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MIMIC: an in vitro model of human immunity

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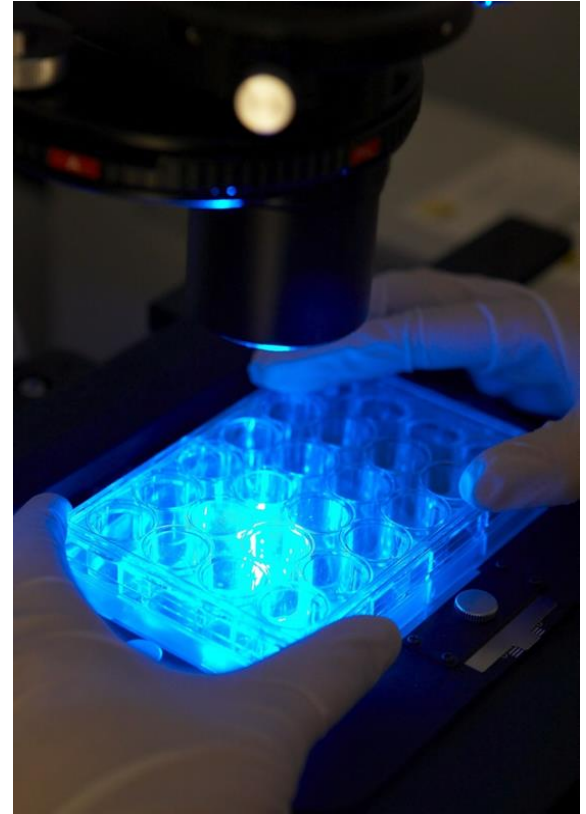


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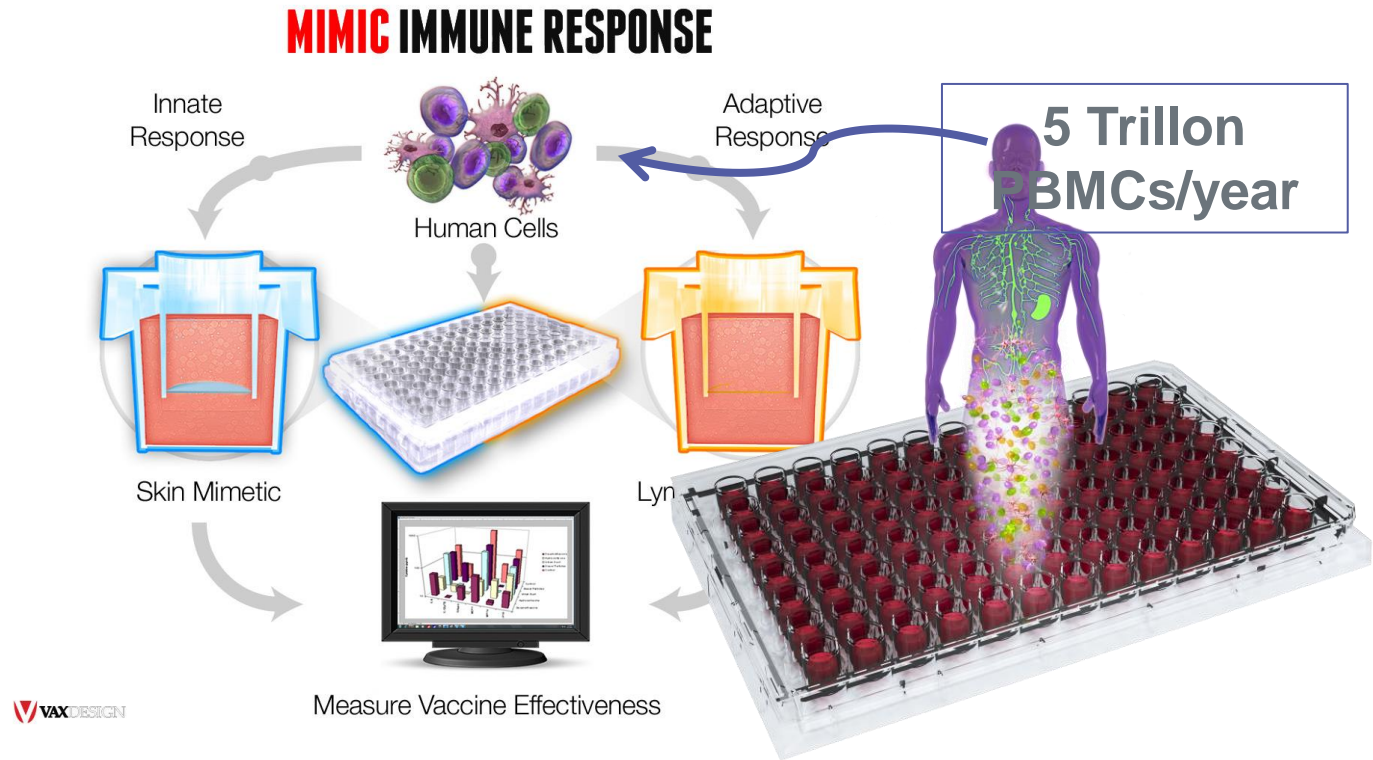
VAXDESIGN CAMPUS

Outline

- **MIMIC (human immune) system overview**
- **Innate (PTE) model**
 - Design principles
 - Physiologic relevance
 - Infection model
- **Adaptive (LTE) model**
 - Design principles
 - Physiologic relevance
 - Malaria T cell epitope analyses



Can we improve vaccine success rates through the development of better pre-clinical tests?



