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*J Immunol* 1999; 162:4790-4795;

http://www.jimmunol.org/content/162/8/4790

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*The Journal of Immunology* is published twice each month by
The American Association of Immunologists, Inc.,
1451 Rockville Pike, Suite 650, Rockville, MD 20852
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Print ISSN: 0022-1767 Online ISSN: 1550-6606.
DNA Vaccination Against the Idiotype of a Murine B Cell Lymphoma: Mechanism of Tumor Protection

Athanasia D. Syrengelas and Ronald Levy

Several studies have shown that immunization with DNA, which encodes the idiotypic determinants of a B cell lymphoma, generates tumor-specific immunity. Although induction of antiidiotypic Abs has correlated with tumor protection, the effector mechanisms that contribute to tumor protection have not been clearly identified. This study evaluated the tumor protective effects of humoral and cellular immune mechanisms recruited by idiotype-directed DNA vaccines in the 38C13 murine B cell lymphoma model. Antiidiotypic Abs induced by DNA vaccination supported in vitro complement-mediated cytotoxicity of tumor cells, and simultaneous transfer of tumor cells and hyperimmune sera protected naive animals against tumor growth. However, in vitro stimulation of immune splenocytes with tumor cells failed to induce idiotype-specific cytotoxicity, and following vaccination, depletion of CD4 or CD8 T cell subsets did not compromise protection. Furthermore, protection of naive recipients against tumor challenge could not be demonstrated either by a Winn assay approach or by adoptive transfer of spleen and lymph node cells. Thus, in this experimental model, current evidence suggests that the tumor-protective effects of DNA vaccination can be largely attributed to idiotype-specific humoral immunity. The Journal of Immunology, 1999, 162: 4790–4795.

Materials and Methods

Mice

Six- to eight-week-old female C3H/HeN mice were obtained from Harlan Sprague-Dawley (San Diego, CA) and housed at the Laboratory Animal Facility at Stanford University Medical Center (Stanford, CA).

Cell lines

General background. 38C13 is a carcinogen-induced B cell lymphoma tumor that expresses IgM/s on its surface and has been previously described (5). All experiments were performed from a working cell bank of uniformly frozen 38C13 cells. 38C13 cells were maintained in RPMI 1640, 10% heat-inactivated FCS, 2 mM l-glutamine, 100 U/ml penicillin, 100 lg/ml streptomycin, and 50 lg M 2-ME (eRPMI-10) at 37°C, 5% CO₂ in a humidified incubator. V1 cells, a surface Ig-positive, idiotypic-negative genetic variant of 38C13 (13), were similarly maintained.

Tumor challenge. 38C13 cells were grown for 72 h, and cells in logarithmic growth phase were washed three times in RPMI 1640 (no additives) and appropriately diluted. From 2 to 3 wk after the last immunization, mice were injected i.p. or s.c. with the designated number of tumor cells in 0.5 ml RPMI 1640. Statistical analysis of survival was performed using the Gehan test.

DNA vaccines

Design. Construction and verification of plasmids used for DNA immunization have been previously described (2), as has the mammalian expression vector from which all DNA vaccines were constructed (14). Briefly, the plasmids used for these experiments, pId-GM and pCtrl-GM, encode chimeric Ig-GM-CSF fusion constructs (Fig. 1). Specifically, the

1 This work was supported by National Institutes of Health-U.S. Public Health Service Grant CA 33399. A.D.S. was supported by a National Institutes of Health immunology training grant (ST32 AI 07290). R.L. is an American Cancer Society Clinical Research Professor.

