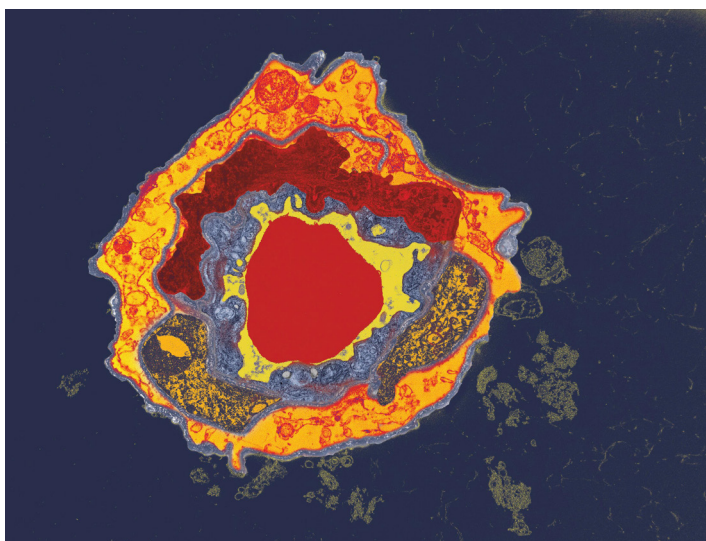


CROSSING THE BLOOD BRAIN BARRIER TO TREAT GLIOBLASTOMA MULTIFORME

BY ANISHA IYER

Blood is the ceaseless tide that washes over the body's diverse cellular civilizations, perpetually revitalizing and maintaining their capabilities. Intricate and extensive, the human body's vasculature provides each organ with the oxygen and nutrients necessary to perform its distinct and necessary function. Chemical therapies and other pharmaceuticals almost always need to travel through the bloodstream to reach their target tissues. When the

Figure 1: TEM of BBB Neurovascular Unit. Neurovascular units are the building blocks of the BBB, with a restrictive diameter of approximately 9 micrometers. This false-coloured transmission electron micrograph (TEM) depicts a neurovascular unit in a mouse brain capillary. A red blood cell is visible in a solid, red-orange color at the center of the image—inside the lumen—which is lined with a layer of endothelial cells in grey and surrounded by various other cell types in the other colors in the image. Image licensed under CC BY 4.0.



"Many newly synthesized pharmaceuticals are unable to cross the BBB, limiting their ability to treat terminal brain diseases including malignant brain cancers such as glioblastoma multiforme."

target tissue is the brain, however, not every drug or compound should be allowed to enter.

As one of the most important organs, the brain possesses its own vasculature that is shielded by the brain's robust protective system: the blood brain barrier (BBB). This barrier is a heavily restrictive border composed of specialized endothelial cells, which are held together by tiny connections called tight junctions (Figure 1).¹ The BBB contains unusually small tight junctions, which heavily restrict the movement of molecules into the brain and provide selective permeability of the vasculature of the central nervous system (CNS).

Despite its necessity, this protective barrier presents a serious obstacle for drug delivery, particularly for drugs with peptides and proteins. Many newly synthesized pharmaceuticals are unable to cross the BBB, limiting their ability to treat terminal brain diseases including malignant brain cancers such as glioblastoma multiforme (GBM).²

GLIOBLASTOMA MULTIFORME

Due to its aggressive, treatment-resistant nature, GBM is the most severe and debilitating type of brain cancer and one of the most lethal cancers worldwide, with a median survival time of only 15 months.^{3,4,5} As both the most common and most deadly primary

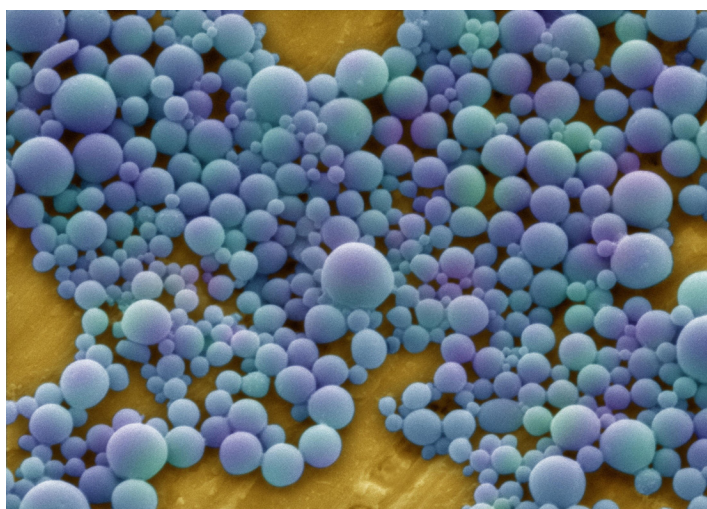


Figure 2: (PLGA) Nanoparticles for drug delivery. This false-colored image depicts nanoparticles ranging in size from 100 nm to 500 nm. The nanoparticles are made of poly lactic-co-glycolic acid (PLGA) and are used as a drug delivery carrier, stabilizing the drugs and allowing them to be released in a sustained manner once inside the body. Image licensed under CC BY-NC 4.0.

