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"In silico allosteric network predicts variation in response for drugs against human kinesin-5: are all anticancer therapies created equal?"

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Anti-cancer therapeutics target the kinesin-5 motor via a common allosteric site, loop-5, with high selectivity. There is no explanation as to how over 100 classes of small molecule inhibitors bind a common site with a wide range of efficacies. Also lacking is the allosteric pathway(s) responsible for communication from loop-5 to the catalytic and microtubule (MT)-binding sites. Our goal herein is to determine the network of key residues responsible for this communication. After obtaining improved alignment of 726 kinesin sequences, our statistical coupling analysis extracted evolutionarily linked clusters of residues for kinesin motor proteins. We identified a network of 56 residues and thermodynamic linkage was experimentally validated using double mutant cycle analysis for 15% of the residues. The network includes residues in the allosteric, active, and MT-binding sites. Importantly, we identified drug-interacting residues for the two most commonly used small molecule inhibitors, monastrol and S-trityl-L-cysteine (STC), in our analysis. The evolutionary linkages for each inhibitor are different: confirming that there is more than one allosteric pathway in the kinesin motor domain. We conclude that our allostery wiring diagram captures an energetic definition of drug signaling pathways for a kinesin-5 motor domain. In addition, this wiring diagram can potentially identify mechanisms of resistance and hypersensitivity to anti-cancer therapeutics.