THEME-BASED RESEARCH SCHEME
PUBLIC SYMPOSIUM 2024
主題研究計劃研討會

Potentiating Host Immunity for HIV-1 Functional Cure

Virological control through functional CD8+ T cells after PD-1-based DNA vaccination and BiIA-SG against pathogenic $SHIV_{SF162P3CN}$ challenge of rhesus macaques

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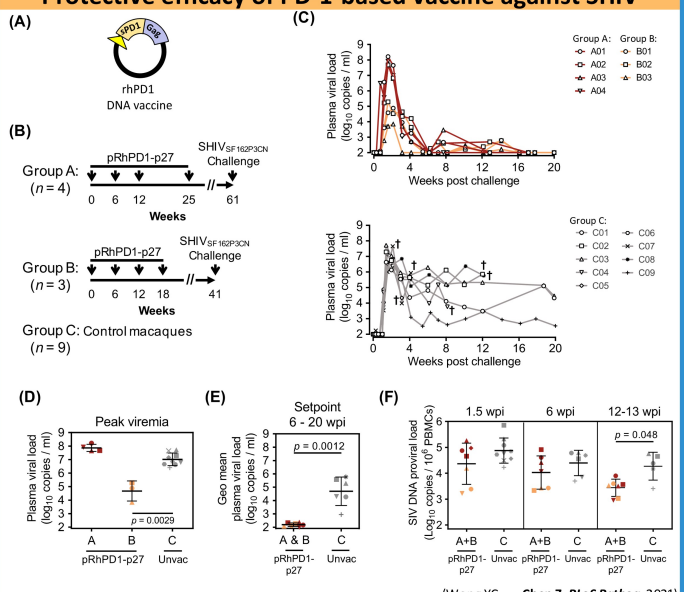
***Project Coordinator (PC): Professor Zhiwei CHEN.**

Background

Although combination antiretroviral therapy (cART) has reduced the number of deaths significantly, HIV/AIDS remains a major global pandemic. Identifying an efficacious vaccine and/or a therapeutic cure to achieve sustained HIV control without cART is essential to eliminate HIV/AIDS. We previously demonstrated that HIV antigen in fusion with a soluble program death-1 (PD-1) domain could effectively promote antigen cross-presentation by dendritic cells that constitutively expressed PD-1 ligands PD-L1/L2. This finding resulted in the third generation of DNA vaccination, which showed highly immunogenic in mice (*Zhou et al. JCI. 2013*). Here, we investigated the efficacy of a PD-1-based DNA vaccine and a tandem bi-specific neutralizing antibody BiIA-SG against pathogenic simian-human immunodeficiency virus challenge in rhesus macaques.

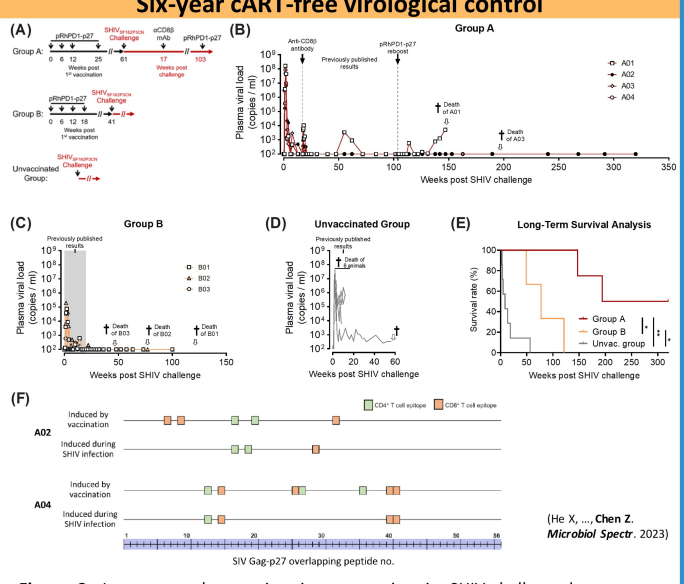
Protective efficacy of PD-1-based vaccine against SHIV



(Wong YC, ..., **Chen Z**. ***PLoS Pathog***. 2021)

Figure 1. Viral suppression in rhesus macaques immunised with the PD1-based pRhPD1-p27 DNA vaccine after high dose pathogenic $SHIV_{SF162P3CN}$ challenge.

Six-year cART-free virological control



(He X, ..., **Chen Z**. ***Microbiol Spectr***. 2023)

Figure 3. Long-term plasma viremia suppression in SHIV-challenged macaques received PD-1-based DNA vaccination.

