Next-generation vaccine development options

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Fish vaccines

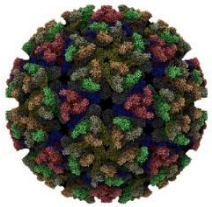
classic vs. alternative technologies

- Classic vaccination → inactivated virus vaccines
  - IPNV
  - SPDV
- Requires large scale virus production
  - Problematic for e.g. PRV, PMCV

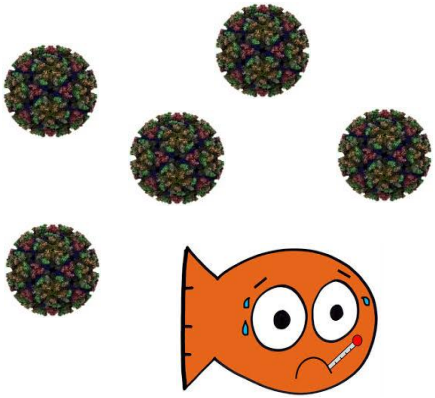
- Alternative technologies
  - Subunit vaccines
  - nucleic acid based vaccines
    - DNA vaccine
    - DNA replicon vaccines
    - RNA vaccine

Inactivated virus vaccine

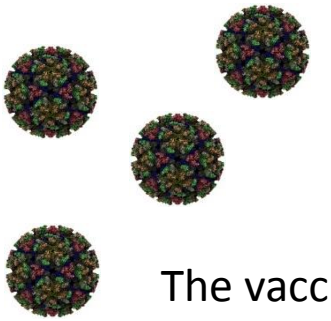
A SPDV virus example



Wild type SPDV particle



Immunity;
Memory generation → Protected upon **second** encounter



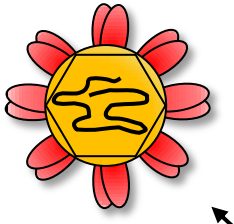
The vaccine:
Inactivated SPDV particles

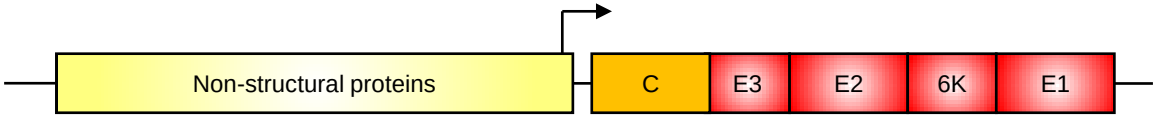
Immunity;
Memory generation → Protected upon **first** encounter

