ISSCR

IS BOSTON

TRANSLATING DISCOVERIES

Pluripotent Stem Cells

17-19 November 2022
Boston, USA

PROGRAM BOOK

Welcome

Dear Colleagues,

On behalf of the International Society for Stem Cell Research (ISSCR), welcome to the 2022 Boston International Symposium, *"Translating Pluripotent Stem Cell Discoveries to the Clinic: Preclinical, Manufacturing and Regulatory Strategies for Success."* We are excited to finally come together for this pandemic-delayed meeting in a city that has become a global hub of innovation and advancement for biotechnology and regenerative medicine approaches.

Pluripotent stem cell-based treatments for human disease are rapidly advancing from the laboratory into early-stage clinical trials and beyond, but unique and complex preclinical, regulatory, and manufacturing challenges increase the time, difficulty, and expense of these processes. The program was deliberately designed to span the translational process and during the next two and a half days of this symposium, a cadre of international scientists and regulators will address many of these issues and share their experience navigating the translational process. Beginning with preclinical strategies to developing a therapy to the final session on delivering your cell product, the goal of the event is to bring experts and stakeholders together to decrease the barriers to and enhance the process of developing pluripotent stem cell-based interventions.

Whether you are in the meeting hall or watching virtually, we invite you to immerse yourself in the science and its application by engaging with the speakers, asking questions during the presentations, and interacting with the sponsors. We hope that you come away from this meeting inspired with new ideas and relationships that will advance the therapeutic applications of stem cells and ultimately improve human health.

Sincerely,

The Boston International Symposium Organizing Committee

Melissa Carpenter, PhD, *ElevateBio, USA*

Derek Hei, PhD, *Clade Therapeutics, USA*

Malin Parmar, PhD, *Lund University, Sweden*

ISSCR INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

ABOUT THE ISSCR

The mission of the International Society for Stem Cell Research (ISSCR) is to promote excellence in stem cell science and applications to human health. The ISSCR is the largest society in the world dedicated to the advancement of responsible stem cell research – a field that strives to advance scientific understanding, treatments, and cures that better human health. We foster junior scientists, give voice and visibility to scientific advancement, and encourage a positive global environment for future discovery and treatment. Our promise is to help the field of stem cell research reach its potential.

Contact Us

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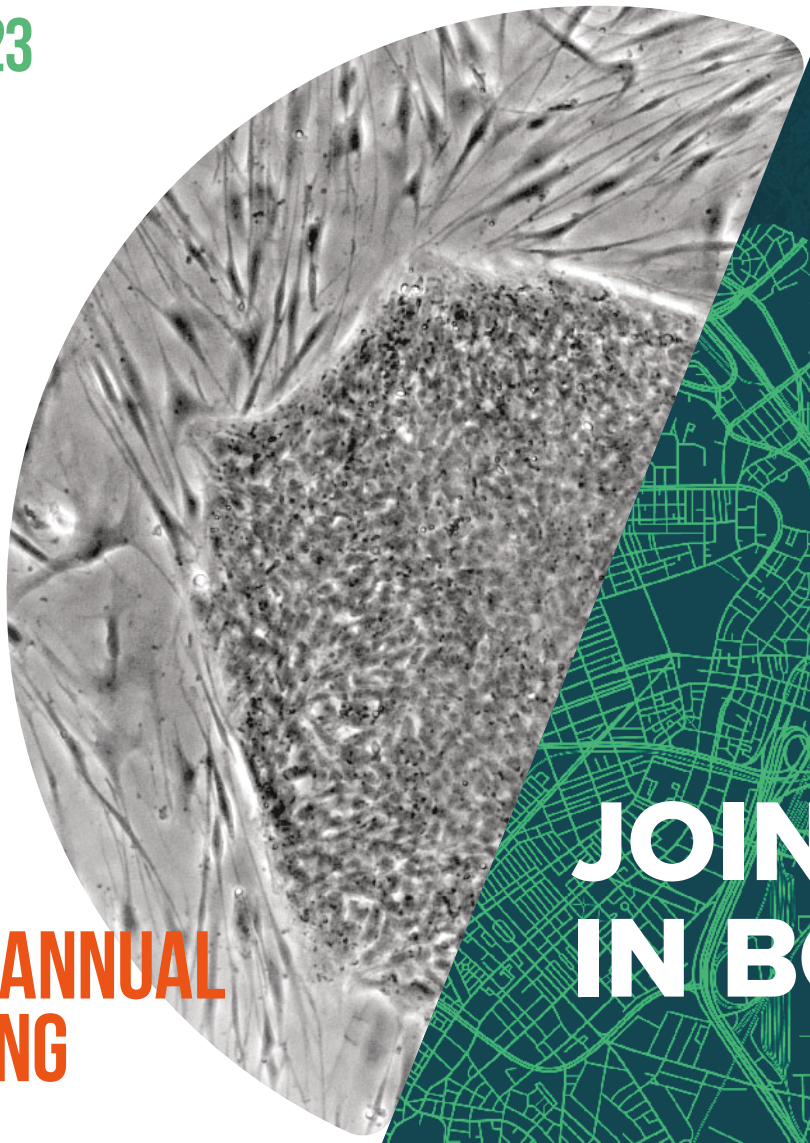

ISSCR ANNUAL MEETING 2023

JOIN US IN BOSTON

14–17 JUNE 2023
BOSTON, MA, USA

Abstracts Open 8 December 2022
Registration Opens January 2023

CO-SPONSORED BY:

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TECHNOLOGIES

Meeting Information

ONSITE BADGE PICK UP

Pick-up your name badge in the **Coat Room Registration Desk** area on the **2nd Floor** of the Boston Marriott Cambridge Hotel during posted hours. Name badges are required for admission to all sessions, social events, and the Exhibit & Poster Hall. Badges may be picked up during the following times:

Thursday, 17 November	7:00 AM – 6:00 PM
Friday, 18 November	7:30 AM – 5:30 PM
Saturday, 19 November	7:30 AM – 1:30 PM

COVID-19 VACCINATION VERIFICATION

The ISSCR requires proof of vaccination for the 2022 Boston International Symposium. **Attendee badges cannot be picked up until vaccination is verified.** Learn more about what is required for all attendees by visiting the Health & Safety page. Every attendee will be required to wear a mask, regardless of vaccination status, during all ISSCR events and gatherings both inside and outside the hotel.

VIRTUAL ASSISTANCE

Access the 2022 Boston International Symposium Virtual Platform and login with your ISSCR credentials. Click on your profile icon located in the upper right corner of the site to access 'Ask ISSCR' and answer any questions. You may also email ISSCRdigital@isscr.org.

INTERNET ACCESS

The ISSCR is pleased to be able to offer complimentary WiFi in our meeting space for all attendees at speeds perfect for basic email and internet browsing.

Network Name: ISSCR Boston
Password: stemcell

RECORDINGS PROHIBITED

Still photography, screen capture, video and/or audio taping/recording of the sessions, presentations and/or posters at the 2022 Boston International Symposium is strictly prohibited. Intent to communicate or disseminate results or discussion presented at the meeting is prohibited until the start of each individual presentation.

GENERAL INFORMATION

Smoking
Smoking is prohibited in the Boston Marriott Cambridge Hotel.

Lost and Found
Please bring found items to the ISSCR Registration Desk in the **Coat Room Registration Desk** area on the **2nd Floor** of the Boston Marriott Cambridge Hotel during posted hours. If you lost an item, stop by during registration hours for assistance.

Parking
The nearest off-site parking garage that services the Boston Marriott Cambridge Hotel is the **Kendall Center Green Garage**, which is 0.1 miles from the hotel. The address to the garage is 90 Broadway St., Cambridge, MA 02142. Overnight parking at the hotel is available, but limited. Hourly and daily parking rates for both the garage and the hotel will vary. Attendees are responsible for paying for their own parking fees.

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At Astellas, we combine the deep experience, expertise and resources of an established global pharmaceutical company with the agility, flexibility and tenacity of a biotechnology start-up. Our open approach to innovation and unique levels of support make us an ideal partner for ambitious organizations pursuing partnership to accelerate their progress.

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STEM CELL REPORTS

SPECIAL ISSUE CALL FOR PAPERS

Image credit: Waddington's landscape and patients receiving PSC-based therapies. Created by Dr. Misaki Ouchida.

Pluripotent stem cell therapies and their path to the clinic

Stem Cell Reports will publish a special issue of the journal with a focus on pluripotent stem cell-based therapies and their path to the clinic.

PSC-based therapies have attracted great interest due to progress in PSC differentiation technology. This special issue will focus on five topics regarding PSC-based therapies: (1) Studies on the effectiveness of PSC-based therapies*, (2) Studies on the safety of PSC-based therapies*, (3) Country-specific regulation and its standardization, (4) Summary of clinical trials over the last 10 years, and (5) Difference from other therapies (e.g., gene therapy) or combination with other therapies.
*Preclinical translational studies are included.

This special issue is expected to publish in May 2023.

Submission deadline: December 15, 2022

Submit your paper now!
https://www.editorialmanager.com/stem-cell-reports/

Questions? Email stemcellreports@isscr.org

Guest editors

Shinya Yamanaka, MD, PhD
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CiRA Foundation, Japan
Gladstone Institutes, University of California, San Francisco, USA

Kazuo Takayama, PhD
Center for iPS Cell Research and Application (CiRA), Kyoto University, Japan

ISSCR

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Meeting Policies

CODE OF CONDUCT

The ISSCR is committed to providing a safe and productive meeting environment that fosters open dialogue and discussion and the exchange of scientific ideas, while promoting respect and equal treatment for all participants, free of harassment and discrimination.

All participants are expected to treat others with respect and consideration, follow venue rules and alert staff or security, if onsite, of any dangerous situations or anyone in distress. Attendees are expected to uphold standards of scientific integrity and professional ethics.

These policies comprise the Code of Conduct for ISSCR Meetings, which will be followed for this event, and apply to all attendees, speakers, exhibitors, staff, contractors, volunteers, and guests at the meeting and related events.

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ISSCR prohibits any form of harassment, sexual or otherwise. Incidents should immediately be reported to ISSCR meetings staff at the Registration Desk or isscr@isscr.org.

RECORDING POLICY

By registering for this meeting, you agree to the ISSCR's Recording Policy. It is strictly prohibited to record (photographic, screen capture, audio and/or video), copy, or download scientific results from the sessions, presentations and/or posters at the 2022 Boston International Symposium. Intent to communicate or disseminate results or discussion presented at the meeting is prohibited until the start of each individual presentation.

EMBARGO POLICY

Abstract content may not be announced, publicized, or distributed before the presentation date and time in any way including blogging and tweeting. ISSCR does permit promotion of general topics, speakers, or presentation times. This embargo policy applies to all formats of abstract publication.

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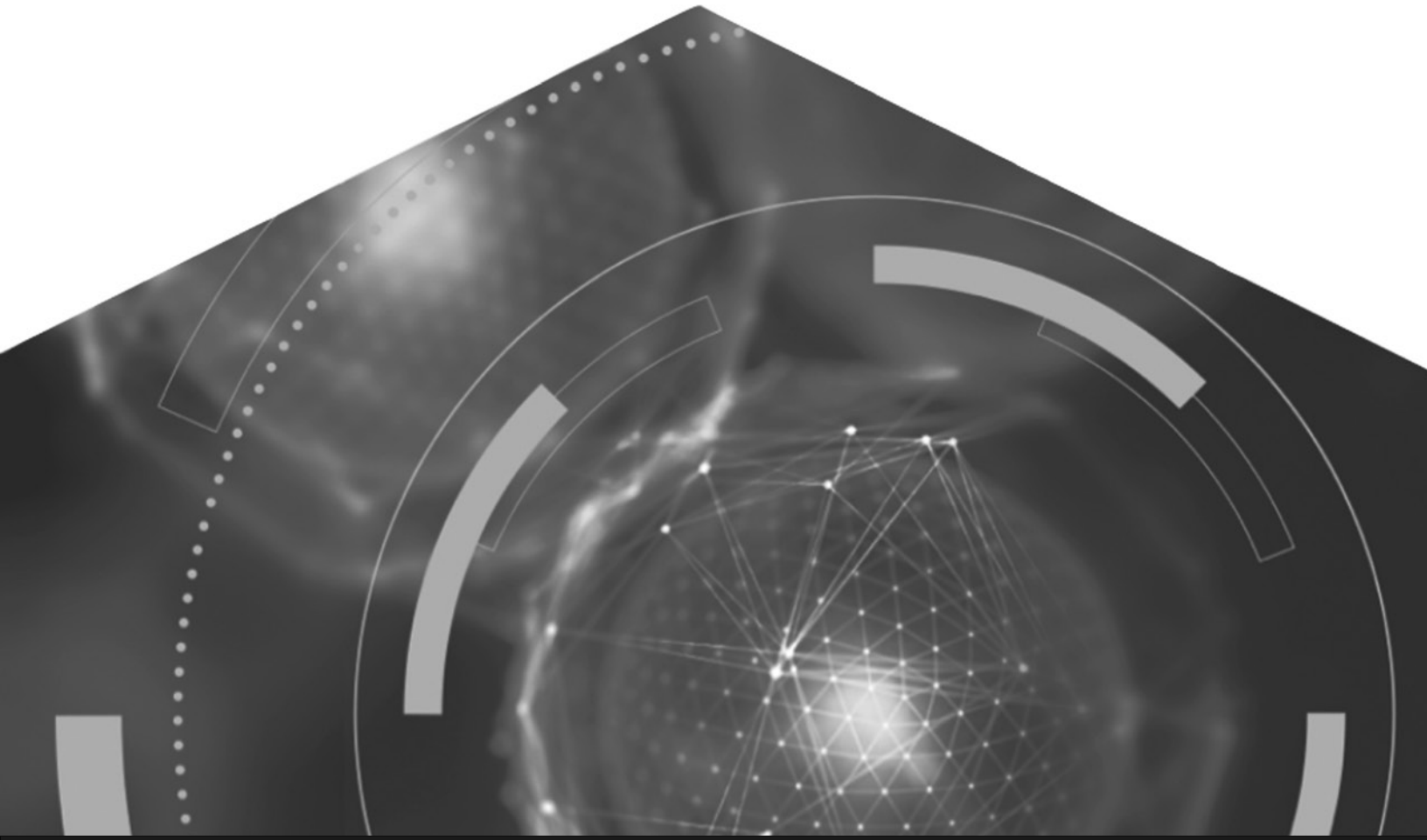

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Engage with ARMI
BioFabUSA this week:

- **Attend the Innovation Showcase and Lunch** to hear about the advanced technologies, automation, process development concepts, data analytics and regulatory strategies that ARMI | BioFabUSA brings to bear to enable the scalable, consistent and cost-effective manufacture of cells, tissues and organs. The session will include a case study on the scalable, modular, automated and closed production of stem cell-derived pancreatic islets, presented by Washington University.
- **Connect with one of our staff attendees** about becoming an ARMI | BioFabUSA member and taking advantage of membership's many benefits.

