Antibody-Mediated Resolution of Light Chain-Associated Amyloid Deposits

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Primary light-chain-associated (AL) amyloidosis is characterized by the deposition in tissue of monoclonal light chains as fibrils. With rare exception, this process is seemingly irreversible and results in progressive organ dysfunction and eventually death. To determine whether immune factors can effect amyloid removal, we developed an experimental model in which mice were injected with amyloid proteins extracted from the spleens or livers of patients with AL amyloidosis. Notably, the resultant amyloidomas were rapidly resolved, as compared to controls, when animals received injections of an anti-light-chain monoclonal antibody having specificity for an amyloid-related epitope. The reactivity of this monoclonal antibody was not dependent on the V_L or C_L isotype of the fibril, but rather seemed to be directed toward a β -pleated sheet conformational epitope expressed by AL and other amyloid proteins. The amyloidolytic response was associated with a pronounced infiltration of the amyloidoma with neutrophils and putatively involved opsonization of fibrils by the antibody, leading to cellular activation and release of proteolytic factors. The demonstration that AL amyloid resolution can be induced by passive administration of an amyloid-reactive antibody has potential clinical benefit in the treatment of patients with primary amyloidosis and other acquired or inherited amyloid-associated disorders. (*Am J Pathol* 2000, 157:1239–1246)

Primary amyloidosis is a monoclonal plasma cell dyscrasia characterized by the pathological deposition as fibrils of immunoglobulin light-chain-related components (ie, AL amyloid) in the heart, kidney, liver, tongue, nerves, and other anatomical sites throughout the body.^{1–4} The relentless accumulation of fibrillar protein within these tissues leads to progressive organ dysfunction and eventually death.⁵ Heretofore, treatment of patients with this devastating disorder has focused on reducing the syn-

thesis of amyloidogenic precursor light chains using anti-plasma cell chemotherapy given in conventional or, more recently, in high doses combined with autologous stem cell transplantation.^{5–15} Such efforts have extended survival and, in some cases, resulted in improvement of organ function over time.^{13–16} However, certain patients, eg, the elderly or those with extensive cardiac amyloid deposition, are not candidates for such intensive therapy and their prognoses remain exceedingly poor.^{11–15} More recently, the administration of an experimental chemotherapeutic agent, the iodinated anthracycline I-DOX, was found serendipitously to accelerate removal of AL amyloid deposits without seemingly decreasing the bone-marrow plasma-cell population or the concentration of the precursor monoclonal Ig.¹⁷ Although this compound binds to various types of amyloid,¹⁸ the process that leads to resorption of fibrils is unknown. Further, the clinical usefulness of I-DOX is limited because of its hematological toxicity and the fact that the most striking therapeutic responses have occurred in patients with soft-tissue amyloid deposits, whereas little or no improvement has been noted in those with heart, kidney, or liver involvement.¹⁹

Amyloid deposition, thus, is not necessarily an irreversible process.^{20–22} In the case of AL, the existence of endogenous mechanisms that can effect amyloid removal has been evidenced by the finding that proteins extracted from pathological deposits most often consist of fragments formed from the degradation of the carboxyl-terminal portion of their precursor light chain molecules, presumably by neutrophil-derived proteases.¹ That AL fibrils are not eliminated totally may result from their nonforeign nature and the body's consequent failure to mount an effective immune response to this material. Additionally, the presence of other molecules co-deposited with amyloid, eg, P component²³ and certain glycosaminoglycans,^{24,25} has been alleged to interfere with amyloidolysis.^{26–28}

To investigate factors that could promote amyloid resolution, we have developed an *in vivo* experimental model involving mice in which amyloidomas were produced by

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the subcutaneous injection of human AL extracts. We now report the results of studies in which it was shown that this material was in fact removed by an immune mechanism associated with the formation of anti-amyloid antibodies and a resultant neutrophil cellular reaction. Based on these observations, we have generated a murine monoclonal antibody (mAb) that recognizes an epitope present on AL amyloid fibrils, as evidenced by enzyme-linked immunosorbent assay (ELISA), immunoblotting, and immunohistochemistry. This reagent, when administered to mice bearing human AL amyloidomas, bound to the fibrils and elicited a neutrophil response. Notably, this process resulted in rapid and complete elimination of the amyloid tumors, as compared to untreated animals. The demonstration that this anti-amyloid antibody can effect amyloidolysis *in vivo* provides a potentially novel means of therapy for patients with primary amyloidosis.

