Is a Human CD8 T-Cell Vaccine Possible, and if So, What Would It Take?

Could a CD8⁺ T-Cell Vaccine Prevent Persistent HIV Infection?

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Vaccines that stimulate CD8⁺ T cells could clear early virus infection or control ongoing infection and prevent disease. This could be valuable to combat human immunodeficiency virus type 1 (HIV-1) where it has not yet been possible to generate broadly reacting neutralizing antibodies with a vaccine. However, HIV-1 vaccines aimed at stimulating CD8⁺ T cells have had no success. In contrast, a cytomegalovirus vectored simian immunodeficiency virus (SIV) vaccine enabled clearance of early SIV infection. This may open the door to the design of an effective HIV vaccine

GREAT DEBATES

What are the most interesting topics likely to come up over dinner or drinks with your colleagues? Or, more importantly, what are the topics that *don't* come up because they are a little too controversial? In ***Immune Memory and Vaccines: Great Debates***, Editors Rafi Ahmed and Shane Crotty have put together a collection of articles on such questions, written by thought leaders in these fields, with the freedom to talk about the issues as they see fit. This short, innovative format aims to bring a fresh perspective by encouraging authors to be opinionated, focus on what is most interesting and current, and avoid restating introductory material covered in many other reviews.

The Editors posed 13 interesting questions critical for our understanding of vaccines and immune memory to a broad group of experts in the field. In each case, several different perspectives are provided. Note that while each author knew that there were additional scientists addressing the same question, they did not know who these authors were, which ensured the independence of the opinions and perspectives expressed in each article. Our hope is that readers enjoy these articles and that they trigger many more conversations on these important topics.

Editors: Shane Crotty and Rafi Ahmed

Additional Perspectives on Immune Memory and Vaccines: Great Debates available at www.cshperspectives.org

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Cite this article as *Cold Spring Harb Perspect Biol* 2018;10:a029124

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This review will address the question of whether it is possible to design a prophylactic vaccine that stimulates protective CD8⁺ T cells that will control or eradicate infection with a virus that routinely establishes persistent infection. It focuses on human immunodeficiency virus (HIV) vaccines because this is a particularly challenging vaccine problem, of which it has not yet been possible to find a vaccine that can stimulate neutralizing antibodies reactive with enough virus variants to be protective. This raises the question of whether a vaccine that stimulates protective broadly reactive CD8⁺ T cells would be a possible alternative, or whether a complementing combination of a CD8⁺ T-cell-inducing vaccine and a partially protective antibody-inducing vaccine might offer the most likely route to an effective prophylactic vaccine.

RATIONALE

There are many examples in experimental animal models where vaccine-induced CD8⁺ T cells protect against virus infections. These include lymphocytic choriomeningitis virus (LCMV), influenza virus, and respiratory syncytial virus (Yap and Ada 1978; Webster and Askonas 1980; Bachmann et al. 1997; Flynn et al. 1998). Not surprisingly, CD8⁺ T cells do not prevent infection, because normally they can only recognize and respond to infected cells, but they can effect rapid virus clearance. CD8⁺ T cells can also prevent long-term persistence of LCMV in mice (Bachmann et al. 1997) and hepatitis C virus in chimpanzees (Folgori et al. 2006), but HIV poses a greater challenge.

In humans, there is strong evidence for a role for CD8⁺ T cells in the control of early influenza virus infection (McMichael et al. 1983), as well as a considerable evidence that CD8⁺ T cells control chronic infection with Epstein–Barr virus (Rickinson and Moss 1997) and cytomegalovirus (CMV), ensuring good health without eliminating the virus (Riddell et al. 1991; Klenerman and Oxenius 2016). In these examples, there is often an additional complementary role for CD4 T cells (Wilkinson et al. 2012) and often a role for natural killer (NK) cells, particularly in

controlling herpes virus infections (Lopez-Botet et al. 2004).

There is also extensive evidence that CD8⁺ T cells are effective at controlling HIV infection (reviewed in McMichael et al. 2010; Carrington and Walker 2012); however, this control ultimately fails in the absence of antiretroviral drug therapy. The evidence for CD8⁺ T-cell control includes the complementary kinetics of the early T-cell response and viral load, rapid and extensive selection of virus escape mutants, and the strong impact of HLA-I type on control of virus. Additional evidence comes from the monkey simian immunodeficiency virus (SIV) model system where CD8⁺ T-cell depletion impairs and restoration reestablishes virus control (Jin et al. 1999; Schmitz et al. 1999).

