ORAL DISEASES

Oral Diseases (2010) 16, 655–660. doi:10.1111/j.1601-0825.2010.01671.x

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ORIGINAL ARTICLE

Attenuation of radiation- and chemoradiation-induced mucositis using gamma-D-glutamyl-L-tryptophan (SCV-07)

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OBJECTIVE: To evaluate the efficacy of a novel immunomodulating peptide (SCV-07) in attenuating the course of radiation-induced mucositis in an established animal model of oral mucositis (OM).

MATERIAL AND METHODS: In three separate experiments, golden Syrian hamsters received either an acute radiation challenge to the buccal mucosa of eight fractionated doses of 7.5 Gy of radiation over a 2-week-period, or a combination of acute radiation and cisplatin. In each experiment, animals were treated with varying doses or schedules of SCV-07 or placebo. OM was scored in a blinded fashion using digital images obtained during the experimental period.

RESULTS: We found that SCV-07 reduced the severity and duration of both acute and fractionated radiation-induced OM. Similarly, when radiation and chemotherapy were used to induce OM, treatment with SCV-07 significantly reduced the duration of ulcerative OM. The therapeutic benefit was dependent on both dose and schedule of administration.

CONCLUSION: Taken together, we found SCV-07 was able to modify the duration and severity of oral mucositis and was dependent on schedule and dose.

Oral Diseases (2010) **16**, 655–660

Keywords: *SCV-07*; gamma-D-glutamyl-L-tryptophan; radiation; mucositis; animal models

Introduction

Oral mucositis (OM) is a painful, treatment-limiting, debilitating, and resource-draining toxicity associated with radiation and drug therapy used for the treatment of cancer. OM significantly affects virtually all patients who receive radiation, with or without chemotherapy, for the management of mouth or oropharyngeal tumors, and over two-thirds of those individuals with cancers of the larynx or hypopharynx (Rubenstein *et al*, 2004).

The pathobiology of OM, once thought simply to be the complete consequence of radiation- or chemotherapy-mediated basal stem cell death, has proven to be much more complex. Mounting evidence demonstrates that OM is the consequence of a multifactorial process in which numerous pathways, activated in the cells and tissues of the submucosa, induce apoptosis and necrosis of the overlying epithelium to produce the clinical phenotype which defines OM (Sonis, 2007). While the pathobiology of OM is far from being comprehensively defined, a five stage model has been described which serves to organize the various steps thought to be important in OM development (Sonis, 2004).

The clinical sequence and changes that define radiation-induced OM are well-characterized and correspond to the cumulative dose of radiation delivered to the tissue (Sonis, 2000). In general, early clinical and symptomatic mucosal changes occur with radiation doses as low as 20 Gy, with ulceration developing by 30 Gy, usually by the end of the third week of therapy. Ulcerative mucositis generally continues throughout the remainder of treatment and persists for an additional 2–3 weeks, often necessitating the use of opioids for pain control and gastrostomy tube feedings for nutrition (Vera-Llonch *et al*, 2006).

There is currently no approved intervention for the prevention or treatment of radiation-induced OM. Several strategies are being actively explored, which are based on the mechanistic interruption of one or more of the pathobiological pathways associated with the condition. The role of immune modulation in mucositis has not been well studied. While T-helper 1 (Th1) cytokines, particularly pro-inflammatory cytokines such as IFN-γ and IL-2, have been implicated in a range of diseases and conditions including mucositis, as important mediators of mucosal injury, T-helper 2 (Th2) cytokines have been less well studied. It has been observed that the percentage of oral mucosal CD8 + lymphocytes increased marginally following

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Received 19 October 2009; accepted 13 November 2009

radiation (Handschel *et al*, 2001). The same investigators also reported an increase in the median value of the total number of CD4 + and CD8 + lymphocyte subpopulations in radiated mucosa. However, the specific roles of T-helper cell populations have not been studied with respect to OM, although Th1 cells have been implicated as important in the genesis of mucosal injury associated with Crohn's disease. Furthermore, a comparison of canonical pathways demonstrated a commonality of many seen in OM and those reported for a range of autoimmune diseases including lupus erythematosus and rheumatoid arthritis (Zhang L, personal communication).

