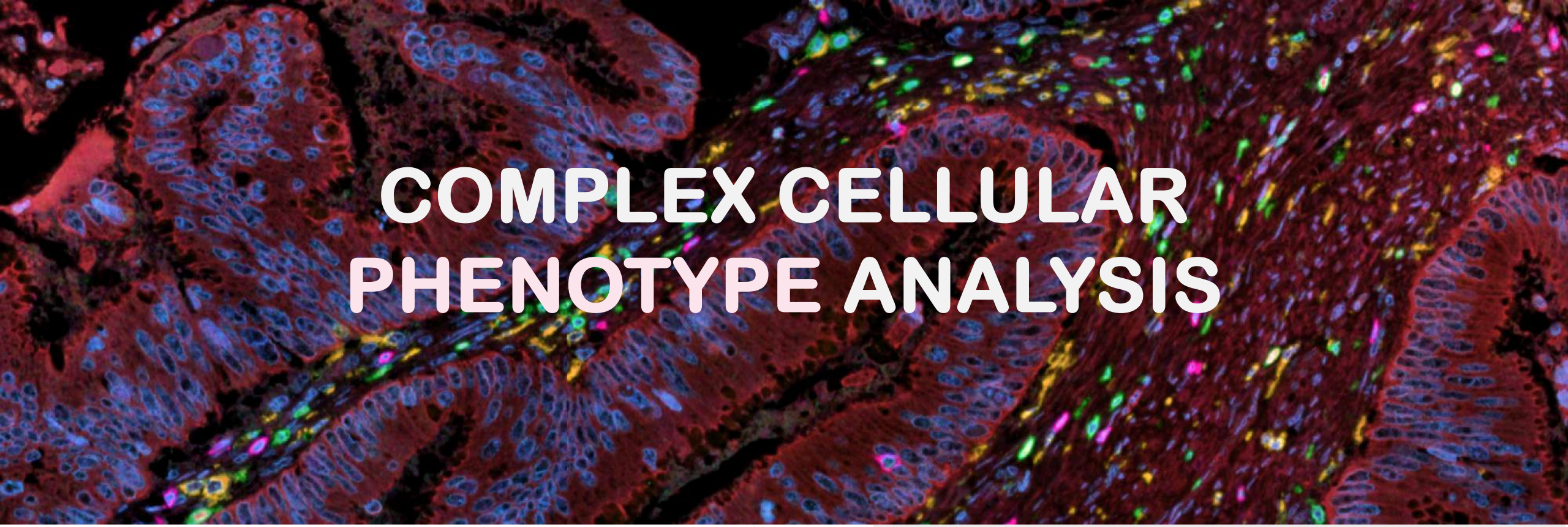
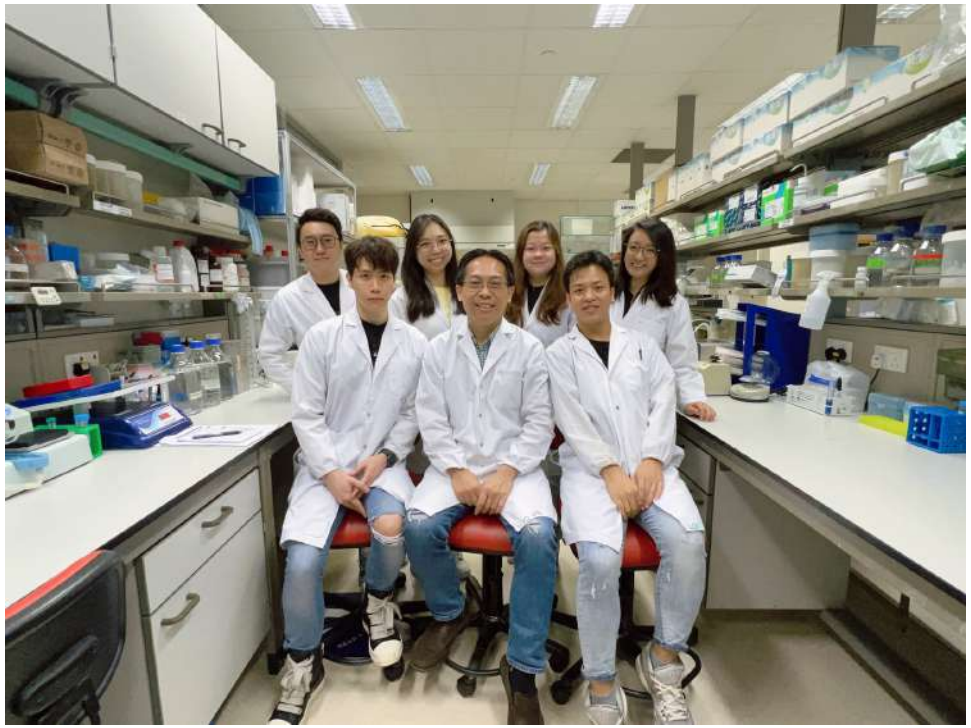


COMPLEX CELLULAR PHENOTYPE ANALYSIS

Loo Lit Hsin
Senior Principal Investigator
Bioinformatics Institute, A*STAR
loolh@bii.a-star.edu.sg

Bioinformatics Institute
BII

COMPLEX CELLULAR PHENOTYPE ANALYSIS GROUP



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Spatial profiling of cells and tissues

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Digital medicine for cancers

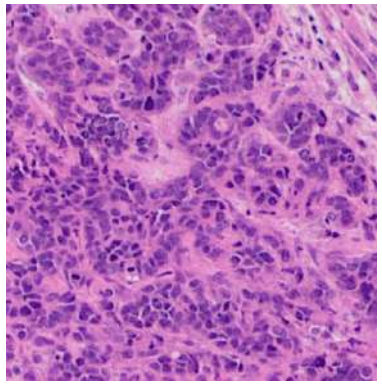
- Biomarkers for patient stratification and targeted intervention
- Pathogenicity of mutations

Predictive models for therapeutic development

- Tumor-associated antigen prediction
- Xenobiotic-induced toxicity prediction

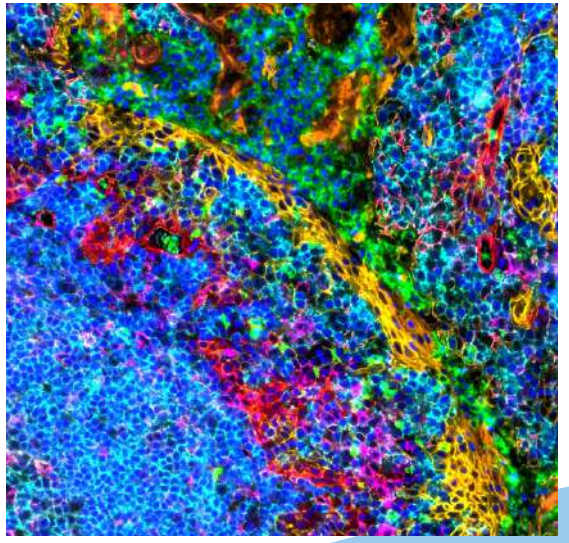
The Quest of Spatial Biology

The goal is to map and visualize biology across biological scales, from DNAs to RNAs to proteins to metabolites to phenotypes



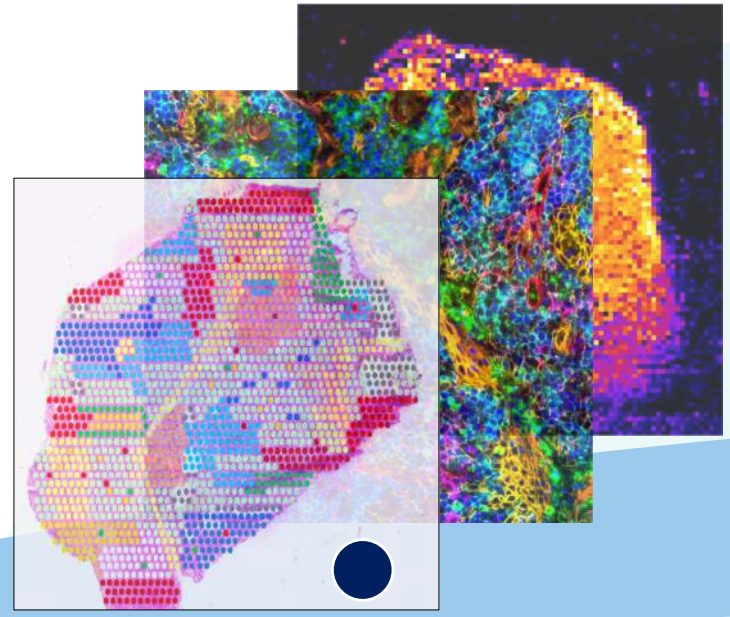
Bright-field imaging

- **Histology**
- Tech: H&E, IHC and MxF imaging
- 1 or 2 markers



Multiplex imaging

- **DNAs, RNAs, or Proteins**
- Tech: Vectra, CODEX, COMET , MERFISH, MIBI, IMC
- 5 to 100 markers



Spatial omics

- **Genomics, Transcriptomics, Proteomics or metabolomics**
- Tech: Visium, Xenium, GeoMX, CosMX, StereoSeq, MALDI-MSI, DESI-MSI
- 1,000 to 20,000 markers

