Correlates

Andrew J Pollard
Professor of Paediatric Infection and Immunity
Why do we need correlates?

• Efficacy is enough

• Avoiding expensive or non-feasible trials

• Bridging to new populations

• Keep regulators happy
How do we measure correlates

• Blood tests to measure immune responses

• Do they relate to protection – efficacy studies
Correlate: An immune response that is responsible for and statistically interrelated with protection

Absolute Correlate: A specific level of response highly correlated with protection: a threshold

Relative Correlate: Level of response variably correlated with protection

Co-Correlate: One of two or more factors that correlate with protection in alternative, additive, or synergistic ways.

Surrogate: An immune response that substitutes for the true immunologic correlate of protection, which may be unknown or not easily measurable
Correlates of what?
What correlates?
Figure 2 Confirmed cases of severe varicella by age (n = 112).

Cameron, J C et al. Arch Dis Child 2007;92:1062-1066

Correlate of what?

All varicella
Varicella

- Viral infection
  - Protection mediated by ?
Child with AIDS – Disseminated VZV
X-linked agammaglobulinaemia

- No antibody
- Course of illness with primary VZV is the same as individual who is not immunodeficient
Perinatal VZV

- Postnatal exposure VZV unlikely or very mild if mother immune
- Maternal VZV 5 days before to 2 days after delivery
- ZIG is not detectable in blood after im injection – very small amount needed for protection
- With VZIG still 30-40% develop disease
- VZIG reduces severity in perinatal exposure
- Reduction in complications and mortality

Reviewed in Isaacs 2007
Vaccine Immunogenicity

- One dose
- > 5 gpELISA units in 92-98%
- Lower seroconversion in adolescents
- 4-fold rise in antibody in 78-87%
- 98-100% persistence for 6 years

Shinefield 2002
Vaccine Efficacy

- 5 years = 90%
- 97% effective against severe and moderately severe disease
- Breakthrough cases 5-7% over 5 years

Correlate of protection

• Level and type of T cells required to limit disease in an individual is unknown
• Passive antibody provides protection but we don’t know the quality of IgG or absolute level for protection
• gpELISA correlates
• FAMA correlates better
Why are T cells not correlates of protection?

- Varicella Infection
- VZ Immunoglobulin
- Maternal antibody
- Varicella Vaccine
- T cells (HIV, pregnancy)

Temperature

36.8° - 40°

Time

10-21 days - 5 days
Zoster (Shingles)

• Need T cells
• Role of antibody?
Zoster vaccine efficacy

**Post-herpetic neuralgia**

**Herpes Zoster**

*Figure 2.* Kaplan–Meier Estimates of the Effect of Zoster Vaccine on the Cumulative Incidence of Postherpetic Neuralgia (Panel A) and Herpes Zoster (Panel B) in the Modified Intention-to-Treat Population.

Incidence rates of postherpetic neuralgia (PHN) and herpes zoster (HZ) were significantly lower in the vaccine group than in the placebo group (*p*<0.001, by a stratified log-rank test that pooled the results of the log-rank test from the two age groups). Cumulative incidence, expressed as a percentage of the subjects at risk, is the probability of the development of the disease during the period from 30 days after vaccination to the follow-up time.
Zoster Vaccine

- Vaccine contains large amounts of infectious and non-infectious varicella virus

- VZ antigen stimulates flagging cellular immunity in the elderly

- Correlate of protection is VZ-specific CD4+ lymphocyte proliferation stimulation index

Hata et al. NEJM 2002
Zoster vaccine in transplanted adults

(Heat-inactivated vaccine)

Hata et al.  NEJM 2002
CD4 T cell Stimulation index

Hata et al. NEJM 2002
CD4 T cell SI and reduction in Zoster

<table>
<thead>
<tr>
<th>Stimulation Index</th>
<th>Reduction in risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.6</td>
<td>68</td>
</tr>
<tr>
<td>3.0</td>
<td>76</td>
</tr>
<tr>
<td>4.0</td>
<td>83</td>
</tr>
<tr>
<td>5.0</td>
<td>93</td>
</tr>
</tbody>
</table>

