Development of Drugs to Treat NAFLD/NASH using Quantitative Systems Pharmacology Modeling

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DILIsym Services

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Session Description and Objectives

Description

- This session will provide scientific background and overview of the application of quantitative systems pharmacology (QSP) modeling in drug development to treat NALFD/NASH
- A case study will be presented where NAFLDsym, a QSP modeling platform, was employed to support clinical development of an acetyl-CoA carboxylase inhibitor (ACCi) to treat NAFLD/NASH

Objectives

- To explore components and scientific backgrounds of quantitative systems pharmacology (QSP) modeling of NAFLD/NASH
- To understand the mechanistic representation of pathophysiology of NAFLD/NASH within NAFLDsym
- To understand how QSP modeling was employed to support clinical development of an ACCi to treat NAFLD/NASH

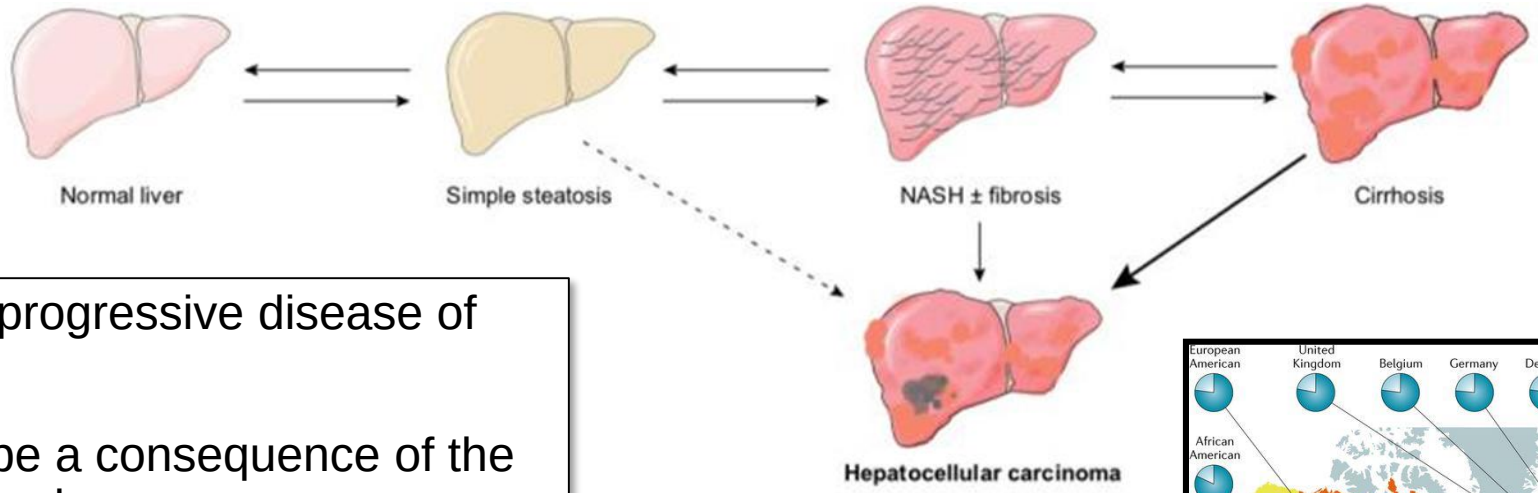
Biography and Contact Information

- Scientist for DILIsym Services, Inc. and software developer working on the DILI-sim Initiative modeling team
- Research focuses on the quantitative systems pharmacology/toxicology (QSP/QST) modeling of drug-induced liver injury (DILI) and treatment of radiation injury
- B.S. in pharmacy and M.S. in pharmacokinetics from Seoul National University, South Korea; Ph.D. in Pharmaceutical Sciences from University of North Carolina at Chapel Hill
- Published scientific papers in the areas of drug metabolism and transport, regulation of drug metabolizing enzymes during pregnancy, and QST modeling of DILI
- Invited to speak at multiple scientific meetings including FDA DILI Conference and ASCPT Annual Meeting
- Email: kyang@DILIsym.com

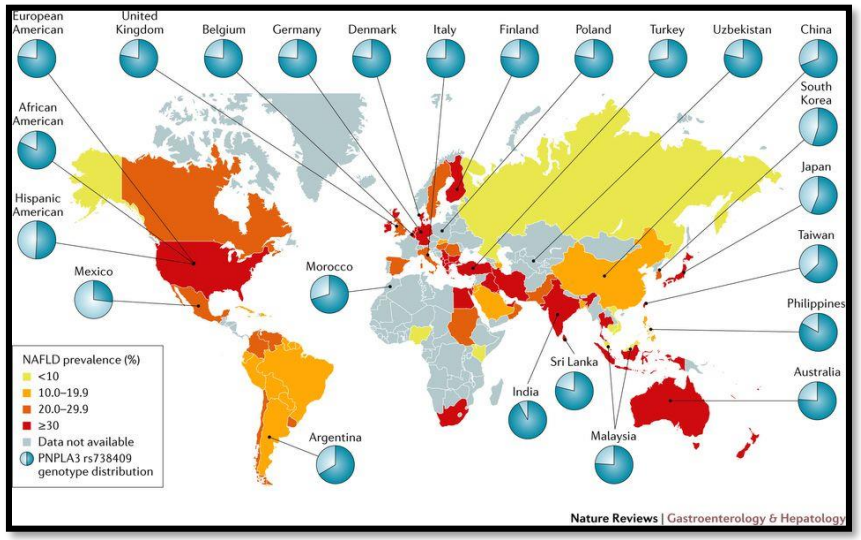
Agenda

- Introduction
  - Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH)
  - Quantitative systems pharmacology (QSP) modeling
- QSP modeling of NAFLD/NASH
  - NAFLDsym overview
  - Steatosis-lipotoxicity
  - Inflammation
  - Fibrosis
  - Effects of weight loss/gain on NASH disease progression
- Example NAFLDsym application
  - Development of an acetyl-CoA carboxylase inhibitor (ACCi)

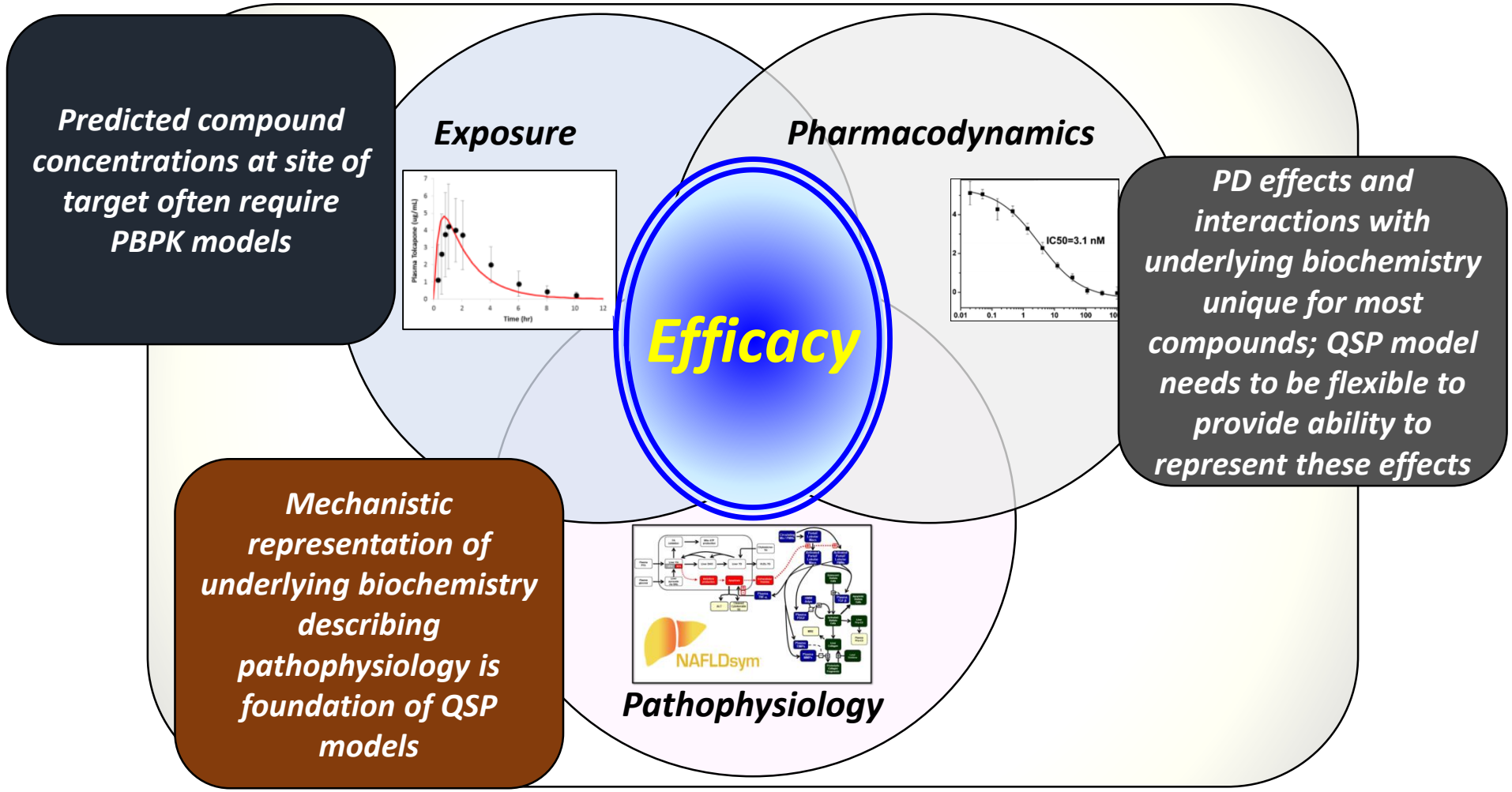
NAFLD and NASH Is a Progressive Condition with Distinct Stages



