

Vaccine Europe position on the IPROVE Industry R&D priorities

Introduction

The Innovation Partnership for a Roadmap on Vaccines in Europe (IPROVE) collaboration has been tasked with preparing the first-ever strategic European roadmap outlining the science and technology investments required for vaccines innovation. The result of this collaboration, the IPROVE Roadmap, has recently been published¹. As described in a separate publication², this roadmap contains 82 recommendations focused around 7 challenges, each specified in main priorities.

The current communication focuses on the first challenge, vaccine R&D, for which five main priorities were identified (see P1-P5 in Table 1 below), and a total of 22 specific recommendations were made. Based on these recommendations, the European vaccines industry (which has, through Vaccines Europe, played an active part in the generation of the roadmap) subsequently conducted an internal prioritisation exercise, to select those that are most relevant for the vaccine industry, are of common interest, and require more investments in research and innovation in the coming years. As a result, 7 key recommendations (R1-R7) have been selected across the five priorities, as presented in Table 1.

Table 1. Selected R&D recommendations

Priorities in the R&D challenge	Selected key recommendations
P1 Support an integrated, multidisciplinary approach to antigen selection	R1 Explore emergent in-vitro bioassay technologies and improve in-vitro assays for antibody functional screening
	R2 Research for selection and analysis of epitopes
	R3 Support research on structural vaccinology
P2 Strengthen the science of vaccine adjuvants	R4 Create a toolbox of adjuvants with well-defined profiles to shape the immune response
P3 Sustain research on vectors and alternative routes of immunisation	R5 Better approach to a combined use of vectors, adjuvants, routes of immunisation
P4 Innovative design and harmonisation of clinical trials data & development of analyses frameworks	R6 Identify innovative designs of clinical trials and methodologies to profile volunteers in these trials at an earlier stage
P5 Continue to invest in biomarkers of safety in vaccines, and correlates of protection and of efficacy	R7 Develop expertise and support infrastructures to perform controlled challenges in humans.

Here, Vaccines Europe presents the proposed measures to implement the key recommendations. Two different approaches are envisaged. On the one hand, development or reinforcement of research networks and collaborations should be pursued, which could

¹ A strategic European roadmap for the vaccines of tomorrow: A joint stakeholder reflection (2016). Accessible at: <http://iprove-roadmap.eu/>; (accessed 12 March 2018).

² Medaglini, D., R. De Azero, M., Leroy, O., Bietrix, F., Denoel, P. (2018). Innovation Partnership for a Roadmap on Vaccines in Europe (IPROVE): A vision for the vaccines of tomorrow. *Vaccine*. 36 (9) p. 1136-1145. Accessible at: <https://linkinghub.elsevier.com/retrieve/pii/S0264410X17316808>; (accessed 21 February 2018).

help to gather key European scientists and the vaccines industry partners to increase the knowledge base, propose new approaches or share data for vaccines development. On the other hand, the vaccines community should encourage the funding of more targeted research, as well as the development and innovation projects involving vaccines manufacturers, small/medium-sized enterprises (SMEs), academic partners, and clinicians.

P1. Support an integrated, multidisciplinary approach to antigen selection

R1. Explore emergent in-vitro bioassay technologies and improve current in-vitro assays for antibody functional screening

We identified the need for a new generation of assays to be used in antigen discovery and as readouts in clinical trials, to allow better screening of human samples for both functional antibodies and T-cell functions relevant to protection from diseases. For example, we could envisage the development of high-throughput (HTP) automated antibody functional assays to evaluate bacterial killing capacity or inhibition of adhesion. Once identified, antibodies and target antigens should be better characterized to help identify protective epitopes and novel mechanisms of protection.

These efforts could be realized by stimulating research collaborations tasked with either:

- the development of new standards, technologies, as well as methods for assays that assess vaccine correlates of protection (e.g. robotics, HTP assays, systems serology, bacterial killing assays).
- the development of new read-outs for characterisation of antibody and T-cell functionalities.

R2. Research for selection and analysis of epitopes

At present, there is a lack of knowledge of structural relationships between natural immunity, vaccine-induced immunity as well as cross-reactivity, and especially further knowledge of the epitopes guiding this immunity is needed. Specifically, we need to focus on identifying **conserved epitopes**, particularly for highly variable pathogens (e.g. influenza virus, norovirus), and **epitopes linked to functional antibody or cellular activity**, to guide the design of improved vaccines or vaccines against new indications.

To support epitope selection and analysis, and to further our understanding of the mechanisms of disease, targeted research and innovation collaborations are required.

R3. Support research on structural vaccinology

Scientific advances have enabled a paradigm shift from an empirical approach to vaccine design based on 'isolate, inactivate and inject' to the more rational and systemic approach of 'sequence, select and synthesize'. A rational approach inherently depends on a better understanding of the pathogen, the immunology of key antigens and of the mechanistic aspects of host-pathogen interactions. New tools are needed to further our understanding of the structural relationships between natural immunity and vaccine-induced immunity/cross-reactivity, and to respond to the challenge of pathogen diversity and antigen variability. A promising innovative approach in this context is structural vaccinology, "a genome-based approach combined with structural biology, with the idea

that protective determinants can be used to selectively engineer the antigens that can be re-designed and simplified for inclusion in vaccine combinations”³.

Research efforts, to be conducted by partnerships between vaccine manufacturers and external partners, should focus on targeted diseases, in order to validate antigen candidates.

