Kinetics of the Immune Response and Regression of Metastatic Lesions following Development of Humoral Anti-High Molecular Weight-Melanoma Associated Antigen Immunity in Three Patients with Advanced Malignant Melanoma Immunized with Mouse Antidiotype Monoclonal Antibody MK2-23


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ABSTRACT

Active specific immunotherapy has been implemented in patients with advanced malignant melanoma, utilizing the mouse antidiotype (anti-id) monoclonal antibody (mAb) MK2-23 which bears the internal image of high molecular weight-melanoma associated antigen (HMW-MAA). In a previous study, development of anti-HMW-MAA immunity in patients with advanced malignant melanoma immunized with anti-id mAb MK2-23 was found to be associated with a statistically significant survival prolongation. Since no information is available about the relationship between development of immunity and clinical response in patients immunized with anti-id mAb, the present study has characterized the kinetics of the immune response in three patients with advanced malignant melanoma who experienced regression of metastatic lesions following immunization with the anti-id mAb MK2-23. The three patients developed anti-mouse IgG antibodies, anti-anti-id antibodies and anti-HMW-MAA antibodies. The anti-HMW-MAA antibodies are mainly IgG, suggesting that the immune response elicited by anti-id mAb MK2-23 is T-cell dependent. The development of anti-HMW-MAA immunity preceded the reduction in the size of metastatic lesions. This temporal relationship suggests but does not prove that the anti-HMW-MAA immunity elicited by anti-id mAb MK2-23 has a beneficial effect on the clinical course of the disease in patients with malignant melanoma. This finding in conjunction with minor side effects associated with repeated administrations of mouse anti-id mAb MK2-23 suggest that active specific immunotherapy with anti-id mAb which bear the internal image of melanoma-associated antigen represents a viable therapeutic approach to malignant melanoma.

INTRODUCTION

The expression of MAA by human melanoma cells (for review, see Refs. 1–3) provides targets for active specific immunotherapy. Interest in this type of therapy has been rekindled by the lack of any effective therapy in malignant melanoma, once the tumor has metastasized (4), and by the recent progress in biotechnology which has facilitated the preparation of reagents to be used as immunogens. During the last few years, several clinical trials have been implemented to evaluate the ability of the available immunogens to induce anti-MAA immunity and its effect on the clinical course of the disease (5–13).

We have focussed our investigations on active specific immunotherapy of malignant melanoma with anti-id mAb which bear the internal image of the human HMW-MAA. The latter has been selected as a target because of its expression in a high percentage of melanoma lesions with limited heterogeneity and its restricted distribution in normal tissues (for review, see Ref. 2). Furthermore, HMW-MAA appears to play a role in the metastatic potential of melanoma cells (14–17). Therefore, inhibition of the functional properties of HMW-MAA with antibodies elicited by anti-id mAb is expected to reduce or suppress the metastatic potential of HMW-MAA-bearing melanoma cells.

In a recent study, we have shown that the mouse anti-id mAb MK2-23, which mimics the determinant defined by the anti-HMW-MAA mAb 763.74 (18), induces humoral anti-HMW-MAA immunity in about 60% of patients with advanced malignant melanoma (13). The development of anti-HMW-MAA antibodies is associated with a statistically significant prolongation of survival and with regression of metastatic lesions in some of the immunized patients (13). No information is available in the literature about the kinetics of the immune response elicited by anti-id mAb in patients with malignant melanoma and about the relationship between development of immunity to a well-defined MAA and regression of metastatic lesions. Therefore, in the present study we have investigated the kinetics of the humoral immune response in three patients with advanced malignant melanoma who experienced regression of metastatic lesions following development of humoral anti-HMW-MAA immunity elicited by anti-id mAb MK2-23.

MATERIALS AND METHODS

Patients. Of the three patients investigated in this study, one had documented, measurable stage III and two had documented, measurable stage IV melanoma.

