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Correction to "Improved Coiled-Coil Design Enhances Interaction with Bcr-Abl and Induces Apoptosis"

Improved Coiled-Coil Design Enhances Interaction with Bcr-Abl and Induces Apoptosis

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Abstract

The oncoprotein Bcr-Abl drives aberrant downstream activity through trans-autophosphorylation of homo-oligomers in chronic myelogenous leukemia (CML).^{1,2} The formation of Bcr-Abl oligomers is achieved through the coiled-coil domain at the N-terminus of Bcr.^{3,4} We have previously reported a modified version of this coiled-coil domain, CCmut2, which exhibits disruption of Bcr-Abl oligomeric complexes and results in decreased proliferation of CML cells and induction of apoptosis.⁵ A major contributing factor to these enhanced capabilities is the destabilization of the CCmut2 homo-dimers, increasing the availability to interact with and inhibit Bcr-Abl. Here, we included an additional mutation (K39E) that could in turn further destabilize the mutant homo-dimer. Incorporation of this modification into CCmut2 (C38A, S41R, L45D, E48R, Q60E) generated what we termed CCmut3, and resulted in further improvements in the binding properties with the wild-type coiled-coil domain representative of Bcr-Abl. A separate construct containing one revert mutation, CCmut4, did not demonstrate improved oligomeric properties and indicated the importance of the L45D mutation. CCmut3 demonstrated improved oligomerization via a two-hybrid assay as well as through colocalization studies, in addition to showing similar biologic activity as CCmut2. The improved binding between CCmut3 and the Bcr-Abl coiled-coil may be used to redirect Bcr-Abl to alternative subcellular locations with interesting therapeutic implications.