



First Clinical Study Initiated for DNX-2440, DNAtrix's Next Generation Armed Oncolytic Virus

New treatment combining virus and immunotherapy to be tried out on brain tumors for the first time

The Clínica Universidad de Navarra (Spain) is the only center to start clinical trials with the new therapy designed for adult patients with recurrent glioblastoma

The new type of genetically modified virus has been developed by DNAtrix Inc. (USA) and designed by the laboratory of doctors Juan Fueyo and Candelaria Gómez-Manzano at the MD Anderson Cancer Center in Houston (USA)

Pamplona, Spain - 24 October 2018. For the first time a new therapy that combines a genetically modified virus with immunotherapy is to be tried out on patients. The trial shall be conducted by a team at the Clínica Universidad de Navarra, who shall apply the new treatment to the most aggressive brain tumor, the glioblastoma. The agent employed to destroy the tumor cells (oncolytic) in this case is the **genetically modified virus DNX-2440**, produced by the company DNAtrix, which has an added new feature: "The new virus makes a unique contribution and that is that once it has infected the tumor cell it makes the cell produce OX40L, a co-activating molecule of the immune system", says Dr. Ricardo Díez Valle, neuro-surgeon and head of the Brain Tumors Section of the Clínica Universidad de Navarra.

This pioneering clinical trial with the new immunotherapeutic molecule contains a radically new element in comparison to previous research with genetically modified viruses. In previous studies, it was shown that oncolytic viruses can induce an immune response that attacks the tumor, but **this is the first virus in the world that is expressly designed to boost the response.**

The Clínica shall be the only center to commence research on patient using the new therapy, **geared towards adults with recurrent glioblastoma** (patients already treated for the tumor, which has developed once again). The main priority of the Phase I study, which commenced this October, will be to check the safety of the therapy.

The treatment using a virus modified with the co-activating molecule of the immune system was designed by the laboratory of doctors Juan Fueyo and Candelaria Gómez-Manzano, of the MD Anderson Cancer Center, and developed by the biopharmaceutical company DNAtrix, both in Houston (Texas, USA).

Research into this treatment for glioblastoma is of special interest because it the most aggressive brain tumor known to exist. Its incidence is 3 new cases a year per 100,000 inhabitants and the age interval in which it most frequently appears is between 45 and 70 years.

Background

A number of clinical trials have been conducted to test the efficacy and safety of treatment with viruses genetically modified to acquire oncolytic properties (destruction of tumor cells). The Clínica team, led by Dr. Díez Valle and Dr. Sonia Tejada, neuro-surgeon at the Clínica, and Dr. Marta Alonso, director of the

brain tumor biological therapy laboratory of The Clínica and CIMA, participated with Dr. Fueyo's team in previous research published in February in the [Journal of Clinical Oncology](#). The therapy used then on patients with glioblastoma consisted of injections of the DNX-2401 virus, whose oncolytic actions were demonstrated.

The results of the research were promising inasmuch as long-term survivals in cases of recurrent high-grade gliomas were achieved. The study's conclusions related the **efficacy of the therapy to the oncolytic effects of the virus followed by an immune response against the brain tumor**. The new virus is designed to increase these responses.

The Clínica is currently maintaining a line of basic (Dr. Alonso) and clinical research with oncolytic viruses. Dr. Tejada shall continue along the same lines with another clinical trial using this virus, designed for children with diffuse pontine tumors.

Co-activator of the immune system

The virus to be used is an adenovirus (common virus that mostly affects the respiratory tract) that has been modified to make it effective for treating glioblastoma. Three genetic modifications are carried out on the adenovirus to eliminate the tumor cells. Two were already present in the previous version: part of the genetic chain of the DNA that codifies one of the most important proteins of the virus has been eliminated. By removing the function of this protein, the virus lacks capacity to multiply in a normal healthy cell, which makes it harmless in that regard", says doctor Díez Valle.

A feature of tumor cells is their tendency to always be activated for multiplication, which enables the modified virus to replicate inside them until the cells are killed by lysis". Another feature is that a change has been made to the way it is inserted into the cells, making it easier for them to enter the cancer cells than the healthy ones.

In the new virus, the immune response is boosted thanks to the third change made to the virus DNX-2440. It induces synthesis in the infected cells of a co-activated molecule in the patient's immune system. The new therapy arose from a finding made in previous trials with oncolytic viruses. The researchers observed that when the therapies were applied there was a natural activation of the patient's immune system against the tumor cells after inoculation with the virus.

As a result, the laboratory of Drs. Fueyo and Gómez-Manzano designed the new treatment in which the action of the virus in destroying the tumor is boosted with this immune activation thanks to a new specific molecule, OX40L, **which makes the boosted effect of the immune system activity take place solely in the tumor, and not in the rest of the body, which makes it more effective and less toxic.**

Trial procedure

The trial methodology commences with a biopsy of the cancerous tissue to corroborate the diagnosis of recurrence of the disease. After establishing that the glioblastoma has reappeared, the virus is injected directly into the tumor. To inoculate the virus in the brain tissue, the team has a special cannula to administer the injection to facilitate diffusion of the virus inside the tumor. The system used is a radically new one designed by the American company, Alcyone Lifesciences.

The specialists expect the tumor to progressively decrease in size over the course of several weeks, in much the same way as in previous trials. Dr. Díez Valle has commented that patients with glioblastoma who took part in other trials using therapies with genetically modified viruses have remained free of the disease years after participating in the trial.

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