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Research-oriented development

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"Human Immunogenicity Trials" in Vaccine Development

WHY?

- **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 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

"Experimental Medicine Trials" in HIV Vaccine Development

WHAT?

- **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
- Provide opportunities for early iterations between preclinical and clinical research (para-clinical approach)
- Early validation and sequential iterations for structural design based approaches
- Early test of 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.

“Experimental Medicine Trials” 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	~10-30
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

"TEST CASE 1" DNA vaccines

Advantages

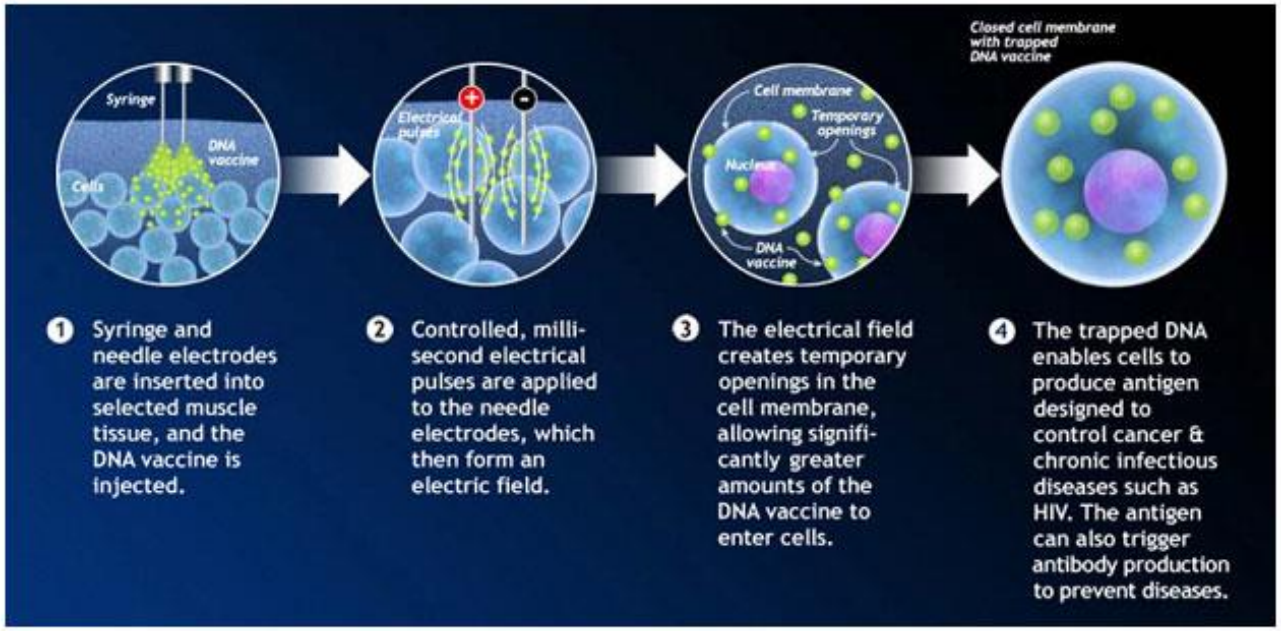
- Cheap and fast to manufacture (1/10) of cost for recombinant protein
- Generic preclinical toxicology to support testing of multiple common inserts within the same pDNA backbone

Disadvantages

- Traditionally seen as poorly immunogenic in humans

Can optimized DNA vaccination to identify protective HIV envelope immunogens?

- Codon optimization
- Promotor selection
- Route
- Dose
- Interval
- Electroporation
- Adjuvantation



Current Opinion in Immunology 2011, 23:421–429

"TEST CASE" DNAVAC

Feasibility of using DNA to screen human immunogenicity

- High level of seroconversion ≥70%
- Sufficient enrichment of antigen specific plasmablasts and memory B cells for repertoire analysis and mAb cloning
- Here DNA is used as a tool to screen immunogens and not as a practical vaccine strategy
- Maybe augmented by generic/consensus boost (protein/vector)
- Ideally suitable for Experimental Trials

"TEST CASE 2" envelope proteins

Time lines for CN54gp140 manufacture

- 1. Genetic construct (generation and validation)
  - 3 months
- 2. Generation of stable producer cell line
  - 9 months
- 3. Generation of Master Cell Bank (2 months)
- 4. Process development
  - 6 months
- 5. GMP manufacture
  - 4 months

- Total = About 36 months from gene to GMP production
- Total cost to GMP >1.54 million US dollars
- Total cost to phase 1 approximately 2 million US dollars

Lessons learnt

Set-backs:

- Underestimated time for contract negotiation/finalization
- Underestimated amount of product needed (500mg needed 1 gram)
- Master cell bank ensured reproducibility
- Delays caused by multiple audit reports (lack of standardization) – regulatory approval should be paramount

Successes:

- The material proved to be extremely stable, enabling material to be used for multiple phase I studies (8 at the last count)
- The material was safe and immunogenic
- Bedside mixing strategy for adjuvants provided maximal flexibility
- Small product development team – streamlined decision making

