MINIREVIEW

Internal Image Concept Revisited[1] (44033)

CONSTANTIN A. BONA[2]

Department of Microbiology, Mount Sinai School of Medicine, New York, New York 10029

Abstract. **Internal image of the antigen represents an essential element of network theory. From theoretical standpoint this concept considers that the idiotypes which are phenotypic markers of variable region of antigen receptor of lymphocytes represent links between the universe of self and foreign antigens and the immune system. This concept had seen rapid practical applications. Ensuing years may see whether these applications are beneficial or rather represent research tools in biological sciences.**
[P.S.E.B.M. 1996, Vol 213]

Internal image concept is pivotal for idiotype network theory. This concept proposes that the idiotypes represents links between the outside world of the antigens and the inner immune repertoire (1, 2). The antigen receptor of lymphocytes (i.e., immunoglobulin [Ig] of B cells, or T-cell receptor [TCR] in the case of T cells) expresses antigenic determinants that can be recognized and can elicit a humoral or cellular immune response in xenogenous, allogeneic, syngeneic, or autologous animals (3–6). The idiotypes are phenotypic markers of variable region of lymphocytic antigen receptor (7).

The completeness of the immune system is due to the ability of lymphocytic receptor to recognize entire universe of foreign and self antigens. This property is related to enormous diversity of lymphocytic receptor resulting from multiple V-germline genes encoding Ig receptor (VH, VK, Vλ) or TCR (Vα, Vβ, V, δ, Vγ), the pairing of VH with various VL or Vβ with Vα or with D, J segments. Furthermore, the addition or deletion of nucleotides during the rearrangement of V genes and somatic mutations occurring in the rearranged V genes also contribute to the diversity of the immune repertoire.

The diversity of antigen receptor is reflected in the diversity of idiotypes. Thus, as a statistical necessity the network theory introduced the concept of internal image proposing that the idiotypes of lymphocytic receptor reflect the antigen diversity (1). This concept is not a simple consequence of the "lock and key" rule of the complementary of the antigen-antibody reaction but rather is based on the principle of 3-dimensional mimicry; that is, two molecules that may differ greatly in their gross chemical structure may appear similar to lymphocytic antigen receptor because they both exhibit specific chemical functional groups in appropriate configuration for their interaction.

Crystallographic analysis of Ig or TCR showed that while the combining site represents a cleft, the idiotypes like the antigenic determinants represent protuberances. This implies that the variable region of antigen receptor possesses a particular structure able to interact with the antigen and also able to interact with the receptor of other lymphocyte by virtue of their idiotypes.

An internal image is defined by anti-idiotype antibodies which cross-react with foreign antigens, meaning that their idiotypes represent the positive imprint of the antigen.

[1] This manuscript is an update of a previously published minireview entitled, "Internal Antigen and Immune Network," Proc Soc Exp Biol Med **178**:189–195, 1985.

[2] To whom requests for reprints should be addressed at Department of Microbiology, Mount Sinai School of Medicine, 1 Gustave L. Levy Place, New York, NY 10029.

0037-9727/96/2131-0032$10.50/0
Copyright © 1996 by the Society for Experimental Biology and Medicine

The most significant idea inherent to the internal image concept that idiotypes connect not only the foreign antigens with inner immune repertoire but also the immune system with other systems. This was clearly illustrated by Sege and Peterson (8) who demonstrated that anti-Id antibodies against rat-bovine insulin antibodies bound to insulin receptor and mimicked some functions of insulin.

Heterogenicity of Anti-Idiotype Antibodies

The idiotypes can be located on various segments of variable region of heavy and light chains. Early efforts to locate the idiotypes were based on serological methods, particularly, the competition by antigen of the binding of anti-idiotypes to idiotypes. Such methods led to classification of idiotypes in idiotypes associated with the combining site which are antigen inhibitable (9) and idiotypes associated with the frameworks which are antigen noninhibitable (10). Serological experiments combined with electron microscopic studies of monoclonal antibodies specific for Streptococcal group A polysaccharide demonstrated that the idiotopes can be located over the entire surface of V region extending from paratope to the junction with first exon of constant region (11).

These observations raised the question of heterogeneity of anti-idiotype antibodies recognizing idiotopes located in various segments of V regions. Based on these observations, Jerne *et al.* (12) defined two categories of anti-idiotype antibodies (Ab_2): $Ab_2\alpha$-anti-idiotypes recognizing framework associated idiotypes and $Ab_2\beta$-anti-idiotypes recognizing paratope associated idiotypes. Heinz Kohler and I (13), after a thorough analysis of the properties of anti-idiotypes antibodies, classified the Ab_2s into four categories:

1. $Ab_2\alpha$ are anti-idiotypes recognizing idiotypes associated with the framework of variable region since their binding to corresponding idiotopes is not inhibited by antigen. These anti-Id antibodies can suppress or prime the clones expressing idiotypes, but they cannot mimic the antigen. Huang *et al.* (14) have shown that $Ab_2\alpha$ can induce a T-dependent, MHC-restricted proliferation of B cells followed by their differentiation into antibody producing cells. It was also shown that $Ab_2\alpha$ directed to antibodies specific for HBsAg (15) or influenza virus neuraminidase (16) can induce specific antibodies without subsequent exposure to viral antigen. Antibodies elicited by immunization with $Ab_2\alpha$ were able to inhibit Id-anti-Id reaction, indicating that they express Id of Ab_1.

2. $Ab_2\gamma$ are anti-idiotype antibodies recognizing paratope associated idiotopes. Such anti-Id antibodies can inhibit the binding of antigen to the parotope. The inhibition is due to alteration of 3-dimensional structure of paratope preventing the interaction with the epitope (13). Like $Ab_2\alpha$, the $Ab_2\gamma$ cannot mimic the antigen.

A particular category of $Ab_2\gamma$ interact with regulatory idiotopes (17) which play an important role in idiotype-regulated immune responses. Regulatory idiotopes exhibit the following properties: (a) they are antigen inhibitable (18) and markers of germline genes (19, 20); (b) they may function as autoimmunogens since they can induce synthesis of autoantiidiotyic antibodies (18); (c) they can be shared by several members of idiotype network (e.g., Ab_1 and Ab_3 or Ab_2 and Ab_4 (17) but also by antibodies with different specificities (21, 22); and (d) they have the potential to become dominant because they are recognized by T cells (23). The immune repertoire contains not only B cells producing $Ab_2\gamma$ specific for regulatory idiotopes (17, 18) but also T cells recognizing regulatory idiotopes (24, 25).

3. $Ab_2\beta$ are anti-Id antibodies recognizing antigen-inhibitable idiotopes which mimic the antigen. These antibodies represent the internal image of the antigen since their idiotypes cross-react with foreign or self epitopes. This means that among the multitude of 3-dimensional structures of idiotopes of variable regions one could find structures or shapes which are similar, if not identical, to the epitopes of self and nonself antigens.

4. $Ab_2\epsilon$ (epibodies) represent a special category of anti-Id antibodies which bind to idiotopes as well as the antigen interacting with antibodies expressing the idiotopes. We have described these antibodies in rheumatoid factor (RF) system in which we demonstrated that the binding of epibody to a IdX of a RF was inhibited by Fc fragment. In addition, we showed that monoclonal epibodies bound to Fc fragment which is the antigen interacting with RFs (26). Epibodies were described among anti-Id antibodies specific for idiotypes of anti-AchR autoantibodies (27) anti-DNA autoantibodies (28) and anti-allotype antibodies (29). The epibody may represent a particular category of internal image because its paratope interacts with both idiotope and epitope.

In spite of the fact that our classification represents perhaps an oversimplification of immunochemical and functional properties of anti-idiotype antibodies, the ensuing years have seen its utility in characterization of anti-idiotype antibodies.

