GHIT Fund

Global Health Innovative Technology Fund

# Appendix.1 New Investments

| ID/Status | Project Title | Collaboration Partners | Disease/Intervention | Stage | Awarded Amount (¥) | Awarded Amount ($) |
|---|---|---|---|---|---|---|
| G2020-208 Continued project | First-In-Human Trial of the Pan-Malaria Transmission-Blocking Vaccine AnAPN1 | Ajinomoto Bio-Pharma Services (Aji-Bio), CellFree Sciences Co. Ltd. (CFS), Centre de Recherches Médicales de Lambaréné (CERMEL), University of Florida (UF), University of Tübingen (UKT) | Malaria Vaccine | Preclinical to Clinical Development (Phase 1) | ¥648,622,379 | $6,104,681 |
| G2020-201 Continued project | Product Development of LFA platform for improving sensitivity of Point-of-Care assays for infectious disease with main focus on Tuberculosis | Asahi Kasei Corporation, Biopromic AB | Tuberculosis Diagnostics | Product Design | ¥226,625,704 | $2,132,948 |
| G2020-213 New project | Lead optimization and preclinical candidate selection from the NTD Drug Discovery Booster series S07 for visceral leishmaniasis | Takeda Pharmaceutical Company Ltd., Drugs for Neglected Diseases *initiative* (DND*i*) | Leishmaniasis Drug | Lead Optimization | ¥225,744,281 | $2,124,652 |
| G2020-112 Continued project | Structured-based approach to develop a novel mechanism-of-action antimalarial with multistage activity | Eisai Co., Ltd., Broad Institute, International Centre for Genetic Engineering and Biotechnology (ICGEB), The Scripps Research Institute | Malaria Drug | Lead Optimization | ¥412,723,601 | $3,884,457 |
| G2020-115 New project | Optimization of multistage inhibitors of Plasmodium falciparum lysyl t-RNA synthetase for the treatment of malaria | Eisai Co., Ltd., Medicines for Malaria Venture (MMV), University of Dundee | Malaria Drug | Lead Optimization | ¥353,873,865 | $3,330,578 |
| H2020-201 Continued project | Hit-to-lead development of new antimalarial compounds from DDI library | The University of Tokyo, Medicines for Malaria Venture (MMV) | Malaria Drug | Lead Identification | ¥116,744,280 | $1,098,770 |
| H2020-202 Continued project | Hit-To-Lead development for Neglected Tropical Diseases | Mitsubishi Tanabe Pharma Corporation, Drugs for Neglected Diseases *initiative* (DND*i*) | Chagas disease, Visceral leishmaniasis Drug | Lead Identification | ¥117,066,370 | $1,101,801 |
| H2020-203 Continued project | Hit-to-Lead Development of Hits Identified in the Phenotypic Screening against *Mycobacterium tuberculosis* (Mtb) | Astellas Pharma Inc., TB Alliance | Tuberculosis Drug | Lead Identification | ¥80,136,368 | $754,225 |
| S2020-231 New project | Screening project between Daiichi Sankyo RD Novare and TB Alliance | Daiichi Sankyo RD Novare, TB Alliance | Tuberculosis Drug | Hit Identification | ¥11,830,099 | $111,342 |
| T2020-252 New project | Evaluation of a malaria vaccine candidate comprised of full-length recombinant CSP formulated with SA-1 adjuvant, using RTS,S/AS01 as a benchmark | Ehime University, Sumitomo Dainippon Pharma Co., Ltd., PATH | Malaria Vaccine | Antigen Identification | ¥99,973,317 | $940,925 |

*All amounts are listed at the exchange rate of USD1 = JPY106.25, the approximate exchange rate on February 26, 2021.

GHIT Fund
Global Health Innovative Technology Fund

Appendix.2 Project Details
Summary of each project below was extracted from their project overview on the GHIT website.

