The single biggest risk factor for the vast majority of chronic diseases is old age. For many diseases, in fact, a person's birth date is a larger red flag than all other known risk factors combined. But for too long, physicians thought that the aging process was impossible to modify or slow down. Like death and taxes, growing old—and the medical problems that come with it—was considered inevitable. That's starting to change. In this special news focus on aging, *Nature Medicine* looks at the progress being made in drug interventions for the elderly and the hurdles that remain in the pursuit of a pharmaceutical elixir for healthy aging.

Drug development for progeria yields insights into normal aging

Life is short—especially for children with Hutchinson-Gilford progeria syndrome, a rare disease in which individuals rapidly develop symptoms of old age, such as hair loss, wrinkled skin, arthritis and cardiovascular weakness. Affected patients typically die by the time they enter their teens. Medications exist that can ease symptoms, but there are currently no drug treatments approved specifically for this disease.

So, there was excitement when a team led by Leslie Gordon, a pediatrician at Brown University's Warren Alpert Medical School in Providence, Rhode Island, reported that an experimental drug called lonafarnib—first developed for treating cancer in 1990s but later abandoned after it failed in that setting—might buy some time for children with progeria. "We learned for the first time that progeria can be improved," says Gordon, who cofounded the Progeria Research Foundation in 1999 after her son Sam was born with the disease. In a two-year, open-label trial involving 25 affected children, lonafarnib offered slight but statistically significant improvements in bone density, vascular stiffness and other disease symptoms[1].

Progeria Research Foundation

Good old boy: Kids like Sam Berns provide drug leads for the elderly.

The findings, published last year, have since buoyed the small but active progeria community. And the results have potentially wider implications for researchers studying the much larger field of 'normal' aging in the elderly, too.

"With the discovery of the genetic defect [behind progeria] and the opportunity to understand exactly what goes on, it has now become quite clear at the molecular level that this is an interesting model of aging," Francis Collins, director of the US National Institutes of Health (NIH) in Bethesda, Maryland, told *Nature Medicine*. Ten years ago, Collins led the team that first demonstrated the cause of progeria: mutations in the gene encoding lamin A, an important structural component in the membrane that lines the cell nucleus[2].

Of note, mutated lamin A protein (known as progerin) also accumulates in the cells of elderly people without progeria, albeit at much lower levels and with a slower buildup[3]. Thus, some researchers expect that efforts aimed at finding therapies to treat progeria—a disease that affects just one in 8 million newborns—could serve as test bed for drug development to prevent normal aging, a problem that affects almost everybody.

"At the cellular level, progeria and normal aging are remarkably similar," says Tom Misteli, a cell biologist at the NIH's National Cancer Institute. "We have found our animal models of [progeria] to be very useful investigating different questions relevant for normal aging, but at an accelerated pace, which makes the work much easier to perform," adds Carlos López-Otín, a biochemist at the University of Oviedo in Spain. For example, rapamycin and resveratrol—two compounds thought to slow the aging process generally (see page 520)—also delay symptoms of progeria in mouse models of the disease[4,5].

Finding a repurpose

In addition to lonafarnib, two other drugs have been clinically tested in children with progeria: pravastatin and zoledronic acid, both of which, like lonafarnib, block the process of farnesylation, which anchors the toxic progerin protein to the nuclear membrane. Pravastatin and zoledronic acid were tested together in a recently completed, four-year trial involving 15 children with progeria in France (the results of which have not been made public), and they are currently being evaluated in a triple-drug regimen, along with lonafarnib, in a two-year trial involving 45 children in the US.

Both pravastatin (a cholesterol-reducing statin) and zoledronic acid (a bisphosphonate for treating osteoporosis) are already approved to treat specific age-related diseases in the general population. If they prove beneficial in progeria, could they now be used as antiaging agents more broadly? "These are the kinds of pathways toward the future that deserve a lot of attention," says Collins.

There are important distinctions between progeria and normal aging, though. For instance, children with progeria age without cancer, neurodegenerative disease or cognitive decline. Even atherosclerosis in progeric children presents differently, as cholesterol deposition occurs too slowly to affect them over the course of their lives. Thus, not everyone is sold on the idea that drugs for progeria will get prescribed more widely. "Studying progeria addresses some mechanisms of cellular aging, but it doesn't address many of the common problems as we age," says Howard Worman, a physician-scientist at Columbia University in New York. "It's at best giving a piece of the puzzle."

Nonetheless, Collins expects that the valuable insights generated by progeria studies into even small aspects of the aging process could someday lead to much larger rewards. "I think we can celebrate the fact that the study of this very rare disease has shed light on a universal condition," he says.

Kevin Jiang

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