Criteria Defining Ab_2-Internal Image

Very rarely in science has a theoretical concept seen rapid practical application. However, this was the case of internal image concept, as when Nisonoff and Lamoyi (30), and Roitt *et al.* (31) exploited the concept to propose the utilization of $Ab_2\beta$ as vaccines. Internal image immunoglobulins were also largely

used to study the function of cell receptors binding the hormones, to isolate and characterize cell receptors interacting with a variety of biological active ligands or drugs, as anti-tumor therapeutical agents or as tools for understanding the production of autoantibodies. Taking into account these broad applications, investigators tried to find precise criteria to define $Ab_2\beta$. Nisonoff and Lamoyi (30) proposed that $Ab_2\beta$ be defined by their ability to recognize antigen-inhibitable idiotype. However, both $Ab_2\gamma$ and $Ab_2\beta$ recognize antigen-inhibitable idiotype and so far it appears that they are quite different with respect to network considerations and their functions. At the Nobel symposium in 1987, together with Ertl (32), we proposed three criteria to define internal image antibodies.

Immunochemical Criterion. $Ab_2\beta$'s antigen-inhibitable capacity to interact with paratope-associated idiotype is useful to distinguish $Ab_2\beta$ from $Ab_2\alpha$. However it cannot be used to distinguish $Ab_2\beta$ from $Ab_2\gamma$.

Functional Criterion. The functional criterion is based on the ability to $Ab_2\beta$ to mimic a given antigen and therefore to induce the synthesis of antibody specific for a nominal self or foreign antigen. It was demonstrated that some $Ab_2\alpha$ also can activate clones expressing corresponding idiotypes. However, the outcome of the activation of clones by $Ab_2\alpha$ or by $Ab_2\gamma$ is different from that induced by $Ab_2\beta$. An $Ab_2\alpha$ or $Ab_2\gamma$, which binds to idiotope of Abs, presumably activates three types of clones: Ag^+Id^+, which can bind the antigen that elicited the production of Ab_1 antibody, Ag^-Id^+, the parallel sets; and Ag^-Ig^-, a true anti–anti-Id antibody (Ab_3). $Ab_2\beta$, which mimics the antigen, also activates three different types of clones: Ag^+Id^+, Ag^+Id^-, and true Ab_3 (i.e., Ag^-Id^-).

A particularity of $Ab_2\beta$, which expresses an idiotype mimicking the antigen, is its ability to elicit antibodies specific for the same antigen in various species. This property is related to the ability of $Ab_2\beta$ to interact with the paratope of antibodies that exhibit similar antigen specificity but can be encoded by various V_H and V_L genes in different species.

Structural Criterion. Structural identity between an epitope of the antigen and a segment of variable region of antibody may represent the most faithful criterion to define an $Ab_2\beta$. The idiotype of $Ab_2\beta$, being identical to the epitope of the antigen, will interact with lymphocyte antigen receptor alike the antigen. It was actually shown that the $Ab_2\beta$ shares identical sequences with the antigen. Roth *et al.* (33) prepared anti-Id monoclonal antibodies (mAbs) against polyclonal antibodies specific for GAT ($Glu^{60}Ala^{30}Tyr^{10}$) synthetic terpolymer. The sequencing of two monoclonal anti-Id antibodies showed the presence of shared sequences Tyr, Tyr, Glu, or Glu, Glu, Tyr between the D segment and the synthetic terpolymer peptide in which Glu-Tyr represents the immunodominant epitope.

Immunization of mice with the synthetic peptide corresponding to the D segment of $Ab_2\beta$ mAb elicited an anti-GAT antibody response similar to original antigen with an important difference: while they exhibited binding to GT, the immunodominant epitope of GAT terpolymer, they did not express GAT IdX characteristic of antibodies induced by GAT synthetic peptide (34). Bailey *et al.* (35) had prepared several mAbs from MRL/lpr and C_3H/HeJ mice injected with HP20-$Ab_2\beta$ mAb raised in GAT system (33). Analysis of immunochemical properties of mAbs obtained from mice immunized with HP 20 mAb showed that they exhibited similar Ka for GT and also for self antigens such as DNA Sm or Fc fragment of IgG. Among 24 mAbs studied, only 6 expressed GATIdx. The analysis of V_H and V_K gene families encoding their specificity showed that they drew their V genes from various V_H and V_K families. This is in striking contrast with canonical anti-GAT antibodies encoded by genes derived from V_HJ558 and V_K1 families (36), indicating that mAbs induced by $Ab_2\beta$ did not derive from the pool of precursors of GAT specific B cells. These data clearly demonstrated that $Ab_2\beta$, by virtue of its ability to mimic the antigen, stimulates both Ag^+Id^+ and Ag^+Id^- clones, and that the paratope of these clones can be encoded by V genes deriving from various families. Bruck *et al.* (37) also reported a shared tetrapeptide between an epitope of the hemagglutinin (HA) of reovirus and the CDR2 of the light chain of a monoclonal anti-Id antibody raised by immunization with anti-reovirus antibody.

Van Cleave *et al.* (38) analyzed the sequence of V_H and V_K genes of two mAbs obtained from mice immunized with rabbit Igs bearing a1 allotypes. The V_H region of both antibodies contain an unique sequence of identity with rabbit V_H segment bearing a1 allotypic determinant but in a novel configuration. The V_H sequence of murine internal image antibody was in the reverse orientation. The peptides corresponding to these sequence were able to inhibit the binding of labeled rabbit Ig a1 to an anti-a1 mAb.

While the structural criterion may be the best for designation of $Ab_2\beta$ raised by immunization with antibodies specific for protein antigens, the immunochemical and functional criteria can be used to define $Ab_2\beta$ raised against antibodies specific for polysaccharides, lipoproteins, nucleotides, or synthetic drugs.

Internal Image Immunoglobulin "à la Carte"

The advent of molecular biology allowed the construction of chimeric molecules in which peptides of microbial antigens or lymphokines were expressed in bacterial, viral, or mammalian genes. These molecules

were produced to deliver vaccinating epitopes or biologically active ligands. This methodology was also used to prepare chimeric immunoglobulins in which microbial epitopes were added to CDR3 of V_H genes (39) or replaced the CDR of V_H genes (40). These chimeric molecules obtained by genetic engineering represent $Ab_2\beta$ because they fulfill the structural criterion, namely, the sharing of identical sequences with the nominal antigen.

Obviously, while these molecules may represent faithful copies of linear epitopes recognized by T cells and rarely by B cells, they cannot mimic conformational self or foreign epitopes. Billeta *et al.* (40) showed that the addition of a peptide corresponding to the tandem repeat of circumsporozoite protein (CSP) to CDR3 of a V_H gene of an autoantibody elicited antibodies capable of inhibiting the invasion of hepatocytes by sporozoites. This $Ab_2\beta$ "à la carte" was able to induce anti-CSP antibodies because the tandem repeat is a linear epitope.

Zaghouani *et al.* (41) prepared a humanized chimeric Ig in which the CDR3 of V_H region of an anti-arsonate antibody was replaced with 19 amino acids residues corresponding to principal neutralizing determinants of hypervariable region 3 (V_3) loop of HIV-1 virus. The replacing of D segment by HIV-1 peptides was accompanied by loss of anti-arsonate activity. One chimeric Ig molecule expressed a 19 amino acid residues peptide corresponding to consensus sequence predicted from the sequences of 245 isolates and the second of WMJ_2 strain. Injected in baboons, the chimeric Ig induced antibodies which bound to V_3 peptide, native gp120 envelope glycoprotein, and neutralized HIV-1 virus. In addition, these chimeric Ig were able to stimulate *in vitro* production of antibodies specific for HIV-1 virus by lymphocytes from HIV-1–infected human subjects. Previous studies have investigated anti-CD4 antibodies as models of internal image Igs of the HIV viral gp120 binding site for CD4. This approach was based on the concept that the paratope of anti-CD4 antibody structurally mimics the receptor of HIV1-gp120 glycoprotein.

