The use of single-cell multi-omics in immuno-oncology

Qin Ma, PhD
Associate Professor
Section Chief of Computational Biology and Bioinformatics
Department of Biomedical Informatics

Leader of the Immuno-Oncology Informatics Group
Pelotonia Institute for Immuno-Oncology

THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER

Immuno-Oncology Informatics Group (IOIG) - PIIO

- Assemble and organize a team full of expertise in biostatistics, bioinformatics, and deep learning to systematically solve immuno-oncological problems.

- Enhance and promote collaborations and communications among PIIO members, aiming to bridge different research communities and facilitate program/grant development.

- Other priorities will include but not limited to training sections that engage and invigorate PIIO faculty and students and inviting reputed researchers within and outside OSU for seminar series.

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Dr. Zihai Li, PIIO director

The IOIG team

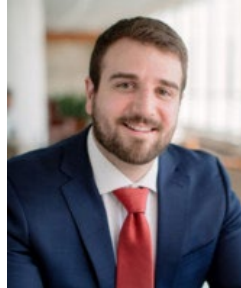**Qin Ma, PhD**
Associate Prof
scMulti-omics and deep learning

Dongjun Chung, PhD
Associate Prof
Spatial transcriptomics and statistical modeling

Brian Searle, PhD
Assistant Prof
Genomic and proteomic

Anjun Ma, PhD
Research Scientist
IOIG coordination and scMulti-omics

Jordan Krull, PhD
Postdoc
Cancer immunology, bioinformatics

Yuzhou Chang
PhD candidate
Spatial multi-omics data analysis and immuno-informatics

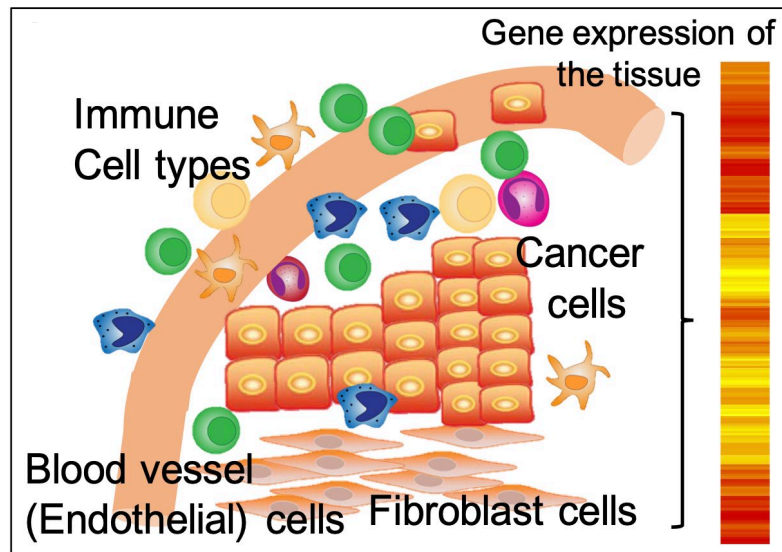## Committee board

Zihai Li

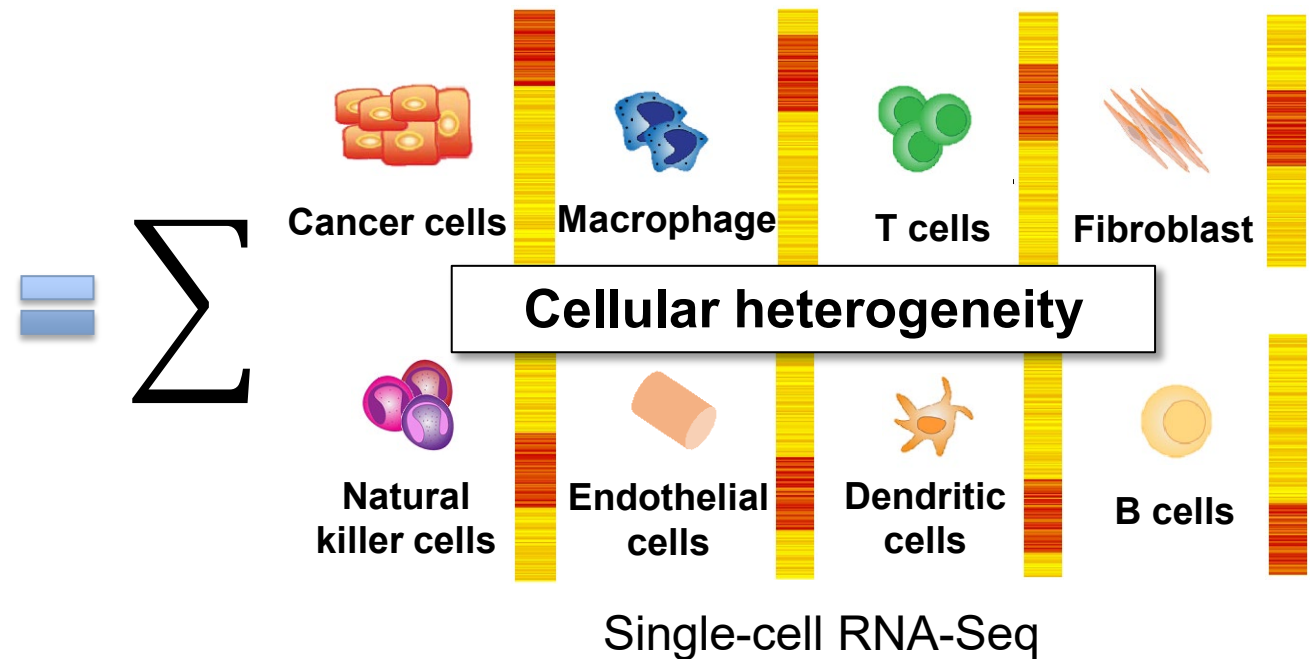Kevin P. Weller

Tamra Brooks

James Fant

Komal Das

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Bioinformatics and Mathematical Biosciences Lab (BMBL)

