

## **DC Hearing Notes (May 14, 2008)**

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Thank you Chairman Kohl and Ranking Member Smith. I am very pleased and honored to be here this morning to address the Special Committee on Aging.

I am a Professor of Neurology at Harvard Medical School and a geneticist at Massachusetts General Hospital.

25 years ago, as a student at Harvard Medical School, I participated in the very first human genome mapping effort to locate a disease-causing gene. That gene was responsible for Huntington's disease, a horrible neurodegenerative movement disorder. Shortly thereafter, I focused my attention on mapping the genes for early-onset familial Alzheimer's disease, the type affecting Mr. Jackson.

In 1987, my lab discovered the first AD gene and we identified two more in 1995, all three causing early-onset AD. This morning, I will summarize the tremendous amount we have learned about the causes of AD and the ongoing trials of new Alzheimer's drugs made possible by studies of these early-onset AD genes.

Before getting into the science, I would like to make three important points:

First, none of the discoveries or drug trials I will mention this morning would have been possible without the courageous involvement of patients, like Mr. Jackson.

Second, few, if any, novel Alzheimer drugs being developed by the pharmaceutical industry today would have been possible without the original seeds of creativity and basic biological and genetic discoveries that have come from academic research, primarily supported by federal and other non-profit funding for Alzheimer's research.

Third, it generally takes about 20 years for basic research findings to reach the stage of clinical trials in patients. This is the case for the discovery of the first Alzheimer's genes in 1987, biological studies of those genes, and current clinical trials in 2008.

By studying the genetic defects in the three early-onset AD genes over the past two decades, we have learned that the culprit in Alzheimer's is a tiny protein we call A-beta. As it accumulates to excessive levels in the brain, it short-circuits communication between nerve cells, ultimately killing them. The result is major cognitive dysfunction and memory loss.

While current Alzheimer's drugs only treat the symptoms offering minimal and only temporary benefit to patients, several new Alzheimer's therapies currently in clinical trials are aimed at actually stopping the progression of the disease by curbing accumulation of toxic A-beta molecules in the brain.

This can be achieved in three ways: 1. Limiting the production of A-beta; 2. Clearing A-beta out of the brain; and, 3. Neutralizing A-beta's toxic properties. Novel drugs of all three classes are currently in clinical trials, including a promising one that my lab helped develop over the last ten years. And, I would be happy to provide more details about these therapies.

While I am optimistic about the success of these trials, history dictates that the first drugs out of the gate are not always the best ones. We will clearly need to take many shots on goal to cure this disease; and, will most likely, someday, be prescribing a cocktail of different drugs to effectively treat Alzheimer's.

The most promising new drugs have been made possible from the knowledge gained from the studies of the gene defects causing early-onset Alzheimer's. However, these three genes together with one other (for late onset) account for only 30% of the inheritance of Alzheimer's disease. Imagine what we could do with the other 70% identified.

To find these, my lab at MGH is currently heading up the "Alzheimer's Genome Project", (primarily funded by a non-profit foundation and the NIMH). A paper describing the first set of genes is currently under review at a major scientific journal, and we expect to announce several novel Alzheimer's genes this summer. I would be happy to provide you with more details here, as well.

As history has shown, every new Alzheimer's gene provides a novel avenue for potential treatment while also improving our ability to predict risk for Alzheimer's early in life. Ultimately, the convergence of genetic knowledge and effective Alzheimer's drugs will allow for a "personalized medicine" approach to this devastating disease: "early prediction, early intervention". These are the pioneering days of that vision.

So, while there is good reason to be optimistic, there is also a lot more work to do before we reach our goal. Scientists will need to work more closely then ever with clinicians, patients, the government, non-profits, and pharma to make this happen.

Thank you.