Consequently, in this study, we investigated the effect of a novel immune modulator, SCV-07, a water-soluble synthetic peptide (gamma-D-glutamyl-L-tryptophan), on the development and course of radiation-induced OM. SCV-07, being clinically developed primarily for infectious disease applications, has been shown to have a direct stimulatory effect on Th1 cells, and to negatively impact Th2 cell function (Simbirtsev *et al*, 2003). Our results demonstrate that SCV-07 has the ability to modulate the severity and course of radiation-induced OM by both acute and fractionated regimens. Furthermore, we found that SCV-07 was also effective in attenuating mucositis induced following a course of a combined treatment with acute radiation and cisplatin. The mechanism(s) by which this unanticipated effect is mediated has yet to be defined.

Materials and methods

Reagents

SCV-07 (gamma-D-glutamyl-L-tryptophan) was provided as a lyophilized powder (SciClone Pharmaceuticals Inc., Foster City, CA, USA) and dissolved in sterile PBS immediately prior to administration. For each dose, SCV-07 was subcutaneously administered in a volume of 0.1 ml per 100 g of body weight. Cisplatin for injection was purchased from Bedford Laboratories (Bedford, OH, USA) and stored at room temperature.

Animals

All animal studies were approved by the Institutional Animal Care and Use Committee (IACUC) and performed under veterinary supervision. Male LVG golden Syrian Hamsters (Charles River Laboratories, Wilmington, MA, USA), aged 5–6 weeks and weighing approximately 80 g at study start, were used. Animals were individually numbered using an ear punch and acclimated for 1 week prior to study initiation. Animals were given food (Purina Labdiet® 5061) and water *ad libitum*.

Radiation source

Radiation was administered using a Philips 160 kVp, 18.75 ma X-ray source (Philips Medical Systems, Valhalla, NY, USA) at a focal distance of 30 cm, with a 3.0 mm hardened Al filtration system. This source was periodically calibrated using a Victoreen model 530 dosimeter (Fluke Biomedical, Everett, MA) to provide a consistent dose rate of 3.32 Gy min^{-1}.

Acute radiation-induced mucositis

Acute mucositis was induced using a standard technique that has been described previously (6). Briefly, following the induction of general anesthesia with ketamine (160 mg kg^{-1}) and xylazine (8 mg kg^{-1}) administered by intraperitoneal injection, the left buccal pouch was everted, fixed and isolated using a lead shield to prevent irradiation of the rest of the animal. A single dose of 40 Gy was delivered to the left buccal pouch mucosa at a rate of 3.32 Gy min^{-1} on study day 0. Animals were given a subcutaneous dose of 100 μg kg^{-1} of SCV-07 once or twice a day from days –1 to 20. Mucositis was evaluated starting on study day 6 and continuing on alternate days until study day 28.

Fractionated radiation-induced mucositis

Use of fractionated radiation in this model, which more closely resembles clinical dosing schedules, has also been previously described (Sonis, 2002). Hamsters received a cumulative dose of 60 Gy of radiation, partitioned into eight fractions of 7.5 Gy each on days 0–3 and 7–10, with a 3-day rest period between (days 4–6). Radiation was selectively delivered to the left buccal pouch with lead shielding the rest of the animal as described above. Animals were treated with vehicle or SCV-07. Vehicle control animals were dosed once daily from day –1 to 29. SCV-07-treated animals received 100 μg kg^{-1} administered in one of three schedules: days 1–29, 0–3 and 6–9, or days 1, 4, 5 and 10–29 (Table 1).

OM was evaluated clinically on alternate days from day 7 until day 35.

Combination cisplatin and acute radiation-induced mucositis

Oral mucositis was induced by a combination of cisplatin (5 mg kg^{-1}) administered on day 1, and radiation given as a single 35 Gy dose on day 0 in a fashion similar to what has been described above. Beginning on

Group Number	*Number of Animals*	*Treatment*	*Treatment Schedule*
1	10 males	Vehicle (PBS), sc, qd	Day -1 to Day 29
2	10 males	SCV-07, sc, qd 100 μg/kg	Day -1 to Day 29
3	10 males	SCV-07, sc, qd 100 μg/kg	Day 0 to Day 3 Day 6 to Day 9
4	10 males	SCV-07, sc, qd 100 μg/kg	Day -1, Days 4, 5 Day 10 to Day 29

Table 1 Fractionated radiation: study design. All animals were irradiated with a cumulative dose of 60 Gy partitioned into eight fractions of 7.5 Gy each on days –0–3 and 7–10. SCV-07 was administered 30 min prior to irradiation. qd, once daily

day 1 (day of cisplatin injection) and then continuing until day 20, animals were treated with daily doses of vehicle or SCV-07 at varying doses (Table 2). Mucositis was evaluated on alternate days from study day 6 until study day 28.