Hata et al.  NEJM 2002
Comparison of varicella-zoster virus (VZV)-specific immune responses in immunology substudy subjects who developed herpes zoster (HZ) and those who did not

<table>
<thead>
<tr>
<th>Time immune assay</th>
<th>Clinical endpoint</th>
<th>Vaccine</th>
<th>Placebo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Observed geometric mean (95%) CI</td>
<td>Observed geometric mean (95%) CI</td>
<td></td>
</tr>
<tr>
<td>Before rash onset</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Responder Cell Frequency (H^3)</td>
<td>HZ</td>
<td>2.3 (2.1–6.9)</td>
<td>2.4 (1.3–4.4)</td>
<td>.006</td>
</tr>
<tr>
<td></td>
<td>Matched control</td>
<td>6.5 (5.3–8.0)</td>
<td>5.6 (4.8–6.5)</td>
<td></td>
</tr>
<tr>
<td>IFNg ELISPOT</td>
<td>HZ</td>
<td>28.6 (7.1–114.2)</td>
<td>28.8 (17.2–48.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Matched control</td>
<td>99.8 (80.8–123.2)</td>
<td>56.7 (47.3–68.0)</td>
<td></td>
</tr>
<tr>
<td>gpELISA</td>
<td>HZ</td>
<td>252.4 (126.1–504.9)</td>
<td>181.3 (122.3–268.8)</td>
<td>.030</td>
</tr>
</tbody>
</table>

Levin et al, JID, 2008
T cells as effectors and correlates

Varicella-Zoster

Temperature

36.8° 40°

5 days

Decades

Waning immunity

Time

T cells
Principle 1

Must Define Protection

Against

Infection ?

(Disease ?)

(Local or Disseminated or even colonisation/carriage)

(Mild or severe)

Cost to the health system

Hospitalisation
Varicella

• Define as short-term protection against clinical (severe) disease

Rotavirus

• Define as prevention of hospitalisation or severe disease
What are used to look for a correlate

<table>
<thead>
<tr>
<th>Serum Antibody</th>
<th>CD4+ T cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutralizing</td>
<td>B cell help (Th2)</td>
</tr>
<tr>
<td>Non-neutralizing</td>
<td>T cell help (Th1)</td>
</tr>
<tr>
<td>Functionality (opsonophagocytosis)</td>
<td>Help to inflammation (Th17)</td>
</tr>
<tr>
<td>Avidity (cytotoxicity, etc.)</td>
<td>Cytokines</td>
</tr>
<tr>
<td></td>
<td>Lysis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mucosal Antibody</th>
<th>CD8+ T cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA locally produced</td>
<td>Lysis</td>
</tr>
<tr>
<td>IgG diffused from serum</td>
<td>Avidity</td>
</tr>
</tbody>
</table>
MALARIA

Prime-boost vaccination with chimpanzee adenovirus and modified vaccinia Ankara encoding TRAP provides partial protection against *Plasmodium falciparum* infection in Kenyan adults


Table 2. Vaccine efficacy by Cox regression. \( N \), number of participants; \( n \), number of end points identified. Efficacy figures are estimated from Cox regression, where efficacy \( = (1 - HR) \times 100\% \).

<table>
<thead>
<tr>
<th></th>
<th>ME-TRAP</th>
<th>Control</th>
<th>Unadjusted efficacy</th>
<th>Adjusted efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( N )</td>
<td>( n )</td>
<td>( N )</td>
<td>( n )</td>
</tr>
<tr>
<td>Any PCR positivity</td>
<td>61</td>
<td>11</td>
<td>60</td>
<td>28</td>
</tr>
<tr>
<td>&gt;10 parasites/ml</td>
<td>61</td>
<td>4</td>
<td>60</td>
<td>19</td>
</tr>
<tr>
<td>New genotype</td>
<td>61</td>
<td>5</td>
<td>60</td>
<td>14</td>
</tr>
</tbody>
</table>
How Correlates Are Determined

