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Theoretical Article

Towards an HIV vaccine based on immune network theory

Geoffrey W. Hoffmann[1,*], Sybille Muller[2] and Heinz Kohler[3]

[1]Network Immunology Inc., Vancouver B.C. V6S 1Z7, Canada. [2]Immpheron Inc., Lexington, KY 40509, [3]Department of Microbiology, Immunology & Molecular Genetics, University of Kentucky College of Medicine, Lexington, KY 40506, USA

ABSTRACT

Immune network theory is a framework for understanding the adaptive immune system. In this paper we briefly review important aspects of the symmetrical immune network theory, and describe how it leads to a possible HIV vaccine based on a monoclonal antibody called 1F7. A central aspect of the theory is a process called co-selection, namely the mutual selection of members from two diverse populations that have complementary shapes.

KEYWORDS: immune network theory, co-selection, IJ paradox, Oudin-Cazenave paradox, repertoire freeze, 1F7 monoclonal antibody, HIV vaccine

ABBREVIATION

BnAb - broadly neutralizing anti-HIV antibody

INTRODUCTION

In the 1960's work on idiotypic interactions began in rabbits. Oudin pioneered the concept by showing that it was possible to induce antibodies against rabbit antibodies in outbred rabbits [1, 2]. Subsequently Potter and colleagues induced anti-idiotypic antibodies in mice against murine plasmacytoma antibodies [3]. They identified a group of anti-phosphorylcholine (PC) antibodies that shared common (idiotypic) determinants using anti-sera against these antibodies raised in a different mouse strain. These antibodies became useful reagents in characterizing specific antibodies and their genetic control of expression [4, 5]. In 1972 Cosenza and Kohler used antiidiotypic antibodies to suppress the effector function of anti-PC antibodies to lyse PC-coated red blood cells in the hemolytic plaque assay [6] and also to suppress the anti-PC response [7]. The immune response was induced by immunizing mice with the PC antigen. Similar experiments in the anti-arsonate system were reported by Nisonoff and colleagues [8].

Partly on the basis of this early work, in 1974 Niels Jerne translated several puzzling phenomena about immune system regulation into the grand vision that the immune system resembles the brain in that it is a network, and that we would only be able to understand it if we managed to understand it as a network [9]. He was most concerned with phenomena that did not make sense in the context of the clonal selection theory, without taking into account idiotypic network interactions. Chief among these was the then recently discovered phenomenon of suppression, in which some lymphocytes specifically and actively suppress others [10]. How could one lymphocyte specifically suppress another unless the V regions of the former recognize the V regions of the latter? Additional phenomena he cited as supportive of his network perspective included low dose tolerance [11], antigenic competition [12] and the fact that antibodies in the immune response to different epitopes on an antigen can share idiotypes [2].

*Corresponding author
hoffmann@networkimmunologyinc.com

Antiidiotypic antibodies can be used as very specific reagents to detect and characterize antibodies and also to manipulate the immune response in adult animals [7, 8] and in neonatal mice to suppress the development of idiotype expressing B-cell clones for months [13, 14]. While these data demonstrated how powerful antiidiotypic antibodies are to manipulate the immune response, the "Idiotypic Network Theory" of Jerne lacked essential experimental support to show that idiotype and antiidiotype are part of a normal immune response and may play a role in the regulation of the response. Support of co-existing idiotype and antiidiotype during an immune response was provided in 1974 by Kluskens and Kohler [15] and confirmed later [16].

Symmetry in idiotypic interactions

The concept of symmetry pervades many aspects of physics. Kohler was the first to postulate symmetry also in interactions between idiotypes and antiidiotypes [17], and he made the case that this leads to the possibility of a functional network [18]. With antigen-specific antibodies denoted Ab1 and antiidiotypic antibodies denoted Ab2, and so on to Ab3 and Ab4, he envisaged Ab2 being induced that may down-regulate the Ab1 response, and if Ab2 mimics the antigen it may also augment the Ab1 response by further inducing Ab3 that is functionally equivalent to Ab1. Experiments in rabbits demonstrated the possibility of an idiotypic cascade going as far as Ab4, in which Ab1 binds to Ab2 and Ab4, while Ab2 binds to Ab1 and Ab3 [19-21].

