Report from the Center for mRNA Technology Development and Transfer

Petro Terblanche on behalf of the Afrigen Team
Who/MPP mRNA Technology Transfer Meeting
Cape Town
17 April 2023
LET’S NOT FORGET……..

- While the rapid development and effective scale up of Covid19 vaccines marks a landmark for vaccine development, the access to life saving vaccines in the poor countries of the world were no reality;

- Despite efforts from COVAX and partners, LMIC could not access vaccines and started first population vaccination up to 6 months after vaccines were available. Even while 2\textsuperscript{nd} and 3\textsuperscript{rd} boosters were administered in high income countries were supplies to LMICs remain ad hoc;

COVID-19 vaccine doses administered per 100 people, Mar 7, 2022

All doses, including boosters, are counted individually. As the same person may receive more than one dose, the number of doses per 100 people can be higher than 100.

Source: Official data collated by Our World in Data – Last updated 8 March 2022, 10:10 (London time) OurWorldInData.org/coronavirus • ©
**MRNA TT Program: 12 Months to Mobilise 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 announces Egypt, Kenya, Nigeria, Senegal, South Africa and Tunisia and Bangladesh, Indonesia, Pakistan, Serbia and Vietnam as spokes
- **March**: WHO announces India as spoke
- **April**: Intro training on mRNA technology initiates at mRNA TT hub
- **November**: WHO announces establishment of global biomanufacturing training hub in Republic of Korea

**Call for expression of interest to: Contribute to the establishment of a COVID-19 mRNA vaccine technology transfer hub**

Provide training on general biomanufacturing processes in an industrial-type setting

**Intro training on mRNA technology initiates at mRNA TT hub**

WHO announces establishment of global biomanufacturing training hub in Republic of Korea
Objective driven implementation at the Center for mRNA technology development and transfer required 3 key elements in preparation of multi lateral technology transfer aligned with the access model of the mRNA technology programme:

- HARDWARE
- SOFTWARE and
- BRAINWARE

Packaged for transfer as we progress - sense of urgency without compromising substance

**OBJECTIVES:**

1. Establish or enhance **sustainable mRNA vaccine manufacturing capacity** in regions with no or limited capacity

2. Build human capital for regulation and biomanufacturing in LMICs
THE HARDWARE
Facilities equipped to enable end-to-end mRNA technology development and manufacturing

- +2000 m² End-to-end sterile vaccine development facility at Afrigen Biologics
- Plasmid manufacturing/BSL 1/2 microbial cultivation
- mRNA synthesis (IVT)
- Formulation (Knauer installed and operational)
- Fill/Finish 2R-20R multidose vials (3 million vials per annum)
- Visual Inspection, labelling & packaging
- Cold storage

Construction completed
- Undergoing HVAC qualification
- SAHPRA Inspection

- R&D and Analytical Laboratories
  - Cell culture for Potency assay under development
- QC Labs
  - Includes Isolator for Sterility assay
- Stability Room
  - Multiple stability chambers
  - Fridges/Freezers
  - Accelerated – 6 months
  - Long term Zone 2 and 4b – 24 to 36 months

- Storage of Master and Working Cell Banks
- Cryogenic Facility
- Semi-Industrial Manufacturing Facility
- Class B Fill & Finish Area
Facility readiness assessment done on Unit 5, 6, 7, 8
Completion of “snap” list end March

Utilities
HVAC in PQ phase, completed end April
WFI delayed due to TOC Start mid April
Compressed air completed successfully

Equipment
Quantoom installation in process
FPC 60 – Afrigen Team view the mock-up in Ireland and added valuable changes
Equipment validation process is ongoing
Experience still delays by supplier information and documentations
Risk assessments – critical equipment had been completed and are in close out phase
THE SOFTWARE

Systems development/optimization: QMS conforming to highest regulatory and quality standards, data management and security and mRNA product and process design
Quality Management System
Dr Imelda Jordaan 13:30 session on 17/4

Management Responsibilities and Requirements
✓ Quality Policy
✓ Quality Plan
✓ Site Master File
✓ Organisational Chart
  o Product reviews
✓ Validation Master Plan
✓ Master Equipment list

Resource Requirements & Management
Human Resources:
✓ Training Policy,
✓ Staff system
  o Competency

Facility and Equipment:
✓ Facility design
✓ System Impact assessment
  o Equipment design & control Maintenance

Control outsourced Operations:
  o Supplier external audits

Manufacturing Operations
Product:
  o Specifications

Client Related processes:
✓ Product information
✓ Contracts Complaint

Material purchase:
  o Control process
  o Verification

Manufacturing:
  o Process control
  o In-process testing
  o Release criteria
  o Storage

Monitoring and measuring:
✓ Management review
  o Annual product review
✓ Internal audits
✓ Customer complaint

Deviation:
  o Root cause analysis
  o CAPA
✓ Deviation reports

Analysis Data:
  o Monitor trends
  o Process improvements

Evaluation Activities
Make quality improvements
Progress on product and process development with data presentation by Dr Caryn Fenner 15:00 on 18 April

