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New tool in the fight against tropical diseases

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A novel tool exploits baker's yeast to expedite the development of new drugs to fight multiple tropical diseases, including malaria, schistosomiasis, and African sleeping sickness. The unique screening method uses yeasts which have been genetically engineered to express parasite and human proteins to identify chemical compounds that target disease-causing parasites but do not affect their human hosts.

Parasitic diseases affect millions of people annually, often in the most deprived parts of the world. Every year, malaria alone infects over 200 million people, killing an estimated 655,000 individuals, mostly under the age of five. Unfortunately, our ability to treat malaria, which is caused by Plasmodium parasites, has been compromised by the emergence of parasites that are resistant to the most commonly used drugs. There is also a pressing need for new treatments targeting other parasitic diseases, which have historically been neglected.

Currently, drug-screening methods for these diseases use live, whole parasites. However, this method has several limitations. First, it may be extremely difficult or impossible to grow the parasite, or at least one of its life cycle stages, outside of an animal host. (For example, the parasite *Plasmodium vivax*, responsible for the majority of cases of malaria in South America and South-East Asia, cannot be continuously cultivated in laboratory conditions.) Second, the current methods give no insight into how the compound interacts with the parasite or the toxicity of the compound to humans.

In an effort to develop new drugs to fight parasitic diseases, scientists

from the University of Cambridge have collaborated with computer scientists at Manchester University to create a cheaper and more efficient anti-parasitic drug-screening method. The clever screening method identifies chemical compounds which target the enzymes from parasites but not those from their human hosts, thus enabling the early elimination of compounds with potential side effects.

Professor Steve Oliver, from the Cambridge Systems Biology Centre and Department of Biochemistry at the University of Cambridge, said: "Our screening method provides a faster and cheaper approach that complements the use of whole parasites for screening. This means that fewer experiments involving the parasites themselves, often in infected animals, need to be carried out."

The new method uses genetically engineered baker's yeast, which either expresses important parasite proteins or their human counterparts. The different yeast cells are labelled with fluorescent proteins to monitor the growth of the individual yeast strains while they grow in competition with one another. High-throughput is provided by growing three to four different yeast strains together in the presence of each candidate compound. This approach also provides high sensitivity (since drug-sensitive yeasts will lose out to drug-resistant strains in the competition for nutrients), reduces costs, and is highly reproducible.

The scientists can then identify the chemical compounds that inhibit the growth of the yeast strains carrying parasite-drug targets, but fail to inhibit the corresponding human protein (thus excluding compounds that would cause side-effects for humans taking the drugs). The compounds can then be explored for further development into anti-parasitic drugs.

In order to demonstrate the effectiveness of their screening tool, the scientists tested it on *Trypanosoma brucei*, the parasite that causes African sleeping sickness. By using the engineered yeasts to screen for

chemicals that would be effective against this parasite, they identified potential compounds and tested them on live parasites cultivated in the lab. Of the 36 compounds tested, 60 per cent were able to kill or severely inhibit the growth of the parasites (under standard lab conditions).

Dr Elizabeth Bilsland, the lead author of the paper from the University of Cambridge, said: "This study is only a beginning. It demonstrates that we can engineer a model organism, yeast, to mimic a disease organism and exploit this technology to perform low-cost, fully-automated drug screens to select and optimise drug candidates as well as identify and validate novel drug targets."

"In the future, we hope to engineer entire pathways from pathogens into yeast and also to construct yeast strains that mimic diseased states of human cells."

More information: The research is published today, 27 February, in the journal *Open Biology*.

Provided by University of Cambridge