MATWIN
MATURATION & ACCELERATING TRANSLATION **WITH INDUSTRY**

TECHNOLOGY OFFER

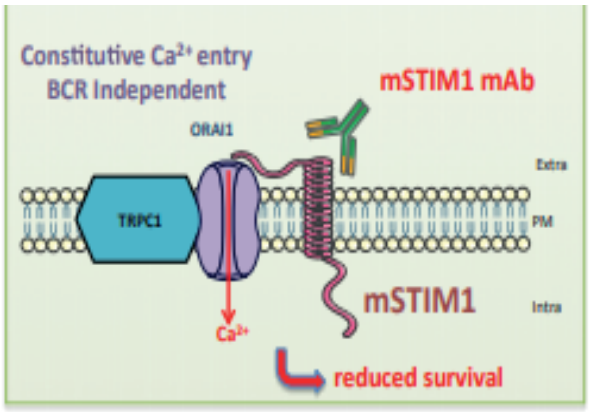
SUPPORTING INNOVATION AND TECHNOLOGY TRANSFER IN ONCOLOGY

STIM-CLL

Sensing and Treating the IMmune calcium signal in Chronic Lymphocytic Leukemia

CONTEXT & BACKGROUND

Chronic lymphocytic leukemia (CLL) is the leading cause of leukemia in Western countries. Chemotherapies associated with anti-CD20 monoclonal antibodies (mAbs) such as rituximab (RTX) are used and show interesting results in terms of survival. In these patients no remission is observed, side effects are frequent and more than 50% of patients will relapse within 5 years. To date no treatment, including the promising novel therapies offers a complete and long-term remission, and it is noteworthy that the rate of treatment suspensions and toxicity remain elevated for these patients. It is therefore crucial to discover new therapeutic alternatives with less toxicity and resistance. We propose to use a monoclonal antibody directed against the STIM1 protein (Stromal Interacting Molecule 1) as a first in class therapeutic tool for CLL treatment. This protein is abnormally expressed in B lymphocytes from CLL patients and is implicated in calcium signaling disturbances associated with aggressiveness of this disease.



- *We iden' fied* : A new independent and pro-survival pathway, clinically relevant for CLL. Synergy with exis=ng therapies and a new therapeu=c target mSTIM1 (2 patents)

  an= STIM1 mAbs blocks this pro-survival Ca^{2+} entry and lymphoprolifera=on

- *We developed* : proprietary an=-STIM1 mAbs and we got *in vitro* and *in vivo* POC of their poten=al use for CLL treatment (Not limited to CLL: SLE, LAM, Pancrea=c cancer…)

SCOPE

A new therapeutic proposal for Chronic Lymphocytic Leukemia

KEYWORDS

Chronic Lymphocytic Leukaemia;
Calcium Signalling,
immunotherapy

INNOVATIVE COMPONENT & TECHNOLOGY

Immunotherapy: the originality of the project is based on the discovery of a novel survival pathway in chronic lymphocytic leukaemia (CLL) and the development of a specific proprietary monoclonal antibody (mAb) targeting this pathway. The target itself, mSTIM1, is an absolutely new therapeutic target in different pathology.

OBJECTIVES

The ultimate objective is to conduct a non-inferiority trial with a better safety hypothesis in CLL patients based on the utilization of a chemotherapy-free immunotherapy that blocks an alternative signalling pathway, and such immunotherapy can be used alone or in association with existing drugs targeting the BCR-pathway. We intend to propose a new first in class immunotherapy to prevent and reverse therapeutic escape in CLL patients.
The objective of the present project is to realize all the preclinical studies and to end up with a humanized anti-mSTIM1 mAb ready for use in a clinical trial oriented production.

DEVELOPMENT & MATURATION STAGE

We obtained the preclinical proof of concept for using mAb targeting mSTIM1 in CLL treatment. We are now realizing all the preclinical development and validation of two proprietary humanized mAb targeting mSTIM1.
We propose now to validate our proposal in another CLL murine model and to humanize selected anti-mSTIM1 mAb.

INTELLECTUAL PROPERTY & PATIENT CO-OWNER(S)

Two patents – co-owner: SATT Ouest Valorisations
- Method of screening of compounds using membrane STIM1: PCT number EP14290232,9
- Processes for the diagnosis, prognosis and monitoring of the progression of Chronic Lymphoid Leukaemia (CLL) and/or of
Systemic Lupus Erythematosus (SLE) using membrane STIM: PCT number: EP15156694,0

TARGET POPULATION

The treatment will be dedicated to CLL patients refractory to first line treatment for patients who suspend their therapy, older patients (>70 years), and for high-risk patients. Such therapeutic approach might also benefit especially young patients.
Given the unmet needs highlighted in CLL, our treatment may also be beneficial for elderly patients as a first line treatment in association with drugs targeting the BCR pathway such as rituximab and ibrutinib.

TARGET PROFILE

The STIM1 (stromal interaction molecule 1), a single pass transmembrane protein is a key regulator for Ca2+ homeostasis in lymphocytes, portion of STIM1 is located in the plasma membrane (mSTIM1) at levels very significantly increased in B 2 Lymphocyte from CLL patients.
The utilization of an antibody to block plasma-membrane mSTIM1 is effective both to control in vivo lymphoproliferation and in vitro B cell survival when used alone or in association with drugs targeting the B cell receptor pathway Monoclonal antibody: humanized anti-mSTIM1 mAb will be beneficial to inhibit a pro-survival constitutive extracellular Ca2+ entry.

STRENGHTS & COMPETITIVE ADVANTAGES

We believe that the modulation of a BCR-independent and novel Ca2+ signalling pathway would provide a totally new approach that will improve the efficacy of the existing treatments, propose a chemotherapy-free approach, and reduce the side effects and/or reverse a relapse in CLL patients.
There is absolutely no doubt that the mSTIM1 is a new therapeutic target. There is no patent published and filed on plasmamembrane mSTIM1 other than ours giving us a strong leadership position.
No drugs targeting either constitutive Ca2+ entry or mSTIM1 are in pre-clinical or clinical development. Our approach is completely original, innovative and able to provide a clinical breakthrough in CLL management if considering the additive or synergic potential from association of an anti-calcium pathway inhibitor with a drug targeting the BCR-pathway.

INDUSTRIAL APPLICATIONS & OPPORTUNITIES

CLL: Despite development of novel therapeutics in chronic lymphocytic leukaemia (CLL) the complete rate of complete longtime remission is low, the rate of side effects remains elevated, and the number of patients that stop treatment prematurely remain high, thus suggesting the need to develop new and first in class therapeutic proposal for CLL.
Additional indications
-Cancer: Acute Myeloid leukaemia, multiple myeloma and in solid cancers such as pancreatic cancer.
- Autoimmune diseases: We have already demonstrated the benefits of the anti-mSTIM1 mAb in a lymphoproliferative and lupus prone mice model (MRL/Lpr). In systemic lupus erythematous (SLE), the higher level of mSTIM1 expression on B cells is associated with disease activity as described in the patents EP14290232,9 & EP15156694, 0

CONTACT | MATWIN : Lucia Robert: Lucia.Robert@matwin.fr