

**Information required for submission of Letter of Interest (LOI) to Medicines for Malaria
Venture's 17th Call for Proposals for
Malaria Drug Discovery Projects**

Deadline for receipt in MMV office: 12 noon (CET) March 29th, 2019

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). 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 later in 2019. 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:

1. Compounds addressing the key priorities of the malaria eradication agenda

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

- kill or reactivate hypnozoites for use as part of a *P. vivax* radical cure; or
- have activity against sexual stage V gametocytes and evidence of transmission blocking in SMFA.

2. Compounds having activity against asexual liver and/or blood stages

Novel chemical series with $EC_{50} < 500\text{nM}$ and which have one or more of the following key features:

- A known, novel mechanism of action;
- An inability to select resistant mutants *in vitro*;
- Activity at more than one life-cycle stage;

- A long half-life (ideally >4h in rodents) and confirmed *in vivo* efficacy.

For advanced series, we are seeking novel compounds with, ideally, a predicted human half-life >100h and a predicted oral single human dose <500mg or an *i.m.* dose that can be administered in <1mL and sufficient for up to 3 months' protection in humans.

3. Novel approaches for screening

To help identify new phenotypic and/ or target based hits, as well as confirm activity of MMV compounds on all human malaria asexual blood stages, new screening proposals are sought amongst the three categories below:

- Validated *Plasmodium* target-based assays, ideally with evidence of target essentiality beyond asexual blood stages. Biological validation should be supported by a biological target based screening assay suited for identification of novel chemical series.
- Novel whole cell phenotypic screening paradigms to potentially identify new relevant chemistry.
- Asexual blood stage assays for *vivax* and *ovale* malaria.

Please see the published [MMV Target Candidate Profile](#) for more information. Early target validation 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 following [template](#). If the proposal involves knowledge of a biological target, you should also fill and submit this [target 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

- 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.
 - ⇒ Chemical structures of lead compounds should be provided along with medicinal chemistry comments; as with all other information these will be treated confidentially.
 - ⇒ Please give a full overview of any novel screening paradigm including validation, throughput and cost per well.

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, as a founder member of 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:

- The Plasmodium whole cell EC50 <1uM and the chemical structure can be shared
- A minimum of 10mgs of compound can be provided to the consortium
- The provider completes the one page .xls template found [here](#).

SUBMISSION CONTACT DETAILS:

Deadline for receipt in MMV office: 12 noon CET March 29th, 2019

Send your 3 page letter of interest, Target information .xls or Application for Target ID, electronically to: proposals@mmv.org