INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

AI AND BIOLOGY: ACCELERATING DISCOVERY AND THERAPIES

An ISSCR International Symposium

9-10 OCTOBER 2025
SEATTLE, USA

PROGRAM & ABSTRACT BOOK

ABOUT THE ISSCR

INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

The International Society for Stem Cell Research
+1-224-592-5700
isscr.org

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

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

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

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

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

Learn more at isscr.org.

ABOUT *STEM CELL REPORTS*

STEM CELL REPORTS

Stem Cell Reports

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

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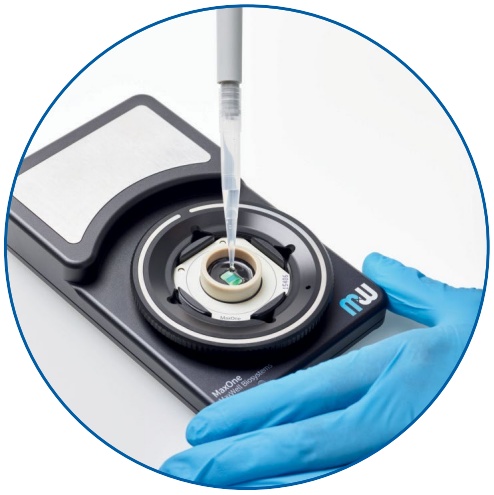

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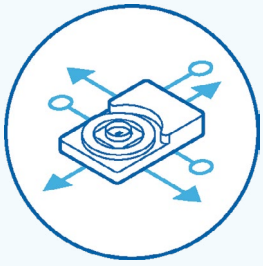

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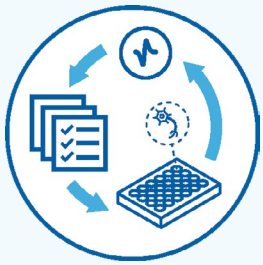

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11-12 DECEMBER 2025 | BOSTON, USA

SUMMIT ON ACCESS AND AFFORDABILITY IN CELL AND GENE THERAPIES

20 MARCH 2026 | LOS ANGELES, USA

IN COLLABORATION WITH:

CIRM California Institute for Regenerative Medicine

UCLA Broad Stem Cell Research Center

ISSCR 2026 ANNUAL MEETING

THE GLOBAL STEM CELL EVENT
8-11 JULY 2026 | MONTRÉAL, CANADA

CO-SPONSORED BY: STEMCELL™ TECHNOLOGIES

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

KYOTO INTERNATIONAL SYMPOSIUM
20-22 OCTOBER 2026 | KYOTO, JAPAN

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

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STEM CELLS IN DISEASE MODELING AND DRUG DISCOVERY

SAN DIEGO INTERNATIONAL SYMPOSIUM
14-16 DECEMBER 2026 | SAN DIEGO, USA

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MEETING INFORMATION

ONSITE BADGE PICK UP

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

Registration Desk Hours | Lobby of Block 41

Thursday, 9 October	**8:00 AM – 6:30 PM**
Friday, 10 October	**8:00 AM – 4:00 PM**

ISSCR PROGRAM AGENDA

There will be no printed program book for the 2025 Seattle International Symposium. You can access the online version of the program agenda here: Full Schedule

LIVESTREAMING

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

ABSTRACT REVIEWERS

Anthony Asmar, Rafael Carazo Salas, Ci Chu, Rodrigo Cristofoletti, Kaustubh Joshi, Ajamete Kaykas, Marinna Madrid, Roy Maimon, Bar Makovoz, Jian Shu, Christina Theodoris, Cole Trapnell, Wei Xie, Ke Zhang

SMOKING

Smoking or the use of e-cigarettes is prohibited throughout the venue.

LOST AND FOUND

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

POSTER INFORMATION

Each poster will be presented during a 60-minute session in the Bert & Tot Ballroom on level 2 of Block 41. Poster presenters must adhere to the scheduled date and time of their poster display and presentation.

Poster presenters are responsible for removing their posters on Friday, 10 October between 3:20 PM – 3:50 PM. Any posters not removed at the end of their session will be discarded.

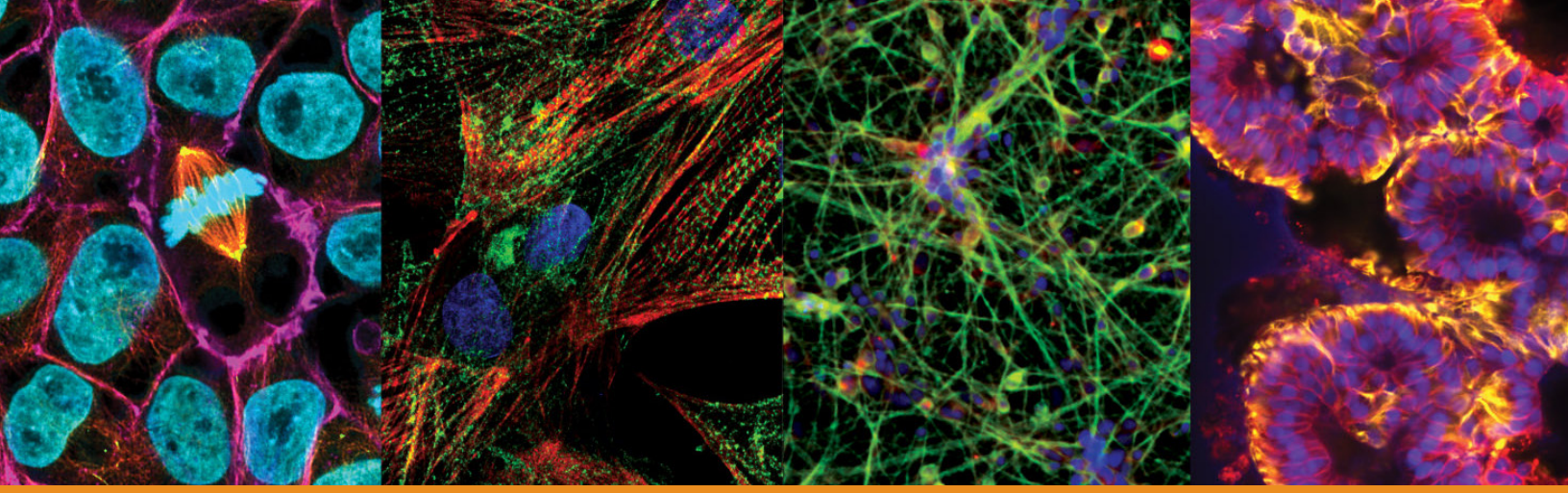
POSTER PRESENTATION SCHEDULE

Thursday, 9 October 2025

10:30 AM – 11:00 AM	**All posters to be put up**
4:30 PM – 5:30 PM	**Poster Session 1 ODD**
5:30 PM – 6:30 PM	**Poster Session 2 EVEN**

Friday, 10 October 2025

3:20 PM – 3:50 PM	**All posters to be taken down**



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

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The Chan Zuckerberg Biohub Network is a group of nonprofit research institutes that bring together physicians, scientists, and engineers with the goal of pursuing grand scientific challenges on 10- to 15-year time horizons.

COLLABORATIVE DRUG DISCOVERY (CDD VAULT)

https://www.collaborativedrug.com/

Collaborative Drug Discovery (CDD) provides an intuitive software suite extensively used by creative biologists and chemists working in academic, biotechnology and pharmaceutical settings. Their flagship product, CDD Vault, enables researchers to intuitively organize and analyze both biological and chemical data, and to collaborate with partners through a straightforward web interface. CDD Vault helps scientists register entities, track inventory, manage bioassay data, capture experiments, calculate Structure-Activity Relationships (SAR), and mine their data for drug candidates. It also functions as an Electronic Laboratory Notebook (ELN) to capture and share experimental results. CDD Vault is differentiated through its intuitive design, superior performance, and workflows for secure, collaborative data sharing capabilities. CDD was founded in 2004 and presently serves thousands of researchers doing drug discovery all around the world.

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Parse Biosciences is a global life sciences company whose mission is to accelerate progress in human health and scientific research. Empowering researchers to perform single cell sequencing with unprecedented scale and ease, our pioneering approach is enabling groundbreaking discoveries in cancer treatment, tissue repair, stem cell therapy, kidney and liver disease, brain development, and the immune system. Founded based on a transformative technology invented at the University of Washington, Parse has raised over $100 million and our tools are trusted by 3,000 labs across the world. Our growing portfolio of products includes Evercode Whole Transcriptome, Evercode TCR, BCR, Gene Capture, and Trailmaker, a software tool for data analysis. Headquartered in Seattle, Washington's vibrant South Lake Union district, Parse Biosciences recently opened a 34,000 square foot headquarters and state-of-the-art laboratory.

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The Sartorius Group is a leading international partner of biopharmaceutical research and the life-sciences industry. With innovative laboratory instruments and consumables, the Group's Lab Products & Services Division concentrates on serving the needs of laboratories performing research and quality control at pharma and biopharma companies and those of academic research institutes. We are at the forefront of innovation, merging the realms of artificial intelligence (AI) and biology to transform live-cell imaging. This cutting-edge approach is pivotal for understanding the dynamic biology of living cells, offering real-time insights into their health, behavior, morphology, and function as they interact with their environment. As the demand for comprehensive research grows, Sartorius leverages high-throughput, automated live-cell analysis to streamline workflows, minimize errors, and enhance data reliability. The incorporation of AI and machine learning into this domain is set to revolutionize data mining, enabling quicker and more profound insights. Predictive software, powered by AI algorithms, can analyze vast imaging datasets, identifying patterns and correlations beyond human perception. This capability paves the way for predictive models that forecast cellular responses to treatments, facilitating the development of more targeted and effective therapies. Through these innovations, Sartorius is redefining the landscape of biological research and therapeutic development.

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

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At the heart of CellVoyant is FateView, our AI-powered SaaS platform. FateView enables biologists to visualize, track, and forecast cell differentiation in real-time. It supports high-throughput experimentation and model inference, combining microscopy, computer vision, cloud infrastructure, and AI to serve cutting-edge stem cell research and manufacturing.

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Building on this progress, we are now leveraging our genome engineering platform to create advanced iPSC libraries for genetic perturbation studies. By applying machine learning, we aim to revolutionize the design of genetically engineered cells for superior therapeutic performance. We are seeking collaborations with AI companies to develop predictive models for multi-gene perturbation in iPSCs, unlocking new insights at the intersection of biology and artificial intelligence. This is where we believe the future of regenerative and other cell-based medicine lies.

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

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Located in the heart of Seattle's innovation hub, the Institute for Stem Cell and Regenerative Medicine (ISCRM) brings together scientists from over 150 labs who are using stem cells to drive discovery and treatment. By studying the body's natural ability to heal, they're pioneering technologies that target the root causes of major medical challenges—safely and effectively.

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10x Genomics was founded on the vision that this century will bring advances in biomedicine and transform the way we understand and treat disease. We deliver powerful, reliable tools that fuel scientific discoveries and drive exponential progress to master biology to advance human health. Our end-to-end single cell and spatial solutions include instruments, consumables, and intuitive software, letting you unravel highly intricate biological systems, while bringing into focus the details that matter most. Asuragen, ExosomeDx, Lunaphore, Novus Biologicals, ProteinSimple, R&D Systems and Tocris Bioscience.

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SPEAKER ABSTRACTS

All times are listed in Pacific Daylight Time (PDT)

THURSDAY, 9 OCTOBER 2025
9:20 AM – 10:30 AM
DECODING STEM CELLS

9:30 AM - 9:50 AM
ABSTRACT NOT AVAILABLE AT THE TIME OF PUBLISHING

Rafael E. Carazo Salas, *University of Bristol, CellVoyant, UK*

9:50 AM - 10:10 AM
DECODING AND TRANSLATING THE LANGUAGES OF BIOLOGY

Jian Shu, *Harvard Medical School, USA*

Decoding the biological "languages" underlying cellular states is a major challenge. Single-cell omics offer deep insights but are expensive and destructive, limiting their use for tracking live cells over time. In contrast, imaging is scalable, non-destructive, and low-cost, but often difficult to interpret. My lab develops scalable experimental and computational frameworks that use generative AI to bridge diverse biological data modalities. For instance, we've built technologies that predict single-cell omics from imaging, reconstruct molecular dynamics in live cells, and generate tissue and cellular images from gene expression profiles. These tools enable real-time, scalable prediction and querying of multi-omics and imaging data across both microbial and mammalian systems. By integrating live-cell, label-free imaging with genetic and chemical perturbations, we've developed high-throughput screening systems to explore cell function and behavior in space and time. Translating these distinct "languages" (data modalities) of biology unifies different perspectives of cell and tissue biology, reduces the need for multiple destructive measurements and brings us closer to our ultimate goal: building digital simulators of multicellular systems.

11:00 AM - 12:00 PM
KEYNOTE - PROTEIN DESIGN

11:00 AM – 12: 00 PM
DESIGN OF NEW PROTEIN FUNCTIONS USING DEEP LEARNING

David Baker, *Institute for Protein Design, University of Washington, USA*

Proteins mediate the critical processes of life and beautifully solve the challenges faced during the evolution of modern organisms. The focus of our lab is the design of a new generation of proteins that address current-day problems not faced during evolution. In contrast to traditional protein engineering efforts which modify naturally occurring proteins, we design new proteins from scratch to optimally solve these problems. We develop and use deep learning methods to design these new proteins with new functions, produce synthetic genes encoding the designs, and characterize them experimentally. In this talk, I will describe the design of proteins to address current challenges in health, technology, and sustainability.

1:00 PM - 2:30 PM
APPLYING AI IN MANUFACTURING AND CLINICAL ADVANCES

1:10 PM - 1:30 PM
BUILDING AN EXPERT SYSTEM FOR QUANTITATIVE MONITORING OF INDUCED PLURIPOTENT STEM CELLS (IPSC) DURING EXPANSION

Anne L. Plant, *National Institute of Standards and Technology, USA*
Anthony J. Asmar, *National Institute of Standards and Technology, USA*
Ndeye Y. Ndiaye, *National Institute of Standards and Technology, USA*

The ability to quantitatively image human induced pluripotent stem cells (hiPSC) in real time to analyze their state of pluripotency and differentiation in a non-invasive and non-destructive manner is important for establishing better metrics for monitoring cultures, optimizing culture conditions and analytical parameters, and assuring consistency and efficiency in hiPSC manufacturing. We will discuss how we have implemented computer and computational capabilities to establish an imaging and image analysis pipeline for quantifying the relationships between critical biological characteristics. Our pipeline

allows turnkey, automated and real-time collection, processing, and storage of image data from tens of thousands of individual hiPSCs and their progeny using phase contrast microscopy. The system performs segmentation and tracking of nuclei over time and over multiple cell divisions. The U-Net-based AI model for this analysis is trained with hundreds of thousands of cells identified through automated segmentation of fluorescent nuclei. This obviates the need for manual annotation and provides access to the large diversity of cells within an isogenic population. The rapid imaging (all cells are interrogated every 2 minutes) allows the counting and tracking of all cells and their daughters with a high rate of accuracy. Reliability was confirmed by comparing data over 10 replicate experiments. Our AI pipeline trained on human iPS cells shows good accuracy (F1 score ≈0.96) for inferencing individual pluripotent nuclei in phase contrast images. The automated pipeline allows real time monitoring of the biological characteristics of cell populations with data and metadata continually fed into a central database. A dashboard controls real-time interrogation and visualization of the data. Quantitative metrics from different datasets allow comparison of the effects of cell culture conditions and of computational parameters. The database is designed to be queried using appropriate LLM prompts to return aspects of morphology, migration rate, mitosis rate, time between mitoses, expression of fluorophores associated with transcription factors, and spatial and temporal relationships between these characteristics.

1:30 PM - 1:50 PM
FROM DATA TO DISCOVERY: ACCELERATING CHEMICAL REPROGRAMMING THROUGH IN SILICO PREDICTION

Hongkui Deng, *Peking University, China*

Chemical reprogramming provides a precise and flexible method to control cell fate, enabling the generation of desired cell types for biomedical applications. Our recent success in reprogramming human somatic cells into PSCs using purely chemical methods underscores the promise of this approach and its advantages for clinical translation. However, the discovery and screening of effective small molecules for cell fate conversion remain challenging, largely due to the labor-intensive and time-consuming nature of conventional methodologies. To overcome this hurdle, we developed a computational platform that leverages single-cell RNA sequencing data to systematically categorize and prioritize chemical compounds. Our approach integrates a large compendium of single chemical perturbation profiles with a network model to identify molecules that can effectively target key transcription factors driving cellular conversions. This platform

successfully predicted both known and novel compounds across diverse reprogramming contexts, providing a powerful tool to accelerate the discovery of chemical cocktails. Looking ahead, the next frontier is predicting the synergy of small molecule combinations. This requires developing advanced computational models in parallel with generating high-throughput, multi-omic data from multi-drug perturbations. Successfully uniting these efforts will enable the precise, combinatorial fine-tuning of chemicals required to engineer cell fate.

