Pacritinib is a high Potent Inhibitor of Pro-Survival Signaling that Overcomes BTK Mutation-Mediated Resistance and Induces Apoptosis in Waldenström's Macroglobulinemia

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Introduction: MYD88 mutations are prevalent in B-cell malignancies such as Waldenström Macroglobulinemia (WM), primary CNS lymphoma, ABC DLBCL, marginal zone lymphoma, and CLL. These mutations activate pro-survival pathways involving HCK-directed BTK, ERK, SYK, and IRAK1/IRAK4. While BTK inhibitors are effective, resistance often arises due to BTK mutations. Pacritinib, an FDA-approved kinase inhibitor, targets pathways associated with mutant MYD88, including IRAK1, JAK2, and SRC, but its potential in MYD88-mutated B-cell malignancies including WM is underexplored.

Main Points: Pacritinib induced higher apoptosis in MYD88-mutated WM (BCWM.1) and ABC DLBCL (TMD8) cells, and primary MYD88-mutated WM cells, compared to ibrutinib or zanubrutinib. This effect was dose-dependent, with significant apoptosis at 0.5 μM. Pacritinib inhibited JAK2 and IRAK1 activation and suppressed p-HCK (Y411) and p-BTK (Y223) in MYD88-mutated cells. It also showed synergy with BTK inhibitors and venetoclax in inhibiting cell growth. Pacritinib, alone or with venetoclax, induced high apoptosis in $BTK^{Cys481Ser}$-expressing BTK inhibitor-resistant MYD88-mutated cells. In a $BTK^{Cys481Ser}$ BCWM.1 xenograft model, pacritinib significantly suppressed tumor growth compared to controls.

Conclusion: Pacritinib effectively targets pro-survival signaling in MYD88-mutated cells, shows superior apoptotic activity, and overcomes mutated BTK-associated resistance. These findings support further investigation, with a phase II clinical trial initiated for relapsed/refractory WM.

Biography:

Dr. Shirong Liu, MD, PhD, is a Senior Scientist and the Lee and Michael Bell Waldenström's Macroglobulinemia (WM) Fellow at the Dana-Farber Cancer Institute, Harvard Medical School. He earned his medical degree from Jiangxi Medical College and practiced internal medicine in China. Transitioning to research, he obtained a Master of Science degree in Immunology from Peking Union Medical College, where he studied a gene linked to thymus atrophy during aging. Dr. Liu then completed his PhD at Saarland University in Germany, identifying TLR2 as a key receptor in Alzheimer's disease-related neuroinflammation. In 2012, Dr. Liu moved to Boston for postdoctoral training and subsequently became a faculty member at Brigham and Women's

Hospital and Harvard Medical School. There, he discovered that microRNAs in the gut shape microbiome composition and regulate immune responses. He identified miR-30d, which can expand *Akkermansia muciniphila* in the gut, and demonstrated its potential in treating multiple sclerosis. In 2021, Dr. Liu joined Genentech Inc., where he developed therapeutics for inflammatory bowel diseases using human intestinal organoids. In 2022, he joined Dana-Farber, where he focuses on basic oncology, the tumor microenvironment, and developing new therapies for WM.