VACCINATION STUDIES

Demonstration that CD8⁺ T cells contribute to virus control in people infected with HIV-1 does not necessarily mean that vaccine induction of CD8⁺ T cells will be beneficial. That demonstration requires vaccination ahead of natural HIV infection, or vaccination followed by challenge with SIV in monkeys. Vaccination in humans has so far been disappointing. Very large-scale, expensive, and time-consuming clinical trials are needed for efficacy studies and only two CD8⁺ T-cell vaccines that have so far been tested for efficacy. Both were based on recombinant adenovirus-5 with or without an initial DNA prime. Neither showed evidence of protection (see Table 1). However, that does not necessarily mean that the concept is wrong; the immune responses stimulated might have been inadequate. In contrast, there was a 31% reduction in HIV infection seen in the RV144 trial where a recombinant canarypox vaccine primed and an envelope protein boosted, but that protection could not be attributed to CD8⁺ T cells nor to neutralizing antibody (Rerks-Ngarm et al. 2009). Most likely antibody-dependent cell-mediated viral inhibition was associated with the rather short-lived protection seen (Haynes et al. 2012).

The SIV model has yielded more encouraging results. The first attempts at stimulating CD8⁺ T cells in monkeys used SIV nonenvelope

Table 1. Efficacy of vaccines in human trials

Human Trial	Vaccine	Insert	Efficacy?	References
STEP	Adenovirus-5	HIV Gag, Pol, Nef	No protection	Buchbinder et al. 2008
HVTN505	DNA + adenovirus-5	Gag, Pol, Nef, Env	No protection	Hammer et al. 2013
RV144	Canarypox + Env protein	Gag, Pol, Env + Env gp120	31% reduction in acquisition (attributed to non-neutralizing antibody)	Rerks-Ngarm et al. 2009

proteins expressed by plasmid DNA or vectors such as modified vaccinia virus ankara (MVA), adenovirus-5, or vesicular stomatitis virus (VSV). CD8⁺ T-cell responses were generated and there were reduced virus loads after challenge with SHIV89.6P (Rose et al. 2001; Barouch et al. 2002; Amara et al. 2005). That challenge virus (SIV with an HIV envelope) was chosen because it was very aggressive with a rapidly fatal decline in host CD4 T-cell numbers. Paradoxically, SHIV89.6P turned out to be relatively easy to control by any immune response and was

misleading therefore. The more natural isolate SIVmac239 was shown to be much more rigorous as a challenge virus (Casimiro et al. 2005). Protection against SIVmac239 offered by the same types of vaccines as above was less impressive, although some control could be obtained (Casimiro et al. 2005; Liu et al. 2009; Martins et al. 2015). These positive SIVmac239 results are not necessarily inconsistent with the failed HIV vaccine trials, because the induced CD8⁺ T-cell responses were much weaker in the human studies (Fig. 1) (Liu et al. 2009; Haynes et al. 2016).

Figure 1. Relationship between magnitude and breadth of CD8⁺ T-cell responses and protection. Plots, based on data, are shown for the STEP human immunodeficiency virus type 1 (HIV-1) vaccine trial, and simian immunodeficiency virus (SIV) mac239—CD8⁺ T-cell vaccine-challenge studies, where the primary aim was to stimulate CD8⁺ T-cell responses. The y-axis shows the peak magnitude of the vaccine-stimulated T-cell response as spot forming units (SFU)/million peripheral blood mononuclear cells (PBMCs) in the interferon- γ enzyme linked immunospot (ELISPOT) assay and the x-axis shows the breadth of the vaccine-induced T-cell responses shown as the number of epitopes the vaccine stimulated. Indicated are the upper limits of each type of T-cell response and the outcome. Further details can be found in Haynes et al. (2016).