Oral mucositis evaluation and scoring

For the evaluation of mucositis, the animals were anesthetized with isoflurane and the left pouch everted and photographed. At conclusion of the study's clinical phase, digital images were randomly numbered and then scored in blinded fashion by two observers. A validated and well-described five point scoring system (Alvarez *et al*, 2003) was used that applied the following numerical scores to buccal lesions: 0 – normal mucosa; 1 – erythema and vasodilation; 2 – severe erythema and vasodilation with edema and superficial epithelial sloughing; 3 – frank ulceration of the mucosal surface of which the cumulative area involved is ≤25% of the mucosal surface and pseudomembrane formation may be evident; 4 – Severe erythema and vasodilation and cumulative size of ulcers involved >25% and ≤50% of mucosal surface with general loss of mucosal pliability; 5 – diffuse, extensive ulceration, loss of pliability, pouch can only partially be extracted from mouth. The reported scores represent the average of the observations from the two blinded observers. In this model, a score of ≥3 represents a score that is clinically equivalent to an NCI-CTC or WHO score of at least two.

Oral mucositis severity was calculated using group scores on each observation day (mean ± s.e.m.). For each evaluation day, groups were compared using a Mann–Whitney rank-sum test. The duration of severe OM for each group was also determined using animal scores and was represented as a percentage (percentage of animal days with a score ≥3). Chi-squared analysis for significance was performed to evaluate the differences between the groups. A score was considered significantly different if a chi-square analysis demonstrated a probability value of <0.05. For these analyses, treatment success is considered as a statistically significant lowering of scores in the treated group on two or more days from day 6 until the end of the study as well as a statistically significant difference in the percentage of animal days with a score ≥3.

Results

Effect of SCV-07 on oral mucositis induced by acute radiation

Daily doses of SCV-07 administered at 100 μg kg^{-1} on days –1–20 markedly attenuated the course and duration of ulcerative mucositis. Whereas peak mucositis on day 18 in the vehicle control group was 3.0, it was only 2.2 in the test group (Figure 1a). Hamsters receiving SCV-07 had mucositis scores of ≥3 on only 6.3% of the animal days evaluated, compared to 28.1% in vehicle treated hamsters ($P < 0.001$).

Dose ranging studies demonstrated that doses of SCV-07 less than 100 μg kg^{-1} were ineffective in influ-

