developing science
delivering therapies
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Live Biotherapeutics

- Single-strain commensal bacteria encapsulated for oral delivery
- Highly favourable toxicity/side-effect profile
- Accelerated preclinical development and early in-patient data

Industry leader with differentiated approach

- 4D pharma is an integrated platform & product company
- Mechanistic approach focused on function: targeting and addressing known disease pathways via effector molecules
- Sector-leading IP estate; more than 550 granted patents
- Multiple value inflection points; proof-of-concept clinical data on the horizon

Breakthrough class of medicines with potential to change the way we treat disease
### CORE PIPELINE ADDRESSING KEY GLOBAL DISEASES

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<td><strong>Immuno-oncology</strong></td>
<td>MRx0518</td>
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<td><em>Solid tumours – Combination study with Keytruda®</em></td>
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<td>Autism</td>
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Phase I/II study enrolling
Phase I study enrolling
Phase I study opening H2 2019
Phase II study enrolling
Phase II in planning
Phase I/II opening Q2 2019
Focus Programme:
Neurodegenerative Disorders
GUT MICROBIOME IS EMERGING AS A NEW FRONTIER IN NEURODEGENERATION

• The gut microbiota exerts important effects on brain functions and can affect physiological processes such as host stress responses, behaviour and pathophysiology such as depression and anxiety.  

• Recent studies point towards gut microbiota alterations in PD and other neurodegenerative disorders when comparing patient faecal samples to age-matched healthy controls.

• Gut constipation can manifest as a pre-motor or prodromal symptom years before any clinical manifestation of central nervous system (CNS) neurodegeneration is confirmed.

1Cryan and Dinan, Nat Rev Neurosci 2012;  
2Foster et al, Neurobiol Stress 2017;  
3Scheperjans et al, Mov Disord 2015;  
4Bedarf et al, Genome Med 2017;  
5Stirpe et al, Eur J Neurol 2016
Our assay development screening platform is designed to reproduce both environmental and genetic triggers associated with PD pathology and to inform on appropriate preclinical models and biomarkers identification.

Selected candidates show efficacy in MPTP mouse model.

Neurons, microglia, astrocytes, reporter cell lines

Neuroinflammation
Neurodegeneration

Primary and secondary metabolites analysis

Inflammation
Gut permeability
PD-specific markers

Intestinal epithelial cell models

MicroRx® bacteria

MRx0005 and MRx0029 – NDDs
MRx0005
Gram-negative, anaerobe
*Porphyromonadaceae* family
Non-motile, non-sporulating

- Decreases IL-6 secretion in glioblastoma cells; and co-culture of glioblastoma and differentiated neuroblastoma cells
- Decreases gene expression of IL-6 in amygdala from healthy mice fed with MRx0005
- Protects several brain-derived cells (glioblastoma, microglial and differentiated neuroblastoma cells) from oxidative stress
- Metabolites: increased production of succinic acid, C1-C3 SCFA
- Induces partial protection from MPTP-induced cytotoxicity in differentiated neuroblastoma cells and in a MPTP model of PD

MRx0029
Gram-negative, anaerobe
*Veillonellaceae* family
Non-motile, non-sporulating rods

- Decreases IL-6 secretion in glioblastoma cells; and co-culture of glioblastoma and differentiated neuroblastoma cells
- Protects differentiated neuroblastoma cells from oxidative stress
- Induces MAP2 gene expression in SH-SY5Y cells
- Metabolites: increased production of C4-C6 SCFA
- Increases gut-barrier function
- Induces complete protection from MPTP-induced cytotoxicity in differentiated neuroblastoma cells and in a MPTP model of PD
MRx0005 AND MRx0029 DOWN-REGULATE IL-6 SECRETION INDUCED BY DIFFERENT STIMULI

*Elevated plasma concentrations of IL-6 correlate with increased risk of PD*

- MRx0005 and MRx0029 reduced secretion of IL-6 after LPS treatment in U373 cells
- MRx0005 and MRx0029 reduce secretion of IL-6 after TNF-α treatment in HMC3 cells

Gene expression of IL-6 is decreased in the amygdala of brains from mice fed with MRx0005