Big Data
generated by
High-throughput Sequencing ⟶ **Bioinformatics** ⟶ **Knowledge** *in* **Transcriptional Regulation**

Microarray & Bulk RNA-Seq

Single-cell RNA-Seq
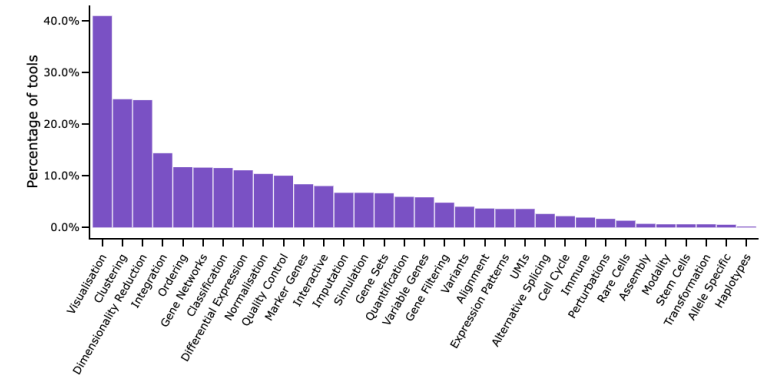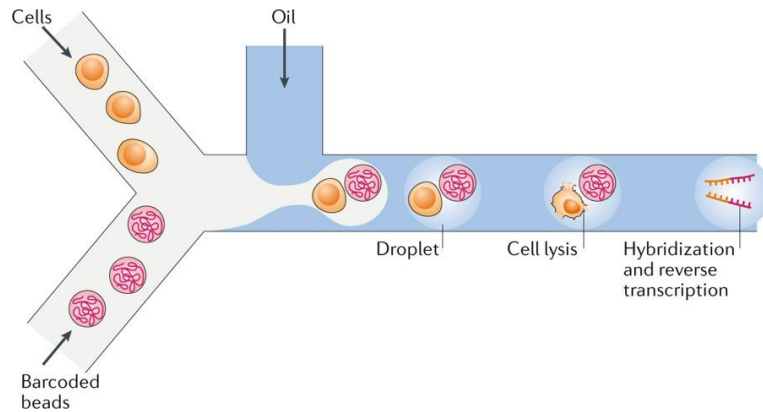
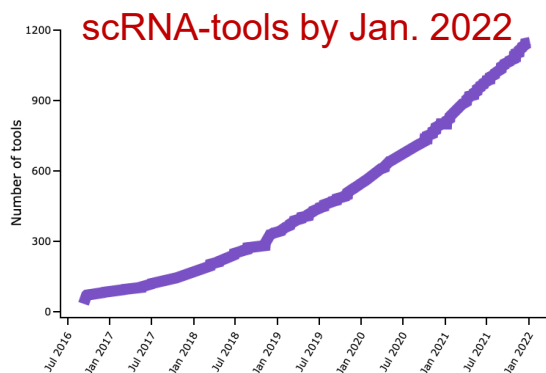*Complex tissue* is composed of more than one kind of cells

- **Cell-cell interactions among diverse cell types**
- **Microbiota in tumor microenvironment**

Single-cell sequencing technology may save the day

Cells

Oil

Barcoded beads

Droplet Cell lysis Hybridization and reverse transcription

...in over **30** categories

scRNA-tools by Jan. 2022

Number of tools

We currently track **1147** tools...

scRNA-seq

What is the contribution of my research lab in this fast-developing field?

R01GM131399: Construction of cell-specific gene co-regulation signatures based on single-cell transcriptomics analysis

2019

- Statistical modeling
- Qualitative representation of regulatory signal
- Improve cell clustering, DEG, module detection

