

## Chapter 16. HIV and AIDS pathogenesis

Acquired immune deficiency syndrome (AIDS) was discovered in 1981 as an infectious disease of homosexual men transmitted by sexual intercourse. The human immunodeficiency virus (HIV) was soon discovered and shown to be the causative agent, and additional risk groups and modes of infection were identified. The virus could also be transmitted by blood transfusions and contaminated needles. HIV infects a small population of helper T cells and the helper T cell count decreases, at first slowly, and then, after a variable length of time, precipitously. The patient typically loses weight, has chronic diarrhea and is susceptible to multiple infections and cancers.

There are many puzzling aspects of HIV pathogenesis within the framework of the conventional viewpoint that HIV kills helper T cells directly. An alternative concept is that HIV triggers autoimmunity, and was first published by Ziegler and Stites<sup>237</sup>, by Andrieu et al.<sup>238</sup>, and by Shearer<sup>239</sup>, based on the fact that there is serological cross-reactivity between HIV components and MHC class II. There is however no evidence of anti-MHC class II antibodies in AIDS patients.

My colleagues and I have developed an autoimmunity theory of AIDS pathogenesis in the context of the symmetrical network theory, including the resolution of the I-J paradox described in chapter 13. In this chapter I will first outline the autoimmunity model, then discuss the ways in which it accounts better for many aspects of the disease than the conventional model, in which HIV kills helper T cells directly. The model is based on the idea that there is an MHC class II image centre-pole also in humans, analogous to the I-J centre-pole in mice, and that this is susceptible to autoimmunity triggered by HIV.

### AIDS pathogenesis models involving autoimmunity

Our network model of HIV pathogenesis was developed in two stages. The first stage appeared in papers published from 1988 to 1991, and involved autoimmunity triggered by a combination of allogeneic lymphocytes and

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<sup>237</sup> J. L. Ziegler and D. P. Stites (1986) Hypothesis: AIDS is an autoimmune disease directed at the immune system and triggered by a lymphotropic retrovirus. *Clin. Immunol. Immunopathol.*, 41, 305-313.

<sup>238</sup> J. M. Andrieu, P. Even and A. Venet (1986) AIDS and related syndromes as a viral-induced autoimmune disease of the immune system. *AIDS Res.* 2, 163-174.

<sup>239</sup> G. M. Shearer (1986) AIDS: An autoimmune pathologic model for the destruction of a subset of helper T lymphocytes. *Mount Sinai J. Med.* 53, 609-615.

HIV.<sup>240</sup> An improved version of this theory was published in 1994<sup>241</sup> and 1995<sup>242</sup>, when an additional postulate was added. The model was kept reasonably simple, or minimal, by concomitantly dispensing with the earlier postulated obligatory role for allogeneic lymphocytes. The added postulate was that HIV-specific helper T cells are preferentially infected with HIV. This was a plausible postulate, since HIV has MHC-mimicking determinants, and helper T cells are selected to recognize MHC class II antigens. In other words, it was postulated that, in addition to CD4, CXCR4 and CCR5, which are known to be receptors for HIV, the antigen-specific receptor of HIV-specific helper T cells is a coreceptor for infection by HIV. HIV would then bind specifically to at least some helper T cell receptors. This postulate was validated by Douek et al. in 2002.<sup>243</sup>

HIV is not identical to MHC class II, so we would expect it to bind to the V regions of the receptors of some but not all helper T cells. Douek et al. showed that helper T cells that specifically recognise HIV are preferentially infected. These helper T cells can be assumed also to be stimulated by HIV to proliferate. The postulated stimulation by HIV of HIV-specific T cells to proliferate is consistent with an observed increase in the fraction of HIV-specific T cells following HIV infection. Strains of HIV that are recognized by the largest number of helper T cells then preferentially replicate. Helper T cell clones that are specific for the largest number of HIV virions are preferentially stimulated. There is then co-selection of some HIV variants and the corresponding HIV-specific helper T cells.

A diverse population of similar elements is called a “quasi-species”. This term was originally applied to related macromolecules in an origin of life scenario<sup>244</sup>. HIV is a rapidly mutating virus, and a consequently diverse array of viruses can be referred to as a quasi-species.

As described in chapter 13, helper T cells are highly diverse, but are nevertheless generally selected to have some affinity for self MHC class II. In

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<sup>240</sup> G. W. Hoffmann, M. Grant and T. A. Kion (1991) An Idiotypic Network Model of AIDS Immunopathogenesis. *Proc. Nat. Acad. Sci. (USA)*, 88, 3060-3064 (1991).

<sup>241</sup> G. W. Hoffmann (1994) Co-selection in Immune Network Theory and in AIDS Pathogenesis. *Immunology and Cell Biology*, 72, 338-346, 1994.

<sup>242</sup> G. W. Hoffmann (1995) The T Cell Receptor and AIDS Pathogenesis. *Scand. J. Immunol.*, 41, 331-337.

<sup>243</sup> Douek D. C., J. M. Brenchley, M. R. Betts, D. R. Ambrozak, B. J. Hill, Y. Okamoto, J. P. Casazza, J. Kuruppu, K. Kunstman, S. Wolinsky, Z. Grossman, M. Dybul, A. Oxenius, D. A. Price, M. Connors and R. A. Koup. (2002) HIV preferentially infects HIV-specific CD4<sup>+</sup> T cells. *Nature* 417, 95-98.

