

# CANCER DRUG MIGHT HELP KIDS WITH FATAL "AGING" SYNDROME

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Johns Hopkins scientists have discovered that a drug currently being tested against cancers might help children with a rare, fatal condition called Hutchinson-Gilford progeria syndrome, which causes rapid, premature aging.

Children with progeria appear normal until they're 6 months to a year old, but then begin developing symptoms normally associated with old age -- wrinkled skin, hair loss, brittle bones and atherosclerosis, which usually causes their deaths by about age 13. There's no known treatment.

But the new Hopkins research, and similar results from other labs, shows that a class of drugs known as farnesyl transferase inhibitors, or FTIs, can reverse an abnormality in laboratory-grown cells engineered to mimic cells from progeria patients. Such cells have nuclei that aren't round like normal nuclei but instead have multiple "lobes" and can even look like a cluster of grapes or bubbles.

In the laboratory, however, treating these engineered cells with an FTI already in clinical trials in cancer patients restored the cells to a normal appearance, the researchers report Sept. 26 in the advance online section of the [\*Proceedings of the National Academy of Sciences\*](#). The drug blocks the first step in processing the faulty protein that causes the syndrome.

"We've been hopeful that our two decades of research on how proteins are processed and modified in cells might ultimately help people with certain forms of cancer," says [Susan Michaelis, Ph.D.](#), professor of [cell biology](#) at [Johns Hopkins' Institute for Basic Biomedical Sciences](#).

"But for progeria, we and others only recently learned that it involves the one of the modified proteins we've been studying, a nuclear protein called lamin A. As a basic scientist, it is really exciting to have leapfrogged from studying a fundamental process to finding evidence that an existing drug might be useful in treating a devastating disease in children," she says.

Michaelis emphasizes that no one knows whether making the cells' nuclei look normal will be enough to reverse the disease process or slow it down. "If it does, this will be a wonderful example of how understanding basic biology can lead to new medical treatments," she says.

The class of drugs they tested prevents the first step in cells' processing of certain critical proteins in yeast and mammals. For more than 20 years, Michaelis has been studying this complex process.

The process starts with a fully assembled protein, then adds a fatty appendage called farnesyl very close to the protein's end, and then a tiny modification called a methyl group to a nearby building block. Finally, somewhat inexplicably, two proteins known to be modified in this way then undergo an additional step. For these two proteins, and maybe more, the modified end and the adjoining 15 building blocks -- a fraction of the proteins' original length -- are chopped off by an enzyme discovered in Michaelis's lab.

In yeast, the protein that gets the full treatment helps the single-celled organisms reproduce -- and the useful protein is the smaller part with all the fancy modifications. In cells' processing of lamin A in mammals, however, the plain, big chunk is the active part, and it's critical for the proper function and organization of cells' nuclei.

In children with progeria, however, a genetic mutation causes a piece of the original lamin A protein to be deleted, a discovery made by National Institutes of Health researchers and reported in 2003. The Hopkins researchers immediately noticed that also missing was the specific point at which the modified end would normally be chopped off -- a biologically crucial event.

"The normal mammalian protein, lamin A, doesn't have all those modifications; the modified part is thrown away," says Michaelis. "With the disease mutation, however, that fails to occur. Although the failure to make normal lamin A could have wreaked havoc in a number of ways, we hypothesized at the time that the problems in progeria arose specifically because the modifications persist."

So Michaelis and postdoctoral fellow Monica Mallampalli, Ph.D., set out to test that idea. Mallampalli genetically engineered a human cell line (HeLa) to have either of two mutations in the gene for lamin A. One mutation halted the process at the very beginning, by preventing addition of the fatty farnesyl appendage. The other affected the end of the process by preventing cleavage of the otherwise normal, fully modified protein.

"Neither has the correct lamin A protein, but only one has a modified protein hanging around," says Michaelis. "We found that only the cells with the farnesyl-modified protein had the problems seen in cells with the HGPS mutation."

Mallampalli also altered the version of the gene that produces the abnormal, persistently modified, disease-causing protein, called progerin, to uncover the effect of preventing the addition of farnesyl. Sure enough, even though the cells still didn't have normal lamin A, their nuclei looked normal when the faulty protein couldn't get modified.

The researchers then obtained an FTI compound made by Michael Gelb and Pravin Bendale at the University of Washington in Seattle to see whether interfering with the enzyme that adds farnesyl would have the same normalizing effect.

"We were thrilled that, as our genetic studies predicted, the experimental drug did the trick," says Michaelis. "Because FTIs are already in advanced clinical trials with cancer patients and seem to be quite well-tolerated, it's hopeful that they could be tested in patients with progeria fairly quickly."

Cancers are much more common than the progeria syndrome, which only affects about one in 8,000,000 births a year in the United States. Such rare disorders don't usually attract the attention of drug developers, but the fortunate coincidence that progeria is caused by a protein that requires farnesyl for processing means that existing drugs might help.

FTIs prevent addition of farnesyl to all proteins that have a particular molecular tag. In cancer, the key target among these proteins is one called Ras, which is activated by the same farnesyl-triggered process as lamin A and which promotes cancerous growth when there's too much of it.

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**On the Web:**

<http://www.pnas.org>

<http://www.progeriaresearch.org>