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

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14D Pharma plc is a pharmaceutical company focused on developing Live Biotherapeutic products (LBPs) derived from the human gut microbiome. LBPs are 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 anti-tumorigenic 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 TLSR and NF-κB activator.

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

Results: Transcriptional analysis

MRx0518 significantly modulates gene expression in the tumor and the colon

MRx0518 therapeutic activity was associated with upregulation of genes involved in immune cell adhesion and migration, such as Cd38 and Gzma, Gzmb, Klrb1, Klrd1, Klrk1, Nkg7, Prf1 genes.

MRx0518 modulates immune cell populations

Immune cell populations including NK, T cells and cytotoxic cells were increased by MRx0518 treatment in both colonic tissue and the tumor microenvironment.

MRx0518 Clinical development

MRx0518 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 TLSR expression within the tumor tissue

MRx0518 Mechanism of Action

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

Transcripts analysis of the tumoral (A), ileal (B) and colonic (C) tissue in the mouse model of breast cancer (EMT6) was conducted using the PanCancer IQ 360 NanoString gene expression panel.

KEGG database was used to annotate the transcripts isolated from tumoral (D), ileal (E), and colonic (F) tissues and to conduct pathway identification.

Genes previously shown to be characteristic of various immune cell populations (Table A) were used to measure the abundance of populations for cell type profiling. Heat maps represent tumor (B), ileum (C) and colon (D) immune cell population abundance for untreated, vehicle-treated and MRx0518-treated animals in the EMT6 model.

Results: Tumor growth

MRx0518 monotherapy induces a reduction in EMT6 tumor burden

• From D-14, mice received vehicle or 2x10^9 CFU MRx0518 daily until termination.
• On D0, mice were engrafted with EMT6 tumor cells subcutaneously.
• Anti-CTLA-4 (10 mg/kg, IP, BiW) was used as positive control.
• Tumor length and width as well as body weight were measured 2-3 times a week. No side effect of the treatment was observed.