting unspecific stimulated T cells. Second, we tested various combinations of siRNA targeting 2 or 3 different genes in functional GvH and GvL assays. We identified a mixture of 3 siRNAs (containing RAN siRNA) with the desired potency and specificity: up to 75% inhibition of T cell proliferation upon allogeneic stimulus ($p= 0.007$, $N= 3$), while no effect on GvL effect or T cell proliferation upon unspecific stimulus. Surprisingly, the exchange of any one of the 3 siRNAs diminished (by 2-7-fold) the T cell inhibitory effect, suggesting that specific genes regulate T cell activation and proliferation in a synergistic manner. Furthermore, our siRNAs induced a shift in T cell phenotype towards regulatory T cells. Our data provide proof-of-principle for siRNA mixes as a precision immunomodulatory therapy for GvHD and can be envisioned as a clinical concept for *ex vivo* treatment of stem cell grafts and /or donor lymphocytes.

Keywords: siRNA therapy; T lymphocytes; Immunotherapy

Biography:
Anastasia Kremer completed her Bachelor of Science in Biochemistry at the University of Regensburg (2013-2016) and her Master of Science in Biochemistry at the University of Regensburg (2017-2020). She completed her Master's thesis at MiNA Therapeutics Limited, London, focusing on the development of small activating RNA drugs. She started her PhD in 2021 in the lab of Reka A. Haraszti, working on the development of siRNA-based immune therapy for Graft-versus-Host Disease.

SESSION: ADVANCEMENTS IN CELL AND STEM CELL-BASED THERAPIES

Assessing T Cell Potency Using Enrich TROVO System.

Qi Zhao*, Yichong Zhang, Kirby Madden-Hennessey, and Jordan Urbani
Enrich Biosystems Inc., CT, USA

Abstract:
An effective assay to functionally partition and quantify bystander, tumour-reactive, and dysfunctional T cells is crucial for assessing cell therapy product potency and discovery of optimal TCR/CAR construct. We here present an innovative solution that leverage microscopy to visualize cytotoxicity, proliferation and chemotaxis of T cells. Utilizing our TROVO machine, we can print hydrogel-based microwell patterns on standard cell culture containers. This method allows for the separation of T cells based on their long-term persistence, cytotoxicity, and chemotaxis. The simultaneous evaluation of all these parameters can serve an effective potency/wellness metric for TIL/CAR-T samples as well as an isolation step in T cell production.
Keywords: Cell therapy; Solid tumor; T cell potency; Chemotaxis; Persistence

Biography:
Dr. Qi Zhao is a biophysicist, obtained his Ph.D in Tsinghua and training in Yale. He is the founder of Enrich Biosystems Inc. (Enrich Therapeutics Inc.), where he has led the company since January 2019. With a focus on next-generation cell manipulation platform, he has successfully secured a NIAID grant for the commercialization of the Enrich cell isolation platform. Previously, Dr. Zhao held positions at Abcam and AxioMx, focusing on antibody discovery and bioinformatics. His expertise includes device design, computational b0iology and drug discovery platforms. He is based in Branford, CT.

SESSION: GENE THERAPY: METHODS, STRATEGIES & CLINICAL APPLICATIONS/ PRECISION GENE THERAPY FOR SPECIFIC DISORDERS

Gene Therapy for Spinocerebellar Ataxia

Luis Pereira de Almeida
CNC UC, Portugal

Biography:

Dr. Luís Pereira de Almeida is a Group Leader and coordinates the CNC-Center for Neuroscience and Cell Biology and the Center for Innovative Biomedicine and Biotechnology - Associated Laboratory (CIBB) at the University of Coimbra, where he is also an Associate Professor at the Faculty of Pharmacy. He received his doctorate from the Lausanne CHUV Gene Therapy Center in Switzerland and has worked in the field of gene therapy for brain diseases such as Machado-Joseph disease. He is involved in several initiatives including the coordination of GeneT - a Teaming project of schedule Horizon Europe, to create a new Center of Excellence in Gene Therapy.

SESSION: GENE THERAPY: METHODS, STRATEGIES & CLINICAL APPLICATIONS/ PRECISION GENE THERAPY FOR SPECIFIC DISORDERS

Next Generation Synthetic DNA

E. Cuevas

4basebio Discovery Ltd., United Kingdom

Abstract:

mRNA production is limited by availability of high quality, GMP grade DNA. Synthetic DNA produced enzymatically can address the draw backs associated with plasmid derived DNA templates.

opDNA is a synthetic DNA template with a 3' open end, which can feed directly into IVT processes without the need for linearisation. opDNA is devoid of a bacterial backbone and can be designed with long continuous poly-(A) tails encoded within the sequence

opDNA achieves significantly higher mRNA yields, comparable proinflammatory cytokine/chemokine responses, and equivalent gene expression as compared to plasmid derived templates.

Next generation delivery systems such as Hermes™ nanoparticles, which offer enhanced long term stability and comprise a targeting mechanism, can enable wider use of nanoparticle based delivery across a range of therapeutic areas.

Keywords: Synthetic DNA; Cell-free DNA; mRNA therapies; Vaccines; AAV

Biography:

Elisa Cuevas is a neurodevelopmental and molecular biologist with over 15 years' experience in academia and the biotechnology industry. Elisa earned her PhD from the Free University in Berlin, where she investigated the role of miRNA-target genes during CNS development, using gene editing techniques. She then moved to a postdoctoral fellowship at UCL, where she explored the use of cell and gene therapy to treat ophthalmological conditions. She then served as Laboratory Director at a startup company spun out from UCL. Currently, she leads the New Project Development team at 4basebio, leveraging her scientific expertise to expand their commercial portfolio.

CELL & GENE THERAPY SUMMIT-2024

The Global Cell & Gene Therapy Summit 2024

July 08-10, 2024 (Hybrid) | Boston, MA

Monday, July 08, 2024

SESSION: GENE THERAPY: METHODS, STRATEGIES & CLINICAL APPLICATIONS/ PRECISION GENE THERAPY FOR SPECIFIC DISORDERS

Integrated Bioanalytical Approach to Characterize the Cellular Kinetics and Biodistribution to Support *ex vivo* and *in vivo* Gene Therapy

Hiroshi Sugimoto

Takeda Development Center Americas Inc., Cambridge, MA, USA

Abstract:

The definition and characterization of the cellular kinetics and biodistribution for *in vivo* and *ex vivo* gene therapy products are complex and challenging due to the multiple assay platform requirements to determine the pharmacokinetics and pharmacodynamics. In the case of *ex vivo* gene therapy (i.e., CAR-T cell therapy), the pharmacokinetic measurement includes cellular kinetics in systemic and biodistribution to the tumor or other tissues. The bioanalytical assay platform may include qPCR/ddPCR for transgene copy number, flow cytometry for the CAR expression and imaging technique. In the case of *in vivo* gene therapy, the pharmacokinetic measurement includes biodistribution and vector shedding. The bioanalytical assay platform may include qPCR/ddPCR for vector genome, RT-qPCR/ RT-ddPCR for transgene mRNA, and LBA or LC/MS for transgene protein. In addition, quantitative measurements of enzymatic activity resulting from the expression of a transgene protein are often required as a part of the pharmacodynamic assessment and downstream pathway-related biomarker measurements. This presentation will showcase the multifaceted approaches in supporting the AAV-based gene and CAR-T cell therapies in the nonclinical pharmacokinetics and pharmacodynamics study.

Biography:

Dr. Sugimoto is the Associate Director at Takeda Development Center Americas Inc. currently leading the research project support team for the cell therapy drug discovery and genomic biomarker. He has orchestrated the strategic assay platform for Takeda's cell/gene therapy research and development program to better understand the mechanism of action and biodistribution in drug discovery and development process. He served as a chair of the Bioanalysis Center of Excellence for Takeda Boston, San Diego and Japan to lead the discussion with a stronger scientific outcome. Previously, he served as a DMPK representative in oncology and neuroscience in Japan.

Dr. Sugimoto received Ph.D. in pharmaceutical science in 2016. He has been a member of the Applied Pharmaceutical Analysis organizing committee, the AAPS Gene and Cell Therapy BA leadership and a key opinion leader at the WRIB meeting. He has contributed to multiple scientific journals including Analytical Chemistry, The AAPS Journal, Drug Metabolism and Disposition and patent submission.

SESSION: GENE THERAPY: METHODS, STRATEGIES & CLINICAL APPLICATIONS/ PRECISION GENE THERAPY FOR SPECIFIC DISORDERS

Non-Lipid Polymer-based Nanoparticles - A Safe and Efficient Alternative for Gene Delivery

Shira Orr, Trinayan Kashyap, Tomer Bonshtein, and Asiel Mana
Envoya Inc., MA, USA

Abstract:
Non-lipid polymer-based nanoparticles for gene therapy are distinguished by their superior safety profile and non-immunogenic nature. Envoya's nanoparticles are crafted from FDA-approved polymers for clinical applications. Their core advantage lies in their efficient encapsulation capabilities, adeptly housing plasmid DNA and RNA within their structure. Averaging in size around 70nm in diameter, the nanoparticles are optimal for cellular uptake. This size allows the nanoparticles to easily navigate through biological barriers and reach their target sites within the body. Envoya's non-lipid polymer-based nanoparticles demonstrate effective cellular entry and subsequent release of genetic material, leading to high levels of transfection *in vitro* and *in vivo*. The polymers are chosen for their biodegradability and low toxicity, ensuring that the nanoparticles can be safely metabolized and eliminated from the body after fulfilling their therapeutic role. Additionally, the versatility of these polymers allows for the customization of the nanoparticles' properties. Overall, Envoya's non-lipid polymer-based nanoparticles represent a significant advancement in the field of gene therapy delivery. Their superior safety profile, non-immunogenic nature, and efficient encapsulation and transfection capabilities make them an attractive alternative to traditional vectors ultimately contributing to more effective and safer treatments for a wide range of genetic conditions.

Keywords: Gene therapy delivery; Drug delivery; Polymer; Nanotechnology; Polymer nanoparticles; Immunogenicity

Biography:
Shira is a pioneering force in the domain of drug delivery systems. She has been developing biopolymers for 25 years starting in the Israeli Technology Intelligence unit at the age of 18. Following her military service Shira completed her BSc. And MSc. cum laude at Tel Aviv University. Throughout her Ph.D. studies she received the distinguished Kraitman excellence scholarship, followed by a postdoc at Harvard Medical School. Following her postdoctoral work, Shira has gained experience in the pharma industry. Shira believes that biopolymer based nanoparticles delivery system is the answer to gene therapy and will reshape the boundaries of drug delivery and patient care.

SESSION: GENE THERAPY: METHODS, STRATEGIES & CLINICAL APPLICATIONS/ PRECISION GENE THERAPY FOR SPECIFIC DISORDERS

In vivo Precision Gene Therapy for Beta-hemoglobinopathies

C. Li*, and A. Lieber

Medical Genetics, University of Washington, WA, USA

Abstract:

For patients with hemoglobinopathies, hematopoietic stem cell transplantation represents the only curative option available. However, donor cell availability, technical complexity and high cost of current stem cell transplantation strategies present challenge for scalable applications. My presentation will focus on a simplified *in vivo* HSC gene therapy approach that does not require HSC harvesting and *ex vivo* manipulation. It is performed by transiently mobilizing HSCs from the bone marrow into the peripheral blood and transducing them with virus vectors administered intravenously. By utilizing precision genome editors, we have achieved therapeutic levels of genome editing in HSCs of murine models of β-thalassemia or sickle cell disease after *in vivo* transduction/selection. Editing strategies include base editing of critical motifs controlling repression of fetal haemoglobin, and prime editing to directly repair the sickle mutation. The treated animals showed phenotypic improvements without noticeable adverse effects. The safety and efficacy of *in vivo* HSC transduction/selection is also demonstrated in rhesus macaques, a more relevant large animal model to humans. This technically simple strategy has the potential for applications in resource-limiting regions where hemoglobinopathies are prevalent.