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DNA vaccines contain murine tumor Ig V region sequences, human Ig γ1 and κ C region sequences, and the murine GM-CSF sequence fused to that of the heavy chain C termini using a Gλy-Gλy linker as previously described (2, 15). “Id” refers to the relevant 38C13 heavy and light chain V regions (5), and “Ctrl” refers to those from another murine B cell lymphoma, BCL1 (16). Ig heavy and light chains are independently encoded within each plasmid, and transcription of each chain is driven by separate cytomegalo-virus promoters. For the purpose of DNA immunization, other eukaryotic drug resistance genes were removed (14). Only coding regions were cloned into the constructs, and each gene was followed by a downstream poly(A) tail. All plasmids contain the bacterial ampicillin resistance gene.

**Protection.** Plasmids were electroporated into E. coli XL1-Blue and grown from single colonies for 20–24 h at 37°C in the presence of 50 μg/ml ampicillin. Closed circular plasmid DNA was then isolated using the Wizard Megaprep Purification Kit (Promega, Madison, WI). Purified DNA was precipitated, washed with 70% ethanol, and resuspended in saline at a final concentration of 1.0 μg/ml. The ratio of OD260/280 ranged from 1.8 to 2.0, and each preparation was analyzed by restriction digest mapping. The DNA was stored at −20°C in 1.0 ml aliquots until the day of immunization.

**Immunizations.** Plasmids were injected i.m. three times at 1-wk intervals using a 0.3-ml ultraline insulin syringe. Mice received a total of 100 μg of DNA, 50 μg (50 μl) in each quadrirect. From 2 to 3 wk after the final immunization, immune sera were collected by tail vein bleeding and assayed for the presence of anti-Id Abs as previously described (2). For tumor challenge experiments, mice were then injected i.p. or s.c. with 38C13 tumor cells.

**Protein vaccines**

The term “Id-GM protein” (Fig. 1) refers to the product of the pId-GM plasmid, which has been described above. Id-GM protein was produced and affinity purified as previously described (15) and brought to 0.25 mg/ml in PBS. Mice were immunized two times at 2-wk intervals with 200 μl (50 μg) i.p.

**Complement-mediated cytotoxicity**

Immune serum was collected on the same day from mice immunized two times with the chimeric Id-GM protein or three times with pId-GM or pCtrl-GM DNA (10 days after the last protein vaccine or 17 days after the last DNA vaccine). The pId-GM vaccine induced humoral responses that were approximately two orders of magnitude below those generated by the Id-GM protein. To equalize the concentration of anti-idiotypic Abs, serum from mice vaccinated with Id-GM protein was first appropriately diluted into normal mouse serum. Using activated complement medium (RPMI 1640 containing 0.3% BSA, 50 μM L-2,ME, and 25 mM HEPES), 50 μl containing 10 4 51 Cr-labeled 38C13 cells were added to a 96-well U-bottom tissue culture plate containing 50 μl of activated complement medium at an effector:stimulator ratio of 20:1 and allowed to incubate for 24 h at 37°C. The plate was then incubated on ice for 45 min to allow binding of immune serum to labeled cells. After this period, the plate was spun for 5 min at 1000 rpm. The majority of the supernatant was carefully removed, and 200 μl activated complement medium containing a 1:10 dilution of rabbit complement (Low-Tox-M rabbit complement, Cedarlane Laboratories, Hornby, Ontario, Canada) was added to each well. The plate was incubated for 1 h at 37°C, 5% CO2 in a humidified incubator. Following this incubation, the plate was similarly spun, and 100 μl supernatant was removed from each well in order to measure release of 51Cr. To determine maximum 51Cr release, labeled 38C13 or V1 cells were lysed with Triton X-100. The percentage of cytotoxicity was determined by [(sample cpm − spontaneous cpm)/(maximum cpm − spontaneous cpm)] × 100.

