Inhibition of Murine Tumor Growth by an Interferon-inducing Imidazoquinolinamine¹

Younan A. Sidky, Ernest C. Borden,² Charles E. Weeks, Michael J. Reiter, James F. Hatcher, and George T. Bryan

Cancer Center, Medical College of Wisconsin, Milwaukee, Wisconsin 53226 [Y. A. S., E. C. B.], 3M Pharmaceuticals, 3M Company, St. Paul, Minnesota 55144 [C. E. W., M. J. R.], and the University of Wisconsin Clinical Cancer Center, Madison, Wisconsin 53792 [J. F. H., G. T. B.]

ABSTRACT

The low-molecular-weight imidazoquinolinamine derivative, 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine (imidiquimod, previously described as R-837), induced α-interferon (IFN-α) in mice. IFN induction was identified at oral doses as low as 3 mg/kg. The 10% lethal dose for daily treatment with imiquimod was 200 mg/kg. Oral treatment with 30 mg/kg imiquimod once every three days significantly inhibited MC-26 colon carcinoma. Delay of treatment from day 1 to day 5, when tumors were easily palpable, did not reduce benefits. Ten daily treatments were slightly more effective than five. However, delivery of the same total dose of imiquimod either once every day for 20 days, once every 4 days, once every 7 days, or once every 10 days inhibited tumor growth to the same level. The antitumor effects of imiquimod were significantly abrogated by an antiseraum to murine IFN-α, suggesting that the antitumor effect was to a substantial extent mediated by IFN induction. Imiquimod also significantly reduced the number of lung colonies in mice inoculated i.v. with MC-26 tumor cells. Combination of treatment with imiquimod and cyclophosphamide was significantly (P < 0.01) better than treatment with either drug alone. Combination treatment with cyclophosphamide led to cures in some of the mice inoculated either s.c. or i.v. with MC-26 cells. Treatment with imiquimod also inhibited the growth of RIF-1 sarcoma and Lewis lung carcinoma but was ineffective for P388 leukemia. Imiquimod is an oral IFN-α inducer with antitumor effectiveness for transplantable murine tumors.

INTRODUCTION

Since the discovery of IFNs¹ as antiviral and later as antineoplastic proteins, a research focus has been the identification of potent, chemically defined IFN inducers. In 1967 polyribonucleotides were discovered to induce high levels of serum IFN and subsequently demonstrated antiviral and antitumor activity in experimental models (1). Several additional low-molecular-weight inducers including tilorone, pyrimidinones, and acridines were described (2–3). Few of these molecules induced high levels of IFN in humans (4). Thus the search for effective inducers, particularly those which might be orally active, has continued.

The low-molecular-weight (240) imidazoquinolinamine derivative, 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine, coded imiquimod (Fig. 1), when administered intravenously in a gel or cream formulation, protected guinea pigs from herpes virus challenge (5) but did not inhibit herpes virus replication in vitro (6). The level of effectiveness of imiquimod corresponded to an IFN titer induced in the guinea pig in response to treatment with imiquimod (7). Imiquimod proved effective for the treatment of primary genital herpes simplex virus type 2 (6, 8), cytomegalovirus infection (9) in guinea pigs, and arbovirus infection in mice (10, 11). Oral imiquimod induced high levels of circulating IFN-α in mice, rats, and guinea pigs (12). Imiquimod was also shown to induce IFN-α in monkeys following single or multiple daily oral doses (13).

We postulated that imiquimod might be effective against transplantable murine tumors. After preliminary studies identified antitumor activity, as a focus for study we chose MC-26 colon carcinoma and assessed different doses, schedules, combinations of imiquimod with cytotoxic agents, and routes of inoculation of MC-26 cells. To probe effectiveness in other murine tumor models we also assessed effects on tumors of varying histogenesism.

MATERIALS AND METHODS

Agents. Imiquimod as well as the vehicle were prepared and provided by 3M Pharmaceuticals (St. Paul, MN). Imiquimod was suspended as a fine powder in 2% Klucel LF vehicle (hydroxypropylcellulose). The vehicle or the imiquimod suspension was given to mice by gavage and was not used beyond 10 days after preparation.

