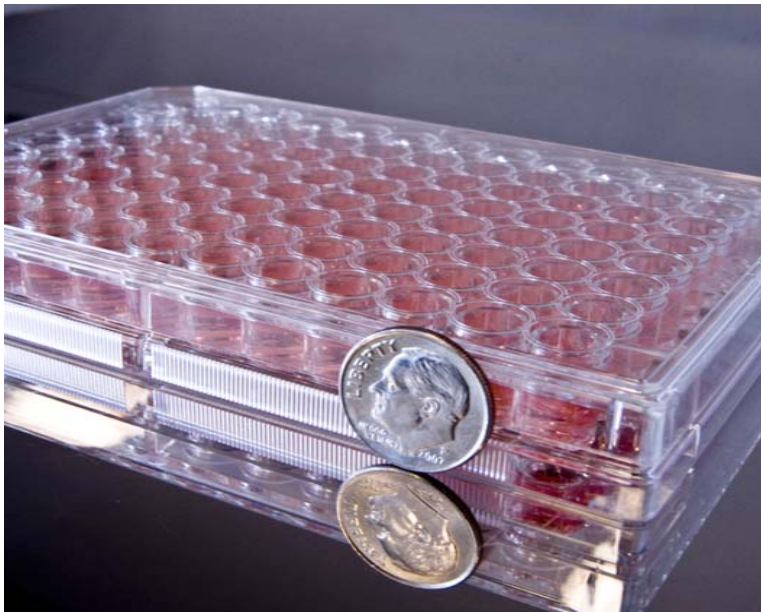


Engineering an *in vitro* human immune system for rapid vaccine evaluation

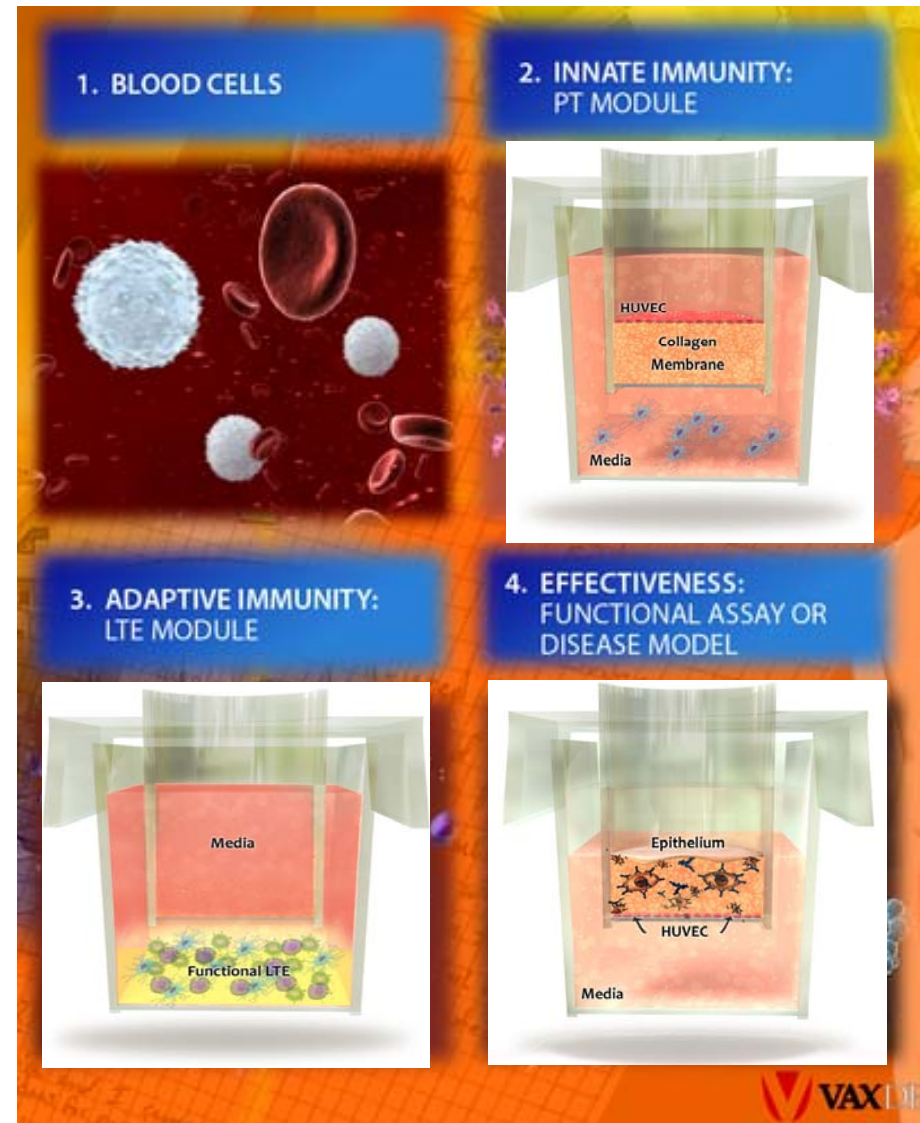


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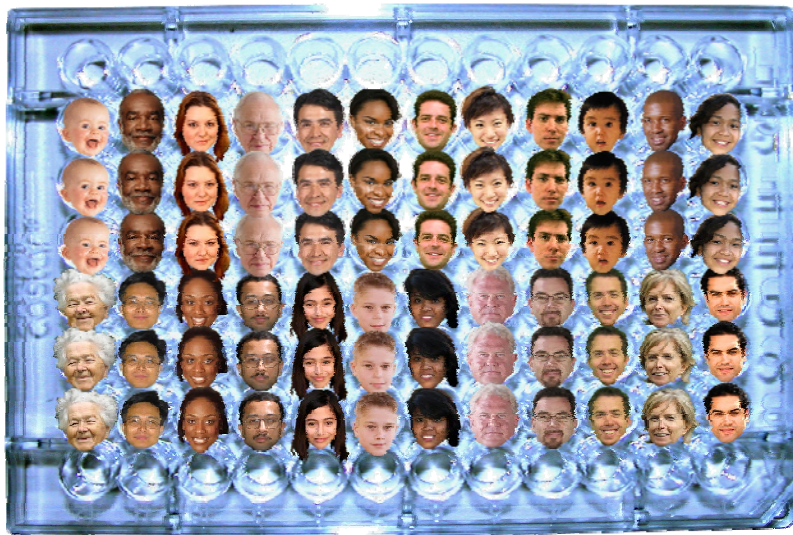
MIMIC™ Technology Overview

MIMIC: an *in vitro* biomimetic of the human immune response:

1. Collect leukocytes from human donors
2. Simulate innate immunity with the Peripheral Tissue (PT) Module
3. Simulate adaptive immunity with the Lymphoid Tissue Equivalent (LTE) Module
4. Measure the effectiveness of the immune response or immune modulator product



Benefits: Vaccine Trial in a Well



