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

www.zapi-imi.eu

1st One Health IMI project

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)	EFPIA coordinator
• Boehringer Ingelheim Animal Health	EFPIA partner
• AstraZeneca / Medimmune	EFPIA partner

Public consortium partners:

Erasmus Medical Center NL	Univ. Klin. Bonn DE
WBVR Lelystad NL	Viroclinics Biosciences NL
Utrecht University NL	CSIC Madrid SP
Leyden University NL	IRTA-CReSA SP
FLI Riems DE	TiHo Hannover DE
Institut Pasteur FR	Aix-Marseille Univ. FR
IABS-EU FR / BE	

SMEs	Dyadic NDL Wageningen NL	Artemis NL
	Harbour Antibodies Rotterdam 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[1] and Benjamin J. Cowling[2]

Promising data for candidate vaccines against Zika virus infection reported by Abbink *et al.* (*1*) on page 1129 of this issue raise 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(H1N1)pdm09, Ebola virus, and Zika virus. Developing effective vaccines is a central goal for such pathogens.

Repeatedly, emerging infections have caught us by surprise, with no vaccine candidate or only very early-stage candidates available. Human safety and immunogenicity must be established before starting large-scale efficacy studies. These studies consume valuable time while the epidemic spreads. During the 2014–2015 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 indicative of efficacy (*3*). Yet, delays in vaccine availability in many locations meant that the vaccine arrived too late to affect the course of the first pandemic waves.

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

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 for performing human safety and immunogenicity studies on candidate vaccines against a range of pathogens before the next emergency (*5*, *6*) would enhance preparedness against known pathogens that could become greater threats if they become more common or geographically widespread. Moreover, for pathogens (*3*, *7*) that have at least one proven efficacious vaccine, discovering correlates of protection (*8*) could justify initial reliance on immunogenicity (and safety) data in the use of subsequent vaccines or formulations against the same pathogen. The new field of systems vaccinology, 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 for candidate vaccines against Ebola virus (*2*), or for adapting existing designs to meet the logistical challenges of the disease and the populations 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 one has 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 ethics and political acceptability of individually randomized or placebo-controlled trials in the context of a highly lethal infection (*11*). Zika virus raises a different spectrum of challenges. As with trial design, a consensus effort is needed, during a period when there is not an immediate emergency, to raise, debate, and reach consensus about ethical issues that can arise in trials of candidate vaccines. For example, the World Health Organization defined conditions under which placebos could be used in vaccine trials (*12*). Future efforts will require not only study, rigor and openness to multiple perspectives, but also imagination to anticipate distinctive ethical challenges that could be posed by future emergencies caused by different types of pathogens.

Many challenges for Zika vaccines arose 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 fetuses 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 harm fetuses 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-

