INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

ACCELERATING PSC-DERIVED CELL THERAPIES: STARTING WITH THE END IN MIND

An ISSCR International Symposium

11-12 DECEMBER 2025

BOSTON, USA

PROGRAM & ABSTRACT BOOK

ABOUT THE ISSCR

INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

The International Society for Stem Cell Research
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isscr.org

The International Society for Stem Cell Research (ISSCR) is a 501c(3) nonprofit organization with a mission to promote excellence in stem cell science and applications to human health. Our vision is a world where stem cell science is encouraged, ethics are prioritized, and discovery improves understanding and advances human health.

The ISSCR represents nearly 5,000 scientists, students, educators, ethicists, and business leaders from more than 80 countries. Each ISSCR member makes a personal commitment to uphold the ISSCR Guidelines for Stem Cell Research and Clinical Translation, an international benchmark for ethics, rigor, and transparency in all areas of practice.

Our work is made possible through generous support from our members and allied organizations towards strategic initiatives that support the mission:

- **Regulatory Affairs:** The ISSCR helps members navigate the regulatory landscape while assisting regulators by making scientifically informed recommendations for the development of stem cell therapies.
- **Policy:** The ISSCR advocates globally to support research funding, enforce ethical guidelines, and guard against unproven therapies.
- **Education:** The ISSCR provides resources for patients, clinicians, educators, policymakers, and the interested public. Aboutstemcells.org and ISSCR's Patient Handbook provide trusted information for those considering stem cell treatments. Clinicians can also access dedicated resources, including the new continuing education course with Harvard and updated disease-specific fact sheets.
- **Standards and Guidelines:** The ISSCR sets international guidance for ethical and rigorous research, adopted by public and private organizations, regulatory bodies, funders, and publications. These references strengthen the pipeline of research and therapies, ultimately to benefit the patient.
- **International Conferences:** The ISSCR hosts a portfolio of international and digital meetings designed for knowledge sharing and collaboration to further the field. Discover upcoming programs, including the ISSCR 2026 Annual Meeting.
- **Publishing:** The ISSCR publishes *Stem Cell Reports*, an open access journal communicating basic discoveries in stem cell research alongside translational and clinical studies.

Our Board of Directors and Committees represent leaders across research, academia, and industry who are committed to advancing the Society's mission.

Learn more at isscr.org.

ABOUT *STEM CELL REPORTS*

STEM CELL REPORTS

Stem Cell Reports

www.cell.com/stem-cell-reports/home

Stem Cell Reports is an open access forum communicating basic discoveries in stem cell research, in addition to translational and clinical studies. *Stem Cell Reports* focuses on manuscripts that report original research with conceptual or practical advances that are of broad interest to stem cell biologists and clinicians. *Stem Cell Reports* participates in Cell Press Multi-Journal Submission, allowing authors to simultaneously submit their papers for consideration by multiple journals at once.

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CCRM Commercializing Living Therapies

Genentech
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Inserm
La science pour la santé
From science to health

Korean Society for Stem Cell Research

LUNDS UNIVERSITET

Mytos

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SCOTTISH NATIONAL BLOOD TRANSFUSION SERVICE

TreeFrog therapeutics

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ISSCR UPCOMING PROGRAMS

SUMMIT ON ACCESS AND AFFORDABILITY IN CELL AND GENE THERAPIES

20 MARCH 2026 | LOS ANGELES, USA

IN COLLABORATION WITH:

CIRM California Institute for Regenerative Medicine

UCLA Broad Stem Cell Research Center

ISSCR 2026 ANNUAL MEETING

THE GLOBAL STEM CELL EVENT

8-11 JULY 2026 | MONTRÉAL, CANADA

CO-SPONSORED BY: STEMCELL™ TECHNOLOGIES

20 YEARS OF IPSC DISCOVERY: A CELEBRATION AND VISION FOR THE FUTURE

KYOTO INTERNATIONAL SYMPOSIUM

20-22 OCTOBER 2026 | KYOTO, JAPAN

IN PARTNERSHIP WITH: Center for iPS Cell Research and Application, Kyoto University CiRA

CO-SPONSORED BY: JSRM

DISEASE MODELING AND DRUG DISCOVERY SYMPOSIUM

SAN DIEGO INTERNATIONAL SYMPOSIUM

14-16 DECEMBER 2026 | SAN DIEGO, USA

CO-SPONSORED BY: maxwell BIOSYSTEMS

Learn more at **isscr.org/upcoming-programs**

BlueRock Therapeutics is proud to sponsor ISSCR's 2025 PSC-Derived Therapies Symposium in Boston.

BlueRock THERAPEUTICS

BLUEROCKTX.COM

MEETING INFORMATION

ONSITE BADGE PICK UP

Pick up your name badge in the designated area during the hours below. Name badges are required for admission to all sessions, social events, meals/breaks, and the Exhibit & Poster area. Badges can be picked up during the following times:

Registration Desk Hours | Lobby of the Hyatt Regency Cambridge Boston

Thursday, 11 December	**7:30 AM – 6:00 PM**
Friday, 12 December	**7:30 AM – 3:30 PM**

ISSCR PROGRAM AGENDA

There will be no printed program book for the 2025 PSC-Derived Therapies Symposium. You can access the online version of the program agenda here: Full Schedule

LIVESTREAMING

Livestream will not be available for this event. However, registrants can access the audio and slide recordings on-demand after the event by logging into the Member Library with their ISSCR credentials. An email will be sent approximately two weeks after the event to notify attendees that the on-demand content is ready for viewing.

ABSTRACT REVIEWERS

Xiaowen Bai, Jan Willem Buikema, Thomas H.R. Carlsen, Claire Henchcliff, Ana Hildago, Ran Jing, Andrew Kahlil, Henning, Kempf, Howard Kim, Erin Kimbrell, Jane Lebowski, Tenneille Ludwig, Chad MacArthur, Heather Main, Jørn Petersen, Amanda Rickard, Shreya Shukla, Mark Tomishima, Yongting Wang, Juliana Ya-Chu, Wolfram Zimmermann

SMOKING

Smoking or the use of e-cigarettes is prohibited.

LOST AND FOUND

Please bring found items to the ISSCR Registration Desk during posted hours. If you lose an item, visit the registration desk during posted hours for assistance.

POSTER INFORMATION

Each poster will be presented during a 60-minute session in the Amesbury Ballroom ABC and Foyer space on the lobby level of the Hyatt Regency Boston / Cambridge. Poster presenters must adhere to the scheduled date and time of their poster display and presentation.

Poster presenters are responsible for removing their posters on Friday, 12 December between 3:10 PM – 3:25 PM. Any posters not removed at the end of their session will be discarded.

POSTER PRESENTATION SCHEDULE

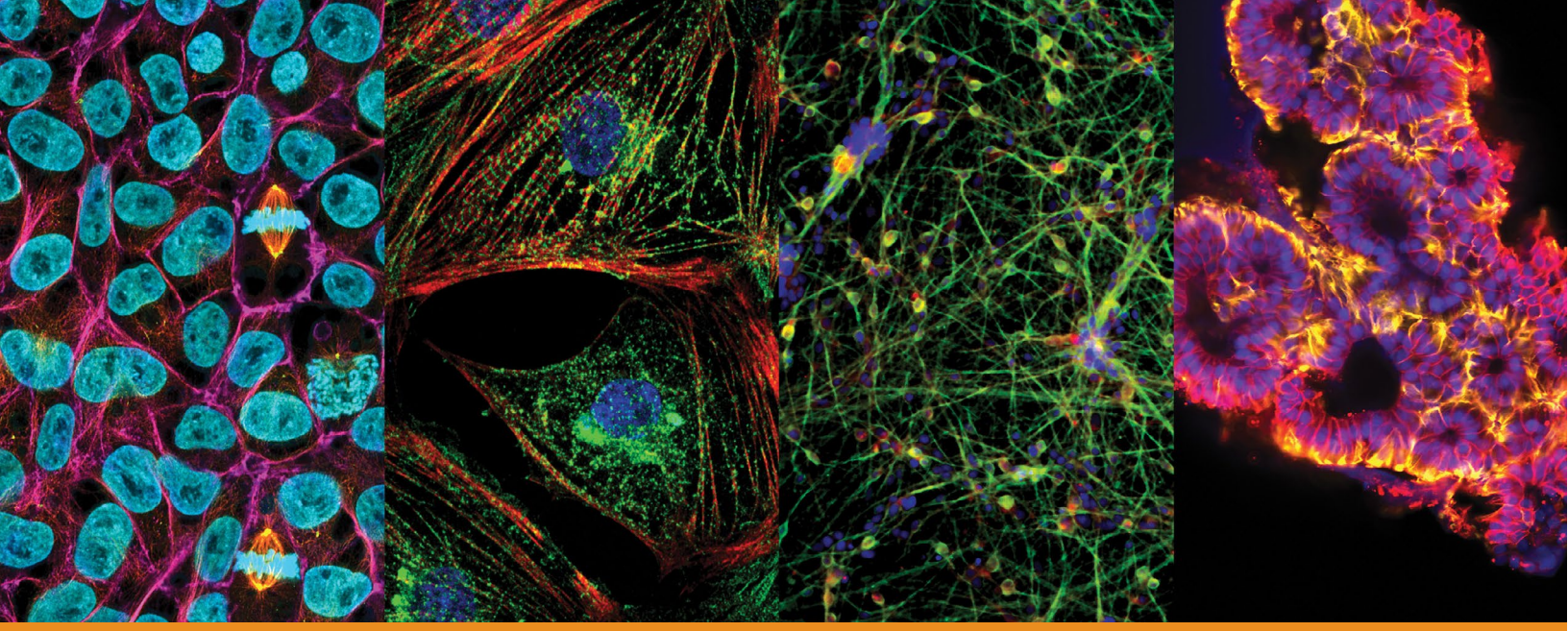
Thursday, 11 December 2025

10:20 AM – 10:45 AM	**All posters to be put up**
5:15 PM – 6:15 PM	**Poster Session 1 ODD**
6:15 PM – 7:15 PM	**Poster Session 2 EVEN**

Friday, 12 December 2025

3:10 PM – 3:25 PM	**All posters to be taken down**


ISSCR
Your Access to a World of Stem Cell Discoveries
JOIN OUR GLOBAL COMMUNITY
The ISSCR supports members with access to breakthrough science, career resources, global advocacy, and collaboration through global events. There is strength in numbers, and our numbers are growing.
LEARN MORE AT
https://www.isscr.org/membership



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BLUEROCK THERAPEUTICS

https://www.bluerocktx.com/

BlueRock Therapeutics LP is a clinical stage cell therapy company focused on creating cellular medicines to treat devastating diseases. We are harnessing the power of cell therapy to create a pipeline of new medicines for people suffering from neurological and ophthalmic diseases. Two of our novel investigational cell therapies, bemdaneprocel (BRT-DA01) for the treatment of Parkinson's disease and OpCT-001 for the treatment of primary photoreceptor diseases are clinical stage programs. Bemdaneprocel has RMAT (Regenerative Medicine Advanced Therapy) and Fast Track designation from the US FDA (Food and Drug Administration) and is being tested in a Phase III clinical trial, exPDite-2. OpCT-001 has Fast Track designation from the FDA and is being tested in a Phase 1 clinical trial, Clarico. BlueRock Therapeutics is a wholly owned, independently operated subsidiary of Bayer AG. Our culture is defined by the courage to persist regardless of the challenge, the urgency to transform medicine and deliver hope, integrity guided by mission, and community-mindedness with the understanding that we are all part of something bigger than ourselves. For more information, visit www.bluerocktx.com.

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ASTELLAS

https://www.astellas.com/en/

Astellas is a global life sciences company committed to turning innovative science into VALUE for patients. We provide transformative therapies in disease areas that include oncology, ophthalmology, urology, immunology and women's health. Through our research and development programs, we are pioneering new healthcare solutions for diseases with high unmet medical need. Learn more at www.astellas.com.

ELI LILLY AND COMPANY

https://www.lilly.com/

Lilly is a medicine company turning science into healing to make life better for people around the world. We've been pioneering life-changing discoveries for nearly 150 years, and today our medicines help tens of millions of people across the globe. Harnessing the power of biotechnology, chemistry and genetic medicine, our scientists are urgently advancing new discoveries to solve some of the world's most significant health challenges: redefining diabetes care; treating obesity and curtailing its most devastating long-term effects; advancing the fight against Alzheimer's disease; providing solutions to some of the most debilitating immune system disorders; and transforming the most difficult-to-treat cancers into manageable diseases. With each step toward a healthier world, we're motivated by one thing: making life better for millions more people. That includes delivering innovative clinical trials that reflect the diversity of our world and working to ensure our medicines are accessible and affordable.

EVOTEC

https://www.evotec.com/solutions/next-gen-platforms/ipsc-cell-therapies

Evotec is a life science company pioneering drug discovery and development through deep disease expertise, AI-driven platforms, and advanced technologies. Working across modalities, our fully integrated R&D value chain and flexible partnering models accelerate the journey from concept to cure - faster, smarter, and with greater precision. One of Evotec's key areas is cell therapy, where we offer a fully integrated end-to-end platform to move iPSC-based projects from inception to the clinic, including in-house GMP manufacturing capabilities with clinical supply. Our platform is one of the broadest in the industry and includes cell types for anti-tumor therapies (NK cells, macrophages, αβ T cells, γδ T cells), regenerative therapies (beta cells, cardiomyocytes, photoreceptors) and immune-modulation therapies. In addition, Evotec provides integrated drug development solutions, covering safety assessment, CMC, process and analytical development, regulatory and clinical services for autologous and allogeneic cell therapy candidates.

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MAXWELL BIOSYSTEMS

https://www.mxwbio.com/

MaxWell Biosystems is a technology leader providing instrumentation and solutions to boost scientific research and development in neurosciences, stem cell and tissue engineering, ophthalmology, and other fields involving electrogenic cells. The company engineered advanced high-density microelectrode arrays (HD-MEAs) as the core of easy-to-use platforms, MaxOne (single-well) and MaxTwo (multi-well), that equip scientists to record electrical signals of neurons in in-vitro 2D and 3D models. MaxWell Biosystems' HD-MEA technology allows to capture neuronal activity across multiple scales, from sub-cellular to single cells, up to full networks in unprecedented detail. Ultimately, MaxWell Biosystems' platforms facilitate the understanding of neurological diseases, enhance the efficiency of cell-based assays for toxicity and safety pharmacology, and accelerate drug discovery.

STEMCELL TECHNOLOGIES

https://www.stemcell.com/

At STEMCELL Technologies, science is our foundation. Driven by our mission to advance research globally, we offer over 2,500 tools and services supporting discoveries in stem cell research, regenerative medicine, immunotherapy, and disease research. By providing access to innovative techniques like gene editing and organoid cultures, we are helping scientists accelerate the pace of discovery. Inspired by knowledge, innovation, and quality, we are Scientists Helping Scientists

SYNTAX BIO

https://www.syntax-bio.com/

Syntax Bio's regenerative medicine discovery platform overcomes the longstanding challenges in stem cell-derived therapies by directly controlling and accelerating cell differentiation. A shorter and more reliable iPSC differentiation process improves patient access by making stem cell discovery and manufacturing faster, less costly and scalable. Synatx's proprietary Cellgorithm technology mimics human development using a sequential synthetic biology CRISPR-based system to generate a wide diversity of functional cell types to enable new cell and gene therapy product opportunities.

SILVER SPONSORS

APPLIED STEMCELL

https://appliedstemcell.com/

Founded in 2008 to provide industry and academic researchers with the ability to leverage the power of gene editing and induced pluripotent stem cells (iPSC), Applied StemCell continues to use our innovative technologies to power the discovery and development of advanced therapeutics. With a focus on genome engineering products and services, our patented technologies ensure a clear IP path to commercialization.

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BIO-TECHNE

https://www.bio-techne.com/

Get to know Bio-Techne Bio-Techne is headquartered in Minneapolis, Minnesota and employs over 3,000 people globally at 34 locations worldwide. As a global developer, manufacturer and supplier of high-quality reagents, analytical instruments and precision diagnostics, Bio-Techne has an extensive catalog of over 500,000 products. Incorporated in 1981 as R&D Systems, the company changed its name to Bio-Techne in 2014. Our growth has been accelerated through acquisitions, organic investments, diversification of our customer base and expansion into new markets. In fiscal year 2023, Bio-Techne delivered net sales of over $1.1 billion. Bio-Techne includes the following brands: ACD, Asuragen, Lunaphore, Novus Biologicals, ProteinSimple, R&D Systems and Tocris Bioscience.

CATALENT

https://www.catalent.com/

Catalent, Inc. is a leading global contract development and manufacturing organization (CDMO) championing the missions that help people live better and healthier lives. Every product that Catalent helps develop, manufacture and launch reflects its commitment to improve health outcomes around the world through its Patient First approach. Catalent provides unparalleled service to pharma, biotech and consumer health customers, delivering on their missions to transform lives. Catalent tailors end-to-end solutions to meet customers' needs in all phases of development and manufacturing. With thousands of scientists and technicians and the latest technology platforms at more than 40 global sites, Catalent supplies billions of doses of life-enhancing and life-saving treatments for patients annually.

THE CELL AND GENE THERAPY CATAPULT

http://ct.catapult.org.uk/

The Cell and Gene Therapy Catapult (CGT Catapult) is an independent innovation and technology organisation committed to the advancement of the CGT industry with a vision of a thriving industry delivering life changing advanced therapies to the world. Its aim is to create powerful collaborations which overcome challenges to the advancement of the sector. With around 300 experts covering all aspects of advanced therapies, it applies its unique capabilities and assets, collaborates with academia, industry and healthcare providers to develop new technology and innovation.

THE CENTRE FOR COMMERCIALIZATION OF REGENERATIVE MEDICINE

http://ccrm.ca/

TCCRM, a Canadian public-private partnership established with seed funding by the Government of Canada, the Province of Ontario, and leading academic and industry partners, supports the development of regenerative medicines and associated enabling technologies, with a specific focus on cell and gene therapy. A network of academic researchers, leading companies, investors and entrepreneurs, CCRM accelerates the translation of scientific discovery into new companies and marketable products for patients, with specialized teams, funding and infrastructure. CCRM sources and evaluates IP from around the globe, conducts development projects with partners, and establishes new companies built around strategic bundles of IP. In 2022, CCRM established OmniaBio Inc., a pre-clinical to commercial-scale CDMO for manufacturing gene-modified cells and viral vectors. CCRM is hosted by the University of Toronto and launched in 2011.technology and innovation.

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GENENTECH

https://www.gene.com/

Our ability to bring transformative medicines to patients depends on the positive experience, engagement and resilience of everyone who works here. Our employees are the heart of Genentech and the driving force behind the progress that brings important new medicines to the people who need them. We believe a great people experience is critical for revolutionizing healthcare and living Our Promise. That's why we're committed to cultivating an environment where people feel valued, included and able to thrive.

THE FRENCH INSTITUTE OF HEALTH AND MEDICAL RESEARCH INSERM

http://www.inserm.fr/

NSERM, the National Institute of Health and Medical Research (www.inserm.fr) is the largest public health and medical research organization in France. It coordinates several national research infrastructures that support high-level competitive translational research and innovation.

CiTHERA, (https://cithera-ipsc.com) the Center for IPS Cell Therapies of INSERM linked to PARIS SACLAY University, hosts the National iPSC HAPLOBANK Platform and translates Stem Cell research into advanced, breakthrough cellular therapies in collaboration with leading biotech and pharmaceutical partners.

Korean Society for Stem Cell Research (KSSCR)

https://www.ksscr.org/en/main/

Founded in 2005, the Korean Society for Stem Cell Research (KSSCR) is Korea's leading scientific society dedicated to advancing stem cell and regenerative medicine research, with a membership of approximately 2,000 researchers and clinicians. The Society brings together scientists, clinicians, and policy leaders to promote research excellence, foster clinical translation, and strengthen global collaboration. KSSCR works closely with the ISSCR through participation in guideline development, regulatory dialogue, scientific programs, and patient-education initiatives.

Lund University

https://www.stemcellcenter.lu.se/

Lund Stem Cell Center at Lund University in Sweden is funded by the StemTherapy grant and is a national initiative of stem cell research for regenerative medicine.

MYTOS

https://www.mytos.bio/

Mytos is a vertically integrated automated CDMO for regenerative medicines. We've integrated our proprietary closed, flask-based automation to deliver scalable, consistent, and cost-effective manufacturing solutions for regenerative medicines.

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PBS BIOTECH

https://www.pbsbiotech.com/

PBS Biotech manufactures single-use Vertical-Wheel® Bioreactors optimized for homogenous expansion, differentiation, and scale-up of multiple cell types for cell and gene therapy applications. PBS' Bioprocess R&D team offers CDO services to expedite your process development for scalable, reproducible, and cost-effective cell therapy manufacturing. For more information, please contact sales@pbsbiotech.com

SCOTTISH NATIONAL BLOOD TRANSFUSION SERVICE

https://www.at-tcat.nhs.scot/

SNBTS have over 20 years' experience delivering autologous and allogeneic products for in vivo studies and First in Human, Phase 1 and Phase 2 trials. As an NHS establishment we are uniquely positioned to support academic and other early-stage developers in the translation of their 'proof of concept' stage products into GMP-compatible processes, and to manufacture these products for early-stage clinical trials. We have proven expertise working with somatic cells, pluripotent stem cells and their derivatives, and genetically modified cell therapies. Alongside our GMP capability we have extensive in-house Quality Control capacity specifically developed for Advanced Therapy Medicinal Products (ATMPs). SNBTS is the sole provider of Apheresis services in Scotland for procurement of autologous and allogenic hematopoietic stem cells.

TREEFROG THERAPEUTICS

https://treefrog.fr/

TreeFrog Therapeutics is an R&D biotech advancing a pipeline of cell therapies based on a proprietary technology platform, C-Stem™ that overcomes several of the major challenges in cell therapy development - producing safe, high-quality, cell therapies at scale. C-Stem™ is the world's first GMP-compliant cell encapsulation device capable of generating over 1,000 capsules per second. It enables the seeding of up to 10-liter bioreactors and delivers 15 billion cells in a single batch run

THE UNIVERSITY OF HONG KONG

https://www.hku.hk/

The University of Hong Kong is a world-leading university transforming humanity's future with a mission to attract, nurture, and inspire future leaders to create knowledge, address global challenges, advance humanity and promote sustainability, to leverage our unique heritage and global position to connect and impact East and West through an extensive network of intellectual hubs, and to transform our University by exploiting and exploring artificial intelligence to its fullest.

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BIT.BIO

https://www.bit.bio/

bit.bio designs and manufactures consistent, defined, and scalable human cells for research, drug discovery, and cell therapy. bit.bio has a partnership strategy that enables access to its proprietary opti-ox, deterministic cell programming technology, and cell identity coding platform. These technologies can reproducibly and consistently generate billions of defined human cells in days, not months.

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CARR BIOSYSTEMS

https://www.carrbiosystems.com/

Headquartered in Clearwater, Florida, and part of the Barry-Wehmiller family of companies, CARR Biosystems partners with leading therapy developers worldwide to advance the next generation of cell and gene therapies - helping bring life-changing treatments to patients faster.

CELLVOYANT

www.cellvoyant.com

CellVoyant is a biotechnology company that predicts stem cell differentiation using live cell microscopy and artificial intelligence. We use this approach to optimise and unlock human cell manufacturing for research and therapeutics applications. We aim to understand and solve important health issues, make a long-lasting positive impact on society and change the world. At the heart of CellVoyant is FateView™, our AI-powered SaaS platform. FateView™ enables biologists to visualize, track, and forecast cell differentiation in real-time. It supports highthroughput experimentation and model inference, combining microscopy, computer vision, cloud infrastructure, and AI to serve cutting-edge stem cell research and manufacturing.

KENAI THERAPEUTICS

www.kenaitx.com

Kenai Therapeutics is a biotechnology company pioneering next generation approaches to cure neurological conditions. The Company utilizes induced pluripotent stem cell (iPSC) technology, a Nobel Prize-winning breakthrough that enables scientists to manufacture any human cell, to generate Kenai's off-the-shelf neuron replacement therapeutics. By focusing on an iPSC technology platform, and forging partnerships with global leaders in surgical delivery and clinical development, Kenai is dedicated to advancing a best-in-class pipeline targeting neurological conditions. Kenai Therapeutics closed an $82 million Series A financing in 2024, co-led by Alaska Permanent Fund Corporation, Cure Ventures and The Column Group, with participation from Euclidean Capital and Saisei Ventures.

LOGOMIX BIOTECHNOLOGY

https://logomix.bio/

Logomix Biotechnology is reshaping iPSC engineering through its proprietary genome platform, Geno-Writing™. The platform's unique power lies in its ability to deliver precise, allele-specific, and high-throughput modifications on a megabase scale, with minimal off-target effects. This capability enables rapid iPSC engineering breakthroughs, such as stable expression of up to 12 transgenes from our original landing pad locus in human iPSCs within 2.5 months. Furthermore, we can directly delete all major HLA gene loci and induce stable expression of any HLA allotypes within 4 months to generate hypoimmunogenic iPSC lines. These cutting-edge capabilities are highly versatile, allowing us to collaborate with multiple partners seeking to enhance the functionality or confer novel properties to human cells for diverse applications. Geno-Writing™ also fuels our internal programs, notably our Type 1 Diabetes program, focused on developing iPSC-derived cells with enhanced therapeutic potential to address key clinical and manufacturing

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challenges. Moreover, we are automating the Geno-Writing process to allow for the simultaneous, high-speed creation of thousands of iPSC lines, each with a distinct genome design. Crucially, this high-throughput capability is the foundation for developing sophisticated algorithms and perturbation models that can propose optimal genome designs, dramatically accelerating the enhancement of iPSC functionality on Geno-Writing™ platform.

MASSACHUSETTS LIFE SCIENCES CENTER

https://www.masslifesciences.com/

The Massachusetts Life Sciences Center (MLSC) is a quasi-public economic development investment agency dedicated to supporting the growth and development of the life sciences in Massachusetts, home to the most verdant and productive life sciences ecosystem in the world. Through public-private funding initiatives, the MLSC supports innovation, research and development, commercialization, and manufacturing activities in the fields of biopharma, medical device, diagnostics and digital health. Since 2008, the MLSC has strategically deployed more than $1.1 billion in Massachusetts, through a combination of grants, loans, capital infrastructure investments, tax incentives and workforce development programs. These investments have created thousands of jobs and propelled the development of new therapies, devices and scientific advancements that are improving patient health and well-being in Massachusetts and beyond.

NOVARTIS

www.novartis.com

Novartis is an innovative medicines company. Every day, we work to reimagine medicine to improve and extend people's lives so that patients, healthcare professionals and societies are empowered in the face of serious disease. Our medicines reach 296 million people worldwide.

WICELL

https://www.wicell.org/

From bench to clinic, WiCell is your source for cGMP-compliant starting materials and the cGMP assays you need to support your cell therapy and product development up to, and beyond, regulatory submission. A trusted partner in the industry for over 25 years, WiCell has the experience in cell banking and testing required to ensure high quality and consistent material for your clinical program. Additionally, WiCell has the cGMP karyotype, FISH, and STR testing services to ensure the genetic stability and identity of your products. WiCell offers this testing for a variety of species and cell types, including hESC, iPSC, MSC, Fibroblast, and T-Cells. WiCell also offers non-cGMP testing for karyotype, FISH, STR, undifferentiated status, pluripotency, SNP microarray, and mycoplasma detection as well as a diverse cell-line catalog of over 1500 stem cell lines in a wide range of disease models. Let WiCell be your trusted partner on your path to the clinic with the cells and testing services you need.

EXHIBITORS

ACROBiosystems Group

https://www.acrobiosystems.com/

ACROBiosystems Group, founded in 2010 and listed in 2021, is a biotechnology company aimed at being a cornerstone of the global biopharmaceutical and healthcare industries by providing products and business models innovation. The company spans across the globe and maintains offices, R&D centers, and production bases in over 10 different cities within the United States, Switzerland, England and Germany. ACROBiosystems Group has established numerous long-term and stable partnerships with the world's top pharmaceutical enterprises, including Pfizer, Novartis, and Johnson & Johnson, and numerous well-known academic institutes. The company comprises of several subsidiaries such as ACROBiosystems, bioSeedin, Condense Capital, and ACRODiagnostics.

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ACROBiosystems' brands include FLAG, Star Staining, ViruStop, Aneuro, ComboX, GENPower, and many others. Its main products and services are recombinant proteins, kits, antibodies, scientific services, and other related products. ACROBiosystems employs a strict quality control system for its products that are used in biopharmaceutical research and development, production, and clinical application. This includes targeted discovery and validation, candidate drug screening/optimization, CMC development and pilot production, preclinical research, clinical trials, commercial production, and clinical application of companion diagnostics.

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AMSBIO

https://www.amsbio.com/

Accelerate your discovery with Amsbio, a premier life sciences supplier with over 35 years of expertise. Dedicated to supporting diverse research needs, Amsbio offers high-quality products and advanced, customizable services. Amsbio's focus on underserved areas like Glycobiology reflects a commitment to advancing niche fields in life science. Amsbio is ISO9000 Certified to ensure easy partnerships, and with European, US, and UK distribution hubs, global shipping and no minimum order quantities, Amsbio is committed to making products accessible to researchers worldwide.

BioLamina

BIOLAMINA

https://www.biolamina.com

BioLamina is a biotechnology company with a scientific base and heritage in matrix biology and cell culture research. It supports scientists who have struggled for decades to grow pluripotent stem cells and other primary cells in the lab. By providing tools for efficient and easy cell culture, BioLamina aims to ease the path towards safe and effective cell therapies and make better cell assays and models for increasing accuracy in drug discovery and development. The power of Biolaminin® substrates, developed by BioLamina, has been demonstrated in numerous publications, and they will continue to provide vital support to the stem cell community, from scientific concepts to clinical studies.

CaseBioscience®
INNOVATIVE QUALITY BIOSOLUTIONS

CASEBIOSCIENCE

www.casebioscience.com

CaseBioscience® is advancing next-generation cryopreservation and culture media solutions to support the safe and reliable development of PSC-derived cell therapies. By uniting insights from stem cell science and assisted reproductive technology (ART), we are redefining how sensitive cells are preserved, handled, and prepared for translational applications.

At ISSCR 2025 Boston International Symposium, CaseBioscience will present a poster exploring how artificial intelligence can accelerate the discovery of safer and more effective cryopreservation solutions for stem cell applications, including the identification of potential DMSO-free cryoprotectants—demonstrating innovative approaches to improve post-thaw cell survival and functionality.

In addition to our research, CaseBioscience offers a comprehensive cryopreservation media portfolio and provides contract and custom media manufacturing services, helping partners design, optimize, and scale high-quality formulations tailored to their applications.

Operating under ISO 13485:2016 certification, cGMP standards, and within an FDA-registered facility, we are committed to delivering the highest levels of quality, consistency, and performance.

Visit our poster and table to discover how CaseBioscience is developing next-generation tools to enable PSC-derived research and therapies, including CaseCryo® CTG DMSO and CaseCryo® CTG NON-DMSO, both Cell Therapy Grade, along with our growing portfolio of cryopreservation solutions optimized for quality, safety, and consistency.

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MEDCHEMEXPRESS LLC

https://www.medchemexpress.com

MedChemExpress (MCE) is a trusted global supplier of high-quality research chemicals and biochemicals, dedicated to advancing scientific innovation. We offer a comprehensive portfolio of reagents essential for biomedical and pharmaceutical research.

Our catalog includes 80,000+ selective inhibitors and agonists targeting over 1,000 proteins across 20 major signaling pathways. There are 11,000+ recombinant proteins, 5,000+ antibodies, 8,000+ natural products, 200+ fully customizable compound libraries and 200+ biochemical assay kits. These products are widely used in key research areas such as cancer, neuroscience, immunology, and infectious diseases. In addition to our extensive product range, MCE provides a suite of custom services, including chemical synthesis, oligonucleotide synthesis, peptide/protein/antibody production, high-throughput screening, and analytical chemistry support. Backed by an experienced scientific team, we tailor our services to meet the evolving demands of the biopharmaceutical industry and accelerate scientific discovery. At MCE, quality is our top priority. Every product undergoes rigorous quality control - such as HNMR, LC-MS, HPLC, stability analysis, and bioactivity validation - to ensure identity, purity, and performance. We are committed to being your reliable partner in driving drug discovery and life science research forward.

PEPTIGROWTH

https://peptigrowth.com/en/

PeptiGrowth Inc., a joint venture of Mitsubishi Corporation and PeptiDream, develops innovative synthetic peptides that match or surpass the activity of conventional recombinant growth factors and cytokines. Our PG-peptides (Synthetic Peptide Growth Factors) are fully chemically synthesized, eliminating lot-to-lot variability and risks associated with animal-derived components. This ensures consistent quality, safety, and reliability—making them ideally suited for stem cell research, cell therapy, and regenerative medicine. Compared to traditional growth factors, PG-peptides demonstrate superior stability during both storage and culture conditions. Our expanding product lineup includes synthetic peptide growth factors for HGF, BDNF, Noggin, VEGF, Wnt3a, TPO, FGF2, and KGF, with IL-15 scheduled for launch in late 2025. At PeptiGrowth, we are dedicated to advancing next-generation cell and regenerative medicine by providing high-quality, synthetic alternatives to recombinant growth factors.