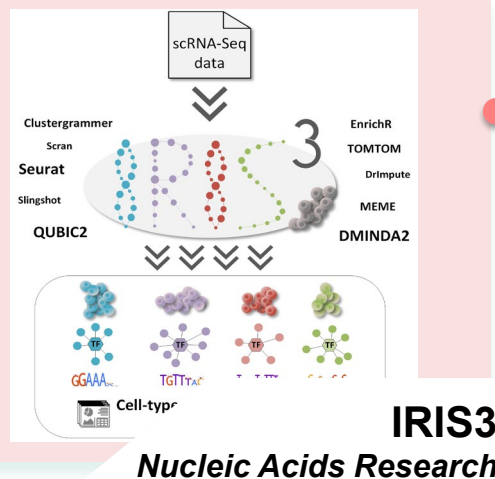**LTMG**
Nucleic Acids Research
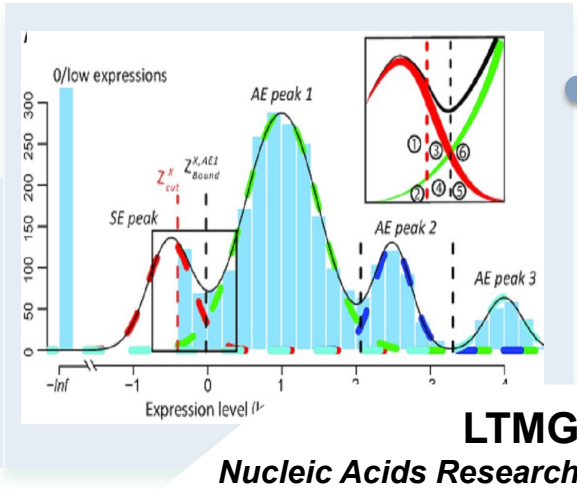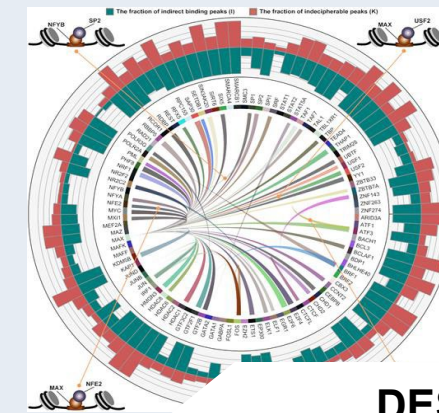
- Deep learning (Convolutional neural network)
- ChIP-seq analysis
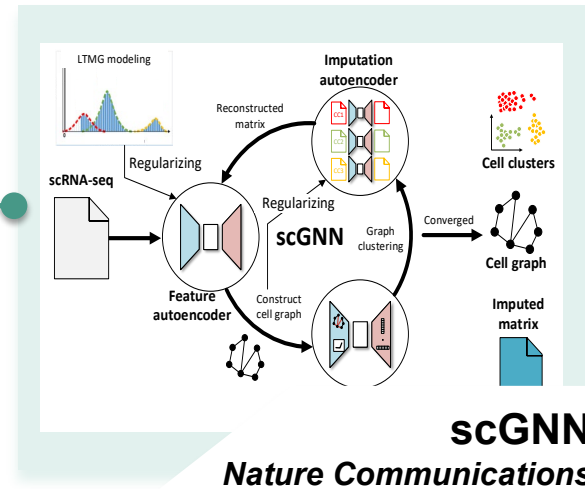- Motif prediction
- Shape motif
- Tethering binding

DESSO
Nucleic Acids Research

2020

- First cell-type-specific regulon pipeline
- Composable framework
- scRNA-seq analyses
- Heterogeneous regulatory mechanism
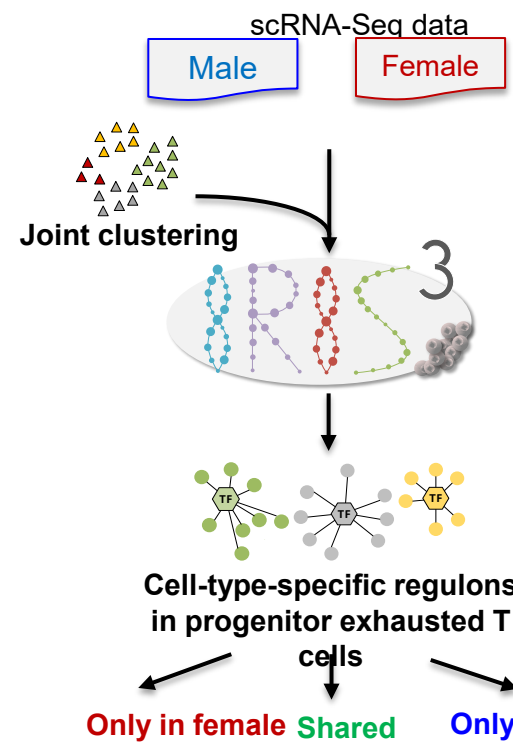- Web interface

