GHIT Fund Hit-to-Lead Platform (HTLP)
Request for Proposals
Reference Number: GHIT-RFP-HTLP-2025-001

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1. GHIT Fund Background

Over a billion people worldwide suffer from infectious diseases, and particularly in low-income countries and lower middle-income countries (LICs and LMICs), there is a need for new low-cost, high-impact health technologies. Responses to this need in recent years have led to the development of new products in recent years, mostly as a result of partnerships between pharmaceutical companies, academia and research institutions, and Product Development Partnerships (PDPs). These partnerships have proven to be an effective way to develop high-impact global health technologies.

The Global Health Innovative Technology Fund (GHIT Fund) is a non-profit organization focused on promoting the discovery and development of new health technologies, including drugs, vaccines and diagnostics for infectious diseases prevalent in LICs and LMICs. The first fund of its kind in Japan, the GHIT Fund is supported by the Japanese Government, Japanese pharmaceutical/healthcare companies, the Wellcome Trust and the Bill & Melinda Gates Foundation. The GHIT Fund aims to advance Japan's wealth of health technology innovation to discover and develop new technologies for patients and populations affected

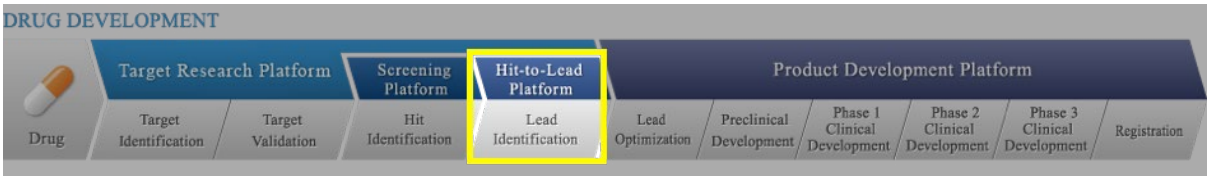
by neglected infectious diseases. To this end, the GHIT Fund will catalyze R&D partnerships between Japanese and non-Japanese organizations and support these partnerships through GHIT Fund investments.

There is an urgent need for new drugs (medicines) for diseases that disproportionately affect the poor. Many compounds are in early- and late-stage development for drugs against malaria, tuberculosis, Chagas disease 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 novel mechanisms of action.

2. Funding Opportunity

The GHIT Fund endeavors to further facilitate collaboration and funding for 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 medicinal chemistry expertise in Japan and facilitate access to relevant and diverse compounds from Japanese companies or academic organizations for drug development to address the unmet needs of malaria, tuberculosis, Chagas disease, and visceral leishmaniasis.

The HTLP focuses on the aspect of the drug discovery and development process that advances 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 GHIT's Product Development Platform that begins with the lead-optimization step.



Qualified drug hits that meet the eligibility criteria will be considered for HTLP funding. **The goal and key requirement of the Hit-to-Lead Platform is to convert drug hits derived from Japanese compound libraries into lead series through a comprehensive assessment of chemical integrity, synthetic accessibility, scalability and novelty, 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 because it is the earliest point at which knowledge-based decisions can be made about compounds. Early, rigorous allows resources to be focused on the most promising lead series. To address the high attrition rate in the early stages of drug discovery, it is preferable that applications include multiple hit series.

3. Project Scope and Eligibility

3.1 Criteria for Eligibility[1]

Proposals must meet the criteria below in order to be eligible for consideration.

Cellular potency consistent with potential to deliver lead series (typically *Plasmodium spp.* IC_{50} <1μM, *T. cruzi* intracellular IC_{50} <10 μM, *L. donovani* intracellular IC_{50} <10μM, and *Mycobacterium tuberculosis* MIC <10μM)

- Compounds originated/derived from Japan

[1] Katsuno, K., Burrows, J., Duncan, K. *et al.* Hit and lead criteria in drug discovery for infectious diseases of the developing world. *Nat Rev Drug Discov* **14,** 751–758 (2015). https://doi.org/10.1038/nrd4683

- 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

3.2 Project Outcomes[1]

3.2.1 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 >10µM, 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

3.2.2 Criteria for 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: ED_{90} <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; ED_{90}<50mg/kg

*For more information regarding TCPs and TPPs, please refer to the following URL:
https://www.mmv.org/research-development/information-scientists/target-product-profiles-target-candidate-profiles

3.2.3 Criteria for 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

3.2.4 Criteria for 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.*)

3.2.5 Criteria for 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.*

4. Partnership Eligibility

The GHIT Fund **requires** each HTLP project to partner with one of the three leading drug development PDPs as a partner: **Medicines for Malaria Venture (MMV)**, **Drugs for Neglected Diseases initiative (DNDi), and TB Alliance. A partnership with one of the above PDPs must be in place at the time of ITA submission.**

There is no set format for a collaborative project. However, it is important that each partner makes a significant contribution to the collaboration. For example, an international organization working only with a Japanese Contract Research Organization (CRO) would not qualify for funding.

