Brainwaves
in drug delivery

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Delivering drugs through the blood-brain barrier has always confounded scientists, but new developments in both non-invasive targeted brain delivery and brain-implanted drug formulations may provide a way forward.

Getting drug therapies into the brain to treat life-threatening illnesses is one of the most challenging issues in drug delivery. Many drugs display excellent affinity for their targets in cell cultures and isolated preparations, but remain undeveloped because they cannot get access to the brain. Companies working on the central nervous system may be able to translate potent molecules into significant patient advances if they only considered the delivery and targeting issues more carefully.

According to a 2004 study by the Tufts Centre for the Study of Drug Development, central nervous system (CNS) drugs are more costly and take longer to develop than other therapeutic classes, but the rewards extend over a longer period. The study found they take, on average, 115 months to develop, at a cost of US$527 million; lifecycle sales peak at US$849 million, nine years after launch. If delivery issues could be resolved at earlier stages of development, leads might emerge more quickly.

A number of false dawns in the 1990s suggested the blood-brain barrier (BBB) could be breached using either a range of drugs to reversibly loosen the BBB cells or by chemically modifying drugs, making them more likely to permeate it. These approaches failed, however, because of a lack of sustained and adequate delivery and also safety issues. This has led to scepticism about new delivery approaches, even though preclinical research suggests breakthroughs may be possible.

Gene delivery to the brain

At the annual meeting of the Controlled Release Society (CRS) in Hawaii in June 2004, Dr William Pardridge of the University of California highlighted some of the pioneering work of his laboratory – on delivering gene medicine to the brain by targeting receptors on the BBB. Typically, the BBB keeps water-soluble agents out of the brain and favours access for small fat-soluble drugs such as diazepam. Water-soluble molecules such as levodopa and glucose can, however, cross the barrier by being carried on capillary membrane transporters, many of which are still undiscovered.

One problem is usually enough for most scientists, but Pardridge is trying to solve both brain and gene delivery using a single molecular targeting tool[1]. In justifying his methods, he argues that the more conventional approach – using transcranial injections of genes in viral carriers – gives rather weak results in confined brain regions, which is not much use for diseases that spread throughout the brain such as Alzheimer's and some advanced cancers. In addition, there are concerns about the inflammatory and autoimmune side-effects associated with the viral carrier itself.

What Pardridge is trying to do is administer tiny fatty particles loaded with genes to the blood, which brings the particles to the brain capillaries of the BBB as it circulates around the body (see box on page 24). The particles are specifically targeted to capillary endothelial cell receptors to which antibodies on the particle surface can bind. Once across the barrier, the gene is then free to disseminate within the brain and be expressed in all or selected regions. This approach is non-invasive and would not require surgery.

These particular receptor targets were chosen as a result of promising rodent data. Somewhat unexpectedly,

DELIVERING GENES VIA LIPOSOMES

The University of California's laboratory work on delivering gene medicine to the brain uses particles long-established in drug delivery products, fatty globules (liposomes). The liposome construction comprises 85-nm-diameter multi-lamellar anionic units coated with polyethylene glycol (PEG) polymer. It is, in other words, a negatively charged non-sticky onion-like system. PEG was used in order to avoid recognition and removal of immunoliposomes by macrophages; hence it improves particle stability and circulation time. A small proportion of the PEG is then attached to monoclonal antibodies designed to target endothelial cell peptide receptors for either transferrin or insulin. Plasmid DNA containing the gene was entrapped in the liposomes and the exteriorised material chemically removed.

the particles had traversed the barrier and entered brain neurons. Data presented at the meeting showed widespread delivery of gene markers throughout the brains of rodents and monkeys using loaded particles targeting the transferrin and insulin receptors respectively. In one pre-clinical example, intravenous injections of particles containing genes for a deficient enzyme improved motor function in a rat model of Parkinsonism[2].

A second example demonstrated a 100% increase in survival time in mice implanted with an experimental human brain cancer following weekly injections of an agent to silence gene expression of a cancer-associated growth factor[3]. Specific growth factors encourage cell proliferation and their receptors tend to be expressed in many cancers in an unregulated way. These data from Pardridge suggest his approach to silencing genes coding for cancer-implicated receptors may be appropriate to take into humans. They showed a 90% reduction in gene expression for the suspect receptor.

A PARCEL WITH TWO ADDRESSES

Pardridge's particle system is a complex formulation and one of the first to demonstrate targeting from two antibodies on the same particle. It has been described as a parcel with both a primary delivery address (to the BBB) and a secondary forwarding address (to the brain cancer). The particle therefore acts as a Trojan horse, and the cargo is released only when the particle enters the cancer and is activated by a tissue-specific trigger.

