GHIT Fund

Global Health Innovative Technology Fund

Appendix.1 New Investment

ID/Status	Project Title	Collaboration Partners	Disease/ Intervention	Stage	Awarded Amount
G2019-102 New project	Optimization and pre-clinical development of a *Trypanosoma cruzi* Cyp19 knock-out strain as a live vaccine for Chagas disease.	Institute of Tropical Medicine (NEKKEN) Nagasaki University, Ohio State University, Ohio University	Chagas disease Vaccine	Lead Optimization	¥109,792,791 (US$1,031,596)
G2019-105 New project	Commercial Development of a Saliva-based Malaria Asymptomatic and Asexual Rapid Test (SMAART-1)	CellFree Sciences Co. Ltd., Frontier Institute Co., Ltd., University of Florida, Oasis Diagnostics Corp., ERADA Technology Alliance, Ltd.	Malaria Diagnostics	Product Design	¥138,269,665 (US$1,299,161)
G2019-111 New project	Co-delivery of Pfs230C1 and CSP with CoPoP, a versatile, potent liposomal adjuvant system for multistage malaria vaccine	Ehime University, PATH Malaria Vaccine Initiative, University at Buffalo, The State University of New York	Malaria Vaccine	Antigen Identification	¥97,295,110 (US$914,170)
H2019-101 Continued project	Proteasome inhibitors as new potent antimalarials	Takeda Pharmaceutical Company Limited, The University of Melbourne's Bio21 Molecular Science and Biotechnology Institute, Medicines for Malaria Venture	Malaria Drug	Hit-to-Lead	¥52,614,000 (US $494,353)
H2019-104 New project	Development of nucleoside sulfamates as novel antimalarials	Takeda Pharmaceutical Company Limited, The University of Melbourne's Bio21 Molecular Science and Biotechnology Institute, Medicines for Malaria Venture	Malaria Drug	Hit-to-Lead	¥101,612,940 (US$954,740)
H2019-107 Continued project	Hit-to-Lead Development of Phenotypic and Mechanism-based Screen Hits	Takeda Pharmaceutical Company Limited, Global Alliance for TB Drug Development	Tuberculosis Drug	Hit-to-Lead	¥111,205,860 (US$1,044,873)
S2019-111 New project	Screening project between Takeda and Medicines for Malaria Venture	Takeda Pharmaceutical Company Limited., MMV	Malaria Drug	Hit Identification	¥4,196,250 (US$39,427)
S2019-121 New project	Screening project between Mitsubishi Tanabe Pharma Corporation and Drugs for Neglected Diseases *initiative*	Mitsubishi Tanabe Pharma Corporation, Drugs for Neglected Diseases *initiative*	Chagas disease, Leishmaniasis Drug	Hit Identification	¥15,000,000 ($140,938)

*All amounts are listed at the exchange rate of USD1 = JPY106.43, the approximate exchange rate on August 30, 2019.

