27O-ISMS22 **Development of Protein Degradation Inducers of Oncogenic BCR-ABL Protein by Conjugation of ABL Kinase Inhibitors and IAP Ligands**

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Chromosomal translocation occurs in some cancer cells, which results in the expression of aberrant oncogenic fusion proteins that include BCR-ABL in chronic myelogenous leukemia (CML). Inhibitors of ABL tyrosine kinase, such as imatinib and dasatinib, exhibit remarkable therapeutic effects, although emergence of drug resistance hampers the therapy during long-term treatment. An alternative approach to treat CML is to downregulate the BCR-ABL protein. Recently, we have devised a protein knockdown system by hybrid molecules named Specific and Nongenetic inhibitor of apoptosis protein [IAP]-dependent Protein Erasers (SNIPER), which is designed to induce IAP-mediated ubiquitylation and proteasomal degradation of target proteins. In this study, we tested various combinations of ABL inhibitors and IAP ligands, and the linker was optimized for protein knockdown activity of SNIPER(ABL). The resulting SNIPER(ABL)-39, in which dasatinib is conjugated to an IAP ligand LCL161 derivative by polyethylene glycol × 3 linker, shows a potent activity to degrade the BCR-ABL protein. Mechanistic analysis suggested that both cIAP1 and XIAP play a role in the degradation of BCR-ABL protein. Consistent with the degradation of BCR-ABL protein, the SNIPER(ABL)-39 inhibited the BCR-ABL kinase signaling pathway, and suppressed the growth of BCR-ABL-positive CML cells. Since the SNIPER(ABL)-39 contain dasatinib moiety, it also inhibit ABL kinase, which complicates the importance of the BCR-ABL degradation in the CML growth inhibition by degraders. We developed a control compound containing an N-methylated LCL161 derivative (SNIPER(ABL)-59), which inhibits kinase activity but does not degrade the BCR-ABL protein. When CML cells were treated for 48 h, SNIPER(ABL)-39 shows slightly weaker activity than SNIPER(ABL)-59 to inhibit cell growth. However, drug removal after 12-h treatment with SNIPER(ABL)-59 resulted in the quick recovery of the CML cell growth whereas that with SNIPER(ABL)-39 showed more sustained growth inhibition. Consistently, SNIPER(ABL)-39 showed a long-lasting effect on the BCR-ABL protein degradation. These results suggest that SNIPER(ABL)-39 could be a candidate for a degradation-based novel anti-cancer drug against BCR-ABL-positive CML.