Proof-of-concept that Variable Onset and Severity of T cell-mediated Drug-Induced Liver Injury is Reproduced in a Simulated Human Population

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OBJECTIVE

Idiosyncratic drug-induced liver injury (iDILI) is a rare, but often serious, adverse reaction that can compromise drug development. For some iDILI compounds[1], the adaptive immune system is implicated in the observed liver injury. Previous work extended an existing quantitative systems toxicology (QST) model, DILIsym®, to include human CD8+ T cell responses to hepatocyte-expressed amodiaquine (AQ) related neo-antigen[2,3]. Here, a human simulated population (SimPops™) of patients was developed with variability in characteristics related to T cell responsiveness, including susceptibility to AQ toxicity mechanisms, naïve CD8+ T cell numbers, and T cell differentiation rates. Using this SimPops, this work aimed to examine liver injury profiles and evaluate the key characteristics leading to specific responses.

METHODS

- Liver exposure of AQ predicted using previously developed PBPK representation[3]
- Leveraged previously developed QST model of adaptive immune responses in the liver to simulate liver injury response to AQ in a simulated population[2,3]
- Designed exploratory SimPops, i.e., frequency of response in SimPops is not representative of expected iDILI frequencies in a normal healthy population, to investigate range of potential T cell responses
- Simulated human SimPops (N=1000) with 600 mg AQ dosed weekly for 20 weeks[4] assuming a maximum of 30% of hepatocytes express AQ-related neo-antigen
- All individuals in SimPops assumed to have limited capacity for exhaustion for initial examination, informed by mouse studies with knockout PD-1 and anti-CTLA-4 administration[5]

RESULTS

Key T Cell Parameters and Relevant Ranges Identified for SimPops Construction

Parameters were identified for inclusion in SimPops based on expected variability between individuals and suspected key parameters with few experimental constraints (Table 1). Ranges for SimPops exploration were determined by leveraging biologically relevant values (e.g., naïve baseline T cells) or simulated dynamic range of response (e.g., T cell differentiation). Parameter ranges were uniformly sampled to create simulated individuals.

Parameter	Unit	Min	Max
T cell differentiation	Dimensionless	0.05	0.15
Baseline naïve CD8+ T cells	1e9 Cells	1.6e-7	1.6e-5
Max ER stress clearance	1/hour	0.02	2
ER stress prod'n const 1	1/hour	0.5	500
ER stress prod'n const 2	1/hour	0.5	500
HC EV release	Vesicles/1e9 Cells	2e7	2e10
T cell avidity	Dimensionless	0	1
T cell exhaustion	1/hour	0.001	1.0

Table 1: Parameters varied in T cell SimPops and the minimum and maximum of each range. T cell exhaustion is limited and fixed for the initial analysis but varied for follow-on analysis.

