POTENT INDOLINE CD4 MIMETICS ENABLE ANTI-CORECEPTOR BINDING SITE ANTIBODIES TO MEDIATE ADCC

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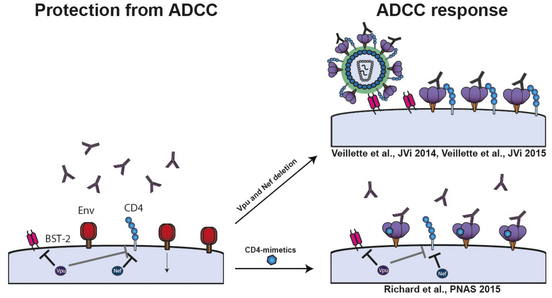
Richard J.[1,2], Zhu L.[3], Marchitto L. [1,2], Bourassa C.[1], Tolbert W.D.[4], Boodapathi T.S.[3], Yang D.[5], Beaudoin-Bussière G.[1,2], Benlarbi M.[1,2], Sodroski J.[7,8], Smith III A.B.[5], Pazgier M P.[4] Kumar P.[3*] **Finzi A.[1,2,*,#]**

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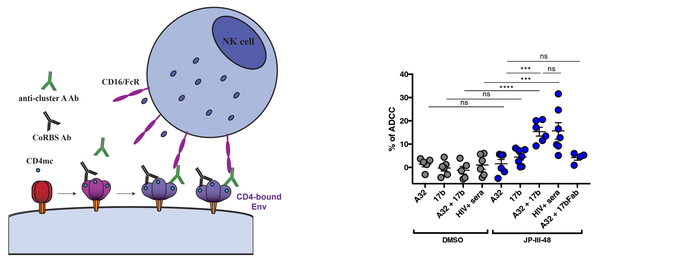
*co-corresponding # lead contact

BACKGROUND

Protection from ADCC / ADCC response

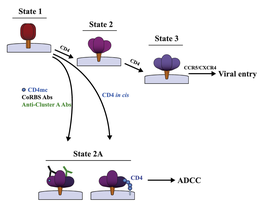


Two families of CD4i nnAbs contribute to eliminate HIV-1-infected cells in the presence of a CD4mc: the anti-cluster A and the anti-coreceptor binding site (CoRBS) Abs

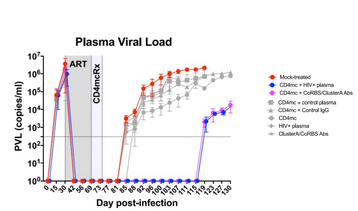


Richard *et al.*, EBioMedicine 2016; Anand *et al.*, JVirol 2019

The combination of anti-Cluster A Abs/anti-CoRBS Abs/indane CD4mc stabilizes a new conformation (State 2A), reduces the size of HIV-1 reservoir and significantly delays viral rebound after ART interruption in humanized mice

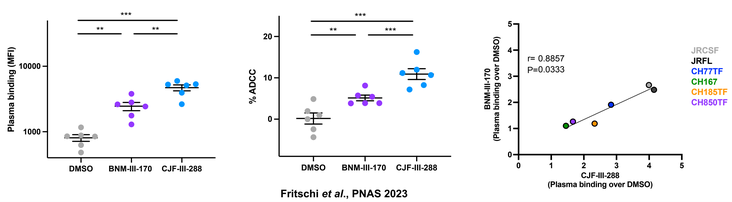


Alsahafi, Bakouche, Kazemi *et al.*, Cell Host Microbes 2019



Rajashekar, Richard *et al.*, Cell Host Microbes 2021

New indoline CD4mcs with improved potency and breath over indane CD4mcs were recently described



Fritschi *et al.*, PNAS 2023

METHODS

- The capacity of anti-CoRBS Abs to mediate ADCC against primary CD4 T cells infected with HIV-1 *in vitro* or *ex vivo*-expanded form ART-treated individuals, in the presence of indane and indoline CD4mcs, was assessed by flow cytometry.
- The capacity of anti-CoRBS Abs delay viral rebound *in vivo* , in the presence of CD4mc, was evaluated using HIV-1-infected humanized NSG-IL15 mice.

