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Molecular flexibility shown to help pharmaceutical drugs bind to their targets

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Scientists have discovered an alternative way to create a stronger binding between pharmaceutical drugs and the part of the body they are targeting - a development that can be used to fight a variety of diseases, including breast cancer. The study published in *PLOS Computational Biology* shows that flexible molecules, instead of rigid ones, as previously thought, can bind more effectively to the proteins causing the disease.

Being a tight binder is important for a molecule to be a good pharmaceutical drug. When designing a pharmaceutical drug, scientists typically make molecules - which are naturally flexible - rigid so that they can strongly bind, like a lock and key, with the disease causing protein in the body.

When molecules bind to their partners they usually decrease their flexibility which leads to the so-called entropy penalty. Having a large entropy penalty has been shown to be bad for creating a tight bindings. Scientists aim to reduce it so that the drug can stay on the target protein and alter its functional behavior for good. However, one key problem to this approach is that scientists are reaching the limit of how much rigidity can be produced in order to reduce entropy penalty and result in tighter binders.

Researchers, led by Wanli You (University of California), found that keeping the molecules flexible, as opposed to making them rigid, both reduced the entropy penalty and created a stronger binding. One of the authors, Chia-en A. Chang, notes that "This was really unexpected and

opens up a new direction for designing pharmaceutical drugs".

In order to discover this, the researchers examined the thermodynamic properties of different ligands binding to a promiscuous modular protein, Breast-cancer-gene 1 (BRCA1) C-terminal (BRCT). The authors used molecular dynamics simulations and a rigorous free energy calculation method to study ligands binding to BRCT, understand promiscuous molecular recognition and guide inhibitor design. Flexible ligands, the researchers found, may utilize multiple conformations in their bound states to keep good attractions with BRCT whilst also reducing entropy cost.

The research focused on breast cancer drugs, but the principles could be applied in drug development targeting other diseases and also in basic cell biology studies.

More information: You W, Huang Y-mM, Kizhake S, Natarajan A, Chang C-eA (2016) Characterization of Promiscuous Binding of Phosphor Ligands to Breast-Cancer-Gene 1 (BRCA1) C-Terminal (BRCT): Molecular Dynamics, Free Energy, Entropy and Inhibitor Design. *PLoS Comput Biol* 12(8): e1005057. DOI: 10.1371/journal.pcbi.1005057