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# Zoonoses Anticipation and Preparedness Initiative

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## How to deliver vaccines and therapeutic antibodies under very short timelines ?

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# Zoonoses Anticipation and Preparedness Initiative

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[www.zapi-imi.eu](http://www.zapi-imi.eu)

## 1st One Health IMI project

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# IMI Basic Principles



## Key concepts underlying IMI



Open innovation in  
public-private consortia

Non-competitive collaboration  
between large pharma companies

A new ecosystem for sustainable healthcare  
across Europe, involving all stakeholders

# 20 Partners in ZAPI consortium



## EFPIA partners :

- **Merial (now part of Boehringer Ingelheim)**
- **Boehringer Ingelheim Animal Health**
- **AstraZeneca / Medimmune**

**EFPIA coordinator**

**EFPIA partner**

**EFPIA partner**

## Public consortium partners:

**Erasmus Medical Center NL**

**WBVR Lelystad NL**

**Utrecht University NL**

**Leyden University NL**

**FLI Riems DE**

**Institut Pasteur FR**

**IABS-EU FR / BE**

**Univ. Klin. Bonn DE**

**Viroclinics Biosciences NL**

**CSIC Madrid SP**

**IRTA-CReSA SP**

**TiHo Hannover DE**

**Aix-Marseille Univ. FR**

## SMEs

**Dyadic NDL Wageningen NL**

**Harbour Antibodies Rotterdam NL**

**Artemis NL**

**Finovatis FR**

# The Reason for ZAPI: facing the unknown, and the need to be able to react rapidly



INSIGHTS

**PERSPECTIVES**

INFECTIOUS DISEASE

## Zika vaccine trials

There are new and familiar challenges in the race for timely and effective vaccines

By Marc Lipsitch<sup>1</sup> and Benjamin J. Cowling<sup>2</sup>

Examining data for candidate vaccines against Zika virus infection reported by Altmink et al. (1) on page 1120 of this issue raises hopes that one or more Zika virus vaccines may soon be ready for efficacy trials. Recent years have seen a barrage of emerging infectious diseases, including those caused by new pathogens such as Middle East respiratory syndrome (MERS) coronavirus, and those that are newly salient because of increased geographic spread, higher incidence, or genetic change, such as influenza A(H5N1) pandemic, Ebola virus, and Zika virus. Developing effective vaccines is a central goal for such pathogens.

**Developing effective vaccines have caught us by surprise with no vaccine candidates available very early-stage candidates available.** Human safety and immunogenicity must be established before starting large-scale efficacy studies. Those studies consume valuable time while the epidemic spreads. During the 2014–2016 Ebola epidemic, the urgency of exponentially growing incidence gave way to the urgency of declining incidence, which threatened the ability to test vaccine efficacy. The effectiveness of one Ebola vaccine was proven just as the epidemic ended (2). During the 2009–2010 influenza A(H1N1) pandemic, efficacy testing was not required because demonstrating immunogenicity for influenza vaccines is accepted as indirect evidence of efficacy (3). The biggest vaccine availability challenge in many locations is that the vaccine arrived too late to affect the course of the first pathogenic waves.

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**A key principle of preparedness is to do as much work as possible before an emergency happens, so that the response can be decisive and efficient.** Several approaches would speed vaccine availability in future emergencies, such as the ring-opening trial used to test an Ebola vaccine (2), or for adapting existing designs to meet the logistical challenges of the disease and the population in which it is spreading (10). Adaptive designs that test multiple candidate vaccines and put more resources toward those showing the most promise may be needed, particularly for emerging-disease vaccines, to avoid ethical issues that could arise in testing vaccines after they have been proven effective. The properties of such trial designs should be understood before they are needed.



Earlier this year, the US National Institute of Allergy and Infectious Diseases launched a safety and immunogenicity clinical trial of a vaccine candidate to prevent Zika virus infection.

a range of pathogens before the next emergency (4) would enhance preparedness against known pathogens that could become greater threats if they become more common or geographically widespread. Moreover, for pathogens (5, 7) that have at least one proven effective vaccine, discovering correlates of protection (6) could justify initial reliance on immunogenicity (and safety) data in the use of subsequent vaccines or formulations against the same pathogen. The more field or systems vaccination which uses thousands of measurements on vaccinated persons to identify correlates and possible mechanisms of immune protection (9), could accelerate such discovery.

