Modernizing malaria research through a new, interdisciplinary approach

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(Medical Xpress)—Despite a relatively low incidence of malaria in the United States since the 1950s, the disease continues to pose a major threat to nearly half the world's population.

According to the World Health Organization

(WHO), an estimated 3.4 billion people in 97 countries live in areas at risk of

malaria transmission. In 2012, according to WHO estimates, there were 207 million cases of malaria worldwide resulting in 627,000 deaths.

"The literature on malaria is over a hundred years old," says Manuel Llinás, an associate professor of biochemistry and molecular biology at Penn State. "It's a very well-studied disease. It's one of the most classic illnesses of humankind. And yet we currently still have no great ways to actually tackle this thing."

The main reason for this, he argues, "is that we just simply don't understand the parasite that causes malaria very well yet."

Llinás has been working on malaria for nearly a decade, beginning with an early interest in emerging genome-sequencing technology.

"Initially," he explains, "I was working in a completely different field. But when the malaria genome was sequenced in 2004, it provided an

opportunity to start asking genome-wide-level questions with regard to how the malaria parasite develops, and so we designed the first DNA microarray to be used to analyze the malaria parasite as it replicates in red blood cells as it does during the infection."

Now, having firmly established itself in the malaria field, Llinás's lab focuses specifically on the 48-hour blood stage of the Plasmodium parasite.

Half of the lab's researchers are investigating the parasite's regulation of DNA transcription during the blood stage, "with the idea," says Llinás, "that if we can understand how the parasite's genes regulate its development in red blood cells, then we can attack it."

But of the roughly 5,400 genes in the Plasmodium genome, it's only for about half of them, Llinás notes, that "we can make good guesses at what they probably do. I look at the other half and wonder why there is 50 percent of this organism that we have no understanding of at all. I think it's likely that parasite-specific biological processes are functioning through those genes, and in there lies tremendous potential for coming up with new ways to attack the parasite."

So while some researchers in the Llinás Lab employ genomics techniques to better understand the Plasmodium parasite's blood-stage transcription regulation, other researchers study the parasite's metabolism during the blood stage, using mass spectrometry to examine small molecular byproducts of metabolism, known as metabolites.

"There's this new wave of research known as metabolomics," Llinás says, "and we jumped into this, being the first ones to start looking at the malaria parasite in this way. The idea is that if we can we understand the nutritional requirements between the host and the parasite – what molecules it takes in and what it spits back out, how we respond to those

molecules, whether they're different from the ones we make – then that may open up the possibility for novel therapies targeting the parasite's metabolism."

As his approach to studying the Plasmodium parasite may suggest, Llinás isn't a classically trained parasitologist; but as a result, he says, "I feel like I come into this field with a lot of freedom to move through territory where there are currently a lot of biases."

Llinás recently moved his lab from Princeton University to the Millennium Science Complex at Penn State, where he will be launching the Center for Malaria Research (CMaR) this spring with a cadre of other well known and respected Penn State malaria researchers.

"My vision," says Llinás, "was to come here and build a small malaria research center around this group of people to really focus on this disease – to foster creative new research ideas, funding opportunities, and teaching outlets – and to draw on all the expertise we have around us."

"There are very few places in the world currently that have the capabilities that Penn State has to do all aspects of parasite biology," he declares. "I'm surrounded by people who work on all stages of the malaria parasite's development, on the ecology of the disease, people with field sites. Probably we're one of three places in the world currently that can move the malaria parasite from blood into mosquitoes, back into the liver, back into the blood, and complete the full cycle, asking any question along the whole trajectory of the complete life cycle of the malaria parasite – and that's very enviable."

"Of course," Llinás continues, "the Huck Institutes and my department in Biochemistry and Molecular Biology just have a tremendous number of resources and expertise in so many fields – biochemistry, genetics,

parasitology, vector biology – all these things that are clearly really important to what we do in my lab."

Llinás also notes what he says is "a real strength at Penn State in genomics" research.

"To bring classic, traditional malaria research into the 21st century," he says, "I'm all about trying to move us into the genome-centric world – how we do things at the cutting edge, just like is being done in human cancer studies or yeast biology or fly developmental biology – to really innovate and bring those kinds of tools to parasitology. I see a ton of opportunity here to do experiments that I would never have been able to do before coming to Penn State."

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