RESULTS

Indoline CD4mc CJF-III-288 sensitizes HIV-1 infected cells to ADCC mediated by various anti-CoRBS Abs.

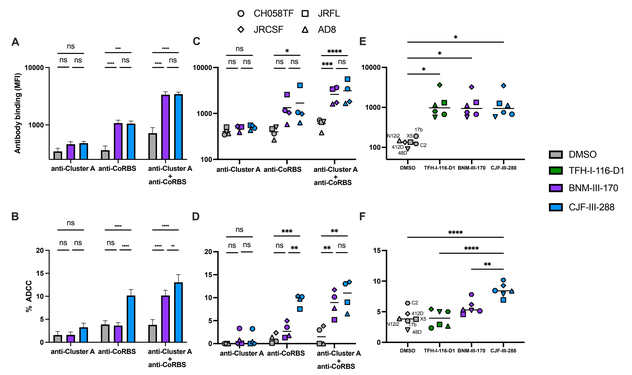


Figure 1. (A) Recognition and (B) ADCC-mediated elimination of primary CD4+ T cells infected with CH058TF by A32, 17b or A32+17b +/- CD4mc (50uM). (C) Mean of recognition and (D) ADCC-mediated elimination of primary CD4+ T cells infected with indicated IMCs by A32, 17b or A32+17b +/- CD4mc (50uM). (E) Recognition and (F) ADCC-mediated elimination of primary CD4+ T cells infected with CH058TF by various anti-CoRBS Abs +/- CD4mc (50uM)

Indoline CD4mc CJF-III-288 expose the CoRBS at concentration where indane CD4mc remain ineffective.

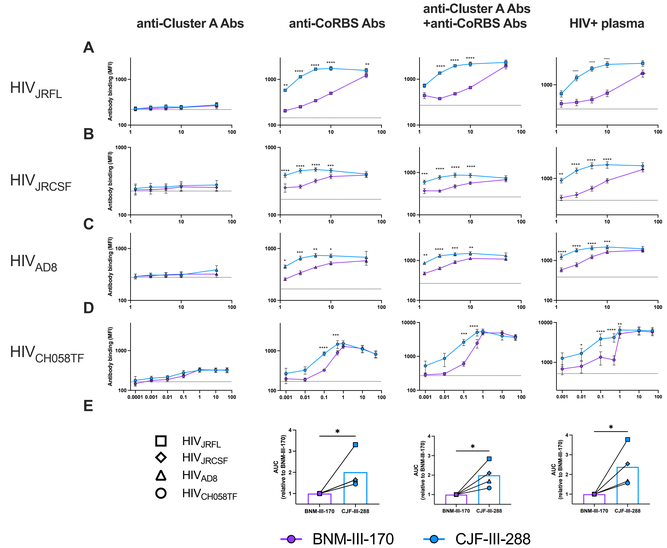


Figure 2. Recognition of primary CD4+ T cells infected with (A) HIV$_{JRFL}$, (B) HIV$_{JRCSF}$, (C) HIV$_{AD8}$ or (D) HIV$_{CH058TF}$ by A32, 17b, A32+17b or HIV+ plasma in the presence of different concentration of CD4mc. (E) Area under the curve (AUC) values of antibody/plasma binding in the presence of indicated CD4mc for each IMCs.

Indoline CD4mc CJF-III-288 sensitize HIV-1-infected cells to ADCC mediated by anti-CoRBS and HIV+ plasma at concentration where indiane CD4mc remain ineffective.

