



Experimental Medicine Vaccine Trials EMVTs Opportunities and Challenges

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EMVT definition -1

However, for this presentation Experimental Medicine Vaccine Trials are defined as:

“Clinical investigations undertaken to test or generate a scientific hypothesis that advances vaccine discovery/development but provide no direct prophylactic or therapeutic benefit to the participant”.

EMVT definition -2

These differ from product development trials where plausible vaccine candidates are positioned to progress through phase I-IV testing

While most often conducted under phase I guidelines the focus of EMVTs is to accelerate vaccine science rather than progress individual products.

They are likely iterative by nature

With little or no expectation that these will progress further in their own right

Why EMVTs?

- **Scientific:**
 - Animal models are not fully predictive of human responses
 - There are germ-line differences between humans and experimental animals
 - Recognized need for human immunogen discovery
 - NGS, B cell cloning, systems biology etc., approaches can provide valuable information from a few subjects
- **Financial:**
 - Unsustainable to continue to put “wishful” candidates into expensive phase 3 trials
 - Better allocation of resources needed to increase likelihood of success
- **Logistical:**
 - Public Health need to accelerate HIV vaccine development
 - Increasing difficulty of conducting large scale efficacy trials
- **Ethical:**
 - Enrolling volunteers in vaccine trials with higher probability of success
 - Reducing the number of volunteers exposed to unsuccessful vaccine candidates
 - **But** requires clear communication around the lack of benefit to the participant

The EMVT approach

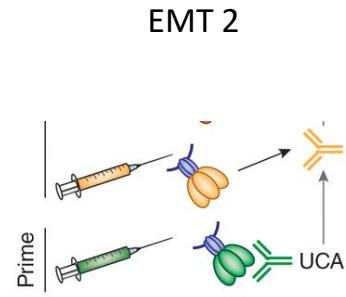
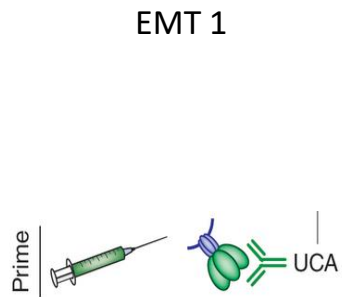
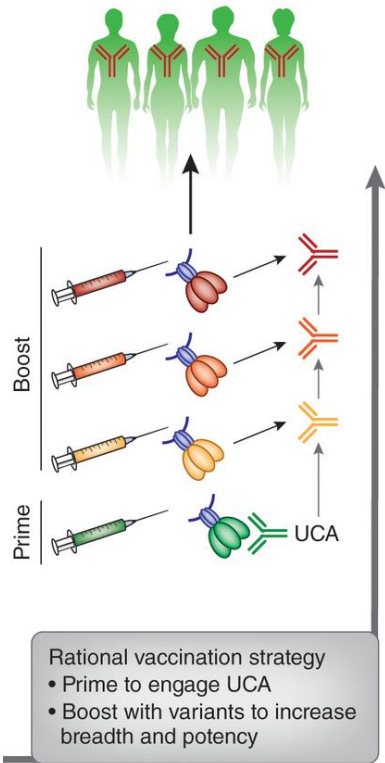
- **Designed to accelerate HIV vaccine development, increasing the probability of success for products moving into clinical evaluation.**
- Address questions that are not capable of definitive solution solely in animal models – *humans are the best model of humans*
- Provide opportunities for early iterations between preclinical and clinical research (para-clinical approach)
- Early validation and sequential iterations for structural based-design
- Evaluate novel concepts prior to formal product development – *hypothesis testing*
- Involve in depth analysis of human specimens (eg. NGS to analyze antibody germ line engagement and evolution)
- May involve intense sampling, such as mucosal or lymph node biopsies, daily blood samples, etc.

