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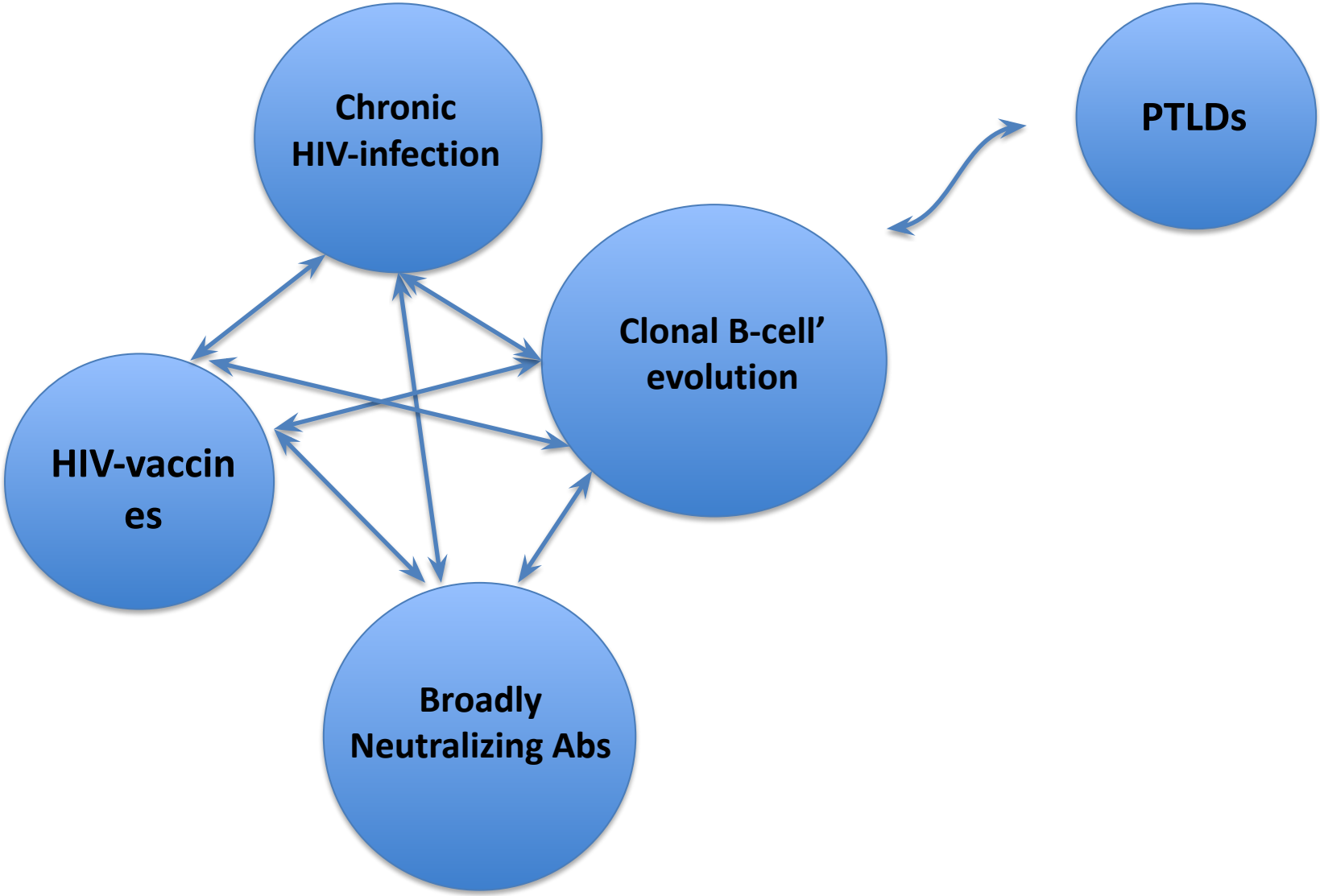
Санкт-Петербург, 2017


Chronic HIV-infection
PTLDs
Clonal B-cell' evolution
HIV-vaccines
Broadly Neutralizing Abs

LIVEJOURNAL ГЛАВНАЯ ТОП ВОЙТИ СОЗДАТ

SHVARZ

Yegor Voronin

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Below are the 25 most recent journal entries recorded in the "Yegor Voronin" journal:

[<< Previous 25 entries]

July 11th, 2019

02:21 pm **Журнал**

Журналу исполнилось 13 лет.

