

CMC Strategies to achieve saRNA transition from Discovery through to Clinic

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Ziphius



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Ziphius



Founded in 2019 with the mission to **develop self-amplifying RNA-based vaccines and/or medicines** for

- Prevention of a broad range of **infectious diseases**
- Treatment of **rare genetic disorders**

+45 employees



Ziphilus Mission



Infectious Diseases

Reduce the global impact of **infectious diseases** by development of transformational **prophylactic and therapeutic vaccines**



Protein Supplementation

Offer highly effective **protein supplementation therapy**



IP & Platform

All this, by leveraging the unique features of our **proprietary platforms (saRNA & LNP library)**



Potential advantages of saRNA

	mRNA	saRNA	
	STANDARD	OUR PRODUCT	
 in vivo expression of GOI in transfected cells	Short expression	Long expression	saRNA library offers several options for the desired antigen expression profile (peak value and duration) → potential for protein supplementation therapy (e.g. Cystic Fibrosis)
 (minimal) Effective dose needed	30µg ¹	5µg ¹	Lower dose needed for equivalent efficacy Increased capacity, lower COGS, Improved safety profile
 Humoral immune response	Fast decay of antibodies	Better persistence of antibodies	Less boosters needed
 Anticipated CD4 / CD8 response	Moderate Low	High High	CD8 offers the potential for therapeutic applications in ID and Oncology

saRNA library offers several options for the desired antigen expression profile (peak value and duration)
→ potential for protein supplementation therapy (e.g. Cystic Fibrosis)

Lower dose needed for equivalent efficacy
Increased capacity, lower COGS, Improved safety profile

Less boosters needed

CD8 offers the potential for therapeutic applications in ID and Oncology

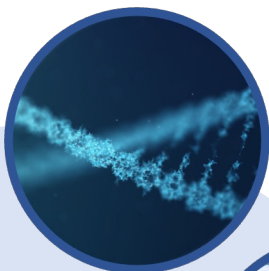
¹Oda, Y., Kumagai, Y., Kanai, M., Iwama, Y., Okura, I., Minamida, T., Yagi, Y., Kurosawa, T., Greener, B., Zhang, Y., & Walson, J. L. (2023). Booster dose of self-amplifying SARS-CoV-2 RNA vaccine vs. mRNA vaccine: a phase 3 comparison of ARCT-154 with Comirnaty. *medRxiv*, 2023.07.13.23292597. <https://doi.org/10.1101/2023.07.13.23292597>





What makes Ziphilus unique ?

Ziphilus



Strong believers in the advantages of saRNA over mRNA, as recognized in the scientific community¹.



Recognize the challenge of innate responses in order to transform saRNA advantages into safe and efficient medicines



Aiming for best-in-class medicines by considering specific design of the saRNA, new LNPs and improved formulation

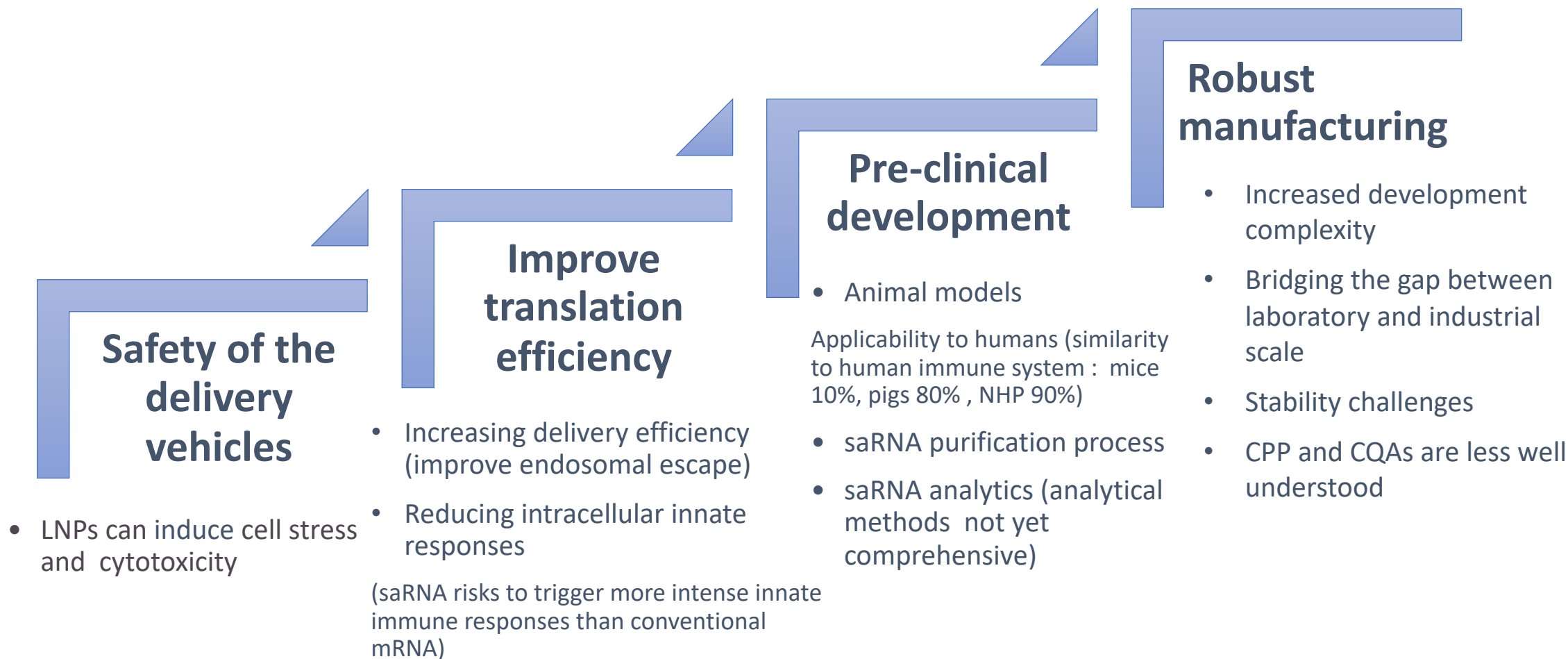


Vision driven by results (*in vivo* & *in vitro*)

