What's the future for animal vaccines?

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Outline

• Importance of Veterinary vaccines
• Veterinary vs human vaccines
• Advances in Veterinary Vaccinology
• Forecast for animal vaccines
• Research at SDSU
  • Viral vectors
  • Vectored vaccine
• Final thoughts
Importance of veterinary vaccines

• Allow safe and efficient food production

• Control of zoonotic diseases

• Control of emerging and exotic diseases of animals and people
  - Eradication of Rinderpest (2011)
  - Rabies control (reduction number of human cases)

• Reduction of the need for antibiotics

Food safety vaccines

- *E. coli* O157:H7 vaccine for use in cattle
- *S. enteritidis* vaccine for use in poultry

Reduce shedding of pathogens that may contaminate animal products
Importance of veterinary vaccines

- Main purpose is to prevent infectious diseases, but it depends on animal species/groups.
  - Livestock vaccines: improve the efficiency of production of food animals
  - Companion animal vaccination similar to humans – health and welfare of individual animal
  - Vaccination against zoonotic or foodborne pathogens – used to reduce or eliminate the risk to people
  - Wildlife – prevent transmission of zoonotic infections to humans
    - Oral bait vaccines for rabies
    - Brucellosis vaccines for bison and elk

Recombinant vectored vaccine
Global vaccine market

• Veterinary vaccines comprise ~23% of market of animal health products
• Sector experienced consistent growth
  • Technological advances
  • Drug resistance by pathogens
  • Emergence of new diseases
  • Reduction on antibiotics use - VFD

Veterinary vaccines vs human vaccines

• Disadvantages
  • Lower $$ returns to industry (lower sales prices and market sizes)
    • *Gardasil vs FMDV + M. hyo*
  • Lower investment in R&D

• Advantages
  • Less stringent regulatory and pre-clinical trial requirements
  • Shorter time to market launch and return on investment
  • Can be immediately tested in relevant target animal species

~50 human vaccines vs ~300 animal/veterinary vaccines worldwide

$1 billion

$100-200 million
Advances in veterinary vaccinology

• **First-generation vaccines**
  • Prepared by physical or chemical modification of the organisms
  • Inactivation
  • Modification of virulence by cultivation in artificial media or on alternate hosts

• **Second-generation vaccines**
  • Advances in technology led to second generation vaccines
    • Tissue culture systems (viral vaccines)
    • Large scale production
    • Led to eradication of rinderpest
    • Control of several animal diseases

• **Third-generation vaccines**
  • Latest molecular biology approaches

http://www.sanidadanimal.info/cursos/inmun/noveno1.htm
Advances in veterinary vaccinology

- Science behind animal vaccines changed little until ~25 years ago
- First genetically engineered vaccines were developed and licensed
  - PRV – gene-deleted virus vaccine
  - Recombinant vector rabies vaccines
- Significant technological advances in last 25 years. Today we have:
  - 15 live vector vaccines
  - 7 non-replicating recombinant antigen-vaccines
  - 4 live-gene-deleted vaccines
  - 3 nucleic acid vaccines
Examples of available animal vaccines and their characteristics

<table>
<thead>
<tr>
<th>Brand name (Company)</th>
<th>Target species</th>
<th>Purpose/Use</th>
<th>Characteristics</th>
<th>Route of administration</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccines for domesticated animals</td>
<td></td>
<td></td>
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<tr>
<td>Apex-IHN (Novartis)</td>
<td>Salmon</td>
<td>IHN virus infection</td>
<td>DNA vaccine</td>
<td>Parenteral</td>
<td>[12]</td>
</tr>
<tr>
<td>AquaVac ERM (Schering-Plough Animal Health)</td>
<td>Fish</td>
<td><em>Vibrio</em> <em>vulnificus</em> infection</td>
<td>Killed vaccine; antigen protection vehicle used</td>
<td>Oral</td>
<td>(1)</td>
</tr>
<tr>
<td>Art Vax (Schering-Plough Animal Health)</td>
<td>Turkeys</td>
<td><em>Salmonella</em> <em>enteritidis</em> infection</td>
<td>Live temperature-sensitive mutant strain</td>
<td>Oral or inhalation</td>
<td>[23]</td>
</tr>
<tr>
<td>Bayovac CSF E2 (Bayer Leverkusen)</td>
<td>Pigs</td>
<td>Classical swine fever</td>
<td>Baculovirus recombinant E2 protein</td>
<td>Parenteral</td>
<td>[14]</td>
</tr>
<tr>
<td>Improvac (Pfizer Animal Health)</td>
<td>Male pigs</td>
<td>Control of boar taint</td>
<td>LHRH-protein conjugate; plus adjuvant</td>
<td>Parenteral</td>
<td>[154]</td>
</tr>
<tr>
<td>Ovastim (Virbac)</td>
<td>Ewes</td>
<td>Increased ovulation / twinning</td>
<td>Androstenedione-protein conjugate; plus adjuvant</td>
<td>Parenteral</td>
<td>(1)</td>
</tr>
<tr>
<td>Suvaxyn PCV2 (Fort Dodge)</td>
<td>Pigs</td>
<td>PCV2 infection</td>
<td>Inactivated PCV1-2 chimera; plus adjuvant</td>
<td>Parenteral</td>
<td>[15]</td>
</tr>
<tr>
<td>Vectormune FP-ND (Biomune)</td>
<td>Poultry</td>
<td>Newcastle disease</td>
<td>Fowlpox virus vectored</td>
<td>Parenteral</td>
<td>[17, 18]</td>
</tr>
<tr>
<td>Vaccines for wildlife</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Gonacon, (now registered by USDA)</td>
<td>Deer</td>
<td>Fertility control</td>
<td>GnRH-protein conjugate in mycobacterium-oil adjuvant</td>
<td>Parenteral</td>
<td>[19, 20]</td>
</tr>
<tr>
<td>Raboral (Merial)</td>
<td>Canine</td>
<td>Rabies control</td>
<td>Recombinant Vaccinia virus vectored vaccine</td>
<td>Oral</td>
<td>[6, 8]</td>
</tr>
</tbody>
</table>