GHIT Fund

Global Health Innovative Technology Fund

Appendix.2 Project Details

G2019-102

Project Title	Optimization and pre-clinical development of a *Trypanosoma cruzi* Cyp19 knock-out strain as a live vaccine for Chagas disease
Collaboration Partners	Institute of Tropical Medicine (NEKKEN) Nagasaki University, Ohio State University, Ohio University
Disease	Chagas disease
Intervention	Vaccine
Stage	Lead Optimization
Awarded Amount	¥109,792,791 (US$1,031,596)
Status	New project
Summary	Human infection by the parasite *Trypanosoma cruzi* causes Chagas disease which is the leading infectious cause of heart failure in Latin America. Approximately 20-30% of those chronically infected develops cardiac fibrosis and associated cardiomyopathy. Chagas disease is increasingly found outside of Latin America mainly due to trans-migration of chronically infected individuals and affects at least 300,000 people in the United States and 8-11 million worldwide. There are increasing numbers of people infected by *T. cruzi* in the lower 20 of the United States due to exposure to infected insect vectors. Identification and treatment of infected people are challenging and only two rather antiquated drugs (nifurtimox and benznidazole) are available to treat the infection but are ineffective to completely clear the parasites from the host and have significant side effects which hamper their use. Thus there is an urgent need to develop a safe vaccine for prevention of *T. cruzi* infection and to develop more therapeutic strategies for treatment. Our laboratory is currently characterizing the biochemical and biological properties of *T. cruzi* cyclophilin 19 (Cyp19), a peptidyl-prolyl-isomerase that catalyzes the cis-trans isomerization of various cellular proteins acting as a chaperone. We created a double allelic knock-out parasite (DKO) line devoid of Cyp19 expression, which has shown *T. cruzi* Cyp19 as an indispensable protein for parasite infectivity and virulence supporting the hypothesis that this protein represents a potential critical target for small molecule inhibitors to treat the infection. Although unable to cause disease in animals, repeated immunization with live DKO parasites stimulates anti-parasitic immunity which is completely protective to mice in a model of acute Chagas disease, demonstrating proof-of-concept that this is a promising live attenuated vaccine strain. The long-term goal of this proposal is to generate a safe and highly efficacious live attenuated vaccine for Chagas disease for use in humans and in animals. The specific objectives are: 1) engineering a Cyp19 DKO (CC-DKO) vaccine strain using CRISPR/Cas9 and confirming its potential to provide protection in mice; 2) understanding of the T- and B-cell response responsible for protective immunity generated by this vaccine strain; 3) demonstrating that the CC-DKO vaccine is efficacious at preventing acute and chronic Chagas disease in mice and cross-protects from multiple strains and understand the duration of immunity; 4) understanding if the vaccine is safe in immunosuppressed hosts; and 5) understand if the CC-DKO is transmissible through the insect vector. The overall design of the project is divided into the following specific aims: Aim 1: Engineer and test a Cyp19 DKO line using CRISPR/Cas9 technology and perform characterization, stability, safety, and toxicity of this version of the vaccine. Aim 2: Test CC-DKO-strain vaccinated animals for the determinants of protective immunity, to understand what profile of T- and B-cell immunity is provoked by vaccination and to optimize the vaccine strategy. Aim 3: Determine if DKO vaccination leads to protection of chronic Chagas disease in the mouse model of infection, test the duration of immune-protection and the ability of the vaccine to cross-protect from diverse strains of *T. cruzi*. Aim 4: Test the ability of the DKO strain to grow, survive in triatomine insects and be transmitted between animals and insects.
Project Detail	https://www.ghitfund.org/investment/portfoliodetail/detail/143/en

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G2019-105

Project Title	Commercial Development of a Saliva-based Malaria Asymptomatic and Asexual Rapid Test (SMAART-1)
Collaboration Partners	CellFree Sciences Co. Ltd., Frontier Institute Co., Ltd., University of Florida, Oasis Diagnostics Corp., ERADA Technology Alliance, Ltd.
Disease	Malaria
Intervention	Diagnostics
Stage	Product Design
Awarded Amount	¥138,269,665 (US$1,299,161)
Status	New project
Summary	Malaria remains a major global heath burden with as much as a third of the global population at risk of disease. Importantly, it is the leading cause of death for children under five, especially in Sub-Saharan Africa. The malaria elimination and eradication effort has stalled in recent years and the World Health Organization Strategic Advisory Group on Malaria Eradication, has renewed the call for new, innovative tools to overcome the current limitations of our current tools. Malaria rapid diagnostic tests (RDTs) have been a critical component of the eradication arsenal but recent studies suggest that the *Plasmodium falciparum* parasite has developed mutations that effectively limit the diagnostic capacity of current RDTs to confirm parasitic infection in the field. Our project addresses this limitation by producing a commercial RDT that can either use saliva or blood as input material, have high enough sensitivity to diagnose asymptomatic cases with high reliability, and greater acceptability, designed especially for easier diagnostic screening of children. The University of Florida identified a new *P. falciparum* protein marker PSSP17 that could replace presently used parasite markers like the *Plasmodium* histidine-rich protein-2 (HRP-2), which has become increasingly ineffective due to a growing prevalence of parasite mutations. The PSSP17 protein is present in infected red blood cells and is also present as a soluble molecule in the saliva of individuals with clinical and subclinical infections. Our recent data using a prototype test demonstrated that this marker allows the identification of children with subclinical malaria infection with high precision. Based on these promising results, we are developing and validating a commercial PSSP17-based RDT for highly sensitive detection of malaria infection at the point of care (clinic) and point of need (villages). We propose three objectives for the development and validation of Saliva-based Malaria Asymptomatic and Asexual Rapid Test (SMAART-1): **Objective 1** – Design and small-scale production of 2,000 SMAART-1 kits, which contains a saliva-collection device and a lateral flow immunoassay cassette. **Objective 2** – Quality-assured medical device production conditions of heat-stable, high-affinity recombinant humanized monoclonal antibodies for capture and detection of PSSP17 on a lateral flow test. **Objective 3** – Thorough testing and validation of the commercial SMAART-1 test in the Democratic Republic of Congo (DRC), a priority malaria endemic country, or in Uganda as an alternative trial site. During these studies, the acceptability, usability, sensitivity and reliability of the SMAART-1 RDT will be compared to the most sensitive molecular laboratory tests used in malaria detection. The overall outcome of the project is to fulfill all the criteria for obtaining CE marking and subsequent WHO prequalification of the SMAART-1 kit.
Project Detail	https://www.ghitfund.org/investment/portfoliodetail/detail/144/en