IRIS3
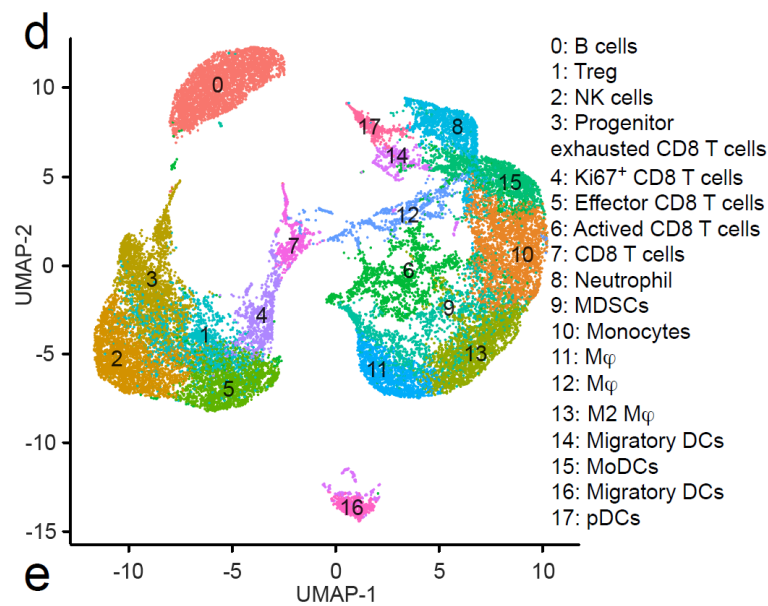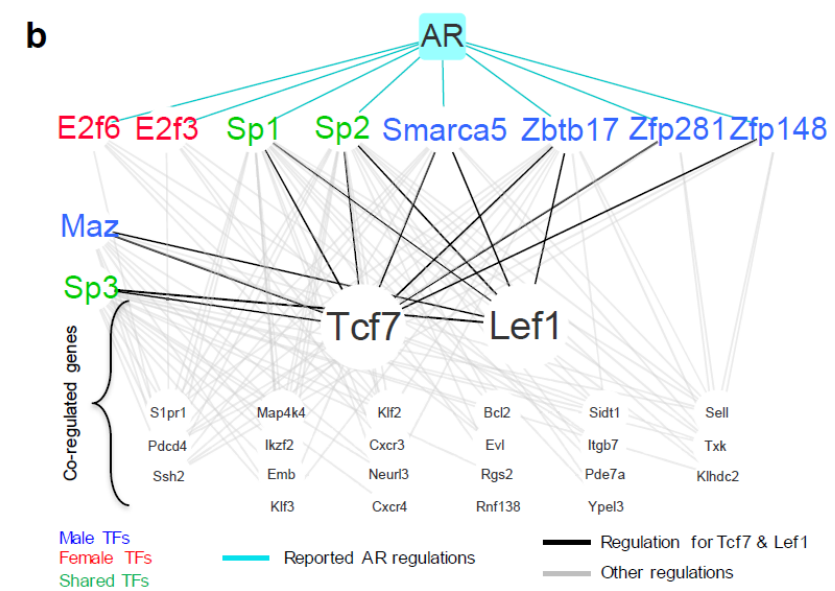*Nucleic Acids Research*

2021

- First graph neural network (GNN) model for scRNA-seq
- Gene imputation
- Cell clustering
- Cell-cell communications
- Iterative autoencoder

scGNN
Nature Communications

6

Informatics contributes to immuno-oncology projects, for example…

Use published tools and pipelines for single cell clustering and signature gene identification in Susd2−/− CD8+ T cells

d

0: B cells
1: Treg
2: NK cells
3: Progenitor exhausted CD8 T cells
4: Ki67⁺ CD8 T cells
5: Effector CD8 T cells
6: Actived CD8 T cells
7: CD8 T cells
8: Neutrophil
9: MDSCs
10: Monocytes
11: Mφ
12: Mφ
13: M2 Mφ
14: Migratory DCs
15: MoDCs
16: Migratory DCs
17: pDCs

scRNA-Seq data

Male   Female

Joint clustering

Cell-type-specific regulons in progenitor exhausted T cells

Only in female   Shared   Only in male

Apply in-house tools to identify unique sex-biased regulatory mechanisms

b

AR

E2f6 E2f3 Sp1 Sp2 Smarca5 Zbtb17 Zfp281 Zfp148

Maz

Sp3

Tcf7   Lef1

Co-regulated genes:
S1pr1 Map4k4 Klf2 Bcl2 Sidt1 Sell
Pdcd4 Ikzf2 Cxcr3 Evl Itgb7 Txk
Ssh2 Emb Neurl3 Rgs2 Pde7a Klhdc2
       Klf3 Cxcr4 Rnf138 Ypel3

Male TFs
Female TFs
Shared TFs

Regulation for Tcf7 & Lef1
Reported AR regulations
Other regulations

Sushi domain containing 2 suppresses CD8+ T cell antitumor immunity by targeting IL-2 receptor signaling.
Nature Immunology. 2022

Androgen conspires with the CD8+ T cell exhaustion program and contributes to sex bias in cancer.
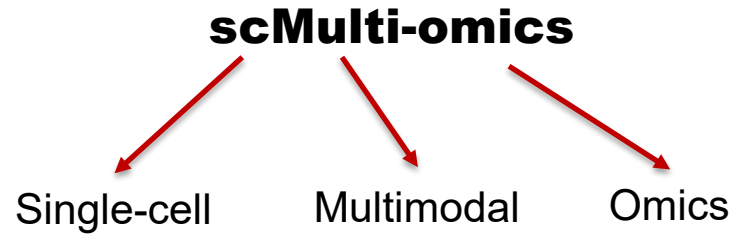*Science Immunology. 2022*

NCI-R01: Targeting immune inhibitory molecule SUSD2 to reverse immunosuppression. (2021-2026)

NCI-R01: Targeting GRP94-TGF-beta pathway for cancer immunotherapy. (2021-2026)