Study of anti-Id antibodies raised against anti-CD4 mAbs showed that, while they could induce anti-CD4 antibodies in mice, no such response was detected in other species (42). Lanza *et al.* (43) used chimeric Igs to stimulate a protective response against HIV-1. They added to CDR3 of V_H62 gene used by anti-thyroglobulin autoantibody a nucleotide sequence encoding a 7-mer or a 15-mer corresponding to the first domain of human CD4, which is the major receptor for HIV-1 virus. While these chimeric Ig molecules injected in rabbit and mice, like anti-Id anti-CD4 antibodies of Healy *et al.* (42), were able to elicit the synthesis of anti-CD4 antibodies, they were unable to elicit the synthesis of neutralizing antibodies in monkeys (Kennedy, personal communication). This can be related to their inability to break the tolerance, since Goodnow *et al.* (44) have demonstrated that the B cells specific for cell membrane–associated antigens like CD4 are deleted in the bone marrow during ontogeny. In addition, one may ask whether the induction of anti-CD4 antibodies is beneficial for AIDS patients. While the anti-CD4 antibody inhibits *in vitro* the penetration of the virus, it may also have a deleterious effect *in vivo* by killing CD4 T cells by an ADCC mechanism or by promoting apoptosis like gp120 protein. I have discussed this case in length because I believe that $Ab_2\beta$ has a great potential for vaccines. However, in designing $Ab_2\beta$ "à la carte" the investigators should take into consideration fundamental knowledge, since antibodies as well as T cells, while beneficial in host defense against microbes, sometimes can be deleterious.

Another approach to prepare $Ab_2\beta$ "à la carte" was imagined by Blalock (45). His approach consists of producing anti-Id antibodies by immunization with peptides specified by complementary sense or antisense RNA nucleotide sequences. Using this approach, Bost *et al.* (46) were able to induce anti-Id antibodies subsequent to immunization with complementary peptides. Monoclonal anti-Id antibodies produced by this methodology were able to suppress the production of antibodies by hybridomas bearing the corresponding idiotype (47). It therefore appears that this approach also provides a method to produce $Ab_2\beta$ "à la carte."

Molecular Characteristics of Internal Image Immunoglobulins

While the sequencing of V region genes expressing individual or cross-reactive idiotypes provided a deep insight into structural correlates of idiotypes, we searched a long time for information on 3-dimensional structure of $Ab_2\beta$-idiotype-antigen crystals. Fields *et al.* (48) determined the crystal structure of an idiotype and anti-idiotype to a nominal resolution of 1.9A. Fv fragments were obtained from D1.3, a mAb specific for lysozyme, and from E5.2, anti-idiotypic mAb. E5.2 exhibited the properties of an $Ab_2\beta$ in that when injected in BALB/c or C57BL/6 mice it elicited the production of anti-lysozyme antibodies.

Of the 18 residues that contact anti-Id antibody and the 17 that interact with lysosyme, 13 were in contact with both lysozyme and anti-Id antibody. The position of atoms by which anti-idiotype contacts anti-lysozyme antibody is close to that by which D1.3 contacts the lysozyme. The structural mimicry observed involves van dar Waals forces, hydrogen bonds, and solvent interaction. Ban *et al.* (49) determined the crystal structure of Fab complex of mAb specific for

E2 peptomer of feline infectious peritonitis virus and of an anti-Id antibody. This anti-Id also exhibited $Ab_2\beta$ properties in that when it was injected in animals it elicited the production of viral neutralizing antibodies. The two Fab fragments interact by direct juxtaposition of their complementary CDRs. CDR loops of two Fab were in contact through van der Walls forces and hydrogen bonds between 58 atoms of antibody and 59 atoms of anti-idiotype. In total, 19 residues of idiotype and 17 residues of anti-idiotype participate in interaction. In CDR1 loop of light and heavy chains, a near identity with the sequences of an hexapeptide of the antigen was found. These two regions of homology of CDR1 of light and heavy chain of Ab_2 provide important contact with the idiotype of antibody specific for viral antigen. These results indicate that the structural correlates of $Ab_2\beta$ mimicry can be related to conformational determinants because the contact residues can be located in various CDR loops. However, in other cases, such as feline peritonitis virus system, some linear peptides located in CDRs can play a major role in antigen mimicry.

Internal Image Immunoglobulins and T Cells

In contrast to B cells, which can recognize linear or conformational epitopes on native antigens, T cells recognize peptides derived from the processing of self or foreign antigens in association with MHC class I or II antigens (50). The recognition of idiotypes by T cells followed the same rules. It was shown that CTLs-($CD8^+$) recognize idiopeptides generated *via* endogenous pathway in association with class I antigens (51, 52). Similarly, CD4 T cells recognize idiopeptides in association with class II antigens (24, 53, 54). It is worthwhile to point out that CD4 T cells recognize idiopeptides generated *via* endogenous pathway rather than in the endosomal compartment following the internalization of Igs. Generation of idiopeptide in ER was elegantly demonstrated by Weiss and Bogen (55).

In 1988 we proposed that an internal image immunoglobulin mimicking a T-dependent antigen should be obligatorily recognized by T cells in a genetically restricted manner, namely, in association with MHC antigens (56). Since $CD8^+$ T cells recognize nonamer peptides and $CD4^+$ T cells recognize 8- to 20-mer peptides it results that internal image Ig should be processed to generate peptides able to bind to class I or II molecules. No internal image Igs sharing 8–20 amino acid residues linear peptides with foreign antigens are yet available to study the generation of internal image idiopeptides by processing natural $Ab_2\beta$. Therefore, we decided to investigate the molecular basis of the recognition of internal image Igs by T cells preparing "à la carte" chimeric Ig expressing linear viral epitopes. For this purpose, we prepared by genetic engineering method, a V_H gene in which the CDR3 was replaced with a peptide corresponding to 147–161 amino acid residues of PR8 influenza virus nucleoprotein (N147–161) and another corresponding to 110–120 amino acid residues of hemagglutinin (HA110–120). While N147–161 peptide is recognized by CD8 T cells in association with class I-K^d antigen (57), the HA110–120 peptide is recognized in association with class II I-E^d antigen (58).

The chimeric V_H genes were co-transfected with V_H gene and respective transfectomas produce an Ig molecule expressing N147–161 peptide that we designated as Ig-NP (39) and another expressing HA110–120 peptide that we designated IgHA (59). We have shown that Ig-NP cannot sensitize target cells to be killed by NP-specific CTL or to induce the proliferation of the CTL upon incubation *in vitro* with various APC (40). IgNP was unable to prime NP-specific CTL subsequent to parental administration in adults or neonates, or by transfer to fetuses *via* the placenta (60). These results clearly showed that IgNP molecule taken up by APC and processed in endosomes cannot generate NP147–161 class I complex which is recognized by CTL. By contrast, transfectoma bearing chimeric V_H NP gene were lysed in a genetically restriction fashion by CTL and were able to prime the CTL precursors when injected into mice of $H2^d$ haplotype (40, 60).

The conclusion of these observations is very clear. The translated product of chimeric V_HNP gene should be processed like viral nucleoprotein in endogenous pathway to generate the NP peptide which once complexed with class I antigen is translocated on the surface where it may be recognized by T cells. This conclusion suggests that an internal image Ig *per se* cannot be recognized by T cells through a mimicking of the foreign antigens with the exception of a V region sharing a nonapeptide structurally identical to a foreign antigen. This view was supported by a recent observation of Cao *et al.* (61), who found that hybridomas expressing a V_H gene from V_H7183 family, which shares a peptide with the A/Japan influenza virus hemagglutin, were killed by HA-specific CTLs.