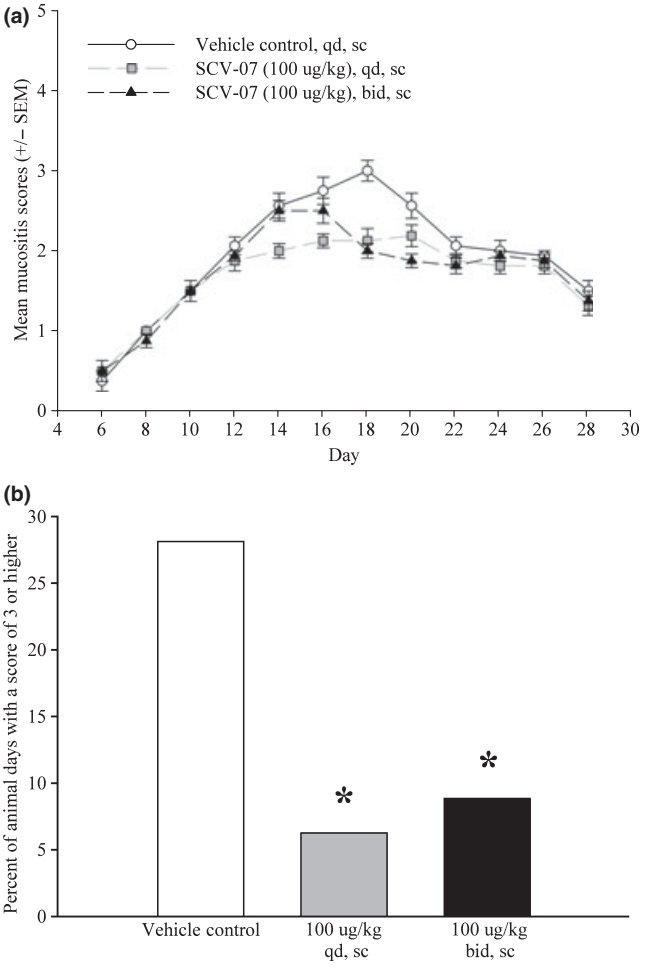

Figure 1 Acute radiation schedule determination. **(a)** Mean group mucositis scores were calculated for each day of evaluation. Error bars represent the standard error of the means (s.e.m.). **(b)** To examine the levels of clinically significant mucositis, as defined by presentation with open ulcers (a score of ≥3), the total number of days in which an animal exhibited an elevated score was summed and expressed as a percentage of the total number of days scored. Asterisks denote statistically significant scores when compared to the control using a chi-squared test

Table 2 Combination therapy: study design. All animals were irradiated with 35 Gy on day 0. SCV-07 was administered 30 min prior to irradiation. qd, once daily

Group Number	*Number of Animals*	*Treatment*	*Treatment Schedule*	*Cisplatin*
1	10 males	Vehicle (PBS), sc, qd	Day -1 to Day 20	5 mg/kg Day 1
2	10 males	SCV-07, sc, qd 1 μg/kg	Day -1 to Day 20	5 mg/kg Day 1
3	10 males	SCV-07, sc, qd 100 μg/kg	Day -1 to Day 20	5 mg/kg Day 1
4	10 males	SCV-07, sc, qd 1.0 mg/kg	Day -1 to Day 20	5 mg/kg Day 1

encing the severity or course of OM induced by acute radiation. While higher doses (1 mg kg^{-1}) provided equivalent efficacy, they were not superior to the 100 μg kg^{-1} dose (data not shown). Dosing twice per day was also no more effective than daily dosing (Figure 1); hamsters receiving SCV-07 at 100 μg kg^{-1} twice daily had mucositis scores of ≥3 on only 8.9% of the animal days evaluated ($P < 0.001$ compared to the vehicle control). Using the Mann–Whitney rank sum analysis, animals treated with SCV-07 at 100 μg kg^{-1} once daily on days –1–20 showed statistically significant improvement on days –14 ($P = 0.011$), 16 ($P = 0.002$) and 18 ($P = 0.001$) of the study relative to the saline controls. The group treated with SCV-07 at 100 μg kg^{-1} twice daily on days –1–20 showed significant improvement relative to controls only on days 18 and 20 ($P < 0.001$ and $P = 0.003$, respectively).

Effect of SCV-07 induced by fractionated radiation schedule

The ability of SCV-07 to modulate OM induced by fractionated doses of radiation was dependent on dosing schedule (Figure 2). Whereas SCV-07 administered daily at concentrations of 100 μg kg^{-1} effectively reduced the duration of ulcerative mucositis when given only on days of radiation (days 0–3, 6–9), it was ineffective if administered throughout the radiation period (days 1–29), or only on days between radiation dosing periods and following the completion of radiation (days –1, 4, 5, 10–29).

Vehicle-treated control animals had a mucositis score of ≥3 on 36% of the animal days evaluated (Figure 2a). Animals treated throughout the study (100 μg kg^{-1} SCV-07, days –1–29) had a mean mucositis score of ≥3 on 32.7% of the animal days in the study; but this was lowered to 24% for animals treated only on days of radiation (days –0–3 and 6–9). The latter result was significantly different from vehicle treated control animals ($P = 0.002$). Animals treated only on days before or after radiation (days –1, 4, 5, 10–29) however showed mucositis scores of ≥3 on only 30.7% of the animal days, which was not statistically different from vehicle-treated control animals ($P = 0.204$).