- NAFLD is a progressive disease of the liver
- Believed to be a consequence of the Metabolic Syndrome
- Lipotoxicity causes hepatocellular apoptosis, inflammation, and fibrosis
- Cirrhosis and HCC are possible consequences of NAFLD/NASH



QSP Models Predict Efficacy via the Intersection Between Pathophysiology Mechanisms, Compound Exposure, and PD



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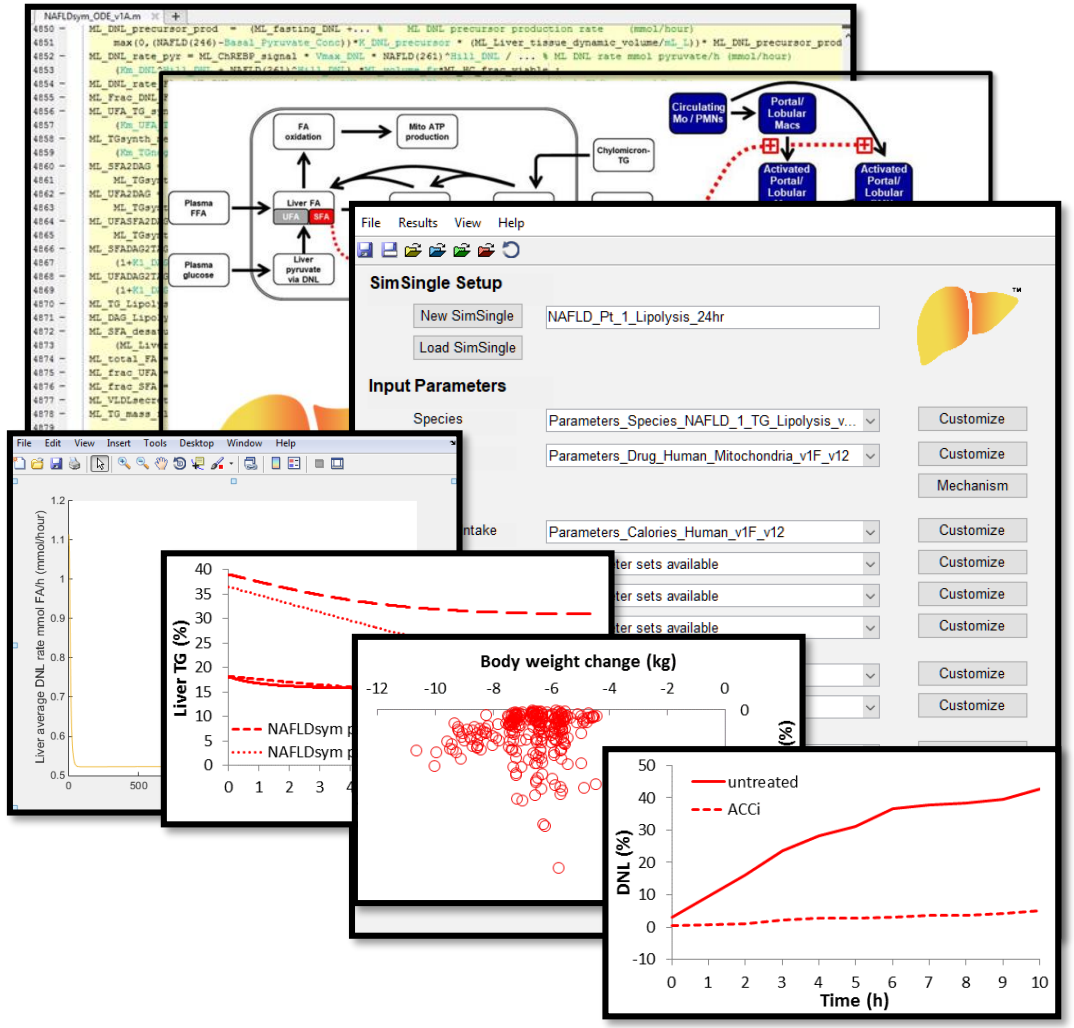
NAFLDsym Is Designed to Support Drug Development with Efficacy Predictions

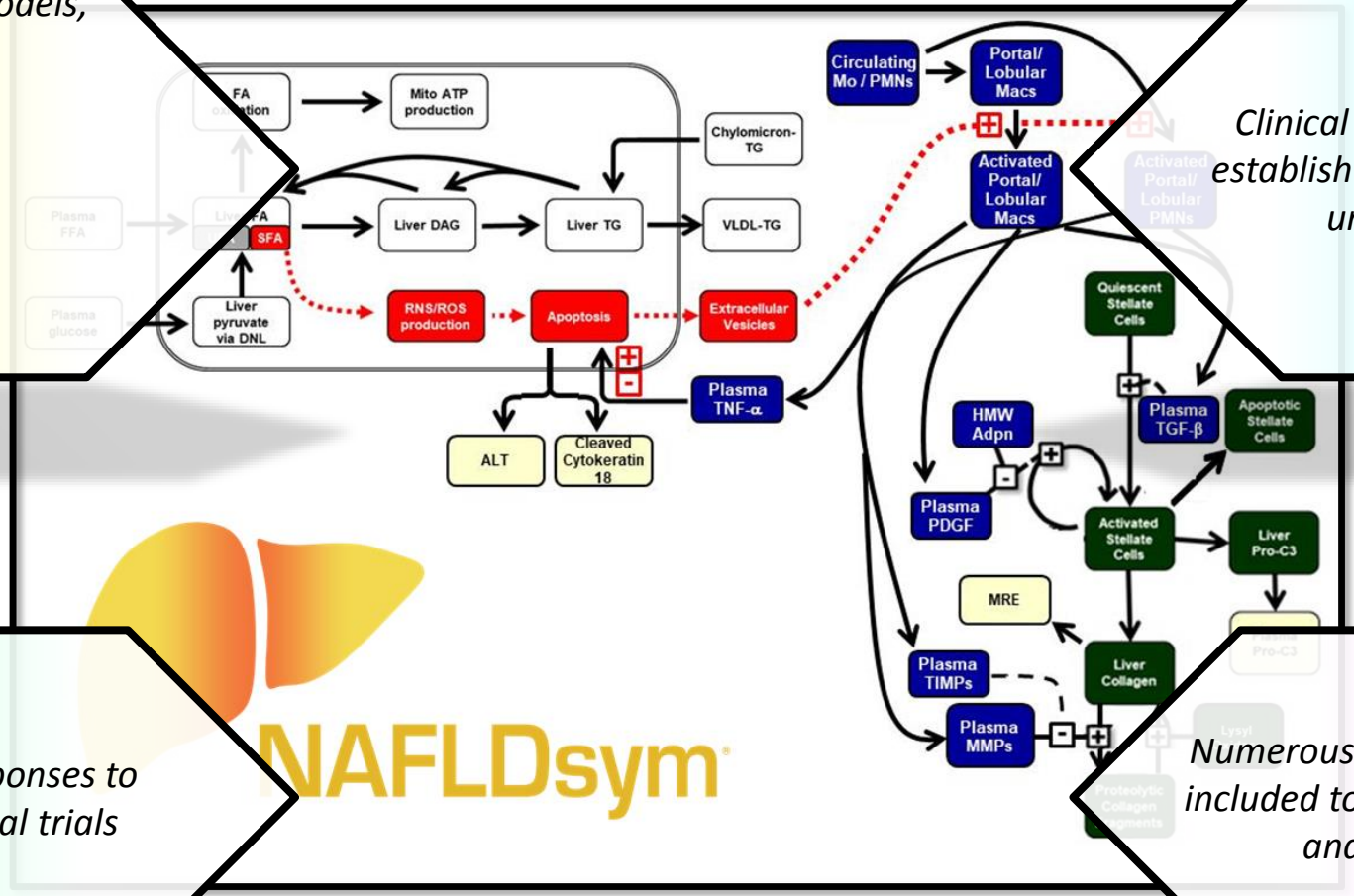
- NAFLDsym is a QSP model of NAFLD/NASH
  - NAFLDsym v2A includes steatosis, lipotoxicity, inflammation, and fibrosis sub-models
  - Includes pathophysiologically diverse simulated patients in SimPops
- NAFLDsym can be used to support NAFLD drug development
  - Combines PK, PD, pathophysiology to predict efficacy of novel treatments
  - Flexible framework facilitates addition of new targets as needed
  - Can be used to optimize clinical trial protocols and identify key hypotheses related to mechanistic underpinnings of predicted response to treatment
  - Provides ability to evaluate combinations of treatments with different mechanisms of action
- NAFLDsym has been used in collaborative research agreements with Pfizer, Gilead and other companies to inform clinical programs



