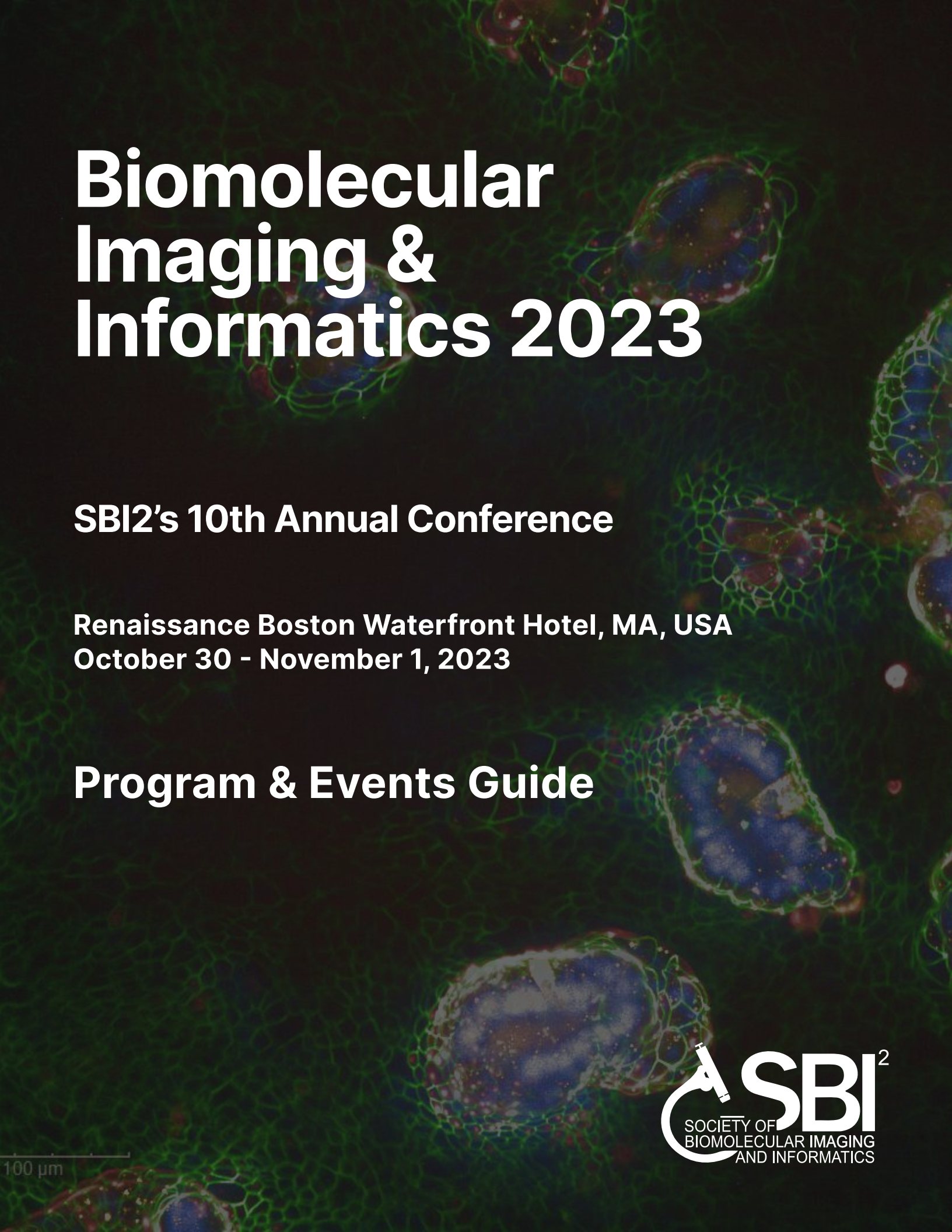
Biomolecular Imaging & Informatics 2023

SBI2's 10th Annual Conference

Renaissance Boston Waterfront Hotel, MA, USA
October 30 - November 1, 2023

Program & Events Guide



SBI²
SOCIETY OF BIOMOLECULAR IMAGING AND INFORMATICS

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Sponsors Description

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10
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President’s Welcome

I'm delighted to welcome you to the 10th annual meeting of the Society of Biomolecular Imaging and Informatics (SBI2) - on behalf of the entire board, we're so glad you've joined us. I could not be more excited about this year's program, starting with our outstanding keynote speakers: Lans Taylor from University of Pittsbugth on Tuesday, and Rong Fan from Yale University on Wednesday. I'm also looking forward to our extended poster session, which we had to lengthen since we received a record number of submitted abstracts this year!

We will start our first full 3-day meeting since 2019 with 9 fantastic educational sessions covering everything from basic principles to applications, followed by a can't-miss Colloquium on the Joint Undertaking for Morphological Profiling (JUMP Consortium) chaired by Anne Carpenter, whose SBI2 chairing chops go all the way back to the very first SBI2 annual meeting’s educational program. SBI2's Scientific Organizing Committee, chaired this year by Katherine Hales, have put then together 2 amazing days of scientific talks covering AI/ML, functional genomics, spatial omics, and advances in high content imaging. Please join me in thanking Katherine, our outstanding 2023 SoC (Stephen Walker, David Shum, Neil Carragher, Kristin Halfpenny), and our fantastic session chairs (Jovan Tanevski, Safiye Celik, Manuel Leonetti, and Melaney Bailey), and the speakers themselves. Of course, none of this would have been possible without our tremendous sponsors and vendors, who make this meeting what it is and contribute so much scientifically and technologically to our community.

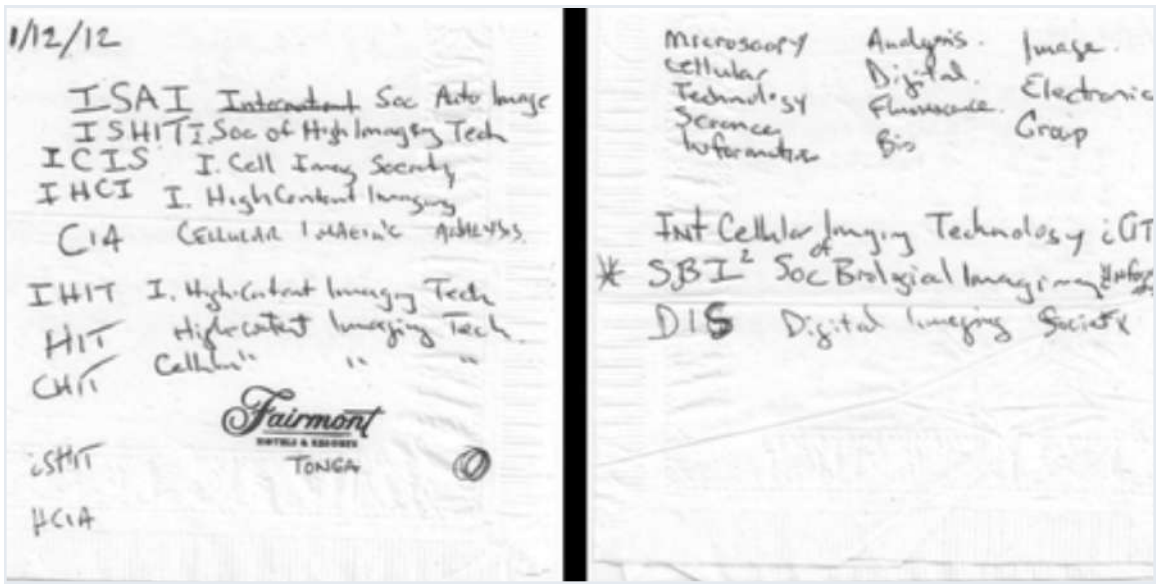
Reaching the milestone of a 10th meeting occasions a look back on just how much the society and the field have grown in the course of 10 years. I recently returned to the original paper describing the founding of the society and announcing the first meeting, and especially was struck by the missions the society set out to serve: “promoting technological advancement, discovery, and education", "quantitatively interrogat[ing] biological models to provide high context information at the cellular level", and "increasing the understanding, utility and rigor of quantitative imaging or high content analysis.”

The explosion of new imaging assays, technologies, and analytical techniques in the past 10 years have been truly inspiring, and I'm proud to be part of a society pushing these developments and, just as importantly, helping disseminate them such that our community (and the size of our poster hall!) keeps growing. While space prohibits listing every board member and contributor over 10 years, all are gratefully acknowledged, especially this year's officers, Past President Neil Carragher, new Treasurer Jim Finley and new Secretary John Moffat, and our new community manager Shruti Ganapathy. As the society enters our "tween years", we've hit our share of growing pains, but it's exciting to see the society mature in a way that will make it more stable and expandable for years to come.

Please enjoy the next 3 days of learning, networking, brainstorming, seeing old friends, and hopefully making some new ones: we hope that if you end up scribbling some ideas for new projects on a napkin, they're as fruitful as the napkin below was. If you enjoy the meeting, as a volunteer-run society, we're always looking for colleagues to help us serve the SBI2 mission, so please reach out and get involved - board self-nominations are currently open but will be closing soon. We look forward to welcoming you back to Boston next year from September 18th-20th for our 11th annual meeting!

Beth A Cimini
President

Broad Institute



About SBI2

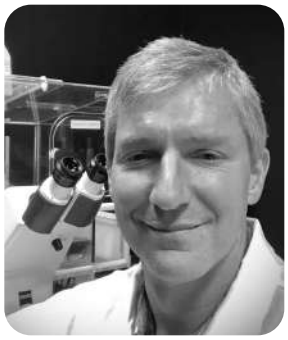
The Society of Biomolecular Imaging and Informatics (SBI2) is an international community of leaders, scientists, and students promoting technological advancement, discovery, and education to quantitatively interrogate biological models to provide high context information at the cellular level.