BioFabUSA, a program of the Advanced Regenerative Manufacturing Institute (ARMI), *is a public-private partnership with the Department of Defense. BioFabUSA has more than 170 members in industry, academic institutions and not-for profit organizations. Our mission is to make practical the scalable, consistent and cost-effective manufacturing of cells, tissues and organs—and to develop the trained and ready workforce necessary for that manufacturing.*

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https://ct.catapult.org.uk/

Program Schedule

Thursday, 17 November

2022 Boston International Symposium:
Translating Pluripotent Stem Cells Discoveries

Thursday
17 November 2022

8:00 AM – 9:00 AM — BREAKFAST & SPONSORED INNOVATION SHOWCASE

Grand Ballroom Salons 1-3

Presented by: **Cell and Gene Therapy Catapult**

8:00 AM – 9:00 AM

INTRODUCTION TO THE CELL AND GENE THERAPY CATAPULT
**Pick up your breakfast from the Grand Ballroom Foyer area and bring it with you to enjoy during the Innovation Showcase*

9:00 AM – 9:25 AM — BREAK

Grand Ballroom Foyer

9:25 AM – 11:20 AM — PRECLINICAL STRATEGIES

Grand Ballroom Salons 1-3

Sponsored by: **Astellas Institute for Regenerative Medicine**
Chair: **Derek Hei**, *Clade Therapeutics, USA*

9:25 AM – 9:30 AM

Welcome and Opening Remarks
Derek Hei, *Clade Therapeutics, USA*

9:30 AM – 10:00 AM

Opening Keynote
Douglas A. Melton, *Harvard University and Vertex Pharmaceuticals, USA*
STEM CELL-DERIVED ISLETS FOR THE TREATMENT OF DIABETES

10:00 AM – 10:30 AM

Su-Chun Zhang, *Duke-NUS Medical School, Singapore, and University of Wisconsin, USA*
CELL THERAPY FOR NEUROLOGICAL DISORDERS

10:30 AM – 11:00 AM

April Craft, *Boston Children's Hospital, USA*
OFF THE SHELF TISSUE FOR CARTILAGE REPAIR

11:00 AM – 11:20 AM

Kareen Coulombe, *Brown University, USA*
REGENERATION IN INFARCTED RAT HEARTS BY HUMAN IPSC-DERIVED CARDIAC TISSUE WITH PATTERNED ENGINEERED VESSELS

11:20 AM – 12:45 PM — LUNCH BREAK

Grand Ballroom Salons 4-7

Program Schedule

Thursday, 17 November

11:45 AM – 12:45 PM LUNCH & SPONSORED INNOVATION SHOWCASE

Grand Ballroom Salons 1-3

Presented by: **STEMCELL Technologies**

11:45 AM – 12:45 PM

DIFFERENTIATION TO MEGAKARYOCYTES TO SUPPORT TRANSLATIONAL RESEARCH AND SCALABLE EXPANSION OF HUMAN PLURIPOTENT STEM CELLS IN SUSPENSION CULTURE

**Lunches may be brought into the session room to enjoy during the Innovation Showcase*

1:00 PM – 2:30 PM SELECTING YOUR CELL LINE: DERIVATION AND CHARACTERIZATION

Grand Ballroom Salons 1-3

Sponsored by: **ElevateBio**
Chair: **Melissa Carpenter**, *ElevateBio, USA*

1:00 PM – 1:30 PM

Tenneille Ludwig, *WiCell Research Institute, USA*
TRANSLATIONAL SUCCESS: MINDING YOUR P's AND Q'S

1:30 PM – 2:00 PM

Jennifer Dashnau, *Century Therapeutics, USA*
REGULATORY CONSIDERATIONS FOR GENETICALLY-ENGINEERED, INDUCED PLURIPOTENT STEM-CELL DERIVED ALLOGENEIC CELL THERAPIES: A PROPOSED RISK-BASED APPROACH FOR ADDRESSING CHEMISTRY, MANUFACTURING, AND CONTROLS

2:00 PM – 2:30 PM

Nissim Benvenisty, *Hebrew University, Israel*
GENETIC AND EPIGENETIC CHARACTERIZATION OF HUMAN PLURIPOTENT STEM CELLS

2:30 PM – 2:50 PM REFRESHMENT BREAK

Grand Ballroom Salons 4-7

2:50 PM – 4:20 PM WHAT IS IN YOUR PRODUCT?

Grand Ballroom Salons 1-3

Chair: **Kapil Bharti**, *National Institutes of Health, USA*

2:50 PM – 3:20 PM

Deborah Hursh, PhD, *US Food and Drug Administration, USA*
CMC CONSIDERATIONS FOR PLURIPOTENT STEM CELL DERIVED PRODUCTS: FDA PERSPECTIVES
**Virtual Presentation*

3:20 PM – 3:50 PM

Bob Valamehr, *Fate Therapeutics, Inc, USA*
FT819 AND FT596: FIRST-OF-KIND OFF-THE-SHELF CAR19 T-CELL AND NK CELLS FOR B CELL MALIGNANCIES

3:50 PM – 4:20 PM

Angela Keightley, *BlueRock Therapeutics, Cambridge, MA*
ANALYTICAL DEVELOPMENT STRATEGIES FOR EARLY-STAGE CELL THERAPY PRODUCT CHARACTERIZATION

4:30 PM – 6:30 PM WELCOME RECEPTION & POSTER NETWORKING SESSION

Grand Ballroom Salons 4-7

4:30 PM – 5:15 PM **POSTER SESSION I ODD**

5:45 PM – 6:30 PM **POSTER SESSION II EVEN**

Friday
18 November 2022

8:00 AM – 9:00 AM BREAKFAST & SPONSORED INNOVATION SHOWCASE

Grand Ballroom Salons 1-3

Presented by: **MaxWell Biosystems**

8:00 AM – 9:00 AM

NEXT-GENERATION IN-VITRO ASSAYS: CHARACTERIZING THE ACTIVITY OF HUMAN IPSC-DERIVED NEURONS IN 2D AND 3D CULTURES AT HIGH RESOLUTION
**This Innovation Showcase will be available in-person and on the virtual meeting platform.*
***Pick up your breakfast from the Grand Ballroom Foyer area and bring it with you to enjoy during the Innovation Showcase*

9:00 AM – 9:30 AM BREAK

Grand Ballroom Foyer

9:30 AM – 11:40 AM NEW TECHNOLOGIES/WHERE ARE WE GOING?

Grand Ballroom Salons 1-3

Chair: **Sonja Schrepfer**, *Sana Biotechnology and University of California, San Francisco, USA*

9:30 AM – 10:00 AM

Kapil Bharti, *National Institutes of Health, USA*
DEVELOPING AUTOLOGOUS iPS CELL THERAPY FOR MACULAR DEGENERATION: FROM BENCH-TO-BEDSIDE

10:00 AM – 10:30 AM

Peter Zandstra, *University of British Columbia, Canada*
SIGNALING DYNAMICS DURING T-CELL DEVELOPMENT FROM PLURIPOTENT STEM CELLS
**Virtual Presentation*

10:30 AM – 11:00 AM

Howard Kim, *New York Stem Cell Foundation Research Institute, USA*
LEVERAGING AUTOMATION AND AI TO STREAMLINE IPSC PRODUCTION AND RESEARCH

11:00 AM – 11:20 AM

Kévin Alessandri, *TreeFrog Therapeutics, France*
FROM 50 MILLION TO 15 BILLION HUMAN IPS CELLS WITHIN A WEEK: HIGHLY REPRODUCIBLE EXPONENTIAL IPS EXPANSION IN 10L BIOREACTORS WITH MAINTENANCE OF CELL QUALITY

11:20 AM – 11:40 AM

Kiera Dwyer, *Brown University, USA*
ONE BILLION CELLS: ENGINEERING CARDIAC TISSUE WITH HUMAN INDUCED PLURIPOTENT STEM CELL DERIVED CARDIOMYOCYTES FOR THERAPEUTIC IMPACT

11:40 AM – 1:00 PM LUNCH BREAK

Grand Ballroom Salons 4-7

11:50 AM – 12:50 PM LUNCH & SPONSORED INNOVATION SHOWCASE

Grand Ballroom Salons 1-3

Presented by: **Pluristyx, Inc.**

11:50 AM – 12:50 PM

MANUFACTURING THE NEXT GENERATION OF PLURIPOTENT STEM CELL-BASED THERAPIES
**This Innovation Showcase will be available in-person and on the virtual meeting platform.*
***Lunches may be brought into the session room to enjoy during the Innovation Showcase*

Program Schedule

Friday, 18 November

1:00 PM – 2:30 PM IMMUNOLOGY FOR CELL THERAPIES

Grand Ballroom Salons 1-3

Chair: **Bob Valamehr**, *Fate Therapeutics, Inc, USA*

1:00 PM – 1:30 PM
Ran Jing, *Harvard Medical School/Boston Children's Hospital, USA*
EPIGENETIC ENGINEERING OF IPSC-DERIVED T CELLS

1:30 PM – 2:00 PM
Sonja Schrepfer, *Sana Biotechnology and University of California, San Francisco, USA*
ENGINEERING OF ALLOGENEIC DONOR CELLS FOR ACCEPTANCE BY THE HOST'S IMMUNE SYSTEM

2:00 PM – 2:30 PM
Shin Kaneko, *Kyoto University, Japan*
DEVELOPMENT OF IPSC-DERIVED FUNCTIONAL LYMPHOCYTES FOR IMMUNE CELL THERAPY
**Virtual Presentation*

2:30 PM – 3:00 PM REFRESHMENT BREAK

Grand Ballroom Salons 4-7

3:00 PM – 4:30 PM BALANCING SCIENCE AND REGULATORY REQUIREMENTS IN EMERGING FIELDS

Grand Ballroom Salons 1-3

Sponsored by: **Cellino**
Chair: **Jane Lebkowski**, *Regenerative Patch Technologies, USA*

3:00 PM – 3:30 PM
Gesine Paul-Visse, *Lund University and Skånes University Hospital, Sweden*
STEM-PD TRIAL: CLINICAL TRIAL DESIGN AND REGULATORY CHALLENGES
**Virtual Presentation*

3:30 PM – 4:00 PM
Anthony Oro, *Stanford University School of Medicine, USA*
SCALEABLE, SAFE, AND EFFECTIVE GENETICALLY-CORRECTED TISSUE MANUFACTURING AND DELIVERY

4:00 PM – 4:30 PM
Melissa Carpenter, *ElevateBio, USA*
DEVELOPING PLURIPOTENT STEM CELL-DERIVED THERAPIES

4:30 PM – 4:50 PM BREAK

Grand Ballroom Salons 4-7

4:50 PM – 5:50 PM CAREER DEVELOPMENT SESSION

Grand Ballroom Salons 1-3

Chair: **Marinna Madrid**, *Cellino Biotech, USA*

Panelists:

Ibrahim Domian, MD, PhD, *BlueRock Therapeutics*
Julie Perlin, PhD, *Ten Bridge Communications*
Kimberly Snyder, MS, *STEMCELL Technologies*
Austin Thiel, PhD, *ElevateBio*

Saturday

19 November 2022

8:00 AM – 9:00 AM BREAKFAST & SPONSORED INNOVATION SHOWCASE

Grand Ballroom Salons 1-3

Presented by: **Astellas Institute for Regenerative Medicine**

8:00 AM – 9:00 AM

CANCER CELL THERAPY AT ASTELLAS
**Pick up your breakfast from the Grand Ballroom Foyer area and bring it with you to enjoy during the Innovation Showcase*

9:00 AM – 9:30 AM BREAK

Grand Ballroom Foyer

9:30 AM – 11:00 AM HOW TO ACCELERATE WITH ACCELERATED DESIGNATIONS

Grand Ballroom Salons 1-3

Chair: **Anthony Oro**, *Stanford University, USA*

9:30 AM – 10:00 AM

Masayo Takahashi, *Vision Care Inc., Japan*
RETINAL CELL THERAPY AS A SUSTAINABLE CATEGORIZE MEDICINE
**Virtual Presentation*

10:00 AM – 10:30 AM

Jane S. Lebkowski, *Regenerative Patch Technologies, Menlo Park, CA, USA*
DEVELOPMENT OF MANUFACTURING PROCESSES FOR PLURIPOTENT CELL BASED THERAPIES: CONSIDERATIONS FOR ACCELERATED APPROVAL PATHWAYS

10:30 AM – 11:00 AM

Jacqueline Barry, *Cell and Gene Therapy Catapult, UK*
EU AND UK ACCELERATED APPROVAL PATHWAYS

11:00 AM – 12:30 PM LUNCH BREAK

Grand Ballroom Salons 4-7

11:15 AM – 12:15 PM LUNCH & SPONSORED INNOVATION SHOWCASE

Grand Ballroom Salons 1-3

Presented by: **ARMI | BioFab, USA**

11:15 AM – 12:15 PM

PAVING THE ROAD TO TRANSLATION THROUGH SCALABLE, MODULAR, AUTOMATED AND CLOSED MANUFACTURING
**Lunches may be brought into the session room to enjoy during the Innovation Showcase*

Program Schedule

Saturday, 19 November

12:30 PM – 2:00 PM DELIVERING YOUR CELL PRODUCT: STRATEGIES FOR SUCCESS

Grand Ballroom Salons 1-3

Sponsored by: **Vertex Pharmaceuticals**
Chair: **Derek Hei**, *Clade Therapeutics, USA*

12:30 PM – 1:00 PM
Timothy Kamp, *University of Wisconsin, USA*
HUMAN IPSC-DERIVED CARDIAC PROGENITOR CELLS FOR MYOCARDIAL REPAIR

1:00 PM – 1:30 PM
Cory R. Nicholas, *Neurona Therapeutics, USA*
PHASE I/II CLINICAL INVESTIGATION OF HUMAN INHIBITORY NEURON CELL THERAPY FOR CHRONIC FOCAL EPILEPSY

1:30 PM – 2:00 PM
CLOSING KEYNOTE
Peter Marks, *US Food and Drug Administration, USA*
THE REGULATORY FRAMEWORK FOR CELLULAR THERAPIES IN THE UNITED STATES

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At the Astellas Institute for Regenerative Medicine (AIRM), we are investigating novel pluripotent stem cell-derived therapeutic products that have the potential to rejuvenate, regenerate and replace damaged tissues. Our goal is to develop "off-the-shelf" cell-based therapies that can be used in any patient. Our lead program is in the ocular space, with a developmental pipeline encompassing innovative therapies that can be used in many other therapeutic areas, including cancer, autoimmune conditions and vascular diseases. Our new 262,000 square foot, state-of-the-art facility allows us to combine both our research and manufacturing capabilities in the same complex, giving us the means to develop new treatments while scaling manufacturing for future commercialization needs.

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MAXWELL BIOSYSTEMS

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www.pluristyx.com

Table 4

Pluristyx is an advanced therapy tools company helping companies and researchers solve manufacturing challenges in the field of drug development, regenerative medicine, and cell and gene therapy. Pluristyx provides seamless client support by offering CMC consulting, contract cryopreservation and development services, and research- and clinical-grade Ready-to-Use (RTU™) and Ready-To-Differentiate® (RTD™) Pluripotent Stem Cells at a commercial scale.

Sponsor and Exhibitor Directory

GOLD SPONSORS

STEMCELL TECHNOLOGIES

1618 Station St
Vancouver, BC V6A1B6 Canada
+1 604-675-7575
info@stemcell.com
www.stemcell.com

Table 1
Interactive Virtual Exhibit

At STEMCELL, 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're helping scientists accelerate the pace of discovery. Inspired by knowledge, innovation and quality, we are Scientists Helping Scientists.

VERTEX PHARMACEUTICALS

50 Northern Ave
Boston, MA 02210-1862 USA
+ 1 617-341-6100
www.vrtx.com

Vertex, a global biotechnology company, invests in scientific innovation to create transformative medicines for people with serious diseases. The company has multiple approved medicines that treat the underlying cause of cystic fibrosis (CF) and continues to advance its research in CF. Vertex has a broad and deep pipeline, including small molecule approaches, and cell and genetic therapies, for other serious diseases like sickle cell disease, beta thalassemia, type 1 diabetes, APOL1-mediated kidney disease and pain.

SILVER SPONSORS

ARMI | BIOFABUSA

400 Commercial Street
Manchester, NH 03054 USA
+1 603-666-3905
info@armiusa.org
www.armiusa.org

The Advanced Regenerative Manufacturing Institute (ARMI) is a member-based, nonprofit organization whose mission is to advance the bioeconomy of the United States. BioFabUSA, a program of ARMI, is a public-private partnership with more than 170 members, including companies, academic institutions and not-for profit organizations. The mission of BioFabUSA is to bring together the fundamental tenets of good manufacturing processes and the science of regenerative medicine to create regenerative manufacturing and the trained and ready workforce necessary for that manufacturing.

CELL AND GENE THERAPY CATAPULT

12th Floor Tower Wing, Guy's Hospital
Great Maze Pond, London SE1 9RT UK
+20 3728 9500
info@ct.catapult.org.uk
ct.catapult.org.uk

The Cell and Gene Therapy Catapult is an independent innovation and technology organisation committed to the advancement of cell and gene therapies 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 over 400 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 Cell and Gene Therapy Catapult works with Innovate UK. For more information, visit ct.catapult.org.uk or http://www.gov.uk/innovate-uk.

Sponsor and Exhibitor Directory

SILVER SPONSORS

CELLINO

501 Massachusetts Ave
Cambridge, MA, 02139 USA
connect@cellinobio.com
www.cellinobio.com

Cellino is on a mission to make stem cell-derived cell therapies accessible for patients. Stem cell-derived regenerative medicines are poised to cure some of the toughest diseases within this decade, including Parkinson's, diabetes, and heart disease. However, current therapeutic production processes are not scalable due to extensive manual handling, high variability, and expensive facility overhead. Cellino's vision is to make personalized regenerative medicines viable at large scale for the first time.

Cellino's platform combines label-free imaging and high-speed laser editing with machine learning to automate cell reprogramming, expansion, and differentiation in a closed cassette format, enabling thousands of clinical-grade cell samples to be processed in parallel in a single facility.

ELEVATEBIO

200 Smith Street
Waltham, MA 02451 USA
info@elevate.bio
www.elevate.bio

ElevateBio is a technology-driven company built to power the development of transformative cell and gene therapies today and for many decades. The company has industry-leading talent, state-of-the-art facilities, and diverse technology platforms, including gene editing, iPSCs, and protein, vector, and cellular engineering, necessary to drive innovation and commercialization of cellular and genetic medicines. In addition, BaseCamp in Waltham, MA, is a purpose-built facility offering process innovation, process sciences, and cGMP manufacturing capabilities. It was designed to support diverse cell and gene therapy products, including autologous, allogeneic, and regenerative medicine cell products such as iPSC and viral vector manufacturing capabilities.