**Continued innovation during “peacetime” in designing and studying (through simulation) vaccine efficacy trials that address the challenges of emergencies is needed to enhance quick responses.** Getting results rapidly using immunogenicity and safety data in humans calls for innovative trial designs, such as the ring-opening trial used to test an Ebola vaccine (2), or for adapting existing designs to meet the logistical challenges of the disease and the population in which it is spreading (10). Adaptive designs that test multiple candidate vaccines and put more resources toward those showing the most promise may be needed, particularly for emerging-disease vaccines, to avoid ethical issues that could arise in testing vaccines after they have been proven effective. The properties of such trial designs should be understood before they are needed.

Trials for emerging infectious disease countermeasures pose novel ethical questions. For Ebola, there was an intense debate about the ethical and political acceptability of individually randomized or placebo-controlled trials in the case of a highly lethal infection (11). Zika virus raises a different spectrum of challenges. As with trial design, a preparatory effort is needed, during which there is not an immediate emergency, to raise, debate, and reach consensus about ethical issues that can arise in trials of countermeasures. For example, the World Health Organization defined emergency use conditions under which placebos could be used in vaccine trials (12). Researchers will require not only clearly stated and open to multiple interpretations, but also mechanisms to anticipate distinct ethical challenges that could be posed by future countermeasures against different types of pathogens.

Many challenges for Zika vaccine arise from the severity of the infection. Zika virus infection, by contrast, is mild or asymptomatic in most patients but severe in a few, causing congenital malformations in the fetus of some women infected during pregnancy (13). This pattern raises distinct challenges: What is the most relevant outcome for clinical trials? We do not yet know how much a mild or asymptomatic infection contributes to transmission or whether it could have fitness if it occurs in a pregnant woman. Therefore, infection, rather than symptoms, could be an important trial end point. However, this raises challenges for monitoring trial participants, especially because serologic tests for Zika virus infection are im-

A key principle of preparedness is to do as much work as possible before an emergency happens, so that the response can be decisive and efficient. Several approaches would speed vaccine availability in future emergencies. For pathogens we have not yet encountered, there is a need for platform technologies that rapidly produce test vaccine lots and, if successful, mass-produce vaccines against a new pathogen (4). Further, innovative proposals

Continued innovation during “peacetime” in designing and studying (through simulation) vaccine efficacy trials that address the challenges of emergencies is needed to enhance quick responses. Getting results rap-

