GVIRF 2018 Workshop 1: Emerging Vaccine Strategies & Technologies	
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Session Outline	**Chair:** Paula Bryant (Senior Scientific Officer, NIAID) **Presentations:** *MIMIC: an in vitro model of human immunity*, Donald Drake (Director, Sanofi Pasteur VaxDesign) *New Vaccine Strategies Using Cytomegalovirus,* Klaus Frueh (Professor, Vaccine & Gene Therapy Institute) *A novel vaccine technology platform Plasmid Launched Live Attenuated Virus (PLLAV) vaccines*, Johan Neyts (Professor, University of Leuven)
Objectives of the session	*To discuss:* • Emerging systems and technologies and how they can be applied to advance research and development of vaccine candidates.
Main outcome	"Traditional vaccines work by mimicking the immune responses elicited by a given pathogen, using a safe alternative to the pathogen. However, traditional vaccine approaches struggle to elicit protective immune responses for infectious diseases that do not elicit protective immunity upon natural exposure. Since we cannot mimic natural immunity, we need new approaches that elicit immune responses that are different and more efficacious than those induced by each pathogen." – Klaus Fruh
Summary	The MIMIC system is a modular and flexible *in vitro* model of the human immune system intended to function as a "clinical trial in a test tube", providing clinically relevant information much earlier in the development process. The MIMIC system uses human donor peripheral blood mononuclear cells and is comprised of a Peripheral Tissue Equivalent (PTE) Module that is designed to stimulate the innate immune response and a Lymphoid Tissue Equivalent Module (LTE) that stimulates the adaptive (B and T cells) immune response. Gene activation in the PTE module correlates well with dendritic cell activation *in vivo*. A MIMIC-based assessment of influenza vaccines using cells from 24 donors gave results that were comparable to a Phase 3 clinical trial with 2400 subjects. The MIMIC is now being used to identify malaria peptides with strong CD4+ T cell response profiles for consideration in a novel malaria vaccine. In nonhuman primates, vaccine vectors based on rhesus cytomegalovirus (RhCMV) elicit and maintain high frequency "effector memory" T cell responses in mucosal sites, lymphoid tissues, and parenchymal organs. Because they efficiently re-infect and persist despite robust anti-CMV immunity, CMV-based vectors can be used repeatedly in CMV-immune recipients to induce immune responses against different antigens. These responses are uniquely "programmable": deletions and inversions in the RhCMV 68-1 vaccine strain shift the immune response from canonical MHC-I restricted epitopes to non-canonical, nonpolymorphic MHC-Ib (i.e., MHC-E) restricted or MHC II-restricted T cell epitopes[a] RhCMV strategies are being applied to HIV vaccine

	development. In a non-human primate AIDS model, RhCMV/SIV vaccine was the first to control highly virulent SIV. Ongoing experiments are testing protection by different CD8+ T cell programs. A highly attenuated human CMV vectored HIV vaccine targeting unconventional CD8+ T cells is now in cGMP manufacturing and slated for clinical trial in 2019. RhCMV-vectored TB and malaria vaccine constructs are also being evaluated. Plasmid Launched Live Attenuated Vaccines (PLLAV) are *E*. *coli*-produced DNA vaccines based on the live-attenuated Yellow Fever vaccine, YFV-17D. Upon administration, PLLAV replicate in mammalian cells, assemble into virus particles, and infect and are amplified in surrounding cells. They can serve as an effective live-attenuated yellow fever vaccine as demonstrated by proof-of-concept studies in small animals and non-human primates. PLLAV can also be utilized as a platform to generate chimeric vaccines against additional flaviviruses such as Japanese Encephalitis and Zika, or transgenic vaccines against other targets such as hepatitis B, rabies, and Lassa fever virus. Advantages of this technology include scalable, high yield production; modularity and high vector capacity; thermostability; and needle-free delivery.
Key references or quotes	a. Früh, K., & Picker, L. (2017). CD8+ T cell programming by cytomegalovirus vectors: applications in prophylactic and therapeutic vaccination. *Current Opinion in Immunology*, *47*, 52-56. DOI: 10.1016/j.coi.2017.06.010