



# ***DILIsym Services***



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## **DILIsym: Modeling Drug-Induced Liver Injury & Beyond**

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*\*DILIsym<sup>®</sup>, NAFLDsym<sup>®</sup>, MITOsym<sup>®</sup>, ADMET Predictor<sup>®</sup>, GastroPlus<sup>®</sup> and SimPops<sup>®</sup> are registered trademarks, and SimCohorts<sup>™</sup>, IPFsym<sup>™</sup>, and RENAsym<sup>™</sup> are trademarks, of DILIsym Services Inc. and/or SLP for computer modeling software and for consulting services.*



- DILIsym:  
Modeling  
Drug-  
Induced  
Liver Injury  
& Beyond**
- Introduction to  
DSSI
- QSP Modeling
- Platforms
- Summary

# INTRODUCTION TO DILISYM SERVICES INC.

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# DILIsym Services, Inc., a Simulations Plus Company

- DILIsym Services, Inc. (DSSI) is a Simulations Plus company
  - Simulations Plus develops modeling and simulation software for pharmaceutical and biotechnical industries
  - Software designed to support drug discovery, clinical development research, and regulatory submissions
- DSSI uses quantitative systems pharmacology (QSP) and quantitative systems toxicology (QST) to support the pharmaceutical industry
- DSSI has developed numerous modeling software platforms to support the development of safe and effective drug therapies
  - Focused on improving drug safety through QST models and supporting development of efficacious treatments through QSP models

DILIsym:  
Modeling  
Drug-  
Induced  
Liver Injury  
& Beyond

Introduction to  
DSSI

QSP Modeling

Platforms

Summary

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# The DILIsym Services Team



**Paul B. Watkins**

DILI-sim Initiative Founder and  
Scientific Advisory Board Chair  
RTP, NC



**Scott Q Siler**

Chief Scientific Officer  
Bay Area, CA



**Brett Howell**

President  
RTP, NC



**Shawn O'Connor**

CEO, Simulations Plus Inc.  
Lancaster, CA

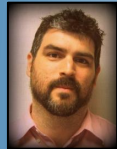


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Modeling  
Drug-  
Induced  
Liver Injury  
& Beyond

## DILIsym Services

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Introduction to  
DSSI

QSP Modeling

Platforms

Summary



# Relatively Small Team Means Each Member Contributes to Multiple Aspects on Multiple Projects

- The team consists of:
  - mathematicians
  - engineers (biomedical, chemical)
  - life scientists (nutrition, immunology, pharmaceutical sciences)
- For most projects, teams consist of a mix of “engineers” and life scientists who work closely to accurately construct and validate models based on physiological considerations
- In our small team dynamic environment, everyone wears multiple hats
- Many modelers on the team work remotely so effective communication skills are crucial

DILIsym:  
Modeling  
Drug-  
Induced  
Liver Injury  
& Beyond

Introduction to  
DSSI

QSP Modeling

Platforms

Summary

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# DILI-sim Initiative Built on a Public-Private Partnership

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Modeling  
Drug-  
Induced  
Liver Injury  
& Beyond

- DILI-sim Initiative membership consists of numerous pharmaceutical companies
- Members have common interest in improving drug safety and understanding mechanisms that contribute to toxicity
  - Guide areas for model development
  - Provide insight into novel biomarkers, mechanisms of toxicity
- FDA has been active contributor to DILIsym efforts
  - Previously supported 2 ORISE fellows within the DILIsym team
  - Obtained multiple licenses for validating DILIsym software
- Overall goals
  - Improve patient safety through QST
  - Reduce the need for animal testing
  - Reduce the costs and time necessary to develop new drugs

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## History

- Officially started in 2011
- 19 major pharmaceutical companies have participated
- Members have provided compounds, data, and conducted experiments to support effort

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# DSSI Develops Software to Support Safety and Efficacy

*“Our vision is safer, effective, more affordable medicines for patients through modeling and simulation.”*