G2020-208

| | |
|---|---|
| **Project Title** | First-In-Human Trial of the Pan-Malaria Transmission-Blocking Vaccine AnAPN1 |
| **Collaboration Partners** | Ajinomoto Bio-Pharma Services (Aji-Bio), CellFree Sciences Co. Ltd. (CFS), Centre de Recherches Médicales de Lambaréné (CERMEL), University of Florida (UF), University of Tübingen (UKT) |
| **Disease** | Malaria |
| **Intervention** | Vaccine |
| **Stage** | Preclinical to Clinical Development (Phase 1) |
| **Awarded Amount** | ¥648,622,379 (US$6,104,681) |
| **Status** | Continued project |
| **Summary** | [Project objective]<br>A very promising approach to reduce malaria transmission is the development of so-called "Transmission Blocking Vaccines" or "TBVs" that could block the transmission of the parasite from humans to the mosquito. Targeted vaccination of individuals in high transmission areas promise an immediate and effective reduction in the number of malaria cases. Although a TBV would not directly prevent immunized individuals from developing the disease, it has a clear, delayed clinical benefit for the population. Moreover, a TBV could provide effective means to prevent the spread of antimalarial drug-resistant parasites, and parasites that break through the most advanced malaria vaccine (Mosquirix™) to date. Thus, the development of new TBVs is one of the research priorities for a cost-effective intervention that can directly support the malaria eradication effort. The development of TBVs has mostly focused on *P. falciparum* ookinete surface protein 25 (Pfs25) and its *P. vivax* homolog Pvs25, for which Phase 1 clinical trials have been initiated, as well as gametocyte proteins such as Pfs48/45 and Pfs230. However, successful suppression of malaria transmission in most parts of the world will require TBVs that effectively block transmission of both *P. falciparum* and *P. vivax*, as the most common causes of disease. A parasite-centric approach requires the development of multiple TBVs using protein immunogens from different species. Instead, the partners focused our studies on developing a vaccine based on a highly conserved mosquito protein that acts as a receptor for the parasite and has the potential to block malaria transmission regardless of the Plasmodium species, i.e., a so-called universal malaria TBV.<br><br>[Project design]<br>The anopheline mosquito midgut-specific alanyl aminopeptidase N (AnAPN1) is a luminal midgut surface protein involved in blood meal digestion. At present, AnAPN1 is the only TBV candidate, which blocks parasite transmission of *P. falciparum* and *P. vivax* in different *Anopheles* species. Working with a mosquito protein further reduces the risk that the parasite could develop resistance against the intervention, potentially allowing for a long-term use of the vaccine under elimination settings.<br><br>AnAPN1 has been studied extensively in transmission-blocking experiments, where the protein induced very high titers in immunized animals. A detailed analysis of the protein structure and consecutive mapping of epitope domains identified critical transmission-blocking epitopes of AnAPN1 that can elicit antibodies that completely reduced parasite development in the mosquito. Since any TBV will require very high antibody titers within vaccinated individuals to be effective, it is mandatory to develop an optimized antigen to ensure transmission-blocking activity. The partners have achieved this goal, by re-designing the AnAPN1 antigen and immuno-focusing the humoral response to the key epitopes. The optimized AnAPN1 immunogen, UF6b, has no purification tags, and when formulated with the GLA-LSQ adjuvant elicits potent transmission-blocking activity in mice and non-human primates against natural P. falciparum strains.<br><br>This project represents a joint effort by the University of Florida, CellFree Sciences, Ajinomoto Bio-Pharma Services, Center of Medical Research Lambaréné (CERMEL), and the University Hospital Tübingen. The partners envision that during the two-stage project they will complete preclinical manufacturing of UF6b and toxicology testing to obtain ethical approval for use of the vaccine and then enter directly into Phase IA/B clinical trials in Lambaréné, Gabon. As the end points of the clinical trial, safety and dose will be confirmed. Antibodies obtained from immunized individuals will be fully evaluated using a set of functional, immunological, and biological assays established at the University of Florida and CERMEL. |

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| **Project Detail** | https://www.ghitfund.org/investment/portfoliodetail/detail/185/en |