Downloaded from http://science.sciencemag.org/ on September 9, 2016

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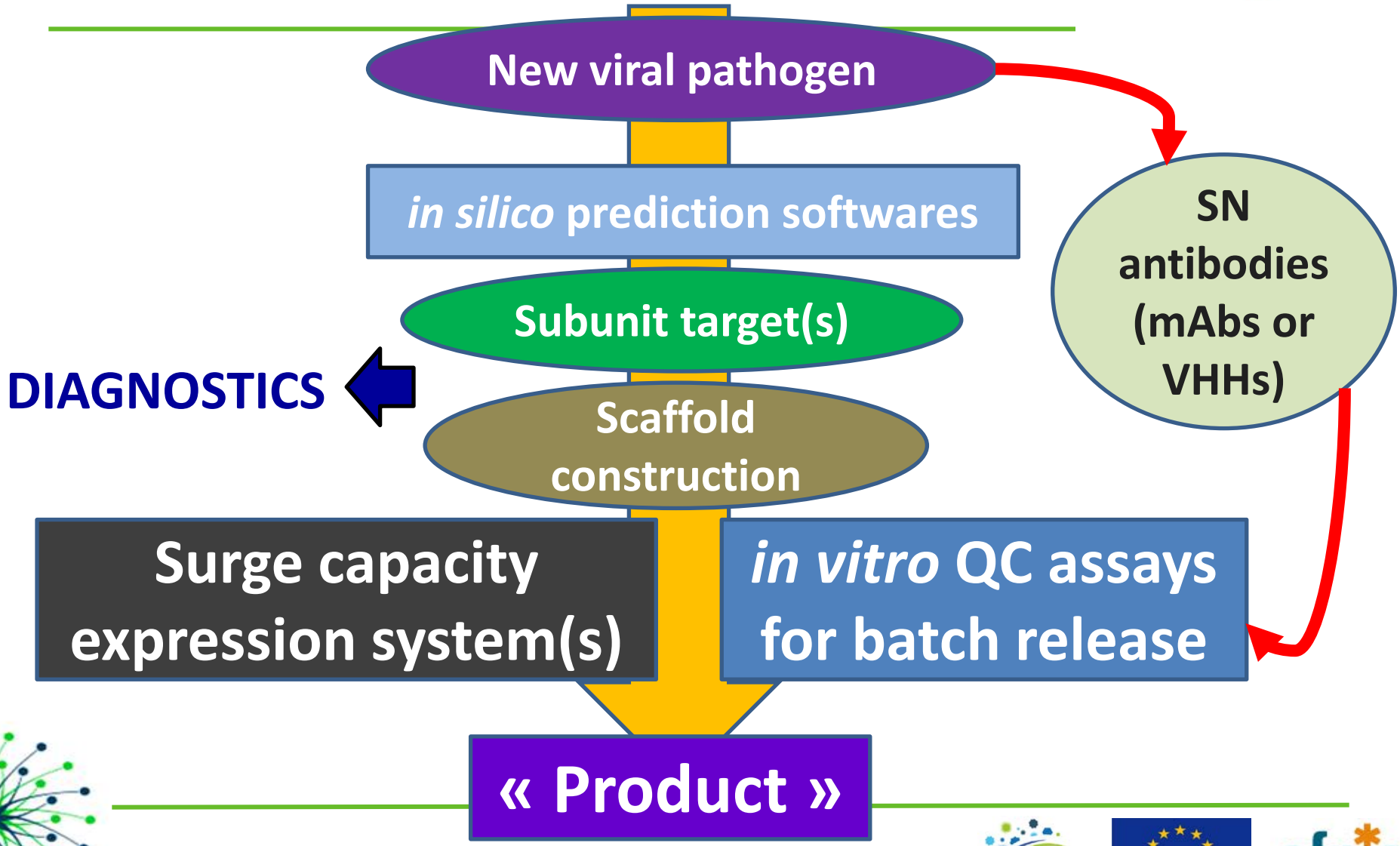
Continued innovation during "peacetime" in designing and studying (through simulation) vaccine efficacy trials that address the challenges of emergencies is needed to enhance quick responses. Getting results rap-

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) (Bunyaviridiae, 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

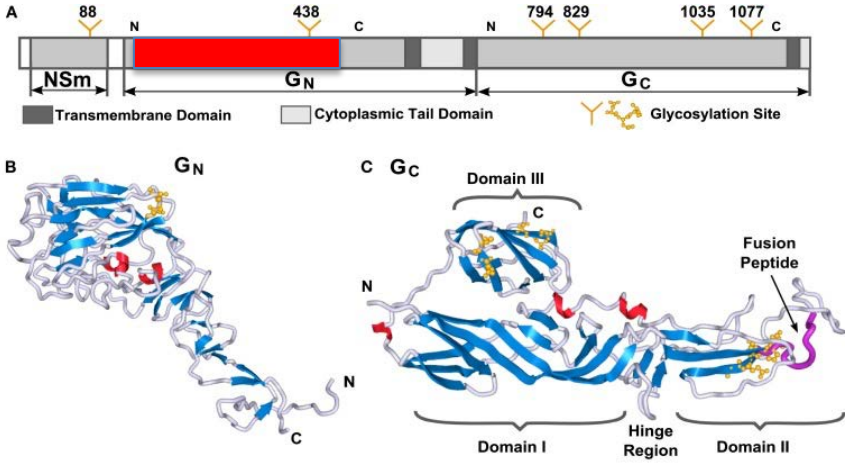
Objectives & Challenges for ZAPI Vaccines Strategy

