Principles and Practice of Vaccine Development

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Conflicts of interest

• GSK Adjuvant Advisory Board (previously)
• Expert witness in a court matter (ongoing)

• No funding received from any companies whose products mentioned

• Acknowledge the provision of slides from GSK, Dr. Birgit Beisner (these slides should be obvious)
Outline

• Vaccine Development 101
  • Costs and other parameters of drug and vaccine development
  • opportunities

• What is new(ish)?
  • Adjuvants – “danger” (Matzinger), “immunologists dirty little secret” (Janeway)
  • Checkpoint inhibitors – a new dawn for cancer vaccines
  • Tissue resident memory
  • New vaccines – Shingrix™

• Where are we heading?
  • Multivalency – improving efficacy or marketing?
  • Anti-Vax lobby
Drug (and vaccine) development

• Very expensive (some exc e.g. influenza)
• Tufts Uni do periodic costing – weight R&D costs against FDA-approved products, ie. ”failure incorporated”
• R&D costs of 106 randomly selected new drugs obtained from 10 pharmaceutical firms
• Journal of Health Economics 47: 2016, 20-33
• US$ 2013 $2.6B pre-approval + $300M post-approval

= $2.9B/approved product

=> Vaccine (like drug) development is limited to ‘deep pocketed’ companies
R&D investment recovered via pricing

• “Differential pricing” – buyin from vaccine Pharma
• GAVI post-EPI getting the vaccines to the poorest countries, but countries “graduate each year”
• Vaccines – volume tends to be less of an issue (to-date)

• What if there is insufficient volume?
• Niche vaccines for e.g. hospital infections
• Vaccines for Indigenous Australians
• Will need a high price driven by development costs to counter volume impact - who would pay?
30 day script costs in US in 2016

Data from Express Scripts (US PBM)

What is a vaccine that prevents e.g. a CMV or a KPC infection in a cardiac transplant patient worth?

http://lahealthexchange.com/blog/category/fda/page/2/
Vaccine development 101

• Years of laboratory work 10-25+ post etiology, phylogeny
• Gather resources – VC, MRCF…. need health informatics
• Pre-clinical studies – toxicology, immunogenicity, seed lots..
• Phase 1 – safety, dose escalation (1a/1b, immunogenicity?)
• Phase 2 – proof of concept - immunogenicity
• Correlate of protection fundamental – human challenge?
• Phase 3 – field studies (can be 1000->50,000) = pivotal trial
• Case definition important, infrastructure for diagnosis….
• Phase 4 – post-marketing surveillance

http://www.euvaccine.eu/vaccines-diseases/vaccines/stages-development
Attrition major issue in drug development

Raghavendra et al., International Journal of Academic Research, 2012
Clinical studies

### Early Phase

- **Phase I**
  - N=20–80
  - Safety
  - Immunogenicity
  - Proof of concept
  - Dose ranging

- **Phase II**
  - N=>100s
  - Safety
  - Immunogenicity
  - Efficacy

- **Phase III**
  - N=1000s–10,000s
  - Safety
  - Immunogenicity
  - Effectiveness

- **Phase IIIb/IV**
  - N=millions
  - Safety
  - Immunogenicity
  - Effectiveness
  - New indications

### Safety Evaluation:
- Local
- Systemic
- AE
- SAE

### Pharmacovigilance

AE, adverse event; SAE, severe adverse event

Vaccine manufacture is a multi-step process

Antigen manufacture

Growing the organism

Purifying the antigen

Formulation & Filling

Formulating the vaccine

Filling the vaccine

Freeze-drying

Packaging & Distribution

Packaging the vaccine

Storing the vaccine

Release

(Internal & by the authorities)

Distribution

Quality Assurance & Quality Control

Do vaccine clinical trials happen here?


• Search revealed 25 "vaccine" trials occurring, inc:
  • The B-VAX Project: Providing hepatitis B vaccinations through assertive outreach to people who inject drugs
  • ...effect of 10-valent pneumococcal-\textit{Haemophilus influenzae} protein D conjugate vaccine (PHiD-CV, Synflorix™) on the frequency of non-typeable \textit{Haemophilus influenzae} (NTHi) infection
  • Human Papillomavirus (HPV) infection in young men who have sex with men
  • Optimising Rotavirus Vaccine in Aboriginal Children
  • Opportunities, vaccine companies (4 large = Sanofi, GSK, Merck and Pfizer, 20-25% $)
After all this - is there money in vaccines?