NAFLDsym v2A Overview

Multiple interacting sub-models, including

- *Steatosis*
- *Lipotoxicity*
- *Inflammation*
- *Fibrosis*
- *Biomarkers*
- *Weight gain/loss*



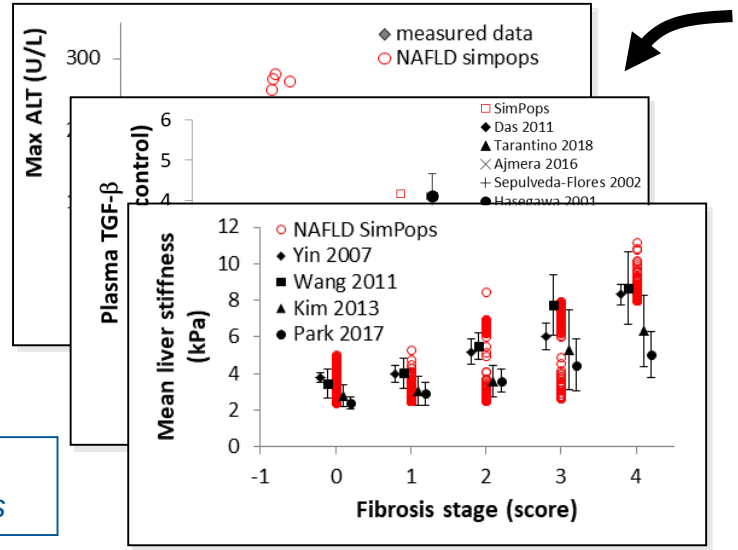
Clinical data from literature used to establish quantitative relationships for underlying biochemistry

Provides ability to predict responses to treatment in simulated clinical trials

Numerous simulated patients (SimPops) included to account for pathophysiologic and clinical heterogeneity

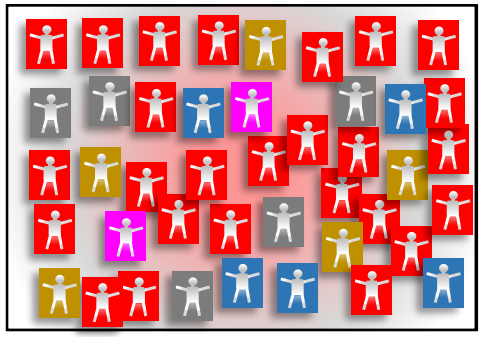
Pathophysiologic Variability Represented in NAFLDsym with NAFLD/NASH SimPops

- SimPops are population samples with variability across key areas of NAFLD/NASH pathophysiology
- Multiple parameters are varied to produce diverse possible simulated patients
- Simulated patients are compared with a multitude of clinical data to validate pathophysiology
- Response data (e.g., dietary intervention) have been used to validate the SimPops



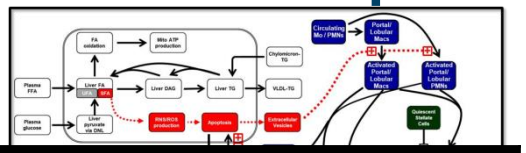
Clinical Data and Simulation Results

Maximos 2015, Das 2011, Tarantino 2018, Ajmera 2016, Sepulveda-Flores 2002, Hasegawa 2001, Yin 2007, Wang 2011, Kim 2013, Park 2017



