Developing Live Biotherapeutics to Target the Gut-Brain Axis
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4D PHARMA - INTEGRATED DEVELOPMENT FROM CONCEPT TO CLINIC

4D pharma is a leader in the development of single strain LBPs, a novel class of drug derived from the human gut microbiome

- Bench to bedside in-house – true end-to-end microbiome company
- Fully developed infrastructure and expertise, from strain isolation through to manufacturing
- Significant experience in navigating the regulatory landscape to deliver clinic-ready candidates

MicroRx® platform - extensive library of strains, focus on functionality, adaptable platform
Research collaboration with MSD in vaccines
World-leading IP estate with multi-layered protection facilitated by detailed mechanistic understanding

3000L, cGMP-certified manufacturing capabilities, unique in the microbiome space
CMC and ‘manufacturability’ integrated early into candidate development to accelerate progression into the clinic
Production for 4 clinical trials in parallel

4 clinical-stage candidates across multiple TAs
Clinical collaboration with MSD in I-O
Positive early signals for MRx0518 + Keytruda
### CORE PIPELINE ADDRESSING KEY GLOBAL DISEASES

<table>
<thead>
<tr>
<th>Programmes</th>
<th>DISCOVERY</th>
<th>PRECLINICAL</th>
<th>DEVELOPMENT</th>
<th>PHASE I</th>
<th>PHASE II</th>
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<tr>
<td><strong>Immuno-oncology</strong></td>
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<td>MRx0518 Solid tumours – Combination study with Keytruda®</td>
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<td>MRx0518 Solid tumours – Monotherapy study (Tx naive neoadjuvant)</td>
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<tr>
<td>MRx0518 Pancreatic cancer – Monotherapy study (neoadjuvant)</td>
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<td>MRx0573 New solid tumour types</td>
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<td>MRx1299 HDACi – New solid tumour types</td>
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<td><strong>Gastro-intestinal</strong></td>
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<td>Blautix® Irritable Bowel Syndrome</td>
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<td>Thetanix® Crohn’s Disease</td>
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<td><strong>Respiratory</strong></td>
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<td>MRx-4DP0004 COVID-19</td>
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<td>MRx-4DP0004 Asthma</td>
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<td><strong>CNS</strong></td>
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<td>MRx0005 Neurodegeneration</td>
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<td>MRx0029 Neurodegeneration</td>
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<td><strong>Platform</strong></td>
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<td>Vaccines</td>
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<td>Autoimmune</td>
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FOCUS ON FUNCTIONALITY: MicroRx® PLATFORM

**Product development**
- Integrated scale-up and optimization
- Strain-specific fermentation and formulation

**Strain engineering**
- Gene disruption/deletion
- Recombinant protein expression

**Isolation**
- Significant culturomics expertise
- Broad coverage and diversity
- Previously unisolated organisms

**Discovery**

**Proteomics/lipidomics**
- Cell surface shaving
- Characterisation of secreted proteins
- Targeted and driven by host signalling data

**Genome mining**
- Whole genome sequencing
- Comparative genomics and bioinformatics

**Host-response assays**
- Suite of host cells, spheroids/organoids
- Rodent models (disease, SPF, GF)

**Metabolomics**
- Metabolomic fractionation
- Exhaustive profiling of effector molecules

**Isolation**

**Discovery**

**Pathways**

**Isolation**
The Gut-Brain Axis: MicroRx® Drug Discovery Platform
The gut-brain axis plays a critical, yet poorly defined role in the aetiology of neurodegenerative and psychiatric disorders, highlighting the crucial role of the gut and the microbiome on central nervous system processes

- The gut microbiota can affect neurological processes and pathophysiology, from stress responses to neurodegenerative disorders

- Significant differences in the gut microbiota of patients with neurological disorders compared to age-matched healthy controls

- Gastrointestinal symptoms are a common comorbidity of CNS disorders and often manifest years before any clinical CNS manifestations are confirmed

