Preclinical evaluation of polyethylenimine-mediated RNA interference of Polo-Like Kinase 1 gene for ultrasound image-guided treatment of hepatocellular carcinoma

G.B. About¹, E. Thiebaut¹, A. Guimond¹, P. Reilly¹, M. Wattenhofer-Donze¹, E. Robinet², T.F. Baumert², P. Erbacher⁵, T. Sorg¹, Y. Herault¹.

¹ Institut Clinique de la Souris-ICS-MCI, PHENOMIN, CNRS UMR7104, INSERM U964, Université de Strasbourg, 1 rue Laurent Fries BP 10142 Parc d’Innovation 67404 Illkirch, France;
² U1110, INSERM,
³ IHU Strasbourg
⁴ Strasbourg University Hospital
⁵ PolyPlus Transfection, Strasbourg, France

Virus-induced chronic hepatitis is a leading cause of HepatoCellular Carcinoma HCC in France and Europe. In the developed Western world, only 10-15% of cases can be attributed to hepatitis B virus (HBV) infection, while chronic hepatitis C appears to be the major risk factor for HCC (up to 70% of cases) in Europe. Indeed, HCC is the second cause of cancer death worldwide, and due to limited treatments options, the 5-year overall survival rate is <20%.

Unsatisfactory therapeutic options are due too several hurdles, such as a poorly understood pathogenesis, heterogeneity of HCC, limited number of targets and small animal models only partially addressing pathogenesis. Our goal within the Therahcc program was to develop relevant animal models for pathogenesis and preclinical therapeutic studies.

In particular, Ultra-Sound (US) image-guided orthotopic injection of human HCC tumor cells in the liver parenchyma has been set-up and validated. In a first series of experiments, US image-guided injection of Huh-7 cells in immunodeficient mice was successfully performed, leading to tumor engraftment in the targeted hepatic lobe with a similar efficacy as after injection under laparotomy.

In a second series of experiments, we evaluated in vivo a therapeutic innovative approach based on image-guided local delivery of Doxorubicine or siRNA targeting the Polo-Like Kinase 1 (PLK1) using a polyethylenimine (PEI)-based nanovector. We were able to show improved efficacy of doxorubicin upon local versus IP administration, strong tumor growth reduction and a potent antitumor effect of the PLK1 nanovector.

The use of US imaging for intra-hepatic or intra-tumoral injections allows thus to refine this model, in agreement with the 3R rules of animal experimentation. These data also provide support to the in vivo applicability of PLK1 nanovector administration for HCC treatment and hints for further developments.