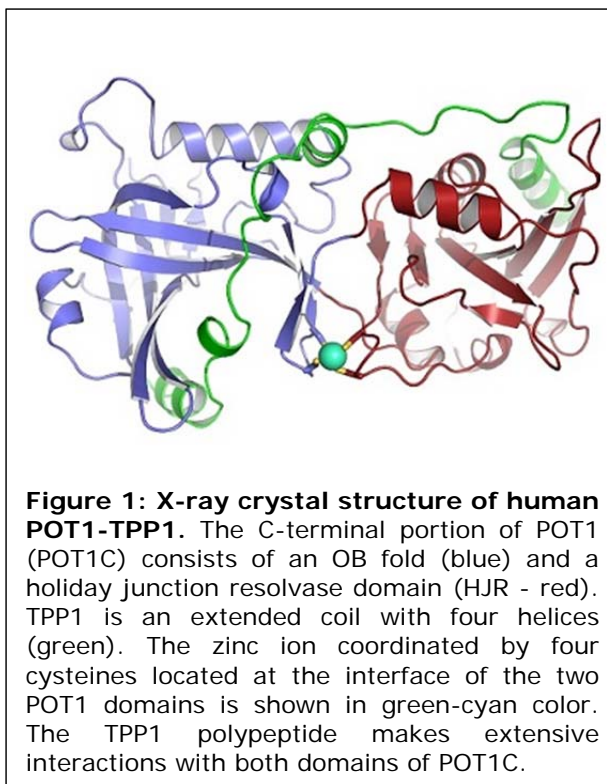


## Elucidating the Role of POT1 C-terminal Mutations in Cancer

The ends of our chromosomes are protected by nucleoprotein complexes known as telomeres. The hetero-hexameric shelterin complex (POT1, TPP1, TRF1, TRF2, TIN2 RAP1) binds single and double-stranded telomeric DNA and plays a critical role in telomere length regulation and maintenance [1]. POT1, a protein component of shelterin, binds single stranded telomeric DNA with high affinity and specificity using its two N-terminal OB folds. The C-terminus of POT1 is involved in TPP1 binding and together they are involved in regulating telomerase access to the telomeric overhang and suppression of undesired ATR dependent DNA damage response at telomeres. Naturally occurring mutations of POT1 are associated with familial melanoma and glioma and chronic lymphocytic leukemia [2-4]. How these two proteins interact with each other to form a functional telomeric complex and how POT1 naturally occurring mutations contribute to malignant cancer is currently unknown.

Using the method of single-wavelength anomalous dispersion (SAD) and a mercury derivative the structure of POT1 C-terminal domain (POT1C) in complex with its TPP1 interacting domain to 2.1 Å resolution was determined. The data was collected at SSRL BL12-2 and the study was published in [Nature Communications](#), 8:14928 (April 2017). The structure revealed that POT1C consists of an OB fold and a holiday junction resolvase domain both of which are involved in extensive contacts with the TPP1 polypeptide, a long coil with four helices (Figure 1). The atomic structure of POT1C-TPP1 was then used to design a host of biochemical and cell based assays geared toward understanding the role of POT1C naturally occurring mutations in cancer. Biochemical and cell based studies show that several of the POT1C cancer mutations partially disrupt the POT1-TPP1 complex. Partial disruption of the POT1-TPP1 complex affects POT1's affinity for the telomeric DNA overhang. Weak DNA binding by POT1 leads to persistent telomerase activity at telomeres and the generation of long telomeric overhangs. Long telomeric overhangs are fragile and susceptible to telomere loss. Significant telomere loss promotes undesirable DNA damage response at the end of our chromosomes, genomic instability and cancer.



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