Cell Lines. Cultured human melanoma cells Colo 38 and M14/13; cultured human B-lymphoid cells L14, which are autologous to M14/13 cells; and cultured human B-lymphoid cells LG-2 were grown in medium RPMI 1640 supplemented with 10% serum plus (JRH Bioscience, Lenexa, KS) and 2 mM L-glutamine.

mAb and Conventional Antisera. Mouse mAbs 149.53 (an IgG1), 225.28 (an IgG2a), and 763.74 (an IgG1) to distinct and spatially distant determinants of HMW-MAA; the mouse anti-intercellular adhesion molecule-1 mAb Cl207.14 (an IgG1) and the mouse anti-id mAbs MF11.30 and MK2-23 (both IgG1) to idiotopes within the antigen combining sites of the immunizing mAbs 225.28 and 763.74, respectively; and the mouse anti-HLA-DQ3 mAb KS13 (an IgG2b) and the mouse anti-id mAb K03-34 (an IgGl) to an idiotope within the antigen combining site of the immunizing mAb KS13 were developed as described (19–23).

mAbs were purified from ascitic fluid by sequential precipitation with caprylic acid and ammonium sulfate (24). The purity of the mAbs was monitored by SDS-PAGE (25).

Affinity-purified goat antibodies to human IgM, IgG, and IgG+F(ab')2 were purchased from Jackson ImmunoResearch Laboratories (Avondale, PA). Antibodies were labeled with 125I utilizing the Iodo-Gen method (26).

Immunization Schedule. Patients were immunized on days 0 and 7 with s.c. injections of anti-id mAb MK2-23 (2 mg/injection) conjugated to KLH and mixed with 0.1 ml (1 × 106 organisms) of Tice BCG (Organon, West Orange, NJ); then on day 28, patients were immunized with mAb MK2-23 conjugated to KLH. Additional injections of mAb MK2-23 conjugated to KLH but without BCG were given if, on day 35, the titer of the anti-anti-id antibodies which
obtain the binding of $^{125}$I-mAb MK2-23 to anti-HMW-MAA mAb 763.74 by at least 90% was lower than 1:8.

**Clinical and Laboratory Monitoring.** A complete blood cell count was obtained weekly; liver and renal function tests were performed monthly. Sentinel lesions were measured monthly and lesions measurable by X-ray, CAT scan, and MRI were evaluated every 4 months. Response was defined according to guidelines previously described by the National Cancer Institute, Bethesda, MD. Briefly, complete remission was defined as complete disappearance of all measurable melanoma lesions for at least 4 weeks. Partial remission was defined as 50% reduction of the bidimensional diameters of all measurable melanoma lesions for at least 4 weeks. Minor remission was defined as greater than 25% and less than 50% reduction of the bidimensional diameters of all measurable lesions for at least 4 weeks. Stable disease was defined as no change in the size of all measurable melanoma lesions. Progression of disease was defined as greater than 25% increase in the bidimensional diameters of all measurable melanoma lesions after the induction phase had been completed. Duration of response was determined after the patients received therapy for at least 4 weeks.

**Serological Assays.** The indirect binding assay with whole immunoglobulin of mAb-coated microtiter plates to measure human anti-mouse IgG antibodies and the inhibition assay to measure human anti-anti-id antibodies were performed in 96-well U-bottomed polyvinylchloride microtiter plates (Dynatech Laboratories, Alexandria, VA) as described elsewhere (12). The indirect binding assay to measure antibodies reacting with cells was performed in 96-well U-bottomed Falcon flexible microtiter plates (Becton Dickinson Labware, Oxnard, CA) as described elsewhere (12). Absorption was performed by incubating patient’s serum with cells (1 ml of serum/4 $\times 10^7$ cells) for 4 h at 4°C on a rotator. Serum was then harvested by centrifugation.

**Immunohistochemical Methods.** Antibodies were conjugated to Affigel 10 (Bio-Rad Laboratories, Richmond, CA) at the concentration of 15–20 mg/ml gel following the manufacturer’s instructions. Human anti-mouse IgG antibodies were absorbed by passing serum diluted with an equal volume of PBS through a mouse IgG mAb column. Absorption of human anti-mouse IgG antibodies was monitored by testing serum reactivity with an unrelated mouse IgG mAb in a binding assay with $^{125}$I-anti-human IgG + xenoantibodies.

Labelling of cells with $^{125}$I, solubilization with Nonidet P-40, indirect immunoprecipitation, SDS-PAGE, and autoradiography were performed as described (12, 13).

