GHIT Fund

Global Health Innovative Technology Fund

Appendix.1 New Investment

Project Title	Treating schistosomiasis in preschool-aged children: development, registration and access to L-praziquantel orally disintegrating tablet formulation
Collaboration Partners	Astellas Pharma Inc., Lygature, Merck KGaA, Swiss Tropical and Public Health Institute, Farmanguinhos, Schistosomiasis Control Initiative (SCI), Université Félix Houphouët Boigny (UFHB), Kenya Medical Research Institute (KEMRI)
Disease	Schistosomiasis
Intervention	Drug
Stage	Phase III - Registration
Awarded Amount	¥452,329,597 (US$4,078,348)
Status	Continued project
Summary	Schistosomiasis, also known as bilharzia and endemic in 78 developing countries, is a chronic inflammatory neglected tropical disease caused by parasitic worms. The disease affects more than 206 million people, including 100 million children, globally. It is one of the most prevalent tropical diseases in the world after malaria, and represents an important health burden in developing countries, especially in Africa where more than 90% of the infections occur. The current gold standard recommended treatment for schistosomiasis, praziquantel (PZQ), is available in oral tablets for adults and children, but the effective dose for children < 4 years is currently not known as pharmacokinetics or dose-finding clinical studies have never been systematically conducted in this age group until recently. In addition, a pediatric formulation of praziquantel that would be appropriate for preschool age children, infants and toddlers, and would permit accurate dosing and enhanced compliance in these patients is non-existent and highly needed. The development of a new pediatric formulation of praziquantel is to be seen in the context of the WHO's 2020 Roadmap and with respect to the initiative of "Uniting to combat Neglected Tropical Diseases" under which the global community agreed on control and elimination of schistosomiasis. The Pediatric Praziquantel Consortium is an international not-for-profit partnership that aims to reduce the global disease burden of schistosomiasis by addressing the medical need of infected preschool-age children. Its mission is to develop, register and provide access to a suitable pediatric praziquantel formulation for treating schistosomiasis in this age group. The pediatric formulation under investigation has been designed to be smaller, exhibit an improved palatability and be orally dispersible compared to the current commercial formulation. The Consortium was established in July 2012 by Merck KGaA, Darmstadt, Germany (Merck KGaA), Astellas Pharma Inc. (Astellas), Swiss Tropical and Public Health Institute (Swiss TPH) and Lygature (formerly TI Pharma). At the beginning of 2014, Farmanguinhos and Simcyp, a Certara company, joined the Consortium as full partners. The Schistosomiasis Control Initiative (SCI) joined in 2016. At the end of 2017 Simcyp completed all its tasks around PK modeling and left the Consortium. In Jan 2018 Université Félix Houphouët Boigny (UFHB) and Kenya Medical Research Institute (KEMRI) joined the consortium as new partners. Since the start, all partners have been efficiently working together to progress the project and achieve the pre-clinical, clinical phase I-III and registration objectives. All partners are bound by a Consortium agreement, which arranges their roles and responsibilities and includes a formal governance structure with a Consortium Board as the highest decision-making body, and Lygature as independent Coordinator. An external expert panel is called by the Consortium prior to each clinical development stage to provide an independent evaluation of the project. The partners have formed a core project team, led by Merck KGaA, comprising one representative of each partner and/or expertise area that meets every month. The core project team is supported by various subteams focusing on specific technical and operational aspects to implement the consortium's program.
Project Detail	https://www.ghitfund.org/investment/portfoliodetail/detail/138/en

Project Title	Preclinical development of an anti-Dengue virus antibody that neutralizes all four serotypes
Collaboration Partners	Chugai Pharmaceutical Co., Ltd. and its subsidiary in Singapore, Chugai Pharmabody Research Pte. Ltd., Singapore Immunology Network, Agency for Science, Technology and Research
Disease	Dengue
Intervention	Drug
Stage	Preclinical Development
Awarded Amount	¥489,273,750 (US$4,411,448)
Status	Continued project
Summary	Dengue fever is a mosquito-borne viral infection found in tropical and subtropical regions around the world. There are 4 distinct, but related, serotypes of dengue virus (DENV) that cause dengue fever. The viral infection leads to symptoms that can include high fever, severe headache, joint, muscle and bone pain and skin rash. Mild bleeding is often observed because DENV inhibits the blood clotting function. In severe cases, plasma leaks out from blood vessels and the fluid loss can be fatal. A recent study estimates that approximately 390 million people are infected, and 500,000 people with severe dengue require hospitalization each year. A specific treatment for dengue has not been established yet. This Project aims to develop a safe and highly effective anti-DENV antibody that neutralizes all 4 serotypes for treatment of dengue fever without a risk of antibody-dependent enhancement (ADE), which is assumed to be related to severe disease during secondary DENV infection. Chugai and SIgN are working on preclinical development of the novel anti-DENV antibody. The objectives of the continuing project are shown below. 1) Manufacturing of drug substance and drug product under GMP conditions for the First-in-Human (FIH) clinical trial (Phase I) 2) Completion of preclinical studies (e.g. GLP-toxicology studies) enabling the Investigational New Drug (IND) application for testing in human
Project Detail	https://www.ghitfund.org/investment/portfoliodetail/detail/134/en

