Into the Clinic: Challenges & Opportunities

Alex Stevenson, Chief Scientific Officer

1st Microbiome Movement – Oncology Response
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With all new therapeutic modalities there are challenges to be met and opportunities to leverage

Manufacturing

• Challenge: How to adapt for CMC when pioneering a new therapeutic modality

• Opportunity: Integrate CMC to increase speed to clinic and develop further IP

Regulatory

• Challenge: Navigating areas of regulatory uncertainty

• Opportunity: Unique characteristics of LBPs encourage favourable perspectives, accelerating clinical development

Clinical Study Design + Analysis

• Challenge: Additional endpoints and biomarker analysis selection

• Opportunity: Use of standard efficacy measures and additional LBP-specific endpoints to generate confidence in microbiome medicines and develop mechanistic understanding
Research
- Single-strain commensal bacteria encapsulated for oral delivery
- MicroRx® discovery platform
- Focus on function, addressing understood disease pathways

CMC
- Glass to stainless steel in-house facility
- cGMP certified commercial-scale production

Regulatory
- Multiple studies approved by regulators
- Extensive experience with both US and EU regulators

Clinical
- Four active clinical studies across multiple therapeutic areas
- Including two oncology trials in multiple tumour types
- Extensive clinical operations team to deliver results
### INTO THE CLINIC: MULTIPLE PROGRAMMES IN MULTIPLE THERAPEUTIC AREAS

<table>
<thead>
<tr>
<th>Focus</th>
<th>DISCOVERY</th>
<th>PRECLINICAL</th>
<th>DEVELOPMENT</th>
<th>PHASE I</th>
<th>PHASE II</th>
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<td><strong>Immuno-oncology</strong></td>
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<td>MRx0518 Solid tumours – Combination study with Keytruda®</td>
<td>Phase I/II study enrolling</td>
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<td>MRx0518 Solid tumours – Monotherapy study (Tx naïve neoadjuvant)</td>
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<td>MRx0518 Pancreatic cancer – Monotherapy study (neoadjuvant)</td>
<td>Phase I study opening H2 2019</td>
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<td>Blautix® Irritable Bowel Syndrome</td>
<td>Phase II enrolling</td>
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<td>Thetanix® Crohn’s Disease</td>
<td>Phase II in planning</td>
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<td>MRx-4DP0004 Asthma</td>
<td>Phase I/II study enrolling</td>
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<td>MRx0002 Multiple Sclerosis</td>
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<td>Autism</td>
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Manufacturing:
In-House or Outsource
MANUFACTURING: DIY OR OUTSOURCING?

For any new therapeutic modality, viable cost-effective manufacturing at scale is often a significant hurdle/bottle neck

Internalising CMC capability offers many advantages to companies in the microbiome space

- Bandwidth to match clinical objectives
- Increased control & flexibility over process
- Develop internal expertise & IP
- Early integration into candidate selection
- Accelerated time to clinic
OVERVIEW OF 4D PHARMA MANUFACTURING CAPABILITY

Fully-Equipped Development Lab
- CMC an early consideration in candidate selection and product development
- Accelerated development and translation from lab to patient
- In-house CMC expertise and development of manufacturing IP

Commercial-Scale Manufacturing
- Cell bank with cultures of bacterial strains from 4D pharma’s proprietary library
- 3000L production plant to supply growing business with API for clinical studies
- End-to-end cGMP certified process (AEMPS/ANSM; ICH QbD Q8/9/10/11)

Global Quality Control & Assurance
- Ultimate control of materials, process, quality, purity and potency
Regulatory:
A Challenge or an Opportunity
**USA Regulatory Environment**

- Internal FDA expertise in LBP products has led to well-defined guidance for development
- FDA issued first guidance in 2012, updated in 2016 to be more extensive
- Guidelines cover CMC, in support of preclinical and clinical investigations; LBPs still covered by Medicines regulations

Guidance enables rapid translation to Phase II clinical development

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**European Regulatory Environment**

- European LBP expertise derived from National Agencies; extent of expertise varies between territories
- European Pharmacopoeia guidelines published April 2018, effective from April 2019
- Guidelines focused on quality and CMC, with broader regulations captured under the EU Medicines Directive

Many similarities to FDA guidelines, with published standards for approved products

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4D Pharma has interacted with seven different regulatory bodies in respect of early clinical development
LBPs possess unique properties that enable accelerated clinical development.

- LBPs are expected to have inherently favorable safety profiles.
- Significantly reduced risk of preclinical/clinical tox failure.
- Regulators happy to conduct first-in-man studies in patients.
- Access to patients earlier in disease progression than other modalities.
- Single dosing level.
- Accelerated generation of meaningful clinical data.
Clinical Study Design & Analysis:
Endpoints & Biomarkers
What is the target patient population? What is the treatment setting?
- Which tumour types?
- Treatment naïve?
- Monotherapy or combo?

What are the endpoints for trials of LBPs?
- Usual measurement of clinical outcomes
- Different/additional endpoints for LBPs?

