

Organ Pathobiology and Therapeutics Institute

Liver Acinus Microphysiological System (LAMPS) for Determining Drug Candidate Dosing in Clinical Trials of Liver Disease

Multi-Pis:

Mark Schurdak, PhD - OPTIn, Dept Comp & Sys Bio (Contact PI)

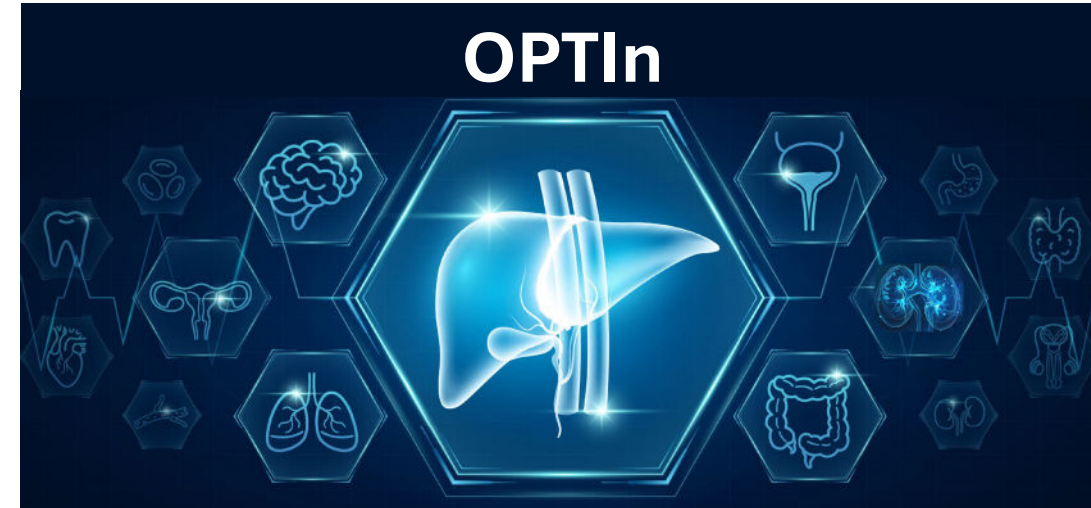
D. Lansing Taylor, PhD – OPTIn, Dept Comp & Sys Bio

Mark Miedel, PhD - OPTIn, Dept Pharmacology and Chemical Biology

Lawrence Verneti, PhD - OPTIn, Dept Comp & Sys Bio

27th NIH Tissue Chip Consortium Meeting and CIVM Qualification Public Workshop

March 5, 2026



[Pitt Trace](#)

Understanding How to Effectively Translate Pharmacokinetic Data From Healthy Volunteers to a Patient Population With Liver Disease to Inform Decisions on Dosing Is an Unmet Need



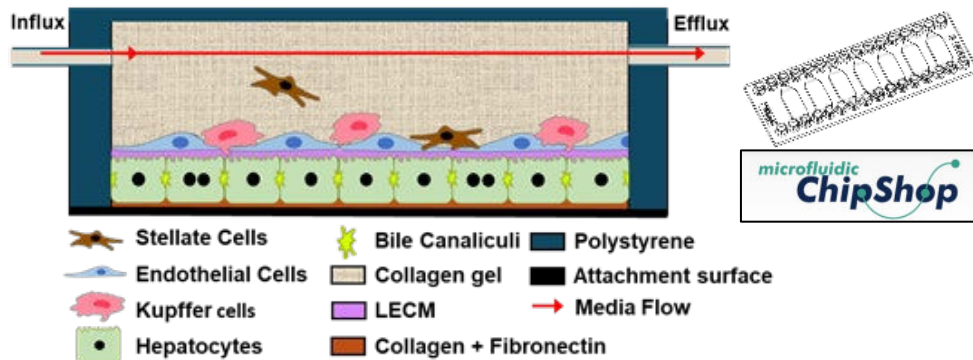
- “Until a sponsor can characterize a drug’s initial tolerability, preliminary safety, and pharmacokinetics, patients with evidence of abnormal liver synthetic function should be excluded from early phase trials (i.e., phase 1 and early proof-of-concept (POC) clinical trials).” (*FDA Guidance NASH drug development, 2018*)
- “. . . sponsor should study the effects of hepatic impairment on the drug’s pharmacokinetics early during the drug development program in a dedicated hepatic study to support appropriate dosing and dose adjustment across the spectrum of NASH liver disease.” (*FDA Guidance NASH drug development, 2018*)
- “Despite extensive efforts, no single measure or group of measures has gained widespread clinical use to allow estimation in a given patient of how hepatic impairment will affect the PK and/or PD of a drug.” (*FDA Guidance PK in patients with hepatic impairment, 2003*)
- There are no generally available tests to correlate drug disposition changes with degree of hepatic impairment. (*Zgheib et. al., Atkinson’s Principals of Clinical Pharmacology, 2022*)

Goal: Qualify Our Biomimetic Liver MPS Platforms as a Drug Development Tool (DDT) to address this unmet need

CoU: The LAMPS is a DDT to establish the hepatic clearance of drug candidates in patients with MASLD and assist in the determination of drug candidate dosing in clinical trials when patients with MASLD are included.