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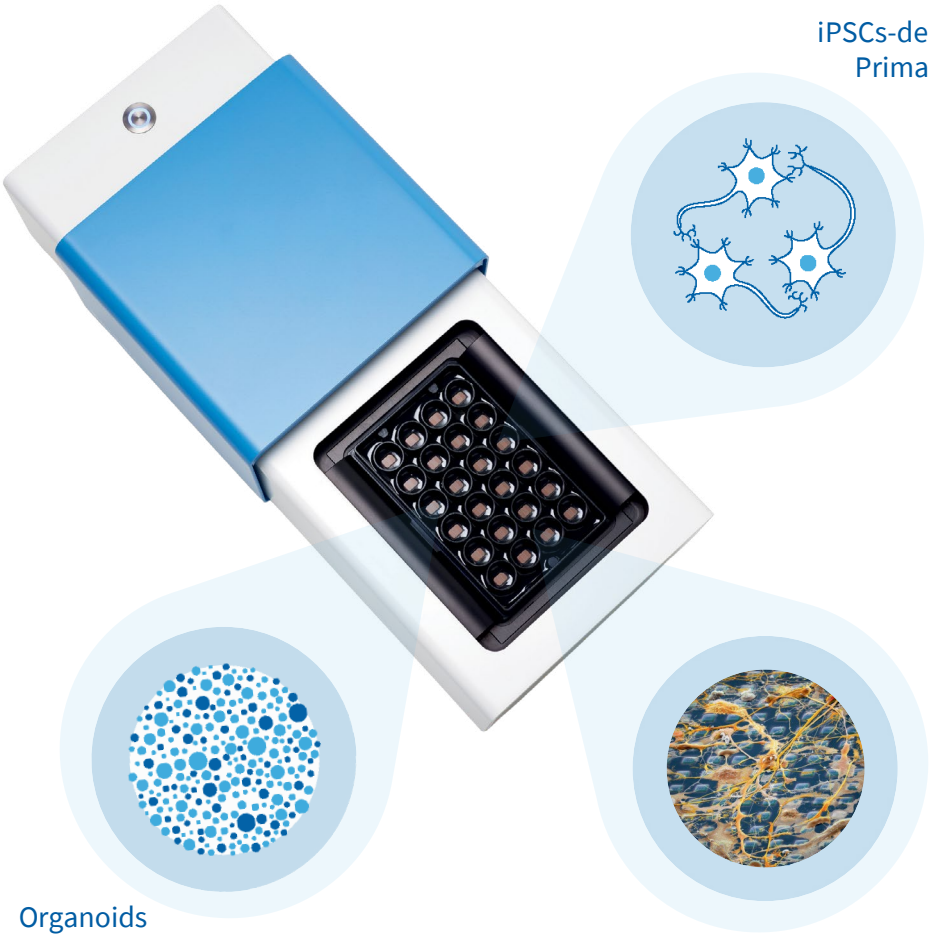

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SPEAKER ABSTRACTS AND SPONSORED INNOVATION SHOWCASES

All times are listed in Eastern Standard Time (EST)

THURSDAY, 11 DECEMBER 2025

9:00 AM – 10:20 AM

PSC CLINICAL TRIALS: PHASE II & BEYOND PART I

Sponsored by BlueRock Therapeutics

9:00 AM - 9:03 AM
OPENING REMARKS

Keith Alm, *CEO, ISSCR*

9:03 AM - 9:06 AM
WELCOME FROM GAiT

Jacqueline Barry, *CGT Catapult & GAiT, UK*

9:06 AM - 9:09 AM
STEM CELL REPORTS UPDATE

Janet Rossant, *Gairdner Foundation & Stem Cell Reports, Canada*

9:09 AM - 9:20 AM
PROGRAM INTRODUCTION & OVERVIEW

Claire Henchliffe, *Vert University of California, Irvine, USA*

9:20 AM - 9:50 AM

DEVELOPMENT OF STEM CELL DERIVED ISLET CELL THERAPIES FOR TYPE 1 DIABETES

Felicia Pagliuca, *Vertex Pharmaceuticals, USA*

ABSTRACT NOT AVAILABLE AT THE TIME OF PUBLISHING

9:50 AM - 10:20 AM

TOWARD THE FIRST POTENTIALLY REGISTRATIONAL TRIAL OF A PSC-DERIVED CELL THERAPY FOR PARKINSON'S DISEASE: CLINICAL DEVELOPMENT OF BEMDANEPROCEL

Joohi Jimenez-Shahed, *Mount Sinai, USA*

Bemdaneprocel is an investigational cell therapy composed of human embryonic stem cell-derived midbrain dopaminergic neuron progenitor cells in development for Parkinson's disease (PD). In exPDite (NCT04802733), a completed Phase 1 open-label study, predefined safety, tolerability, and feasibility criteria were met at 1 year, and trends toward improvement or stability in clinical assessments were observed through 2 years post transplantation. Twelve participants received low-dose (n=5; 0.9 million cells/putamen) or high-dose (n=7; 2.7 million cells/putamen) bemdaneprocel injected bilaterally into the postcommissural putamen in a single surgical session. A 1-year immunosuppression regimen began immediately preoperatively. Following study completion, all participants enrolled in a continued-evaluation study through 5 years post transplantation (NCT05897957). Participants (N=12) were a median of 67.0 years of age, 75% male, and 67% White. Median time since PD diagnosis was 9.0 years. Through 2 years post transplantation, 12 participants experienced 89 treatment-emergent adverse events, mostly mild or moderate in severity. Three treatment-emergent serious adverse events, all unrelated to bemdaneprocel, were reported: COVID-19 (low dose), gastrointestinal hemorrhage (high dose), and seizure (high dose) possibly related to surgery. There were no deaths or graft-induced dyskinesias. No intracerebral hemorrhages or mass lesions were observed by magnetic resonance imaging. In the high-dose cohort at 2 years post transplantation, mean (SD) changes from baseline in participant-reported ON times without troublesome dyskinesia (+1.8 hours [2.6]) and OFF times (−1.9 hours [2.6]) and MDS-UPDRS Part III OFF scores (−21.9 points [7.8]) showed a continuing trend toward improvement; non-motor assessments were stable. Outcomes in the low-dose cohort were stable. Overall, bemdaneprocel demonstrated a favorable safety profile and trended toward dose-dependent improvement or stability across clinical assessments through 2 years post transplantation, supporting a Phase 3 multicenter, multisite, randomized, sham

surgery-controlled, double-blind trial (exPDite-2, NCT06944522) to evaluate the efficacy and safety of bemdaneprocel. Results through 3 years will be presented at the congress.

10:20 AM – 10:45 AM

REFRESHMENT BREAK

10:45 AM – 11:45 AM

PSC CLINICAL TRIALS: PHASE II & BEYOND PART II

10:45 AM – 11: 00 AM
DEVELOPMENT AND CLINICAL EVALUATION OF A HUMAN PLURIPOTENT STEM CELL-DERIVED INHIBITORY INTERNEURON CELL THERAPY CANDIDATE FOR CHRONIC FOCAL EPILEPSY

Yves Maury, *Neurona Therapeutics, USA*
Marina Bershteyn, *Neurona Therapeutics, USA*
Luis Fuenteabla, *Neurona Therapeutics, USA*
Robin Zhou, *Neurona Therapeutics, USA*
Geetha Subramanyam, *Neurona Therapeutics, USA*
Chun Chen, *University of California San Francisco, USA*
Li Zhou, *University of California San Francisco, USA*
Seonok Lee, *Neurona Therapeutics, USA*
Sonja Kriks, *Neurona Therapeutics, USA*
Steven Havlicek, *Neurona Therapeutics, USA*
Mansi Parekh, *Neurona Therapeutics, USA*
Arnold Kriegstein, *University of California San Francisco, USA*
Jorge Palop, *University of California San Francisco, USA*
Michael Watson, *Neurona Therapeutics, USA*
Derek Anderson, *Neurona Therapeutics, USA*
Meliz Sezan, *Neurona Therapeutics, USA*
Anastasia Nesterova, *Neurona Therapeutics, USA*
Wai Au, *Neurona Therapeutics, USA*
Juan Salvatierra, *Neurona Therapeutics, USA*
Alessandro Bulfone, *Neurona Therapeutics, USA*

John Nixon, *Neurona Therapeutics, USA*
Sheri Madrid, *Neurona Therapeutics, USA*
Gautam Banik, *Neurona Therapeutics, USA*
John Hixon, *Neurona Therapeutics, USA*
Sheri Madrid, *Neurona Therapeutics, USA*
Gautam Banik, *Neurona Therapeutics, USA*
Catherine Priest, *Neurona Therapeutics, USA*
Cory R. Nicholas, *Neurona Therapeutics, USA*

Inhibitory GABAergic pallial interneurons (pIN), which primarily originate prenatally from the medial ganglionic eminence (MGE) in the ventral forebrain, are essential to maintain the balance between neuronal excitation and inhibition in the cerebral cortex. Inhibitory interneuron cell therapy represents a promising therapeutic approach to restore physiological activity to local hyperactive circuits, such as the hippocampus of patients diagnosed with drug-resistant mesial temporal lobe epilepsy (MTLE), the most common focal epilepsy in adults. Here, we present the preclinical development of NRTX-1001, a pallial MGE-type GABAergic interneuron cell therapy candidate, derived from human pluripotent stem cells (hPSCs) alongside emerging clinical data from two ongoing open-label Phase 1/2 clinical trials for drug-resistant MTLE (NCT05135091, NCT06422923). By exploring hPSC differentiation trajectories in vitro, we identified key patterning cues to reproducibly generate MGE-type progenitors and direct their subsequent differentiation into post-mitotic GABAergic pINs, with high efficiency and fidelity to endogenous human MGE-derived pINs. Multiple lots of cryopreserved hPSC-derived pIN were characterized extensively in vitro and in vivo, in both naïve and epileptic rodent models, demonstrating consistent cell attributes, robust migration, and functional integration into recipient rodent cortex and hippocampus. Intra-hippocampal administration in a mouse model of chronic MTLE, resulted in significant, reproducible and stable seizure reduction. Implementation of sc-RNA sequencing, FISH, immunohistochemistry, and electrophysiological analyses, revealed rapid emergence of somatostatin and parvalbumin MGE pIN subtypes, followed by gradual maturation of regular- and fast-spiking membrane properties. In addition, the latest clinical data from ongoing open-label clinical trials in adults with drug-resistant MTLE will be presented, with up to two years follow-up. Interim results to date demonstrate substantial and durable seizure reduction, improved quality of life, and absence of serious adverse events related to NRTX-1001. Altogether, these clinical and pre-clinical findings underscore the potential of human interneuron cell therapy for drug-resistant focal epilepsy.

Funding source: CIRM Awards TRAN1-11611; CLIN2-13355; CLIN2-17135.

11:00 AM – 11:15 AM

ADVANCEMENT OF A CRYOPRESERVED ALLOGENEIC BIOENGINEERED HESC-DERIVED PIGMENTED EPITHELIAL CELL (RPE) IMPLANT FOR GEOGRAPHIC ATROPHY TO A PHASE2B CLINICAL TRIAL

Jane S. Lebowski, *Regenerative Patch Technologies LLC, USA*
Mark Humayun, *University of Southern California, USA*
Dennis Clegg, *University of California Santa Barbara*, *USA*
Briteney S. Pennington, *Regenerative Patch Technologies LLC, USA*
Mohamed S. Faynus, *Regenerative Patch Technologies LLC, USA*
Megan S. Treu, *Regenerative Patch Technologies LLC, USA*
Adam S. Akkad, *Regenerative Patch Technologies LLC, USA*
April S. Ingram, *Regenerative Patch Technologies LLC, Canada*
Linc S. Johnson, *Regenerative Patch Technologies LLC, USA*
Jeffrey S. Bailey, *Regenerative Patch Technologies LLC, USA*
Jeffrey S. Lin, *Regenerative Patch Technologies LLC, USA*

The CPCB-RPE1 implant, composed of hESC-derived RPE cells seeded on a parylene substrate, is in developed for the treatment of geographic atrophy (GA) secondary to dry age-related macular degeneration. Safety and preliminary efficacy of the implant were assessed in an open-label Phase 1/2a clinical trial where the implant was delivered to the subretinal space of the legally-blind eye of 15 HLA-mismatched participants during outpatient surgery. Patients were followed for a mean of 36.9 months (range 12-54). Ocular SAE's observed in Cohort 1 were mitigated in Cohort 2 by improved hemostasis during surgery. As of last follow-up, 27% of treated eyes showed a >5 letter gain in visual acuity compared to 7% of the untreated fellow eyes. A larger proportion of nonimplanted eyes demonstrated >5 letter loss (80% vs 47%) compared to the treated eye. Histological analysis of the implant from one patient that passed away two years post-implantation showed that polarized donor RPE cells remained on the implant despite the allogeneic environment. The implant tested in the Phase 1/2a clinical trial was "fresh", not cryopreserved. To facilitate the logistics of production and implantation of the CPCB-RPE1 implant, a cryopreserved formulation was developed and shown to have similar composition and function to the non-cryopreserved implant. Stability studies have demonstrated that the implant is stable in structure, phenotype, and function for at least 3 years. The implant is thawed in the operating room and directly delivered to the subretinal

space. The cryopreserved implant is now being assessed in a Phase 2b clinical trial which is open for enrollment. The Phase 2b trial is an assessor-masked trial where participants are randomized 3:1 to receive the implant or serve as a control. The trial is serving to assess the implantation, safety and efficacy of the cryopreserved CPCB-RPE1 implant at multiple clinical trial sites. GA patients with an eye with a best corrected visual acuity of 20/63 to 20/200 are eligible. Patients will be assessed for several visual parameters such as retinal sensitivity, best corrected visual acuity, and adaptive sensory function, outcome measures of importance for regulatory registration. Updates on the Phase 2b clinical trial will be provided at the meeting.

Funding Source: California Institute of Regenerative Medicine; The Marcus Foundation.

11:15 AM – 11:45 AM

PSC-DERIVED THERAPIES: THE FUTURE OF CELL THERAPY AND DESTINED TO STAY THAT WAY?

Katy Spink, *Dark Horse Consulting Group, USA*

PSC-derived therapies have been in development for more than 25 years, since the original isolation of human embryonic stem cells in 1998. iPSCs were first isolated in 2007, and the first clinical trial of an hESC derived therapy (Geron's GRNOPC1 for Spinal Cord Injury) was initiated in 2009. Yet in 2025 there remain no approved therapies based on this promising technology. This presentation will review the history and current state of PSC-derived therapeutic development, posit lessons learned, and propose key success factors for future development of this long delayed but still promising class of therapeutics.

11:45 AM – 1:15 PM
LUNCH & SPONSORED INNOVATION SHOWCASES

12:00 PM – 12:20 PM
CLOSING THE TRANSLATIONAL GAP: BIOTECH-PHARMA COLLABORATION AT WORK

Sponsored Innovation Showcase
Presented by Eli Lilly
Thomas Hopkins, *Eli Lilly, USA*
Vinny Jindal, *Secretome, USA*

This session offers an informal yet incisive look into how Eli Lilly shapes their external dealmaking playbook. Discover how they offer scientific entrepreneurs' access to pharma expertise, resources, and a streamlined path from discovery to clinical proof of concept. Explore the power of collaboration to solve challenges and deliver life-changing medicines faster to the patients in need. Join us for a candid conversation revealing what drives strategic choices to reshape the way breakthrough therapies are discovered and developed in today's evolving biotech landscape, and how it has helped one of the many CEOs Lilly ExploR&D has collaborated with.

12:20 PM – 12:30 PM
MASSACHUSETTS LIFE SCIENCES CENTER BIOBANK PROGRAM: ENABLING ACCESS TO DIVERSE PATIENT SAMPLES AND DATA

Sponsored Innovation Showcase
Presented by Massachusetts Life Sciences Center
Asmi Chakraborty, *Massachusetts Life Sciences Center, USA*

Guided by an ecosystem-wide Phase 1 survey, the inaugural focus areas are Alzheimer's Disease and Colorectal Cancer. Through partnerships with leading institutions statewide, the MLSC aims to build a shared, high-impact resource that benefits both non-profit and for-profit organizations and strengthens the life sciences ecosystem in Massachusetts.

12:30 PM – 12:40 PM
FATEVIEW™: AI-POWERED, NON-DESTRUCTIVE LIVE CELL ANALYTICS AND CELL FATE FORECASTING

Sponsored Innovation Showcase
Presented by CellVoyant
Rafael Carazo Salas, *CellVoyant, UK*

Endpoint cell analytical methods - like immunohistochemistry and omics – are unable to yield continuous insights into cell fate dynamics and transitions, which can only be

inferred. By contrast real-time analysis using e.g. genetically-encoded fluorescent reporters can highlight cell fates 'live' in a population and yield continuous fate dynamics but is lengthy to implement, cell-type specific and can report only on few cell states simultaneously. We developed FateView™, an online web-based platform that leverages live-cell imaging, computer vision and AI to enable real-time, non-invasive scalable and predictive monitoring of cell fate dynamics at single-cell level in heterogeneous cell populations. FateView™, works flexibly across cell types and applications and uses only label free ('white light') microscopy imaging for cell predictions, thus requiring no lengthy cell line generation and enabling multiple cell fates to be co-monitored. FateView™, provides current cell state readouts, predicts future cell states, measures quality attributes and differentiation potential, all without sacrificing or disaggregating cells or interrupting cell differentiation processes. By providing a robust flexible and non-invasive platform for monitoring cell fate live, FateView™, paves the way for novel discoveries and offers a powerful technology to improving cell-based therapies and disease modelling.

12:40 PM – 1:00 PM
UNLOCKING ALLOGENEIC THERAPIES WITH HYPOIMMUNOGENIC IPSCS

Sponsored Innovation Showcase
Presented by Applied StemCell
Simon Wu, *Applied StemCell, USA*

At Applied StemCell, we are combining our proprietary genome engineering technology—the TARGATT™ large knock-in platform—with our iPSC expertise to establish a hypoimmunogenic cell line platform for use in the next wave of cell therapies. This talk will highlight a few different approaches to building a hypoimmunogenic cell line and the progress we've made towards creating a hypoimmunogenic iPSC platform.

1:15 PM – 3:20 PM
PSC CLINICAL TRIALS: EARLY TRIALS

1:15 PM – 1:45 PM
HUMAN IPSC-DERIVED CARDIOMYOCYTE SPHEROIDS FOR LEFT VENTRICULAR REMUSCULARIZATION IN SEVERE ISCHEMIC HEART FAILURE: EARLY SAFETY AND EFFICACY FROM THE LAPIS STUDY

Takehiko Kaneko, *Heartseed Inc., Japan*

Patients with severe ischemic heart failure remain at high risk despite revascularization. LAPiS is a first-in-human, single-arm, open-label, phase I/II multicenter study in Japan evaluating allogeneic human iPSC-derived ventricular cardiomyocyte spheroids (HS-001). Transplantation is via multiple intramyocardial injections using a specially designed needle; spheroids are ~150-μm to aid retention. Two sequential cohorts receive total doses of 50 million or 150 million cells. Candidates are ischemic heart failure patients scheduled for CABG with reduced ejection fraction (key eligibility: LVEF 15–40%, NYHA ≥II, and 1–3 prior heart failure hospitalizations). Immunosuppression is administered per protocol, and follow-up is 12 months. Enrollment of 10 patients was completed in January 2025. At Tokyo Women's Medical University (n=5; low-dose n=4, high-dose n=1), baseline echocardiography showed LVEF 26±4% in the low-dose subgroup and 19% in the high-dose case. At 26 weeks, LVESVI improved from 101±14 to 73±18 ml/m^2, LVEF rose to 34±7% and NT-proBNP reduction by 37–80%. Responders by LVESVI (≥15% reduction) were 4/5, and NT-proBNP improved in 3/5. Safety was favorable: three SMC reviews found no SAEs impeding progress; no tumor formation or clear rejection was noted. No life-threatening arrhythmia occurred; no early sustained ventricular tachycardia was seen, including in high-dose. Transient, asymptomatic accelerated idioventricular rhythm appeared around 2 weeks and diminished thereafter. Infections attributable in part to immunosuppression occurred although they were managed by dose adjustment. These findings support the feasibility of combining surgical revascularization with targeted delivery of iPSC-derived cardiomyocyte spheroids and suggest reverse remodeling driven by remuscularization (engraftment of new cardiomyocytes) in severe ischemic heart failure, warranting controlled evaluation of durability and dose response.

Funding Source: Heartseed Inc.

1:45 PM – 2:00 PM

HUMAN IPSCS-BASED THERAPIES FOR SPINAL CORD INJURY: FIRST-IN-HUMAN TRIAL AND ITS BEYOND

Hideyuki Okano, *Keio University, Japan*

Spinal cord injury (SCI) is a devastating neurological condition with no established regenerative treatment. To address this unmet need, our group has pursued stem cell–based strategies for over 25 years, progressing from fetal neural stem/progenitor cell

(NS/PC) studies to induced pluripotent stem cell (iPSC)-derived NS/PC transplantation. Preclinical studies demonstrated functional recovery in rodent and non-human primate models, with graft-derived neuronal activity, synaptic integration, and remyelination identified as key mechanisms of action. Rigorous safety and quality control pipelines were established in collaboration with CiRA, enabling the clinical application of iPSC-derived NS/PCs. Based on these foundations, we initiated the world's first first-in-human clinical study of iPSC-derived NS/PC transplantation for subacute complete SCI (AIS A, 2–4 weeks post-injury). Four participants underwent transplantation of two million cells each into the lesion epicenter, followed by one year of observation. The primary endpoint of safety was achieved: no tumor lesions were observed in the transplanted area on MRI examination up to 52 weeks post-transplantation, and no serious adverse events were attributable to the cells. Importantly, two patients demonstrated neurological improvement on the American Spinal Injury Association Impairment Scale (AIS A→C and A→D, respectively), while the median improvement in total motor score on the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI, full score 100) was 13 points at 52 weeks. In comparison, historical registry data typically show only a 4–7 point improvement, underscoring the potential therapeutic benefit observed in our trial. Although responder variability was noted, this trial established both the feasibility and safety of iPSC-NS/PC therapy for SCI, warranting further controlled studies. Building on this milestone, we are preparing a new physician-led clinical trial targeting patients with chronic incomplete SCI—a population that represents the majority of cases yet remains resistant to conventional therapies. In chronic incomplete SCI, some axons are preserved but undergo severe demyelination, accompanied by a significant loss of oligodendrocytes, whereas the number of neurons is relatively maintained. Based on these pathological features, we employed spinal cord–type gliogenic iPSC-derived NSCs in preclinical studies and demonstrated that they differentiated into neurons and oligodendrocytes in response to the microenvironment, promoted axonal regeneration, and improved locomotor recovery in chronic injury models. The upcoming trial, scheduled to begin in 2026, will combine transplantation with advanced neurorehabilitation protocols, including robotic assistive technologies such as the Hybrid Assistive Limb (HAL). By optimizing graft type, ameliorating the hostile chronic environment, and integrating rehabilitation, we aim to overcome barriers specific to chronic SCI. This next step represents not only an expansion of clinical indications but also a critical bridge toward scalable, regulatory-approved regenerative therapies for neurological disorders. In summary, our first-in-human trial demonstrated the safety and preliminary efficacy of iPSC-derived NS/PCs in subacute complete SCI. We now seek to extend these advances to chronic incomplete SCI through

innovative trial design, with the long-term goal of establishing iPSC-based regenerative medicine as a viable therapeutic paradigm for spinal cord injury and beyond.

Funding Source: AMED under Grant Numbers JP24ym0126118 and 24bm1223008.

2:00 PM – 2:20 PM

ACCELERATING CELL THERAPY DEVELOPMENT WITH GMP-GRADE HUMAN IPSC LINES AND MATCHED RESEARCH-GRADE EQUIVALENTS

Sponsored Innovation Showcase
Presented by STEMCELL Technologies
Andrew Gaffney, *STEMCELL Technologies, Canada*
Janet Rothberg, *CCRM, Canada*

The generation of high-quality human induced pluripotent stem cell (hiPSC) lines is essential for producing reproducible and biologically relevant human model systems. STEMCELL Technologies has developed standardized workflows for reprogramming, gene editing, scaling up, and banking to ensure the consistency, genetic stability, and traceability acrossits hiPSC portfolio. Each line undergoes comprehensive qualification, including genomic integrity assessments, pluripotency validation, sterility and identity testing, and evaluation against established ISSCR research quality standards. The collection encompasses healthy control, patient-derived, and genome-edited lines designed to capture key genetic and ancestral diversity, supporting the development of more predictive and translatable in vitro models. This presentation will describe the methodologies and quality control frameworks underlying the production of robust, well-characterized hiPSC lines and their role as a foundation for disease modeling, drug discovery, and translational research.

2:20 PM – 2:35 PM

JOURNEY AND PHASE 1B CLINICAL TRIAL STATUS UPDATE FOR ASP7317: A PSC-BASED RPE CELLULAR REPLACEMENT THERAPY FOR GEOGRAPHIC ATROPHY SECONDARY TO AMD

Erin Kimbrel, *Astellas Pharma Inc., USA*

Age-related macular degeneration (AMD) is a worldwide leading cause of visual impairment. The combination of various risk factors, including advancing age, genetics, and environmental factors lead to the progressive dysfunction and degeneration of retinal pigment epithelium or RPE, a cell type with a critical role in supporting the health of the retina. Areas of geographic atrophy (GA) can appear in regions of the retina where swaths of RPE degeneration have led to the erosion of light-sensing photoreceptors and underlying retinal layers, leading to the loss of visual acuity particularly in macula, an area responsible for central vision. Approved therapies such as complement inhibitors can slow the rate of GA progression yet cannot stop it. Cellular replacement therapies may be able to stabilize and/or potentially reverse the loss of visual acuity due to GA through functional replacement of lost RPE and provide new hope to patients with high unmet need. Here, we discuss interim results from an ongoing multicenter phase 1b clinical trial (7317-CL-0003) testing the safety and tolerability of a subretinally-delivered pluripotent stem cell (PSC)-based RPE cellular suspension, ASP7317 in patients with GA secondary to AMD. The open label, dose-escalation and expansion clinical study design includes 3 cohorts of patients with moderate vision loss (>20/200 to ≤ 20/50) and 3 cohorts of patients with severe vision loss (≥ 20/500 to ≤ 20/200). We will present six months of safety and tolerability data as well as changes in best corrected visual acuity (BCVA) over time as a way to assess emerging preliminary signs of efficacy. Important aspects and lessons learned in the product development and optimization journey to bring this PSC-based therapy to humans will be discussed.

2:35 PM – 2:50 PM

THE PHASE 1 CLINICAL STUDY OF IPSC-DERIVED HUMAN FOREBRAIN NEURAL PROGENITOR CELLS (HNPC01) TREATING CHRONIC ISCHEMIC STROKE

Jing Fan, *Hopstem Biotechnology, USA*
Guangzhu Zhang, *Chinese PLA General Hospital, China*
Dingyang Liu, *Xiangya Medical Center and Zhongnan University, China*
Shuning Zhang, *Hopstem Bioengineering, China*
Anxin Wang, *Hopstem Bioengineering, China*
Fang Ren, *Hopstem Bioengineering, China*
Jing Fan, *Hopstem Bioengineering, China*
Zhiquan Yang, *Xiangya Medical Center and Zhongnan University, China*
Yiwu Dai, *Chinese PLA General Hospital, China*

Chronic motor dysfunction post 6 months of ischemic stroke onset represents a severe, disabling condition with limited therapeutic options. The hNPC01 injection, a GMP-manufactured cell injection containing mostly human induced pluripotent stem cell (hiPSC)-derived forebrain neural progenitor cells (hNPCs), offer a regenerative solution for this unmet medical need. Two phase I studies enrolled a total of 23 participants at 6 to 60 months post ischemic stroke with modest to severe motor dysfunctions under IND (CXSL2300229) with NMPA, China and an investigator-initiated trial (IIT, N=9), both following Good Clinical Practices. The two studies are both single-arm, open-label, dose-escalation study with 3 cohorts: participants in each cohort received either 1.5×10^7, 3.0×10^7, or 6.0×10^7 hNPC01 cells via intracerebral stereotactic injection, with 1-2 months of cyclosporine-based immunosuppression. Except for 3 participants loss-to-follow up, all the rest 20 participants have reached the 12-months observation endpoint, and 3 participants have finished their 18-months visit. No dose-limiting toxicities, deaths, uncontrollable or irreversible adverse events or tumorigenicity were observed to date. Most participants demonstrated sustained motor function improvements over 12 months, and 8 out of 20 participants had 1-grade reduction in Modified Rankin Scale (mRS). At 12-months post hNPC01 transplantation, the IIT low-dose cohort participants had a mean ± SEM of 16 ± 4.0 points improvement in Fugl-Meyer Motor Scale (FMMS), while the high-dose cohort participants improved 22 ± 5.6 points. The upper limb part of FMMS improvements are 11.3± 3.8 points and 13.7 ± 4.7 of these two cohorts, respectively. All IIT participants with focal basal ganglia infarct achieved clinically meaningful FMMS gains of 6 points, and about 80% of these participants achieved clinically significant improvement of 10 points in FMMS. In addition, 100% of the 4 participants in IIT study with language deficits or dysarthria improved 1 point in their corresponding section of National Institutes of Health Stroke Scale (NIHSS). Magnetic resonance imaging (MRI) confirmed evidence of tissue regeneration and long-term survival of grafts up to 12-months in all responders. Unlike findings from prior clinical studies of primary cell products, hNPC01 exhibited continuous FMMS improvements through 12 months to 18 months, which is consistent with its proposed mechanism of neural replacement and circuitry integration supported by previous preclinical studies.

Funding Source: The IIT study is supported by the National grant of China under 2021YFA1101700.

2:50 PM – 3:20 PM
DEVELOPMENT OF IPS CELL–BASED CORNEAL EPITHELIAL REGENERATIVE THERAPY: FIRST-IN-HUMAN OUTCOMES AND FUTURE PROSPECTS

Yoshinori Oie, *Osaka University, Japan*

Limbal stem cell deficiency (LSCD) causes severe corneal opacity and vision loss, with limited access to graft sources. We developed a regenerative therapy using human iPSC-derived corneal epithelial cell sheets (iCEPS) produced by the SEAM method, and conducted the first-in-human clinical study. This single-arm, open-label study was conducted at the University of Osaka Hospital and included four eyes of four patients with bilateral LSCD. After removal of fibrovascular pannus, allogeneic iCEPS were transplanted onto the corneal surface. Manufacturing followed GCTP standards with shipment criteria. The first two eyes received systemic low-dose cyclosporine; the remaining two were treated without systemic immunosuppression other than topical corticosteroids. No serious adverse events, immune rejection, or tumorigenesis occurred during 52-week follow-up and a 1-year extension. Three eyes maintained stage IA LSCD at 1 year; one eye (toxic epidermal necrosis) regressed to stage IIB after transient recovery. Corrected distance visual acuity improved by 10.0, 11.8, and 6.6 logMAR lines in three eyes, and by 2.8 lines in the fourth. Corneal opacity and neovascularization regressed in all cases. Quality-controlled manufacturing yielded stable, reproducible iCEPS lots, supporting the feasibility of a banked, immediate-use product. This first-in-human experience suggested the safety and potential efficacy of iCEPS transplantation and demonstrated that systemic immunosuppression may be minimized or avoided in selected cases. The use of iPSC haplobank-derived cells enables an “off-the-shelf” strategy, improving scalability and scheduling flexibility. A multicenter trial is planned to further confirm efficacy and safety. Lessons learned highlight the importance of designing pluripotent-cell-derived products “with the end in mind,” balancing manufacturing robustness, immune compatibility, and surgical workflow for real-world application.

3:20 PM – 3:35 PM

HUMAN PLURIPOTENT STEM CELL (HPSC) LINES AVAILABLE FOR USE IN CLINICAL APPLICATIONS: A COMPREHENSIVE REVIEW

Melissa Carpenter, *Carpenter Consulting Corporation, USA*
Tenneille E. Ludwig, *WiCell, USA*

For researchers developing hPSC derived therapies, selecting starting material to use in clinical manufacturing is one of the most important decisions they will make. It is also one

of the biggest pain points they will encounter. Recent reports show that at least 115 clinical trials using hPSCs have been initiated, using at least 24 unique hPSC lines (Kirkeby et al., 2025). However, the majority of the hPSC cell lines used in the manufacturing of these therapeutics are privately held and not available for licensing. Information about available lines is often not readily accessible, and the overall number of available cell lines suitable for clinical development is difficult to assess. Furthermore, information about the lines and how to obtain and/or license them can be limited or unclear. Therefore, as the number of groups advancing through translation to clinical application increases, so does the need for readily available, good quality, clinically compliant cell lines for the development of hPSC-derived therapeutics. The ability of researchers to access these materials "off-the shelf / ready to use" rather than deriving bespoke materials can save considerable expense and years of development time. We have identified 153 readily available hPSC lines from 17 distributors globally that appear to be suitable for generating hPSC-derived products: 30 hESC lines, and 123 hiPSC lines. The majority were derived under GMP or the Principles of GMP, and 11 have been previously used in clinical trials. We provide basic information on each identified line including licensing contact, distributor, information on Donor informed consent, reprogramming technology, quality systems, characterization information, and regulatory compliance. This information will enable researchers to evaluate, identify and acquire appropriate materials more readily, expediting translation of hPSC research to clinical outcomes.

3:35 PM – 4:05 PM

REFRESHMENT BREAK

4:05 PM – 5:00 PM

PATIENT PERSPECTIVES PANEL DISCUSSION

Sponsored by Kenai Therapeutics

Moderator: **Luke Rosen,** *KIF1A.org, USA*

Panelists:

Maria L. De Leon, *The Michael J. Fox Foundation, USA*

Martha Steel, *Foundation Fighting Blindness, USA*

Carrie Khouri, *Breakthrough T1D, USA*

5:00 PM – 7:30 PM

Welcome Reception & Poster Presentations

Sponsored by BlueRock Therapeutics

FRIDAY, 12 DECEMBER 2025

8:00 AM – 10:30 AM

"I WISH I WOULD HAVE": LESSONS LEARNED IN PRODUCT DEVELOPMENT

Sponsored by Eli Lilly

8:00 AM – 8:25 AM

EXPLORING NEW APPROACHES TO EFFICIENT AND COST-EFFECTIVE CLINICAL MANUFACTURING OF CELL THERAPIES

Greg Russotti, *Century Therapeutics, USA*

All companies intending to conduct clinical trials face the choice of contracting a CDMO or building in-house manufacturing to meet clinical supply needs. Having one's own manufacturing facility offers several advantages, including greater flexibility of the manufacturing schedule; closer coordination between research, development, and operations teams; better visibility to manufacturing data; and limited exposure to competitors. So why doesn't everyone choose to build their own manufacturing capabilities? Typically, companies preparing to begin clinical trials lack the time, money and/or expertise to build their own manufacturing facility. Century was very fortunate to be able to build its own GMP manufacturing facility three years ago and hire a team with deep experience in a variety of cell therapy types. However, in today's economic environment, where cash preservation is paramount, it is especially difficult for new companies to justify the capital expenditures necessary to build, potentially leaving them no choice but to contract a CDMO. This presentation will explore the possibility of a new paradigm: one in which two or more companies share both the financial burden and the many advantages of

an in-house facility. Building a multi-suite, multi-product facility is only marginally more expensive than building a limited number of suites, considering all the infrastructure necessary to support GMP manufacturing facility. Hence, the cost model for two or more companies sharing a facility could be extremely favorable, allowing cost and risk to be spread while maintaining the advantages of having one's own facility.