Меня зовут Егор Воронин, хотя последние 19 лет (с тех пор как я приехал в Штаты) я чаще пишу свое имя как Yegor Voronin. Хотя в этом журнале я пишу всегда лишь о том, что лично мне в данный момент интересно, опрос в комментах к этой записи говорит, что большинство читателей ко мне приходят за постами о науке, в основном о ВИЧ. Я изучал этот вирус (и его родственников) в лаборатории лет 12, а последние 7 лет я работаю в очень маленькой организации Global HIV Vaccine Enterprise, которая поддерживает работу очень большого альянса организаций, работающих над вакциной от ВИЧ.

[Link]

Большинство записей в журнале помечены тэгами, пользуйтесь ими для того, чтобы найти то, что вам интересно. Под катом в этом посте - небольшая выборка из написанного за 13 лет, чтобы вам проще было сориентироваться.

(Read more...)

Tags: ЖЖ

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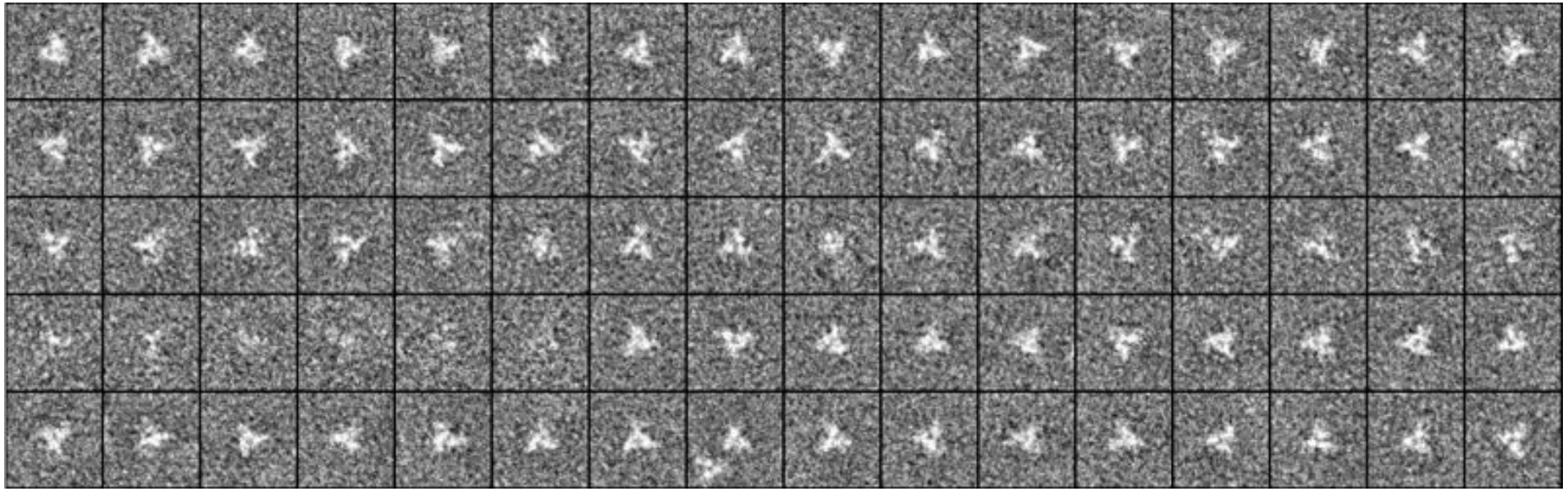
February 17th, 2017

04:42 pm **Олигонуклеотиды как лекарство**

Жена навела на интересную историю. Часто доводится писать об открытиях, которым до клиники еще годы, а тут открытию уже лет десять примерно и буквально месяц-другой назад оно как раз добралось до клиники.

Есть такая очень страшная генетическая болезнь - spinal muscular atrophy (SMA), поражает примерно одного на 10,000 новорожденных.