<sup>244</sup> Eigen M., J. McCaskill and P. Schuster (1988) The molecular quasi-species. *J. Phys. Chem.* 92: 6881-6891.

the symmetrical network theory there is a population of suppressor T cells that are selected according to the criterion of being able to recognise, stimulate and be idiotypically stimulated by as many helper T cells as possible. This suppressor T cell population is also quasi-species, with the similarity in its idiotypes being the result of the uniform selection criterion for all of these cells. There is co-selection of helper T cells and these suppressor T cells. The suppressor T cell quasi-species of idiotypes is a family that comprises an internal image of MHC class II in the context of the helper T cells that are selected to have some complementarity to MHC class II. The internal image quasi-species of T cell idiotypes is a central regulating element of the system. In mice it is known as I-J, and practically it can be detected in mice using well defined anti-I-J antibodies.

HIV and the suppressor T cell population are then subject to the same selection pressure, namely to recognise as many helper T cell idiotypes as possible (Figure 16-1). Those HIV variants that have complementarity to the largest number of helper T cell V regions would then infect helper T cells in the largest numbers, and these HIV variants proliferate preferentially. The helper T cells with receptors that bind HIV are preferentially stimulated and proliferate. There is co-selection of the helper T cell population and HIV. The suppressor T cells and HIV are subject to the same selection pressure, namely to have complementarity to as many helper T cells as possible. The consequence of being subject to the identical selection pressure is that the HIV quasi-species and the suppressor T cell quasi-species converge in shape space, meaning that with time the average shape of the HIV population looks more and more like the average shape of the suppressor T cell V regions. This is a natural selection process that takes place in the context of the repertoire of helper T cell idiotypes. There is also an evolutionary process for the helper T cell repertoire. In the presence of HIV, helper T cells are selected that recognize not only MHC class II and the suppressor T cell quasi-species, but also the HIV quasi-species (Figure 16-2). As the HIV quasi-species and the suppressor T cell quasi-species converge in shape space, the anti-HIV antibodies produced cross-react with the V regions of the suppressor T cell quasi-species, and this central regulating element of the system comes under attack by those antibodies. The suppressor T cell centre-pole subsequently collapses, and the original set of helper T cells is no longer adequately stimulated and co-selected

Figure 16-1. Model of HIV pathogenesis. Helper T cells are selected to have some complementarity to MHC class II. Suppressor T cells are selected such that their V regions have complementarity to as many helper T cell V regions as possible, as shown also in Figure 13-2. In addition to CD4, CXCR4 and CCR5, the T cell receptor of HIV-specific helper T cells is a coreceptor for HIV. HIV variants that are recognized by the largest number of helper T cells are preferentially produced and also stimulate these helper T cells to proliferate. In other words, there is co-selection of helper T cells and HIV variants. There is also co-selection of helper T cells and suppressor T cells. Since HIV and the suppressor T cells are subject to the same selection criterion, there is a natural selection process in which HIV proteins and the V regions of the suppressor T cells converge in shape space. Anti-HIV immunity then becomes specific for the suppressor T cell centre-pole. Immunity against this central regulating element of the system results in the collapse of the system. The suppressor T cells no longer adequately stimulate and regulate the helper T cells, that then are free to inappropriately help immune responses against self components, and autoimmunity ensues. The autoimmunity includes cytotoxic T cell activity against CD4 helper T cells. Adapted from G. W. Hoffmann (1994) *Immunol. and Cell Biol.* 72, 338-346.

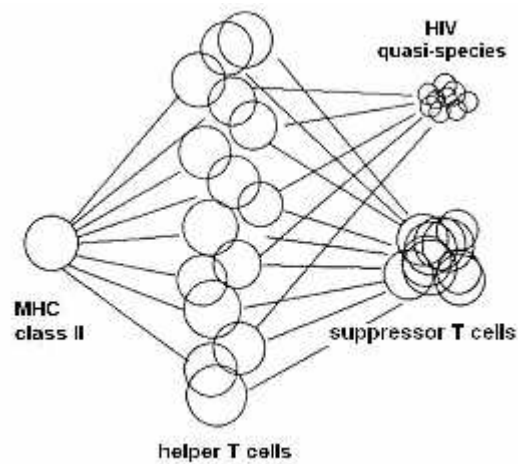
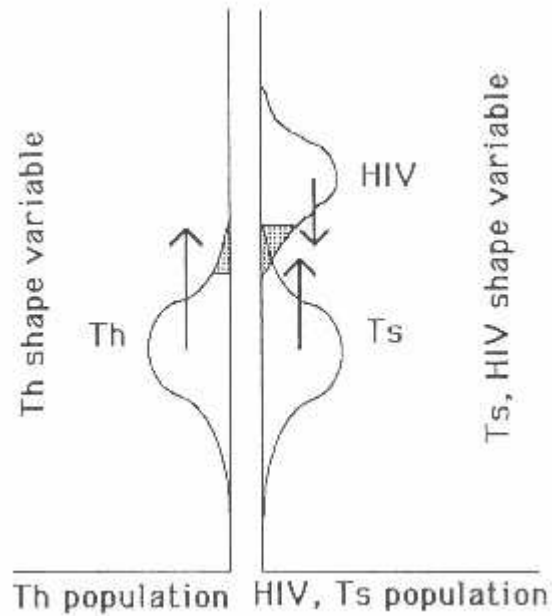


