Human Anti-Murine Immunoglobulin Responses in Patients Receiving Monoclonal Antibody Therapy


ABSTRACT

Human anti-murine immunoglobulin responses were assessed in serum from three groups of patients receiving murine monoclonal antibody therapy. Each of the three patient groups responded differently. Chronic lymphocytic leukemia patients demonstrated little or no preexisting murine immunoglobulin G-reactive antiglobulin prior to treatment, while the cutaneous T-cell lymphoma and melanoma patients demonstrated preexisting antiglobulin levels in the same range as those demonstrated in healthy controls. None of 11 chronic lymphocytic leukemia patients receiving the T101 monoclonal antibody demonstrated an antiglobulin response, whereas all four of the cutaneous T-cell lymphoma patients receiving the same antibody developed increased levels of antiglobulins. Three of nine malignant melanoma patients receiving the 9.2.27 monoclonal antibody showed an increase in antiglobulin titer. In patients developing antiglobulin responses, the response was rapid, typically being detectable within 2 weeks. The antiglobulins were primarily immunoglobulin G and, with the exception of a single melanoma patient in whom the response appeared to have a substantial 9.2.27-specific component (i.e., antiidiotype), were cross-reactive with most murine immunoglobulin G preparations tested. This pattern of results suggested that the antiglobulin was a secondary immune reaction with elevation of the levels of preexisting antiglobulin which was cross-reactive with the mouse antibody administered. While the presence of serum antiglobulin would be expected to present major complications to monoclonal antibody therapy, no clinical toxicity related to antiglobulin responses was observed in these patients, and no inhibition of antibody localization on tumor cells was seen.

INTRODUCTION

Attempts at serotherapy of human tumors date back to the treatment of chronic myelogenous leukemia with antisera by Lindstrom (6) in 1927. However, due to the difficulty in obtaining large quantities of antisera of sufficient specificity, and the many side effects of crude antisera, this form of therapy has not come into general use. The development of monoclonal antibodies of defined specificity and unlimited availability has rekindled interest in the use of passively administered antibody as a form of cancer therapy (13).

The development of host antibodies against passively administered immunoglobulin, with possible neutralization of the administered immunoglobulin and anaphylactic or other immune reactions, has been viewed as a potential major complication to serotherapy. Recent reports of clinical trials with murine monoclonal antibodies have confirmed that human anti-mouse immunoglobulin antibodies may be induced (1, 2, 10, 14, 17). Miller et al. (10) reported development of anti-mouse immunoglobulin antibodies in 4 of 7 T-cell lymphoma patients treated with the anti-Leu-1 monoclonal antibody. In 3 of these 4 patients, the development of anti-mouse immunoglobulin antibodies appeared to contribute to tumor escape from therapy. Similarly, Dillman et al. (1) attributed the lack of response to therapy, in 2 of 4 cutaneous T-cell lymphoma patients receiving the T101 monoclonal antibody, to the presence of human anti-mouse immunoglobulin antibodies. Sears et al. (17) also reported the presence of human anti-mouse immunoglobulin antibodies in 9 of 18 gastrointestinal tumor patients receiving the monoclonal antibody 1083-17, 1A. However, other studies did not report that human antiglobulin responses presented major problems in monoclonal antibody therapy (3, 7–9, 15). The relatively small number of reports in the literature of monoclonal antibody clinical trials, the variety of diseases treated, and the lack of uniformity in the design of these trials makes it difficult to draw general conclusions as to the conditions under which host anti-mouse immunoglobulin responses would be expected to develop.

The Biological Therapeutics Branch of the National Cancer Institute has recently completed Phase I clinical trials with the IgG2a monoclonal antibody T101 in patients with CLL and CTCL and the IgG2a monoclonal antibody 9.2.27 in patients with malignant melanoma (2, 3, 14). The T101 antibody recognizes the T65 antigen present on the cell surface of both normal and malignant T-cells, as well as some B-cell cancers, including CLL (16). The 9.2.27 antibody recognizes a M, 250,000 glycoprotein-proteoglycan associated with melanoma (11). In this paper, the host anti-mouse immunoglobulin responses observed during these trials are summarized, with a comparison of the differences and similarities in the responses elicited within the 3 disease groups, and an analysis of the specificity of the detected antibodies.