Subunit vaccination

A SPDV virus example

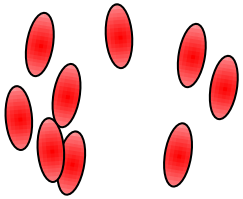
Inactivated virus vaccine

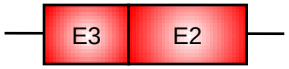




Viral outside is important for immune responses

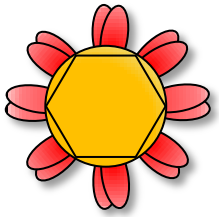
Subunit vaccine





Not protective in Atlantic salmon

Virus-like particle (VLP) vaccine

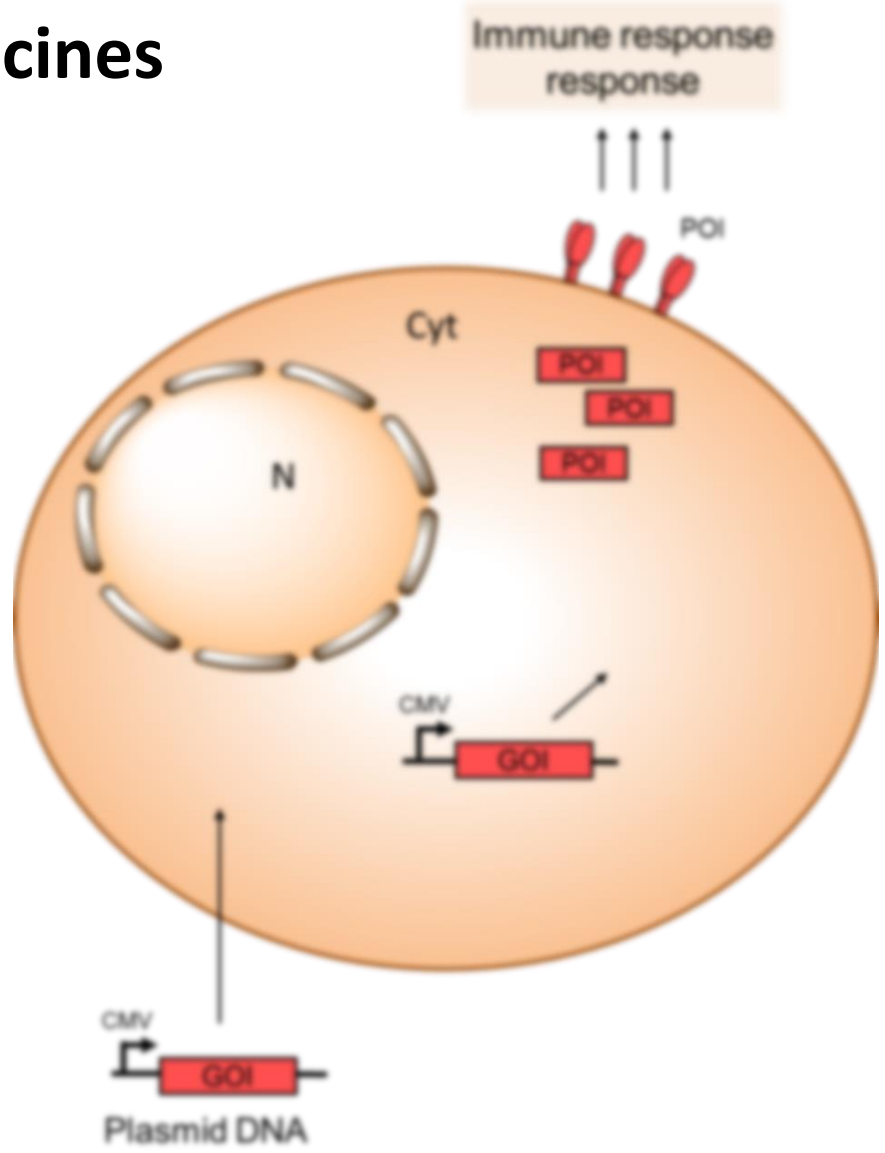


Not protective in Atlantic salmon

Nucleic acid vaccines

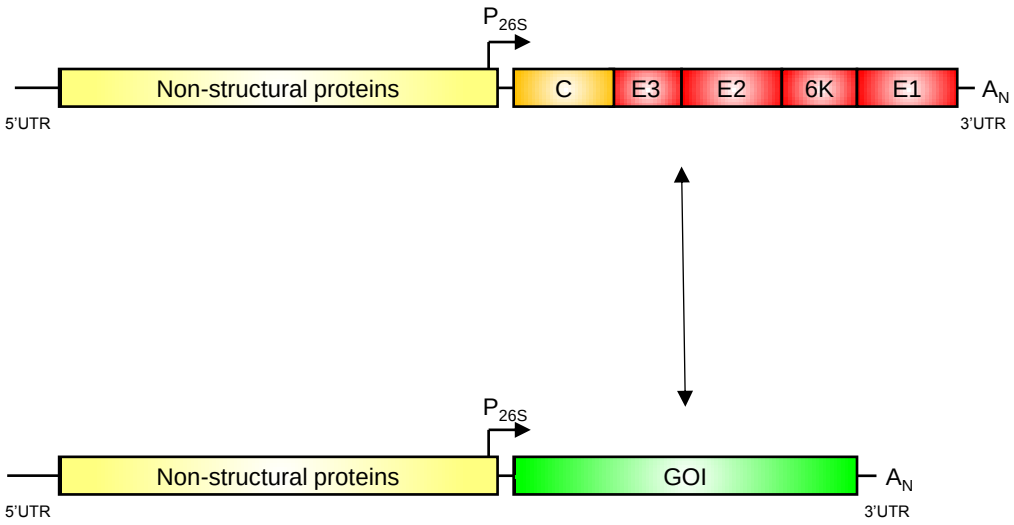
DNA vaccination

- 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



SPDV complete Genome

SPDV Replicon

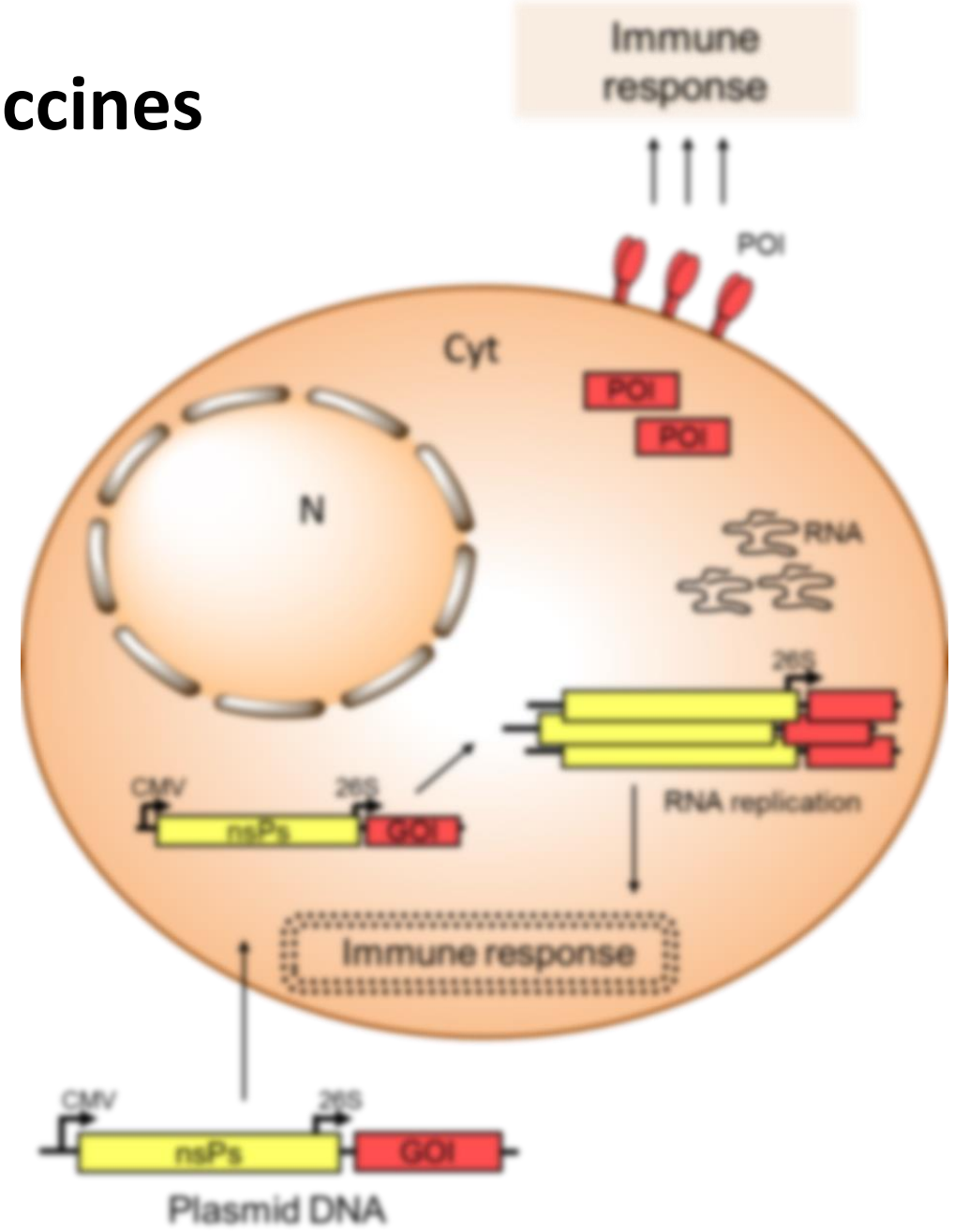
Structural genes of SPDV can be replaced by a gene of interest, e.g.