IFN-α/β (Lot 87075) was purchased from Lee BioMolecular (San Diego, CA) with a specific activity of 3.6 × 10⁷ units/mg. It was provided as a lyophilized powder in vials containing 1.2 × 10⁷ units and was reconstituted just before use with 1 ml sterile distilled water. Further dilutions were made with glycerol buffer, pH 3.5. Rabbit anti-mouse IFN-α/β (Lot 88098, with 51,000 NIH neutralizing units/ml) as well as normal rabbit serum (Lot 90006) were also purchased from Lee BioMolecular. They were reconstituted with 1 ml sterile distilled water. Further dilutions were done with PBS. Rabbit anti-mouse TNF-α (IP-400) was purchased from Genzyme Corp. (Cambridge, MA). One μl neutralized 1000 units of TNF-α. The antiserum was diluted 1:100 with 1% bovine serum albumen in PBS.

CY and VLB were purchased from Sigma Chemical Co. (St. Louis, MO).

Mice. Virus-free female BALB/c × DBA/2 F₁ hybrids (CDF₁) weighing 18–20 g, as well as male and female CFW (20–25 g) mice were purchased from the Charles River Company. Female C57BL/6 mice (18–20 g body weight) were obtained from Sprague-Dawley. C3H/Km mice (18–22 g) were a gift from Dr. J. E. Moulder (Medical College of Wisconsin, Milwaukee, WI). Mice were housed in plastic cages with no more than 5 mice/cage. They were fed Wayne Rodent Blox (Continental Grain Co., Chicago IL) and HCl-acidified (pH 2.7–3.0) tap water ad libitum and were housed in a room with controlled temperature (22.2–24.4°C), 40% humidity, and a 12-h light-dark cycle. Mice were included in experiments after at least 1 week after their arrival from the supplier.

Tumors. P388 leukemia, MC-26 colon carcinoma, and Lewis lung carcinoma were obtained from the Frederick Cancer Research Facility, National Cancer Institute (Frederick, MD). RIF-1 sarcoma was a gift from Dr. J. E. Moulder. P388 was passaged once every week by i.p. inoculation in CDF₁ mice. The remaining tumor cell lines were grown as a monolayer in 75-cm² polystyrene flasks (Corning Glass Works, Corning, NY) in Dulbecco’s modified Eagle’s medium supplemented with 10% heat-inactivated fetal calf serum, nonessential amino acids, sodium pyruvate, minimum essential medium vitamin solution, and 1-
MURINE TUMOR INHIBITION BY AN INTERFERON INDUCER

**RESULTS**

The approximate LD_{50} for a single oral dose of imiquimod in CFW mice was about 500 mg/kg. When imiquimod was given daily for 5 days, the LD_{10} was 200 mg/kg for CDF1 mice. CDF1 mice treated with 100 mg/kg imiquimod daily for 5 days had a reversible body weight loss of about 12%. CDF1 mice receiving 50 mg/kg daily or 100 mg/kg once every 4 days tolerated treatment well and did not lose weight. Similar body weight patterns were observed in other mouse strains.

Imiquimod, administered orally to mice, was confirmed to induce IFN-α. Peak levels occurred at 2 h after a single dose in a typical mouse strain (Table 1). The use of antibodies to murine IFNs to neutralize serum antiviral activity identified only IFN-α. IFN induction was not affected when mice were pretreated with cyclophosphamide or vinblastine, oral imiquimod induced similar levels of IFN-α in the other mouse strains used for tumor studies, and similar levels of IFN were induced in males and females (data not shown).

Effects of Imiquimod on MC-26 Colon Carcinoma

Subcutaneous Tumors. CDF1 mice inoculated s.c. on day 0 with MC-26 colon carcinoma and treated orally with 100 mg/kg imiquimod daily on days 1–5 had significantly smaller tumors than those of control vehicle-treated mice (P < 0.02) in all days of measurement (Fig. 2A). Imiquimod inhibited tumor growth more effectively than treatment with 5 × 10^6 units IFN-α/β injected i.p. daily on days 5–9 (Fig. 2C; P < 0.05 in all days of measurement). The approximate LD_{50} for a single oral dose of imiquimod

![Structure of imiquimod](image_url)

**Fig. 1. Structure of imiquimod.**

Measurements were made three times a week and continued until a humane sacrifice was required. In the case of i.v. inoculation, cells were injected in a volume of 0.2 ml. Lungs were harvested on day 14 and fixed, and the number of lung colonies was evaluated.

