# Stony Brook University
# The Graduate School

Doctoral Defense Announcement

## Abstract

**Chromosomal instability accelerates the evolution of resistance to anti-cancer therapies**

By

**Devon Lukow**

Aneuploidy is a ubiquitous feature of human tumors, but the acquisition of aneuploidy is typically detrimental to cellular fitness. To investigate how aneuploidy could contribute to tumor growth, I triggered periods of chromosomal instability (CIN) in human cells and then exposed them to a variety of different culture environments. While chromosomal instability was universally detrimental under normal growth conditions, I discovered that transient CIN reproducibly accelerated the ability of cells to adapt and thrive in the presence of anti-cancer therapeutic agents. Single-cell sequencing revealed that these drug-resistant populations recurrently developed specific whole-chromosome gains and losses. Along with collaborators, we independently derived one aneuploidy that was frequently recovered in cells exposed to paclitaxel and found that this chromosome loss event was sufficient to decrease paclitaxel sensitivity. Finally, we demonstrated that intrinsic levels of CIN correlate with poor responses to a variety of systemic therapies in a collection of patient-derived xenografts. In total, my results show that while chromosomal instability generally antagonizes cell fitness, it also provides phenotypic plasticity to cancer cells that can allow them to adapt to diverse stressful environments. Moreover, these findings suggest that aneuploidy may function as an under-explored cause of therapy failure in human tumors.

**Date**: August 24, 2022
**Time**: 2:00pm
**Place**: Virtual Conferencing*

**Program**: Genetics Program
**Dissertation Advisor**: Jason Sheltzer

*If an outside member of the community would like to attend the defense, please contact the Stony Brook Genetics Program Director (Martha.Furie@stonybrookmedicine.edu)