

A Novel Modular Polymer Platform for the Treatment of Head and Neck Squamous Cell Carcinoma in an Animal Model

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Objective: To evaluate the therapeutic efficacy of a novel modular polymer platform in the treatment of head and neck squamous cell carcinoma (HNSCC).

Design: In vivo study.

Setting: Academic research laboratory.

Subjects and Methods: C3H/HeJ mice and SCID/beige mice were randomized to receive implantation of no polymer, plain polymer, plain polymer with local cisplatin injection, or cisplatin polymer. The 2 groups of mice implanted with cisplatin polymer or no polymer were further randomized to receive 4 Gy of external beam radiation for 4 days or no radiation. Tumor size was measured until the mice were humanely killed. At necropsy, the tumors were excised and weighed.

Results: There was a significant reduction in tumor growth using this novel polymer platform. The cisplatin-

secreting polymer effectively reduced human head and neck tumor growth in SCID mice by 17-fold and SCC VII/SF tumors in C3H/HeJ mice by more than 16-fold compared with the control, plain polymer, and plain polymer + intratumoral cisplatin injection groups ($P = .01$ for both). We also observed a statistically significant lower tumor weight in mice treated with cisplatin polymer and concomitant radiation compared with the radiation alone and control groups.

Conclusions: We demonstrate the efficacy of a novel polymer platform in delivering cisplatin to a partially resected SCC in a murine model. This polymer may represent a new therapeutic modality for patients with HNSCC. Once this polymer platform is optimized, we will plan for validation in the context of a prospective trial in patients with unresectable advanced or recurrent HNSCC.

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HEAD AND NECK SQUAMOUS cell carcinoma (HNSCC) is the sixth most common cancer in the world. Patients with HNSCC are at considerable risk for mortality, with more than 300 000 deaths attributable to the disease annually.¹ Aggressive surgical resection, with or without adjuvant chemoradiotherapy, is the cornerstone of treatment for early disease. In many patients, the necessary surgery can be disfiguring and may also affect everyday functioning, with a profound effect on quality of life.² During the past 30 years, the 3- to 5-year survival rate of patients with advanced T3 and T4 HNSCC has remained poor (20%-30%) despite considerable advances in surgical techniques and radiation delivery and improvements in chemotherapeutic strategies. Because 50% of patients with advanced and unresectable disease fail primary management, salvage in these patients is of paramount importance.³ Many of these pa-

tients undergo radiotherapy (RT) as definitive or adjuvant therapy, which makes retreatment a challenge. Currently, the standard of care for recurrent disease is surgical salvage. However, many advanced head and neck cancers are unresectable owing to their proximity to vital structures, such as the carotid artery or the skull base. Although palliation by chemotherapy is often attempted, systemic toxicity and its effect on patient quality of life prevents its wider clinical application.⁴ Given these dismal figures, new advances are needed in the effective treatment of HNSCC.

The science of polymer technology for drug delivery has evolved considerably since 1990.⁵ Polymers have been developed to deliver different types of drugs, including anticancer agents and antibiotics.⁶⁻⁸ Because most head and neck cancers and their cervical metastatic nodes are clinically accessible, local treatment with a polymer matrix may have significant clinical applications.

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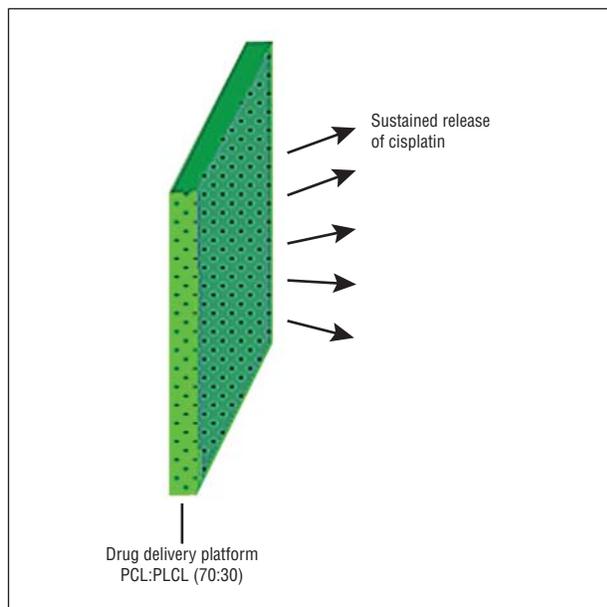


Figure 1. Cisplatin-releasing polymer. Cisplatin release is sustained for 6 weeks by the drug delivery platform, which consists of a blend of pure poly- ϵ -caprolactone (PCL) and a co-polymeric blend of poly(DL-lactide-co- ϵ -caprolactone) (PLCL).

