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Significance

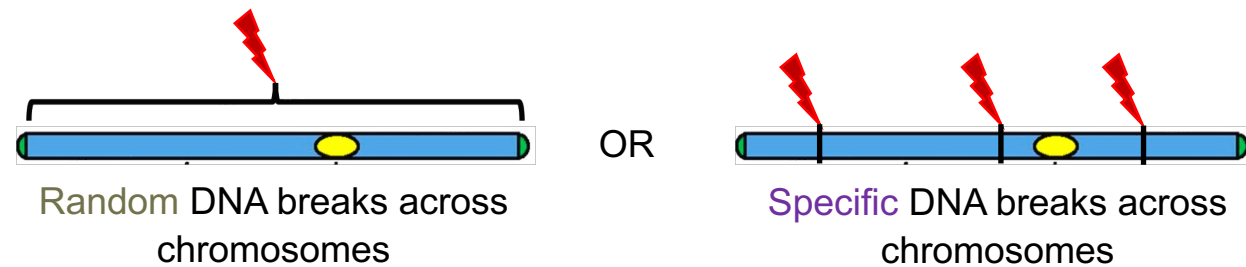
Identifying genomic biomarkers that predict response to therapy is critical for precision medicine. Yet characterizing cancers with an evolving and dynamic genome remains a challenge. BreakSight's vision is to address this challenge by harnessing new technologies that enable discovery of novel DNA sequence biomarkers from DNA break signatures associated with targeted cancer therapeutics and the unique biology of cancer cells.

Our technique, originally developed at Penn, identifies weak points in the genome of proliferating cancer cells, revealed by the treatment of different targeted cancer drugs or in the presence of cellular deficiencies that lead to heightened DNA damage. DNA break signatures discovered by our platform can offer a greater depth of understanding on drugs, the pathways they target, and mechanisms of genomic instability previously left uncharted.

Through our offered services, BreakSight can illuminate genome-wide landscapes of DNA damage and potentially new sequence biomarkers with site-specific precision.

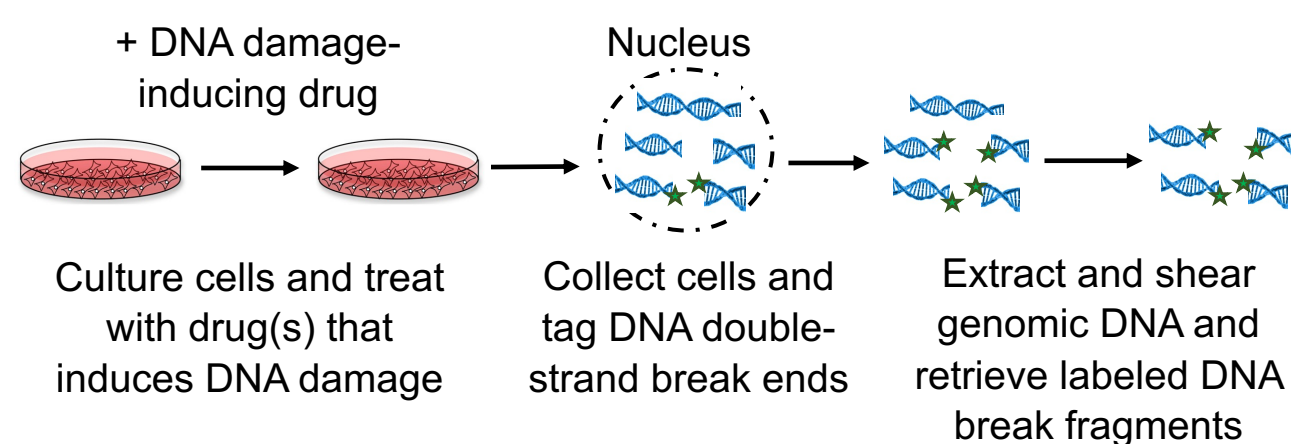
Targeted Cancer Drugs

A major class of cancer drugs target DNA Damage Response (DDR) pathways. This increases the level of DNA damage and breaks in cancer cells that are already defined by genomic instability.