8:25 AM – 8:50 AM

ADVANCED MANUFACTURING OF HUMAN PLURIPOTENT STEM CELLS FOR HEART REPAIR

Robert Zweigerdt, *Medizinische Hochschule Hannover and Hannover Medical School, Germany*
Felix Manstein, *Medizinische Hochschule Hannover and Hannover Medical School, Germany*
Kevin Ullmann-Cyrys, *Medizinische Hochschule Hannover and Hannover Medical School, Germany*
Nils Kriedemann, *Medizinische Hochschule Hannover and Hannover Medical School, Germany*
Caroline Halloin, *Medizinische Hochschule Hannover and Hannover Medical School, Germany*
Wiebke Triebert, *Medizinische Hochschule Hannover and Hannover Medical School, Germany*
Ina Gruh, *Medizinische Hochschule Hannover and Hannover Medical School, Germany*
Sara Szadocka, *Medizinische Hochschule Hannover and Hannover Medical School, Germany*
Veronika Fricke, *Hannover Medical School, Germany*
Andreas Martens, *Medizinische Hochschule Hannover and Hannover Medical School, Germany*
Serghei Cebotari, *Medizinische Hochschule Hannover and Hannover Medical School, Germany*
Tobias Goecke, *Hannover Medical School, Germany*
Annette Schrod, *German Primate Center and Leibniz Institute for Primate Research, Germany*
Susann Boretius, *German Primate Center and Leibniz Institute for Primate Research, Germany*

Christian Veltmann, *Hannover Medical School, Germany*
David Dunker, *Hannover Medical School, Germany*
Kuleshova Anna, *Hannover Medical School, Germany*
Alexandra Haase, *Hannover Medical School, Germany*
Arjang Ruhparwar, *Hannover Medical School, Germany*
Ulrich Martin, *Medizinische Hochschule Hannover and Hannover Medical School, Germany*

The talk will present advanced matrix-free human pluripotent stem cells (hPSCs) bioprocessing in stirred tank bioreactors (STBR) in 3D suspension culture. This will include process inoculation directly from cryopreserved cell stocks for omitting the need for conventional surface-attached 2D precultures and promoting closed system manufacturing and automation. Lineage-directed differentiation of hPSC into cardiomyocytes in up to 2L STBR scale will be discussed followed by the transplantation of process-derived cardiac aggregates into the heart in a non-human primate model of heart failure. In parallel, cells' functional assessment via an in vitro bioartificial cardiac tissue (BCT) "potency assay" will be shown. Lessons learned on process development, cell line heterogeneity, and challenges for the clinical translation of cell therapies to the heart will be highlighted.

Funding Source: EU Horizon project HEAL, contract 101056712; authors explicitly express that funding was used for research on human induced pluripotent stem cells (hiPSC) only in frame of the published research.

8:50 AM – 9:10 AM

COMPLIANCE BY DESIGN – LESSONS LEARNED FROM CREATING GMP iPSCs FOR USE IN CELL THERAPIES AND PATIENT CURES

Sponsored Innovation Showcase
Presented by Catalent
Frederic Cedrone, *Catalent, France*

In the iPSC derived Cell Therapy field, accessing a suitable iPSC line is a key step, but not the only one. Taking an iPSC line to the clinic means gathering the full information related to the line, its characteristics, its manufacturing, the quality controls applied, but also the information and data package that are regulatory commercially acceptable, all must have

but none are trivial. At Catalent, we have started with the end in mind: iPSC lines are for clinical use in cell therapy and for developing patient cures. The lines are GMP from day one, built with validated GMP workflows for reprogramming, expansion, banking and comprehensive quality control assays. Each line comes with a full regulatory package. However, we have learned lessons when scaling up and taking those lines to our community, including when preparing the full information and regulatory package for Health Authorities, with donor eligibility, donor consent and reconsent for commercial use. This presentation aims to share challenges, solutions and lessons learned when creating GMP iPSCs for use in cell therapies development.

9:10 AM – 9:35 AM

BRIDGING INNOVATION AND TRANSLATION: CRITICAL INSIGHTS FOR CELL THERAPY DEVELOPMENT

Uma Lakshmipathy, *Thermo Fisher Scientific, USA*

Induced pluripotent stem cell (iPSC)-derived therapies hold transformative potential for treating a wide range of diseases, yet translating these products from early discovery into clinical application presents complex scientific, operational, and regulatory challenges. Scaling academic protocols to GMP manufacturing often reveals gaps in process design, differentiation consistency, and safety controls. Decisions between allogeneic and autologous approaches influence immune risk, manufacturing scale, and clinical strategy. The development of reliable potency assays linked to mechanism of action, assessment of tumorigenicity, and strategies for immune compatibility are all important design choices that must be incorporated early to inform clinical translation. Ensuring genomic and epigenetic stability of iPSC lines, establishing robust lineage-specific differentiation, and mitigating risks from residual pluripotent cells or off-target populations are critical considerations that can impact both safety and efficacy. Manufacturing considerations, including closed-system scalability, batch comparability, validated cryopreservation, and reproducible quality control, further influence readiness for clinical trials. Lessons from other programs show that such early choices around cell source, differentiation strategy, product format, and patient-focused requirements profoundly shape downstream success. This presentation shares practical strategies to efficiently translate therapies from concept to scalable, clinically ready products.

9:35 AM - 10:30 AM

"I WISH I WOULD HAVE": LESSONS LEARNED IN PRODUCT DEVELOPMENT PANEL DISCUSSION

Moderator: **Thomas Carlsen,** *Cellerator, Denmark*
Panelists:
Greg Russotti, *Century Therapeutics, USA*
Robert Zweigerdt, *MHH, Germany*
Uma Lakshmipathy, *Thermo Fisher Scientific, USA*
Frederic Cedrone, *Catalent, USA/France*
Tim Hunt, *ARM, USA*
Teisha Rowland, *CBER, FDA, USA*

10:30 AM – 11:00 AM
REFRESHMENT BREAK

11:00 AM – 12:35 PM

NOW YOU SEE ME, NOW YOU DON'T: ENSURING CELL SURVIVAL

11:00 AM – 11:30 AM

BIOPRINTED TISSUE THERAPEUTICS (BTTS) CONTAINING ALLOGENEIC CELLS HAVE THE POTENTIAL TO FUNCTIONALLY CURE MULTIPLE ENDOCRINE AND METABOLIC DISEASES

Samuel J. Wadsworth, *Aspect Biosystems Ltd., Canada*

Aspect Biosystems is developing a pipeline of Bioprinted Tissue Therapeutics (BTTs) – "off-the-shelf", implantable, allogeneic cell therapies that can replace, repair, or restore damaged function – that could provide a functional cure for some of the most elusive diseases without the need for immunosuppression. Underpinning these BTTs is Aspect's full-stack tissue therapeutic platform, which integrates proprietary AI-powered bioprinting technology, computational design tools, therapeutic cells, and advanced biomaterials to manufacture a new class of cellular medicines. Aspect is developing BTTs for a variety of endocrine and metabolic disorders using different therapeutic cell payloads. In vitro and in vivo data demonstrates that multiple types of therapeutic cells from PSC or cadaveric

sources can be bioprinted into implantable BTTs with high viability, using semi-permeable biomaterials that enable diffusion of oxygen and growth factors, while shielding the cells from immune attack. Primary adrenal insufficiency is one example endocrine disorder where replacing function of the affected gland could have a transformative impact on patient health and quality of life We have demonstrated that implantation of human adrenal cell-containing BTTs into adrenalectomized mice results in a sustained elevation of plasma cortisol, as well as an increase in survival. A robust response to exogenously administered adrenocorticotropin hormone (ACTH) was observed, resulting in a rapid and significant increase in plasma cortisol in mice implanted with adrenal BTTs. ACTH responsive cortisol secretion was observed throughout the six month study. Plasma cortisol and ACTH levels were measured mornings and evenings to assess whether implanted adrenal BTTs responded to physiological circadian fluctuations in endogenous mouse ACTH levels. Results showed that plasma cortisol levels followed the same diurnal rhythm as endogenous ACTH in the adrenalectomized mice. These results demonstrate the ability of Aspect's adrenal BTTs to release cortisol in response to the natural diurnal variation in ACTH, mimicking the function of a healthy adrenal gland. This work highlights that Aspect's BTTs could provide a curative and transformative therapy for patients living with primary adrenal insufficiency. Aspect's BTT platform also shows promise in the treatment of diseases such as type 1 diabetes and acute liver failure without the need for long-term systemic immune suppression.

11:30 AM – 11:45 AM

PERMANENTLY CROSSLINKED HYDROGELS ENABLE STEM CELL AND ISLET TRANSPLANTATION INTO MICE AND RATS

Harald Stover, *Allarta Life Science, Canada*

The dangers of Type I diabetes (T1D) stem from its potential to cause severe, long-term health complications affecting multiple organ systems. While islet transplantation using primary or stem cell-derived sources is a viable clinical option, it remains constrained by limited donor availability and the requirement for lifelong immunosuppression. Physically shielding transplanted cells from immune attack while allowing metabolic exchange, is a compelling solution to minimize or eliminate systemic immunosuppression. Allarta's chemically crosslinked hydrogels are non-immunogenic devices, that are mechanical stable, yet flexible. Different forms of bioprinting enable the encapsulation of cells into customizable formats. Novel formulations include coatings that allow fine-tuning of size-

exclusion properties and immune protection, and enhanced mechanical resilience. We utilized human induced pluripotent stem (hiPSCs) cells to demonstrate the materials' ability to support sensitive, highly metabolically demanding cells. The hiPSCs demonstrated good viability and growth over multiple weeks in vitro. The device was also compatible with genetically modified cells. Donor islets from human non-transplantable pancreases, and Wistar and Lewis rats, known to contain tissue resident stem cells, were studied as therapeutic cell types. These encapsulated islets remained viable (AO/EthD) and functional, as assessed by GSIS (stimulation index >1), in vitro for at least 7 days. In vivo, they effectively reduced blood glucose levels (<200 mg/dL) in STZ-diabetic animals, for 75 days in immunocompromised NSG mice and for over 45 days in immunocompetent C57BL/6J mice and Lewis rats. Explanted devices showed minimal host cell attachment and encapsulated cells were viable and functional. Interestingly, geometry strongly influences host responses. High-surface-area devices promote cell migration throughout, but not into, the device. To support the logistical challenges of bringing islets and material to the patient, Allarta further developed cryogels, that aid in storage and transport of cells. The combination of therapeutic primary and stem cell-derived cells with the protective and tunable properties of Allarta's hydrogel platform offers a promising path towards a functional cure for people with T1D.

Funding Source: Breakthrough T1D (formerly JDRF), Natural Research Council Canada (NRC), Ontario Centre of Innovation (OCI).

11:45 AM – 12:05 PM

SPONSORED INNOVATION SHOWCASE: TREEFROG THERAPEUTICS
Maxime Feyeux, *TreeFrog Therapeutics, France*

ABSTRACT NOT AVAILABLE AT THE TIME OF PUBLISHING

12:05 PM – 12:35 PM

IMMUNE EVASION ENGINEERING OF IPSC-DERIVED CAR AND TCR T CELLS FOR OFF-THE-SHELF THERAPY

Daniel Kemp, *Shinobi Therapeutics, USA*

Shinobi Therapeutics is developing iPSC-derived allogeneic T cell therapies engineered with chimeric antigen receptors (CARs) and T cell receptors (TCRs) for the treatment of solid tumor cancers and autoimmune diseases. iPSCs offer a scalable and renewable source for uniform cell products, but immune rejection remains a major barrier to effective and durable therapy. To overcome this, Shinobi has created a proprietary immune evasion platform that enables iPSC-derived T cells to persist and function in immunocompetent patients. Our approach employs multiplex genome engineering to modulate key immune recognition pathways, producing cells capable of evading both innate and adaptive immune responses. Edits are introduced at the iPSC stage, allowing consistent and scalable manufacturing of immune-evasive T cell therapies. Importantly, by minimizing host immune recognition, Shinobi's platform not only enhances initial engraftment and anti-tumor efficacy but also enables the potential for re-dosing, a key advantage for managing relapsed or refractory disease. Preclinical data demonstrate that immune-evasive CAR and TCR T cells maintain cytotoxic function and persist in immune-competent models. By embedding immune cloaking directly into the genome of iPSC-derived T cells, Shinobi aims to deliver scalable and cost-efficient off-the-shelf therapies with improved durability, broader patient access, and the flexibility to re-dose without immunosuppression.

12:35 PM – 1:45 PM
LUNCH & SPONSORED INNOVATION SHOWCASES

12:50 PM – 1:00 PM
AUTOMATED MANUFACTURING: REMOVING BOTTLENECKS & REDUCING COSTS

Sponsored Innovation Showcase
Presented by Mytos
Ignacio Willats, *Mytos, USA*

Mytos is a vertically integrated automated CDMO for Regenerative Medicine. Mytos leverages it's proprietary closed, flask-based automation to deliver scalable, consistent, and cost-effective manufacturing. Manual manufacturing has long been the achilles heel of regenerative medicines with critical hiring and training bottlenecks risking programmes being unfeasible to scale. Hear how leading teams leverage Mytos' automation to avoid delays and reduce costs.

1:00 PM – 1:10 PM
ADVANCING ORGANOID CULTURE: CULTREX™ SYNTHETIC HYDROGEL AND AI-MODIFIED PROTEINS

Sponsored Innovation Showcase
Presented by Bio-Techne
Paul Tetteh, *Bio-Techne, USA*

Dr. Paul Tetteh will present recent advancements in organoid culture leveraging (1) AI-modified engineered proteins (thermostable FGF10 and Wnt3a agonists) to improve organoid culture workflows and (2) a fully defined synthetic-component derived hydrogel matrix to mimic the extracellular matrix as an alternative to BME. This combination was tested for its compatibility across human stem cell-derived intestinal, liver, and lung organoid cultures. Dr. Tetteh will discuss the benefits of combining defined matrices with engineered proteins to overcome organoid workflow limitations for more reproducible, scalable, and clinically relevant alternatives to traditional reagents. These advancements have the potential to improve key organoid applications including disease modeling and therapeutic development, opening the door to more effective organoid workflow development and clinically translatable platforms.

1:10 PM – 1:20 PM
PRECISION IPSC GENOME ENGINEERING FOR T1D CELL THERAPY

Sponsored Innovation Showcase
Presented by Logomix
Yasunori Aizawa, *Logomix, Japan*

Recent years have seen successful progress in multiple clinical trials involving iPSC-derived therapeutic cells. Recognizing from our founding that an advanced iPSC genome engineering platform would be indispensable for developing the next generation of iPSC-based cell therapies, we have dedicated ourselves to developing a versatile, safe, quick and precise technology for iPSC genome modification, crucial for maximizing therapeutic efficacy and streamlining manufacturing. Our primary focus is leveraging this powerful technology to develop highly enhanced cell products for our Type 1 Diabetes (T1D) pipeline. In this presentation, we will first provide an overview of our proprietary iPSC genome engineering platform, Geno-Writing™. Geno-Writing™ enables precise, allele-specific, and high-throughput modifications on a mega-base scale with minimal off-target

effects. We will then demonstrate how we utilize the full potential of this platform in our internal programs for the treatment of T1D, specifically by achieving robust immune tolerance and significantly enhancing cell differentiation and insulin secretion. Our work underscores how Logomix's integrated platform offers a robust solution for next-generation, allogeneic iPSC-derived cell therapies, promising more effective and widely accessible T1D treatments.

1:20 PM – 1:30 PM
MEET MINIPRO™: INDEPENDENT CONTROL AND SCALABLE CONFIDENCE FOR CELL THERAPY DEVELOPMENT

Sponsored Innovation Showcase
Presented by PBS Biotech
Sharon Harvey, *PBS Biotech, USA*

PBS Biotech introduces MiniPRO™, a compact, fully automated bioprocessing system engineered for cell and gene therapy development. Built on PBS's proven Vertical-Wheel® technology, MiniPRO™ enables independent control of up to 24 cultures - each with customizable parameters and workflows. It delivers consistent, low-shear mixing and closed-system reliability across every run. Onboard sensors monitor pH, dissolved oxygen, temperature, and agitation in real time. The closed design supports sterile sampling, media additions, and perfusion-based exchange. The system operates as a standalone unit or integrates with enterprise automation platforms. As a true scale-down model, MiniPRO™ mirrors the fluid dynamics of PBS's GMP-scale bioreactors (3L, 15L, 80L), ensuring consistent performance and predictable outcomes from R&D to manufacturing. Key features include independent operation of 1-24 bioreactors, automated control of key process parameters, closed-system sterility and perfusion support, integration-ready with enterprise automation platforms, and direct scalability to PBS GMP systems.

1:45 PM – 3:10 PM

NEXT GENERATION CELL THERAPIES PIPELINE I

Sponsored by ISSCR Consortium for Advanced Stem Cell-Based Models in Drug Discovery & Development

1:45 PM – 2:10 PM

FORWARD PROGRAMMING OF PLURIPOTENT STEM CELLS ENABLES AI-GUIDED CELL FATE DESIGN AND PLUG-AND-PLAY MANUFACTURING

Alex Ng, *GC Therapeutics, USA*

Pluripotent stem cell (PSC)-derived therapies have advanced from preclinical proof-of-concept to promising late-stage clinical results, yet two major bottlenecks persist. From the discovery perspective, the current reliance on stepwise, cell-external cues makes differentiation protocol development slow and difficult to generalize, thereby constraining the pipeline of new therapeutic cell types. From the manufacturing angle, multi-step protocols that yield low-purity populations and are difficult to scale limit affordability and scalability, restricting broad patient access. Here, we present advances in forward programming that address both fronts. First, our discovery engine powered by the TFome™ library, the first comprehensive collection of >1,700 human transcription factors (TFs), integrates high-throughput screening and AI-guided design to identify TF recipes for PSC differentiation. Millions of TF-perturbed single-cell transcriptomes spanning all three germ layers train foundation models to predict and nominate factors for cell fate, infer identity, and reverse-engineer cell states. As one example, we discovered a TF recipe producing oligodendrocyte progenitor cells (OPCs) for myelin repair in a one-step, four-day process at >90% purity with high consistency across diverse donor backgrounds. Single-cell transcriptomics show high homogeneity and fidelity to reference atlas. OPCs mature into myelinating oligodendrocytes and form myelin sheaths in vitro and in preclinical models. Once a TF recipe is selected for clinical application, our manufacturing platform installs it into PSCs using clinically compatible starting material. Because TF recipes can be exchanged to produce other cell types with minimal re-optimization, this constitutes a “plug-and-play” manufacturing paradigm. These advances establish our forward programming strategy as a powerful means to expand the therapeutic pipeline and accelerate translation of PSC-derived cell therapies.

2:10 PM – 2:25 PM

ENGINEERED HUMAN CARDIAC PATCHES REPAIR THE HEART FOLLOWING INFARCTION IN SMALL AND LARGE ANIMAL MODELS

Andrew R. Laskary, *QIMR Berghofer, University of Queensland, and Murdoch Children's Research Institute, Australia*
Daniel Donner, *Baker Institute, Australia*

Christian Brizard, *The Royal Children's Hospital, Australia*
Rebecca Fitzsimmons, *QIMR Berghofer, Australia*
Adam Piers, *Murdoch Children's Research Institute, Australia*
Kevin Watt, *Murdoch Children's Research Institute, Australia*
Neda Mehdiabadi, *Murdoch Children's Research Institute, Australia*
Hayley Pointer, *Murdoch Children's Research Institute, Australia*
Rebecca Sutton, *Murdoch Children's Research Institute, Australia*
James Hudson, *QIMR Berghofer, Australia*
Enzo Porrello, *Murdoch Children's Research Institute, Australia*

Ischemic heart disease often progresses to heart failure, a global health crisis with no curative treatment beyond whole-heart transplantation—an approach constrained by donor shortages and lifelong immunosuppression. While cardiac cell therapy holds promise, efficacy is limited by poor retention and arrhythmogenicity. To address these challenges, we developed engineered cardiac patches (ECPs) from human pluripotent stem cells as a structurally and functionally integrative transplant therapy for myocardial repair. We established a fabrication pipeline enabling small- and large-scale ECP manufacture for murine and porcine/human studies, respectively. ECPs consisted primarily of cardiomyocytes with epicardial and endothelial progenitors. To direct progenitor differentiation and enhance hypoxia tolerance, we designed a Transplant Medium (TM) optimized for high glucose, low calcium, and growth factor conditions, compared to widely used Standard Medium (SM). Single-nucleus RNA-sequencing revealed TM significantly enriched vascular populations versus SM. TM also reprogrammed metabolism toward glycolysis, conferring superior survival and function following 20-hour hypoxia challenge in vitro. To assess therapeutic benefit, TM-conditioned ECPs (TM-ECPs) were transplanted following myocardial infarction (MI) in mice. One-month post-transplantation, TM-ECPs prevented adverse structural remodeling, promoted neovascularization, and supported maturation of human-derived cardiomyocyte grafts. TM-ECP recipients demonstrated a 17% recovery in ejection fraction compared with SM-ECP recipients. In a porcine MI model, TM-ECP transplantation completely preserved cardiac structure and rescued ejection fraction by 19%— back to healthy baseline, three months post-transplantation. Furthermore, no evidence of arrhythmogenesis or other adverse events were observed. These findings demonstrate for the first time that vascularized, metabolically adapted ECPs are capable of reversing structural and functional decline in a large-animal MI model. Currently, ECP development is moving toward Good Manufacturing Practice and first-in-human trials. With further validation, ECP

transplantation holds promise as a transformative clinical intervention for patients suffering with heart failure.

Funding Source: The Novo Nordisk Foundation Center for Stem Cell Medicine is supported by Novo Nordisk Foundation grant (NNF21CC0073729).

2:25 PM – 2:45 PM

HD-MEA FUNCTIONAL READOUTS FOR TRANSLATING IPSC-DERIVED MODELS TOWARD PRECLINICAL APPLICATIONS

Sponsored Innovation Showcase
Presented by MaxWell Biosystems
Francesca Puppo, *MaxWell Biosystems, USA*

The complexity and heterogeneity of many diseases, particularly neurodegenerative disorders, underscore the urgent need for personalized therapeutic strategies. At the same time, growing ethical and translational limitations of animal research have accelerated the search for alternative approaches. Induced pluripotent stem cells (iPSCs) have emerged as a transformative tool to model disease and enable drug discovery directly in human-relevant systems. Several iPSC-based therapies are already advancing toward clinical application, yet realizing their full potential requires technologies capable of delivering precise, high-content functional insights. MaxWell Biosystems' High-Density Microelectrode Arrays (HD-MEAs), including the MaxOne and MaxTwo platforms, provide a powerful, non-invasive approach to capture high-resolution electrophysiological data from iPSC-derived neuronal networks. These platforms enable researchers to assess neural activity and maturation with exceptional detail and reproducibility. In this Innovation Showcase, we highlight how HD-MEAs can provide essential functional readouts to accelerate the translation of iPSC-derived models toward therapies suitable for preclinical evaluation.

2:45 PM – 3:10 PM

ADVANCING STEM CELL THERAPIES FOR OCULAR SURFACE REPAIR: PRECLINICAL INSIGHTS FOR TRANSLATION

Tanja Ilmarinen, *StemSight, Finland*

Blindness places a significant burden on both the patients and society. To advance curative treatments for patients suffering from severe ocular surface disorders, such as limbal stem cell deficiency (LSCD) or persistent epithelial defects, we are developing an allogeneic iPSC-derived limbal stem cell (LSC) therapy. LSCD is a rare form of corneal blindness primarily affecting young and working-age adults, with an estimated prevalence of approximately 3 cases per 100,000 people. Therapeutic cells are manufactured from a clinical-grade, off-the-shelf, hypoimmunogenic iPSC-line with a process enabling made-to-order production within one week. Our ongoing preclinical studies focus on establishing a GMP-compliant manufacturing process and robust preclinical in vivo models to support first-in-human (FIH) studies. Key aspects addressed will include demonstration of proof-of-concept, as well as establishing safety studies for assessment of biodistribution, tumorigenicity and toxicologic potential in both rodent and large-animal models. Key translational challenges include optimizing delivery to maintain cell viability and ensure engraftment across species, translatability of potency assays, and addressing logistics for transporting live cultures. Extensive testing across in vitro, ex vivo, and in vivo platforms has provided critical insights into product performance and safety, enabling refinement of the delivery method, dosing strategy, and potency assay selection, as well as logistical considerations from the manufacturing site to the clinic. These findings directly inform the design of FIH clinical trials and support the development of a robust regulatory strategy for advancing iPSC-derived LSC therapy toward clinical application.

3:10 PM – 3:25 PM

REFRESHMENT BREAK

3:25 PM - 5:30 PM

NEXT GENERATION CELL THERAPIES PIPELINE II & CLOSING KEYNOTE

3:25 PM – 3:40 PM

ALLOGENEIC IPSC-DERIVED CAR-NK CELLS TARGETING OVARIAN CANCER

Alan Trounson, *Cartherics Pty Ltd, Australia*

Chimeric Antigen Receptor T cell (CAR-T) technologies targeting haematological malignancies have revolutionised cancer treatment. However, current autologous CAR-T therapies face major challenges, including limited success against solid tumours, barriers to broad adoption, and treatment-associated toxicities. Allogeneic immune cell therapies, particularly natural killer (NK) cells, are rapidly emerging treatment modalities that have the potential to overcome some of the current limitations associated with autologous CAR-T therapies. Accordingly, we have developed an allogeneic, gene-modified, induced pluripotent stem-cell (iPSC)-derived CAR NK cell product that targets ovarian cancer expressing tumour-associated glycoprotein-72 (TAG-72). Using CRISPR/Cas9, an iPSC line derived from a homozygous HLA cord blood sample, was gene edited to express an anti-TAG-72 CAR and Diacylglycerol Kinase□□ (DGK) gene deletions (KOs) which enhance T cell/NK cell persistence and function. These TAG-72-CAR-DGK-KO iNK cells (termed CTH-401) have demonstrated significant cytotoxicity against an ovarian cancer model in vitro and in vivo i.p., but not against non-tumour cells. CTH-401 is manufactured using a proprietary, feeder-free process, which expands and differentiates iPSCs into functional NK cells in 40 days using bioreactors. We have produced a gene-edited iPSC cell line that has been fully characterised by comprehensive genomic and functional assessment. Particularly critical was the safety-driven genomic analysis, including Whole Genome Sequencing (96X) to verify the absence of significant pathogenic mutations. A GMP-compliant master cell bank (MCB) of a clone selected for genomic integrity and gene edited homozygosity was generated for preclinical and clinical use. Procedures were endorsed at a pre-IND meeting with the FDA and CTH-401 is being manufactured in house at clinical-scale for Phase I/II clinical studies and preclinical testing. In summary, CTH-401 is a promising clinical candidate for treatment of ovarian cancer and other adenocarcinomas expressing TAG-72. Our gene-edited iPSC platform/MCB provide limitless, on-demand supply of standardised allogeneic CAR-iNK-KO cells with potentially no or minimal treatment-associated toxicities.

Funding Source: Australian Government Cooperative Research Centres Project CRC-P-489.

3:40 PM – 4:00 PM
CREATING COMPETITIVE AND SAFE GENE EDITED ALLOGENIC IPSC-DERIVED CELL THERAPY PRODUCTS FOR REGENERATIVE MEDICINE AND ONCOLOGY

Sponsored Innovation Showcase
Presented by Evotec
Matthias Austen, *Evotec, Germany*

Evotec has built a comprehensive end-to-end platform to provide services to develop and manufacture off-the-shelf iPSC-based cell therapeutics, covering the bandwidth from conceptualization, process development/upscaling, gene editing strategies, GMP gene editing and genetics QC, formal preclinical tox/safety to GMP manufacturing of clinical material. We also conduct R&D to develop innovative and flexible therapeutic cell type-based platforms to accelerate generation of product candidates and pipeline building with our partners, focusing e.g. on iPSC-derived islets, immune and retinal cells, as treatment of diabetes, cancer or retinal degeneration. Most of our work uses targeted gene editing for improved functionalization and/or hiding of target cells from allograft rejection. We have established full capabilities to perform gene edits efficiently and in a GMP compatible manner, and have developed a proprietary combination of gene edits for effective immune-shielding in vivo. Advanced models with human primary immune cells are available to assess effectiveness of immune shielding. By accessing disease know-how across Evotec, therapeutic cells can be tested using state-of-the art iPSC-based or animal disease models. Our presentation provides an overview of our innovative solutions and recent progress on upscaling of manufacturing, and discusses data from ongoing RnD projects aimed at the generation of innovative allogenic iPSC-derived therapeutics.

4:00 PM – 4:15 PM

A CLOSED, AUTOMATED AND CONTROLLED END TO END SCALED PLURIPOTENT STEM CELL EXPANSION PLATFORM FOR SUSTAINABLE THERAPY DEVELOPMENT AND MANUFACTURING

Jahid Hasan, *Cell & Gene Therapy Catapult, UK*
Mudith Jayawardena, *Cell & Gene Therapy Catapult, UK*
Alexandru Podovei, *Cell & Gene Therapy Catapult, UK*
Coralie Nerincx, *Cell & Gene Therapy Catapult, UK*
Ofure Awonusi, *Cell & Gene Therapy Catapult, UK*
Saadat Wadud, *Cell & Gene Therapy Catapult, UK*
Patrick Statham, *Cell & Gene Therapy Catapult, UK*
Molly Tregidgo, *Cell & Gene Therapy Catapult, UK*
Natacha Agabalyan, *Cell & Gene Therapy Catapult, UK*

Juline Guenat, *Cell & Gene Therapy Catapult, UK*
Marcia Mata, *Cell & Gene Therapy Catapult, UK*

Allogeneic cell therapies utilising induced Pluripotent Stem Cells (iPSCs) offer scalability and sustainability benefits over current autologous manufacturing processes in meeting high-dose indications and cell replacement therapies. iPSCs are ideal for platform processing due to their unlimited expansion potential and ability to differentiate into multiple therapeutic cell types. Advances in bioprocess automation and control and the ability to expand iPSCs as 3D aggregates make them ideal candidates for continued development of end-to-end platforms taking advantage of novel technologies and methods to address the challenge of manufacturing at scale. Intensified production of iPSCs in a closed end-to-end bioprocessing platform has the potential to accelerate patient access to transformative allogeneic cell therapies by achieving essential reductions in manufacturing cost. The Cell and Gene Therapy Catapult (CGT Catapult) has developed a perfusion-based bioprocessing platform to generate high-quality iPSC aggregates. To determine the scalability of the platform, as well as its potential for improved automation and control, the expansion process was transferred from 300 mL to 3 L scale. In addition, procedures and technologies were investigated to close and automate passage between systems, allowing for integrated passage and seamless downstream processing of iPSCs, either as single cells for further expansion or aggregates for differentiation. Here, we showcase successful scaling of our iPSC expansion platform, generating 1E9 iPSCs at the 300 mL scale, subsequently propagated to generate 10E9 iPSCs at the 3L scale and maintaining the key quality attributes of iPSCs. By leveraging the additional capabilities offered by concentrate-and-wash systems, we've demonstrated a closed end-to-end bioprocessing system where iPSC aggregates can be dissociated and re-seeded for subsequent expansion cycles at a larger scale or concentrated as aggregates for full media exchanges and downstream differentiation purposes. Additionally, we have implemented in-line imaging and spectroscopic tools as in process controls within our platform, allowing us to embed feedback loops for perfusion rates and action process variations faster, with limited manual handling.

4:15 PM – 4:40 PM

REBUILDING THE BODY'S INTERFACES: CELL THERAPY FOR NEUROSKELETAL AND SURFACE TISSUES

Gabsang Lee, *Johns Hopkins University, USA*

Human pluripotent stem cells (hPSCs) have unveiled unprecedented opportunities for next-generation regenerative medicine by providing an unlimited and diverse array of cell types capable of repairing and replacing damaged tissues in patients. Our research group has developed novel methodologies to guide hPSCs into multiple cell types, primarily neuroskeletal and surface tissues. Notably, we have reported the derivation and prospective isolation of engraftable skeletal muscle stem cells (hPSC-SkMSCs) generated from hPSCs. hPSC-SkMSCs exhibited typical molecular and cellular characteristics of muscle stem cells and were capable of adhering to niche areas as quiescent cells after transplantation into immunodeficient mice. Additionally, the transplantation of hPSC-SkMSC can functionally rescue mouse models of Duchenne and facioscapulohumeral muscular dystrophies. Another example is our effort to utilize sensory neurons derived from hPSCs (hPSC-SNs) for pain disorders. Our sensory neuron protocol can generate a specific subset of human sensory neurons exhibiting characteristic features including polymodal responsiveness to a number of pain and itching stimuli. Interestingly, ectopic transplantation of hPSC-SNs into the knee joint of osteoarthritic (OA) mice reduced pain and promoted bone and cartilage repair. Mechanistically, our proteomics data suggest that hPSC-SNs act as decoys by sequestering inflammatory ligands while secreting reparative factors in joint tissues. These findings uncover a fundamental role of human sensory neurons in tissue repair, providing a multi-targeted, disease-modifying strategy for OA and chronic pain. In this talk, I will share our recent progress in the hPSC-SkMSCs and hPSC-SNs. Furthermore, our group is currently engaged in the development of additional cell types for the purpose of cell therapy aimed at treating medical conditions and diseases in neuroskeletal and surface tissues.

4:40 PM – 5:25 PM

ABSTRACT AND TITLE NOT AVAILABLE AT THE TIME OF PUBLISHING

George Church, *Wyss Institute, Harvard University, and MIT, USA*

POSTER ABSTRACTS

All times are listed in Eastern Standard Time (EST)

THURSDAY, 11 DECEMBER 2025

POSTER SESSION 1: 5:15 PM – 6:15 PM

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A 3D BIOREACTOR PLATFORM FOR IPSC EXPANSION AND HEPATIC DIFFERENTIATION

Oliver Kraemer, *Fl68 Inc., USA*
Nathalie Chretien, *FL68 Inc.*, *USA*
Pratibha Tripathi, *FL68 Inc.*, *USA*
Lauren Jansen, *FL68 Inc.*, *USA*
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Chris Ramsborg, *FL68 Inc.*, *USA*

Generating clinically relevant quantities of functional hepatocytes from induced pluripotent stem cells (iPSCs) remains a central challenge in regenerative medicine. We report the development of an integrated 3D stirred tank bioreactor system that supports both iPSC expansion and directed differentiation into hepatocytes within a single platform, marking a noteworthy step forward in bioprocess development and manufacturing. Media formulations and real-time sensor-driven control loops were optimized for each phase. This process enabled high iPSC yields, followed by efficient hepatic differentiation. The system generates sufficient differentiated cells to support in vivo rodent studies, indicative of a clear path to clinical doses after scale-up. Derived cells exhibit definitive hepatic characteristics, including elevated expression of alpha-1 antitrypsin and albumin as well as ammonia detoxification and ureagenesis. When comparing bioreactor-derived hepatocytes with primary and 2D-derived hepatocytes, no statistically significant differences in ammonia detoxification rates were found, thereby indicating functional equivalence in this key cellular function. These findings highlight the potential of the integrated bioreactor approach to meet the cell quantities and quality requirements for clinical applications. Ongoing work focuses on further functional characterization and process refinement to support scale-up and in vivo testing.