We developed a novel modular drug delivery device that reproducibly reduces tumor growth in vivo. In this study, we used a partial tumor resection model in the mouse, replicating the difficult situation we see in patients in which the entire tumor is not resectable. The polymer platform we developed is a flexible sheet that was designed to be applied intraoperatively to the surgical bed after removing or debulking the tumor, and it was engineered to adapt and adhere to the surgically resected tissue contours. Cisplatin has been widely used in combination with radiation as a radiosensitizer in pre-clinical and clinical studies.⁷ We hypothesized that the local delivery of cisplatin is expected to maximize the therapeutic index, minimize systemic adverse effects, and enhance postoperative RT.

METHODS

POLYMER FABRICATION

The cisplatin-releasing polymer was designed to be adequately flexible to adapt to irregular tissue contours without tearing. To meet this requirement, a wide range of mixing ratios involving 2 polymers, poly- ϵ -caprolactone (PCL) and a co-polymeric blend of poly(DL-lactide-co- ϵ -caprolactone) (PLCL), were evaluated in a pilot study. A 70:30 ratio of PLCL:PCL was found to offer the optimal flexibility and malleability of the PCL sheet, allowing for more facile handling by surgeons during implantation in vivo (**Figure 1**). Both PCL and PLCL were obtained from Boehringer Ingelheim and are manufactured in Good Manufacturing Practices-compliant and International Organization for Standardization-certified facilities, qualifying these materials' availability for future clinical testing. Polymers were dissolved in chloroform in a 70:30 ratio of PLCL:PCL for 24 hours until gentle mixing.⁹ Fresh cisplatin (4 mg/kg) was added to the polymer solution before spreading onto a glass or polyethylene surface to form the thin sheets. After spreading, the

sheets were dried overnight, vacuum packed, and protected from ambient light. This polymer device is designed to degrade gradually over time to prevent extrusion and long-term giant cell foreign body response. Furthermore, material selection was limited to those used in Food and Drug Administration-approved devices. Therefore, the intact polymer and its degradation products are known to be well tolerated in humans.

MOUSE MODEL

The animals used in this study were 6-week-old C3H/HeJ mice or 6-week-old SCID/beige mice (both from The Jackson Laboratory). The care and use of the animals was in accordance with the guidelines of the Animal Research Committee of the University of California at Los Angeles. The mice were maintained under specific pathogen-free conditions, and sterilized food and water was available ad libitum. The animals were housed in the University of California at Los Angeles vivarium according to National Institutes of Health guidelines, and all the procedures were conducted under institutionally approved animal protocols.

ANIMAL MODEL SURGICAL PROCEDURE

For testing the polymer platform, 2 animal models were used: (1) 5×10^6 cells from the well-established human oral SCC line TU686¹⁰ were injected into 6-week-old SCID/beige mice and (2) 4×10^5 cells from the well-established C3H/HeJ mouse SCCA cell line SCC VII/SF were injected into 6-week-old C3H/HeJ mice. The SCC VII/SF cell line is a spontaneously arising SCC syngeneic to C3H/HeJ mice.¹¹ The TU686/SCID model allowed us to test the efficacy of the polymer against a human oral SCC cell line. Eight mice were injected in each group unless otherwise specified. All the mice were injected subcutaneously over the right flank. Tumor growth was assessed using calipers 3 times per week after polymer implantation for 18 to 31 days to evaluate the antitumor efficacy of the different treatments. (Tumor growth was assessed for 18-31 days as this was the time point at which control animals required euthanasia owing to tumor burden as determined by the Animal Research Committee of the University of California at Los Angeles.) The length, width, and height of the tumors were measured, and tumor volume was calculated according to the following formula: Tumor Volume = $\pi/6 \times \text{Length} \times \text{Width} \times \text{Height}$.

When the tumors reached an average size of 0.5 to 1.0 cm³, all the animals underwent surgery to debulk their tumors by 50% to approximate the surgical situation when a patient's tumor is unresectable and some tumor is left behind before polymer therapy. Animals were then randomly assigned to the different treatment groups: (1) no polymer, (2) plain polymer, (3) plain polymer with local cisplatin injection, and (4) cisplatin polymer. No systemic cisplatin was given. Each tumor bed was completely covered with the polymer according to treatment group. The polymer was placed over each tumor and draped over the tumor edges.