SBI2 Leadership

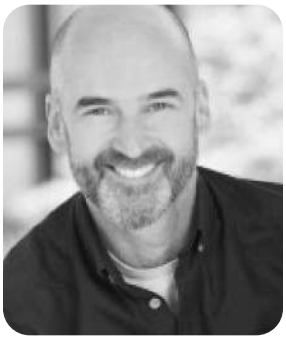
Executive Positions

Beth A Cimini
Broad Institute

Neil Carragher
University of Edinburgh



James Finley
Pfizer



John Moffat
Genentech

Katherine Hales
Pfizer

John Bassett
Merck

David Shum
Institut Pasteur Korea

Donald Apanovitch
Syngene

Stephen Walker
Abbvie

Victor Wong
Core Life Analytics

Angeline Lim
Molecular Devices

SBI2 Leadership

Council

Maggie Vantangoli Policelli
Spring Science

Nicholas M. Radio
Thermo Fisher Scientific

Richard Kasprowicz
GSK

Sheila Kantesaria
Pfizer

Heba Sailem
University of Oxford

Greg Way
University of Colorado

Conference at a Glance

Monday, October 30, 2023

8:00 AM - 9:00 AM	**Breakfast**
9:00 AM - 12:00 AM	**Education Sessions**
12:15 PM - 1:00 PM	**Lunch**
1:00 PM - 4:30 PM	**Colloquium**

Tuesday, October 31, 2023

7:00 AM - 7:00 PM	**Exhibit Hall Opening / Networking**
8:00 AM - 9:00 AM	**Breakfast**
9:00 AM - 10:00 AM	**Tuesday Keynote Session**
10:45 AM - 1:00 PM	**Session 1: Artificial Intelligence / Machine Learning: Data Integration and Analytics for Biomolecular Imaging**
1:00 PM - 1:45 PM	**Lunch and Learn**
1:45 PM - 4:30 PM	**Session 2: Functional Genomics, pooled optical and genetic screening advancement**
4:30 PM - 6:00 PM	**Exhibit Viewing and Poster Session**
6:00 PM - 7:30 PM	**Reception**

Wednesday, November 1, 2023

8:00 AM - 600 PM	**Exhibit Hall Opening / Networking**
8:00 AM - 9:00 AM	**Breakfast**
9:00 AM - 10:00 AM	**Keynote Session**
10:00 AM - 10:15 AM	**Best Poster Award Ceremony**
10:45 AM - 1:00 PM	**Session 3: Spatial Omics and advances in platform capabilities for multi omics**
1:00 PM - 1:45 PM	**Lunch and Learn**
1:45 PM - 4:30 PM	**Session 4: Advances in High Content Imaging: Next Generation Phenotypic Screening Assays**
5:00 PM - 6:15 PM	**SBI2 AGM**

Program Agenda

Monday, October 30, 2023

8:00 AM - 9:00 AM	**Breakfast**
9:00 AM - 12:00 AM	**Education Sessions**
12:15 PM - 1:00 PM	**Lunch**
1:00 PM - 4:30 PM	**Colloquium**

Education Sessions

9:00 AM - 10:00 AM	**Session I (Pacific Ballroom Salon F)** **Assay statistics for Spatial Biology applications** Bartek Rajwa Purdue University
9:00 AM - 10:00 AM	**Session I (Pacific Ballroom Salon G)** **Into to High Content Imaging (Complex models/ assays focus)** Paul Johnston University of Pittsburgh
9:00 AM - 10:00 AM	**Session I (Pacific Ballroom Salon H)** **Cell Painting Best Practices** Regis Doyonnas Pfizer
10:00 AM - 11:00 AM	**Session II (Pacific Ballroom Salon F)** **Intro to ML/ Deep Learning Applications using HCI** Beth A Cimini Broad Institute, MIT
10:00 AM - 11:00 AM	**Session II (Pacific Ballroom Salon G)** **3D Cell Culture: Introduction to 3D Spheroid Imaging and Analysis** Ozlem Yavas Insphero

Education Sessions

10:00 AM - 11:00 AM

Session II (Pacific Ballroom Salon H)
Metrics and best practices for assay development and standardization

Joe Trask
Revvity Health Sciences Inc

11:00 AM - 12:00 PM

Session III (Pacific Ballroom Salon F)
Intro to Spatial Biology

Paulo Cadinu
Boston Children's Hospital and Harvard Medical School

11:00 AM - 12:00 PM

Session III (Pacific Ballroom Salon G)
Elevate Your Drug Discovery Game:Guide to 3D Cell Culture, High-Content Imaging, and Automation

Angeline Lim
Molecular Devices

11:00 AM - 12:00 PM

Session III (Pacific Ballroom Salon H)
Strategies for performing image data analysis at scale

David Stirling, Emil Rozbicki, Erin Diel
Glencoe Software

Colloquium Title:
JUMP Cell Painting Insights and Tools

Chair:
Anne Carpenter and Shantanu Singh, Broad Institute

1:00 PM to 4:30 PM

Anne Carpenter

Dr. Carpenter is an Institute Scientist at the Broad Institute of Harvard and MIT. Her research group develops algorithms and strategies for large-scale experiments involving images. The team's open-source CellProfiler software is used by thousands of biologists worldwide and their Cell Painting assay has been adopted throughout the pharma industry to accelerate drug discovery. She led the JUMP Cell Painting Consortium.

Shantanu Singh

Shantanu Singh, Ph.D. is a Senior Group Leader at the Broad Institute, where he co-leads the Carpenter–Singh lab. His lab's central research theme is using cell imaging to probe biological processes toward finding new therapies for diseases. He is excited about bringing together the many rapidly developing fields of high-dimensional biology to tackle the challenges of improving human health.

What is Cell Painting and what can it do?

Cell morphology holds valuable information about the mechanisms and functions of cell structures, and microscopy has been instrumental in uncovering biological phenomena. However, images of cell structures contain more information than what meets the eye. With the advancements in image analysis and deep learning, this rich information can be captured and quantified to drive progress in basic biology research and drug discovery. Image-based profiling using fluorescence microscopy assays such as Cell Painting can reveal the impact of diseases, drugs, and genes on cells, uncover mechanisms of action for small molecules, identify disease-associated phenotypes, detect response to drugs, and predict the biological impact and toxicity of compounds, among other applications. This has led to a growing impact on the pharmaceutical industry as cell morphology becomes a powerful data source for systems biology alongside molecular omics readouts.

Shantanu Singh
Broad Institute

The JUMP Cell Painting dataset

Image-based profiling has emerged as a powerful technology for basic biological and pharmaceutical discovery, but the community has lacked a large, public reference dataset. The Joint Undertaking for Morphological Profiling (JUMP)-Cell Painting Consortium, a collaboration between 10 pharmaceutical companies, six supporting technology companies, and two non-profit partners, was formed with the express goal of creating such a dataset.

This dataset constitutes over 8 million images, CellProfiler-based classical features and deep learning-based features for over 1.5 billion cells perturbed by 116,750 unique compounds, over-expression of 12,602 genes, and knockout of 7,975 genes using CRISPR-Cas9. The dataset is estimated to be over 250 TB in total. Apart from its size, the other strengths of the dataset are its robustness (generated at 12 sites using different microscopes) and its diversity of perturbations (both chemical and genetic). However, these strengths also pose challenges such as data alignment, which the consortium is working on addressing. Nevertheless, the dataset is already being used for various purposes, such as learning new representations of cells, exploring relationships between phenotype and gene functions and predicting the mechanism of action of compounds.

Niranj Chandrasekaran
Broad Institute

Talk previews

Dr. Carpenter will provide highlights of talks to be presented later in the week that make use of JUMP-Cell Painting data.

Anne Carpenter
Broad Institute

Optimizing the Cell Painting assay for JUMP

Cell microscopy images contain a vast amount of information about the status of the cell: whether it is diseased, how it is responding to a drug treatment, or whether a certain pathway has been disrupted, for example. These profiles can be analyzed to identify subtle cellular patterns, potentially biologically meaningful but undetectable to the human eye.
The JUMP-Cell Painting Consortium, a group of pharmaceutical companies and non-profits, created a critical mass of such cellular imaging data to empower discoveries about cell biology that can inform drug discovery and development.
Here, we provide an updated protocol for the most popular assay for image-based profiling, Cell Painting.

Sakshi Garg
Merck KGaA

Microscopes for the Cell Painting assay: it's all good

One relatively unique aspect of the JUMP Consortium was the number of kinds and configurations of microscopes involved: 5 different microscopes with 8 optical configurations. Additionally, we hope new users will wish to start running Cell Painting on their own samples to compare to the JUMP dataset; it would not be reasonable to suggest such users purchase one particular microscope with one particular configuration. We therefore wanted to ensure Cell Painting is compatible with a large number of microscopes, as well as to generate recommendations for settings either individually or across the board. We will report on efforts to assess the performance of Cell Painting across various microscopes, in partnership with the microscope vendors.

Beth Cimini
Broad Institute

Brightfield images alongside the Cell Painting assay

We have developed a data analytics workflow that is both scalable and computationally efficient, while providing significant, biologically relevant insights for biologists estimating and comparing the effects of different drug treatments.
The two main objectives of our work include: 1) a simple, yet sophisticated, scalable data analytics metric that utilizes negative controls for comparing morphological cell profiles. We call this metric the equivalence score (“Eq. score”). 2) A workflow to identify and amplify subtle morphological image profile changes caused by drug treatments, compared to the negative controls. In summary, we provide a data analytics workflow to assist biologists in interpreting high-dimensional image features, not necessarily limited to morphological ones. This enhances the efficiency of drug candidate screening, thereby streamlining the drug development process. By increasing our understanding of using complex image-based data, we can decrease the cost and time to develop new, life-saving treatments.

