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Zoonoses Anticipation and Preparedness Initiative

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ZAPI modular vaccine design approach as an answer to pandemics / panzootics threats

**Pandemics! A One Health view of Emerging Infectious Diseases
H4A CWG & STAR-IDAZ Webinar, June 30th, 2020**



Facing pandemics or panzootics

- One cannot predict where exactly and to which target species an emerging / re-emerging virus will trigger the next pandemic or pan-epizootic event.
- All outbreaks in humans and veterinary species in the past 20 years (SARS-CoV, Ebola, MERS-CoV, H1N1, WNV, BTV-8, BTV-1, Schmallenberg virus) have occurred unexpectedly and as full surprises regarding time and location.
- But we can have good guesses on the most likely suspects:

contact, air transmission

Paramyxoviruses

Orthomyxoviruses

Coronaviruses

insect-borne

Bunyaviruses RVFV

Orbiviruses BTV, AHSV

Flaviviruses WNV



Facing pandemics or panzootics



The only way to face unexpected viral outbreaks is to develop our capacity to execute an « immediate and decisive intervention ».

This strategy raises a dilemma for industrial manufacturing of (human or veterinary) vaccines:

- How to react very fast and:
 - not chasing false alerts for « non events » / self-resolving outbreaks
 - avoiding to invest huge levels of resources with high risk to fail
- How to address exponential needs while manufacturing capacity increase can only be « low arithmetics » (2x or 3x)



Facing pandemics or panzootics



Even for veterinary vaccines, developing new vaccines is a very long process (ethical need to validate safety and efficacy and development process) based on years of work.

3 different time periods for a vaccine development:

- **Scientific time**
- **Technical & Industrial time**
- **Regulatory / Registration time**

Can we decrease these 3 timelines to be effective against outbreaks that spread around the world in a few months?



Facing pandemics or panzootics

Need to shorten timelines for:

- **Scientific time**
 - Faster and faster today
- **Technical & industrial time (capability & capacity)**
 - « Industrial vaccine » by design approach = ZAPI core objective
- **Regulatory / registration time?**
 - Lowering requirements shall be in line with societal and technical adaptation (use of safe and sustainable vaccines by design)
 - Moving from **Risk / benefit** balance to a **Benefit / risk** balance



ZAPI pandemics vaccines

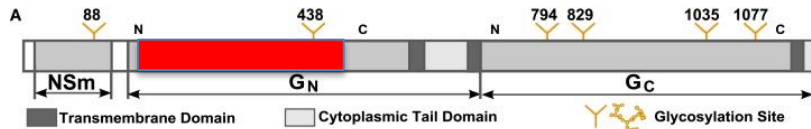
Key drivers for the ZAPI vaccine design and surge capacity manufacturing approach:

- **Flexible platform** fitting with all potential viral vaccine targets
- **Lean and sustainable** manufacturing platform
- Simple, **portable** technologies, available worldwide
- **No bottlenecks** for manufacturing raw materials or key ingredients
- **Very rapid cycle time** (including *in vitro* QC)
- Thermostable vaccines for easy distribution and supply chain in LMIC

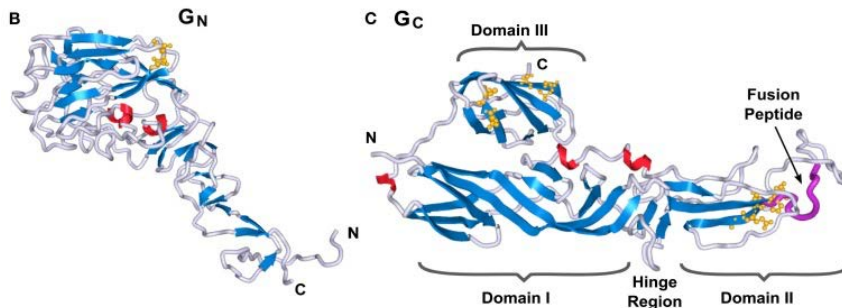
ZAPI demonstration project using 3 zoonotic viral prototypes



