Hepatotoxicity of Compound V Evaluated with Quantitative Systems Toxicology

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DILIsym Services

A SIMULATIONS PLUS COMPANY

Session Description and Objectives

Compound V is a small molecule with potential therapeutic benefits in patients with obesity. An early clinical safety trial produced two patients with liver enzyme elevations. This presentation discusses the combination of *in vitro* assays and *in silico* modeling to investigate the hepatotoxicity of Compound V. DILIsym, a quantitative systems toxicology (QST) model of drug-induced liver injury, was used to evaluate what mechanisms may be involved and if the compound concentration in the liver plays a role. Simulation results predict Compound V can injure hepatocytes and reveal the primary mechanism of injury: Reactive Oxidative Stress. This prediction of hepatotoxicity is highly sensitive to the value of the liver:blood partition coefficient (Kp). These results demonstrate the ability for QST modeling, specifically DILIsym, to propose plausible rationales for difficult-to-explain clinical liver toxicity data, and to suggest which further experiments would be most useful for understanding the underlying mechanisms of certain DILI cases.

I also have a poster with more details on this project!
Poster ID: 891035

- Upon completion, participants will be able to recognize how *in silico* QST modeling and simulations identify data gaps, thereby guiding future *in vitro* experiments and *in vivo* studies.
- Upon completion, participants will be able to design and execute a set of QST simulations to determine which mechanism(s) of injury is driven by a compound of interest.
- Upon completion, participants will be able to identify and develop *in vitro* assays that are most useful for parameterizing a QST model like DILIsym.

Biography and Contact Information

- Dr. Lakhani's primary role is to improve the SimPops capabilities, including size and tools, across all the software platforms developed by DSSI.
- He is often a technical lead on DILIsym consulting projects, such as the project discussed here.
- He contributes to the model development of DILIsym, RENAsym, and RADAsym.

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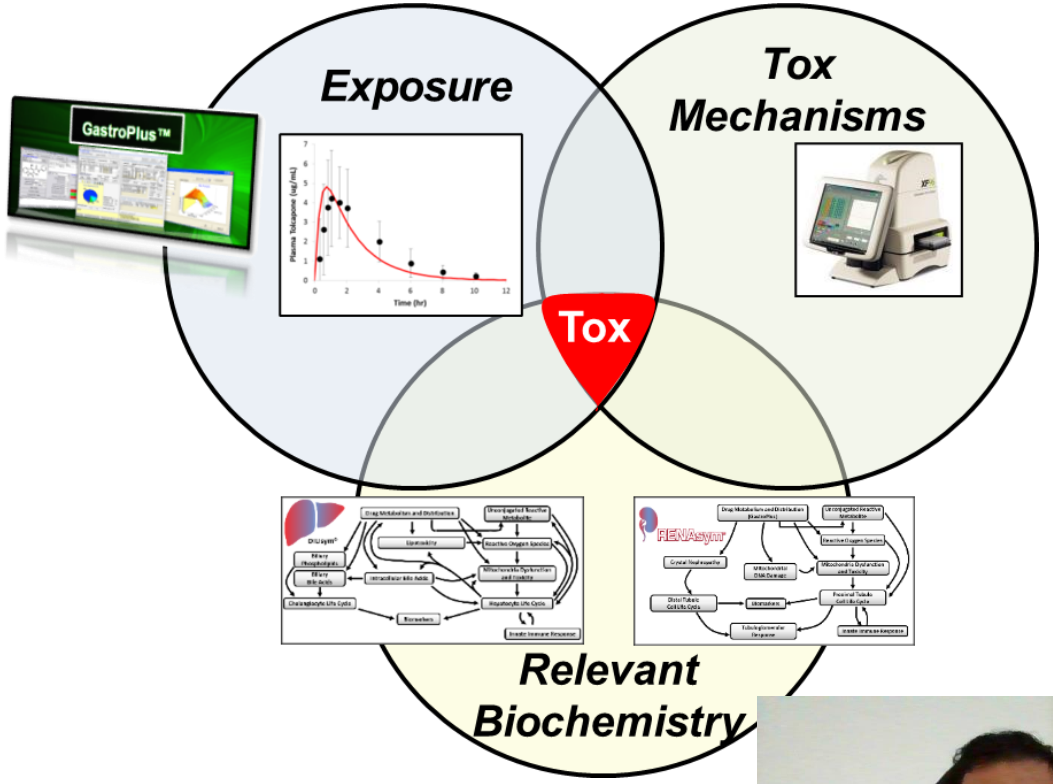
Introduction, Background, and Methods

The Molecule of Interest

- Compound V is a small, lipophillic molecule with potential therapeutic benefits for patients with obesity.