Specifically, these efforts should:

- Leverage epidemiology studies to conduct molecular epidemiology and biodiversity studies among pathogens collected in the field; and
- Exploit the expanding knowledge of human immunology and new immunoassay technology to identify biomarkers and novel mechanisms and correlates of protection
- Lead to development of new products helping the body to fight against a broad range of diseases by activating the immune system

P2: Strengthen the science of vaccine adjuvants

R4. Create a toolbox of adjuvants with well-defined profiles, in order to shape the immune response

To better potentiate or tailor the immune responses to a vaccine antigen, we need to promote the development of new adjuvants, improve adjuvant manufacturing and characterization, and further our understanding of their modes of action. Specifically, this requires us to:

- Investigate for some adjuvants the mechanisms of actions by which they enhance an immune response;
- Investigate the mechanisms underlying immunosenescence to allow the rational use of adjuvants in vaccines for elderly;
- Increase our clinical experience with adjuvants by increasing the number of clinical studies that deliver the early Proof of Concept in humans;
- Develop the European capacities to rapidly develop GMP manufacturing processes for clinical material (ie., fast pilot plant capability).

To accomplish this, the European bioinformatics expertise should be further developed and large “-omics” technology platforms in should be stimulated. Collectively, these efforts will improve our understanding of adjuvant mechanisms of actions, and initiate the creation of a European database.

P3. Sustain research on vectors and alternative routes of immunisation

R5. Improve the approach to a combined use of vectors, adjuvants, routes of immunisation

There is a need to improve our understanding of the mechanisms by which the (decline in) immune response is regulated, in order to develop or improve the current technology

³Quoted from: Cozzi, R., Scarselli, M. & Ferlenghi, I. Structural vaccinology: a three-dimensional view for vaccine development. *Curr. Top. Med Chem.* 13, 2629-2637 (2013).

platforms, vaccines and vaccination programs **for every age-group**. Furthermore, there is a lack of evidence-based research of the opportunities to **combine technologies and approaches** improving vaccine efficacy including i, vectors and other antigen delivery systems (nanoparticles, nucleic acids); ii, adjuvants; and iii, routes and schedules of immunisation.

Europe's vaccine industry identified three types of actions to fill these knowledge gaps:

- Develop the European bio-informatics expertise and large platform technologies in “-omics” to help characterise and understand the interactions, modes of action of adjuvants, and associated immunobiological aspects.
- Initiate research collaboration(s) to compile data from adjuvanted vaccine (pre)clinical studies from all industrial stakeholders in a mineable dataset, in order to further our understanding of adjuvant efficacy and safety.
- Initiate targeted research projects, e.g. development of oral immunisation routes for some diseases, intranasal delivery for respiratory vaccines, alternative routes of needle-free immunisation (mucosal, oral, intranasal), and prime-boost strategies (DNA, vectors, peptides, proteins) in order to improve both safety and efficacy of future vaccines, etc.

P4. Innovative design and harmonisation of clinical trials data and development of analyses frameworks

R6. Identify innovative design of clinical trials and methodologies to profile volunteers earlier on in the process

To improve clinical trials and reduce the number of enrolled trial subjects, we need to:

- Define settings, conditions and regulatory frameworks for adaptive clinical trial design, coping with the differences in the standards of care between countries;
- Set up effective and widely accepted criteria and tests, with the aim to down-select the number of subjects to be enrolled (e.g. in nosocomial disease settings such as for *Pseudomonas* and *S. aureus*);
- Identify innovative endpoints for therapeutic vaccines (e.g. HSV);
- Set up registration trials for vaccines targeting low-incidence diseases (e.g. Guillain-Barré syndrome, MenB).

This requires the funding and implementation of trans-disciplinary research collaboration(s) with industry and specialised, non-infectious disease biotech companies, with the aim to:

- develop the methodologies and platforms to screen and select subjects;
- better understand disease in humans (through translational research) with well-defined biomarkers of disease susceptibility and/or progression;
- better understand the impact of the genetic makeup of subjects on their susceptibility to infectious disease.

R7. Develop expertise and support infrastructures to perform controlled challenges in humans (vaccines safety, correlates of protection and safety)

To date, the vaccines industry is facing a lack of success on human challenge studies. Furthermore, the vaccines community did not reach a consensus on documents on either the proposed conduct of human challenge trials, or on pathogen characterisation. There is an immediate need to develop (1) innovative designs for trial delivering proof of efficacy for licensing; (2) new predictive *in silico* tests or animal models, in order to study vaccine efficacy in humans; and (3) a new regulatory infrastructure in Europe with experts to conduct human challenge trials.

To accomplish this, there is a need to prioritize three immediate actions, which should be supported by public funding in Europe, which should aim to:

- Set-up a European platform composed of the vaccine industry, public health institutes, regulators, and research and clinical centres. This platform will be tasked with coordination of the research efforts, and the exchange of information and practices between the stakeholders.
- Finance research collaboration(s) to develop expertise and infrastructures, in order to conduct controlled infection challenge studies in humans focusing on a variety of non-chronic infectious diseases for which vaccine development is technically possible, e.g. Shigella, enterotoxigenic *Escherichia coli* (ETEC), Rhinovirus, Dengue virus, respiratory syncytial virus (RSV) infections.
- Finance targeted research efforts to run retrospective studies into correlates of protection and antibody functionality using marketed vaccines.

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