Live Biotherapeutics

From Concept to Clinic in Immuno-Oncology

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4D pharma PLC
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COMPANY BY NUMBERS

2014
Company formation

Proprietary bacteria
6500+

Scalable platforms
2

Sites
5

Scientists
60+

LBP patient trials
2

LBP programmes
17

Company formation

£100 million+
Capital raised to date

Granted patents
300+

Fermenters
3000L

Patent applications
300+

Capsules
20+ million
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>Disease Area</th>
<th>Preclinical</th>
<th>Development</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
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<tr>
<td><strong>Gastro-intestinal</strong></td>
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<td>Blautix <em>Irritable Bowel Syndrome</em></td>
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<td>Thetanix <em>Crohn’s Disease</em></td>
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<td>Rosburix <em>Ulcerative Colitis</em></td>
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<td><strong>Immuno-oncology</strong></td>
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<td>MRx0518 <em>Solid tumours</em></td>
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<td><strong>Respiratory</strong></td>
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<td>MRx0004 <em>Asthma</em></td>
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<td>MRx0001 <em>Allergic Asthma</em></td>
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<td><strong>Autoimmune</strong></td>
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<td>MRx0002 <em>Multiple Sclerosis</em></td>
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<td>MRx0006 <em>Rheumatoid Arthritis</em></td>
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<td><strong>Others</strong></td>
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<td><strong>CNS</strong></td>
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<td>Neurodegeneration</td>
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<td>Autism</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
# Research
- MicroRx platform
- Focus on bacterial functionality
- 17 programmes

# Development + Manufacturing
- Concept to clinic in-house
- Stable, repeatable processes
- GMP certified, commercial-scale

# Clinical
- Phase Ib IBS complete
- Phase Ib CD nearing completion
- Up to 4 clinical studies by end 2018
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
LITERATURE EVIDENCE SUPPORTING 4D APPROACH IN IMMUNO-ONCOLOGY

Microbiome impacts efficacy of checkpoint inhibition in patients

- Anti-PD-1-responsive patients have significantly increased microbiome diversity compared with non-responders (Gopalakrishnan et al., 2018, Routy et al., 2018)

This effect is causative, not just a correlation

- Animals humanised with ‘responder’ microbiota have delayed tumour growth and enhanced response to anti-PD-1 therapy (Gopalakrishnan et al., 2018)

Single-strain LBPs inhibit tumour growth and increase microbiome diversity

- Single-strain live biotherapeutics are effective in reducing tumour growth (Sivan et al., 2015, Vetizou et al., 2015, 4D pharma data) and increase microbiome diversity (4D pharma data) in animal models

Clinical data supports MRx0518 intervention

- NSCLC patients who respond to checkpoint inhibition have an increased abundance of MRx0518 species in their microbiome (Routy et al., 2018)
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 – Immuno-oncology
Significant increase in microbiome diversity

- Microbiome diversity is known to significantly affect response to checkpoint inhibitors in the clinic (Gopalakrishnan et al., 2018; Routy et al., 2018)
- MRx0518 treatment leads to an increase in microbiome diversity in animal models
- Strongly supportive of combination therapy with checkpoint blockade
- MicroDx platform: Proven in-house capability to perform full microbiome analysis
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 SELECTION – STRONG IMMUNOSTIMULATORY PROFILE IN NUMEROUS HUMAN CELL TYPES

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 RNAsSeq)

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<thead>
<tr>
<th>MRx0518: Host response</th>
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<tbody>
<tr>
<td>CCL20</td>
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<td>CxCL1</td>
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<td>CXCL3</td>
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<td>CXCL8</td>
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<td>TNF</td>
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**Surfacome/secretome**
- ID of MRx0518 MAMPs
- Multiple targets of interest related to host signalling

- MRx0518
- MRx0518 Δlic

**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
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 \emph{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