

Agent-based models of immune-mediated P450 down-regulation using modularity and integration techniques

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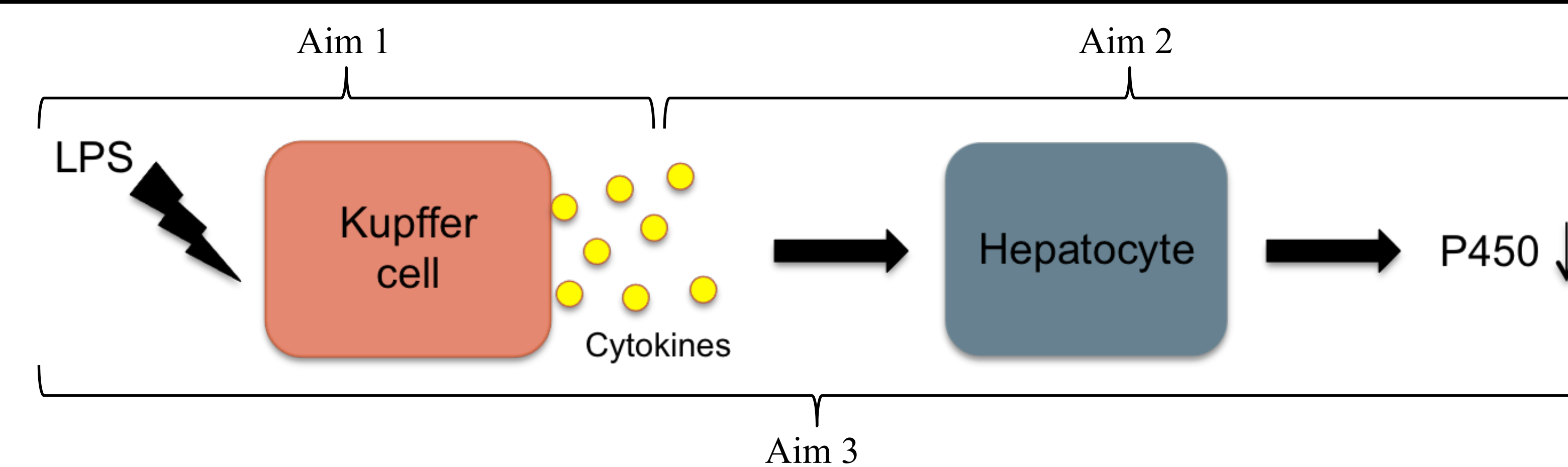
Abstract

We use synthetic, agent-based modeling and simulation methods to instantiate and challenge concrete, mechanistic hypotheses. The objective is to explore plausible mechanisms of the roles of immune system components in drug metabolism. We achieve validation targets for several in silico mechanisms using a variety of wet-lab data.