In contrast, we found the IgHA expressing HA110–120 peptide can activate *in vitro* CD4 T-cell hybridomas or can prime *in vivo* the precursors of HA110–120–specific CD4 T cells (59). Our studies showed that IgHA is mainly internalized *via* FcR, that it is degraded in endosomal compartment where the peptide is sorted by I-E^d molecules, and that the peptide-class II complex translocated on the cell surface is recognized by CD4 T cells. It is important to point out that we extracted from I-E^d antigen of APC pulsed with the synthetic peptide chimeric IgHA or PR8 influenza virus an 11-mer peptide with identical structure (62). This observation clearly demonstrates that the generation of idiopeptide from internal image Ig or

Table I. Hormones Mimicked by Internal Image Immunoglobulins

$Ab_2\beta$-mimicked hormones	Receptors
Insulin	Insulin receptor (8)
Gonadotropin	Gonadotropin receptor (66)
Aldosterone	Aldosterone binding proteins (67)
Thyrotrophin hormone	Thyrotrophin receptor (68)
Growth hormone	Growth homone receptor (65)

from viral protein obeys the same rules of processing and presentation of foreign antigens as APC.

In aggregate, our results showed that the viral epitopes recognized by CD4 or CD8 T cells inserted within the CDR3 of Ig are antigenic, as they are expressed by the viral proteins, and therefore these chimeric molecules can be used as tools to investigate the molecular mechanisms of recognition and stimulation of T cells by internal image Igs.

This conclusion is supported by two experimental findings. Pride *et al.* (63) showed that T cells from mice immunized with hepatitis virus or with an $Ab_2\beta$ mimicking HBsAg proliferate *in vitro* upon incubation with viral antigen, synthetic peptide, or heavy chain of $Ab_2\beta$. This response was ablated when APC were prefixed with glutaraldehyde or when they were incubated with anti–class II (i.e., I-A) antibodies. Similarly, Brumenau *et al.* (64) showed that resting CD4 T cells from a transgenic mouse expressing TCR genes of a hybridoma recognizing HA110–120 peptide developed a strong proliferative response when incubated with the synthetic peptide, PR8 virus, chimeric IgHA, or bromelin-prepared HA. The stimulation was also ablated by the prefixation of APC with formaldehyde or preincubation with cholorquine or anti–class II (i.e., I-E) antibodies.

Therefore, it clearly appears that the idiopeptides of $Ab_2\beta$ which are recognized by T cells are processed by APC and presented in a genetically restricted manner like the peptides derived from foreign antigens.

Table II. Biologically Active Ligands Mimicked by Internal Image Immunoglobulins

$Ab_2\beta$-mimicked ligands	Receptor
Formyl peptide	Chemotactic receptor (69)
Laminin	Laminine β receptor (70)
Factor H	β_1H-globulin receptor (71)
Bradykinin	Kinin receptor (72)
Albumin	Endothelial cell albumin receptor (73)
Polymeric Albumin	Polymeric human albumin receptor of hepatitis B virus (74)
β-Glycan	Monocyte β-glycan receptor (75)
TNFα	TNF receptor (76)

Table III. Drugs of Organic Origin Mimicked by Internal Image Immunoglobulins

$Ab_2\beta$-mimicked drugs	Drug receptor
Alprenelol	β-Adrenergic receptor (77)
Morphine	Opiate receptor (78)
Cyclosporine	Cyclophilin (79)
Adenosine	Adenosine receptor (80)
Bis Q	Acetylcholine receptor (81)

Practical Applications of Internal Image Igs

There are very few examples, other than internal image of the antigen, of a theoretical biological concept that has such rapid and practical application. The secret of this impetus may be attributed to two facts: first, the demonstration of Sege and Paterson (8) that an $Ab_2\beta$ can mimic a hormone, second, the idea of Nisonoff and Lamoyi (28), and Roit *et al.* (29) that $Ab_2\beta$ can be used as a new generation of safe vaccines.

The demonstration that an $Ab_2\beta$ can mimic some functions of insulin strongly suggested that an $Ab_2\beta$ can mimic biologically active ligands. We have shown that a monoclonal anti-Id specific to anti-porcine growth hormone antibody was able to promote the growth of somatotrop-deficient animals prepared by hypophysectomy (65). Table I illustrates $Ab_2\beta$s mimicking hormones. It was shown that $Ab_2\beta$ against anti-hormone antibodies can mimic completely or partially the biochemical and/or molecular intracellular events induced by the binding of hormones to their corresponding cell receptor. Furthermore, it was shown that $Ab_2\beta$ can mimic not only hormones but also the binding to receptors of other biologically active ligands (Table II). All the examples cited in Table II showed the possibility of obtaining antibodies by a ligand-specific receptor in the absence of the receptor itself. $Ab_2\beta$ can also mimic some organic drugs (Table III) and various proteins or at least some of their antigenic

Table IV. Proteins Mimicked by Internal Image Immunoglobulins

$Ab_2\beta$-mimicked proteins	Type of response
Vitamin A transport protein	Binding to pre-albumin (82)
HLA-DR	HLA antigens (83)
IgE	Basophilic IgE receptor (84)
IgE	IgE binding factor (85)
Rheumatoid factor	Fcγ binding protein of HSV type I (86)
Fc fragment	RF-receptor of B cells (87)
Taxol	Tubulin-microtubule (88)

Table V. Self Antigens Mimicked by Internal Image of Immunoglobulins

	Disease
Autoantigens	
C3/C5 convertase	Membrane proliferative glomerulonephritis (89)
Factor VIII	Hemophilia A (90)
CD4	HIV-1 seropositive with thrombocytopenia (91)
Tumor-associated antigens	
GD2	Melanoma (92)
High molecular weight melanoma antigen	Melanoma (93)
gp37	Human T cell leukemia (94)
Colon carcinoma antigen	Colon cancer (95)
Human mammary tumor virus antigen	Breast tumor (96)
gp52 of mammary mouse tumor virus	Breast cancer (97)
SV40 large tumor antigen	Tumor in mice (98)
L1210 tumor	Murine leukemia (99)

determinants (Table IV). In principle, internal image immunoglobulins should mimic not only the foreign antigens but also self antigens. While there are a few examples of $Ab_2\beta$ that mimic the self antigen, there are numerous examples demonstrating that $Ab_2\beta$ mimic tumor-associated antigens (Table V). $Ab_2\beta$ mimicking tumor-associated antigen potentially may have an immunotherapeutic applications aimed at hardening the immune response against tumors that are tolerated by host. Indeed, there are trials aimed at evaluating the efficacy of internal image Igs in the treatment of melanoma or colon cancer.

During the last decade, much hope was put on the use of internal image Igs as vaccines based on the prediction of Nisonoff and Lamoyi (30) that idiotypes of $Ab_2\beta$ would mimic the foreign antigens. Rubinstein *et al.* (100) was one of the first to demonstrate that $Ab_2\beta$ can mimic a bacterial polysaccharidic antigen. BALB/c mice injected after birth with minute amounts of a monoclonal antibody specific for A48Id expressed on a levan binding myeloma protein, activated B clones producing antibodies specific for β2-6 fructosan. IEF analysis of these clones shown that, in spite of the fact that they expressed A48Id, they showed a different pI from that of antibodies produced by mice immunized with bacterial levan.