Conclusion and Implication

PD-1-based DNA vaccine and BiIA-SG strategies hold promise as effective clinical immunotherapy for long-term HIV-1 suppression. Our results warrant clinical trials of PD-1-based DNA vaccines for achieving HIV-1 cART-free virologic control and for further studies on its combinational use with other biomedical interventions such as BiIA-SG.

Functional CD8+ T_{EM} cells induced by PD-1-based vaccine

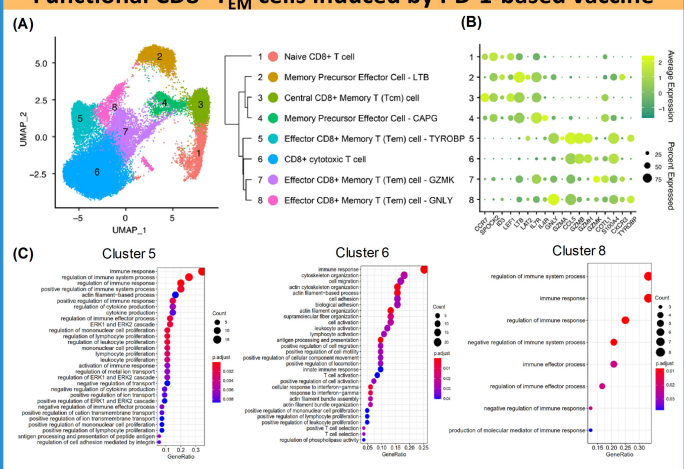
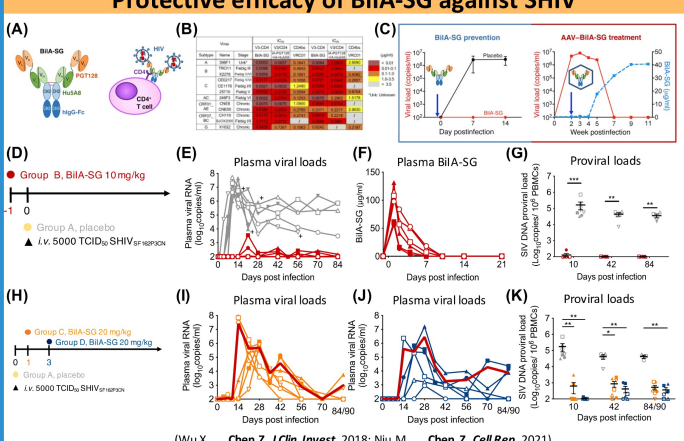


Figure 2. ScRNA-seq analysis of CD8+ T cells induced by PD-1-based vaccination.

Protective efficacy of BiIA-SG against SHIV



(Wu X, ..., **Chen Z**. ***J Clin Invest***. 2018; Niu M, ..., **Chen Z**. ***Cell Rep***. 2021)

Figure 4. The preventive and protective efficacies of BiIA-SG against HIV or SHIV.

Related publications

[1] Wong YC, Liu W, Yim LY, Li X, Wang H, Yue M, Niu M, Cheng L, Ling L, Du Y, Chen SMY, Cheung KW, Wang H, Tang X, Tang J, Zhang H, Song Y, Chakrabarti LA, **Chen Z***. Sustained viremia suppression by $SHIV_{SF162P3CN}$-recalled effector-memory CD8+ T cells after PD1-based vaccination. ***PLoS Pathog***. 2021 Jun 14;17(6):e1009647.

[2] He X, Wong YC, Zhong M, Mo Y, Li B, Yim LY, Li X, Liu W, Du Y, Wang H, Zhang H, **Chen Z***. A follow-up study: 6-year cART-free virologic control of rhesus macaques after PD-1-based DNA vaccination against pathogenic $SHIV_{SF162P3CN}$ challenge. ***Microbiol Spectr***. 2023 Dec 12;11(6):e0335023.

[3] Wu X, Guo J, Niu M, An M, Liu L, Wang H, Jin X, Zhang Q, Lam KS, Wu T, Wang H, Wang Q, Du Y, Li J, Cheng L, Tang HY, Shang H, Zhang L, Zhou P, **Chen Z***. Tandem bispecific neutralizing antibody eliminates HIV-1 infection in humanized mice. ***J Clin Invest***. 2018 Jun 1;128(6):2239-2251. doi: 10.1172/JCI96764.

