

## **Efficacy of Superoxide Dismutase Mimetic M40403 in Attenuating Radiation-Induced Oral Mucositis in Hamsters**

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**Abstract Purpose:** M40403 is a small-molecule superoxide dismutase mimetic that has shown efficacy in animal model disease states in which superoxide anions are thought to play a key role. Radiation treatment and chemotherapy for cancer generate free oxygen radicals that are hypothesized to trigger unwanted side effects in healthy tissue. For some patients undergoing these antineoplastic treatments, one of the most prevalent side effects is oral mucositis, which is a painful, often dose-limiting condition. Preclinical and clinical studies of this condition have shown the positive effect of treatment with compounds that decrease free oxygen radicals. This study investigated the efficacy M40403 in a clinically relevant hamster model of acute, radiation-induced oral mucositis.

**Methods:** Oral mucositis was induced in hamsters by irradiation of the cheek pouch. The ability of i.p. administered M40403 to decrease the duration and severity of oral mucositis was assessed after treatment at different doses and dosing schedules. Oral mucositis was scored using the WHO grading scale.

**Results:** Compared with placebo-treated animals, those irradiated on day 0 and treated twice daily with 30 mg/kg M40403 had significantly less severe and shorter duration mucositis over a range of treatment schedules, including from days -1 to 3, day 0 to 3, and day 0 alone. Similar efficacy was achieved at doses of 10 and 3 mg/kg twice daily on days -1 to 3.

**Conclusions:** These results implicate free oxygen radicals in the onset of oral mucositis and also provide the basis for further development of M40403 in the prevention of this condition in at-risk cancer patients.

Oral mucositis is a dose-limiting and painful side effect of radiation and/or chemotherapy in cancer patients. It occurs in almost all patients undergoing radiochemotherapy for treatment of head and neck cancers and in the majority of patients receiving conditioning regimens in preparation of autologous stem cell transplant (1). In addition, between 20% and 60% of patients undergoing treatment for other types of cancer experience significant mucositis (1). Among patients receiving myeloablative chemotherapy, mucositis is the toxicity most often mentioned by patients as being the most debilitating side effect encountered (2). Oral mucositis is associated with increased morbidity and mortality in addition to significant additional hospital costs (3, 4).

Onset of oral mucositis is a biologically complex process that has been partially elucidated at the molecular level (1, 5–7). Radiation and chemotherapy lead to the generation of reactive oxygen species (ROS), which in turn activate several signaling pathways in the submucosa and epithelium (5, 8). Among these, nuclear factor- $\kappa$ B is thought to be important as it mediates the release of cytokines and cytokine mediators, cell adhesion molecules, acute-phase proteins, and stress response genes. This, in turn, leads to loss of epithelial cell renewal, apoptosis, atrophy, and ulcer formation. Amplification of these events can also occur through the subsequent infection of compromised mucosal barrier by oral bacteria.

Studies using either the superoxide dismutase enzyme or small-molecule ROS scavengers have reinforced the hypothesis that ROS are an important early trigger leading to oral mucositis. Superoxide dismutases are a class of oxidoreductase enzymes that dismutate superoxide anions into oxygen and hydrogen peroxide (9). In one experimental model of oral mucositis, mice administered the human Mn-superoxide dismutase gene, SOD2, intraorally in plasmid/liposomes before irradiation were protected from oral ulceration compared with controls (10). Vitamin E, a free radical scavenger, delayed the onset and reduced the severity of oral mucositis in a rat model of radiation-induced oral mucositis (11). In clinical studies, orgotein (bovine Zn-Cu-superoxide dismutase enzyme) treatment resulted in decreased radiation-related toxicity in patients with head and neck, bladder, or rectal cancer (12–14). Two other oxygen radical scavengers, amifostine (15) and RK-0202

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Received 10/19/07; revised 2/15/08; accepted 3/6/08.