- **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

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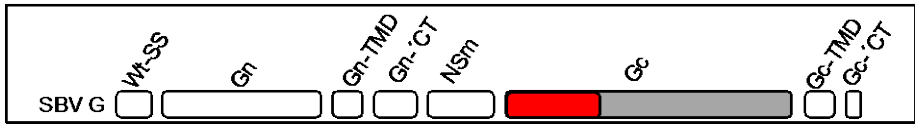
SBV

FLI



GcAmino

Identified domains:

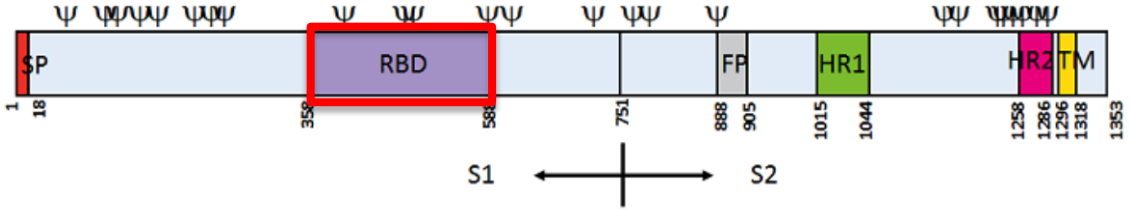
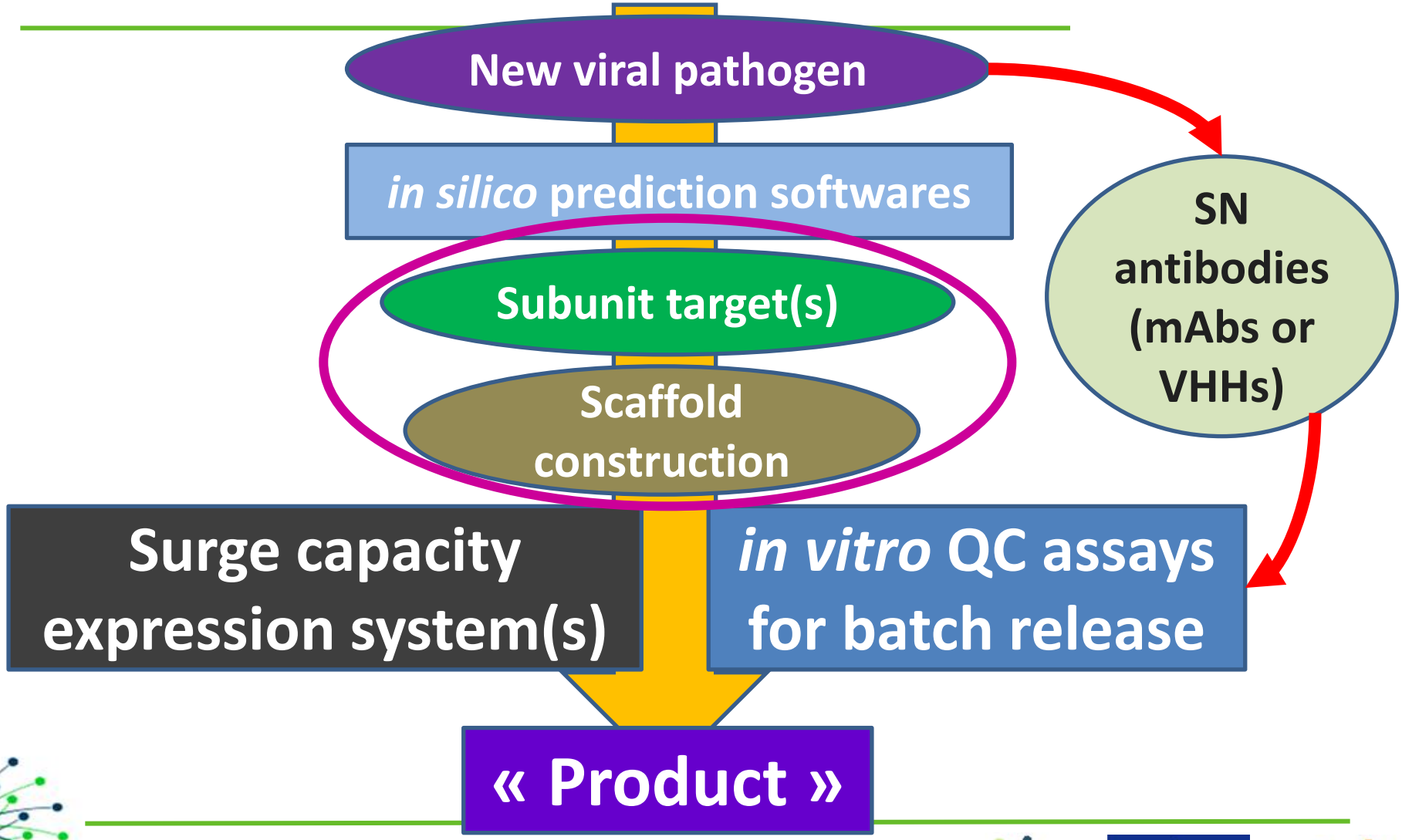