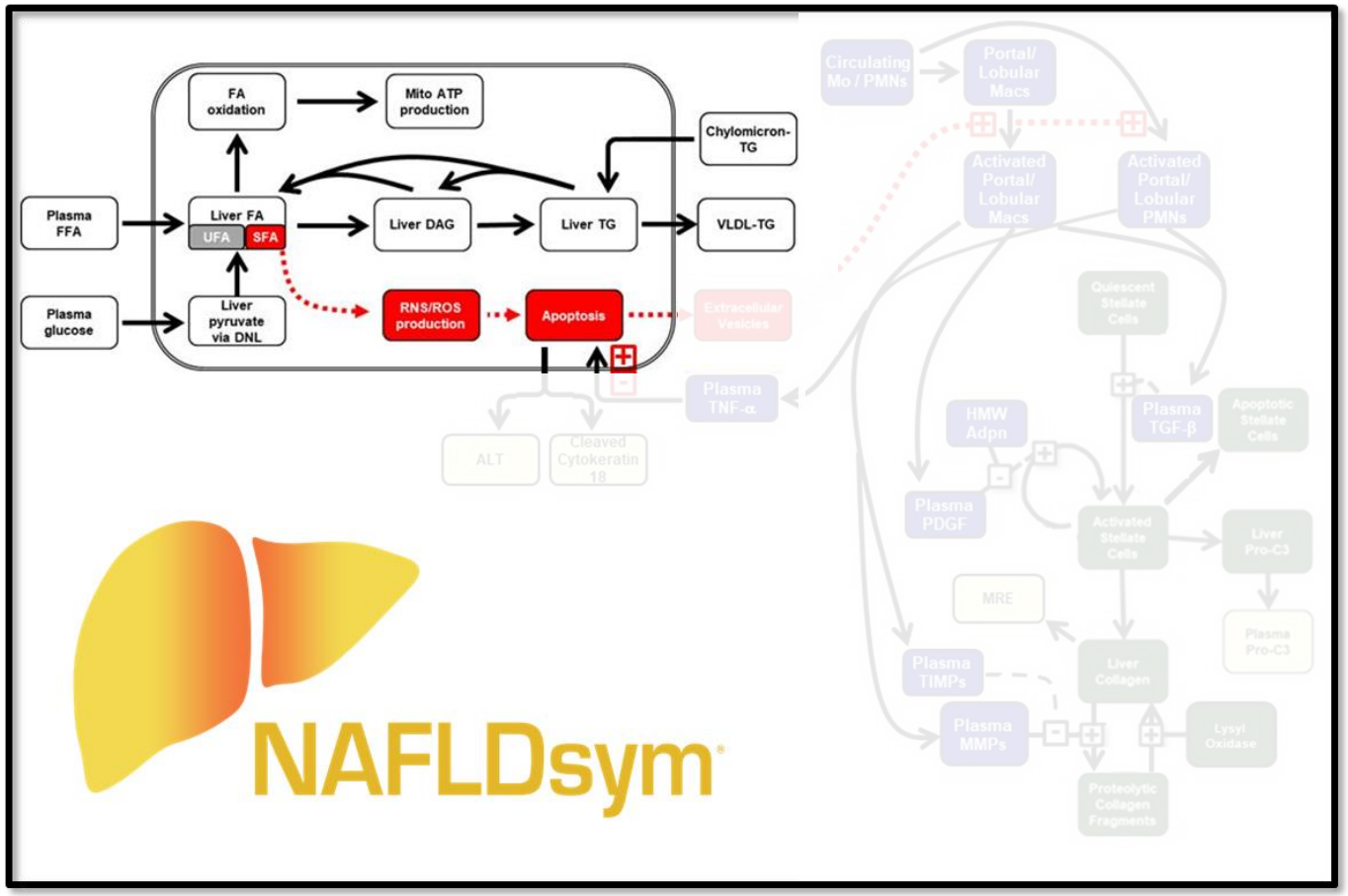
◆ Measured data

○ Simulation results



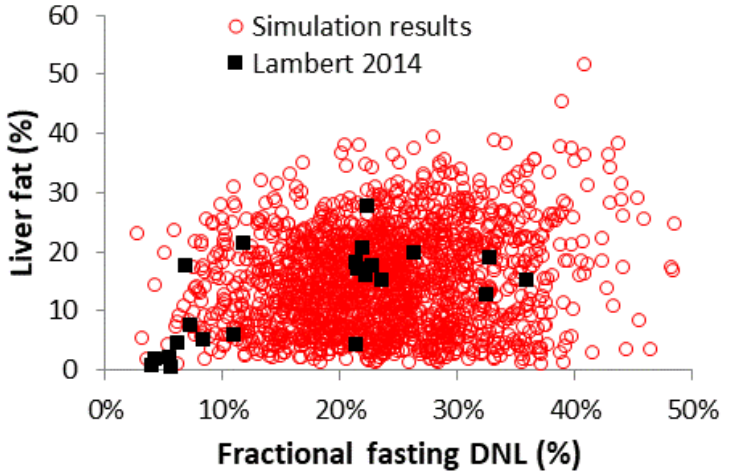
Variables Used to Construct the NAFLDsym v2A SimPops
Body weight
Adipose FA release
De novo lipogenesis
RNS-ROS clearance
Mitochondria function
VLDL-TG secretion rates
Plasma glucose
Hepatic glucose uptake
Plasma TG clearance
Apoptotic sensitivity to RNS-ROS
Necrotic sensitivity to ATP reductions
Hepatocyte regeneration
Extracellular vesicle release
Inflammatory mediator production
Stellate cell activation
Collagen synthesis and degradation

NAFLDsym v2A Overview: Steatosis-Lipotoxicity

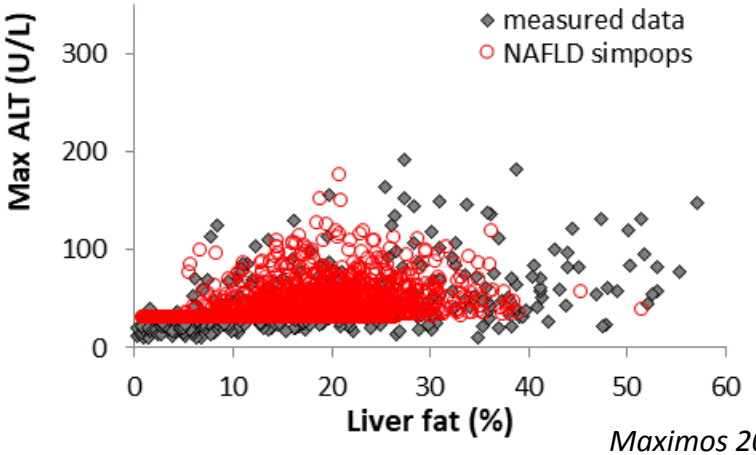


NAFLDsym v2A Includes Simulated Patients with Steatosis, DNL, and Liver Injury Consistent with Clinical Data

- Simulated patients have wide range of contributions to steatosis from DNL
  - Consistent with Lambert 2014 observation that frequency of elevated DNL higher in patients with extensive steatosis
- Majority of simulated patients within range of liver fat-ALT clinical data (Maximos 2015)
  - Indicates that relationship between steatosis and lipotoxicity is captured within SimPops



