# GHIT Fund Hit-to-Lead Platform (HTLP)

# Request for Proposals

# Reference Number: GHIT-RFP-2014-002

# Summary

The GHIT Fund endeavors to further facilitate collaboration & funding of global health technology R&D, to build momentum, and to demonstrate action and results. The Hit-to-Lead Platform (HTLP) is designed to leverage the Product Development Partnerships (PDPs)’ active platform for neglected and tropical diseases in partnership with Japanese companies or academic organizations that have relevant compounds. The intention is to facilitate access to the chemical diversity in Japanese research organizations and to the medicinal chemistry expertise in Japan.

# Project Descriptions and Definitions

# There is an urgent need to bring forward new drugs for diseases that disproportionately affect the poor. Many compounds are in early- and later-stage development for drugs against malaria, tuberculosis, Chagas, and visceral leishmaniasis. However, there is still a need to expand the drug pipeline for these diseases by bringing forward compounds that have not been previously screened or that are known to target mechanisms of action in a novel manner.

The HTLP projects will focus on the aspect of the drug discovery and development process that progresses hits, identified through compound library screening, into lead compounds that can then be optimized into drug candidates. This platform will provide a bridge from early drug discovery into our typical Grant-making Mechanism that begins at the lead-optimization step.

Target Identification

Lead Optimization

Hit to Lead

Hit Identificationn

Assay Development

Target Validation

Outside of GHIT Scope

GHIT Screening Platform

GHIT Hit-to-Lead Platform

GHIT Grant-making Mechanism

Qualified drug hits that meet the entry criteria will be considered for HTLP funding. The goal of a Hit-to-Lead program is to convert drug hits derived from Japanese compound libraries into lead series through a comprehensive assessment of chemical integrity, synthetic accessibility, functional behavior, and structure-activity relationships (SAR), as well as bio-physiochemical and absorption, distribution, metabolism and excretion (ADME) properties. This lead-generation step is critical as it is the earliest point at which knowledge-driven decisions about compounds can be made. An early, rigorous assessment can focus resources on the most promising lead series and projects. To address the high attrition rate at the early stage of drug discovery, it is preferable that applications include multiple hit series.

# Criteria for Entry

Cellular potency consistent with potential to deliver lead series (typically *Plasmodium spp.* IC50 <1µM, *T. cruzi* intracellular IC50 <10 µM, *L. donovani* intracellular IC50 <10µM, and *Mycobacterium tuberculosis* MIC <10µM)

* Novel hit structures confirmed
* Primary results validated on hit compounds (>90% pure)
* Acceptable *in vitro* concentration-response curves
* Preliminary SAR with existing analogues
* Progressable chemotypes
* >10-fold selectivity for cytotoxicity using a mammalian cell line (e.g. HepG2)
* Adequate selectivity in counter assay(s)
* No blocking intellectual property (IP)
* No major synthesis or formulation issues anticipated

# Project Outcomes

**Generic criteria**

* TPP (Target Product Profile)/TCP (Target Candidate Profile) defined
* Acceptable *in vitro* potency. Oral efficacy in appropriate disease model (see below)
* Potential to deliver compounds with sufficient potency and favorable physicochemical properties (i.e. tractable SAR and structure liability relationships) with properties within the series within 10 fold of the TCP/ TPP
* Synthetic chemistry amenable to rapid series expansion preferred
* >10 fold selectivity with respect to cytotoxicity
* Acceptable physicochemical properties (typically solubility in PBS >10M, acceptable lipophilicity)
* Manageable ADME/Toxicity profile (liver microsome stability, plasma binding, permeability, CYP inhibition, hERG inhibition and, typically, secondary pharmacology selectivity profile)
* Oral bioavailability in rodents demonstrated (> 25%)
* No known toxicophores or undesirable reactive groups and no chemical feature with a liability associated with the pharmacophore; however, if required for biological activity, some indication that its toxicity can be managed
* No acute toxicity from *in vivo* efficacy studies
* Liabilities of the series understood and a rationale generated for why they can be overcome in the subsequent optimization phase
* No apparent IP obstacles for progression of this series