Vehicle-treated control animals had a mean peak mucositis score of 3.2 on day 19 (Figure 2b). Animals receiving SCV-07 on days –1–29 had a peak mean mucositis score of 3.3 (day 19) and those receiving SCV-07 on the days of radiation delivery (0–3 and 6–9) had a peak mean mucositis score of 3.0 on day 17. In combination with fractionated radiation, therefore, SCV-07 did not significantly reduce observed peak OM scores.

The Mann–Whitney rank-sum test was used to compare each treatment group to the vehicle control on each day of mucositis on each day of mucositis. Rank sum comparison for the mean daily mucositis scores for SCV-07 treated animals with the vehicle control showed that daily administration of 100 μg kg^{-1} SCV-07 from days –1 to 29 or days –0 to 3 and 6 to 9 significantly reduced the severity of OM for 3 or 6 days, respectively. Animals which received SCV-07 from days –1, 4, 5, 10–29 also had significantly lower mucositis scores on only three consecutive observation days when compared to the control animals.

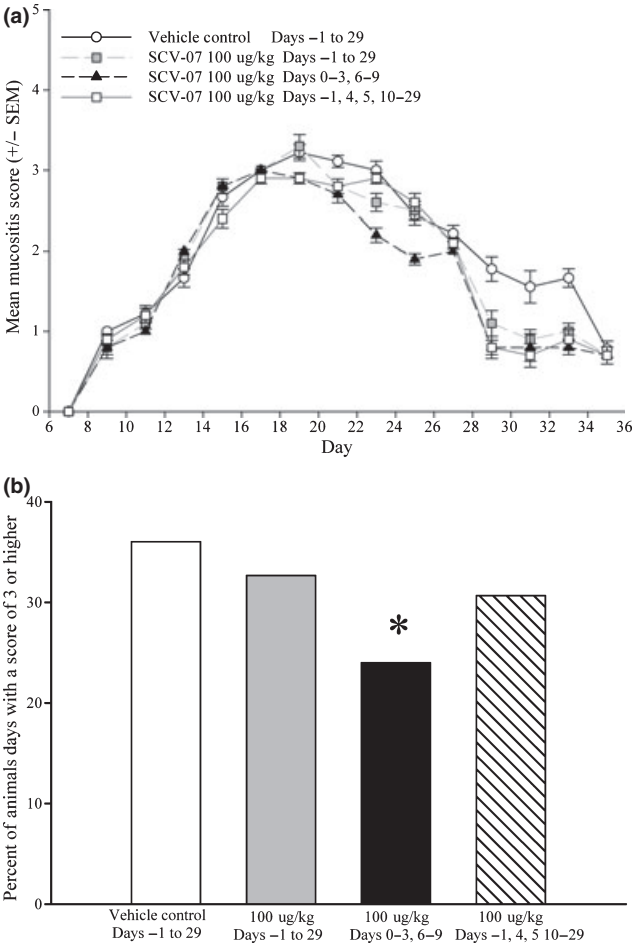

Figure 2 Fractionated radiation study. **(a)** Mean group mucositis scores were calculated for each day of evaluation. Error bars represent the standard error of the means (s.e.m.). **(b)** To examine the levels of clinically significant mucositis, as defined by presentation with open ulcers (a score of ≥3). The total number of days in which an animal exhibited an elevated score was summed and expressed as a percentage of the total number of days scored. Asterisks denote statistically significant scores when compared to the control using a chi-squared test

Though we observed a lowering of scores on two or more days for each treatment group, indicating that OM severity was decreased, we only observed a significant reduction compared to control animals in the duration of severe OM only for animals receiving SCV-07 on days of radiation (days –0–3 and 6–9).

Effect of SCV-07 on oral mucositis induced by radiation and chemotherapy

Treatment with SCV-07 significantly reduced the severity of OM induced by combined chemoradiation. Single daily doses of SCV-07 administered from day –1 to 20 at 10 μg kg^{-1}, 100 μg kg^{-1} or 1 mg kg^{-1} attenuated the course and duration of ulcerative mucositis (Figure 3a).