By Marc Lipsitch<sup>1</sup> and Benjamin J. Cowling<sup>2</sup> sciencemag.org SCIENCE  
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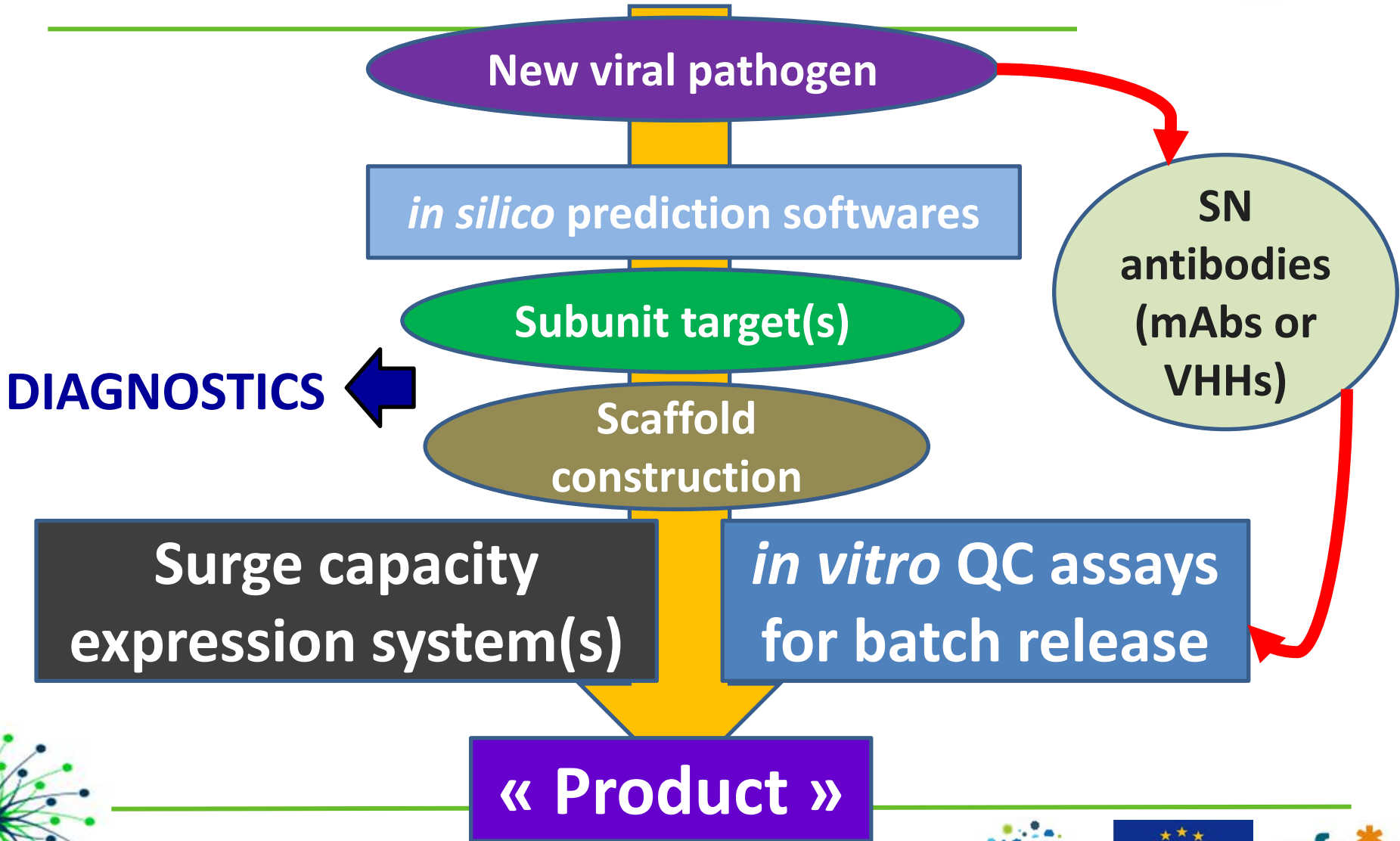
# ZAPI Overall Objectives



- ZAPI's outcome will be a methodology which works for several targets.
- ZAPI will provide a technology and selection method for the industrialization of therapeutic / preventive solutions.
- ZAPI will provide a methodology which will enable fast manufacturing and batch release, avoiding to stockpile.
- ZAPI aims at providing effective tools that will stop the disease progress in animals before it spreads to humans.



# ZAPI vaccine approach



# Prototyping ZAPI methodology with 3 viral models



- **3 “zoonotic” viral models are used in the ZAPI project:**
  - Rift Valley Fever Virus (RVFV) (Bunyaviridae, Phlebovirus)