**Malaria**

* *In vitro*potency against wild type and resistant strains within 10 fold of Target Candidate Profile (TCP)
* Frontrunners tested  across the entire malaria life-cycle and specialist mechanistic assays so series’ profile and potential for each TCP understood
* *In vivo*efficacy criteria
* Blood stages (TCP1 and TCP2): Observed parasite clearance in a *P. falciparum* infected SCID mouse model when given orally:  ED90 <50mg/kg
* Anti-relapse (TCP3a): no *in vivo*criteria – demonstrated anti-hypnozoite activity *in vitro*
* Transmission-blocking (TCP3b): Potency in functional gametocyte assay (gamete formation) in a similar range to the *in vitro*asexual blood stage potency
* Chemoprotection (TCP4): Efficacy in a prophylaxis model of malaria; ED90<50mg/kg

\*For more information regarding TCPs and TPPs, please refer to the following URL:

[http://www.mmv.org/research-development/essential-information-scientists/target-product-profiles](http://www.mmv.org/research-development/essential-information-scientists/target-product-profiles%22%20%5Ct%20%22_blank)

**Tuberculosis**

* Good *in vitro* activity against replicating and preferably also non-replicating *M. tuberculosis* (MIC under aerobic conditions (MABA)<5 µM and/ or under anaerobic conditions (LORA)<20 µM)
* Bactericidal activity preferred
* Preliminary indication of safety and efficacy demonstrated in mice (greater than 0.5 log CFU reduction at doses equal to or less than 400 mg/kg in a mouse acute infection model)
* No cross resistance with existing TB drugs

 **Chagas disease**

* *In vitro* potency within 10 fold of TPP
* Acute mouse model of Chagas disease: 80% parasitaemia reduction or no parasites detected at the end of treatment and an increase in life span (10 x 50mg/kg *p.o.*)

**Visceral leishmaniasis**

* *In vitro* potency within 10 fold of TPP
* Mouse (or hamster) model (infected with *L. donovani* or *L. infantum*): >70% reduction in liver parasitaemia after 5 x 50mg/kg *p.o. q.d.* or *b.i.d.*

# Eligible Collaboration Partners

Projects will require a commitment to collaborate with one of the three leading drug development PDPs: **Medicines for Malaria Venture (MMV)**, **Drugs for Neglected Diseases Initiative (DNDi), and the Global Alliance for TB Drug Development (GATB).** There is no need to solidify a partnership with the PDP prior to proposal submission; however, the proposals should be written on a basis of such partnership.

There is no set format for a collaborative project. However, it is important that each partner is contributing something significant to the collaboration. For example, an international organization working only with a Japanese contract research organization would not qualify for funding.

GHIT has data access and product access policies that must be followed by grantees (<http://www.ghitfund.org/afag/policies/en>). Both parties will need to sign an agreement with GHIT that includes access principles (data/ IP and product). **The funding for HTLP will be milestone-based and subject to review at each critical milestone.**

# Applicant Instructions

All correspondence and documents relating to this RFP shall be written in English. The applicant shall bear all costs associated with the preparation and submission of the proposal, including costs associated with proposal presentation and contract negotiation.

## *Intent to Apply*

Interested applicants must complete the *GHIT\_HTLP\_RFP2014-002\_Intent\_To\_Apply.docx* document and return it by email to HTLPResponse@ghitfund.org no later than 10:00 am Tokyo time September 10, 2014, (use email subject line: GHIT-HTLP\_RFP-2014-002 Intent to Apply).

Applicants who submit the Intent to Apply document will receive a confirmation email and the GHIT Fund’s required proposal template.

## Proposal Submission

Eligible applicants who submit an Intent to Apply form will receive the GHIT Fund HTLP Proposal, Timeline and Budget templates. Applicants are required to completeand submit them to HTLPResponse@ghitfund.org no later than 10:00 am Tokyo time on October 10, 2014 (use email subject line: GHIT-HTLP\_RFP-2014-002 Proposal). All proposal submissions will receive an acknowledgement from GHIT Fund staff. Proposal submissions may not be modified after the submission closing date.

The GHIT Fund may, at its own discretion, extend the closing date by notifying applicants who have submitted an *Intent to Apply* document. Proposals received after the closing date for submission, without prior agreement, will be ineligible for consideration, but may be resubmitted in response to future RFPs.