Keywords: Gene therapy; Gene editing; In vivo; Hematopoietic stem cells; Sickle cell disease

Biography:

Dr. Li earned his Ph.D. in Biochemistry and Molecular Biology from the University of Chinese Academy of Sciences. He completed his post-doctoral fellowship at the University of Maryland and the University of Washington, where he is currently a faculty member in the Division of Medical Genetics. Dr. Li has a long-term research interest in the development of safe, simple, and affordable gene therapy strategies for genetic disorders and infectious diseases.

DAY 2: KEYNOTE SESSION

RNA Immunotherapies for Cancer: The World's First CAR-mRNA-LNP Experience in Humans. *In vivo* Programming of Immune Cells Using mRNA-LNP Chimeric Antigen Receptors

J. Chal*, Y. Wang, J. Ding, R. Hofmeister, and Daniel Getts*

Myeloid Therapeutics, MA, USA

Abstract:

Myeloid Therapeutics has pioneered the world's first mRNA-CAR-LNP technology, now in clinical trials for TROP2-expressing tumors. This presentation explores how the company leverages mRNA and protein biology to reprogram immune cells, specifically myeloid lineage cells within the tumor microenvironment (TME). By utilizing lipid nanoparticles (LNPs) to deliver mRNA, Myeloid reprograms these cells with chimeric antigen receptors (CARs), enabling them to recognize and kill tumor cells. Myeloid's *in vivo* engineering platform targets myeloid cells, inducing broader anti-tumor immunity. These CARs utilize ITAM signaling adaptors, exclusive to immune cells, to achieve specific tumor lysis and cytokine responses. The technology demonstrates potent tumor killing in multiple cold tumor models and is backed by a robust GMP manufacturing platform, enabling clinical-stage therapies for TROP2+ tumors and GPC3+ liver cancer.

Keywords: RNA immunotherapies; Myeloid cells; Cell programming; Cancer; Clinical program

Biography:

Dr. Chal is Senior Vice President, Head of CMC at Myeloid Therapeutics. Dr. Chal brings over twenty years of experience in the biotechnology industry across multiple cell and gene therapies in R&D and CMC capacities, and landmark achievements in the field. Dr. Chal received a Ph.D. in Stem Cell and Molecular Developmental Biology from Sorbonne University /Stowers Institute (Kansas City, MO). Dr. Chal is a decorated scientist with multiple patents and over twenty peer-reviewed publications in the fields of biotechnology and cell and gene therapy.

DAY 2: KEYNOTE SESSION

MECP2. Gene Regulation and Therapeutic Approaches to Autism

Rudolf Jaenisch

Professor of Biology, MIT, MA, USA

Biography:

Dr. Rudolf Jaenisch is a Professor of Biology at MIT and a founding member of the Whitehead Institute for Biomedical Research. He is a pioneer of transgenic science. His research focuses on using pluripotent cells (such as embryonic stem cells and induced pluripotent stem cells) to study the genetic and epigenetic basis of human diseases, including Parkinson's, Alzheimer's, autism, and cancer.

DAY 2: KEYNOTE SESSION

AI-driven Decision Making for Cell & Gene Therapy Production

Irene Rombel
BioCurie, DE, USA

Abstract:
Genetic medicines – spanning cell, gene, and nucleic acid therapies (CGT) – have the unprecedented potential to treat and cure rare genetic diseases, cancer, and many other devastating diseases. However, the future of CGT is seriously hampered by very real and practical challenges in process development and manufacturing. Today, next-gen technologies are producing a multiplicity of data that could be transformed into actionable knowledge for production – with the help of AI, which has the potential to be a game-changer in improving human health. In this session, we will explore

- The potential to leverage AI across the CGT value chain, as well as the hype, pitfalls, and limitations
- AI as an enabler of Smart Manufacturing *aka* Biopharma 4.0
- The mAI BioCurie Platform™, a scalable AI-driven software platform for CGT process development and manufacturing.

BioCurie's mAI-driven software will enable biopharma companies and contract manufacturers to improve product quality, safety, commercial viability, and ultimately, increase patient access. Developed by Richard Braatz, thought leader in AI and advanced modeling for biomanufacturing, the mAI BioCurie Platform™ was designed to transform the current state of CGT production from today's labor-intensive, brute-force "hit-or-miss" approach to a new data-driven paradigm.

Biography:
Dr. Irene Rombel is the CEO, President and Co-Founder of BioCurie. She is an industry veteran with 25+ years of leadership experience spanning biotechnology, big pharma, consulting, investing, and academia. Prior to BioCurie, Irene was Chief of Staff, Research, at Spark Therapeutics; Senior Director of Strategy and External Innovation at Janssen, J&J; Founder and President of Biomedical Intelligence LLC; biotechnology hedge fund analyst; and Assistant Professor at UT Southwestern Medical Center in the Center for Biomedical Inventions. Dr. Rombel is on Columbia University's Translational Therapeutics Accelerator Steering Committee and the Columbia University Irving Cancer Drug Discovery Advisory Board.

SESSION: CGT ADVANCES IN CANCER: PRECISION THERAPIES AND IMMUNOMODULATION

A New Approach to Tackle Cancer Therapies Using Programmable Cytotoxic Nucleases

Krohn M*, R Medert, E Kleinert, D Ritzmann, T Fauth, A Knapp, R Back, D Sombroek, and P Scholz
Akribion Genomics, Germany

Abstract:

The utilization of the prokaryotic immune defense system CRISPR-Cas for mammalian applications has significantly boosted genome engineering for basic research and medical applications in the last decade and has promoted the mining for new Cas variants with advantageous editing properties. The identification and engineering of novel Cas nucleases allows for the development of a wide variety of applications including more targeted and advanced cancer therapies. However, one major hurdle to overcome is to ensure highly selective killing of cancer cells without scattered damage of surrounding healthy tissue. In a metagenome screening Akribion Genomics revealed a novel Cas variant termed G-dase E that later on has been assigned to the Cas12a2 family with an unexpected mode of action. G-daseE forms a ribonucleoprotein (RNP) complex containing both the Cas12a2 enzyme and a specific guide RNA (gRNA) that identifies and binds a target RNA molecule. Following gRNA-mediated recognition of the target RNA (e.g. mRNA), the collateral activity of G-daseE is activated, catalyzing non-specific cleavage of RNA and DNA, which ultimately leads to cell death. Here we report that G-daseE possesses an RNA guided, ‘collateral’ nuclease activity that can be employed to achieve selective depletion of cells that are defined by a specific marker RNA. The programmable collateral activity of the G-daseE nuclease opens up a new possibility of cancer treatment by targeting and eliminating cancer cells based on an oncogenic RNA marker.

Biography:

Michael Krohn studied Molecular Biology with a PhD from the Heinrich-Heine University / Düsseldorf and did his PostDoc at the Max-Planck Institute for Immunology / Freiburg with focus on developmental biology. He started his industrial career at BRAIN Biotech AG in 1997. Since 2001 he is working in the upper management at BRAIN Biotech AG. In 2013 he became member of the executive committee at BRAIN and accompanied the IPO in 2016. In 2018 he became executive Vice President and Head of R&D at BRAIN Biotech AG and is now part of the co-founding process of Akribion Genomics as Co-CEO.

SESSION: CGT ADVANCES IN CANCER: PRECISION THERAPIES AND IMMUNOMODULATION

New Immune Checkpoints: From Discoveries to Novel Drugs to Clinical Trials

Xingxing Zang
Albert Einstein College of Medicine, NY, USA

Abstract:
We recently discovered a new functional B7 immune checkpoint molecule called HHLA2 (HERV–H LTR Associating 2) and its two functionally opposite receptors including the costimulatory receptor TMIGD2 (transmembrane and Ig domain containing 2) and the coinhibitory receptor KIR3DL3 (killer cell immunoglobulin-like receptor, three Ig domains and long cytoplasmic tail 3). We found that HHLA2 was widely expressed in a broad spectrum of human cancers, particularly in PD-L1 negative tumors. KIR3DL3 was mainly expressed on CD56dim NK and terminally differentiated effector memory CD8 T (CD8 TEMRA) cells, whereas TMIGD2 was mainly expressed on naïve T and NK cells. The HHLA2-KIR3DL3 pathway inhibited immune function, whereas the HHLA2-TMIGD2 pathway stimulated immune function. Finally, we have developed novel immunotherapies targeting HHLA2/KIR3DL3/TMIGD2. I will discuss our results from discoveries to novel therapies to clinical trials.

Biography:
Dr. Zang is a Professor and Director of Institute for Immunotherapy at the Albert Einstein College of Medicine, New York. His lab has been at the forefront of new immune checkpoints and immunotherapies from discoveries to novel drugs to clinical trials.

SESSION: CGT ADVANCES IN CANCER: PRECISION THERAPIES AND IMMUNOMODULATION

Programming mRNA for Cancer Immunotherapy

Jaspreet Khurana
Strand Therapeutics Inc., MA, USA

Abstract:

We have developed a platform in which we design RNA-encoded programmable genetic "circuits" that detect molecular cues in a cell to specifically express a payload protein in cells that exhibit a particular molecular signature. We applied this platform to the development of our program which entails systemic delivery of lipid nanoparticle (LNP)-encapsulated mRNA-bearing programmable genetic circuitry to selectively express a therapeutic payload within target cells.

Biography:

Dr. Jaspreet Khurana is an RNA molecular biologist by training who is passionate about transforming innovative platforms into meaningful therapies for patients. Following a PhD in Biomedical Sciences from UMass medical school, Worcester, he joined Princeton and Columbia University for a postdoc where he utilized functional genomics to study genomic rearrangements. With 13+ years of post-PhD expertise in RNA molecular biology, he has proven experience leading cross-functional teams across early stages of drug development. Currently he is overseeing the mRNA platform development for immunotherapy programs at Strand Therapeutics.

CELL & GENE THERAPY SUMMIT-2024
The Global Cell & Gene Therapy Summit 2024
July 08-10, 2024 (Hybrid) | Boston, MA
Tuesday, July 09, 2024

SESSION: CGT ADVANCES IN CANCER: PRECISION THERAPIES AND IMMUNOMODULATION

OBX-115, an Interleukin 2 (IL2)-sparing Engineered Tumour-infiltrating Lymphocyte (TIL) Cell Therapy, in patients (pts) With Immune Checkpoint Inhibitor (ICI)-resistant Unresectable or Metastatic Melanoma

R.N. Amaria[1], J.L. McQuade[1], M.A. Davies[1], I.C. Glitza Oliva[1], S. Jose[1], E.N.K. Cressman[1], A.L. Clausell[1], R. Bassett[1], S.P.P Patel[1], A. Diab[1], H.A. Tawbi[1], M.K. Wong[1], A.P. Ikeguchi[1], C. Haymaker[1], S-A Lee[1], M. Jagasia[2], G. Ramsingh[2], P. Prabhakar[2], R. Duan[2], and P. Hari[2*]

[1]*MD Anderson Cancer Center, Houston, TX, USA*

[2]*Obsidian Therapeutics, Cambridge, MA, USA*

Abstract:

Background: Unengineered TIL cell therapy has shown promising activity in ICI-resistant metastatic melanoma but requires systemic high-dose IL2, which has well-described high-grade toxicity frequently requiring specialized management and limiting patient eligibility. OBX-115 autologous engineered TIL cell therapy does not require co-administration of IL2 due to its regulatable expression of membrane-bound IL15 (mbIL15) using the FDA-approved small-molecule drug acetazolamide (ACZ) to provide cytokine support for TIL expansion and persistence.