¹Current Topics in Microbiology and Immunology
ISBN 978-3-031-18069-9 ISBN 978-3-031-18070-5 (eBook)
<https://doi.org/10.1007/978-3-031-18070-5>



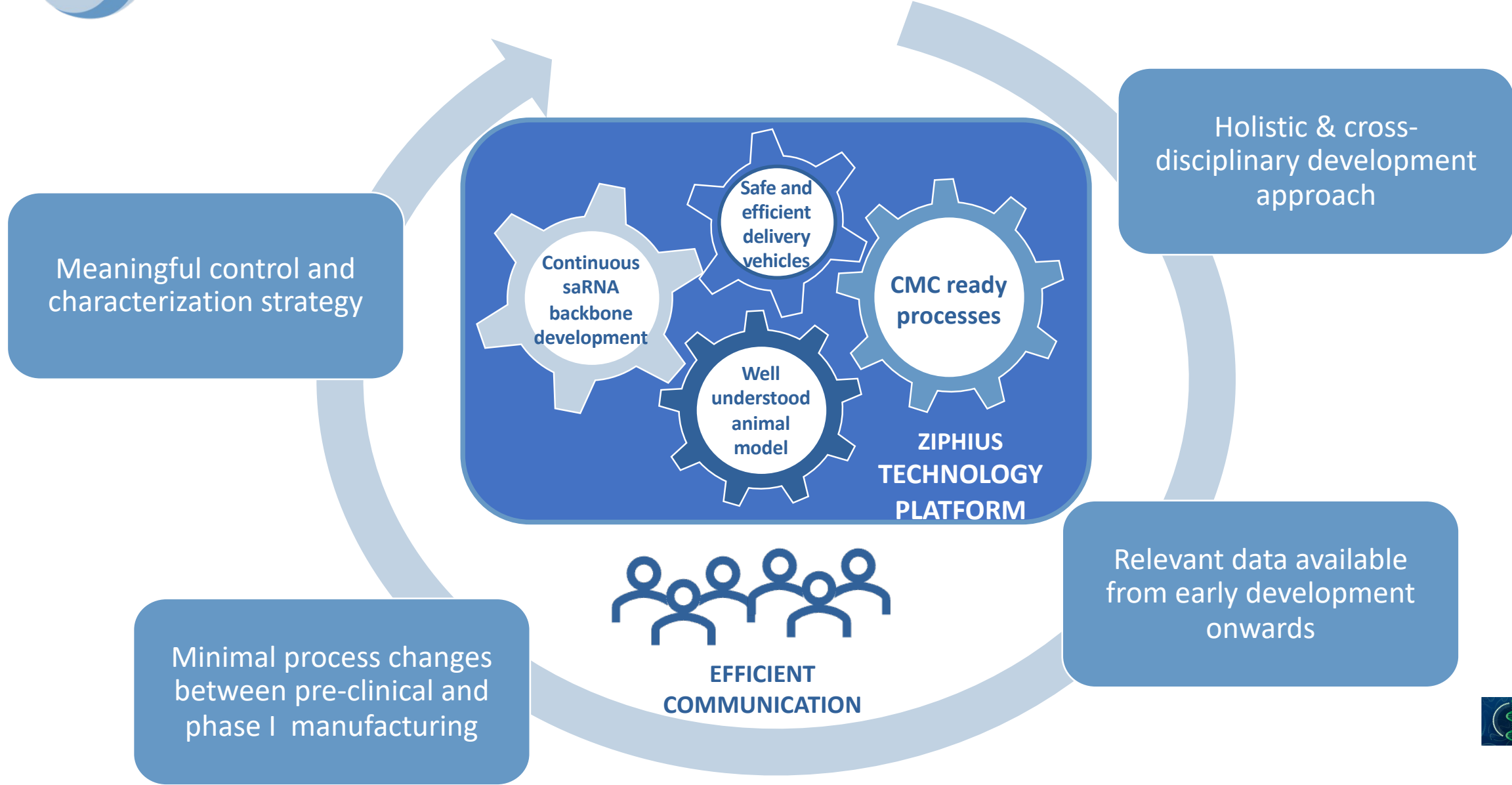
Technical challenges still to be addressed*



**some of these specific for saRNA – other for all mRNA -based approaches*



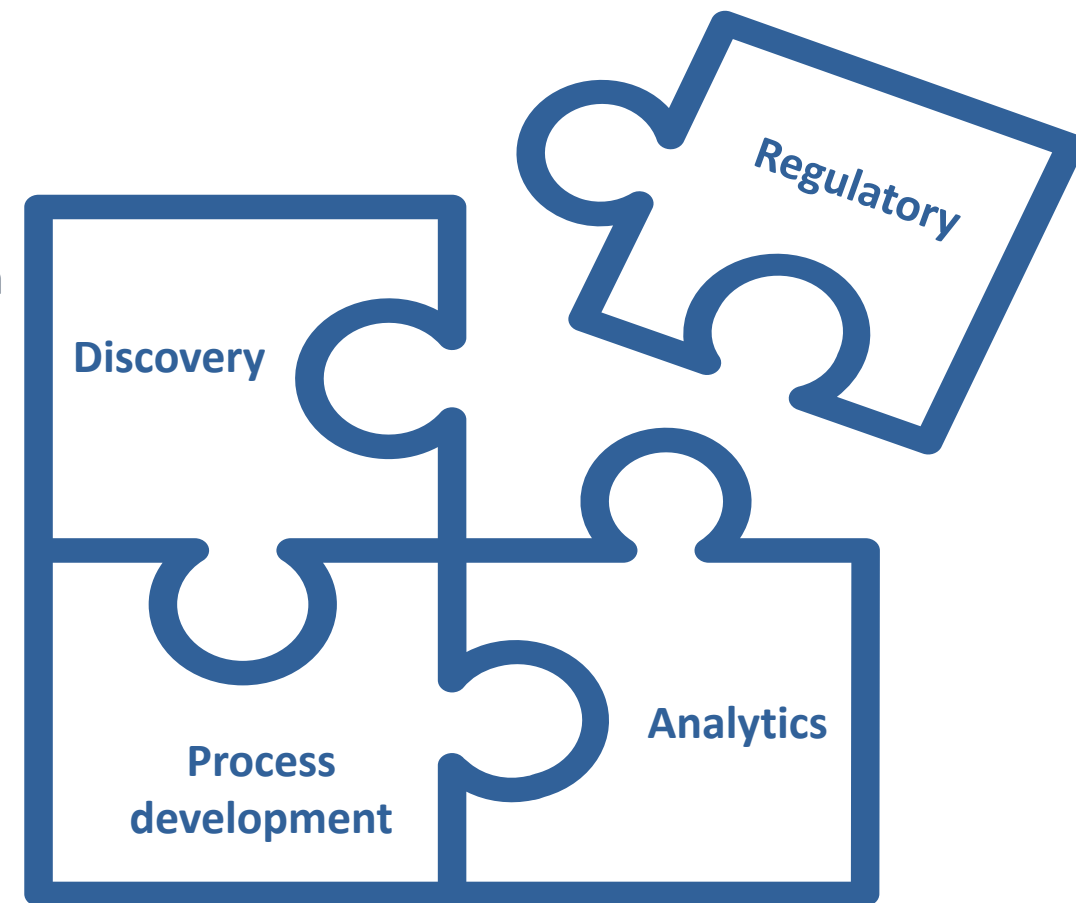
Ziphilus approach for a fast transition to clinic