MATERIALS AND METHODS

Patients. Patients considered for the clinical trial with T101 were adults with histologically confirmed diagnosis of CLL or CTCL. Patients with malignant melanoma were considered as candidates for treatment with the 9.2.27 antibody. Patients received no radiation or immunosuppressive drugs for at least 4 weeks prior to entry into these trials. Prior to treatment, all patients were fully ambulatory and had no serious unrelated disease, and their tumor cells were positive for reactivity with the antibody to be used in therapy. The mean and range of age of each patient population was: CLL, 59, 43 to 81; CTCL, 56, 42 to 68; melanoma, 46, 23 to 72 years.

The abbreviations used are: CLL, chronic lymphocytic leukemia; CTCL, cutaneous T-cell lymphoma; ELISA, enzyme-linked immunosorbent assay.
The control population used in this study consisted of 11 healthy individuals with no history of cancers and no previous therapy with murine-derived agents and ranged in age from 20 to 45 years, with a mean of 31 years.

**Study Plan.** Patients were treated with either T101 or 9.2.27 monoclonal antibody. Details of the design and clinical findings of each trial have been reported elsewhere (3, 14). Briefly, patients with CLL or CTCL received T101 antibody i.v. at fixed-dose levels of 1, 10, 50, or 100 mg. Patients were treated twice weekly for 4 weeks. Initially, patients received the total dose of antibody in 100 ml of 0.9% NaCl solution (saline) with 5% human albumin over 2 hr. Due to pulmonary toxicity associated with the rapid rate of infusion, this was later amended so that antibody was administered at a rate of no more than 1 to 2 mg of T101 antibody per hr. Melanoma patients received the 9.2.27 antibody by i.v. infusion in 100 ml of saline with 5% human serum albumin over 2 hr. Each patient received single doses of antibody twice weekly on an escalating dose schedule of 1, 10, 50, 100, and 200 mg or 10, 50, 100, 200, and 500 mg. A summary of the number of patients treated and the amount of antibody administered is presented in Table 1.

**Assay for Human Anti-Mouse Antibody.** Sera used in all assays were separated from peripheral blood and stored at -20° until use. Antiglobulins in dilutions of serum were measured using solid-phase antiglobulin test kits obtained from Kallestad Laboratories, Austin, TX. Immunofluorescent Staining of Melanoma Specimens. Tumor cells were prepared as single-cell suspensions by teasing tissues which were obtained from skin lesions. To assess in vivo localization of the murine 9.2.27 antibody, the cell suspensions were incubated with fluorescein isothiocyanate-conjugated goat anti-mouse IgG (Tago, Inc., Burlingame, CA) for 30 min at 4°. The cells were then washed by centrifugation and analyzed on a Cytofluorograf 50H (Ortho Diagnostic Systems, Westwood, MA). A similar goat antibody directed against mouse IgM (Tago) was used as a negative control, and incubation in the presence of excess 9.2.27 antibody served as a positive control. All biopsy specimens were obtained 24 hr following infusion of the 9.2.27 antibody.

**Statistical Evaluation.** Serum antioglobin levels for a given patient were considered significantly increased at antoglobulin levels greater than 2 S.D.s above the mean of the healthy control group.

## RESULTS

**Development of Antiglobulin Responses.** In order to determine the level of mouse-reactive antiglobulins which could be detected in healthy individuals by our ELISA, antoglobulin levels were assessed in 11 normal donors. As illustrated in Chart 1, the control population demonstrated detectable levels of IgG and IgM antoglobulin reactive with both the T101 and 9.2.27 antibodies. These preexisting antoglobulin levels in the CLL patients prior to therapy were significantly lower (p < 0.005 by Student’s t test) than those demonstrated by the healthy controls. Serum immunoglobulin levels were determined on the same specimens. Both serum IgG and IgM levels were significantly lower in the CLL group as compared to the control group. However, CLL serum immunoglobulin levels were roughly one half that of controls, while CLL antoglobulin levels were less than one tenth of that of control antoglobulin levels.