Edvin Forsgren
Umeå University

Aligning Cell Painting data via batch correction, leveraging single-cell data in image-based profiling

Batch effects confound many high-throughput experiments. High-throughput microscopy datasets are no exception. Comprising billions of cells from millions of samples at a much lower cost than other profiling technologies, image data has comparable or better predictive power for diverse biological applications. However, batch effects are a major obstacle confounding real biological signals, especially for data collected across different data collection laboratories and equipment. Here, we evaluate seven top-ranked batch correction strategies in the context of a newly released large public Cell Painting dataset of image-based profiles. Overall across five scenarios that span the simplest (multiple experimental batches within a single laboratory) to the complex (multiple laboratories using different microscopes) we find that Harmony (and to a lesser extent, Scanorama), consistently outperforms the other tested methods. We provide a framework, benchmark, and metrics for the future assessment of new batch correction methods on image-based profiles.

John Arevalo
Broad Institute

Break

Diving into JUMP Data

Public portal for exploring Cell Painting data

Adi Prakash
Spring Science

Navigating phenotypic and structural representations with the PhenAID JUMP-CP Data Explorer

JUMP-CP is the world's largest publicly available Cell Painting data set, generated by 10 industry and academic partners with the aim to validate and scale up image-based drug discovery strategies. It contains data from over 140,000 samples, including treatments with 117,000 compounds, 13,000 overexpressed genes, and 8,000 genes knocked down by CRISPR-Cas9.

As a supporting partner of the consortium, Ardigen has developed the phenAID JUMP-CP Data Explorer, a free web-based application that facilitates exploration of this data set. The application displays phenotypic and structural representations of the JUMP-CP data as a UMAP, and enables scientists to view images and corresponding metadata. Phenotypic representations of chemical and genetic perturbations are generated based on CellProfiler features provided by the JUMP-CP consortium, whereas structural representation is given by the Extended-Connectivity Fingerprint (ECFP) representation of each compound. Representations are aggregated across all replicates generated by different partners, resulting in one representation per compound or genetic perturbation.
The user can search for corresponding data of the perturbation of interest using its name or chemical structure (SMILES) with regard to compound data. The application also displays the full chemical structure and information about the activity and mode of action for compounds, and directly links to ChEMBL and PubChem databases if they are publicly available. For genetic perturbations, the link to the Uniprot database is provided.
The find neighbors function enables exploration of chemical or genetic perturbations inducing phenotypic changes similar to the compound or gene of interest. The application automatically calculates up to 100 of the closest compounds or closest genes. It is possible to view the corresponding images and metadata and finally download a csv file with the list of neighbors for further investigation.
The JUMP-CP Data Explorer is a part of the PhenAID platform; an artificial intelligence based tool that enables analysis of multimodal data, combining high content screening images and molecular structures to facilitate the following predictive and generative tasks: Mode of Action and biological propriety prediction, hit identification, virtual screening and much more.
During this short presentation, we will demonstrate the functionalities of phenAID and explain how they can be applied to leverage the value of JUMP-CP data set.

Magdelena Otrocka
Ardigen

Weakly supervised learning for feature extraction

Traditionally, image-based profiling relies on manually engineered features and pre-trained convolutional neural networks which are insufficient in their expressive power. Weakly supervised learning strategy allows to model associations between treatments and images with increased sensitivity and robustness. However, those associations encode not only biologically meaningful information, but also confounding factors (batch-effects). To find a way to facilitate their separation, we investigated the effect of data distribution modification with respect to phenotypic or technical variation. We found that increasing the technical variation and reducing biological variation to treatments with strong phenotypic effect leads to biologically relevant representations in Cell Painting benchmark datasets. We used those observations to construct a new training dataset composed of images from different sources to maximize experimental diversity. With this dataset, we have trained a reusable Cell Painting CNN model with EfficientNet as the base architecture.

A comprehensive evaluation was performed with three benchmark datasets: one with gene overexpression and two with chemical perturbations. The results show that Cell Painting CNN is able to extract representations performing up to 25% better than classical features in the downstream analysis (biological matching task). Those results indicate that large datasets with diverse phenotypic effects can be used to train a single model for feature extraction that generalizes to different experiments without additional training. All model training and feature extraction experiments were performed with DeepProfiler software https://github.com/cytomining/DeepProfiler.

Sam Chen
Broad Institute

Multi-modal representation learning with JUMP-CP

Image-based profiling techniques are scalable and can generate large datasets of cellular morphologies as induced by perturbagens. However, their application is constrained to perturbagens that have been imaged or are available for imaging. To overcome this limitation, we develop MoCoP, a multimodal contrastive learning approach that jointly learns representations of molecules and cellular morphologies. We further demonstrate that scaling of MoCoP to approximately 100K compounds and 600K morphological profiles available in JUMP produces highly transferable molecular representations for a range of downstream tasks. These results highlight the untapped potential of the wealth of information available in Cell Painting dataset

Cuong Nguyen
GSK

Contextual Vision Transformers for Robust Representation Learning

We present Contextual Vision Transformers (ContextViT), a method for producing robust feature representations for images exhibiting grouped structure such as covariates. ContextViT introduces an extra context token to encode group-specific information, allowing the model to explain away group-specific covariate structures while keeping core visual features shared across groups. Specifically, given an input image, Context-ViT maps images that share the same covariate into this context token appended to the input image tokens to capture the effects of conditioning the model on group membership. We furthermore introduce a context inference network to predict such tokens on the fly given a few samples from a group distribution, enabling ContextViT to generalize to new testing distributions at inference time. We illustrate the performance of ContextViT through a diverse range of applications. In supervised fine-tuning, we demonstrate that augmenting pre-trained ViTs with additional context conditioning leads to significant improvements in out-of-distribution generalization on iWildCam and FMoW. We also explored self-supervised representation learning with ContextViT. Our experiments on the Camelyon17 pathology imaging benchmark and the cpg-0000 microscopy imaging benchmark demonstrate that ContextViT excels in learning stable image featurizations amidst covariate shift, consistently outperforming its ViT counterpart.

Yujia Bao
Insitro

Single-cell phenotype classification to aid image-based profiling

Phenotypic drug screening applies drugs to cells to observe the unbiased effects of drug treatments and improve drug discovery. One of the most common approaches used in phenotypic drug screening is to collect unbiased fluorescence microscopy images of cells exposed to these perturbations and apply advanced computers to quantify perturbation impact. These perturbations impact cells in various ways, and we measure these impacts in heterogeneous single cells. However, current computational pipelines are limited to analyzing phenotypic drug screening data after bulk aggregation, which ignores single-cell heterogeneity. This approach obscures results and prevents us from refining compound mechanisms per phenotype class.

Jenna Tomkinson
University of Colorado-Anschutz

Post Colloqium Reception - 4:30 PM to 6:30 PM

Matching genetic and chemical perturbations via Cell Painting profiles

Finding new chemicals that target genes or pathways of interest is a major bottleneck in the process of finding new drugs and useful tool compounds. Current pipelines rely almost entirely on an expensive, time-consuming step of screening millions of compounds using target-specific assays to find those that have the desired activity of targeting the gene or pathway of interest. In this work, we show that microscopy images of chemically or genetically perturbed cells could be used to computationally search for chemical modulators of a gene target. The same approach can also be used to identify the target of a potential therapeutic. Overall, the approach has the potential to dramatically accelerate the drug discovery process as well as reduce costs. Using a small pilot dataset generated for this study, we show a seven-fold improvement over a random baseline in predicting already annotated gene-compound matches.

Niveditha Subramanyam Iyer
Stanford

Tuesday, October 31, 2023

7:00 AM - 7:00 PM	**Exhibit Hall Opening / Networking**
8:00 AM - 9:00 AM	**Breakfast**

Keynote: Evolution, Implementation, and Future of High-Content Imaging

9:00 AM to 10:00 AM

High Content Screening (HCS)/High Content Imaging (HCI) was first introduced in 1997 as a commercial platform by Cellomics. The concept was to transition away from the then state-of-the-art focus on generating high quality microscope images with the application of interactive metrics on a relatively small number of living and/or fixed cells with limited statistical significance. HCS/HCI changed the paradigm by creating a semi-automated platform that focused on multiplexed and statistically significant cellular data extracted from the images of hundreds to thousands of cells in each experiment. Many research groups and companies have contributed to the evolution of HCS/HCI with instrumentation, reagents and analytics over the last 25 years. Today, I will give a historical overview of the evolution of HCS/HCI from my perspective. In addition, I will discuss our present work in studying the mechanisms of disease progression and drug discovery/drug development using non-alcoholic fatty liver disease (NAFLD) as an example of integrating patient-derived liver microphysiology systems (MPS) with quantitative systems pharmacology (QSP) where HCS/HCI plays an important role.

I will discuss the heterogeneity of the disease, the implementation of disease progression in the liver MPS, the prediction of drugs that could mitigate the disease progression using QSP applied to patient samples and the development of “patient biomimetic twins” as an experimental complement to “patient digital twins” from the same patients. I will include the development of an analytical database for MPS, animal and clinical data and how this will be part of a precision medicine platform. There is an increased effort to integrate multi-modal data sets from HCS/HCI, genomics, proteomics and metabolomics. The emergence of “spatial biology” as a new “omics” linked to the evolution of HCS/HCI will also be outlined. I will finish by describing my perspective on where the field of HCS/HCI is going.