Methods: This Phase 1 study (NCT05470283) assesses OBX-115 in patients with ICI-resistant unresectable/metastatic melanoma. OBX-115 is manufactured from the patient's tumor tissue (surgical excision or core needle biopsy [CNB]). After lymphodepletion (cyclophosphamide, fludarabine), patients receive OBX-115 followed by ACZ once daily (≤7 days); ACZ redosing (≤7 days) is permitted at Week 6 for non-responders. No systemic IL2 is administered. Peripheral blood and tumor tissue is collected for longitudinal immune profiling.

Results: As of 02 Jan 2024, 9 patients (median age, 50 y) with ICI-resistant metastatic melanoma were infused with OBX-115 (median study follow up, 17 weeks; range, 2–58 weeks). Median lines of prior therapy was 3 (range, 1–6). OBX-115 was successfully manufactured for all patients, including from CNB tumor tissue (n=5). The infusion product had a high proportion of CD8+ cells (≥96%) and stem-like cells (CD8+CD39-CD69-; median 76%) with very low PD-1 expression in the CD8+ population (<1%). Post-infusion safety included no DLTs, 3 Gr 3 nonhematologic TEAEs in 2 pts (abdominal pain, ALT elevation, syncope), and no Gr 4 nonhematologic TEAEs. ACZ was redosed and well-tolerated in 4 of 5 eligible pts.

Among patients with ≥12-week follow-up (n=6), ORR (RECIST v1.1) was 50% (2 CR, 1 PR, 3 SD); all responses occurred between Week 6–18 and were ongoing, with longest response >12 months. One patient developed new metastatic disease (liver) and progressed at Week 24, despite continued target lesion reduction; no patient developed brain metastasis. Post-infusion ctDNA was not detectable in any of the responders at Day 14 or 42. Although OBX-115 had <1% NK cells, post-infusion peripheral blood and tumor biopsies showed NK cell expansion, consistent with trans-presentation of mbIL15 to endogenous NK cells. Updated data will be presented.

Conclusions: OBX-115 regulatable engineered TIL cell therapy was well-tolerated and produced consistently deepening and durable responses, indicating that OBX-115 may mediate CRs and durable clinical benefit in ICI-resistant metastatic melanoma without high-dose IL2. OBX-115 investigation continues in this and an ongoing Phase 1/2 multicenter study (NCT06060613).

Keywords: Tumour-infiltrating lymphocytes; Adoptive cellular therapy; Genetic engineering; Cytokines; Protein regulation; Melanoma

Biography:

Parameswaran Hari, M.D., M.S., is Chief Development Officer at Obsidian Therapeutics, Inc. Dr. Hari brings decades of experience designing, managing and leading complex cell and gene therapy clinical programs, including TIL cell therapies. Previously, Dr. Hari was Senior Vice President, Clinical Science at Iovance Biotherapeutics, where he led solid tumor adoptive cell therapy programs across multiple tumor types and indications, including new IND submission, first in human phase 1 studies and BLA submission efforts. Prior to Iovance, Dr. Hari was the Chief of Hematology and Oncology at the Medical College of Wisconsin, where he led national cooperative multi-PI trial groups in cell and gene therapy and multiple myeloma. He also served the American Society of Transplantation and Cellular Therapy (ASTCT) as its secretary. Dr. Hari received his M.B.B.S at Kerala University, M.D. at Central University of Pondicherry, and his M.S. at the Medical College of Wisconsin.

SESSION: CGT ADVANCES IN CANCER: PRECISION THERAPIES AND IMMUNOMODULATION

Translational Development of a Novel CAR-T Cell Therapy, from Bench to Bedside

Yan Luo*, Yaqing Qie Martha E. Gadd, Alak Manna, Rocio Rivera-Valentin, Tommy To, Shuhua Li, Farah Yassine, Hemant S. Murthy, Roxana Dronca, Mohamed A. Kharfan-Dabaja, and Hong Qin

Department of Cancer Biology, Mayo Clinic, FL, USA

Abstract:

Several CD19-targeting CAR-T cell therapies have been employed in the treatment of leukemias and lymphomas. However, relapsed and/or refractory (R/R) disease still poses challenges for a significant number of patients. Furthermore, the efficacy of CD19-CAR-T cell therapies varies across different hematological malignancies, notably in chronic lymphocytic leukemia (CLL). This study introduces the development of a novel CAR-T cell therapy targeting the B-cell activating factor receptor (BAFF-R), a crucial regulator of B-cell proliferation and maturation. A monoclonal antibody against BAFF-R was generated from a hybridoma clone and utilized to construct a novel MC10029 CAR.Through a comprehensive series of *in vitro* and *in vivo* models utilizing the Nalm-6 cell line for leukemia and the Z138 cell line for lymphoma, we demonstrated the antigen-specific cytotoxicity of MC10029 CAR-T cells against tumor cells. Notably, MC10029 CAR-T cells exhibited potent antitumor effects against CD19 knockout tumor cells, effectively mimicking CD19-negative R/R disease. Furthermore, MC10029 CAR-T cells were specifically designed to target CLL, a disease in which BAFF-R expression is nearly ubiquitous. Initial assessment of MC10029 CAR-T cell cytotoxicity was conducted using the MEC-1 CLL cell line, followed by validation using patient-derived samples. Utilizing healthy donor-engineered MC10029 CAR-T cells against enriched primary tumor cells, and subsequently patient-derived MC10029 CAR-T cells against autologous tumor cells, we demonstrated the efficacy of MC10029 CAR-T cells against CLL patient samples. Based on these robust findings, we have progressed to the production of MC10029 CAR-T cells using GMP lentivirus and have successfully obtained an IND approval in preparation for a Phase 1 clinical trial.

Biography:

Dr. Yan Luo is an Assistant Professor in the Department of Cancer Biology at Mayo Clinic in Florida, USA.

SESSION: ADVANCING CGT MANUFACTURING: OPTIMIZATION, TECHNOLOGIES, AND PLATFORMS

Opportunities and Value in Using Process Wide Digital Twins to Support Cell and Gene Therapy Production

Joseph Pekny

Advanced Process Combinatorics Inc., IN, USA

Abstract:

This presentation will describe how to develop process wide digital twins to accurately model and predict the behaviour of cell and gene therapy production. These process wide digital twins can be readily updated with rapid advances in underlying technology and can be used to investigate manufacturing strategies for global accessibility, process scale-up, patient-specific manufacturing approaches, and the impact of next generation manufacturing technologies. The relationship of process wide digital twins to detailed understanding of individual manufacturing steps will be discussed as a foundation for using process wide digital twins to help guide research and development strategies.

Biography:

Dr. Joe Pekny co-founded Advanced Process Combinatorics Inc., in 1993. Dr. Pekny is also a Professor of Chemical Engineering at Purdue University, and was the Founding Director of the Regenstrief Center for Healthcare Engineering in 2005. For over twenty years he has been a leader in the application of industrial engineering techniques to complex industrial challenges, and has been a key leader in the development of products and services for combinatorial optimization for process design, planning, and scheduling. Pekny earned a Ph.D. in Chemical Engineering from Carnegie Mellon University in 1989.

SESSION: ADVANCING CGT MANUFACTURING: OPTIMIZATION, TECHNOLOGIES, AND PLATFORMS

Leveraging a Flexible and Efficient Rapid Development Framework™ to Accelerate Development and Manufacturing of Cell and Gene Therapies

Mindy Sadik

Cell Therapy Sciences, Thermo Fisher Scientific, MA, USA

Abstract:

This presentation will provide an overview of Thermo Fisher Scientific's Rapid Development FrameworkTM to streamline the complexity of regenerative medicine and immunotherapy workflows. Developed with 20+ years of advanced therapy industry experience and expertise, these frameworks for processes and analytics are designed to expedite development and manufacturing while remaining adaptable to the unique needs of each product.

Biography:

Dr. Mindy Sadik joined Thermo Fisher Scientific in 2021 as the Director, Cell Therapy Sciences and oversees the Process Development and Analytical Development teams for the Cell Therapy Business unit for Advanced Therapies. Mindy's teams work closely with partners to provide development and clinical scale services, which include gene and non-gene modified cell processing for autologous and allogeneic cell therapies. In her previous roles, Mindy has led teams of scientists and engineers and the associated R&D and pilot facilities in both large and small organizations concentrating on medical devices, biologics, and tissue products. Her expertise is in process and product development specializing in regenerative medicine, tissue engineering, biomaterials, and stem cells. She completed a postdoctoral fellowship at the University of Pennsylvania in Neurosurgery and received her Ph.D. in Biomedical Engineering from Rutgers University. She also holds an MSc from Columbia University and a BSc from Tulane University, both in Biomedical Engineering.

SESSION: ADVANCING CGT MANUFACTURING: OPTIMIZATION, TECHNOLOGIES, AND PLATFORMS

Resource Effective Development & Operation of CGT Processes with Hybrid Modelling and Transfer Learning

M. von Stosch

DataHow AG, Switzerland

Abstract:

The development and operation of cell and gene therapy processes is cost ad time intensive. Commonly, design of experiment methods is used to provide insight into which process parameters and material changes impact on the process response. This requires the execution of a multitude of experiments, as other sources of knowledge are largely disregarded. By using prior knowledge, in form of data or fundamental knowledge, transfer learning and hybrid modelling provide a cost-effective alternative. In this contribution we first show how hybrid models can be used to increase process understanding, aiding the rational design of cell and gene therapy processes. Secondly, we introduce the concept of transfer learning and present how it supports streamlining the development of a gene therapy process.

Keywords: Process development; Process Operation; Hybrid modelling; Transfer learning

Biography:

Dr. Moritz von Stosch is a thought leader in digital bioprocess development and operation. He is the Chief Innovation Officer at DataHow AG and co-author of more than 50 scientific publications, including the Book “Hybrid Modelling in Process Industries”. Prior to joining DataHow, Moritz led the Process Systems Biology & Engineering Centre of Excellence at GSK Vaccines, for which he received an Innovation Performance and Trust award. He lectured at Newcastle University (England), holds a PhD in Biochemical Engineering from University of Porto (Portugal) and received a Dipl.Ing. in Chemical Engineering from RWTH Aachen University (Germany).

SESSION: ADVANCING CGT MANUFACTURING: OPTIMIZATION, TECHNOLOGIES, AND PLATFORMS

Isolating Full Capsids in AAV Production with IPP Technology

B. Jacobites, A. Ersen, and J.M. Criscione*

Enquyst Technologies Inc., MA, USA

Abstract:

Enquyst Technologies is developing its core, patented isoelectric point purification (IPP) technology to solve unmet needs in the downstream purification of viral vector gene therapies. We have successfully demonstrated the ability of IPP technology to address the empty vs. full capsid problem in adeno-associated virus (AAV) downstream processing by isolating full capsids. Further, our IPP technology comprises novel referenced, multi-channel, in-line process analytical technologies (PATs), including absorption spectroscopy (e.g. A260, A280) and multi-angle light scattering (MALS) detection, to enable real-time characterization of empty vs. full capsid in process. Leveraging real-time monitoring and precise separation based on isoelectric point (pI), charge heterogeneity, and molecular size, Enquyst's IPP technology delivers a preparative scale, high purity solution with seamless integration, flexibility, and virtually no yield loss.