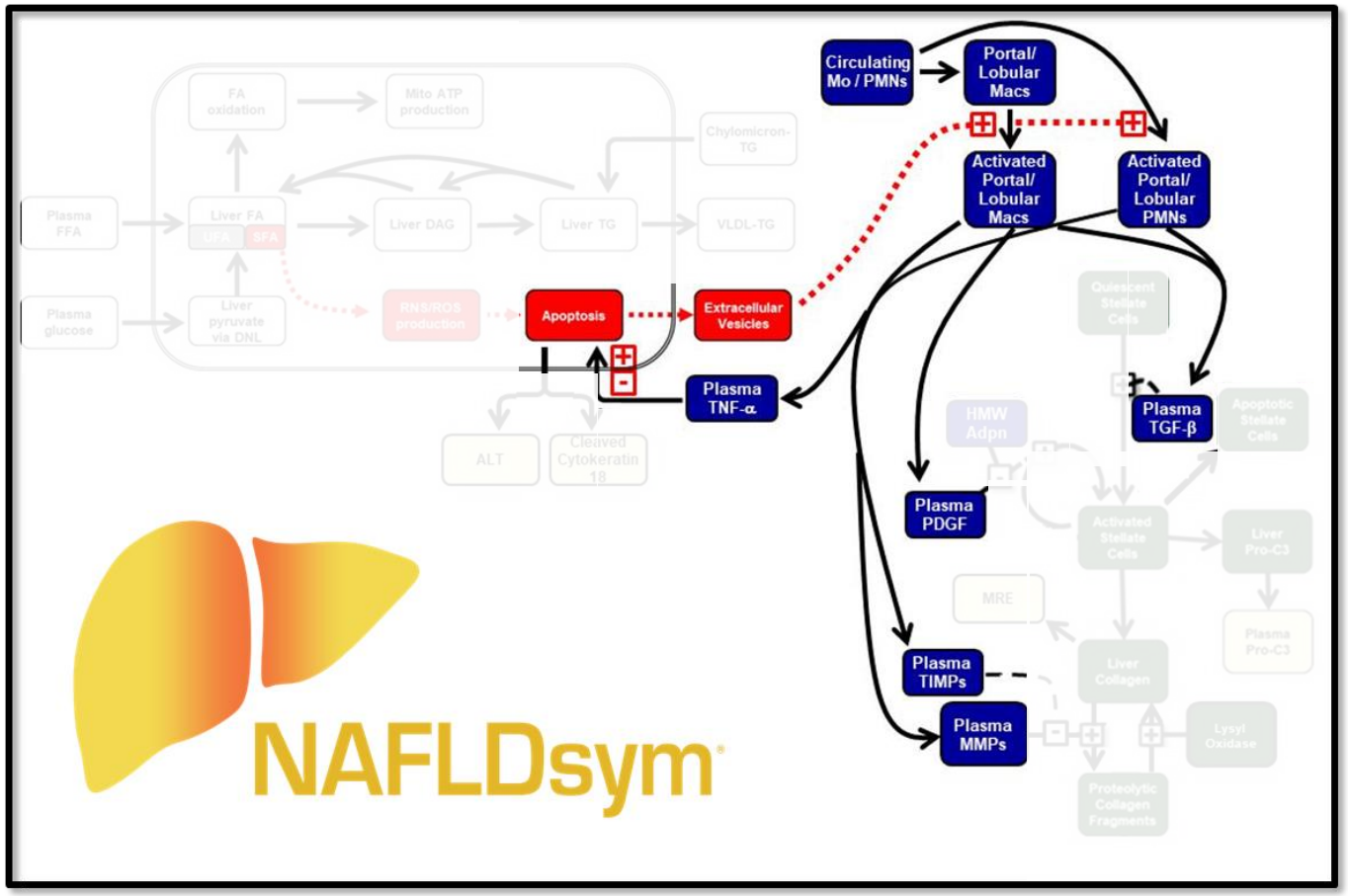
Lambert 2014



Maximos 2015

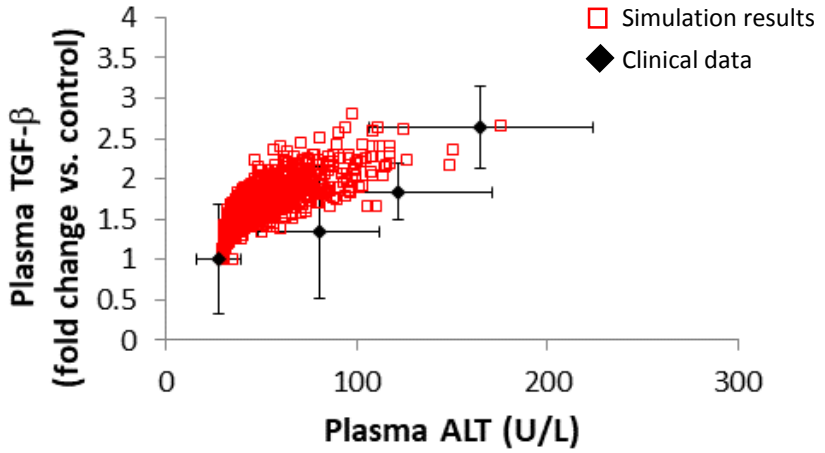
Clinical Data and Simulation Results

NAFLDsym v2A Overview: Inflammation

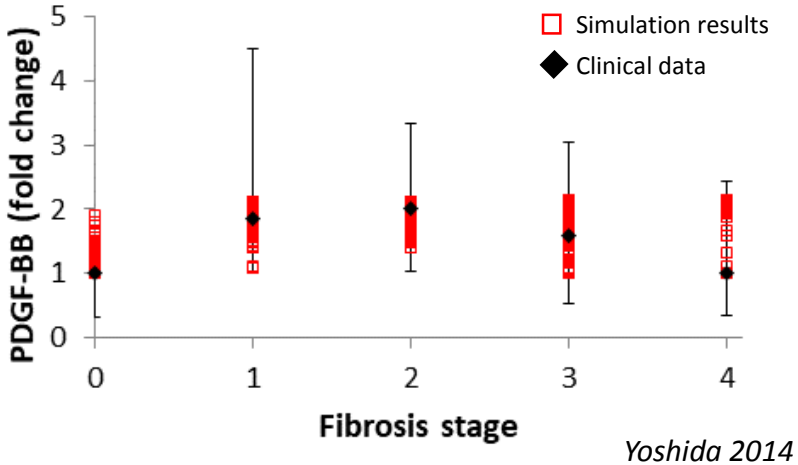


NAFLDsym v2A Include Mediators Consistent with the Majority of Data: TGF-β, PDGF

- Simulation results demonstrate modest increases in TGF-β consistent with the reported range (Das 2011)
  - Other data show no change or modest increases with disease severity



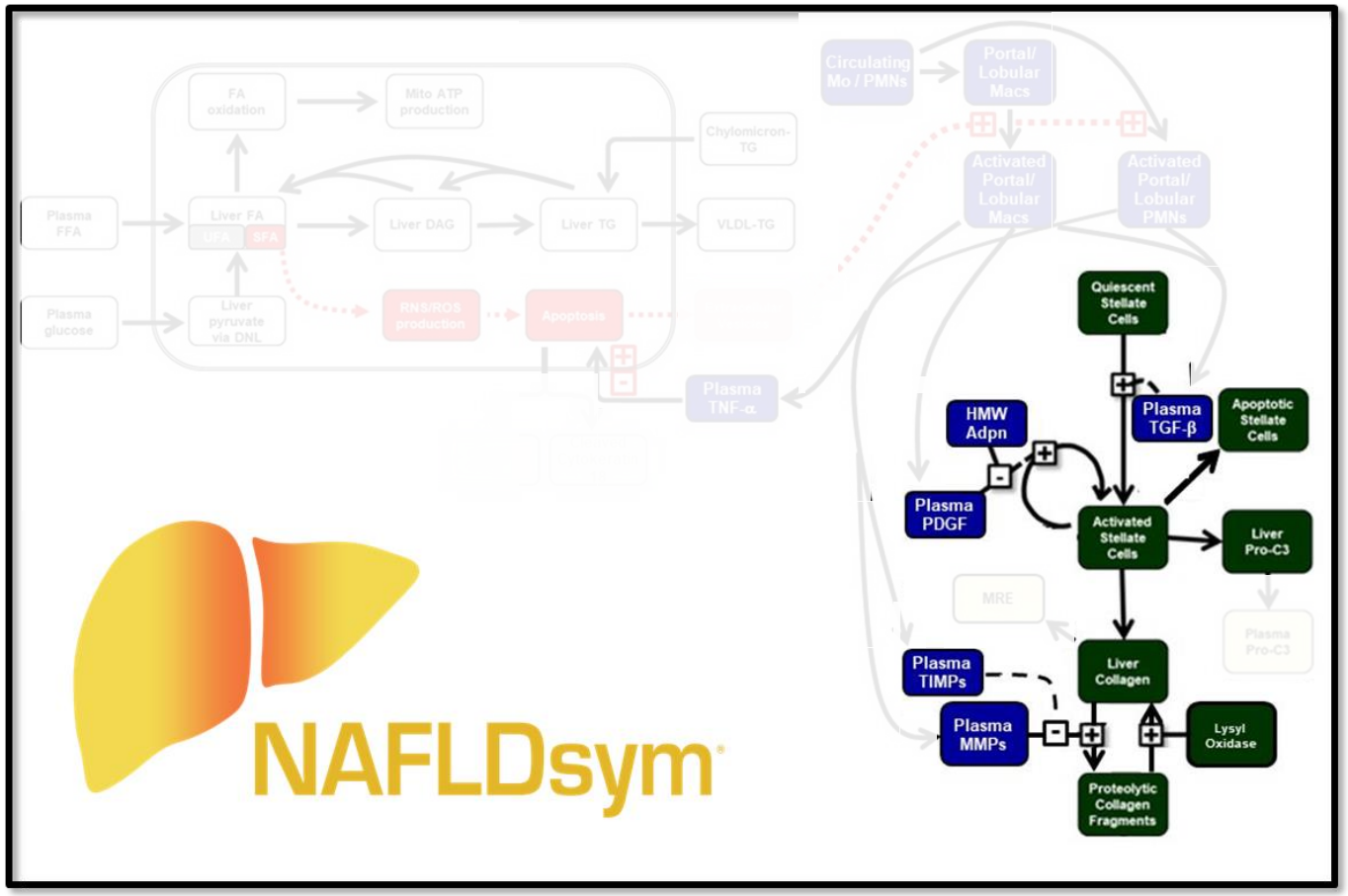
- Simulation results demonstrate modest increases in PDGF consistent with reported increases at lower Metavir fibrosis scores
  - Limited NAFLD data available; Yoshida et al. (2014) report serum levels from a cohort that includes 24% NAFLD patients



Yoshida 2014

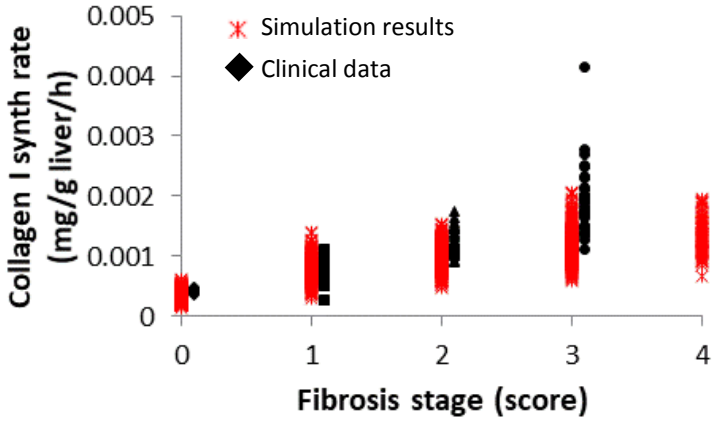
Clinical Data and Simulation Results

NAFLDsym v2A Overview: Fibrosis



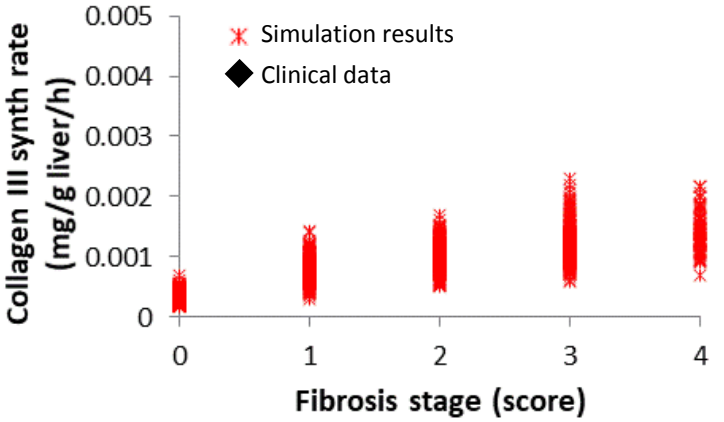
NAFLDsym v2A Has a Range of Collagen Synthesis Rates Consistent with Clinical Data

- Rates of collagen I synthesis are greater in higher fibrosis stages
  - Consistent with clinical data showing increased collagen synthesis rates in NASH patients (Decaris 2017)
  - Rates from Decaris et al. combined with collagen quantities from Masugi et al.



