# Lee Zou, PhD

Cancer is a complex disease driven by genetic and epigenetic alterations in the genome. To prevent these detrimental alterations, cells have evolved an intricate signaling network, called the checkpoint, to detect and signal problems in the genome. During cancer development, the activation of oncogenes and loss of tumor suppressors leads to genomic instability, rendering cancer cells increasingly dependent upon specific DNA repair and checkpoint signaling proteins to survive. **The Zou laboratory** is particularly interested in understanding how the checkpoint detects DNA damage and genomic instability, and how the checkpoint can be targeted in cancer therapy. Our current studies are focused on the activation of ATR and ATM, the master sensor kinases of two major checkpoint pathways. Furthermore, we are developing new strategies to exploit the genomic instability and checkpoint addiction of different cancer cells in targeted cancer therapy.

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## Sensing and Signaling of DNA Damage

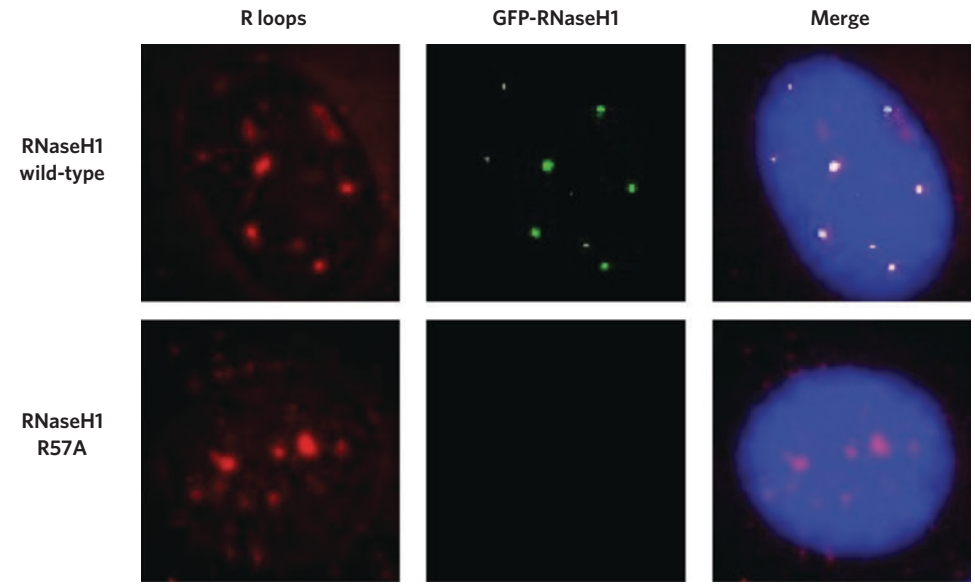
ATM and ATR are two master checkpoint kinases in human cells. In particular, ATR is the key responder to a broad spectrum of DNA damage and DNA replication problems. To understand how ATR is activated, we sought to identify the key DNA structural elements and sensor proteins that activate ATR. We have developed unique biochemical and cell biological assays to dissect the process of ATR activation. Using both proteomic and genomic approaches, we have identified a number of regulators of the ATR checkpoint and novel functions of this pathway. We are currently investigating the regulation of ATR in different physiological, pathological and therapeutic contexts, such as in response to oncogenic stress, in radiation and drug resistant cancer cells, and during cellular aging.

## Checkpoint, DNA Replication, DNA Repair, Telomeres and the Cell Cycle

The ATR checkpoint plays a key role in regulating and coordinating DNA replication, DNA repair, and cell cycle transitions. To understand these functions of ATR, we have identified new substrates of ATR involved in each of the processes. Furthermore, we are using a systems approach to interrogate how ATR orchestrates the network of DNA damage responses in different contexts. Our lab is also exploring the novel functions of ATR at specific chromosomal loci, such as telomeres and fragile sites. These studies may significantly advance our understanding of how the genome is safeguarded during the cell cycle.

## Checkpoint Signaling, Non-Coding RNA, and Epigenetic Regulation

The signaling of DNA damage through the checkpoint pathway is generally viewed as a cascade of protein phosphorylation events. However, recent studies by us and others have revealed that many types of modifications of proteins and chromatin—such as ubiquitylation, SUMOylation, methylation and acetylation—also contribute to DNA damage signaling. Furthermore, noncoding RNAs have also been implicated in this process. We are currently investigating how this network of




*This image shows that GFP-tagged RNaseH1 (green) localizes to sites of R loops (red) through binding to RPA. R loops are transcription intermediates that contain RNA:DNA hybrids and single-stranded DNA (ssDNA). RPA is a protein complex that recognizes ssDNA. RNaseH1 is an enzyme that suppresses R loops by cleaving the RNA in RNA:DNA hybrids. Wild-type RNaseH1 recognizes R loops through binding to RPA, but the R57A mutant of RNaseH1, which is defective for RPA binding, fails to recognize R loops.*

regulatory events is integrated to the DNA damage response.

## Checkpoint Inhibitors and Targeted Cancer Therapy

While the checkpoint is often compromised in cancers, certain checkpoint proteins are uniquely required for the survival of cancer cells because of the oncogenic events within them. We recently found that BRCA1/2 deficient cancer cells became resistant to PARP inhibitors through bypassing the functions of BRCA1/2 in homologous recombination (HR) and protection of stalled replication forks. Remarkably, inhibition of ATR disrupts the rewired HR and fork protection pathways in resistant cells, resensitizing them to PARP inhibitors. Our findings may bring about a new strategy to overcome the resistance of BRCA deficient tumors to PARP inhibitors.

## Selected Publications:

Buisson R, Lawrence MS, Benes CH, and **Zou L**. APOBEC3A and 3B activities render cancer cells susceptible to ATR inhibition. *Cancer Res.* (July 11, 2017, Epub ahead of print).

Nguyen HD, Yadav T, Giri S, Saez B, Graubert TA, and **Zou L**. (2017) Functions of RPA as a Sensor of R Loops and a Regulator of RNaseH1. *Mol. Cell* 65:832-847.

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Buisson R, Joshi N, Rodrigue A, Ho CK, Kreuzer J, Foo TK, Hardy E, Dellaire G, Hass W, Xia B, Masson J, and **Zou L**. (2017) Coupling of Homologous Recombination and the Checkpoint by ATR. *Mol. Cell.* 65:336-346.

Flynn RL, Cox KE, Jeitany M, Wakimoto H, Bryll AR, Ganem NJ, Bersani F, Pineda JR, Suvà ML, Benes CH, Haber DA, Boussin FD, **Zou L**. (2015) Alternative lengthening of telomeres renders cancer cells hypersensitive to ATR inhibitors. *Science*. 347:273-7.

Flynn RL, Centore RC, O'Sullivan RJ, Rai R, Tse A, Songyang Z, Chang S, Karlseder J, **Zou L**. (2011) TERRA and hnRNPA1 orchestrate an RPA-to-POT1 switch on telomeric single-stranded DNA. *Nature*. 471:532-6.