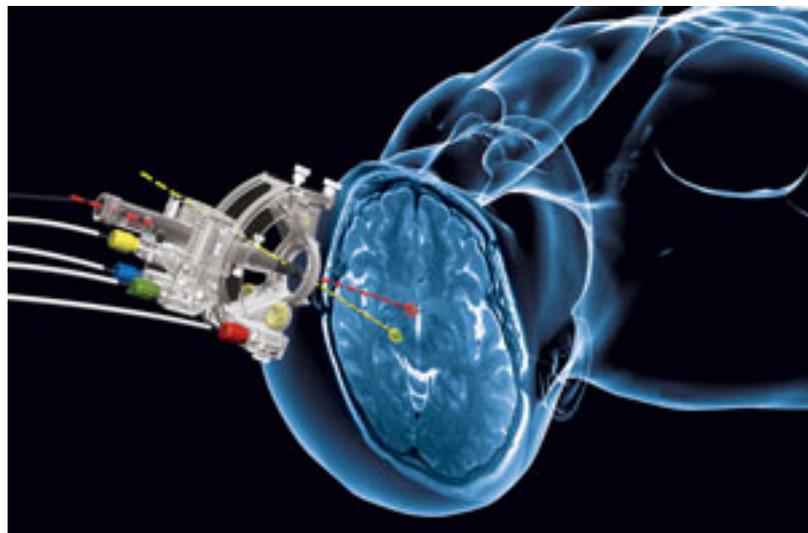


Safer Drug Delivery to the Brain

Lindsay Hock, Managing Editor



Delivering drugs into the brain to treat neurological diseases and disorders has been a challenge. The current best and easiest way to get drugs anywhere in the body is to take them orally or to administer them intravenously. But the challenges for these routes of drug delivery for targets in the brain are multiple.

For one, there is the blood-brain barrier, a highly selective permeability barrier that separates the circulating blood from the brain extracellular fluid in the central nervous system. The blood-brain barrier blocks about 98% of all small molecules and about 100% of all large molecules from targets. If drugs can pass the blood-brain barrier, there are sometimes issues with selectivity to neurological targets. If a really powerful drug is delivered into the brain, it not only affects the target area, but also affects wiring in other parts of the brain. It also requires significantly higher dosages to do this.

Systemic side effects are also faced with the common standard of drug delivery into the brain. These can amount to liver toxicity to heart issues, as the drug has the potential to travel throughout the body and not just to its target.

The obvious solution to these challenges and the barriers faced with standard drug delivery to the brain is to deliver drugs directly into the neurological target. For example, putting a needle into the putamen and delivering a gene therapy that will help patients who suffer from Parkinson's disease. There are many positives to this solution in that there is no blood-brain barrier issue, no systemic side effects (the drug doesn't go through the whole body system), it is selective to the neurological target and it requires much less drug. But the question is, how does one do this? Is it as simple as placing a needle into the putamen?

The answer is no; it isn't simple at all. The standard technique that is commonly used is called conventional neuro stereotaxy. Sterotaxy is the methodology involved

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in the 3-D localization of structures within the brain, based on diagnostic image information, and the use of surgical instruments to reach these points. Traditionally, stereotaxy has been used to place electrodes within the brain for stimulation or EEG recording and approach deep-seated brain lesions with a probe, a cannula or a high-energy ionizing radiation beam. Conventional stereotaxy makes use of a frame attached to the patient's head and some form of catheter or cannula to administer the drug, and was first used in 1908 on small animals and in 1947 on humans.

However, several clinical trials have been run to try this route of administration, and have proved that it doesn't work—the idea of placing a catheter or cannula with neuro stereotaxy into the neuro target delivering the drug doesn't work. One of the most cited papers is an article by Dr. John H. Sampson in the *Journal of Neurosurgery* in 2010. The paper looked at the Neopharm PRECISE trial. Neopharm had a very powerful drug therapy for treating glioblastoma multiform, a form of brain cancer. In a Phase 3 clinical trial, Neopharm placed a group of neurosurgeons at different centers to place 572 catheters to deliver drugs into brain tumors. Of those 572 catheters inserted, they missed the target 51% of the time.

Why didn't this technique work? It's a blind procedure. The placing of the catheter to deliver the drugs is done using indirect targeting methods based on previously obtained images. There is no intraprocedural visualization during the procedure. Inherent inaccuracies from brain shift, co-registration errors and system limitations can't be overcome. And as seen from the Neopharm data, it doesn't work.

MRI Interventions Inc., Irvine, Calif., saw a need to fix these barriers and developed the ClearPoint system, a combination of hardware, software and disposable components that all work together in a seamless manner to deliver a simple workflow for neurosurgeons to deliver drugs to the brain. The ClearPoint system allows neurosurgeons to see the target and see the catheter as it goes into the brain and tumor to watch the drug get infused. The procedure is performed in MRI suite, where the patient is inside the MRI scanner bore, and collects images of the patient during the procedure. A trajectory is pivoted until the neurosurgeon finds their target and a safe path to get there.

The plan is developed using the SmartFrame trajectory guide, which is mounted on a patient's head and has four degrees of freedom—pitch, roll and x and y motion—increasing accessibility to nearly any point in the brain. The SmartFrame device is filled with MRI-visible fluid, which helps the MRI scanner to sense the device. The technology's software knows where the device is pointing and knows the plan trajectory that the neurosurgeon develops. The ClearPoint software guides the surgeon in adjusting the trajectory of the SmartFrame, until the trajectory of the SmartFrame is co-linear with the planned trajectory and then the surgeon is ready to insert a catheter to deliver the drug.

ClearPoint is FDA approved and CE marked. It is involved in a number of clinical trials as the delivery platform for investigational therapeutic agents. Using direct MRI guidance with the ClearPoint system, delivery of a cancer fighting gene therapy, Toca 511, into as many as four locations in a brain tumor, at flow rates of up to 30 uL/min has been achieved without reflux, according to the study

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showcased at the 2013 annual meeting of the Society for Neuro-Oncology.

“The study overall underscores that real-time MRI-guided delivery is more reliable than delivery based on previous scans,” says Kimble Jenkins, President and CEO of MRI Interventions. The system also shows an accuracy of 0.2-mm radial error in cadaver and 0.6-mm radial error *in vivo*. “To put these numbers into perspective, 0.6-mm radial error means we can hit a target the size of a sesame seed anywhere in the brain,” says Jenkins. “We hope that we can continue to collaborate with leading researchers and drug companies with our solution for intracranial drug delivery.”

These collaborations could be the next wave of hope for patients suffering from a range of neurological diseases.

Overall, the company is excited to change the paradigm in the way that patients with neurological diseases can be treated. “We want to give patients, their caregivers and their neurosurgeons a broader arsenal of tools to fight brain tumors, Parkinson’s and a range of other neurological diseases that are often considered incurable. In doing so, we aim to provide hope against these terrible illnesses,” says Jenkins. This hope all falls upon the delivery of life-saving drugs.

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