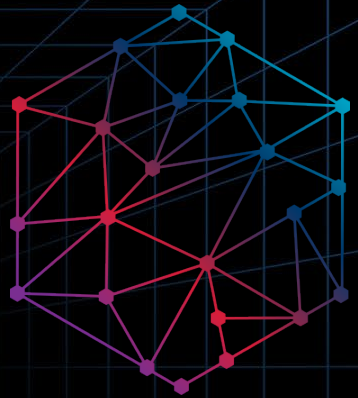
Model-Informed Drug Development

MIDD+

2021 Virtual Conference



Working with Cognigen

Kevin Dykstra, PhD FCP
Vice President, Consulting Services

SimulationsPlus
Cognigen | DILIsym Services | Lixoft

Drug Development Success is Measured in the Big Picture

Regulatory Success

Efficiency

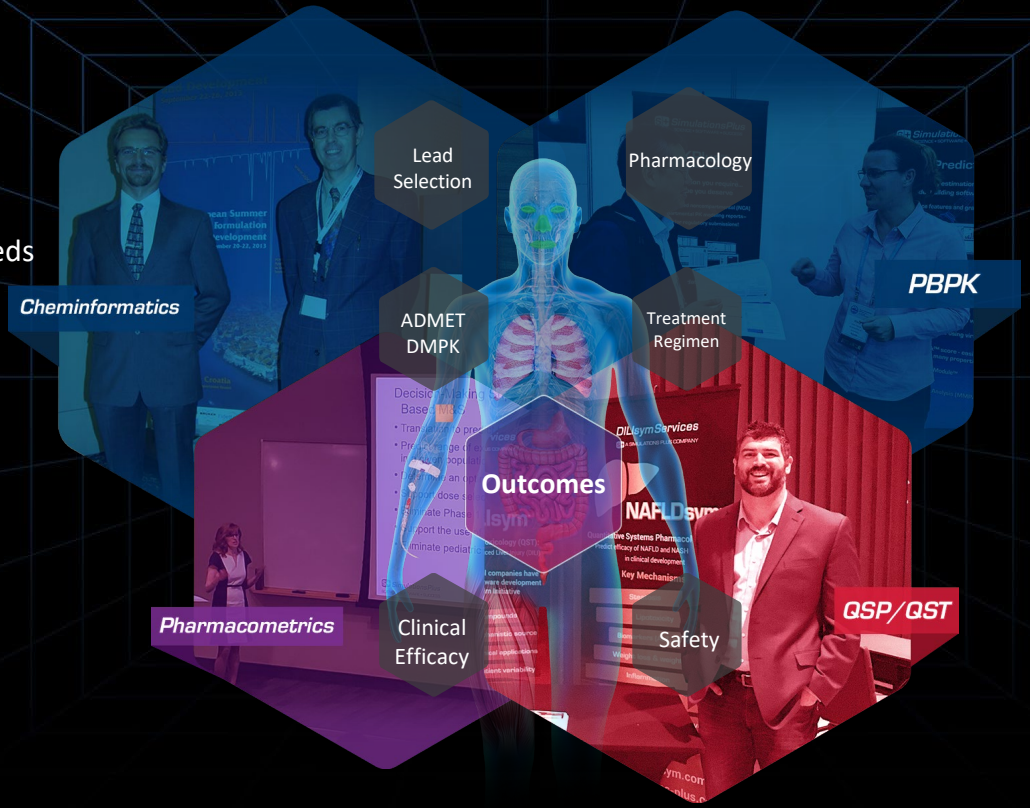
Patient Benefit

Commercial Success

At *SimulationsPlus* We Put It All Together

Science

- Seamless collaboration
- Integrated, innovative solutions to meet <u>your</u> needs



Business

- Resources available to get the job done on time
- One-stop shopping – single vendor for all of your *in silico* drug development needs

We have the *Solutions* and the *People* to Address <u>*Your*</u> Drug Development Questions!

What it is Like to Work With Us?

