

# **Stony Brook University The Graduate School**

## **Doctoral Defense Announcement**

### **Abstract**

Understanding Lineage Dependencies in Rhabdomyosarcoma

By

**Cristian Cleary**

Rhabdomyosarcoma (RMS) is the most common extra-cranial solid tumor in the pediatric population of the United States by incidence. RMS is a high-grade neoplasm composed of cells that resemble skeletal myoblasts and express some markers of myogenic differentiation but do not form functional myotubes. The standard systemic therapy for RMS consists of intensive multi-agent chemotherapy and has not significantly changed in nearly five decades. These compounds target general vulnerabilities of rapidly dividing cells and are not specific to the pathophysiology of RMS. As such, treatment is accompanied by a suite of toxicities with potentially lifelong repercussions in pediatric patients. Approximately 20% of RMS patients present with metastatic disease at diagnosis, and the failure-free survival rate for these patients is only 30% after five years. Hence, there is a pressing need for specific yet potent therapies for RMS.

Recently, high-throughput, negative-selection genetic screens across cell lines of varying tumor types have identified myogenic differentiation 1 (MYOD) as the most potent genetic growth dependency specific to RMS. MYOD is a member of the basic Helix-Loop-Helix family of transcription factors and is a master regulator of muscle differentiation. MYOD is one of the predominant myogenic markers used in the clinical diagnosis of RMS but has long been thought to be functionally inactive in RMS, as this cancer does not complete the myogenic differentiation program. Considering the results of genetic screening in cancer cell lines, we hypothesized that RMS exploits the powerful transcriptional activity of MYOD to support neoplastic growth.

Using functional genetics and genomics techniques, we have identified the key structural elements MYOD requires to support RMS, the genes that modulate its expression, and cooperating proteins required for its function. Notably, we have found that its canonical heterodimerization partners, the E-proteins, exhibit functional redundancy, and knockout of all three family members is required to abolish MYOD activity. These findings further our understanding of MYOD's role in RMS pathophysiology on a molecular level and provide a foundational context for downstream developments to therapeutically target MYOD activity in this disease.

**Date:** May 16, 2023

**Time:** 12:30 pm

**Place:** Bush Auditorium, Cold Spring Harbor Laboratory

**Program:** Graduate Program in Genetics

**Dissertation Advisor:** Christopher Vakoc