In 1975 Hoffmann published a symmetrical idiotypic network model that includes roles for the two main players in the immune system, B cells and T cells [22]. The model includes three types of symmetrical interactions, namely stimulation, inhibition and killing. Symmetrical stimulation is postulated to follow from activation of lymphocytes involving the cross-linking of receptors. Symmetrical inhibition is ascribed to specific T cell factors ("tabs") that block complementary lymphocyte receptors, and symmetrical killing was ascribed to IgM and IgG antibodies that kill lymphocytes with complementary receptors. A mathematical model showed that these postulates can lead to the existence of four stable states for any antigen, namely a virgin state, an immune state, a suppressed state and an anti-immune state. Surprisingly, this could be done in a model with only two variables, representing the amounts of antigen-specific and antiidiotypic lymphocytes respectively [23]. An animal in the virgin state for an antigen has not been exposed to the antigen. In the immune state there is an elevated level of antigen-specific lymphocytes and a lower amount of antiidiotypic lymphocytes, while in the suppressed state there is an elevated level of both antigen-specific and antiidiotypic lymphocytes.

The theory was based on the existence of suppressor T cells that are antigen-specific [10, 24]. Such suppressor T cells were shown in the 1970s to express CD8 [25, 26], and contrary to a widely held misconception they are not the same as the more recently described Treg cells that express CD4 and CD25 [27, 28], for which the effector function is not antigen-specific [29].

The impact of IJ on the symmetrical immune network theory

In 1976 two groups of leading immunologists reported that suppressor T cells [30] and suppressor tabs [31] express determinants that can be detected by "anti-IJ antibodies". Anti-IJ antibodies are antibodies that can be produced in certain allo-immunizations, and using many recombinant inbred strains of mice putative IJ gene(s) were mapped to within the MHC class II part of the mouse genome. Suppression was not well understood, but it was clearly important, so the discovery of this serological marker of suppressor T cells and of T cell derived antigen-specific molecules that mediated suppression was an exciting development.

After having mapped the IJ gene or genes to within the mouse MHC the next obvious step was to find the genes and sequence them. But in 1982 it emerged that there was no IJ gene or genes where it was expected on the basis of the mapping studies [32]. This was a shock. IJ was no fly by night phenomenon. About 1000 papers were published with IJ in the title, and a much larger number of publications contributed to IJ science. The absence of an IJ gene was a paradox and led to much consternation among those who had worked on suppressor T cells and suppressor tabs

that expressed IJ. Immunology was faced with a conflict between immunogenetics based on serology and immunogenetics based on DNA. DNA called the shots, and with time immunologists chose to reject not only all the data on IJ but also a much bigger library of data about classic suppressor T cells that express CD8 and about specific T cell factors, including suppressor tabs and helper tabs. The most complete version of immune network theory, which is based on suppressor T cells and on specific T cell factors, was also a casualty. However, we will see that the IJ paradox can be resolved in the context of immune network theory, in a way that leads to a new concept for an HIV vaccine. We will see that, as is so often the case in scientific quandaries, both sides can be right. There is no IJ gene, while IJ as a serologically defined entity exits.

"Co-selection" is a recurring theme in the symmetrical immune network theory [33]. Co-selection is mutual selection between complementary populations that can initially both be diverse populations, whereby one of the two populations typically becomes much less diverse with time. CD4 helper T cells in general are selected to have some affinity for MHC class II, and hence can be classified as "anti-self". Our model for IJ includes the idea that the helper T cells are also co-selected with CD8 suppressor cells that are then "anti-anti-self" and express serologically detectable IJ determinants as shown in Figure 1. The CD8 suppressor T cells are selected to have complementarity to as many CD4 helper T cells as possible, and the helper T cells are selected to have complementarity not only to MHC class II but also to the V regions of the CD8

