World Health Organization

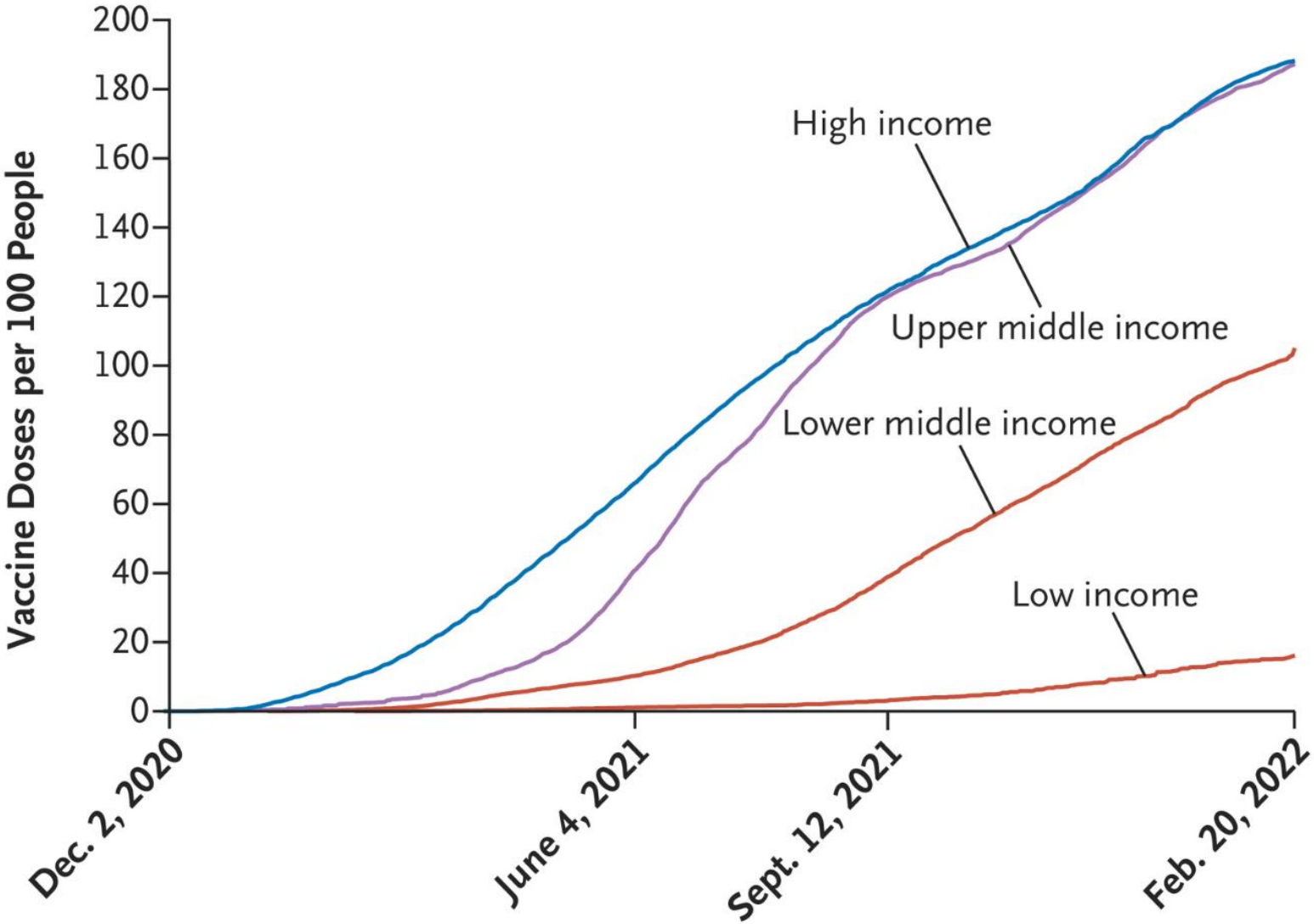
mRNA Vaccine R&D in LMICs

Update to PDVAC

Dr. Martin Friede

Department Immunization, Vaccines and Biologicals

Inequity in Covid vaccine supply

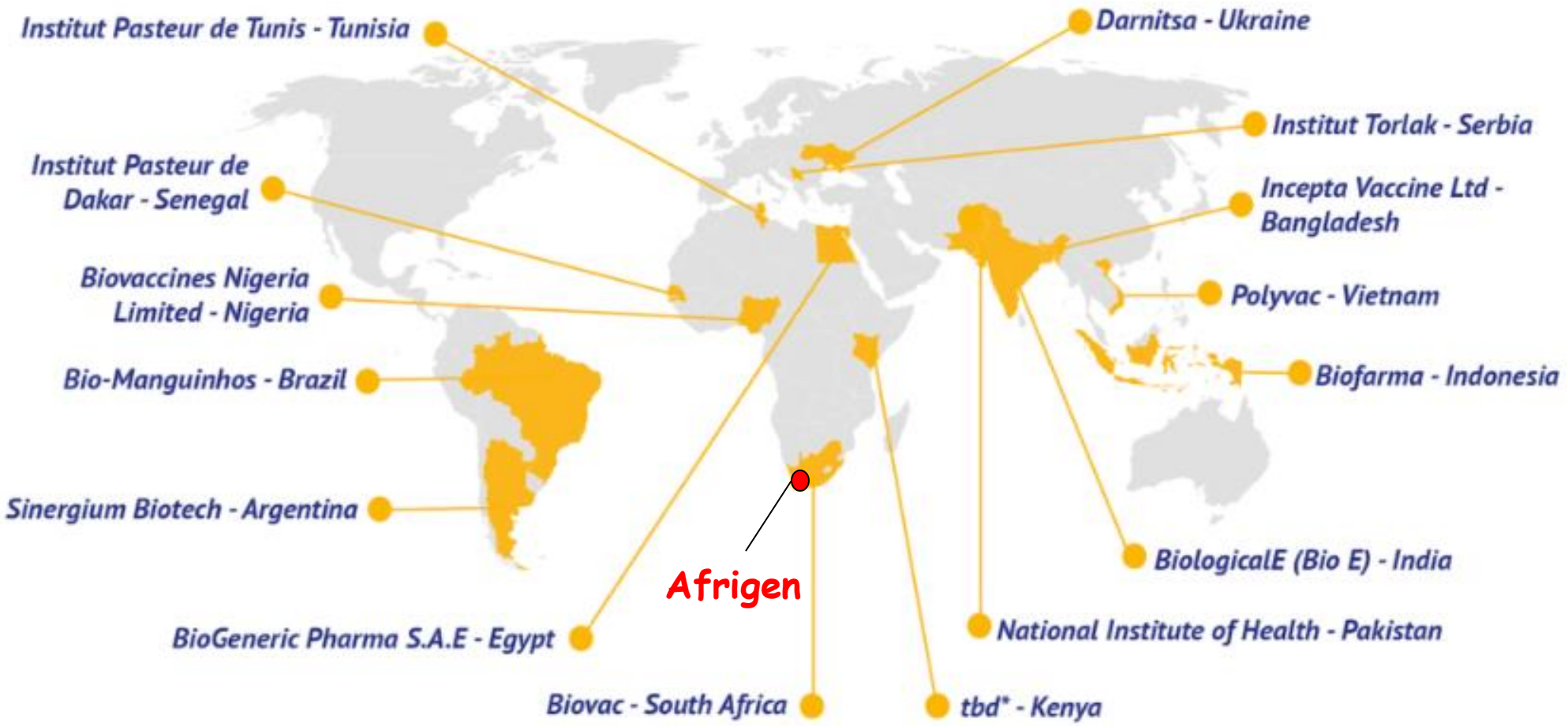


Response for LMICs ?