RADIOTHERAPY

After tumor debulking (described previously herein), animals were assigned to various treatment groups. For the RT experiments, the treatment groups were as follows: (1) no treatment (no polymer addition, surgical debulking only); (2) no treatment (no polymer addition, surgical debulking only) plus RT, (3) cisplatin polymer alone, and (4) cisplatin polymer plus RT. On postsurgical day 3, the mice were anesthetized and positioned in a Lucite jig with lead shielding the body except for the tumor site, which was irradiated using a Gammacell 40 ir-

radiator (Cs-137 source; Atomic Energy of Canada Ltd) at a dose rate of approximately 0.6 Gy/min. Tumors were irradiated with a total dose of 16 Gy given in 4-Gy fractions on 4 consecutive days. Dosimetry was performed using a LiF: Mg,Cu,P dosimeter (TLD-100H; Thermo Electron) and film (GAFCHROMIC EBT2; International Specialty Products) and was calibrated against a clinical cobalt-60 irradiator (Theratron 1000; MDS Nordion), indicating that leakage and scatter of gamma rays to the shielded areas reached approximately 10.9% to 14.1% of the total dose. Dose fractionation was chosen to allow for repair, which is required for radiosensitization by cisplatin. The size of the dose was based primarily on the fact that these tumors grow considerably more rapidly than in the clinic and that standard 2-Gy doses are inadequate to compensate for rapid cell division. In addition, doses greater than 2 Gy per fraction are becoming increasingly popular clinically either as planned homogeneous or inhomogeneous dose distributions, so the use of 4-Gy fraction sizes is not clinically irrelevant.¹² Cisplatin is a known radiosensitizer, and the polymer platform releasing 4 mg/kg of cisplatin in the radiation field will allow us to amplify the radiation dose in a localized manner.^{13,14} We were studying the benefits of cisplatin as a radiosensitizer and, therefore, were not administering the drug systemically. The length, width, and height of each tumor were measured using calipers 3 times a week. After the animals were humanely killed, a gross necropsy and histopathologic examination of the tissues surrounding the implant site were conducted. The inflammatory response to the implanted polymer was determined based on the average number of cell types present in the surrounding tissue. Tissue responses were found to be minimal (data not shown). Histopathologic examination of all the tissues and tumors was performed with the assistance of the pathologists at the University of California at Los Angeles.

STATISTICS

Tumor growth curves were compared between treatment arms using repeated-measures analysis of variance models. These models contained terms for time, treatment effects, and the interaction between time and treatment. For tumor growth experiments in which there was a significant treatment \times time interaction effect (demonstrating differences in tumor growth rates between groups), we compared mean tumor sizes between treatment arms of interest at specific time points using Bonferroni-corrected 2-sample *t* tests. Tumor weight was compared between groups using a 2-way analysis of variance model containing terms for cisplatin polymer and radiation. In both types of tumor models, the log transformation was used to reduce the effect of outliers. Statistical significance was set at $P = .05$.

RESULTS

THE MODULAR POLYMER DEVICE IS SAFE AND BIOCOMPATIBLE IN THE ANIMAL MODEL AND IS FACILE FOR SURGICAL USE

Although the tissue biocompatibility of the backbone of the polymers is well documented in the literature,¹⁵ we initially tested the safety and biocompatibility of the chemotherapeutic layer of the device in the mouse model. To accelerate clinical translation, we selected materials that are currently used in medical devices with known characteristics in terms of toxicity, hypersensitivity, mutagenesis, and inflammatory responses.

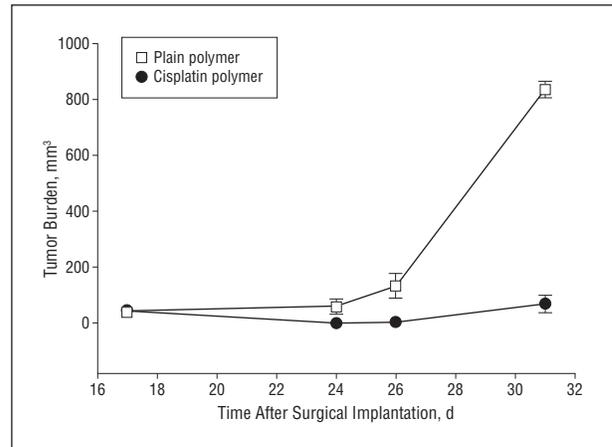


Figure 2. Cisplatin polymer effectively reduces the growth of human head and neck squamous cell carcinoma (HNSCC). TU686 HNSCC cells (5×10^6) were inoculated in SCID/beige mice. The implanted cisplatin-secreting polymer significantly reduced tumor growth kinetics compared with the control polymer. There were 8 mice per group. Error bars represent SD.