Project Title	Preclinical development of a novel mechanism-of-action antimalarial drug with multistage activity
Collaboration Partners	Eisai Co. Ltd, Broad Institute
Disease	Malaria
Intervention	Drug
Stage	Preclinical Development
Awarded Amount	¥536,822,427 (US$4,840,163)
Status	Continued project
Summary	Treatment and ultimately elimination of malaria remains a massive challenge due, mainly, to the emergence of drug-resistant strains of Plasmodium falciparum, the most lethal species in humans. It is therefore necessary to discover lead candidates unaffected by existing mechanisms of resistance to traditional antimalarial chemotypes. Additionally, while prophylaxis and transmission-blocking drugs are needed to prevent epidemics and to protect vulnerable populations, standard-of-care antimalarials do not address all of the requirements for pan-lifecycle activity. The Broad Institute, in collaboration with Eisai Ltd., has discovered a series of antimalarial compounds with a novel mechanism of action (targeting Plasmodium falciparum cytosolic phenylalanine tRNA synthetase (PfcPheRS)) (Nature, doi:10.1038/nature19804). Our unique bicyclic azetidine series exhibits potent activity both in vitro and in vivo against blood-, liver- and transmission-stage P. falciparum parasites. The current proposal builds on the progress made with GHIT support (G2014-107 and G2016-219) that delivered multiple compounds with excellent therapeutic profiles and improved synthetic routes. These advances will enable completion of preclinical development studies and Investigational New Drug (IND)-enabling Good Laboratory Practice (GLP) studies, with the goal of nominating a

	candidate for Phase I clinical studies aligned with the target candidate profiles defined by Medicines for Malaria Venture (MMV). The project is designed to generate in-depth preclinical data around the most promising candidate of the bicyclic azetidine chemical series, with the goal of nominating an antimalarial candidate for Phase I clinical studies. The main objectives of the project include: 1) physicochemical profiling of the candidate and selection of salt form; 2) preparation of material in accordance with Good Laboratory Practice (GLP) guidelines; 3) development of dosage form; 4) Investigational New Drug (IND)-enabling non-clinical safety studies.
Project Detail	https://www.ghitfund.org/investment/portfoliodetail/detail/137/en

Project Title	Preclinical development of a new class of Plasmodium DHODH inhibitor for the treatment of malaria
Collaboration Partners	Eisai Co. Ltd , Broad Institute
Disease	Malaria
Intervention	Drug
Stage	Lead Optimization
Awarded Amount	¥421,418,717 (US$3,799,646)
Status	New project
Summary	To be updated on the GHIT website.
Project Detail	https://www.ghitfund.org/investment/portfoliodetail/detail/133/en

Project Title	Live attenuated prophylactic vaccine for leishmaniasis
Collaboration Partners	Institute of Tropical Medicine (NEKKEN) Nagasaki University, The Ohio State University, McGill University, Gennova Biopharmaceuticals Ltd.
Disease	Leishmaniasis
Intervention	Vaccine
Stage	Preclinical Development
Awarded Amount	¥399,898,983 (US$3,605,617)
Status	Continued project
Summary	The leishmaniases comprise a number of diseases caused by obligate intracellular parasites of the genus *Leishmania* that is transmitted by the bites of infected sandflies. With over 350 million people worldwide at risk of contracting leishmaniasis, the WHO classifies leishmaniasis as a neglected tropical disease. Visceral leishmaniasis (VL) is the most severe form of the disease which is fatal without treatment. It is well documented that patients who recover from leishmaniasis including VL develop protective immunity against reinfection, which altogether indicates that a vaccine is feasible. Our team has developed a live attenuated vaccine for leishmaniasis by generating an attenuated dermotropic *Leishmania* by deleting a key gene to be critical for parasite virulence and persistence in the host. The overall objective of this project is to advance the preclinical development of this vaccine candidate. The aims of this project are: 1) Undertake pre-clinical toxicology studies on the vaccine as per regulatory guidelines, 2) Manufacture clinical grade GMP vaccine for clinical trials. Using CRISPR-Cas technology, we have successfully generated antibiotic selection marker free *centrin* gene deficient *L. major* (*LmCen*$^{-/-}$) and have established their safety and efficacy in pre-clinical laboratory studies. Our team will produce *LmCen*$^{-/-}$ vaccine under GLP conditions, undertake pre-clinical toxicology testing in animals as per regulatory guidelines and manufacture sufficient quantities of clinical grade GMP *LmCen*$^{-/-}$ for clinical testing.
Project Detail	https://www.ghitfund.org/investment/portfoliodetail/detail/135/en