Figure 1. Schematic representation of MERS-CoV S protein. The signal peptide (SP), receptor binding domain (RBD), fusion peptide (FP), heptad repeat region (HR) and transmembrane domain (TM) are indicated. The RBD of MERS CoV has been mapped based on the predicted location and structure of the RBD of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

MERS-CoV

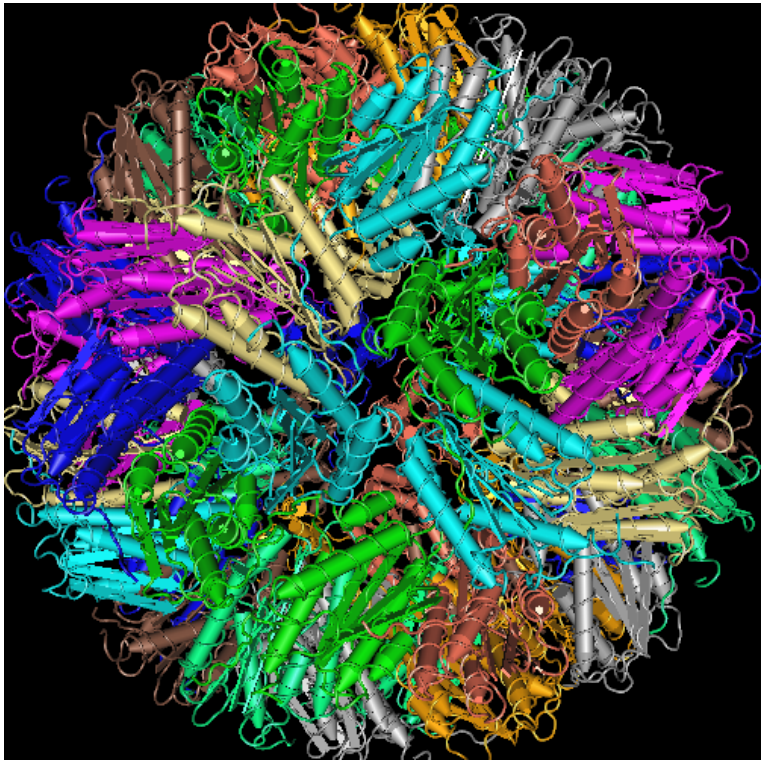
Utrecht University

ZAPI vaccine approach

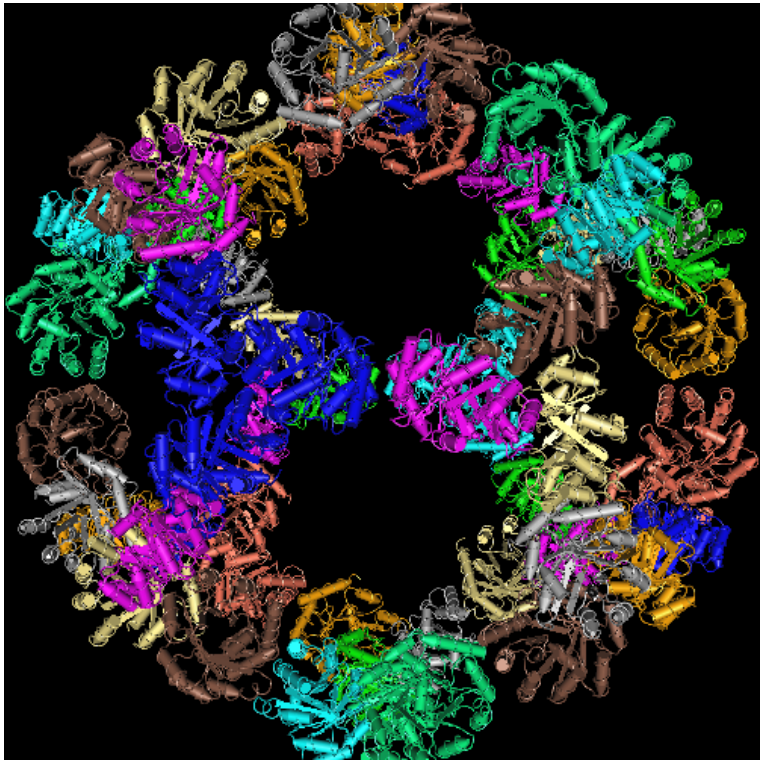