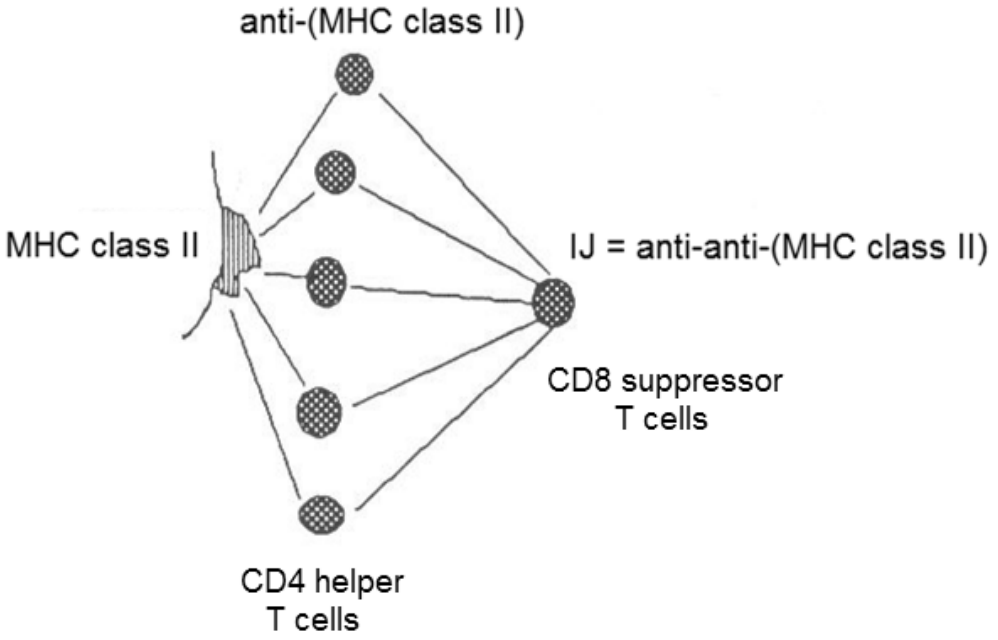

Figure 1. This figure is a model for the emergence of IJ determinants in the absence of allo-immunization. Helper T cells that express CD4 and have affinity for MHC class II are co-selected with classical suppressor T cells that express CD8 and are anti-anti-(self MHC class II). The suppressor T cells with affinity for the largest number of helper T cell V regions are preferentially selected, and the helper T cell clones shown here are selected not only on the basis of their V regions having affinity for MHC class II, but also on the basis of having V regions with affinity for suppressor T cell V regions. The suppressor T cells are thus indirectly selected via the helper T cells. This indirect selection explains the fact that there is no intrinsically designated IJ gene or genes. The sharp selection of IJ via co-selection means that IJ is a well-defined alloantigen that can stimulate an anti-IJ immune response. (Adapted from Hoffmann, G. W. 1994, Immunol. Cell Biol., 72, 338 with permission from Nature Publishing Group).

suppressor T cells that express IJ. This constraint results in IJ being a sharply defined and serologically detectable entity. IJ maps to the MHC region of the genome because IJ determinants are indirectly selected via helper T cell V regions that are in turn selected partially by MHC class II. The genes encoding V regions of T cells expressing IJ are normal T cell V region genes. No genes that specifically encode IJ are needed. Furthermore, not only MHC class II but all of the self antigens of a vertebrate may contribute to the selection of IJ, in which case IJ may play a central role in self-tolerance.

The antibodies in an A anti-B serum, where A and B are, for example, two strains of mice, are complementary to the antibodies in a B anti-A serum. This concept is known as "second symmetry" [34]. Using the Greek letter α as an abbreviation for "anti-", we can resolve the IJ paradox by postulating that an A anti-B serum contains AαB, AααA and AαααB antibodies, while a B anti-A serum contains BαA, BααB and BαααA antibodies, as shown in Figure 2. We have shown that the interactions between AαB, BαA, AααA and BααB exist as shown. The AααA and BααB antibodies are anti-anti-self, while the AαααB and BαααA antibodies are postulated to be anti-IJ^B and anti-IJ^A respectively. This model leads to the prediction that anti-IJ^B antibodies present in an A anti-B serum bind to BααB antibodies present in a B anti-A serum, and anti-IJ^A antibodies in a B anti-A serum bind to AααA antibodies present in an A anti-B serum. With regard to experiments to potentially confirm this prediction, we have shown that serum enriched in AααA antibodies can be obtained by absorbing an A anti-B serum with B strain lymphocytes, and serum enriched in BααB antibodies can be obtained by absorbing a B anti-A serum with A strain lymphocytes [34].

Resolution of the Oudin-Cazenave paradox

Figure 3 shows a co-selection model of how the immune system reacts to an antigen or pattern Ag with two features A and B. The symbol α is again an abbreviation for "anti-". The interactions between clones are symmetrical. The αA and αB clones are stimulated by ααA/ααB clones and vice versa. The clones with receptors that have affinity for the antigen are diverse, and there is