**RESULTS**

Serial sera obtained from patients LM, AM, and AK immunized with mAb MK2-23 were tested with the immunizing mAb MK2-23 and with the isotype-matched mAb MF11-30 to monitor the level and specificity of human anti-mouse IgG antibodies. Furthermore, sera were tested for their ability to inhibit the binding of $^{125}$I-mAb MK2-23 and MF11-30 to the corresponding immunizing anti-HMW-MAA mAb 763.74 and 225.28, respectively, to determine the level and specificity of anti-anti-id antibodies. Lastly, sera were tested for their reactivity with HMW-MAA-bearing cultured human melanoma cells and with cultured human B-lymphoid cells, which do not express HMW-MAA, to monitor the level and specificity of antibodies reacting with melanoma cells. The reactivity of the anti-anti-id antibodies with HMW-MAA was assessed by SDS-PAGE analysis of the antigens immunoprecipitated from radiolabeled melanoma cells from patients’ immune sera.

Patient LM, a 64-year-old man, had a history of primary superficial spreading melanoma lesion with a 1.2-mm thickness which was removed from his midback when he was 63 years old. No evidence of lymph node involvement was detected at that time. Four months following surgery, he noted a mass in his right groin and underwent dissection for metastatic melanoma. Eighteen of 20 lymph nodes in the right groin were found to have metastatic melanoma. A CAT scan showed enlargement of retroperitoneal lymph nodes (Fig. 1). He was evaluated and entered into the clinical trial using anti-id mAb MK2-23.

A 50% decrease of retroperitoneal paraaortic lymph nodes was demonstrated in a CAT scan in the 20th week, 4 weeks after the detection of antibodies reacting with melanoma cells M14/13 (Fig. 1). An additional reduction in the size of the retroperitoneal lymph nodes was observed in a CAT scan performed in the 75th week when a metastatic lesion was detected in the patient’s right axilla. The patient underwent lymph node dissection and elected to continue therapy with mAb MK2-23. A 50% decrease of retroperitoneal paraaortic lymph nodes in patient LM immunized with mouse anti-id mAb MK2-23. Patient LM was immunized with s.c. injections of mAb MK2-23 (2 mg/injection) conjugated to KLH and mixed with BCG. Sequential CAT scans of the abdomen taken before the patient was immunized (top) and in the 20th week of treatment following six immunizations (bottom) show a decrease in the size of paraaortic lymph nodes (arrows). Although the sections shown appear to be at slightly different levels, they are fully representative of the complete scans which were compared.
with s.c. injections of mAb MK2-23 (2 mg/injection) conjugated to KLH and mixed with BCG. Sera were drawn in the indicated weeks.

Patient LM was immunized in the weeks indicated by the arrows with s.c. injections of mAb MK2-23 (2 mg/injection) conjugated to KLH and mixed with BCG. Unabsorbed sera (--) and sera that had been absorbed with isotype-matched mouse IgG (- - -) were incubated with 125I-anti-idiotype mAb MF11-30 (○) and K03-34 (□) for 4 h at 4°C. Then the mixture was added to anti-HMW-MAA mAb 225.28 (○), mAb 763.74 (□), and anti-HLA-DQ3 mAb K513 coated 96-well microtiter plates (1 μg/well). The specificity of the reaction was assessed by testing sera with autologous cultured human B-lymphoid cells L14 (□). The latter do not express HMW-MAA.

Patient AM is a 49-year-old male who had enucleation of his right eye because of ocular melanoma in 1971 at the age of 29 years. He did well until April 1987 when he noted recurrence of multiple cutaneous nodules on his abdomen. A biopsy revealed metastatic melanoma. He refused chemotherapy and chose to be treated by macrobiotic diet. In December 1987, he started to complain of back pain associated with difficulty in ambulation. A physical examination showed that he had numerous cutaneous lesions ranging from 1 x 1 to 2 x 1 cm on his back and abdomen. Furthermore, lymph nodes were palpable in the supraclavicular, axillary, and inguinal areas. A MRI scan demonstrated a large paraspinal mass causing cord compression with difficulty to ambulate and tumor replacement of the L4 vertebral body. In March 1989, therapy was initiated with anti-id mAb MK2-23.

