# Information required for submission of Letter of Interest (LOI) to Medicines for Malaria Venture’s 21st Call for Proposals for

# Malaria Drug Discovery Projects

**Deadline for receipt in MMV office: 12 noon (CET) 31st March, 2023**

*Please read the instructions carefully. Submissions should be completed on* ***3 pages of A4*** *as per template. Please use only black Arial 11 font. MMV will only receive submissions electronically in Word format; please see the accompanying templates and contact details at the end of this document.*

There are two stages to the process of seeking funding of a project through the Medicines for Malaria Venture.

The first stage is a concise 3-page LOI outlining the project using the guidelines and templates provided. These letters will be competitively assessed by MMV and MMV’s Expert Scientific Advisory Committee (ESAC) during **May 2023**. A short-list of projects will then be invited for the submission of a more detailed proposal, which will be presented and discussed with MMV and the MMV ESAC in **Q4 2023.** Experience has shown that MMV funding is highly competitive and it is in your interest to present all relevant data as completely and as concisely as possible. Some guidelines on this are provided below.

**Please note: If you have several approaches or potential projects that you wish to propose for funding, then each approach should be submitted as a separate project application.**

Please remember when preparing the application that MMV and the MMV ESAC is already familiar with the key issues of malaria, malaria chemotherapy and the need for antimalarial drugs. So please focus on key information, chemical structures and data. Your proposal should restrict itself to details placed in the context of drug discovery.

MMV has highlighted three key areas necessary for the control and eradication of malaria. They are:

**Compounds having activity against Plasmodium** [**falciparum blood stages in vitro**](https://www.mmv.org/research-development/information-scientists) **(TCP1-TPP1) for use in treatment or chemoprevention (TCP1-TPP2)**

Novel chemical series with asexual blood stage EC50<500nM and which have one or more of the following key features:

* A known, novel mechanism of action without cross resistance to clinical or marketed antimalarials. Priority will be given to mechanisms that are not represented in the MMV portfolio.
* An inability to select resistant mutants *in vitro* after at least 60 days’ incubation with compound
* Potency on early stage gametocytes similar to that for asexual blood stages
* Potency on stage V gametocytes (TCP5) similar to that for asexual blood stages and evidence of transmission blocking to the mosquito
* Potency on *P. falciparum* liver stages similar to that for asexual blood stages
* A long half-life (ideally >4h in rodents) and confirmed in vivo efficacy. Compound series with very long rodent half-lives (>10h) are of particular interest.

For advanced series, we are seeking novel compounds with, ideally, a predicted human half-life >100h and a predicted oral single human dose <500mg

**Compounds addressing the key priorities of the malaria eradication agenda (TCP3, and TCP6)**

**Novel families of molecules in the hit-to-lead or lead optimization stages, without G6PD deficiency liabilities that either:**

* kill or reactivate hypnozoites for use as part of a *P. vivax* radical cure;

or

* have oral endectocide activity suggesting human single monthly dose <100mgs

In each of the above, where possible, example compounds in the series should have measured in vitro physical property and metabolism data, e.g. solubility, LogD, microsomal intrinsic clearance (Clint). The [MMVsola](https://www.mmvsola.org/) tool can be used to predict a human half-life and dose.

**Please see the published** [**MMV Target Candidate Profile**](https://malariajournal.biomedcentral.com/articles/10.1186/s12936-016-1675-x) **for more information.** [**The Frontrunner templates**](https://www.mmv.org/research-development/information-scientists) **are also a useful aid for project teams to evaluate frontrunner compounds against the criteria associated with the next project milestone.**

**Early target validation and screening falls** outside of our mandate.

Our ultimate ambition is to deliver treatments that are completed with, ideally, a single dose so as to ensure patient compliance, have a low cost of goods and which are likely to have activity against all known resistant strains, including those resistant to artemisinin.

**The following information will assist you in preparing a focused application.**

To apply with a LOI you should use the template provided on the [website](https://www.mmv.org/21st-call-proposals). If the proposal involves knowledge of a biological target, you should also fill and submit the target information template.

**The 1st page of your application should outline:**

* Project title
* Contact details of Principal Investigator, and partners with areas of responsibility of within the project and a succinct description of their professional expertise and contribution to the team.
* Target information if appropriate
* Overall goals of the project and the Target Candidate Profile focus
* Proposal Phase – to clarify the position of the proposal within the drug development continuum (delete as appropriate)

**The 2nd page of your application should include:**

* Scientific basis for the project and justification vs. the call for proposals criteria e.g.
* Biology rationale
* Chemistry rationale
* Evidence of site capacity to run an assay and relevance/ benefit of said assay (as appropriate)
* Comparative advantages of approach (and compounds) over existing drugs and other approaches
* Top 3 strengths and issues associated with the proposal
* Project status:

Give a clear account what has been achieved to date giving the latest full data and information.

* Identify where the project is in relation to its goals and include any key results
* Include pharmacokinetic and safety data when available
* Clearly state activities of any lead compounds

(a) *in vitro* against enzyme / molecular target e.g., IC50 / Ki

(b) in culture against parasite strains e.g. EC50 along with mammalian cytotoxicity data;

(c) in animal models e.g., ED50, indicating route of application and precise model. Compound exposure should always be reported to interpret the efficacy data

* Chemical structures of lead compounds should be provided along with medicinal chemistry comments; as with all other information these will be treated confidentially.
* Include measured data where available to support the application (for example Log D, metabolic stability as a Clint not t1/2, hERG potency, solubility, in vivo efficacy)

**The 3rd page of your application should include:**

* Highlight the critical issues and explain the mitigation strategy
* Give a summary of the medicinal chemistry plan specifically focusing on how the critical issues will be solved whilst maintaining the attractive properties
* Identify gaps in knowledge or a bottleneck that need to be addressed to validate the biological approach, compound or screen
* Give specific timed milestones for the progression of the project towards the final goal
* Outline project approach and methodologies to be used
* Likely resource requirements and how these would be allocated to: project partners, consumables, etc.
* Include budget for year 1.
* Costs may be approximate at this stage.
* Please note that MMV has a zero indirect cost policy.
* Maximum 3 literature references if any.

If accepted, the project will be integrated into the MMV portfolio as soon as a legal agreement is reached between MMV and the relevant parties. As part of the MMV portfolio, we will strive to aid movement of the project toward drug development and registration for fast access to the markets in developing countries.

**Compounds for Target Identification**

MMV also welcomes requests for support to investigate the mechanism of action of compounds:

MMV is a founder member of the Malaria Drug Accelerator (MalDA). MalDA, a consortium funded by the Bill and Melinda Gates Foundation and led by Prof. Elizabeth Winzeler (UCSD), is working on a project to identify mechanisms of action of antimalarial compounds having phenotypic activity. Compounds can be considered for such target identification activities provided that the following criteria are met:

* Plasmodium whole cell EC50 <1uM and the chemical structure can be shared
* At least 10mgs of compound can be provided to the consortium
* The provider completes the one page Excel template available on the [website](https://www.mmv.org/21st-call-proposals).