Project Title	Mitsubishi Tanabe Lead Optimization of Anti-Malarials
Collaboration Partners	Mitsubishi Tanabe Pharma Corporation (MTPC), Medicines for Malaria Venture (MMV)
Disease	Malaria
Intervention	Drug
Stage	Lead Optimization
Awarded Amount	¥192,247,534 (US$1,733,365)
Status	Continued project
Summary	Screening of an (approximately) 50,000 member library of unique compounds from the Mitsubishi Tanabe Pharma Corporation (MTPC) library identified several antimalarial hits from diverse series of molecules. Development of structure-activity relationships (SAR) for three series of focus (Series 1, 2 and 3) in a "Hit-to-Lead" project revealed that Series 1 was the most attractive series for further optimization, as the series is fast-killing, exhibits high antimalarial potency across the lifecycle (Target Candidate Profiles (TCP1,4 and 5) potential), has good physicochemical and pharmacokinetic properties and shows efficacy in the mouse model of malaria. Three of these Lead Compounds have formally met the MMV Early Lead criteria and will form the basis of this Lead Optimization project. The primary objective of the project will be to identify 1-3 late leads within 18 months, as defined by MMV's progression criteria, and further profile them in the final 6 months to select a preclinical candidate capable of progression to first-in-human clinical trials. As an additional objective, the project will endeavor to confirm the proposed mode of action. By doing so, the project will be able to assess the likelihood that these compounds will have the ability to safely treat malaria in areas where resistance to existing drugs is emerging. The project will be conducted as a multi-disciplinary drug discovery effort, utilizing the diverse skills and experiences of medicinal chemists, molecular modelers, parasitologists, pharmacokineticists and toxicologists. Starting with the identified Early Lead Molecules, systematic modification of these drug candidates will be undertaken to further improve the pharmacological, selectivity, physicochemical, pharmacokinetic and toxicological properties based on state-of-the-art capabilities at MMV, MTPC and our partners. As the putative target of these molecules is an enzyme that is essential to the growth of the malaria parasite, and structural information is available from analogous bacterial proteins, a structure-based drug design (SBDD) approach will be applied. This will provide the opportunity to more rapidly focus on compounds with a higher likelihood of achieving the project objectives.
Project Detail	https://www.ghitfund.org/investment/portfoliodetail/detail/136/en

Project Title	New Hit-to-Lead Activity for New Anti-Malarials between MMV and Takeda
Collaboration Partners	Takeda Pharmaceutical Company Limited., Medicines for Malaria Venture
Disease	Malaria
Intervention	Drug
Stage	Lead Identification
Awarded Amount	¥52,800,000 (US$476,062)
Status	Continued project
Summary	Malaria, a mosquito-borne parasite, can still infect over 200 million people per year. There were an estimated 445,000 malaria deaths worldwide in 2016 (1). Novel classes of antimalarial medicines targeting different parasite stages are urgently needed to provide both effective alternatives when resistance to current therapies will inevitably progress and the ingredients needed to meet the malaria eradication agenda (2). The project team is now working on three confirmed chemical hit series inhibiting the asexual blood stage of the parasite life cycle. The prioritized series is directly repurposed from Takeda portfolio, the other two series are from the GHIT Screening Platform with

