The Fly Boy

Dr. Ross Cagan's approach to drug discovery aims to show how flies can be used to screen for new targets.

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Dr. Ross Cagan

The traditional process of finding a new drug starts by screening chemicals for their effect on a given target through cell-based screens. Modern drug discovery automates this, but it is still a process that depends on multiple screens of multiple chemicals to find a "hit" against a certain target. What follows is preclinical testing, which is expensive, time-consuming, and may not be predictive of clinical results.

Now a Mount Sinai researcher and his contract company are aiming to create a more efficient screening process — by using flies — that has the potential to lead to better classes of drugs.

Medros Inc. and Co-founder Ross Cagan, M.D., who is also a professor in the department of development and regenerative biology, and associate dean, graduate school of biological sciences at Icahn School of Medicine at Mount Sinai, have developed a method for using flies to model diseases such as cancer and diabetes.

Dr. Cagan's method is able to address the complexity of diseases because it uses a "whole animal" approach rather than using single cells. His process has the potential to lead to product candidates that have better efficacy and with lower risk for toxicity. The technology involves growing fruit flies that target disease.

"Flies allow us to take advantage of a century of tool building and embrace genomics," he says. "Let's take cancer as an example. We are learning from genomics that there are many mutations in a tumor; some of them matter and some of them don't. Flies allow us, patient by patient, to figure out which mutations are functional drivers and then rebuild those drivers in flies. My lab has been building fly models with eight or more hits, something that we can't do with any other model."

The biggest advantage of using flies, he says, is having the ability to do whole-animal screening, which can lead to a different class of drugs that can address the complexity of human disease.

"By using flies and a whole animal approach, we can reimagine and embrace the complexity of drug discovery," Dr. Cagan says. "First, there is a cost advantage. I can screen 50,000 drugs in a fly. I can't do 50,000 screens in a mouse. Flies have a very short lifecycle so building complex flies is straightforward and easier than other more complex model organisms. We identify drugs that act both in the tumor and elsewhere in the body, something that can't be done with cell lines. Flies fit in the sweet spot of being able to build complex models and then screen them readily and rapidly."

Dr. Cagan says flies also offer a powerful entry point for improving compounds.

"Flies can point us in a different discovery direction, while helping chemists," he says. "For example, say a compound hits two or three targets and we have figured out that some targets are detrimental to the drug's therapeutic index. We call these anti-targets. Chemists can then to work to delete that specific activity from a compound. We can determine the targets that need to be enhanced within the context of a whole animal, which is important for lowering toxicity. Subsequently, we can dramatically improve the therapeutic index."

One company that has used this approach is AstraZeneca as part of its development plan for Caprelsa (vandetanib). The therapy for advanced medullary thyroid cancer (MTC) was approved in the United States in April 2011 and in Europe in February 2012. MTC is a rare disease that can be fatal.

Most patients with MTC have an activating mutation in a receptor called RET, Dr. Cagan says.

"We put oncogenic RET into the fly, specifically in the eye since the fly doesn't have a thyroid," he says. "We got a tumor-like phenotype and we then used that to screen drugs. We helped identify vandetanib as useful for MTC, a drug originally developed as VEGF receptor antagonist. With the fly data and the cell line data, this drug was taken into clinical trials. It is now first-line therapy for MTC." PV

Creating Personalized Drug Cocktails

Ross Cagan, M.D., professor in the department of development and regenerative biology, and associate dean, graduate school of biological sciences at the Icahn School of Medicine at Mount Sinai, started the Mount Sinai Center for Personalized Cancer Therapeutics (CPCT) in September 2013. The goal of the center is to create novel cancer treatments that are based on a patient's own cancer genome.

"We are focusing on three different tumor types — medullary thyroid cancer, colorectal cancer, and triple negative breast cancer," he says.

For example, a colorectal patient may have 100 mutations. The center will test all 100 of them, one by one, using Dr. Cagan's fly model as a functional test to determine which mutations are drivers and which are passengers. From there, Dr. Cagan's Center creates a fly with the collective drivers of that person's cancer. Essentially, Dr. Cagan creates a fly with the same cancer as the patient.

Robotics then screen thousands of drug combinations, and use each patient's fly line to develop a customized treatment for that patient.

"We will do a full on drug screen of FDA-approved drugs looking for a two- to three-drug cocktail that shows an optimal therapeutic index on that fly," he says. "Then we source mammalian data and go back to the patient and the physician with a proposal for a treatment."