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The poor results in the human trials of vaccines that stimulated CD8⁺ T cells without neutralizing antibody (see Table 1) led to the idea of mixing in an HIV envelope (Env) vaccine so that both T cells and antibody could be generated. This was the rationale for the RV144 trial in Thailand (Table 1), although that vaccine barely stimulated any CD8⁺ T cells. Similar vaccine combinations in monkeys using an adenovirus-env-gag-pol to prime with an Env protein boost to stimulate both CD8⁺ T cells, CD4⁺ T cells, and non-neutralizing antibody have given up to 50% protection from SIV acquisition after six repeated low-dose mucosal SIVmac239 challenges (Barouch et al. 2015). In animals that became infected, virus load was slightly reduced, which could be attributed to the vaccine-induced CD8⁺ T-cell response, in line with earlier studies. If the RV144 trial result is reproducible in current human trials, the virus vector prime plus Env protein boost approach could offer partial protection. However, by testing this type of vaccine in humans exposed to a much higher HIV-1 risk than the original Thai cohort, the small reduction in HIV-1 infection seen in the RV144 trial may be obscured. Whatever the result, such studies are unlikely to answer the question posed here because the CD8⁺ T-cell responses are not optimized and there is an antibody component. Furthermore, because the protection in humans and monkeys has only been seen early in infection or with a limited number of SIV challenges, respectively, there is a risk that this approach will not offer broad and long-lasting protection in humans.

Thus, conventional vaccine approaches using recombinant adenoviruses, pox viruses, and/or DNA have given some encouraging results in monkeys but no protection in humans. The limited protection seen in the RV144 trial could not be attributed to CD8⁺ T-cell responses. These results led to a common perception that CD8⁺ T cells would not be useful in a prophylactic vaccine. That view was then challenged by studies using recombinant CMV-vectored vaccines in an SIV model system (Hansen et al. 2009, 2013a).

CMV-VECTORED VACCINE

The original aim of the CMV-vectored vaccine was to try to get SIV-specific CD8⁺ T-cell responses similar in magnitude to the very strong anti-CMV CD8⁺ T-cell responses seen in humans chronically infected with human CMV (HCMV) (Hansen et al. 2009). Also it was expected that such T cells would be of the effector memory phenotype and therefore ready to act on SIV-infected cells with little further differentiation. This was achieved in the first experiments, which showed, unexpectedly, that half of the animals were able to completely clear infection with SIVmac239 when challenged a year after vaccination (Hansen et al. 2009, 2013a). The animals became infected soon after challenge, but they then eradicated virus over 1–6 months. While similar to clearance of an acutely infecting virus such as an influenza virus, this was unprecedented for a lentivirus, which establishes a reservoir of latent provirus infected cells soon after infection.

Hansen et al. (2009) have argued very strongly that this protection was mediated by vaccine-induced CD8⁺ T cells. Although the animals were immunized with a recombinant rhesus monkey cytomegalovirus strain 68-1 (RhCMV68-1) that included all of SIV except Vif, there was no SIV-specific-neutralizing antibody generated and only low levels of non-neutralizing antibodies (Hansen et al. 2009). This makes any form of antibody-mediated protection unlikely. Furthermore, the nature of the protection seen was very different from that seen in the RV144 trial (Haynes et al. 2012) and in similar studies in monkeys (Barouch et al. 2015), where there was reduced acquisition but no evidence of viral clearance once infection occurred. In contrast, the CMV-based vaccine induced very strong CD8⁺ T-cell responses and the pattern of virus elimination over a few weeks was very similar to CD8⁺ T-cell-mediated clearance of many acutely infecting viruses (Yap and Ada 1978; Flynn et al. 1998). Although T cells and NK cells often work together to clear acute virus infections, in this case a dominant role for innate immune responses is unlikely because all of the vaccinated animals were already infected

with natural RhCMV. Although NK cells are activated by acute CMV infection, they are unlikely to be further enhanced by “chronic” superinfection with the vaccine. Therefore, the vaccine stimulated CD8⁺ T-cell responses were almost certainly responsible for clearance of SIV after challenge.

If this interpretation is correct, it raises the question of why this particular T-cell response could eradicate early SIV infection in >50% of SIV-challenged animals, whereas T cells stimulated by SIV itself or by other vaccines could not. There are several possible explanations:

1. The T-cell responses were of much greater magnitude and/or breadth than previous vaccine- or SIV-induced responses.
2. The function and state of activation, or preparedness, of the T cells was more effective than with previous vaccines or in acute SIV infection.
3. Other qualities of the T cells were different.

