

AI for Biomedicine:

Lecture 1 *Unmet Needs in Biomedical Research: Insights from Fundamental Science to Patient Care*

Yasuko Iwakiri, PhD, Yale University School of Medicine

Croucher Foundation, November 27, 2025



Croucher Foundation
裘槎基金會



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Professor of Medicine

Yale University

- Not a computational biologist
- Least technical expertise in AI among the speakers
- Perspective from vascular liver biology
- Focus on where current models and data fall short
- Sets the stage for why we need AI (Lecture 2)



Career path



Postdoc training at Yale

Roberto Groszmann, MD



- **Physician Scientist**
- Mechanisms of portal hypertension

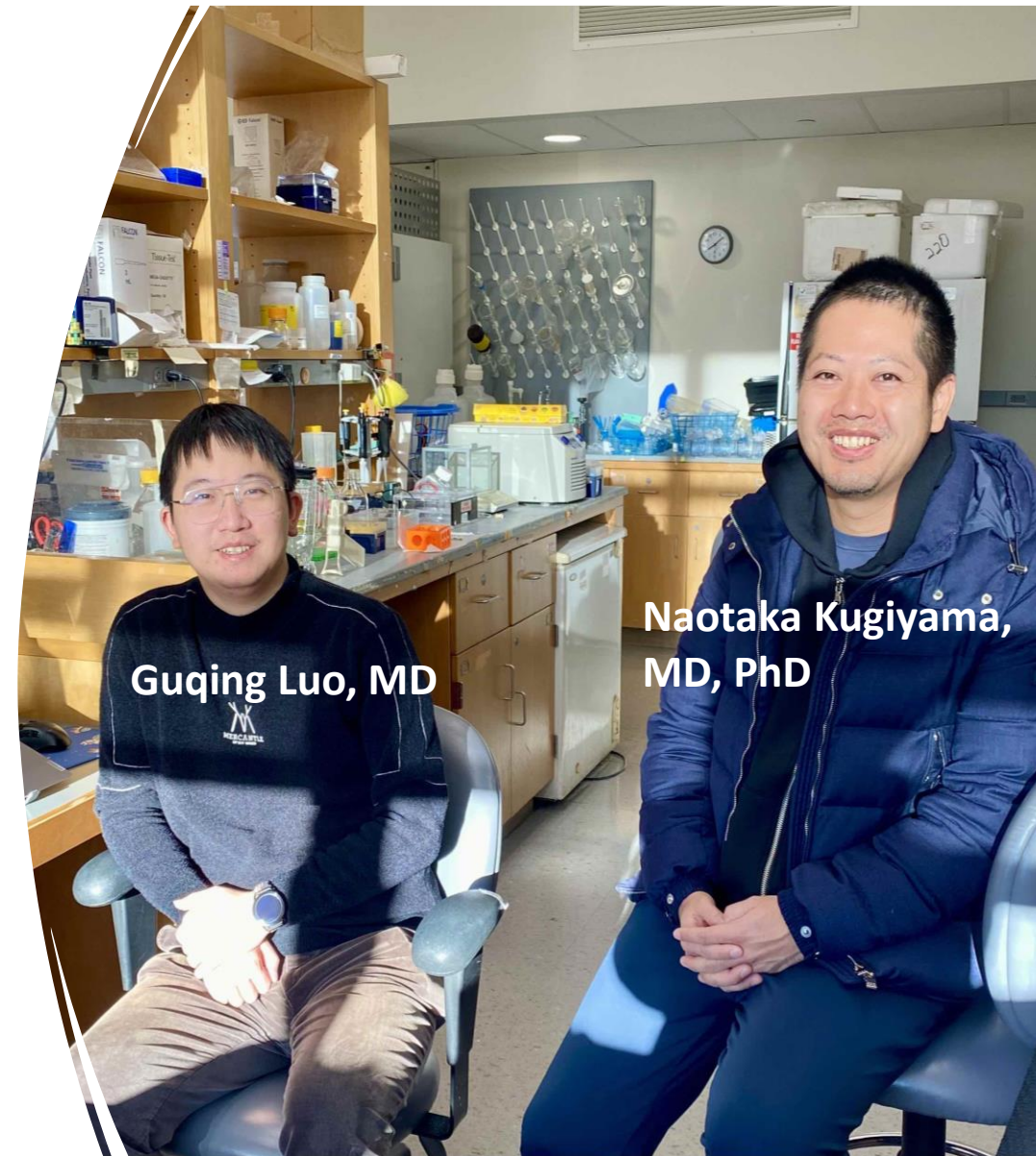
William Sessa, PhD



- **Basic scientist**
- Vascular & endothelial cell biology
- Pharmacology

Lecture 1 - Overview

1. Introduction
2. Human-relevant platforms
3. Challenges in Biomedical Research
4. Background: Omics & Systems Biology
5. Liver Biology
6. Unmet Needs in Liver Research
7. Real-World Examples in Liver Research
8. Key Takeaways



Section I

Introduction

New NIH office to reduce use of animals in research

Agency plans to promote alternative methods and address “bias” toward animal studies in grant review

30 APR 2025 • 5:00 PM ET • BY [SARA REARDON](#)



A New Direction in U.S. Biomedical Research

<https://www.science.org/content/article/new-nih-office-reduce-use-animals-research>

A New Direction in U.S. Biomedical Research

- Shift toward **human-relevant platforms**: organ-chips, organoids, large human datasets, and AI-based modeling.
- Not everyone agrees: some are excited about cutting animal studies, others question whether the alternatives are ready



SCIENCEINSIDER | SCIENTIFIC COMMUNITY

New NIH office to reduce use of animals in research

Agency plans to promote alternative methods and address "bias" toward animal studies in grant review

30 APR 2025 • 5:00 PM ET • BY SARA REARDON



Section II

Human-relevant platforms



Organoids & Organ-on-chip

Organoid: advanced *in vitro* culture system

Definition

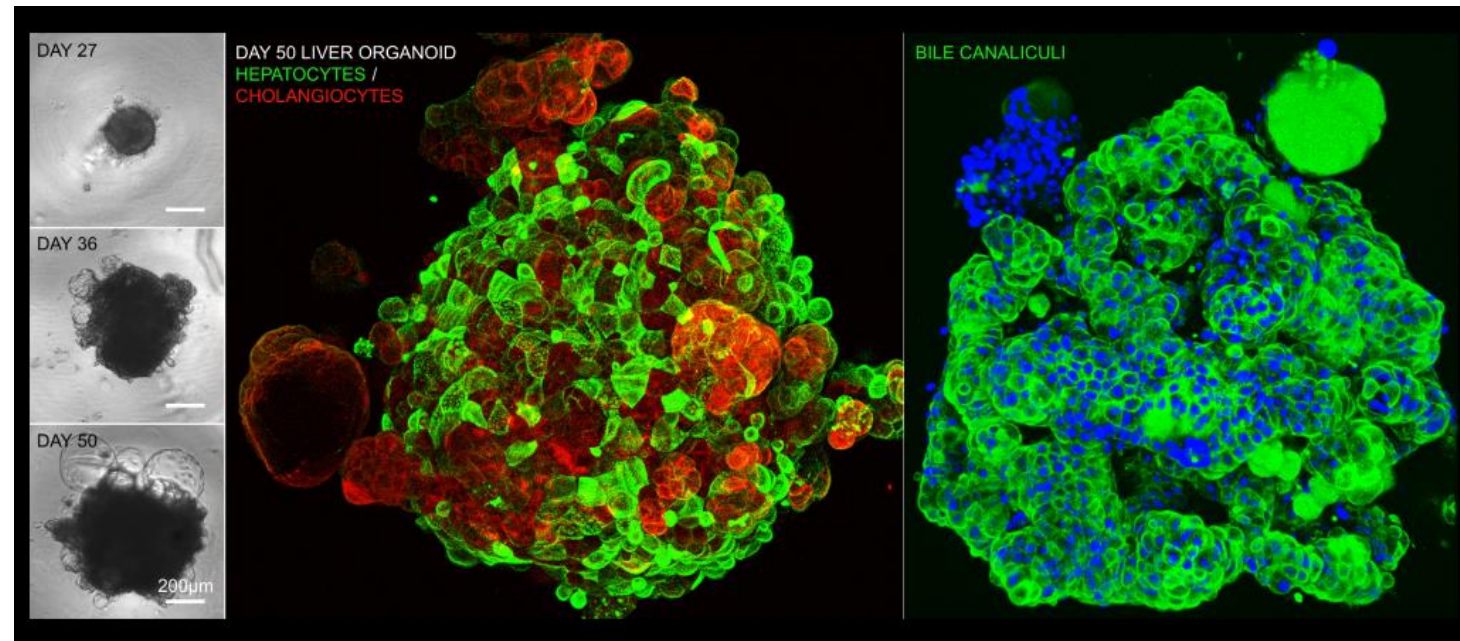
- A **3D structure** of cells that self-organize through cell-cell and cell-matrix interaction

Origin

- Primary stem/progenitor cells
- iPSCs

Applications

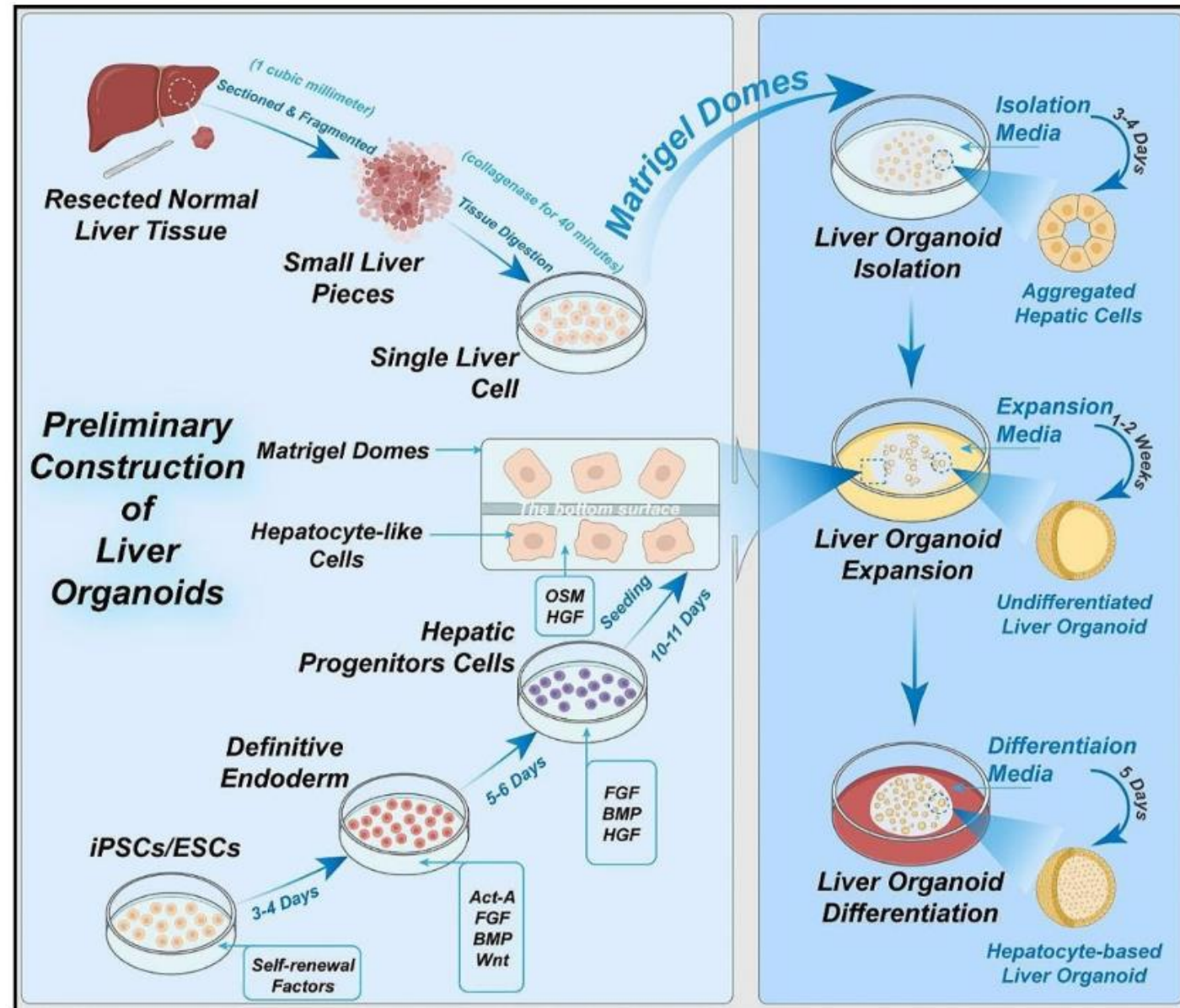
- Drug discovery, toxicity, mechanistic study



<https://www.a-star.edu.sg/News/astarNews/news/press-releases/singapore-scientists-develop-advanced-human-liver-organoids>

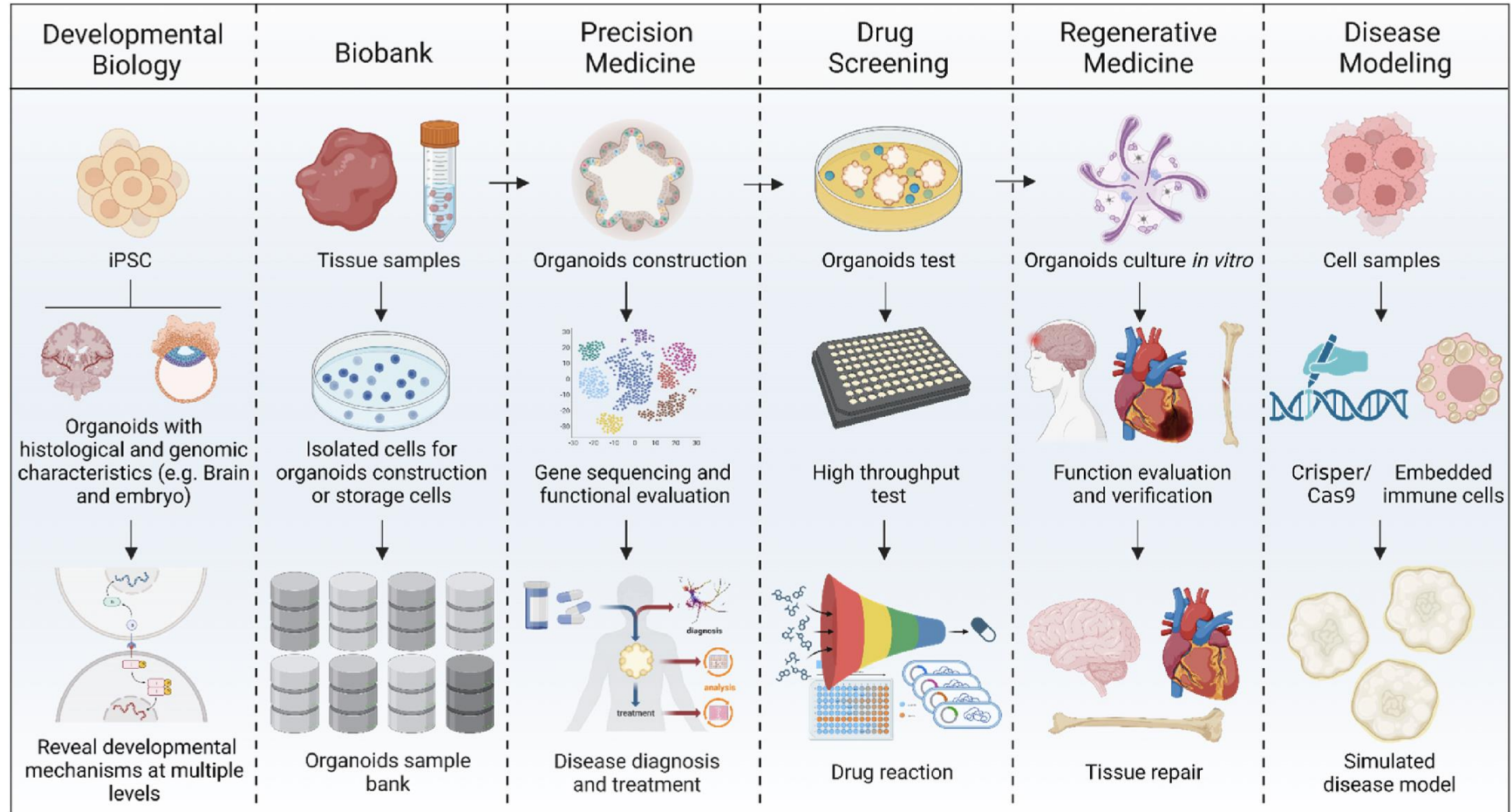
Organoid: advanced *in vitro* culture system

