Apogenix: immuno-oncological protein drugs for the treatment of malignant diseases

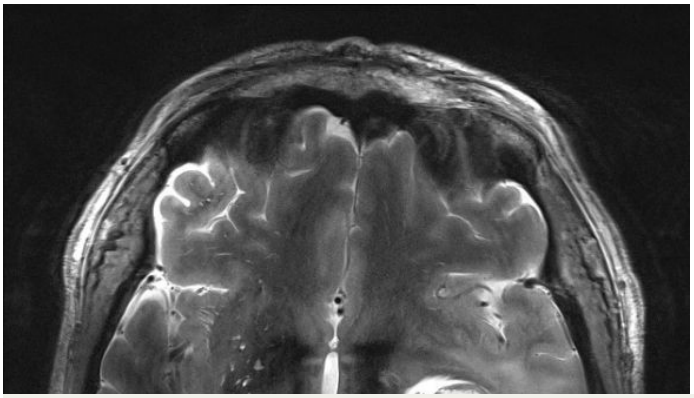
Apogenix AG, a biopharmaceutical company from Heidelberg that specialises in immuno-oncology, develops protein drugs that target central signalling pathways involved in regulating the growth, migration and apoptosis of malfunctioning cells and thus offer novel treatment options for cancer and other malignant diseases. The company's most advanced drug candidate, APG101, has already demonstrated its effectiveness in the treatment of glioblastoma, the most aggressive of human cancers, in a Phase II clinical trial. The same drug also achieved good results in a Phase I clinical trial with myelodysplastic syndrome.

Apogenix AG, a spin-off from the German Cancer Research Center (DKFZ) in Heidelberg, develops immuno-oncological protein drugs for treating cancer and other life-threatening diseases. Since its foundation in 2005, the company has developed a promising portfolio of innovative compounds that target central signalling pathways involved in growth, migration and apoptosis and represent novel treatment options for oncological and haematological indications.

Glioblastoma treatment with APG101

Apogenix' most advanced drug candidate, APG101, is a genetically engineered, fully human, soluble fusion protein consisting of two extracellular domains of the CD95 receptor and the Fc domain of immunoglobulin G1. APG101 binds to the CD95 ligand, which is important for the activation of CD95, and thus blocks the signalling cascades triggered by the receptor. This reduces the invasive growth and migration of tumour cells. The efficacy of APG101 has already been demonstrated in a controlled Phase II study assessing the second-line treatment of glioblastoma (i.e. tumour that has regrown following primary treatment). Patients whose tumour had a new epigenetic biomarker (which is associated with the CD95 ligand) were particularly responsive to treatment. In a cooperative project (CancerMark) with a diagnostics company called R-Biopharm AG funded by the German Federal Ministry of Education and Research (BMBF), Apogenix is developing a companion diagnostic test for this biomarker. The biomarker is also being validated in another clinical study with regard to its suitability in personalised APG101 glioblastoma therapy.

Dr. Thomas Höger, CEO of Apogenix AG, called the study an important milestone on the path to the approval of APG101 for treating glioblastoma as part of a personalised treatment approach. Höger explains: "We are very pleased that the BMBF has decided to fund the CancerMark project. These



funds bring total funding raised by Apogenix for developing innovative protein drugs against cancer and other malignant diseases to more than 11 million euros." Since its establishment in 2005, the company has acquired third-party funds from investors, public funds and licensing deals worth more than 90 million euros.

The "death receptor" CD95 and its ligand CD95L

The CD95 receptor and its functions were characterised by immunologist Prof. Peter Krammer and his colleagues at the DKFZ in Heidelberg. They identified CD95 as a cell surface switch that triggers apoptosis (programmed cell death) when a messenger molecule, the CD95 ligand (CD95L), binds to the receptor. This is why CD95 is referred to as the "death receptor". The researchers subsequently elucidated the complex signalling pathways that are trigged by the death receptor. Research carried out by the

Heidelberg researchers, and especially by Prof. Dr. Ana Martin-Villalba (now director of the

Department of Molecular Neurobiology at the DKFZ), showed that many cancer cells, including glioblastoma cells, lose the ability to undergo apoptosis and the activation of the receptor by CD95L does not lead to cell death. Quite the contrary: receptor activation stimulates uncontrolled tumour growth. This in turn triggers another signalling cascade, a signalling pathway called NF-κB, which promotes the proliferation, migration and metastasis of tumour cells. APG101, a compound developed on the basis of research carried out by Krammer and colleagues, turned out to be a solution to the problem. APG101 is a soluble CD95-like fusion protein that captures the CD95 ligand before it can bind to the CD95 receptor of cancer cells and wreak havoc.

APG101 and MDS

In addition to its proven effect on the most aggressive brain tumour in humans, APG101's unique mechanism of action also makes the compound an excellent candidate for treating solid tumours such as prostate, pancreatic and breast cancers. CD95L has also been shown to inhibit the formation of erythrocytes (erythropoesis) in myelodysplastic syndrome (MDS), a disease that affects the haematopoietic cells in the bone marrow.

MDS can lead to severe anaemia, which then needs to be treated with blood transfusions. Blood transfusions can lead to liver and organ damage as a result of iron overload. At the same time, the number of thrombocytes (needed for blood clotting) and leukocytes (needed for immune defences) decrease, with the result that MDS patients also suffer from sudden bleeding and life-threatening infections over time. In addition, there is a risk that the disease may develop into acute myeloid leukaemia (AML), a malignant cancer of the haematopoietic system. By blocking the CD95 ligand, APG101 addresses the cause of the disorder and could thus potentially provide a cure for MDS.

Dr. Harald Fricke, Chief Medical Officer of Apogenix AG.

After Apogenix had shown that blocking the CD95 ligand by APG101 can restore erythropoesis, a Phase I clinical study was carried out with blood transfusion-dependent MDS patients who did not respond to erythropoietin-stimulation substances and had a low to intermediary risk of developing AML.

The study showed that APG101 was safe and well tolerated. In June 2016, Dr. Harald Fricke, Apogenix' Chief Medical Officer, commented: "We were particularly excited to see that APG101 appeared to decrease the number of transfusions required by this very sick patient population. Our next step will be to initiate a Phase II trial in MDS to evaluate APG101 in various doses in combination with an erythropoietin-stimulating agent."

The HERA technology platform

In addition to APG101, Apogenix owns a promising pipeline of immuno-oncological drug candidates that stimulate the immune response of anti-tumour immune cells to cancer cells by activating or inhibiting signalling pathways in which proteins of the TNF/TNFR superfamily play a crucial role (TNF stands for tumour necrosis factor and TNFR for TNF receptor). The company's highly qualified scientific team has also developed a proprietary technology platform called HERA (hexavalent TNF superfamily (TNFSF) receptor antagonists) that is used to construct novel biologics. TNFSF proteins only show biological activity when their three polypeptide chains form one receptor-binding domain, which in turn binds three receptors. This technology is therefore superior to other biologics that target TNFSF pathways, such as agonistic antibodies which only bind two TNFSF receptors in a spatially undefined manner. As each agonist binds and clusters six receptor molecules, a sufficient level of appropriate signal is transmitted into the target cell. The TRAIL receptor agonist APG880, a drug candidate produced with the HERA platform, has already been licensed to AbbVie, a global pharmaceutical company with a research and production site in the city of Ludwigshafen in southern Germany.

Article

05-Sep-2016
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The article is part of the following dossiers

Cancer therapy and cancer diagnostics

Boosting the immune system can improve cancer prevention and treatment

cancer | metastases | signalling pathway | receptor | immune system | immunotherapy | cancer immunotherapy