1. Levels of passively administered or maternal antibody that protect

2. Analysis of immune responses in protected and susceptible individuals in efficacy trials

3. Analysis of immune responses in protected cohorts in effectiveness studies

4. Observations made on vaccine failures, e.g. immunosuppressed individuals

5. Human challenge studies

6. Extrapolation from animal challenge studies
Principle 2

The Mechanism of Protection by Vaccination is \textit{NOT} Necessarily the Same Mechanism as Recovery From Infection
Varicella

- Antibody neutralises the virus and prevents disease

- T cells kill viral infected cells and limit disease
<table>
<thead>
<tr>
<th>Mechanism of Disease Prevented by the Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Viral</strong></td>
</tr>
<tr>
<td><strong>Viraemia:</strong></td>
</tr>
<tr>
<td><strong>Mucosal replication:</strong></td>
</tr>
<tr>
<td><strong>Neuronal Invasion:</strong></td>
</tr>
<tr>
<td><strong>Neuronal reactivation</strong></td>
</tr>
<tr>
<td><strong>Bacterial</strong></td>
</tr>
<tr>
<td><strong>Bacteremia:</strong></td>
</tr>
<tr>
<td><strong>Colonisation</strong></td>
</tr>
<tr>
<td><strong>Mucosal Replication:</strong></td>
</tr>
<tr>
<td><strong>Toxin Production:</strong></td>
</tr>
<tr>
<td><strong>Macrophage Replication:</strong></td>
</tr>
</tbody>
</table>

Adapted from Plotkin S. *C.R. Acad. Sci.* 1999;322:943-951.
Principle 3

A Large Challenge Dose Can Overcome Immunity

Well recognised for viral infections – severity is associated with dose

This is a caution to those working in vaccine development using challenge studies to guide clinical development programmes
“Challenge” of Poliovaccine by OPV

% Infected 7 days after challenge

<table>
<thead>
<tr>
<th></th>
<th>Low dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPV Vaccinees</td>
<td>3%</td>
<td>15%</td>
</tr>
<tr>
<td>IPV Vaccinees</td>
<td>30%</td>
<td>70%</td>
</tr>
</tbody>
</table>
Principle 4

Current Vaccines were almost exclusively developed to Protect Through Antibodies

(Be suspicious of anyone who believes in T cells)
Infections for which Passive Immunity is Clearly Useful

Diphtheria
Pertussis
Tetanus
Staph
Group B Strep
Hib
Pneumo

Hepatitis A
Hepatitis B
RSV
CMV
VZV
Parvovirus B19
Enteroviruses (polio)
Measles
Rubella
Vaccinia
Anti-PRP Antibody and Hib Colonization

Fernandez J, et al. JID 2000;182:1553-6
Antibody is used to derive quantitative correlates

Table 4. Some quantitative correlates of protection after vaccination.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Test</th>
<th>Correlate of protection</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria</td>
<td>Toxin neutralization</td>
<td>0.01–0.1 IU/mL</td>
<td>[14]</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>ELISA</td>
<td>10 mIU/mL</td>
<td>[15]</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>ELISA</td>
<td>10 mIU/mL</td>
<td>[16]</td>
</tr>
<tr>
<td>Hib polysaccharides</td>
<td>ELISA</td>
<td>1 mcg/mL</td>
<td>[17]</td>
</tr>
<tr>
<td>Hib conjugate</td>
<td>ELISA</td>
<td>0.15 mcg/mL</td>
<td>[18]</td>
</tr>
<tr>
<td>Influenza</td>
<td>HAI</td>
<td>1/40 dilution</td>
<td>[19]</td>
</tr>
<tr>
<td>Lyme</td>
<td>ELISA</td>
<td>1100 EIA U/mL</td>
<td>[20]</td>
</tr>
<tr>
<td>Measles</td>
<td>Microneutralization</td>
<td>120 mIU/mL</td>
<td>[7]</td>
</tr>
<tr>
<td>Pneumococcus</td>
<td>ELISA; opsonophagocytosis</td>
<td>0.20–0.35 mcg/mL (for children); 1/8 dilution</td>
<td>[21, 22]</td>
</tr>
<tr>
<td>Polio</td>
<td>SN</td>
<td>1/4–1/8 dilution</td>
<td>[23]</td>
</tr>
<tr>
<td>Rabies</td>
<td>SN</td>
<td>0.5 IU/mL</td>
<td>[24]</td>
</tr>
<tr>
<td>Rubella</td>
<td>Immunoprecipitation</td>
<td>10–15 mIU/mL</td>
<td>[25, 26]</td>
</tr>
<tr>
<td>Tetanus</td>
<td>Toxin neutralization</td>
<td>0.1 IU/mL</td>
<td>[27]</td>
</tr>
<tr>
<td>Varicella</td>
<td>SN; gpELISA</td>
<td>≥1/64 dilution; ≥5 IU/mL</td>
<td>[28, 29]</td>
</tr>
</tbody>
</table>

