# Researchers slash pre-drug screening time from years to days

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Researchers at Ben-Gurion University of the Negev (BGU) and The Hebrew University of Jerusalem (HU) have developed a powerful tool that will streamline and accelerate the development of disease therapies, transforming a multi-year process into just a few days.

Until now, existing technologies only enabled scientists to observe one mutation at a time, each one taking weeks or months. Constructing

protein mutants and measuring their effect on binding affinity—the strength with which proteins interact with their target proteins in cells—slows the study of how and why diseases progress. With thousands of potential mutations for every protein-protein interaction (PPI), the process was costly, labor-intensive and time-consuming.

The new approach, published in *Nature Communications*, simultaneously evaluates the effect of thousands of mutations in protein-protein complexes. It is an important step for both applied and theoretical scientists. Most of the promising new drugs in production are proteins that destroy certain disease-associated protein-protein interactions, which control virtually all processes in the cell. It will help researchers design protein drugs that are both potent and specific, causing minimal side effects.

"Our new approach will increase the understanding of the mechanisms and evolutionary origins of specific PPIs, and facilitate the rational design of specific inhibitors that can discriminate between structurally similar protein targets," says Prof. Niv Papo of BGU's Avram and Stella Goldstein-Goren Department of Biotechnology Engineering and the National Institute for Biotechnology in the Negev (NIBN).

"Indeed, as many disease-related proteins belong to large families of related proteins, increasing target selectivity is a highly desirable but challenging goal in drug development. This tool offers great promise for designing novel target-specific therapeutics," he says.

As cancer researchers, BGU's Prof. Papo and HU Prof. Julia Shifman were facing a bottleneck in their work, which led them to develop the tool. They needed to understand the relationships created by cellular proteins, particularly the mutations that occur when those relationships go awry. To streamline the process of mapping and cataloguing the reactions, they combined a sophisticated protein library screening

technology, deep sequencing and data normalization to identify and categorize protein mutations according to their function.

"Just like people, proteins maintain 'social networks,'" says Prof. Shifman, a member of HU's Department of Biological Chemistry. "Some 'couples' partner for the long-term, while others prefer numerous and promiscuous interactions. When the proteins act the way they are supposed to, the body is healthy. But when the binding affinity becomes affected—that is, when stable relationships break up too quickly, or fleeting ones fail to disengage—that's when disease happens."

Profs. Papo and Shifman intend to apply their unique approach to map the binding specificity landscapes of broad-spectrum inhibitors of the human matrix metalloproteinases (MMPs) and serine proteases and test the therapeutic efficacy of these inhibitors in cellular and pre-clinical models of bone diseases and cancer. Ultimately, the inhibitors will be commercialized.

**More information:** Michael Heyne et al, Generating quantitative binding landscapes through fractional binding selections combined with deep sequencing and data normalization, *Nature Communications* (2020). DOI: 10.1038/s41467-019-13895-8

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