RESEARCH GRANTS COUNCIL
THEME-BASED RESEARCH SCHEME (TRS)

Completion Report on Funded Project

Project start date: *1st January, 2019*
Project completion date: *31 December, 2023*

1. Project Title: Potentiating Host Immunity for HIV-1 Functional Cure

2. Names and Academic Affiliations of Project Team Members#

Project team member	Name / Post	Unit / Department / Institution	Average number of hours per week spent on this project in the whole project period
Project Coordinator (PC)	Chen Zhiwei / Professor	AIDS Institute / Microbiology / HKU	10
Co-Principal Investigator(s)	Cheng Sze Lok Alfred / Professor	School of Biomedical Sciences / CUHK	10
	Lee Shui Shan / Professor	Stanley Ho Centre for Emerging Infectious Diseases / CUHK	8
	Song Youqiang / Associate Professor	School of Biomedical Sciences / HKU	8
	Kok Kin Hang / Associate Professor	Microbiology / HKU	8
	Chu Hin / Assistant Professor	Microbiology / HKU	8

	Liu Li / Research Assistant Professor	AIDS Institute / Microbiology / HKU	8
	Tan Zhiwu / Research Assistant Professor	AIDS Institute / Microbiology / HKU	8
	Mo Yufei[1] / Postdoc Fellow	AIDS Institute / Microbiology / HKU	8
Collaborators	Zhang Linqi / Professor & Director	Comprehensive AIDS Research Centre / Tsinghua University, PRC	N.A.
	Zhou Tongqing / Co-head & senior staff scientist	Vaccine Research Ctr, National Institute of Allergy and Infectious Diseases / NIH, US	N.A.
	Chakrabarti Lisa / Associate Professor	Head of Structure / Dept. of Virology / Pasteur Institute, France	N.A.
	Gao Fu / Director & Professor	Chinese Centre for Disease Control and Prevention / PRC	N.A.
	Jin Xia / Associate Director	CAS Key Lab of Molecular Virology & Immunology / Institute Pasteur/Shanghai, PRC	N.A.
	Wei Qiang / Professor	Pathogen center at Institute of Lab. Animal Sciences / Chinese Academy of Medical Sciences, PRC	N.A.
	Qin Chuan / Professor	Pathogen center at Institute of Lab. Animal Sciences / Chinese Academy of Medical Sciences, PRC	N.A.
	Wang Hui / Director	AIDS clinical research unit / Shenzhen Third People's Hospital	N.A.
	Zhang Haoji / Professor	Dept. of Veterinary Medicine/Foshan University, PRC	N.A.
	Zhang Qi / Head	TrinoKure Biotech, Beijing, PRC	N.A.
	Cheung Wai Hung / Director	Immuno Cure BioTech Limited	N.A.

 # Please highlight the approved changes in the project team composition and quote the date when the RGC granted approval of such changes. For changes in the project team composition, please submit a separate request, together with the justification and the curriculum vitae of the new member(s), to the RGC three months prior to the intended effective date of the change.

1. The RGC has approved on August 10, 2021 to replace one Co-Principal Investigator Dr. Yik Chun Wong with Dr. Lok Yam Yim, who has been further replaced by D. Mo Yufei (approved by RGC

on August 7, 2023).

3. Project Objectives

Summary of objectives addressed/achieved:

Objectives*	Percentage achieved	Remarks**
1. To determine correlates of PD1-based vaccine- and BiIA-SG-induced protection in $SHIV_{162P3}$-infected rhesus macaques	1. 100%	Completed
2. To determine immunogenicity and efficacy of GLP-grade human PD1-based vaccine and BiIA-SG in animal models in support of IND application	2. 100%	Completed
3. To investigate the possible functional cure of HIV-1 infection in patients by PD1-based vaccine and BiIA-SG immunotherapies	3. 100%	Completed

* *Please highlight the approved changes in objectives and quote the date when the RGC granted approval of such changes.*

****** *Please provide reasons for significantly slower rate of progress than originally planned.*

6. Research Highlights and Outputs

6.1 What are the most exciting research accomplishments of the project?
(Please list five or more of the team's best research accomplishments, such as journal and conference papers, software codes, research infrastructure, etc. For each item, please clearly justify how it has achieved international excellence (e.g. best paper award, invited presentation, citations, product licensed to industry, etc.)

To potentiate host immunity for HIV-1 functional cure (now called ART-free virological control), our TRS project focused mainly on pre-clinical studies of immunotherapeutic interventions primarily using bi-specific antibodies and/or dendritic-cell-targeting PD-1-based vaccines during the funding period. Under the guidance of our external scientific advisors and the UGC TRS Sub-committee, our multi-disciplinary and multi-institutional research team has successfully conducted all proposed studies under three originally proposed themes despite of the lock down and negative impacts caused by COVID-19 pandemic. We have made significant accomplishments in basic, translational, and clinical studies in the field of HIV/AIDS immunotherapy. Most importantly, we have exceeded our objectives as initially proposed under *Theme III* by translating the rhesus PD1-based AIDS vaccine into ICVAX, the clinical grade human PD1-based HIV-1 vaccine for clinical trial. We have already successfully launched a dose-escalating, randomized, double-blind, placebo-controlled phase I study has been to evaluate the safety, tolerability, and immunogenicity of ICVAX in clinically stable PLWH under ART treatment since February 14, 2023. Here, we provide following six of our team's best research accomplishments.

[1] Preventive and therapeutic efficacies of BiIA-SG against AIDS in monkey models

Our research team has completed the evaluation of both preventive and post exposure therapeutic efficacy of an innovative tandem bi-specific neutralizing antibody namely BiIA-SG in two different animal models, HIV-infected humanized mice and SHIV-infected Chinese-origin rhesus macaques (CRMs). For monkey experiments, GLP-grade BiIA-SG was kindly provided by TrinoKure Biotech through external collaborations. In the preventive efficacy study, CRMs received prophylactic BiIA-SG treatment (10 mg/kg) via intramuscular (n=3) or intravenous (n=3) injections 24 hours prior to the intravenous $SHIV_{SF162P3CN}$ challenge. There was no productive plasma viral RNA detected longitudinally in all CRMs 6/6 (100%) after they were intravenously challenged with pathogenic $SHIV_{SF162P3CN}$. Proviral DNA load also remained undetectable over 12 weeks in 6/6 (100%) CRMs. Although the average half-life of BiIA-SG in the challenged animals was 1.32 days, plasma BiIA-SG maintained at levels exceeding the *in vitro* neutralization IC_{50} value against $SHIV_{SF162P3CN}$ for around 10-14 days post-infection (dpi). We concluded that BiIA-SG prevents $SHIV_{SF162P3CN}$ infection completely via both prophylactic intramuscular or intravenous injections. In the therapeutic efficacy study, a single dose of BiIA-SG (20 mg/kg) was administrated via intramuscular injection on 1 day post infection (dpi, n=7) and 3 dpi (n=6) after a high dose of intravenous $SHIV_{SF162P3CN}$ challenge. All animals were infected despite of delayed peak plasma viral RNA loads between 14 to 28 dpi. However, none of these BiIA-SG-treated CRMs developed acute symptoms including progressive diarrhea, body weight loss, or CD4 lymphocytopenia. Importantly, the single dose of BiIA-SG post-exposure treatment prevented the death of all (13/13) infected CRMs with a significant survival advantage compared with untreated controls. A total of 8/13 (61.5%) treated CRMs became controllers with undetectable plasma viral loads around 84 dpi, of which 5/7 (71.4%) were in the 1-dpi group and 3/6 (50%) in the 3-dpi group. The subsequent anti-CD8β antibody (clone CD8b255R1) depletion experiment on day 119 after viral challenge, demonstrated the crucial role of $CD8^+$ T cells in BiIA-SG-induced long-term protection. We concluded that the single intramuscular injection of BiIA-SG as early as 1 dpi does not achieve complete post-exposure prevention

against a high dose of intravenous infection. Early post exposure BiIA-SG intervention, however, actively suppressed pathogenic infection and prevented disease progression in all 13 BiIA-SG-treated CRMs during the study period through the induction of T cell immunity. These findings have been published in ***Niu et al., Cell Reports. 2021;36(8):109611***, which may warrant the clinical development of BiIA-SG for HIV-1 prevention and immunotherapy.

