Transcript Details
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Engineering Autoimmunity: A New Model for Studying MS Progression and Remyelination

Announcer:
You're listening to *NeuroFrontiers* on ReachMD. On this episode, Dr. Christian Cordano will discuss a new cell-mediated disease model for multiple sclerosis research. Dr. Cordano is an Associate Researcher of Neurology at the University of California, San Francisco Weill Institute for Neurosciences, and he spoke on this topic at the ACTRIMS Forum 2025. Let's hear from him now.

Dr. Cordano:
We were inspired by the fact that we are not satisfied with the animal models that we have. There are multiple kinds. The more-used is called EAE—experimental autoimmune encephalomyelitis—in which we induce a disease that is similar to MS. We have a single episode of inflammation, demyelination, and axonal loss that happen in the same moment, so it's very complicated to dissect out the different neuropathological aspects, but the biggest problem that we have is that these animal model doesn't have recurring disease progression or discrete lesions. With the model that we described during ACTRIMS, we are able to have an improvement because we improved reproducibility; we ensured more uniform expression of disease, a disease that is initiated strictly by design using autoreactive adaptive immune response. And also, we saw prominent discrete lesions that are never seen in EAE or other animal models of MS.

Many people treating AI disease have thought about CAR T-cell as a therapeutic approach, including our group, which has focused on designing cells that can help us with eliminating encephalitogenic or autoreactive immune cells. However, as we imagined targeting cells to the CNS, we also thought about creating autoreactive cells which could induce disease in animals. CAR T-cells allow us to hijack the biology of the T-cell. There is a highly specific immunological target, and the cell gets activated, and we can understand through these cells what happens when they are activated. These could be used to help us understand if targeted autoreactive lymphocytes are sufficient to induce a disease that has some fidelity for MS. And we asked if specifically targeting a myelin antigen with a T-cell is enough to induce a more reproducible form of EAE with the hope that it would have demyelination and neuronal loss and will be more consistent than the currently used approach. MOG is a glycoprotein that has been used because it is highly immunogenic to induce disease, so for this reason we decided to use MOG.

When we used clemastine in this new model, we saw an improvement of the visual evoked potential latency, and we also showed that the lesions that were extremely important in terms of dimension were way smaller both looking at Caspr staining—that is a staining for paranodes—and at MBP staining—that is a staining for myelin. Thus far it has been impossible to use inflammatory animal models of demyelination to answer a crucial question that arose from the first successful clinical trial studying remyelination. Do remyelinating compounds promote the formation of new myelin only in the context of normal-appearing white matter or also within lesions? We published in December 2017 the first successful clinical trial using clemastine in *The Lancet*, and in 2023, we showed that in those patients we were able to quantify remyelination using myelin water fraction within the normal-appearing white matter of the corpus callosum while we didn't see an effect of the drug within lesions.

Another group, in Cambridge, also did something similar. They had a successful remyelinating clinical trial, and they looked with brain imaging at potential signs of remyelination, and they found some effect of the drug within lesion using another sequence—MTR. So there is still a doubt about the area of the brain where we are having an effect with this kind of treatment.

We knew from a previous manuscript published by our group in 2022 that when giving clemastine in the very first days of EAE, we are able to obtain an improvement of the visual evoked potential latency already after seven days in the extreme first phase of inflammation. So the results from this animal model confirm what we believed, but now we have one more important piece that is related to the formation of lesion, so we have one more reason to get excited about the ReCOVER clinical trial that is enrolling here at UCSF, in

London, and in Paris in patients with acute optic neuritis.

This proof of principle model could open a new frontier in the application of engineered cells. We can look at other cells in the future—so, for example, other lymphocytes and engineer them—or we can look at other antigens. We use MOG. That is the most used. But there are multiple other ones that have been described able to induce inflammatory disease and optic neuritis. And then after this first step in which we engineered cells from healthy donors, we will be able to try to engineer cells from patients with different forms of disease, different accumulation of disability, anything that we can think of. We will also be able to use the specific animal model for studying new remyelinating therapies in the context of acute inflammation and discrete lesions.

Announcer:
That was Dr. Christian Cordano discussing a novel approach to therapeutic development for multiple sclerosis. To access this and other episodes in our series, visit *NeuroFrontiers* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!