The Graduate School of Biomedical Sciences
Cancer Biology

Announces the PhD Thesis Defense of

SUMEET NAYAK

TRANSLESION SYNTHESIS MEDIATED REPLICATION GAP SUPPRESSION, A CANCER VULNERABILITY

Wednesday, July 22, 2020 at 10 a.m. Via Zoom Meeting

Error-free DNA replication is paramount to maintaining genomic integrity. Despite being highly regulated, the process of DNA replication is often challenged by various intrinsic and extrinsic sources of replication stress. Failure to maintain the DNA replication quality reduces genomic stability, cell survival and results in diseases, such as cancer. Thus, cells rely on the replication stress response that detects perturbations in DNA replication and pauses or arrests cellular replication. Similar to other intrinsic replication obstacles, oncogene expression also induces the replication stress response that acts as a barrier to cancer, thereby mystifying how cancer develops.

Here, we demonstrate that oncogene expression, similar to other replication stress inducing agents, induces single-stranded DNA (ssDNA) gaps that reduce cell fitness unless counteracted by translesion synthesis (TLS). Moreover, we find that TLS subverts the replication stress response in a wide range of cancer cell lines indicating that TLS is a previously unappreciated and unique cancer vulnerability. Mechanistically, we reveal that upon replication stress, TLS restricts replication fork slowing, reversal, and fork degradation, while maintaining continuous replication. Furthermore, we demonstrate that a small molecule inhibitor targeting the TLS factor, REV1, not only disrupts DNA replication and cancer cell fitness, but also synergizes with other therapies that induce replication gaps. Thus, our study places TLS at the center of cancer cell fitness as a necessary adaptation to overcome replication stress.

Mentor	Dissertation Exam Committee
Sharon Cantor, PhD	Craig Ceol, PhD (Chair)
	Craig Peterson, PhD
	Kendall Knight, PhD
	Paul Kaufman, PhD
	Mitch McVey, PhD (Tufts University)- External Member