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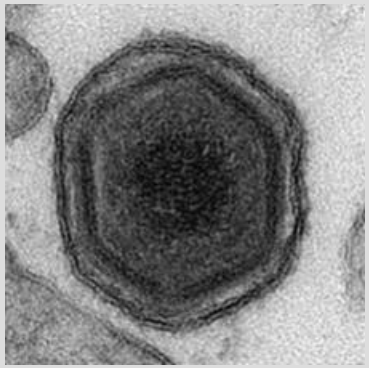
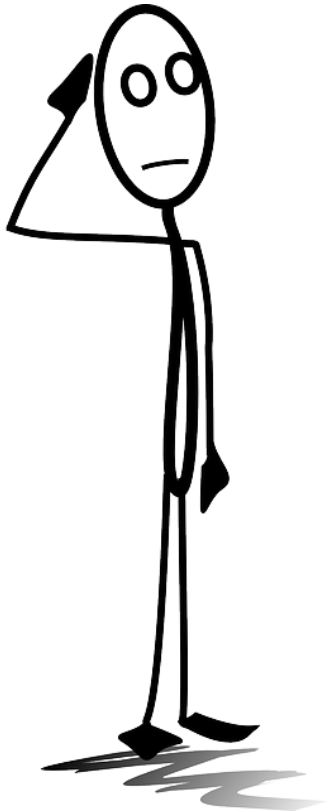
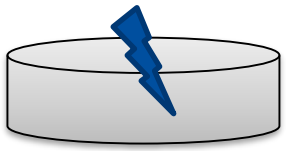
African swine fever vaccines – history and state of play

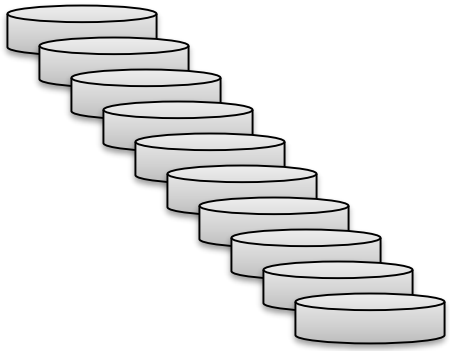


What does the little virologist do when he wants to develop a vaccine?