What attributes are critical for our success?

- **Automation**

- For precision and quality (data and sample management)

- **Regulatory engagement**

- The system has been extensively reviewed by the FDA in two formal briefings
- A German regulatory (PEI) meeting is slated to occur in late 2018

- **Flexibility**

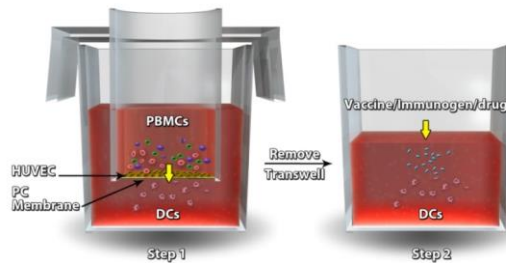
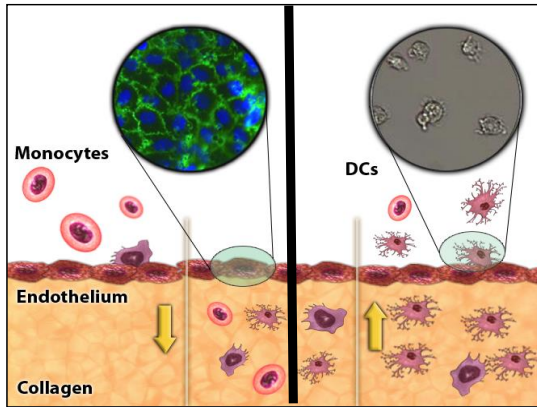
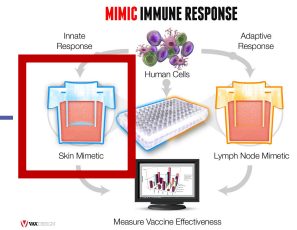
- The system is modular and adaptable for the evaluation of a variety of immunological questions and vaccine/adjuvant types

- **Donor program**

- As required, diverse donors (age, ethnicity, disease state) can be recruited for specific studies