Example: Liver organoid



Organoid: advanced *in vitro* culture system

Applications



Organ-on-a-chip: advanced *in vitro* culture system

Definition

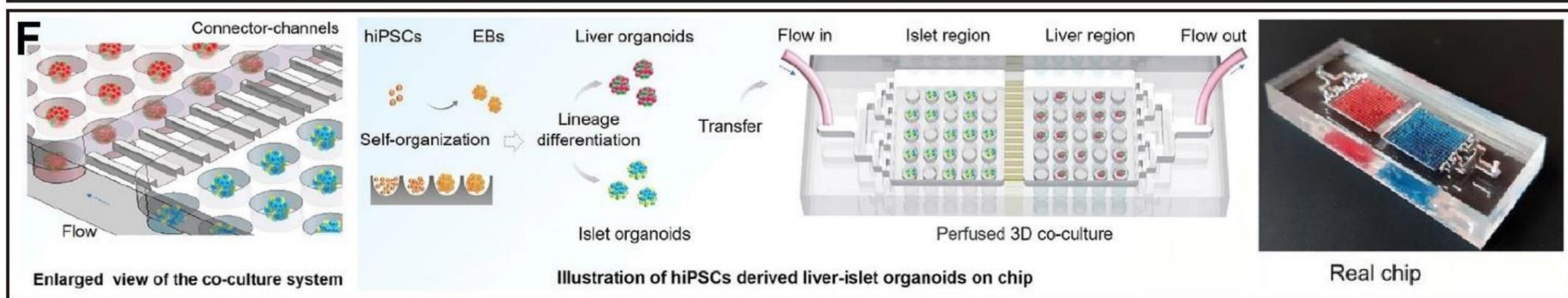
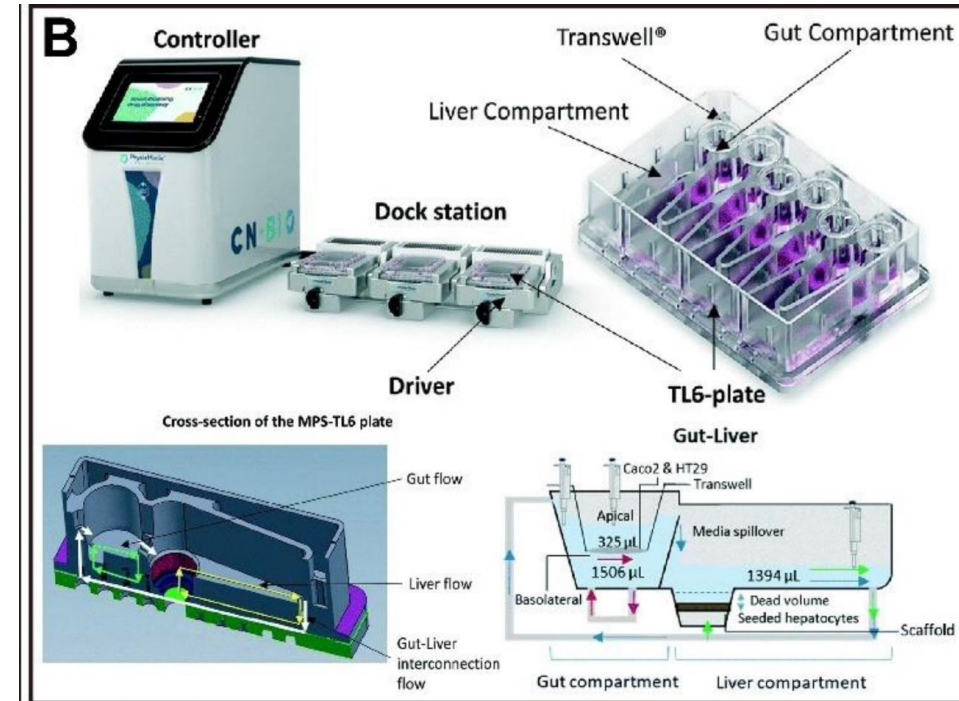
- An *in vitro* microphysiological system used for mimicking the human body environment, representing a simplified but realistic model of its organ level.
 - e.g., Microfluidics

Applications

- Drug testing,
- disease modeling,
- personalized medicine, etc

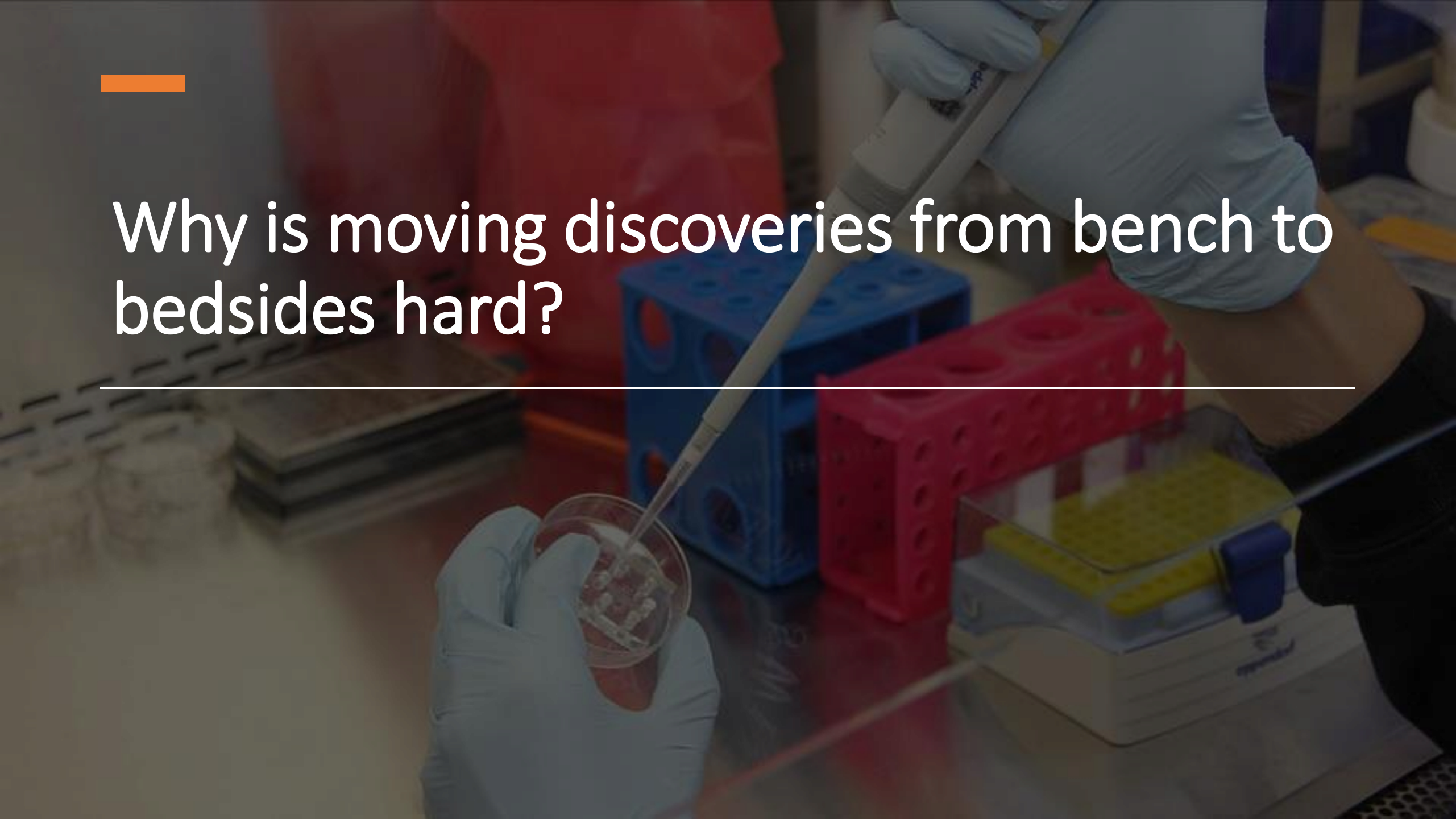
Cell sources

- Primary cells or cell lines
- organoid
- iPSC



Section III

Challenges in Biomedical Research

A person wearing a white lab coat and blue gloves is using a pipette to transfer liquid from a multi-well plate to a small vial. The background shows a laboratory setting with various equipment and containers. The text "Why is moving discoveries from bench to" is overlaid on the image, followed by a horizontal line and the text "bedsides hard?".

Why is moving discoveries from bench to
bedsides hard?

Challenges in Biomedical Research

1. Technical limitations

- Experimental models remain imperfect

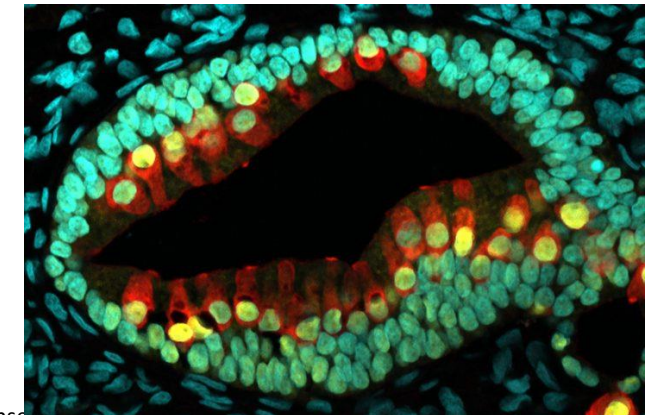
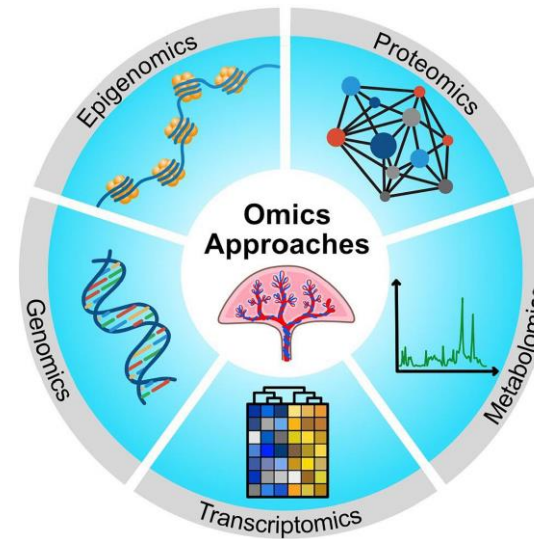


2. Data fragmentation and reproducibility

- Omics data set stored in separate formats/platforms
- Incomplete metadata and protocol validation

