Gene Tests in Yeast Aid Work on Cancer

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People have been searching for new medicines for thousands of years, and yet we have barely explored the universe of possibilities. Recently chemists at the University of Bern in Switzerland tried to estimate how many promising molecules have yet to be tested. In June they published [their best guess](http://pubs.acs.org/doi/abs/10.1021/cn3000422): over a million billion billion billion billion billion billion. Blindly testing those molecules one at a time is not practical, and most of them will turn out to be useless anyway. So many scientists are looking for strategies they can use to zero in more quickly on promising candidates.

At the University of Texas at Austin, a team of biologists is speeding the search by [exploring our evolutionary history](http://www.nytimes.com/2010/04/27/science/27gene.html). They are finding surprising links between the biology of humans and that of our most distant relatives — links that point the way to new drugs. On Tuesday in the journal PLoS Biology, the researchers [describe the first fruit of this approach](http://www.plosbiology.org/article/info%3Adoi/10.1371/journal.pbio.1001379): a drug that shows a promising ability to shrink [tumors](http://health.nytimes.com/health/guides/disease/tumor/overview.html?inline=nyt-classifier). Its [cancer](http://health.nytimes.com/health/guides/disease/cancer/overview.html?inline=nyt-classifier)-fighting ability has been hiding in plain sight since the 1960s, when it was approved to treat fungal infections. Until the new research, no one had thought to test the drug against cancer.

One reason that drug hunting is so vexing is that scientists still don’t know much about the functions of many genes in humans. It’s much easier to study the genes in other species. Scientists have systematically mutated more than 6,000 genes in yeast, for example, observing the changes those mutations activate in the organism.

Humans and yeast share a common ancestor that lived some 1.2 billion years ago. That single-celled creature had already evolved clusters of genes that worked together to do particular jobs, like dividing cells or resisting stress.

The lineage that led to humans and the lineage that led to yeast both inherited the same clusters of genes. Over the next 1.2 billion years, the clusters took on different jobs. But many of the genes in the original cluster remained, working together on the new tasks.

Dr. Edward Marcotte, a molecular biologist at the University of Texas, reasoned that he might be able to uncover human gene clusters by looking at their counterparts in other species. In yeast, for example, he and his colleagues identified 68 genes that work together to build cell walls. Dr. Marcotte and his colleagues then looked at the scientific literature about the human versions of those genes. Five of them, they found, are involved in building blood vessels.

It’s next to impossible, statistically speaking, that this overlap was the result of chance. It’s far more likely that the cell-wall cluster in yeast and the blood-vessel cluster in humans evolved from an ancestral cluster of genes. Aside from the five genes that were known to be involved in blood vessel formation, Dr. Marcotte and his colleagues found other human genes matching those in the yeast cluster. But no one knew the function of those genes.

Dr. Marcotte hypothesized that they also helped build blood vessels. To find out, he and his colleagues did experiments on frog embryos. The researchers found eight additional genes that also helped build blood vessels, bringing the total to 13 so far.

This strategy has allowed Dr. Marcotte and his colleagues to make discoveries about hundreds of other genes. Plants have a network of genes for sensing gravity, for example. Dr. Marcotte and his colleagues have discovered a human version of the network, which helps build the nervous system. Mutations to this nerve network can cause [deafness](http://health.nytimes.com/health/guides/symptoms/hearing-loss/overview.html?inline=nyt-classifier).

Dr. Marcotte and his colleagues then used this strategy to search for new drugs. The scientific literature is packed with studies on how potential drugs affect other species. Dr. Marcotte’s research hinted that there were connections to human health hidden in the results.

Genes that guide the formation of blood vessels may offer targets for cancer drugs, for example. [Tumors](http://health.nytimes.com/health/guides/disease/tumor/overview.html?inline=nyt-classifier) grow so quickly that they need extra blood vessels to supply them with oxygen and nutrients. They release signals that spur nearby blood vessels to sprout new branches.

Dr. Marcotte suspected that a drug that attacks the yeast cell-wall cluster would also attack blood vessels in cancer cells. “We could make a blind prediction,” he said.

Hye Ji Cha, a graduate student on Dr. Marcotte’s team, programmed a computer to search through millions of test results of different drugs on yeast. She found a handful of molecules that targeted the cluster of genes that builds cell walls.

The drug that excited the scientists most was a compound known as thiabendazole. It was thrilling in its familiarity: Thiabendazole was approved by the Food and Drug Administration for fighting fungal infections back in 1967. One of the biggest worries in the search for drugs is that a promising compound will turn out to have toxic side effects. Thiabendazole’s long track record made it unlikely that Dr. Marcotte and his colleagues would get such an unpleasant surprise.

“We were particularly interested in it because it was human-approved,” Dr. Marcotte said.

To see if thiabendazole would attack blood vessels as they predicted, the scientists began by rearing frog tadpoles. Ordinarily, the tadpoles start to develop blood vessels three days after hatching. But when Dr. Marcotte and his colleagues gave thiabendazole to the tadpoles, their blood vessels disintegrated into free-floating cells. “The cells actually let go of each other,” Dr. Marcotte said.

The effects of thiabendazole were precise and limited. As soon as the scientists washed the drug out of the tadpoles, they immediately started rebuilding their blood vessels.

Dr. Marcotte and his colleagues then tried out thiabendazole on human blood vessel cells. Normally, the cells organize themselves into tubes. But when exposed to the drug, they fell apart.

These experiments gave Dr. Marcotte and his colleagues the confidence to try out thiabendazole on tumors. They transplanted human tumors into mice. Left untreated, the tumors grow rapidly, fueling their growth by coaxing the mice to build blood vessels.

In mice treated with thiabendazole, on the other hand, the tumors grew much more slowly. After 27 days, the drug-treated tumors were only about a quarter of the size of the untreated ones.

“I’m really excited about this coming out,” Dr. Morris Groves, the director of the Texas Oncology—Austin [Brain Tumor](http://health.nytimes.com/health/guides/disease/brain-tumor-adults/overview.html?inline=nyt-classifier) Center, said of the new research. Despite his excitement, he warned that thiabendazole might not prove effective on cancers in people.

“Ninety-five percent of drugs are probably going to fail,” he said. “You just build your world around it.”

Even if thiabendazole doesn’t reach the clinic, Dr. Groves thinks that Dr. Marcotte’s strategy for systematically exploring evolution will accelerate the discovery of drugs. “You can mechanize that and make it a lot faster,” Dr. Groves said. “That’s a great step forward.”