Next-generation vaccine development options

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PD TriNation, oct 2016
Fish vaccines
classic vs. alternative technologies

• Classic vaccination $\rightarrow$ inactivated virus vaccines
  • IPNV
  • SPDV
• Requires large scale virus production
  • Problematic for e.g. PRV, PMCV

• Alternative technologies
  • Subunit vaccines
  • nucleic acid based vaccines
    • DNA vaccine
    • DNA replicon vaccines
    • RNA vaccine
Inactivated virus vaccine
A SPDV virus example

Wild type SPDV particle

The vaccine:
Inactivated SPDV particles

Immunity;
Memory generation → Protected upon second encounter

Immunity;
Memory generation → Protected upon first encounter
Subunit vaccination
A SPDV virus example

Inactivated virus vaccine

Viral outside is important for immune responses

Subunit vaccine
Not protective in Atlantic salmon

Virus-like particle (VLP) vaccine
Not protective in Atlantic salmon
Nucleic acid vaccines
DNA vaccination

- Antigen expression in the fish
- DNA plasmid directly expresses the antigens of interest
- Positive examples
  - SPDV
  - VHSV
  - IHNV
- Immune responses are provoked by antigen exposure
**Nucleic acid vaccines**

**DNA SPDV replicons**

Structural genes of SPDV can be replaced by a gene of interest, e.g.

- ISAV
- PRV
Nucleic acid vaccines
DNA SPDV replicons

• RNA launched from DNA plasmid

• RNA replication provokes immune responses

• Antigen expression inside the fish

• Expression of antigen provokes immune responses
Nucleic acid vaccines
DNA SPDV replicons

Non-structural proteins

SPDV Complete genomic sequence

Non-structural proteins

SPDV DNA replicon

DNA SPDV replicons
Example 1 - Vaccination against SPDV

Non-structural proteins

SPDV DNA replicon (1)

Non-structural proteins

SPDV DNA replicon (2)
Conclusion: DNA replicon vaccination against SPDV is effective, but only when both major structural proteins are present

[Hikke et. al, 2014, Vaccine]
Expression of the structural proteins at the cell surface is important for induction of a good immune response.
DNA SPDV replicons

Example 2 - vaccination against ISAV

SPDV DNA replicon expressing the HE gene of ISAV

[Wolf et. al, 2012, Vaccine]
Vaccines based on nucleic acid

- DNA plasmids raise some regulatory/legislation hurdles, based on
  - the theoretical possibility of DNA integrating into fish genome
  - bioactive plasmids into nature

- Solution: Replacement of DNA by RNA

- But RNA is unstable and would need to be protected. Doable?

Harrisvaccines is now part of MSD Animal Health

Replicon particle (RP) vaccine based on Venezuelan equine encephalitis virus
SPDV Replicon particles (RP)
a potential vaccine against other fish pathogens
Immune response

(Production)

(Cell entry)

(Immune response)

(Vaccination)
Final remarks

• New technology for fish vaccines needed to develop more virus vaccines in the future
• Several new vaccine technologies developed for other species work in fish after “fish adjustments”
• Many of the new technologies have implementation hurdles in Europe due to “outdated” GMO/gentechnology legislation.
• In Norway the Norwegian Biotechnology Advisory board is addressing the legislations on governmental level.

Open meeting in Oslo scheduled November 14th 2016
Acknowledgements

Wageningen University
• Gorben Pijlman
• Just Vlak
• Corinne Geertserda

MSD Animal Health
• Sjo Koumans
• Stephane Wilsing
• Luc Grisez
• Petter Frost
• Kjartan Hodneland

Norwegian School of Veterinary Science
• Espen Rimstad
• Stine Braaen