Materials and Methods

Amyloid Extraction and Chemical Characterization

The method used to prepare water-soluble amyloid extracts was essentially that described by Pras et al.²⁹ Briefly, 30 to 40 g of fresh-frozen (-80°C) or 10 g of lyophilized spleen or liver obtained postmortem from patients with AL amyloidosis were homogenized in ~ 300 ml of cold saline with a Virtis-Tempest apparatus (Virtis, Gardiner, NY). The homogenates were centrifuged at 6°C for 30 minutes at 17,000 rpm and residual saline-soluble material was removed by repeated homogenization and washing until the resultant supernatant had an OD of <0.10 at A_{280} . The pellet was then repeatedly homogenized, washed with cold deionized water, centrifuged, and the amyloid-containing supernatants lyophilized. The amount of protein recovered represented approximately one-third to one-fifth the weight of the starting material.

The light chain composition and V_L subgroup of the amyloid was determined by amino acid sequencing (Pro-cise Protein Sequencing System; Applied Biosystems, Foster City, CA) and ionizing mass spectroscopy (PE SCIEX API 150 EX; Perkin Elmer, Norwalk, CT) of high-performance liquid chromatography-separated peptides obtained by trypsin digestion of reduced and pyridylethylated protein³⁰ extracted from the water-soluble material with 6 mol/L guanidine HCl. The presence of the proteoglycan heparan sulfate was established using an Azure A assay.³¹

Monoclonal Antibody

A lyophilized sample of a V_{κ} fragment derived from endopeptidase cleavage of a $\kappa 4$ Bence Jones protein³² was dissolved in a 1 mol/L sodium acetate buffer, pH 4.9, to a final concentration of 1 mg/ml, precipitated from solution by heat treatment at 56°C for 15 minutes, and resuspended in phosphate-buffered saline (PBS) before injection into BALB/c mice. The techniques used to gen-

erate and characterize the murine mAb 11-1F4 were as previously described,^{33,34} as were those to fluorescein-label, obtain through pepsin digestion an F(ab')_2 fragment, and biotinylate the antibody.³⁵

Immunochemical Assays

For solid-phase ELISA,³³ 96-well flat-bottomed microwell plates (Corning CoStar, Corning, NY) were filled with 50 μl of a 10 $\mu\text{g/ml}$ solution of human light chain containing fibrils extracted from amyloidotic livers and spleens or with recombinant V_L fibrils^{36,37} and allowed to dry overnight by incubation at 37°C . After blocking and washing, appropriately diluted samples of mouse serum, culture fluid supernatant, or purified mAb were added to each well. Detection of bound antibody was accomplished using a peroxidase-labeled goat anti-mouse IgG antiserum (BioRad, Richmond, CA) and a 2,2'-amino-bis [3-ethylbenzthiazoline-6-sulfuric acid] substrate solution (Kirkegaard and Perry Laboratories, Gaithersburg, MD). Color development was terminated after 15 minutes by the addition of 2% oxalic acid and measured at an OD of 415 nm using an ELISA plate reader (Bio-Tek Instruments, Winooski, VT).

For Western blotting, amyloid extracts were subjected to sodium dodecyl sulfate-polyacrylamide gel electrophoresis under reducing conditions using the NuPAGE electrophoresis system (Novex, San Diego, CA). The proteins were electrotransferred to 0.45- μm Immobilon membranes (Millipore, Bedford, MA) and, after blocking, were exposed to mouse sera, purified murine anti-light chain mAbs,³⁴ or an anti-P component reagent (Calbiochem, La Jolla, CA). The blots were washed and treated with an alkaline phosphatase-labeled horse anti-mouse IgG antiserum (ABC kit, Vector Laboratories, Burlingame, CA). Bound protein was detected with the Western Blue Stabilized Substrate (Promega, Madison, WI). Immunohistochemical analyses were performed using the ABC technique as specified by the manufacturer (Vector) on 4- μm -thick deparaffinized tissue sections mounted on poly-L-lysine-coated slides. The primary and secondary antibodies and substrate used were 11-1F4, an affinity-purified goat anti-mouse IgG horseradish-peroxidase conjugate (Bio-Rad), and diaminobenzidine (Vector), respectively.