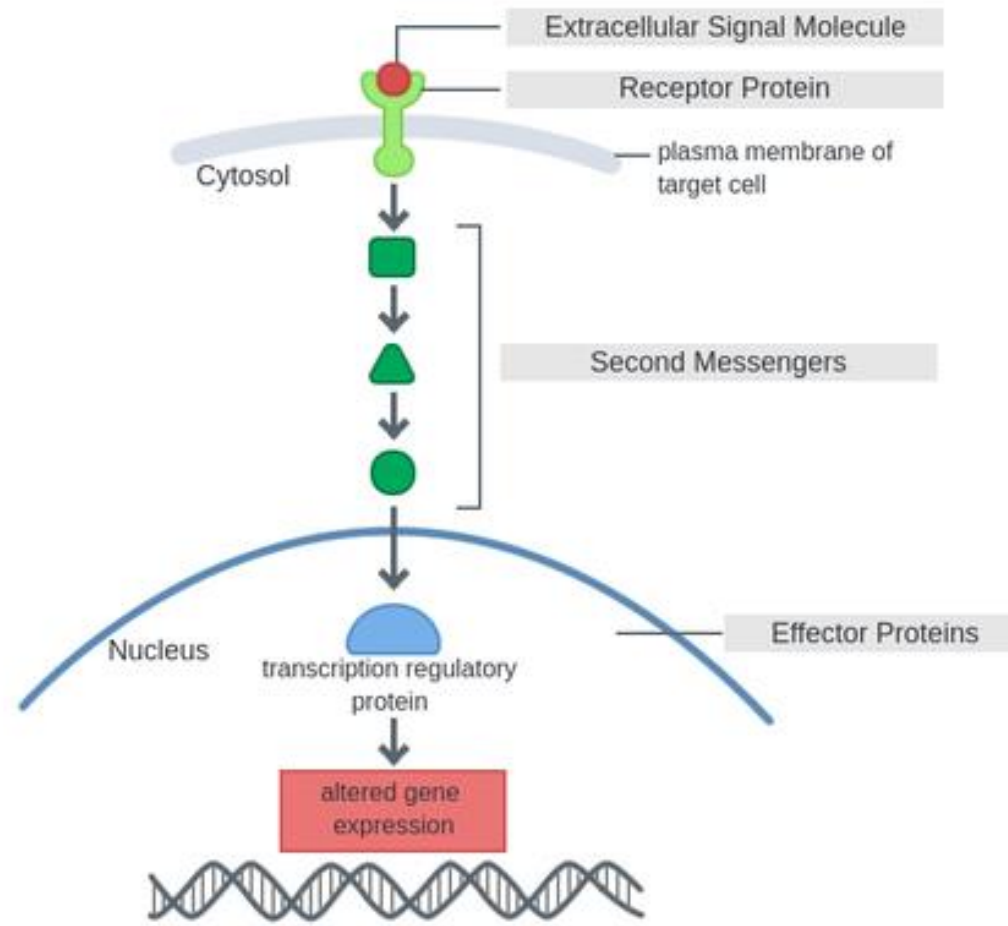


3. Biological complexity

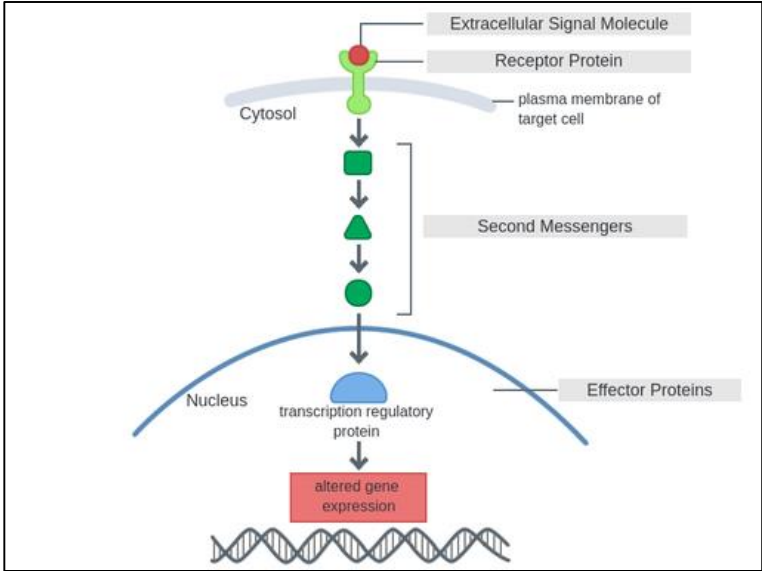


3. Biological complexity

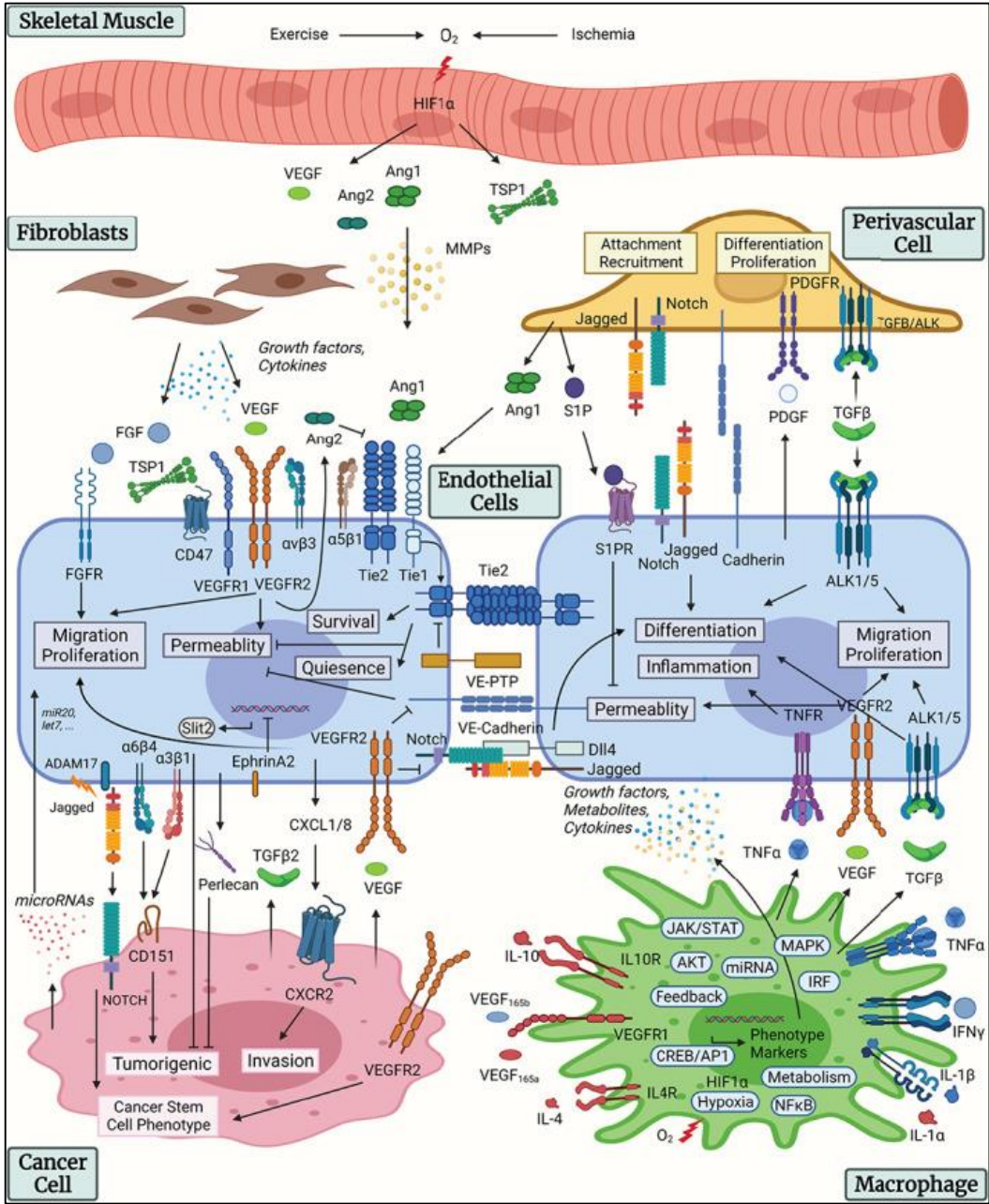
Cell



3. Biological complexity



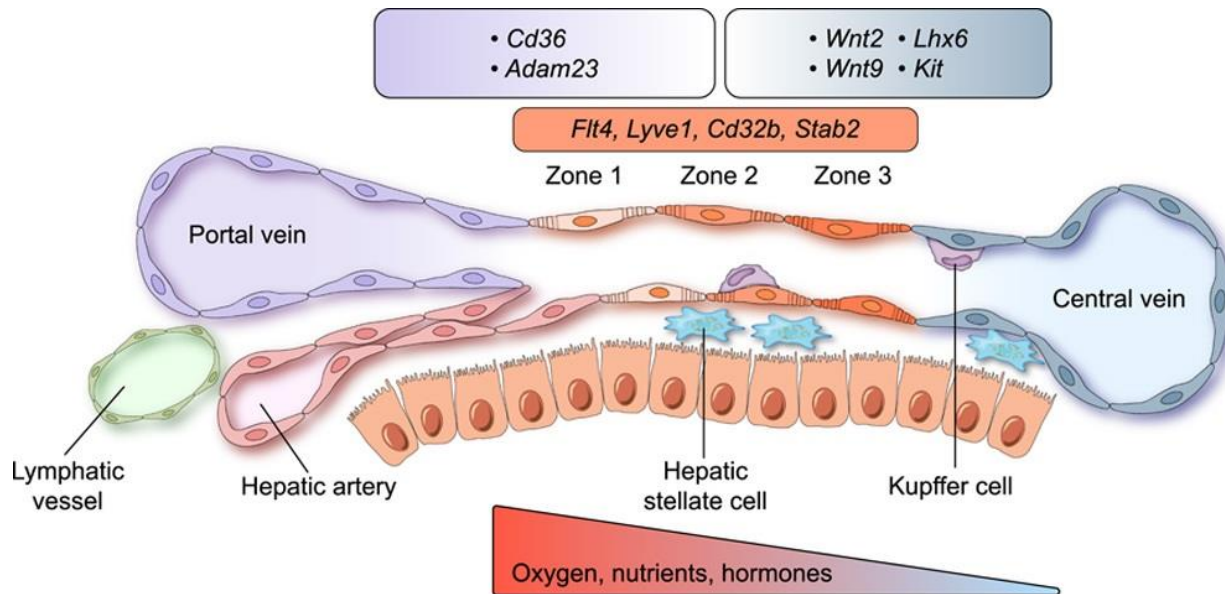
Angiogenesis Signaling Pathways



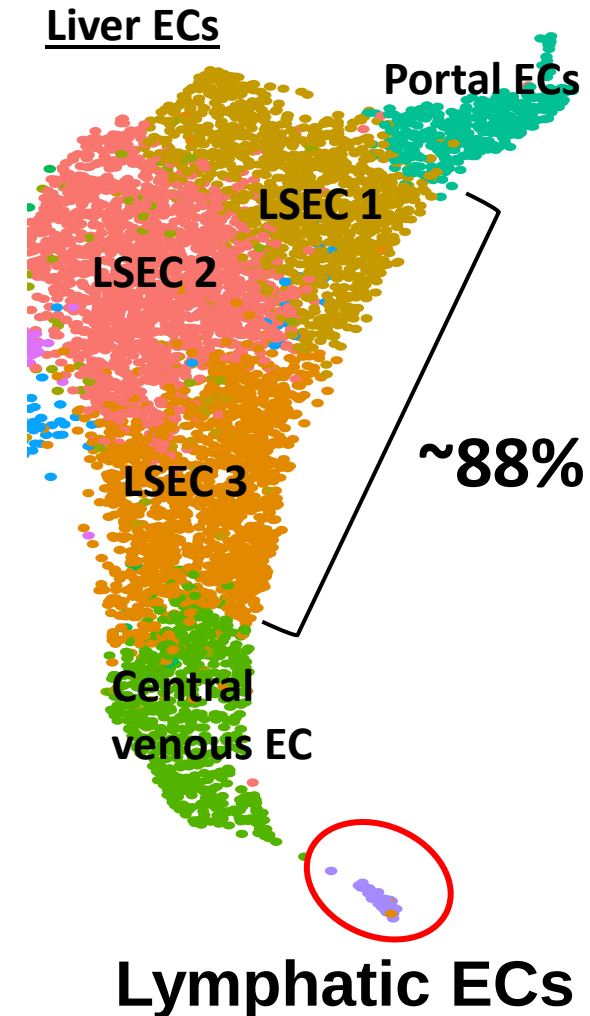
3. Biological complexity

Cell heterogeneity

Example: liver endothelial cells



McConnell, Kostallari, Ibrahim, Iwakiri.
Hepatology. 2023; 78(2): 649-669

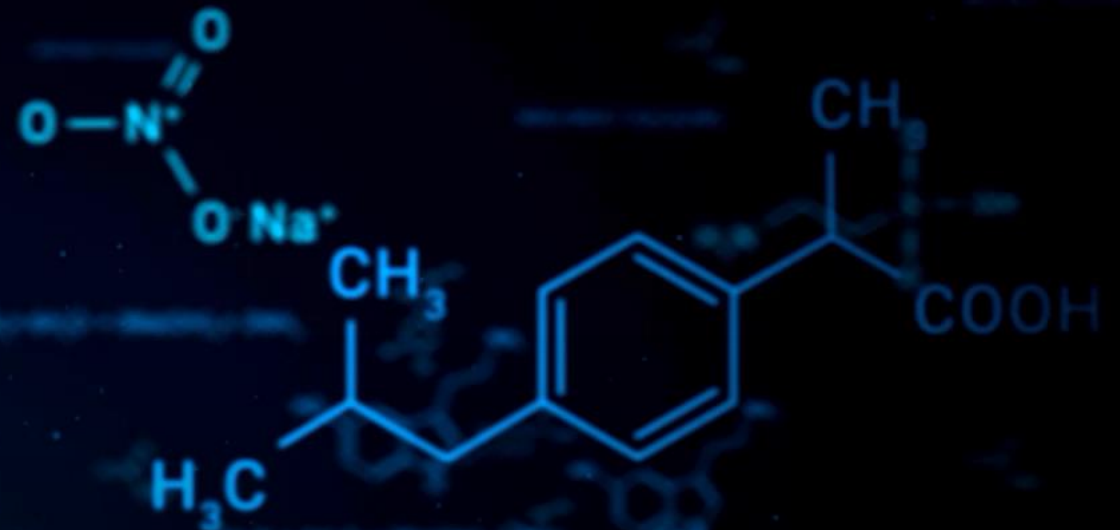
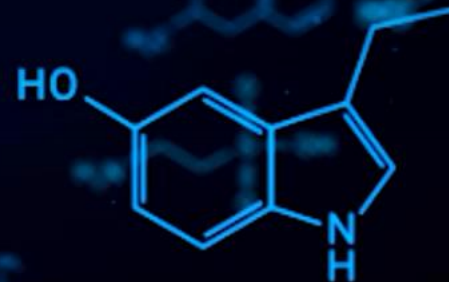


Su T, Iwakiri Y, et al. CMGH. 2021;11(4):1139-1161.

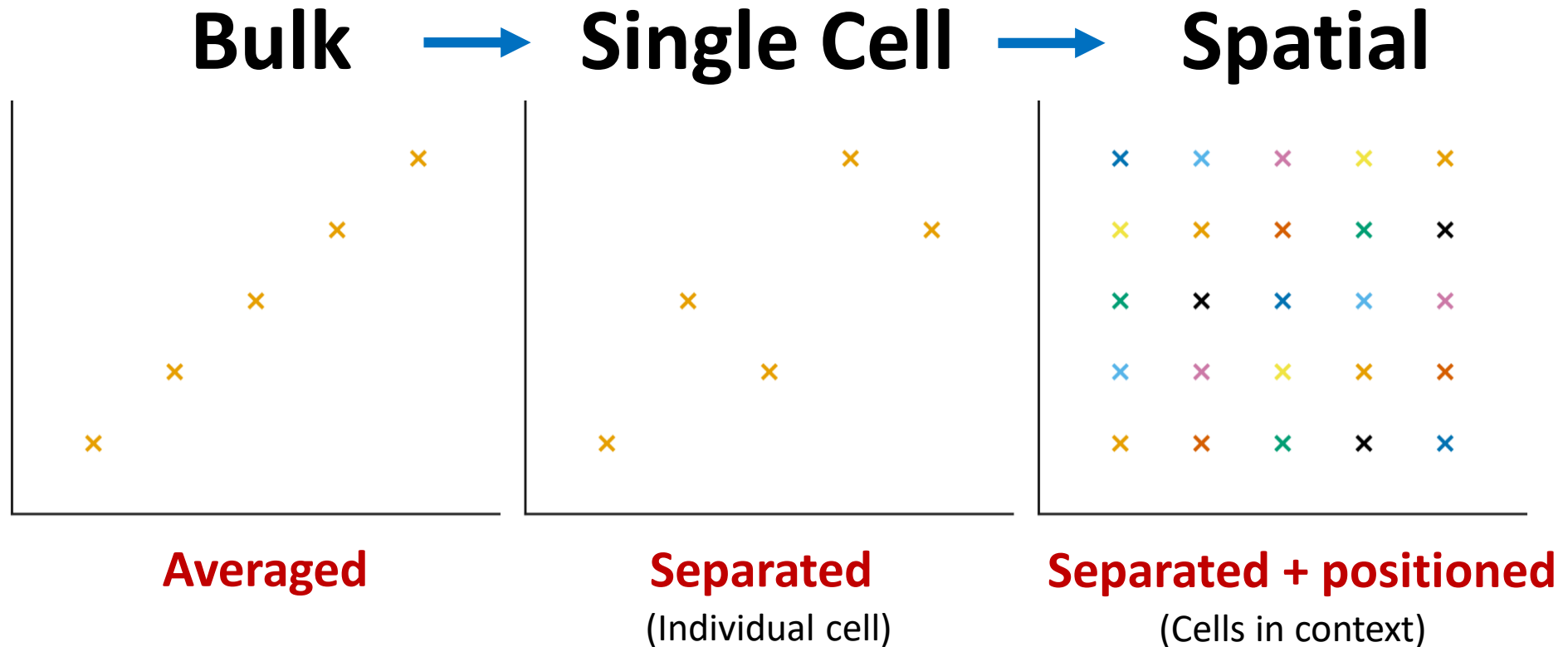
Section IV

Background: Omics & Systems Biology

Omics



How Omics Technologies Have Evolved



Transcriptomics: from bulk to single cell and spatial level

Single cell RNA-seq

* Live cell only – no dead cells!

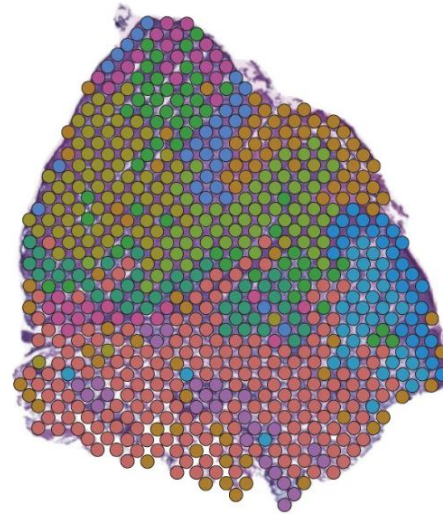
Single nucleus RNA-seq

- Cells can be frozen
- Suitable for those samples difficult to get in live (e.g., human samples)

Spatial RNA-seq

- Non-fixed frozen sections
- Data quality in paraffin section is not ideal

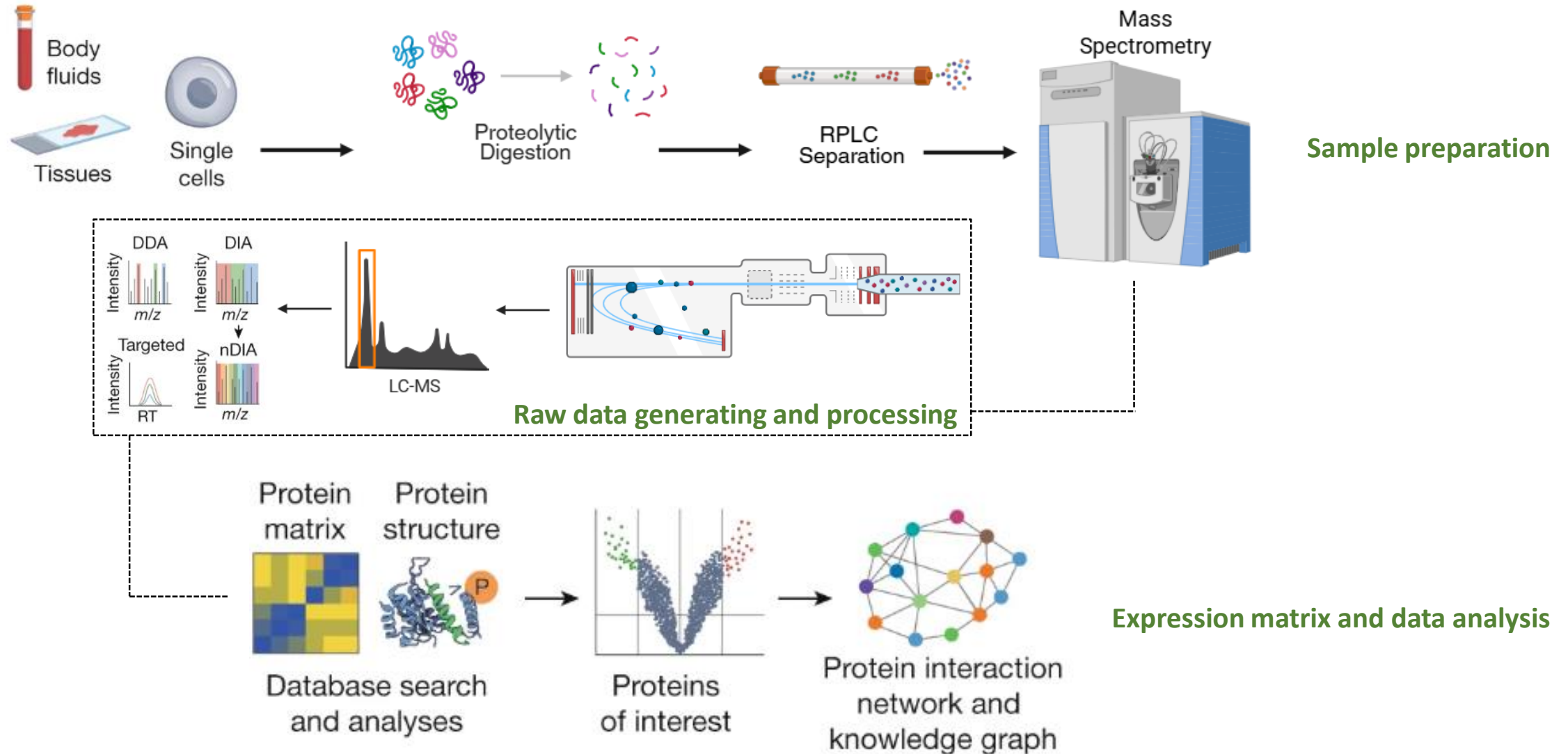
Integration



- **Locational information**
from **Spatial**
- **Transcriptome depth**
from **Single cell**

Proteomics: from bulk to single cell and spatial level

- Key technique: *Mass Spectrometry (MS)*

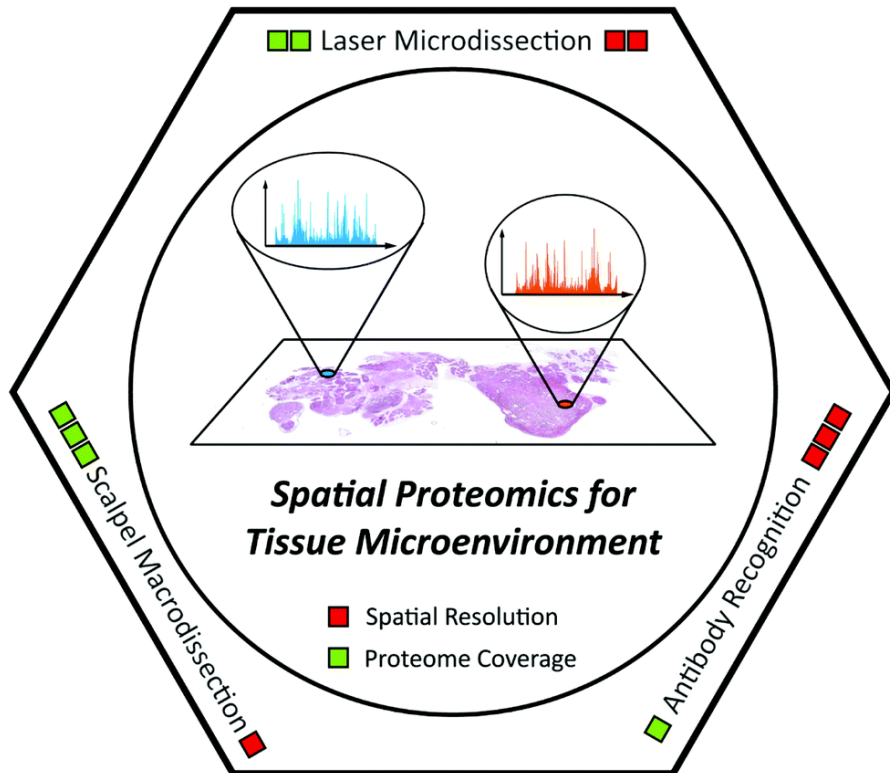


Proteomics: from bulk to spatial and single cell level

- Spatial level: know “*where*”