scMulti-omics analysis refines knowledge of biological systems

scMulti-omics

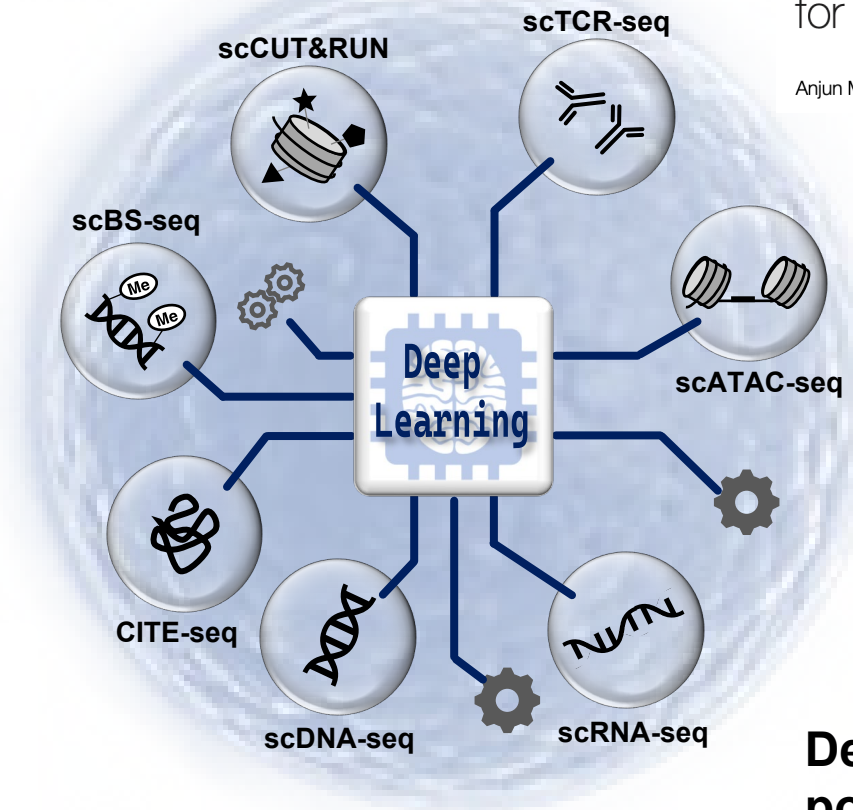Single-cell   Multimodal   Omics

Anjun Ma [1,7,@] Adam McDermaid [2,3,7] Jennifer Xu [1,4] Yuzhou Chang [1] and Qin Ma [1,5,6,*,@]
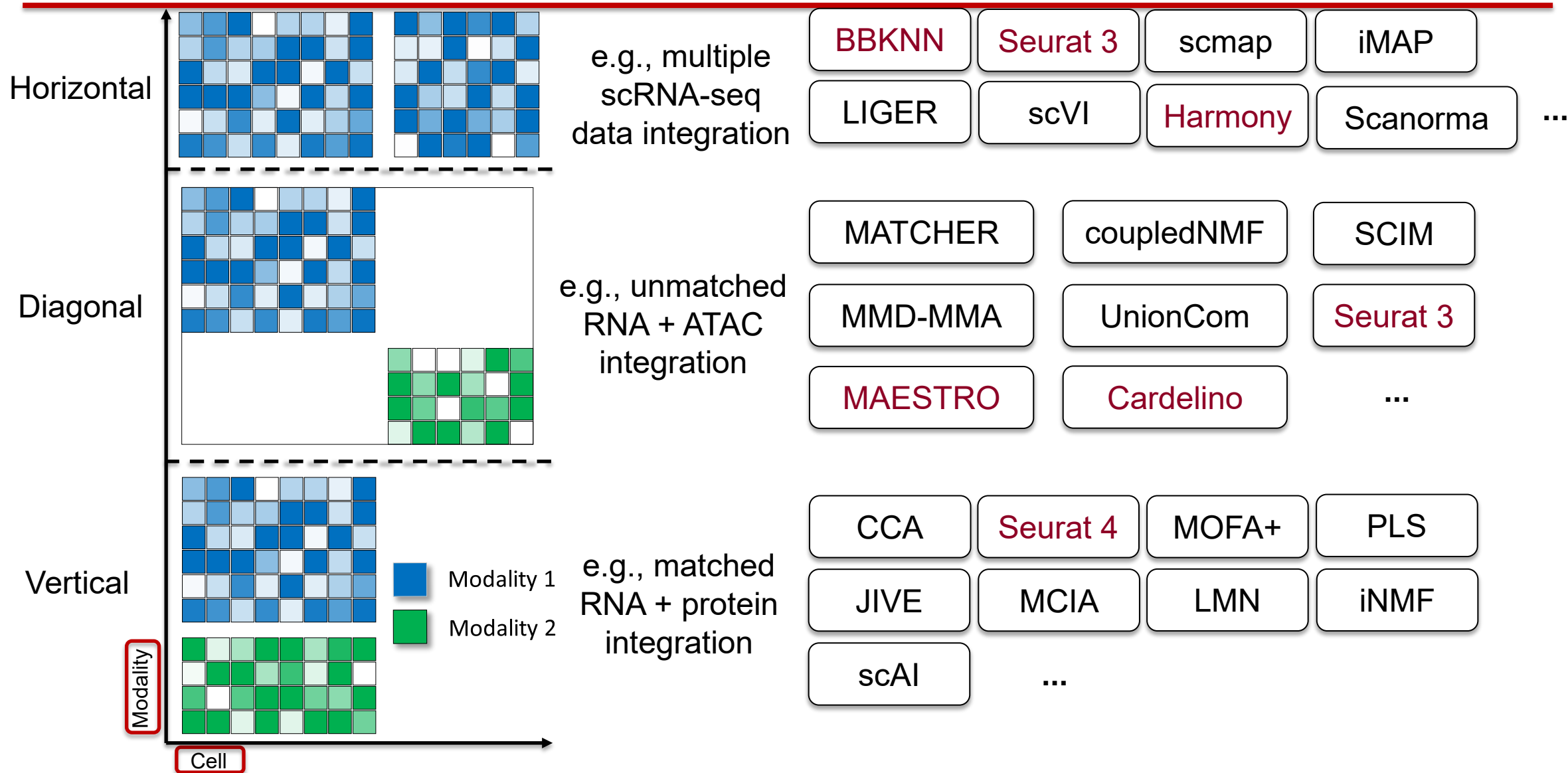
Large scale;
Sparsity;
Heterogeneity;
Intrinsic connections among
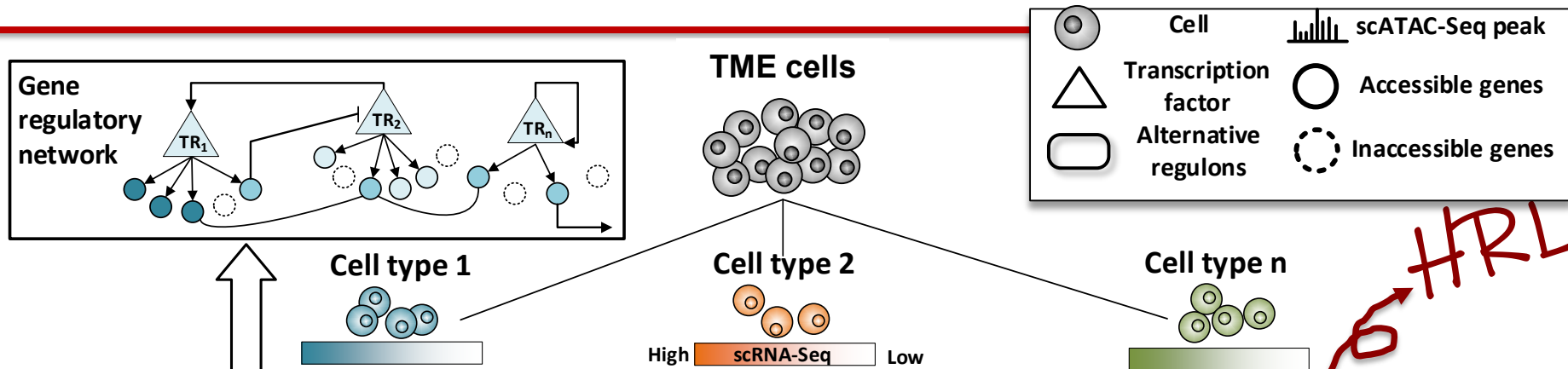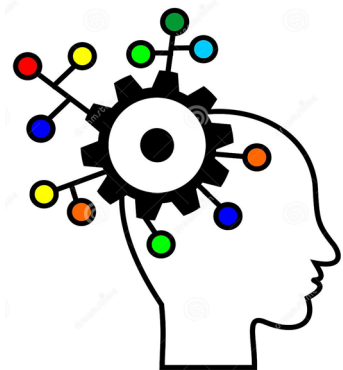Different modalities