To prepare for clinical development, we examined the neutralizing activity of BiIA-SG against the diverse panel of 72 HIV-1 pseudoviruses, in collaboration with one of our TRS advisors, Prof Linqi Zhang at Tsinghua University. The potency against this panel was consistently superior to the VRC01 positive control antibody as we reported (***Wu et al. Journal of Clinical Investigation. 2018. pii: 96764.***). These results demonstrated that BiIA-SG is broadly reactive against all Chinese HIV-1 strains/subtypes tested including multiple circulating subtypes found throughout China. **The Chinese patent of BiIA-SG was licensed to TrinoKure Biotech by HKU TTO** to proceed for mid-scale BiIA-SG production under GMP condition. This company and we have done further modification of BiIA-SG, generating a variant called gBiIA-TMLS. This variant has an LS mutation in the Fc region to extend its half-life, and a mutation to reduce the affinity of the IgG1 Fc region for Fcγ receptors to eliminate antibody-dependent cytotoxicity (ADCC) towards $CD4^+$ T cells of recipients for safety reason. This variant showed consistent antiviral activities and breadth. These findings have been presented by **PC** as an invited speaker in ***Cent Gardes Conference: HIV Vaccines in 2019*** in France and and by ***Niu et al., the 17th International Congress of Immunology in 2019***. Unfortunately, the COVID-19 outbreak caused severe damages to this project. First, all national monkeys were used mainly for SARS-CoV-2 research and the price of each monkey raised to 200,000 RMB, far beyond our TRS budgets. We, however, managed to test gBiIA-TMLS using 3 CRMs in preventive and post exposure therapeutic efficacy groups, respectively. Similarly, gBiIA-TMLS (10 mg/kg) was intravenously administrated one day before and 3dpi against the same high-dose $SHIV_{SF162P3CN}$ challenge. Full protection was achieved in 2/3 CRMs during the preventive experiment, whereas 3/3 CRMs showed similarly delayed peak viremia and lower viral loads but one death during the period of 80 weeks post-infection. These results demonstrated that gBiIA-TMLS is effective in monkey models for viral prevention and immunotherapy. Second, due to the national policy of COVID-19, the GMP was used for antibody production against SARS-CoV2. TrinoKure Biotech, therefore, stopped gBiIA-TMLS GMP and returned the patent of BiIA-SG back to HKU TTO on 27 May 2022 (Appendix **1**).

It should be noted that our platform of bi-specific antibody engineering has contributed significantly to the success of the HKU InnoHK program, namely Centre for Virology, Vaccinology & Therapeutics (CVVT), for engineering novel bi-specific antibodies against emerging infectious diseases (https://www.cvvt.hk/research-focus).

[2] Sustained virological control elicited by the PD-1-based vaccination in monkeys.

Our previous study has demonstrated the immunogenicity of PD-1-based vaccine in mice by eliciting potent CD8 T cells through antigen cross-presentation (***Zhou et al. Journal of Clinical Investigation. 2013; 123(6):2629–2642.).*** To determine the efficacy of PD-1-based vaccine in monkey models, we generated a rhesus monkey PD1-based DNA vaccine, namely RhPD1-p27, to express a rhesus sPD1 in fusion with SIV Gag-p27 capsid antigen. Since this vaccine also induced strong CD8 T cell responses in mice, we established the standard operation procedure (SOP) for the monkey-scale RhPD1-p27 DNA vaccine production by GLP biotech manufacturer. The $SHIV_{SF162P3CN}$-infected CRM model was then used for evaluating the *in vivo* efficacy of this vaccine. In two sperate monkey experiments, T cell responses elicited by the pRhPD1-p27 vaccination conferred protection against pathogenic $SHIV_{SF162P3CN}$ challenge in 7 CRMs. Moreover, we found that pRhPD1-p27-induced T cells in vaccinated CRMs had polyfunctional memory phenotype with breadth targeting at multiple epitopes of the capsid p27 antigen. Critically, strong anamnestic p27-specific CD8 T cell

responses were recalled in vaccinated CRMs after $SHIV_{SF162P3CN}$ challenge, leading to sustained ART-free viral logical control in 6/7 monkeys. The crucial role of vaccine-induced $CD8^+$ T cells in mediating the sustained virologic control was determined by an *in vivo* CD8 T cell depletion experiment using anti-CD8β antibody (clone CD8b255R1). Moreover, subsequent boosting immunisation of pre-vaccinated CRMs at 103 weeks after the viral challenge was able to maintain viremia control and did not activate productive viral rebound. To understand the immune pathways in $CD8^+$ T cells activated by RhPD1-p27 vaccination, our co-PI Dr. Youqiang Song performed single-cell RNA transcriptome analysis on peripheral $CD8^+$ T cells purified from CRMs. We found three effector memory $CD8^+$ T cell subsets that expressed gene signatures important in mediating antigen recognition and cytotoxic functions during viral challenge. These findings have been published in ***Wong et al., PLoS Pathog. 2021 Jun 14;17(6):e1009647***, and was presented in ***the 17th International Congress of Immunology in 2019.*** The first author Dr. Wong won the prestigious **New Investigator Award at the HIVR4P** meeting in Madrid in 2018 after his oral presentation.

After COVID-19 pandemic, we surprisingly found that 9 controller monkeys remained healthy without measurable viral loads whereas all 7 un-vaccinated monkeys died before 60 weeks post viral challenge. We then conducted a follow-up study to investigate survived macaques that received either RhPD1-DNA vaccine or BiIA-SG antibody. A prolonged survival period of over 6 years was found with two pRhPD1-p27-vaccinated CRMs that had no detectable viremia in the absence of cART. Meantime, they maintained polyfunctional effector-memory p27-specific CD8 T cells. The pRhPD1-p27-vaccinated macaques possessed advantages in viremia control by long-term vaccine-induced T cell responses as compared to BiIA-SG-treated CRMs. These findings have been published in ***He et al., Microbiol Spectr. 2023 Dec 12;11(6):e0335023***. We concluded that PD1-based vaccine-induced polyfunctional effector-memory CD8 T cells play critical roles in sustaining over 6-year virological control in SHIV/macaque models. The PC was invited for a plenary presentation at the 9th National Academic Conference on HIV/AIDS (April 2024).

[3] Translating human PD-1-based vaccine ICVAX for fighting HIV/AIDS

To determine ART-free viral control in people living with HIV-1 (PLWH), we designed two HIV-1 mosaic Gag-p41 antigens, namely, mos1 and mos2, to cover the diversity of over 500 viral strains circulating in China and surrounding countries (***Liu et al. Vaccine. 2018;36(31):4621-4632***). To test antigen cross-reactivities, we collaborated closely with our co-PI Prof Shui Shan Lee from CUHK and Dr Hui Wang from the Shenzhen 3rd People's Hospital, China. We performed the cross-reactivity assay using peptide pools of these two mosaic antigens. More than 90% of ART-naive (n=87) and ART-treated (n=79) PLWH had T cells responding to these mosaic antigens, although ART-treated PLWH showed significantly lower levels. <u>These results demonstrated the broad antigenicity of these mosaic antigens among both cART-treated or cART-naive PLWH</u>. Next, for vaccine construction, we generated **ICVAX**, which a codon-optimized human PD1-based bivalent HIV-1 Gag-p41 mosaic DNA vaccine expressing a human soluble PD1 domain fused to mos1 and mos2 antigens. This vaccine could induce enhanced cross-reactive and polyfunctional effector-memory T cell responses against multiple HIV-1 subtypes in both mice and CRMs (***Chen et al., J Virol. 2022 Apr 13;96(7):e0216121***.). **The patent of ICVAX was licensed to Immuno Cure HK Ltd by HKU TTO** to proceed for GMP production. In collaboration with Immuno Cure, 3 lots of GMP-grade ICVAX (gICVAX) were manufactured. We tested gICVAX for the toxicity, stability and immunogenicity in mice and CRMs. Like the CRM study with ICVAX produced in our own laboratory, the gICVAX was equally immunogenic, as measured by T cell responses induced against the peptide pools of HIV-1 subtype AE Gag-p41 antigen. Specific antibody response against HIV-1 p24 was also successfully elicited by gICVAX vaccination. The magnitude and polyfunctionality of antigen-specific effector-memory T cells induced by the gICVAX vaccine were maintained after a delayed

boost vaccination at 24 weeks after the completion of the initial vaccination schedule. These results demonstrated the readiness of gICVAX for clinical development. During the preparation of the phase I ICVAX clinical trial, our co-PI Prof Shui Shan Lee from CUHK designed a Mobile App tailored to the needs of PLWH in Hong Kong, to enable the forming of the HIV Research Partner's Network. Upon registration, users of the Apps would (a) have access to information on HIV treatment and health risks relating to HIV; and (b) be able to assess one's health risk through the measurement of various scores. A beta version was released in June 2022. Moreover, a survey on awareness, attitude, and acceptability of PLWH towards clinical trials related to functional cure was completed. PLWH, especially those sexually active, showed a positive attitude towards functional cure and willingness to join related clinical trials despite low awareness. The results have been reported in ***Kwan et al., BMC Infect Dis. 2022 Apr 15;22(1):383***.