After 7 weeks of treatment with anti-id mAb MK2-23, the patient's back pain improved, and he was able to ambulate without any difficulty. A physical examination showed greater than 50% decrease of his skin lesions. A repeat MRI of his spine showed a 50% decrease in the size of the paraspinal mass but did not detect any change in the size of the metastatic lesion at the L4 vertebral body (Fig. 5). Furthermore, his anemia improved. This response continued until the 88th week when he started to complain of increasing back pain and difficulty in ambulation. A physical examination showed recurrence of his skin metastasis and a repeat MRI showed an increase in the size of his
paraspinal mass. The patient was taken off of the study and treated with 4-(dimethyltriazeno)imidazole-4-carboxamide, 1,3-bis(2-chloroethyl)-1-nitrosourea, cisplatin, tamoxifen, and α interferon. Following one cycle of this combination, the patient required admission to the hospital because of nadir sepsis, and he expired during this hospitalization.

Fig. 6 shows the kinetics of the development of anti-mouse immunoglobulin antibodies, of anti-anti-id antibodies, and of antibodies reacting with melanoma cells. The reactivity pattern of the three types of antibodies in patient AM are similar to those described in patient LM. The antibodies reacting with melanoma cells are both IgM and IgG (Fig. 7). Furthermore, anti-anti-id antibodies purified from patient AM immunoprecipitated HMW-MAA from radiolabeled melanoma cells (Fig. 8).

Patient AK, a 78-year-old female, noted a mole on her left foot when she was 76 years old. She underwent a biopsy which was entered into this clinical trial and received three immunizations when she was 76 years old. She underwent a biopsy which was AM immunoprecipitated HMW-MAA from radiolabeled melanoma cells. As described elsewhere, no change was detected in the size of the metastatic lesion at the L4 vertebral body. Sequential MRI scans taken before the patient was immunized (left) and in the 12th week of treatment following three immunizations (right) show reduction in the size of metastatic lesions in the paraspinal area and in the intradural cavity. In contrast, no change was detected in the size of the metastatic lesion at the L4 vertebral body.

DISCUSSION

The present study has analyzed for the first time the characteristics of the humoral immune response in three patients with advanced malignant melanoma who experienced partial or minor clinical responses following development of humoral anti-HMW-MAA immunity elicited by immunizations with the mouse anti-id mAb MK2-23. The latter bears the mirror image of the determinant defined by anti-HMW-MAA mAb 763.74 (13, 18). Although the extent of the investigations has been restricted by the availability of sera from the three patients, the present study has provided valuable information about the kinetics of the immune response elicited in patients with malignant melanoma by a mouse anti-id mAb which bears the internal image of HMW-MAA. The development of anti-HMW-MAA antibodies in the three immunized patients is indicated by most, if not all, of the following lines of evidence: (a) sera displayed a higher reactivity with HMW-MAA-bearing melanoma cells than with autologous cultured B-lymphoid cells which do not express HMW-MAA; (b) the reactivity of the immune sera with melanoma cells was not affected by extensive absorption with cultured human B-lymphoid cells; and (c) anti-anti-id antibodies isolated from patients' sera immunoprecipitated HMW-MAA from radiolabeled melanoma cells. As described elsewhere (13), patients' immune sera inhibit the binding of anti-HMW-MAA mAb 763.74 to melanoma cells, suggesting that the latter mAb and anti-anti-id antibodies recognize the same (or spatially close) determinant(s).

Following immunizations with mAb MK2-23, the three patients' sera displayed a higher titer with the immunizing mAb than with the isotype-matched mAb MF11-30. Furthermore, in one patient antibodies reacting with the immunizing anti-id mAb MK2-23 were detected at an earlier stage in the course of the immunization than those reacting with the isotype-matched mAb MF11-30. These results suggest that the immune response elicited by the idiotopes of mAb MK2-23 is higher than that elicited by isotypic determinants and framework regions of mouse IgG. It is also of interest that the anti-anti-id antibodies elicited by mAb MK2-23 do not react with determinants in the antigen combining site of anti-id mAb elicited by anti-HMW-MAA mAb that recognize determinants different from...
with s.c. injections of mAb MK2-23 (2 mg/injection) conjugated to KLH and mixed with BCG. Serum was absorbed with cultured human B-lymphoid cells LG-2 (100 μl serum/4 × 10^6 cells) for 4 h at 4°C. The immunoglobulin class of antibodies reacting with melanoma cells was determined by testing absorbed serum with cultured melanoma cells Colo 38 (—) in a binding assay with 125I-anti-human IgG (□) and IgM (△) xenoantibodies (1 × 10^5 cpm/well). Results are expressed as bound cpm/well. Cultured human B-lymphoid cells LG-2 (-) were used as specificity controls.