The growing world of multimeric protein scaffold particles (MPSP)

Lumazine Synthase
Aquifex aeolicus or Brucella spp



Aldolase I3-01
artificial protein

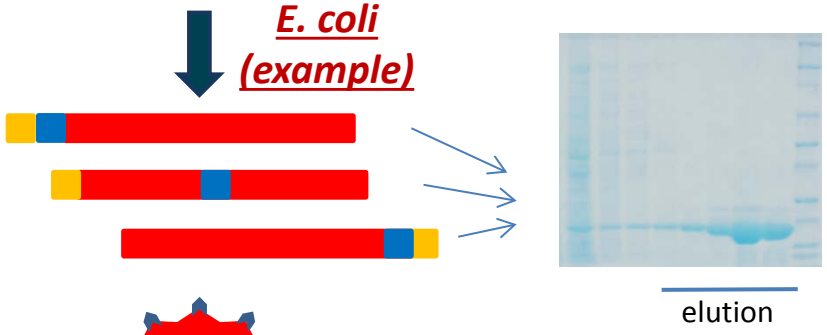


Entrez 3D Structure database

Modular scaffold system with bacterial superglue

Produce MPSP-SpyTag™ in most convenient system

E. coli (example)



MMPS

Protein-Scaffold Spy-Tag™

Produce antigen-SpyCatcher™ in most convenient expression system

Baculovirus Expression (example)