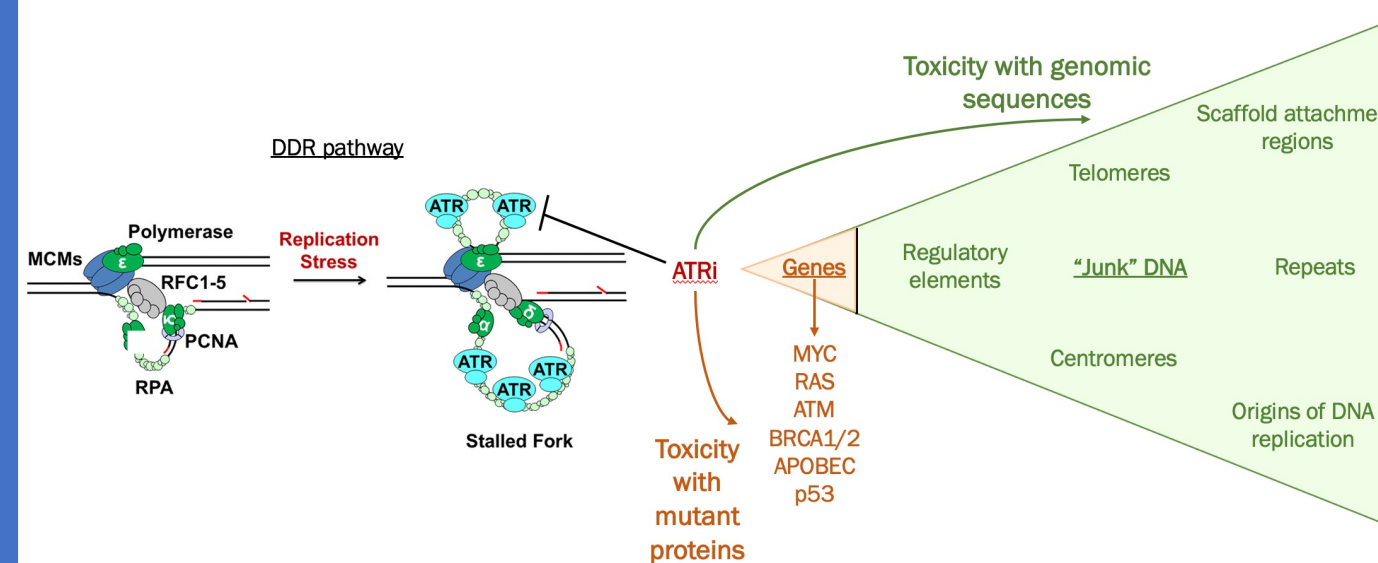
DNA breaks can occur randomly throughout the genome or at specific vulnerable sites. By selectively capturing DNA breaks along the cell's chromosomes, we can discover genomic sites and sequences that offer unique information about the drug's genome-wide effect. These sequences can potentially serve as markers of response to targeted treatments.

