MATWIN
MATURATION & ACCELERATING TRANSLATION **WITH INDUSTRY**

TECHNOLOGY OFFER

SUPPORTING INNOVATION AND TECHNOLOGY TRANSFER IN ONCOLOGY

THERAPY

TITANT

Development of small molecules inhibitors of ADP/ATP translocation to mitochondria with anti-tumor activity

CONTEXT & BACKGROUND

The company is an innovative one specialized in detection of compounds-induced mitochondrial damages through their proprietary screening platforms. Founders know-how led to a better understanding of the role of mitochondrial proteins like the ADP/ATP translocator (ANT) found in the inner mitochondrial membrane and associated with ATP synthase (Various publications, 2006-2010).

Among the four ANT isoforms, ANT2 is overexpressed in highly proliferative cells including tumor cells. ANT2 plays a crucial role in the maintenance of mitochondrial integrity in tumor cells by importing the glycolytic ATP into the mitochondrial matrix (reviewed in Chevrollier et al, 2010). Thus, ANT2 is required for tumor cell survival and has an anti-apoptotic function (reviewed in Brenner et al, 2011). In addition, several RNA interference studies (si/shRNA) clearly showed that the invalidation of ANT2 induced growth retardation and/or apoptosis in several tumor cell types (Jang et al, 2010-2012-2013) and sensitized to anti-tumor treatments (Kim et al, 2013; Choi et al, 2013; Jang et al, 2010-2013; Le Bras et al, 2006). More recently, ANT2 upregulation was shown to promote Sorafenib resistance in hepatocellular carcinoma (HCC) (Lu et al, 2017) and EGFR-TKI resistance in NSCLC (Jang et al, 2016).

Considering ANT2 role in tumor cell metabolism, the team identified small molecule inhibitors of ANT translocase activity. Compounds were identified first by virtual screening of compounds library on 3D model of human ANT2. Three chemical families of compounds (PCT/IB2009/006076) inhibit ADP/ATP translocation in vitro and induce apoptosis in cancer cell lines. ANT2 was identified as the in vitro target of MTL101 Hit (Family 1) by cellular knock-down of ANT isoforms and affinity chromatography on immobilized ligands.

The team optimized ANT2 ligands leading to MTL105 and MTL107 which specifically induce cell death in a panel of tumor cell lines around 1 µM. It is noteworthy that no effect on normal cells is observed up to 100 µM, suggesting a strong safety margin. Thus, ligands demonstrated higher efficacy on several tumor cell lines than other reference drugs and insensitivity to PgP efflux. Thus, ANT2 ligands constitute a first-in-class candidate in cancer therapy with this mode of action which might be particularly interesting to overcome multidrug-resistant cancers.

SCOPE

Inhibition of anti-apoptotic ANT2 protein in tumors

KEYWORDS

ADP/ATP translocase, ANT2, Mitochondria, Apoptosis, Cancer

INNOVATIVE COMPONENT & TECHNOLOGY

Through a rational approach of drug design, the team identified active and specific ANT2 small molecule inhibitors and began their optimization. These molecules display interesting anti-tumor activity in vitro by inducing apoptotic cell death but also a promising safety, opening the way to treatments with high therapeutic index.

OBJECTIVES

The aim of the company is to optimize and develop ANT2-ligands in collaboration with the pharmaceutical industry. The industrial partner will bring expertise in chemical synthesis to run SAR studies with the use of the company expertise and tools in the mitochondrial field to generate drug candidate and initiate pre-clinical development with such compound for a first-in-man administration.

DEVELOPMENT & MATURATION STAGE

ANT2 targeting and MoA well characterized in vitro
Chemical optimization required before in vivo testing.

INTELLECTUAL PROPERTY & PATIENT CO-OWNER(S)

PCT IB2009/006076
Ongoing national phases in Europe, Japan
Patent granted in USA and Canada
Co-owners: the company, CNRS and UVSQ

TARGET POPULATION

Human malignancies requiring maintenance of ANT2 activity as well as multidrug-resistant cancers.
Sensitive cancer types might be pancreatic cancer, colorectal and hepatocellular carcinoma, melanoma and NSCLC.

TARGET PROFILE

ANT2 is overexpressed in cancer cells and allows import of ATP produced by glycolysis to mitochondria to maintain transmembrane potential and tumor cell survival.

STRENGHTS & COMPETITIVE ADVANTAGES

Novel MOA, tumor specific, first-in-class product, favourable safety profile and tolerability, no competition.

INDUSTRIAL APPLICATIONS & OPPORTUNITIES

NCE to treat cancers and multidrug resistant cancers
Co-development or licensing opportunities

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