Potential savings (time and money) for Experimental Vaccine Trials

- Use of BAC technology for rapid establishment of stable cell lines (time saved: 6 months)
- Adoption of generic manufacturing process (risk – low or lack of expression – mitigated by advancing multiple candidates)
- Smaller scale batch production (risk – insufficient or unstable product, little saving on analytics and documentation)
- Adoption of generic release and stability criteria (risk – regulatory approval)
- Acceptance of generic toxicology for multiple Env products produced by common manufacturing process
- Savings through parallel rather than sequential production of multiple products (gains in process development

Cost saving for contracting multiple similar proteins
Reduce timeline from concept to clinic from 36 to 24 months
Increased evidence base for rationalized animal toxicology

New time lines for gp140 manufacture

	Previous (months)	Projected
Synthesis of Expression vector	3	1
Generation of stable producer cell line	9	3
Master Cell Bank (Polymun)	2	2
Process development	6	1
GMP manufacture	4	4
	24	**11**

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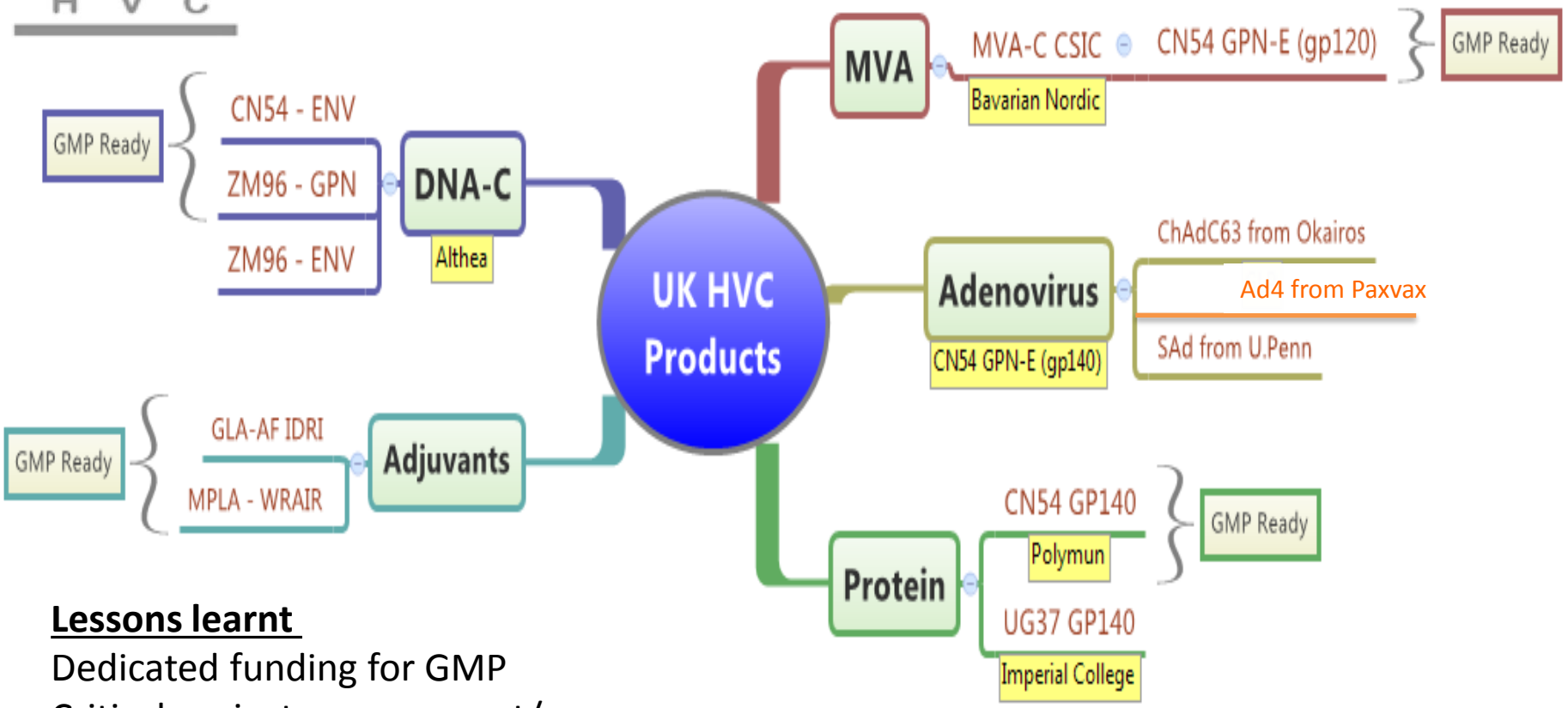
"TEST CASE " product portfolio