Vehicle-treated control animals had a mucositis score of ≥3 on 50% of the animal days evaluated (Figure 3b). In contrast, animals which received 10 μg kg^{-1} of SCV-

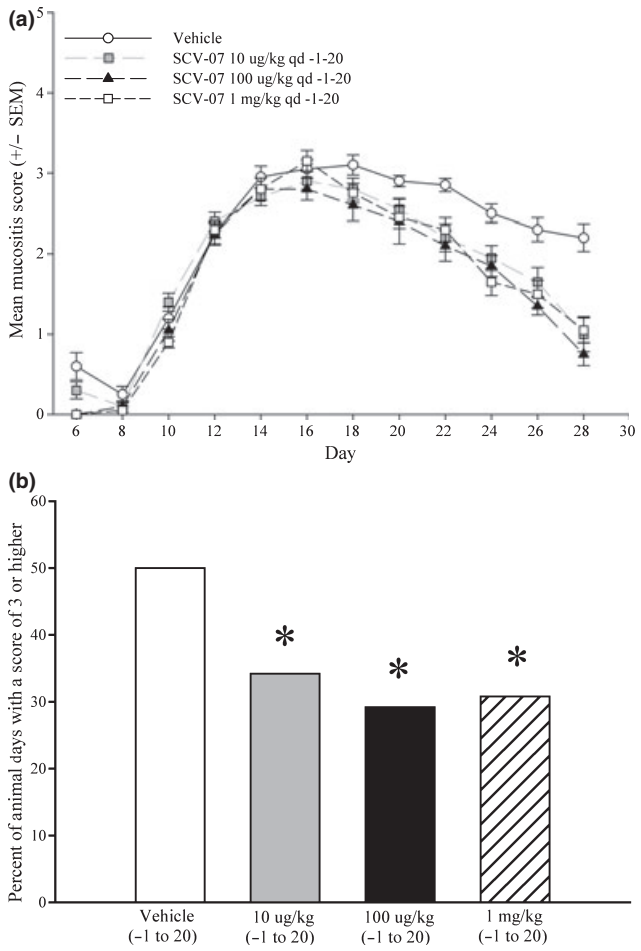

Figure 3 Combination radiation and cisplatin study. **(a)** Mean group mucositis scores were calculated for each day of evaluation. Error bars represent the standard error of the means (s.e.m.). **(b)** To examine the levels of clinically significant mucositis, as defined by presentation with open ulcers (a score of ≥3). The total number of days in which an animal exhibited an elevated score was summed and expressed as a percentage of the total number of days scored. Asterisks denote statistically significant scores when compared to the control using a chi-squared test

07 (days -1–20) had a mean mucositis score of ≥3 on only 34.2% of the animal days in the study, while animals that received 100 μg kg^{-1} SCV-07 had a mean mucositis score of ≥3 on only 29.2% of the animal days evaluated, and animals treated with 1 mg kg^{-1} SCV-07 had a mean mucositis score of ≥3 on only 30.8% of animal days. All animals treated with SCV-07, regardless of dose, had significantly fewer days of severe OM compared to vehicle treated control animals ($P < 0.001$).

There were no differences in peak mucositis scores when the groups were compared. The peak mean mucositis score for vehicle treated animals was 3.1 (day 18). Animals that received 10 μg kg^{-1} had a peak mean mucositis score of 2.9 (day 16), those animals that received 100 μg kg^{-1} had a peak mean mucositis score of 2.8 (days 14 and 16), and animals that received 1 mg kg^{-1} had a peak mean mucositis score of 3.2 (day 16) (Figure 3a).

However, when we compared daily mean mucositis scores using the Mann–Whitney rank-sum analysis for each treated group to control animals, we observed a significant lowering of scores on more than two observation days. Animals that received 10 μg kg^{-1} SCV-07 had significantly lower mucositis scores on four observation days when compared to the control animals. Animals that received 100 μg kg^{-1} SCV-07 had significantly lower mucositis scores on five observation days compared to the control animals. Animals that received 1 mg kg^{-1} SCV-07 had significantly lower mucositis scores on six observation days when compared to the control animals.

Taken together, these data indicate that daily administration of SCV-07 at doses of 10 μg kg^{-1}, 100 μg kg^{-1} or 1 mg kg^{-1} on days –1–20 in combination with chemoradiation significantly decreased the severity and duration of OM.

