

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
26 February 2009 (26.02.2009)

PCT

(10) International Publication Number
WO 2009/025830 A1

- (51) International Patent Classification:
A01N 43/38 (2006.01) A61K 38/00 (2006.01)
A61K 31/40 (2006.01)
- (21) International Application Number:
PCT/US2008/009932
- (22) International Filing Date: 21 August 2008 (21.08.2008)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
60/957,530 23 August 2007 (23.08.2007) US
- (71) Applicant: SCICLONE PHARMACEUTICALS, INC.
[US/US]; 950 Tower Lane, Suite 900, Foster City, California 94404 (US).
- (72) Inventor; and
- (75) Inventor/Applicant (for US only): TUTHILL, Cynthia W. [US/US]; 645 Woodland Avenue, Menlo Park, California 94025 (US).
- (74) Agents: REPPER, George R. et al.; 1425 K Street, N.W., Suite 800, Washington, District Of Columbia 20005 (US).

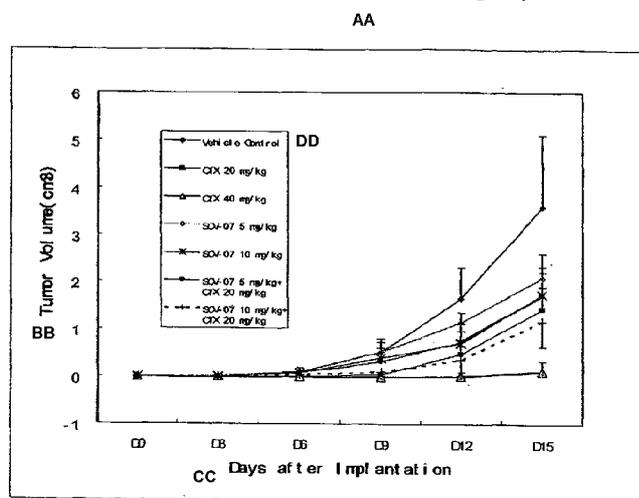
- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.
- (84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— of inventorship (Rule 4.17(iv))

Published:
— with international search report

(54) Title: TREATMENT OF LUNG CANCER

Figure 1: Tumor growth curves in all treatment groups



AA Courbes de croissance tumorale dans tous les groupes de traitement
 BB Volume tumorale
 CC Jours après implantation
 DD Véhicule témoin

(57) Abstract: An immunomodulatory compound is administered to treat, prevent, inhibit, or reduce lung cancer in a subject.

WO 2009/025830 A1

TREATMENT OF LUNG CANCER

BACKGROUND OF THE INVENTION

[001] The present application claims the benefit of U.S. Provisional Application Serial No. 60/957,530, filed August 23, 2007, the disclosure of which is incorporated herein in its entirety by reference.

Field of the Invention

[002] The present invention relates to the field of treatment of lung cancer.

Description of Background Art

[003] Lung cancer is the malignant transformation and expansion of lung tissue, and is responsible for 1.3 million deaths worldwide annually. It is the most common cause of cancer-related death in men, and the second most common in women.

[004] Current research indicates that the factor with the greatest impact on risk of lung cancer is long-term exposure to inhaled carcinogens, especially tobacco smoke. The occurrence of lung cancer in others (less than one tenth) appears to be due to a combination of genetic factors. Radon gas and air pollution may also contribute to the development of lung cancer.

[005] Treatment and prognosis depend upon the histological type of cancer, the stage (degree of spread), and the patient's performance status. Current treatments include surgery, chemotherapy, and radiotherapy. Overall, the five-year survival rate is about 14%.

[006] There are two main types of lung cancer categorized by the size and appearance of the malignant cells seen by a histopathologist under a microscope: *non-small cell* (80%) and *small-cell* (roughly 20%) lung cancer. This classification, although based on simple histological criteria, has very important implications for clinical management and prognosis of the disease.

[007] The non-small cell lung cancers (NSCLC) are grouped together because their prognosis and management are roughly identical. There are three main sub-types: squamous cell lung carcinoma, adenocarcinoma and large cell lung carcinoma.

[008] Squamous cell carcinoma, accounting for 29% of lung cancers, also starts in the larger bronchi but grows slower. The size of these tumours varies on diagnosis.

[009] Adenocarcinoma is the most common subtype of NSCLC, accounting for 32% of lung cancers. It is a form which starts near the gas-exchanging surface of the lung. Most cases of adenocarcinoma are associated with smoking. However, among people who have never smoked ("never-smokers"), adenocarcinoma is the most common form of lung cancer. A subtype of adenocarcinoma, the bronchioloalveolar carcinoma, is more common in female never-smokers, and may have different responses to treatment.

[0010] Large cell carcinoma is a fast-growing form, accounting for 9% of lung cancers, that grows near the surface of the lung.

[0011] Small cell lung cancer (SCLC, also called "oat cell carcinoma") is a less common form of lung cancer. It tends to start in the larger breathing tubes and grows rapidly becoming quite large. The oncogene most commonly involved is *L-myc*. The "oat" cell contains dense neurosecretory granules which give this an endocrine/paraneoplastic syndrome association. It is initially more sensitive to chemotherapy, but ultimately carries a worse prognosis and is often metastatic at presentation. This type of lung cancer is strongly associated with smoking.

[0012] Other types of lung cancers include carcinoid, adenoid cystic carcinoma (cylindroma) and mucoepidermoid carcinoma.

Metastatic cancers

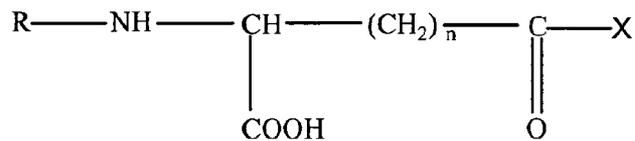
[0013] The lung is a common place for metastasis from tumors in other parts of the body. The adrenal glands, liver, brain, and bone are the most common sites of metastasis from primary lung cancer itself.

[0014] There remains a need in the art for methods of treatment for treating, preventing, inhibiting or reducing lung cancer.

SUMMARY OF THE INVENTION

[0015] In accordance with the present invention, a method of treatment for treating, inhibiting, reducing or at least partly preventing lung cancer, a metastasis thereof, or a metastasis in a lung from a cancer outside the lung, or for treating, inhibiting, reducing or at least partly preventing growth of lung cancer cells, a metastasis thereof, or a metastasis of

cancer cells in a lung from cancer cells outside the lung, in a subject, comprises administering to the subject a treatment-effective amount of an immunomodulator compound of formula A



(A)

wherein, n is 1 or 2, R is hydrogen, acyl, alkyl or a peptide fragment, and X is an aromatic or heterocyclic amino acid or a derivative thereof, so as to treat, inhibit, reduce or at least partly prevent said lung cancer, a metastasis thereof, or a metastasis in a lung from a cancer outside the lung in the subject, or treat, inhibit, reduce or at least partly prevent growth of said lung cancer cells, a metastasis thereof, or a metastasis of cancer cells in a lung from cancer cells outside the lung, in the subject.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] Fig. 1 graphically depicts tumor growth in one study of one embodiment at different dosages.

[0017] Fig. 2 graphically depicts tumor weight in the study of one embodiment at different dosages.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0018] In accordance with one embodiment, the present invention relates to a method of treatment for treating, at least partly preventing, inhibiting, or reducing lung cancer by administering an immunomodulator compound to a mammalian subject, preferably a human patient.

[0019] In certain embodiments, the disease is lung cancer, a metastasis thereof, or a metastasis in a lung from a cancer outside the lung. The invention can be utilized to treat, at least partly prevent, inhibit or reduce growth of lung cancer cells, a metastasis thereof, or a metastasis of cancer cells in a lung from cancer cells outside the lung, in a subject. In some

and lymphocyte proliferation, increases Con-A-induced interleukin-2 (IL-2) production and IL-2 receptor expression by spleen lymphocytes, and stimulates expression of Thy-1.2 on bone marrow cells. In vivo, SCV-07 has a strong immunostimulatory effect on 5-FU-immune-suppressed animals and in a model of immunization with sheep red blood cells.

[0025] The Formula A compounds may be administered at any effective dosage, e.g., at dosages in the range of about 0.001-1000 mg, preferably about 0.1-100 mg and most preferably about 10 mg. Dosages may be administered one or more times per week, e.g., on a daily basis, with dosages administered one or more times per day. Administration can be by any suitable method, including orally, nasally, transdermally, sublingually, by injection, periodic infusion, continuous infusion, and the like. The dosages may be administered by intramuscular injection, although other forms of injection and infusion may be utilized, and other forms of administration such as oral or nasal inhalation or oral ingestion may be employed. Aerosols, solutions, suspensions, dispersions, tablets, capsules, syrups, etc., may be utilized.

[0026] Dosages may also be measured in milligrams per kilogram, with dosages in the range of about 0.00001-1000 mg/kg, more preferably within the range of about 0.01-100 mg/kg, still more preferably about 0.1-50 mg/kg, and still more preferably about 1-20 mg/kg.

[0027] Included are biologically active analogs having substituted, deleted, elongated, replaced, or otherwise modified portions which possess bioactivity substantially similar to that of SCV-07, e.g., an SCV-07 derived peptide having sufficient homology with SVC-07 such that it functions in substantially the same way with substantially the same activity as SCV-07.

[0028] According to one embodiment, a Formula A compound may be administered to a subject so as to substantially continuously maintain an effective amount of the Formula A compound in the subject's circulatory system during a treatment or prevention period. Although much longer treatment periods are contemplated in accordance with the present invention, embodiments of the invention include substantially continuously maintaining an effective amount of the Formula A compound in the patient's circulatory system during treatment periods of at least about 6, 10, 12 hours, or longer. In other embodiments, treatment periods are for at least about a day, and even for a plurality of days, e.g., a week or longer. However, it is contemplated that treatments, as defined above, in which effective amounts of the Formula A compound are substantially continuously maintained in the

subject's circulatory system, may be separated by non-treatment periods of similar or different durations.

[0029] In accordance with one embodiment, the Formula A compound is continuously infused into a subject, e.g., by intravenous infusion, during the treatment period, so as to substantially continuously maintain an effective amount of the Formula A compound in the subject's circulatory system. The infusion may be carried out by any suitable means, such as by minipump. Alternatively, an injection regimen of the Formula A compound can be maintained so as to substantially continuously maintain an effective amount of the Formula A compound in the subject's circulatory system. Suitable injection regimens may include an injection every 1, 2, 4, 6, etc. hours, so as to substantially continuously maintain the effective amount of the Immunomodulator compound peptide in the subject's circulatory system during the treatment period.

[0030] Although it is contemplated that during continuous infusion of the Formula A compound, administration will be for a substantially longer duration, according to one embodiment the continuous infusion of the Formula A compound is for a treatment period of at least about 1 hour. More preferably, continuous infusion is carried out for longer periods, such as for periods of at least about 6, 8, 10, 12 hours, or longer. In other embodiments, continuous infusion is for at least about one day, and even for a plurality of days such as for one week or more.

[0031] In some embodiments, the Formula A compound is present in a pharmaceutically acceptable liquid carrier, such as water for injection, physiological saline, or similar, at concentrations within a range of about 0.001-1000 $\mu\text{g/ml}$, more preferably about 0.1-100 $\mu\text{g/ml}$.

[0032] Effective amounts of Formula A compound can be determined by routine dose-titration experiments.

[0033] The Formula A compound also can be administered with other agents. For example, with treatments of cancer such agents include chemotherapy agents and/or radiation.

[0034] Radiation may be administered by any suitable method, and at any suitable dosage and dosage regimen administered in the art. For example, radiation can be administered at a dosage rate of approximately 1 Gy/minute, and radiation can be

administered, for example, at two doses per day of, e.g., about 4 Gy/dose on separate days of administration, separated by a day of non administration of radiation.

[0035] Chemotherapy agents that may be administered in a treatment regimen along with the Formula A compounds include any suitable chemotherapy agent, such as, without limitation, cisplatin, 5-fluorouracil (5-Fu), DTIC, and/or the like. Such chemotherapy agents may be administered at any suitable dosage and/or dosage regimen, including those set forth in the examples herein.

Example 1

Abbreviations

CTX	Cyclophosphamide
F	Female
g	Gram
IR	Inhibition Rate
Ip	Intraperitoneal
Kg	Kilogram
L	Length
M	Male
mL	Milliliter
sc	Subcutaneous
SD	Standard Deviation
W	Width

Summary

[0036] In this study, SCV-07 was tested for its inhibitory effect on growth of murine lung tumor in C57/BL6 mice. A total of 70 mice were implanted subcutaneously with murine Lewis lung cancer (LLC) cells, followed by treatment with SCV-07 or cyclophosphamide (CTX) alone or in combination for 14 consecutive days. SCV-07 was administered daily by sc injection,

while CTX was administered by *ip* injection every other day. In total, 7 groups were used: Group 1: vehicle; Group 2: CTX 20 mg/kg; Group 3: CTX 40 mg/kg; Group 4: SCV-07 5 mg/kg; Group 5: SCV-07 10 mg/kg; Group 6: SCV-07 5 mg/kg plus CTX 20 mg/kg; Group 7: SCV-07 10 mg/kg plus CTX 20 mg/kg. Tumor volume and body weight were measured every three days, and tumor weights were measured on Day 16 (necropsy day) at the end of the study.

[0037] Throughout the course of the study, animal death was not found in any group. Moreover, the statistical results of body weights showed no significant differences between SCV-07 alone groups and vehicle control group, indicating no effect of SCV-07 on animal growth. By contrast, from Day 6 onwards, CTX treatment groups showed a significant decrease in body weight, especially in the groups administered with a high dose of CTX.

[0038] For the tumor growth, on day 3, all of groups except Group 4 showed statistically significant inhibition of tumor volume compared to Group 1 (vehicle control). On Day 6, only Group 2 and Group 3 showed the inhibition. On Day 9, Group 2, Group 3 and Group 7 showed the inhibition. On Day 12, all groups except Group 4 showed the inhibition. On Day 15, the mean tumor sizes of all groups were statistically significantly smaller than Group 1. On Day 16, the mean tumor weights of all treatment groups were lower than the vehicle control group. The tumor weight inhibition rate of Group 2, Group 3, Group 4, Group 5, Group 6 and Group 7 were 45.54% ($p < 0.01$), 90.25% ($p < 0.01$), 18.08% ($p = 0.07$), 30.60% ($p < 0.01$), 48.57% ($p < 0.01$) and 62.63% ($p < 0.01$), respectively.

[0039] In conclusion, the tumor model used in this study is valid because vehicle group showed significant tumor growth, while the positive control drug CTX effectively reduced the tumor growth. Daily administration of SCV-07 (10 mg/kg) for 14 days significantly inhibited the tumor growth. Tumor weights in treated animals were significantly reduced in comparison with those of in the vehicle control group. Moreover, the combined treatment of CTX at the suboptimal dose (20 mg/kg) with high dose of SCV-07 (10 mg/kg) showed increased anti-tumor efficacy.

Introduction

[0040] This study tests the anti-tumor effect of SCV-07 with murine lung cancer model to explore its potential as an anti-tumor drug in lung cancer. CTX is used as positive control. The

combination effects of SCV-07 and CTX is also tested to determine if there exists additive or synergistic effect.

Materials and Methods

Test and Control Articles

[0041] PBS was used as the negative control article (vehicle), and CTX as the positive control. CTX was purchased from Sigma-Aldrich and aliquoted to 10 mg/vial. PBS was added to achieve the proper dose level as indicated in the study design table. The formulation was kept on ice, protected from light, and used immediately. Test article (SCV-07) is dissolved in PBS to achieve the proper dose levels as indicated on the study design table; kept on ice, protected from light, and used within one week.

Test System and Animal Husbandry

Murine Lung Cancer Cells (LLC)

[0042] Murine Lewis lung cancer cells were obtained from the Cell Culture Center of Chinese Academy of Medical Sciences (CAMS; Beijing, P. R. China). The cancer cells were adapted in C57BL/6 mice before use in experiment. Please refer to Section 4.3.1 for details on cell adaptation.

Test System

[0043] Thirty-five male and thirty-five female healthy, naive, C57BL/6 mice were received from the Institute of Laboratory Animal Science, CAMS, Beijing, P. R. China. The animals were six weeks old and weighed between 18 and 22 grams at the start of the study.

Animal Husbandry

[0044] Animals were group-housed in autoclaved shoe box cages with autoclaved wood chips as the bedding materials. The temperature of the animal room was maintained at 22 to 25°C, and the relative humidity was maintained at 40 to 60%. A 12-hour light/12-hour dark cycle was maintained except when interrupted by study-related events. Animals were fed *ad libitum* with sterile water and Beijing KeAoXieLi Rodent Diet (certified). All animals were acclimated for 3 days before tumor inoculation.

Experimental Procedures

Tumor Cell Adaptation

[0045] As per aseptic tissue culture procedures, one vial of murine lung cancer cells was thawed and centrifuged at 1000 rpm, 20-25°C for 5 minutes. The cell pellets were suspended in 0.5 mL normal saline (NS) and subcutaneously injected into the right axilla of each mouse (approximately 1×10^6 cells/mouse). When the tumor diameter reached approximately 1 cm, the animals were euthanized with CO₂ asphyxiation and the tumor was excised. Tumor cells were suspended in normal saline as previously described and the cell adaptation cycle was repeated one more time.

Tumor Cell Inoculation

[0046] 1×10^6 LLC cells in a volume of 0.1 mL of normal saline were subcutaneously injected into the right axillary area of the mouse. The day of tumor inoculation was defined as Day 0.

Study Design and Treatment Regimen

[0047] On Day 1, the animals were randomized into seven different groups based on their body weights so that the mean body weights were not statistically significantly different among groups. Dosing was initiated on Day 1. SCV-07 was administered once daily for 14 consecutive days via subcutaneous (sc) administration in a dose volume of 0.1 mL/20 g body weight, and CTX was administered by intraperitoneal injection every other day at the same dose volume. The vehicle was also dosed once daily for 14 consecutive days via sc administration of PBS at the same dose volume. Treatment regimens for all groups are outlined in Table 1.

Table 1: Treatment Regimen and Study Design

Group Number	Group Name	Treatment	Number of Animals	Dosing Days	Necropsy Day
1	Vehicle Control	PBS	10	1 through 14	Day 16
2	Positive Control 1	CTX 20 mg/kg, i.p., every other day	10		
3	Positive Control 2	CTX 40 mg/kg, i.p., every other day	10		
4	Test Article 1	SCV-07, 5 mg/kg, s.c., daily	10		
5	Test Article 2	SCV-07, 10 mg/kg, s.c., daily	10		
6	Combination 1	SCV-07, 5 mg/kg, s.c., daily + CTX 20 mg/kg, i.p., every other day	10		
7	Combination 2	SCV-07, 10 mg/kg, s.c., daily + CTX 20 mg/kg, i.p., every other day	10		

Evaluation of Anti-tumor Effect

[0048] Throughout the course of the study, the tumor sizes and body weights of all animals were measured every 3 days --- tumor size measured by caliper and body weight by laboratory balance. Animal mortality and morbidity were daily monitored and recorded. On Day 16, the animals were euthanized by CO₂ asphyxiation, and the tumors were excised, separated, and weighed.

Tumor volume was calculated using the following formula:

$$\text{Tumor Volume} = \text{Length} \times \text{Width} \times \text{Width} / 2$$

[0049] Tumor volume inhibition rate (IR) was calculated according to the formula below:

$$\text{IR(TV)} = (\text{TV}_{\text{vehicle}} - \text{TV}_{\text{drug treated}}) / \text{TV}_{\text{vehicle}} \times 100\%$$

[0050] Where, TV is the tumor volume on the day of measurement, "vehicle" denotes the group receiving PBS, and "drug treated" denotes groups receiving SCV-07 and/or CTX.

[0051] The anti-tumor effect of SCV-07 used alone or in combination with CTX was also evaluated by tumor weight. The tumor weight of each mouse was recorded after euthanasia, and the inhibition rate of tumor weight was calculated according to the formula below:

$$\text{IR(TW)} = (\text{Tumor weight}_{\text{vehicle}} - \text{Tumor weight}_{\text{drug treated}}) / \text{Tumor weight}_{\text{vehicle}} \times 100\%$$

[0052] Mean and standard deviations were calculated using Excel.

