4D pharma PLC
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Revolutionary new medicines from the human gut microbiome

Using its MicroRx platform, 4D pharma is pioneering the development of an emerging class of therapeutics known as live biotherapeutic products to treat a range of indications from cancer and respiratory disease to neurodegeneration.

The gut microbiome—the microorganisms inhabiting the human gastrointestinal tract—plays important roles in health and disease, affecting not only the local environment but also the immune, metabolic and even nervous systems, modulating diverse disease pathways throughout the body.

Defining the microbiome space is 4D pharma and its pioneering live biotherapeutic products (LBPs), an emerging class of medicines based on single strains of commensal bacteria. “We understand mechanistically how specific bacteria interact with the host, and exploit this functionality to treat a range of diseases,” said CEO Duncan Peyton.

From its extensive library of bacterial strains, 4D uses its MicroRx platform to identify and characterize candidates that modulate disease pathways (Fig. 1). “MicroRx gives us a comprehensive understanding of how specific bacteria impact the human body at the molecular level, allowing us to rationally select live biotherapeutic candidates with profiles relevant for particular aspects of disease,” explained Alex Stevenson, CSO. “Each strain is selected for its functionality, via a defined mechanism of action, in a targeted drug-discovery approach.”

Therapeutic activity is then validated using industry standard animal models before entering the clinic. 4D has multiple clinical-stage programs in immuno-oncology, COVID-19, irritable bowel syndrome, inflammatory bowel disease and asthma, and pre-clinical programs in neurodegenerative and autoimmune conditions. The end-to-end company also has its own current good manufacturing practice (cGMP)-certified manufacturing facility.

LBPs are developed to meet the same safety and efficacy standards as any other drug, but having been refined by millennia of co-evolution do not require optimization. “By avoiding the toxicity that often compromises conventional drugs, development timelines and risk are dramatically reduced,” explained Stevenson.

The productivity of 4D’s MicroRx platform is exemplified by its pipeline and the largest intellectual property portfolio in the space. Its MicroRx platform and approach to live biotherapeutic development attracted a research collaboration with Merck & Co. in 2019 to discover LBPs for use in novel vaccines, building on an existing clinical collaboration in oncology.

First oncology clinical data for a live biotherapeutic

4D’s lead immuno-oncology candidate, MRx0518, is in a phase I/II trial in combination with Merck & Co.’s Keytruda (pembrolizumab) for solid tumors with acquired resistance to checkpoint immunotherapy.

Mechanistic work identified the MRx0518 bacterial flagellin protein as a potent TLR5 agonist, stimulating innate and adaptive anti-tumor immune responses. MRx0518 demonstrated anti-tumor activity in multiple animal models of cancer, as a monotherapy and in combination with checkpoint inhibitors.

Demonstrating the rapid development of LBPs, 4D moved from discovery to first-in-class proof-of-concept clinical data for a live biotherapeutic in oncology in just 4 years. Data from the ongoing trial indicate that MRx0518 can re-engage response to checkpoint immunotherapy in heavily pre-treated patients with acquired resistance. “Using MRx0518 to increase response in refractory patients with no other therapeutic options is hugely significant for the industry,” said Peyton.

Targeting the gut-brain axis

More recently, MicroRx has identified two bacterial strains, MRx0005 and MRx0029, with potentially disease-modifying activity targeting multiple processes involved in neurodegenerative diseases such as Parkinson disease (PD).

Motor function deterioration characteristic of PD is due to accumulation of misfolded α-synuclein and loss of dopamine-producing neurons; patients also typically suffer from gastrointestinal symptoms and ‘leaky gut’. MRx0005 and MRx0029 have multiple effects, reducing α-synuclein-induced neuroinflammation, protecting from oxidative stress and increasing expression of tight-junction proteins, improving gut barrier integrity. Interestingly, MRx0029 can induce a dopaminergic phenotype in undifferentiated neuronal cells, suggesting a potential ‘neuroregenerative’ capability.

The neuroprotective therapeutic effects of these complementary functions have been demonstrated in an animal model of PD. 4D is now planning a first-in-man study in patients with PD. “By targeting multiple aspects of disease pathology, our LBPs offer a potentially disease-modifying treatment for patients with neurodegenerative diseases,” said Stevenson.

Wide-spectrum partnering

4D is seeking to partner at all stages—from platform collaborations utilizing MicroRx in new areas, to co-development of clinical or clinic-ready programs, including expanding development of immuno-oncology candidate MRx0518 with new combination therapies, following the first-in-class proof-of-concept data.

“MicroRx is a highly productive platform and our pipeline demonstrates the breadth of its potential. We have generated first-in-class positive oncology data, validating our approach. A fully integrated company, with expertise from discovery through manufacturing to regulatory and clinical, 4D is the perfect partner, with a new approach to therapeutics that is safer and quicker than traditional drug development,” said Peyton. “Live biotherapeutics have the potential to transform the way many diseases are treated.”

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