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Project of the Year 2020

The brilliance of resistance profiling

Each year, a project is selected by Medicines for Malaria Venture's (MMV's) independent Expert Scientific Advisory Committee (ESAC) as Project of the Year. This highlights an exciting drug discovery and development project in the MMV portfolio and recognizes the scientific excellence of partners involved. The winner of Project of the Year 2020 is the malaria drug resistance profiling project, led jointly by Prof. David Fidock (Columbia University, USA) and Dr Didier Leroy (MMV). This project profiles potential new antimalarials to discern their potential to select for resistance – and to characterize any resistance – before projects are progressed into human studies.

Resistance to antimalarial medicines is an ongoing concern in malaria, leading to failure of frontline therapies. Broadening our understanding of resistance mechanisms is key to addressing this major issue. By investigating new antimalarials in the laboratory, the project team can better predict how resistance can develop in a real-world setting. This profiling also improves efficiency in drug discovery by identifying drug candidates exhibiting higher risks early and characterizing favourable compounds that can progress into more advanced and costly studies. Such an approach has also increased our understanding of resistance mechanisms in older drugs including chloroquine, piperaquine and artemisinin.

Prof. David Fidock
C.S. Hamish Young Professor of Microbiology & Immunology and Medical Sciences, Columbia University, USA

Dr Didier Leroy
Senior Director, Drug Discovery, MMV

Prof. David Fidock and Dr Didier Leroy discuss the malaria drug resistance profiling project.

Could you briefly describe the profiling project? When did it begin and how has it evolved?

Dr Leroy: The drug discovery profiling project is central to MMV's drug development pipeline. Its purpose is to interrogate the biology of the malaria parasite in terms of drug resistance, using laboratory-based techniques to predict the risk of resistance in the field. The Fidock lab started coordinating with MMV in 2008 to investigate the drug discovery and development portfolio and identify resistance risks.

Prof. Fidock: Profiling is done throughout drug development, from early drug discovery to lead compounds and candidate selection, allowing for de-prioritization of series with unacceptable risks. Through whole-genome sequence analyses of cultured, drug-pressured resistant parasites, we can investigate the genetic basis of *Plasmodium falciparum* resistance. This increases our understanding of the parasite's biology and helps us identify novel mechanisms of action that won't be compromised by resistance mechanisms already existing in the field. Our technology has evolved to allow for accelerated processes in the laboratory, whole-genome sequencing analyses and reverse-genetic approaches to confirm the impact of point mutations or copy number variations on resistance. In addition, data accumulated in recent years has shown that our laboratory results closely match what is seen in human volunteer infection studies, humanized mouse models and clinical trials, showing that the drug discovery profiling project can accurately predict paths to resistance.

Why is it an exciting project?

Dr Leroy: This project is exciting because, for the first time, we are at a point in malaria drug discovery where we can investigate compounds and relate resistance data to the real-world setting. In turn, discovery can be guided by clinical data, effectively 'closing the loop' in malaria drug development.

Prof. Fidock: Beyond this, our project has interrogated key pathways in the malaria parasite and helped to increase our understanding of its biology, particularly its vulnerabilities from a therapeutic perspective.

How does the project fit into MMV's overarching strategy on resistance risk assessment?

Dr Leroy: This profiling project is integrated into MMV's overarching strategy as a key tool in assessing the risk of resistance throughout the pipeline. Resistance could be interrogated in clinical trials, however, the ability to identify resistance risks during the drug development process allows MMV to make strategic decisions much earlier to deliver higher-quality antimalarial candidates and combinations.

Why is it important to define the resistance risks of antimalarials?

Dr Leroy: It is highly cost-effective to have a platform that can predict the risk of resistance early. Re-prioritization through defined risk criteria allows resources to be used more efficiently and results in higher-quality products. In addition, our understanding of resistance can be used to inform future antimalarial development, particularly the choice of combination partners.

What led you to develop this project and decide to work together?

Prof. Fidock: This project presented a very appealing convergence of interests. Our lab was initially focused on understanding clinical resistance of first-line antimalarial medicines, but it became clear that investigating drug resistance in antimalarial candidates is key to helping guide drug discovery and development efforts. In this way, MMV and our lab were motivated to work together to develop and deliver next-generation medicines for malaria. This has been, and continues to be, an extremely enriching partnership that benefits from the extensive experience of all partners.

What has the impact of this project been on MMV's portfolio and the drug discovery process?

Dr Leroy: So far, 180 compounds have been investigated and 18 drug targets and mechanisms of resistance have been identified. This has had an extensive impact on the development and quality of compounds in MMV's pipeline. MMV is a global leader in coordinating malaria drug discovery and development, and this project has benefitted academia, industry and pharmaceutical research by streamlining development and highlighting the need to identify resistance early.

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