Statistical Analysis

[0053] Inter-group comparison was performed in terms of tumor volume, tumor weight and body weight, using a student's t test. P values of less than 0.05 were considered to be statistically significant.

Results and Discussion

Mortality

[0054] No animal deaths were observed in the study.

Tumor Size

[0055] Raw measurement data of tumor size are listed in Appendixes 1-10. The calculated tumor inhibition rates and statistical comparison of each treatment group versus vehicle group are listed in the Tables 2-6. The tumor growth curves are illustrated in Figure 1. Based on tumor volume data, all groups except Group 4 showed significant inhibition of tumor growth on Day 3. Group 2 and Group 3 showed inhibition on Day 6. On Day 9, the mean tumor sizes of Group 2, Group 3 and Group 7 were statistically significantly smaller than Group 1 (vehicle). On Day 12, the mean tumor sizes of all treatment groups except Group 4 were statistically significantly smaller than Group 1. On Day 15, the mean tumor sizes of all groups were statistically significantly smaller than Group 1. Among combination treatment groups, high dose of SCV-07 showed additive effect with CTX.

Tumor Weight

[0056] Raw data of tumor weight were shown in Appendix 11, while statistical comparison results between each of treatment groups and vehicle control group are tabulated in Table 7. As shown in Table 7, the mean tumor weights measured on Day 16 of all treatment groups were lower than the vehicle control group. The tumor inhibition rates in Group 2, Group 3, Group 4, Group 5, Group 6, and Group 7 were 45.54% ($p < 0.01$), 90.25% ($p < 0.01$), 18.08% ($p = 0.07$), 30.60% ($p < 0.01$), 48.57% ($p < 0.01$), and 62.63% ($p < 0.01$), respectively. There was no statistically significant difference in tumor inhibition between Group 2 (CTX 20 mg/kg) and Group 6 (CTX 20 mg/kg + SCV-07 5 mg/kg). By contrast, the inhibition rate in Group 7 (CTX

20 mg/kg + SCV-07 10 mg/kg) was statistically significantly greater than in Group 2 (CTX 20 mg/kg), indicating an additive effect when using CTX in combination with SCV-07.

[0057] Figure 2 illustrates the tumor weight for all groups at the end of the study (Day 16).

Body weight

[0058] Raw data of body weight measurement were listed in Appendixes 12-17. The results of statistical comparison of each treatment group versus vehicle group are listed in the Tables 8-13.

[0059] As shown in the tables, there are no significant differences between each of treatment groups and vehicle control group on Day 3. On Day 6, Group 3 (CTX 40 mg/kg) exhibited a body weight inhibition rate of 10.82% ($P < 0.05$). There was no significant difference of body weights for other groups. On Day 9, the inhibition rates for group 2 (CTX 20 mg/kg), group 3 (CTX 40 mg/kg) and group 6 (CTX 20 mg/kg + SCV-07 5 mg/kg) were 12.35% ($p < 0.01$), 16.12% ($p < 0.01$) and 7.22% ($p < 0.01$), respectively. With the addition of SCV-07 in Group 6, the inhibition rate of body weight gain was decreased. There was no significant difference of body weights for other groups, indicating that SCV-07 had no effect on animal body weight gain. On Day 12 the inhibition rates for Group 2 (CTX 20 mg/kg), Group 3 (CTX 40 mg/kg), and Group 6 (CTX 20 mg/kg + SCV-07 5 mg/kg) were 14.83% ($p < 0.01$), 21.97% ($p < 0.01$), and 10.28% ($p < 0.01$), respectively. On Day 15, the inhibition rate in Group 3 (CTX 40 mg/kg) was 25% ($p < 0.01$). There was no significant difference of body weights for other groups. This result indicated that CTX inhibited the body weight gain probably due to its toxicity and SCV-07 could partially reserve the inhibition, probably due to its alleviation of CTX toxicity.

Conclusion and Discussion

[0060] In conclusion, the tumor model used in this study is valid as tumor growth can be inhibited by positive control drug CTX. Daily administration of test article, SCV-07 at 10 mg/kg for 14 days is also effective against the tumor growth. Tumor sizes in animals of all SCV-07-treated groups were significantly reduced in comparison with those of the vehicle control group from Day 12 onwards. Tumor weights, which are measured on Day 16, are also significantly reduced in the group receiving 10 mg/kg SCV-07 alone and in the groups receiving combination therapy, but not in the group receiving 5 mg/kg SCV-07 alone. Furthermore, the combined use of 10 mg/kg SCV-07 and 20 mg/kg SCV-07 collectively

produced 62.63% inhibition of tumor growth, in comparison to 30.6% and 45.54% inhibition obtained when using 10 mg/kg SCV-07 or 20 mg/kg CTX alone. These results suggest that combined use of SCV-07 with CTX produces an additive effect towards the tumor growth inhibition.

[0061] The mean animal body weights in CTX treatment groups were significantly decreased, indicating a toxic effect. However, with the addition of SCV-07 in the combination therapy groups, it appears that the toxic effect of CTX can be attenuated at least partially by SCV-07. The phenomenon is apparent on Day 9, when CTX 20 mg/kg alone produces statistically significant inhibition of body weight gain, but the inhibition is abolished in the combination treatment group (CTX 20 mg/kg + SCV-07 10 mg/kg). We did not test protective effect of SCV-07 in combination with higher dose of CTX (i.e., 40 mg/kg) that produced more pronounced inhibition of body weight gain. The protective effect of SCV-07, if verified by future studies, shall be very useful when considering SCV-07 and CTX combination therapy. Taken together, combination of suboptimal dose of CTX (20 mg/kg) with high dose of SCV-07 (10 mg/kg) showed increased anti-tumor efficacy and less toxicity.

Tables

Table 2: Statistical results of tumor sizes on Day 3

Group Number	Group Name	Treatment	Number of Animals Surviving	Average Weight (x ± SD)	IR (TV) %	P value
1	Vehicle Control	PBS	10	0.0172±0.0078		
2	Positive Control 1	CTX 20 mg/kg, i.p., every other day	10	0.0022±0.0043	87.21	0.0000
3	Positive Control 2	CTX 40 mg/kg, i.p., every other day	10	0.0014±0.0043	91.86	0.0000
4	Test Article 1	SCV-07, 5 mg/kg, s.c., daily	10	0.0173±0.0137	-0.29	0.9921
5	Test Article 2	SCV-07, 10 mg/kg, s.c., daily	10	0.0072±0.0068	58.43	0.0066
6	Combination 1	SCV-07, 5 mg/kg, s.c., daily + CTX 20 mg/kg, i.p., every other day	10	0.0094±0.0100	45.35	0.0677
7	Combination 2	SCV-07, 10 mg/kg, s.c., daily + CTX 20 mg/kg, i.p., every other day	10	0.0070±0.0058	59.30	0.0038

Table 3: Statistical results of tumor sizes on Day 6

Group Number	Group Name	Treatment	Number of Animals Surviving	Average Weight (x ± SD)	IR (TV) %	P value
1	Vehicle Control	PBS	10	0.1091±0.0857		
2	Positive Control 1	CTX 20 mg/kg, i.p., every other day	10	0.0217±0.0248	80.15	0.0062
3	Positive Control 2	CTX 40 mg/kg, i.p., every other day	10	0.0067±0.0196	93.86	0.0017
4	Test Article 1	SCV-07, 5 mg/kg, s.c., daily	10	0.0908±0.0224	16.78	0.5216
5	Test Article 2	SCV-07, 10 mg/kg, s.c., daily	10	0.0871±0.0366	20.17	0.4648
6	Combination 1	SCV-07, 5 mg/kg, s.c., daily + CTX 20 mg/kg, i.p., every other day	10	0.0824±0.0560	24.44	0.4209
7	Combination 2	SCV-07, 10 mg/kg, s.c., daily + CTX 20 mg/kg, i.p., every other day	10	0.0601±0.0406	44.89	0.1199

Table 4: Statistical results of tumor sizes on Day 9

Group Number	Group Name	Treatment	Number of Animals Surviving	Average Weight (x ± SD)	IR (TV) %	P value
1	Vehicle Control	PBS	10	0.5252±0.2953		
2	Positive Control 1	CTX 20 mg/kg, i.p., every other day	10	0.0582±0.0100	88.92	0.0001
3	Positive Control 2	CTX 40 mg/kg, i.p., every other day	10	0.0085±0.0195	98.39	0.0000
4	Test Article 1	SCV-07, 5 mg/kg, s.c., daily	10	0.5286±0.1945	-0.66	0.9757
5	Test Article 2	SCV-07, 10 mg/kg, s.c., daily	10	0.4001±0.2034	23.82	0.2845
6	Combination 1	SCV-07, 5 mg/kg, s.c., daily + CTX 20 mg/kg, i.p., every other day	10	0.3324±0.1944	36.71	0.1018
7	Combination 2	SCV-07, 10 mg/kg, s.c., daily + CTX 20 mg/kg, i.p., every other day	10	0.0998±0.0602	81.01	0.0003

Table 5: Statistical results of tumor sizes on Day 12

Group Number	Group Name	Treatment	Number of Animals Surviving	Average Weight (x ± SD)	IR (TV) %	P value
1	Vehicle Control	PBS	10	1.6607±0.6599		
2	Positive Control 1	CTX 20 mg/kg, i.p., every other day	10	0.4864±0.1807	70.71	0.0000
3	Positive Control 2	CTX 40 mg/kg, i.p., every other day	10	0.0149±0.0333	99.11	0.0000
4	Test Article 1	SCV-07, 5 mg/kg, s.c., daily	10	1.1649±0.2079	29.85	0.0360
5	Test Article 2	SCV-07, 10 mg/kg, s.c., daily	10	0.7196±0.2452	56.67	0.0005
6	Combination 1	SCV-07, 5 mg/kg, s.c., daily + CTX 20 mg/kg, i.p., every other day	10	0.7505±0.3700	54.81	0.0013
7	Combination 2	SCV-07, 10 mg/kg, s.c., daily + CTX 20 mg/kg, i.p., every other day	10	0.3573±0.2481	78.49	0.0000

Table 6: Statistical results of tumor sizes on Day 15

Group Number	Group Name	Treatment	Number of Animals Surviving	Average Weight (x ± SD)	IR (TV) %	P value
1	Vehicle Control	PBS	10	3.5911±1.5089		
2	Positive Control 1	CTX 20 mg/kg, i.p., every other day	10	1.4398±0.4698	59.91	0.0004
3	Positive Control 2	CTX 40 mg/kg, i.p., every other day	10	0.1222±0.2207	96.60	0.0000
4	Test Article 1	SCV-07, 5 mg/kg, s.c., daily	10	2.0853±0.5227	41.93	0.0080
5	Test Article 2	SCV-07, 10 mg/kg, s.c., daily	10	1.7460±0.4757	51.38	0.0017
6	Combination 1	SCV-07, 5 mg/kg, s.c., daily + CTX 20 mg/kg, i.p., every other day	10	1.7240±0.6097	51.99	0.0019
7	Combination 2	SCV-07, 10 mg/kg, s.c., daily + CTX 20 mg/kg, i.p., every other day	10	1.1728±0.5247	67.34	0.0001

Table 7: Statistical results of tumor weights on Day 16

Group Number	Group Name	Treatment	Number of Animals Surviving	Average Weight (x ± SD)	IR (TW)	P value
1	Vehicle Control	PBS	10	4.062±1.0113		
2	Positive Control 1	CTX 20 mg/kg, i.p., every other day	10	1.806±0.5407	55.54	0.0000
3	Positive Control 2	CTX 40 mg/kg, i.p., every other day	10	0.396±0.5509	90.25	0.0000
4	Test Article 1	SCV-07, 5 mg/kg, s.c., daily	10	3.329±0.6713	18.05	0.0722
5	Test Article 2	SCV-07, 10 mg/kg, s.c., daily	10	2.819±0.7946	30.60	0.0068
6	Combination 1	SCV-07, 5 mg/kg, s.c., daily + CTX 20 mg/kg, i.p., every other day	10	2.089±0.7854	48.57	0.0001
7	Combination 2	SCV-07, 10 mg/kg, s.c., daily + CTX 20 mg/kg, i.p., every other day	10	1.518±0.6677	62.63	0.0000

Table 8: Statistical results of body weights on Day 0

Group Number	Group Name	Treatment	Number of Animals Surviving	Average Weight (x ± SD)	IR (BW) %	P value
1	Vehicle Control	PBS	10	20.75±1.2869		
2	Positive Control 1	CTX 20 mg/kg, i.p., every other day	10	20.86±1.2267	-0.53	0.8471
3	Positive Control 2	CTX 40 mg/kg, i.p., every other day	10	20.74±1.0490	0.05	0.9850
4	Test Article 1	SCV-07, 5 mg/kg, s.c., daily	10	20.62±1.3935	0.63	0.8309
5	Test Article 2	SCV-07, 10 mg/kg, s.c., daily	10	20.84±1.2267	-0.43	0.8746
6	Combination 1	SCV-07, 5 mg/kg, s.c., daily + CTX 20 mg/kg, i.p., every other day	10	20.62±1.3139	0.63	0.8256
7	Combination 2	SCV-07, 10 mg/kg, s.c., daily + CTX 20 mg/kg, i.p., every other day	10	20.75±1.2704	0.00	1.0000

Table 9: Statistical results of body weights on Day 3

Group Number	Group Name	Treatment	Number of Animals Surviving	Average Weight (x ± SD)	IR (BW) %	P value
1	Vehicle Control	PBS	10	20.56±1.5742		
2	Positive Control 1	CTX 20 mg/kg, i.p., every other day	10	20.36±1.3954	0.97	0.7671
3	Positive Control 2	CTX 40 mg/kg, i.p., every other day	10	19.80±1.0414	3.70	0.2191
4	Test Article 1	SCV-07, 5 mg/kg, s.c., daily	10	20.14±1.3468	2.04	0.5295
5	Test Article 2	SCV-07, 10 mg/kg, s.c., daily	10	20.08±1.2444	2.33	0.4592
6	Combination 1	SCV-07, 5 mg/kg, s.c., daily + CTX 20 mg/kg, i.p., every other day	10	19.98±1.4328	2.82	0.4002
7	Combination 2	SCV-07, 10 mg/kg, s.c., daily + CTX 20 mg/kg, i.p., every other day	10	20.17±1.6446	1.90	0.5946

Table 10: Statistical results of body weights on Day 6

Group Number	Group Name	Treatment	Number of Animals Surviving	Average Weight (x ± SD)	IR (BW) %	P Value
1	Vehicle Control	PBS	10	20.51±1.5581		
2	Positive Control 1	CTX 20 mg/kg, i.p., every other day	10	18.89±2.0041	7.90	0.0587
3	Positive Control 2	CTX 40 mg/kg, i.p., every other day	10	18.29±1.5344	10.82	0.0049
4	Test Article 1	SCV-07, 5 mg/kg, s.c., daily	10	20.33±1.6674	0.88	0.8059
5	Test Article 2	SCV-07, 10 mg/kg, s.c., daily	10	20.44±1.4909	0.34	0.9194
6	Combination 1	SCV-07, 5 mg/kg, s.c., daily + CTX 20 mg/kg, i.p., every other day	10	19.59±1.1921	4.49	0.1554
7	Combination 2	SCV-07, 10 mg/kg, s.c., daily + CTX 20 mg/kg, i.p., every other day	10	19.58±2.3766	4.53	0.3144

Table 11: Statistical results of body weights on Day 9

Group Number	Group Name	Treatment	Number of Animals Surviving	Average Weight (x ± SD)	IR (BW) %	P value
1	Vehicle Control	PBS	10	22.45±1.0835		
2	Positive Control 1	CTX 20 mg/kg, i.p., every other day	10	19.68±2.1856	12.35	0.0024
3	Positive Control 2	CTX 40 mg/kg, i.p., every other day	10	18.83±1.9922	16.12	0.0001
4	Test Article 1	SCV-07, 5 mg/kg, s.c., daily	10	21.96±1.5551	2.18	0.4243
5	Test Article 2	SCV-07, 10 mg/kg, s.c., daily	10	21.42±1.7453	4.59	0.1303
6	Combination 1	SCV-07, 5 mg/kg, s.c., daily + CTX 20 mg/kg, i.p., every other day	10	20.83±1.1016	7.22	0.0038
7	Combination 2	SCV-07, 10 mg/kg, s.c., daily + CTX 20 mg/kg, i.p., every other day	10	21.14±2.1966	5.84	0.1080

Table 12: Statistical results of body weights on Day 12

Group Number	Group Name	Treatment	Number of Animals Surviving	Average Weight (x ± SD)	IR (BW) %	P value
1	Vehicle Control	PBS	10	23.26±2.1665		
2	Positive Control 1	CTX 20 mg/kg, i.p., every other day	10	19.81±2.1231	14.83	0.0021
3	Positive Control 2	CTX 40 mg/kg, i.p., every other day	10	18.15±1.3168	21.97	0.0000
4	Test Article 1	SCV-07, 5 mg/kg, s.c., daily	10	22.21±1.8071	4.51	0.2545
5	Test Article 2	SCV-07, 10 mg/kg, s.c., daily	10	21.97±1.6371	5.55	0.1504
6	Combination 1	SCV-07, 5 mg/kg, s.c., daily + CTX 20 mg/kg, i.p., every other day	10	20.87±1.2623	10.28	0.0075
7	Combination 2	SCV-07, 10 mg/kg, s.c., daily + CTX 20 mg/kg, i.p., every other day	10	20.98±2.4512	9.80	0.0408

Table 13: Statistical results of body weights on Day 15

Group Number	Group Name	Treatment	Number of Animals Surviving	Average Weight (x + SD)	IR (BW)%	P value
1	Vehicle Control	PBS	10	24.01±1.9076		
2	Positive Control 1	CTX 20 mg/kg, i.p., every other day	10	22.75±2.3590	5.25	0.2056
3	Positive Control 2	CTX 40 mg/kg, i.p., every other day	10	17.98±1.9240	25.11	0.0000
4	Test Article 1	SCV-07, 5 mg/kg, s.c., daily	10	23.05±2.1423	4.00	0.3039
5	Test Article 2	SCV-07, 10 mg/kg, s.c., daily	10	23.19±1.5538	3.42	0.3058
6	Combination 1	SCV-07, 5 mg/kg, s.c., daily + CTX 20 mg/kg, i.p., every other day	10	22.52±1.4695	6.21	0.0661
7	Combination 2	SCV-07, 10 mg/kg, s.c., daily + CTX 20 mg/kg, i.p., every other day	10	22.43±2.3641	6.58	0.1174

Appendix 1: Tumor measurements (cm) on Day 3

Group	Treatment	F1		F2		F3		F4		F5		M1		M2		M3		M4		M5	
		0.3	0.4	0.3	0.4	0.3	0.3	0.4	0.4	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
1	Vehicle Control	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2	CTX 20 mg/kg	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3	CTX 40 mg/kg	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4	SCV-07 5 mg/kg	0.4	0.3	0.3	0.4	0.4	-	-	-	0.3	0.3	0.4	0.4	-	-	0.2	0.2	0.3	0.3	0.4	0.4
5	SCV-07 10 mg/kg	0.3	0.3	0.3	0.3	0.3	-	-	-	-	-	0.3	0.3	0.2	0.2	-	-	0.3	0.3	-	-
6	SCV-07 5 mg/kg+ CTX 20 mg/kg	0.4	0.2	0.2	0.3	0.3	-	-	-	0.3	0.3	0.3	0.3	0.2	0.2	-	-	0.3	0.3	-	-
7	SCV-07 10 mg/kg+ CTX 20 mg/kg	0.2	0.2	0.2	0.2	0.2	0.3	0.3	-	-	-	0.3	0.3	-	-	0.3	0.3	0.3	0.3	0.2	0.2

- Not measurable

Appendix 2: Tumor volumes* (cm³) on Day 3

Group	Treatment	F1		F2		F3		F4		F5		M1		M2		M3		M4		M5	
		0.0135	0.032	0.0135	0.032	0.0135	0.032	0.0135	0.032	0.0135	0.032	0.0135	0.032	0.0135	0.032	0.0135	0.032	0.0135	0.032	0.0135	0.032
1	Vehicle Control	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	CTX 20 mg/kg	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	CTX 40 mg/kg	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	SCV-07 5 mg/kg	0.032	0.0135	0.0135	0.032	0.032	0	0	0.0005	0	0.0135	0.032	0	0	0	0.004	0.004	0.0135	0.0135	0	0
5	SCV-07 10 mg/kg	0.0135	0.0135	0.0135	0.0135	0.0135	0	0	0	0	0	0.0135	0.0135	0.004	0.004	0	0	0.0135	0.0135	0	0
6	SCV-07 5 mg/kg+ CTX 20 mg/kg	0.032	0.004	0.0135	0	0.0135	0	0	0	0.0135	0.0135	0.0135	0.0135	0.004	0.004	0	0	0.0135	0.0135	0	0
7	SCV-07 10 mg/kg+ CTX 20 mg/kg	0.004	0.004	0.004	0.004	0.004	0.0135	0.0135	0	0	0	0.0135	0.0135	0	0	0.0135	0.0135	0.0135	0.0135	0.004	0.004

* Tumor volumes were calculated using the formula "Tumor Volume=Length*Width*Width/2" based on the data listed in Appendix 1.