[4] Phase I clinical trial of ICVAX

To determine the potential of our innovative PD1-based dendritic cell targeting vaccine in HIV immunotherapy, the biggest challenge is to conduct human studies. In collaboration with Immuno Cure, 3 lots of GMP-grade gICVAX were tested for quality and toxicity through contracts by CFDA-recognized CDMO professional companies. The IND application of gICVAX was approved by Center for Drug Evaluation (CDE) in mainland China in May 2022 (**approval ID: 2022LP00868**). After obtaining ethical approval of the Phase I clinical trial at the Shenzhen 3rd People's Hospital National Clinical Trial Center and the approval from China Human Genetics Resources, a dose-escalating, randomized, double-blind, placebo-controlled Phase I clinical trial of gICVAX was initiated in Shenzhen 3rd People's Hospital in ART-treated PLWH in February 2023. Three dose groups tested 1mg/ml, 2mg/ml and 4mg/ml. Each group included 12 vaccinees and 3 placebos. Each subject was vaccinated four times at a monthly interval, then boosted 24 weeks later. Based on the trial protocol approved by the **Data Safety Management Committee** (**DSMC**) consisted of external professionals, the recruitment of the 2-mg group was initiated at 6 weeks after the initiation of the 1-mg group, whereas the recruitment of the 4-mg group was initiated at 6 weeks after the initiation of the 2-mg group. During the trial, 36 subjects were documented with treatment emergent adverse events, whereas 23 subjects reported various types of adverse reactions. The adverse effects related to ICVAX vaccination were mainly related to injection site pain and rash. There were no viral rebound post vaccinations. CD4 T cell count and CD8 T cells did not show any decrease 4 weeks after ICVAX vaccination. Based on the DSMC recommendation, we have successfully recruited all study subjects and finished their vaccinations. Based on the DSMC report, we concluded that gICVAX vaccination is safe in ART-treated PLWH. Although the funding period of this TRS project is completed at the end of 2023, we continue the monitoring of clinical outcomes and long-term immune responses among these vaccinated individuals in close collaboration with Immuno Cure Ltd, CRO company, and the trial hospital. The primary immunogenicity results showed that majority of vaccinees had Gag-specific T cell responses including degranulating $CD107a^+$ CD8 T_{EM} cells by ELIspot and ICS assays. Part of the trial results was presented in **the plenary presentation by PC at the 9th National Academic Conference on HIV/AIDS (April 2024)**. This trial is ongoing and will be officially unblinded in August 2024. The safety data has been selected for presentation at **AIDS 2024** conference in Germany. Our findings demonstrated that gICVAX is not only safe but also immunogenic in human, supporting upcoming phase II trial and highlighting the first-in-class HIV-1 therapeutic vaccine made by HKU scientists in clinic (https://www.immunocure.hk/upload/news/21/file_1/673d6240e531b.pdf).

[5] Modulating host immunity for improving HIV/AIDS therapy

To study the host immune modulation in HIV/AIDS, our research team focused on the following three aspects: (i) to understand the role of immunosuppressive cells in HIV/AIDS

immunotherapy; (ii) to understand how HIV latency is established or maintained and how it can be eliminated at the epigenetic level; and (iii) to explore novel therapeutic methods in modulating host immune cells during HIV infection.

First, since HIV-1 cannot infect mice and monkeys are two expensive, we used the immunocompetent EcoHIV/mouse model to understand the immunosuppressive cell types during the PD-1-based-vaccine immunotherapy. The prophylactic-alone or prophylactic plus therapeutic immunization of murine PD1-p24fc DNA vaccine was conducted in BALB/c mice with EcoHIV infection. We found that the proportion of H2-Kd-GAG A-I tetramer$^+$CD8$^+$ T cells was significantly higher in mice that received the prophylactic plus therapeutic immunization than mice that received prophylactic vaccination alone, suggesting that therapeutic vaccination further boosted virus-specific CD8$^+$ T cell responses. We observed a high expression of Tim3 and PD-1 in CD8$^+$ T cells in spleens of mice that received either prophylactic-alone or prophylactic plus therapeutical vaccinations, along with the increased frequencies of immunosuppressive cells, for instance, regulatory T (Treg) cells and myeloid-derived suppressive cells (MDSCs). Therefore, our study indicated the importance of overcoming the immunosuppressive cells during HIV immunotherapeutic interventions, which has been published by ***Liu et al., EBioMedicine. 2020;60:103008*** and presented in the **17th International Congress of Immunology**. Meantime, we made a major discovery on a novel human B cell inhibitory receptor, namely Δ42PD-1, which was an isoform of PD-1. We found that Δ42PD-1 is upregulated on a subset of total B cells (up to 28%) in both ART-naïve and ART-treated PLWH. Δ42PD-1 induction primarily occurs in response to BCR stimulation, resulting in B cell cycle arrest, apoptosis, and cell death through suppressing the AKT1/FOXO1 pathway. Furthermore, treatment with anti-Δ42PD-1 antibody restored the functionality of naive and HIV-1 ENV-specific memory B cells in some PLWH. Importantly, targeting Δ42PD-1 may serve as a potential therapeutic strategy to restore HIV-1-specific antibody responses. The results have been presented at the ***IAS2023 conference*** in Australia, and the manuscript is under revision in ***Cell Reports***. Subsequently, we tested the heterologous DNA prime plus intranasal LAIV-HK68-HIVp41 mosaic boost regimen, which elicited robust mucosal tissue resident memory T cells (TRM) against tumor expressing HIV-1 Gag. We demonstrated that TRM cells were derived from DNA vaccine-induced T_{CM} essential for mucosal protection (***Xu et al., Cancer Research 2024***).

Second, we established an *in vitro* HIV latency model using primary memory CD4$^+$ T cells to study epigenetic regulation in reversing HIV latency. During the latency model establishment, we illustrated the importance of TGF-β upregulation during acute HIV-1 infection for promoting rapid latency reservoir establishment, especially in resting memory CD4$^+$ T subsets. The finding has been published in ***Yim et al., J Virol. 2023;97(5):e0027023***. Meantime, co-PIs Dr. Hin Chu from HKU and Prof Sze Lok Alfred from CUHK screened potential latency-reversing agents (LRAs) from an epigenetic drug library. We discovered that I-BRD9, an inhibitor that targets bromodomain 9 protein (BRD9) of the BET family, is a new drug candidate in reactivating HIV-1 latency in T cells. BRD9 directly binds to the HIV-1 LTR-Gag gene region in HIV-1 infected resting memory CD4$^+$ T cell model. The binding between BRD9 protein and HIV-1 genes could be reversed by BRD9 inhibition. Moreover, we delineated the underlying mechanism of how BRD9 regulates HIV-1 expression by performing the Cut&Run followed by a DNA sequencing experiment and RNA sequencing experiment. I-BRD9 could be useful for the "shock and kill strategy". These findings were selected for a poster presentation at the ***IAS 2023 conference*** and in ***AIDS 2024 conference***. The manuscript is under revision in ***PNAS***.

Third, we explored the metabolic regulation of nicotinamide mononucleotide (NMN) on host immune cells in HIV-1 infection. We found that NMN significantly reduced the expression of late activation markers CD25 and HLA-DR upon PMA/Ionomycin activation on resting CD4$^+$ T cells derived from PLWH. Using the *in vitro* HIV-1 infection model of primary CD4$^+$ T cells, we found a significant decrease of intracellular p24 level in

$CD25^+CD4^+$ T cells under NMN treatment, but not in $CD25^-CD4^+$ T cells, correlating with the frequency of proliferating p24-expressing cells. Using *in vivo* HIV-1 infection model of humanized mice without or with the treatment of cART and/or NMN, we found that NMN plus cART treatment could quickly reconstitute CD4+ T cell frequency after HIV-1 infection. In contrast, NMN treatment changed neither plasma viral load nor $CD4^+$ T cell frequency. There results suggested that NMN is useful to reconstitute $CD4^+$ T cells in combination with ART or immunotherapy against HIV/AIDS. These results have been selected for the poster presentation at the ***IAS 2023*** **conference** and for an invited oral presentation at ***AIDS 2024*** **conference**. A full research article has been published by ***Mo et al., EBioMedicine. 2023;98:104877***.