The MIMIC PTE construct

An endothelial cell-based innate immune assay



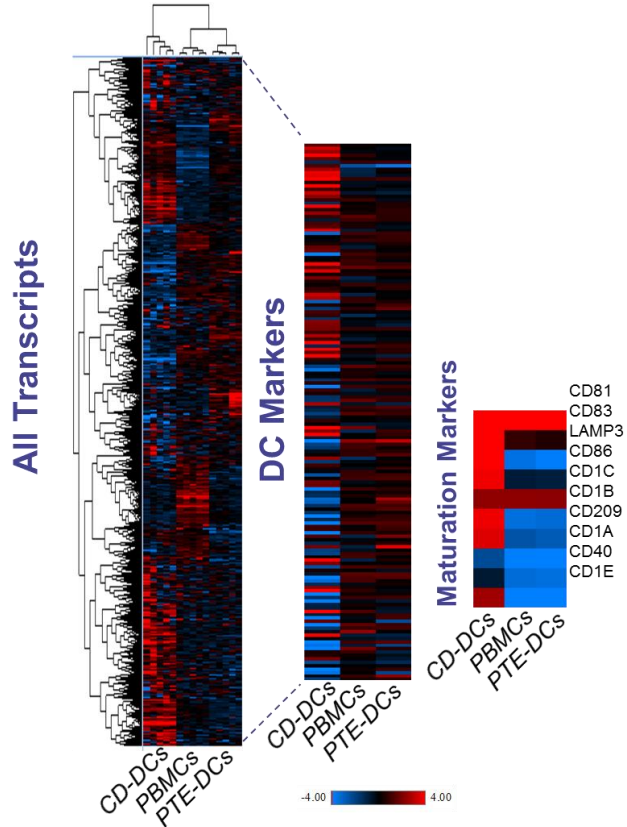
• Physiological Relevance

- No exogenous cytokines
- DC subset heterogeneity

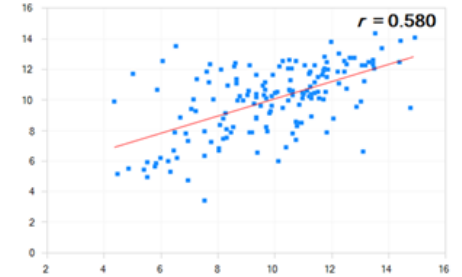
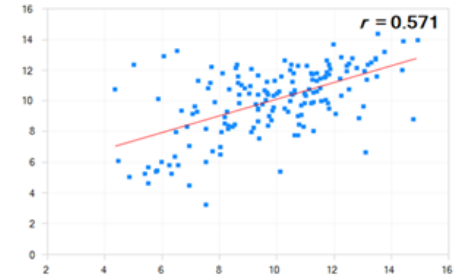
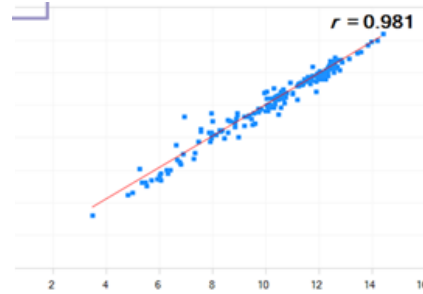
• Functional Outcomes

- APC phenotyping
- Inflammatory profiling
- T cell priming assays

PTE and *in vivo* DCs are well-correlated



Innate gene correlations



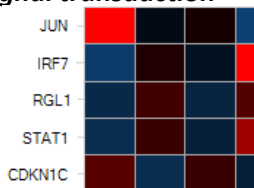
PBMCs

PTE-DCs

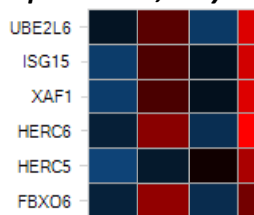
CD-DCs

Comparable activation of innate genes against YF-VAX was observed in MIMIC and *in vivo*

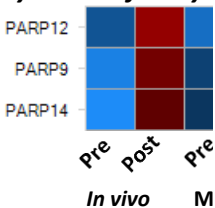
Signal transduction



Ubiquitination, ISGylat



Poly (ADP-ribose) polymerase family



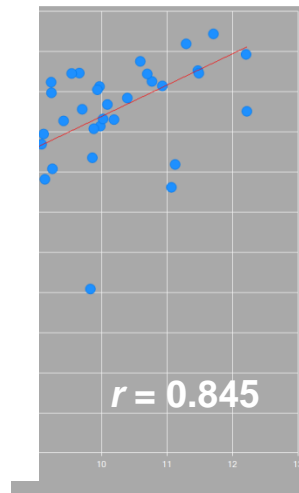
Antiviral Antiviral con't Cell Adhesion Cytoskeleton, chemotaxis



Apheresis (PBMCs)

In vivo vaccinate

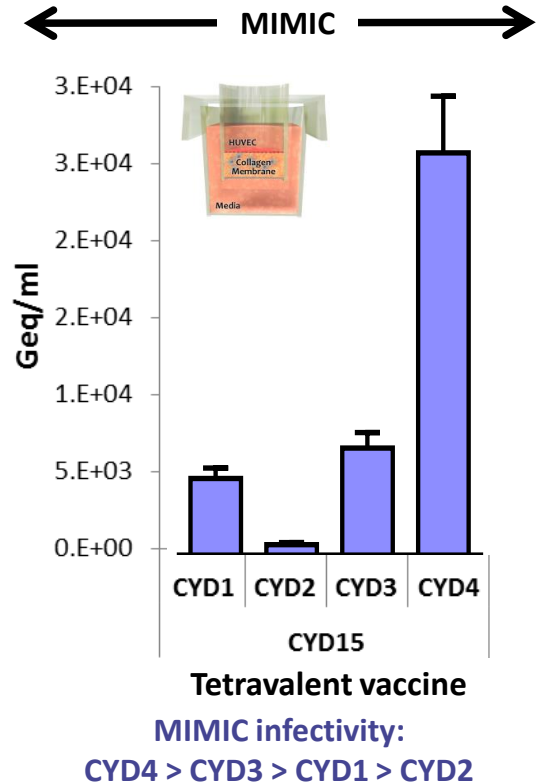
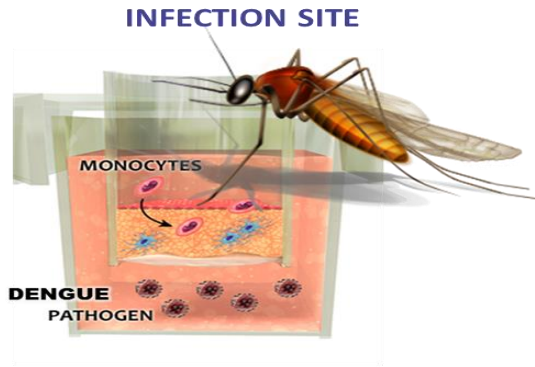
Apheresis (PBMCs)