ONE Ziphilus team

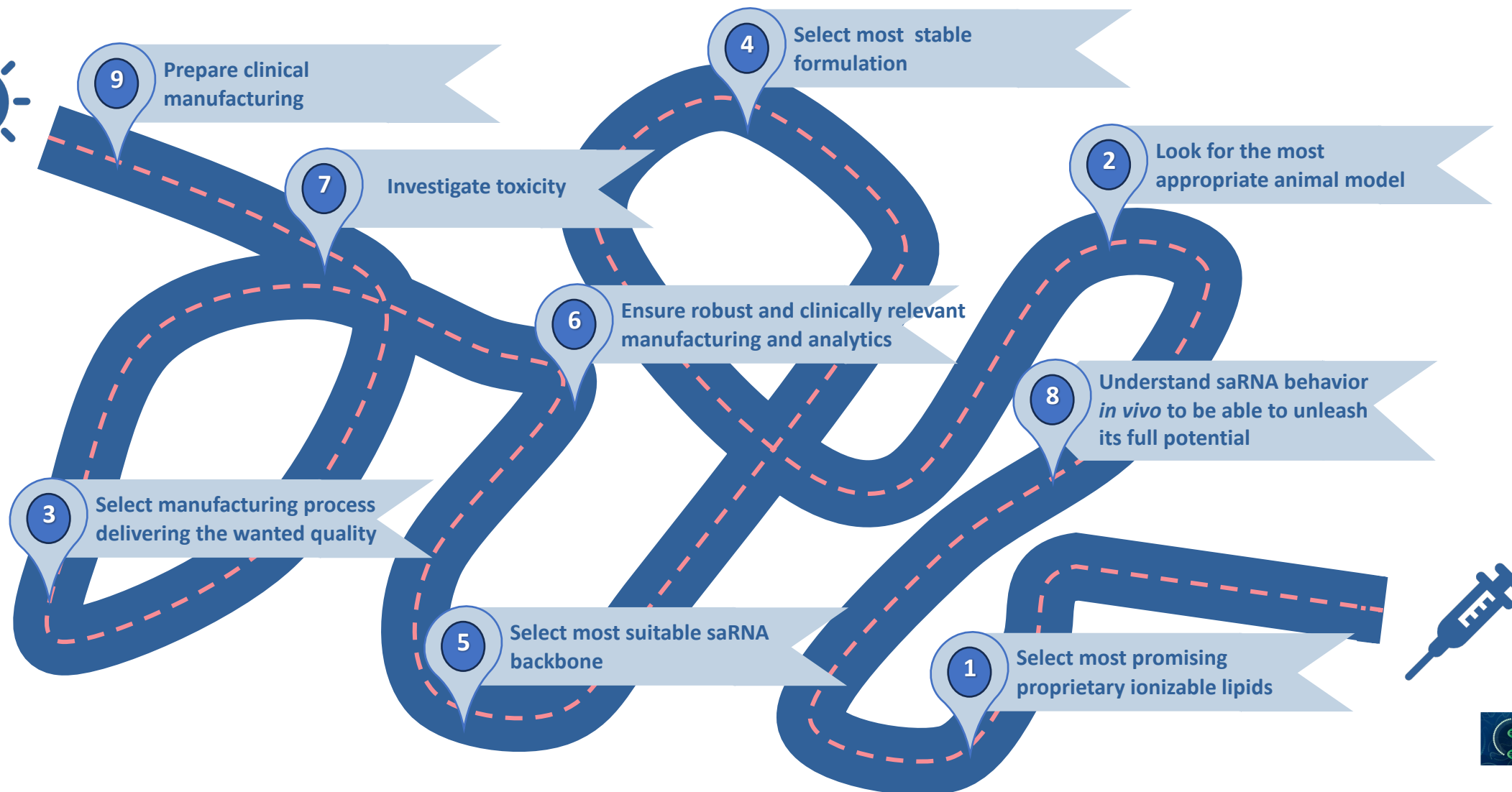
- Clear vision → focus and strategy
- Dialogue between Discovery and CMC is initiated from start of a project → agility and flexibility
- Constantly learning from each other:
 - *in vivo* results feed-back
 - IVT resulting in higher purity and efficiency
 - saRNA purification process GMP ready
 - Improved analytical methods to understand purity and integrity of the saRNA (HPLC)
 - Looking into extended characterization of saRNA and LNPs
- Integrate fast the lessons learned along the way