- Predictive high-throughput *in vitro* immunology to assess novel vaccine candidates
- Measure immune response in diverse population
- Faster cycle time for discovery
- Better selection of vaccine candidates for clinical evaluation
- New ways to design clinical trials
- Reduce the time and costs to bring vaccines to the market

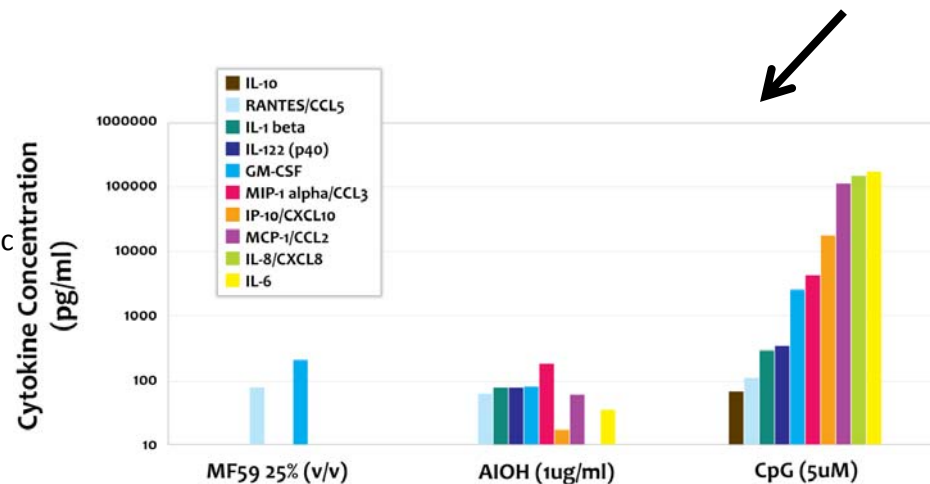
Examples of *In Vitro* Vaccine Projects

1. Assessing adjuvant responses
2. Immunotoxicology/immunoregulation of biologicals
3. Quantity and Quality of T cell/CMI responses
4. Quantity and Quality of B cell/Ab responses
5. Rapid immunogen screen/Engineering immunology