Biography:

Dr. Criscione is an applied science and engineering entrepreneur with a unique expertise that covers chemistry, spectroscopy, materials science, physics, biochemistry, biophysics, and biomedical engineering. Dr. Criscione has 10+ years of experience in successfully building interdisciplinary technical teams and leading innovation. Dr. Criscione received his PhD in Biomedical Engineering from Yale University. He also holds a MPhil in Biomedical Engineering from Yale University, a MS in Biomedical Engineering from Yale University, a MS in Physical Chemistry from Michigan State University, and a BA with High Honors in Chemistry and a concentration in Neuroscience from Oberlin College.

SESSION: ADVANCING CGT MANUFACTURING: OPTIMIZATION, TECHNOLOGIES, AND PLATFORMS

Development of HEK293 Cell Line for Optimal Production of Novel Capsids with Enhanced Brain Tropism

Z. Guillemin*, V. Venkatesan, A. Ibe-Enwo, C. Gagnon, S. Sharma, and K. Dhanasekharan

Voyager Therapeutics Inc., MA, USA

Abstract:

Voyager has developed-novel AAV capsids with significantly enhanced brain tropisms and achieved transgene expression that is superior to conventional AAV serotypes in non-human primates. These capsids have the potential to increase the safety and effectiveness of AAV gene therapy. To accelerate clinical studies of therapeutic candidates using novel capsids, rapid process development leading to a cost-effective manufacturing process is the next challenge. HEK293 cells are the most widely used cell-line for rAAV production and Voyager has internally developed a HEK293 cell line to support our portfolio of AAV gene therapy assets. The VYGR-293 cell line was developed by adapting a serum-fed adherent cell line to a serum-free suspension culture. Further, VYGR-293 cells were optimized for maximum productivity throughout the production process from cell seeding to lysis. Triple transfection parameters of total plasmid amount, cell density at transfection, plasmid to transfection reagent ratio and molar plasmid ratio (Transgene: Rep-Cap: Helper) were tested using Design of Experiment (DOE) studies. Optimal parameters that enabled the highest productivity and %Full capsids were thus selected. The upstream process was further developed by examining optimal N-1 to N split ratios, amino acid utilization during production and time of harvest studies. In addition, multiple additives and commercial transfection additives are explored. VYGR-293 cells achieved 2-4x increase in volumetric titer after these optimization studies, reaching above 2E11 vg/mL. rAAV obtained from VYGR-293 cell line had good product quality profile including high % full capsids. In summary, this cost-efficient cell line can be utilized to produce high quality novel rAAV for its next generation drug candidates in-line to treat many neurogenerative disorders.

Keywords: AAV gene therapy; Process development; Upstream; Cell line; Optimization

Biography:

Zeynep Guillemin received her PhD degree from Boston College. She is working as scientist in Upstream Process Development for 7 years, and currently in Voyager Therapeutics as senior scientist.

SESSION: ADVANCING CGT MANUFACTURING: OPTIMIZATION, TECHNOLOGIES, AND PLATFORMS

An Automated Rapid CAR T Cell Manufacturing Process on a Single Platform

Liping Yu*
Applied Cells, Inc., CA, USA

Abstract:

Autologous cell therapy using genetically modified T cells to express chimeric antigen receptor (CAR) has yielded durable responses in patients. However, currently only a small portion of patients are privileged to receive the therapy. High cost and long manufacturing time contribute to the key limitations on a broader adoption. Researchers have recently demonstrated a process of generating functional CAR T cells within 24 hrs with greater potency. This rapid process provides a new hope in making CAR T therapy affordable and accessible. The reported rapid manufacturing process is still manual operation and involves use of multiple tools. To automate the rapid process for quality cell production, we developed a rapid CAR T manufacturing process on a single platform.

Rapid process eliminates *in vitro* cell expansion and requires much smaller doses compared to conventional process. Manufacturing of CAR-T cells is simplified to: (1) T cell selection, (2) viral transduction, and (3) cell purification. Fresh peripheral blood can now replace leukopak as starting material. We conducted feasibility study on a platform equipped with 3x magnetic cell separation modules. Magnetic cell separation process is column-free automated operation within enclosed sterile lines. First, T cells were isolated directly from peripheral blood from a healthy donor using CD4/CD8 nanomagnetic beads. Then isolated T cells were released using cell culture medium. eGFP expressing lentivirus were added to the enriched T cells with other reagents required for viral transduction. After 20 hrs incubation, transfected T cells were purified on a second magnetic module to remove free viruses and transduction medium. T cells were then released and collected in saline solution ready for injection.

Starting from 20mL of peripheral blood, we isolated T cells with 95% purity and 70% recovery. >99% of lentivirus was rinsed off during purification. After transduction, >17.5% T cells became GFP positive, with 80% viable cells. Compared to reported process, single platform process saves multiple cell washing steps, achieves high cell recovery and purity, and reasonable transduction efficiency.

In summary, we demonstrated rapid manufacturing of CART cells on an automated platform is feasible. The platform can be the solution for rapid autologous manufacturing of CAR T cells at close-to-patient settings.

SESSION: ADVANCING CGT MANUFACTURING: OPTIMIZATION, TECHNOLOGIES, AND PLATFORMS

Keywords: Automation; Magnetic separation; Closed; Rapid

Biography:

Dr. Liping Yu obtained her Ph.D. in physical chemistry and biophysics from Carnegie Mellon University and took the postdoc training at Beckton Dickinson. She had worked in biotech industry for over 15 years where she led innovation projects and managed academic collaborations. She has technical expertise in cell analysis, cell separation, microfluidics as well as process development.

SESSION: ADVANCING CGT MANUFACTURING: OPTIMIZATION, TECHNOLOGIES, AND PLATFORMS

Enabling Compliant Development and Manufacturing of iPSC-Derived Therapies

Lynne Frick*, and Karen Weisinger
Cell X Technologies, Inc., OH, USA

Abstract:

Cell therapy processes are subject to significant variability due to labour-intensive manual processes. Tasks such as imaging, cell culture maintenance, passaging, and offline assays, when performed by multiple operators, contribute to this variability. Long processing times, inconsistency, disparate data collection and the subjective evaluations of cell colonies (is it time to passage or feed?) all contribute to processes that are difficult to fully characterize, reproduce and transfer.

iPSC cultures are particularly prone to variability issues, especially given the lengthy and complex differentiation protocols they often require. Each step in these protocols is essential, and operator error or inter-operator variability is additive, impacting the overall outcome. In addition, standardizing data collection is necessary for establishing critical quality attributes (CQAs). Data quality is essential, and maintaining an unchanging workflow is vital. Consistent and accurate data collection ensures that the relevant CQAs can be established, providing a solid foundation for process optimization and regulatory compliance.

By minimizing human intervention, automation improves contamination rates and ensures consistent and reliable processes. An automated platform with real-time, detailed records of every action, can help therapeutic developers retrieve essential information and begin this record keeping much earlier in the process.

In this presentation, we will discuss and show examples of how automation can be used to streamline the development of iPSC-derived therapies, leading to consistent, reliable, and efficient production process.

Keywords: iPSCs; Automation; Manufacturing; Cell therapy; Adherent cell culture

Biography:

Lynne Frick is the President and Chief Executive Officer at Cell X Technologies in Cambridge, Massachusetts. As an experienced entrepreneur and founder, Lynne has a proven track record of elevating startup life sciences technology, product, and service companies. She is a strong business development professional skilled in corporate development, strategy, marketing, leadership, communications, investor relations, and bio-pharmaceutical discovery, development, and manufacturing.

SESSION: ADVANCING CGT MANUFACTURING: OPTIMIZATION, TECHNOLOGIES, AND PLATFORMS

Access to an ISO5 Cell Therapy Production Space Anywhere

A.D. Henn*, and R. Yerden

BioSpherix, Ltd., NY, USA

Abstract:

Cleanroom space has been more difficult to obtain since the pressures of the COVID19 pandemic. We designed a closed system, the Xvivo System, to provide an ISO 5 cell handling and incubation space that is production process agnostic. These systems use compressed tanked gases, excluding room air from the system. They also exclude people, the biggest sources of microbial risk in the cleanroom environment. This allows exquisite control of relative humidity, which, in turn, helps control microbial risks. Operating costs are reduced compared to traditional cleanrooms and the lack of connection to HVAC systems mean these can be located anywhere. Desiccation has been used for centuries to preserve food from microbial breakdown. Controlling RH in cell handling spaces allows us to use the atmospheric conditions to inactivate microbes that otherwise would threaten cell cultures. Using tanked dry gases also provides the ability to always control oxygen to physiologic levels as well as constant CO2. This allows us to provide the kind of reproducibly cytocentric conditions for cells that aren't possible in open cleanrooms. Here, we share data on studies of the recovery of 5 different problem microbes under different controlled atmospheric conditions as well as cell therapy production media runs. Attendees will gain understanding of a fundamentally new approach to protecting cells from microbes, using the physical attributes of the environment without antibiotics, chemical biocides, or cleanrooms. This approach can provide cell production capacity anywhere, without building a cleanroom, for a more manageable distributed manufacturing model.

Keywords: Cleanroom alternative; Cell therapy production

Biography:

Alicia D. Henn, PhD., MBA, is Chief Scientific Officer for BioSpherix, Ltd. She interviews Cytocentric Visionaries for the company blog. Dr. Henn also owns the *In Vitro* Reproducibility and Physiologic Cell Manufacturing groups on LinkedIn. Her mission is to improve scientific reproducibility through clonable, physiologically relevant cell and tissue production environments.

SESSION: ADVANCING CGT MANUFACTURING: OPTIMIZATION, TECHNOLOGIES, AND PLATFORMS

Novel Opportunities to Advance Cell Therapy Cryopreservation and Logistics

Stella Vnook,
Likarda Inc., MO, USA

Abstract:

Cell therapies and many biologics, such as vaccines and proteins, are highly sensitive to temperature fluctuations and require storage at extremely low temperatures to maintain their stability and efficacy. These temperatures typically range from -80°C (-112°F) to cryogenic temperatures achieved using liquid nitrogen, reaching as low as -196°C (-320.8°F). While these ultra-low temperatures are necessary to prevent degradation and preserve the biological activity of these materials, the process of cryopreservation itself can introduce a host of challenges and stresses that can negatively impact the viability and functionality of the cells or biologics.

During the cryopreservation process, the formation of ice crystals is one of the primary sources of stress for biological materials. As the temperature drops, water molecules within the cells or surrounding the biologics begin to freeze, forming ice crystals that can cause mechanical damage to cell membranes, organelles, and protein structures. This damage can lead to reduced cell viability, loss of critical cellular function, and decreased potency of the therapeutic material.

In addition to the physical damage caused by ice crystals, the cryopreservation process can also induce osmotic stress on cells. As ice forms in the extracellular space, the concentration of solutes in the remaining liquid phase increases, creating a hyperosmotic environment. This can lead to the dehydration of cells as water moves out of the cell to maintain osmotic balance, causing the cell to shrink and potentially leading to membrane damage and cell death.