ONE organic team able to react and adapt fast

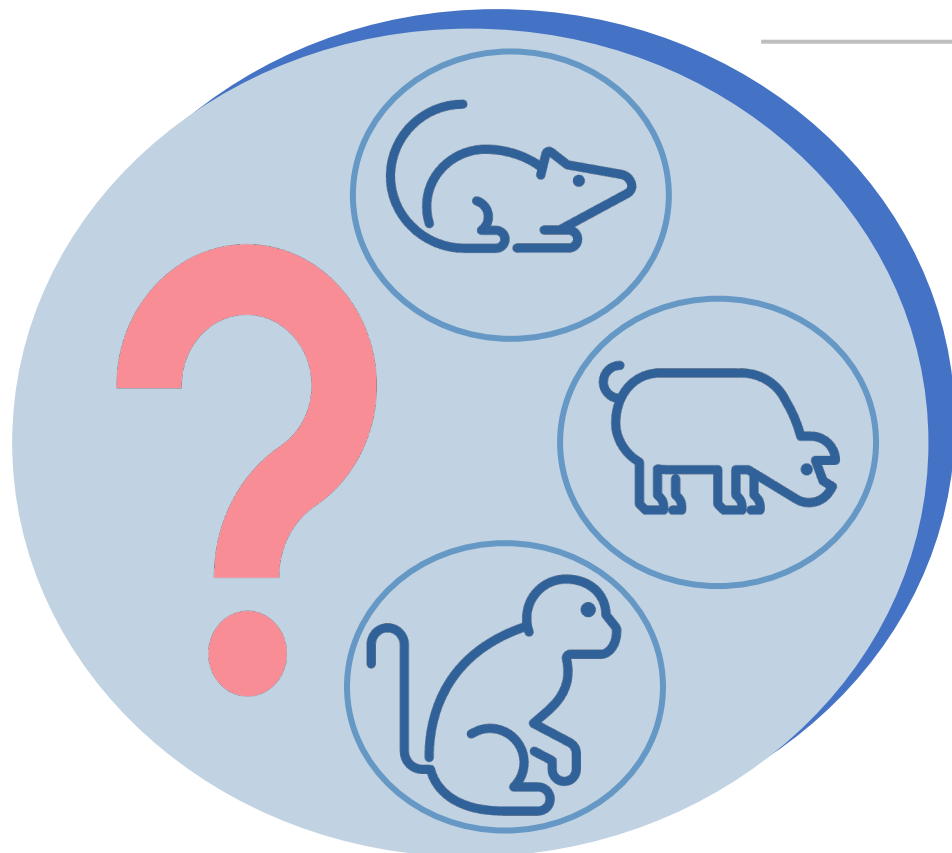


Our roadmap to clinic





Evaluate the most appropriate animal model for vaccination studies



Ethical considerations

Accurate prediction of vaccine immunogenicity, toxicity and safety in humans ?

Relevant data to elucidate pathogenesis and anti-infectious approach?

Anatomical, genetic and physiological similarity to humans?

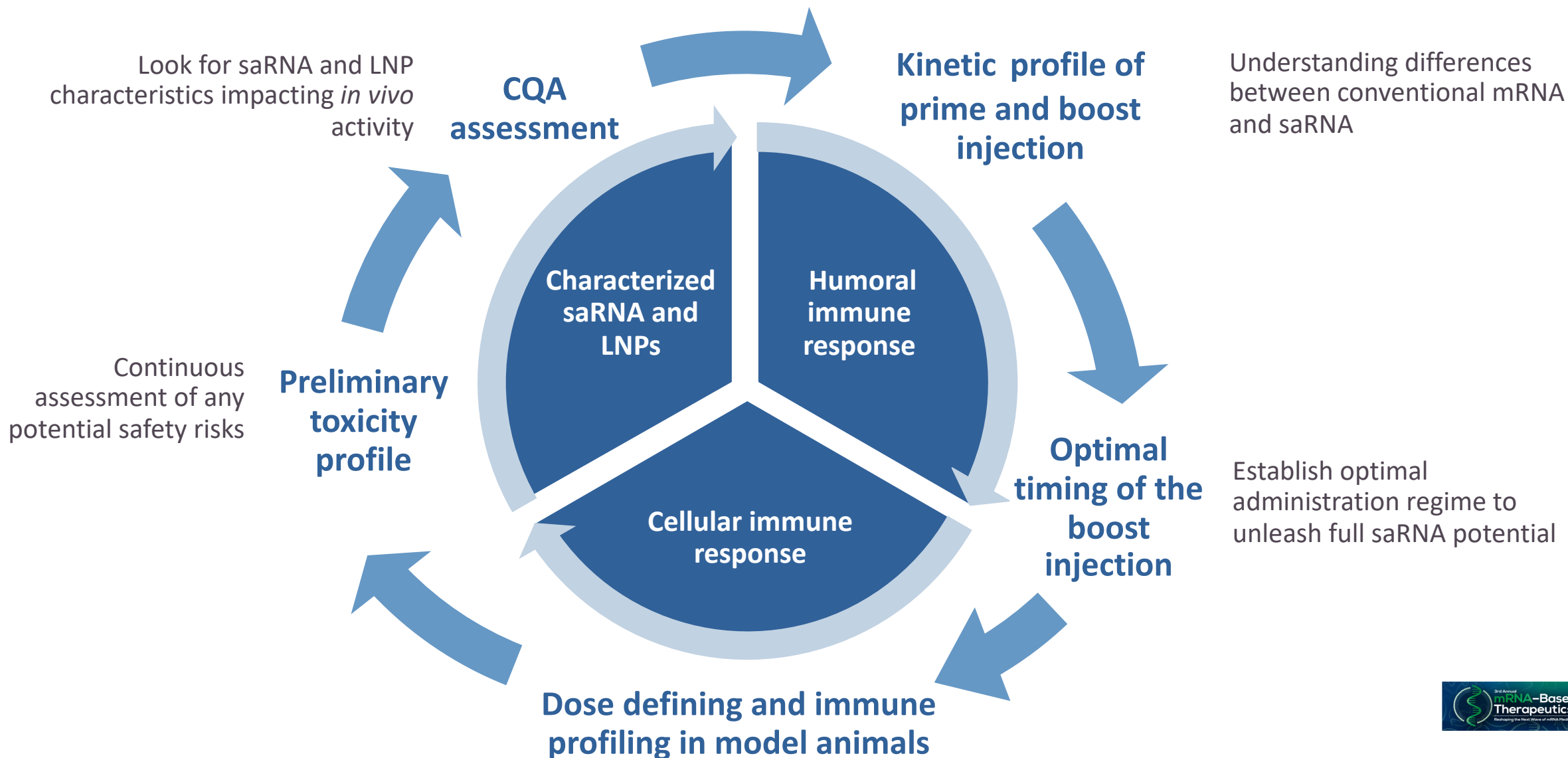
Model similarity relative to human immunological and inflammatory response to infection - is 20% difference close enough?

