Researchers develop a multi-target approach to treating tumors

June 7 2012

Researchers from Mount Sinai School of Medicine developed a cancer model built in the fruit fly *Drosophila*, then used it to create a whole new approach to the discovery of cancer treatments. The result is an investigational compound AD80 that precisely targets multiple cancer genes. Tested in mouse models, the drug proved far more effective and less toxic than standard cancer drugs, which generally focus on a single target. This is the first time that whole-animal screening has been used in a rational, step-wise approach to polypharmacology. The study appears online in the journal *Nature*.

Conventional drug design embraces the "one gene, one drug, one disease" philosophy. Polypharmacology focuses on multi-target drugs and has emerged as a new paradigm in drug discovery. The hope is that AD80—showing unparalleled effectiveness in fly and mouse models—will be tested in Phase I clinical trials.

"We've come up with one drug that hits multiple targets through 'rational polypharmacology,' and our approach represents a new concept we believe will have great success in suppressing tumors," said Ross L. Cagan, Ph.D., Professor and Associate Dean at Mount Sinai School of Medicine, and senior author on the study. "Scientists are beginning to recognize that single-target drugs can be problematic. I believe that, within the next five years, we'll see more drugs entering clinical trials that use rational polypharmacology as the basis of drug discovery."

The study represented an unusual collaboration between fly geneticists

and medicinal chemists. Typically, scientists use human tumor cell lines to screen for single target anti-cancer drugs. In this project, Dr. Cagan, along with co-authors Tirtha Das, Ph.D, from Mount Sinai and their collaborators Arvin Dar, PhD and Kevan Shokat, Ph.D. from the University of California, San Francisco, used their fly cancer models to screen a large chemical library for novel drug leads that shrunk the tumors. They then combined classical fly genetic tools with chemical modeling to develop second-generation drugs to better hit specific targets.

"Many successful drugs now in the marketplace have, by chance, wound up hitting several tumor targets, which is probably why they work," said Dr. Cagan. "The intention of our research was to hit multiple targets purposefully. By using fruit fly genetics we identified, step-by-step, the targets we needed. To my knowledge, this has never been done before. It's also a cost effective model and my prediction is there is going to be more emphasis on whole animal polypharmacology approaches in cancer drug research in the future."

For the study, investigators started out with Ret, the kinase that drives the growth of medullary thyroid tumors in people whose Ret has a cancer-activating mutation; a subset of lung cancer patients also have activated Ret. Researchers engineered a cancer form of Ret into fruit flies. The flies grew tumors wherever Ret was expressed. The investigators then tested dozens of drugs with the goal of curing the tumor.

One challenge is that Ret has many normal cellular roles and shutting it down everywhere in the body would lead to toxicity, a major problem with cancer drugs. "Our goal did not include the assumption that Ret needed to be shut down," said Dr. Cagan. "We wanted to see what worked on the tumors, and then figure out why it worked."

Researchers determined that their lead drug, AD57, suppressed several cancer signals emanating from Ret. These signals include some of the best-known cancer proteins such as Raf, Src, and Tor. Ret itself was not entirely shut down, which suggested to scientists that a patient would experience fewer side effects. The researchers then set out to improve AD57. They manipulated genes in the presence of the original drug hit, a process that had never been done before. As a result, they found that if they lowered the amount of Raf signaling in the presence of AD57, the drug would work even better.

Raf therefore was found to act as a desirable "target." Reducing Tor made AD57 more toxic, so researchers christened Tor an "anti-target," a new concept in drug discovery. Armed with an ideal target/anti-target profile, the Shokat laboratory then developed a derivative of AD57 called AD80.

"When we fed AD80 to the fruit flies, it was like a super drug," said Cagan. "It was remarkable how much AD80 you could give these flies and they didn't mind. This drug wiped the tumors out in a way AD57 or any other drug did not."

Tested in mice models with the same cancer, AD80 performed 500 times better on human cell lines, and far better in mice with very low toxicity, than a cancer drug that the FDA had recently approved for the same cancer type." That drug, vandetanib, is an orphan drug for patients with late-stage medullary thyroid cancer who are not eligible for surgery. Vandetanib was validated in similar fly models from the Cagan laboratory some years earlier.

"We hope that our research will influence the debate between those who favor pursuing drugs that address single vs. multiple tumor targets," said Cagan, who believes the rational polypharmacology model's success in identifying AD80 will prompt scientists and drug companies to pursue

broader approaches to attack tumors.

Provided by The Mount Sinai Hospital