Fig. 7. IgM and IgG components in the antibody populations reacting with cultured human melanoma cells in patient AM immunized with mouse anti-id mAb MK2-23. Serum was obtained on day 133 from patient AM who had been immunized on days 0, 7, 28, and 112 with s.c. injections of mAb MK2-23 (2 mg/injection) conjugated to KLH and mixed with BCG. Serum was absorbed with cultured human B-lymphoid cells LG-2 (100 μl serum/4 × 10^6 cells) for 4 h at 4°C. The immunoglobulin class of antibodies reacting with melanoma cells was determined by testing absorbed serum with cultured melanoma cells Colo 38 (□) in a binding assay with 125I-anti-human IgG (□) and IgM (△) xenoantibodies (1 × 10^5 cpm/well). Results are expressed as bound cpm/well. Cultured human B-lymphoid cells LG-2 (-) were used as specificity controls.

Fig. 8. SDS-PAGE analysis of antigens immunoprecipitated from cultured human melanoma cells by anti-anti-id antibodies purified from patients AK and AM immunized with mouse anti-id mAb MK2-23. Anti-anti-id antibodies were purified from sera obtained at a late stage of immunization from patients AK (Lane B) and AM (Lane C) by affinity chromatography on mAb MK2-23 following removal of anti-mouse lgG antibodies. A Nonidet P-40 extract of 125I-labeled cultured human melanoma Colo 38 cells was immunoprecipitated with insolubilized anti-anti-id antibodies. Antigens were then eluted from the immunoadsorbents and analyzed by SDS-PAGE in 5% slab gels in the presence of 2% β-mercaptoethanol. Gels were processed for autoradiography using Kodak XAR-5 film (Eastman Kodak Co., Rochester, NY). Left, migration of molecular weight standards. Anti-HMW-MAA mAb 763.74 (Lane A) and anti-mouse IgG antibodies purified from the pools of sera from patients AK (Lane D) and AM (Lane E) by affinity chromatography on unrelated mouse IgG mAb were used as controls.

Fig. 6. Kinetics of the development of anti-mouse IgG antibodies, anti-anti-id antibodies, and antibodies reacting with melanoma cells in patient AM immunized with mouse anti-id mAb MK2-23. Patient AM was immunized in the weeks indicated by the arrows with s.c. injections of mAb MK2-23 (2 mg/injection) conjugated to KLH and mixed with BCG. Sera were drawn in the indicated weeks. A, anti-mouse IgG antibodies were measured by testing sera with the immunizing mouse anti-id mAb MK2-23 (□) in a binding assay with 125I-anti-human IgG +M xenoantibodies. Results are expressed as the highest dilution of serum giving 50% of the maximal binding to mAb MK2-23. The specificity of the reaction was assessed by testing sera with the unrelated isotype-matched anti-id mAb MF11-30 (■). B, anti-anti-id antibodies were measured by testing sera for the ability to inhibit the binding of 125I-labeled melanoma cells M14/13 (13) in an inhibition assay. Results are expressed as the highest dilution of serum giving 90% inhibition of the binding of 125I-mAb MK2-23 to mAb MK2-23 as compared to the binding in the presence of preimmune serum. The specificity of the inhibition was assessed by testing the sera for the ability to inhibit the binding of 125I-labeled unrelated isotype-matched anti-id mAb MF11-30 (■) to anti-HMW-MAA mAb 763.74 (□) in an inhibition assay. Results are expressed as the highest dilution of serum giving 90% inhibition of the binding of 125I-mAb MK2-23 to mAb MK2-23 as compared to the binding in the presence of preimmune serum. The specificity of the inhibition was assessed by testing sera with cultured melanoma cells M14/13 (□) in a binding assay with 125I-anti-human IgG +M xenoantibodies. Results are expressed as the highest dilution of serum giving 50% of the maximal binding to melanoma cells M14/13. The specificity of the reaction was assessed by testing sera with autologous cultured human B-lymphoid cells L14 (■). The latter do not express HMW-MAA.

those recognized by mAb 763.74. The latter finding implies that interference with the immunogenicity of anti-id mAb by anti-anti-id antibodies formed in the course of the immunization may be overcome by changing the immunizing anti-id mAb. Lastly, the markedly higher reactivity of anti-anti-id antibodies with mAb MK2-23 than with melanoma cells suggests that the areas of mAb MK2-23 which do not mimic the structure of HMW-MAA are markedly more immunogenic than those that do. The latter conclusion parallels similar results derived from the analysis of sera from BALB/c mice immunized with mAb MK2-23 (17).