- An early clinical safety trial produced 2 out of 16 patients with liver enzyme elevations.

DILIsym QST Model



In vitro Assays Signaled Compound V has Potential for Hepatotoxicity

- DILIsym represents 3 distinct mechanisms of toxicity
  - Bile Acid Transporter Inhibition (Solvo Biotechnology)
    - BSEP, NTCP, MRP3, MRP4
  - Mitochondrial Dysfunction (Cyprotex)
    - SeaHorse XF Analyzer with HepG2 cells
    - Inhibition of proteins in the electron transport chain
    - Mitochondrial Membrane Uncoupling
  - Production of ROS/RNS (Cyprotex)
    - Cytotoxicity High Content Screen in HepG2 cells

IC_{50} values estimated for all four transporters

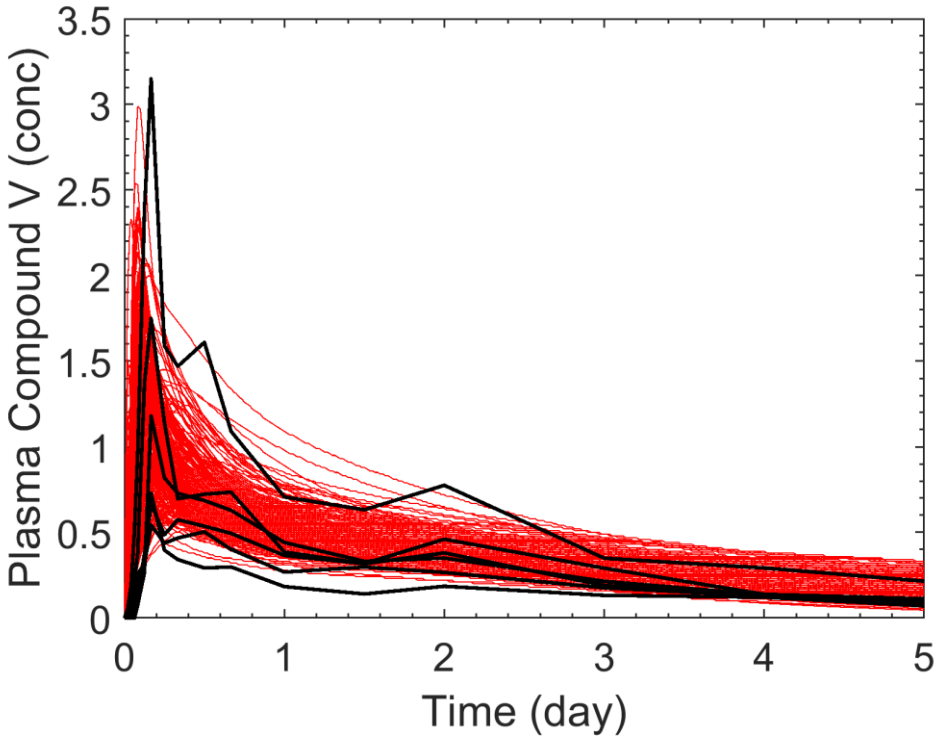
K_M and V_{max} for inhibition of electron transport chain