Figure 16-2. Convergence in shape space of the suppressor T cell centre-pole quasi-species and the HIV quasi-species, resulting from the suppressor T cells (Ts) and HIV being subject to the same selection criterion. Points that are close on each of the vertical axes correspond to closely related shapes. Points on the left axis are complementary to corresponding points on the right axis. There is an evolution of the helper T cell (Th) population, with the preferential selection of helper T cell clones that recognize both the suppressor T cell population and HIV (shaded). These helper T cells cause the preferred proliferation of the corresponding HIV and Ts (also shaded), such that the centre of the distribution of HIV moves downward and the centre of the Ts distribution moves upwards with time. Meanwhile the centre of the Th population moves upwards. From G. W. Hoffmann (1995) *Scand. J. Immunol.* 41, 331-337.



by the suppressor T cell centre-pole. A collapse of the helper T cell population also ensues, as evidenced by the well-known fall in the helper T cell count that occurs as an HIV infected person progresses to AIDS. The original helper and suppressor T cell repertoires play a role in self tolerance, and as they collapse, the remaining helper cells are no longer properly regulated by the suppressor T cells, and autoimmunity ensues. The autoimmunity may be largely T cell mediated. Rapid helper T cell depletion correlates with the presence of cytotoxic T cells specific for normal helper T cells.<sup>245</sup>

### What the theory can do

We now consider both findings that are supportive of autoimmunity models in general, and phenomena that support our model more specifically. I am not aware of any phenomena that contradict the model.

1. Some strains of HIV can kill some lymphocytes in vitro, but this ability does not correlate with pathogenicity in vivo. Thus a strain of HIV that kills chimpanzee cells in vitro does not cause disease in the chimpanzee.<sup>246</sup> A different HIV strain that does not kill human cells in vitro causes a rapid loss of helper T cells in an experimental mouse, that has an implanted immune system consisting of human T cells.<sup>247</sup> These findings are consistent with autoimmunity models in general, as opposed to HIV directly mediated cytotoxicity models.

2. Instead of a correlation between HIV disease and the ability of the virus to kill cells, there is a correlation between HIV disease and HIV induced autoimmunity. Autoimmunity against T cells is seen in HIV-infected humans.<sup>248,249</sup> Autoimmunity can also be seen in a monkey model of HIV,

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<sup>245</sup> Grant, M. D., Whaley, M. D., Mayne, A., Hoffmann, G. W. and Ansari A. A. (1996) Similar abnormalities of idiotype and immunoglobulin light chain expression and of cell-mediated cytotoxicity in HIV-infected humans and simian immunodeficiency virus (SIV)-infected rhesus macaques. *Immunology and Cell Biology*, 74, 38-44.

<sup>246</sup> M. Watanabe, D. J. Ringler, P. N. Fultz, J. J. MacKey, J. E. Boyson, C. G. Levine, and N. L. Letvin (1991) A chimpanzee-passaged human immunodeficiency virus isolate is cytopathic for chimpanzee cells but does not induce disease. *J. Virol.*, 65, 3344-3348.

<sup>247</sup> D. E. Mosier, R. J. Gulizia, P. D. MacIsaac, B. E. Torbett, J. A. Levy. (1993) Rapid loss of CD4+ T cells in human-PBL-SCID mice by noncytopathic HIV isolates. *Science* 260, 689-692.

<sup>248</sup> J. M. Zarlring, J. A. Ledbetter, J. Sias, P. Fultz, J. Eichberg, G. Gjerset and P. A. Moran (1990) HIV-infected humans but not chimpanzees have circulating cytotoxic T lymphocytes that lyse uninfected CD4+ cells. *J. Immunol.* 144, 2992-2998.

caused by the HIV-like virus SIV (simian immunodeficiency virus). SIV causes an AIDS-like disease in some monkeys (macaques), but not in others (African green monkeys). It likewise causes autoimmunity in the macaques but not in the African green monkeys.<sup>250</sup> The same correlation is seen with HIV in humans and chimpanzees; HIV causes both autoimmunity and AIDS in humans,<sup>251,252</sup> but neither autoimmunity nor AIDS in chimpanzees.<sup>248</sup> These striking correlations strongly support the concept that AIDS is primarily an autoimmune disease.

3. Several HIV proteins have serologically demonstrated MHC and immunoglobulin mimicking properties. This could be interpreted as consistent with HIV inducing autoimmunity. On the other hand, experimental HIV vaccines consisting of HIV recombinant proteins do not induce autoimmunity, so any autoimmunity theory based on similarity between HIV proteins and MHC molecules needs to be able to explain this aspect. Our model involves a change with time in HIV, so that anti-HIV immunity can zero in on the suppressor T cell centre-pole. Recombinant protein vaccines have a fixed form and cannot evolve as HIV does in our model. This explains the inability of the vaccines to induce autoimmunity, and leaves our model, with a dynamic role for evolving HIV virions, intact. The inability of conventional experimental HIV vaccines to induce autoimmunity is therefore evidence against a simpler autoimmunity model, but is compatible with our dynamic model.

4. There is a long, unpredictable, latent period following infection, prior to the onset of the clinical symptoms of AIDS. During this period immunity to HIV has presumably not yet converged to become synonymous with immunity to the centre-pole. Our interpretation is that full-blown AIDS occurs when that convergence takes place, immunity is directed at the centre-pole, and regulation by the suppressor T cell centre-pole collapses.

5. There are differences between AIDS in Africa and in the United States, including differences in the distribution between sexes, that may be due to genetic factors in the people, differences in the virus, or both. The evolution of the virus within a given individual involves the interaction between a "swarm"

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<sup>249</sup> M. D. Grant, F. M. Smaill, K. Laurie and K. L. Rosenthal (1993) Changes in the cytotoxic T cell repertoire of HIV-1 infected individuals: relationship to disease progression. *Viral Immunol.* 6, 85-95.