- ISAV
- PRV

Nucleic acid vaccines

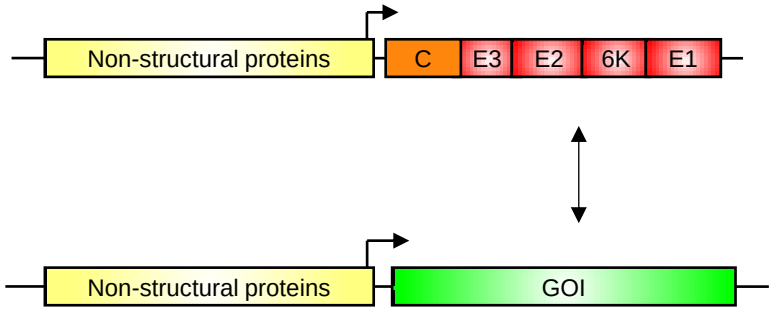
DNA SPDV replicons

- 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

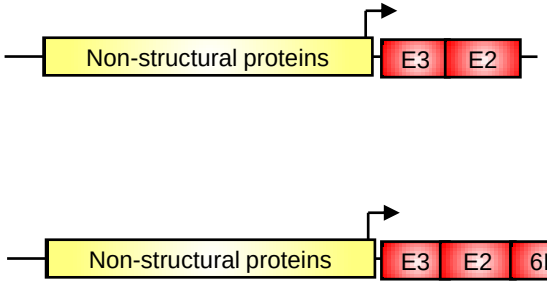


SPDV Complete genomic sequence

SPDV DNA replicon

DNA SPDV replicons

Example 1 - Vaccination against SPDV

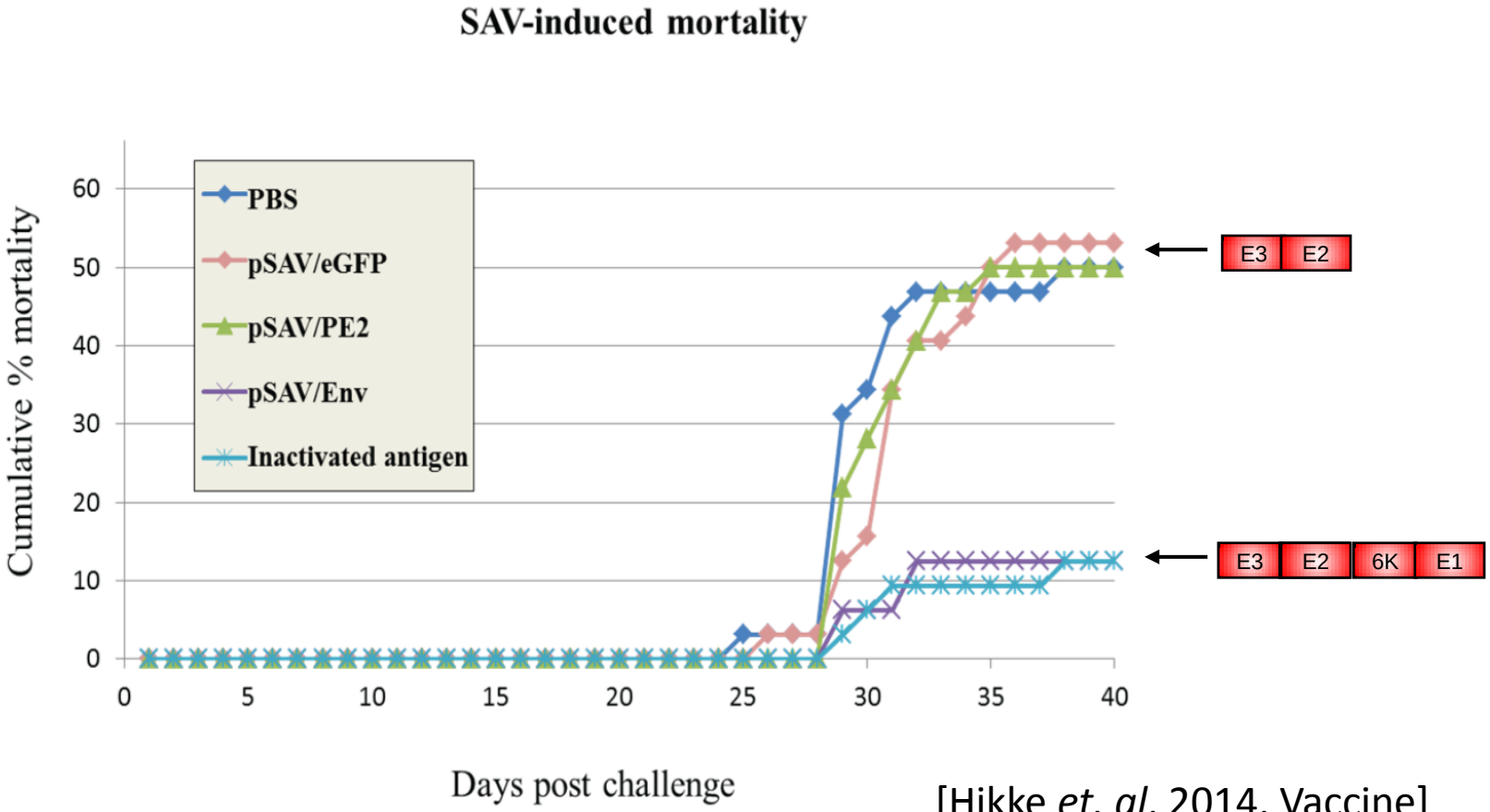


SPDV DNA replicon (1)

SPDV DNA replicon (2)