K_M, V_{max} and n_{Hill} for ROS production

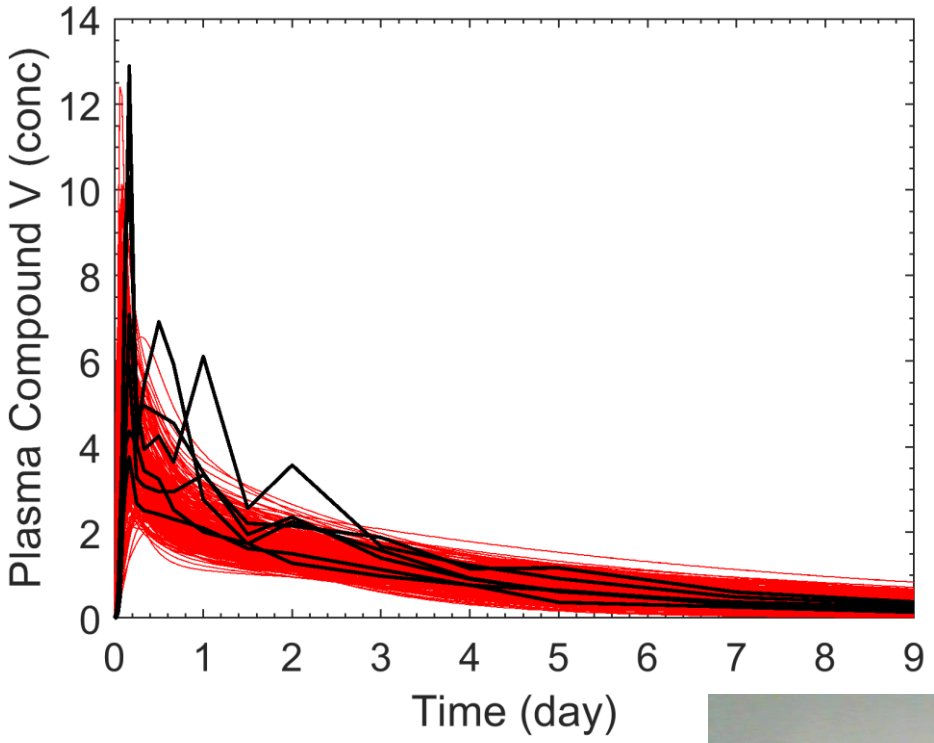
Compound	BA Transport signals	Mitochondrial dysfunction signals	Oxidative stress signals
Compound V	Yes	Yes	Yes