The GHIT Fund has data access and product access policies that must be followed by development partners (https://www.ghitfund.org/applyforfunding/accesspolicy/en). All partners to the partnership must sign an agreement with the GHIT Fund that includes access principles (data/ IP and product).

5. 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 development, presentation, and contract and agreement negotiation (unless otherwise noted by the GHIT Fund).

To receive and manage applications, the GHIT Fund uses Editorial Manager® (http://www.editorialmanager.com/ghitfund/), an online document submission system dedicated for this funding program. Please note that Intent to Apply documents or Proposals that are not submitted through the above-mentioned system will not be accepted.

Step 1 - Intent to Apply

Interested applicants must complete the Intent to Apply form (*GHIT-RFP-HTLP-2025-001_IntentToApply.docx*) and submit it to the GHIT Fund via Editorial Manager® no later than:

10:00 am Tokyo time on January 10, 2025

The *Intent to Apply* form is available on the GHIT Fund website: https://www.ghitfund.org/applyforfunding/htlp/en. Any application that does not use the designated *Intent to*

Apply form provided for this RFP will not be accepted. Please do not attach any documents to the *Intent to Apply* form.

When submitting the *Intent to Apply* form on the Editorial Manager®, please list all the collaboration partners involved in the project, including the name and contact information (including e-mail address) of at least one representative from each organization must be indicated.

Applicants who submit the *Intent to Apply* document will receive a confirmation email. The GHIT Fund Management Team will then conduct an initial partnership and scope eligibility assessment. **Only eligible applicants will be invited to submit the full proposal and will receive the proposal templates from the GHIT Fund**. In addition, each eligible proposal will be assigned a unique project ID.

Step 2 - Proposal Submission

Applicants invited to submit a full proposal to the GHIT Fund are required to do so via Editorial Manager® no later than:

10:00 am Tokyo time on March 14, 2025

Applicants who successfully submit their proposal documents will receive a confirmation e-mail. Proposals may not be changed after the submission due date.

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

The GHIT Fund may, at its sole discretion, extend the deadline by notifying applicants. Proposals received after the deadline for submission without prior agreement will be ineligible for consideration, but may be resubmitted in response to future RFPs.

6. Proposal Evaluation

6.1 Preliminary Examination of Proposals

Proposals will initially be examined to determine or evaluate:

- whether the partnership meets GHIT Fund eligibility criteria
- whether the project objectives are aligned with the RFP-specified scope
- whether the proposal is complete and addresses all required content
- that an organizational credit check (so-called "Due Diligence") reveals no significant issues or concerns*

* Each applicant should submit the certificated copy of organization registration and the financial statement that was audited by an independent auditor from the most recent three years.

Applicants will be notified by e-mail of their proposal's readiness for technical evaluation. The GHIT Fund Management Team may ask clarifying questions or request additional information, as needed, to qualify proposals for evaluation.

6.2 Technical Evaluation

All eligible proposals will be evaluated based on the following criteria by the External Panel, which is comprised of several experts in the discovery and development of global health technologies, each of whom possesses the experience to objectively evaluate the proposal content.

- 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., collaboration 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.

After the review process, the External Panel will provide funding recommendations to the HTLP Subcommittee, which is comprised of selected GHIT Selection Committee members, who review and approve funding recommendations.

Please note that the GHIT Fund Management Team does not have influence, authority, or decision power on the review and evaluation, funding recommendations, and award or non-award decisions of submitted proposals by the Expert Panel, Selection Committee, Subcommittee, and the Board of Directors. In addition, submission of the Intent to Apply form and proposal documents to the GHIT Fund does not guarantee an automatic funding approval for your proposal.

6.3 Budget Evaluation, Organizational Credit Check

All proposals that pass the other requirements of preliminary evaluation will also be subject to evaluation of budget and an organizational credit check in detail according to the following criteria:

1. The detailed, consolidated budget for each category provided by the Designated Development Partner is reasonable and appropriate to address all contemplated R&D activities of the project by phase/activity/milestone.**
2. Each detailed budget for each category provided by each collaboration partner is reasonable and appropriate to address the project's R&D activities to be conducted by each Collaboration Partner by phase/activity/milestone.
3. Results of the organizational credit check reveal no significant issues or concerns.

** The Designated Development Partner should submit a detailed, consolidated budget for each category outlining the project's expenditures as a part of the Project Full Proposal.