Back Issues

OPENING THE ENVELOPE

The premier gathering of HIV vaccine researchers showcased a healthy dose of progress in understanding HIV's structure and how it can be utilized to engineer better vaccine candidates

*By Yegor Voronin and Noah Sather**

"Three atomic-level structures of HIV envelope were released over the past two years," said Peter Kwong of the Vaccine Research Center at the National Institute of Allergy and Infectious Diseases (NIAID). "At this meeting, I've already seen six new trimer structures, and the meeting is barely half over."

The meeting was the Keystone Symposium on HIV Vaccines, which took place March 22-27 in Banff, Canada, and, for the record, Peter counted a total of 10 new HIV envelope (Env) structures that were unveiled there, reflecting the rapidly accelerating pace of progress in defining the structure of HIV's outer surface protein. This sentiment extended to the whole meeting, as several directions of HIV vaccine research, none of which are completely new, showed spectacular progress in the recent months.

Epitope mapping reveals surprises

New structures of Env illuminate how the genetic diversity of HIV results in the diversity of protein structures, which allows the virus to efficiently evade the immune system. They also reveal the conserved motifs that are targeted by antibodies capable of neutralizing a broad swath of HIV isolates (so-called broadly neutralizing antibodies or bNAbs). At Keystone, Pamela Bjorkman from the California Institute of Technology presented data showing that an antibody referred to as 8ANC195 binds to HIV Env in a manner different from all previously identified bNAbs. Although initial analysis showed that 8ANC195 competes with antibodies targeting the CD4 binding site (CD4bs) on Env, crystal structures revealed that it actually binds to a distinct region nearby and that its epitope spans the gp120 and gp41 subunits of Env.

NATURE MEDICINE | COMMENTARY

The 2010 scientific strategic plan of the Global HIV Vaccine Enterprise

The Council of the Global HIV Vaccine Enterprise, Seth Berkley, Kenneth Bertram, Jean-François Delfraissy, Ruxandra Draghia-Akli, Anthony Fauci, Cynthia Hallenbeck, Madame Jeannette Kagame, Peter Kim, Daisy Mafubelu, Malegapuru W Makgoba, Peter Piot, Mark Walport, Mitchell Warren & Tadataka Yamada for Members of the Enterprise, José Esparza, Catherine Hankins, Margaret I Johnston, Yves Lévy & Manuel Romaris for Alternate members, Rafi Ahmed & Alan Bernstein for Ex-officio members

Affiliations | Corresponding author

Nature Medicine **16**, 981–989 (2010) | doi:10.1038/nm0910-981

Subject terms: HIV infections · Public health · Vaccines

AIDS Research and Human Retroviruses
Mary Ann Liebert, Inc. publishers
Journals | Search | Alerts

AIDS Res Hum Retroviruses. 2016 Nov 1; 32(10-11): 944–946.
Published online 2016 Nov 1. doi: 10.1089/aid.2016.0120
PMCID: PMC5067853

The Landscape of Targeted Immune Responses in the HIV-1 Vaccine Field

Jeffrey T. Safrit,[1] Georgia D. Tomaras,[2] Tomáš Hanke,[3] Allan C. deCamp,[4] and Yegor Voronin[5]

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HIV-1 VACCINE DEVELOPMENT is rapidly advancing numerous diverse vaccine candidates based on a variety of hypotheses about what constitutes protective HIV-1 immunity.[1–3] It is common to differentiate vaccine candidates as being antibody-based, T-cell-based, or both, which is a useful classification, but it does not provide enough granularity to capture the multiple hypotheses regarding the contribution of particular immune responses to protection against HIV-1.

We conducted a landscape analysis of the immune responses that are viewed as potentially protective by HIV-1 vaccine researchers (Fig. 1). We interviewed 10 investigators involved in 12 current phase I/IIa studies and asked them to list the immune responses that they wished to elicit with their vaccine candidate(s) divided into the following three categories:

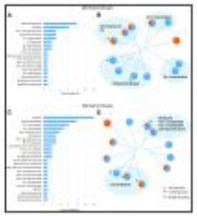
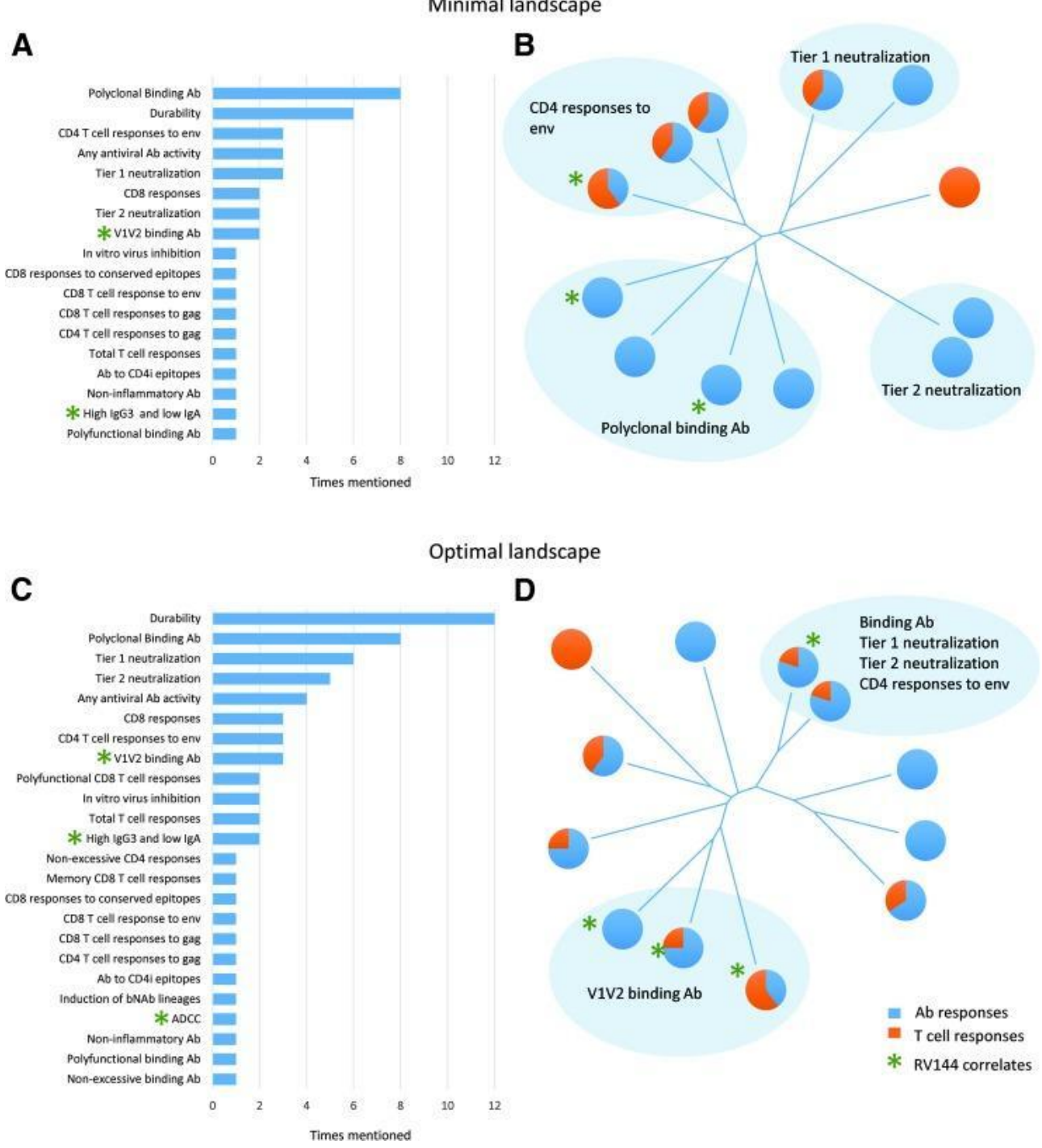


FIG. 1.
Immune landscape of candidates based on the minimal **(A, B)** or the optimal **(C, D)** desired immune responses. **(A, C)** show frequency distribution of immune responses identified as desired for the surveyed vaccine candidates. The numbers represent the number ...