NOTE: gp, glycoprotein; HAI, hemagglutination inhibition; Hib, Haemophilus influenzae type b; SN, serum neutralization.
HAI

Hemagglutination and hemagglutination-inhibition test

Virus + RBC \rightarrow \text{Hemagglutination}

Virus + Antibodies from patient's serum + RBC \rightarrow \text{No Hemagglutination}

Dilution

Sample

1/40
Influenza vaccines in children

<2 years efficacy 75%

MF59 adjuvanted vaccine

<2 years efficacy 2%

Vesikari et al, NEJM 2011
HAI

- Factors affecting correlation with immunity
  - Age
  - Strain H3N2, H1N1, H5N1, H7N9
  - Virus Match
  - Co-morbidity
  - Previous exposure
Principle 5

Correlates may be relative

Which means that the situation is more complex
Distribution of serum neutralizing titers in hospitalized and non-hospitalized adult subjects with RSV

Complex situation – dose of virus, level of antibody and quality of antibody

Walsh EE. JID 2004;189:233.
Principle 6

Antibodies must be FUNCTIONAL

Do we need to measure them and are we are measuring the right thing?
Meningococcal Disease

Goldschneider 1969
Measuring immunity against meningococcus – bactericidal assay

Complement

Immune serum

N. meningitidis

Measures high avidity antibody that binds complement

Growth
The complement system
## ELISA and Bactericidal Antibodies After Group C Meningococcal Polysaccharide Vaccination

<table>
<thead>
<tr>
<th>Age (Yrs)</th>
<th>ELISA % Pos.*</th>
<th>Bactericidal % Pos.#</th>
<th>Efficacy in Canada</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>93</td>
<td>18</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>94</td>
<td>35</td>
<td>41%</td>
</tr>
<tr>
<td>3</td>
<td>92</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>94</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>84</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>Adult</td>
<td>100</td>
<td>100</td>
<td>83%</td>
</tr>
</tbody>
</table>

* ≥ 2 mcg/ml  # ≥ 1/8

Complement deficiency

• 0.3% of those with meningococcal disease have complement deficiency

• Rare serogroups:
  – W 135: 54 people (56%): 16/54 (30%) with complement deficiency
  – X: 9 people (9%) of whom 3 (33%) with complement deficiency
  – Y: 23 people (24%) of whom 11 (48%) had complement deficiency
  – Z: 1 person (1%) — no one had complement deficiency
  – 29E: 2 people (2%) — no one had complement deficiency
  – non-groupable; 8 people (8 %) of whom 2 (25%) had complement deficiency

• After B and C disease complement deficiency very very rarely reported but SBA correlates with protection
Pneumococcal Disease

- Increase risk in asplenia
- T cell deficiency (HIV)
- Antibody deficiency
- Complement deficiency

- Protection mediated by opsonophagocytosis
- Licensure based on measurement of ELISA antibody
  - Contains both high and low avidity antibody
Opsonophagocytic Antibodies

Response to Pneumococcal Vaccine with Age

Romero-Steiner, CID, 1999

What are you actually measuring in the laboratory?