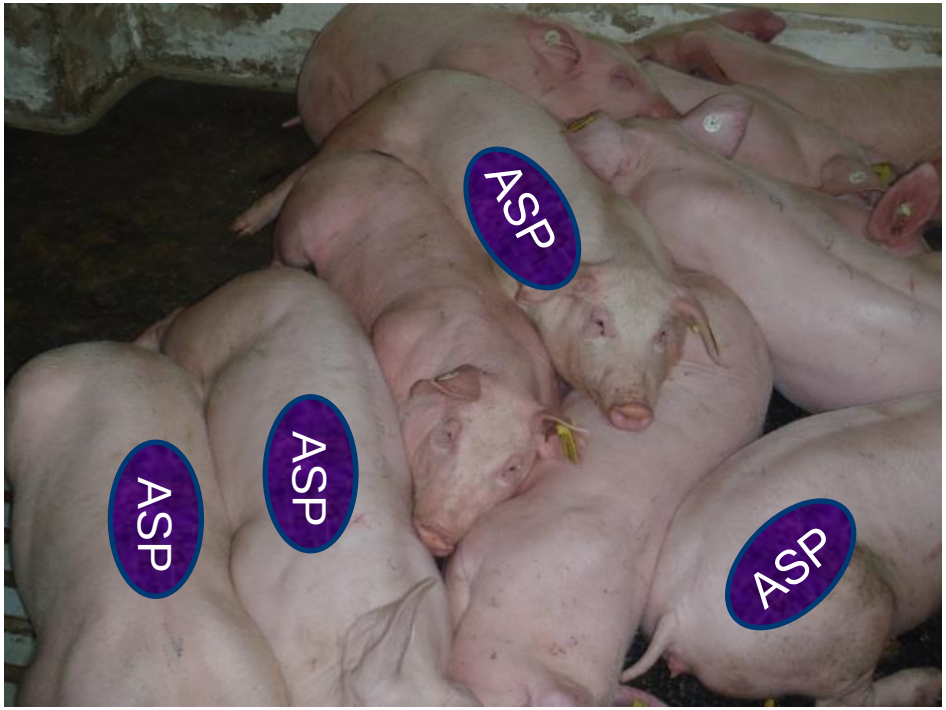




Inactivate whole virus



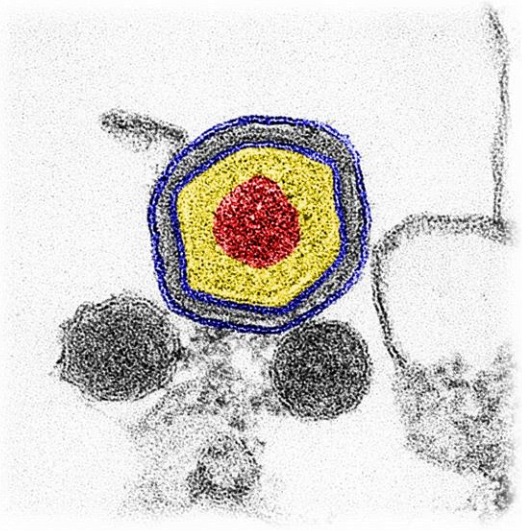
Passage the virus in cell culture or in animals



- Huge virus with DNA genome
- Can replicate in mononuclear cells
- Field strains do not grow on cell cultures
- Antibodies do not neutralize the virus
- So far, no subunits conferred sufficient protection
- Live attenuated vaccines have safety and potency issues

- Small virus with RNA genome
- Can replicate in mononuclear cells but also cell cultures
- Antibodies neutralize the virus
- The main immunogen E2 is sufficient to confer protection (at high level)
- Live attenuated vaccines are safe and efficacious

ASFV



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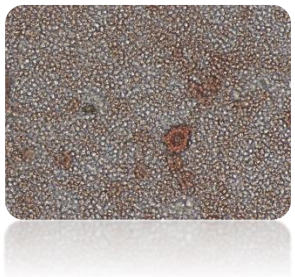

