MedicalXpress

Scientists find new uses for existing drugs by mining gene-activity data banks

August 17 2011

Researchers at the Stanford University School of Medicine have paired up medicines and maladies with help from a molecular "Match.com." When the scientists applied an "opposites attract" algorithm to publicly available databases, surprising sparks flew: They found potential compatibilities between numerous existing drugs and diseases for which those drugs had never before been thought to be beneficial.

So far, preclinical tests have borne out at least two of these findings: Cimetidine — a widely used, cheap, over-the-counter anti-ulcer drug — may be a good fit for a form of lung cancer; and topiramate — an off-patent anti-seizure drug with a solid safety profile — may be therapeutic for inflammatory bowel disease.

Scientists led by Atul Butte, MD, PhD, associate professor of systems medicine in pediatrics, combed public databases with a sophisticated computer algorithm and identified numerous drug-and-disease pairs that may have a therapeutic future together. The coupling is based on the opposing directions in which a given disease and a given drug alter various genes' activity in tissues.

The results of this new study establish proof of principle for an approach that could significantly speed progress in combating difficult diseases with drugs that are already approved for other indications (a procedure called drug repositioning). They will be published online Aug. 17 in two separate studies (one each for the cimetidine and topiramate findings) in *Science Translational Medicine*. Butte, who is also director of the Center

for Pediatric Bioinformatics at Lucile Packard Children's Hospital, is the senior author of both studies.

What may be most counterintuitive of all, Butte said, is the degree to which a drug that is effective in a disorder, for instance epilepsy, may prove effective in one disorder as seemingly different as, say, Crohn's disease. Likewise, one wouldn't ordinarily assume an ulcer drug might be useful in fighting lung cancer.

But such leaps do occur in the medical world, albeit typically by accident instead of by systematic search. To name one popular example, a compound originally developed for heart problems turned out to be effective for erectile dysfunction and, eventually, for a severe lung disorder called pulmonary hypertension. That drug, sildenafil, is more commonly known by its brand name, Viagra.

In the early 2000s, Butte began assembling a systematic way to mine the wealth of underused information in public databases. "I was wondering: Can we predict these intersections, instead of stumbling across them?" he said.

The working hypothesis was simple, said Butte: "If a drug exerts a change on gene-activity pattern that is opposite to that exerted by a disease, then that drug may have a therapeutic effect on that disease."

Many studies aim to determine which of the approximately 30,000 genes contained in each cell of a given tissue are working hardest and which are quiescent. Every disease or drug affects cells' overall pattern of gene activity in its own way, pointing at genes that may be important in that disease's or drug's effects on that tissue.

New technologies have rendered routine the simultaneous measurement of activity levels of every gene in a cell or tissue. Today there are

750,000 results of such analyses in publicly available databases, nearly a 30-fold increase since 2004, said Butte. "For various reasons, very few scientists use the data that's already entered. So we thought we'd make use of this info."

The Stanford researchers restricted their database search to analyses in which human biopsy samples and normal tissues, or drugged and non-drugged samples, were compared in the same experiment, yielding more-accurate comparisons. About 100 diseases and 164 approved drugs met this narrow criterion. (That was five years ago, when the search now being reported began. The same screen initiated today, Butte said, would deliver profiles on about 1,500 diseases and more than 300 drugs.)

Butte's algorithm grouped diseases by how they changed gene activity instead of by the organ affected, and then paired them off against drugs whose gene-activity effects opposed those changes. Just like that celebrated little old lady of yore, the yenta, the algorithm suggested matches that, however startling, would prove to be made in heaven.

Butte's team chose two seemingly oddball pairings: cimetidine, an ulcer drug, for adenocarcinoma of the lung, which accounts for about 30-40 percent of all lung cancers; and topiramate, an anti-seizure drug, for Crohn's disease, an inflammatory bowel disorder.

Provided by Stanford University Medical Center