These hypotheses are not mutually exclusive. The total magnitude of the T-cell responses was not much higher than with previous vaccines (Hansen et al. 2009), making this the least likely of these explanations. On the other hand, the T-cell responses were extraordinarily broad (Hansen et al. 2013b). Epitopes recognized by the CD8⁺ T cells occurred on average every 30 amino acids of the SIV proteome, so >100 epitopes were recognized by each animal in total (Hansen et al. 2016). This contrasts with 10–30 for previous vaccine approaches or after SIV infection. Responses in HIV-infected humans are even narrower, probably because there are fewer classical HLA class I loci in humans than in rhesus macaques (Wiseman et al. 2013). Narrowly immunodominant T-cell responses, seen in acute SIV/HIV infection and with most vaccines, rapidly select virus escape mutants and compromise control of virus (Liu et al. 2013). Here, the extremely broad T-cell responses, which lacked clear immunodominance hierarchies, could make it impossible for the virus to escape. So the great breadth of the response could be very important to protection.

The CD8⁺ T cells that expanded after RhCMV68-1 vaccination were activated effector memory cells, continuously stimulated by the replicating virus (Hansen et al. 2009). This contrasts with the resting memory T cells generated following immunization with nonpersisting vaccine vectors. A need for activated effector memory T cell protection is reminiscent of the finding that murine CD8⁺ T-cell-mediated protection against LCMV required T cells recently restimulated by virus (Bachmann et al. 1997).

Finally, the T-cell responses elicited by the RhCMV68.1 vector were very unusual in quality. Two-thirds of the CD8⁺ T cells were restricted by the major histocompatibility complex class II (MHC-II) and one-third by the nonclassical MHC-E molecules (Hansen et al. 2013b, 2016). These unusual T-cell responses might be protective because these MHC molecules were highly permissive in the peptides they presented in Hansen et al. (2013b, 2016), resulting in extreme response breadth. MHC-II- and MHC-E-specific CD8⁺ T cells might also be particularly effective in cells that have down-regulated classical MHC class I proteins. Furthermore, the atypical T cells might be particularly effective if the long-lived latently SIV-infected cells in the virus reservoir, such as CD4⁺ T follicular helper (T_{FH}) cells in the lymphoid follicles (Fukazawa et al. 2015), express MHC-II or MHC-E. The latter seems more likely because MHC-II expression is enhanced on T-cell activation, as are SIV/HIV replication, so is unlikely to define latently infected T cells. In contrast, there is evidence in mice and humans that T_{FH} cells can be regulated in lymphoid follicles by lytic and nonlytic CD8⁺ T cells restricted by H2-Qa1 (the H-2 HLA-E equivalent) (Kim et al. 2010) or HLA-E, respectively (Jiang et al. 2010).

If the unusual nature of these protective T-cell responses is important for protection, the findings may also provide an explanation for why 45% of vaccinated monkeys were not protected. Hansen et al. (2016) have identified several RhCMV68-1 genes that are essential to the generation of the MHC-II- and MHC-E-restricted CD8⁺ T-cell responses. For SIV-infected cells to be recognized by these CD8⁺ T cells, they must display MHC-II- or MHC-E-containing

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virus peptides at their surface. CD8⁺ T cells can recognize target cells that express less than 10 peptide–MHC complexes on the surface (Purbhoo et al. 2004). In contrast, priming a T-cell response requires much more peptide on the antigen-presenting cells (Met et al. 2003). Thus, while SIV lacks the genetic mechanisms that RhCMV68-1 uses to favor the binding of epitope peptides to MHC-E and prime these unusual responses, it can put enough peptides into MHC-E to generate targets (Fig. 2). However, SIV-infected cells in some animals may present better than others, and only the former would be protected. There is more polymorphism of MHC-E in monkeys compared to humans and some peptides or allotypes may present better than others. This hypothesis and alternative hypotheses that the lack of protection is the result of some other as-yet-undetermined property of the vaccine-induced T cells need to be tested.

WHAT WOULD IT TAKE?