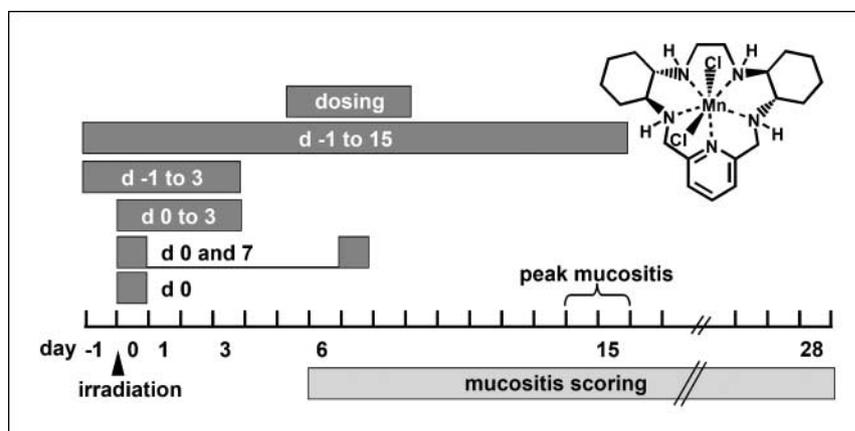
**Grant support:** ActivBiotics; Amgen, MedImmune, and Novartis (S.T. Sonis).

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doi:10.1158/1078-0432.CCR-07-4669

**Fig. 1.** Dosing schedules used in this study. In initial experiments, animals were treated with M40403 (*inset*) on days -1 to 15 or days -1 to 3. Subsequent experiments to refine the dosing schedule administered treatment on days -1 to 3, days 0 to 3, day 0 and 7, and day 0 only.



(*N*-acetylcysteine in a proprietary topical formulation; now called EN-3285; 16), have shown promise in the treatment of radiation-induced side effects including mucositis.

M40403, is a nonpeptidic, manganese-containing macrocyclic molecule that specifically catalyzes the dismutation of superoxide anions, a reaction that is also carried out by native human Mn-superoxide dismutase (SOD2; Fig. 1; ref. 17). M40403, in contrast to superoxide enzymes, is more stable, and its small size affords possible advantages of cell permeability and lack of immunogenicity. M40403 has specificity among reactive species and interacts exclusively with superoxide anions (18). The efficacy of M40403 and analogues has been shown in a wide variety of animal models of inflammation, ischemia-reperfusion injury, and pain (17). M40403 has also been investigated in approximately 700 subjects/patients as an i.v. formulation in several clinical trials for the treatment of pain. No significant safety trends have been detected to date in these trials (data not shown).

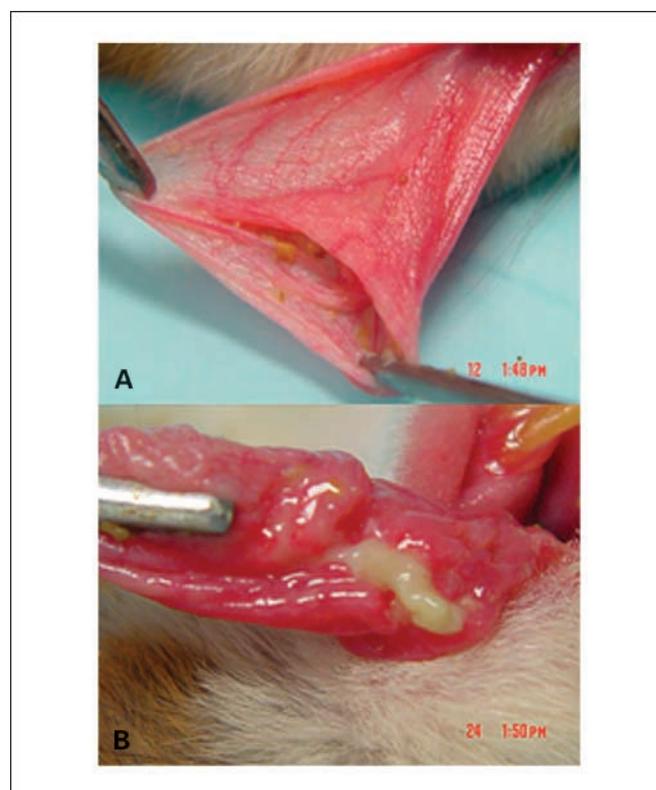
Based on the clear medical need for new therapies for oral mucositis, the molecular evidence for the role of ROS in the development of oral mucositis, and the preclinical and clinical studies establishing the efficacy of free radical scavengers, the concept of applying M40403 in this therapeutic area is compelling. The present studies were undertaken to assess the efficacy of M40403 in a hamster model of radiation-induced mucositis. The hamster model has been developed to test the efficacy of agents in both delaying the onset and lessening the severity of oral mucositis induced by acute irradiation (19). In this model, the hamster cheek pouch can be everted and specifically irradiated so that localized mucositis is elicited. The progression and resolution of mucositis in this animal model is very similar to that seen in the human condition. In addition, this model has been clinically validated with respect to the dosing schedule of therapeutic agents (20, 21). The present study tests the ability of M40403 to prevent oral mucositis in this model and suggest its possible utility as a human therapeutic.