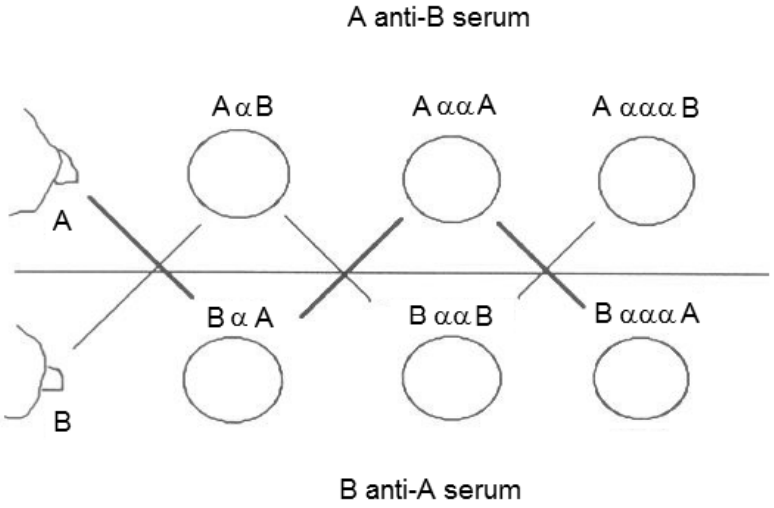

Figure 2. The specific antibodies present in an A anti-B allo-antiserum are believed to be complementary to those that are present in a B anti-A serum. This set of relationships is called "second symmetry". The Greek letter α is an abbreviation for "anti-". The αA and αB antibodies are the usual alloantibodies. The sera have been shown to also contain ααA and ααB, which are also known as anti-anti-self antibodies [34]. According to our model for IJ the A anti-B serum also contains αααB antibodies that are anti-IJ^B and the B anti-A serum contains αααA antibodies that are anti-IJ^A. These are each predicted to bind to anti-anti-self antibodies in the converse antiserum.

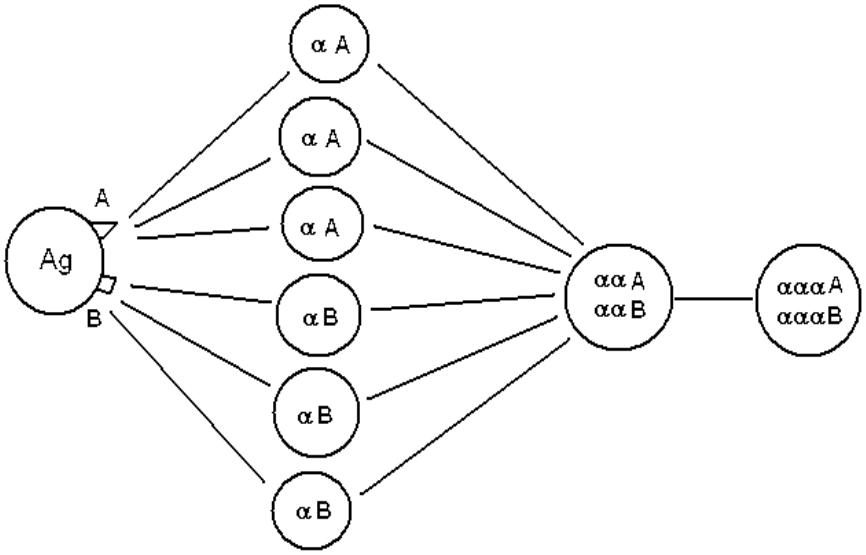

Figure 3. This figure is a co-selection model that accounts for the Oudin-Cazenave paradox. The antigen has two antigenic determinants A and B. These determinants stimulate clones that are αA and αB respectively. There is co-selection of these clones with clones that are both ααA and ααB. Due to the co-selection process, the latter clones become homogeneous, possibly monoclonal, and become a stronger antigen than the antigen itself. The ααA/ααB population stimulates αααA/αααB, some of which are αA, some are αB, and some of which are neither αA nor αB, and all of which bind to ααA/ααB antiidiotypic antibodies.

co-selection involving firstly αA and αB clones and secondly ααA/ααB clones. Clones that are only ααA or only ααB are not selected as strongly as those that are both ααA and ααB. The criterion for the selection of ααA/ααB clones is that they recognize as many αA and αB clones as possible. This criterion together with the diversity of the αA and αB clones and the non-linear autocatalytic co-selection process results in the selection of the homogeneous ααA/ααB "internal image" of the antigen. This homogeneous population emerges as a stronger "antigen" than the Ag itself, and stimulates αααA/αααB clones. Any clone that has complementarity to the ααA/ααB clones is αααA/αααB, so the nomenclature becomes ambiguous, with αααA/αααB including αA and αB clones and clones that have complementarity to ααA/ααB but are neither αA nor αB. This model explains the Oudin-Cazenave paradox, in which antibodies to different parts of an antigen share an idiotype, and some antibodies expressing the idiotype do not bind to the antigen at all [2]. The mutual selection of (a) diverse αA and αB clones and (b) less diverse ααA/ααB clone or clones sharply defines a polarization of the network that is associated with the antigen. The αααA/αααB clones which are neither αA nor αB are generalizations of the Ag pattern along the ααA/ααB-αααA/αααB shape space axis.

