Accelerating Clinical Trials for Vaccine Development

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Missing Vaccines

• The Big Three:
  • HIV / AIDS
  • Malaria
  • improved TB

• Viruses
  – CMV, Dengue, EBV, hepatitis C, HSV, norovirus, rhinovirus, universal influenza

• Bacteria
  – Campylobacter, Chlamydia, E. coli, gonococcus, H. pylori, Shigella, Strep A & B

• Other
  – Leishmaniasis, Schistosomiasis, Hookworm
  – Allergies
  – Autoimmunity
  – Cancer
Vaccinology

• The science underlying the most cost-effective medical intervention ever

• Vaccines saves million of lives every year
  – with an ever-broadening scope

• True global reach
  – But a European strength scientifically and commercially
Vaccine Impact

• Rapid commercial growth over the last decade to $>25$ billion p.a.

• Improved vaccine access globally
  – Many new vaccines and larger populations served

• Vaccines are key to disease eradication
  – Smallpox, polio, measles, rinderpest, malaria…

• …and food security, biosecurity, maintained antimicrobial utility, and economic growth
A Very Translational Activity

• The only real test of human vaccines is in humans

• Efficacy can be tested in small numbers of people in many diseases

• Vaccine development can happen very quickly, especially in pandemics
The RTS,S Malaria Vaccine Candidate

Rutgers et al., 1988; Biotechnology 6:1065-1070
Clinical Development of Vaccines takes a Long Time

• Safety
  – Every larger trial sizes
  – Ever costlier documentation

• Population heterogeneity

• Disease incidence falls in trial sites
Some Suggested Solutions

• Innovative designs
  – Adaptive trial designs
  – New analytical approaches

• More phase IV safety and effectiveness studies

• Commercial incentives
  – e.g. Advance market commitments
Experimental Medicine Studies

A More Urgent Need

Small-scale rapid clinical trials aiming to

1. Test concepts
2. Compare vaccines types
3. Search for efficacy signals
4. Identify biomarkers of efficacy
1. Testing Concepts

• How can we induce mucosal immunity?
  – Biopsy studies in HIV

• Can CD8+ T cells protect humans?
  – Prime-boost studies in malaria

• Will new routes of immunisation help?
  – Aerosol immunisation in TB
2. Comparing Vaccines

• What are the most potent immunogens?
  – DNA, virus-like particles, viral vectors, RNA

• Which adjuvants are most useful?

• Which are the best antigens from complex pathogens?

Head to head comparisons in the clinic are very rare
3. Efficacy in Small Trials

• Controlled human microbial infections
  – Started in 1796
  – Key to malaria vaccine development
  – Underused for at least 12 other vaccine types
Controlled Human Microbial Infections

- malaria
- influenza
- cholera
- norovirus
- RSV
- typhoid
- paratyphoid
- rhinovirus
- *Shigella*
- *E. coli*
- dengue
- BCG for TB
- pneumococcus
- *H. pylori*
- hookworm
- gonococcus
4. Identify Biomarkers of Efficacy

• Preferably in small scale CHMI trials
  – Usually immune correlates
  – Immensely powerful new immunoassays

• To de-risk investment and guide further development

• And even allow licensure
## Are There Any Biomarkers?

<table>
<thead>
<tr>
<th>YES</th>
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<td>Diphtheria</td>
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<tr>
<td>MMR</td>
<td>Japanese encephalitis</td>
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</table>
New Assays for Difficult Diseases

• **Malaria**
  – CSP antibody titre
    • Anti-sporozoite immunity
  – CD8+ T cells using flow cytometry
    • Anti-liver-stage immunity
  – Growth inhibition and membrane feeding assays
    • Functional assays for blood-stage and transmission-blocking stages

• **Tuberculosis**
  – Mycobacterial growth inhibition assay
    • May correlate with vaccine efficacy

• **HIV**
  – Neutralisation assays
  – New anti-viral suppression assays of cellular immunity
Transcriptomic Technologies Now Allow New Correlate Identification

Stronger responders

Weaker responders

Case

Control

Same genes separate cases and controls among weaker responders
Crossing the “Valley of Death”