**Immune serum transfer**

Ten C3H/HeN mice per group were immunized with pId-GM or pCtrl-GM as described above. From 2 to 3 wk after the third immunization, mice were sacrificed, and spleens and draining lymph nodes (inguinal and paraaortic) were collected and pooled within each group. Single cell suspensions were prepared using the frosted ends of sterile glass slides, and RBC were removed using a Lympholyte M density gradient (Cedarlane Laboratories). Cells were washed with RPMI 1640 medium and resuspended at 6 × 107 cells/ml in 5.0 ml RPMI 1640 medium supplemented with 2% normal mouse serum. 38C13 tumor cells were prepared as described above and brought to a final concentration of 400 cells/ml using RPMI 1640 medium (no additives). A total of 5 ml of the 38C13 cell suspension was added to the 5 ml pId-GM or pCtrl-GM lymphocyte suspension. Thus, each 10 ml suspension now contained 38C13 cells at 200 cells/ml, 1% normal mouse serum, and relevant or control lymphocytes at 3 × 106 cells/ml. The suspensions were incubated in 75-ml tissue culture flasks at 37°C, 5% CO2 in a humidified incubator for 1 h. Following the incubation, two groups of 10 naive mice were injected i.p. with 1 ml of the relevant or control suspension (200 38C13 cells and 3 × 107 relevant or control lymphocytes, effector:target cell ratio of 1.5 × 107). Animals were followed for survival.

**Winn assay**

Ten C3H/HeN mice per group were immunized with pId-GM or pCtrl-GM as described above. From 2 to 3 wk after the third immunization, mice were sacrificed, and spleens and draining lymph nodes (inguinal and paraaortic) were collected and pooled within each group. Single cell suspensions were prepared using the frosted ends of sterile glass slides, and RBC were removed using a Lympholyte M density gradient (Cedarlane Laboratories). Cells were washed with RPMI 1640 medium and resuspended at 6 × 107 cells/ml in 5.0 ml RPMI 1640 medium supplemented with 2% normal mouse serum. 38C13 tumor cells were prepared as described above and brought to a final concentration of 400 cells/ml using RPMI 1640 medium (no additives). A total of 5 ml of the 38C13 cell suspension was added to the 5 ml pId-GM or pCtrl-GM lymphocyte suspension. Thus, each 10 ml suspension now contained 38C13 cells at 200 cells/ml, 1% normal mouse serum, and relevant or control lymphocytes at 3 × 106 cells/ml. The suspensions were incubated in 75-ml tissue culture flasks at 37°C, 5% CO2 in a humidified incubator for 1 h. Following the incubation, two groups of 10 naive mice were injected i.p. with 1 ml of the relevant or control suspension (200 38C13 cells and 3 × 107 relevant or control lymphocytes, effector:target cell ratio of 1.5 × 107). Animals were followed for survival.

**Adoptive transfer of immune lymphocytes**

Nine C3H/HeN mice per group were immunized three times with pId-GM or pCtrl-GM as described above. The presence of specific anti-idiotypic Abs was confirmed by ELISA as previously described (2). Approximately 2 wk after the last immunization, mice were sacrificed, and spleens and draining lymph nodes (inguinal and paraaortic) were collected, pooled within each group, prepared as described for the Winn assay, and resuspended in 3.0 ml RPMI 1640 (no additives). Two groups of nine naïve C3H/HeN mice, which had been sublethally irradiated with 400 rad earlier in the day, were injected i.v. with 0.3 ml (about 4 × 107 cells) of the relevant or control lymphocyte suspension. Five days later, mice were challenged i.p. with 200 tumor cells in 0.5 ml RPMI 1640 as described above. Mice were followed for survival.