<sup>250</sup>P. Fultz, personal communication.

<sup>251</sup> M. D. Grant, F. M. Smaill, K. L. Rosenthal (1994) Cytotoxic T-lymphocytes that kill autologous CD4+ lymphocytes are associated with CD4+ lymphocyte depletion in HIV-1 infection. *J. AIDS* 7, 571-579.

<sup>252</sup> R. B. Stricker, T. M. McHugh, D. J. Moody, W. J. W. Morrow, D. P. Stites, M. A. Schuman and J. A. Levy. (1987) An AIDS-related cytotoxic autoantibody reacts with a specific antigen on stimulated CD4+ T cells. *Nature* 327, 710-713.

of virus mutants and the diverse population of HIV-specific helper T cell V regions. This constitutes a non-linear selection process, the outcome of which can depend sharply on initial conditions. There is also a higher level, non-linear selection process of the HIV species present within populations of people (as opposed to selection within individuals). Both HIV and the centre-pole change with time in each individual during these selection processes, as does the population of helper T cell V regions. The point of convergence in space shape for HIV and the centre-pole is likely to depend very strongly on the initial conditions, and it may be similar for two individuals, if they have similar backgrounds of antigenic exposures, and one of them is infected by the other. At the population level, this could account for stable differences between HIV in Africa and HIV in the United States.

6. HIV can cause an otherwise rare cancer, Kaposi's sarcoma, but this occurs almost exclusively in homosexuals. This finding can be plausibly related to the immune surveillance theory of the origin of cancer. According to this theory, we have many more cancers than we ever notice, and the immune system "deals with them" as they arise. A collapse of the immune system, due to autoimmunity against the centre-pole, could have any one of several modes, corresponding to which of various key idiotypes are attacked and eliminated first. The various modes of collapse would result in susceptibility to various complications of AIDS. Kaposi's sarcoma is one of the complications, and would correspond to a particular mode of collapse. Various opportunistic infections would accompany other modes of collapse. The fact that AIDS related Kaposi's sarcoma is seen primarily in AIDS in homosexuals would be a result of sensitivity of the mode of collapse to initial conditions, including the HIV mutants, and the spectrum of specificities of helper and suppressor T cells. If AIDS related Kaposi's sarcoma occurred first in homosexuals, that mode of collapse could propagate exclusively in homosexuals, since they are typically infected from each other, and similar initial conditions could cause the same mode of collapse.

7. The viral load is particularly high in the lymph nodes. This would be due to the fact that a large number of replicating helper T cells are to be found in the lymph nodes, and the HIV-specific helper T cells are the ones that produce virus.

8. The fraction of HIV infected cells increases gradually during disease progression. During acute infection the viral load reaches a very high level, but nevertheless fails to infect many peripheral blood lymphocytes. We ascribe the fact that most helper T cells do not become infected to the fact that it is the HIV-specific T cells are infected. At the same time, the simultaneous selection of HIV and complementary HIV-specific T cells results in a gradually increasing fraction of the T cells being infectable and thus infected.



9. If a monkey has been infected with an attenuated strain of SIV, it can be difficult or impossible to infect it also with a second strain of SIV<sup>253</sup>. One might have expected that the immune system is weakened by a first virus, so that it could be more readily infected with a second virus, but this is not the case. We say that the monkey is resistant to superinfection by other strains of SIV. This could be ascribed to SIV-induced immunity, but such immunity should be more specifically directed against the first strain than the second strain. On the contrary, protection can be provided against a pathogenic strain of SIV by immunization with a less pathogenic strain if the less pathogenic strain persists.<sup>254</sup> This can be understood in terms of co-selection taking place that involves primarily the helper T cells and the first virus, and because this virus is there first, its selection dominates. There is a positive feedback loop involving the first virus, and while there is also the potential for a positive feedback loop involving the second virus, the initial conditions favour the first virus. The mutual positive selection of the first SIV strain and of T cells specific for that strain, results in the T cell population becoming tailored (selected) to preferentially recognise the first strain of SIV, such that these T cells are infected by, and favour the production of, the first strain. The dominating strain customizes its T cell environment to suit itself, and a second strain of SIV cannot readily compete. Similarly, chimpanzees that are infected with one strain of HIV are resistant to superinfection with another strain of HIV<sup>255</sup>. Further support for these ideas comes from the finding that SIV infected monkeys have expanded populations of clonally restricted CD4<sup>+</sup> T cells, and evidence that these CD4<sup>+</sup> T cells may be SIV-specific.<sup>256</sup>

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<sup>253</sup> F. Titti, L. Sernicola, A. Geraci, G. Panzini, S. Di Fabio, R. Belli, F. Monardo, A. Borsetti, M. T. Maggiorella, M. Koanga-Mogtomo, F. Corrias, R. Zamarchi, A. Amadori, L. Chieco-Bianchi, P. Verani (1997) Live attenuated simian immunodeficiency virus prevents super-infection by cloned SIVmac251 in cynomolgus monkeys. *J. Gen. Virol.* 78 2529-39.

<sup>254</sup> G. A. Mackay, Z. Liu, D. K. Singh, M. S. Smith, S. Mukherjee, D. Sheffer, F. Jia, I. Adany, K. H. Sun, S. Dhillon, W. Zhuge and O. Narayan (2004) Protection against late-onset AIDS in macaques prophylactically immunized with a live simian HIV vaccine was dependent on persistence of the vaccine virus. *J. Immunol.* 173, 4100-4107.

