# First-in-class Brain-penetrant EGFR/EGFRvIII Inhibitor Against Gliomas

With High Penetration, Potency and Selectivity

## Overview

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| **Drug Name** | BioLink1006 |
| **Description** | BioLink1006 is a brain blood barrier (BBB) penetrable EGFR/EGFRvIII inhibitor in early clinical development for the potential treatment of glioblastoma, anaplastic astrocytoma, and other brain cancers.<br>BioLink1006 has been granted Orphan Drug Designation by the FDA for the treatment of gliomas including glioblastoma and anaplastic astrocytoma and received R01 grant from the FDA to support the ongoing phase I/IIA clinical development. |
| **Target** | EGFR/EGFRvIII |
| **Drug Modality** | Small molecule |
| **Indication** | Gliomas |
| **Product Category** | Tyrosine kinase inhibitor |
| **Mechanism of Action** | Inhibiting EGFR signaling |
| **Status** | Phase II |
| **Patent** | Granted |

### Collaboration Opportunity

Protheragen Inc. is actively seeking partnership for BioLink1006. Potential collaboration can be strategic alliance, licensing, or marketing agreement.
We look forward to hearing from you.

## Target

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## Epidermal Growth Factor Receptor

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| **Introduction** | The epidermal growth factor receptor (EGFR) is a transmembrane receptor tyrosine kinase of the ErbB family. EGFR is expressed in many normal human tissues, and activation of the proto-oncogene results in elevated EGFR expression in many types of human tumors. The extracellular domain of the EGFR binds to ligands such as epidermal growth factor (EGF), transforming growth factor alpha (TGF-α), amphiregulin, betacellulin, epigen or epiregulin. Ligand binding activates the tyrosine kinase activity of the intracellular domain of the EGFR, triggering cell division and proliferation, and tumor cell dissemination and escape from apoptosis. |
| **Approved Name** | Epidermal growth factor receptor |
| **Official Symbol** | EGFR |
| **Gene Type** | Protein coding |
| **Synonyms** | ERBB; ERBB1; ERRP |
| **Ensembl** | ENSG00000146648 |
| **Gene ID** | 1956 |
| **mRNA Refseq** | NM_005228.5 |
| **Protein Refseq** | NP_005219.2 |
| **OMIM** | 131550 |
| **UniProt ID** | P00533 |
| **Chromosome Location** | 7p11.2 |

## Clinical Resources

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| **Gene Function** | The EGFR is overexpressed in a variety of human epithelial tumors. Deletions and point mutations of EGFR gene are found frequently in glioblastoma. Among EGFR deletions, EGFRvII and EGFRvIII are oncogenic. The deletion of exons 2-7 of the EGFR gene renders EGFRvIII incapable of binding any known ligand, and EGFRvIII is constitutively active. The co-expression of EGFR and EGFRvIII contributes to tumorigenesis and progression. |
| **Major Conditions** | Cancer |

# Drug Modality

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### Small Molecule

BioLink1006 is a novel small molecule that selectively inhibits EGFR/EGFRvIII. Unlike most small-molecule inhibitors of EGFR that competitively block the ATP-binding pocket of the receptor, BioLink1006 is a noncompetitive inhibitor of the ATP-binding domain. In preclinical studies, BioLink1006 showed potent activity, excellent blood-brain barrier penetration, good safety profile, anti-tumor efficacy, and highly selective over other kinases.

## Indication

### Gliomas

There are more than 120 primary tumors affecting the brain and spinal cord, of which more than 90% arise in the brain, with the remainder affecting the meninges, spinal cord, and cranial nerves. These tumors together are referred to as brain cancer or neurologic cancer. Brain cancers are rare, accounting for just 1% of invasive cancers diagnosed in the USA, albeit with a disproportionate burden of morbidity and mortality. But brain tumors are the most common solid tumors diagnosed in children and adolescents. In adults, approximately half of central nervous system (CNS) tumors are malignant, while more than 75% of those in pediatric patients are malignant. In addition, the brain is also a common site of metastasis from other primary tumors, especially melanoma, lung, breast, and colorectal cancer.

Gliomas are a class of tumors that develops from glial cells and ranges from benign low-grade tumors to aggressive high-grade malignancies. Gliomas are the most common type of brain cancer in adults and children. More than 35% of primary brain tumors are gliomas. About half of these patients have glioblastoma, the most aggressive form of glioma. Anaplastic astrocytoma is a high-grade glioma that arises from astrocytes, a type of glial cell. Anaplastic astrocytoma and glioblastoma are two of the most common primary brain tumors in adults. Chemotherapy is usually combined with surgical debulking and radiation therapy to treat patients with brain cancer. The main issues limiting the use of chemotherapy in the treatment of neurological cancers are the blood-brain barrier (BBB) and the blood-tumor barrier, both of which limit penetration of systemically administered agents into the tumor at a therapeutically effective dose.

# Mechanism of Action

## Inhibiting EGFR Signaling

The EGFR has been identified as a relevant therapeutic target in glioblastoma. Engagement of the extracellular domain of EGFR with its ligand activates the intracellular tyrosine kinase domain and triggers a cascade of events involved in cell proliferation, gene transcription and apoptosis. Oncogenic missense mutations in the EGFR gene, which lead to constitutive activation of the receptor, have been identified in patients with glioblastoma. These mutations are suggested to increase the risk of this form of brain cancer, and the most common of which is EGFRvIII.

A broad spectrum of drugs targeting EGFR has failed to significantly prolong glioblastoma patient survival. This lack of efficacy has been attributed to the factors including the poor blood-brain barrier (BBB) penetrance of most inhibitors, involvement of efflux transporters, adaptive signaling responses and drug resistance, disease heterogeneity, and the presence of EGFR mutations in glioblastoma that are distinct from those seen in diseases more amenable to EGFR inhibition. These obstacles have led many to dismiss EGFR-targeted therapy as a viable strategy for treating glioblastoma.

The first-in-class small-molecule kinase inhibitor BioLink1006 is developed to address many of these challenges. Most EGFR small-molecule inhibitors competitively block the ATP-binding pocket of the receptor, which often causes mutations in this region leading to the emergence of resistance. BioLink1006, a noncompetitive inhibitor of the ATP-binding domain, has good BBB penetration but poor substrate specificity for common efflux transporters. These features make BioLink1006 a promising therapeutic candidate for glioblastoma.

# Status

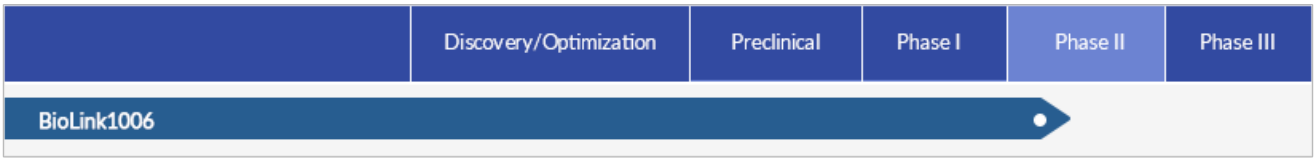
## The Status of BioLink1006

The phase IIA clinical trial of BioLink1006 is ongoing in the United States. In the phase I dose escalation trial, BioLink1006 demonstrated favorable pharmacokinetics with a clinical benefit rate (CBR) of 100% in the target patient population.

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