

GENES THAT CURE

Genetic engineering is now a reality.
If used wisely, it can be beneficial for humans.
A good example is offered by gene therapies
that put viruses to work.



**Prof. Miroslaw Zabek,
PhD, DSc, MD**

is the head of the Department of Neurosurgery at the Medical Center for Post-Graduate Education (CMKP) and a long-standing national consultant in neurosurgery. He has introduced and performed numerous innovative and pioneering surgeries of the brain and spine.

zabek.cmc@gmail.com




**Paweł Obierzyński,
MD**

is a physician earning a specialty in neurosurgery. He is passionate about neuroanatomy and neuroscience. His professional interests focus above all on neuro-oncology, functional neurosurgery, and the search for modern treatments of degenerative and metabolic diseases of the central nervous system.

pawel.obierzynski@gmail.com


Adrian Drożdż, MD

is a physician earning a specialty in neurosurgery, and an assistant at the Department of Descriptive and Clinical Anatomy, Center for Biostructure Research, Medical University of Warsaw. He is interested in brain surgery, the use of modern technologies and gene therapy in neuro-oncology and the treatment of neurodegenerative diseases.

ad.drozd@gmail.com

**Mirosław Ząbek
Paweł Obierzyński**

Interventional Neurology Center (INC)
Department of Neurosurgery
Medical Center for Post-Graduate Education (CMKP)
Department of Neurosurgery,
Bródno Mazovian Hospital in Warsaw

Adrian Drożdż

Interventional Neurology Center (INC)
Department of Neurosurgery
Bródno Mazovian Hospital in Warsaw
Department of Descriptive and Clinical Anatomy,
Center for Biostructure Research
Medical University of Warsaw

Neurodegenerative diseases are a diverse group of conditions that may be congenital or acquired and take a chronic and progressive course, involving a gradual loss of cells in the nervous system. In their initial stages, such diseases often remain asymptomatic for a long time. Their first clinical symptoms are non-characteristic and only appear when the number of damaged cells of the nervous system is already significant. Neurodegenerative diseases pose an important public health problem: they lead to a gradual loss of function and independence, and the deteriorating neurological state of patients generates numerous systemic complications (including recurrent or chronic pneumonia, bedsores, difficulties with food intake, and depressive disorders). Over time, these complications impair patients' quality of life and lead to death. Some neurodegenerative disorders (such as ataxia-telangiectasia syndrome) are associated with an increased risk of cancer.

Unfortunately, modern-day medicine knows no cure for congenital neurodegenerative diseases, and comprehensive care for patients is usually limited to symptomatic treatment and rehabilitation. Currently, there is a great deal of interest in the scientific study of the mechanisms responsible for the development and course of these diseases. Their fuller understanding is the next step towards the discovery of causal treatments for many congenital neurodegenerative diseases.

Therapy

One of the methods that offer a great deal of hope for real progress in the treatment of congenital neurodegenerative diseases is gene therapy. It makes use of genetic engineering technologies that allow the cor-

