Recent progress to deliver Microbiome-based therapeutics in asthma and immuno-oncology
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COMPANY BY NUMBERS

2014
Company formation

5
Sites

60+
Scientists

2
LBP patient trials

2
Scalable platforms

6500+
Proprietary bacteria

£100 million+
Capital raised to date

300+
Granted patents

300+
Patent applications

3000L
Fermenters

17
LBP programmes

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

What are live biotherapeutics?
• 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
### 4D PHARMA - PIPELINE ADDRESSING KEY DISEASE AREAS

<table>
<thead>
<tr>
<th>Category</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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<td><strong>Gastro-intestinal</strong></td>
<td>Blautix Irritable Bowel Syndrome</td>
<td>Thetanix Crohn’s Disease</td>
<td>Rosburix Ulcerative Colitis</td>
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<td><strong>Immuno-oncology</strong></td>
<td>MRx0518 Solid tumours</td>
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<td><strong>Respiratory</strong></td>
<td>MRx0004 Asthma</td>
<td>MRx0001 Allergic Asthma</td>
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<td><strong>Autoimmune</strong></td>
<td>MRx0002 Multiple Sclerosis</td>
<td>MRx0006 Rheumatoid Arthritis</td>
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<td>Neurodegeneration</td>
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<td><strong>Autism</strong></td>
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PROPRIETARY PLATFORMS = TARGETED RAPID DEVELOPMENT

**MicroRx**
- 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

**MicroDx**
- Age-Matched Cohort
  - Capability: Microbiota, urine samples, patients vs. healthy
  - Ongoing: Breath analysis, expand disease areas

- 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

Early Diagnosis and Intervention

Developing science
Programme:
MRx0518 – Immuno-oncology
GUT MICROBIOME IS EMERGING AS NEW FRONTIER IN 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

- 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 microbiome diversity; 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

Cowie *et al.*, in submission
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 BOOSTS THE EFFICACY OF CHECKPOINT BLOCKADE

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

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
**MRx0518 PUTATIVE EFFECTOR MOLECULES**

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

**Surfacome/secretome**
- 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
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
Programme:
MRx0004 – Asthma
**Bifidobacterium breve** MRx0004 protects against airway inflammation in a severe asthma model by suppressing both neutrophil and eosinophil lung infiltration

Emma J. Raftis¹, Margaret I. Delday¹,², Philip Cowie³, Seánín M. McCluskey¹, Mark D. Singh¹, Anna Ettorre¹ & Imke E. Mulder¹
Disease phenotype

Asthma is a phenotypically heterogeneous disease, characterized by either predominant eosinophilic or neutrophilic, or even mixed eosinophilic/neutrophilic inflammatory patterns. Eosinophilic inflammation is associated with the whole spectrum of asthma severity, from mild-to-moderate to severe uncontrolled disease, whereas neutrophilic inflammation occurs mostly in more severe asthma. Neutrophilic asthma is mostly dependent on Th17 cell-induced mechanisms. Therapies targeting inflammatory pathways linked to allergic asthma are often not effective against severe neutrophilic asthma.

Study protocol

Day -14 to day 17
- Daily administration of MRx0004 per oral.

Day 0, 7
- Sensitization with HDM in CFA s.c.
- Administration of anti IL-17 i.p.

Day 13, 15, 17
- Challenge with HDM in 30ul PBS i.n.

Day 14, 15, 16, 17
- Sacrifice of all animals for analysis.

Experimental readouts

- Quantification and characterisation of airway infiltrating cell types
- Lung histology; disease severity score
- HDM-specific IgG1 and IgG2a production
- Measurement of inflammatory mediators in lung tissue
INTRODUCTION: ASTHMA

MRx0004
- *Bifidobacterium breve* strain isolated from the gut microbiome of a healthy human

Asthma
- Chronic inflammatory lung disease: recurrent, reversible airway obstruction and increased bronchial hyper-responsiveness (330 M people worldwide)
- Clinical presentations ranging from mild to severe
- Additional 100 million people by 2025

Endotypes
- Multiple disease endotypes, stratified immune cell infiltration (eosinophilic/neutrophilic/mixed)
- Divisions based on eosinophilic inflammation (T<sub>H2</sub>-high and T<sub>H2</sub>-low/non-T<sub>H2</sub> phenotypes)
- Severe asthma is refractory to steroid treatment
- Characterised by molecular phenotypes, biomarkers and responses to therapy
- T<sub>H1</sub> and T<sub>H17</sub> pathways play a role in the pathology of severe neutrophilic asthma.