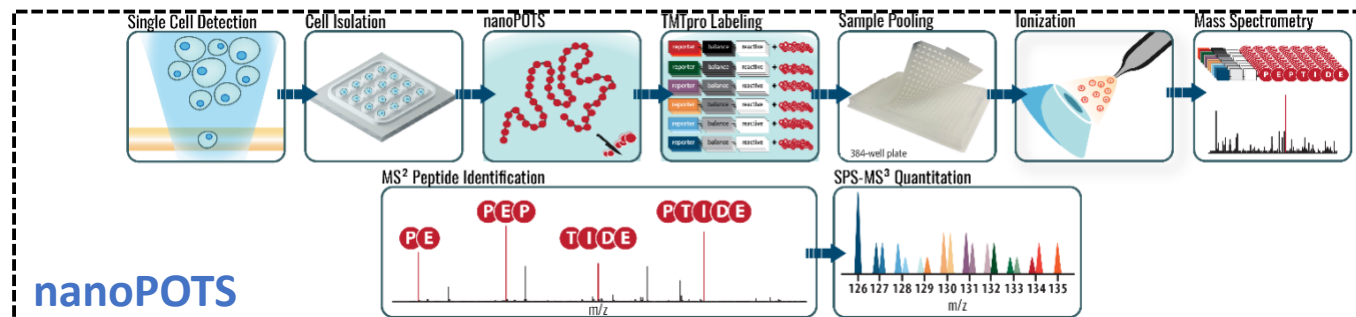
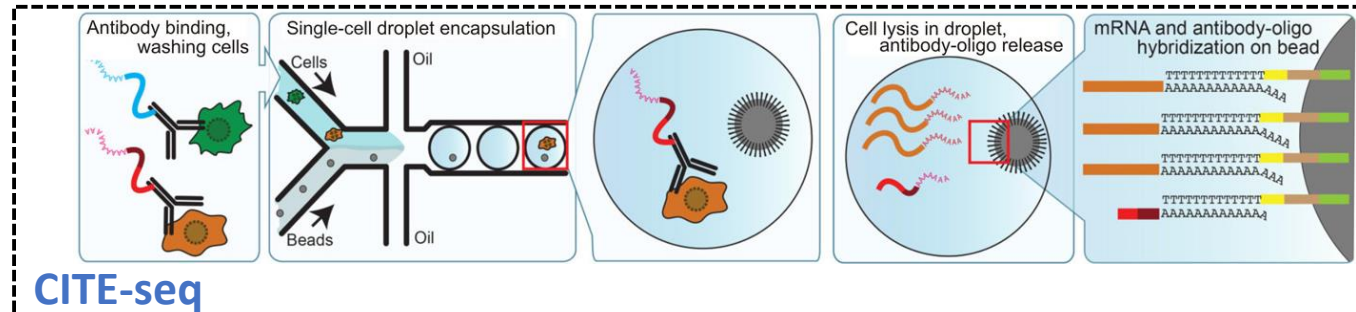
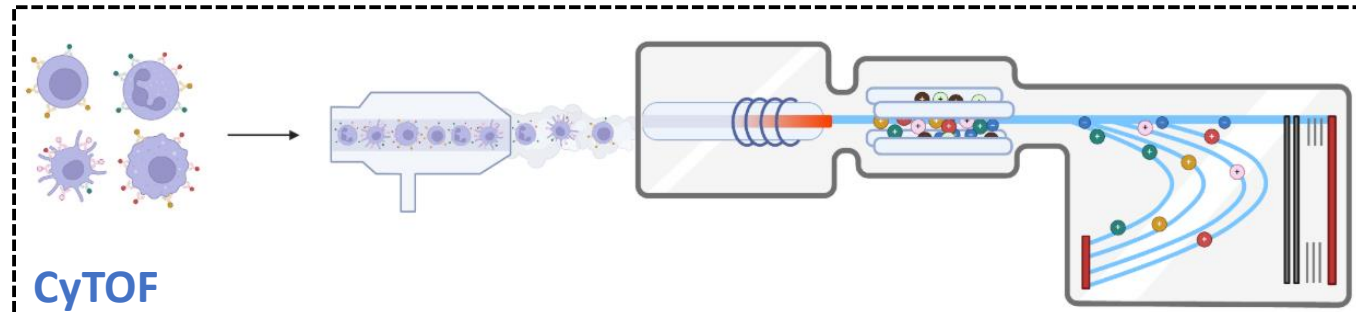
Depth
↓ ↑
Resolution

- Mass spectrometry imaging
- Laser capture microdissection
- Antibody recognition



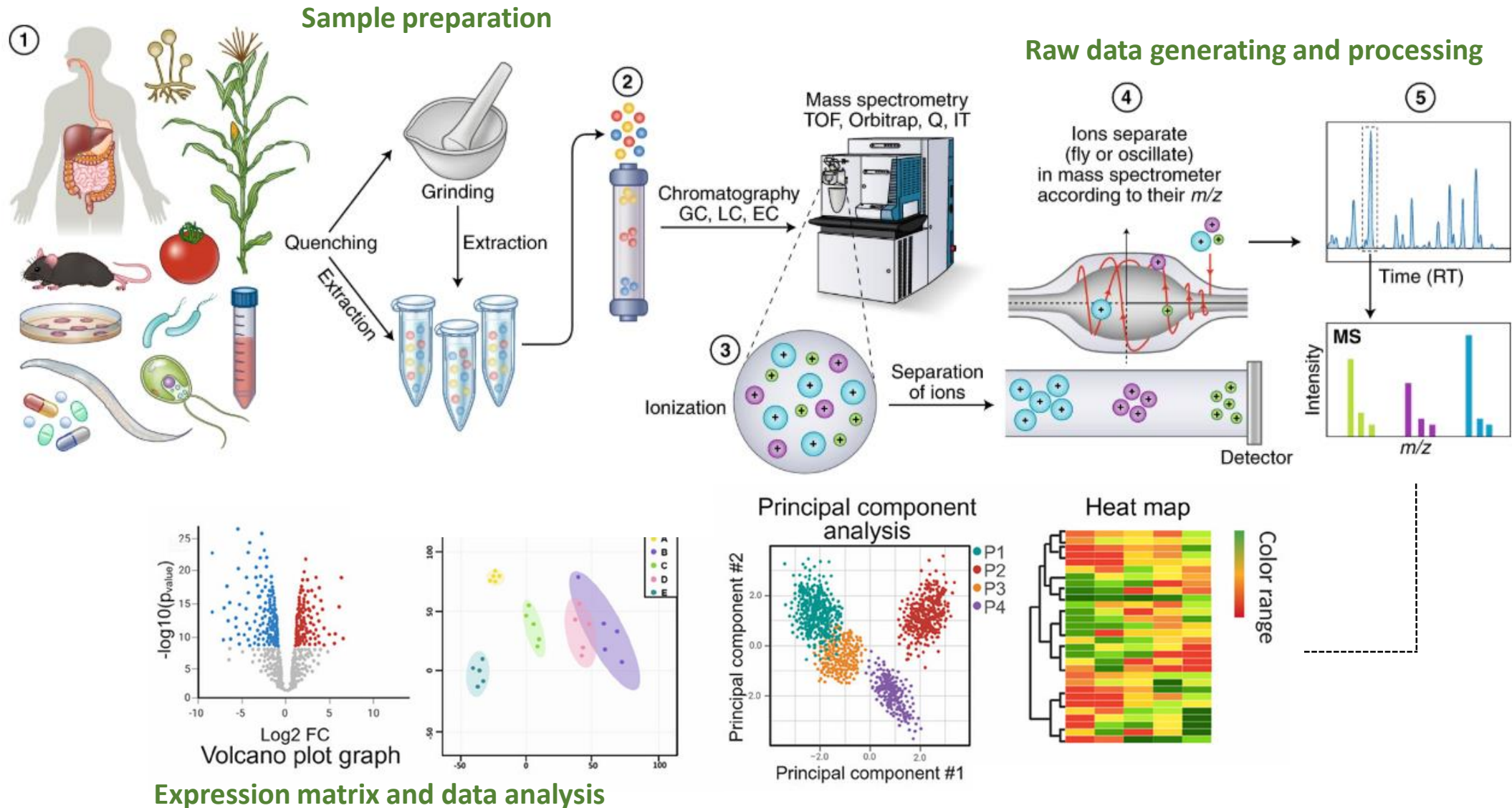
- Single cell level:

- CyTOF: flow cytometry-like MS
- CITE-seq: scRNA-seq with surface protein mark
- TMT-labeled: nanoPOTS, SCoPE-mS



Metabolomics: from bulk to single cell and spatial level

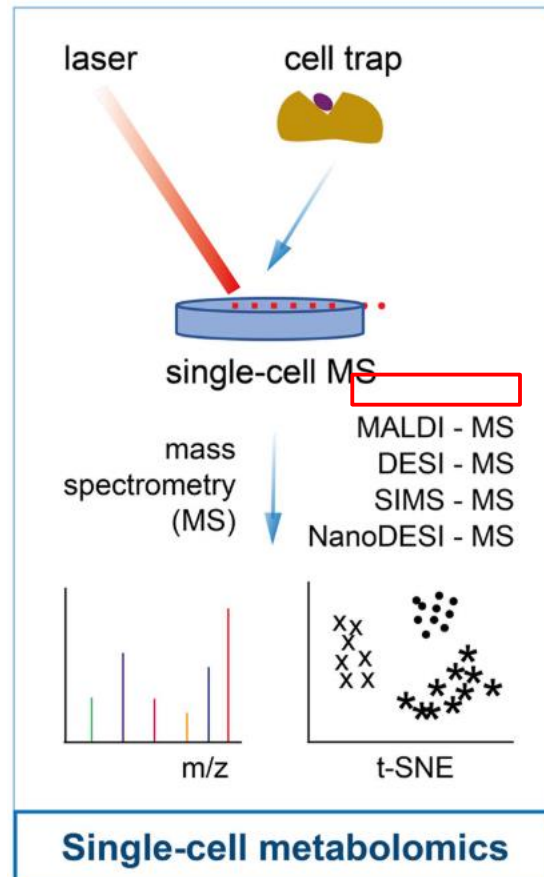
- Key techniques: **Mass Spectrometry (MS)** and **Nuclear Magnetic Resonance (NMR)**



Metabolomics: from bulk to single cell and spatial level

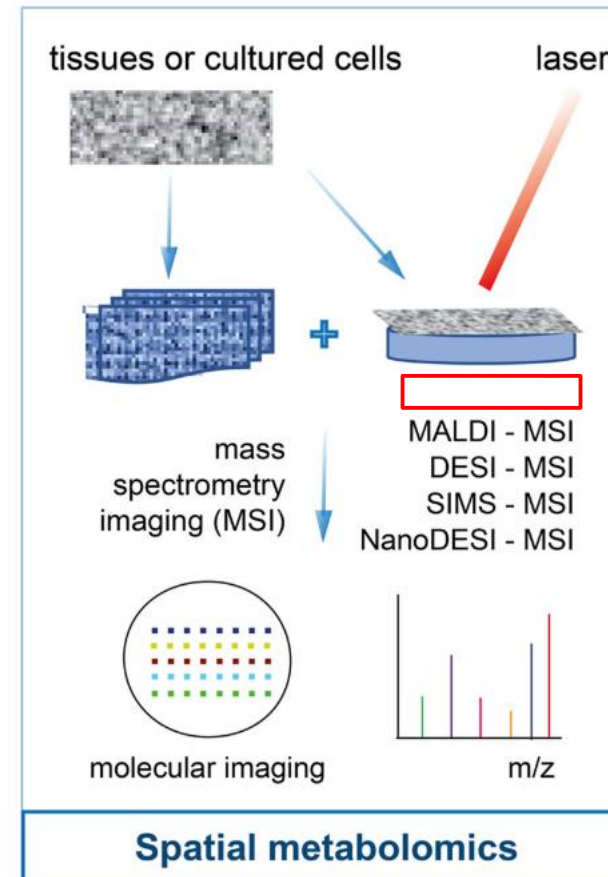
Single cell level

Mass Spectrometry (MS)



Spatial level

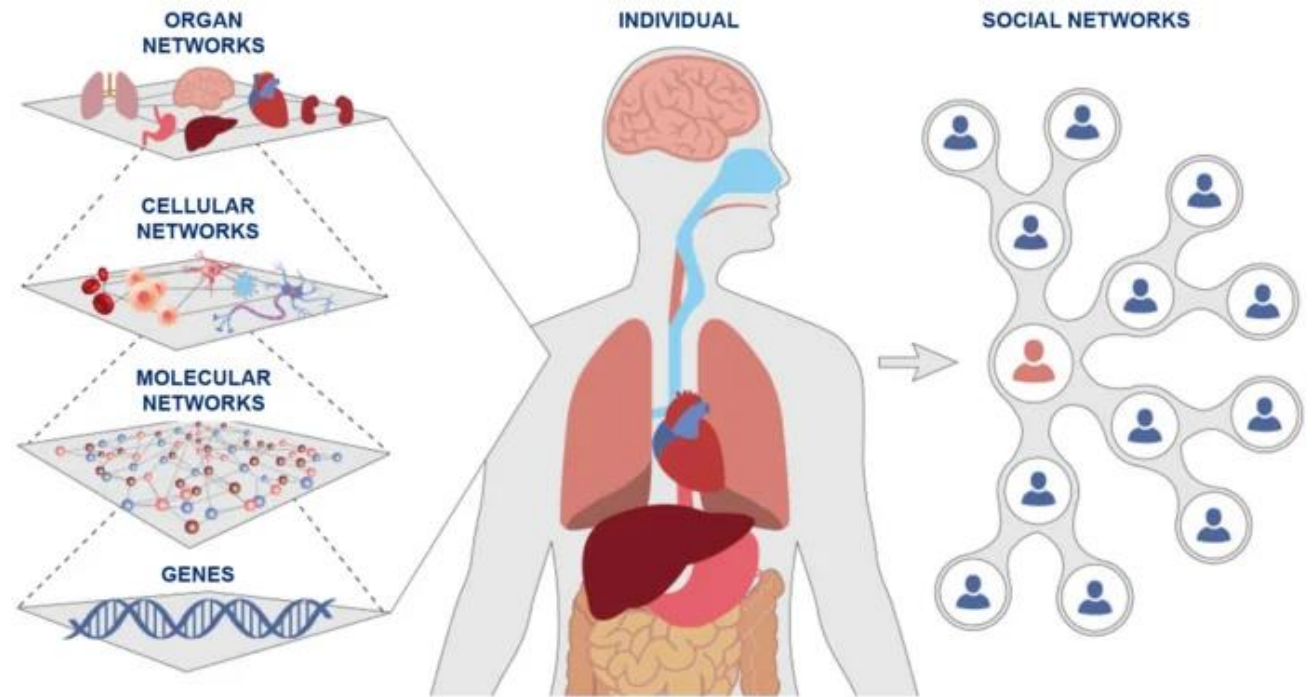
Mass Spectrometry Imaging (MSI)



Systems biology

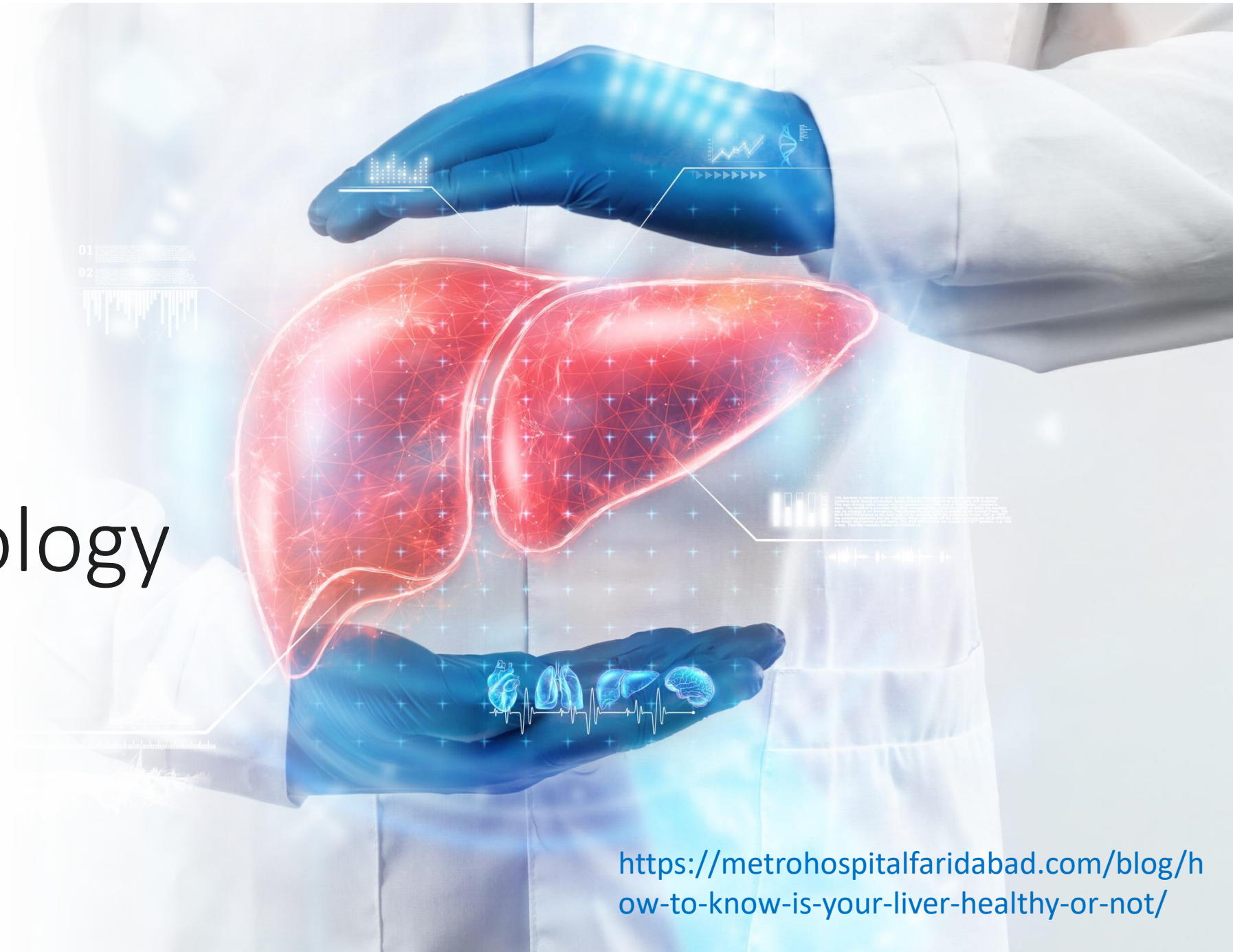
Definition:

- An approach in biomedical research to understanding the larger picture
- To understand complex biological systems by looking at how all their interconnected parts work together, rather than studying them in isolation