Decaris 2017, Masugi 2018

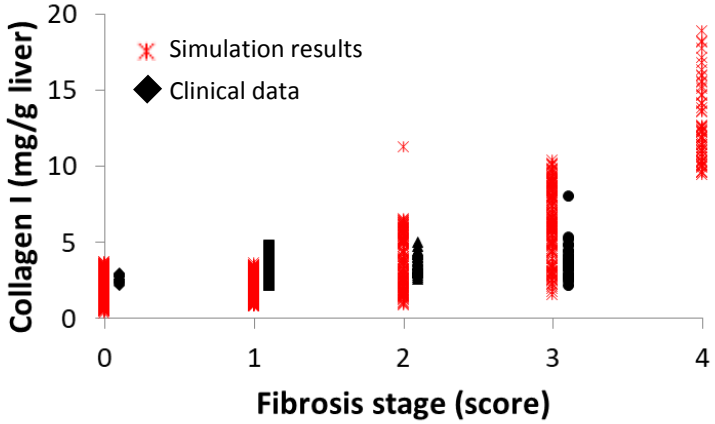
- Rates of collagen III synthesis are predicted to be greater in higher fibrosis stages
  - No clinical data in NASH patients for collagen III synthesis rates
  - Comparable to collagen I synthesis rates



Clinical Data and Simulation Results

NAFLDsym v2A Has a Range of Hepatic Collagen Levels Consistent with Clinical Data

- Hepatic collagen I levels are comparable in fibrosis stages 0, 1, 2, 3
  - Consistent with clinical data showing collagen levels in NASH patients (Masugi 2018)
  - Histologic assessment of collagen levels by Masugi et al. converted to collagen quantities by incorporating data from Aycock and Seyer and Nakabayashi et al.
- F3 and F4 collagen levels can dramatically exceed levels in F0-F2
  - Wide variability in clinical data and simulation results



Masugi 2018, Aycock 1989, Nakabayashi 1993

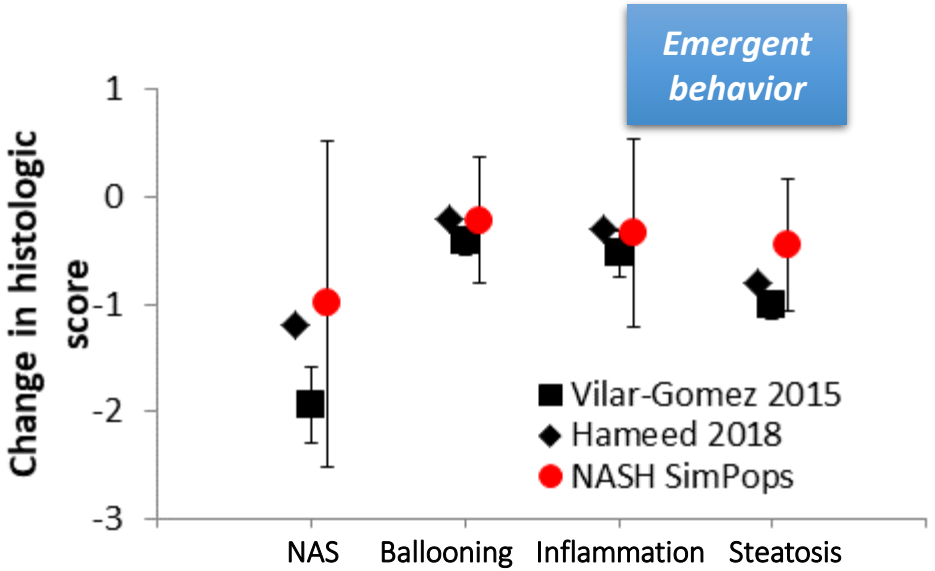
Clinical Data and Simulation Results

NAFLDsym v2A SimPops Patients Include Common Measurements of Treatment Efficacy

Plasma Biomarkers	Histology Measurements	Imaging measurements
Plasma TG	Steatosis score	Liver fat percentage (MRI)
Plasma ALT	Ballooning score	Liver stiffness (MRE)
Plasma cytokeratin cleaved 18 (cK18)	Inflammation score	
Plasma free fatty acids	NAFLD Activity Score (NAS)	
Plasma adiponectin	Fibrosis stage	
Plasma TNF-α	Activated hepatic stellate cells	
Plasma TGF-β	Hepatic collagen	
Plasma Pro-C3		

NAFLDsym v2A SimPops Predicted Response to Weight Loss is Consistent with Clinical Data: NAS

- Weight loss has been shown to improve NASH and fibrosis
  - Current standard of care
  - Greater efficacy with greater weight loss
- Simulated ≈5% weight loss over 1 year
  - Comparable to data from clinical studies by Vilar-Gomez 2015 and Hameed 2018
  - Compared predicted changes in NASH biomarkers with clinical data
  - Good agreement between predicted changes in NAS score and components and clinical data
- Provides validation for NAFLDsym v2A SimPops

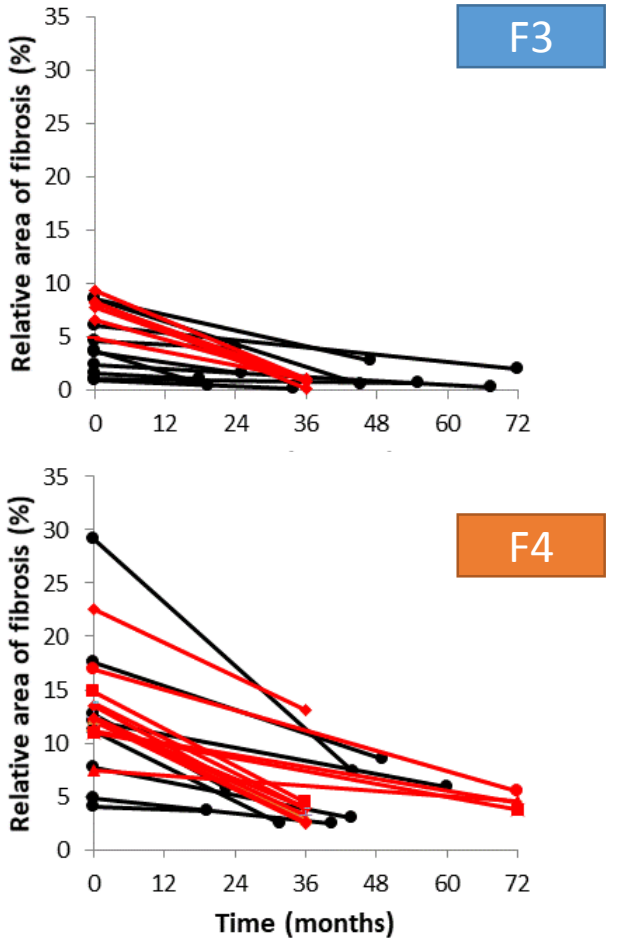


Vilar-Gomez 2015, Hameed 2018

Clinical Data and Simulation Results

Inclusion of Mature Collagen Pools in NAFLDsym Predicts Appropriate Collagen Reduction with Treatment

