QSP Modeling of Liver AMPK Activation Using NAFLDsym Is Predicted to Reduce Steatosis in NAFLD Patients

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) currently has few available treatment options. Bringing effective treatments rapidly to market is paramount. Quantitative systems pharmacology (QSP) modeling can accelerate clinical development by reducing the number of required experiments. One therapeutic target that holds promise is hepato-selective AMP Kinase activation (hAMPKa), with multiple steato-modulatory mechanisms. We used NAFLDsym, a novel QSP model of NAFLD originally derived from DILIsym, to predict the efficacy for hAMPKa. NAFLDsym mechanistically represents many of the key components of steatosis and lipotoxicity.

A simulated cohort (SimCohorts) of 144 NAFLD patients, previously validated based on steatosis reductions due to weight loss, was used to predict changes in liver triglycerides (TG) and lipotoxicity (plasma ALT) with 12 weeks of mid or high hAMPKa. The simulations included hAMPKa-mediated effects on multiple enzymes that regulate de novo lipogenesis (DNL), fatty acid oxidation and TG synthesis.

hAMPKa was predicted to reduce liver TG from 21±14% to 19±14% (mid) and 17±13% (high) after 12 weeks. However, maximal effects had not been achieved in 15% of the SimCohorts within 12 weeks. Plasma ALT was also reduced from 67±44 U/L to 60±39 U/L (mid) and 50±31 U/L (high). Normalization of plasma ALT was achieved in 30% of the SimCohorts.

The NAFLDsym predictions suggest that hAMPKa holds potential for reducing steatosis and lipotoxicity in NAFLD patients. AMPK needs to be activated to a high degree to provide clinically meaningful efficacy. The simulations indicate that clinical trials need to extend for >12 weeks, as a significant proportion of the SimCohorts did not reach maximal liver TG reductions within this time frame.

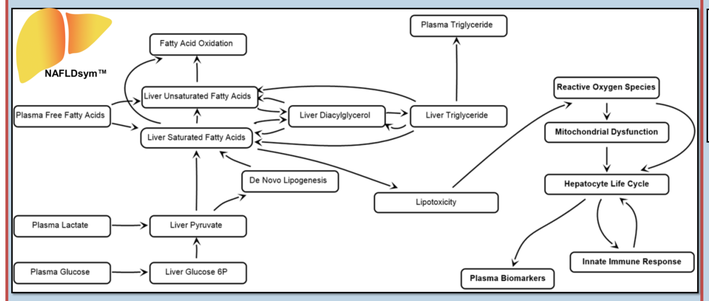
INTRODUCTION

- There is a substantial worldwide incidence of patients with NAFLD, yet there are not effective pharmaceutical treatments currently available for these patients [1]
- NAFLD patients have substantial heterogeneity in pathophysiologic and clinical characteristics
- We have developed NAFLDsym, a QSP model of NAFLD pathophysiology to assist in the development of NAFLD treatments
- AMPK activation in the liver could yield beneficial improvements in liver lipids and relief of lipotoxicity
- NAFLDsym was used to evaluate hAMPKa as a target for treating NAFLD

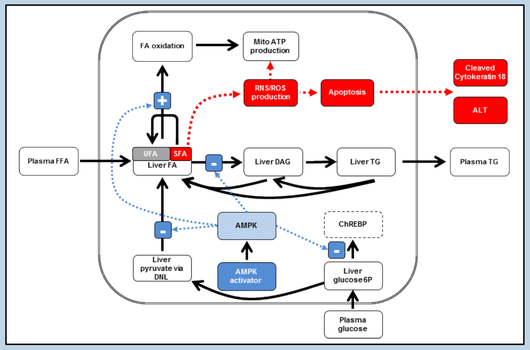
NAFLDsym™

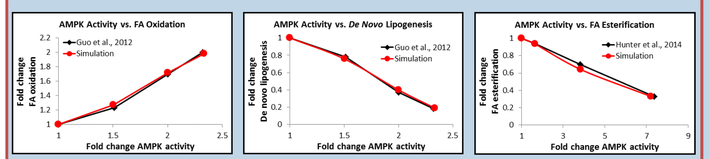
RESULTS

NAFLDsym Overview



Representation of hAMPK Activation in NAFLDsym

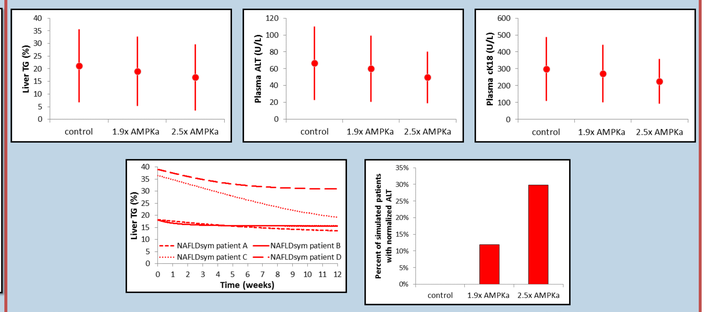




hAMPK Activation effects represented in NAFLDsym and optimized utilizing published *in vitro* pharmacodynamic data

- Fatty acid (FA) oxidation effects optimized with data from Guo 2012 [2]
- De novo lipogenesis effects optimized with data from Guo 2012 [2]
- FA esterification effects optimized with data from Hunter 2014 [3]