**In vitro cytotoxicity against tumor cell line**

Mice were immunized as described (except vaccines were given every 3 wk instead of every 1 wk) with pId-GM or pCtrl-GM. From 4 to 8 wk after the last immunization, mice were sacrificed, and spleens were harvested and prepared as described for the Winn assay. Briefly, splenocytes were incubated at 37°C, 5% CO2 in a humidified incubator in cRPMI-10 with irradiated 38C13 tumor cells (3000 rad) and 1-U/ml human IL-2 (added after 24 h) at an effector:stimulator cell ratio of 100:1 or 10:1. Six days later, cells were washed and similarly incubated with [3H]thymidine-label- ed 38C13 tumor target cells (3 × 104) at an effector:target cell ratio of 20:1, labeled with 4 μCi/ml for 6–10 h) in 96-well V-bottom tissue culture plates at specified E:T ratios. Four hours later, cells were harvested onto glass fiber filter paper (Tomtec Harvester 96, Orange, CT), and incorporation of radioactivity was measured by scintillation counting (Wallac Microbeta 1450, Gaithersburg, MD). In this assay, CTL lysis results in the breakdown of target cell DNA 200 cells/ml, and the amount of radioactive DNA captured by the filter paper (17). Thus, maximum signal is derived from spontaneous target cell death in medium alone. The percentage of cytotoxicity was determined by [(maximum cpm − sample cpm)/maximum cpm] × 100.
FIGURE 1. DNA and protein vaccines. The pld-GM construct expresses a secreted, chimeric Ig with murine GM-CSF fused to the heavy chain C termini (Id-GM protein). mVκ is the murine 38C13 κ light chain V region, mVH is the murine 38C13 heavy chain V region, hCκ is the human κ-chain C region, and hCγ1 is the human IgG1 heavy chain C region. “Id” refers to the idiotype of the 38C13 murine B cell lymphoma. As a control, a plasmid encoding another murine idiotype, “Ctrl,” was also constructed and designated pCtrl-GM (not shown). Plasmids were used in their uncut state for all immunizations.

All points were performed in duplicate or triplicate (six wells for medium alone), and data are presented as mean cpm ± SD.

Results

Vaccines

The antiidotypic DNA and protein vaccines used in this study have been previously described (2, 15). Briefly, DNA vaccines pld-GM and pCtrl-GM encode a chimeric Ig-GM-CSF fusion construct (Fig. 1). The use of the chimeric Ig-cytokine fusion constructs was based on results from prior work with DNA vaccines encoding Ig. Specifically, xenogeneic C regions were required for the induction of humoral immunity (2) as well as tumor protection (data not shown). Additionally, the use of the murine GM-CSF sequence was found to induce earlier Ab responses in a higher proportion of immunized animals. In this study, DNA-immunized mice consistently developed Abs against the appropriate idiotype (data not shown).

Protective role of humoral immunity

Prior work with DNA immunization against idiotypic determinants has shown that protection against tumor growth correlates with the induction of a threshold level of approximately 1 μg/ml antiidiotypic Abs (2, 3). In the present work, the role of humoral immunity was further assessed using both in vitro and in vivo approaches. In in vitro assays of complement-mediated cytotoxicity, incubation of 38C13 tumor cells with serum from mice immunized with pld-GM DNA resulted in lysis of tumor (Fig. 2). The pld-GM immune serum did not mediate lysis of a surface Ig-positive, idiotype-negative genetic variant of this tumor, and serum from mice immunized with pCtrl-GM DNA or Id-GM protein, the product of pld-GM DNA, did not appreciably lyse tumor (Fig. 2). The ability of immune serum to inhibit tumor growth was also tested in vivo. Naïve recipients given a mixture of pld-GM-immune serum and an otherwise lethal dose of tumor cells were protected against tumor growth, whereas mice similarly treated with pCtrl-GM immune serum were not protected (Fig. 3A). The presence of anti-idiotypic Abs did not affect in vitro tumor growth (data not shown). This result was consistent with that of a previous study in which the presence of anti-idiotypic mAbs had no effect on the in vitro growth of 38C13 cells (6, 18).

FIGURE 2. Complement-mediated cytotoxicity. Immune serum was collected from mice immunized with Id-GM protein, pld-GM DNA, or pCtrl-GM DNA. Serum from Id-GM protein-immunized mice was diluted into normal serum in order to equalize the anti-idiotypic Ab titers among the groups. Several dilutions of immune serum were incubated in vitro with 51Cr-labeled 38C13 or V1, a surface Ig-positive but idiotype-negative genetic variant of 38C13, and rabbit complement as described. Complement-mediated cytotoxicity was measured by 51Cr release into supernatant. Each point represents the average ± SD of triplicate wells. Symbols represent the same groups in both graphs.