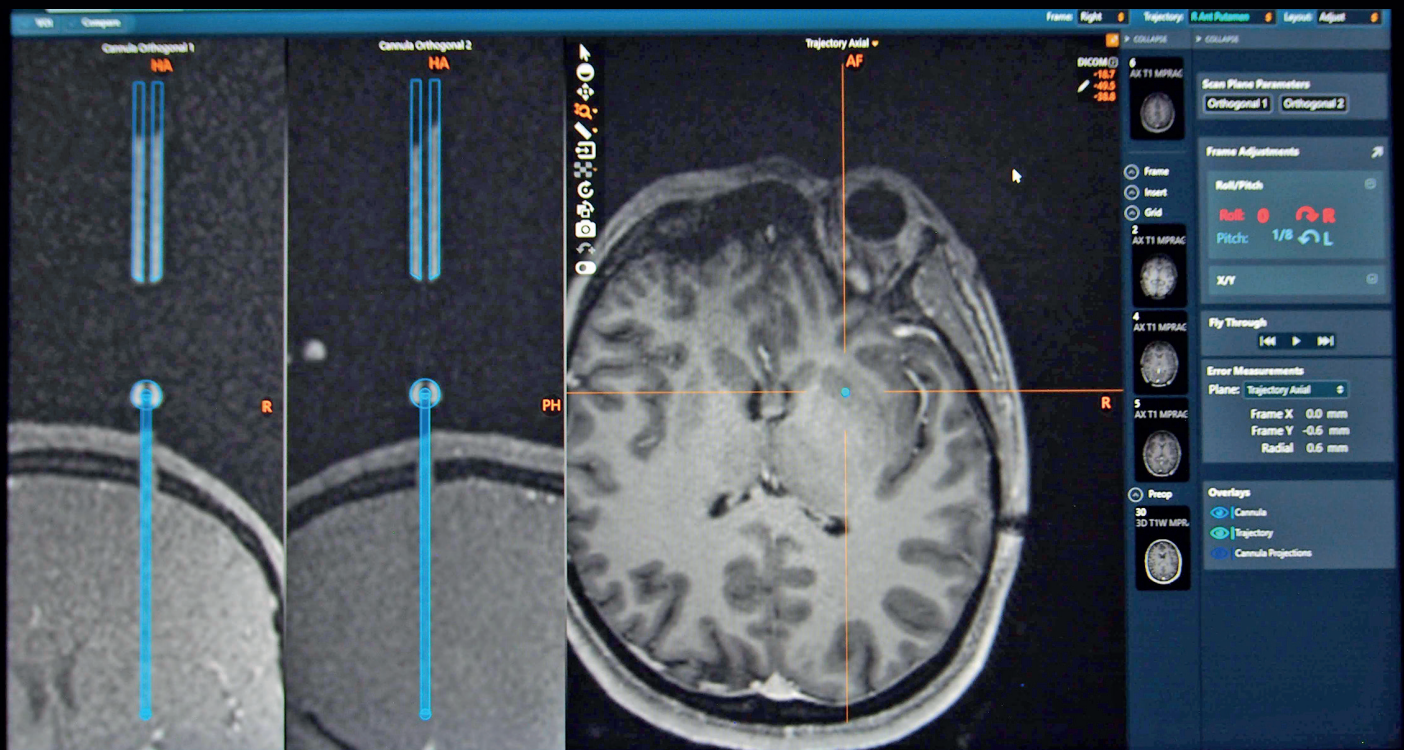
rect version of a gene to be introduced into a patient's body, thus repairing the mutation underlying the development of a disease. In most cases, this involves inserting into the patient's body the correct mRNA sequence, as an "instruction" for the body to begin to synthesize the deficient protein associated with a specific disease. In other cases, gene therapy involves delivering molecules of siRNA (small interfering RNA) into the body to block the patient's mRNA sequence responsible for the expression of the abnormal protein. Short-chain, synthetic, single-stranded nucleic acids (antisense oligonucleotides, or ASOs) can also be introduced into the body, which makes it possible to "switch off" the defective fragment of the patient's gene. The genetic material thus introduced into the body is called a "transgene."

One type of "vehicle" used to deliver the therapeutic genetic material into the human body is called a viral vector. These typically consist of adenoviruses or lentiviruses that have been attenuated (weakened so that they cannot cause disease, but they can interact with host cells) or adeno-associated virus (AAV) vectors. The latter have been widely used in gene therapy of neurodegenerative diseases for reasons related to how easily they can cross the blood-brain barrier (the natural morphological and biochemical barrier between blood vessels and nerve tissue responsible for the selective exchange of substances between blood and neurons, glia, and cerebrospinal fluid). Registered drugs or drugs at the stage of testing that contain a viral vector may be administered to a patient suffering from a neurodegenerative disease orally, intravenously, or through intrathecal and intracerebral infusions (into the spinal canal and into the brain).