“EMVTs” in HIV Vaccine Development

	Traditional phase I	EM phase I
Purpose of the trial	Product development	Scientific information
Next step	Hopefully Phase II	Improve Vx design / Phase I
Number of Volunteers	~20-100	Defined by scientific question
Use of Controls/Placebo	Yes	Potentially No
Duration (months)	~12-18	Usually <12
Laboratory monitoring of volunteers	Safety/mostly regular immunogenicity	Safety/mostly special assays
Preclinical (animal) evaluation	Extensive (up to protection)	Limited/generic for platform (safety)
Vaccine Manufacturing	Scalable product (reproducibility/MCB etc)	Pilot/ small scale lot
Product characterization	Suitable for Ph3 trials; long term stability	Description of product (qualified assays): Purity, potency, stability
Safety/toxicity	Extensive	Limited
Regulatory	IND /IMPD	IND/IMPD
Ethics	IRB approval; Involves large communities	IRB approval; Involves individuals
Industrial partner	Highly desirable	Desirable, but not essential

EMVT example 1

- Clinical evaluation of a germline targeting immunogens (eg. eOD GT8)
- Tests the scientific concept that a certain immunogen design can stimulate relevant germline B cells in a significant number of individuals
- While a critical scientific question, induced antibodies provide no (or very unlikely) benefit to the participant

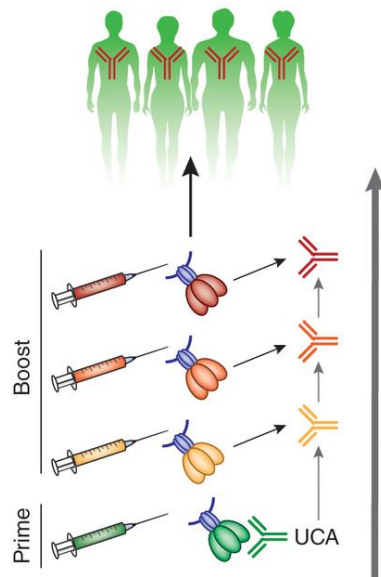


EMVT example 2

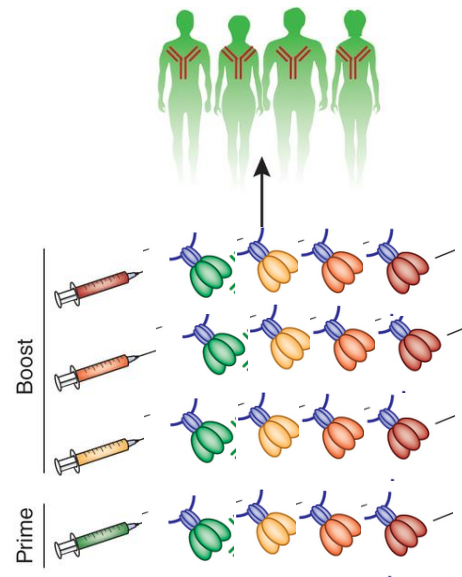
- Utilization of native like trimers as challenge agents to further understanding of the pathways to induction neutralizing antibody breadth
- Supported by a single pivotal toxicology package
- Use of phase appropriate small batch manufacturing
- Highly exploratory – hypotheses generating
- Challenge immunogens unlikely to provide any meaningful level of protection in their own right
- Provides significant savings in time and cost accelerating insight into the use of native like trimers

A large number of iterative EMVTs are likely needed to identify a series of immunogens able to induce broadly neutralizing responses before a realistic product is identified

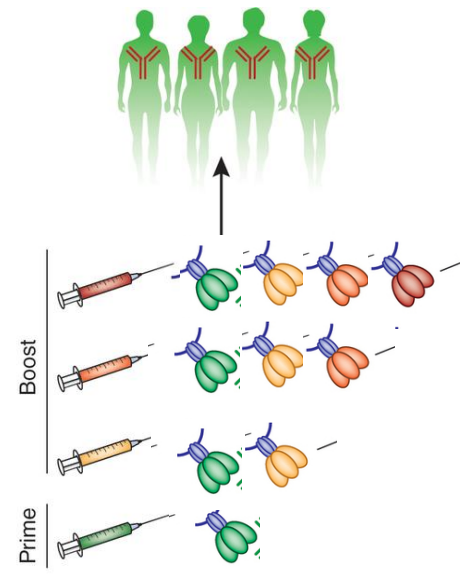
EMT 1



EMT 2



EMT 3



Potential savings (time and money) for Experimental Vaccine Trials

- Adoption of generic manufacturing process (platform approach: rec protein, vector, mRNA etc.)
- Smaller scale batch production (phase appropriate)
- Adoption of generic release and stability criteria (rapid regulatory approval, increased safety database)
- Acceptance of generic toxicology for multiple products produced by common manufacturing process
- Savings through parallel rather than sequential production of multiple products (gains in process development)