Cytokine Analysis. IFN levels were determined in mouse serum by Lee BioMolecular by use of a bioassay. Briefly, a microtiter serial dilution assay using L929 cells challenged with encephalomyocarditis virus was used. A standard reference curve using murine IFN was used as a positive control and for normalization (15). The type of IFN induced was determined with an antibody neutralization assay. Induction of IFN by imiquimod was independently affirmed in the laboratory of Dr. Sidney Grossberg at the Medical College of Wisconsin utilizing an antiviral different assay method (16).

Serum levels of TNF (17), IL-2 (18), and IL-1 (Genzyme enzyme-linked immunosorbent assay kit) from CDF1 mice treated with different doses of imiquimod were evaluated.

Statistics. Student’s two-tailed t test was used to assess the statistical significance of differences between pairs of means. Results were considered and described as significant only if P < 0.05. Data from single experiments are presented, but for confirmation all results reported are based upon repeated experiments.
MURINE TUMOR INHIBITION BY AN INTERFERON INDUCER

Fig. 3. Effects of length of treatment (A) and time of start of treatment (B) with 50 mg/kg imiquimod applied p.o. on the growth of MC-26 colon carcinoma inoculated s.c. on day 0 in CDF1 mice. Klucel vehicle daily on days 1–5 (C); bars, SEM. A, imiquimod daily on days 1–5 (V); imiquimod daily on days 1–10 (A); B, imiquimod on days 1, 5, 9, 13, 17 (A); imiquimod on days 5, 9, 13, 17, 21 (O).

Fig. 4. Effects of fractionation of the same total dose of imiquimod (210 mg/kg/mouse) into 10 mg/kg daily for 21 days, 40 mg/kg once every 4 days, 70 mg/kg once every 7 days, or 110 mg/kg once every 10 days on the growth of MC-26 colon carcinoma inoculated s.c. on day 0 in CDF1 mice: Klucel vehicle on days 1, 5, 9, 13, 17, 21 (D); 10 mg/kg imiquimod on days 1–21 (A); 40 mg/kg on days 1, 5, 9, 13, 17 (O); 70 mg/kg on days 1, 8, 15 (O); 110 mg/kg imiquimod on days 1 and 11 (V).

Fig. 5. Effects of treatment with rabbit antisera to mouse IFN-α/β or TNF-α on the effectiveness of imiquimod against MC-26 colon carcinoma. Bars, SEM. A, effects of antiserum to mouse IFN-α/β: Klucel vehicle on days 3, 9, 15 (C); 100 mg/kg imiquimod on days 3, 9, 15 + 1 ml reconstituted normal rabbit serum simultaneously (O); 100 mg/kg imiquimod on days 3, 9, 15 + 1 ml reconstituted rabbit anti mouse IFN-α/β (capable of neutralizing 1000 units TNF-α) simultaneously (Δ). B, effects of treatment with antiserum to mouse TNF-α: Klucel vehicle on days 1, 5, 9, 13, 17 + 0.1 ml 100 dilution normal rabbit serum simultaneously (D); 100 mg/kg imiquimod on days 1, 5, 9, 13, 17 + 0.1 ml 100 dilution normal rabbit serum simultaneously (O); 100 mg/kg imiquimod on days 1, 5, 9, 13, 17 + 0.1 ml 100 dilution rabbit anti mouse TNF-α (capable of neutralizing 1000 units TNF-α) simultaneously (Δ).

measurements made up to day 27). Five treatments with 50 mg/kg imiquimod were as effective as 100 mg/kg. Five treatments with 100 mg/kg imiquimod once every 4 days inhibited tumor growth more effectively than treatments once daily for 5 days (Fig. 2A; P < 0.02 for measurements on days 15 and 18). Treatment with 10 mg/kg imiquimod once every 3 days for five doses resulted in the nonsignificant inhibition of tumor growth (Fig. 2B). However, 30 mg/kg once every 3 days or higher doses once every 4 days were equally effective, suggesting that maximal benefit for the treatment of MC-26 with imiquimod was achieved with 30 mg/kg (Fig. 2B).

Ten treatments were slightly although nonsignificantly more inhibitory than five (Fig 3A; the variance of measurements is indicated by SE bars for this experiment; comparable variances occurred in other experiments but are not indicated on graphs, to enhance clarity). A delay of the start of treatment from day 1 to day 5 did not affect the level of inhibition (Fig. 3B). This was true whether imiquimod was given daily or once every 4 days.