In principle, therefore, vaccine-induced CD8⁺ T cells can clear early SIV infection (Hansen et al. 2009, 2013a). These findings ought to be translatable into humans. However, there are many differences between human and rhesus CMVs (Powers and Fruh 2008), between the MHC of humans and monkeys (Wiseman et al. 2013), and more generally in the immune responses (Haigwood and Walker 2011). Also SIV and HIV-1 have differences that go beyond simple sequence variation (Sharp and Hahn 2011). A full understanding of how the RhCMV68-1-induced CD8⁺ T cells actually protect in the rhesus monkey SIV model may be needed before such protection can be reproduced in humans.

Most likely a vaccine will need to stimulate strong, very broad persisting effector memory CD8⁺ T cells that are restricted by HLA-E and/

Figure 2. How RhCMV68-1-SIV and simian immunodeficiency virus (SIV) differ in presenting SIV peptides to CD8⁺ T cells. The diagram shows a cell (of unknown type) infected by the tropism restricted RhCMV68-1-SIV on the *left* and an activated CD4⁺ T-cell infected with SIV on the *right*. The relative levels of major histocompatibility complex (MHC)-E, classical MHC-I, and MHC-II are shown together with the epitopes expressed on the cell surface that may lead to priming of a CD8⁺ T-cell response or make the cell a target for CD9⁺ T cells (based on McMichael and Picker 2017). NK, Natural killer.

or HLA-II. The simplest approach would be to use an HCMV vector that is equivalent to RhMV68-1. However, RhCMV68-1 has unusual features that are critical to its ability to prime these responses and protect (Hansen et al. 2013b, 2016), in particular, the loss of the RhCMV equivalents to the HCMV UL128 and UL131 genes that contribute to virus tropism, and the presence of the equivalent of HCMV US11, which down-regulates classical MHC class I molecules. There may be additional genes or deletions that are critical, and these need to be identified to design an HCMV that elicits the same type of T-cell responses.

The use of HCMV as a vaccine may carry some risk because CMV can be a pathogen (Griffiths et al. 2015). HCMV infection down-regulates antigen presentation so it is possible for HCMV-infected individuals to be superinfected. Therefore, volunteers from the >50% of humans who are naturally chronically infected with HCMV would be tested first. This will eliminate the risk of introducing CMV for the first time, but the modifications in HCMV needed to make it equivalent to RhCMV68-1 may cause problems. Potential issues might be circumvented by the insertion of suicide genes into the vaccine HCMV vector so that a drug treatment could remove the vaccine virus after response priming if needed.

An alternative approach will be to use other vectors or DNA plasmids to elicit the desired T-cell responses (e.g., HLA-E-restricted responses). It is known, for instance, that *Mycobacterium tuberculosis* (Mtb) and bacille Calmette–Guérin (BCG) naturally prime HLA-E-restricted T-cell responses in humans (Joosten et al. 2010). This appears to be dependent on antigen processing in, and T-cell priming by, Mtb-infected macrophages (Grotzke et al. 2009). Therefore, a BCG vector is attractive, although it has the disadvantage that the recombinant gene or genes are only a tiny part of the whole Mtb genome and so it may not be efficient in stimulating T-cell responses specific for the inserted HIV gene. However, once more is known about how these responses are primed it may be possible to use other approaches.

Is a Human CD8 T-Cell Vaccine Possible?

CONCLUDING REMARKS

Conventional approaches to a CD8⁺ T-cell-stimulating vaccine have so far failed to generate T-cell responses that are capable of protecting and clearing SIV or HIV infection. In contrast, an RhCMV-based SIV vaccine does this in half the monkeys subsequently challenged with SIV. It is highly likely that CD8⁺ T cells are responsible for that protection. Those CD8⁺ T cells have unusual features, being restricted by MHC class II or MHC-E. The exceptional breadth of these effector memory T-cell responses likely contributes to their effectiveness, but their target specificity could also be critical. The MHC-E-rather than the MHC-II-restricted T cells seem most likely to be responsible for the SIV control, but this needs to be shown experimentally. Then these findings will need translating into an HIV vaccine that is effective. Because not all monkeys are protected by the RhCMV vaccine, it is possible that incomplete protection could also be a problem in humans. Even so, this is the most exciting and promising of all HIV vaccine approaches at present. Once fully understood, this type of vaccine could also have potential in several other contexts, including infections and cancer.

COMPETING INTEREST STATEMENT

The author has no conflicts of interest.

