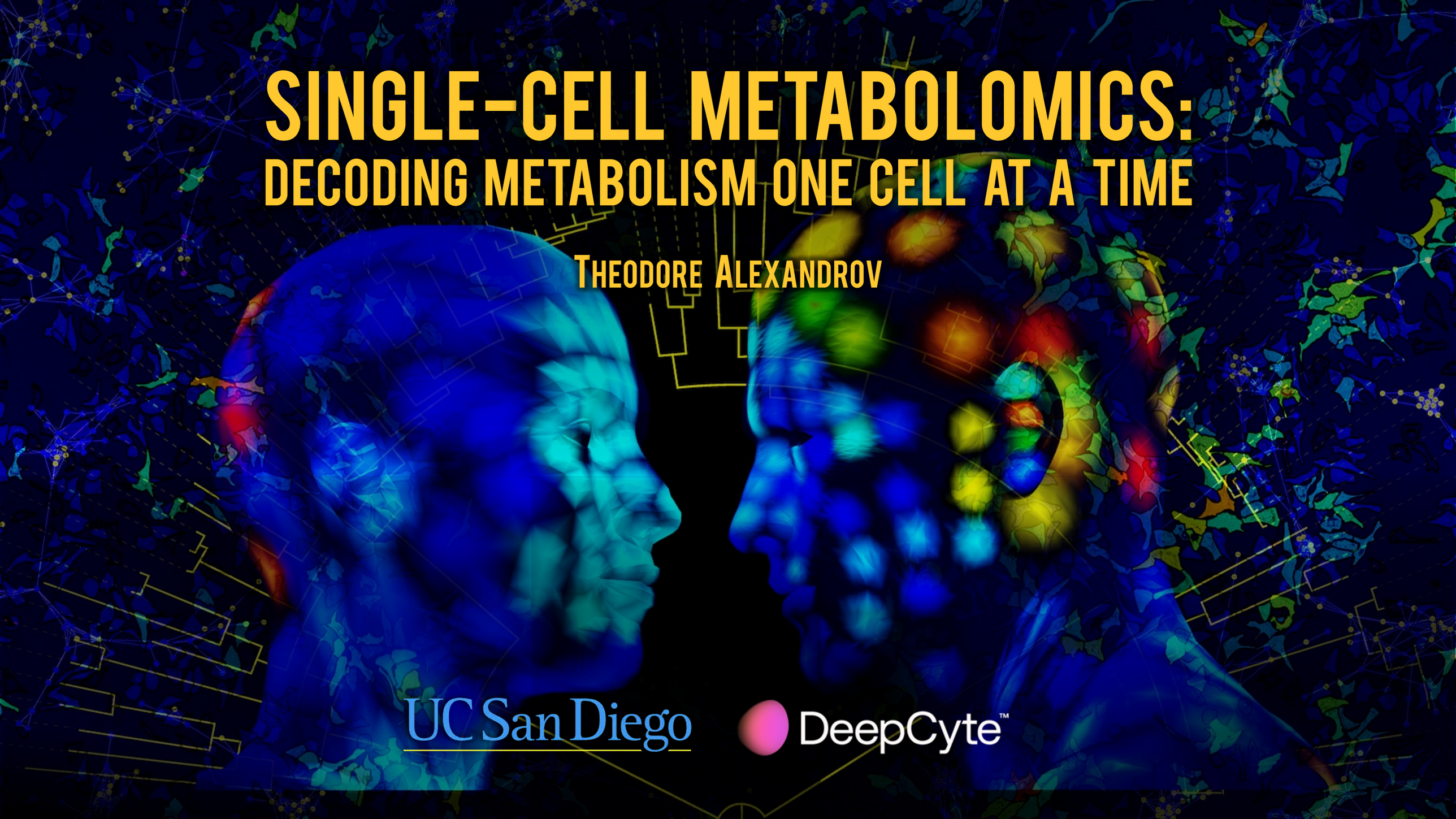
SINGLE-CELL METABOLOMICS:
DECODING METABOLISM ONE CELL AT A TIME

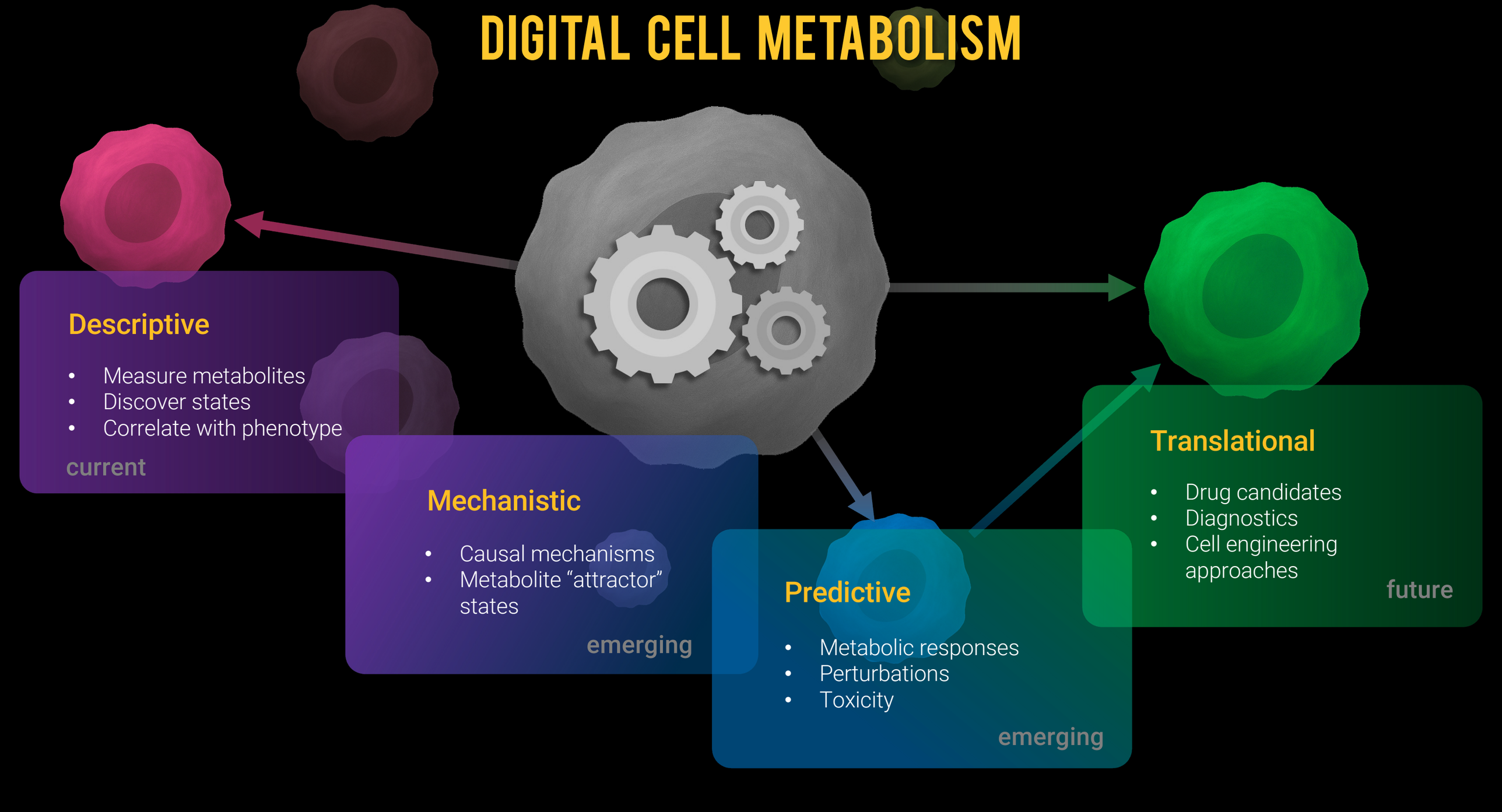
THEODORE ALEXANDROV



UC San Diego

DeepCyte™

DIGITAL CELL METABOLISM



Descriptive

- Measure metabolites
- Discover states
- Correlate with phenotype

current

Mechanistic

- Causal mechanisms
- Metabolite “attractor” states

emerging

Predictive

- Metabolic responses
- Perturbations
- Toxicity

emerging

Translational

- Drug candidates
- Diagnostics
- Cell engineering approaches

future

ENABLER: SINGLE-CELL METABOLOMICS

Alexandrov, Zamboni (2026) *Nature*

- Scalable (simple sample prep)
- High throughput (x10 cf. scRNAseq)
- Affordable (x100 cf. scRNAseq)
- Can be combined with protein & RNA detection

