mRNA Innovations for Sustainability: Establishing an Enabling Environment

Prof Petro Terblanche, Dr Caryn Fenner and Dr Amin Khan
Afrigen Biologics, the mRNA Programme Center
The **mRNA Technology Transfer Program**: 12 months to mobilize a network for sustainable future pandemic/epidemic preparedness and **vaccine equity**

2021
- **April**: WHO call for EOI to contribute by providing technology or hosting a hub, or both
- **June**: WHO DG, French President and SA president announcing establishment of SA mRNA TT hub at Afrigen in CT
- **September**: WHO/PAHO announce selection of Argentina and Brazil as spokes in LatAm

2022
- **February**: WHO call for EOI for additional spokes and WHO call for EOI to establish workforce training hub
- **March**: WHO announces Egypt, Kenya, Nigeria, Senegal, South Africa and Tunisia as spokes
- **April**: WHO announces India as spoke

- **September**: WHO announces establishment of global biomanufacturing training hub in Republic of Korea
- **November**: Intro training on mRNA technology initiates at mRNA TT hub

**Call for expression of Interest (EOI)**: Contribute to the establishment of a COVID-19 mRNA vaccine technology transfer hub

- Provide training on general biomanufacturing processes in an industrial-type setting
- WHO announces Bangladesh, Indonesia, Pakistan, Serbia and Vietnam as spokes
mRNA Hub Programme Vision and Objectives

**Vision**

Improve health security in LMICs through local and/or regional production of mRNA vaccines

**Future pandemic readiness**

mRNA-based vaccine manufacturing platform and transfer to Programme Partners

**Interpandemic sustainability**

manufacturing of a pipeline of vaccines addressing local market needs & next generation mRNA technologies
mRNA Technology Transfer Programme:
A partnership network straddling 4 continents and connecting 15 countries (LMICs)

Partner countries constitute ~3 billion people (~40% global population)
KEY ENABLERS FOR mRNA product innovation

- FUNDING (the key role of WHO and MPP)
- THE RIGHT PEOPLE AND ENOUGH OF THEM
- PLATFORMS AND FACILITIES
- PROCESSES AND PRODUCTS
- REGULATORY AND QUALITY
- LOTS OF WISE ADVISORS
- DESIGNED FOR INNOVATION
- PARTNERS PARTNERS PARTNERS
- PURPOSE DRIVEN

mRNA Center at Afrigen case study
FUNDING IS THE FIRST ENABLER

SA CONSORTIUM
Funding sources

PARTNERS
Funding sources

NOTES:
1. Afrigen, Biovac, SAMRC and Secretariat
2. Sites assessment, GxP bio-manufacturing training, critical equipment, regulatory strengthening
3. Exchange rates of 31Mar 2023

Overall funding mobilised:
US$ 122m

27% 73%
SA Consortium Partners
IT IS ALL ABOUT THE PEOPLE!

Employee Status & Projection

Aug 2020

Aug 2023
SARS-CoV2 vaccine development: The backbone for a sustainable platform and future product pipeline

Second generation products and technologies addresses:
- Potency, reactogenicity and thermostability
- Reduced cost of goods
- Freedom to operate

Ongoing research and innovation a priority (SAMVAC)
COVID-19 vaccine: mRNA platform vs product development

- mRNA technology platform (AfriVac 2121* as PoC)
- Robust science
- Technology transfer
- COVID-19 vaccine development (XBB.15 monovalent)
- Regulatory requirements
- Clinical trial application

*Monovalent based on index virus (Wuhan)
AfriVac2121 performs comparably in multiple end points to an approved mRNA SARS-CoV2 vaccine.