Fractionation of the same total dose of imiquimod of 210 mg/kg into 10 mg/kg daily for 21 days, 40 mg/kg once every 4 days, 70 mg/kg once every 7 days, or 110 mg/kg on days 1 and 12 resulted in the comparable inhibition of tumor growth (Fig. 4). Tumors of all treated groups were significantly smaller than those of control mice (P < 0.05), and there were no significant differences in the tumor size among the treated groups.

Antisera to IFN. Treatment with 100 mg/kg imiquimod induced about 6000 units IFN-α/ml serum (Table 1). To determine whether the antitumor effects of imiquimod were mediated by the induced IFN-α, a neutralizing antiserum to mouse IFN was administered to mice inoculated with MC-26 and treated with imiquimod. Control mice were treated simultaneously on days 3, 9, and 15 with 100 mg/kg imiquimod p.o. and 1 ml normal rabbit serum i.p. This resulted in the considerable and significant inhibition of tumor growth as expected (P < 0.01; Fig. 5A). Mice treated with 100 mg/kg imiquimod and 1 ml rabbit anti-IFN-α/β serum simultaneously had tumors which were significantly smaller than those of control mice but significantly larger than those of mice treated with the combination.
imiquimod and normal rabbit serum ($P < 0.05$). This indicated that induction of IFN-α represented an important part of the effectiveness of treatment with imiquimod but perhaps not the only mechanism.

Mice treated with the normal rabbit serum lost 4.5% of their body weight, but none died. Those treated with the immune rabbit serum lost 7.7% of their body weight, and 5 of 10 died. The first mouse died on day 17, when differences were already apparent (Fig. 5A), and the remaining four died on day 20. The experiment was thus repeated using lower doses of antisera (2.5x or 5x dilution); under these conditions no mice died. Serum taken from these mice 2 h after treatment with 100 mg/kg imiquimod and normal rabbit serum had detectable IFN-α levels (125 or 255 units/mI serum). Serum from mice treated with imiquimod and immune rabbit serum (2.5x or 5.0x) had no measurable IFN-α. This indicated that even the 5.0x dilution neutralized all the IFN-α induced by imiquimod. The treatment with the antisera similarly abrogated imiquimod antitumor effects to a large extent and was not toxic. Mice treated with imiquimod and the anti-IFN-α antiserum diluted 5x had significantly larger tumors than those of mice treated with imiquimod plus normal rabbit serum ($P < 0.05$ in all days of measurement). Their tumors were smaller than those of vehicle-treated mice, but the difference was not statistically significant.

Antiserum to TNF. Treatment with 100 mg/kg imiquimod induced 100–200 units TNF in CDF1 mice. Peak levels were observed at 1 h after treatment and declined rapidly thereafter (data not shown). Tumors of mice treated with 100 mg/kg imiquimod and 1 μl rabbit anti-murine TNF-α serum (enough to neutralize 1000 units) had significantly ($P < 0.001$) smaller tumors than those treated with the vehicle plus normal rabbit serum but slightly and nonsignificantly larger tumors than those of mice treated with 100 mg/kg imiquimod plus normal rabbit serum (Fig. 5B).

Combination with Cytotoxic Drugs

Subcutaneous Tumors. Treatment with 50 mg/kg imiquimod orally on days 1, 5, 9, 13, 17, 21, and 25 significantly inhibited the growth of MC-26 as expected ($P < 0.02$ in all days of measurement). Treatment with 150 mg/kg CY alone on day 9 and on day 3 also inhibited tumor growth significantly (more so on day 3) (Fig. 6A; $P < 0.001$). The difference in tumor size of mice treated with CY on day 3 and on day 9 was significant on all days of measurement ($P < 0.001$) up to day 24. Treatment with CY on day 3 inhibited initial tumor growth substantially, but starting on day 17 tumors grew in an accelerated manner and caught up by day 24 with tumors of mice treated with CY on day 9. When CY treatment was combined with treatment with imiquimod, significant further inhibition occurred, especially in mice treated with CY on day 9 (Fig. 6A; $P < 0.003$ in all days of measurement). Of the mice treated with the combination of CY on day 9 and imiquimod on days 1, 5, 9, 13, and 17, 2 of 10 in one experiment and 1 of 10 in another were tumor-free for more than 60 days.

