

842 **EXOSOME MEDIATED REPROGRAMMING OF TUMOR ASSOCIATED MACROPHAGES BY EXOASO-STAT6 FOR THE TREATMENT OF HEPATOCELLULAR CARCINOMA (HCC)**

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**Background** Tumor associated macrophages (TAMs) play a critical role in tumor immunosuppression and resistance to immune checkpoint blockade. Reprogramming ‘M2’ TAMs to a proinflammatory ‘M1’ phenotype by selectively silencing M2 phenotype-driving transcription factors, such as STAT6, is a promising strategy to relieve TAM-induced immunosuppression. We have developed exoASO-STAT6™, an investigational therapeutic candidate consisting of exosomes loaded with anti-sense oligonucleotides (ASOs) targeting STAT6. By leveraging the TAM tropism of exosomes, exoASO-STAT6™ is the first systemically administered exosome designed to selectively silence STAT6 in TAMs. Preclinical biodistribution studies demonstrated that the liver is the main organ targeted by exoASO after intravenous (IV) dosing.

**Methods** We evaluated the translational potential of exoASO-STAT6 to treat hepatocellular carcinoma through pharmacokinetics (PK), pharmacodynamic (PD) and anti-tumoral efficacy studies in preclinical models, as well as computational analysis of human HCC datasets.

**Results** PK/PD were evaluated in naïve mice dosed IV with a single dose of exoASO-STAT6. PK analysis showed that the STAT6-ASO is rapidly cleared from plasma. Retention of the ASO in liver was dose-dependent and observed for at least 21 days. exoASO-STAT6 induced significant Stat6 mRNA knock-down (KD) in liver tissue with maximum KD at day 7 (70% KD at the 30 ug dose). IV administration of exoASO-STAT6 in an orthotopic, CPI resistant HCC model attenuated tumor growth and induced complete remission of tumor lesions in 50% of mice, while combination therapy with anti-PD1 antibodies further enhanced anti-tumor activity (75% complete remissions). Gene expression and histological analysis of the liver showed effective remodeling of the tumor microenvironment including a significant increase in interferon and cytotoxic T-cell gene signatures and iNOS expression. PD studies were also performed in cynomolgus monkeys that demonstrated a dose-dependent and durable silencing of STAT6 mRNA (50% and 31% at 1- and 3- weeks post-dose, respectively). STAT6 knockdown correlated with a reduction in STAT6 target genes, IL4R and EGR2, confirming modulation of the STAT6 pathway. Finally, we identified a STAT6 macrophage transcriptional signature and show high expression in human HCC tumors, both in immune cell-rich and TAM-rich/CD8 T-cell low tumors that correlates with worse survival.

**Conclusions** In summary, we demonstrate that exoASO-STAT6 has a durable PK/PD profile in the liver of several species and potent antitumoral efficacy in a preclinical model of HCC. Furthermore, we identify an inverse correlation between the STAT6 macrophage signature and survival in human HCC tumors. Altogether our data support the systemic administration of exoASO-STAT6 as a promising therapy for liver cancer.

**Ethics Approval**

**For Mice** Mice were maintained and treated at the animal care facility of Codiak Biosciences in accordance with the regulations and guidelines of the Institutional Animal Care and Use

Committee (CB2017-001). Animal housing and experimental procedures (mice) were conducted according to the French and European Regulations and the National Research Council Guide for the Care and Use of Laboratory Animals and Institutional Animal Care and Use Committee of Oncodesign (Oncomet) approved by French authorities (CNREEA agreement N° 91). For cynomolgus monkeys: All animals were maintained and treated at the animal care facility of Altasciences in compliance with the Animal Welfare Act and recommendations set forth in the Guide for the Care and Use of Laboratory Animals (National Research Council 2011).

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