Spatial multi-omics

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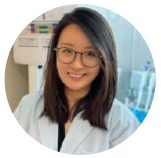
Spatial Proteomics

Joey Lee


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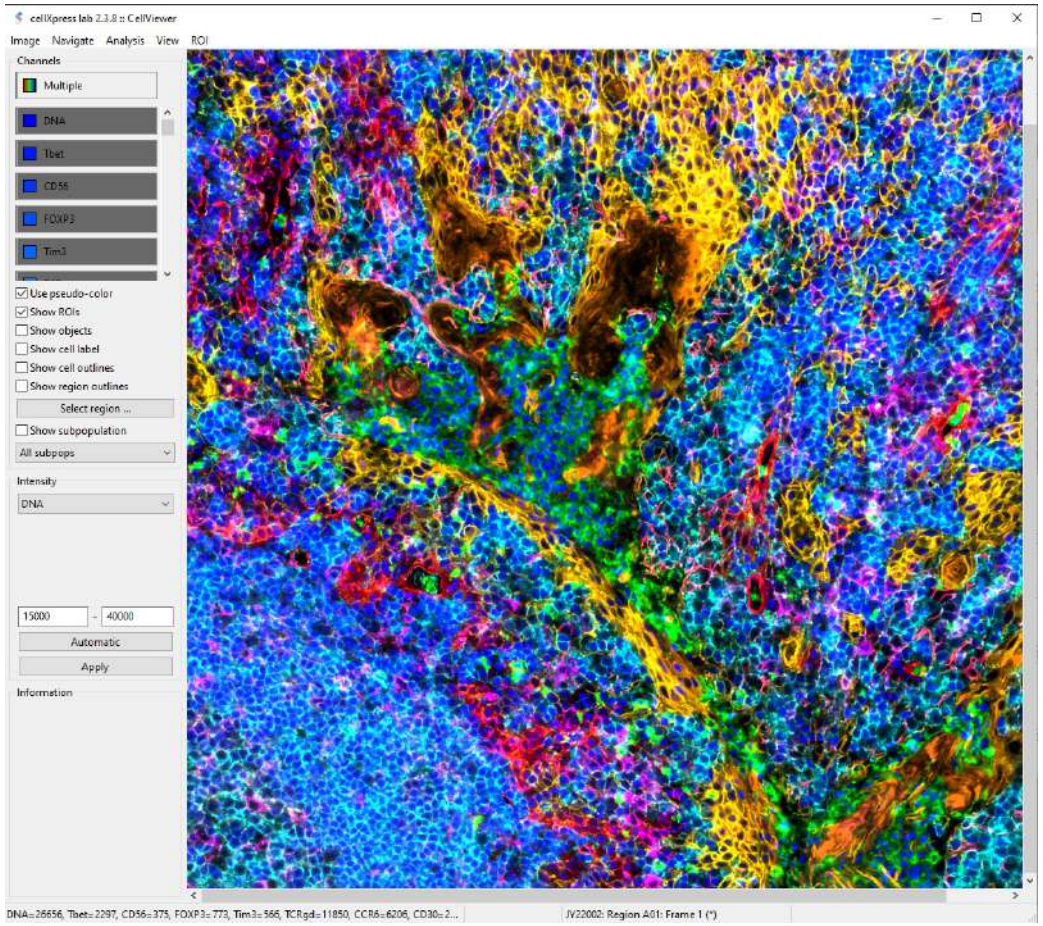
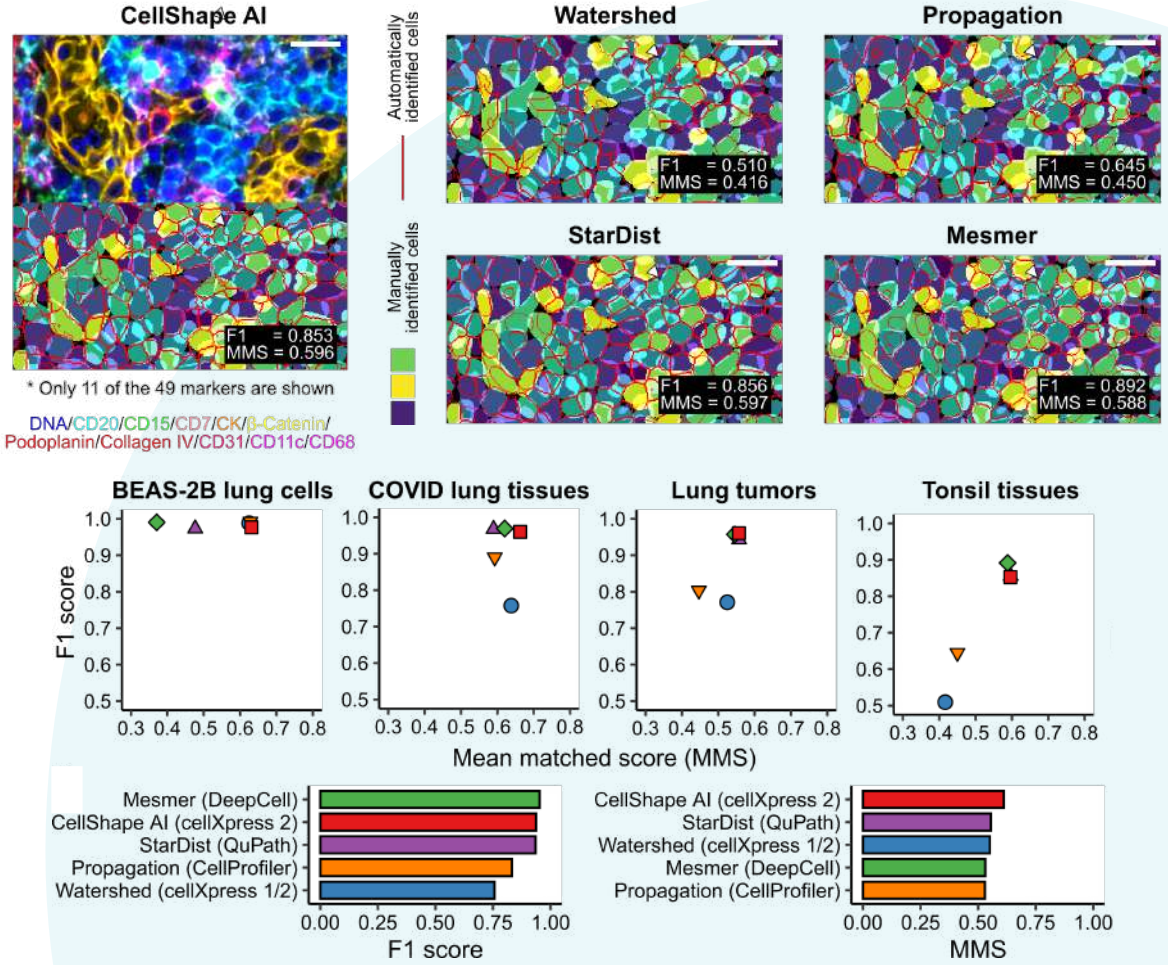
Sizun Jiang

HARVARD MEDICAL SCHOOL

cellXpress 2 https://cellXpress.org

- We have updated cX2 to handle large hyperplexed tissue images
- An example of a tonsil tissue stained with 49 protein markers using the CODEX technology
- We have developed CellShapeAI to segment diverse and overlapping cell types at tissues





Spatial Metabolomics

Joey Lee

Wang Yulan

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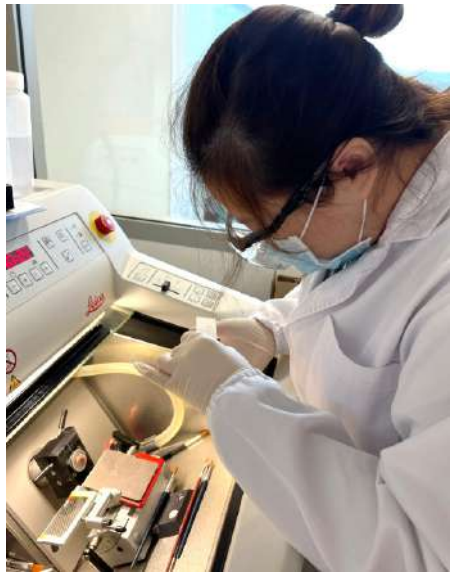
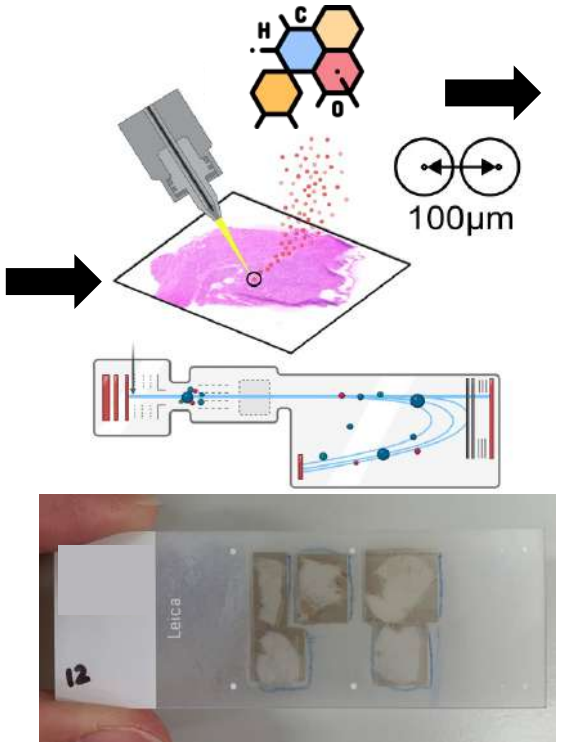
SCHOOL OF MEDICINE