All models are wrong,
but some are useful.

George Box, British statistician (1919 – 2013)

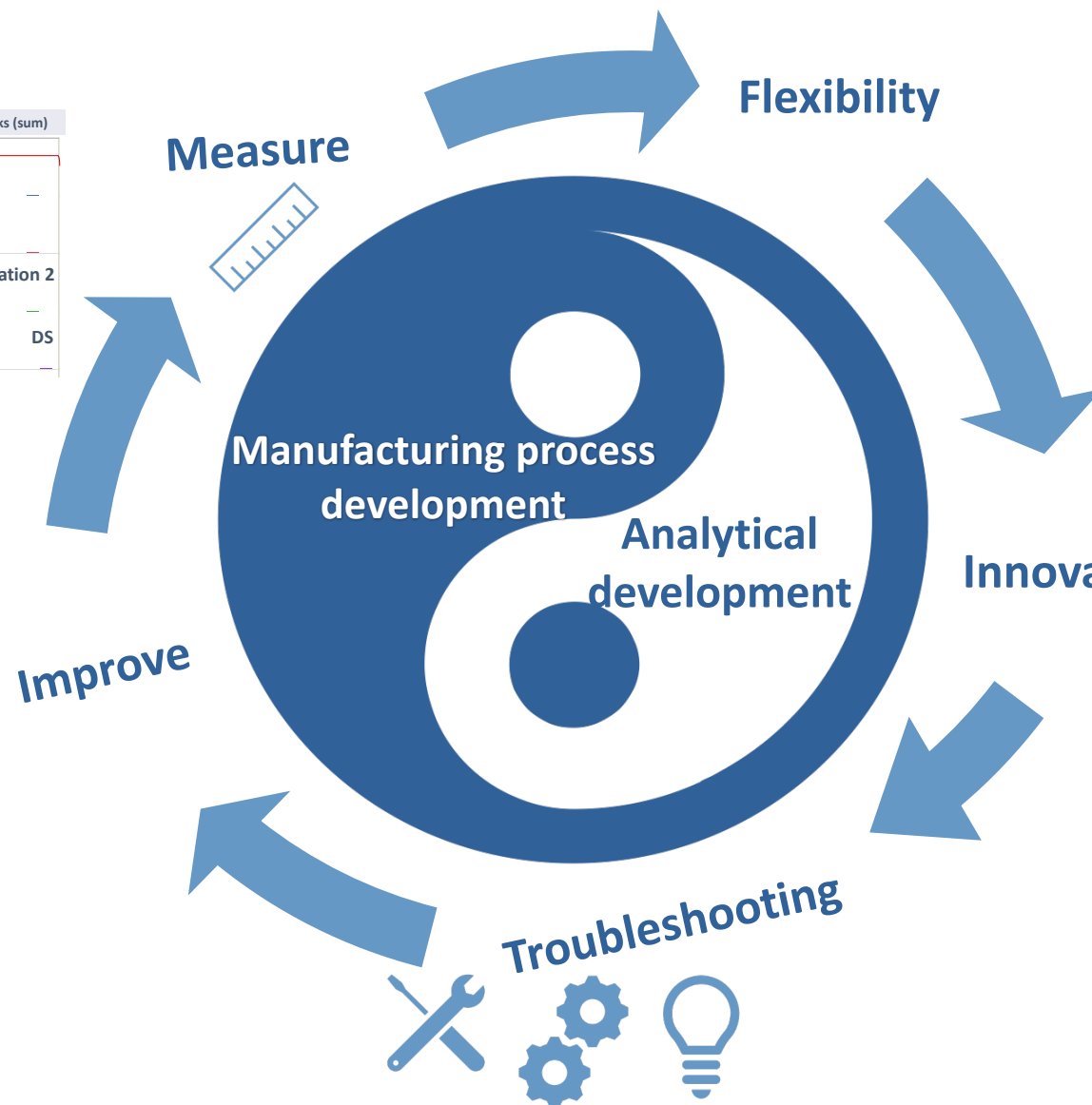
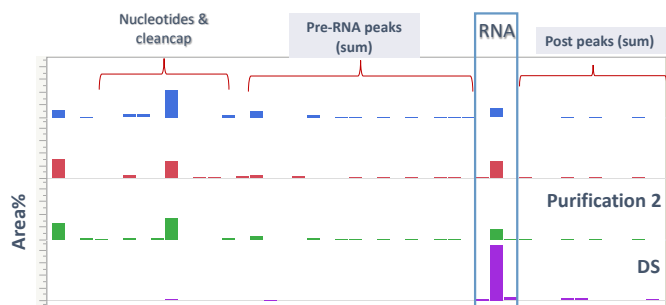


