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A new druggable site to rescue p53 folding and activity

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The tumor suppressor protein p53 is mutated or deleted in more than half of human cancers. The most frequently occurring of these loss-of-function mutations are localized to the p53 "core domain," but do not involve surface residues directly responsible for function. Rather, these point mutants reduce the thermodynamic stability of this marginally stable protein, such that cellular activity is diminished because an insufficient amount of p53 is correctly folded. We sought to identify compounds that bind and stabilize correctly folded p53, expecting that stabilization through this mechanism will restore activity to this most frequently occurring class of p53 point mutants, and further will restore activity to these destabilized mutants.

Using new computational tools developed in my lab, we have discovered a new druggable site on the surface of the p53 core domain, and identified compounds designed to interact with this surface. Through biochemical assays we find that these compounds are effective at stabilizing multiple different p53 mutants. We further find that these compounds can restore transcriptional activity in cell lines harboring destabilized mutants of p53, without affecting cells that have wild-type p53.

Thus, this new druggable site may provide a starting point for developing a new class of therapeutics that selectively re-activate p53 – regardless of precisely which mutation is responsible for the underlying loss of protein function.We also expect that refinement of our novel screening platform will additionally enhance its utility for identifying reactivators of other select proteins that are frequently deactivated in human cancers by destabilizing mutations.

Biography:

John Karanicolas is currently an Associate Professor at the Fox Chase Cancer Center, in the Molecular Therapeutics Program. He was granted a PhD from Charlie Brooks' lab at The Scripps Research Institute in 2003, for his work using molecular dynamics simulations to study protein folding. He then moved to a postdoc in David Baker's lab at the University of Washington, where he studied protein design and added a wetlab component to his research. He started his lab at the University of Kansas in 2008, focusing on developing structure-based approaches for modulating protein function using small-molecules. He moved his lab to Fox Chase in 2016, where his research follows two parallel themes: the first is re-engineering proteins so that a small-molecule can be used to "turn on" function, and the second is identifying small-molecules that naturally complement and occlude a protein interaction sites to "turn off" function.