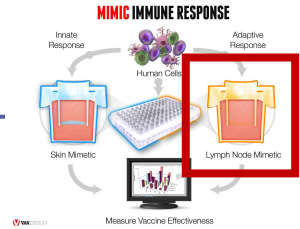
In vivo MIMIC

In vivo MIMIC

MIMIC early stage viral infectivity reflects human dengue vaccine viremia

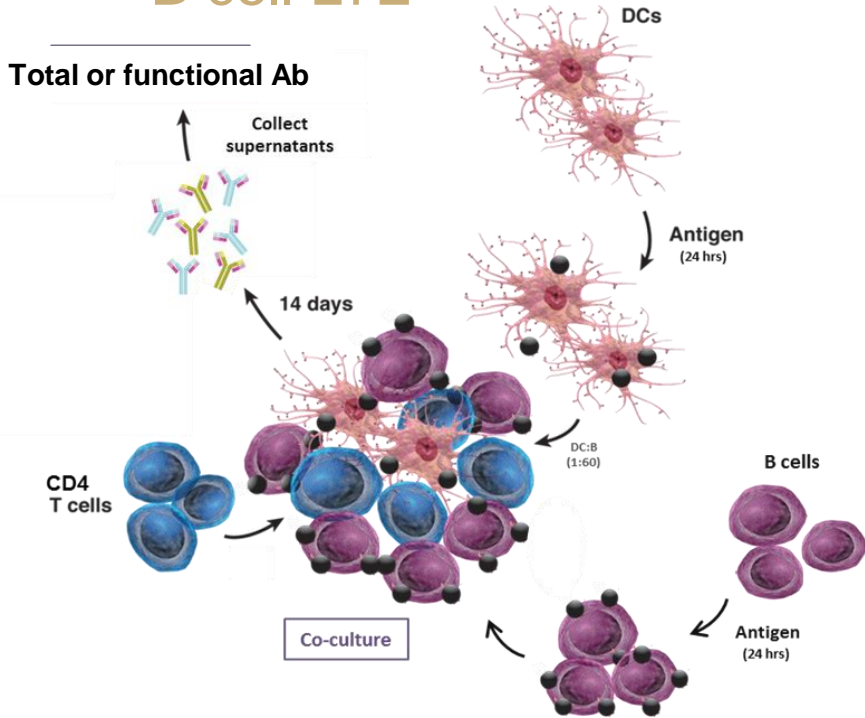


Distinct assays to evaluate T and B cell immunity

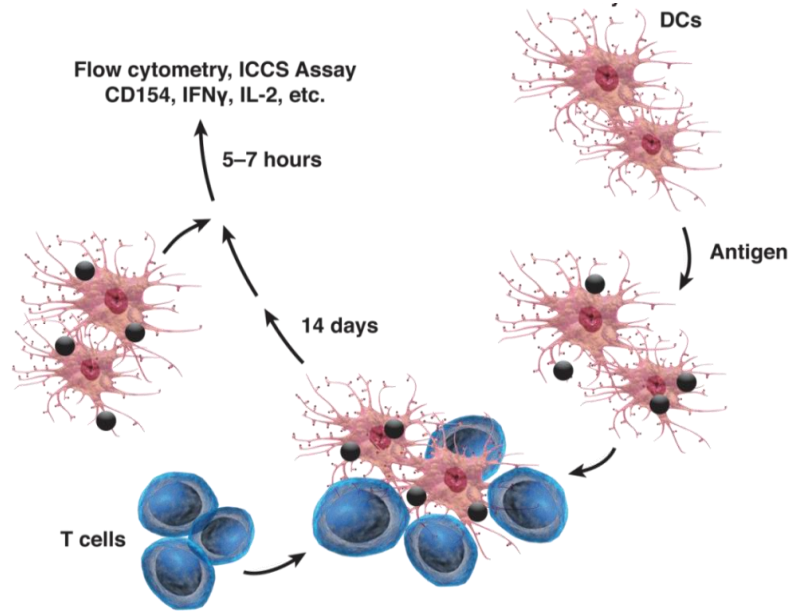


B cell LTE

Total or functional Ab



T cell LTE



MIMIC-based assessment of flu vaccines compared to phase 3 non-inferiority trial

	California	Victoria/Perth	Brisbane B	Texas B
TIV-ID1 = TIV Licensed	Light Blue	Light Red	White	Light Green
TIV-ID2 = TIV Investigational	Light Blue	Light Red	Light Purple	White
QIV-ID = QIV Bulk	Light Blue	Light Red	Light Purple	Light Green
	A/H1N1	A/H3N2	Victoria Lineage	Yamagata Lineage

- **Clinical topics of interest for this study**
 - Is QIV non-inferior to TIV for the 3 common strains?
 - Is there low cross-reactivity between B strains to justify the quadrivalent vaccine?
 - **How does MIMIC compare to a PhIII clinical trial, prospectively?**