[4] Niu M, Wong YC, Wang H, Li X, Chan CY, Zhang Q, Ling L, Cheng L, Wang R, Du Y, Yim LY, Jin X, Zhang H, Zhang L, **Chen Z***. Tandem bispecific antibody prevents pathogenic $SHIV_{SF162P3CN}$ infection and disease progression. ***Cell Rep***. 2021 Aug 24;36(8):109611. doi: 10.1016/j.celrep.2021.109611.

Acknowledgement

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THEME-BASED RESEARCH SCHEME
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主題研究計劃研討會

Potentiating Host Immunity for HIV-1 Functional Cure

A Novel PD-1-Enhanced HIV Therapeutic DNA Vaccine in PLWH under cART : A Phase 1, Randomized, Double-blinded, Placebo-controlled, and Dose-escalation Study

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Background

cART has saved millions of lives, but it cannot cure HIV-1 infection. The persistent need for lifelong treatment and the associated challenges underscore the importance of developing novel therapeutic approaches. We previously showed that a third-generation DNA vaccine technology using PD-1-enhanced DC-targeting strategy conferred cART-free virologic control for over 6 years in rhesus macaque model of SHIV infection, whereas all control monkeys died within 1.5 years after pathogenic SHIV challenge.

Here, we report interim findings of ICVAX, a third-generation therapeutic HIV DNA vaccine that incorporates the PD1-enhanced DC-targeting approach and HIV-1 mosaic Gag antigen design, in a first-in-human Phase 1 clinical trial.

Phase 1 Clinical Trial Design

Clinical Trial Design	Primary Objective
• Randomized, double-blind, placebo-controlled, dose-escalation	• To evaluate the safety and tolerability of ICVAX
Participants	**Secondary Exploratory Objective**
• 45 people living with HIV (PLWH) under effective cART (viral load <50 copies/mL)	• To determine the immunogenicity of ICVAX and its impact on peripheral virus reservoir
Grouping and Sample Size	**Objectives**
• Three dosage groups: 1mg, 2mg, 4mg • 15 subjects per group • Ratio of IP to Placebo = 4:1	• Intramuscular injection of ICVAX into the deltoid muscle, followed by electroporation (EP) with a proprietary device

Treatment regimen

Participant Demographics

Group	Low dosage group 1mg (n=15)	Medium dosage group 2mg (n=15)	High dosage group 4 mg (n=15)
Age (yr)			
Mean±SD	36.3±6.58	34.1±5.55	37.0±8.18
Gender			
Male, n (%)	15(100.0)	15(100.0)	14（93.3）
Female, n (%)	0(0)	0(0)	1（6.7）
Ethnicity			
Han, n (%)	15(100.0)	14(93.3)	14(93.3)
Others, n (%)	0(0)	1(6.7)	1(6.7)
Height (cm)			
Mean±SD	172.30±8.581	170.60±6.687	168.20±6.064
Weight (kg)			
Mean±SD	67.83±11.625	72.80±13.545	60.63±12.32
Duration of HIV diagnosis (yr)			
Mean±SD	5.71±3.337	5.21±2.255	5.63±2.614
Duration of ART(yr)			
Mean±SD	5.31±2.899	4.93±2.614	5.49±3.40
ART regimen			
NRTI+NNRTI, n (%)	6(40.0%)	8(53.3%)	7 (46.7%)
NRTI+INSTI, n (%)	8(53.3%)	7(46.7%)	8 (53.3%)
NRTI+PIs, n(%)	1(6.7%)	0(0.0%)	0 (0.0%)
HIV subtype distribution			
CRF01_AE, n (%)	4(26.7%)	4(26.7%)	6(40.0%)
CRF07_BC, n (%)	5(33.3%)	5(33.3%)	6(40.0%)
CRF55_01B, n (%)	2(13.3%)	2(13.3%)	0 (0.0%)
others, n (%)	1(6.7%)	0 (0.0%)	0 (0.0%)
NA, n(%)	3(20.0%)	4(26.7%)	3(20.0%)

Related Publications

[1] Liu W, Wong YC, Chen SMY, Tang J, Wang H, Cheung AKL, **Chen Z***. DNA prime/MVTT boost regimen with HIV-1 mosaic Gag enhances the potency of antigen-specific immune responses. ***Vaccine***. 2018 Jul 25;36(31):4621-4632. doi: 10.1016/j.vaccine.2018.06.047.