Section V

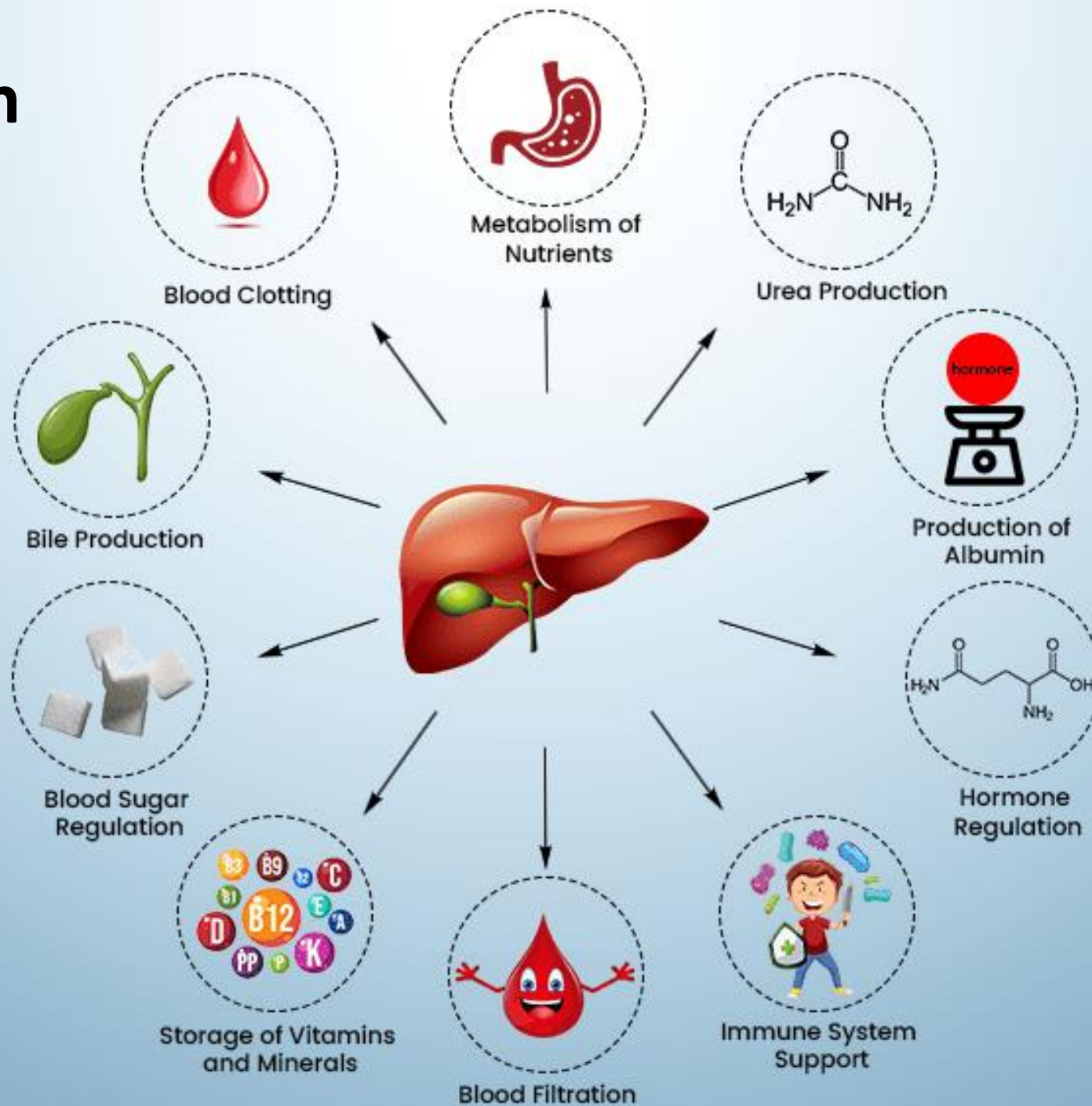
Liver biology



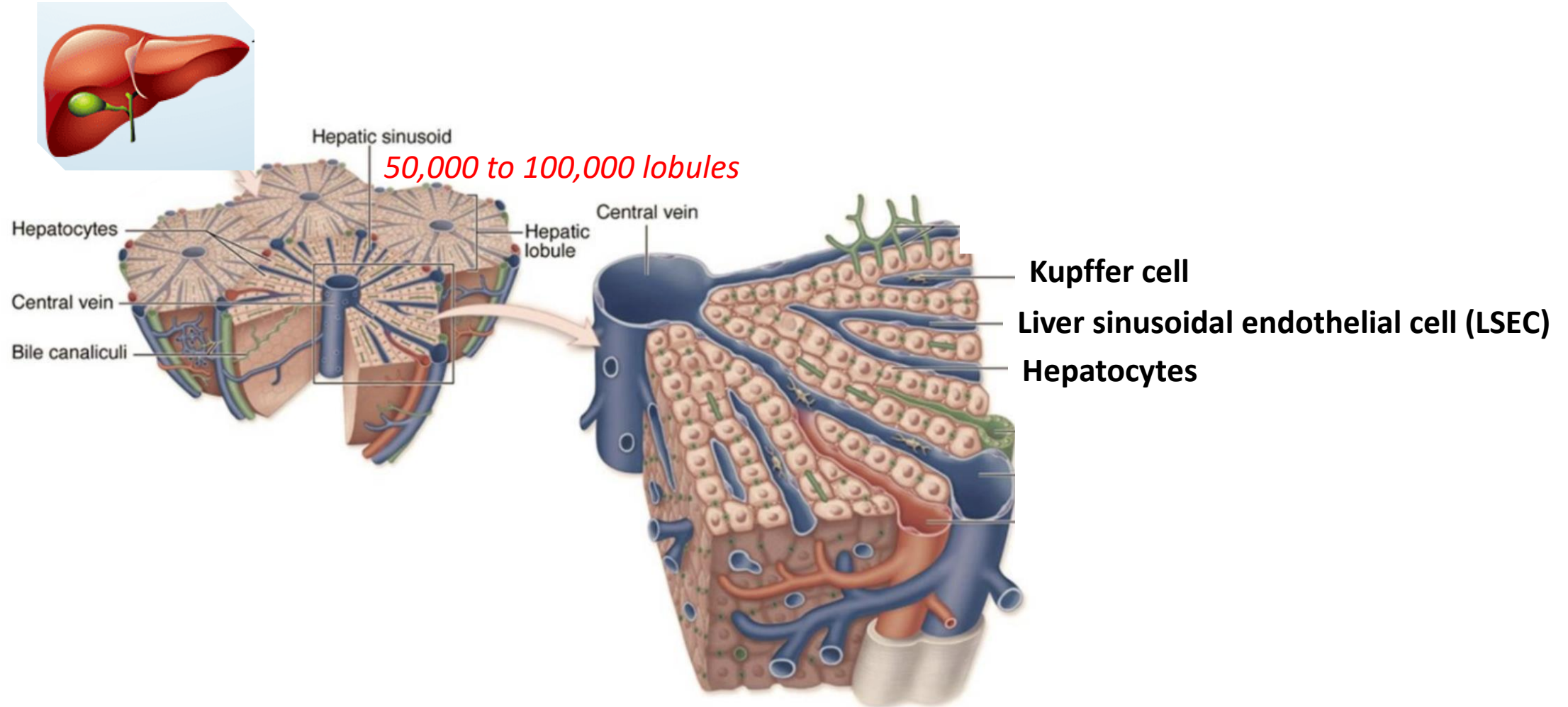
<https://metrohospitalfaridabad.com/blog/how-to-know-is-your-liver-healthy-or-not/>

Liver function

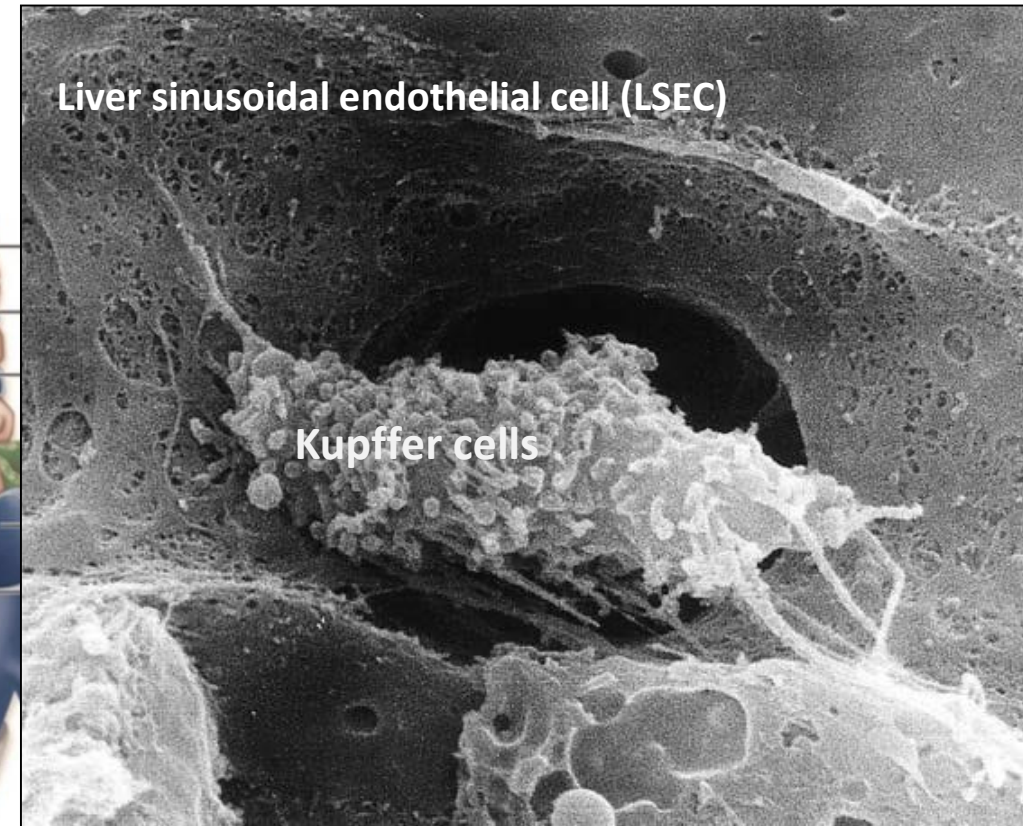
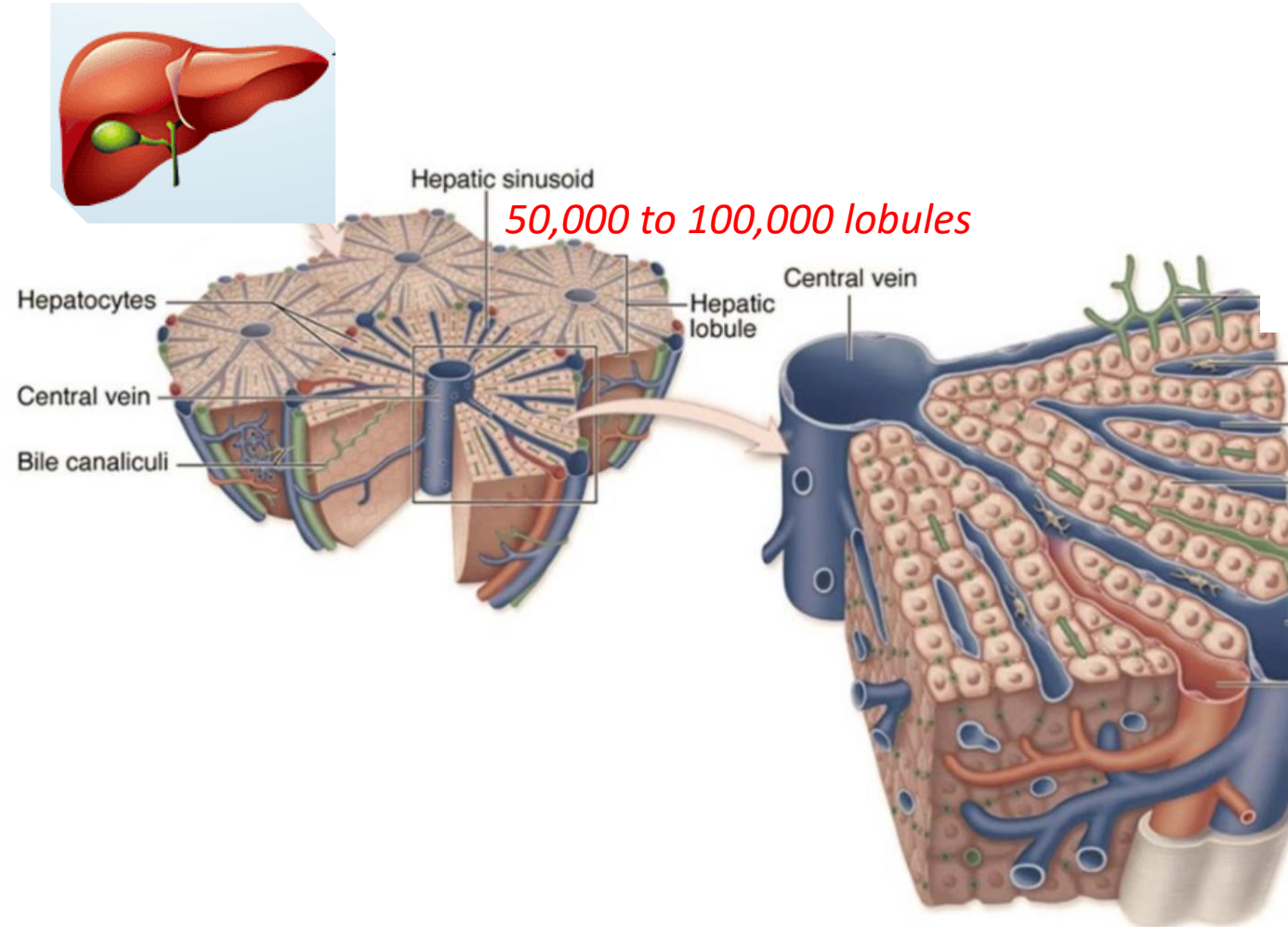
Drug
detoxification



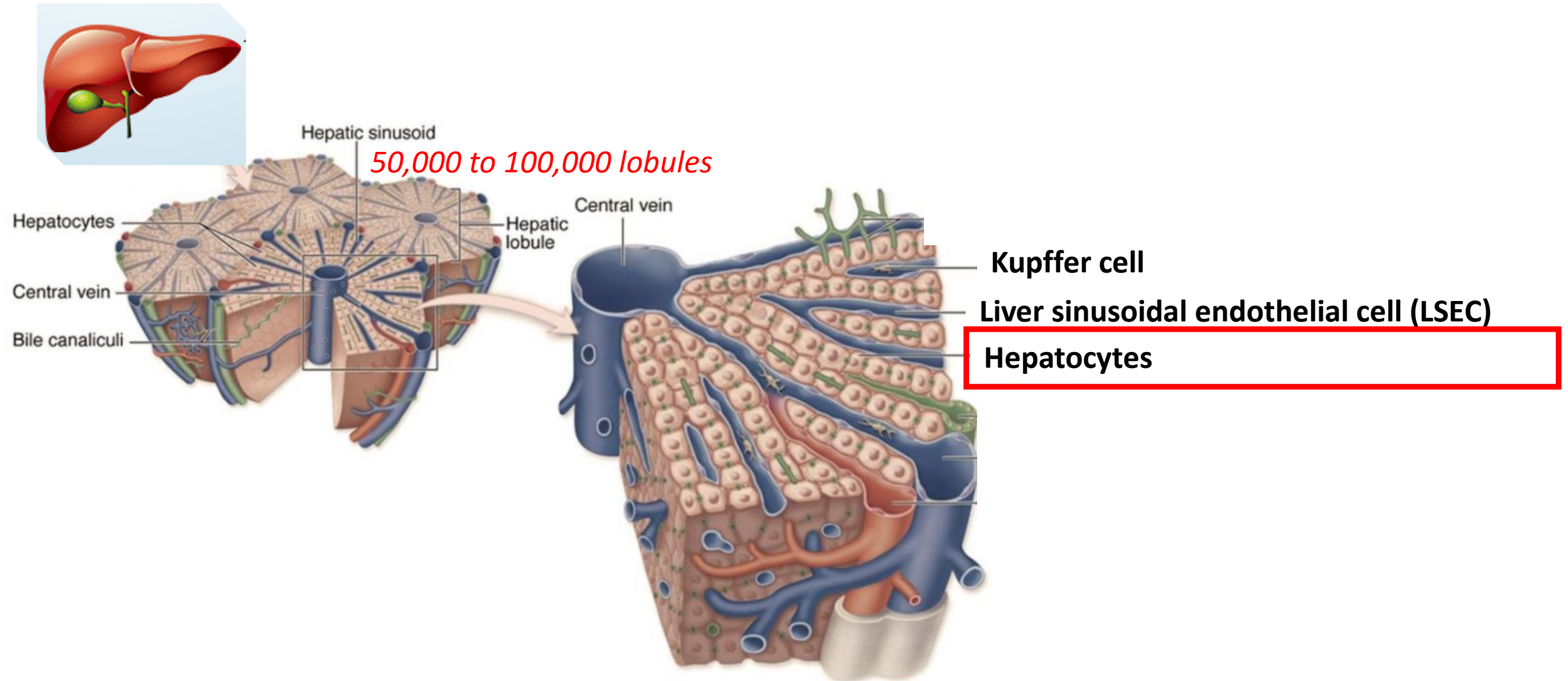
Architecture plus cell diversity = liver function



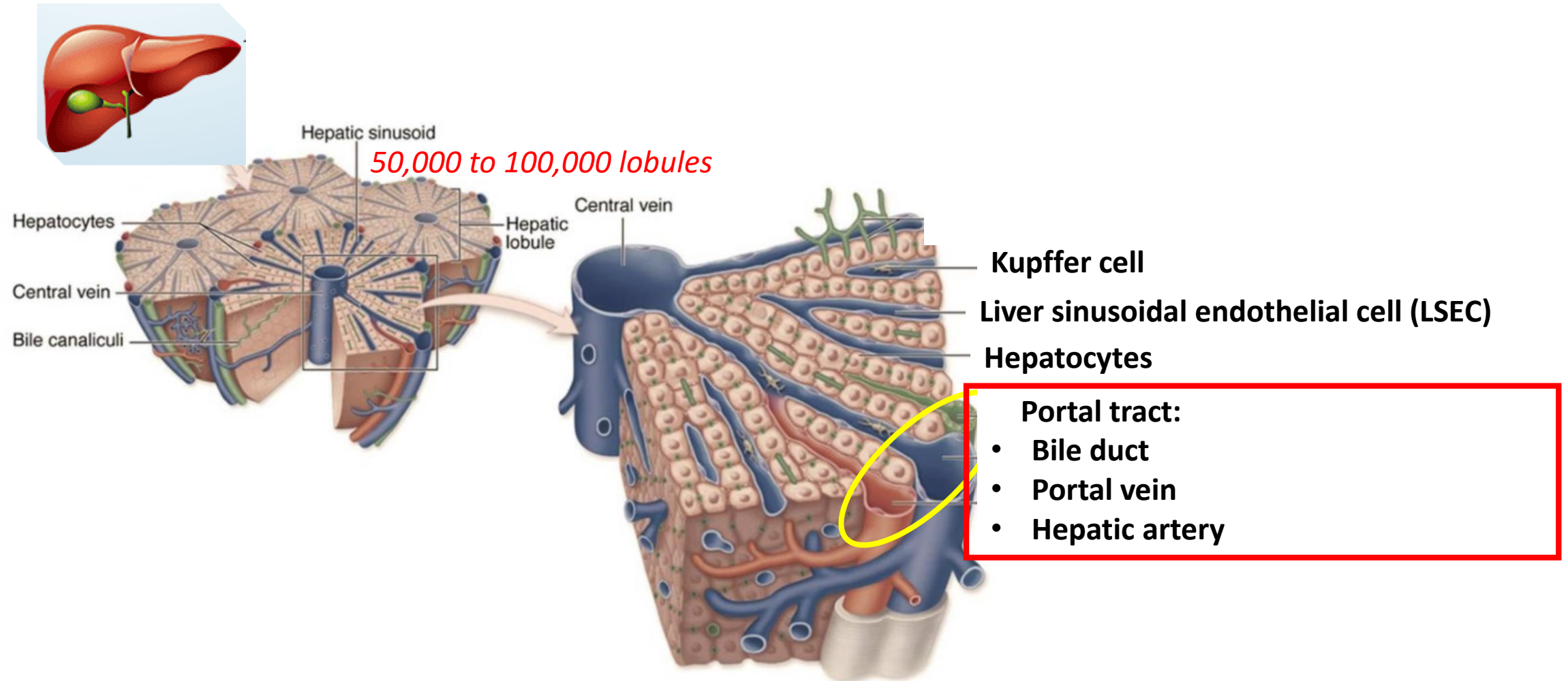
Architecture plus cell diversity = liver function