DILIsym™



RENAsym™



IPFsym™



NAFLDsym™



RADAsym™

- DILIsym Services, Inc. offers comprehensive program services:
  - **DILIsym** software licensing, training, development (DILI-sim Initiative)
  - **NAFLDsym** software licensing, training, development
  - **DILIsym** and **NAFLDsym** simulation consulting projects
  - Consulting and data interpretation; *in vitro* assay experimental design and management
  - **RADAsym**, **RENAsym**, and **IPFsym** software in development

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DILIsym:  
Modeling  
Drug-  
Induced  
Liver Injury  
& Beyond

Introduction to  
DSSI

QSP Modeling

Platforms

Summary



# Work at DSSI is Distributed Between Consortium and Proprietary Projects

## Consortium projects

- Directed by Initiative members' input each year
- Modeling and incorporating new exemplars into the software
- Adding new submodels that may contribute to hepatotoxicity (e.g. adaptive immune system)
- Creating new simulated populations to use for toxicity predictions
- Adding additional preclinical species for toxicity comparisons
- Improving software speed and performance

## Proprietary projects

- Contracted by various pharmaceutical companies (big and small)
- Predict hepatotoxicity risk
- Investigate mechanistic causes (and possibly remedies) for observed toxicity
- Predict safety/exposure range for new therapeutics
- Compare new drug safety profile against that of existing drugs on market in same class
- Develop novel QSP/QST model in area of interest

DILIsym:  
Modeling  
Drug-  
Induced  
Liver Injury  
& Beyond

Introduction to  
DSSI

QSP Modeling

Platforms

Summary

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**DILIsym:  
Modeling  
Drug-  
Induced  
Liver Injury  
& Beyond**

Introduction to  
DSSI

QSP Modeling

Platforms

Summary

# QSP MODELING

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# QSP Modeling

- QSP models are designed to characterize biological systems, representing details such as disease pathophysiology, drug pharmacology, and pathways of toxicity
- Models typically depict interactions between drugs and the biological system of interest
- QSP model development may help identify data gaps and guide future *in vitro* or *in vivo* experiments to yield more insightful data
- Importantly, the importance of QSP models is now widely recognized within the pharmaceutical industry and by regulatory agencies
  - Increasingly being used to explore target feasibility and selection, drug efficacy and safety, dose optimization, etc.
  - Utilized to inform decision-making at all points in drug development pipeline, from discovery through trials to post-market
- Technical skills required for QSP modeling:
  - Mathematical modeling
  - Parameter estimation/optimization
  - Coding and debugging
  - Quantitative reasoning
  - Network biology, physiology

NIH QSP White Paper (2011): <https://www.nigms.nih.gov/News/reports/Documents/SystemsPharmaWPSorger2011.pdf>

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# QSP Models Built to Answer Key Questions

- QSP or QST models can answer questions related to key mechanistic or physiologic effects as well as understand areas of uncertainty
  - Compare to pharmacokinetics, pharmacometrics, machine learning, and/or artificial intelligence methods – these methods tend to be based in statistics, address different key questions, and may provide different levels of mechanistic insight
- Models constantly updated and expanded to fit available data and needs of clients
  - Ability to branch into new areas of interest using pre-existing mathematical models of relevant biological systems
- Software developed by DSSI built using systems of ODEs
  - Systems treated as averaged “well-mixed tanks (or compartments)” across organs and body systems
  - Mechanistic knowledge of interactions required, can combine with sparse data
- DSSI models currently designed in MATLAB environment
  - Team investigating C++ and Julia simulation speeds

**DILIsym:  
Modeling  
Drug-  
Induced  
Liver Injury  
& Beyond**

Introduction to  
DSSI

QSP Modeling

Platforms

Summary

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# DSSI Model Development

- Constantly researching new topics, developing/implementing new mathematical models, and predicting safety/efficacy of novel therapeutics
  - Consortium guides modeling direction for DILIsym
  - Clients identify new diseases/organs of interest and/or new therapeutic targets
  - Recent scientific findings may require model updates
- Maintain model integrity through public forums
  - Attend conferences to present seminars, talks, and posters
  - Host training sessions to support model use in academia and industry
  - Publish papers in prominent journals