G2020-201

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|---|---|
| **Project Title** | Product Development of LFA platform for improving sensitivity of Point-of-Care assays for infectious disease with main focus on Tuberculosis |
| **Collaboration Partners** | Asahi Kasei Corporation, Biopromic AB |
| **Disease** | Tuberculosis |
| **Intervention** | Diagnostics |
| **Stage** | Product Design |
| **Awarded Amount** | ¥226,625,704 (US$2,132,948) |
| **Status** | Continued project |
| **Summary** | [Project objective]<br>The main objective is to validate a Rapid Diagnostic Test which is currently developed by Asahi Kasei and Biopromic for diagnosis of tuberculosis in TB patients irrespective of HIV status. Moreover, the test should meet the WHO TPP criteria.<br><br>[Project design]<br>Asahi Kasei´s and Biopromic´s RDT test will be evaluated by analysis of more than 1000 well-characterized clinical samples collected from South Africa and Uganda to determine the accuracy of the test. |
| **Project Detail** | https://www.ghitfund.org/investment/portfoliodetail/detail/182/en |

G2020-213

| | |
|---|---|
| **Project Title** | Lead optimization and preclinical candidate selection from the NTD Drug Discovery Booster series S07 for visceral leishmaniasis |
| **Collaboration Partners** | Takeda Pharmaceutical Company Ltd., Drugs for Neglected Diseases *initiative* (DND*i*) |
| **Disease** | Leishmaniasis |
| **Intervention** | Drug |
| **Stage** | Lead Optimization |
| **Awarded Amount** | ¥225,744,281 (US$2,124,652) |
| **Status** | New project |
| **Summary** | [Project objective]<br>The overall objective is to deliver a preclinical candidate compound for VL from the chemical series S07 fulfilling the Target Candidate Profile (TCP) for VL developed and used by DND*i*.<br><br>Specific Objectives:<br>1. Expand current selection of compounds meeting candidate level efficacy<br>2. Investigate and determine PK/PD drivers for the S07 series<br>3. Support compound development with preliminary CMC activities<br>4. Nominate one compound for preclinical development IND enabling studies<br><br>[Project design]<br>The overarching strategy for progression of the S07 series towards candidate nomination is to identify 3-5 optimized leads with potential to fulfill the TCP for in-depth profiling. From this optimized lead profiling, 2-3 of the most promising leads will be profiled in exploratory toxicology, and the best compound then nominated for progression to preclinical studies. The decision regarding which compound to progress will be made by a data review and candidate nomination meeting composed of all project members and external experts. To identify 3-5 optimized leads, the partners will:<br>a) complete profiling of the existing leads identified via the NTD Drug Discovery Booster program |

| | |
|---|---|
| | b) use SAR knowledge from previous work to produce new leads for profiling |
| **Project Detail** | https://www.ghitfund.org/investment/portfoliodetail/detail/186/en |

G2020-112

| | |
|---|---|
| **Project Title** | Structured-based approach to develop a novel mechanism-of-action antimalarial with multistage activity |
| **Collaboration Partners** | Eisai Co., Ltd., Broad Institute, International Centre for Genetic Engineering and Biotechnology (ICGEB), The Scripps Research Institute |
| **Disease** | Malaria |
| **Intervention** | Drug |
| **Stage** | Lead Optimization |
| **Awarded Amount** | ¥412,723,601 (US$3,884,457) |
| **Status** | Continued project |
| **Summary** | [Project objective]<br>The goal of this proposal is to leverage structural data on the target parasite protein to guide the design of next-generation antimalarials with higher efficacy, with potentially lower costs of treatment, and improved safety profiles.<br><br>[Project design]<br>We will use a combination of structural biology and computational chemistry to guide the design of novel antimalarials, which will be synthesized and profiled in vitro and in vivo. Promising compounds will be advanced to in vivo safety studies with the goal of selecting a preclinical development candidate. |
| **Project Detail** | https://www.ghitfund.org/investment/portfoliodetail/detail/169/en |