[6] Contribution of our TRS platform of technology in response to COVID-19 pandemic

During the unexpected emerging COVID-19 pandemic, our TRS platforms of technology made great contributions the fight against SARS-CoV-2. Using our multi-color FACS panel of antibodies, we demonstrated that acute SARS-CoV-2 infection impairs dendritic cell and T cell responses (***Zhou R. et al., Immunity 2020***). Using our phage antibody display method, we demonstrated that the robust nasal transmission and replication of SARS-CoV-2 outcompeted systemic antibody and vaccine-induced antibody for breakthrough infections (***Zhou D et al., Cell Host & Microbe 2021*** – Most Picked Award by Cell Press). Using our single B cell antibody cloning methos, we discovered human neutralizing antibodies against COVID-19 by us (***Zhou B et al.,*** *Nature Commun 2022*) and with our collaborators (*Nature 2020, Cell 2021, Nature Commun 2021, Cell Host & Microbe 2022, Nature 2022, Sci Trans Med 2022*). We co-invented the flu-based LAIV-RBD COVID-19 nasal vaccine (*EBioMedcine 2022*), which won Gold Medal in Inventions Geneva Evaluation 2021 and has been licensed by China FDA for emergency use. More importantly, using our PD-1-based vaccine platform, we made the ICCOV vaccine by fusing human sPD1 with SARS-CoV-2 RBD antigen. We demonstrated that the heterologous ICCOV prime plus the flu-based COVID-19 nasal vaccine boost regimen is the only successful vaccination strategy to prevent the nasal transmission of SARS-CoV-2 compared with others, including mRNA and inactivated vaccines tested in parallel (***Zhou et al., EBioMedicine. 2022;75:103762.***). Based on these findings, we contributed to the success of HKU-leading RGC TRS program on COVID-19 (TRS T11-709/21-N). These results have significant implications for HIV-1 control in mucosal tissues. This study was invited for a plenary presentation in the 2023 meeting of Grand Challenge for HIV-1 Cure in Beijing Dec 2023. In addition, we tested a single-dose AAV-vectored PD1-based vaccine for enhanced protection against mesothelioma (***Tan et al., Mol Ther Oncolytics. 2021 Jan 21;20:373-386***). We have also optimized our AAV system for antibody in vivo delivery to promote human translational application (***Yang et al. J Virol. 2024;98(4): e00242-24***).

In summary, during the TRS-funded period, our research team have made significant contributions to the basic, translational, and clinical study on HIV/AIDS immunotherapy, based on originally proposed studies. We acknowledged TRS for funding support in all our scientific publications, presentations and events. We also thank our industry partner Immunoe Cure for providing additional fundings and gICVAX for conducting the clinical trial against HIV/AIDS. Our findings not only have enriched the knowledge on vaccinology, immunology and translational research but also lay solid foundation for next stage of clinical studies of gICVAX for cART-free HIV-1 control among PLWH.

The detailed report on projects/research activities in relation to the project objectives under each theme has been attached with this submission in ***Appendix 1***, with the figures and figure legends in ***Attachment for Appendix 2***.

6.2 What was the added value of the TRS funding, rather than standard project grant funding?
(For example, could this work have been achieved with other funding scheme, such as the General

Research Fund or Collaborative Research Fund? If not, why?)

Our research outputs have demonstrated that TRS is a great funding mechanism, allowing us to bring ICVAX from laboratory bench to bedside of patients within 5 years. Such great value is not possible by other fundings such as General Research Fund (GRF) or Collaborative Research Fund (CRF). TRS is also a truly transparent and externally reviewed funding mechanism, allowing university professors for free submission without any issues of bureaucratic internal shortlist process. During the funding period, our TRS promoted the establishment of Immuno Cure startup company in Feb 2021 in Hong Kong Science Park based on platforms of technology generated by our research team (https://www.immunocure.hk/en/). Such big impact is also not possible by GRF and CRF. In addition, our TRS provided excellent training opportunities to more than 32 postgraduate students and post-doctoral fellows, in addition to over 50 employees hired by Immuno Cure. We have also developed more collaboration opportunities between team members and external and international collaborators, leading to the growth of biomedical research and development talents in Hong Kong.

6.3 If the project has not met its original objectives, why?

All original objectives in our TRS project have been achieved within the report period**.**

6.4 (a) Please provide details of each peer-reviewed journal publication arising directly from this project by completing the table at **Annex** *(one for each publication)*.

The details of each peer-reviewed journal publication arising directly from this project have been completed in **Annex 1-20.**

The list of all peer-reviewed journal publications acknowledging this project has been attached with this submission in ***Appendix 3***.

(b) Please provide details of recognised international conference(s) in which paper(s) related to this project was/were delivered by completing the following table:
(Please attach a copy of each conference abstract)

Month/Year/ Place	Title	Conference name	Submitted to the RGC *(indicate the year ending of the relevant progress report)*	Attached to this report *(Yes or No)*	Acknowledged the support of the RGC *(Yes or No)*	Accessible from the institutional repository *(Yes or No)*
Sept. 2019 France	Potency of Tandem Bispecific Neutralizing Antibody against Pathogenic SHIV Infection	Cent Gardes Conference: HIV Vaccines	2020	No	Yes	No
Oct/2019/ Hangzhou, PRC	PD1 疫苗功能性治愈艾滋病的研究	The 6th National Academic Conference on HIV/AIDS	2020	No	Yes	No

Month/Year/ Place	Title	Conference name	Submitted to the RGC *(indicate the year ending of the relevant progress report)*	Attached to this report *(Yes or No)*	Acknowledged the support of the RGC *(Yes or No)*	Accessible from the institutional repository *(Yes or No)*
Oct/2019/ Beijing, PRC	Tandem bispecific neutralizing antibody prevents fully and induces prolonged T cell immunity against pathogenic SHIV in monkey models	17th International Congress of Immunology	2020	No	Yes	No
Oct/2019/ Beijing, PRC	Sustained control of a highly pathogenic simian-human immunodeficiency virus infection by PD1-based DNA vaccine-induced CD8+ T cells	17th International Congress of Immunology	2024	Yes	Yes	No
Oct/2019/ Beijing, PRC	Aberrant innate immune activation facilitates EcoHIV evasion from vaccine-induced protection	17th International Congress of Immunology	2024	Yes	Yes	No
Oct/2020/ Virtual Congress	Perceptions of HIV infected men who have sex with men as regards functional cure of HIV infection	*HIV Glasgow Congress 2020*	2022	Yes	Yes	No
July/2023/ Brisbane, Australia	HIV-1-induced isoformic PD-1 undermines Env-specific B cell response	*IAS 2023, the 12th IAS Conference on HIV Science*	2024	Yes	Yes	No
July/2023/ Brisbane, Australia	Nicotinamide mononucleotide impacts HIV-1 infection by modulating immune activation in T lymphocytes and humanized mice	*IAS 2023, the 12th IAS Conference on HIV Science*	2024	Yes	Yes	No
July/2023/ Brisbane, Australia	Delineating the role of transcription factor BRD9 in HIV-1 latency reactivation	*IAS 2023, the 12th IAS Conference on HIV Science*	2024	Yes	Yes	No
October / 2023 / Warsaw	Attitude of HIV-negative MSM towards functional cure of HIV infection	19th European AIDS Conference	2024	Yes	Yes	No
October/2020 /Japan	Enhancer dysregulation of myeloid-derived suppressor cells in hepatocellular carcinoma	The 79th Annual Meeting of the Japanese Cancer Association 2020	2024	Yes	Yes	Yes
September/ 2021/Hong Kong	Enhancer dysregulation of myeloid-derived suppressor cells in hepatocellular carcinoma	International Digestive Disease Forum 2021	2024	Yes	Yes	Yes
September/2022/Hong Kong	A selective class I HDAC inhibitor recovers intratumoral interferon signaling to overcome immune-checkpoint blockade resistance in hepatocellular carcinoma	International Digestive Disease Forum 2022	2024	Yes	Yes	Yes
May/2023/USA	Investigating the Role of HDAC8 in $CD4^+$ T Cells	The American Association of Immunologists, Inc.(AAI) 2023	2024	Yes	Yes	Yes

Month/Year/ Place	Title	Conference name	Submitted to the RGC *(indicate the year ending of the relevant progress report)*	Attached to this report *(Yes or No)*	Acknowledged the support of the RGC *(Yes or No)*	Accessible from the institutional repository *(Yes or No)*
June/2023/Hong Kong	Epigenetic activation of tumoral IFNγ response and pyroptosis overcomes immunotherapy resistance in hepatocellular carcinoma	International Digestive Disease Forum 2023	2024	Yes	Yes	Yes

(c) RGC funding should have been acknowledged in all publication(s)/conference papers listed in (a) and (b) above. If no acknowledgement has been made in any of the publications/ papers, please indicate and provide explanations.