We used the partial tumor resection model in the mouse. After implantation, the mice were observed daily for overt toxic effects. The animals tolerated the implant well and were not observed to pick or scratch at the polymer. No signs of bleeding, swelling, or infection were noted at the incision site. When the animals were humanely killed, a histopathologic examination of the tissues surrounding the implant site was conducted. The inflammatory response to the implanted polymer was found to be minimal (data not shown).

CISPLATIN-SECRETING POLYMER REDUCES TUMOR BURDEN IN HEAD AND NECK CANCER

We evaluated the antitumor efficacy of the chemotherapeutic layer of the polymer platform in murine models of head and neck cancer. Results using this novel polymer platform demonstrate a significant reduction in tumor growth. The cisplatin-secreting polymer effectively reduced TU686 human head and neck tumor growth in SCID mice by 17-fold on day 31 (**Figure 2**) and SCC VII/SF tumors in C3H/HeJ mice by more than 16-fold on day 25 (**Figure 3**) compared with the control (surgical debulking only), plain polymer, and plain polymer plus intratumoral cisplatin injection groups ($P = .01$ for both). We confirmed this decrease in tumor burden by excising the tumors that had been treated with cisplatin polymer (**Figure 4**). The present data show that cisplatin-secreting polymer is more effective against head and neck cancer than is plain polymer plus cisplatin given as an intratumoral bolus injection.

CISPLATIN-SECRETING POLYMER ENHANCES THE EFFICACY OF RT

Mice treated with radiation, with or without cisplatin polymer implantation, demonstrated a significant reduction in tumor regrowth compared with the control group (radiation alone: 22% the size of control, $P = .005$; radiation with cisplatin polymer: 12% the size of control, $P = .003$).

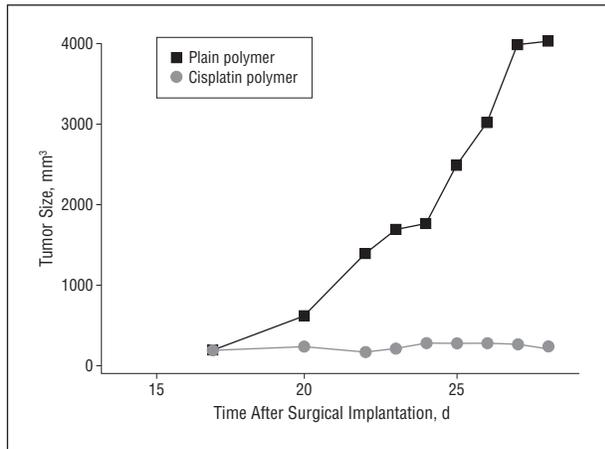


Figure 3. Cisplatin polymer effectively reduces the growth of mouse SCC VII/SF. SCC VII/SF tumor cells (4×10^5) were inoculated in C3H mice. The implanted cisplatin polymer significantly reduced tumor growth by more than 16-fold compared with control. There were 8 mice per group.

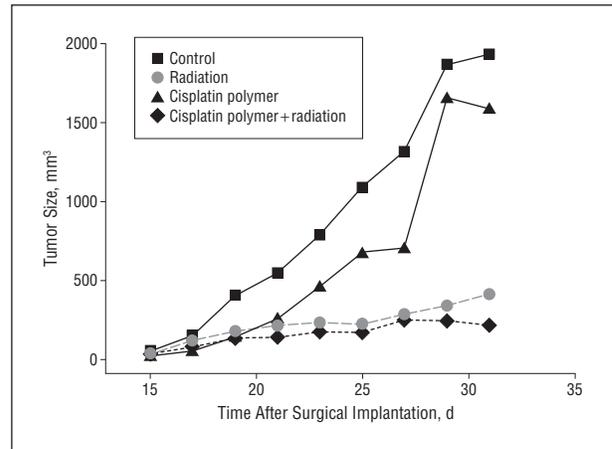


Figure 5. Time-series plot of tumor size in the 4 treatment arms. The effects of treatments were assessed using a repeated-measures analysis of variance model. Treatment with cisplatin polymer and radiation resulted in significantly reduced tumor size over time ($P = .03$ and $.001$, respectively).