GastroPlus Model Trained on Single Dose Clinical Data

1x Single Dose

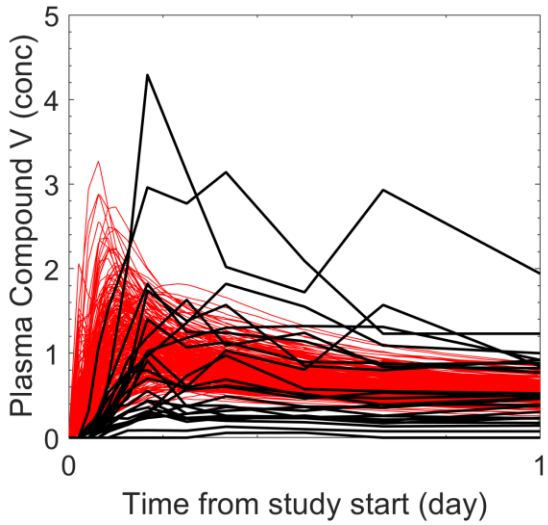


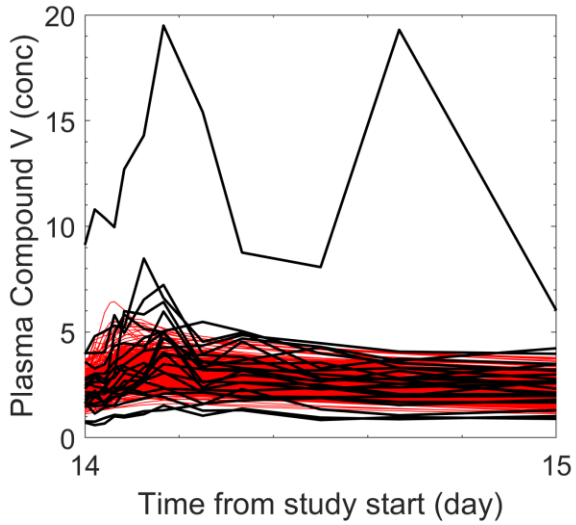
4x Single Dose

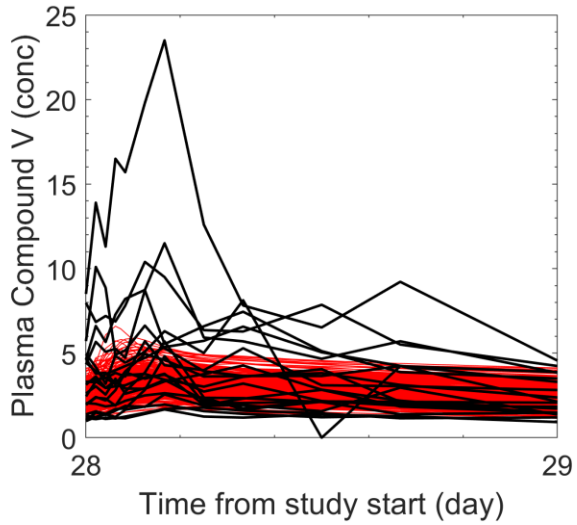


GastroPlus Model Validated on Multiple Dose Clinical Data

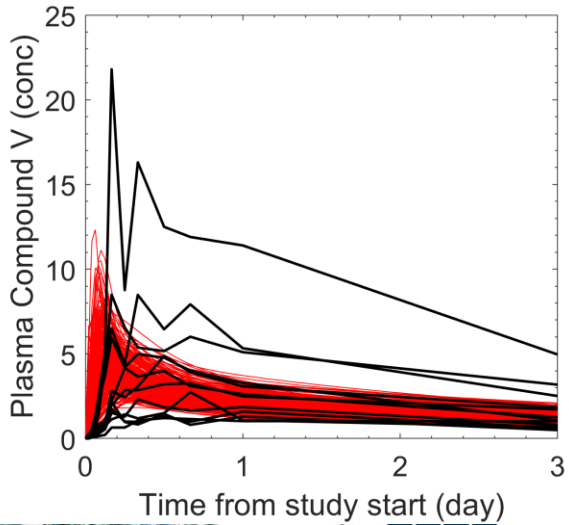
1x QD Multiple Dose

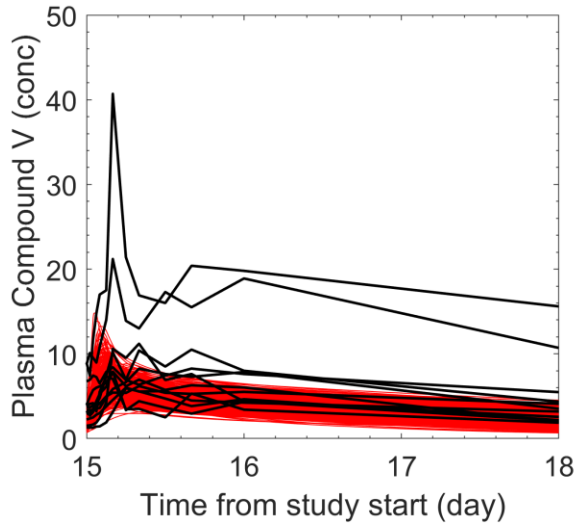


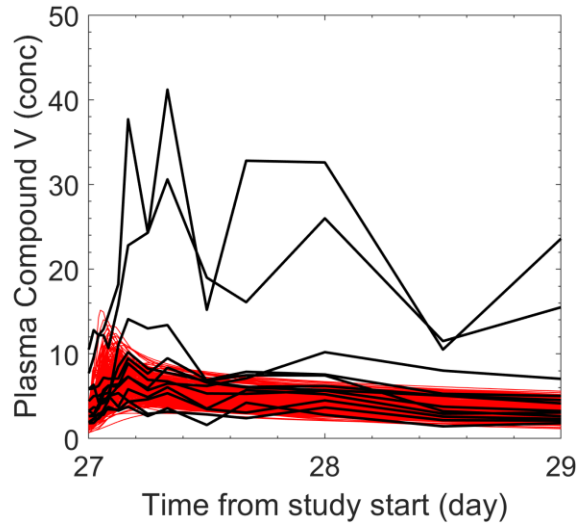