Understand saRNA behavior *in vivo*





Platform development - process development



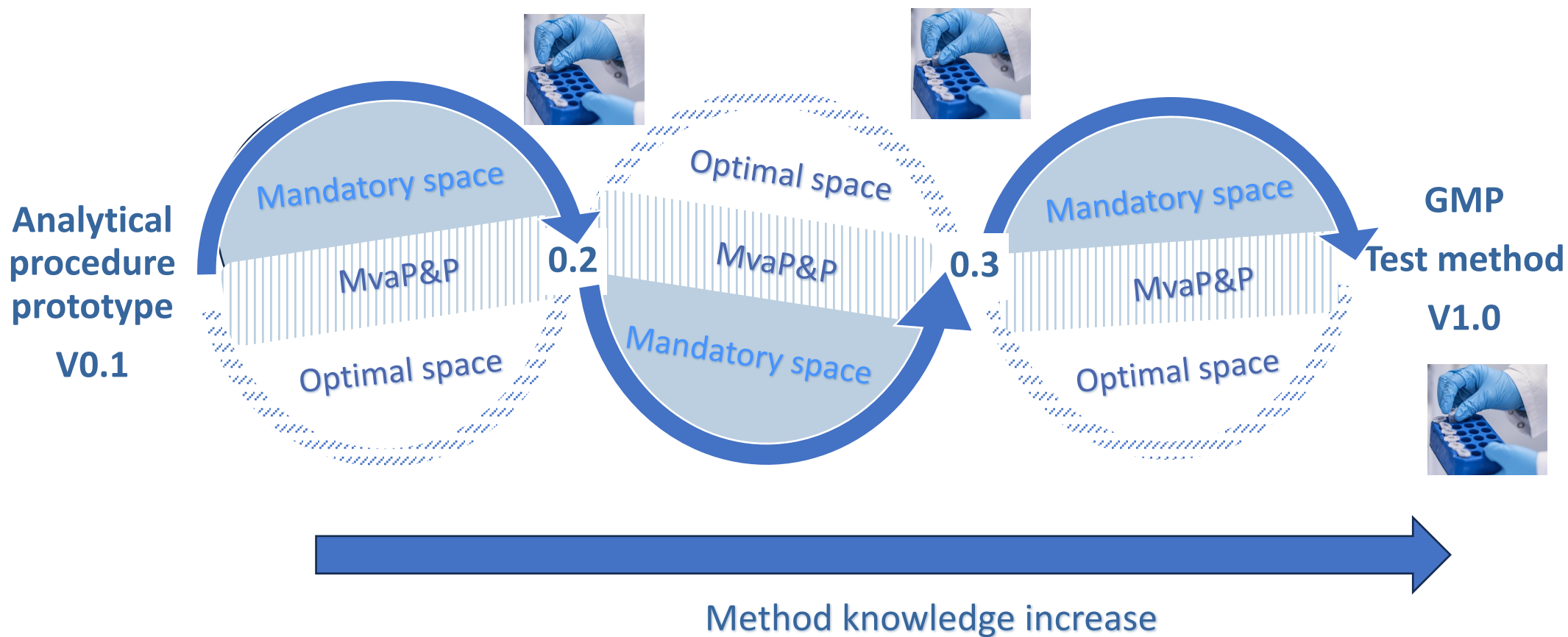
- New constructs
- Different sample matrixes
- Smaller sample volumes
- Higher material requirements

- Evaluate need for new analytical technique
- Adjust process based on results

- Unconventional approaches
- Combining techniques



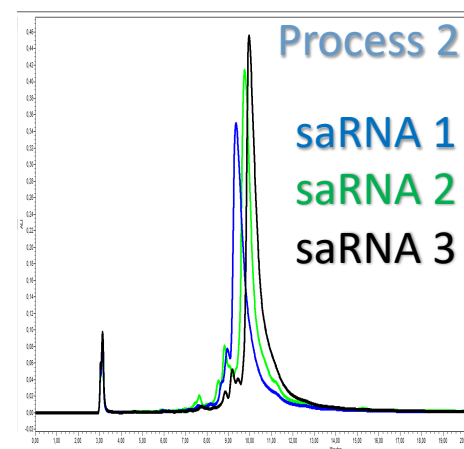
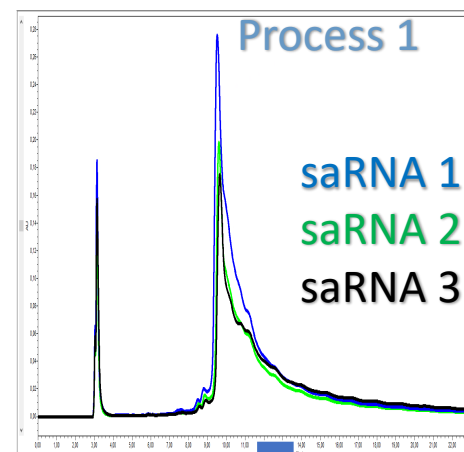
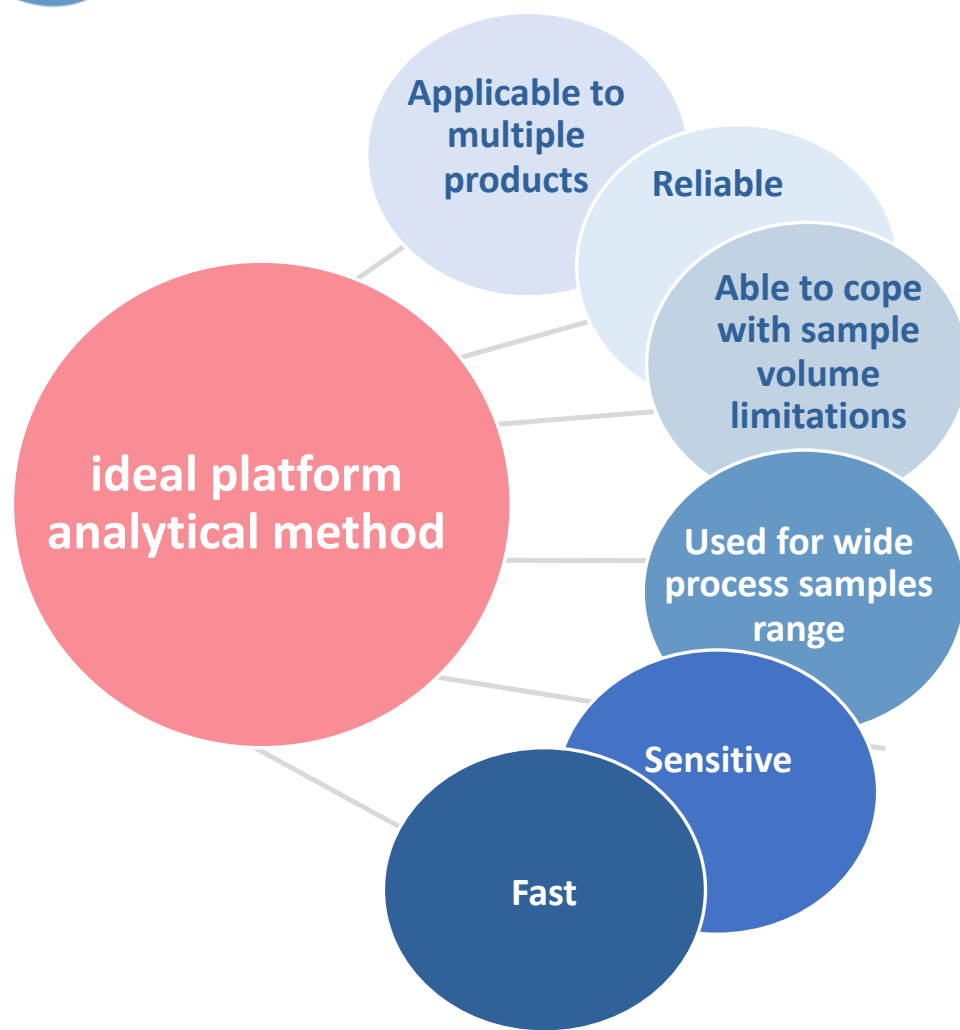
Using analytical development loops



