Enhanced Drug Delivery Across the Blood-Brain Barrier: pH-Dependent Antibodies Targeting the Transferrin Receptor

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WARF: P150370US02

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The Wisconsin Alumni Research Foundation (WARF) is seeking commercial partners interested in developing targeting antibodies for cancer or brain delivery, with significantly increased intracellular accumulation.

Overview

Drug delivery to the brain is hampered by the presence of the blood-brain barrier (BBB), which excludes more than 98 percent of small molecule pharmaceuticals and nearly 100 percent of all protein and gene therapeutics.

One promising delivery method involves antibodies that target receptor-mediated systems at the BBB. Drug molecules can be attached to the antibodies and transported into brain tissue. Antibodies that target the transferrin and insulin receptor systems currently are available, but these systems are expressed throughout the body, leading to the mistargeting of expensive pharmaceuticals.

Nevertheless, the transferrin receptor (TfR) presents a valuable therapeutic target both on normal and cancerous cells, and can be antagonized directly or exploited indirectly as an intracellular drug delivery vector. Needed in the field is an antibody with pH-sensitive binding capability; this would enable the antibodies to bind TfR at physiological pH and release rapidly at endosomal pH.

The Invention

UW–Madison researchers have developed several new single-chain antibody fragments to the transferrin receptor which exhibit increased dissociation at pH 5.5. Such targeting antibodies could have immense potential for drug delivery into and across target cells including cancer cells and the BBB.

Unlike other anti-TfR antibodies in development for cancer or brain delivery, the new antibodies have been endowed with pH-sensitivity resulting in differential trafficking and increased intracellular accumulation up to 2.6 times their wild-type parent.

Applications

- Drug delivery to the brain
- Treating cancer
- May enable new methods of treating disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease, ALS, autism, multiple sclerosis, brain cancer and stroke

Key Benefits

- Non-invasive delivery
- Potentially selective and efficient

- May minimize side effects that can result when drugs are mistargeted
- Antibody fragments are fully human, lowering the risk of immunogenic reactions that can result when non-human antibodies are used.

Stage of Development

The researchers subjected an anti-TfR single-chain antibody to histidine saturation mutagenesis at a single CDR (CDR1) known to participate in TfR binding. The resulting library was screened and eight antibodies with increased dissociation at pH 5.5 were identified. One of these (M16) was dosed onto live cancer cells *in vitro* and exhibited intracellular accumulation 2.6 times greater than its parent antibody.

Additional Information

For More Information About the Inventors

- Eric Shusta

Related Technologies

- WARF reference number P140126US02 describes two specific antibodies previously developed by the researcher which bind to rat brain endothelial cells and show specificity for brain vasculature.
- WARF reference number P06056US describes several other antibody fragments previously identified by the researcher.
- WARF reference number P130017US02 describes an improved in vitro model of the BBB for screening compounds and researching brain function.

Tech Fields

- Drug Delivery : Other drug delivery technologies

For current licensing status, please contact Jennifer Gottwald at jennifer@warf.org or 608-960-9854