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Fighting resistance to antimalarial drug

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When it comes to the emergence of antimalarial drug resistance, it's not a question of 'if' but 'when'. In order to keep up with the quickly evolving Plasmodium parasite - the cause of malaria - new ways to treat and control the disease must be found. But many of today's antimalarial drugs, such as artemisinin, were developed without a great understanding of how the drug actually killed the parasite.

Now the EU-funded project MALSIG, which ended in 2012, may have

provided important insight into the parasite's biology. Kinases are vital enzymes involved in signalling pathways in all cells. But project researchers gained a good understanding of which specific kinases play key roles in the life cycle of the parasite. Project coordinatorGordon Langsley, a researcher at the Institute Cochin in Paris, France, believes targeting kinases may be one of the most promising routes to developing new antimalarial drugs.

Why kinases? "Because they are drug targets in cancer and many other diseases," Langsley tells youris.com. "Some of the early cancer drug leads were not very efficacious against the human enzymes. But the idea is that they could work against the parasite enzymes." Since developing new antimalarial drugs is not at the top of the list for most pharmaceutical companies, 'piggybacking' on the drug development for other diseases like cancer is an especially valuable approach in malaria research, he adds.

Even though the project brought some advances, Langsley says there's still a vast amount of work to do to identify the proteins that kinases phosphorylate, or activate, in the cell. Once phosphorylated, these proteins go on to perform vital cellular functions, the arrest of which can lead to cell death. Understanding the ins and outs of these protein-kinase interactions will give researchers the ability to develop new drugs that cause less side effects in humans. But also it could enable scientists to find a common thread among all the Plasmodium variants around the world. Such knowledge could lead to an effective vaccine.

One expert appreciates the magnitude of the problem and the importance of the project. "This is complex, big biology. Whole genome wide and proteome wide approaches will be required to understand the [kinase] pathways. And those kinds of technologies are only just emerging," says Julian Rayner, a senior group leader at the Wellcome Trust Sanger Institute near Cambridge, in the UK. "So I don't think it's a

surprise that, while the project has been very successful in identifying targets, there is still more work to do."

Rayner believes two issues usually hinder malaria research – funding and the complexity and uniqueness of the parasite. "There's no question that [malaria] receives less attention than other diseases that have a more economic upside," he notes. The Plasmodium parasite is also, like humans, a eukaryotic organism. This means that its cellular biology is more complex than that found in other organisms like bacteria or viruses. In addition, its genome is quite unique, as many of its genes are not clearly related to others in eukaryotes. These characteristics make developing techniques to study Plasmodium difficult and that's why collaborations like this project are important, according to Rayner. He also tells youris.com: "It's not always obvious which way is the best way forward, so we have to share approaches and knowledge."

But another expert is concerned that there is no golden ticket to solving this global health issue. Targeting kinases "is a very valuable approach, but we should target as many different approaches as possible if we really want to tackle the very complicated life cycle of and disease caused by this parasite," says Maria Mota, a researcher at theUniversity of Lisbon's Institute for Molecular Medicine in Portugal.

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