brain tumor in adults, GBM has been the target of extensive research, which is limited by the disease's localization in the CNS.⁴

Beyond its treatment-resistance and high incidence, GBM is especially difficult to treat because of the BBB.⁴ Unlike regular blood vessels, blood vessels of the CNS are specialized to better maintain homeostasis and prevent injury and disease. Endothelial cells, which make up the walls of blood vessels, allow only small, hydrophobic molecules to pass. Tight junctions, meanwhile, closely regulate the movement of molecules, ions, and cells between the blood and the CNS and prevent large compounds like proteins and peptides from passing.¹

Although it shields the brain from toxins and harmful compounds, the BBB presents an obstacle for treatments that target the brain because it rejects drugs and chemical therapies that normally help radiation and surgeries treat or excise damaged tissue.³ In GBM specifically, brain tumors contain various cellular populations that respond differently to chemical treatments (Figure 3). Much like with bacterial resistance, the tumors' heterogeneity can often lead to treatment-resistance. As a result, GBM requires multimodal treatment regimens that can reach beyond the BBB.⁶ To overcome the BBB's hindrances, scientists are developing alternative drug delivery systems.

ALTERNATIVE DRUG DELIVERY SYSTEMS

Alternative drug delivery systems help scientists carry drugs beyond the BBB by preventing these drugs from degrading before they reach their target site. Chemical delivery systems, for example, modify the chemical structure of a drug in order to carry it across the BBB. One such system is the lipid-mediated transport system, which increases a drug's hydrophobicity to trigger the BBB's natural permeability to hydrophobic molecules.² Biological delivery systems, on the other hand, re-engineer pharmaceuticals to increase their

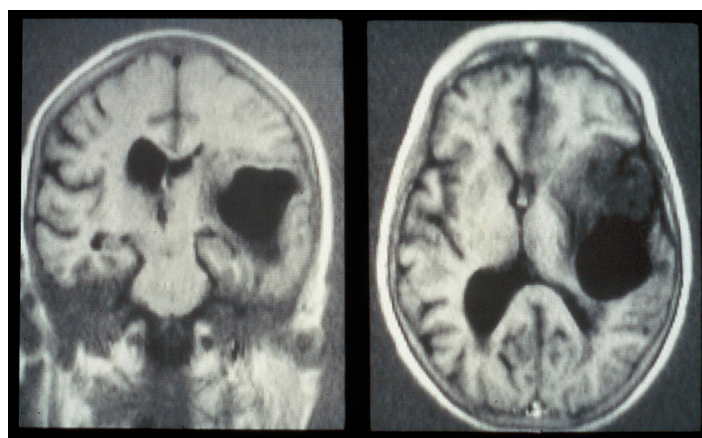


Figure 3: MRI scan; brain cancer (glioblastoma). This magnetic resonance image (MRI) scan visualizes the neuroanatomy of a 33-year-old patient with glioblastoma. Visible in the right hemisphere, the tumor is a large mass, colored black by MRI, which causes focal neurologic signs or seizures. Image licensed under CC BY 4.0.

ability to cross through endogenous transporters within a layer of the brain's capillaries. Other delivery systems modify tight junctions to disrupt the blood brain barrier, use antibodies to transport large molecules across the barrier, or take advantage of already present receptor-mediated transport systems to move molecules into the brain.²

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While effective, these systems sometimes present health risks or are not efficient. Chemically modifying pharmaceuticals can decrease their strength, making them less effective. Re-engineering pharmaceuticals, as in biological delivery systems, requires scientists to devise specific re-engineering strategies for each compound, which does not provide a unilateral solution. Modifying tight junctions in the BBB can lead to uncontrolled permeability, which prevents the barrier from protecting the brain from toxins and pathogens and causes additional complications in patients.⁷

NANOPARTICLES AND FOCUSED ULTRASOUND TO CROSS THE BBB

Many new drug delivery systems involve nanoparticles, which act as physical carriers to transport drugs across the BBB safely and

