Li Lan, MD, PhD

Lan Laboratory

Boya Gao
Li Lan, MD, PhD
Laiyee Phoon
Jayanth Rao
Xudong Wang, PhD
Yao Xiao, MD
Haibo Yang, PhD
Haoran Yu

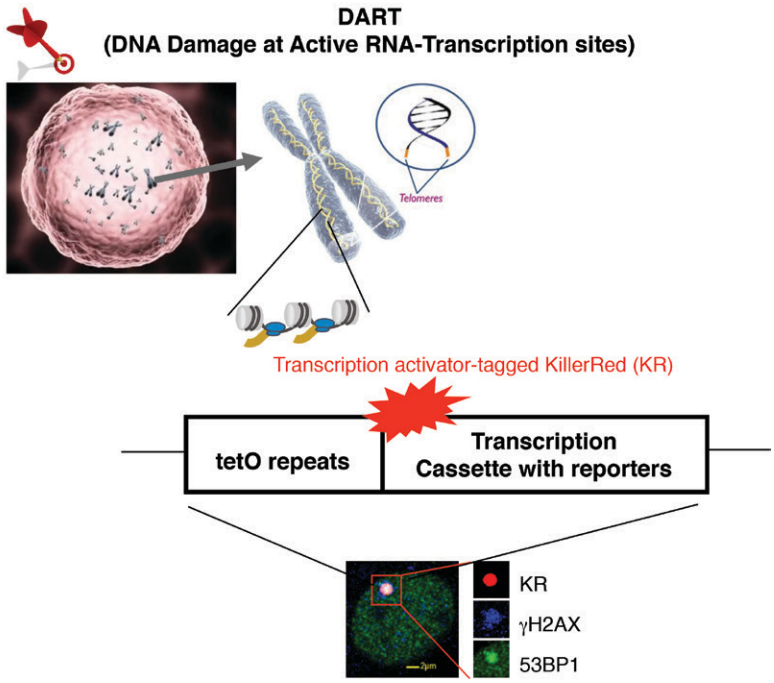
Elevated oxidative stress and DNA replication stress are common in cancers. On one hand, these intrinsic stresses in cancer cells promote tumor initiation and progression. On the other hand, these stresses render cancer cells sensitive to radiation and chemotherapies. **The Lan laboratory** is especially interested in understanding how cancer cells respond to oxidative and replication stresses through DNA repair pathways and developing new strategies to target these pathways in cancer therapy. The Lan lab developed the first molecular assay to study the oxidative damage response at specific chromosomal loci. Recently, we discovered and delineated a novel DNA repair pathway—mRNA-mediated repair—that protects the transcribed regions of the genome. We also study mechanisms of telomere protection, a cancer survival mechanism, in cancer therapy and investigate cross-talk between DNA damage response and immune response. We aim to open new avenues to understanding the oxidative DNA damage response in different chromosomal environments.

Targeting RNA modifying enzymes and R-loops in homologous recombination proficient breast and ovarian cancer

PARP inhibitors (PARPi) are DNA repair targeted drugs that have improved outcomes for tumors which are resistant to hormone therapy and exhibit homologous recombination (HR) deficiency (HRD). However, PARPi are effective only in ~10% of breast or ovarian cancer patients, and patients treated with PARPi inevitably develop drug resistance. Therefore, it is critical to identify HRD-independent vulnerabilities of cancer cells and find new therapeutic targets to complement PARPi therapy. My group has provided fundamental insights into HR in breast cancer and is one of the first to discover an RNA-loop and mRNA-dependent DNA Repair (RDDR) pathway, which is upregulated in cancer and maintains cancer cell survival. We set up platforms to validate RDDR activity, keep identifying novel factors of RDDR, develop and validate RDDR inhibitors for cancer therapy. We are also developing RDDR biomarkers to identify tumors harboring increased RDDR activity and predict drug sensitivity. We currently focus on understanding the function and targeting mRNA modifying enzymes of RDDR. RDDR inhibitors should be effective in treating a significant fraction of breast cancer patients, including those who do or do not have HRD and significant fraction of PARPi and hormone therapy-resistant breast cancer patients.

