Live Biotherapeutics

From Concept to Clinic in Immuno-Oncology

Imke Mulder
4D pharma PLC
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COMPANY BY NUMBERS

- **2014**
  - Company formation

- **2**
  - Scalable platforms

- **5**
  - Sites

- **60+**
  - Scientists

- **2**
  - LBP patient trials

- **17**
  - LBP programmes

- **3000L**
  - Fermenters

- **6500+**
  - Proprietary bacteria

- **300+**
  - Granted patents

- **300+**
  - Patent applications

- **£100 million+**
  - Capital raised to date

- **£100 million+**
  - Capital raised to date

- **20+ million**
  - Capsules
WHAT DO OUR LIVE BIOThERAPEUTICS LOOK LIKE?

4D live biotherapeutics

- Single strain
- Commensal anaerobic bacteria
- Attractive safety profiles
- Oral delivery
- Local action; distal effects

Why single strain?

- Profound effects in industry-standard animal models
- Ability to impact the structure of the gut microbiota
- Reproducible, consistent manufacture at scale
- More straightforward regulatory pathway
GLOBAL MICROBIOME COMPANY

- Rapid development with early in-patient data
- Deep, broad pipeline across multiple therapeutic areas
- True end-to-end capability from bench to capsule
- In-patient data with IBS and Crohn’s; moving into cancer and asthma
- Largest intellectual property estate in the microbiome space
<table>
<thead>
<tr>
<th>Disease Area</th>
<th>DISCOVERY</th>
<th>PRECLINICAL</th>
<th>DEVELOPMENT</th>
<th>PHASE I</th>
<th>PHASE II</th>
<th>PHASE III</th>
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<tbody>
<tr>
<td>Gastro-intestinal</td>
<td>Blautix</td>
<td>IBS</td>
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<td>Irritable Bowel Syndrome</td>
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<td>Thetanix</td>
<td>Crohn's Disease</td>
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<td>Rosburix</td>
<td>Ulcerative Colitis</td>
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<td>Immuno-oncology</td>
<td>MRx0518</td>
<td>Solid tumours</td>
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<td>Respiratory</td>
<td>MRx0004</td>
<td>Asthma</td>
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<td></td>
<td>MRx0001</td>
<td>Allergic Asthma</td>
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<td>Autoimmune</td>
<td>MRx0002</td>
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<td>MRx0006</td>
<td>Rheumatoid Arthritis</td>
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<td>Others</td>
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<td>CNS</td>
<td>Neurodegeneration</td>
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<td>Autism</td>
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PROPRIETARY PLATFORMS = TARGETED RAPID DEVELOPMENT

**Library**
- **Capability:**
  - 6500+ strains
  - Broad coverage and species diversity
- **Ongoing:**
  - Continually expand

**LBP screening**
- **Capability:**
  - Host response
  - Microbial metabolomics
  - Cell culture
  - Primary cells/tissues
- **Ongoing:**
  - Ex vivo, 3D models
  - Additional diseases

**Preclinical Models**
- **Capability:**
  - Expertise in humanised microbiota models (IBS)
- **Ongoing:**
  - RA, asthma, IO, CNS

**Early Diagnosis and Intervention**

**MicroRx**
- Demonstrated concept in IBS
- Ongoing:
  - Verify in larger cohort
  - Investigate other diseases

**MicroDx**
- Microbiome Profiling Capability:
  - Demonstrated concept in IBS
- Ongoing:
  - Verify in larger cohort
  - Investigate other diseases

**Metabolomic Profiling**
- **Capability:**
  - Metabolic capacity of patient microbiome
  - Signals in IBS
- **Ongoing:**
  - Identify VOC markers
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<tr>
<th>Research</th>
<th>MicroRx platform</th>
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<tr>
<td></td>
<td>Focus on bacterial functionality</td>
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<td>17 programmes</td>
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<td>Development + Manufacturing</td>
<td>Concept to clinic in-house</td>
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<td>Stable, repeatable processes</td>
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<td></td>
<td>GMP certified, commercial-scale</td>
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<tr>
<td>Clinical</td>
<td>Phase Ib IBS complete</td>
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<td>Phase Ib CD nearing completion</td>
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<td>Up to 4 clinical studies by end 2018</td>
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Programme:
MRx0518 – Immuno-oncology
Microbiome and immuno-oncology