1a. CMC: Drug substance process scale-up
1b. CMC: Drug product
1c. CMC: Analytics
1d. CMC: Fill/Finish
2. Preclinical studies
3. Clinical development
4. Quality & Regulatory
5. Technology transfer & training
THE BRAINWARE

Investment in relevant integrated rapid skills development training - equip our people
BUILDING A CAPABLE WORKFORCE

GROWING THE AFRIGEN STAFF COMPLEMENT OVER THE LAST YEAR

300% Increase in no. of employees
Knowledge Transfer to the Network
Dr Caryn Fenner presentation 15:00 18/4

- The following spokes training has been scheduled:
  - Nigeria: 15 – 17 May 2023
  - Pakistan: 15 – 17 June/July 2023
  - Kenya and Ukraine Q3 2023

- International Vaccine Institut (IVI) provided Good Laboratory Practices, Good Manufacturing Practices and Good Clinical Practices training at Afrigen (21 – 25 Nov 2022)

**11/15 Spokes have already received an introductory training to the mRNA Technology from Afrigen**
Technology Transfer Packages: Platform and Product Based
The key role of Biovac, MPP and partners

Staggered Technology Transfer Approach ensuring multiple access points to mRNA vaccine technology

1. **Package 1 - R&D GMP process, suitable to produce Phase I/II clinical trial material***
   a. Hands-on training at Afrigen;
   b. Documentation (detailed in the contract);
   c. Post-training remote support (+ visit at Spoke post training to support technology transfer).

2. **Package 2a - Industrial scaled up non-validated process**
   a. Documentation (detailed in the contract);
   b. Remote support (+ visit at Spoke to support technology transfer).

3. **Package 2 - Industrial scaled up validated process, suitable to produce Phase III clinical trial material**
   a. Documentation (detailed in the contract);
   b. Remote support (+ visit at Spoke to support technology transfer).

4. **Package 3 - Marketing Authorization Application**
   a. Documentation - standard, as per local national regulatory authority requirements.
DRIVING SUSTAINABILITY BEYOND THE PANDEMIC
Opportunities

- Platform manufacturing and testing processes
- Multi-product production facility is feasible
- Small footprint and cost-efficient manufacturing
- Potential application to many vaccine targets
- Versatility for complex antigens/multi-valency
- Safety and efficacy demonstrated in widespread application for Covid-19
- Short lead times to clinical development
- Enables rapid iteration in exploratory medicine trials

Challenges

- Core mRNA immunology is still evolving
- Fundamental structure-function understanding of mRNA architecture still being developed
- Vaccine product (LNP) temperature stability is yet to be adequately addressed
- Capabilities beyond CMC are required for antigen design:
  - Understand host-pathogen interactions for wide variety of infectious diseases
  - Antigen design and vaccinology
  - Preclinical functional assay development
- Durability & breadth of protective immune response (is covid-19 vaccine typical?)
- Intellectual property minefield
COVID-19 Vaccine Development: The Backbone for a Sustainable Platform
(Dr Amin Khan presentation 9:15 19/4)

The general structure of the antigen-encoding mRNA of AfriVac 2121

High level process flow chart for mRNA vaccine production

Antigen selection or design → mRNA cassette design → Plasmid design & cloning → Plasmid production → mRNA synthesis via IVT & capping → Purification of mRNA → Formulation in lipid nanoparticle → Fill-Finish into vials

CRADAs

Existing antigens, access need for novel antigens

RNA structure improvement

Cell-based: E.coli platform → Cell-free (enzymatic) synthesis

Modified nucleotides

Encapsulation technology → Novel lipids

Preclinical screening, safety & toxicity

CLINICAL TRIALS

Next-gen product

Proof of concept product – COVID-19
Strategic alliances and Collaborative Research for Optimization and Sustainability

- Process optimization to improve thermostability for 2nd generation vaccine(s) and therefore reduce cost of goods and supply chain complexities (FTO and improved product target profile)
- Novel immunogenicity targets for diseases of interest for pipeline development (long term sustainability and maximum public health impact)
- Long term development of improved process and identification of novel lipids and enzymes and delivery systems (FTO, continuous optimization and customization to ensure competitive advantage for mRNA production network)
mRNA Program Local Innovation Platform

Build innovation capacity and develop pipeline of homegrown products

**SAMVAC** – South African mRNA Vaccine Consortium

- Genomics (NGS-SA, CERI)
- Immunology (NICD)
- Vaccine construction (WITS)
- Lipid carriers (WITS)
- Enzyme production (SUN)
- Process development (UCT)
- Process scale-up, GMP manufacturing (Afrigen)
- Preclinical (PUDAC, NWU)
CONTRIBUTION AND RECOGNITION

WHO
Medicines Patent Pool (MPP)

Funders: France, Belgium, Germany, Norway, Canada, Switzerland, South Africa, EC/EU.
SA Government DSI
AU and Africa CDC (PAVM)
SAMRC
Biovac
Civil Society Groups
mRNA Hub Steering Committee
mRNA Hub Scientific Advisory Committee
PATH
NIH/VRC

University of the Witwatersrand, NICD and other SA Universities
Afrigen Team and Supporting Stakeholders and Shareholders