We believe the relationships we build with our clients are critical and a highly interactive collaboration not only allows us to deliver results as quickly as possible, but also ensures a higher quality deliverable

- Regular interactions ensure the relevancy of results as the knowledge-base continues to evolve
- Transparency provided by progress updates eliminates surprises
- Synergies come from a shared knowledge-base of expertise and experience
- We welcome involvement, participation, and input from stakeholders outside of M&S

We have the experience and capacity to meet your development needs on time

- Currently over 50 scientists and technologists …. and growing!
- Experience in most therapeutic areas and all phases of drug development
  - Oncology: tumor size, cell counts, OR, PFS, OS
  - Psychiatry and other CNS diseases: disease progress model, characterization of placebo response, E-R efficacy and safety models for categorical endpoints
  - Small molecules, mAb, biologics, ADCs, liposomes
  - Concentration-QT models and risk assessment
  - Anti-virals/anti-infectives: Viral load, MIC, disease burden, TA analyses
  - Diabetes and obesity: PK/PD models of efficacy and safety endpoints
  - Pediatrics: PIP development, dose selection based on exposure-matching, adjustments by age, weight
- Well-established quality management system and successful client audit record

We have the Systems Infrastructure to ensure data integrity and secure access

- Fully validated, private “cloud” computing to address computational requirements in regulated industries
- Redundant enterprise-grade storage
- Uninterruptable power supply protects entire datacenter
- Comprehensive off-site backup facilities
- Diesel generator provides long-term backup power
- Continuous system-wide environmental monitoring

THANK YOU

We look forward to collaborating!

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Q&A

Questions & Answers

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Partner With Us...

John DiBella

President, Simulations Plus Division

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Brett Howell

President, DILIsym Services Division

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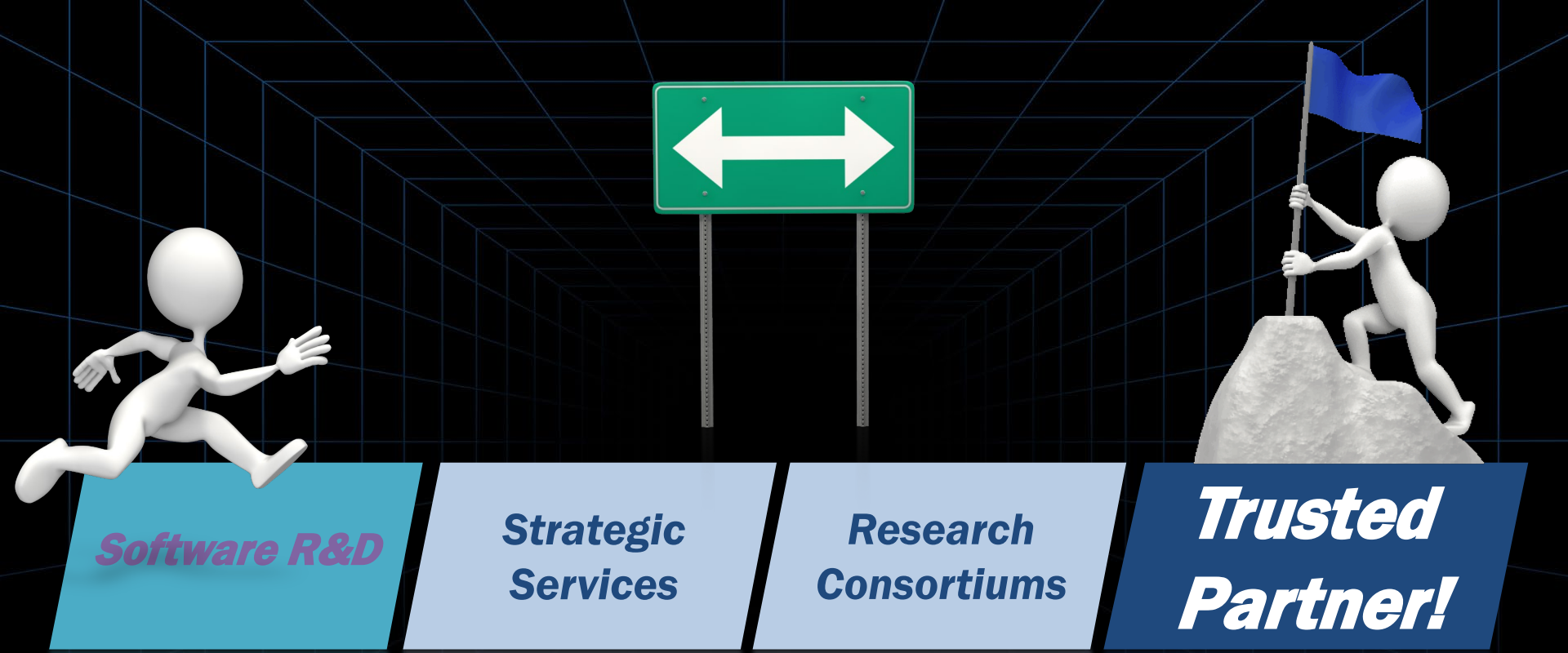
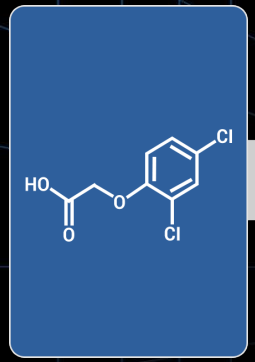
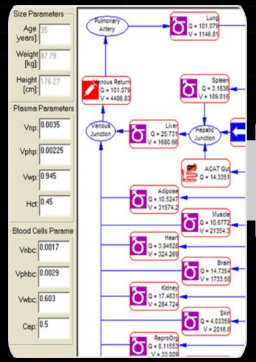