- Changes in gut-brain communication could lead to neural network defects and CNS disorders, including:
  - Gut permeability
  - Production of neuromodulatory compounds
  - Activation of the enteric nervous system (ENS)
  - Vagus nerve function
  - Peripheral immune system, microglia and astrocytes
• Previous approaches to NDDs have failed to achieve disease modification
• High unmet need for new therapeutic strategies for brain-related conditions
• MicroRx® has generated clinical candidates in oncology, respiratory and gastrointestinal disease
• Now taking 4D into neurodegeneration, specifically targeting neuroinflammation and neuroprotection
• Focus on restoring gut-brain axis communication by assessing inter-tissue signalling between gut, periphery and CNS
• Combination of *in vitro* and *ex vivo* cell-derived functional systems and *in vivo* translational models

**Commensal effector molecules**
- Neuroprotection
- Neuroinflammation
- Neurodifferentiation
- Protein misfolding and aggregation
- Blood-brain barrier function

**Commensal signalling molecules**
- Neurotransmitters
- Anti-inflammatory mediators
- Antioxidants
- Indoles
- Tryptophan
- Polyphenols

**Commensal bacterial strains**
- Gut barrier function
- Anti-inflammatory properties
- Gut dysbiosis
- Short-chain fatty acids
- Tryptophan, Indole
- Protein misfolding and aggregation
- Drug interactions

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Neurodegenerative Disorders:
Parkinson’s Disease
Parkinson’s Disease

- Most common movement disorder: ~10M people worldwide
- Two forms of PD: idiopathic and familial
- Deterioration of motor function due to loss of dopamine-producing brain cells in the motor region of the brain
- Linked to accumulation or dysfunction of misfolded α-synuclein in Lewy bodies

The gut microbiome in PD

- PD patients experience GI symptoms and gut microbiome changes decades before motor symptoms and CNS involvement
- Transplantation of faecal microbiota from PD patients into mice leads to motor deficits and neuroinflammation
- Presence of α-synuclein in the mucosal and submucosal nerve fibres and ganglia of individuals with Parkinsonian syndrome
- Gut microbiome could influence the course of neurological disorders via interfering with medications such as L-DOPA
MicroRx® platform has identified two gut commensal bacterial strains which show strong potential for the treatment of neurodegenerative diseases, such as PD:

- MRx0029 – *Megasphaera massiliensis*
- MRx0005 – *Parabacteroides distasonis*

**SUMMARY OF NEURODEGENERATION PROGRAM TO DATE**

- Reduction of neuroinflammation (cytokine production, TLR4/NF-kB signalling)
- Protection of neuronal cells from oxidative stress
- Promotion of intestinal barrier integrity
- Induction of dopaminergic neuronal differentiation
- Protection of dopaminergic neurons and increased dopamine and DOPAC

LBP candidates progressing through development cycle

Rapid progression into first-in-man trial in patients
ANIMAL MODELS OF PARKINSON’S DISEASE (PD)

Different models (environmental & genetic) replicate different features of PD:
• Degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc)
• Deficiency of striatal dopamine (DA) and metabolites (DOPAC and HVA)
• Aggregation of α-synuclein (Lewy body-like pathology) in the CNS, PNS and ENS
• Neuroinflammation, associated with alterations to many cell types (microglia)
• Gastrointestinal and olfactory dysfunction
• Progressive motor dysfunction and cognitive decline

<table>
<thead>
<tr>
<th>Neurotoxic-induced Parkinsonian syndrome</th>
<th>Transgenic models of PD-related genes</th>
<th>Viral vector-based models of PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 6-hydroxydopamine (6-OHDA) and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)</td>
<td>• SNCA, PINK1, PARK7, DJ-1, Parkin and LRRK2</td>
<td>• Viral (AAV/Lentiviral) delivery vehicle</td>
</tr>
<tr>
<td>• Degeneration of dopaminergic neurons</td>
<td>• No dopaminergic neuron degeneration</td>
<td>• Irregular forms of α-synuclein</td>
</tr>
<tr>
<td>• Reduced DA, DOPAC and HVA levels</td>
<td>• No reduction in DA, DOPAC and HVA</td>
<td>• Degeneration of dopaminergic neurons</td>
</tr>
<tr>
<td>• Limited α-synuclein aggregation, restricted to chronic MPTP model</td>
<td>• α-synuclein aggregation apparent, restricted to A53T and A30P models</td>
<td>• Reduced DA, DOPAC and HVA levels</td>
</tr>
<tr>
<td>• Limited behavioural readouts</td>
<td>• Prominent behavioural deficits</td>
<td>• Delivery of α-synuclein to SNc results in Lewy body-like pathology</td>
</tr>
<tr>
<td>• Useful to study mechanism of cell death</td>
<td>• Useful to study roles of α-synuclein aggregation and mutations related to PD</td>
<td>• Prominent behavioural deficits</td>
</tr>
<tr>
<td>• Environmental pesticides also implicated</td>
<td></td>
<td>• Useful to study PD-pathology including cell death and α-synuclein aggregation</td>
</tr>
</tbody>
</table>