- Full list of vaccines and other biologics licensed in the US:
"In the years to come, we expect to see the continued emergence of recombinant vaccines with multiple antigens to address our evolving customer needs, with improved efficacy and safety," said Dr Marcus Remmers, global head of biologics R&D at Merial.
Ceva notes molecular biotech impact

Dr. Yannick Gardin, the company's director of science and innovation, told Animal Pharm: "The coming few years will see further dramatic changes already evident in the world of veterinary vaccines. Vaccines and concepts developed with molecular biotechnologies (recombinant, vector, nucleic acid, platforms, etc.) will become ever more dominant."
Delivery systems are key, says Hester

Like Ceva, Indian firm Hester Biosciences is driving strong sales growth with poultry vaccines. "The effectiveness of a vaccine is not only in itself but also as much the delivery system." said Rajiv Gandhi.
Research at SDSU

• Development of viral vector platforms for vaccine delivery in livestock
• Recombinant DNA technologies being applied to generate novel vaccine delivery platforms and improved vaccines

Parapoxvirus Orf virus
**Viral vectors**

- Viruses that can be used as vehicles to carry specific genes/proteins into cells

**What is needed to construct viral vectors?**
- Remove genes that are important for virulence/pathogenesis
- Insert genes encoding the desired function (i.e., protective antigens)
ORFV as a delivery vector

• Properties of ORFV
  - Novel and potent IMPs
  - Local (restricted to skin) and self-limiting infection
  - Repeated infections in natural host/lack of neutralizing antibodies (repeated immunizations)
  - Large genome that can potentially accommodate large DNA insertions

• Rational approach
  - Optimize ORFV as a delivery vector platform (10+ IMPs)
  - Deletion of IMPs that contribute to virus virulence and pathogenesis
Immunogenicity of a recombinant parapoxvirus expressing the spike protein of *Porcine epidemic diarrhea virus*

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- Confirm immunogenicity of ORFV vector in swine
- Develop a novel vaccine delivery platform for PEDV based on the parapoxvirus Orf virus (ORFV) expressing PEDV S
Generation of ORFV-PEDV-S

A

PEDV spike primers

B

Anti-PEDV spike (mAb HV37-11)

C

MW

Spike
Animal Immunization studies – Experimental Design

**ORFV-PEDV-S**

### Experimental Design

- **Prime Immunization**
- **Booster Immunization**
- **Booster Immunization**
- **Challenge**

#### PEDV Challenge

- Days post immunization/challenge

<table>
<thead>
<tr>
<th>Group</th>
<th>Route</th>
<th>Dose</th>
<th>Challenge</th>
</tr>
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<tbody>
<tr>
<td>G1: ORFV-G</td>
<td>IM + TC</td>
<td>$2 \times 10^{7.3}$</td>
<td>-</td>
</tr>
<tr>
<td>G2: ORFV-PEDV-S</td>
<td>TC</td>
<td>$2 \times 10^{7.3}$</td>
<td>PEDV CO13</td>
</tr>
<tr>
<td>G3: ORFV-PEDV-S</td>
<td>IM</td>
<td>$2 \times 10^{7.3}$</td>
<td>PEDV CO13</td>
</tr>
<tr>
<td>G4: ORFV-G</td>
<td>IM + TC</td>
<td>$2 \times 10^{7.3}$</td>
<td>PEDV CO13</td>
</tr>
</tbody>
</table>
Antibody Responses

Challenged Oral PEDV (2 x 10^5 TCID50)

Clinical Outcome
Summary

Example of how the latest vaccinology approaches can be used to develop improved delivery systems and vaccines for livestock

- ORFV represents a promising delivery platform for livestock
- Induces protective immunity
Final thoughts...

What's the future for animal vaccines?

Vaccines will continue to play a major role for animal health and public health.

- Universal delivery platforms
- Novel delivery systems and administration routes (microneedle patches or needle free)
- Improved immunological adjuvants
- Rational approaches combined with traditional vaccines (MLV and killed vaccines)
- Autogenous – combine autogenous with third generation delivery systems
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