A new drug targeting EGFR in glioblastoma tumors

By Warren Froelich

A drug designed by UCLA researchers has shown a unique ability to cross the blood-brain barrier to specifically target genetically altered epidermal growth factor receptors (EGFR), one of the most commonly mutated genes in glioblastoma, according to preclinical studies. The drug, dubbed ERAS-801, was 4 times more effective in penetrating patient-derived glioblastoma tumors in laboratory mice than currently approved EGFR inhibitors. About 60 percent of glioblastoma in patients contains EGFR alterations. What’s more, life was extended in more than 90 percent of these diverse glioblastoma models.

These results—coupled with the use of an imaging biomarker that tracks the drug’s activity in the brain—have placed ERAS-801 on track for an investigational new drug submission during the first quarter of 2022.

“Given the unique properties of ERAS-801 and extensive preclinical data in clinically relevant models of glioblastoma, this drug has the potential to improve on the outcomes of patients with glioblastoma that have EGFR alterations,” said David A. Nathanson, PhD, Associate Professor of Molecular and Medical Pharmacology at UCLA. He presented preclinical studies—generated in collaboration with Timothy Cloughesy, MD, Professor and Director of the Neuro-Oncology Program at UCLA—during a special virtual conference on brain cancer held in October by the American Association for Cancer Research.

Nathanson cautioned that, although these preclinical studies were derived from tissue from glioblastoma patients, “no model is able to fully capture the behavior and predictability in response to new drugs.” That said, he added that his team “approached this study with high translational relevance.”

Much-needed research

Glioblastoma is a particularly deadly form of cancer which, despite aggressive standard of care established in 2005 consisting of surgery, radiation, and chemotherapy, has a mean patient survival of 15 months. Numerous clinical trials using targeted therapies, including approved EGFR inhibitors that have shown success against other tumors including the lung and breast or contemporary approaches such as immunotherapy, have failed against glioblastoma.

“For glioblastoma, there has been no improvements over standard of care during this same time period,” said Nathanson. “So, there is clearly a high unmet need for glioblastoma.”

To tackle this critical problem, the UCLA team worked with a suite of approaches and tools, including specific medicinal chemistry to create compounds that would not only have high brain penetration and potency, but also would inhibit both mutated and wildtype forms of EGFR.

The blood-brain barrier can be viewed as a gatekeeper or border that’s evolved to allow only a select few molecules such as water and oxygen to enter the brain, thus offering protection against potentially harmful molecules. Unfortunately, this same barrier to toxic substances also keeps out therapies meant to treat a variety of brain disorders, including glioblastoma. For example, less than 10 percent of plasma drug levels reach the brain for all FDA-approved EGFR inhibitors.

Besides penetrating the brain, the UCLA team recognized that EGFR alterations take on different shapes that are specific to glioblastoma and not found in other tumor types. These structural anomalies imposed an additional factor needed to be considered in the design of a new EGFR drug to treat glioblastoma.

For example, about a third of all EGFR mutations in glioblastoma are found in the extracellular domain (ECD) of the receptor’s structure, with EGFRvIII being the most prevalent. These mutations adopt a shape that favors treatment with a Type 2 EGFR inhibitor, such as lapatinib. Conversely, lung cancer mutations are found in the kinase domain of the receptor, whose shape favors binding to Type 1 EGFR inhibitors such as erlotinib.

Also, nearly one-quarter of glioblastoma patients have increased or amplified wild-type EGFR activity with no mutations; this form of the receptor also binds to Type 1 EGFR inhibitors. Even patients with ECD mutations, such as those with active EGFRvIII, express high levels of wild-type EGFR.

“Collectively, these data support the need to hit both wild-type EGFR and mutant EGFR in patients with EC domain mutant EGFR tumors,” Nathanson said. “Given the fact that there are currently no EGFR inhibitors that effectively target both the EC domain mutant forms of EGFR, amplified wild-type EGFR, and is also CNS [central nervous system] penetrant, our team felt there was a clear unmet need to develop such a molecule.”

In collaboration with Michael Jung, PhD, Distinguished Professor of Chemistry at UCLA, the team synthesized several novel compounds that, through physical and chemical changes in the structure of existing EGFR drugs, were expected to improve penetration across the blood-brain barrier, while targeting EGFR alterations common to glioblastoma. After testing surprisingly few of these synthesized compounds, one in particular—ERAS-801—was found to fit all criteria.

“We hypothesized that if we took this approach to drug development, we could create an effective EGFR inhibitor for glioblastoma, as always in science, certain chemical modifications that we made impacted the key properties [brain penetration and potency] to a degree or in ways that were unexpected,” Nathanson said.

“Since this effort was done in academia—which lacks the financial resources to quickly make and test hundreds to thousands of compounds—these unexpected findings enabled us to quickly identify a clinical candidate from a relatively small number of synthesized compounds and, therefore, much fewer resources than typical drug development programs,” he added.

Results suggested they were on the right track. Among other things, ERAS-801 was found to penetrate the brain at more than 100 percent.
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brain to plasma, a measurement of the levels of EGFR inhibitor that gets into the brain relative to what is circulating in the blood. These findings were about 4 times greater for CNS penetration compared to the next closest approved EGFR inhibitor.

In engineered cell lines, ERAS-801 was found to be highly potent or even better than the approved EGFR drug erlotinib at inhibiting wild-type EGFR. For ECD activity, ERAS-801 was as potent or better than lapatinib at inhibiting EGFRvIII.

Could the Molecule Prolong Life?
In a study of highly diverse patient-derived glioblastoma tumors in genetically engineered mice—also known as orthotopic patient-derived xenograft (PDX) models—about 93 percent had an improved outcome with ERAS-801, Nathanson confirmed.

“Our data has shown that ERAS-801 is highly penetrant, highly specific for EGFR, and appears to have strong activity against several orthotopic EGFR PDX models,” he said. “So, this would suggest that ERAS-801 is a really strong clinical candidate for glioblastoma patients.”

He added that a substantial challenge to translating any new therapy for brain disorders such as glioblastoma is the limited ability to collect tissue samples to determine if the drug is reaching its target, and if it is adequate to produce a positive clinical response.

In previous work, Nathanson and others showed that mutated EGFR in glioblastoma increases the consumption of glucose or sugar, an essential nutrient needed for tumor growth. An imaging method called fluorodeoxyglucose PET (FDG-PET) can non-invasively measure the intake of glucose by the GBM tumor at extremely early time-points, making it a useful tool to measure a drug’s activity in the brain.

The PDX studies with ERAS-901 showed that, when mutated EGFR is effectively inhibited in glioblastoma, the uptake of sugar into the tumor is likewise stunted.

“Collectively, these data suggest that FDG can serve as a robust non-invasive surrogate of EGFR inhibition with ERAS-801 and rapidly—we’re talking within hours—predict long-term benefit to continued ERAS-801 treatment,” Nathanson said.

“Given the unique properties of ERAS-801 and extensive preclinical data in clinically relevant models of glioblastoma, this drug has the potential to improve on the outcomes of patients with glioblastoma that have EGFR alterations.”

—David A. Nathanson, PhD, Associate Professor at UCLA

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Learning Objectives for This Month’s Activity:
After participating in this activity, readers should be better able to: 1. Identify pathophysiological features of glioblastomas. 2. Assess issues related to the treatment of glioblastomas, including results from preclinical studies of ERAS-801.

Disclosure: The author(s), faculty, staff, and planners in any position to control the content of this activity, have disclosed that they have no financial relationships with, or financial interests in, any commercial companies relevant to this educational activity.

Warren Froelich is a contributing writer.