## Materials and Methods

**Animals.** Male LVG Syrian golden hamsters (Charles River Laboratories), ages 5 to 6 weeks and weighing between 74 and 101 g, were used throughout the study. Animals were individually numbered using an ear punch and housed in small groups of approximately eight

animals per cage. Animals were acclimatized for 3 days before study commencement and were housed in rooms that were set to maintain a minimum of 12 to 15 air changes per hour. The room was on an automatic timer for a light/dark cycle of 12 h on and 12 h off with no twilight. Purina Labdiet 5061 rodent diet and water were provided *ad libitum*. Animals were randomly and prospectively divided into treatment groups before irradiation. The study was done at Biomodels, an Association for Assessment and Accreditation of Laboratory Animal Care-accredited facility in Cambridge, MA. Approval for this study was obtained from Biomodels Institutional Animal Care and Use Committee, which adhered strictly to the USPHS Policy on Humane Care and Use of Laboratory Animals.

**Dosing preparations.** M40403 powder, provided by ActivBiotics, was dissolved in 26 mmol/L sodium bicarbonate buffered saline



**Fig. 2.** Clinical appearance of (A) normal hamster cheek pouch mucosa and (B) cheek pouch mucosa with grade 3 mucositis following acute irradiation with 40 Gy. Ulcerative mucositis in the hamster presents in a manner similar to that seen in humans. An ulcerative base is covered by a whitish/yellowish pseudomembrane.

solution immediately before use. The pH was adjusted to between 8.1 and 8.3 with NaOH. All treatment solutions were passed through a 0.22  $\mu\text{m}$  polyvinylidene fluoride filter. Groups of eight animals were included for each dose group.

**Mucositis induction and treatments.** Mucositis was induced using a standardized acute radiation protocol on day 0 of the study (19). Before irradiation, animals were anesthetized with an i.p. injection of ketamine (160 mg/kg) and xylazine (8 mg/kg). The hamsters' left buccal pouch was then everted, fixed, and isolated using a lead shield. A single, focused dose of radiation (40 Gy) was administered to the pouch at a rate of 3.2 Gy/min. Radiation was generated with a 250 kV potential (15 mA) source at a focal distance of 50 cm, hardened with a 0.35 mm Cu filtration system. This dose of radiation predictably elicits mucositis that progresses to a mucositis score of between 3 and 4 at peak (see below and Figs. 3 and 4). Clinically detectable mucositis generally occurs in this model by day 6, with peak mucositis at about days 14 to 15.

Throughout the study, M40403 was administered twice daily via i.p. injection. The dosing schedules for each group are described in Fig. 1. In all cases, initial doses on day 0 were administered 30 min before irradiation. Control, irradiated animals were treated with vehicle (bicarbonate buffered saline vehicle). The maximum i.p. dose of M40403 used in hamsters was based on acute toxicity studies (data not shown).

**Quantitation of radiation damage and M40403 efficacy.** For the evaluation of mucositis, the animals were anesthetized with isoflurane and the left cheek pouch was everted and photographed every 2 days beginning on day 6. At the conclusion of the study (day 28), the photographs were randomized and analyzed by two independent, blinded observers. Mucositis was scored visually by comparison with a validated photographic scale (19), ranging from 0 for normal to 5 as follows: 0, completely healthy mucosa; 1, light to severe erythema and vasodilation, with no erosion of the mucosa; 2, severe erythema and vasodilation, erosion of superficial aspects of mucosa leaving denuded areas and decreased stippling of the mucosa; 3, severe erythema and vasodilation, including formation of off-white ulcers, which may be pseudomembranous, in a cumulative area of about one fourth of the cheek pouch; 4, severe erythema and vasodilation with ulcers covering about half of the cheek pouch, loss of pliability; 5, virtually all of pouch is ulcerated, with loss of pliability (pouch can only be partially extracted from the mouth). Mucositis scores of  $\geq 3$  in this animal model correspond to National Cancer Institute or WHO clinical scores of  $\geq 3$ . Figure 2 illustrates the difference between a normal cheek pouch and one that has grade 3 (severe) mucositis.