Software R&D
Strategic Services
Research Consortiums
Trusted Partner!

The Vision:

Saying “I do” to the Machine Learning / PBBM-PK / QST(P) / Pharmacometrics marriage…



Permeability, solubility vs. pH, pKa(s), logD vs. pH, Fup, blood:plasma ratio, tissue Kps, CLint, CLfilt



Local & systemic exposure, drug distribution, parent and metabolite levels, patient variability

ADMET Predictor™

GastroPlus™

PKPlus™ DDDPlus™

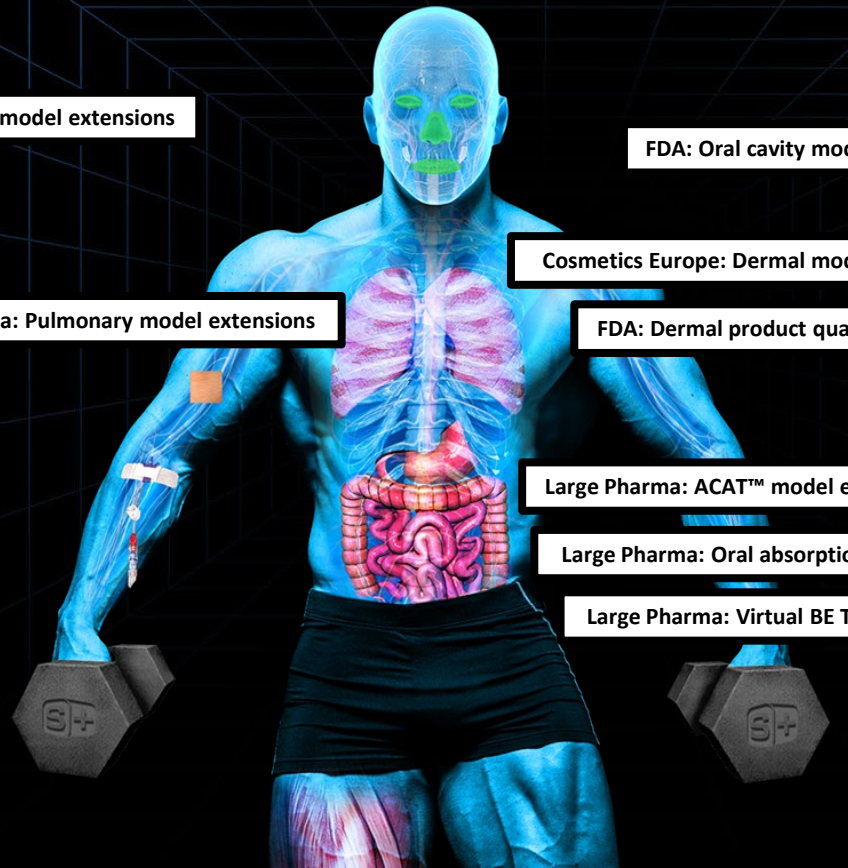
MembranePlus™

RENAsym™ DILIsym™

IPFsym™ NAFLDsym™

>10% in total revenues invested in software R&D in 2020
(additional funding from collaboration partners)

