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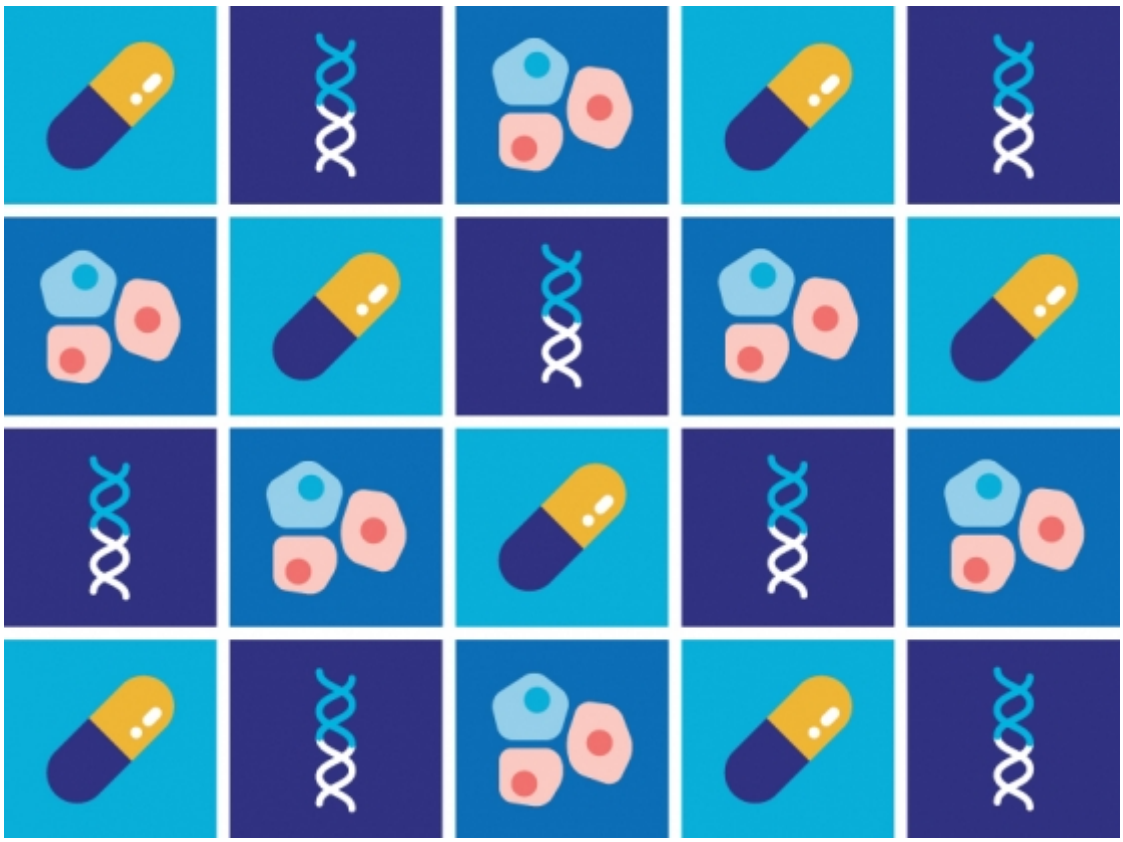
AN EFFORT TO MAP CANCER'S WEAK SPOTS IS STARTING TO REVEAL NEW DRUG TARGETS



Credit : Susanna M. Hamilton

By Nicole Davis

Through the Broad's Cancer Dependency Map, researchers are searching for genetic vulnerabilities in cancer cells that could lead the way to better precision drugs.

Physicians and scientists have been on a decades-long mission to find drugs with both the power and precision to thwart tumor growth. They initially lacked a detailed understanding of the enemy, but even with ever-increasing biological knowledge of cancer, trial and error still remains a common approach to cancer drug development.

"That's not a really great strategy. It'd be much better to know, based on preclinical insights, which approaches are most likely to be the winning ones," said Todd Golub, chief scientific officer of the Broad and director of its Cancer Program. "We believe

systematic methods can help us figure out which ideas we should bring into the clinic in the first place."