Lans Taylor
University of Pittsburgh

Lans began his career at Harvard University developing and applying “high content” light optical methods and fluorescence-based reagents to investigate the dynamics of living cells, including cell migration and cell division. This trend of developing and applying new technologies involving “high content” imaging methods to biomedical challenges has been the focus of his career. At the University of Pittsburgh, we have been applying quantitative systems pharmacology (QSP) to multiple disease areas including non-alcoholic fatty liver disease, type 2 diabetes, solid tumors and traumatic brain injury. We are emphasizing the integration of QSP with human, biomimetic microphysiology systems (MPS) to generate physiological and pathophysiological experimental and computational models to create a powerful paradigm in drug discovery and development. In addition to Harvard, Lans has been a professor at Carnegie Mellon University and spent a number of years starting and leading biotechnology companies including Biological Detection Systems (acquired by Amersham Biosciences), Cellomics (acquired by Thermo Fisher), Cellumen (acquired by Cyprotex, now part of Evotec) and Cernostics (acquired by Castle Biosciences). He recently co-founded PredxBio, a precision medicine pathology company focusing on solid tumors. He also co-founded BioSystics, a comprehensive computational and systems analytical platform company designed to access, manage, analyze, share and computationally model complex data sets from in vitro experimental models of disease and ADME-TOX, animal models and human clinical data. The BioSystics-Analytics Platform generates actionable knowledge that will accelerate and optimize drug discovery, development and personalized medicine. BioSystics recently merged with Nortis, Inc to form Numa Biosciences, a precision medicine company harnessing the strengths of patient derived MPS (patient biomimetic twins) and patient digital twins from the same patients.

Vendor Spotlight: Advancing Innovation at Revvity

10:00 AM to 10:15 AM

Revvity represents our continued commitment to revolutionizing next generation breakthroughs that create a healthier humankind.

Joe Trask

Coffee Break - 10:15 AM to 10:45 AM

Session I:
Artificial Intelligence/Machine Learning: data integration & analytics for biomolecular imaging.

Chairs:
Kristin Halfpenny (Araceli Biosciences)
Jovan Tanevski (Heidelberg University, Germany)

10:45 AM to 1:00 PM

Jovan Tanevski

Jovan Tanevski is a research area leader at the Institute for Computational Biomedicine, Heidelberg University Hospital, Germany. He is also a research associate at the Department of Knowledge Technologies, Jožef Stefan Institute, Ljubljana, Slovenia where he also obtained his PhD in the area of machine learning for systems biology. He is a researcher of computational scientific discovery in biomedicine by bridging knowledge and data-driven approaches. At the Institute for Computational Biomedicine, he is leading the development of machine learning and optimization methods for analysis of spatially resolved omics and their application to problems of understanding the relationship between structure and function, mechanisms of dysregulation and response to treatment.

Learning explainable models for spatial data representation and exploration

10:45 PM to 11:15 PM

With the advancement of technologies for spatially resolved omics we gain an unprecedented, deeper insight into the composition and structure of tissues. To tackle the complexity of this data and acquire novel insights into the emergence of the structure-function relationship, we require new computational models. Explainable machine learning and optimization based approaches are well suited to flexibly and efficiently capture different aspects of organization in spatial omics data and offer a more detailed view of the underlying tissue biology. We developed MISTy, a scalable multi-view machine learning framework, with the goal of enabling versatility of analysis by combining different types of complex spatially resolved data with prior knowledge. Our framework facilitates exploration of condition specific and differential patterns of cell states, investigation of channels of intra and intercellular signaling in different spatial contexts, as well as integration of different spatially resolved omics. Our explainable tissue specific models are used for data exploration and hypothesis generation, in contrast to being deployed in a standard predictive context. The hypotheses are based on the robust and persistent structural and functional relationship patterns in the data captured by the spatial-context-specific models, ranging from the subcellular to the broader tissue context. As a next step, the relationships distilled from the data represent a basis for higher level representation of tissues. The association of this representation to available clinical observations lends itself to further learning and optimization tasks. As such, it can be used to better understand the molecular basis of spatial coordination and its role in disease progression and response to treatment.

Jovan Tanevski
Heidelberg University, Germany

Automated segmentation of cellular and subcellular structures with Cellpose

11:15 AM to 11:45 AM

Many biological applications require the segmentation of cell bodies, membranes and nuclei from microscopy images. We thus developed a generalist, deep learning-based segmentation algorithm called Cellpose, which can very precisely segment a wide range of image types out-of-the-box. To achieve generalist performance, we created a new dataset of highly varied images of cells, containing over 70,000 segmented objects, and trained Cellpose on this dataset. We also created a three-dimensional (3D) extension of Cellpose that reuses the two-dimensional (2D) model and does not require 3D-labeled data. However, we found this model still does not work in all cases: some users have specific segmentation styles or specific image types that may not work well. Therefore we created Cellpose 2.0, a new package that includes an ensemble of diverse pre-trained models as well as a human-in-the-loop pipeline for rapid prototyping of new custom models. Models pre-trained on the Cellpose dataset can be finetuned with only 500-1,000 user-annotated regions of interest (ROIs) to perform nearly as well as models trained on entire datasets with up to 200,000 ROIs. This approach can also be extended to enable accurate segmentation of many organelles across different tissue types. We provide software tools like an annotation GUI, a model zoo, and a human-in-the-loop pipeline to facilitate the use of Cellpose.

Carsen Stringer
Janelia Research

Carsen Stringer is a group leader at HHMI Janelia Research Campus. Her lab develops machine learning tools for understanding large-scale neural, behavioral, and imaging data. These tools include Cellpose, a general segmentation tool for cellular imaging data, and Suite2p, a fast and accurate pipeline for processing recordings of 50,000+ neurons, both of which are used by hundreds of labs.

Deep learning identifies antibiotic drug modes of action from brightfield images

11:45 AM to 12:15 PM

The antibiotic resistance crisis urgently calls for antibacterial compounds with novel modes of action. Phenotypic drug screening by high-throughput imaging is a target-agnostic approach to identify compounds with antimicrobial activity, but time-consuming follow-up studies are needed to identify drug targets and modes of action. In a collaboration with microbiologists and imaging experts, we explore the potential of deep learning to directly determine modes of action from images alone. We will present preliminary results from an ongoing study suggesting that deep learning can extract subtle phenotypes of drug-treated bacteria (H. pylori and E. coli) and predict the mode of action of compounds by comparison with known reference antibiotics using brightfield imaging alone. These results constitute a first stepping stone towards a computational pipeline to predict the modes of action or molecular targets of chemical compounds from high-throughput imaging data, with the goal of speeding up phenotypic drug discovery.

Christophe Zimmer
Institut Pasteur; Joint International Unit Artificial Intelligence for Image-based Drug Discovery & Development

AutoHCS: AI-based scoring of dose-response high- content JUMP dataset predicts mechanisms of action from morphological clustering.

12:15 AM to 12:30 PM

Modern drug development increasingly depends on high-content compound screens where automation is the key to rapid, impactful discoveries. AutoHCSTM is an AI-based analysis tool for high content screens (HCS) developed by ViQi Inc. that automatically detects and scores phenotypic responses to drugs. Because the system does not depend on segmentation, it works non-parametrically with multichannel fluorescence, a combination of fluorescence and brightfield, or brightfield alone. The only inputs to the analysis are images from any automated plate imager and a plate map specifying drugs, concentrations, replicates, and controls. A few core AutoHCS analytical tools are: 1) comparing compounds of interest against negative and positive controls or target phenotypes 2) evaluating the dose response of compounds of interest and 3) computing morphological clusters across many different compounds. Importantly, AutoHCS AIs can conduct each of these analyses independently or in combination. For example, comparing the dose response of a compound of interest against positive controls will determine which dose, if any, is most similar to a known target phenotype. Whereas, investigating dose-dependent responses independently of controls permits the discovery of novel phenotypes, and clustering similar drug-induced phenotypes. AutoHCS entirely determines its training parameters using the experimental conditions rather than user input, which eliminates subjective criteria selection that may bias phenotype scoring. It is cloud-based, meaning there is no software or specialized computing hardware to install locally. Accordingly, AutoHCS is scalable to millions of images and works regardless of contrast method, cell type, or cellular responses generated. A key function of AutoHCS is its ability to morphologically cluster compounds according to their induced phenotype. To further investigate the significance of these clusters, and potentially gain insight into underlying mechanisms of action, we used AutoHCS to analyze a subset of the JUMP dataset, a public HCS dataset with many compounds and replicates. We converted our morphological clusters into gene lists using standard databases of compounds and their gene targets, and conducted pathway analysis on these gene lists. We found that gene lists from our morphological clusters resulted in a high degree of overlap in database-queried mechanisms of action when compared with randomly generated clusters. By using common open source pathway analysis tools like g-profiler and pathway db, we conclusively demonstrate that automated morphological clustering can lead to functional insight. As we build our knowledge base using the JUMP dataset and others, this bioinformatics-based approach to cluster validation will not only allow us to make predictions about novel compounds, but may provide deeper insight into functional pathways that lead to similar phenotypes. With all its capabilities, AutoHCS harnesses the pattern recognition abilities of modern AIs to precisely score and phenotypically profile high- content screens in an entirely automated, objective manner.

Teresa Findley
ViQi Inc.

Leveraging Artificial Intelligence to describe Cell Painting images

12:30 PM to 12:45 PM

Adriana Borowa
Ardigen

Illuminating life like never before: revolutionizing 3D bioimaging to elevate human health at LifeCanvas Technologies

12:45 PM to 1:00 PM

Molecular phenotyping has led to a growing appreciation of cell type diversity and function thereby transforming our understanding of the brain among other organs. Detection of protein in fixed tissues via immunohistochemistry (IHC) has been a major driver of those findings, with a cell's precise microenvironment within tissue providing essential physiological context. However, detection of protein in fixed tissue requires thin sectioning of tissue paired with time- consuming and error-prone post-hoc reconstruction. Tissue clearing and 3-dimensional imaging has the potential to revolutionize the field of biology by enabling researchers to evaluate protein expression in 3 dimensions across an entire organ, rather than focusing on individual regions at a time. At LifeCanvas Technologies, we are an industry leader in tissue clearing, labeling, imaging, and analysis, and are the only company to provide a full pipeline for 3D histology. We leverage the tissue transformation technique SHIELD to preserve tissue integrity and preserve endogenous fluorescence and complete active delipidation of up to 12 samples (i.e. clearing) using our SmartBatch+ device. Samples are then index matched using EasyIndex and imaged on our light sheet microscopes (SmartSPIM/MegaSPIM). This pipeline empowers researchers to reliably complete 3D histology either in their own labs or alternatively utilize our contract research services and send samples to LifeCanvas Technologies for the full pipeline.