Emergence of AIDS and the discovery of HIV

AIDS (Acquired Immunodeficiency Syndrome) was first recognized in the United States as a disease in 1981. Now with 40 million people infected with the Human Immunodeficiency virus (HIV-1 and HIV-2) world-wide, Sub-Saharan Africa accounts now for 29 million of people living with HIV of AIDS [35]. Thereby AIDS has shifted from an orphan disease as seen in the 1980s, and described at first in the Western world, to a global threat. Despite the advent of powerful antiviral drugs there is no cure except for a very few resistant to HIV, and no method for the complete eradication of the virus in infected individuals [36].

Looking for a vaccine began soon after the discovery of HIV by Montagnier 1983 [37], and

the introduction of screening tests by the Gallo group [38]. For instance, the core protein p24 was chosen by Salk for one of the first clinical trials in vaccine development [39]. Later on massive efforts were undertaken to use the recombinant HIV envelope protein gp160, and its parts gp120 and gp41, respectively, as well as peptides from the hyper variable region of gp120 for vaccine development, but have failed as well [40, 41]. Induction of neutralizing antibodies to gp120 did not protect against the emerging escape variants of HIV in AIDS patients [42].

The lack of an AIDS vaccine is not entirely due to lack of efforts and resources. The reason that HIV evades vaccination resides in the nature of this fast mutating retrovirus. HIV has mustered several strategies to spoil vaccine effects that lie in the high frequency of viral escape variants by changing the composition of its envelope protein, and using different receptors for entry into the host's cell [43], outsmarting the immune response. HIV-infection can be also seen as an "autoimmune" disease that affects the very cells that are important for the host's immune response [44-46].

Therefore it is important to continue to look for approaches to develop passive and active (protective) vaccines in order to curb the world wide threat of HIV infection. In this review some considerations on how to approach a vaccine solution for HIV are laid out.

Discovery and properties of the monoclonal antibody 1F7

As the idiotype network concept could provide tools to regulate the humoral immune response to HIV-infection new anti-Id antibodies were needed. Such antibodies would have to be different from those described in the original Jerne model [9]. The anti-Id for inducing protection against HIV-1 infection would meet these criteria: 1) to recognize B-cells producing broadly neutralizing antibodies against different virus clades; 2) the recognized idiotope would have to not interfere with the antigen binding site (anti-Id of Ab2 alpha type). 3) the anti-Id should bind to B-cells producing broadly neutralizing antibodies in an outbreed population, i.e. humans. To produce an anti-Id meeting these criteria the typical protocol of using monoclonal antibodies as Ab1 had to be changed. Muller *et al.* [47] used IgG from a serum pool of HIV-1 infected humans (HIVIG) to produce and screen hybridomas. The 1F7 hybridoma clone produced antibodies meeting the criteria of an anti-Id reacting with antibodies against different HIV-1 proteins from a pool of infected individuals but not with sera from normal individuals. This unique property of 1F7 prompts one of us (Kohler) to expand the classification of anti-Id beyond Ab2 alpha [48], Ab2 beta [49] and Ab2 gamma [50] by coining the term Ab2 delta (see Table 1) for 1F7 type antiidiotypes.

Surveys of sera from normal and HIV-1 infected individuals have shown that about 73% of HIV-1 positive sera are recognized by 1F7 and none of negative sera reacted with 1F7 [47]. 1F7 also reacted with neutralizing human monoclonal antibodies [47]. Interestingly, sera from SIV macaques also react with 1F7. The therapeutic utility of 1F7 was tested in infected macaques, based on the hypothesis that 1F7 could suppress the restricted and dominant expression of antibodies that fail to neutralize SIV [51, 52]. When SIV-1 infected macaques were treated with 1F7 new neutralizing antibodies were detected [53, 54]. These data show that the Ab2δ 1F7 detects human neutralizing and non-neutralizing antibodies in different viral HIV-1 proteins. Binding of 1F7 to B-cells can inhibit production of 1F7 positive antibodies, as inferred from the

Table 1. Types of antiidiotypic antibodies, Ab2.