Clients Driving Software R&D: Active Funded Collaborations



FDA: Ocular model extensions

FDA: Oral cavity model extensions

Cosmetics Europe: Dermal model extensions

Large Pharma: Pulmonary model extensions

FDA: Dermal product quality attributes

Large Pharma: ACAT™ model enhancements

Large Pharma: Oral absorption of peptides

Large Pharma: Virtual BE Trial Simulator

Other Software

- RENAsym™: Drug-induced kidney injury QST
- IPFsym™: Pulmonary fibrosis QSP
- ADMET Predictor®: HT-PBPK simulations
- PKPlus™: HT-PK data analysis

Software R&D Collaborations: Roles and Responsibilities

Sponsor provides:

1. Scientific guidance based on subject knowledge
2. Selected internal data to validate proposed modifications
3. Feedback on implementation (e.g., GUI design, workflows, deployment within sponsor's IT system)
4. Funding of FTE(s) to prioritize and accelerate development
5. Assistance with the preparation of draft manuscripts for publication

Simulations Plus provides:

1. Project management
2. Scientific expertise building mathematical models
3. Algorithmic and logic code updates into the simulation engine
4. Beta versions of the software for testing
5. Pre-built compound models for future internal use by sponsor
6. Assistance with the preparation of draft manuscripts for publication

Software R&D Collaborations: We Are All Winners!

WINNER! Sponsor receives:

1. Customized functionality within commercially qualified/maintained software
2. Validated compound models developed using sponsor data
3. Free licenses to new features
4. Publications describing the modeling methodology and validation
5. Recognition from industry/regulatory agencies for advancing the utility of modeling & simulation

WINNER! Simulations Plus receives:

1. Data, funding and scientific expertise to support model development
2. Ability to distribute new functionality to other clients (IMPORTANT: no data is ever shared!)
3. Presentations and publications describing the modeling methodology and validation

WINNER! Regulatory agencies and industry receive:

1. Access to innovative, validated science to develop safe, effective medicines more efficiently

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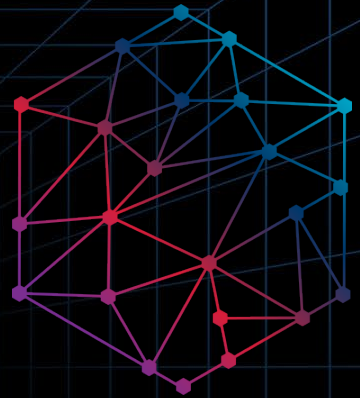

Collaborating With Us – Consortium Membership

Brett Howell, President of DILIsym Services Division

SimulationsPlus

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Summary

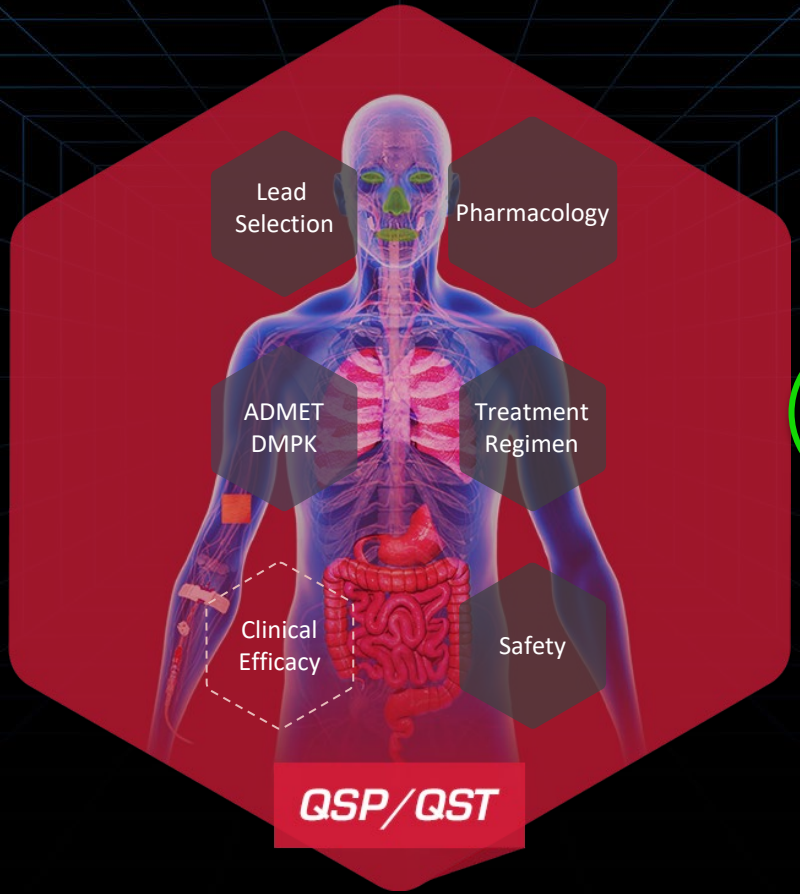
- QST model development is more effective within a consortium style setting
  - Collaboration
  - Sharing
  - Common deliverables
- DILIsym and RENAsym are developed within consortia
  - Partner with us today via membership!
- Licensing, consulting, and training options are available outside of membership as well