Appendix 3: Tumor measurements (cm) on Day 6

Group	Treatment	F1		F2		F3		F4		F5		M1		M2		M3		M4		M5	
		L	W	L	W	L	W	L	W	L	W	L	W	L	W	L	W	L	W	L	W
1	Vehicle Control	0.5	0.5	0.4	0.4	0.5	0.5	0.5	0.5	0.5	0.5	0.8	0.8	0.8	0.8	0.5	0.5	0.7	0.7	0.5	0.5
2	CTX 20 mg/kg	0.3	0.3			0.3	0.3					0.4	0.4	0.4	0.4	0.5	0.5	0.1	0.1	0.5	0.5
3	CTX 40 mg/kg					0.5	0.5	0.2	0.2											0.1	0.1
4	SCV-07 5 mg/kg	0.6	0.6	0.6	0.6	0.4	0.5	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.5	0.5	0.6	0.6	0.6	0.5	0.5
5	SCV-07 10 mg/kg	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.5	0.5	0.7	0.7	0.5
6	SCV-07 5 mg/kg+ CTX 20 mg/kg	0.4	0.4	0.6	0.6	0.5	0.5	0.3	0.3	0.5	0.5	0.7	0.7	0.7	0.7	0.4	0.4	0.6	0.6	0.5	0.5
7	SCV-07 10 mg/kg+ CTX 20 mg/kg	0.5	0.5	0.6	0.6	0.6	0.3	0.3	0.5	0.5	0.5	0.5	0.5	0.3	0.3	0.6	0.6	0.6	0.6	0.5	0.5

- Not measurable

Appendix 4: Tumor volumes* (cm³) on Day 6

Group	Treatment	F1		F2		F3		F4		F5		M1		M2		M3		M4		M5	
		L	W	L	W	L	W	L	W	L	W	L	W	L	W	L	W	L	W	L	W
1	Vehicle Control	0.0625	0.0625	0.032	0.032	0.0625	0.0625	0.0625	0.0625	0.0625	0.0625	0.256	0.256	0.256	0.256	0.0625	0.0625	0.1715	0.1715	0.0625	0.0625
2	CTX 20 mg/kg	0.0135	0.0135	0	0	0.0135	0	0	0	0	0	0.032	0.032	0.032	0.032	0.0625	0.0625	0.0005	0.0005	0.0625	0.0625
3	CTX 40 mg/kg	0	0	0	0	0.0625	0.004	0.004	0	0	0	0	0	0	0	0	0	0	0	0.0005	0.0005
4	SCV-07 5 mg/kg	0.108	0.108	0.072	0.0625	0.0625	0.108	0.108	0.108	0.108	0.108	0.108	0.108	0.0625	0.108	0.0625	0.108	0.108	0.108	0.0625	0.0625
5	SCV-07 10 mg/kg	0.0625	0.0625	0.0625	0.0625	0.0625	0.0625	0.0625	0.0625	0.108	0.108	0.108	0.108	0.108	0.108	0.0625	0.0625	0.1715	0.1715	0.0625	0.0625
6	SCV-07 5 mg/kg+ CTX 20 mg/kg	0.032	0.032	0.108	0.108	0.0625	0.0135	0.0135	0.0135	0.0625	0.0625	0.1715	0.1715	0.1715	0.1715	0.032	0.032	0.108	0.108	0.0625	0.0625
7	SCV-07 10 mg/kg+ CTX 20 mg/kg	0.0625	0.0625	0.108	0.108	0.0135	0.0135	0.0135	0.0625	0	0	0.0625	0.0625	0.0625	0.0135	0.108	0.108	0.108	0.108	0.0625	0.0625

* Tumor volumes were calculated using the formula "Tumor Volume=LengthxWidthxWidth/2" based on the data listed in Appendix 3.

Appendix 5: Tumor measurements (cm) on Day 9

Group	Treatment	F1		F2		F3		F4		F5		M1		M2		M3		M4		M5	
		L	W	L	W	L	W	L	W	L	W	L	W	L	W	L	W	L	W	L	W
1	Vehicle Control	0.8	0.8	0.9	0.9	1.2	1.1	0.9	0.9	0.8	0.8	1.2	1.2	1.3	1.3	0.8	0.8	1.2	1.2	1.0	1.0
2	CTX 20 mg/kg	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.4	0.5	0.5	0.5	0.4	0.4	0.5	0.5
3	CTX 40 mg/kg	0.2	0.2			0.5	0.5	0.3	0.3	0.2	0.2									0.1	0.1
4	SCV-07 5 mg/kg	1	0.5	1	0.7	1.1	1.1	1.2	1.1	0.9	0.9	1.2	1.2	1	1	1	1	1	1	1	1
5	SCV-07 10 mg/kg	0.8	0.8	0.7	0.7	0.9	0.9	0.9	0.9	1	1	1.0	1.0	1.0	1.0	0.8	0.8	1.2	1.2	0.8	0.7
6	SCV-07 5 mg/kg+ CTX 20 mg/kg	0.8	0.8	1.1	1	0.7	0.7	0.7	0.7	1	1	0.8	0.8	1	1	0.7	0.7	0.7	0.7	0.7	0.7
7	SCV-07 10 mg/kg+ CTX 20 mg/kg	0.5	0.5	0.7	0.7	0.4	0.4	0.6	0.6	0.2	0.1	0.5	0.5	0.6	0.6	0.7	0.7	0.7	0.7	0.6	0.6

- Not measurable

Appendix 6: Tumor volumes* (cm³) on Day 9

Group	Treatment	F1	F2	F3	F4	F5	M1	M2	M3	M4	M5
1	Vehicle Control	0.256	0.3645	0.792	0.3645	0.256	0.5	1.0985	0.256	0.864	0.5
2	CTX 40 mg/kg	0.0625	0.0625	0.0625	0.0625	0.0625	0.0625	0.05	0.0625	0.032	0.0625
3	SCV-07 0.01 mg/kg	0.004	0	0.0625	0.0135	0.004	0	0	0	0	0.0005
4	SCV-07 0.1 mg/kg	0.25	0.35	0.6655	0.792	0.3645	0.864	0.5	0.5	0.5	0.5
5	SCV-07 1.0 mg/kg	0.256	0.1715	0.3645	0.3645	0.5	0.5	0.5	0.256	0.864	0.224
6	SCV-07 5 mg/kg+ CTX 20 mg/kg	0.605	0.605	0.1715	0.1715	0.5	0.256	0.5	0.1715	0.1715	0.1715
7	SCV-07 10 mg/kg+ CTX 20 mg/kg	0.0625	0.1715	0.032	0.108	0.002	0.0625	0.108	0.1715	0.1715	0.108

* Tumor volumes were calculated using the formula "Tumor Volume=Length×Width×Width/2" based on the data listed in Appendix 5.

Appendix 7: Tumor measurements (cm) on Day 12

Group	Treatment	F1		F2		F3		F4		F5		M1		M2		M3		M4		M5	
		L	W	L	W	L	W	L	W	L	W	L	W	L	W	L	W	L	W	L	W
1	Vehicle Control	1.2	1.2	1.2	1.2	1.7	1.7	1.5	1.5	1.5	1.3	1.7	1.7	1.6	1.5	1.2	1.2	1.7	1.7	1.5	1.4
2	CTX 20 mg/kg	0.9	0.9	1.1	1.1	0.8	0.8	1	1	0.8	0.8	1	1	1	1	1.1	1.1	0.9	0.9	1.2	1.1
3	CTX 40 mg/kg	0.3	0.3	-	-	0.6	0.6	0.3	0.3	0.3	0.3	-	-	-	-	-	-	-	-	-	-
4	SCV-07 5 mg/kg	1.2	1	1.5	1.2	1.3	1.3	1.3	1.3	1.3	1.3	1.5	1.3	1.5	1.2	1.3	1.3	1.3	1.3	1.4	1.3
5	SCV-07 10 mg/kg	1.2	1.2	1.1	1.1	1	1	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1	1	1.3	1.3	0.8	0.8
6	SCV-07 5 mg/kg+ CTX 20 mg/kg	1	1	1.6	1.2	1	1	1	1	1	1	1.1	1.1	1.4	1.3	1.1	1.1	1.2	1.2	1	1
7	SCV-07 10 mg/kg+ CTX 20 mg/kg	0.9	0.9	1	1	0.5	0.5	1	1	0.3	0.3	0.8	0.8	0.8	0.8	1.2	1.2	1	1	0.8	0.8

-not measurable

Appendix 8: Tumor volumes* (cm³) on Day 12

Group	Treatment	F1	F2	F3	F4	F5	M1	M2	M3	M4	M5
1	Vehicle Control	0.864	0.864	2.4565	1.6875	1.4625	2.4565	1.92	0.864	2.4565	1.575
2	CTX 20 mg/kg	0.3645	0.6655	0.256	0.5	0.256	0.5	0.5	0.6655	0.3645	0.792
3	CTX 40 mg/kg	0.0135	0	0.108	0.0135	0.0135	0	0	0	0	0
4	SCV-07 5 mg/kg	0.72	1.35	1.0985	1.0985	1.0985	1.4625	1.35	1.0985	1.0985	1.274
5	SCV-07 10 mg/kg	0.864	0.6655	0.5	0.864	0.864	0.72	0.864	0.5	1.0985	0.256
6	SCV-07 5 mg/kg+ CTX 20 mg/kg	0.5	1.536	0.5	0.5	0.5	0.6655	1.274	0.6655	0.864	0.5
7	SCV-07 10 mg/kg+ CTX 20 mg/kg	0.3645	0.5	0.0625	0.5	0.0135	0.256	0.256	0.864	0.5	0.256

* Tumor volumes were calculated using the formula "Tumor Volume=Length×Width×Width/2" based on the data listed in Appendix 7.

Appendix 9: Tumor measurements (cm) on Day 15

Group	Treatment	F1		F2		F3		F4		F5		M1		M2		M3		M4		M5	
		L	W	L	W	L	W	L	W	L	W	L	W	L	W	L	W	L	W	L	W
1	Vehicle Control	1.5	1.5	1.8	1.8	2	1.7	2.4	1.8	2	1.5	2.4	2	1.8	1.8	1.5	1.5	2.4	2	2	1.8
2	CTX 20 mg/kg	1.4	1.3	1.6	1.2	1.3	1.2	1.5	1.5	1.7	1.5	1.3	1.3	1.2	1.2	1.7	1.5	1.3	1.2	1.5	1.4
3	CTX 40 mg/kg	0.5	0.5			1.1	1.1	0.9	0.9	0.5	0.5			0.5	0.5					0.2	0.2
4	SCV-07 5 mg/kg	1.7	1.4	1.7	1.1	1.7	1.4	1.7	1.7	1.4	1.4	2	1.5	1.8	1.5	1.4	1.6	1.4	1.4	1.8	1.6
5	SCV-07 10 mg/kg	1.4	1.4	1.7	1.7	1.7	1.7	1.4	1.4	1.4	1.4	1.5	1.5	1.4	1.4	1.5	1.5	1.7	1.6	1.4	1.4
6	SCV-07 5 mg/kg+ CTX 20 mg/kg	1.2	1.2	1.7	1.6	1.2	1.2	1.4	1.4	1.5	1.5	1.7	1.7	1.7	1.7	1.7	1.7	1.5	1.5	1.5	1.4
7	SCV-07 10 mg/kg+ CTX 20 mg/kg	1.4	1.4	1.4	1.4	1	1	1.3	1.3	0.5	0.5	1.4	1.3	1.5	1.5	1.5	1.4	1.5	1.5	1.5	1.3

Appendix 10: Tumor volumes* (cm³) on Day 15

Group	Treatment	F1		F2		F3		F4		F5		M1		M2		M3		M4		M5	
		L	W	L	W	L	W	L	W	L	W	L	W	L	W	L	W	L	W	L	W
1	Vehicle Control	1.6875	1.6875	2.916	2.916	3.4	3.4	5.184	5.184	3	3	5.76	5.76	2.916	2.916	1.6875	1.6875	5.76	5.76	3.6	3.6
2	CTX 20 mg/kg	1.274	1.274	1.536	1.536	1.014	1.014	1.6875	1.6875	2.1675	2.1675	1.0985	1.0985	0.864	0.864	2.1675	2.1675	1.014	1.014	1.575	1.575
3	CTX 40 mg/kg	0.0625	0.0625	0	0	0.6655	0.6655	0.3645	0.3645	0.0625	0.0625	0	0	0.0625	0.0625	0	0	0	0	0.004	0.004
4	SCV-07 5 mg/kg	2.023	2.023	1.5895	1.5895	2.023	2.023	2.4565	2.4565	1.372	1.372	3	3	2.43	2.43	1.575	1.575	1.792	1.792	2.592	2.592
5	SCV-07 10 mg/kg	1.372	1.372	2.4565	2.4565	2.4565	2.4565	1.372	1.372	1.372	1.372	1.6875	1.6875	1.372	1.372	1.6875	1.6875	2.312	2.312	1.372	1.372
6	SCV-07 5 mg/kg+ CTX 20 mg/kg	0.864	0.864	2.312	2.312	0.864	0.864	1.372	1.372	1.6875	1.6875	2.4565	2.4565	2.4565	2.4565	2.1675	2.1675	1.6875	1.6875	1.372	1.372
7	SCV-07 10 mg/kg+ CTX 20 mg/kg	1.372	1.372	1.372	1.372	0.5	0.5	1.0985	1.0985	0.0625	0.0625	1.274	1.274	1.6875	1.6875	1.575	1.575	1.6875	1.6875	1.0985	1.0985

* Tumor volumes were calculated using the formula "Tumor Volume=Length×Width×Width/2" based on the data listed in Appendix 9.

Appendix 11: Tumor weight* (g) on Day 16

Group	Treatment	F1	F2	F3	F4	F5	M1	M2	M3	M4	M5
1	Vehicle Control	3.01	3.61	4.49	4.20	2.90	5.34	5.33	2.79	5.23	3.72
2	CTX 20 mg/kg	2.05	1.64	1.44	1.72	1.72	1.63	1.43	2.90	1.05	2.48
3	CTX 40 mg/kg	0.29	0.12	1.80	0.84	0.39	0.28	0.02	0.03	0.15	0.04
4	SCV-07 5 mg/kg	2.87	2.05	3.23	4.03	2.94	4.40	3.18	3.11	3.71	3.77
5	SCV-07 10 mg/kg	2.86	2.96	4.03	2.05	2.7	3.18	2.20	2.42	4.10	1.69
6	SCV-07 5 mg/kg+ CTX 20 mg/kg	1.60	3.40	1.26	1.60	1.40	2.46	3.39	2.07	2.21	1.50
7	SCV-07 10 mg/kg+ CTX 20 mg/kg	1.57	2.00	0.56	2.53	0.47	0.99	1.67	2.00	1.96	1.43

Appendix 12: Body weights (g) on Day 0

Group	Treatment	F1	F2	F3	F4	F5	M1	M2	M3	M4	M5
1	Vehicle Control	19.5	19.4	19.7	19.5	19.6	21.9	21.8	22.2	22.2	21.7
2	CTX 20 mg/kg	19.8	19.7	19.1	20.2	19.9	22.2	22.1	21.5	22.2	21.9
3	CTX 40 mg/kg	19.3	20.1	19.5	19.7	20.3	21.7	21.7	21.7	21.7	21.7
4	SCV-07 5 mg/kg	19.8	19.2	19.2	19.9	18.7	21.9	21.3	22.4	22	21.8
5	SCV-07 10 mg/kg	19.9	19.3	19.6	19.7	20	21.9	22.2	21.6	22	22.2
6	SCV-07 5 mg/kg+ CTX 20 mg/kg	19.2	19.1	19.5	19.5	19.7	22.1	21.4	21.8	22.2	21.7
7	SCV-07 10 mg/kg+ CTX 20 mg/kg	20	19.5	19.6	19.4	19.4	21.6	22.4	21.5	21.9	22.2

Appendix 13: Body weights (g) on Day 3

Group	Treatment	F1	F2	F3	F4	F5	M1	M2	M3	M4	M5
1	Vehicle Control	19.5	18.4	19.8	19	18.9	21.9	21.6	22.4	21.9	22.2
2	CTX 20 mg/kg	18.7	19.6	18.6	19.7	18.9	21.5	22	21.1	21.5	22
3	CTX 40 mg/kg	18.9	19.1	18	18.8	20.1	20.1	20.5	20.5	20.7	21.3
4	SCV-07 5 mg/kg	19.2	18.9	19.3	19.6	17.8	21.9	21.2	21.3	21.2	21
5	SCV-07 10 mg/kg	18.8	19	19	19	19.3	21.6	22.3	20.7	20.8	20.3
6	SCV-07 5 mg/kg+ CTX 20 mg/kg	18.4	18.1	19	19.1	18.9	21	21.6	21.9	21.4	20.4
7	SCV-07 10 mg/kg+ CTX 20 mg/kg	19.3	18.1	19	19	18.1	21.6	22	22.4	21.4	20.8

Appendix 14: Body weights (g) on Day 6

Group	Treatment	F1	F2	F3	F4	F5	M1	M2	M3	M4	M5
1	Vehicle Control	18.7	18.8	19.6	20	18.7	21.8	21.8	22.5	22.5	20.7
2	CTX 20 mg/kg	17	16.6	17.3	16.7	17.8	20	22	20.2	20.6	20.7
3	CTX 40 mg/kg	17	17.6	15.8	16.7	17.8	19.7	19.3	19.4	19	20.6
4	SCV-07 5 mg/kg	20.4	19	18.2	19.5	17.8	22.9	21.7	21.8	21.2	20.8
5	SCV-07 10 mg/kg	18.5	19.6	19.1	19.2	19.5	22.2	22.9	21.7	20.5	21.2
6	SCV-07 5 mg/kg+ CTX 20 mg/kg	17.8	20.1	18.4	18.4	19	21.4	20.5	19.2	20.7	20.4
7	SCV-07 10 mg/kg+ CTX 20 mg/kg	16.5	18.2	17.9	16.9	17.4	21.6	21.4	22.2	22.1	21.6

Appendix 15: Body weights (g) on Day 9

Group	Treatment	F1	F2	F3	F4	F5	M1	M2	M3	M4	M5
1	Vehicle Control	21.5	21.8	21.6	21.2	21.2	23.6	22.9	23.8	23.3	23.6
2	CTX 20 mg/kg	17.5	18.8	17.	17.5	18	21.4	22.5	22	20	21.2
3	CTX 40 mg/kg	17.5	19.1	15.4	17.1	17.2	20.4	20.3	18.8	21.5	21
4	SCV-07 5 mg/kg	21.8	21.6	19.5	20.6	20	24.	23.7	23	23.2	22.2
5	SCV-07 10 mg/kg	18.9	20.7	19.7	20.1	20.3	23.3	24.4	22.4	22.2	22.2
6	SCV-07 5 mg/kg+ CTX 20 mg/kg	19.9	21.1	18.6	21.2	19.9	22	22.2	20.9	20.8	21.7
7	SCV-07 10 mg/kg+ CTX 20 mg/kg	18.3	20.8	18.9	20	18.4	21.9	23.5	24.5	22.6	22.5

Appendix 16: Body weights (g) on Day 12

Group	Treatment	F1	F2	F3	F4	F5	M1	M2	M3	M4	M5
1	Vehicle Control	21.5	21.5	20.7	21.8	20.8	25.7	25.0	24.4	25.8	25.4
2	CTX 20 mg/kg	17.9	18.3	17.9	18.3	17	20.9	22.7	22.1	21.9	21.1
3	CTX 40 mg/kg	17.3	20	16.7	17	18.2	18.5	17.4	16.8	20	19.6
4	SCV-07 5 mg/kg	21.7	20.8	20	19.9	20.4	23.8	23.8	23.8	23.9	24
5	SCV-07 10 mg/kg	19.7	21.2	20.5	20.4	21.5	23.7	25	23	22.4	22.3
6	SCV-07 5 mg/kg+ CTX 20 mg/kg	19.2	21.7	18.9	20.7	20.2	21.5	23	20.7	22.1	20.7
7	SCV-07 10 mg/kg+ CTX 20 mg/kg	17.5	19.6	18.7	19.8	18.6	22.2	23.4	24.5	23.7	21.8

Appendix 17: Body weights (g) on Day 15

Group	Treatment	F1	F2	F3	F4	F5	M1	M2	M3	M4	M5
1	Vehicle Control	22.5	22.9	22.7	22.3	21.4	25.7	24.5	25.4	25.4	27.3
2	CTX 20 mg/kg	23.7	25.1	25.4	23.0	24.2	21.3	20.9	18.7	25.1	20.1
3	CTX 40 mg/kg	16.9	19.8	17.9	17.6	16.7	18.2	15.2	16.0	20.7	20.8
4	SCV-07 5 mg/kg	22.4	21.3	20.3	20.5	21.8	26.3	24.6	23.0	25.6	24.7
5	SCV-07 10 mg/kg	20.7	22.4	22.4	21.5	22.7	24.0	26.0	24.0	24.5	23.7
6	SCV-07 5 mg/kg+ CTX 20 mg/kg	20.5	23.2	20.2	22.6	21.3	23.1	25.1	23.1	23.3	22.8
7	SCV-07 10 mg/kg+ CTX 20 mg/kg	20.8	21.3	19.8	20.5	19.0	23.6	25.1	25.4	25.0	23.6

Example 2

An Evaluation of SCV-07 in Combination with Radiation for Efficacy in the Reduction of Tumor Growth.

