Promising new one-dose malaria drug discovered

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Researchers have discovered a promising new malaria drug with the potential to treat resistant strains of the deadly disease in a single dose, according to a study published Thursday in the journal *Science*.

An international team led by scientists from The Scripps Research Institute, the Swiss Tropical Institute, the Genomics Institute of the Novartis Research Foundation and the Novartis Institute for Tropical Diseases has discovered a promising new drug candidate that represents a new class of drug to treat malaria. Clinical trials for the compound are planned for later this year.

The research was published on September 3, 2010, in the prestigious journal *Science*.

"We're very excited by the new compound," said Elizabeth Winzeler, a Scripps Research associate professor and member of the Genomics Institute of the Novartis Research Foundation (GNF) who led the research with Thierry Diagana of the Novartis Institute of Tropical Diseases. "It has a lot of encouraging features as a drug candidate, including an attractive safety profile and potential treatment in a single oral dose."

The Problem with Malaria

Malaria is a nasty and often fatal disease, which may lead to kidney

failure, seizures, permanent neurological damage, coma, and death. The disease is caused by Plasmodium parasites, transmitted through the bite of infected mosquitoes.

Despite a century of effort to globally control malaria, the disease remains endemic in many parts of the world. According to the World Health Organization, in 2008 there were 247 million cases of malaria and nearly one million deaths - mostly among children living in Africa. The need for new treatments is made more urgent by the spread of drug-resistance to current medications.

While some 40 percent of the world's population lives in malaria-infected areas, little economic incentive for pharmaceutical companies to develop new treatments exists, since malaria-infected areas correspond with the some of the world's most impoverished nations.

To help surmount this barrier, concerned individuals have formed public-private partnerships to help spur research on much-needed treatments. The current study is the result of one such partnership. In addition to in-kind contributions by the pharmaceutical company Novartis (including its decade-old Novartis Malaria Initiatives) and the scientific expertise of scientists in academic laboratories around the world, the research was made possible by the support of the nonprofit organizations Medicines for Malaria Venture, the Wellcome Trust, and the W. M. Keck Foundation, as well as funding from government agencies in the United States (the National Institutes of Health (NIH) National Institute of Allergy and Infectious Diseases (NIAID) and Singapore (Agency for Science, Technology, and Research (A*STAR)).

In Pursuit of a New Drug

The impetus for the new study began in the Scripps Research Winzeler laboratory about seven years ago when Winzeler received funding from

the Keck Foundation to develop new antimalarial drugs by pursuing target-based drug discovery methods (designing a drug based on known molecular interactions). The approach was not yielding many interesting compounds, so Winzeler and her collaborators at GNF decided to take a different tack.

Noting that serendipity and observation played a role in all previous breakthrough antimalarials (for example, the drug artemisinin was derived from an herb used in traditional Chinese medicine), the team decided to pursue cell-based screening. The Winzeler lab at GNF then developed a high-throughput screen to look for compounds active against the malaria parasite Plasmodium falciparum. Scientists at Novartis, which had compiled a library of 12,000 purified natural products, then offered their library for the screen.

The first screen returned a set of 275 compounds with anti-malarial activity. Subsequent screens weeded out those with little activity against multi-drug resistant parasites and those toxic for mammalian cells. Seventeen compounds remained in the running.

An evaluation of the remaining compounds' toxicity and pharmacokinetic profiles provided additional information to evaluate their potential drug candidates. One compound—belonging to a chemical class of molecules called spiroindolones, which had never before been associated with anti-malarial activity—stood out as particularly promising.

Novartis Institute for Tropical Medicine's project team head Bryan Yeung noted, "Of the remaining compound classes, the spirotetrahydro-beta-carbolines or spiroindolones displayed the desired physicochemical properties for drug development, as well as a mechanism of action distinct from the currently used therapies based on aminoquinolines and artemisinin derivatives."

In an effort based at the Novartis Institute of Tropical Diseases in Singapore, the chemistry team synthesized and evaluated some 200 derivatives of this molecule to optimize its safety profile and pharmacokinetic properties. At the end of several hundred rounds of medicinal chemistry and efficacy testing at the Swiss Tropical and Public Health Institute, the team advanced NITD609 as the best candidate for proceeding to clinical trials.

Shining Light in the Black Box

The new study, however, doesn't stop there. To gain insight into how NITD609 worked, Winzeler applied a distinctive and elegant evolutionary approach.

Winzeler noted, "One of the disadvantages of doing cellular screening has been chemists will say, 'You don't know what the target is. You don't know if the parasites are going to become resistant to it. It's a huge black box.' It has been extremely difficult to find the genes involved in malarial drug resistance using traditional methods. So what we've been doing in my lab is developing ways to find single-base changes in drug-exposed genomes."

In this case, Case McNamara at GNF, a lead author, took a parasite and cloned it to create two identical organisms. One was allowed to reproduce in regular culture. The other was placed in a culture with a sub-lethal dose of the anti-malarial drug candidate. After three to four months and many generations, the parasites in the culture with NITD609 started to display low-level drug resistance.

At that point, the team used an advanced tiling array to compare the 26 million base pairs of coding sequence in the genome of the drug-exposed organisms to the genome of the control organisms.

"We were expecting hundreds or thousands of mutations because we grew the parasites for many generations," Winzeler said. "We got only a handful."

When McNamara analyzed the genomes of the six resistant clones, it turned out that all of the mutant strains had at least one mutation mapping to a single gene, pfatp4. This suggests that the protein PfATP4 is either the target for the new drug candidate or is involved in the parasite's resistance to it in some other way.

"PfATP4 is a cation transporting ATPase, so it is a very well validated drug target," said Winzeler. "That class of proteins, for example, is the target of antacids. It hasn't really been explored in malaria. This is one of the first cases where an evolution study has been used to identify the action of a compound in a parasite cell."

More information: "Spiroindolones, a new and potent chemotype for the treatment of malaria," Matthias Rottmann et al., *Science*, Sept 3 2010. DOI:10.1126/science.1193225

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