BRONZE SPONSORS

HEIDOLPH NORTH AMERICA

Heidolph North America
1235 N Mittel Blvd Suite B
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sales@heidolph.com
www.heidolphna.com

Heidolph North America is a German laboratory manufacturer that sells and services premium solutions and installation services for cell culture cultivation, chemical synthesis, process development, work-up and evaporation chemistry applications. Our product portfolio includes best-in-class, high quality laboratory and research capital equipment designed to focus on cost reduction, safety, and ease of use operation. All Heidolph manufactured offerings include an industry leading 3-year full-service warranty and a 10 year lifespan. Heidolph North America Portfolio Offerings include: 3D Cell Culturing Plates, Smart Incubators, Platform Shakers, Autoclaves/ Sterilizers, High Quality Peristaltic Pumps for Biology or Chemistry Applications, Rotary Evaporators, Chillers, Vacuum Pumps, Magnetic Stirring Hotplates, Overhead Stirrers, Chemical Reactors, Control Software, Glove Boxes for Air Sensitive Applications.

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Our mission is to discover new ways to improve and extend people`s lives. Our vision is to be a trusted leader in changing the practice of medicine.

We use science-based innovation to address some of society's most challenging healthcare issues. We discover and develop breakthrough treatments and find new ways to deliver them to as many people as possible.

Sponsor and Exhibitor Directory

BRONZE SPONSORS

TAKEDA ONCOLOGY

www.takedaoncology.com

At Takeda Oncology, we aspire to cure cancer, with inspiration from patients and innovation from everywhere. We are structured within Takeda to ensure a tight connection from research to development to commercialization and rapidly meet the needs of the cancer community, optimizing our ability to bring transformative medicines to patients. With demonstrated leadership in the treatment of hematologic cancers and solid tumors, we are propelling cutting-edge science around the power of innate immunity to enhance and broaden responses to cancer therapy.

We complement our deep in-house expertise with symbiotic partnerships to unlock promising science wherever it emerges.

For more information: www.takedaoncology.com.

EXHIBITORS

ADVANCED INSTRUMENTS

Two Technology Way
Norwood, MA 02062 USA
+1 (339) 206-3373
www.aicompanies.com

Table 15

Advanced Instruments is a global company offering a novel portfolio of analytical tools including, OsmoTECH®, a robust line of micro-osmometers to support bioprocessing and quality control (QC), and Solentim, a portfolio of best in class imaging and single-cell deposition technologies for cell line development workflows and assurance of clonality for regulatory bodies.

ALTIS BIOSYSTEMS

6 Davis Drive
Durham, NC 27709 USA
+1 919-885-4823
info@altisbiosystems.com
www.altisbiosystems.com

Table 3

RepliGut® is a unique, stem cell derived platform that recreates the human small intestine and colonic epithelium for more biologically relevant screening of compounds, disease modeling, and microbiome research.

With a scalable platform, actionable data, high throughput screening to test thousands of compounds, and an unrivaled biobank, RepliGut® is the future of in vitro testing during drug development.

Sponsor and Exhibitor Directory

EXHIBITORS

AMSBIO

1035 Cambridge Street
Cambridge, MA 02141 USA
+1 (617) 945 5033
info@amsbio.com
www.amsbio.com

Table 8

AMSBIO supplies high-quality products for cell and gene therapy. Our portfolio includes stem cells from various sources, reprogramming agents, feeder cells, and GMP-qualified cryopreservation media. We offer stem cell characterization tools, differentiation reagents, unique assay platforms, and packaging of AAV and lentivirus. AMSBIO carries the industry's largest selection of recombinant ECMs, and xeno-free culture media which provide unrivalled productivity and easy regulatory adoption.

BIOLAMINA

One Broadway
Cambridge, MA 02142 US
www.biolamina.com

Table 16

We offer an expansive portfolio of defined human recombinant laminin matrices, Biolaminins, for a variety of applications, such as expansion of human pluripotent stem cells and differentiation and maintenance of different specialised cell types. The biologically relevant cell-matrix interaction leads to improved cell functionality, robust culture systems and safe cells for therapy. BioLamina's laminin technology has been scientifically validated in many high impact journals.

CELLBOX SOLUTIONS, INC.

451 N. Hungerford Drive, Suite 119-333
Rockville, MD 20850 USA
enquiries@cellbox-solutions.com
www.cellbox-solutions.com

Table 7

THE NEW GENERATION FOR LIVE CELL SHIPMENTS. Cellbox 2.0 - a fully conditioned portable CO2 incubator to transport live cells and biological material under laboratory conditions.

Cellbox Solutions is a young technology company developing and marketing innovative logistics solutions for the BioMedTech, Pharmaceutical and Academic sectors.

Our flagship product, the Cellbox 2.0 - a portable CO2 incubator, offers the unique opportunity to incubate and cultivate cells during transport - saving time & effort - while maintaining high cell viability and improving the outcome of downstream applications and assays.

NAMOCELL

2485 Old Middlefield Way, Suite 30
Mountain View, CA 94043 USA
www.namocell.com

Table 6

Namocell is a leading provider of high-performance single cell sorting and dispensing systems to empower single cell research, therapeutics development and diagnostics. Namocell's Single Cell Dispensers are the fastest and easiest solution to identify and isolate single cells, nuclei, protoplasts, bacteria, yeast and fungi, and enable users to accomplish single cell sorting and dispensing in one step while being gentle to the cells to preserve cell viability and integrity. We serve researchers and scientists in a wide range of applications, including cell line development, CRISPR and cell engineering, single cell genomics, cell and gene therapy, antibody discovery, rare cell isolation, single cell proteomics, and synthetic biology. Learn more at www.namocell.com, watch our product video here, and follow us on LinkedIn: https://www.linkedin.com/company/namocell/.

Sponsor and Exhibitor Directory

EXHIBITORS

NEW ENGLAND OVIS

Headquartered in New Hampshire with clients nationwide.
+1 (603) 781-1149
juliehurleydvm@gmail.com
neosheep.com

Table 18

Two veterinarians, Richard and Julie Hurley, with extensive experience in sheep production and use of animals in research, developed innovative strategies that have created a commercial flock of specific pathogen free (SPF) sheep. New England Ovis (NEO) SPF Sheep are free of over 50 pathogens which is a flock health status unparalleled in the world. This includes zoonotic diseases such as Q Fever. These animals provide the most humane and safest source of sheep, lambs, cells, tissues, and organs available today.

OPTICS11 LIFE INC.

Hettenheuvelweg 37, 1101
BM Amsterdam, Netherlands
www.optics11life.com

Table 17

Optics11 Life develops nanoindentation instruments for biomechanical characterization (stiffness, viscoelasticity, etc.) of soft biomaterials. Integrated with advanced microscopy and high throughput capacity, the new Pavone nanoindenter is capable of screening a broad range of samples.

PBS BIOTECH, INC.

4721 Calle Carga
Camarillo, CA 93012-8560 USA
+1 (805) 482-7272
sales@pbsbiotech.com
www.pbsbiotech.com

Table 10

PBS Biotech, Inc. aims to be the leading provider of innovative, single-use bioreactors and to deliver superior value to customers with our products and services. Our single-use bioreactors are fully scalable for any stage of the cell culture process, from R&D to clinical to cGMP production. We provide efficient, cost-effective disposable systems and top-notch technical services to help our customers solve their cell culture challenges.

REPROCELL

9000 Virginia Manor Rd. Suite 207
Beltsville, MD 20705 USA
+1 301-470-3362
info-us@reprocell.com
www.reprocell.com

Table 5

REPROCELL is a global leader providing iPSC services including clinical and research reprogramming, differentiation, expansion and banking. Our clinical service empowers our clients therapeutic reprogramming needs via a customized approach of manufacturing iPSC GMP Master Cell Banks. Through our Bioserve Tissue network, we provide the donor samples necessary to begin your project. In addition, we provide REPROCELL and Stemgent brand products for stem cell research.

WICELL

504 South Rosa Road, Suite 101
Madison, WI 53719 USA
+1 608-291-6100
Info@wicell.org
www.wicell.org

Table 11

As a recognized world leader in pluripotent stem cell banking, distribution, characterization, and storage services, WiCell provides the stem cell community with high-quality cell lines, accurate and reliable characterization testing, and long term LN2 storage with WiCellSAFE.

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Ready-to-Differentiate® (RTD™) Pluripotent Stem Cells

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- Scalable workflow
- NO stem cell expansion
- Efficient product development/ manufacturing

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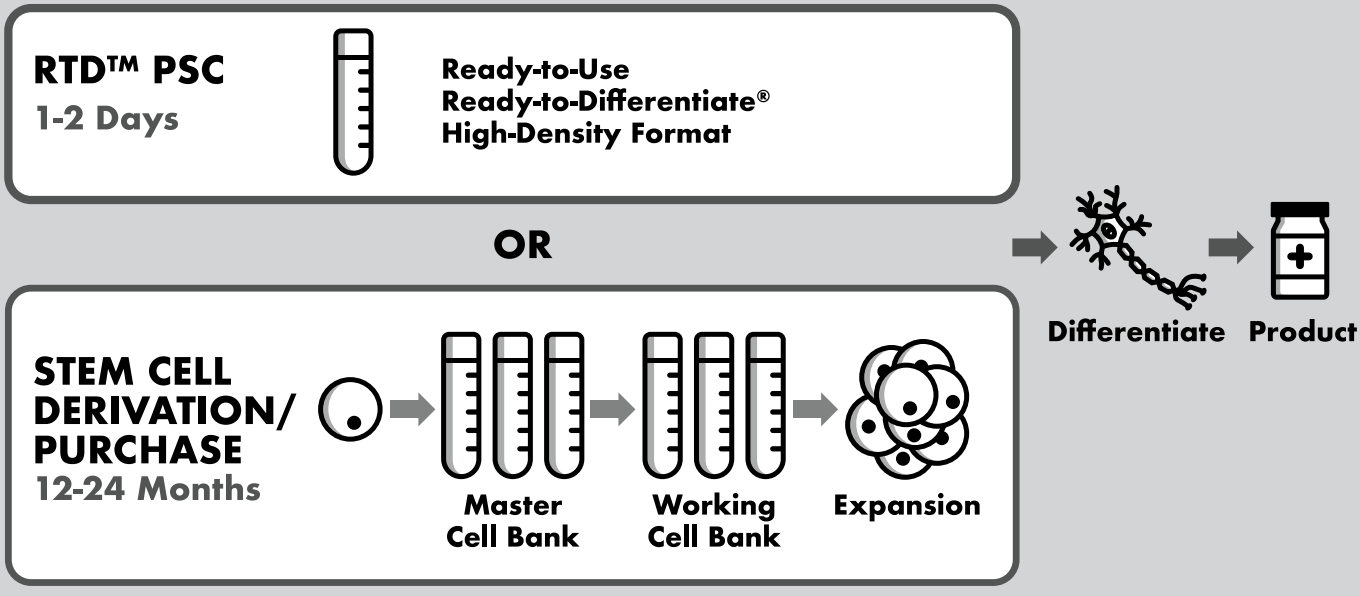

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A PODCAST WITH MARTIN PERA

SEASON 2 EPISODE 3

MODELING NEUROPSYCHIATRIC DISORDERS IN A DISH

CAROL MARCHETTO, PHD
UNIVERSITY OF CALIFORNIA, SAN DIEGO, USA

RUSTY GAGE, PHD
SALK INSTITUTE FOR BIOLOGICAL STUDIES, USA

SEASON 2 EPISODE 4

INTERSPECIES CHIMERISM: ADVANCES, APPLICATIONS, AND CHALLENGES

ORI BAR-NUR, PHD
ETH ZURICH, SWITZERLAND

JOEL ZVICK
ETH ZURICH, SWITZERLAND

JUN WU, PHD
UT SOUTHWESTERN, USA

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Speaker Abstracts

THURSDAY, 17 NOVEMBER

All sessions will take place in Grand Ballroom Salons 1-3

8:00 AM – 9:00 AM
SPONSORED INNOVATION SHOWCASE

Presented by: Cell and Gene Therapy Catapult

8:00 AM – 9:00 AM

INTRODUCTION TO THE CELL AND GENE THERAPY CATAPULT

Barry, Jacqueline, Hoest-Ragab, Anan

The Cell and Gene Therapy Catapult, UK

The Cell and Gene Therapy Catapult (CGT Catapult) is an independent innovation and technology organization committed to the advancement of cell and gene therapies 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 over 400 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 move to allogeneic off-the shelf therapeutic products includes the use of induced pluripotent stem cells (iPSCs) as well as embryonic stem cells (ESCs) to derive specific cell lineages of interest. CGT Catapult's Technology and Process Innovation laboratories, under the Allogeneic Cell Therapies Programme, have developed robust, scalable manufacturing processes for pluripotent stem cell production (PSC) including knowledge of high-throughput and high-content metabolomics, secretomics and transcriptomics analyses. Key aspects include the development of solutions and mitigations to ensure GMP compliant processes and products, closing and controlling upstream processes, characterisation of starting material and lineage biases, as well as integrated at-line and in-line process analytical technology e.g. RAMAN technology for optimal control.

9:25 AM – 11:20 AM
PRECLINICAL STRATEGIES

Sponsored by: Astellas Institute for Regenerative Medicine

Opening Plenary

9:30 AM – 10:00 AM
OPENING KEYNOTE ADDRESS

STEM CELL-DERIVED ISLETS FOR THE TREATMENT OF DIABETES

Melton, Douglas A.

Harvard University and Vertex Pharmaceuticals, Boston, MA, USA

The directed differentiation of human pluripotent stem cells into functional islets has been achieved and clinical trials are ongoing. New work aimed at gaining better control of islet composition and addressing immune tolerance will be presented.
Keywords: diabetes, human pluripotent stem cells

10:00 AM – 10:30 AM

CELL THERAPY FOR NEUROLOGICAL DISORDERS

Zhang, Su-Chun

Program in Neuroscience & Behavioral Disorders, Duke-NUS Medical School, Singapore, and University of Wisconsin, Madison, WI, USA

Cell therapy for neurological diseases requires not only the replacement of diseased or lost cells but also the reconstruction or modification of the faulty circuit in order to restore the appropriate function. That necessitates the therapeutic products, often neural progenitors, to be (sub)type-specific with a high purity and a predictable differentiation outcome in vivo and the lack of unwanted neural types that may make aberrant connections in order to ensure efficacy and safety. The nature of the living cell products also demands a special formulation/packaging/delivery system to maximize the success in clinical operation. I will discuss these issues of preclinical preparation for cell therapy.
Keywords: Cell transplantation, Neurological disorders, Primate

10:30 AM – 11:00 AM

OFF THE SHELF TISSUE FOR CARTILAGE REPAIR

Craft, April M.

Orthopedic Surgery, Boston Children's Hospital, Boston, MA, USA

Orthopedic pain is a $54 billion dollar industry. Joint injuries and the associated progressive deterioration of the joint-lining articular cartilage and other connective tissues (commonly known as osteoarthritis) are highly prevalent across all demographics, affecting our ability to move our bodies and participate in activities of daily living without pain. Current therapies are inadequate. Here we will describe our preclinical approach to establish a novel, low-risk, cost-effective, single-step treatment for sustained cartilage repair derived from allogeneic stem cells. Replacement of damaged cartilage will restore joint function long-term, providing significant benefits for patients, their families, the clinicians and surgeons who treat them, and the overall healthcare industry.

Keywords: iPSCs, cartilage, large animal model

11:00 AM – 11:20 AM

REGENERATION IN INFARCTED RAT HEARTS BY HUMAN IPSC-DERIVED CARDIAC TISSUE WITH PATTERNED ENGINEERED VESSELS

Coulombe, Kareen L., Kant, Rajeev, Dwyer, Kiera

Engineering, Brown University, Providence, RI, USA

Cardiovascular disease is the leading cause of death globally. Despite therapeutic advances in cardiovascular health, there are patients who, after surviving a myocardial infarction (MI), are refractory to treatment options and progress into chronic heart failure (HF). Current research in heart regeneration using stem cell-derived cardiomyocytes (CMs) is accelerating as seen in large animal and human clinical trials; however, delivery of CMs by intramuscular injection or epicardially-implanted engineered cardiac tissues (ECTs) often fail to consider the need for a robust oxygen supply to ensure the engraftment and survival of cells in the harsh environment of the infarct. To this end, we have developed a remuscularization-revascularization therapy to regenerate the heart post-MI that is evaluated in a rodent model of ischemia-reperfusion myocardial infarction. Our work details the differentiation, expansion, and maturation of human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) using multi-stage biphasic Wnt signaling. ECTs are then formed by mixing hiPSC-CMs and 5% human primary cardiac fibroblasts into a collagen-1 hydrogel. Sacrificial gelatin-alginate fibers coated with endothelial cells are embedded in ECTs to pattern patent, arteriole-scale channels 400 µm in diameter. ECTs are cultured under dynamic perfusion conditions for two weeks prior to implantation to study inosculation, revascularization, and remuscularization of the heart. We quantitatively evaluate host vascular remodeling and origin-tracking of inosculated host vessels with implant vasculature using micro-CT based 3D vascular reconstructions. Ex vivo optical coherence tomography reveals capillary-scale vascular morphology in remote, infarct, and implant regions. Immunohistochemical staining shows robust engraftment of hiPSC-CMs and chimeric vascular ingrowth into implants that are persistent at 1 month after implant. Our remuscularization-revascularization therapy, featuring innovative approaches to study host-implant vascular inosculation and vascular remodeling, provides building blocks to enhance ECT function for future application as a regenerative therapy.