Mass spectrometry imaging (MSI) can measure the spatial expressions of metabolites, such as **amino acids, lipids, steroids**, and other small molecules in human tissues

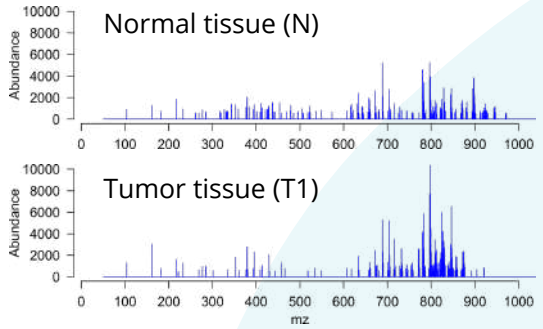
We have developed computational pipelines to process, QC, analyze, and visualize MSI data



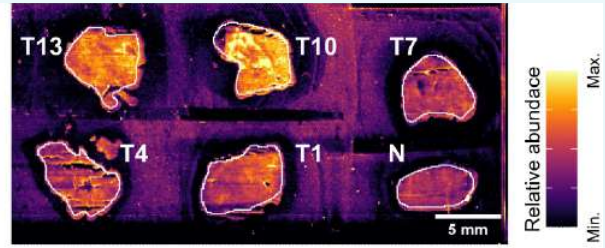
Tissue sectioning (Our PhD student, Claresta)



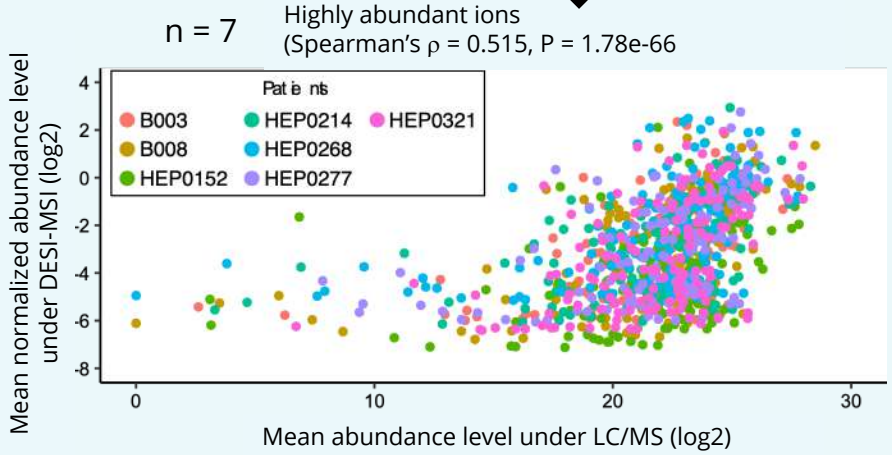
Multiple sections from one patient



Total ion current from MSI



Comparing spatial (MSI) and bulk metabolomics (LC/MS)



COMPLEX CELLULAR PHENOTYPE ANALYSIS GROUP

Cuithbert, Carmen, Claresta, Joey Oscar, Lit-Hsin, Guorui

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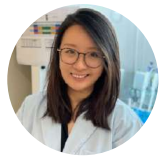
Predictive models for therapeutic development

- Tumor-associated antigen prediction
- Xenobiotic-induced toxicity prediction

Online public portal for immuno-oncology images and markers

Joey Lee



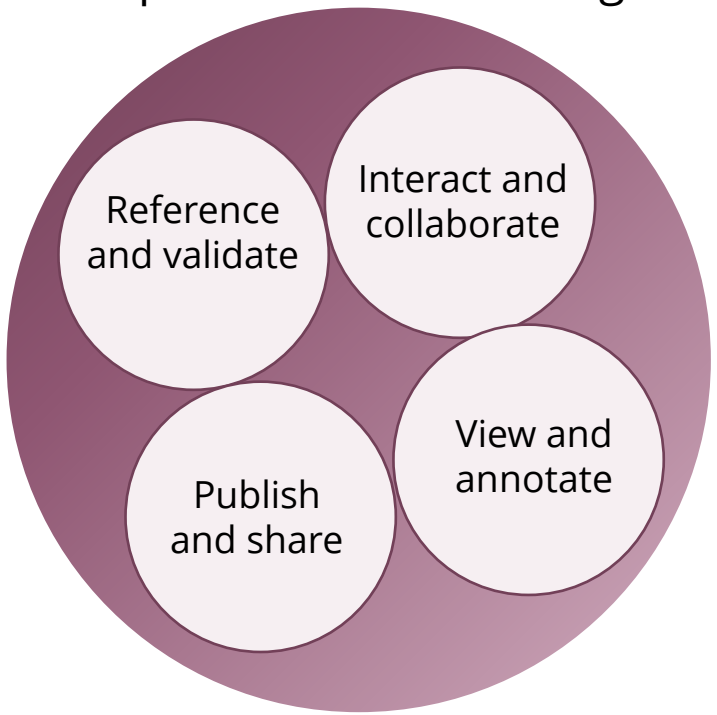
Joe Yeong

Bioinformatics Institute BII

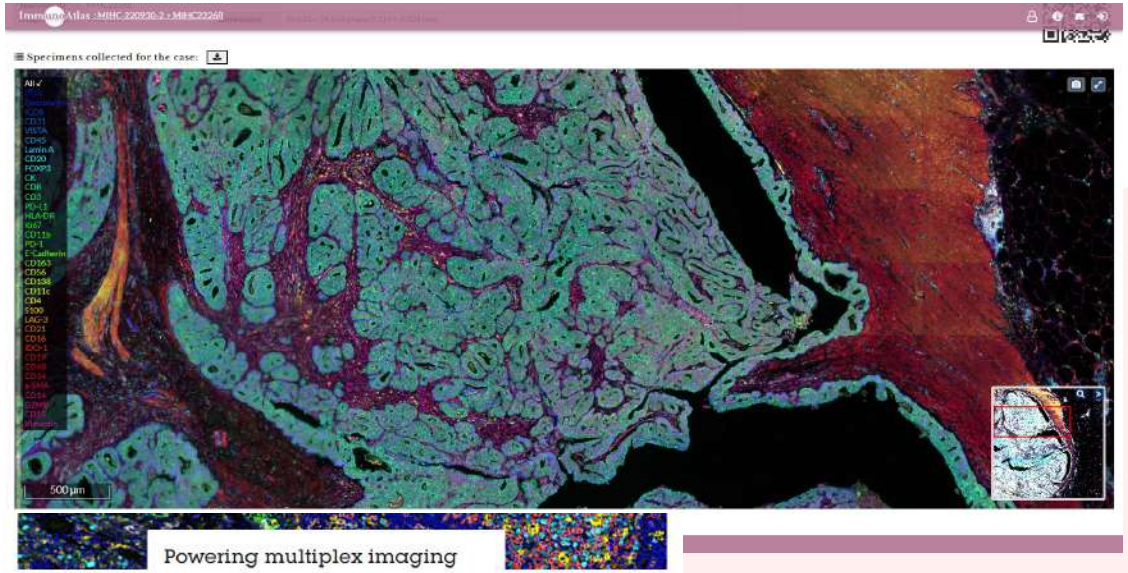
Institute of Molecular and Cell Biology IMCB

