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Representing the American Society for Cell Biology

Senate Special Committee on Aging

Regarding"Exploring the Promise of Embryonic Stem Cell Research"

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Mr. Chairman, members of the Committee, thank you for inviting me here today and thank you for allowing me to join you by way of teleconference. My name is Larry Goldstein. I am a Professor of Cellular and Molecular Medicine at the University of California, San Diego, School of Medicine and an Investigator with the Howard Hughes Medical Institute. My research is focused on understanding the molecular mechanisms that are used to move vital materials inside neurons such as brain cells, and testing the role that failures of movement in brain cells play in the development of neurodegenerative diseases such as Alzheimer's Disease, Huntington's Disease, and others including mad cow disease.

I serve as Secretary of the American Society for Cell Biology, a professional society of almost 12,000 basic biomedical researchers in the United States and in 50 other nations. I am also the Chair of the Public Policy Committee of the American Society for Cell Biology and Chair of the Government Affairs and Policy Committee of the International Society for Stem Cell Research.

I want to thank you for holding this hearing today, and for your long-standing support of the Federal investment in basic biomedical research at the NIH and the NSF. Every year this vital research brings new understanding and new treatments for the many diseases that afflict our friends and families.

I am here today to discuss how my research, and that of other scientists, is trying to take advantage of the enormous scientific and medical opportunity provided by human embryonic stem cells. I want to be cautious and stress that scientific progress in the fight against diseases such as Alzheimer's is difficult and sometimes agonizingly slow-even when the best tools are available; importantly, guarantees are hard to come by. Nonetheless, I, and many of my colleagues think that human embryonic stem cells potentially hold the key to major advances in the search for new understanding of, and new treatments for, these terrible diseases.

To explain why I think there is so much promise with these cells, I want to make a few general points about how human brain diseases are generally studied using Alzheimer's Disease as a specific example. An important basic principle is that we can rarely do the kinds of biochemical and cellular experiments on brain cells of human patients while they are still alive and in the earliest, and we hope treatable, stages of Alzheimer's Disease. Thus, much of what we learn about the basic cell biology and biochemistry of human

brain cells that have Alzheimer's Disease comes from studying brain cells of people who have died of the disease, and hence were in late stages of the disease. Thus, we are often relegated to studying the biology of the brain and its component cells after the ravages of Alzheimer's Disease have destroyed most of the normal functions. In some ways, this is like trying to learn how to detect and prevent plane crashes simply from studying the pattern of wreckage on the ground after a plane has already crashed. While valuable, what we most need is the "black box" to reveal what went wrong in the earliest stages of failure-the nature of the cellular mistakes and malfunctions so that we can learn how to prevent them or to treat them. Thus, in our search for understanding and for new treatments, we are effectively searching for the "black box" of Alzheimer's Disease.

The question then is how to find the "black box" so that we can learn what cellular events and mistakes cause Alzheimer's Disease and how we might fix them. One very important approach has been to take advantage of rare forms of Alzheimer's Disease caused by known genetic changes. These genetic changes can be introduced into laboratory animals such as mice and the cellular changes in the mouse brain can be studied. A great deal has been learned from this approach and a number of important ideas about what causes brain cells to malfunction in Alzheimer's Disease have been proposed. But, people are not just big mice-there are many important cellular differences, particularly in the brain. As a result, ideas that come from studying mice with some but not all symptoms of Alzheimer's Disease must be tested in human cells and ultimately human patients. This, however, is hard for the reasons I have already described. This is where my lab is trying to use human embryonic stem cells to develop a new, and I believe, very important approach to solving this problem. By learning to induce human embryonic stem cells to become the types of brain cells that malfunction in Alzheimer's Disease, and by introducing into them the genetic changes that cause Alzheimer's disease in people, we are working to test the different ideas for what goes wrong at the earliest stages in brain cells afflicted with this disease. As we learn which ideas are likely to be correct, these very cells may be important test-beds to evaluate or develop candidate drugs for treatment.

Another problem that we face in understanding and treating Alzheimer's Disease comes from the simple observation that most people who develop this disease develop what we call sporadic disease. In sporadic Alzheimer's disease, we do not know of simple genetic changes that cause the disorder, but, we suspect that several, or perhaps many genetic changes combine together, and perhaps combine with environment to cause disease. In this regard, we suspect that each of us has a unique susceptibility profile, or potentially resistance, to Alzheimer's Disease. To my knowledge, we have no way to study this major form of the disease in laboratory animals or to evaluate some of the proposed genetic components that have been found from painstaking genetic studies in humans. This is where I think that human embryonic stem cells have a second, and potentially even more important contribution to make. For it is here where the availability of many diverse human embryonic stem cell lines may help us. Each stem cell line has a specific and unique genetic constitution; each line in principle may be induced to form brain cells that fail in Alzheimer's Disease, and evaluated at the cellular and biochemical level to test how the genetic variability found in humans may contribute to the disease state.

Again, there may be great value in taking advantage of this variability to test the response of brain cells with different genetic variants to different drugs so that we might begin to learn to predict which people will respond best to different types of treatments.

The ideas and methods I have just described are not limited specifically to Alzheimer's Disease but could be used profitably with Huntington's Disease, Parkinson's Disease, and perhaps Lou Gehrig's Disease. Only time will tell, but many of my scientific colleagues and I are prepared to devote our careers to these goals if given the chance. Thank you for taking the time to listen to my testimony today. I would be happy to respond to questions if you have any.