DNA SPDV replicons

Example 1 - vaccination against SPDV

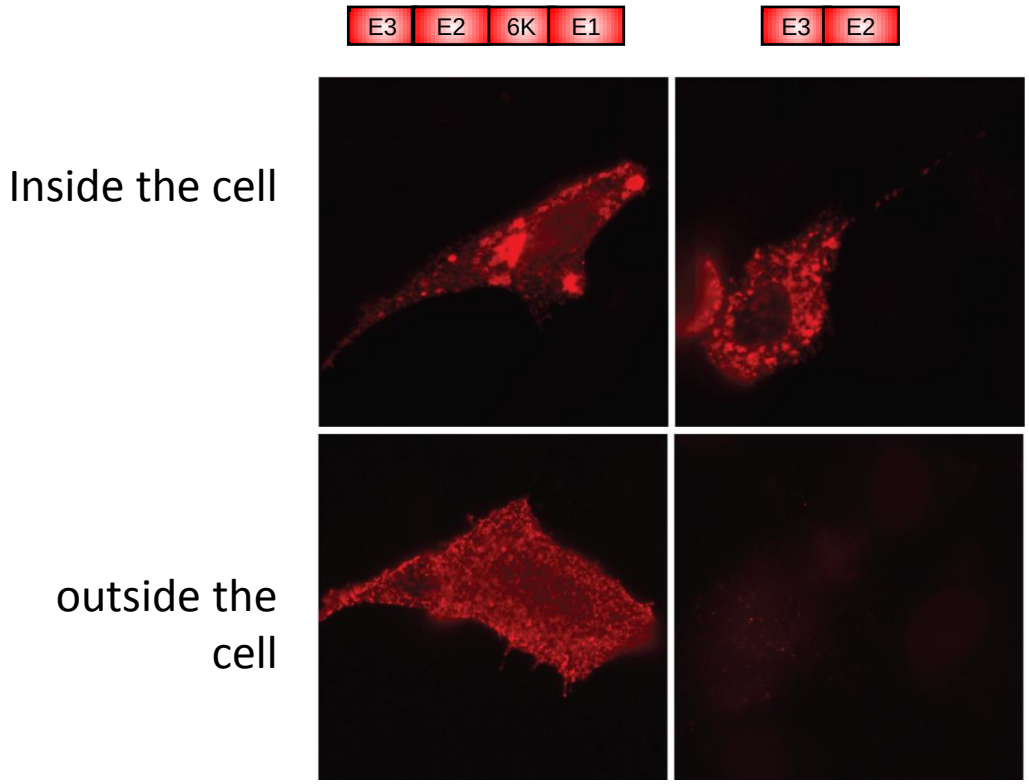


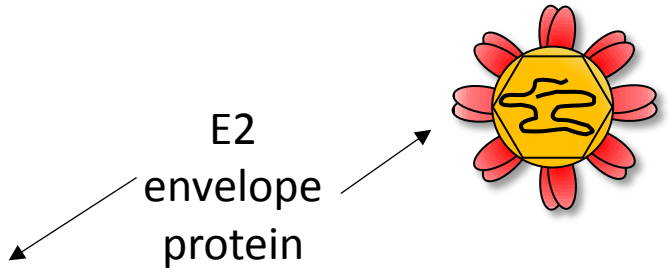
[Hikke *et. al*, 2014, Vaccine]

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

DNA SPDV replicons

vaccination against SPDV

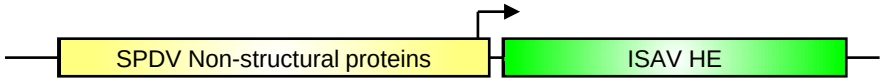