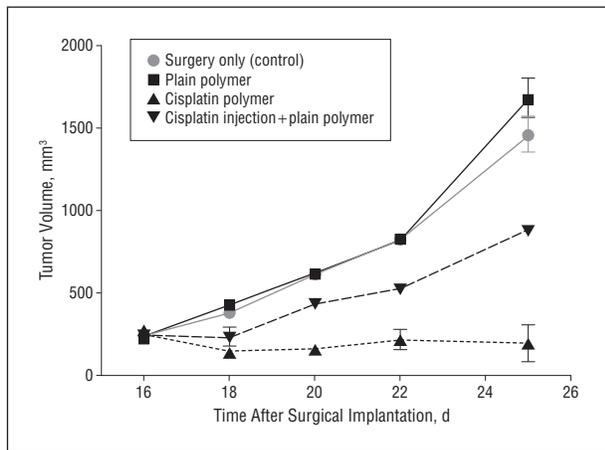


Figure 4. Cisplatin polymer is more effective at reducing tumor growth than cisplatin injection. The implanted cisplatin polymer significantly reduced tumor growth kinetics compared with plain polymer and cisplatin injection plus plain polymer. There were 8 mice per group. Error bars represent SD.

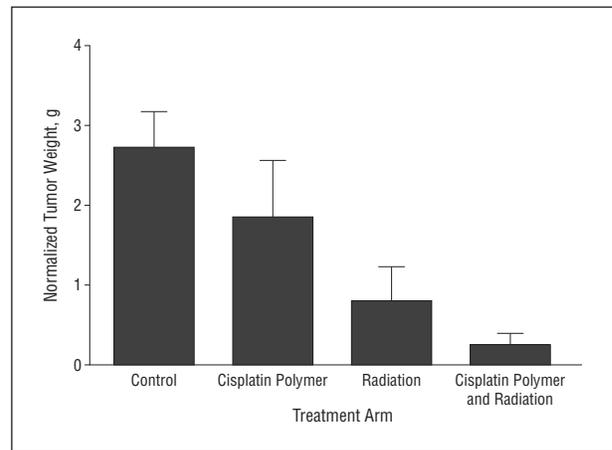


Figure 6. Mean tumor burden at sacrifice in the 4 treatment arms. Analysis of variance models determined that cisplatin polymer and radiation significantly reduced tumor weight ($P = .04$ and $.001$, respectively). Error bars represent SD.

Table. Final Tumor Weight by Treatment Group

Group	Tumor Weight, Mean (SD), g
Control	2.79 (1.19)
Cisplatin polymer	1.90 (1.91)
Radiotherapy	0.82 (0.73)
Cisplatin polymer + radiotherapy	0.26 (0.17)

A closer comparison between the 2 different RT groups revealed lower tumor burden in the group also implanted with cisplatin polymer (**Table** and **Figure 5**) (53% the size of the radiation alone group). An overall analysis of the 4 treatment arms found that cisplatin polymer and radiation resulted in significantly reduced tumor size over time ($P = .03$ and $.001$, respectively). This observation was corroborated by the statistically significant lower tumor weight noted in mice treated with cisplatin polymer and concomitant radiation compared with the radiation alone and control groups (32% the weight

of the radiation alone group, $P = .05$; 9% the weight of the control group treated with debulking alone, $P < .001$) (**Figure 6**). These results are promising that the polymer platform can direct the highest dose of RT to the tumor and spare the surrounding normal tissues.

COMMENT

We developed a novel modular drug delivery device that reproducibly reduces tumor growth and enhances the efficacy of RT in vivo after partial tumor resection. We used this partial tumor resection model in the mouse, replicating the difficult situation we see in patients in which the entire tumor is not resectable. The device we developed is a flexible sheet that was designed to be applied intraoperatively to the surgical bed after removing or debulking the tumor, and it was engineered to adapt and adhere to the surgically resected tissue contours.