G2019-111

Project Title	Co-delivery of Pfs230C1 and CSP with CoPoP, a versatile, potent liposomal adjuvant system for multistage malaria vaccine
Collaboration Partners	Ehime University, PATH Malaria Vaccine Initiative, University at Buffalo, The State University of New York
Disease	Malaria
Intervention	Vaccine
Stage	Antigen Identification

Awarded Amount	¥97,295,110 (US$914,170)
Status	New project
Summary	Malaria remains one of the leading causes of deaths in young African children. Transformative tools are urgently needed to ensure global control, elimination and eventual eradication goals are met; our vaccine approach has the potential to serve as one such transformational tool. Building on recent advances in the identification of leading malaria vaccine targets and novel delivery platforms, this project seeks to develop a vaccine to induce immunity that blocks parasite transmission between humans and mosquitoes. We will evaluate the capacity of CoPoP, a novel liposomal delivery platform, to co-deliver Pfs230 and CSP, two lead malaria vaccine candidates, to block parasite transmission from human-to-mosquito and mosquito-to-human, respectively. The planned work will generate necessary evidence to support a go/no-go decision to advance the candidate vaccine to preclinical development. ・Evaluate CSP immune enhancement using CoPoP liposomes coupled with immunestimulants (called CoPoP adjuvant in short thereafter). ・Evaluate feasibility of co-delivery of Pfs230C1 and CSP with CoPoP adjuvant for enhanced functional immunogenicity and protective efficacy in preclinical models. ・Evaluate immunogenicity of selected formulations in a second animal species suitable for GLP toxicology studies; develop analytical assays and release specifications for drug substance and drug product. We will first apply knowledge and experience obtained from Pfs230C1 formulated with CoPoP adjuvant to evaluate the potential of CoPoP adjuvant for enhancing immunogenicity of CSP. We will then evaluate the capacity of co-formulating CSP and Pfs230 with CoPoP adjuvant, and the immune enhancement by CoPoP adjuvant to both CSP and Pfs230. Antigen incorporation and the stability of antigen-CoPoP formulations will be optimized using biochemical and biophysical methods. The functional immunogenicity of the antigen-CoPoP formulation will be evaluated by established functional assays: the standard membrane-feeding assay (SMFA) for Pfs230 and an in vivo mouse transgenic parasite challenge model for CSP. Aiming to advance Pfs230-CSP-CoPoP vaccine candidate toward preclinical development, we will also conduct a pilot study in additional animal species in order to inform future design of GLP toxicology study, and will develop assays in order to inform future establishment of product release specifications.
Project Detail	https://www.ghitfund.org/investment/portfoliodetail/detail/145/en

H2019-101

Project Title	Proteasome inhibitors as new potent antimalarials
Collaboration Partners	Takeda Pharmaceutical Company Limited, The University of Melbourne's Bio21 Molecular Science and Biotechnology Institute, Medicines for Malaria Venture
Disease	Malaria
Intervention	Drug
Stage	Hit-to-Lead
Awarded Amount	¥52,614,000 (US $494,353)
Status	Continued project
Summary	The proteasome is a multienzyme complex found in all eukaryotic cells that functions to maintain homeostasis of intracellular proteins. As an organism that undergoes rapid growth and cell division, the malaria parasite is highly reliant on its ubiquitin proteasome system, making the proteasome a promising target for antimalarial drug discovery. With the previous support of the GHIT Fund (T2015-134; H2017-101), our Takeda Pharmaceuticals/ University of Melbourne/ Medicines for Malaria Venture team has already identified promising early leads for a drug discovery campaign. We screened a peptide boronate library of human proteasome inhibitors for antiparasitic activity then further characterized the hits, by comparing their activities against purified *P. falciparum* and human 20S proteasome and assessing their activities as inhibitors of the growth of *P. falciparum* and human cells. We identified three hit series and performed further exploration to define structure activity relationships, ultimately arriving at a preferred series. Our lead 'DAG' series are potent inhibitors of only the two beta-5 subunit's catalytic centers in the plasmodium proteasome. Examples also have high potency against the parasite (3D7 ED50 <10nM), selectivity over human cell lines (>100-fold), are fast-acting (equivalent to artemesinin), have good