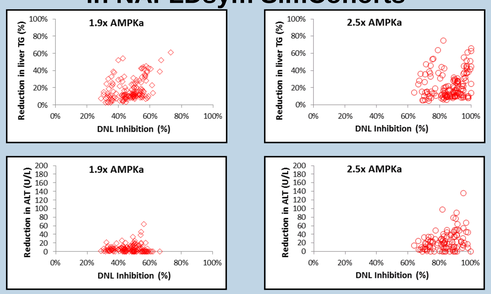
Predicted Efficacy in NAFLDsym SimCohorts



Predicted changes in liver TG, plasma ALT, and cK18 with hAMPKa

- hAMPKa was predicted to reduce liver TG from 21±14% to 19±14% and 17±13% (mean±SD) after 12 weeks
- Plasma ALT was also reduced from 67±44 U/L to 60±39 U/L (mid) and 50±31 U/L (high). Comparable results were predicted for cK18 as well.
- Normalization of plasma ALT (to ≤40 U/L) and cK18 was achieved in 30% of the SimCohorts.
- Maximal liver TG reductions were not achieved within 12 weeks in some simulated patients; Illustrative patient responses to 2.5x hAMPKa shown

Contribution of DNL Reductions to Predicted Efficacy in NAFLDsym SimCohorts

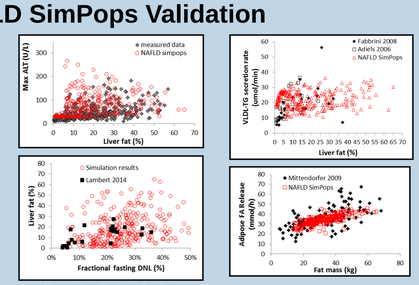


Influence of DNL inhibition on predicted liver TG and plasma ALT reductions

- In general, increasing inhibition of DNL provided greater efficacy for hAMPKa as illustrated by scatter plot of patients in SimCohort.
- The substantial underlying inter-patient variability in DNL contributes to heterogeneity in predicted efficacy

NAFLD SimPops Validation

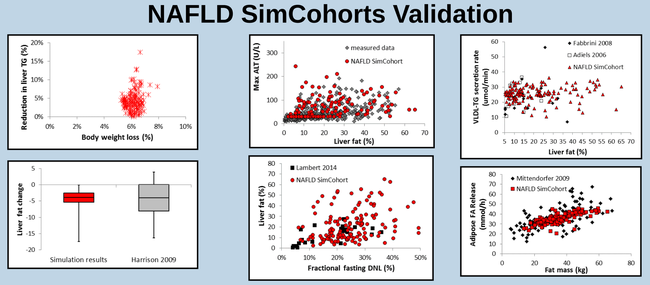
Variables Used to Construct the NAFLD SimPops™
Body weight
Adipose FA release
De novo lipogenesis
RNS-ROS clearance
Mitochondria function
VLDL-TG secretion rates
Plasma glucose
Hepatic glucose uptake
Plasma TG clearance
Apoptotic sensitivity to RNS-ROS
Necrotic sensitivity to ATP reductions
Hepatocyte regeneration



Construction and validation of NAFLD SimPops

- Simulated NAFLD patients (n=304) include combinations of parameter ranges based on reported responses from literature [5, 6, 7, 8].
- Simulated patients within SimPops have pathophysiologic and clinical characteristics consistent with what has been reported in literature [4, 5, 6, 7, 8]

NAFLD SimCohorts Validation



Simulated patient selection for and validation of NAFLD SimCohorts

- A subset of all simulated patients were selected to provide liver TG reductions with weight loss that was comparable to the range of responses reported in Harrison 2009 [9].
- This SimCohort maintained an appropriate range of pathophysiologic and clinical characteristics

METHODS

Overview NAFLDsym was utilized for all simulations. NAFLDsym includes a representation of the primary pathways controlling liver fatty acid and triglyceride fluxes in addition to the effects of lipotoxicity on hepatocellular health. ALT and cK18, biomarkers of hepatocellular loss, are also represented. Simulated levels of liver and plasma TG are also outputs of NAFLDsym.

Simulated patients A simulated population of patients with the pathophysiological aspects of NAFLD are included in NAFLDsym. This SimPops (n=306) includes a number of characteristics that are consistent with the observed heterogeneity of pathophysiologic and clinical features of NAFLD. For this study, a subset of all simulated patients (SimCohorts, n=144) with a validated reduction in steatosis in response to dietary intervention, was utilized.

Simulated effects of hAMPKa AMPK activation elicits a number of downstream effects in the liver, and those effects relevant to lipid partitioning were represented in NAFLDsym. These include effects on fatty acid oxidation [2] and de novo lipogenesis [2] (due to ACC inhibition) and reductions in fatty acid esterification [3] due to reduced activity of GPAT. Reductions in ChREBP expression were also represented [10]. The quantitative relationship between AMPK activation and these downstream effects were established from data in the literature [2,3] and included in NAFLDsym. AMPK was activated to 1.9x and 2.5x above baseline for 24 hours a day during each subsequent simulation.

Simulated Protocols AMPK activation in the liver was simulated in the SimCohorts for 12 weeks. Predicted changes in liver TG, plasma ALT, and plasma cK18 were the primary simulation results used to predict hAMPKa efficacy.

CONCLUSION

- hAMPKa is predicted to have potential for reducing steatosis and lipotoxicity in NAFLD patients.
- Clinical trials with hAMPKa need to extend >12 weeks to allow all patients to reach maximal reductions in steatosis

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