Anti-Id Class	Property	Reference
Ab2 alpha	Regulatory anti-Id	Bona [48]
Ab2 beta	Internal antigen image anti-Id	Jerne [49]
Ab2 gamma	Near antigen binding site anti-Id	Kohler [50]
Ab2 delta	Non binding site, disease-specific and species-shared anti-Id	Kohler 2012, this review

macaque study [54, 55]. 1F7 also blocks T-cells from SIV-1 infected macaques [55]. It remains to be tested whether 1F7 can be used in a vaccine to induce immunity against HIV-1 infection. Below we describe a model based on co-selection that makes this plausible.

Wang *et al.* [56] identified a region (FR3-CDR3) on 3 human monoclonal antibodies directed to gp120 and p24, respectively, binding to 1F7, and have designed a peptide mimicking this region. The selection of the peptide was based on the molecular recognition theory [57], i.e., regions of inverse hydropathy between the variable sequence of 1F7 and the human monoclonal antibodies which are assumed to be involved in the idiotype-antiidiotype contacts were selected for the peptide design. Human anti-HIV serum antibodies from a variety of HIV infected individuals could bind to this peptide, indicating an auto-antiidiotypic humoral immune response to the 1F7 idiotype [56]. 1F7 is able to induce apoptosis of CD4+ and CD8+ cells derived from PBMC of HIV infected individuals [58]. 1F7 positive T cells are involved in cytotoxic effector cell function [55]. This adds further evidence for the biological role of 1F7 in AIDS. The HIV-1 infection related idiotype recognized by 1F7 is also expressed on antibodies to the env glycoprotein of SIV and SHIV-infected rhesus monkeys [54]. Since this is a widely shared idiotype/clonotype some cross-reactivity with antibodies directed to similar structures is not surprising.

Grant *et al.* found that the 1F7 idiotype is selectively expressed on CD5+ B cells and is elevated in chronic hepatitis C virus infections [59, 60]. It was concluded that distinct pathogens establishing chronic infection during strong humoral responses select antibodies along a common idiotypic axis of the immune network. More studies are necessary to decipher the action mechanism of 1F7 idiotype in chronic HIV infection.

Wang *et al.* [56] investigated the idiotope region of the neutralizing antibody that is recognized by 1F7. Using molecular recognition theory [57], regions of inverse hydropathy between the variable sequence of 1F7 and human monoclonal anti-HIV-1 antibodies were identified that are assumed to be involved in idiotype-antiidiotype contacts. A peptide from the proposed contact in FR3-CDR3 of the heavy chain sequence of human antibodies was synthesized. This inhibits the binding of 1F7 to human anti-HIV-1 antibodies which express the 1F7 idiotype. A survey of normal and HIV-1-infected sera revealed the presence of antibodies in infected sera which bind to the FR3-CDR3 peptide. The involvement of CDR3 in the 1F7 contact indicates that 1F7 detects mutations that are selected by HIV-1 antigens. It remains to be discovered how these CDR3 are important in the antibody response to HIV-1 infection.

Repertoire freeze

The antibodies in HIV-1 infected individuals are not typical. Normally, the immune response to bacterial and viral infection is highly diverse, reflecting a polyclonal B-cell response. Some antigens, such as allergens, selectively mount an IgE response, which is still polyclonal. In contrast, the antibody repertoire induced by HIV-1 infection is skewed [56]. Sera of HIV-1 infected individuals contain antibodies against the HIV-1 core protein (p24), HIV-1 envelope glycoprotein (gp120) and reverse transcriptase (RT). These antibodies against p24 and gp120 are characterized by a skewed light chain isotype expression that is unique in each serum and constant over several years independently of disease progression. These observations [52] led to the conclusion that the B-cell repertoire is selected early in infection and does not change during infection. This repertoire freeze [51] may play a significant role in the pathogenesis of the disease by limiting the recruitment of new uncommitted B cells to produce antibody against the evolving virus populations. This concept prompted the hypothesis of *Deceptive Imprinting* of the B-cell repertoire against the infecting viral clade/variant producing a clonal dominance of selected B-cells with the inability to adapt to emerging viral escape variants [51, 52, 61]. The potential impact of a dominant B-cell repertoire in HIV-1 infection on the development of protective and therapeutic vaccines has been discussed [62, 63].