N/A.

6.5 To what extent this project has strengthened inter-institutional collaborations and other partnerships?

This TRS project brought the expertise available in the fields of basic, translational, and clinical research together in Hong Kong, allowing our team to tackle the HIV/AIDS epidemic issue with novel biomedical products discovered and developed in Hong Kong. With close intra-institutional or inter-institutional collaborations, we achieved three objectives of this project, with collaborative accomplishments presented in ***Section 6.1***, joint publications listed in ***Section 6.4***, several collaborative products listed in ***Section 6.7***, joint symposia and seminars in ***Section 6.8***, other newly approved grant applications mentioned in ***Section 7.1***, and several collaborative patents listed in ***Section 7.4***.

During the collaborative TRS work, we have built a strong platform of the PD-1-based ICVAX vaccine, shared up-to-date research skills, and opened new avenues of research. Some examples include: (1) For the clinical translation of the ICVAX vaccine, our PC, Immuno Cure Ltd (one of external collaborators), and Dr Hui Wang (from Shenzhen 3rd People's Hospital, one of external collaborators) worked closed to obtain all approvals required for the launching of Phase I clinical trial in mainland China (*ClinicalTrials.gov Identifier: NCT06253533*). (2) For the up-to-date research technology sharing, our PC, Dr. Youqiang Song, and Prof Sze Lok Alfred Cheng shared knowledge and experimental skills of single-cell transcriptome techniques with each other, resulting in several high impact publications using single-cell RNA sequencing techniques. (3) For new avenues of research, our PC, Prof Shui Shan Lee (one co-PI), Immuno Cure Ltd are working closely for the next stage of ICVAX trials in Hong Kong. Meantime, Prof Shui Shan Lee, Dr. Hui Wang, and Prof S Lewin (one of our SAB members) are working closely to prepared for a multi-centre phase II trial and to conduct analytical treatment interruption in ICVAX-vaccinated PLWH.

Our project also promoted close collaboration with our external TRS scientific advisors in the field of virology, immunology, and immunotherapy. For example, (1) we collaborated with Prof DD Ho (our TRS SAB Chairman) working on the anti-SARS-CoV-2 antibodies in response to the COVID-19 pandemic, published by Zhou et al., Cell Host Microbe. 2021 Apr 14;29(4):551-563.e5, Zhou et al., Emerg Microbes Infect. 2023 Dec;12(2):2245921, and Luo et al., Emerg Microbes Infect. 2023 Dec;12(1):2146538. (2) We also collaborated with Prof Linqi Zhang (our TRS SAB member) working on the fields of HIV-1 and SARS-CoV-2 and generated 4 publications together in recent five years.

6.6 Research students trained (registration/awards):

Name	Degree registered for	Date of registration	Date of thesis submission/ graduation
Ling Lijun	PhD	2015-09-01	2019-08-31
Niu Mengyue	PhD	2015-09-01	2020-05-31
Zhou Dongyan	PhD	2017-09-01	2021-08-31
Li Shuang	PhD	2017-09-01	2021-08-31
Yue Ming	PhD	2017-09-01	2021-08-31
Yang Qing	PhD	2018-09-01	2022-08-31
Zhou Biao	PhD	2019-09-01	2022-08-31
Yee Ming	PhD	2018-09-01	2022-08-31
Chen Ruijun	PhD	2018-09-01	2022-08-31
Huang Huarong	PhD	2019-09-01	2023-08-31
Xu Haoran	PhD	2019-09-01	2023-08-31
Liu Wenjing	PhD	2019-09-01	2023-08-31
Luk Tsz Yat	PhD	2020-09-01	2024-08-31 (expected)
Peng Qiaoli	PhD	2020-09-01	2024-08-31 (expected)
Lim Chun Yu Hubert	PhD	2020-09-01	2024-08-31 (expected)
Zhao Meiqiang	PhD	2021-09-01	2025-08-31 (expected)
Chen Baohao	PhD	2021-09-01	2025-08-31 (expected)
Liu Na	PhD	2021-09-01	2025-08-31 (expected)
Luo Mengxiao	PhD	2021-09-01	2025-08-31 (expected)
Ma Tianyu	PhD	2022-09-01	2026-08-31 (expected)
Wang Jinlin	PhD	2022-09-01	2026-08-31 (expected)
Zhang Pengfei	PhD	2022-09-01	2026-08-31 (expected)
Liu Wenxuan	PhD	2023-09-01	2027-08-31 (expected)

Our PhD student **Dr. Zhou Dongyan** won Faculty Outstanding Research Output Award in 2023, Poster Presentation Winner in the 25th Research Postgraduate Symposium of HKU in 2021, Poster Presentation Award, Hong Kong Society for Immunology in 2020 and Award of Pilot Scheme on International Experience for PRg Students of HKU in 2019; PhD Student **Dr. Niu Mengyue** won Faculty Postgraduate Research Presentation Award in 2019; PhD student Ms **Luo Mengxiao** awarded YS ad Christabel Lung Postgraduate Scholarship in 2024.

6.7 Specific products (e.g. software or netware, instruments or equipment developed):

Products:

[1] gICVAX vaccine

In collaboration with Immuno Cure Ltd, gICVAX has been made for phase I clinical trial. It has become a potential therapeutic vaccine for HIV-1 functional cure.

[2] gBiIA-SG

In collaboration with TrinoKure Biotech, we have generated gBiIA-SG for preclinical study in animals. Although the company suspended the gBiIA-SG manufacturing due to COVID-19 pandemic, it is possible that we can find other company for future collaboration. To this end, we have recently developed AAV-vectored BiIA-SG to reduce the GMP cost.

Book(s):

In collaboration with local HIV/AIDS clinicians and international HIV/AIDS researchers, the

PC shared some knowledge and literature in two published books, as shown in the following:

[1] A01 Virology and immunology (by Zhiwei CHEN), HIV Manual (Fourth edition), Published by : Department of Health, Centre for Health Protection , Stanley Ho Centre for Emerging Infectious Diseases of the Chinese University of Hong Kong. (Link: https://hivmanual.hk/)

[2] Monkey Models and HIV Vaccine Research (by Zhiwei CHEN), HIV Vaccines and Cure: The Path Towards Finding an Effective Cure and Vaccine (Advances in Experimental Medicine and Biology, 1075), by Springer. (Link: https://doi.org/10.1007/978-981-13-0484-2)

Software(s):

- **A beta version of CU+ App:**

For Research Partners' Network formation among HIV+ patients, the CU+ Mobile App (β version) was developed and tested. It is now downloadable by patients in Hong Kong. This App can recruit patients for clinical trials, and patients can see their CD4 count and viral load from the App. It can also evaluate whether this is a good way of communication between clinicians and patients, especially less communication during COVID-19. (Reference website: https://cuplus.hk/en/)

6.8 Other education activities and/or training programmes developed:

[1] To benefit PLWH in Hong Kong:

CU+ (Circuit U plus) is an Apps designed to promote health for people living with HIV/AIDS in the setting of Hong Kong. The bilingual Apps (in both android and iOS version) were developed with updated information on HIV therapies (https://cuplus.hk/zh-hant/).

[2] To benefit the educational and research environment in the field of HIV/AIDS or the field of immunotherapy:

First, our TRS team has trained 23 postgraduate students and 9 post-doctoral fellows, in the research fields of immunology, virology, cellular biology, and bioinformatics. In addition, we also provide short-term projects and training for 5 undergraduate students.