4x Q3D Multiple Dose

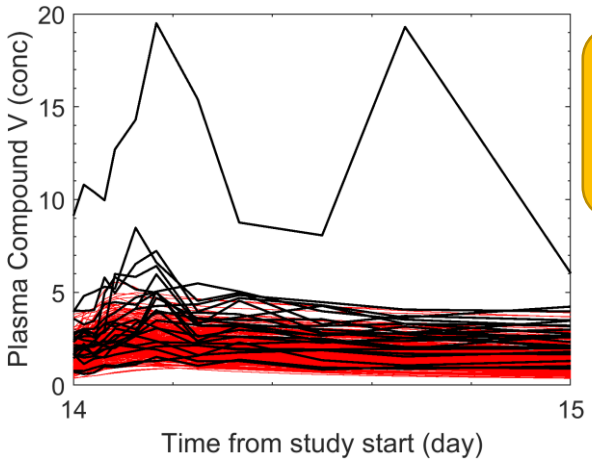




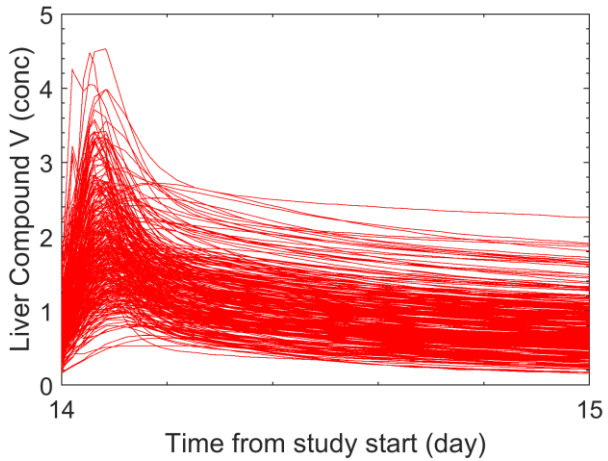


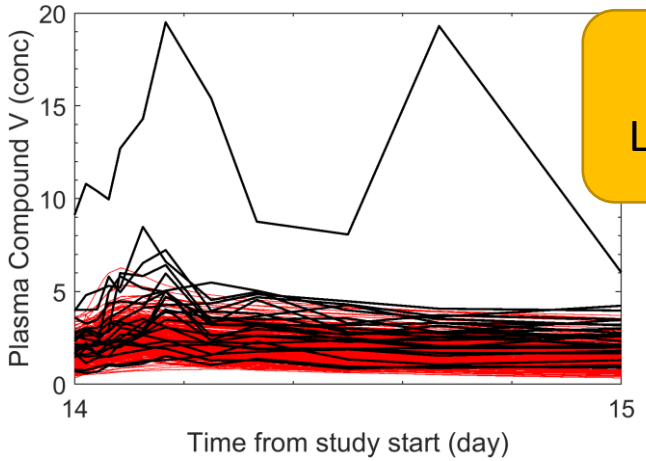
Large Range of Possible Liver K_P Value Makes Predictivity Complicated

- No measurements of preclinical species' Liver K_P was available
- An *in silico* prediction by GastroPlus gave a value of 0.33
- An *in vitro* estimate with HepG2 cells gave a value of 3.3