- Gut microbiome modulates efficacy of checkpoint inhibitors
- LBPs – opportunities as monotherapies; or combination therapies to boost response rates

4D IO programme

- MRx0518 – 4D Live Biotherapeutic candidate in immuno-oncology
- Highly immunostimulatory host-response profile
- Efficacy in murine models of breast, lung and renal cancer
MRX0518 – IMMUNO-ONCOLOGY OVERVIEW

MRx0518

- Gram-positive, motile, anaerobic bacterium of the _Enterococcus_ genus
- Selected for immunostimulatory host response profile, unique within the 4D strain library

**Efficacy in vivo**

- Monotherapy: reduction of tumour volume in three syngeneic cancer models
- Combination: boosts efficacy of checkpoint inhibition

**Mechanism of action**

- Increases tumour CD8+/Treg ratio
- Immune stimulation through action of bacterial flagellin on TLR5

**Upcoming clinical studies**

- Phase Ib neoadjuvant biomarker study (UK)
- Combination study with anti-PD-1 (US)
MRX0518 MONOTHERAPY INHIBITS TUMOUR GROWTH IN DIFFERENT CANCER TYPES

Efficacy in multiple tumour types
- Inhibition of tumour growth in different preclinical models
  - Breast cancer (EMT6)
  - Lung cancer (LLC1)
- Increased survival in EMT6 model

Complementary efficacy profile
- Efficacy in models not responsive to monotherapy checkpoint blockade

Benchmark
- MRx0518 outperforms Bifidobacterium and Bacteroides – reported to have anti-tumour effects (Sivan et al., 2015; Vetizou et al., 2015)
- The effect of MRx0518 is not genus-specific
MRX0518 AFFECTS CD8+ CELL POPULATIONS

Effect of MRx0518 on CD8+/FoxP3+ ratio

- MRx0518 and anti-CTLA-4 increase the ratio CD8+/FoxP3+ cells
- MRx0518 increases CD8α cells in the crypt region of the ileum

Effect of MRx0518 on ileal CD8α cells

Ileum cryosections immunolabelled with antibodies against CD8α (green) and DAPI (blue)
Terminal ileum sections

MRx0518 – Immuno-oncology
MRX0518 BOOSTS THE EFFICACY OF CHECKPOINT BLOCKADE

EMT6 Breast Carcinoma Model

- **Mice:** Balb/c
- **Tumour induction:** $10^6$ EMT6 cells SC
- **MRx0518 dosing:** D-14 to D24
- **Anti-CTLA-4 dosing:** TWx2 from D10
- **Readouts:** Tumour volume; tumour, spleen, serum, MLN, intestinal immunology; microbiome analysis; others

**Anti-CTLA-4 combination further reduces tumour growth**

- MRx0518 and anti-CTLA-4 combination therapy assessed in EMT6 breast carcinoma model
- MRx0518 monotherapy reduced tumour volumes comparably to anti-CTLA-4 treatment
- MRx0518 + anti-CTLA-4 combination virtually eradicated mouse tumours
- Immunology, microbiome, metabolomics, statistical analysis currently ongoing
Caco-2 response

- Strong upregulation of a number of immuno-stimulatory transcripts:
  - TNFα, CXCL1, CXCL3, CXCL10, CCL20, IL-8

THP-1 response

- Strong and significant increases in:
  - TNF-α, IL-1β and IL-23, CXCL9 and CXCL10
- Very large induction of IL-8 beyond detection limit

PBMC response

- Strong and significant induction of pro-inflammatory cytokines:
  - IL-6, IL-8, TNF-α
MRx0518 PUTATIVE EFFECTOR MOLECULES

