MATWIN
MATURATION & ACCELERATING TRANSLATION **WITH INDUSTRY**

TECHNOLOGY OFFER

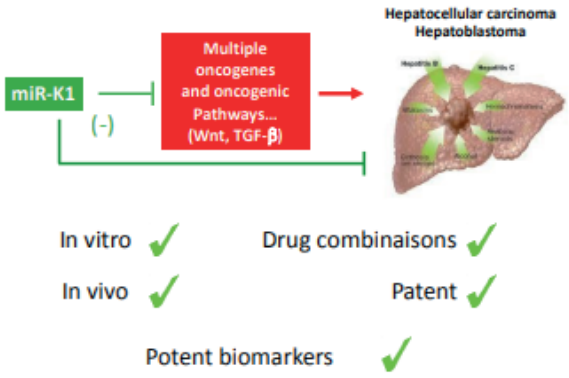
SUPPORTING INNOVATION AND TECHNOLOGY TRANSFER IN ONCOLOGY

Liver µtherapy

MIR-K1, A MULTITARGET THERAPEUTIC AGENT FOR THE TREATMENT OF LIVER CANCER

CONTEXT & BACKGROUND

Hepatocellular carcinoma (HCC) is a frequent and deadly primary liver neoplasm in adults, which kills 782,000 people per year in the world (half in China) [1, 2].There is currently no curative therapy for a large proportion of patients who generally present an unresectable and advanced tumor and decreased hepatic functions due to liver cirrhosis. Moreover HCC tumors are molecularly very heterogeneous and many gene drivers and oncogenic pathways participate in liver carcinogenesis. For all these reasons, patients usually do not respond to chemotherapy and most targeted therapies have failed to show any benefit in this cancer with the exception of sorafenib that slightly increases life expectancy of patients with advanced tumors. In this context, microRNA-replacement therapy is a new strategy for the treatment of patients with liver cancer as exemplified by the current phase I with miR-34a-5p, the first microRNA reaching the clinical trial step in cancer. Using bioinformatic analyses and functional screening approaches, we selected miR-K1 as a strong regulator of various oncogenes in tumoral hepatic cells. Indeed miR-K1 decreased the expression of several key factors involved in cell proliferation, survival and differentiation and inhibited the two oncogenic TGF- -catenin pathways. Moreover, whereas MiR-K1 is abundant in most organs and human tissues including liver, this microRNA is strongly decreased in all types of HCC and in hepatoblastoma, a primary tumor of the liver in children under 5 year of age. At a cellular level, miR-K1 efficiently reduced the tumoral growth of liver cancer cell lines in vitro and in vivo, and induced their death through apoptosis. Besides, miR-K1 sensitized tumoral hepatic cells to drugs currently used in clinic as a first-line treatment for patient with advanced, metastatic and/or unresectable liver tumor (Sorafenib, cisplatin...). These data are of particular interest as these drugs are sometimes associated with severe toxicity and only barely increase patients' overall survival in HCC. In conclusion, miR-K1 acts as a strong tumor suppressor in liver by inhibiting multiple oncogenes and pathways. At this stage, our objectives are the development of miR-K1-replacement therapy, associated or not with standard clinical drugs, using various route of administration (locoregional, intra-arterial, systemic...) and the transfer of miR-K1 to the clinic for the treatment of patients with liver cancer. **Figure: Key points of our innovative miR-K1 approach in liver cancer. The tumor-suppressive role of miR-K1 has been validated in vitro and in vivo. This molecule is patented and can be combined with other drugs. Its target genes constitute good biomarkers to evaluate the response of patients to miR-K1- replacement therapy.**



References

1. Llovet, J.M., et al., Advances in targeted therapies for hepatocellular carcinoma in the genomic era. Nat Rev Clin Oncol, 2015.
2. Attwa, M.H. and S.A. El-Etreby, Guide for diagnosis and treatment of hepatocellular carcinoma. World J Hepatol, 2015. 7(12): p. 1632-51.

