# Exploring the eIF4A RNA Helicase as a New Cancer Drug Target

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Abstract: The RNA helicase eIF4A (DDX2A) is highly expressed in many cancers and acts as an oncogenic driver in murine models of leukemia and lymphoma. The Wendel lab (MSKCC) described the precise mechanism of eIF4A action in cancer. We found that eIF4A is specifically required to unwind G-quadruplex (GQ) structures in the 5´UTRsof eIF4A dependent mRNAs. Importantly, these eIF4A target genes include MYC, NOTCH, CDK6 and other oncogenes (Figure 1)(Wolfe et al. 2014). Biochemical and genetic evidence has identified silvestrol as a selective inhibitor of eIF4A (Bordeleau et al. 2005, Bordeleau et al. 2008, Cencic et al. 2009, Sadlish et al. 2013, Chu et al. 2016). In this project, we will explore the biological and therapeutic effects of eIF4Ainhibitors in cancer. We have developed assays to probe eIF4A activity and preliminary data with a natural-product inhibitor (silvestrol) showing promising results. The Joshua-Tor lab (CSHL) will pursue structural studies of human eIF4A1 with the small-molecule inhibitors in the presence and absence of RNA. This will yield insights into the molecular action of eIF4A and facilitate the design of novel inhibitors. The Joshua-Tor lab has expertise in structural studies of protein-RNA complexes and is ideally suited to carry out these studies. The Tan lab (MSKCC) will pursue a novel synthesis-informed design strategy to develop new eIF4A inhibitors that are inspired by the silvestrol structure but are much more synthetically accessible, allowing for facile analogueing and scale-up. Inhibitors of the eIF4A RNA helicases have not been tested clinically and our results indicate that eIF4A inhibition is an effective and feasible means to block the production of oncogenes such as c-MYC.