1:50 PM - 2:10 PM
AN AI-DRIVEN BIOMANUFACTURING TECHNOLOGY TO SCALE PRODUCTION OF AUTOLOGOUS IPSC-BASED CELL THERAPIES

Bar Makovoz, *Cellino Biotech, USA*

Regenerative medicines have the potential to cure chronic degenerative diseases. Autologous iPSC (induced pluripotent stem cell)-derived therapies enable treatment without immunosuppression or donor matching, improving patient access. However, current manufacturing methods require manual labor, qualitative human decision-making, and open systems- resulting in high variability, low scalability, and high cost ($800k/dose per Huang et al., 2019). Cellino uses an AI-driven optical biomanufacturing technology for consistent, scalable production of autologous iPSC-derived therapies. Cells are frequently imaged, AI-based image analysis algorithms characterize cells in-process, and laser-generated bubbles selectively remove cells as needed. Cellino's AI-based image analysis algorithms detect all living cells in the growth area, discern between pluripotent stem cells and undesired spontaneously differentiated cells, and calculate local cell density in regions of interest. This in-process characterization enables consistent management of the stem cell culture, which has a direct positive effect on quality and health of the cells. Using these AI-based image analysis algorithms and derived metrics, Cellino demonstrates an autonomous optical bioprocess for iPSC manufacturing. The optical bioprocess enables cell production in closed cassettes, and as such enables sterile, parallel manufacturing of multiple patient samples at a time, at significantly reduced costs. Cellino is proud to collaborate with Mass General Brigham in Boston, to launch a personalized iPSC foundry at point-of-care, with an autologous Parkinson's disease cell therapy trial as the first clinical application.

2:20 PM – 2:30 PM

MODELLING GRAFT–HOST INTERACTIONS IN A MULTI-OMICS FRAMEWORK TO IMPROVE CARDIOMYOCYTE ENGRAFTMENT

Elsa Lawrence, *University of Cambridge, UK*
Anne F. Grangaard, *University of Cambridge, UK*
Vincent Knight-Schrijver, *University of Cambridge, UK*
Catherine H. Wilson, *University of Cambridge, UK*
Adam J. Reid, *University of Cambridge, UK*
Sanjay Sinha, *University of Cambridge, UK*
Lay Ping Ong, *University of Cambridge, UK*

Up to a billion heart cells die following a myocardial infarction (MI) which leads to heart failure. Human embryonic stem cell (hESC)-derived cardiomyocytes can remuscularize the heart with improved cardiac function in subacute MI animal models. Thus, cell therapy holds significant promise to regenerate the injured failing human heart. However, mechanisms governing successful engraftment of cells into infarcted host tissues remain poorly understood. Unsuccessful engraftment leads to tachyarrhythmias which pose a significant barrier to clinical translation. Here, we present a novel multi-omics framework to map graft–host interactions with the goal of identifying molecular targets and predicting compounds to enhance engraftment outcomes and reverse heart failure. We obtained tissues from chronic heart failure rat model engrafted with distinct cellular compositions: sham, neonatal rat ventricular cardiomyocytes, hESC-derived cardiomyocytes, and hESC-derived cardiomyocytes co-delivered with hESC-derived epicardial cells. Using spatial transcriptomics, single-nucleus RNA sequencing (snRNA-seq), and single cell Assay for Transposase-Accessible Chromatin with high-throughput sequencing (scATAC-seq), we dissected the cellular composition, spatial organisation, and chromatin accessibility of the graft–host interface. Our analytical workflow includes these three phases: (1) spatial deconvolution to allow mapping of cellular niches and prediction of ligand–receptor interactions to characterise graft–host crosstalk, (2) construction of gene regulatory networks (GRNs) to identify key transcription factors that regulate graft–host communication, and (3) development of a predictive machine learning (ML) model to identify compounds capable of improving engraftment, trained on the multi-modal omics data and informed by in vitro high throughput compound testing. We present findings from multi-omic data integration and analyses, revealing regional cellular niches in the graft and host tissue, putative ligand–receptor interactions and niche-specific cell communication dynamics between graft and host cells. Our integrative, multi-modal approach aims not

only to map the biological mechanisms of engraftment, but to also directly inform strategies for its enhancement.

Funding Source: BHF UKRI Rosetrees AstraZeneca.

3:00 PM - 4:20 PM
GENETIC VARIABILITY OF CELL LINES AND DATA

3:00 PM – 3:20 PM
UNRAVELING THE COMPLEXITY USING GENETICALLY DIVERSE HUMAN CELLULAR MODELS

Ralda Nehme, *Broad Institute of MIT and Harvard, USA*

Growing evidence suggests that human genetic variation associated with complex traits—such as psychiatric disorders— disrupts communication between specific brain cell types. Yet, the nature of these interactions, and whether they represent shared mechanisms across diverse risk alleles, remains poorly understood. To address this, we use human induced pluripotent stem cells (iPSCs) to model neurons and astrocytes derived from genetically diverse individuals, along with targeted CRISPR technologies to study risk variants in the context of the human genetic background. I will discuss newly developed resources and assays that we established to measure genetic influences on living human cells. Using a combination of multiplexed and pooled approaches (such as cell villages) along with arrayed, non-pooled measurements, we have identified transcriptional signatures and morphological fingerprints linked to genetic and pharmacological perturbations. We found that cell-type specific gene expression programs that govern specific morphological features underlie astrocyte-neuron communications and are altered in the context of psychiatric disorders. Together, these findings underscore the power of multi-donor cellular models to reveal genotype-dependent cellular responses and nominate new avenues for therapeutic discovery in psychiatric disease.

3:20 PM – 3:30 PM
MACHINE LEARNING RESOLVES FUNCTIONAL PHENOTYPES AND THERAPEUTIC RESPONSES IN KCNQ2 DEVELOPMENTAL EPILEPTIC ENCEPHALOPATHY IPSC MODELS

Evangelos Kiskinis, *Northwestern University, USA*

Pathogenic KCNQ2 mutations are associated with developmental and epileptic encephalopathy (KCNQ2-DEE), a devastating disorder characterized by neonatal seizures and neurodevelopmental deficits with no effective treatments. KCNQ2 encodes the voltage-gated potassium channel KV7.2, which regulates action potential threshold and repolarization. However, the relationship between KV7.2 dysfunction and abnormal neuronal excitability remains unclear. Here, we use human induced pluripotent stem (iPSC)-derived neurons from five patients with loss-of-function mutations and CRISPR/Cas9-corrected isogenic controls to explore pathophysiological mechanisms of KCNQ2-DEE. We identify a common dyshomeostatic enhancement of Ca2+-activated SK channels, which drives larger post-burst afterhyperpolarizations in patient neurons. We use microelectrode arrays (MEAs) to record over 18 million extracellular spikes from >8,000 neurons during five weeks in culture and apply supervised and unsupervised machine learning algorithms to dissect time-dependent functional neuronal phenotypes and define both patient-specific and shared firing features across KCNQ2-DEE patients. We identify irregular spike timing and enhanced bursting as functional biomarkers of KCNQ2-DEE and demonstrate the significant influence of genetic background on phenotypic diversity. Critically, using unbiased machine learning models, we show that early and chronic treatment with the Kv7 activator retigabine restores the temporal pattern of disease-associated functional phenotypes with variable efficacy. Our work establishes SK channel upregulation as a key pathophysiological mechanism underlying KCNQ2-DEE and provides an MEA-based machine learning platform that can be used to decipher phenotypic diversity amongst patients, discover disease biomarkers, and evaluate precision medicine interventions in personalized iPSC neuronal models.

3:30 PM - 3:40 PM
CONTINUOUS REPRESENTATIONS AND LABEL-FREE DIFFERENTIAL ANALYSIS OF SINGLE-CELL DATA

Dominik J. Otto, *Fred Hutchinson Cancer Center, USA*
Erica Arriaga-Gomez, *Fred Hutchinson Cancer Center, USA*
Elana Thieme, *Fred Hutchinson Cancer Center; University of Washington, USA*
Ruijin Yang, *Fred Hutchinson Cancer Center, USA*
Stanley C. Lee, *Fred Hutchinson Cancer Center, USA*
Manu Setty, *Fred Hutchinson Cancer Center, USA*

Single-cell technologies generate vast, high-dimensional profiles that capture the full continuum of cell states across development, aging, and disease. Yet most analysis pipelines collapse this complexity into clusters or pseudotime bins, obscuring rare or intermediate states and limiting opportunities for mechanistic and machine-learning based modeling. We present a unified framework, Mellon and Kompot, that preserves single-cell diversity in continuous, probabilistic representations optimized for quantitative interrogation and downstream AI applications. Mellon infers smooth, differentiable density functions over the entire cell-state space using intrinsic-dimensionality guided nearest-neighbor distributions, and Gaussian processes. These densities quantify local population structure, reveal rare transitional states, and serve as rich substrates for statistical and computational modeling. By providing a continuous manifold with uncertainty estimates, Mellon and Kompot enable downstream procedures such as regression, classification, or dynamical inference to operate directly on the full data distribution rather than discrete labels. Building on Mellon's densities, Kompot performs label-free differential analysis on the learned manifold. For differential abundance, Kompot computes log-fold changes in density between conditions at every cell-state and derives posterior tail probabilities for statistical calibration, yielding volcano-style plots in which each point represents an individual cell-state. For differential expression, it learns smooth, condition-specific mappings from cell-state coordinates to gene expression via Gaussian processes. By predicting counterfactual expression levels and comparing them to observations with a Mahalanobis-distance based significance metric, Kompot sensitively detects localized transcriptional rewiring such as stress-response or lineage-priming programs that cluster-based tests miss. We illustrate this framework on an aging murine hematopoiesis dataset. Kompot's differential abundance reveals subtle shifts in stem-progenitor densities consistent with altered proliferation and turnover, while the differential expression component uncovers stage-specific regulation of oxidative-stress and MHC-II gene changes with age. We further demonstrate Kompot's extension to multimodal assays (for example, ATAC-seq and CITE-seq) and its scalability to millions of cells. Both tools are implemented in JAX for efficient CPU/GPU acceleration, integrate seamlessly with Scanpy and scverse workflows, and are released as open-source packages with pretrained models, synthetic benchmarks, and comprehensive documentation. We will conclude with a brief outlook on incorporating mechanistic drift-diffusion-growth partial differential equation formulations into these continuous representations to supply biologically grounded loss functions for future AI-based simulations of cell fate dynamics. By maintaining the full continuum of single-cell diversity and quantifying uncertainty on a data-driven manifold, Mellon and Kompot provide a robust foundation for interpretable analysis, mechanistic

modeling, and the next generation of AI-accelerated discoveries in regenerative medicine, immunology, and precision therapeutics.

3:40 PM - 4:00PM
THE CIRM IPSC REPOSITORY – LEARNINGS FROM THE JOURNEY

Uta Grieshammer, *California Institute for Regenerative Medicine (CIRM), USA*

In 2013, CIRM funded the creation of a large research-grade induced pluripotent stem cell (iPSC) bank, using blood or skin donated by more than 2000 participants. The goal was to enable iPSC-based modeling of polygenic, genetically complex diseases such as Alzheimer's disease, liver disease, neurodevelopmental disorders, and other diseases. The repository operated for 10 years and was decommissioned in July 2025. While not currently active, the collection remains intact and could be reactivated in the future. I will discuss some of the strengths and some of the challenges that arose from the design of the repository and reflect on the ancestral diversity it represented. The lessons learned may be of value when designing new iPSC collections.

4:00 PM - 4:20 PM
ABSTRACT AND TITLE NOT AVAILABLE AT THE TIME OF PUBLISHING

Jonah Cool, *Anthropic, USA*

FRIDAY, 10 OCTOBER 2025
9:00 AM - 10:10 AM
MACHINE LEARNING FOR OMICS DATA

9:00 AM – 10:00 AM
WHERE FORM MEETS FUNCTION: DECODING TISSUE ARCHITECTURE

Dana Pe'er, *Sloan Kettering Institute, MSK, USA*

ABSTRACT NOT AVAILABLE AT THE TIME OF PUBLISHING

10:40 AM - 12:00 PM
FOUNDATIONAL MODELS

10:40 AM - 11:00 AM
MACHINE LEARNING ENABLED ALS-TARGET & THERAPEUTIC DISCOVERY

Ajamete Kaykas, *Insitro, USA*

Amyotrophic lateral sclerosis (ALS) remains a devastating neurodegenerative disease with limited therapeutic options. At insitro, we are leveraging machine learning (ML) and high-throughput, multimodal screening platforms to accelerate target and drug discovery for ALS. By combining large libraries of engineered iPSC-derived motor neurons with multiplexed pooled optical screening (POSH) and transcriptomic perturbation assays, we generate rich genotype–phenotype datasets. Our ML pipelines identify predictive disease phenotypes, novel genetic modifiers of TDP43 dysfunction and rescue of cryptic splicing. This integrative approach has uncovered ALS-1, a promising target that restores splicing fidelity and neurite regrowth without cytotoxicity. Together, these advances illustrate how ML-enabled platforms can reveal new biological insights and actionable targets for ALS and beyond.

11:00 AM - 11:20 AM
TRANSFER LEARNING TO ENABLE PREDICTIONS IN NETWORK BIOLOGY

Christina V. Theodoris, *Gladstone Institutes, USA*

Mapping gene networks requires large amounts of transcriptomic data to learn the connections between genes, which impedes discoveries in settings with limited data, including rare diseases and diseases affecting clinically inaccessible tissues. However, there has been a rapid expansion in the amount of single-cell transcriptomics data available from human tissues more broadly, which may be leveraged through the machine learning approach of transfer learning to improve predictions in settings where data remains limited. To address this, we developed a foundational artificial intelligence (AI) model, Geneformer, pretrained on a large-scale corpus of human single-cell transcriptomes (initially ~30 million, now >100 million) to enable context-specific predictions in settings with limited data in network biology. During pretraining, Geneformer gained a fundamental understanding of network dynamics, encoding network hierarchy in the attention weights of the model in a completely self-supervised manner. With both zero-shot learning and fine-tuning with limited task-specific data, Geneformer consistently boosted predictive accuracy in a diverse panel of downstream tasks relevant to chromatin

and network dynamics. In silico perturbation with zero-shot learning identified a novel transcription factor in cardiomyocytes that we experimentally validated to be critical to their ability to generate contractile force. In silico treatment with limited patient data revealed candidate therapeutic targets for cardiomyopathy that we experimentally validated to significantly improve the ability of cardiomyocytes to generate contractile force in an iPSC model of the disease. Now, we have applied transfer learning to reveal how gene network states affect neighboring cells within tissues across space and how perturbations propel cells over temporally dynamic trajectories over time. Overall, our foundational AI models for network biology can now be democratized to a vast array of downstream tasks to accelerate discovery of key network regulators and candidate therapeutic targets for human disease.

11:40 AM - 11:50 AM
GENERATION OF CELLULAR AND TISSUE IMAGES FROM SINGLE-CELL EXPRESSION PROFILES WITH GENVINCI

Xingjian Chen, *MGH/Harvard Medical School, USA*

Cells were first discovered and characterized through imaging hundreds of years ago, while recent advances in single-cell genomics have enabled their systematic cataloging through comprehensive molecular profiling. However, both approaches typically capture only a single modality at a time, requiring substantial effort to obtain multiple views and often resulting in seemingly disparate representations of cellular identity. Recent breakthroughs in generative AI offer a transformative solution by enabling the synthesis of multiple views through non-linear transformations, providing a unified perspective on cellular and tissue biology. Here, we introduce GenVinci, a transformer-based generative model that learns a universal cell representation to reconstruct morphological information from single-cell and spatial gene expression profiles. GenVinci is pretrained on over 120 million dissociated and spatially resolved single-cell gene expression profiles across more than 80 tissues from both humans and mice. The model is then fine-tuned to generate diverse types of cellular and tissue imaging data, including electron microscopy images, fluorescence microscopy images, neuron morphologies, and histological stains (hematoxylin and eosin (H&E)), from various molecular profiles at different resolutions. GenVinci generates highly accurate cellular and tissue images that align with ground-truth morphologies, cell types, and pathological annotations. Notably, we demonstrate that GenVinci enables in silico

perturbation experiments by generating previously unseen morphologies from perturbed gene expression data. This capability bridges molecular states with imaging phenotypes, facilitating the modeling of cellular behaviors and functions in silico. Furthermore, we show that GenVinci can be flexibly applied to a range of downstream tasks, including image generation, multi-modal clustering, zero-shot classification, and data augmentation. By unifying different views of cellular and tissue biology, GenVinci significantly reduces the need for multiple experimental measurements, advancing the ultimate goal of virtual cell and tissue simulation.

11:50 AM - 12:00 PM
DECIPHERING MOLECULAR UNDERPINNINGS OF CELL STATES AND STATE TRANSITIONS WITH A GLOBAL CELL-STATE MANIFOLD

Xingjie Pan, *Harvard University, USA*
Reuben Saunders, *Harvard University, USA*
Joseph Replogle, *Massachusetts General Hospital, USA*
Jonathan Weissman, *Massachusetts Institute of Technology, USA*
Xiaowei Zhuang, *Harvard University, USA*

Mammalian organisms comprise numerous types of cells with distinct gene-expression states, which arise from single zygotes differentiating on a complex landscape of cell states. Thus, a global cell-state map will be foundational for understanding the molecular basis of normal tissue functions and dysfunction in diseases. Although single-cell transcriptomic data offer the possibility of constructing such a map, it remains a challenging task that requires computationally efficient integration of many large datasets and accurate removal of artifactual batch effects. Here, we developed a contrastive learning model, single-cell manifold generator (SCMG), which combines the strong batch-correction power of pairwise integration with the computational scalability of deep learning, outperforming other state-of-the-art foundation models for dataset integration. We used SCMG to construct a highly interpretable global map of cell states, which encompasses most of the embryonic and mature cell types of human and mouse. The resulting global cell-state manifold enabled the zero-shot projection and annotation of cell states, the generation of developmental trajectories, and the prediction of causal genes driving cell-state transitions. To further illustrate its power for understanding the molecular basis of cell-state transitions, we performed a genome-scale perturb-seq experiment on human embryonic stem cells by profiling 1.3 million cells with a library of 6,638 sgRNAs for CRISPR inhibition (CRISPRi) of 2,978 genes. We systematically analyzed the relationships

between perturbation-induced cell states and the naturally occurring ones on the global cell-state manifold. We identified numerous gene modules that were co-regulated in response to genetic perturbations, some of which, but not all, represent transcriptional programs observed during normal development. Projection of the perturbed cells onto the global cell-state manifold revealed distinct classes of cell-state transitions and their driver genes, including transitions that reflect germ layer development, resemble mesenchymal transitions, or are orthogonal to natural development. Our global cell-state manifold and related computational tools provide a powerful framework for understanding cell-state transitions, interpreting perturbation data, and constructing genotype-phenotype maps in health and disease.