Challenge[2]

scMulti-omics was selected as Method of the Year 2019 by *Nature Methods*

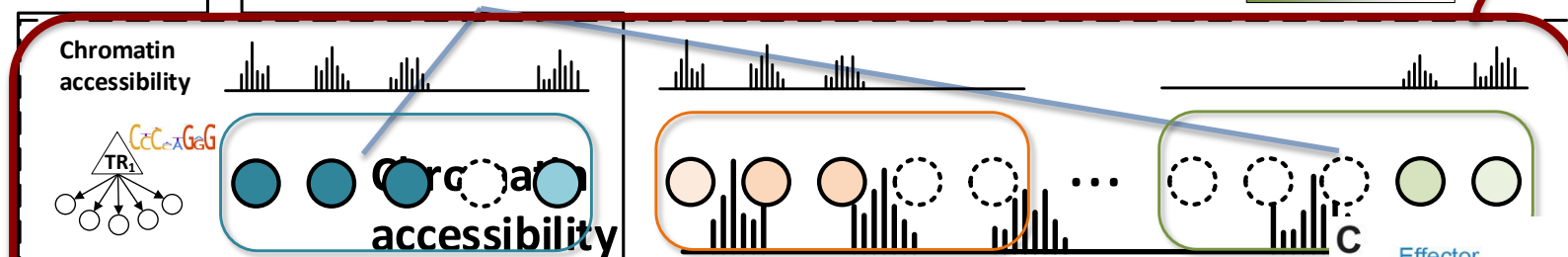**Deep learning has unique power in defining and shaping scMulti-omics data analyses**

Integration strategies and corresponding tools

Ricard Argelaguet, et al., *Nature Biotechnology* (2021)

Infer heterogeneous gene regulatory landscape in IO

Gene regulatory network

TME cells

Cell | scATAC-Seq peak
Transcription factor | Accessible genes
Alternative regulons | Inaccessible genes

Cell type 1 | Cell type 2 | Cell type n

High — scRNA-Seq — Low

HRL

Chromatin accessibility

Chromatin accessibility

Pending ITCR U01
U01CA258401 (28)