	bioavailability (rat >50%) and show efficacy in the SCID mouse model of *P.falciparum* malaria (ED_{90}<50mg/kg 4 x b.i.d). Data from the clinical development of Takeda's new oral human proteasome inhibitor, ixazomib (NINLARO®) suggests that molecules in this chemical class can have pharmacological and pharmaceutical properties consistent with MMV's Target Candidate Profile (TCP) for new antimalarial medicines. Thus, with further improvements in selectivity, we are poised to deliver a novel antimalarial drug lead that can be a valuable contribution to treatment in its own right, and in addition, potentiate the action of artemisinins and overcome artemisinin resistance. The Project aims: 1) To discover potent inhibitors of *P. falciparum* proteasome with high selectivity over the human enzyme which meet MMV's criteria for entry into lead optimization; 2) To assess potent, specific *P. falciparum* proteasome inhibitors for concordance with the Malaria Target Product Profiles *i.e.* for treatment and/or chemoprotection. We will pursue a H2L medicinal chemistry program supported by a well-defined test cascade to deliver early lead(s) which meet MMVs criteria for entry into lead optimisation. We need to improve selectivity over the human beta-5 subunit and to improve the half-life in order to ultimately identify safe candidates with single dose potential. Differences in the substrate binding site between the human and *P. falciparum* enzymes will aid the rational design of highly selective inhibitors. Furthermore, our experience with boronate inhibitors has taught us that good pharmacokinetic properties (oral bioavailablity, low clearance and long half-lives, good solubility and suitable LogP) can be obtained. The inhibitor design will take advantage of our understanding of *P. falciparum* 20S proteasome active site obtained from modelling and cryoEM structural studies.
Project Detail	https://www.ghitfund.org/investment/portfoliodetail/detail/146/en

H2019-104

Project Title	Development of nucleoside sulfamates as novel antimalarials
Collaboration Partners	Takeda Pharmaceutical Company Limited, The University of Melbourne's Bio21 Molecular Science and Biotechnology Institute, Medicines for Malaria Venture
Disease	Malaria
Intervention	Drug
Stage	Hit-to-Lead
Awarded Amount	¥101,612,940 (US$954,740)
Status	New project
Summary	Malaria is a debilitating disease caused by Plasmodium parasites. Every year ~200 million new infections are established, causing more than 400,000 deaths. There is an urgent need to develop new antimalarial drugs that are safe, fast-acting, active against different stages and all strains, effective as a single dose and suitable for both treatment and prophylaxis. We have identified a class of nucleoside sulfamates that show potential to meet these demanding criteria. Our front-runner compounds exhibit long in vivo half-lives, very high potency against malaria parasite cultures and very low toxicity against mammalian cell lines. We have demonstrated single dose efficacy in a mouse model of human malaria. This project seeks to undertake Hit-to-Lead studies on our nucleoside sulfamates series to identify compounds which meet MMV's early lead criteria for entry into lead optimization. Specifically, the Project aims: i) To undertake a medicinal chemistry program to improve oral bioavailability of the nucleoside sulfamate series, while maintaining selectivity and potent anti-parasitic activity. ii) To undertake a detailed analysis of the activity of orally bioavailable nucleoside sulfamates in a testbed of assays against different life stages of Plasmodium to define the potential product profile (*i.e.* treatment and/or chemoprotection). iii) To demonstrate efficacy and tolerability of orally bioavailable nucleoside sulfamates in a SCID mouse model of *P. falciparum* malaria. iv) To confirm the mode of action and to understand the potential for resistance generation. The target of the nucleoside sulfamate front-runner compound has been identified as an important protein synthesis enzyme, called tyrosine tRNA synthetase. The target enzyme is divergent from its human homologue, consistent with good selectivity of the inhibitors. We will establish biochemical assays and a well-defined test cascade to support a medicinal chemistry program to improve oral availability and deliver nucleoside sulfamates with drug-like properties that maintain potency and

	selectivity. We anticipate that good pharmacokinetic properties (oral bioavailablity, low clearance and long half-lives, good solubility and suitable LogP) can be obtained. Within one year of project funding, we will identify nucleoside sulfamate compounds that inhibit the growth of 3D7 *P. falciparum* with an IC_{50} value less than 100 nM and show more than 25% bioavailability in rats.
Project Detail	https://www.ghitfund.org/investment/portfoliodetail/detail/147/en