	Takeda 20,000 compound library against the asexual blood, liver and sexual stages of malaria. The screening was performed at MMV testing centres in USA (Prof. Elizabeth Winzeler – University of California, San Diego) and in Australia (Prof. Vicky Avery – Griffith Institute for Drug Discovery, Griffith University) against the liver (3), blood asexual (4) and sexual (5) stages of the malaria parasite. The objectives for the project are to transform these hits into Lead series with proven in vivo efficacy at the animal disease models so as to identify before March 2020 at least one compound series that meets the GHIT/MMV criteria for progression to Lead Optimization stage. During the first phase of the project, frontrunner compounds from the three series selected for hit-to-lead progression will be profiled in the parasite life cycle assays to confirm their Target Candidate Profile (TCP). In parallel, medicinal chemistry will be carried out and analogues will be profiled in parasitology and cytotoxicity assays. The physicochemical properties, stability and ADMET characteristics will also be determined. Then the most promising compounds will be evaluated in rodents PK experiments and in the disease model of human malaria to demonstrate in vivo efficacy. After further optimization of their properties, the goal is to select a couple of lead molecules which will be the basis of a new proposal to GHIT for a Lead Optimization program.
Project Detail	https://www.ghitfund.org/investment/portfoliodetail/detail/141/en

Project Title	Hit-to-Lead Development of Novel anti-TB Natural Products
Collaboration Partners	Daiichi Sankyo RD Novare, TB Alliance
Disease	Tuberculosis
Intervention	Drug
Stage	Lead Identification
Awarded Amount	¥119,244,000 ($1,075,142)
Status	Continued project
Summary	Most TB drugs currently in use were discovered 40-50 years ago and little has changed over this period. To treat people with drug-sensitive TB, it takes on average 6 months of treatment with multiple drugs a day. In the case of drug-resistant TB, the situation is much worse, often requiring continued medication for at least 18 months and sometimes less effective and toxic drugs. The treatment success rate for multidrug-resistant TB is currently estimated at 54%. Therefore, new TB drugs are urgently needed to shorten the treatment duration and to combat drug-resistant strains of Mycobacterium tuberculosis (M tb), the causative agent of TB. Identification of lead compounds that can result in effective new tuberculosis drugs including treatment shortening and cure for both drug-sensitive and drug-resistant TB. This project was a result of screening effort among Daiichi Sankyo RD Novare, TB Alliance, and the Research Institute of Tuberculosis (Japan Anti-tuberculosis Association) which began with a support from the GHIT Fund. Daiichi Sankyo RD Novare's original natural product library created from microorganisms such as actinomycetes and fungi, consisting of 30,000 extracts and 600 purified natural compounds. The Research Institute of Tuberculosis evaluated bactericidal activity against TB using the natural product library. Through close cooperation of these three research institutes, a group of hit compounds were identified and the structures of the active components were determined. The active components were further studied for their biological properties and a research plan was developed to generate additional fermentation products for structural modifications and biological evaluations. The medicinal chemistry program was developed by consultation between Daiichi Sankyo RD Novare and TB Alliance.
Project Detail	https://www.ghitfund.org/investment/portfoliodetail/detail/142/en

Project Title	Further development of a new asexual blood-stage malaria vaccine candidate
Collaboration Partners	Ehime University (Ehime), European Vaccine Initiative (EVI), iBET
Disease	Malaria

Intervention	Vaccine
Stage	Antigen Identification – Technology Platform Identification
Awarded Amount	¥93,057,133 ($839,033)
Status	New project
Summary	Despite intensive control efforts over the past decade, malaria remains one of the most significant global public health problems, leading to substantial morbidity and mortality. Given the low efficacy and other potential limitations of the currently most advanced malaria vaccine candidate (RTS,S, or Mosquirix), a more effective second-generation malaria vaccines is urgently needed. In this proposal, we plan to advance the development of a novel blood-stage antigen that in the future may form part of a more effective multi-antigen-multistage malaria second-generation malaria vaccine. Goal of this project is to further advance the development of a new asexual blood-stage malaria vaccine candidate, based on the PfRipr5 protein of the malaria parasite *Plasmodium falciparum*, which was discovered by researchers in Ehime University in collaboration with Sumitomo Dainippon Pharma Co., Ltd., Japan. Different expression systems for the antigen will be tested and compared, subsequently the immunogenicity of the antigen formulated with two different adjuvants already in use in humans will be tested in different model systems. The project work plan has been structured according to the three research objectives defined. First objective will be to produce the PfRipr5 antigen in different scalable expression systems, with the ultimate goal to identify the expression system most suitable for further product development. Subsequently, objective two aims to formulate the antigen with two different adjuvants. Third and last objective of the project will be to evaluate the immunogenicity and anti-malarial efficacy of the adjuvanted in an animal model and in in *in vitro* growth inhibition assay.
Project Detail	https://www.ghitfund.org/investment/portfoliodetail/detail/139/en

