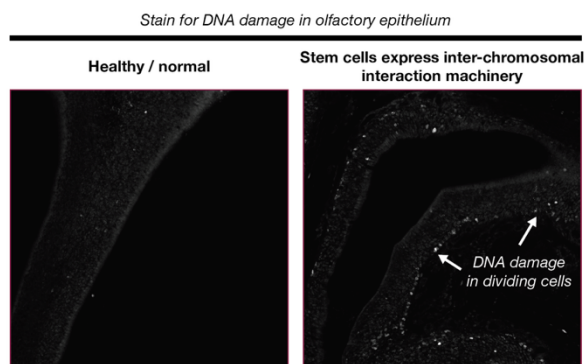


The Florence and Herbert Irving Endowment

Our lab studies one of biology's most elegant puzzles: how does each olfactory neuron choose to express just one olfactory receptor from among hundreds of possibilities? Over the past two decades, we discovered that neurons solve this problem by physically “Velcroing” DNA elements from different chromosomes together, creating stable interchromosomal contacts that lock in a single receptor choice for the life of the cell.

This mechanism is exquisitely controlled. The molecular machinery that drives these chromosomal contacts is normally restricted to non-dividing cells like neurons, protecting dividing cells from the genome instability that such contacts could cause. But a striking pattern in cancer genomics suggests this protection can break down: many tumors carry highly reproducible chromosomal translocations, whereby the same genomic regions are fused together across patients and cancer types, with a specificity that mirrors what we observe in olfactory neurons.



Stain for DNA damage in mice where dividing stem cells express interchromosomal interaction machinery that is normally only in mature neurons.

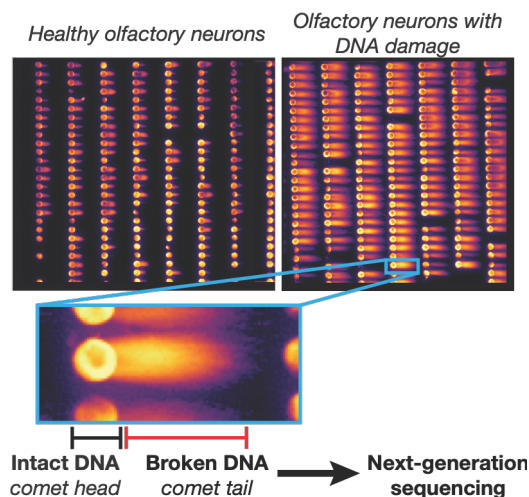
The Florence and Herbert Irving Endowment allows us to pursue the transformative idea that these cancer-associated translocations may arise through the same interchromosomal interaction machinery we study in neurons. Our current work spans five directions:

- **DNA damage in dividing cells.** We are testing whether aberrant expression of neuron-specific chromosomal “Velcro” proteins in dividing cells causes DNA damage and drives cancer.
- **DNA breaks in olfactory neurons.** Using a novel high-throughput sequencing approach (COMET-seq), we are mapping the precise locations and rates of DNA breaks in

olfactory neurons.

- **Recurrent cancer translocations.** We are developing genetic tools to detect and study interchromosomal interactions at loci that are frequently translocated in human cancers.
- **Therapeutic discovery.** We are leveraging the unique properties of olfactory neurons to screen for small molecules that can weaken pathological interchromosomal contacts.
- **Structural biology.** In collaboration with biophysicists, we are investigating how DNA sequence and three-dimensional genome architecture govern the stability of these interactions.

By connecting olfactory neurobiology, cancer genetics, genomics, and biophysics, we aim to uncover a fundamental mechanism of genome instability and to open new avenues for understanding and ultimately preventing the chromosomal catastrophes that drive tumor progression. The Irving Endowment made this cross-disciplinary vision possible, enabling our lab to bring a fresh perspective to one of cancer biology’s most enduring mysteries.



COMETseq allows identification of the specific locations in the genome where DNA breaks occur.