UC San Diego
UC San Diego News Center

March 13, 2012 | By Scott LaFee

A New Approach to Faster Anticancer Drug Discovery

Tracking the genetic pathway of a disease offers a powerful, new approach to drug discovery, according to scientists at the University of California, San Diego School of Medicine who used the approach to uncover a potential treatment for prostate cancer, using a drug currently marketed for congestive heart failure. Their findings are published in the current online issue of the *Proceedings of the National Academy of Sciences*.

“The science of genomics – the study of all of the genes in a person and how these genes interact with each other and the environment – has revealed many fundamental aspects of biology, including the mechanisms of diseases like cancer. But it has not yet been truly exploited to find new medicines to treat those diseases,” said Xiang-Dong Fu, PhD, professor of cellular and molecular medicine and senior author of the *PNAS* paper.

Fu, with colleagues at UC San Diego and elsewhere, describe a unique screening strategy that compares genes associated with specific disease phenotypes (traits) with small molecules capable of intervening with disease-linked gene-expression events. The high-throughput process, capable of analyzing large numbers of genes and drugs simultaneously, emphasizes investigation of the entire genetic pathway of the disease against a large set of internal controls, rather than its limited phenotype or any particular molecular or cellular target.

Historically, drug discovery has been driven by phenotype- or target-based methodologies.

“For 50 years, the standard phenotype approach emphasized the final outcome without worrying about the mechanism,” said Fu. “The process has produced some very good drugs, but researchers often didn’t know exactly how or why the drug worked. Aspirin is an example. It’s been around for more than a century, but we still don’t understand the mechanism in great detail.”

More recently, many drug designers have focused upon targeting particular components of a disease, such as a vital molecule or receptor involved in the pathogenic process. The approach has a stronger, more rational scientific basis, said Fu, but remains beset by two fundamental

difficulties: “You can create a drug that disrupts a specific disease target, but you also run the risk of causing unforeseen, adverse side effects that might be worse than the disease. Second, there are many places inside of a cell that are essentially ‘undruggable.’ They are difficult, if not impossible, to intervene with.”

The new approach attempts to avoid these problems by emphasizing investigation of the genetic pathways associated with disease processes and how they might be altered to produce a healthful benefit.

“The idea is to identify the genetic troublemakers associated with a disease and then find a way to contain them, not crush them,” said Fu. “No gene was ever designed to cause disease. The goal is to find new drugs or ways to convert these genes or the affected cells back to a normal state. In many disease paradigms, you don’t want to kill cells. You want to modify them to become healthy again.”

While the idea of conducting multi-target screenings is not new, the technology to do so has been limited. Deep sequencing, said Fu, is ideally suited for the purpose.

To illustrate the efficacy of their high-throughput, gene-sequencing approach, Fu and colleagues applied the strategy to prostate cancer, which sometimes becomes resistant to standard antiandrogen hormone therapy. The scientists found that Peruvoside, a cardiac glycoside, strongly inhibits both androgen-sensitive and androgen-resistant prostate cancer cells without triggering severe side effects. Interestingly, a related cardiac glycoside called Digoxin has been used to treat congestive heart failure. A large epidemiological study found protective effects against prostate cancer on patients treated with Digoxin, compared to control cohorts.

“High-throughput genetic sequencing and screening allows you to look deeply into cells and analyze millions of molecules at the same time. The technology is constantly improving and getting cheaper. We think it’s a promising strategy for drug discovery,” said Fu.

Co-authors include Hairi Li, Dong Wang, Jinsong Qiu, Yu Zhou, UCSD Department of Cellular and Molecular Medicine; Hongyan Zhou and Sheng Ding, Gladstone Institute of Cardiovascular Disease; Xianqiang Li, Signosis, Inc.; and Michael G. Rosenfeld, Howard Hughes Medical Institute, UCSD Department of Medicine.

Funding for this research came, in part, from the Prostate Cancer Foundation and the National Human Genome Research Institute.

UC San Diego's Studio Ten 300 offers radio and television connections for media interviews with our faculty, which can be coordinated via studio@ucsd.edu. To connect with a UC San Diego faculty expert on relevant issues and trending news stories, visit https://ucsdnews.ucsd.edu/media-resources/faculty-experts.