Treat aging, not the diseases of age, says geneticist

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After meeting four siblings from the same family, all of whom lived over 100 healthy years, Nir Barzilai, MD, asked himself, “What secret do they have in their lifestyle, in their blood, in their genes that allows them to live healthy and happy and productive lives?”

Dr. Barzilai and his research team have now studied over 600 families of centenarians—those who live past 100. They looked at “really old people who were independent and we tried to figure out [through their medical, social and psychological history] what is it in their blood content, in their genome that can help us understand them,” Dr. Barzilai said in a presentation at this year’s TEDMED conference.

“We also immortalized some of their white blood cells so we can study them even after they are dead,” he said. Dr. Barzilai is a professor in the departments of medicine and genetics at the Albert Einstein College of Medicine and directs the school’s Institute for Aging Research.

Before detailing his research team’s findings, Dr. Barzilai explored why so many people fear aging. Quoting Woody Allen, he said, “‘I’m not afraid of dying, I just don’t want to be there when it happens.’ But that’s not really what we’re afraid of.”

“We’re afraid of the diseases of aging,” he said. “We’re afraid of getting a disease and getting a treatment. The treatment is effective against the disease [but there are] side effects, and then we get another disease and another treatment and very soon we’re accumulating three or more diseases with many treatments that have side effects and also interaction between them.”

There are many age-related diseases. For cardiovascular disease, the risk of death can increase a thousand-fold as you grow older, Dr. Barzilai said. Cancer has a similar increase in risk the longer you live. “Treating one disease at a time, the most that you can expect is to exchange one disease for another,” he said.

“If you get a myocardial infarction, you walk into the emergency room, you get a stent or you get a bypass,” Dr. Barzilai said. “You know those people that are now saved from a local treatment to the

heart, in two or three years a lot of them are getting diabetes and cancer and Alzheimer's because we never treated or thought of treating their aging. Just one disease at a time, and that doesn't work so well."

What is different about centenarians

Dr. Barzilai presented data showing that many of the centenarians he studied were disease-free compared with the controls. Among the control group of noncentenarians, "everybody is pretty much healthy and then at a certain age they're starting to be sick, and at age 80 most of them are sick," he said. But in the centenarians that is all delayed. "They're starting to get sick later and at a later age a lot of them don't have diseases."

"You might say, 'OK, but after all we learned about their interaction between the environment and aging maybe [the centenarians are] just doing what the doctors are telling us to do now," Dr. Barzilai said. "The answer is no. Fifty percent of them are overweight or obese. Fifty percent of them are smoking. Less than 50 percent are doing even moderate exercise."

"We discovered clusters of mutations that changed the function of some proteins," he said. Some of the proteins, for example, are important to lipid metabolism. The centenarians Dr. Barzilai has studied, and their families, have high levels of HDL cholesterol, which is associated with some of their protein mutations.

And some of the centenarians have clustered functional mutations in their growth hormones, he said. "Which suggests actually that giving growth hormones to the elderly … is really not safe." Some drug companies are using Dr. Barzilai's data to develop drugs that target specific diseases.

"So how can we move toward targeting aging?" he asked. Animal models have played a significant role in his research, because they age in ways similar to humans. "In the lab we took worms and mice, we took flies and rats and primates, and treated them either by genetic manipulation or interaction with the environment or drugs, [some of which] are in human use, and we were successful in extending not only life span, but [also] health span, in those animals."

Dr. Barzilai gave an example. "There is a very interesting chemical that is called rapamycin, [which is] used in people after an organ transplant," he said. "It's an immune modulator [and it] affects the nutrient sensing pathway," and when given to mice they live longer.

In one study, researchers gave rapamycin to elderly people before immunization and “their immune response was better against the virus,” Dr. Barzilai said. “Unfortunately, this drug is still not safe for chronic use so it needs more development. What can we do in the meantime? How can we go from animal studies to human studies?”

A diabetes drug that may do more

Diabetic patients use metformin to control their condition, Dr. Barzilai said. “But … when you give it to animals they live longer and they live healthier … but it has curious side effects.”

“People with diabetes, if they’re on metformin, as compared to other drugs … have 30 percent less cardiovascular disease,” he said. And the occurrence of cancer is 30 percent less as well. Those patients also have less cognitive decline and the occurrence of Alzheimer’s disease is less, he said.

“Metformin can be a really great tool in order to target aging,” Dr. Barzilai argued. “Why am I saying that metformin is a tool? Well, first of all, we have to do the study and we have to do it right. With the help of the American Federation for Aging Research, we launched a study that’s called Targeting Aging with Metformin.”

In this study, Dr. Barzilai and his colleagues will select and randomize 3,000 elderly people. They will look at the onset and types of diseases and evaluate whether metformin changes the rate of aging, he said. The team will work with the Food and Drug Administration to approve metformin as a possible treatment for aging so that pharmaceutical companies can try to develop versions of the drug that are safe for chronic use among patients without diabetes.

“My colleagues have shown that even a modest increase in health span, like over two years, will result in $7 trillion in savings by the year 2050,” Dr. Barzilai said. “If we do that, we can really ask ourselves, ‘What if?’ What if, instead of taking care of our parents, our parents are going to take care of [our] children and our grandchildren? … This is not science fiction, it’s science now.”