RACHEL FLYNN believes that if you can attack the enzyme ATR kinase, you can stop cancer in its tracks.

A New Tactic for Fighting Cancer

DEEPER UNDERSTANDING OF TELOMERES MAY LEAD TO TARGETED CANCER TREATMENTS / BY BARBARA MORAN

By a quirk of biology, every time an adult cell divides, a bit of DNA gets lopped off the end of the double helix. This seems like a recipe for disaster—imagine a crazed librarian ripping the last chapter off a book every time it got checked out. Soon, the book would be useless. So would truncated DNA, if not for structures called telomeres, long sequences of repetitive base pairs—the same meaningless TTAGGG over and over—that cap each end of our DNA. Every time a cell divides, it's a bit of telomere that gets chopped off, rather than vital genes.

But biologists have long understood telomeres to be a double-edged sword. When they get too short, cells stop dividing. We see this as aging: hair turns gray, skin sags. But some cells are able to keep their telomeres long, effectively becoming immortal and dividing forever. Sometimes, the immortal cells become a cancer.

Now, scientists led by Rachel L. Flynn, a School of Medicine assistant professor of pharmacology and experimental therapeutics and medicine, have found a new way to kill certain cancers by targeting mechanisms of telomere elongation. The research, funded by the National Institutes of Health, the Foster Foundation, and the Karin Grunebaum Cancer Research Foundation, and published in the January 15, 2015, issue of *Science*, may lead to new therapies for certain rare and deadly cancers that often appear in children.

Cells that are able to lengthen their telomeres, and thereby divide indefinitely, use two known methods to do so. The more common is to use an enzyme called telomerase, which is active in embryonic stem cells but repressed as cells become specialized. The less common method, and the one Flynn studies, is called ALT (alternative lengthening of telomeres). The ALT pathway is most prevalent in certain cancers, including the bone cancer

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pediatric osteosarcoma, and glioblastoma, a type of brain cancer.

"In terms of the possible clinical applications, this research could be a game changer," says Karen Antman, provost of the Medical Campus and dean of MED. "This exciting finding could allow us to target any cancer that uses the ALT pathway to maintain telomeres. Such cancers are often resistant to common treatment options and have a poor prognosis."

Although discovered almost two decades ago, the ALT pathway is still poorly understood, according to Flynn. "We know that ALT is a mechanism that relies on recombination—one telomere basically hijacks another and uses it to replicate and elongate itself," she says. "But we didn't know how the pathway was maintained until now."

Flynn's paper suggests how cancer cells may be able to maintain the ALT pathway—by depending on an enzyme called ATR kinase. This enzyme is what's known as a "master regulator," she says. In a normal cell, it recognizes DNA damage when a cell is preparing to divide, and leads to either DNA repair or cell death. ALT cancer cells are constantly undergoing DNA repair at the telomere and are more reliant on ATR kinase activity than other cancer cells. Therefore, ATR promotes immortality by helping telomere elongation. Attack this enzyme, Flynn says, and you stop the cancer cell in its tracks.

"When you take ATR kinase out of the picture, it shuts down a whole chain of events," she says. "The cancer cell tries to promote telomere elongation, but it can't, and the cell dies."

There are several drugs already on the market that act as ATR kinase inhibitors, but none is used individually to treat these types of cancers. "The cool thing about these drugs is that the cancer cells actually die incredibly fast, as opposed to just slowing down cell growth," Flynn says. She also notes that since the drugs affect only cancer cells using the ALT pathway, normal cells should be left unharmed.

Flynn's next step is to get the existing drugs into clinical testing for targeted use. She is working with a group at Massachusetts General Hospital who will test them on mice with glioblastomas. Eventually, she hopes, her work will lead to a new treatment for these deadly diseases.

"The dream is that this research will eventually give kids with devastating cancers an option for individualized treatment," says Flynn, "something that will hopefully improve outcomes."

Every time a cell divides, a bit of telomere gets chopped off, rather than vital genes.

JACKIE RICCIARDI

Hipsters and the Fast Crowd

WIDE HIPS DON'T MAKE YOU A BAD BIPED / BY KATE BECKER

Anthropologists have long believed that a wide pelvis was bad for bipedalism. Kristi Lewton decided to test the assumption.

What can you learn from a pelvis? Among the qualities that make humans unique are two physical features: our way of walking and running upright on two legs and our newborn babies' very large heads. Those two traits of humanity meet at the pelvis, a set of bones that includes the ilium, ischium, pubis, and sacrum.

For more than 50 years, anthropologists have believed that the human pelvis was shaped by an evolutionary tug-of-war between the competing demands of bipedalism and childbirth.