Drug and vaccine pipeline: 10 – 20 years

Concepts
- T cell vaccines
- Internal adjuvants
- Epitope strings
- Prime-boost regimes
- Over-expressing bacteria
- Simian vectors
- Sugar + membrane stabilisation

Products
- AIDS vaccine
- Malaria vaccine
- Foot and mouth vaccine
- Universal flu vaccine
- Meningitis B vaccines
- TB vaccines
- Fridge-free vaccines
THE JENNER INSTITUTE

a partnership between Oxford University and the Pirbright Institute

- Developing innovative vaccines
- Partnering with industry
- Driving the One Health agenda
### Oxford Human Vaccines Pipeline

<table>
<thead>
<tr>
<th>Disease Area</th>
<th>Number of GMP Vaccines</th>
<th>Preclinical</th>
<th>Phase I</th>
<th>Phase IIa</th>
<th>Phase Ib</th>
<th>Phase IIb</th>
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<th>Licensure</th>
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</table>

The busiest pipeline of any non-profit vaccine institute
Centre National de Recherche et de Formation sur le Paludisme, Burkina Faso

Scientific Staff: Group of Sodiomon Sirima

- 10 PhDs (Epidemiology, Immunology, Entomology, Socio-anthropology, Biochemistry and Pharmacology)
- 6 MDs, 1 specialising in Clinical Development
- 3 Pharm D (2 with an MSc in Clinical Pharmacology and Parasitology)
- 4 MSc in Biology
- 2 BSc in Biology and Parasitology
- 1 MSc in Demography
Cerebral Malaria
Malaria
A Complex Life Cycle

Mosquito Stage

Sporozoite Stage

Liver Stage

Blood Stage

vertebrate host
anopheles mosquito
sporozoites

RBC
within mosquito gut

schizonts
merozoites
Killer T-Cell Attack on an Infected Liver Cell

Parasites

Cytoplasm

Liver Cell

Killer T Cell

HLA = Human Leucocyte Antigen

Human Leucocyte Antigen Receptor

KILLING
Viral Vector Vaccines

to Maximise Cellular Immunogenicity

Adenovirus Prime 8 weeks  MVA Boost

Malaria, HCV, HIV, influenza, TB, RSV
Sukuta Infant Vaccine Clinic
The Gambia
ChAd63-MVA MeTRAP in Gambian 10 week olds
An Innovative Malaria Trial Design

- Randomized controlled trial
- ChAd63 + MVA ME-TRAP vs Rabies control
- Healthy adult volunteers in Kilifi, Kenya, n = 120
- Primary Endpoint: Time to PCR +ve infection after anti-malarial drug treatment to clear any baseline infection
- Drugs = Atovaquone, Proguanil, Artesunate

Ogwang et al. Submitted 2013
A Sporozoite and Liver-Stage Vaccine

a combination two-hit approach

Sporozoite Stage:
Antibodies clear most sporozoites

Liver Stage:
T Cells clear the remaining liver cells
## Combining Vectors with RTS,S/AS01
An Oxford University - GSK Collaboration

<table>
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<tr>
<th>Week</th>
<th>Group 1 (n=20)</th>
<th>Group 2 (n=20)</th>
<th>Group 3 (n=6)</th>
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<td>10</td>
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<td>12</td>
<td>CHMI</td>
<td>CHMI</td>
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Other Ways to Save Time and Money

• Review biomanufacturing regulations for small trials
  – Often the cost of manufacture exceeds trial costs

• Support open access adjuvants and vectors

• Continue to resource trial capacity in developing countries
Summary Recommendations

• Support more experimental medicine trials
  – Smaller, faster, less costly & comparative

• Add mechanistic analysis to all efficacy trials

• Regulators could help even more
  – biomanufacturing regulations for small trials
  – More use of biomarkers and CHMI for licensure
Edward Jenner’s Clinical Development Plan

- 1796: phase I / IIa trial of the first vaccine
  - inoculation and challenge of James Phipps in Berkeley, UK

- 1798: first London smallpox vaccinations

- 1800: most European countries using vaccination

- 1801: Thomas Jefferson vaccinated
  Empress of Russia supports vaccination

- 1802: widespread use begins in USA, India, Ceylon