Peripheral Tissue Module Replicates Innate Immune Response

- Adjuvants and immunopotentiators
 - “Alum”, MF59, CpG, poly I:C, etc.
- Innate response profiles of vaccines
 - DTaP, Influenza, Hep B, Yellow Fever, Rabies, etc.
- Innate response to biologics
 - TNF α , CD154, OKT3, Avastin
- Immunosuppressant effects
 - Dexamethasone, Cyclosporine, Hydrocortisone, etc
- Cytokine profiles of pathogens
 - Viruses, bacteria

Adjuvant	DC Development	DC Maturation	Cytokine Production
Alum	0/+	-/0	++
MF59	++++	++++	0/+
CpG	++++	++++	++++



With Jeff Ulmer & Andreas Wack, Novartis Vaccines

Examples of *In Vitro* Vaccine Projects

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How Do We Measure a “Good” T Cell Response to a Vaccine?

- Magnitude of a T-cell response
 - Quantitative measurement of the T-cell response,
 - the frequency of CD4+ or CD8+ T cells that are Ag-specific.
 - total cytokine secretion, cytolytic activity or proliferation.
- Quality of the T-cell response
 - Combination of T cell functions
 - Proliferation, organization of immune cells, effector cells
 - Multifunctional T cells have been shown to correlate with disease non-progression and protection (HIV, EBV, CMV, Influenza, etc.)

Betts, M. R. et al. Blood **107**, 4781–4789 (2006).

Harari, A., Petitpierre, S., Vallelian, F. & Pantaleo, G.. Blood **103**, 966–972 (2004).

Younes, S. A. et al. J. Exp. Med. **198**, 1909–1922 (2003)

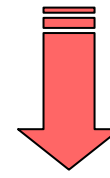
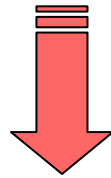
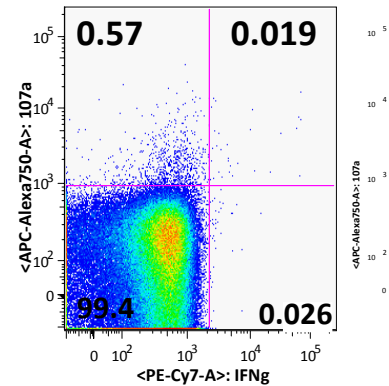
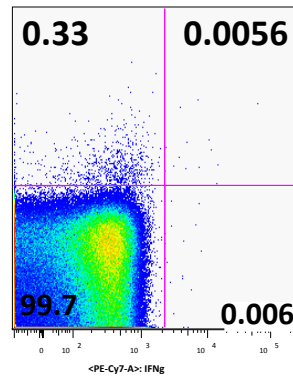
Robert A. Seder, Patricia A. Darrach, Mario Roederer, Nat. Rev. Immunology **8**, 257 (2008)

Magnitude of Primary *In Vitro* CTL Responses to Yellow Fever *CD8 T cells recognize "naïve" antigen*

Primary
Stimulation
(7 days)

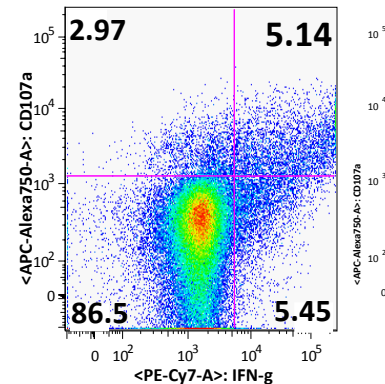
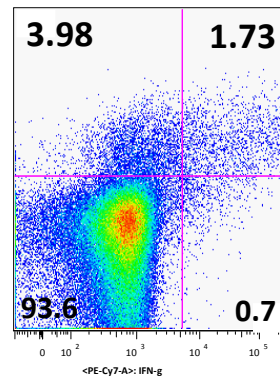
no Antigen

