TESTIMONY BEFORE THE
SENATE COMMITTEE ON HEALTH, EDUCATION, LABOR AND PENSIONS:
SUBCOMMITTEE ON RETIREMENT SECURITY AND AGING

Hearing on Alzheimer's disease: Current and Future Breakthrough Research

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Good morning, Madam Chairman, Senator Burr and members of the Subcommittee. Thank you for holding today's hearing and for inviting me to provide testimony on the very important subject of breakthrough research on Alzheimer's disease.

My name is Dr. J. Donald deBethizy, and I am President and Chief Executive Officer of Targacept, Inc, a publicly traded biopharmaceutical company located in Winston-Salem, North Carolina. I would like to speak today about the promising research our company is doing in the area of cognitive disorders and specifically in Alzheimer's disease, a devastating disease that affects more than 37 million people worldwide.

At Targacept, we are engaged in the design, discovery and development of a new class of drugs for the treatment of multiple diseases and disorders of the central nervous system. Alzheimer's disease is a primary area of focus for us, and we have also conducted clinical research in other conditions on the spectrum of cognitive decline that too often culminates in Alzheimer's.

We call our pharmaceutical product candidates 'NNR Therapeutics' because they modulate the activity of a class of specialized proteins in the body known as neuronal nicotinic receptors, or NNRs. As you may recall from your basic biology class, nerve cells, or neurons, are the primary element in the human nervous system and act like electrical wires to send various signals to the brain and throughout the body. However, unlike the kinds of electrical circuits we have in our homes, the communication between nerve circuits is not controlled mechanically, but chemically. In this process, the electrical impulses of a neuron are converted into essential chemicals such as serotonin, dopamine, acetylcholine and norepinephrine. These chemicals are released by the neuron and then land, so to speak, on another neuron – where they trigger the release of essential chemicals by the second neuron. This process then repeats itself, usually resulting in the successful transmission of signals and the normal functioning of our nervous system. NNRs are the landing sites on the neurons and, as such, are responsible for modulating the transmission of these essential chemicals. I like to use the metaphor that NNRs are like the volume knobs of the central nervous system. They boost the degree of neuron communication if the nervous system is understimulated and reduce the degree of neuron

communication if the system is overstimulated. If NNRs don't do their job correctly, it can lead to a chemical imbalance that is associated with a number of debilitating CNS diseases and disorders, such as Alzheimer's disease. This is why NNRs are important therapeutic targets.

Targacept is the leader in the development of NNR Therapeutics. We have extensive experience in the biology and chemistry of the NNR receptor family and hold the largest patent estate in the NNR space. Our history began with a program initiated by R.J. Reynolds Tobacco Company in 1982 to study the activity and therapeutic effects of nicotine, which is the prototypical NNR modulator. Nicotine's ability to enhance attention, learning and memory is well documented, and there are a number of studies showing the lower prevalence of diseases such as Alzheimer's disease and Parkinson's disease in smokers as compared to non-smokers. As another example, more than 70 percent of people suffering with schizophrenia smoke. It is believed that in smoking, these people could be actually medicating themselves, by providing nicotine that helps them focus and enhances their cognitive performance. Nicotine, of course, is not viable as a drug because it causes a number of deleterious side effects. The reason for this is that, in addition to NNRs, nicotine affects other receptors in the body's muscles and ganglia that are associated with the side effects.

The researchers at Reynolds recognized that drugs capable of modulating NNRs could remedy the chemical imbalance characteristic of nervous system diseases like Alzheimer's disease. However, to be useful, these drugs had to target specific NNRs while at the same time avoiding interaction with nicotinic receptors associated with harmful side effects. This recognition of the need to exploit only Targeted Receptors led to the creation of Targa Cept. Our scientists' 20-plus years of focused NNR research has led to a particular expertise in designing and developing pharmaceutical product candidates that have the required NNR selectivity.

We are conducting some very promising work in the area of Alzheimer's disease as well as other cognitive disorders. Our lead product candidate is a novel small molecule that we refer to as TC-1734. TC-1734 selectively modulates specific NNRs, which creates the potential for therapeutic benefit and reduces the risk of side effects. This product candidate has been evaluated in 12 clinical trials to date, involving a total of about 540 subjects.

As reported in a very recent issue of Nature Reviews (Drug Discovery), the economic burden of Alzheimer's is massive, with an estimated direct and indirect annual cost of patient care estimated at $100 billion in the U.S. alone. The number of therapeutic options for Alzheimer's is severely limited and only a fraction of patients respond well to those that are on the market. Moreover, none of the approved treatments have demonstrated the ability to substantially delay the progressive deterioration and death of neurons in the brain that can lead to more severe stages of cognitive impairment and debilitation. The need for more effective drugs is clear.

What we find very exciting about NNR-based therapeutics is their potential at every stage of cognitive dysfunction. As I mentioned earlier, Targacept has conducted clinical research in other conditions on the spectrum of cognitive decline. I'm speaking specifically of conditions known as age associated memory impairment, or AAMI, a condition associated with normal aging, and mild cognitive impairment, or MCI, which is a condition that is more severe than AAMI but less severe than Alzheimer's disease. In fact, we would argue that perhaps the most effective and efficient manner for addressing Alzheimer's disease would be to treat these earlier stages of cognitive decline, which could potentially mean that a patient may never suffer from Alzheimer's disease. TC-1734 has shown evidence of neuroprotective properties in our preclinical testing. This means that it had the effect of protecting neurons under conditions that would otherwise have caused them to deteriorate and die. If it has the same effect in humans, our position regarding prevention as the optimum way to address Alzheimer's disease and other neurodegenerative diseases would only be strengthened.

In 2006, Targacept completed a Phase II clinical trial TC-1734 in age associated memory impairment (AAMI). In the trial, TC-1734 achieved statistically significant results on all three co-primary endpoints, demonstrating its cognitive-enhancing potential. The development of AAMI has been set aside in favor of Alzheimer's disease, for now, largely due to the difficult and uncertain path to regulatory approval for AAMI. However, if that path were clarified so as to support the substantial investment of large-scale Phase III clinical trials, we would be well on our way to developing a drug that could act in early intervention against cognitive dysfunction. Moreover, the data from these trials could be extremely useful as TC-1734 is developed to address Alzheimer's disease directly. A Phase II clinical trial of TC-1734 in approximately 500 patients with mild to moderate Alzheimer's disease is scheduled to get underway in mid-2007, as is a similar size Phase II clinical trial in cognitively impaired patients with schizophrenia.

We recognize that Alzheimer's disease has impacted the lives of millions of people and represents an area of enormous unmet medical need. It is extremely gratifying to us to contribute to the body of knowledge in this area and to help people understand potential treatments for this disease.

Thank you.