**DILIsym:  
Modeling  
Drug-  
Induced  
Liver Injury  
& Beyond**

Introduction to  
DSSI

QSP Modeling

Platforms

Summary

***DILIsym Services***

**S+** A SIMULATIONS PLUS COMPANY



**DILIsym:  
Modeling  
Drug-  
Induced  
Liver Injury  
& Beyond**

Introduction to  
DSSI

QSP Modeling

Platforms

Summary

# DSSI PLATFORMS

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# DILIsym Services, Inc. Platforms

DILIsym:  
Modeling  
Drug-  
Induced  
Liver Injury  
& Beyond

Introduction to  
DSSI

QSP Modeling

Platforms

Summary



## DILIsym

- Development motivated by FDA
- Very successful consortium (DILI-sim Initiative) sponsored development
- Assess liver toxicity



## NAFLDsym

- Development motivated by corporate sponsors Pfizer (v1) and BMS (v2)
- Steatosis, inflammation, and fibrosis to assess treatment efficacy



## RENAsym

- Development motivated by DILI-sim Initiative members
- Sponsored by SBIR grant
- Recruiting members for consortium
- Assess renal toxicity



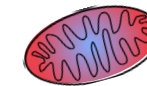
## IPFsym

- Development motivated by corporate sponsor
- Lung fibrosis and function loss to assess treatment efficacy



## RADAsym

- Development motivated by sponsor
- Model for prediction of effects of radiation and the impact of interventions on radiation syndrome
- Utilized to help garner approval for treatment under the Animal Rule



## MITOsym®

## MITOsym

- Developed to generate parameter inputs from key *in vitro* assay system
- Sponsored by DILI-sim Initiative

