Live Biotherapeutics
Form Follows Function
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FROM COMPLEX MIXTURES TO NEW THERAPEUTIC CLASSES

- Targeted small-molecules
- Antibodies
- Fungal broths
- Serum therapy
- Plant extracts
- Vaccines
- Blood transfusions
- Cytotoxic small-molecules
- Therapeutic proteins
SERUM THERAPY AND THE BIRTH OF ANTIBODY BIOLOGICS

- Emil von Behring pioneered ‘serum therapy’ to treat infection
- Breakthrough new treatments for diphtheria and tetanus
- Over next 70 years, antibodies from serum identified and characterised
- Polyclonal antibodies from serum used in clinic in late 1960s
- First monoclonal antibody produced in mice in 1975
- First approval 1986

The discovery and development of antibodies

- 1890s: Von Behring develops ‘antitoxin’ for diphtheria
- 1901: Von Behring wins 1st Nobel Prize for Medicine
- 1959: ‘Skymed’ immune globulin first administered in clinic
- 1968: Edelman and Porter characterise antibody structure
- 1975: First monoclonal antibody produced in mice
- 1986: First licenced mAb, Orthoclone OKT3, approved
- 2017: Global mAb market > $100 bn
• First successful blood transfusion in humans occurred in the early 19\textsuperscript{th} century

• Late 19\textsuperscript{th} century, scientists observed that plasma from anaemic rabbits can stimulate blood cell production

• Not until mid-20\textsuperscript{th} century that EPO was identified from blood

• Low serum concentrations meant that recombinant DNA tech required to produce meaningful amounts

• Epogen became Amgen’s first product in 1989
16th century Chinese physician Li Shizhen documented the use of ‘yellow soup’ containing fresh, dried or fermented stool to treat abdominal diseases.

FMT first reported in western medical literature in 1958 as treatment for infectious colitis (now known to be caused by *C. diff*).

Numerous efforts to standardise/improve practicality of FMT including use of frozen and freeze-dried material.

First live biotherapeutic clinical study conducted in 2005 by Oxthera.

The development of FMT and live biotherapeutics:

- **4th Century**: Faecal matter used in Chinese medicine to treat food poisoning and diarrhoea.
- **1500s**: Li Shizhen uses ‘yellow soup’.
- **1958**: Ben Eiseman uses FMT to treat fulminant pseudomembranous colitis (CDI).
- **1983**: First report of rectal infusion of faeces for CDI.
- **1989**: First reported use of FMT for IBD.
- **2005**: First LBP clinical trial (Oxthera).
Complex mixtures contain functionality, but are poorly defined

Historical dominance of small molecules, antibodies, proteins

Based on single ‘validated target’ hypothesis

Biological pathways do not operate in isolation

All of the top ten drugs have significant side-effect profiles

None of these are effective in all patients
WHOLE CELL BIOLOGICS – FORM FOLLOWS FUNCTION?

- Functionality in complex organisms exists at different levels
- Organs, tissues, cells
- Cells are the simplest unit of independent biological functionality
- Potential to deliver therapeutically relevant effects ‘in context’
- If this can be harnessed and controlled, the effects can be remarkable
- CAR-T, stem cell therapy

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OncLive
CAR-T Cell Response Rate Tops 80% in NHL Trial

Forbes
New Immunotherapy Treatment Removes All Tumors In Woman With Advanced Metastatic Breast Cancer

The New York Times
T-Cell Therapy Puts Leukemia Patients in Extended Remission

nature
Reprogrammed cells relieve Parkinson's symptoms in trials
• Microbiome has significant functionality relevant to human health

• Single strains of bacteria are the simplest unit of contained functionality in the microbiome

• Is it possible to harness that functionality and create single strain live biotherapeutic products?

• What is the breadth of their potential applications?
developing science delivering therapies
• Deep, broad pipeline across multiple therapeutic areas
• Largest intellectual property estate in microbiome space
• Only microbiome company with true ‘end-to-end’ capability
• In patient data with IBS and Crohn’s; first mover in cancer and asthma
• Targeting four clinical programmes by end 2018
COLLABORATIONS

**MERCK**

- Immuno-oncology
- MRx0518 combination with Keytruda

**Imperial College London**

- Immuno-oncology
- MRx0518 Phase Ib neoadjuvant study

**MD Anderson Cancer Center**

- Immuno-oncology
- Multiple studies of MRx0518

**apc Microbiome Ireland**

- IBS, CNS, cancer
- Preclinical models
- Microbiome profiling

**BCM**

- Pre-clinical
- Germ-free animal models

**HOUstON Methodist**

- Irritable bowel syndrome
- Blautix Phase II study

**INRA**

- Irritable bowel syndrome
- Germ-free animal models
### 4D PHARMA - PIPELINE ADDRESSING KEY DISEASE AREAS

