Study identifies an enzyme inhibitor to treat Gulf War illness symptoms

June 6 2017, by Lauren Ingeno

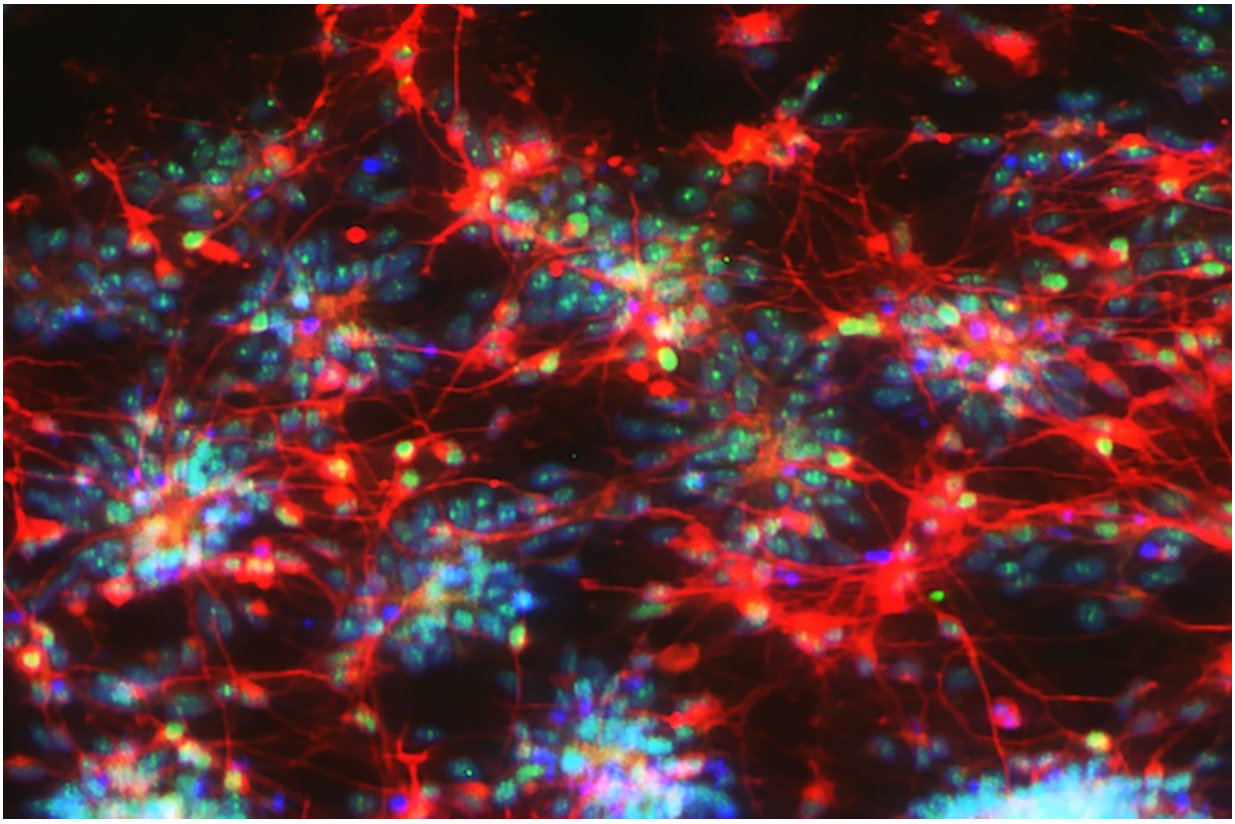

Image reveals a nucleus and two neuronal markers, validating the conversion of adult blood cells that have been “reprogrammed” into pluripotent cell lines and then differentiated into neurons. Credit: Peter Baas Laboratory

At least 100,000 military veterans who served in the 1990-1991 Gulf War were exposed to chemical weapons, released into the air after the

United States bombed an ammunition depot in Khamisiyah, Iraq. Today, many are still suffering from Gulf War Illness, a mysterious, multi-symptom disease that experts believe is linked to organophosphate nerve agents sarin and cyclosarin.

A new paper by researchers at Drexel University sheds light on the neurological consequences of exposure to low-levels of these nerve agents and suggests that drugs like tubacin could treat some of the toxins' neurological effects. The results were recently published in the journal *Traffic*.

To model Gulf War Illness, the researchers treated cultures of human and rat neurons with an organophosphate called diisopropyl flurophosphate, which is an analog of sarin. They also pretreated the neurons with stress hormones to better mimic the stressors of war.

Within the neurons, the research team was looking for deficits in the activity of microtubules, hollow cylinders that act as the cell's conveyor belt, which the investigators believe might go awry in Gulf War Illness patients. Organophosphates can affect a variety of proteins and pathways in cells, and the impacts on microtubules and microtubule-related proteins are likely to be many. The researchers wanted to find whether particular microtubule-related deficits could be identified and corrected pharmacologically to improve Gulf War Illness symptoms.

"In addition to being an architectural element that helps to shape the cell, the microtubule also acts as a railway, which transport organelles throughout the cytoplasm," said Peter Baas, PhD, a professor in the Department of Neurobiology and Anatomy at Drexel's College of Medicine. "We hypothesized that toxins would change the typical way microtubules are chemically modified in neurons and that a drug like tubacin could restore those modifications to normal, thereby treating the disease."

Once treated with tubacin, which makes the microtubules more chemically modified, the researchers observed a restoration in everything that went wrong with the microtubules due to the toxin and stressor treatments.

Surprisingly, they also found that once they corrected the microtubule deficit, defects in dopamine release also markedly improved. Fluctuations in dopamine are thought to be connected to many of the neurological symptoms that Gulf War Illness sufferers face, including insomnia, cognitive problems and headaches. This study's results suggest that dopamine alterations after toxin exposure are in part due to changes in microtubules, and restoring microtubule function to a more normal state could help to alleviate symptoms.

"The fact that a microtubule-based therapy would correct the problem with dopamine release is really encouraging," Baas said.

Baas' research group is part of a multi-institution Gulf War Illness Consortium, a group of investigators dedicated to uncovering the source and treatment for Gulf War Illness. As described in the journal Neurology, Drexel University and Boston University recently received funding from the U.S. Department of Defense to create a Gulf War Illness human stem cell repository, to be shared with researchers across the country for a deeper understanding of this disease.

To create the repository, the researchers are taking blood cells from Gulf War veterans and "reprogramming" them into their "pluripotent" state, which can then be transformed into any type of cell, from a kidney to a neuron. These "pluripotent cell lines" will be especially groundbreaking for studying Gulf War Illness, because they preserve the genetic and possibly epigenetic factors specific to disease susceptibility.

For the study published in *Traffic*, the researchers did not use

pluripotent cells lines derived from Gulf War veterans, but said they plan to use veterans' cells in the future for more refined results.

Since the use of organophosphate pesticides is widespread around the world, and growing evidence indicates a link between these pesticides and disorders such as Parkinson's disease, Baas said that a deeper investigation of low-level OP exposure is critical for preventing and treating neurological conditions arising from such exposures, in addition to Gulf War Illness. Baas also noted that the use of sarin is a concern for the growing threat of bioterrorism, so preparedness for treating victims is paramount.

"We're living in an increasingly toxic world," Baas said. "It's likely that this kind of disease is going to repeat itself if we don't educate ourselves as to its causes, as well as how to prevent and treat it."

More information: Anand N. Rao et al, Pharmacologically increasing microtubule acetylation corrects stress-exacerbated effects of organophosphates on neurons, *Traffic* (2017). DOI: 10.1111/tra.12489

Provided by Drexel University