Treatment with 2.7 mg/kg VLB (LD$_{10}$) on day 3 inhibited MC-26 growth to a lesser degree than 50 mg/kg imiquimod. The difference between the two treatments was not significant. Treatment with VLB on day 9, in contrast to the case of CY, was ineffective. Treatment with the combination resulted in smaller tumors than in case of either drug alone, but the differences were not significant (data not shown).

Intravenous Tumors. Treatment with 50 mg/kg imiquimod orally once every 4 days significantly inhibited the number of lung colonies caused by i.v. inoculation with 4 x 10$^4$ viable MC-26 cells (Fig. 6B). Treatment was started on day 1 and repeated on days 5, 9, and 13. Mice were sacrificed on day 14, and macroscopic lung colonies were quantitated. Treatment with 100 mg/kg CY or a higher dose on day 3 resulted in the total prevention of the development of any lung colonies in mice inoculated i.v. with MC-26. Treatment with 50 mg/kg imiquimod orally on days 1, 5, 9, and 13 or 50 mg/kg CY on day 3 caused a significant inhibition in the number of lung colonies ($P < 0.01$; Fig. 6B). The difference between the effects of CY and those of imiquimod was not significant ($P = 0.17$). The combination of CY on day 3 and imiquimod resulted in a significant further reduction in the number of lung colonies ($P < 0.001$). Of mice treated with the combination, lungs of 4 of 10 were totally free of any colonies. In a repeat experiment 2 of the 10 lungs were colony-free.

In mice inoculated on day 0 with 10$^4$ viable MC-26 cells, treatment with 50 mg/kg imiquimod on days 1, 5, 9, and 13 caused, as expected, a significant reduction in the number of lung colonies from a mean of 170 to 99 ($P < 0.001$). Treatment with 2.7 mg/kg VLB on day 3 was ineffectual (mean, 163 colonies). The combination resulted in lower colony counts (mean, 70 colonies; $P < 0.003$).

Other Tumors

Lewis Lung Carcinoma. Lungs of mice inoculated i.v. with Lewis lung carcinoma and treated with 150 mg/kg imiquimod...
on days 1, 5, 9, 13, and 17 had significantly fewer lung colonies than control mice (Table 2), suggesting the sensitivity of Lewis lung carcinoma to treatment with imiquimod. The mean number of lung colonies of the control group was 6.4 and for the treated group was 0.2 ($P < 0.01$).

**RIF-1 Carcinoma.** C3H/Km mice were inoculated s.c. with $10^5$ viable RIF-sarcoma cells on day 0. Tumors were palpable on day 7. Mice were treated with the vehicle or 100 mg/kg imiquimod on days 3, 7, 11, and 15. Imiquimod-treated mice had significantly ($P < 0.02$) smaller tumors than vehicle-treated mice, starting with measurements made on day 14 (Fig. 7).

**P388 Leukemia.** P388 leukemia inoculated i.p. or s.c. was refractory to treatment with even toxic levels of oral imiquimod regardless of the time of start of treatment, the number of applications, the length of time between successive treatments, or the tumor load at the start of treatment (data not shown). Combination treatment with imiquimod did not alter the antitumor effectiveness of CY.

**DISCUSSION**

It was previously shown that imiquimod, when administered orally, induced high levels of circulating IFN-α in mice, rats, guinea pigs, and monkeys (12, 13) and that antiviral activity was related to IFN levels (6). Imiquimod (<1 μg/ml) induced in vitro IFN-α in human peripheral blood mononuclear cells, but polyriboinosinic-polyribocytidyl acid or 2-amino-5-bromo-6-phenyl-4(3H)pyrimidinone, potent IFN inducers in mice, failed to initiate any IFN production at levels of up to 50 μg/ml (19). In vitro, imiquimod demonstrated no direct antiviral (6, 7) or cytotoxic effects at drug levels achieved in vivo (data not shown). In the current study oral imiquimod demonstrated the ability to induce IFN effectively at doses less than 1% of the LD$_{50}$. The peak time of IFN induction and extent of induction were similar in different mouse strains. In general there were no detectable levels of IFN in the serum at 30 min and low levels at 1 h, peaking at 2 h and decreasing rapidly after that. Observed differences in the level of IFN measured at 2 h probably result from changes in the temporal peak of antiviral activity.