**U373 cells**

**HMC3 cells**

**il6 Amygdala**
MRx0005 AND MRx0029 INDUCED CELL-DEPENDENT DOWN-REGULATION OF NFκB ACTIVATION AND IL-6 SECRETION BY αSYN PROTEINS

αSyn, A53T, E46K and A30P mutated forms of α-synuclein are linked to familial PD and early disease onset

• In HEK-TLR4 cells treated with αSyn WT and mut proteins, MRx0005 significantly decreased NFκB activation that is αSyn mut-dependent

• In U373 cells co-cultured with SH-SY5Y cells treated with αSyn WT and mut proteins, both MRx0005 and MRx0029 decreased IL-6 secretion

• Interestingly, and in contrast with HEK-TLR4 cells, MRx0029 significantly reduced secretion of IL-6, suggesting a specificity associated with MRx0029 but not MRx0005
MRx0005 and MRx0029 protect from oxidative stress

- MRx0029 and MRx0005 showed an intrinsic antioxidant and ROS-scavenging capacity in several biochemical assays.
- MRx0005 protects astrocytoma, microglia and differentiated neuroblastoma cells from THBP-induced ROS.
- Interestingly, MRx0029 only protects differentiated neuroblastoma cells from oxidative stress.

- MRx0029 completely rescued mitochondria damage induced by MPP+, while MRx0005 showed only a partial protection, albeit still significant.
- These findings suggest that MRx0029 might have a specific tropism for neuron-like cells.
GUT BACTERIA PRODUCE METABOLITES RELEVANT FOR NEUROPROTECTION IN PD

Bacterial metabolites can directly influence the host response to oxidative stress and cell-to-cell communication

- MRx0005 and MRx0029 have distinct metabolite signatures:
  - MRx0005 produces C1-C3 SCFA (acetic acid, propionic acid)
  - MRx0029 produces C4-C6 SCFA (butanoic, pentanoic, hexanoic acid)

- Succinic acid was notably higher in MRx0005, while 4-hydroxy-phenyl acetic acid was produced in significant amounts by MRx0029

- SCFAs are responsible for the decrease of IL-6 secretion in vitro in U373 cells after challenge with LPS
GUT-BRAIN AXIS: MRx0029 INCREASES TIGHT JUNCTION PROTEIN IN VITRO, IN VIVO AND EX VIVO

‘Leaky gut’ in PD patients is linked to systemic circulation of molecules like LPS, ultimately associated to neuroinflammation

- MRx00029, but not MRx0005, increased gene expression of proteins associated to barrier function
  - **In vitro** (HT29-MTX)
  - **In vivo** (mice fed with our strains)
  - **Ex vivo**

---

**In vitro**

- Villin
- Occludin
- TJP1
- TJP2

**In vivo**

- TJP1
- Occludin

**Ex vivo**

- FITC (μM/mL)
MRX0029 INDUCES A DOPAMINERGIC-LIKE NEURON PHENOTYPE IN NEUROBLASTOMA CELLS

*Microtubule-associated protein 2 (MAP2) is considered a marker of terminal neuronal differentiation*

- MRx0029 induces neuronal differentiation in SH-SY5Y cells via upregulation of MAP2 at the gene and protein level

- MRx0029 induces expression of DAT and LMX1B which are considered markers of dopaminergic neurons
ORAL ADMINISTRATION OF MRx0005 AND MRx0029 INDUCED DOPAMINERGIC NEURONS PROTECTION IN A MPTP MODEL

- Administration of MRx0005 and MRx0029 did not cause weight loss, showing high tolerability for both strains
- Oral delivery of this bacterial strain successfully protected tyrosine hydroxylase positive (TH+) dopaminergic neurons from cell death
Our functional screening platform has been designed to target different aspects of the ‘multiple hit hypothesis’ of neurodegeneration and has led to the discovery of two gut-derived bacteria that can modulate relevant cell types and pathways via the gut-brain axis.

The two strains have complementary characteristics and mechanisms of action.

MRx0005 has a predominantly anti-inflammatory signature.

MRx0029 is potentially able to promote neurodifferentiation and protect neurons from cytotoxicity induced by both environmental and familial triggers.

Both strains have shown efficacy in an industry-standard animal model.

4D is preparing plans to quickly generate clinically-relevant in-patient data.