G2020-115

| | |
|---|---|
| **Project Title** | Optimization of multistage inhibitors of Plasmodium falciparum lysyl t-RNA synthetase for the treatment of malaria |
| **Collaboration Partners** | Eisai Co., Ltd., Medicines for Malaria Venture (MMV), University of Dundee |
| **Disease** | Malaria |
| **Intervention** | Drug |
| **Stage** | Lead Optimization |
| **Awarded Amount** | ¥353,873,865 (US$3,330,578) |
| **Status** | New project |
| **Summary** | [Project objective]<br>The aim of this project is to discover improved compounds with potential to treat human infection. In particular we want to identify a compound suitable for single dose treatment of malaria.<br><br>[Project design]<br>The initial part of the project will be further optimization studies to identify an improved molecule with potential for single dose treatment. Work will then focus on profiling the compound to understand it in more detail. This will include a raft of experiments in “test-tubes” and disease models to try and understand if it should be possible to obtain sufficient levels of compound in the body to treat the malaria infection (pharmacokinetics) and experiments to make sure that toxicity is not seen at the levels at which the compound will be given. |
| **Project Detail** | https://www.ghitfund.org/investment/portfoliodetail/detail/180/en |

H2020-201

| | |
|---|---|
| **Project Title** | Hit-to-lead development of new antimalarial compounds from DDI library |
| **Collaboration Partners** | The University of Tokyo, Medicines for Malaria Venture (MMV) |
| **Disease** | Malaria |
| **Intervention** | Drug |
| **Stage** | Lead Identification |
| **Awarded Amount** | ¥116,744,280 (US$1,098,770) |
| **Status** | Continued project |
| **Summary** | [Project objective]<br>The University of Tokyo and MMV will generate structurally optimized lead compounds effective against malaria parasites, based on the hit compounds identified by the partners in the previous screening campaign in 2018-2020, supported by GHIT Fund. In the preceding project, the partners identified a number of hits that kill the malaria parasites under micromolar concentrations, by phenotypic screening of 210,000 structurally defined compounds from Drug Discovery Initiative, Japan. In the present project, the partners will conduct structural optimization of the selected six series to develop new antimalarial leads. The partners aim at new compounds with a novel scaffold, mechanism of action, and improved efficacy and safety.<br><br>[Project design]<br>The University of Tokyo and MMV will work together to generate a few series of new compounds that kill malaria parasites by structural modifications of the initial hit series. The new compounds will be further tested for efficacy against both drug-sensitive and resistant malaria strains and also for in vitro safety. It will be also elucidated how the new compounds kill the parasites. Malaria parasites are transmitted between humans and mosquitoes. The partners will also evaluate what developmental stages of parasites the new compounds are efficacious to, e.g., parasites in the human liver, erythrocytes, mosquito gut, and the salivary gland. |
| **Project Detail** | https://www.ghitfund.org/investment/portfoliodetail/detail/189/en |

H2020-202

| | |
|---|---|
| **Project Title** | Hit-To-Lead development for Neglected Tropical Diseases |
| **Collaboration Partners** | Mitsubishi Tanabe Pharma Corporation, Drugs for Neglected Diseases *initiative* (DND*i*) |
| **Disease** | Chagas disease, Visceral leishmaniasis |
| **Intervention** | Drug |
| **Stage** | Lead Identification |
| **Awarded Amount** | ¥117,066,370 (US$1,101,801) |
| **Status** | Continued project |
| **Summary** | [Project Objective]<br>The objective of this project is to identify at least one series meeting DND*i* lead stage criteria for Chagas disease and/or visceral leishmaniasis in line with DND*i* published Target Product Profiles (TPPs) for new chemical entities. Medicinal chemistry efforts will be carried out in priority on the three most promising series.<br><br>[Project Design]<br>Screening cascade defined by DND*i* for both diseases will be used to assess and progress T. cruzi and Leishmania active series. Compounds will be designed to address the identified liabilities of the series and explore the most promising chemical subset of activity based on structure activity relationship (SAR) identified to date. Any new compound qualifying as a hit in line with the in vitro activity and selectivity criteria will be considered for further profiling and progression in ADME in vitro assays and eventually PK studies assuming favorable ADME profile in vitro is confirmed. Plasma and culture medium protein binding measurements will be performed on promising compounds to evaluate the levels of drug available as free fraction and eventually correlate in vitro |