The importance of effective cryopreservation cannot be overstated. In a study published in the journal Biopreservation and Biobanking, researchers found that the viability of human mesenchymal stem cells (hMSCs) was significantly improved when they were cryopreserved using a combination of trehalose, a natural cryoprotectant, and a hydrogel-based scaffold (Bissoyi et al., 2016). The study demonstrated that this approach not only enhanced cell survival but also maintained the crucial therapeutic properties of the hMSCs, highlighting the potential of hydrogels in preserving the integrity of cell therapies during storage. Likarda's own hydrogel technology has demonstrated the ability to ship cells across international lines on dry ice for cells that normally required liquid nitrogen shipping conditions.

In addition to their protective properties during freezing, hydrogels also offer valuable benefits during the transportation phase. By providing an extra layer of insulation and cushioning, hydrogels can help to mitigate the impact of temperature fluctuations that may occur during shipping. This is particularly important for cell therapies, which are highly sensitive to even minor temperature deviations. By maintaining a stable environment, hydrogels can significantly improve post-thaw recovery rates, ensuring that more of the precious therapeutic material remains viable and effective.

Session: Advancing CGT Manufacturing: Optimization, Technologies, and Platforms

Likarda designed a hydrogel for cell therapies that could maintain the cells on dry ice rather than liquid nitrogen. This reduced the shipping cost, but also allowed the veterinarian the ability to store the product in their clinic in a cooler with dry ice until administration into the patient.

Biography:

Dr. Stella Vnook is a distinguished pharmaceutical executive, serial entrepreneur, highly respected CEO and founder of multiple biotech companies and visionary leader with a proven track record of success in the biotechnology and life sciences industries. With over 25 years of experience, Dr. Vnook has played a pivotal role in shaping the future of Companies, such as Merck and Co, Jazz Pharmaceuticals and Catalent, and small start-ups through her leadership, innovation, and commitment to advancing medical science.

As a CEO of Likarda, Vnook is poised to propel the company to new heights by leveraging her extensive experience and innovative vision. Under her leadership, Likarda aims to expand its presence in the biotech industry by pioneering groundbreaking solutions in cell therapy and regenerative medicine. With a focus on research and development, strategic partnerships, and operational excellence, Dr. Vnook is committed to driving Likarda towards achieving significant advancements in the field of biotechnology. Likarda Biotech is a pioneering drug-delivery biotechnology specializing in advanced cell therapy solutions.

CELL & GENE THERAPY SUMMIT-2024

The Global Cell & Gene Therapy Summit 2024

July 08-10, 2024 (Hybrid) | Boston, MA

Tuesday, July 09, 2024

SESSION: OPTIMIZING AAV MANUFACTURING: ENGINEERING, PROCESSING, AND ANALYSIS

Novel Cell Engineering Platform for High-Yield AAV Production and Improved Manufacturability

L. Forman*, K. NGO, and L. Chasin

CHO Plus, CA, USA

Abstract:

Adeno-associated virus (AAV) has emerged as a significant therapeutic modality in gene therapy. Challenges such as poor yield and variable product quality persist in the viral vector manufacturing space, and we have addressed these problems using our cell engineering technology.

Our cell engineering platform for improved AAV manufacturing addresses the critical challenges in gene therapy manufacturing and presents an innovative modality for improving cells for production of viral vector therapeutics. Our platform, yielding cells with improved AAV production and CQAs, can significantly bolster the efficiency and cost-effectiveness of gene therapy manufacturing, and can accelerate current development timelines.

We used a directed-evolution approach based on repeated cell fusions to shuffle the cell genome, and to amplify chromosomes of HEK-293 host cells. Engineered clones enriched for mitochondria phenotypes were isolated, then used as transient-transfection hosts, and for creating stable packaging and producer cell lines. For generation of stable packaging and producer cell lines, we developed a novel inducible system that maximizes the capabilities of the inherent viral production machinery.

Engineered HEK-293 clones grown in suspension culture exhibited up to 15-fold productivity improvement via triple transient transfection for AAV1, AAV2, AAV5, and AAV9 serotypes with capsid titers as high as 10^{17} viral particles/L (vp/L)—at least 10-fold higher than current industrial manufacturing processes. Selection for certain mitochondria phenotypes resulted in a 2-fold improvement in full-to-empty ratio—up to 55% full in crude supernatants. Finally, our engineered stable packaging and producer cell lines achieved capsid titers of up to 10^{16} vp/L.

We demonstrated a multi-modal cell-engineering platform that has significantly improved yield and manufacturability for transient transfection and for stable packaging and producer cell line methods. We further propose a model regarding the role of mitochondria for enhancing capsid percent full. Taken together, our disruptive platform technologies provide solutions for meeting current—and future—gene therapy manufacturing challenges.

Biography:

Larry Forman is a biologist by training. He worked at Genentech from 1980-1996 where his focus was mammalian cell culture process development. After Genentech, Larry worked for other pharmaceutical companies involved with the production of human therapeutic proteins via mammalian cell culture. In 2014 Larry founded CHO Plus to (successfully) develop cell-engineering methods for significantly increasing the specific productivity of mammalian cells used for biomanufacturing: engineered CHO cells for recombinant therapeutic protein production; engineered HEK-293 cells for AAV production.

SESSION: OPTIMIZING AAV MANUFACTURING: ENGINEERING, PROCESSING, AND ANALYSIS

Lyophilization as an Effective Tool to Develop AAV8 Gene Therapy Products for Refrigerated Storage

Li Zhi*, Yao Chen, Kuan-Yu, Nick Lai, Jonathan Wert, Shuai Li, Xiaoyan Wang, Xiaolin (Charlie) Tang, Mohammed Shameem, and Dingjiang Liu*

Formulation Development Group, Regeneron Pharmaceuticals, Inc., NY, USA

Abstract:

Recombinant adeno-associated virus (rAAV) has emerged as the leading gene delivery platform for treatment of monogenic disorders. Currently, for clinical and commercial products, rAAVs are typically formulated and stored below −65 °C as frozen liquid. Their long-term storage is often far from ideal because it may result in shorter drug product (DP) shelf-life compared to recombinant protein-based biologics and presents challenges for supply chain and inventory management. Consequently, there is great interest in developing robust lyophilized AAV DPs that are stable at 2 to 8 °C. In this study, we evaluated formulation excipients required for stable lyophilized AAV8 products including buffers, salts, cryoprotectants/lyoprotectants, surfactants, and bulking agents, and optimized the concentrations and ratios between the excipients. This led to the identification of the lead formulation that demonstrated short-term in-solution stability at 25 °C and, upon lyophilization, sufficient long-term stability at 2 to 8 °C. Our study demonstrated that, in the presence of 110 mM salts, mannitol can serve as an effective bulking agent with the appropriate formulation and lyophilization process design, and the sucrose to mannitol ratio is critical to maintain the stability and cake appearance of the lyophilized AAV8 DP. Thorough characterization of the effect of formulation components on the properties and quality of the lyophilized DP led to an optimized AAV8 lyophilized DP. This approach could be applied to streamline the future development of lyophilized AAV gene therapy products with various target transgenes and capsid serotypes.

Biography:

Nick Lai is a Senior Scientist at Regeneron Pharmaceuticals, a leading manufacturing company founded in 1988 with approximately 13,400 employees. Based in Tarrytown, New York, Nick holds a degree from the University of Illinois at Urbana-Champaign. With his expertise and experience, he contributes significantly to Regeneron's innovative efforts in the biopharmaceutical industry.

SESSION: OPTIMIZING AAV MANUFACTURING: ENGINEERING, PROCESSING, AND ANALYSIS

AAV Analytical Tools - Start to Finish

J. Kay*, D. Holzinger, and C. Odenwald
Biotechnik GmbH, Germany

Abstract:

PROGEN is a leading provider for AAV analytical tools, and we are strongly committed to supporting scientists making new discoveries and ground-breaking research within AAV gene therapy. Our exclusive, serotype-specific AAV ELISAs for the accurate determination of AAV capsid titers, represent one of the gold standard methods for titer determination. Besides, PROGEN offers a variety of analytical tools supporting work across the whole value chain of gene therapy development, from manufacturing to clinical evaluations. In addition to the PROGEN ELISAs which are suitable for crude lysate as well as highly purified material and being used from early development to analytical safety evaluations, we also offer an exclusive portfolio of AAV directed antibodies for the optimization of manufacturing processes, purification, analytical assessment of AAV particles up to serological evaluation of patient sera. To enable comparability from start to finish PROGEN´s highly characterized AAV protein standards as well as full and empty AAV particle standards are used calibration or validation of the commonly used assays along the value chain.

The global distribution of our products as well as the reliability and reproducibility of the data allow their application across departments, laboratories and even varying organizations without the need for expensive equipment, special training or technology transfer. This allows for consistent data to be generated by all involved in AAV production, from researchers to CDMOs producing at high capacity.

Biography:

Jesse Kay is currently the Business Development Manager at PROGEN, Inc, responsible for collaborative efforts to bring PROGEN products to more customers as well as direct sales. With extensive experience in different life science industries, such as food microbiology, automated liquid handling, and NGS, he has successfully led and managed teams as well as contributing to technical support and sales growth. Jesse holds a PhD in Medical Science from the University of Florida and a B.S. in Biological Science from Vanderbilt University.

SESSION: OPTIMIZING AAV MANUFACTURING: ENGINEERING, PROCESSING, AND ANALYSIS

Upstream and Downstream Process Development of AAV Production Platform

Huiren Zhao

Precision Biology, Amgen, Thousand Oaks, CA, USA

Abstract:

A design-of-experiment (DOE) methodology was used to optimize rAAV production in a HEK293T suspension cell system and resulted in higher production yields across 13 serotypes and capsid variants. The results also revealed a unique set of parameters compared to previously described protocols. Recently, we further optimized the upstream and downstream processing of this rAAV production platform. Our results showed that adding peptones (yeastolate, Trypton N1 or both) increased production yield by 2.8- to 3.4-folds, while addition of sodium butyrate lowered the production yield. For downstream processing, a variety of wash buffers for an affinity resin, POROS™ CaptureSelect™ (PCS)-AAVX, were tested for their effects on rAAV8 purity, including NaCl, $MgCl_2$, arginine, Triton X-100, CHAPS, Tween 20, octyl β-d-1-thioglucopyranoside (OTG), and low pH. The results showed that the OTG wash significantly improved the rAAV purity to 97% and reduced endotoxins to an undetectable level (<0.5 EU/mL), while retaining the yield at 92.3% of the phosphate-buffered saline (PBS) wash. The OTG wash was successfully applied to purifications of rAAV1, rAAV2, and rAAV5 using PCS-AAVX, and rAAV9 using PCS-AAV9. rAAV8 purified with OTG wash showed comparable transduction efficiency in HEK 293T cells to the rAAV8 purified with PBS wash. The optimized rAAV production process yielded 5.5–6.0 × 10^{14} and 7.6 × 10^{14} vector genome per liter of HEK 293T cells for purified rAAV8- and rAAV5-EF1α-EGFP (enhanced green fluorescent protein), respectively. The platform described in this study is simple with high yields and purity, which will be beneficial to both research and clinical gene therapy.

Biography:

Huiren Zhao is a Principal Scientist at Amgen Research in South San Francisco, CA, USA. Zhao's research focused on systematically evaluating various factors, including transgene, packaging, and helper plasmid ratios, total DNA concentration, and cell density. He has published several high impact peer-reviewed paper in quality journals.