- Inactivated ?
- Viral vector ?
- Recombinant ?
- mRNA ?

- Which technology is most likely to be sustainable- ie able to be used to make other things?
- **Answer: mRNA**

Establishing a mechanism to ensure global ability to make mRNA



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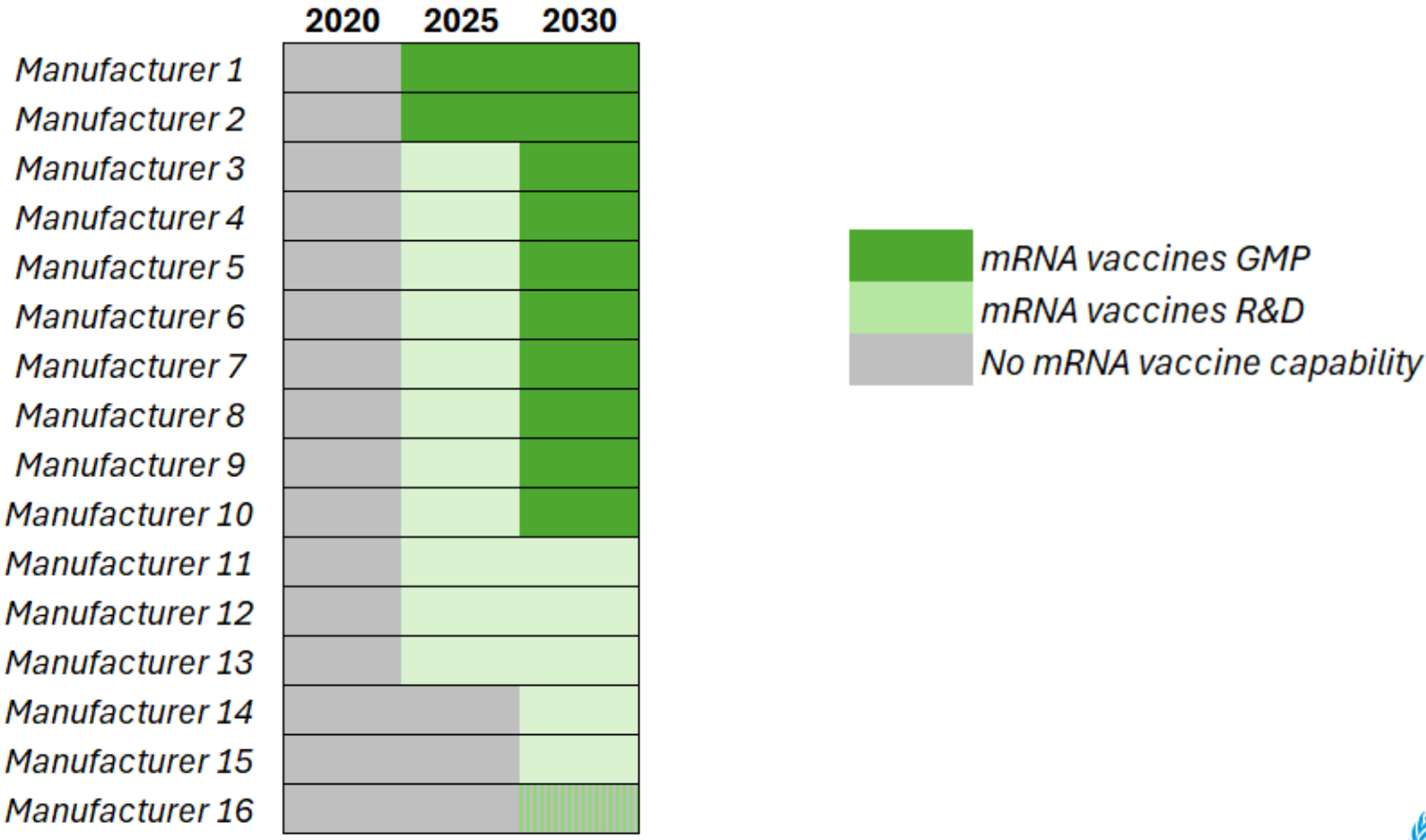
A better prepared Global South

Through the programme, we expect that **11 manufacturers could produce mRNA vaccines for human use by 2030**, **if suitably funded.**



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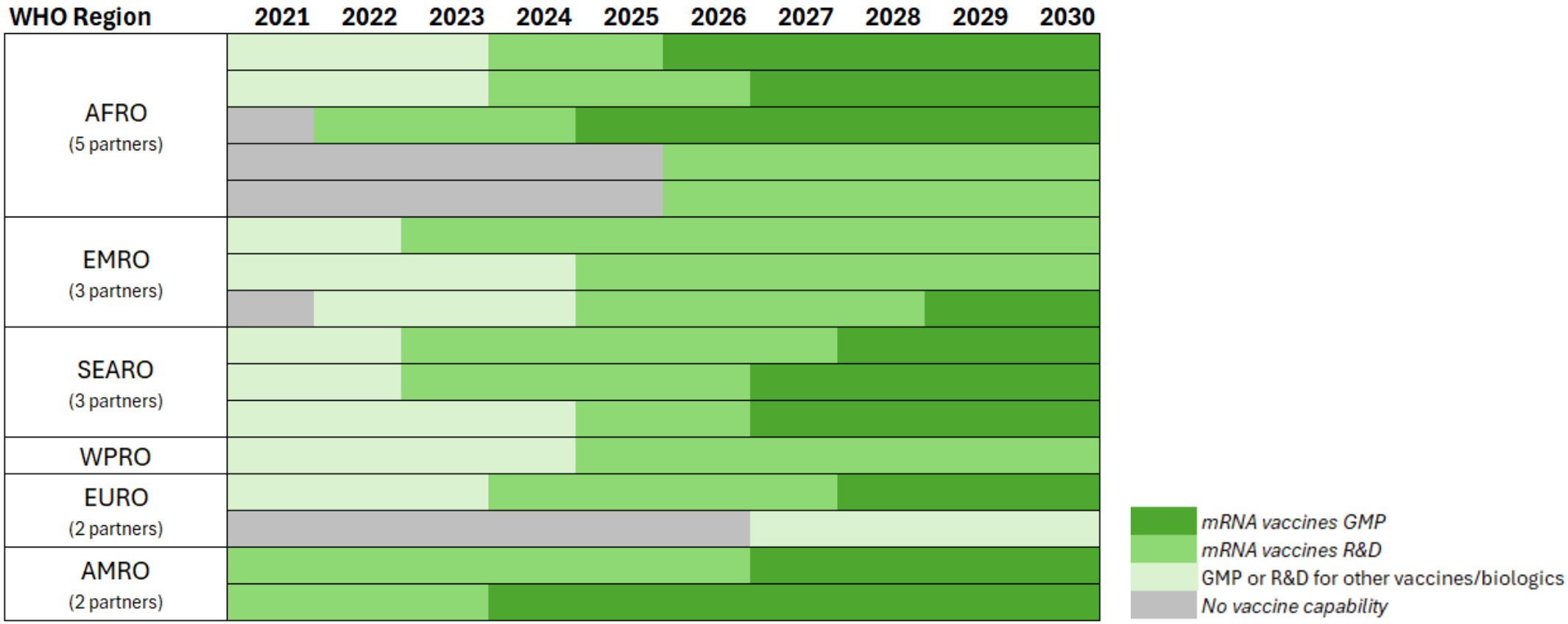
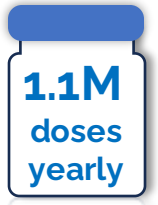


Establishing pandemic preparedness

By 2029 and Interpandemic Period
(36.4k doses/batch)



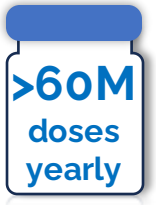
30µg mRNA / dose.