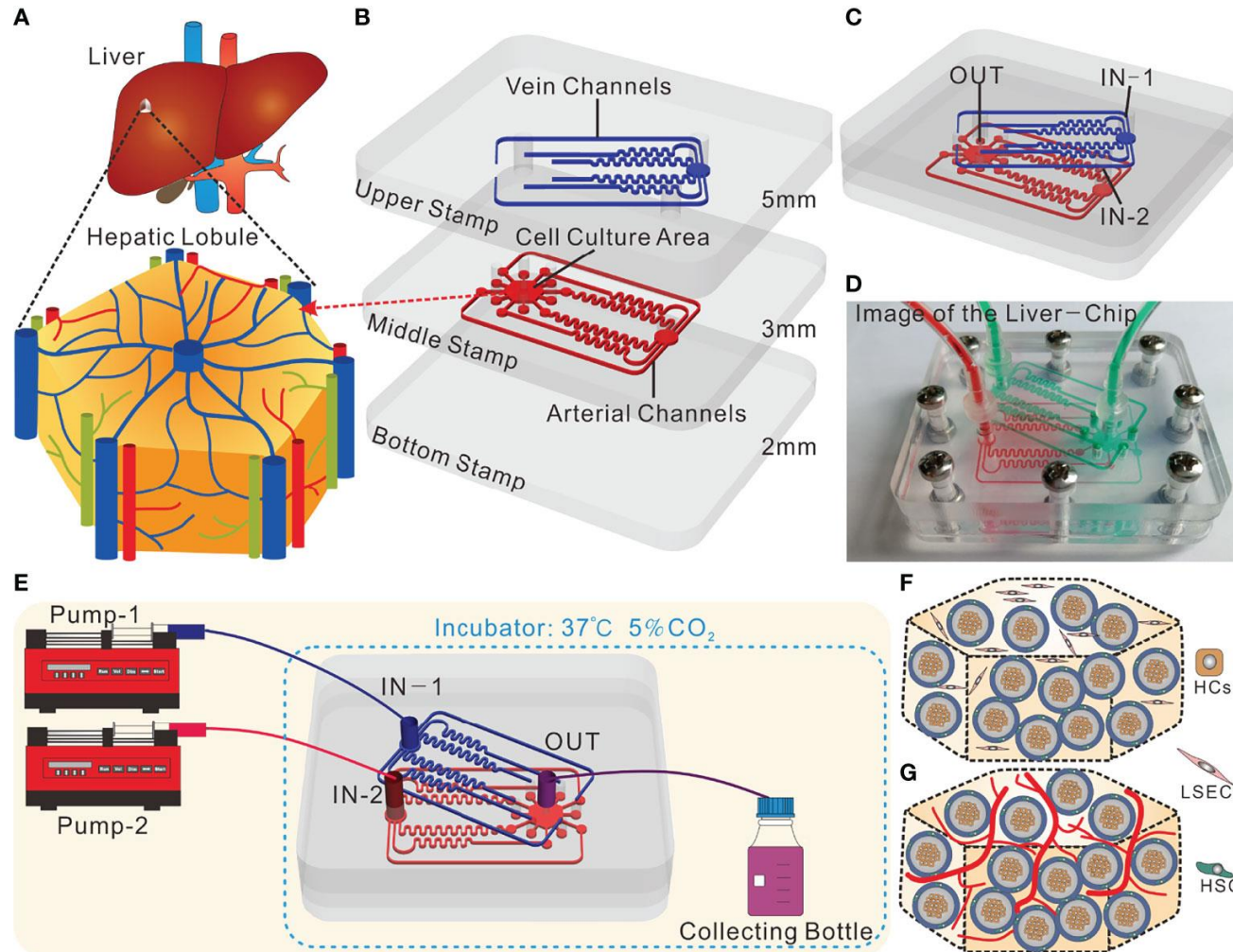
Architecture plus cell diversity = liver function



Architecture plus cell diversity = liver function



Liver-on-a-chip



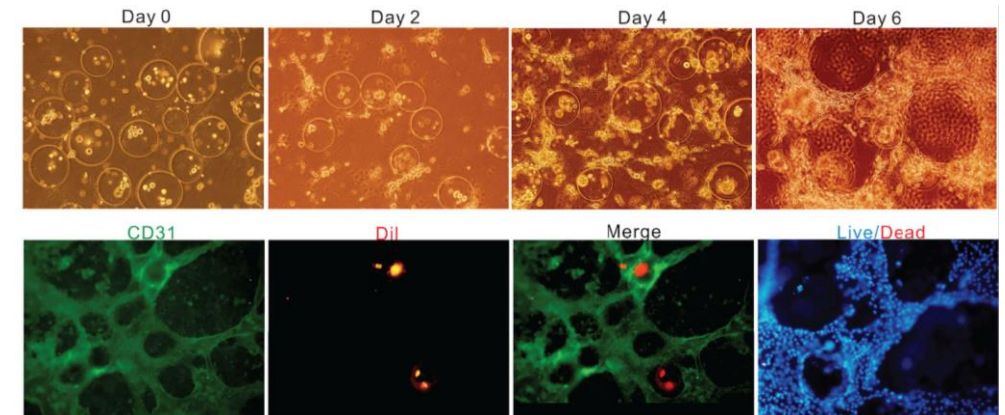
Tri-vascular LoC: Mimic hepatic lobule

Origin

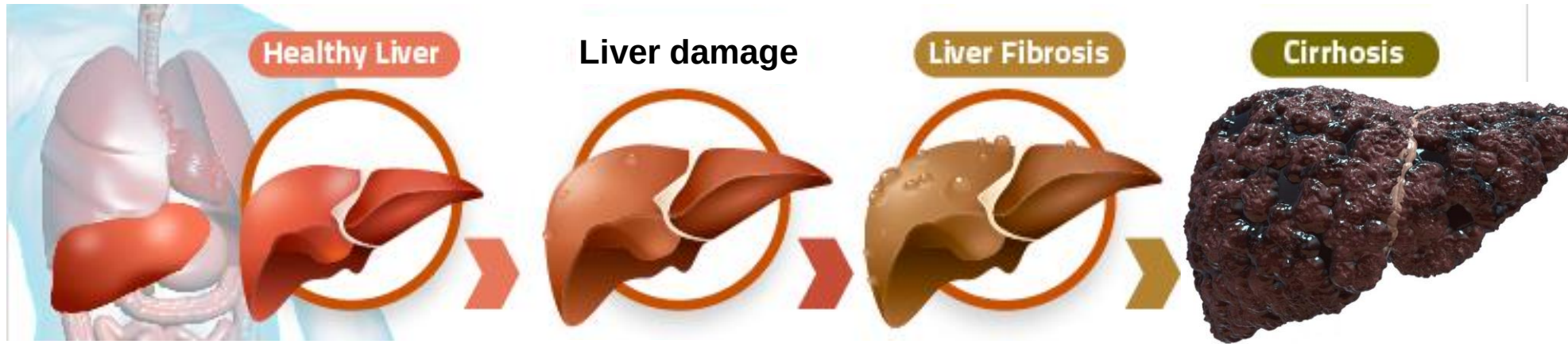
- Liver cells: LSECs, hepatocytes, HSCs

Key elements

- Bilayer **3D-organized cells**
- Simulation of **functional unit** on microfluidic chip
 - Portal vein, hepatic artery, and central vein
- Embed with matrix and growth factor
 - Survival and **LSEC vascularization**



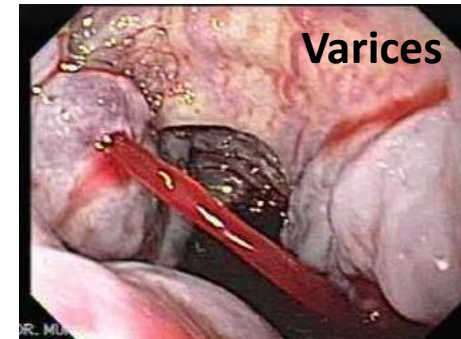
Stages of liver disease progression



- Virus
- Toxin
- Diet (high fat, high sugar)
- Alcohol
- Bile accumulation
- Drug overdose

Portal hypertension

Ascites
Esophageal varices
Hepatic encephalopathy



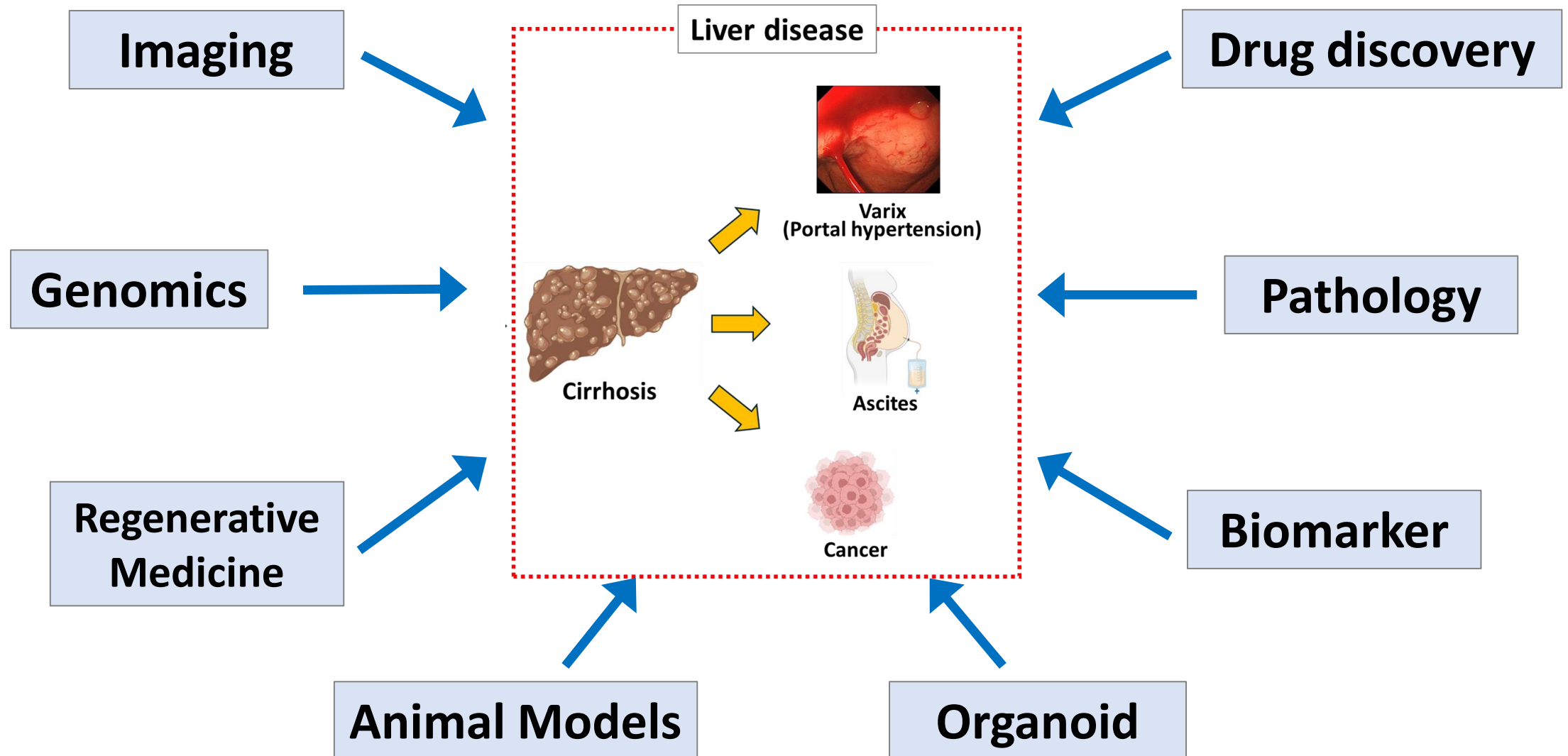
Hepatic encephalopathy



Section VI

Unmet Needs in Liver Research

Research approaches to liver diseases



Unmet Needs in Liver Research



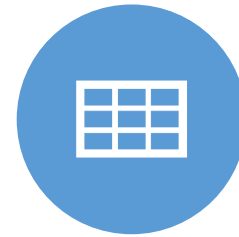
INCOMPLETE
MECHANISTIC
UNDERSTANDING.



ANIMAL MODELS FALL
SHORT.



LIMITED HUMAN-
RELEVANT
PLATFORMS.



FRAGMENTED DATA
ACROSS SYSTEMS.



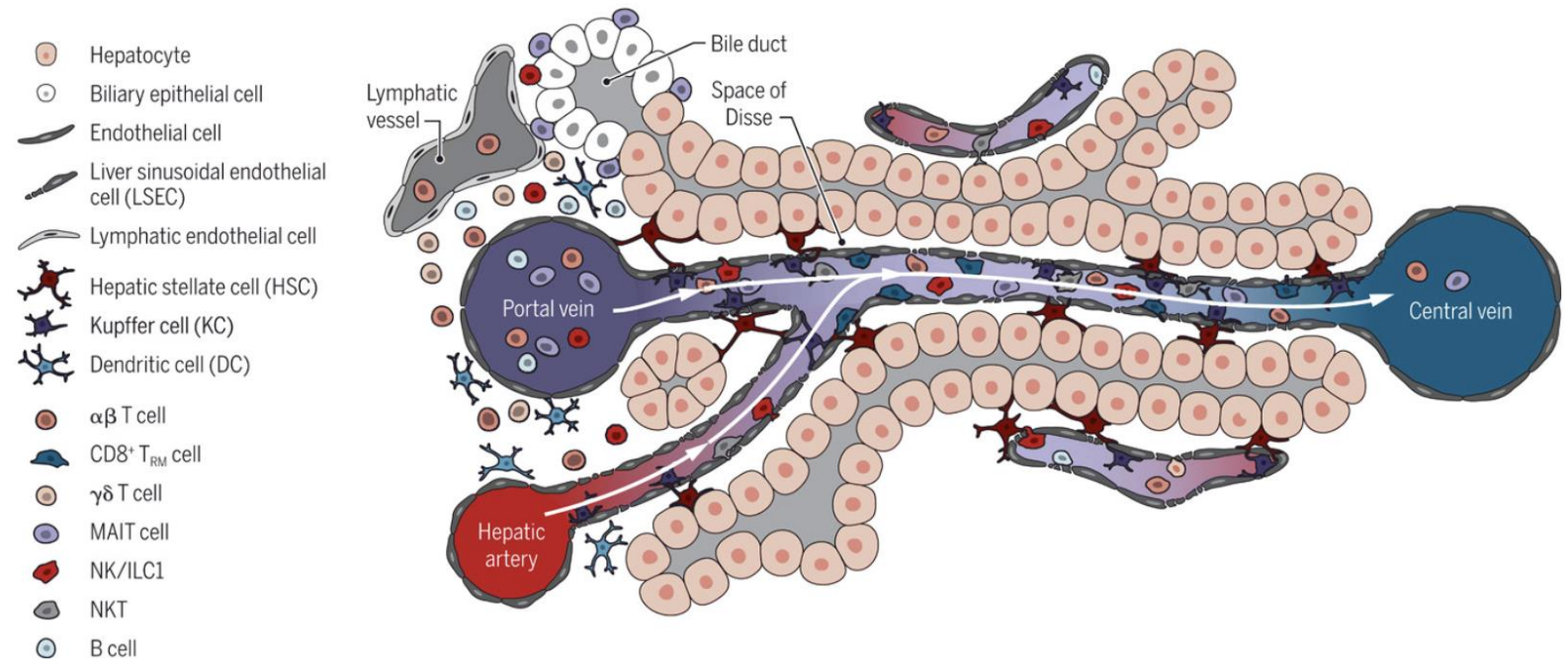
WEAK TRANSLATION
TO THERAPIES.