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A CRITICAL EXAMINATION OF CLINICAL DATA FOR REMESTEMCEL-L-RKND

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Sarah R. Tingley, *UCSF*, *USA*
Rita Redberg, *UCSF*, *USA*

Ryoncil (remestemcel-L-rknd) is the first mesenchymal stromal cell (MSC) therapy approved by the Food and Drug Administration (FDA) as second-line treatment for pediatric steroid-refractory acute graft-versus-host disease (SR-aGVHD) in patients ≥2 months old. The proposed mechanism for this off-the-shelf, donor-derived MSC product involves immunomodulatory paracrine signaling (e.g., IFNγ and IL-2Rα inhibition) dampening donor-derived T-cell activity. Before its FDA approval in December 2024, Ryoncil, previously known as Prochymal, had a long (27-year) regulatory history. It has received multiple special designations by FDA, including Orphan Drug, Fast Track, and Priority Review. We performed a review of the clinical evidence to evaluate Ryoncil's safety and efficacy. FDA approval documents were obtained from the "FDA Approval History, Letters, Reviews, and Related Documents for Ryoncil" packet (June 18, 2025). PubMed, Embase, Google Scholar, and ClinicalTrials.gov were searched through July 20, 2025, using trial identifiers, enrollment numbers, conditions, and remestemcel-specific keywords. Twenty-five studies were identified, including 14 prospective treatment trials, five follow-up safety trials, three Expanded Access Program studies, and additional emergency/compassionate-use reports. Data were tabulated by design, indication, and endpoints. Approval was based primarily on a single-arm multicenter trial of 55 pediatric patients. The pivotal trial's primary endpoint, prevalence of an overall response at day 28, relied on surrogate measures and was not as rigorous as other endpoints used in the field such as a 28-day durable complete response. Of the 25 studies, 3 matched the final approved population, dosing, and indication. Ten were randomized controlled trials; 17 lacked placebo controls. Six allowed unstandardized concomitant medications. Across studies, 42.7% of participants died during follow-up of a median of 140 days; infection was the most common adverse event (38.9%). Evidence supporting Ryoncil's approval was limited in relevance, scale, and rigor. These findings highlight the need for robust, controlled trials to ensure MSC therapies for rare conditions meet both regulatory and clinical standards for safety and efficacy.

Funding: UCSF Summer Explore Research Grant.

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A PLATFORM FOR MULTIPLEXED RNA-BASED CELL ENGINEERING TO DRIVE DIFFERENTIATION IN HUMAN STEM CELLS VIA MECHANOPORATION

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Alec Barclay, *Portal Biotechnologies, USA*
Armon Sharei, *Portal Biotechnologies, USA*

The ability to generate diverse functional cell types rapidly and efficiently from induced pluripotent stem cells (iPSCs) holds transformative potential for disease modeling, drug discovery, and regenerative medicine. Protocols have been derived to differentiate iPSCs into several different cell types; however, these methods come with limitations such as low efficiency, variability between batches, and long production times. Herein we describe a novel mechanoporation technology that allows for cytosolic delivery of cargos (e.g. nucleic acids, proteins, peptides) by means of rendering cell membranes temporarily permeable through mechanical stress. The technology has demonstrated compatibility across multiple cell types and materials, while having minimal effects on endogenous gene expression. Our approach is scalable, reproducible, and minimizes some of the safety concerns associated with other delivery methods. Our results show that mechanical delivery of mRNA encoding Neurogenin 2 (NGN2) can enable differentiation of iPSCs into neuronal precursors via increased expression of early neuronal markers and a decrease in pluripotency markers. These data illustrate the potential to overcome current limitations associated with differentiation while maintaining a viability of 75% at a RNA expression level of over 70%. Additionally, we show that our technology enables delivery of circular RNA, antibodies, and other impermeable cargos, such as DNA-encoded libraries, which can be used for diverse cell engineering and drug discovery applications. At a larger scale for clinical processes that meet GMP requirements, we have demonstrated delivery of over 1 billion cells per minute. By continuing to simplify stem cell modification, we aim to further unlock the biological potential of iPSCs while simultaneously reducing manufacturing complexity and safety concerns associated with other delivery modalities.

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A PRECLINICAL PLATFORM FOR HUMAN THYMIC EPITHELIAL CELL REGENERATION FROM IPSC

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Rosa G. Bacchetta, *Stanford School of Medicine*, *USA*
Vittorio G. Sebastiano, *Stanford School of Medicine*, *USA*

The thymus is an essential immune organ that instructs T cell development and central tolerance, yet its function declines rapidly with age, driving immunosenescence. Recent evidence has revealed that thymic function is even more critical than previously appreciated. A landmark study from Harvard University (Kooshesh et al., NEJM 2023) demonstrated that adult patients who underwent thymectomy experienced a two-fold increase in cancer incidence and nearly a three-fold rise in all-cause mortality within five years - stark evidence of the thymus's role in preventing age-related disease. Despite this importance, no clinically relevant strategies to regenerate thymic function exist, and its potential to direct immune function for therapeutic purposes has not yet been tapped into. Given its small size and simple organ structure, the thymus is an attractive target for iPSC-based tissue regeneration. To elucidate pathways guiding the commitment and specialization of human thymic epithelial stroma, we employed complementary single-cell transcriptomic approaches (Mohammed et al., Sci Immunol 2025). We identified hematopoietic niche-derived signals as critical regulators of thymic epithelial cell (TEC) differentiation and maturation. Building on these insights, we developed a morphogen-based protocol to drive iPSCs into thymic epithelial cells (iTECs). iTECs generated by this approach displayed strong transcriptional fidelity to human fetal TECs and exhibited a diverse MHC class I and II immunopeptidome. To assess functionality, we transplanted iTECs into athymic humanized NSG-nude mice. In this model, iTECs supported the development of naïve and memory effector T cells as well as regulatory T cells with TCR repertoires comparable to controls transplanted with human thymus. iTECs further enabled the generation of antigen-specific vaccine responses, $CD8^+$ T cell–mediated cytotoxicity, and tolerance to "self" in mixed lymphocyte reactions. Together, these findings provide proof-of-concept that transplantable human iTECs can recapitulate the

key functions of the thymus. This work establishes a preclinical platform for iPSC-derived thymic therapeutics to address unmet clinical needs spanning lethal congenital immunodeficiencies, transplant-related complications, and the fundamental biology of aging.

Funding: CIRM DISC2, Emerson Collective, Stanford High Impact Technology Award, Philanthropic support.

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ACCELERATING ALLOGENEIC CELL THERAPIES THROUGH CLINICALLY COMPLIANT IPSC LINE GENERATION

Stefan Braam, *Cellistic, Netherlands*

Progress in iPSC-based allogeneic therapies is hindered by the use of research-grade lines, creating inefficiencies and extending development timelines. Once a therapeutic candidate is defined, cell line development often must be repeated under GMP conditions, causing rework, delays, and cost escalation. Here we present a case study on the generation of the Allo Chassis™ cell lines, produced using the PulseTM platform to deliver Advanced Therapy Medicinal Product (ATMP)-compliant starting material, integrating precision reprogramming, gene editing, and robust quality control. The process began with GMP-compliant leukopaks from two healthy donors, enriched for $CD34^+$ and $CD4^+$ subsets. Cells were reprogrammed using a non-integrative method, minimizing genomic disruption. Colonies were selected and expanded, with QC confirming normal karyotypes (46,XX; 46,XY) and high expression (>85%) of pluripotency markers OCT3/4, NANOG, SSEA-4, and TRA-1-60. Selected clones were advanced into gene editing with the STAR-CRISPR™ platform. Editing reagents were delivered as ribonucleoprotein complexes, preventing integration risk and reducing off-target activity. Single-cell sorting with double clonality assurance enabled the establishment of true monoclonal populations. Editing introduced frameshift mutations in B2M and CIITA to generate HLA class I/II-null iPSCs, validated by next-generation sequencing (>50,000x coverage). Clones meeting specifications were expanded and banked as ATMP-grade pre-MCBs, seamlessly aligning with GMP cell banking and available for downstream use or customization (e.g., CAR, TCR). This case study demonstrates how early integration of GMP-aligned workflows, donor-derived reprogramming, precise gene editing, and monoclonality assurance can generate clinically compliant iPSCs. Embedding these quality-driven processes upstream minimizes R&D-to-CDMO bottlenecks and supports the scalable development of immune-evasive allogeneic therapies.

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ADVANCING CORNEAL ENDOTHELIAL REGENERATION USING HIGH-PURITY FUNCTIONAL CELLS DERIVED FROM HUMAN IPSCS WITH A NOVEL WASH-OUT STRATEGY

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Yeji Yoon, *Asan Medical Center, University of Ulsan College of Medicine, South Korea*
Jiyoon Park, *University of Ulsan College of Medicine, Asan Medical Center, South Korea*
Ryun Hee Lee, *University of Ulsan College of Medicine, Asan Medical Center, South Korea*
Sung Jin Kim, *Asan Medical Center, University of Ulsan College of Medicine, South Korea*
Ji Woo Lee, *Asan Medical Center, University of Ulsan College of Medicine, South Korea*
Hun Lee, *Asan Medical Center, University of Ulsan College of Medicine, South Korea*

Failure of corneal endothelial function leads to loss of corneal transparency and vision impairment, with corneal transplantation currently being the only treatment option. However, due to the shortage of donor corneas, it is critical to establish robust methods for generating corneal endothelial-like cells (CECs) from induced pluripotent stem cells (iPSCs). Here, we developed a novel wash-out method to generate homogeneous CEC populations by removing undifferentiated stem cells, and we demonstrated their therapeutic efficacy and safety in an animal model of corneal endothelial dysfunction (CED). Using clinical GMP-grade human iPSCs derived from cord blood, we induced CEC differentiation with or without the neural crest cell (NCC) stage by plating iPSCs onto VTN-coated culture dishes for 14–28 days. Differentiation into CECs was confirmed by single-cell RNA sequencing, Western blotting, immunocytochemistry, and functional assays. The wash-out protocol allows more differentiated CECs to adhere to a VTN-coated surface in the initial stage, whereas the remaining population, with relatively weaker attachment ability, is washed out and removed. We identified robust CEC-specific markers in iPSC-derived CECs displaying hexagonal morphology. The wash-out method significantly improved both the purity and efficiency of CEC differentiation. Single-cell transcriptomic analysis further revealed that wash-out–enriched iPSC-CECs closely resembled human primary CECs, sharing differentially expressed genes (DEGs) involved in focal adhesion, cell–substrate junctions, mitochondrial protein complexes, metabolic activity, and extracellular vesicle function. In vivo, transplantation of iPSC-CECs into a rabbit CED model confirmed their safety and therapeutic efficacy, restoring corneal transparency, with transplanted cells persisting on the endothelium for up to 16 weeks. In summary, we

successfully differentiated clinical GMP-grade human iPSCs into CECs using a direct differentiation strategy combined with a novel wash-out method. The robust in vitro characterization and the notable recovery of corneal clarity in vivo, without evidence of graft rejection, highlight the strong therapeutic potential of iPSC-derived CECs as a promising cell source for treating CED.

Funding: Grant by the Korean government: (1711174348, RS-2020-KD000148); (21C0723L1-21); (RS-2023-00214125); (RS-2023-00302193); (RS-2024-00438366); Asan Medical Center (2023IP0069-2, 2024IP0066-1).

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ADVANCING NEURAL CELL FUNCTIONALITY: LAMININS AS KEY ECM COMPONENTS IN CELLULAR MODELS AND TRANSLATIONAL RESEARCH

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Cells within tissues interact directly with an extracellular matrix (ECM), a protein-rich framework essential for cellular adhesion, proliferation, differentiation, and maturation. The ECM family of laminins is composed of 16 different isoforms all critical for healthy tissue development and homeostasis. The laminin isoforms vary in expression both temporally and spatially and act as an active part in both the stem cell niches and differentiation. The successful recapitulation of in vivo laminin expression has been demonstrated in various neural applications. For example, groundbreaking work by Kirkeby et al. (2016), demonstrated the use of Biolaminin 521 and -111 to significantly enhance and standardize protocols for PSC-derived dopaminergic neurons. This approach increased cell yield by over 40-fold and facilitated clinical translation, setting a new benchmark for neural differentiation protocols. Biolaminin-111 and -521 have also been shown to enhance neural differentiation and reduce neuroinflammation in human 3D brain organoids, enabling long-term functional midbrain and cerebral organoid generation. Here we demonstrate that Biolaminin 521 can support PSC-derived neural crest differentiation with high purity and yield. The monolayer culture simplifies the differentiation with equivalent or better results compared to the often-used aggregate differentiation. We further demonstrate that Biolaminin 521 in combination with -221 can support PSC-derived astrocyte differentiation, increase standardization, and accelerate differentiation, shortening the protocol by up to one week. In conclusion, in vitro recapitulation of the natural cell niches, with recombinant laminin proteins, can lead to increased yield of desired target cells, simplified and accelerated protocols, as well as enabling clinical translation.

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AN AI-ASSISTED LITERATURE SCREENING APPROACH IDENTIFIES POTENTIAL DMSO-FREE CRYOPROTECTANTS FOR OPTIMAL PRESERVATION OF HUMAN PLURIPOTENT- AND NEURAL- PROGENITOR CELLS

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Jillian Kuizenga, *CaseBioscience*, *USA*
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Current regenerative medicine manufacturing workflows rely heavily on cryopreservation at multiple stages of the product lifecycle. Pluripotent stem cells (PSCs), intermediate progenitor cells, and differentiated cell types are typically preserved using solutions containing dimethyl sulfoxide (DMSO). While effective, these solutions have limitations, including reduced post-thaw cell survival and function, along with known cellular and systemic toxicity. To identify safer and more effective alternatives to DMSO, we utilized open-access large language models (LLMs) to systematically search the scientific literature for non-DMSO cryoprotective agents (CPAs), with the goal of creating an optimized cryopreservation solution for use with human PSCs and neural progenitor cells (NPCs). Using identical search terms across three different LLMs, we generated comprehensive lists of previously reported non-DMSO CPAs used to preserve human cells and tissues. Cross-referencing the results initially yielded ten cell-permeable candidate molecules for further ex vivo screening. Each candidate was evaluated in combination with sucrose, a standard non-permeating CPA, through toxicology assessments and cryopreservation assays, with direct comparison to DMSO. The panel included both well-studied CPAs, such as glycerol, ethylene glycol, and propylene glycol, and less commonly utilized CPAs, such as betaine, neutral amino acids, and urea. Following initial screenings, targeted combinations of CPAs were tested for their ability to support long-term post-thaw survival of PSCs and neural stem cells (NSCs). Ethylene glycol, alone or in combination with other CPAs, demonstrated superior performance, significantly improving long-term PSC and NSC survival compared to other DMSO-free formulations. Glycerol also demonstrated satisfactory performance, however to a lesser degree than ethylene glycol. Further optimization of DMSO-free CPA formulations matched, if not exceeded, the performance of commercial DMSO based cryopreservation solutions. Subsequent testing verified the post-thaw functionality of PSCs and NSCs in differentiation and neuronal development assays, respectively. This LLM literature mining approach enabled the rapid,

systematic identification and validation of alternative CPAs, ultimately leading to the development of DMSO-free cryopreservation solutions with improved safety and efficacy profiles.

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AN ANIMAL ORIGIN-FREE SEEDING SUPPLEMENT TO ENHANCE HUMAN PLURIPOTENT STEM CELL SURVIVAL IN 2D AND 3D CELL CULTURE SYSTEMS

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Cell survival is a major bottleneck in human pluripotent stem cell (hPSC)-derived manufacturing workflows, particularly during stressful procedures, such as gene editing, cloning, and transitioning between culture environments. Poor cell survival reduces yields, increases run-to-run variability, and can elevate production costs impacting the manufacturability. To address this, we developed a novel Animal Origin-Free Seeding Supplement (AOF-SS) to support hPSCs during periods of cell stress and enhance their survival in 2D and 3D culture applications. We evaluated the impact of AOF-SS by comparing against a commercially available small molecule based cell survival supplement (C-SS) and Rho kinase inhibitor Y-27632. Using an animal component-free workflow, hPSCs maintained in TeSR™-AOF on CellAdhere™ Laminin-521 were seeded at 1 cell per well in 96-well plates. After 8 days in culture, colonies were quantified using whole-well imaging. Conditions containing AOF-SS outperformed conditions containing either Y-27632 or C-SS, with cloning efficiencies of 28 ± 12%, 9.5 ± 8%, and 11 ± 8%, respectively (mean ± SD; n = 4 cell lines; n = 7 biological replicates). Additionally, we assessed the ability of AOF-SS to support the transition of hPSCs from 2D adherent to 3D suspension culture and their continued expansion in 3D. hPSCs maintained in 2D adherent culture were dissociated into 50 - 200 µm clumps, seeded into 6-well plates at 5 x 10^4 cells/mL in

TeSR™-AOF 3D medium supplemented with either AOF-SS or Y-27632, and maintained on an orbital shaker. After 4 days of expansion, aggregates were dissociated into single cells before counting and re-seeding into 3D suspension culture. Addition of AOF-SS during the 2D to 3D adaptation passage increased cell yields by 65% compared to Y-27632, resulting in a fold expansion of 13.6 ± 2.6 and a total yield of 6.8 ± 1.3 x 10^5 cells / mL culture volume (mean ± SD; n = 5 cell lines; 1 - 4 biological replicates). Inclusion of AOF-SS during the 4 day expansion passage increased cell yields by 30%, resulting in a fold expansion of 14.9 ± 3.5 and total yield of 7.4 ± 1.8 x 10^5 cells / mL culture volume (mean ± SD; n = 4 cell lines; 3 biological replicates). In summary, AOF-SS enhances cell survival during stressful 2D and 3D bioprocessing, providing a valuable tool for scalable hPSC manufacturing and therapeutic development.

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ASSAY STANDARDIZATION AND CRITICAL QUALITY ATTRIBUTES FOR ADVANCING PATIENT-SPECIFIC PSC-DERIVED THERAPIES

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The retinal pigment epithelium (RPE) is a polarized monolayer essential for photoreceptor maintenance and visual function. Progressive RPE degeneration results in photoreceptor loss and irreversible vision impairment, for which no curative therapies currently exist. To address this unmet need, we are developing an autologous induced pluripotent stem cell (iPSC)–derived RPE replacement therapy. Patient-specific fibroblasts are reprogrammed into iPSCs and differentiated into RPE cells suitable for transplantation. Achieving lot-to-lot manufacturing consistency remains a central hurdle, particularly for autologous iPSC-derived products where intrinsic donor-specific variation imposes additional complexity on process control and product release. To overcome this, we developed a quality control

(QC) framework to define and evaluate critical quality attributes (CQAs) across four domains: Identity, Purity, Safety, and Potency. Defining these attributes required iterative assay development, cross-validation across platforms, and correlation with functional benchmarks. The resulting QC panel integrates complementary molecular and cellular methods, including flow cytometry, microscopy, quantitative gene expression profiling and differential protein secretion. Expression of RPE-specific lineage markers (MITF, RPE65, MerTK, BEST1) confirms identity, while purity is ensured by excluding residual undifferentiated iPSCs. Safety assays assess sterility through presence or absence of microbial contamination, and potency is demonstrated through functional assays of differential cytokine secretion, and tight junction integrity. By systematically addressing the challenges of heterogeneity and assay reproducibility, we established a standardized assay panel that enables robust definition of CQAs, ensuring the safety, reproducibility, and therapeutic potential of autologous iPSC-RPE products. These lessons learned in assay development and standardization provide a generalizable approach for advancing other PSC-derived cell therapies.

Funding: CIRM UCLA BSCRC.

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AUTOMATED IPSC CULTURE AND DIFFERENTIATION ON THE MYTOS IDEM PLATFORM: FROM BENCH PROTOCOLS TO LARGE-SCALE CLINICAL MANUFACTURING

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Ali Afshar, *Mytos*, *UK*
Jordina Casanova, *Mytos*, *UK*
Rebecca Powell, *Mytos*, *UK*
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Pluripotent stem cell (PSC) derived therapies are showing great promise in late-stage trials and have the potential to treat tens of millions of patients - but today their potential is limited by the high cost and low scalability of manual manufacturing. Culture protocols get developed manually in flasks, and then require years of process redevelopment to be scalable in bioreactors. The Mytos iDEM platform is an alternative route to scalable, low cost manufacturing, without having to redevelop manual protocols. iDEM fully automates PSC culture in a closed flask-based cartridge, enabling manually-developed flask-based protocols to be directly translated to large automated production for PD and

manufacturing. We demonstrate automated iPSC maintenance and differentiation across multiple lineages on iDEM. Using STEMdiff™ Hematopoietic, we generated ~9.5×10^6 hematopoietic progenitor cells (HPCs) per T175 with consistent marker profiles (CD34+ >95%, CD45+ >60%, SSEA4+ <5%, TRA-1-81+ <5%; n=2). Dopaminergic neurons (DAs) produced via a published protocol (Kriks et al., 2011) exhibited >95% viability and flow-cytometry profiles comparable to manual differentiation (TUJ1+ >95%, FOXA2+ >95%, MAP2+ >80%, TH+ >65%; n=3). We have also completed proof-of-concept differentiation to retinal pigment epithelium (RPE), supporting the platform's suitability for extended, adherent protocols. Beyond these case studies, iDEM is now being applied to a wide range of therapeutic cell types through active manufacturing collaborations with StemSight (iPSC-derived corneal cells), Rinri Therapeutics (otic neural progenitors for sensorineural hearing loss), and Novadip (adipose-derived cell therapies for large bone defects). These collaborations demonstrate a practical path from research-grade processes to early clinical and commercial-ready manufacturing on the same automated platform. Collectively, the iDEM platform reduces variability, minimizes operator intervention, and preserves culture integrity in a closed system. By enabling robust, scalable differentiation workflows across diverse lineages, iDEM accelerates time-to-clinic and lowers the cost of goods for developers advancing cell-based therapies.

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AUTOMATED MORPHOLOGICAL QUALITY CONTROL OF IPSC-DERIVED RPE USING DEEP LEARNING: A PLATFORM FOR BIETTI CRYSTALLINE DYSTROPHY AND RETINAL THERAPY DEVELOPMENT

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Bietti crystalline dystrophy (BCD), an inherited retinal disease (IRD) caused by pathogenic variants in CYP4V2, leads to progressive retinal pigment epithelium (RPE) atrophy and vision loss, with no effective therapy currently available. In this study, we established a patient-specific disease model using induced pluripotent stem cell (iPSC)-derived RPE cells harboring distinct CYP4V2 mutations alongside their CRISPR-corrected isogenic counterparts. Bright-field imaging revealed that BCD-iPSC-derived RPE (BCD-iPSC-RPE) cells recapitulated mutation-specific morphological abnormalities, establishing a direct correlation between genotype and pathological phenotype and reflecting mutation-dependent disease severity. To enable robust and scalable phenotypic characterization, we developed a convolutional neural network (CNN)-based deep learning model trained on large-scale RPE imaging datasets. The model accurately distinguished diseased from

corrected RPE and quantitatively graded morphological variation across different CYP4V2 mutations, providing an unbiased readout of cellular phenotypes. By integrating AI-assisted image analysis with patient-derived cellular models, this approach establishes a rigorous framework for preclinical evaluation of gene-corrected RPE cells prior to transplantation. This platform is broadly applicable to other IRDs and degenerative diseases in which RPE dysfunction is central. The ability to automate mutation-specific morphological quality control has the potential to accelerate the translation of iPSC-derived RPE into clinical applications, ensuring the safety and efficacy of autologous cell replacement therapies. Collectively, our findings highlight the power of combining stem cell–based disease modeling with AI-driven analytics as a scalable and generalizable strategy to advance regenerative therapies for retinal disorders.

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CLOAKED RPE CELL REPLACEMENT: ENAHNCING SURVIVAL AND IMMUNE EVASION IN RETINAL THERAPY

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Retinal degeneration (RD) is a major cause of irreversible blindness worldwide, with profound impacts on patient quality of life. RD encompasses a range of diseases, including age-related macular degeneration (AMD) and inherited retinal dystrophies (IRDs). AMD alone affects nearly 200 million people globally - a figure projected to nearly double by 2040 - underscoring the urgent need for new therapeutic strategies. Most forms of RD involve the degeneration of both retinal pigment epithelium (RPE) and photoreceptor (PhR) cells. Effective, long-term vision restoration will likely require replacement of both cell types. While PhR transplantation is relatively immune-privileged due to low MHC class I expression, RPE cells pose a greater immunological challenge. Despite the immune-

privileged status of the eye, RPE cells are introduced into a pro-inflammatory microenvironment during transplantation, especially in late-stage retinal disease. Moreover, RPE cells naturally express MHC class I and can upregulate MHC class II in response to inflammation, reflecting their physiological role in retinal immune regulation. While beneficial in homeostasis, these features make allogeneic RPE transplants more immunogenic, typically requiring recipients to undergo immunosuppressive regimens. To address this, we have developed genetically engineered, “cloaked” allogeneic RPE cells derived from a fully characterized, GMP-compliant human iPSC line. These cells are designed to evade immune detection while maintaining full differentiation potential. Using a proprietary, cost-efficient, and scalable protocol compatible with GMP standards, we achieved robust, high-yield, and high-purity production of cryopreservable cloaked RPE cells. Our engineered cells show the the inserted and deleted immune-evasive transgenes at both RNA and protein levels, while maintaining key RPE differentiation and maturation markers. The modifications are designed to protect RPE cells from T cell- and NK cell-mediated killing, with the goal of improving survival following transplantation. Taken together, our results represent a significant advancement in the development of immune-evasive, off-the-shelf RPE cell therapies.

Funding: Evotec International GmbH.

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CO TRANSCRIPTIONALLY FOLDING RNA NANOSTRUCTURES TO TARGET CANCER STEM CELLS

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Nucleic acid nanotechnology is an emerging discipline at the intersection of chemistry, biology, physics, and biotechnology, with the potential to transform how we design programmable molecular tools. A central approach, DNA origami, exploits the predictable base-pairing rules of DNA to fold long strands into precise nanoscale architectures under controlled conditions. More recently, the concept of RNA co-transcriptional folding has gained momentum. Unlike DNA origami, this strategy harnesses the natural folding dynamics of RNA as it emerges from RNA polymerase, enabling the spontaneous formation of functional RNA structures without requiring extensive post-synthetic manipulation. Although co-transcriptional folding has been demonstrated in bacterial systems, its

application in mammalian cells remains largely unexplored. Here, we present the first demonstration of abundant expression, folding, and function of co-transcriptionally folded RNA nanostructures in human cells. We engineered synthetic DNA templates encoding RNA sequences that fold into programmable monomeric units during transcription, which then self-assemble into higher-order RNA nanostructures. Remarkably, these assemblies preferentially localized within the nuclei of human cells, suggesting novel opportunities for spatially targeted applications. To evaluate functionality, we incorporated miRNA sponging motifs into our RNA designs. These constructs are being implemented to sequester oncogenic miRNAs frequently upregulated in cancer. Through this strategy, we anticipate reduced cancer cell proliferation and downregulation of cancer stem cell markers. This dual demonstration of structural programmability and biological activity highlights the versatility of RNA nanostructures as intracellular tools. Our work establishes a proof-of-principle for designer RNAs as a new modality in mammalian synthetic biology. By coupling predictable co-transcriptional folding with rationally designed functionality, this approach opens the door to programmable regulation of gene expression, cellular pathways, and stem cell fate decisions. More broadly, RNA nanotechnology may provide a foundation for therapeutic interventions, from targeting oncogenic networks to engineering regenerative potential in stem cells.

Funding: NIH R01 DK139790.

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COMPARATIVE EFFICACY AND SAFETY OF INTRACAVERNOSAL PLATELET-RICH PLASMA AND AUTOLOGOUS BONE MARROW MESENCHYMAL STEM CELLS IN PATIENTS WITH ERECTILE DYSFUNCTION

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Erectile dysfunction (ED) is a prevalent condition with significant impact on quality of life, particularly in patients unresponsive to phosphodiesterase type 5 inhibitors. Novel regenerative strategies are needed for this population. This prospective case-control study

evaluated the efficacy and safety of intracavernosal platelet-rich plasma (PRP) and autologous bone marrow-derived mesenchymal stem cells (BM-MSCs). Sixty men aged 37–65 years with moderate to severe organic ED refractory to first-line therapy were randomized into three groups of 20: Group 1 received 4 mL PRP in two sessions, Group 2 received 6 mL PRP in two sessions, and Group 3 received a single BM-MSC injection. Outcomes were assessed using the International Index of Erectile Function-5 (IIEF-5) and the Erection Hardness Score (EHS) at 1.5, 3, and 6 months. Both PRP and BM-MSC interventions were well tolerated without serious adverse events. Improvements in erectile function were observed in all groups, peaking at three months and declining by six months. Although intergroup differences were not statistically significant, trends favored higher PRP volume and BM-MSCs, with the latter showing a tendency toward more sustained benefits. These findings demonstrate that both PRP and BM-MSC therapy are safe and provide short-term clinical improvement in refractory ED, while stem cell therapy may offer more durable effects. Further randomized controlled trials are required to standardize methodology, optimize dosing and frequency, and evaluate long-term outcomes of regenerative therapies in ED management.

Funding: This research has been funded by the Science Committee of the Ministry of Science and Higher Education of the Republic of Kazakhstan (Grant No. AP23488303).

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COMPARING PSC-DERIVED PERICYTES FOR VASCULAR NETWORK STABILISATION

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Pericytes are essential regulators of vascular stability, but their generation from pluripotent stem cells (PSCs) remains poorly characterised compared with endothelial cell (EC) differentiation. Pericyte-like cells can be derived from the CD34– fraction of EC differentiation protocols, offering a more streamlined approach that reduces time, cost, and waste by generating two vascular cell types in parallel. Efficient and reproducible derivation of functional ECs and pericytes will be critical for developing PSC-derived vascular networks and cell suspension therapies, yet how EC differentiation strategy

shapes pericyte function remains unclear. We investigated the effects of two EC differentiation protocols on downstream pericyte function using Shef1.3 hESCs. A baseline protocol (BP) using CHIR-mediated mesoderm induction followed by bFGF/VEGF for vascular specification was compared with a modified protocol (MP) incorporating stage-specific TGFβ modulation and an increased volume-to-surface area ratio. In both cases, the CD34– fraction was directed towards pericyte-like cells using three post-sorting strategies: pericyte medium (PCM), PCM with bFGF and PDGF-BB (factor treatment), or factor treatment with subsequent expansion. BP-derived pericytes consistently proliferated in response to PDGF-BB, whereas MP-derived pericytes were less responsive. Expansion further reduced proliferative potential in both groups. When co-cultured with ECs in 3D hydrogels, pericytes influenced capillary-like network morphology and stability in distinct ways. MP-derived pericytes promoted more continuous networks, while BP-derived pericytes produced more variable outcomes. Both populations supported lumen formation and aligned with CD31+ EC networks. Confocal imaging also revealed heterogeneous pericyte morphologies, with relative proportions differing by protocol. This suggests that EC differentiation strategy shapes pericyte heterogeneity, which may affect their ability to stabilise vascular networks. Together, these findings demonstrate that protocol design impacts EC and pericyte functionality, and that optimising these lineages in parallel will be critical for advancing PSC-derived vascular cell therapies and accelerating their translation into clinic.

Funding: The Michael Oren Foundation. The Sir Joseph Hotung Charitable Settlement.

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CREATION OF THE FIRST GLOBAL CONTINUING EDUCATION COURSE FOR HEALTHCARE PROFESSIONALS ON STEM CELL MEDICINE

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The field of stem cell medicine is advancing rapidly, with several interventions progressing to clinical trials. Despite this progress, there is a rise of unproven stem cell treatments that presents significant challenges. This transformative era in stem cell medicine has the potential to revolutionize treatment options in the coming years, but effective integration into clinical practice requires clinicians to have authoritative, evidence-based knowledge for optimal patient care. To address this, the ISSCR, in partnership with Harvard Medical School, has developed an open-access Continuing Education course, Stem Cell Medicine: From Scientific Research to Patient Care. The course was developed in three phases: 1) global consultation to identify unmet needs in stem cell education for clinicians; 2) prioritization of content and educational delivery methods; and 3) development of on-demand, online training material. The course consists of seven modules covering topics from basic stem cell biology to effective patient communication strategies. Key content includes distinguishing between approved, investigational, and unproven stem cell treatments, and the transition from preclinical research to clinical trials and applications. Examples from the scientific literature are used throughout to illustrate key concepts. The final module synthesizes the content focusing on patient communication and explores the concept of therapeutic hope and persuasive communication to support informed decision-making among patients and their families. Launched in May 2025, this open-access course offers AMA PRA Category 1 Credits™ and ANCC contact hours. It serves as an essential resource for clinicians, scientists, and healthcare providers, empowering them to navigate the evolving field of stem cell medicine. Future disease-specific courses will expand on areas where stem cell medicine has seen significant progress.

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DEFINED SYNTHETIC HYDROGEL AND AI MODIFIED PROTEINS FOR CULTURING HUMAN INTESTINAL, LIVER, AND LUNG ORGANOIDS

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3D organoid culture often relies on animal component-derived matrices, such as basement membrane extract (BME), along with thermally unstable growth factors, such as FGF10 and Wnt3a. Historically, these proteins have demonstrated manufacturing difficulties and required frequent supplementation. Additionally, end users of these matrices may also experience restricted reproducibility, poor scalability, and compliance challenges for downstream clinical path goals, Collectively, these factors increase the total costs and labor of organoid workflows. To overcome these challenges, a two-pronged strategy was implemented: (1) leverage AI-modified proteins (thermostable FGF10 and Wnt3a agonists) to improve cell culture workflows manufacturability and (2) use a fully defined synthetic-component derived hydrogel matrix to mimic the extracellular matrix as an alternative to BME. This combination was tested for its compatibility across human stem cell-derived intestinal, liver, and lung organoid cultures. The results demonstrate that the synthetic hydrogel supports robust organoid growth while maintaining key markers, such as LGR5 for intestinal cultures, and expected characteristic organoid morphology (e.g. cyst formation). The designer Wnt agonists effectively activated β-catenin signaling at lower concentrations than wild type Wnt3a protein, further improving organoid culture efficiency while reducing the cost and variability associated with these factors. Thermostable FGF10 also promoted robust organoid growth. This innovative approach highlights the synthetic matrix's ability to address a range of tissue compatibility and shows the benefits of combining defined matrices with designer proteins to overcome organoid workflow limitations for more reproducible, scalable, and clinically relevant alternatives to traditional reagents. These advancements have the potential to improve key organoid applications including disease modeling and therapeutic development, opening the door to more effective organoid workflow development and clinically translatable platforms.