Network of **10 GMP pilot facilities**

3 lots / year / site

May not have a product to sustain costs.

Immediate Pandemic Response from 2029
(36.4k doses/batch)



30µg mRNA / dose.

Network of 10 GMP pilot facilities

Full capacity

Running costs offset by product profit.

Pandemic Response from 2029 Increased capacity
(364k doses/batch)

30µg mRNA / dose.

Network of 10 facilities **increase production scale by 10-fold;**

Additional funding required for equipment;

Running costs offset by product profit.

Investment required depends on each partner.
These figures are used for scenario-building purposes, and they do not reflect recommendations.
Estimations based on current process as developed by Afrigen. Running costs do not consider possible increase in HR for capacity increase.

mRNA Technology Transfer Programme

World Health Organization

Nothing can go ~~wrgon~~ ~~wgorn gworn~~ wrong!

The biggest barrier to national and regional investment in mRNA facilities is the current lack of commercially viable products that could be manufactured and sold.

Manufacturers / governments hesitant to invest

building facilities to manufacture vaccines is easy – keeping them **sustainable** is very difficult.

Multi-use technology a key driver: mRNA beats eggs..

Criteria to assess commercial feasibility of a candidate R&D products

PTRS: *Probability of Technical and Regulatory Success*

- ***what makes you think the immune response will be protective ?***
- ***-are you really sure there is a regulatory pathway with reasonable time/ cost ?***

PPDP: *Probability of Policy Development and Procurement* ***(unique to vaccines !)***

- ***Will immunization policy bodies issue favorable policy ?***
- ***Will procurement agencies decide to buy the vaccine for the population ?***
  - ***efficacy and cost effectiveness vs existing interventions ?***
  - ***feasibility of health impact , complexity of delivery etc?***

PPAU: *Probability of Population acceptance and use*

- *If the disease burden not visible resistance builds up*
- *-If the disease burden visible resistance can build up (hesitancy)*

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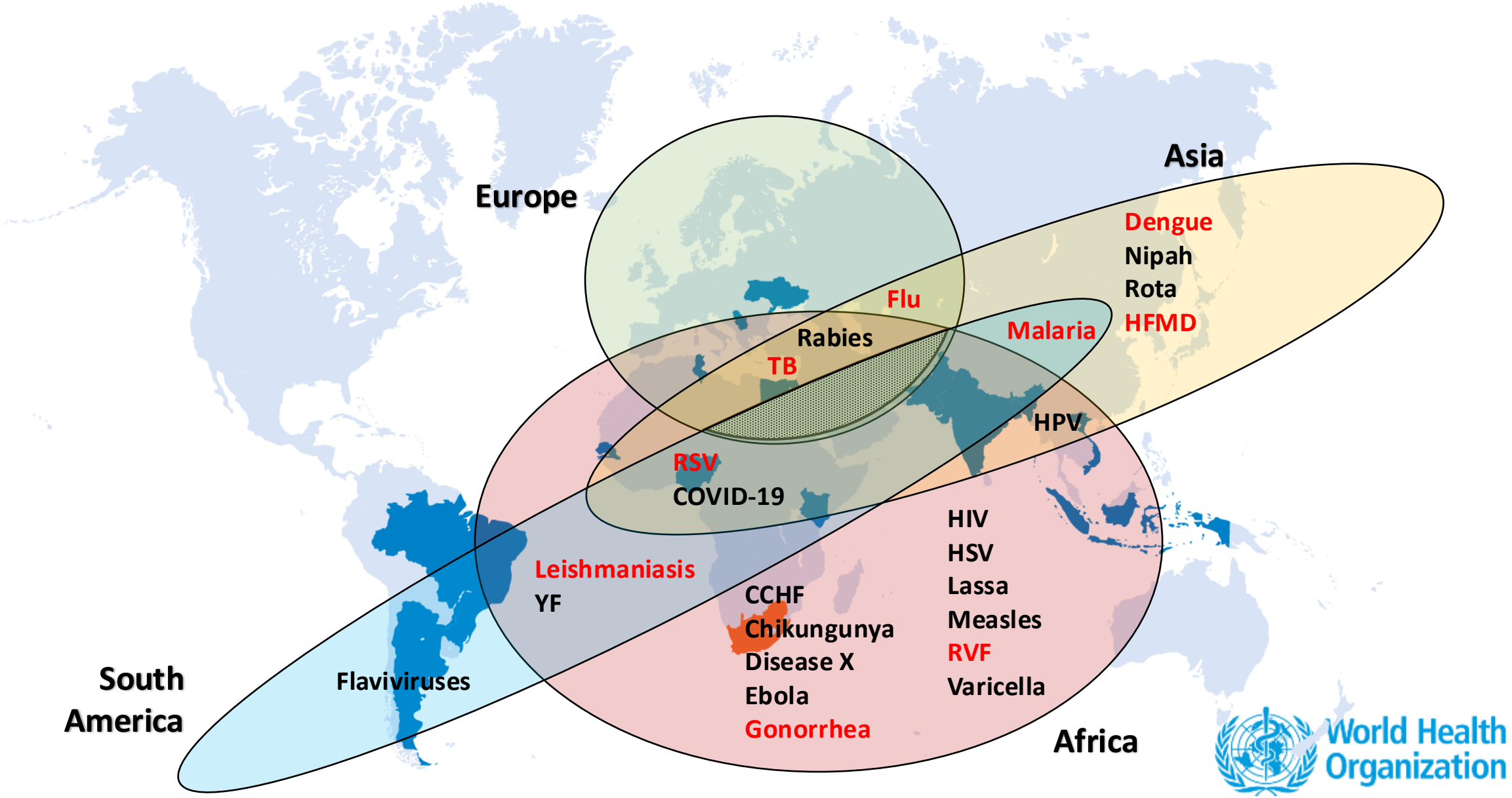
2023: Programme Partners Disease Targets by region