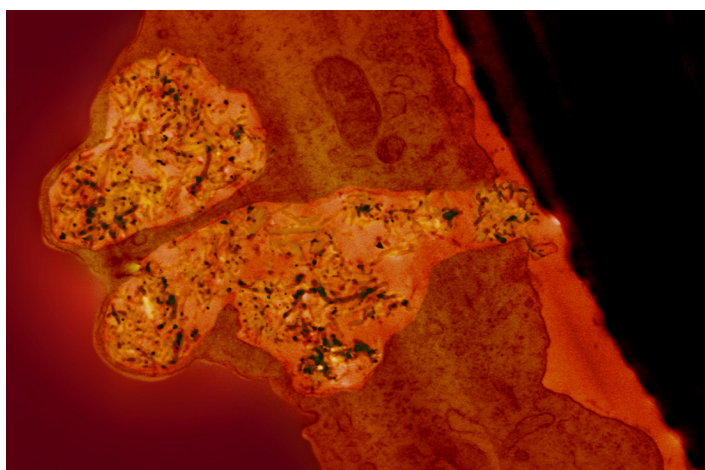
efficiently (Figure 2).⁷ Nanoparticle-based systems include three components: the drug, the stabilizer, and the nanoparticle itself. Because of the system's multiple components, scientists can find an optimal combination of the three to maintain stability during circulation, carry the drug across the BBB, and prevent the body's systems from dissolving nanoparticles in enzymes.⁴

Poly(lactic-co-glycolic acid) (PLGA) nanoparticles, for instance, were designed to optimize nanoparticle composition, thereby improving one component of this system. PLGA and other types of polymeric nanoparticles encapsulate drugs, allowing them to cross the BBB through endocytosis (Figure 4). PLGA was a component of a successful system in which scientists effectively crossed the BBB with a chemotherapy drug called paclitaxel. Scientists loaded paclitaxel onto PLGA nanoparticles and used an additional technique, focused ultrasound (FUS), to make the BBB more permeable to the nanoparticles.

FUS is a particularly important technique because it can produce localized and selective BBB permeability while simultaneously being non-invasive. While still effective, FUS is applied from the outside of the skull, or transcranially, and is therefore non-invasive to the patient. Using ultrasound waves, FUS makes microbubbles inside neurovascular units oscillate. This oscillation produces mechanical forces against the tight junctions of endothelial cells that line the BBB. When the microbubbles collapse, they create channels between endothelial cells that act as microjets to draw cargo through in a fast and favorable way. Together, the two techniques disrupt the tight junctions of CNS endothelial cells and provided greater antitumor efficacy of the paclitaxel.⁸

Moreover, the forces produced by FUS against tight junctions

Figure 4: Nano-needles shuttling the blood brain barrier, TEM. This false-colored transmission electron micrograph shows nano-needles (yellow tubular structures) crossing the blood-brain barrier (orange cell layer) to deliver the therapeutic cargo they contain from the blood (left; dark red space) to the brain (right; black). The nano-needles depicted here are formed from carbon nanotubes (CNTs), which are tubular nanostructures made of rolled-up layers of graphene. Much like nanoparticles, these CNTs are a current research topic due to their ability to act as nanocarriers to deliver drugs or genes to brain tumors blocked by the BBB. Image licensed under CC BY 4.0.



"While still effective, FUS is applied from the outside of the skull, or transcranially, and is therefore non-invasive to the patient."

are reversible, with BBB permeation only lasting 4–6 hours. Attempts to permanently disturb the BBB are particularly dangerous because they can cause ion dysregulation, cellular communication problems, failure to maintain homeostasis, and the acceptance of immune cells and other molecules into the central nervous system—all of which can lead to neuronal dysfunction and degeneration. For patients with neurological diseases, traumatic brain injuries, or neurodegenerative disorders, interfering with the BBB's properties can often escalate the pathology and progression of the disease.⁹ Through its reversibility, FUS avoids the serious dangers associated with permanent BBB disturbance. As a result, drug delivery using nanoparticles and FUS is especially promising because nanoparticle-based systems can be optimized and FUS is non-invasive and impermanent.

CONCLUSION

Cancerous or benign, brain tumors present the distinct difficulty of requiring intervention beyond the brain's protective barrier. With GBM in particular, brain tumors require multimodal treatment regimens due to their cellular heterogeneity and resulting treatment-resistance. Thus, scientists have innovated several alternative drug delivery systems to enable drugs to cross the BBB.

While many systems compromise treatment efficacy or affect the integrity of the BBB as a protective barrier, nanoparticles provide an effective alternative that preserves treatment efficacy, especially when combined with FUS, which only disrupts the BBB temporarily to prevent permanent damage to this crucial protective structure.

As scientists innovate novel techniques beyond enhanced drug delivery to conquer GBM, immunotherapies like vaccines to overcome GBM's heterogeneity and immune checkpoint inhibitors to amplify immune response foreshadow an optimistic future for the field of neuro-oncology. At the same time, alternative drug delivery systems, especially those with nanoparticle-delivery systems that work with FUS, provide a promising means to cross the BBB and work in tandem with these immunotherapies to fight GBM.

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IMAGE REFERENCES

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