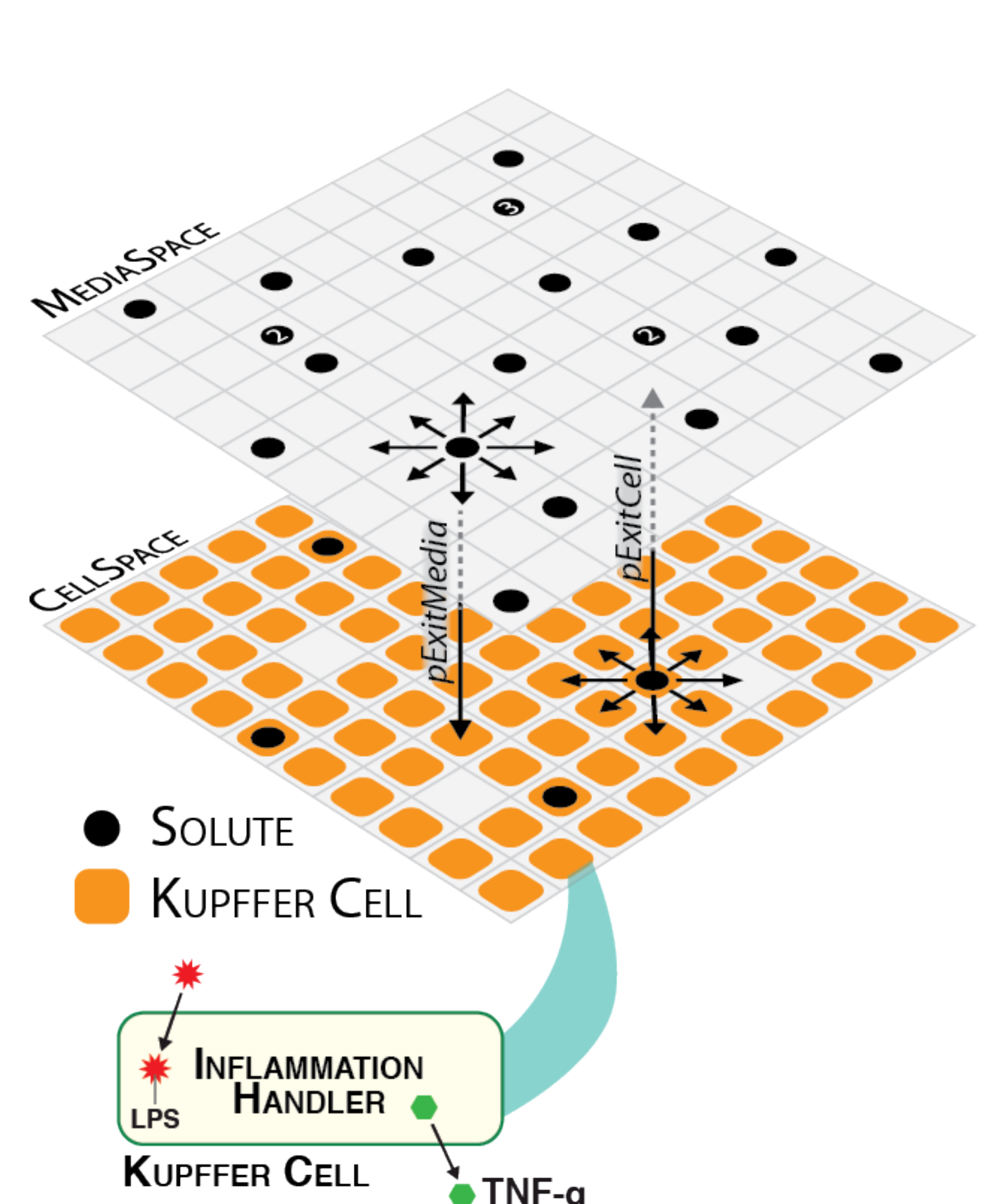