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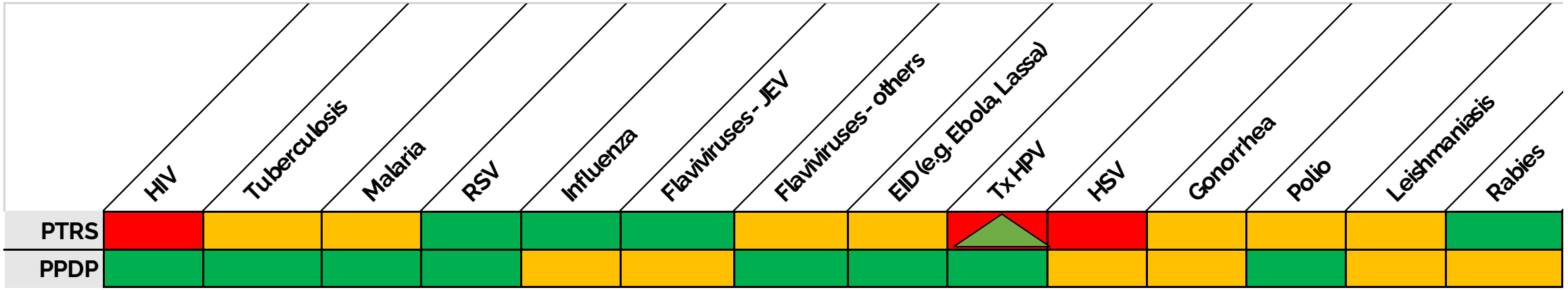
WHO/MPP mRNA meeting, April 2023
Summary of PTRS/PPDP assessment in LMICs



April 2023 to October 2024
What a difference a year makes !
Several initial assessments now seen to be too pesimistic !
Eg Tx HPV – PTRS perhaps good…. Others being re-evaluated and new ones added.

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Building consortia to lead on mRNA vaccine research to support regional manufacturers: 4 Asian consortia

News & Publications » News & Press Releases » Press Releases, MRNA

Pioneering Partnerships: The mRNA Technology Transfer Programme Inks Groundbreaking mRNA Vaccine R&D Consortia at Singapore Scientific Colloquium

HPV Tx: Chula

P. Vivax: Mahidol

HFMD: Hilleman

Dengue: IVI

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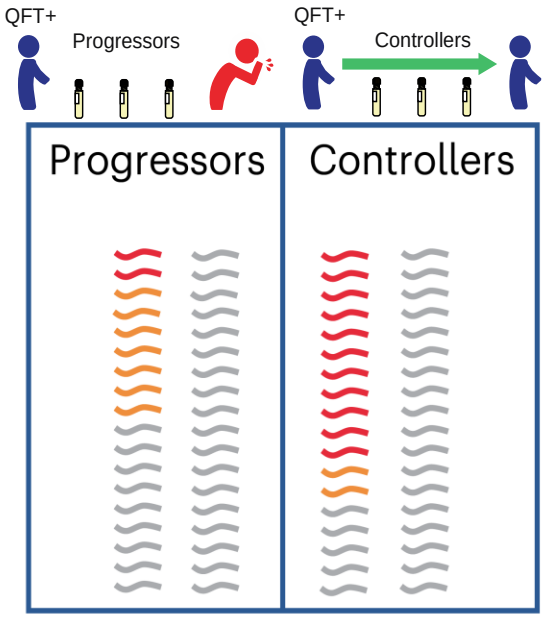
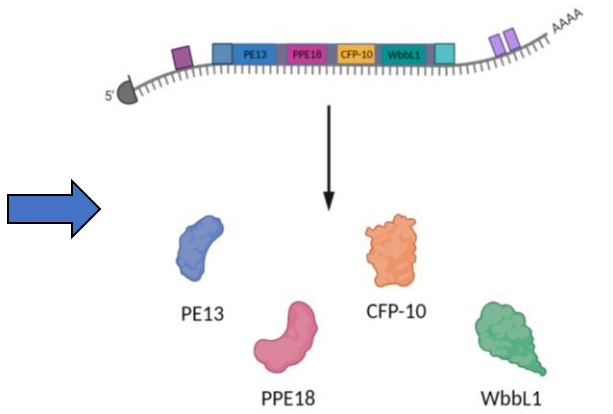
TB vaccine consortium

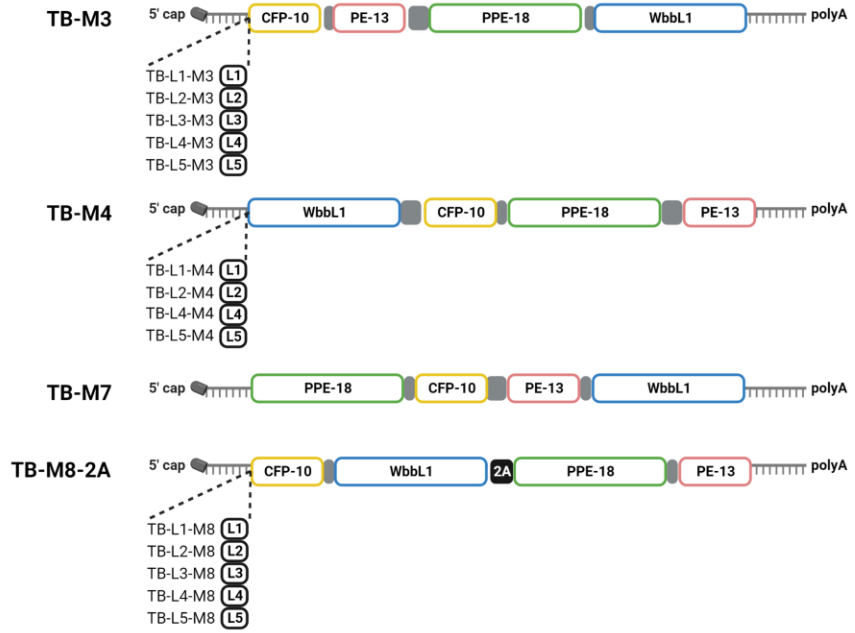
- South African UCT SATVI TB vaccine discovery and development unit, Afrigen.



Musvosvi, M., et al. Nat Med 29, 258–269 (2023)



TITAN-01 mRNA TB vaccine



- CD4 response to these antigens is associated with control of disease
  - PTRS: moderate – clinical trials long and very expensive: endpoint is prevention of progression
  - PPDP: high (massive disease burden) – but other candidates more advanced