Yellow Fever



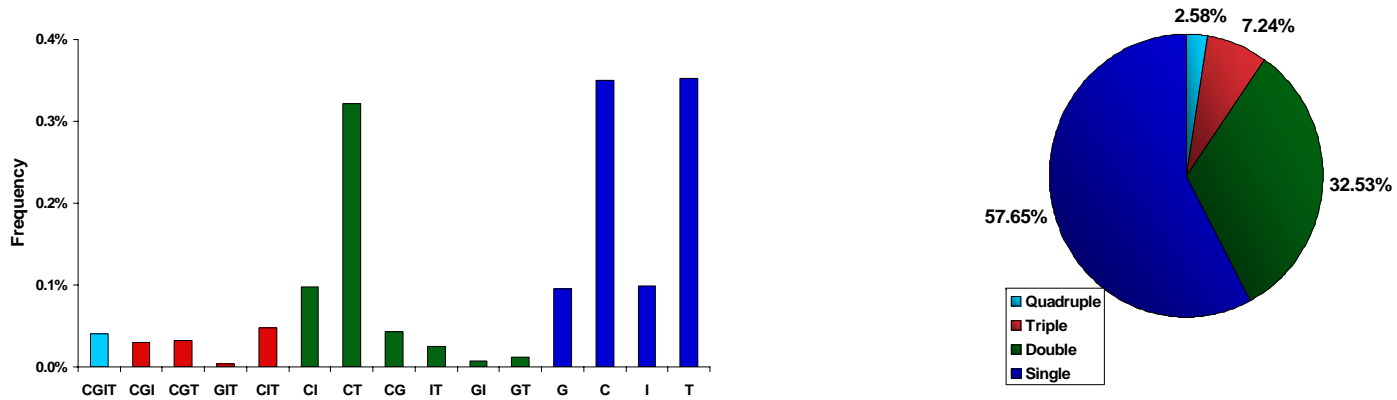
Secondary
Stimulation (12 days)