Second, our TRS team has organized and participated in several symposia or seminars to share their research interests and activities for facilitating public education and international collaborations, listed as the following:

[1] Seminar: T-cell based immunotherapy for virus infections and cancers – Speaker: Professor Xiao-Ning XU, Imperial College London, 1 August 2019

[2] Seminar: HIV or not, does it make a difference under COVID-19? – Speaker:Dr Wilson Lam, Specialist in Infectious Disease at Gleneagles Hospital, 16 September 2021

[3] Seminar: Heterologous Prime-Boost Vaccination: from COVID-19 to HIV – Speaker: Professor Shan LU, University of Massachusetts Medical School Worcester, USA, 14 December 2022

[4] Seminar: EM based Epitope Mapping and Vaccine Development – Speaker: Dr Renee Yuhe YANG, National Center for Nanoscience and Technology, 5 May 2023

[5] Seminar: Cardiovascular Sequelae of Long COVID-19 in Adults – Speaker: Dr Susan Xiuqing ZHAO, Stanford University, 9 August 2023

[6] Seminar: Engineering Next-Generation of Viral Vectors for Gene Therapy – Speaker: Dr Bonnie Danqing ZHU, 15 March 2024

6.9 Please highlight any deliverables indicated in the project implementation timetable endorsed by the RGC which have not been covered or achieved as per sections 6.1 to 6.8 above, and explain/ elaborate.

All deliverables indicated in the project implementation timetable endorsed by the RGC have been achieved in the reporting period.

Project Management

6.10 Please elaborate how the PC has played his/her role in coordinating and managing the project.

The principal coordinator (PC) of this TRS programme, Prof Zhiwei Chen, has played an essential role in coordinating and managing the project. He organized regular executive committee meetings with co-PIs (A copy of the minutes is attached as ***Appendix 4***) and weekly students/postdocs meetings. He chaired all these meetings and directed team discussions. The PC overseed major issues of the project and coordinates with co-PIs to meet research deliverables according to the project timetable. During COVID-19 pandemic, the physical meetings were replaced by virtual online meetings via Zoom. He provided direct daily supervisions to postgraduate students, postdocs and research assistants working with our team. For internal collaboration, every Co-PI has made contributions in their working areas with their names properly cited in ***Section 6.1***.

Our PC also coordinated with our Scientific Advisory members, including Prof DD Ho, Prof KY Yuen, Prof R Schooley, Prof L Zhang, Prof S Lewin, Prof CC Mayer and Prof X Xu, actively seeking for their advice on the project. During COVID-19, he and Prof S Lewin coordinated weekly, then bi-weekly, then monthly Zoom meetings with Prof DD Ho, Prof KY Yuen, Prof L Zhang, leading to establishment of PRA in Dec 2023 besides many joint publications. He coordinated with Prof DD Ho and Prof X Xu to join InnoHK, resulting in the establishment of Centre for Virology, Vaccinology and Therapeutics (CVVT) in Hong Kong Science Park. He also assisted Prof X Xu with a joint grant funded by Wellcome Trust in UK on viral immunology. In addition, Prof G Shaw hosted PC's visit in Philadelphia and discussed work in Cent Garde's meeting in 2019. Prof CC Mayer provided SHIV challenge virus, visited HK twice, and commented on our ICVAX papers. L Zhang visited HKU twice and led a GATES grant with our participation. R Schooley had zoom meetings although his visit to HKU was cancelled during COVID-19, but he recently visited us for the SAB meeting. Overall, our external advisors have helped a lot to our TRS project.

For industry collaborations, our PC collaborated with Immuno Cure Ltd and TrinoKure Biotech with solid progress for developing gICVAX and gBiIA-SG into a therapeutic product, respectively. Our PC has regularly met and discussed with representatives of the companies to ensure the production, quality controls and testing of gICVAX and gBiIA-SG could be delivered in a timely manner. To enhance the collaboration among researchers in the field of immunotherapy or HIV/AIDS, in 2019 and 2020, the PC took Chairmanship of Hong Kong Society for Immunology, and hosted HKSI 2019 and HKSI 2020 meeting. In 2023 or 2024, the PC has joined as a scientific committee member in IAS2023/AIDS2024 international conferences. Team members in this TRS project also actively attended these conferences or meetings and disseminated the important findings of our TRS project to the scientific community.

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7. Awards and Recognition

7.1 Have any research grants been awarded that are directly attributable to the results obtained from this project?

Since 2020, a total of 10 research grants directly related to this TRS project have been awarded to team members collaboratively, as listed below:

[1] Prof Zhiwei Chen (PC of this TRS), Prof Haoji Zhang (one external collaborator of this TRS); #19180672; Optimisation of adeno-associated viral vectors for prolonged in vivo expression of a highly potent bi-specific neutralising antibody against HIV; HKD 1,499,832; *Health and Medical Research Fund*; 2020-09-01 ~ 2024-02-29.

[2] Dr Li Liu (one co-PI of this TRS), Prof Zhiwei Chen (PC of this TRS); #19180632; Δ42PD1 regulate metabolic alterations to compromise the B cell immunity in HIV-infected viremic individuals; HKD 1,500,000; *Health and Medical Research Fund*; 2020-09-01 ~ 2023-08-31.

[3] Prof Zhiwei Chen (PC of this TRS), Dr Tan Zhiwu (one co-PI of this TRS); #17104919 Mechanism of a Δ42PD-1-specific humanized antibody huCH101 in treating HIV/AIDS; HKD 1,115,993; *General Research Fund (GRF)*; 2020-01-01 ~ 2022-12-31.

[4] Prof Zhiwei Chen (PC of this TRS); #AR200035; PD1-COVID19-RBD vaccine project; HKD 4,000,000; *Friends of Hope Education Fund Limited*; 2021-01-01 ~ 2025-12-31.

[5] Prof Zhiwei Chen (PC of this TRS); #17121420; Combined BiIA-SG and anti-TRABD2A antibody for HIV-1 Functional Cure; HKD 1,195,502; *General Research Fund (GRF)*; 2021-01-01 ~ 2023-12-31.

[6] Prof Zhiwei Chen (PC of this TRS), Dr Runhong Zhou; #17117422; Mechanism of vaccine-induced mucosal immune responses against SARS-CoV-2 infection; HKD 1,179,038; *General Research Fund (GRF)*; 2023-01-01 ~ 2025-12-31.

[7] Dr Hin Chu (one co-PI of this TRS), Dr Jasper Fuk Woo Chan, Prof Kwok-Yung Yuen (one SAB member of this TRS); #17119122; Epigenetic modulation as a novel approach to establish antiviral state for the control of emerging viral pathogens; HKD 1,160,548; *General Research Fund (GRF)*; 2023-01-01 ~ 2025-12-31.

[8] Dr Zhiwu Tan (one co-PI of this TRS), Prof Zhiwei Chen (PC of this TRS); #AR220025; Preclinical Study of PD1-based TWIST1 Vaccination Approach-Promoting its Translation into Clinical Use; HKD 1,985,520; *Pneumoconiosis Compensation Fund Board - General Award*; 2023-04-01 ~ 2025-3-31.

[9] Prof Zhiwei Chen (PC of this TRS), Dr Mo Yufei (one co-PI of this TRS); #17119723; Role of HIV-1-specific antibodies cloned from Δ42PD-1 positive memory B cells; HKD 1,576,960; *General Research Fund (GRF)*; 2024-01-01 ~ 2026-12-31.

[10] Prof Zhiwei Chen (PC of this TRS), Dr Liu Li, Dr Tan Zhiwu (co-PIs of this TRS), Dr Runhong Zhou; #C7156-20G, Mechanism of immune control against COVID-19; HKD 8,979,578; Collaborative Research Fund (CRF); 2021-06-30 ~ 2024-06-29.

7.2 Have any project team members participated as invited speakers in or organisers of international conferences as a result of this project?

Our PC, Prof Zhiwei Chen, participated as an invited speaker in the below international conferences:

1) Cent Gardes Conference: HIV Vaccines – 2019, France

2) The 6th National Academic Conference on HIV/AIDS – 2019, Hangzhou, China

3) The Asia-Pacific AIDS & Co-Infections Conference – 2020, Thailand

4) The 5th International Conference & Expo on HIV & AIDS, the HIV-AIDS Summit – 2020, Philadelphia, USA

5) The 3rd Symposium on Global Health – 2021, Shenzhen, China

6) Webinar on Advances in COVID Management Vaccines/ Treatment and Technologies – 2022, Hong Kong

7) The 3rd The University of Hong Kong – Peking University Chinese Medicine and Integrative Medicine Summit – 2023, Hong Kong

8) The 12th International AIDS Scociety Conference on HIV Science – 2023, Brisbane, Australia

9) The 8th National Academic Conference on HIV & AIDS – 2023, Xiamen, China

10) 传染病防控和检测技术学术交流会 – 2023, Fuzhou, China

11) 广东省免疫学会2023年学术年会 – 2023, Zhuhai, China

12) The 15th Annual Meeting of Chinese Scoiety for Immunology – 2023, Suzhou, China

13) The 8th Hong Kong-Shenzhen International Oncology Conference cum 6th Sanming Project Conference – 2023, Futian, China

14) 2023年"艾滋病大挑战"专家研讨会 – 2023, Beijing, China

15) 中国免疫学会感染免疫分会2023年学术年会暨第二届感染性疾病与免疫国际论坛– 2023, Beijing, China

PC also served as one of the scientific committee members for this meeting.