Overview of the Liver Acinus MPS (LAMPS) Platform as a DDT For Assessing Drug Candidate Clearance

Liver Acinus Microphysiology Systems (LAMPS)



- 3D layered biomimetic constructed with four liver cell types
 - Tight junctions and bile canaliculi
 - Space of Disse
 - Extracellular matrix facilitating intercellular communication, and cellular polarity
- Amenable to inducing disease states
 - e.g., metabolic dysfunction-associated steatotic liver disease (MASLD) stages F0 – F3.
- Applications include:
 - ADME-Tox studies
 - Studying liver disease progression
 - Precision medicine platform with patient iPSC derived liver cells

The four hepatic cell types are necessary for inducing the disease state

- Hepatocytes – accumulates lipid, are the drug metabolizing cells.
- Liver sinusoidal endothelial cells (LSECs) – contribute to the pro-inflammatory response.
- Hepatic stellate cells (HSCs) – contribute to fibrotic response.
- Kupffer-like cells (KCs) - resident macrophage immune cells initiate the immune response.

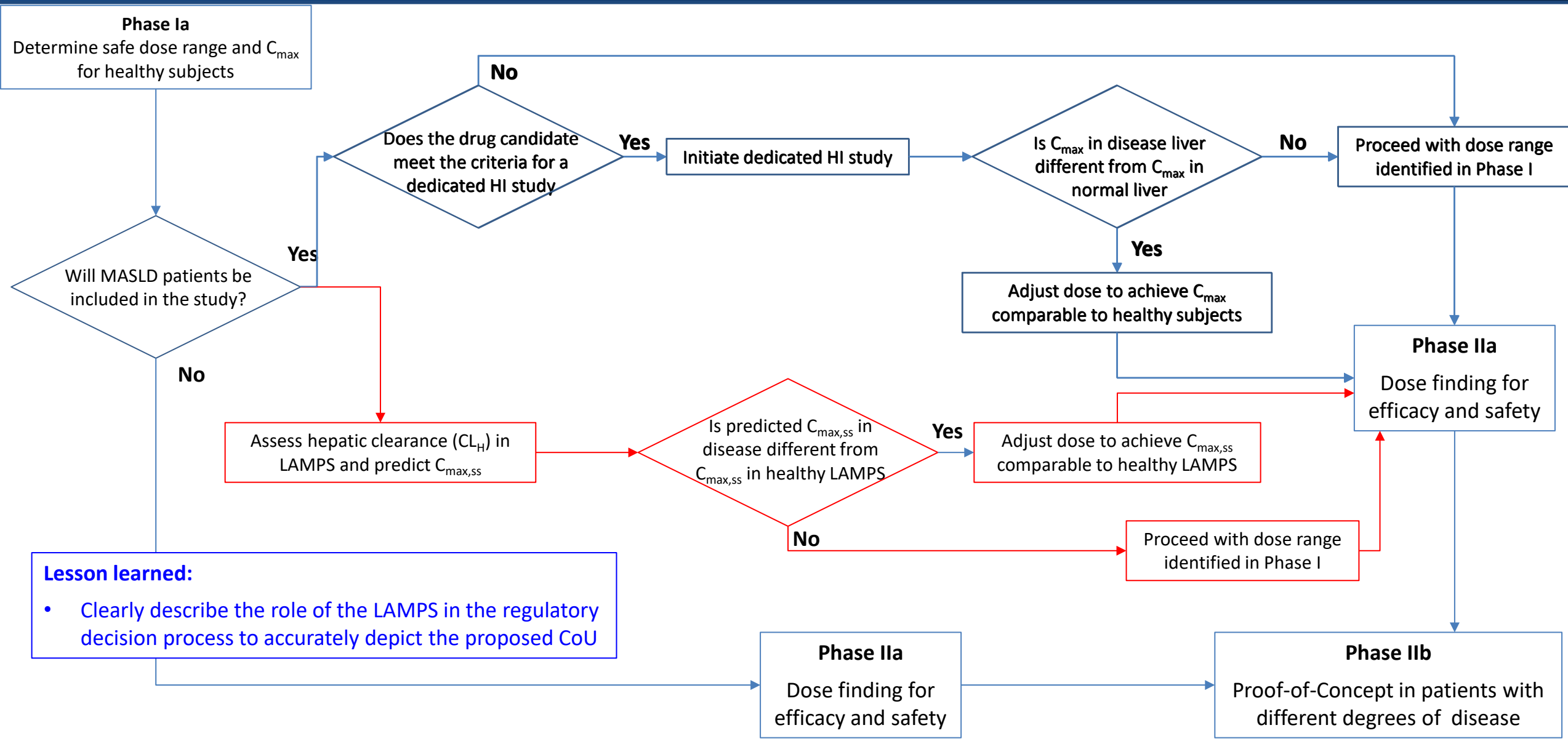
Advantages of the LAMPS for predicting hepatic clearance and drug metabolism.

