Development of a Direct CD8+ T Cell Activation QSP Model for Ovalbumin in the Context of Liver Injury Advances Groundwork for Mathematical Representation of Idiosyncratic Drug-Induced Liver Injury (iDILI)

Zackary Kenz, Christina Battista, Lisl Shoda

DILIsym Services, Inc., Research Triangle Park, NC, a Simulations Plus Company

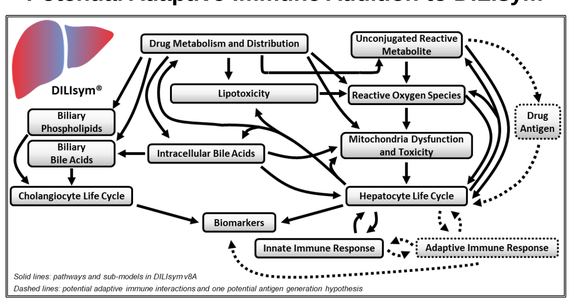
INTRODUCTION

- 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 appear immune-mediated based on delays between treatment initiation and DILI onset and more rapid injury upon drug re-challenge. 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 seek to expand the scope of DILIsym (figure below, "Potential Adaptive Immune Addition to DILIsym"), utilizing an iDILI expansion framework laid out in [2], to reconcile clinical data implicating the immune response with mechanistic data characterizing liver-specific CD8+ T cell responses. The aim is 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.

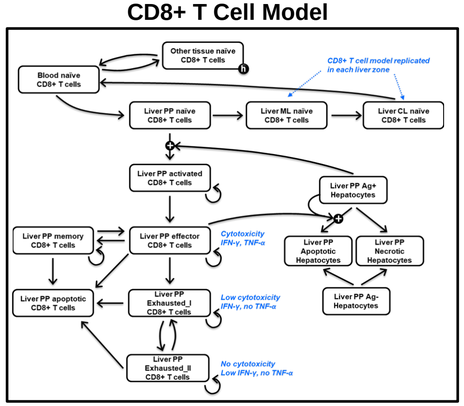
METHODS

- Developed a mechanistic model (figure below, "CD8+ T Cell Model") of well-characterized CD8+ T cell responses to hepatocyte-expressed ovalbumin [3], linked antigen presenting hepatocytes to T cell activation, and dynamically represented cytotoxic T cell antigen clearance through hepatocyte loss. Antigen is a critical determinant of CD8+ functional responses in the liver, above antigen affinity or antigen presenting cells, based on examinations of preclinical data in [3,4].
- Mediator production modeled as constant rate of production per effector T cell, with reduced production from exhausted T cells.
- Assessed model response to changes in CD8+ functional avidity, qualitatively comparing to ovalbumin altered peptide ligand data [4,5], as prelude to simulation of drug antigen.

Potential Adaptive Immune Addition to DILIsym



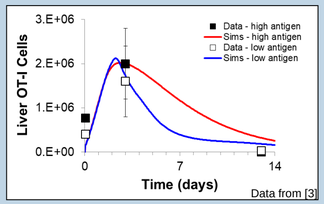
CD8+ T Cell Model



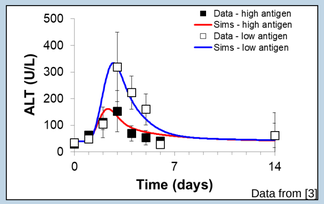
RESULTS

Mechanistic Modeling of T Cell Activation Due to Ovalbumin

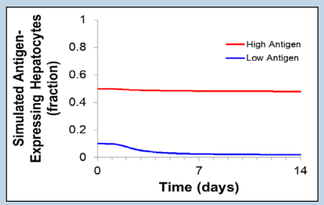
- Experimental models of CD8+ T cell responses to liver-expressed antigens have identified antigen load as a key regulator of the response [3,5].
- At lower antigen levels, effector CD8+ T cells effectively kill OVA-expressing hepatocytes, with associated ALT release.
- At higher antigen levels, commensurate with the inability to clear OVA-expressing hepatocytes, effector CD8+ T cells assume an exhausted phenotype, with associated ALT release.



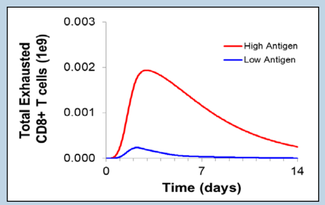
Simulated CD8+ T cells expand in both high and low antigen scenarios consistent with mouse data (by design).



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



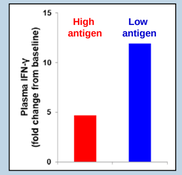
Simulated high antigen is not cleared, (by design) leading to generation of exhausted CD8+ T cells and less ALT release.

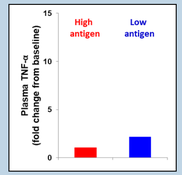


Exhausted T cells are dominant in high (but not low) antigen scenario (by design).

Mediator Production by T Cells

- Mediators contribute to T cell interactions with other sub-models.
  - IFN-γ representative of effector function and immunomodulatory response.
  - TNF-α contributes to inflammation response and potentially to hepatotoxicity.

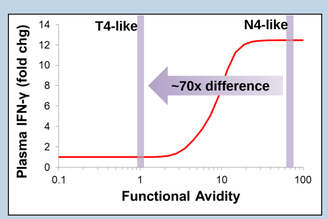




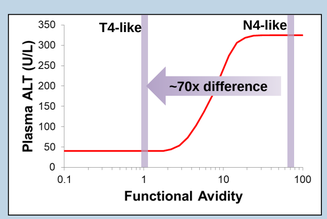
Simulated T cells produce more IFN-γ and TNF-α in the presence of low relative to high antigen, qualitatively consistent with measured data [3] by design. The difference in cytokine production reflects functional differences in effector and exhausted T cells.

Simulated Functional Avidity Response to Ovalbumin Altered Peptide Ligands

- Drug antigen likely to have significantly weaker avidity compared with ovalbumin, impacting T cell response to antigen.
- Examination of ovalbumin altered peptide ligands from full binding (N4-like) to 70x weaker binding (T4-like) indicates model capability to represent range of avidity responses and reduction in generation of effector T cells.



Reduced IFN-γ response observed over ~70x change in functional avidity, consistent with [4,5] by design.



Loss of T cell activity demonstrated by reduced plasma ALT, consistent with [4,5] by design.

CONCLUSIONS

- The mechanistic model can reproduce different outcomes in response to OVA antigen levels and functional avidity, including the generation of exhausted T cells which is one mechanism of tolerance that may contribute to the rarity of iDILI. These findings set the stage for further systematic investigation of immune-mediated DILI, particularly drug-mediated T cell cytotoxicity.
- Continued refinement of the model response timing, frequency, 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), particularly related to the next modeling stage where mouse amodiaquine experiments [6] will be simulated, and to enhance the accuracy of prospective predictions.

REFERENCES

[1] Shoda, et al. Biopharm Drug Dispos. (2014); 35.1:33-49.
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[3] Ochel A, et al. Cell. and Mol. Immun. (2016); 13.6:805-815
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