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THERAPY

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 (SIRPα), 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, αv integrins, β1 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 led 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 it**s 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 in not altered.

SCOPE

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

KEYWORDS

TSP-1, CD47, cancer immunotherapy, therapeutic peptide

OBJECTIVES

The team seeks industrial partnership for R&D collaborations and licensing. Their general aim is to develop the drug candidate until direct translation of the product in the clinics. Intermediate goals are (i) formulation and TAX2 peptide production scale-up (CMC), (ii) safety assessment of developed formulation (toxicology studies) prior to (iii) regulatory approval and first-in-man trials.

DEVELOPMENT & MATURATION STAGE

Proof-of concept for TAX2 anti-cancer efficacy (either as a stand-alone treatment or in combination) 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** (glioblastoma), and 4 **immunocompetent syngeneic models** (ovarian carcinoma and melanoma).

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** through regulatory frameworks (toxicology & safety, pharmacology, production-CMC) so as to help TAX2 translation to the clinics.

TARGET POPULATION

Human malignancies showing TSP-1 overexpression within tumors, i.e. ovarian carcinoma, glioblastoma, pancreatic carcinoma, melanoma, colorectal cancer, NSCLC, head & neck cancer (non-exhaustive list). TSP-1 targeting may also be relevant for the treatment of non-Hodgkin lymphoma.

INTELLECTUAL PROPERTY & PATIENT CO-OWNER(S)

A patent application has been filed claiming the use of a 12-mer peptide in either linear or cyclic forms. Patent has already been granted in Europe (EP2729495), USA (US2014296477), Japan (JP2014525740) and Canada (CA2840719).
Co-owners: Reims Champagne-Ardenne University, CNRS.

TARGET PROFILE

The MOA of the therapeutic peptide implies disruption of TSP-1:CD47 interaction, therefore inhibiting tumor-associated vascularization and promoting and overall anti-cancer immune response. TAX2 peptide also stimulates intra-tumor infiltration of T lymphocytes. Such approach is distinct from conventional check-point inhibitors and overcomes undesired effects related to broad CD47 inhibition (i.e. using monoclonal antibodies).
TAX2 peptide synthesis is fully automated and the peptide is suitable for long-term storage. It displays no unintended immunogenicity, adverse events or toxicity. Interestingly, TAX2 peptide displays additive effect when combined to targeted therapy or immune checkpoint inhibitors.

STRENGHTS & COMPETITIVE ADVANTAGES

- Original and differentiated mode of action leading to angiostatic and immunomodulatory dual effects
- Selective targeting of TSP-1 being overexpressed within tumor stroma
- No adverse side-effects related to broad CD47 inhibition (no unintended immunogenicity, adverse event or toxicity)
- TAX2 overcomes many of usual peptides' limits (CMC concerns, stability, solubility/aggregation, low membrane permeability…)
- Fully-automated synthetization of TAX2 peptide (SPPS) hence potentially reducing production costs

INDUSTRIAL APPLICATIONS & OPPORTUNITIES

The team intends to develop TAX2 peptide as a scalable anti-cancer medication, until direct translation of the product in a clinical trial. TAX2 may be used whether as a stand-alone therapy or in combination with other modalities. Indeed, relevant pre-clinical data strongly suggest additive effects of TAX2 peptide treatment when used together with 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.

CONTACT | MATWIN : contact@matwin.fr