Unmet Needs in Liver Research



**INCOMPLETE MECHANISTIC
UNDERSTANDING.**

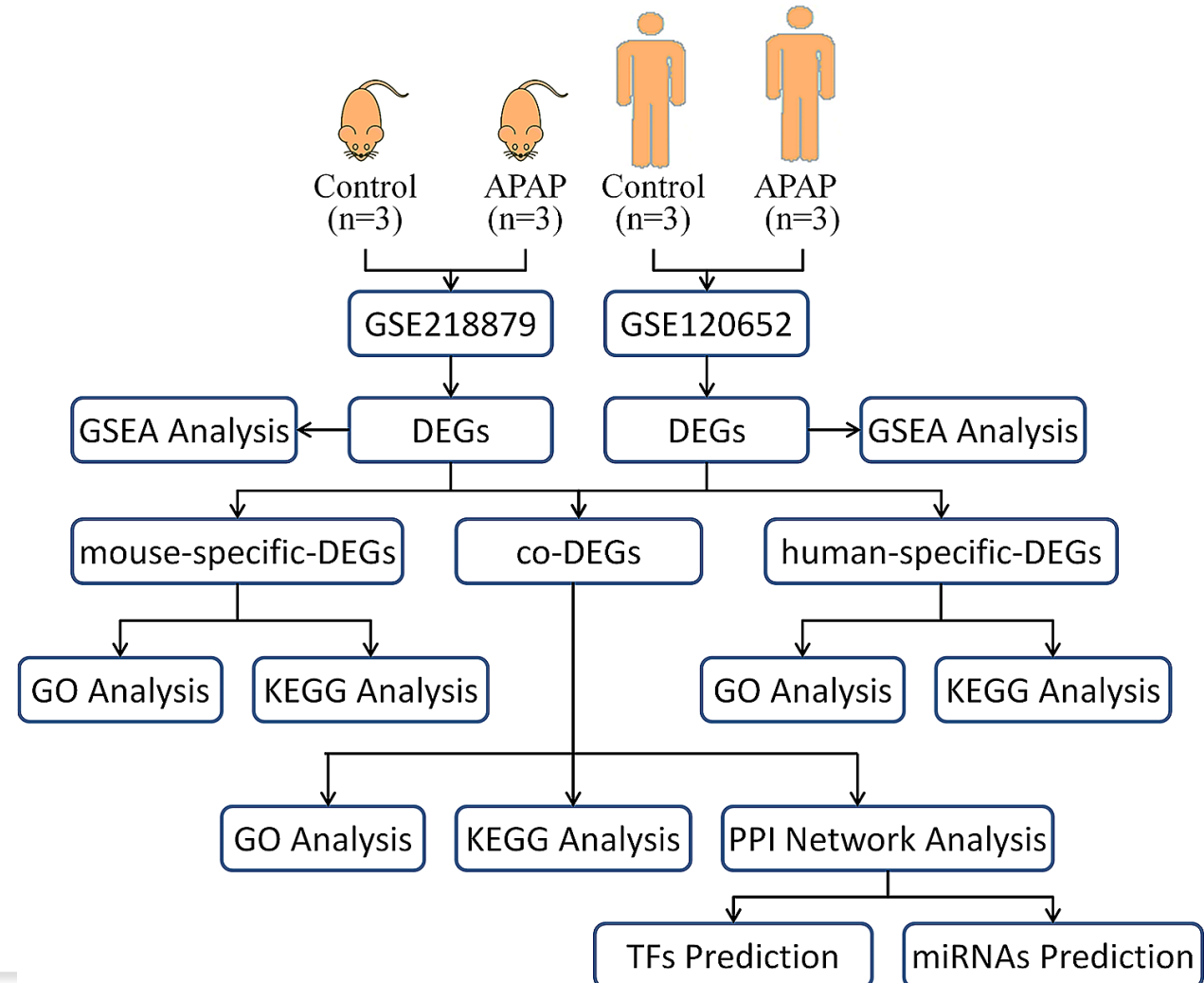
C Histology of liver parenchyma



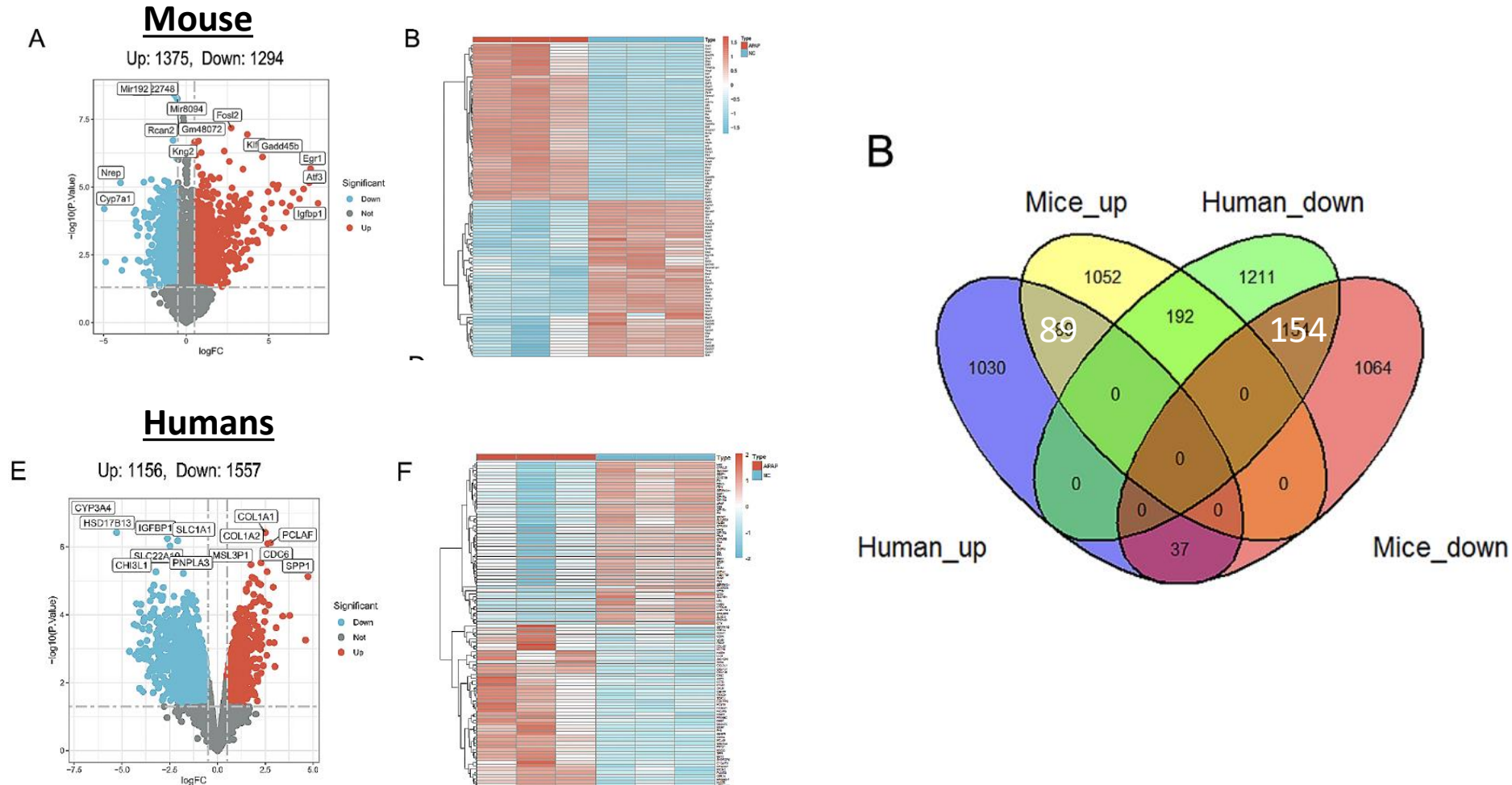
Unmet Needs in Liver Research



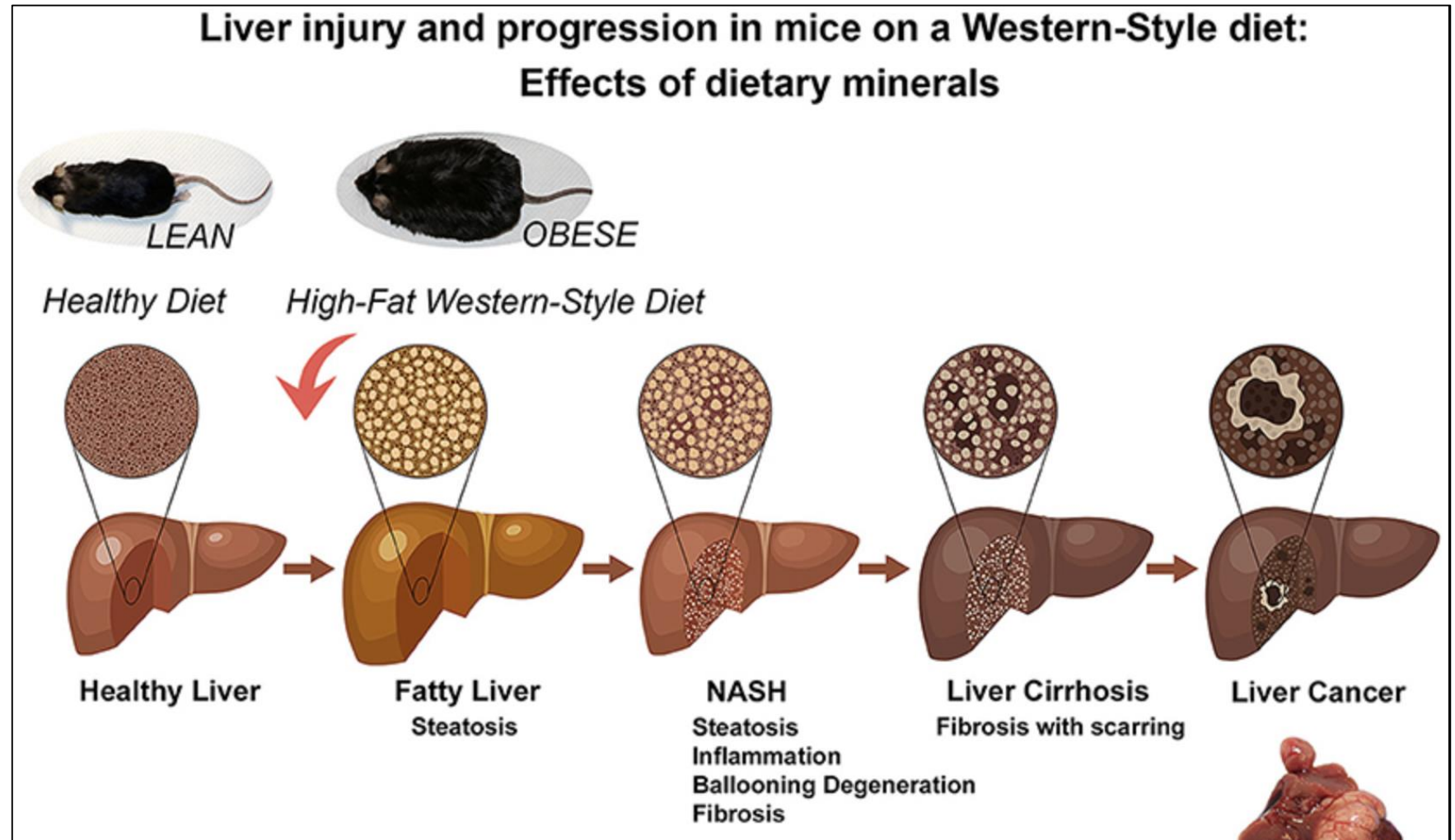
**ANIMAL MODELS FALL
SHORT**



Significant differences in gene expression in APAP-livers between mice and humans

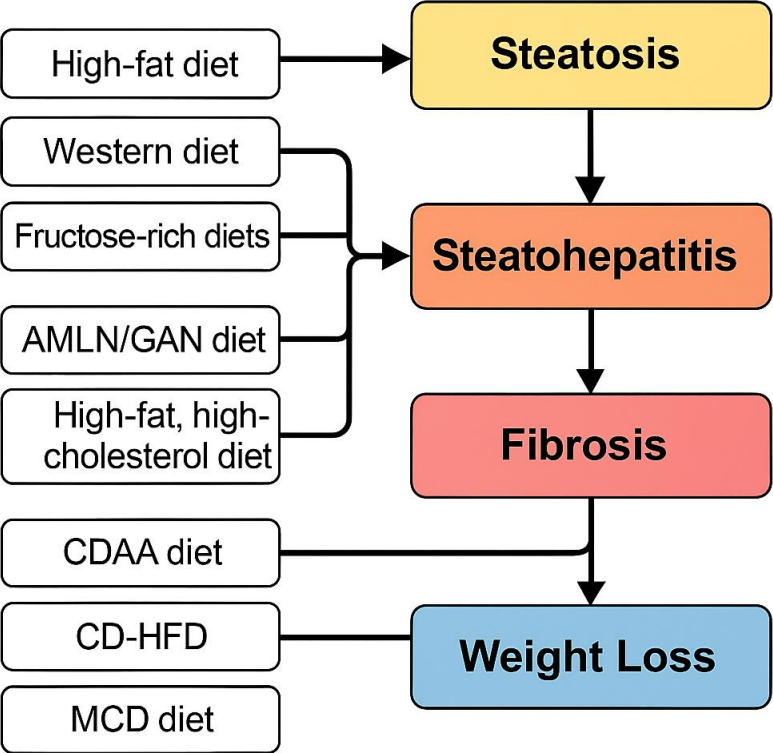


Example – Studies on MASLD (metabolic dysfunction-associated steatotic liver disease)



Many diets, many combination

– complex interpretation and wide variations

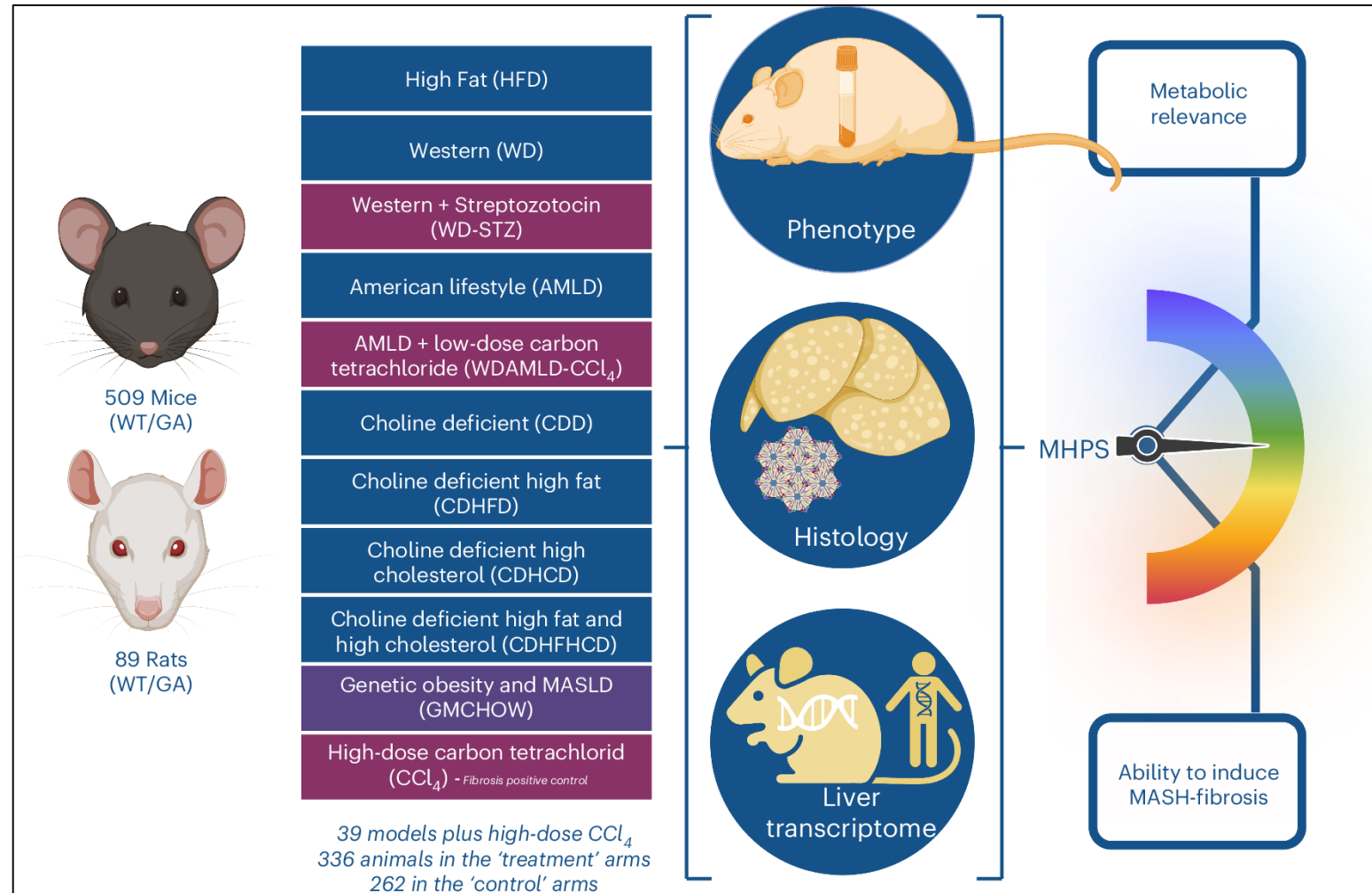


Vendor	Diet Name	Catalog Number	Key Features	Typical Phenotype	
Research Diets	Western Diet	D12079B	41% fat, sucrose-rich	Steatosis → mild NASH	
Research Diets	Fast-Food NASH Diet	D09100310	40% fat, 2% cholesterol, high fructose	Strong steatohepatitis	
Research Diets	AMLN Diet	D09100301	High fat, high cholesterol, high fructose	Obesity, IR, NASH, fibrosis	
Research Diets	GAN Diet	D17010101	AMLN update without trans-fat	NASH + fibrosis	
Research Diets	MCD Diet	D05010402	Methionine–choline deficient	Rapid steatohepatitis, weight loss	
Research Diets	CDAA Diet	D06011801	Choline-deficient AA-defined	Chronic fibrosis	
Research Diets	High-Fat Diet	D12492	60% fat	Obesity + steatosis	
Envigo/Teklad	Western Diet	TD.88137	High fat, high sucrose	Steatosis, mild NASH	
Envigo/Teklad	Western + Cholesterol	TD.160130	+1% cholesterol	Ballooning + inflammation	
Envigo/Teklad	NASH Variant	TD.180423	Western + cholesterol + fructose	Steatohepatitis + fibrosis	
Envigo/Teklad	High-Fat Diet	TD.06414	60% fat	Steatosis, obesity	
Envigo/Teklad	MCD Diet	TD.90262	Methionine–choline deficient	Rapid NASH	
Envigo/Teklad	CDAA Diet	TD.140709	Choline-deficient AA-defined	Fibrosis model	
Dyets	MCD Diet	518810	AIN-76 base	Rapid NASH	
Dyets	CDAA Diet	518754	L-AA defined	Chronic fibrosis	
Dyets	Cholesterol Diets	104779/104780	1–2% cholesterol	Inflammation, fibrosis	
Bio-Serv	Western Diet	F3666	High fat + sucrose	Steatosis / mild NASH	
Bio-Serv	HFHC NASH Diet	S3282	High fat + 1% cholesterol	Robust NASH	
Bio-Serv	MCD Diet	S4203	Methionine–choline deficient	Rapid NASH/fibrosis	

- Duration
- + • Mouse species
- Chemicals (CCl4, LPS, etc)

A study "An unbiased ranking of murine dietary models based on their proximity to human MASLD By Vacca et al. *Nature Metab.* 2024; 6(6): 1178-1196

- **Objective:** The study aimed to rank 39 murine dietary models based on their resemblance to human MASLD.
- **Methodology:**
 - Conducted a retrospective review of 598 animals (509 mice and 89 rats).
 - Evaluated models based on metabolic phenotype, liver histopathology, and transcriptome.
 - Developed the MASLD Human Proximity Score (MHPS) to rank models based on metabolic relevance and ability to induce MASH-fibrosis.