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|---|---|
| | activity with drug plasmatic concentration in vivo. Compounds associated with sufficient drug exposure levels will be submitted to secondary assays as well as submitted in parallel to PD studies in acutely infected Chagas disease or leishmaniasis animal models to establish a PoC of in vivo efficacy. Compounds meeting the DND*i* lead stage criteria are set as the final milestone of this 2-year project. |
| **Project Detail** | https://www.ghitfund.org/investment/portfoliodetail/detail/190/en |

H2020-203

| | |
|---|---|
| **Project Title** | Hit-to-Lead Development of Hits Identified in the Phenotypic Screening against Mycobacterium tuberculosis (Mtb) |
| **Collaboration Partners** | Astellas Pharma Inc., TB Alliance |
| **Disease** | Tuberculosis |
| **Intervention** | Drug |
| **Stage** | Lead Identification |
| **Awarded Amount** | ¥80,136,368 (US$754,225) |
| **Status** | Continued project |
| **Summary** | [Project Objective]<br>Astellas in collaboration with TB Alliance have identified two chemical series in our screen of the 20,000-compound library offered by Astellas. The partners intend to develop them in a hit-to-lead phase by preparing a set of analogues for each to finetune their structure-activity relationships (SAR) and to acquire data on their pharmacokinetic (PK) properties and safety profiles. Consolidating the cumulative data, the partners aim to identify candidate compounds, ideally from both series, to test in a mouse acute infection model of TB. If successful, this project will provide a candidate for the lead optimization (LO) phase.<br><br>[Project Design]<br>New analogues in the two series will be synthesized and tested for the in vitro activity against Mtb and any promising analogues will be evaluated for PK and toxicity. Analogues selected after the PK and toxicity studies will be scaled up to test them in a mouse acute infection model. |
| **Project Detail** | https://www.ghitfund.org/investment/portfoliodetail/detail/191/en |

S2020-231

| | |
|---|---|
| **Project Title** | Screening project between Daiichi Sankyo RD Novare and TB Alliance |
| **Collaboration Partners** | Daiichi Sankyo RD Novare, TB Alliance |
| **Disease** | Tuberculosis |
| **Intervention** | Drug |
| **Stage** | Hit Identification |
| **Awarded Amount** | ¥11,830,099 (US$111,342) |
| **Status** | New project |
| **Summary** | This is a screening project between Daiichi Sankyo RD Novare and TB Alliance. |
| **Project Detail** | https://www.ghitfund.org/investment/portfoliodetail/detail/192/en |

T2020-252

| | |
|---|---|
| **Project Title** | Evaluation of a malaria vaccine candidate comprised of full-length recombinant CSP formulated with SA-1 adjuvant, using RTS,S/AS01 as a benchmark |
| **Collaboration Partners** | Ehime University, Sumitomo Dainippon Pharma Co., Ltd., PATH |

