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Novel Strategies for Targeting Myc in Aggressive Lymphoma

Myc is a critical oncogene involved in lymphomagenesis, and its overexpression is associated with aggressive tumor growth and poor patient outcome. The Myc oncoprotein has a very short half-life, and its translation is highly dependent on the eukaryotic initiation factor 4F (eIF4F) comprised of eIF4E, eIF4A, and eIF4G. Our preliminary results have demonstrated combinations of proteasome and PI3K inhibitors are highly synergistic in models of human lymphoma. A phase I/II clinical study evaluating this combination strategy is expected to be open for enrollment within 4-5 months. The current proposal aims to gain further insight into the mechanistic basis of the synergy, and find novel strategies to further improve the treatment of Myc associated lymphoma and highly chemo-resistant “double hit” lymphoma characterized by concurrent gene rearrangements involving Myc and Bcl2.

Specific Aims

Aim 1: Elucidate the mechanism underlying the potent synergy of PI3K and proteasome inhibitors.

1a. Establish that the synergistic combination of proteasome and PI3K inhibitors potently inhibits the translation of c-Myc, using dual renilla luciferase/IRES-firefly luciferase reporters carrying the G-quadruplex sequence or the 5’UTR of Myc.

1b. Establish that forced overexpression of c-Myc and eIF4E reduces the synergy of proteasome and PI3K inhibitors.

1c. Identify the signature of genes whose downregulation is uniquely associated with the potent synergy of proteasome and PI3K inhibitors.

Aim 2: Discover novel combination regimens that effectively downregulate both Myc and Bcl2.

2a. Conduct cytotoxic studies using high-throughput methods to investigate the synergy of various Bcl2 targeting agents and Myc targeting treatments, including PI3K and proteasome inhibitors, in models of Myc-expressing lymphoma and double hit lymphoma.

2b. Determine the effects of the synergistic combination of the expression of Myc and Bcl2.

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1a. Establish that the synergistic combination of proteasome and PI3K inhibitors potently inhibits the translation of c-Myc, using dual renilla luciferase/IRES-firefly luciferase reporters carrying the G-quadruplex sequence (gift of Dr. Hans-Guido Wendel, Memorial Sloan Kettering Cancer Center) or the 5'UTR of Myc.
1b. Establish that forced overexpression of c-Myc (gift of Dr. Adolfo Ferrando, HICCC of CUMC) and eIF4E (gift of Dr. Suzanne Lentzsch, HICCC) reduces the synergy of proteasome and PI3K inhibitors.
1c. Identify the signature of genes whose downregulation is uniquely associated with the potent synergy of proteasome and PI3K inhibitors (Collaborator: Dr. Nicholas Tatonetti of HICCC).

Aim 2: Discover novel combination regimens that effectively downregulate both Myc and Bcl2.
2a. Conduct cytotoxic studies using high-throughput methods (collaborator: Dr. Charles Karan of HICCC) to investigate the synergy of various Bcl2 targeting agents and Myc targeting treatments, including PI3K and proteasome inhibitors, in models of Myc-expressing lymphoma and double hit lymphoma.
2b. Determine the effects of the synergistic combination of the expression of Myc and Bcl2.