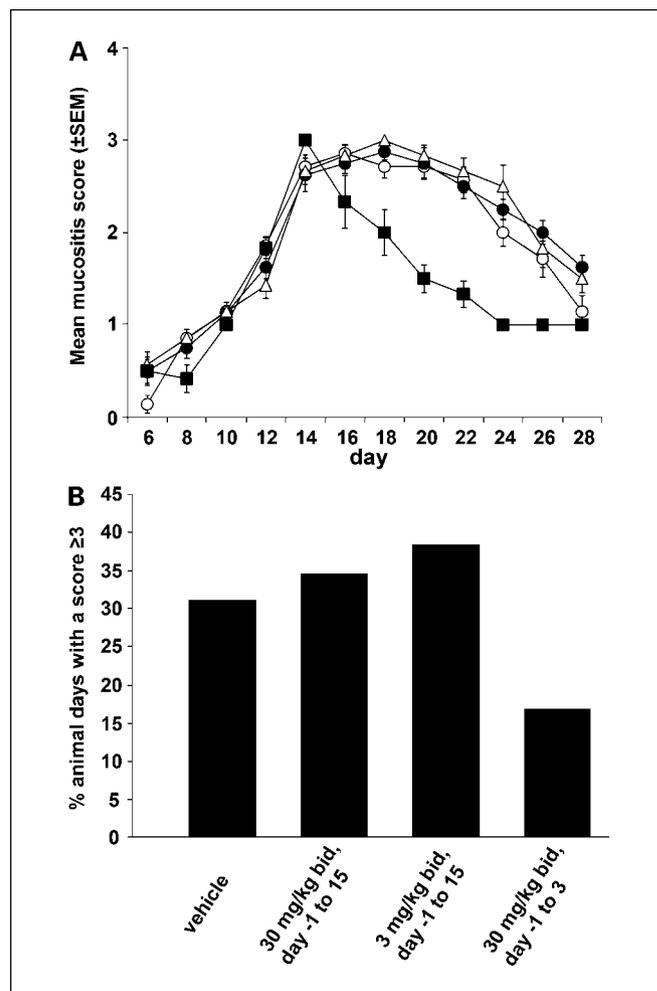
The efficacy of M40403 was assessed in three ways. First, the mean  $\pm$  SE daily mucositis scores for each treatment group and the controls were plotted over time to determine the effect of treatment on the kinetics of progression of oral mucositis. Second, the percentage of observed days hamsters in each group had ulcerative (score  $\geq 3$ ) mucositis was determined. Treatment groups were compared with the control group and statistical significance was determined by  $\chi^2$  analysis. Efficacy, in this analysis, is defined as a significant reduction ( $P < 0.05$ ) in the number of days that a treated group of animals had ulcerations (scores  $\geq 3$ ) when compared with the control group. Third, the rank-sum differences in daily mucositis scores were calculated. On each evaluation day, the scores of the control group were compared with those of the treated groups using nonparametric (Mann-Whitney) rank-sum analysis. Treatment success was considered as a statistically significant ( $P < 0.05$ ) lowering of scores in a treated group on  $\geq 2$  days between days 6 and 28.