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DEVELOPING A BIOLOGICALLY INFORMED WORKFLOW FOR EFFICIENT PARATHYROID CELL PRODUCTION

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Loss or dysfunction of parathyroid (PT) glands leads to hypoparathyroidism, a challenging condition characterized by insufficient levels of parathyroid hormone (PTH) that disrupts calcium homeostasis. Unlike progress in many endocrine disorders to monitor and stabilize homeostasis, current treatment approaches for hypoparathyroidism lack feedback mechanisms. Pluripotent stem cell (PSC)-derived PT cells represent a potentially curative therapeutic avenue if optimal conditions or strategies could be derived. Here, we present efforts to optimize biologically informed transdifferentiation strategies to efficiently transition human pluripotent stem cells through definitive endoderm (DE), anterior foregut endoderm (AFE), pharyngeal endoderm (PE), and PT stages using single cell (sc)RNA-seq predicted Transcription Factors (TFs) and Growth Conditions. Specifically, we nominated TF modules via a densely sampled atlas of mouse parathyroid development that spans E6.5 epiblast to bifurcating PT-thymus progenitors at E11.5 in 12-hour increments. Our approach tests small molecule modulation of key signaling pathways, such as BMP, WNT, and SHH, ectopic transcription factor expression, and synergy between these approaches on the overall efficiency of PT-like cell production. Nucleofection of TF modules into PSCs induced distinct cellular patterning and morphological cues of differentiation within 3 days, and scRNA sequencing performed on PSCs nucleofected with TF modules produces large fractions of cells that clearly map to cells within the PE/parathyroid-thymus primordial state. When directed differentiation through DE and AFE was combined with delivery of TF modules, immunofluorescence microscopy revealed discrete clusters of cells with high levels of GATA3, a parathyroid-enriched transcription factor. Additional characterization of these cells supports the feasibility of this approach for rapidly prioritizing and testing developmental factors for their ability to support directed differentiation of functional cell types. By bridging stem cell biology with developmental genetics, this work is advancing toward a functional cure for hypoparathyroidism.

Funding: NIH, Mathers Foundation.

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DEVELOPING A FLEXIBLE CELL PROFILING PLATFORM TO QUALIFY RAW CELLULAR MATERIALS AND FINAL THERAPEUTICS

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Precise characterization of cellular composition is critical for quality control in ex vivo cell manufacturing, where dynamic shifts in immune populations can directly influence therapeutic efficacy and safety. Conventional methods for cell profiling are often time-consuming or lack flexibility across different sample types. To address this challenge, we developed a rapid and adaptable cell profiling platform based on multi-parameter flow cytometry with fluorescence-conjugated antibodies. This system enables clear identification of T, B, and NK lymphocyte subsets in less than 30 minutes, providing a standardized approach for monitoring both raw cellular materials and final therapeutic products. We applied this platform to peripheral blood mononuclear cells (PBMCs) undergoing feeder-free T cell activation and expansion. At initiation, cultures contained 97.2% CD45+ lymphocytes, with 45.1% CD3+ T cells and 32.5% NK cells. By day 13, T cells expanded to 96.6% of the population, while NK and B cells declined to below 1%, consistent with expected enrichment of activated T cells during manufacturing. These results demonstrate that the platform reliably captures population dynamics throughout the process, with high precision and reproducibility. In addition, the assay's adaptability allows it to be applied to diverse cell therapy products, including CAR-T and other engineered lymphocytes. Together, these findings establish a rapid and flexible strategy for cell profiling that supports real-time quality control during cell therapy development. By integrating speed, adaptability, and scientific rigor, this approach offers a practical solution for advancing consistent, high-quality manufacturing in both autologous and allogeneic settings, thereby strengthening the translational potential of cell-based immunotherapies.

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DEVELOPING A SEAMLESS WORKFLOW TO TRANSITION PSCS FROM ADHERENT TO SUSPENSION CULTURE WITH CELL THERAPY GRADE CULTURE SYSTEMS

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Pluripotent stem cells (PSCs) hold great promise for regenerative medicine and the development of cell therapies. Despite the potential for unlimited PSC expansion in vitro, conventional workflows still have many challenges to overcome. These challenges include minimizing cytotoxic stress during single cell workflows such as gene editing; efficiently scaling PSC cultures to meet manufacturing needs; robust differentiation protocols; and access to regulatory compliant, cell therapy grade cell culture reagents. To address these needs, we developed several fit-for-purpose cell therapy-grade PSC tools, including CTS StemFlex Medium and CTS StemScale PSC Suspension Medium, designed to ease transition from bench scale to clinical manufacturing processes. These platforms allow for a seamless PSC workflow that supports PSC growth from small-scale adherent cultures to large-scale suspension bioreactors. We demonstrate that monolayers of PSCs cultured in CTS StemFlex maintain high expression levels of pluripotency markers (e.g. >95% OCT4/NANOG); display trilineage differentiation potential in spontaneous and directed differentiation assays; and maintain a normal karyotype for a minimum of 10 passages. This medium system also supported gene editing protocols and clonal expansion efficiency with maintenance of pluripotency markers after electroporation. We then transitioned PSCs to suspension culture in CTS StemScale medium which maintained pluripotency marker expression and genomic stability for more than 30 passages, confirming the PSCs were successfully adapted to this format. In this culture system, PSCs displayed 8-10 fold expansion per passage in well plates, shake flasks, and stirred tank reactors, while also maintaining their differentiation potential. For example, suspension PSCs could be differentiated into highly pure, cytotoxic populations of iPSC-derived natural killer cells. These results demonstrate the successful integration of adherent and suspension PSC media systems to enable workflows at application appropriate scales while maintaining critical PSC attribute.

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DEVELOPING A STEM-CELL BASED THERAPY FOR HUNTINGTON'S DISEASE TREATMENT

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Cell replacement therapy (CRT) for Huntington's Disease (HD) aims to restore neural circuits by replacing the striatal projection neurons (SPNs) lost during disease progression. Human pluripotent stem cells (hPSCs) offer a renewable source to generate these neurons in vitro. However, clinical translation needs robust, reproducible, and Good Manufacturing Practice (GMP)-compliant processes to ensure product quality, scalability, and safety. Here we describe the development and validation of a fully GMP-compliant scalable platform for the expansion, cryopreservation, and differentiation of hPSCs into transplantable striatal-committed neural progenitor cells (S-NPCs). We optimized seeding densities and evaluated adhesion rates to achieve consistent hPSC expansion while maintaining morphology, pluripotency, and genomic stability, as confirmed by immunocytochemistry, flow cytometry, and G-banding. Using this foundation, we differentiated hPSC into S-NPCs that expressed canonical LGE progenitor markers, exhibited high viability, and retained the capacity to mature into functional SPNs in vitro. Importantly, product specifications were determined by single-cell transcriptomic analyses of both human fetal tissue and hPSC-derived progenitors, enabling the identification of key markers that define a clinically relevant S-NPC population signature. To ensure product stability and availability, we also implemented a controlled rate freezing (CRF) strategy with optimized cell densities to improve recovery rates and maintain viability of both hPSCs and NPCs. Crucially, NPCs recovered after thawing maintained their capacity to differentiate into functional SPNs in vitro, ensuring product potency after long-term storage. Together, these advances establish a reproducible, scalable workflow for producing clinical-grade NPCs, supporting batch release, distribution, and the progression of CRT toward first-in-human trials for HD.

Funding: Ministerio de Ciencia e Innovación (PID2021-126961OB-I00 and PID2024-155342OB-I00; and TERAV, RD21/0017/0020, and RD24/0014/0016, ISCIII); and Generalitat de Catalunya (2021 SGR 01094), Spain.

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DEVELOPMENT OF A CLINICAL-GRADE CBU DERIVED HOMOZYGOUS HLA IPSC HAPLOBANK FOR THE UNITED STATES POPULATION

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Autologous cell sources of induced pluripotent stem cells (iPSCs) have the potential to deliver regenerative cell therapies without risk of rejection, but clinical challenges such as patient cell quality and comorbid diseases, compounded by manufacturing challenges such as scalability, time requirements, consistency, and quality control have rendered such sources as impractical for most applications . Allogeneic cell sources, on the other hand, enable reproducible, off-the-shelf solutions for iPSC cell therapy manufacturing, but have significant risk of graft rejection in recipients. A variety of strategies to create universal iPSC cell lines with limited rejection potential have emerged, such as genetic ablation of HLA genes and overexpression of 'markers of self' (i.e. CD47), however these strategies require genetic editing and impair engagement with the recipient immune system. Indeed, HZ-HLA iPSCs would not require genetic editing, and would preserve natural immune surveillance capabilities thus leaving in place safeguards against viral infections and oncogenic transformation. To enable the broadest possible use of HZ-HLA iPSCs, New York Blood Center's (NYBC) National Cord Blood Program identified in inventory >350 FDA-licensed cord blood units (CBUs) from HZ-HLA consented donors and using CD34+ cells have generated iPSC lines to begin HZ-HLA iPSC Haplobank. Using HLA-A, -B, and -DRB1 allelic typing, we calculate that the 25 most frequent HLA haplotypes in the NYBC master cell bank when fully established would be HLA compatible with >50% of the United States population across a broad range of ethnic backgrounds. Now, having successfully developed a GMP iPSC master cell bank from a HZ-HLA CBU, we herein report the development of this NYBC iPSC Haplobank for use in research, clinical and commercial iPSC applications. We have developed cGMP CD34+ isolation and iPSC manufacturing process workflows to enable scalability and established quality control standards to ensure reproducibility of cell lines that will maximize the long-term viability of the Haplobank. Developing global resources of HZ-HLA iPSCs hold immense potential to mitigate the risks associated with allogeneic iPSC-derived graft rejection and to advance patient accessibility to emerging transplant and regenerative medicine therapies. Ultimately, the Haplobank will support the expanded uses of iPSC-driven technologies and enhance the quality of life for iPSC-derived cell therapy recipients.

Funding: NHLBI R01 HL155574.

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DEVELOPMENT OF A STEROIDOGENIC HORMONE RESPONSIVE OVARIAN IMPLANT FOR THE TREATMENT OF MENOPAUSE

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Despite the substantial impact of menopause on women's health, there are few available treatment options, with most targeting only specific symptoms or consisting of hormone replacement therapy (HRT), which has limited efficacy and safety. This study details the development of a steroidogenic, hormone responsive subdermal implant that aims to treat menopause by integrating into native signalling pathways and restoring hormonal balance. First, a set of allogeneic human induced pluripotent stem cell (hiPSC) lines were evaluated using transcription factor (TF)-directed differentiation into ovarian support cells (OSCs). Resultant OSCs were screened for hormone responsiveness following exposure to follicle stimulating hormone (FSH) and androstenedione (A4) by measuring estradiol (E2) production, and the lead clone GTO-101 was selected based on the highest level of E2 production. Next, parallel differentiation experiments were performed under various conditions to optimize hormone production, with results showing that supplementation with Forskolin, ITS, and SAG, as well as 3D differentiation, increased hormone production. Differentiated OSCs were then encapsulated in core-shell alginate microbeads, and results showed that OSCs retained both viability and functionality following encapsulation. To establish a source of exogenous androgens, A4 was incorporated into a medical-grade polymer matrix and cylindrical A4-containing rods to ensure slow controlled release. Finally, encapsulated OSCs and the A4 rod were loaded into a 3D printed porous resin implant housing, and analysis of hormone secretion demonstrated that the cells retained functionality, based on E2 production, as well as viability. Collectively, these data demonstrate the successful generation of a steroidogenic ovarian implant consisting of alginate encapsulated allogeneic ovarian-like cells. As the in vitro results demonstrate the feasibility and functionality of the implant, the next stages in development will include pilot in vivo studies to evaluate safety and efficacy.

Funding: This work was supported by the Advanced Research Projects Agency for Health (ARPA-H) and Gameto, Inc.

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DEVELOPMENT OF AN OFF-THE-SHELF UNIVERSAL CAR T CELL

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Chimeric Antigen Receptor (CAR) T cell therapies are efficacious in treating blood cancers due to their capacity for targeted killing of cancer cells. However, costly and delicate methods to produce CAR T cells limit their wide-spread use. We seek to create an off-the-shelf CAR T cell using induced pluripotent stem cells (iCAR T cells). iCAR T cells will be immune privileged and express a facultative CAR, replacing T-cell receptor alpha beta (TCRab), to prevent host-vs-graft and graft-vs-host responses, respectively. Our goal is to engineer an immune privileged iPSC line with the capacity to differentiate into an iCAR T cells. Further, our immune privileged iPSCs could be applied to cellular engraftment procedures for other forms of disease. Immune privilege gene edits will be performed on iPSCs using CRISPR/cas9 and then confirmed using PCR amplification, sequencing, karyotyping and flow cytometry. Both immune privileged and wildtype iPSCs will be differentiated into T cells using an established protocol. T cell phenotypes and expression of CAR and T cell markers will be analyzed using flow cytometry. We successfully performed the gene knockouts and knockins granting immune privilege and CAR capabilities, confirmed after differentiating into hemogenic endothelium and lung basal cells. Yet, immune privileged iCAR Ts did not adequately express CARs, even when TCRab was not detected. While the immune privilege was confirmed, majority of iCAR Ts showed TCR gamma delta expression preventing expression of the CAR under the TCR alpha promotor. Recent investigations have revealed the benefit of using iPSCs-derived from CD3+ T cell population (TiPS), that circumvent the natural yet cumbersome DNA recombination events that restructure the DNA sequences encoding TCRa and TCRb. The TiPS also demonstrated expression of a CAR at the hallmark T cell double positive (CD4+ and CD8+) demonstrating iPSC-derived T cell advancement through late developmental phases. Future studies will investigate mechanistic and transcriptional events that underly T cell development when comparing cells derived from iPSCs or TiPS. These studies are

impactful to further elucidate developmental mechanisms of T cell subsets while providing a novel iPSC-based CAR T cell platform for translational medicine in cancer.

Funding: TL1/CTSI Training Program in Regenerative Medicine (5TL1TR410-9) Boston University Kilichand Fellowship, Multicellular Design Program.

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DRIVING NEXT-GENERATION IPSC-BASED CELL THERAPIES THROUGH RIGOROUS CELLULAR AND GENOMIC CHARACTERIZATION

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The discovery of induced pluripotent stem cells (iPSCs) has transformed regenerative medicine by enabling new opportunities in disease modeling, drug discovery, and cell-based therapies. Realizing this promise requires not only advances in differentiation protocols but also robust, well-characterized iPSC lines that can be manufactured at clinical grade. A persistent challenge in the field is ensuring reproducibility, quality, and genomic stability across large-scale, GMP-compliant production systems. To address these needs, FUJIFILM Cellular Dynamics, Inc. (FCDI) has built an integrated iPSC platform that combines reprogramming, banking, genome engineering and comprehensive quality control testing with advanced genomic characterization, including next-generation sequencing, to strengthen understanding of iPSC biology and stability. These capabilities complement FCDI's extensive cell differentiation experience and have enabled the

successful translation of multiple iPSC-derived concepts into clinical programs, including therapies targeting ocular, neurodegenerative, cardiac, and immune diseases. Embedding rigorous genomic and phenotypic characterization into the platform provides critical safeguards to de-risk clinical translation and improve product consistency. This presentation will detail our current strategies, which not only comply with but often exceed regulatory requirements, setting new industry benchmarks for the future of cell-based therapies. Moving forward, FCDI will continue to advance high-quality iPSC manufacturing while leveraging strategic partnerships and CDMO offerings to accelerate the development of novel cell therapies.

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SAFETY AND TOLERABILITY OF RPE STEM CELL-DERIVED RPE (RPESC-RPE) IMPLANTATION IN PATIENTS WITH DRY AGE-RELATED MACULAR DEGENERATION (AMD): EARLY LOW DOSE CLINICAL OUTCOMES

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In non-exudative age-related macular degeneration (dry AMD), atrophy of retinal pigment epithelium (RPE) cells leads to deterioration of photoreceptor cell function and ultimately to vision loss. There are currently no approved vision-improving therapies for dry AMD patients. Multiple approaches for RPE cell replacement therapy are under clinical investigation. Our unique strategy utilizes adult RPE stem cell-derived RPE cultured to an

intermediate 4-week progenitor stage of differentiation (RPESC-RPE-4W). IND-enabling studies demonstrated a strong safety profile in Rowett Nude rats and durable vision rescue in the Royal College of Surgeons rat model of retinal degeneration. Our first-in-human Phase 1/2a clinical trial is underway with interventions completed for 6 subjects in 50,000-cell low dose Cohort 1. Participants were enrolled in worse-seeing group 1a (20/200 – 20/800) or better-seeing group 1b (20/70 – <20/200) based on baseline screening. Post-surgical primary and secondary endpoint measurements have been completed to 12 months for Group 1a and 6 months for Group 1b. Primary safety endpoints were met with no product-related serious adverse events (SAEs), no significant inflammation and no tumor formation. Vision improvements were observed in all subjects. Worse-seeing Group 1a subjects improved by an average of +22 letters on the EDTRS eye chart at 12 months, while better-seeing Group 1b subjects improved by an average of +3.3 letters at 6 months. Following Data Safety Monitoring Committee review, the trial has advanced to the second cohort receiving the middle dose of 150,000 cells. The promising clinical outcomes with potential to address the significant unmet medical need of dry AMD patients, coupled with strong manufacturing methodology, were recognized by Regenerative Medicine Advanced Therapy (RMAT) designation from the FDA.

Funding: The IND-enabling studies and clinical trial are sponsored by NIH NEI Regenerative Medicine Innovation Program cooperative agreements (U01EY030581, UGEY031810) and Luxa Biotechnology.

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ENABLING ROBUST AND EFFICIENT IPSC-DERIVED THERAPY MANUFACTURING UP TO 80L VIA LINEAR SCALE-UP AND INTERMEDIATE HIGH-DENSITY CELL BANKING

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Efforts have been made to develop scalable processes for producing human induced pluripotent stem cell (iPSC)-derived products. Cell therapy manufacturing processes are complex, involving various unit operations such as expansion, differentiation, harvest, fill/finish, and cryopreservation. Developing each of the processes at scale for sensitive iPSCs and their derivatives is extremely challenging. For example, multiple studies have demonstrated non-linearity in the scale-up of iPSC expansion processes. Moreover, manufacturing processes for iPSC-derived therapies typically require prolonged periods of

seed-train stages, including planar culture. Planar culture has disadvantages such as a lack of process control and monitoring, and a requirement for matrix substrates. These challenges are compounded by subsequent passaging, which may adversely impact cell quality even before bioreactor inoculation. To overcome such manufacturing challenges, we have developed scalable iPSC expansion processes, addressing key requirements for linear scale-up. Specifically, we successfully developed large-scale 3D cell culture processes using the Vertical-Wheel® Bioreactor family, up to 80L scale, and efficient, scalable, and reproducible bioreactor harvest protocols (including cell aggregate dissociation, wash, and concentration). This accomplishment of linear scale-up in the iPSC expansion process enabled the establishment of high-density working cell banks (HD-WCBs) to cryopreserve bioreactor-expanded iPSCs at 50-150E6 cells/mL. Furthermore, we have generated various HD-WCBs during serial passages of bioreactor culture to cryopreserve cells with different levels of bioreactor adaptation. The HD-WCBs demonstrated normal growth when thawed and inoculated into bioreactors and maintained pluripotency phenotype and karyotype stability. Additionally, the iPSCs were differentiated into insulin-producing cells in both planar and suspension cultures, and other cell types. These results demonstrate linear scale-up of the iPSC expansion process and the successful application of a bioreactor-adapted HD-WCB strategy, eliminating the need for 2D seed-train culture, shortening the manufacturing process, and significantly improving the manufacturability of iPSC-based therapies.

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MACHINE LEARNING-DRIVEN IDENTIFICATION OF GENETIC PERTURBATIONS ENHANCING CELL SURVIVAL AND INTEGRATION FOR CNS CELL REPLACEMENT THERAPIES

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Cell replacement in the central nervous system (CNS) is being investigated to treat neurodegenerative diseases (NDDs), stroke, brain injuries, and other ailments. Induced pluripotent stem cell (iPSC)-derived therapeutics for certain NDDs are challenged by poor cell survival and integration. Genetic engineering of cells prior to engraftment is a strategy to overcome these limitations. Here, we elucidate perturbations that may enhance graft survival and resilience to the hostile microenvironment. Using publicly available perturbation datasets and machine learning, we uncover gene expression patterns that may drive resilience across stress states in transplantation via in silico transcriptome

prediction tools. We analyze these features to nominate iPSC perturbation candidates for future testing. We curated datasets from the CRISPRbrain platform, including CRISPR screens on iPSC-derived glutamatergic neurons and microglia, with various survival-related phenotypes. Beneficial perturbations were filtered, and transcriptomic profiles of cells post-perturbation were modeled using transformer-based state prediction tools. Predicted transcriptomic profiles were clustered to identify groups of resilient profiles while pathway enrichment analyses identified candidate biological processes linked to survival. A logistic regression classifier was trained and used to extract defining pathways of the resilient clusters. A likelihood ratio test was applied to rank driver pathways, and Gene Ontology analysis further refined a subset of approximately 250 high-priority genes linked to apoptosis, neuronal development, axonal guidance, and synaptic integration. This work introduces a pipeline for identifying perturbation candidates that may enhance transplantation efficacy. Winnowing down to a tractable list of candidates may inform future preclinical transplantation studies with engineered cell lines designed to overcome key bottlenecks in CNS neuronal replacement therapies.

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ENHANCING CELL MANUFACTURING EFFICIENCY WITH NOVEL POLYMERS FP003B AND FP006

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Nowadays, cell therapy is becoming increasingly widespread, leading to the development of large cell manufacturing processes using multi-layer flasks or microcarriers. We have developed a useful polymer, FP003B, which maintains cells in suspension without shaking or agitation for suspension culture or non-cryopreserved cell transportation. Recently, we found that FP003B also helps prevent the formation of large cell aggregate in agitation culture. Human adipose-derived mesenchymal stromal cells (AD-MSCs) were cultured with microcarriers in 125 mL spinner flasks under agitation. After 4 days, the average aggregation size was smaller in the FP003B condition compared to the control, and the number of harvested cells increased by 1.34-fold. This indicates that FP003B suppressed cell aggregation and that led to easier dissociation from microcarriers and improving cell yield. Also, we are evaluating the effect of FP003B in agitation culture of human induced pluripotent stem cells (iPSCs). In addition, we have developed novel polymer, FP006,

which behaves as a plastic fluid below 25 degrees and as a liquid at 37 degrees to support 2D culture. The multi-layer flasks are difficult to control for uniform cell seeding on a large scale and if cells are seeded unevenly, it may result in low cell yield or reduced cell quality due to over-confluence in certain areas. We evaluated the effect of FP006 on cell seeding. AD-MSCs were seeded with or without FP006 into 5-layer flasks (875 cm2) and cultured for 5 days. The cell suspension contained a lot of cell aggregates that were not dispersed into single cells even strong pipetting in the control. In contrast, the FP006 condition showed fewer aggregates and a 1.16-fold increase in cell number. This result showed that there were a lot of over-confluent areas in control so that the number of obtained single cells decreased, and FP006 improved this situation by seeding uniformly. Similarly, we confirmed that iPSCs were also seeded more uniformly using FP006. In conclusion, our unique polymers, FP003B and FP006, enhance cell yield in both 2D and 3D culture systems and offer promising solutions for large-scale cell manufacturing.

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EXOSOME PRECONDITIONING ENHANCES STAT3-MEDIATED CARDIO-PROTECTION AND STEM CELL SURVIVAL AGAINST ISCHEMIA/REPERFUSION INJURY

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Myocardial ischemia causes lactic acidosis with a pH range of 6.0–6.5, and a significant number of stem cells (95%) die once transplanted, posing the biggest threat to therapy. Therefore, pharmacologically preconditioned MSC-derived exosomes were used to investigate the cardioprotective effect of exosomes on the Ischemic/reperfusion (I/R) injury model of H9C2 cardiomyocytes. The MSCs were isolated from Wharton's jelly of the Umbilical Cord and preconditioned with 100µM Tadalafil. Following Preconditioning, the exosomes were purified and identified by NTA and western blot assays, using CD63 and CD81 as markers. After characterization, I/R injured H9C2 (2h 0.5% hypoxia and 4h Reperfusion) cells were conditioned with 300µg/ml exosomes for 24h and 48h to evaluate cardioprotective efficacy. MTT, CCK8, and apoptosis necrosis (Y-Pro & PI) methods were used to detect H9C2 cell growth and survival. Confocal and Transmission electron microscopy (TEM) reveal sub-cellular details of restored mitochondrial potential (ΔΨm) with intact cristae, decreased ROS concentration, and enlarged mitochondria showing exosomes, enhanced cardioprotection ($P<0.05$). We found that prolonging the exposure duration promoted cell survival, compared to higher concentrations of exosomes.

Accordingly, immunoblot also revealed that STAT3 expression was highly increased after exosome conditioning of injured H9C2 at 48h. In conclusion, the present study demonstrated that tadalafil preconditioned MSC-derived exosomes enhanced the activation of the cardioprotective JAK-STAT3 pathway in I/R injured H9C2 in a time dependent manner. In the future, this study can be used as a non-invasive inhalable cardioprotective therapy.

Funding: Science and Engineering Research Board, Anusandhan National Research Foundation (SERB-ANRF).

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FRESH 3D PRINTED ECM-BASED SCAFFOLDS SUPPORT VIABILITY OF IPSC-DERIVED BETA CELL CLUSTERS

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Type 1 diabetes (T1D) affects ~2 million Americans, including children and adolescents and represents a collective national cost of $813 billion annually. Cell replacement therapies hold promise for treating T1D, but clinical translation has been hindered by limited donor islet availability and poor engraftment in extrahepatic sites such as the subcutaneous space. Using our FRESH 3D bioprinting platform, we previously demonstrated that cadaveric donor islet scaffolds printed from extracellular matrix (ECM) restore normoglycemia when transplanted subcutaneously into diabetic SCID mice, establishing proof-of-concept that scaffolds engineered from ECM instead of traditional foreign and synthetic polymers can aid in overcoming this site's notable challenges. However, primary islets remain constrained by donor variability and supply limitations for which there is currently no alternative. Induced pluripotent stem cell (iPSC)-derived beta cells represent a scalable and patient-specific source of insulin-producing beta cells, but challenges remain regarding their survival, maturation, and function to achieve successful clinical translation. To begin evaluating the use of iPSC-derived beta cells in our system as next-generation alternative to primary islets, we generated spheroids from commercially available iPSC-derived beta cells and printed them into extracellular matrix-based scaffolds using the same approach optimized for cadaveric islets. Compared to primary human islets

maintained in traditional 2D culture, iPSC-derived beta cell clusters cultured within 3D printed scaffolds exhibited significantly higher viability at 7 days (75% vs. 53%) and beyond. These findings demonstrate that iPSC-derived beta cell clusters benefit from the 3D ECM-based microenvironment provided by FRESH printed scaffolds, maintaining greater viability than primary islets under conventional conditions. While further optimization is needed to enhance functional maturation and confirm therapeutic efficacy, this work establishes a critical step toward integrating iPSC-derived beta cells within bioprinted scaffolds, advancing the development of scalable, clinically translatable cell-based therapies for diabetes.

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FROM BENCH TO BEDSIDE: IPSC-DERIVED NEPHRON/RENAL PROGENITORS FOR RENAL REGENERATION

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Chronic kidney disease (CKD) is a silent and progressive condition with high global prevalence. Irreversible CKD results in structural damage and functional decline of the kidney, ultimately requiring renal replacement therapy such as dialysis or transplantation. Despite advances in management, the development of effective therapeutic strategies for CKD remains challenging. Renal progenitor cell–based therapy has emerged as a promising approach to regenerate damaged renal tissue, restore function, and slow disease progression. We investigated the therapeutic potential of iPSC-derived renal progenitor cells (iPS-RPCs) in mice with acute kidney injury (AKI) and in AKI-to-CKD transition models. Our preliminary data showed that ischemia–reperfusion injury (IRI) induced mild increases in BUN and creatinine, which were not significantly reduced by RPC implantation. However, cystatin C levels were markedly decreased in iPS-RPC–treated mice. Histological analyses demonstrated preservation of proximal tubular brush borders following RPC injection, while untreated IRI mice exhibited indistinct structures. Human nuclear staining revealed that exogenous RPCs engrafted into renal tubules, particularly within the cortical region. Furthermore, Masson's trichrome staining indicated reduced collagen deposition in RPC-

treated kidneys, suggesting attenuation of fibrosis. These findings support the potential of iPS-RPCs to protect renal structure and function in the setting of AKI and CKD progression. Ongoing studies are focused on further characterizing their in vivo roles during the AKI-to-CKD transition. To facilitate future clinical translation, we are also integrating automated manufacturing processes for the scalable production of clinical-grade iPS-RPCs.

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FROM iPSCS TO PAIN RELIEF: PRECLINICAL DEVELOPMENT OF IPSC-DERIVED NOCICEPTOR FOR THE CELL THERAPY OF KNEE OSTEOARTHRITIS

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Osteoarthritis (OA), affecting over 250 million people worldwide, most commonly impacts the knee and causes chronic nociceptive and neuropathic pain that limits mobility and quality of life. Non-opioid analgesic development remains challenging due to sensory neuron heterogeneity and complex pain pathways. Human iPSCs enable scalable generation of physiologically relevant sensory neurons, and we developed an iPSC-derived nociceptor therapy (SN101) as an off-the-shelf, non-opioid intervention for chronic knee OA pain. Through optimized differentiation and purification, we generated homogeneous sensory neurons expressing TRPV1+, SCN9A+, and MRGPRX1+. Transcriptomic profiling confirmed alignment with human dorsal root ganglia signatures, establishing iPSC-nociceptors as physiologically relevant and scalable for translational use. Manufacturing emphasizes reproducibility, scalability, and cGLP standards. In vitro, iPSC-nociceptors responded to capsaicin, mustard oil, menthol, and OA patients' synovial fluid. In vivo, transplantation into murine anterior cruciate ligament transaction (ACLT) knee OA models demonstrated reduced pain behaviors, mechanical hypersensitivity (PWF, PAMWT), and injury/pain markers (ATF3, CGRP) by sequestering inflammatory mediators and intercepting nociceptive signals. These results demonstrate therapeutic potential and highlight broader applications for hiPSC-derived nociceptors as engineered, targeted cell therapies beyond classical regenerative approaches. In conclusion, iPSC-nociceptor represents a next-generation cell-based therapy that integrates advances in stem cell biology, cell therapy manufacturing, and functional validation. By combining scalable

production with demonstrated preclinical efficacy, iPSC-nociceptor treatment may establish a novel cell therapy approach for chronic osteoarthritis pain.

Funding: Maryland Stem Cell Research Fund (MSCRF) 2025-R2-MSCRFCO-00006.

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FULL-LENGTH LAMININS CRUCIAL FOR RECREATING THE CELLULAR NICHE IN VITRO

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Laminins, a family of 16 distinct ECM proteins, are crucial for tissue formation, maintenance, and homeostasis, with expression tightly regulated in space and time. As key components of basement membranes (BM), intact laminins are vital for healthy tissue function, while mutations in laminin genes result in diseases like Pierson syndrome and Epidermolysis bullosa, affecting organs such as muscles, nerves, and skin. Laminin proteins interact with integrin and non-integrin receptors, such as dystroglycan and syndecan, and bind essential growth factors (GF), modulating GF release. As large trimeric proteins, intact laminins provide structural integrity and bioactivity critical for BM functionality. In contrast, fragmented laminins lack these properties, are not naturally produced in healthy tissues, and fail to support tissue homeostasis. Studies show pluripotent stem cells (PSCs) with LAMA5-KO cannot survive without exogenous laminin 521, supporting the essential role of laminin 521 for PSC survival and expansion. Our study demonstrates the superiority of full-length recombinant laminin-521 in supporting human PSCs compared to fragmented laminins. Full-length laminin-521 significantly enhances PSC survival, proliferation, and migration, enabling single-cell seeding without the need for ROCK inhibitors. Importantly, PSCs cultured on intact laminin-521 exhibit enhanced migratory capacity, achieving complete wound closure in migration assays, whereas fragmented laminins support only 50% closure under the same conditions. These findings highlight the importance of full-length laminin-521 in recreating natural cellular microenvironments, which is crucial for advancing PSC culture techniques, improving differentiation protocols, and refining disease modeling and gene-editing strategies.

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IMPROVING PROCESS ROBUSTNESS FOR EFFICIENT HUMAN PLURIPOTENT STEM CELL-DERIVED CARDIOMYOCYTE PRODUCTION THROUGH INTEGRATIVE MULTI-OMIC ANALYSIS

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Human pluripotent stem cells (hPSCs) represent an unlimited source of human cell types for cell therapy, disease modeling, and drug testing. While protocols for deriving terminal cell types including cardiomyocytes have existed for over a decade, there are no currently approved cell therapies utilizing hPSC-derived terminal cell types. One of the substantial barriers to clinical translation and widespread use of hPSC-cardiomyocytes (hPSC-CMs) is the significant variability in differentiation success or the ability to reliably generate pure hPSC-CMs (cTnT+ cells) from cell line to cell line and from batch to batch. To more deeply understand early divergence from hPSC-CM fate commitment, we temporally profiled the transcriptome, proteome, intracellular metabolome, and extracellular metabolome of high and low efficiency hPSC-CM differentiations throughout the differentiation of hPSCs to CMs. Using this multi-omic approach, our objectives were to 1) provide biological insight into the early stages of hPSC-CM fate commitment, 2) identify progenitor markers capable of predicting terminal hPSC-CM purity, and 3) leverage multi-omic discoveries to enhance hPSC-CM differentiation process purities and robustness. Assessment of multi-omic features throughout early hPSC-CM progenitor trajectories in high and low efficiency hPSC-CM differentiations identified significant divergence as early as the Wnt inhibition stage of differentiation (+IWP2 differentiation step). While a majority of top pathways between high and low efficiency differentiations exhibited shared temporal dynamics, major pathways underlying fate divergence were driven by WNT, NOTCH, MAPK, calcium, and glucose metabolism. Notably, nonlinear models utilizing gene expression data of top differentially expressed genes were able to accurately predict hPSC-CM purity (percentage of cTnT+ cells) as early as the +IWP2 differentiation step. In several cases, these models performed better than models constructed with canonical hPSC-CM differentiation markers alone. Finally, multi-omic insights informed process perturbations, including prolonged WNT inhibition and the addition of MAPK inhibition, that produced higher CM purities and yields.

Funding: NHLBI: 5R01HL148059, 1R01HL178095-01, 1F30HL173988-01 NIH: T32 GM140935, T32 AG000213, T32 GM135066 NSF: CMaT EEC-1648035.

