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UNDERSTANDING ALZHEIMER'S

One in 10 Americans over the age of 65 has Alzheimer's disease, a debilitating neurological disorder that slowly destroys memory and cognitive function and for which there is no cure. According to the National Institutes of Health (NIH), because the risk of developing the disease increases with age and more people are living longer, the number of people suffering from Alzheimer's is likely to grow dramatically over the next few decades. Despite years of research by scientists all over the world, Alzheimer's is still poorly understood.

Prof. Joel Sussman

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Prof. Joel Sussman of the Weizmann Institute of Science's Department of Structural Biology, who studies nervous system proteins involved in Alzheimer's disease and other neurological disorders, is working to change that. For more than 20 years, he and Prof. Israel Silman of the Department of Neurobiology have been studying the three-dimensional (3D) structures of these proteins in order to better understand how they function in biological processes. This research also helps them develop ideas for improving existing Alzheimer's drugs, as well as designing new ones that are more effective and have fewer side effects. Prof. Sussman compares the process to "getting a better view of a lock so you can design a key that would fit inside it."

Much of Prof. Sussman's research focuses on a brain enzyme called acetylcholinesterase (AChE) that is thought to play a crucial role in Alzheimer's disease. Memory loss and other cognitive deficits in Alzheimer's patients result from the deterioration of brain cells that release a substance called acetylcholine—a neurotransmitter that carries messages between brain cells. The acetylcholine shortage that ensues is compounded by the action of AChE, the enzyme that breaks down acetylcholine in the body. "One of the ways of treating Alzheimer's is to slow down the activity of this enzyme [AChE] and, thus, artificially raise the levels of acetylcholine," says Prof. Sussman.

Prof. Sussman and his colleagues were the first to determine the 3D structure of AChE. Their research in the early 1990s showed that AChE has a very deep chasm known as the "aromatic gorge," where acetylcholine is broken down. "What we found was totally unexpected," says Prof. Sussman, "and it gave us great insight into thinking of ways to slow this enzyme down."

Since then, they've determined the 3D structure of several FDA-approved drugs used to treat Alzheimer's, including donepezil (Aricept®), rivastigmine (Exelon®), and galanthamine (Razadyne®, formerly known as Reminyl®). These studies revealed the exact nature of the interaction between these compounds and AChE. All the com-

pounds work by inhibiting AChE activity in order to restore acetylcholine levels. They don't cure Alzheimer's disease, but they can help counteract memory loss and prevent symptoms from becoming worse for a period of time.

Prof. Sussman also unraveled the 3D structure of huperzine A, an extract from a Chinese herb used for centuries to treat memory disorders. Collaborating with scientists at the Mayo Clinic in Jacksonville and at Georgetown University, his team found that although huperzine A differed in chemical structure from the FDA-approved Alzheimer's drugs, it worked in the same way—by blocking AChE activity. "As far as we know, this is the first example anywhere of taking a traditional herbal medicine from China and seeing how it functions [on the molecular level]," says Prof. Sussman.

Prof. Sussman conducts much of his research at the Israel Structural Proteomics Center (ISPC), a facility for the study of protein structures. He helped establish the center, which is located on the Weizmann Institute campus, in 2003, and serves as its director. Scientists at the ISPC have revealed the structures of more than 50 proteins, investigated drug-protein interactions, and designed new proteins with novel functions. The ISPC has already earned an international reputation for its high-quality research and is widely regarded as a model facility, frequently visited by scientists from other institutions who wish to establish their own structural proteomics laboratories. "When you can see the molecules you are studying at atomic resolution," Prof. Sussman says, "it gives you enormous insight into so many biological questions."

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Prof. Joel Sussman is the incumbent of the Morton and Gladys Pickman Professorial Chair in Structural Biology.

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