## Results

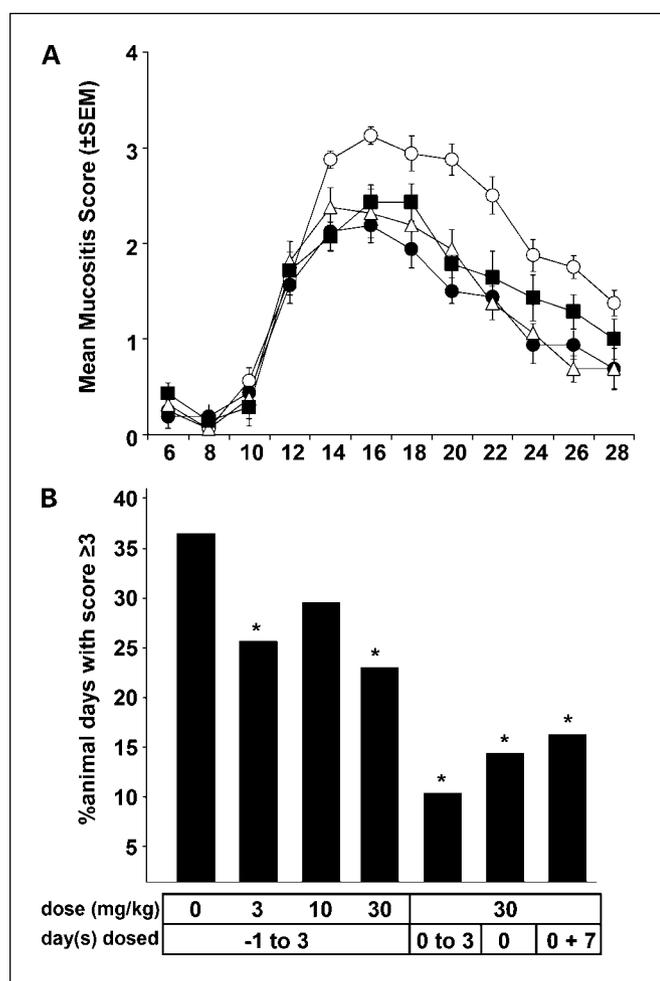
**Initial experiments to determine the efficacy of M40403.** Based on the mechanism of action of M40403 and the role that superoxide anions are thought to play in the initial stages of oral mucositis, therapy was scheduled starting on the day before irradiation (day -1) and carried through either day 3 or

15 postirradiation. Animals were dosed i.p. twice daily with M40403 at 3 or 30 mg/kg. On the day of irradiation (day 0), M40403 was administered 30 minutes before irradiation to increase the chance of significant levels of the drug during the initiating events of mucositis. In irradiated, untreated animals, clinical mucositis was evident starting on days 8 to 10 and peaked on day 16, with a mean mucositis score of 2.9 (Fig. 3A). The natural resolution of the mucositis was evident by day 28 in the vehicle-treated group, which regressed to a mean mucositis score of 1.1. The progression of severe mucositis was not significantly affected in the groups receiving either 30 or 3 mg/kg twice daily M40403 over days -1 to 15 (Fig. 3). Animals dosed at 30 mg/kg twice daily for days -1 to 3 had mucositis that progressed to a peak at day 14 (mean score of 3) similar to the control animals; however, mucositis resolution was markedly accelerated over days 16 to 24.

To determine the significance of the effect of M40403 on duration of mucositis in the model, the percentage of animal days with severe, ulcerative mucositis (a mucositis score  $\geq 3$ )



**Fig. 3.** Efficacy of M40403 in the hamster model of mucositis induced by acute irradiation. Animals were treated with M40403 as follows: 30 mg/kg twice daily on days -1 to 15 ( $\Delta$ ), 3 mg/kg twice daily on days -1 to 15 ( $\bullet$ ), 30 mg/kg twice daily on days -1 to 3 ( $\blacksquare$ ), or vehicle twice daily ( $\circ$ ). A, mean mucositis scores for each treatment group were calculated and plotted over the course of the study. B, for each treatment group, the percentage of animal days at or below a mucositis score of 3 was determined. The 30 mg/kg twice daily on days -1 to 3 treatment group's effect was significant when compared with the control using  $\chi^2$  test.



**Fig. 4.** Effect of reduced dosing regimens on oral mucositis in the hamster model. **A**, daily mean mucositis scores are shown for animals treated with 30 mg/kg M40403 twice daily on days 0 to 3 ( $\bullet$ ), day 0 only ( $\blacktriangle$ ), days 0 and 7 ( $\blacksquare$ ), or vehicle ( $\circ$ ). **B**, percent of animal days with mucositis scores  $\geq 3$  for each group. \*,  $P < 0.05$ , statistically significant from the control group ( $\chi^2$  analysis).

were determined for each of the groups (Fig. 3B). Vehicle-treated animals had severe mucositis 31% of the total of scored animal days. Animals treated with M40403 (either 30 or 3 mg/kg twice daily) on days -1 to 15 had severe mucositis for a slightly higher percentage of days (34.4% and 38.2%, respectively). In contrast, the group treated on days -1 to 3 with 30 mg/kg twice daily had severe mucositis for significantly less time (16.7%;  $P = 0.005$ ,  $\chi^2$  test). The efficacy of the 30 mg/kg twice daily dose for days -1 to 3 provided the basis for further experiments to refine treatment regimens.