Funding Source: We acknowledge the support of the Howard Hughes Medical Institute and the Jane Coffin Childs Memorial Fund for Medical Research for this project.

1:00 PM - 2:10 PM
AI INFRASTRUCTURE AND ACCESSIBILITY

1:00 PM – 1:20PM
MULTIMODAL GENERATIVE AI FOR PRECISION HEALTH

Hoifung Poon, *Microsoft and University of Washington, USA*

The dream of precision health is to develop a data-driven, continuous learning system where new health information is instantly incorporated to optimize care delivery and accelerate biomedical discovery. The confluence of technological advances and social policies has led to rapid digitization of multimodal, longitudinal patient journeys, such as electronic health records (EHRs), imaging, and multiomics. Our overarching research agenda lies in advancing multimodal generative AI for precision health, where we harness real-world data to pretrain powerful multimodal patient embedding, which can serve as digital twins for patients. This enables us to synthesize multimodal, longitudinal information for millions of cancer patients, and apply the population-scale real-world evidence to advancing precision oncology in deep partnerships with real-world stakeholders such as large health systems and life sciences companies.

1:20 PM – 1:40 PM
UNLOCKING THE FUTURE OF SCIENTIFIC DISCOVERY WITH AI AND QUANTUM COMPUTING

Ester de Nicolas Benito, *Microsoft, USA*

As the life sciences community pushes the boundaries of regenerative medicine and cellular therapies, the need for transformative computational tools has never been greater. This session introduces Microsoft's scalable quantum computing platform and its integration with AI and high-performance computing (HPC) to accelerate discovery in biology and chemistry. We will explore how quantum-trained AI models are enabling first-time-right predictions in molecular simulations, drug efficacy, and materials design—reducing years of research to hours. Attendees will gain insight into the architecture of reliable quantum systems, the role of logical qubits in achieving practical quantum advantage, and how hybrid quantum-HPC-AI workflows are reshaping the future of scientific innovation.

1:40 PM – 2:00 PM
ABSTRACT AND TITLE NOT AVAILABLE AT THE TIME OF PUBLISHING

Theofanis Karaletsos, *Chan Zuckerberg Initiative, USA*

2:20 PM - 3:20 PM
MULTIMODAL IMAGING AND COMPUTER VISION

2:20 PM – 2:40 PM
AI-POWERED MULTIMODAL APPROACH TO DECIPHER CELL STATE TRANSITIONS USING HIPSC-DERIVED ENDOTHELIAL CELLS

Ruwanthi N. Gunawardane, *Allen Institute, USA*

Endothelial Cells (ECs) play a critical role in the vasculature. They are subject to shear stress as blood flows through the vessels they line, which influences their structure, function, and morphology. Here, we use the alignment and re-alignment of human induced pluripotent stem cell-derived ECs (hiPSC-ECs) under fluid shear stress as a tractable model system to investigate cell state transitions and developed a novel, segmentation-

and tracking-free machine learning framework to decipher the underlying principles of these dynamic cellular changes. We differentiated endogenously tagged hiPSC lines from the Allen Cell Collection (www.allencell.org) into hiPSC-ECs and performed 3D, live cell imaging as they respond to fluid shear stress to capture their morphology, behavior, and organization. We found that hiPSC-ECs exhibited distinct responses to different magnitudes of applied shear stress. When the magnitude of shear stress is switched from high to low or vice versa, the hiPSC-ECs responded with distinct cellular changes to their collective migration behavior and organization. To quantify these distinct cell state transitions that occurred in response to the shear stress magnitudes, we developed a segmentation-free machine learning framework to extract single-cell features directly from microscopy images that bypassed the need for traditional, error-prone segmentation and in an interpretable manner. Using these features, we applied a deep learning method to infer the underlying dynamical rules that drive the re-alignment of ECs under varying fluid shear stress. This data-driven approach allowed us to create vector fields that inform the dynamics of these cell state transitions under low, intermediate, and high shear stress. We are currently developing this workflow using paired bright field images and images of fluorescently tagged VE-cadherin to integrate data from time lapse and fixed imaging datasets. This AI-powered analysis of dynamic imaging data will not only deepen our understanding of endothelial biology but also demonstrate a powerful new paradigm for studying cell state transitions from imaging and multimodal data to inform stem cell and regenerative biology.

2:40 PM – 3:00 PM
ABSTRACT AND TITLE NOT AVAILABLE AT THE TIME OF PUBLISHING

Loïc A. Royer, *Chan Zuckerberg Biohub, USA*

3:00 PM – 3:20 PM
COMPUTATIONAL MICROSCOPY FOR PHASE, 3D AND SUPER-RESOLUTION IMAGING

Laura Waller, University of California, Berkeley, USA

Computational imaging involves the joint design of imaging system hardware and software, optimizing across the entire pipeline from acquisition to reconstruction. Computers can replace bulky and expensive optics by solving computational inverse problems, or new imaging modalities can be enabled by reconstructing invisible quantities or higher-

dimensional information from carefully-designed measurement. This talk will describe end-to-end learning for development of new microscopes and space-time algorithms that use computational imaging to enable 3D phase and fluorescence measurement with high resolution and dynamic samples. We demonstrate these concepts with a programmable-illumination microscope having an LED array for illumination, or a system with patterned illumination achieved with random diffusers (Scotch Tape). Traditional model-based image reconstruction algorithms are based on large-scale nonlinear non-convex optimization; we combine these with neural networks to learn both the image and its algorithmic self-calibration.

3:50 PM – 4:55 PM
REASONING AND PERTURBATION PREDICTION

3:50 PM – 4:10 PM
X-ATLAS/ORION: GENOME-WIDE PERTURB-SEQ DATASETS VIA A SCALABLE FIX-CRYOPRESERVE PLATFORM FOR TRAINING DOSE-DEPENDENT BIOLOGICAL FOUNDATION MODELS

Ci Chu, *Xaira Therapeutics, USA*

The rapid expansion of massively parallel sequencing technologies has enabled the development of foundation models to uncover novel biological findings. While these have the potential to significantly accelerate scientific discoveries by creating AI-driven virtual cell models, their progress has been greatly limited by the lack of large-scale high-quality perturbation data, which remains constrained due to scalability bottlenecks and assay variability. Here, we introduce “Fix-Cryopreserve-ScRNAseq” (FiCS) Perturb-seq, an industrialized platform for scalable Perturb-seq data generation. We demonstrate that FiCS Perturb-seq exhibits high sensitivity and low batch effects, effectively capturing perturbation-induced transcriptomic changes and recapitulating known biological pathways and protein complexes. In addition, we release X-Atlas: Orion edition (X-Atlas/Orion), the largest publicly available Perturb-seq atlas. This atlas, generated from two genome-wide FiCS Perturb-seq experiments targeting all human protein-coding genes, comprises eight million cells deeply sequenced to over 16,000 unique molecular identifiers (UMIs) per cell. Furthermore, we show that single guide RNA (sgRNA) abundance can serve as a proxy for gene knockdown (KD) efficacy. Leveraging the deep sequencing and

substantial cell numbers per perturbation, we also show that stratification by sgRNA expression can reveal dose-dependent genetic effects. Taken together, we demonstrate that FiCS Perturb-seq is an efficient and scalable platform for high-throughput Perturb-seq screens. Through the release of X-Atlas/Orion, we highlight the potential of FiCS Perturb-seq to address current scalability and variability challenges in data generation, advance foundation model development that incorporates gene-dosage effects, and accelerate biological discoveries.

4:10 PM – 4:20 PM
RECONSTRUCTING TRANSCRIPTIONAL STATES USING DESIGNED COMBINATORIAL PERTURBATIONS

Thomas Norman, *Memorial Sloan Kettering Cancer Center, USA*

Cell atlas projects have revealed that familiar cell types exhibit distinct, recurrent transcriptional states, but the roles of these states in health and disease remain largely unclear. In this talk, I will share our ongoing efforts to reconstruct these states through systematic Perturb-seq experiments targeting transcription factors. One outcome of this approach is tractable in vitro models for studying the regulation and functional properties of specific states. For example, a large-scale CRISPRa screen activating all human transcription factors in fibroblasts recovered key cell states and revealed regulatory relationships between them, including suppression of a disease-linked inflammatory state by a “universal” fibroblast program. However, many states remain inaccessible via single perturbations, and the space of transcription factor combinations is too vast for brute-force search. This challenge provides an ideal setting to develop and test computational methods for designing combinatorial perturbations. I will present a strategy based on Multiome Perturb-seq for predicting synergistic transcription factor pairs based on the chromatin accessibility changes induced by individual perturbations. Our goal is to establish a simple, mechanistically grounded framework for guiding large-scale genetic interaction experiments and, ultimately, rational engineering of cell state.

4:20 PM – 4:30 PM
RECONSTRUCTING SIGNALING HISTORIES OF SINGLE CELLS VIA PERTURBATION SCREENS AND TRANSFER LEARNING

Nicholas T. Hutchins, *Massachusetts Institute of Technology, USA*
Miram Meziane, *Whitehead Institute, USA*
Pulin Li, *Whitehead Institute, USA*
Claire Lu, *MIT, USA*
David Fischer, *Medical University of Vienna, Austria*
Maisam Mitalipova, *Whitehead Institute, USA*

Manipulating the signaling environment is an effective approach to alter cellular states for broad-ranging applications, from engineering tissues to treating diseases. Such manipulation requires knowing the signaling states and histories of the cells in situ, for which high-throughput discovery methods are lacking. Here, we present an integrated experimental-computational framework that learns signaling response signatures from a high-throughput in vitro perturbation atlas and infers combinatorial signaling activities in in vivo cell types with high accuracy and temporal resolution. Specifically, we generated signaling perturbation atlas across diverse cell types/states through multiplexed sequential combinatorial screens on human pluripotent stem cells. Using the atlas to train IRIS, a neural network-based model, and predicting on mouse embryo scRNAseq atlas, we discovered global features of combinatorial signaling code usage over time, identified biologically meaningful heterogeneity of signaling states within each cell type, and reconstructed signaling histories along diverse cell lineages. We further demonstrated that IRIS greatly accelerates the optimization of stem cell differentiation protocols by drastically reducing the combinatorial space that needs to be tested. This framework leads to the revelation that different cell types share robust signal response signatures, and provides a scalable solution for mapping complex signaling interactions in vivo to guide targeted interventions.

Funding Source: This work was supported by National Institute of Health DP2, Allen Distinguished Investigator Award, and a Paul G. Allen Frontiers Group advised grant of the Paul G. Allen Family Foundation.

4:30 PM - 4:50
ABSTRACT AND TITLE NOT AVAILABLE AT THE TIME OF PUBLISHING

Cole Trapnell, *University of Washington, USA*

POSTER ABSTRACTS

All times are listed in Pacific Daylight Time (PDT)

THURSDAY, 9 OCTOBER 2025
POSTER SESSION 1 (ODD): 4:30 PM – 5:30 PM

101
DEEPBLASTOID: A DEEP LEARNING-BASED HIGH-THROUGHPUT CLASSIFIER FOR HUMAN BLASTOIDS USING BRIGHTFIELD IMAGES WITH CONFIDENCE ASSESSMENT

Zejun Fan, *King Abdullah University of Science and Technology, Saudi Arabia*
Zhenyu Li, *King Abdullah University of Science and Technology, Saudi Arabia*
Yiqing Jin, *King Abdullah University of Science and Technology, Saudi Arabia*
Arun Chandrasekaran, *King Abdullah University of Science and Technology, Saudi Arabia*
Ismail Shakir, *King Abdullah University of Science and Technology, Saudi Arabia*
Yingzi Zhang, *King Abdullah University of Science and Technology, Saudi Arabia*
Aisha Siddique, *King Abdullah University of Science and Technology, Saudi Arabia*
Mengge Wang, *King Abdullah University of Science and Technology, Saudi Arabia*
Yeteng Tian, *King Abdullah University of Science and Technology, Saudi Arabia*
Peter Wonka, *King Abdullah University of Science and Technology, Saudi Arabia*
Mo Li, *King Abdullah University of Science and Technology, Saudi Arabia*

Recent advances in human blastoids have opened new avenues for modeling early human development and implantation. Human blastoids can be generated in large numbers, making them suitable for high-throughput screening, which often involves analyzing vast numbers of images. However, automated methods for evaluating and characterizing blastoid morphology are still underdeveloped. We developed a deep-learning model capable of recognizing and classifying blastoid brightfield images into five distinct quality categories based on developmental features. The model processes 273.6 images per second with an average accuracy of 87%, without signs of overfitting or batch effects. By integrating a Confidence Rate (CR) metric, the accuracy was further improved to 97%, with low-CR images flagged for human review. In a comparison with human experts, the model matched their accuracy while significantly outperforming them in throughput. We demonstrated the value of the model in two real-world applications: (1) systematic assessment of the effect of lysophosphatidic acid (LPA) concentration on blastoid formation, and (2) evaluating the impact of dimethyl sulfoxide (DMSO) on blastoids for drug

screening. In the applications involving over 10,000 images, the model identified significant effects of LPA and DMSO, which may have been overlooked in manual assessments. The deepBlastoid model is publicly available and researchers can train their own model according to their imaging conditions and blastoid culture protocol. deepBlastoid thus offers a precise, automated approach for blastoid classification, with significant potential for advancing mechanism research, drug screening, and clinical in vitro fertilization (IVF) applications.

Funding Source: KAUST Center of Excellence for Generative AI, award No. 5940 (PW). KAUST Center of Excellence for Smart Health, award No. 5932 (ML). KAUST Office of Sponsored Research, award No. BAS/1/1080-01 (ML).

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GHOST CYTOMETRY ENABLES MORPHOLOGICAL PROFILING AND SORTING OF DYNAMIC CELL STATES

Hiroko Nomaru, *ThinkCyte K.K., Japan*
Yuri An, *ThinkCyte K.K., Japan*
Yuichi Yanagihashi, *ThinkCyte K.K., Japan*
Mika Uematsu, *ThinkCyte K.K., Japan*
Kohjin Suzuki, *Juntendo University Graduate School of Medicine, Technology Innovation, and Sysmex Corporation, Japan*
Keisuke Wagatsuma, *ThinkCyte K. K., Japan*
Hirofumi Nakayama, *ThinkCyte K.K., Japan*
Juliet Packiasamy, *ThinkCyte K.K., USA*
Romain Ballet, *ThinkCyte K.K, USA*
Tomoiku Takaku, *Juntendo University Graduate School of School of Medicine and Saitama Medical University Hospital, Japan*
Sadao Ota, *ThinkCyte K.K., and The University of Tokyo, Japan*

Cell morphology is a key indicator of cell status, reflecting intricate intracellular changes in response to intra-/extracellular stimuli, differentiation processes, and disease states. Ghost cytometry (GC) captures label-free, high-resolution morphological information, generating high-resolution morphological signatures from each cell as one-dimensional ghost motion imaging (GMI) waveforms. Previously, GC relied on supervised machine-learning classifiers trained using known ground truth labels, such as antibodies. This

limited the scope of GC applications and potentially introduced bias when interpreting continuously evolving morphological changes. To overcome these limitations, we developed an unsupervised approach integrating Uniform Manifold Approximation and Projection (UMAP) dimensionality reduction with GC. This allows unbiased exploration and sorting of cell populations based solely on their inherent morphology. To demonstrate the effectiveness of this method, we first applied it to human iPSC differentiation towards hepatocytes: by mixing cells from various time points (Day 0 iPSC, Day 3 definitive endoderm, Day 7 hepatoblast, Day 15 hepatocyte) and analyzing their GMI waveforms via UMAP. By projecting each time point onto the UMAP space, three morphologically distinct subpopulations were identified. These subpopulations were gated, sorted and confirmed as the expected differentiation stage using qPCR analysis with marker gene expressions. Second, we demonstrated UMAP-sort's potential in disease profiling using lineage-depleted bone marrow samples from Chronic Myelogenous Leukemia (CML) patients and healthy controls. UMAP was generated from mixed samples, and the CML-enriched population was gated. The gated population was sorted from CML and control samples, respectively, for scRNA-seq analysis. Transcriptomic analysis revealed an increased ratio of specific cell clusters within the CML-sorted samples. Overall, our technology provides a powerful, scalable tool for morphological profiling and sorting of live cells. Its applications span regenerative medicine, disease diagnosis, drug discovery and beyond, offering new insights and accelerating discoveries by unlocking new perspectives through its unique morphological profiling capabilities.