<table>
<thead>
<tr>
<th>Disease Area</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
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<tbody>
<tr>
<td><strong>Gastro-intestinal</strong></td>
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<tr>
<td>Blautix <em>Irritable Bowel Syndrome</em></td>
<td>✔️</td>
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<tr>
<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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<tr>
<td>MRx0518 <em>Solid tumours</em></td>
<td>✔️</td>
<td>✔️</td>
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<tr>
<td><strong>Respiratory</strong></td>
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<tr>
<td>MRx0004 <em>Asthma</em></td>
<td>✔️</td>
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<tr>
<td>MRx0001 <em>Allergic Asthma</em></td>
<td>✔️</td>
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<tr>
<td><strong>Autoimmune</strong></td>
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<tr>
<td>MRx0002 <em>Multiple Sclerosis</em></td>
<td>✔️</td>
<td>✔️</td>
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<tr>
<td>MRx0006 <em>Rheumatoid Arthritis</em></td>
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<tr>
<td>Others</td>
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<tr>
<td><strong>CNS</strong></td>
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<tr>
<td>Neurodegeneration</td>
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<td>✔️</td>
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<td>Autism</td>
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MRX0518

• Gram-positive, flagellated, 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 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 RNASeq)

<table>
<thead>
<tr>
<th>MRx0518:Host response</th>
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<tbody>
<tr>
<td>CCL20</td>
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<tr>
<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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**Surfaceome/secretome**
- ID of MRx0518 MAMPS
- Multiple targets of interest related to host signalling

![Surface Proteins 593] ![Secreted Proteins 399]

**Flagellin**
- Flagellin identified as potential contributing molecule
- In depth investigation of MRx0518 flagellin has identified strain-specific signalling effects
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 shedding of flagellin into the supernatant

Dose-response with recombinant flagellins

- Purified recombinant flagellins activate TLR5
- MRx0518 flagellin is more potent than the reference flagellin at low concentrations

Caly et al., in submission
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
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 shed 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 cancer 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
HYPOTHESIS TESTING

- Single strain LBPs aren’t able to deliver functionality in vivo
- Engraftment is necessary in order to see an effect
- You can’t get IP on LBPs
- LBPs can’t be manufactured to pharmaceutical standards
- The regulatory environment isn’t clear
- Big pharma and biotech will never be interested in LBPs
• Single-strain LBPs aren’t able to deliver functionality in vivo

• Engraftment is necessary in order to see an effect

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• LBPs can’t be manufactured to pharmaceutical standards

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• Big pharma and biotech will never be interested in LBPs
IBS: What’s Rome got to do with it? (Abstract 469)
Dr. Ian Jeffery (4D Pharma Cork Ltd), Dr. Eileen O’Herlihy (4D Pharma Cork Ltd), Ms. Meenakshi Pradhan (4D Pharma Cork Ltd), Prof. Paul O’Toole (4D Pharma Cork Ltd), Prof. Fergus Shanahan (4D Pharma Cork Ltd)

Unravelling the molecular mechanisms underlying the therapeutic effects of Bifidobacterium breve MRx0004 (Abstract 474)
Dr. Mary O’Connell Motherway (APC Microbiome Ireland and School of Microbiology, University College Cork, Cork, Ireland), Dr. Emma Hennessy (4D Pharma Research Ltd), Dr. Delphine Caly (4D Pharma Research Ltd), Dr. Emma J. Raftis (4D Pharma Research Ltd), Dr. Imke E. Mulder (4D Pharma Research Ltd)

Identification and characterisation of gut bacterial strains able to modulate neuroinflammation and neurodegeneration (Abstract 475)
Dr. Anna Ettorre (4D Pharma Research Ltd), Dr. Suaad Ahmed (4D Pharma Research Ltd), Dr. Parthena Fotiadou (4D Pharma Research Ltd), Dr. Imke E. Mulder (4D Pharma Research Ltd) et al.

Bifidobacterium breve MRx0004 suppresses both neutrophil and eosinophil lung infiltration and protects against airway inflammation in a severe asthma model (Abstract 476)
Dr. Emma J. Raftis (4D Pharma Research Ltd), Mrs. Margaret I. Delday (4D Pharma Research Ltd), Dr. Philip D. Cowie (4D Pharma Research Ltd), Dr. Seánín M. Mccluskey (4D Pharma Research Ltd), Dr. Nicole Reichardt (4D Pharma Research Ltd), Dr. Imke E Mulder et al.