Cell line
Exogenous complement
Serum
Principle 7

More than One Factor May Protect Co-Correlates

For example: Mucosal Antibodies
## Correlates of Immune Protection After Live Influenza Vaccine or Natural Infection (Artificial Challenge in Children)

<table>
<thead>
<tr>
<th>Serum HAI</th>
<th>Nasal IgA</th>
<th>Shedding</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>-</td>
<td>63%</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>19%</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>15%</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>3%</td>
</tr>
</tbody>
</table>

Belshe, JID, 2000
- HAI antibodies in serum and on mucosa correlate with protection

- However, in the elderly antibody responses are poor. CD8+ responses, rather than CD4+ responses correlate with antibody rises, and CD8+ CTL independently correlates with protection

Pertussis co-correlates
Exposure to Pertussis and PT

Exposure to Pertussis and FHA

Exposure to Pertussis and Pertactin

<table>
<thead>
<tr>
<th>Yes</th>
<th>Depends on Ab on Mucosa</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dengue</td>
<td>Hib</td>
<td>Rota</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>HPV</td>
<td></td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Influenza</td>
<td></td>
</tr>
<tr>
<td>Lyme</td>
<td>Measles</td>
<td></td>
</tr>
<tr>
<td>Rabies</td>
<td>Pertussis</td>
<td></td>
</tr>
<tr>
<td>(Tetanus)</td>
<td>Polio</td>
<td></td>
</tr>
<tr>
<td>Yellow Fever</td>
<td>Rubella</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Varicella</td>
<td></td>
</tr>
</tbody>
</table>
Principle 8

Memory may be a Surrogate (but not always)
Anti-HBs response to a 1-μg booster dose of recombinant-derived vaccine administered to persons vaccinated with plasma-derived vaccine 5-7 years earlier

Percentage with <10 S/N at time of booster dose 46% (24/52)

Percentage with anamnestic response 90% (47-52)

Long Term Efficacy of Hepatitis B Vaccine Despite Antibody Loss

(Chinese infants assessed 15 yrs. after vaccination)

<table>
<thead>
<tr>
<th></th>
<th>Anti-HBs</th>
<th>HBs Ag+</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine</td>
<td>50%</td>
<td>1.9%</td>
<td>89%</td>
</tr>
<tr>
<td>Controls</td>
<td>33%</td>
<td>16.7%</td>
<td></td>
</tr>
</tbody>
</table>

Liao SS Vaccine, 1999
Invasive Hib infections by age group, 1990-2002

Hib, >10,000 cases prevented since 1992

Source: Dr M Ramsay, Health Protection Agency CDSC, Colindale

Lee et al, 2007
Principle 9
Its probably more complicated than you think
Principle 9
Antibody “correlates” should contain the absolute correlate but may measure something more, or less

- Hib antibody level >0.15mcg/ml correlates with protection

- AJP
  - 100mcg/ml
  - Avidity very low
  - Complement binding antibody probably important
2 examples of ways to measure immune responses to influenza vaccines

MN (microneutralisation)

HAI (haemaglutination inhibition assay)
Principle 10

Main correlate for protecting susceptibles may be herd immunity rather than a direct correlate in the individual

• Is herd immunity a measurable correlate?
Herd Immunity
Herd Immunity
Herd Immunity might be the most important correlate for your protection – measure through carriage studies?

Effectiveness of meningococcal serogroup C conjugate vaccine 4 years after introduction

Caroline I. Trotter, Nick J. Andrews, Edward B. Kaczorowski, Elizabeth Miller, Mary E. Ramsay

See Comment page 309
Statistics, Economics, and Modelling Department (C I Trotter PhD, N J Andrews MS) and Immunisation Department (E Miller FRCPa, M E Ramsay FFP-HM), Health Protection Agency Communicable Disease Surveillance Centre, 61 Colindale Avenue, London NW9 5EQ, UK, and Health Protection Agency Meningococcal Reference Unit, Manchester Royal Infirmary, Manchester, UK (E B Kaczorowski FRCPa)
Correspondence to: Dr Mary Ramsay mary.ramsay@hpa.org.uk

Figure: Cases of laboratory-confirmed meningococcal serogroup C disease by age group and quarter, 1995–2004.
Carriage of meningococci

Christensen 2010
Principle 11

We might have to use Surrogates
Definition of a “surrogate”:

“A biomarker that is closely correlated to another marker, that is in turn statistically related to and responsible for protection from a disease”

i.e. a surrogate is one step removed from the correlate
It is confusing

- **Surrogate**: An immune response that substitutes for the true immunologic correlate of protection, which may be unknown or not easily measurable (Plotkin 2010)

