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Cancer's next magic bullet may be magic shotgun

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A new approach to drug design, pioneered by a group of researchers at the University of California, San Francisco (UCSF) and Mt. Sinai, New York, promises to help identify future drugs to fight cancer and other diseases that will be more effective and have fewer side effects.

Rather than seeking to find magic bullets—chemicals that specifically attack one gene or protein involved in one particular part of a disease process—the new approach looks to find "magic shotguns" by sifting through the known universe of chemicals to find the few special molecules that broadly disrupt the whole diseases process.

"We've always been looking for magic bullets," said Kevan Shokat, PhD, a Howard Hughes Medical Institute Investigator and the Chair of the Department of Cellular and Molecular Pharmacology at UCSF. "This is a magic shotgun—it doesn't inhibit one target but a set of targets—and that gives us a much, much better ability to stop the cancer without causing as many side effects."

Described in the June 7, 2012 issue of the journal *Nature*, the magic shotgun approach has already yielded two potential drugs, called AD80 and AD81, which in fruit flies were more effective and less toxic than the drug vandetanib, which was approved by the U.S. Food & Drug Administration last year for the treatment of a certain type of thyroid cancer.

Expanding the Targets to Lower a Drug's Toxicity

Drug design is basically all about disruption. In any disease, there are numerous molecular interactions and other processes that take place within specific tissues, and in the broadest sense, most drugs are simply chemicals that interfere with the proteins and genes involved in those processes. The better a drug disrupts key parts of a disease process, the more effective it is.

The toxicity of a drug, on the other hand, refers to how it also disrupts other parts of the body's system. Drugs always fall short of perfection in this sense, and all pharmaceuticals have some level of toxicity due to unwanted interactions the drugs have with other molecules in the body.

Scientists use something called the therapeutic index (the ratio of effective dose to toxic dose) as a way of defining how severe the side effects of a given drug would be. Many of the safest drugs on the market have therapeutic indexes that are 20 or higher—meaning that you would have to take 20 times the prescribed dose to suffer severe side effects.

Many cancer drugs, on the other hand, have a therapeutic index of 1. In other words, the amount of the drug you need to take to treat the cancer is the exact amount that causes severe side effects. The problem, said Shokat, comes down to the fact that cancer drug targets are so similar to normal human proteins that the drugs have widespread effects felt far outside the tumor.

While suffering the side effects of drugs is a reality that many people with cancer bravely face, finding ways of minimizing this toxicity is a big goal pharmaceutical companies would like to solve. Shokat and his colleagues believe the shotgun approach is one way to do this.

The dogma that the best drugs are the most selective could be wrong, he

said, and for cancer a magic shotgun may be more effective than a magic bullet.

Looking at fruit flies, they found a way to screen compounds to find the few that best disrupt an entire network of interacting genes and proteins. Rather than judging a compound according to how well it inhibits a specific target, they judged as best the compounds that inhibited not only that specific target but disrupted other parts of the network while not interacting with other genes and proteins that would cause toxic side effects.

More information: The article, "Chemical genetic discovery of targets and anti-targets for cancer polypharmacology" by Arvin C. Dar, Tirtha K. Das, Kevan M. Shokat and Ross Cagan appears in the June 7, 2012 issue of the journal Nature. See: dx.doi.org/10.1038/nature11127

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