Funding Source: METI R&D Support Program for Growth-oriented Technology SMEs Grant Number JPJ005698.

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MODELING CHROMOSOMAL ANEUPLOIDY DURING EARLY HUMAN EMBRYOGENESIS ON MICRORAFT ARRAY PLATFORM

Ian Jan, *University of Washington, USA*
Andrew Cearlock, *University of Washington, USA*
Jacob I. Evarts, *University of Washington, USA*
Jason Y. Cain, *University of Washington, USA*
Po-Hao Chiu, *University of Washington, USA*
Neda Bagheri, *University of Washington, USA*
Min Yang, *University of Washington, USA*

Nancy L. Allbritton, *University of Washington, USA*

Human 2D gastruloids model the spatial patterning that occurs during gastrulation, which is otherwise inaccessible because of ethical and technical limitations. Specifically, this highly reproducible system enables quantitative analysis of cell signaling and fate decisions during embryogenesis. Although gastruloids can provide insights into the molecular mechanisms underlying early embryonic development, their potential for large-scale screens is limited by low-throughput analytical approaches. Furthermore, no current technology can sort single adherent cell colonies efficiently for downstream analysis. Through a multidisciplinary collaboration spanning from engineering to systems biology, we developed an innovative platform that can screen and sort gastruloids via high-throughput and -content imaging. We culture gastruloids on a microraft array, which is a poly(dimethylsiloxane)-supported array of optically clear and releasable polystyrene cell carriers ("microrafts"). These microrafts are embedded with magnetic beads for collection following release by an actuated microneedle. Photopatterning circular Matrigel islands onto each microraft to geometrically confine human pluripotent stem cells, we induce differentiation of tissue layers reflecting the germ layers and trophectoderm in a developing embryo. The automated microraft system images the cell-patterned array, performs sophisticated image processing using deep learning to detect simple-to-complex phenotypic features, and sorts gastruloids for transcriptomic analysis. We have established foundational technologies including large microrafts for culturing millimeter-sized gastruloids, reliable micropatterning protocols, and a computational pipeline that processes each gastruloid. Currently, we are using the platform to systematically assess the heterogenous patterning in gastruloids with euploid or aneuploid cells. Because aneuploidy (chromosomal abnormalities) can complicate pregnancy outcomes, we can use this platform to better understand the process of aneuploidy depletion for the recovery of healthy development. Moreover, large scale screens of gastruloids can provide insights into pregnancy losses, congenital birth defects, and tissue regeneration.

Funding Source: NIH F31 1F31HD115304-01A1 NIH R01 CA289291 Frank and Julie Jungers Endowment Funds.

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HIGH CELL DENSITY MANUFACTURING OF HUMAN INDUCED PLURIPOTENT STEM CELLS (HIPSCS) AND MESENCHYMAL STEM CELLS (MSCS) WITH ARTIFICIAL INTELLIGENCE (AI) SUPPORT

Luis G. Villa-Diaz, *Oakland University, USA*
Jack Rauch, *CellGro Technologies, USA*
Nathan Fredericks, *CellGro Technologies, USA*
Madison Clark, *Oakland university, USA*
Ana L. Gama Manon, *Oakland university, USA*
Niraj Chaudhary, *Oakland university, USA*
Hendrik Viljoen, *CellGro Technologies, USA*

Stem cell's ability to self-renew and differentiate into multiple cell lineages makes it an ideal source for cell therapies and tissue engineering. However, successful treatment strategies require large numbers of cells, ranging from 106 to 1012. To produce these large amounts with well-defined characteristics at affordable costs remains a challenge. Current culture systems include two-dimensional monolayer cultures, three-dimensional extracellular matrix-based hydrogels, three-dimensional spheroids, and hollow fibers. Despite these advancements, there is still a need for large-scale manufacture of hiPSCs and MSCs at high cell densities, while controlling the biophysical effects on the cells and maintaining uniformity of the phenotype for downstream applications. Culturing cells in hollow alginate tubes, which shield cells from shear stress, but concomitantly allow nutrients and metabolites to pass, addresses the issues of phenotype preservation and high cell production. The manufacture of alginate tubes with specified dimensions is challenging as the tube structure depends on the flow rates and physical properties of three fluids that are combined in the extruder. AI has been used to develop an automated process to extrude cells at a typical seeding density of 10^6/mL into hollow alginate tubes. This process has also been adapted to extrude micro-carriers into the alginate tubes to produce adherent cells. Once formed, the cell loaded alginate tubes are placed in a specialized bioreactor to meet a high demand for nutrients and oxygen. In these conditions, hiPSCs expanded to cell densities of 500 million/mL within the hollow alginate tubes. On the other hand, alginate tubes containing 30% (vol.) micro-carriers yield up to 80 million MSCs/mL of available space. This method achieves a ten- to twenty-fold intensification of the process, bringing us closer to large-scale manufacture of stem cells.

Funding Source: MTRAC Advanced Materials, NSF PFI 2234541.

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NEURAL NETWORKS ENABLE EARLY DETECTION OF PLURIPOTENT STEM CELL DIFFERENTIATION FOR IMPROVED ATMP QUALITY CONTROL

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Jane Synnergren, *University of Skövde, Sweden*
Nidal Ghosheh, *University of Skövde, Sweden*
Catharina Brandsten, *Takara Bio Europe Swedish Filial, Sweden*
Amin Forootan, *Multid Analyses AB, Sweden*
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Advanced therapy medicinal products (ATMPs) represent an emergent medical field, where the quality of starting material is crucial to the success of the final product. Pluripotent stem cells (PSCs) are widely used as starting material in ATMP production due to their ability to self-renew and differentiate into all three germ layers. PSCs are highly sensitive to genetic, epigenetic, and environmental perturbations, which can compromise their undifferentiated state and impact ATMP quality. Current methods for assessing PSC quality rely on the expression of established markers to identify their undifferentiated state. However, these methods fail to detect early shifts in PSC state as marker expression remains stable during the initial stages of differentiation, highlighting the need for novel approaches to accurately identify early drifts in PSC state and ensure the generation of fully undifferentiated and pluripotent PSCs. To tackle this challenge, we used Artificial Intelligence algorithms, specifically Neural Networks, which excel at modelling complex relationships and providing accurate predictions. Using single-cell RNA sequencing on six human embryonic stem cell lines, we trained a multilayer perceptron (MLP) model to accurately classify PSCs based on cell state shifts occurring as early as three days into spontaneous differentiation (undifferentiated versus early differentiated). The MLP classifier achieved an average area under the receiver operating characteristic curve (AUROC) of 88.3% when applied to test data. Feature importance analysis identified the most influential genes for MLP classification, enabling the selection of 100 key features. This reduced the model's complexity while maintaining a high performance, achieving an average AUROC value of 80.1% in discriminating PSC states. Interestingly, only 9 (3.9%) of the top-ranked genes overlap with the 228 genes reported in the ISSCR guidelines as associated with undifferentiated PSC and their differentiation. Overall, this study addresses current challenges in PSC quality assessment by accurately detecting early PSC differentiation and identifying 93 novel genes linked to PSC state. This approach enhances quality assessment of PSCs and holds potential for adaptation into an affordable, qPCR-based assay for industrial use.

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

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Allogeneic stem cell-derived therapies are being investigated for several clinical indications and represent a promising avenue for innovative therapeutic development. Despite significant advances, the rising cost of cell manufacturing underscores the need for robust methods to ensure the consistent production of potent cell products. Over the years, evidence has emerged of preferential differentiation in specific cell lines, a phenomenon commonly referred to as 'lineage bias.' Lineage bias is theorised to be influenced by intrinsic factors, including differences in gene expression and epigenetic modifications, as well as extrinsic cues from the cellular microenvironment. These external factors may involve culture conditions, cell-secreted factors, genetic variations and, in the case of induced pluripotent stem cells (iPSCs)— the tissue of origin from which the cells were derived. During in vitro differentiation processes, this can result in distinct subpopulations predisposed toward specific germinal lineages, limiting the efficiency of manufacturing the final cell product, or even preventing the final cell phenotype from being attained. This poses a critical challenge for manufacturing of cell therapies, where precise control over the trajectory of cell differentiation is essential to produce a safe, efficacious product in clinically relevant quantities. To investigate the molecular and metabolic drivers of this phenomenon, multiple hPSC lines were differentiated into derivatives of the three germ layers (ectoderm, mesoderm, and endoderm) under controlled conditions. Different methodologies were used to explore novel phenotypic signatures associated with

differentiation potential, from a range of multiomic and traditional analytical datasets. The study found differences between cells at the pluripotent stage, and temporal differences in the progression of differentiation between cell lines. These may underpin mechanisms of lineage bias, however, it is as yet unclear whether these differences are inherently biological or due to process variation. Insights gained could inform strategies to minimise lineage bias, optimise differentiation protocols, and improve the scalability and efficiency of cell manufacturing [SW1.1][MS1.2]processes for clinical applications.

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USING DEEP LEARNING BASED SEGMENTATION MODEL TO IDENTIFY THE MORPHOGENETIC PRINCIPLES OF TUBULAR ORGANOGENESIS IN VIVO

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Many major organs consist primarily of folded and branched tubes, whose correct formation is essential for proper physiological function. This project investigates the cellular mechanisms of 3D tube formation using in vivo imaging of the developing Drosophila renal system, the Malpighian tubules. Their tractable structure and the genetic accessibility of Drosophila, provides a powerful system for studying how cells sculpt tubes. I aim to characterize the coordinated and spatially patterned changes in cell shape and neighbor relationships that drive precise elongation and folding of the tubules. This project will uncover three key aspects of tubule morphogenesis: (1) characterization of dynamic shape changes of individual cells, (2) determine region-specific patterns of cell packing and shape changes in time, and (3) examination of the spatiotemporal coordination between cell intercalation and cell shape. Preliminary data show that tubule cells rapidly deform and change shape within tens of seconds during cell intercalation. These deformations vary across all cells along the tubule and the cells adopt a diverse range of 3D geometries such as scutoid shapes, complex 3D shapes characterized by a neighbor exchange along the length of the cell. During intercalation, the tubule cells initially displayed frustum-like geometries and progressively transitioned into a scutoid shape. Notably, intercalation speeds at the curve of the tubule were ~14 min, faster than the 24-49 minute range reported at the straight, distal region. The difference in speed suggests regional differences in cell dynamics that may be important for sculpting the tubule such as to balance mechanical stress during morphogenesis. These findings add to previous 2D analysis of tubule morphogenesis and underscore the value of full 3D cell geometry

analysis in revealing complex, spatially patterned cell behaviors. To fully characterize the diversity of all tubule cell dynamics, I am developing a deep learning-based pipeline for 3D cell segmentation and tracking to quantify cellular changes and morphological patterns. Understanding these processes will uncover general principles of cell coordination in organ formation offering insight into when these processes are disrupted in developmental disorders and disease states.

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PROTEIN LANGUAGE MODEL MEDIATED ENGINEERING OF AN INHIBITOR-RESISTANT RECEPTOR TYROSINE KINASE

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Receptor tyrosine kinases (RTKs) are critical regulators of cellular signaling pathways that govern proliferation, survival, and differentiation, making them central to therapeutic strategies in cancer, immunology, and regenerative medicine. Engineering RTKs to modulate their signaling or alter drug sensitivity offers a powerful route to fine-tune cellular responses in a variety of therapeutic contexts. However, systematically tuning RTK activity remains challenging, as it typically requires time-intensive and expensive mutagenesis studies to dissect how individual residues affect receptor function and inhibitor response. We used a protein language model, developed with OpenAI, trained on homologous protein sequences to generate a focused library of RTK variants conditioned on RTK sequences known to confer resistance to a clinically relevant inhibitor of the wild-

type (WT) receptor. This library was screened in a high-throughput fashion for both receptor phosphorylation and resistance in the presence of the inhibitor, enabling identification of variants with preserved signaling activity and inhibitor insensitivity. Several variants showed robust expression and phosphorylation while maintaining ligand dependent signaling function in the presence of the inhibitor treatment. Our results establish a generalizable framework for precision engineering of RTKs using language model-guided sequence design coupled with functional screening. This approach enables rapid development of RTK variants with tailored properties, offering a powerful platform for advancing engineered cell and gene therapies that require tunable receptor activity.

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CZ CELLXGENE DISCOVER: A SINGLE-CELL DATA PLATFORM FOR SCALABLE EXPLORATION, ANALYSIS AND MODELING OF AGGREGATED DATA

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CZ CELLxGENE Discover (cellxgene.cziscience.com) is a free-to-use online data portal hosting a growing corpus of more than 1800 single-cell datasets comprising over 115 million unique cells from the major human and mouse tissues. All data have been curated to include consistent cell metadata, such as cell type, tissue, and donor age and disease, each standardized to a community ontology. The metadata schema and required raw counts indexed by Ensembl gene identifiers enables searchability and reusability of the data. Recent updates to the schema has allowed for support of ATAC-seq, Visium, and Slide-seq assays. The CELLxGENE Explorer displays an interactive 2-dimensional representation of cells in a dataset and allows users to color cells by metadata (e.g. cell type, disease, metadata features etc.) or gene activity. Users can also subset and analyze subgroups of cells, perform differential gene expression and create scatter plots of gene expression. The Gene Expression feature allows querying the expression of any gene across all human and mouse cell types available in the portal, and enables lookup of differentially enriched genes for any cell type. The Cell Guide feature allows users to explore an interactive encyclopedia of 900+ cell types that provides detailed definitions, marker genes, lineage, and relevant datasets in one place. The Differential Expression tool allows for calculation of differentially expressed genes between custom groups of cells across the CELLxGENE corpus. The CELLxGENE Census is a cloud based platform that allows for

data access, efficient cell-based queries and analysis of cells regardless of the dataset of origin. Standardized metadata allows for subsetting and slicing of the data in AnnData, Seurat, and SingleCellExperiment objects. The Census also hosts pre-calculated embeddings and pretrained models, enabling cell type prediction and data projection of new query data. CELLxGENE is a tool intended for community use and contributions. By supporting multiple modalities and data generated by labs around the world, the CELLxGENE suite of tools and data aims to maximize rapid use of high quality data describing the phenotypes of cells and tissues. To date, CELLxGENE supports data sharing from worldwide labs as well as consortia such as the CZ Biohub Tabula projects, LungMap, BICCN, Allen Institute for Brain Science, KPMP, HTAN and the Human Cell Atlas. Groups interested in submitting their own data can inquire about the inclusion of your data and the submission process by contacting the CELLxGENE team at cellxgene@chanzuckerberg.com.

Funding Source: Chan Zuckerberg Initiative.

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A COMPUTATIONAL METHOD TO CAPTURE HIGH-RESOLUTION HIERARCHICAL RELATIONSHIPS IN CELL POPULATIONS TO FACILITATE SINGLE-CELL ANALYSIS AT SCALE

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Advances in single-cell technologies have enabled the high-resolution profiling of complex biological systems at unprecedented scales. While this wealth of information has the potential to uncover insights across tissues, developmental stages, and disease states, it also presents formidable computational challenges. In particular, the pace of data generation is rapidly outstripping our capacity to analyze and interpret it, underscoring the need to develop efficient strategies to extract meaningful insights without sacrificing rigor and resolution. Here, we present MILK (Multi-resolution Integration of Large-scale and high-dimensional Kernel information), a recursive, distance-based approach to capture the hierarchical structure of cell populations in linear time. Applied to a human fetal cell atlas composed of 4-million single-cells, we demonstrate how this hierarchical information can be leveraged to generate representative subsamples that can mitigate technical noise, thereby enriching for robust biological signal. Next, we applied MILK to a 12-million-cell mouse prenatal developmental atlas, where we show that the cell relationships effectively

capture dynamic gene expression patterns consistent with established trajectory inference methods. Finally, we applied this method to the Chan-Zuckerberg CELLxGENE census, where we demonstrate how it can facilitate comprehensive benchmarking analyses of foundation models in biology at multiple resolutions. We further extend this analysis to showcase how access to the global hierarchical relationships can represent a powerful means to explore the dysregulation of cells in various disease contexts, potentially uncovering linkages between seemingly unrelated cell states. By focusing efforts on exploring the massive amounts of data we have, this method aims to enable more accessible and approachable large-scale inference to identify emergent biological properties using economic computing resources.

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KNOWLEDGE GRAPH GUIDED IMAGE EMBEDDING, UNDERSTAND THE PERTURBATION FROM CELLULAR IMAGES

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Cell Painting, a high-content screening (HCS) assay that uses up to six fluorescent dyes to stain subcellular structures, has emerged as a powerful tool for identifying compounds that alter cellular phenotypes in drug discovery. Traditionally, morphological features extracted from Cell Painting images have been used to infer the biological effects or mechanisms of action (MOA) of these perturbations. However, current approaches often treat MOA as isolated, categorical labels in classification tasks, overlooking the intricate interactions that occur within biological systems. In reality, drug targets are interconnected through complex biological pathways, and a single drug can act on multiple targets. Additionally, drugs with different MOAs may share common targets, suggesting that the distance or relationship between drugs should reflect their target and pathway interactions. To address this, we propose a novel representation learning method that integrates cellular morphological analysis with a biological knowledge graph. First, we generate drug embeddings based on their associations with biological targets and

pathways. These embeddings are then used to guide feature extraction from Cell Painting images, ensuring that the extracted morphological features not only provide insights into the compound's MOA but also capture relationships between different MOAs. This approach allows for a more nuanced understanding of drug mechanisms by combining visual phenotypic data with biological network information, potentially leading to more accurate predictions of drug behavior and interactions in complex biological systems.

