Targeted Herpesvirus-derived Oncolytic Vectors for Liver Cancer European Network

Keywords
HSV-1, hepatocellular carcinomas, oncolytic vectors, targeting

Summary
The overall objective of THOVLEN is to develop safe and efficient herpes simplex virus type 1 (HSV-1)-derived oncolytic vectors, designed to strictly target and eradicate human hepatocellular carcinomas (HCC), the most common liver cancer of adults. HSV-1 is certainly one of the most promising viral platforms for the development of improved oncolytic vectors, as anticipated by the unique biological properties of this virus and confirmed by the encouraging results coming from clinical trials in gliomas. However, the first generations of oncolytic HSV-1 vectors have also shown limitations regarding efficacy and safety. New generations of innovative HSV-1 vectors with improved potency and safety are required before the oncolytic strategy using HSV-1 becomes a standard therapeutic reality against cancer, and this is the goal of THOVLEN. One of the most important innovative contributions of our project concerns the overall approach towards the improvement of HSV-1-based oncolytic viruses. Instead of focusing on the development of vectors carrying deletions in particular virus genes, we will engineer competent, but replication-restricted, HSV-1 vectors, strictly targeted to HCC. These vectors will combine multiple HCC-targeting approaches, both at the level of entry and at the level of gene expression and replication, and will be able to multiply and spread only in HCC, while displaying no virulence in normal healthy tissues. Additionally, an important innovation is related to the ability of the HSV-1 vectors to permit a sophisticated and flexible combined approach against HCC. That is, in addition to optimising the oncolytic properties of HSV-1 vectors, THOVLEN will exploit the very large transgenic capability of HSV-1 to generate vectors that will simultaneously display multiple and multimodal anti-tumour activities acting either locally or systemically, including combined expression of anti-angiogenic, immune-modulatory and oncolytic proteins.

Problem
Data from epidemiological studies indicate that HCC accounts for 80% of all primary liver cancers and is one of the most prevalent malignant diseases worldwide. It is the fifth most common cancer, with an estimated average of about 0.45 million new cases diagnosed each year, and it ranks fourth in mortality rate. Furthermore, the incidence of HCC has increased noticeably over the past two decades and has become progressively associated with younger age groups. Despite development of novel therapeutic methods in recent years, prognosis of advanced HCC remains very poor, with a life expectancy of about six months from time of diagnosis and a less than 3% survival rate for untreated cancer over five years. This disease therefore represents a major challenge for public health in Europe and in the world. It decreases human longevity, impairs citizens’ quality of life and represents an immense burden to Europe’s healthcare services. New therapeutic strategies are clearly needed to improve this situation. The possibility of developing an anti-cancer therapy whose activity increases with time, while retaining tumour-specificity and expressing multiple anti-tumour activities is a new and still uncharted area of cancer therapy and, in this context, the administration of HSV-1 oncolytic vectors shows a considerable promise. Therefore, by developing our project, THOVLEN will ultimately serve to accelerate the development of new, safer and more effective treatments.
Aim

The central goal of THOVLEN is to design HCC-targeted virus vectors that will simultaneously display multiple targeting elements acting at different steps of the virus life cycle, in order to ensure maximum aggressiveness for HCC cells with minimum or no virulence for healthy tissues. In addition, the unique advantage of the HSV genome to carry about 40 kbs of foreign DNA will be exploited in the context of designing a multimodal approach for cancer therapy, required for improvement of the inherent anti-tumour activity of the virus. The availability and the expertise in using several well-defined animal models for liver cancer will allow us to evaluate safety and efficacy of our vectors in relevant systems. Through fundamental research, we will generate novel genomic and proteomic information on the interactions between the oncolytic vectors and the normal and cancer cells, which will guide the rational design of vectors targeted to HCC cells, therefore resulting in the improvement of the vector oncolytic potency, and the improvement of safety.

Expected results

We will investigate different ways of producing HSV-1 vectors conceived to penetrate specifically, express genes and replicate into HCC, therefore killing these cells and allowing the spread of the virus to infect other tumour cells. In addition to their inherent targeted oncolytic potential, these vectors will express enhancing transgenic sequences, encoding immune-modulators, anti-angiogenic molecules, fusion proteins, or toxic proteins, which are expected to have an additive negative action on tumour growth. Our expectation is to produce, by the end of the project, a number of such vectors, combining targeting and enhancing functions, which will be fully evaluated for efficacy and toxicity on different HCC animal models, including standard and transgenic mice, and woodchucks.

Potential applications

Treatment of primary liver cancers (hepatocellular carcinomas).

Project website: no definitive website address