Microbiome link
- Lower abundance of *Bifidobacterium* species has been associated with long-term asthma
- Oral delivery of *Bifidobacterium* strains alleviates allergen-specific T<sub>H2</sub> responses and suppresses airway inflammation in allergic asthma

Treatments
- Inhaled corticosteroids and long-acting β-agonists
- No neutrophil specific (non-T<sub>H2</sub>) therapeutics currently available
MRx0004 PREVENTATIVE TREATMENT: BALF CELL COUNTS

Effect of MRx0004 on BALF cell counts

Key parameter: neutrophil recruitment

HDM-sensitised mice:
- Higher number of BALF cells/ml vs untreated mice.
- Severe inflammation and large neutrophilic influx.

MRx0004
- Reduces total BALF cell count vs HDM
- Reduces both # and % of neutrophils vs HDM and vehicle groups.
- Reduces % eosinophil lung infiltration vs Anti-IL-17.

Anti-IL-17
- Reduces both # and % of neutrophils vs HDM and vehicle groups.
- Increases % of eosinophils vs MRx0004 and untreated groups.
Effect of MRx0004 on lung histopathology and inflammatory scores

- Cellular infiltration evident in whole lung sections and around bronchioli and blood vessels.
- Lung histological appearance similar in both MRx0004 and untreated animals.
- MRx0004: strong reduction in peribronchiolar and perivascular inflammatory cell infiltration.
- Similar inflammatory infiltrate levels in anti-IL-17, HDM and vehicle groups.
- MRx0004 and untreated groups: low levels of CD4⁺ cell infiltrations vs all other groups.
- MRx0004 inflammatory scores not significantly different from untreated animals.
- Anti-IL-17 did not reduce lung inflammatory scores.
Disease progression is associated with a trend towards increased IL-1α, IL-1β, IFN-γ, CXCL1 and CXCL2 in HDM and vehicle-treated animals.

MRx0004 reduced (n.s.) pro-inflammatory cytokines IL-1α, IL-1β and chemokine CXCL2.

Anti-IL-17 significantly increased IL-1α vs all other treatments.
Effect of therapeutically-dosed MRx0004 on BALF cell counts

Prevent or limit airway inflammation during the active disease?

Stronger neutrophilic phenotype in therapeutic vs prophylactic study

**MRx0004**
- Reduced airway neutrophil infiltration vs HDM and vehicle groups.
- Reduction due to lower total BALF number vs prophylactic study.
- Trend towards a reduction in eosinophil.

**Anti-IL-17**
- Large reduction in total # and % of neutrophils.
- Increased eosinophils, macrophages and lymphocytes in the BALF vs all other groups.
Impact of MRx0004 on T cell numbers and activation status.

(a) Total number of CD4+ cells  
(b) Total number of CD8+ cells  
(c) MFI of the CD44 marker of activation on CD4+ and CD8+  
(d) Total number of CD4+FoxP3+ cells

Capped bars illustrate the maximum and minimum data points within each treatment group. *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001 between treatment groups. Mean Fluorescence Intensity (MFI).

**MRx0004**
- Reduces both the number and activation state of pulmonary T cells.
- CD4+ T cell numbers comparable to untreated animals
- Only treatment to increase expression of the effector/memory T cell marker CD44

**Anti-IL-17**
- CD8+ T cell numbers elevated vs all other groups.
- Increased CD4+FoxP3+ regulatory T cell populations vs HDM and vehicle groups
MRx0004 THERAPEUTICALLY-DOSED: T CELL AND DENDRITIC CELL NUMBERS AND ACTIVATION STATUS.

Impact of MRx0004 on dendritic cell numbers and activation status.

Expression of MHCII, CD40, CD80 and CD86 used to activated dendritic cells

MRx0004

• Trend towards reduced CD11b+ MHCII+ dendritic cell numbers vs HDM animals.
• Similar trend for activation markers CD40 and CD80.
• Reduction in CD86 compared to HDM animals.

Anti-IL-17

• Reductions in the number and activation of DCs were not observed for anti-IL-17 treatment.
CLINICAL DEVELOPMENT AND UPCOMING TRIALS

Target Product Profile
- Long-term therapy to control symptoms and prevent exacerbations
- Daily oral treatment in addition to ICS/LABA inhalers

Working clinical study design
- Patient population: eosinophilic, neutrophilic, mixed
- 90 patients
- Phase Ib to open 2019

Primary endpoint: safety and tolerability
Secondary endpoints:
- Sputum eosinophils, neutrophils
- ACQ

Biomarkers:
- Full MicroDx analysis
- Sputum & serum immune markers