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UNLEASHING THE POWER OF AI-DRIVEN DRUG DISCOVERY WITH A 100 MILLION SINGLE CELL ATLAS

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Single cell RNA sequencing has transformed our ability to profile heterogeneous biological systems by capturing cell-type-specific transcriptional responses with high resolution. This granularity is especially valuable for drug discovery, where understanding how individual cells respond to perturbations can reveal mechanisms of action, pathways driving resistance, and novel biomarkers. As AI becomes central to drug discovery, the need for

large-scale, high-resolution datasets has grown. Yet most existing datasets lack the scale and complexity required to effectively train machine learning models.To bridge this gap, we applied our novel high-throughput combinatorial barcoding approach to generate an atlas of over 100 million single cell transcriptomes from cancer cell lines exposed to hundreds of drugs. This resource sets a new benchmark for enabling predictive modeling of drug response. In this first-of-a-kind study, 50 proprietary cancer cell lines (Tahoe Therapeutics) were co-cultured then treated with 379 drugs at three concentrations. Following treatment, cells were dissociated, fixed, and pooled for combinatorial barcoding using Parse Biosciences' GigaLab platform, enabling batches of >10 million cells per run while maintaining transcriptome integrity. Post-barcoding steps, including cDNA capture, PCR, library preparation, and clean up were automated in 96-well format. The entire experimental workflow from cell treatment through library generation was completed in less than 5 weeks. Sublibraries were converted for the UG 100™ sequencer (Ultima Genomics), and the resulting data were processed with Parse's pipeline and demultiplex using Demuxlet. Spanning over 100 million cells and 56,000 conditions, this dataset represents a unique and scalable resource for AI-based biological modeling and therapeutic discovery, supporting next-generation efforts in drug response prediction and systems-level perturbation analysis.

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FLOW-REGULATED PATHOGENESIS OF HYPOPLASTIC LEFT HEART SYNDROME IN A 3D BIOPRINTED HUMAN HEART TUBE

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Hypoplastic left heart syndrome (HLHS) is a severe congenital heart defect (CHD) marked by the underdevelopment of the left heart. Despite the prevalent theories of genetic and hemodynamic perturbations being the potential causes, molecular mechanisms underlying the HLHS pathogenesis remain obscure. Recently, we reported a human

induced pluripotent stem cell (hiPSC)-based 3D bioprinted embryonic heart tube (eHT) model that shows recapitulation of robust cardiac function and cardiogenic cellular activities upon hemodynamic flow initiation. To delineate the individual and synergistic effects of genetic and hemodynamic perturbations in HLHS, we generated wildtype (WT) vs. HLHS cardiomyocytes (CMs) and endocardial cells (ECs) from hiPSCs via WNT and BMP10 signaling modulation. 2D monocultures and 3D eHT perfusion cocultures were conducted and assessed for HLHS-associated gene expression, contractile function, and cellular structure and interactions using qPCR, video-based contractility analysis, single-cell RNA-sequencing, and immunohistochemistry. Computational simulation characterized the hemodynamic-contractile coupling under varying contractility and flow conditions. Further, integrated perfusion-electrical conditioning was applied chronically to WT vs. HLHS eHTs, modeling HLHS phenotype induction in response to developmental cardiac loading and electrophysiological changes. Transcriptomic and immunohistochemistry analyses in 2D monocultures revealed intrinsic proliferation defects in CMs and novel endocardial defects in ECs derived from HLHS hiPSCs. In 3D, both WT and HLHS eHTs demonstrated long-term viability and cardiac function under flow perfusion, while the additional electrical conditioning enhanced contractile adaptation over time. Preliminary data from flow perfusion also suggested an effect of hemodynamic perturbations on developmental EC gene expression. This study highlights the causal and exacerbatory interactions of intrinsic genetics and extrinsic hemodynamic perturbations in HLHS pathogenesis in a 3D bioprinted eHT model, suggesting novel therapeutic targets.

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HUMAN GENE REGULATORY NETWORK INFERENCE THROUGH A CUSTOM PETER-CLARK ALGORITHM

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A human gene regulatory network (GRN) illustrates transcriptional gene regulatory cascades within cells. Deciphering the cascades of causal regulator genes and their target

genes through biological measurements to understand disease progression and development has become a major focus in biology today. While many existing GRN inference algorithms leverage large-scale single-cell RNA sequencing data using regression models, they suffer from high false-positive rates, due to the intricacy of transcription regulatory network causing many gene pairs to numerically correlate even if they are not TF-gene pairs. In contrast, causal discovery algorithms, particularly the Peter-Clark (PC) algorithm, effectively eliminate false causal relationships. However, PC tends to over-prune true regulator–target pairs and has high computational costs. To address these challenges, we propose two key modifications to the PC algorithm: (1) reducing uninformative statistical tests through graph theory to avoid accidental removal of true TF-gene edges, and (2) introducing biased causal discovery to enable a divide-and-conquer approach for large datasets by leveraging local sample agreement. Furthermore, to improve computational efficiency, we implemented our custom PC algorithm, termed PCC, in C programming with dynamic multithreading acceleration, achieving a runtime reduction of over three orders of magnitude compared to the current de facto standard implementation of PC in Python. Our implementation has been shown capable to achieve de novo discovery of E. coli GRN. We believe PCC could enable robust human GRN inference through the PC concept, potentially resulting in a more robust understanding of gene regulation in broader biology research.

Funding Source: United Therapeutics Corporation, Canadian Institutes of Health Research, CIFAR, Canada Foundation for Innovation.

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GAT2I: A BIOLOGICALLY INSPIRED GRAPH ATTENTION NETWORK FOR INTERPRETABLE PREDICTION OF A-TO-I RNA EDITING SITES

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Adenosine-to-inosine (A-to-I) RNA editing, catalyzed by ADAR enzymes, is a widespread and functionally important post-transcriptional modification in metazoans. Despite decades of research — from classical biochemical assays and high-throughput sequencing pipelines to machine learning and deep learning models — computational

prediction of editing sites remains a challenging problem. Prior methods have demonstrated limited success in terms of sensitivity, specificity, or biological interpretability. We introduce GAT2I, a novel biologically inspired Graph Attention Network (GAT) architecture designed specifically for predicting A-to-I editing sites by integrating both RNA sequence and secondary structure into a unified graph representation. The model is trained on approximately 20,000 labeled RNA segments, comprising validated editing sites. Unlike previous models that treat sequences linearly or employ opaque neural architectures, GAT2I constructs explicit RNA graphs, where nucleotides serve as nodes and both sequential and base-pairing interactions form the edge structure. This biologically grounded design enables the model to capture cis-regulatory dependencies of ADAR editing — including stem-loop contexts and position-specific sequence motifs — without relying on engineered features or black-box encodings. The use of graph attention layers not only enhances predictive performance but also enables interpretability: attention weights reveal which sequence or structural neighbors contribute most to each prediction. We validate this interpretability through an attention-based reverse analysis using XGBoost and SHAP, showing that attention patterns alone retain substantial predictive power, confirming their biological informativeness. Empirically, GAT2I outperforms previous models across 16 cross-tissue scenarios, achieving F1-scores above 0.8 and demonstrating strong generalization. Notably, our extended experiments show that performance scales positively with more data, highlighting the model's capacity to learn increasingly complex editing determinants from biologically noisy contexts. These insights are increasingly relevant, as ADAR-based RNA editing is emerging as a promising therapeutic strategy for correcting pathogenic mutations without altering the genome.

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MIRAGE: MANIFOLD-INFORMED GENE-MODULE EXTRACTION FOR DISENTANGLING SIMULTANEOUS DYNAMICS IN SINGLE-CELL RNA-SEQ

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Single-cell RNA-seq (scRNA-seq) enables fine-grained tracking of how pluripotent or induced progenitor cells navigate complex differentiation landscapes, yet multiple concurrent programs, such as cell-cycle, stress responses, intercellular signalling, can still blur these trajectories and mask key biologies. For instance, the transcriptomic programs regulating the dynamics of cell cycling could be distinct from those regulating DNA damage repair. These concurrent programs can result in existing pseudotime or RNA velocity methods to either conclude there are no meaningful trajectories, or conclude overly complex and misleading trajectories. To address this limitation with existing methods, we develop MIRAGE (Manifold-Informed Gene-module Extraction) to provide a novel hypothesis-testing framework based on cellular manifold structure to untangle and characterize such concurrent biological programs to assist with biological discoveries. MIRAGE first constructs a k-nearest-neighbor cell graph for every preliminary gene set, then examines genes outside those sets, which we term as bystander genes. For each graph it computes a Laplacian score that captures how smoothly a bystander's expression changes across neighboring cells. If the two score distributions are indistinguishable under a permutation test, the modules are merged, progressively yielding a biologically coherent catalogue of transcriptional programs. We apply MIRAGE to understand development in the human fetal pancreas, where it 20 preliminary clusters into three statistically distinct programs that highlight beta vs alpha cell identity, progenitor maturation, and cycling ductal cells, respectively, whereas canonical correlation collapses into a single module. We also apply MIRAGE to the CellTag lineage-tracing dataset that follows the reprogramming of mouse embryonic fibroblasts (MEFs) into induced endoderm progenitors (iEPs), integrating clonal barcodes with the manifolds discoveries in MIRAGE to expose how cell-cycle and lineage-commitment programs interact during reprogramming. By nominating program-specific regulators, MIRAGE can provide a ranked list of CRISPR targets to test causal roles of each module.

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INTERACTIONS OF TRANSCRIPTION FACTOR AP2A AND TRANSCRIPTION FACTOR 4 PREDICTED BY ALPHAFOLD3 AND THEIR INFLUENCE ON OSTEOGENIC DIFFERENTIATION DURING IN VITRO AGING HBMSCS

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Due to their scarcity, usually, only limited quantities of primary tissue-derived stem cells (TDSCs) can be isolated from tissues. To generate sufficient cells for research and therapeutic applications, in vitro expansion of primary TDSCs is needed. However, it is known that in vitro expansion causes a loss of stemness (proliferation and differentiation potentials) in TDSCs, a significant challenge preventing the production of large quantities of high-potential TDSCs through cell culture. The underlying mechanism causing the loss of differentiation potential is mainly unknown. We found that transcription factor AP2a (AP2a) and transcription factor 4 (TCF4) increased expression during in vitro expansion of human bone marrow stem cells (hBMSCs), which coincided with the loss of osteogenic differentiation ability of the cells. Importantly, the knockdown of AP2a and TCF4 could additively or synergistically rescue (restore) the compromised osteogenic differentiation ability due to the in vitro expansion of the cells. Using AlphaFold3 in the neurosnap platform, we predicted the interactions of AP2a and TCF4, suggesting that they can form protein complexes, which may explain their additive or synergic role in regulating hBMSC differentiation, and their perturbation may cause the loss of osteogenic differentiation observed during in vitro expansion of hBMSCs.

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SINGLE-CELL MULTI-OMICS UNCOVERS DISTINCT TRANSCRIPTOMIC AND EPIGENETIC DYNAMICS DRIVING REPROGRAMMING HETEROGENEITY IN HUMAN IPS CELL INDUCTION

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Somatic cell reprogramming into human induced pluripotent stem cells (iPSCs) is highly heterogeneous, and improving its efficiency remains a major challenge for its application in regenerative medicine. While early-stage transcriptomic heterogeneity has been linked to reprogramming outcomes, its relationship with epigenetic regulation remains not fully understood. To address this question, we performed time-series single-cell multiome

analysis of human dermal fibroblasts undergoing iPSC induction. By inferring cell trajectories between discrete time points using an optimal transport algorithm, we identified “early primed” subpopulations that were predicted to ultimately undergo successful reprogramming even prior to the induction of reprogramming factors. These subpopulations were characterized by the intersection of “early priming” marker genes previously identified through barcode-based lineage tracing along with distinctive functional features such as accelerated proliferation and enrichment of cell cycle progression markers. However, chromatin accessibility analysis revealed that enhancers associated with these marker genes in a specific manner for this subpopulation were rarely detected. Instead, we observed large-scale epigenomic changes in genes located upstream or downstream of these markers within the regulatory network. To dissect the regulatory system underlying the early primed state, we performed deep learning–based motif analysis across different time points. Given that cooperative transcription factor binding plays a key role in reprogramming, we systematically explored conditions under which both proximal and distal interactions could be inferred. This approach revealed the epigenetic regulatory landscape of heterogeneous cell populations and identified key factors that govern the transition from the early primed state to successful reprogramming.

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SCALING PROTEOMICS FOR AI/ML: INSIGHTS FROM QUANTIFYING 1,000 PROTEINS IN 20,000 HUMAN CELL LINE SAMPLES

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Perturbation screens are increasingly used to explore system responses, dependencies, vulnerabilities, and regulatory pathways. The resulting data support drug discovery, the development of foundation models, and in silico biology initiatives such as the virtual cell. These studies require large-scale, biologically relevant readouts. While morphology-based profiling and transcriptomics are widely used, proteomics has the potential to be a more powerful read-out as it yields ground-truth insights into the functional state of cells. However, the application of high plex proteomics to high-throughput perturbation screens has been limited by high cost, the difficulty of scaling throughput, and lack of quantitative

interoperable data. The nELISA is an affinity-based proteomics platform that quantifies >1000 proteins in parallel, at high throughput and low cost, making it suitable for perturbation screening. We used nELISA to measure 1,000 proteins across 20,000 samples, generating 20 million data points. Supernatants were collected from hepatocytes, cardiomyocytes, and microglia treated with 510 compounds at three concentrations. Perturbations were applied with or without relevant stimuli—thapsigargin (ER stress), angiotensin II (cardiac hypertrophy), or LPS (neuroinflammation). This diverse screen enabled the identification of >30,000 compound–protein interactions in hepatocytes alone, yielding signatures associated with cell type, disease context, and compound mechanism. For example, bortezomib strongly potentiated thapsigargin toxicity in hepatocytes, consistent with its role as a proteasome inhibitor that impairs protein degradation and exacerbates ER stress. In contrast, the mTOR inhibitor temsirolimus mitigated thapsigargin-induced toxicity by enhancing stress-response protein synthesis and reducing global translation, thereby relieving ER burden. Temsirolimus also partially reversed the thapsigargin-induced protein signature, including changes in metabolic proteins such as IGFBP3 and folding regulators like QSOX1—consistent with modulation of the Unfolded Protein Response (UPR). Other compounds targeted distinct UPR arms: for example, tacrolimus targets the calcium-induced inflammatory response, and thus suppressed thapsigargin-driven changes in chemokines (e.g., CCL7, CCL8, CCL22). In addition to recapitulating known regulatory pathways, protein profiles provided insights into compound toxicities. Thus, classically toxic compounds such as staurosporin, ouabain, and actinomycin D resulted in extensive cell death, and increased presence in the supernatant of canonical inducers of apoptosis such as caspases, and other generally intracellular proteins such as GAPDH. These toxicity signatures were dose dependent, and could be distinguished from biologically active changes in cellular phenotypes at sub-toxic doses. Importantly, these signatures predicted clinical toxicities of several compounds, highlighting the potential of proteomic screens to capture toxicities earlier in drug development pipelines. We will discuss the dataset's applicability to improve foundational models for toxicity predictions and other AI-enabled applications, such as the virtual cell.

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A MANUFACTURING PLATFORM THAT ENABLES AI SOFT-SENSOR MODELING IN CULTIVATED MEAT PRODUCTION

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Bioprocess manufacturing of commercial products in multi-cellular organisms has rapidly expanded with the rise of biotherapeutics, cell therapies, and more recently, cultivated meat. Despite transformative progress, high costs and product variability remain key challenges in biomanufacturing, highlighting the growing need for soft-sensor modeling. Leveraging AI tools and infrastructure, these models offer the potential to improve process control, enable early failure identification, and enhance product consistency. Here we present the Manufacturing Intelligence (MI) platform, a framework for collecting, integrating, and structuring diverse bioprocess data, as well as for building, deploying, and maintaining AI models across development and manufacturing. It captures real-time sensor data across bioreactor scales, experimental designs, multi-platform analytical assays, and final product critical quality attributes. The platform supports cultured cell processes scaling up over 80-fold and cell lines transitioning from biopsy to commercial-scale production. We describe the foundational infrastructure—built using tools like LabKey, Snowflake, and AWS—that underpins data harmonization and ML readiness. We then demonstrate two soft-sensor models developed using our mammalian stem-cell-derived lines. The first predicts viable cell density (VCD) and metabolite concentrations (glucose, lactate) from process parameters and in-line sensors, enabling proactive control based on early consumption trends. Using 10-fold cross-validation on ~2,000 data points, it achieved an R^2 of 0.93 for VCD and 0.67 for glucose. The second model applies an LSTM autoencoder for real-time anomaly detection and early failure identification. Both models operate within a continuous learning environment using version control and cloud compute, and can be extended to hybrid ML–mechanistic frameworks. We conclude by showcasing the platform's dashboard and alerting tools, which surface key insights to scientists, executives, operators, and model developers. This work provides a practical, extensible foundation for accelerating AI-enabled biomanufacturing in commercial bioprocessing applications.