**Transcriptomics**
- Whole genome sequencing and genome mining
- Targeted bacterial effector and host response
- Mono-colonised mice (dual RNASeq)

<table>
<thead>
<tr>
<th>MRx0518:Host response</th>
<th>HT29-MTX Response to MRx0518</th>
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<tbody>
<tr>
<td>CCL20</td>
<td>Inflammation upstream to signalling</td>
</tr>
<tr>
<td>CxCL1</td>
<td>Translation initiation</td>
</tr>
<tr>
<td>CXCL3</td>
<td>Apoptosis ER Stress</td>
</tr>
<tr>
<td>CXCL8</td>
<td>Antigen presentation</td>
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<tr>
<td>TNF</td>
<td>Inflammation &amp; Cell Proinflammatory</td>
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**Surfacome/secertome**
- ID of MRx0518 MAMPs
- Multiple targets of interest related to host signalling

**Flagellin**
- Flagellin identified as potential contributing molecule
- Activation of TLR5 by flagellin known to inhibit tumour proliferation in vivo
- In depth investigation of MRx0518 flagellin has identified strain-specific signalling effects

MRx0518 – Immuno-oncology
FLAGELLIN IS RESPONSIBLE FOR MRX0518 TLR5 ACTIVATION

Flagellin in MRx0518 culture activates NF-κB and TLR5 signalling

• Little to no NF-κB/TLR5 activation when flagellin is knocked out
• Supernatant of the reference strain does not activate TLR5
• Effects of MRx0518 were exacerbated by higher abundance of flagellin in the supernatant

Dose-response with recombinant flagellins

• Purified recombinant flagellins activate TLR5
• MRx0518 flagellin is more potent than the reference flagellin at low concentrations
MRX0518 FLAGELLIN IS IMMUNOSTIMULATORY IN IECS

Inactivation of MRx0518 flagellin gene abolishes immunostimulatory effects

- No stimulation of immune response gene expression in comparison with MRx0518 when flagellin gene is inactivated
- Stimulatory effect of MRx0518 recombinant flagellin
- IL-8 stimulation abolished by flagellin gene inactivation
- Stimulatory effect of MRx0518 recombinant flagellin

Caly et al., in submission
Increased immunostimulatory effects of MRx0518 translates into increased performance in preclinical cancer models

• MRx0518 is a flagellated bacterium and host TLR5 signalling contributes to its immuno-stimulatory effects

• The active flagellin protein, FliC, is produced by the bacterium

• The MRx0518 FliC is a more potent TLR5 agonist than homologous flagella from other strains of the same species

• MRx0518 outperforms reference strain in *in vivo* syngeneic tumour models
GMP MATERIAL AND REGULATORY PROFILE

**Fermentation**
- Live bacteria
- Strictly anaerobic environment
- Strain-specific protocols

**Lyophilisation**
- Highly moisture sensitive
- Strain-specific protocols

**Encapsulation**
- Highly moisture sensitive
- Heat sensitive

**MRx0518 Clinical material**
- Manufactured at GMP in-house facility
- Size 0 capsules
- Maximum dose $10^{11}$ per capsule
- Long-term stability data

**Regulatory profile**
- Commensal, found in 25% of population
- No AEs preclinically; no cytokine ‘storm’
- No further safety studies required for FiM
- Q3/4 commencement of monotherapy study in UK
**UK neoadjuvant ‘window’ study**
- Window study: dosing between diagnosis and surgery
- Up to 120 patients; multiple solid tumour types
- Placebo-controlled (4:1 randomisation)
- Clean background: treatment-naïve patients

**Trial design overview**
- Primary endpoint: safety and tolerability
- Suite of immunological biomarkers
  - Tumour and serum T cell populations
  - TCR clonality
  - Tumour marker response, Ki67, neoantigen analysis + others
- Full MicroDx microbiome analysis
- Further clinical studies planned in US
developing science delivering therapies