SUMMARY

[0062] In this study, the impact of SCV-07 on tumor growth with or without radiation treatment was tested using the H146 lung cancer model in mice. Tumor bearing mice were treated with saline or SCV-07 with or without radiation therapy once a day for twenty days. SCV-07 showed no evidence of toxicity in this study based on observations of survival and weight change and it did not alter the response of H146 tumors to radiation. When given alone, SCV-07 was effective in reducing tumor growth in a dose dependent manner, with animals receiving SCV-07 twice daily for 20 days at 1 mg/kg showing tumor growth inhibition of 9.1% and animals receiving SCV-07 twice daily for 20 days at 10 mg/kg showing 35.9% tumor growth inhibition. When combined with a single dose of radiation therapy, treatment with SCV-07 at 10 mg/kg twice daily for 20 days resulted in a 78.3% tumor growth inhibition, or a TGI of 40.5% relative to the animals treated with radiation alone. Based on these observations, SCV-07 appears to be effective in reducing the growth of tumors in a lung cancer model when given either alone or in combination with radiation therapy.

OBJECTIVE

[0063] To evaluate the efficacy of SCV-07 in inhibiting tumor growth using a NCI H146 small cell lung cancer model in mice, both as mono-therapy and in conjunction with radiotherapy.

STUDY DESIGN

[0064] Ninety-Six (96) female nude mice (nu/nu) were be randomly assigned into 8 treatment groups. Each mouse wasl inoculated into their lower left flank with 1×10^5 NCI-H146 (H146) lung cancer cells in a volume of 0.1 mL with Matrigel. Treatment began once tumors reached a volume of 75-125 mm³. The groups were treated with vehicle, radiation, SCV-07 or radiation and SCV-07 as detailed in Table 2.1. Initiation of drug treatment was

designated as day 1. Mice in groups 1 and 4 received vehicle by subcutaneous (sc) injection for 20 days. Mice in groups 2-4 and 6-8 received SCV-07 in vehicle once a day by sc injection on days 1 through 20, and mice in groups 6-8 received radiation (2 doses of 4 Gy/dose on days 0 and 2). Radiation was done by anesthetizing the mice in these groups with ketamine (120 mg/kg) and xylazine (6 mg/kg), and placing them under a lead shield such that the region of the flank with tumor was exposed to the radiation. Radiation was delivered using a Philips 160 kV source at a focal distance of approximately 40 cm, and a dose rate of approximately 1.0 Gy/min. Tumors were measured on alternating days throughout the duration of the study. Mice in groups 1-8 were sacrificed on day 21 and remaining tumors were excised, measured, weighed, photographed and fixed in formalin for later analysis.

Table 2.1 SCI-05: Study Design

Group	Number of animals	Tumor cell inoculum	RT Days 0 and 2	Drug Treatment & Dosing	Route	Frequency	Schedule
1	12	1 x 10 ⁵	none	Vehicle	sc	bid	Day 1 to 20
2	12	1 x 10 ⁵	none	SCV-07 100 µg/kg	sc	bid	Day 1 to 20
3	12	1 x 10 ⁵	none	SCV-07 1.0 mg/kg	sc	bid	Day 1 to 20
4	12	1 x 10 ⁵	none	SCV-07 10.0 mg/kg	sc	bid	Day 1 to 20
5	12	1 x 10 ⁵	4 Gy focal	Vehicle	sc	bid	Day 1 to 20
6	12	1 x 10 ⁵	4 Gy focal	SCV-07 100 µg/kg	sc	bid	Day 1 to 20
7	12	1 x 10 ⁵	4 Gy focal	SCV-07 1.0 mg/kg	sc	bid	Day 1 to 20
8	12	1 x 10 ⁵	4 Gy focal	SCV-07 10.0 mg/kg	sc	bid	Day 1 to 20

Weights and Survival

[0065] To assess possible toxicity, animals were weighed every day and their survival recorded. Any animals exhibiting a loss of >20% of starting weight during the course of the

study were euthanized. Any animals whose tumors grew to over 4000 mm³ were also euthanized.

MATERIALS AND METHODS

Tissue Culture.

[0066] H146 human lung cancer cells were obtained from ATCC. These cells were grown in DMEM supplemented with 10% Fetal Calf Serum (FCS), 1% penicillin and streptomycin, and 2mM L-Glutamine. Cells were sub-cultured by removing the medium, rinsing twice with sterile calcium- and magnesium-free phosphate buffered saline (PBS) and adding 1 to 2 ml of 0.25% trypsin/ 0.03% EDTA solution. The flask was incubated at 37°C until cells detached. Cells were then sub-cultured at a ratio of 1:3.

Location of Study Performance

[0067] The study was performed at Biomodels AAALAC accredited facility in Watertown MA. Animal use approval for this study was obtained from Biomodels IACUC.

Animals

[0068] Female nude mice, homozygous for the *nu* gene (*nu+ / nu+*) (Charles River Labs), aged 5 to 6 weeks, with a mean pre-treatment body weight of 24 grams were used. Animals were individually numbered using an ear punch, housed in groups of 6 animals per cage, and acclimatized prior to study commencement. During the acclimatization period of at least 2 days, the animals were observed daily in order to reject animals that presented in poor condition.

Housing

[0069] The study was performed in animal rooms provided with filtered air at a temperature of 70°F +/- 5 ° F and 50% +/- 20% relative humidity. Animal rooms 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 hours on and 12 hours off with no twilight.

[0070] Sterilized *Bed-O-Cobs*[®] bedding was used. Bedding was changed a minimum of once per week.

[0071] Cages, tops, bottles, etc. were washed with a commercial detergent and allowed to air dry. Prior to use, these items were wrapped and autoclaved. A commercial disinfectant was used to disinfect surfaces and materials introduced into the hood. Floors were swept daily and mopped a minimum of twice weekly with a commercial detergent. Walls and cage racks were sponged a minimum of once per month with a dilute bleach solution. A cage card or label with the appropriate information necessary to identify the study, dose, animal number and treatment group marked all cages. The temperature and relative humidity were recorded during the study, and the records retained.

Diet

[0072] Animals were fed with sterile Labdiet[®] 5053 (pre-sterilized) rodent chow and sterile water was provided *ad libitum*.

Animal Randomization and Allocations

[0073] Mice were randomly and prospectively divided into eight (8) groups prior to the initiation of treatment. Each animal was identified by ear punching corresponding to an individual number. A cage card was used to identify each cage and marked with the study number (SCI-05), treatment group number and animal numbers.

Assessment of Results

[0074] Statistical differences between treatment groups were determined using Student's *t*-test, Mann-Whitney U test and chi-square analysis with a critical value of 0.05.

Experimental Procedures

[0075] Tumors were measured once every two days with micro-calipers, and tumor volume was calculated as $\frac{4}{3}\pi r^3$, where r is equal to the sum of the length and the width divided by 4. The tumor growth index (TGI) was calculated using the formula $100 \cdot (V_c \cdot 100 / V_t)$, where V_c is the mean volume of the tumors in the control group and V_t is the mean volume of the tumors in the test group.

RESULTS AND DISCUSSION

Survival

[0076] No animal deaths occurred as a direct result of treatment during the course of this study.

Animal Weights

[0077] There were no significant differences in mean daily weight changes between vehicle-treated groups and animals who received SCV-07 as a mono-therapy ($p=0.7$) or in animals who received radiation only and SCV-07 in conjunction with radiotherapy ($p=0.68$). The mice receiving vehicle only gained an average of 13.2% of their starting weight by Day 21. Mice treated with either 100 $\mu\text{g}/\text{kg}$, 1.0 mg/kg or 10 mg/kg SCV-07 gained between 10.2% and 12.3% of their starting weight by Day 21. Mice treated with vehicle and exposed to radiation gained an average of 3.2% of their starting weight by Day 21. Mice treated with either 100 $\mu\text{g}/\text{kg}$, 1.0 mg/kg or 10 mg/kg SCV-07 and were exposed to radiation gained between 2.8% and 3.6% of their starting weight by Day 21.

[0078] The significance of these differences was evaluated by calculating the mean area under the curve (AUC) for the percentage weight change for each animal and comparing the groups using a One-Way ANOVA test.

Tumor Volumes

[0079] Tumor volumes were calculated from the length and width measurements taken on alternating days by calculating the mean radius (r), which was the sum of length and width divided by 4, and using the formula $\frac{4}{3} \pi r^3$ to calculate the volume.

[0080] Tumors from animals treated with 100 $\mu\text{g}/\text{ml}$ grew at rates faster than vehicle control animals. Among the non-irradiated animals, mice treated with 10 mg/kg of SCV-07 showed the best improvement in tumor growth inhibition. The mean tumor volume at the end of the study period for vehicle treated animals was 4436.6 mm^2 , 4923 mm^2 for 100 $\mu\text{g}/\text{kg}$ SCV-07 treated animals, 4033.4 mm^2 for 1 mg/kg SCV-07 treated animals, and 2842.4 mm^2 for 10 mg/kg SCV-07 treated animals.

[0081] Among the irradiated animals, mice treated with 10 mg/kg of SCV-07 showed the best improvement in tumor growth inhibition. The mean tumor volume at the end of the study period for vehicle treated animals was 1618.5 mm^2 , 1322.3 mm^2 for 100 $\mu\text{g}/\text{kg}$ SCV-07 treated animals, 1923.9 mm^2 for 1 mg/kg SCV-07 treated animals, and 962.8 mm^2 for 10 mg/kg SCV-07 treated animals.

[0082] Further analysis of the data was performed by calculating the mean area under the curve (AUC) for the tumor volume for each animal and comparing the groups using a One-Way ANOVA test. This analysis did not reveal significant differences between any of the treated groups and the saline control group ($p=0.13$ for the non-irradiated animals, and $p=0.14$ for irradiated animals). However, a direct comparison of vehicle treated and 10 mg/kg SCV-07 with a Mann-Whitney Rank Sum analysis was significantly different ($p=0.026$).

[0083] The tumor growth inhibition (TGI) was calculated using the formula $100 - (V_c \cdot 100 / V_t)$, where V_c is the mean volume of the tumors in the control group and V_t is the mean volume of the tumors in the test group. Table 2.2 shows the tumor growth inhibition for animals treated with 100 $\mu\text{g}/\text{kg}$, 1 mg/kg , 10 mg/kg SCV-07 alone or in combination with radiation. When compared to unirradiated controls, animals treated with 1 mg/kg SCV-07 alone had a tumor growth inhibition of 9.1%, and animals treated with 10 mg/kg SCV-07 alone had a tumor growth inhibition of 35.9%. Animals treated with radiation alone had a TGI of 63.5% when compared to unirradiated controls, while animals treated with SCV-07

plus radiation had TGI values of 70.2% (100 µg/kg), 50.3% (1 mg/kg) and 78.3% (10 mg/kg). When compared to the group receiving radiation plus vehicle the groups treated with radiation plus SCV-07 had a TGI of 18.3% at 100 µg/kg and 40.5% at 10 mg/kg.

Table 2.2

Group	RT Days 0 and 2	Drug Treatment & Dosing	Mean Tumor Volume (mm ³)	TGI (%)	
1	-	Vehicle	4436.5	-	
2	-	SCV-07 100 µg/kg	4922.8	**	
3	-	SCV-07 1.0 mg/kg 2.0	4033.4	9.1	
4	-	SCV-07 10.0 mg/kg	2842.4	35.9	TGI (%)
5	4 Gy focal	Vehicle	1618.5	63.5	-
6	4 Gy focal	SCV-07 100 µg/kg	1322.3	70.2	18.3
7	4 Gy focal	SCV-07 1.0 mg/kg 2.0	1923.9	50.3	**
8	4 Gy focal	SCV-07 10.0 mg/kg	962.8	78.3	40.5

Table 2.2. Tumor Growth Inhibition (TGI). TGI was calculated from the last tumor measurement using the formula $100 - (V_c * 100 / V_t)$, where V_c is the mean volume of the tumors in the control group and V_t is the mean volume of the tumors in the test group. **Mean tumor volumes in groups 2 and 7 exceeded the vehicle control animals (9.8% and 15.87%, respectively).

CONCLUSIONS

[0084] SCV-07 showed no evidence of toxicity in this study based on observations of survival and weight change.

[0085] Animals treated with 10 mg/kg SCV-07 alone showed significant reduction in tumor growth inhibition (TGI=68%) compared to vehicle control animals (P=0.026).

[0086] Although not statistically significant, animals treated with 100 µg/kg SCV-07 alone or with 1 mg/kg SCV-07 alone showed reductions in tumor growth compared to animals who received vehicle only.

[0087] Although not statistically significant, irradiated animals treated with SCV-07 at 100 µg/kg or 10 mg/kg showed reductions in tumor growth relative to irradiated vehicle control animals.

Appendix 2.1. Daily Animal Weight

Group	No.	Weight	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21	
1	1	24.22	23.81	23.97	23.63	23.56	25.61	23.71	24.2	24.9	24.86	24.85	25.04	25.32	25.44	26.43	26.7	27.62						
1	2	26.48	27.72	27.62	27.73	28.78	27.71	26.36	26.63	26.71	26.69	27.56	27.53	28.21	27.51	28.63	28.19	29.51						
1	3	22.49	22.8	23	23.11	23.34	23.21	23.01	23.63	23.56	23.35	23.38	23.28	24.15	23.8	24.08	24.78	25.38	25.54	25.41	25.19			
1	4	24.89	25.39	25.94	26.71	26.7	28.32	26.85	27.52	27.81	27.06	27.48	27.35	28.08	28.07	29.28	28.96	29.32						
1	5	25.69	25.58	25.8	25.9	25.87	26.23	26.57	26.03	26.75	26.69	26.72	26.94	27.62	28.75	28.16	30.54	31.74						
1	6	24.97	26.54	27.55	29.86	27.7	26.65	25.93	23.93	26.78	27.02	25.66	26.15	26.71	26.56	26.43	26.89	27.13	27.25	26.5	27.43	28.37		
1	7	26.64	27.18	27.39	27.87	28.14	27.48	28.21	28.44	29.11	29.41	30.24	29.65	29.02	27.73	29.23	31.18	26.71						
1	8	27.43	28.12	28.37	28.56	28.72	29.75	29.39	29.93	31.55	31.41	31.86	31.87	33.03	31.77	30.86	30.95	29.79						
1	9	27.24	29.48	29.61	27.56	30.1	30.02	28.98	29.49	29.18	28.77	29.38	28.25	28.62	27.74	27.64	27.7	28.26						
1	10	25.86	24.09	24.59	24.62	25.01	25.4	24.83	25.07	25.34	24.63	24.92	24.89	25.13	25.38	25.07	26.32	27.29	25.84	25.92	25.45	25.87		
1	11	25.04	25.31	25.54	26.03	26.25	26.11	25.31	26.02	26.04	26.3	26.11	26.4	26.11	26.4	25.05	25.37	25.97	26.19					
1	12	25.56	25.86	26.49	25.96	26.02	27.33	26.07	26.81	27.61	27.72	28.4	28.91	28.74	29.76	31.51	31.62	34.89						
2	13	23.33	24.24	23.54	23.25	22.95	23.19	22.44	22.45	22.32	21.63	21.55	21.12	21.27	20.98	26.31	21.55	21.85	22.27	22.56	21.88	23.21		
2	14	23.49	24.15	24.31	24.83	24.17	24.63	24.41	25.4	24.63	24.52	24.68	25.14	25.5	24.94	25.45	25.58	25.81	26.93	26.87	26.82	28.81		
2	15	21.12	21.62	21.57	22.26	22.13	22.87	22.25	23.39	23.39	23.32	24.31	24.12	24.4	23.42	23.95	24.04	24.69						
2	16	25.34	27.17	27.05	27.87	27.63	28.32	27.57	23.43	28.44	28.39	28.42	28.63	28.09	29.02	29.26	29.34	30.14						
2	17	23.81	24.75	24.23	24.51	23.62	24.73	23.65	24.2	24.12	23.75	23.95	24.81	24.69	24.51	24.82	24.86	26.29						
2	18	26.25	27.62	27.72	28.09	27.38	28.41	27.66	27.81	28.18	27.17	27.9	27.09	28.31	27.64	27.53	25.33	27.77						
2	19	23.52	23.55	23.75	24.23	23.98	24.17	24.37	24.12	24.62	24.21	24.76	24.69	25.03	25.71	25.46	27	27.41						
2	20	27.05	28.22	28.04	28.63	28.59	29.52	29.36	31.1	32.42	32.28	33.1	34.51	35.6	36.51	36.88	39.72	39.18	20.08	21.18	22.97	24.47		
2	21	22.89	24.07	24.19	24.54	24.34	24.43	24.43	24.33	24.96	25.24	25.05	25.74	26.22	24.9	25.44	27.65	26.23	19.73	20.08	21.18	22.97	24.47	
2	22	27.22	28.42	27.98	28.47	27.95	29.85	28.35	29.11	27.73	28.12	27.95	28.02	28.93	27.98	24.56	28.01	28.59	29.42	29.76	30.57	31.9		
2	23	24.41	26.08	24.72	24.81	24.42	25.02	24.86	25.63	24.61	24.71	25.01	25.22	25.62	24.64	21.63	25.35	24.08	25.41	25.04	25.04	25.72		
2	24	23.73	24.13	24.83	25.45	24.92	24.63	24.82	24.81	24.8	24.86	24.81	24.8	24.86	26.34	24.13	25.13	24.78	27.14					
3	25	25.6	27.18	27.14	27.96	27.63	28.33	28.33	29.98	28.73	28.68	29.12	28.82	28.13	27.87	26.98	26.7	25.39						
3	26	24.48	25.72	25.6	25.35	25.79	26.31	25.73	25.62	25.99	26.27	25.88	26.65	27.21	26.39	28.39	26.83	27.8						
3	27	24.53	25.21	25.71	25.56	25.23	25.83	25.6	25.34	25.75	2.89	26.11	26.59	27.33	27.02	27.6	27.84	28.91						
3	28	26.48	27.22	26.81	26.82	26.44	26.32	26.14	26.52	26.71	26.76	26.69	27.07	28.31	27.32	27.85	28.03	28.27	27.6	27.85	28.52	28.38		
3	29	26.69	26.89	26.61	27.01	26.81	27.52	27.78	28.06	28.17	27.92	27.84	28.16	28.35	27.72	24.2	28.72	28.18	29.45	29.08	28.73	29		
3	30	23.08	23.45	23.45	23.71	23.81	22.45	24.45	24.81	25.24	25.4	25.72	26.54	26.07	27.71	26.73	27.32	28.44						
3	31	21.47	22.3	22.44	22.49	22.8	24.65	22.6	23.04	23.66	23.85	23.72	23.81	26.41	24.58	24.81	26.4	26.25	26.01	26.47	27.1	28.13		
3	32	27.76	29.54	29.27	29.91	28.77	29.51	29.23	29.95	29.94	29.74	29.44	29.91	30.71	29.75	29.87	30.68	31.4	31.52	33.23	32.54	34.72		
3	33	25.54	26.22	26.23	26.39	25.75	26.85	26.02	26.6	26.62	26.81	27.34	28.09	28.13	28.69	30.12	30.53	31.38						
3	34	28.85	29.47	28.9	29.55	29.01	29.63	28.63	29.19	28.82	29.02	28.41	29.04	24.08	28.48	28.98	28.1	30.11						
3	35	23.89	24.89	24.3	24.82	24.54	24.78	24.83	24.00	24.69	24.43	24.31	24.6	24.55	27.2	25.14	25.13							
3	36	24.13	24.89	24.81	25.01	24.28	24.48	24.01	24.65	24.57	24.65	24.51	24.05	23.71	23.87	23.56	22.98	23.83						
4	37	24.58	25.71	25.71	26.31	23.6	24.12	25.77	25.5	26.46	26.44	26.58	26.08	26.43	26.23	26.5	26.37	26.34	21.6	21.66	22.28	23.08		
4	38	20.02	20.51	19.65	19.79	19.38	20.16	19.24	19.57	19.41	19.38	19.41	19.78	19.36	19.45	19.75	20.46							
4	39	25.88	27.38	27.55	27.37	27.19	27.27	27.32	27.95	27.52	27.55	27.85	27.68	27.61	26.73	26.98	27.26	27.38	23.41	24.23	25.08	25.71		
4	40	20.19	22.33	22.26	22.76	22.92	23.1	22.18	22.21	22.56	22.37	23.11	22.55	22.52	22.05	22.31	22.46	23.34	25.88	28.51	27.22	28.04		
4	41	23.92	25.08	24.56	25.59	25.28	26	25.12	25.19	24.94	25.29	25.66	23.41	25.47	24.42	24.23	23.54	23.85	26.95	27.51	28.16	28.12		
4	42	23.36	25.16	24.82	25.2	24.94	25.29	24.89	24.75	24.56	24.41	24.66	25.02	25.22	24.77	24.17	23.76	26.99						
4	43	23.39	23.33	23.29	23.86	24.32	24.46	24.81	25.58	26.05	25.73	25.84	25.81	25.42	24.52	25.33	24.96	25.19	22.94	22.94	22.94	22.94		
4	44	23.49	24.53	24.49	25.06	24.61	24.45	23.43	23.44	22.79	22.71	23.58	23.09	22.97	21.73	22.43	22.07	22.55	22.94	22.79	23.7	24.01		
4	45	24.75	24.68	24.07	23.84	23.69	23.68	22.81	22.48	21.68	21.03	21.18	20.51	21.32	21.66	21.75	22.04	22.16	22.05	22.22	21.59	21.59		
4	46	25.62	27.02	26.11	26.58	24.98	26.68	28.1	26.24	26.24	26.34	26.11	26.1	24.46	25.69	23.5	25.58	27.28						
4	47	22.16	23.43	23.24	23.52	23.24	26.19	23.4	24.2	26.66	23.62	26.87	24.1	25.32										
4	48	24.93	25.52	25.16	25.52	25.62	26.55	25.96	25.99	25.68	25.32	28.01	26.18	26.16	25.54	26.18	26.32	26.78						