To substantiate that the assay used was in fact detecting human anti-mouse immunoglobulin antibody, 2 control experiments were performed. To demonstrate that the binding of human immunoglobulin to the ELISA plate was not nonspecific, control and patient specimens were incubated on plates coated with either the T101 or 9.2.27 antibodies, or left uncoated. Table 2 demonstrates that binding did not occur in the absence of mouse immunoglobulin on the plates and that binding was roughly equivalent irrespective of the antibody used to coat the plates. To further substantiate that the preexisting human antibody activity was indeed reactive with mouse immunoglobulin, we performed the ELISA for human anti-mouse immunoglobulin activity in the presence of a 1000-fold-greater concentration of the soluble inhibitor murine IgG2a antibodies 9.2.27, T101, D3, or RPC-5 as compared to the solid-phase target immunoglobulin.

### Table 1

**Summary of monoclonal antibody therapy**

<table>
<thead>
<tr>
<th>No. of patients treated</th>
<th>Disease</th>
<th>Total dose received (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CLL</td>
<td>6</td>
</tr>
<tr>
<td>1</td>
<td>CLL</td>
<td>8</td>
</tr>
<tr>
<td>1</td>
<td>CLL</td>
<td>50</td>
</tr>
<tr>
<td>1</td>
<td>CLL</td>
<td>150</td>
</tr>
<tr>
<td>1</td>
<td>CLL</td>
<td>300</td>
</tr>
<tr>
<td>1</td>
<td>CLL</td>
<td>400</td>
</tr>
<tr>
<td>1</td>
<td>CTCL</td>
<td>8</td>
</tr>
<tr>
<td>1</td>
<td>CTCL</td>
<td>66</td>
</tr>
<tr>
<td>1</td>
<td>CTCL</td>
<td>80</td>
</tr>
<tr>
<td>1</td>
<td>CTCL</td>
<td>162</td>
</tr>
<tr>
<td>7</td>
<td>Melanoma</td>
<td>361</td>
</tr>
<tr>
<td>2</td>
<td>Melanoma</td>
<td>860</td>
</tr>
</tbody>
</table>

CANCER RESEARCH VOL. 45 FEBRUARY 1985

880

Downloaded from cancerres.aacrjournals.org on April 12, 2017. © 1985 American Association for Cancer Research.
Table 3
Inhibition of 9.2.27-reactive human antiguobulin activity in normal human serum
with murine IgG2a

<table>
<thead>
<tr>
<th>Monoclonal antibodies</th>
<th>Titer</th>
<th>% of inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>70 ± 45&lt;sup&gt;b&lt;/sup&gt;</td>
<td>42 ± 5</td>
</tr>
<tr>
<td>9.2.27</td>
<td>42 ± 30</td>
<td>34 ± 27</td>
</tr>
<tr>
<td>T101</td>
<td>43 ± 36</td>
<td>51 ± 10</td>
</tr>
<tr>
<td>D3</td>
<td>34 ± 27</td>
<td>57 ± 17</td>
</tr>
<tr>
<td>RPC-5</td>
<td>35 ± 36</td>
<td>57 ± 17</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reciprocal of the dilution yielding an absorbance at 405 nm of 0.3.
<sup>b</sup> Mean ± S.D.

Values represent the mean of 5 healthy control specimens.

Antiglobulin levels were assessed in patients over the period of treatment with either T101 or 9.2.27 antibodies as the target antigens. In the T101 trial, serum specimens were obtained before the third, fifth, and seventh doses. These specimens were obtained immediately prior to doses in order to minimize the possibility of circulating free mouse IgG being present in the specimen. To confirm that serum mouse IgG levels were low, mouse IgG levels were quantitated in all serum samples. Specimens from CLL and CTCL patients all demonstrated mouse IgG levels of less than 1 µg/ml. Specimens from melanoma patients demonstrated somewhat higher levels of mouse IgG but, in all cases, were less than 25 µg/ml. As depicted in Chart 2, CLL patients treated with T101 failed to develop detectable antiguobulin levels over the period of therapy. In contrast, while CTCL patients demonstrated rather low antiguobulin levels prior to receiving T101 antibody, a significant increase in IgG levels of antiguobulin developed over the course of therapy in all 4 patients (Chart 3). Three of these 4 patients also demonstrated rises in IgM antiguobulin levels over the course of therapy, but not to the same magnitude as IgG responses.

Of the 9 melanoma patients in the 9.2.27 trial, 3 developed significant levels of IgG antiguobulin (Chart 4). These same 3 patients demonstrated lower, but yet significant, levels of IgM antiguobulin during the course of therapy. All 3 individuals who developed antiguobulin levels received a total of 361 mg of 9.2.27 antibody.