Table VI. Microbial Antigen Mimicked by Internal Image Immunoglobulin

	Antigen Mimicked by $Ab_2\beta$	Function of antibodies
A. Bacterial species		
C. levanicum	Levan	Anti-β-6 fructosan antibodies (100)
E. coli	Capsular polysaccharide	Protective antibodies (102)
S. pneumonia	Phosphocholine	Protective antibodies (101)
S. pyogenesis	Group A carbohydrate	Protective antibodies (103)
Gram-negative	Lipid A	Protective antibodies (104)
P. aeruginosa	Capsular antigen	Protective antibodies (105)
C. diphtheria	Toxin	Protection of Vero cells (106)
L. pneumonia	Cytolysin	Non-neutralizing antibodies (107)
B. Viruses		
HIV	gp120	Neutralizing antibodies (108, 109)
	p24	Non-neutralizing antibodies (110)
Reovirus type 3	Hemagglutinin	Neutralizing antibodies (111)
Poliovirus type II	Neutralizing epitope	Neutralizing antibodies (112)
Influenza virus	Hemagglutinin	Neutralizing antibodies (113, 114)
Rabies virus	Virus glycoprotein	Neutralizing antibodies (115)
SV40	T antigen	Suppressive antibodies (116)
Coxsackie virus B4	Binding receptor	Non-neutralizing antibodies (117)
Corona virus	MHV-A59 epitope	ND[a] (118)
Blue tongue virus	Not defined	Neutralizing antibodies (119)
FMDV	Surface epitopes	Non-neutralizing antibodies (120)
Hepatitis virus	HBs Ag	ND (121, 122)
C. Parasites		
Schistosoma mansoni	Glycoprotein 68KD	Cytotoxic and protective Ab (123, 124)
Trypanosoma	VAT	Protective immunity (125)
Trichothecene	Mycotoxin T2	Protective antibodies (126)

[a] Not determined.

In the years following the initial observation of Rubinstein *et al.* (100), several investigators demonstrated that $Ab_2\beta$ can mimic bacterial polysaccharides as well as bacterial protein antigens (Table VI). These findings clearly demonstrated that a mimicry of polysaccharides by $Ab_2\beta$ cannot be due to sequence homology of antigen and $Ab_2\beta$ but rather to their sharing of functional chemical groups that interact with the combining site of anti-polysaccharide antibodies. It was also shown that $Ab_2\beta$ are able to mimic viral antigens of protein origin. The results of these studies are summarized in Table VIB. In some cases, $Ab_2\beta$-like viral antigens were able to elicit protective or neutralizing antibodies, whereas in other cases non-neutralizing antibodies resembled an Ab_3 rather than an Ab_1.

However, one may ask why idiotype vaccine approach was not adopted by vaccinologists and why any idiotype vaccine was not evaluated in human trials in spite of the fact that their efficacy was proved in preclinical trials. I believe that idiotype vaccines' failure to penetrate the human vaccination arsenal has several explanations. First, no human $Ab_2\beta$ able to function as idiotype vaccine was characterized or produced in sufficient amounts for a clinical trail. Utilization in humans of xenogenous (rabbit or murine) idiotype vaccines is unrealistic, because of undesirable antibody response against foreign Igs. Secondly, even in animals the idiotype vaccines were not demonstrated to elicit superior quantitative (titer) or qualitative (affinity) antibody responses compared with classical killed or live attenuated vaccines. Third, little effort was made to determine whether the idiotype vaccine confers memory like the classical vaccines. Induction of immunological memory is critical for the efficacy of vaccine.

1. Jerne NK. Towards a network theory of the immune response. Ann Immunol Paris **125C**:373–389, 1974.
2. Lindemann J. Homobodies: Do they exist? Ann Immunol Institute Pasteur **130C**:311–318, 1973.
3. Oudin J, Michel M. Une Nouvelle forme d'allotypie des globulines du serum de lapin apparement lie a la fonction et a la specificite anticorps. CR Acad Sci Paris **257**:805–808, 1963.
4. Kunkel HG, Mannick M, Williams RC. Individual antigenic specificity of isolated antibodies. Science **140**:1218–1219, 1963.
5. Infante AJ, Infante PD, Gillis S, Fathman CG. Definition of T-cell idiotopes using antiidiotypic antisera produced by immunization with T-cell clones. J Exp Med **155**:1100–1107, 1982.
6. Gascoigne NRJ, Waters S, Elliott JF, Victor-Kobrin C, Goodnow C, Davis MM, Bona CA. Expression of T-cell receptor genes in an antigen-specific hybridoma and radiation-induced variants. J Exp Med **164**:113–130, 1986.
7. Grey HM, Mannik M, Kunkel HG. Individual antigenic specificities of myeloma proteins. Characteristics and localization to subunits. J Exp Med **121**:561–575, 1965.
8. Sege K, Paterson PA. Use of antiidiotypic antibodies as cell-surface receptor probes. Proc Natl Acad Sci U S A **75**:2443–2447, 1978.
9. Brient BW, Nisonoff A. Quantitative investigation of idiotypic antibodies. IV. Inhibition by specific haptens of the reaction of anti-hapten antibody with its idiotypic antibody. J Exp Med **132**:951–962, 1970.
10. Mudgett M, Coligan JE, Kindt TJ. Isolation and characterization of distinct antibody populations from antisera directed against idiotypes of rabbit homogenous antibodies. J Immunol **120**:293–301, 1978.
11. Greenspan NS, Monafo WJ. Topographic analysis with monoclonal antiidiotopes: Probing the functional anatomy of immunoglobulin variable domains. Int Rev Immunol **2**:391–417, 1987.
12. Jerne NK, Roland J, Cazenave PA. Recurrent idiotopes and internal images. EMBO J **1**:243–247, 1982.
13. Bona CA, Kohler H. Antiidiotype Antibodies and Internal Images in Monoclonal and Antiidiotypic Antibodies: Probes for Receptor Structure and Function. Alan R. Liss, New York, pp141–149, 1984.
14. Huang JH, Ward RE, Kohler H. Idiotype antigens (Ab2α and Ab2β) can induce in vitro B cell proliferation and antibody production. J Immunol **137**:770–776, 1986.
15. Schick MR, Dreesman GR, Kennedy RD. Induction of an anti-hepatitis B surface antigen response in mice by non-internal image Ab2α antiidiotypic antibodies. J Immunol **138**:3419–3425, 1987.
16. Mayer R, Ioanides C, Moran T, Johansson B, Bona C. Effect of syngeneic antiidiotypic antibody on influenza virus neuraminidase antibody response. Viral Immunol **1**:121–134, 1987.
17. Bona CA, Heber-Katz E, Paul WE. Idiotype-antiidiotype regulation. I. Immunization with a levan-binding myeloma protein leads to the appearance of autoanti(antiidiotype) antibodies and to the activation of silent clones. J Exp Med **153**:951–967, 1981.
18. Victor-Kobrin C, Barak Z, Bonilla FA, Bona C. Network and regulation of the idiotypic repertoire In Szentivanyi A, Maurer PH, Janicki BW, Eds. Antibodies: Structure, Synthesis, Function and Immunologic Intervention in Disease. New York: Plenum Publ. Corp., pp91–105, 1987.
19. Goldberg B, Paul WE, Bona CA. Idiotype-antiidiotype regulation. IV. Expression of common regulatory idiotopes in fructosan-binding and non-fructosan binding monoclonal immunoglobulin. J Exp Med **158**:515–528, 1983.
20. Victor-Kobrin C, Barak ZT, Bonilla FA, Kobrin B, Sanz I, French D, Rothe J, Bona C. A molecular and structural analysis of the VH and VK regions monoclonal antibodies bearing A48 regulatory idiotype. J Immunol **144**:614, 1990.
21. Bonilla FA, Zaghouani H, Rubin M, Bona CA. VK gene usage idiotype expression and antigen binding among clones expressing the VHX24 gene family derived from naive and antiidiotype immune BALB/c mice. J Immunol **145**:616–622, 1990.
22. Zaghouani H, Bonilla FA, Meek K, Bona CA. Molecular basis for expression of the A48 regulatory idiotope on antibodies encoded by V genes from various families. Proc Natl Acad Sci USA **86**:2341–2345, 1989.
23. Rubinstein LJ, Yeh M, Bona CA. Idiotype-antiidiotype network II. Activation of silent clones by treatment at birth with idiotopes is associated with the expansion of idiotype-specific helper T cells. J Exp Med **156**:506–521, 1982.
24. Waters SJ, Bona CA. Characterization of a T-cell clone recognizing idiotopes as tumor-associated antigens. Cell Immunol **111**:87–93, 1988.
25. Gleason K, Kohler H. Regulatory idiotopes T helper cells recognized a shared VH idiotype on phosphorycholine-specific antibodies. J Exp Med **156**:539–549, 1992.
26. Bona CA, Finley S, Waters S, Kunkel HG. Anti-immunoglobulin antibodies. III. Properties of sequential antiidiotypic antibodies to heterologous anti-γ-globulins. Detection of reactivity of antiidiotype antibodies with epitopes of Fc fragments (homobodies) and with epitopes and idiotopes (epibodies). J Exp Med **156**:986–999, 1982.
27. Dwyer D, Vakil M, Kearney JF. Idiotypic network connectivity and possible cause of myastenia. J Exp Med **164**:1310–1319, 1986.
28. Puccetti A, Migliorini P, Sabbanga J, Madaio MP. Human and murine anti-DNA antibodies induce the production of antiidiotypic antibodies with autoantigen binding properties (epibod-

ies) through immune network interactions. J Immunol **145:** 4229, 1990.