The combined use of RT and chemotherapy has been effective in improving the therapeutic index of RT for a variety of human cancers.¹⁴ Cisplatin is a highly effective

tive anticancer agent that has been widely used in combination with radiation as a radiosensitizer in preclinical and clinical studies.¹⁴⁻¹⁶ The successful use of chemotherapeutic agents as radiosensitizers depends on enhanced tumor cell killing without increased normal tissue toxicity. The local delivery of synergistic agents is expected to maximize the therapeutic index, minimize systemic adverse effects, and enhance postoperative RT. The present data show that cisplatin-secreting polymer is more effective against head and neck cancer than is plain polymer plus cisplatin given as an intratumoral bolus injection. This enhanced antitumor activity is likely due to a more durable sustained release of cisplatin from the polymer platform, increasing the interaction time with the tumor cells.

Some advantages of this polymer system over conventional brachytherapy are better control of dose distribution and elimination of radioprotection and safety issues for the patient, the patient's family, and treating personnel. An important psychological factor is that the patient's daily activities are not restricted during the entire treatment time. An additional benefit of this polymer system includes prophylaxis against tumor recurrence after resection. Viable SCC cells have been recovered from the surgical wound after neck dissection and were shown to be capable of growing as colonies *in vitro*; theoretically, these may implant and cause cancer recurrence.¹⁷ Therefore, exposing such cells to this polymer system in combination with external beam RT before they implant (while they are isolated and fragile) may decrease the chance of implantation.

Previous studies in oral and head and neck cancers have looked at combining cisplatin with collagen as a protein carrier. Kanekal et al¹⁸ noted that this combination allowed for higher intratumor drug levels for up to 48 hours. In addition, Yapp et al¹⁹ evaluated the use of biodegradable polymer implants to deliver cisplatin compared with delivery by systemic injection and by osmotic pump. In contrast to the latter 2 systems, cisplatin levels were found to be higher in the tumor than in the blood and kidney when the drug was delivered using the polymer implant. Herein, we introduced the advantages of the polymer platform in directing the highest dose of RT to the tumor and sparing surrounding normal tissues. Another attractive addition to the modular platform is the concept of polymer delivery of immunomodulators, which will increase the efficiency of tumor cell killing by the host's immune system. Patients with HNSCC have been well documented to exhibit local immunosuppression with depressed T-cell-mediated responses and depressed natural killer cell and antibody-dependent cell cytotoxic effects.²⁰ Gene therapy approaches include replacement gene therapy, suicide gene therapy, and immunotherapy. Despite these many approaches, gene therapy still has been limited significantly.⁴ The role of cytokines in tumor regression is now well established.²⁰ The major limitation to the clinical use of cytokines is the lack of a simple and effective protocol for local and sustained delivery of cytokines to the tumor milieu.

Although the polymer used herein is currently used in Food and Drug Administration–approved devices and

the intact polymer and its degradation products are known to be well tolerated in humans, the exact polymer-tissue interactions in the vicinity of a dynamic tumor environment is unknown. In the present work, we did not explicitly evaluate biocompatibility in such an environment and instead focused on demonstrating the overall utility of this modular approach. Now that feasibility has been demonstrated, the next step of our research program is to optimize the polymer platform to improve handling, cell delivery, and drug delivery.

We propose to develop the optimal combination of the bilayers to improve the outcome for patients with advanced or recurrent HNSCC. The modular nature of this polymer platform provides an elegant approach to future dosing modifications and device improvements, allowing us to incorporate changes into 1 layer without altering the chemical-physical properties of the other layer. The C3H/HeJ mouse model has an intact functional immune system that permits further optimization of the polymer platform with potentially synergistic immunomodulators, unlike previous xenograft models in immunodeficient mice used for other polymers.¹⁶ The robustness of this design will also enable us to dissect underlying mechanisms of immune activation and expansion, which will, in turn, help us design additional strategies to block the inactivation and death of the cytotoxic effectors in patients with aggressive HNSCC. We obtained promising results from pilot *in vivo* studies using a single-layer polymer releasing cisplatin only. We are in the process of developing the optimal combination of the bilayers to improve the outcome for patients with advanced or recurrent HNSCC. Once this polymer platform is optimized in an *in vivo* model, we will plan for ultimate validation in the context of a prospective trial in patients with unresectable advanced or recurrent HNSCC.