Pardridge told the conference that this was one of the first drug delivery technologies to prolong life in animals and that it should soon be ready for clinical trials to deliver nerve growth factors (neurotrophins) for stroke. Outcomes in man are unknown, however, and could fail for many reasons. One issue is whether humans have sufficient BBB receptors to transport enough particles. Another is whether there will be sufficient drug or gene delivery from each injection to treat chronic brain disease. Despite these unknowns, the technology has come a long way. Many doubted whether such a complex tri-partite system could work even in animal models.

Dr Jorg Kreuter of the University of Frankfurt, Germany, also provided convincing pre-clinical data at the CRS conference that supports the thesis that drug-loaded particles can be delivered to the brain. His somewhat larger particles were made from a glue-like polymer, and coated with a detergent (polysorbate 80). Kreuter believes the detergent coating attracts lipid carrier proteins in the blood, and then binds to cholesterol-related (low density lipoprotein) receptors on the BBB, leading to particle uptake by the brain. He also suggests the particles could open the tight junctions between the cells of the BBB capillaries, further aiding absorption to the brain. They also block the BBB efflux transporters on the capillaries that normally act in a protective fashion to send toxins back from the brain to the blood. By the same token, efflux transporters also prevent the delivery of clinically useful agents to the brain.

Irrespective of the mechanism, however, data showed that poorly-delivered agents such as the anticancer, doxorubicin, could be made more effective against solid cancers in rats when these particles were used. A second example was the induction of pain relief in rats using an opiate as the cargo. There seems little doubt that the capacity of particles to deliver drugs and genes to the brain has been underestimated.

ANY ADVANCE ON WAFERS?

An alternative approach to getting drugs to the brain has been to bypass

The particle acts as a Trojan horse, releasing its cargo only when it enters the cancer

Drugs discarded due to poor pharmacokinetics could be retried using the new delivery systems

the BBB altogether and implant localised controlled release formulations directly into areas of brain lesions. This is an invasive approach that has had relative success in man. In 1996, Guilford Pharmaceuticals' Gliadel 'Wafer' was approved by the FDA as a treatment for recurrent high grade malignant brain glioma, a condition in which patients typically succumb within 12 months. Seven or eight dime-sized wafers are implanted into the cavity left by the surgical removal of the recurrent glioma. The wafers are made of a biodegradable polyanhydride polymer and contain the anticancer, carmustine, which is released in the cavity as the polymer dissolves.

In theory, the controlled release of the agent should kill any cancer cells not removed by surgery. Controlled release of localised carmustine also suggests the drug's side-effects may be less than when administered intravenously. A major issue with these types of formulations, however, is how to prevent dose dumping in the brain. In a recent clinical trial of Gliadel, the median survival in selected patients with severe types of glioma was reported to have increased by 41% from 20 to 28 weeks. An eight-week extension of life is regarded as significant for this kind of malignant brain cancer, which has few treatment options. Importantly, Gliadel has recently gained a wider indication from the FDA and wafers can now be inserted at the time of the initial surgery and diagnosis. In combination with surgery and subsequent radiation, this change in labelling has expanded the Gliadel market. In 2003, annual sales were US$20 million at an average cost of US$10,000 per patient, a 32% increase over 2002.

Another paper presented at the conference, by Dr Jon Weingart of Johns Hopkins University in the US, described recent studies to further develop wafer technology for other cargos and to tailor the device to release drug cocktails in a programmed manner. Positive pre-clinical studies were described in which two other anticancer agents (paclitaxel and camptothecan) were formulated into biodegradable polymers and used to treat rodents with glioma implants. Other wafer formulations include anti-angiogenesis agents, cancer vaccines and gene-silencing agents.

There is also significant potential to combine intracranial implantation of chemo-therapeutics with the systemic delivery of a secondary agent to achieve additional benefit. One example is the use of a wafer-laden antibiotic (minocyclin) in combination with intravenous carmustine to treat glioma in rats[4]. This technology extends the design kinetics of how cargos are released. By using implanted biodegradable scaffolds, anti-cancer agents that would normally only be able to reach the required sites in cytotoxic levels, can be delivered directly to experimental CNS models of solid tumours. The university-based group are also working with Guilford Pharmaceuticals to screen new classes of more stable and potent anti-cancer agents for their suitability for local brain glioma therapy in future clinical trials.

While wafer implant technology is promising and appropriate for life-threatening malignant localised gliomas, the potential for non-invasive particle-based delivery systems cannot be overlooked. These particles have shown they can access receptors expressed on the blood-brain barrier and deliver cargo to animals. Intravenously-administered targeted particles carrying genes and drugs that can access lesions in the brain would represent a significant breakthrough in the way a range of CNS diseases is treated. These delivery systems could be used to re-examine drugs that have been discarded because of their poor pharmacokinetics and also to optimise the delivery of new candidates. The question now is whether these new particle systems can work as well in human trials as they have done in animals.

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