ImmunoAtlas

https://ImmunoAtlas.org



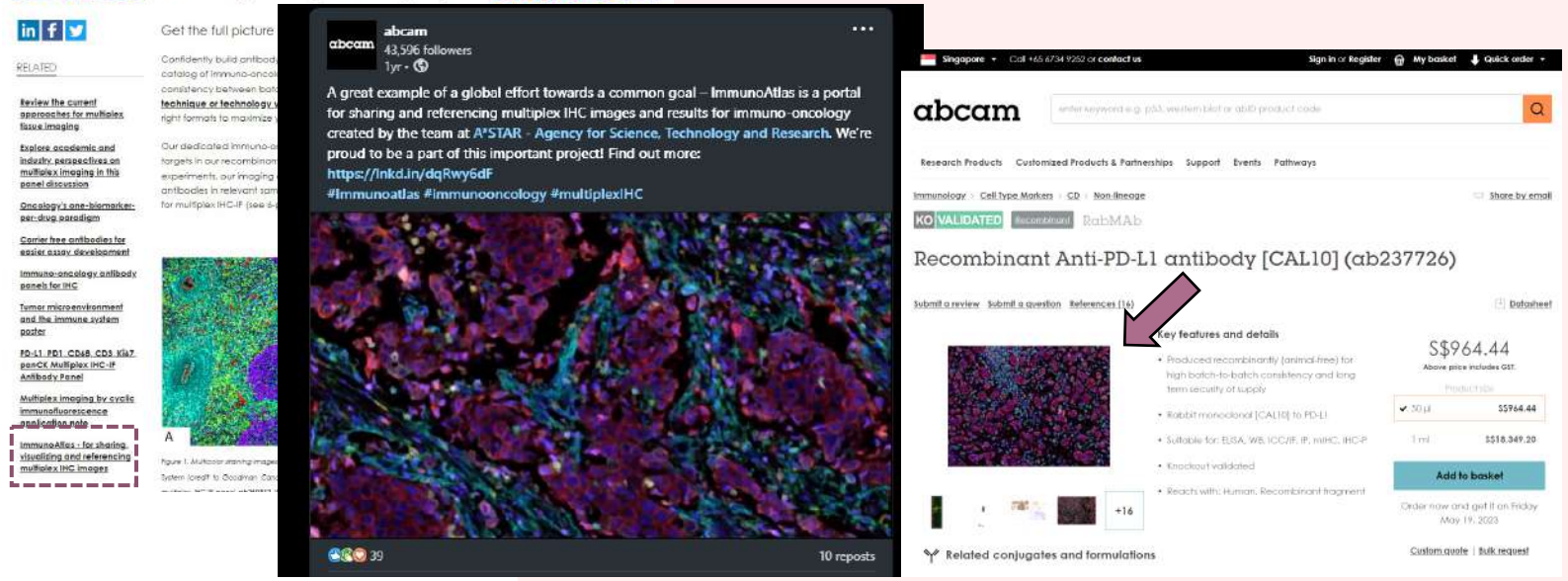
Marketing campaign with abcam (April 2022)!



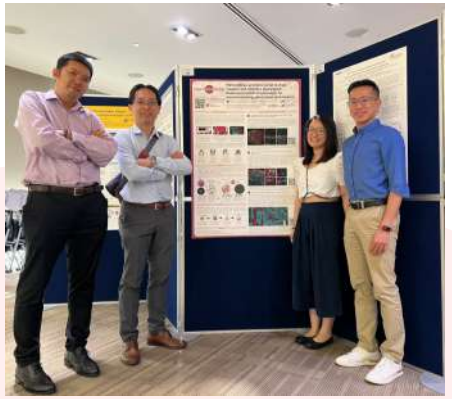
Support whole-slide hyperplexed images

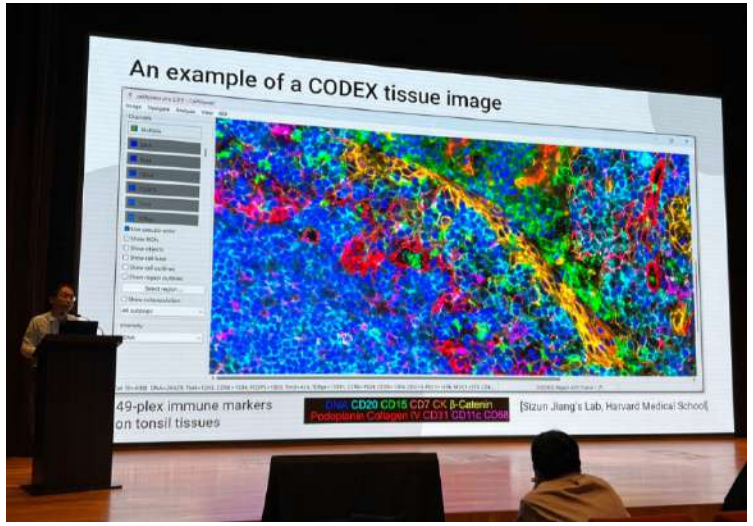
Over 30 markers and 180GB!!

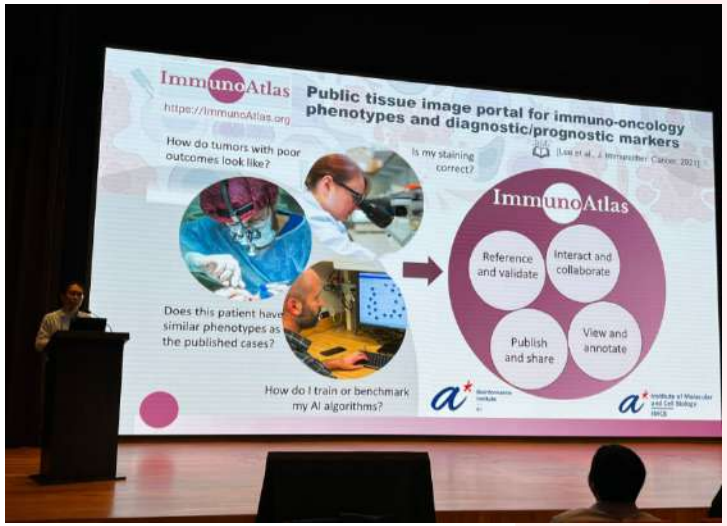
Find out more!

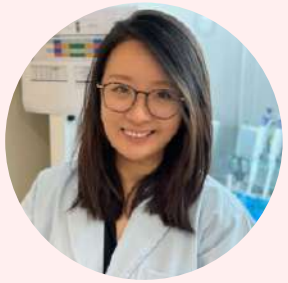


SingHealth Immunopathology Workshop
(8th – 9th May 2023)







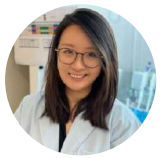


Joey Lee

Poster award
(Second Prize)

HistoPath Analytics (HPA) Platform

Joey Lee



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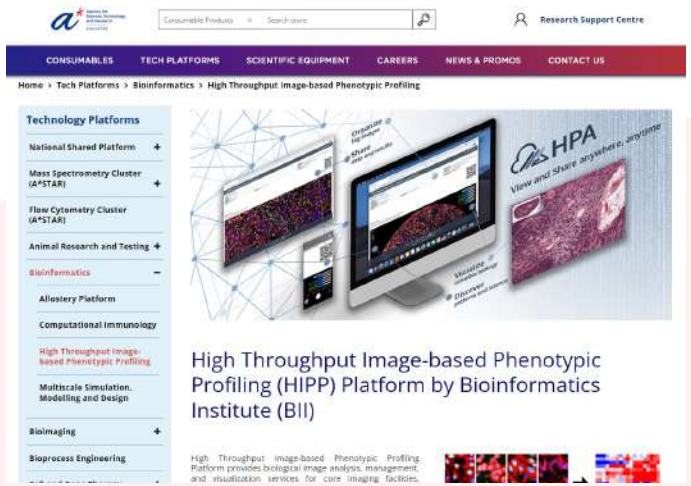
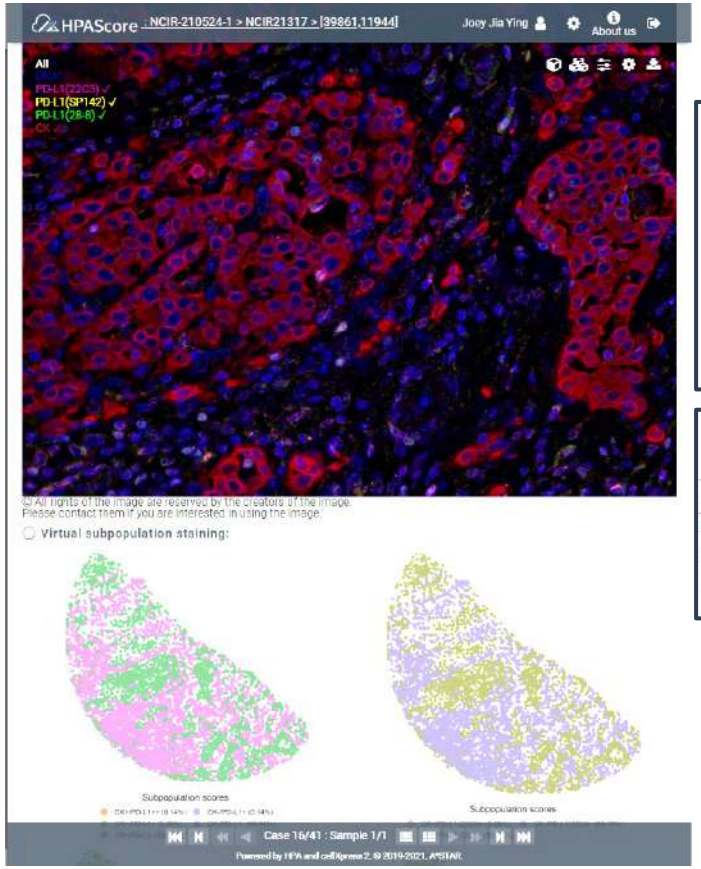
HPA
View and share anywhere, anytime

- Cloud-based digital platform for organizing, sharing, visualizing, and analyzing large histological images
- Offering as a service via A*STAR RSC since 2019





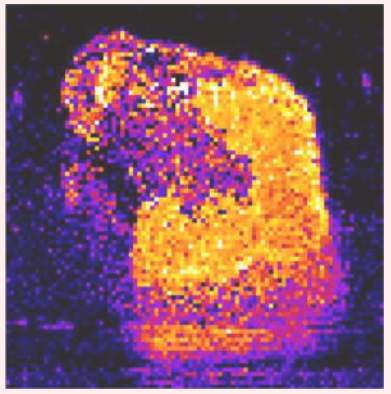
HPA currently supports **spatial proteomics** images