- Simulated 3-6 years of sustained weight loss in small SimCohorts
  - F3 and F4 simulated patients
  - 5% weight loss
  - Reductions in steatosis, ballooning, inflammation
- Predicted magnitude of fibrosis reduction consistent with clinical data from HCV patients
  - Degradation of mature pool is slower than labile collagen pool
  - F4 simulated patients have greater amounts of mature collagen
  - Arima 2004
- Predicted collagen levels converted to approximate relative area of fibrosis
  - Employed data from Acock and Sayer 1989, Masugi 2018



Arima 2004

Clinical Data and Simulation Results

Weight Gain Correlated with NASH Disease Progression

- NASH patients studied longitudinally, including liver biopsies and histology
  - Wong 2010
  - n=52 patients
  - 3 year time interval between biopsies
- Change in body weight appeared to influence NASH disease progression
  - Based on histologic scoring
  - Patients with increased NAS had increased BMI
- Other studies have shown equivocal results for weight loss effect on progression
  - Variability in body weight over time likely factor
- Disease progression in NAFLDsym driven primarily by changes in body weight
  - Variable alterations in lipids, inflammation and fibrosis

Clinical Data

Table 4 Factors associated with increased non-alcoholic fatty liver disease (NAFLD) activity score from baseline to month 36

Factors	Increased NAFLD activity score	Static or decreased NAFLD activity score	p
N	26	26	
Age (years)	45±9	44±9	0.65
Male gender, n (%)	16 (62)	18 (69)	0.56
Diabetes mellitus, n (%)	15 (58)	11 (42)	0.27
Hypertension, n (%)	12 (46)	14 (54)	0.58
Metabolic syndrome, n (%)	18 (69)	17 (65)	0.77
Body mass index (kg/m^2)	27.4±4.1	27.4±3.3	0.99
Change in body mass index (kg/m^2)*	0.6±1.6	−0.8±1.7	0.003
Waist circumference (cm)	92.8±11.1	92.5±6.7	0.91

Table 3 Distribution of fibrosis stage at baseline and month 36

Month 36	F0	F1	F2	F3	F4	Total
Baseline						
F0	17	7	0	1	1	26
F1	7	7	1	2	0	17
F2	4	1	0	1	1	7
F3	0	0	1	0	0	1
F4	0	0	0	0	1	1
Total	28	15	2	4	3	52

Table 2 Distribution of disease activity at baseline and month 36

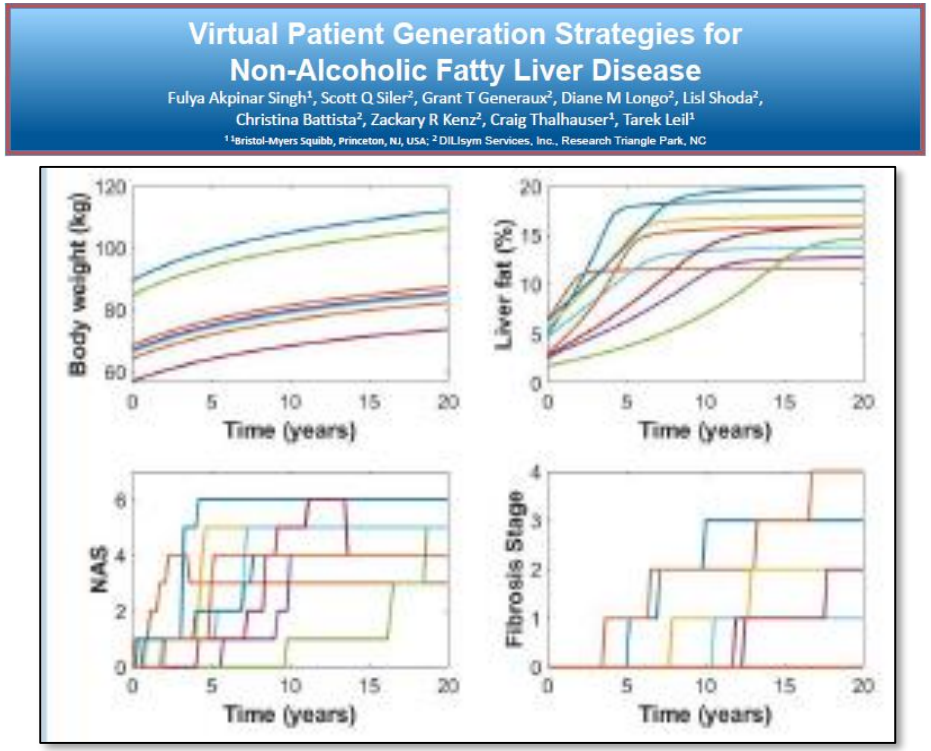
NAFLD activity score at month 36	<3	3–4	≥5	Total
NAFLD activity score at baseline				
<3	12	16	1	29
3–4	5	10	3	18
≥5	0	5	0	5
Total	17	31	4	52

NAFLD, non-alcoholic fatty liver disease.

Wong 2010

NASH Disease Progression via Weight Gain Predicted in NAFLDsym

- Simulated weight gain over 20 years in SimCohorts
  - 20-30% increase in body weight
  - McTigue 2002
- Increase in food intake and weight gain elicit increases in steatosis
  - Driven by increases in de novo lipogenesis and adipose fatty acid release
- Increased NAS score over time due to lipotoxicity and increased hepatocellular apoptosis and hepatic inflammation
  - Release of pro-fibrotic mediators also drives increased fibrosis



Akpinar Singh 2019

Simulation Results

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- Example NAFLDsym application
  - Development of an acetyl-CoA carboxylase inhibitor (ACCi)

NAFLDsym Was Used to Support the Clinical Development of the ACCi GS-0976

- Early clinical results indicated GS-0976 MoA may be more complex than initially believed

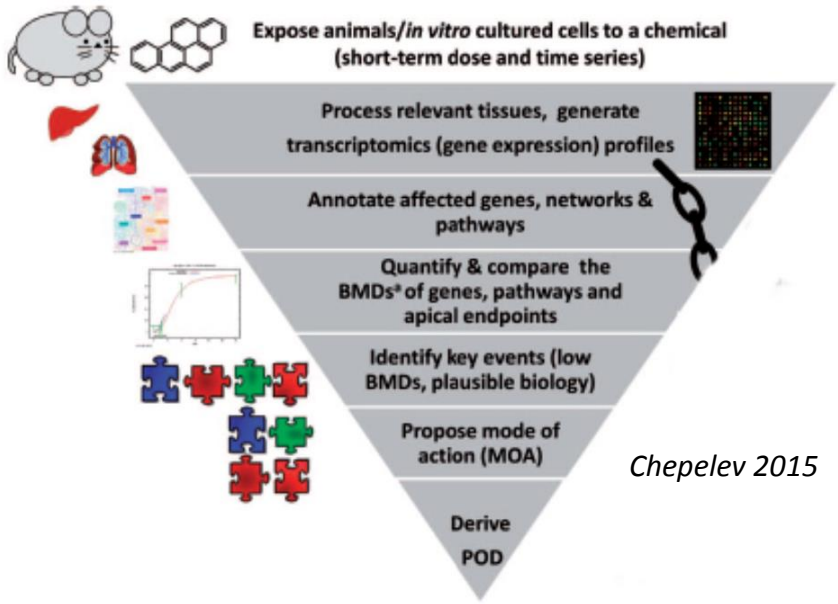
- NAFLDsym employed to evaluate MoA hypotheses
  - Developed PBPK model of GS-0976 (exposure)
  - Utilized existing preclinical and clinical data to determine PD parameters
  - Utilized existing simulated patients to generate appropriate SimCohorts

- Simulation study conducted in parallel with Phase 2 clinical trial; comparison between clinical data and NAFLDsym predictions provided validation
  - Further validated in comparisons with MK-4074

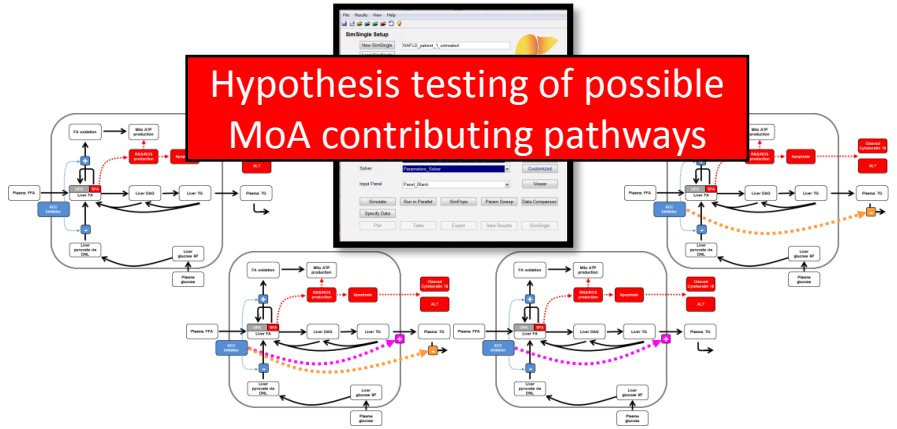
- Simulation study identified key pathways that were activated via downstream gene expression effects and contributed to clinical response
  - Enhanced understanding of MoA helped provide guidance to clinical development program

