University of Massachusetts Medical School

GRADUATE SCHOOL OF BIOMEDICAL SCIENCES

CANCER BIOLOGY PROGRAM

Ph.D. THESIS DEFENSE

YULIAN ELLIS

MENTOR: Alonzo Ross, PhD

FRIDAY 8/7/2015 at 10:00 a.m.

LRB 816

"EXPLORING NOVEL STRATEGIES TO OVERCOME RESISTANCE IN GLIOBLASTOMA MULTIFORME"

Glioblastoma multiforme (GBM) tumors are highly malignant and despite aggressive therapy, long-term survival is uncommon. We sought novel strategies to overcome resistance in GBMs.

In our first approach, the cellular responses of GBM cell lines to two new temozolomide (TMZ) analogues, DP68 and DP86, are reported. The efficacy of these compounds was independent of MGMT and the MMR pathway. DP68-induced damage includes interstrand DNA crosslinks, and there is a distinct cell cycle arrest with accumulation of cells in S phase that is not observed for TMZ. DP68 induces a strong DNA damage response and suppression of FANCD2 expression or ATR expression/kinase activity enhanced anti-glioblastoma effects of DP68. Collectively, these data demonstrate that DP68 is a novel and potent anti-glioblastoma compound that circumvents TMZ resistance.

Our second approach stems from previous work in which we showed that the combination of TMZ with Notch inhibition using a gamma secretase inhibitor (GSI) enhances GBM therapy. Efficacy of TMZ + GSI treatment is partially due to cells becoming senescent. We identified miRNAs that mimicked the effects of TMZ + GSI as an alternative approach to enhance GBM therapy. MiR-34a expression was highly upregulated in response to TMZ and TMZ+DAPT treatment. Exogenous expression of miR-34a revealed that it functions as a tumor suppressor and mimicked the *in vitro* effects of TMZ + GSI treatment. The down-regulation of Notch family receptors by miR-34a appears to mediate the anti-tumor effects we observed as constitutively active Notch intracellular domain (NICD) rescued cells from miR-34a anti-proliferative effects.

Mentor(s)

Alonzo Ross, PhD

Dissertation Exam Committee

Leslie Shaw, PhD (Chair)
Arthur Mercurio, PhD
Miguel Esteves, PhD
Daniel G. Jay, PhD