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REFERENCES

1. Ferlay J, Bray F, Pisani P, et al. *GLOBOCAN 2000: Cancer Incidence, Mortality and Prevalence Worldwide, Version 1.0*. Lyon, France: IARC Press; 2001. IARC CancerBase No. 5.
2. Shikani AH, Domb AJ. Polymer chemotherapy for head and neck cancer. *Laryngoscope*. 2000;110(6):907-917.
3. Ross DA, Hundal JS, Son YH, et al. Microsurgical free flap reconstruction outcomes in head and neck cancer patients after surgical extirpation and intraoperative brachytherapy. *Laryngoscope*. 2004;114(7):1170-1176.
4. Xian J, Yang H, Lin Y, Liu S. Combination nonviral murine interleukin 2 and interleukin 12 gene therapy and radiotherapy for head and neck squamous cell carcinoma. *Arch Otolaryngol Head Neck Surg*. 2005;131(12):1079-1085.
5. Domb AJ, ed. *Polymeric Site-Specific Pharmacotherapy*. New York, NY: John Wiley & Sons Inc; 1994:1-464.
6. Domb AJ, Kost J, Wiseman D, eds. *Handbook for Biodegradable Polymers*. Amsterdam, the Netherlands: Harwood Academic Publishers; 1997:1-513.
7. Cohen EM, Ding H, Kessinger CW, Khemtong C, Gao J, Sumer BD. Polymeric micelle nanoparticles for photodynamic treatment of head and neck cancer cells. *Otolaryngol Head Neck Surg*. 2010;143(1):109-115.
8. Colella G, Cannavale R, Vicidomini A, Rinaldi G, Compilato D, Campisi G. Efficacy of a spray compound containing a pool of collagen precursor synthetic aminoacids (l-proline, l-leucine, l-lysine and glycine) combined with sodium hyaluronate to manage chemo/radiotherapy-induced oral mucositis: preliminary data of an open trial. *Int J Immunopathol Pharmacol*. 2010;23(1):143-151.
9. Wang L. *Sequential Layer Polymer Deposition* [master's thesis]. Los Angeles, CA: UCLA Biomedical Engineering; September 2010.
10. Zhang X, Chen ZG, Choe MS, et al. Tumor growth inhibition by simultaneously blocking epidermal growth factor receptor and cyclooxygenase-2 in a xenograft model. *Clin Cancer Res*. 2005;11(17):6261-6269.
11. O'Malley BW Jr, Cope KA, Johnson CS, Schwartz MR. A new immunocompetent murine model for oral cancer. *Arch Otolaryngol Head Neck Surg*. 1997;123(1):20-24.
12. Stuschke M, Pottgen C. Altered fractionation schemes in radiotherapy. *Front Radiat Ther Oncol*. 2010;42:150-156.
13. Deurloo MJ, Kop W, van Tellingen O, Bartelink H, Begg AC. Intratumoural administration of cisplatin in slow-release devices, II: pharmacokinetics and intratumoural distribution. *Cancer Chemother Pharmacol*. 1991;27(5):347-353.
14. Ning S, Yu N, Brown DM, Kanekal S, Knox SJ. Radiosensitization by intratumoural administration of cisplatin in a sustained-release drug delivery system. *Radiother Oncol*. 1999;50(2):215-223.
15. Göpferich A. Mechanisms of polymer degradation and erosion. *Biomaterials*. 1996;17(2):103-114.
16. Yu NY, Conley FK, Luck EE, Brown DM. Response of murine tumors to matrix-associated cisplatin intratumoural implants. *NCI Monogr*. 1988;6(6):137-140.
17. Vikram B, Mishra S. Permanent iodine-125 implants in postoperative radiotherapy for head and neck cancer with positive surgical margins. *Head Neck*. 1994;16(2):155-157.
18. Kanekal S, Joo J, Bublik M, et al. Retention of intratumour injections of cisplatin in murine tumors and the impact on laser thermal therapy for cancer treatment. *Eur Arch Otorhinolaryngol*. 2009;266(2):279-284.
19. Yapp DT, Lloyd DK, Zhu J, Lehnert SM. Cisplatin delivery by biodegradable polymer implant is superior to systemic delivery by osmotic pump or i.p. injection in tumor-bearing mice. *Anticancer Drugs*. 1998;9(9):791-796.
20. Jewett A, Cacalano NA, Teruel A, et al. Inhibition of nuclear factor kappa B (NF- κ B) activity in oral tumor cells prevents depletion of NK cells and increases their functional activation. *Cancer Immunol Immunother*. 2006;55(9):1052-1063.