<sup>255</sup> R. Shibata, C. Siemon, M. W. Cho, L. O. Arthur, S. M. Nigida Jr., T. Matthews, L. A. Sawyer, A. Schultz, K. K. Murthy, Z. Israel, A. Javadian, P. Frost, R. C. Kennedy, H. C. Lane and M. A. Martin MA (1996) Resistance of previously infected chimpanzees to successive challenges with a heterologous intraclade B strain of human immunodeficiency virus type. *J. Virol.* 70, 4361-4369.

<sup>256</sup> Z. W. Chen, Y. Shen, Z. Kou, C. Ibegbu, D. Zhou, L. Shen, P. Morrison, C. Bogle, H. M. McClure, A. J. Nahmias, P. K. Sehgal and N. L. Letvin (2000) Prolonged dominance of clonally restricted CD4<sup>+</sup> T cells in macaques infected with simian immunodeficiency viruses *J. Virol.* 74, 7442-7450.

10. HIV strains vary widely in their infectivity for various CD4 T cell lines, with differences of up to 100,000 fold.<sup>257</sup> This can be plausibly ascribed to differences in the T cell receptors of the different lines. There are also big differences between different HIV strains infecting peripheral blood lymphocytes from a given donor.<sup>258</sup> This too is consistent with something other than only CD4 being important for infectivity, plausibly the specific receptors of T cells that are selected by MHC molecules. The concept that the selection of the T cell repertoire by MHC molecules influences susceptibility to infection and hence to HIV disease is also supported by the finding of Flores-Villanueva et al. that some HLA haplotypes are associated with rapid progression to AIDS, while others are associated with slow progression.<sup>259</sup> That study points to a role for MHC class I molecules in susceptibility and resistance, and is a reminder that both MHC class I and MHC class II are important in the selection of the T cell repertoire.

11. Only a small fraction of the T cells are infected, yet the entire helper T cell population declines to a very low level. This would not be the case if being infected were synonymous with being killed, as in the conventional model, with direct killing of helper T cells by HIV. In the autoimmunity model the demise of the suppressor T cell centre-pole results firstly in cytotoxic T cell immunity against helper T cells, and secondly in the normally selected repertoire of helper cells no longer being so effectively co-selected by the centre-pole.

12. The level of helper T cells in a patient does not correlate with the amount of HIV. Some patients with very low helper T cell counts have barely detectable HIV. Similarly, antivirals can deplete HIV levels 1000 fold, with little change in helper T cell levels. If HIV were directly killing the helper T cells, we could expect such a large reduction in HIV levels to be accompanied by a substantial increase in helper T cell levels. This difficulty does not arise in the autoimmunity model, since HIV is not responsible for killing the T cells.

13. Serious disease follows rather than precedes the development of the induction of immunity to HIV. HIV-specific immunity does not protect infected individuals against disease. This is consistent with autoimmunity causing the disease.

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<sup>257</sup> M. W. Cloyd and B. E. Moore (1990) Spectrum of biological properties of human immunodeficiency virus (HIV-1) isolates. *Virology*. 174, 103-116.

<sup>258</sup> L. M. Williams and M. W. Cloyd (1991) Polymorphic human gene(s) determines differential susceptibility of CD4 lymphocytes to infection by certain HIV-1 isolates. *Virology*. 184, 723-728.

<sup>259</sup> P. O. Flores-Villanueva, H. Hendel, S. Caillat-Zucman, J. Rappaport, A. Burgos-Tiburcio, S. Bertin-Maghit J. A. Ruiz-Morales, M. E. Teran, J. Rodriguez-Tafur, J. F. Zagury (2003) Associations of MHC ancestral haplotypes with resistance/susceptibility to AIDS disease development. *J. Immunol.* 170, 1925-1929.

14. The T cell repertoire is typically skewed following infection of an individual with HIV. Some V regions are present in much larger quantities than prior to the infection, while other V regions are present in much smaller amounts. This would be expected if there is autoimmunity against T cell idiotypes.<sup>260</sup>

The following remarkable experimental findings were obtained by Tracy Kion<sup>261</sup> and Abdulaziz Al-Fahim<sup>262</sup> in my laboratory:

15. Alloimmune mice make anti-HIV antibodies, even though they have never been exposed to HIV.<sup>261</sup> This can be rationalized in the context of our model. The alloimmune mice make anti-I-J antibodies that cross-react with HIV because of the similarity between HIV and the suppressor T cell centre-pole. Accordingly, at least some anti-I-J antibodies are predicted to react with HIV.<sup>263</sup>

16. Mice of a strain that is considered to be a model for the human autoimmune disease *systemic lupus erythematosus* (SLE), namely the MRL-*lpr/lpr* mouse, make anti-HIV antibodies, even though the mice have never been exposed to HIV.<sup>261</sup> This finding constitutes a link between the production of anti-HIV antibodies that are plausibly directed against the and autoimmunity.

17. MRL-*lpr/lpr* mice also make anti-anti-self ("MHC class II image") antibodies, even though they have not been immunized with allogeneic lymphocytes.<sup>261</sup> Anti-anti-self antibodies are likewise present in aged C57BL/6 mice,<sup>262</sup> that also develop autoimmunity.<sup>264</sup> This suggests that autoimmunity involves both MHC class II image and anti-MHC class II image T cells. There are many similarities between AIDS and SLE, and the model formulated for AIDS pathogenesis may also have relevance for lupus.

