BMGF strategy to advance mRNA vaccine manufacturing

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Vaccine Development, CMC
Covid-19 vaccine rollout has shown that a regional vaccine manufacturing strategy is critical component for preparedness.

As of June 2021, vaccinations in HICs and UMICs dramatically outpace any LIC campaigns.

...countries with early rollout largely correlates with concentration of production capacity in US, EU, India and China.

Lack of production capacity in Gavi-served LMICs meant that local production is not an option for COVID-19.

Source: Our World in Data; Linksbridge; M4IA Public Database, WHO / UNICEF; Gavi

Last updated: June 2021
MRNA TECHNICAL CHALLENGES AND OPPORTUNITIES FOR LMIC

- Access to mRNA doses to costs approaching $1/dose or less.
- Find alternative reagent supply solution
- Use of new production methods

- Develop Liquid and/or Dry form Thermostable Solution
- Use of new delivery devices

- Access to methods to produce mRNA
- Provide access to mRNA key critical reagents (modified nucleoside, cap enzymes, cationic lipids)
- Freedom to Operate (FTO)

- Develop new mRNA modular technology
- Avoid scale problems
- Provide high output
- Design in consideration of deployment in LMIC

Cost of Goods (COG)
Thermostability
Reagents and Methods Access
Scale/Deployment
Univercells, a biotechnology Group of Affiliates on a common mission: making biologics available to all

**Univercells Technologies**
- Next-generation cell-based manufacturing technologies (scale-X™, NevoLine™)

**Quantum BioSciences**
- Technology innovator focused on mRNA from sequence up to mass production (Nfinity™ platform)

**Unizima**
- Project Management & Operational partner for in-country bioproduction facility setup

**Exothera**
- Best-in-class GMP-certified CDMO specialized in the development and manufacturing of viral vectors

**RLm consulting**
- Regulatory affairs support at all stages of medicinal product development

**Since 2013: Biologics for All**
- Proven track record in scaling production and bioprocessing
- Technology-driven affordability to support access and promote sustainability
- We address the needs of the health value chain

- 500 people from 40 nationalities
- +250 million EUR in equity & non-dilutive funding

**Univercells**
- Biologics for all
Reduction in facility size based on process intensification has multiple benefits

Ten-fold reduction in capital costs

Each production train can be readily placed in a BSL3+ GAPIII compliant facility providing increased assurance of environmental safety

Each unit operation can be hosed in an isolator (glove box) providing increased assurance of operator safety

Source: Univercells
mRNA PRODUCTION SYSTEM - DESIGN PRIME DIRECTIVES

- Use known mRNA and LNP reagents
- Maintain low cost of good operation
- Scale out - not scale up
- Fully automated – better control
- New purification methods (avoid complex system such as tangential flow filtration)
- Wide range of output with the same machine
- R&D operation and GMP operation with the same machine
DENSIFICATION: RNA IN VITRO TRANSLATION UNIT

- Lower footprint
- Bioburden controlled cabinet
- Lower CAPEX
WP3 – RNA Production Equipment Development & Prototype

Machine installed (qualification ongoing) in the mobile lab @Quantoom
Ntensify™ – 3 models designed for increasing RNA capacity requirements

1. **Mini**
   - R&D BENCHTOP
   - Drug Discovery and Pre-Clinical Phase (< 175 K doses over a year)
   - 500 µg
   - < 1 day

2. **Midi**
   - GMP SMALL SCALE
   - Clinical Phases & annual production of max 7.3 M doses
   - 1 g
   - Max 1 day

3. **Maxi**
   - GMP LARGE SCALE
   - Clinical Phase III & Commercial Production of max 100 M doses
   - 30 g
   - 1 day
   - 200 g
   - 6 days

Capacity (drug substance) / batch
Note: 1 dose assumed to be 50µg
CHAINING: DNA TO RNA TO LNP

• Chaining reduces the safety issues and batch-to-batch variations associated with physical handling

• Because the processes are essentially closed, there is also less likelihood of contamination. “Chaining reduces the safety issues and batch-to-batch variations associated with physical handling,”
LNP FORMULATION SYSTEM - DESIGN PRIME DIRECTIVES