Institute of Molecular and Cell Biology
IMCB

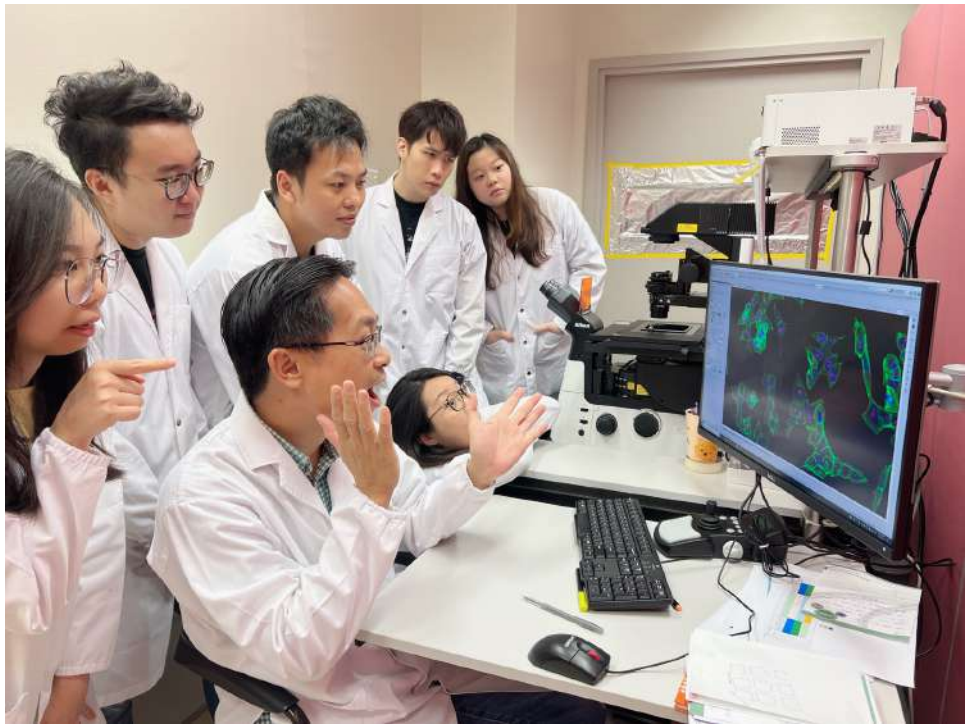
CSI SINGAPORE
CANCER SCIENCE INSTITUTE OF SINGAPORE
National University of Singapore

NUHS
National University Health System

We will support **spatial transcriptomics and metabolomics** soon!



COMPLEX CELLULAR PHENOTYPE ANALYSIS GROUP



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Biomarkers for Liver Cancer

- Liver cancer is the third most common cause of cancer death in Singapore
- There is currently NO predictive biomarker for hepatocellular carcinoma (HCC) immunotherapy

Pierce Chow

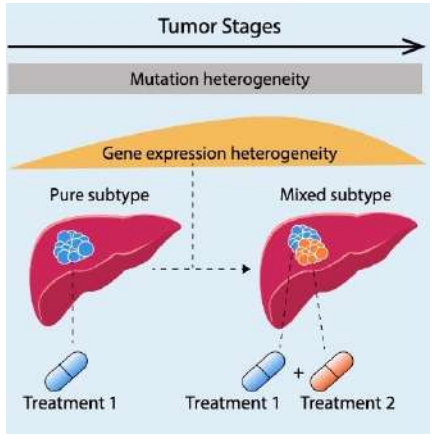
National Cancer Centre Singapore
SingHealth

Institute of Molecular and Cell Biology
IMCB

Precision Medicine in Liver Cancer across an Asia Pacific Network (PLANet)

PLANet 1 (2016-2021)

Characterized the dynamic evolutionary and heterogeneity in HCC



PLANet 2 (2022-2027)

To identify predictive biomarkers for HCC

Current Trials

PLANet 2.0 – AHCC12 and AHCC13	
AHCC12 & AHCC13	**Precision Medicine in Liver Cancer across an Asia Pacific Network 2.0 (PLANet 2.0)** **AHCC12:** **Deep, Multi-omics Phenotyping to Predict Response, Resistance and Recurrence to Adjuvant Atezolizumab plus Bevacizumab in Resected Hepatocellular Carcinoma (HCC)(EMPHASIS)(NCT05516628)** **AHCC13:** **Liquid Biopsy based Identification of Predictive Biomarkers of Response in Intermediate/Locally Advanced HCC receiving Y90 +/- Atezolizumab plus Bevacizumab (NCT05377034)**

Curated data for >1000 patient samples

Spatial, single - cell and bulk genomics

Epigenomics

Metabolomics

Immunomics

Patient-derived models

Spatial multi-omics data before and after treatments

National Cancer Centre Singapore
SingHealth

- Spatial transcriptomics
- Spatial proteomics
- Spatial metabolomics
- Histology

BII will use the HPA Platform to **integrate and analyze** all the generated spatial multi-omics data

↓

Biomarker for patient stratification

HPA
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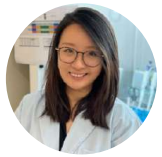
Spatial metabolomics landscape of Liver Cancer

Joey Lee 

Wang Yulan

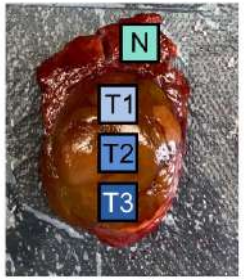
Bioinformatics Institute BII

National Cancer Centre Singapore SingHealth

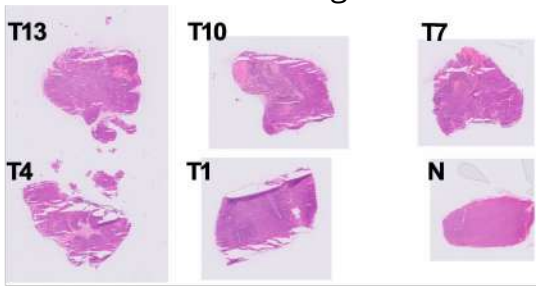
Singapore General Hospital SingHealth

National Cancer Centre Singapore SingHealth

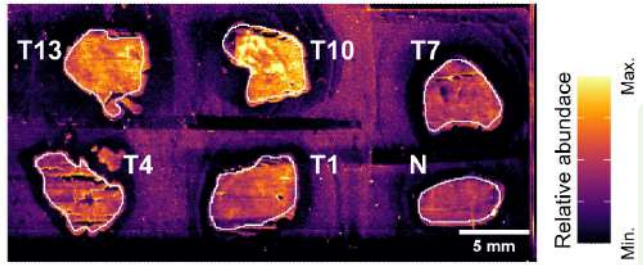
24 HCC patients



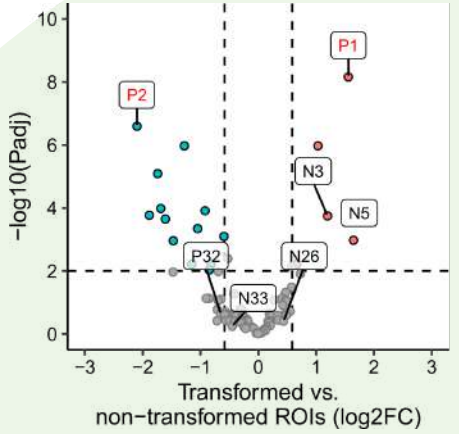
H&E image



DESI-MSI (neg. mode)



We used machine learning to integrate **histopathological and spatial metabolomics** information and identify potential markers for the normal and tumor tissues



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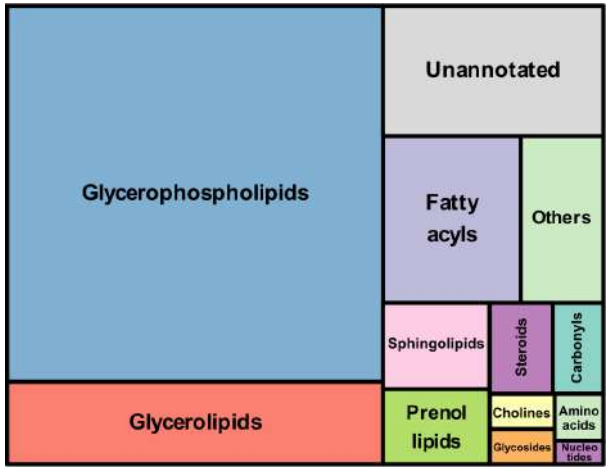
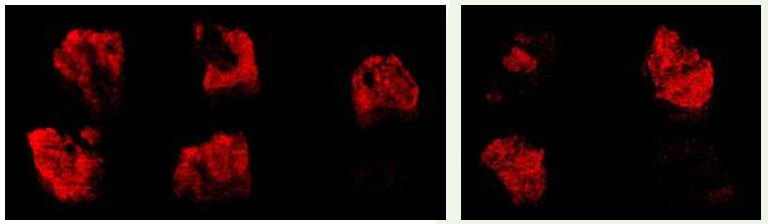
Our analysis found highly-abundant metabolites in both MSI and LC/MS samples