  - Schmallenberg Virus (SBV) (Bunyaviridae, Orthobunyavirus)
  - MERS-CoV (Betacoronavirus)
- **2 main targets for ZAPI Vaccines:**
  - RVFV and SBV (MERS-CoV evaluated at small scale only)
- **2 main targets for ZAPI Therapeutic Antibodies:**
  - MERS-CoV and RVFV





# Objectives & Challenges for ZAPI Vaccines Strategy



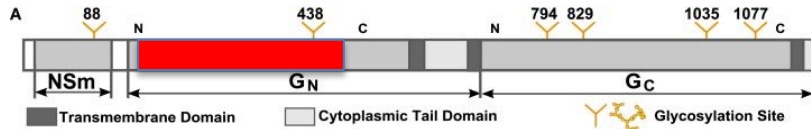
- **Define key immunogen subunits which are:**
  - Large enough to bear key protective epitopes and to be immunogenic
  - Small enough to be soluble / secreted at high yields *in vitro*
  - Well defined / characterized by specific antibodies

## Design manufacturing process which can :

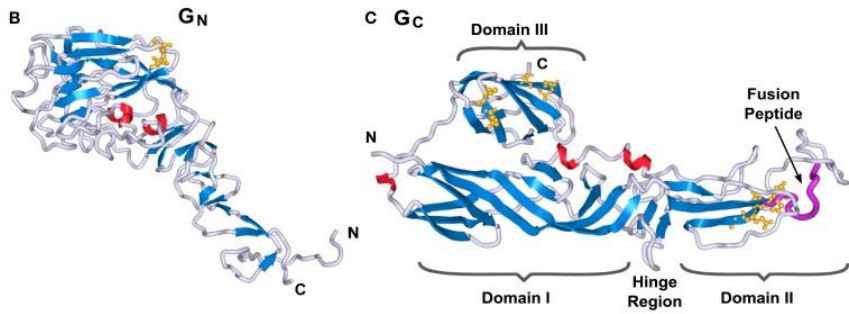
- achieve « surge capacity » (millions of doses in a few weeks)
- be deployed easily