Dopaminergic neurons in SNc in an MPTP model

α-synuclein accumulation in A53T transgenic mice

α-synuclein accumulation and loss of dopaminergic neurons in an AAV-A53T model
THE MPTP MOUSE MODEL OF PD

Model summary

- **Model**: 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine (MPTP)-Induced Parkinsonian Syndrome
- **Disease Induction**: MPTP administered i.p. at a dose of 20mg/kg, twice a day for five days
- **Animal Strain**: Male C57BL/6 mice (7 weeks of age)
- **Positive Control**: 7-nitroindazole (50 mg/kg; i.p.; b.i.d.)
- **Length of Model**: 35 days (14 days pre-treatment + 21 days in vivo)

Key readouts

- DA transporter levels
- Dopamine and metabolites
- Quantification of dopaminergic neurons
- 16S microbiome analysis
- Cytokine analysis
- Metabolomics
- Inflammatory mediators
- Histopathology
- Permeability
- Short chain fatty acid analysis

Study design

- **D-21**: Animal acclimation
- **D-14**: Dosing commences
- **D1 to D5**: MPTP administered i.p. at a dose of 20mg/kg, twice a day for five days
- **D21**: Termination & tissue collection

<table>
<thead>
<tr>
<th>Group</th>
<th># of Animals</th>
<th>Disease Induction</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>Saline</td>
<td>PBS</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>MPTP</td>
<td>PBS</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>MPTP</td>
<td>MRx0005</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>MPTP</td>
<td>MRx0029</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>MPTP</td>
<td>Peanut Oil</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>MPTP</td>
<td>7-Nitroindazole</td>
</tr>
</tbody>
</table>
ASSESSMENT OF DISEASE MODIFYING POTENTIAL IN THE MPTP MOUSE MODEL OF PD

TH+ cell numbers
- MRx0029 protected from loss of tyrosine hydrolase (TH)+ neurons in MPTP-induced brain lesions
- Neuroprotection is comparable to positive control 7-Nitroindazole (7-NI).

Dopamine and DOPAC Quantification
- MRx0005 protected from loss of striatal dopamine and DOPAC in MPTP-treated mice. The effect is similar to that of the positive control 7-NI.
**Intestinal barrier function**

- MRx0029 increased gene expression of tight junction proteins associated with gut barrier function (occludin and TJP)
- MRx0029 decreased gut permeability (as measured by FITC/Ussing chambers)

**Neuroprotection**

- MRx0029 completely rescued mitochondrial damage induced by MPP+

![Graphs and images showing gene expression and permeability changes](image-url)
MRx0005 AND MRx0029: DATA FROM CNS DISCOVERY PLATFORM

**Neuroinflammation**

- MRx0005 and MRx0029 reduce secretion of IL-6 after LPS treatment in glioblastoma astrocytes (U373) U373 cells and TNF-α treatment in microglia cells (HMC3)

- MRx0005 significantly decreased NF-κB activation in HEK-TLR4 cells treated with LPS and mutated α-syn proteins

- MRx0005 and MRx0029 decreased IL-6 secretion in U373 cells co-cultured with SH-SY5Y cells treated with αSyn WT and mutated proteins

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**IL-6 secretion in U373 cells**