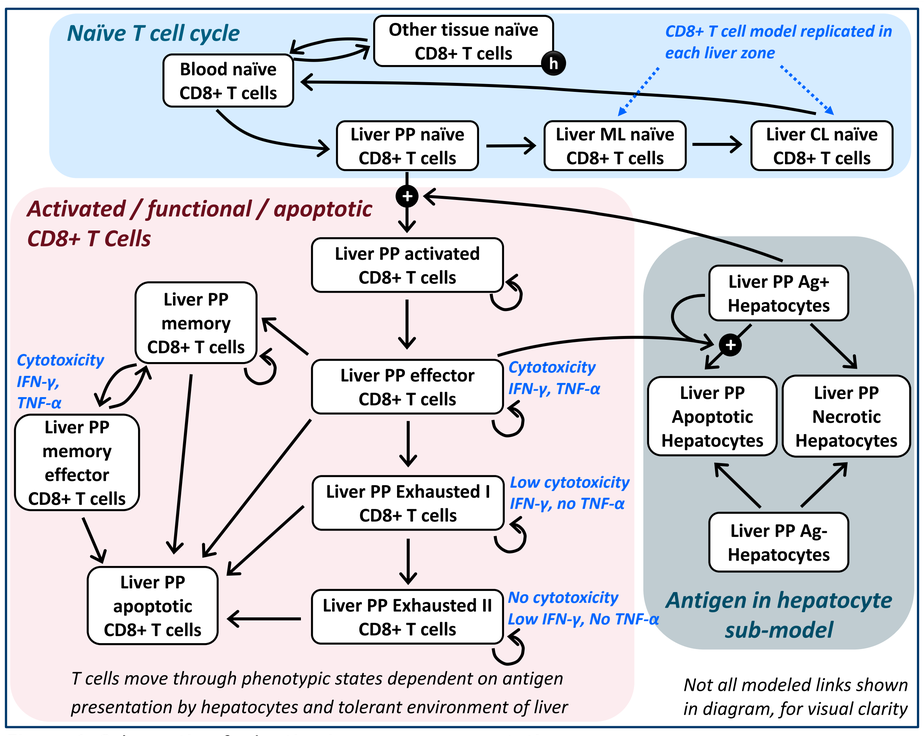

Figure 1: Schematic of adaptive immune representation.

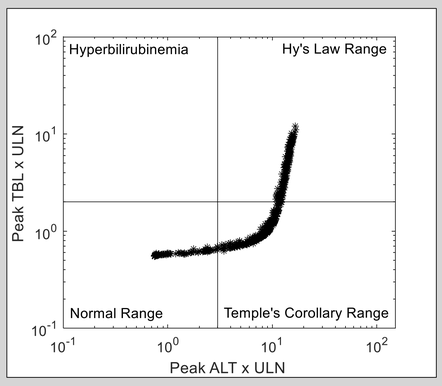

Figure 2: Evaluation of drug-induced serious hepatotoxicity (eDISH) plot of SimPops (N=1000) simulated for 20 weeks with 600 mg AQ weekly.

Liver Injury Profiles from T Cell SimPops Capture Range of Clinical Responses

SimPops outcomes capture a range of response from no injury to mild ALT elevations, to Hy's Law cases (Fig 2). The magnitude of these responses are qualitatively consistent with a range of responses seen in case studies (Table 2). Resultant variability in time to onset of ALT elevations (first time ALT > 3xULN) in simulated population is consistent with clinically reported variability (Table 2). Simulated individuals demonstrate a variety of ALT dynamics, including individuals with progressive ALT increases, stabilizing ALT, and resolving ALT profiles.

Outcome	Clinically Reported	SimPops Results
Time to onset of ALT elevation (ALT > 3xULN)	Observed by 4-12 weeks[6]	1-13 weeks
Observed max ALT	1-70xULN[6]	1-20xULN

Table 2: SimPops results vs. clinical characterization of putative iDILI following AQ administration. Upper limit of normal (ULN) ALT defined as 40 U/L.

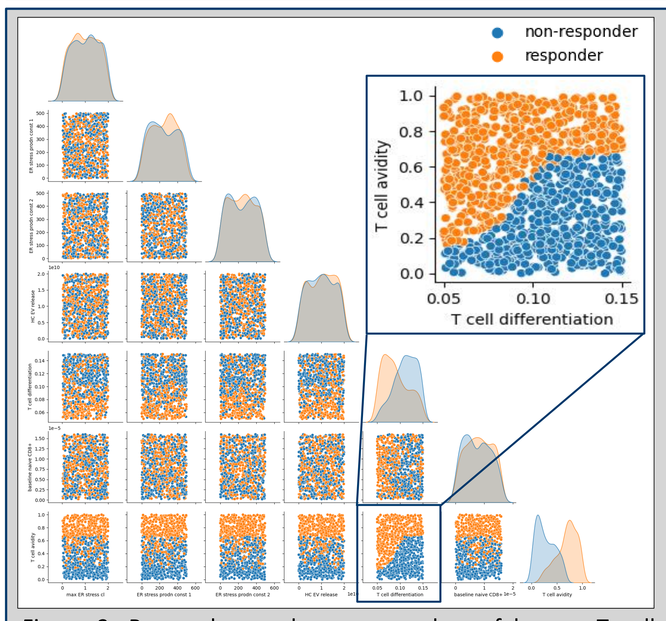

Figure 3: Responders and non-responders of human T cell SimPops plotted in pair plots of SimPops parameters. Distribution of responders and non-responders for single parameter plotted on the diagonal. Inset shows zoom in of pair plot for T cell differentiation vs T cell avidity.