**Effect of dosing schedule and level on M40403 efficacy in oral mucositis.** An ascending dose-conventional dose-response profile was carried out from days -1 to 3 to investigate efficacy in more detail. The mean daily mucositis scores and percentage of days that animals displayed a mucositis score of  $\geq 3$  are summarized in Fig. 4. The rank-sum analysis is summarized in Table 1. Doses of 3, 10, and 30 mg/kg were administered twice daily on days -1 to 3. As was seen in the first set of dosing experiments, the 30 mg/kg twice daily dose was again effective in significantly lowering the percentage of animal days with severe mucositis from 36.2% in the control group to 22.2% ( $P = 0.03$ ) in the treatment group (Fig. 4B).

Doses of 10 and 3 mg/kg twice daily for days -1 to 3 lowered the percentage of animal days with a mucositis score of  $\geq 3$  to 29.2% and 25%, respectively. Although the 3 mg/kg twice daily dose effect was significant ( $P = 0.02$ ,  $\chi^2$  analysis), the 10 mg/kg twice daily dose had a borderline trend toward efficacy when compared with the control group for this variable ( $P = 0.16$ ). Mann-Whitney rank-sum analysis for the 3 mg/kg twice daily dose group scored 3 days as statistically different than controls (days 14, 22, and 28; Table 1). None of the 10 mg/kg twice daily dose group showed a difference by this test. In addition, no difference was observed when the mean daily mucositis scores of these animals were plotted versus untreated animals (data not shown).

The effect of dosing schedule was further examined by reducing the days of treatment to 1 (day 0 only), 2 (days 0 and 7 only), or 4 (days 0-3) and comparing results with the days -1 to 3 dosing schedule that previously showed efficacy (Fig. 4B). An unanticipated finding was that the reduction of dosing was in every case more effective in reducing the hamster days of severe mucositis than the days -1 to 3 schedule (Fig. 4B). Even the day 0 only treatment was more efficacious than the 5-day schedule of the days -1 to 3 group, although the greatest efficacy was observed in the days 0 to 3 group. The days 0 to 3, days 0 and 7, and day 0 only treatment groups had percent of animal days with severe mucositis (score  $\geq 3$ ) of 9.4%, 15.5%, and 13.5%, respectively. These values represent a 74%, 58%, and 63% decrease in days with severe oral mucositis compared with controls, respectively, and are not statistically different from one another. Figure 4A shows that animals subjected to these dosing regimens also had lower mean peak mucositis when compared with controls and resolved the condition in a shorter time frame.

A third analysis was applied to the data to determine the extent of M40403 efficacy in the model. The scores for the M40403-treated groups were compared with the control on each observation day of scoring using the Mann-Whitney rank-sum test. Two or more days of significant lowering of scores for treated animals versus controls was considered treatment success. In the first set of experiments, animals treated with M40403 at 30 mg/kg twice daily from days -1 to 3 had significant lowering of their mucositis scores from days 18 to 26 (Table 1). Dosing at this level or at 3 mg/kg for days -1 to 15 failed to show significant differences on any of the observation days. Applying this analysis to results from the second set of experiments revealed that the 30 mg/kg dose at days -1 to 3 had only 1 day that was significantly different and 5 other days that trended toward significance when compared with the control group. The 10 mg/kg group for this schedule failed to show any days that trended toward a difference. Curiously, the 3 mg/kg group had 3 days that were significantly different; however, these were not on contiguous observation days. Shortening the dosing schedule had a striking effect as visualized by this rank-sum test. Treating animals with 30 mg/kg twice daily for days 0 to 3, day 0 only, and days 0 and 7 resulted in a significant lowering of mucositis scores for 8, 7, and 5 days, respectively, compared with controls.