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TRANSCRIPTIONAL RESURRECTION IN IPSC-DERIVED MOTOR NEURONS TO BOOST POOLED OPTICAL SCREENING EFFICIENCY

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Optical pooled CRISPR screening (OPS) methods enable the investigation of high-content, imaging-based phenotypes resulting from genetic perturbations made to individual cells in a pool. At insitro, we built the Pooled Optical Screening in Human Cells (POSH) platform, in which the repetitive in situ sequencing (ISS) liquid handling and microscopy steps are conducted on an automation workcell. This platform has enabled insitro to rapidly conduct POSH screens and discover novel genetic targets for multiple disease areas. We leverage the POSH platform for target discovery in neurodegenerative disease areas using iPSC-derived motor neurons (hNILs) with overexpression of neurogenin 2 (NGN2), islet 1 (ISL1) and LIM homeobox containing 3 (LHX3) transcription factors. However, optical screening in hNILs is difficult in part due to inefficient transcription of sgRNAs leading to poor barcoding efficiency. To address this limitation, we adopted an emerging OPS method which introduces a U6-T7 hybrid promoter to drive T7 in vitro transcription (IVT) of barcodes in fixed cells after phenotyping and before ISS. Amplicons generated from performing padlock probe binding, gap-fill, and rolling circle amplification on the highly abundant T7 transcripts are large, bright, and localized to the nucleus. These changes in signal intensity and localization greatly enhance the ease and accuracy of barcode calling and assignment to cells. With this approach, we achieved at least a threefold increase in the number of correctly barcoded cells compared to conventional OPS. Further, we successfully paired this method with FISH, CellPaint, and antibody staining, ensuring the compatibility of the in vitro transcription protocol with multiplexed phenotyping in hNILs. Funded through our BMS partnership.

Funding Source: Funded through our BMS partnership.

THURSDAY, 9 OCTOBER 2025
POSTER SESSION 2 (EVEN): 5:30 PM – 6:30 PM

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INFERRING TRANSCRIPTION FACTORS DRIVING CELL FATE DECISIONS IN EARLY-STAGE HUMAN DEVELOPMENT USING TERATOMA AS A MODEL

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Understanding of early-stage human development has been hindered by ethical constraints in establishing causality via in vivo perturbation experiments. Model organisms which capture conserved developmental processes fail to reveal human-specific features. Teratoma, a pluripotency benchmarking assay derived from human pluripotent stem cells, has been shown to enable multi-lineage differentiation into fetal-like cell types, complex cell-cell interactions among nonhomogeneous cell types, and systematic CRISPR-based perturbations. In this study, we leverage the teratoma assay to model early-stage human development and investigate transcriptional regulation in both human fetal and teratoma-derived tissues across developmental stages using a gene regulatory network (GRN) inference tool. We observed that GRNs reconstructed from teratoma-derived cell types share key features with those derived from human fetal tissues, supporting the developmental relevance of the teratoma model. The identified candidate transcription factors involved in lineage specification and cell fate transitions and the genes they regulate are validated against with previously published data. Lastly, we proposed transcription factor recipes based on GRN and perturbation prediction results for directed differentiation towards fetal-like cell types in teratoma. Our approach presents a framework of applying GRN inference tools in developmental systems to alleviate experimental burden in differential protocol design and enable scalable generation of physiologically relevant, perturbable fetal-like cell types.

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DEVELOPING CARDIAC-SPECIFIC PERTUBATION DATASETS FOR ML/AI-GUIDED CARDIAC DRUG DISCOVERY

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Perturbation datasets including Connectivity Map/LINCS, DepMap, and RxRx have been critical for AI-driven drug discovery and repurposing, with LINCS L1000 providing over 3 million profiles from 80,000 perturbagens across 70+ cell lines. However, these foundational resources are overwhelmingly cancer-focused. Equivalent perturbation resources for cardiac biology remain absent, creating a critical bottleneck for AI-guided cardiac drug discovery. To address this, we have completed phase 1 of the first cardiac-specific perturbation dataset designed for AI/ML applications. We have profiled functional (contraction force and kinetics) and transcriptional signatures for 80 endogenous ligands and 10 small molecule agonists targeting 103 cell membrane receptors in multicellular human cardiac organoids (hCOs). For the throughput and reproducibility required, we have developed semi-automated capacity across the pipeline and are able to produce >1000 hCO per week. Standardization and liquid handling supports the cell differentiation, organoid formation, and culture. Tempo.ai, a cloud-based platform, was implemented to automate hCO quality control and analysis of contractile data including force and kinetic parameters. A semi-automated single hCO RNA-seq pipeline was developed to generate transcriptional signatures for all compounds. Together these enable paired functional-transcriptional datasets with the required reproducibility and format for supervised learning approaches. Human heart failure with preserved ejection fraction (HFpEF) is an unmet clinical need with limited therapeutic targets. We employed supervised regression modeling to identify gene expression patterns associated with impaired relaxation rate – the diastolic dysfunction that causes HFpEF. This analysis identified NPPB a clinically used heart failure biomarker as a confirmatory positive control, in addition to markers related to actin cytoskeleton function and pathological remodeling (including ANKRD1 and XIRP1) – forming a set of putative therapeutic targets. This work establishes phase 1 of the first comprehensive cardiac-specific perturbation resource - Cardiopedia. This will provide critical datasets for AI and machine learning applications in heart failure drug discovery pipelines.

Funding Source: This work has been funded by Snow Medical.

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CARDIAC PHENOMAPPING FOR MULTI-MECHANISM DRUG CLASSIFICATION

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Enzo R. Porrello, *Murdoch Children's Research Institute, Australia*

Development of therapeutic drugs for cardiac diseases is exceptionally challenging. Meeting the multiple of targets of maximizing on-target efficacy of lead candidates, while negating harmful off-target effects, continues to hamper preclinical drug development, pushing all stakeholders to look at new methods, models and approaches. Our human pluripotent stem cell-derived cardiac organoid (hCO) model has been developed to aid in the target discovery and preclinical development of new therapeutics. They have displayed their utility in the early pre-clinical development of regenerative compounds, and in the repurposing of a bromodomain and extraterminal protein inhibitor. We have recently made significant improvements to the hCOs, demonstrating, with increased maturity, their ability to recapitulate aspects of complex cardiac diseases, and respond faithfully to multiple classes of cardioactive drugs. As identifying a putative mechanism of action early in therapeutic discovery is important, we have sought to enable a mechanism-informed phenotypic screening approach by training a supervised machine learning model on a diverse set of drug-perturbation data. So far, this includes 3-7 concentrations of 25 drugs, belonging to 8 drug classes, totalling >800 individual samples. An ExtraTrees model trained to classify the mechanism being activated or perturbed by these drugs achieved >70% test accuracy. Drug classes included, Gq/IP3R activators, Gs/cAMP activators, phosphodiesterase inhibitors, sarcomeric activators, sarcomeric inhibitors, sodium channel blockers, potassium channel blockers, and calcium channel blockers. We are currently expanding our training set to include other drug mechanisms. We are also exploring the use of a multitask classification model that can handle the mixed-mechanisms of action of many cardioactive drugs. We hope that the integration of efficacy and safety profiling the hCOs provide, enhanced with mechanism-of-action prediction, will interface naturally with existing pre-clinical drug development pipelines.

Funding Source: This research was supported by Snow Medical Research Foundation grant no. SMRF2019-060.

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IMPORTANCE OF HIGH-DENSITY MICROELECTRODE ARRAYS FOR RECORDING MULTI-SCALE EXTRACELLULAR POTENTIAL AND LABEL-FREE CHARACTERIZATION OF NETWORK DYNAMICS IN IPSC-DERIVED NEURONS

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Advances in microelectrode array (MEA) technology for in-vitro electrophysiological recordings have made it possible to investigate neuronal networks at multiple scales, ranging from subcellular features to overarching network dynamics. These systems are essential for studying neurological disorder phenotypes and accelerating drug discovery, offering detailed insights into neuronal network behaviour. Electrode characteristics, including density, spacing, and size, play a key role in signal quality, noise, and sensitivity. To comprehensively characterize neuronal networks, MEAs must combine single-cell and subcellular resolution with high-throughput capabilities, while maintaining sensitivity to small extracellular action potentials to capture the full range of network activity. In this study, the MaxOne high-density (HD) MEA system (MaxWell Biosystems, Switzerland) was used to record activity from induced pluripotent stem cell-derived neurons. HD-MEA data was compared to simulated low-density recordings, generated by clustering adjacent electrodes to emulate the signal characteristics of larger, lower-density electrodes. In addition, the AxonTracking Assay – an automated tool for simultaneously analysing axonal arbours from multiple neurons – was utilized to assess axonal structure and network functionality in the cultures. The findings indicated that higher electrode density and smaller electrode size enhance sensitivity, enabling the detection of smaller spikes and capturing the complete spectrum of network dynamics. The combination of high-resolution analysis of network activity with subcellular insights from the AxonTracking Assay, offers a robust platform for drug screening and disease modelling.

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

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A HIGH-THROUGHPUT, ISOGENIC IPSC PLATFORM FOR ADVANCING SINGLE-CELL FOUNDATION MODELS

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Current single-cell foundation models for predicting cellular responses to genetic perturbations are limited by data derived from conventional methods like CRISPR or RNAi, which often lead to incomplete gene knockout. We here developed a high-throughput platform leveraging Geno-Writing™ technology to generate an induced pluripotent stem cell (iPSC) library with complete and precise inactivation of target genes. Our platform can

produce hundreds of distinct, single-gene knockout iPSC lines within approximately 100 days in a semi-automated fashion. We then differentiate these precisely engineered iPSCs into major organ lineages relevant for regenerative medicine, followed by single-cell RNA sequencing (scRNA-seq). Originating from a single, parental iPSC clone, the library can be highly isogenic, which significantly reduces experimental noise and yields high-fidelity perturbation data. This data can dramatically enhance single-cell foundation models to inform genome design principles for developing iPSCs with improved differentiation efficiency into desired organ lineages and a reduced risk of unintended differentiation or dedifferentiation after transplantation. We believe our data generation platform will accelerate advancements in regenerative medicine and future medicine.

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INTERPRETABLE REPRESENTATION LEARNING FOR 3D MULTI-PIECE INTRACELLULAR STRUCTURES IN HUMAN INDUCED PLURIPOTENT STEM CELLS (hiPSCs) USING POINT CLOUDS

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A key challenge in understanding subcellular organization is quantifying interpretable measurements of intracellular structures with complex multi-piece morphologies in an objective, robust and generalizable manner. To address this, we introduce a deep learning framework that learns compact and interpretable representations of morphology, independent of the structure's 3D orientation. Our method converts 3D microscopy images

into point clouds and employs a rotation-invariant autoencoder to analyze their shape. Using a large dataset of fluorescently-tagged human stem cell lines, we benchmark our framework on punctate (DNA replication foci) and polymorphic (nucleoli) structures. Compared to standard image-based autoencoders, our morphology-aware approach is more effective at the unsupervised discovery of distinct morphological sub-clusters. We showcase a practical application by using the framework for phenotypic profiling of nucleoli following drug perturbations. To accelerate research in this area, we provide all models in our open-source Python package, CytoDL, alongside the extensive 3D image datasets and analysis tools at allencell.org.

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PIXEL-BASED COMPUTER VISION APPROACH FOR ENDOTHELIAL CELL JUNCTION ANALYSIS IN HUMAN BRAIN MICROVESSEL IMAGES

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Ying Zheng, *University of Washington, USA*

Understanding the morphological integrity of endothelial cell junctions is essential for in-depth investigation of endothelial dysfunctions and identifying therapeutic strategies for diseases. Conventional imaging analysis tools often rely on segmentation-based workflows that attempt to delineate individual cells or junction structures using predefined thresholds or trained models. However, these methods can be biased by subjective parameters, fail in low signal-to-noise conditions, and struggle with morphologically diverse or disrupted junctional structures. To address these limitations, we developed a novel pixel-based computer vision tool designed to extract and interpret quantitative features from endothelial junctions without relying on explicit segmentation. Our method focuses on high-resolution confocal immunofluorescence images of human brain microvessels stained with VE-cadherin (for adherens junctions) and DAPI (for nuclear localization). Using nuclei centroids extracted through Cellpose, we define spatially meaningful regions between nearest-neighbor nuclei by constructing bisector-aligned rectangular sampling windows. Within each region, we extract 21 parallel pixel intensity profiles along the VE-cadherin channel, capturing junction continuity and organization. From these profiles, we computed biologically interpretable features including peak intensity, signal spread, entropy, tortuosity, and fractal dimension, which reflect both the sharpness and complexity of junction morphology. Unlike segmentation-based methods, our approach is unbiased,

does not require manual annotations or training on labeled masks, and preserves nuanced morphological variations that may be lost in binary segmentations. The pixel-centric analysis enables the detection of subtle, continuous changes in junction architecture—critical for studying transitional or abnormal states of cell-cell contact. We applied ensemble learning models to classify regions into junctional phenotypes: stable, tortuous, and internalized or disrupted, which are characteristic of different vascular responses in disease contexts. We then trained and tested our model on approximately 200 images from controlled 3D vessel environments, with preliminary results showing a strong correlation between extracted features and expert annotations. Next, we used dimensionality reduction (PCA) and clustering methods to explore natural groupings of junction morphology across datasets. This unsupervised analysis highlighted previously underappreciated morphological gradients and lays the groundwork for building an explainable AI (XAI) pipeline that offers interpretable visual feedback for users and researchers. In this project, we developed a computational tool capable of analyzing subtle morphological variances in VECAD junctions. One of the core strengths of this method is its scalability and generalizability,;. The non-segmentation-based approach enables the analysis toolkit to be readily applied to a wide variety of vascular imaging datasets, including different endothelial cell types (arterial, venous, and microvascular), various experimental conditions (e.g., hypoxia, drug treatment), and other imaging modalities. By quantifying endothelial junctional morphology in a scalable, interpretable, and unbiased manner, this tool has the potential to accelerate both basic research and therapeutic screening in vascular biology, particularly in applications involving injury, regeneration, and drug response. Future work aims to focus on expanding the pipeline to include additional datasets, including various endothelial cell phenotypes and pathological states, to build a robust feature database that supports automated vascular phenotyping across contexts beyond VECAD junctional analysis.

Funding Source: Funded by the University of Washington and the Institute for Stem Cell and Regenerative Medicine (ISCRM).

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BUILDING A PIPELINE FOR LARGE-SCALE PHENOTYPIC DRUG SCREENING WITH HESCS-CARDIOMYOCYTES – LESSONS LEARNT

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The adult mammalian heart is the least regenerative organ in the body. Up to ~ a billion cardiomyocytes are lost after a heart attack. Recent advances to replace lost muscle (primary remuscularization) and recover cardiac function relied strongly on the relative accessibility of human embryonic stem cells (hESCs)-derived cardiomyocytes (CMs). To successfully regenerate the injured heart, hESCs-CMs must survive, proliferate, mature and integrate in vivo. However, the long-term behaviour of hESCs-CMs in vivo remains unpredictable, compounded by its pro-arrhythmic nature. Thus, we adapted a commonplace practice in drug development e.g. large-scale phenotypic drug screening, to systematically perturb each regulatory pathway in hESCs-CM to determine its composite behaviour in vitro in both injury and non-injury settings. We first developed a robust pipeline to enable small-scale phenotypic drug screening of hESCs-Cardiomyocytes with clinically applicable compounds such as beta-blockers, myosin inhibitors. Our outputs include fluorescence-labelled Ca2+ kinetics, subcellular live-cell imaging. However, we found that the hESC-CMs were highly variable with different maturation and contractility rates. To optimize the signal-to-noise ratio in our readouts, we aim to utilise the real-world data generated by our large-scale phenotypic drug screen to develop an in silico perturbation model of hESC-CMs. Ultimately, this data science-intensive approach would enable a better prediction of hESC-CMs behaviour in vitro and in vivo with wide-ranging applications in both cardiac regeneration and cardiovascular medicine.

Funding Source: Astra Zeneca, Rosetrees, The Royal Society, Biotechnology and Biological Sciences Research Council.

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CROSS-SPECIES MORPHOLOGY LEARNING ENABLES NUCLEIC ACID-INDEPENDENT DETECTION OF MUTANT BLOOD CELLS

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Nucleic acid sequencing-/hybridization-based molecular diagnostics are routinely used for detection of malignancy-associated mutations in molecular diagnostics. However, the low cost-efficiency of nucleic acid-based assays hinder their application in pre-malignant screening, i.e. detecting rare circulating mutant blood cells in asymptomatic individuals. In both neonates and adults, the presence of malignancy-associated mutations in circulation correlates with higher risks of developing neoplasms later in life, which can reach 100% penetration for certain mutations such as KMT2A-rearrangement. Pre-malignant screening, if feasible, can create an opportunity for early interventions and even disease prevention. Here, we present a high-throughput single-cell computer vision platform capable of identifying mutant peripheral blood (PB) cells by recognizing their distinctive morphological features. Our cross-species morphology learning platform consists of two main modules: (1) mouse genetic / PDX models, designed to generate chimeric PB samples containing mutant mouse / human cells for ML training and testing; and (2) single-cell imaging and ML, achieved by comprehensive sampling of the best-performing ML models (including convolutional neural network, vision transformer, and feature-aware decision tree learning) and optimizing of the winning model. Layered technical variations were incorporated into the platform design to ensure robustness and generalizability, including geographically separated sample acquisition, geographically separated image recording, and blinded biological cross validations. The best performing model (XGBoost with CellProfiler in feature extraction) achieved balanced accuracies of 0.83 ~ 0.96, AUC-ROC of 0.93, and AUC-PR of 0.74, in detecting KMT2A-MLLT3 mutation. Top features used for mutant cell detection are related to cell size and cell texture, reflecting KMT2A-MLLT3 mutation-associated expression changes in genes regulating cell size as a function of increased metabolic activity. Our study created a generalizable method for cost-effective detection of mutations in live blood cells, potentially translatable to pre-malignant screening in asymptotic neonates and adults.