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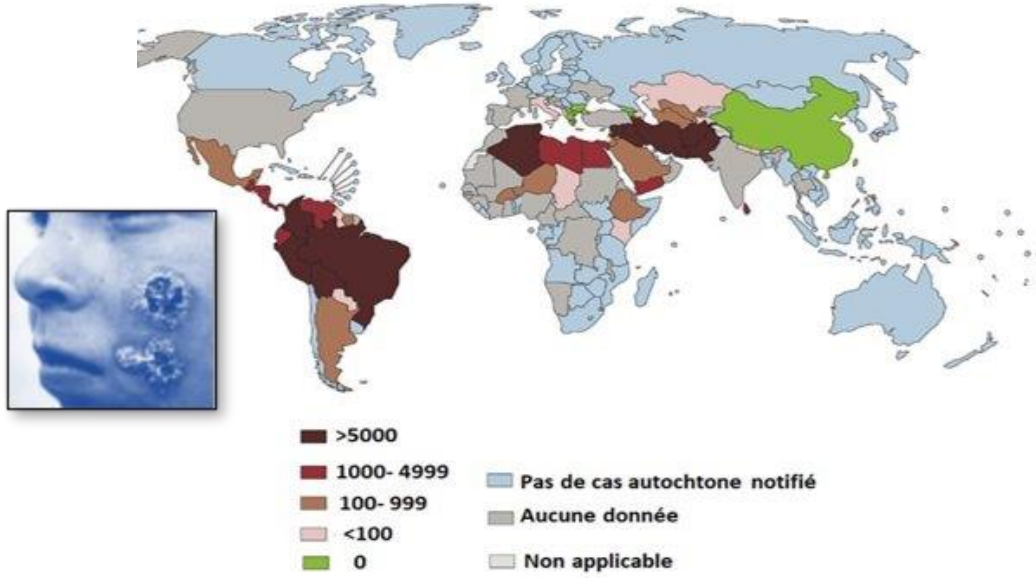
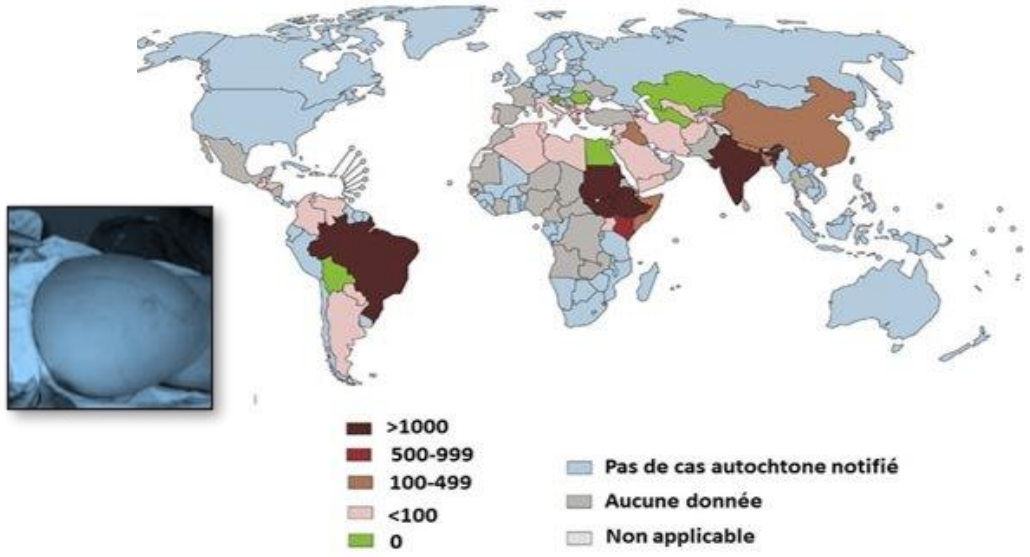
Leishmaniasis mRNA vaccine consortium (MOU not yet signed)

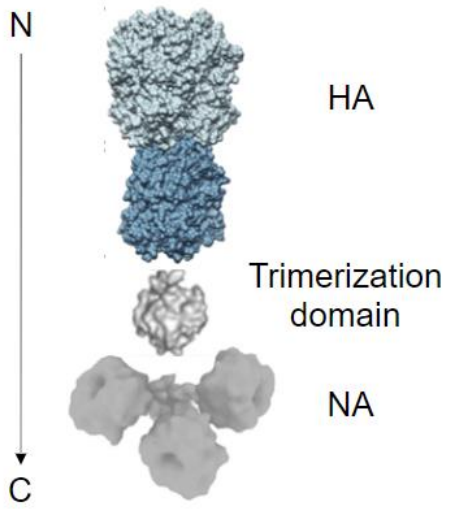
- Fiocruz (**Brazil**), UFMG (**Brazil**) Institute Pasteur Tunis (**Tunisia**) and Institute Pasteur **Korea** are developing a mRNA leishmaniasis vaccine using different antigens and different preclinical pathways.
- Key challenges for vaccine development – genetic diversity (22 species), target antigens (how to select), and challenges in defining protection in animal models,
- Next steps: agree on a common vaccine TPP and facilitate access to a parasite bank and will fundraise to advance a candidate vaccine to Phase 1.
- PTRS ? PPDP ?... TBD
- Other candidates in pipeline: live attenuated !



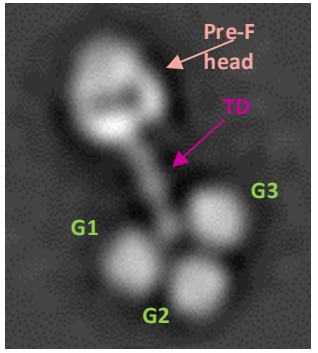


Influenza mRNA vaccine consortium
Led by Sinergium (Argentina) in collaboration with Bio-Manguinhos and global experts.

- Sinergium has launched a H5 influenza mRNA program – sharing the reagents and protocols with other mRNA partners.
- R&D program to seek to make seasonal (trivalent) vaccine with improved efficacy through incorporation of Neuraminidase component.
- Seek to control cost through fusion of HA and NA (otherwise vaccine will contain > 6 mRNA components each needing QC.
  - Reactogenicity….
  - Cost….



Pre-F/G



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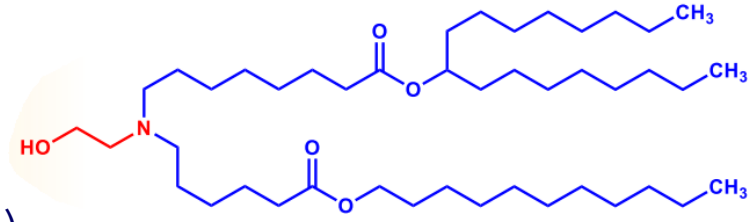
Guillaume Stewart-Jones, Rebecca Loomis et al. Frontiers Immunology 2020 Jun 11; 11:842. doi:

A consortium to develop ioniseable lipids and LNPs for LMIC use

- **key limitations** that limit suitability for use in LMICs
  - Freedom-to-operate
  - Cost, Ease of Manufacturing
  - Imperfect potency
  - Need for regional production (e.g. lipids, supply chain)



SM-102
Moderna

- Loose consortium: WITS university, Chulalongkorn, - adding others…

- Establish a standardized protocol and standard reagents to enable head-to-head comparisons of LNPs
  - Standard mRNA (eg Wuhan candidate from Afrigen)
  - Standard ioniseable lipid GMP quality (eg SM102 from Afrigen)
  - Standard mouse serum taken from pooled material
  - Standard immunization protocol, Standard ELISA protocol

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In a Nutshell: WITS University (South Africa)

Cashew nut shells:

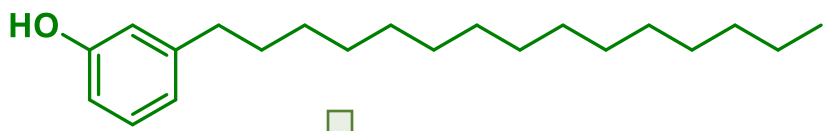
1. Distillation
2. Hydrogenation

Cashew nut shell liquid:

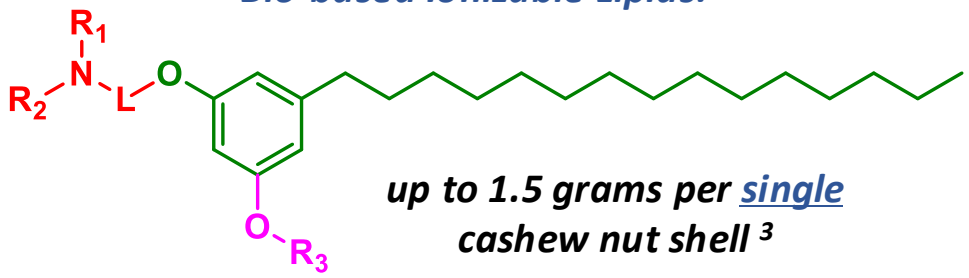
~ 450 000 tons discarded per year [1,2]

0.5 $/Kg

Hydrogenated Cardanol:



Bio-based Ionizable Lipids:



up to 1.5 grams per single cashew nut shell [3]

Photograph: Worker at Biotan factory, Tanzania, deshelling cashew nuts. Taken by Eva Helmeth

1. Chem. Soc. Rev., 2013, **42**, 427
2. World Acad. Sci., Engg. Technol., 2011, **58**, 889.
3. Journal of Agriculture and Food Research, 2021, **6**, 100219

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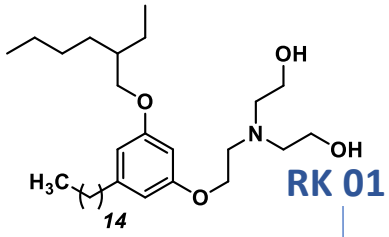
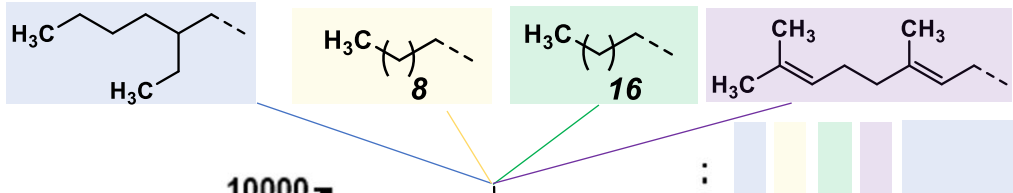
in-vivo Screening:



RK 011

SAR *screening*



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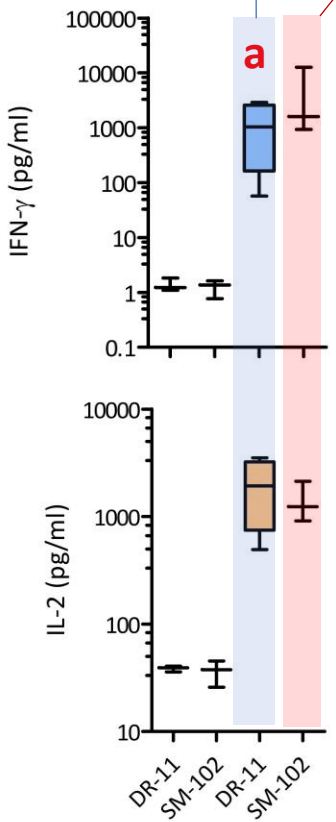