Funding Source

We gratefully acknowledge funding from NIH R01 HL135091 to KLC.

Keywords: remuscularization, inosculation, engineered cardiac tissue

11:45 AM – 12:45 PM
SPONSORED INNOVATION SHOWCASE

Presented by: STEMCELL Technologies

11:45 AM – 12:45 PM

DIFFERENTIATION TO MEGAKARYOCYTES TO SUPPORT TRANSLATIONAL RESEARCH AND SCALABLE EXPANSION OF HUMAN PLURIPOTENT STEM CELLS IN SUSPENSION CULTURE

Jervis, Eric

STEMCELL Technologies, BC, Canada

In this showcase, we will highlight two human pluripotent stem cells (hPSCs) technologies: the scale of up hPSC aggregate culture, and the differentiation of hPSCs to generate megakaryocytes (MKs) for platelet production. TeSR™ 3D fed-batch-based media products have been developed for efficient and scalable suspension culture of hPSCs as aggregates. Cell expansion experiments to 500 mL in vertical wheel bioreactors were conducted using multiple human embryonic and induced pluripotent stem cell lines. TeSR™ 3D media formulations and protocols routinely enabled greater than 1.5- to 1.9-fold expansion per day (cell line dependent), > 85% viability, > 90% expression of OCT4 and TRA-1-60, the capacity to differentiate to three germ layers, and normal karyotypes. The STEMdiff Megakaryocyte Differentiation Kit is a feeder- and serum-free culture system that promotes differentiation of hPSCs from multiple cell lines into polyploid MKs. This differentiation occurs in two stages: a 12-day endothelial-to-hematopoietic transition, and a 5-day MK maturation step that results in the production of polyploid MKs capable of generating platelets. Together, these technologies offer an attractive method for expanding hPSC-derived MKs for translational research.

1:00 PM – 2:30 PM SELECTING YOUR CELL LINE: DERIVATION AND CHARACTERIZATION

Sponsored by: ElevateBio

1:00 PM – 1:30 PM
TRANSLATIONAL SUCCESS: MINDING YOUR P'S AND Q'S

Ludwig, Tenneille

WiCell Stem Cell Bank, WiCell Research Institute, Madison, WI, USA

As more groups work to translate discoveries, it is clear that even the best research can be waylaid by issues that have little to nothing to do with the science. Careful selection of cell lines and initial characterization can make the difference between a successful project, and one that is doomed before it even begins. This talk will focus specifically on cell line selection, and the provenance, patent, procurement, paperwork and quality issues that must be considered to avoid significant pitfalls and ultimate regulatory failure.

Keywords: cGMP, translation, cell line selection

1:30 PM – 2:00 PM
REGULATORY CONSIDERATIONS FOR GENETICALLY-ENGINEERED, INDUCED PLURIPOTENT STEM-CELL DERIVED ALLOGENEIC CELL THERAPIES: A PROPOSED RISK-BASED APPROACH FOR ADDRESSING CHEMISTRY, MANUFACTURING, AND CONTROLS

Dashnau, Jennifer L.

Analytical Development & Quality Control, Century Therapeutics, Philadelphia, PA, USA

Advances in a number of key technologies related to cellular reprogramming and gene editing have enabled a new class of products based on genetically-engineered, induced pluripotent stem-cell derived cell therapies, which have the potential to treat a wide range of diseases. As the processes for developing these therapies have rapidly evolved, regulatory considerations for their derivation and characterization are slowly forming. Leveraging existing concepts for biotechnological products along with emerging guidance for autologous and donor-derived cell and gene therapies, a risk-based approach for chemistry, manufacturing, and controls is presented to address the unique considerations for this class of therapies associated with donor selection, cell line derivation, master cell banking and characterization.

Keywords: CMC, donor selection, cell line derivation, master cell banking, characterization, regulatory

2:00 PM – 2:30 PM
GENETIC AND EPIGENETIC CHARACTERIZATION OF HUMAN PLURIPOTENT STEM CELLS

Benvenisty, Nissim

Department of Genetics, Hebrew University, Israel

Human pluripotent stem cells (hPSCs) are being increasingly utilized worldwide in investigating human development, in modeling human disorders, as well as a source for cellular therapy. Yet, since the first isolation of human embryonic stem cells (hESCs), followed by the successful reprogramming of human-induced pluripotent stem cells (hiPSCs), various studies shed light on genetic and epigenetic abnormalities that sometimes accumulate in these cells in vitro. It is well established that alongside their immense potential, hPSCs undergo culture adaptations that can result in genetic aberrations including recurrent chromosomal abnormalities. Some of these aberrations correspond to abnormalities found in human tumors. hPSCs were also shown to carry point mutations. Specifically, recurrent point mutations in TP53 have been demonstrated in hPSCs by both whole-exome sequencing (WES) and by analysis of RNA-seq data. These mutations were shown to gradually take over the culture, suggesting that they provide a powerful selective advantage to the cells. hPSCs were also demonstrated to acquire mutations in other cancer-related genes, although in much lower frequency. In addition to genetic aberrations, epigenetic alterations can also occur as a result of culture adaptations. These include alterations in DNA methylation patterns, parental imprinting, and X chromosome inactivation. These aberrations may depend on the origin of hPSCs and have distinct consequences for their use. Various methodologies can identify genetic and epigenetic aberrations, and a routine quality control of hPSCs may be critical for both basic research and clinical applications.

Keywords: Human pluripotent stem cells Genetics Epigenetics

2:50 PM – 4:20 PM
WHAT IS IN YOUR PRODUCT?

2:50 PM – 3:20 PM
CMC CONSIDERATIONS FOR PLURIPOTENT STEM CELL DERIVED PRODUCTS: FDA PERSPECTIVES

Hursh, Deborah

US Food and Drug Administration, USA

Dr. Hursh will outline US FDA regulatory expectations for chemistry, manufacturing and controls (product quality) for regenerative medicine products derived from pluripotent stem cells

Keywords: US FDA, regulatory, cell therapy

3:20 PM – 3:50 PM
FT819 AND FT596: FIRST-OF-KIND OFF-THE-SHELF CAR19 T-CELL AND NK CELLS FOR B CELL MALIGNANCIES

Valamehr, Bob

Research & Development, Fate Therapeutics, Inc, CA, USA

The use of induced pluripotent stem cells (iPSCs) to derive immune effector cells offers distinct advantages for immune therapy over existing patient- or donor- derived platforms, not only in terms of scalable manufacturing and precision genetic engineering at the clonal level, but also in allowing the generation of multiple effector cell types each with distinct characteristics. Taking cues from the natural propagation of innate to adaptive effector responses, here I describe the development of both FT596 and FT819 multi-engineered iPSC-derived chimeric antigen receptor (CAR) natural killer (iNK) and T (iT) cells, respectively, in order to exploit the unique properties of each cell type to achieve both depth and durability of response for hematological malignancies. As innate cells, NK cells are characterized by the capacity for spontaneous reactivity, either in response to cell surface antigen or downregulation of class I MHC, and the rapid kinetic under which NK cells operate make them an ideal candidate to achieve a depth of response that outpaces the limiting effects of cytokine support. FT596 was developed as a dual-targeted iNK cell platform engineered to express both a CD19-directed, NK cell-optimized (NKG2D-2B4-CD3ζ) CAR and a high-affinity, non-cleavable Fc receptor (hnCD16), enabling multi-targeting through combination with therapeutic antibodies. The activity of each receptor is further enhanced by the expression of an IL15-IL15Ra fusion receptor, which also allows the cells to expand in the absence of exogenous cytokine support and prolongs cell survival in vitro and in vivo. T cells are exquisitely specific and undergo rapid clonal expansion and differentiation in response to target antigen, and antigen driven persistence has been demonstrated as a key determinant in efficacy in primary CAR-T cell immune therapy. FT819 is an iT cell platform engineered to express a functionally optimized CD19-CAR (1XX) that has been genome edited into the T cell receptor (TCR) alpha constant (TRAC) locus to provide ideal CAR activity and to prevent TCR expression, thereby avoiding the complications of GVH reactivity in an allogeneic setting.

Keywords: CAR T cells, NK cells, induced pluripotent stem cells, cancer immunotherapy

3:50 PM – 4:20 PM
ANALYTICAL DEVELOPMENT STRATEGIES FOR EARLY-STAGE CELL THERAPY PRODUCT CHARACTERIZATION

Keightley, Angela

Assay Development, BlueRock Therapeutics, Canada

Product characterization is key to successful cell therapy development and analytical methods are essential tools throughout the product development life cycle. But how do we identify critical analytics in early-stage process development that can be leveraged to develop robust downstream quality control tests? Examples will illustrate how new analytical techniques, such as single-cell multi-omics, combined with novel bioinformatic approaches have been successfully used to develop pipelines for Critical Quality Attribute discovery in early-stage bioprocess to generate a deeper understanding of product quality and derive control strategies to improve product manufacturing.

Keywords: analytical development, quality attribute, cell therapy

FRIDAY, 18 NOVEMBER

All sessions will take place in Grand Ballroom Salons 1-3

8:00 AM – 9:00 AM
SPONSORED INNOVATION SHOWCASE

Presented by: MaxWell Biosystems

8:00 AM – 9:00 PM

NEXT-GENERATION IN-VITRO ASSAYS: CHARACTERIZING THE ACTIVITY OF HUMAN IPSC-DERIVED NEURONS IN 2D AND 3D CULTURES AT HIGH RESOLUTION*

Obien, Marie[1], Sundberg, Maria[2], Pak, Chang Hui[3], McSweeney, Danny[4]

[1]MaxWell Biosystems, Switzerland, [2]Boston Children's Hospital, MA, USA, [3]University of Massachusetts, MA, USA, [4]University of Massachusetts-Amherst, MA, USA

Both 2D and 3D brain models derived from human induced pluripotent stems cells (hiPSCs) are emerging as promising tools for investigating brain development and disease progression, as well as to test drug toxicity and efficacy in-vitro. In order to adopt hiPSC-derived 2D and 3D neuronal networks for rapid and cost-effective phenotype characterization and drug screening, it is necessary to assess their cell type composition, gene expression patterns, and physiological function.

In this innovation showcase, our invited speakers will showcase studies where MaxWell Biosystems' advanced high-density microelectrode arrays (HD-MEAs) as the core of easy-to-use platforms, MaxOne (single-well) and MaxTwo (multi-well), allowed to capture neuronal activity across multiple scales, from sub-cellular to single cells, up to full networks and facilitated the characterization of the neuronal activity of hiPSC-derived neurons. During this session speakers will introduce how brain development disorders are modeled in 2D and 3D in-vitro.
Overall, the presentations will provide an overview on how HD-MEA technology can efficiently advance research in 2D and 3D hiPSC-derived brain models and accelerate drug discovery for neurodegenerative diseases.
*This Innovation Showcase will be available in-person and on the virtual meeting platform.

9:30 AM – 11:40 AM
NEW TECHNOLOGIES/WHERE ARE WE GOING?

9:30 AM –10:00 AM

DEVELOPING AUTOLOGOUS IPS CELL THERAPY FOR MACULAR DEGENERATION: FROM BENCH-TO-BEDSIDE

Bharti, Kapil

National Institutes of Health, Bethesda, MD, USA

Induced pluripotent stem cells (iPSCs) can provide autologous and allogeneic replacement tissues, potentially for all degenerative diseases. Autologous tissues offer the advantage of not requiring immune-suppressive drugs that may cause severe side-effects. However, feasibility of autologous iPSC-based therapies hasn't been established. Here, we developed an autologous iPSC-based therapy for age-related macular degeneration (AMD), a blinding eye disease that affects over 30 million people world-wide. AMD is caused by the progressive degeneration of retinal pigment epithelium (RPE), a monolayer tissue that maintains photoreceptor function and survival. Combining developmental biology with tissue engineering we developed clinical-grade iPSC-derived RPE-patch on a biodegradable scaffold. This patch performs key RPE functions like photoreceptor phagocytosis, water transport, and polarized cytokine secretion. We confirmed the safety of this patch in an immune-compromised rat model and confirmed its efficacy in a swine RPE injury model. A phase I/IIa Investigational New Drug (IND)-application for iPSC-derived ocular tissue to treat AMD was recently cleared by the FDA. This Phase I/IIa clinical trial will test safety, feasibility, and integration of an autologous iPSC-derived RPE-patch in twelve advanced AMD patients. This work is helping leverage other similar autologous cell therapies in various other degenerative diseases.
Keywords: iPS cell, cell therapies, autologous cell therapy, eye disorders

10:00 AM – 10:30 AM
SIGNALING DYNAMICS DURING T-CELL DEVELOPMENT FROM PLURIPOTENT STEM CELLS

Zandstra, Peter

School of Biomedical Engineering, University of British Columbia, Canada

T-cells have showed promising efficacy as cellular therapeutics. However, obtaining primary T-cells from human donors is expensive and variable. Pluripotent stem cells (PSCs) have the potential to provide a renewable source of T cells, but differentiating PSCs into hematopoietic progenitors with T-cell potential remains an important challenge. We are using bioengineering and synthetic biology strategies to engineer control of notch and TCR signaling dynamics during T-cell development. This is revealing insights into key decision points during T-cell development, and enabling the production of different T-cell types using efficient and chemically defined strategies.
Keywords: T-cells, pluripotent stem cells, Notch, Bioengineering

10:30 AM – 11:00 AM
LEVERAGING AUTOMATION AND AI TO STREAMLINE IPSC PRODUCTION AND RESEARCH

Kim, Howard

Cell Therapy Programs, New York Stem Cell Foundation Research Institute, New York, NY, USA

In order to successfully model complex genetic diseases with induced pluripotent stem cells (iPSCs), the capability for generating and handling multiple (tens to hundreds) of lines in parallel is essential, in a reproducible manner that enables subtle biological signals to be detected above technical noise. To meet this need, we developed the NYSCF Global Stem Cell Array®, a fully automated robotic platform integrating liquid handlers, robotic arms, automated imagers, and other peripheral devices. Across several 'clusters' of instruments, we have developed automated workflows capable of iPSC reprogramming, expansion, and differentiation, with the ability to handle multiple cell lines and media formulations in parallel. Custom software tracks all data through our system, from donor information to method parameters to cell doubling times. Our goal has been, and remains, to develop novel infrastructure to perform stem cell biology at a population scale, such that we may ask questions that cannot be answered with small sample sizes. In establishing these platforms, we have been able to transfer much of our basic knowledge into a therapeutic setting. We have recently established GMP facilities within the NYSCF Research Institute where we are currently developing clinically relevant cell lines. Here we will present recent progress in the development of our automated research platform, our progress in combining it with artificial intelligence and our work in progressing toward a clinical trial.
Keywords: iPSC, Automation, Deep Learning, AI, Manufacturing

11:00 AM – 11:20 AM
FROM 50 MILLION TO 15 BILLION HUMAN IPS CELLS WITHIN A WEEK : HIGHLY REPRODUCIBLE EXPONENTIAL IPS EXPANSION IN 10L BIOREACTORS WITH MAINTENANCE OF CELL QUALITY

Alessandri, Kévin[1], Becheau, Odette[1], Luquet, Elisa[2], Pletenka, Justine[2], De Marco, Maelle[2], Jamet, Emilie[2], Wurtz, Helene[2], Cohen, Philippe[3], Moncaubeig, Fabien[1], Lanero Fidalgo, Michael[2], Alessandri, Kevin[4], Feyeux, Maxime[1]

[1]Research & Development, TreeFrog Therapeutics, Pessac, France, [2]Process Development, TreeFrog Therapeutics, Pessac, France, [3]Research & Development, TreeFrog Therapeutics, Imagine Institute, Pessac, France, [4]TreeFrog Therapeutics, Pessac, France

2D cell culture has been widely used to manufacture the first generation of cell therapies. However, due to the drawbacks of scale-out processes (footprint, workforce use, variability and subsequent QC expenses), the industry is shifting towards the goldstandard for bioproduction scale-up, i.e. bioreactors, with the goal of addressing mass-markets with standardized and affordable products. The main format in bioreactor culture is aggregates. Aggregate culture has demonstrated a number of limitations, including scalability challenges, mostly due to mixing conditions and the associated shear stress, severely impacting yields and quality. So far, only a few teams have publicly shared results showing the successful cultivation of pluripotent stem cells in large-scale bioreactors. One notable recent achievement by Huang et al. (2020) is the production of a batch of 37 billion human induced pluripotent stem cells (hiPSC) in a 10L bioreactor in 6 days, with an amplification factor of 40-fold. Here using new C-Stem™ technology based on a high-speed cell encapsulation microfluidics, we report the production of two single batches of 15 billion hiPSCs in 10L bioreactors with an unprecedented 276-fold amplification within a week. Data demonstrates high-reproducibility and maintenance of best-in-class cell viability and pluripotency. Also documenting the scale-independent amplification profile obtained with C-Stem™ in 30mL, 500mL, 1.5L and 10L bioreactors, we argue that the C-Stem™ technology is amenable to produce commercial-size batches of stem cells in larger bioreactors.
Funding Source
Cell Therapy
Keywords: 3D Cell Culture, Cell Therapy, Bioreactor

11:20 AM – 11:40 AM

ONE BILLION CELLS: ENGINEERING CARDIAC TISSUE WITH HUMAN INDUCED PLURIPOTENT STEM CELL DERIVED CARDIOMYOCYTES FOR THERAPEUTIC IMPACT

Dwyer, Kiera, Coulombe, Kareen L.K.