Targeting R-loop-dependent telomere protections upon damage in cancer

Oxidative DNA damage at telomeres is a source of genomic instability, which fuels both aging and tumorigenesis. To bypass senescence, cancer cells have to extend and maintain telomeres during cell division. While the majority of human cancers activate telomerase, a small but significant fraction (~10-15%) of cancers use the alternative lengthening of telomere (ALT) pathway to extend telomeres. We discovered a novel DNA repair pathway contributing to telomere



The Lan laboratory developed the DNA Damage at RNA Transcribed sites (DART) method to precisely introduce oxidative DNA damage at specific transcribed loci in a dose-dependent manner. This is achieved by site-specific positioning of the photo-excitable and ROS-releasing protein KillerRed (KR). This unique method provides a tool to understand how oxidative DNA damage response is differentially regulated in transcribed and un-transcribed regions, and in dividing and non-dividing cells.

maintenance. This pathway involves TERRA, a non-coding RNA generated at telomeres and R-loops. Our goal is to understand and develop new strategies to exploit the cellular dependency on telomerase, ALT, and R-loop-mediated repair pathways to kill cancer cells harboring high telomeric oxidative damage.

Crosstalk between DDR and immune response upon damage in cancer

DNA sensor cGAS triggers STING-dependent innate immune response and subsequently alters the tumor microenvironment to enhance anti-tumor immunity. The Lan laboratory focuses on 1) understanding how DDR inhibition and/or damage trigger cGAS-STING activation; and 2) how the function of cGAS in the nucleus regulates replication, transcription, and chromatin accessibilities in cancer cells. Our goal is to elucidate the function of cGAS and efficiently target it with the combination with DDR-based therapy in cancer.

Selected Publications:

Yang H, Wang Y, Xiang Y, Yadav T, Shi Y, Zou L, **Lan L*** FMRP Promotes transcription-coupled homologous recombination via Facilitating TET1-mediated m5C RNA modification De-methylation. *Proc Natl Acad Sci USA*. 2022 Mar 22; 119(12): e2116251119.

Petermann E*, **Lan L***, and Zou L*. Sources, resolution and Impact of R-loops and other RNA-DNA hybrids. *Nature Reviews Molecular Cell Biology* 2022. *In press*.

Ouyang J, Yadav T, Zhang JM, Yang H, Rheinbay E, Guo H, Haber DA, **Lan L**, Zou L. RNA transcripts stimulate homologous recombination by forming DR-loops. *Nature*. 2021 Jun;594(7862):283-288.

Zhu X, Wang X, Yan W, Li H, **Lan L**. Ubiquitination-mediated degradation of TRDMT1 regulates Homologous Recombination and therapeutic response. *NAR Cancer*. 2021. 3,1:zcab010.

Chen H, Chen H, Zhang J, Wang Y, Simoneau A, Yang H, Levine AS, Zou L, Chen Z, **Lan L**. cGAS Suppresses Genomic Instability as a Decelerator of Replication Forks. *Sci Adv*. 2020 Oct 14;6(42):eabb8941.

Chen H, Yang H, Zhu X, Yadav T, Ouyang J, Truesdell SS, Tan J, Wang Y, Duan M, Wei L, Zou L, Levine AS, Vasudevan S, **Lan L**. m5C modification of mRNA serves a DNA damage code to promote homologous recombination. *Nat Commun*. 2020 Jun 5;11(1):2834.

Tan J, Duan M, Yadav T, Phoon L, Wang X, Zhang JM, Zou L, **Lan L**. An R-loop-initiated CSB-RAD52-POLD3 pathway suppresses ROS-induced telomeric DNA breaks. *Nucleic Acids Res*. 2020 Feb 20;48(3):1285-1300.

Tan R, Nakajima S, Wang Q, Sun H, Xue J, Wu J, Hellwig S, Zeng X, Yates NA, Smithgall TE, Lei M, Jiang Y, Levine AS, Su B, **Lan L**. Nek7 Protects Telomeres from Oxidative DNA Damage by Phosphorylation and Stabilization of TRF1. *Mol Cell*. 2017 Mar 2;65(5):818-831.e5.

*Co-corresponding authors