CD107a
↑
IFN γ

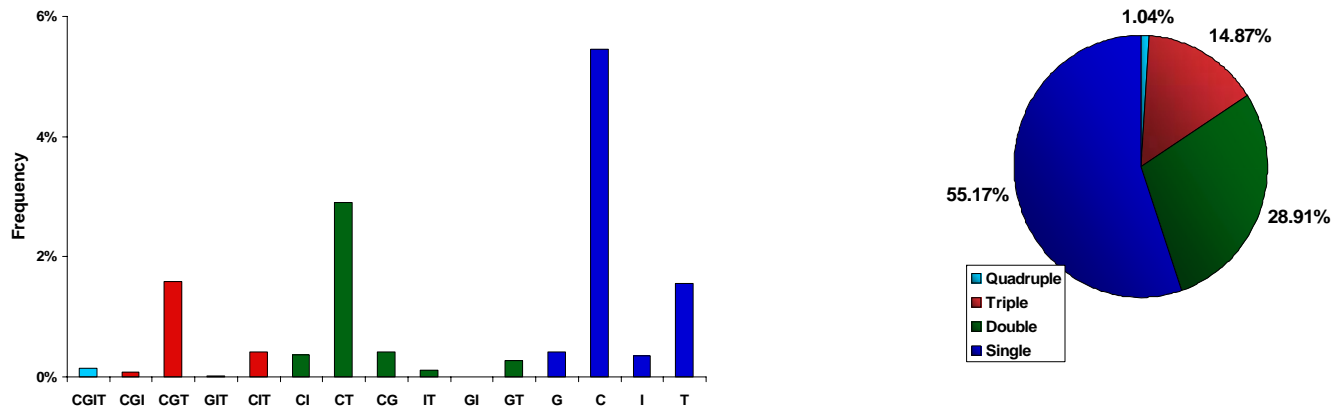


Quality of CD8 T Cell Responses: *In Vitro* Yellow Fever Vaccination

Day 7



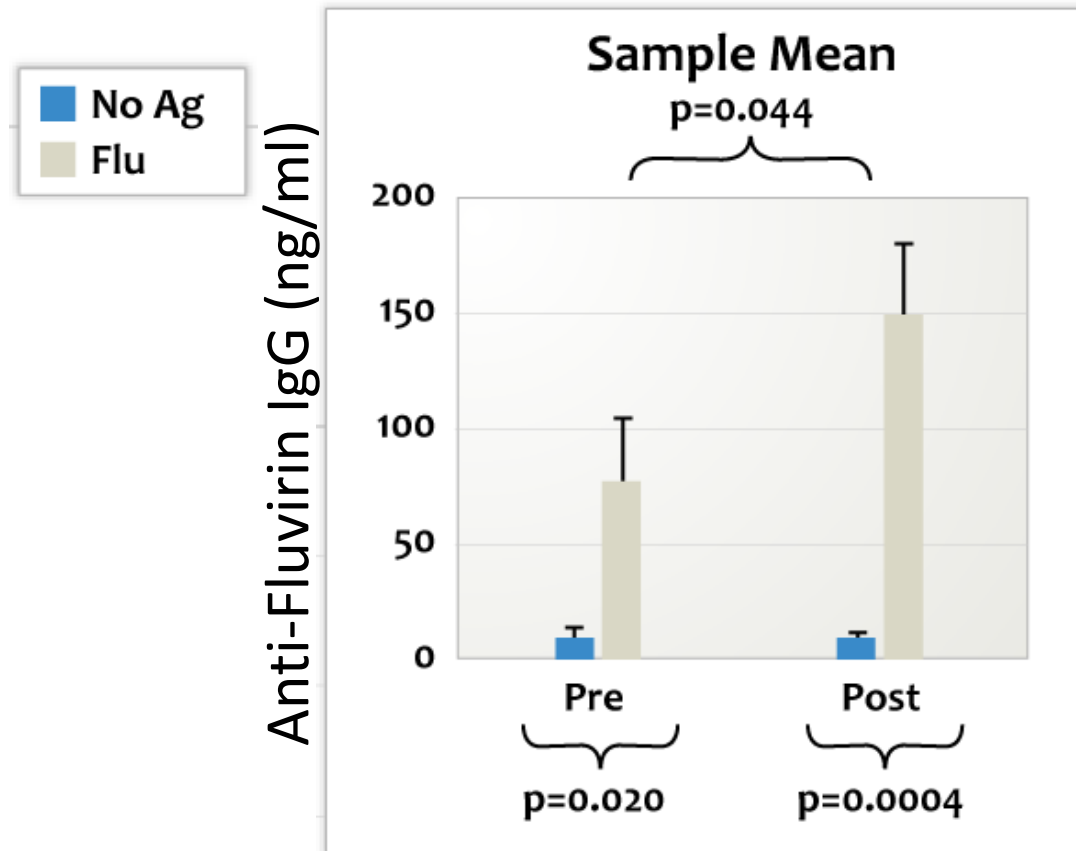
Day 15 Re-stimulation



Examples of *In Vitro* Vaccine Projects

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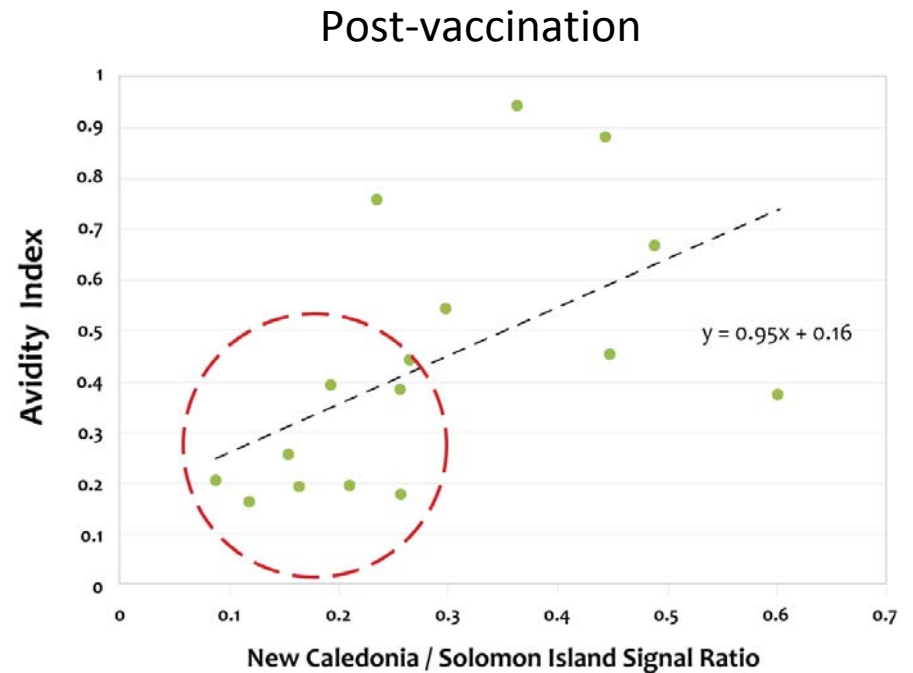
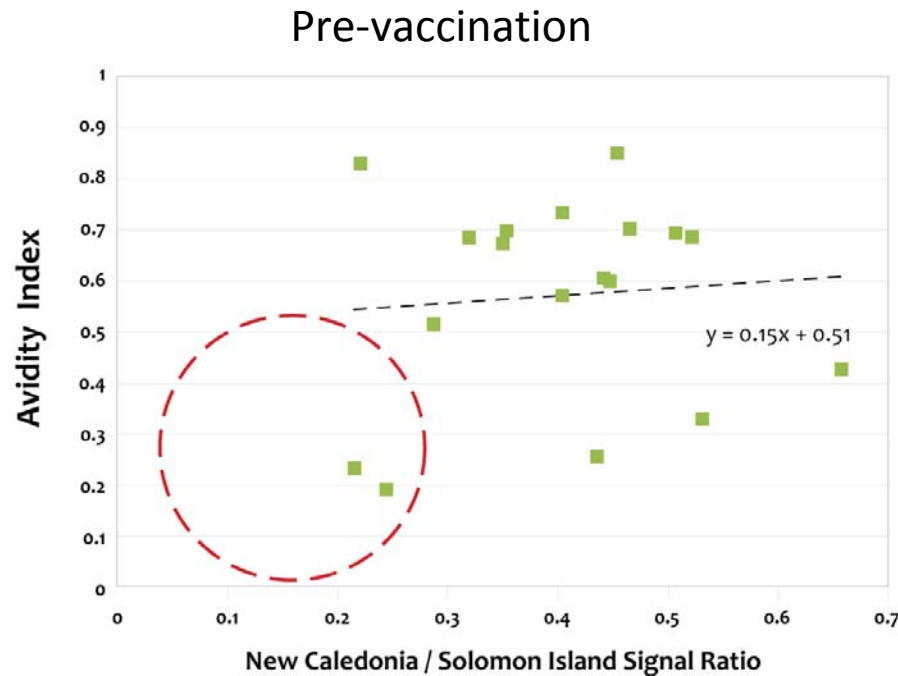
Quantity: Pre/Post Influenza Vaccine Stimulation: Anti-Fluvirin IgG