Minimal Residual Disease

Pigment

therapeutic challenge

MITF

PAX3

Invasion

BRAFi
MEKi

AP-1

SMC state

RXRγ

Drug-naïve Melanoma

RXR antagonist

Effector → Heterogeneous Regulatory Landscape

Exhausted → Heterogeneous Regulatory Landscape

ICB-responsiveness

ICB therapy

Rejuvenated → Heterogeneous Regulatory Landscape

Dual: Cellular heterogeneity and underlying molecular program

- **Rare cell population**
- **Cell-cell communications**

# DeepMAPS: Single-cell biological network inference from scMulti-omics
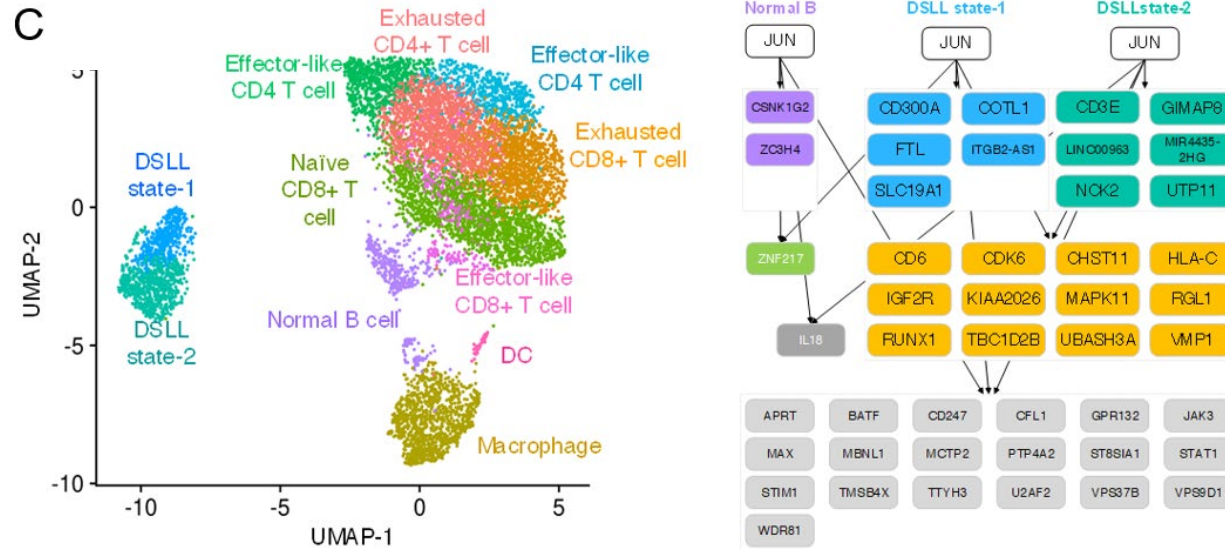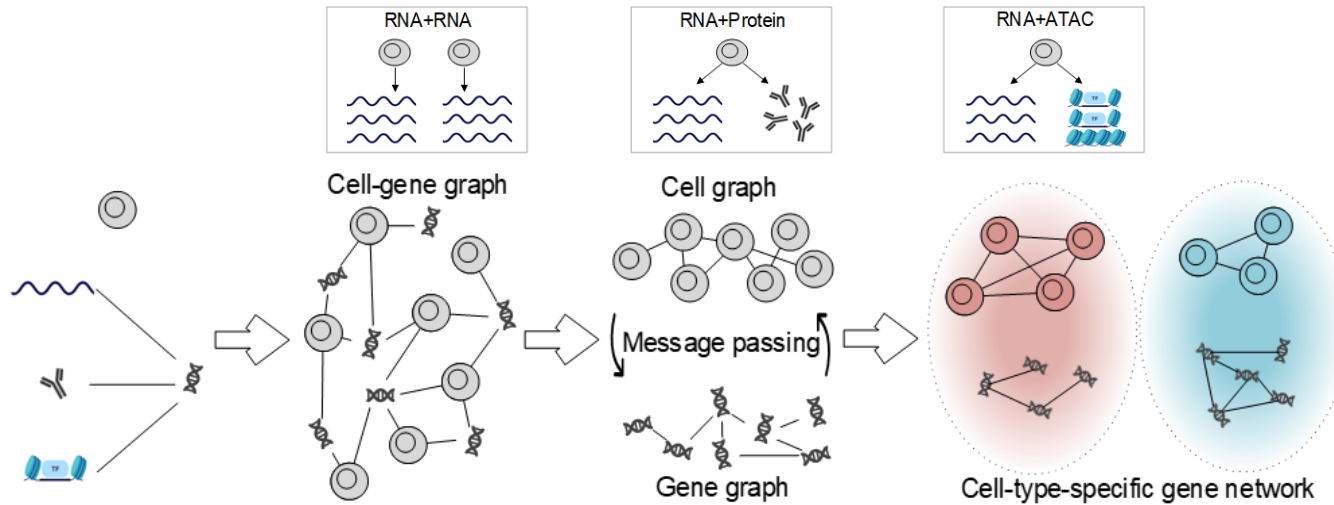
- DeepMAPS: **Deep** learning-based **M**ulti-omics **A**nalysis **P**latform for **S**ingle-cell data.

- First-of-its-kind model: Simultaneous cell clustering and biological network inference on a **heterogeneous graph**.

- Adopts a **multi-head graph attention mechanism** to model the overall topological information and neighbor message passing.

- Identified distinct gene regulatory networks among normal B cells and two diffuse small lymphocytic lymphoma development states.