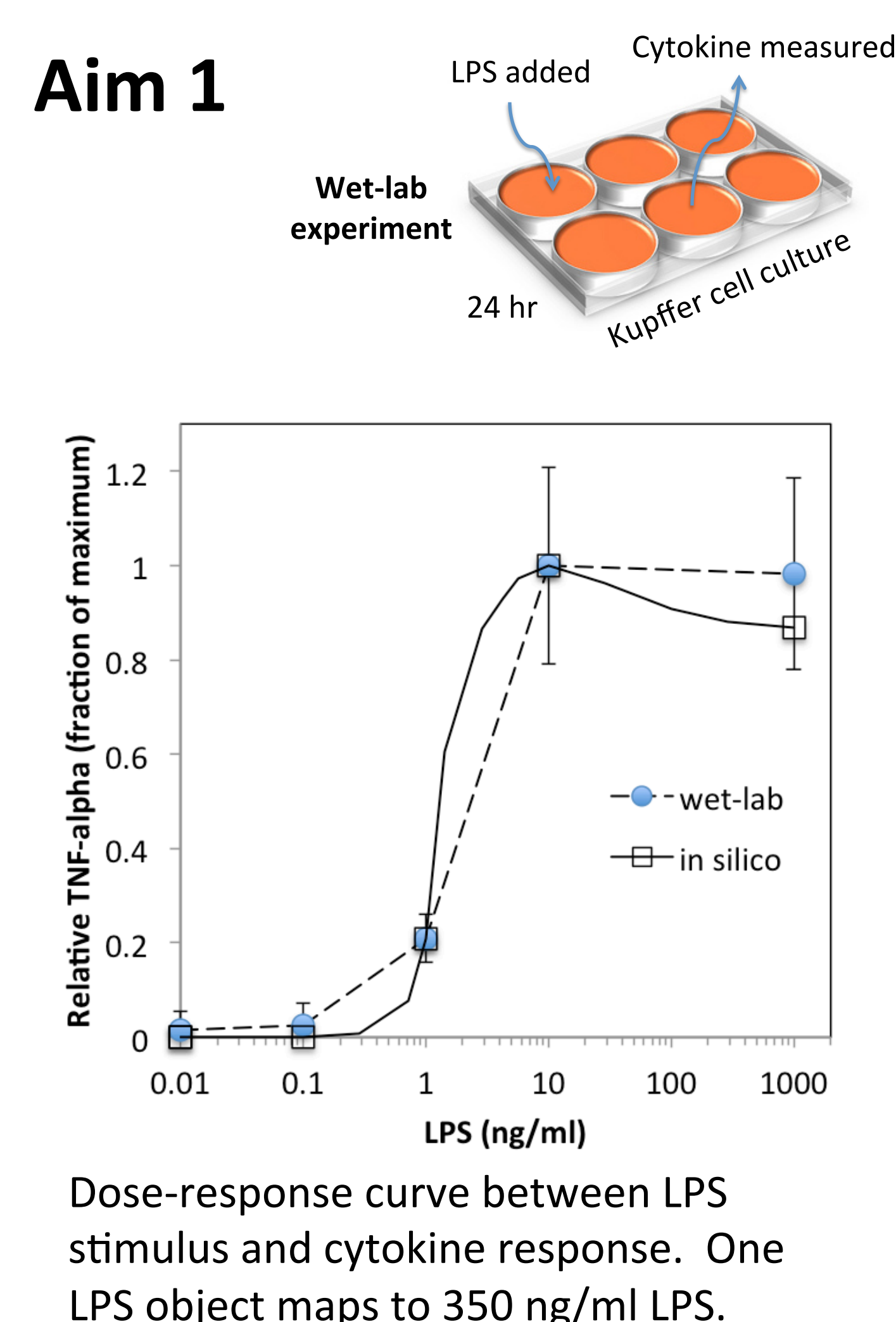
Validation targets