MvaP&P = minimal valuable product and process
Sanders M, Mainil R, Chahim W, Introducing a New Concept for Value-Driven Acceleration in Biopharma Development. *BioPharm International*. 2022; 35 (10): 34-41.



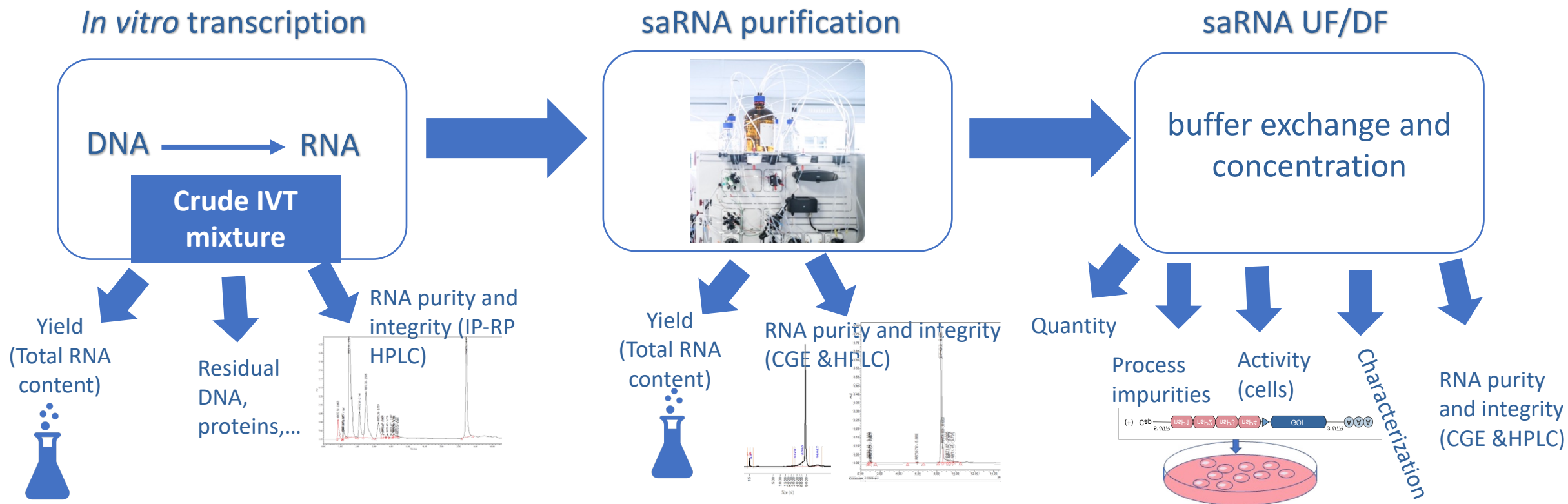
Platform development – analytical development



- Methods are continuously evaluated and optimized as the development progresses
- Sometimes complementary/unconventional approaches to capture subtle impact of process changes
- Development stage appropriate method verification
- Standard workflows for fast transition between projects



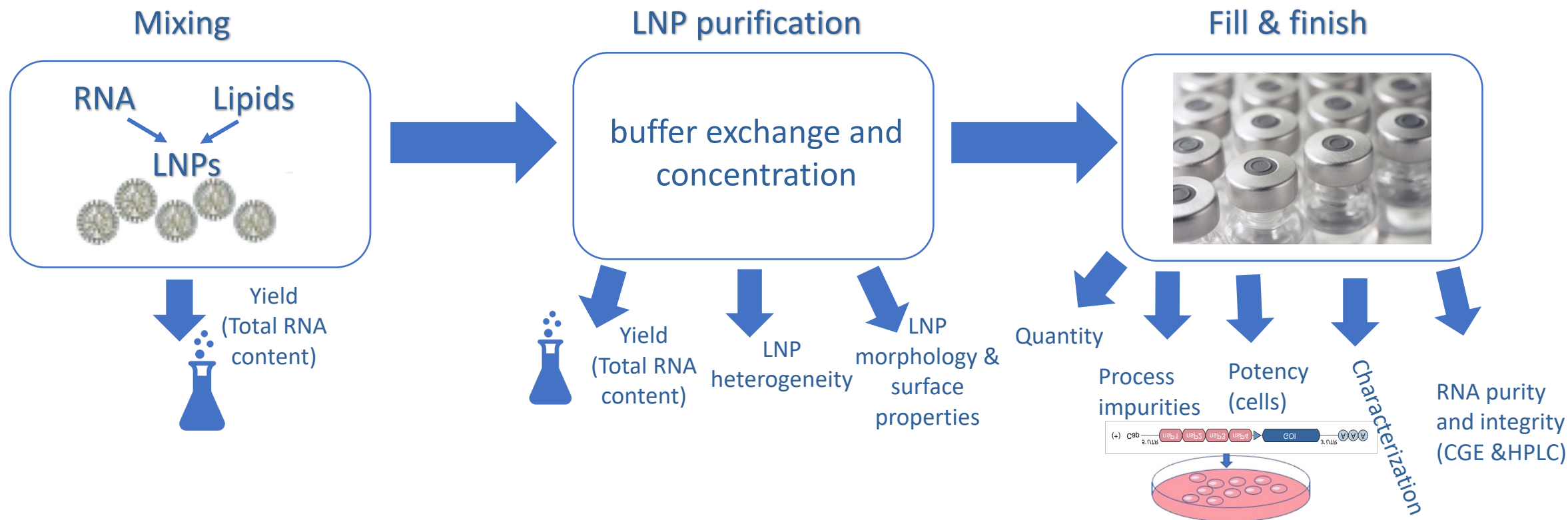
Platform development – saRNA manufacturing



