REPRESENTATION OF FIBROSIS STAGE WITHIN MECHANISTIC MODEL OF NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)/NON-ALCOHOLIC STEATOHEPATITIS (NASH) ALIGNS WITH HISTOLOGIC ASSESSMENTS

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OBJECTIVE

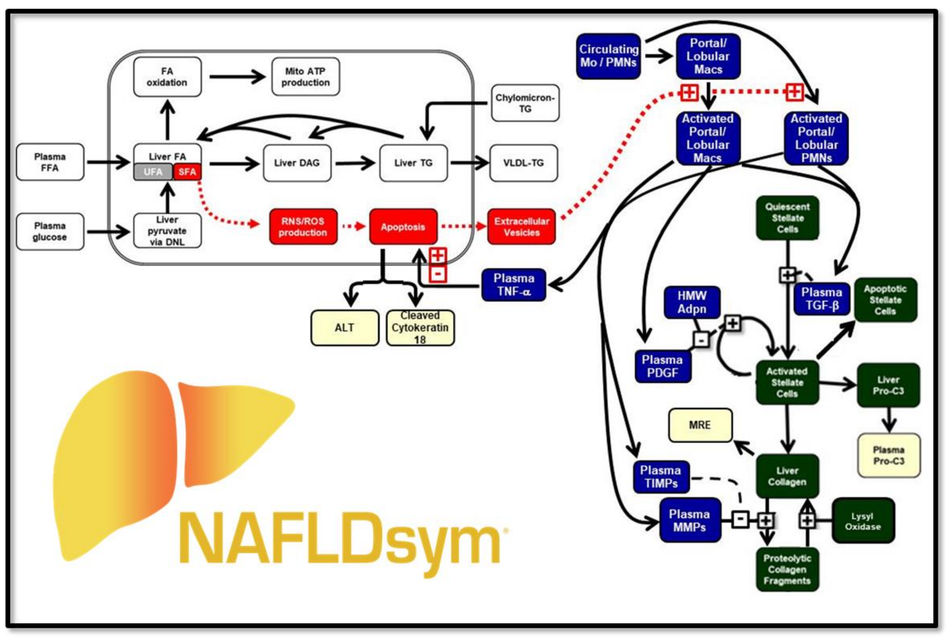
NAFLD encompasses a histological spectrum of liver pathophysiology ranging from steatosis to NASH and may result in cirrhosis and ultimately liver failure. A reduction in fibrosis stage, which has been cited as the strongest predictor for disease-specific mortality[1], is a standard primary outcome when investigating efficacy of potential treatments for NASH patients. Therefore, capturing changes in fibrosis stage is critical to enable accurate predictions of efficacy for treatments within NAFLDsym®, a quantitative systems pharmacology (QSP) model that describes NAFLD pathophysiology[2,3].

METHODS

To maximally leverage available collagen and fibrosis data, a multivariate regression model[4] was used to infer percent fibrosis (or collagen index) from reported serum levels of fibrosis markers for different fibrosis stage patients in multiple studies[5,6,7]. Additionally, a relationship between liver hydroxyproline content and percent fibrosis was used to convert liver hydroxyproline content to total hepatic collagen per wet weight[8,9,10]. Using the aforementioned data, known spatiotemporal dynamics of collagen deposition, and insight into histologic fibrosis scoring methods[11], a computational logic scheme was devised to sequentially compare zonal[12] dynamic collagen amounts and categorize a simulated individual into their appropriate fibrosis stage F0-F4 based on each individual's healthy (i.e., non-NAFLD/NASH) comparator status. The calculations are included within NAFLDsym.