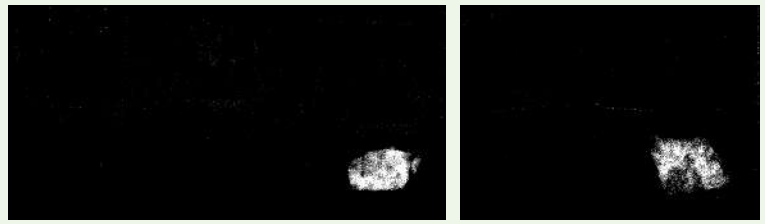


P1 (m/z = 810.6001)



HEP0152 B0003

P2 (m/z = 437.3528)

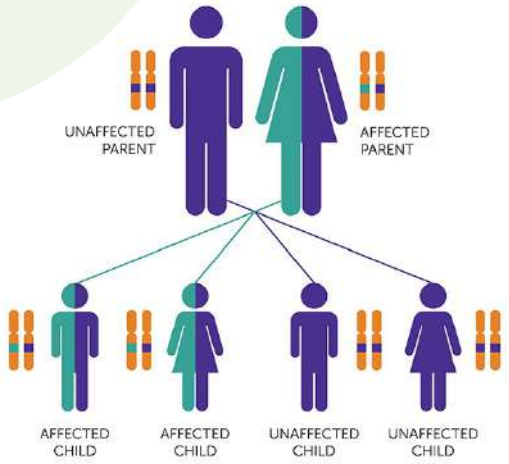


HEP0152 B0003

The 5th Singapore Liver Cancer Consortium Scientific Symposium (1 June 2023)

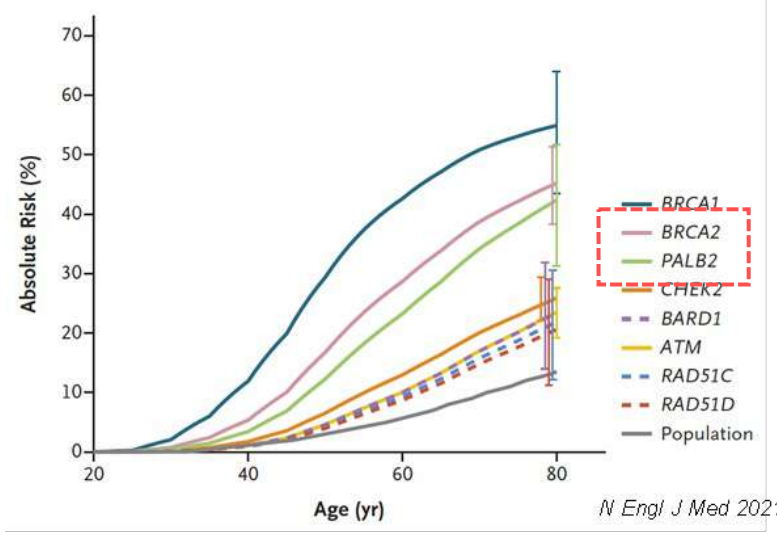
Hereditary mutations associated with cancers

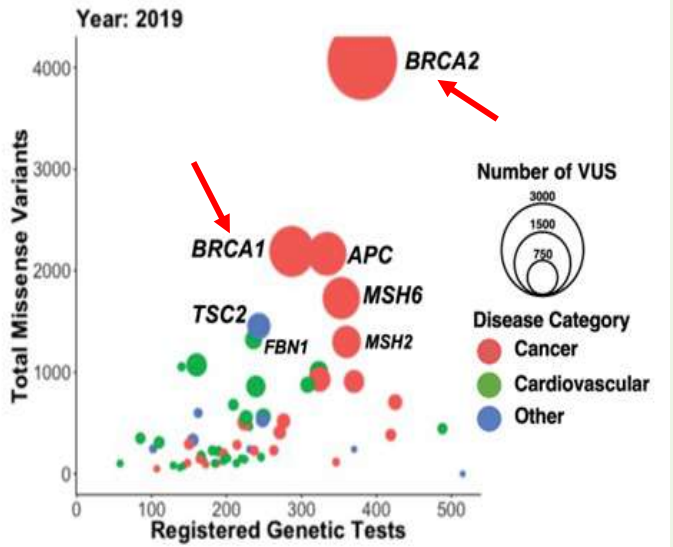
Joanne Ngeow

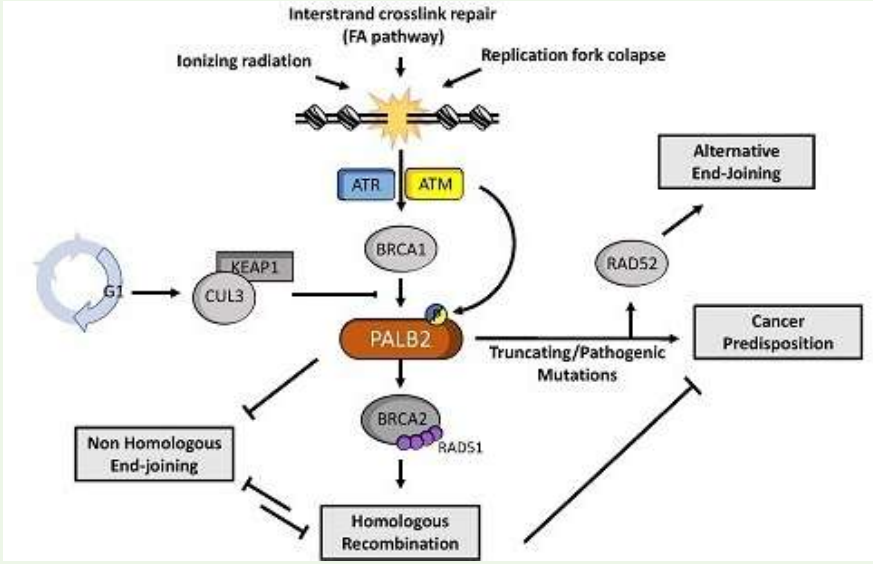


Variants of Uncertain Significance (VUS)

When analysis of a patient's genome identifies a variant, but it is unclear if the variant is actually connected to a health condition