INNOVATIVE COMPONENT & TECHNOLOGY

- A new microRNA with antitumoral properties validated in vitro on 4 hepatoma cell lines and in vivo (chick CAM model).
- miR-K1 is more effective in vitro than miR-34a-5p, the microRNA currently tested in phase-I clinical trial in unresectable and metastatic liver cancer in adults.
- miR-K1 sensitizes tumoral hepatic cells to the first-line clinical drugs (Sorafenib, Cisplatin...).
- miR-K1 is downregulated in human HCC and in hepatoblastoma.
- miR-K1 targets several key oncogenes and pathways involved in liver carcinogenesis and hepatic tumoral cell survival and proliferation.

=> miR-K1 is an excellent candidate for miRNA-replacement therapy

SCOPE

A new multitarget drug for the treatment of adult and pediatric liver cancers

KEYWORDS

MicroRNA, liver, cancer, Hepatocellular carcinoma, Hepatoblastoma, Oncogenes, tumour suppressor.

OBJECTIVES

- Development of a miR-K1-replacement therapy for treating liver cancer in adult and children.
- Development of a multidrug therapy (miR-K1 + standard clinical drug) for treating liver cancer in adult and children.
- Evaluation of the relevance of miR-K1-replacement therapy in other cancers.
- Perform preclinical studies for lead optimization, formulation selection, GMP production, toxicity, ADME and PK

DEVELOPMENT & MATURATION STAGE

- Anti-tumoral activity obtained with chemically modified miR-K1 candidates from different sources
- In vivo efficacy of our candidate based on a peritumoral injection of miR-K1/In vivo-JetPEI nanoparticles in mice with subcutaneous HCC tumor xenografts
- Selection of the delivery system depending on the administration route (naked, adenovirus, lentivirus, liposomes, beads…)
- In vivo efficacy of our candidate based on a systemic injection of miR-K1/ selected nanoparticles in mice with orthotopic liver tumors.
- Comparison of miR-K1 with miR-34a-5p, the first-in-class microRNA entering the clinic
- Evaluation of miR-K1 as a tumor suppressor in another frequent cancer in adults

INTELLECTUAL PROPERTY & PATIENT CO-OWNER(S)

- Pending European patent application “Use of Glypican-3-targeting microRNAs for treating liver cancer” (Application: EP 15 306107.2/ Priority: 2015/07/07). Patent co-owners: INSERM, Bordeaux University
- Strong IP

TARGET POPULATION

- Treatment of patients with liver cancer by miR-K1-replacement therapy in association or not with drug (sorafenib, cisplatin…):
- Adult patients with hepatocellular carcinoma (HCC).
- Possibly pediatric hepatocellular carcinoma (teenagers and young adults above 15 of age).
- Children (below 15 of age) with Hepatoblastoma (HBL).
- Patients with advanced, metastatic and/or unresectable liver tumor

TARGET PROFILE

- miR-K1 negatively regulates various oncogenes that are overexpressed in liver cancer. These oncogenes play a key role in liver carcinogenesis and are involved in hepatic tumoral cell survival, proliferation and differentiation. Moreover, our candidate selection is confirmed by our retrospective analysis underlying the under-expression of miR-K1 in all types of liver cancers

STRENGHTS & COMPETITIVE ADVANTAGES

- Modality that could be used as a monotherapy or in combination to potentiate the anti-tumoral effect of current drugs (Sorafenib or possibly doxorubicin for HCC, Cisplatin for HBL).
- Modality more efficient in vitro compared to the miR-34a-5p modality currently tested in a phase I clinical trial.
- A new report showing miR-34a-5p as an oncogene rather than a tumor suppressor in half of HCC.

INDUSTRIAL APPLICATIONS & OPPORTUNITIES

- New therapeutic strategy for cancers lacking efficient treatment options
- HCC indication: common cancer associated with a bad prognosis (half of patients being in China)
- Big market size with unmet medical needs
- Possibility to be used in combination with standard chemotherapies
- Co-development or licensing opportunities

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