Research offers clues to Alzheimer's disease

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An organic compound found in red wine - resveratrol - has the ability to neutralize the toxic effects of proteins linked to Alzheimer's disease, according to research led by Rensselaer Professor Peter M. Tessier. The findings, published in the May 28 edition of the *Journal of Biological Chemistry*, are a step toward understanding the large-scale death of brain cells seen in certain neurodegenerative diseases.

"We've shown how resveratrol has very interesting selectivity to target and neutralize a select set of toxic peptide isoforms," Tessier said. "Because resveratrol picks out the clumps of peptides that are bad and leaves alone the ones that are benign, it helps us to think about the structural differences between the peptide isoforms."

Isoforms are different packing arrangements of a particular peptide. Deformations of a particular peptide - the Aβ1-42 peptide - have been linked to Alzheimer's disease. Improperly folded peptides have been shown to collect in accumulations called "plaques" within the brain. Those plaques are often found near areas of cell death in diseased brains.

It is not clear that resveratrol is able to cross the blood-brain barrier, Tessier said. However, the molecule has garnered interest in recent years for its potential impact on cancer and aging.

In their research, Tessier and his co-authors generated Ab peptides packed together in five unique isoforms, or "arrangements" (monomer, soluble oligomer, non-toxic oligomer, fibrillar intermediates and amyloid fibrils). In their experiments, three of these arrangements were toxic to

human cells, two were not.

Next, the researchers introduced resveratrol.

The resveratrol reacted with the toxic arrangements of the Aβ1-42 peptide, neutralizing their toxicity.

It did not affect the non-toxic arrangements.

"The surprise is that this molecule can target some of these packing arrangements that are toxic and rearrange them into packing arrangements that are not toxic. For those forms that are non-toxic, it doesn't change them," Tessier said.

Intriguingly, Tessier said, one of the toxic arrangements (the soluble oligomer) and one of the non-toxic arrangements (the non-toxic oligomer) were indistinguishable by various methods. And yet the resveratrol only affected the toxic arrangement.

The point, Tessier concludes, is that the seemingly identical non-toxic and toxic arrangements must have some distinguishing feature yet to be discovered, raising questions for future study.

"We have two things that look very similar, but one is toxic and the other isn't," Tessier said. "What is it that makes the bad one bad and the good one good?"

The research produced several other findings, Tessier said, including reliable methods of generating the arrangements Tessier's team produced, and formation of one arrangement which had previously been unknown.

Last week, Tessier was named as a 2010 Pew Scholar in the Biomedical

Sciences by the Pew Charitable Trusts.The distinction includes an award of $240,000 over four years and inclusion into a select community of scientists that includes three Nobel Prize winners, three MacArthur Fellows, and two recipients of the Albert Lasker Medical Research Award, according to the Pew Charitable Trusts.

Tessier was also recently awarded a five-year, $411,872 Faculty Early Career Development Award (CAREER) from the National Science Foundation (NSF) for research in the related field of protein thermodynamics and aggregation.

Provided by Rensselaer Polytechnic Institute