SEBASTIAN NIJMAN

MOLECULAR TEASER

New tools to probe how drugs perturb the interconnected biochemical and genetic networks within cells hold great promise for cancer drug design.

One of the enduring frustrations physicians encounter in treating cancer patients is how unpredictable treatments can be. In two people with ostensibly the same cancer, the same drug can induce remission in one but have little effect on the other. Some mysterious interplay of the cancer cell's molecular circuitry and the drug's intended target is to blame, of course, but what precisely? And how might that same circuitry be better defined, contextualized and targeted to undo the unique malignancy of each patient's cancer?

Sebastian Nijman, who joined Ludwig Oxford in November 2014, seeks to answer these questions. To that end, he has developed powerful new cell- and silicon-based technologies to investigate how drugs interact not only with one gene, or the protein it encodes, but also with the variegated genetic landscape of malignancies—an endeavor known as pharmacogenomics. He is, in other words, interested in the full suite of knock-on effects induced within the cell by that antagonistic encounter. "Many more tools are now coming online that will allow us to begin to address this problem in a much more systematic manner," he says.

A study Nijman published in early 2015, reporting work he did at the Austrian Academy of Sciences, in Vienna, is a case in point. He and his team identified a group of compounds that kill triple-negative breast cancer (TNBC) cells, a deadly tumor type that does not respond to current treatments.

To do this, they generated cancer cells genetically engineered to be similar to triple-negative cancers, with a similar set of genes turned on and off. They then exposed these cells to a vast library of more than 20,000 compounds, including experimental and approved drugs. About 100 compounds could kill the cancer cells—including one, PKC412, that has already been extensively tested in humans as a potential leukemia drug.

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Through desktop experimentation and computer modeling, they then asked what made PKC412 so special. What did it hit inside the cancer cells? And how did those interactions play out across the circuitry of malignant cells, according to the team's computer models? Their studies revealed that the drug induced suicide in a subset of TNBC cells, and suppressed tumor growth in animal models. Unexpectedly, the target of PKC412 is a signaling molecule called SYK, which turns on a second signaling protein that drives the growth of that subset of cells.

Nijman is eager to move this work forward at Ludwig Oxford. This goal will certainly be helped along by his additional appointment as director of functional genomics of the Target Discovery Institute in Oxford. This new institute, supported in part by Ludwig, is devoted to finding new drugs and drug targets, and it will provide Nijman with easy access to all sorts of new drug discovery technologies.

Nijman is also eager to establish collaborations with Ludwig colleagues who have expertise in the biology of various cancers, and who can help him test the compounds he identifies in mice and human tissues—and, eventually, in clinical trials.

"All these things together made it irresistible to come to Ludwig," said Nijman. "I see a lot of possibilities."