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MATURATION & ACCELERATING TRANSLATION **WITH INDUSTRY**

TECHNOLOGY OFFER

SUPPORTING INNOVATION AND TECHNOLOGY TRANSFER IN ONCOLOGY

THERAPY

SK3-SCAN (SK3-Screen CANcer)

Development of preventing bone anti-metastatic drugs, inhibitors of SK3-based channel complex, in targeted cancer therapy

CONTEXT & BACKGROUND

If cancer is the leading cause of death, it is almost always linked to the development of distant metastases. However, there is currently no anti-metastatic treatment available. The SK3-SCAN is a project dedicated to the development of original drugs for the prevention of bone metastases in targeted cancer therapy. The discovery of this new class of drugs is based on the finding of a new mechanism of cell migration observed only in cancer cells. This mechanism is not universal but depends on the abnormal presence of a protein on the surface of cancer cells: the SK3 ion channel protein. This channel that is expressed in lipid rafts with the Orai1 calcium channel was not observed in non tumor cells and is specific to cancer cells. Based on our experiments in small rodents, when cancer cells expresses SK3 channel, bone metastases are observed.

The proof of concept of the existence of this new mechanism promoting both in vitro and in vivo cancer cell migration was also established by the identification of a new molecule that inhibits SK3 channel activity, Ohmline (1-O-hexadecyl-2-O-methyl-snglycero-3-lactose), which is the subject of this project. Ohmline was found to specifically reduce the migration of SK3-expressing cancer cells (prostate, breast), the development of bone metastases and the Akt pathway following a mechanism that involves its incorporation into lipid rafts. Importantly, the action of Ohmline is selective for SK3 channel since no effect on many other ion channels (hERG, L-type Ca2+, Nav) and receptors (PAF receptor, PKCs) was detected. The clinical relevance of SK3 channel in cancer is ongoing. The analysis of a first series of samples from human cancer patients with bone marked tropism (prostate, breast, kidney) shows that SK3 channel is expressed in more than 60% of bone metastases. Furthermore, the expression of SK3 protein by cancer epithelial cells was also found in 60% of primary prostate tumors but non tumoral epithelial cell do not expressed SK3. Importantly, recent data indicate a surexpression of SK3 protein in biopsies of patients with advanced-stage prostate cancer.

Our lead molecule Ohmline and derivatives have already passed the chemical optimization phase including their synthesis. Ohmline has a good tolerance and an apparent safety in rodents (eg no observable tissue damage by a pathologist). The preclinical studies performed in vitro have shown no adverse biological activity and no toxicity or genotoxicity of Ohmline at in vitro concentrations lower than 10 µM

INNOVATIVE COMPONENT & TECHNOLOGY

The originality of our project is the development of bone anti-metastatic compounds, acting on cancer cells and based on the discovery of the first specific inhibitor of SK3 channel Ohmline. This would be the first compound for the prevention of bone metastases.

SCOPE

Prevention of bone metastases

KEYWORDS

KEYWORDS Anti-metastatic drug, ion channel, lipids, prevention, personalized therapy

OBJECTIVES

The SK3-SCAN project aims to complete the preclinical development of a new class of anti-metastatic drugs in order to position Ohmline in clinical trials in 3 years. The two first goals are 1- Determination of the minimal pharmacological active dose of Ohmline in combination with androgen-deprivation drugs; 2- Determination of the clinical relevance of SK3 expression in cancers with bone tropisms. To reach these goals, we need first to develop an analytical method for Ohmline quantification by HPLC/MS and the galenic formulation of Ohmline in order to evaluate: the stability of the compound, its potential adverse side effects and toxicity and its pharmacokinetic. Finally, we propose to reinforce the strength of our patents by additional patents (new Ohmline analogs, formulation and SK3 detection kit). Thus, we expect to obtain a definitive proof of concept on SK3 channel as a drugable target and we propose to position Ohmline for the prevention of bone colonization in patients with advanced-stage prostate cancer because these patients have a high risk to develop bone metastases.

DEVELOPMENT & MATURATION STAGE

Preclinical development of Ohmline to consolidate the proof of concept on SK3 channel as a drugable target and to position Ohmline as a drug candidate for phase II clinical studies for the prevention of bone colonization in patients with prostate cancer and who have a high risk to develop bone metastases

INTELLECTUAL PROPERTY & PATIENT CO-OWNER(S)

Patent N°1: « Method for the in-vivo screening of anti-cancer compounds that inhibits SK3 activity and said anti-cancer
compounds » patented on 2006-08-03 (n° EP06118417, 2, USA, Japan, Europe).
Co-owners: University of Tours and INSERM.

Patent N°2: -« Method for Preventing Cancer Metastasis» patented on 2010-02-18 (n°EP10305169, 4, USA, Japon, Europe).
Co-owners: University of Tours, University of Bretagne Occidentale and INSERM

TARGET POPULATION

The treatment will be dedicated to patients having tumor cells that express SK3. Such therapeutic approach might be benefit to patients that are predisposed to develop bone metastases, such as, according to incidence of bone metastasis, cancers of prostate, breast, lung and kidney. Note that we propose to first position Ohmline in the prevention of bone metastases in prostate cancer patients, a cancer in which the likelihood of bone metastases occurrence is very high and quick.

TARGET PROFILE

- Ion channel: SK3 channel is a potassium channel localised in lipid rafts. Our concept is based on the inhibition of the activity of this plasma membrane protein.
- Ohmline: Ohmline is an amphiphilic compound, retained at the plasma membrane that displace SK3 channel from lipid rafts. It has a glyco-glycero-ether lipid chemical formula and its synthesis can be readily performed using standard organic chemistry protocols.

STRENGHTS & COMPETITIVE ADVANTAGES

First compound for the prevention of bone metastatses. Development of a new and original therapeutic approach (drug integrate on tumor lipid rafts and on SK3 channel localized in tumor lipid rafts). Originality of the target (SK3) and of the amphiphile compounds in cancer. Attractiveness of a new target expressed in more than half of Breast/ and Prostate tumors. Non tumoral epithelial cells do not expressed SK3. The expression of SK3 can be observed using already developed immunohistochemistry kit. Drugs used in targeted and personalized cancer therapy.
At present, there is no drug available to prevent bone metastasis development. Such therapeutic can complement the action of existing drugs targeting bone metastases: bisphosphonates, denozumab and alpharadin. Should Ohmline totally prevent bone metastasis development it would replace the existing drugs, Bisphosphonates, Denozumab and Alpharadin, dedicated to reduce skeletal related events in established bone metastases.

INDUSTRIAL APPLICATIONS & OPPORTUNITIES

Bone anti-metastatic drugs in targeted and personalized cancer therapy: targeted to SK3 channel and dedicated to patients with tumor cells expressing the SK3 channel. These drugs will prevent bone colonisation by cancer cells. Such therapy would be used mostly as an adjuvant therapy and in association with therapeutics for SK3-positive cancers with a high risk of bone metastases formation. Advanced-stage prostate cancer constitutes a first therapeutic target because nearly all patients will develop bone metastases.

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