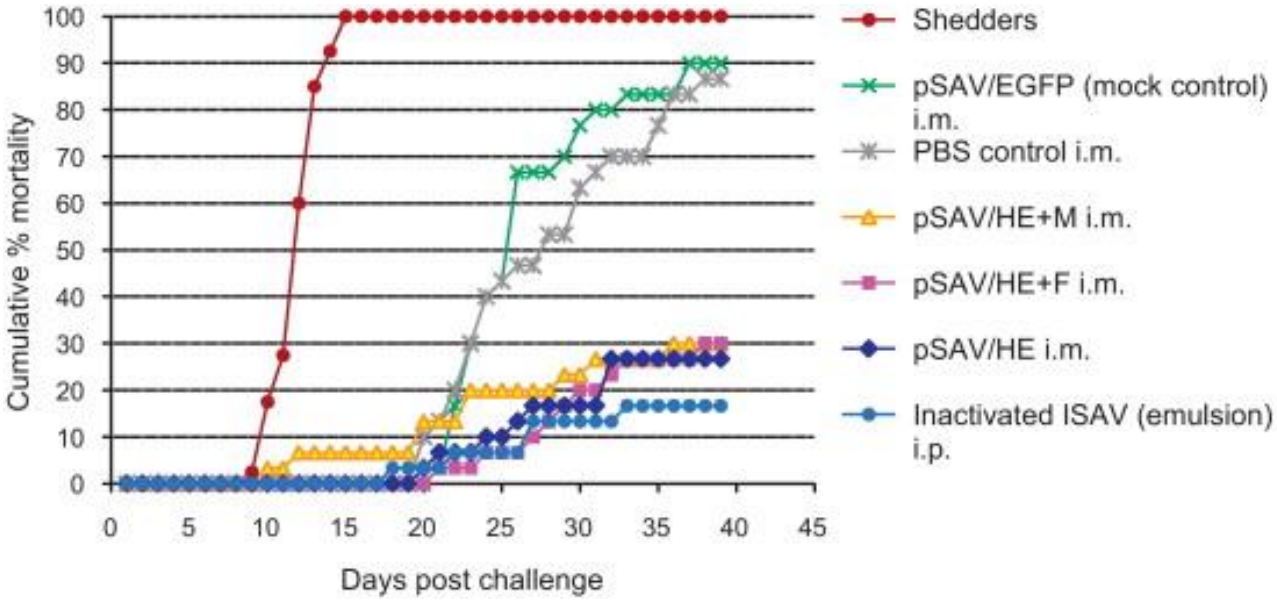
Expression of the structural proteins at the cell surface is important for induction of a good immune response

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 theoredical possibility of DNA integrating into fish genome
  - bioactive plasmids into nature