18. There are anti-anti-self antibodies also in alloimmune mice, as described already in chapter 14. Together with the anti-anti-self antibodies present in MRL-*lpr/lpr* autoimmune mice, this again suggests that the type of system breakdown seen in the MRL-*lpr/lpr* mouse has features in common with AIDS. In chapter 14 we concluded that alloimmune sera contain three populations, namely anti-foreign MHC, antibodies that are an image of self MHC, and

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<sup>260</sup> Confirmed prediction.

<sup>261</sup> T. A. Kion and G. W. Hoffmann (1991) Anti-HIV and anti-anti-MHC antibodies in alloimmune and autoimmune mice. *Science* 253, 1138-1140.

<sup>262</sup> A. Al-Fahim and G. W. Hoffmann (1998) Second symmetry in the BALB/c-C57BL/6 (B6) system, and anti-anti-self antibodies in aging B6 mice. *Immunol. and Cell Biol.* 76, 27-33.

<sup>263</sup> Prediction.

<sup>264</sup> Y. Hatashi, M. Utsuyama, C. Kurashima, K. Hirokawa. (1989) Spontaneous development of organ-specific autoimmune lesions in aged C57BL/6 mice. 78, 120-126.

anti-(foreign MHC class II image) antibodies. Alloimmunity and autoimmunity may both involve the production of antibodies or cellular immunity along the MHC class II—anti-MHC class II—MHC class II image—anti-MHC class II image axis of shape space.

### **Predictions of the co-selection model of HIV pathogenesis**

The co-selection model makes some interesting, experimentally testable predictions. It predicts that there is a change with time in both the virus quasi-species and the helper T cell quasi-species within a given individual, such that with time each is progressively recognized by a larger fraction of the other. This can be tested by a longitudinal study that involves isolating both HIV and CD4 helper T cells at various time points following infection, then stimulating the CD4 helper T cells obtained at the various time points with HIV obtained at the various time points. The model predicts that the strongest stimulation would be observed using the latest HIV isolates together with the latest CD4 helper T cell preparations.<sup>265</sup>

Another prediction is that there should be a relationship between the degree of HLA-relatedness between infector and infectee and the rate of progression to AIDS. The model suggests that a high degree of HLA-relatedness should correlate with rapid disease progression.<sup>266</sup> Prior to infection two HLA-identical individuals would have centre-poles that are more similar than those of HLA-unrelated individuals. Following infection of the first one, HIV and the centre-pole of that individual evolve towards each other. HIV then infects the second one, and due to its evolution in the first one, it is closer to the centre-pole of the second one than it would be in an HLA-unrelated individual.

### **Towards a preventive AIDS vaccine**

The above idiotypic network model of HIV pathogenesis leads to a novel HIV vaccine concept. The network model firstly explains why the conventional HIV vaccine approach does not work, and it provides a rationale for a preventive AIDS vaccine consisting of MHC class II from a different species. We will see that this vaccine concept is also supported by a considerable amount of experimental evidence that has already been published. But first we review the conventional approach for developing vaccines to pathogens.

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<sup>265</sup> Prediction

<sup>266</sup> Prediction

### **AIDS vaccines that don't work**

Conventional vaccines to most infectious agents are able to eliminate the pathogen completely from the body. Such vaccines typically consist of an inactivated or weakened version of the pathogen, or components of the pathogen. The immune system makes antibodies against the pathogen, and there is memory associated with the immune response, such that when the immunized person is infected with the pathogen, there is a secondary immune response and the pathogen is quickly eliminated from the system. HIV vaccines involving this approach differ from vaccines to other pathogens in two respects. The immunized person (or macaque monkey in the case of an SIV vaccine) does not typically completely eliminate the virus on infection; it only keeps it at a low level compared with the level that is typical in unimmunized infected individuals. Secondly, this limited protection is specific for the particular SIV or HIV used in the immunization; the protection does not extend to other SIV or HIV variants. Since HIV is a very diverse virus, we need a vaccine that provides broad protection.

### **A vaccine paradox**

In 1991 E. J. Stott published the paradoxical finding that macaque monkeys can be protected from SIV infection by immunization with human cells, without any SIV being present in the inoculum.<sup>267</sup> Four macaques were vaccinated with inactivated SIV-infected killed human cells (group A) and four with uninfected cells (group B). When the animals were challenged with live virus given intravenously, three macaques in group A and two in group B were protected. There was no significant difference in the amount of protection induced by the two vaccines. While the uninfected vaccine did not induce any detectable antibodies to SIV, the mean titre of antibodies to the human cells in all of the immunized animals was highly correlated with the probability of being protected. Subsequently Arthur *et al.* immunized two macaques with human MHC class II molecules, namely HLA-DR, and found they were protected against SIV infection that had been passaged in human cells. These findings were paradoxical in the context of the standard point of view that a vaccine works by inducing the production of antibodies against the pathogen.

### **Related findings**

In the same year Tracy Kion and I reported that mice immunized with lymphocytes of another strain make antibodies that bind to the HIV proteins

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<sup>267</sup> Stott E. J. (1991) Anti-cell antibody in macaques. *Nature* 353: 393.

gp120 and p24, even though they have never been exposed to the virus.<sup>268</sup> A plausible interpretation in the context of extended second symmetry (chapter 14) and the above model of HIV pathogenesis is that the allo-antibodies involved are anti-I-J antibodies, with HIV determinants being similar to I-J. This interpretation implies that I-J in mice is similar to an analogous centre-pole in humans. Then selection of HIV variants in the human population results in HIV becoming similar to the centre-pole in humans.