[2] Chen SMY, Wong YC, Yim LY, Zhang H, Wang H, Lui GCY, Li X, Tang X, Cheng L, Du Y, Peng Q, Wang J, Kwok HY, Huang H, Lau TT, Chan DPC, Wong BCK, Liu L, Chakrabarti LA, Lee SS, **Chen Z***. Enhanced Cross-Reactive and Polyfunctional Effector-Memory T Cell Responses by ICVAX-a Human PD1-Based Bivalent HIV-1 Gag-p41 Mosaic DNA Vaccine. ***J Virol***. 2022 Apr 13;96(7):e0216121. doi: 10.1128/jvi.02161-21.

[3] Xu H, Yue M, Zhou R, Wang P, Wong MY, Wang J, Huang H, Chen B, Mo Y, Tam RC, Zhou B, Du Z, Huang H, Liu L, Tan Z, Yuen KY, Song Y, Chen H, **Chen Z***. A Prime-Boost Vaccination Approach Induces Lung Resident Memory CD8+ T Cells Derived from Central Memory T Cells That Prevent Tumor Lung Metastasis. ***Cancer Res***. 2024 Oct 1;84(19):3173-3188. doi: 10.1158/0008-5472.CAN-23-3257.

Results

Preliminary analysis:

1. ICVAX vaccine with IM/EP delivery is safe and well-tolerated, with no vaccine-related severe adverse events (SAEs), potential immune-mediated diseases, or Grade 3 or higher adverse events (AEs).
2. The primary clinical AEs reported were mild injection site pain and rash (Figure 1). No significant laboratory AEs attributable to ICVAX were observed. There was no clinically significant change in CD4 T cell count or VL occurred following the injection of ICVAX.
3. No anti-PD1 antibody (Figure 2) nor ICVAX plasmid (data not shown) were detected in peripheral blood after vaccination. There was no significant increase in various inflammatory cytokines tested after ICVAX injection (Figure 3).
4. In exploratory analyses, most vaccine recipients generated potent T-cell immune responses (pending for unblinding), as detected by the ELISPOT assay.

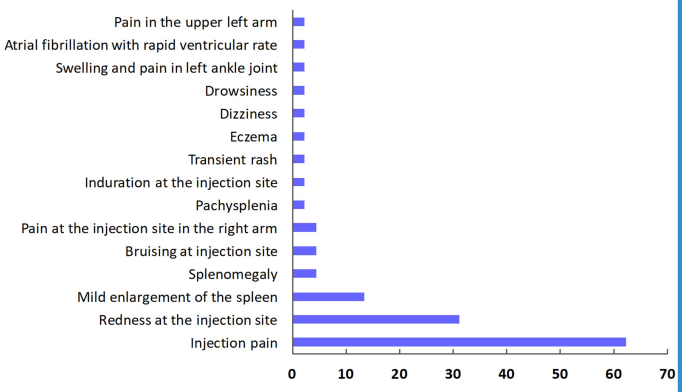

Figure 1. Adverse events that may or may well be related to ICVAX vaccination or placebo injection (n=45) (Unblinded safety data were collected up to 25 May 2024)

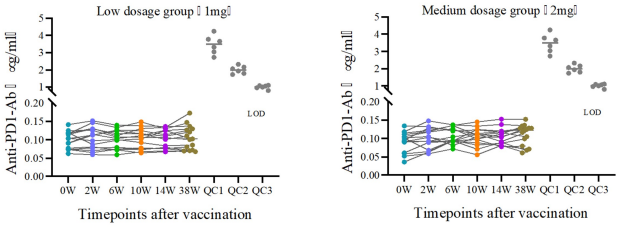

Figure 2. Anti-PD1-Ab in serum after vaccination or placebo injection in low and medium dosage groups

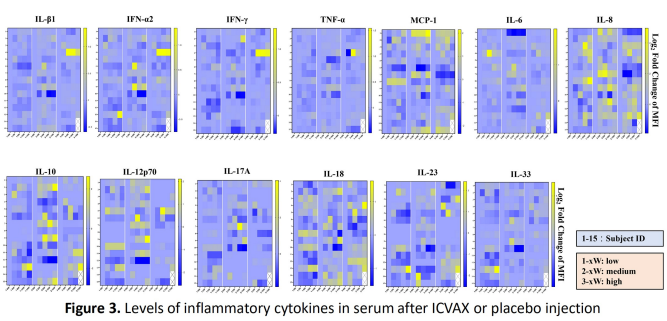

Figure 3. Levels of inflammatory cytokines in serum after ICVAX or placebo injection

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Conclusions

These data suggest that ICVAX in cART-suppressed people living with HIV is safe and immunogenic. Larger clinical trials are warranted to investigate the therapeutic effects of ICVAX to achieve cART-free virologic control.