COMPOUND INTEREST

The Broad is testing drugs already approved as safe to see if they can be repurposed for cancer and other diseases.

In a robotized freezer on the third floor of the Broad Institute are more than 6,000 of all the 11,000 small-molecule drugs ever made, dating back to the 19th century.

This collection is the Drug Repurposing Hub (clue.io/repurposing)—an innovative effort by the Broad's Cancer Program to accelerate the pace of drug discovery. Launched thanks to the generosity of the Carlos Slim Foundation and now being supported by an anonymous donor from Switzerland, the Hub was started with the aim of finding already-existing drugs that can kill cancer cells. Most of these drugs have already been approved as safe in humans, which means a fast-track path to clinical trials if they do prove to have cancer-killing abilities.

Even more critically, the Broad's collection—unlike similar ones—is carefully curated. Each compound is annotated with relevant scientific and clinical information, which helps to quickly illuminate the biology targeted by these drugs.

Scores of drugs go into clinical trials, but many are shelved because they're ineffectual against their original indication or because they trigger side effects. Side effects, however, are sometimes a clue that a drug could have unexpected therapeutic benefits for another disease area. For example, thalidomide, a notorious morning-sickness drug that caused severe birth defects, now treats a blood cancer called multiple myeloma.

"It's really hard to get pure specificity for one target and nothing else," explained Florence Wagner, an institute scientist at the Broad and director of medicinal chemistry in the Broad's Center for the Development of Therapeutics (CDoT), who helps oversee the Hub's efforts. "That's why a lot of drugs have side effects—they might modulate a second protein somewhere else in your body. But that side effect can also be a target effect. Once you understand what other proteins are involved, you can go back, screen a different target, and create a novel molecule that is more selective."

Excitingly, other researchers beyond the Cancer Program are also tapping into this resource to find cures for diseases ranging from malaria to kidney disorders. Here's a closer look at the Drug Repurposing Hub.
—Anna Fiorentino ■

1 THE CHALLENGE: LENGTH AND COST OF DEVELOPING NEW DRUGS

From basic science to post-approval research, the development of a single drug typically costs more than $1 billion over a span of 10 to 15 years. Repurposing a drug shaves off hundreds of millions—about a third of the cost—and anywhere from three to six years.

2 THE RESPONSE: LEVERAGING THE POWER OF ALREADY-EXISTING DRUGS

The Hub team—led by its founder, Steven Corsello, who is a member of the Cancer Program and an attending physician at the Dana-Farber Cancer Institute—has catalogued and barcoded thousands of drugs in vials on shelves in a massive refrigerator at the Broad. In addition, the researchers synthesize molecules to develop drugs they cannot obtain through chemical vendors, continually expanding the Hub with new compounds.

3 THE RATIONALE: SCIENTISTS HAVE DISCOVERED NEW CLINICAL BENEFITS FOR OLD DRUGS BEFORE

The most famous discoveries include aspirin for treating coronary artery disease and the blood pressure drug, Sildenafil, to treat impotence, before it was labeled Viagra. And Leukine, the first drug approved to improve an immune system weakened by chemotherapy, was approved last year for radiation sickness from a nuclear explosion.

4 THE TESTING: AFTER SCREENING COMPOUNDS, BROAD RESEARCHERS GET A SENSE OF A DRUG'S SECONDARY TARGETED EFFECTS

The Broad uses a patented molecular barcoding system, pooling and testing multiple cell lines simultaneously and running predictive modeling algorithms to identify biomarkers of sensitivity or resistance. This system, called PRISM (Profiling Relative Inhibition Simultaneously in Mixtures), addresses a persistent problem in cancer research: how to test drugs in a way that reflects the genetic heterogeneity of a disease like cancer. PRISM allows researchers to test a compound against hundreds of cell lines—each containing distinct mutations—all in one go.

5 THE PROOFS-OF-CONCEPT: CHEMOTHERAPY–RESISTANT CANCERS AND KIDNEY DISEASE

Corsello has found that tepoxalin—a drug first approved to reduce inflammation in animals—also appears to be effective in targeting chemotherapy–resistant cancers through a mutation that often confers drug resistance. Corsello is now conducting *in vivo* studies to further understand its mechanism. "Having a treatment to target these chemotherapy–resistant cancers would be very helpful in the clinic," he said.

Anna Greka, a Broad institute member and director of the Kidney Disease Initiative and a physician at Brigham and Women's Hospital, has used the collection to discover a pre-clinical compound that could potentially become the first drug to treat medullary cystic kidney disease, a rare, devastating disease caused by mutations in the MUC1 gene. "We can hopefully harness existing knowledge about a drug's properties and safety profile to leap faster to proof-of-concept studies in the clinic," she said. Greka and her team are now working nonstop to develop a therapy from the compound—and to avail that therapy to patients as quickly as possible. It's findings like this that demonstrate the promise the Hub has in curing people from diseases.

6 THE BENEFITS: ACCELERATING DRUG DISCOVERY AND HELPING PATIENTS SOONER

The Broad's library is a resource that any nonprofit researcher can access. Laura Pisarsky, a researcher at the Fred Hutchinson Research Center, identified about a dozen drugs that could be the first to kill chemo-resistant, dormant metastatic breast cancer cells. These cells can cause metastases and result in long-term patient relapse, even if they have been dormant for a decade. Pisarsky noted that promising drug leads are often shelved because they prove too toxic to animal models and humans. "Whereas if you identify an efficient drug using the drug repurposing library, you know that it has been safe enough to be used in humans." That, in turn, provides a faster track to clinical trials, and hopefully, regulatory approval.