MATWIN
MATURATION & ACCELERATING TRANSLATION **WITH INDUSTRY**

TECHNOLOGY OFFER

SUPPORTING INNOVATION AND TECHNOLOGY TRANSFER IN ONCOLOGY

THERAPY

COGITh

CYP **O**ncology **G**ene and **I**mmune **Th**erapy

CONTEXT & BACKGROUND

Based on previous research and expertise in biochemical engineering, cancer immunology and minimally invasive interventional medicine, a completely new approach of cancer treatment was developed consisting in:

- Sensitization of tumors to a **prodrug** thanks to a **modified gene** (patented).
- Triggering of a secondary and specific **immune response** against tumor cells.

The first step consists in introducing, into the tumor, an optimized gene (engineered in our lab and patented) that transforms, **cyclophosphamide (CPA)** into toxic metabolites very efficiently. The second step is the treatment with CPA. In **mice**, CPA **completely eradicated ectopic pulmonary tumors** containing CYP2B6TM-RED, without any recurrence up to 24 months after stopping the treatment. The triggered **immune response** was synergic with the toxicity of CPA metabolites, **protected** against **recurrence** of the **primary tumor** and prevented the development of **metastases** (Amara et al, *J Control Rel* 2016).

To introduce the modified-gene into the tumors, **Mesenchymal Stem Cells (MSCs)** were used as **vector** since they migrate into the tumors and home there. The highly positive results obtained in mice were confirmed in an orthotopic VX2 hepato-carcinoma rabbit model; transduced MSCs were injected, intra-arterially (IA) close to the tumor. After two injections of MSCs-CYP2B6TM-RED and CPA, tumors reduced significantly as compared to controls. In addition, no metastasis was seen in 2/3 of the rabbits, which has never been observed previously in this very aggressive type of tumor, with any other type of treatment (Pellerin et al, *Cardiovasc Intervent Radiol.* 2018).

INNOVATIVE COMPONENT & TECHNOLOGY

The lead product consists in an optimized gene (named CYP2B6TM-RED), derived from Cytochrome P450 2B6. It is able to convert very efficiently (13 times more efficiently than wild type CYP2B6) a prodrug, cyclophosphamide (CPA), into its toxic metabolites, with the aim of treating solid tumors. It is a gene-directed enzyme prodrug therapy (GDEPT) that consists in bringing the optimized gene into the tumors, thanks to an intra-arterial (IA) administration and an efficient vector, mesenchymal stem cells (MSCs). There, it eradicates the tumor and triggers a specific immune response, resulting in a vaccinating effect (see Figure 1).

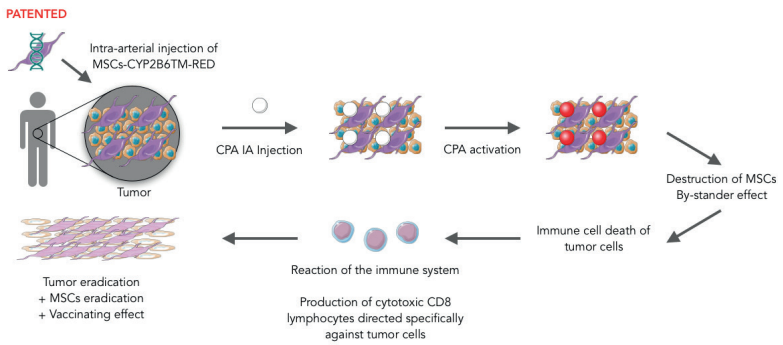

Figure 1: COGITh's GDEPT approach: a trojan horse strategy

SCOPE

A gene immunotherapy for the treatment of solid tumors, with a first focus on hepatocellular carcinoma and prostate, kidney or breast cancer.

KEYWORDS

Gene & Cell therapy – Immuno-oncology – Immunotherapy – Cancer – Hepatocellular Carcinoma – Platform technology

OBJECTIVES

The team's business model is based on the creation and development of a pipeline of high value therapeutic products. Indeed, the product has the properties of a technology platform as the same product, MSC-CYP2B6TM-RED, can be used in different indications to treat most solid tumors. The team will develop its products up to the clinical phase I/II and from there it will partner (co-development) the products to pharmaceutical companies for further development and commercialization.