Microscopy

Four- to 6- μm -thick tissue sections were cut for light microscopy. Stains for leukocyte esterases were performed using naphthol AS-D chloroesterase and α -naphthyl acetate solutions (Sigma Diagnostics, St. Louis, MO), according to the manufacturer's directions. To detect amyloid, the sections were treated with a freshly prepared alkaline Congo red solution and viewed under polarized light using a filter polarizer (Leitz, Rockleigh, NJ) with a gypsum plate and a filter analyzer. For electron microscopy, precipitates were applied to formvar carbon-coated copper grids, air-dried, stained with 1% phosphotungstic acid, and viewed with a Hitachi H-600

electron microscope (Hitachi Science Systems, Ltd., Ibaraki, Japan).

Amyloidoma Formation

Lyophilized water-soluble amyloid extracts were suspended in 25 ml of sterile saline and homogenized with a PCU-2 Polytron apparatus (Brinkman, Luzerne, Switzerland). The fibrils were sedimented by centrifugation at 6°C for 30 minutes at 17,000 rpm; the resultant pellet was resuspended in 1 ml of sterile saline and rehomogenized. This solution was injected subcutaneously between the scapulae of mice using an 18-gauge needle attached to a 6-ml syringe. The size of the resultant amyloidoma was measured by daily palpation and confirmed at necropsy. High-resolution X-ray-computed tomography images were acquired using a microCat apparatus (Oak Ridge National Laboratory, Oak Ridge, TN).

Mice

BALB/c, CD-18 null, and C.B-17 SCID mice were purchased from Charles River Laboratories (Wilmington, MA), Jackson Laboratories (Bar Harbor, ME), and Taconic (Germantown, NY), respectively. All mice were treated in accordance with National Institutes of Health regulations under the aegis of a protocol approved by the University of Tennessee's Animal Care and Use Committee.

Results

To investigate humoral or cellular factors that can facilitate amyloid removal, we developed an *in vivo* experimental model in which 6-week-old BALB/c mice were injected subcutaneously between the scapulae with 50 to 200 mg of water-soluble AL amyloid extracts. The composition of this material was established by chemical, immunoblotting, amino acid sequence, and ionizing mass spectroscopic analyses where the predominant protein species were found to be κ or λ light chain-related molecules that, in most cases, consisted primarily of the variable region (V_L) plus the first ~50 residues of the constant region (C_L) and, in others, V_L fragments or intact molecules. Additionally, these extracts contained the expected amyloid-associated P- component,²³ as well as the proteoglycan

Figure 1. Human AL amyloidoma model. **Top:** Appearance of a mouse injected subcutaneously between the scapulae with 200 mg of a human AL κ amyloid extract (**left**) and resolution of the amyloidoma after 14 days (**right**). **Bottom:** Radiographic (CT scan) images of a mouse after injection of a human AL κ amyloid extract (**left**) and 21 days later (**right**).

heparan sulfate.²⁴ The injected material formed a readily visible, palpable mass on the backs of animals, the size of which depended on the amount of material injected (eg, 0.2 to 2.5 cm in maximum diameter). The amyloidoma remained localized and unchanged for ~10 to 24 days, as evidenced by high-resolution X-ray-computed tomography; after that point, the tumors began to regress and eventually disappeared throughout an ~4-day period (Figure 1). This response occurred regardless of the κ or λ nature or the V_L subgroup of the amyloid extract; however, in studies involving five different κ and seven λ amyloidomas, AL λ extracts typically resolved more slowly than did AL κ (AL λ , 18 ± 6 days *versus* AL κ , 13 ± 3 days). Sufficient material was available to repeat experiments at least four times in eight of the 12 cases where it was found that this effect was reproducible in healthy, young animals regardless of the tissue source of the amyloid. However, dissolution of the induced amyloid-

Figure 2. Infiltration of regressing amyloidoma by polymorphonuclear leukocytes. Amyloid tumor excised on day 10 and formalin-fixed, paraffin-embedded sections stained with Congo red (**left**); hematoxylin-eosin (**middle**); and naphthol AS-D chloroacetate (**right**). Original magnifications, $\times 400$, $\times 400$, $\times 1,000$, respectively).

omas was consistently delayed beyond 3 months in aged (>18 months) and immunodeficient (SCID) mice.

Histological studies to determine the fate of the regressing amyloidomas demonstrated that the amyloid was not redistributed to other mouse tissues, as evidenced by Congo red staining. Additionally, the tumors were infiltrated by naphthol AS-D chloroacetate-positive, α -naphthyl acetate-negative, polymorphonuclear cells, ie, neutrophils (Figure 2). In contrast, this cellular response did not occur in CD-18 null mice³⁸ where resolution of human AL amyloidomas required a considerably longer time period (ie, ~3 months). Further, amyloidolysis was delayed in animals rendered profoundly neutropenic by co-administration of 250 μ g of the anti-neutrophil mAb Gr-1³⁹ given at the time of amyloidoma induction and again on day 3.

