# Nature of the yeast

*By Lauren Martz, Staff Writer*

**University of Toronto** researchers have developed a yeast-based strategy to identify off-target effects of psychoactive drugs.[1] The approach could provide an early screen to find compounds with improved side effects and has already been licensed by a handful of biopharma companies. The unanswered question is whether findings in yeast will correlate with effects in humans.

Targets of traditional antipsychotics include dopamine receptors. Side effects associated with these first-generation drugs range from sexual and reproductive issues to seizures.[2] The impact on quality of life and patient compliance with these drugs prompted development of the next generation of drugs, dubbed atypical antipsychotics, which often target both serotonin (5-HT) and dopamine receptors. Atypical antipsychotics have been linked to cardiovascular and neurological problems such as myocarditis and agranulocytosis.[3]

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> *—Yona Geffen, BioLineRx Ltd.*

Corey Nislow and colleagues at the University of Toronto have developed a screening method that uses a library of yeast strains with single gene deletions to help identify the genes or pathways potentially responsible for a compound's side effects. In their *PLoS Genetics* paper describing the method, the researchers propose that the approach might help identify compounds with improved side-effect profiles.

According to Nislow, because yeast does not express the primary targets of either typical or atypical antipsychotics, any effects of a compound on yeast growth can be attributed to activity on secondary targets.

The hypothesis is that the equivalent human genes and pathways may be responsible for the side effects of antipsychotic drugs in humans.

The researchers first tested the effect of 214 psychoactive compounds on wild-type yeast and identified 81 that inhibited yeast growth. The other 133 may have been present at concentrations too low to have an effect or could have been pumped out of the yeast cells via drug and ion transporters.

The researchers subsequently screened the 81 compounds with the single-deletion yeast library. Computational analysis of the over 500,000 growth measurements obtained from the screen identified cellular processes affected by the drugs, such as secretion, protein folding and RNA metabolism.

## Brewing plans

Nislow thinks the screening technology will be most valuable as an early screening step in preclinical development. Although many companies want to see a firmer link between yeast and human results, others told *SciBX* there could be even broader uses for the screening method, such as drug reprofiling.

"Adding this screening system has the potential to improve drug discovery," said Kenneth Henry, senior research associate at **Case Western Reserve University**. "It gives you an idea of what to look at when moving forward to preclinical studies in other model organisms."

Case Western and **Diagnostic Hybrids Inc.** are developing and commercializing yeast-based diagnostic assays for HIV and other infectious diseases under a 2005 sponsored research agreement.

Yona Geffen, senior drug development manager at **BioLineRx Ltd.**, was less optimistic that the findings in yeast will mesh with results in humans. "It is not yet possible to correlate between cellular processes and actual profiles of side effects in humans. There is a need to understand the functional outcome of those off-target effects in humans," she said.

The method reported in *PLoS Genetics* "is at the level of cellular processes, but there is a need to understand the impact of those cellular processes on the entire human body," Geffen said.

BioLineRx's BL-1020, a dopamine and γ-aminobutyric acid A receptor ($GABA_A$ receptor) antagonist, is in Phase II testing to treat schizophrenia.

Nislow told *SciBX* that it's possible to make associations between yeast and human systems if the focus is on core cellular functions. "Cellular proliferation, vesicle trafficking and cell polarity—things absolutely conserved between yeast and man—can be analyzed," he said. "When you move to organ-specific processes and processes specific to differentiated cell types, you don't want to make any predictions and the method falls apart."

Henry agreed that certain cellular processes do translate from yeast to humans.

"I think you will find a lot of the same targets in yeast and other larger organisms, so I expect it to translate relatively well," he said. "If you consider a cellular process such as vesicle trafficking, which is secreting and taking up molecules, the relationship is clear. Compounds such as serotonin must be secreted by one cell type and taken up by another, and this occurs in both the human body and yeast populations."

He added: "If we use mice or monkeys, we will gain a better understanding of the compounds' effects on cell-cell interactions."

However, Henry said, "I don't think this method will serve as a substitute for identifying off-target effects through animal or clinical trials. We can't say that because it happened in yeast it must happen in animals. But it is a good starting point and I think more drugs should initially be evaluated this way."

Lon Cardon, SVP of genetics at **GlaxoSmithKline plc**, was interested in the technology's ability to help reprofile drugs. He said that because the paper identifies genes involved in cellular processes

targeted by psychoactive compounds, those compounds could be of interest to treat other disorders that involve the same processes.

GlaxoSmithKline has several compounds to treat schizophrenia in clinical development, including 773812, a mixed serotonin and dopamine receptor antagonist that is in Phase II testing. The company also markets depression therapeutics including Paxil paroxetine, a selective serotonin reuptake inhibitor (SSRI), and Wellbutrin bupropion, a norepinephrine and dopamine reuptake inhibitor.

## Next steps

Although the Toronto group's screening technology took advantage of the lack of primary targets including the dopamine and serotonin receptors in yeast, Nislow said his team is now seeking to engineer yeast that express the human targets. By doing so, he said, the group will be able to see the effects of drugs on the primary and secondary targets simultaneously and to determine how changes in the potency of drugs might be related to side effects.

Nislow said about half of the human cellular targets that are not naturally present in yeast could be expressed.

"It is also possible and relatively simple to modify the assays to consider almost all molecules," he said.

For example, Nislow said, because it can be difficult to observe the effects of the drugs on the yeast cellular processes before they are excreted from the cells, "it might be beneficial to reengineer the deletion strains with deleted efflux pumps as well. Our goal now is to determine which pumps can be deleted in order to keep the cells as healthy as possible but also as sensitive to the drugs as possible."

The screening method has been patented by **Stanford University**. Nislow told *SciBX* it has been nonexclusively licensed to several undisclosed companies and is available for licensing.

## REFERENCES

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## COMPANIES AND INSTITUTIONS MENTIONED

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