Engineering, Brown University, Providence, RI, USA

It is estimated that 1 billion cardiomyocytes are killed during a myocardial infarction (MI). Ongoing work in the field of cardiac regenerative engineering is aimed at developing strategies to restore both cellular and functional loss from MI. Delivery of cardiomyocytes derived from human embryonic or human induced pluripotent stem cells (hiPSC-CMs) through engineered tissue or intramuscular injection after such injury has emerged as a promising means to stabilize cardiac function. Delivery of CMs through epicardially-implanted engineered cardiac tissues (ECTs) is especially advantageous as increased CM maturity, improved engraftment and increased mechanical support of the cardiac wall have been reported as compared to intramuscular CM injection, and new data suggests lower incidence of arrhythmia. To date, however, a lack of rigorous studies exploring the biomanufacturing design space for clinical translation of ECTs poses an immense hurdle to their use in translation. To this end, we are focused on understanding how scaling up ECTs in size, CM number and density, and matrix density impact the electromechanical function of the tissue. Our work details the differentiation and proliferative expansion of hiPSC-CMs to achieve the quantity and quality of hiPSC-CMs required for clinically scaled ECTs. We fabricate ECTs by mixing hiPSC-CMs with 5% human cardiac fibroblasts in a collagen-1 hydrogel with electromechanical function assessed through optical mapping of action potentials and tensile mechanical testing. We report compromised electromechanical function and structural organization of ECTs with scale up in size alone. Because such tissues must deliver enough CMs to have a therapeutic impact, we explore increasing cell density in ECTs, reporting decreased compaction during formation (6-fold increase, assessed by cross-sectional area), elastic modulus (20-fold decrease) and active stress generation (6.5-fold decrease) with increasing cell density from 5M/mL to 50M/mL. By understanding the design space and functional changes, this work supports the translational feasibility of using hiPSC-CMs within ECTs as a regenerative treatment to remuscularize the failing heart.

Funding Source

We gratefully acknowledge funding from NIH R01 HL135091, NIH CPVB IDeA-COBRE P20 GM103652, NSF-GRFP, and Brown University.

Keywords: engineered tissue, cardiomyocytes, preclinical

11:50 AM – 12:50 PM
SPONSORED INNOVATION SHOWCASE

Presented by: Pluristyx, Inc.

11:50 AM – 12:50 PM

MANUFACTURING THE NEXT GENERATION OF PLURIPOTENT STEM CELL-BASED THERAPIES*

Hawkins, Brian

Pluristyx, Inc., WA, USA

Pluripotent stem cells promise to revolutionize future medicine by eliminating or replacing organs, tissues, and cells compromised by disease or old age. Unfortunately, the timeframe to realize these medical advances is currently decades due to the complexity and inherent variability required to expand stem cells into sufficient numbers before every development or manufacturing run. Bringing these future medicines to current reality requires the elimination of just-in-time manufacturing and the transformation of stem cells from an artisan craft into a highly qualified raw material. When available as a raw material, pluripotent stem cells in a Ready-to-Differentiate® format should be primed for differentiation to eliminate unnecessary cell manipulation and expansion and enable on-demand and reproducible product development and production. This presentation will introduce the audience to the challenges associated with pluripotent stem cell-based therapies, and discuss how Pluristyx provides solutions to tackle these challenges during commercial development.

*This Innovation Showcase will be available in-person and on the virtual meeting platform.

1:00 PM – 2:30 PM
IMMUNOLOGY FOR CELL THERAPIES

1:00 PM – 1:30 PM
EPIGENETIC ENGINEERING OF IPSC-DERIVED T CELLS

Jing, Ran

Stem Cell Program, Harvard Medical School/Boston Children's Hospital, Boston, MA, USA

Adoptive T cell therapy holds great promise for the treatment of immune deficiency, viral infection, autoimmunity, and cancer. However, the broader application has been impeded by the cumbersome, labor-intensive protocols for engineering autologous patient-specific cells. Human induced pluripotent stem cells (iPSCs) represent an appealing source for scalable manufacture for cell therapy, which when coupled to strategies for immune matching or cloaking, could represent "off-the-shelf" products. Prior studies have engineered iPSC-derived T cells with chimeric antigen receptors (CAR) and shown proof-of-principle for cancer immunotherapy, however, iPSC-derived T cells are not as robustly functional as mature peripheral blood T cells. Here we discuss how epigenetic reprogramming strategies could be used to facilitate the production of mature, functional CAR T cells from iPSCs.
Keywords: CAR T cell therapy, iPSC, epigenetic, cell engineering

1:30 PM – 2:00 PM
ENGINEERING OF ALLOGENEIC DONOR CELLS FOR ACCEPTANCE BY THE HOST'S IMMUNE SYSTEM

Schrepfer, Sonja

Surgery and Genomic Immunology, Sana Biotechnology Inc. and University of California, San Francisco, CA, USA

To address the challenge of allogeneic immune recognition and cell death, our team turned to the field of fetal maternal tolerance. During pregnancy, the maternal immune system is tolerant of allogeneic paternal antigens through a series of multiple complex changes that have evolved over time and occur during placental implantation and early embryonic development. The Schrepfer lab examined syncytiotrophoblast cells which form the interface between maternal blood and fetal tissue and attempted to identify pathways and factors that are critical for immune tolerance. Over the course of a decade and multiple experiments, the lab uncovered that modification of HLA class I and II expression and overexpression of CD47 were important genetic modifications to evade immune recognition. CD47, a membrane protein that interacts with signal regulatory protein-alpha (SIRPa) on innate immune cells, is a key for evasion of innate immune cells, including NK cells and macrophages which can immediately kill implanted cells (J Exp Med 2021;218(3):e20200839). It was recognized that this combination of genetic modifications might support allogeneic transplantation without the need for immunosuppression and enable a new class of therapies. This concept was illustrated in several publications involving hypoimmune induced pluripotent stem cells (mouse, NHP, and human) which were differentiated into multiple cell types for in vivo transplantation studies (e.g. Nat Biotechnol 2019;37(3):252-258 and Proc Natl Acad Sci U S A 2021;118(28):e2022091118).
Keywords: allogeneic transplantation, immune evasion, hypoimmune, induced pluripotent stem cells, immune hurdle

2:00 PM – 2:30 PM
DEVELOPMENT OF IPSC-DERIVED FUNCTIONAL LYMPHOCYTES FOR IMMUNE CELL THERAPY

Kaneko, Shin

Center for iPS Cell Research and Application, Kyoto University, Japan

Due to their unlimited proliferative capacity and multidifferentiation ability into all cell types in our body, iPS cells are expected to be a cell source for regenerative immunotherapy. Since the essence of iPS cell generation is epigenetic reprogramming, we had focused on the fact that genomic reset to germline sequence does not occur in this process and successfully rejuvenated antigen-specific CD8 killer T cells through pluripotency reprogramming and redifferentiation. We further revealed that antigen-specific TCR gene modified CD8 killer T cells can be induced from non-T cell-derived iPS cells with desired TCR transduction, in addition, additional antigen specificity could be conferred also with CAR gene transfer to iPS/iPS-T cells. On the other hand, in the course of iPS-T cell development, it also became clear that innate lymphoid cells such as NK cells could be induced not passing through CD4/CD8 double positive T cells. In this talk, I would like to introduce the characteristics of CD8 killer T cells and NK cells regenerated from iPS cells and our attempts to apply those immune cells for clinical use.
Keywords: iPS cells, T cells, NK cells, antigen-specific, immunotherapy

3:00 PM – 4:30 PM
BALANCING SCIENCE AND REGULATORY REQUIREMENTS IN EMERGING FIELDS

Sponsored by: ***Cellino***

3:00 PM – 3:30 PM
STEM-PD TRIAL: CLINICAL TRIAL DESIGN AND REGULATORY CHALLENGES

Paul-Visse, Gesine

Neurology, Lund University and Skånes University Hospital, Sweden

We are currently preparing to perform a multicentre, single arm, dose escalation, first in human advanced therapy investigational medicinal product (ATiMP) trial investigating the safety and tolerability of intraputamenal transplantation of human embryonic stem cell derived dopaminergic cells for Parkinson's disease (STEM-PD product) in Sweden. The trial is performed at Skånes University Hospital in Lund in collaboration with Lund University, Cambridge University, UK and Cambridge University Hospital. In this talk we will present the clinical trial design and highlight ethical and regulatory challenges on the path to clinical implementation.
Keywords: Clinical trial, study design, Parkinson's disease

3:30 PM – 4:00 PM
SCALEABLE, SAFE, AND EFFECTIVE GENETICALLY-CORRECTED TISSUE MANUFACTURING AND DELIVERY

Oro, Anthony[1], Wernig, Marius[2], Neumayer, Gernot[2], Torkelson, Jessica[2], McCarthy, Kelly[2], Zhen, Hanson[2], Tang, Jean[2], Vangipuram, Madhuri[2], Jackow, Joanna[2], Christiano, Angela[2], Rami, Avina[2]

[1]Program in Epithelial Biology and Department of Dermatology, Stanford University School of Medicine, Stanford, CA, USA, [2]Stanford University School of Medicine, CA, USA

Despite the promise of Induced pluripotent stem cells (iPSCs) for treatment of human genetic disease, critical process development, regulatory, and delivery roadblocks have hampered development and clinical application of genetically-corrected tissue therapies. Here We have developed Dystrophic Epidermolysis Bullosa Cell Therapy (DEBCT), a GMP-compatible, reproducible and scalable platform to produce autologous clinical grade iPSC-derived tissue stem cells to treat the incurable wounds of patients lacking type VII collagen (C7). In my presentation, I will identify several of the roadblocks and discuss how process development innovation led to current solutions that can be applied to the development of other cell based therapies.
Keywords: Epidermolysis bullosa, induced pluripotent cell, CRISPR technology

4:00 PM – 4:30 PM
DEVELOPING PLURIPOTENT STEM CELL-DERIVED THERAPIES

Carpenter, Melissa

ElevateBio, MA, USA

Abstract not available at time of printing.

SATURDAY, 19 NOVEMBER

All sessions will take place in Grand Ballroom Salons 1-3

8:00 AM – 9:00 AM
SPONSORED INNOVATION SHOWCASE

Presented by: Astellas Institute for Regenerative Medicine

8:00 AM – 9:00 PM

CANCER CELL THERAPY AT ASTELLAS

Starling, Gary[1], Yuraszeck, Carlos[2]

[1]Xyphos, an Astellas Company, CA, USA, [2]Astellas Institute for Regenerative Medicine, MA, USA

The over-arching goal of the Astellas Immuno-Oncology strategy is to deliver curative treatment options for patients with cancer, specifically for the majority of patients who do not respond to currently available immunotherapies. There are two key elements to our strategy. First, is the development of a cell therapy platform technology at Xyphos (an Astellas company) known as ACCEL (Advanced Cellular Control through Engineered Ligands) which consists of a convertible chimeric antigen receptor (cCAR) targeted to cancer cells using a modified monoclonal antibody (MicAbody). Preclinical data using transduced normal donor T cells shows activity in a range of cancer types. The second element is the creation of our Universal Donor Cells platform, derived from engineered iPSC at Universal Cells (an Astellas company), that can be used to create a wide range of allogeneic cell types. Combining the ACCEL platform with iPSC-derived cytotoxic cells may enable a flexible, off-the-shelf therapy for patients of many cancer types. Finally, to enable clinical production of these therapies, Astellas has invested in a state-of-the-art cell manufacturing facility within the Astellas Institute for Regenerative Medicine.

9:30 AM – 11:00 AM
IMMUNOLOGY FOR CELL THERAPIES

9:30 AM – 10:00 AM

RETINAL CELL THERAPY AS A SUSTAINABLE CATEGORIZE MEDICINE

Takahashi, Masayo

Vision Care Inc. Kobe, Japan

Our goal is to develop an outer retinal layer cell therapy using iPS cells. First in 2014, we performed autologous iPS-derived retinal pigment epithelium (RPE) cell transplantation to demonstrate the safe use of iPS cells. In an allogeneic transplantation clinical study from 2017, we confirmed that the immune response to transplanted cells can be controlled by topical steroids alone if HLA mismatch is avoided, that lead us to the HLA partial KO iPS cells. Currently, we expanded our target diseases to RPE impaired diseases to understand the categories of diseases for phase 2 clinical study. In terms of cell manipulation, we are using a humanoid robot to ensure true validation of cell culture not only equipment The next challenge is photoreceptor replacement. iPSC-retinal organoid transplantation was conducted for two cases of retinitis pigmentosa with the POC in the animal models such as, (1) maturation of grafted retinal sheets, (2) synapse formation with host secondary neurons, (3) electrophysiological response to light, and (4) The blinded mice could response to light stimuli in the behavior test after transplantation. We are currently counting the number of synapses and preparing the next generation of retinal sheets to increase it. Based on these experiences, we believe that we should prepare therapies for each category of outer retinal diseases. In addition, since replacement therapies are surgical treatments, there is a gap between the end product and the treatment that does not exist in drug development. Therefore, for an ideal treatment, we need to rstrictly select the right cases for each therapy and work with clinical teams to improve surgical techniques. Otherwise, cell therapy will become an expensive gamble. I will talk about the current status and future vision of retinal cell therapy.

Keywords: RPE, photoreceptor, patient selection

10:00 AM – 10:30 AM

DEVELOPMENT OF MANUFACTURING PROCESSES FOR PLURIPOTENT CELL BASED THERAPIES: CONSIDERATIONS FOR ACCELERATED APPROVAL PATHWAYS

Lebkowski, Jane S.

Regenerative Patch Technologies, Menlo Park, CA, USA

There are numerous considerations that must be addressed in the manufacturing of a stem cell-based therapy. These key points range from: 1) the starting materials, reagents, process, and facility used to manufacture the therapeutic cells, 2) the procedures to characterize the composition, functionality, stability, and adventitious agent profile for release of the therapeutic product, 3) determination of the delivery devices, dose, and route of administration and 4) the scale and costs of manufacturing that can allow cost coverage by healthcare providers. Specific therapeutic designs must be conceptualized and advanced by scientists, engineers, and physicians during the development of a cell-based therapy to ensure that manufacturing, safety, clinical and other needs are addressed to provide a safe, efficacious, and cost-effective product to patients. This presentation will address these key considerations in manufacturing of a stem cell-based therapy and will include specific case study examples. Special manufacturing development considerations with respect to accelerated approval pathways will be discussed.

Keywords: stem cells, manufacturing, accelerated approval

10:30 AM – 11:00 AM

EU AND UK ACCELERATED APPROVAL PATHWAYS

Barry, Jacqueline

Cell and Gene Therapy Catapult, UK

Key regulatory challenges for developing Advanced Therapy Medicinal Products in the EU and UK. The registration process for ATMP in Europe (EU & UK) spans several legislative domains; Tissues and Cells, Gene Modified Organisms, Clinical Trial and Medicinal Product. This can add to complexity and cost to the registration process for these products. This talk will cover practical aspects of registering ATMP for clinical trial and marketing Authorisation in Europe including a discussion of the accelerated pathways available to developers.