profiling to predict pathogenic mutations

Zhong Guorui

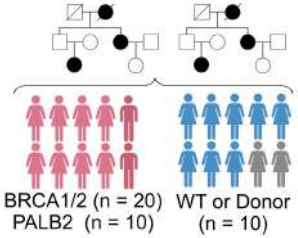
Bioinformatics Institute BII

LEE KONG CHIAN SCHOOL OF MEDICINE

National Cancer Centre Singapore SingHealth

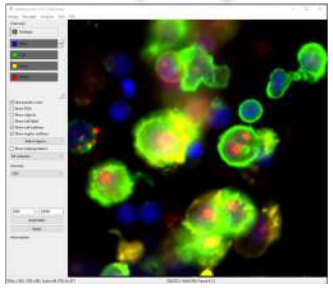
Cancer Genetic Service

Germline mutations with clinical data



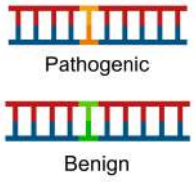
PBMCs

cellXpress 2



Phenotypic profiling

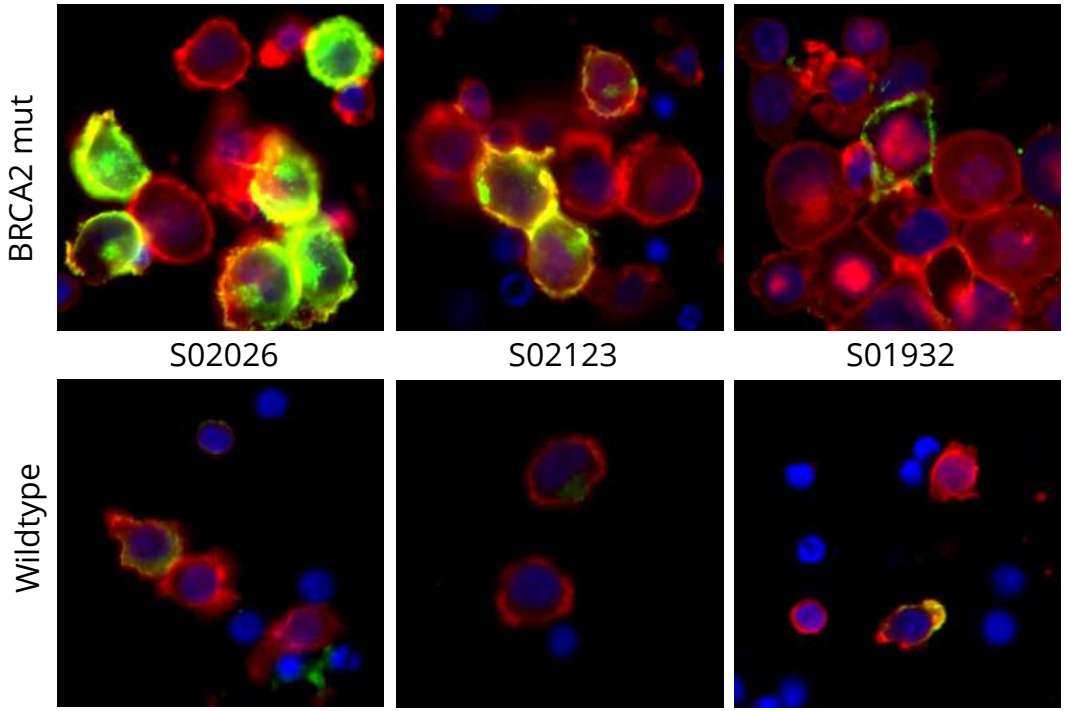
VUS classification

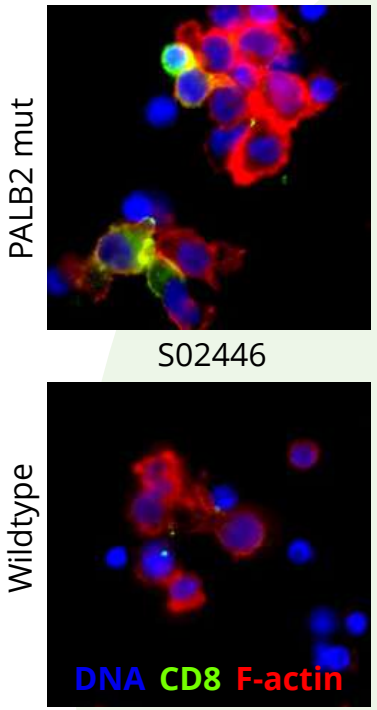


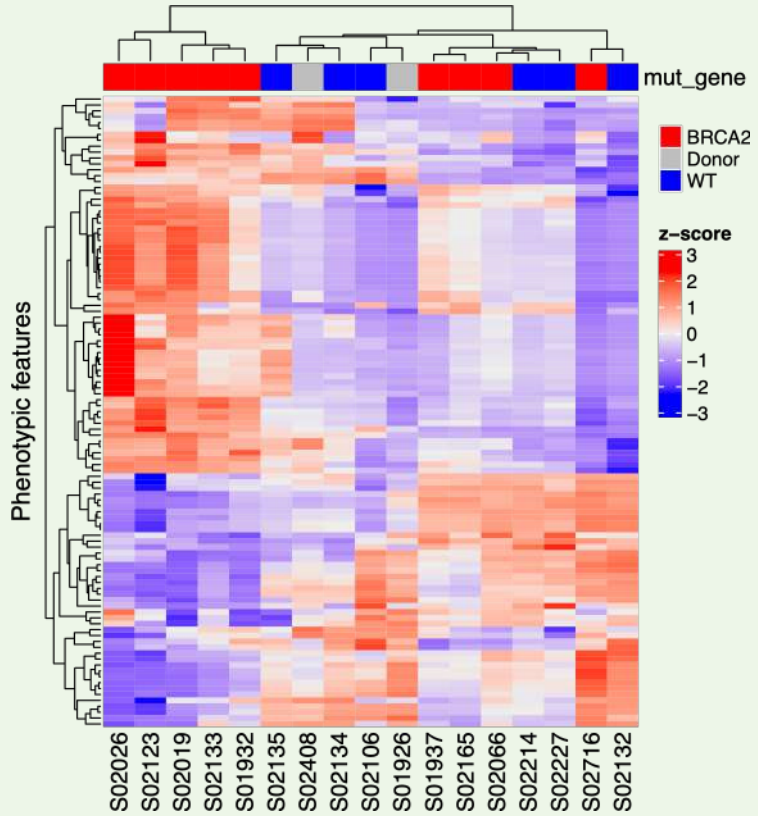
HPA

View and share anywhere, anytime

Clinical management







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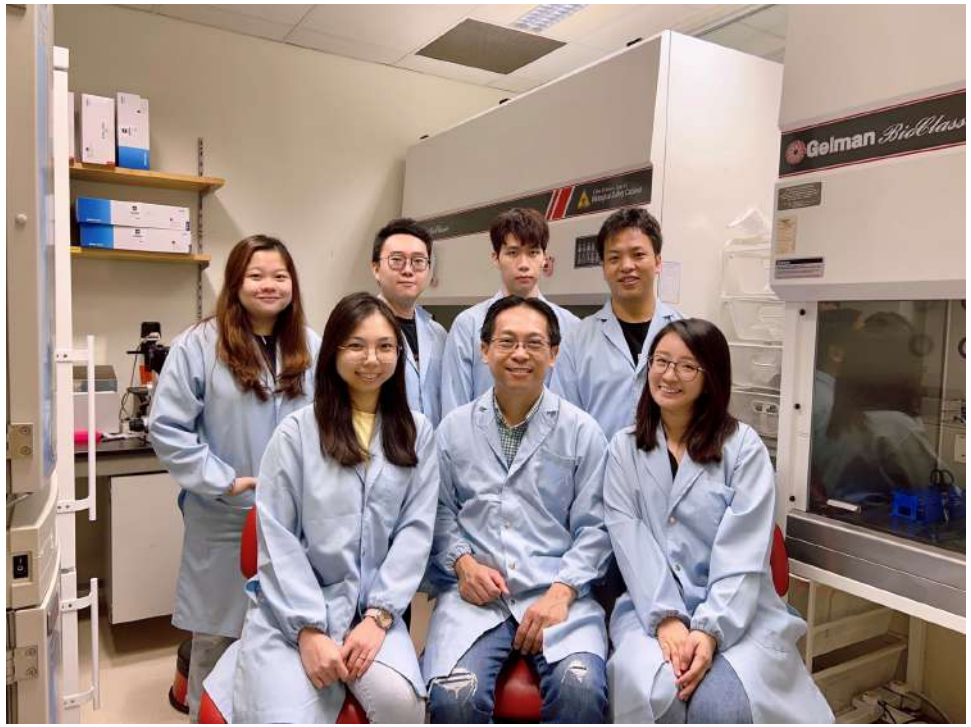

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Spatial profiling of cells and tissues

- Spatial multi-omics profiling of human tissues
- High-throughput image-based phenotypic profiling

Bioimage databases and portals

- Visualization and sharing of cellular and tissue images
- HistoPath Analytics (HPA) Platform and ImmunoAtlas

Digital medicine for cancers

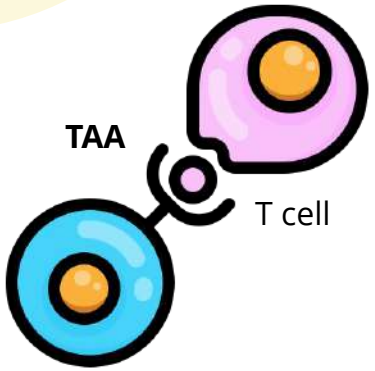
- Biomarkers for patient stratification and targeted intervention
- Pathogenicity of mutations