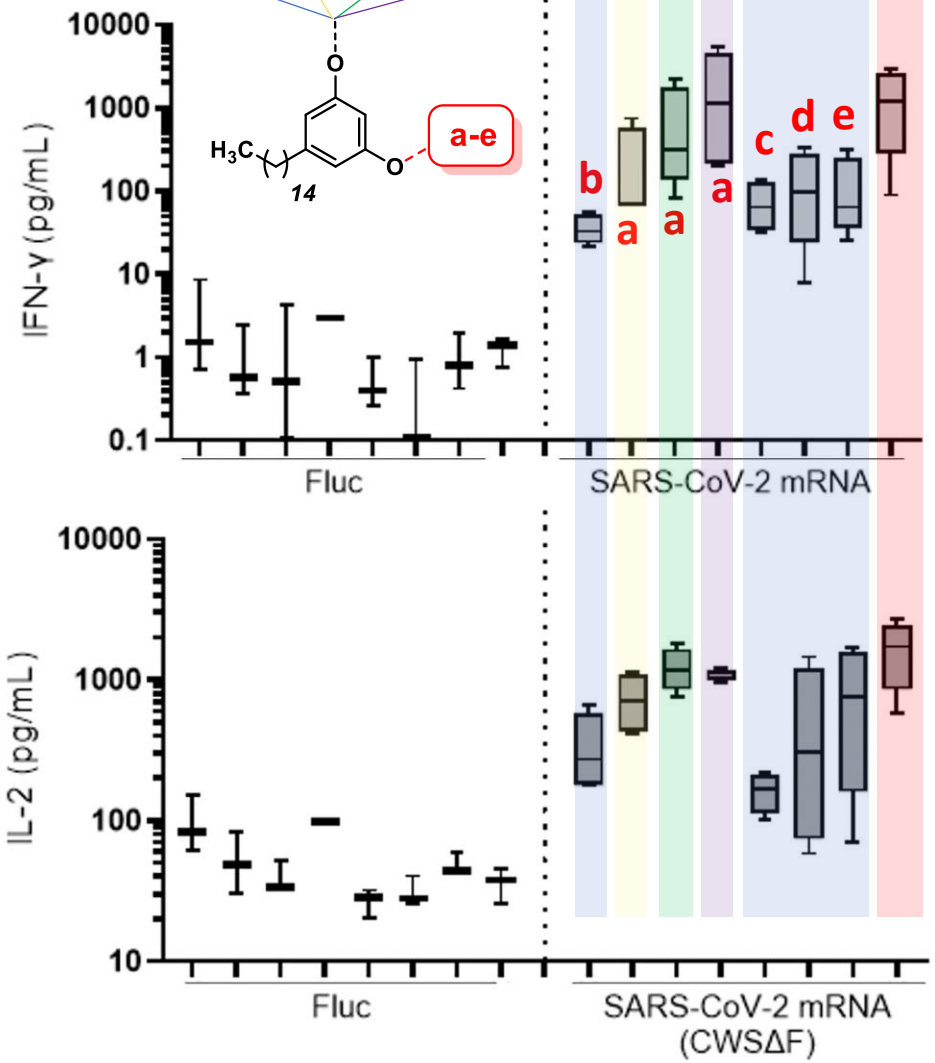

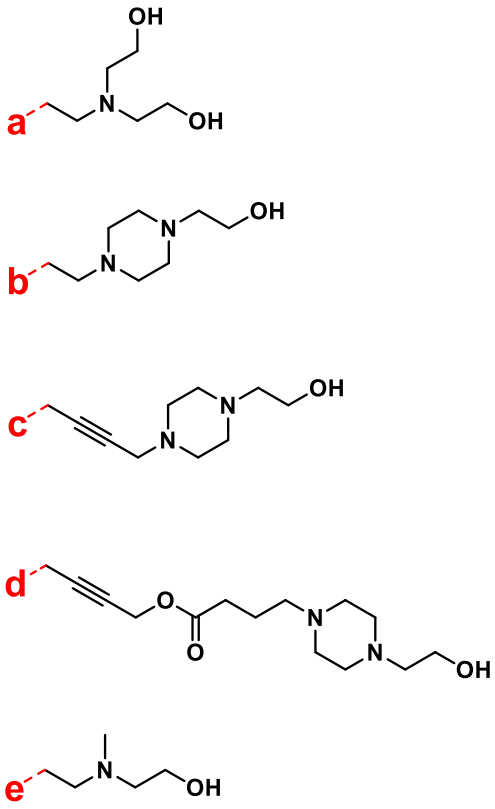

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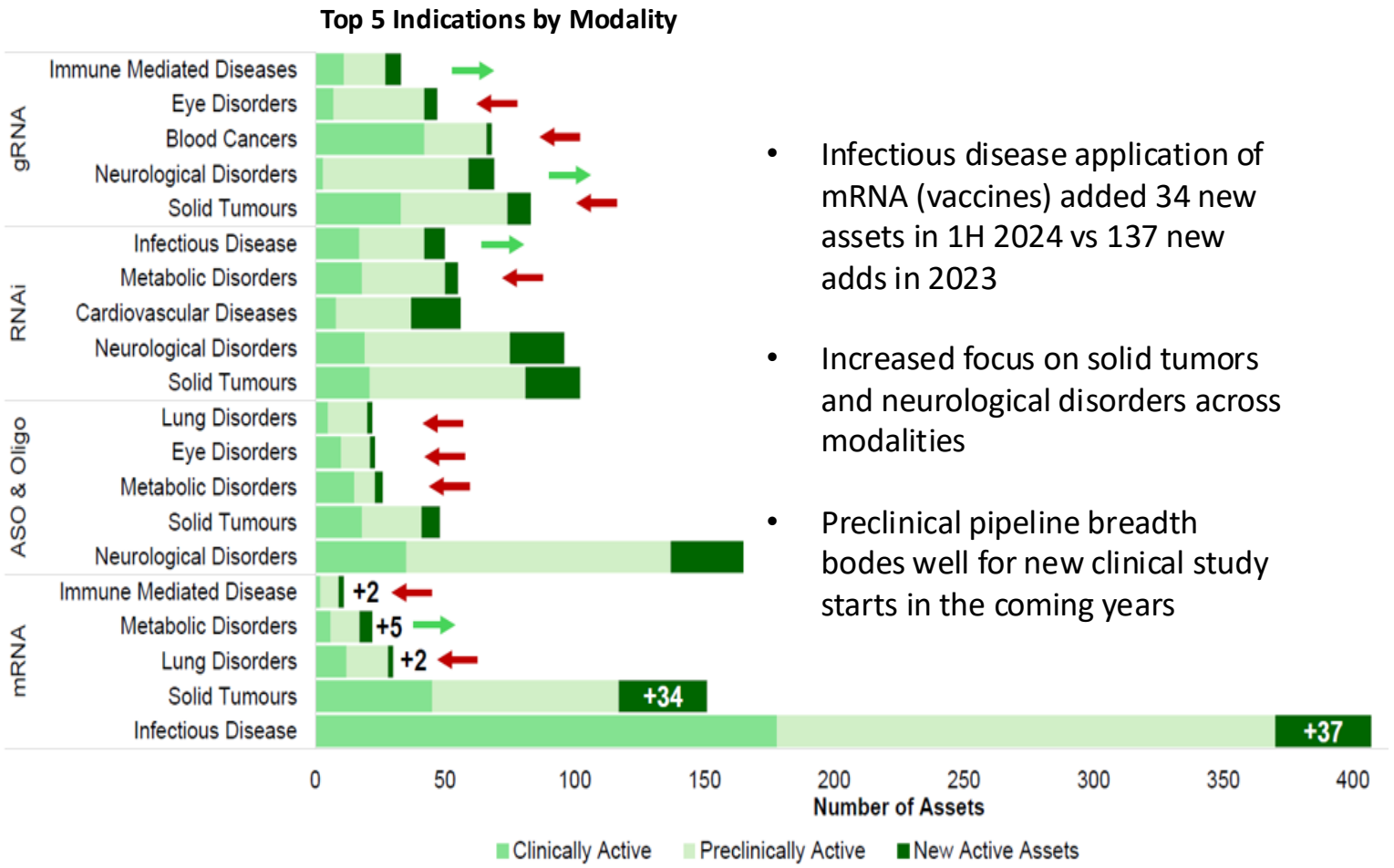
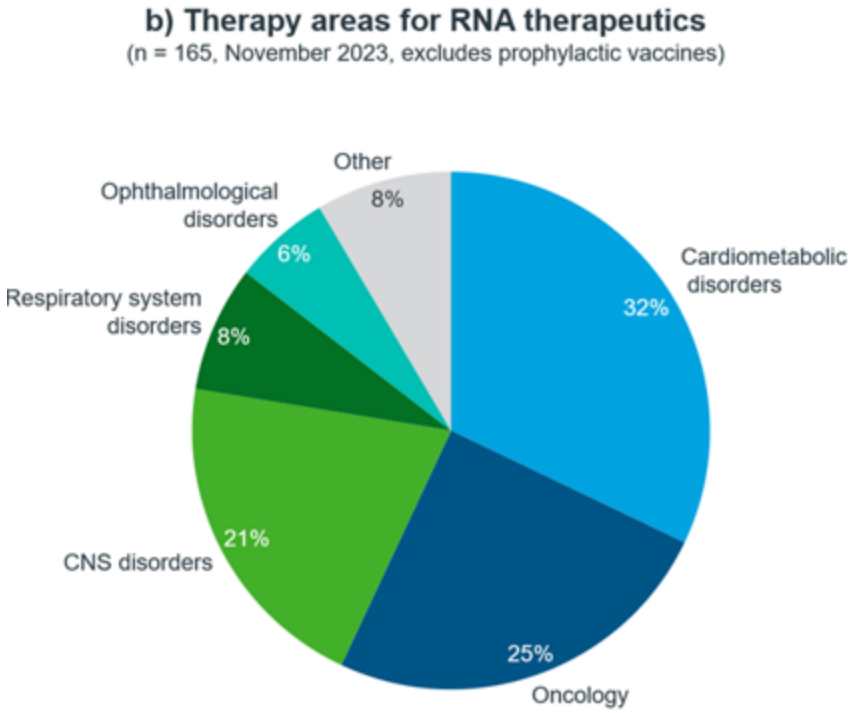
Sustainability: therapeutic applications may be key



- Infectious disease application of mRNA (vaccines) added 34 new assets in 1H 2024 vs 137 new adds in 2023
- Increased focus on solid tumors and neurological disorders across modalities
- Preclinical pipeline breadth bodes well for new clinical study starts in the coming years



RNA Therapeutics - IQVIA

Adapted from
Beacon | H1 2024 RNA Landscape Review | (beacon-intelligence.com)