Keywords: Regulation, Accelerated, Europe

11:15 AM – 12:15 PM
SPONSORED INNOVATION SHOWCASE

Presented by: ARMI | BioFabUSA

11:15 AM – 12:15 PM

PAVING THE ROAD TO TRANSLATION THROUGH SCALABLE, MODULAR, AUTOMATED AND CLOSED MANUFACTURING

Bollenbach, Thomas[1], Hogrebe, Nathaniel[2], McCorry, Mary Clare[1], McFarland, Richard[1]

[1]ARMI | BioFabUSA, NH, USA, [2]Washington University in St. Louis, MO, USA

Decades of fundamental regenerative medicine research has laid the technical foundations for a revolution in medicine. However, that revolution continues to lie just around the corner due mainly to challenges associated with manufacturing. The mission of the BioFabUSA program is to make practical the scalable, consistent and cost-effective manufacturing of cells, tissues and organs through a strategic investment from the Department of Defense and collaborations with nearly 180 members from industry, academic, not-for-profit institutions and government. This community is driving the field towards scalable, modular, automated and closed (SMAC) manufacturing systems, which are being successfully prototyped in the context of diverse tissue types (e.g., ligament, pancreatic islets) demonstrating their generalizability. SMAC system capabilities are being augmented through technology development, including novel non-destructive sensors, rapid chemically-defined media formulation and new types of preservation methods. These systems are also supported through the institute's deep tissue characterization core, which facilitates big data-driven Quality by Design process development for scalability and GMP-readiness. Given the regulatory expectations inherent in translating innovative scientific concepts into safe and effective therapies for routine clinical use, BioFabUSA complements its technology development activities with a robust regulatory program that spans both specific projects and strategic priorities. Regulatory projects include regulatory consulting for members' product developments and a public private partnership (PPP) agreement with CBER, which is paving the way to smoother regulatory pathways for all complex advanced therapies. These advanced concepts will be presented in the context of a case study.

12:30 PM – 2:00 PM
DELIVERING YOUR CELL PRODUCT: STRATEGIES FOR SUCCESS

Sponsored by: Vertex Pharmaceuticals

12:30 PM – 1:00 PM

HUMAN IPSC-DERIVED CARDIAC PROGENITOR CELLS FOR MYOCARDIAL REPAIR

Kamp, Timothy J.

Medicine, University of Wisconsin, Madison, WI, USA

Introduction: iPSC-derived committed cardiac progenitor cells (CCPs) have potential to remuscularize infarcted myocardium; however, little is known about the ability of CCPs to engraft and differentiate. We hypothesized that transendocardial injection of CCPs with an injectable cardiac fibroblast derived extracellular matrix (cECM) retention agent would result in cardiac tissue grafts in an immunosuppressed porcine ischemic heart failure model. Methods: Coronary artery balloon-occlusion myocardial infarction was induced in 48 Yucatan mini-swine. After 1 month, 200M CCPs with and without 50 mg ECM particles were delivered in 15 intramyocardial injections to the border zone and infarct zone using a steerable Myostar injection catheter with NOGA XP mapping. Immunosuppressed swine were sacrificed up to 2 months following treatment. Histopathology, continuous ECG recording, cardiac MRI, and P-V analyses were performed. Results: Human grafts were identified using Ku80+ human cell specific antibody and human-specific mitochondrial antibody. Immunolabeling for cardiomyocyte-specific and endothelial-specific markers showed that CCPs differentiated primarily into TnI-positive cardiomyocytes and to a lesser extent endothelial cells. Cardiac MRI following one month treatment did not show a significant change in EF or infarct size, but pressure-volume loop analysis demonstrated that CCPs with or without cECM improved dobutamine-induced functional reserve. No procedural complications and no significant ventricular arrhythmias were observed, but 10 animals were terminated due to opportunistic infections and sepsis. Conclusions: Intramyocardial injection of CCPs in an ischemic failing porcine heart resulted in engraftment and differentiation of CCPs to generate grafts containing human cardiomyocytes and endothelial cells. After one month there was evidence for an improvement in cardiac functional reserve without evidence of ventricular arrhythmias.

Funding Source

NIH Regenerative Medicine Innovation Program

Keywords: IPS cells, cardiac progenitor cells, myocardial infarction, cardiac regeneration

1:00 PM – 1:30 PM

PHASE I/II CLINICAL INVESTIGATION OF HUMAN INHIBITORY NEURON CELL THERAPY FOR CHRONIC FOCAL EPILEPSY

Nicholas, Cory R.

Neurona Therapeutics, South San Francisco, CA, USA

Drug-resistant seizures represent a significant unmet medical need for more than one-third of people diagnosed with epilepsy. Surgical resection or ablation of the seizure focus can be an option for chronic focal-onset epilepsy, however, these surgeries are destructive to surrounding tissue, can cause serious adverse cognitive effects, and many patients are not eligible. Alternative non-destructive therapeutic options are needed, and we have developed a human inhibitory neuron candidate, NRTX-1001, to potentially provide a regenerative cell therapy option. NRTX-1001 is derived from human pluripotent stem cells and comprises GABAergic inhibitory neurons of a specific pallial interneuron lineage, and specific post-mitotic, migratory stage. An investigational new drug (IND) application was recently cleared by the FDA to allow a phase I/II clinical trial (NCT05135091) of NRTX-1001 for drug-resistant temporal lobe epilepsy (TLE). We will discuss the IND-enabling preclinical data package, including the molecular and functional criteria used to release three lots of cGMP clinical product, definitive safety and efficacy data, and the intracerebral cell delivery strategy. We will also present early data from the first-in-human clinical trial.

Keywords: Epilepsy, GABA, Interneuron

1:30 PM – 2:00 PM
CLOSING KEYNOTE

1:30 PM – 2:00 PM

THE REGULATORY FRAMEWORK FOR CELLULAR THERAPIES IN THE UNITED STATES

Marks, Peter

Center for Biologics Evaluation and Research, US Food and Drug Administration, Silver Spring, MD, USA

Cellular therapies are regulated as biologic products by the U.S. Food and Drug Administration (FDA). There are two major classes of cellular therapies: those that require premarket authorization and those that do not. Pluripotent stem cells generally fall into the former category. Establishing a well defined, high quality manufacturing process is critical for success, and integral to such manufacturing is the development of critical quality attributes, and whenever possible, a potency assay, in order to insure consistency of product manufacture over time. FDA has several different programs to help developers advance their products through the development process.

Keywords: cellular therapies, regulation, critical quality attributes

Poster Abstracts

THURSDAY, 17 NOVEMBER

Poster Session I – ODD
4:30 PM – 5:15 PM

CHARACTERIZATION OF THE FINAL CELL PRODUCT

101

INDUCED PLURIPOTENT STEM CELL DERIVED HUMAN PRIMARY ASTROCYTES ROBUSTLY EXPRESS CANONICAL WNT/B-CATENIN PATHWAY

Shetty, Amogh[1], Narasipura, Srinivasa[2], Shull, Tanner[2], Zayas, Janet[2], Al-harthi, Lena[2]

[1]Pathogens and Immunity, Rush University Medical Center and Illinois Mathematics and Science Academy, Chicago, IL, USA, [2]Pathogens and Immunity, Rush University Medical Center, Chicago, IL, USA

Astrocytes are one of the most abundant cell types in the central nervous system (CNS), important for regulating glutamate uptake, immunoinflammatory response, permeability of the blood brain barrier, and neuronal health. In the past, astrocytes were mainly sourced from adult deceased brains, gliomas, aborted human fetal tissues, and mice/rat brains. However, such sources can be difficult to access and can pose limitations due to lack of biological relevance and legal implications. Recently, hiPSCs (human induced pluripotent stem cells) were successfully demonstrated to differentiate into induced astrocytes (iAs), which have become an important tool in studying astrocyte biology and function. The Wnt/β-catenin pathway is an important pro-survival that is robustly expressed in primary astrocytes and regulates vital functions such as glutamate uptake, immunoinflammatory response, and viral transcription in all types of astrocytes. However, this pathway is not yet characterized in iAs. Here, by using multiple approaches, such as RT-qPCR, Western blot, and TOPflash reporter assay, we show that 1) Tumor CFs/LEF, the downstream transcription factors of the pathway are present in abundance at mRNA level 2) β-catenin, the central mediator of the pathway is robustly detected at protein level and can be significantly induced in the presence of CHIR99021 (CHIR: an agonist of the pathway) and 3) The pathway is highly active and can be significantly induced in the presence of CHIR. Finally, by employing the CRISPR/Cas9 approach we successfully knocked out β-catenin in the iAs, which was confirmed through western blot, TOPflash reporter assay, and Sanger sequencing. Our study not only establishes the iAs robust expression of the Wnt/beta-catenin pathway, but also helps to assess the functional aspects of this pathway in these biologically relevant central nervous system cell types.
Keywords: induced astrocytes, Wnt/β-catenin pathway, CHIR99021

IMMUNOLOGY FOR CELL THERAPIES

103

ENABLING ALLOGENEIC T CELL-BASED THERAPIES: SCALABLE STIRRED-TANK BIOREACTOR MEDIATED MANUFACTURING

Gatla, Himavanth[1], Bennun, Inbar[2], Levinson, Yonatan[2], Ramaswamy, Senthil[2], Sargent, Alex[2], Uth, Nicholas[2]

[1]Cell and Gene Therapy, Lonza, Gaithersburg, MD, USA, [2]Cell and Gene Therapy, Lonza, Rockville, MD, USA

Allogeneic T cells are key immune therapeutic cells to fight cancer and other clinical indications. High T cell dose per patient and increasing patient numbers result in a clinical demand for large number of allogeneic T cells. This necessitates a manufacturing platform that can be scaled-up, while retaining cell quality. Here we present a closed and scalable platform for T cell manufacturing to meet clinical demand. Upstream manufacturing steps of T cell activation and expansion are done in-vessel, in a stirred-tank bioreactor. T cell selection, which is necessary for CAR-T based therapy, is done in the bioreactor itself, thus maintaining optimal culture conditions through the selection step. Platform's attributes of automation and performing the steps of T cell activation, expansion and selection in-vessel, greatly contribute to enhancing process control, cell quality, and to reduction of manual labor and contamination risk. In addition, the viability of integrating a closed, automated, downstream process of cell concentration, is demonstrated. The presented T cell manufacturing platform has scale up capabilities, while preserving key factors of cell quality and process control. This platform could be applied, in principle, not only to donor-derived T cells, but to T cells derived from Pluripotent stem cells (PSCs), facilitating the enabling of "off-the-shelf" PSC-derived cell therapy.
Keywords: T cell manufacturing, bioreactors, CAR T cells

NEW TECHNOLOGIES FOR CELL THERAPY

105

SMALL MOLECULE-MEDIATED GENERATION OF A MULTIPOTENT REPROGRAMMING INTERMEDIATE FROM FORESKIN FIBROBLASTS

Singh, Rishabh D.[1], Kim, Kyeong[2]

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Direct conversion of fibroblasts to induced pluripotent stem cells (iPSCs) using a set of four transcription factors (TFs) opened a new avenue of research in patient-specific regenerative medicine, disease modelling and drug discovery. However, the low reprogramming efficiency and remarkably slow process have called attention to the study of underlying molecular players. Mechanistic studies have highlighted the involvement of key developmental regulators which are indispensable for the generation of reprogramming intermediate preceding iPSCs formation. Here, we demonstrate the use of a chemical cocktail to generate a multipotent intermediate stage from foreskin fibroblasts. Using the cocktail, we have targeted a set of signalling pathways well known to regulate the developmental regulators involved during embryonic development. The treatment of human foreskin fibroblasts with this cocktail for a specific time period generates a reprogramming intermediate which upon exposure to different reprogramming media, can generate cells from three germ layers. The intermediate stage is characterized by an extensive epigenetic remodelling permissive for the activation of gene regulatory networks governing different lineages. Our chemical approach provides a platform to understand both, the molecular players which impart plasticity during reprogramming, and lineage-specific barriers resulting in varying efficiencies. This study demonstrates the use of a chemical cocktail for a rapid and efficient generation of cells from three germ layers bypassing a pluripotent stage which can be used for multiple therapeutic applications.

Keywords: Small molecules, Direct reprogramming, Development regulators

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CDX2 CELLS FOR CARDIOVASCULAR REGENERATION

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Inadequate renewal of adult human cardiomyocytes and the subsequent inability of the heart to repair itself explains, in large part, the extensive morbidity and mortality of heart disease. Development of novel strategies for cell therapies is critical for cardiac regeneration. We previously demonstrated that murine end-gestation placentas contain multipotent Cdx2 cells of trophoblast lineage capable of cardiac repair. These cells displayed unique homing ability to the sites of cardiac injury and regenerated injured myocardium. Since trophoblast-mediated placentation is a conserved phenomenon, our current study is a translational approach for novel therapeutic development. Here we show that human term placenta harbors CDX2-expressing cells and these cells may be uniquely poised for cardiogenesis. Using a multiparametric approach including transcript analysis and sanger sequencing, immunoblot and immunofluorescence analysis, and with subsequent screening of different anatomical sites, we demonstrated that CDX2 is present in the chorionic (fetal cytotrophoblast) portion of human term placentas. We used a CDX2 promoter driven lentiviral vector, expressing mCherry fluorescence, to isolate viable CDX2mCherry cells from the chorion. These cells co-expressed HLA-G and cytokeratin-7 confirming trophoblast progenitor identity. Ultra-low input RNA sequencing in comparison with human embryonic stem cells (H9) revealed a downregulation of pluripotency markers and upregulation of genes for migration, mesodermal/cardiovascular commitment, and gene function that reflect low immune cell specificity. In subsequent experiments, we observed that CDX2mCherry cells generated beating organoids within a span of 5 days when cultured on neonatal cardiomyocyte feeders and later differentiated into cardiomyocytes expressing human α-sarcomeric actinin. In a similar approach, we show that CDX2mCherry cells gave rise to cells of endothelial lineage (vWillebrand Factor+) suggesting the potential of both cardiac and endothelial cell formation. Our study signifies the regenerative potential of human placental CDX2 cells and thus uncovers a novel and clinically viable cell source from healthy placentas that can be a potential target for cell-based approaches for cardiovascular regeneration.

Funding Source
NIH/NHLBI New York State Stem Cell Board
Keywords: Cell therapy, Novel placental cell source, cardiac regeneration

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TOWARDS SAFE CURATIVE THERAPIES FOR CHRONIC ENDOCRINE DISORDERS BY COMBINING STEM CELL ENGINEERING AND ENCAPSULATION TECHNOLOGY

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Current treatments for endocrine disorders such as type I diabetes increase the patient's quality of life but are usually not curative. Transplantation of stem cells holds the promise of curative therapy but requires evidence that stem cells can provide a safe source of insulin. To reduce the risk of immune rejection or aberrant growth of transplanted cells, we combined a safe source of stem cells with encapsulation technology. Ganciclovir eliminates proliferative human stem cells, reducing the risk of tumor formation. Encapsulation protects the transplanted cells from the immune system while still allowing the exchange of nutrients and hormones such as insulin. Defined stem cell clusters of less than 250mm in diameter survived within alginate capsules (1wt%) for at least six weeks in vitro. Their proliferation, however, was reduced compared to standard tissue culture conditions. Incorporating extracellular matrix molecules (ECM) such as fibronectin, vitronectin, or laminin increased proliferation; however, this caused cellular escape from uncoated capsules within a few days. To combat cellular escape, we reinforced the capsule surface with a strong, chemically cross-linked barrier that is not degradable and designed to avoid fibrotic responses in vivo. Coating the capsules sequentially with poly-L-lysine (PLL) and 50% hydrolyzed poly(methyl vinyl ether-alt-maleic anhydride, PM50) slowed or eliminated cellular escape, depending on the shell-former concentrations used. These shells have shown good persistence and immune evasion in C57BL/6 mouse models for empty and islet-containing capsules. The current data shows that it is vital to demonstrate the containment of strongly proliferative cells within capsules and that a cross-linked coating can reduce, if not eliminate, cellular escape. Together with the safe-cell line, this might be one way to provide curative treatments for people with chronic endocrine disorders, such as diabetes.

Keywords: Biomaterials, Pluripotent Stem Cells, Diabetes

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MULTI-LINEAGE LUNG REGENERATION BY STEM CELL TRANSPLANTATION ACROSS MAJOR GENETIC BARRIERS USING A SAFER CONDITIONING REGIMEN AND CLINICAL GRADE REAGENTS

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Respiratory diseases are among the leading causes of death worldwide, causing more than 9 million deaths per year. Although lung transplantation can offer a curative option for patients with end-stage respiratory disease, the difficulty of finding matched lung donors has led to an extensive search for alternative tissue sources for transplantation. Induction of lung regeneration by transplantation of lung progenitor cells is a critical preclinical challenge. Recently, we demonstrated that robust lung regeneration can be achieved if the endogenous host stem cell niches in the recipient's lung are vacated by sub-lethal preconditioning (Milman Krentsis et.al. 2018, Rosen et.al. 2015). However, overcoming MHC barriers is an additional requirement for clinical application of this attractive approach. More recently, we have demonstrated that durable tolerance towards mis-matched lung progenitors and their derivatives can be achieved without any need for chronic immune suppression, by virtue of co-transplantation with hematopoietic progenitors from the same donor. Initial proof of concept of this approach was attained by transplantation of fetal lung cells comprising both hematopoietic and non-hematopoietic progenitors. Furthermore, an even higher rate of blood (more than 80%) and epithelial lung chimerism (30.7±6.4% of lung area was occupied by donor derived cells) was attained by using adult lung cells (8*106) supplemented with bone marrow hematopoietic progenitors (25*106) (Hillel et. al. 2020). Furthermore, very recently using this approach for tolerance induction in lung stem cell transplantation, we have defined the minimal levels of irradiation combined with other non-myeloablative clinical grade agents that can allow safer conditioning prior to transplantation of lung and hematopoietic progenitors. These include T cell debulking with anti CD4 and anti-CD8 antibodies, 2 GY TBI and cyclophosphamide. These results lay the foundation for repair of lung diseases, such as IPF and COPD, through a simple procedure akin to allogeneic bone marrow transplantation.

