A longer lifespan comes with a catch; an increase in the percentage of the population living into advanced old age brings with it a sharp increase in the number of people with Alzheimer’s disease and other dementias, placing unexpected emotional and financial burdens on loved ones. A University of California biostatistician predicts that Alzheimer’s diagnoses will quadruple by 2050, so that one in eighty-five people will have the disease.

The exact cause of Alzheimer’s disease is still unknown. The condition is characterized by two types of abnormal brain structures: amyloid-beta (Aß) plaques and neurofibrillary tangles. Aß plaques are sticky clumps of protein fragments that accumulate around and attack brain cells, leading to their death. Neurofibrillary tangles are twisted fibers of protein that build up inside the neurons of Alzheimer’s patients. The memory loss and communication problems typical of the disease don’t generally appear until after age sixty because it takes time for these structures to amass.

Eventually, Alzheimer’s kills, but not before it takes everything away from you.

— Alzheimer’s Association
Identifying the Cause

All people have Aβ proteins. The proteins carry out several functions for the brain, including cholesterol transportation and protection against free radicals. Alzheimer’s disease is associated with the pathological accumulation of Aβ proteins in specific regions of the brain; for example, patients lose their memories, but are still able to walk. The reasons why some people get Alzheimer’s and why certain regions are affected have been elusive because samples of brain tissue cannot be removed from living patients, making comparisons impossible.

A Better Way to Study Disease

Harvard Stem Cell Institute (HSCI) scientists use a different set of tools to understand disease. With the advent of induced pluripotent stem cell technology – the biological reprogramming of mature cells into stem cells – it is possible to generate stem cells from the skin of an adult Alzheimer’s patient and then direct these cells to become different types of brain cells. HSCI investigators can direct patient stem cells to become brain cells both affected and not affected in Alzheimer’s disease. Our scientists plan to examine the types and amounts of Aβ proteins generated by these cell types, and to look at how the different cell types respond to plaques.

None of the Food and Drug Administration approved treatments on the market for Alzheimer’s tackle the underlying cause of the disease. Rather, they attempt to alleviate symptoms associated with the loss of brain cells. Using stem cells, HSCI scientists can reveal potential targets for therapeutic intervention by studying the differences between brain cell types, and between those suffering from the disease and those who are healthy.

Screening for Treatments

Most current pharmaceutical research is aimed at preventing the formation of Aβ plaques by inhibiting the enzyme (called gamma-secretase) responsible for generating toxic versions of the protein. Both industry and academia have spent billions of dollars to develop thousands of compounds that target the enzyme. Instead of being tested on brain cell types affected by Alzheimer’s disease, these compounds are often first screened with non-brain cells or random collections of brain cells. The result is that the vast majority of the compounds are thrown out in these early screening rounds due to a lack of potency. This screening process may be causing the premature disregard of some of the most promising future drugs because the compounds are not being tested on diseased cells.

HSCI scientists are developing a screening method using induced pluripotent stem cells directed to become multiple brain cell subtypes in order to examine the effect of potential drugs in the cell types most relevant to Alzheimer’s disease. The new test will be able to examine how compounds act on tens of thousands of individual cells at one time. Preliminary tests of the screening method have allowed our scientists to detect Aβ proteins generated from single cells. The further development of this new technology will allow for a more careful examinations of the effects of potential drugs on certain cell types and, through collaborative efforts, screen through several types of compounds for those that correctly target the cells in the brain most affected in this devastating disease.

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