Predictive models for therapeutic development

- Tumor-associated antigen prediction
- Xenobiotic-induced toxicity prediction

High-throughput assays and AI models for tumor-associated antigen classification

Joe Yeong



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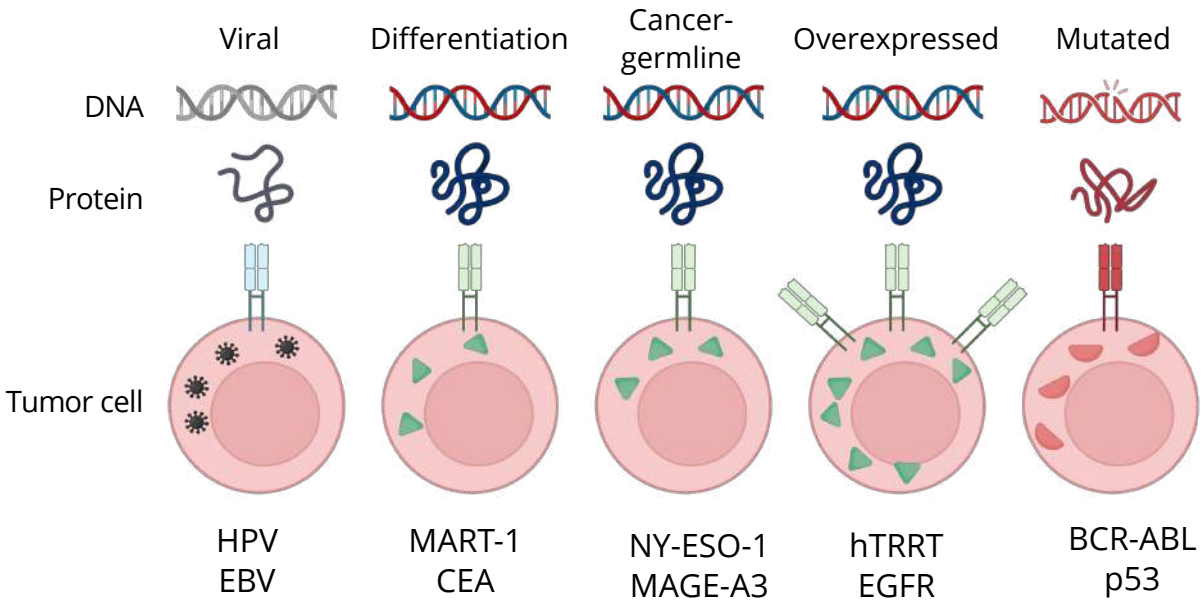
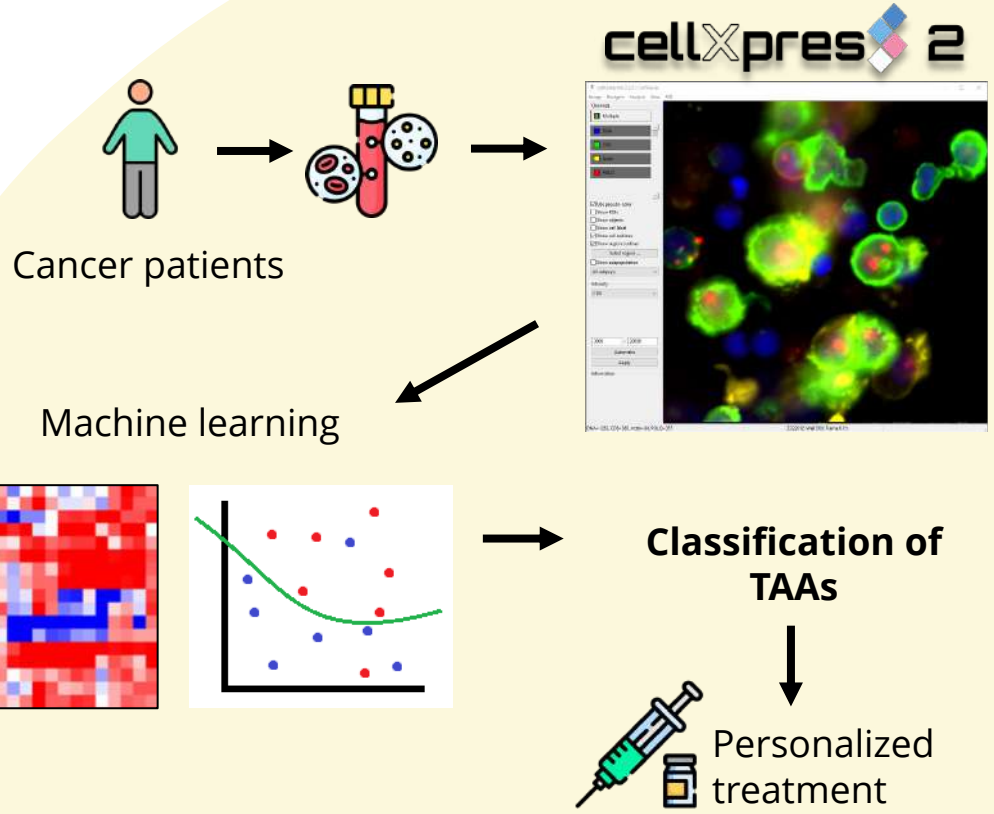
(1 Sept 2022 to 31 Aug 2025)

Tumor-associated antigens (TAAs)





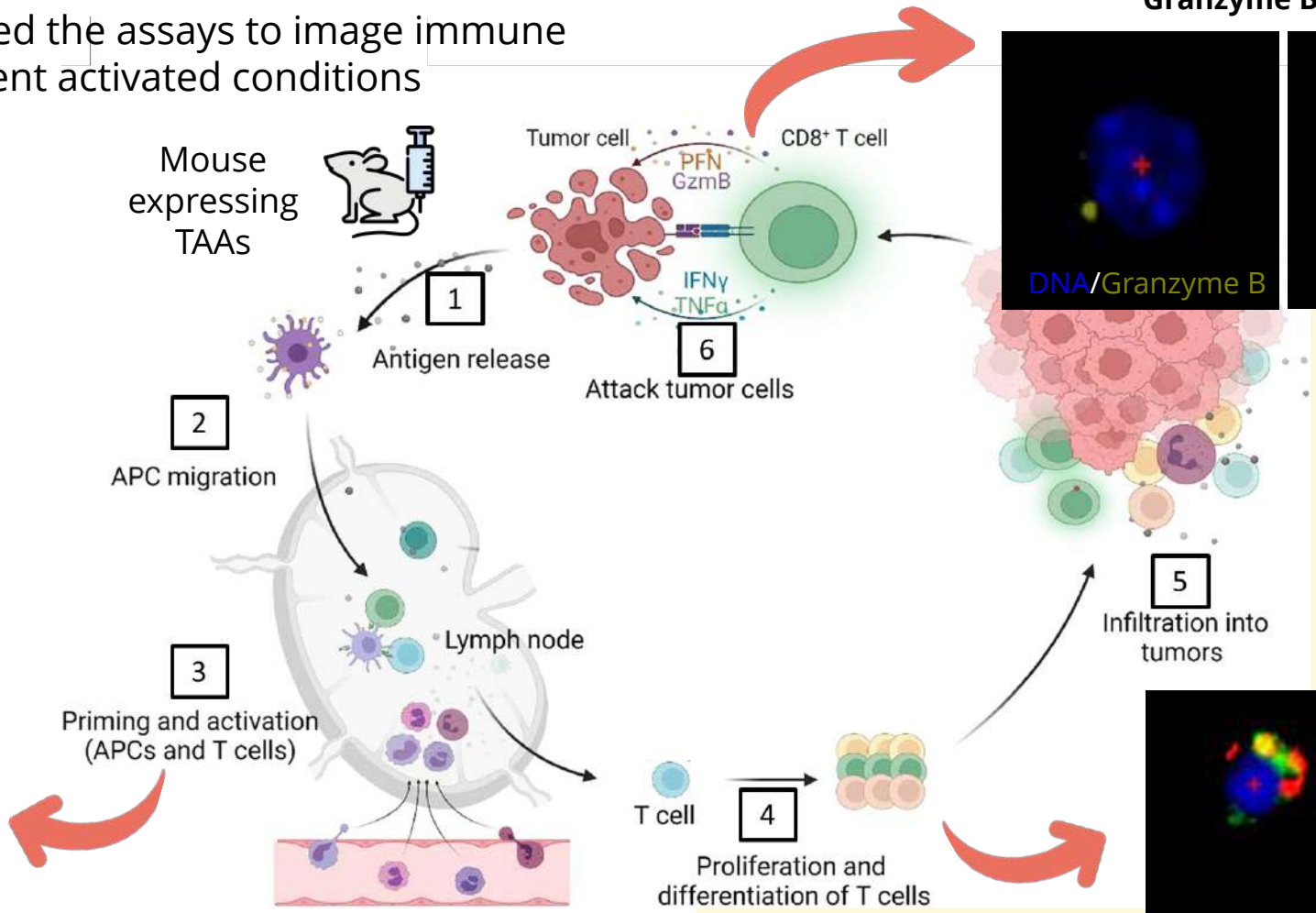
Imaging-based phenotypic profiling to predict tumor-associated antigens

Oscar Fu

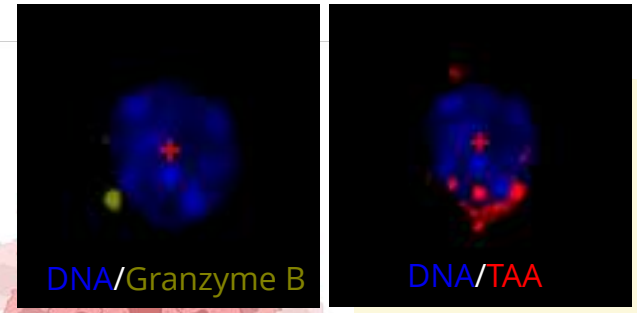
Bioinformatics Institute BII

Institute of Molecular and Cell Biology IMCB

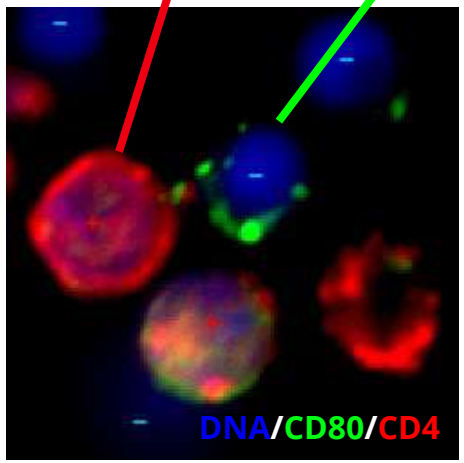
We have developed the assays to image immune cells under different activated conditions



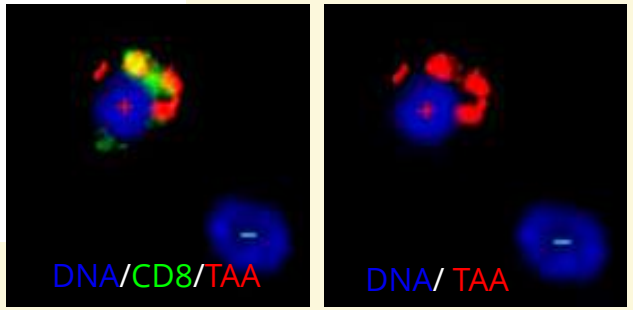
Granzyme B + TAA



CD80 (APC) + CD4 (T Cells)



CD8 + TAA



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Claresta, Cuithbert, Oscar, Guorui Carmen, Lit-Hsin, Joey

Thank you

Institute of Molecular and Cell Biology
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- Dr Abdul Aziz Aiderus

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SingHealth

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- Yeo Yao Yu

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ImmunoAtlas

HPA
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