Zoonoses Anticipation and Preparedness Initiative

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

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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

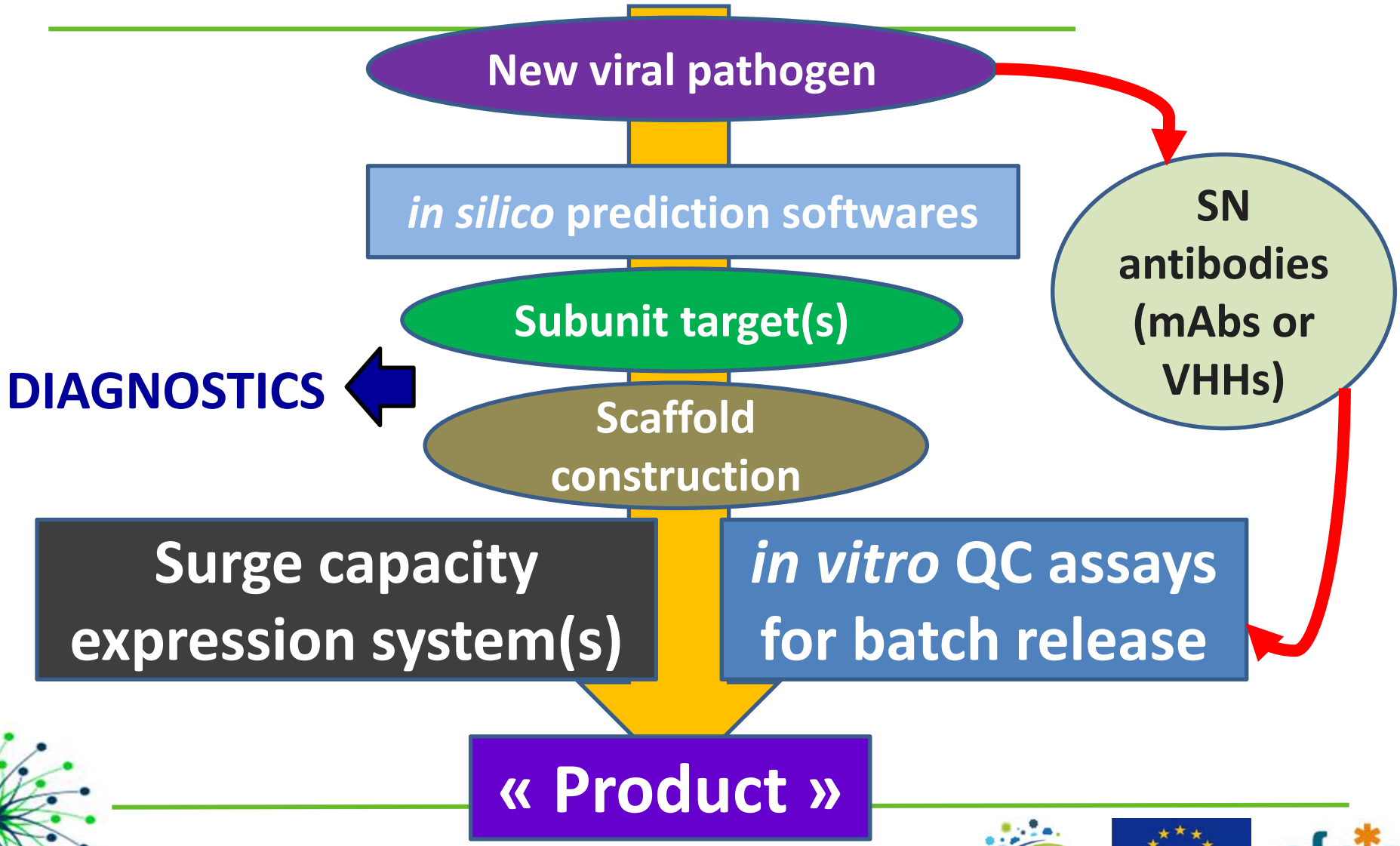
A key principle of preparedness is to do as much work as possible before an emergency happens, so that the response can be decisive and efficient. Several approaches would speed vaccine availability in future emergencies. For pathogens we have not yet encountered, there is a need for platform technologies 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-