AIDS Res Hum R


Minimal landscape
A
Polyclonal Binding Ab
Durability
CD4 T cell responses to env
Any antiviral Ab activity
Tier 1 neutralization
CD8 responses
Tier 2 neutralization
V1V2 binding Ab
In vitro virus inhibition
CD8 responses to conserved epitopes
CD8 T cell response to env
CD8 T cell responses to gag
CD4 T cell responses to gag
Total T cell responses
Ab to CD4i epitopes
Non-inflammatory Ab
High IgG3 and low IgA
Polyfunctional binding Ab
0 2 4 6 8 10 12
Times mentioned
B
Tier 1 neutralization
CD4 responses to env
Tier 2 neutralization
Polyclonal binding Ab
Optimal landscape
C
Durability
Polyclonal Binding Ab
Tier 1 neutralization
Tier 2 neutralization
Any antiviral Ab activity
CD8 responses
CD4 T cell responses to env
V1V2 binding Ab
Polyfunctional CD8 T cell responses
In vitro virus inhibition
Total T cell responses
High IgG3 and low IgA
Non-excessive CD4 responses
Memory CD8 T cell responses
CD8 responses to conserved epitopes
CD8 T cell response to env
CD8 T cell responses to gag
CD4 T cell responses to gag
Ab to CD4i epitopes
Induction of bNAb lineages
ADCC
Non-inflammatory Ab
Polyfunctional binding Ab
Non-excessive binding Ab
0 2 4 6 8 10 12
Times mentioned
D
Binding Ab
Tier 1 neutralization
Tier 2 neutralization
CD4 responses to env
V1V2 binding Ab
Ab responses
T cell responses
RV144 correlates

PLoS Pathog. 2017 Feb 24;13(2):e1006182. doi: 10.1371/journal.ppat.1006182. [Epub ahead of print]

Boosting of HIV envelope CD4 binding site antibodies with long variable heavy third complementarity determining region in the randomized double blind RV305 HIV-1 vaccine trial.

Easterhoff D[1], Moody MA[1], Fera D[2], Cheng H[3], Ackerman M[3], Wiehe K[1], Saunders KO[1], Pollara J[1], Vandergrift N[1], Parks R[1], Kim J[4], Michael NL[4], O'Connell RJ[5], Excler JL[4,6], Robb ML[4], Vasan S[5], Rerks-Ngarm S[7], Kaewkungwal J[8], Pitisuttithum P[9], Nitayaphan S[9], Sinangil F[10], Tartaglia J[11], Phogat S[11], Kepler TB[12], Alam SM[1], Liao HX[1], Ferrari G[1], Seaman MS[13], Montefiori DC[1], Tomaras GD[1], Harrison SC[2], Haynes BF[1].

⊕ Author information

Abstract

The canary pox vector and gp120 vaccine (ALVAC-HIV and AIDSVAX B/E gp120) in the RV144 HIV-1 vaccine trial conferred an estimated 31% vaccine efficacy. Although the vaccine Env AE.A244 gp120 is antigenic for the unmutated common ancestor of V1V2 broadly neutralizing antibody (**bnAbs**), no plasma bnAb activity was induced. The RV305 (NCT01435135) HIV-1 clinical trial was a placebo-controlled randomized double-blinded study that assessed the safety and efficacy of vaccine boosting on B cell repertoires. HIV-1-uninfected RV144 vaccine recipients were reimmunized 6-8 years later with AIDSVAX B/E gp120 alone, ALVAC-HIV alone, or a combination of ALVAC-HIV and AIDSVAX B/E gp120 in the RV305 trial. Env-specific post-RV144 and RV305 boost memory B cell VH mutation frequencies increased from 2.9% post-RV144 to 6.7% post-RV305. The vaccine was well tolerated with no adverse events reports. While post-boost plasma did not have bnAb activity, the vaccine boosts expanded a pool of envelope CD4 binding site (bs)-reactive memory B cells with long third heavy chain complementarity determining regions (HCDR3) whose germline precursors and affinity matured B cell clonal lineage members neutralized the HIV-1 CRF01 AE tier 2 (difficult to neutralize) primary isolate, CNE8. Electron microscopy of two of these antibodies bound with near-native gp140 trimers showed that they recognized an open conformation of the Env trimer. Although late boosting of RV144 vaccinees expanded a novel pool of neutralizing B cell clonal lineages, we hypothesize that boosts with stably closed trimers would be necessary to elicit antibodies with greater breadth of tier 2 HIV-1 strains.