1) The 17th International Congress of Immunology – 2019, Beijing, China

2) The 7th National Academic Conference on HIV/AIDS –2021, Xiamen, China

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7.3 Have any project team members taken leadership positions in editorial boards, scientific and professional organisations?

(I) Several TRS team members are in leadership positions on editorial boards of international refereed journals, listed as the following:

Prof Zhiwei Chen:
[1] Editorial Board Member: *AIDS* – 2017-01 to Present, *Journal of Acquired Immune Deficiency Syndromes* – 2010-01 to Present, *Journal of Neuroimmune Pharmacology* – 2015 and *ournal of Medical Primatology* – 2008 to Poresent; Academic Editor, *PLoSOne* – 2010 to Present; Founding Editorial Board Member, *Immunotherapy Advances* – 2020-01 to Present,
[2] Guest Editor: *Journal of Leukocyte Biology* – 2020-01 to Present, *Current Opinion in HIV and AIDS* – 2020

Prof Shui Shan Lee:
[1] Editorial Board Member: Editor-in-Chief, *International Journal of Infectious Diseases* – 2022-08 to Present

Prof Sze Lok Alfred Cheng:
[1] Editorial Board Member: *Frontiers in Genetics* – 2016-01 to Present, *Frontiers in Cell and Developmental Biology* – 2016-01 to Present, *Cancers* – 2019-01 to Present, *Cellular & Molecular Immunology* – 2022-01 to Present, *Tumor Discovery* – 2023-01 to Present
[2] Guest Editor: *Journal of Leukocyte Biology* – 2020-01

Dr Hin Chu:
[1] Editorial Board Member: *npj Viruses* – 2023 to Present
[2] Special Topic Editor: *BMC Infectious Disease* – 2024 to Present

(II) Our PC also has served leadership positions in scientific and professional organisations, listed as the following:

[1] Scientific Committee Member: Asia-pacific AIDS & Co-Infection Conference – 2020 to Present
[2] Section Chair of 5th International Conference & Expo on HIV and AIDS, the HIV-AIDS Summit, Philadelphia, USA – 2020
[3] Chairman of Hong Kong Society for Immunology – 2018 to 2020
[4] Vice-Chair for the Academic Committee for this Largest Annual Conference on HIV/AIDS in China – 2015 to 2022
[5] Member of Abstract Selection Panel of World's Largest Scientific Conference on HIV (Brisbane) by International AIDS Society – IAS 2023
[6] Member of the American Society for Microbiology – 2012 to Present
[7] Member of the American Association of Immunologists – 2008 to Present
[8] Member of Hong Kong Society for Immunology – 2015 to Present
[9] Board Director of Hong Kong AIDS Foundation Hong Kong SAR – 2019 to Present
[10] Secretary-designate of *Pandemic Research Alliance* – 2023 to Present

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7.4 Any documentary proof of the application of technologies arising directly from this project?

Technologies:
[1] ICVAX – CFDA approval (ID: 2022LP00868) reported in 2nd review report.
[2] ICCOV – ClinicalTrials.gov (NCT number): NCT05102643, reported in 2nd review report.
[3] CU+ Mobile App – Reference website: https://cuplus.hk/en/**.**

7.5 Other awards and recognitions as a result of this project (please specify):

The outstanding research achievements of our TRS team members have been awarded and recognized as the following:

Prof Zhiwei Chen:
[1] Faculty Outstanding Research Output Awards, for the ***Gut 2023*** paper with **Dr. Zhiwu Tan** as the 1st author
[2] Conferment of the title of Chair Professor by the president of the University of Hong Kong – 2023
[3] Ranked by Clarivate Analytics as the top 1% worldwide by citations and one of HKU academics among Highly Cited Researchers –2023
[4] Ranked by Clarivate Analytics as the top 1% worldwide by citations and one of HKU academics among Highly Cited Researchers – 2022
[5] Faculty Outstanding Research Output Awards, for the ***Cell Host Microbe 2022*** paper with **Zhou Dongyan** as the 1st author
[6] Bronze Medal of Geneva Invention – 2022
[7] Most Picked Award – 2021 Chinese Scientists with Cell Press (Cell Press).
[8] Outstanding Researcher Award of The University of Hong Kong – 2021

[9] Outstanding Research Student Supervisor Award of The University of Hong Kong – 2021
[10] Faculty Knowledge Exchange (KE) Excellence Award of The University of Hong Kong – 2019

Dr. Hin Chu:
[1] Clarivate Analytics' Essential Science Indicators (ESI) Highly Cited Researcher – 2021 to 2023
[2] National Natural Science Foundation of China (NSFC) Excellent Young Scientists Fund (Hong Kong and Macau) – 2021
[3] Research Output Prize of The University of Hong Kong – 2022 to 2023
[4] Outstanding Young Researcher Award – 2022 to 2023

Our postdoc **Dr. Wong YC** won New Investigator Award of HIVR4P held in Madrid 2018.

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8. Impacts

8.1 What are the current and expected impacts of the project on the long-term development of Hong Kong (social or economic development, e.g. patent, technology transfer, collaboration with external organisations, etc.)?

[1] Technology transfer

Our overall objective is to potentiate host immunity to achieve a functional cure for HIV-1 infection, a status of suppressed viremia below the limit of detection, for benefiting PLWH without receiving ART. Here, our TRS project successfully brought the ICVAX vaccine into Phase I clinical trial and illustrated the translational success of our scientific discoveries into clinical development step by step. It leads a promising "made in Hong Kong" immunotherapeutic candidate for cART-free HIV-1 functional cure. The patents of ICVAX and PD1-based vaccine platforms have been licenced to Immuno Cure, leading to its establishment and development into a clinical stage startup company of over 50 people in Hong Kong Science Park.

[2] Collaboration with external organizations

This TRS project enabled us to establish a Hong Kong consortium of leading scientists in close collaboration with renowned international experts, scientific advisors, and biomedical R&D companies to develop novel immunotherapeutic strategies for HIV-1 functional cure. During the TRS period, we have jointly published numerous high impact publications for the fight against AIDS and COVID-19 pandemics. Our research outputs promoted the recent establishment of the global Pandemic Research Alliance (PRA) in December 2023 with HKU as the leading inauguration institution. PRA includes currently six renowned institutions including Columbia University, University of Melbourne, National University of Singapore, Tsinghua University, Guangzhou National Laboratory and University of Hong Kong. Our PC not only is one of the founding members of PRA but also serves as the first PRA secretory, promoting the international collaboration in emerging infectious diseases including HIV/AIDS.
(https://www.med.hku.hk/en/news/press/20231204-Leading-global-scientists-launch-the-Pandemic-Research-Alliance)

[3] Education

For the short-term impact, this TRS project has already created many job opportunities for Hong Kong's new generations of technologists, postgraduate students, post-doctoral

fellows, and importantly young principal investigators. For the long-term impact, it can promote our future biomedical research and product development in infectious diseases and biomedical research in general.

In this project, our TRS team investigated both immune activation and suppressive mechanisms underlying the immunotherapeutic strategies. The findings not only generated consistently high-impact peer-reviewed publications in leading scientific journals in the short term but also enriched our knowledge on potentiating host immunity against HIV/AIDS significantly in the long term.

8.2 Others (please specify):

N/A.

9. Sustainability of the Project

9.1 Whether there are new ideas evolved directly from this project?

Yes, there are new ideas evolved directly from this project, including following scientific questions:
(1) What is the mechanism underlying PD1-based vaccine-mediated 6-year cART-free virologic control in SHIV-infected rhesus monkeys?
(2) What is the impact of PD1-based vaccine on HIV-1 reservoir among cART-treated PLWH?
(3) Can ICVAX-treated PLWH achieve sustained cART-free HIV-1 virologic control after analytical treatment interruption?
(4) Can ICVAX-based combination immunotherapy in PLWH achieve sustained cART-free HIV-1 virologic control after analytical treatment interruption?