Parameter	Primary hepatocytes and microsomes	LAMPS
Cell disease state	Healthy	Healthy and/or induced to disease
Metabolic stability	Limited to few hours	Prolonged over days
Drug exposure	Non-steady state	Steady state and non-steady state
Metabolic format	Single cell or simple enzyme mixture	Multi-cell biomimetic architecture with metabolic zonation

Lessons learned:

- Explain the role of all of the cell types in the LAMPS.
- Justify why this NAM is better than a more simplified hepatocyte only model.
- Define the limitations of the LAMPS.

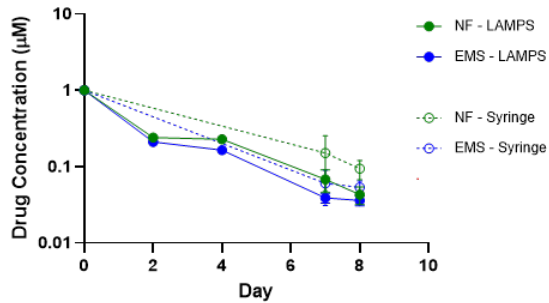
The LAMPS DDT Is to Be Used as a Co-Decisional Tool to Recommend Dose Adjustment in MASLD Patients



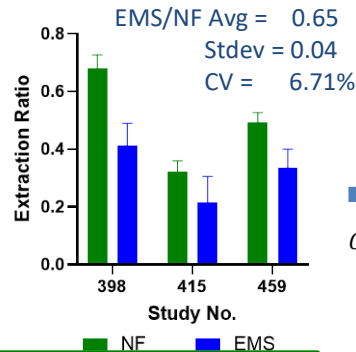
Analytical Approach for Recommending Dose Adjustments in MASLD Using the LAMPS

1. Establish the LAMPS performance

- Cell viability
- Hepatocyte function
- MASLD induction



$$ER = \frac{Conc_{in} - Conc_{out}}{Conc_{in}}$$



3. Determine hepatic extraction ratio

Lessons learned:

- Be comprehensive in describing the analytical approach.
- Provide methods for the calculations.
- Provide analytical reference criteria.
- Provide data for every step in the workflow.

$$CL_H \left(\frac{ml}{min} \right) = ER \times Q \times \frac{N_{cells}}{g \text{ liver}} \times \frac{1}{ND_{cells}} \times g \text{ liver}$$

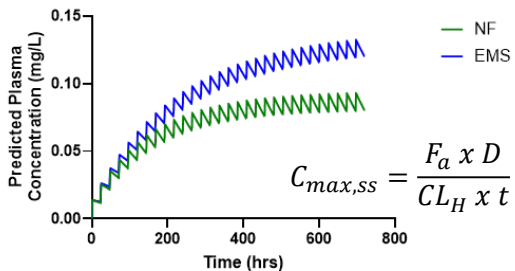
Prediction of Omeprazole hepatic clearance.

Parameter	NF	EMS
Chip (µM)	0.043 ± 0.011	0.036 ± 0.005
Syringe (µM)	0.094 ± 0.026	0.054 ± 0.011
ER	0.498 ± 0.103	0.321 ± 0.057
Predicted CL _H (ml/min)	60.5 ± 12.5	38.9 ± 6.9

Mean ± SEM, n = 3 studies.

2. Measure drug conc.

4. Predict hepatic clearance (CL_H)



$$D_{adj} = D_i \div \frac{C_{max,ss} \text{ disease}}{C_{max,ss} \text{ non-disease}}$$

Recommendation for Omeprazole dose adjustment.