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INTEGRATING AUTOMATION AND KNOWLEDGE GRAPH-BASED AI FOR ROBUST CQA DISCOVERY IN IPSC-DERIVED HUMAN CARDIOMYOCYTE MANUFACTURING

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The successful scale-up and clinical translation of iPSC-based therapies demand robust, reproducible, and efficient manufacturing processes. A major barrier lies in achieving scalability with reduced variability of product across iPSC workflows, from R&D all the way through to manufacturing. AI has shown promise in manufacturing, yet its true transformative impact is maximized only when tightly integrated with automated systems that generate high-quality, process-linked datasets. This synergy is essential for building predictive models that can drive early intervention and execute workflows with batch-to-batch consistency. We developed an integrated AI-manufacturing platform that combines automation of iPSC differentiation workflows with a machine vision system powered by a knowledge graph-based model - linking different types of data to find meaningful patterns. This platform automates the full manufacturing workflow—from iPSC expansion and maintenance, to iPSC differentiation —while capturing detailed process metadata. Using this infrastructure, we analyzed two iPSC lines with distinct and quantitative cardiomyocyte differentiation outcomes (high-quality and low-quality). All process steps, phenotypic observations, and orthogonal datasets were fed into our knowledge system, which used multimodal data to extract early, mid, and late CQAs. The knowledge model was trained to recognize patterns predictive of differentiation success and failure. Our platform demonstrated equivalent or superior performance of manual workflows to the automated workflows. Notably, for the suboptimal cultures, automated corrective interventions enabled recovery to phenotypic and molecular quality levels comparable to optimal starting material—an outcome not feasible with manual handling. Leveraging the full spectrum of data captured, our knowledge-driven analysis successfully identified a Sentinel panel of early-stage markers predictive of cardiomyocyte differentiation success, offering a reliable tool for early decision-making in manufacturing. This study underscores the essential interplay between automation and AI for advancing clinical-grade iPSC manufacturing. Beyond data generation, our platform enables dynamic process correction, deep phenotypic characterization, and early CQA identification—capabilities foundational to analytical development, scale-up, and regulatory alignment. As cell therapy

manufacturing evolves, such integrated systems will be key enablers of scalable, high-fidelity production pipelines.

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TRACING CELLULAR DYNAMICS DURING INTESTINAL TUMORIGENESIS AND METASTASIS

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Interactions between tumour cells and the surrounding microenvironment contribute to tumour progression, metastasis and recurrence. Although mosaic analyses in Drosophila have advanced our understanding of such cellular interactions during tumour initiation, parallel approaches have remained challenging to engineer in mammalian systems. Here, we present an oncogene-associated, multicolour reporter mouse model, the Red2Onco system, that allows differential tracing of mutant and wild-type cells in the same tissue. Applied to the small intestine, we show that oncogene-expressing mutant crypts alter the cellular organization of neighbouring wild-type crypts, driving accelerated clonal drift. Crypts expressing oncogenic KRAS or PI3K secrete BMP ligands that suppress local stem cell activity, while induced changes in PDGFRlo CD81+ stromal cells by crypts with oncogenic PI3K alter the Wnt signalling environment. Together, these results show how oncogene-driven paracrine remodelling creates a niche environment that is detrimental to the maintenance of wild-type tissue, promoting field transformation dominated by oncogenic clones. To further extend the research programme towards analysing clonal behaviours during tumour progression and metastasis, we establish robust frameworks including advanced spatial transcriptomics and live imaging with the cell cycle reporting system.

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MULTIMODAL DECODING OF CELLULAR SENESCENCE WITH SENNETRAMANOMICS

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Cellular senescence contributes to aging and age-related diseases, yet its genetic, biochemical, and spatial heterogeneity remains poorly understood due to the lack of integrated tools capable of capturing molecular and biochemical information in intact tissues. To address this, we developed SenNetRamanOmics, a modular experimental and computational platform that combines label-free, nondestructive hyperspectral Raman imaging with single-cell and spatial transcriptomics and AI-powered multi-modal data integration. This platform leverages computer vision techniques and machine learning models to align biochemical signals with gene expression at cellular resolution, enabling non-invasive, spatially resolved profiling of senescent cells across tissues and aging stages. Applying this approach to aged mouse lung and skin, we identified key tissue-specific aging signatures, such as extracellular matrix (ECM) remodeling and insulin signaling in lung, and keratinization and cell cycle arrest in skin, revealed by transcriptomic data. Hyperspectral Raman imaging further uncovered corresponding biochemical changes, such as lipid and saccharide composition, which were computationally linked to senescence-related pathways using multimodal data integration. We discovered lipid-associated Raman peaks were linked to ECM remodeling in lung and keratinization in skin, while saccharide-associated Raman peaks were linked with anti-apoptotic signaling and muscle contraction. These results demonstrate the power of combining multimodal imaging and computer vision with spatial transcriptomics to uncover molecular mechanisms of aging. Together, SenNetRamanOmics highlights a scalable strategy for non-invasive characterization of senescence and aging and illustrates how AI and multimodal imaging can accelerate discovery in aging and regenerative biology.

Funding Source: NIH Cellular Senescence Network (SenNet) UG3CA275687, UH3CA275687.

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DECODING DEVELOPMENTAL BRANCHPOINTS WITH CONFORMAL AND SEMI-SUPERVISED CLASSIFICATION VIA SCOPE

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Branchpoints in cellular differentiation represent pivotal decision points in developmental biology and offer promising therapeutic targets for disease intervention. For instance, manipulating differentiation branchpoints has been used to treat acute promyelocytic leukemia and beta-thalassemia. These branchpoints also identify transcriptomic regions where cells commit to various differentiating or reprogramming fates. However, current trajectory inference methods do not explicitly define the transcriptomic identity of such branchpoints, leaving a methodological gap. To address this, we introduce SCOPE, a statistical framework for Semi-supervised COnformal Prediction in dEvelopmental biology that identifies branchpoints in single-cell data. SCOPE formalizes branchpoints as regions of both high uncertainty in fate prediction and high local cell density. Using conformal inference, we generate statistically valid multi-label prediction sets per cell, capturing the ambiguity inherent to progenitor states. Our method integrates manifold-aware semi-supervised learning, density-based clustering, and pseudotime-informed modeling. Applied to clonal single-cell data from mouse hematopoiesis, SCOPE identified a Meg–Ery branchpoint characterized by a significant decrease in entropy along pseudotime (p-value = 0.001996) and maximal variance in clonal velocity fields, validating its biological plausibility. In therapeutic contexts such as stem cell engineering, our framework may help identify optimal intervention points by pinpointing the branchpoints at which reprogrammed cells can be most effectively guided toward specific fates prior to reinfusion into the patient. Our work provides a principled approach for uncovering developmental bifurcations and supports future efforts in regenerative medicine and multi-omics integration.

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STATISTICAL LEARNING ON A LARGE-SCALE CHEMICAL PERTURBATION SCREEN IN CANCER CELL LINES REVEALS NOVEL DRUG MECHANISM OF ACTIONS

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Cellular response to drugs is heterogeneous depending on factors, such as genetic background, and on-/off-target engagement. Current large-scale cancer cell profiling

shows substantial differences in mutation status, protein expression, and drug sensitivity. However, to date, existing large-scale drug perturbation experiments are limited to one or a few cell lines, owing to the rapid expansion of candidate drugs. Unfortunately, this often means sacrificing understanding of the diverse molecular contexts of different cellular models to enable the analysis of larger cohorts of small-molecule compounds. Thus, accurate study of drug MOA will require more comprehensive inclusion of variations in genetic backgrounds to improve ongoing efforts in drug development. We generated a chemical perturbation dataset for 24 lung cancer cell lines containing different oncogenic driver gene mutations, treated with DMSO control and 15 drugs, including 2 HDACi, 8 RTKi, 2 cell cycle inhibitors, 1 MAPKi, 1 MEKi and 1 proteosome inhibitor. Bridge samples were also included for bach correction and normalization. Consequently, protein samples were labelled with 18-plex TMT reagents and analyzed on Orbitrap Eclipse mass. Real-time search was integrated to enhance the throughput, accuracy, and sensitivity. In total, 360 proteomic datasets of each cell line by drug were collected. Random Forest was applied to predict mutation effects on drug responses, ranking mutations by feature importance. Lasso regression identified proteins most strongly linked to cell viability, selected via cross-validation. Our dataset showed high reproducibility ($r = 0.62–1$ across 72 bridge samples) and low variation (98.9% of CV < 30%). In total, we quantified 11,966 proteins and 10,387 phosphosites. Drug responses were highly variable. For instance, bortezomib (proteasome inhibitor), 30 proteins were consistently regulated in more than 20 cell lines, including SNRNP70 ser 410, which was consistently reduced. Since SNRNP70 is a U1 snRNP component degraded by the proteasome, this suggests that proteasome inhibition alters alternative splicing regulation. In contrast, gefitinib (EGFR inhibitor) showed mutation-specific effects. Most regulated proteins were cell-line specific, with less than half cell lines sharing similar proteomic changes. Random Forest identified EGFR mutation (importance = 0.36) as the strongest predictor of gefitinib response, followed by FAT2 (0.13) and POLQ (0.11). Welch's t test analysis revealed 14 proteins and 11 phosphosites significantly different between EGFR mutants and non-mutants. Among them, ERRFI1, a negative EGFR regulator, was significantly reduced in EGFR-mutants ($p = 0.006$, Cliff's delta = 1.00, median difference = 1.04). In addition, we identified 135 proteins and 15 phosphosites correlated with cell viability post-treatment. LARP1 ser 774 phosphorylation was the top-ranked predictor of viability, which is a downstream protein of mTORC1 signaling.

Funding Source: CARE.

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AI-ASSISTED AUTOMATED COMPOUND SCREENING FOR TOXICITY EFFECTS USING HUMAN 3D LIVER ORGANOIDS

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Prathyushakrishna Macha*, Molecular Devices, USA*
Judi Wardwell, *In Sphero, Switzerland*

The most common side effect of developing drugs is their toxicity to liver. Drug-Induced Liver Injury (DILI) is the leading contributor to the withdrawal of approved drugs and black-box warnings. Traditional cell or animal studies have shown only limited predictivity of drug toxicity testing. More predictive In vitro assays could potentially reduce drug attrition rates and save lives. Understanding liver toxicity Mode of Action would facilitate the development of improved drug versions and help predict DILI risk in clinic. In vitro assays using organoids can evaluate toxicity effects to the liver and provide essential information in the process of drug development. In this study we utilized 3D liver spheroids provided by InSphero (InSightTM Human Liver Microtissues) to develop imaging-based In Vitro assay for toxicity evaluation. High Content Imaging and AI-enabled image analysis were used for analysis and quantitation of multi-parametric effects of various compounds on liver micro-tissues. We treated liver microtissues with twelve compounds that have been shown to cause liver toxicity (ketoconazole, tamoxifen, etc.), also included other compounds that don't show any clinical toxicity effects (ampicillin). Compounds were applied in triplicates or quadruplicates in various concentrations. Phenotypic changes and drug responses were observed after staining microtissues with variety of dyes, including viability, nuclear, mitochondria, RNA, cytoskeleton markers, also lipid markers. Hamilton liquid handler was used for drug addition, media exchanges and staining microtissues. Microtissues were imaged using the ImageXpress HCS.ai automated confocal imaging system. Various dyes allowed to measure multiplexed High Content Imaging endpoints that represent major DILI-related mechanisms of action: cell death, mitochondrial health, cell membrane integrity, apoptosis, as well as steatohepatitis. We used machine learning approaches (by In Carta software) for analysis and phenotypic characterization of compound effects. First, the microtissues were identified (segmented) by machine learning, then nuclei and cells were defined inside microtissues. Spheroid objects, also individual cells were characterized by various imaging read-outs, including fluorescence intensities for different markers, object areas, sizes, cell numbers, textures, uniformity, and number of other measurements. Concentration dependent changes of individual read-outs (e.g. viability, cytoskeleton integrity, mitochondria potential, nuclear intensity, lipid content, etc.) were

used to characterize potential mechanism of action of various compounds. Then, the integrated information from multiple read-outs (171) and concentration-dependent phenotypic changes in organoids were analyzed by AI tools in software through multi-parametric feature extraction. These features were used in a machine-learning classifier to automatically distinguish different classes of phenotypes caused by compound treatments. Automated classification was applied to distinguish affected from unaffected phenotypes, also to classify other phenotypes related to lipid accumulation, apoptosis, or mitochondria damage. This method is suitable for automating toxicity assessment studies which significantly reduces manual image processing. AI-powered data analysis automates complex analysis steps, enabling efficient and reproducible compound testing.

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THE ROLE OF FULL-LENGTH LAMININS IN ENHANCING IN VITRO CELLULAR MICROENVIRONMENTS

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Laminins, a family of 16 distinct ECM proteins, are crucial for tissue formation, maintenance, and homeostasis, with expression tightly regulated in space and time. As key components of basement membranes (BM), intact laminins are vital for healthy tissue function, while mutations in laminin genes result in diseases like Pierson syndrome and Epidermolysis bullosa, affecting organs such as muscles, nerves, and skin. Laminin proteins interact with integrin and non-integrin receptors, such as dystroglycan and syndecan, and bind essential growth factors (GF), modulating GF release. As large trimeric proteins, intact laminins provide structural integrity and bioactivity critical for BM functionality. In contrast, fragmented laminins lack these properties, are not naturally produced in healthy tissues, and fail to support tissue homeostasis. Studies show pluripotent stem cells (PSCs) with LAMA5-KO cannot survive without exogenous laminin

521, supporting the essential role of laminin 521 for PSC survival and expansion. Our study demonstrates the superiority of full-length recombinant laminin-521 in supporting human PSCs compared to fragmented laminins. Full-length laminin-521 significantly enhances PSC survival, proliferation, and migration, enabling single-cell seeding without the need for ROCK inhibitors. Importantly, PSCs cultured on intact laminin-521 exhibit enhanced migratory capacity, achieving complete wound closure in migration assays, whereas fragmented laminins support only 50% closure under the same conditions. These findings highlight the importance of full-length laminin-521 in recreating natural cellular microenvironments, which is crucial for advancing PSC culture techniques, improving differentiation protocols, and refining disease modeling and gene-editing strategies.

Funding Source: BioLamina AB, Löfströms Allé 5, 172 66 Sundbyberg, Sweden.

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DESIGNING CELL FATES USING THE TFome™ PLATFORM

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Cell fate programming technologies hold immense potential for regenerative medicine, yet discovering potent transcription factor (TF) combinations to achieve specific, functional cell states remains a central challenge. We developed the TFome™ platform, the first comprehensive library of 1,732 human TFs for optimized high-throughput experimental screening. Our platform discovers TF combinations for highly efficient (up to 99%), streamlined (single-step in days), and “plug-and-play” (single culture media) conversions of pluripotent stem cells into diverse cell types, including oligodendrocyte progenitor cells, vascular endothelial cells, stromal cells, and neurons. Iterative combinatorial screening enables deeper exploration of programming space, exemplified by the identification of microglia programming factors. Our survey of the transcription factor programming landscape has generated an unprecedented dataset of over one million single-cell transcriptomes from TF-perturbed cells spanning all three germ layers and major cell-type classes inferred from transcriptional identity. This is complemented by multimodal phenotypic data, including cell morphology, protein expression, in vitro function, and in

vivo assays, which create a uniquely rich foundation for data-driven cell fate design. We leveraged our unique datasets to train and benchmark AI foundation models for cell fate inference and reverse engineering cell fate. Our model achieved high accuracy in inferring cell identity from TF combinations: 6 out of 14 queries correctly predicted the target cell type as the top-ranked result, and 9 of 14 within the top five. These span a variety of cell types including neurons, endothelial cells, OPCs, and stromal cells. When challenged with specific target identities, the models successfully nominated TFs known to generate those cell types, demonstrating meaningful predictive power across a broad cell fate space. Importantly, several features of our programming paradigm make it uniquely compatible with AI modeling: (1) TFs act as direct, intrinsic regulators of fate without confounding small-molecule or media perturbations; (2) TF expression is introduced in a single step, avoiding temporal complexity; and (3) single-cell genomic outputs directly link phenotype to TF dosage and stoichiometry. Overall, these results demonstrate the power of AI-guided TF programming. With our ongoing feedback loops between experimental screening and computational inference, we are transitioning cell programming from a trial-and-error approach into a rational, design-driven discipline. We envision TFome™ as a foundational platform that unlocks the full potential of cell programming technologies to enable the accelerated development of next-generation cell therapies.