Wang *et al.* found that alloimmunization induces HIV-specific suppressor factors and resistance to HIV infection in women<sup>269</sup>. In a recent paper the same group found that even unprotected sexual intercourse between regular heterosexual partners results in an alloimmune response, that is associated with the inhibition of *in vitro* HIV infectivity<sup>270</sup>. This finding supports the notion that the induction of immunity to foreign MHC is safe. Spear *et al.* subsequently reported that antibodies to MHC alloantigens can mediate lysis and neutralization of HIV-1<sup>271</sup>.

Further strong evidence for a connection between alloimmunity and protection from HIV infection comes from the Nairobi perinatal transmission study<sup>272</sup>. HIV-infected mothers and their infants were tested for HLA discordance at the A, B and C loci. The mother and infant share loci inherited from the mother, so the study tested whether vertical (mother to child) transmission is associated with the degree of discordance between maternal and paternal MHC class I antigens. There was an approximately 2.5-fold increased risk for each MHC class I matched allele.

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<sup>268</sup> Kion T. A., and G. W. Hoffmann (1991) Anti-HIV and anti-anti-MHC antibodies in alloimmune and autoimmune mice. *Science* 253, 1138-1140.

<sup>269</sup> Y. Wang, L. Tao, E. Mitchell, C. Bravery, P. Berlingieri, P. Armstrong, R. Vaughan, J. Underwood and T. Lehner (1999) Allo-immunization elicits CD8+ T cell derived chemokines, HIV suppressor factors and resistance to HIV infection in women. *Nature Med.* 5, 1004-1009.

<sup>270</sup> B. Peters, T. Whittall, K. Babaahmady, K. Gray, R. Vaughan and T. Lehner (2004) Effect of heterosexual intercourse on mucosal alloimmunizations and resistance to HIV-1 infection. *Lancet* 363, 518-524.

<sup>271</sup> G. T. Spear, G. G. Olinger, M. Saifuddin and H. M. Gebel. (2001) Human antibodies to major histocompatibility complex alloantigens mediate lysis and neutralization of HIV-1 primary isolate virions in the presence of complement. *J. Acquir. Immune Defic. Syndr.* 26, 103-110.

<sup>272</sup> K. S. MacDonald, J. Embree, S. Njenga, N. J. Nagelkerke, I. Ngatia, Z. Mohammed, B. H. Barber, J. Ndinya-Achola, J. Bwayo and F. A. Plummer (1998) Mother-child class I HLA concordance increases perinatal human immunodeficiency virus type I transmission. *J. Infect. Dis.* 177, 551-556.

Leith *et al.* found that infertile women undergoing leukocyte immunotherapy through alloimmunization make antibodies capable of neutralizing HIV *in vitro*<sup>273</sup>. Furthermore, women who have recurrent spontaneous abortions make anti-HLA antibodies that neutralize HIV *in vitro*.

These findings suggest that a vaccine strategy for the prevention of HIV infection can be based on immunization with foreign MHC class II.

### **Theory of a novel HIV vaccine method that uses foreign MHC class II**

A theoretical basis for the above results is needed, in order that we have a more complete framework for the further development of a preventive vaccine. The theory that follows links the pathogenesis model described above to the above experiments on prevention of HIV infection by alloimmunity and xenoimmunity, and is expected to lead to a more focused pursuit of this approach.

The conclusion that was originally derived from the above autoimmunity model of HIV pathogenesis was that we should endeavour to eliminate HIV-specific T cells, since they are the “factories” that produce the virus. That can however be expected to be extremely difficult, given the diversity of the helper T cells and the diversity of the virus. Surprisingly, the model can be reinterpreted in a way that explains how alloimmunity and xenoimmunity can be protective.

Helper T cells that recognise both HIV and suppressor cell idiotypes play a key role in the convergent selection process. When HIV infection occurs, those clones are especially selected, and they lead to the selection of suppressor T cell clones with V regions that resemble the dominant HIV variants. The average shape of the HIV quasi-species thus undergoes selection in virus carriers to resemble the average shape of the suppressor T cell idiotypes. If however, at the time of the exposure to HIV, the average shape of the suppressor T cell idiotypes in an individual differs sufficiently from the average shape of the HIV with which an individual is infected, the population of helper T cells with which HIV interacts may be effectively distinct from the population of helpers interacting with the suppressor T cells. Then there are potentially two separate co-selection processes, and the convergence may not occur. A novel vaccine based method for the prevention of HIV infection accordingly involves immunization with foreign MHC class II, that causes a change in the repertoire of helper T cells, and a resultant change in the repertoire of co-selected suppressor T cells.

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<sup>273</sup> J. G. Leith, D. A. Clark, T. J. Matthews, K. L. Rosenthal, M. A. Luscher, B. H. Barber and K. S. MacDonald. (2003) Assessing human alloimmunization as a strategy for inducing HIV type 1 neutralizing anti-HLA responses. *AIDS Res. Hum. Retrovir.* 19, 957-965.