Antigen stimulation & vaccination boosted MIMIC anti-Fluvirin IgG

Quality of Ab Responses: Avidity Indices and Cross Reactivity

Last year's flu vaccine, esp. Solomon Island H1 component, is associated with reduced Ab avidity and reduced cross-reactivity



Stronger NC memory, high avidity, response in pre-vaccinated donors

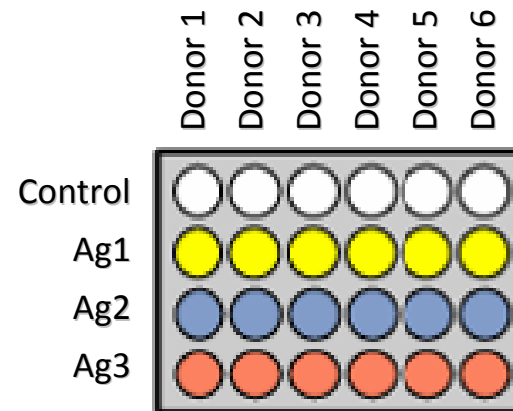
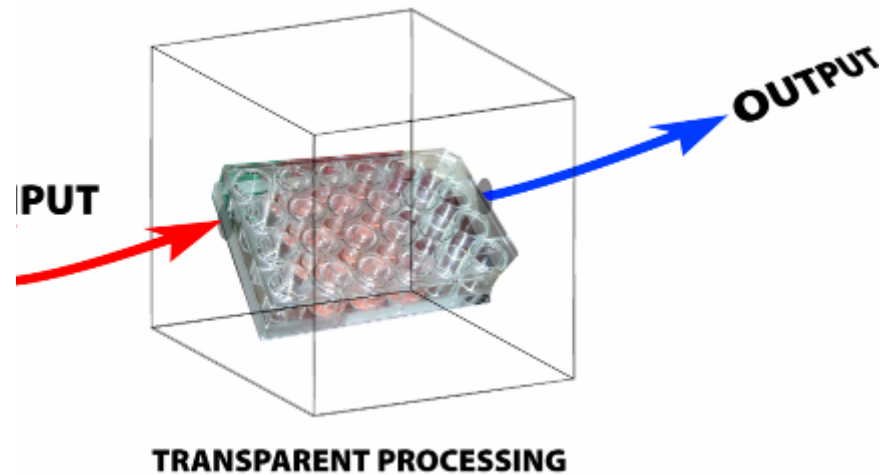
Stronger SI, low avidity, response in post-vaccinated donors