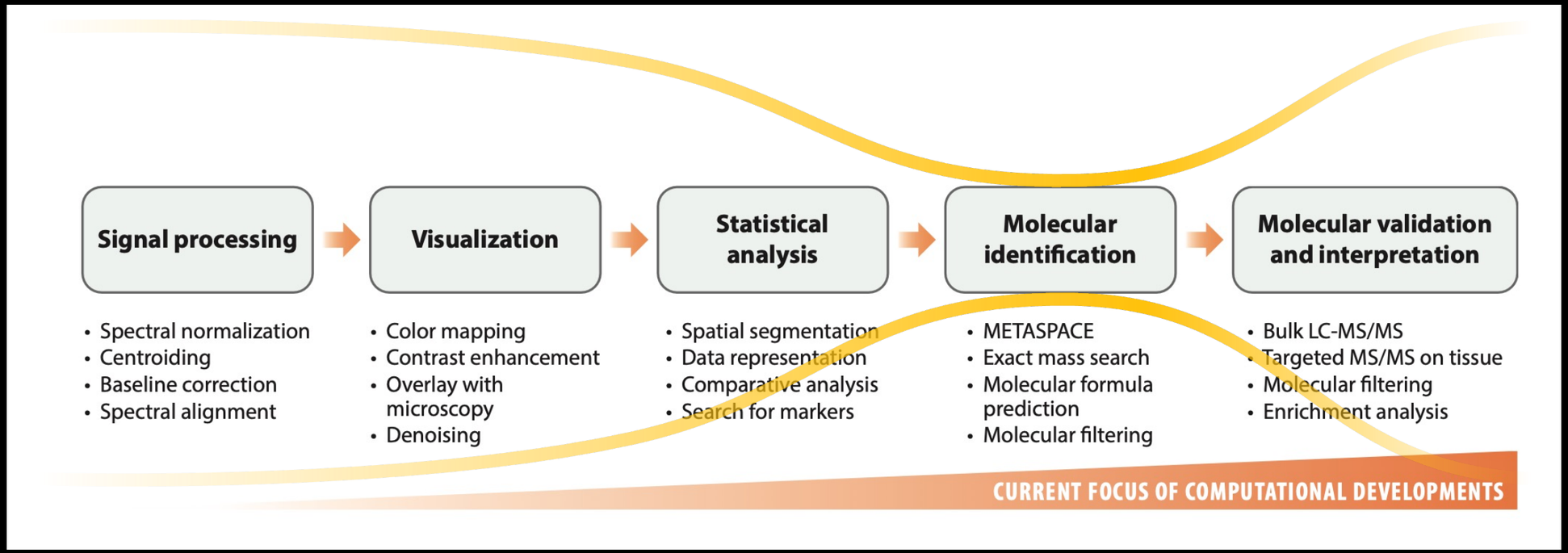
ENABLING THE ENABLER: MALDI–IMAGING MASS SPEC





A KEY BOTTLENECK IN SPATIAL & SINGLE-CELL METABOLOMICS

Alexandrov, *Annu Rev Biomed Data Science* 2020

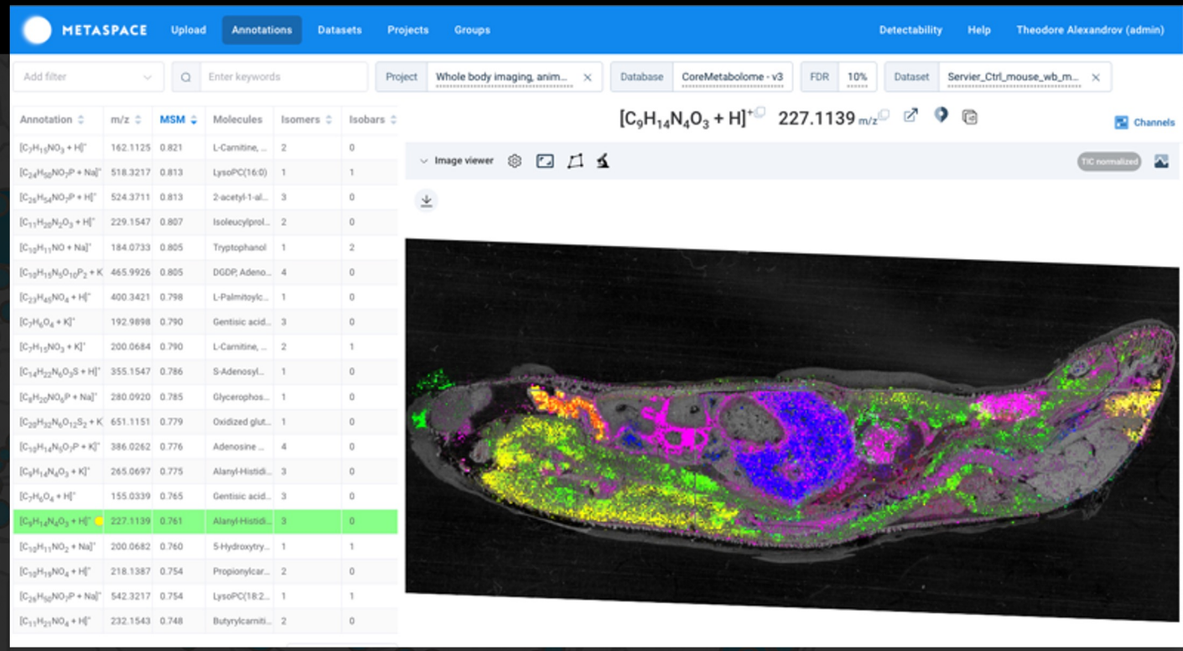


METASPACE: CLOUD PLATFORM FOR SPATIAL METABOLOMICS

- Addressed the bottleneck: metabolite ID

  Palmer et al, Nature Methods 2017

- Data analysis, visualization, sharing
- Knowledge base of spatial metabolomes



Big data

- 70,000+ datasets
- 5,000+ users
- 70+ TB of data

Scientific impact

- 400+ publications



Lucas Vieira



Bishoy Wadie

Collaborative

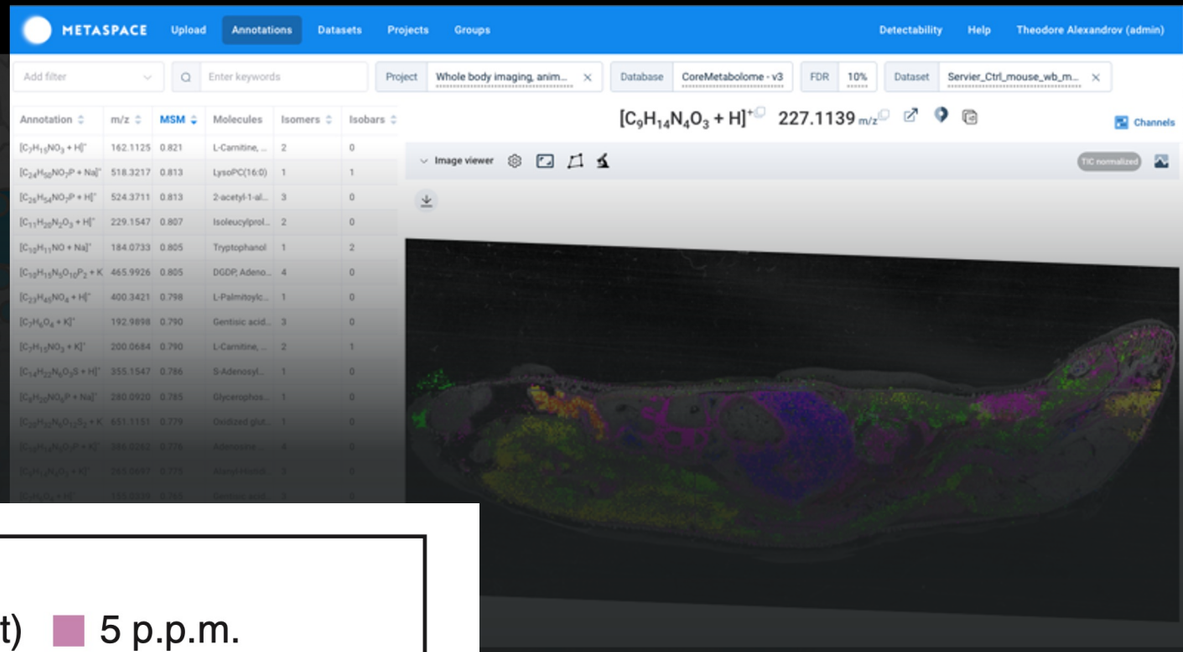
- Free, open source, open data
- NIH atlases (KPMP, LungMAP2)

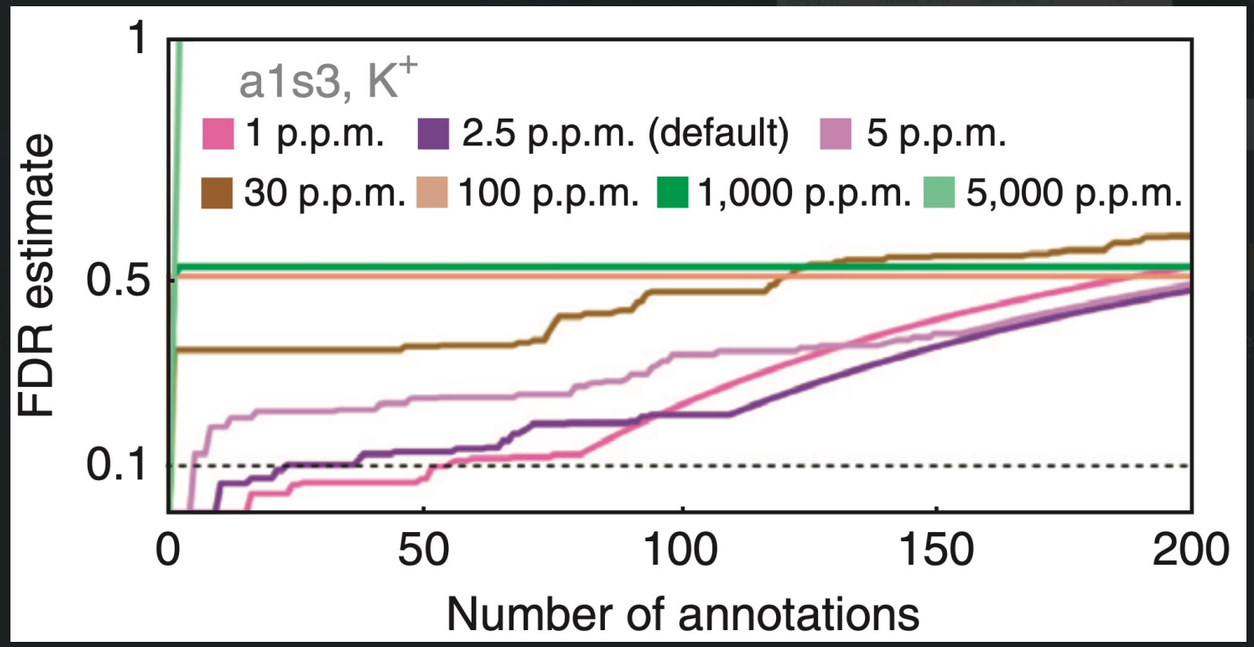
METASPACE: CLOUD PLATFORM FOR SPATIAL METABOLOMICS

- Addressed the bottleneck: metabolite ID

  Palmer et al, Nature Methods 2017

- Data analysis, visualization, sharing
- Knowledge base of spatial metabolomes





HRMS & high accuracy are essential for metabolite ID in MALDI-imaging

IMAGING MASS SPEC AS A FOUNDATIONAL TECHNOLOGY

Alexandrov, *Nature Metabolism* 2024



Comment

https://doi.org/10.1038/s42255-023-00881-0

Spatial metabolomics: from a niche field towards a driver of innovation

Check for updates

spectrometry (imaging MS)[2] also referred to as mass spectrometry imaging, which integrates spatially resolved molecular ablation with online capture of desorbed material followed by MS-based molecular analysis. Spatial metabolomics is the main application of imaging MS, which can also be used for protein detection. Among various approaches for imaging MS, matrix-assisted laser desorption ionization (MALDI) is the key and the most popular technology[12]. Multiple vendors offer comprehensive solutions for spatial metabolomics, including reagents, imaging mass spectrometers, sprayers and software. A number of core facilities and contract research organizations offer services in this area. A range of open-source software packages is available, including MSIReader, Cardinal and METASPACE. In addi-