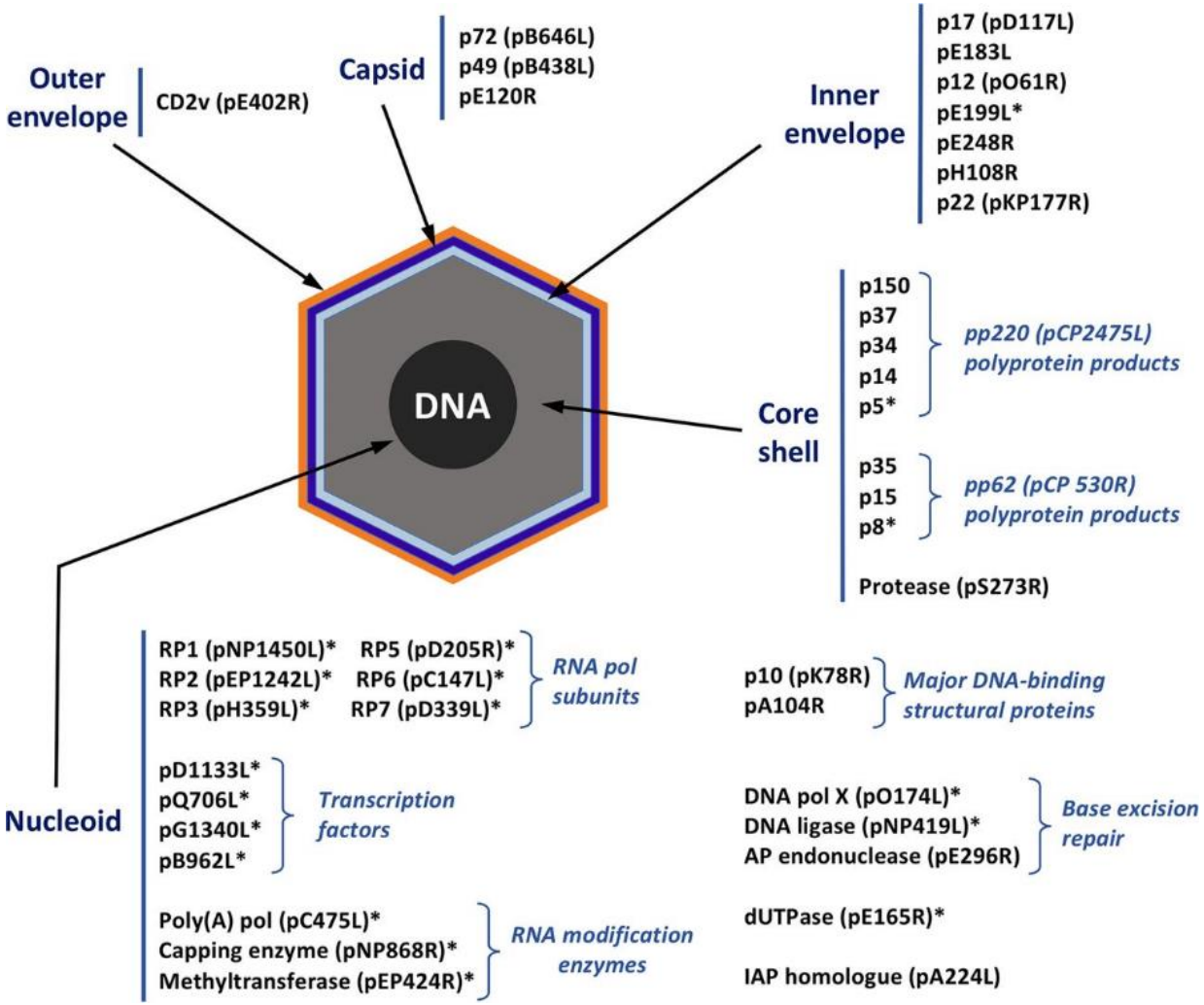

Alejo et al., 2018

Why we still think it‘s possible…

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Animals surviving an ASFV infection are protected against reinfection or challenge with related viruses

… and are not long-term carriers

Veterinary Microbiology 206 (2017) 52–58

Contents lists available at ScienceDirect

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journal homepage: www.elsevier.com/locate/vetmic

Rock 2017

Challenges for African swine fever vaccine development—" . . . perhaps the end of the beginning."

D.L. Rock*

Department of Pathobiology, College of Veterinary Medicine, University of Illinois at Urbana-Champaign, Urbana, IL, USA

vaccines

MDPI

Review

Approaches and Perspectives for Development of African Swine Fever Virus Vaccines

Marisa Arias [1,*], Ana de la Torre [1], Linda Dixon [2], Carmina Gallardo [1], Ferran Jori [3], Alberto Laddomada [4], Carlos Martins [5], R. Michael Parkhouse [6], Yolanda Revilla [7], Fernando Rodriguez [8] and Jose-Manuel Sanchez-Vizcaino [9]

Arias et al., 2017

Inactivated virus preparations

- Very old reports show protective effects of formalin-fixed virus preparations
- Other preparations showed no protective effect
- „Modern“ adjuvants did not increase protection …
- Discussion: „metabolic active“ preparations (Psoralen, irradiation)

… not really …

Live attenuated vaccines

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- Conventionally attenuated viruses and naturally occurring strains of low virulence are able to protect against severe clinical signs and reduce virus shedding upon challenge with related strains
- Severe side-effects for some variants, reported from Spain and Portugal, joint and skin lesions, chronic ASF
- Lower rate of side-effects with variants like NHV and OURT88/3

… almost …

Rational deletions

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- Attempts to optimize the existing attenuated strains
- Deletions of TK, 9GL (B119L), DP71L (NL) or MGF 360 and 505
  - TK und 9GL: defect in macrophage replication
  - DP71L: Prevents host-shutoff
  - MGF: Interferon answer
- Problem 1: Deletions are not easily transferred among strains
- Problem 2: double deletions, that should lead to further attenuation abrogated protection (e.g. 9GL and MGF 360/505 cluster or DP71L and DP96 R)
- Very limited dose range
- Sometimes pathology in „protected“ animals

… better …

Mission (im)possible?