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DE NOVO MINI-AGONISTS UNLOCK A GENERALIZABLE PLATFORM FOR HYPER-STABLE, RECEPTOR-SPECIFIC GROWTH FACTOR SIGNALING

Ashish Phal, *University of Washington, USA*

Advances in generative AI now let us design proteins with atomic precision. We harness three deep-learning engines—RFdiffusion (diffusion generative model), ProteinMPNN (sequence optimization network) and AlphaFold 3 (structure predictor)—in an iterative loop that designs, scores and ranks millions of candidates entirely in silico. Picomolar interface binders produced by RFdiffusion are sequence-refined by MPNN, then assembled into rigid multivalent scaffolds drawn from an AI-generated backbone library. AlphaFold 3 and Rosetta docking filter the designs, automatically selecting the ~10% predicted to fold and enforce the active geometry of growth-factor receptor dimers/oligomers. We applied this AI pipeline to many unrelated signaling families such as FGF, NGF and BMP—creating a library of hyper-stable mini-agonists that solve long-standing liabilities of native growth factors: rapid proteolysis, cofactor dependence and receptor promiscuity. All expressed solubly in

E. coli, purified in a single ion-exchange step, and most melted above 90°C. SPR confirmed sub-nanomolar affinities; two designs crystallized exactly as modelled (<1.2 Å Cα RMSD), validating AI accuracy at the atomistic level. Without heparan sulfate or latent-complex activation, the FGF, TrkA and BMP mimetics sustained their canonical pathways (pERK/pPLCγ, pERK/pAKT, pSMAD2/3) for ≥72 h while leaving off-axis reporters silent. Standardized functional assays—scratch closure, neurite extension and SMAD-luciferase—showed each mini-agonist outperformed its native counterpart on a molar basis. We demonstrated therapeutic feasibility in vivo: blood-vessel organoids differentiated with the heparan-independent FGFR-c agonist C6-79C_mb7 were implanted under the kidney capsule of NOD-SCID mice. After 20 days, extensive human VE-cadherin^{+}/CD31^{+} vasculature had anastomosed with host vessels, confirming that AI-designed mini-agonists can drive complex tissue outcomes without native growth factors. By unifying AI-driven binder discovery, scaffold engineering and stability tuning, our platform delivers a general, low-cost class of growth-factor mimetics that eliminate cofactors, off-target signaling and cold-chain logistics—opening new avenues for regenerative therapeutics and fully defined cell-culture media.

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3D BRAIN ORGANOID GENERATION FOR APOE E4 FAMILIAL ALZHEIMER'S DISEASE MODELING AND EXPLORATION

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Aofei Liu, *Insitro, USA*
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Alzheimer's disease (AD) is a progressive, neurodegenerative disease and the leading cause of dementia world-wide. For over three decades, human genetics has shown that variants in the apolipoprotein E (APOE) gene are closely correlated to AD risk. However, despite a strong genetic link, traditional animal models and 2D in vitro cultures only recapitulate a fraction of AD mechanisms due to their inability to recapitulate human brain-specific tissue structure, function, and cellular diversity. The emergence of three-dimensional (3D) cerebral organoids using tissue engineering and induced pluripotent stem cell (iPSC) technology now offer an opportunity to model aspects of human brain tissue with more physiological relevance. Our aim is to explore whether in vitro 3D human

brain models can better recapitulate APOE variant–related disease phenotypes. At insitro, we are developing a robust protocol for generating human cerebral organoids using iPSC lines with diverse APOE genetic backgrounds. The cell lines being examined include iPSC lines with their respective isogenic APOE mutations (KO/KO, E4/E4, and E3/E3). Over the course of organoid formation, we expect to find a wide range of cells from neural progenitor cells to neurons, astrocytes, and other glial cells.Using FACS, single-cell RNA sequencing (scRNA-seq), and histological analyses, we are developing comprehensive transcriptional and proteomic signatures of APOE variant–associated phenotypes within these cell types. Additionally, we have developed methods to barcode and pool multiple cell lines, combining principles of CRISPR screening with a “village-in-a-dish” approach. Using these methods, we have generated organoids from a pooled mixture of nine isogenic iPSC lines with distinct APOE variants, enabling us to interrogate how intercellular interactions modulate AD-related phenotypes in these complex 3D systems.

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DIGITAL RECONSTRUCTION OF 3D SPATIAL TISSUE ARCHITECTURE REVEALS CELLULAR NICHE REWIRING IN SKIN DISEASE

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Haochun Huang, *Massachusetts General Hospital, USA*
Jian Shu, *Massachusetts General Hospital, USA*

Reconstructing 3D tissue architecture in health and disease is a fundamental challenge in tissue biology. Pioneering tissue-mapping technologies, such as spatial transcriptomics, generate high-resolution molecular profiles with spatial context, but they are limited to 2D sections and require substantial costs. In contrast, hematoxylin and eosin (H&E) staining offers detailed morphological information at a low cost but lacks molecular resolution. To overcome these limitations, we developed 3DST, an integrated experimental and computational framework that integrates H&E imaging with spatial transcriptomics to infer 3D and spatially resolved molecular profiles of complex tissues from H&E images with foundation models. We applied 3DST to investigate the molecular and cellular mechanisms underlying alopecia, including Lichen planopilaris (LPP) and Frontal fibrosing alopecia (FFA), a skin disorder predominantly characterized by hair loss on the scalp or other locations of the body, affecting nearly 7 million people in the U.S. and around 150 million people worldwide. We used 3DST that inputs H&E to predict 3D spatially resolved

gene expression profiles in alopecia. This 3D approach pinpoints dysregulated cellular and tissue niches and interactions, such as inflammatory signaling, in 3D contexts between lesion states. 3DST offers a versatile and modular framework to reconstruct complex tissue architectures in diseases at low cost and high throughput, laying the foundation for building virtual tissue models to study a broad range of diseases.

Funding Source: Massachusetts General Hospital.

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MULTIOMICS INTEGRATION OF HUMAN IPSC MODEL AND BRAIN BANK DATA UNCOVER APOE4-DRIVEN SPLICING DEFECTS DISRUPTING NEURITE PROJECTION IN EXCITATORY NEURONS IN ALZHEIMER'S BRAINS

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Alexandre Pelletier, *Boston University Chobanian, Avedisian School of Medicine, USA*
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The allele e4 of the apolipoprotein E gene (APOE4), present in around 20% of the population, is the leading genetic risk factor of late-onset Alzheimer's disease (AD), with APOE4 homozygote (APOE 44) having more than 90% chance undergoing AD biology at 65 years old. Despite this near full penetrance, major gaps remain in our understanding of APOE4-mediated neuropathology. We used human iPSC-derived mixed cortical culture (hiMCC) from APOE 44 and AD neutral APOE3 allele carriers in neurons and astrocytes integrating proteomics and deep sequencing of transcriptomics data. We further validated our findings using APOE genotype CRISPR/Cas9-edited isogenic hiMCC and postmortem brain multi-omics data from large and highly phenotyped brain bank cohorts. While transcriptomics and proteomics integration confirm the impacts of APOE4 in extracellular matrix and lipid transport pathways, we found that APOE4 induces a robust reduction of the mRNA spliceosome machinery at protein level. Analyzing high depth RNA-seq data, we further identify that APOE4 systematically induces mRNA splicing defects, and more specifically intron retention in genes regulating neuronal projection. By analyzing scRNA-seq data from hiMCC, we found that APOE4 induces this splicing defect specifically in a subpopulation of excitatory neurons with intense mRNA splicing activity for cytoskeletal reorganization. Finally, analyzing postmortem brain proteomics and transcriptomics data, we confirmed this splicing defect with neuronal projection impact and found strong

association with amyloid plaque and Neurofibrillary tangles burden. This integrative genomics analysis highlights the disruption of excitatory neurons mRNA splicing and subsequent neuronal projection as one key element of the neuropathology induced by APOE4 and suggests new therapeutic pathways to overcome it.

Funding Source: NIH NIA R01AG082362, R01AG083941.

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MICROVASCULAR TISSUE-ON-A-CHIP PLATFORM POWERED BY AI FOR HIGH-THROUGHPUT DRUG DISCOVERY TO PROMOTE HEALTHY AGING AND FIGHT AGING-ASSOCIATED DISEASES

Yan Ting Zhao, *Ora Biomedical Inc., USA*
Ben Blue, *Ora Biomedical Inc., USA*

Aging is one of the greatest risks for vascular dysfunction and contributes significantly to the progression of neurodegenerative diseases such as Alzheimer's disease (AD). Despite their potential efficacy, therapies targeting vascular aging remain underdeveloped. One limiting factor is that current tissue-on-a-chip technologies are constrained by overly complex instrumentation, low throughput, high costs, and the requirement for specialized personnel. This is coupled with a lack of relevant candidate molecules that have the potential to be validated in a more optimized platform. To address the medical unmet need and overcome the technical limitations, Ora Biomedical aims to develop an automated microvascular tissue-on-a-chip platform to model the blood-brain barrier (MicroBBB-AI) and validate several lead candidates for their efficacy in modulating microvascular aging. Ora Biomedical Inc. is a longevity biotechnology company that identifies and develops therapeutics for healthy aging across multiple clinical endpoints, utilizing artificial intelligence and advanced robotics. Our current screening pipeline is conducted on a massively high-throughput whole-animal phenotypic drug testing platform, Caenorhabditis elegans: the WormBot-AI. Ora currently has several lead small molecules that have been identified via their efficacy in modulating C. elegans aging and validated in existing tissue models. However, to best transition candidate molecules from pre-clinical discovery to clinical validation, novel and high-throughput vascular tissue modeling pipelines and their supporting technology must be developed and validated. Ora has three primary goals: 1) utilize predictive AI on Ora's existing longevity-promoting compounds to develop and synthesize molecules that are best targeted at vasculature aging, 2) develop MicroBBB-AI,

an advanced neurovascular tissue-on-a-chip platform powered by AI for preclinical drug testing in healthy vs AD models of the synthesized molecules, and 3) further validate the efficacy of the top performing candidates in an AD mouse model. The ultimate goal is to accelerate the discovery and clinical validation of therapies for aging-associated diseases, such as AD. This project will result in new gerotherapeutics for AD treatment or prevention and a novel microvascular tissue-on-a-chip pipeline well-suited for large-scale drug discovery across multiple neurodegenerative diseases.

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TOWARDS THE MODELLING OF TIME-VARYING GENE REGULATORY NETWORK TOPOLOGIES DURING DEVELOPMENT WITH IQCELL2

Divy Raval, *University of British Columbia, Canada*
Tiam Heydari, *University of British Columbia, Canada*
Martin Hirst, *University of British Columbia, Canada*
Peter Zandstra, *University of British Columbia, Canada*

The inference of gene regulatory networks (GRNs) and their dynamics is critical for understanding cell-fate transitions which occur during healthy and diseased development. GRNs model how transcription factors control gene expression and can be used in silico to simulate the effects of gene perturbations. Single-cell transcriptomic (scRNA-seq) and chromatin accessibility (scATAC-seq) measurements inform transcriptional activity and regulatory potential, enabling multiomics-driven GRN inference based on motif evidence. In our work, we adapt multiomics-driven GRN inference to IQCELL2 – a platform for GRN dynamics simulation – and demonstrate its application in early T-cell development. Existing methods can infer GRNs locally across time (or pseudotime), but few integrate this into dynamic simulation frameworks. Our approach supplies IQCELL2 with a time-varying GRN topology inferred from paired multiomics data. This enables modelling how regulatory edges evolve as cells differentiate. Future extensions will aim to model changes in chromatin accessibility alongside transcriptional changes, providing a more comprehensive view of regulatory dynamics during perturbation studies. Ultimately this approach contributes to constructing more realistic, time-resolved models of gene regulation during development.

INNOVATION SHOWCASES

All times are listed in Pacific Daylight Time (PDT)

THURSDAY, 9 OCTOBER 2025
10:10 AM – 10:30 AM
DECODING BRAIN DEVELOPMENT: ADVANCED FUNCTIONAL ANALYSIS WITH ORGANOIDS

Presented by MaxWell Biosystems
Tal Sharf, *MaxWell Biosystems, USA*
Francesco Modena, *MaxWell Biosystems, Italy*

Deciphering how the human brain develops remains one of the central challenges in neuroscience. Neural organoids derived from human induced pluripotent stem cells (h-iPSCs) have emerged as powerful models to study how neurons organize, mature, and interact during early stages of brain development. To fully harness their potential, however, technologies that deliver reliable, high-resolution functional data are essential. MaxWell Biosystems' High-Density Microelectrode Arrays (HD-MEAs), including the MaxOne and MaxTwo platforms, provide a robust, non-invasive means to investigate neural activity, connectivity, and function in organoid systems.
In this Innovation Showcase, invited speaker Assoc. Prof. Dr. Tal Sharf will highlight the importance of electrophysiology in advancing neurodevelopmental research. This session will explore how neuronal firing sequences emerge, highlighting the use of advanced analytical approaches applied to electrophysiological data to uncover new insights into the dynamic processes that shape brain circuit formation.

2:10 PM – 2:20 PM
AI-ENHANCED, CHEMICALLY AWARE WORKFLOWS FOR NEXT-GENERATION DRUG DISCOVERY

Presented by Collaborative Drug Discovery (CDD Vault)
James White, *CDD Vault, USA*

CDD Vault supports researchers at the intersection of AI, chemistry, and biology by unifying multimodal data including structures, sequences, cell lines, and assay results within a

secure, context-rich platform. From small molecules to biologics, peptides, and engineered cells, CDD Vault standardizes and integrates datasets across disciplines, enabling deep learning–driven searches for novel compounds and bioisosteres, as well as 3D protein folding and docking via AlphaFold2, ESMFold, and DiffDock. Chemically aware registration bridges experimental biology and medicinal chemistry, ensuring data are findable, accessible, interoperable, and reusable (FAIR). This architecture not only maximizes the value of built-in AI analysis, it also positions datasets for use in downstream or future models. By aligning chemists, biologists, and data scientists in a single collaborative environment, CDD Vault's AI ecosystem enables teams to transform multidisciplinary data into actionable breakthroughs and accelerate discovery.

FRIDAY, 10 OCTOBER 2025
10:00 AM – 10:10 AM
SCALING SINGLE CELL SEQUENCING: DRIVING DISCOVERY IN AI ENABLED BIOLOGY

Presented by Parse Biosciences
Charlie Roco, *Parse Biosciences, USA*

Single cell datasets are rapidly growing in size and complexity, creating unprecedented opportunities along with some challenges. In this talk, we'll share how Parse Biosciences' platform enables researchers to seamlessly scale from thousands to millions of cells without compromising data quality. We'll spotlight our collaboration with Tahoe Therapeutics on a groundbreaking 100-million-cell dataset that unlocked novel biological insights.

11:20 AM – 11:30 AM
INNOVATIVE LIVE-CELL ANALYSIS: ADVANCING MEDICINE WITH REAL-TIME IMAGING AND AI

Presented by Sartorius
Cicely Schramm, *Sartorius, USA*

The dynamic economic and scientific environment of the last year has highlighted the need for instruments capable of delivering more with an easy and intuitive approach. In addition to insights from more complex biological models, there is an increasing expectation for

streamlined methods that provide high-quality, reproducible data with quick turnaround times. The Sartorius portfolio has delivered in many areas, and we are dedicated to creating innovative solutions that enhance the development of superior medicines and research. This presentation will showcase recent exciting developments in live-cell analysis which facilitate real-time imaging of 3D cell models, capturing dynamic cellular changes through imaging techniques such as spinning disk confocal and wide field fluorescence. Intuitive software aids in the straightforward acquisition and interpretation of complex data. We will also highlight computational tools we have developed for label-free live-cell analysis. These tools were developed using AI neural network models trained on annotated datasets from various cell types. Data will illustrate the application of these tools in advancing iPSC research. Instruments are supported with aligned reagents, in-depth protocols and example application datasets to simplify integration into existing customer workflows.

11:30 AM – 11:40 AM
PRECISION IPSC GENOME ENGINEERING: FUELING THE FUTURE OF AI-POWERED CELLULAR DESIGN

Presented by Logomix
Yasunori (Yas) Aizawa, *Logomix, Japan*

Building on this progress, we are now leveraging our genome engineering platform to create advanced iPSC libraries for genetic perturbation studies. By applying machine learning, we aim to revolutionize the design of genetically engineered cells for superior therapeutic performance. We are seeking collaborations with AI companies to develop predictive models for multi-gene perturbation in iPSCs, unlocking new insights at the intersection of biology and artificial intelligence. This is where we believe the future of regenerative and other cell-based medicine lies.

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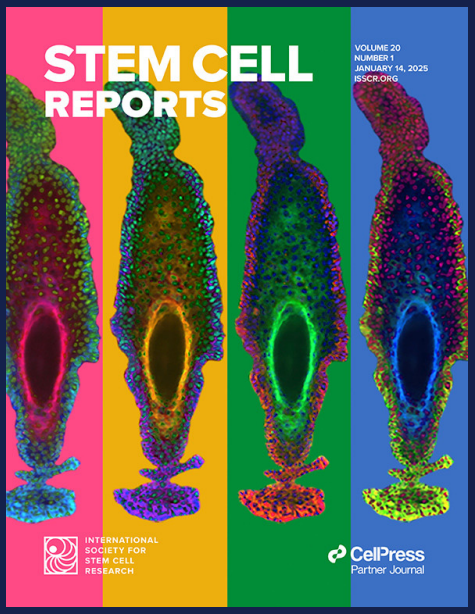

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THE STEM CELL REPORT PODCAST

Join editor-in-chief of *Stem Cell Reports,* Janet Rossant, on The Stem Cell Report Podcast as authors go "beyond the paper" and share new insights on their breakthroughs and explore questions about the future of the field.

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Douglas Melton, PhD


Masayo Takahashi, MD, PhD


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