Hoffmann described a co-selection model of HIV pathogenesis in 1994 [33]. The model was based on the postulate that HIV-specific T cells are preferentially infected. This postulate was validated by Douek *et al.* in 2002 [64]. In this model there

is co-selection of HIV and HIV-specific helper T cells, that is similar to the co-selection of normal CD4 helper T cells and normal CD8 suppressor T cells. In this model, HIV is subject to the same selection pressure as the CD8 suppressor T cells, namely to have affinity for as many helper T cell V regions as possible. Then there is convergence in the shapes of HIV and the suppressor T cell V regions, and with time immunity against HIV becomes immunity against the suppressor T cell V regions that are a central regulating element of the system.

In a related model, three coupled co-selection processes may account for repertoire freeze in HIV infection as shown in Figure 4. HIV preferentially infects helper T cells that are specific for HIV. These helper T cells are preferentially stimulated to proliferate, and the HIV strains that infect the largest number of helper T cells are preferentially produced. In other words, there is again co-selection of helper T cells with the HIV species that is most recognized by the helper T cells. Secondly, there is co-selection of anti-HIV helper T cells with anti-anti-HIV suppressor T cells. This two stage co-selection process for anti-anti-HIV suppressor T cells results in the suppressors being a particularly sharply defined and stable population. A third co-selection process involves the anti-anti-HIV suppressors and anti-HIV B cells, and is responsible for the anti-HIV B cells being an idiotypically stable population. Stimulation of the anti-HIV B cells with affinity to the co-selected anti-anti-HIV suppressor T cells is believed to be more important than stimulation of the B cells by HIV itself. Because of the stability of the co-selected anti-anti-HIV suppressor T cells, a stable population of anti-HIV B cells is selected and remains selected, independent of any mutational changes in HIV. In other words, the three co-selection processes shown here lead to repertoire freeze. The co-selected anti-HIV B cells secrete anti-HIV antibodies that tend to eliminate HIV, but they do so inefficiently because they are co-selected on the basis of affinity to anti-anti-HIV suppressor T cells, rather than affinity for circulating HIV itself. The V region of 1F7 plausibly mimics the V region of the anti-anti-HIV suppressor T cell population.

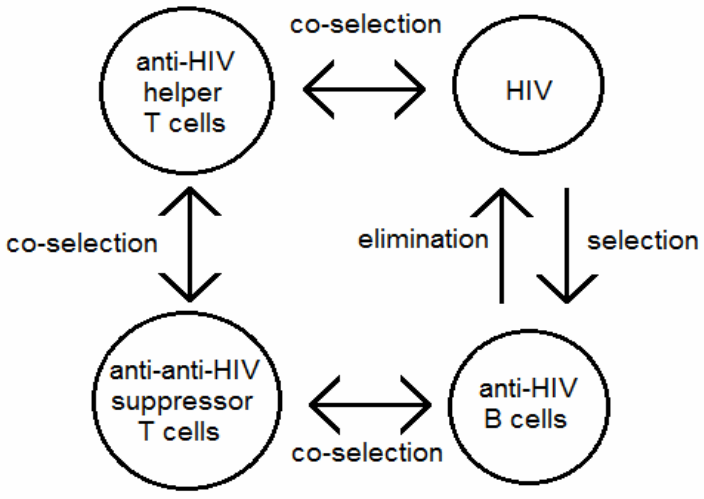

Figure 4. This figure shows how three coupled co-selection processes may account for repertoire freeze. These include co-selection of HIV with HIV-specific helper T cells, co-selection of HIV-specific helper T cells with anti-anti-HIV suppressor T cells, and co-selection of anti-anti-HIV suppressor T cells with anti-HIV B cells. The repertoire is frozen because a stable population of anti-anti-HIV suppressor T cells emerges, that is more important in stimulating HIV-specific B cells than various forms of HIV itself. The anti-HIV B cells secrete anti-HIV antibodies that tend to eliminate HIV.

Implications for HIV vaccine development

The co-selection model for the resolution of the Oudin-Cazenave paradox (Figure 3) is also a model for understanding 1F7 and HIV. In this case A and B are HIV antigens, αA and αB clones have V regions with some affinity for A and B respectively, 1F7 belongs to the antiidiotypic ααA/ααB category, and the αααA/αααB clones include B cells that secrete broadly neutralizing antibodies (BnAbs). Remarkably, 1F7 binds to six well-characterized BnAbs, namely b12, 2G12, VRC01, 2F5, 4E10 and Z13e1 [65]. That makes it a molecule of great interest for HIV vaccine development, since one of the major challenges has been to find an immunization method that induces broadly neutralizing antibodies. 1F7 has not previously been considered a candidate as an HIV vaccine because 1F7 binds outside the antigen-binding region of anti-HIV antibodies. According to this model, however, 1F7 is a potential HIV vaccine molecule because when given in appropriate immunogenic form it may induce αααA/αααB clones that include broadly neutralizing antibodies. In Kohler's nomenclature 1F7 is an Ab2 delta antibody.