Examples of *In Vitro* Vaccine Projects

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Rapid T and B Cell Immunogen Screening

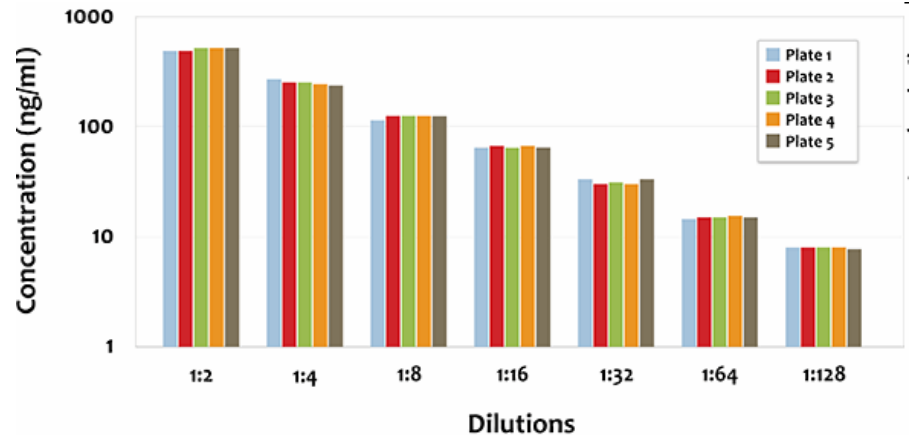
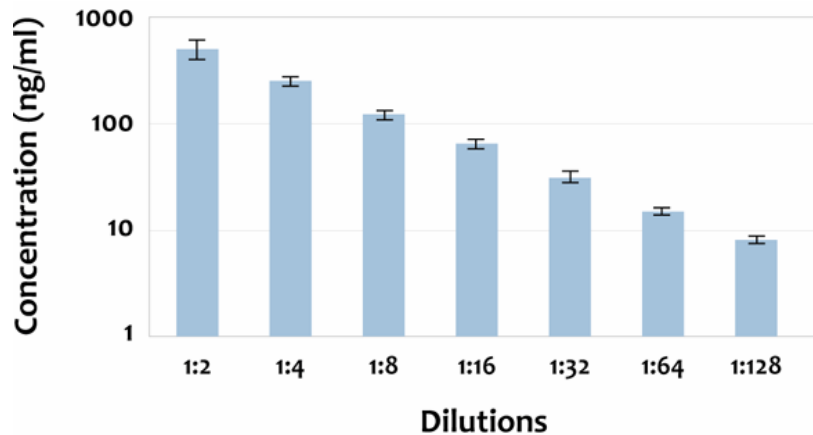
- Reduce the complexity of the human immune system into a series of modular bioengineered *in vitro* constructs
- Highly sensitive approach for assessing the magnitude and functionality of specific T and B cells
- Permits the evaluation of primary and recall responses



Significant Time/Cost Savings via Automation

	Manual	Automation
Blood Processing Labor Hours	2.5 hrs	1 hr
Vaccination Site Hours per 32 plates	24 hrs	6 hrs
ELISA Hours per 36 plates	40 hrs	3 hrs
ELISPOT Hours per 32 plates	40 hrs	10 hrs

Automated ELISA Results



Conclusions

1. MIMIC system appears to replicate human immunity, further validation will improve the situation
2. Data appears encouraging as a biomimetic of the human immune system
 - vaccine responses
 - immunogenicity
 - immunotoxicity
 - *in vitro* infectious disease models
3. Applications for vaccines: entire drug development timeline
 - preclinical down-selection
 - design adaptive clinical trials
 - manufacturing

Acknowledgements



***Thank
You***



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To sanofi pasteur for providing the yellow fever vaccine