Amyloid removal also was dependent on a humoral murine response to the human light-chain-containing material. Approximately 10 to 20 days after amyloidoma induction, we showed in immunoblotting experiments that mouse sera contained antibodies that recognized, not only the light chain constituent of the amyloid protein injected, but also that of heterologous AL κ or AL λ extracts (Figure 3). In contrast, there was no reactivity with the homologous amyloid precursor protein, ie, Bence Jones protein or any other monoclonal light chain tested. When the same amyloid preparation was re-administered to these immunized animals, its rate of disappearance increased approximately twofold. Additionally, in other experiments, elimination of amyloid tumors was accelerated when the extracts were incubated overnight with mouse immune serum before injection. A similar response occurred when serum-treated extracts were injected into SCID mice.

Based on these experiments, we hypothesized that the seemingly irreversible nature of amyloid deposition results from the patient's inability to elicit an immune response directed toward this material. We thus reasoned that, if available, the passive administration of anti-amyloid antibodies could expedite amyloid resolution and, thus, potentially provide a new therapeutic approach to this disease. To test this theory, we injected mice with a V_L fragment obtained by proteolytic cleavage of a human κ 4 Bence Jones protein³² that, on thermal denaturation under acidic conditions, formed material that possessed the characteristic features of amyloid,¹ namely, after Congo red staining, it exhibited green birefringence when viewed by polarizing microscopy and, by electron microscopy, appeared fibrillar. Spleen cells harvested from the immunized animals were fused with SP2/0 cells and culture fluid supernatants from the resultant hybridomas were screened for reactivity in a solid-phase ELISA³³ using as capture proteins κ and λ amyloid fibrils. Selected hybridoma colonies were injected intraperitoneally into pristane-primed BALB/c mice and the resultant mAbs purified from ascitic fluid by gel filtration. Among those tested, one, an IgG1 antibody (designated 11-1F4), exhibited the greatest degree of reactivity with both types of molecules. Notably, the binding of mAb 11-1F4 was unrelated to the V_L or C_L isotypic properties of the amyloid proteins tested, ie, there was no correlation between

Figure 3. Humoral immune response to AL amyloidoma. Detection by immunoblotting of murine anti-human AL fibril antibodies. **Top:** AL κ HIG amyloid extract stained with Coomassie blue (lane 2) and blotted with an anti- κ light chain mAb (lane 3), nonimmune serum obtained from a normal mouse (lane 4), serum obtained from a mouse 20 days after HIG amyloidoma induction (lane 5), and serum obtained from a mouse 20 days after BAL amyloidoma induction (lane 6). **Bottom:** AL λ BAL extract stained with Coomassie blue (lane 2) and blotted with an anti- λ light chain mAb (lane 3), nonimmune serum obtained from a normal mouse (lane 4), serum obtained from a mouse 20 days after BAL amyloidoma induction (lane 5), and serum obtained from a mouse 20 days after HIG amyloidoma induction (lane 6). The M_s of the molecular mass markers located in lane 1 are indicated in kd.

the V _{κ} /V _{λ} subgroup or C _{κ} /C _{λ} nature of the light chain constituent and the interaction with this antibody. Alternatively, when tested in a liquid-phase ELISA³³ against a panel of Bence Jones proteins representative of the four major V _{κ} and five V _{λ} subgroups, this reagent was specific only for κ 4 light chains.

The anti-amyloid reactivity of 11-1F4 also was evidenced immunohistochemically. As shown in Figure 4, both AL κ and AL λ deposits were recognized by this antibody. Most importantly, we found that mAb 11-1F4 bound to AL amyloid *in vivo*. In one such experiment, a mouse injected with an AL κ 1 amyloid extract was inoculated concomitantly in the thigh with 100 μ g of fluorescein-labeled antibody. The animal was sacrificed 36 hours later and the excised amyloidoma examined by fluorescence microscopy (Figure 5). The labeled antibody localized only to the amyloidoma and not to any mouse tissue. Similarly, this reagent did not react with normal human tissue.

Figure 4. Reactivity of mAb 11-1F4 with AL κ and AL λ amyloid tissue deposits. Histochemical and immunohistochemical analyses of liver and spleen tissue obtained from AL κ 1 patient HIG (**top**) and AL λ 1 patient SHE (**bottom**), respectively. **Left:** Polarizing microscopy of Congo red-stained sections. **Right:** Immunoperoxidase staining with the mAb 11-1F4. Original magnifications, $\times 200$.