The model for explaining the Oudin-Cazenave paradox and for explaining the relationship of 1F7 to broadly neutralizing antibodies leads to the following novel HIV vaccine concept. The vaccine consists of complexes of 1F7 and an HIV antigen. Complexes are produced by mixing 1F7 and the HIV antigen and using a cross-linking reagent, or by some other method that results in aggregation of proteins. Figure 5 shows how the vaccine is expected to work. Here Ab2 is 1F7. Ab2 stimulates Ab3 clones and Ag stimulates Ab1 clones. Complexes are used in order to prevent antigenic competition between 1F7 and the HIV antigen. There is then only one antigen consisting of both antiidiotypic and HIV determinants. There is co-selection of (a) some of the Ab3 clones and (b) some of the Ab1 clones with (c) those lymphocytes that are both Ab4 and Ab2. This Ab4/Ab2 population becomes the strongest antigen in the system, and it induces the Ab3 lymphocytes on the right that include B cells that secrete broadly neutralizing anti-HIV antibodies. The co-selected Ab3, Ab1 and Ab4/Ab2 populations of this figure are expected to be primarily T cells, since these populations would be most efficiently

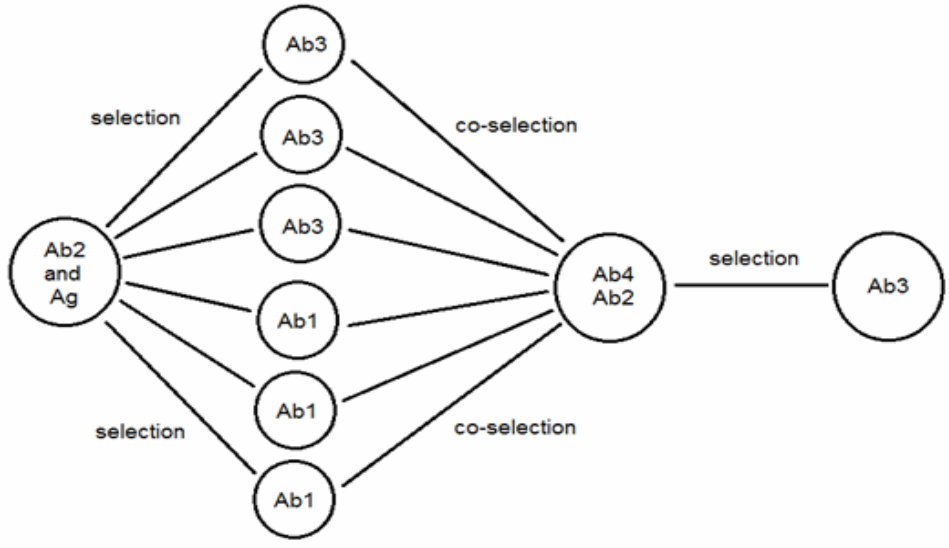

Figure 5. A model for how 1F7 complexed to an HIV antigen is expected to be effective as an HIV vaccine. Here 1F7 is Ab2 and an HIV antigen is Ag. 1F7 stimulates Ab3 and the HIV antigen stimulates Ab1. There is co-selection of (a) Ab3 clones and (b) Ab1 clones with (c) Ab4/Ab2 clones, leading to the Ab4/Ab2 clones becoming the strongest antigen in the system. These clones stimulate Ab3 clones that secrete broadly neutralizing anti-HIV antibodies.

co-selected via specific T cell factors adsorbed onto the surfaces of non-specific accessory cells including macrophages [66].

In conclusion, the discovery of 1F7 and the fact that 1F7 binds to six broadly neutralizing anti-HIV antibodies leads to a co-selection model of HIV pathogenesis based on co-selection of HIV and HIV-specific T cells, co-selection of HIV-specific helper T cells and anti-anti-HIV suppressor T cells, and co-selection of HIV-specific B cells and anti-anti-HIV suppressor T cells. This model provides an explanation for the antibody repertoire freeze seen in HIV infection. Most significantly, it also suggests that 1F7 can be used as a key component of an HIV vaccine. An effective vaccine is expected to comprise 1F7 complexed to an HIV antigen.

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