Targeted Rescue of the Destabilized p53 Mutant Y220C -
In silico and Biophysical Screening in a “Novel” Binding Site

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The tumour suppressor p53 is inactivated because of mutations in some 50% of human cancers. About a third of the mutations lower the melting temperature of the protein, leading to its rapid denaturation. Small molecules that bind to those mutants and stabilize them could be effective anti-cancer drugs.[1] The mutation Y220C, which occurs in ~75,000 new cancer cases per annum, creates a surface cavity that destabilizes the protein by 4 kcal/mol, at a site that is not functional.[2] Using a structure-based in-silico screening approach, we were able to identify a structural scaffold binding to this “novel” binding site. The virtual high throughput-screening was complemented by biophysical screening and characterisation of the hits and was followed by rational and computational drug design.[3] PhiKan083, a leadlike structure containing the carbazole scaffold, binds to the “novel” cavity with a dissociation constant of ~150 µM. It raises the melting temperature of the mutant and slows down its rate of denaturation. We have solved the crystal structure of the protein-PhiKan083 complex at 1.5 Å resolution. The structure implicates key interactions between the protein and ligand and conformational changes that occur on binding, which provide a basis for lead optimization. We have studied structure-activity relationships of various carbazole derivatives to learn more about the binding site. Further rounds of in silico screening and design have yielded additional scaffolds with interesting new binding modes. We have found that the Y220C mutant is a “druggable” target well suited for developing and testing novel anti-cancer drugs based on protein stabilization.

Literature: