MATWIN
MATURATION & ACCELERATING TRANSLATION **WITH INDUSTRY**

TECHNOLOGY OFFER

SUPPORTING INNOVATION AND TECHNOLOGY TRANSFER IN ONCOLOGY

THERAPY

EPISENS

Epigenetic regulations as new therapeutic targets in oncology

CONTEXT & BACKGROUND

Epigenetics refers to heritable and reversible changes of gene expression that do not derive from alterations of the nucleotide sequence of DNA. In particular, epigenetic modifications include the DNA methylation and histone post-translational modifications. These different processes (methylation, acetylation and others) are dynamic phenomenon within the cells that involve a high number of proteins in a **network of interactions**. In cancer cells, the exacerbate methylation pattern of tumor suppressor genes reduces their expression, while reduced methylation of oncogenes leads to increased expression. Accordingly, the correction of epigenetic defects at the level of specific genes would represent an attractive strategy. However, this highly specific epigenetic editing was not available so far.

The currently approved drugs that target the methylation mechanisms are inhibitors of DNA methyl transferase (DNMTs), which favour the demethylation of all genes, regardless of their oncogenic or tumor suppressing roles. The clinical benefits remain limited, due to this default in specificity and the dose-limiting toxicities. However, a major positive result is that epigenetic drugs can potentiate the anti-cancer activity of standard chemotherapy, radiotherapy and targeted therapies.

In their proof-of-concept experiments, the team identified :
1) a **molecular target** involved in the resistance of cancer cells to therapeutic agents, namely the ISGF3/DNMT3A complex,
2) a **peptidic drug** that re-sensitizes glioblastoma cells to the current standard-of-care treatment (temozolomide + irradiation), via the restoration of some important pro-apoptotic molecules, and,
3) a mechanistically-related **companion diagnostic**, based on blood sample testing.

The identification of the precise mechanism of action is fully disruptive compared to wide-spectrum DNMT inhibitors. Beside the initial description in glioblastoma, recent data have shown that the target is relevant in other cancer types, notably lung, prostate, oesophagus.

INNOVATIVE COMPONENT & TECHNOLOGY

In general terms, the team's innovation is based on the targeting of precise protein/protein complexes from the epigenetic network, that are responsible for defects in the methylation pattern of gene promoters. The defective methylation of promoters results in intrinsic- or induced-resistance to therapeutic agents in cancer cells.

They have developed a **technology platform** to identify the mechanisms responsible for the aberrant methylation of genes of interest, based on our specific know-how. Common genes of interest are oncogenes, tumor-suppressing genes, immune checkpoint genes, which are relevant across a variety of cancers.
Given that the approach starts from the identification of the mechanism of action and the drug design and evaluation follow, the main advantages of it are :
1) to focus drug-candidate development on the pre-identified target,
2) to limit the off-target effects,
3) to have a companion biomarker available at an early step.

Based on this platform, the team started the EXD2 program for the **preclinical and clinical development** of the drug candidate to target the ISGF3/DNMT3A complex. This new drug is designed to potentiate the radio-chemotherapy via the restoration of the apoptotic pathway. The indication remains to be selected among the different cancers of interest. The key benefit from the approach is to provide a new and strong rationale for the most appropriate potentiation of the treatment (radio-, chemo- or targeted therapy) in a personalised medicine perspective.

SCOPE

Innovative approach to increase the efficacy of anti-cancer therapy

KEYWORDS

DNA Methylation, potentiation, drug combination

OBJECTIVES

Based on this technology platform and on the lead program, the objectives are :
1) to expand the use of the **technology platform** of target identification across different cancers. The team seeks to establish collaborative agreements with partners to potentiate several classes of treatments, including chemotherapy, immune checkpoints therapy and other targeted therapies.
2) to obtain clinical proof-of-concept of safety and efficacy for the disruption of the DNMT3A/ISGF3 molecular complex in **EXD2 program**.

DEVELOPMENT & MATURATION STAGE

The technology platform is available for operation.

EXD2 program:
Pre-clinical proof-of-concept in vivo is obtained.
Optimization of the drug candidate and formulation is planned.

INTELLECTUAL PROPERTY & PATIENT CO-OWNER(S)

EXD2 program:
1.European Patent filed (March 2015), PCT extension submitted (March 2016), designation of UE, USA and Japon (Sept 2018) by INSERM-Transfert
2. Exclusive license to company planned

TARGET POPULATION

The incidence of glioblastoma is estimated to be 115,000 new cases worldwide per year. The target population positive for the DNMT3A/ISGF3 molecular complex represents 45% of the patients treated with the standard-of-care treatment.
In other indications, the target populations range from 15% to 80% representing significant fractions of patients in each indication.

TARGET PROFILE

Positioning: synergy with drugs commonly used or in development.

STRENGHTS & COMPETITIVE ADVANTAGES

• The precise targeting represents the development of a new generation of DNMT inhibitor, with a clear differentiation over the existing inhibitors that display wide-spectrum inhibition and numerous side effects.
• The combination of the therapeutic drug and its companion diagnostic allows to guide the rational use of the drug. The expected impact is to increase the efficacy of the current standard-of-care, in a significant fraction of patients (e.g. 45% in glioblastoma).

INDUSTRIAL APPLICATIONS & OPPORTUNITIES

In oncology, managing the sensitivity of cancer cells to treatment remains a major challenge. Then, the potentiation of marketed drugs (or drugs in development) can be a promising approach in different directions, notably :
1) increasing the efficacy,
2) reducing the side effects,
3) overcoming the intrinsic and the treatment-induced resistances (e.g. in anti-PD1 treated patients).

The **technology platform** is dedicated to the identification of pivotal epigenetic mechanisms which drive the resistance of cancer cells to treatment. These mechanisms represent starting point to develop:

- epigenetic drugs that can synergize with other drugs, such as chemotherapeutics or immune checkpoint inhibitors by stabilizing the expression of their target, and,
- relevant biomarkers to stratify the patient population.

The **EXD2 program** is initiated and relies on sensitizing cancer cells to chemotherapy via the restoration of an apoptotic pathway. Partnerships for extending this program to specific indications (e.g. lung and prostate cancers) are sought.

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