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# Alzheimer's Research Advance

## Structure Causing Enhancement of Aβ Fibril Formation is Identified

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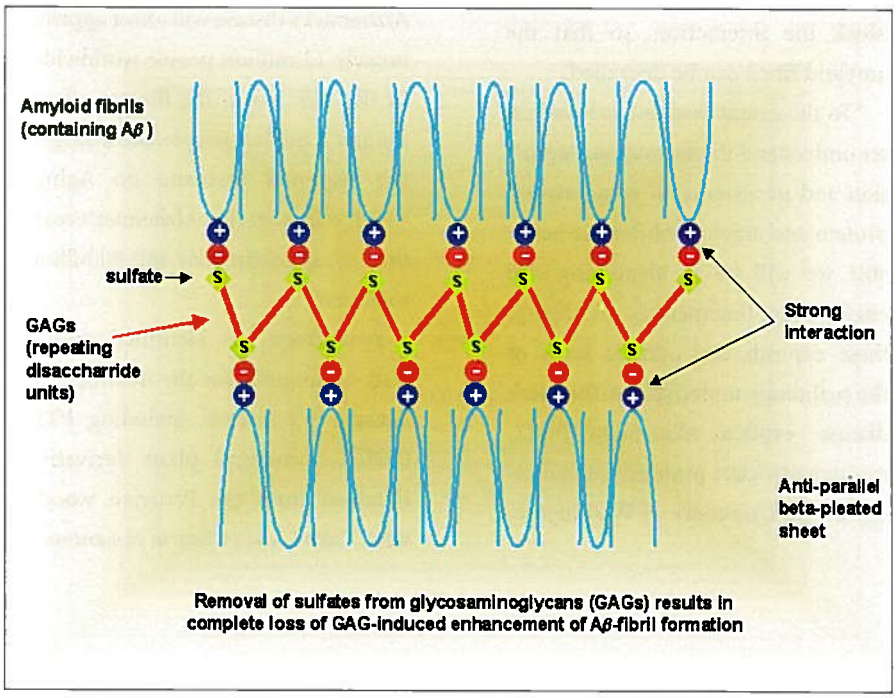
Researchers from the University of Washington (Seattle), along with Gerardo Castillo, Ph.D., director of biochemistry at **ProteoTech, Inc.** (Redmond, WA), have pinpointed the sulfate portion of glycosaminoglycans as being critical for the enhancement of beta-amyloid protein (Aβ) fibril formation that occurs in Alzheimer's disease.

It is now well accepted that the formation and deposition of amyloid fibrils in the brain is a cause of Alzheimer's disease, according to Dr. Castillo. In Alzheimer's patients, there is an increase in production of these fibrils, as well as a decrease in their degradation once formed. Aβ is a 39-43 amino acid peptide present in the amyloid plaques.

Proteoglycans, glycoproteins found in the extracellular matrix of connective tissue, contain carbohydrate portions, called glycosaminoglycans. A number of different glycosaminoglycans, one of which is heparan sulfate, have previously been identified in the amyloid plaques present in Alzheimer's disease. These polysaccharides have been shown not only to enhance the formation of Aβ fibrils, but also to contribute to the stability of the amyloid fibrils once they are formed.




Removal of sulfates from glycosaminoglycans (GAGs) results in complete loss of GAG-induced enhancement of Aβ-fibril formation

Courtesy of Milestones

### Sulfate Structures

With the purpose of identifying which structures within glycosaminoglycans are responsible for these effects, the researchers removed all of the sulfates from heparin. This led to a corresponding complete loss of Aβ fibril enhancement. Furthermore, removal of the *O*-sulfate led to a partial loss of the enhancement of Aβ fibril formation, as did, to a lesser

extent, removal of the *N*-sulfate, according to the study. Results of the study were reported in the April issue of the *Journal of Neurochemistry.*

"This is direct proof that the sulfate structures are critical for enhancement of Aβ fibril formation," says Dr. Castillo. This new information could speed the development of Alzheimer's drugs. He explains, "If we can prevent the association between the glycosaminoglycan and the amyloid fibril by using a drug to block the interaction, we can avoid deposition and accelerate the removal of the fibrils." The goal is to block the interaction, so that the amyloid fibril can be degraded.

"To the extent that researchers better understand the formation, deposition and persistence of beta-amyloid protein and amyloid fibrils, the better able we will be at identifying and engineering therapeutics to disrupt these deposits and address some of the pathology underlying Alzheimer's disease," explains Alan Snow, Ph.D., research associate professor of pathology at the University of Washington, and one of the co-founders of ProteoTech.

**ProteoTech, Inc.**

ProteoTech, Inc. is a drug-discovery company focused on therapeutics for human disease that involve proteoglycans in the disease pathogenesis. Proteoglycans are synthesized by virtually all cells of the body and play a significant role in the pathogenesis of a number of human diseases, including Alzheimer's disease, Down's syndrome, diabetes, cancer, arthritis, atherosclerosis, heart disease and AIDS.

By the year 2000, it is estimated that Alzheimer's disease will affect approximately 12 million people worldwide. In the U.S. alone, the disease affects around 4 million people, according to the National Institute on Aging, which estimates that Alzheimer's costs the U.S. approximately $80-90 billion each year.

ProteoTech has identified several lead compounds for the treatment of Alzheimer's disease, including PTI-00703™, a natural plant derivative obtained from the Peruvian woody vine, Cat's Claw (*Uncaria tomentosa*). PTI-00703 has been shown to inhibit amyloid fibril formation and growth. The compound is licensed on an exclusive worldwide basis to **Rexall Sundown** (Boca Raton, FL) in the dietary supplement field-of-use. ProteoTech retains rights to develop the active amyloid inhibitory ingredients within PTI-00703 as prescription pharmaceuticals.

In April, ProteoTech received a $227,501 SBIR Phase I award from the NIH to further isolate and identify the active amyloid inhibitory ingredients in PTI-00703. The research project, titled "PTI-00703: A Potent Amyloid Inhibiting Agent for the Treatment of Alzheimer's Disease and Other Amyloidoses," will be led by Dr. Castillo.

ProteoTech also received a $143,986 SBIR Phase I award from the NIH to further investigate the discovery of a proteoglycan structural abnormality that may be critical for the formation of the amyloid plaques and neurofibrillary tangles of Alzheimer's disease.

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