BIOSCIENTIST
The Salford Biomedicine Society Magazine

Fast-tracking anti-malarial drug discovery through re-positioning

Prathyusha Vishwanathan

Malaria is one of the oldest diseases known to mankind and among one of the top three infectious killer diseases[1]. It is caused by a parasite genus known as Plasmodium. Over the years, scientists have developed many drugs to treat the disease, but “drug resistance” is known to affect all well-known categories of anti-malarial drugs including the front-line artemisinins[2]. Unfortunately, the traditional discovery pipeline to develop new drugs could take about 15-17 years[3].

Prof. Niroshini Nirmalan, Head of Biomedicine at the University of Salford, leads the Malaria research group which has been conducting research aiming to find a fast-tracked solution for malaria via ‘re-positioning’ of drugs which involves identifying new therapeutic drugs by modifying existing drugs[4]. We have interviewed her about her research below.

Firstly, what type of Plasmodium is this research focusing on? & can you please give us a brief idea about your research?

We are focusing only on *Plasmodium falciparum* because it causes the deadliest version of malaria. It is the only species that causes cerebral malaria, which accounts for most of the deaths globally. The main aspect of this research is to use drug re-positioning to fast-track drug discovery. It is the re-positioning of existing FDA approved drugs in diseases other than those it was originally invented for. We began this research 8 years ago and have had several PhD and MRes students involved in different aspects of the project.

Initially, we screened 1250 FDA approved drugs on in-vitro *P. falciparum t*o identify approximately 50 drugs repositioning in Malaria. As we went further, one plant derived anti-amoebic drug named Emetine dihydrochloride seemed to be impressive in our screens as a viable option for repositioning in Malaria. Since then, we have been focusing on re-positioning and developing the compound and its analogues as a potential drug to fight against *P. falciparum.*

Can you highlight the most important laboratory techniques you used as part of this research?

This research contains very specialized cultures. We culture the parasites in human blood and monitor the parasite life cycles in the red cells that repeats itself. Other specialized techniques include in vitro antimalarial drug screening, Calcusyn drug synergy analysis, in-silico modelling, lead optimization and analogue synthesis and natural product drug discovery methods.

DOI: https://doi.org/10.57898/biosci.166

We know that drug re-positioning has been successful in diseases like cancer. But has this technique proved to work in Malaria earlier?

No, not yet. I suppose we were one of the first research groups to apply this technique to fast-track drug discovery in malaria.

Emetine was not used since it was replaced by metranidazole since the 1970s. What made you so determined to take up this research and how did you tackle the concerns surrounding side effects?

Oh yes, initially when I asked many researchers about Emetine, they asked me not to touch it and said it was a poison. But my memory was good, and I remembered that it was widely used to treat amoebic dysentery and hepatic abscesses in South East countries like India & Srilanka . So, I decided to perform a little bit of research to check this. We resynthesized emetine analogs with better safety profiles and modelled it. Our work showed that the doses of emetine required for malaria was a thousand-fold less than the effective dose for amoebiasis. We know that the side effects are dose dependent, and we now have evidence to hypothesize that the component is not harmful when used in proper doses.

Another most important bit that will surprise you is, we have discovered that we would require only an extremely tiny quantities of emetine to treat *P. falciparum* as in nanomolar concentration to be precise. Our work is constantly expressed on the public domain. Initially we made our first publications in 2014 and were considered as one of the first ever drug repositioning papers in malaria. We have also published various journals over all these years in regards to our research. Our most recent publications in 2020, was a very high-profile paper on a synthetic derivative of emetine called Dehydroemetine. Recently, many researchers have acknowledged our work, appreciated it and have started to perform various tests using this compound.

Emetine is known to have some cardiovascular side effects in patients when treated for Amoebiasis. Did you think the side effects will occur even when it is treated as an anti-malarial drug?

Those side effects caused by emetine are all dosage based and can be controlled. In Malaria, since the usage is in extremely lower concentrations, we can strongly argue that the side effects will be minimal in most cases. However, we are yet to study this in a very detailed manner.

Research is a never-ending process. We might not necessarily start off from one point and directly travel towards the same path we planned. In between, the process might lead us on to different pathways where we might witness completely different or new aspects which we weren't even aware of and might have to divert our focus onto that. Have you experienced any similar instance in this research?

Oh yes, there were several leads like that. As I said, initially we screened 50 drugs. These 50 drugs showed positive results at first, but as we proceeded further, we encountered some errors and while we investigated them, we found them either to be not effective or only effective in extremely high doses. So yes, there were many times we had taken up the leads and we had to do so much to go beyond that point and get back on track.

DOI: https://doi.org/10.57898/biosci.166

In terms of action, When the parasite encounters the drug at the binding site, how much time would it likely require to showcase its effect?

It looks like an early acting drug. We can see activity in 24 hours.

However, while Emetine is capable of combating the deadliest strain of the parasite, do you think it would also be able to fight against other versions like *P.vivax* , when re-positioned accordingly?

Yes, it is most likely to be effective is *P. vivax* as well. All current antimalarials are active against both strains. So, the same is likely to be seen with emetine which is currently effective at low nanomolar concentrations.

What is the most recent work you have performed as part of the project?

Recently, we carried our project on to the next level and performed a preliminary animal work on mice – and I must say it is very promising!

What would be the next phase of the project?

Regarding Emetine, the next phase would be performing animal trials on a larger scale followed by safety trials. On the other hand, apart from Emetine, we have also started to look out for many other natural products like mushrooms, some native African plants etc as sources of future drugs and we have got quite a few interesting data coming up from that as well.

References

1. WHO. Malaria. Published 2021. Accessed April 4, 2021. https://www.who.int/news-room/fact-sheets/detail/malaria
2. Phyo AP, Win KK, Thu AM, et al. Poor response to artesunate treatment in two patients with severe malaria on the Thai–Myanmar border. *Malar J*. 2018;17(1):30. doi:10.1186/s12936-018-2182-z
3. Drug Discovery and Development. *Basic Clin Pharmacol Toxicol*. 2014;115:92-161. doi:10.1111/bcpt.12259_3
4. Persaud-Sharma V, Zhou S-F. Drug Repositioning: A Faster Path to Drug Discovery. *Adv Pharmacoepidemiol Drug Saf*. 2012;01(06). doi:10.4172/2167-1052.1000e117

Further resources

Matthews H, Deakin J, Rajab M, Idris-Usman M, Nirmalan NJ. Investigating antimalarial drug interactions of emetine dihydrochloride hydrate using CalcuSyn-based interactivity calculations. Bogyo M, ed. *PLoS One*. 2017;12(3):e0173303. doi:10.1371/journal.pone.0173303

Matthews H, Usman-Idris M, Khan F, Read M, Nirmalan N. Drug repositioning as a route to anti-malarial drug discovery: preliminary investigation of the in vitro anti-malarial efficacy of emetine dihydrochloride hydrate. *Malar J*. 2013;12(1):359. doi:10.1186/1475-2875-12-359

Panwar P, Burusco KK, Abubaker M, et al. Lead Optimization of Dehydroemetine for Repositioned Use in Malaria. *Antimicrob Agents Chemother*. 2020;64(4). doi:10.1128/AAC.01444-19

DOI: https://doi.org/10.57898/biosci.166