Potential challenges -1

Financial:

If EMVTs are performed along classical Phase I designs, there may be little savings in time or money (dependent on trial design and depth of IND specification)
Alternative pathways exist in different countries but may be relatively unique

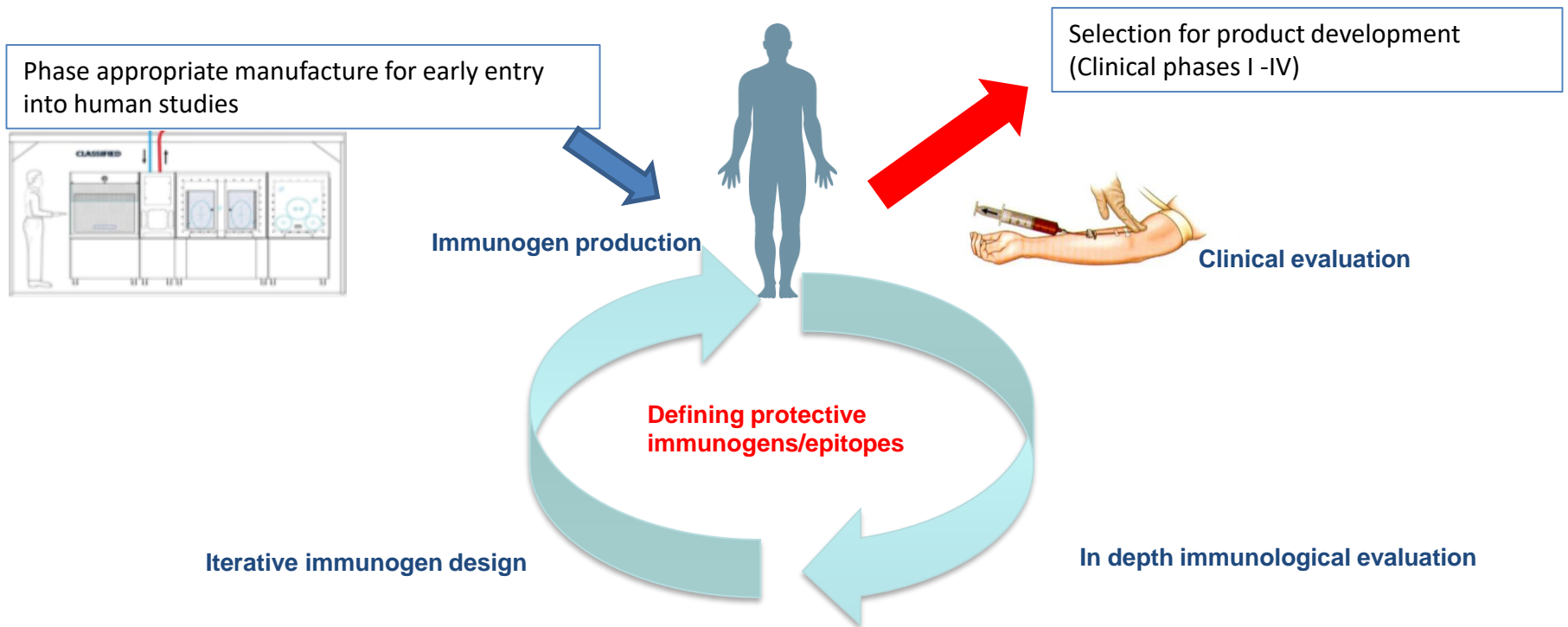
Logistical:

Development of phase appropriate manufacturing often not commercially attractive
Use of highly adaptable trial designs can be complex to communicate to regulatory and ethical bodies

Ethical:

Communication of “lack of benefit”, where volunteers are “research partners”
Changes risk-benefit discussion
Potential need for greater incentivization
Communication to vulnerable groups, children, minors, those with a low educational background etc., is more complex.
Avoidance of the Guinea Pig label

Iterative EMVTs



An urgent need to change the paradigm for HIV vaccine research has the potential to drive innovative use of EMVT that will provide wider benefit to vaccinology for many unmet needs

Thank you for your attention