QSP Modeling and Gene Expression Analyses Have Complementary Approaches

- Gene expression analyses provide large amounts of data in evaluation of drug MoA
  - Identifies specific enzyme(s) that may participate in drug action
  - Challenging to identify causative roles
  - Challenging to determine biochemical context
- QSP modeling provides insight into plausibility of contributions of specific pathways
  - Provides insight into dynamics of pathways affected by drug actions
  - Challenging to identify specific enzyme(s) that may participate in drug action
- Combination of NAFLDsym simulation analyses and preclinical data provided insight into GS-0976 MoA
  - Changes to liver fat and plasma TG

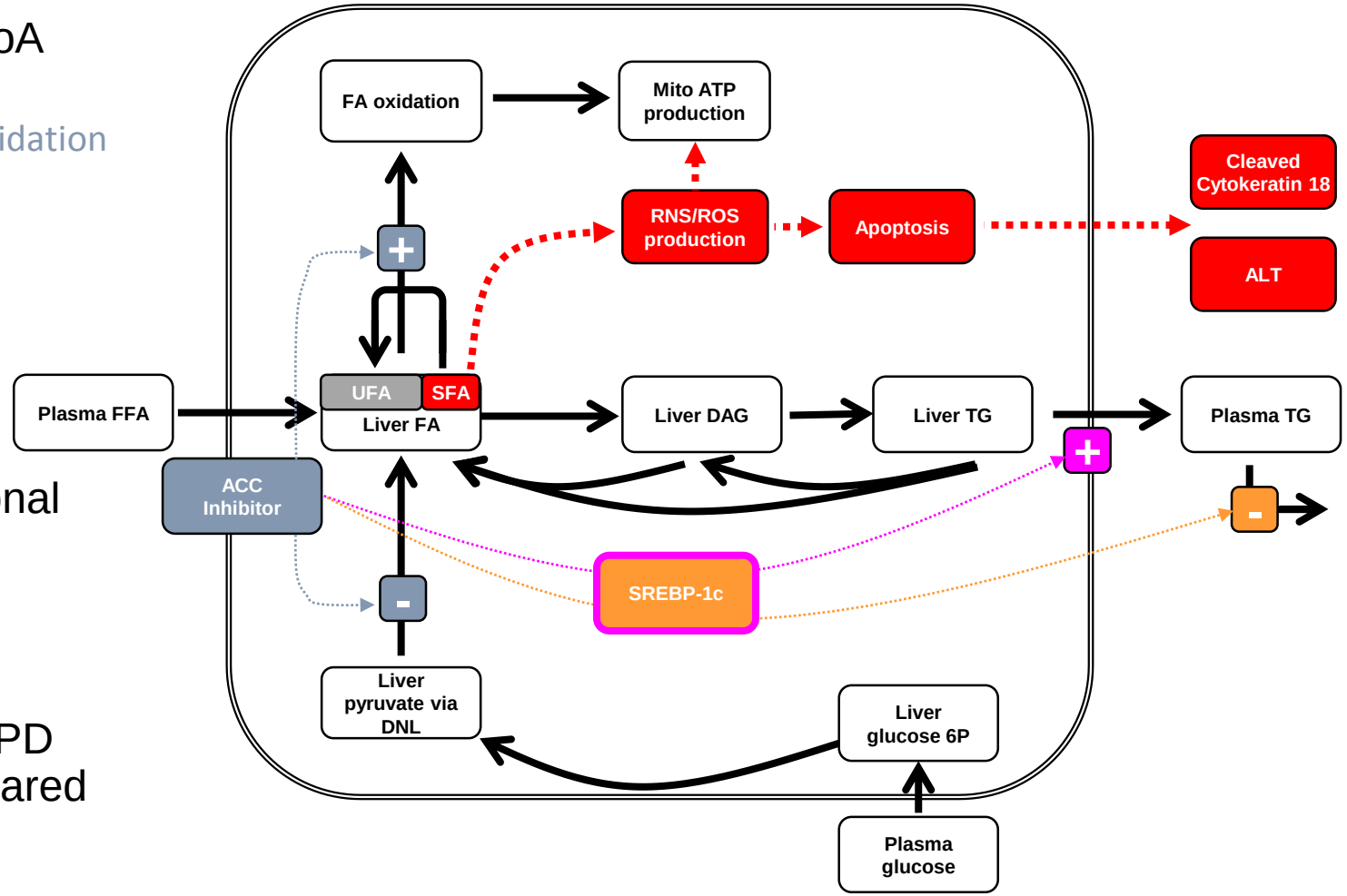


Chepelev 2015



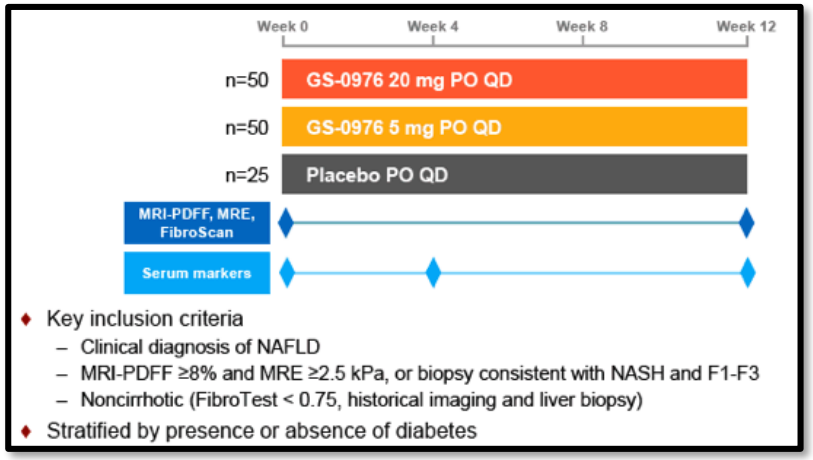
GS-0976 Direct and Downstream PD Effects Included in NAFLDsym

- ACC inhibitor directly reduces Malonyl CoA levels
  - Increases potential for increased fatty acid oxidation (ACC2)
  - Decreases de novo lipogenesis (ACC1)



- Preclinical experiments revealed additional downstream effects
  - Likely due to PPAR-α and/or SREBP-1c
  - ↑ VLDL-TG secretion
  - ↓ Plasma TG clearance
- Performed simulations including varying PD combinations of each pathway and compared with clinical data to determine feasibility

Good Agreement between GS-0976 Phase 2 Clinical Data and NAFLDsym Simulation Results Validates MoA Hypotheses



Loomba et al.
The Liver Meeting (AASLD)
2017

Measure	Dose	Sampling time	Clinical data	Simulation results
Liver fat (%)	20 mg	Baseline	16.3	16.5
Liver fat (%)	20 mg	Week 12	11.6	11.0
Liver fat (%)	5 mg	Baseline	16.4	16.5
Liver fat (%)	5 mg	Week 12	14.9	12.7
Plasma TG (mg/dL)	20 mg	Baseline	181.3	187.3
Plasma TG (mg/dL)	20 mg	Week 12	251.9	231.9
Plasma TG (mg/dL)	5 mg	Baseline	173.3	187.3
Plasma TG (mg/dL)	5 mg	Week 12	209.8	223.1
Plasma ALT (U/L)	20 mg	Baseline	64.7	69.9
Plasma ALT (U/L)	20 mg	Week 12	49.8	48.4
Plasma ALT (U/L)	5 mg	Baseline	70.2	69.9
Plasma ALT (U/L)	5 mg	Week 12	65.9	56.9

Clinical Data and Simulation Results

Acknowledgments

The DILIsym Services Team

Questions

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