Discussion

SCV-07 (gamma-D-glutamyl-L-trytophan) is a novel water soluble synthetic peptide with a broad range of immunomodulating properties. In animals infected with *Mycobacterium bovis-bovinus 8*, SCV-07 reduced lung damage, produced a shift to a T-helper 1 (Th1)-like immune response characterized by increased levels of interferon-γ (IFN-γ), decreased the Th2 cytokine interleukin-4 (IL-4), and enhanced phagocytosis by peritoneal macrophages (Simbirtsev *et al*, 2003). In a cell-based luciferase reporter assay, SCV-07 inhibited the expression of signal transducer and activator of transcription-3 (STAT-3) responsive genes and inhibited nuclear translocation of STAT-3 (Nagabhushanam *et al*, 2008).

Once characterized as the sole consequence of direct clonogenic cell death, it is now clear that oral mucositis is markedly more biologically complex. Although Th1 cytokines have been consistently reported to be increased in both tissue and serum following the administration of ionizing radiation (3, 10), the ratio of Th1:Th2 populations are skewed in the opposite direction (Logan *et al*, 2007). In particular, increased levels of Th1 pro-inflammatory cytokines such as IL-6 have been observed, while Th1:Th2 clone ratios are reportedly shifted to highly favor Th2 cells (Park *et al*, 2005). This shift is accompanied by an over production of IL-4 by Th2 cells. This Th1/Th2 imbalance may contribute to the disruption of tissue homeostasis and lead to toxicity. It thus seemed of interest to evaluate the ability of SCV-07 to modulate radiation-induced mucositis in established models of the condition.

We studied the effect of SCV-07 on three hamster models of radiation-induced oral mucositis. To evaluate proof of concept, we used an established model in which a single, stomatotoxic radiation dose was targeted to isolated oral mucosa, and found that a 100 μg kg^{-1} of SCV-07 administered as a daily dose beginning the day before radiation and continuing for 16 days thereafter was able to attenuate the duration of ulcerative mucositis. The length of the dosing schedule was designed to coincide with the well-known ascending curve of mucositis development in the model. While the duration of

ulcerative mucositis was favorably affected with this dose and schedule (data not shown), we found that increasing the duration of exposure to SCV-07 so that it extended beyond the peak period of risk for maximum mucositis (increasing dosing from days -1–16 to days -1–20) resulted in additional efficacy (data not shown and Figure 1). Taken together, these data indicate that once daily dosing of 100 μg kg^{-1} of SCV-07 from days -1 to 20 favorably effects OM in the acute model and that the effects seen are both dose and schedule dependent.

While the acute radiation model is useful as a screening model for efficacy, it does not reproduce the radiation sequence used clinically, in which fractionated dosing is used. Consequently, we evaluated three dosing schedules of SCV-07 in a fractionated radiation model and found that SCV-07 was most efficacious in attenuating oral mucositis when it was administered on days of radiation. This observation, coupled with the finding that optimal SCV-07 dosing was seen when the peptide was administered during the period of mucositis development (rather than resolution) following acute radiation may suggest a cytoprotective mechanism to account for our observations.

The majority of radiation regimens for head and neck cancer include the concomitant use of radiosensitizing chemotherapy. Hence we tested SCV-07's ability to modulate mucositis following a combination treatment with radiation and cisplatin. SCV-07 showed efficacy in reducing the duration and severity of OM in this model as well. Animals who were administered concurrent chemotherapy and radiation with SCV-07 showed significant improvement in OM.

There are currently no studies which specifically address a purported mechanism of action for SCV-07 in mucositis. However, based on its reported activities, we can speculate on how the peptide may function in the context of oral mucositis. Radiation therapy results in increased levels of IL-6 levels, which subsequently results in the activation of STAT-3. STAT-3 activation is associated with general immune evasion including prevention of leukocyte and T-cell recruitment, inhibition of macrophage and dendritic cell maturation, and inhibition of apoptosis (Sengupta *et al*, 1996; Shen *et al*, 2001; Otero *et al*, 2006). Preliminary data suggest that SCV-07 effectively inhibits the STAT-3 pathway (Nagabhushanam *et al*, 2008). Thus, it is possible that the effect of SCV-07 on STAT-3 results in an enhanced local immune response which attenuates tissue damage. Alternatively, SCV-07 might also function by its ability to repress the radiation-mediated upregulation of IL-4, through maintenance of a favorable Th1/Th2 balance. Finally, although their roles require more study, the observation of quantitative differences in CD8 + cells and the abrupt increase in RM3/1 macrophages in patients' oral mucosa following radiation (Sonis, 2002) is at least suggestive of a possible role for these cells in the pathogenesis of the condition and as possible targets for SCV-07's activity.