Group	No.	Weight	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21
5	49	25.45	23.69	23.64	22.77	22.99	22.34	23	24.43	23.46	22.09	22.34	22.27	22.51	23.92	23.93	23.93	23.96	24.25	23.71	23.84	24.04	23.88	23.88
5	50	22.69	21.55	21.6	21.13	21.46	21.29	21.97	22.44	22.14	21.96	22.24	22.03	21.99	22.84	22.9	22.96	22.85	22.26	23.37	22.72	23.1	23.09	23.06
5	51	22.49	21.91	21.72	21.36	22.23	22.52	21.94	22.09	22.29	21.85	22.18	22.21	23.01	22.75	22.59	22.49	22.77	22.34	22.71	22.92	22.71	23.06	23.06
5	52	24.85	23.65	23.98	21.15	24.35	24.05	25	23.17	24.61	24.96	25.26	25.44	25.9	26.42	26.25	27.7	27.02	27.14	27.6	28.89	28.4	28.89	28.4
5	53	24.48	23.51	23.84	22.35	23.47	23.63	24.1	24.5	24.36	23.71	24.9	23.27	23.47	23.95	24.22	23.9	23.83	24.12	24.58	24.2	24.24	24.38	24.38
5	54	22.5	21.97	21.72	23.02	21.72	22.27	22.82	22.81	22.48	21.74	22.04	21.96	22.48	23.62	22.83	23.06	22.01	23.18	22.49	23.29	23.29	23.49	23.49
5	55	22.92	22.02	22.58	23.35	21.87	21.2	22.66	24.63	22.56	22.81	22.6	22.36	21.98	22.27	22.26	22.84	22.54	22.68	22.83	22.83	22.83	22.83	22.83
5	56	22.11	21.65	22.34	21.64	21.6	21.65	21.7	22.44	22.25	22.12	21.93	23.4	22.05	22.85	23.44	23.4	23.3	23.17	24.02	23.94	23.31	23.62	23.62
5	57	24.7	23.84	24.03	23.52	23.11	23.34	24.09	23.91	23.46	23.5	23.91	23.4	23.52	23.31	24.24	23.8	24.34	24.01	24.64	23.95	24.14	24.31	24.31
5	58	23.36	22.3	22.63	23.39	22.28	22.91	23.18	23.19	22.74	22.6	22.37	22.12	22.98	23.82	24.05	24.13	23.72	24.07	23.32	23.98	24.17	24.17	24.17
5	59	20.78	20.82	21.29	21.95	21.08	21.18	22.18	22.5	22.69	21.8	22.4	22.36	22.29	22.5	22.63	22.72	22.34	22.29	22.82	22.54	22.85	22.9	22.9
5	60	23.92	22.52	22.39	21.95	22.16	21.74	23.12	23.14	23.12	23.47	23.09	23.83	24.33	24.26	24.64	25.61	25.34	24.49	25.32	24.44	24.81	24.3	24.3
6	61	22.89	21.71	25.97	21.95	22.16	22.13	24.02	23.7	25.46	23.56	22.12	22.95	23.05	23.1	23.91	23.04	23.36	23.07	26.33	23.31	23.35	22.89	22.89
6	62	24.82	23.09	24.21	23.47	22.91	23.05	25.92	23.81	23.29	23.21	22.07	22.86	23.1	23.12	23.82	23.59	23.85	23.87	24.11	23.92	24.69	24.49	24.49
6	63	23.65	23.25	22.8	21.63	21.92	21.2	23.09	23.1	22.96	22.85	22.83	23.05	23.41	23.35	24.42	24.02	24.3	23.95	25.3	24.55	24.5	24.5	24.5
6	64	24.93	24.12	24.3	24.45	23.21	23.62	24.57	25.81	25.21	25.2	24.96	25.12	25.3	25.96	27	26.72	27.14	26.99	28.62	28.12	28.4	28.41	28.41
6	65	23.84	22.14	23.43	22.79	22.89	22.42	24.34	24	24.33	23.84	23.86	23.95	24.28	24.28	24.35	24.12	24.25	24.34	24.36	24.17	24.89	24.72	24.72
6	66	26.09	25.53	25.98	26.26	26.19	25.9	26.74	26.36	24.52	25.47	23.72	25.4	25.34	25.84	26.7	25.82	25.86	24.7	26.38	26.39	26.28	26.28	26.28
6	67	23.31	22	22.91	22.7	23.01	23.14	23.95	23.8	23.98	23.56	23.62	23.77	23.68	23.84	24.67	23.71	24.02	21.74	22.02	23.92	24.14	24.47	24.47
6	68	22.97	21.12	23.22	22.21	22.45	22.42	24.25	24.5	24.08	24.2	24.34	24.07	24.18	24.19	24.52	24.09	24.06	23.41	24.03	23.56	23.77	24.13	24.13
6	69	23.84	22.63	23.68	22.79	22.05	22.4	23.89	23.62	23.69	22.64	23.69	23.51	23.6	23.52	23.56	23.25	23.41	23.15	23.53	23.24	23.29	23.05	23.05
6	70	23.82	22.31	22.74	22.16	21.1	21.99	22.23	22.23	22.49	24.04	21.86	23.05	21.74	22.19	22.88	22.37	22.62	22.74	23.6	22.98	23.17	23.32	23.32
6	71	26.44	24.89	22.06	25.35	25.13	24.83	25.75	26	22.15	25.49	25.05	25.43	25.42	25.84	26.4	25.92	26.09	25.37	25.42	25.86	25.47	26.12	26.12
6	72	21.95	22.06	22.2	22.22	22.3	22.22	22.65	22.58	23.05	22.61	22.69	22.95	23.09	22.96	23.62	23.01	23.3	23.14	23.9	23.27	23.71	23.96	23.96
7	73	22.83	22.26	23.32	22.78	22.8	22.95	23.76	25.4	23.21	22.92	24.16	23.14	23.28	22.7	23.61	23.01	23.68	22.9	23.58	22.76	23.57	23.38	23.38
7	74	26.37	28.09	28.17	27.24	27.65	26.79	28.34	27.5	21.55	28.06	28.21	28.34	28.69	29.35	30.05	29.92	30.36	29.74	30.97	30.28	30.88	30.92	30.92
7	75	24.41	24.1	25.07	24.22	24.66	23.59	25.14	25.06	24.48	24.17	23.19	24.9	25.28	25.08	25.3	25.04	25.57	25.48	26.88	26.73	27.24	26.61	26.61
7	76	21.98	21.87	22.43	21.12	21.73	21.43	22.72	22.83	25.59	22.67	22.72	22.06	23.54	22.78	23.81	25.21	25.12	24.35	25.3	23.58	25.41	24.83	24.83
7	77	26.33	25.4	25.08	25.22	24.83	24.4	26	26.19	25.39	25.82	21.48	26.1	26.43	25.71	26.99	26.69	26.69	26.26	26.26	25.84	26.66	26.49	26.49
7	78	25.94	25.13	25.6	24.85	24.27	23.71	24.63	25.18	24.93	24.82	25.22	25.25	25.56	25.83	27.3	27.12	27.53	27.62	28	28.37	29.64	30	30
7	79	25.68	23.05	23.34	22.79	23.14	22.89	24.14	24.71	23.65	23.74	23.82	24.55	24.72	24.83	25.53	23.22	23.63	22.96	24.21	24.13	25.01	25.3	25.3
7	80	25.4	22.96	22.97	22.8	22.98	22.23	23.44	23.15	22.89	22.35	22.58	22.54	22.8	22.93	23.51	23.04	23.42	23.11	24.06	23.26	24.04	24.43	24.43
7	81	23	22.7	22.97	22.7	23.73	23.51	24.73	25.38	24.1	24.28	24.56	24.18	24.22	24.12	24.77	24.26	24.45	23.58	24.66	23.28	24.33	23.67	23.67
7	82	25.84	22.8	23.04	22.92	22.45	22.39	23.47	23.84	23.58	23.74	23.4	23.83	23.92	23.94	24.6	24.48	25.02	24.62	25.5	25.12	25.77	26.98	26.98
7	83	24.81	23.44	23.52	23.88	23.27	23.05	24.04	24.06	23.54	23.11	2.1	22.92	22.92	23.26	24.15	23.41	23.73	23.42	23.4	23.26	23.89	23.49	23.49
8	85	20.9	20.3	20.66	20	20.98	21.13	21.2	21.34	21.13	21.07	24.83	21.43	21.42	21.55	21.86	21.25	21.48	21.21	21.63	20.67	21.22	21.14	21.14
8	86	24.4	24.05	24.64	24.33	24.59	24.49	24.42	24.55	24.53	24.78	24.21	22.94	24.99	24.78	25.47	24.65	24.92	24.85	25.25	23.82	24.6	24.4	24.4
8	87	23.39	22.8	22.18	22.23	22.24	21.56	23.84	23.26	22.42	22.39	25.01	23.27	23.29	24.39	23.58	23.62	23.44	24.28	23.31	23.62	23.38	23.38	23.38
8	88	24.43	23.33	23.76	22.92	23.42	23.44	24.67	25	23.87	23.48	24.73	23.7	23.96	24.1	24	23.48	23.85	23.71	23.54	23.68	24.15	23.94	23.94
8	89	24.05	23.35	23.76	23.45	24.65	24.16	25.63	25.26	24.19	24.41	24.62	24.73	24.96	24.54	25.61	25.07	25.59	25.42	25.98	25.74	26.05	26.01	26.01
8	90	25.52	22.27	23.37	22.53	23.46	24.26	24.66	24.58	24.52	24.76	21.15	24.87	24.13	25.02	25.14	25.62	25.23	25.14	25.97	26.08	25.97	26.08	26.08
8	91	20.28	19.98	22.79	20.98	20.46	20.32	20.87	20.8	20.45	23.6	21.7	21.49	21.66	23.7	22.67	22.05	23.3	22.13	22.33	21.76	22.16	22.13	22.13
8	92	24.88	24.09	24.75	24.12	25.01	24.12	25.41	25.5	25.19	24.83	23.38	25.45	25.79	25.77	26.68	26.97	25.91	25.87	25.63	25.31	25.37	25.44	25.44
8	93	25.69	24.97	25.07	24.28	24.77	23.02	23	22.6	22.53	22.94	23.96	24.51	24.14	23.96	25.65	24.89	25.59	25.1	26.14	25.55	26.35	25.44	25.44
8	94	23.88	23.13	23.35	22.98	22.9	22.54	23.33	24.9	23.89	20.91	25.51	21.43	23.87	23.44	23.92	23.12	23.42	23.17	23.93	23.27	24.25	24.42	24.42
8	95	23.66	23.6	23.22	23.92	22.6	22.27	21.5	23.8	24.9	23.89	20.91	25.51	21.43	23.87	23.44	23.92	23.12	23.42	23.17	23.93	23.27	24.25	24.42
8	96	23.71	23.14	21.22	23.25	23.78	23.54	24.61	24.41	24.18	23.72	23.72	23.63	23.69	24.99	25.81	25.44	23.69	23.22	23.72	22.86	23.38	23.42	23.42

Appendix 2.2. Tumor Dimensions

Group	No.	Day 1		Day 3		Day 5		Day 7		Day 9		Day 11		Day 13		Day 15		Day 17		Day 19		Day 21	
		Dim 1	Dim 2	Dim 1	Dim 2	Dim 1	Dim 2	Dim 1	Dim 2	Dim 1	Dim 2	Dim 1	Dim 2	Dim 1	Dim 2								
1	1	11.23	6.75	13.44	8.83	14.47	9.6	14.02	10.75	9.85	14.29	16.52	14.44	21.32	14.99	21.35	14.76	20.58	16.71				
1	2	6.51	4.01	7.53	5.82	6.77	8.31	8.16	9.9	10.12	10.96	13.53	11.71	14.06	12.14	16.09	15.87	16.35	18.98				
1	3	4.77	7.57	8.29	5.57	6.24	9.06	8.36	6.27	6.73	7.77	12.71	8.85	13.45	8.38	14.28	11.05	17.99	13.4	13.85	19.42	22.3	17.45
1	4	8.27	6.22	9.6	9.1	11.04	9.94	77.67	12.07	12.55	11.35	18.17	14.51	18.13	15.99	21.29	19.38	16.76	23.73				
1	5	8.16	10.21	11.38	8.81	13.41	9.91	10.29	17.33	16.09	10.81	15.96	13.5	17.45	14.31	15.75	17.07	12.92	17.4				
1	6	3.46	3.67	4.89	7.05	4.59	6.72	6.44	7.48	8.13	12.38	9.66	13.63	10.62	15.14	14.67	16.49	15.61		17.74	18.2	20.47	18.67
1	7	13.81	10.99	17.4	13.99	15.29	20.56	21.5	17.35	22.19	18.02	25.16	21.95	24.02	22.39	16.47	22.3	23.66	20.94				
1	8	11.45	10.85	14.07	12.06	15.37	13.72	15.13	18.73	20.43	18.34	23.77	21.23	28.22	22.3	26.22	23.8	18.27	20.22				
1	9	6.97	5.1	9.81	6.33	8.99	5.79	9.91	8.11	8.35	8.74	13.99	10.9	13.21	12.03	12.23	13.97	16.11	16.94				
1	10	12.56	7.66	13.52	10.15	15.22	10.4	14.35	11.46	16.27	10.62	19.28	13.71	19.5	14.35	14.96	21.79	24.59	16.15				
1	11	6.19	7.19	6.74	5.01	6.9	4.88	5.84	4.41	3.04	4.11	6.95	4.97	6.29	4.77	6.75	7.06	7.61	7.54	8.53	7.75	10.73	9.41
1	12	8.89	8.57	12.78	10.4	15.82	13.3	15.55	14.08	15.47	15.91	25.78	21.27	27.33	24.59	27.39	24.56	28.2	32.78				
2	13	4.84	4.53	5.08	4.06	7.53	5.59	8.12	5.97	5.25	7.18	10.04	6.98	11.2	7.32	10.84	7.86	9.76	14.5	15.2	11.81	11.65	17.98
2	14	3.54	5.66	6.88	5.36	6.63	6.29	7.82	6.6	6.96	6.86	13.55	10.75	12.85	10.32	12.45	12.17	18		17.11	19.26	23.23	15.62
2	15	6.42	8.48	8.34	7.4	8.24	8.73	10.19	10.57	9.69	12.41	17.02	13.82	16.14	15.71	15.79	16.01	18.84	20.51				
2	16	6.89	7.29	8.77	8.13	11.89	9.32	14.72	10.48	13.17	11.54	22.2	16.26	24.46	16.15	21.06	16.57	21.33	19.04				
2	17	8.38	6.42	9.6	7.75	9.32	10.5	10.45	9.54	12.71	10.67	15.68	13.61	17.05	13.82	16.79	17.23	17.77	18.64				
2	18	4.05	4.15	7.29	4.45	6.98	5.28	5.6	8.47	6.34	7.1	12.8	9.45	14.32	9.81	14.88	14.31	13.15	16.82				
2	19	10.05	6.81	13.57	8.24	14.72	9.63	10.53	18.09	12.48	19.39	25.23	17.05	18.23	16.25	25.51	22.54	30.53					
2	20	12.12	12.56	13.9	11.89	18.42	12.63	16.3	20.47	20.7	16.15	26.53	19.84	26.76	24.31	32.03	31.56	33.33	29.77				
2	21	10.25	8.18	13.2	8.91	13.91	9.32	8.65	14.5	10.76	15.12	19.82	16.32	13.18	10.73	10.37	13.46	16.79	14.4	17.8	18.91	18.09	21.6
2	22	4.77	5.84	7.02	6.41	7.24	6.5	6.86	7.3	6.18	5.04	11.01	9.3	11.85	8.77	21.41	17.2	12.74	16.81	22.38	20.76	23.51	18.06
2	23	5.99	4.81	6.89	4.51	5.03	6.28	4.24	6.5	4.39	6.24	8.54	7.08	8.94	6.24	6.26	8.57	8.8	11.28	11.93	11.45	9.88	10.99
2	24	5.76	4.2	5.96	4.57	5.54	4.42	6.88	6.48	6.14	6.01	10.64	8.96	20.32	16.24	20.23	16.57	21.3	20.29				
3	25	9.69	8.01	12.16	10.13	14.51	11.34	18.26	14.58	19.51	16.81	22.36	19.62	23.61	20.15	14.4	15.98	18.93	18.17				
3	26	5.53	3.9	7.45	6.39	7.41	8.2	7.97	9.75	9.39	10.2	14.88	12.62	15.64	13.6	12.94	16.9	17.15	20.18				
3	27	6.17	6.66	8.76	6.86	8.82	7.75	6.87	12.04	9.43	11.69	16.35	11.46	17.6	13.56	19.41	17.28	19.16	23.35				
3	28	6.74	3.05	9.08	5.81	8.28	4.4	5.68	8.91	6.62	8.06	11.61	7.89	11.74	7.05	12.99	8.78	14.08	9.5	11.06	12.96	15.08	13.54
3	29	7.15	8.85	9.65	7.53	8.09	8.23	6.18	6.63	5.76	7.41	14.25	14.32	13.21	11.2	13.23	13.41	15.05	13.89	16.57	17.01	17.88	15.95
3	30	11.72	9.87	20.48	11.1	21.87	10.89	11.71	22.31	12.86	21.75	28.05	16.89	30.33	16.65	30.61	23.09	18.18	28.13				
3	31	6.98	9	10.68	7.52	13.18	7.81	11.11	9.86	11.3	11.28	15.86	11.71	13.73	10.5	21.06	15.59	16.56	20.96	19.42	22.48	18.14	24.31
3	32	3.62	3.69	5.36	4.4	5.43	4.77	5.62	6.73	6.76	7.29	11.7	9.53	12.07	8.72	13.55	14.5	17.04	17.67	21.72	23.21	20.87	24.54
3	33	9.12	6.29	11.14	8.03	12.06	7.9	14.05	10.38	10.03	15.54	22.54	13.52	23.17	14.48	23.12	19.47	19.81	26.93				
3	34	4.55	6.01	7.04	4.84	6.23	5.22	6.51	7.47	7.14	7.64	11.31	10.08	10.33	14.85	12.13	15.14	12.96	15.14				
3	35	7.14	6.32	7.8	5.36	7.77	5.16	8.42	6.01	7.12	8.04	11.4	9.88	12.78	10.49	16.96	19.19	15.96	12.68				
3	36	10.31	11.39	14.47	14.08	13.00	12.78	15.83	14.87	16.31	24.69	21.6	19.63	21.43	20.15	19.31	19.88	20.77	20.89				
4	37	9.04	7.21	12.55	8.46	13.59	10.41	10.01	15.32	14.14	13.4	18.11	15.42	19.86	15.86	20.45	18.74	23.04	19.09				
4	38	7.09	5.5	8.32	5.72	7.12	4.91	6.23	6.1	6.39	7.39	11.37	9.07	11.11	10.18	11.18	13.29	12.74	13.63	18.16	17.13	23.01	19.45
4	39	8.65	7.98	9.65	6.35	6.59	7.45	8.25	10.87	11.42	9	15.86	10.8	14.8	9.05	16.45	13.87	11.89	18.66				
4	40	6.12	5.22	9.09	6.36	7.67	7.8	6.5	9.14	5.82	7.17	10.87	8.75	14.35	8.41	14.28	8.45	18.58	10.26				
4	41	7.38	4.89	8.72	6.19	7.06	6.88	7.32	9.37	6.89	8.22	13.85	10.31	14.74	9.73	13.23	13.2	14.22	16.73				
4	42	3.97	7.08	6.98	6.5	8.9	10.25	9.34	8.63	9.02	11.35	14.75	13.85	16.48	15.74	19.32	17.88	14.88	20.38				
4	43	10.34	8.19	12.71	9.88	10.54	12.11	11	9.47	11.69	10.5	13.68	11.98	13.49	11.45	12.88	11.79	13.66	13.5				
4	44	4.47	3.88	5.33	4.7	5.16	5.3	5.02	5.57	4.75	5.31	6.11	6.52	8.62	6.81	7.85	5.06	11.55	12.82				
4	45	7.65	3.88	7.64	4.56	6.32	4.64	3.88	7.24	2.9	6.06	9.27	4.88	8.65	3.92	8.42	7.96	6.19	7.81				
4	46	4.5	5.66	7.46	5.54	7.11	6.5	6.18	8.11	7.82	6.55	12	9.93	14.6	15.54	12.63	11.89	16.77	14.28				
4	47	7.28	6.59	9.49	8.19	9.39	10.33	12.59	12.84	13.18	13.46	17.15	15.96	13.45	12.32	14.45	14.12	15.7	13.55				
4	48	9.23	8.72	10.64	10.48	9.93	11.81	11.32	12.52	11.93	12.38	16.47	14.18	16.54	15.08	16.45	14.87	15.73	17.1				

