Progress on Replication-Defective Live Virus Vaccines

Vaccines using live DNA viruses that are chemically treated so that they don’t reproduce could be quickly and inexpensively developed, a study in Cell Reports Methods suggests.

The authors noted that, if developed, such vaccines would likely be more effective than inactivated virus or virus subunit vaccines against a wide range of human disease-causing DNA viruses, including herpesviruses, adenoviruses, papillomaviruses, and enteroviruses.

Currently, there is no established method for producing live-attenuated replication-defective virus for vaccine development, according to the authors. But their study suggests appropriate treatment with a chemical compound called centanamycin may render many DNA viruses unable to replicate, making them safe for use in vaccines.

Centanamycin in high concentrations inactivates viruses completely; at lower concentrations it blocks replication without killing the virus. Preclinical research has demonstrated that the resulting replication-defective viruses infect cells near the vaccine injection site but do not cause systemic infection. The infected cells are thought to present a broader range of antigens than inactivated or subunit viruses, stimulating more robust humoral and cellular immune responses.

In the current study, treatment with centanamycin produced human cytomegalovirus, herpes simplex virus 2, and mouse cytomegalovirus (MCMV) that infected, but did not reproduce in, cultured human cells. A replication-defective MCMV vaccine injected into mice produced enough serum neutralizing antibodies to protect the animals from developing disease after injection of wild-type MCMV. Mice injected with serum from the vaccinated mice were also protected from wild MCMV.

The researchers noted that their inexpensive, scalable approach can be adapted to any type of DNA virus but not to RNA viruses such as SARS-CoV-2 or HIV. Future research is needed to determine the safety and efficacy of replication-defective live virus vaccines among humans.

Trial Tests Combined Cell and Gene Therapy for ALS

In an early clinical trial, human neural progenitor cells genetically engineered to produce a potentially neuroprotective factor were safely transplanted into the spines of patients with amyotrophic lateral sclerosis (ALS) and continued to produce the factor for up to 42 months, researchers reported in Nature Medicine.

The treatment also may have preserved limb function and neurons in some patients, although these differences were not statistically significant overall.

The phase 1 and 2a study involved 18 patients injected with cultured donor cells engineered to produce glial cell line-derived neurotrophic factor (GDNF), which can be neuroprotective. To detect differences between treated and untreated neural pathways, the cells were injected into the lumbar spine on just one side. Immunosuppression was administered for 12 months after surgery.

Though the study reached its primary safety end point, most patients reported dysesthesia, paresthesia, or pain in the anterior thigh, which is the region innervated by the spinal injection site. Common adverse events included falls, extremity pain, nausea, back pain, and muscular weakness associated with ALS, immunosuppression, and surgery. No serious adverse events were due to treatment.

Functional outcomes declined for all patients at a rate typical of ALS trial participants. On average, treated legs lost strength at a slower rate than untreated legs, but the difference was not statistically significant. One participant showed markedly preserved function of the treated leg 3 years after transplant.

Postmortem studies of 13 patients who died from ALS progression showed evidence of GDNF only on the treated side, though no overall differences in motor neurons were seen between the sides. However, GDNF was detected primarily in the dorsal spinal horn, which incorporates sensory neurons, rather than the ventral horn, which incorporates motor neurons. This may explain why postsurgery pain was prevalent, as well as the lack of significant overall functional and motor neuron gains. Small benign tumors also were found in some participants. One individual showed many more motor neurons preserved on the treated side.

“Given encouraging outcomes from this initial trial, a combined cell and gene therapy approach holds great promise as a therapeutic option for ALS and other neurodegenerative diseases,” the authors wrote.

Open-source Closed-Loop System Is Effective for Type 1 Diabetes

Automated insulin delivery (AID) systems—also known as closed-loop or artificial pancreas systems—for type 1 diabetes are growing in popularity. In a recent study, an unregulated open-source AID system was more effective for blood glucose control in type 1 diabetes than a conventional sensor-augmented insulin pump.

The “do-it-yourself” AID system tested in the trial, called OpenAPS, included an insulin pump, continuous glucose monitoring, and an insulin-delivery algorithm accessed through a smartphone app.

Among 97 children and adults with type 1 diabetes, the system kept blood
glucose between 70 and 180 mg/dL 71% of the time during the last 2 weeks of the 24-week test period, up from 61% at baseline. By comparison, a control group using a commercial insulin pump with continuous glucose monitoring was in range 54% of the time at the end of the test period, down from 58% at baseline. The between-group differences translated to an additional 3 hours and 21 minutes per day in range for the AID group.

The AID group, but not the control group, had better glucose control overnight than in the day. At the end of the trial, average glycated hemoglobin levels were also lower in the AID group. Among children, the average glycated hemoglobin level was 7% in the AID group and 7.6% in the control group. Among adults, the glycated hemoglobin level was 6.8% in the AID group and 7.5% in the control group.

No severe hypoglycemia or diabetic ketoacidosis occurred in either the AID or control groups. Two patients in the AID group withdrew from the trial due to device connectivity issues.

The study adds to a growing body of evidence that AID systems, including commercial AIDs, are “remarkably consistent” in keeping blood glucose in target range, according to an editorial that accompanied the findings in the New England Journal of Medicine. Open-source AIDs may be more customizable and more widely available than commercial systems, though these potential benefits should be balanced against possible difficulties configuring open-source systems, lack of regulatory approval, and limited trial data, the editorial’s author noted. – Howard D. Larkin

Note: Source references are available through embedded hyperlinks in the article text online.