TRIAL REGISTRATION: ClinicalTrials.gov NCT01435135.

PMID: 28235027 DOI: 10.1371/journal.ppat.1006182

PMC full text: Virol J. 2015; 12: 3.
Published online 2015 Jan 24. doi: 10.1186/s12985-014-0221-0

Table 1

Summary of immunogen design strategies and progress in evaluation

Design strategy	Expected outcome	*In vitro* evaluation	Animal trials	Human trials	Key ref.
1. Mimicking native trimer: remove non-functional Env from VLP	bNAb	Recognised by NAb but not non-NAb	-	-	[29,31]
2. Mimicking native trimer: soluble SOSIP-modified Env trimer	bNAb	Recognised by bNAb but not non-NAb Resembles Env trimer by electron microscopy	-	-	[39]
3. Stabilised bNAb epitope: epitope-scaffolds	bNAb	Bound to bNAb	Ones tested did not elicit NAb	-	[33,46,47]
4. Stabilised bNAb epitope: targeting germline and driving maturation	bNAb	Potently activated germline and mature VRC01 B cells	-	-	[49]
5. Stabilised bNAb epitope: fragment immunogen	bNAb	Ab induced in rabbits neutralised tier I, II and III viruses	Induced b12 bNAb in rabbits	-	[51]
6. Mosaic immunogens	T cell responses to diverse strains, reduce escape	Processed and expressed by human T cells	Increased breadth and depth of T cell responses Reduced per exposure probability of infection by ≈ 90%	-	[67,70-72]
7. Conserved element immunogens	T cell responses to diverse strains, reduce escape/attenuate virus	T cell responses elicited in humans inhibited viruses	Highly immunogenic	High magnitude and breadth of T cell responses in 100% vaccinees	[21,81]
8. Escape-cornering immunogens (computational model)	Reduce escape/attenuate virus	Fitness testing of mutants supported model predictions	-	-	[84,86]
9. Immunogens using CMV vectors	Persistent T cell responses to act early	-	50% monkeys clear SIV infection early Persistent, unusually broad T cell responses	-	[55,91,92]

ref – references; VLP – virus-like particles; bNAb – broadly neutralising antibodies; NAb – neutralising antibodies; SOSIP - disulphide bond between gp120 and gp41 and gp41 trimer stabilising mutation I559P; Env – envelope; CMV – cytomegalovirus; SIV – simian immunodeficiency virus.

WILEY IMMUNOLOGICAL REVIEWS

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PMCID: PMC5299500

Immunologic characteristics of HIV-infected individuals who make broadly neutralizing antibodies

Persephone Borrow[1] and M. Anthony Moody[2]

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Summary

Go to:

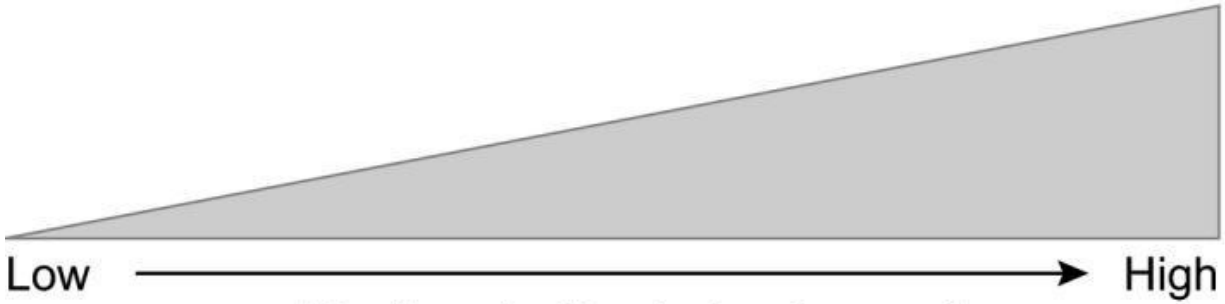
Induction of broadly neutralizing antibodies (bnAbs) capable of inhibiting infection with diverse variants of human immunodeficiency virus type 1 (HIV-1) is a key, as-yet-unachieved goal of prophylactic HIV-1 vaccine strategies. However, some HIV-infected individuals develop bnAbs after approximately 2-4 years of infection, enabling analysis of features of these antibodies and the immunological environment that enables their induction. Distinct subsets of $CD4^+$ T cells play opposing roles in the regulation of humoral responses: T follicular helper (Tfh) cells support germinal center formation and provide help for affinity maturation and the development of memory B cells and plasma cells, while regulatory $CD4^+$ (Treg) cells including T follicular regulatory (Tfr) cells inhibit the germinal center reaction to limit autoantibody production. BnAbs exhibit high somatic mutation frequencies, long third heavy-chain complementarity determining regions, and/or autoreactivity, suggesting that bnAb generation is likely to be highly dependent on the activity of $CD4^+$ Tfh cells, and may be constrained by host tolerance controls. This review discusses what is known about the immunological environment during HIV-1 infection, in particular alterations in $CD4^+$ Tfh, Treg, and Tfr populations and autoantibody generation, and how this is related to bnAb development, and considers the implications for HIV-1 vaccine design.