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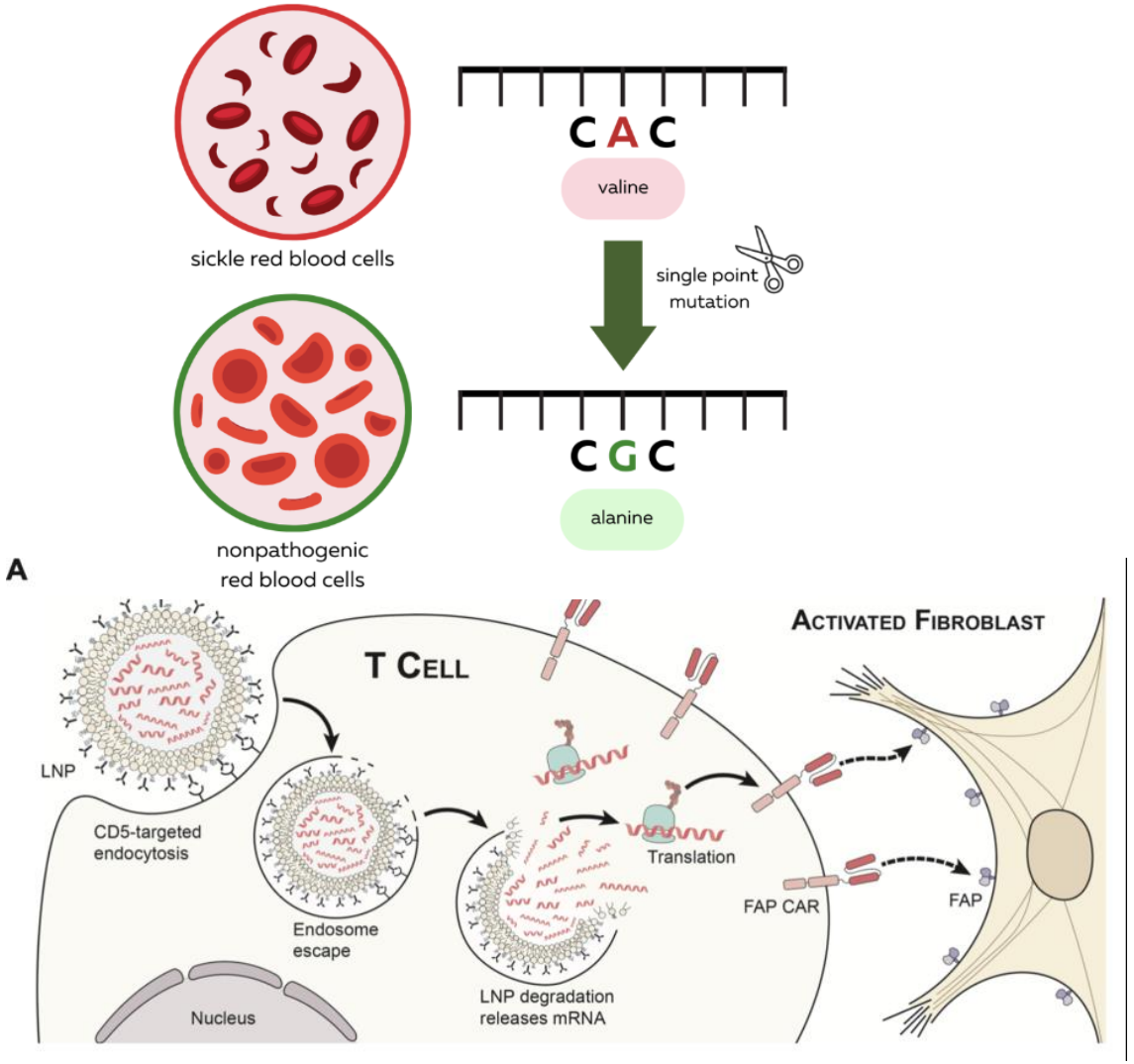
U. Penn labs committed to sharing portfolio with WHO/MPP mRNA programme. MOU under negotiation

- Sickle-cell anemia
- Thalassemia
- CD19 CAR-T cells for autoimmunity
- CD5 CAR-T for cardiac injury
- Others….

Seeking similar commitments from other academic research institutes



Rurik et al 2022

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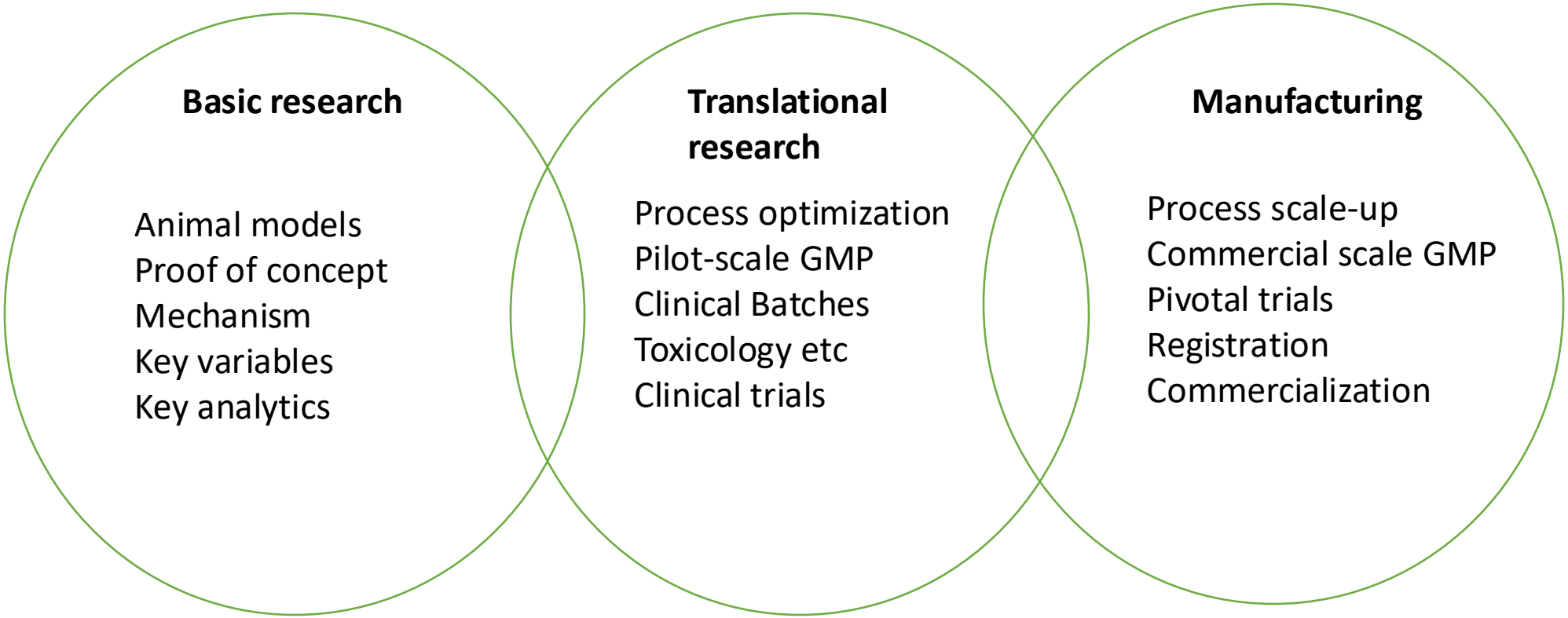
Critical role of translational research infrastructure
Need to build ENTIRE R&D ecosystem



Most academic research centres lack the know-how / infrastructure for product development
Most manufacturers lack the know-how / pilot facilities for early product development
WHO perspective: this is the key bottle-neck to work on next.

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Thank you

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