Activation of CD8+ T Cells in the Context of Amodiaquine-Induced Liver Injury Advances Groundwork for Mathematical Representation of Idiosyncratic Drug-Induced Liver Injury (iDILI)

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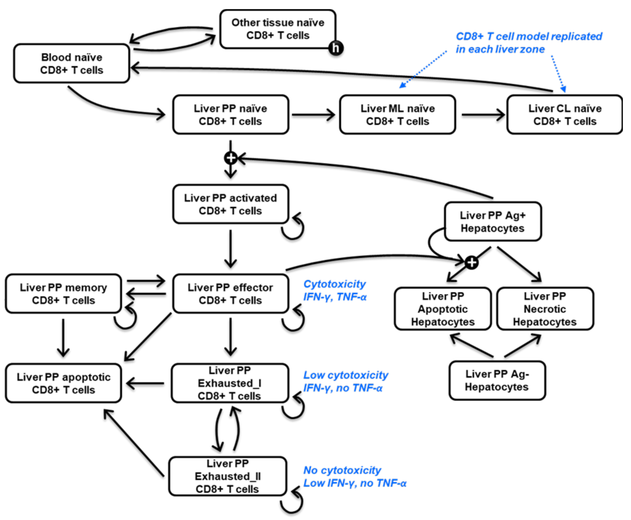
INTRODUCTION

- Extensive progress has been made in identifying mechanisms for dose-dependent drug-induced liver injury (DILI) and in developing screening assays to reduce its incidence. However, idiosyncratic DILI (iDILI), or rare, often severe, adverse reactions that are not obviously dose-dependent, remain poorly predicted and extremely costly, both for patient health and for drug development companies.
- Some iDILI events are thought to be immune-mediated, based on delayed onset and rapid re-injury after resuming drug. Immune involvement has been further supported by the identification of HLA risk alleles for some drugs.
- DILIsym® software applies a quantitative systems toxicology (QST) approach to the understanding of dose-dependent DILI. It integrates *in vitro* mechanistic toxicity data, *in vivo* dynamic drug disposition, known biochemistry, and patient characteristics to predict the hepatotoxic potential of new drug candidates. Simulations can also provide a mechanistic rationale to account for liver signals observed in the clinic. [1]
- We now seek to expand the scope of DILIsym to reconcile clinical data implicating the immune response with mechanistic data characterizing liver-specific CD8+ T cell responses.
- Incorporation of CD8+ T cell mediated hepatocyte death in DILIsym is designed to synthesize available data into a quantitative framework for hypothesis testing, further experimental design, and to increase knowledge of the preclinical/clinical potential to mitigate the occurrence of iDILI.

METHODS

- Developed a mechanistic model (depicted below) of well-characterized CD8+ T cell responses to hepatocyte-expressed ovalbumin (OVA) [2], linked antigen presenting hepatocytes to T cell activation, and dynamically represented cytotoxic T cell antigen clearance through hepatocyte loss.
- Begun examination of model predictions and analysis with amodiaquine administration in order to reproduce CD8+ T cell mediated DILI in a mouse model [3].



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[1] Shoda, et al. Biopharm Drug Dispos. (2014); 35.1:33-49.

[2] Ochel A, et al. Cell. and Mol. Immun. (2016); 13.6:805-815.

[3] Mak and Uetrecht. Chem Res Toxicol. (2015); 28.8:1567-73.

[4] Tay, et al. PNAS. (2014);111.25:E2540-E2549.

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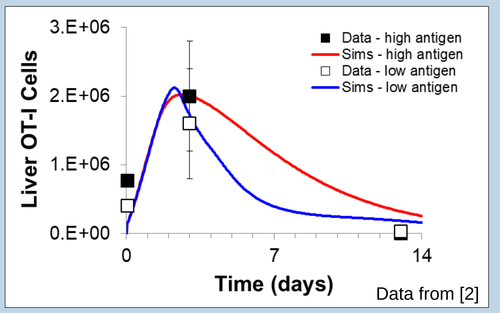
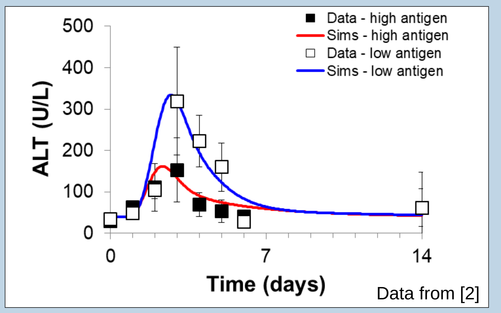
RESULTS

Mechanistic Modeling of T Cell Activation Due to Ovalbumin

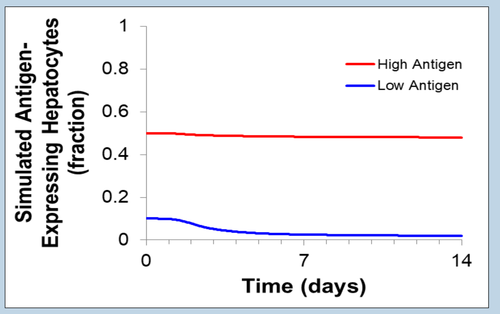
- Experimental models of CD8+ T cell responses to liver-expressed antigens have identified antigen load as a key regulator of the response [2,4].
- At lower antigen levels effector CD8+ T cells clear antigen with related higher ALT release.
- At higher antigen levels effector CD8+ T cells are unable to clear antigen and assume an exhausted phenotype with corresponding lower ALT release.