- Solution: Replacement of DNA by RNA

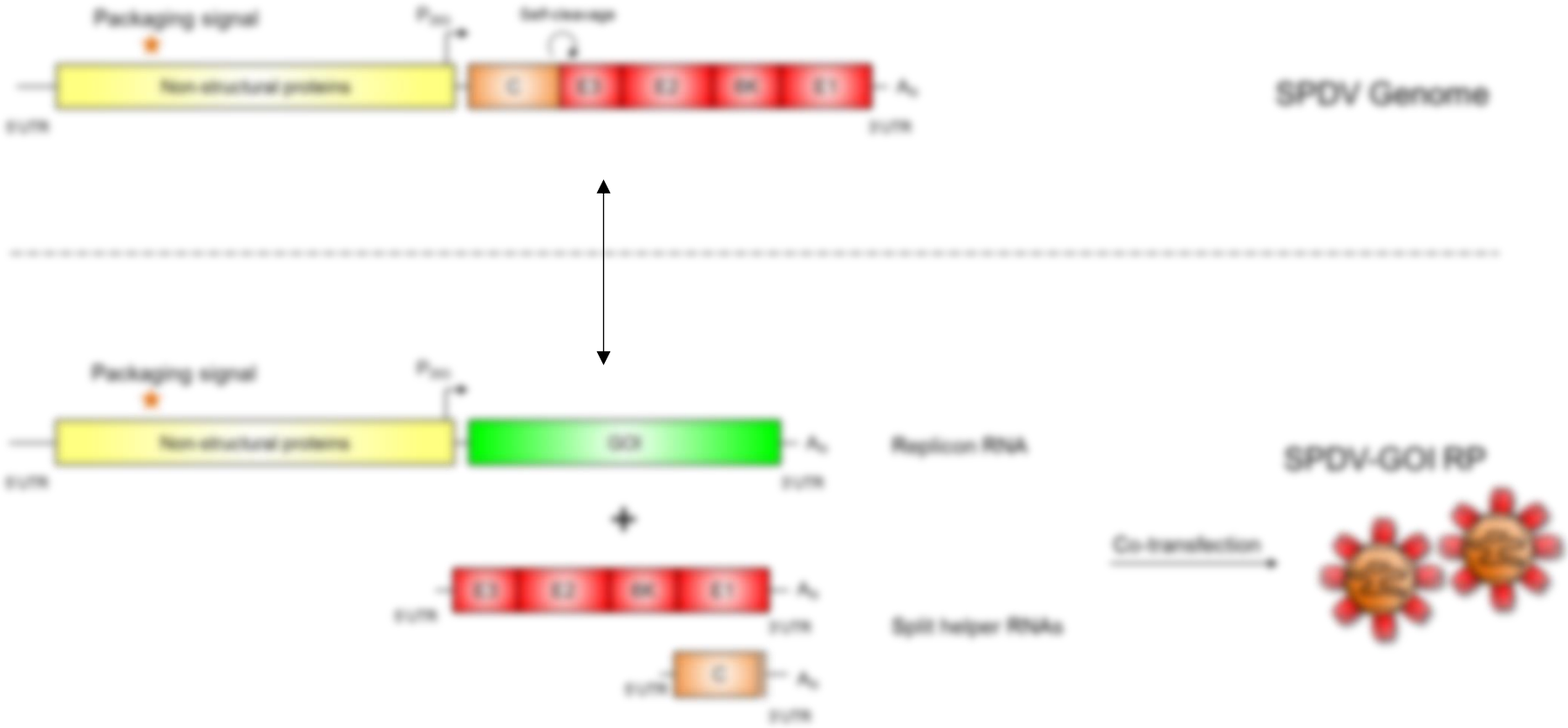
- But RNA is unstable and would need to be protected. Doable?