Breanna Fearey
LifeCanvas Technologies

Lunch and Learn: Revolutionizing High Content Screening - From 2 hours to 10 minutes a plate

1:00 PM to 1:45 PM

High content screening at speed requires compromise: sacrificing resolution, sample coverage or both. This has limited high content screening's utility as a high throughput tool. In order to scale up a screen, several instruments may be required, introducing more variables. Araceli's Endeavor high content screening system can image a 96, 384 or 1536 well microplate in under 10 minutes with full well coverage and sub-micron resolution, enabling high content screening at high throughput speeds without compromising resolution or coverage. This presentation details the technology underlying these improvements and its validation, as well as a novel quality control tool designed to assess large quantities of images at the level of content. After an overview of Endeavor's capabilities on real-world assays, I'll cover how Endeavor uniquely leverages several key technical innovations to achieve high content screening at scale. I'll describe how Endeavor's proprietary parallelized optical paths and ground up design with no moving parts coalesce into an instrument that scanned forty-one 384-well plates at submicron resolution in an 8-hour workday. This produces >250,000 images: deciding which are worth further analysis is challenging. To that end, I'll present a novel quality control algorithm to identify sample aberrations such as out of focus wells, dust, or pipet tip strikes. Overall, this presentation highlights the underlying technology that makes Endeavor the fastest high content screening platform available today, allowing you to scale up your assays without introducing errors or compromising quality.

Matt Boisvert
Application Scientist at Araceli Biosciences

Lunch and Learn: Molecular Devices
Scale up and automate your 3D cell culture research: A complete workflow for automated high-throughput applications

1:00 PM to 1:45 PM

A significant barrier to widespread adoption of organoids in drug discovery is that organoid production is a costly and highly labor-intensive process. Moreover, organoid culture is a skilled manual process, and thus there can be significant variability between operators.
Join us for this lunch and learn session to find out more about the solutions offered by Molecular Devices to help you overcome the challenges in scaling up your 3D biology research.
Do not miss out on the sneak preview of our latest automated cell culture system – the CellXpress.ai™ Automated Cell Culture System, offering a revolutionary solution that gives you total control over demanding cell culture feeding and passaging schedules. Allowing you to automate and schedule your cell culture workflows 24/7.

Angeline Lim, Senior Application Scientist
Misha Bashkurov, Product Manager

Session II:
Functional genomics, pooled optical and genetic screening advancements.

Chairs:
David Shum (Institut Pasteur Korea), Safiye Celik (Recursion)

1:45 PM to 4:30 PM

Safiye Celik

Dr. Safiye Celik is a machine learning scientist, software engineer, and team leader with 10 years of industry experience, specializing in statistical machine learning applied to multi-omics data. During her Ph.D., she developed algorithms to address high-dimensionality in systems biology applications and identified robust biomarkers for complex diseases like Alzheimer's and cancer. Currently leading a cross-functional team at Recursion, Dr. Celik drives the development of phenomics-driven models and metrics to industrialize the drug discovery process, collaborating closely with biologists, chemists, and engineers to build a comprehensive "map of biology."

Image-based profiling of cells at scale with Optical Pooled Screening

1:45 PM to 2:15 PM

Paul C. Blainey
Broad Institute of MIT and Harvard; Dept. of Biological Engineering, MIT

CellPaint POSH: an ML-enabled pooled morphological CRISPR screening platform for mapping genetic functions and target discovery in neurological diseases

2:15 PM to 2:45 PM

Pooled CRISPR screening has emerged as a powerful method of mapping gene functions. Recently, the emergence of pooled optical screening combines pooled genetic screening and microscopy-based assays in studying the NFkB pathway, essential human genes, cytoskeletal organization and antiviral response. The applications thus far employ hypothesis-specific assays. Here, we enable hypothesis-free reverse genetic screening for generic morphological phenotypes by re-engineering the Cell Painting technique to provide compatibility with pooled optical screening in human cells (CellPaint-POSH).

We validate CellPaint-POSH using well-defined morphological genesets (124 genes), compared classical image analysis and self-supervised learning methods using a mechanism-of-action (MOA) library (300 genes), and performed discovery screening on the druggable genome (1640 genes) in A549 cells, demonstrating clustering of genes by biological functions without the need for target-specific biomarkers. We further applied CellPaint-POSH in drug target discovery in an iPSC based disease model for tuberous sclerosis complex (TSC), which is a multisystem autosomal dominant genetic disorder that leads to refractory epilepsy in ~80% of patients. We found multiple disease modifying targets by biomarker and ML phenotype analysis. These targets can be corroborated by orthogonal screening (perturb-seq), and validated by genetic association with relevant clinical phenotypes and functional assays measuring neuronal firing activities. In summary, we describe a unique pooled optical screening platform that combines rich morphological data and deep learning and leads to better discovery of gene functions and drug targets.

Ci Chu
Insitro

Break for Coffee and Exhibit Viewing - 2:45 PM to 3:15 PM

Correcting for chromosome-arm-scale truncations induced by CRISPR-Cas9 editing

3:15 PM to 3:45 PM

CRISPR-Cas9 is a powerful tool for introducing targeted mutations in DNA, but recent studies have shown that it can have unintended effects such as structural changes. However, these studies have not yet looked genome-wide or across data types. In this study, a phenotypic CRISPR-Cas9 scan was performed targeting 17,065 genes in primary human cells, revealing a "proximity bias" where CRISPR knockouts show unexpected similarities to unrelated genes on the same chromosome arm. This bias was found to be consistent across cell types, labs, Cas9 delivery methods, and assay modalities. The data suggests that proximity bias is caused by telomeric truncations of chromosome arms, with genes related to cell cycle and apoptotic pathways playing a mediating role. Additionally, a simple correction is demonstrated to mitigate this pervasive bias while preserving biological relationships. This uncharacterized effect has implications for functional genomic studies using CRISPR-Cas9, with applications in discovery biology, drug-target identification, cell therapies, and genetic therapeutics.

Safiye Celik
Recursion

Presidents Award:
Learning interpretable single-cell morphological profiles from 3D Cell Painting Images

3:45 PM to 4:15 PM

Quantifying the phenotypic effects of experimental perturbations from high-throughput imaging assays, a feature extraction process known as morphological profiling, is a necessary and challenging step in the analysis of Cell Painting data. Whereas traditional methods use handcrafted image processing algorithms to extract human-designed descriptors of cellular morphology, recent methods have taken a deep learning approach, training neural networks to extract features learned to be relevant from raw imaging data. While learned morphological profiles have been shown to enable better performance in downstream analysis tasks, the question of interpretability limits deep learning-based approaches: how can we ensure that the morphological profiles extracted by black-box deep learning models actually capture biologically relevant information about single cells, rather than exploiting confounding factors present in image data to minimize training loss (e.g., batch effects)? To address this uncertainty, we propose combining morphological profiles obtained using supervised learning with Gradient-weighted Class Activation Mapping (Grad-CAM), a technique that uses the gradients produced by a deep learning model to localize which regions of an input image the model paid the most attention to when making its prediction. Using single-cell segmentations produced by CellPose (a generalist segmentation algorithm), we can measure, for each learned morphological profile, what proportion of the model's attention is concentrated on the cell of interest versus the background. Using this interpretability metric, we can identify which morphological profiles capture biologically relevant components of the input image, helping to visualize the influence of confounders on the extracted features. Using a 3D convolutional neural network, we demonstrate how to scale this technique to 3D Cell Painting images: in a dataset of single-cell z-stacks, we find that only 47% of learned morphological profiles have Grad-CAMs that overlap with the cell's segmentation map. This demonstrates that supervised feature extractors can cheat by exploiting non-biological information in microscopy data. Motivated by this disadvantage of supervised learning, we also explore self-supervised approaches for learning interpretable morphological profiles from single-cell 3D Cell Painting images.

Vivek Gopalakrishnan is a third-year PhD candidate in Medical Engineering and Medical Physics at the Harvard-MIT Program in Health Sciences and Technology, advised by Dr. Polina Golland. The goal of his research is to address unmet clinical needs through the development of biomedical machine-learning methods that deepen our ability to understand and treat disease. His current focus is making minimally invasive neurosurgery easier for clinicians and safer for patients by designing fast 3D computer vision algorithms (neural fields) that advance the standard of intraoperative image guidance.