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GENERATION OF EFFECTOR CD4+ T CELLS FROM HUMAN IPSC

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T cells form a core element of immune response, possessing the capability to direct other cells and exert cytotoxic effector functions themselves. T cells are often taken from patients and genetically modified for autologous cell therapies, however, uniquely manufacturing cell therapies on an individual basis comes with large costs in time, money and consistency. By using an alternative cell source, such as induced pluripotent stem cells (iPSCs) many of these costs could be bypassed. Mimicking T cell developmental cues in vitro directs iPSCs to differentiate into T cell progenitors. Historically, iPSC derived T cell progenitors can be differentiated to one of two major T cell lineages, CD8+ cytotoxic T cells, but not the second major lineage of CD4+ helper T cells. Both CD4+ and CD8+ cells are important for optimal function of therapies based on T cells. The cues responsible for CD4+ T cell lineage commitment, particularly in iPSC derived T cells, remain poorly understood. We have been able to generate iPSC derived CD4 positive cells (iCD4+ cells) through the removal of Notch signaling during stimulation of the developing T cell receptor at the DP stage. Using a combination of transcriptomic and protein level analysis of iCD4 cells we show remarkable similarity to primary CD4+ T cells. We demonstrate conventional surface marker profiles, including CD3, CD4 and T cell receptor expression alongside transcription of key lineage transcription factors. Beyond identity by surface markers iCD4+ T cells produce characteristic CD4+ cytokines in response to stimulation as interrogated by a combination of multiplexed ELISA, scRNA-Seq and CyTOF at unprecedented resolution. Further, in response to T cell receptor stimulation we observe proliferation alongside upregulation of classical activation markers. We believe this robust yet simple platform represents a key step towards iPSC T cell therapies incorporating both helper and cytotoxic iT cells.

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GENERATION OF NORMALIZED LIMBAL EPITHELIAL PROGENITOR CELLS FROM DIABETIC LIMBAL-DERIVED INDUCED PLURIPOTENT STEM CELLS

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Diabetes mellitus is the most widespread blinding disease in working-age adults. It causes many corneal complications, including recurrent epithelial defects (keratopathy) and impaired wound healing due to limbal epithelial stem cell (LESC) deficiency (LSCD). LSCD may be treated with keratolimbal grafts and transplantation of cultured limbal epithelial cells. However, both modalities have limitations due to the need of a standardized bankable source of LESCs. A novel concept is the derivation of normalized differentiated corneal cells from diabetic induced pluripotent stem cell (iPSC)-derived limbal cells. This may become a therapeutic strategy for autologous transplantation in severe cases of diabetic keratopathy. Previously, we generated iPSCs from diabetic and non-diabetic LESC and hypothesized that the diabetic LESC reprogramming into iPSC would essentially remove epigenetic disease signatures of parental cells and yield more normal corneal epithelial progenitors. In the present work, we showed that the DNA methylation pattern of a set of genes in diabetic limbal-derived iPSCs was similar to the primary non-diabetic cells and distinct from the primary diabetic cells, indicating the normalization of diabetes-altered DNA methylation signatures. We differentiated diabetic iPSCs into LESC-like cells using two previously described protocols, eventually adopting one. Immunostaining at day 14 of differentiation showed that pluripotency marker Oct4 was abolished and epithelial cell marker ΔNp63 was expressed. From the day 21 of differentiation, the expression of putative LESC markers ΔNp63, keratins 15 and 17, and N-cadherin was observed at similar levels in both non-diabetic and diabetic iPSC-derived LESC-like cells. Experiments are underway to test the functionality of the diabetic iPSC-derived LESC-like cells using scratch wound healing assay. Altogether, these results support the potential generation of

normalized LESCs from impaired-diabetic LESCs by the process of iPSC redifferentiation. With further investigation, this novel approach may serve as a potential therapeutic transplantation modality for LSCD and diabetic keratopathy.

Funding: This work is supported by NIH grants R01 EY031377, EY013431 and funding from the Cedars Sinai Board of Governors Regenerative Medicine Institute.

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GMP SMALL MOLECULES: THE KEY “ACCELERATOR” FOR CELL THERAPY

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Cell and gene therapy (CGT) is emerging as the next therapeutic paradigm after small molecule and biologic drug. CGT has demonstrated remarkable success in treating chronic diseases, rare genetic disorders, and hematologic malignancies. However, widespread of application of CGT is still hindered by challenges in efficacy, safety, and scalable, cost-effective manufacturing. Good Manufacturing Practice (GMP) standards are essential for ensuring the safety and consistency of CGT products. MedChemExpress (MCE) addresses this need by offering a comprehensive portfolio of GMP-grade small molecules to support various aspects of stem cell therapy, including rapid cell reprograming, robust self-renewal, and controlled differentiation into specific cell types. Each batch of GMP products undergoes rigorous quality control, such as assessments of substance purity, water content, residual solvents, bioburden, endotoxin levels, elemental impurities levels, and solubility profiles. Using MCE’s GMP-grade CHIR99021 and Y-27632, researchers achieved a 3.2-fold increase in stem cell expansion and a 2.7-fold improvement in differentiation efficiency toward neural lineages, with minimal off-target effects and consistent batch-to-batch performance. MCE supports the entire CGT development process from Investigational New Drug (IND) enabling studies to New Drug Application (NDA) submission, as well as on-site audits by providing relevant research data and regulatory documentation. To date, we have produced more than 30 GMP small molecules for pluripotent stem cell (PSC) culture and served over 130 clients globally. Notably, the fastest progressing CGT project supported by MCE has entered Phase III clinical trials. Our kilogram-scale production facility has successfully passed EU Qualified Person (QP) and US FDA audits, ensuring reliable delivery of GMP-grade products on a large scale. Through its robust R&D and synthesis capabilities, MCE is accelerating the advancement of stem cell therapy by enabling safer, more efficient, and scalable solutions for clinical translation.

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HARNESSING ARTIFICIAL INTELLIGENCE TO HEAT-STABILIZE FGF4 FOR IPSC-DERIVED INTESTINAL ORGANOIDS

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Induced pluripotent stem cell (iPSC) differentiation into organoids typically requires the use of protein growth factors, many of which degrade under standard culture conditions. The FGF family is well-known for thermal instability, and in some cases rapidly loses signaling activity. This instability can result in necessity for high concentrations and daily replenishment, which reduces reproducibility and efficiency of deriving organoids. To address this challenge, we applied AI-guided protein engineering to develop a thermostable variant of FGF4 that retains signaling activity following prolonged heat exposure. We tested this heat-stable variant in the mid-hindgut patterning stage of intestinal differentiation, which normally requires high concentrations (500 ng/mL) of FGF4. Preliminary results indicate that the engineered FGF4 supports comparable growth and viability to wild-type FGF4 while requiring lower concentrations. By improving the stability and performance of a key signaling input, our engineered heat-stable FGF4 may enhance the scalability, consistency, and translational utility of intestinal organoid models.

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HIGH MULTIPLEX DIGITAL PCR FOR RESIDUAL IPSCS AND GENOMIC STABILITY TESTING

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Residual undifferentiated cells and genomic stability are two key quality and safety attributes of induced Pluripotent Stem Cell (iPSC) derived therapies that require sensitive and precise methods to deliver reproducible and accurate testing. The QIAcuity digital PCR (dPCR) system provides sensitive and precise nucleic acid analysis along with high multiplexing capability for quantification of up to 12 targets per reaction. Interrogating an increased number of targets enables more robust testing and increased information with

less sample material. In this work, dPCR testing was applied to highlight its capability for key quality and safety attributes of iPSC derived therapies. Detection and quantification of several commonly used RNA markers was performed on samples containing low levels of iPSCs spiked into a background of primary fibroblasts to demonstrate sensitive detection by multiplexed dPCR. In addition, assessment of genomic stability was demonstrated by a 12-plex dPCR reaction to test for an array of copy number variation mutations. High multiplex dPCR enables rapid genomic stability screening for in-process testing of cells in culture and can compliment traditional karyotypic analysis by targeting specific genomic regions for smaller alterations. The QIAcuity digital PCR system offers the benefit of sensitive and precise analysis along with the flexibility and efficiency of high multiplexed nucleic acid testing to provide solutions throughout the iPSC development workflow.

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HIGH-RESOLUTION HUMAN FETAL RETINA AND RETINAL ORGANOIDS SINGLE-CELL ATLAS TO GUIDE RETINAL CELL DIFFERENTIATION AND REPLACEMENT EFFORTS

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The complexity of the mammalian retina arises from the unique combination of extrinsic and intrinsic factors in its development. Several single-cell RNA seq datasets have been generated to study retina and retinal organoids. We propose to investigate human retinal development and the questions of cell fate specification, cell class and cell type heterogeneity, and regulation of cell trajectory by intrinsic and extrinsic factors. We start with the scRNA-seq data for human developing healthy retina and retinal organoids. We focus on the methods of data transformation (Harmony, scVI, ForceAtlas2) and cell-cell interactions analysis (CellChat, Scriabin), cell fate trajectory reconstruction and time transformation (scvelo, scFates, CytoTRACE2). We establish a human fetal retina (100k cells) and human retinal organoids atlas (0.5M cells) by integrating scRNA-seq datasets intoa high-resolution map of retinal development. We use pseudotime with the cell fate trajectory reconstruction, potency and trajectory density methods to deconvolute the transcriptional signal. We demonstrate the application of pseudotime approaches in reconstruction of retinal ganglion cells (RGC) development to unravel the heterogeneity behind cell maturation. We discover hundreds of de novo development-oriented targets from both cell-intrinsic and cell-extrinsic prospectives of retina and RGC maturation. We show how maturation states contribute to forming the environment sufficient for retina

development. Our findings confirm developing retina to be a closed and self-supporting system. We demonstrate the comparison of 12 organoids differentiation protocol with such metrics as cell commitment, similarity to native retina, development timepoint correlation, and transplantation probability prediction. We integrate and publish two new tools for the data analysis: a human fetal retina and human retinal organoids atlas. We show how switching from canonical timepoint to pseudotime in studying the cell fate changes the understanding of fate driving genes. Both the atlases can be used as a community tool for analyzing, reference mapping and annotation of the sequencing data. The resulting reference map, publicly available at CELLxGENE portal, serves as a template for cell differentiation, reprogramming, and transplantation.

Funding: NIH/NEI–5U24EY029893-05 (P.B.), NIH/NEI–P30EY003790 (Core Facility Grant), Bright Focus Foundation G2020231 (P.B.), Gilbert Family Foundation–GFF00 (P.B.), Department of Defense - VRP FTTSA (P.B).

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HUMAN AUTOLOGOUS ENGINEERED NEURAL TISSUE FOR SPINAL CORD INJURY TREATMENT

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Spinal Cord Injury (SCI) is a debilitating condition affecting hundreds of thousands of people globally each year, leading to major disabilities and imposing heavy economic and social burdens. Unfortunately, despite extensive research, a definitive cure has yet to emerge. Current advancements in tissue engineering technologies offer hope for SCI patients. However, these technologies often use synthetic materials or donor cells, imposing a significant risk for immune responses and transplant rejection. This underscores the urgent need for alternative treatments. Matricelf has developed an innovative platform for the formation of engineered neural tissue fully derived from the patient's own cells and tissue. In this process, induced pluripotent stem cells, generated from the patient's blood cells, are differentiated into neuronal lineage within an Extracellular Matrix scaffold made from the patient's omentum (abdominal fatty tissue). The result is a fully autologous 3D neural tissue tailored to each patient. Characterization of the engineered tissue reveals prominent transcript and protein expression of neuronal markers, including microtubule elements, neurofilaments, motor neuron-specific indicators, synaptic markers, and cholinergic neuron markers. Moreover, widespread electrical activity is detected within the tissue using a high-density microelectrode array. Spontaneous and synchronized firing patterns indicate the successful formation of neural

networks within the 3D architecture of the engineered tissue. Proof of concept in vivo studies conducted in a SCI contusion model showed that 80% of treated rats exhibited significant functional recovery, as evaluated by the BBB locomotor rating scale. Furthermore, 100% of treated nude rats in a 6-month preliminary safety study presented a safe profile with no evidence of teratomas. In light of these remarkable pre-clinical results, and due to the autologous approach, which reduces the risk of immune response, along with the expected beneficial potency attributed to the generation of a 3D functional tissue, Matricelf is preparing to initiate a safety and efficacy clinical study in traumatic complete SCI patients.

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PSC-DERIVED SPINAL ORGANOIDS AS A NEXT-GENERATION CELL THERAPY FOR SPINAL CORD INJURY: A SYSTEMATIC REVIEW OF PRECLINICAL EVIDENCE

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Spinal cord injury (SCI) leads to irreversible neural loss and chronic motor deficits, affecting over 15 million people globally. Emerging evidence suggests that cell replacement strategies, particularly those using PSC-derived neural progenitor cells and engineered spinal cord organoids, hold promise for replenishing lost cells thus promoting neural regeneration and restoring function. This systematic review evaluates the therapeutic efficacy and integration capacity of human spinal organoid transplantation in preclinical models of SCI. A comprehensive literature search was conducted across PubMed, Google Scholar, and MEDLINE in accordance with PRISMA guidelines using the keywords: spinal cord injury, pluripotent stem cell, organoids, transplantation, and animal model. Inclusion criteria comprised vertebrate models receiving transplants of human spinal cord organoids derived from NPCs or directly reprogrammed astrocytes with at least one primary outcome assessing motor function (BBB scores). Lack of functional end-points, in vitro-only experiments, and non-English publications were excluded. Of 196 screened records, 5 studies met all eligibility criteria. Risk of bias was assessed using the SYRCLE tool. All studies reported successful graft survival, neuronal differentiation, and integration into host spinal circuits. Raw BBB scores at 6–12 weeks post-transplantation ranged from 11.6 to 16.3 in treatment groups, versus 6.0 to 10.2 in controls. Immunohistochemistry revealed consistent expression of MAP2, TUJ1, and GFAP, while NeuN and synaptophysin were reported in four of five. While, 3 out of 5 studies reported recovery of motor evoked potentials (MEPs) with enhanced amplitude and reduced latency, suggesting partial

restoration of corticospinal conduction. No tumorigenesis or graft overgrowth was observed. Transplanted PSC-derived spinal organoids demonstrate consistent survival, neuronal differentiation, and integration into host circuits, yielding reproducible improvements in motor function and electrophysiological recovery in preclinical SCI models. These findings establish organoid-based transplantation as a credible pipeline cell replacement therapy, with translational relevance for circuit reconstruction and functional restoration in spinal cord injury.

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HUMAN PARP-REGULATED BLASTOMERE-LIKE STEM CELLS WITH IMPROVED HEMATOVASCULAR AND CHIMERA COMPETENCY

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PARP proteins play formative roles in preimplantation development by regulating the proteogenome of totipotent blastomere and pluripotent epiblast states. We have derived Tankyrase/PARP1 Inhibitor-Regulated Naïve Stem Cells (TIRN-SC) using a PARP-mediated reprogramming method that chemically reverts primed, conventional human iPSC to a functionally improved stem cell state with augmented differentiation potencies. TIRN reversion eliminated interline variability of multi-lineage differentiation, significantly enhanced functional in vivo performance of differentiated progenitors, and contributed efficiently to interspecific chimeras. TIRN-SC-derived vascular progenitors maintained greater genomic stability and were more efficient in migration, engraftment, and re-vascularization of the deep neural layers of the ischemic adult retina. TIRN-SC hematopoietic differentiation produced two-fold higher CD34+CD45+ hematopoietic progenitors and generated 5-to-50-fold greater numbers of induced granulocyte-macrophage progenitors (i-GMP). Single TIRN-SC injection into 8C-16C-staged murine embryos resulted in efficient integration of human cells to both extra-embryonic (trophectoderm, placenta) and embryonic (neural, hematopoietic) lineages of blastocyst and fetal chimeras, including human CD34+CD45+ hematopoietic progenitors in murine fetal livers. TIRN-SC chimerism efficiencies reached up to 20-50% using combinations of chemical complementation, immunosuppression, or ectopic expression of murine-E-

Cadherin; the latter strategy promoted enhanced targeting to neural and hematopoietic organs (e.g., AGM, fetal liver). TIRN-SC achieved human cell chimerism rates of 2-80% and 2-18% in whole murine E14.5 feti and fetal livers, respectively. TIRN-SC represent a new class of human stem cells with de-repressed epigenetic plasticity and 2C-8C blastomere-like functionality, including totipotent-like contribution of differentiated human cells to developing animal embryos. TIRN-SC and TIRN-SC-derived hematovascular progenitors with improved in vivo contribution will be valuable for future interspecific chimera and human xenotransplantation studies. TIRN-SC may serve as a gateway to deriving more clinically useful human stem cells for regenerative medicine.

Funding: This work was supported by the NIH (R01EY032113), Research to Prevent Blindness (Stein Innovation Award), The Maryland Stem Cell Research Fund (2024-MSCRFV-6248), and The Lisa Dean Moseley Foundation.

THURSDAY, 11 DECEMBER 2025

POSTER SESSION 2: 6:15 PM – 7:15 PM

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HUMAN T CELL-DERIVED INDUCED PLURIPOTENT STEM CELLS: A QUALITY ASSESSEMENT OF ALL COLONIES PICKED AND PRACTICAL CONSIDERATIONS FOR MANUFACTURING

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We present an example of a practical iPSC manufacturing process that generated a total of 20 iPSC colonies after reprogramming activated, human T cell-enriched healthy male donor PBMCs using commercially available GMP-compliant Sendai virus vectors. In this example, all colonies contained >85% OCT-4/TRA-1-60 (with less than 1% SSEA-1) expressing iPSCs. Eighteen iPSC colonies are derived from T cells as concluded from TCR gene arrangement analysis. Three colonies appear to be derived from T cells in which both alleles of the rearranged B chain gene are productively expressed. Detailed analysis of oncogenes indicates that the natural TCR gene arrangement process often results in loss of

the serine protease1 gene (PRSS1). G-banded karyotyping revealed the presence of an extra Y chromosome in 1 iPSC colony. We identified 6 different types of iPSC colonies: (1) T cell-derived iPSC clones with heterozygous loss of PRSS1, (2) T cell-derive iPSC clones with homozygous loss of PRSS1, (3) T cell-derived iPSC clones with extra Y chromosome, (4) T cell-derived iPSC colonies without allelic exclusion of TCR beta chain rearrangement, (5) Mixtures of 2 different T cell-derived iPSC clones, and (6) Non T cell-derived iPSC colonies. Ultimately, this process example generated 10 unique T cell-derived iPSC clones that passed all release criteria. In addition, we describe the implementation of practical approaches to improve management of personnel and expiration-prone materials involved in iPSC manufacturing processes in small to medium-sized GMP-compliant work environments.

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IDENTIFYING BIOMARKERS TO IMPROVE AN NK CELL MANUFACTURING PROCESS USING A MULTI-OMICS APPROACH

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While allogeneic cell therapy using induced Pluripotent Stem Cells (iPSCs) offer an exciting avenue to the scalable manufacture of immunotherapy products, significant increases in productivity and quality are hindered by inadequate process characterisation and control. Process analytics, such as large-scale omics analyses, are essential in enhancing process understanding and provide ample scope for improvement and development, in particular through identification of biomarkers linked to specific process outcomes. This identification process can be facilitated by the parallel collection of various omics data alongside conventional process data (e.g. protein and gene expression, measures of potency). However, analysis of each omics type is often performed in isolation, without integration of the datasets, limiting the potential for deeper process characterisation and understanding of the linkages between process steps, biological readouts and process outcome. Cell and Gene Therapy Catapult (CGT Catapult) performed iterative optimisation experiments on an iPSC-derived haematopoietic progenitor cell (HPC) and natural killer (NK) differentiation process and established epigenomic, transcriptomic, proteomic and metabolomic pipelines for biomarker discovery and selection. In this study, we tested and

implemented five multi-omics integration methods to identify biomarkers linked to improved productivity of the manufacturing process. We found that most integration methods could accurately model the target outcome of our process (percentage of NK cells as identified by protein expression), with some differences in model performance. Each integration method identified multiple candidate biomarkers from the different omics data, which we compared to assess how well each integration method performed for biomarker identification. We also assessed the suitability of each integration method to the dataset provided and developed a roadmap and best practice guidance to better plan future multi-omics and process optimisation projects and ensure to leverage the value of the multi-omics datasets. Overall, this study identified multiple candidate biomarkers for the improvement of the NK cell production process, as well as promising integration methods for use in future studies.

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GASTROINTESTINAL ORGANOID THERAPY; THE ROAD TO DELIVERY

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As many as 11 percent of Americans have gastrointestinal (GI) tract acute inflammatory conditions. A small yet significant percentage do not respond to existing therapies resulting in severe chronic conditions. GI organoid therapies are a disease agnostic approach that may provide clinically feasible solutions to regenerate all regions of the GI tract, dramatically improving quality of life and resolving morbidities. To realize the goal to use iPSC derived GI tissues to transform clinical care, we have initiated preclinical work that includes establishing methods to generate GMP GI organoids and a preclinical transplant model. A multidisciplinary team of clinical, basic science, translational and engineering academicians and industry experts has been selected to 1. define criteria for patient enrollment and optimal route of application; 2. develop cGMP scalable in vitro iPSC to GI organoids culture methods; 3. validate GMP GI organoids engraftment using a pre-clinical model; 4. implement automation to scale production; and 5. obtain an Investigational New Drug (IND) clearance. We have established a clinical advisory team to define criteria for patient enrollment and optimal route of application of cell therapy product, and to establish clinical protocols and objective measures of outcome. We have validated the use of cGMP iPSC lines by confirming the formation of GI organoids and appropriate tissue patterning upon transplantation into an animal model. We have introduced a comprehensive automation system to standardize organoid culture and reduce variability.

We are preparing to submit a regulatory application for first-in-human GI iPSC cell therapy in 2025. Combining in-house developed GI organoid technology with excellence in patient centered care provides a unique opportunity to accomplish this work. iPSC and organoid therapies will revolutionize 21st century medicine. With safety defining our mission, Cincinnati Children's is preparing to deliver GI organoid therapy to patients.

Funding: Farmer Family Foundation and Cincinnati Children's Research Foundation.

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IN VITRO AND IN VIVO EVALUATION OF NANOFIBER MEMBRANE IMPLANTS COMBINED WITH FUNCTIONAL IPSC-DERIVED CORNEAL ENDOTHELIAL CELLS FOR ENDOTHELIUM REPLACEMENT

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Functional corneal endothelial cells (CEC) maintain corneal transparency by regulating fluid balance. Currently, corneal transplantation using donor tissue is the only treatment for endothelial failure, but the limited availability of donor tissue presents a significant challenge. In response, tissue engineering strategies utilizing cell-based implants have emerged as promising alternatives to traditional corneal transplantation. In this study, we have developed a novel cell-seeded nanofiber membrane implant specifically designed for corneal endothelium replacement and comprehensively evaluated its performance through in vitro and in vivo experiments. To overcome the limited availability of clinically viable corneal endothelial substitutes, we independently developed a differentiation

protocol to generate corneal endothelial-like cells (CEC) from induced pluripotent stem cells (iPSCs). These iPSC-derived CECs were seeded onto a biocompatible membrane to fabricate a cell-seeded nanofiber membrane implant, which was then evaluated through comprehensive in vitro and in vivo experiments. In vitro characterization confirmed robust expression of ZO-1, CD166, and Na+, K+-ATPase, key markers of CEC, indicating successful differentiation and cellular functionality on the membrane. Furthermore, we confirmed high cell viability and a low level of proliferation on the membrane. For in vivo assessment, the membrane was transplanted into a rabbit corneal endothelial dysfunction model. Post-implantation, a significant improvement in corneal opacity and pachymetry were observed within one or two weeks, demonstrating the therapeutic potential of the implant in restoring corneal clarity and thickness. These findings suggest that our corneal endothelial implant, combined with an optimized iPSC differentiation protocol, offers a promising strategy for corneal endothelium regeneration and functional recovery. Furthermore, this work highlights a novel approach to overcoming donor limitations and advancing regenerative therapies in ophthalmology.

Funding: Grant by the Korean government: (1711174348, RS-2020-KD000148); (21C0723L1-21); (RS-2023-00214125); (RS-2023-00302193); (RS-2024-00438366); Asan Medical Center (2023IP0069-2, 2024IP0066-1).

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IND-ENABLING SAFETY AND EFFICACY OF RPESC-RPE-4W, AN ADULT RPE PROGENITOR CELL THERAPY FOR DRY AGE-RELATED MACULAR DEGENERATION

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Dry age-related macular degeneration (AMD) is a prevalent blinding disorder. It is characterized by loss of retinal pigment epithelium (RPE) cells, resulting in central vision impairment. Here, we describe preclinical studies supporting the allowance of an Investigational New Drug (IND) application of adult RPE stem cell-derived RPE (RPESC-RPE) for cell replacement therapy. We established donor-to-donor reproducibility and Good Manufacturing Practice (GMP) processes, and evaluated the GMP cell product in preclinical studies conducted in accordance with Good Laboratory Practice principles. Efficacy experiments in Royal College of Surgeons rats showed that subretinal implantation of the 4-week, postmitotic, progenitor-stage product (RPESC-RPE-4W) produced significant and durable vision rescue compared to vehicle control. Biodistribution and safety studies in immunocompromised Rowett Nude rats demonstrated a favorable safety profile, with long-term, localized engraftment and no serious adverse effects (SAEs) related to the cell product. These results enabled an Investigational New Drug allowance and an ongoing first-in-human Phase 1/2a clinical trial (NCT04627428), with initial outcomes from the low-dose Cohort 1 recently reported. These data also contributed to Regenerative Medicine Advanced Therapy (RMAT) designation from the FDA. Advancement of Chemistry, Manufacturing and Controls (CMC) to further improve RPESC-RPE-4W manufacturing has continued in parallel with clinical study. In addition, we are collaborating with the In-Depth Cell Characterization Hub and Biodata Catalyst under the Regenerative Medicine Innovation Project (RMIP) to perform deep molecular profiling of the cell product.

Funding: This work was supported by the Empire State Stem Cell Fund (NYSTEM) through NYSDOH contract C029158, NIH (R01EY032138, R01EY029281, RMIP awards U01EY030581 and UG3EY031810) and by Luxa Biotechnology.

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INTRAVENOUS CHICK EARLY AMNIOTIC FLUID AS A SAFE AND EFFECTIVE THERAPY FOR CARDIAC INSUFFICIENCY, A PRELIMINARY TRIAL REPORT

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We previously reported that intravenous injection of chick early amniotic fluid (ceAF), which is secreted by early embryonic cells, efficiently rescued damaged cardiac tissue, stimulated cardiac repair, and significantly improved heart function in adult mice and swine models of myocardial ischemic injury. We further demonstrated that no noticeable abnormalities were observed in the treated animals, and that no systemic inflammation or immune reactions occurred after 7 daily repeated IV injections of ceAF in rats and monkeys, even at a dosage 15 times higher than the desired therapeutic dose. To evaluate the safety and therapeutic value of ceAF (labeled as EE001) in humans, an clinical trial (NCT06884111) was conducted. Two healthy adults were administrated two 35 ml EE001 doses intravenously, with a 4-hour interval between doses. In addition, one healthy adult and 3 patients with cardiac insufficiency received 2-3 IV infusions of 35 ml EE001 per day for 7 consecutive days. The 3 patients with cardiac insufficiency were classified as follows: 1) NYHA II with a pacemaker and incomplete left bundle branch block; 2) NYHA III; and 3) NYHA IV with a pacemaker and complete left bundle branch block. No side effects or immune reactions were observed in any of the 6 volunteers, as assessed by routine blood counts, blood biochemistry, urine routines, coagulation functions, immune factors, and clinical examinations. All 3 patients showed noticeable improvements in left ventricular ejection fraction (LVEF) and arterial fibrillation after 7 days of treatment. Additional improvements were observed in parameters such as the the 6-minute walk test (6MWT), NT-proBNP levels, and other clinical indicators, as well as in self-reported symptoms. Interestingly, there was a consistent pattern of reduced inflammatory cytokines, e.g. CXCL4, CXCL9, CXCL10, CXCL11, CCL2, CCL5, CCL17, MMP1, MMP2, MMP7, MMP9, MMP12, IL-1α, IL-1β, IL-6, IL-12, IL-13, IL -17α, IL-18,IL -23, IL-27, CD31, CD62p; SYK, KMT5A, CNBP, IFN-γ, TNF-α, VEGF-A, and increased anti-inflammatory cytokines, e.g. IL-4,

IL-10, iNOS, NQO1, in 44 tested factors across all 6 volunteers. Given that EE001 is a natural reagent, no single dominant factor has been identified. We therefore believe that EE001 acts synergistically through multiple pathways/mechanisms, similar to the way ES cells work. Taken together, our data indicates that intravenous injection of EE001 could be a novel, highly beneficial, and safe non-invasive therapy for cardiac insufficiency and heart failure.

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INVESTIGATING MECHANISMS UNDERLYING THE HUNTINGTON'S DISEASE ONSET-DELAYING DNA LIGASE 1 K845N VARIANT

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Huntington's disease (HD) is an autosomal dominant fatal neurodegenerative disorder caused by a CAG repeat expansion in the Huntingtin (HTT) gene. It leads to a triad of motor, cognitive, and psychiatric symptoms. Even though currently there is no cure for HD, we have a much deeper understanding of disease biology which forms the forefront of current scientific research and clinical trials. This is the result of the identification, via genome-wide association studies (GWAS) of genetic modifiers that alter clinical phenotypes. A subset of these acts by modifying the somatic expansion in brain of the CAG repeat tract, while others act via other, as yet unknown, mechanisms. Importantly, modifier genes provide human-validated drug targets. A notable genetic modifier is DNA ligase 1 (LIG1; Chr 19). The GWAS identified two independent LIG1 modifier signals—19AM1 and 19AM3. The top variant for 19AM3, rs145821638 (K845N), is a rare allele (MAF 0.2% in Europeans) producing a 7–8 year delay in age of HD motor onset, making it one of the strongest modifiers discovered. The profound impact of this variant provides a strong rationale for understanding its underlying mechanism of disease modification due to the potential to translate this knowledge into a therapy that could substantially delay disease onset. Our

recently published preprint shows that 1)The K845N variant preserves LIG1 activity on canonical base-paired substrates but reduces activity on mismatched and oxidatively damaged DNA, thus increasing DNA ligation fidelity; 2)The K845N protects the genome against oxidative stress-induced damage in an overexpression system and in patient-derived lymphoblastoid cell lines; 3) The orthologous mutation (K843N) suppresses somatic CAG expansion in HD knock-in mice brain. Given our preliminary data, there is a strong rationale for further investigating the impact of K845N on both HTT CAG instability and on global DNA repair. As part of this effort we are using patient derived iPSC lines and differentiated neurons that harbor the LIG1 K845N variant. As these lines are rare and on a background of a low CAG length, we are also generating isogenic K845N knock-in iPSCs with long CAG repeats that will facilitate the analyses of CAG instability

Funding: Support for this study was provided by the National Institutes of Health (5 R01 NS127866-02) and by the CHDI Foundation.

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IPSC-DERIVED ARTIFICIAL PLATELET AS A NOVEL THERAPEUTIC APPROACH FOR OSTEOARTHRITIS

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Purpose Osteoarthritis (OA) is a degenerative joint disease characterized by cartilage degradation, driven by mechanical stress, aging, sex differences, and chronic inflammation. While various therapeutic strategies—such as stem cell therapies and platelet-rich plasma (PRP)—have been investigated, PRP's therapeutic efficacy is often limited by donor variability and inconsistent composition. To address these limitations, we developed a platform for generating artificial platelets (aPLTs) derived from human induced pluripotent stem cells (iPSCs). This study aims to evaluate the therapeutic potential of aPLTs in OA treatment. Human iPSCs were differentiated into megakaryocytes (MKs) through hematopoietic stem cell intermediates. MKs were characterized using electron microscopy, flow cytometry, and DNA ploidy analysis. The aPLTs were compared with

peripheral blood-derived platelets in terms of morphology, surface marker expression (CD41a, CD42b, CD61), membrane integrity, functionality (PMA-induced PAC-1 and CD62p expression), RNA profiles, and growth factor content (e.g., PDGF-AA, EGF, bFGF). To assess therapeutic efficacy, re-differentiated human chondrocytes cultured in alginate beads were treated with IL-1β to simulate OA-like conditions. aPLT treatment was evaluated for its effects on the mRNA and protein expression of anabolic markers (e.g., aggrecan, type II collagen, SOX9), catabolic enzymes (e.g., MMP1, MMP3, ADAMTS5), and inflammatory cytokines (e.g., IL-6, IL-8, IL-1β). In vivo efficacy was tested in anterior cruciate ligament transection (ACLT)– and ACLT + destabilization of the medial meniscus (DMM)–induced OA models via intra-articular injection, followed by behavioral tests and histological analysis over 8 weeks. aPLTs exhibited platelet-specific surface markers and functional responses to stimulation, closely resembling native platelets in phenotype and transcriptomic profile. They also contained a diverse array of regenerative growth factors. In IL-1β–stimulated chondrocytes, aPLT treatment significantly upregulated anabolic factors and downregulated catabolic enzymes and inflammatory cytokines. Protein expression analyses confirmed increased ACAN, SOX9, and TIMPs, and decreased MMP1, MMP3, and phosphorylated NF-κB. In vivo, aPLT administration alleviated joint pain, preserved cartilage structure, and enhanced proteoglycan synthesis in OA animal models. iPSC-derived aPLTs closely resemble blood-derived platelets in structure, function, and molecular composition. In both in vitro and in vivo OA models, aPLTs promoted anabolic cartilage gene expression and suppressed inflammatory and catabolic pathways, leading to functional and structural improvement. These findings support the potential of aPLTs as a standardized, cell-free, regenerative therapeutic candidate for osteoarthritis.

Funding: This research was supported by the Korean Fund for Regenerative Medicine (KFRM) grant funded by the Korea government (the Ministry of Science and ICT, the Ministry of Health & Welfare). (23C0104L1).

