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First spherical nucleic acid drug injected into humans targets brain cancer

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The first drug using spherical nucleic acids to be systemically given to humans has been developed by Northwestern University scientists and approved by the Food and Drug Administration as an investigational new drug for an early-stage clinical trial in the deadly brain cancer glioblastoma multiforme.

A clinical trial has just been launched at the Robert H. Lurie Comprehensive Cancer Center of Northwestern University and Northwestern Medicine.

The new drug is able to cross the challenging blood-brain barrier to reach tumors in animals, where it turns down a critical cancer-causing gene. Now, the Phase 0 clinical trial will investigate the drug's ability to reach tumors in humans.

The glioblastoma drug represents a revolutionary new class of drugs. The novel spherical nucleic acid platform it is based on can be applied to other types of neurological diseases, such as Alzheimer's and Parkinson's, by similarly turning down the genes that lead to those diseases.

It's highly unusual for a drug to be developed in preclinical research at a university, shepherded through FDA approval as an investigational new drug and studied in a clinical trial—all within the same university and without funding from a pharmaceutical company. In most cases, a drug is developed and licensed to a pharmaceutical company.

"We want to get the drug to patients as quickly as possible," said Jay Walsh, vice president for research at Northwestern. "We want to move the drug forward because there are patients with a disease with no current cure."

The drug, called NU-0129, will have to go through many more phases before it is approved for general use in a clinical environment.

"We know this drug works in mice. Now we need to know if it can cross the human blood-brain barrier and accumulate in the tumor of a human being," said Alexander Stegh, an assistant professor of neurology at Northwestern University Feinberg School of Medicine.

Stegh developed the drug with Chad A. Mirkin, the George B. Rathmann Professor of Chemistry at the Weinberg College of Arts and Sciences and director of Northwestern's International Institute for Nanotechnology (IIN).

"If the spherical nucleic acids cross the barrier and localize in the brain, the implications go beyond glioblastoma," Mirkin said. "This would give us the ability to target diseases of the brain by targeting pathways that we know are associated with different diseases, including Huntington's, Parkinson's and Alzheimer's diseases."

The drug, which consists of short snippets of RNA densely arranged on the surface of spherical gold nanoparticles, changes the genetic makeup of the tumor cells and dampens their ability to divide. The drug targets the gene BCL2L12, which is involved in apoptosis, or programmed cell death. Mirkin and his group invented spherical nucleic acids, and Stegh identified the gene to target.

Glioblastoma patients are treated with chemotherapy, radiation and surgery, but there is no cure. The life expectancy for the estimated

30,000 people in the U.S. who are diagnosed with the aggressive brain cancer each year is 14 to 16 months.

"We desperately need an effective treatment for this deadly disease," said Dr. Priya Kumthekar, an assistant professor of neurology and hematology-oncology at Feinberg and a Northwestern Medicine neuro-oncologist. Kumthekar is the lead investigator of the Northwestern trial, which will recruit six to eight glioblastoma patients.

The study will recruit individuals who have had regrowth of their tumors and are candidates for tumor removal. They will receive the drug intravenously prior to surgery. Following tumor removal, Kumthekar and her team will study the tumor's drug content to determine how well the drug crossed the blood-brain barrier in patients.

"Based on animal studies, there is good penetration into the tumor," Kumthekar said. "We predict that will be the case here, too."

"Northwestern is very focused on delivering better therapy to patients," said Dr. Frank Giles, who serves as Northwestern University's sponsor representative on the investigational new drug application and clinical study. "Applying new scientific knowledge is the best way to develop truly paradigm-changing novel therapies."

Kumthekar, Stegh, Mirkin and Giles are members of the Lurie Cancer Center.

"This was a complex, meticulous process requiring intense collaboration across many facets and groups within the University and Northwestern Medicine," noted Ann Adams, associate vice president for research at Northwestern and one of the quarterbacks who led the FDA application process with Giles and Caroline Ko, a research associate in the department of chemistry and chief scientific officer of the IIN.

Dr. Leon Platanias, director of the Lurie Cancer Center, said, "The technology of spherical nucleic acids used in this first-in-human study is very powerful and may result in new, more effective approaches for the treatment of brain tumors and possibly other tumors in the future."

The birth of the drug: spherical nanoparticles meet genetics

Stegh and Mirkin have been collaborating since 2009 to tackle the difficult problem of developing better treatments for glioblastoma. They first came together through Northwestern's Center of Cancer Nanotechnology Excellence, funded by the National Cancer Institute.

Mirkin had the perfect tool: spherical nucleic acids, new globular forms of DNA and RNA—rather than linear—which are nontoxic to humans. The nucleic acid sequence is designed to match the target gene.

Stegh had the gene: in 2007, he and colleagues identified the gene BCL2L12 as one that is overexpressed in glioblastoma tumors and related to glioblastoma's resistance to conventional therapies.

How the therapeutic works

The therapeutic, because of its novel structure, is actively taken across the blood-brain barrier, allowing it to reach the brain tumor. Once inside cancer cells, the drug silences the disease-causing gene. The RNA's programmed sequence acts as a dimmer switch, selectively impeding the cells from producing specific proteins related to the disease. The result is selective cancer cell death and reduced cell growth.

Key to the drug's success is the nanostructure's 3-D spherical shape and nucleic acid density. Normal (linear) nucleic acids cannot get into cells or cross the blood-brain barrier, but these spherical nucleic acids can. Strands of RNA attach to and surround a gold nanoparticle like a shell;

the nucleic acids are densely packed and form a tiny sphere. The gold nanoparticle core is only 13 nanometers in diameter.

Pivotal animal study

In 2013, Mirkin and Stegh were the senior co-authors of an animal study published in *Science Translational Medicine*. Their research team was the first to demonstrate delivery of a drug by intravenous injection that turns off a critical cancer-causing gene in glioblastoma, reducing tumor progression and increasing survival rates significantly in mice with the deadly disease.

In mice with glioblastoma, approximately 1 percent of the injected dose accumulated in the intracranial brain tumor tissue. Interestingly, once in the brain, the spherical nucleic acids selectively accumulated in tumor tissue over normal brain tissue. This is likely due to the ability of nanoparticles to accumulate in tumor tissue because of leaky blood vessels created by the tumor.

The survival rate of the animals increased nearly 20 percent, and tumor size was reduced three to four fold, as compared to the control group.

Mirkin first developed the nanostructure platform used in this study at Northwestern in 1996. This new development targeting glioblastoma was the first realization that the nanostructures injected into an animal naturally find their target in the brain and can deliver an effective payload of therapeutics.

Mirkin also is a professor of medicine, chemical and biological engineering, biomedical engineering and materials science and engineering.