DEVELOPMENT & MATURATION STAGE

The first drug candidate, named C... 01, is currently in the preclinical phase of the development. First-in-human clinical trials should start in 2022. Major progress achieved to date:

- Optimization of CYP2B6: new patented gene 13 times more efficient than wild type for CPA metabolization.
- Evaluation of several vectors and demonstration of the inefficacy of viruses (lentivirus and poxvirus), and of the pertinence of allogeneic MSCs to carry and express the gene.
- In vitro proof of concept in different human cancer cell lines insensitive to CPA (breast, colorectal and head and neck).
- In vivo proof of concept in mice: ability to kill tumor cells through direct toxicity, by-stander effect and specific immune response protecting the mice after a rechallenge experiment.
- In vivo proof of concept in rabbits: significant decrease in tumor size and no metastases in 2 out of 3 rabbits treated (has never been observed in this very aggressive tumor model). Validation of the intra-arterial administration route.
- Characterization of the secondary immune response, which is mainly due to immunological cell death.

Next steps:

- Comparison to gold-standard (IA doxorubicin + lipiodol) in 30 rabbits with VX2 tumors: sponsored by an industrial.
- Characterization of the secondary immune response (article in revision in OncoImmunology).
- Creation of the start-up in January 2019 and filing of additional patents.

TARGET POPULATION

This approach to GDEPT, based on MSCs expressing the CYP2B6TM-RED gene plus CPA, is well suited for the treatment of most solid tumors. The first clinical target will be hepatocellular carcinoma (HCC). HCC is the sixth most common cancer in terms of incidence (782,000 new cases/year) and the second leading cause of cancer deaths worldwide. Other targets are envisioned such as prostate, kidney and breast cancer. Therapeutic approaches for the treatment of advanced HCC are currently very limited and are not effective enough as five-year survival rate for HCC is around 17% and has not increased in the past 20 years.

INTELLECTUAL PROPERTY & PATIENT CO-OWNER(S)

The patent (EP 2 705052B1) covers both the optimized gene (CYP2B6TM-RED) and its vector. It was filed in 2012 (EP, US, WO) and it was delivered. Owner: Institut National de la Santé et de la Recherche Médicale (INSERM).
An exclusive license has been granted to the company created.

TARGET PROFILE

- Allogeneic human mesenchymal stem cells expressing a modified gene, CYP2B6TM-RED + Cyclophosphamide
- Intra-arterial route of administration

STRENGHTS & COMPETITIVE ADVANTAGES

This therapeutic approach presents key advantages compared to other similar approaches:

- An increased therapeutic index thanks to a higher toxin concentration at tumor site only. This is due to a targeted route of administration, an efficient vector with a natural tropism for tumor cells, and to our optimized and proprietary gene, which is 13 times more efficient to metabolize CPA.
- A strong direct by-stander effect (free diffusion of CPA toxic metabolites).
- A specific and long-lasting anti-tumor immune response, which protects against recurrence and metastases.
- In vivo proof of concept in two relevant animal models.

A complementary team and the expertise of recognized experts:

- The company's scientific co-founders are specialists of human CYPs (pharmacogenetics, toxicology, immuno-toxicology, oncology). One was Head of Clinical Chemistry Department in Paris, Professor of Biochemistry at Paris-Descartes and Director at INSERM and the other holds 2 PhD and is currently working on the scientific aspects of the project with a PhD student and a Master student.
- Two recognized experts and key opinion leaders in interventional radiology.

INDUSTRIAL APPLICATIONS & OPPORTUNITIES

- Technology platform as the same product, MSC-CYP2B6TM-RED, can be used in several indications to treat most solid tumors (e.g. prostate, kidney, breast) → Big market size, co-development or licensing opportunities.
- HCC indication: high unmet medical need for which the IA route of administration is already used as a standard of care. By targeting HCC as a first clinical target, we expect to get an orphan drug designation for C...01 in USA and EU, which will give substantial advantages to maximize the probability of a successful outcome.
- The team have already established a partnership with an industrial to conduct a new proof of concept study in 30 rabbits.

CONTACT | MATWIN : contact@matwin.fr