This vision goes hand-in-hand with precision medicine — where patients would provide a blood sample or bit of tumor for molecular analysis, and then receive a list of drugs that are most likely to work.

Yet this world is still emerging. While the tools and technologies for characterizing tumors at the molecular level have advanced in recent years, the information that comes out is still largely uninterpretable.

This lack of clarity is one reason why the majority of cancer patients are not benefitting from targeted therapies. Scientists have so far identified mutations in some 500 genes that are associated with cancer. But only 20 to 50 of them are targeted by FDA-approved drugs. "So, we've been asking ourselves, what do we need to do to make the vision of precision medicine a reality, not just for some but for all cancer patients?" said Golub, who is also the Charles A. Dana Investigator in Human Cancer Genetics at the Dana-Farber Cancer Institute.

One answer is an ambitious, international effort based at the Broad known as the Cancer Dependency Map, or DepMap for short. This project catalogues key vulnerabilities in cancer cells with the aim of spurring drug makers to design new compounds that target them. It has taken a major step in that direction, partnering with several biopharmaceutical companies to boost discovery efforts and bring promising new treatments to the clinic.

"If one of our goals is to influence drug discovery, we need to engage drug companies at the very beginning," said Jesse Boehm, who serves as scientific director of the DepMap and associate director of the Broad's Cancer Program.

Tumors are riddled with genetic mutations -- some normally fatal -- but cancer cells cleverly find ways to survive. They end up depending heavily on molecular work-arounds — for example, ramping up another gene's activity — but if a drug blocks those workarounds, it could kill the cells. The goal of the DepMap project is to reveal these work-arounds, or dependencies, as possible drug targets, among hundreds of genes across many cancer types.

To do this, Broad researchers and their colleagues are analyzing hundreds of cancer cell lines, exposing them to a large collection of drugs to see which ones kill the cells. They are also using a suite of genetic technologies, including RNA interference (RNAi) and CRISPR-Cas9 genome editing, to systematically turn off hundreds of genes, one at a time, and home in on key genes the cancer cells need to survive.

"There is no question that the best oncology drugs are yet to be discovered or developed, and these genetic perturbations will point us to which drugs need to be developed in the future," said Golub.

The project is already showing promise, with a recent report of a striking cancer dependency involving a gene called *WRN* in a significant fraction of cell lines from ovarian, endometrial, gastric and colon tumors. DepMap researchers, led by people from the Broad, including co-senior author and DepMap associate director Francisca Vazquez, reported that *WRN* could be a drug target for certain types of cancers.

"We have been working in close collaboration with colleagues at several of our affiliated hospitals to identify and validate novel therapeutic strategies for cancer patients," said Vazquez. "It's very exciting that we are beginning to see progress both in drug discovery and clinical trials."

GREATER THAN THE SUM OF ITS PARTS

The DepMap is not a new endeavor. It's based on nearly 15 years of research at the Broad Institute and other leading research organizations characterizing the genetic activity and mutations in different cancer cell types.

"Each component that makes up the DepMap is an incredibly large and complicated effort," said William Hahn, an institute member of the Broad's Cancer Program who is also the chief research strategy officer and an oncologist at the Dana-Farber Cancer Institute. "By putting them all together, we're doing something that is really unprecedented and potentially transforming."

The project's leaders say an effort of this magnitude requires collaboration. "Something this important really shouldn't be the work of just one institution," said Golub. That is why the Broad is working together with scientists at the Wellcome Sanger Institute in Hinxton, near Cambridge, UK.

"We are excited to be working in partnership with the Broad Institute on this initiative. As two of the largest data producers of this type in the world, we can create a bigger, better map — and do it faster," said Mathew Garnett, a group leader at the Sanger Institute and lead scientist for its DepMap efforts.