29. Boca CA, Goldberg B, Metzger D, Urbain J, Kunkel HG. Anti-immunoglobulin antibodies IV. Crossreacion of antiidiotypic antibodies specific for rabbit and murine anti-α_1 allotype antibodies with Fc fragment of human immunoglobulins. Eur J Immunol **14:**548–552, 1984.
30. Nisonoff A, Lamoyi E. Implications of the presence of an internal image of the antigen in antiidiotypic antibodies: Possible application to vaccine production. Clin Immunol Immunopathol **21:**397–406, 1981.
31. Roitt IM, Male DK, Guarnotta G, de Carvalho LD, Cooke A, Hay FC, Lydyard PM, Thanavala Y, Ivanyi J. Idiotype networks and their possible exploitation for manipulation of the immune response. Lancet **1:**1041–1045, 1981.
32. Ertl HCJ, Bona C. Criteria to define antiidiotypic antibodies carrying the internal image of an antigen. Vaccine **6:**80–84, 1988.
33. Roth C, Rocca-Serra J, Somme G, Fougereau M, Theze J. Gene repertoire of the anti-poly (Glu60, Ala30, Fyr10) GAT immune response: comparison of VH, VK and D regions used by anti-GAT antibodies and monoclonal antibodies produced after antiidiotypic immunization. Proc Natl Acad Sci USA **83:**4788–4792, 1985.
34. Mazza G, Guigou V, Moinier D, Corbet S, Ollier P, Fougereau M. Molecular interactions in the GAT idiotype network: an approach using synthetic peptides. Ann Inst Pasteur **138:**3–17, 1987.
35. Bailey NC, Fidanza V, Mayer R, Mazza G, Fougereau M, Bona C. Activation of clones producing self-reactive antibodies by foreign antigens and antiidiotype antibody carrying the internal image of the antigen. J Clin Invest **84:**744–756, 1989.
36. Fougereau M, Roca-Serra J, Schiff C, Tonelle C. Analysis of the GAT B repertoire. In: Reen MI, Nisonoff A, Eds. The Biology of Idiotypes. New York: Plenum Press, Vol **97:**p116, 1984.
37. Bruck C, Co SM, Slaoui M, Gaulton GN, Smith T, Fields BN, Mullins JI, Green MI. Nucleic acid sequence of an internal image-gearing monoclonal antiidiotype and its comparison to their sequence of the external antigen. Proc Natl Acad Sci USA **83:**6578–6582, 1986.
38. Van Cleave WH, Naeve CW, Metzger DW. Do antibodies recognize amino acid side chains of protein antigens independently of carbon backbone? J Exp Med **167:**1841–1848, 1988.
39. Biletta R, Hollingdale MR, Zanetti M. Immunogenicity of an engineered internal antibody. Proc Natl Acad Sci USA **88:**4713–1717, 1991.
40. Zaghouani H, Krystal M, Kuzu H, Moran T, Shah H, Kuzu Y, Schulman J, Bona CA. Cells expressing a heavy chain immunoglobulin gene carrying a viral T cell epitope are lysed by specific cytolytic T cells. J Immunol **148:**3604–3609, 1992.
41. Zaghouani H, Anderson SA, Sperber KE, Daian C, Kennedy RC, Mayer L, Bona C. Induction of antibodies to the human immunodeficiency virus type 1 by immunization of baboons with immunoglobulins molecule carrying the principal determinant of the envelope protein. Proc Natl Acad Sci USA **92:**631–635, 1995.
42. Healey DG, Dianda L, Beverley PCL. A network antigen for human CD4. J Immunol **148:**821–826, 1992.
43. Lanza P, Billeta R, Antonenko S, Zanetti M. Active immunity against the CD4 receptor by using an antibody antigenized with residues 41–55 of the first extracellular domain. Proc Natl Acad Sci USA **90:**11683–11687, 1993.
44. Adelstein S, Pritchard-Briscoe H, Basten A, Goodnow CC. Induction of self-tolerance in T cells but not B cells of transgenic mice expressing little self-antigen. Science **251:**1223–1228, 1991.
45. Smith LR, Bost KL, Blalock E. Generation of idiotypic and antiidiotypic antibodies by immunization with peptides encoded by complementary RNA: A possible molecular basis for the network theory. J Immunol **168:**7–9, 1987.
46. Bost KL, Smith EM, Blalock JL. Similarity between the corticotropin (ACTH) receptor by a peptide encoded by an RNA that is complementaray to ACTH mRNA. Proc Natl Acad Sci USA **82:**1372–1375, 1985.
47. Zhou SR, Han CC, La Gauke CC, Whitaker JN. Comparison of properties of murine monoclonal antiidiotypic antibodies generated with idiotype-bearing monoclonal antibodies to myelin basic protein peptides or their complementary peptides. Clin Immunol Immunopathol **70:**251–259, 1994.
48. Fields B, Goldbaum, FA, Ysern X, Poljak RJ, Mariuzza RA. Molecular basis of antigen mimicry by an antiidiotype. Nature **374:**739–742, 1995.
49. Ban N, Escobar C, Garcia R, Hasel K, Day J, Greenwood A, McPherson A. Crystal structure of an idiotype-antiidiotype Fab complex. Proc Natl Acad Sci USA **91:**1604–1608, 1994.
50. Braciale TL, Braciale VL. Antigen presentation: Structural themes and functional variations. Immunol Today **12:**124–129, 1992.
51. Chakarabarti D, Ghosh SK. Induction of syngeneic cytotoxic T lymphocytes against a B cell tumor. II. Characterization of antiidiotypic CTL lines and clones. Cell Immunol **144:**443–454, 1992.
52. Chakarabarti D, Ghosh SK. Induction of syngeneic cytotoxic T lymphocytes against a B cell tumor. III. MHC class I resticted CTL recognizes the processed form of idiotype. Cell Immunol **144:**455–464, 1992.
53. Bikoff E, Bona C. Influence of IgH-C and MHC-linked genes on the activity of immunoglobulin-recognizing T cells. J Immunol **131:**103–108, 1983.
54. Bogen B, Malissen B, Haas W. Idiotope-specific T cells clones that recognize syngeneic immunoglobulin fragments in the context of class II molecules. Eur J Immunol **16:**1373–1378, 1986.
55. Weiss S, Bogen B. MHC class II-restricted presentation of intracellular antigen. Cell **64:**767–776, 1991.
56. Bona C. Antiidiotypes. In: Bona C, Ed. Biological Applications of Antiidiotypes. Boca Raton FL CRC Press, Vol **1:**pp1–13, 1988.
57. Taylor PM, Askonas BA. Influenza nucleoprotein-specific cytotoxic T cell clones are protective in vivo. Immunology **58:**417–420, 1986.
58. Haberman AM, Moller C, McCreedy D, Gerhard WV. A large degree of functional diversity exists among helper T cells specific for the same antigenic site of influenze hemagglutinin. J Immunol **145:**3087–3094, 1990.
59. Zaghouani H, Steinman R, Nonacs R, Shah H, Gerhard W, Bona C. Presentation of a viral T cell epitope expressed in the CDR3 region of a self-immunoglobulin molecule. Science **259:**224–227, 1993.
60. Kuzu Y, Kuzu H, Zaghouani H, Bona C. Priming of cytolytic T lymphocytes at various stages of ontogeny with transfectoma cells expressing a chimeric heavy chain gene bearing an influenza virus nucleoprotein peptide. Int Immunol **5:**1301–1307, 1993.
61. Cao W, Myers-Powell BA, Braciale TJ. Recognition of an immunoglobulin VH epitope by influenza virus-specific class I major histocompatibility complex-restricted cytolytic T lymphocytes. J Exp Med **179:**195–202, 1994.
62. Brumeanu T, Swiggard WJ, Steinman RM, Bona CA, Zaghouani H. Efficient loading of identical viral peptide onto class II molecule by antigenized immunoglobulin and influenza virus. J Exp Med **178:**1795–1799, 1993.
63. Pride MW, Thakur A, Thanavala Y. Mimicry of the α determinant of hepatitis B surface antigen by an antiidiotype antibody. J Exp Med **177:**127–134, 1993.
64. Brumeanu TD, Casares S, Harris PE, Dehazya P, Wolf I, von Bolhomes H, Bona C. Immunopotency of a viral peptide assembled on the carbohydrate moieties of self-immunoglobulins. Nature Biotech **14:**722–725, 1996.
65. Wang VS, Zhang RJ, Bona C, Moran TM. Promotion of animal growth with a monoclonal antiidiotype specific to anti-porcine growth hormone antibody. Mol Immunol **31:**651–656, 1994.
66. Moyle WR, Ehrlich PH, Canfield RE. Use of monoclonal antibodies to subunits of human gonadotropin. Proc Natl Acad Sci USA **79:**2245–2248, 1982.
67. Lombes M, Edelman IS, Erlanger BF. Internal image proper-