## Discussion

The onset of oral mucositis is multifactorial and has several adverse consequences for the cancer patient. Apart from causing

severe pain, and an overall effect on quality of life, oral mucositis has significant effect on patient survival due to the increased risk of infection and curtailment of the antineoplastic treatment. Currently, the only approved drug for the treatment of oral mucositis is the biologic Kevivance® (palifermin, a member of the fibroblast growth factor family). Although it is currently approved only for use in patients undergoing conditioning therapy for autologous hematopoietic stem cell transplant (22), several clinical trials examining its safety and efficacy in other cancer treatment settings are under way (<http://clinicaltrials.gov>). Orgotein, which has also shown efficacy in small human trials, is currently not approved for human use in the United States due to its immunogenicity, which can lead to anaphylactic reactions in patients receiving the therapy. Additional agents that could be used in other cancer patient populations or that have mechanisms of action distinct from palifermin could be valuable in oral mucositis treatment or prevention.

Several lines of evidence have implicated ROS as key mediators in the initiation of oral mucositis and related radiation and chemotherapy induced conditions. Radiation itself is known to result in the generation of ROS from water, and subsequently ROS have been shown to activate NFκB (5). The latter transcription factor has been postulated to elicit expression of a variety of inflammatory cytokines and other mediators of tissue damage (23). Further association between oxidative stress and oral mucositis has been borne out of several studies in animals and humans using superoxide dismutase enzyme and ROS scavengers (10–14).

M40403 specifically catalyzes the dismutation of superoxide anions at the same rate as the native enzyme, which provides a logical mechanism for its efficacy in preventing oral mucositis in the hamster model. M40403 is stable in the presence of peroxynitrite, which inactivates the native enzyme, and does not react with nitric oxide, which is a key anti-inflammatory mediator and has tissue protective properties. It is interesting

that M40403 was also efficacious in experimental models of inflammation (17).

M40403 efficacy in this model was most sensitive to variations in dose schedule. In contrast to our expectations, minimal dosing of M40403, on day 0 alone, was markedly more effective than extended dosing regimens. M40403 administered for a prolonged period at the higher dose was not efficacious in the hamster model. The result of this 17-day dosing schedule was instead a significant reduction in weight gain compared with control animals, which were irradiated and treated with placebo (data not shown). When the total dose of compound was reduced (and the reduction of weight gain diminished), M40403 showed marked efficacy. The optimal regimen was 30 mg/kg delivered from days 0 to 3. However, it is important to note that a dose-response curve at this schedule awaits further experimentation. That the day 0 only treatment at 30 mg/kg was efficacious compared with the control group raises the possibility that favorable effects could be gained clinically by two doses on the day of irradiation. In any case, in this acute model, it appears that treatment over longer periods is not advantageous. The reason for this may be that superoxide anions are involved in the signaling of the healing process that occurs in the days postirradiation and that the extensive removal of superoxide anions by M40403 during this specific time window may interfere with the healing process.

Our finding that two doses of M40403 on the day of irradiation are efficacious suggests a mechanism of action in which superoxide anions are removed from the tissue at the time of irradiation. We expect that, in this regimen, plasma levels of M40403 would be high during radiation exposure based on plasma pharmacokinetics in rodents, dogs, and man (data not shown) and the fact that the initial dose was administered not more than 1 hour before irradiation. It will be interesting to determine whether a single dose before irradiation will be as efficacious as two doses on day 0. It is also

**Table 1.** Mann-Whitney rank-sum test analysis of daily mucositis scores for M40403-treated groups versus the control, vehicle-treated group

Dose (mg/kg twice daily)	Schedule (d)	Day											
		6	8	10	12	14	16	18	20	22	24	26	28
3	-1 to 15												
30	-1 to 15												
30	-1 to 3												
30*	-1 to 3												
10	-1 to 3												
3	-1 to 3												
30	0 to 3												
30	0												
30	0 and 7												

NOTE: Days on which the scores were significantly different are shaded black and those that trended toward significance ( $P \leq 0.15$ ) are shaded gray.

\*The 30 mg/kg bid dose was also tested in a second experiment.

possible that lower doses could be efficacious for this schedule. These data show that M40403 was efficacious after a single large radiation dose, indicating the potential of M40403 for decreasing the severity and duration of oral mucositis in patients undergoing radiotherapy for cancer. Because patients being treated for head and neck cancers undergo a fractionated radiation dosing regimen, it would be interesting to extend this

work with preclinical studies employing a fractionated radiation dose schedule of treatment.

### Disclosure of Potential Conflicts of Interest

S. Sonis received a grant from Amgen, MedImmune, and Novartis. S. Sonis also has ownership interest in Mucosal Therapeutics.

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*Clin Cancer Res* 2008;14:4292-4297.

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