To test the therapeutic efficacy of mAb 11-1F4, a series of experiments were initiated in which 100- μ g doses of reagent were given to pairs of mice bearing human AL amyloidomas. In the case of AL κ , studies involving two different extracts (HIG and GRA) revealed that even a single injection of the antibody resulted in rapid and complete disappearance of the amyloid tumor, as compared to untreated animals (Table 1). As illustrated in

Figure 5. Localization of fluorescein-labeled mAb 11-1F4 within an AL κ amyloidoma (fluorescent microscopy, original magnification, $\times 400$).

Figure 6 (top), the mass of an AL κ 1 amyloidoma was reduced $>90\%$ within 4 days after antibody injection, as compared to control animals. However, to achieve a similar response in certain AL λ -type amyloidomas, multiple doses of the reagent were required. These were given as a series of 100- μ g injections beginning at the time when the amyloidoma was induced (day 0) and then again on days 2, 4, and 6 (Figure 6, bottom). As summarized in Table 1, in experiments in which five different human AL λ amyloidomas were tested in the mouse model (JON, SHE, FIE, BUE, and BAL), it was found that treatment with mAb 11-1F4 decreased by as much as fourfold the time in which the amyloid tumors were eliminated. Notably, although single or repeated doses of two other anti-light chain mAbs³⁴ that recognized AL fibrils (eg, 31-8C7) expedited amyloidolysis, the 11-1F4 reagent was unique in that it accelerated removal of both AL κ and AL λ amyloid. In contrast, three anti-light chain mAbs that lacked such reactivity were ineffective.

In other studies, it was demonstrated that for amyloidolysis to occur, the complete 11-1F4 IgG molecule was required, as evidenced when a biotinylated pepsin-derived F(ab')₂ fragment of this antibody, although localizing to the human amyloidoma, did not accelerate amyloidolysis. Further, histological examination of residual amyloid tumors removed from 11-1F4-treated mice revealed the presence of a pronounced neutrophilic infiltration, whereas little or no cellular response was seen in the unresolved material taken from control animals within the same time period (ie, 5 to 6 days). Additionally, based on ELISA and immunoblotting analyses, neither group of mice had detectable serum antibodies to the injected amyloid in these short-term experiments (data not shown).

Discussion

We have shown that amyloidomas formed by subcutaneous injection of human AL amyloid extracts into healthy mice were resolved within 14 to 26 days by an immune-mediated mechanism involving the generation of anti-amyloid antibodies and a resultant polymorphonuclear leukocyte response. The sera obtained from such animals contained antibodies that recognized antigenic determinants not only present on the injected protein, but also common to both AL κ and AL λ amyloid fibrils. Pre-incubation of the amyloid extracts with immune serum

Table 1. Monoclonal Antibody-Mediated Amyloidolysis in Mice Bearing Human AL κ and AL λ Amyloidomas

Amyloidoma (V _L subgroup)	Single dose*		Untreated	Multiple doses†		Untreated
	Treated			Treated		
	11-1F4‡	31-8C7‡		11-1f4	31-8C7	
ALκ(1) HIG	4§	12	14	NT¶	NT	NT
ALκ(1) GRA	4	8	15	NT	NT	NT
ALλ(6) JON	8	11	14	NT	NT	NT
ALλ(1) SHE	9	19	21	9	20	24
ALλ(1) FIE	17	24	24	9	18	26
ALλ(2) BUE	24	NT	25	6	NT	25
ALλ(3) BAL	28	NT	28	7	NT	28

*100 μ g day 0; †100 μ g days 0, 2, 4, and 6; ‡mAb designation; §time (days); ¶NT, not tested.

Figure 6. Monoclonal anti-amyloid antibody-mediated resolution of human AL amyloidomas. **Top:** Appearance of residual AL κ amyloid tumor on day 4 in a mouse given a single 100- μ g injection of mAb 11-1F4 at the time of amyloidoma induction (**left**) and in an untreated animal (**right**). **Bottom:** Appearance of residual AL λ amyloid tumor on day 7 in a mouse given 100- μ g injections of mAb 11-1F4 at the time of amyloidoma induction (day 0) and then again on days 2, 4, and 6 (**left**) and in an untreated animal (**right**).

resulted in more rapid resolution of the induced amyloidomas in normal and SCID mice.