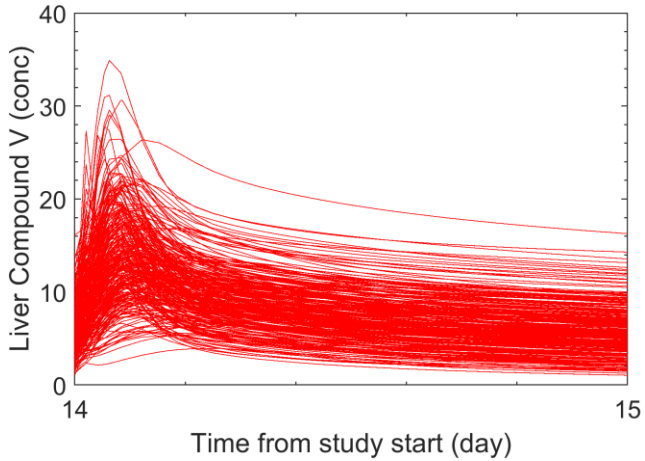


1x QD
Liv K_P = 0.33





1x QD
Liv K_P = 2.4

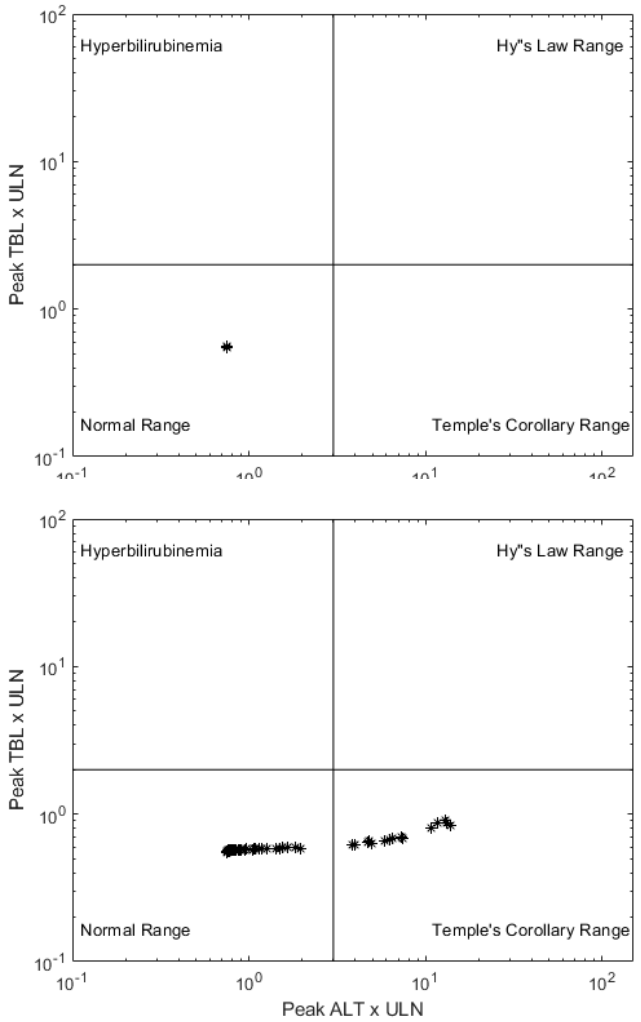


DILIsym Prediction of Toxicity is Heavily Dependent on the Liver K_P Value

Simulated Individuals with ALT >3x ULN		
Liver K_P	1x QD	4x Q3D
0.33	0.00% (0/285)	0.00% (0/285)
1.72	0.00% (0/285)	4.91% (14/285)
2.1	2.46% (7/285)	12.6% (36/285)
2.4	5.26% (15/285)	20.7% (59/285)
3.3	61.4% (175/285)	92.3% (263/285)

1x QD
Liv K_P = 0.33

1x QD
Liv K_P = 2.4



DILIsym Mechanistic Analysis Shows ROS Production as the Necessary and Sufficient Mechanism for Compound V to Cause Hepatotoxicity

1x QD
Liv K_P = 2.4

Mechanisms OFF	Mechanisms ON	Simulated ALT >3x ULN Frequency
None	All	15/15
ROS	ETCi, BAi	0/15
ETCi	BAi, ROS	15/15
BAi	ETCi, ROS	15/15
ETCi, BAi	ROS	15/15
BAi, ROS	ETCi	0/15
ETCi, ROS	BAi	0/15

- DILIsym allows each mechanism of toxicity to be individually turned ON or OFF

ETCi = electron transport chain inhibition
BAi = bile acid transporter inhibition
ROS = reactive oxygen species generation

Insights from DILIsym Modeling for Compound V

- Data Gap
  - The Liver K_P Value is a critical gap in knowledge for assessing hepatotoxicity of Compound V
  - A value of 2.1 can be estimated based on comparing DILIsym's predicted frequency of ALT elevations with clinical observations
- Culprit Mechanism of Injury
  - Based on the mechanistic sensitivity analysis, DILIsym shows the production of ROS is necessary and sufficient for Compound V hepatotoxicity
- Additional Insights discussed on poster

Poster ID: 891035

References

- We have extensively published on the DILIsym model. Please see the following review paperas a great starting point
  - Watkins Curr Opin Toxicol. 2020
  - Watkins PB. DILIsym: Quantitative systems toxicology impacting drug development. Curr Opin Toxicol. 2020;23–24: 67–73. doi:10.1016/j.cotox.2020.06.003

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Questions

- DSS is also developing a QST model for Acute Kidney Injury (**RENAsym**)
- DSS has developed a QSP model capable of assessing the efficacy of compounds to treat NAFLD or NASH (**NAFLDsym**)
- Some other QSP models under development
  - **IPFsym** – Idiopathic Pulmonary Fibrosis
  - **RADAsym** – Acute Radiation Injury

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