DEPARTMENT OF CHEMISTRY AND ENVIRONMENTAL SCIENCE
SEMINAR SERIES
FALL 2023

WEDNESDAY, FEBRUARY 22, 2023
TIERNAN HALL – LECT. HALL 2
1:00PM-2:20PM

GUEST SPEAKER

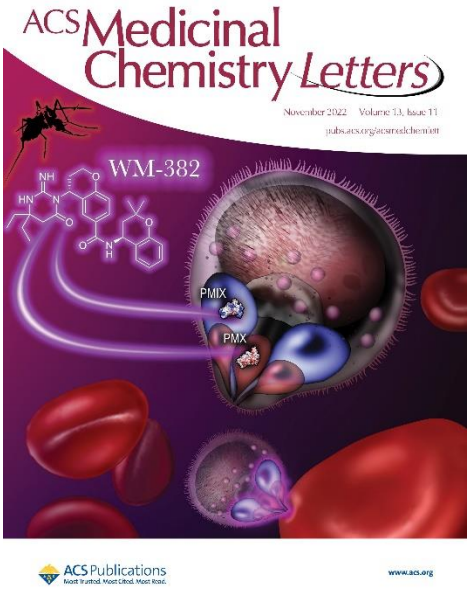
Dr. Manuel de Lera Ruiz
Principal Scientist
Discovery Chemistry, Merck

TOPIC

Plasmepsin IX/X Dual Inhibitors: A Novel Mechanism to Treat Artemisinin-Resistant Malaria

ABSTRACT

Malaria is a devastating disease that directly effects over half a million people each year with the most devastating and debilitating effects on young children.



Antimalarial drug discovery by and large is focused on the identification of novel drugs to treat and prevent the disease due to the emergence and spread of *Plasmodium* strains resistant to existing medicines. In particular arteminisin resistance which has now spread from SE Asia and is firmly established in Africa (as reported at ASTMH in Seattle Oct 2022).

The Merck Research Labs and the **Walter and Eliza Hall Institute of Medical Research (WEHI)** (led by Prof. Alan Cowman), have teamed up on identifying novel drug candidates by targeting the Plasmodium parasite via newly identified essential aspartyl proteases. The team has been greatly assisted in this endeavor with generous funding for the collaboration from the Wellcome Trust. The team was successful at identifying potent dual protease targeting hits that lead to the identification of an important tool compound WM382 with subnanomolar inhibitory potency in vitro. This was accomplished through targeted phenotypic screening and structure-guided medicinal chemistry to optimize orhan (MoA unknown) hit compounds. WM382 was also used to establish impressive in vivo proof-of-concept efficacy not only on blood stage parasitemia but also potent pharmacodynamic effects in the sexual/mosquito and liver stages of replication. Finally, Justin Boddey's team determined that defective parasites under WM382 drug coverage yield some interesting immunological effects in vivo that may be discussed.

Portions of this work focused on the medicinal chemistry has recently been accepted for publication in the journal *ACS Medicinal Chemistry Letters* (The Invention of WM382, a Highly Potent PMIX/X Dual Inhibitor toward the Treatment of Malaria).

The reviews of this work were very positive and the team was invited to submit for approval cover art for the journal. The picture shown here is the cover art that was approved by the journal for publication. Note: in previous publications, (← use attached links) the team utilized compounds from the program to decipher exact molecular mechanism of the leads and decipher much *P. falciparum* biology/biochemistry. and obtained crystal structures of PMX and PMX-drug complexes. This work was supported by The Wellcome Trust (109662/Z/15/Z, 2027/Z/16/Z).

BIO

Manuel de Lera Ruiz received his B.Sc. in chemistry from the Universidad Autónoma of Madrid in 1997. After completion of his Ph.D. in 2001 from the University of Nottingham, he joined Professor Leo A. Paquette research labs as a postdoctoral fellow. In 2003, he started a career in Medicinal Chemistry at Schering-Plough Research Institute in New Jersey. Manuel moved to Merck's West Point site in 2012 where he worked for three and a half years in Discovery Process Chemistry. In 2016 he moved back to medicinal chemistry at West Point where he is currently co-leading the Malaria plasmepsin inhibitors program.

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