Keywords: autoantibody, broadly neutralizing antibody, $CD4^+$ T follicular helper cell, $CD4^+$ T follicular

Factors correlated with bnAb development

Preserved early CD4 count
lower viral load
short time since infection
no autoantibodies

Early CD4 loss
early high viral load
longer time of infection
presence of autoantibodies
reduced circulating Treg
high circulating Tfh
high PD-1 expression on Treg and Tfr



Possibly correlated with bnAb development

Subtype C infection
HLA-A*03

Env diversity

Not correlated with bnAb development

Gender
Age

Geographical origin
Mode of transmission/risk factor

www.sciencemag.org/cgi/content/full/340/6133/751/DC1

Supplementary Materials for

Delineating Antibody Recognition in Polyclonal Sera from Patterns of HIV-1 Isolate Neutralization

Ivelin S. Georgiev, Nicole A. Doria-Rose, Tongqing Zhou, Young Do Kwon, Ryan P. Staupe, Stephanie Moquin, Gwo-Yu Chuang, Mark K. Louder, Stephen D. Schmidt, Han R. Altae-Tran, Robert T. Bailer, Krisha McKee, Martha Nason, Sijy O'Dell, Gilad Ofek, Marie Pancera, Sanjay Srivatsan, Lawrence Shapiro, Mark Connors, Stephen A. Migueles, Lynn Morris, Yoshiaki Nishimura, Malcolm A. Martin, John R. Mascola,* Peter D. Kwong*

*Corresponding author. E-mail: jmascola@nih.gov (J.R.M.); pdkwong@nih.gov (P.D.K.)

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DOI: 10.1126/science.1233989

This PDF file includes

Molecular Therapy

Volume 25, Issue 3, p570–579, 1 March 2017

ORIGINAL ARTICLE

Engineering HIV-Resistant, Anti-HIV Chimeric Antigen Receptor T Cells

Malika Hale, Taylor Mesojednik, Guillermo S. Romano Ibarra, Jaya Sahni, Alison Bernard, Karen Sommer, Andrew M. Scharenberg, David J. Rawlings, Thor A. Wagner

DOI: http://dx.doi.org/10.1016/j.ymthe.2016.12.023 | CrossMark

Article Info

Altmetric 7

The treatment or cure of HIV infection by cell and gene therapy has been a goal for decades. Recent advances in both gene editing and chimeric antigen receptor (CAR) technology have created new therapeutic possibilities for a variety of diseases. Broadly neutralizing monoclonal antibodies (bNAbs) with specificity for the HIV envelope glycoprotein provide a promising means of targeting HIV-infected cells. Here we show that primary human T cells engineered to express anti-HIV CARs based on bNAbs (HIVCAR) show specific activation and killing of HIV-infected versus uninfected cells in the absence of HIV replication. We also show that homology-directed recombination of the HIVCAR gene expression cassette into the *CCR5* locus enhances suppression of replicating virus compared with HIVCAR expression alone. This work demonstrates that HIV immunotherapy utilizing potent bNAb-based single-chain variable fragments fused to second-generation CAR signaling domains, delivered directly into the *CCR5* locus of T cells by homology-directed gene editing, is feasible and effective. This strategy has the potential to target HIV-infected cells in HIV-infected individuals, which might help in the effort to cure HIV.