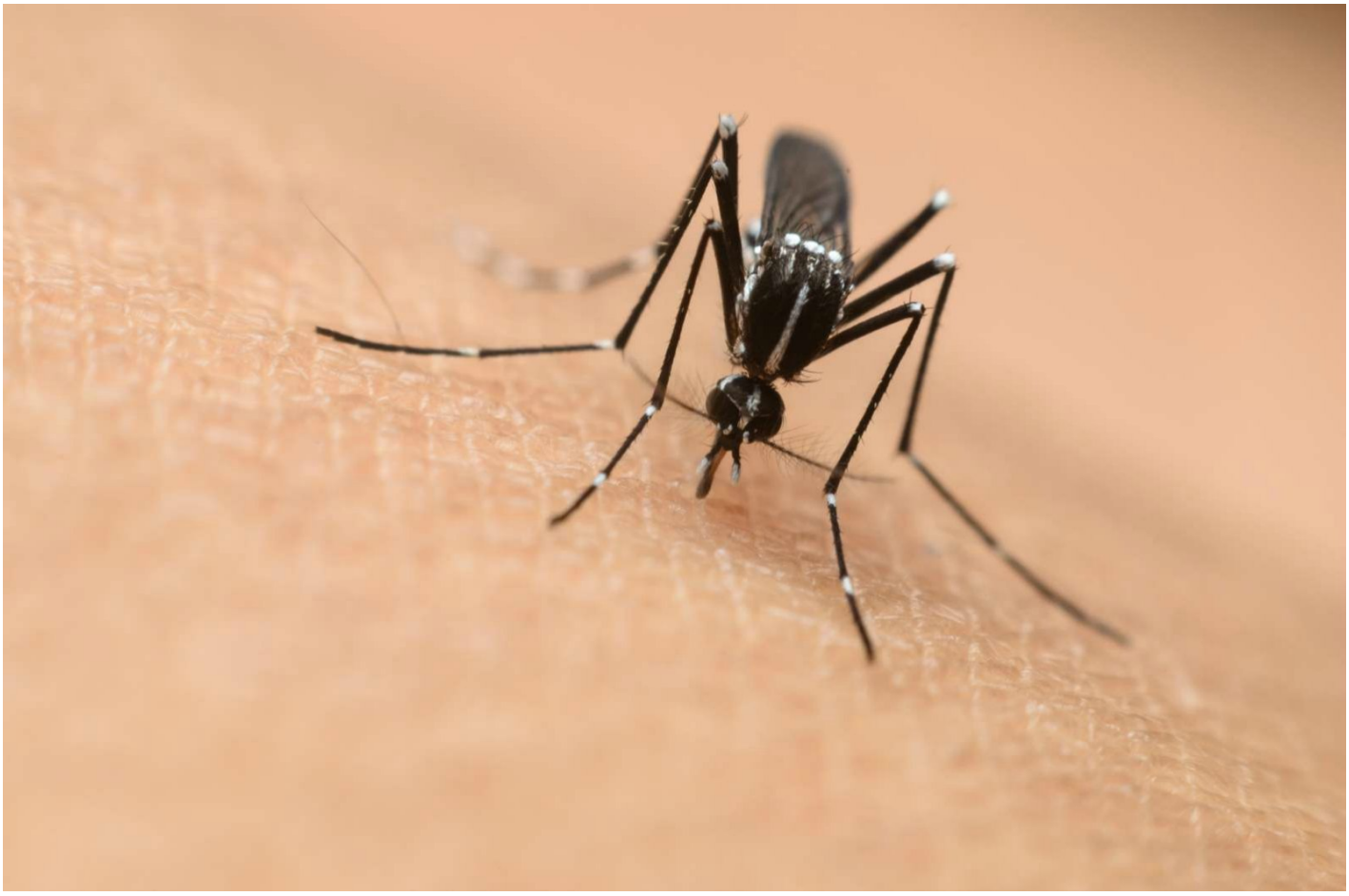
Malaria: A New Approach Takes On An Old Disease

Portland State University



As a professor of chemistry specializing in nuclear magnetic resonance spectroscopy at Portland State University in the 1990s, David Peyton, Ph.D., was studying the structures of molecules when a colleague asked him for assistance with spectroscopic analysis of a new class of drugs.

That collaboration two decades ago was Peyton's introduction to malaria, a scourge that annually infects more than 300 million people and causes 1 million deaths worldwide, according to the National Institutes of Health. From that early collaboration, he developed a deep concern about the disease.

"First and foremost," Peyton says, "malaria is a human problem. More than 40 percent of the Earth's population lives in areas where it is a health risk — primarily in Africa and Asia. It's estimated that a child dies from malaria somewhere in the world every 40 seconds."

Children and pregnant women are especially at risk. If young children survive their first malaria infection, their risk of death from subsequent bouts is diminished, since their immune systems will have adapted somewhat. But their

vulnerability during the first infections is very high. Pregnant women are vulnerable because their immune systems are lowered by their condition. Unborn children are also greatly at risk.

"Frustratingly," Peyton says, "there are drugs for malaria that have been effective in the past — particularly chloroquine — but that have lost their potency as the malaria parasite evolved an ability to resist them."

Today, Peyton is still a professor of chemistry at Portland State University (PSU) and still immersed in nuclear magnetic resonance spectroscopy, but now he is the inventor of a potentially significant breakthrough in the treatment of malaria. By chemically bonding chloroquine with drugs called resistance reversal agents, he's created a new, hybrid agent more effective than either one alone. He calls it reversed chloroquine.