No protective role of cellular immunity

In addition to recruiting humoral immunity, DNA immunization may have also induced idiotype-specific cellular immunity. To further explore this possibility, in vitro assays of cellular immunity were initially conducted. Although specific proliferative responses against human C regions were reproducibly demonstrated, in vitro stimulation of immune lymphocytes with native tumor Ig failed to demonstrate idiotype-specific proliferative response (data not shown). Furthermore, immune lymphocytes that had been stimulated with irradiated tumor cells also failed to exhibit detectable, idiotype-specific cytotoxicity against this tumor (Fig. 4).

Despite this inability to demonstrate in vitro idiotype-specific cellular immune responses, T cells may still have been necessary for protection against tumor in vivo. To determine if T cells contributed to protection, mice were immunized with pld-GM or pCtrl-GM DNA, depleted of CD4+ and/or CD8+ T cells, and challenged with tumor cells. Flow cytometry analysis of lymph node and PBL 1 day prior to tumor challenge confirmed greater than 98% depletion of the appropriate T cell subset, and depletion was maintained to the same degree for at least 2 wk following tumor challenge (data not shown). As shown in Fig. 5, depletion of both CD4 and CD8 T cells did not compromise protection against tumor growth. Similar results were obtained when only one T cell subset (either CD4+ or CD8+) was depleted in relevantly immunized animals (data not shown).

Since anti-idiotypic Abs induced by DNA immunization confer protection against tumor in the absence of immune lymphocytes (Fig. 3A), a protective effect of idiotype-specific CD4+ and/or CD8+ T cells in the depletion studies may have been masked by the presence of anti-idiotypic Abs, which were detected in all vaccinated animals. To eliminate the effect of humoral immunity, naïve recipients were treated with lymphocytes that were harvested from immunized donors. In vitro incubation of tumor cells and immune lymphocytes followed by injection of this suspension into naïve recipients (Winn assay) did not inhibit tumor growth (Fig. 3B). Additionally, adoptive transfer of immune lymphocytes into sublethally irradiated recipients failed to protect animals against a subsequent challenge with tumor (Fig. 3C). Anti-idiotypic Abs...
were not detected in serum samples taken from these recipients immediately prior to tumor challenge (data not shown).

Discussion

In the present study, the effector mechanisms recruited against the 38C13 idiotype using naked DNA as the immunogen have been further characterized. Using both in vitro and in vivo approaches, our results confirmed the protective effect of anti-idiotypic Abs against B cell lymphoma but failed to demonstrate any evidence of idiotype-specific cellular immunity. Specifically, DNA vaccination induced complement-fixing anti-idiotypic Abs but failed to generate both idiotype-specific proliferative and cytotoxic cellular responses. Moreover, naive animals that had been transplanted with tumor cells precoated with hyperimmune serum were protected against tumor growth, whereas passive transfer of immune lymphocytes did not afford tumor protection.

Although the protective effects of humoral immunity have been demonstrated in prior studies of protein vaccination in the 38C13 model (7), it is possible that DNA vaccines induce a humoral response that is preferable to that induced by protein vaccines. In our
previous study, the anti-idiotypic Ab response induced by immu-

nization with pld-GM DNA was predominantly of the IgG2a iso-
type, whereas that induced by immunization with the protein

product of the DNA vaccine, namely Id-GM protein, was predomi-
nantly of the IgG1 isotype (2). Studies of passive immunization

using anti-idiotypic mAbs have clearly demonstrated the superior

antitumor effects of Abs of the IgG2a isotype (19). Using isotype-

switch variants containing identical V regions, IgG2a anti-
idiotypic mAbs induced superior in vitro Ab-dependent cellular

