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Old Smoking Gun Of AD Dementia Blows Smoke

## New Hypothesis Aims To Upend Received Wisdom Anent Fibrils, Plaques, Tangles Of Alzheimer's

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Science Editor

A 51-year-old demented woman, known to medical history as Auguste D., was the first patient ever diagnosed with Alzheimer's disease (AD). Her physician, neuropathologist Alois Alzheimer (1864-1915), cared for her from 1901 until her death in 1906, then sought in her brain tissue the root cause of her disease.

What Alzheimer saw was a mess of lesions inside and outside of her neurons – the now familiar senile neuritic plaques and fibrillary tangles. They bore out his bold contention that dementia was not the result of aging but a specific cerebral disorder. Now, nearly a century later, a new, still-unproven, hypothesis is challenging accepted wisdom as to the etiology of AD.

It's put forward in the April 2001 issue of the Elsevier journal, *Trends in Neurosciences*, under the title: "Targeting small A $\beta$  oligomers: the solution to an Alzheimer's disease conundrum?" The article's corresponding author is neuroscientist William Klein, at Northwestern University's Cognitive Neurology and Alzheimer's Disease Center in Evanston, Ill. Its second and third co-authors are neurobiologist Caleb Finch, who directs the Alzheimer's Disease Center at the University of Southern California (USC), Los Angeles, and NWU Professor of Molecular Pharmacology, Grant Krafft.

"The bottom line," Finch told *BioWorld Today*, "is learning the details of how this novel toxic amyloid that we've discovered aggregates, and how it participates in AD in humans. Until a few years ago," he continued, "the field at large was completely convinced that the fibrils of amyloid were toxic agents. We're showing that it's something much more slippery and smaller, what we call ADDLs – amyloid-derived diffusible ligands. When you centrifuge and homogenize the AD brain, you will find ADDLs in the liquid part.

“ADDLs have remarkable selectivity as to which cells are damaged. Bill Klein and Grant Krafft at NWU showed most recently,” Finch said, “that the cerebellum, which is not damaged in AD, is not damaged by ADDLs, and the hippocampus, which is damaged in AD, is damaged by ADDLs.”

### **ADDL Receptors Clue In Therapeutic Drugs**

“The other aspect of this is that these forms of the beta peptide also have short-term effects, which are not lethal, but which disrupt memory-like processes in the electrical activity of brain cells. The proof of the principle,” Finch said, “will be when we know exactly which receptor molecules on the cell surface ADDLs interact with. Then, we can begin to look at therapeutic drugs that block their interaction with cells.”

Finch said that “for more than a decade, AD researchers have focused on large clumps of amyloid – fibrils – which coalesce into even larger deposits in the brain – plaques. Their case against amyloid fibrils was one of guilt by association. Since autopsies invariably discovered plaques in the brains of AD victims, and fibrils were shown to kill neurons in culture, a consensus rapidly developed that fibrils and plaques were the crux of the AD problem.

“Our hypothesis,” he said, “still lays the blame for AD on the amyloid beta molecule, but diverges sharply from there. It describes a new, never-before-suspected form of amyloid, whose toxicological profile neatly fits AD’s pathology, and redefines the basic cause of dementia in the disease’s early stages.

“People saw these plaques,” co-author Krafft commented, “and concluded: ‘This has to be the smoking gun.’ But we concluded the plaques are just smoke; the gun lies elsewhere.”

Finch said that, “unlike the comparatively hulking amyloid fibrils, ADDLs are soluble, which means they float freely and diffuse everywhere in the brain. Fibrils, being insoluble, are confined to the specific locations where they first form. Those locations correspond poorly with the brain areas that wither as AD progresses – an inconvenient fact that the fibril hypothesis could never explain.”

For clinical purposes, the co-authors are pursuing two main avenues – drug discovery and vaccine development.

“To optimize the efficacy of our vaccine,” Klein told *BioWorld Today*, “it would be crucial to establish the ADDLs as the antigenic target of the antibody. It turns out that the ADDLs are truly effective, so this is very promising. And here’s the key: The amyloid beta monomer that’s present in those solutions is a normal molecule, so we won’t raise antibodies against it. And the oligomers – the ADDLs – are foreign species. An AD patient’s immune system will recognize them as such, and start to make antibodies against them.

“In the early stages of AD,” Klein said, “our theory says that memory loss is not due to nerve cell death. Our theory says it’s reversible, because it’s due to synaptic dysfunction instead of initially killing neurons. If you can get an antibody in at these early stages, the prediction would be that memory impairment will go away. The beauty of it is of course, that the same toxin would play a role in later stages of the disease, ultimately building up to a level that kills the neurons. And this toxin would be neutralized by the same antibody. In vivo testing in rodents is essentially under way.”

### **In Works: Vaccine, Diagnostic Blood Test**

On the trail of ADDL receptors, Klein observed, “We hope to use our existing systems to start looking for drug candidates that block the toxic aspects of amyloid. In the short term it disrupts memory-like processes. In the long term it kills nerve cells.

“However, in the light of the ADDL hypothesis,” he said, “some drug-finding approaches could inadvertently make things worse. For example, blocking the formation of fibrils or breaking down plaques – a major objective of pharmaceutical research – could increase the supply of dissolved amyloid, which would then be free to assemble into virulent ADDLs.”

It’s axiomatic that the only 100 percent reliable diagnosis of AD is posthumous – detecting plaques and tangles in the post-mortem brain. “We’ve developed an immunochemical assay,” Klein said, “that’s remarkably sensitive for detecting the ADDLs, and eventually making a simple diagnostic blood test possible.”

On April 17, 2001, the U.S. Patent Office issued a composition-of-matter and methods patent, No. 6,218,506, jointly to NWU and USC. Klein said it covers “amyloid beta protein globule, assembly and uses thereof.” Krafft, Klein, and Finch are its principal co-inventors. Krafft, on leave from NWU, is CEO of a newly founded virtual biotech company, Acumen Inc., of Glenview, Ill., to which the patent is licensed.

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