- **Surrogate endpoint**: Laboratory or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful endpoint that is the direct measure of how a patient feels, functions or survives and that is expected to predict the effect of the therapy. US FDA

- **Surrogate**: The term surrogate refers to markers [that are statistically associated with clinical protection and] that lie on the causal pathway leading to protection (WHO 2013)

- **Serological surrogate**: A predefined antibody concentration correlating with clinical protection. EMA
Magnitude of primary B cell responses may determine persistence of antibody

What about T cells?
## Correlates for paediatric vaccines

<table>
<thead>
<tr>
<th>Antibody correlates</th>
<th>Cell mediated correlates (T cell)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria, antibody (toxin neutralisation)</td>
<td></td>
</tr>
<tr>
<td>Tetanus, antibody (toxin neutralisation)</td>
<td></td>
</tr>
<tr>
<td>Hib, antibody (ELISA)</td>
<td></td>
</tr>
<tr>
<td>MenC, antibody (serum bactericidal assay)</td>
<td></td>
</tr>
<tr>
<td>Pneumococcus, antibody (ELISA)</td>
<td></td>
</tr>
<tr>
<td>Hepatitis A, antibody (ELISA)</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B, antibody (ELISA)</td>
<td></td>
</tr>
<tr>
<td>Measles, antibody (microneutralisation)</td>
<td></td>
</tr>
<tr>
<td>Rubella, antibody (immunoprecipitation)</td>
<td></td>
</tr>
<tr>
<td>Varicella, antibody (serum neutralisation or gp ELISA)</td>
<td></td>
</tr>
<tr>
<td>Influenza, antibody (HAI)</td>
<td></td>
</tr>
<tr>
<td>Polio antibody (serum neutralisation)</td>
<td></td>
</tr>
<tr>
<td>Rabies, antibody (serum neutralisation)</td>
<td></td>
</tr>
</tbody>
</table>
Conclusion

• There are no paediatric T cell correlates of protection
T cells

- Needed to recover from disease after viral infections
- Measurement probably not sophisticated enough yet
- CD4 T cells necessary to help B cells
- CD4 T cells producing IL-23 probably important in response to BCG
- CD8 T cells maintain latency in TB
- CD4 frequency T cells correlate with Zoster protection
- CD4 T cells correlate long term immunity (mice and pigs)
B cell help

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>T cell involvement?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria, tetanus antitoxin, pertussis</td>
<td>B cell help</td>
</tr>
<tr>
<td>Hib, MenC, PCV antibody</td>
<td>B cell help</td>
</tr>
<tr>
<td>Measles, Rubella, Mumps, Polio, Varicella</td>
<td>B cell help</td>
</tr>
</tbody>
</table>

So why don’t we have T cell surrogates?

Immune response

Measurement

Blood  | Blood  | Blood  | Blood  | Blood

antigen

B cell  | T cell help  | B cell  | Plasma cell  | Antibody

Lymphoid tissue  | Lymphoid tissue  | Bone marrow  | Mucosa Blood

Primary location of action
It’s a bit more complicated
Measuring B cell help

- T cells which provide B cell help likely correlate with protection

- BUT difficult to measure
  - Access to the location of relevant cells
  - Definition of the right subset of cells
  - Standardised assay not available that specifically measures B cell help (assays for proliferation etc)
  - Relevant testing has not been done in efficacy trials to define T cell, B helper responses as a surrogate
FhT cells correlate with antibody response

Induction of ICOS+CXCR3+CXCR5+ TH cells correlates with antibody responses to influenza vaccination at 7 days
More T cells

• CD4 T cell responses correlate with protection against Zoster
• Standardisation of assays needed

But what about other infections…….. TB, malaria?
TB – T cells should be the correlate

- No established correlate.
- Need efficacy trials to establish the correlate.
- Last trial in infants in 1968 until 2013 study
MVA85A

• Boosting BCG with MVA85A
  – improves BCG-induced protection against mycobacterial challenge in animals.
  – induces antigen-specific Th1 and Th17 cells in infants (thought to be important in protection)
MVA85A
1st infant TB trial since 1968