ties of a monoclonal autoantiidiotypic antibody and its binding to aldosterone receptors. J Biol Chem **268**:2528–2536, 1989.
68. Braun JM, Marion S, Charreire J, Ropars A. Production of $Ab_2\beta$, antiidiotypic monoclonal antibodies, specific for human thyrotropin receptor. Cell Immunol **148**:316–330, 1993.
69. Marasco WA, Becker EL. Antiidiotype as antibody against formyl peptide chemotaxis receptor of the neutrophil. J Immunol **128**:963–968, 1982.
70. Lassoued K, Danon F, Brouet JC. Human autoantibodies to lamin B receptor are also antiidiotypic to certain anti-lamin B antibodies. Eur J Immunol **21**:1959–1962, 1991.
71. Lambris JD, Ross GD. Characterization of the lymphocyte membrane receptor for Factor H (β1H-globulin) with an antibody to anti-factor H idiotype. J Exp Med **155**:1400–1411, 1982.
72. Hassermann M, Buschko J, Faussner A, Roscher AA, Hoebeke J, Burch RM, Muller-Esteri W. Antiidiotypic antibodies bearing the internal image of a bradykinin epitope. Production, characterization and interaction with the kinin receptor. J Immunol **147**:3882–3892, 1991.
73. Dobrila L, Antohe F, Heltianu C, Simionescu M. Albumin binding proteins of endothelial cells identified by antiidiotypic antibodies. Int Immunol **4**:789–796, 1992.
74. Colucci G, Waksal SD. Production of monoclonal antiidiotypes which recognize hepatitis B virus surface antigen. Eur J Immunol **17**:365–370, 1987.
75. Czop JK, Gurish MF, Kadish JL. Production and isolation of rabbit antiidiotypic antibodies directed against the human monocyte receptor for yeast β-glucans. J Immunol **145**:995–1001, 1990.
76. Galloway CJ, Madanat MS, Sarr T, Espevik T, Dumas ML, Mitra G, Ranges GH. Anti-tumor necrosis factor receptor and tumor necrosis factor against activity by an antiidiotypic antibody. Eur J Immunol **22**:3045–3048, 1992.
77. Schreiber AB, Courand PO, Andre C, Vray B, Strossberg A. Anti-alprenelol anti-Id antibodies bind to β-adrenergic receptors and modulate catecholamine-sensitive adenylate cyclase. Proc Natl Acad Sci USA **77**:7385–7389, 1980.
78. Glasel JA, Myers WE. Rabbit anti-Id antibodies raised against monoclonal anti-morphine IgG block μ and δ opiate receptor site. Life Science **36**:2523–2528, 1985.
79. Cacalano N, Cleveland WL, Erlanger BF. Characterization of a monoclonal antiidiotypic antibody that mimics cyclosporine A in a single binding system. J Immunol **147**:3012–3017, 1991.
80. Ku HH, Cleveland WL, Erlanger BF. Monoclonal antibodies to adenosine receptor by an autoantiidiotypic approach. J Immunol **136**:2376–2384, 1987.
81. Cleveland WL, Wasserman NH, Sarangarajan P, Penn AS, Erlanger BF. Monoclonal antibodies to the acetylcholine receptor by a normally functioning autoantiidiotypic mechanism. Nature **305**:56–57, 1983.
82. Sege K, Pete PA. Antiidiotypic antibodies against anti-Vitamin A transporting protein react with prealbumin. Nature **271**:167–168, 1978.
83. Perosa F, Ferone S. Murine antiidiotypic monoclonal antibodies that bear the internal image of HLA-DR allospecificities. J Clin Invest **84**:907–914, 1989.
84. Baniyash M, Eshhar Z. Anti-anti-IgE idiotypic antibodies mimic IgE in their binding to the Fcε receptor. Eur J Immunol **17**:1337–1342, 1987.
85. Sarafati M, Duncan D, Delespesse G. Production and characterization of rabbit antiidiotypic antibodies specific to mouse monoclonal anti-human IgE and reaching with IgE binding factors and lymphocyte receptors for IgE. Eur J Immunol **16**:325–331, 1981.
86. Tsuchiya N, Williams RC, Hutt-Fletcher LM. Rheumatoid factors may bear the internal image of the Fcγ binding protein of herpes simplex virus, Type 1. J Immunol **144**:4742–4748, 1990.
87. Fong S, Gilberston TA, Chen PP, Vaugham JH, Carson DA. Modulation of human rheumatoid factor-specific lymphocyte responses with a crossreactive antiidiotype bearing the internal image of antigen. J Immunol **132**:1183–1189, 1984.
88. Leu JG, Chen BX, Diamanduros AW, Erlanger BF. Idiotype mimicry and the assembly of a supramolecular structure: An antiidiotypic antibody that mimics taxols in its tubulin-microtuble interaction. Proc Natl Acad Sci USA **91**:10690–10694, 1994.
89. Spitzer RE, Stitzel AE, Tsokos GC. Autoantibody to the alternative pathway C3/C5 convertase and its antiidiotypic response. J Immunol **148**:137–141, 1992.
90. Lubahn BC, Reisner HM. Characterization of monoclonal antiidiotypic antibodies to human anti-factor VII antibodies. Proc Natl Acad Sci USA **87**:8232–8236, 1990.
91. Karpatkin S, Nordi MA, Kouri YH. Internal-image antiidiotypic HIV-1 gp120 antibody in human immunodeficiency virus 1 (HIV-1) seropositive individuals with thrombocytopenia. Proc Natl Acad Sci USA **89**:1487–1491, 1992.
92. Salek MN, Stapleton JD, Khazaeli MB, LoBuglio AF. Generation of a human antiidiotypic antibody that mimics the GD2 antigen. J Immunol **151**:3390–3398, 1993.
93. Chen ZJ, Yang H, Ferrone S. Human high molecular weight melanoma-associated antigen mimicry by mouse antiidiotypic monoclonal antibody MK2-23. J Immunol **147**:1082–1090, 1991.
94. Buattacharya-Chatterjee M, Chatterjee SK, Vasile S, Seon BK, Kohler H. Idiotype vaccines against human T cell leukemia. J Immunol **141**:1398–1403, 1988.
95. Herlyn D, Ross AH, Iliopoulos D, Koprowski H. Induction of specific immunity to human colon carcinoma by antiidiotypic antibodies to monoclonal antibody CD17-1A. Eur J Immunol **17**:1649–1652, 1987.
96. Smorodinsky NI, Ghendler Y, Bakimer R, Chaitchuk S, Keydar I, Shoenfeld Y. Towards an idiotype vaccine against mammary tumors. Eur J Immunol **18**:1713–1718, 1988.
97. Raychandhuri S, Saeki Y, Chen JJ, Iribe H, Fuji H, Kohler H. Tumor-specific idiotype vaccine. J Immunol **139**:271–278, 1987.
98. Shearer MH, Lanford RL, Kennedy RC. Monoclonal antiidiotypic antibodies induce humoral immune responses specific for simian virus 40 large tumor antigen in mice. J Immunol **145**:932–939, 1990.
99. Saeki V, Chen JJ, Shi L, Raychandhuri S, Kohler H. Characterization of regulatory idiotype-specific T cell clones to a monoclonal antiidiotypic antibody mimicking a tumor associated antigen. J Immunol **142**:1046–1056, 1983.
100. Rubinstein LJ, Goldberg B, Hiernaux J, Stein KE, Bona CA. Idiotype-antiidiotype regulation. V. The requirement for immunization with antigen and monoclonal antiidiotypic antibodies for the activation of $\beta \rightarrow 6$ and $\beta \rightarrow 1$ polyfructosan reactive clones in BALB/c mice treated at birth with minute amounts of anti-A48 idiotype antibodies. J Exp Med **158**:1129–1144, 1985.
101. McNamara MK, Ward RE, Kohler H. Monoclonal idiotype vaccine against *Streptococcus pneumoniae* infection. Science **226**:1325–1326, 1985.
102. Stein K, Soderstrom J. Neonatal administration of idiotype or antiidiotype primes for protection against *Escherichia coli* K13 infection in mice. J Exp Med **160**:1001–1011, 1984.
103. Monafo WJ, Greenspan NS, Cebra-Thomas JA, Davie JM. Modulation of the murine immune response to streptococcal group A carbohydrate by immunization with monoclonal anti-idiotope. J Immunol **139**:2702–2707, 1987.
104. Su S, Ward MN, Apicella MA, Ward RE. A nontoxic, idiotope vaccine against gram-negative bacterial infections. J Immunol **148**:234–238, 1992.
105. Schreiber JR, Nixon KL, Tosi MF, Pier GB, Patawaran MB. Antiidiotype-induced, lipopolysaccharide-specific antibody response to Pseudomonas aeruginosa. II. Isotype and functional activity of the anti-idiotype-induced antibodies. J Immunol **146**:188–193, 1991.
106. Rolf JM, Gaudin HM, Tirrell SM, MacDonald AB, Eidels L. Antiidiotypic antibodies that protect cells against the action of diphtheria toxin. Proc Natl Acad Sci USA **86**:2036–2039, 1989.
107. Spitsin SV, Drobyshevskaya EI, Barkhatova OI, Belyi YF, Tartakovsky IS, Nesterenko VG. Induction of the immune response to Legionella pneumophila cytolysin by monoclonal and antiidiotypic antibodies. J Immunol **147**:2001–2005, 1991.
108. Zaghouani H, Goldstein D, Shah H, Anderson S, LaCroix M, Dionne G, Kennedy R, Bona CA. Induction of antibodies to

