New immuno-therapy for malignant brain tumors

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Animal experiments show that it is relatively easy to treat cancer in the early stages. However, it is far more difficult to successfully treat advanced cancer. Treatment of brain tumors is particularly challenging because regulatory T-cells accumulate in brain tumors and suppress an immune attack.

In several steps using a new strategy and a novel drug, Burkhard Becher's team from the Institute of Experimental Immunology at the University of Zurich has now succeeded in doing exactly this in the case of glioblastoma, one of the most dangerous brain tumors. First step, they stimulated the body's own immune system in such a way that it recognised and then killed the brain tumor cells even in advanced stages of the disease.

The initial objective of their new study was to break through the tumor's protective shield. "We wanted to establish whether we can actually elicit an immune response to a tumor growing within the brain", explains Burkhard Becher. To this end, the team used the immune messenger substance, Interleukin-12. When Interleukin-12 is produced in the tumor, immune cells are stimulated locally in such a manner that the tumor is attacked and rejected. Once this procedure had worked well in the early stages of the tumor, the researchers waited in the next stage until the tumor was very large and the life expectancy of the untreated test animals was less than three weeks. "We only began treatment when it was, in fact, already too late", says the first author of the study Johannes vom Berg. The success rate was low, Berg adds. "We then

injected biopharmaceutical Interleukin-12 into the large brain tumor. This did induce an immune response but only led to tumor rejection in one-quarter of the animals."

From 25 to 80 percent: combined treatment leads to success

The researchers were successful when they drew on a new development in skin cancer treatment. They combined intra-tumoral Interleukin-12 treatment with the intravenous administration of a novel immunostimulating drug that suppresses the regulatory T-cells. The rejection of the tumor then worked in 80 percent of the test animals. "I have rarely seen such convincing data in preclinical glioma treatment", says Michael Weller, neurooncologist and Director of the Clinic for Neurology at the University Hospital Zurich. He added, "That's why this development should be tested as soon as possible in clinical trials."

In a joint trial, the team then tested the treatment in a further tumor model which mimics the clinical situation of the brain tumor patient even better. And once again they were successful.

The next step: a clinical trial as soon as possible

The findings of the current research work have been published in the *Journal of Experimental Medicine*. Their promising results do not mean that the treatment can already be as effective in brain tumor patients. This has to be examined in the next phase for which the team now actively seek commercial partners. Burkhard Becher puts it like this, "We are cautiously optimistic but it's time that we adopted completely new strategies to really get to grips with this fatal tumor"

More information: Johannes vom Berg, Melissa Vrohlings, Sergio

Haller, Aladin Haimovici, Paulina Kulig, Anna Sledzinska, Michael Weller and Burkhard Becher. Intratumoral IL-12 combined with CTLA-4 blockade elicits T cell mediated glioma rejection. The *Journal of Experimental Medicine* (*JEM*). November 25, 2013.DOI: 10.1084/jem.20130678