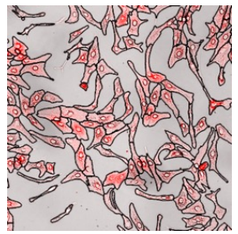
Enabling & driving other technologies

- Spatial single-cell metabolomics
- High-throughput screening
- Intra-operative mass spectrometry
- Spatial fluxomics
- Spatial multi-omics

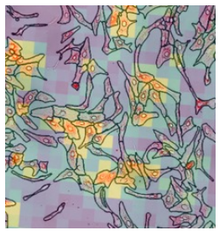
SpaceM FAMILY OF METHODS FOR SINGLE-CELL METABOLOMICS

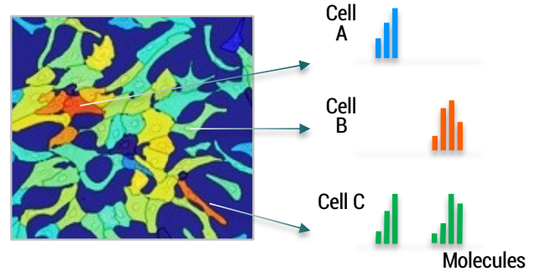
Cells → High-content imaging → Detection of metabolites, lipids or protein markers → Image analysis → Single-cell profiles











SpaceM: lipids Rappez et al, *Nature Methods* 2021

13C-SpaceM: flux Buglakova et al, *Nature Metabolism* 2024

HT SpaceM: high-throughput & small molecule-metabolites

Delafiori et al, *Cell* 2025

100K cells/100 samples in 10h

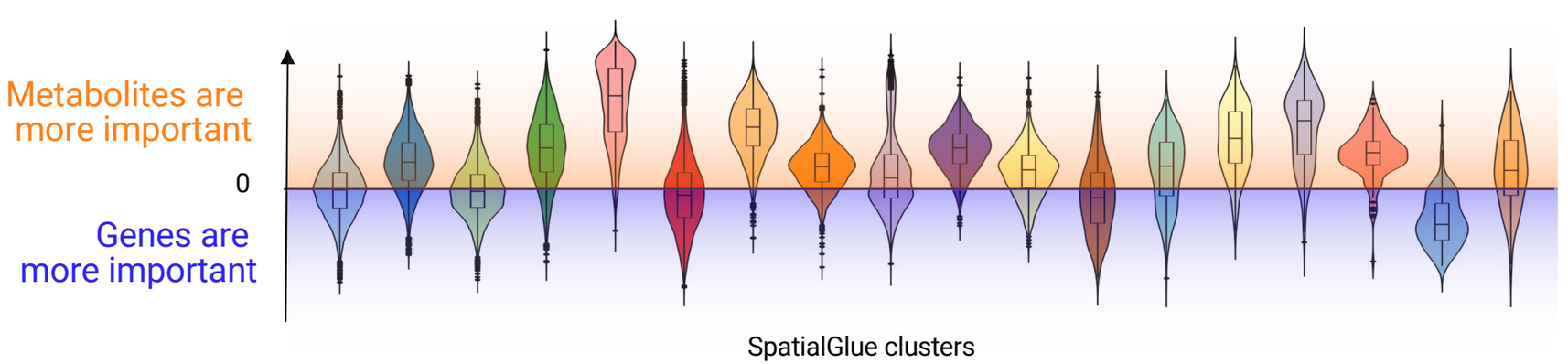
x10 faster, x100 cheaper than scRNAseq

100+ metabolites, 500+ lipids, protein markers

ARE METABOLITES USEFUL FOR CELL IDENTITY?

Wadie et al, unpublished

Single-cell importance of metabolites vs genes in defining cell identity
(spatial single-cell multi-omics of mouse brain)



