Constitutively activated PI3K/AKT/mTOR pathway plays a critical role in the proliferation and survival of cancer cells. Through the expression of numerous pro-survival and proliferative genes. Specific inhibitors of the various isoforms of PI3K have shown promising activity in the treatment of indolent B-cell lymphoma. However, they have not shown similar activity in aggressive lymphoma. Notable examples of such signals regulated by mTOR include the expression of the pro-survival and pro-proliferative genes, NF-kappaB (NF-κB) pathway, and the eukaryotic initiation factor 4E (eIF4E). Through a feed-forward loop, eIF4E controls the expression of c-Myc, a well established oncoprotein in many cancers including highly aggressive lymphomas.

**Hypothesis**

If both the proteasome and PI3K are involved in activation of mTOR, then combinations of proteasome and PI3K inhibitors will be able to potently inhibit the mTOR-eIF4F-Myc axis and kill Myc dependent cancer.

**Future Direction**

- Determine whether down-regulation of c-Myc is caused by disruption of the feed-forward loop of eIF4F-Myc in lymphoma
- Investigate other mechanisms of the synergy
- Determine the in vivo effects of combining carfilzomib and TGR-1202
- A clinical trial combining carfilzomib and TGR-1202 will be open for enrollment soon.