Exhibit Viewing and Poster Sessions - 4:15 PM to 6:00 PM

Reception - 6:00 PM to 7:30 PM

Wednesday, November 1, 2023

8:00 AM - 600 PM	**Exhibit Hall Opening / Networking**
8:00 AM - 9:00 AM	**Breakfast**

Keynote: Spatial Multi-Omics for Mapping Tissue Development, Aging, and Diseases

9:00 AM to 10:00 AM

Despite latest breakthroughs in single cell sequencing that revealed cellular heterogeneity, differentiation, and interactions at an unprecedented level, the study of multicellular systems needs to be conducted in the native tissue context defined by spatially resolved molecular profiles to better understand the role of spatial heterogeneity in biological, physiological and pathological processes. In this talk, I will begin with discussing the emergence of a whole new field – “spatial omics”, and then focus mainly on a new technology platform called Deterministic Barcoding in Tissue (DBiT) for spatial omics sequencing developed in our laboratory over the past years. We conceived the concept of “spatial multi-omics” and demonstrated it for the first time by co-mapping whole transcriptome and proteome (~300 proteins) pixel-by-pixel directly on a fixed tissue slide in a way compatible with clinical tissue specimens including FFPE. It has been applied to the study of developing mouse brain, human brain, and human lymphoid tissues associated with normal physiology, disease, or aging. Recently, our research enabled another new field – “spatial epigenomics” – by developing multiple DBiT-based spatial sequencing technologies for mapping chromatin accessibility (spatial-ATAC-seq), histone modification (spatial-CUT&Tag), or further combined with transcriptome or proteins for spatial epigenome-transcriptome co-profiling. These new technologies allow us to visualize gene expression regulation mechanisms pixel by pixel directly in mammalian tissues with a near single cell resolution. The rise of NGS-based spatial omics is poised to fuel the next wave of biomedical research revolution including human cancer research. Emerging opportunities and future perspectives will be discussed with regard to clinical cancer biomarker discovery and therapeutic development.

Rong Fan
Yale University

Dr. Rong Fan is the Harold Hodgkinson Professor of Biomedical Engineering at Yale University and Professor of Pathology at Yale School of Medicine. He received a Ph.D. in Chemistry from the University of California at Berkeley and completed the postdoctoral training at California Institute of Technology before joining the faculty at Yale University in 2010. His current interest is focused on developing microtechnologies for single-cell and spatial omics profiling to interrogate functional cellular heterogeneity and inter-cellular signaling network in human health and disease (e.g., cancer and autoimmunity). He co-founded IsoPlexis, Singleron Biotechnologies, and AtlasXomics. He served on the Scientific Advisory Board of Bio-Techne. He is the recipient of a number of awards including the National Cancer Institute’s Howard Temin Career Transition Award, the NSF CAREER Award, and the Packard Fellowship for Science and Engineering. He has been elected to the American Institute for Medical and Biological Engineering (AIMBE), the Connecticut Academy of Science and Engineering (CASE), and the National Academy of Inventors (NAI).

Introduction to Thermo Fisher Scientific High-Content Screening Technologies

10:00 AM to 10:15 AM

High Content Analysis has adapted to handle many different sample types used for making discoveries. In this spotlight seminar we will examine how the CellInsight HCA platforms enable robust automated image acquisition and analysis. We will also highlight the wide array of reagents and resources available for researchers.

Mark A Clark, Sr Product Specialist, Thermo Fisher Scientific

Award Ceremony: Best Posters - 10:15 AM to 10:20 AM

Coffee Break - 10:20 AM to 10:45 AM

Session III:
Spatial omics & advances in platform capabilities for multi-omics.

Chairs:
Manuel Leonetti (Chan Zuckerberge BioHub), Katherine Hales (Pfizer)

10:45 AM to 1:00 PM

Manuel Leonetti

A Group Leader at the CZ Biohub San Francisco, Leonetti leads a multidisciplinary team of biologists, engineers, and data scientists that strive to understand how human cells are built. Their projects seek to characterize fundamental mechanisms in physiology and disease, but also to "reverse engineer" the cell—to understand the details of how it is built in order to be able to predictably tune its properties and behavior. In particular, Leonetti and colleagues develop and deploy technologies to characterize the network of proteins that govern cellular function using a combination of genome engineering, live-cell imaging and mass spectrometry. One their goals is to build open datasets, software, and protocols for the entire scientific community to use and explore. Check out their flagship project, OpenCell, at opencell.czbiohub.org.

OpenCell: Intracellular Cartography of the Human Proteome

10:45 AM to 11:15AM

New methods are enabling us to address key questions in cell biology with a new level of scale and comprehensiveness. Mapping the localization of all proteins within the cell and the interaction network that connects them would provide a reference map of cellular organization. Quantifying how this organization changes between cell types or cell states promises new insights into physiology and disease. Here, I will present the experimental and analytical frameworks that my team is developing to map sub-cellular architecture. We are combining high-throughput CRISPR editing, live-cell imaging and interaction proteomics to create OpenCell (opencell.czbiohub.org), a systematic effort to map the sub-cellular localization of human proteins and the interactions between them. Notably, our imaging dataset from >1,300 fluorescently tagged cell lines enabled us to develop a self-supervised deep learning strategy for the quantitative comparison of localization patterns.

We are also building new open-source tools to automate and accelerate cell biology workflows, from the design and analysis of gene editing experiments to cell sorting and passaging. Finally, we are generating a novel proteomics dataset to comprehensively define the proteome of cellular organelles. Overall, I will illustrate how we are integrating scalable engineering solutions (from genome engineering to software to hardware) for the study of cell biology.

Manuel Leonetti
Chan Zuckerberg BioHub

Next generation tools for Spatial Genomics

11:15 AM to 11:45 AM

Tissue functions are highly cell non-autonomous. While single-cell analysis has begun to elucidate the cellular components that participate in tissue function and dysfunction; interactions – and their spatial variation across tissue structures – remain challenging to explore. Here, we'll describe advances in situ and single cell transcriptomic sequencing tools which aim to capture both the spatial context of cells as well as their dynamics within tissues. In particular, we'll describe a new technology, which we call Slide-tags, in which single nuclei within an intact tissue section are 'tagged' with spatial barcode oligonucleotides derived from DNA-barcoded beads with known positions. A major benefit of Slide-tags is that it is easily adaptable to virtually any single cell measurement technology. We adapted Slide-tags for T cell receptor sequencing to spatially map T cell clonality in single nuclei. We also implemented Slide-tags to quantify genetic alterations at single-nucleus spatial resolution by targeted sequencing of single-nucleotide variations captured in the transcriptome. To demonstrate the utility of Slide-tags in tumor biology, we spatially profiled human melanoma samples. We identified geographically segregated cancer clones with distinct genetic and transcriptomic profiles, as well as different levels of T cell clone infiltration. The technological advances of Slide-tags facilitate high-resolution analysis of cell-cell interactions, allow for spatial tumor lineage tracing, and grant more statistical power to detect changes in gene expression across cell types in space. Slide-tags offers a universal platform for importing established single cell measurements of gene expression, epigenetic regulation, and antibody-based quantification into the spatial genomics repertoire. More broadly, we'll discuss the promise and challenges of spatial transcriptomics for tissue genomics.

Fei Chan
Broad Institute

Dr. Fei Chen is currently a Core Faculty member at the Broad Institute, and Assistant Professor at Harvard Stem Cell and Regenerative Biology. During the course of his doctoral research, Chen co-invented expansion microscopy, a breakthrough technique that allows for super-resolution imaging of biological samples with conventional light microscopes. As an independent Fellow at the Broad, his lab continued to pioneer novel tools at the intersection of genomics and microscopy to uniquely illuminate biological pathways and function. These include, Slide-seq, a novel technology for transcriptome-wide gene expression profiling with near-single-cell spatial resolution. At Harvard and the Broad Institute, Chen's laboratory sets out to build a set of tools which will bridge single-cell genomics with space and time – to enable discoveries of where cell types are localized within intact tissues, when relevant transcriptional modules are active. To do this, the lab is developing novel technologies at the intersection of microscopy, genomics, and synthetic biology. We are applying these tools to learn organizational principles governing neurodevelopment, and cellular mechanisms of disorganization during neuronal injury and disease. Chen obtained his Ph.D. in Biological Engineering from the Massachusetts Institute of Technology with Ed Boyden. Afterward, Chen was a Schmidt Fellow at the Broad Institute. His awards include the National Institutes of Health Director's Early Independence Award and the Allen Distinguished Investigator Award.

Direct fluorescence imaging of specific lipid trafficking pipelines in cells

11:45 AM to 12:15 PM

Lipids are used by cells to build membranes, store energy, and transmit signals. Because lipid composition determines organelle identity and function, dysregulation of lipid distribution in cells is at the center of many diseases and often a cause for clinical trials to fail. Cells rely on two different mechanisms to maintain lipid homeostasis in their membranes: vesicular and non-vesicular lipid transport. Despite extensive research, it still remains unclear what the relative contributions of the two transport pathways to membrane lipid homeostasis are. This is due to two main reasons: (1) our inability to monitor transport of native lipids under the microscope and (2) the complexity of the cellular lipidome that features thousands of chemically distinct lipid species that in many cases only vary in small, yet biologically relevant structural details. Until recently, direct visualization of lipid transport in cells under the microscope has proven difficult. This is because lipids are a product of metabolism and the genetic tools that cell biologists have developed cannot be used to fluorescently tag lipids in a comprehensive manner. Furthermore, chemical modifications that render lipids fluorescent require large alterations of the chemical structure of the parent molecules that disrupt how the cellular proteins interact with the labeled lipid. To overcome these issues, chemical biology laboratories have synthesized a small number of so-called bifunctional lipids (also known as photoactivatable and clickable, pac) and prodrug-versions of lipids that have the advantage to behave close to their native counterparts. In recent years we have developed a library of more than 20 bifunctional lipids and streamlined their synthesis. With this diversity we can start to understand how, for example, small differences in lipid saturation degree and acyl chain position determine lipid transport and metabolism. By combining our expertise in chemical synthesis, biology and image analysis, we have generated a pipeline to quantify intracellular lipid transport using confocal fluorescence microscopy. Furthermore, we can provide a direct link between intracellular lipid localization and lipid metabolism by mass spectrometry. Our data suggest that non-vesicular lipid transport provides both higher molecular specificity and faster kinetics compared to both vesicular lipid trafficking and metabolism. Organelle membrane compositions and intracellular lipid homeostasis are thus likely maintained by non-vesicular lipid transport. We also find that phosphatidylcholine regioisomers possibly contribute to distinct acyl-CoA pools for neutral lipid synthesis. This suggests a highly coupled reaction sequence of fatty acid cleavage, acyl-CoA synthesis and incorporation into triacylglycerols and cholesterol ester.