the envelope protein of the human immunodeficiency virus by immunization with monoclonal antiidiotypes. Proc Natl Acad Sci USA **88**:5645–5649, 1991.
109. Kang CY, Nara P, Chamat S, Caralli V, Chen A, Nguyen ML, Yoshima H, Morrow JW, Ho DD, Kohler H. Antiidiotype monoclonal antibodies elicits broadly neutralizing anti-gp120 antibodies in monkey. Proc Natl Acad Sci USA **89**:2546–2550, 1992.
110. Hohmann A, Peters V, Comacchio R, Bradley J. Mouse monoclonal antiidiotypic antibodies to HIV P24: Immunochemical properties and internal imagery. Mol Immunol **30**:521–527, 1993.
111. Gaulton GN, Sharpe AH, Chang DW, Fields BN, Green MI. Syngeneic monoclonal internal image antiidiotypes as prophylactic vaccines. J Immunol **137**:2930–2936, 1986.
112. Uytdehaag FGCM, Osterhaus ADME. Induction of neutralizing antibody in mice against poliovirus type II with monoclonal antiidiotypic antibody. J Immunol **134**:1225–1229, 1985.
113. Anders EM, Kapaklis-Daliyannis GP, White DO. Induction of immune response to influenza virus with antiidiotypic antibodies. J Virol **2**:103–115, 1989.
114. Dinca L, Newirth S, Schulman J, Bona C. Induction of antihemagglutinin antibodies by polyclonal antiidiotype antibodies. Viral Immunol **6**:75–84, 1993.
115. Regan KJ, Wunner WH, Wiktor T, Koprowski H. Antiidiotypic antibodies induce neutralizing antibodies to rabies virus glycoproteins. J Virol **48**:660–666, 1983.
116. Kennedy RC, Dreesman GR, Butel JS, Lanford RE. Suppression of in vivo tumor formation induced by simian virus 40-transformed cells in mice receiving antiidiotypic antibodies. J Exp Med **161**:1432–1449, 1985.
117. McClintock PR, Prabhakar BS, Notkins AL. Antiidiotypic antibodies to monoclonal antibodies that neutralize Coxsackie virus B4 do not recognize viral receptors. Virology **150**:352–360, 1986.
118. Lamarre A, Lecomte J, Talbot PJ. Antiidiotypic vaccination against murine coronavirus infection. J Immunol **147**:4256–4262, 1991.
119. Grieder FB, Schultz KT. Antiidiotypic antibody mimicry of a bluetongue virus neutralizing antigen. J Immunol **144**:2627–2631, 1990.
120. Baxt B, Garmendia AE, Morgan DO. Characterization of antiidiotypic antibodies generated against foot-and-mouth disease virus neutralizing monoclonal antibodies. Viral Immunol **2**:130–138, 1989.
121. Kennedy RC, Eichberg JW, Lanford RE, Dreesman GR. Antiidiotype antibody vaccine for type B viral hepatitis in chimpanzees. Science **232**:220–223, 1986.
122. Thanavala YM, Bond A, Tedder R, Hay FC, Roitt IM. Monoclonal internal image antiidiotypic antibodies of hepatitis B antigen. Immunology **55**:197–204, 1985.
123. Grzyck JM, Capron M, Lambert PH, Dissons C, Torres S, Capron A. An antiidiotypic vaccine against experimental schistosomiasis. Nature **316**:74–76, 1985.
124. Kresina TF, Olds GR. Antiidiotypic antibody vaccine in murine Schistosomiasis mansoni. Comprising the internal image of antigen. J Clin Invest **83**:912–920, 1989.
125. Sachs DL. Induction of protective immunity using antiidiotypic antibodies: Immunization against experimental trypanosomiasis. In: Kohler H, Urbain J, Cazenave PA, Eds. Idiotypy in Biology and Medicine. New York: Academic Press, pp401–416, 1984.
126. Chanh TC, Rappocciolo G, Hewetson JF. Monoclonal antiidiotype induces protection against the cytotoxicity of the trichothecene mycotoxin T-2. J Immunol **144**:4721–4728, 1990.