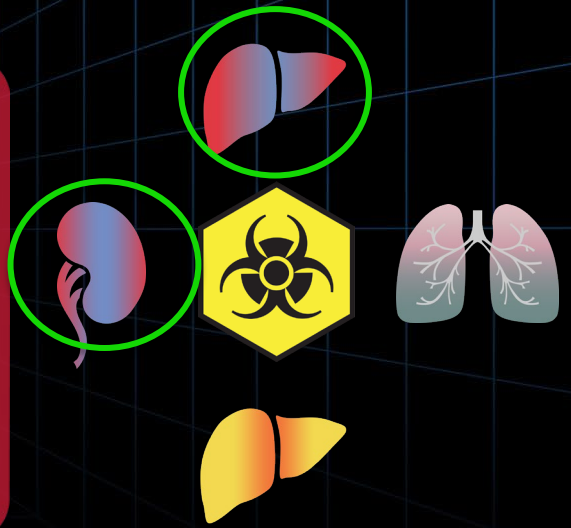
Our *QSP/QST* Solutions Employ Comprehensive, Mechanistic Models to Address Key Drug Development Areas

DILIsym®
RENAsym®
NAFLDsym®
IPFsym™
RADAsym™

Services

QSP Consulting
QST Consulting





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The DILI-sim Initiative is a Partnership Between DILIsym Services and Pharmaceutical Companies to Minimize DILI

DILIsym Services
A SIMULATIONS PLUS COMPANY

janssen
gsk GlaxoSmithKline
GILEAD
DILIsym
abbvie
SERVIER

Select Sample of Current Companies Licensing DILIsym

For a comprehensive review of progress, see ***Watkins 2019: Clin Transl Sci***

- *Overall Goals*
  - *Improve patient safety*
  - *Reduce the need for animal testing*
  - *Reduce the costs and time necessary to develop new drugs*
- *History*
  - *Officially started in 2011*
  - *20 major pharmaceutical companies have participated*
  - *Members have provided compounds, data, and conducted experiments to support effort*
  - *Over $10 million total invested in project*
- ***At least 29 cases of use for regulatory purposes***
- ***Over 30 publications***

Top DILIsym Related Content from 2020

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OXFORD SOT Society of Toxicology academic.oup.com/toxsci

TOXICOLOGICAL SCIENCES, 177(1), 2020, 84–93

doi: 10.1093/toxsci/kfaa093
Advance Access Publication Date: 24 June 2020
Research Article

Mechanistic Investigations Support Liver Safety of Ubrogepant

Brenda Smith,* Josh Rowe,*,1 Paul B. Watkins,† Messoud Ashina,‡ Jeffrey L. Woodhead,§ Frank D. Sistare,¶ and Peter J. Goadsby‖

*Allergan plc, Irvine, California; †Eshelman School of Pharmacy and Institute for Drug Safety Sciences, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; ‡Department of Neurology, Danish Headache Center, Faculty of Health and Medical Sciences, University of Copenhagen, Københavns, Denmark; §DILIsym Services, Durham, North Carolina; ¶Merck & Co., Inc., West Point, Pennsylvania and ‖NIHR-