Poster Presentations

Development of an Allogenic Cell Therapy for Parkinson's Disease Using Low-immunogenic Dopaminergic Progenitors Differentiated from Gene-edited Induced Pluripotent Stem Cells in an Experimental Animal Model

Y.-H. Chen, Y.-T. Chen, Y.-J. Yang, C.-Y. Lu, C.-P. Wang, and C.-L. Hsieh*

Development Center for Biotechnology, Taiwan

Abstract:

Parkinson's disease (PD) is the second most common neurodegenerative disorder of aging in which dopamine-producing neurons are progressively lost. Current treatment strategies for PD are focused solely on symptom management and with no curative treatment available. Regenerative medicine using dopamine-producing neural cells derived from stem cells raises hope for developing new therapeutics to reform neural networks and restore motor function to patients. Clonal induced pluripotent stem cells (iPSCs) derived from healthy donors offer the distinct advantages over existing patient-therapeutic approaches to generate unlimited number of homogeneous and off-the-shelf cell therapy products in a highly scalable manufacturing process. In this study, we aimed to develop an allogenic cell therapy by taking the advantages of current iPSC and gene editing technologies. Herein, we generated a low-immunogenic human iPSC line (Li-iPSC) using gene editing approach to eliminate cell-surface expression of HLA class I, which effectively reduced the proliferation of allogeneic PBMCs in a mixed lymphocyte reaction. Subsequently, the Li-iPSCs were further differentiated into dopaminergic progenitor cells (Li-iPSC-DAPs) using our clinically transferable protocol. These Li-iPSC-DAPs were well characterized with dopamine neuron–specific and other neural markers, dopamine secretion and electrophysiological properties *in vitro*. The therapeutic function of Li-iPSC-DAPs was assessed by transplanting cells into the striatum of 6-OHDA-lesioned PD rats following a 6-months monitoring period of motor behaviour using apomorphine-induced rotation and the stepping test. PD rats that received Li-iPSC-DAPs transplantation showed a significant decrease in rotation scores in a dose-dependent manner at 5 months post-grafting compared with vehicle group. Similar recovery effect was also observed in the stepping test where animals in the cell transplanted group reversed behavioural impairments at 18-weeks post-grafting. Immunopathological analysis in brain tissues confirmed the survival and neuron maturation of transplanted Li-iPSC-DAPs at the area of cell injection. Owing that population ageing is an irreversible global trend, regenerative medicine has become a new mainstream approach to innovation in pharmaceutical and biotech industry. Our data provided the proof of concept that Li-iPSC-derived cell products have benefits for PD therapeutics and could extend to other aging-related diseases in the field of regenerative medicine.

Keywords: Allogenic cell therapy; Induced pluripotent stem cell; Parkinson's disease; Dopaminergic progenitors; Gene

Biography:

Dr. Chia-Ling Hsieh is currently served as the Deputy Executive Director of Institute for Drug Evaluation Platform in Development Center for Biotechnology (DCB), leading the research team to develop iPSC-based cell therapy products toward the stage of clinical application. She is also affiliated with Taipei Medical University as an associate professor since 2013. Dr. Hsieh's research interests span both cancer biology and translational science. Much of her work has been on improving the understanding of the biological role of tumour microenvironment, and the development of clinically useful biomarkers and effective gene and cell therapy approach to overcome the unmet medical needs and challenges of cancer diagnosis and treatment. Dr. Hsieh continuedly conducts government-sponsored research projects and has published over 60 peer-reviewed articles at present.

POSTER PRESENTATIONS

Navigating Genetics of Dementia in the Indian Sub-continent

Karan Gujarati[1], Aparna Ganapathy[1], Aditi Chatterjee[1], Shrutee Jakhanwal[1], Sanjeev Jain[2], Meera Purushottam[2], Biju Viswanath[2], Chinu Patra[2], Ebin Joseph[2], Radhakrishna Bettadapura[1], and Ramesh Hariharan[1]*

[1]*Strand Life Sciences, Bengaluru, India*

[2]*Molecular Genetics Laboratory, Department of Psychiatry, NIMHANS, Bengaluru, India*

Abstract:

Dementia is associated with a wide group of neurodegenerative disorders and encompasses a range of symptoms associated with progressive decline in brain function. Around 55 million people worldwide are affected with dementia with nearly 10 million cases being added every year. Dementia has high heritability thereby making it crucial to understand the genetic underpinnings underlying its pathogenesis. We have developed a genome-wide association studies (GWAS) pipeline and performed analyses for dementia patients using the UK Biobank dataset. A plethora of genome-wide association studies have uncovered several hundred SNP associations with dementia on European ancestry, but the relationship between these SNPs in populations with complex genetic substructure like South Asians have not been thoroughly examined. The disease types for dementia in this analysis included Alzheimer's disease, dementia in other diseases and unspecified dementia. To understand population-specific genes in the Indian cohort, we performed a second analysis using similar criteria on an in-house dataset from the Indian subcontinent. GWAS analysis on the UK Biobank dataset showed strong SNP associations in genes like *APOE, TOMM40, NECTIN2, BCAM, CBLC, BCL3, APOC4, NKPD1, CLPTM1, EXOC3L2, PILRA, CLU*. GWAS analysis on the Indian cohort revealed only a weak association of the well-established APOE gene with dementia, highlighting population-specific differences in genetic associations. Interestingly, analysis on the Indian cohort uncovered associations of novel SNPs in genes like *COPZ2, CDC27, CTBP2, RAI1, and ATG12*. While these novel associations are currently not statistically significant, we believe that these findings provide insights into the genetic landscape of dementia. Understanding the role of these genes in neurological functions will contribute to unraveling the complexity of dementia. A subsequent expansion of our cohort will not only help establish the significance of these findings in the Indian population but can aid in identification of variants which may be potential drug targets for precision gene therapy.

Keywords: Dementia; GWAS; Genetic associations; Drug discovery; Gene therapy

POSTER PRESENTATIONS

Aberrant Expression of TIM-4-L is a Common Feature of AML and a Potential Target for Engineered T Cell Therapy

B. Cieniewicz, A. Bhatta, E. Oliveira, B. Yu, Z. Yang, H. Ning, and D. Corey*

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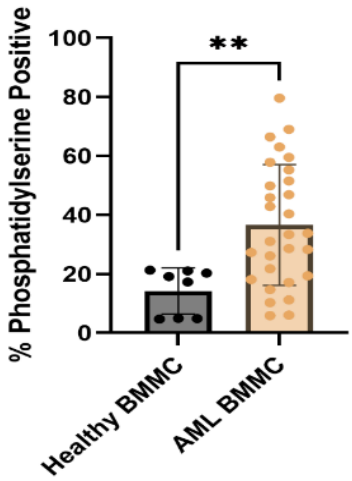
Abstract:

Development of targeted T cell therapies for acute myeloid leukemia (AML) has had limited success, in part due to clinical and biological heterogeneity of the disease, and the similarity of the surface proteome with healthy hematopoietic stem and progenitor cells. Phosphatidylserine, the ligand for TIM-4 (TIM-4-L), is a membrane phospholipid maintained on the intracellular leaflet of the plasma membrane and exposed during apoptosis, where it mediates phagocytosis of dying cells. Aberrant expression of TIM-4-L in AML and other cancers has been observed, which could act as a novel target for engineered T cell therapy. We screened a panel of bone marrow aspirates from 29 treatment-naïve AML patients for expression of TIM-4-L and found 25/29 (86.2%) had increased TIM-4-L as compared to healthy controls. AML blasts ranged from 5.9-79.7% TIM-4-L positive, with a TIM-4-L expression ratio of 0.4-26.4-fold as compared to healthy controls. Although our sample size was limited, TIM-4-L positivity was observed in AML across WHO classifications. The frequency and level of expression of TIM-4-L are comparable to other AML cell therapy targets.

We tested the ability of a TIM-4-L-targeting Chimeric Engulfment Receptor (CER)-1236 T cell to eliminate the AML cell lines MV-4-11 and Kasumi-1. CER-1236 T cells bind TIM-4-L via a TIM-4 extracellular binding domain, while inducing T cell cytotoxicity, cytokine secretion, and proliferation via CD28, CD3ζ, and TLR2 intracellular signalling domains. CER-1236 mediated 83.0 or 84.6% cytotoxicity against Kasumi-1 and MV-4-11 AML lines, respectively, at a 2:1 E:T ratios, and showed secretion of IFN-γ and antigen-induced proliferation. Interestingly, secreted factors from CER-1236 T cells could further induce TIM-4-L expression on both MV-4-11 and Kasumi-1 cells. *In vivo* xenograft models of AML using Kasumi-1 in NSG MHC dKO mice were eliminated by a single infusion of 7.5e6 CER-1236 T cells. CER-1236 T cells showed early expansion after engraftment, peaking at 7 days post infusion in the peripheral blood and contracting out to day 44. No morbidity or loss of body weight were observed in treated mice.



Assessment of TIM-4-L expression on healthy HSPCs from WT or xenografted mice revealed minimal TIM-4-L expression, suggesting that TIM-4-L expression was limited to malignant cells. Overall, these data identify aberrant TIM-4-L expression as a common feature of AML that can be targeted with cytotoxic T cell therapy. Importantly, TIM-4-L expression is not shared with healthy HSPCs, suggesting CER-1236 T cell treatment may have less on-target off-tumor hematotoxicity than other AML cell therapies.

Keywords: AML; T cell therapy; CER T cell; Phosphatidylserine

Biography:

Brandon has been at CERo for 4 years developing the CER-T technology across multiple indications. He is keenly interested in developing novel ideas in cellular therapy to treat human diseases. He has Rich experience in academic (12 years) and corporate segments across several sectors including people management, product management, operations management, client management and business development. Areas of expertise include population genetics, data curation, precision medicine, CRISPR-Cas and protein biochemistry.

POSTER PRESENTATIONS

Spinal Muscular Atrophy and Pompe Disease Gene Therapy Clinical Trials in China

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Abstract:

Spinal muscular atrophy (SMA) and Pompe disease (PD) are both rare diseases that can be life-threatening and significantly impact the quality of life. GC101 and GC301 are AAV-based gene therapy drugs specifically designed to treat SMA and PD, respectively.

Currently, Beijing GeneCradle Therapeutics in China is sponsoring registered phase I/II clinical trials (NCT05824169, NCT05901987, and NCT05793307) that involved 3 types of SMA patients, while trials for PD patients are also ongoing. Initial findings indicate remarkable progress. For SMA type 2 patients who completed a three-month follow-up after receiving an intrathecal injection of GC101 at a dosage of 1.2x1014 vg/person, the average improvement in Hammersmith Functional Motor Scale Expanded (HFMSE) exceeded 4 points.

In additional exploratory studies, both type 1 (ChiCTR2200056833 (Chinese Clinical Trial Registry, Chictr.org.cn) and ChiCTR2200063230) and type 2/3 (ChiCTR2100054441) SMA patients were treated with intrathecal GC101. These studies showed promising results, with improved survival and motor function for SMA type 1 patients, achievement of new motor milestones for SMA 2/3 patients.

In a previous pilot study (NCT05567627/ChiCTR2200063229), three out of four infantile-onset PD (IOPD) patients treated with GC301 via intravenous infusion at a dosage of 1.2x1014 vg/kg survived beyond 18 months of age, experiencing significantly improvements in both cardiac and motor function. These patients also reached new development milestones. Another study (ChiCTR2200065664) demonstrated that six IOPD patients who had previously undergone enzyme replacement therapy (ERT) maintained stability and achieved new developmental milestones without the need for further ERT following GC301 treatment.