So far, the project has analyzed more than 500 cancer cell lines, and the researchers want to study many more — from very rare to common forms of the disease. Achieving that goal requires scale. Researchers will need to look at thousands of different cancer cell types to find key dependencies and potential drugs that target them. "Perturbing

these cells at scale in a meaningful way to define dependencies is a huge technical challenge that should not be underestimated," said Garnett.

Similarly, interpreting and integrating distinct types of data — from genomic sequencing to large-scale screens using drugs, RNAi, and CRISPR — is a monumental task that is led by Aviad Tsherniak, associate director of the Cancer Data Science group (http://www.cancerdatascience.org/) at the Broad. His team develops and applies state-of-the-art machine learning approaches to identify novel cancer drug targets. The team also builds models that predict the vulnerabilities of a tumor from its molecular characteristics.

Last April, DepMap researchers unveiled depmap.org, a publicly accessible web portal that allows researchers, including those with no computational background, to explore and analyze DepMap data, as well as relevant datasets generated by other efforts worldwide. Already, the portal is accessed by more than 700 researchers each day.

Sharing data openly and in a timely manner is a top priority for the DepMap team. Tsherniak and his colleagues release data quarterly through the DepMap portal, regardless of whether there are accompanying scientific journal publications.

"Part of the DepMap's value is enabling the broader research community to make discoveries," said Tsherniak. "We believe sharing data early, with no restrictions, will help others do great science."

MEASURING IMPACT

While the DepMap's ultimate goal — improving cancer treatment — is still in the distance, there are already signs of progress. For example, the recent *WRN* discovery points to a new potential therapeutic strategy for cancers that have a certain type of cellular defect called microsatellite instability (MSI).

"This is an exciting potential drug target for multiple reasons," said Vazquez. "There is a relatively large number of patients with MSI tumors and we can readily identify them." She adds that normal cells don't have this defect so they hopefully won't be affected by a potential drug.

Remarkably, two other research groups also published papers describing the same *WRN* finding, including Garnett's team at the Sanger Institute and a group at pharmaceutical company Boehringer Ingelheim.

Other encouraging developments include a dependency identified about three years ago by two independent teams, one at the Broad and one at the Novartis Institutes for

Biomedical Research. These findings have spurred new drug discovery projects centered on the gene *PRMT5*. A slew of other discoveries in pediatric cancers, including neuroblastoma and certain kidney tumors, sprung from DepMap data and could also lead to promising new treatments.

MOVING CLOSER TO PATIENTS

As the DepMap continues gaining momentum, its leaders will need to figure out how to bridge the gap between a research-grade map — constructed using cancer cells grown in the laboratory — and a clinically useful one. That means building a resource that is not only useful for drugmakers, but also doctors, who want to know which treatments are most likely to be effective, based on the molecular profiles of their patients' tumors.

The DepMap team is addressing this challenge by figuring out how to collect data from tumor cells isolated directly from patients, rather than from cancer cells grown in the laboratory. "If we want to represent human cancer as part of a dependency map, we need laboratory models that really reflect human cancers," said Boehm.

Scientists at the Broad and elsewhere are working toward this goal through a variety of efforts, including a project known as the Cancer Cell Line Factory. Launched five years ago, it aims to create new cancer cell models that more fully capture the diversity of human cancers, and share them with researchers worldwide. This work has also spurred a broader effort, sponsored by the National Cancer Institute, that involves a consortium of research organizations across the globe to create a new generation of human cancer models. In addition, Broad scientists are exploring ways to incorporate immune cells into these new cancer models to better mimic the important role of the immune system in cancer.

Cancer researchers also need to understand and study the experiences of patients. The Broad is partnering with a new non-profit organization called Count Me In, which enables cancer patients from across the U.S. and Canada to share their medical information, personal experiences, and tumor samples for genetic analysis. The hope is that the patient data, in combination with DepMap insights, will advance cancer research and therapeutic discovery.

"To really make progress, we need the patient experience and the laboratory experience running hand-in-hand, informing each other," Golub explained. "That's why having a comprehensive DepMap is going to be so vital."