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

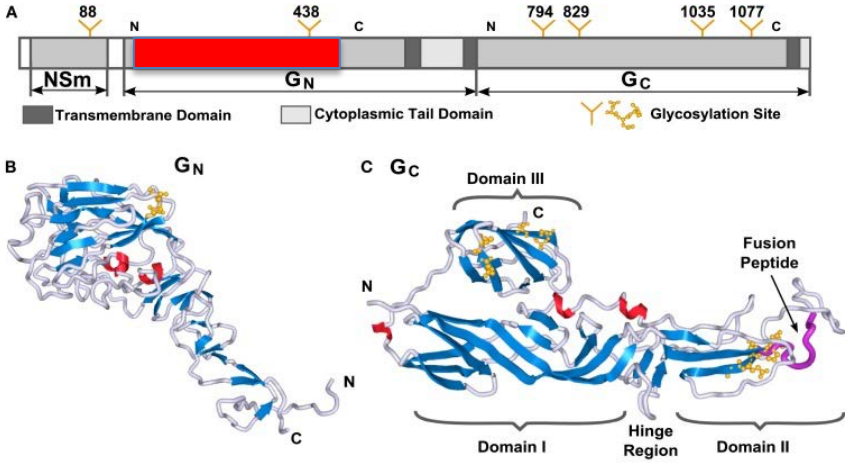
Objectives & Challenges for ZAPI Vaccines Strategy

- **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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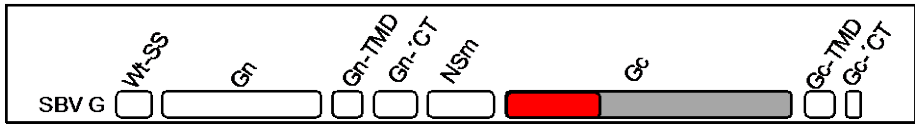
SBV

FLI



GcAmino

Identified domains:

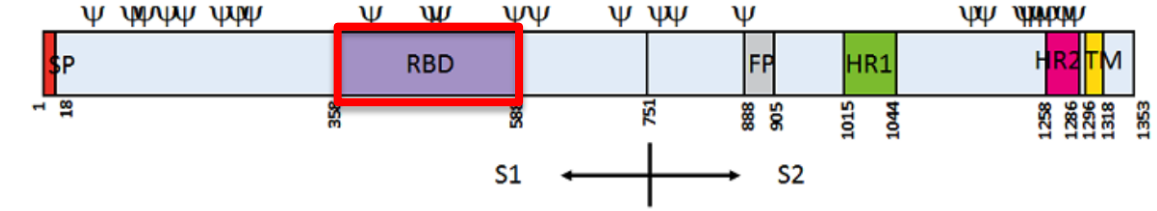
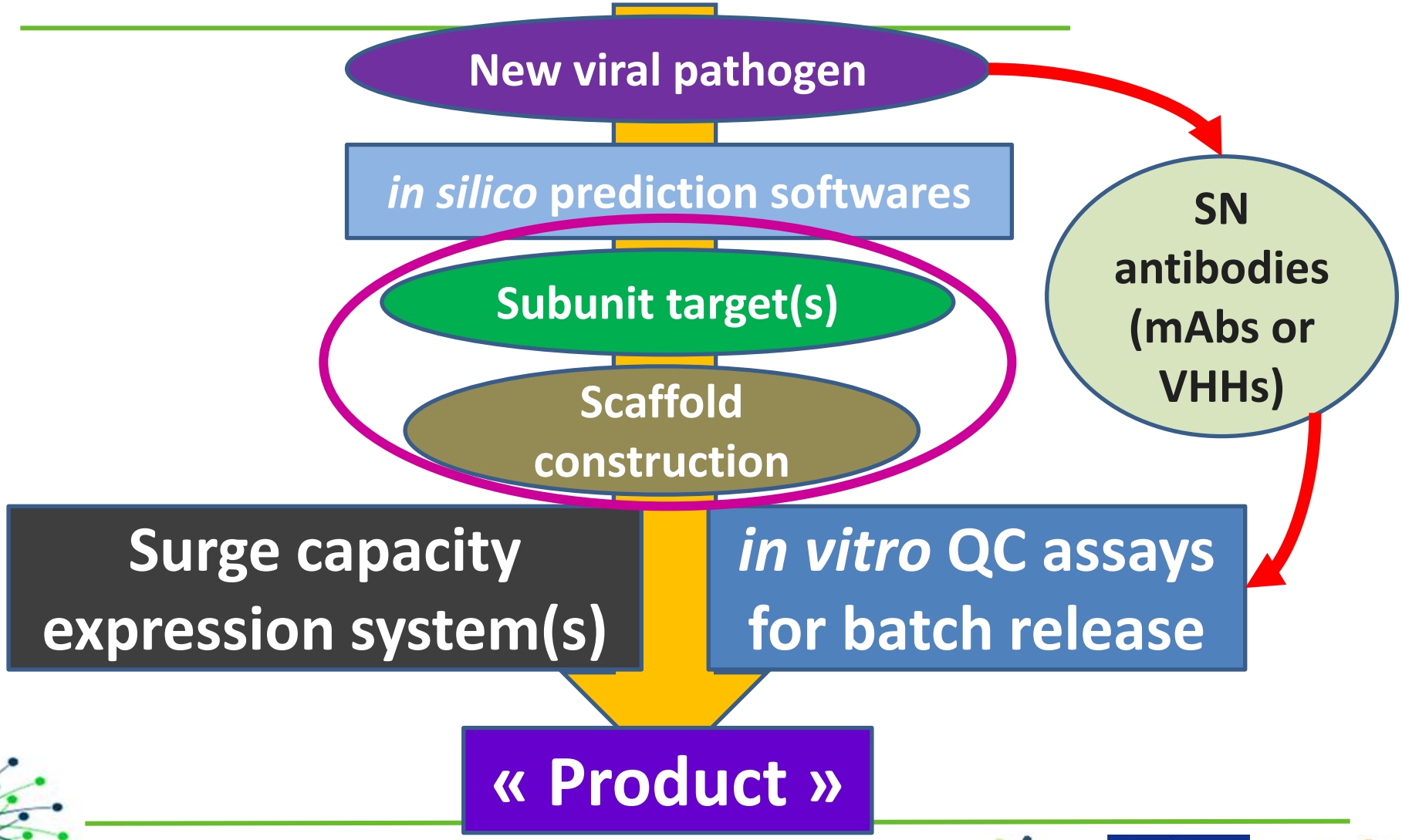


Figure 1. Schematic representation of MERS-CoV S protein. The signal peptide (SP), receptor binding domain (RBD), fusion peptide (FP), heptad repeat region (HR) and transmembrane domain (TM) are indicated. The RBD of MERS CoV has been mapped based on the predicted location and structure of the RBD of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

