



## SUPPORTING INNOVATION AND TECHNOLOGY TRANSFER IN ONCOLOGY

### TAX2

**PROPOSITION OF A CD47/TSP-1 ORTHOSTERIC ANTAGONIST ACTING AT A UNIQUE ANGLE AT THE INTERFACE BETWEEN IMMUNOMODULATION AND ANTI-ANGIOGENIC TREATMENT.**



### CONTEXT & BACKGROUND

CD47, also known as Integrin-associated protein (IAP), is a ubiquitously expressed transmembrane protein that in humans is encoded by the CD47 gene. CD47 belongs to the immunoglobulin superfamily and represents an integrative node in multiple cellular pathways controlling a range of cellular functions including apoptosis, proliferation, adhesion, and migration. In addition, **CD47 plays a key role in both immune and angiogenic responses**. CD47 physically interacts in cis- and/or in trans- with several membrane-bound or soluble ligands including **TSP-1**, integrins, signal-regulatory protein alpha (SIRP $\alpha$ ), VEGFR2 or CD95 (FASR). TSP-1 is a multi-domain matrix glycoprotein that has been shown to be a natural regulator of neovascularization and tumorigenesis in healthy tissue. TSP-1 interacts with CD47 as well as at least 11 surface receptors, including CD36,  $\alpha$ v integrins,  $\beta$ 1 integrins, syndecan, reelin receptors, ApoER2 and VLDLR. It also interacts with numerous proteases involved in angiogenesis, including plasminogen, urokinase, matrix metalloproteinases, thrombin, cathepsin, and elastase. **While CD47 displays ubiquitous expression, TSP-1 was reported to be overexpressed within tumor stroma in several cancer types**. Besides, **TSP-1 binding to CD47 is known to inhibit T lymphocytes differentiation, proliferation and activation**. Therefore, specific targeting of the TSP-1/CD47 signaling axis provides exciting new directions in the treatment of cancer.



### INNOVATIVE COMPONENT & TECHNOLOGY

The intervention modality concerns a **CD47/TSP-1 interaction orthosteric antagonist acting as a competing cyclic peptide (TAX2)**. TAX2 competes with CD47 for TSP-1 interaction, therefore preventing TSP-1-mediated activation of CD47 downstream signalling.

To date, most efforts have focused on developing CD47-targeting mAbs to restore an anti-tumor immune response, and first-in-man phase 1 clinical trials are currently underway. Given the **ubiquitous expression of CD47**, systemically administered anti-CD47 mAbs will inevitably come across a huge number of CD47 copies on red blood cells (RBCs), and may therefore lead to phagocytic-induced excessive reduction in erythrocytes count and subsequent severe anemia. Besides, CD47 also plays fundamental physiological roles by limiting nitric oxide signaling in RBCs, platelets, and endothelium. Therefore, **the use small antagonistic molecules may be of a better interest**.

Through its **original mechanism of action** which implies specific disruption of TSP-1:CD47 interaction through direct targeting of tumor-overexpressed TSP-1, **TAX2 inhibits tumor progression while limiting many of the undesired side effects of broadly inhibiting important physiological functions of CD47**. Indeed, both **TSP-1 other domains and CD47 remains free to interact with other ligands/co-receptors under TAX2 treatment**, while CD47 expression is not altered.

### SCOPE

Anti-cancer therapy by anti-angiogenesis and immune system restoration

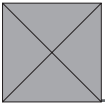
### KEYWORDS

TSP-1, CD47, cancer immunotherapy, therapeutic peptide



### OBJECTIVES

**We seek industrial partnership for R&D collaborations and licensing.** Our general aim is to develop our drug candidate and reinforce its proof-of-concept for anti-cancer efficacy as an immunotherapeutic approach until direct translation of the product in a clinical trial. Intermediate goals are (i) to further document the peptide tissue distribution in vivo, (ii) to complete efficacy studies in heterotopic and orthotopic syngeneic models and (iii) develop a test based on TAX2 companion biomarkers.



## DEVELOPMENT & MATURATION STAGE

Proof-of concept for TAX2 anti-cancer efficacy has already been provided **in a wide range of TSP-1-overexpressing models**, including 7 **xenografts models** (melanoma, neuroblastoma, pancreatic carcinoma, ovarian carcinoma), 2 **orthotopic PDX models**, and 2 **syngeneic models**. While PK profile was determined, no adverse element was reported in standard ADME/toxicology assays, particularly regarding those commonly reported using CD47-blocking mAbs. Developments detailed above indeed expose an optimized candidate with advanced characterization (i.e. TRL4++), yet the overall purpose of further developments is **to improve risk perception for potential future partners** that may help TAX2 translation to the clinics.



## TARGET POPULATION

Human malignancies showing TSP-1 overexpression within tumors, i.e. melanoma, paediatric neuroblastoma, pancreatic, carcinoma, ovarian carcinoma, glioma (non-exhaustive list).



## TARGET PROFILE

The MOA of our therapeutic peptide implies disruption of TSP-1:CD47 interaction, therefore inhibiting tumor-associated vascularization and promoting and overall anti-cancer immune response. TAX2 peptide is expected to contribute to immune restoration while stimulating T cell proliferation, inhibiting Treg differentiation and stimulating Th1 maturation. Such approach is distinct from conventional check-point inhibitors and overcomes undesired effects related to broad CD47 inhibition (i.e. using monoclonal antibodies).



## STRENGTHS & COMPETITIVE ADVANTAGES

- Original and differentiated MOA: angiostatic + immunomodulatory dual action
- Selective targeting of TSP-1 being overexpressed within tumor stroma
- No adverse side-effects related to broad CD47 inhibition
- TAX2 overcomes many of usual peptides' limits (i.e. CMC concerns, stability, solubility/aggregation, low membrane permeability...)



## INDUSTRIAL APPLICATIONS & OPPORTUNITIES

-We intend to validate TAX2 as an anti-cancer approach to be used whether alone or in combination with other modalities (for example targeted therapy or immune checkpoint inhibitors). TAX2 approach is expected to take place among a new generation of immunomodulatory agents targeting the CD47 axis, with distinct and original mechanism of action and limited secondary effects.



## INTELLECTUAL PROPERTY & PATIENT CO-OWNER(S)

A patent application has been filed claiming the use of a R1R2R3SQQKGR4R5R6 peptide in either linear or cyclic forms. USA, Canada and Japan national stages are going while the patent has already been granted in Europe (EP2729495B1). Inventors: S. Dedieu, N. Floquet, L. Martiny, C. Schneider, A. Jeanne, E. Sick, M. Dauchez. Co-owners: Reims Champagne-Ardenne University, CNRS.