For identities of most cells, metabolites are more important

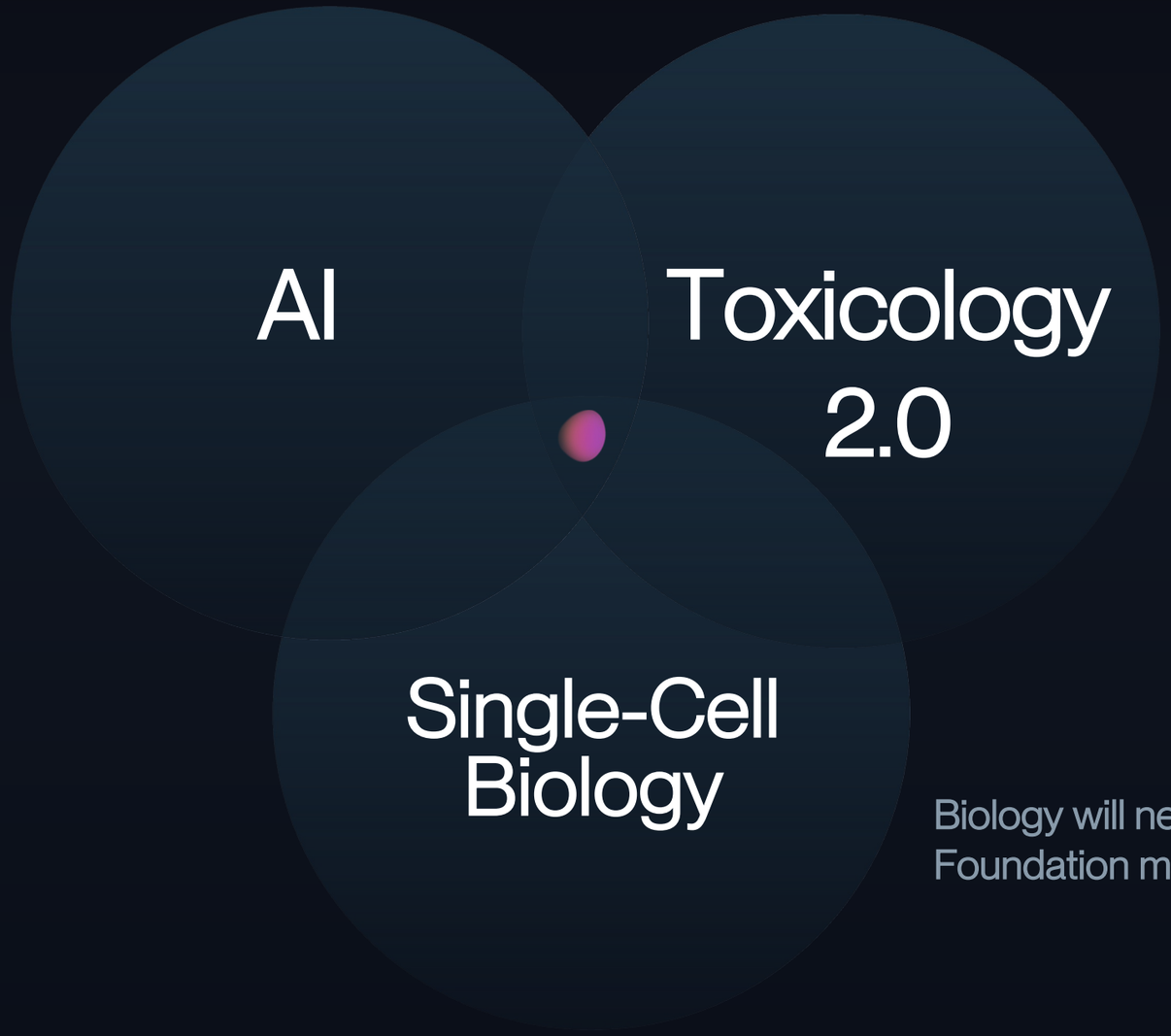
Biological interpretation:

- Transcriptionally similar cells can be metabolically distinct
- Metabolic states add information beyond cell type
- Metabolic states are independent cell attributes