6.4 Award Administration and Conditions

After the HTLP Subcommittee approval, the GHIT Fund will notify applicants of the award decision by email. **Please note that GHIT Fund is not able to provide formal feedback to applicants receiving a non-award decision.**

Please also note:

・Investments will be executed subject to the condition that our funding partners contribute funds to the GHIT Fund in a sufficient amount to support such investments.

・By submitting an application, applicants agree that the GHIT Fund may rescind any awarded investment in its sole discretion at any time.

If the proposal is selected and the applicant receives an award notification, all partners are required to sign the Investment Agreement with the GHIT Fund and also submit a collaboration partners' contractual agreement which clearly defines the roles and responsibilities of all collaboration partners, within one month from award notification. Please be aware that the award may be void if this condition is not met.

Applicants are required to identify the Designated Development Partner (investment recipient) and all other collaboration partners. 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 GHIT Fund discussions and negotiations.

The GHIT Fund has the right to revoke the award if the following conditions are not agreed upon:

1. Funding and Use of the Investment

The funding granted by the GHIT Fund (Investment) may be used by the collaboration partners solely for the project in accordance with the Budget (as defined below). Any portion of the Investment unused or uncommitted at the end of the period for the Investment must be promptly returned to the GHIT Fund; and the return of any such portion of the Investment upon an early termination of the period for the Investment will be made in accordance with the termination clause of the relevant Investment Agreement. Any amounts not used properly in accordance with the Budget for the project shall be reimbursed to the GHIT Fund upon its written request.

The designated development partner and the collaboration partners for each project should submit a detailed, categorized budget outlining the projected expenditures for the project as a part of the Project Proposal (such budget as approved by the GHIT Fund, the "Budget"). Only immaterial changes may be made to the projected expenditures for any Budget category without the GHIT Fund's approval, and under all circumstances, changes of ten percent (10%) or more or amounting to more than JPY500,000, whichever is larger, to the projected expenditures for any budget category must be approved in writing by the GHIT Fund in advance of such expenditures. The designated development partner and the collaboration partners may not use the Investment to reimburse expenses incurred prior to the effective date of the Investment Agreement.

The designated development partners shall ensure that the collaboration partners use the Investment strictly in accordance with the preceding two paragraphs.

2. Reporting Procedures

The designated development partner is required to submit bi-annual reports, in accordance with the reporting and payment schedule regarding the expenditure of Investment funds and the progress on the project to be attached to the Investment Agreement. The report templates and submission guidelines will be provided by the GHIT Fund. These templates and guidelines are subject to change upon confirmation by the GHIT Fund. The reports should be submitted electronically to the GHIT Fund in accordance with the instructions shown in each template. The Designated Development Partner also agrees to submit such other reports as the GHIT Fund may reasonably request. The GHIT Fund reserves the right to demand interim status and other reports at any time.

3. Survival

Each Collaboration Partner's obligations will be continuous and survive expiration or termination of the project or the Investment Agreement as expressly provided in the Investment Agreement or otherwise required by law or intended by their nature.

Investments will be awarded for a period of up to two years and reflecting the agreed activities and conditions based on the award notification from the GHIT Fund. The funding allocation/disbursement will be "by milestone/deliverable" or "on an annual basis", or in the form of "disbursement in advance", "deferred disbursement/disbursement after confirmation of delivery of deliverable" or "disbursement by installments (in advance disbursement and deferred disbursement) based on the risk of project. The GHIT Fund has the right to terminate the Investment Agreement if, but not limited to:

- 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

In the event an Investment Agreement 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 or terminate participation in the project or the existing Investment Agreement by one or multiple collaboration partners.

6.5 Access Policy

Details about the GHIT Access Policy can be found here:

https://www.ghitfund.org/applyforfunding/accesspolicy/en.

7. Key RFP Milestone Dates

RFP Release	**November 1, 2024**
Intent to Apply Due	No later than **10:00 am Tokyo time on January 10, 2025** Submit via **Editorial Manager®** (**https://www.editorialmanager.com/ghitfund/**)
Full Proposal Due	No later than **10:00 am Tokyo time on March 14, 2025** Submit via **Editorial Manager®** (**https://www.editorialmanager.com/ghitfund/**)
Proposal Evaluation	March 2025 - July 2025
Notification of Results	July 2025
Investment Agreement Fully Executed (Awarded Proposals)	September 2025

8. Inquiries

For any inquiries, please contact RFPresponse@ghitfund.org (please use the e-mail subject line: **GHIT-RFP-HTLP-2025-001_Questions**)

A Frequently Asked Questions (FAQ) page is available on the GHIT Fund website: (https://www.ghitfund.org/applyforfunding/investmentfaq/en).

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