DNA sequencing method can detect where and how small molecule drugs interact with their targets

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Many life-saving drugs directly interact with DNA to treat diseases such as cancer, but scientists have struggled to detect how and why they

work—until now.

In a paper published in the journal *Nature Biotechnology*, University of Cambridge researchers have outlined a new DNA sequencing method that can detect where and how small molecule drugs interact with the targeted genome.

"Understanding how drugs work in the body is essential to creating better, more effective therapies," said co-first author Dr. Zutao Yu from the Yusuf Hamied Department of Chemistry. "But when a therapeutic drug enters a cancer cell with a genome that has three billion bases, it's like entering a black box."

The powerful method, called Chem-map, lifts the veil of this genomic black box by enabling researchers to detect where small molecule drugs interact with their targets on the DNA genome.

Each year, millions of cancer patients receive treatment with genome-targeting drugs, such as doxorubicin. But despite decades of clinical use and research, the molecular mode of action with the genome is still not well-understood.

"Lots of life-saving drugs directly interact with DNA to treat diseases such as cancer," said co-first author Dr. Jochen Spiegel. "Our new method can precisely map where drugs bind to the genome, which will help us to develop better drugs in the future."

Chem-map allows researchers to conduct in situ mapping of small molecule-genome interactions with unprecedented precision, by using a strategy called small-molecule-directed transposase Tn5 tagmentation. This detects the binding site in the genome where a small molecule binds to genomic DNA or DNA-associated proteins.

In the study, the researchers used Chem-map to determine the direct binding sites in human leukemia cells of the widely used anticancer drug doxorubicin. The technique also showed how the combined therapy of using doxorubicin on cells already exposed to the histone deacetylase (HDAC) inhibitor tucidinostat could have a potential clinical advantage.

The technique was also used to map the binding sites of certain molecules on DNA G-quadruplexes, known as G4s. G4s are four-stranded secondary structures that have been implicated in gene regulation, and could be possible targets for future anti-cancer treatments.

"I am so proud that we have been able to solve this longstanding problem—we have established a highly efficient approach which will open many paths for new research," said Yu.

Professor Sir Shankar Balasubramanian, who led the research, said, "Chem-map is a powerful new method to detect the site in the genome where a small molecule binds to DNA or DNA-associated proteins. It provides enormous insights on how some drug therapies interact with the human genome, and makes it easier to develop more effective and safer drug therapies."

More information: Shankar Balasubramanian, Chem-map profiles drug binding to chromatin in cells, *Nature Biotechnology* (2023). DOI: 10.1038/s41587-022-01636-0.
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