Correlations Between SimPops Parameters and Responses Identify Key Drivers of Injury

Pair plot correlations of SimPops parameters demonstrate drivers of ALT response (Fig 3). Responders (max ALT > 40 U/L; orange) correlate strongly with T cell avidity and T cell differentiation (Fig 3 inset). Clustering responses based on max ALT shows clear separation of groups based on T cell avidity and differentiation, indicating these two parameters as key drivers of the ALT response (Fig 4 left).

SimPops outcomes assumed limited ability for T cells to become exhausted, maintaining T cell effector function. Adding variability to exhaustion capacity as an additional SimPops parameter weakens the max ALT dependency on T cell avidity and differentiation (Fig 4 right). This implies susceptibility to exhaustion as an additional influence on propensity for iDILI in response to AQ.

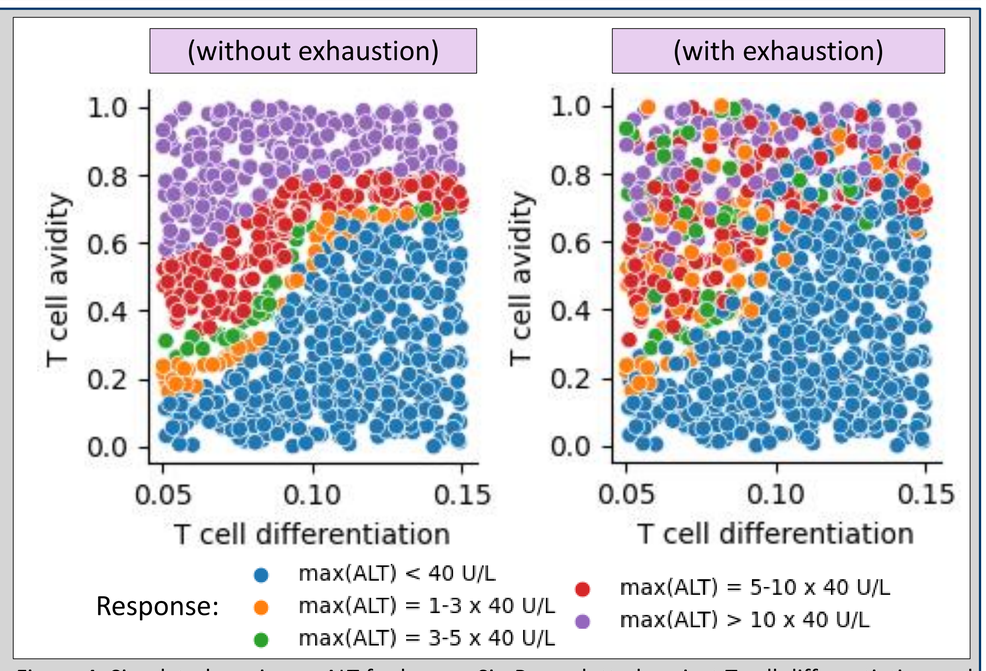

Figure 4: Simulated maximum ALT for human SimPops plotted against T cell differentiation and T cell avidity. Outcomes when exhaustion pathway is limited and fixed across individuals (left) compared to when exhaustion scalar is included as a varied parameter in the SimPops (right).

CONCLUSION

- Exploratory SimPops simulations provide proof-of-concept that reasonable parameter variation in T cell activation and response during AQ dosing allows a broad range of T cell response, including non-response, mild injury, self-resolving injury, and severe injury
- Emergent variability in simulated time to injury is consistent with range reported in literature case studies
- Of the parameters included in this SimPops, response vs parameter correlations identify T cell avidity, differentiation, and exhaustion as key drivers in AQ-mediated liver injury (ALT response)
- Analysis suggests high T cell avidity and limited exhaustion capacity can increase susceptibility to iDILI with AQ administration

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