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>2016 Sales (in million U.S. dollars)</th>
<th>2022 Sales (in million U.S. dollars)</th>
<th>Per Annum Sales</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevnar (pneumococcus)</td>
<td>2,513</td>
<td>2,488</td>
<td>$6.0B</td>
</tr>
<tr>
<td>Gardasil (HPV)</td>
<td>2,128</td>
<td>1,654</td>
<td>$2.5B</td>
</tr>
<tr>
<td>Pentacel (DTaP+IPV+Hib)</td>
<td>2,068</td>
<td>1,683</td>
<td>$1.7B</td>
</tr>
<tr>
<td>Fluzone (influenza HD/Q)</td>
<td>1,170</td>
<td>528</td>
<td>$1.7B</td>
</tr>
<tr>
<td>Bexsero (MenB)</td>
<td>528</td>
<td>1,170</td>
<td>$0.5B</td>
</tr>
</tbody>
</table>

https://www.statista.com/
Adjuvants

• Polly Matzinger and the ”danger” hypothesis c.1994
• Paradigm shift – self vs non-self -> recognizing “danger”
• Created nexus between innate immune system -> inflammation and adaptive immune system (inflammation licensing of DCs.. -> T cells)
• “Danger” is seen as product(s) of pathogens (or cells under stress) that are detected by a growing network of sensors
  • Toll like receptors (TLRs)
  • NOD-like receptors and inflammasomes
  • https://www.adipogen.com/pub/media/Catalogs/PDFs/Inflammasome-1_2010_final_1.pdf?___store=kr
• Adjuvants work by activating innate sensors, even Alum (+ depot)
  • Li H, Nookala S, Re F. Aluminum hydroxide adjuvants activate caspase-1 and induce IL-1beta and IL-18 release. J Immunol. 2007 178(8):5271-6 and others
Adjuvants

• “Immunologists dirty little secrets” (Charles Janeway)
• New understanding of innate signaling – new adjuvants triggering TLRs, inflammasomes…. create better danger
• Hard to divorce potency from inflammation

• Used to ‘dose spare’ during epidemic e.g.H1N1
• Opportunities for increasing deployment, elderly use....
• e.g. MF59, AS03 = squalene, oil-in-water (o/w) emulsions
• Antigen reduction, potency has stimulated anti-Vax lobby
Checkpoint inhibitors

• US clinical trials.gov > Keytruda, Opdivo et al. >1300 trials
• What do they do?
  • Observation: period of activity, the immune system is regulated
  • This ‘natural’ regulation (or checkpoint) reduces immunopathology but also limits immune control of esp. cancer
  • Regulation mediated through ligands (e.g. PD-L1) and receptors (e.g. PD-1)
  • If antibodies can block
  • T cells keep working

http://www.curetoday.com/articles/fda-approves-frontline-opdivo-for-braf-mutant-melanoma
Checkpoint inhibitors

• Rely on the development of an immune response
• New dawn for cancer vaccines, to be used in tandem

• Link between viruses and cancers
• Viral antigens may (again) become cogent cancer targets
• Therapeutic vaccine opportunities more generally

• Risks – autoimmunity, immunopathology
Immunological memory

Phenomenon mediated by adaptive immune system, through engagement, activation, then clonal expansion (then contraction) of specific T and B cells.

Some of the specific cells persist through the contraction phase – these cells are memory cells (esp. memory T cells).

Memory is programmed by transcription factors.
Immunological memory

- Vaccines, with a few exceptions (e.g. tetanus) rely on immunological memory, which persists for years
- Memory no longer simple – effector memory (EM), central memory (CM) and tissue resident memory (RM)

Rosato et al. Current Opinion in Virology 2017
Immunological memory

- Parabiosis can establish which is most important – $T_{RM}$ are being linked with protection inc. viruses
- One mouse immunized then joined to naïve animal
- Share $T_{EM}$ and $T_{CM}$
- Don’t share $T_{RM}$
- Separate and test immunity
- Can attribute role to $T_{RM}$

http://www.youngbloodinstitute.org/aging--blood.html
New vaccines

- Recombinant DNA-based biotechnology was supposed to solve most of problems with vaccine development e.g. pathogens that can’t be grown (easily) 1980s
- “Malaria vaccine within 5 years” c.1985
- HepB vaccine, HPV vaccines, RTS-S but progress slow
- Shingrix™
  - ...”is lyophilized varicella zoster virus glycoprotein E (gE) antigen component with the accompanying AS01<sub>B</sub> adjuvant suspension component” FDA product insert
- AS01<sub>B</sub> is a new adjuvant QS-21 + MPL (LPS derived), drives T+B
  - Didlerlaurent <i>et al.</i>, 2017 Expert Reviews in Vaccines 16:55-63
- Produced in Chinese Hamster Ovarian (CHO) cells
New vaccines