In response to an inflammatory stimulus like lipopolysaccharide (LPS), Kupffer cells down-regulate hepatic P450 enzyme expression via cytokines. This can result in reduced intrinsic clearance of xenobiotic both in vitro and in vivo.

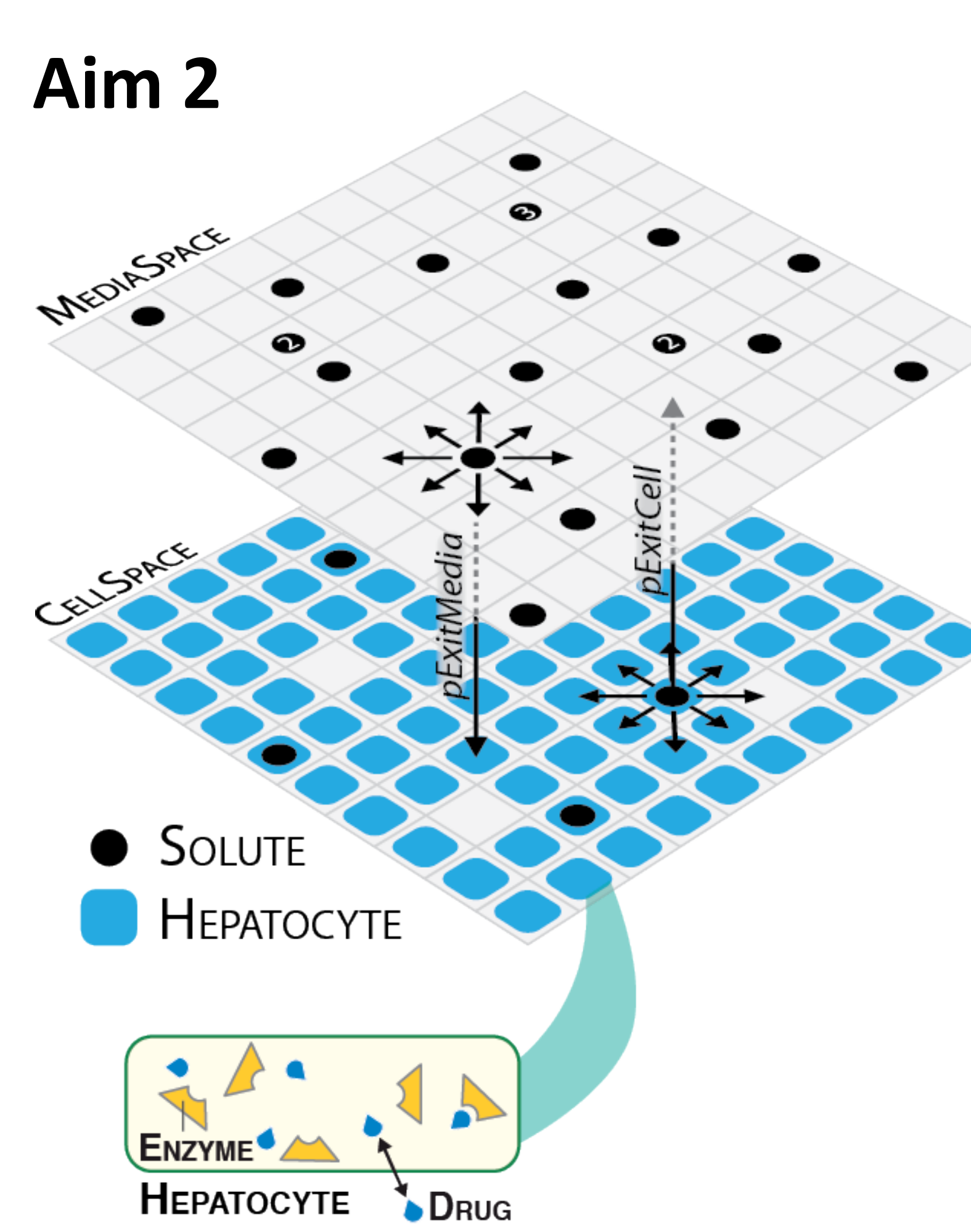
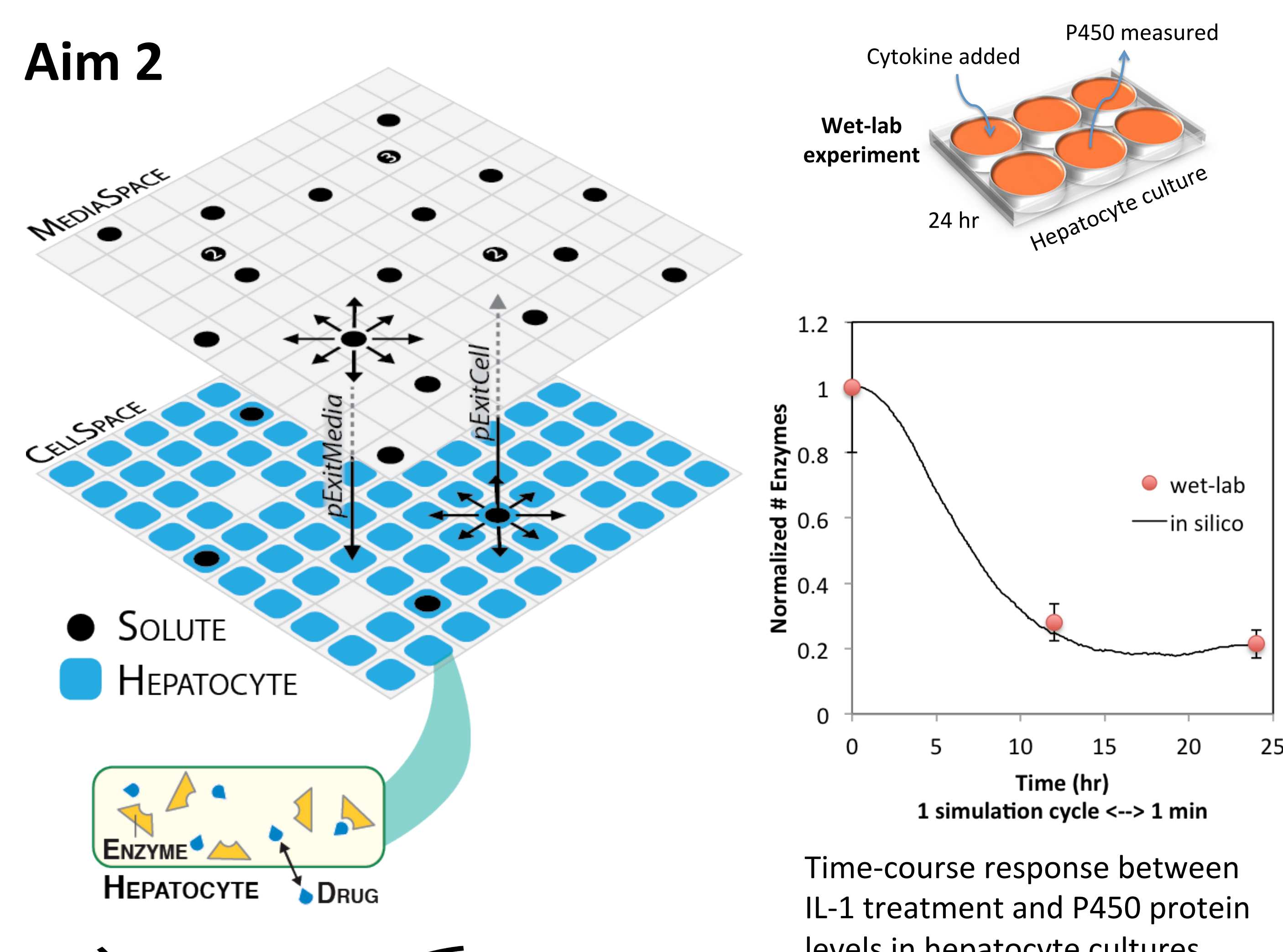
- Aim 1: Develop a Kupffer Cell analog that yields a dose-response between LPS and Cytokine.
- Aim 2: Add Hepatocyte mechanisms that down-regulate P450 levels in response to Cytokine.
- Aim 3: Integrate the Kupffer Cell and Hepatocyte analogs to simulate immune-mediated P450 down-regulation in response to LPS.



