Development of covalent binders of *c-Myc* mRNA

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Allowing potent and selective inhibition of desired targets, covalent drugs incorporate a mildly reactive functional group to form a covalent bond with the target site. Covalent inhibitors have several advantages, including use of lower dosages, higher target occupancy, and decreased likelihood of developing drug resistance. We aim to target *c-Myc*, the mRNA encoding for MYC protein, a transcription factor overexpressed in greater than 70% of human cancers. Direct inhibition of *c-Myc* has been shown to cause rapid tumor regression in mice with reversible and mild side effects, suggesting this to be a viable therapeutic target. Here, we use a covalent binding molecule containing an analogue of the duocarmycin class, due to their mechanism of bioactivity and the modularity of their structures. Additionally, other covalent molecules containing electrophilic groups, such as pyrrolobenzodiazepine (PBDs) and chlorambucil, will be synthesized. These bifunctional small molecules will be tested *in vitro* in HeLa cells. A potential mode of action encountered may be ribosomal stalling, the process wherein translating ribosomes are obstructed during elongation and trigger No-Go Decay (NGD) pathways, leading to the degradation of the oncogenic transcript.

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