

**Stony Brook University
The Graduate School**

Doctoral Defense Announcement

Abstract

Specification of Origins of DNA Replication in *Yarrowia lipolytica*

By

Narges Zali

The regulation of DNA replication is critical for maintaining genomic integrity and stability. Disruptions in replication processes can lead to severe consequences, including genetic defects during germ cell production, disorders such as autism and schizophrenia, and genomic instability in somatic cells, which are linked to cancer. Both *Yarrowia lipolytica* and humans lack key domains in the origin recognition complex (ORC) responsible for sequence-specific origin recognition. This shared feature suggests potential mechanistic similarities in how ORC identifies replication origins and initiates DNA replication in these organisms.

Despite its differences from higher eukaryotes, *Y. lipolytica* provides a simplified model for studying replication due to its smaller genome, making it an ideal system for identifying the key steps and components involved in origin specification. In this study, I characterized replication origins across all six chromosomes of *Y. lipolytica* using high-throughput sequencing, genetic manipulation, and biochemical approaches. The results revealed a novel sequence motif, YATR.....C.AWTT.....Y.YAA, which includes major and minor groove contacts critical for ORC and CDC6 binding. Functional assays confirmed that disrupting these contacts abolished origin activity, underscoring the motif's critical role in replication initiation. Structural features, such as DNA bending, were also found to be crucial for origin function, highlighting the importance of sequence context and structural plasticity in replication initiation. These findings bridge critical knowledge gaps in replication biology, establishing *Y. lipolytica* as a valuable model for understanding eukaryotic DNA replication.

Date: February 4, 2025

Program: Genetics

Time: 1:00 p.m.

Dissertation Advisor: Dr. Bruce Stillman

Place: Cold Spring Harbor Laboratory, James Building, James Library Room 15.

To attend virtually, contact the Program Director at martha.furie@stonybrook.edu.