A powerful partnership

Paediatrician and oncologist **Dr Manuel Ramírez** explains the novel approach his team is bringing to the treatment of childhood cancers, and describes the exciting next steps that have them searching for new collaborators in project development

Can you outline what the CELYVIR treatment is and the origins of your study on the Safety and Efficacy of Repeated Infusion of CELYVIR in Children and Adults with Metastatic and Refractory Tumours?

The clinical trial we are now developing represents the continuation of a trial first launched in 2005, where we used CELYVIR as a treatment for children with refractory tumours. Prior to this, we had already conducted such a wealth of experimental work that we were convinced the treatment was worth testing in patients. The name CELYVIR is derived from the Spanish 'células y virus', which means cells and virus, and we use it to refer to a new medicine consisting of mesenchymal stem cells (MSCs) obtained from each patient carrying an oncolytic adenovirus inside them. CELYVIR is therefore composed of a cell capable of finding the cancer, and a virus that is able to remove the cancer when it is found.

Neither cell nor virus is an effective antitumour agent when separated, but together they can be converted into a powerful and intelligent weapon. We work in a children's hospital and I am a specialist in paediatric oncology, so it is not surprising that our first patients were children with cancer.

How would you summarise past efforts to utilise MSCs? Can you explain how prior research has informed your current project?

MSCs are one of the most popular cell types in human regenerative cell therapy, and are also being tested in clinical trials for their immunomodulatory properties. Other groups have also shown MSCs' capacity to migrate towards pathological regions in the body, including areas of wound healing, ischaemic tissues or tumours. In addition to their tumour-targeting capacity, MSCs allow adenoviral replication, and may prevent the oncolytic virus from neutralising antibodies and innate immune responses for the first few hours immediately following intravenous infusion. The tumour-trophic characteristic of adult stem cells can be used to deliver anticancer agents such as suicide genes, cytotoxic drugs or immunomodulatory molecules. Basically, we are using MSCs as cellular vehicles to deliver the oncolytic adenovirus to the right places.

You have observed mixed mechanisms of action: oncolysis and antitumour immune response. Can you elaborate on your discoveries?

These results have already been described by other authors – pioneers in oncolytic virotherapy. Virus replication in malignant cells causes tumour destruction, but also – because of the danger signals generated by the viral infection and other mechanisms not yet completely known – oncolytic viruses stimulate an antitumour immune response that was previously inefficient. This point is being exploited through the manufacture of oncolytic viruses that produce immunostimulatory molecules during viral replication, enhancing the immune effect of the therapy.

Who are you collaborating with in order to conduct this research, and what do they contribute to your overall objectives?

The CELYVIR strategy is the result of our collaboration with two teams of researchers, both of which are key to the project. On the one hand, Dr Ramon Alemany's group at the Catalan Institute of Oncology (ICO) in Barcelona is responsible for all of the work we conduct relating to the oncolytic adenovirus. On the other hand, Dr Javier García-Castro's group at the Carlos III Institute of Health (ISCIII) in Madrid, Spain, is responsible for everything related to the stem cells. García-Castro worked with us at the hospital when we started the project. Finally, recruitment of adult patients for these clinical trials is conducted by Dr José A López at the Hospital Universitario 12 de Octubre's oncology service in Madrid.

In which areas are you now hoping to develop the project and what types of expertise are you planning to add to the current consortium?

We realise that the next steps for this project will require us to move beyond the experience of the academic field in which we have developed to date. As we continue to improve this new antitumour treatment strategy, we will conduct a phase II trial, and will therefore require the advice and guidance of groups with expertise in biomedical and biotechnological project development. One option we are evaluating at the moment is the creation of a spinoff that can take on this challenge – but ultimately, we are looking for new collaborative links.