2797 infants enrolled
BCG or BCG+ MVA85A

Tameris et al, The Lancet 2013
Without potent efficacy, not possible to establish a clear correlate
Malaria – establishing a correlate or a surrogate

Difficult to pin down protective responses without potent vaccines but T cells and antibodies should be candidates.
RTS,S vaccine efficacy of 30.1% (95% confidence interval, 23.6 to 36.1)

NEJM 2012
RTS,S malaria vaccine in a challenge model

circumsporozoite protein (CSP)

Both antibody and CD4 T cells are surrogates

White et al, Plos One 2013
T cells in TB and Malaria

• The hunt for T cells for TB and malaria correlates continues………..

• TB
  – We can measure T cell responses in a sophisticated way
  – but without efficacy data we cant identify a correlate

• Malaria
  – Both T cells and antibodies may be surrogates or correlates

• Other approaches?
Principle 12
Look harder and the correlates may be out there
Increase sophistication

Gene regulation

Gene Expression
- Promoter
- Exon 1
- Intron 1
- Exon 2
- Intron 2
- Exon 3
- Intron 3
- Exon 4

Gene (DNA)

Transcription
Primary transcript (RNA)

Splicing
Mature transcript (mRNA)

Protein synthesis
Protein

©Wellcome Trust
Yellow fever vaccine

Querec et al, Nature Immunology 2009
Predicting neutralising antibody titres

<table>
<thead>
<tr>
<th>Symbol</th>
<th>UniGene</th>
<th>Day</th>
<th>Pearson r</th>
<th>P-value</th>
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<td>7</td>
<td>0.530</td>
<td>0.00667</td>
</tr>
</tbody>
</table>

Querec et al, Nature Immunology 2009
Genomic signatures that correlate with the magnitude of the CD8$^+$ T cell response

Separate high and low responders on gene expression

Querec et al, Nature Immunology 2009
Influenza

Nakaya et al, Nature Immunology 2011

Gene expression signatures correlate with influenza antibody (HAI)

Future studies – will gene expression on day 1 be predictive of protection 1 year later?
Plotkin and Gilbert have recently proposed that correlates are simply divided into mechanistic and non-mechanistic correlates.
Pathway and Effector correlates

**Antibody**
- bactericidal antibody
- neutralizing antibody
- opsonophagocytic antibody
- high avidity antibody
- antibody concentration
- antibody dependent cellular cytotoxicity

**T cells**
- cytotoxic T cells
- CD4 T cell proliferation

**T helper cells**
- TfH cells
- memory B cells
- plasma cells
- cytokines

**Transcription factors**
- cytokines
- transcriptional or proteomics profiles

**Effector T cell responses**
- Antibody
  - bactericidal antibody
  - neutralizing antibody
  - opsonophagocytic antibody
  - high avidity antibody
  - antibody concentration
  - antibody dependent cellular cytotoxicity

**Pathway correlates of protection**
- Antigen recognition
- Innate responses
- Adaptive immune responses
- Protection
Conclusions

How to make a correlate – Step 1

• Choose a disease and decide what your vaccine will protect against (infection, disease, severe disease, hospitalisation, death)

• Use observations from disease, (immuno)deficiency, passive immunity, challenge studies and clinical study evidence to determine what mediates protection
Step 2

• If the answer is T cells, employ an army of immunologists, as the road ahead is uncertain or choose a new disease/change jobs

• If the answer is antibody (celebrate and), find a lab test that is easy to measure that is related to protection and can be justified
• Call it a correlate so everyone knows you are serious even though it might be a relative correlate, contain the correlate or even be just a surrogate
• While functionality is critical, If you have a simple correlate, take care not to be distracted by complex in vitro assays of functionality unless the regulator asks as this risks holding up vaccine development

• Consider memory and persistence of immunity and colonisation (mucosal bacteria) as a surrogate for diseases for which risk continues for a long time after vaccination (possibly in addition to a short term correlate)
• Whatever you do, make sure you find a correlate or surrogate as it will save you much time and money during development of your vaccine
If you have no correlate you need a lot of self belief (and then efficacy trials)