

GHIT Fund Hit-to-Lead Platform (HTLP) Request for Proposals Reference Number: GHIT-RFP-HTLP-2016-001

Summary

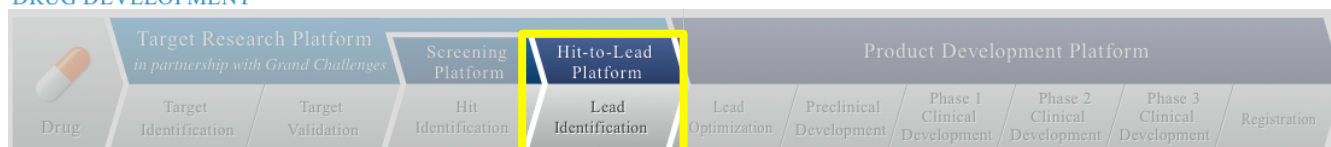
The GHIT Fund endeavors to further facilitate collaboration & funding of global health technology R&D, to build momentum, and to demonstrate action and results. The Hit-to-Lead Platform (HTLP) is designed to leverage the Product Development Partnerships (PDPs)' active platform for neglected and tropical 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 to our product development platform that begins with the lead-optimization step.

DRUG DEVELOPMENT



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 >10m0, 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-hyponozoite 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>

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)**. A partnership with a PDP needs to have been solidified at the time of proposal submission.

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.

The GHIT Fund has data access and product access policies that must be followed by development partners (<http://www.ghitfund.org/afag/policies/en>). Both partners to the partnership will need to sign an agreement with the GHIT Fund that includes access principles (data/ IP and product).

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-RFP-HTLP-2016-001_IntentToApply.docx* document and return it by email to HTLPResponse@ghitfund.org no later than **10:00 am Tokyo time March 28, 2016** (use email subject line: GHIT-RFP-HTLP-2016-001_Intent to Apply). Please do not attach any documents to the *Intent to Apply* form.

Applicants who submit the *Intent to Apply* document will receive a confirmation email. The GHIT Fund staff will then perform an initial partnership and scope eligibility assessment. Eligible applicants will receive a full GHIT Fund proposal template to support proposal development. Also, an individual Project ID will be assigned to each eligible proposal.

Proposal Submission

Applicants are required to submit their completed proposal to HTLPResponse@ghitfund.org no later than **10:00 am Tokyo time on April 27, 2016** (use email subject line: [Project ID] GHIT-RFP-HTLP-2016-001_Proposal). Applicants who successfully submit their proposal document will receive a confirmation email. Proposals may not be modified after the submission due date.

Proposals must be reviewed and approved by all the collaboration partners who are participating in the project prior to submission. The *Collaboration Partners' Approval* form (***Collaboration_Partners'_Approval.docx***) must be signed by all the collaboration partners and a PDF copy must be submitted along with other proposal documents.

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.

RFP Questions

Prospective applicants may also submit RFP questions to HTLPResponse@ghitfund.org no later than **10:00 am Tokyo time on April 18, 2016** (please use email subject line: GHIT-RFP-HTLP-2016-001_Questions). Please note that it may take time for the GHIT Fund Management Team to respond to your inquiries, so make sure to address your questions well in advance of the submission deadlines.

A Frequently Asked Questions (FAQ) page is available on the GHIT Fund website: <https://www.ghitfund.org/afag/seekersfaq/en>

Proposal Evaluation

Preliminary Examination of Proposals

Proposals will initially be examined to determine whether the:

- Partnership meets the 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 be able to provide formal feedback to applicants receiving a non-award decision.

Applicants are required to identify the designated development partner (investment recipient) and all other collaboration partners of the award decision. The designated development partner will be responsible for the performance of all its collaborating partners. A representative of the designated development partner will serve as the main GHIT Fund point of contact and will be responsible for all discussions and negotiations with the GHIT Fund.

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

- The partnership disbands prior to satisfying its investment project obligations
- The progress of work is such that the obligations undertaken by the partnership will not be fulfilled
- The partnership fails to meet the milestones or goals specified in the investment agreement

If an investment contract is terminated, the GHIT Fund reserves the right to cancel future 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 investment agreement.

Data Access Policy

The aim of our Data Access Policy is to articulate the principles that promote the transparency of and accessibility to data related to the safety and efficacy of healthcare technologies. This policy and its principles apply to data generated through activities primarily funded by the GHIT Fund, including but not limited to, those related to the discovery, development, and/or delivery of healthcare technologies.

All data and its processes for access will be transparent and clearly defined with the aim to ensure data quality, security, and equitable access. All data and findings will be disclosed in a broad and prompt manner in order to optimize prospects for the translation of findings in the global advancement of new healthcare technologies. Development partners should utilize public-access repositories and, if unavailable, should use alternatives for access that can ensure the transmission of new scientific findings to the larger research and development community globally.

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 and respect for such should be fully recognized where necessary or required by law or regulation.

Any and all existing data and findings owned by a development partner at the initiation of a project, including but not limited to information, know-how or intellectual property, will remain that of the original holder. The original holder may share, assign, or license their rights to a third party.

Ownership of any and all data and findings that is obtained or created through activities funded by the GHIT Fund and that can be applied for any intellectual property rights will be discussed and negotiated between participants and/or development partners of a project. All final agreements shall be in alignment with the licensing and pricing principles outlined below.

Any existing data owned by a development partner and/or any new data obtained through activities funded by the GHIT Fund may be disclosed by the GHIT Fund to a third party if such data is used in a patent application for a product which was derived from the activities funded by the GHIT Fund; provided, however: (1) the disclosure of such data shall be limited to the proposed title of the invention, a draft of the abstract, the international non-proprietary name (INN) where applicable, and an outline of the specifications of such patent

application; and (2) such third party shall take reasonable measures to keep confidential any such data received from the GHIT Fund.

Product Access Policy

The aim of the Product Access Policy is to articulate the principles that improve access to products primarily developed with funding from the GHIT Fund, where such products refer to healthcare technologies approved for market by a national regulatory authority.

When development partners/participants are successfully granted a patent deriving from projects funded by the GHIT Fund, development partners/participants will grant royalty-free licenses to users operating in Least Developed Countries (LDCs) as categorized by the United Nations and Low-Income Countries (LICs) as categorized by the World Bank. License-related matters concerning middle income countries (MICs) will be reviewed on an individual basis with the goal of ensuring reasonable royalty licenses.

For LDCs, LICs, and MICs, partners/participants will set prices for products on the basis of a no gain/no loss policy to improve access to the product for patients and citizens of these LDCs, LICs, and MICs.

Key RFP Milestone Dates

RFP Release	February 26, 2016
Intent to Apply	No later than 10:00 am Tokyo time on March 28, 2016 Submit Intent to Apply form to HTLPResponse@ghitfund.org Email Subject Line: GHIT-RFP-HTLP-2016-001_Intent to Apply
Q & A	No later than 10:00 am Tokyo time on April 18, 2016 Submit questions to HTLPResponse@ghitfund.org Email Subject Line: GHIT-RFP-HTLP-2016-001_Questions
Full Proposal	No later than 10:00 am Tokyo time on April 27, 2016 Submit proposal to HTLPResponse@ghitfund.org Email Subject Line: GHIT-RFP-HTLP-2016-001_Proposal
Award Notification	No later than August 1, 2016
Investment Agreement	No later than September 1, 2016