A complicating factor in this approach emerges however from a study by Arthur et al.<sup>274</sup> They initially immunized two macaques four times with human MHC class II, and two weeks after the final immunization the animals were challenged with SIV that had been propagated in human cells. Both animals were fully protected against this challenge, including being negative by recovery of virus and by PCR. Hence immunity to xenogeneic MHC class II was fully protective in this case (sterilizing immunity). The macaques were however subsequently boosted by another immunization with human MHC class II, and two weeks later were challenged with SIV that had been propagated in macaque cells. They both became infected. In the context of the above theory, the failure of the vaccine in the second case can be attributed to SIV and MHC molecules in the challenge preparation stimulating a set of helper T cells other than the set that was selected by the vaccine. This set of helpers select a different set of suppressors. There is a positive feedback loop for this second set of helper and suppressor T cells, and the second positive feedback loop competes against the positive feedback loop of the vaccine-specific helper T cells and their corresponding co-selected suppressor T cells. It appears likely that the vaccine-specific feedback loop can be made dominant by additional activating doses of the vaccine applied at time points that are close to time points of possible HIV exposure, namely within hours. The mechanism that is envisaged to result in the first feedback loop, involving the foreign MHC class II of the vaccine, prevailing over the second feedback loop is that of antigenic competition, as described in chapter 10. The time window for the activating doses to be effective can be determined experimentally, initially in the macaque and SIV model.

The vaccine will not need to contain live cells or dead cells. The main component in the vaccine, that causes the required shift in the T cell repertoires, is foreign MHC class II molecules. The foreign MHC class II can in principle be xenogeneic or allogeneic MHC class II, or an altered version of either human or xenogeneic MHC class II. A single allogeneic MHC class II molecule, that is present in some members of the population, would not be so good, because some individuals will normally have that molecule as a self antigen, and hence immunization of those individuals with it cannot be expected to cause the required change in the immune system.

An attractive option is for the vaccine to contain xenogeneic MHC class II molecules from a species that is more phylogenetically different from both humans and macaque monkeys, than humans are phylogenetically different from macaque monkeys. For example, the vaccine can consist of mouse MHC class II. On account of the phylogenetic relationships, the immune

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<sup>274</sup> L. O. Arthur, J. W. Bess Jr., R. G. Urban, J. L. Strominger, W. R. Morton, D. L. Mann, L. E. Henderson and R. E. Benveniste. (1995) Macaques immunized with HLA-DR are protected from challenge with simian immunodeficiency virus. *J. Virol.* 69: 3117-3124.



response of a macaque to mouse MHC class II can be expected to be similar to that of a human to the mouse MHC class II. Hence the described vaccine based method can be expected to prevent both SIV infection in macaques and HIV infection in humans. The same agent can then go directly from an animal trial in macaques to clinical trials in humans, enabling optimally rapid development of this MHC class II based method for the prevention of HIV infection.

The initial injection with MHC class II would be given in an adjuvant in order to induce a strong IgG response with memory. In unpublished work we have found that mice immunized intramuscularly with a single dose of only 3 micrograms of human MHC class II in alum make a strong IgG response. Since the amount of antigen needed in such immunizations is essentially independent of the size of the immunized vertebrate, this result bodes well for the cost of production of the vaccine being low. I envisage that the initial immunizations will be xenogeneic MHC class II in alum, while the activating doses will not include an adjuvant.

Someone using this method for protection against HIV infection would need to have a supply of the activating doses on hand, for use on each occasion when he or she engages in unsafe sex. Potential users of the method include people who are not yet in stable monogamous relationships and tourists.

This vaccine based method for the prevention of infection with HIV is for people who are not already infected with HIV. For people who are HIV positive the concept of activating doses close to times of possible exposure to HIV does not make any sense, and it is possible that using the vaccine would be counterproductive. In a worst case scenario, it is conceivable if not probable that widespread use of the vaccine by HIV positive persons could lead to the emergence of HIV variants that are immune to the vaccine.

The main obstacle to the development of an HIV vaccine has been the great diversity of the virus. In this vaccine based method that difficulty is overcome by the vaccine being something that is quite different from the virus, and the antibodies induced by the vaccine do not need to bind to the virus.

How then is HIV eliminated when this vaccine is used? It is notable that HIV is not a highly infectious virus. Healthy people can have unprotected sex multiple times with HIV positive partners without become infected, a risky behaviour that is of course not recommended. If HIV were a highly infectious virus the fraction of HIV positive people could be expected to be much higher than it is. In chapter 17 I suggest that the relatively low infectivity of HIV is related to serum IgG being a quasi-species that mimics the human equivalent of I-J, while natural IgM has complementarity to the human equivalent of I-J, and therefore natural IgM also has some complementarity to HIV. In this model IgM plays an important role in clearing HIV from people who are transiently infected and do not seroconvert, and thus plays a key role in the low infectivity of HIV. When the vaccine is used, the feedback loop involving foreign

MHC class II specific helper T cells and the corresponding suppressor T cells is activated, rather than HIV-specific helper T cells and the corresponding suppressor T cells. Then the IgM with complementarity to HIV clears the virus without leaving any record of the infection. So the idea is that natural IgM clears the virus without seroconversion to the production of anti-HIV IgG antibodies occurring. In the absence of the vaccine the helper T cells are more strongly HIV-specific. HIV causes more activation of the HIV-specific helper T cells, there is a higher probability of these helper T cell becoming infected with HIV, and there is more HIV production, leading to the production of large amounts of HIV and then seroconversion.

This foreign MHC class II based vaccine method for the prevention of HIV infection is of course not the ultimate goal of HIV vaccine research. But in the continuing absence of success for more conventional vaccines, it has the potential to be a component in the our efforts to slow and eventually halt the epidemic. In addition, evidence that this approach works would be evidence of progress towards understanding HIV pathogenesis, and consequently may lead to further advances.