Importantly, the safety profile of both GC101 and GC301 is reassuring. There have been no drug-related serious adverse events (SAEs) reported. The only adverse events (AEs) observed were Grade 1 or 2, consisting of elevations in liver enzyme and dyslipidaemia, which resolved without any need for intervention.

In conclusion, the intrathecal administration of GC101 and intravenous administration of GC301 have demonstrated safety and provided clinically significant improvement in overall motor function and achievement of motor milestones, which were not previously expected in patients with SMA and PD.

Keywords: SMA; Pompe disease; Gene therapy; Clinical trials; Safety and efficacy

Biography:

Xiaodong Wang, Ph.D, is trained in human genetics, is in charge of medical affairs in GeneCradle Therapeutics. She participates in protocol designs, data analysis and results discussion with investigators.

POSTER PRESENTATIONS

Influence of Cell Division on Plasmid Nuclear Entry and Expression

J. Sylvers, Y. Wang, and F. Yuan*

Department of Biomedical Engineering, Duke University, NC, USA

Abstract:

The nucleus in mammalian cells is the target for DNA based gene delivery. For nonvirally delivered plasmid DNA (pDNA), nuclear entry can occur via two known mechanisms: passive inclusion in the nucleus following cell division when the nuclear envelope breaks down and then reforms; and active transport of the pDNA through nuclear pore complexes. To investigate the relative importance of these pathways for pDNA nuclear entry and subsequent transcription and translation, we electrotransfected naked pDNA encoding enhanced green fluorescent protein (EGFP) into cell-cycle arrested and unarrested mammalian cells and developed a sensitive imaging method to quantify the pDNA in nuclei based on a DNA hybridization probe with amplified fluorescence signals and automatic image analysis. The method allowed us to detect pDNA in cells at single molecule resolution. Meanwhile, we used an RNA hybridization probe targeting mRNA to measure EGFP transcript, and flow cytometry to quantify EGFP protein level in transfected cells. Two distinct pDNA distribution patterns were observed in cell nuclei at 16 hours post transfection: punctate and diffuse, prevalent in cell cycle arrested and unarrested cells, respectively. The cell cycle arrest reduced diffuse pDNA and increased punctate pDNA, resulting in a net decrease in total intranuclear pDNA. Moreover, cell cycle arrest boosted EGFP mRNA synthesis but minimally affected EGFP protein production. These findings indicate that efficient pDNA nuclear entry during cell division does not guarantee high transgene expression and suggest that punctate pDNA is more transcriptionally active than diffuse pDNA in nuclei. Results from the study can aid future research on nonviral gene delivery mechanisms for increasing transgene expression.

Keywords: Nonviral gene delivery; Electrotransfection; Nuclear entry; Transcription compartment

Biography:

Justin Sylvers is a PhD candidate in Dr. Fan Yuan's lab at Duke University. He received a BS in bioengineering from University of Maryland, College Park in 2019, after which he joined Fan Yuan's lab and started studying nuclear entry of Plasmid DNA.

POSTER PRESENTATIONS

Non-lipid Polymeric Nanoparticle-encapsulated siRNA is Effective *in vitro* and *in vivo*

T. Kashyap*, T. Bonshtein, A. Mena, and S. Orr

Envoya Inc, MA, USA

Abstract:

The success of gene therapy is measured by the ability to deliver genetic material safely and precisely to target cells within the body; however, biological and physiological barriers present formidable challenges. As such, efficient delivery systems must overcome hurdles such as immune responses, off-target effects, and limited cellular uptake. We have developed biopolymer-based nanoparticles (Envoyer), which are formulated with external gelation-based microfluidics methodology that offers greater control over particle formation size. Here, we examined the consistency of the analytical properties of Envoyer, and determined its immunogenicity and efficacy, in both *in vitro* and *in vivo* experimental models. Transmission electron microscopy showed that Envoyer particles encapsulating siRNA maintain a consistent size, of 20-30 nm. At the working concentration of the siRNA (~50 nM to 140 nM), Envoyer-encapsulated scrambled siRNA did not significantly activate toll-like receptor 4 compared to lipopolysaccharides (LPS), suggesting that Envoyer particles are non-immunogenic. Furthermore, intraperitoneal injection of Envoyer-encapsulated scrambled siRNA to mice did not induce inflammatory related cytokine levels. We also demonstrated that Envoyer-encapsulated survivin siRNA are internalized by the cells and act in a dose- and time-dependent manner. Transfection of PANC1 cells with Envoyer-encapsulated survivin siRNA showed that the threshold dose for significant reduction in survivin mRNA and protein levels was ~62.5 nM, with higher concentrations (125 and 250 nM) further decreasing both mRNA and protein levels. A time course analysis showed that Envoyer-encapsulated survivin-targeted siRNA decreased survivin mRNA and protein levels as early as 3 hours post transfection and this trend continued throughout the 48-hour incubation period. Freeze-thaw cycles and storage of Envoyer-encapsulated survivin siRNA at -80°C did not impact the transfection efficiency of the particles. Lastly, intratumoral injection of Envoyer-encapsulated NUF2 siRNA in NOD-SCID gamma mice showed inhibition of tumor growth by 60% but did not induce any changes in body weight. Further analysis of the tumors confirmed successful delivery of the Envoyer and target engagement by the siRNA, indicating that Envoyer nanoparticles are both safe and effective in rodent models of tumorigenesis. Collectively, these data highly suggest that Envoyer encapsulation of siRNA is a stable and efficient delivery system for gene therapy.

Keywords: Biopolymer nanoparticles; siRNA; Gene therapy; Immunogenicity; Drug delivery

Biography:

Trinayan has over 14 years of extensive expertise in the entire drug development process, spanning from discovery through clinical development of small molecules and tRNA-based therapies targeting both oncology and non-oncology indications. Before joining the Envoya team, Trinayan served as the Executive Director of Research at hC Biosciences, where he successfully led proof-of-concept studies for an innovative engineered tRNA. His career includes an 11-year tenure at Karyopharm Therapeutics, where he played pivotal roles in the bench-to-bedside development of Xpovio (selinexor), the first-in-class selective inhibitor of nuclear export (SINE) compound, targeting various hematological malignancies. Trinayan led successfully translational research efforts, encompassing biomarker initiatives to validate clinical trial findings. He earned his MS in Biology from the University of Massachusetts, Lowell, and is currently pursuing an MBA from the Isenberg School of Management at the University of Massachusetts, Amherst.

POSTER PRESENTATIONS

Low Volume Wash, Formulation and Fill Strategies for T Cell Therapies

S. Prakash*, P. Ahuja, and J. Cram
ElevateBio, MA, USA

Abstract:
While many approved cell therapies typically infuse between 50 - 70 mL or more, certain therapies call for a lower infusion volume, such as Lisocabtagene Maraleucel, which is supplied as less than 5 mL aliquots of individual dose components in cryogenic vials. Efforts in the cell therapy space, directed towards improving cell potency and persistence, will likely drive further reduction in the number of cells administered per dose. Given that there is a minimum cell concentration at which these cells can be cryopreserved while maintaining sufficient post-thaw stability, this requires working with much lower volumes in manufacturing. The accuracy and precision required to wash, formulate, and fill small volumes in a closed system requires new and innovative solutions. Final product containers must also be evaluated for suitability with desired administration procedures and their compatibility with fill platforms. Although instruments capable of processing lower volumes are being developed, there is still limited data characterizing their effective operating ranges and practical limitations.

In this study, we evaluate and optimize state-of-the-art modular solutions for low volume wash, formulation and fill, that can easily be incorporated into existing cell manufacturing platforms. We compare individual instruments for wash, formulation and fill, in tandem with platforms capable of performing two or more operations simultaneously. Critical metrics evaluated here include cell recovery, viability, fill accuracy and consistency, as well as the homogeneity of the formulated cell product. We also assess post-thaw viability of the cell therapy drug product that correlates with stress encountered by the cells during processing. To support the choice of a final product container, we measure the recoverable volume via syringe and needle-less adaptors. We also assess the ease of clinical handling and administration. Finally, we provide a cost and time assessment to help drive a complete understanding and identify gaps for future development.

Keywords: Cell therapies; Low volume; Automation; Wash; Formulation; Fill

Biography:

Supriya Prakash is a Scientist I in the Cellular Process Development Department at ElevateBio, working on the accelerating the development of cell therapies for clinical applications. She has obtained her Ph.D. from the John A. Paulson School of Engineering and Applied Sciences where she explored the use of biomaterials for immune cell modulation, with a focus on NK cells and B cells.

POSTER PRESENTATIONS

Single Cell Fluorescence Lifetime Imaging for Subcellular Enzyme Activity

B. T. Harvey, and C. I. Richards*
University of Kentucky, KY, USA

Abstract:
Increasing emphasis has been placed on studying single cell enzyme activity and intracellular localization to better understand the influence of cellular heterogeneity on disease state. However, this is not feasible with many traditional methods due to their ensemble approach, lack of spatial information, or destructive nature. Fluorescence lifetime imaging microscopy (FLIM) offers a non-destructive approach that provides quantitative and spatial information without artifacts associated with other intensity-based imaging methods. Here, we utilized cells engineered to express endoplasmic reticulum localized CYP1 enzyme and the unmodified substrate ethoxyresorufin, which undergoes a lifetime change upon conversion to product. By monitoring fluorescence lifetime contribution by substrate and product, we show FLIM can extract enzyme kinetics of individual cells and subcellular enzyme activity, as well as distinguish enzymes of different activity levels. Additionally, we demonstrate organelle-localized enzyme activity can be visually resolved and sensitivity can be tailored by modifying excitation wavelength. Thus, FLIM can be applied to directly monitor enzyme activity for visualization and quantification of subcellular enzyme kinetics without requiring substrate engineering.
Keywords: Enzymes; Cytochrome P450; Fluorescence lifetime

Biography:
In pursuit of his PhD at the University of Kentucky, Brock Harvey has focused on investigating exosome-mimetic nanovesicles for therapeutic applications, in addition to developing techniques to monitor single cell enzyme activity using fluorescence lifetime. During his graduate career, he has been published in multiple journals, including Advanced Healthcare Materials, Frontiers in Oncology, and ACS Omega. Upon completion of his PhD, he hopes to continue exploring approaches to immune system modulation and developing novel assays and techniques to probe ultramodern biomarkers and the mechanism of action of immune-oncology therapies.

POSTER PRESENTATIONS

Validation of an Impedance-based *in vitro* Potency Assay for Repeatability and Precision

Danielle Califano,
Axion BioSystems, NY, USA

Abstract:

Cell-based immunotherapies, such as CAR T cells, are emerging as a promising approach to therapeutic intervention against cancer. Developing cell and gene therapy products requires reliable and reproducible methods of quantifying critical quality attributes, such as potency, to ensure product strength and consistency. A variety of assays can be used to assess potency; however, it is crucial that these tests are qualified for assay performance to ensure intra- and inter-assay precision. Biological assays, although inherently variable, are often the best methods to investigate a product's mechanism of action and predict clinical outcomes. Previous work has shown that impedance-based potency assays provide a non-invasive, real-time measure of effector cell-mediated cytotoxicity, thus reducing cell manipulation that impacts data reliability. Here, we describe an *in vitro* potency assay that demonstrates low variability and high precision across replicates, analysts, and days. Effector cell-mediated cytotoxicity was performed using a CD19-positive liquid tumor cell line (Raji) tethered to the well surface using an anti-CD40 antibody. CD19-specific CAR T effector cells were added 24 hours after the target cells and co-cultured with the target cells across a range of E: T ratios and cytolysis was monitored for three days. Real-time measurement of cell-mediated cytotoxicity also allowed for the calculation of kill time 50 (KT50), defined as the time required for 50% cytolysis of the target cells. Repeatability was calculated across three replicates per E:T ratio. The co-culture experiment was performed in duplicate by a second analyst and on two subsequent days for a comparison of three plates as well as two operators to evaluate inter-assay precision. In addition to this, CAR T-mediated cell killing in a multiplate impedance system was also investigated for plate-to-plate variability. The percent coefficient of variation (% CV), a statistical measure that describes the precision and repeatability of an assay, was calculated to assess variability between assay replicates, operators, and plate replicates. In all conditions tested, the percent CV for all E:T ratios was below 20% illustrating the repeatability and precision of the assay. These data support the use of an impedance-based potency assay for the evaluation and characterization of immunotherapy products.