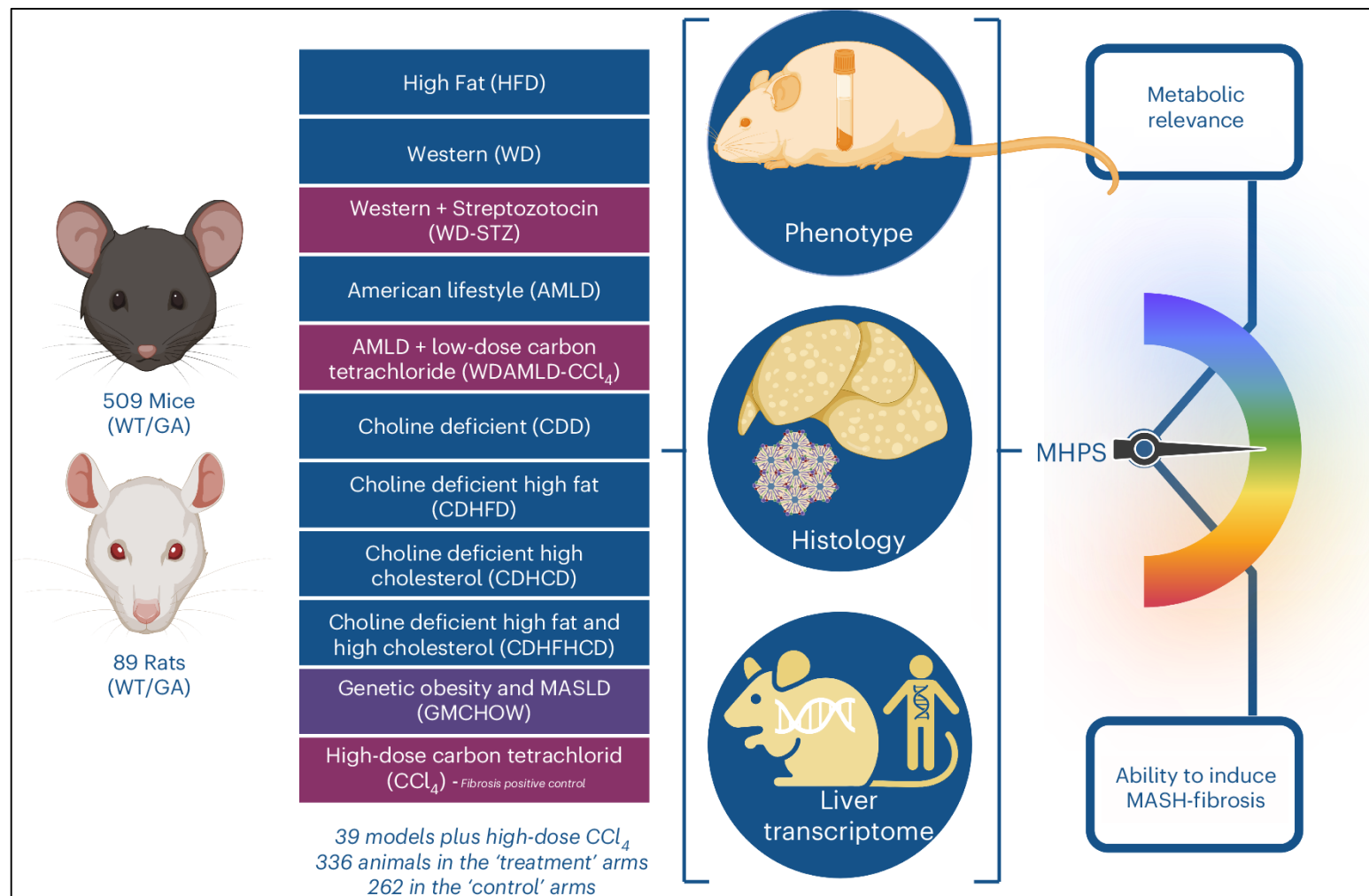
A study "An unbiased ranking of murine dietary models based on their proximity to human MASLD

By Vacca et al. *Nature Metab.* 2024; 6(6): 1178-1196

- **Key Findings:**

- Western diets closely align with human MASH.
- Choline-deficient models rapidly induce MASH-fibrosis within 12 weeks or less but show poor translatability to human disease.

- **Conclusion:** The ranking of murine models based on their proximity to human MASLD aids in selecting appropriate *in vivo* models to accelerate preclinical research.

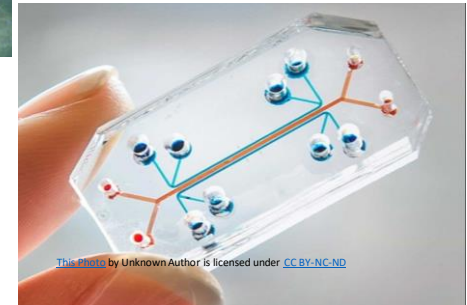
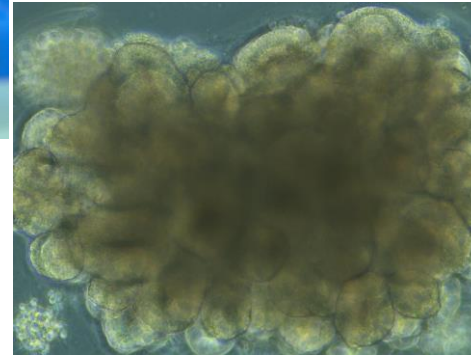
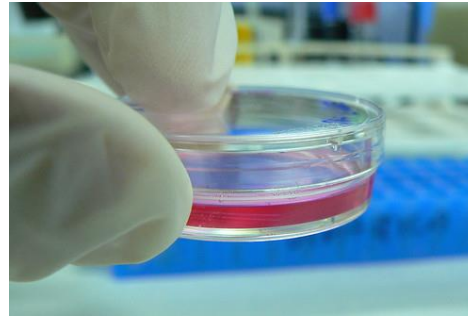


Unmet Needs in Liver Research

* Not fully capture in vivo complexity or reproducibility.



**LIMITED HUMAN-
RELEVANT PLATFORMS.**



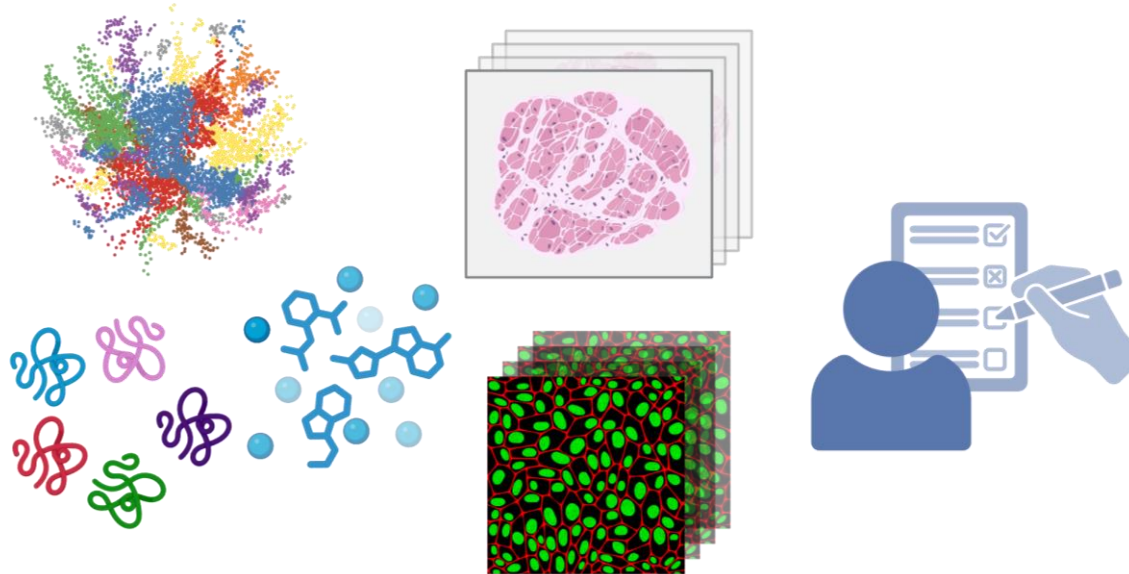
This Photo by Unknown Author is licensed under [CC BY-NC-ND](#)

Unmet Needs in Liver Research



**FRAGMENTED DATA
ACROSS SYSTEMS.**

* Different type of data - omics, imaging, and clinical records – sit in separate places, so it's hard to put them together a coherent picture of how disease evolves.



Unmet Needs in Liver Research



**WEAK TRANSLATION
TO THERAPIES.**

* Mechanistic insights rarely advance to clinical testing, and reliable biomarkers for progression or treatment response remain scarce.

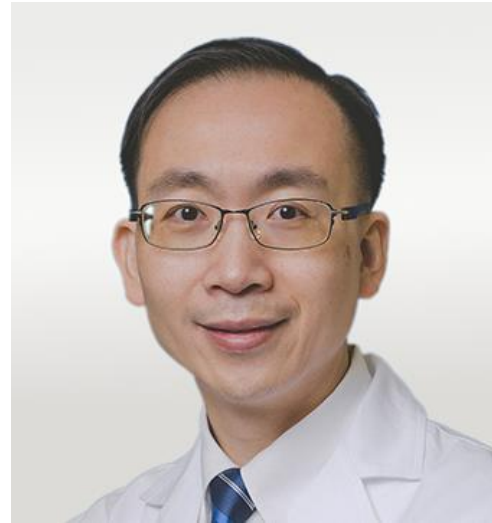


Section VI

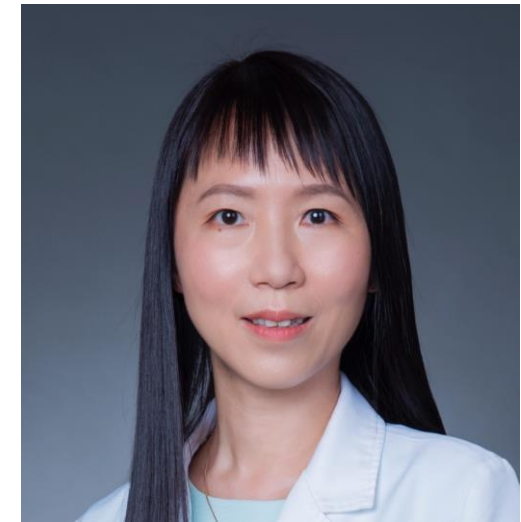
Real-World Examples in Liver Research



Dr. Terry Yip



Dr. Vincent Wong



Dr. Grace Wong

Foundations of Artificial Intelligence in Hepatology: What a Clinician Needs to Know[☆]

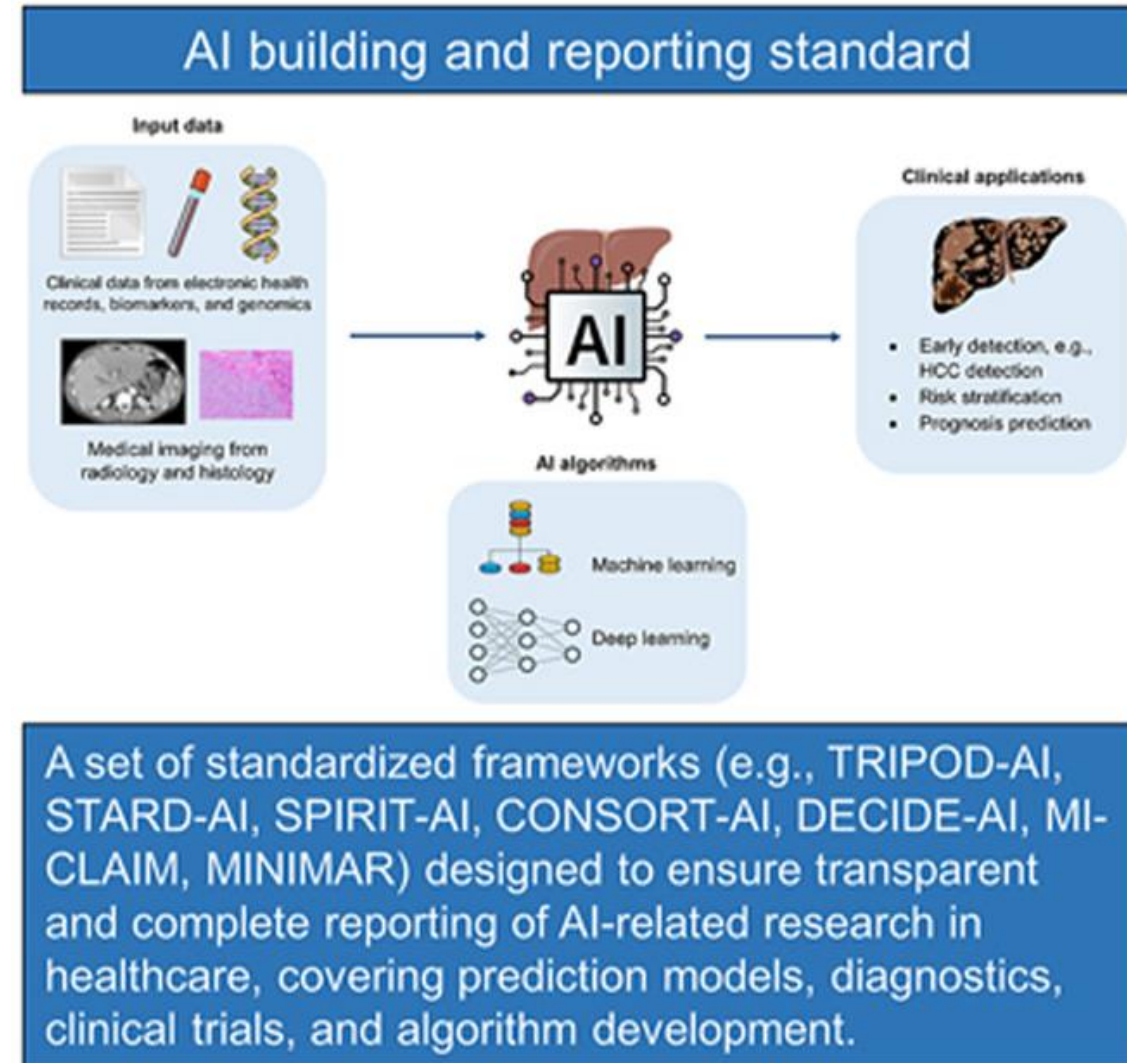


Nana Peng^{*,†,a}, Sherlot J. Song^{*,†,a}, Vicki Wing-Ki Hui^{*,†}, Jimmy Che-To Lai^{*,†,‡,§}, Grace Lai-Hung Wong^{*,†,‡},
Vincent Wai-Sun Wong^{*,†,‡}, Terry Cheuk-Fung Yip^{*,†,‡,§}

Journal of Clinical and Experimental Hepatology. 2026; 16(1): 103183

Foundations of AI in Hepatology

- **Overview:** AI's role in transforming hepatology through enhanced diagnosis, risk assessment, and management of liver diseases using large-scale data
- **Highlights:** AI improves detection accuracy for liver conditions and offers personalized risk stratification and treatment guidance
- **Key takeaways:** AI can revolutionize hepatology, but successful integration requires collaboration and understanding of AI vs. traditional statistics.
- **Future Directions:** Focus on integrating AI into clinical workflows, addressing data and privacy challenges, and establishing best practices for AI use in hepatology



AI-driven Innovation in Liver Disease Diagnosis: The ALADDIN Model

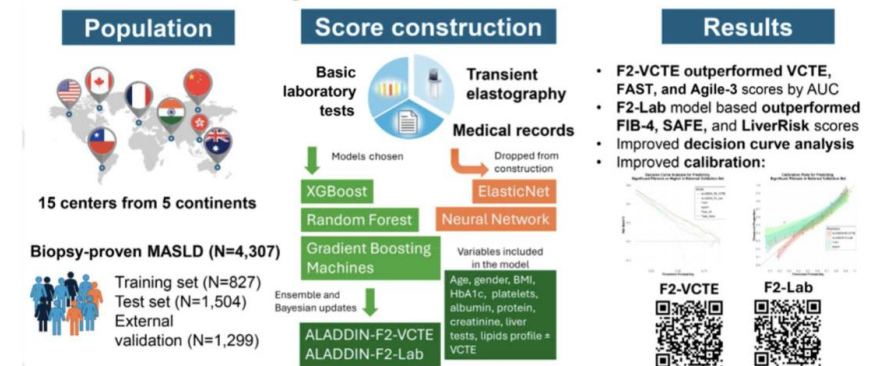
- **Overview:** AI-driven clinical research in liver disease, focusing on predicting significant fibrosis in MASLD
- **Methodology:** Integrates routine lab parameters with/without VCTE, offering a noninvasive, accurate and accessible approach
- **Key outcomes:** ALADDIN model outperforms existing diagnostic methods; enhances patient selection for treatment like resmetirom.

ALADDIN: A Machine Learning Approach to Enhance the Prediction of Significant Fibrosis or Higher in Metabolic Dysfunction-Associated Steatotic Liver Disease

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ALADDIN: A Machine Learning Approach to Enhance the Prediction of Significant Fibrosis in MASLD



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Section VII

Key Takeaways

Key Takeaways 1:

Where the Unmet Needs Really Are



We still don't capture biological complexity well enough.

Most models miss the multi-layered signaling and cell–cell interactions that drive real disease.



Human relevance is still limited.

We rely heavily on systems that don't fully reflect human physiology, which slows translation.



Our data are scattered.

Omics, imaging, and clinical information live in different places and don't talk to each other, making it hard to build a complete picture.

Key Takeaways 2:

Where the Unmet Needs Really Are



Reproducibility lags behind discovery.

Missing metadata, inconsistent protocols, and siloed datasets weaken otherwise strong science.



Mechanistic insight is slow to emerge.

We often identify associations but struggle to connect them to real causal pathways.



Clinical translation remains the final hurdle.

Even with rich datasets, we struggle to predict who progresses, who responds, and why.



Q & A