Juan M. Iglesias-Artola
Max Planck Institute of Molecular Cell Biology and Genetics

Short Talk:
Subcellular Spatial Omics Decode RNA and Protein Networks and Neighborhoods in Single Cells

12:15 PM to 12:30 PM

The spatial organization of cells in tissues and subcellular networks provides a quantitative metric for determining health and disease states. Single-cell analyses of molecular profiles with in-situ detection methods dissect spatial heterogeneity of distinct cell types. Such detailed cellular digital maps shed light on the spatial regulation mechanisms of many disorders. The next challenge in spatial biology is to link the cellular functional responses to the cell identities in their native three-dimensional (3D) environments. To achieve this important goal, image-based multiparameter molecular profiling has the potential to decode “high-dimensional dynamics of molecular neighborhoods and networks” at the subcellular and molecular levels in cultures and tissues. Here, I will introduce subcellular spatial omics modalities (spatial genomics, spatial proteomics, and spatial metabolomics) to decipher and model the spatio-temporal regulation of single cells at macromolecular resolution in synthetic biosystems and native human biospecimens for (1) systems immuno-engineering and immune-aging, (2) subcellular precision oncology, and (3) personalized regenerative medicine applications.

Automated machine learning algorithms in this single-cell big data impact biomedical practice and clinical care. In the first part, I will introduce a spatially resolved gene neighborhood network (SpaGNN) concept to decipher RNA-RNA proximity in multiplexed fluorescence in situ hybridization (FISH) data and how it can impact cell type classification. The spatial and temporal decision-making of single cells is regulated by such gene neighborhood networks at macromolecular resolution in 3D-engineered organoids and various human tissues. In the second part, I will present a spatial signaling network model based on multiplexed proteomic signatures of signaling factors and proximity pairs. Such a spatial signaling network model will predict drug responses using graph-based convolutional networks and machine learning algorithms. In the third part, I will demonstrate a spatial organelle network approach that can distinguish stem cell identities for regenerative medicine applications. The image-based subcellular networks of organelles will inform functional analyses of single cell molecular organization for controlling bioenergetics and organelle communication. Co-localization of organelles and signaling molecules will further shed light on complex subcellular control of molecular wiring in single cells. In the last part, digital technologies interfacing with cellular interactive media will be presented using the virtual reality of 3D spatial omics. Single-cell biotechnologies and digital cellular media tools synergistically complement each other for next-generation bioengineering, crowd-sourced education, and collaborative discovery platforms.

Ahmet F Coskun
Georgia Institute of Technology

High-throughput Imaging Transcriptomics in 2D and 3D cell models

12:30 PM to 12:45 PM

Image-based profiling in 2D and 3D cells is a well-established strategy at the Victorian Centre for Functional Genomics (VCFG), reducing the rich information present in biological images to a multidimensional profile of image-based features. These readouts can help understand disease mechanisms and predict a drug's activity, toxicity, or mechanism of action. However, mechanistic changes that are not reflected in a change in cell morphology can be missed, especially in organoids and spheroids, and imaging features are often hard to interpret in isolation. Therefore, we have developed "Imaging Transcriptomics", which aims to integrate data from high-content imaging and high-throughput transcriptomics. Multiplexed Analysis of Cells (MAC-seq) allows for multiplexed sequencing of samples from 384-well plates at a fraction of the cost and we have optimized this method to be applied to spheroids and organoids grown in Matrigel. This application will allow us to characterize not just morphological changes to minimal amounts of patient-derived organoids over time, during drug-treatment, and during development of resistance but for the first time also their transcriptional changes in a high-throughput fashion in 384-well plates.

Kaylene J Simpson
Peter MacCallum Cancer Centre

Vendor Spotlight: CytoTronics
Electrical imaging: A new paradigm for generating live cell high-dimensional functional data

12:45 PM to 1:00 PM

At CytoTronics, we integrate semiconductor microchips into microplates to bring electrical live-cell measurements to high-throughput. Our non-invasive, label-free technology offers real-time measurements spanning live-cell function, electrophysiology, and morphology. With the ability to capture over 20 parameters throughout experiments, our semiconductor 96-microplate platform opens new avenues to understand cellular behavior across diverse biological applications.

Jeffrey Abbott, PhD
Co-founder & CEO, CytoTronics Inc

Lunch and Learn: Integrated Spatial Multiomic Approaches to Biomarker Discovery and Tissue Phenotyping

1:00 PM to 1:45 PM

The MACSima™ Spatial Multiomic Imaging Platform is a fully automated cyclic immunofluorescence imaging system that integrates liquid handling with sensitive multichannel microscopic detection. Biomarker discovery as well as tissue phenotyping can readily be performed by investigating >100 markers on one sample. The platform does not require antibody validation or complicated experiment set-up allowing multiparameter staining/detection of various antigens in one staining cycle and transcript detection on the same tissue sample.

Robert Pinard
Director of Sequencing Chemistry & Molecular Technologies

Lunch and Learn: Carl Zeiss Microscopy
Flexible End-toEnd Solutions for Spatial Biology Workflows with ZEISS Imaging and Analysis Platforms

1:00 PM to 1:45 PM

As a leading manufacturer of microscopes ZEISS offers inspiring solutions and services for your life sciences and materials research, teaching and clinical routine. Reliable ZEISS systems are used for manufacturing and assembly in high tech industries as well as exploration and processing of raw materials worldwide.

Keving O'Keefe, PhD

Session IV:
Advances in High Content Imaging: next-generation phenotypic screening assays.

Chairs:
Melaney Bailey (University of Surrey), Stephen Walker (Abbvie)

1:45 PM to 4:30 PM

Melanie Bailey

Melanie Bailey is a Professor of Analytical Science. She is Director of the BBSRC SEISMIC national research facility for spatially resolved single and sub-cellular "omics". She also holds a prestigious EPSRC fellowship which is developing strategies for correlative imaging of elemental and molecular biomarkers at single cell resolution. She is an elected member of the Royal Society of Chemistry Analytical Measurement Community and is a member of a number of international committees relating to analytical science.

The SEISMIC UK National Research Facility for Spatially Resolved Single and Sub-Cellular Omics

1:45 PM to 2:15 PM

The SEISMIC facility for single and sub-cellular omics is a new UK national facility. SEISMIC is based on a new technology from the Yokogawa Corporation, which allows the extraction of single living cells, or their sub-cellular compartments into capillary tips. The extraction of cellular material is performed under microscope observation. Essentially, this is a platform technique for extracting single cells or their sub-cellular contents. This therefore enables the analysis of lipids, metabolites proteins, metals, transcripts and genes. We will report on progress, challenges and opportunities for this tool to add value to biological investigations, with a particular focus on mass spectrometry "omics".

Melaney Bailey
University of Surrey

Multimodal Tissue Imaging and Machine Learning to Advance Precision Medicine

1:00 PM to 4:30 PM

The effective treatment of cancer and many other diseases is increasingly dependent on a precision approach in which the quantification of molecular features at the level of individual patients is used to guide treatment plans. Currently, cancer diagnosis and staging are performed primarily via direct examination of biopsy and resection specimens by histopathologists. However, these classical methods provide insufficient molecular insight to guide the use of targeted and immunotherapies even when supplemented by knowledge of tumor genotypes. Fortunately, the last few years has witnessed the introduction of innovative new methods for performing 20-100 plex imaging of histological specimens at subcellular resolution. When processed to extract single cell data, high-plex tissue images promise to combine the historical strength of histopathology with deep insight into cancer biology.

In a research setting such data are a natural complement to dissociative single cell sequencing, in the context of clinical trials, they can provide unprecedented insight into mechanism of action and pharmacodynamics, and in a diagnostic setting, they promise to improve outcomes and reduce the burden of therapy. Realizing these benefits requires the development of new instruments, reagents, and machine-learning algorithms. I will describe progress in these areas with reference to the characterization of immune landscapes in primary melanoma and predicting tumor progression in colorectal cancer.

Peter K. Sorger
Harvard Medical School

Vendor Spotlight: Spring Science
Public portal and benchmarks for exploring Cell Painting data analysis

2:45 PM to 3:00 PM

SPRING

The JUMP-CP dataset is available for public exploration and analysis using Spring's AI-based image analysis suite at http://app.springscience.com. We're excited to share this portal, our set of benchmark metrics for JUMP-CP aimed at representative tasks in drug discovery, and novel insights emerging from this analysis.
On JUMP-CP's public portal: Spring's imaging suite generates powerful and novel insights across many preclinical questions, including quantifying single cell behaviors at scale, unbiased phenotypic modeling, differentiating top hits, and phenotypic similarity scoring. This toolkit is applied to the JUMP-CP dataset and available for you to explore on Spring's platform at http://app.springscience.com. On JUMP-CP benchmarks: Spring defined a set of benchmark metrics aimed at representative tasks in drug discovery. Specifically, we measured the accuracy for retrieving and matching treatment replicas as well as for distinguishing a treatment-induced phenotype from a control condition. We present the impact on these metrics of different algorithmic choices in building phenotypic profiles and computing similarity scores.

Ben Kamens
Founder and CEO, Spring Discovery

Break for Coffee and Exhibit Viewing - 3:00 PM to 3:30 PM

Towards therapeutics for metabolic disease: Linking genetic variation to cell biology

3:30 PM to 4:00 PM

The motivation of my research program has been that those genetic studies succeeded in identifying 1,000s of associations between genetic loci and cardiometabolic disease in humans. Yet, the next grand challenge — systematically dissecting the mechanisms by which these variants affect disease — has still to be solved and scaled. We have previously developed V2F frameworks for going from variants to genes to cells to biological pathways for the FTO obesity risk locus (NEJM 2015), and shown that this framework generalizes to other genetic risk loci. A major focus of my lab has been to develop and deploy a cardiometabolic disease-oriented scalable, high-dimensional image-based profiling tool, LipocyteProfiler, across hundreds of individuals to map genetic determinants of cell functions in adipocytes (GWAS-in-a-dish). In this talk, I will introduce LipocyteProfiler and show its power to ascertain the effects of polygenic risk scores for metabolic disease on cellular phenotypes.