Malaria in Brief

Malaria is caused by tiny, single-celled parasites of the genus Plasmodium. There are more than 100 species, and different species of malaria are found in many kinds of birds and animals. Humans are vulnerable to just four species.

One, P. falciparum, is responsible for the great majority of the most serious human infections and for most deaths, especially in Africa.

Key to human Plasmodium infection is the Anopheles mosquito. Infected Anopheles inject the parasite into humans as they feed on their blood. The parasites then begin a cycle of invading their human hosts' liver cells and releasing merozoites that invade the red blood cells. Some of these transform into sexual forms that, ingested by mosquitoes as they prey on humans, repeat the cycle.

Chloroquine was developed in 1934, but ignored until after World War II, when it became widely used to treat — and prevent — malaria. Optimally, it works by establishing itself in a Plasmodium's digestive vacuole, binding with heme, a component of hemoglobin released by its digestion. This binding prevents the parasite from sequestering the toxic heme and leads to the death of the parasite. But over time, P. falciparum evolved an ability to eject the chloroquine from its vacuole, rendering the drug ineffective.

Resistance Reversal Agents

Peyton settled on the concept of combining resistance reversal agents with chloroquine because he believed that restoring the effectiveness of a standout medication like chloroquine was more promising than trying to develop a new malaria drug from scratch.

"Resistance reversal agents are drugs that have little or no anti-malarial properties of their own," he says. "In fact, they include things like antidepressants and blood pressure medications. But administered in combination with chloroquine, they help it overcome the parasite's resistance. The catch is, as separate medications in the combination, they have to be used in very large doses. I wondered what would happen if they could be chemically bonded to chloroquine." He and his graduate student, Steven Burgess, decided to find out.

> *"What happened in laboratory tests was that a hybrid version of chloroquine and resistance reversal agent proved remarkably effective in remarkably lower doses — much lower than either when used alone.*

The specific mechanisms are unclear, but Peyton suspects that when a reversal agent is administered with chloroquine as two separate parts of a simple cocktail, the reversal agent has trouble getting into the Plasmodium's digestive

vacuole where it is needed to keep choloroquine from being ejected. Thus, large doses are required. In a chemically bonded hybrid, he suggests, the chloroquine pulls the reversal agent along with it all the way into the digestive vacuole where it does its work.

An important aspect of the approach, Peyton notes, is that as the parasite evolves to resist the new drug, the hybrid can be reengineered with new resistance reversal agents.

In 2005, Peyton informed PSU's technology transfer office that he might be onto something. PSU submitted its first patent application for the work that year. Thus far, outside funding included National Institutes of Health grants. The next step was to find funding to move the research and development forward.

"David was so concerned with advancing the research that he became involved in the search for a company," notes Dana Bostrom, the university's director of innovation and industry alliances. "We sent him to a weeklong 'boot camp for scientists' at the university called Lab2Market. It focuses on technology transfer and commercialization. One part is a mentorship program, matching them with experienced entrepreneurs. Through it, he met Lynn Stevenson and Sandra Shotwell."

Designing DesignMedix

Stevenson and Shotwell had both been technology office directors at separate universities before they joined together to form a consulting firm, Alta Biomedical Group, based in Portland, Ore. Since each had had experience with malaria drugs in the past, they were intrigued by Peyton's work.

"As a team," Shotwell says, "we decided the next step in moving the technology forward was getting funding for focused drug development." They felt that by forming a company, they could pursue federal small business grants.

DesignMedix was established in 2006. Stevenson serves as the chief executive officer, Shotwell as the chief operations officer and Peyton — still full time at PSU — as chief scientific officer.

"We were lucky enough to get a Phase I small-business grant on the first try," Shotwell notes, "and the results of that work were exciting." This helped DesignMedix get a larger Phase II grant, as well as private equity funding from investors, including the Oregon Angel Fund.

In 2009, DesignMedix won the top prize in the Angel Oregon competition, sponsored by the Oregon Entrepreneurs Network. By 2010, they had six employees, including Burgess (by now a doctorate), an active laboratory and were moving into formal preclinical studies. Support from the university was essential to their progress.

"Portland State is committed to fostering entrepreneurship," says PSU's Bostrom. "We operate a 40,000-square-foot Business Accelerator to support startups. It houses 20 companies and will soon add more than 2,000 square feet of wet-lab space, including a new laboratory for DesignMedix."

DesignMedix/PSU ties are financial as well as logistical — in 2008, the university negotiated a license with DesignMedix. One provision dictates that in any commercialization of the technology, the university won't receive royalties from sales in specified developing nations — reflecting a concern that, often, the people most in need of such medicines are the ones who can least afford them.

Preclinical Studies and a Pipeline

As 2010 began, reversed chloroquine was in preclinical studies. The product has been through laboratory and animal

tests, with highly encouraging results. DesignMedix hopes to go to the U.S. Food and Drug Administration to seek approval for clinical trials within two years.

In the meantime, the company has licensed additional technology from the Portland VA Medical Center and the Oregon Health & Science University for a different class of antimalaria molecules and has begun research on applying Peyton's hybrid techniques to overcoming resistance in bacteria such as methicillin-resistant Staphylococcus aureus (MRSA), an increasingly common, infection-causing bacterium that has been highly resistant to treatment.

How does David Peyton the chemistry professor react to the prospect of being David Peyton the entrepreneur — and creator of a significant drug?

"This is the first time I've even been involved in commercialization," he says. "I do spectroscopy. I study molecules. We're all involved in academia because we enjoy learning. This isn't academic, but, boy, has there been a learning curve!"

He adds: "The process is arduous, but the end result may be a solution to a terrible disease that affects millions of people. It's worth it."

This story was originally published in 2010.

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