ACKNOWLEDGMENTS

I thank Persephone Borrow and Louis Picker for many discussions on the topics reviewed here. A.J.M. is funded by the National Institutes of Health (NIH) Center for HIV AIDS Vaccine Immunology Immunogen Discovery Grant No. UM1 AI 00645-02 and the Medical Research Council Programme Grant MR/K012037/2.

REFERENCES

- Amara RR, Patel K, Niedziela G, Nigam P, Sharma S, Stappans SI, Montefiori DC, Chenareddi L, Herndon JG, Robinson HL, et al. 2005. A combination DNA and attenuated simian immunodeficiency virus vaccine strategy provides enhanced protection from simian/human

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- immunodeficiency virus-induced disease. *J Virol* **79**: 15356–15367.
- Bachmann MF, Kundig TM, Hengartner H, Zinkernagel RM. 1997. Protection against immunopathological consequences of a viral infection by activated but not resting cytotoxic T cells: T cell memory without “memory T cells”? *Proc Natl Acad Sci* **94**: 640–645.
- Barouch DH, Kunstman J, Kuroda MJ, Schmitz JE, Santra S, Peyerl FW, Krivulka GR, Beaudry K, Lifton MA, Gorgone DA, et al. 2002. Eventual AIDS vaccine failure in a rhesus monkey by viral escape from cytotoxic T lymphocytes. *Nature* **415**: 335–339.
- Barouch DH, Alter G, Broge T, Linde C, Ackerman ME, Brown EP, Borducchi EN, Smith KM, Nkolola JP, Liu J, et al. 2015. Protective efficacy of adenovirus/protein vaccines against SIV challenges in rhesus monkeys. *Science* **349**: 320–324.
- Buchbinder SP, Mehrotra DV, Duerr A, Fitzgerald DW, Mogg R, Li D, Gilbert PB, Lama JR, Marmor M, Del Rio C, et al. 2008. Efficacy assessment of a cell-mediated immunity HIV-1 vaccine (the Step Study): A double-blind, randomised, placebo-controlled, test-of-concept trial. *Lancet* **372**: 1881–1893.
- Carrington M, Walker BD. 2012. Immunogenetics of spontaneous control of HIV. *Annu Rev Med* **63**: 131–145.
- Casimiro DR, Wang F, Schleif WA, Liang X, Zhang ZQ, Tobery TW, Davies ME, McDermott AB, O'Connor DH, Fridman A, et al. 2005. Attenuation of simian immunodeficiency virus SIVmac239 infection by prophylactic immunization with DNA and recombinant adenoviral vaccine vectors expressing Gag. *J Virol* **79**: 15547–15555.
- Flynn KJ, Belz GT, Altman JD, Ahmed R, Woodland DL, Doherty PC. 1998. Virus-specific CD8⁺ T cells in primary and secondary influenza pneumonia. *Immunity* **8**: 683–691.
- Folgori A, Capone S, Ruggeri L, Meola A, Sporeno E, Ercole BB, Pezzanera M, Tafi R, Arcuri M, Fattori E, et al. 2006. A T-cell HCV vaccine eliciting effective immunity against heterologous virus challenge in chimpanzees. *Nat Med* **12**: 190–197.
- Fukazawa Y, Lum R, Okoye AA, Park H, Matsuda K, Bae JY, Hagen SI, Shoemaker R, Deleage C, Lucero C, et al. 2015. B cell follicle sanctuary permits persistent productive simian immunodeficiency virus infection in elite controllers. *Nat Med* **21**: 132–139.
- Griffiths P, Baraniak I, Reeves M. 2015. The pathogenesis of human cytomegalovirus. *J Pathol* **235**: 288–297.
- Grotzke JE, Harrieff MJ, Siler AC, Nolt D, Delepine J, Lewinsohn DA, Lewinsohn DM. 2009. The Mycobacterium tuberculosis phagosome is a HLA-I processing competent organelle. *PLoS Pathog* **5**: e1000374.
- Haigwood NL, Walker CM. 2011. Commissioned paper: Comparison of immunity to pathogens in humans, chimpanzees, and macaques. In *Chimpanzees in biomedical and behavioral research: Assessing the necessity* (ed. Altevogt PD, et al.). National Academies Press, Washington, D.C.