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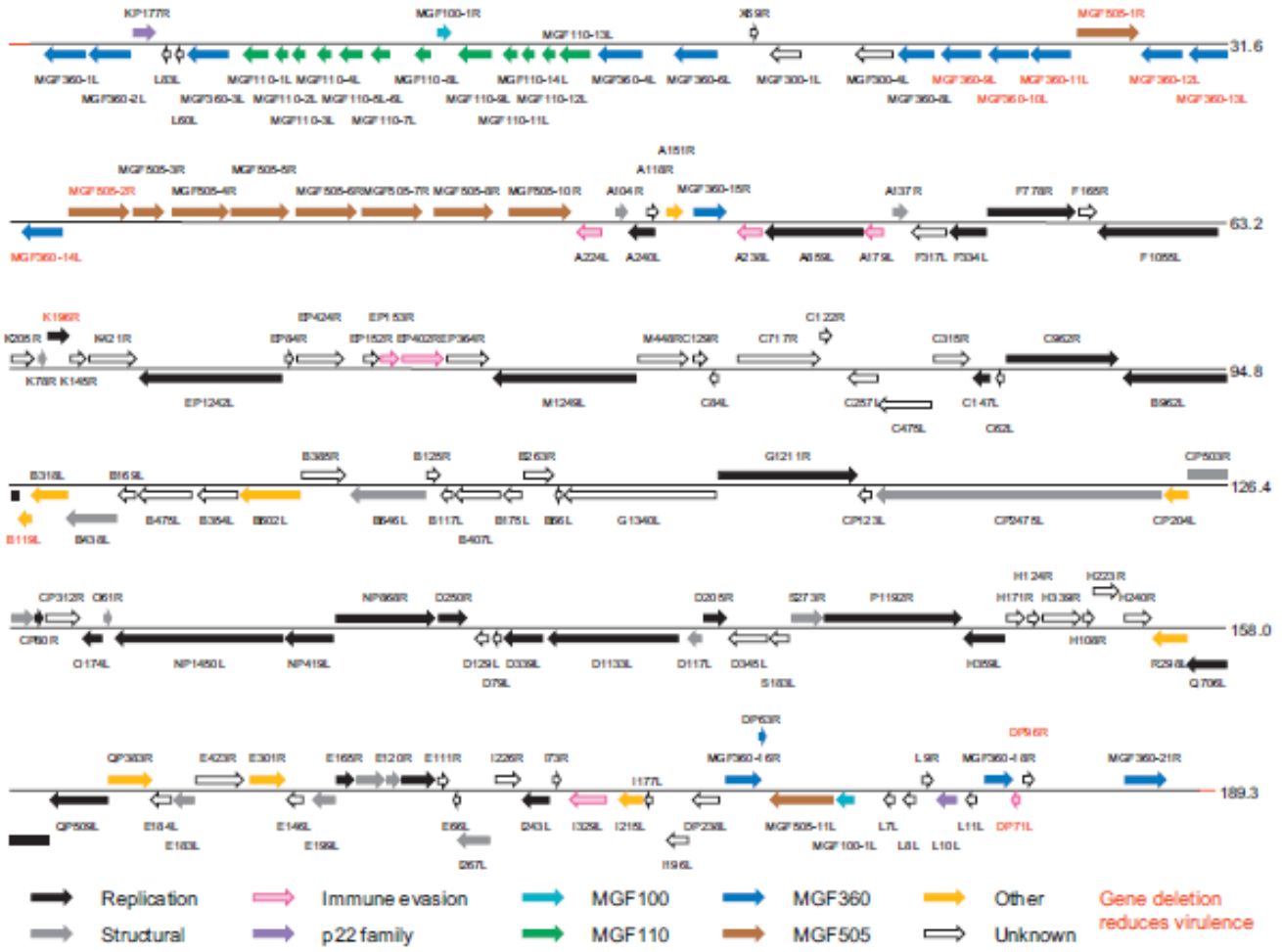

Fig. 1. Genome organisation of the African swine fever virus genome. The organisation of open reading frames (ORFs) on the genome of the virulent ASFV isolate Georgia 2007/1 is shown. ORFs are shown as arrows to indicate their size and direction they are read. The colours indicate ORFs with known functions. Black indicates ORFs encoding enzymes and factors involved in genome replication, repair or transcription. Grey indicates ORFs encoding structural proteins. Pink indicates ORFs encoding proteins involved in evading the host defences. Turquoise, blue, green, brown and mauve indicate members of multigene families. ORFs encoding proteins with other predicted functions are shown in yellow. ORFs encoding proteins of unknown function are shown in white. Red text indicates ORFs whose deletion reduces virus virulence.

Vector vaccines and subunits

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- Known antibodies e.g. against p30, p54 and p72…
- Partial protection through p30 and p54 antibodies…
- DNA immunization using a fusion protein of CD2v, p30, p54 and ubiquitin showed also partial protection
- Baculovirus expressed p30, p54, p72 or p22 did not protect
- Partial protection through CD2v immunization
- Vector based systems lack knowledge about antigens
- *in silico* prediction did not show promising results
- Standard proteins in diverse vector systems did not show reliable protection (it is NOT a matter of the vector)

… safety first? …

Deletion of the African swine fever virus gene DP148R does not reduce virus replication in cult - Internet Explorer

https://www.ncbi.nlm.nih.gov/pubmed/28978700

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J Virol. 2017 Oct 4. pii: JVI.01428-17. doi: 10.1128/JVI.01428-17. [Epub ahead of print]

Deletion of the African swine fever virus gene DP148R does not reduce virus replication in culture but reduces virus virulence in pigs and induces high levels of protection against challenge.