# Proposal Evaluation

## *Preliminary Examination of Proposals*

Proposals will initially be examined to determine whether the:

* Partnership meets GHIT Fund eligibility criteria
* Project objectives are aligned with the RFP-specified scope
* Proposal is complete and addresses all required content

Applicants will be notified by email of their proposal’s readiness for technical evaluation. GHIT Fund staff may ask clarifying questions or request additional information, as needed, to qualify proposals for evaluation.

## *Technical Evaluation*

All proposals passing the preliminary examination will be evaluated and prioritized based on the following criteria:

* Scientific and technical merit (e.g., sound approach and methodology, level of innovation, overall quality and comprehensiveness)
* Potential Impact (e.g., how it will address a global health priority)
* Partnership and project management (e.g., capabilities and expertise, project history and performance, risk management, budget)

If a proposal has already been deemed technically or scientifically sound and aligned with global health needs by an established independent scientific or technical advisory committee (such as those established by PDPs), the partnership is expected to include a summary of the outcome of that review in their proposal submission.

# Award Administration and Conditions

The GHIT Fund will notify applicants of their selection status by email. The GHIT Fund will not provide formal feedback to applicants receiving a non-award decision.

Applicants are required to identify the designated grantee and all collaboration partners. The grantee will be the funding recipient and will be responsible for the performance of its collaborating partners. A representative of the designated grantee will serve as the main GHIT Fund point of contact and will be responsible for all GHIT Fund discussions and negotiations.

Grants will be awarded for a period reflecting the expected time required to complete agreed activities. **The funding will be milestone based.** The GHIT Fund has the right to terminate the grant agreement if:

* The partnership disbands prior to satisfying its grant obligations.
* The progress of work is such that the obligations undertaken by the partnership will not be fulfilled.
* The partnership fails to meet the critical milestones specified in the grant agreement.

In the event a grant is terminated, the GHIT Fund reserves the right to cancel future fund payments, reclaim paid funds, or mandate that paid funds be redirected to other charitable activities. In lieu of termination, the GHIT Fund may choose to renegotiate the terms of the existing grant agreement.

**Data and Product Access**

The aim of the GHIT Fund Data and Product Access Policies are to articulate the principles that promote the transparency of, and accessibility to, data related to the safety and efficiency of healthcare technologies. The policy and its principles apply to data or products generated through the activities funded primarily by the GHIT Fund, including but not limited to, data related to the discovery and development of healthcare technologies, and products approved for introduction by a national regulatory authority.

All data, and processes for its access, will be clearly defined by the applicant. Appropriate data and project outcomes will be disclosed in a broad and prompt manner to optimize the translation of findings in the global advancement of new healthcare technologies. Ideally, grantees should utilize public-access repositories, whenever available; if this is not feasible due to confidentiality concerns, the project team should define a timeline with GHIT at which point data from the funded project will be made available freely to the community.

Respect must be given to individuals and communities from or about whom data are collected. Respect must also be given to all matters of confidentiality and attribution as they pertain to researchers, evaluators, and their collaborators. Confidentiality prior to obtaining IP should be fully recognized when requested or when required by law or regulation.

Existing data or project outcomes owned by a grantee at the initiation of a GHIT Fund project, including but not limited to information, know-how or intellectual property, will remain the property of the original holder. The original holder may share, assign, or license their rights to this property to a third party.

Proprietorship of data and project outcomes achieved or created through activities funded by the GHIT Fund that can be considered an intellectual property right, will be negotiated prior to grant completion.

**Key RFP Milestone Dates**

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| RFP Release  | August 6, 2014 |
| Intent to Apply  | 10:00 am September 10, 2014Submit *GHIT\_HTLP\_RFP2014-002\_Intent\_To\_Apply.docx* to HTLPResponse@ghitfund.org Email Subject Line: GHIT-HTLP\_RFP-2014-002 Intent to Apply |
| Q & A  | Submit Questions to HTLPResponse@ghitfund.org Email Subject Line: GHIT-HTLP\_RFP-2014-002 Questions |
| Application | 10:00 am Tokyo Time October 10, 2014Submit GHIT Fund HTLP Proposal, Timeline and Budget templates to HTLPResponse@ghitfund.orgEmail Subject Line: GHIT-HTLP\_RFP-2014-002 Proposal |
| Award Notification  | No later than January 31, 2015 |
| Agreement  | No later than February 28, 2015 |