DeepCyte™

Developing Single-Cell Mechanistic AI for Toxicity Prediction

AI promises to transform all aspects of drug discovery

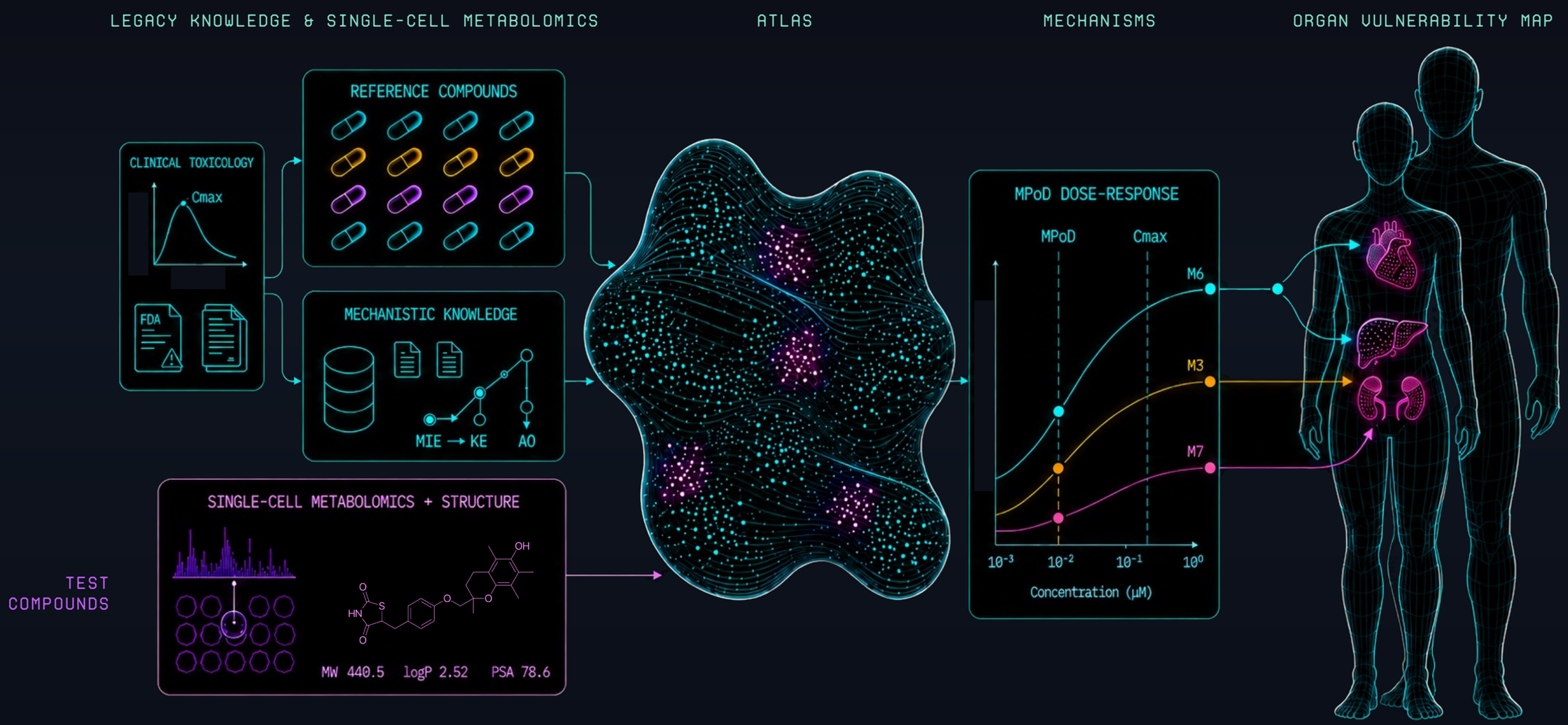


FDA Modernization Act 2.0.
March 2026 NAM guidance

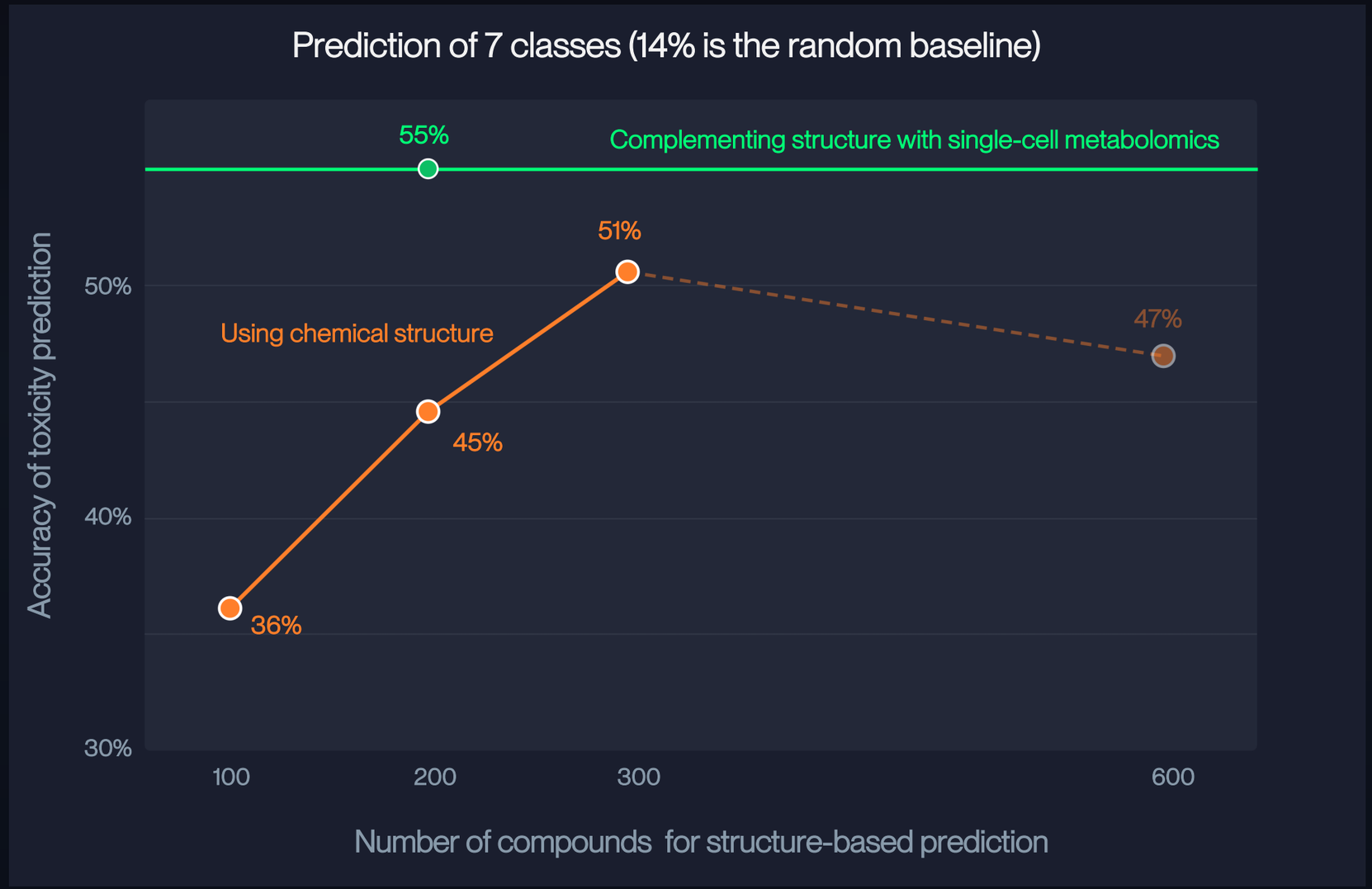
Biology will never be the same
Foundation models promise virtual cells

