New technologies deliver in treating neurological diseases

New techniques that use RNA interference (RNAi) and osmotic pumps to deliver medicines are moving to clinical trials after proving successful in animal models of amyotrophic lateral sclerosis (ALS). If the methods are successful in humans, researchers say, the results may be applicable to other neurological disorders.

Delivering therapies to the cells that need them is a daunting obstacle in treating neurodegenerative diseases, such as Parkinson disease and Huntington disease. Researchers have had some success in animal models, but none of the therapies have yet proven effective in people. Some researchers say that may be because the medicines did not reach the target cells at high enough concentrations.

"We know we have effective concepts, but we need to deliver them to the cells at risk," says Don Cleveland, a neuroscientist at the University of California in San Diego.

ALS is a fatal degeneration of the nerve cells that control muscles. In most cases, the root cause is unknown, but about five percent of cases are inherited. Familial ALS—often related to a genetic defect in the antioxidizing enzyme SOD1—is usually fatal within nine months. "It makes sense for ALS to be the proof of principle because the prognosis is so fast and so well defined," says Cleveland. He and others presented their work at the Society for Neuroscience annual meeting in November.

Targeting treatment to the brain is difficult because the blood-brain barrier blocks many drugs. Gene therapy can bypass the barrier with viruses engineered to carry signals marking them for transport into nerve or muscle cells. Osmotic pumps implanted into ventricles—fluid-filled cavities in the brain—can deliver medicine directly to the cerebrospinal fluid, where it is ultimately taken up into neurons.

In RNAi, small fragments of double-stranded RNA bind to the target RNA sequence, preventing it from producing protein. A Swiss team used the technique to silence defective copies of the SOD1 gene using a carrier that can bypass the blood-brain barrier. To restore function, they also built a normal copy of the gene into the vector. The method improves muscle function in a mouse model of ALS, says lead researcher Patrick Aebischer.

Another approach is to deliver gene silencers directly into the ventricles. In a technique similar to RNAi, Cleveland's team used an osmotic pump to deliver short sequences of DNA that bind to the SOD1 RNA and target its destruction. Unlike RNAi delivered by viruses, however, the pump can be stopped if necessary, assuaging concerns about gene therapy in the brain. The technique can effectively silence the gene encoding SOD1 in rats and is being tested in skin cells from a patient with familial ALS.

It's too soon to predict how effectively the pump will deliver therapy through the length of the human spinal cord, but the medicine should reach the target neurons and delay disease progression, Cleveland says.

The benefits of gene silencing will be limited to diseases with known genetic mutations, notes Jeffrey Rothstein, a researcher at Johns Hopkins University. "But the therapy could have enormous impact for people who only have nine months to live," he says.

Scientists are testing more broadly applicable techniques to deliver growth factors to ailing cells. A pump system is also being tested in a few Parkinson disease patients.

Scaling up therapy from rodents to humans has been notoriously difficult, says Cleveland, but "one of these techniques has a real chance of being effective."

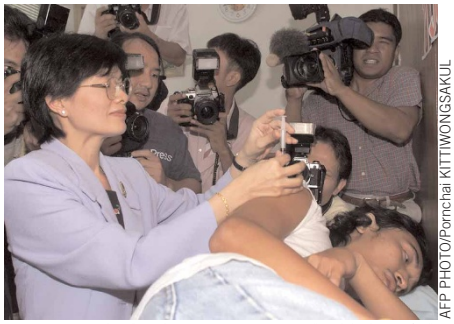
Emily Singer, San Diego

Despite snags and skepticism, Thai vaccine trial lumbers on

The US Food and Drug Administration (FDA) may not license for use in the US an AIDS vaccine now in large-scale trials in Thailand because it has "a relatively low level of efficacy," the agency says. But despite controversy surrounding the vaccine, the FDA continues to support the trials in Thailand.

The Thai health ministry and the US Army launched the trial in October 2003 amid strong criticism from leading HIV researchers, who described the scientific rationale for the $119 million project as "extremely weak" (*Science* 303, 316; 2004).

The vaccine is a combination of Aventis Pasteur's canary pox vector (ALVAC) and VaxGen's controversial AIDSVAX vaccine. ALVAC stimulates the production of cytotoxic T lymphocytes, the 'killer cells' that destroy HIV-infected cells, and the booster AIDSVAX is intended to stimulate the production of neutralizing antibodies that prevent new cell infection. The combination is primarily designed to protect against clade E of the virus, predominant in Thailand, but also contains a few genes from clade B, which circulates in the US and Europe.



AFP PHOTO/Pornchai KITTIWONGSAKUL

Experts say Thailand's HIV vaccine trial is likely to fail

The vaccine is unlikely to work, as the immunological responses so far "have not been impressive," and the data has been "overstated," says David Markovitz, an HIV researcher at the University of Michigan.

Critics note that neither component has had much success. In phase 2 trials, the ALVAC component stimulated cytotoxic T lymphocytes in 23% of patients over the course of the trial and only 5–8% at a single time frame. Researchers also tested cell cultures, which are easier to neutralize than clinical isolates, Markovitz says.

In its phase 3 trials, AIDSVAX did not stimulate detectable levels of neutralizing antibodies and had no effect on the viral loads of more than 8,000 volunteers in the US and Thailand. Adding the two components is "like hoping zero plus zero gives you more than zero," says David Ho, director of the Aaron Diamond AIDS Research Center in New York.

Despite the low efficacy, UNAIDS officials in Bangkok are confident the vaccine will benefit the Thai population.

The FDA concluded after the September meeting that although the vaccine might be ineffective in the US, "it could have beneficial impact in Thailand." The trial has been presented as a 'proof-of-concept' study to provide correlates of immune protection and a safety profile for vaccination. But with 16,000 volunteers, the trial is well over the average 1,500–3,000 volunteers for a proof-of-concept study.

In Thailand, trial organizers have been able to recruit fewer than 6,000 volunteers. Experts caution that the trial exploits the volunteers' goodwill and runs the risk of further damaging public confidence in AIDS vaccine trials, experts say. "It is hard to understand why they decided to go ahead with the trial," says Markovitz.

T. V. Padma, New Delhi