ELSEVIER Regulatory Toxicology and Pharmacology

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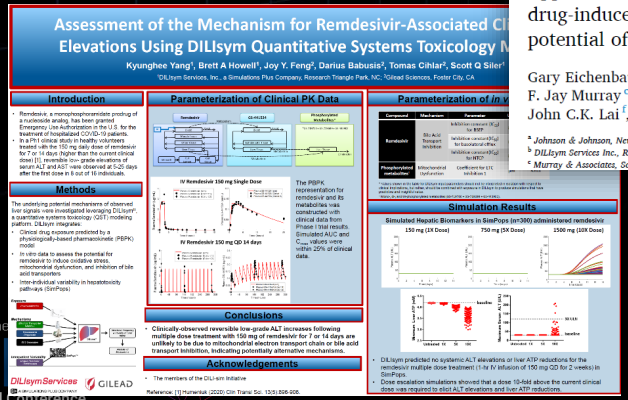

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DILIsym®

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*Now includes **RENAsym™ Consortium** membership at no additional cost!*

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RENAsym Scientific Advisory Board

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Dr. K Melissa Hallow
Assistant Professor
School of Chemical, Materials, and Biomedical Engineering
University of Georgia

Dr. Zheng Dong
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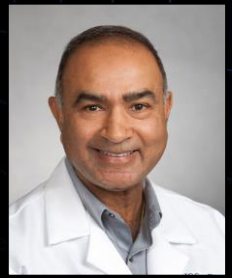
Senior Career Scientist, Director of Research
Charlie Norwood VA Medical Center

Lauren Aleksunes, PharmD, PhD, DABT
Associate Professor, Graduate Director
Pharmacology and Toxicology
Rutgers University

Dr. Frank Sistare
Former Executive Director of the Department of Laboratory Sciences and Investigative Toxicology within Safety Assessment at Merck
Former Co-Chair, Nephrotoxicity Working Group, PSTC
Formerly also with FDA/CDER for 15 years



Dr. Ravinder L Mehta
Professor of Medicine in the Division of Nephrology and Associate Chair for Clinical Affairs
Department of Medicine
University of California, San Diego (UCSD)

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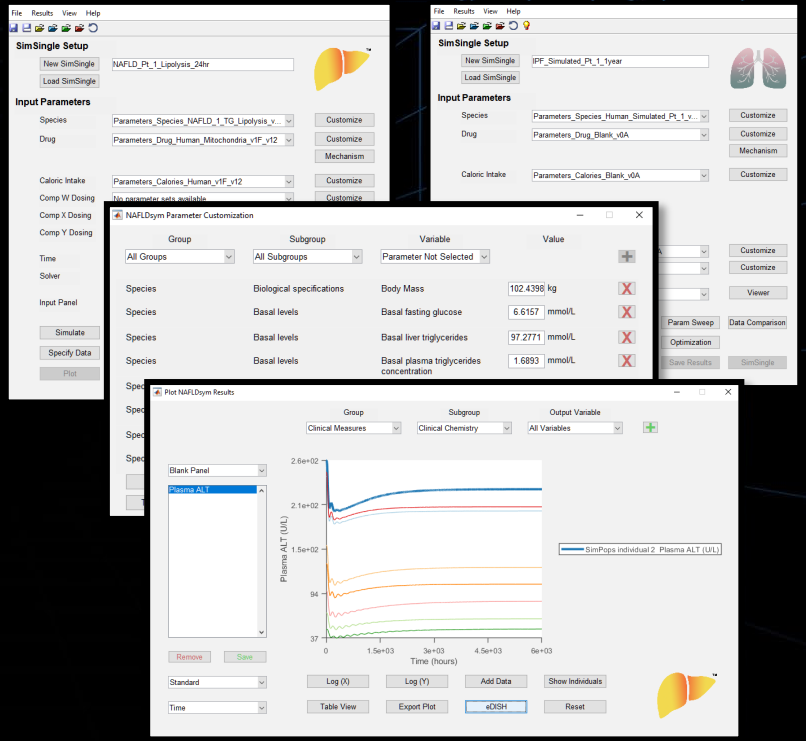
Areas of Focus for RENAsym Consortium