**TIV-Licensed is the licensed 2012/2013 TIV-ID containing B/Texas

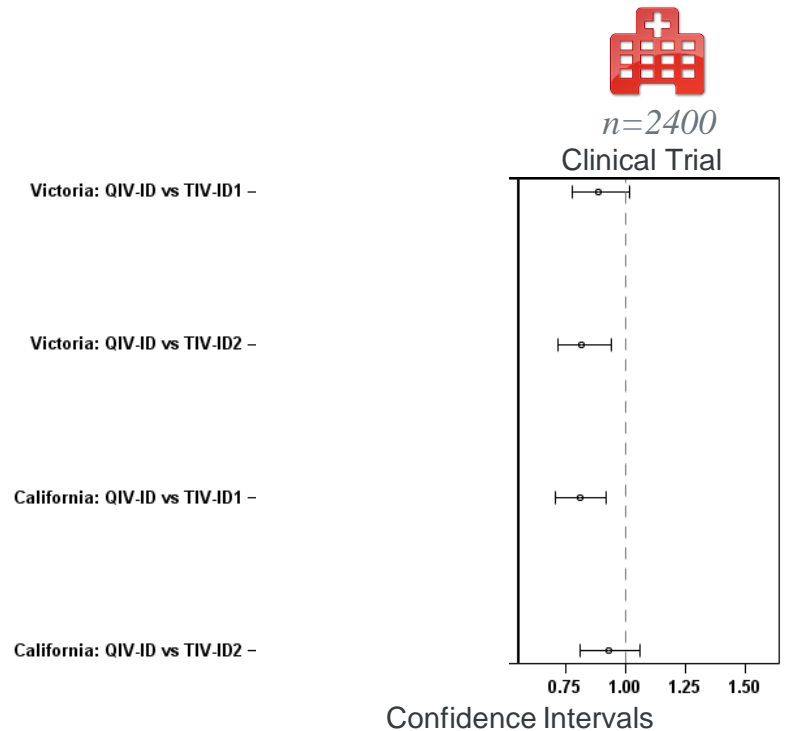
MIMIC datasets prospectively provided the same conclusions as a Phase III Trial

- **Analysis parameters**

- HAI functional readout
- The deciding factor is whether the lower end of the confidence interval (CI) is above 67% to show non-inferiority between QIV-ID and TIV-ID

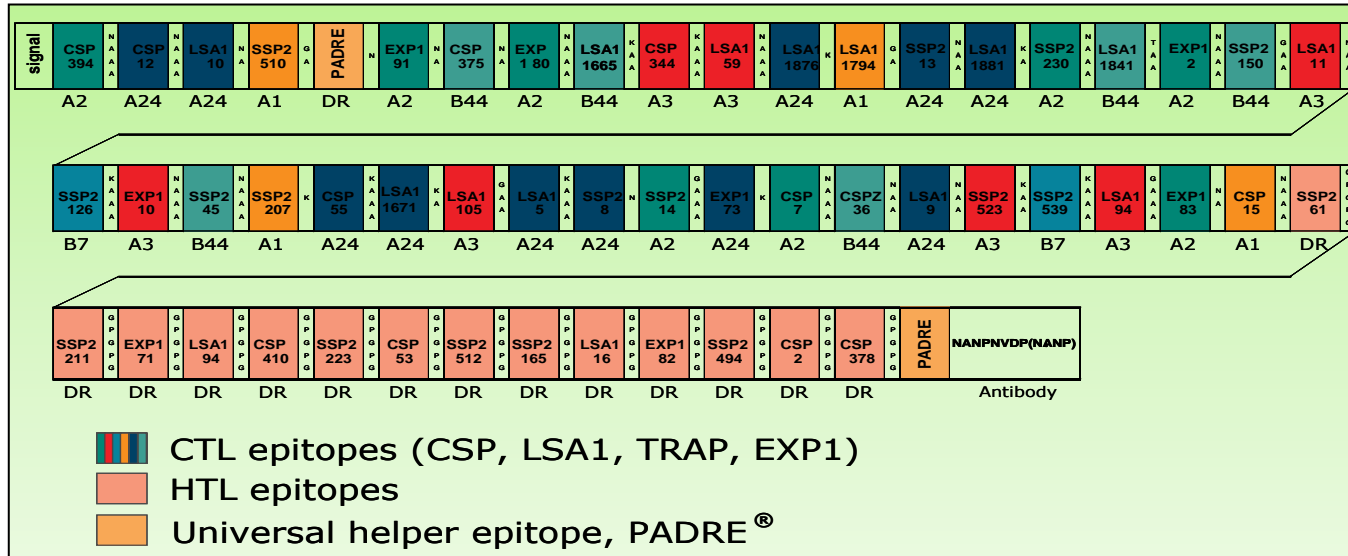
- **Conclusions**

- The MIMIC generated comparable results to the clinical trial, with only 24 donors
- This was achieved through a randomized complete block design statistical approach