Keywords: CART; Immunotherapy; Potency; reproducibility; Cytotoxicity

Biography:

Danielle Califano is a biotech specialist with over 15 years of experience in immunology and research project development. Currently working in business development with a focus on immuno-oncology at Axion BioSystems, From 2019 to 2021, Danielle worked as a Field Application Scientist at Bio-Rad Laboratories and NanoCellect Biomedical, Inc. Prior to that, Danielle served as a Postdoctoral Fellow and Manager of the Flow Cytometry Core at Albany Medical Center. During her time as a Ph.D. Student at Albany Medical College, Danielle's research focused on T cell migration in autoimmune diseases, with a particular emphasis on multiple sclerosis.

CELL & GENE THERAPY SUMMIT-2024

The Global Cell & Gene Therapy Summit 2024

Wednesday, July 10, 2024

July 08-10, 2024 (Hybrid) | Boston, MA

SESSION: REGULATORY LANDSCAPE AND COMMERCIALIZATION STRATEGIES

Preclinical Considerations for Cell and Gene Therapy Products

Kimberley Buytaert-Hoefen

QPS Holdings, LLC, CO, USA

Abstract:

An Investigational New Drug (IND)/Clinical Trail Application (CTA) application is the first regulatory step developers must take when preparing a Cell and Gene Therapy (CGT) for human clinical studies. The specific product characteristics and mechanism(s) of action (MOA(s)), the target disease indication, and the method of product delivery should be considered to define the elements and design of the preclinical testing program. Preclinical *in vitro* assays intended to assess aspects of the biological activity of an investigational CGT product also can provide supporting Proof of Concept (POC) information. *In vitro* studies are important for identification of potential safety issues and MOA of an investigational CGT product. For *in vivo* preclinical testing, animal models of disease/injury should be used to allow for the characterization of resulting morphological changes in conjunction with observable functional/behavioral changes. Due to the biological attributes of the CGT products, the conduct of studies to assess the potential for reproductive/developmental toxicity and carcinogenicity/tumorigenicity is essential.

This presentation will review specific preclinical testing considerations for CGT products and emphasize the importance of having early engagement with regulatory agencies to ensure an adequate preclinical assessment to fulfil requirements for first in human clinical studies.

Biography:

Dr. Kimberley Buytaert-Hoefen earned a bachelor's degree in psychology from the State University of New York at Binghamton, followed by Master's and Doctorate degrees in Neuroscience from the University of Colorado at Boulder. She completed post-doctoral fellowships specializing in embryonic and adult stem cell research at the University of Colorado Health Sciences Center. In 2005, she transitioned to private industry as a Lead Scientist at Navigant Biotechnologies. By 2009, Dr. Buytaert-Hoefen joined the FDA as a Consumer Safety Officer, focusing on pharmaceutical inspections, particularly in biotechnology and sterile processing. As a Consultant, she specializes in Biologics, Gene and Cellular Therapies, and Medical Devices, assisting companies with regulatory document authoring, interactions with regulatory agencies, and compliance with GLP, GCP, and GMP regulations.

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The Unknown Unknowns - New Ways of Identifying and Leveraging Stakeholders in Order to Optimally Operationalize Innovation

Rachel Salzman,

Global Head, Corporate Strategy, Armatus Bio, OH, USA

Abstract:

Gene and cell therapies have proved to be transformational medicines addressing serious unmet medical need, however, the fact remains that these drugs are expensive and often not readily accessible. As a result, patients and their families involuntarily experience both financial and physiological adverse outcomes. In the pursuit of enhancing affordability, while maintaining industry's economic incentives, traditional approaches are evolving to incorporate novel sources of innovation. This presentation explores the integration of diverse stakeholders—scientists, patient groups, payers, policy makers, and others who may still remain to be identified— while underscoring the importance of fostering a sense of urgency to drive transformative advancements in the field.

The discussion begins by acknowledging the persistent challenges in making cell and gene therapies accessible, which often restrict their broad impact on patient populations. Conventional innovation strategies have predominantly focused on technological advancements and regulatory frameworks. However, circumstances call for a notable shift towards embracing unconventional avenues of innovation.

Scientists, renowned for their technical acumen, are increasingly valued not only for their expertise but also for their potential to catalyze cost-effective solutions through interdisciplinary collaboration and disruptive thinking. Patient groups contribute crucial insights derived from firsthand experience with healthcare system deficiencies, thereby illuminating practical realities and unmet therapeutic needs. Policy makers are recognized as pivotal in shaping the innovation landscape. By fostering supportive regulatory environments and incentivizing economically viable research and development initiatives, they play a crucial role in expediting the translation of scientific breakthroughs into accessible treatments.

Central to the discussion is the cultivation of a collective sense of urgency among stakeholders. The evolving landscape necessitates a proactive and open-minded approach to identify and mobilize diverse interest groups with a mission of comprehensive integration towards the common objective. Furthermore, the presentation emphasizes the untapped potential of these stakeholders, highlighting the breadth of interests, pressures, and collaborative opportunities that could contribute to overcoming pricing, reimbursement, and accessibility challenges. This recognition underscores the ongoing necessity for dialogue, experimentation, and adaptive strategies aimed at universally enhancing access to cell and gene therapies.

This talk will reflect upon the unacceptable current state, while encapsulating the imperative for novel collaborative efforts and strategic adaptations to propel advancements in this crucial area of healthcare innovation. It is only via the identification and integration of stakeholders, particularly those who do not traditionally share spaces, that will allow us to make meaningful progress in order to overcome heretofore existential barriers.

Biography:

Dr. Rachel Salzman, CEO of Armatus Bio, specializes in drug development for rare diseases, navigating complex biological and business challenges to address critical medical needs. Previously, she served as Executive Vice President at Alcyone Therapeutics, focusing on precision medicines for neurological disorders. Dr. Salzman co-founded SwanBio Therapeutics in 2017 and held roles including CEO and President until January 2021. She also founded UltraSquared Bio, a nonprofit dedicated to advancing gene therapies for ultra-rare conditions. Earlier, Dr. Salzman served as Chief Science Officer at The Stop ALD Foundation, dedicated to innovative approaches for X-linked adrenoleukodystrophy (ALD). She holds a B.S. in Animal Science from Rutgers University and a DVM from Oklahoma State University in Veterinary Medicine.

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Operational Complexity in Phase-I GMP Cell Therapy Manufacturing: A Compliance Perspective

*N.C. Kotecha

Gates Institute/ University of Colorado, Anschutz Medical Campus, Aurora, CO, USA

Abstract:

In the field of cell therapy, the transition from research laboratory to clinical application poses significant challenges, especially during the critical phase of first-in-human, early-phase clinical trials. These trials are foundational for both safety and efficacy as therapies progress toward commercialization. In my talk, I will discuss the intricate operational complexities encountered in the manufacturing of cell therapy products for early-phase clinical trials, focusing on adherence to Good Manufacturing Practices (GMP) and the implications for a wide range of stakeholders including sponsors, innovators, and regulatory professionals.

A primary challenge in Phase-I manufacturing is the technology transfer process, wherein laboratory protocols are adapted to GMP-compliant production environments. This includes the transfer, material controls analysis, analytical support, and scale-up processes, which must be meticulously managed to secure the target product profile despite the inherent variability of biological materials derived from patient samples.

Effective management of manufacturing process design and change, coupled with adherence to regulatory guidelines on product comparability and quality risk management, is essential to maintain product quality and safety. Development of robust methods to ensure batch-to-batch consistency amidst biological diversity is critical, requiring advanced technological solutions and precise process controls.

Regulatory compliance and quality oversight are crucial components in these trials, with emphasis on the U.S. FDA and global regulatory bodies advocating a phase-appropriate GMP compliance. This approach allows for some procedural flexibility for the early phases but insists on stringent controls over sterility, cell viability, safety, and batch consistency. Unique to the Gates Biomanufacturing Facility (GBF), an academic contract drug manufacturing organization (CDMO), is our bespoke approach to technology transfer, risk management framework and phase-appropriate quality system. We do not merely follow protocols but adapt and innovate, customizing our methods to meet the unique challenges of each new therapy. Our forward-looking, risk-based approach assesses each step from raw material procurement to final product shipping, ensuring strategic evaluation throughout the product development lifecycle. This approach, coupled with our adaptive quality systems, ensures that we not only meet but exceed the highest safety standards, thus reinforcing the trust placed in us by our partners and patients.

My discussion aims to highlight the importance of integrating phase-appropriate yet robust quality systems and a proactive risk management framework to navigate the complexities of early-phase cell therapy manufacturing, ensuring that each transition from concept to clinic is as smooth and successful as possible.

Biography:

Dr. Kotecha serves as the Program Director of Regulatory Affairs at the Gates Institute, a role through which she passionately supports the advancement of transformative cell and gene therapies. With a PhD in Pharmaceutical Sciences, she has dedicated over a decade to diverse roles, from academic researcher and hands-on scientist to strategic quality and compliance leader. Always eager to learn and share knowledge, she values the opportunities to contribute to and influence the regulatory landscape. Deeply committed to her field, she is always striving to bridge the gap between scientific innovation and patient care with a unique blend of expertise, humility and enthusiasm to create a meaningful impact.

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SESSION: REGULATORY LANDSCAPE AND COMMERCIALIZATION STRATEGIES

Maximizing Regulatory and Patent Strategy for Cell and Gene Therapy Manufacturing Success

Susan M. Faust, and Sally Gu

Hogan Lovells LLP, DC, USA

Abstract:

The average time it takes for a patent application filed with the United States Patent and Trademark Office (USPTO) to become an enforceable patent is currently 25.4 months. The time to an FDA approval is even longer - > 10 years on average. Expediting these processes is critical for enhanced financing opportunities, gaining competitive advantages, and generating revenue quickly. In this session, we will discuss considerations for efficiently navigating regulatory and patent processes to avoid unnecessarily delays and expediting product development.

Biography:

Susan M. Faust, Ph.D., draws on her diverse experience in scientific research, academic technology transfer, patent prosecution, and business development to help build and manage strategic patent portfolios for life science companies. Dr. Faust also founded a gene therapy startup which received Series A and B investments and an issued patent on the company's platform technology which lists her as an inventor. She earned her Ph.D. from the University of Michigan and performed a postdoctoral fellowship at the University of Pennsylvania.

Sally Gu, JD, is a life sciences regulatory attorney at Hogan Lovells. She leverages her experience and understanding of the complex US regulatory landscape to counsel clients on strategies for development, approval, marketing, and distribution of regenerative medicine therapies. She has extensive experience in guiding clients through the investigational new drug (IND) and marketing application processes, as well as handling post-approval compliance issues such as advertising and promotion, good manufacturing practices, and market access strategies.