Keywords: Lung, Transplantation, Allogeneic

PRECLINICAL STRATEGIES

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OPTIMIZATION OF A LARGE-SCALE PRODUCTION METHOD FOR THE 2D-EXPANSION OF HUMAN PLURIPOTENT STEM CELLS IN CGMP ANIMAL ORIGIN-FREE CULTURE MEDIUM AND COMPATIBILITY WITH STEMDIFF PROTOCOLS

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Successful transition of human pluripotent stem cell (hPSC)-based therapies to the clinic is reliant on demonstrating safety of the cell product and of the components in contact with the product throughout the manufacturing process. In addition, efficient expansion of hPSCs is critical for applications requiring a large number of high-quality cells for production of cell banks and directed differentiation. The development of large-scale multilayer tissue culture plastics and stabilized hPSC maintenance media have led to improved methods for 2D expansion of hPSCs. We have an optimized protocol for the expansion of hPSCs in a 10-layer cell factory using TeSR™-AOF. TeSR™-AOF is manufactured under relevant cGMPs, developed with animal-free raw materials with traceability to at least the secondary level of manufacturing, and was optimized to improve plating efficiency and expansion of hPSCs compared to low-protein formulations. Typically, plating efficiency in TeSR™-AOF was enhanced by 27.1 ± 4.71% (mean ± STDEV; n = 3 cell lines); however, in select hPSC lines with historically low plating efficiency in low-protein media formulations, the plating efficiency was improved by 80 to 140% (n = 2 cell lines) in TeSR™-AOF. To assess the regenerative potential and differentiation efficiency of hPSCs maintained in TeSR™-AOF, we assessed compatibility with several clinically-relevant directed differentiation protocols. hPSCs expanded in TeSR™-AOF efficiently differentiated to megakaryocytes using the STEMdiff™ Megakaryocyte Differentiation Kit, with 79.2 ± 5.76% CD41+/CD42+ double-positive cells (n = 2 cell lines), and into natural killer cells using the STEMdiff™ NK Cell Kit, with 89.9 ± 7.63% CD56+ cells (n = 2 cell lines). In summary, TeSR™-AOF was designed with quality and safety in mind, and formulated to improve attachment efficiency, consistency, and reproducibility. TeSR™-AOF enables versatile workflows and efficient scale-up to support high-quality hPSCs in large-scale long-term culture.

Keywords: Scale-up, scale-out, animal-free

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THE CROSSTALK BETWEEN CAMP, MAPK, WNT/Β-CATENIN SIGNALING, SHH SIGNALING, AND RETINOIC ACID SIGNALING PATHWAYS IN DIFFERENTIATION OF STEM CELLS INTO NEURONS

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Neurons derived from stem cells have attained serious eminence in research and regenerative medicine. In the last few decades, stem cells' potential to differentiate into functional neurons has been well explored. Though the potentiality of stem cells to be transformed into neurons has been proved, there is still no universal protocol for the same. As reported in various studies, the differentiation process involves activation/deactivation of several signaling pathways, but there isn't any study to our knowledge that explores the integration or crosstalk between those significant pathways. The lack of computational studies in this area points out the uncertainty and exhaustiveness of cell culture experiments and addresses the gap that needs to be fulfilled if one wants to successfully differentiate stem cells into functional neurons. This study has selected five major pathways viz. cAMP, MAPK, Wnt/β-catenin signaling, Sonic Hedgehog (SHH) Signaling, and Retinoic acid signaling based on their significance in neuronal differentiation. These pathways were studied and integrated to explore the crosstalk mechanism between them to create a slight impact towards the approach of the researches intended towards neuronal differentiation. The insilico research of the intricate orchestration of various signaling pathways involved in stem cell differentiation will be helpful in designing and standardizing the protocols for in-vitro differentiation experiments more efficiently.

Funding Source

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Keywords: Signaling pathways crosstalk, Neurons, Stem cells differentiation

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CRISPR PERTURBATION IN IPSC-DERIVED HUMAN HEPATIC STELLATE CELLS REVEALS ROLE FOR TNF-DRIVEN INTERFERON RESPONSE IN CHRONIC LIVER DISEASE

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Activation of hepatic stellate cells (HSC) by inflammatory cytokines plays a central role in the progression of fibrosis. We aimed to: (i) define the interplay between NF-kappa-B and TGF-beta pathways using iPSC-derived hepatic stellate cells (iHSCs); and (ii) discover insights that align with non-alcoholic steatohepatitis (NASH) progression. We developed an iHSC model that showed evidence of cellular maturation and extracellular matrix production. We used Cas9-engineered cells and 400 guide RNAs to execute pooled optical screening in human cells (POSH); and single-cell RNA-seq to analyze cytokine-treated iHSCs. To characterize NASH phenotypes, we used 4,641 whole-slide images of liver biopsies from multiple trials. We trained deep convolutional neural networks (CNN) to predict histological features [Casale et al, EASL 2020]. RNA-seq was performed on matched samples. For each clinical endpoint, we assessed the (multiple-hypothesis corrected) enrichment of TNFa and IL1b response genes at multiple cutoffs using GSEA (using the gseapy prerank module). We identified genes critical for TNFa and IL1b-mediated activation of NF-kappa-B p65 response in iHSCs. Molecular characterization of gene expression changes demonstrated that NF-kappa-B induces type I interferon response genes in iHSCs, constituting a distinct activation state as compared to TGF-b. Supporting the disease relevance of these signatures, we observed that TNFa and IL1b signatures were enriched for genes associated with the CNN fibrosis stage and progression, as well as the serum fibrosis biomarker ELF score at FDR 5%. This work constitutes an advancement above the state-of-the-art methodology, with optimized protocols and cell lines for genetic editing of iHSCs. Notably, this constituted the first time that POSH with image-based phenotyping has been achieved in iPSC derived cells. These studies also revealed a model of cytokine-driven fibrosis that aligned with clinical histological and biomarker features of NASH progression. Finally, we highlight the identification of NF-kappa-B p65 induced type I interferon in iHSCs. These results provide insights that will support the development of new therapeutic approaches for NASH.

Keywords: iPSC-derived Stellate Cells, CRISPR, Liver Disease

SELECTING YOUR CELL LINE: DERIVATION AND CHARACTERIZATION

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ROLE OF STORE OPERATED CALCIUM ENTRY (SOCE) IN HUMAN INDUCED PLURIPOTENT STEM CELL LINE FROM AN AUTOSOMAL RECESSIVE PARKINSON'S DISEASE PATIENT WITH A HOMOZYGOUS PLA2G6 -C.2222G>A (P. ARG741GLN) MUTATION

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c.2222G>A (p. Arg741Gln) accounts for the majority of the PLA2g6-Parkinsonism in India. We describe the generation and characterization of a human-induced pluripotent stem cell (hiPSC) from a young (20-year-old) PD patient with a homozygous c.2222G>A (p. Arg741Gln) mutation and unaffected non-symptomatic familial control with the mutation in a monoallelic condition. The patient born out of consanguineous parentage presented with history of catatonia in the form of reduced speech output, reduced oral intake, immobility and rigidity. Exome sequencing and correlation with the clinical symptoms confirmed him to be suffering from Parkinson disease 14 (PARK14). An integration-free feeder-free approach using episomal nucleofection of the Yamanaka factors was used to derive iPSC lines from the peripheral blood mononuclear cells of the patient and mother. The new generated lines were positive for pluripotency markers, could be further differentiated to cells expressing all trilineage markers, and presented a normal karyotype. PLA2g6 is thought to play

an important role in the activation of endogenous store-operated Ca2+ entry (SOCE), an ER-driven intracellular Ca2+ signaling pathway. Since iPSCs faithfully mirror the patient's genetic background, we used this control and patient-derived iPSCs to study basal calcium levels and SOCE induced by ER-depletion with Thapsigargin (Tg). In parallel, we also used CRISPR-edited PLA2G6 mutant line and its isogenic control to look at overlapping phenotypes between the patient-derived and genome edited hiPSC lines. These patient derived iPSC lines provide new avenues by serving as a scalable source for generating NPCs and dopaminergic neurons with the relevant PD-associated mutations. Further, changes in SOCE ensuing the disease pathology in ARPD can be investigated systematically in the neural cell type of interest.

Funding Source

This work was supported by the DBT/Wellcome Trust India Alliance Early Career Fellowship [IA/E/18/1/504319] awarded to the presenting author, Dr. Renjitha Gopurappilly.

Keywords: Parkinson's disease, PLA2G6, Disease modeling

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ELECTROPHYSIOLOGICAL PHENOTYPE CHARACTERIZATION OF HEALTHY AND DISEASED HUMAN IPSC-DERIVED MOTOR NEURONS BY MEANS OF HIGH-DENSITY MICROELECTRODE ARRAYS

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Induced pluripotent stem cell (iPSC) technology has increasingly made it easier to access human neurons for in-vitro studies. Additionally, the study of neurodegenerative diseases benefited from the combination of iPSC and gene editing technologies: the diseases can now be modelled with human neurons, and the mechanisms behind these pathologies can be analysed. In parallel, high-density microelectrode arrays (HD-MEAs) have become more widely used to non-invasively record extracellular activity of iPSC-derived neurons in vitro over weeks at unprecedented spatiotemporal resolution. In this work, we combined both HD-MEA and iPSC technologies to study the functional phenotype and development of a human motor neuron line modelling amyotrophic lateral sclerosis (ALS) and its respective isogenic healthy line. We used an HD-MEA platform featuring 26'400 electrodes to explore the network, single-cell and subcellular-resolution electrophysiology metrics, such as network-burst properties, neuronal firing rate, and axonal conduction velocity. The two iPSC lines showed significant differences in network characteristics such as network burst duration, frequency, and shape, and in neuronal firing rate. Additionally, we extracted axonal features of the motor neurons and quantified functional and morphological metrics in a label-free approach. In summary, this work demonstrates that the combination of iPSC and HD-MEA technologies allows to successfully characterise healthy and diseased motor neurons and to identify their phenotypical differences. The presented methodology can potentially be utilised as a screening platform in the early phases of drug discovery for neurodegenerative diseases, such as ALS.

Funding Source

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Keywords: microelectrode arrays, iPSC, electrophysiology

Poster Session II – EVEN
5:45 PM – 6:30 PM

CHARACTERIZATION OF THE FINAL CELL PRODUCT

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A TRADE-OFF BETWEEN SYNAPTOGENESIS AND ASTROGLIAL CONTENT IN HUMAN TELENCEPHALIC BRAIN ORGANOIDS BALANCED BY EXTRINSIC FACTORS IN CULTURE MEDIA

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Brain organoids derived from human pluripotent stem cells (hPSCs) have remarkable and evolving utility in the modeling of CNS disease biology and functional assessments of therapeutic candidates.Many prior studies have demonstrated synapse formation and functional synaptic connectivity in brain organoids that in general mirrors human brain development. However, there is a lack of systematic analyses on how organoid culture conditions may affect synapse formation. Here we present assessments of multiple extrinsic factors in culture media as independent variables that may affect synapse formation

in organoids. The use of dissolved matrigel impaired expression of synaptic proteins and resulted in increase of GFAP expressing cells. Furthermore, the use of NeurobasalPlus/B-27Plus media during organoid maturation resulted in fewer axons and dendrites and increase of GFAP expressing cells. The mixture of Neurobasal:DMEMF12 media, with or without subsequent switch to BrainPhys medium were shown to better support the development of pre- and post-synaptic compartments and axon-dendritic network among the experimental conditions assessed.
Keywords: Brain organoids, Synapses, axons and dendrites

NEW TECHNOLOGIES FOR CELL THERAPY

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IPSC MANUFACTURING FOR THE FIRST AUTOLOGOUS IPSC-DERIVED THERAPEUTIC PRODUCT TRANSPLANTED IN THE USA

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Human iPSCs are an unprecedented cell source for regenerative medicine therapeutics, especially for autologous cell therapy products. However, the manufacturing process should be efficient, reproducible, and cGMP-compliant with the appropriate quality check (QC) assays to meet the critical quality attributes (CQAs) of the transplant. Using the iPSC technology, the surgeons at the National Eye Institute (NEI) have successfully transplanted the first patient in the USA with an autologous cell therapy product, the retinal pigment epithelium (RPE)-patch, for a patient with advanced-stage geographic atrophy (GA) of the eye. For the autologous therapy product manufacturing, from a starting sample of ~100 mL of patient blood, CD34+ cells were isolated, expanded, and reprogrammed using episomal OriP/EBNA1-based plasmids expressing reprogramming transcription factors. Twelve iPSC clones were generated and continued up to iPSC passage 10, at which they underwent a battery of QC tests, including purity assay, karyotyping assay, plasmid loss assay, oncogene panel sequencing, sterility & mycoplasma tests, endotoxin test, and HLA & STR identity tests. Based on the QC assays results, three best iPSC clones were selected for further differentiation to mature RPE on a biodegradable polymer scaffold sheet which was transplanted into the GA patient's eye after meeting FDA-approved release specifications for viability, morphology tests, identity tests, purity, absence of iPSCs, sterility & mycoplasma tests, and endotoxin assay. Here, we describe our defined cGMP-compliant manufacturing process permitted by the FDA, as it was used for this patient product manufacturing with focus on reprogramming, generation, and selection of iPSC clones.
Keywords: clinical cGMP iPSC, RPE, National Eye Institute

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TRANSPLANTATION OF HUMAN INDUCED PLURIPOTENT STEM CELL (IPSC)-DERIVED NEURAL PROGENITOR CELLS (NPC) PROVIDE NEUROPROTECTION IN A RAT MODEL OF PARKINSON'S DISEASE

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Repacement of lost or damaged dopaminergic neurons leading to restoration of brain function is the final goal of cell replacement strategies for Parkinson's Disease (PD). However, there are several challenges associated with such approaches. On the other hand, unique abilities of Neural Progenitor Cells (NPC) to generate different neural and glial cell types, release trophic factors and cause immunomodulation are considered favourable for their application in the treatment of PD. Our study explores the neuroprotective role of Induced Pluripotent Stem Cells (iPSC)- derived NPCs in restoring pre-motor and motor functions in 1-methyl- 4-phenyl-1,2,3,6-tetrahydroperidine (MPTP) induced chronic rat PD model. First, we designed an efficient and scalable method to produce NPCs from hiPSCs via dual SMAD and Wnt inhibition using small molecules. De novo generated NPCs were characterized for identity and purity by immunochemistry, flow cytometry, RNA sequencing and RT-PCR. Post intra-nasal instillation of freeze-thawed NPCs in diseased rats, behavioural studies comprising of olfactory discrimination, motor-coordination (rotarod) & locomotor activity (actimeter) were carried out and dopamine levels was measured by dopamine release assay. Homing and retention of NPCs in the different compartments of the brain and other organs were analysed by Near Infra Red (NIR) imaging and immunohistochemistry to understand biodistribution. Taken together, our results indicate that iPSC-derived NPCs exhibit all the key markers and are potentially effective in alleviating the symptoms of PD in MPTP induced rats without any safety concerns.
Keywords: Neural progenitor cells (NPCs), MPTP-rat model, Parkinson's Disease (PD)

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NOVEL RNA VIRAL VECTORS CONTROL MYOGENIC DIFFERENTIATION IN MOUSE EMBRYONIC STEM CELLS BY A SMALL MOLECULE

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Regulation of transgene expression in vertebrate cells without genomic insertion has many applications in regenerative medicine. Vesicular stomatitis virus (VSV) is a cytoplasmic RNA virus that replicates without a DNA intermediate; therefore does not integrate into the host chromosome. Previously, a VSV vector equipped with a guanine-responsive riboswitch was shown to regulate transgene expression in BHK-21 cells reversibly. In this study, introduction of several mutations in the VSV genome, including two newly found ones (+a and mL), allowed its stable replication in mouse embryonic stem cells (ESCs) as indicated by fluorescent reporter gene expression while maintaining pluripotency. Moreover, the reporter gene expression diminished as the differentiation progressed through embryoid body formation, suggesting the possibility of spontaneous viral vector removal upon differentiation. To apply the novel VSV vector for stem cell differentiation, a differentiation factor (MyoD) and a selection marker (PuroR) were incorporated into the vector. Mouse ESCs infected with the vector were cultured in the presence of guanine and puromycin to suppress the transgene expression. Seven days of induction of MyoD expression by removing guanine resulted in significant upregulation of the endogenous myogenic differentiation markers (myogenin and MHC) accompanied by a morphological change typical of myocytes. On the other hand, differentiation into myogenic lineage was suppressed in the cells cultured in the presence of guanine. In conclusion, the novel VSV vectors allow genetically-induced stem cell differentiation without chromosomal alteration in a scalable manner.