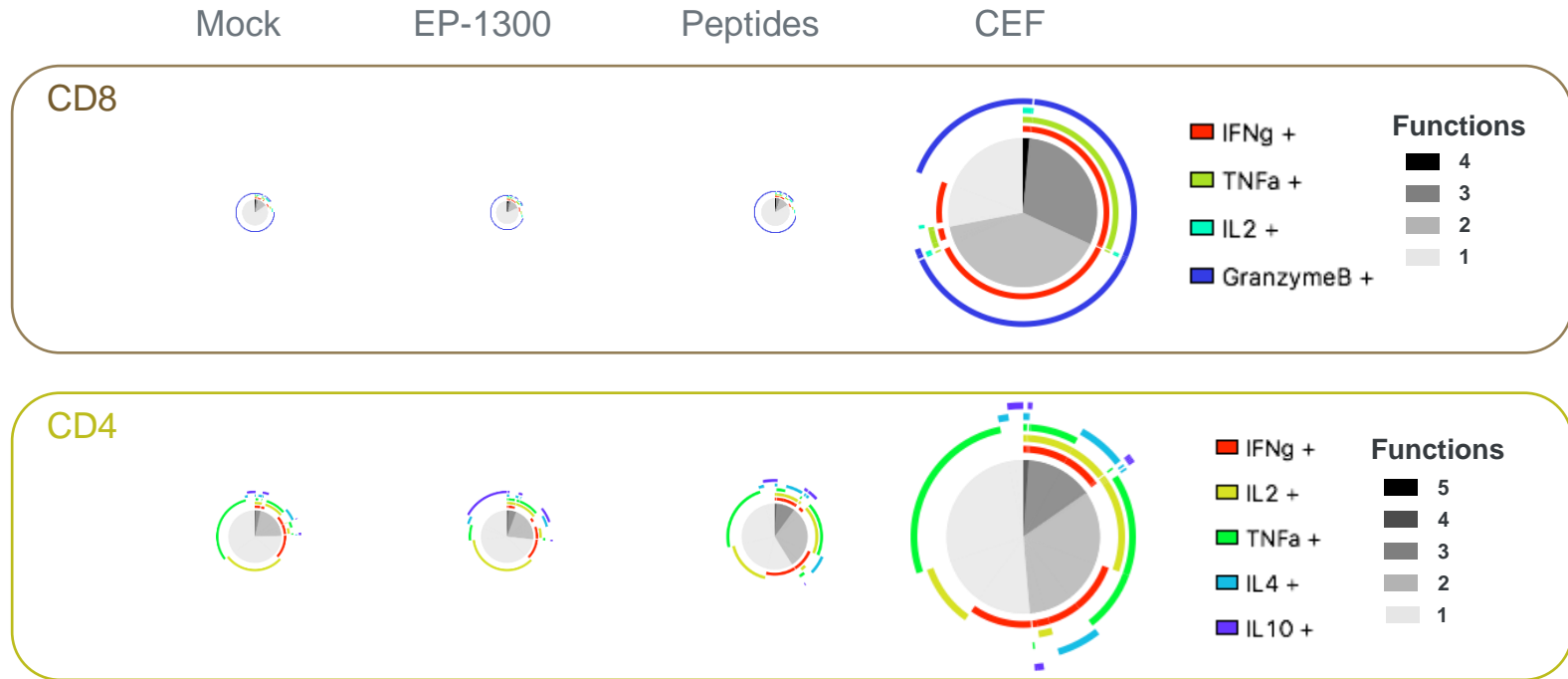


MIMIC-based assessment of a malaria liver-phase DNA vaccine candidate

- EP-1300 is a polyepitope plasmid expressing 38 cytotoxic T cell epitopes and 16 helper T cell epitopes



EP-1300 failed to engage human CD4 and CD8 T cells in MIMIC assays



***In vitro results were consistent with published clinical observations (PMID: 27697302)

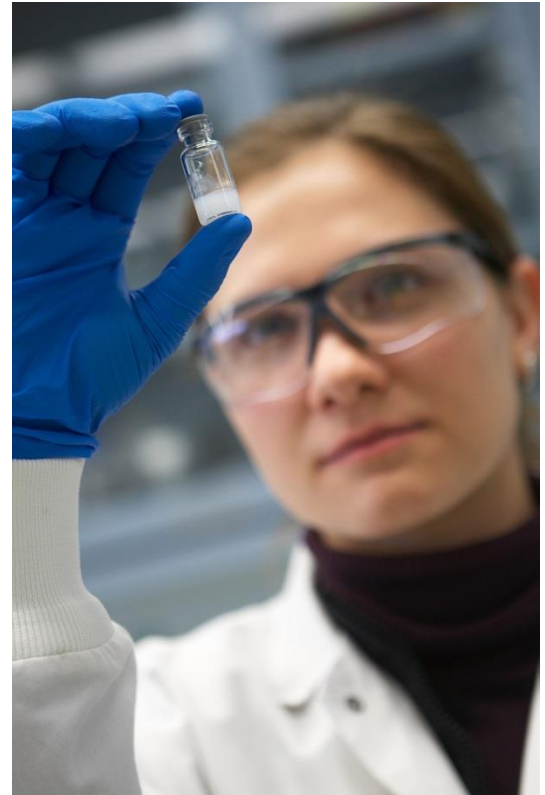
Working toward developing a novel malaria liver-stage vaccine