# Can we identify immunogenic subunit domains ?

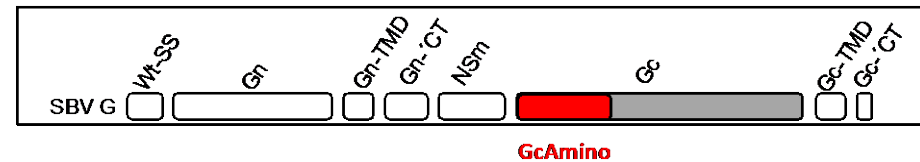


**RVFV**

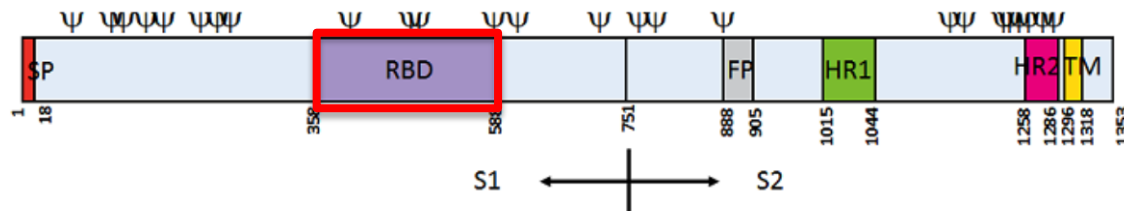


**SBV**

**FLI**



## Identified domains:



**MERS-CoV**

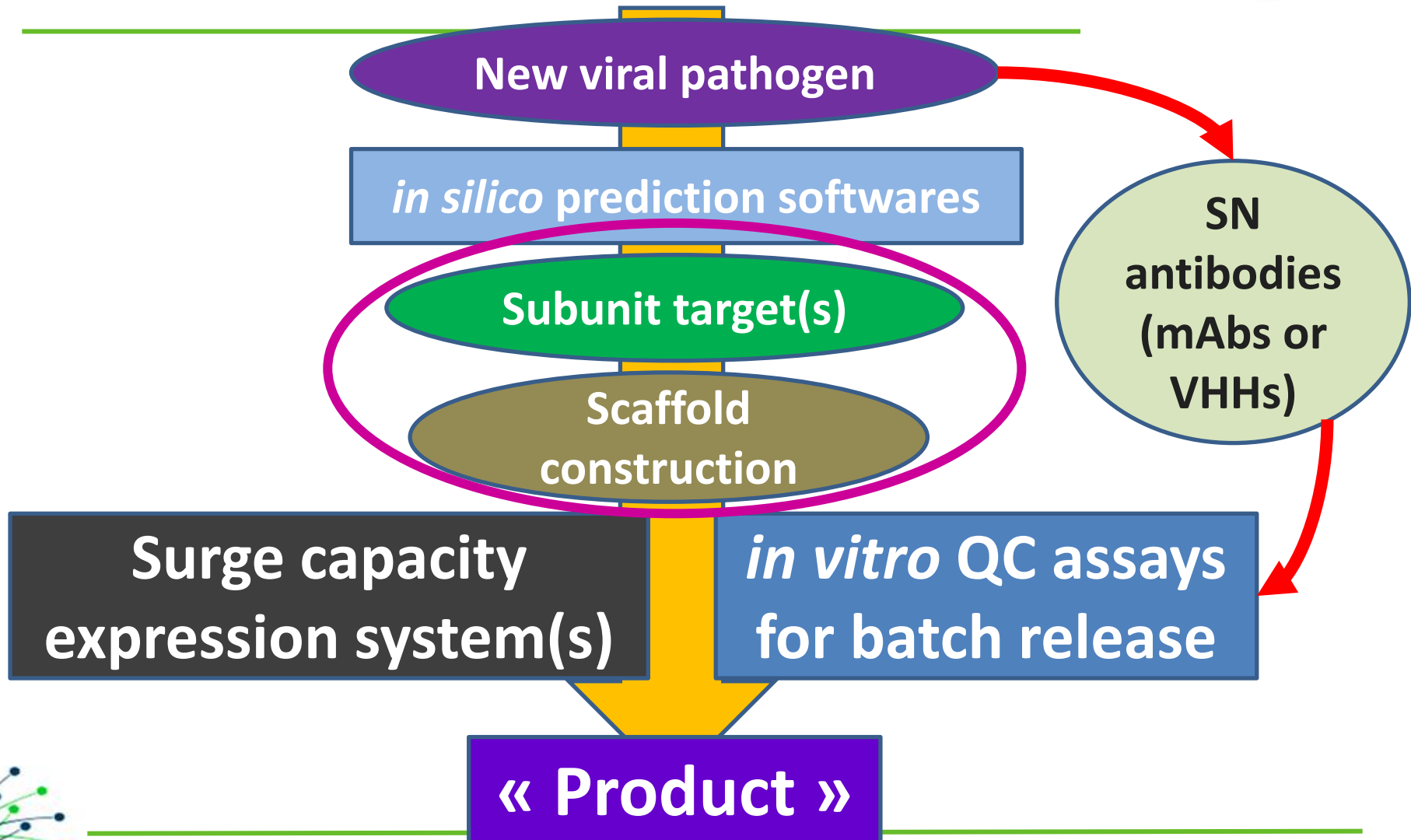


Utrecht University

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 RBC 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 ClustalW<sup>1</sup>. The other domains are assigned using predictor software as listed above.