H2019-107

Project Title	Hit-to-Lead Development of Phenotypic and Mechanism-based Screen Hits
Collaboration Partners	Takeda Pharmaceutical Company, Limited, Global Alliance for TB Drug Development
Disease	Tuberculosis
Intervention	Drug
Stage	Hit-to-Lead
Awarded Amount	¥111,205,860 (US$1,044,873)
Status	Continued project
Summary	In the fight against TB the number of drugs available is quite limited and many of them are 40 to 50 years old. They need to be administered to the patients for at least 6 months in the best case and much longer in the case of drug-resistant TB. New drugs are needed to shorten the treatment duration and to combat drug-resistant strains. In order to identify prototypes of potential new TB drugs (hits) Takeda Pharmaceutical Company (Takeda) and TB Alliance jointly carried out screening campaigns. We ultimately identified two series of compounds, one from phenotypic screening a large number of compounds with Takeda library for their ability to kill *Mycobacterium tuberculosis* (*Mtb*, the pathogen causing TB), and another from mechanism-based screening for their ability to inhibit a particular enzyme in *Mtb* from Takeda internal portfolio. In this Hit-to-Lead project we intend to improve their potency and properties to make them suitable for treatment. The objectives of this project are to improve the potency of the hits to kill *Mtb* but at the same time to make them safe to be used in humans. We also want to prove that the eventual drugs derived from these prototypes can be dosed orally and in reasonable doses to be widely accepted among TB patients worldwide. To achieve these objectives, we will synthesize several dozens of analogues in each series to evaluate them in the assays related to the objectives above. We will test selected analogues in mice to evaluate their activity in animal models. The design, synthesis, and testing are an iterative process until we identify a compound best satisfying the objectives above.
Project Detail	https://www.ghitfund.org/investment/portfoliodetail/detail/148/en

S2019-111

Project Title	Screening project between Takeda and Medicines for Malaria Venture
Collaboration Partners	Takeda Pharmaceutical Company Limited., MMV
Disease	Malaria
Intervention	Drug
Stage	Hit Identification
Awarded Amount	¥4,196,250 (US$39,427)
Status	New project
Summary	This is a screening project between Takeda Pharmaceutical Company Limited. and MMV.
Project Detail	https://www.ghitfund.org/investment/portfoliodetail/detail/149/en

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S2019-121

Project Title	Screening project between Mitsubishi Tanabe Pharma Corporation and Drugs for Neglected Diseases *initiative*
Collaboration Partners	Mitsubishi Tanabe Pharma Corporation, DND*i*
Disease	Chagas disease, Leishmaniasis
Intervention	Drug
Stage	Hit Identification
Awarded Amount	¥15,000,000 ($140,938)
Status	New project
Summary	This is a screening project between Mitsubishi Tanabe Pharma Corporation and DND*i*.
Project Detail	https://www.ghitfund.org/investment/portfoliodetail/detail/150/en

*All amounts are listed at the exchange rate of USD1 = JPY106.43, the approximate exchange rate on August 30, 2019.

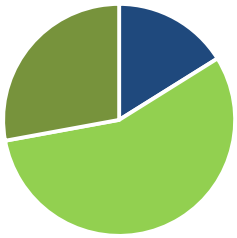
Appendix.3 Investment Overview (As of September 30, 2019)

1. Investment to date

Total Investments 17.6 billion yen (US$165.6 million*)
Total Invested Projects 86（Active projects 47, Completed projects 39）

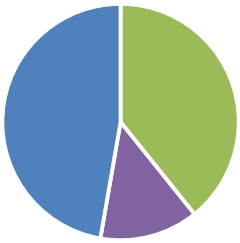
2. Portfolio Analysis (Active + Completed)

Stage



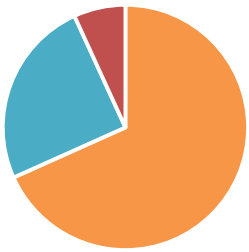
- Discovery ¥3,120,868,061 (US$29,323,199) 17.7%（50 projects）
- Preclinical ¥9,765,019,536 (US$91,750,630) 55.4%(25 projects)
- Clinical ¥4,737,846,333 (US$44,516,079) 26.9%（11 projects）

Disease



- Malaria ¥7,062,002,174 (US$66,353,492) 40.1%（38 projects）
- Tuberculosis ¥2,405,493,461 (US$22,601,649) 13.6%（18 projects）
- NTDs ¥8,156,238,295 (US$76,634,767) 46.3%（30 projects）

Intervention



- Drugs ¥11,890,600,038 (US$111,722,259) 67.5%（58 projects）
- Vaccines ¥4,434,160,782 (US$41,662,696) 25.1%（20 projects）
- Diagnostics ¥1,298,973,110 (US$12,204,953) 7.4%（8 projects）

To know more about GHIT investments, please visit

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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 = JPY106.43, the approximate exchange rate on August 30, 2019.