These observations led us to immunize mice with human V_L fibrils and to generate an antibody that recognized an amyloid-related epitope, as demonstrated immunochemically. Based on the pattern of reactivity, we

established that this determinant was not necessarily related to the κ or λ nature of the AL fibrils or to the V_L subgroup of the immunogen used to prepare the antibody. Thus, we posited that this anti-amyloid reagent recognized a β -pleated structure common to AL fibrils; that such material contains antigenic sites not exposed

on the soluble light chain precursor protein has been shown by other investigators.^{40,41} We also found that mAb 11-1F4 recognized other forms of amyloid, as evidenced in immunohistochemical analyses of AA-, ATTR-, ALyS-, AApoA1-, and A β -containing tissues. In each case, similar patterns of reactivity were obtained with 11-1F4 and antibodies specific for these five different types of amyloid proteins (Wall J, Macy S, Weiss DT, Solomon A, unpublished studies).

The therapeutic potential of mAb 11-1F4 was demonstrated in our *in vivo* experimental model where its administration to normal or SCID mice in which human AL amyloidomas had been induced resulted in marked acceleration of amyloidolysis, as compared to untreated animals. This antibody was shown to localize within the amyloid tumors and, further, rapid resolution of this material occurred before the mice could mount a detectable humoral immune response to the human proteins contained within the AL extracts. Although a single 100- μ g injection of antibody 11-1F4 resulted in rapid amyloidolysis in mice bearing the two AL κ amyloidomas, for three of five AL λ amyloid tumors studied, several doses were required to achieve complete resolution. The apparent resistance of AL λ versus AL κ fibrillar deposits to immune-mediated lysis also was noted in nonantibody-treated mice. Although it has been postulated that the presence of the amyloid-associated P component or glycosaminoglycans may protect fibrils from degradation by cellular or humoral processes,^{26–28} amyloidolysis occurred in both treated and control animals despite the presence of these components in the amyloid extracts used for injection.

Antibody-mediated amyloid resolution in our experimental AL mouse model was associated with an infiltration of neutrophils within the amyloid. The essentiality of these cells in effecting AL amyloid dissolution was demonstrated in studies involving neutropenic, as well as CD-18 knockout mice in which a component of the neutrophil β -integrin cell-surface adhesion molecule is lacking and, thus, extravascular diapedesis of neutrophils is prevented.³⁸

Based on our experimental data, we posit that amyloidolysis resulted from a three-step process that included: 1) the binding or opsonization of fibrils by the anti-amyloid mAb; 2) attraction and activation of neutrophils via an interaction between their Fc γ receptors and the Fc γ portion of the antibody molecule; and 3) enzymatic and/or chemical proteolysis^{42–44} of the amyloid by neutrophil-derived endopeptidases or free radicals, respectively.

Although subcutaneous amyloidomas occur in patients with AL amyloidosis, most often, pathological fibrillar deposits are found in organs throughout the body.² Because of the lack of a suitable animal model of this disease process, it remains to be determined if administration of an anti-amyloid antibody would expedite lysis of systemically deposited material. However, because mAb 11-1F4 also recognizes other types of amyloid proteins, eg, AA, we have tested it in our transgenic AA amyloidotic mice⁴⁵ that develop extensive hepatic fibrillar deposits and found that there was a rapid and marked diminution of this material in the livers of animals given this

reagent (Wall J, Schell M, Wooliver C, Wolfenbarger DA, Weiss DT, Solomon A, unpublished studies). Indeed, that humoral immunity may effect amyloidolysis has been inferred from the report by Schenk et al⁴⁶ who demonstrated using a transgenic mouse model of Alzheimer's disease that older animals immunized with a synthetic A β peptide had considerable reduction in cerebral A β amyloid plaques.

The use of anti-amyloid antibodies to effect removal of pathological fibrillar deposits would provide a novel means to treat patients with primary (AL) amyloidosis. Currently, efforts are underway to prepare a chimerized or humanized version of the murine 11-1F4 mAb that eventually can be tested clinically. Although conventional or high-dose anti-plasma cell chemotherapy still would be required to eliminate the synthesis of the AL precursor light chain, the previous administration of such a reagent would serve to reduce the total body amyloid burden and possibly improve organ function. The development of therapeutic strategies designed to eliminate pathological fibrillar deposits by passive or active⁴⁶ immunotherapy would represent a major advance for patients with primary amyloidosis, as well as those with other acquired or inherited amyloid-associated disorders.

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