BrTL: an Assay to Capture DNA Double-Strand Breaks



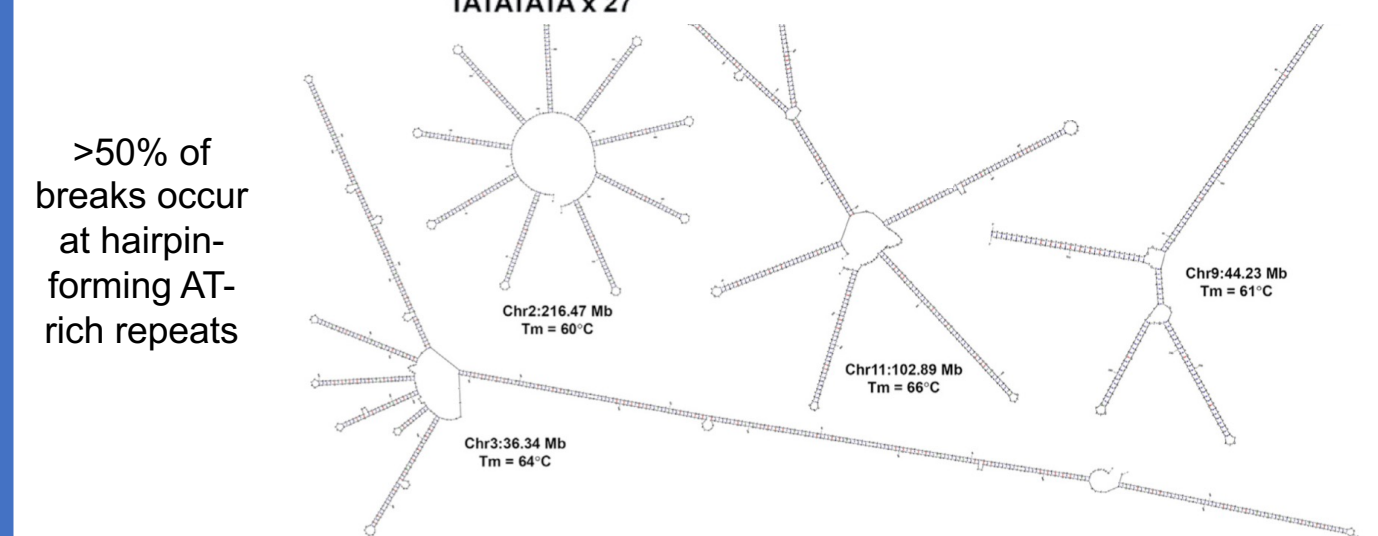
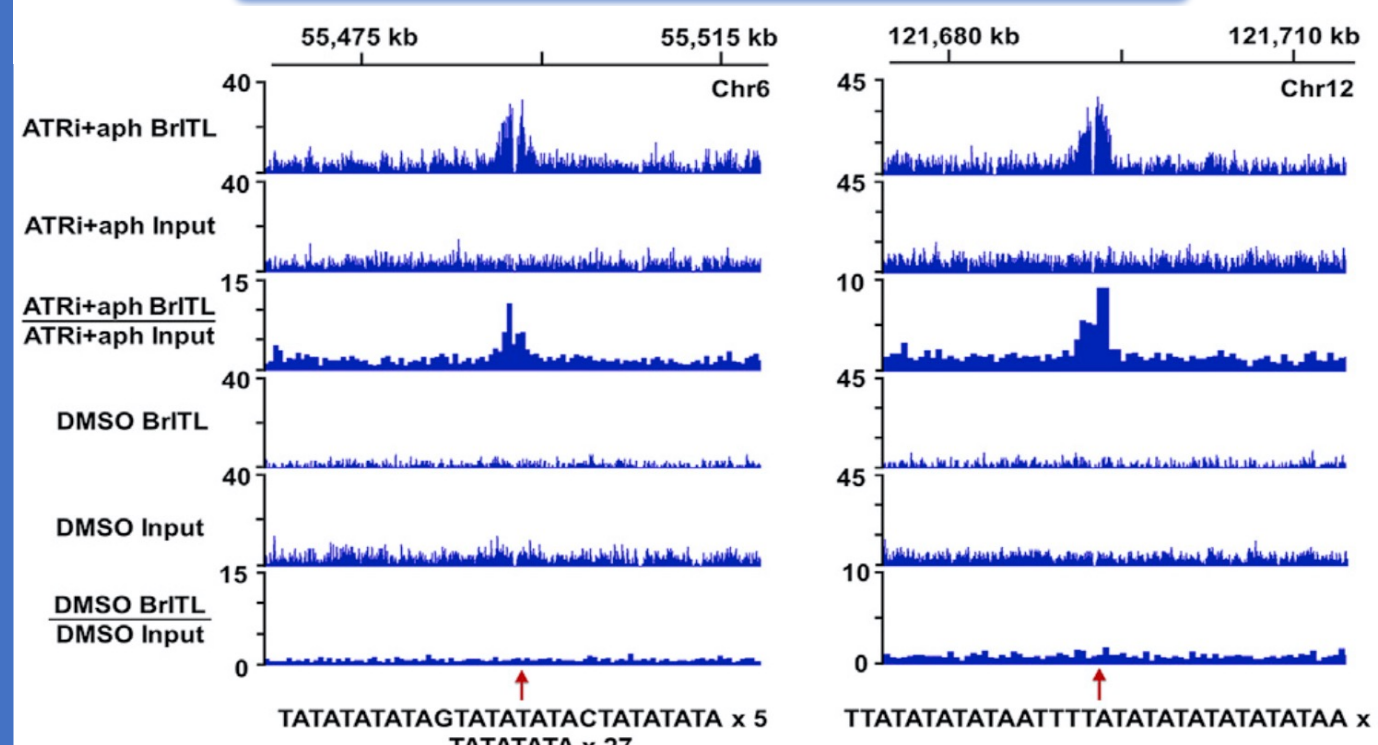
Sites of Breakage as Biomarkers of Drug Efficacy