- Untreated
- LPS
- Media
- MRx0005
- MRx0029

**IL-6 secretion in HMC3 cells**

- Untreated
- TNF-α
- Media
- MRx0005
- MRx0029

**NF-κB activation in HEK-TLR4 cells**

- Untreated
- LPS
- Media
- MRx0005
- MRx0029

**α-Synuclein induced inflammation in U373 Cells**

- Untreated
- A53T
- A53T + MRx0005
- A53T + MRx0029
- E46K
- E46K + MRx0005
- E46K + MRx0029
  
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Neurodevelopmental Disorders: Autism Spectrum Disorder
AUTISM SPECTRUM DISORDER (ASD) AND THE GUT MICROBIOME

**Autism Spectrum Disorder**
- Neurological development disorder: 1 in 160 children affected
- Cause is unknown: genetic, environmental, psychological, and neurological factors implicated
- ASD categorised in two ways: primary or secondary
- Wide range of symptoms: social interaction, language and communication, patterns of thoughts and physical behaviour

**The gut microbiome in ASD**
- Gastrointestinal symptoms are a comorbidity in ASD
- Altered gut microbial composition in ASD and in animal studies
- Germ-free mice exhibit hallmark autistic behaviours after undergoing gut microbiota transplantation from humans with ASD
- Administration of single bacterial strains can reverse ASD-related behavioural and gastrointestinal changes in humans and animals
- Children with ASD given microbiota transfer therapy show reductions in gastrointestinal symptoms and improvements in ASD behaviours
MicroRx® platform has identified a gut commensal bacterial strain which show strong potential for the treatment of neurodevelopmental disorders, such as ASD:

- MRx0006 – *Blautia stercoris*

**MRx0006**

- Modulates neuropeptide gene expression *in vitro* and *ex vivo*
- Anti-inflammatory effects *in vitro* and *in vivo*
- Decreased stereotyped behaviour, suggesting reversal of repetitive behaviours *in vivo*
- Increased social behaviour, reduced anhedonia
- Decreased anxiety-like behaviour in open-field test

LBP candidate progressing through development cycle
THE BTBR MOUSE MODEL - A GENETIC MODEL OF ASD

Model summary

- **Model**
  BTBR genetic mouse model of ASD

- **Animal Strain**
  Male BTBR mice (8 weeks of age)

- **Length of Model**
  11 weeks

Key readouts

- **Social**
  - Three chamber social test
  - Social transmission of food preference
  - Marble burying test
  - Grooming behaviour

- **Stereotyped**
  - Elevated plus maze
  - Open field test

- **Anxiety**
  - Forced swim test
  - Female urine sniffing test

- **Depression**
  - Novel object recognition

- **Cognition**
  - Ussing chambers
  - Carmine red

- **Ileum and Colon**
  - Cytokine profiling

- **Blood**

Study design

- **Week 0**
  Animal acclimation

- **Week 1-3**
  Dosing commences

- **Week 4**
  Marble burying and grooming test

- **Week 5**
  Three chamber social test and elevated plus maze
  Female urine sniffing test

- **Week 6**
  Open field, novel object recognition and social transmission of food preference

- **Week 7**
  Female urine sniffing test

- **Week 8**
  Elevated plus maze
  Carmine red

- **Week 9**
  Forced swim test

- **Week 10**
  Termination & tissue collection
### THE MIA MOUSE MODEL - AN ENVIRONMENTAL MODEL OF ASD

#### Model summary

<table>
<thead>
<tr>
<th>Model</th>
<th>Maternal immune activation (MIA)</th>
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<tbody>
<tr>
<td>Animal Strain</td>
<td>Male C57BL/6N mice (8 weeks of age)</td>
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<tr>
<td>Length of Model</td>
<td>10 weeks</td>
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</tbody>
</table>

#### Key readouts

- **Social**
  - Three chamber social test
  - Marble burying test
  - Grooming behaviour