Aim 1



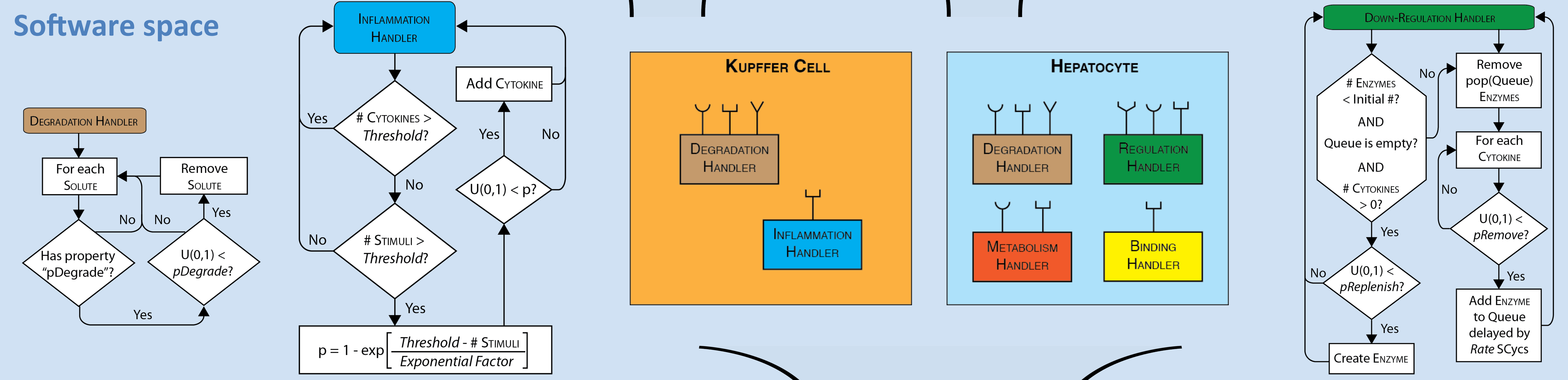
Aim 2



Methods: iterative refinement

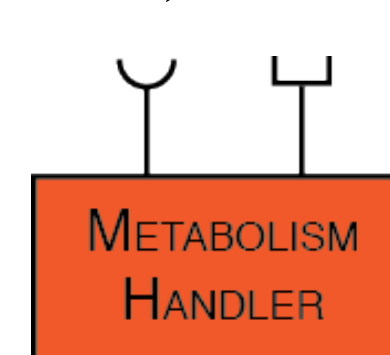
- 1 Assemble & prioritize a diverse set of experimental observations—Targeted Attributes (TAs)—that characterize multiple key aspects of interest at different scales.
- 2 Select a subset, initially small; they are the validation targets for the current cycle.
- 3 (Re)Specify measurements & granularity.
- 4 (Re)Specify mechanisms to be modularized, mechanism users, and relevant mechanism state information.
- 5 Partition state information and expose each partition as a physiommimetic parametric container.
- 6 Encapsulate the behavior of the mechanism as a physiommimetic mechanism module.
- 7 (Re)Specify Similarity Measures (SMs) & their target values.
- 8 Revise physiommimetic mechanism modules (&/or implement analog counterparts to published mechanistic scenario); select competing analogs; follow parsimony guideline.
- 9 (Re)Specify modules, components, model use case(s), parameters, rules, & parameterization ranges.
- 10 Conduct and measure many simulation experiments that predict TAs & achieve SMs.
- 11 Effort fails: mechanism falsified (new knowledge) return to Step 8 or 9. Effort successful: achieved a degree of validation; study sensitivity analysis results; return to step 7 & increase SM stringency. SM targets achieved: go to Step 12.
- 12 Specify next validation milestone by expanding the set of TAs &/or increasing SM stringency.