RESULTS

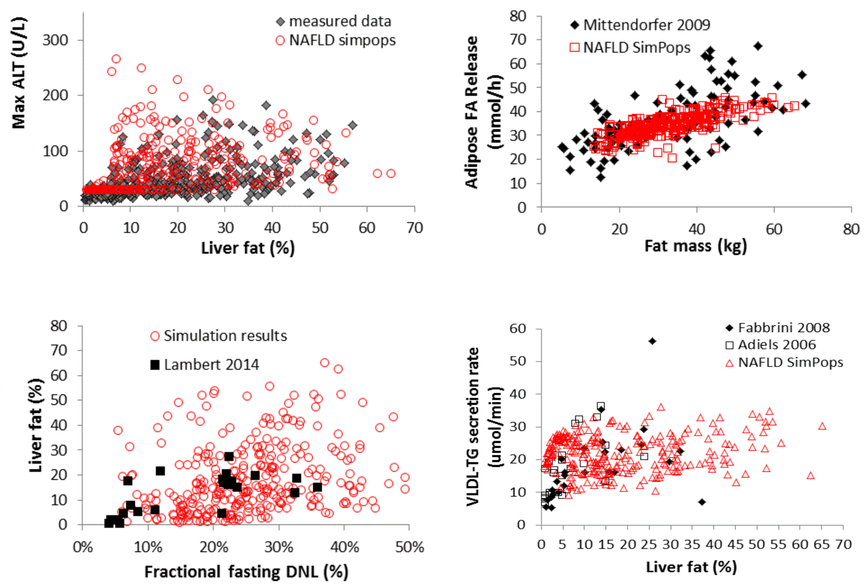
NAFLDSYM OVERVIEW DIAGRAM



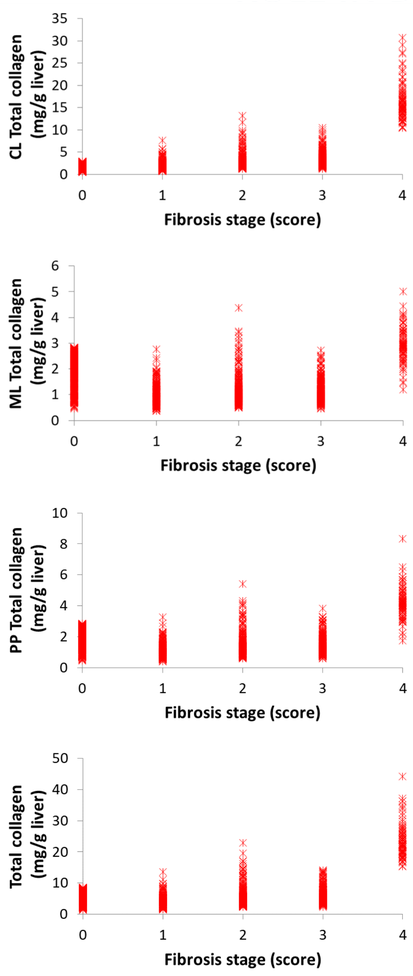
SIMPOPS™ CAPTURE DIVERSE PATHOPHYSIOLOGY OF NAFLD/NASH PATIENTS

Variables Used to Construct the NAFLD 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

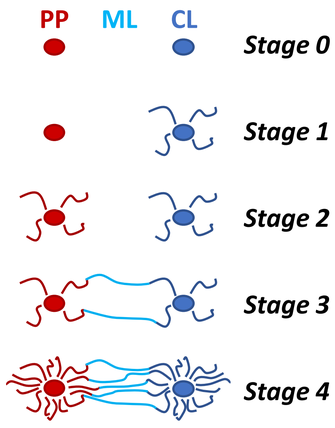
- Simulated NAFLD patients include combinations of parameter ranges based on reported responses from literature[3]
- SimPops incorporate variability in steatosis and lipotoxicity pathways
- SimPops incorporate variability in inflammation and fibrosis sub-models



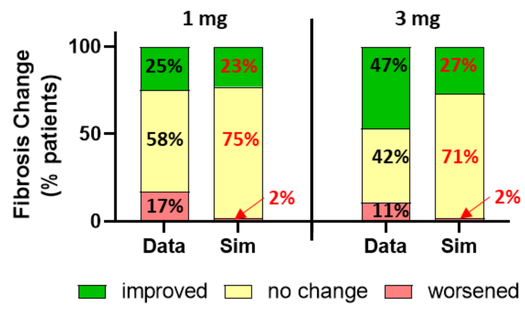
SPATIOTEMPORAL DYNAMICS OF COLLAGEN PLAY A CRUCIAL ROLE IN DETERMINING FIBROSIS STAGE