**DATA IS KING**

Live viral neutralisation titers in mice 2 weeks post 2-dose vaccination

Body weight, lung viral burden and lung histopathology after SARS-CoV2 viral challenge of vaccinated Syrian hamsters

Collaboration with Xavier De Lamballerie, University of Marseille, France
BUILDING End-to-End Capabilities
COST COMPETITIVENESS AT HEART

Quality Management System (GMP)
- Qualified Utilities
- Material Handling
- QC Laboratories & Stability

Research & Development
- Plasmid Design & Development
- Antigen Design
- Process Development (DS + DP)

Biotech Production (GMP)
- Master & Working Cell Banks
- Plasmid Manufacturing
- DS & Bulk DP Manufacturing

Analytics (GMP)
- Characterization Assays
- Drug Substance Release Assays
- Drug Product Release Assays

Aseptic Filling & Finishing (GMP)
- Sterile Filling Line
- Visual Inspection, Label & Pack
- Shipping
mRNA technology innovation strategy

Manufacturing Technology

Formulation Research

DNA & RNA Development

Additional Disease Targets

Alternative Delivery Methods

01 These would assist in streamlining the process and looking at cost effective approaches

02 This focuses on optimizing stability, vaccine efficacy and immunogenicity

03 The sharing of expertise, access to complementary resources and accelerate progression

04 Expanding preventative measures for unmet medical needs and improving patient outcomes.

05 These methods have the capability of expanding vaccine accessibility, enhance immunization coverage and improve patient acceptance to name a few aspects
Collaborations are critical to the continued building of the mRNA platform.

DNA & RNA Development

Manufacturing Technology

Alternative Delivery Method

Formulation Research

Additional Disease Targets
Afrigen DS comparability study

mRNA Review

Confidential presentation
Nivelles, September 2023

Afrigen Drug Substance comparability study

QUANTOOM ANALYSIS RESULTS

- Similar RNA integrity results
- 78% of capping efficiency for P220016, close but below the specification of 80% for DS23001 and DS23002 present capping efficiency above 90%
- Similar PolyA tail length results
- Higher level of mRNA (G35 & KAN), above the specification of 100 ng/mg RNA
- dsRNA results are below the LOQ
- Low ratio of Protein/RNA, 0.11% for P220016 and <LOQ for DS23001 and DS23002*

*Afrigen analytical methods under development: rpDNA, dsRNA, capping efficiency.

Similar results are obtained by both Analytical teams on Afrigen DS:

- Residual NTPS results: <LOQ
- Endotoxin: <LOQ
- Spike protein expression: positive
- RNA Sequence matches description (UQTM >99.9%)
- pH

Process performance comparison

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<th>mRNA Yield</th>
<th>UQTM process</th>
<th>AFRIGEN process</th>
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<td>IVT mRNA yield (mg/ml)</td>
<td>2.96 (Post 1st TFF)</td>
<td>5</td>
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<td>Active mRNA pre purification (mg/ml)</td>
<td>0.73</td>
<td>0.9</td>
</tr>
<tr>
<td>Active mRNA post purification (mg/ml)</td>
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Building an end to end R&D and manufacturing ecosystem to leverage the power of mRNA

1. Antigen design
2. Target selection
3. Lipid design & testing
4. mRNA design & testing
5. mRNA manufacturing
6. LNP manufacturing
7. Preclinical experiments
8. Clinical trial design & execution
9. Manufacturing process/ COGS optimization
10. Assay development
11. mRCA center & partners

Flowchart:
- Antigen design linked to Target selection
- Target selection linked to Lipid design & testing
- Lipid design & testing linked to mRNA design & testing
- mRNA design & testing linked to mRNA manufacturing
- mRNA manufacturing linked to LNP manufacturing
- LNP manufacturing linked to Preclinical experiments
- Preclinical experiments linked to Clinical trial design & execution
- Clinical trial design & execution linked to Manufacturing process/ COGS optimization
- Manufacturing process/ COGS optimization linked to Assay development
- Assay development linked to mRNA center & partners
- mRNA center & partners linked back to Antigen design
Pipeline development and partnerships for sustainability and **public health impact**
### Summary of PTRS/PPDP assessment in LMICs