Funding Source

The research was funded by Okinawa Institute of Science and Technology Graduate University and Japan Society for the Promotion of Science (JSPS) KAKENHI grants 20K15669 and 19H02855.

Keywords: embryonic stem cells, riboswitch, RNA virus

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OPTIMISING THE PROCESS DEVELOPMENT PROTOCOLS FOR PROMOTING HIGHEST VIABILITY GROWTH OF IPSC'S DURING SINGLE-CELL CLONING

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The potential of Human Induced Pluripotent Stem Cells (iPSC's) in the allogeneic treatment of many disease types has grown considerably over the past 5 years. Optimisation of iPSC's at the single-cell cloning stage can provide a high yield of healthy and stable clones, essential for cell banks providing high quality patient material for cell therapies. We will present data on the optimisation of iPSC single-cell cloning, focusing on time-efficiency and the production of straightforward single-cell standard operating procedures using GMP-compatible reagents. Further, we will elaborate on the benefits of single-cell seeding, whole well imaging and clone documentation of iPSC's on the VIPS instrument to streamline your iPSC workflows.

Keywords: GMP-compatible, Cell therapy, Single-cell cloning

PRECLINICAL STRATEGIES

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PRECLINICAL SAFETY AND LONG-TERM SURVIVAL OF HUMAN IPSC-DERIVED CARDIOMYOCYTES SUPPORTING CLINICAL TRIALS IN THE TREATMENT OF UNIVENTRICULAR CONGENITAL HEART DISEASE

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Univentricular heart (UVH) disease is a complex congenital heart disorder and the survival of high-risk patients with this disease after staged palliation is highly reduced. Currently, no viable long-term treatment option for patients with cardiac failure, other than heart transplantation. The induced pluripotent stem cell studies have advanced rapidly with cell-based therapies and are now advancing to therapeutic application. Recent studies demonstrated that h-iPSC-derived cardiomyocytes offer functional benefits to damaged hearts in non-human primates. However, the question remains about the low-graft survival of the transplanted cells,

the risk of arrhythmia, and the tumorigenic potential of residual human pluripotent cells present in the final product. To address this safety concern, we have performed randomized, controlled studies, and under-blinded labels with staggered dosing cohorts in humanized mice for facilitating patient safety in clinical application. Male and female NOD-scid mice were randomly distributed in equal numbers to receive a single dose of human iPSC-derived cardiac lineage (iPSC-CL) or cardiomyocyte media for the vehicle control group without cells. An intracardiac injection was performed through an epicardial approach at a dose of 3 million cells/animal via 4 injections of 20 ul each. In addition, we determined the impurities in the cell product's tumorigenic potential using an intracardiac injection, we spiked iPSC-CL with 1% and 10% with day 0 undifferentiated iPSCs. During the 1, 4, and 9-month follow-up period, daily cage-side observation , arrhythmia, mortality, body weight changes, tumorigenicity, and terminal hematological and blood chemistry parameters were recorded. The treated mice were sacrificed and subsequently performed for cell graft formation and biodistribution studies. Results demonstrate iPSC-CL achieved enhanced survival of human cells and long-term engraftment within the myocardium, no sign of tumor formation, and no significant risk factors such as arrhythmia. The ability of bioengineered cardiac lineage to long-term survival in the myocardium, and the maturation of cardiomyocytes make them a promising safe therapeutic cardiovascular cell product to repair damaged heart muscles in patients with chronic heart failure.

Funding Source
Todd and Karen Wanek Family Program for Hypoplastic Left Heart Syndrome (HLHS)
Keywords: iPSC-derived cardiomyocytes, Congenital heart disorder, Univentricular heart disease

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MACHINE LEARNING METHODS FOR DETAILED CHARACTERIZATION OF TGFB-INDUCED SIGNATURES IN A LARGE IPSC-DERIVED HEPATIC STELLATE CELL COHORT

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Activation of hepatic stellate cells (HSCs) by TGF-beta plays a key role in fibrotic changes in Non-Alcoholic Steatohepatitis (NASH). We aimed to establish a screenable system for identification of anti-fibrotic targets in activated HSCs. This required the development of a machine learning (ML) framework which was used to characterize a cohort of control and NASH iPSC-HSCs (iHSCs). We differentiated iHSCs from 56 iPSC lines and characterized them using high content imaging and single cell (sc) RNA-seq. For ML image analysis, we derived a deep learning method that was tasked with producing informative featurizations of segmented cell images, followed by covariate correction. Transcriptomic datasets were featurized using a state-of-the-art archetypal analysis. Using each of our transcriptomic and imaging datasets separately, we quantified three quality metrics for iHSCs: (i) predictiveness of TGF-beta response in an ML classifier trained on pHSCs as ground truth; (ii) separation between TGF-beta and DMSO in an unsupervised ML model; (iii) similarity of the overall cell state distribution between iHSCs and pHSCs. The established ML framework provided informative featurizations of cellular data and allowed for correction of experimental artifacts. We showed robustness of TGF-beta-induced ML phenotype in pHSCs in both modalities (mean AUC 0.96 for out-of-line assessment in imaging; mean AUC 0.98 in transcriptomics). Interpretation of ML phenotypes revealed insights into the TGF-beta responsiveness of pHSCs, allowing use of multi-parametric criteria to evaluate the cohort of iHSCs. We observed a strong correlation between transcriptomic and imaging characterizations used for the ranking of iHSC lines (spearman = 0.66, p = 8.7 * 10-5). In summary, we developed a state-of-the-art approach for the characterization of HSC morphological and transcriptional phenotypes. Using the developed framework, we successfully modeled TGF-beta-induced activation signatures in HSCs. These image-based phenotypic assays paired with high-performance ML models present unique opportunities for genetic and chemical screens and the discovery of novel fibrosis targets.

Keywords: Machine Learning, iPSC-derived hepatic liver cells, Liver Disease

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FUNCTIONAL HUMAN IPSC-DERIVED THYMIC EPITHELIAL PROGENITOR CELLS RECONSTITUTE T CELL DEVELOPMENT AND FUNCTION IN AN IN VIVO MODEL OF THYMIC APLASIA

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The thymus is an essential primary lymphoid organ in which T cells mature and proliferate. In the thymus, specialized thymic epithelial cells (TECs) select a broad and self-tolerant T cell receptor repertoire. During aging, thymic involution leads to immune senescence. There is no evidence of thymic stem cells that could contribute to thymus regeneration throughout life. Genetic forms of complete thymic aplasia lead to severe T cell immunodeficiency and are fatal unless immune reconstitution is achieved by allogeneic thymus transplantation (ATT). Shortage of donor tissue and lack of HLA-matching limits the use of ATT. Thymic injury can also occur from conditioning medications, irradiation and/or graft-versus-host disease (GVHD) after hematopoietic stem cell transplantation. This compromises T cell immune reconstitution leading to poor outcomes. Thus, there is a critically unmet need to provide regenerative thymic tissues for any patient with thymic insufficiency. Using various iPSC-lines (tissue source, donor age and sex), we have developed a robust in vitro TEC differentiation protocol that sequentially induces all stages of human thymic ontogeny including bipotent third pharyngeal pouch endoderm (PPE), ventral PPE, and thymic epithelial progenitor cells (TEPCs). iPSC-derived TEPCs (iTEPCs) express key markers of TEC fate and function: FOXN1, PAX1, PAX9, and HLA-DR. Upon transplantation into humanized (hCD34+ HSCs engrafted) athymic NSG mice (NSG Foxn1null), iTEPCs promote human T cell development with physiologic CD4:CD8 ratio and native and memory phenotypes. Similar levels of T cells are found in mice that receive human fetal thymus transplants, while T cells are not detected in athymic NSG mice without thymus graft. Mice receiving iTEPCs show no clinical signs of autoimmunity or GVHD. In vivo matured iTEPCs grafts show robust protein expression of FOXN1, PAX1, PAX9, DLL4, PSMB11 and CD205 protein comparable to primary thymus grafts. Our protocol reliably produces functional iTEPCs that support T cell differentiation in vivo. We anticipate that iPSC-derived, HLA-matched TEPCs will offer a clinically safer thymic replacement therapy alternative that will benefit a larger cohort of patients, i.e. HSCT recipients, and elderly populations in addition to those with congenital thymic aplasia.

Funding Source
CIRM Grant (California Institute of Regenerative Medicine), Philanthropic Funding

Keywords: Thymic epithelial cells, iPSC-derived cells, T cell immune reconstitution

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ASSESSING CONTRACTILITY OF 3D IPSC-DERIVED MUSCLE MODELS FOR SAFETY AND DISCOVERY USING A NOVEL, HIGH-THROUGHPUT, AND LABEL-FREE INSTRUMENTATION PLATFORM

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Stem cell models hold promise for improving the predictive power of preclinical in vitro assays for new therapies, drug discovery, basic research, and disease modeling. 3D Engineered Muscle Tissues (EMTs) fabricated from primary or iPSC-derived cells can directly measure tissue contractility, a challenge in conventional 2D platforms where cells are rigidly attached to a surface. However, traditional methods to fabricate EMTs demand extensive bioengineering expertise and measuring contractility often involves laborious and low-throughput optical measurements. Here, we report on the design, fabrication, and validation of a novel 3D EMT platform that uses 1) facile and scalable bioengineering approaches to generate tissues from a variety of cell sources, and 2) a label-free parallel measurement technique. Our tissue casting approach has a success rate of >96% (n > 100) and produces consistently-sized constructs with a standard deviation of +/- 9% across 6 experiments. The substrate features an embedded magnet; as tissues contract, the magnet's displacement is quantitatively detected in a highly-parallel manner using specialized sensors. The simultaneous detection of contractility in 24 tissues is measured at a rate of 100Hz, which is suitable for capturing various aspects of contraction, such as upstroke velocity, decay time, and fatigue. Engineered cardiac tissues show acute and chronic effects of toxicants like doxorubicin, sunitinib, and BMS-986094. Chronically-dosed tissues show statistically significant dose-dependent reduction in twitch frequency over a multi-day time course ($p < 0.05$). We will also show that our platform can be used to generate physiologically-relevant skeletal muscle constructs capable of achieving tetanic responses upon stimulation. In addition to modeling healthy tissue, we are developing patient-specific models, e.g. Duchenne Muscular Dystrophy, for the testing of personalized gene therapies. In summary, we have designed a novel system that can leverage the complexity of 3D cellular models in a scalable format and can be tailored for specific applications. The platform will provide a stand-alone tool capable of screening significant numbers of compounds for the rapid safety evaluation of drug candidates, thereby accelerating drug discovery and development.

Keywords: 3D Organoids, 3D Engineered Muscle Tissues, High-throughput

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REPRESENTATIVE DRUG PRODUCT FOR CELL THERAPIES USED IN NONCLINICAL STUDIES

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The US Code of Federal Regulations, FDA Guidance documents, ICH guidelines, and industry white papers were reviewed for information on general nonclinical program design and test material to be evaluated in investigational new drug-enabling nonclinical laboratory investigations. IND-enabling definitive/pivotal hybrid pharmacology/safety, biodistribution/toxicology, and tumorigenicity studies should be conducted with drug product that is representative of the product administered to the patient. It is expected each lot of drug product used in nonclinical in vitro and in vivo studies should be characterized according to phase-appropriate criteria. As product development continues and phase-appropriate manufacturing or formulations changes are implemented, it must be demonstrated these changes do not impact product quality such that product tested in nonclinical studies is no longer representative of clinical drug product. Demonstration of comparability can be particularly challenging for cell therapies where proof of concept and early nonclinical studies are conducted with material made in the research setting versus clinical product made in a GMP facility. Lack of comparability of the nonclinical study test material, to the clinical product, can limit the ability of the nonclinical data to support the design of an early clinical study and can lead to an FDA Information Request during IND review, which can become a clinical hold issue if not resolved properly. If comparability is not demonstrated, then additional in vitro and/or in vivo preclinical studies may be needed to bridge the two products. Therefore, in selecting the drug product to be used in nonclinical studies, to ensure the drug product tested will be representative of the clinical product it is recommended to take a risk-based approach when implementing changes, which should include consideration of cell source, material characteristics, and manufacturing processes in place.

Keywords: Representative material, comparability, Nonclinical

SELECTING YOUR CELL LINE: DERIVATION AND CHARACTERIZATION

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GENERATION AND CHARACTERIZATION OF SEX CHROMOSOME ANEUPLOIDY IPSC LINES

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Sex chromosome aneuploidies (SCAs) are genetic conditions defined by carriage of a sex chromosome dosage other than XX or XY. These conditions can increase risk for atypical brain development and represent models of genetic risk for psychopathology and naturally occurring models of sex chromosome dosage effects on the human brain. SCA effects on brain structure and function presumably reflect the downstream consequences of SCA effects on cellular phenotypes, although these cellular effects have proved hard to model in humans. As a path towards addressing this need, we have developed a library of induced pluripotent stem cell (iPSC) lines from SCA patients as a resource for in vitro modeling of cellular effects of SCA in humans. We recruited 27 participants, three individuals from the nine following sex chromosome dosage groups: XO, XX, XXX, XXXX, XY, XXY, XYY, XXYY, XXXXY. We obtained upper arm skin-punch biopsies to generate fibroblasts that were reprogramed into iPSCs by non-integrative Sendai virus method and OSKM transcription factor cocktail. These iPSCs were characterized to confirm their pluripotency, differentiation capacity, and genetic stability, while cell culture sterility was monitored. Pluripotency was confirmed by immunocytochemistry staining, flow cytometry analysis evaluated nuclear and surface pluripotency markers, and tested by Nanostring Pluripotency Scorecard assay. Differentiation capacity into the three germ layers was determined by Nanostring 3 Germ Layer Scorecard Analysis. Expected aneuploidy of iPSC lines was confirmed by G-band karyotyping. Identity test by Fluidigm SNP Trace Panel confirmed the genetic origin of iPSC lines with their parental fibroblast cell lines. All iPSC lines were cultured about 20 passages and quantitative real-time polymerase chain reaction confirmed the absence of Sendai virus. Finally, the cell culture was screened for mycoplasma contamination. These 27 patient-derived iPSC aneuploidy lines are a valuable cellular bioresource. They serve as a cellular in vitro model to study the pathological mechanism of sex aneuploidy and a role of sex chromosome dosage in neurodevelopmental disorders. These iPSCs will be further differentiated into neural progenitor cells and various CNS cell types, and they will be used for downstream multi-omics studies.

Funding Source
National Institute of Mental Health Intramural Research Program

Keywords: iPSC, Aneuploidy, Characterization

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HUMAN GINGIVA DERIVED MESENCHYMAL STEM CELLS (GMSCS) EFFICIENTLY DIFFERENTIATE INTO MESODERMAL AND ECTODERMAL LINEAGES IRRESPECTIVE OF DONOR AGE

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In the past two decades, there has been significant advancement in stem cell research and regenerative medicine. Adult stem cell sources such as blood, bone marrow, dental pulp, and adipose tissue have been extensively studied with respect to their application in tissue engineering. Furthermore, mesenchymal stem cells (MSCs) gained extensive attention due to their high proliferative and self-renewal properties. Moreover, when required MSCs can be differentiated to a specific lineage. Despite such advancements in stem cell research, the well-researched sources of stem cells unveil certain limitations in terms of availability of large numbers of clinically competent MSCs and the inability of adult MSCs to differentiate into practically any cell type. Further, these MSCs gradually lose their differentiation potential either due to in vitro replicative senescence or due to progression in age of donor. In the past decade gingival tissue has emerged as a prominent new source of MSCs. It provides several advantages over the prevailing stem cell sources, that includes easy tissue harvesting and faster healing of donor site. Further, a small piece of gingival tissue yields large number of MSCs in short duration, that can be transformed into induced pluripotent stem cells to broaden their differentiation lineages. In our study, we demonstrate that irrespective of donor age gingival MSCs (GMSCs) retain their colony formation efficiency, display high expression of MSC surface markers and also efficiently differentiate into both mesodermal (osteogenic) and ectodermal (neurogenic) lineages. Thus, we suggest gingiva to be a promising source of MSCs for tissue engineering/ regeneration applications involving autologous stem cell therapies, irrespective of donor age.

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Keywords: gingiva, mesenchymal stem cell, age

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