1. Can we identify immunogenic subunit domains ?

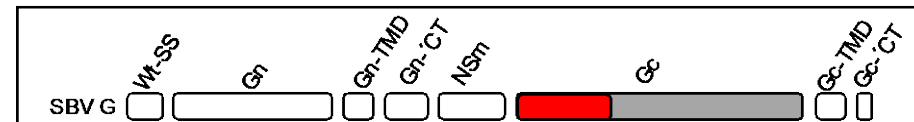


Rift Valley Fever Virus



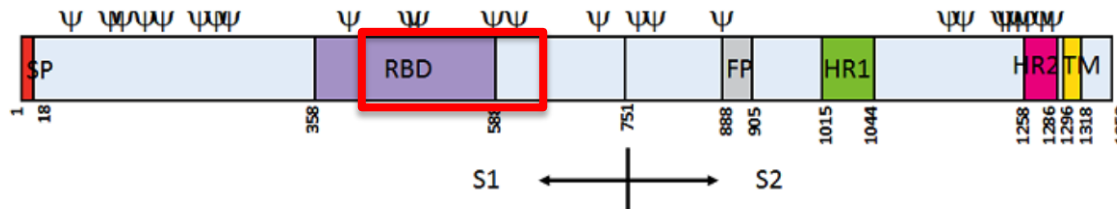
Schmallenberg Virus

FLI



GcAmino

Identified domains:



MERS-CoV



Utrecht University

Figure 1. Schematic representation of MERS-CoV S protein. The signal peptide (SP), receptor binding domain (RBD), fusion peptide (FP), heptad repeat region (HR) and transmembrane domain (TM) are indicated. The RBD of MERS CoV has been mapped based on the predicted location and structure of the RBD of two other *Betacoronavirus*, MHV and SARS-CoV using ClustalW¹. The other domains are assigned using predictor software as listed above.

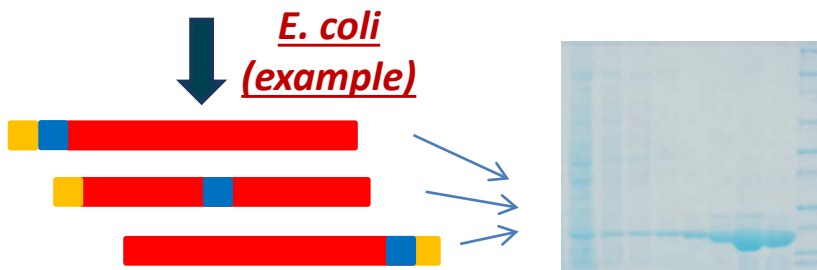


2. Modular scaffold system with bacterial superglue



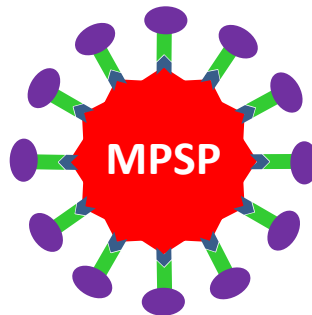
Produce Multimeric Protein Scaffold Particle-SpyTag™ in most convenient system

Produce antigen-SpyCatcher™ in most convenient expression system



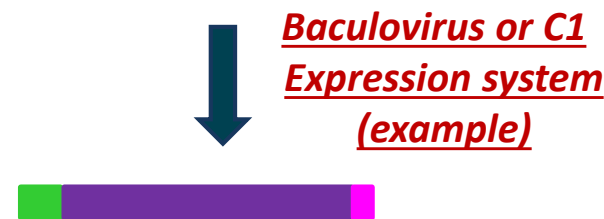
Covalent binding of Spy-Tag and Spy-Catcher

Formulate vaccine by combining particles with antigen



Flexible, high expression, multiple antigens possible

Zakeri B. *et al.* P.N.A.S. 2012. **109**. E690-697
 Veggiani C., Zakeri B. Howarth M. Trends in Biotechnol.. 2014. **32**. 506-512



- Spy-Catcher
- Spy-Tag
- His(6x)-tag
- Strep(2x)-tag

ZAPI modular vaccines efficacy in target species (1)



Comparison of RVFV Gn subunit coupled to 3 different MPSPs (sheep target species)

Immunization of sheep with adjuvanted MPSP complexes. All 3 prototype vaccines were able to induce full clinical protection and protection against viremia (sterile immunity / DIVA capability) against a severe RVFV challenge.

Manuscript in preparation (Wichgers-Schreur P. et al)

SBV Gc subunit coupled to Aldolase MPSP (cattle target species)

Immunization of cattle with adjuvanted MPSP complex. Full clinical protection and protection against viremia (sterile immunity / DIVA capability) against SBV challenge.