Melina Claussnitzer
Broad Institute

Short Talk:
Automated High-Throughput, High-Content 3D Imaging of Intact Pancreatic Islets

4:00 PM to 4:15 PM

Diabetes poses a global health crisis affecting individuals across age groups and backgrounds, with a prevalence estimate of 700 million people worldwide by 2045. Current therapeutic strategies primarily rely on insulin therapy or hypoglycemic agents, which fail to address the root cause of the disease - the loss of pancreatic insulin-producing beta-cells. Therefore, bioassays that recapitulate intact islets are needed to enable drug discovery for beta-cell replenishment, protection from beta-cell loss, and islet-cell interactions. Standard cancer insulinoma beta-cell lines MIN6 and INS-1 have been used to interrogate beta-cell metabolic pathways and function but are not suitable for studying proliferative effects. Screening using primary human/rodent intact islets offers a higher level of physiological relevance to enhance diabetes drug discovery and development. However, the three-dimensionality of intact islets have presented challenges in developing robust, high-throughput assays to detect beta-cell proliferative effects. Established methods rely on either dissociated islet cells plated in 2D monolayer cultures for imaging or reconstituted pseudo-islets formed in round bottom plates to achieve homogeneity. These approaches have significant limitations due to the islet cell dispersion process. To address these limitations, we have developed a robust, intact pancreatic islet imaging platform in 384-well format that is capable of detecting diabetes-relevant endpoints including beta-cell proliferation, chemoprotection, and islet spatial morphometrics. We were then able to apply our method to a preliminary in vivo study of a new scaffold for beta-cell modulation. Islets were isolated from the pancreata of mice after a week of exposure of our compound, GNF-9228. This method proved to be a drastic improvement over classical histological analysis for in vivo beta-cell proliferation and encouraged us to pursue a structure-activity relationship campaign to improve the physical properties of our lead compound.

Sean McCarty
University of Michigan

Live cell painting of drug responses in human primary patient cells

4:15 PM to 4:45 PM

A variety of microscopy and machine learning methods have been proposed to glean information from morphological data about cellular responses to drugs. At the one extreme, limited data about live cells can be recorded at high speed (e.g. bright field or light scattering images). At the other, multiplexed staining patterns from fixed cells provide much richer data but for dead cells. The latter technique, popularized as ‘Cell Painting’, was introduced to maximize the information available from micrographs and generate image-based signatures that can reveal information about a drug’s mechanism of action or phenotypic impact. However, cell painting requires multiple sample processing steps that can result in selective loss of cells during sample handling as well as other sample alterations associated with permeabilization and fixation. Moreover, as an end-point assay, important kinetic information could be missed, which may necessitate assaying independent samples at different time points.

When in the early 2000’s we began developing an automated high throughput technique akin to Live Cell Painting using fluorescent dyes, it became clear that obtaining morphology data in live cells offers more than the obvious advantage of temporal analyses. However, analyzing the data computationally to generate informative signatures was complicated because the observed responses to drugs were convoluted with the response(s) of the cells to the dyes used for imaging. Furthermore, for screening obviating the uneven loss of cells, particularly stressed and or dying cells by eliminating washing steps by using mix and read dyes is a major advantage. This is particularly important for primary patient cells which are inherently heterogeneous populations that may have differing drug responses.

Similarly, primary patient cells can often be limiting to the number of samples that can be imaged therefore, being able to image the same samples at different time points is clearly advantageous. Finally, when using organoids and other 3D cultures of primary patient cells, uneven dye penetration can lead to differences in cell staining that are unrelated to cell physiology or drug responses that further confound interpretation.

For these reasons, we developed both non-toxic Chromalive dyes with minimal effects on cell physiology and genetically encoded stress-sensors that can be used to measure the effects, not only of the dyes, but also other sample manipulations that may change cell responses. Because Chromalive is non-toxic, mix and read dye that reports on cellular metabolic activity it can be added to cultures during the generation of patient derived organoids ensuring even staining. I will describe our progress using automated high throughput Live Cell Painting with 2D and 3D cultures of primary patient cells to identify; patient cohorts with similar drug responses, drugs with common mechanism(s) of action and to identify off-target effects of drugs. Our preliminary results in companion studies for clinical trials suggest that live cell painting can be used as part of a precision treatment regime in oncology.

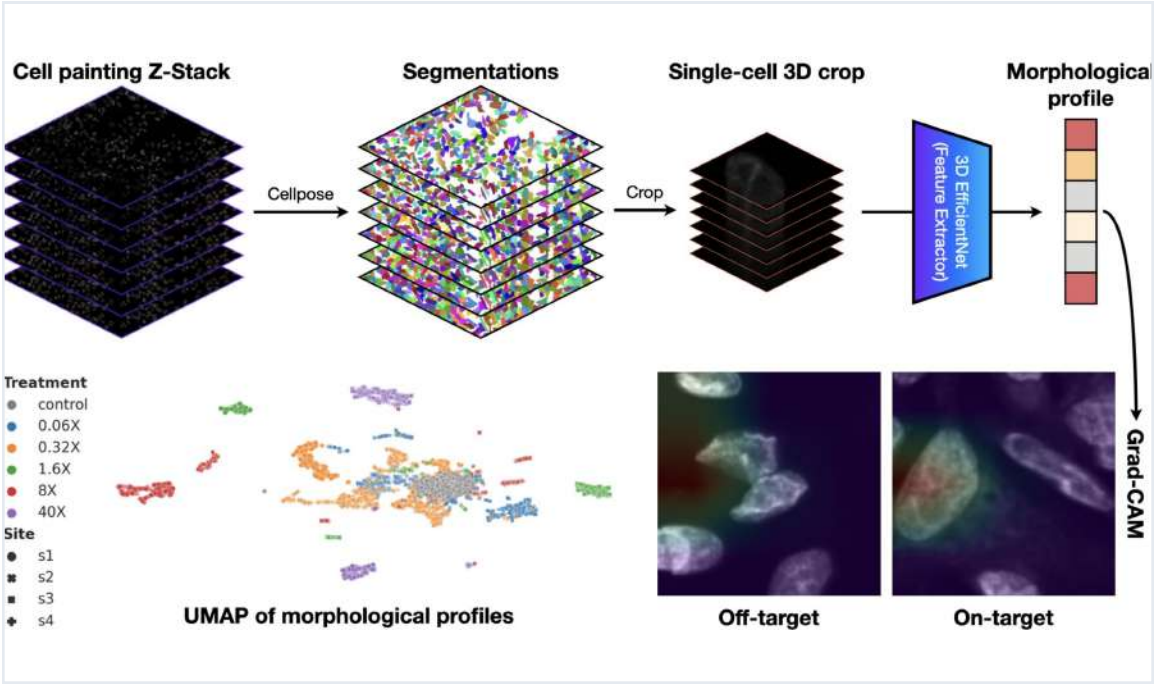
David Andrews
University of Toronto Sunnybrook Research Institute

SBI2 AGM (Open to all attendees) - 5:00 PM to 6:00 PM

Presidents Award Winner

Learning interpretable single-cell morphological profiles from 3D Cell Painting images

Quantifying the phenotypic effects of experimental perturbations from high-throughput imaging assays, a feature extraction process known as morphological profiling, is a necessary and challenging step in the analysis of Cell Painting data. Whereas traditional methods use handcrafted image processing algorithms to extract human-designed descriptors of cellular morphology, recent methods have taken a deep learning approach, training neural networks to extract features learned to be relevant from raw imaging data. While learned morphological profiles have been shown to enable better performance in downstream analysis tasks, the question of interpretability limits deep learning-based approaches: how can we ensure that the morphological profiles extracted by black-box deep learning models actually capture biologically relevant information about single cells, rather than exploiting confounding factors present in image data to minimize training loss (e.g., batch effects)?



To address this uncertainty, we propose combining morphological profiles obtained using supervised learning with Gradient-weighted Class Activation Mapping (Grad-CAM), a technique that uses the gradients produced by a deep learning model to localize which regions of an input image the model paid the most attention to when making its prediction. Using single-cell segmentations produced by CellPose (a generalist segmentation algorithm), we can measure, for each learned morphological profile, what proportion of the model's attention is concentrated on the cell of interest versus the background. Using this interpretability metric, we can identify which morphological profiles capture biologically relevant components of the input image, helping to visualize the influence of confounders on the extracted features. Using a 3D convolutional neural network, we demonstrate how to scale this technique to 3D Cell Painting images: in a dataset of single-cell z-stacks, we find that only 47% of learned morphological profiles have Grad-CAMs that overlap with the cell's segmentation map. This demonstrates that supervised feature extractors can cheat by exploiting non-biological information in microscopy data. Motivated by this disadvantage of supervised learning, we also explore self-supervised approaches for learning interpretable morphological profiles from single-cell 3D Cell Painting images.

Vivek Gopalakrishnan

Vivek Gopalakrishnan is a third-year PhD candidate in Medical Engineering and Medical Physics at the Harvard-MIT Program in Health Sciences and Technology, advised by Dr. Polina Golland. The goal of his research is to address unmet clinical needs through the development of biomedical machine-learning methods that deepen our ability to understand and treat disease. His current focus is making minimally invasive neurosurgery easier for clinicians and safer for patients by designing fast 3D computer vision algorithms (neural fields) that advance the standard of intraoperative image guidance.

The Exhibiting Partners