Improving Influenza vaccines: Looking ahead

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First 20th century pandemic -
The “Spanish Flu”

Influenza A/CDC/1918 virus

Courtesy: A. Garcia-Sastre
History of influenza vaccines

• Experimental vaccinations with active influenza virus (Stokes et al. 1937 J Clin Invest)

• Whole-virus inactivated influenza vaccine in clinical trials (Francis 1945 Am J Hyg, Salk et al. 1945 Am J Hyg)

• Adjuvanted influenza vaccines to enhance antibody responses (Salk et al. 1952 Am J Hyg, Salk et al. 1952 JAMA)

• Subvirion (split) inactivated influenza vaccines (Cate et al. 1977 J Infect Dis, Wright et al. 1977 J Infect Dis)

• Live attenuated influenza virus vaccines: Clinical trials with safety, immunogenicity and efficacy data in children (Alexandrova et al. 1986 Vaccine, Belshe et al. 1984 J Infect Dis)
Seasonal vaccines against human influenza

- DE ~20 Mio doses/year
- egg-(cell) produced
- mostly inactivated (split – subunit), intramuscular
- trivalent (H1, H3, B) or quadrivalent (H1, H3, B_{yam}, B_{vic})
- mostly without adjuvant
- annual strain selection:
  - A/California/07/2009 (H1N1)
  - A/Switzerland/9715293/2013
  - B/Phuket/3073/2013
  - B/Brisbane/60/2008

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Shortcomings of seasonal influenza vaccines

- immunogenicity limited to virus-specific antibodies
- low level memory responses
- vulnerable to immune escape by virus drift variants
- suboptimal efficacy in high risk populations
- no efficacy against new viruses (avian, pandemic)

Strategies:
- need for antigen update every season
- need for repeated immunizations over years
22.02.2015

Experten schlagen Grippe-Alarm

Schon 1,5 Mio. Infizierte +++ Virus besonders aggressiv
Need to improve influenza vaccines!

Objective is to induce broadly protective immunity:

- against virus drift variants within subtypes
- against viruses across all subtypes

Strategies:

- optimizing antigens for immunization
- testing additional antigens for immunization
- strengthen and broaden immunogenicity to elicit virus-specific antibodies and T cells
Induction of antibodies and T cells against conserved influenza virus proteins

Adapted from Subbarao et al., Immunity 2006, TIM 2013
Optimize delivery of influenza antigens

Strategies:
- antigen targeting
- antigen presentation
- antigen modification

to elicit virus-specific antibodies and T cells
Alerting the immune system!
New vaccine technologies under development

- Proteins with adjuvants
- Nucleic acids
- Virus-like particles
- Recombinant viruses
Important properties of new (vector) vaccines against influenza

• high level biological safety
• acceptable safety profile in clinical testing
• capacity to deliver multiple virus antigens
• immunostimulatory capacity (no need for adjuvants)
• broad immunogenicity (cellular & humoral responses)
• induction of long lasting immunity
FLUNIVAC Concept

A influenza universal vaccine development based on Modified Vaccinia virus Ankara (MVA), inducing broad protective and long lasting immunity: “Doing better than Nature”

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<td>Prof. Sutter, LMU</td>
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Modified Vaccinia virus Ankara (MVA)
electron micrograph - D. Spehner/ G. Sutter
Modified Vaccinia virus Ankara (MVA)

- excellent characterization in many preclinical models
- various candidate vector vaccines in clinical testing
- large scale production compliant with GMP regulations

Sutter & Moss PNAS 1992
Sutter Vaccine 1994
Regulatory guidance on Quality, Safety and Efficacy of recombinant MVA vaccines

24 June 2010
EMA/CHMP/VWP/141697/2009
Committee for Medicinal Product for Human Use (CHMP)

Guideline on quality, non-clinical and clinical aspects of live recombinant viral vectored vaccines
Targeting new influenza viruses: A/Vietnam/2004 (H5N1)
MVA-H5 vaccine

Double blind randomized study

MVA-H5-sfMR

1shot * 10^7 pfu
1shot * 10^8 pfu
2shot * 10^7 pfu
2shot * 10^8 pfu

MVA-F6-sfMR

1shot * 10^7 pfu
1shot * 10^8 pfu
2shot * 10^7 pfu
2shot * 10^8 pfu

1) Safety
2) Immunogenicity

80 subjects male/female 18-35 yrs healthy

27 volunteers received additional booster, 1 year post primary vaccination

Kreijtz Lancet Infect Dis 2014
MVA-H5 vaccine induces immunity to influenza H5N1

Kreijtz Lancet Infect Dis 2014
Avian Influenza H5N8 in Asia and Europe in 2014

Highly Pathogenic Avian Influenza A(H5N8) Virus from Waterfowl, South Korea, 2014

Keun Bon Ku,1 Eun Hye Park, Jung Yum,1 Ji An Kim, Seung Kyoo Oh, and Sang Heui Seo

Author affiliation: Chungnam National University College of Veterinary Medicine, Daejeon, South Korea

DOI: http://dx.doi.org/10.3201/eid2009.140390

Emerging Infectious Diseases
September 2014
Induction of influenza H5N8 antibodies by MVA-H5 vaccine

- Cross-clade antibodies in 82% participants receiving $10^8$ pfu MVA-H5
Progress in Vaccine Development: Better Vaccines on the Horizon!

Adaptive humoral response

Neutralization by antibody

B cells

Virus

Adaptive cellular response

Killing by CD8+ CTL

DC function

CD8+

Killing reaction

CD4+

Innate response

Cytokine secretion

T cells
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DZIF
Fluniva
Cooperation
New vaccines against influenza: Technically feasible!

How to get them developed?

Stakeholders
- DE: GOV BMBF, BMG (PEI)
- EU: EC, EMA
- Worldwide: Foundations, Pharm Industry, WHO

Instruments
- DZIF, InfectControl, FLUNIVAC, Horizon2020
- Public Private Partnership

Potential hurdles
- time lines
- regulatory questions
- economical interest