Specificity of Antiglobulin Response. In order to determine the specificity of the antiguobulin responses elicited, sera from patients who demonstrated significant elevations in antiguobulin levels were tested against a variety of immunoglobulins (Table 4). Specimens from the 4 CTCL patients were assessed for reactivity against whole T101 and a Fab fragment of T101, as well as 5 IgG murine myeloma proteins, the IgG and IgM components of normal mouse serum, and a rabbit IgG preparation. Specimens from the 3 melanoma patients who demonstrated antiguobulin responses were tested against a similar panel, with the exception that the F(ab')<sub>2</sub> fragment of 9.2.27 was substituted for the Fab fragment of T101.

Sera from all 4 CTCL patients and the 3 melanoma patients demonstrated substantial reactivity with whole T101 or 9.2.27, most murine myeloma proteins of the different IgG subclasses, and mouse IgG (Table 4). Little or no reactivity was observed against the Fab or F(ab')<sub>2</sub> fragments or to mouse IgM. These results suggest that the antiguobulin response elicited in these patients was directed to determinants common to murine IgG and was not specific for either the T101 or 9.2.27 antibody. Further, the lack of reactivity to Fab or F(ab')<sub>2</sub> fragments suggests that the reactivity is directed against determinants on the Fc region of the immunoglobulin molecule and not determinants.
HUMAN ANTI-MURINE IMMUNOGLOBULIN RESPONSES

Chart 2. Antiglobulin levels in CLL patients. Serum IgG (A) or IgM (B) antibody levels to the T101 antibody are indicated. Points, determinations on serum specimens from 9 patients obtained either prior to therapy (Dose 0) or immediately preceding the indicated dose.

Chart 3. Antiglobulin levels in CTCL patients. Serum IgG (A) or IgM (B) antibody levels to the T101 antibody are indicated. Points, determinations on serum specimens from patients receiving total T101 doses of 8 (---), 66 (---), 80 (---), or 162 (---) mg. Specimens were obtained either prior to therapy (Dose 0) or immediately prior to the indicated dose.

Chart 4. Antiglobulin levels in melanoma patients. Serum IgG (A) or IgM (B) antibody levels to the 9.2.27 antibody are indicated. Points, determinations on serum specimens from 9 patients obtained either prior to therapy (Pre) or immediately preceding the indicated dose. Points from the 3 patients with significant (>2 S.D. above mean of normal controls) responses are connected to indicate the progression of the response.
such as the antibody-combining site or idiotype, which reside in the Fab region. Interestingly, the 3 melanoma patients showed reactivity with rabbit IgG, indicating that the antiglobulin response in these patients was not mouse specific. The antiglobulin response in the CTCL patients, however, appeared to be specific for mouse IgG.

One melanoma patient, Patient C. S., demonstrated substantial reactivity against the 9.2.27 F(ab')2 fragment as well as the whole 9.2.27 antibody (Table 4). However, this reactivity was not restricted to the 9.2.27 antibody but was also present against the murine myeloma proteins and the mouse and rabbit IgG preparations. To further investigate the potential of a 9.2.27 anti-idiotype component in the antiglobulin response of this and the other patients, a series of blocking studies similar to those performed with the murine myeloma proteins and the mouse and rabbit IgG were done. With the exception of Patient C. S., the antiglobulin response was largely inhibitable with all of the murine IgG2a monoclonal antibody preparations, with no evidence of an anti-idiotype component to the antiglobulin response. Patient C. S. demonstrated over 80% inhibition in the presence of soluble 9.2.27 antibody, as compared to roughly 30% inhibition with the other preparations. These data, in combination with the binding studies presented in Table 4, indicate that this patient developed an antiglobulin response which, although not completely specific for the 9.2.27 antibody, consisted of a substantial component which appears to be specific for the 9.2.27 antibody.