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KICKING IPSC THERAPIES INTO HIGH GEAR BY EMBEDDING AUTOMATION AND COLLABORATIONS FROM THE START

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Starting with the end in mind is critical for iPSC-derived therapies, where the lack of reproducible processes wastes resources, escalates costs, blocks clinical progress and, most tragically, prevents life-saving therapeutics from ever reaching patients. Automation offers a path to change this trajectory, if embedded early in development, rather than

treated as a bolt-on at the end. By standardizing workflows from the outset, automation reduces operator-dependent variability while generating structured process data essential for regulatory readiness and scale-up. Importantly, it can execute precision tasks, often beyond human capability. The novel automated cleanup of iPSC cultures, an important feature in this technology, provides a means to enrich high-quality starting material, ensuring that downstream outcomes are built on a stronger foundation in a way not achievable by manual handling. In a comparative study, we provide the first demonstration that automated cleanup of low-quality iPSC cultures can rescue differentiation potential: cleaned cultures produced robust, contractile, cTnT-positive cardiomyocytes, while low-quality cultures failed to yield functional outcomes. Flow cytometry and omics assays confirmed that cleaned populations upregulated key cardiac gene programs aligned with functional maturity, highlighting automation's ability to de-risk development through increased culture quality and early predictive markers. While automation provides the essential foundation, it can only go so far on its own. True transformation in advanced therapeutics requires coupling autonomous operation with rigorously defined, best-in-class reagents and ecosystem collaboration. Our partnership with BioLamina exemplifies how integrating full-length human laminins within automated workflows yields reproducible iPSC cultures, validated by viability, automated confluency algorithms, and doubling time calculations. More broadly, this model of ecosystem-driven innovation defines a blueprint for reproducible, regulator-ready iPSC manufacturing. Together, these advances accelerate the creation of industrialized, patient-ready pipelines, moving regenerative therapies closer to widespread clinical reality.

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LABEL-FREE FUNCTIONAL CHARACTERIZATION OF IPSC-DERIVED NEURONS AT SUBCELLULAR RESOLUTION

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Induced pluripotent stem cell (iPSC)-derived brain models have become a fundamental tool for studying common neurological disorders, such as epilepsy, Alzheimer's disease, and Parkinson's disease. Being able to measure the electrical activity from these in vitro models in real time and label-free offers critical insights into the complexity of neuronal networks. Nowadays, the integration of single cell resolution with high-throughput physiological assays is especially valuable, as it can deepen our understanding of subtype-specific neuronal activity, yet it remains challenging to achieve. In the present study, high-density microelectrode array (HD-MEA) platforms (MaxWell Biosystems, Switzerland), were used to perform in vitro extracellular recordings of action potentials across entire neuronal networks, single neurons and even subcellular compartments. Additionally, we showed the advantages of having HD-MEA systems featuring 26,400 electrodes per well, since they play a crucial role in enhancing the statistical power gathered from iPSC-derived neurons over multiple days/weeks and in capturing even the smallest neuronal signals. Finally, we present the Axon Tracking Assay, a tool for automated recording and analysis of individual axonal arbors of many neurons in parallel. The Axon Tracking Assay enabled the obtention of metrics such as potential conduction velocity, axonal length, and number of axonal branches. Therefore, with this unique method we characterized the function and axonal structure of different iPSC-derived neuronal cell lines. Our HD-MEA platforms and the extracted metrics, such as firing rate, spike amplitude, and network burst profile among several others, provide an extremely powerful and user-friendly approach for in vitro drug screening and disease modelling.

Funding: This work is funded by the HyVIS project, GA 964468, within the H2020 Framework Program of the European Commission.

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LANDMARK TRANSCRIPTION FACTOR DIRECTED MULTIPLE CELL PREPARATION FOR TRANSPLANTABLE LIVER ORGAN PRODUCTION

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Each year in the U.S., over 45,000 organ transplants are performed, yet more than 120,000 patients remain on waiting lists, and roughly 1 in 10 dies before an organ becomes available. The regenerative medicine field is currently at the stage of single cell type-based therapy development. Organoids, on the other hand, are formed mostly by self-assembly of

progenitor cells directed by paracrine signaling from co-differentiating cells within the same spheroid into organ-specific 3D structures of limited complexity. They largely lack spatial and temporal cues to form truly organ-mimicking structures that carry in vivo comparable functions, therefore not suitable for organ replacement. Our technology—using a bioprinted, multi-cell organ part graft—is a disruptive innovation because it aims to fundamentally replace lost organs and restore critical biological functions at the whole organ level, e.g. structural, enzymatic, systemic circulation, and metabolic homeostasis. This approach focuses on regenerative organs to restore the quality of life rather than merely managing the long-term consequences of irreparable damage by most other treatment regimens. A critical technical requirement for this approach is that high-quality iPSCs be consistently created that expand well to the orders of billions without losing pluripotency or differentiation potential in any lineages. Our industry-tested mRNA reprogramming has already met that requirement, even for autologous use to avoid immune suppression. We extended the application of mRNA by designing its structural elements to suit different cell types for mRNA-mediated landmark transcription factor (mLTF) expression, which specifically and potently directs iPSC differentiation towards hepatocytes, liver sinusoidal endothelial cells, hepatic stellate cells, Kupffer cells, cholangiocytes, and endothelial cells, all pre-fabricated and proportionally mixed with bioink and ECM for bioprinting a functional human liver organ, albeit at the initial phase just a right liver lobe, ready for transplantation through surgery. We will present our data of both cell differentiation, functional analysis, and phase I bioprinting as an ongoing ARPA-H project.

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LARGE-SCALE PRODUCTION AND RELEASE OF AN OFF-THE-SHELF ALLOGENEIC HIPSC-DERIVED THERAPY FOR INFERTILITY

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In vitro maturation (IVM) is a fertility treatment that enables oocyte maturation outside of the body, greatly reducing the need for the high hormone doses typically required to retrieve fertilization-ready oocytes. We have recently demonstrated that supplementation of IVM media with hiPSC-derived ovarian support cells (OSCs) significantly improves

oocyte maturation and euploid embryo formation by replicating the complex ovarian environment in vitro. To develop a off-the-shelf therapy capable of meeting the growing demand for assisted reproductive technologies, currently increasing 5-10% worldwide annually, manufacturing capacity must scale up to accommodate that need. In preparation for clinical and commercial manufacturing of this off-the-shelf ex vivo cell therapy, we scaled up OSC production to achieve up to 10,000 vials per lot. This scaling effort involved addressing key challenges, including high-throughput fill-and-finish processes, formulation optimization, and comprehensive lot release strategies to maintain cell therapy standards and ensure product quality across the entire lot. These strategies were designed to maintain the integrity of critical quality attributes such as identity, conformance, potency, and safety. We have demonstrated that our process can accommodate batch sizes from 1,000 to 10,000 doses, ensuring consistent quality across the lots. Our findings support the adoption of similar strategies for high-throughput manufacturing of hiPSC-derived products. Furthermore, this work represents the first description of a large scale hiPSC-derived therapy aimed at enhancing IVF outcomes and advancing women's health, paving the way for broader clinical applications.

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LINEAGE BIAS IN ALLOGENEIC STEM CELL-DERIVED THERAPIES: MECHANISMS AND IMPLICATIONS FOR SCALABLE MANUFACTURING

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Pluripotent stem cell (PSC)-derived therapies hold significant promise for treating a range of diseases, yet challenges remain in ensuring consistent, efficient manufacturing of high-quality, lineage-specific cell products. One key barrier is lineage bias—the preferential differentiation of certain PSC lines toward specific germ layers—posing risks to both yield and therapeutic efficacy. Lineage bias is theorised to be influenced by intrinsic factors,

including differences in gene expression and epigenetic modifications, as well as extrinsic cues from the cellular microenvironment. These external factors may involve culture conditions, cell-secreted factors, genetic variations and, in the case of induced pluripotent stem cells (iPSCs)— the tissue of origin from which the cells were derived. During in vitro differentiation processes, this can result in distinct subpopulations predisposed toward specific germinal lineages, limiting the efficiency of manufacturing the final cell product, or even preventing the final cell phenotype from being attained. This poses a critical challenge for manufacturing of cell therapies, where precise control over the trajectory of cell differentiation is essential to produce a safe, efficacious product in clinically relevant quantities. This study explores the molecular and metabolic drivers of lineage bias in allogeneic PSC-derived products. Multiple human PSC lines were differentiated into derivatives of the three germ layers (ectoderm, mesoderm, and endoderm) under controlled conditions. Different methodologies were used to explore novel phenotypic signatures associated with differentiation potential, from a range of multiomic and traditional analytical datasets. Our findings reveal inter-line variability at the pluripotent stage and distinct temporal dynamics during lineage commitment. While the origin of these differences remains to be fully elucidated—whether biological or process-driven—their impact on differentiation is clear. Understanding these early-stage determinants of lineage bias is critical for guiding differentiation protocol design, improving manufacturing robustness, and ultimately ensuring scalable production of safe, efficacious cell therapies. These insights support a product-focused development approach, aligning with efforts to bring iPSC/ESC-derived therapies from lab to clinic more efficiently and predictably.

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ENDOCANNABINOID SYSTEM OF HUMAN IPSC-DERIVED PRIMORDIAL GERM CELLS AS A POTENTIAL REGULATOR OF GERM CELL COMMITMENT

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Male infertility accounts for about half of all infertility cases, with germ cell aplasia causing azoospermia in 15% of these men. Deriving male germ cells from human induced pluripotent stem cells (hiPSCs) offers a potential autologous germ cell reservoir for patients lacking sufficient sperm. Components of the endocannabinoid system (ECS) are expressed in hiPSCs, human spermatogonial stem cells (hSSCs), and the testes, where activation of CB2R enhances proliferation and differentiation towards male germ cells. However, the role of ECS in human primordial germ cells (hPGCs), the natural precursors of hSSCs, remains unexplored. We hypothesize that ECS is present in hPGCs, where it may serve as a novel regulatory pathway influencing male germ cell fate determination. To test this hypothesis, we differentiated hiPSCs into hPGCs and characterized these hiPSC-derived PGCs using immunofluorescence labelling, flow cytometry, and qPCR; additionally, we analyzed ECS receptors and ligands in hPGCs via qPCR, flow cytometry, and LC/MS. hPGCs express SOX 17 and VASA at 1500- and 4000-fold higher levels relative to hiPSCs ($p<0.0001$ for all). The proportions of BLIMP1+ and VASA+ hPGCs are 67.09-68.78% and 85.87- 86.41%, respectively, compared to 7.24- 7.56% and 21.58- 21.98% in hiPSCs ($p<0.0001$ for all). The hPGCs exhibit homogeneous cytoplasmic labelling for BLIMP1 and VASA. They secrete AEA and 2-AG ligands into the supernatant at pM- nM levels more than hiPSCs ($p<0.0001$ for all), with 2-AG secretion being higher than AEA secretion ($p<0.0001$). hPGCs express CB1R at 0.5-fold and CB2R at 0.1-fold relative to hiPSCs. The proportion of CB1R+ hPGCs ranges from 71.01% to 98.85%, while CB2R+ hPGCs range from 73.25% to 93.81%. AEA and 2-AG at 0.01 µM stimulate the proliferation of hiPSC-derived PGCs. Similarly, doses of AEA and 2-AG between 0.01 and 10 µM enhance the differentiation of hiPSCs into PGCs. This study demonstrates, for the first time, the presence of CB1R and CB2R in hiPSC-derived PGCs, where their activation promotes both proliferation and differentiation. Determining the effective dose ranges of AEA and 2-AG for CB1R and CB2R agonism in vitro will facilitate the validation of these findings in vivo. Ultimately, this approach holds potential for translation into clinical settings as a receptor-targeted, personalized, and autologous hiPSC-based cellular therapy strategy for male infertility.

Funding: The Scientific and Technological Research Council (TÜBİTAK) of Turkey (#120S254, #223S711) funded this study.

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MODELING HEMATOPOIETIC DEFECTS IN SCHWACHMAN-DIAMOND SYNDROME USING PATIENT-DERIVED IPSCS

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Shwachman-Diamond Syndrome (SDS) is an inherited bone marrow failure disorder primarily caused by mutations in the SBDS gene, including the common 258+2T>C splice site mutation, which accounts for approximately 90% of cases. To model SDS and explore therapeutic correction strategies, we have generated and fully characterized over 30 integration-free iPSC lines from one healthy donor and two SDS patients carrying compound heterozygous SBDS mutations (c.258+2T>C and a second pathogenic variant). These iPSCs were generated using a non-integrating, RNA-based reprogramming method, enhancing their translational potential. These patient-derived iPSCs reliably recapitulate SDS-associated hematopoietic phenotype. Hematopoietic differentiation of CD34+ cells derived from SDS iPSCs revealed a significant defect in both erythroid and myeloid lineage output, combined with approximately 70% reduction in colony-forming capacity compared to healthy control. Importantly, these findings reflect the anemia and neutropenia observed in SDS patients. For gene correction, we first demonstrated that SDS iPSCs are amenable to editing via electroporation of cytosine base editor (CBE) mRNA. We then optimized lipid nanoparticle (LNP)-mediated delivery of mCherry mRNA into iPSC-derived $CD34^+$ cells, confirming high transfection efficiency. Our ongoing studies include the use of LNPs to deliver CBE6b-SpRY mRNA to correct the c.258+2T>C mutation in both iPSC-derived and patient-derived $CD34^+$ hematopoietic progenitors. This platform combines disease modeling with precise RNA-based base editing in patient-derived cells, offering a promising approach for developing gene-edited cell therapies for SDS and other inherited hematologic disorders.

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MULTI-CAMERA SCANNER FOR RAPID LONGITUDINAL AND FLUORESCENCE IMAGING OF 3D CORTICAL ORGANOIDS

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Cortical organoids reproduce key cyto-architectural and functional aspects of human cortical development in vitro and reliably capture size phenotypes driven by genetic variation or environmental factors. Imaging is central to both QC and phenotyping across differentiation—from brightfield checks of viability and neuroepithelial budding to fluorescence measurements of cell-type markers and clonal dynamics. Yet traditional single-objective microscopes, and even high-content plate imagers, are throughput-limited: large organoids require stitched mosaics, and fully scanning a 96-well plate typically takes ~20 minutes, prolonging time outside optimal culture conditions. We present a multi-camera array scanner (MCAS) engineered for fast, high-resolution imaging of thick organoids over wide fields. The instrument combines 48 image sensors, each paired with a custom lens achieving ~1.2 µm full-pitch resolution—on par with a standard 10X objective—in an inverted format compatible with standard culture plates. Parallel capture across sensors, together with an automated stage for lateral tiling of large organoids and z-stacking for volume acquisition, enables complete 96-well plate imaging in under 15 seconds. To convert raw data into biological metrics, we built a machine-learning segmentation pipeline that automatically quantifies organoid cross-sectional area, growth trajectories, and responses to drugs and morphogens. We showcase MCAS across core organoid workflows. Longitudinal brightfield imaging resolves condition-dependent differences in survival and growth, guiding optimization of seeding density and media. High-throughput assays measure how compounds and morphogens influence cortical organoid expansion. Flexible plate compatibility (e.g., 96- and 24-well) supports uninterrupted imaging throughout differentiation. In addition, fluorescence modes quantify the fraction and spatial organization of labeled cell populations within organoids and support measurements in 2D neuronal cultures. In sum, MCAS pairs massively parallel acquisition with automated analysis to deliver order-of-magnitude speed gains without

compromising resolution. The platform enables scalable, low-perturbation phenotyping of cortical organoids for teratogen screening and protocol refinement, accelerating studies that require large cohorts and volumetric readouts.

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NEXT-GENERATION MANUFACTURING FOR ALLOGENEIC CELL THERAPIES: THE ECHO™-NK IPSC PLATFORM ADVANTAGE

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The advancement of allogeneic cell therapies hinges on the ability to develop high-quality scalable manufacturing processes. The Echo™-NK platform from Cellistic offers the next-generation solution for the production of iPSC-derived Natural Killer (NK) cells, designed to meet the demands of therapeutic developers for manufacturing their Cell Therapy Product. Echo™-NK is a feeder-free, bioreactor-based process built on well-defined unit operations and GMP-grade materials. The platform achieves high cell yields—exceeding one billion NK cells per liter—and maintains robust in-process controls to ensure product quality and reproducibility. The process has been successfully established and transferred to GMP manufacturing at a 10-liter scale and is engineered for seamless scalability up to 100 liters, supporting both early-phases and pivotal clinical trials. By integrating automation, closed-system processing, and standardized quality control, Echo™-NK enables efficient, scalable, and regulatory-ready manufacturing of allogeneic NK cell therapies. This platform represents a significant step forward in overcoming the logistical and technical barriers to delivering off-the-shelf, allogeneic cell therapies to patients worldwide.

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NEXT-GENERATION PIPELINE THERAPIES FOR HEMOGLOBINOPATHIES: GLOBIN RESTORATION AND PHENOTYPE RESCUE IN PSC-DERIVED ERYTHROID CELLS

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Sickle cell disease (SCD) and β-thalassemia are among the most common inherited hemoglobinopathies and remain major causes of morbidity worldwide. Although autologous gene-modified hematopoietic stem cell (HSC) therapies can be curative, their broader use is limited by donor requirements, conditioning toxicity, and high cost.

Pluripotent stem cells (PSCs) represent a renewable and genetically modifiable source of erythroid cells with potential to deliver donor-independent and scalable treatments. A key translational question is whether PSC-derived erythroid cells can restore globin expression and demonstrate functional phenotype rescue, both essential for therapeutic application. A PRISMA-guided systematic review of PubMed, Medline, and Google Scholar was performed using the terms pluripotent stem cells, erythroid, hemoglobinopathies, and globin. Eligible studies included human iPSC-derived erythroid work reporting quantitative endpoints of globin expression (HbA/HbF/HbS %, β-globin protein) or phenotype rescue (sickling, deformability, CFU-E formation). HSPC-only work, non-erythroid differentiation, and ≥ 5 years studies were excluded. Risk of bias was assessed using the OHAT tool. Of 121 records screened, 4 studies met inclusion. Three demonstrated globin restoration: corrected SCD iPSCs produced only normal β-globin after biallelic repair, while β-thalassemia iPSCs achieved up to 90% monoallelic and 14% biallelic correction with restored β-globin expression and persistence of human erythroid cells in murine marrow for over 10 weeks without tumorigenicity. Phenotype rescue was shown in three studies: SCD iPSCs exhibited reduced hypoxia-induced sickling, thalassemia iPSCs formed more CFU-E colonies, and generated hemoglobin tetramers with oxygen-binding curves overlapping healthy controls, indicating improved deformability. No adverse events were reported. Future progress requires more efficient biallelic editing, optimized adult-type erythropoiesis, long-term in-vivo validation, application of transfusion models to corrected lines, and scalable manufacturing to enable reliable, donor-independent therapies. These findings establish proof-of-concept that PSC-derived erythroid cells can repair molecular and functional defects in hemoglobinopathies.

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NPC-EXOSOMES AS A NOVEL MODALITY TO MITIGATE ALZHEIMER'S DISEASE PROGRESSION

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Alzheimer's disease (AD) is a complex neurodegenerative disorder involving multiple pathological processes. In addition to genetic factors, AD may be driven by protein

aggregation, metabolic dysfunction, and drug-induced complications. Current pharmacological treatments generally target specific symptoms or proteins at certain disease stages, but often require ongoing dose adjustments that can result in severe side effects. Exosomes secreted by neural stem cells have recently been shown to promote neuronal regeneration and enhance neural activity in animal models, yet their therapeutic potential in AD remains insufficiently explored. Here, we investigated the effects of exosomes derived from iPSC differentiated neural progenitor cells (NPCs) in J20 transgenic mice. Behavioral assessments, including Open Field, Novel Object Recognition (NOR), and Morris Water Maze (MWM), were conducted. NPC exosome treatment enhanced exploratory behavior in NOR and significantly improved spatial learning and memory, as demonstrated by reduced latency to locate the hidden platform in MWM. Increased PSD95 expression was also observed, suggesting enhanced synaptic activity. These findings indicate that NPC-derived exosomes may modulate synaptic proteins to promote neuronal signaling. This effect was further examined in vitro using iPSC-derived neurons carrying APP mutations, supporting their disease-relevant activity. Ongoing studies aim to further elucidate the mechanisms through which NPC exosomes enhance neuronal regeneration and exert anti-inflammatory effects. In addition, the integration of automated cellular manufacturing will be presented to support scalable production of clinical-grade cells and exosomes.

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OPTIMIZED DELIVERY STRATEGY FOR CLINICAL APPLICATION OF NEURAL MICROTISSUES IN PARKINSON'S DISEASE

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With the rapid expansion of the field of 3D cultures and organoids, interest in their therapeutic use is growing. However, these innovative formats pose unique challenges for clinical translation as their physical and biological properties substantially differ from those of conventional single-cell-based products. Their handling imposes new constraints, such as much faster sedimentation, which must be addressed from the fill-and-finish stage to the final delivery procedure in the target region to ensure accurate dosing and precise cell placement. In this study, we present the development of a delivery strategy for 3D neural microtissues as a cell therapy for Parkinson's disease. This includes the development of a custom-made delivery solution. Various delivery methods were compared using in vitro tests. The final selected strategy was validated through in-use testing and led to successful engraftment in a non-human primate, with the presence of dopaminergic (DA) neurons observed 1 month after transplantation. The development approach described here holds potential for broader applications in other diseases and supports using next-generation cell therapies employing 3D formats.

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OPTIMIZING IPSC EXPANSION AND DIFFERENTIATION IN STIRRED SUSPENSION BIOREACTORS: ADVANCEMENTS IN PROCESS SCALE-UP AND GMP READINESS

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This presentation will summarize recent advancements in the expansion and differentiation of iPSCs in stirred suspension bioreactor systems, with a focus on optimizing operational parameters to enhance viable cell density and cellular drug product quality. Experimental data demonstrate that optimized media exchange strategies and cell retention technologies improve iPSC aggregate size, circularity, and viability, as well as cell expansion rates, in studies scalable from Ambr15 DOEs to 10L Univessel platform. Scale-

up to perfusion-based iPSC aggregate expansion workflows, coupled with in-line analytics enabled real-time process adjustments, achieving consistent cell yield. The value of in silico computational fluid dynamics simulations to support process scale up decisions will be discussed. Development of key in process analytic tools and release assays for iPSC pluripotency will also be presented. Takeaways will highlight the cross-functional needs necessary for successful scale-up, process intensification, and GMP-readiness of iPSC manufacturing processes.

Funding: This work was funded by Sartorius Corporate Research.

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PARACRINE EFFECT OF IPSC-DERIVED PROGENITOR SMOOTH MUSCLE CELLS ON THE VAGINA

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Pelvic organ prolapse (POP) is common in adult women and it is defined as the downward shift of the pelvic contents, such as the bladder, uterus, vagina, or rectum, beyond the vaginal opening. Although not a life-threatening condition, POP has a severe impact on the quality of life of women. Major risk factors for POP include vaginal delivery, aging, history of pelvic surgery, and obesity. Surgery is the most common treatment but it is suboptimal because of its high recurrence rates. At least 11% of women in the US will undergo surgery to repair POP in their life span, and about 30% of them will need additional surgeries due to recurrence. Therefore, there is a need for non-surgical therapies to restore supportive tissues in the female pelvis of older women. We hypothesized that patient iPSC-derived progenitor smooth muscle cells may exert a paracrine effect through their secretomes on the recipient tissues after transplantation. We reprogrammed patient dermal fibroblasts into induced pluripotent stem cells (iPSCs) and then differentiated these into progenitors smooth muscle cells (pSMCs). We collected the conditioned media (CM) containing pSMC secretomes from the in vitro expansion of the pSMCS to examine the paracrine effect on the surgically injured vagina. Proteomic analysis of the pSMC-CM revealed proteins involved in extracellular matrix (ECM) remodeling. We tested the effects of pSMC-CM in vitro using vaginal fibroblasts from POP patients and in vivo using a rat model of vaginal injury by POP surgery. pSMC-CM treatment improved vaginal contractile function in vivo and ECM protein expression, such as elastin, in the surgically injured vagina. These findings suggest that pSMC-CM may be a possible acellular, non-surgical therapy for prevention of POP recurrence after surgical intervention.

Funding: 1. National Institutes of Health (1 R21 HD102224; PI- B. Chen) 2. California Institute for Regenerative Medicine (TRAN1-10958 and DISC2-13205, PI-B. Chen).

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PERFUSION-FED PLURIPOTENT STEM CELL CULTURE IN MULTI-LITER BIOREACTORS

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The development of pluripotent stem cell (PSC) culture protocols in multi-liter bioreactors is essential to efficiently scale-up PSC yields to manufacturing scales. We have previously shown how PSCs can be expanded as spheroids in 3L stir-tank bioreactors (SBRs). These bioreactors use impellers that continuously mix the culture medium but also generate shear stress that may negatively affect PSC growth. Additionally, protocols that rely on gravity sedimentation of PSC spheroids and manual aspiration of spent medium appear impractical beyond ~3L culture scale. SBRs can be combined with perfusion apparatuses to constantly supply fresh medium and mitigate the need to manually exchange spent culture medium. Here, we describe our ongoing efforts to optimize PSC spheroid growth in perfusion-fed multi-liter bioreactor cultures by balancing stir speeds, shear stress, and medium exchange rates. First, we seeded PSCs into dual pitch blade horizontal impeller-based SBRs at low stir speeds (i.e. low RPM) to promote spheroid formation. The RPM was then gradually increased to prevent spheroid aggregation and maintain culture homogeneity. Unsurprisingly, shear stress was detrimental to spheroid growth at high speeds, though this could be minimized with the addition of Pluronic. Our results indicated that the addition of 0.1 – 0.2% Pluronic enabled spheroids to grow larger and more uniform in size, resulting in greater cell yields. We further evaluated spheroid growth using tangential flow depth filtration (TFDF) and alternating tangential flow (ATF) perfusion systems to perform medium exchanges. We determined that both systems were able to support spheroid expansion with similar efficiencies. In these optimized parameters we observed yields of up to 25 billion PSCs in 2L cultures (~12x106 cells/mL; ~80-fold expansion) after 10 days in culture that maintained high levels of pluripotency marker expression (>95% OCT4+/NANOG+ cells). Overall, these results demonstrate that PSC culture in perfused SBRs is a promising means towards achieving manufacturing scale needs.

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PFAS TREATMENT LEADS TO ACTIVATION OF IPSC-DERIVED HEPATIC STELLATE CELLS AND IMPLIES FIBROSIS DEVELOPMENT IN METABOLIC-ASSOCIATED STEATOHEPATITIS

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Metabolic-dysfunction Associated Steatotic liver disease (MASLD) starts with steatosis but can be further advanced to steatohepatitis (MASH) characterized by lobular inflammation, hepatocyte ballooning, and fibrosis. The environmental risk factors underlying the development of MASLD and MASH remain incompletely understood. Per- and polyfluoroalkyl substances (PFAS), a wide group of synthetic chemicals broadly utilized and integrated in industrial and consumer products, can accumulate in the human body, which has been associated with increased risk for MASLD and MASH. While it is known that PFAS could interfere the lipid metabolism in hepatocytes, it remains elusive whether PFAS could independently induce the activation of hepatic stellate cells (HSCs), the critical cells for secreting fibrogenic factors, playing key role in the fibrosis development in MASH. To investigate this role, the levels of PFAS and HSC activation/fibrosis-related proteins were measured and quantified in 10 human liver samples. Linear regression analysis showed that higher PFAS levels were associated with HSC activation and fibrosis. Additionally, wild-type and LDLR knockout mice were fed PFAS, and results showed that mouse HSCs were activated, and fibrosis was induced in vivo. To further examine the specific role and mechanism of PFAS-induced HSC activation, we used a well-established induced pluripotent stem cell (iPSC)-derived HSC model (iPSC-HSCs), which exhibit a highly quiescent state and strong sensitivity to stimulation. Using this model, we examined the impact of common PFAS species on cellular responses. When treated with varying concentrations of PFAS (including PFNA, PFOA, and PFOS) in vitro for 24 hours, the exposed iPSC-HSCs demonstrated a dose-dependent increase in the expression of fibrogenic proteins such as α-SMA, TIMP1, and collagen I. A dose-dependent response was also observed in cellular toxicity, migration and wound healing capacity, and cytokine release, but not in cell proliferation. Furthermore, RNA sequencing data indicated that

PFAS exposure primarily elevated cell migration, cell death, oxidative stress, and MAPK pathway activation in HSCs. Functionally, PFAS induced oxidative stress during HSC activation, which could be inhibited by antioxidants such as vitamin C. Activation of MAPK pathways, including ERK, JNK, and P38, was also detected in PFAS-treated HSCs. Overall, our study indicates that exposure to PFAS leads to the activation of human HSCs both in vivo and in vitro via multiple pathways, providing new insights into the cellular mechanisms by which PFAS increases the risk for MASH.

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PLURIPOTENT STEM CELL EXPANSION IN A STIRRED-TANK BIOREACTOR: OPTIMIZATION AND AUTOMATION OF FEEDING STRATEGIES FOR ACHIEVING ECONOMIC FEASIBILITY

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Large-scale expansion of human pluripotent stem cells is an evolving field with promising applications in cell therapy and regenerative medicine. Despite significant advances, economic viability of large-scale stem cell culture bioprocesses remains challenging, hampering translation. Costliness of cell culture media is a major hurdle. The current work sought to answer the following question: How does optimizing culture medium composition, perfusion culture, and online monitoring of glucose & lactate concentrations help to reduce culture media associated costs? To answer, experiments were performed using Eppendorf's DASbox Bioreactor System, culturing hiPSCs as free-floating scaffold-free aggregates. Daily samples were drawn from the bioreactor for cell counting, staining for viability and immunocytochemistry for flow. For all media, aggregates presented a hollow morphology and stained positive for Calcein AM throughout 6-7 days of culture. HiDef-S8 led to a fold expansion of 39× in only 6 days. HiDef-B8 and TeSR both led to fold expansions of 33× in 7 days, whereas E8 led to a fold expansion of only 18× in 7 days. TeSR and S8 presented improved cell survival (38% and 37%, respectively). S8 supported a faster expansion. HiDef-S8 and TeSR led to much greater TRA-1-60+ yields over 6 and 7 days, respectively, than either E8 or B8. Despite the similar performance of TeSR and S8 in this metric, S8's substantially lower cost per volume and faster growth rate resulted in substantially lower medium cost. In terms of pluripotency maintenance, only HiDef-S8 and mTeSR1 preserved high expression of key pluripotency markers (>95%) after 6 days and 7 days, respectively. Notably, for extracellular vesicle production it is important that the

culture medium contain as few particles. Nanoparticle analysis showed that TeSR contained substantially higher concentrations of particles across multiple lots compared to HiDef-S8, HiDef-B8, and E8. HiDef-S8, a new optimized medium designed to support high-density suspension human PSC expansion, led to a 34% reduction in culture media associated costs comparatively to TeSR. Perfusion and glucose/lactate monitoring also decreases costs, by facilitating an optimal medium exchange rate. Although focused on hiPSCs, this work's results are applicable to stem cell bioprocesses.

Funding: Fundação para a Ciência e a Tecnologia; I.P. granted to CardioWheel (PTDC/EQU-EQU/29653/2017) and SMART (PTDC/EQU-EQU/3853/2020); to iBB (UIDB/04565/2020 and UIDP/04565/2020).

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PRIMARY MOUSE TRACHEAL BASAL CELLS TRANSPLANTED INTO CFTR-/- MICE RESCUE CFTR FUNCTION

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Replenishing a diseased airway stem cell compartment with normal transplanted autologous basal cells has the potential to treat genetic airway diseases, such as cystic fibrosis (CF). We previously demonstrated the capacity of primary and pluripotent stem cell derived basal cells to durably engraft in mice trachea after injury. Towards the goal of developing cell therapy for CF, we sought to adapt our approach by testing the functional capacity of transplanted basal cells to rescue in vivo CFTR function in a genetic mouse model of CF. Here, we demonstrate the successful transplantation of exogenous wild-type

primary mouse basal cells into the tracheas of gut-corrected CFTR-/- mice, successfully restoring in vivo CFTR expression and function Primary wild type ubiquitin-green fluorescent protein (GFP) C57BL/6 mouse basal cells were isolated and expanded from fresh trachea and subsequently transplanted into heterozygous and gut-corrected CFTR-/- (B6.129P2-KOCftrtm1Unc) mice by oropharyngeal delivery following polidocanol conditioning of the recipient animals as we previously described. Recipient murine tracheae were analyzed after 6 weeks for engraftment efficiency, Cftr expression, and CFTR ion channel function. Donor-derived GFP+ replacement (23.4 ± 3.1% (mean ± SEM)) of endogenous epithelium was detected by epifluorescence in all transplant recipients. To characterize the donor-derived cells, we performed single cell RNA-sequencing analysis of CFTR-/- recipient tracheae which identified the 8 expected airway cell types that make up the tracheal epithelium: basal, secretory, multiciliated, pulmonary neuroendocrine (PNEC), tuft, hillock cells and ionocytes. Finally, Ussing chamber analysis of transplant recipients showed significantly higher CFTR-dependent current in transplanted CFTR-/- than in non-transplanted CFTR-/- mice, comparable to levels of response seen in heterozygous littermate controls.

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PROTOCOL-DEPENDENT BEHAVIOURS OF PSC-DERIVED ENDOTHELIAL CELLS IN 3D MODELS

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The efficient and reproducible generation of endothelial cells (ECs) from pluripotent stem cells (PSCs) is critical for the development of vascular cell therapies. However, current differentiation strategies produce variable yields and functionality, and the impact of protocol design on downstream behaviour in 3D environments remains poorly understood. We compared two differentiation protocols in Shef1.3 hESCs: a baseline protocol (BP) using CHIR for mesoderm induction followed by bFGF/VEGF for vascular specification, and a modified protocol (MP) that incorporated stage-specific TGFβ modulation, and a high volume-to-surface area ratio. Morphological observations revealed protocol-dependent

differences. BP cultures appeared more dispersed after mesoderm induction but compacted following vascular specification, whereas MP cultures initially formed denser colonies that later spread and became irregular, which suggests that the two protocols drive distinct patterns of vascular commitment. Both protocols generated CD34+ EC progenitors, but MP produced significantly higher yields (55.3 ± 4.5%) compared to BP (27.5 ± 3.1%). After maturation, both protocols produced ECs capable of forming capillary-like networks (CLN) in 3D hydrogels, however BP-derived ECs frequently overgrew gel surfaces while MP-derived ECs formed more contained networks. To test whether the addition of VEGF during EC maturation influenced function, EC progenitors were cultured with or without VEGF. Interestingly, VEGF-treated progenitors appeared more elongated, consistent with vascular maturation. However, angiogenesis analysis of CLNs in 3D revealed that VEGF did not significantly alter network formation, despite values trending towards improvement. Confocal imaging confirmed that ECs from both protocols formed lumenised structures when co-cultured with support cells, indicating functional vascular organisation. These results demonstrate that protocol design not only influences yield but also behaviour in 3D culture. This work highlights that marker expression alone is insufficient to predict function and emphasises the need to evaluate protocol-dependent behaviours in 3D models, providing a framework for selecting strategies that accelerate the translation of PSC-derived vascular cells.

Funding: The Michael Uren Foundation. The Sir Joseph Hotung Charitable Settlement.