Efficacy of the Herpes Zoster Subunit Vaccine in Adults 70 Years of Age or Older

Anthony L. Cunningham, M.B., B.S., M.D., Himal Lal, M.D., Martina Kovac, M.D., Roman Chlibek, M.D., Ph.D., Shinn-Jang Hwang, M.D., Javier Diez-Domingo, M.D., Ph.D., Olivier Godeaux, M.D., Myron J. Levin, M.D., Janet E. McElhaney, M.D., Joan Puig-Barberà, M.D., M.P.H., Ph.D., Carline Vanden Abeele, M.Sc., Timo Vesikari, M.D., Ph.D., et al., for the ZOE-70 Study Group

RESULTS

In ZOE-70, 13,900 participants who could be evaluated (mean age, 75.6 years) received either HZ/su (6950 participants) or placebo (6950 participants). During a mean follow-up period of 3.7 years, herpes zoster occurred in 23 HZ/su recipients and in 223 placebo recipients (0.9 vs. 9.2 per 1000 person-years). Vaccine efficacy against herpes zoster was 89.8% (95% confidence interval [CI], 84.2 to 93.7; P<0.001) and was similar in participants 70 to 79 years of age (90.0%) and participants 80 years of age or older (89.1%). In pooled analyses of data from

Vaccine trends

• Historical live, attenuated vaccines both highly efficacious and effective, can be single dose, adjuvants not required
• Increase in immunodeficiency – some contrived, HIV etc.
• General trend towards subunit, multiple doses
• OPV -> IPV
• Live attenuated zoster -> recombinant gE (longevity?)
• Plasma HBV vaccine -> recombinant yeast vaccine
• Some of this is around manufacturing and characterization, but reversion is a theoretical or real (OPV) risk – adjuvants enable different immune correlates
Vaccine trends

Multivalency to address serodiversity

- Individual vaccines — **conjugated pneumococcal vaccine**
  - 7-valent
  - 13-valent
  - 15-valent in development
  - 20-valent in development

Combination vaccines — 5-in-1, MMR....

- Reduction in immunizations with new vaccines coming
- Potential for interactions, new hurdle for introduced vaccines
Anti-vaccination lobby

• Few areas of medicine have received such aggressive pushback, obstetrics?
• Largely driven off ”fake news”, “alternative ‘facts’”, “post truth”
  ...before these were made fashionable

• Debate provides oxygen
• Best approach - read Myths & Realities
  ...but it is 92 pages
Anti-vaccination messages start subtle

https://jameslyonsweiler.com/category/vaccine-safety-research-reform/
RETRACTED: Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children

Andrew Wakefield - MMR, and autism
Andrew Wakefield

Andrew Wakefield’s ‘dishonest and irresponsible’ research into the causes of autism led to his being struck off by the General Medical Council. That would have ended most doctors' careers. Instead, the MMR 'martyr' moved to the US - and into reality TV
Wakefield trying to impact Houston election

Disgraced anti-vaxxer Andrew Wakefield aims to advance his agenda in Texas election

Wakefield sees Houston primary as a new start after his anti-vaccine theories were debunked and medical license revoked
Where the successful candidate will join another anti-Vaxxer
Some very disturbing trends in the US
Outline

• Vaccine Development 101
  • Basic parameters of drug and vaccine development
  • https://www.australianclinicaltrials.gov.au
  • opportunities

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Summary - vaccination and vaccines

• Many new vaccines in the pipeline, and new uses
• Profitability, lack of patent exposure – gaining R&D attention, but some pushback from ant-vaxxers
• Hurdles for approval/use being reassessed
  • WHO Working Group 2016-2017 Typhoid vaccination
  • Changed guidelines to increase vaccine use (SAGE Oct 2017)
  • GAVI allocated funds to support expanded vaccine (Dec 2017)
  • New vaccine (Indian supplier) pre-qualified by WHO (Jan 2018)
  • Published evidence was limited, extensive immunogenicity
  • Human challenge study showing efficacy
  • Jin et al, Lancet 390:10111:2472-80 2017

• Model for other new vaccines?
It takes many years to develop a vaccine

Despite what you read on NHMRC grant proposals........

- Safety surveillance continues indefinitely
- Additional clinical and epidemiological studies may be carried out for new indications or to assess impact and safety