cytotoxicity (ADCC) activity against the 38C13 tumor and, more

importantly, were at least 100-fold more effective at conferring in

vivo tumor protection in comparison to their IgG1 counterparts

(19). Thus, the isotype profile induced by DNA vaccines may re-

sult in more effective targeting of tumor cells despite an anti-
idiotypic Ab tier two orders of magnitude below that generated by

protein immunization (2), whereas the higher titers induced by

protein vaccines most likely compensate for the induction of a

suboptimal class of Ab. Specifically, the predominance of IgG2a

anti-idiotypic Abs following DNA vaccination may have resulted

in more efficient recruitment of Ab-mediated effector mechanisms.

The ability of immune serum from DNA but not protein-immu-
nized animals to engage in vitro complement-mediated cytotoxic-

ity against tumor supports this possibility.

At this time, the mechanism of Ab-mediated inhibition of tumor
growth has not been precisely identified in the case of idiotype-
directed DNA vaccines. Although studies of mAb isotype-switch

variants implicate a role for Ab-dependent effector mechanisms

such as complement and ADCC, these Abs may also inhibit tumor
growth through direct signaling effects. In one study, passive trans-
fer of anti-idiotypic F(ab')2 fragments, which lack the Ig domains

necessary for the recruitment of effector mechanisms such as

ADCC and complement, protected animals against the growth of

38C13 tumor (6). Thus, although anti-idiotypic Abs had no effect

on the in vitro growth of 38C13 (6, 18), they appear to have had a

direct cytotoxic effect in vivo. This isotype-independent mech-

anism may have also contributed to the therapeutic efficacy of Abs

induced by DNA and protein vaccines. Interestingly, in a recent

study also using the 38C13 model, a genetically engineered anti-
idiotypic scFv molecule, which contained only V regions, failed to

show any in vivo therapeutic effect (20). In contrast, its Ig coun-

terpart, which contained the identical V regions as well as C re-

gions, protected animals against tumor growth (20). Since growth

inhibition may depend on the level of surface receptor cross-link-

ing (21), the inability of the monovalent scFv to cross-link tumor

Ig may have abrogated a direct antitumor effect despite its ability
to recognize tumor idiotype. Other studies of anti-idiotypic Ab

have also provided evidence for direct antitumor activity. In a study

of patients whose B cell lymphomas were treated with anti-
idiotypic mAbs, Ab-induced intracellular signaling patterns corre-
lated with clinical regression of the patient’s tumor (22). Addi-
tionally, several animal studies have implicated direct antitumor
activity using various mAbs that target key B cell-signaling mol-

eules, including CD19, CD40, and idiotyp (21, 23–25). One of these

studies clearly demonstrated that in vitro antitumor activity
does not necessarily predict therapeutic efficacy in vivo (25). Thus,

further work regarding the protective role of specific effector

mechanisms should be conducted using in vivo experimental

approaches.

Since depletion of CD4+ and CD8+ T cell subsets partially

compromised the protective effect of protein vaccines (7–9), the

inability of DNA immunization to generate any detectable cellular

immunity in this study was somewhat unexpected. DNA-encoded

Ag should, in theory, be processed and presented through both

endogenous and exogenous pathways, whereas protein Ags should

be processed predominantly through exogenous pathways. Thus,
in comparison to protein immunization, DNA immunization was

expected to have been more rather than less effective at recruiting

idiotype-specific, cytotoxic cellular immunity. Indeed, DNA can-
cer vaccines have induced protective, cytotoxic cellular immunity

in other models of malignant disease using tumor cells that had

been transfected with one of several surrogate, nonself Ags (26–31).