T-mixer

Impingement jet mixer

Microfluidics
# RNA: GAME CHANGER PLATFORM FOR LMIC

## COST OF GOODS (COG)

<table>
<thead>
<tr>
<th>Manufacturing Step</th>
<th>Key Materials</th>
<th>Vaccine 1</th>
<th>Vaccine 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Buy</td>
<td>Make</td>
</tr>
<tr>
<td>mRNA production</td>
<td>pDNA</td>
<td>0.39</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td>2' O-methyl transferase</td>
<td>0.06</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>Guanylyl transferase</td>
<td>0.14</td>
<td>0.05</td>
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<tr>
<td></td>
<td>T7 RNA polymerase</td>
<td>0.02</td>
<td>0.01</td>
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<tr>
<td></td>
<td>Cleanoosp®</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>LNP production</td>
<td>Cationic lipid</td>
<td>4.16</td>
<td>0.04</td>
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<tr>
<td></td>
<td>DSPC</td>
<td>0.01</td>
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</tr>
<tr>
<td></td>
<td>Cholesterol</td>
<td>0.47</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>DMG-PEG</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>5.25</td>
<td>0.27</td>
</tr>
</tbody>
</table>

In-house raw material production 0.25 cents/dose

## MODELING 50-250M DOSES OUTPUT

- 90 batches per year
- Lower footprint (10 fold)
- Lower CAPEX (5 fold)
- 50-250M doses/year

*External assessment commissioned by the foundation based on public data*
MODULAR FACILITIES
What is next?

- saRNA
- circRNA
- xRNA
- New LNP (Ionizable lipids, Adjuvant)
- Microneedle
- Advanced Lyophilization
- Advanced potency assays
- Advanced reagents (enzymes)
Gates Foundation to Accelerate mRNA Vaccine Innovation and Manufacturing in Africa and Globally

DAKAR (October 9, 2023) – Today at the 2023 Grand Challenges Annual Meeting, Bill Gates, Co-chair of the Bill & Melinda Gates Foundation, announced new investments to advance access to mRNA research and vaccine manufacturing technology that will support low- and middle-income countries’ (LMICs) capacity to develop high-quality, lifesaving vaccines at scale.

The move builds on lessons the foundation has learned from more than 20 years of working with vaccine manufacturers in LMICs and the opportunity to leverage recent scientific advances to develop low-cost, high-quality health tools that reach more people around the world. mRNA technology is considered a potential game-changer for a range of infectious diseases, including...
## RNA ACCESS 2023 GRANTS

<table>
<thead>
<tr>
<th>GRANT NUMBER</th>
<th>YEAR</th>
<th>LOCATION</th>
<th>TITLE</th>
<th>AMOUNT</th>
<th>DESCRIPTION</th>
</tr>
</thead>
</table>
| INV-064834   | 2023 | Belgium         | Quantoom Sustainability      | $20M   | • LNP Formulation Unit  
• LNP FTO  
• In Silico Design unit  
• Critical Reagents Internalization |
| INV-064835   | 2023 | West Africa     | DCVM IPD mRNA Enabling       | $5M    | • Establish a R&D mRNA laboratory and pilot scale  
• Training on R&D capabilities and first production at IPD |
| INV-064836   | 2023 | South Africa    | DCVM BIOVAC mRNA Enabling    | $5M    | • Ntensify Midi and Ncapsulate  
• Training at Quantoom |
| INV-XXXXX    | 2024 | TBD             | DCVM XXXXX mRNA Enabling     | $10M   | TBD                                                                                           |
Based on this new mRNA access mission and our desired impact, the Foundation is now focusing on four new strategy pillars:

<table>
<thead>
<tr>
<th>Pillar objective</th>
<th>Desired timing for impact</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Access to mRNA R&amp;D and GMP manufacturing equipment at commercial scale</strong></td>
<td>Next 3-5 years</td>
</tr>
<tr>
<td>Enable DCVMs to acquire R&amp;D and commercial Quantoom units for mRNA development and manufacturing</td>
<td></td>
</tr>
<tr>
<td><strong>Access to mRNA supportive technologies and methods</strong></td>
<td>Next 2-3 years</td>
</tr>
<tr>
<td>Enable DCVMs to access supportive technologies such as thermostability, potency, delivery</td>
<td></td>
</tr>
<tr>
<td><strong>Access to critical raw materials</strong></td>
<td>Next 1-2 years</td>
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<tr>
<td>Enable DCVMs to access critical raw materials, with appropriate freedom-to-operate, and specific focus on LNPs</td>
<td></td>
</tr>
<tr>
<td><strong>Access to mRNA candidate design services</strong></td>
<td>Next 3-5 years</td>
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<tr>
<td>Enable DCVMs to develop their own mRNA vaccine portfolio</td>
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</tr>
<tr>
<td>Provide DCVMs with latest mRNA candidate design &amp; bioinformatics capabilities</td>
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