Obviously, additional studies are necessary to more completely explain the mechanisms by which SCV-07 mediates its effect in modifying mucositis. Nonetheless, the observation that a novel immunomodulating peptide has the ability to attenuate both acute and fractionated radiation injury suggests a possible therapeutic role for this approach.

Acknowledgements

This study was funded by SciClone Pharmaceuticals.

References

Alvarez E, Fey EG, Valax P, *et al*. (2003). Preclinical characterization of CG53135 (FGF-20) in radiation and concomitant chemotherapy/radition-induced oral mucositis. *Clin Cancer Res* **9:** 3454–3461.

Handschel J, Sunderkötter C, Prott FJ, *et al*. (2001). Increase of RM3/1-positive macrophages in radiation-induced oral mucositis. *J Pathol* **193:** 242–247.

Logan RM, Stringer AM, Bowen JM, *et al*. (2007). The role of pro-inflammatory cytokines in cancer treatment-induced alimentary tract mucositis: pathobiology, animal models and cytotoxic drugs. *Cancer Treat Rev* **33:** 448–460.

Nagabhushanam V, Subbarao K, Ramachandran M, Reddy J, Tuthill C. Inhibition of STAT3 driven gene expression in melanoma cells by SCV-07. Presented Abstract at the 2008 American Society of Clinical Oncology General Meeting: Chicago, IL.

Otero DC, Poli V, David M, Rickert RC (2006). Cutting edge: inherent and acquired resistance to radiation-induced apoptosis in B cells: a pivotal role for STAT3. *J Immunol* **177:** 6593–6597.

Park HR, Jo SK, Paik SG (2005). Factors effecting the Th2-like immune response after gamma-irradiation: low production of IL-12 heterodimer in antigen-presenting cells and small expression of the IL-12 receptor in T cells. *Int J Radiat Biol* **81:** 221–231.

Rubenstein EB, Peterson DE, Schubert M, *et al*. (2004). Mucositis study section of the multinational association for supportive care in cancer; International Society for Oral Oncology. *Cancer* **100:** 2026–2046.

Sengupta TK, Schmitt EM, Ivashkiv LB (1996). Inhibition of cytokines and JAK/STAT activation by distinct signaling pathways. *Proc Natl Acad Sci* **93:** 9499–9550.

Shen Y, Devgan G, Darnell JE, Bromberg JF (2001). Constitutively activated Stat3 protects fibroblast from serum withdrawl and UV-induced apoptosis and antagonizes the proapoptotic effects of activated Stat1. *Proc Natl Acad Sci USA* **98:** 1543–1548.

Simbirtsev A, Kolobov A, Zabolotnych N, *et al*. (2003). Biological activity of peptide SCV-07 against murine tuberculosis. *Russ J Immunol* **8:** 11–22.

Sonis ST (2007). Pathobiology of oral mucositis: novel insights and opportunities. *J Support Oncol* **5:** 3–11.

Sonis ST (2004). The pathobiology of mucositis. *Nature Rev Cancer* **4:** 277–284.

Sonis ST, Peterson RL, Edwards LJ, *et al*. (2000). Defining mechanisms of action of interleukin-11 on the progression of radiation-induced oral mucositis in hamsters. *Oral Oncol* **36:** 373–381.

Sonis ST (2002). Animal models of oral mucositis induced by antineoplastic agents and radiation. *Tumor models in cancer research*. Humana Press, Beverly Teicher: New Jersey, pp. 323–335.

Vera-Llonch M, Oster G, Hagiwara M, Sonis S (2006). Oral mucositis in patients undergoing radiation treatment for head and neck carcinoma. *Cancer* **106:** 329–336.