# ZAPI vaccine approach

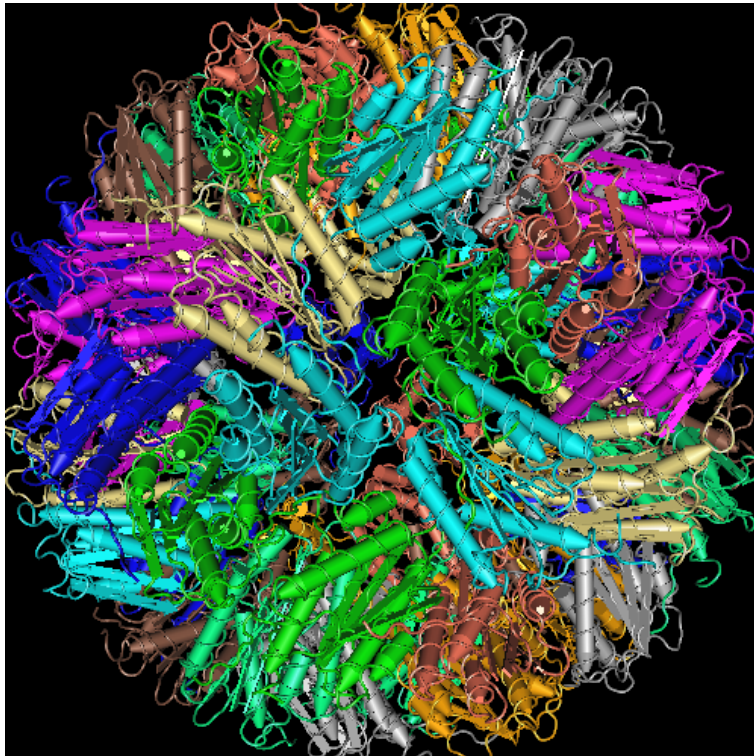


# The growing world of multimeric protein scaffolds (MMPS)



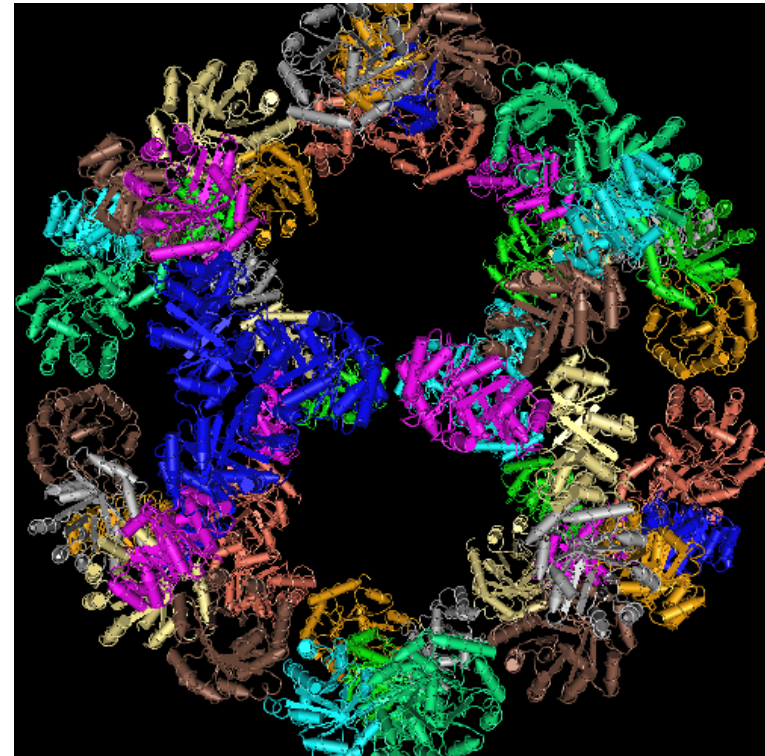
## Lumazine Synthase

*Aquifex aeolicus* or *Brucella* spp



## Aldolase I3-01

artificial protein



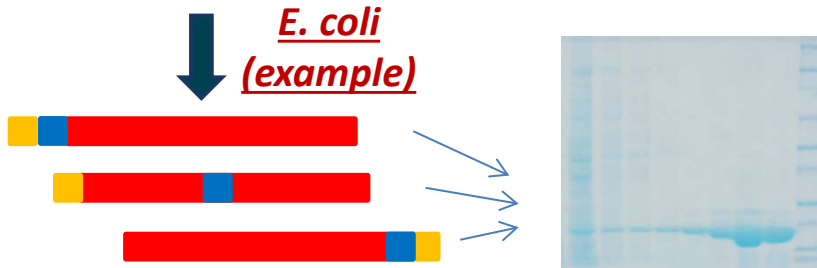
Entrez 3D Structure database



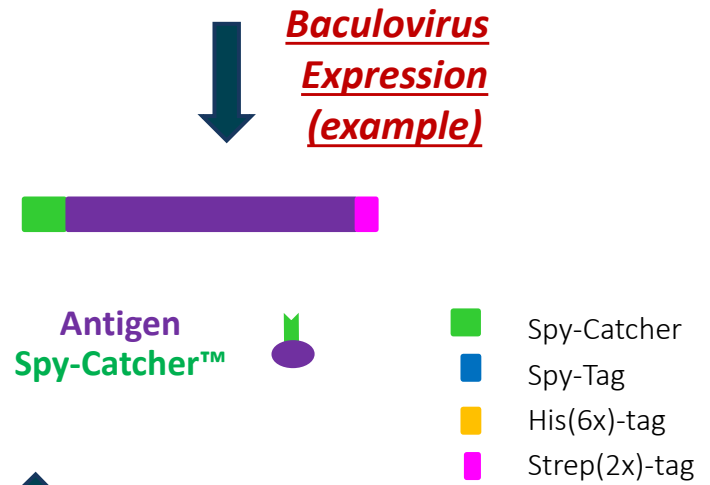
# Modular scaffold system with bacterial superglue



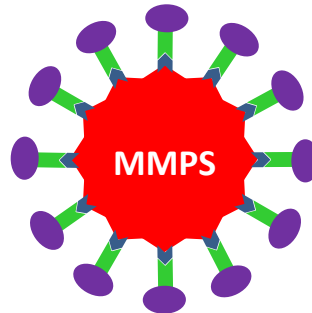
Produce MMPS-SpyTag™ in most convenient system



