The lab focuses on telomeres, protective elements at the ends of chromosomes that are critical for genome integrity and shorten with cell division. de Lange seeks to understand how telomeres are protected from the DNA damage response by a protein complex called shelterin, how they are replicated and maintained, and how telomere shortening contributes to tumor suppression and genome instability in cancer.

Research in the de Lange lab focuses on human and mouse telomeres, which are made up of long arrays of double-stranded TTAGGG repeats that end in a single-stranded (ss) 3’ overhang. The lab identified a six-subunit protein complex, which they named shelterin, that specifically binds to telomeres. de Lange and her colleagues determined the fate of telomeres lacking one or more of the six shelterin subunits, showing that cells perceive their natural chromosome ends as damaged DNA when shelterin is compromised.

Shelterin represses six distinct DNA damage response pathways. These include the two main DNA damage signaling pathways, initiated by the ATM and ATR checkpoint kinases, and the DNA double-strand break (DSB) repair pathways involving homology-directed repair (HDR) and non-homologous end joining (NHEJ). Shelterin also protects telomeres from inappropriate resection by nucleases. Shelterin is compartmentalized such that different subunits repress distinct DNA damage response pathways.

de Lange's group aims to determine the mechanism by which each shelterin subunit inhibits its designated pathway. A major mechanistic insight came from the identification of the t-loop structure of telomeres in which the single-stranded overhang is inserted in the double-stranded repeat array of the telomere, thereby hiding the telomere end from the DNA damage response. This structure is formed by the TRF2 component of shelterin. Since TRF2 is responsible for the repression of the ATM kinase pathway and NHEJ, it is likely that the t-loop structure is critical to prevent these two pathways from acting inappropriately on chromosome ends. In addition, the lab showed that POT1 prevents ATR kinase activation. POT1 binds to the telomeric ssDNA, thereby preventing RPA, the ssDNA sensor in the ATR pathway, from gaining access to the telomere end.

In addition to protecting telomeres, shelterin plays a major role in the maintenance of telomeric DNA. Shelterin recruits telomerase, regulates telomere length, and ensures the maintenance of the C-rich strand of telomeres by recruiting the CST (CTC1/STN1/TEN1) complex. CST is a trimeric ssDNA binding complex that is associated with DNA polymerase primase. The lab has determined the cryo-EM structure of CST/polprimase and studies how it is recruited by shelterin to mediate fill-in synthesis of the telomeric C-strand. They also have revealed an important role for CST/polprimase fill-in synthesis in the repair of DSBs.

The lab also aims to understand how telomere shortening limits cancer development and how telomere dysfunction can lead to genome instability in cancer. Recent data on cancer-prone families with excessively long telomeres showed that telomere shortening is a powerful tumor suppressor mechanism that prevents cancer formation. However, in checkpoint-deficient cells, telomeres can shorten to a point where they become a substrate for NHEJ and form dicentric chromosomes. By modeling this so-called telomere crisis in vitro, the de Lange lab showed that dicentric chromosomes lead to chromothripsis and kataegis, two extreme forms of mutational alteration observed in cancer.

SELECTED PUBLICATIONS
Schmutz, I. et al. TINF2 is a haploinsufficient tumor suppressor that limits telomere length. Elife 9, e51235 (2020).