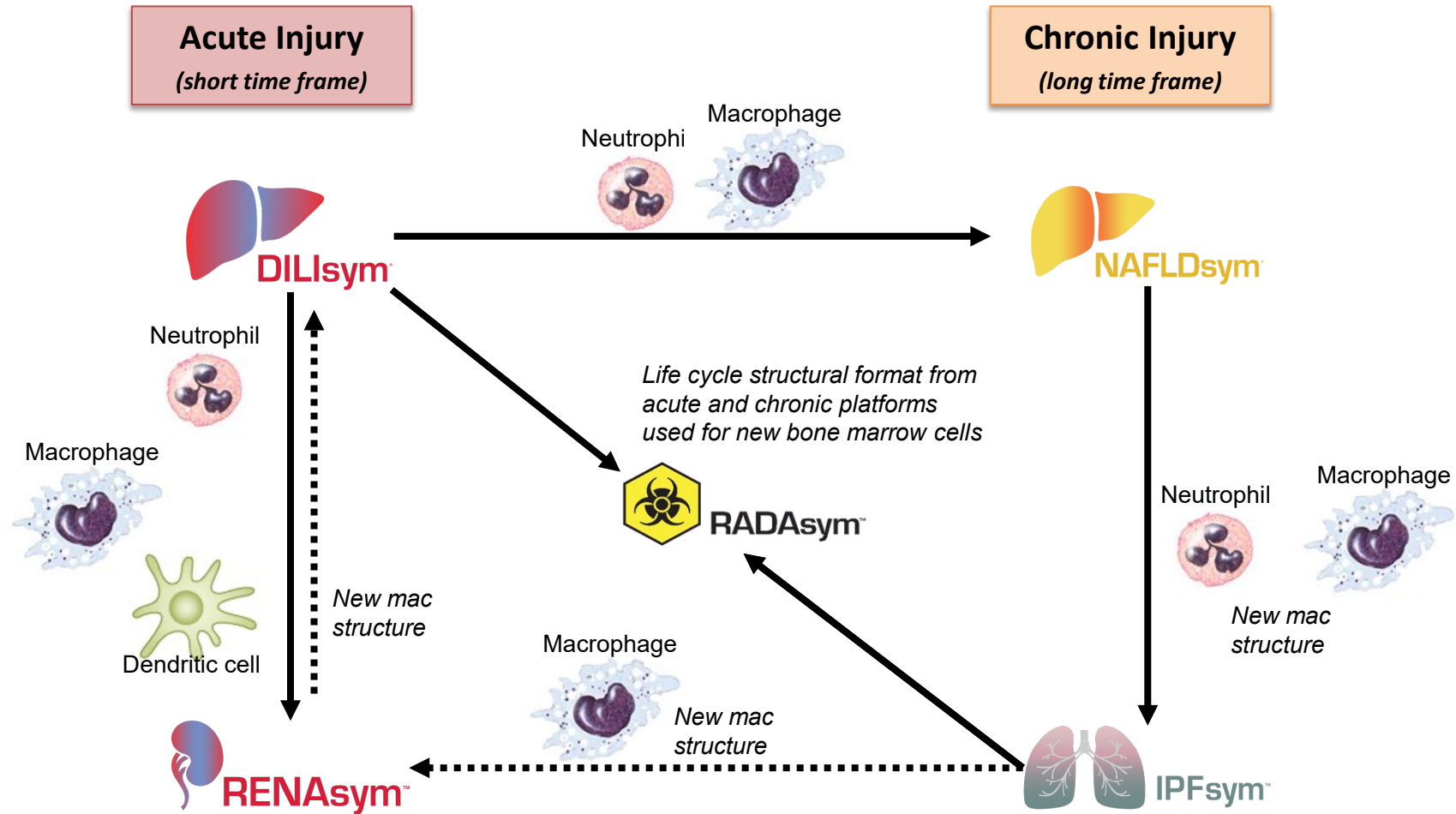
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# Specific Example: Innate Immune Math Model Impacts Platform Development

- DILIsym: Modeling Drug-Induced Liver Injury & Beyond
- Introduction to DSSI
- QSP Modeling
- Platforms
- Summary



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# Cross-Company Modeling Platforms

Discovery	Preclinical	Clinical
MedChem Designer™		
ADMET Predictor™		
GastroPlus™		
	DDDPlus™	
	MembranePlus™	
	PKPlus™	
	DILIsym™	
	IPFsym™	
	RENAsym™	
	NAFLDsym™	
	RADAsym™	
		KIWI™
Consulting Services		

DILIsym:  
Modeling  
Drug-  
Induced  
Liver Injury  
& Beyond

Introduction to  
DSSI

QSP Modeling

Platforms

Summary

NASDAQ: SLP

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S+ A SIMULATIONS PLUS COMPANY





**DILIsym:  
Modeling  
Drug-  
Induced  
Liver Injury  
& Beyond**

Introduction to  
DSSI

QSP Modeling

Platforms

Summary

# SUMMARY

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# Summary

- DSSI provides an exciting and engaging environment with a collaborative, interdisciplinary team
  - Opportunity to contribute to new mathematical models and expand upon already-existing models that directly impact the pharmaceutical industry
- Mathematical modeling can benefit the pharmaceutical industry in many ways
  - Models can be used to predict exposure from chemical structures only
  - Models can predict safety margins for novel therapeutics
  - Models can predict efficacy for diseases which currently have no effective treatment options
  - Full potential for mathematical modeling is being recognized internally by companies and within regulatory agencies to expediate processes and improve efficiency

**DILIsym:  
Modeling  
Drug-  
Induced  
Liver Injury  
& Beyond**

Introduction to  
DSSI

QSP Modeling

Platforms

Summary

***DILIsym Services***

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# QUESTIONS?

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