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PSC BIOMANUFCTURING: ADVANCES IN SCALABLE TECHNOLOGIES WITH THE CORNING® ASCENT® FIXED BED BIOREACTOR SYSTEM

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Induced pluripotent stem cells (iPSCs) have emerged as a promising technology for transformative applications in regenerative medicine, drug discovery, cell therapy, and cell banking. However, the transition from bench to large-scale, clinical-grade production presents significant challenges, including scalability, reproducibility, and regulatory compliance. Current adherent based biomanufacturing systems lack the scalability, automation, and process control required to meet the growing demand for iPSC-based therapies. To address these challenges, we introduce the Corning® Ascent® Fixed Bed Reactor (FBR) platform, engineered for adherent cell cultures. The Ascent platform delivers uniform perfusion of the packed bed substrate, consistent cell distribution, efficient harvesting, and linear scalability. We demonstrate the feasibility and importance of

uniform coating of packed bed bioreactor with biological molecules such as Laminin to enhance cells attachment and proliferation. Critical process parameters necessary for the successful culture of iPSCs on the Ascent system will also be highlighted. 30- fold expansion of iPSC cells in 1m2 bioreactor was demonstrated with total cells yield of 4.8 billion with 96% viability. This scalable and automated platform can address key gaps in iPSC biomanufacturing.

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EFFICIENT REPROGRAMMING OF HUMAN BLOOD-DERIVED CELLS VIA NON-INVASIVE DELIVERY OF SELF-REPLICATING REPRORNA™-OKSGM USING SOLUPORE®

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Self-replicating RNA-based methods (srRNA) for reprogramming somatic cells to generate induced pluripotent stem cells (iPSCs) offer several advantages over traditional methods of reprogramming. The enhanced safety of transient, non-integrating srRNA-based methods eliminate the risk of random genomic insertion and reactivation of reprogramming factors in differentiated progeny. srRNA-based reprogramming methods can also de-risk cell manufacturing by simplifying quality control processes and removing the need to screen for clearance of residual virus. While these methods have been established for many cell types, the efficient and non-toxic delivery of large srRNA constructs to blood cell types via electroporation or lipid-based methods has been a major challenge. In this study, a novel delivery platform, SOLUPORE®, was utilized to reversibly permeabilize the cell membrane to efficiently deliver an srRNA construct containing reprogramming factors, ReproRNA™-OKSGM, to several blood cell types, while minimizing cellular perturbation. Utilizing this technology, we developed an optimized srRNA reprogramming workflow for CD34+/CD45+ cells isolated and expanded from cord blood (CB-CD34+) and mobilized peripheral blood

leukopaks (LP-CD34+), as well as CD71+/GlyA+ erythroid progenitor cells (EPCs) expanded from adult whole blood. On average, post-transfection viability remained >80% across all cell types and donors. Cells adhered and formed pre-iPSC colonies within 6 - 15 days, and formed distinct colonies with iPSC-like morphology by day 21 - 42. We were able to generate iPSCs from CB-CD34+ and LP-CD34+ cells with reprogramming efficiencies of 0.04 ± 0.003% (mean ± SEM; CB-CD34+: n = 7 donors; LP-CD34+: n = 3 donors). Furthermore, we demonstrated for the first time that whole blood-derived EPCs could be reprogrammed with efficiencies of 0.02 ± 0.003% (mean ± SEM; n = 5 donors). Clones reprogrammed using this optimized workflow exhibited the standard human pluripotent stem cell quality attributes, including expression of markers of the undifferentiated state and the ability to differentiate to the 3 germ layers. Together, we have shown that a cell delivery method, that preserves cell health and function, can be used to introduce large srRNA constructs and facilitate reprogramming of human blood cells.

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REGENERATING THE HEART WITH HIPSC-CARDIOMYOCYTES IN COMPOSITE ENGINEERED TISSUES

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Heart attack survivors suffer from reduced cardiac function, as up to 1 billion cardiomyocytes (CMs) die during myocardial infarction (MI) and are not replaced. With 10-20% of MI patients not responding to standard medical therapy and up to 30% of MI patients developing heart failure (HF) within 1 year, there is a critical need to enhance contractility after MI to slow, prevent or reverse loss of heart function as an alternative to later interventions like ventricular assist devices. Therapeutic delivery of hiPSC-derived CMs to the injured heart by injection or engineered tissue implantation is in clinical trials, yet a critical gap exists between the time of intervention and onset of mechanical benefits to the heart. We deliver high densities of hiPSC-CMs (up to 1 billion cells) in engineered human myocardium (EHM) and are integrating the next generation of biomaterial scaffolds for mechanical support of both the implant and injured left ventricular (LV) wall. We optimize the composite scaffold-EHM design through computational modeling, assess mechanics and biodegradability of polycaprolactone (PCL) scaffolds, and evaluate LV

remodeling and contractility after implantation in a rat model of MI. Finite element modeling of the post-MI LV shows that longitudinally aligned fibrous scaffolds and active contraction of the implant improve calculated LV ejection fraction by +3.4% and +15.0%, respectively. The engineered composite EHM has high ease of surgical handling and the implanted hiPSC-CMs significantly mature over 4 weeks in vivo, shown by increased myofilament area (~7-fold), striation development, and ventricular myosin light chain 2 expression (~2-fold). Longitudinal 4D ultrasound reveals dynamic changes in 3D regional strain (a measure of contractility) in the injured wall. PCL alone maintains nearly 80% surface area (SA) strain acutely (day 3), diminishing through 4 weeks. EHM alone enables SA strain recovery from day 3 to >70% of baseline at weeks 1 and 2. The composite PCL-EHM therapy has SA strain preserved at day 3 and improved at 1, 2, and 4 weeks, maintaining higher strain globally at 4 weeks versus all other groups. These results support our ongoing development of a tailored PCL-EHM composite as a cell-based therapy to reinforce, remuscularize and re-engineer function of the post-MI heart.

Funding: Brown University Seed Award (to KLKC), NSF GRFP (to KDD), AAUW Dissertation Fellowship (to KDD).

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RESULTS OF GMP COMPLIANT KARYOTYPE STUDIES TO SUPPORT CELL-THERAPY PRODUCTS

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The use of GMP assays in support of regulatory filings has increased significantly over the last 5 years. The additional oversight and documentation provided by testing in compliance with GMP and EudraLex regulations provides more confidence for translational groups heading to the clinic. WiCell currently offers an array of GMP compliant services suitable for use as release assays to support clinical manufacturing programs including G-banded karyotype, Short Tandem Repeat, and Fluorescence in situ Hybridization. WiCell has previously reported rates of abnormal karyotypes on assays performed using WiCell's Non-GMP characterization services. In this study WiCell compares abnormality rates reported for non-GMP services with the GMP-compliant services performed in support of cellular therapy applications. WiCell has been providing characterization testing for the stem cell community for >20 years and GMP compliant testing in support of the cell therapy applications for >5 years. In the past 5 years WiCell has assessed over 15,000 hPSC

samples through our non-GMP services and >150 samples hPSC samples in compliance with GMPs. While we acknowledge acquisition bias in the GMP data collection, similar biases are acknowledged in the non-GMP data set. In a 5-year time period, WiCell's non-GMP services reveal an overall abnormality rate of 16.8% (of 15,000 samples). In contrast, submissions through GMP compliant services reveal an abnormality rate of only 3.6%. Non-clonal changes were considered normal karyotype results for these studies. This data strongly suggests that cells manufactured under controlled and well-defined conditions show lower rates of karyotypic abnormalities, as one might expect. This also highlights laboratory practice as a major potential source of karyotypic abnormality and suggests that research labs may benefit by using routine characterization (See ISSCR Standards), controlled culture procedures, scheduled equipment maintenance, and other principles of GMP within their workflow to achieve significantly better results.

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ROLE OF HETEROGENEOUS NUCLEAR RIBONUCLEOPROTEINS(HNRNPS) IN MAINTENANCE AND DIFFERENTIATION OF PLURIPOTENT STEM CELLS

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Embryonic Stem cells are distinguished by high pluripotent plasticity, continuous self-renewal, and the ability to generate multilineage cell populations. The perpetuation of pluripotency is intricately orchestration intrinsic gene regulatory networks, metabolic pathways, epigenetic control mechanisms, alternative splicing (AS) machinery. Reports from previous studies suggest that AS is intricately involved in cell fate decisions and embryonic development. In this study, we unveil that a battery of heterogeneous nuclear ribonucleoproteins (hnRNPs) show high expression in pluripotent mouse embryonic stem cells (mESCs) compared to mouse embryonic fibroblasts (MEFs), as evidenced by RT-PCR analysis. We extended our investigation of hnRNP expression in human pluripotent stem cells (TJC8 hiPSCs) by qRT-PCR analysis which validated the elevated hnRNP expression in hiPSC cells. To find the inter-association of these hnRNPs and how they are regulated, promoter regions of these hnRNPs were analyzed by in silico approach. We performed PCR validation which revealed their elevated expression in mESCs. Literature reviews illuminated hnRNPU's pivotal role in important biological process including cranial and cardiac development. To decipher its regulatory significance in stem cell biology, we explored lentiviral-mediated dual-guide RNA CRISPR-Cas9 technology to generate

hnRNPU- knockout human iPSC (icas9) lines. Subsequent molecular analyses demonstrated alterations in pluripotency markers (Oct4, Sox2, C-Myc), muscle progenitor markers (Myogenin, Myf5), and apoptotic gene expression. Future directions aim to unravel the mechanistic intricacies of hnRNPU's influence on pluripotency, lineage commitment, and apoptotic pathways. Through RNA sequencing, organoid model generation, apoptosis assays, splice junction arrays, and overexpression studies, we moving forward to delineate the molecular underpinnings governing hnRNPU's regulatory landscape in stem cell fate decisions.

Funding: BITS PILANI GOA CAMPUS, DBT INDIA.

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ENABLING NEURORETINAL REPAIR. COST-EFFICIENT AND GMP-COMPLIANT CELL THERAPY STRATEGIES FOR VISION RESTORATION

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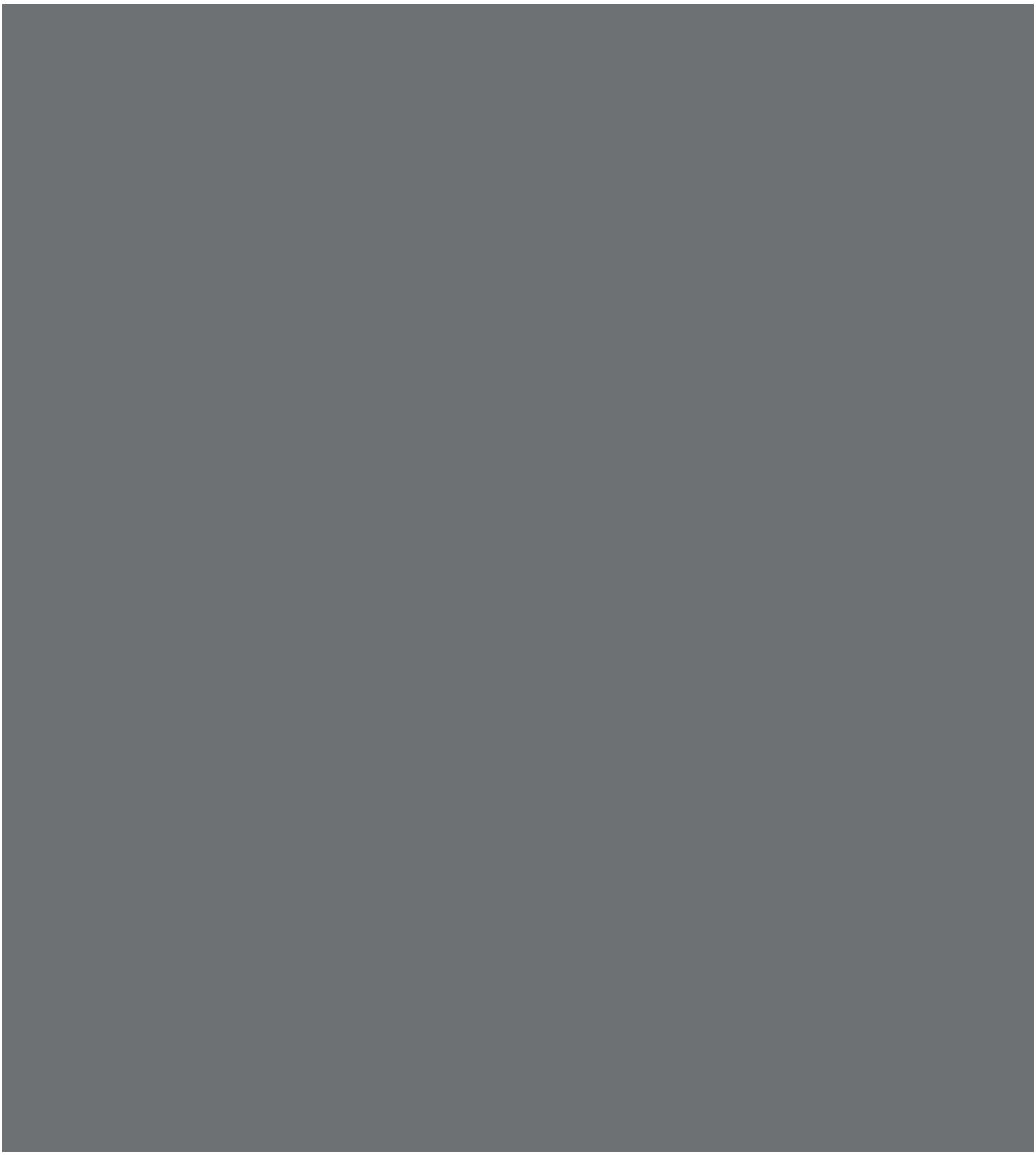
Visual impairment profoundly impacts patients' and their families' quality of life, as well as imposing significant economic burdens on society. Retinal degeneration (RD), including age-related macular degeneration (AMD) and glaucoma (Gl), is the leading causes of blindness in the Western world. AMD alone affects nearly 200 million people globally, a number expected to nearly double by 2040, while glaucoma affects over 80 million worldwide. Current treatments for both diseases do not restore vision already lost, leaving millions suffering from advanced degeneration without effective therapeutic options. Cell replacement therapies—targeting photoreceptors (PhRs) for RD and retinal ganglion cells (RGCs) for Gl -hold promise for restoring vision in these patients. Here, we present Evotec's progress in developing an iPSC-derived cell therapy processes for cost-efficient, GMP-compliant generation of PhRs and RGCs from retinal organoids (ROs). By using a single, proprietary differentiation protocol to produce both cell types, we streamline the workflow,

reduce production timelines and significantly improve cost-efficiency. Importantly, the protocol reduces hands-on time, increases batch size, and accelerates the overall process. Our method ensures robust and consistent RO generation across differentiation runs using a GMP-compliant iPSC line. This consistency is supported by gene expression analyses, histology, and single-nucleus RNA sequencing. Additionally, we demonstrate enrichment of the desired cell types, PhRs and RGCs, which express mature markers and can be isolated and cryopreserved. Post-thaw viability is ~70%, and preliminary in vivo data show survival and maturation of both PhRs and RGCs. By reducing culture time, increasing scalability, and enabling consistent, GMP-compliant production, our approach lowers the cost and complexity traditionally associated with cell therapies in ophthalmology. Taken together, our results represent a significant advancement toward making cell therapy for vision loss more accessible, being a promising step toward off-the-shelf cell therapy solutions for vision restoration.

Funding: Evotec International GmbH.



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SCALABLE PRODUCTION OF DOPAMINERGIC NEURONS PRIMED FOR ENGRAFTMENT

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Pluripotent stem cell-derived (PSC) therapies face several limitations in commercial scale manufacturing. Many of these challenges are associated with traditional 2D culturing systems, which are characterized by an unnatural environment for cells, limited scalability, higher cost of production, and a challenging regulatory path. To address these limitations, we developed a synthetic, fully defined, hydrogel, named AXgelTM, designed for culturing PSCs in 3D environments. This biomimetic hydrogel provides a shear-protective, inert microenvironment for cell expansion and differentiation, free of exogenous extracellular matrix cues. This culturing platform enhances genomic stability and differentiation efficacy and provides cells with the critical extra dimension for expansion, enabling industry-leading yields, with over 5e6 cells/mL produced. We demonstrated production of high-quality midbrain dopaminergic neurons (mDA) for the treatment of Parkinson's Disease, entirely differentiated in the AXgel platform in a perfused bioreactor system. AXgel-produced mDA neurons exhibited ~10% higher post-harvest viabilities ($p<0.0361$), and ~15% higher post-thaw viabilities ($p<0.0001$) compared to mDA neurons produced in standard 2D formats. AXgel mDA cells also exhibited longer and more mature neurite networks, with an average of ~150 um compared to ~100 um in cells generated in 2D ($p<0.0436$). AXgel mDA cells were implanted in a 6-OHDA animal model of Parkinsonism. Animals that received AXgel-produced mDA neurons showed high post-transplantation survival with extensive neurite projections as early as 4-weeks post grafting. This was accompanied by a complete reversion of Parkinson-like motor symptoms by 4 months post-grafting, which is remarkably faster than the reported ~6 months required for standard mDA cells produced in 2D. This data evidences that cells produced in AXgel are primed for engraftment, requiring significantly less time for maturation and engraftment in vivo to exhibit disease alleviation potential. With industry-leading yields, our current scale utilizing a benchtop 2-L AXgel bioreactor is enough to meet clinical and commercial demand, producing up to 2,000 clinical doses per process with ~25x lower costs compared to industry-standard 2D manufacturing.

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SCALABLE STEM CELL-DERIVED NATURAL KILLER CELL DIFFERENTIATION IN AN IN VITRO FEEDER-FREE SYSTEM

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Natural killer (NK) cells are essential mediators of tumor surveillance and immunotherapy, but limited access to functional NK cells remains a major barrier for clinical translation. Induced pluripotent stem cells (iPSCs) provide an attractive renewable source, yet scalable and feeder-free manufacturing solutions are still lacking. We present a robust, fully feeder-free differentiation system that enables efficient and reproducible generation of iPSC-derived NK (iNK) cells suitable for large-scale production. By leveraging a stepwise culture strategy optimized with DLL4 and VCAM-1, iPSCs progressed through hematopoietic and lymphoid intermediates to yield 96.3% CD3–CD56+ iNK cells by day 35. Continued expansion reached over 70,000-fold by day 49 with >90% viability, demonstrating the scalability of this platform. Phenotypic characterization confirmed expression of key NK receptors, including NKp30, NKp44, NKp46, NKG2D, CD16, and KIR. Functional assays revealed potent cytotoxicity and cytokine secretion against K562 leukemia cells, exceeding peripheral blood NK cell controls. This feeder-free system establishes a reliable and clinically relevant method for producing consistent, high-purity iNK cells with strong effector functions. By addressing current limitations in NK cell availability and variability, our platform supports the development of off-the-shelf immunotherapies and highlights ACROBiosystems' commitment to advancing innovative cell therapy manufacturing solutions.

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SCALABLE, DEFINED CARDIAC ORGANOIDS FOR REDUCING POST-INFARCTION CARDIAC FIBROSIS

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Human induced pluripotent stem cell (hiPSC)-derived cardiac organoids (COs) offer promising potential for cardiac regenerative medicine, but scalable and clinically translatable systems remain limited. We developed a robust, serum- and matrix-free platform for generating self-organizing COs in both 96-well plates and scalable suspension bioreactors. These COs comprise major cardiac-relevant cell types, including cardiomyocytes (CMs), cardiac fibroblasts, endothelial cells, smooth muscle cells, pericytes, and other non-myocytes, enabling comprehensive in vitro modeling and therapeutic applications. In an immunosuppressed porcine myocardial infarction acute model, transplanted COs survived, integrated without causing arrhythmias, and improved cardiac function at 30 days post-injury. Multimodal characterization via immunostaining, TEM, flow cytometry, and single-cell RNA sequencing confirmed the presence of key cardiac cell types and maturation features. By day 20, COs exhibited organized sarcomeres (1.7–2 µm), robust expression of maturation markers (e.g., RYR2, PLN), and functional electrophysiology as shown by sharp electrode recordings, optical mapping, and high-density microelectrode arrays. COs were also shipped globally under non-cryogenic conditions with preserved viability and function after 24–48 hours of recovery. Spatial transcriptomics of transplanted COs revealed reduced pro-fibrotic signaling (e.g., TGFβ1, COL1A1) and increased anti-fibrotic/extracellular remodeling markers (e.g., FST, BMP2, MMP2, MMP9) at day 30 compared to day 8. These findings validate a defined, scalable platform that yields functionally mature-like status, multicellular cardiac tissue with regenerative capacity, highlighting its relevance for cell therapies, drug discovery, and global distribution.

Funding: Leitmarkt-NRW project no. EFRE-0801775. Marga and Walter Boll Foundation: JEOL JEM2100 Plus: DFG-INST 216/793-1 FUGG. Spanish Min. of Eco. & Co. (PID2022-142219OB-I00, PID2021-124703OB-I00).

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SIMULTANEOUS RECORDING OF CARDIAC ORGANOID CALCIUM FIRING IN MULTIPLE WELLS, WITH BUILT-IN DOWNSTREAM ANALYSIS

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Human cardiac organoids derived from pluripotent stem cells offer a valuable tool for cardiac disease research. However, current limitations in conventional microscopy's imaging speed hinder large-scale functional screening of cardiac organoid beating and calcium firing, especially for studies requiring temporal precision or time-sensitive comparisons across multiple wells. Ramona Optics' Vireo™ system represents a significant leap forward in the field of cardiac organoid screening by simultaneously imaging 24 wells, thus drastically improving throughput and efficiency. Capitalizing on this technology, we recorded cardiac organoid contractions and calcium flux at the rate of 45 frames per second for 15 seconds, with a resolution of 2.34 µm/pixel, allowing for the rapid completion of a 96-well plate under 90 seconds. Furthermore, using Ramona's Region of Interest tool and a Python-based computational pipeline encompassing a comprehensive analysis of mean fluorescence, $\Delta F/F_0$ normalization to a rolling 10th percentile baseline, and detailed plotting of fluorescence dynamics, the calcium imaging revealed a characteristic firing pattern of spontaneous contractions, evidenced by clear, periodic peaks in fluorescence intensity that correspond to calcium transients. In summary, the Vireo excels at capturing subtle spatial heterogeneities within the organoids and ensures temporal fidelity, which is essential for accurate kinetic analyses. Its output in standard data formats of MP4 and TIFF greatly simplifies integration into existing computational pipelines, including those built with Python and ImageJ, minimizing the need for extensive data conversion or reformatting. This level of speed and precision allows for robust evaluation of cardiac organoid performance, providing researchers with invaluable insights into cardiac function and drug responses.

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SUSTAINED-RELEASED CHASE37 ENABLES SURVIVAL OF TRANSPLANTED HUMAN IPSC-DERIVED NEURAL PROGENITOR CELLS AFTER STROKE

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Ischemic stroke is one of the leading causes of permanent neurological disability worldwide. With few clinical treatments, patients rely mostly on rehabilitation, which has limited therapeutic benefit. Regenerative strategies that harness the plasticity in the brain offer great promise to restore function. Stem cell transplantation offers enormous potential for neural tissue repair through the release of neurotrophic factors and/or replacement of lost cells and integration into the neural circuitry. We hypothesize that the co-delivery of neural stem cells with factors that promote plasticity will lead to improved cellular and functional outcomes in a model of cortical ischemic stroke. To test this, we developed a novel strategy that combines human induced pluripotent stem cell-derived neural progenitor cells (hiPSC-NPCs) with a sustained-release, thermostabilized form of chondroitinase ABC (ChASE37) – a glial scar-degrading enzyme – to promote plasticity and stem cell integration in a rat model of ischemic stroke. hiPSC-NPCs were delivered directly into the stroke cavity using an injectable, in situ-gelling hyaluronic acid-based hydrogel functionalized with laminin to enhance cell survival and integration. To modulate the extracellular matrix and degrade the inhibitory glial scar that forms after stroke, ChASE37 was formulated for affinity-based sustained release (ChASE37-AR) and applied epicortically using an injectable methylcellulose-based hydrogel. Each of NPCs, ChASE37-AR and their combination improved motor outcomes, and only the latter also supported long-term survival and neuronal differentiation of transplanted cells in the stroke-injured brain. After a single ChASE37-AR, glial scar degradation persisted for at least 30 days, and there was no evidence of immunogenicity. These findings suggest that ChASE37-AR effectively creates a permissive microenvironment for repair, allowing the co-delivered NPCs to differentiate into neurons and potentially integrate into the host tissue. This combinatorial approach addresses key barriers to regeneration in the post-stroke brain

and demonstrates the therapeutic potential of engineered enzyme delivery with stem cell transplantation for stroke and potentially other neurological injuries.

Funding: Canadian Institutes of Health Research (CIHR), Heart & Stroke Foundation.

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SYNTHETIC BIOMATERIAL TECHNOLOGY FOR SCALABLE HUMAN PLURIPOTENT STEM CELL PRODUCTION

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Human pluripotent stem cells (hPSCs), with the ability to self-renew and derive all cell types of the body, represent an attractive source for cell replacement therapies (CRTs) to treat diseases of degeneration. However, clinical and commercial translation of hPSC-derived cell products is limited by the scalability of high-quality stem cell production. Diseases of cellular degeneration, such as type 1 diabetes, heart failure, and neurodegenerative disorders can require up to 1e9 cells per patient, and considering the patient population and incidence, may require >1e16 cells per year for the US alone. With conventional 2D cell culture, the surface area necessary to expand enough hPSCs to derive these cell numbers is prohibitive and the approach is limited by low cell yields and genetic instability over multiple passages. Suspension cell culture of hPSC aggregates in bioreactors is limited by low fold changes, genetic instability, and high shear forces that prevent scale-up. To overcome these bottlenecks, we have developed a fully synthetic, scalable, and tunable thermoreversible polymer, termed AXgel(TM), and novel cellular encapsulation devices to unlock the impact of cell replacement therapy. The GMP compatible material and cell encapsulation process allows hPSCs to grow in 3D AXgel(TM) droplets in off-the-shelf bioreactors for scalable expansion of high-quality cells. Cells are retrieved by simply cooling the thermoreversible gel below its LCST to liquefy the hydrogel and release the expanded cells, with no hydrogel material present in the final product. The

release results in near 100% cell retrieval at >95% viability without the need for enzymatic or mechanical degradation of the material. This thermoreversible hydrogel platform enables high expansion fold changes (>170 fold) and high cell yields (>5e6 cells/mL media) while maintaining pluripotency and genetic stability over extended culture periods (>10 passages). Additionally, we have derived potential cell therapy candidates from all three germ layers within the hydrogel platform, demonstrating utility for expansion and differentiation. With the described advantages, the AXgel(TM) 3D cell culture platform overcomes the critical bottlenecks in cell manufacturing and accelerates translation of hPSC-derived CRTs.

Funding: Private Funding.

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SYNTHETIC PEPTIDE GROWTH FACTORS: NEXT-GENERATION TOOLS FOR REGENERATIVE MEDICINE AND CELL THERAPY

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Growth factors derived from conventional sources (ie. FBS or recombinant protein expression) have accompanied regenerative medicine to the threshold of a new era, but in key areas they fall short of the technologies they support such as limited stability, high cost, lot-to-lot variation, animal component contamination risks, and low scalability. PeptiGrowth is a joint venture between PeptiDream and Mitsubishi Corporation that supplies peptides with similar capabilities for receptor activation, cell proliferation, and differentiation as conventional growth factors. Along with greater ease of use, longer shelf life, and no contamination by animal-derived components, these peptides provide uniformity in quality that can improve efficiency and data reproducibility and thus, reduce the cost of R&D, manufacturing, and quality control. PeptiGrowth employs PeptiDream's proprietary Peptide Discovery Platform System (PDPS) technology, enabling the production of highly diverse non-standard libraries containing trillions of peptides and efficiently identifying highly potent and selective macrocyclic peptide candidates. PeptiGrowth is leveraging PDPS to obtain peptides that can specifically bind to target molecules and use them as synthetic peptide growth factors. These peptides are then manufactured from µg to kg scale and tested for biological activity using various reporter assays and cell systems against a recombinant control. PeptiGrowth's FGF2 alternative peptide (PG-011) is a prime example of how these synthetic, cyclic peptides offer many advantages. FGF2 is known to be highly unstable requiring frequent media changes and high concentrations. PG-011 binds to hFGFR1c, activates FGFR1c phosphorylation, and induces proliferation of human

MSCs at one-third the concentration. iPSCs cultured with PG-011 exhibited similar colony morphology, proliferation, and undifferentiated markers as FGF2. PG-011 also showed superior stability in media and during cell culturing at 37 °C. In addition, PeptiGrowth has also successfully developed a KGF alternative peptide (PG-012). This peptide functions as an agonist for human FGFR2b and consists of sequences with high specificity toward FGFR2b. Similar to KGF, PG-012 was confirmed to act as a differentiation inducer of pancreatic islet β cells from iPSCs, suggesting its strong potential as a valuable tool in regenerative medicine approaches for type 1 diabetes. Furthermore, PeptiGrowth is actively developing peptide alternatives for various interleukins, with plans to expand into synthetic peptides applicable to the broader cell therapy field.

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SYNTHETIC RECEPTOR STRUCTURE ENHANCES DIFFERENTIATION OF T CELL-DERIVED INDUCED PLURIPOTENT STEM CELLS

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Induced pluripotent stem cells (iPSCs) iPSCs that express chimeric antigen receptors (CAR) are an attractive self-renewing source for allogeneic cell therapy. We have previously shown that T cell-derived iPSC (TiPS) engineered to express a 1928z-1XX CAR from the TRAC promoter (TRAC-1XX) facilitate differentiation of CD4+CD8αβ double positive (DP) and CD8αβ single positive (SP) TRAC-1XX iPSC-derived T cells (iT). However, TRAC-1XX-iT cells have lower DP induction and have a significantly lower total cell expansion than wild-type (WT) DP iT cells. We hypothesized that a synthetic receptor more similar in structure and signaling to the T cell receptor (TCR) would improve differentiation toward the DP stage. The HLA-independent TCR (HIT) couples the heavy and light chain of an scFv directly to the constant regions of the TCR α and β chains, thereby generating antigen recognition in an HLA-independent manner, while maintaining TCR structure and signaling. TRAC-HIT-TiPS had increased DP formation compared to TRAC-1XX-TiPS but did not reach the same efficiency as WT-TiPS. Additionally, HIT-iT absolute cell yields are similar to those obtained for TRAC-1XX-iT. This suggests that, although closer alignment with the TCR structure supports better DP formation, the HIT does not fully recapitulate the developmental

triggers TCR expression provides. We first looked at HIT and TCR expression levels and observed that HIT is expressed at lower levels than the TCR. Additionally, CD3 and TCR cell surface expression linearly correlate in WT-iT but not in HIT-iT. scFv staining in HIT shows a bimodal distribution, with a population that is clearly negative, whereas all cells express CD3, indicating that CD3 may complexing with chains other than HIT. We therefore determined whether the invariant pre-TCR alpha chain (pTα) may be expressed as it pairs with a functional β chain and CD3. Staining of HIT-iT revealed a higher cell surface level of pTa compared to WT-iT. This suggests that not enough HIT α chain may be expressed from the TRAC locus, thus we transduced the cells with more HIT and observed an increase in cell surface expression of both HIT and CD3. Therefore, HIT cell differentiation may be improved by a stronger expression of the HIT chains. Despite their lower receptor expression, HIT-iT have antigen specificity and cytotoxicity.

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TAILORED POLYCAPROLACTONE SCAFFOLD ARCHITECTURE TO ENHANCE HIPSC-CARDIOMYOCYTE ALGINMENT AND CONTRACTILITY IN ENGINEERED HUMAN MYOCARDIUM TO REMUSCULARIZE THE HEART

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It is estimated that 1 billion cardiomyocytes (CMs) die during a myocardial infarction (MI). Work to curb post-MI heart failure progression is focused on restoring cellular and function loss by delivering human induced pluripotent stem cell-derived CMs (hiPSC-CMs) to regenerate the heart. Delivering CMs by implanting engineered human myocardium (EHM), composed of hiPSC-CMs and collagen hydrogel, on the epicardium offers an advantageous approach to remuscularize the heart with low incidence of arrhythmia. However, our previous work investigating highly dense EHM to deliver clinically relevant CM doses (50M/mL), resulted in a soft tissue with disorganized sarcomeres. To create a robust implant, we are focused on incorporating an anisotropic and biodegradable polycaprolactone (PCL) scaffold into our EHM to direct alignment and bundle formation for increasing contractility, improve surgical handling, reinforce the heart wall, and degrade as CMs mature and healing resolves. Our initial approach used an aligned, electrospun PCL

scaffold to reinforce the EHM and heart wall. Despite successful composite formation in vitro, there was clear delineation of EHM and PCL components and PCL-EHM fragmentation in vivo. This study investigates how in vitro degradation of PCL impacts its mechanical properties and develops a novel 3D PCL architecture to enhance PCL-EHM entwinement, CM alignment, and active contractility. Degradation results show maintenance of the PCL scaffold's mechanical properties over one month in vitro in cell culture medium with physiologically relevant enzyme levels, suggesting an ability to support the EHM during in vitro culture and after implantation. We use melt electro-writing to fabricate a fibrous, anisotropic, and macroporous PCL scaffold and to create a well-integrated PCL-EHM composite that is instructional of hiPSC-CM morphology and mechanically robust for surgical handling. Our ongoing work assesses the composite's contractility, bundle formation, and CM alignment, and evaluates how its structure influences its function. This approach will enable delivery CMs that are strongly contractile and aligned pre-implantation to support the translation of using hiPSC-CMs within EHM as an early intervention to remuscularize and unload the post-MI heart.

Funding: Brown University Seed Funds.

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THE IMPORTANCE OF COMBINING CHROMOSOME KARYOTYPING AND DIGITAL PCR ASSAYS TO ASSESS GENOMIC INTEGRITY

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An important component of the human stem cell research and therapeutic development process is the reliable assessment of genomic integrity. Genomic instability can compromise both the safety and efficacy of derived products, yet each individual characterization method has specific weaknesses. In alignment with the various options for genomic characterization set forth in ISSCR guidelines, we evaluated the combined use of two complementary assays in the case presented: traditional G-band chromosome karyotyping and a recently upgraded 28-probe digital PCR panel for commonly mutated sequences in human pluripotent stem cells. While karyotyping reliably identifies chromosomal rearrangements larger than 10 megabases, digital PCR is able to capture smaller, recurrent sequence alterations that are not always visible cytogenetically. The details of specific samples analyzed within the past six months will be presented to demonstrate the advantages of utilizing both techniques together in the research and development of stem cell therapy products. Considering costs and turnaround times of other genetic characterization assays, this integrated approach provides a more rigorous

and faster assessment thus strengthening quality control practices. Together, these results support a broader adoption of dual genomic integrity testing strategies to safeguard stem cell research and accelerate progress in the cell therapy field.