Fundació Sant Joan de Déu
Laboratory of Oncology
Santa Rosa 39-57
08950 Esplugues de Llobregat (BARCELONA)
Email: amontero@fsjd.org

Treatment of DIPG via intratumoral delivery of oncolytic adenoviruses

Systemic chemotherapy has failed to significantly improve the survival of DIPG patients. In contrast, local radiotherapy alleviates neurologic symptoms and prolongs progression-free survival. Thus, we suggest that local administration of therapeutic agents might circumvent the barriers to systemic delivery and achieve superior antitumor effect. Our research is part of a global strategy to provide a new local treatment approach for our patients, based on oncolytic adenoviruses. The preclinical studies proposed here will provide the rationale for a rapid translation of such approach to the clinic.

Because knowledge of the biology of DIPG is very limited, it is not clear whether therapeutic failure of current systemic treatments is due to the use of inadequate drugs or to the poor penetration of potentially active drugs through the blood-brain barrier (BBB). We assume that the lack of activity of drugs in DIPG is due to the impenetrability of the BBB, but we need experimental confirmation of such assumption, which would provide definitive support for the use of local therapies. Therefore, one aim of our research is to study the integrity of the BBB and its role to limit the penetration of systemic chemotherapy to brainstem and brainstem tumors. In our experiments we will study BBB markers and function in DIPG biopsies and animal models. We will set up techniques to characterize the distribution of anti-cancer drugs in the normal brainstem and in DIPG tumors engrafted in immunodeficient rats.

The antitumor activity of locally administered oncolytic adenoviruses has been promising in preclinical brain tumor models[1-4] and clinical trials have demonstrated the safety of adenovirus-based treatments in cancer patients[5]. Our main working hypothesis is that local DIPG treatments based on stroma-penetrating oncolytic adenovirus will provide enhanced antitumor activity as compared to systemic chemotherapy. The use of locally injected stroma-penetrating adenoviruses for DIPG is supported by the improved intratumoral distribution of adenoviruses with stroma-penetrating activity[6] and by the presence of components of the extracellular matrix such as hyaluronic acid in the normal brainstem and in brain tumors[7,8].

One principal aim of our research is to study the biopharmaceutics, antitumor activity and safety of oncolytic adenoviruses in a preclinical model of DIPG. We suggest that local injection of oncolytic adenoviruses by convection-enhanced delivery (CED)[9] will be safe and active in DIPG. To address such question, we will administer a retinoblatoma-pathway responsive oncolytic adenovirus[10] by systemic and local routes to DIPG-bearing rats and will study its distribution, antitumor efficacy and local and systemic toxicity. Additionally, we will evaluate a stroma-targeting strategy to increase the penetration and activity of adenoviruses. We propose that modified viruses expressing hyaluronidase will propagate better within the tumor[6]. To address this question, we will administer the hyaluronidase-expressing oncolytic adenovirus by CED and will study its distribution, safety and therapeutic effect in animal models. Upon the completion of our experiments we would gather data supporting the use of the oncolytic adenovirus approach in patients.

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Research Team

- Dr Ángel Montero Carcaboso PhD, Laboratory of Oncology, Fundació Sant Joan de Déu
- Dr Jaume Mora MD PhD, Chair of Oncology, Hospital Sant Joan de Déu
- Dr Ioannis Roussos MD, Neurosurgery, Hospital Sant Joan de Déu
- Dr Ramón Alemany PhD, Virotherapy Group, Laboratory of Traslational Research, ICO-IDIBELL and VCN Biosciences (L´Hospitalet de Llobregat, Barcelona)
- Dr Manel Cascalló PhD, Virotherapy Group, Laboratory of Traslational Research, ICO-IDIBELL and VCN Biosciences (L´Hospitalet de Llobregat, Barcelona)
- Eva Rodríguez, Pathology, Hospital Sant Joan de Déu

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