MERS-CoV

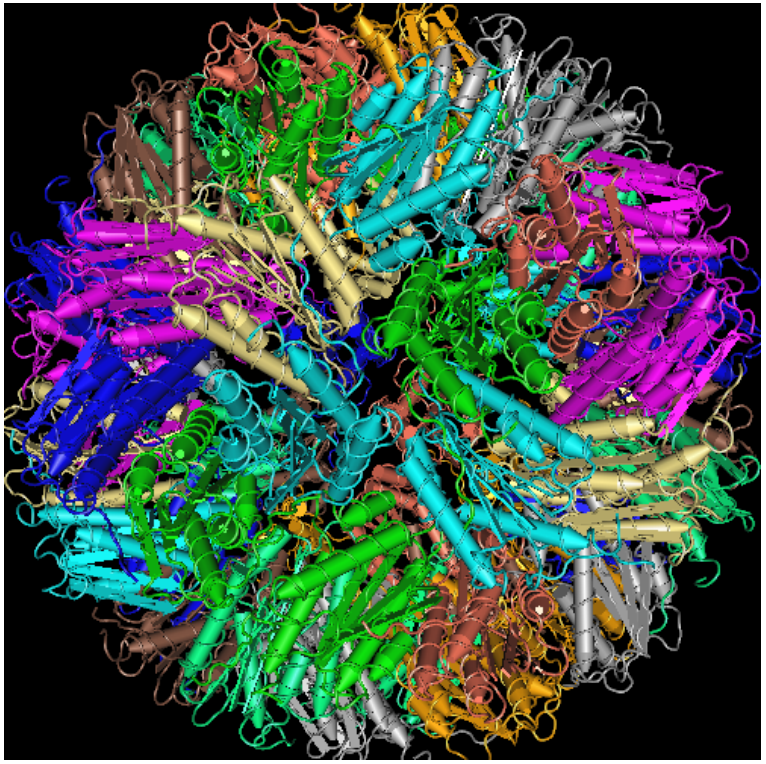
Utrecht University

ZAPI vaccine approach

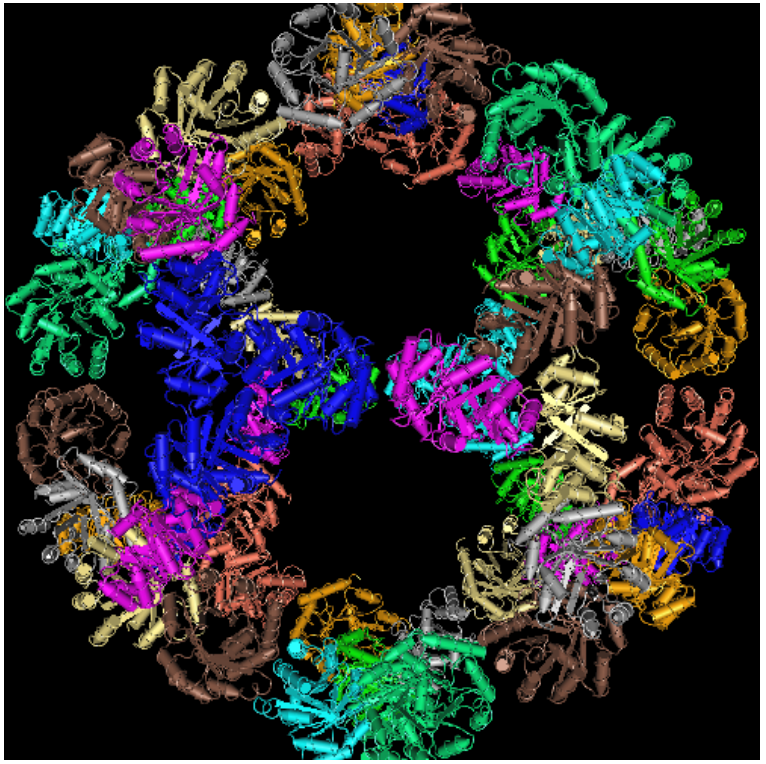


The growing world of multimeric protein scaffolds (MMPS)

