Live Biotherapeutic MRx0518 as a modulator of immune responses in intestinal tissue and breast tumor microenvironment


4D Pharma plc is a pharmaceutical company focused on developing Live Biotherapeutic products (LBPs) derived from the human gut microbiome. LBPs are a regulated, emerging and disruptive new class of medicines, which have the potential to transform the way in which we treat many diseases. 4D Pharma currently has clinical stage programs in cancer, asthma, irritable bowel syndrome (IBS) and Crohn’s disease, and a strong pipeline of pre-clinical programs including immuno-oncology, CNS and autoimmune diseases.

Introduction

The human gut microbiota plays an essential role in modulating both intestinal and systemic immunity. Its importance in regulating antimicrobial responses is now being explored, supported by evidence that functional components of the gut microbiome influence response to cancer therapy, including but not limited to immunotherapies.

We previously demonstrated that the single strain Live Biotherapeutic, Enterococcus gallinarum MRx0518, had strong immunostimulatory properties in vitro, and was a TLR5 and NF-κB activator.

We further investigated whether this bacterial strain displayed anti-tumor efficacy in a murine mammary carcinoma model.

LBPs and the tumor microenvironment

<table>
<thead>
<tr>
<th>Immune cell category</th>
<th>Effects of MRx0518</th>
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<tbody>
<tr>
<td>APCs recruitment and activation</td>
<td>Increased</td>
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<tr>
<td>NK cell recruitment</td>
<td>Increased</td>
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<tr>
<td>Induction of pro-inflammatory cytokines</td>
<td>Increased</td>
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<tr>
<td>PRR activation</td>
<td>Increased</td>
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MRx0518

- Strain of Enterococcus gallinarum
- Gram-positive, motile, anaerobic bacteria
- Oral Live Biotherapeutic
- Originally isolated from the gut microbiome of a healthy human donor
- Selected for immunostimulatory host response profile, relevant for immunoncology
- Immune stimulation primarily through action of bacterial flagellin on TLR5

MRx0518 modulates immunoncology

In vivo efficacy

- Reduces tumor growth in EMT6 model (also LLC and RENCA models, data not shown)
- Increases tumor and intestine immune infiltration: NKS, T cells and cytotoxic cells
- Increases TLR5 expression within the tumor tissue

MRx0518 Mechanism of Action

- Modulation of both the gut immune system and the tumor microenvironment
- Flagellin TLR5 agonism (Lauté-Caly et al. Sci Rep 2019)

Conclusions

MRx0518 in vivo Efficacy

- Phase I/II, open-label, combination with pembrolizumab in anti-PO(L)-1 secondary resistant NSCLC, RCC, melanoma, bladder
- Early signals of activity and clinical response, no serious drug-related adverse events
- Part A enrollment complete
- Phase I, neoadjuvant monotherapy study in treatment-naïve patients awaiting surgical resection of solid tumors; enrolling
- Phase I, pancreatic cancer in combination with radiotherapy; enrolling