GHIT Fund Hit-to-Lead Platform (HTLP)
Request for Proposals
Reference Number: GHIT-RFP-HTLP-2017-001

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 medicinal chemistry expertise in Japan and facilitate access to Japanese companies or academic organizations' relevant and diverse compounds for drugs development to address malaria, tuberculosis, Chagas disease, and visceral leishmaniasis.

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 GHIT's product development platform that begins with the lead-optimization step.

Qualified drug hits that meet the entry 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 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 Eligibility

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
- 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 >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

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: 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

The GHIT Fund **requires** each HTLP project to have a collaboration with one of the three leading drug development PDPs as a partner: **Medicines for Malaria Venture (MMV)**, **Drugs for Neglected Diseases *initiative* (DND*i*), and the Global Alliance for TB Drug Development (GATB). A partnership with one of the above PDPs needs to have been solidified at the time of ITA and proposal submission.**

There is no set format for a collaborative project. However, it is important that each partner is contributing significantly 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). All partners to the partnership will need to sign an agreement with the GHIT Fund that includes access principles (data/ IP and product).

Application Process and 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).

Intent to Apply

Interested applicants must complete the *GHIT-RFP-HTLP-2017-001_IntentToApply.docx* document and return it by email to HTLPResponse@ghitfund.org by **10:00am Tokyo time September 1, 2017** (use email subject line: GHIT-RFP-HTLP-2017-001_Intent to Apply). Please do not submit any other documents to the GHIT Fund other than 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. **Only eligible applicants will be invited to submit the full proposal and will receive the proposal templates from the GHIT Fund**. In addition, an individual Project ID will be assigned to each eligible proposal.

Proposal Submission

Eligible applicants are required to submit their completed proposal to HTLPResponse@ghitfund.org by **10:00am Tokyo time on October 2, 2017** (use email subject line: [Project ID] GHIT-RFP-HTLP-2017-001_Proposal). Applicants who successfully submit their proposal document will receive a confirmation email. Proposals may not be modified after the submission due date (unless applicants receive the request from the GHIT Fund).

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. 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 until **10:00am Tokyo time on September 20, 2017** (please use email subject line: **GHIT-RFP-HTLP-2017-001_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 also available on the GHIT Fund website for reference: 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

GHIT Fund staff may ask clarifying questions or request additional information, as needed, to qualify proposals for evaluation.

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 Sub-Committee, 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, Sub-Committee, 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.

Award Administration and Conditions

After the HTLP Sub-Committee 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.**

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.

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 will be milestone-based. 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

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. Grantees 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 grantee 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 grantees of a project. All final agreements shall be in alignment with the licensing and pricing principles outlined below.

Any existing data owned by a grantee 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.

In LDCs, LICs and MICs, product development partners and/or participants will set prices for products on the basis of a no gains/no loss policy that can improve access to the product for patients and citizens of LDCs, LICs and MICs.

Key RFP Milestone Dates

RFP Release	**July 25, 2017**
Intent to Apply Due	No later than **10:00 am Tokyo time on September 1, 2017** Submit Intent to Apply form to HTLPResponse@ghitfund.org Email Subject Line: GHIT-RFP-HTLP-2017-001_Intent to Apply
Q & A (RFP related questions)	No later than **10:00 am Tokyo time on September 20, 2017** Submit questions to HTLPResponse@ghitfund.org Email Subject Line: GHIT-RFP-HTLP-2017-001_Questions
Full Proposal Due	No later than **10:00 am Tokyo time on October 2, 2017** Submit proposal to HTLPResponse@ghitfund.org Email Subject Line: GHIT-RFP-HTLP-2017-001_Proposal
Proposal Evaluation	October 2017 - January 2018
Award Notification to All Applicants	February 2018
Investment Agreement Fully Executed (For Awarded Proposals)	March 2018

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