- **Approach**

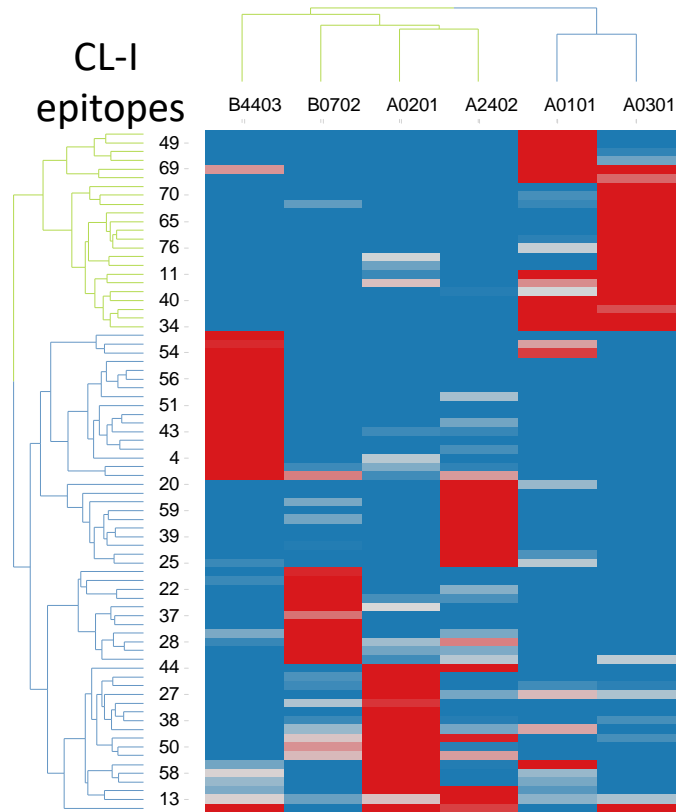
- In silico predictions
- Analysis of MHC binding affinity
- MIMIC analyses of human T cell activity

- **Epitopes chosen from a series of malarial liver-stage antigens**

- **Most immunodominant peptides to be considered for novel malaria vaccine**



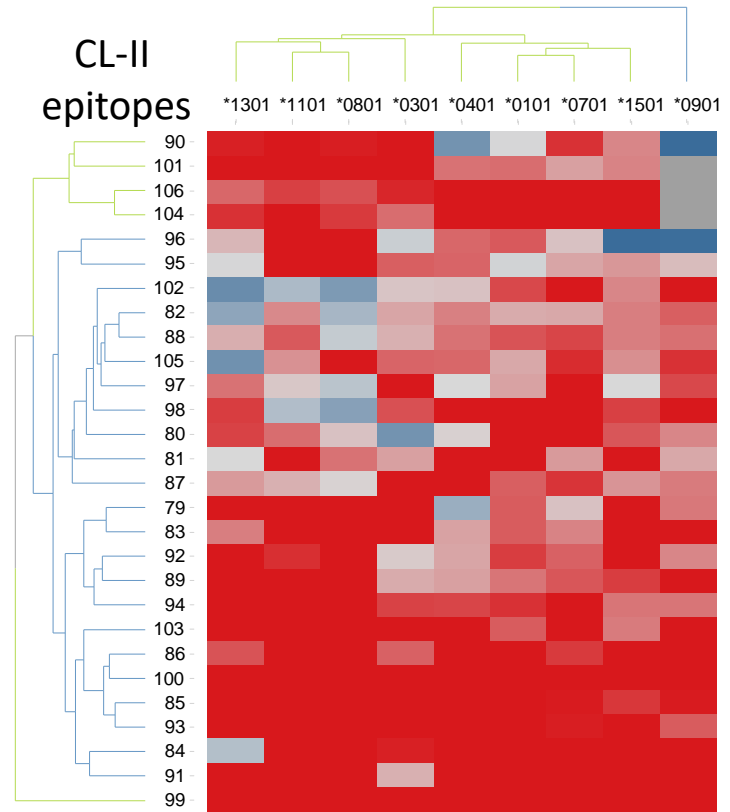
In silico binding predictions of malarial class I and II peptide epitopes