Investigating these questions will enrich the knowledge on mechanisms of immune protection critical for saving PLWH's lives, and for reducing cART toxicity/resistance as well as governmental and patients' financial burden. Recently, AIDS expert Dr. AS Fauci said, "Achieving a sustained, durable ART-free HIV remission by a variety of minimally toxic approaches that are potentially scalable remains an overarching priority in HIV research" in Institut Pasteur at the "40 Years of HIV Science" conference, because "It is likely not economically nor logistically feasible to deliver lifelong antiretroviral therapy to >39 million people with HIV". Therefore, ending the HIV/AIDS pandemic still requires scientific breakthroughs in vaccine and cure research. To answer these grand challenge questions, we submit a new TRS application with focus primarily on investigations of human vaccine immunogenicity and efficacy as well as clinically related mechanisms.

9.2 Whether there are new projects evolved directly from this project?

Yes, stimulated by the strong collaboration in this TRS project, our PC has 6 new projects evolved directly from this TRS one:
(1) **For new projects evolved directly from BiIA-SG**: our PC collaborated with Prof Haoji Zhang to prolong the efficacy time period of BiIA-SG in "Optimisation of adeno-associated viral vectors for prolonged *in vivo* expression of a highly potent bi-specific neutralising antibody against HIV" funded by *Health and Medical Research Fund* (#19180672); we also tried to develop new combinational regimen for BiIA-SG with anti-TRABD2A antibody in HIV/AIDS therapy in "Combined BiIA-SG and anti-TRABD2A antibody for HIV-1

Functional Cure" funded by *General Research Fund* (GRF#17121420).
(2) **For new projects evolved directly from the PD-1-vaccine platform to fight against COVID-19,** our PC designed PD1-COVID19-RBD vaccine in "PD1-COVID19-RBD vaccine project" funded by *Friends of Hope Education Fund Limited* (#AR200035), and tried to develop combinational regimen for inducing mucosal immune responses against SARS-CoV-2 infection in "Mechanism of vaccine-induced mucosal immune responses against SARS-CoV-2 infection" funded by *General Research Fund* (GRF#17117422).
(3) **For new projects evolved directly from the immunosuppressive role of Δ42PD1 in HIV/AIDS,** our PC planned to investigate the "Mechanism of a Δ42PD-1-specific humanized antibody huCH101 in treating HIV/AIDS" funded by *General Research Fund* (GRF#17104919), and to investigate the "Role of HIV-1-specific antibodies cloned from Δ42PD-1 positive memory B cells" funded by *General Research Fund* (GRF#17119723).
(4) **For new projects evolved directly from the clinical trial and HIV latency in PLWH,** our PC is applying for a new TRS project to investigate the "Sustained cART-free HIV-1 control by immunotherapeutic interventions".

Apart from the projects under our PC, based on results obtained from this TRS, other investigators of this TRS project also initiated new projects supported by several funding sources including the Research Grants Council as shown in ***Section 7.1***. A total of 9 research projects have been awarded.

9.3 Whether there are new collaborations developed directly from this project?

Yes, a total of five new collaborations have been established as a direct result of this project. These collaborations try to further explore basic and translational research under the functional cure topic in the field of HIV/AIDS by collaboratively making use of ideas, techniques, and clinical resources, listed below:

[1] Our PC and Prof Qiang Zhang (Beijing Ditan Hospital, China) collaborate for the investigation of the underlying mechanisms of deep HIV-1 latency in bone marrow of PLWH.
[2] Our PC, Dr. Qiaoli Peng (Shenzhen Third Hospital) collaborate for the study of TCR and BCR differences between elite controllers and chronic progressors of PLWH.
[3] Our PC collaborated with Prof Stephen Tsui (CUHK), who have successfully obtained the RGC grant (C4049-23EF) to establish the platform of Long-read-seq, enhancing our collaboration with Prof Xu YU (Ragon Institute, Harvard University) to study latency cells among gICVAX-treated PLWH.
[4] Our PC collaborated with Prof Xinyuan Guan (HKU), who have successfully obtained the TRS grant (T12-703/23-N) to develop PD-1-based DNA vaccine against EBV-associated Nasopharyngeal Carcinoma.
[5] Our PC collaborated with Prof Tao Dong (Oxford Uni) to study the impact of Δ42PD-1 on HIV-1-specific T cell functionality in PLWH and ICVAX-treated PLWH.
[6] We collaborated with Prof Kwan Man (HKU surgery) using a tumor model for developing an upgraded version of PD-1-based vaccine, published in Tan et al., Mol Ther Oncolytics. 2021 Jan 21;20:373-386.

9.4 Please give details on how much money and from which sources has been obtained/requested for the specific purpose of continuing the work started under this project.

Yes, referring to the demonstration in Section 9.2, we would give details on the funded amount and the funding sources of these projects below:

(1) For new projects evolved directly from BiIA-SG: HKD 1,499,832 funded by *Health and Medical Research Fund* (#19180672); and HKD 1,195,502 funded by *General Research Fund* (GRF#17121420).
(2) For new projects evolved directly from PD-1-based vaccine platform to fight against COVID-19, HKD 4,000,000 funded by *Friends of Hope Education Fund Limited* (#AR200035); and HKD 1,179,038 funded by *General Research Fund* (GRF#17117422).
(3) For new projects evolved directly from PD-1-based vaccine platform to fight against COVID-19, RMB 8,000,000 funded by Shenzhen Innovation Fund to support ICCOV GMP.
(4) For new projects evolved directly from PD-1-based vaccine platform to fight against COVID-19, HKD 10,000,000 funded by HMRH to support ICCOV phase I trial in Hong Kong.
(5) For new projects evolved directly from the immunosuppressive role of Δ42PD1 in HIV/AIDS, HKD 1,115,993 funded by *General Research Fund* (GRF#17104919); and HKD 1,576,960 funded by *General Research Fund* (GRF#17119723).

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10. Statistics on Research Outputs

(Please ensure the statistics in this section are consistent with the information presented in other sections of this report.)

	Peer-reviewed journal publications	Conference papers	Scholarly, books, monographs and chapters	Patents awarded	Other research outputs (please specify)	
No. of outputs arising directly from this research project	20	15	2	0	Type	No.
					1.Vanccie 2.Moblie app application	2 1

11. Public Access of Completion Report

(PCs of projects funded in 2010/11 academic year or onwards are required to release the completion reports to the public through the RGC website. Completion reports containing information such as abstracts in non-technical terms, objectives, research output including the list of conference papers / publications / journals and research findings and contact information of PCs should be open to public access.)

Please specify the information, if any, that cannot be provided for public access and give the reasons.

Information that cannot be provided for public access	Reasons
Appendix 2 and its Attachment (The detailed report and its relative figures)	Containing unpublished data.

12. The Layman's Summary

(describe in layman's language the abstracts and research impact of the project.)

HIV/AIDS has been a major health burden worldwide, with currently more than 39.0 million people living with HIV-1 (PLWH). In Hong Kong, the HIV-1 infection rate continues to rise, with more than 11943 accumulative cases reported. Although combined anti-retroviral therapy (cART) is available, it is expensive and does not completely cure PLWH. Life-long

cART causes adverse side effects and drug resistance in PLWH. This TRS project aimed to develop a promising immunotherapeutic strategy to suppress HIV-1 infection to undetectable viremia levels in PLWH without life-long cART. During the TRS-funded period, our team have made significant contributions to the basic, translational, and clinical study on HIV/AIDS immunotherapy, based on originally proposed studies. Based on collaborations with two biomedical companies that provided GLP/GMP-graded PD-1-based DNA vaccine (ICVAX) and bi-specific antibody (BiIA-SG), we tested their preventive and therapeutic efficacies used either alone or in combination in the SHIV-infected rhesus macaque model. We found that both products worked effectively under prophylactic and post-exposure immunotherapeutic conditions, which supported the clinical development of these products for human trials. Although COVID-19 pandemic caused the ceasing of BiIA-SG GMP production, our team successfully completed ICVAX GMP, toxicity/immunogenicity/efficacy tests, IND, research ethics, human genetics and trial approvals, allowing the remarkable launching of phase I clinical trial ahead of our TRS schedule. Our preclinical and clinical findings not only have enriched the knowledge on vaccinology, immunology and translational research but also lay solid foundation for clinical studies of ICVAX for HIV-1 immunotherapy among PLWH. The clinical trial itself also highlights a milestone that the first “made in Hong Kong” HIV-1 immunotherapy has entered a stage of benefiting patients. Our research outputs have laid a solid foundation for clinical research of ICVAX for cART-free HIV-1 control or cure in PLWH.