- **Stereotyped**
  - Elevated plus maze
  - Open field test

- **Anxiety**
  - Forced swim test
  - Female urine sniffing test

- **Depression**
  - Novel object recognition

- **Cognition**
  - Ussing chambers
  - Carmine red

- **Blood**
  - Cytokine profiling

- **Ileum and Colon**
  - Novel object recognition

#### Study design

<table>
<thead>
<tr>
<th>Week 0</th>
<th>Animal acclimation</th>
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<tbody>
<tr>
<td>Week 1-3</td>
<td>Three chamber social test and marble burying</td>
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<tr>
<td>Week 4</td>
<td>Open field, novel object recognition and elevated plus maze</td>
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<tr>
<td>Week 5</td>
<td>Female urine sniffing test and carmine red</td>
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<tr>
<td>Week 6</td>
<td>Grooming and social transmission of food preference</td>
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<td>Week 7</td>
<td>Forc...</td>
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<tr>
<td>Week 8</td>
<td>Termination &amp; tissue collection</td>
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C57BL/6J pregnant mice received a single intraperitoneal injection of the synthetic analogue of viral double-stranded RNA poly(I:C)
ATTENUATION OF AUTISTIC-LIKE BEHAVIOUR IN GENETIC AND ENVIRONMENTAL MOUSE MODELS OF ASD

**Sociability**
- MRx0006 increased the amount of time that animals spent interacting with a mouse over an object compared to vehicle

**Reward-seeking behaviour**
- MRx0006 increased the time spent sniffing urine vs. water
ATTENUATION OF AUTISTIC-LIKE BEHAVIOUR IN GENETIC AND ENVIRONMENTAL MOUSE MODELS OF ASD

Stereotyped behaviour

- MRx0006 decreased the time spent grooming in BTBR-animals compared to vehicle
- MRx0006 decreased the number of marbles buried in MIA-animals compared to vehicle

Depressive-like behaviour

- MRx0006 decreased the immobility time in MIA-animals compared to vehicle

Anxiety-like behaviour

- MRx0006 increased the time spent in the inner zone of the open field in BTBR-animals compared to vehicle
IN VITRO AND EX VIVO PITUITARY NEUROPEPTIDE EXPRESSION

Oxytocin and arginine vasopressin:
- Neuropeptides
- Synthesized in the hypothalamus
- Secreted from the posterior pituitary gland
- Implicated in complex behaviours such as:
  - Social behaviours
  - Trust
  - Romantic bonds
  - Aggression

Increases in oxytocin and arginine vasopressin may be linked to improvement in autistic-like behaviour:
- MRx0006 increased oxytocin and oxytocin receptor mRNA expression in mHypoA2-28 cells
- MRx0006 increased arginine vasopressin in the hypothalamus of BTBR mice

![Oxytocin and Arginine Vasopressin Molecules]

**Pituitary neuropeptides and their receptors**

<table>
<thead>
<tr>
<th>Peptide</th>
<th>mRNA Expression (normalized to β-actin)</th>
<th>Vehicle</th>
<th>MRx0006</th>
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<tbody>
<tr>
<td>Oxytocin Peptide</td>
<td><strong>3.0 ± 0.5</strong></td>
<td>0</td>
<td><strong>3.5 ± 0.3</strong></td>
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<tr>
<td>Arginine Vasopressin Peptide</td>
<td><strong>1.5 ± 0.2</strong></td>
<td>0</td>
<td><strong>2.0 ± 0.4</strong></td>
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</tbody>
</table>

**Oxytocin Peptide in mHypoA2-28 cells**

**Arginine Vasopressin Peptide in Hippocampus of BTBR mice**
Summary
PROGRESS FROM CNS DISCOVERY PLATFORM

• Functional screening platform MicroRx® designed to target different aspects of neurological disorders
• Discovered human gut commensal bacteria that can modulate relevant cell types and pathways via the gut-brain axis
• Demonstrated efficacy in a variety of pre-clinical models

Rational selection of bacterial strains from proprietary culture collection affecting CNS disorders

Targeted *in vitro* screening for mechanisms involved in gut-brain axis communication can identify novel live biotherapeutic candidates

The strains have complementary characteristics and distinct mechanisms of action

All strains have shown efficacy in an industry-standard animal models

4D is preparing plans to quickly generate clinically-relevant inpatient data
developing science delivering therapies