Software space



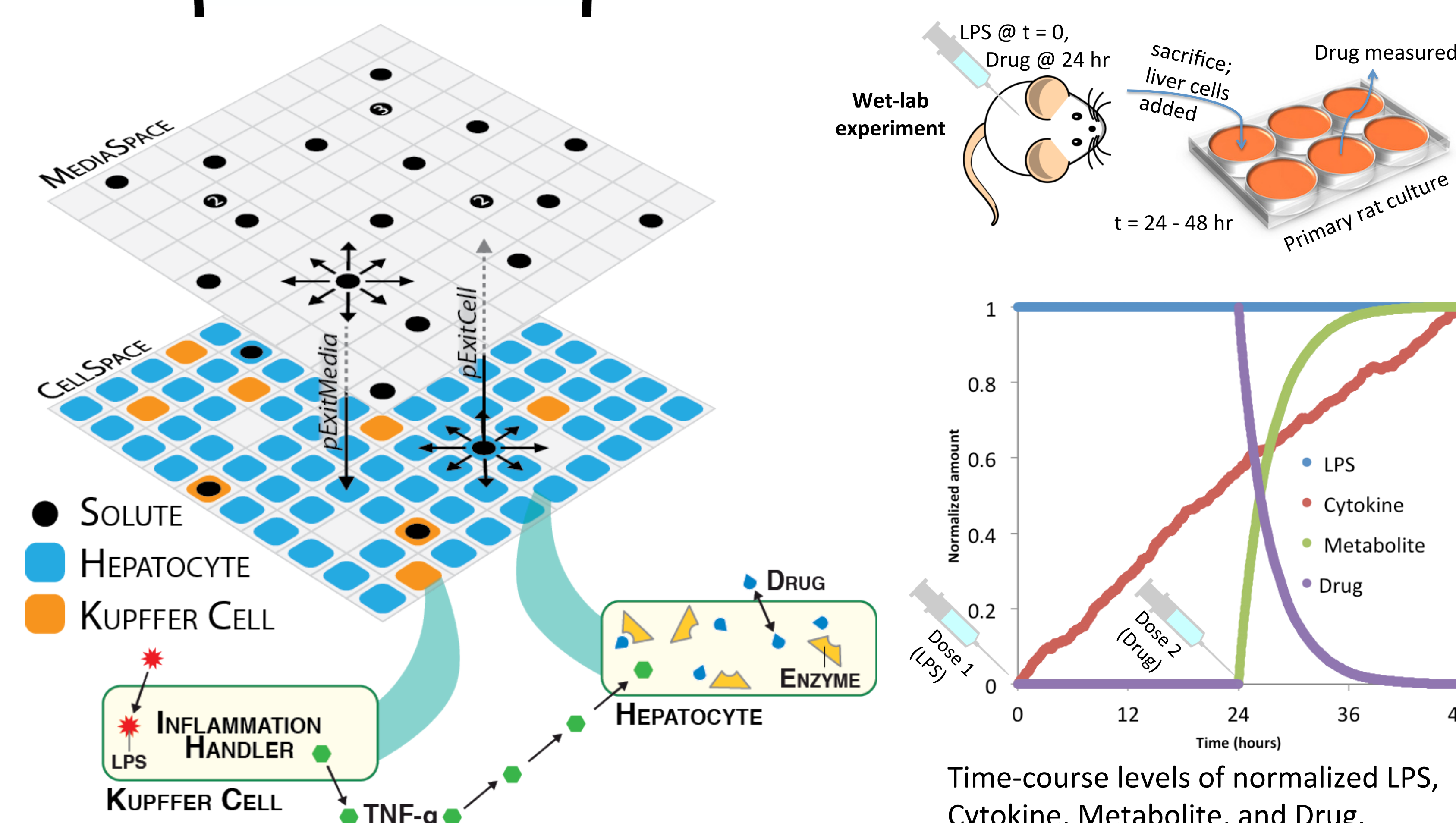
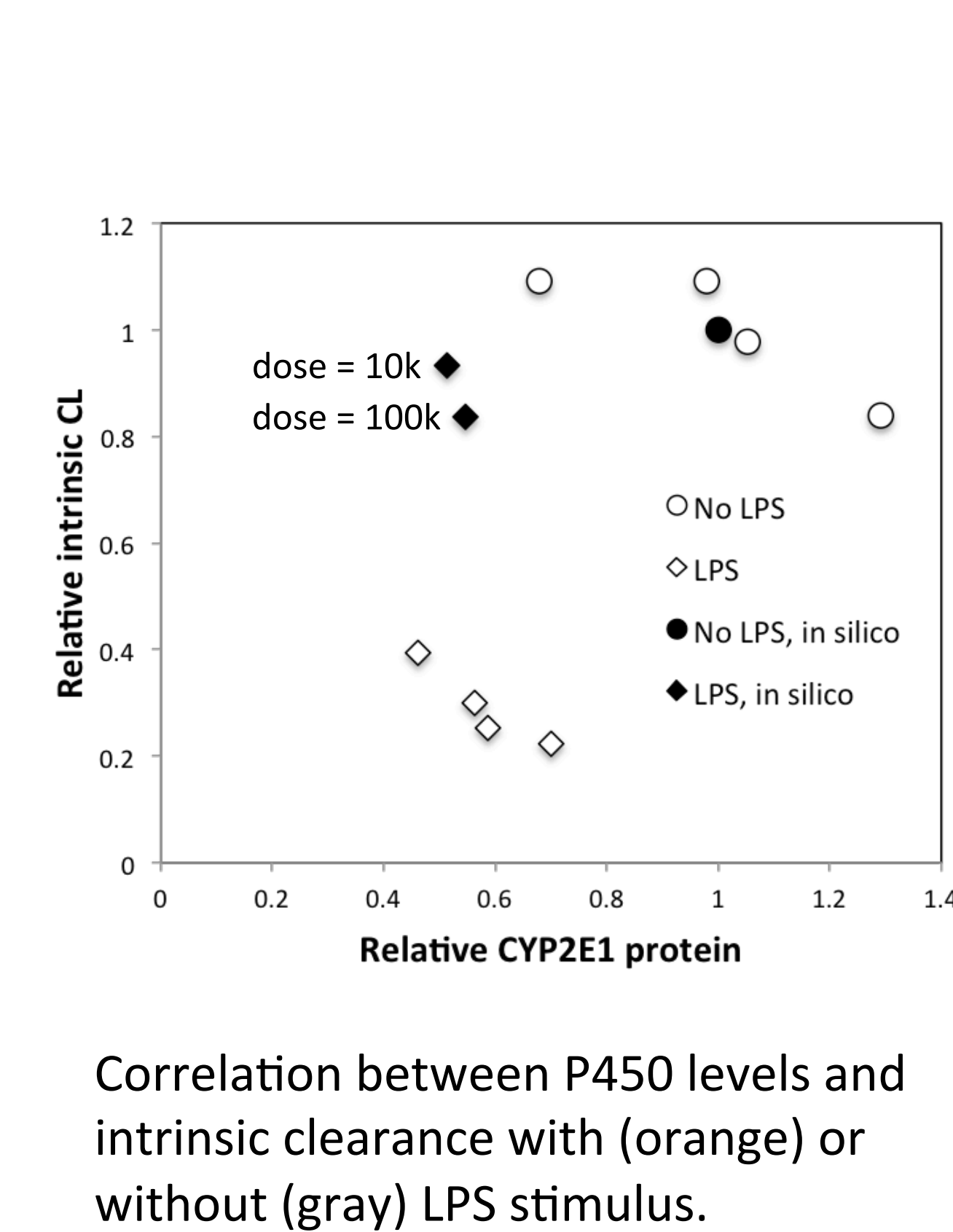
Modularity

Each mechanism is modularized into a software component called a *physiommimetic mechanism module* (PMM), illustrated below.



A mechanism user (i.e. Kupffer Cell, Hepatocyte) uses a PMM by first exposing the correct state information (illustrated using “sockets”), then instantiating it. PMMs facilitate model integration by allowing different models (i.e. liver and immune system) to interact without requiring a priori knowledge of each other.

Aim 3



Conclusions

- Mechanisms and components developed in Aims 1 and 2 achieve validation targets within acceptable levels of similarity. (Similarity criteria: in silico points fall within ± 1 standard deviation of the corresponding wet-lab value.)
- The integrated analog was falsified against wet-lab intrinsic clearance data. Thus, the current mechanisms are too simple to sufficiently explain the wet-lab phenomena. Iterative model refinement will lead to a more complex analog. As additional analogs are falsified, the space of plausible, explanatory mechanisms shrinks, thereby improving mechanistic insight.

References

BK Petersen, GEP Ropella, and CA Hunt, Toward modular biological models: defining analog modules based on referent physiological mechanisms, BMC Systems Biology 8(95) 2014.