Cancer Virotherapy

Semliki Forest Virus: An efficient self-replicative RNA vector for cancer therapy

- **Combination** of immunotherapy and virotherapy, using oncolytic viruses, has shown great promise in cancer therapy.
- **Semliki Forest virus** (SFV) vectors are based on a self-replicating RNA that constitutes a promising tool for cancer therapy due to several intrinsic properties that include high expression levels, induction of type I interferon (IFN) responses and apoptosis in tumor cells.
- SFV vectors able to express immunostimulatory proteins, such as interleukin-12 (IL-12) or IFNα, have been developed.
- Primary indication: **Cancer.**

**Medical Need**

Despite remarkable advances in cancer therapy based on the use of oncolytic vectors and immunomodulatory antibodies:

- Immunomodulatory antibodies do not work in all patients, show toxicity, and are not effective in some tumor types, such as pancreatic cancer, colorectal cancer or hepatocellular carcinoma.
- Oncolytic vectors are limited by the induction of anti-virus immune responses.

**Product profile:**
- SFV vectors can be easily engineered to express immunostimulatory proteins.
- When given intratumorally, SFV vectors express locally high levels of immunostimulatory molecules, resulting in strong antitumor responses with low toxicity.
- The replication of SFV RNA within tumor cells induces potent type I interferon responses that enhance immune responses.
- SFV vectors also induce apoptosis in tumor cells, favoring the release of tumor antigens and epitope spreading.
- SFV do not propagate and their expression is transient, lasting for only 2-3 days, reducing possible toxicity.
- Combination of SFV vectors expressing cytokines with immunomodulatory antibodies has shown potent synergistic effects.
- SFV vectors are poorly immunogenic, allowing repetitive administrations.
- SFV vectors can be used as viral particles, but also directly as RNA. This last possibility facilitates the production of the vector and increases its biosafety.

**Proof of concept**

- Antitumor effects *in vivo* with SFV vectors:

![Graph A](image1.png)

A 100% Survival (% Survival)

![Graph B](image2.png)

B 100% Survival (% Survival)

![Graph C](image3.png)

C 100% Survival (% Survival)

The administration of SFV vectors expressing pro-inflammatory cytokines, like IL-12, induced potent antitumor responses in immunocompetent mice using transplantable colon adenocarcinoma (A) or spontaneous hepatocellular carcinoma (B) tumor models. In addition, this vector showed a potent antitumor synergy when used at a suboptimal dose in combination with immunomodulatory antibodies, like anti-PD-1 (α-PD-1), in colon adenocarcinoma tumors (C).

**References**

1. Quetglas JI *et al.* J. Immunology. 2013. 190:2994-3004
3. Quetglas JI *et al.* Cancer Immunology Research. 2015. 3(5):449-454

**Contact:** Business Development | Email: bdcima@unav.es | Tel: +34 948 194 700

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