Group	Animal	Day 1		Day 3		Day 5		Day 7		Day 9		Day 11		Day 13		Day 15		Day 17		Day 19		Day 21		
		Dim 1	Dim 2	Dim 1	Dim 2	Dim 1	Dim 2	Dim 1	Dim 2	Dim 1	Dim 2	Dim 1	Dim 2	Dim 1	Dim 2									
5	49	9.49	9.71	9.18	10.31	9.7	9.41	9.52	10.04	10.18	10	10.87	9.64	12.09	10.93	11.97	12.13	11.47	10.65	12.97	11.22	12.57	13	
5	50	7.47	6.33	6.75	7.19	9.51	7.36	10.47	8.65	11.33	9.95	11.88	9.53	13.1	10.91	14.74	11.75	10.98	14.4	14.31	16.83	18.2	15.15	
5	51	7.23	5.98	7.35	7.88	7.93	8.95	6.73	9.57	10.26	8.81	9.63	8	10.85	9.53	10.49	9.23	7.76	9.69	9.76	12.34	12.61	10.82	
5	52	7.09	5.57	5.07	5.54	7.05	6.17	7.53	6.12	9.92	8.31	11.56	6.32	10.79	10.01	16.71	10.98	14.97	8.84	15.34	21.77	24.85	18.24	
5	53	9.83	6.12	7.65	6.4	6.31	10	9.58	6.5	12.39	7.05	12.35	7.05	14.12	9.41	15.2	10.08	9.46	14.6	10.58	16.77	18.06	12.73	
5	54	4.08	4.89	4.78	5.1	4.28	4.09	4.64	4.65	5.62	5.37	5.92	4.76	7.75	7	8.1	6.92	7.05	6.53	9.12	8.71	10.77	9.41	
5	55	7.36	6.04	6.49	6.27	7.3	8.33	8.09	9.66	9.34	8.36	9.17	7.74	11.17	11.17	10.93	9.58	12.17	10.03	10.54	11.13	11.85	14.17	12.35
5	56	4.01	4.94	4.26	4.35	4.73	6.33	3.85	6.2	5.43	4.01	5.48	3.53	5.58	4.09	4.27	3.88	12.78	4.55	3.49	3.83	3.9	3.44	
5	58	7.77	13.35	13.18	8.13	14.28	6.22	9.18	14.37	16.21	10.76	17.40	9.94	18.89	12.1	20.31	12.14	10.48	17.07	20.83	13.15	21.61	13.98	
5	59	4.12	4.48	4.25	5	4.03	5.05	4.37	6.06	8.19	7.22	6.54	6.13	9.32	9.7	6.14	6.92	6.6	7.21	9.63	13.39	14.81	11.07	
5	60	9.7	8.58	8.6	9.13	9.31	8.17	7.44	8.49	9.64	7.9	9.31	7.92	10.26	9.23	6.75	9.23	7.94	8.65	8.33	9.96	10.47	9.66	
6	61	6.82	6.46	6.59	6.94	7.69	7.42	7.42	8.01	8.7	7.96	9.44	8.46	10.68	10.4	12.49	10.79	10.16	9.84	11.05	12.89	14.96	12.71	
6	62	4.92	4.6	4.39	4.7	5.76	4.43	6.18	4.31	5.9	4.93	6.2	5.62	6.38	6.19	6.53	6.89	6.32	7.34	2.95	8.1	9.89	8.11	
6	63	9.81	8.57	10.51	8.01	10.51	8.89	9.38	10.24	12.08	10.31	12.44	9.47	13.8	10.89	14.01	11.48	10.3	13.32	11.04	15.63	16.66	12.54	
6	64	5.49	4.8	6	4.06	6.26	4.62	3.92	5.99	8.26	6.58	7.8	5.92	9.84	7.34	10.1	7.97	7.97	9.16	10.69	12.28	14.75	13.16	
6	65	9.3	7.24	9.91	7.86	9.99	8.34	10.59	8.13	12.15	10.83	12.62	10.59	14.37	12.27	14.96	12.79	11.07	14.3	12.98	16.64	18.7	15.76	
6	66	6.33	6.13	7.04	7.37	6.49	7	6.68	8.23	10.54	8.11	9.17	7.88	13.18	13.18	10.01	13.53	10.67	9.79	13.22	11.63	14.52	15.87	12.99
6	67	11.04	9.33	9.11	10.8	11.9	8.92	11.6	8.52	13.57	11.01	14.56	12.47	15.41	13.2	15.09	12.5	10.88	15.16	12.63	17.44	14.04	18.36	
6	68	5.96	3.96	5.07	4.74	4.3	5.71	5.52	7.34	8.3	6.39	8.98	6.33	10.91	8.6	10.9	8.98	7.62	8.25	9.7	11.43	13.98	12.23	
6	69	3.72	6.91	6.15	3.83	3.66	3.93	5.97	2.9	6.87	4.64	4.11	2.86	6.08	4.75	7.01	5	6.68	5.11	9.24	6.8	7.66	10.69	
6	70	5.34	4.53	4.65	5.11	5.87	5.65	7.47	6.97	7.82	6.61	7.56	6.02	8.17	7.51	9.9	8.34	7.42	9.11	9.18	12.12	13.39	10.73	
6	71	8.94	9.19	8.99	9.19	9.84	10.06	8.75	9.25	10.98	10.19	11.64	10.33	12.6	11.64	12.05	11.82	11.03	10.47	11.69	12.15	12.46	12.27	
6	72	5.44	4.16	5.49	4.02	6.27	5.2	4.46	5.1	7.16	6.11	6.62	5.59	7.77	6.9	9.15	8.25	8.52	8.03	10.05	11.17	13.51	11.9	
6	73	5.14	5.89	7.07	4.42	6.69	6.4	5.57	5.56	7.27	7.49	8.24	5.5	7.97	6.81	9.22	8.81	5.31	6.14	7.4	6.85	9.34	6.27	
7	74	3.73	3.54	4.89	4	4.68	5.11	5.97	6.03	7.02	6.52	6.48	6.47	7.98	6.99	9.07	9.21	8.06	7.01	9.67	8.5	10.02	10.26	
7	75	6.56	7.7	8.19	6.93	8.89	8.33	8.93	12.05	11.57	10.46	12.83	10.96	13.55	12.91	19.86	13.64	11.23	15.82	22.18	17.03	21.08	15.7	
7	76	8.1	7.18	7.65	8.7	10.41	9.42	9.19	8.9	11.68	10.55	15.83	12.19	19.36	13.82	12.49	10.27	9.88	11.45	22.24	15.6	25.55	15.85	
7	77	12.47	7.06	13.84	6.89	13.66	8.61	8.85	13.11	15.37	9.72	15.76	10.32	17.14	11.42	17.77	12.71	11.55	16.02	12.12	17.08	18.09	13.08	
7	78	7.13	6.2	6.19	9.41	9.68	9.03	10.73	9.22	14.01	12.06	14.29	9.36	4.59	12.76	19.67	13.85	17.26	14.56	16.31	21.44	21.77	17.17	
7	79	4.88	5.23	5.63	6.06	6.84	6.52	6.35	6.23	7.74	8.21	9.1	7.52	10.24	8.77	14.62	13.84	12.17	12.56	15.01	14.76	14.7	14.45	
7	80	5.98	7.5	7.6	8.5	7.65	7.08	7.24	7.58	9.27	8.19	9.06	7.85	9.96	10.14	12.08	10.21	9	10.96	10.89	13.23	14.65	12.09	
7	81	6.55	7.61	8.32	9.61	8.65	9.78	10.33	8.6	12.19	10.46	11.63	10.14	13.17	11.86	14.48	13.89	12.07	15.04	13.43	16.15	17.68	13.8	
7	82	13.57	13.13	14.97	14.63	15.81	14.44	14.57	16.03	15.44	16.73	17.19	15.63	19.51	18.84	19.88	19.05	14.79	19.22	21.24	17.45	20.1	23.22	
7	83	7.51	8.53	8.47	8.66	9.64	8.21	8.73	8.83	10.54	9.19	12.05	9.04	12.2	10.6	13.11	11.42	9.75	12.22	11.63	13.48	14.51	11.88	
7	84	5.3	4.04	4.65	5.18	5.9	6.05	7.19	6.44	8.44	7.35	7.2	6.37	10.57	8.4	10.82	11.11	6.7	9.94	8.65	11.02	11.18	8.55	
8	85	4.13	5.25	3.91	3.13	5.67	6.5	5.54	3.63	7.09	6.6	5.82	4.57	6.85	5.85	6.26	6.31	6.31	5.82	7.63	6.63	8.49	7.5	
8	86	5.5	4.8	5.19	4.33	10.31	5.89	6.34	4.43	12.06	8.69	6.59	4.62	7.77	6.98	7.81	6.97	7.17	6.54	8.52	6.74	11.8	9.9	
8	87	3.58	4.11	3.73	4.44	6.08	4.28	4.69	5.55	6.47	5.2	9.94	7.62	8.04	6.13	7.69	6.22	6.79	7.66	8.35	8.68	11	9.4	
8	88	7.66	4.17	7.99	4.76	5.31	5.09	8.64	8.99	6.4	10.47	12.63	8.18	13.08	10.51	13.92	10.86	12.97	10.52	12.64	16.14	17.29	14.33	
8	89	4.84	6.8	5.26	7.88	9.43	5.81	6.11	9.03	7.31	6.16	12.53	8.16	10.33	8.18	10.51	13.92	10.86	12.97	10.52	12.64	16.14	17.29	14.33
8	90	5.04	6.53	5.82	6.16	5.11	5.35	4.64	6.47	7.9	6.88	8.72	5.87	8.22	7.34	8.58	6.64	8.04	6.3	8.54	10.85	12.08	9.59	
8	91	6.75	5.46	7.4	5.38	7.02	7.02	8.44	8.42	9.04	9.31	7.38	9.92	11.05	7.99	9.86	10.8	9.5	9.56	11.17	10.96	12.65	13.3	
8	92	6.56	4.56	6.25	6.7	7.8	6.67	7.28	6.73	9.31	7.38	9.92	7.18	10.61	8.24	11.54	9.32	10.43	10.19	11.76	10.26	13.44	10.55	
8	93	10.32	11.25	9.48	11.54	12.53	9.89	11.31	9.47	12.52	10.2	7.59	5.11	13.76	9.84	14.22	12.03	13.13	12.4	11	13.89	14.89	12.07	
8	94	6.92	4.94	6.65	6.51	6.14	7.16	5.96	7.26	9.12	8.71	5.82	4.57	10.52	8.03	9.7	7.6	8.43	9.29	8.2	9.18	10.47	13.37	
8	95	15.76	9.75	8.81	15.01	15.14	9.2	15.76	7.7	11.54	9.42	11.75	9.1	13.44	10.24	13.32	10.93	10.05	11.42	13.82	12.28	13.16	15.81	

Appendix 2.3 Tumor Weights (in grams)

Group	Animal #	Weight
1	1	4.83
1	2	2.2
1	3	3.084
1	4	4.042
1	5	1.38
1	6	5.76
1	7	4.778
1	8	3.488
1	9	1.78
1	10	3.667
1	11	0.416
1	12	10.6
2	13	1.85
2	14	
2	15	2.95
2	16	5.84
2	17	2.56
2	18	1.56
2	19	7.102
2	20	16.56
2	21	3.878
2	22	4.74
2	23	0.866
2	24	2.821
3	25	3.26
3	26	2.64
3	27	3.126
3	28	1.674
3	29	3.22
3	30	5.65
3	31	5.194
3	32	5.36
3	33	5.35
3	34	0.994
3	35	1.01
3	36	2.91
4	37	3.7
4	38	5.116
4	39	0.928
4	40	3.142
4	41	4.344
4	42	9.198
4	43	0.766
4	44	1.77
4	45	0.332
4	46	1.31
4	47	1.448
4	48	1.38

Group	Animal #	Weight
5	49	0.74
5	50	1.36
5	51	0.47
5	52	2.43
5	53	1.04
5	54	0.41
5	55	0.66
5	56	0.7
5	57	0.02
5	58	1.19
5	59	0.57
5	60	0.35
6	61	0.76
6	62	0.17
6	63	0.98
6	64	0.83
6	65	1.76
6	66	0.83
6	67	1.04
6	68	0.63
6	69	0.23
6	70	0.51
6	71	0.68
6	72	0.45
7	73	0.1
7	74	0.3
7	75	2.83
7	76	3.93
7	77	1.32
7	78	3.3
7	79	1.22
7	80	0.72
7	81	1.24
7	82	3.52
7	83	0.91
7	84	0.43
8	85	0.31
8	86	0.39
8	87	0.31
8	88	0.33
8	89	1.05
8	90	0.49
8	91	0.64
8	92	0.48
8	93	0.67
8	94	0.62
8	95	
8	96	0.89

Example 3**An Anti-Tumor Efficacy Study of Combined Treatment of SCV-07 and Cisplatin in Mice Bearing Subcutaneous LLC Tumor****Abbreviations**

BW	Body Weight
CO ₂	Carbon Dioxide
CDDP	Cis-Diamine Dichloroplatinum (Cisplatin)
g	Gram
kg	Kilogram
L	Length
LLC	Lewis Lung Carcinoma
mg	Milligram
mL	Milliliter
PBS	Phosphate Buffered Saline
PI	Percent Inhibition
SD	Standard Deviation
TV	Tumor Volume
TW	Tumor Weight
VBI	Vital Bridge (China), Inc.
W	Width

Summary

[0088] In this study, the inhibitory effect of SCV-07 along with cisplatin (CDDP) was evaluated on the growth of a subcutaneous cancer grown from murine Lewis lung carcinoma (LLC) cells inoculated in C57/BL6 mice. A total of 70 mice were implanted subcutaneously with murine LLC cells, followed by treatment with SCV-07 or CDDP alone or in combination for 14 consecutive days. SCV-07 was administered daily by *sc* injection, while CDDP was administered by *ip* injection on days 1, 6, and 12. In total, 7 groups were used: Group 1: vehicle; Group 2: CDDP 2 mg/kg; Group 3: CDDP 6 mg/kg; Group 4: SCV-07 10 mg/kg; Group 5: SCV-07 20 mg/kg; Group 6: SCV-07 10 mg/kg plus CDDP 2 mg/kg; Group 7: SCV-07 20 mg/kg plus CDDP 2 mg/kg. Body weights were recorded once every 3 days, tumor sizes were measured once every other days, and tumor weights were measured on Day 16 (necropsy day) at the end of the study.

[0089] Throughout the course of the study, no animal died. The statistical results of body weights showed no significant differences between either of SCV-07 treatment alone groups (Groups 4 and 5) and the vehicle control group (Group 1), indicating no effect of SCV-07 on animal growth. By contrast, from Day 3 onwards, the group receiving 6 mg/kg CDDP treatment (Group 3) consistently showed statistically significant decreases in body weight. Group 2, the group receiving 2 mg/kg CDDP treatment, showed statistically significant decreases in body weight only on Day 15, while Group 7, which received 2 mg/kg CDDP in combination with 20 mg/kg SCV-07, consistently exhibited statistically significant decreases in body weight relative to Group 1 from Day 3 onwards.

[0090] Tumor measurement data showed that the mean tumor volumes of Group 2 and Group 3 were statistically significantly smaller than that of Group 1 on Day 6. On Days 8, 10, 12 and 14, the mean tumor volumes of all groups were statistically significantly smaller than Group 1. On Day 16, the mean tumor weights of all treatment

groups were lower than Group 1. The tumor inhibition calculated based on tumor weight were 58.90% ($p < 0.01$), 77.35% ($p < 0.01$), 16.84% ($p < 0.05$), 37.45% ($p < 0.01$), 40.81% ($p < 0.01$) and 56.13% ($p < 0.01$), for Group 2, Group 3, Group 4, Group 5, Group 6, and Group 7, respectively.