The infusion procedure

Our team at the Interventional Neurology Center, based in the Bródno Mazovian Hospital in Warsaw, is currently conducting a phase II clinical trial investigating the use of the intracerebral infusion of a viral vector in patients with early-stage Huntington's disease (HD). HD is a genetic neurodegenerative disease. It is caused by a mutation in the IT15 gene whose expression causes excessive synthesis and accumulation of an abnormal protein called huntingtin in cells. The neurotoxicity of huntingtin is thought to be related to its effects on the mitochondria of nerve cells in the brain. The first symptoms of the disease usually manifest between 30 and 50 years of age, and include motor, cognitive, and mental dysfunction. The average survival is about 15 years after the onset of the first symptoms.

The neurosurgical procedure we are testing involves the real-time MRI-guided infusion of a specific volume of a solution with viral vector material to the



KAJA DANIELAK

brain at a slow rate (on the order of $\mu\text{L}/\text{min}$). The first step of the procedure involves planning a trajectory to determine access to the target region, avoiding large blood vessels and vital brain structures. The cannulas used to deliver the solution are navigated through pre-drilled trepanation holes. Their correct position is determined using a guidance system whose components are attached to the shaved surface of the patient's head during the procedure. It is possible to monitor the location and spatial distribution of the infused solution because it contains gadoteridol, a substance that acts as a contrast agent, making the solution visible on MRI imaging. Monitoring the progress of the infusion makes it possible to modify the position of the ends of the micro-cannulas and the infusion rate. The entire procedure is performed under general anesthesia. Since the infusion procedure is performed in the area of a strong electromagnetic field, the instruments and equipment in the operating room must be made of non-ferromagnetic materials to avoid endangering the patient and the medical staff or distorting the MRI imaging.

Huntington's disease (formerly known as Huntington's chorea) is a genetic condition that manifests as motor and mental dysfunction and dementia. The possible use of gene therapy is currently the only potential causal treatment for HD, and therefore the only hope for patients. Intracerebral viral vector

infusion in patients with HD is at the stage of clinical testing. Patients participating in clinical trials involving intracerebral viral vector infusion are kept under close surveillance, with all information on the course of the disease being collected during the treatment process. So far, our team at the Interventional Neurology Center is the only unit in the world outside the United States that has performed eight intracerebral viral vector infusion procedures as part of an ongoing clinical trial in patients with HD. In June 2022, a second European facility (in Cardiff, Wales) joined the study. More procedures in Warsaw have been scheduled for fall 2022 and beyond. Recruiting patients for the study and following them up after the administration of the viral vector are the responsibility of a team of neurologists from the Institute of Psychiatry and Neurology in Warsaw. In addition to the clinical trial described above, the team of the Interventional Neurology Center in Warsaw is involved in studies using intracerebral infusion of viral vectors in patients with other neurodegenerative diseases (Parkinson's disease, multiple system atrophy), metabolic diseases (congenital deficiency of L-amino acid decarboxylase), and tumors of the central nervous system.

All of the studies described above are currently at various stages of advancement. Full results will be published after the trials are completed – although this could still be more than a decade in the future. ■

Nawigacja miejsca docelowego dla infuzji wektora wirusowego w badaniu klinicznym u chorych na chorobę Huntingtona

Further reading:

Chen W, Hu Y, Ju D. Gene therapy for neurodegenerative disorders: advances, insights and prospects. *Acta Pharm Sin B*. 2020. doi: 10.1016/j.apsb.2020.01.015

Experimental Treatments for Huntington's Disease, www.huntingtonsdiseasenews.com/experimental-treatments-for-huntingtons-disease/

Gene Therapy for Parkinson's Disease, <https://www.apdaparkinson.org/article/gene-therapy-for-parkinsons-disease/>