MATWIN
MATURATION & ACCELERATING TRANSLATION WITH INDUSTRY

TECHNOLOGY OFFER

SUPPORTING INNOVATION AND TECHNOLOGY TRANSFER IN ONCOLOGY

EPIONE Project

The ground-breaking microbiome-based biotherapy to potentialize cancer immunotherapy

THERAPY

CONTEXT & BACKGROUND

One of the most striking innovation in oncology recently is the discovery that the microbiome can potentiate the effects of immune checkpoint blockade (ICB) therapies. Indeed, several species of intestinal bacteria have been associated with enhanced efficacy of ICB drugs, even if the underlying mechanisms are unclear.

We collaborated with the University of Calgary to discover new species of bacteria with therapeutic purpose in the oncology field. Throughout the research program, three bacterial species of interest were identified and isolated, including Bifidobacterium pseudolongum, Lactobacillus johnsonii and Olsenella species, that significantly enhanced efficacy of immune checkpoint inhibitors in different cancer mouse models, notably CRC.

We found that B. pseudolongum enhanced immunotherapy response through production of inosine, a bacterial metabolite. Further, the decrease in gut barrier function induced by immunotherapy increased systemic passage of inosine and subsequent activation of anti-tumor T cells. The effect of inosine was dependent on both T cell expression of the adenosine A2A receptor and co- stimulation. This is the first time that a mechanism of bacteria-host immune system is fully understood. Mechanisms of action elucidation for microbiome-based live biotherapies is key for its clinical translation and drug development.

These data demonstrated that a novel gut bacteria and its metabolite activate the immune pathway and potentiate the therapeutic efficacy of cancer immunotherapies. our objective now is to develop a microbiome-based live biotherapy using B. pseudolongum to potentiate the effect of existing ICB drugs and cure cancer patients.

INNOVATIVE COMPONENT & TECHNOLOGY

Mechanism of action: we have identified through metabolomic approaches inosine as the central metabolite. We showed that inosine could reproduce B. pseudolongum efficacy only when combined with CpG oligonucleotides, activators of dendritic cells. Without CpG costimulation, the inosine is ineffective. In knock-out mice, we have shown that inosine mediates its effect by binding to A2a-receptor on T-cells. This receptor activation plus the co-stimulation of dendritic cells leads to Th1 differentiation and boost T cells activity against cancer cells. Also we measured inosine concentrations in serum of B. pseudolongum monocolonized mice treated with ICB drugs. Inosine was significantly increased in the serum. As inosine is easily measurable in serum, it could be an excellent clinical biomarker of efficacy.

We showed that B. pseudolongum is efficient in combination with ICB in colorectal tumor mice models. We also showed that this combination is efficient in MSI-high Colorectal cancer subtype, using a MSH2 intestinal knock-out model. In addition, the efficacy of B. pseudolongum has been demonstrated in combination with other distinct ICBs including anti PD-L1 and anti PD1. Finally, to open other avenues, we have shown that our biotherapy has a strong potential to be efficient in other cancer models like melanoma & bladder.

KEYWORDS

Immunotherapy, microbiome, Cancer, Drug, Colorectal cancer, Bacteria, Melanoma, Bladder cancer

OBJECTIVES

IImprove the efficacy and patient response to Immune Checkpoint Blockade in cancer patients.

DEVELOPMENT & MATURATION STAGE

We plan to reach clinic with Xla3 in 18 months. To achieve this, we will engage time and resources to setup a library of strains from this species, identify the best clinical candidate among that library, complete all preclinical regulatory activities and develop a CMC process for this specific strain. In parallel, we will discuss with regulatory authorities and prepare and file necessary dossiers to the appropriate health authority, allowing us to treat our first patient and initiate the clinical trial.

We are looking for a pharma partner to accelerate the development of this program toward clinic. The pharma partner will bring its proprietary ICB drug to be combined with our biotherapy, as well as preclinical and clinical expertise in oncology.

TARGET POPULATION

We intend to address patients with melanoma, colorectal and bladder cancer, eventually with MSI-high profiles, who do not respond well to ICB. Only 20% to 40% of patients with these cancers currently respond to ICB drugs. These 3 cancers kill more than 1 million patients per year in the US. Our goal, with Xla3, is to improve the response rate to ICBs in cancer patients.

TARGET PROFILE

We are convinced that our oral biotherapy has the potential to be a first-in-class drug. Our biotherapy is based on a B. pseudolongum commensal bacteria and will be combined with ICB. There is today no microbiome-based therapy on the market, and all are in early-stage clinical development. We expect a very high safety and tolerability profile.

INTELLECTUAL PROPERTY & PATIENT CO-OWNER(S

PCT filed in Nov 2020: HARNESSING THE POWER OF MICROBIOTA AND METABOLITES FOR THE TREATMENT OF CANCER, Calgary University, Canada

STRENHGTS & COMPTETITIVE ADVANTAGES

We will leverage the power of these single-strain bacteria to potentiate the effects of ICBs and treat a lot more cancer patients. We are convinced that this approach is uniquely capable to succeed for several reasons:

- Efficacy: our single-strain bacteria will cure patients by potentiating the effects of ICB in multiple cancer indications
- Convenience and safety: our approach is superior to other microbiome-based therapies (FMT, consortia) or biologics because our biotherapies are taken orally (simple capsule), produced in accordance with pharmacopoeia requirements. It is also safe because our commensal bacteria are present in healthy individuals and we expect no major side effects and no environmental risk
- Well-characterised biology with full understanding of the mechanism of action.
- Controlled manufacturing process: our approach is the only one allowing a full characterization of the drug substance, which is a single keystone bacteria with an understandable mechanism of action.

Based on our unique technology and know-how, we are taking this challenge to develop one of the first-to-market single-strain keystone biotherapies targeting cancer.

INDUSTRIAL APPLICATIONS & OPPORTUNITIES

Improvement of efficacy of current IO drugs is a huge market with a very high medical need.

CONTACT

MATWIN : contact@matwin.fr