- Driving principles: GMP ready & scalable
- Understanding platform performance -> characterization data at platform level
- Standard workflows for fast transition between constructs



Platform development – LNP formulation

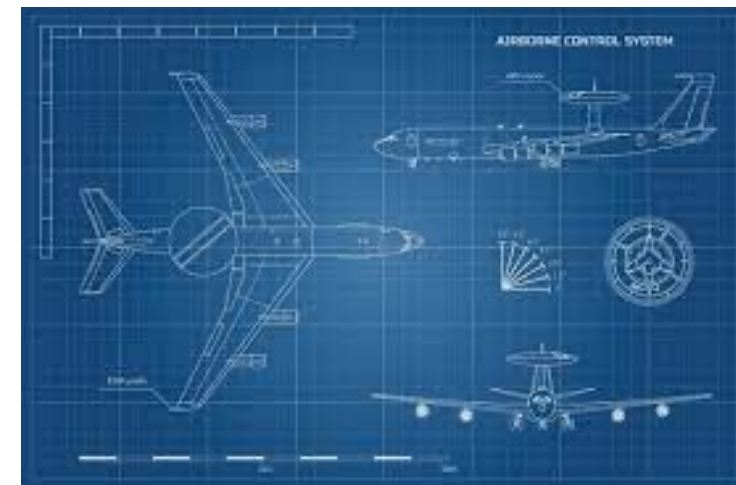


- Driving principles: GMP ready & scalable
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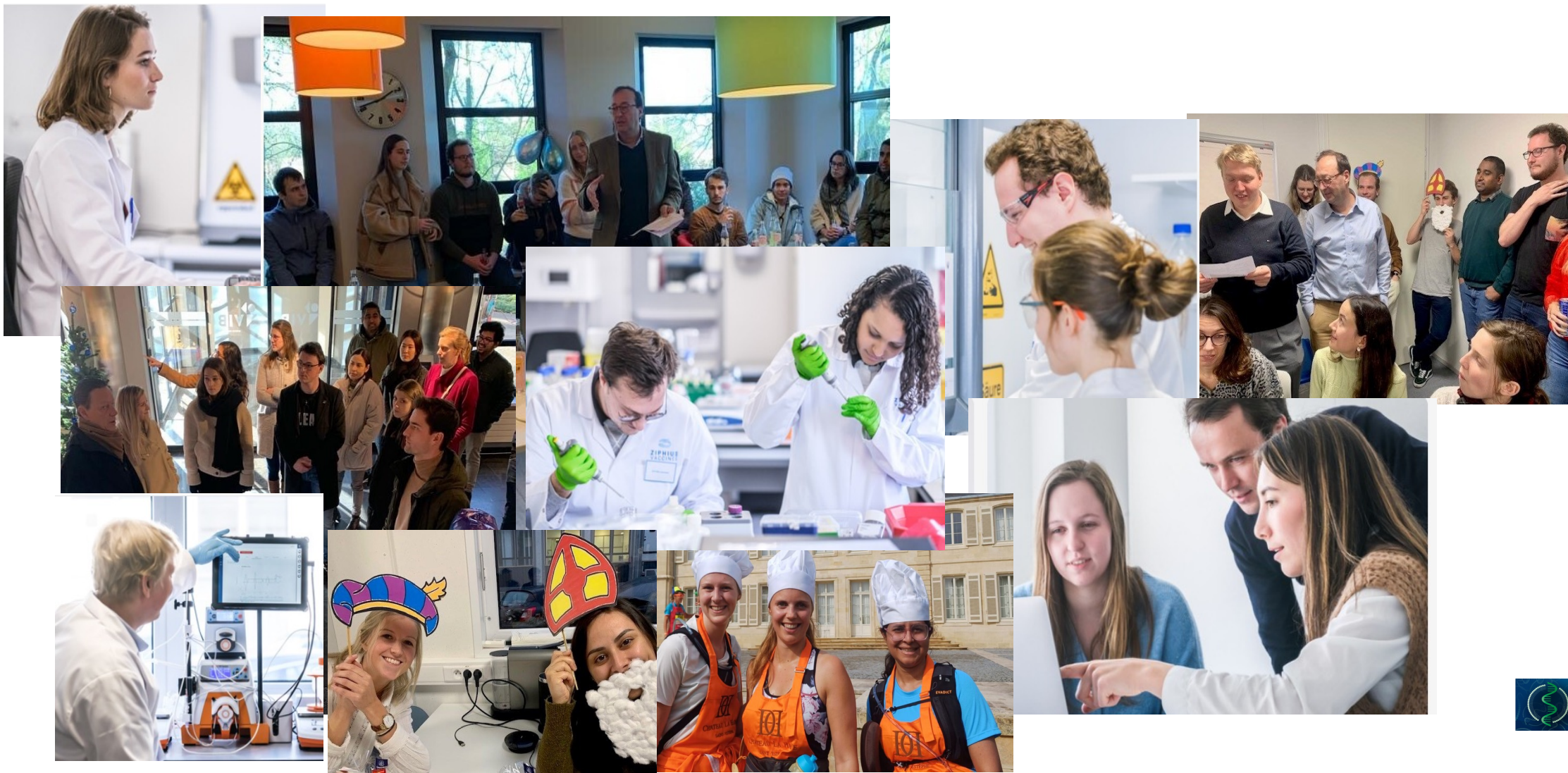
Summary – Ziphius CMC acceleration approach

- Developing a powerful technology platform:
 - Continuous saRNA backbone development
 - Safe and efficient delivery vehicles
 - Well understood animal model
 - CMC ready processes
- Efficient communication
- Invest in platform analytics
- Aim for GMP ready & scalable manufacturing
- Understand platform performance through characterization at platform level
- Implement standard workflows for fast transition between constructs





Acknowledgements to Ziphius team



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