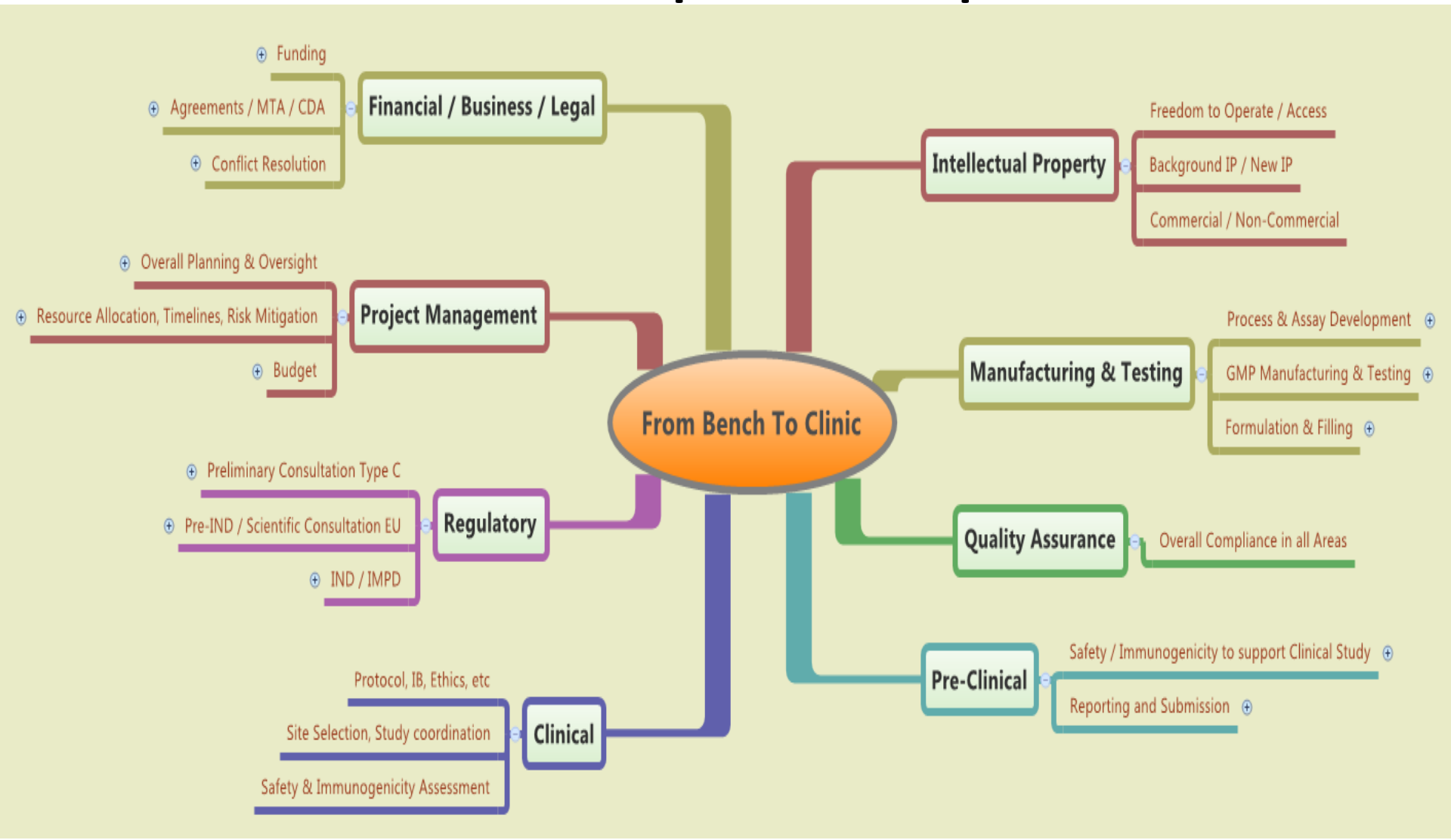
Lessons learnt

Dedicated funding for GMP
Critical project management/manager
Contracts (multiple)
Experienced QP contracted for duration of project
Supporting multiple EM trials (5)

wellcome trust

PI Jonathan Weber, Imperial College

The landscape of expertise



Streamlined product development can be achieved to support small iterative EM phase I trials

Small, experienced teams can provide cost efficient management,

- rapid decision making
- shorter timelines
- fewer tiers of administration
- needed flexibility to address changing scientific priorities

Appropriate for iterative EM studies

- designed to drive early HIV vaccine R&D
- informed by human immunology
- reducing risk of late stage failure
- prior to conventional product development

decentralised

Sharing of best practice

"Experimental Medicine Trials" in HIV Vaccine Development

- Rapid identification of immunogens capable of inducing Tier 2 neutralization
- Selection of immunogens (sequential/pools) designed to drive bnAb breadth
- Use mAbs for vaccine target identification (ability to control infection)
- Down selection of humoral vaccine variables at an early stage (adjuvant type, dose, route, interval)
- Comparison of vectors/immunogens (conserved/mosaic) for breadth of activity/potency
- Assessment of vectors, not only for imunogenicity, but also questions related to mucosal immunology, longevity, inflammation/activation, vector biology, etc.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Enterprise


The Collaboration for AIDS Vaccine Discovery


BILL & MELINDA
GATES foundation

Thank you for your attention