DDR drugs such as ATRi can be synergistically toxic not only with abnormally expressed proteins in cancer, but also with DNA sequences, particularly in repeat-rich regions that are less well researched.



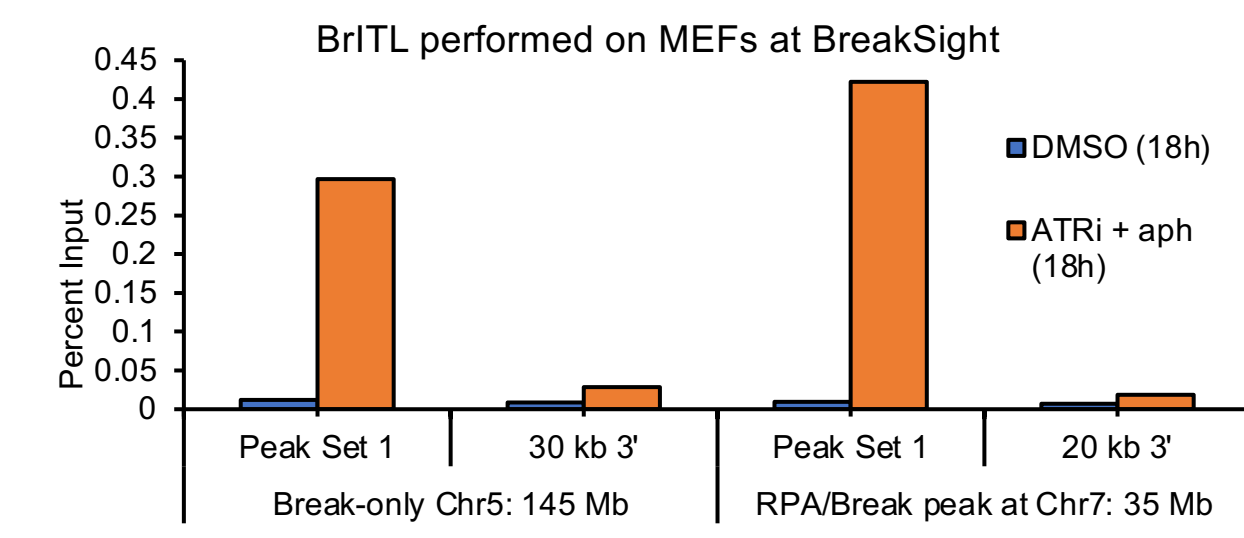
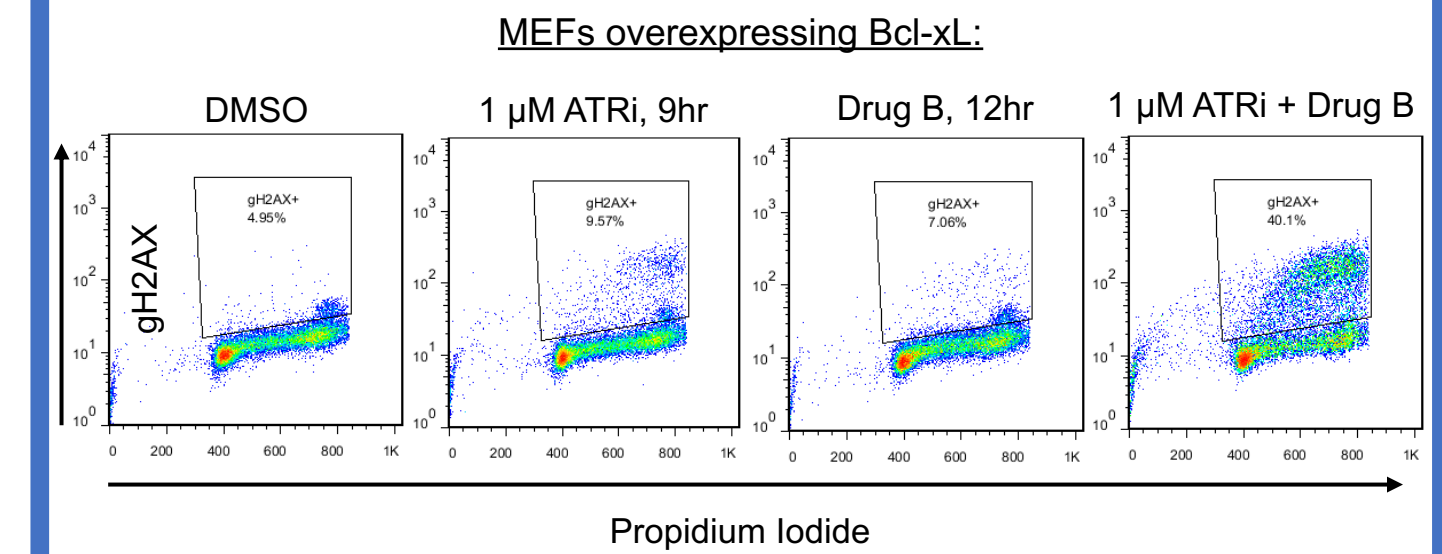
Pathogenic changes to these sequences in the cancer's genome can predict sensitivity to targeted treatments.

BrTL-Seq in MDA-MB-231 Cells Treated with ATRi



>50% of breaks occur at hairpin-forming AT-rich repeats
 "Genome-wide Identification of Structure-Forming Repeats as Principal Sites of Fork Collapse upon ATR Inhibition" (*Molecular Cell*, 2018)

BrTL at BreakSight



Performance of qRT-PCR on DNA break fragments retrieved by BrTL reveals the quantitative enrichment of DNA at different genomic regions, associated here with tandem repeats and hairpin-forming sequences.

Results and Applications

- BrTL-Seq is a method to capture, sequence, and locate sites of DNA double-strand breaks across the genome.
- BrTL-Seq has identified distinct structure-forming repetitive sequences as sites of breakage in MEFs and in MDA-MB-231 cells treated with low-dose aphidicolin and ATRi, a prominent targeted cancer DDR drug that has entered clinical trials.
- There is an unmet need in the field of precision medicine to uncover more diverse DNA sequence biomarkers of drug benefit. Nearly all current DNA biomarkers exist as mutations in expressed genes, which constitute only ~2% of the entire genome. BreakSight's technology can unlock the rich, informative potential of the remaining 98%.
- Overall, DNA break signatures and DNA damage insights revealed by BreakSight's platform of services can ultimately pave the way for discovering new actionable biomarkers that predict therapeutic benefit from the growing number of targeted treatments being developed to treat cancer.