- Methods (described above) utilized to infer connection between histologic fibrosis stage and level of collagen, zonally and in total liver
- Model captures detectable amounts of collagen observed in healthy, non-NASH patients[15]
- Default fibrosis stage status (F1, F2, F3, etc.) for each simulated individual determined relative to the healthy (non-NAFLD/NASH) comparator for that particular individual
  - Fibrosis stages are defined by the extent to which the collagen level in particular zones (CL, ML, PP) is elevated compared to the normal collagen level for that patient
- Changes in collagen are the consequence of the simulated number of activated hepatic stellate cells (aHSCs); this number varies across zones with CL predominance[12]
  - This is consistent with clinical data showing the degree of HSC activation highest in CL in NASH patients[16]
  - Driven by different susceptibilities for HSC activation across zones
- Rates of collagen synthesis are greater in higher fibrosis stages, consistent with clinical data[17]
- Collagen level is reversible, leading to potential reduction in fibrosis stage with treatment



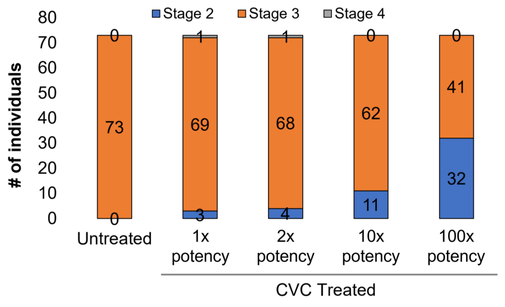
SIMULATED CHANGES IN FIBROSIS STAGE DUE TO NGM282 TREATMENT CONSISTENT WITH REPORTED CLINICAL DATA



	Clinical data		Simulations	
	1 mg (n=24)	3 mg (n=19)	1 mg (n=168)	3 mg (n=168)
NAS ≥2 reduction w/o fibrosis worsening	50%	63%	70.2%	67.9%
Fibrosis ≥1 reduction without NASH worsening	25%	42%	19.6%	23.2%

NGM282, an engineered analogue of FGF19 which interacts with FGFR1 and FGFR4, was simulated in NAFLDsym. Simulations in a SimCohorts (N=168) that mimicked NGM282 clinical patients predicted a change in mean fibrosis stage of -0.2 and -0.3 with 1 and 3 mg QD NGM282 for 12 weeks, respectively, consistent with clinical data[13] that reported a mean fibrosis stage change of -0.1 and -0.5.

SIMULATIONS PREDICT LACK OF FIBROSIS STAGE IMPROVEMENTS FOR CENICRIVIROC, CONSISTENT WITH CLINICAL DATA



Cenicriviroc (CVC), a CCR2/5 antagonist, was simulated in NAFLDsym. Simulations in a NAFLD/NASH SimCohorts (n=73) consisting of individuals with stage 3 fibrosis scores predicted a -0.03 change in mean fibrosis stage with 150 mg QD CVC for 2 years. This was consistent with lack of clinical efficacy that was reported[14] as the cause for termination of the phase 3 clinical trial. Exploratory simulations suggest the possibility of a more potent CCR2/5 antagonist being more efficacious at reducing fibrosis stage and improving NAFLD/NASH outcomes.

CONCLUSION

- NAFLDsym captures the spatiotemporal dynamics of collagen associated with NAFLD/NASH disease progression
- Fibrosis stage in NAFLDsym is defined relative to zonal collagen levels
- NAFLDsym allows for the reversal of collagen levels, enabling potential reductions in fibrosis stage due to interventions
- Accurate predictions of fibrosis stage in NAFLDsym can be used to properly represent the target population for clinical trials and subsequently used to determine efficacy of NAFLD/NASH treatments based on reductions in fibrosis stage

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