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Screening effort turns up multiple potential anti-malaria compounds

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Numerous potential anti-malarial candidate drugs have been uncovered by investigators from the National Institute of Allergy and Infectious Diseases (NIAID) and the National Human Genome Research Institute (NHGRI), both parts of the National Institutes of Health (NIH).

Researchers at the NIH Chemical Genomics Center, administered by NHGRI, used robotic, ultra-high-throughput screening technology to test more than 2,800 chemical compounds for activity against 61 genetically diverse strains of lab-grown malaria parasites. They found 32 compounds that were highly effective at killing at least 45 of the 61 strains. Ten of these compounds had not previously been reported to have anti-malarial action, and seven were more active at lower concentrations than artemisinin, a widely used malaria drug. All the screened compounds are already registered as safe or approved for use in humans or animals, although not necessarily for use against malaria. The most promising compounds revealed in the new screen may thus face a shorter path than usual to development into anti-malarial drugs.

Scientists from NIAID's Laboratory of Malaria and Vector Research also determined that just three parasite genes—the same three genes that confer resistance to currently used malaria drugs—were associated with resistance to many of the screened compounds. This suggests that the malaria parasite has a limited number of ways to develop resistance following exposure to drugs. In theory, if drug combinations could be devised to target activity of all three resistance genes simultaneously, the parasite could be disarmed.

The research also provides a wealth of leads for scientists seeking to combine new or existing compounds into better multi-drug regimens against malaria. For example, the team identified dozens of compounds that act in a manner similar to artemisinin. Combining drugs that act similarly could yield treatment strategies that work better or require fewer doses.

Because malaria parasites can have a single genetic mutation that confers resistance to one drug while simultaneously increasing sensitivity to another drug, the investigators also looked for pairs of compounds with complementary activities. If used together, such complementary drug pairs could slow the emergence of drug resistance in parasites, because the parasite with the mutation—which does not respond well to one compound—would be killed by the other compound to which it has enhanced susceptibility conferred by the mutation. In this regard, the team found many compounds that killed strains of parasites resistant to a standard malaria drug, chloroquine. Since chloroquine-resistant parasites are widespread in many parts of the world, further studies of compounds with complementary activity could lead to new combination treatments for these drug-resistant parasites, the scientists write.

More information: J Yuan et al. Chemical genomic profiling for antimalarial therapies, response signatures and molecular targets. *Science* (2011) DOI: 10.1126/science.1205216 .

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