Reis AL[1], Goatley LC[2], Jabbar T[2], Sanchez-Cordon PJ[2], Netherton CL[2], Chapman DG[2], Dixon LK[2].

Author information

Abstract

Many of the approximately 165 proteins encoded by African swine fever virus do not have significant similarity to known proteins and have not been studied experimentally. One such protein is DP148R. We showed that the DP148R gene is transcribed at early times post-infection. Deletion of this gene did not reduce virus replication in macrophages showing that is not essential for replication in these cells. However deleting this gene from a virulent isolate, Benin 97/1, dramatically reduced the virulence of the virus *in vivo* All pigs infected with the BeninΔDP148R virus survived infection showing only transient mild clinical signs soon after immunisation. Following challenge with the parental virulent virus all pigs immunised by the intramuscular route (11/11) and all except one immunised by the intranasal route (5/6) survived. Mild or no clinical signs were observed after challenge. As expected control non-immune pigs developed signs of acute ASF. Virus genome and infectious virus were observed soon after immunisation coincident with the onset of clinical signs (~10^6 genome copies or $TCID_{50}$/ml). Levels of virus genome declined over an extended period of up to 60 days post-immunisation. In contrast infectious virus was no longer detectable by days 30 to 35. IFN-γ was detected in serum between days 4 and 7 post-immunisation, and IFN-γ producing cells were detected in all pigs analysed following stimulation of immune lymphocytes with whole virus. ASFV specific antibodies were first detected from day 10 post-immunisation.**IMPORTANCE** African swine fever (ASF) is endemic in Africa, parts of the Trans Caucasus, Russian Federation and several European countries. The lack of a vaccine hinders control. Many of the ASF virus genes lack similarity to known genes and have not been characterised. We have shown that one of these, DP148R, is transcribed early during virus replication in cells and can be deleted from the virus genome without reducing virus replication. The gene deleted virus, BeninΔDP148R caused mild clinical signs in pigs and induced high levels of protection against challenge with parental virulent virus. Therefore deletion of this gene can provide a target for rational development of vaccines.

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PMID: 28978700 DOI: 10.1128/JVI.01428-17

Free full text

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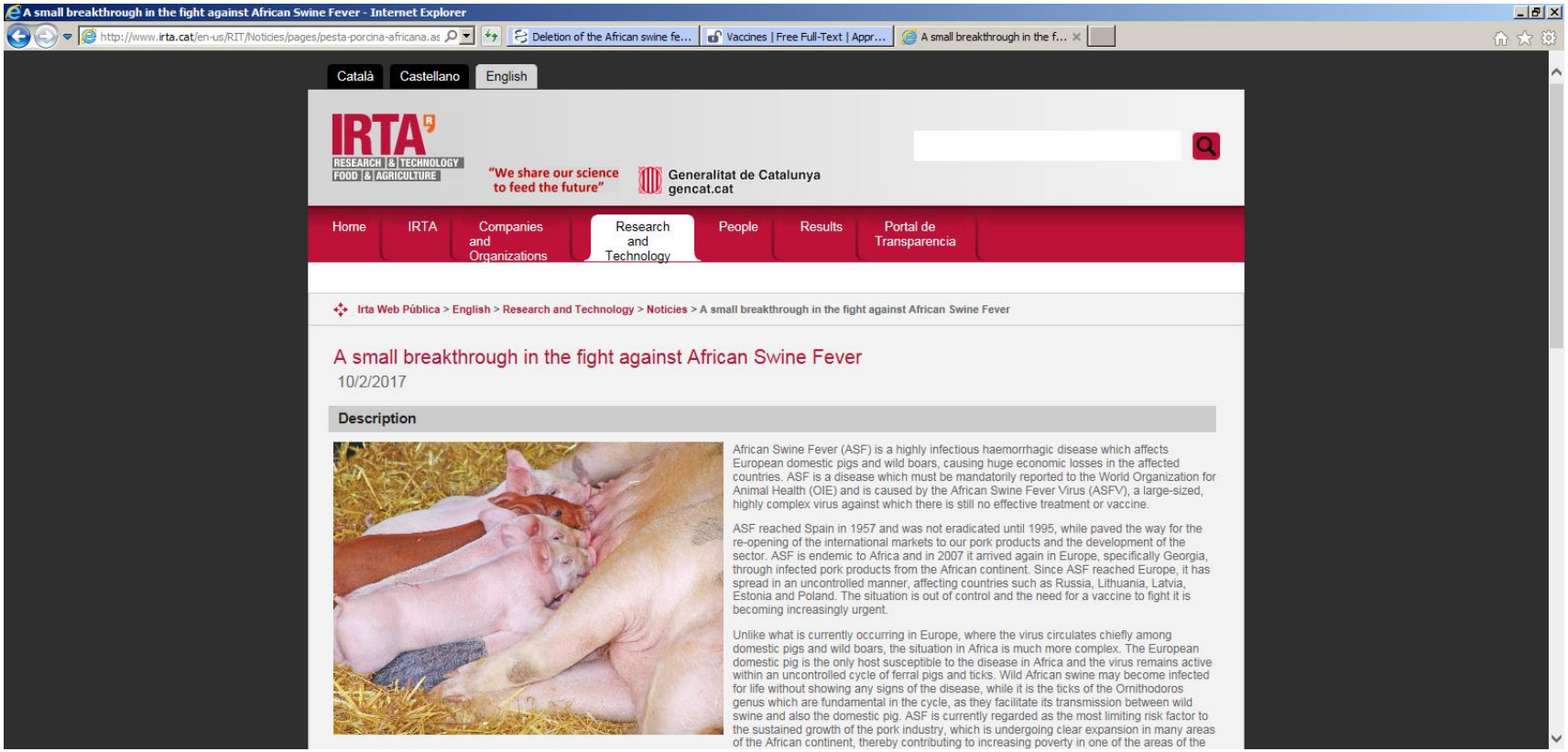
The gene deleted virus, BeninΔDP148R caused mild clinical signs in pigs and induced high levels of protection against challenge with parental virulent virus. Therefore deletion of this gene can provide a target for rational development of vaccines.