- ***Context of Use***: define critical needs from in silico platform to support various aspects of drug development
- ***Oversight***: review progress on RENAsym development and provide feedback and guidance to ensure optimal usefulness
- ***Data Inputs***: collaboratively assess in vitro platforms as useful inputs into RENAsym and provide input on new study designs
- ***Share***: share data, and eventually RENAsym use insight and feedback, with other members
- ***Visibility***: use consortium as a platform to advance the case for human predictions from in vitro systems + simulations; also provides vehicle for engagement with regulators on use of tool

Other Partnership Avenues

QSP Platform License Provides Opportunity to Actively Utilize QSP Model

- Annual licenses to NAFLDsym, IPFsym, and other QSP platforms are available
  - Includes capabilities of predicting effects of treatments on numerous disease aspects
  - Includes 10 hours of training per product
  - Local desktop installations only
  - No network shareable licenses
  - Must be renewed annually
  - Additional licenses can be made available at reduced, volume pricing
- Equations can be viewed by users
  - Can be modified to represent novel targets
  - No original NAFLDsym v2A code can be ported out to other MATLAB files or languages without the permission of DILIsym Services



General Project Timeline and Deliverables

Stage I Project Activities

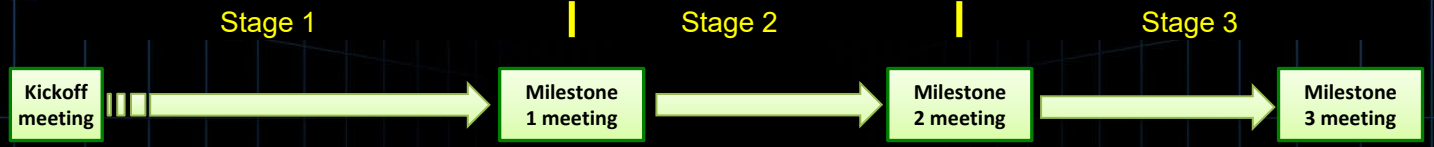
- Updates to NAFLDsym to represent NAFLD therapeutic strategies
- Represent Compound A PK and PD

Stage II Project Activities

- Simulations of Compound A prior studies in representative NAFLD patients
- Simulations of Compound A prior studies in NAFLD human SimPops

Stage III Project Activities

- Simulations of Compound A future clinical trial protocols in representative NAFLD patients
- Simulations of Compound A future clinical trial protocols in NAFLD human SimPops



Final Deliverables

- Final report summarizing findings shortly after project completion

Project costs are dependent upon required resources

Q&A

Questions & Answers

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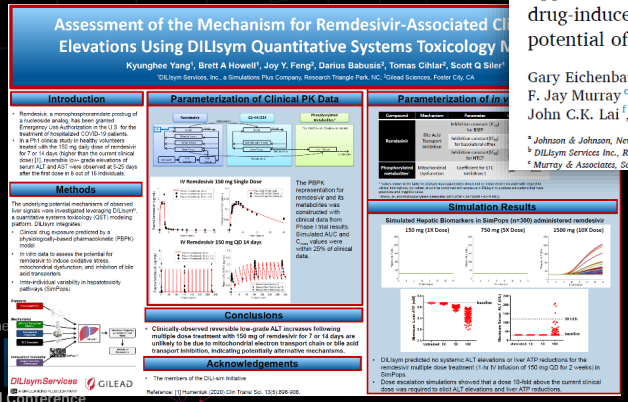

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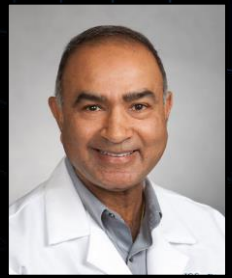
Former Co-Chair, Nephrotoxicity Working Group, PSTC
Formerly also with FDA/CDER for 15 years