Produce antigen-SpyCatcher™ in most convenient expression system



Formulate vaccine by combining MMPS with antigen

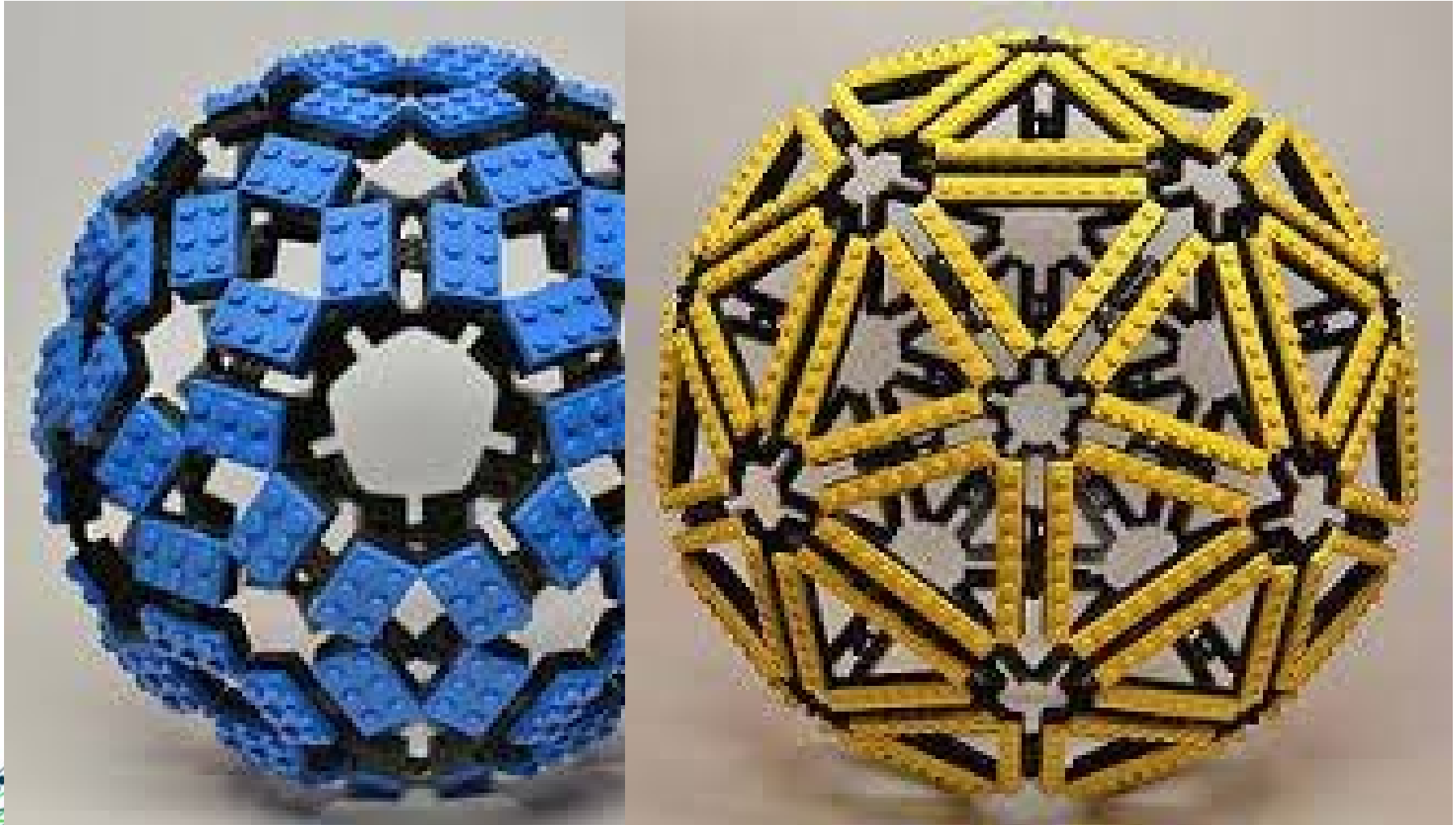


Flexible, high expression, multiple antigens possible

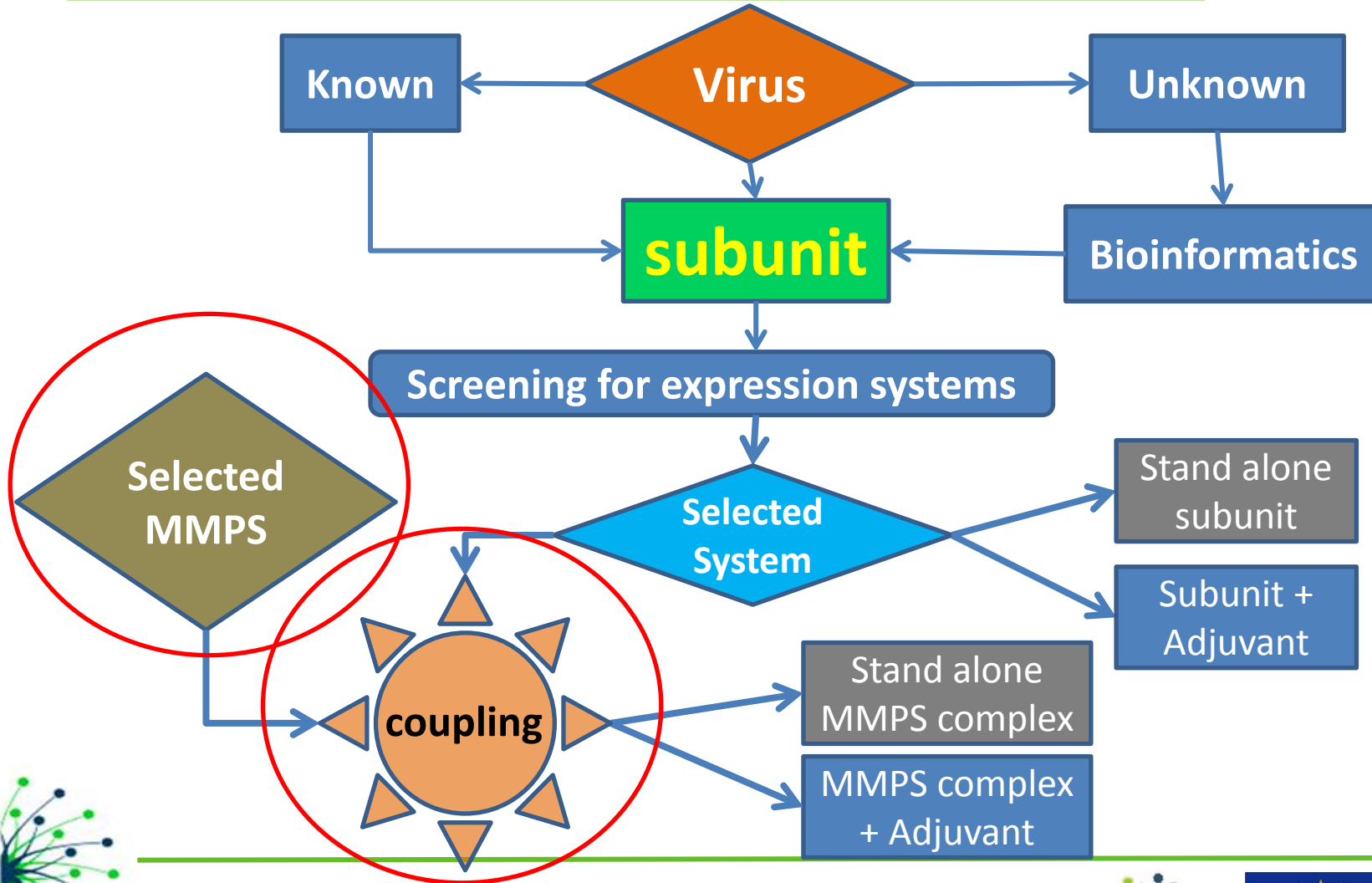
Zakeri B. *et al.* P.N.A.S. 2012. **109**. E690-697  
Veggiani C., Zakeri B. Howarth M. Trends in Biotechnol.. 2014. **32**. 506-512



# ZAPI as a « serious game » methodology



# Decision Tree for "ZAPI Vaccines"



# Coupling immunogens / MMPS to generate vaccine complexes

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- Stand alone subunit formulated with an adjuvant may work as such
- **ZAPI vaccine complex modular methodology should provide a number of advantages:**
  - Robustness in manufacturing
  - Stability (thermostability of the core NP)
  - Efficient targeting of DCs and lymph nodes
  - Quality of the protective immune response





# Conclusions / Perspectives

## Non technical challenges to address

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## Regulatory aspects

- **Acceptability of new platforms under emergency situations**
  - MMPS-subunit « platforms » versus live vaccines or live vectors
  - Actual implementation of the « animal rule » for ZAPI methodology-based vaccines and **neutralizing antibodies**
- **Move from a RISK/benefit balance to a BENEFIT/risk balance**
  - Need to engage the Regulatory Authorities on the changes that the ZAPI project will provide



# Conclusions / Perspectives

## Non technical challenges to address



- Funding for the industrial development and regulatory studies (these One Health emerging diseases are not « markets ») and roadmaps for implementing industrial preparedness ?
- Impact of Nagoya Protocol (NP) for a rapid and free access to the key Genetic Resources, while ensuring fair Access and Benefit Sharing (ABS): how to exempt (re-)emerging infectious diseases strains from the NP obligations ?



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# Zoonoses Anticipation and Preparedness Initiative



## Thank you for your attention



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