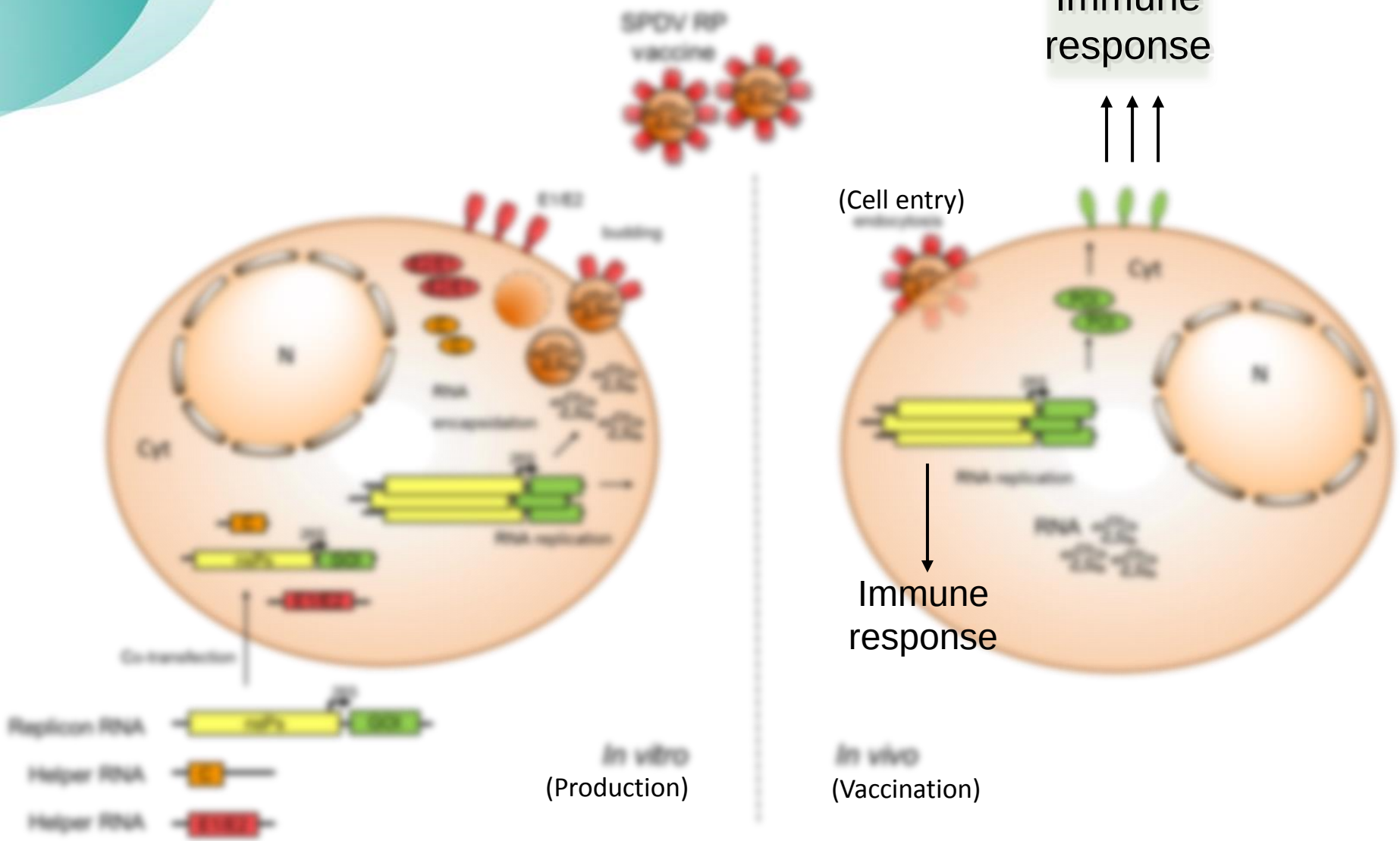
  Harrisvaccines is now part of MSD Animal Health

  Replicon particle (RP) vaccine based on Venezuelan equine encephalitis virus

SPDV Replicon particles (RP)

a potential vaccine against other fish pathogens




SPDV RP
vaccine
Immune
response
(Cell entry)
Cyt
N
RNA
RNA replication
Co-transfection
Replicon RNA
Helper RNA
Helper RNA
Immune
response
In vitro
(Production)
In vivo
(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 legistation.
- In Norway the Norwegian Biotechnology Advisory board is adressing the legistations on governmental level.

Open meeting in Oslo scheduled November 14th 2016

Acknowledgements

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Thank you!!!