Single-Cell Mechanistic AI for Toxicity Prediction

DeepCyte™



Use single-cell metabolomics or just more data?

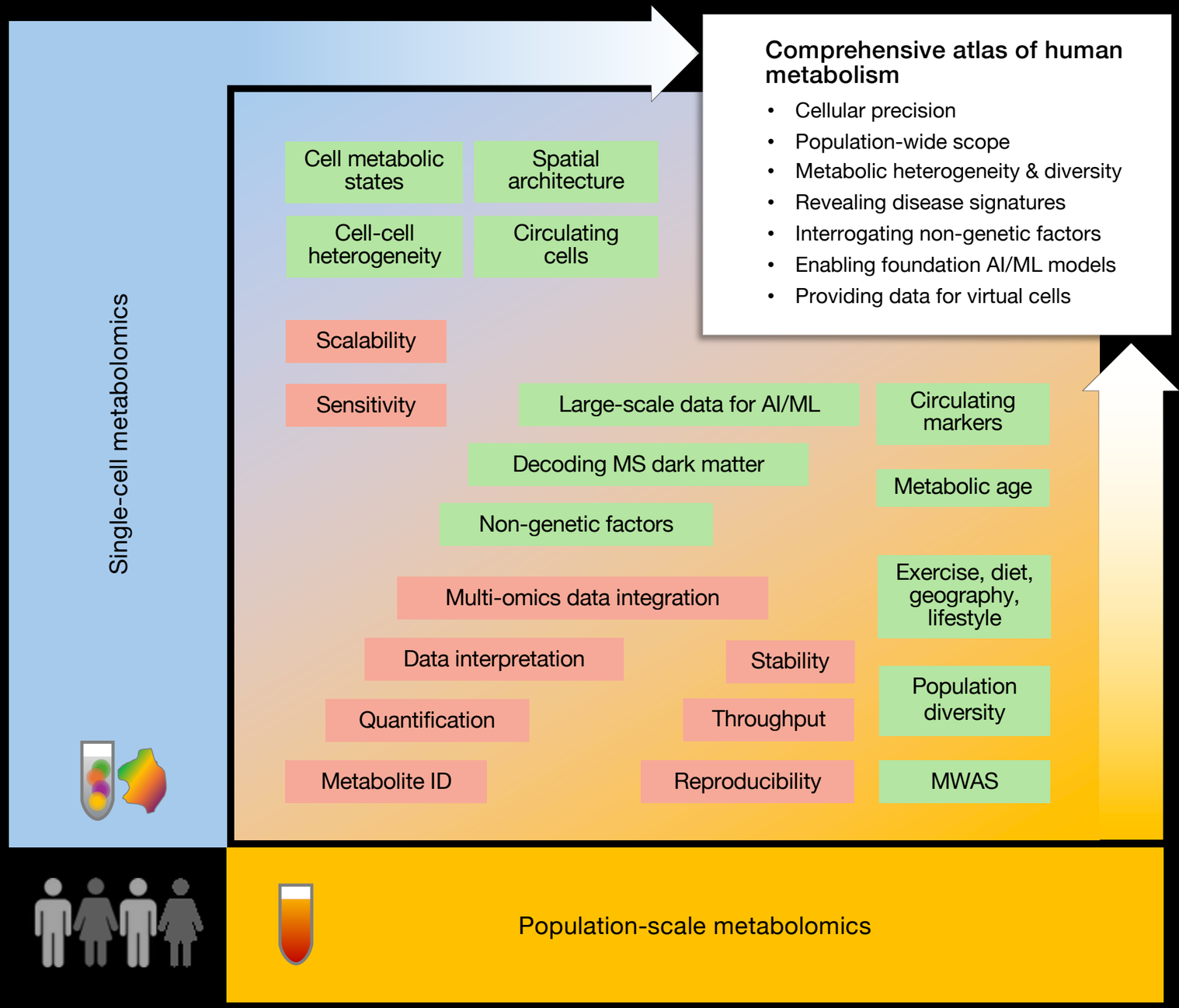


Single-cell metabolomics carries a biochemical signal not represented in the chemical structures alone

=> Improves tox prediction

FUTURE OF SINGLE-CELL METABOLOMICS

Alexandrov, Zamboni (2026) *Nature*





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Rainer Daum
Alexander Makarov

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