MATWIN
MATURATION & ACCELERATING TRANSLATION **WITH INDUSTRY**

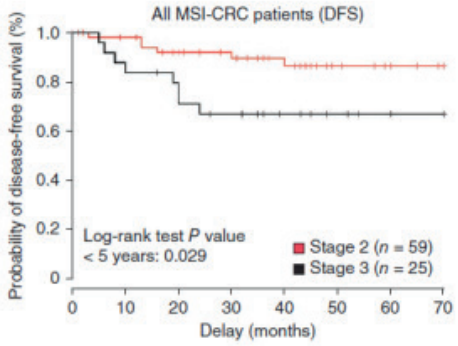
TECHNOLOGY OFFER

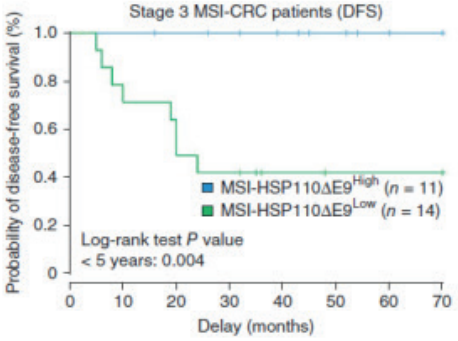
SUPPORTING INNOVATION AND TECHNOLOGY TRANSFER IN ONCOLOGY

TRuTH110
TARGETED THERAPY OF HSP110 FOR CANCER THERAPY

CONTEXT & BACKGROUND

Colorectal cancer (CRC) is the second cause of cancer-related death world-wide. Two subtypes are classically defined to take into account tumor's molecular heterogeneity: microsatellite instable (MSI) and microsatellite stable (MSS). The MSI subtype is caused by a DNA mismatch repair (MMR) deficiency and represents about 15% of colorectal cancers. MSI patients present a higher number of tumor-infiltrating lymphocytes and have a better prognostic than MSS CRCs. We have: i) shown that MSI tumors universally harbor mutations in the heat shock protein HSP110 gene (Dorard et al., Nature Med. 2011) and ii) identified a mutation in a poly T intronic sequence that results in HSP110 exon 9 skipping and expression of a truncated protein, HSP110DE9, that constitutes an early marker of MSI CRCs patients (Patent 2011). HSP110DE9, the first HSPs mutant identified in a cancer so far, completely lacks HSP110 anti-apoptotic and chaperone activity. Further, it acts as a dominant negative that binds HSP110 and blocks its chaperone and oncogenic properties. In cultured colon cancer cells, mice xenografts and patients, HSP110DE9 expression sensitizes tumor cells to chemotherapeutic agents in a dose-dependent manner (Dorard et al., Nature Med. 2011).





INNOVATIVE COMPONENT & TECHNOLOGY

We propose a new target in cancer therapy: HSP110. Other HSPs are being targeted to sensitize cancer cells to chemotherapy.
For instance, many companies are developing inhibitors of HSP90 or HSP27 that are already in clinical trials. However, our last results convincingly demonstrate the interest and superiority or targeting HSP110 over the other HSPs. We have recently Maj mai 2016 published an important work demonstrating the rationale for such an approach: only colon cancer patients that respond to the chemotherapy express an endogenous specific inhibitor of HSP110 (HSP110DE9). This association between the inactivation of HSP110 and good prognosis was demonstrated in a multicentre study including more than 5,000 patients (Collura et al., Gastroenterology 2014). We have also demonstrated that HSP110DE9 was a dominant negative mutant that binds to wild type HSP110 and inhibits the chaperone activity of HSP110; HSP110 is a very important chaperone in cancer cells since not only it has an anti-aggregation activity by its own but also acts as a co-chaperone (nucleotide exchange factor) for other HSPs like HSP70. Therefore by blocking HSP110, the chaperones network in the cell is strongly perturbed as we have already reported (Dorard et al., Nat Med 2011).

SCOPE

Initially : colon cancer patients

KEYWORDS

Targeted therapy, Heat shock Protein 110, small molecules, peptide mimetics

OBJECTIVES

To take advantage of the HSP110DE9 chemosensitizing effect in cancer therapy. We have identified and are developing biologics as well as small molecules inhibitors of HSP110 that mimic the anti-cancer effect of HSP110DE9 and that we could test in phase I clinical trials (with the anticancer center: Centre Georges-François Leclerc (CFGL) in Dijon).

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.

INTELLECTUAL PROPERTY & PATIENT CO-OWNER(S)

A patent application has been filed claiming the use of a R1R2R3SQLLKGR4R5R6 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.

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).

STRENGHTS & 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.

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