Potential Treatment for Prion Diseases

A study in Nucleic Acids Research suggests a possible treatment strategy for patients suffering from prion disease. Prion disease is a rapidly fatal and untreatable neurodegenerative disease. Prion diseases are caused by disrupting the structure of a normal prion protein, producing toxic clumps in the brain. Because prion protein is central to disease, reducing levels of prion protein is a promising therapeutic approach. Previous research has shown that antisense oligonucleotides that reduce levels of prion protein can extend the survival of animals infected with misfolded prions. While these initial data were promising, many critical questions remained before therapeutic development could be possible. The new study reports results of preclinical studies of an antisense therapy against prion disease. In this new work, using an expanded set of prion protein-targeting antisense oligonucleotides, the authors have laid the basis for full-scale clinical development. This research shows that, across multiple treatment paradigms, reducing levels of prion protein in prion-infected lab animals significantly extends their survival. Even reducing prion protein levels by a small amount, which should be easier to achieve clinically, resulted in significant survival benefits. Reduction of prion protein is effective across prion strains and across a battery of different treatment time points. The researchers show that reducing prion protein is effective before any symptoms are seen. They also demonstrate that a single dose of a prion protein-lowering treatment can reverse markers of disease even after toxic clumps have formed in the brain. (Nucleic Acids Res. Published online 10 August 2020; https://doi.org/10.1093/nar/gkaa616.)

Humoral Immune Response Markers in COVID-19 Patients

A recent study identifies five immune response markers that collectively were able to correctly classify both convalescent coronavirus disease 2019 (COVID-19) patients and those who did not survive the disease. The study was published in the journal Immunity. The researchers collected samples from hospitalized COVID-19 patients comprising a cohort of 22 individuals, 12 of whom recovered and 10 of whom died. The team used a systems serology technique, an approach that relies on 60+ assays to create a detailed profile of the immune response, to compare the immune responses of those who had survived to those who had not. The virus that causes COVID-19, SARS-CoV-2, has two main proteins that the humoral immune system responds to: the spike (S) protein and the nucleocapsid (N) protein. The researchers found that patients who had recovered had a humoral immune response that responded mostly to S protein, while deceased individuals had a shift in immunodominance such that they had a stronger immune response to the N protein. This immunodominance shift was more predictive of recovery or death than using demographic factors such as age or sex. (Immunity. Published online 30 July 2020; https://doi.org/10.1016/j.immuni.2020.07.020.)

Peptide Nanofibers Induce Immune Response in Lungs and Lymph Nodes

The ongoing COVID-19 pandemic is shining a spotlight on vaccine development. As numerous vaccines go through clinical trials, physicians and researchers continue to work on developing new vaccine platforms to generate the most effective vaccines with the fewest side effects. A new proof-of-concept study demonstrates the potential for one such platform, using self-assembling peptide nanofibers tagged with antigens to prime the immune system. The research, published recently in Science Advances, showed that these nanofibers can induce an immune response and activate T cells without the use of additional adjuvants. Dendritic cells take up antigens on the surface of invading pathogens and present them on their cell surface to other immune system cells to initiate an immune response. In the study, the researchers employed their nanofiber platform to test a subunit vaccine, which uses a specific protein intended to act as the main antigen to stimulate an immune response. An advantage of subunit vaccines is safety since they do not involve the replication of live pathogens. The researchers believe that the primary strength of their nanofiber scaffolding is that it provides a physical structure that presents the antigens to the dendritic cells, making it easier for the innate immune system to recognize the antigens and initiate a response. While the study
was intended primarily to uncover the mechanism by which the nanofibers can induce an immune response, the results also demonstrate that this platform has great potential for generating safe, effective intranasal vaccines. Image credit: the Collier lab. (Sci Adv. 6, eaba0995; https://doi.org/10.1126/sciadv.aba0995.)

Self-Amplifying mRNA Vaccine Fully Protects against Zika Virus in Rhesus Macaques

Researchers have generated a Zika vaccine based on the self-amplifying mRNA (SAM) platform, which they subsequently show protects non-human primates completely from infection by this virus. Published in Science Advances, this preclinical proof-of-concept study supports the development of SAM technology to combat Zika virus as well as emerging pathogens in a rapid fashion. The number of people infected by Zika virus has fallen significantly since the peak in 2016. Nevertheless, it continues to circulate in the population and is likely to cause occasional future outbreaks. There is particular interest in the development of a Zika vaccine to protect pregnant women from transmitting the virus to developing fetuses. SAM technology is an RNA-based vaccine platform used to rapidly produce vaccines through in vitro transcription. The team first developed candidate vaccines from nine different constructs expressing different versions of the virus’s prM-E antigen. Mice were immunized twice with the candidate vaccines, the second dose being administered 3 weeks after the first and then challenged with virus 49 days later. The most promising two vaccine candidates were next tested in rhesus macaques. Vaccine VRC5283 SAM (CNE) elicited complete protection, without detectable signs of the virus in the blood of vaccinated animals. The researchers suggest future studies may investigate whether including another Zika virus structural protein, called the C protein, in the SAM construct could render the vaccine more effective by enhancing the quality of antibody responses. (Sci Adv. 6, eaba5068; https://doi.org/10.1126/sciadv.aba5068.)

Implanted Neural Stem Cell Grafts Show Functionality in Spinal Cord Injuries

Using stem cells to restore functions lost owing to spinal cord injury (SCI) has long been a goal of scientists and doctors. Nearly 18,000 people in the United States suffer SCIs each year, with another 294,000 persons living with an SCI usually involving some degree of permanent paralysis or diminished physical function, such as bladder control or difficulty breathing. In a new study published recently in Cell Stem Cell, researchers implanted highly specialized grafts of neural stem cells directly into SCIs in mice and then documented how the grafts grew and filled the injury sites within the animals’ existing neuronal network. Previous research had shown improved functioning in SCI animal models after neural stem cell grafts, but the mechanisms behind these effects had not been established. The research team exploited recent technological advances that allow researchers to both stimulate and record the activity of genetically and anatomically defined neuronal populations with light. This allowed them to identify which host and graft neurons were active without the concern of electric currents spreading through the tissue and potentially generating misleading results. The workers discovered that, even in the absence of a specific stimulus, grafted neurons fired spontaneously in distinct clusters with highly correlated activity, much like in the neural networks of the normal spinal cord. When they stimulated regenerating axons coming from the animals’ brains, they found that some of the same spontaneously active clusters of graft neurons responded robustly, indicating that these networks receive functional synaptic connections from inputs that typically drive movement. Sensory stimuli, such as a light touch and pinch, also activated graft neurons. Image credit: Thomas Deerinck, UC San Diego National Center For Microscopy and Imaging. (Cell Stem Cell. Published online 5 August 2020; https://doi.org/10.1016/j.stem.2020.07.007.)