Following immunizations with mAb MK2-23 conjugated to KLH and mixed with BCG, the three patients’ sera displayed an increase in their reactivity not only with cultured melanoma cells but also with cultured B-lymphoid cells which do not express HMW-MAA. This finding suggests that at least part of the antibody populations reacting with melanoma cells may reflect the strong polyclonal response induced by BCG and KLH. In contrast, several lines of evidence argue against the possibility that the HMW-MAA binding antibodies are induced by BCG and KLH: (a) the HMW-MAA binding antibodies express the idiotope recognized by mAb MK2-23 in their antigen binding site; (b) anti-HMW-MAA antibodies have been found occasionally in patients immunized with anti-id mAb MK2-23 without KLH and adjuvant. In contrast, anti-HMW-MAA antibodies have not been detected in patients with malignant melanoma immunized with melanoma cells mixed with BCG (28) as well as in mice immunized with KLH and BCG mixed with mouse anti-id mAb which do not bear binding site.

the internal image of HMW-MAA (22); and (c) in view of the reported cross-reactivity of BCG antigens with MAA (29), it is noteworthy that there is no evidence of cross-reactivity of HMW-MAA with BCG antigens.5

The HMW-MAA-binding anti-anti-id antibodies elicited by mAb MK2-23 are both IgM and IgG. These findings parallel results derived from the analysis of the immunoglobulin class of anti-HMW-MAA antibodies in BALB/c mice (27) and rabbits (18) immunized with mAb MK2-23. The IgG class of HMW-MAA-binding anti-anti-id antibodies indicates that the immune response induced by mAb MK2-23 is T-cell dependent. This possibility is corroborated by the ability of mAb MK2-23 to elicit a delayed-type hypersensitivity reaction to HMW-MAA-bearing melanoma cells in BALB/c mice (27). It is noteworthy that analysis of the immunoglobulin class of the anti-HMW-MAA antibodies formed by patient AK in the course of the immune response to mAb MK2-23 has shown that they are mostly

IgG already in the early phase of the immune response. These results suggest that the anti-id mAb MK2-23 may have boosted and not primed the humoral anti-HMW-MAA immune response. If this interpretation is correct, some patients may be primed by HMW-MAA present in melanoma lesions. This possibility is supported by the occasional detection of anti-HMW-MAA immunity in patients with malignant melanoma (30).

The development of anti-HMW-MAA immunity was associated with a partial clinical remission in the three patients investigated. Although one cannot formally exclude that this association is fortuitous, the temporal relationship between the induction of anti-HMW-MAA immunity and the clinical response strongly argues in favor of a cause-effect relationship between the two phenomena. If the regression of melanoma lesions is caused by immunological mechanisms mediated by HMW-MAA-binding anti-anti-id antibodies, then antibody-dependent cell-mediated cytotoxicity is likely to be the lytic mechanism causing destruction of melanoma cells since anti-HMW-MAA antibodies elicited in rabbits with anti-id mAb MK2-23 do not mediate lysis of melanoma cells in conjunction with human complement.5 Whatever the mechanism, if the immune response elicited by mAb MK2-23 accounts for the clinical responses we have described, immunization with anti-id mAb which bear the internal image of HMW-MAA represents a viable therapeutic approach to malignant melanoma, especially since minimal side effects are associated with repeated administrations of anti-id mAb.

In one patient, regression of metastases in lymph nodes was associated with lack of detectable changes in the size of a metastasis in a vertebra. Two of the three patients relapsed. These phenomena may reflect inaccessibility of melanoma lesions to anti-HMW-MAA antibodies and/or lack or low expression of HMW-MAA in the lesions. If the latter is the case, this limitation of active specific immunotherapy with a single anti-id mAb may be overcome by the use of combinations of anti-id mAb which bear the internal image of distinct MAA with a noncoordinate expression by melanoma cells. Investigations along this line are in progress in our laboratory.

5 Unpublished results.
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