People living today are enjoying a remarkable increase in longevity, with researchers and medical advances having added three decades to life expectancy over the last half century. Notable though, is what has not happened so far: how to delay the onset of common chronic diseases, reduce functional disabilities, and thereby expand not just the lifespan but what biological scientists are terming the “health span.”

“Health span is defined as quality of life over your lifespan,” said Janko Nikolich-Zugich, MD, PhD, chair of GSA’s Biological Sciences Section for 2016–17. “The period of your life over which you enjoy the quality of your life. The idea is to suppress the period of decline to as small as possible and thereby maximize the amount time during which a person enjoys healthier hearts and lungs and has better cognition.”

To create a longer health span, biological researchers are actively looking for ways to change the fundamental basis of aging—and as luck would have it, that may have a lot to do with the fundamental basis of many chronic diseases. “If you can delay aging, you may be able to delay a lot of these chronic diseases,” Nikolich-Zugich said.

New discoveries in four areas are creating excitement in the biological sciences:

- medications that may extend the health span
- discoveries on microbiomes within the human body
- ways molecules from younger organisms can be combined to rejuvenate organs in older organisms
- impressive results in cancer treatment through immunotherapies

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1. Biology of aging

Manipulations of a specific metabolic pathway are routinely extending life of laboratory animals. If these can be replicated clinically, people could move from the current situation—where they already enjoy a life expectancy into the late 70s or early 80s—to one where they live to about 30 years longer than that—to 110 or so, Nikolich-Zugich said.

These interventions rely on “hunker down” signals to the body through caloric restriction. By cutting food intake by about one-third, mice, fruit flies, and other laboratory animals are living about a third longer with fewer chronic diseases.

People—being people—may not want to cut their caloric intake, but they are willing to take a pill. Researchers are finding that currently available drugs may produce these life-extending effects without the need for humans to cut out their Big Macs, Nikolich-Zugich said. For example, rapamycin (marketed as sirolimus) was administered to animals in their last third of a typical lifespan, and the result was extended longevity, indicating that the benefits could help those living today.

The antidiabetic drug metformin showed similar effects in animals and is being tested in the TAME (Taming Aging With Metformin) trial in humans for just this purpose. Rapamycin is an immunosuppressant currently used in high doses to prevent rejection of transplants. Preclinical (animal) research indicates that lower doses of the drug have beneficial effects on the aging process, but the drug causes insulin resistance and has other adverse effects. Fortunately, metformin, an antidiabetic agent that also tends to make people lose weight, can simultaneously counter rapamycin’s negative effects and enable organisms to benefit from the drug’s effects without reducing their caloric intake.

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That these drugs are already approved by the Food and Drug Administration and in wide use throughout the world is a real plus, Nikolich-Zugich explained, in that an expensive research-and-development process need not precede regulatory approval. “Getting these drugs into humans to determine if we have ‘magic bullets’ is really exciting and a new frontier,” he concluded.

2. Microbiomes in human health and disease

The human intestinal tract is fascinating—there are 10 times as many bacteria in the gut as there are human cells in the entire body. The digestive system doesn’t even develop or function properly unless it is colonized with certain symbiotic bacteria. Given this important role of microbes in human health, perhaps it’s not surprising that links are now being made between these bacteria and disease in people.

Surprising, though, are the types of diseases being linked to intestinal microbiomes. Arthritis, depression, and autism are just some of the conditions under study as having a pathogenic link to recently discovered segmented filamentous bacteria (SFB), Nikolich-Zugich said. The importance and number of previously unknown new bacterial species that live in our gut were recognized only over the past few years; they do not grow in the dish when plated, causing scientists to miss them in the past. Researchers have used high-throughput DNA sequencing to find that 95% of the bacteria in the colon were not the familiar *Escherichia coli* and *Salmonella* species.

Electron microscopy has enabled study of tissue samples where the beneficial gut bacteria attach and form microfilms on intestinal epithelial cells that line the gastrointestinal mucosa. That then prevents more harmful gut bacteria, such as SFBs, from invading the body. As people age, the epithelial barrier is known to get weaker, and investigators are looking at the possibility of an aging-related change in the intestinal microbiome as one cause of this, potentially leading to increased inflammation in the body. Clinical studies have shown benefits of fecal transplants in Crohn disease and chronic diarrhea, and
while scientists don’t know for sure why they work, certain gut bacteria are likely a critical, beneficial factor in numerous chronic diseases of aging.

3. Discoveries via parabiosis

With a nod to the science fiction surrounding Frankenstein, scientists have known for nearly two centuries that stitching together the skin of two organisms can lead to their sharing of blood vessels and circulation. In the mid-20th century, it was found that stitching a young and old organism together could make some tissues that can grow “old” or grow “young.” This field of “heterochronic” parabiosis, has experienced a rebirth in the 2000s, Nikolich-Zugich said. In animal experiments, this led to identification of “rejuvenating” and “aging-inducing” individual molecules. The challenge now is to see if current discoveries can translate into clinically applicable means of regrowing, regenerating, and/or remodeling tissues such as skeletal or heart muscle and neurons to their youthful appearance and function.

If successful, such components of tissues could be made into pharmaceuticals or biologic agents that could enter clinical testing for diseases such as cardiomyopathy.

“Science is unpredictable,” Nikolich-Zugich said, “but parabiosis is providing some exciting results and could yield promising candidates for therapy in the near future.”

4. Cancer immunotherapies

As Americans learned during Jimmy Carter’s successful battle with stage 4 melanoma, immunotherapies are gaining “miracle drug” status for tumors even when they have metastasized in a 92-year-old patient like the former president. Cancer immunotherapies rely on ways of taking the brakes off the body’s immune system and creating an army of T-cells directed at the tumor.

Two approaches are involved. The patient’s T cells are isolated ex vivo (outside the body) and engineered to carry cellular chimeric antigen receptors (CARs) that bind to cancer cells in such a way that the receptors trigger cellular signaling machinery to destroy cancer. When the cells are expanded ex vivo and then returned to the patient, they provide a large army that immediately targets the tumor. Checkpoint inhibition provides a second mechanism for increasing the antitumor actions of the patients’ T cells by interfering with natural inhibitory mechanisms that dampen the function of the immune system.

Most cancers occur in people older than 50, but early clinical trials often have younger participants. This presents the greatest challenge for this approach to cancer treatments. “It would behoove us to study immunotherapies in aging patients,” Nikolich-Zugich said.

5. Health is not the absence of disease

“Based on the animal models, it should be possible to extend the human lifespan into the early 100s, with a commensurate extension of the health span, with people being healthy until the end—all but the last 2 years or so,” concluded Nikolich-Zugich. “Health is not the absence of disease, but the ability to live in a satisfying manner—including your social contacts, your spiritual, sexual, and economic well-being, and everything else.”

In support of this effort, GSA plays an important role, the Biological Sciences chair added. “GSA should lead the way by integrating what we have between the sections and moving together in a way that will be meaningful,” he said. “People have long searched for a fountain of youth, and it’s important not to be unreasonably optimistic. But I can confidently say that we are in an era where we as a field will be contributing decisively to human health.”

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For further reading


News reports on the TAME trial:


https://www.fightaging.org/archives/2014/05/suggesting-the-combined-use-of-metformin-and-rapamycin/


Colbert “Cheating Death” segment: http://www.cc.com/video-clips/3rw0tz/the-colbert-report-cheating-death---aging---women-s-health

Images for Reference

http://www.nature.com/news/ageing-research-blood-to-blood-1.16762

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