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<tr>
<th>Condition</th>
<th>PTRS</th>
<th>PPDP</th>
</tr>
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<tbody>
<tr>
<td>HIV</td>
<td>Red</td>
<td>Green</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Yellow</td>
<td>Green</td>
</tr>
<tr>
<td>Malaria</td>
<td>Green</td>
<td>Yellow</td>
</tr>
<tr>
<td>RSV</td>
<td>Green</td>
<td>Yellow</td>
</tr>
<tr>
<td>Influenza</td>
<td>Green</td>
<td>Yellow</td>
</tr>
<tr>
<td>Flaviviruses - JEV</td>
<td>Green</td>
<td>Yellow</td>
</tr>
<tr>
<td>Flaviviruses - others</td>
<td>Green</td>
<td>Yellow</td>
</tr>
<tr>
<td>EID (e.g., Ebola, Lassa)</td>
<td>Green</td>
<td>Yellow</td>
</tr>
<tr>
<td>Tx HPV</td>
<td>Red</td>
<td>Yellow</td>
</tr>
<tr>
<td>HSV</td>
<td>Green</td>
<td>Yellow</td>
</tr>
<tr>
<td>Gonorrhea</td>
<td>Green</td>
<td>Yellow</td>
</tr>
<tr>
<td>Polio</td>
<td>Yellow</td>
<td>Green</td>
</tr>
<tr>
<td>Leishmaniasis</td>
<td>Green</td>
<td>Yellow</td>
</tr>
<tr>
<td>Rabies</td>
<td>Green</td>
<td>Yellow</td>
</tr>
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**PTRS:** Probability of Technical and Regulatory Success  
**PPDP:** Probability of Policy Development and Procurement

- Based on potential targets of interest
- To inform vaccine mRNA pipeline for the 15 Partners
- Needs to take into account regional considerations
mRNA Companies and Locations: Evolving at speed.

<table>
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<tr>
<th>Country</th>
<th>Companies</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>123</td>
</tr>
<tr>
<td>China</td>
<td>34</td>
</tr>
<tr>
<td>South Korea</td>
<td>21</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>16</td>
</tr>
<tr>
<td>Germany</td>
<td>11</td>
</tr>
<tr>
<td>Canada</td>
<td>11</td>
</tr>
<tr>
<td>Japan</td>
<td>7</td>
</tr>
<tr>
<td>India</td>
<td>6</td>
</tr>
<tr>
<td>Switzerland</td>
<td>5</td>
</tr>
<tr>
<td>Netherlands</td>
<td>5</td>
</tr>
<tr>
<td>France</td>
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mRNA Disease Landscape – What’s Next?

- Solid Tumours
- Infectious Diseases
- Blood Cancers
- Metabolic Diseases
- Genetic Disorders

- 57% Solid Tumours
- 14% Infectious Diseases
- 19% Blood Cancers
- 5% Metabolic Diseases
- 5% Genetic Disorders

- mRNA Disease Landscape
- Infection
- www.beacon-intelligence.com
The mRNA IP and Competitive Landscape are in a constant state of flux and subject to significant ongoing change (e.g., market capitalization, opposition and IPR filings, regulatory candidates, alliances, etc. are all constantly changing and will continue to do so on an ongoing basis).

Source: https://www.jdsupra.com/legalnews/the-mrna-patent-and-competitive-7682620/
Closing thoughts...

- There is no doubt that RNA technology and innovation platforms will make a significant contribution to health product development and delivers positive public health benefits.
- Global access to these products needs to be a world priority.
- Lower barriers to entry for mRNA technology provides an opportunity for LMIC’s to become self-sufficient for many vaccines in terms of manufacturing of drug substance and drug product.
- Manufacturing alone is insufficient for sustainability, we must develop the know-how, capability and capacity for vaccines from concept, design, testing/optimization, manufacture and clinical development/registration to ensure sustainable access.
- Success will come more easily through genuine partnership and mutual support through an mRNA/LNP R&D and manufacturing ecosystem.
- RNA has applications beyond vaccines – in human, veterinary and agricultural applications.
RECOGNITION AND APPRECIATION

WHO.
Medicines Patent Pool (MPP).
Funders: France, Belgium, Germany, Norway, Canada, Switzerland, South Africa, EC/EU. Alma Foundation, SA Government DSI.
AU and Africa CDC (PAVM).
SAMRC and SAMVAC consortium.
Biovac.
Civil Society Groups.
mRNA Hub Steering Committee.
mRNA Hub Scientific Advisory Committee.
PATH.
NIH/VRC.
Curapath.
Equipment and technology suppliers.
University of the Witwatersrand, NICD, CeBER-UCT, PCDDP NWU, and other SA Universities.
Afrigen Team and Supporting Stakeholders and Shareholders.
THANK YOU