- Hammer SM, Sobieszczyk ME, Janes H, Karuna ST, Mulligan MJ, Grove D, Koblin BA, Buchbinder SP, Keefer MC, Tomaras GD, et al. 2013. Efficacy trial of a DNA/rAd5 HIV-1 preventive vaccine. *N Engl J Med* **369**: 2083–2092.
- Hansen SG, Vieville C, Whizin N, Coyne-Johnson L, Siess DC, Drummond DD, Legasse AW, Axthelm MK, Oswald K, Trubey CM, et al. 2009. Effector memory T cell responses are associated with protection of rhesus monkeys from mucosal simian immunodeficiency virus challenge. *Nat Med* **15**: 293–299.
- Hansen SG, Piatak M Jr, Ventura AB, Hughes CM, Gilbride RM, Ford JC, Oswald K, Shoemaker R, Li Y, Lewis MS, et al. 2013a. Immune clearance of highly pathogenic SIV infection. *Nature* **502**: 100–104.
- Hansen SG, Sacha JB, Hughes CM, Ford JC, Burwitz BJ, Scholz I, Gilbride RM, Lewis MS, Gilliam AN, Ventura AB, et al. 2013b. Cytomegalovirus vectors violate CD8⁺ T cell epitope recognition paradigms. *Science* **340**: 1237874.
- Hansen SG, Wu HL, Burwitz BJ, Hughes CM, Hammond KB, Ventura AB, Reed JS, Gilbride RM, Ainslie E, Morrow DW, et al. 2016. Broadly targeted CD8⁺ T cell responses restricted by major histocompatibility complex E. *Science* **351**: 714–720.
- Haynes BF, Gilbert PB, McElrath MJ, Zolla-Pazner S, Tomaras GD, Alam SM, Evans DT, Montefiori DC, Karnasuta C, Sutthent R, et al. 2012. Immune-correlates analysis of an HIV-1 vaccine efficacy trial. *N Engl J Med* **366**: 1275–1286.
- Haynes BF, Shaw GM, Korber B, Kelsoe G, Sodroski J, Hahn BH, Borrow P, McMichael AJ. 2016. HIV–host interactions: Implications for vaccine design. *Cell Host Microbe* **19**: 292–303.
- Jiang H, Canfield SM, Gallagher MP, Jiang HH, Jiang Y, Zheng Z, Chess L. 2010. HLA-E-restricted regulatory CD8⁺ T cells are involved in development and control of human autoimmune type 1 diabetes. *J Clin Invest* **120**: 3641–3650.
- Jin X, Bauer DE, Tuttleton SE, Lewin S, Gettie A, Blanchard J, Irwin CE, Safrit JT, Mittler J, Weinberger L, et al. 1999. Dramatic rise in plasma viremia after CD8⁺ T cell depletion in simian immunodeficiency virus-infected macaques. *J Exp Med* **189**: 991–998.
- Joosten SA, van Meijgaarden KE, van Weeren PC, Kazi F, Geluk A, Savage ND, Drijfhout JW, Flower DR, Hanekom WA, Klein MR, et al. 2010. Mycobacterium tuberculosis peptides presented by HLA-E molecules are targets for human CD8 T cells with cytotoxic as well as regulatory activity. *PLoS Pathog* **6**: e1000782.
- Kim HJ, Verbinnen B, Tang X, Lu L, Cantor H. 2010. Inhibition of follicular T-helper cells by CD8⁺ regulatory T cells is essential for self tolerance. *Nature* **467**: 328–332.
- Klenerman P, Oxenius A. 2016. T cell responses to cytomegalovirus. *Nat Rev Immunol* **16**: 367–377.
- Liu J, O'Brien KL, Lynch DM, Simmons NL, La Porte A, Riggs AM, Abbink P, Coffey RT, Grandpre LE, Seaman MS, et al. 2009. Immune control of an SIV challenge by a T-cell-based vaccine in rhesus monkeys. *Nature* **457**: 87–91.
- Liu MK, Hawkins N, Ritchie AJ, Ganusov VV, Whale V, Brackenridge S, Li H, Pavlicek JW, Cai F, Rose-Abrahams M, et al. 2013. Vertical T cell immunodominance and epitope entropy determine HIV-1 escape. *J Clin Invest* **123**: 380–393.
- Lopez-Botet M, Angulo A, Guma M. 2004. Natural killer cell receptors for major histocompatibility complex class I