Antigen Spy-Catcher™

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

Covalent binding of Spy-Tag and Spy-Catcher

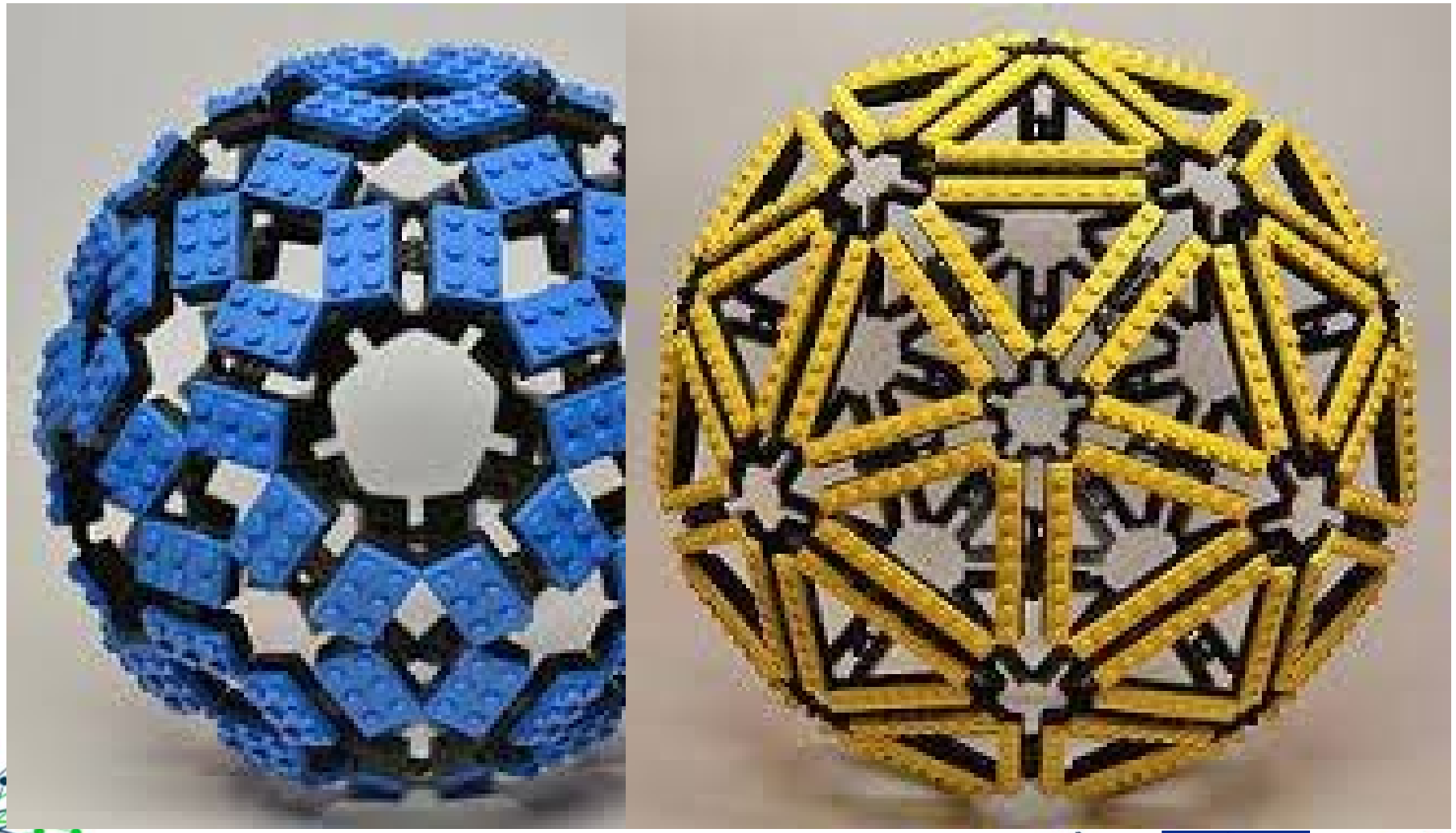
MMPS

Formulate vaccine by combining MPSP with antigen

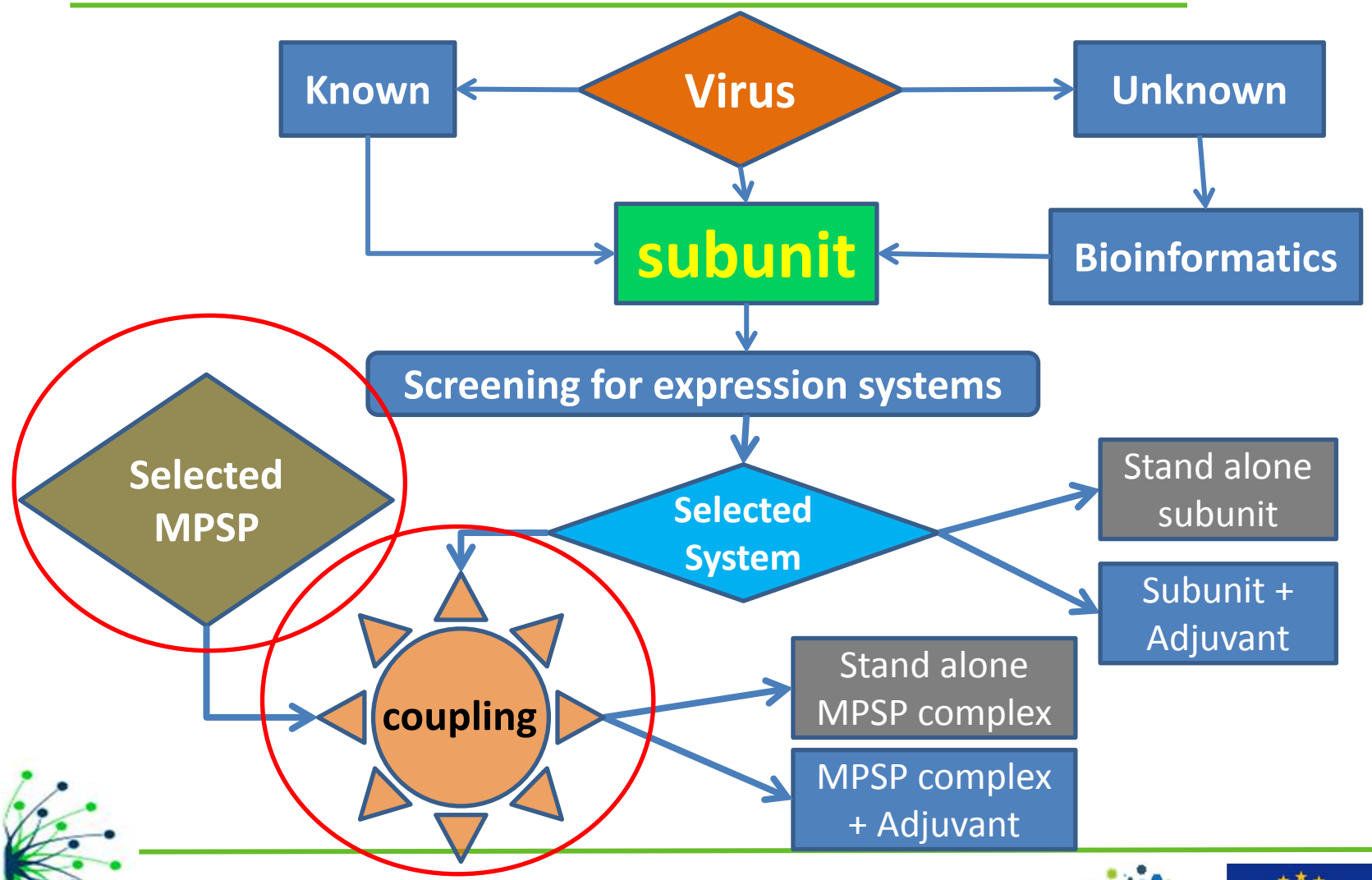
Flexible, high expression, multiple antigens possible

Zakeri B. *et al*. P.N.A.S. 2012. **109.** E690-697
Veggiani C., Zakeri B. Howarth M. Trends in Biotechnol.. 204. 32. 506-512

ZAPI as a « serious game » methodology



Decision Tree for "ZAPI Vaccines"



Coupling immunogens / MPSP to generate vaccine complexes

- 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

Regulatory aspects

- **Acceptability of new platforms under emergency situations**
  - **MPSP-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 ?**

- **<u>Impact of Nagoya Protocol (NP)</u> 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 ?**

Acknowledgements (vaccines)

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Zoonoses Anticipation and Preparedness Initiative

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