MATWIN
MATURATION & ACCELERATING TRANSLATION **WITH INDUSTRY**

TECHNOLOGY OFFER

SUPPORTING INNOVATION AND TECHNOLOGY TRANSFER IN ONCOLOGY

COGITh
CYP Oncology Gene and Immune Therapy

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

COGITh's 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).

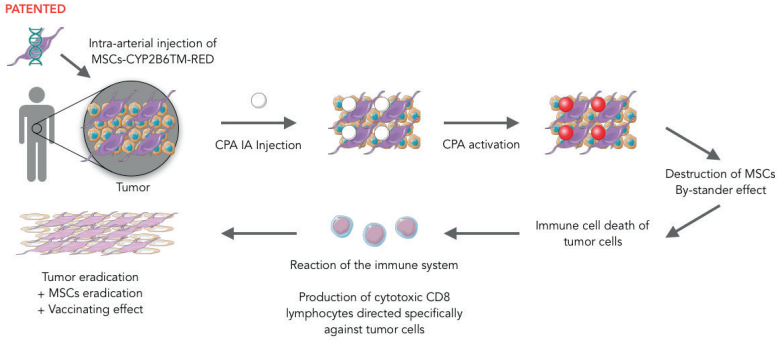

Figure 1: COGITh's GDEPT approach: a trojan horse strategy

SCOPE

A gene immunotherapy for the treatment of solid tumors, with a first focus on hepatocellular carcinoma.

KEYWORDS

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

OBJECTIVES

COGITh's business model is based on the creation and development of a pipeline of high value therapeutic products. Indeed, COGITh 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. COGITh 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

COGITh's first drug candidate, named COGITh 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 September 2018 and filing of additional patents.

INTELLECTUAL PROPERTY & PATIENT CO-OWNER(S)

The patent named Mutant cytochrome P450 2B6 proteins and uses thereof (EP 2705052B1) 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). Agent: SATT IDF Innov.

An exclusive license will be granted to COGITh by SATT IDF Innov upon company creation.

TARGET POPULATION

COGITh's approach to GDEPT, based on MSCs expressing the CYP2B6TM-RED gene plus CPA, is well suited for the treatment of most solid tumors. Our 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. 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.

TARGET PROFILE

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

STRENGHTS & COMPETITIVE ADVANTAGES

COGITh's 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:

- COGITh's scientific co-founders, Pr. Philippe Beaune (PharmD., h=78) and Dr. Isabelle de Waziers (HDR, h=33), are specialists of human CYPs (pharmacogenetics, toxicology, immuno-toxicology, oncology). Pr. Beaune was Head of Clinical Chemistry Department in HEGP Paris, Professor of Biochemistry at Paris-Descartes and Director of INSERM U490. Dr. de Waziers 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, Pr. Marc Sapoval (head of department, HEGP) and Dr. Olivier Pellerin (HEGP).
- Two Industrial Pharmacist, Julie Cervesi and Aymeric Empereur, with a double expertise in pharmaceutical development and business.

INDUSTRIAL APPLICATIONS & OPPORTUNITIES

- Technology platform as the same product, MSC-CYP2B6TM-RED, can be used in several indications to treat most solid tumors → 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 COGITh 01 in USA and EU, which will give substantial advantages to maximize the probability of a successful outcome.

- We have already established a partnership with an industrial to conduct a new proof of concept study in 30 rabbits.

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