Safeguarding the ends of linear chromosomes, known as telomeres, is essential for survival. We are trying to understand how cells keep tabs on their telomeres, how they control cellular proliferation and lifespan and how they regulate the interrelationship of aging and cancer.

Telomeres, the protective ends of chromosomes, become shorter each time cells divide. Often described as the genomic equivalent of the plastic caps that keep shoelaces from fraying, telomeres mask those ends from vigilant repair proteins, which might mistake exposed chromosome ends for broken DNA. When telomeres become critically short and fail to protect the chromosomes, cells cease to grow, or die.

On one hand, this process controls cellular and organismal aging by limiting the number of times cells can divide. On the other hand, this limitation on cellular proliferation ensures that cells do not become immortal and therefore represents a powerful tumor suppressive pathway, illustrating the intricate relationship between aging, proliferation and cancer formation.

Karlseder and his group have recently discovered that the relationship between telomeres and cancer extends much further than previously assumed. The group discovered that if cells take too long to undergo cell division, the telomeres send out a molecular SOS signal. These findings have dual implications for cancer therapy. First, they show how a class of anti-cancer drugs that slows cell division—known as mitotic inhibitors—kills cells. This class includes the commonly used chemotherapy drugs vinblastine, Taxol and Velcade. While these drugs have been in use for decades, it was unclear why they actually killed cancer cells. Research from the Karlseder lab has now demonstrated that exposure to mitotic inhibitors causes telomeres to lose their protective function, and the cells respond with stress signals that eventually lead to the death of cancer cells.

Second, these findings suggest ways to make therapies with mitotic inhibitors more potent; novel strategies could be used in combinatorial cancer chemotherapy regimes, which rely on the synergy between two or more drugs. The theory is that a multi-pronged approach might pack more of a wallop than a sledgehammer alone. By providing the link between mitotic inhibition, telomere deprotection and cell death, Karlseder’s lab continues to unravel the intricate links between chromosome ends, aging and cancer.

For more information, please visit www.salk.edu/faculty/karlseder

From left to right: Liana Goodwin, Daniel Lackner, Makoto Hayashi, Laure Crabbe, Candy Haggblom, Jan Karlseder, Nausica Arnoult, Tony Cesare, Teresa Rivera Garcia, Roddy O'Sullivan