- and related molecules in cytomegalovirus infection. *Tissue Antigens* **63**: 195–203.
- Martins MA, Tully DC, Cruz MA, Power KA, Veloso de Santana MG, Bean DJ, Ogilvie CB, Gadgil R, Lima NS, Magnani DM, et al. 2015. Vaccine-induced simian immunodeficiency virus-specific CD8⁺ T-cell responses focused on a single Nef epitope select for escape variants shortly after infection. *J Virol* **89**: 10802–10820.
- McMichael AJ, Picker LJ. 2017. Unusual antigen presentation offers new insight into HIV vaccine design. *Current Opin Immunol* **46**: 15–81.
- McMichael AJ, Gotch FM, Noble GR, Beare PA. 1983. Cytotoxic T-cell immunity to influenza. *N Engl J Med* **309**: 13–17.
- McMichael AJ, Borrow P, Tomaras GD, Goonetilleke N, Haynes BF. 2010. The immune response during acute HIV-1 infection: Clues for vaccine development. *Nat Rev Immunol* **10**: 11–23.
- Met O, Buus S, Claesson MH. 2003. Peptide-loaded dendritic cells prime and activate MHC-class I-restricted T cells more efficiently than protein-loaded cross-presenting DC. *Cell Immunol* **222**: 126–133.
- Powers C, Fruh K. 2008. Rhesus CMV: An emerging animal model for human CMV. *Med Microbiol Immunol* **197**: 109–115.
- Purbhoo MA, Irvine DJ, Huppa JB, Davis MM. 2004. T cell killing does not require the formation of a stable mature immunological synapse. *Nat Immunol* **5**: 524–530.
- Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, Kaewkungwal J, Chiu J, Paris R, Premisri N, Namwat C, de Souza M, Adams E, et al. 2009. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. *N Engl J Med* **361**: 2209–2220.
- Rickinson AB, Moss DJ. 1997. Human cytotoxic T lymphocyte responses to Epstein–Barr virus infection. *Annu Rev Immunol* **15**: 405–431.
- Riddell SR, Reusser P, Greenberg PD. 1991. Cytotoxic T cells specific for cytomegalovirus: A potential therapy for immunocompromised patients. *Rev Infect Dis* **13**: S966–S973.
- Rose NF, Marx PA, Luckay A, Nixon DF, Moretto WJ, Donahoe SM, Montefiori D, Roberts A, Buonocore L, Rose JK. 2001. An effective AIDS vaccine based on live attenuated vesicular stomatitis virus recombinants. *Cell* **106**: 539–549.
- Schmitz JE, Kuroda MJ, Santra S, Sasseville VG, Simon MA, Lifton MA, Racz P, Tenner-Racz K, Dalesandro M, Scallion BJ, et al. 1999. Control of viremia in simian immunodeficiency virus infection by CD8⁺ lymphocytes. *Science* **283**: 857–860.
- Sharp PM, Hahn BH. 2011. Origins of HIV and the AIDS pandemic. *Cold Spring Harb Perspect Med* **1**: a006841.
- Webster RG, Askonas BA. 1980. Cross-protection and cross-reactive cytotoxic T cells induced by influenza virus vaccines in mice. *Eur J Immunol* **10**: 396–401.
- Wilkinson TM, Li CK, Chui CS, Huang AK, Perkins M, Liebner JC, Lambkin-Williams R, Gilbert A, Oxford J, Nicholas B, et al. 2012. Preexisting influenza-specific CD4⁺ T cells correlate with disease protection against influenza challenge in humans. *Nat Med* **18**: 274–280.
- Wiseman RW, Karl JA, Bohn PS, Nimityongsul FA, Starrett GJ, O'Connor DH. 2013. Haplessly hoping: Macaque major histocompatibility complex made easy. *ILAR J* **54**: 196–210.
- Yap KL, Ada GL. 1978. The recovery of mice from influenza virus infection: Adoptive transfer of immunity with immune T lymphocytes. *Scand J Immunol* **7**: 389–397.

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Andrew J. McMichael

Cold Spring Harb Perspect Biol 2018; doi: 10.1101/cshperspect.a029124 originally published online December 18, 2017

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