Deletion of DP148R → only mild side effects … almost complete protection



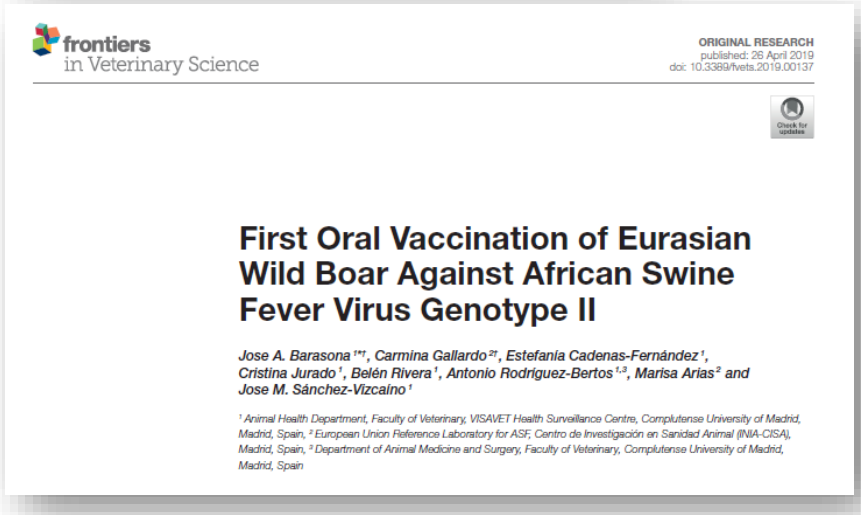
BA71ΔCD2 – promising results but still drawbacks

Schwein / News

ASP-Impfstoff für Wildschweine?

Bislang machten Virologen wenig Hoffnung, dass es in naher Zukunft einen Impfstoff gegen die ASP geben könnte. Das könnte sich jetzt ändern...

12.11.2018 von Agra Europe (AgE)



frontiers in Veterinary Science

ORIGINAL RESEARCH
published: 26 April 2019
doi: 10.3389/fvets.2019.00137

First Oral Vaccination of Eurasian Wild Boar Against African Swine Fever Virus Genotype II

Jose A. Barasona[1†], Carmina Gallardo[2†], Estefanía Cadenas-Fernández[1], Cristina Jurado[1], Belén Rivera[1], Antonio Rodríguez-Bertos[1,3], Marisa Arias[2] and Jose M. Sánchez-Vizcaíno[1]*

[1] Animal Health Department, Faculty of Veterinary, VISAVET Health Surveillance Centre, Complutense University of Madrid, Madrid, Spain, [2] European Union Reference Laboratory for ASF, Centro de Investigación en Sanidad Animal (INIA-CISA), Madrid, Spain, [3] Department of Animal Medicine and Surgery, Faculty of Veterinary, Complutense University of Madrid, Madrid, Spain