However, in this study, in vitro proliferation and cytotoxicity

assays, as well as in vivo adoptive transfer and T cell depletion

experiments, failed to demonstrate the induction of or a protective

role for idiotype-directed cellular immunity. Although prior work

with protein vaccines demonstrated a partial role for cellular im-

munity using T cell depletion experiments (7–9), additional studies

in both the BCL1 and 38C13 models failed to demonstrate either

idiotype-specific in vitro cytotoxicity against tumor (7, 8, 10) or

protection of naive animals following passive transfer of immune

lymphocytes (7, 10). Since the protein vaccines were manufac-
tured from tumor-derived ascites, it is possible that these vaccines

also contained small amounts of another tumor-associated Ag

against which cellular responses could be generated. Alternatively,
since anti-idiotypic Abs remain present in T cell-deficient animals,
it is possible that circulating IgG2a Abs may have recruited effec-
tor mechanisms more effectively in the DNA immunized animals,
thereby masking the effects of a relatively weak cellular response.

However, since studies of both protein (7) and now DNA vaccines

have failed to demonstrate protection following passive transfer of

immune lymphocytes, we believe it is unlikely that cellular im-

munity contributes a significant therapeutic effect against the

38C13 tumor.

Despite the inability to induce detectable idiotype-specific cel-

lular immunity in this study, work with protein vaccines in other

models of B cell malignancy has demonstrated the induction of

idiotype-specific cytotoxicity (32, 33) as well as a protective role

for idiotype-specific cellular immunity (33, 34). In the MOPC-315

plasmacytoma model, several studies have demonstrated that the

protective effects of vaccination against idiotype depended on cel-

lular rather than humoral effector mechanisms (35–37). Addition-

ally, in a recent study of idiotype-directed DNA vaccines, immu-
nization protected animals against the growth of a surface Ig-
negative myeloma, 5T33 (4). In comparison with lymphomas,

myelomas and plasmacytomas exhibit increased secretion and de-

creased surface expression of tumor Ig. As a result, adsorption by

circulating tumor Ig and decreased surface Ig density may com-

promise the protective effect of anti-idiotypic Abs. Thus, depend-

ing on the nature of the B cell malignancy, anti-idiotypic vaccines

should be designed to optimally recruit appropriate effector

mechanisms.

For the purpose of B cell lymphoma immunotherapy, the induc-

tion of antiidiotypic humoral immunity appears to be a reliable

marker of vaccine efficacy. Unlike antiidiotypic cellular effector

mechanisms, antiidiotypic humoral immunity was induced in all of

the aforementioned studies of murine B cell tumors. Furthermore,
in an ongoing clinical trial of protein immunization against tumor

idiotype, prolonged survival has correlated with the induction of

anti-idiotypic Ab responses (38). With regard to cellular immunity,
some tumor Ig may lack the idiotypic MHC epitopes necessary for

the recruitment of tumor-specific helper and/or cytotoxic T cells.

In contrast, idiotype-specific humoral immunity can be consis-
tently induced (2, 15, 39, 40) or enhanced (4, 41, 42) by chemically

or genetically attaching immunogenic, exogenously introduced

helper epitopes to tumor Ig.

In addition to generating humoral immunity, DNA vaccines tar-


ting Ig idiotype should also have the ability to recruit cellular effector

mechanisms in cases in which tumor Ig contains idiotypic
MHC epitopes that can be appropriately processed. This is especially important in the treatment of myeloma and plasma myeloma. These malignancies may be less susceptible to Ab-mediated effector mechanisms. Although the 38C13 idiotype may lack strong T cell epitopes, the isotype profile of the Ab response induced by this method is indicative of a Th1 response. Thus, in addition to possibly eliciting more effective humoral immunity, DNA vaccines may also prime the immune response for the recruitment of cellular immunity when idiotypic T cell epitopes are contained within tumor Ig and appropriately processed. To test this possibility, future work with antiidiotypic DNA vaccines can be conducted using B cell tumor models in which idiotype-specific cytotoxicity has been well documented.

Acknowledgments
We thank Dr. Dale Umetsu for kindly providing the HB129 cell line. A.D.S. dedicates this work to the memory of Deno Bonorris.

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