Engineering a protein to prevent brain damage from toxic agents

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Research at New York University is paving the way for a breakthrough that may prevent brain damage in civilians and military troops exposed to poisonous chemicals—particularly those in pesticides and chemical weapons.

An article in the current issue of the journal *ChemBioChem* outlines the advancement in detoxifying organophosphates, which are compounds commonly used in pesticides and warfare agents. The patent-pending process was developed by NYU School of Engineering Associate Professor of Chemical and Biological Engineering Jin Kim Montclare, along with Richard Bonneau, an associate professor in NYU's Department of Biology and a member of the computer science faculty at NYU's Courant Institute of Mathematical Sciences.

Their work centers on proteins called phosphotriesterases, which have the unique capability of degrading chemicals in a class known as organophosphates, which are found in everything from industrial pesticides to the sarin gas used in chemical warfare.

Organophosphates permanently bond to neurotransmitters in the brain, interfering with their ability to function and causing irreversible damage. The ability of phosphotriesterases to detoxify organophosphates has been previously documented; however, applications using the protein for this purpose have been limited by its short half-life and instability at high temperatures.

Montclare and her colleagues devised a method of re-engineering phosphotriesterases by incorporating an artificial fluorinated amino acid and computational biology. The result: a thermo-stable protein with a longer half-life that retains all the detoxification capabilities of the original version.

"Organophosphates pose tremendous danger to people and wildlife, and sadly it's not unusual for humans to come into contact with these compounds, whether through exposure to pesticide or an intentional chemical warfare attack," explained Montclare. "We've known that phosphotriesterases had the power to detoxify these nerve agents, but they were far too fragile to be used therapeutically," she said.

In a process that married computational biology and experimentation, the collaborators used Rosetta computational modeling software to identify sequences in the fluorinated phosphotriesterase protein that could be modified to increase its stability and make therapeutic applications a reality.

The possibilities for this reengineered protein are considerable. Montclare explained that in addition to therapeutic formulations, which could prevent nerve damage in the event of a gas attack or pesticide exposure and would likely be developed first for military use, the proteins could be critical when stores of toxic nerve agents need to be decommissioned.

"Oftentimes, chemical agent stockpiles are decommissioned through processes that involve treatment with heat and caustic chemical reagents for neutralization, followed by hazardous materials disposal," she said. "These proteins could accomplish that same task enzymatically, without the need for reactors and formation of dangerous byproducts."

Plans are under way to begin developing therapeutic applications for this

modified phosphotriesterase, and the research team believes that its methodology—using computational biology to identify potentially beneficial modifications to proteins—could point the way to future breakthroughs in engineered proteins.

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