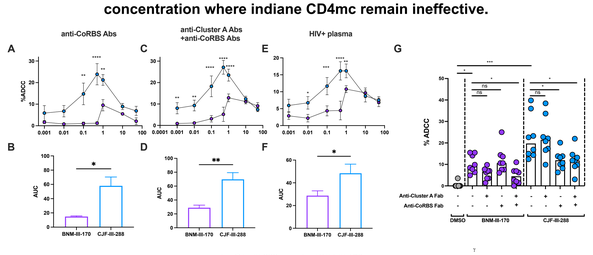


Figure 3. ADCC-mediated elimination of HIV$_{CH058TF}$-infected primary CD4+ T cells by 17b, A32+17b or HIV+ plasma in the presence of different concentration of CD4mc. (B,D,F) Area under the curve (AUC) values of ADCC responses presented in A,C and E. (G) ADCC response mediated by 8 different HIV+ plasma against HIV$_{CH058TF}$-infected primary CD4+ T cells in the presence of A32 or 17b Fabs at 1uM of CD4mc.

Indoline CD4mc CJF-III-288 sensitizes *ex* vivo-expanded CD4 T cells from ART-treated individuals to ADCC mediated by anti-CoRBS Abs

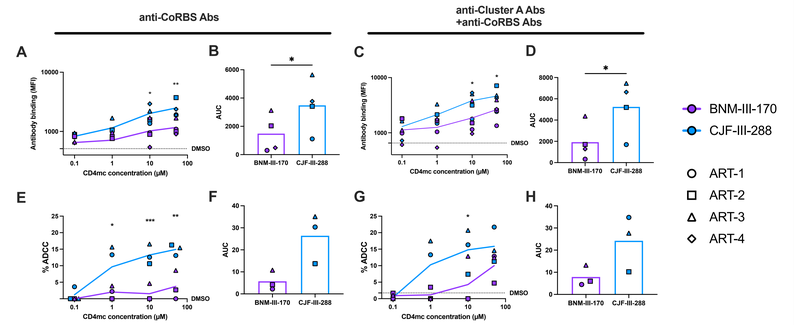


Figure 4. (A,C) Recognition and (E,G) ADCC-mediated elimination of *ex* vivo-expanded CD4 T cells infected from different ART-treated individuals by17b or A32+17b in the presence of different concentration of CD4mc. Area under the curve (AUC) values of (B,D)antibody recognition or (D,H) ADCC responses.

Treatment of HIV-1-infected NSG-IL15 humanized mice with CJF-III-288 and a CoRBS Ab alone delays viral rebound after ART interruption

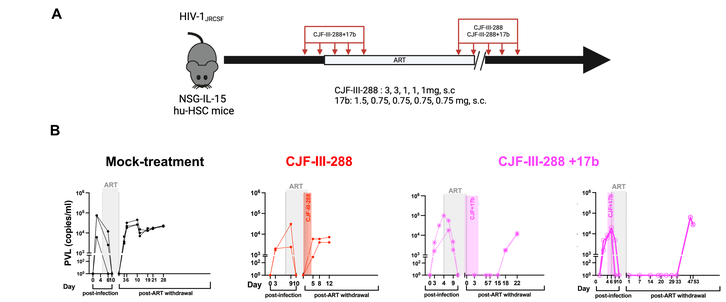


Figure 5. (A) Experimental outine. HIV$_{JRCSF}$-infected NSG-IL15 hu-HSC mice were mock treated or treated with CD4mc CJF-III-288 alone or with 17b at the time of ART initiation or interruption. (B) PVL was measured by quantitative real-time PCR (limit of detection = 300 copies/mL)

CONCLUSIONS

- **The more potent indoline CD4mc CJF-III-288 enables anti-CoRBS Abs to mediate ADCC against HIV-1-infected cells**
- **Treatment of hu-mice with CJF-III-288 and a CoRBS Ab alone delays viral rebound after ART interruption**
- **These results suggest that the indoline CD4mc CJF-III-288 "open" the Env trimer in such a way that the Fc portion of anti-CoRBS Abs is able to engage the Fc gamma receptors on effector cells.**
- **Overall, the indoline CD4mc CJF-III-288 sensitizes HIV-1-infected cells to CoRBS Abs-mediated ADCC responses, thereby improving its therapeutic potential.**

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