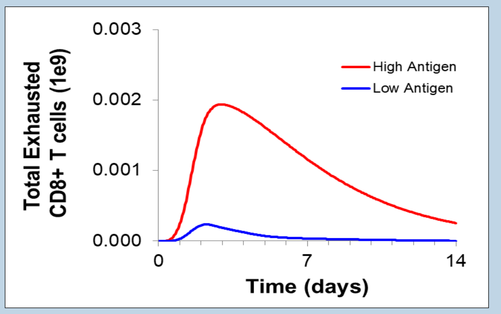
Simulated CD8+ T cells expand in both high and low antigen scenarios consistent with mouse data (by design).



Simulated CD8+ T cells in the low antigen scenario induce more hepatocyte apoptosis and ALT release consistent with mouse data (by design).

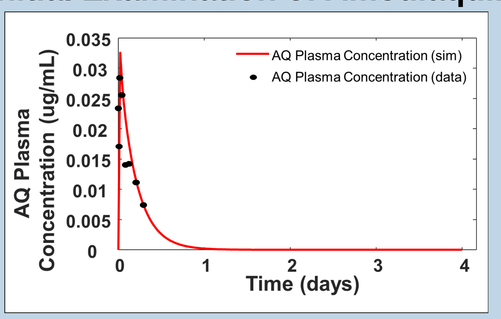


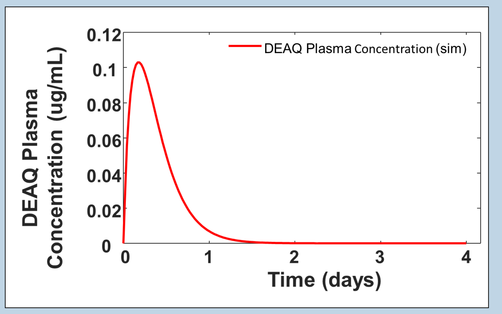
Simulated high antigen is not cleared, (by design) leading to generation of exhausted CD8+ T cells and less ALT release.



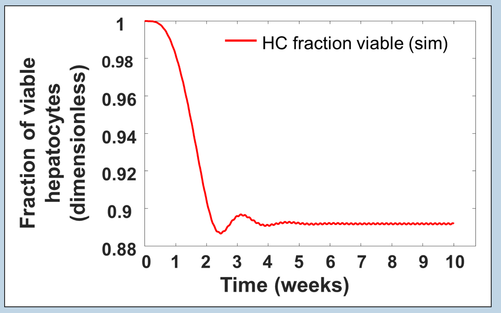
Exhausted T cells are dominant in high (but not low) antigen scenario (by design).

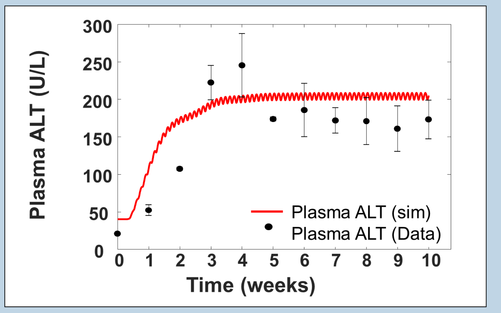
Initial Examination of Amodiaquine and T Cell Mediated DILI in Mice





Simulated plasma profiles in the baseline mouse treated with amodiaquine. Amodiaquine parent simulation and data [5] (left) and major metabolite desethylamodiaquine (right). Model will inform drug exposure in the liver and corresponding antigen levels seen by T cells.





Simulations of hepatocyte death profile (left) which results from fitting a direct apoptosis mechanism to ALT data [3] (right). Simulations indicate potential ALT release timeline and general hepatocyte loss profile which match response to amodiaquine exposure.

CONCLUSION

- The mechanistic model provides the groundwork for quantitative insight into the role of antigen and other key regulators on T cell-mediated liver injury. These findings set the stage for further systematic investigation of immune-mediated DILI.
- Continued refinement of the model response timing, extent, and inter-individual variability of T cell-mediated iDILI is ongoing. This is necessary to better describe immune response to amodiaquine (and potentially additional antigens) and to enhance the accuracy of prospective predictions.