Manuscript in preparation (Aebischer A. et al)



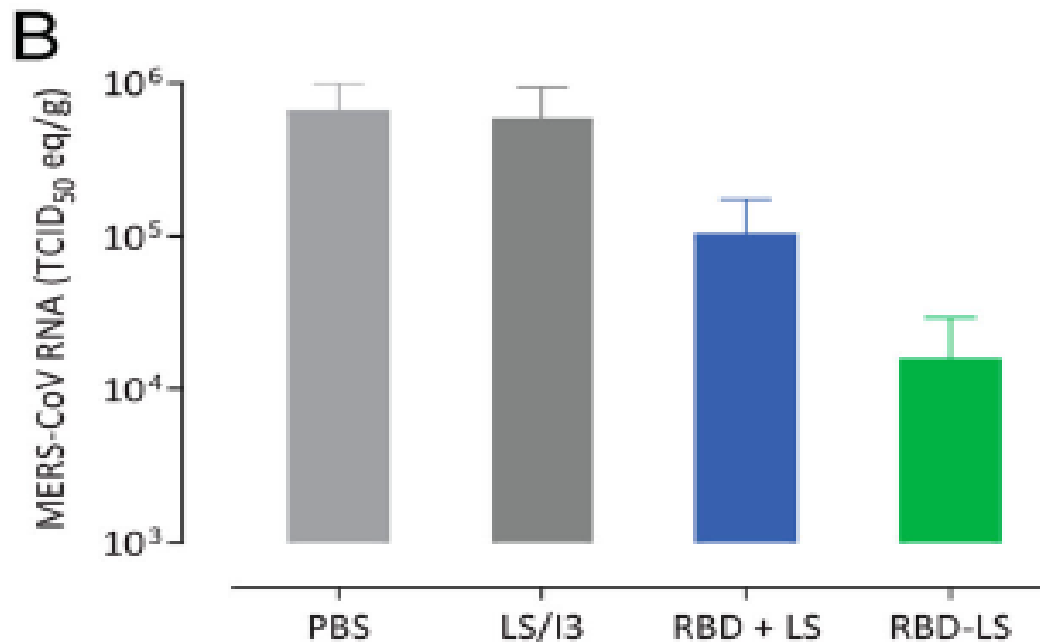
ZAPI modular vaccines efficacy in target species (2)



MERS-CoV RBD subunit coupled to Lumazine-Synthase MPSP (rabbit model)

Very good protection against viral load after intranasal MERS-CoV challenge.
Demonstration of better immunogenicity for the MPSP complex compared to the mixture of uncoupled MPSP and subunit.

Okba N. et al. Emerging Microbes & Infections. 2020.9. <https://doi.org/10.1080/22221751.2020.1760735>





1. Scientific timeline

Accelerated definition of immunogen subunit (few days)

NexGen sequencing technologies

in silico screening

Global knowledge on most suspected viral families

Learnings from veterinary vaccines

Establishment of pertinent animal model (timeline ?)





2. Technical / industrial timeline

Use of robust expression platform with:

- **very high yields / short cycle time**
 - limited impact on manufacturing plant footprint and other vaccines in production
 - very large number of doses in a few months...
- no need for highly specialized site and technical staff



3. Regulatory timeline decrease based on:

- **Quality by Design**
- **Use of an Established Platform**

Vaccine final product inherently safe (target species, environment)

Consistent and robust manufacturing process

- No risk of viral contaminants
- Biophysical criteria used to characterize AI and FP

Platform Master File concept allows now and accelerated licensing procedure (EMA Guidelines for human products published, parallel testing at OMCLs for batch release (EDQM Guidelines published)).

→ New « fast-track process » based on SARS-CoV-2 vaccines learnings?



Conclusion (1)

- Facing a pandemics / panzootics and reacting fast for manufacturing vaccines is similar, for industry, to run a 100-meter Olympic race.
- You can do this and win the race only if you have intensively trained for years at the top level...
- The ZAPI methodology is putting in place the key principles for achieving the surge capacity needed during « war time ».
- The ZAPI project has been a « peace time training ground » for evaluating practical ways to be effective.



Conclusion (2)

- **The industrial training has to be maintained and improved in the coming years.**
- **Call for a ZAPI 2.0 to expand on target examples and process refinements for establishing a solid platform for our future.**
- **Concept for a « ZAPI facility » in which a manufacturing process for a new pandemic vaccine can be rapidly developed and then transferred to multiple facilities in the world if needed.**



Zoonoses Anticipation and Preparedness Initiative



Thank you for your attention



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