Can we use host biomarkers to measure outcomes?
- What immunological markers can we use to measure patient outcomes?
- LBP-specific biomarkers related to effects on host?

How to use microbiome biomarkers to measure outcomes?
- Patient stratification, identification of responders vs. non-responders?
- Surrogate markers of disease progression and therapeutic efficacy?

4D collaborates with world-leaders to complement our expertise and answer these questions
BIOMARKER SELECTION: INTEGRATING HOST & MICROBIOME BIOMARKERS

Selection of Biomarkers for Clinical Studies
• Analysis guided by *in vitro* and *in vivo* preclinical data
• Additional literature evidence informs extensive analysis

Host Tumour and Blood Samples
Understanding effect of LBP on tumour microenvironment and systemic immune compartment
• Extensive immunophenotyping (FACS, nanostring) to profile tumours
• Analysis of tumour gene expression (PD-L1/2, Ca125, Ca153)
• Chemokines, cytokines, immune activation/suppression markers, cytotoxic pathways

Microbiome
Integration of microbiome and metabolomics profiling (MicroDx® platform)
• Analysis of faecal samples: 16S, shotgun metagenomics sequencing, metabolomics data
• Predict responders/non-responders in I-O trials
• Changes in microbiome composition over time as a surrogate marker of response
## Biomarker/MoA Study vs Checkpoint Combination Study

<table>
<thead>
<tr>
<th>What do we want to answer?</th>
<th>Does MRx0518 induce anti-tumour immunity?</th>
<th>Can MRx0518 restore responses to anti-PD-1 in relapsed patients?</th>
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<tbody>
<tr>
<td>Which patient group?</td>
<td>Treatment-naïve – uncompromised immunological background</td>
<td>Relapsed patients, heavily pre-treated population</td>
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<tr>
<td>What setting?</td>
<td>Neoadjuvant monotherapy</td>
<td>Combination with pembrolizumab</td>
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<tr>
<td>Which indications?</td>
<td>Wide range of tumour types to guide downstream clinical development</td>
<td>Assessment of activity in checkpoint approved tumour types</td>
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<tr>
<td>Which endpoints?</td>
<td>Assessment of safety &amp; tolerability</td>
<td>Tumour progression and survival endpoints</td>
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<td></td>
<td>Host biomarkers</td>
<td>Biomarker analysis</td>
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<td>Microbiome profiling</td>
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**Clinical Study Design & Analysis**
MRx0518: NEOADJUVANT MONOTHERAPY STUDY

- Window study: dosing between initial diagnosis and surgery
- Up to 120 treatment naïve patients; multiple solid tumour types
- Principal Investigator: Dr. Jonathan Krell, Imperial College London (UK)

**Primary Outcomes**
- Safety + tolerability (collection of adverse events)

**Secondary Outcomes**
- Tumour marker response (e.g. Ca125 in gynae., Ca153 in breast)
- 2 year survival

**Exploratory Outcomes**
- Changes in T cell populations
- Inhibition of tumour cell proliferation (Ki67 antigen-labelling)
- Host biomarkers
- Microbiota/metabolomic analysis

**Unique design allows novel insights**
- Treatment naïve - clean immunological background
- Multiple sample points, before and after dosing
  - Tumour, serum, urine, stool (MicroDx®)
- Together these will provide a clear signal of LBP effects on host and microbiome
**MRx0518: COMBINATION WITH ANTI-PD-1**

- Patients who have progressed on prior anti-PD-1 therapy
- Four solid tumour types (melanoma, bladder, renal and NSCLC)
- Principal Investigator: Dr. Shubham Pant, MD Anderson

<table>
<thead>
<tr>
<th>Study Part</th>
<th>Primary Outcomes</th>
<th>Secondary Outcomes</th>
<th>Exploratory Outcomes</th>
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<tbody>
<tr>
<td>A (n=12)</td>
<td>Safety + tolerability (collection of adverse events)</td>
<td>-</td>
<td>Host biomarkers • Microbiota/metabolomic analysis</td>
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<tr>
<td>B (n=120)</td>
<td>Safety (collection of adverse events) • Assessment of clinical benefit</td>
<td>Antitumour effect (RECIST/iRECIST – ORR, DOR, DCR, PFS)</td>
<td>Host biomarkers • Microbiota/metabolomic analysis • OS</td>
</tr>
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**Data is already being generated**

- Multiple Part A patients dosed
- Part A recruitment expected completion end 2019
- Baseline and post-treatment biopsies being taken – biomarker data to be generated from parts A & B
- Exploratory biomarker analysis ongoing in first patients
LBPs offer unique opportunities in clinical development ranging from CMC, Regulatory and Clinical trial design

Usage of both standard and LBP-specific endpoints will generate confidence in microbiome medicines and further our understanding of function

- Internal CMC expertise provides significant competitive advantage to LBP developers
- Unique characteristics of LBPs encourage favourable perspectives from regulators, accelerating clinical development and generation of meaningful data
- Use of standard and LBP-specific endpoints, in addition to the integration of immunological and microbiome biomarkers, leverages unique opportunities and answers vital questions quickly
developing science
delivering therapies