[0091] In summary, the tumor model used in this study was valid as the positive control drug CDDP effectively reduced the tumor growth. Treatment with SCV-07 (10 mg/kg or 20 mg/kg) inhibited tumor growth as reflected by the smaller tumor volumes and lower tumor weights in these groups relative to those of the vehicle control group. The treatment regimens of SCV-07 (10 or 20 mg/kg) in combination with CDDP (2 mg/kg) led to higher inhibition of tumor growth than SCV-07 treatment alone, but without increased anti-tumor efficacy compared to CDDP alone (no additive effect).

Introduction

[0092] This study was designed to evaluate the anti-tumor effect of SCV-07 used alone or in combination with CDDP in murine Lewis lung cancer (LLC) model in order to explore its therapeutic potential for the treatment of lung cancer. CDDP was also used as the positive control drug to validate the cancer model.

Materials and Methods

Test and Control Articles

[0093] PBS was used as the negative control article (vehicle), and CDDP as the positive control. CDDP was purchased from PUMC hospital. Manufactured by Qilu Pharmaceutical Co., LTD, each vial of the medicine contains 10 mg CDDP powder. Prior to use, PBS was added to one vial of CDDP to achieve the proper dose level as indicated in the dose formulation table (Table 3.1). The formulation was kept on ice, protected from light, and used immediately. Test article (SCV-07) was dissolved in PBS

to achieve the proper dose levels as indicated on table1; kept on ice, protected from light, and used within one week.

Table 3.1: Dose Formulation

Treatment	Dose level (mg/kg)	Dose Volume (mL/kg)	Concentration (mg/mL)
SCV-07	10	5	2
	20	5	4
CDDP	2	5	0.4
	6	5	1.2

Test System and Animal Husbandry

Murine Lung Cancer Cells (LLC)

[0094] Murine Lewis lung cancer cells were obtained from the Cell Culture Center of Chinese Academy of Medical Sciences (CAMS; Beijing, P. R. China). The cancer cells were adapted in C57BL/6 mice before used in experiment. Refer to Section 4.3.1 for details on cell adaptation.

Test System

[0095] Thirty-five male and thirty-five female, healthy, naive, C57BL/6 mice were received from the Institute of Laboratory Animal Science, CAMS, Beijing, P. R. China. The animals were six weeks old and weighed between 18 and 22 grams at the start of the study.

Animal Husbandry

[0096] Animals were group-housed in autoclaved shoe box cages with autoclaved wood chips as the bedding materials. The temperature of the animal room was maintained at 22 to 25°C, and the relative humidity was maintained at 40 to 60%. A 12-hour light/12-hour dark cycle was maintained except when interrupted by study-related events. Animals were fed *ad libitum* with sterile water and Beijing KeAoXieLi Rodent Diet (certified). All animals were acclimated for 3 days before tumor inoculation.

Experimental Procedures

Tumor Cell Adaptation

[0097] One vial of LLC cells was removed from the liquid nitrogen stock, and placed into a 37 °C water bath. Gentle swirling was conducted until the content of the vial was thawed. Using aseptic tissue culture technique, the cells were immediately centrifuged with a TD5A-WS centrifuge at 1000 rpm, 20-25°C, for 5 min. After centrifugation, the cells were suspended in 0.1 to 0.5 mL normal saline (NS) and then subcutaneously injected into 10 mice (0.1 mL /mouse, about 1×10^6 cells). After 1 or 2 weeks, when the tumor diameter was approximately 1 cm, the animals were euthanized with CO₂ overdose and the tumors excised. The procedure was repeated with another 20 mice to generate a sufficient number of LLC cells with adequate transplantability.

Tumor Cell Inoculation

[0098] On the day of tumor implantation, approximately 1.2×10^6 cells in 0.1 mL were subcutaneously injected on the right axillary area of each mouse. The day of tumor implantation was defined as Day 0.

Study Design and Treatment Regimen

[0099] On Day 1, the animals were randomly assigned into different weight-matched groups, and dosing was started using the regimen according to Table 3.2. Briefly, SCV-07 was administered once daily via subcutaneous injection for 14 consecutive days at a site different from that of tumor cell implantation, while CDDP was intraperitoneally administered on Days 1, 6, and 12.

Evaluation of Anti-tumor Effect

[00100] From Day 1 to Day 14, mortality and morbidity were checked twice daily, the body weights were recorded once every 3 days, and tumors were measured using a caliper once every 2 days. At the end of the study (Day 16), the animals were euthanized by CO₂ asphyxiation, and the tumors were excised and weighed.

Tumor volume was calculated using the following formula:

$$\text{Tumor Volume} = \text{Length} \times \text{Width} \times \text{Width} / 2$$

Tumor volume inhibition (PI) was calculated according to the formula below:

$$\text{PI(TV)} = (\text{TV}_{\text{vehicle}} - \text{TV}_{\text{drug treated}}) / \text{TV}_{\text{vehicle}} \times 100\%$$

[00101] Where, TV is the tumor volume on the day of measurement, "vehicle" denotes the group receiving PBS, and "drug treated" denotes groups receiving SCV-07 and/or CDDP.

[00102] The anti-tumor effect of SCV-07 used alone or in combination with CDDP was also evaluated by tumor weight. The tumor weight of each mouse was recorded after euthanasia, and the percent inhibition of tumor weight was calculated according to the formula below:

$$PI(TW) = (TW_{\text{vehicle}} - TW_{\text{drug treated}}) / TW_{\text{vehicle}} \times 100\%$$

Mean and standard deviations were calculated using Excel.

Table 3.2: Treatment Regimen and Study Design

Group Number	Group Name	Treatment	Number of Animals	Dosing Days	Necropsy Day
1	Vehicle Control	PBS	10	Days 1-14	Day 16
2	Positive Control 1	CDDP 2 mg/kg, i.p., on days 1, 6, and 12	10		
3	Positive Control 2	CDDP 6 mg/kg, i.p., on days 1, 6, and 12	10		
4	Test Article 1	SCV-07, 10 mg/kg, s.c., daily	10		
5	Test Article 2	SCV-07, 20 mg/kg, s.c., daily	10		
6	Combination 1	SCV-07, 10 mg/kg, s.c., daily + CDDP 2 mg/kg, i.p., on days 1, 6, and 12	10		
7	Combination 2	SCV-07, 20 mg/kg, s.c., daily + CDDP 2 mg/kg, i.p., on days 1, 6, and 12	10		

Statistical Analysis

[00103] Inter-group comparisons were performed in terms of tumor volume, tumor weight and body weight, using a student's t test. *P* values of less than 0.05 were considered to be statistically significant.

Results and Discussion

Mortality

[00104] Throughout the course of the study, no animal died.

Tumor Size

[00105] Raw measurement data of tumor size were tabulated in Appendixes 3.1-3.14. The calculated mean tumor volumes and statistical testing results of each treatment group versus the vehicle group were tabulated in the Tables 3-9. Tumors were not measurable in any group on day 2. On day 4, mean tumor volumes in all of groups except Group 4 were statistically significantly smaller than that of Group 1 (vehicle control). On Day 6, only Group 2 and Group 3 showed the smaller mean tumor volumes. On Days 8, 10, 12 and 14, the mean tumor volumes of all groups were statistically significantly smaller than Group 1.

Tumor Weight

[00106] Raw data of tumor weights measured on Day 16 were tabulated in Appendix 3.15. The calculated percent inhibition (PI) values based on tumor weight and the statistical comparison results between each of treatment groups and the vehicle group were tabulated in Table 3.10. As shown in Table 3.10, the mean tumor weights of all treatment groups were lower than that of the vehicle group. The PI values of Group 2, Group 3, Group 4, Group 5, Group 6 and Group 7 were 58.90% ($p < 0.01$), 77.35% ($p < 0.01$), 16.84% ($p < 0.05$), 37.45% ($p < 0.01$), 40.81% ($p < 0.01$) and 56.13% ($p < 0.01$), respectively. Although the combination treatment groups (i.e., Groups 6 and 7) had higher PI values than the corresponding groups (i.e., Groups 4 and 5) that received SCV-07 treatment alone, these PI values were not higher than that of Group 2 which received CDDP treatment alone. There were no statistically significant differences in PI between either of the combination treatment groups and the CDDP treatment alone group (Group 2), indicating no additive effect when using CDDP in combination with SCV-07.

Body weight

[00107] Raw data of body weight measurement were listed in Appendixes 3.16-3.21. The results of statistical comparison of each treatment group versus the vehicle group were tabulated in the Tables 3.11-3.16.

[00108] As shown in the Tables 3.11-3.16, there were no statistically significant differences between each of the treatment groups and the vehicle control group on Day 0. On Day 3, Group 3 (CDDP 6 mg/kg) and Group 7 (CDDP 2 mg/kg + SCV-07 20 mg/kg) exhibited decreases in body weights by 9.33% ($P < 0.01$) and 8.31% ($P < 0.01$), respectively, relative to the vehicle group. There were no statistically significant differences in body weight for other groups in comparison to the vehicle group. On Day 6, the body weights of Groups 3 and 7 were 10.45% ($p < 0.01$) and 6.58% ($p < 0.01$) lower than the vehicle group. On Day 9, the body weights of Groups 3, 6, and 7 were 14.51% ($p < 0.01$), 8.70% ($p < 0.05$), and 11.41% ($p < 0.01$) lower than the vehicle group, respectively. On Day 12, the body weights of Groups 3 and 7 were 13.62% ($P < 0.01$) and 6.65% ($P < 0.05$) lower than the vehicle group, respectively. On Day 15, the body weights of Groups 2, 3, 6, and 7 were 12.51% ($p < 0.01$), 24.38% ($P < 0.01$), 10.42% ($P < 0.05$), and 14.56% ($P < 0.01$) lower than the vehicle group, respectively. Throughout the course of the study, there were no statistically significant differences in body weights of Groups 4 and 5 that received SCV-07 treatment alone, indicating that SCV-07 had no significant effect on animal body weight, when used alone. On the contrary, the CDDP treatment was associated with the loss of body weight, and the observation was especially pronounced in Group 3, the group receiving high dose (6 mg/kg) of CDDP. The combined use of CDDP with SCV-07 did not alleviate the weight loss, but may in fact make the CDDP-associated weight loss more pronounced. Higher weight loss was noted in Group 7, the group receiving CDDP in combination with high dose of SCV-07, than in Group 2 which received CDDP alone.

Conclusion and Discussion

[00109] In conclusion, the tumor model used in this study was valid as tumor growth was inhibited by positive control drug CDDP. Daily administration of test article SCV-07 at 10 mg/kg and 20 mg/kg was effective against the tumor growth. Mean tumor volumes in animals of all SCV-07-treated groups were significantly reduced in comparison to that of the vehicle control group from Day 8 onwards. Tumor weights, which were measured on Day 16, were also significantly reduced in the groups receiving 10 mg/kg or 20 mg/kg SCV-07 alone and in the groups receiving combination therapy. The combined use of 10 mg/kg or 20 mg/kg SCV-07 with 2 mg/kg CDDP produced 40.81% and 56.13% inhibition of tumor growth, in comparison to 16.84% and 37.45% inhibition obtained when using 10 mg/kg or 20 mg/kg SCV-07 alone, and 58.90% and 77.35% inhibition obtained when using 2 mg/kg or 6 mg/kg CDDP alone. These results suggested that the combined use of SCV-07 and CDDP produced no additive effect towards the inhibition of the tumor growth.

[00110] The mean body weights in CDDP treatment groups were significantly decreased, indicating a toxic effect. When used alone, SCV-07 did not cause any statistically significant loss of body weights in all SCV-07-treated groups, indicating that SCV-07 had no effect on animal body weight. However, when SCV-07 was used in combination with CDDP, it may exacerbate the CDDP-associated weight loss, as higher weight losses were noted in Group 7, the group receiving CDDP in combination with higher dose of SCV-07 throughout the course of the study.

Tables

Table 3.3: Mean tumor volume (cm³) on Day 2

Group Number	Group Name	Treatment	Number of Survived Animals	Tumor Volume (Mean ± SD)	PI (TV)	P Value
1	Vehicle Control	PBS	10	0	-	-
2	Positive Control 1	CDDP 2 mg/kg	10	0	-	-
3	Positive Control 2	CDDP 6 mg/kg	10	0	-	-
4	Test Article 1	SCV-07 10 mg/kg	10	0	-	-
5	Test Article 2	SCV-07 20 mg/kg	10	0	-	-
6	Combination 1	SCV-07, 10 mg/kg + CDDP 2 mg/kg	10	0	-	-
7	Combination 2	SCV-07, 20 mg/kg + CDDP 2 mg/kg	10	0	-	-

Table 3.4: Mean tumor volume (cm³) on Day 4

Group Number	Group Name	Treatment	Number of Survived Animals	Tumor Volume (Mean ± SD)	PI (TV)	P Value
1	Vehicle Control	PBS	10	0.007±0.0024		
2	Positive Control 1	CDDP 2 mg/kg	10	0.000±0.0006	93.90	0.0000
3	Positive Control 2	CDDP 6 mg/kg	10	0.000±0.0002	98.66	0.0000
4	Test Article 1	SCV-07 10 mg/kg	10	0.006±0.0040	16.97	0.3989
5	Test Article 2	SCV-07 20 mg/kg	10	0.004±0.0016	42.01	0.0032
6	Combination 1	SCV-07, 10 mg/kg + CDDP 2 mg/kg	10	0.004±0.0039	51.10	0.0168

7	Combination 2	SCV-07, 20 mg/kg + CDDP 2 mg/kg	10	0.003±0.0013	54.15	0.0002
---	------------------	------------------------------------	----	--------------	-------	--------

Table 3.5: Mean tumor volume (cm³) on Day 6

Group Number	Group Name	Treatment	Number of Survived Animals	Tumor Volume (Mean ± SD)	PI (TV)	P Value
1	Vehicle Control	PBS	10	0.071±0.0222		
2	Positive Control 1	CDDP 2 mg/kg	10	0.015±0.0072	78.57	0.0000
3	Positive Control 2	CDDP 6 mg/kg	10	0.004±0.0039	93.76	0.0000
4	Test Article 1	SCV-07 10 mg/kg	10	0.096±0.0348	-35.62	0.0689
5	Test Article 2	SCV-07 20 mg/kg	10	0.069±0.0229	3.31	0.8185
6	Combination 1	SCV-07, 10 mg/kg + CDDP 2 mg/kg	10	0.069±0.0229	3.31	0.8185
7	Combination 2	SCV-07, 20 mg/kg + CDDP 2 mg/kg	10	0.055±0.0241	22.63	0.1384

Table 3.6: Mean tumor volume (cm³) on Day 8

Group Number	Group Name	Treatment	Number of Survived Animals	Tumor Volume (Mean ± SD)	PI (TV)	P Value
1	Vehicle Control	PBS	10	0.449±0.088 0		
2	Positive Control 1	CDDP 2 mg/kg	10	0.089±0.045 8	80.19	0.0000
3	Positive Control 2	CDDP 6 mg/kg	10	0.035±0.029 1	92.13	0.0000

4	Test Article 1	SCV-07 10 mg/kg	10	0.329±0.110 8	26.73	0.0153
5	Test Article 2	SCV-07 20 mg/kg	10	0.270±0.092 9	39.73	0.0003
6	Combination 1	SCV-07, 10 mg/kg + CDDP 2 mg/kg	10	0.185±0.050 4	58.70	0.0000
7	Combination 2	SCV-07, 20 mg/kg + CDDP 2 mg/kg	10	0.161±0.044 9	64.12	0.0000

Table 3.7: Mean tumor volume (cm³) on Day 10

Group Number	Group Name	Treatment	Number of Survived Animals	Tumor Volume (Mean ± SD)	PI (TV)	P Value
1	Vehicle Control	PBS	10	1.102±0.244 2		
2	Positive Control 1	CDDP 2 mg/kg	10	0.221±0.087 3	79.98	0.0000
3	Positive Control 2	CDDP 6 mg/kg	10	0.092±0.065 8	91.67	0.0000
4	Test Article 1	SCV-07 10 mg/kg	10	0.695±0.209 0	36.92	0.0008
5	Test Article 2	SCV-07 20 mg/kg	10	0.621±0.179 5	43.70	0.0001
6	Combination 1	SCV-07, 10 mg/kg + CDDP 2 mg/kg	10	0.402±0.125 6	63.55	0.0000
7	Combination 2	SCV-07, 20 mg/kg + CDDP 2 mg/kg	10	0.393±0.089 2	64.37	0.0000

Table 3.8: Mean tumor volume (cm³) on Day 12

Group Number	Group Name	Treatment	Number of Survived Animals	Tumor Volume (Mean ± SD)	PI (TV)	P Value
1	Vehicle Control	PBS	10	1.565±0.326 4		
2	Positive Control 1	CDDP 2 mg/kg	10	0.481±0.095 1	69.28	0.0000
3	Positive Control 2	CDDP 6 mg/kg	10	0.185±0.116 5	88.16	0.0000
4	Test Article 1	SCV-07 10 mg/kg	10	1.081±0.326 1	30.92	0.0038
5	Test Article 2	SCV-07 20 mg/kg	10	0.902±0.329 4	42.41	0.0003
6	Combination 1	SCV-07, 10 mg/kg + CDDP 2 mg/kg	10	0.649±0.175 7	58.55	0.0000
7	Combination 2	SCV-07, 20 mg/kg + CDDP 2 mg/kg	10	0.648±0.209 6	58.58	0.0000

Table 3.9: Mean tumor volume (cm³) on Day 14

Group Number	Group Name	Treatment	Number of Survived Animals	Tumor Volume (Mean ± SD)	PI (TV)	P Value
1	Vehicle Control	PBS	10	2.388±0.5225		
2	Positive Control 1	CDDP 2 mg/kg	10	0.802±0.0858	66.44	0.0000
3	Positive Control 2	CDDP 6 mg/kg	10	0.374±0.2229	84.35	0.0000
4	Test Article 1	SCV-07 10 mg/kg	10	1.467±0.3658	38.58	0.0002
5	Test Article 2	SCV-07 20 mg/kg	10	1.259±0.2956	47.30	0.0000
6	Combination 1	SCV-07, 10 mg/kg + CDDP 2 mg/kg	10	1.027±0.2889	57.01	0.0000
7	Combination 2	SCV-07, 20 mg/kg + CDDP 2 mg/kg	10	0.907±0.2647	62.03	0.0000

Table 3.10: Mean tumor weight (g) on Day 16

Group Number	Group Name	Treatment	Number of Survived Animals	Tumor Weight (Mean ± SD)	PI (TW)	P Value
1	Vehicle Control	PBS	10	4.08±0.6159		
2	Positive Control 1	CDDP 2 mg/kg	10	1.68±0.4358	58.90	0.0000
3	Positive Control 2	CDDP 6 mg/kg	10	0.92±0.4679	77.35	0.0000
4	Test Article 1	SCV-07 10 mg/kg	10	3.39±0.5793	16.84	0.0193
5	Test Article 2	SCV-07 20 mg/kg	10	2.55±0.4791	37.45	0.0000
6	Combination 1	SCV-07, 10 mg/kg + CDDP 2 mg/kg	10	2.42±0.4954	40.81	0.0000
7	Combination 2	SCV-07, 20 mg/kg + CDDP 2 mg/kg	10	1.79±0.5690	56.13	0.0000

Table 3.11: Mean body weight (g) on Day 0

Group Number	Group Name	Treatment	Number of Survived Animals	Tumor Volume (Mean \pm SD)	PI (BW)	P Value
1	Vehicle Control	PBS	10	17.40 \pm 0.8069		
2	Positive Control 1	CDDP 2 mg/kg	10	17.52 \pm 0.9402	-0.69	0.7629
3	Positive Control 2	CDDP 6 mg/kg	10	17.57 \pm 0.8970	-0.98	0.6612
4	Test Article 1	SCV-07 10 mg/kg	10	17.39 \pm 0.7156	0.06	0.9769
5	Test Article 2	SCV-07 20 mg/kg	10	17.15 \pm 0.5442	1.44	0.4272
6	Combination 1	SCV-07, 10 mg/kg + CDDP 2 mg/kg	10	17.10 \pm 0.9250	1.72	0.4496
7	Combination 2	SCV-07, 20 mg/kg + CDDP 2 mg/kg	10	16.97 \pm 0.6019	2.47	0.1935