Project Title	Development of LFA platform for improving sensitivity of Point-of-Care assays for infectious disease with main focus on Tuberculosis and Malaria.
Collaboration Partners	Asahi Kasei Corporation, Biopromic AB
Disease	Tubeculosis
Intervention	Diagnostics
Stage	Concept Development – Development Feasibility
Awarded Amount	¥100,000,000 ($901,632)
Status	New project
Summary	Despite intense efforts to eliminate malaria, tuberculosis and a number of other infectious diseases only moderate to low success has been achieved. Thus, highlighting the necessity to expand and refine current eradication strategies, in particular those targeting the early detection in endemic areas. Point-of-care (POC) tests dramatically enhanced physician's ability to diagnose patients' diseases rapidly and accurately at a bed side or even by the patient himself. Nevertheless, currently there is only a small number of infections POC tests available and they represent a fraction of the actual demand for this kind of diagnostics (WHO TPP for infectious disease diagnostics). The greatest challenge in POC diagnostics is the very low concentration of antigens in the sample which are easily accessible. Current LFA devices offer analytical sensitivity above 1-5ng/ml. Taking into account that in case of tuberculosis and malaria patients' concentration of antigens in the samples is usually below 100pg/ml there is a clear need for more sensitive LFA systems to be developed. In this project, we plan to develop a new Lateral Flow Assay (LFA) platform aiming at up to 50x improvement of antigen detection from current industry standard. Achieving such a high analytical sensitivity of the LFA tests requires significant improvement and integration of multiple components of the LFA system. . To achieve this goal we will combine, integrate and optimize over 5 technologies which were developed by the project partners, in 3 phases of the project.

	1. Cross-partner technology testing and detailed TPP development where we develop a detailed TPP for the platform. While TPP for each of the technologies exist (or the products are already implemented on the market) a product combining multiple of them would require a separate, balanced approach. 2. Technical feasibility testing of combined technologies and their modifications to work within the platform where at the end of this phase we expect all the potential modifications to be complete and a platform to be ready for the prototype phase. 3. Development of a LFA prototype test and its initial testing In this final stage of the project we aim to build two prototypes of POC-LFA tests which utilize the solutions from phase 2 and validate the designs on laboratory and patient
Project Detail	https://www.ghitfund.org/investment/portfoliodetail/detail/140/en

*All amounts are listed at the exchange rate of USD1 = JPY110.91, the approximate exchange rate on February 28, 2019.

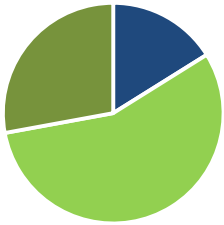
Appendix.2 Investment Overview (As of March 28, 2019)

1. Investment to date

Total Investments 17 billion yen (US$153 million*)
Total Invested Projects 80（Active projects 50, Completed projects 30）

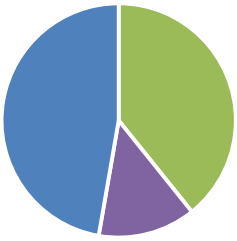
2. Portfolio Analysis (Active + Completed)

Stage



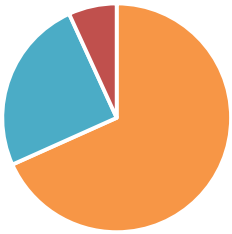
■Discovery ¥2,738,943,901 (US$24,695,193) 16.1%
（46 projects）
■Preclinical ¥9,516,957,080 (US$85,807,926) 56.0%
(23 projects)
■Clinical ¥4,737,846,333 (US$42,717,936) 27.9%
（11 projects）

Disease



■Malaria ¥6,668,014,209 (US$60,120,947) 39.2%
（34 projects）
■Tuberculosis ¥2,294,287,601 (US$20,686,030) 13.5%
（18 projects）
■NTDs ¥8,031,445,504 (US$72,414,079) 47.3%
（28 projects）

Intervention



■Drugs ¥11,605,970,988 (US$104,643,143) 68.3%
（55 projects）
■Vaccines ¥4,227,072,881 (US$38,112,640) 24.9%
（18 projects）
■Diagnostics ¥1,160,703,445 (US$10,465,273) 6.8%
（7 projects）

To know more about GHIT investment, 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

*All amounts are listed at the exchange rate of USD1 = JPY110.91, the approximate exchange rate on February 28, 2019.