In order to determine the specificity of the preexisting antiglobulin in these patients, pretreatment sera from 3 of the CTCL patients and the 3 melanoma patients with elevated antiglobulin levels during therapy were examined for reactivity against the panel of mouse and rabbit immunoglobulin preparations indicated in Table 4. These analyses demonstrated that the specificity of preexisting antiglobulins was very broad, consistent with the broad specificity of posttherapy antiglobulins in these patients. Data from a representative CTCL patient are presented in Chart 6. This particular patient demonstrated detectable IgG antiglobulin to many, but not all, murine immunoglobulin preparations examined and IgM reactivity against all murine immunoglobulin preparations. Elevated antiglobulin responses posttherapy consisted of IgG antibodies.

Effect of Antiglobulin Responses upon Therapy and In Vivo Localization of Antibody. Clinical responses in these Phase I trials were either transient or undetectable (2, 3, 14). The CLL patients all demonstrated transient decreases in leukemia counts but failed to demonstrate lasting effects following cessation of therapy. The CTCL patients had minor regressions of skin lesions but failed to demonstrate lasting effects following cessation of therapy. However, in vivo localization of the 9.2.27 antibody was detected in biopsy specimens removed during the course of therapy. The presence of antiglobulin responses did not appear to affect in vivo localization in the 3 patients with substantial antiglobulin levels. For example, Chart 7 compares in vivo binding of the treatment antibody as detected by immunofluorescence and flow cytometry to the level of serum IgG antiglobulin in one patient. Serum antiglobulin levels as high as...
HUMAN ANTI-MURINE IMMUNOGLOBULIN RESPONSES

Chart 6. Specificity of pretherapy and posttherapy antiglobulins in a CTCL patient. Serum IgG (A) and IgM (B) antiglobulin levels were assessed before and after therapy with the T101 antibody. The target preparation and its subtype if monoclonal are indicated on the abscissa. Absence of a bar indicates an undetectable level of antiglobulin (<0.1 μg/ml).

Chart 7. In vivo localization of 9.2.27 antibody on melanoma cells in the presence of circulating antiglobulin. Binding of the 9.2.27 antibody was assessed in biopsy specimens taken prior to therapy and then at 24-hr intervals following the indicated dose in a single patient. Serum specimens for antiglobulin determinations were obtained immediately prior to the indicated dose, and the values indicate μg of human IgG per ml reactive with the 9.2.27 antibody. Paired serum and biopsy specimens were not obtained at the 10- and 50-mg-dose periods.

175 μg/ml did not inhibit localization of 9.2.27 antibody to melanoma cells in vivo.

DISCUSSION

The development of host antiglobulin responses represents a potential obstacle to effective monoclonal antibody therapy. Such a response would be expected to result in immune complex formation, possibly inducing serum sickness or renal toxicity, or interfering with the efficacy of treatment, either by inhibiting binding of the administered antibody to tumor cells or by increasing the removal of antibody by the reticuloendothelial system. Examples of antiglobulins inhibiting the binding of monoclonal antibodies to tumor cells have been reported (1, 10). In order to better characterize the development of host antiglobulin responses in patients receiving monoclonal antibody therapy, we examined human anti-murine immunoglobulin levels in 3 different patient populations receiving 2 different antibody preparations. This paper represents, to our knowledge, the first detailed investigation of antiglobulin responses of multiple patient populations receiving different murine monoclonal antibodies.

The CLL patients demonstrated little or no detectable levels of antiglobulin prior to therapy. Conversely, the CTCL and melanoma patient groups and the normal control group had measurable levels of preexisting mouse IgG-reactive antiglobulin. While the antiglobulin levels in the CTCL or melanoma patient groups were not significantly increased or decreased as compared to the control group, the 3 melanoma patients who developed increased levels of antiglobulin following therapy demonstrated significantly elevated antiglobulin levels of either IgG or IgM class prior to therapy.

All 3 patient populations received murine IgG2a antibodies. Although the treatment schedule and total dose levels varied among the patient groups, similar dose levels were administered to each group, and the period of therapy (2.5 to 4 weeks) was comparable. Each of the 3 patient groups responded differently. Within those patients receiving T101 antibody therapy, 0 of 10 CLL patients as opposed to all 4 of 4 CTCL patients developed increased levels of antiglobulins. Three of the 9 melanoma patients receiving the 9.2.27 antibody developed increased levels of antiglobulins.

The individuals who developed significant elevations in antiglobulins did so very rapidly. A response was observed in one of the CTCL patients as early as 1 week after initiating therapy, and all CTCL patients responding after 2 weeks of therapy. A similar time course was observed in the melanoma patients developing elevated levels of antiglobulin. The rapid elevation of antiglobulins is consistent with the kinetics of a secondary immune response.