Imiquimod was a potent inhibitor of tumor growth in mice when administered orally at nontoxic doses. While $5 \times 10^5$ units IFN-α/β injected i.p. daily on days 5–9 had nonsignificant inhibitory effects on the growth of the MC-26 tumor, 30 mg/kg imiquimod resulted in significant inhibition. This suggests either that imiquimod induced more IFN-α than that delivered by i.p. treatment with $5 \times 10^5$ units IFN-α/β daily, that an important schedule benefit may exist, or that imiquimod induced other cytokines which participated in the observed benefits.

Imiquimod induced in mice high levels of IFN-α (12), low levels of TNF (20), and no detectable IL-2 or IL-1. Antiserum neutralizing IFN-α significantly reduced the antitumor effectiveness of imiquimod. Despite the complete disappearance of serum IFN levels caused by this antiserum, the antitumor effects of imiquimod were not totally abrogated. The low levels of imiquimod-induced TNF disappeared from the circulation more rapidly than IFN-α. Antiserum to murine TNF-α reduced (but not significantly) the effectiveness of imiquimod, indicating that TNF induction played a minor role in the observed antineoplastic potency of imiquimod. Other mechanisms may be involved in mediating the observed antitumor effects. For example, treatment with imiquimod reduced tumor-induced angiogenesis.5

Fractionation experiments indicated that treatment once every 10 days was as effective in inhibiting tumor growth as treatment with the same total dose once daily or every 4 or 7 days. Close to maximal benefits were achieved against MC-26 tumors with 30 mg/kg every 3 days. The start of treatment could be delayed from day 1 to day 5, when the tumor was easily palpable, without loss of effectiveness.

Imiquimod potentiated the effectiveness of CY in the treatment of MC-26. There was a significant further reduction of tumor growth over that achieved when either drug was used alone. In addition, some of the mice inoculated s.c. or i.v. with MC-26 and treated with the combination remained tumor-free; none of the mice remained tumor-free when treated with either drug alone. The benefits of a combination treatment were less evident when VLB was used. Treatment with imiquimod even at maximally tolerated doses had no effect on the survival of mice inoculated i.p. or s.c. with P388. However, P388 was sensitive to treatment with $5 \times 10^5$ units IFN-α/β injected i.p. daily on days 5–9; this caused a 20% increase in life span (21). When curative doses of CY for P388 leukemia were combined with IFN, mice died (21), indicating the negative effects of combination with IFN. However, a curative dose of CY was not adversely affected by combination with imiquimod in spite of its high potency in the induction of IFN.

Imiquimod proved to be highly potent in the inhibition of a wide range of murine tumors. Thus imiquimod may inhibit tumors induced by chemical carcinogens, as has been described for IFN and IFN-inducing pyrimidinones (22).

These observations suggest that treatment with an IFN inducer may be more beneficial than treatment with exogenous IFN, at least in certain tumor models. Imiquimod induces other cytokines which affect other aspects of the immune response. The set of cytokines and changes in the immune response

---

**Table 2** Effects of treatment with imiquimod on the number of lung colonies after i.v. inoculation of C57BL/6 mice with 10$^5$ viable Lewis lung carcinoma cells

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of lung colonies x ± SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle-treated mice</td>
<td>15, 16, 3, 10, 11, 0, 0, 9, 0</td>
</tr>
<tr>
<td>Imiquimod-treated mice</td>
<td>0, 0, 0, 0, 0, 0, 1, 1, 0</td>
</tr>
</tbody>
</table>

$* P < 0.02$.
initiated by imiquimod inhibited MC-26 colon carcinoma, RIF-1 sarcoma, and Lewis lung carcinoma but were not effective against P388 leukemia. The multiple actions of imiquimod may initiate changes affecting other tumor models differently.

ACKNOWLEDGMENTS

We are grateful to Dr. John E. Moulder for RIF-1 and C3H/Km mice, Steve Reilly and Sheila Gibson for help with the different technical procedures, and Dr. Richard Miller for continuous support and advice. Dr. Lee Kronenberg of Lee BioMolecular performed the IFN assays.

REFERENCES

Inhibition of Murine Tumor Growth by an Interferon-inducing Imidazoquinolinamine

Younan A. Sidky, Ernest C. Borden, Charles E. Weeks, et al.


Updated version
Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/52/13/3528