| | |
|---|---|
| **Disease** | Malaria |
| **Intervention** | Vaccine |
| **Stage** | Antigen Identification |
| **Awarded Amount** | ¥99,973,317 (US$940,925) |
| **Status** | New project |
| **Summary** | [Project Objective]<br>The overall objective of T2020-252 project is to rigorously test a novel vaccine candidate, flCSP/SA-1, comprised of a full-length recombinant CSP adjuvanted with a novel toll-like receptor 7 (TLR7) agonist, SA-1, for superiority to the RTS,S/AS01 benchmark vaccine, to inform whether to advance flCSP/SA-1 to preclinical development. The partners will examine two aspects of the vaccine, adjuvant (SA-1 vs AS01) and antigen (flCSP vs RTS,S), independently and in parallel.<br><br>Our specific objectives are:<br>1. Test whether flCSP/SA-1, compared to flCSP/AS01, for induction of improved durability of antibody responses in NHP model. NHPs are used as the test species because rodents do not adequately model the rapid decline of antibody titer observed with RTS,S/AS01 in humans.<br>2. Test whether flCSP antigen, compared to RTS,S, for induction of stronger protective efficacy in well qualified rodent challenge model.<br><br>[Project Design]<br>*Activity 1. Evaluate antibody response durability in NHP model.* Cynomolgus monkeys will be used as the primary animal model for immunogenicity because of their responsiveness to the TLR7 agonist in SA-1 and the similarity of induced functional antibody pharmacokinetics (PK) seen in humans. Monkeys will be immunized with of flCSP formulated with SA-1 or with AS01.<br><br>*Activity 2.1. Evaluate protective efficacy of antibodies induced by flCSP/AS01 and by RTS,S/AS01.* The partners will next compare the quality of the antibody response induced by flCSP or by RTS,S. Each immunogen will be tested in the same adjuvant, AS01, which is known to be active in mice. The experimental design will be closely based on our previously published qualification of in vivo models.<br><br>*Activity 2.2. Evaluate protective efficacy induced by flCSP/SA-1.* To assure that the combination of flCSP with SA-1 adjuvant results in protective efficacy in the mouse model, the partners will conduct active immunization followed by challenge with sporozoites and measure protection from parasitemia.<br><br>At completion of T2020-252 the partners will conduct a Go/no go decision to recommend preclinical development of flCSP/SA-1. A go decision will require evidence of superior, durable protection. |
| **Project Detail** | https://www.ghitfund.org/investment/portfoliodetail/detail/187/en |

*All amounts are listed at the exchange rate of USD1 = JPY106.25, the approximate exchange rate on February 26, 2021.

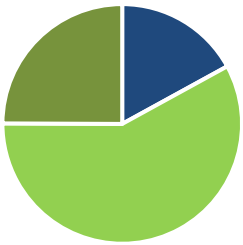
Appendix.3 Investment Overview (As of March 31, 2021)

## 1. Investment to date

Total investments 25.1 billion yen (US$236 million*)
Total invested projects 101 (active projects 57, completed projects 44)

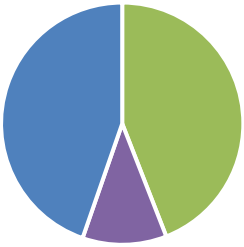
## 2. Portfolio analysis (active projects + completed projects)

Stage



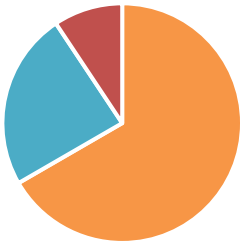
- Discovery ¥4,268,161,589 (US$40,170,933) 17.0% (57 projects)
- Preclinical ¥14,558,696,274 (US$137,023,024) 58.1% (31 projects)
- Clinical ¥6,252,975,417 (US$58,851,533) 24.9% (13 projects)

Disease



- Malaria ¥11,052,661,516 (US$104,025,050) 44.1% (46 projects)
- Tuberculosis ¥2,819,401,619 (US$26,535,545) 11.2% (19 projects)
- NTDs ¥11,207,770,145 (US$105,484,895) 44.7% (36 projects)

Intervention



- Drugs ¥16,717,604,195 (US$157,342,157) 66.7% (66 projects)
- Vaccines ¥6,019,329,759 (US$56,652,515) 24.0% (23 projects)
- Diagnostics ¥2,342,899,326 (US$22,050,817) 9.3% (12 projects)

*All amounts are listed at the exchange rate of USD1 = JPY106.25, the approximate exchange rate on February 26, 2021.

To know more about GHIT investments, please visit
Investment Overview: https://www.ghitfund.org/investment/overview/en
Portfolio: https://www.ghitfund.org/investment/portfolio/en
Advancing Portfolio: https://www.ghitfund.org/investment/advancingportfolio/en
Clinical Candidates: https://www.ghitfund.org/investment/clinicalcandidates/en