In those patients with an increase in levels of antiglobulins, the response was found to represent mainly IgG antibodies. As above, this finding suggests that the response was a secondary or anamnestic immune response. The nature and specificity of the preexisting antiglobulin are unknown; however, the preexisting antiglobulin was found to react with a variety of murine IgG.
HUMAN ANTI-MURINE IMMUNOGLOBULIN RESPONSES

preparations. Anti-globulins are known to exist in healthy individuals (19). It is our hypothesis that, even in the absence of prior exposure to murine immunoglobulin, a portion of this anti-globulin is either specific for or cross-reactive with murine immunoglobulin and that, as a patient is treated with mouse immunoglobulin, an expansion of these B-cell clones occurs. This argument is supported by our observation that the only group without detectable anti-globulin prior to therapy (CLL) failed to develop anti-globulin following therapy.

Our data regarding the specificity of the anti-globulin response indicate that most of the response is directed against determinants common to mouse immunoglobulins. These determinants appear to reside in the Fc region of IgG and not IgM molecules. In only one patient was anti-globulin activity directed against 9.2.27 (Fab')2 fragments. This patient's sera also bound to other mouse IgG preparations of the same and different subclasses, indicating that the specificity was not entirely directed against the idiotypic, although blocking studies confirmed the presence of a substantial anti-idiotypic component. Our findings of general, rather than idiotypic, reactivity are similar to a recent report of Stratte et al. (18), who reported that therapy of primates with murine IgG2a antibody resulted mainly in broad anti-mouse anti-globulin responses and only in one case consisted of a significant anti-idiotypic component. A recent report by Koprowski et al. (5) indicated that several patients treated with an anti-colorectal mononuclear antibody developed anti-idiotypic responses and suggested that development of such an antibody response may correlate with a clinical response to this form of therapy. None of the melanoma patients in this study demonstrated any evidence of a clinical response, including the patient who demonstrated an anti-idiotypic component in the anti-globulin response.

Of primary interest are the variables determining why some individuals developed anti-globulin responses during therapy, while others did not. With the CLL and CTCL patients, this difference may be related to preexisting levels of anti-globulin. CLL patients are hypogammaglobulinemic and incapable of mounting normal humoral responses. However, while CLL serum immunoglobulin levels were one half of the other groups, the low serum immunoglobulin levels alone would not appear to be of sufficient magnitude to account for the extremely low anti-globulin levels in this group. The 3 melanoma patients who demonstrated anti-globulin responses did not differ substantially in their clinical disease state from the 6 patients who did not develop a response nor did they vary from the remaining patients with respect to the type or extent of prior therapy.

No clinical complications were observed in those individuals who developed anti-globulin responses. One of the melanoma patients did experience symptoms clinically indistinguishable from serum sickness, but this patient failed to demonstrate a detectable rise in anti-globulin levels over the course of therapy. Although lasting clinical responses were not observed during these trials, the development of anti-globulin responses did not affect the transient skin responses of the CTCL patients and did not appear to substantially affect the in vivo localization of antibody in the melanoma patients.

In summary, we have found that human anti-murine immunoglobulin responses are not uncommon in patients receiving monoclonal antibody therapy. The development of the response is rapid and appears in most cases to represent a specific response which is cross-reactive rather than a specific response to the immunoglobulin administered. Failure to develop the response can be related to the type of disease to some degree, presumably due to immune deficiency associated with some types of tumors. Within melanoma patients, the ability to develop an anti-globulin response may relate to preexisting anti-globulin levels, or to other as yet undefined variables in the patient population.

ACKNOWLEDGMENTS

The authors wish to acknowledge the contribution of Richard Klein and Margaret Farrell for immunofluorescent staining of melanoma specimens, and Dr. Annette Malush and her laboratory staff for assistance in the processing of clinical specimens.

REFERENCES

19. Maluish and her laboratory staff for assistance in the processing of clinical specimens.
Human Anti-Murine Immunoglobulin Responses in Patients Receiving Monoclonal Antibody Therapy


*Cancer Res* 1985;45:879-885.

Updated version  Access the most recent version of this article at: http://cancerres.aacrjournals.org/content/45/2/879