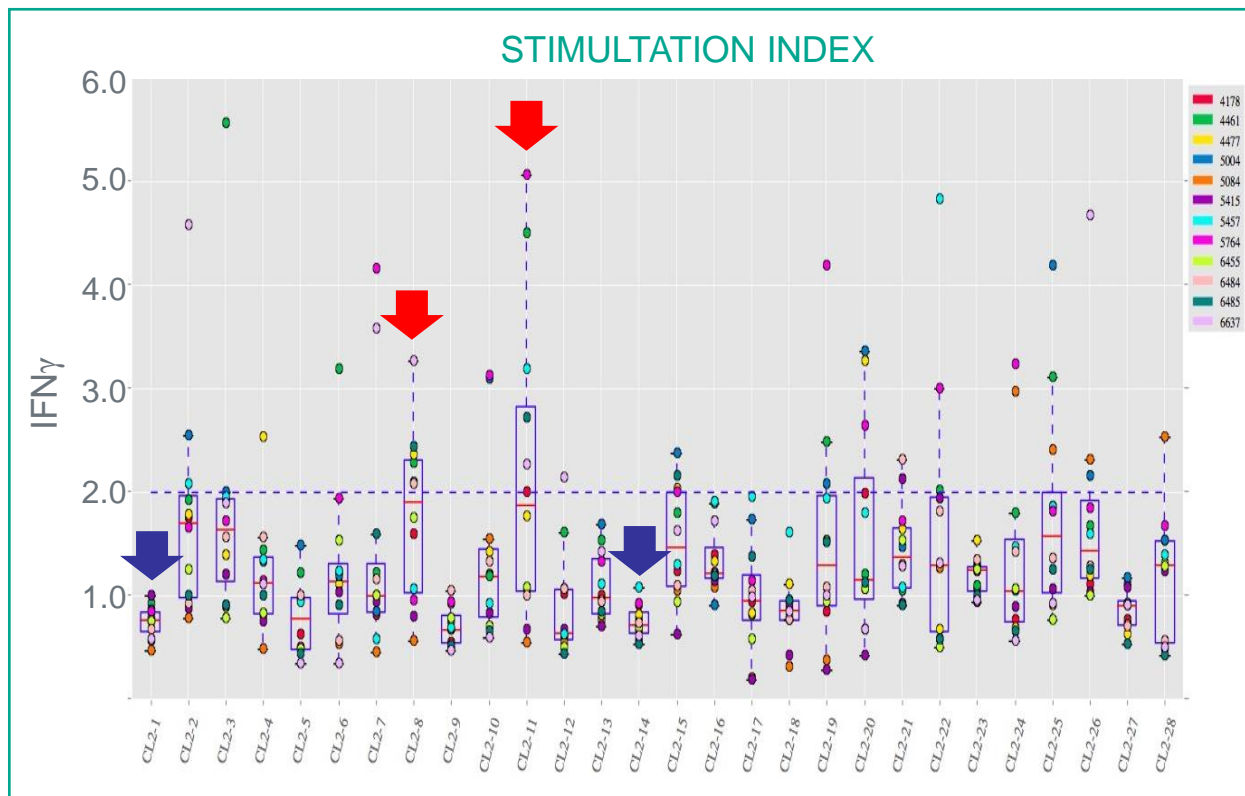
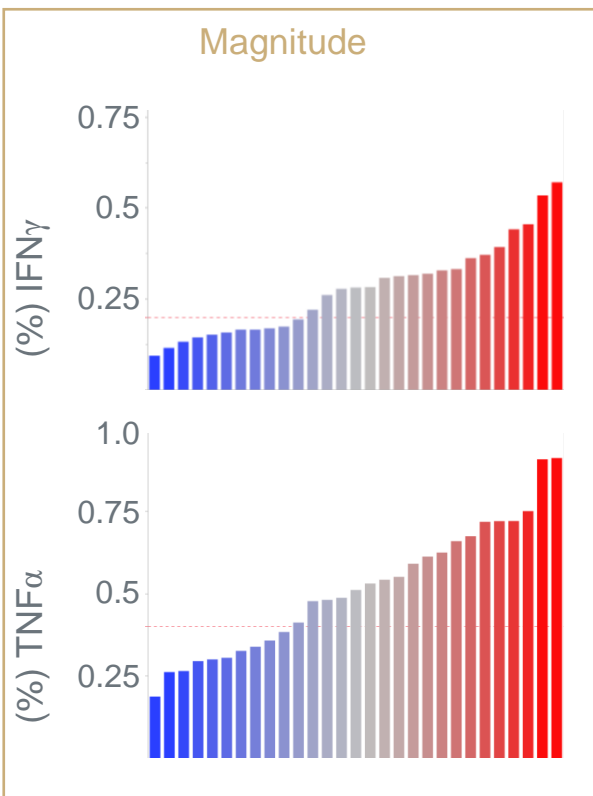
EpiVax

Z-score

- Top 1%
- Top 5%
- <15%



MIMIC-based assessment reveals malaria peptides with relatively strong and weak CD4 response profiles



Conclusions

- **The MIMIC system can be used to examine human innate and adaptive immunity**
- **The system represents a modular and flexible platform to investigate a variety of immunological questions related to the development of vaccines**



Kenneth Tucker



USAID
FROM THE AMERICAN PEOPLE



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