According to Prof. Jose Sánchez-Vizcaíno, virologist at the Faculty of Veterinary Medicine of the University of Madrid and Director of the ASP Reference Laboratory of the World Organisation for Animal Health (OIE) in Madrid, his many years of research into the development of a vaccine have now shown good results. The expert said on Wednesday last week at the Sepor agricultural trade fair in Lorca, southern Spain, that he had concentrated his work on combating the dangerous disease in feral pigs, because the problem in the EU has so far been much greater than with farm animals. The level of protection provided by the currently available oral vaccine is very high. However, there is still a need for research into the stability of the vaccine. The possible consequences of taking several vaccine doses, which cannot be ruled out in the case of oral vaccination of wild animals, are also unclear. As the scientist also reported, he expects the market launch of the new vaccine in two years at the latest. He is already in talks with a multinational company. The aim is to minimise the virus pressure by mass vaccination of wild boar and thereby also to better protect the livestock.

Lv17/WB/Rie1

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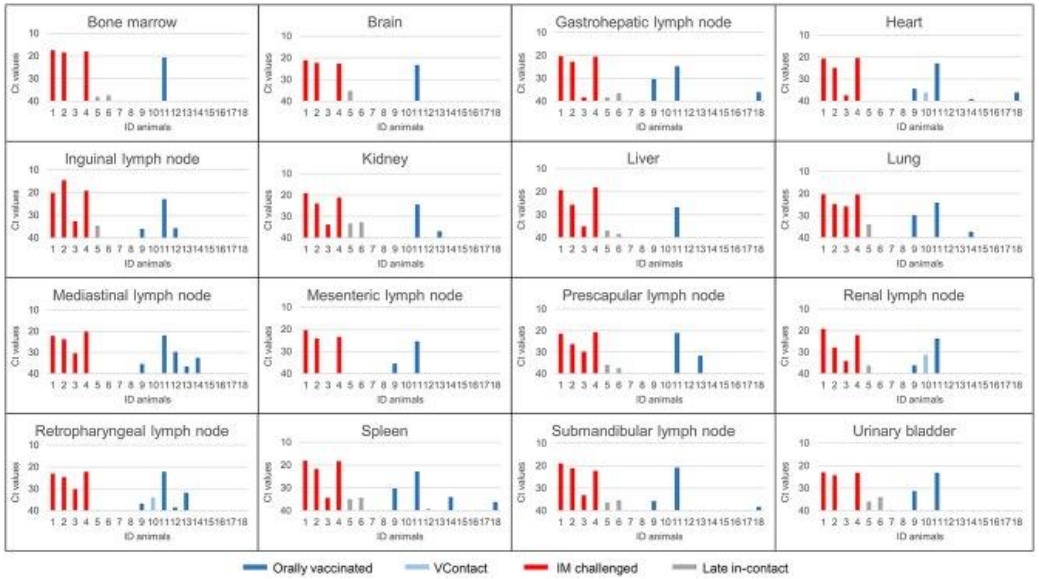


Barasona et al., 2019

Domestic pigs infected with Lv17/WB/Rie1ASFV developed nonspecific clinical signs or, in some cases, remained apparently healthy… Specifically, one inoculated pig (PW17) showed weak peaks of fever (40.3–40.7°C) from 8 to 12 dpi accompanied by the appearance of cyanosis in ears and swelling of joints from 14 to 32 dpi.