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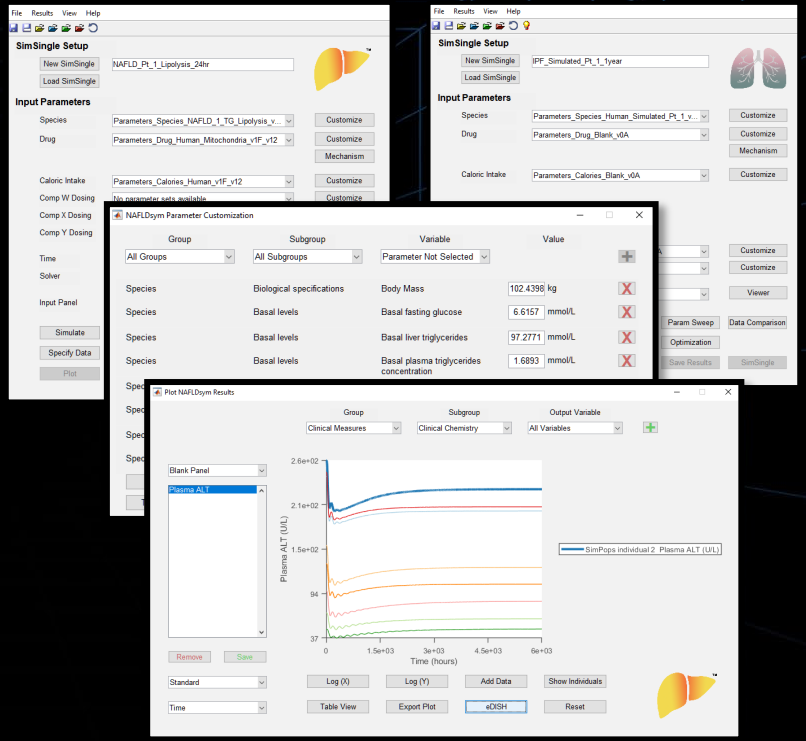
Areas of Focus for RENAsym Consortium

- ***Context of Use***: define critical needs from in silico platform to support various aspects of drug development
- ***Oversight***: review progress on RENAsym development and provide feedback and guidance to ensure optimal usefulness
- ***Data Inputs***: collaboratively assess in vitro platforms as useful inputs into RENAsym and provide input on new study designs
- ***Share***: share data, and eventually RENAsym use insight and feedback, with other members
- ***Visibility***: use consortium as a platform to advance the case for human predictions from in vitro systems + simulations; also provides vehicle for engagement with regulators on use of tool

Other Partnership Avenues

QSP Platform License Provides Opportunity to Actively Utilize QSP Model

- Annual licenses to NAFLDsym, IPFsym, and other QSP platforms are available
  - Includes capabilities of predicting effects of treatments on numerous disease aspects
  - Includes 10 hours of training per product
  - Local desktop installations only
  - No network shareable licenses
  - Must be renewed annually
  - Additional licenses can be made available at reduced, volume pricing
- Equations can be viewed by users
  - Can be modified to represent novel targets
  - No original NAFLDsym v2A code can be ported out to other MATLAB files or languages without the permission of DILIsym Services

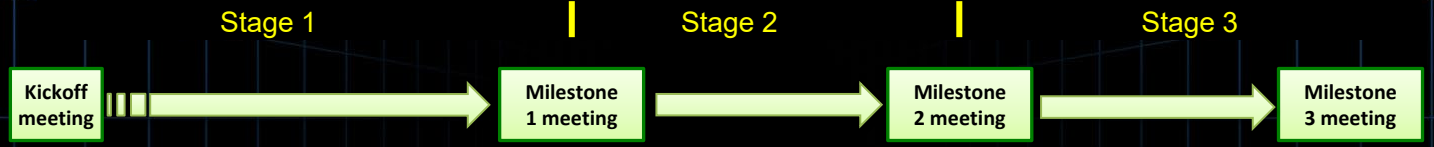


General Project Timeline and Deliverables

Stage I Project Activities
- Updates to NAFLDsym to represent NAFLD therapeutic strategies
- Represent Compound A PK and PD

Stage II Project Activities
- Simulations of Compound A prior studies in representative NAFLD patients
- Simulations of Compound A prior studies in NAFLD human SimPops

Stage III Project Activities
- Simulations of Compound A future clinical trial protocols in representative NAFLD patients
- Simulations of Compound A future clinical trial protocols in NAFLD human SimPops



Final Deliverables
- Final report summarizing findings shortly after project completion

Project costs are dependent upon required resources

Q&A

Questions & Answers

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