Lumazine Synthase
Aquifex aeolicus or Brucella spp



Aldolase I3-01
artificial protein

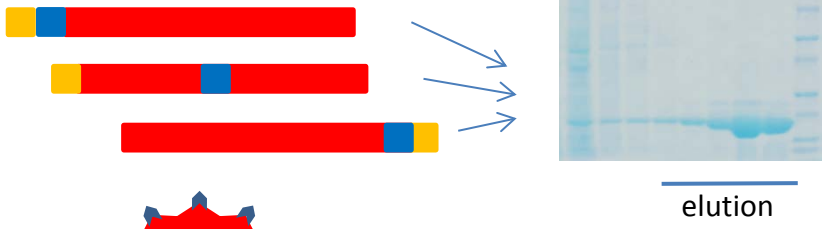


Entrez 3D Structure database

Modular scaffold system with bacterial superglue

Produce MMPS-SpyTag™ in most convenient system

E. coli (example)



elution

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

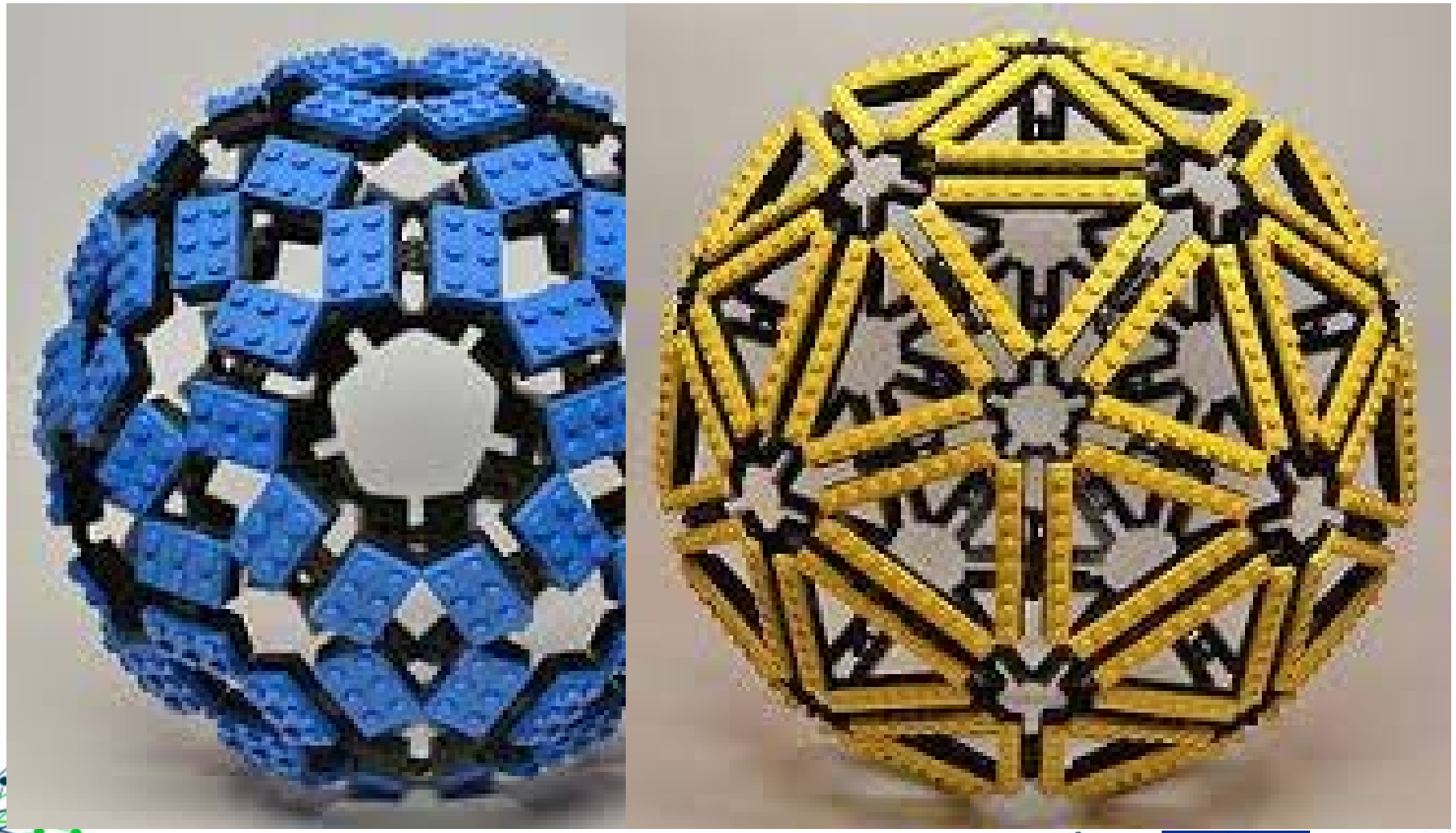
MMPS

Formulate vaccine by combining MMPS with antigen

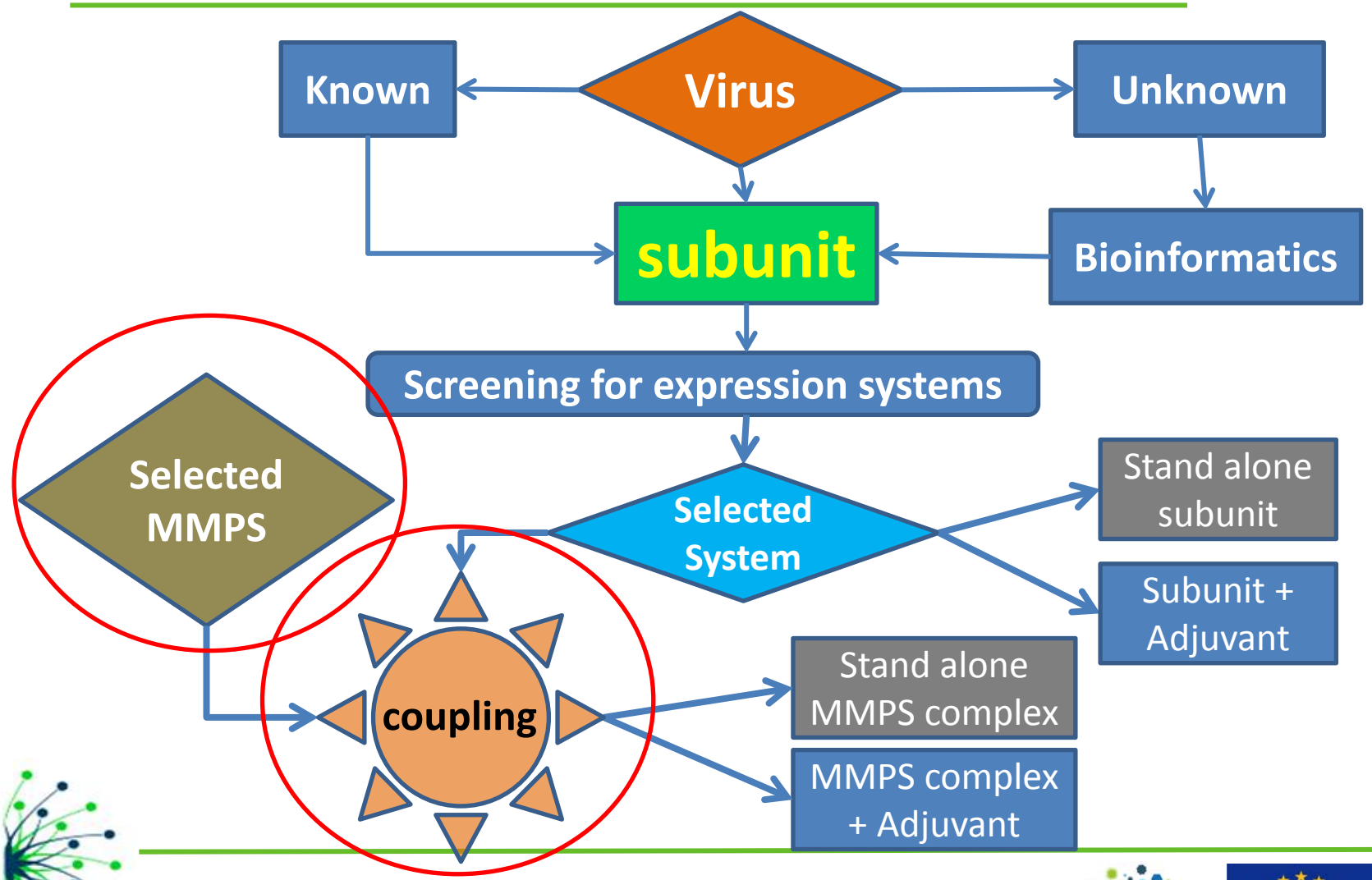
Flexible, high expression, multiple antigens possible

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

ZAPI as a « serious game » methodology



Decision Tree for "ZAPI Vaccines"



Coupling immunogens / MMPS 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**
  - **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 ?**

- **<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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