Parameter	NF	EMS
CL _H (ml/min)	60.5 ± 12.5	38.9 ± 6.9
C _{max,ss} (mg/L)	0.088 ± 0.019	0.134 ± 0.026
C _{max,ss} normalized to NF	-	1.54 (5.9%)
Adjusted Dose (mg)	20	13.0 (5.7%)

Mean ± SEM, n = 3 studies.

5. Simulate drug plasma concentration

6. Calculate dose adjustment

Drugs for LAMPS DDT Validation Were Chosen Based on Dose Recommendations Reported in the Literature

Drug	Dose Adjustment Recommendation
Atorvastatin	Contraindicated in active liver disease
Resmetirom	Reduce
Omeprazole	20 → 10 mg
Acetaminophen	↓ max daily dose by 50%
Paclitaxel	135 → 100 mg/m ²
Azithromycin	No dose adjustment
Metformin	No dose adjustment
Ciprofloxacin	No dose adjustment

Lessons learned:

- Justify the number and selection of drugs for validation.
- Include drugs with a wide degree of clinical dose adjustment needs.
- Reference quantitative clinical data.

Calibrate the LAMPS Phenotypes With Clinical Disease Stage to Identify Patient Population That Would Benefit From the Recommendations

Clinical fibrosis staging metrics.						
Fibrosis Score	NASH-CRN NAS Score	FibroScan (Median)	Steatosis Stage	Lobular Inflammation Stage	Hepatocyte Ballooning Stage	Inflammation Biomarkers
0	None	5.3 kPa	0, 1	0, 1	0	
1	Mild - moderate Zone 3	6.5 kPa	2	0, 1	0, 1	
2	Zone 3, Zone 1	7.0 kPa	2	1, 2	1, 2	IL1 β , IL-6, IL-8, MCP-1, and TNF α are increased in F2 – 4 relative to F0-F1.
3	Bridging fibrosis	10.1 kPa	3	1, 2	2	IL-8, MCP-1, and TNF α are associated with increased ballooning.
4	Cirrhosis	20.9 kPa	3	1, 2	2	IL-1 β increase is associated with increased lobular inflammation. MCP-1 decrease is associated with increased lobular inflammation.

Lessons learned:

- Keep the clinical context in mind.
- Link the *in vitro* metrics to clinical metrics to establish concordance.

Other Lessons Learned

1. Keep up with FDA updates on their website.
2. Take a learn and confirm approach when establishing the clinical concordance of the platform.
3. Recommendations from the DDT should be categorical and not specific numbers.
4. Number of studies required and amount of data being analyzed is greater than originally anticipated.
5. Data management in a standardized database makes analysis more tractable.
6. SOPs are important – need to strive for GLP-like performance to maintain consistency.
7. Know the specific characteristics of the drugs, samples, and analytes.

How Well Have We Learned the Lessons?

We look forward to feedback from I STAND.

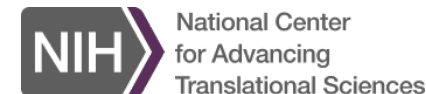
Acknowledgements

Organ Pathobiology and Therapeutics Institute (formerly University of Pittsburgh Drug Discovery Institute)

D. Lansing Taylor, PhD – MPI (Commercialization and automation)
Mark Schurdak, PhD- MPI (Pharmacologist and Database)
Larry Verneti, PhD -MPI (Toxicologist)
Mark Miedel, PhD - MPI (Liver MPS Systems)
Bert Gough, PhD -Co-I (Imaging and Database)
Andy Stern, PhD -Co-I (Therapeutic Strategies)
Jacquelyn Brown, PhD – Co-I (Liver MPS Systems)
Mahboubeh Varmazyad, PhD – Co-I (Liver MPS Systems)
Vinny Negi, PhD – Co-I (Liver MPS Systems)
Summer Xia - Grad Student (Computational Biology)
Julio Aleman - Grad Student (Bioengineering)
Richard DeBiasio - Staff Researcher
Greg LaRocca - Staff Researcher
Allen Wang – Staff Researcher
Dillon Gavlock - Staff Data Scientist/Imaging Specialist
Celeste Reese - Project Manager

UPMC Liver Steatosis and Metabolic Wellness Program Jaideep Behari, MD, PhD - Director

Pittsburgh Liver Research Institute Satdarshan Singh Monga, MD – Director



- **U2CTR004863**
- **1U01FD008657**
- **5R01DK117881**
- **1UG3TR003289-**
- **4UH3DK119973**
- **1UH2TR004124**