- Deployed a code-free web portal to ensure the robustness and reproducibility

Biological network inference from single-cell multi-omics data using heterogeneous graph transformer.
Under peer-review in *Nature Methods.*

Develop DL methods for new IO hypothesis generation

Microbiome-host interactions
Microbiome-infected immune response
Microbiome-drug metabolism
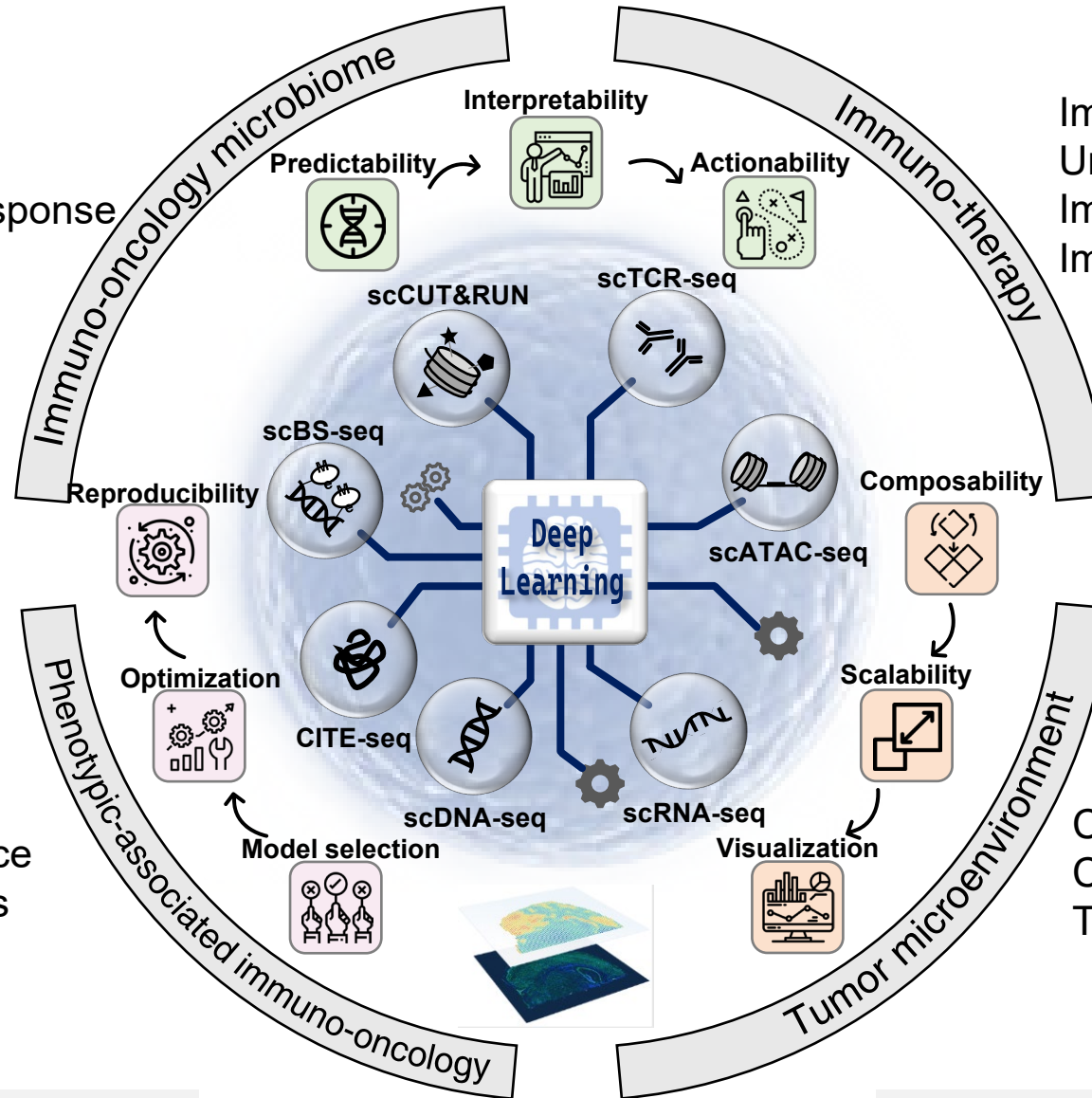
Immune cell landscape
Underlying regulatory mechanisms
Immune cell signatures
Immune evasion

Cancer drug resistance
Sex-bias mechanisms

Cell-cell communication
Clonal evolution
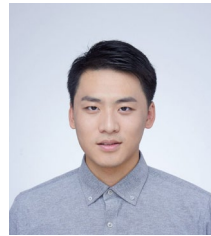Tumor infiltration
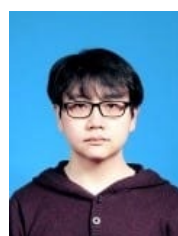
Acknowledgement

Collaborators

Anjun Ma, PhD
Research Sci
*IRIS3, scGNN,
scDEAL, DeepMAPS*

Yang Li, PhD
Postdoc
DESSO

Yuzhou Chang
PhD candidate
IRIS-FGM, RESEPT

Cankun Wang, MS
Bioinformatician
IRIS3, scREAD

Xiaoying Wang
Visiting scholar
DeepMAPS

Adam McDermaid,
PhD
Postdoc
VIDGER

Brandon Monier,
PhD
IRIS-EDA

Jinyu Yang, MS
Graduate student
DESSO, DMINDA2

Jun Xie, MS
Graduate student
QUBIC2

Junyi Chen, PhD
Visiting scholar
scDEAL

Prof. Dong Xu
University of Missouri
Deep learning methods

Prof. Auru Zhang
Duke University
Statistical modeling

Prof. Chi Zhang
Indiana University
Gene regulation

Qin.Ma@osumc.edu   https://u.osu.edu/bmbl/