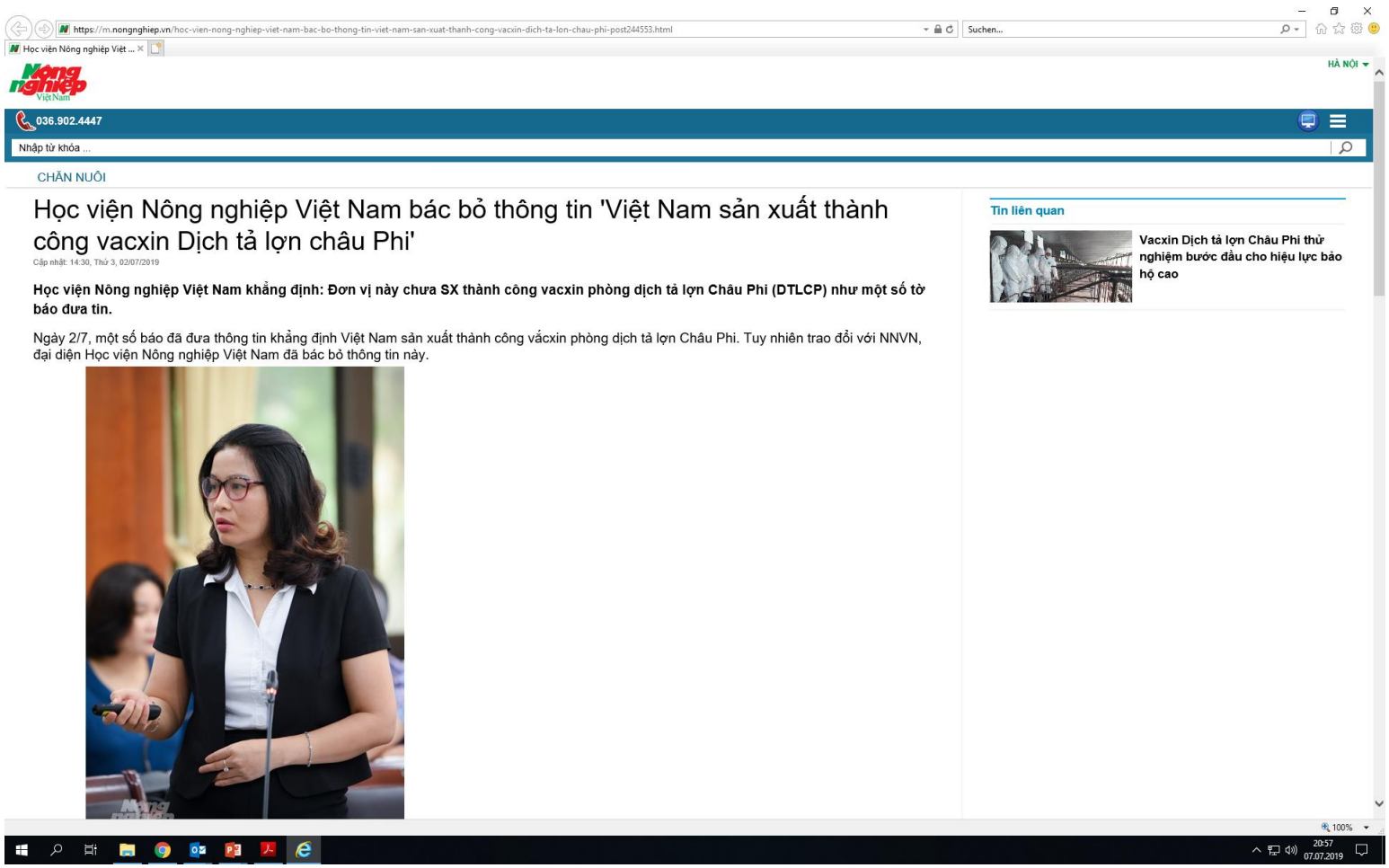
Gallardo et al., 2019

Adenovirus-vectored African Swine Fever Virus antigen cocktails are immunogenic but not protective against intranasal challenge with Georgia 2007/1 isolate
Lokhandwala et al, 2019

Towards the Generation of an ASFV-pA104R DISC Mutant and a Complementary Cell Line-A Potential Methodology for the Production of a Vaccine Candidate.
Freitas et al., 2019

Netherton et al., 2019: **...** we used a gamma interferon ELIspot assay to screen for viral proteins recognized by lymphocytes from ASF-immune pigs... Eighteen antigens that were recognized by ASFV-specific lymphocytes were then incorporated into adenovirus and MVA vectors, which were used in immunization and challenge experiments in pigs. … Pools of viral vectors expressing these genes did not protect animals from severe disease, but did reduce viremia in a proportion of pigs following ASFV challenge.

DNA-Protein Vaccination Strategy Does Not Protect from Challenge with African Swine Fever Virus Armenia 2007 Strain
Sunwoo et al., 2019



Was corrected …

Obstacles

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- There is still a lack of knowledge with regard to infection biology and immunity
- Complexity of the virus, function of several proteins is still unknown, immune modulation
- Correlated of protection are rather unknown
- Reaction pattern of animals with acute-lethal and transient disease courses show only little difference (in the parameters tested)
- Our knowledge about protective antigens is still sketchy
- Efficient expression systems, protein structure
- Rational deletions do not always show the desired effect
- Different ASFV strains do not behave the same way (if deletions are introduced)
- Safety is an issue (late-onset side effects etc.)
- How to grow a vaccine candidate?
- Can we use a vaccine that spreads?

Thanks for your attention!