Table 3.12: Mean body weight (g) on Day 3

Group Number	Group Name	Treatment	Number of Survived Animals	Tumor Volume (Mean \pm SD)	PI (BW)	P Value
1	Vehicle Control	PBS	10	17.57 \pm 0.8486		
2	Positive Control 1	CDDP 2 mg/kg	10	16.56 \pm 1.4592	5.75	0.0747
3	Positive Control 2	CDDP 6 mg/kg	10	15.93 \pm 1.5762	9.33	0.0096
4	Test Article 1	SCV-07 10 mg/kg	10	17.67 \pm 0.7469	-0.57	0.7829
5	Test Article 2	SCV-07 20 mg/kg	10	17.52 \pm 0.3676	0.28	0.8662
6	Combination 1	SCV-07, 10 mg/kg + CDDP 2 mg/kg	10	16.65 \pm 1.3277	5.24	0.0814
7	Combination 2	SCV-07, 20 mg/kg + CDDP 2 mg/kg	10	16.11 \pm 0.9061	8.31	0.0016

Table 3.13: Mean body weight (g) on Day 6

Group Number	Group Name	Treatment	Number of Survived Animals	Tumor Volume (Mean \pm SD)	PI (BW)	P Value
1	Vehicle Control	PBS	10	18.09 \pm 0.7795		
2	Positive Control 1	CDDP 2 mg/kg	10	17.52 \pm 1.2639	3.15	0.2405
3	Positive Control 2	CDDP 6 mg/kg	10	16.20 \pm 1.1402	10.45	0.0004
4	Test Article 1	SCV-07 10 mg/kg	10	18.12 \pm 0.6250	-0.17	0.9254
5	Test Article 2	SCV-07 20 mg/kg	10	17.88 \pm 0.4492	1.16	0.4700
6	Combination 1	SCV-07, 10 mg/kg + CDDP 2 mg/kg	10	17.51 \pm 1.2512	3.21	0.2294
7	Combination 2	SCV-07, 20 mg/kg + CDDP 2 mg/kg	10	16.90 \pm 1.0088	6.58	0.0085

Table 3.14: Mean body weight (g) on Day 9

Group Number	Group Name	Treatment	Number of Survived Animals	Tumor Volume (Mean \pm SD)	PI (BW)	P Value
1	Vehicle Control	PBS	10	18.40 \pm 0.8511		
2	Positive Control 1	CDDP 2 mg/kg	10	17.74 \pm 1.0926	3.59	0.1492
3	Positive Control 2	CDDP 6 mg/kg	10	15.73 \pm 0.7558	14.51	0.0000
4	Test Article 1	SCV-07 10 mg/kg	10	18.59 \pm 0.6173	-1.03	0.5748
5	Test Article 2	SCV-07 20 mg/kg	10	18.24 \pm 0.5522	0.87	0.6240
6	Combination 1	SCV-07, 10 mg/kg + CDDP 2 mg/kg	10	16.80 \pm 1.5463	8.70	0.0103
7	Combination 2	SCV-07, 20 mg/kg + CDDP 2 mg/kg	10	16.30 \pm 0.7394	11.41	0.0000

Table 3.15: Mean body weight (g) on Day 12

Group Number	Group Name	Treatment	Number of Survived Animals	Tumor Volume (Mean ± SD)	PI (BW)	P Value
1	Vehicle Control	PBS	10	19.24±1.4789		
2	Positive Control 1	CDDP 2 mg/kg	10	18.23±1.8233	5.25	0.1905
3	Positive Control 2	CDDP 6 mg/kg	10	16.62±1.6164	13.62	0.0014
4	Test Article 1	SCV-07 10 mg/kg	10	18.89±1.0429	1.82	0.5484
5	Test Article 2	SCV-07 20 mg/kg	10	19.12±0.8522	0.62	0.8266
6	Combination 1	SCV-07, 10 mg/kg + CDDP 2 mg/kg	10	18.29±1.9116	4.94	0.2298
7	Combination 2	SCV-07, 20 mg/kg + CDDP 2 mg/kg	10	17.96±1.1862	6.65	0.0468

Table 3.16: Mean body weight (g) on Day 15

Group Number	Group Name	Treatment	Number of Survived Animals	Tumor Volume (Mean ± SD)	PI (BW)	P Value
1	Vehicle Control	PBS	10	20.06±1.2057		
2	Positive Control 1	CDDP 2 mg/kg	10	17.55±1.6216	12.51	0.0010
3	Positive Control 2	CDDP 6 mg/kg	10	15.17±1.9810	24.38	0.0000
4	Test Article 1	SCV-07 10 mg/kg	10	19.01±1.1939	5.23	0.0661
5	Test Article 2	SCV-07 20 mg/kg	10	19.31±0.8724	3.74	0.1284
6	Combination 1	SCV-07, 10 mg/kg + CDDP 2 mg/kg	10	17.97±1.9647	10.42	0.0102
7	Combination 2	SCV-07, 20 mg/kg + CDDP 2 mg/kg	10	17.14±1.1394	14.56	0.0000

Appendix 3.1: Tumor measurements (cm) on Day 2

Group	Treatment	F1		F2		F3		F4		F5		M1		M2		M3		M4		M5	
		L	W	L	W	L	W	L	W	L	W	L	W	L	W	L	W	L	W	L	W
1	Vehicle Control	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2	CDDP 2 mg/kg	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3	CDDP 6 mg/kg	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4	SCV-07 10 mg/kg	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5	SCV-07 20 mg/kg	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6	SCV-07 10 mg/kg+ CDDP 2 mg/kg	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
7	SCV-07 20 mg/kg+ CDDP 2 mg/kg	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

- Not measurable

Appendix 3.2: Tumor volumes* (cm³) on Day 2

Group	Treatment	F1		F2		F3		F4		F5		M1		M2		M3		M4		M5	
		L	W	L	W	L	W	L	W	L	W	L	W	L	W	L	W	L	W	L	W
1	Vehicle Control	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2	CDDP 2 mg/kg	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3	CDDP 6 mg/kg	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4	SCV-07 10 mg/kg	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5	SCV-07 20 mg/kg	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6	SCV-07 10 mg/kg+ CDDP 2 mg/kg	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
7	SCV-07 20 mg/kg+ CDDP 2 mg/kg	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

*Tumor volumes were calculated using the formula "Tumor Volume=Length×Width×Width/2" based on the data listed in Appendix 3.1.

Appendix 3.3: Tumor measurements (cm) on Day 4

Group	Treatment	F1		F2		F3		F4		F5		M1		M2		M3		M4		M5		
		L	W	L	W	L	W	L	W	L	W	L	W	L	W	L	W	L	W	L	W	
1	Vehicle Control	0.2	0.2	0.2	0.2	0.2	0.2	0.26	0.26	0.26	0.26	0.26	0.26	0.26	0.26	0.26	0.26	0.26	0.27	0.27	0.26	0.26
2	CDDP 2 mg/kg	-	-	-	-	0.1	0.1	-	-	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.16	0.16	-	-	
3	CDDP 6 mg/kg	0	0	0	0	0	0	0.1	0.1	0.1	0	0	0	0	0	0	0	0	0	0.1	0.1	
4	SCV-07 10 mg/kg	0.2	0.2	0.3	0.3	0.2	0.2	0.2	0.2	0.2	0.2	0.3	0.3	0.24	0.24	0.2	0.2	0.2	0.2	0.2	0.2	
5	SCV-07 20 mg/kg	0.2	0.2	0.2	0.2	0.2	0.2	0.26	0.26	0.2	0.2	0.2	0.2	0.17	0.17	0.2	0.2	0.2	0.2	0.2	0.2	
6	SCV-07 10 mg/kg + CDDP 2 mg/kg	0.11	0.11	0.2	0.2	0.11	0.11	0.2	0.2	0.2	0.2	0.2	0.2	0.21	0.21	0.3	0.3	0.1	0.1	0.1	0.1	
7	SCV-07 20 mg/kg + CDDP 2 mg/kg	0.15	0.15	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.1	0.1	

- Not measurable

Appendix 3.4: Tumor volumes* (cm³) on Day 4

Group	Treatment	F1	F2	F3	F4	F5	M1	M2	M3	M4	M5
1	Vehicle Control	0.004	0.004	0.004	0.008788	0.008788	0.008788	0.008788	0.008788	0.009841 ₅	0.008788
2	CDDP 2 mg/kg	0	0	0.0005	0	0.0005	0.0005	0.0005	0.0005	0.002048	0
3	CDDP 6 mg/kg	0	0	0	0.0005	0	0	0	0	0	0.0005
4	SCV-07 10 mg/kg	0.004	0.0135	0.004	0.004	0.004	0.0135	0.006912	0.004	0.004	0.004
5	SCV-07 20 mg/kg	0.004	0.004	0.004	0.008788	0.004	0.004	0.002456 ₅	0.004	0.004	0.004
6	SCV-07 10 mg/kg + CDDP 2 mg/kg	0.000565 ₅	0.004	0.000665 ₅	0.004	0.004	0.004	0.004630 ₅	0.0135	0.0005	0.0005
7	SCV-07 20 mg/kg + CDDP 2 mg/kg	0.001687 ₅	0.004	0.004	0.004	0.004	0.004	0.004	0.004	0.004	0.0005

* Tumor volumes were calculated using the formula "Tumor Volume=LengthxWidthxWidth/2" based on the data listed in Appendix 3.3.

Appendix 3.5: Tumor measurements (cm) on Day 6

Group	Treatment	F1		F2		F3		F4		F5		M1		M2		M3		M4		M5	
		L	W	L	W	L	W	L	W	L	W	L	W	L	W	L	W	L	W	L	W
1	Vehicle Control	0.54	0.54	0.5	0.5	0.4	0.4	0.5	0.5	0.5	0.5	0.53	0.53	0.52	0.52	0.5	0.5	0.59	0.59	0.6	0.6
2	CDDP 2 mg/kg	0.3	0.3	0.4	0.4	0.3	0.3	0.2	0.2	0.3	0.3	0.3	0.3	0.35	0.35	0.3	0.3	0.3	0.3	0.3	0.3
3	CDDP 6 mg/kg	0.18	0.18	0	0	0.2	0.2	0.25	0.25	0	0	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.3	0.3
4	SCV-07 10 mg/kg	0.5	0.5	0.6	0.6	0.6	0.6	0.5	0.5	0.6	0.6	0.6	0.6	0.5	0.5	0.7	0.7	0.6	0.6	0.5	0.5
5	SCV-07 20 mg/kg	0.5	0.5	0.5	0.5	0.6	0.6	0.5	0.5	0.4	0.4	0.5	0.5	0.5	0.5	0.6	0.6	0.5	0.5	0.5	0.5
6	SCV-07 10 mg/kg + CDDP 2 mg/kg	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.6	0.6	0.5	0.5	0.6	0.6	0.4	0.4	0.5	0.5
7	SCV-07 20 mg/kg + CDDP 2 mg/kg	0.4	0.4	0.5	0.5	0.5	0.5	0.6	0.6	0.4	0.4	0.5	0.5	0.5	0.5	0.5	0.5	0.4	0.4	0.4	0.4

Appendix 3.6: Tumor volumes* (cm³) on Day 6

Group	Treatment	F1	F2	F3	F4	F5	M1	M2	M3	M4	M5
1	Vehicle Control	0.078732	0.055296	0.032	0.0625	0.0625	0.0744385	0.070304	0.0625	0.1026895	0.108
2	CDDP 2 mg/kg	0.0135	0.032	0.0135	0.004	0.0135	0.0135	0.0214375	0.0135	0.0135	0.0135
3	CDDP 6 mg/kg	0.002916	0	0.004	0.0078125	0	0.004	0.004	0.004	0.004	0.0135
4	SCV-07 10 mg/kg	0.0625	0.108	0.108	0.0625	0.108	0.108	0.0625	0.1715	0.108	0.0625
5	SCV-07 20 mg/kg	0.0625	0.0625	0.108	0.0625	0.032	0.0625	0.0625	0.108	0.0625	0.0625
6	SCV-07 10 mg/kg + CDDP 2 mg/kg	0.0625	0.0625	0.0625	0.0625	0.0625	0.108	0.0625	0.108	0.032	0.0625
7	SCV-07 20 mg/kg + CDDP 2 mg/kg	0.032	0.0625	0.0625	0.108	0.032	0.0625	0.0625	0.0625	0.032	0.032

*Tumor volumes were calculated using the formula "Tumor Volume=Length×Width×Width/2" based on the data listed in Appendix 3.5.

Appendix 3.7: Tumor measurements (cm) on Day 8

Group	Treatment	F1		F2		F3		F4		F5		M1		M2		M3		M4		M5	
		L	W	L	W	L	W	L	W	L	W	L	W	L	W	L	W	L	W	L	W
1	Vehicle Control	1	1	0.9	0.9	0.8	0.8	0.9	0.9	1	1	1	1	1	1	1	1	1	1	1	1
2	CDDP 2 mg/kg	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.6	0.6	0.5	0.5	0.5	0.5	0.5	0.5	0.7	0.7	0.7	0.7
3	CDDP 6 mg/kg	0.3	0.3	0	0	0.3	0.3	0.3	0.3	0	0	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
4	SCV-07 10 mg/kg	0.7	0.7	1	0.9	1	1	0.8	0.8	0.87	0.87	1	1	0.8	0.8	0.9	0.9	0.8	0.8	0.8	0.8
5	SCV-07 20 mg/kg	0.8	0.8	0.9	0.9	0.8	0.8	0.89	0.89	0.6	0.6	0.9	0.9	0.7	0.7	0.9	0.9	0.7	0.7	0.7	0.87
6	SCV-07 10 mg/kg + CDDP 2 mg/kg	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.8	0.8	0.7	0.7	0.9	0.9	0.6	0.6	0.7	0.7
7	SCV-07 20 mg/kg + CDDP 2 mg/kg	0.6	0.6	0.7	0.7	0.7	0.7	0.8	0.8	0.6	0.6	0.7	0.7	0.7	0.7	0.7	0.7	0.6	0.6	0.7	0.7

Appendix 3.8: Tumor volumes* (cm³) on Day 8

Group	Treatment	F1		F2		F3		F4		F5		M1		M2		M3		M4		M5	
		L	W	L	W	L	W	L	W	L	W	L	W	L	W	L	W	L	W	L	W
1	Vehicle Control	0.5	0.5	0.3645	0.3645	0.256	0.256	0.3645	0.3645	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
2	CDDP 2 mg/kg	0.0625	0.0625	0.0625	0.0625	0.0625	0.0625	0.0625	0.0625	0.108	0.108	0.0625	0.0625	0.0625	0.0625	0.0625	0.0625	0.1715	0.1715	0.1715	0.1715
3	CDDP 6 mg/kg	0.0135	0.0135	0	0	0.0135	0.0135	0.0135	0.0135	0	0	0.0625	0.0625	0.0625	0.0625	0.0625	0.0625	0.0625	0.0625	0.0625	0.0625
4	SCV-07 10 mg/kg	0.1715	0.1715	0.3969	0.3969	0.5	0.5	0.256	0.256	0.329251	0.329251	0.5	0.5	0.256	0.256	0.3645	0.3645	0.256	0.256	0.256	0.256
5	SCV-07 20 mg/kg	0.256	0.256	0.329251	0.329251	0.256	0.256	0.352484	0.352484	0.108	0.108	0.3645	0.3645	0.1715	0.1715	0.1715	0.1715	0.1715	0.1715	0.1715	0.329251
6	SCV-07 10 mg/kg + CDDP 2 mg/kg	0.1715	0.1715	0.1715	0.1715	0.1715	0.1715	0.1715	0.1715	0.1715	0.1715	0.256	0.256	0.1715	0.1715	0.288	0.288	0.108	0.108	0.1715	0.1715
7	SCV-07 20 mg/kg + CDDP 2 mg/kg	0.108	0.108	0.1715	0.1715	0.1715	0.1715	0.256	0.256	0.108	0.108	0.1715	0.1715	0.1715	0.1715	0.1715	0.1715	0.108	0.108	0.1715	0.1715

* Tumor volumes were calculated using the formula "Tumor Volume=Length×Width×Width/2" based on the data listed in Appendix 3.7.

Appendix 3.9: Tumor measurements (cm) on Day 10

Group	Treatment	F1		F2		F3		F4		F5		M1		M2		M3		M4		M5	
		L	W	L	W	L	W	L	W	L	W	L	W	L	W	L	W	L	W	L	W
1	Vehicle Control	1.2	1.2	1.1	1.1	1.2	1.3	1.4	1.4	1.3	1.5	1.3	1.25	1.4	1.4	1.3	1.3	1.4	1.4	1.3	1.3
2	CDDP 2 mg/kg	0.6	0.6	0.7	0.7	0.7	0.7	0.8	0.8	0.7	0.7	0.7	0.7	0.7	0.7	0.8	0.8	0.9	0.9	0.9	0.9
3	CDDP 6 mg/kg	0.5	0.5	0	0	0.5	0.5	0.5	0.5	0	0	0.6	0.6	0.6	0.6	0.6	0.7	0.7	0.7	0.7	0.7
4	SCV-07 10 mg/kg	1	1	1.1	1.1	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1	1	1.23	1.23	1	1	0.9	0.9
5	SCV-07 20 mg/kg	1.09	1.11	1.2	1.1	1.05	1.05	1.1	1.1	0.8	0.8	1.19	1.2	0.9	0.9	1.1	1.1	1	1.2	1.1	1.23
6	SCV-07 10 mg/kg + CDDP 2 mg/kg	0.9	0.9	0.8	0.8	0.9	0.9	0.97	1.1	0.9	0.9	1	1	0.9	0.9	1.1	1.1	0.8	0.8	0.9	0.9
7	SCV-07 20 mg/kg + CDDP 2 mg/kg	0.9	1.1	0.9	0.9	1	1	1	1.12	0.8	0.8	0.9	0.9	0.99	0.99	0.9	0.9	0.85	0.85	0.9	0.9

Appendix 3.10: Tumor volumes* (cm³) on Day 10

Group	Treatment	F1	F2	F3	F4	F5	M1	M2	M3	M4	M5
1	Vehicle Control	0.864	0.6655	0.936	1.372	1.2675	0.976562 ₅	1.372	1.0985	1.372	1.0985
2	CDDP 2 mg/kg	0.108	0.1715	0.1715	0.256	0.1715	0.1715	0.1715	0.256	0.3645	0.3645
3	CDDP 6 mg/kg	0.0625	0	0.0625	0.0625	0	0.108	0.108	0.1715	0.1715	0.1715
4	SCV-07 10 mg/kg	0.5	0.702464	0.864	0.864	0.864	0.864	0.5	0.930433 ₅	0.5	0.3645
5	SCV-07 20 mg/kg	0.659395 ₅	0.7018	0.578812 ₅	0.6655	0.256	0.84966	0.3645	0.6655	0.72	0.74415
6	SCV-07 10 mg/kg + CDDP 2 mg/kg	0.3645	0.256	0.3645	0.517495	0.3645	0.5	0.3645	0.6655	0.256	0.3645
7	SCV-07 20 mg/kg + CDDP 2 mg/kg	0.4455	0.3645	0.5	0.56	0.256	0.3645	0.40095	0.3645	0.307062 ₅	0.3645

* Tumor volumes were calculated using the formula "Tumor Volume=LengthxWidthxWidth/2" based on the data listed in Appendix 3.9.

Appendix 3.11: Tumor measurements (cm) on Day 12

Group	Treatment	F1		F2		F3		F4		F5		M1		M2		M3		M4		M5	
		L	W	L	W	L	W	L	W	L	W	L	W	L	W	L	W	L	W	L	W
1	Vehicle Control	1.4	1.4	1.3	1.4	1.4	1.5	1.6	1.6	1.5	1.5	1.5	1.5	1.5	1.5	1.6	1.6	1.3	1.3	1.4	1.4
2	CDDP 2 mg/kg	1	1	1	1	1	1	1	1	0.9	0.9	0.9	0.9	0.9	0.9	1	1	1.1	1.1	1.1	1.1
3	CDDP 6 mg/kg	0.7	0.7	0.3	0.3	0.7	0.7	0.6	0.6	0.1	0.1	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.9	0.9
4	SCV-07 10 mg/kg	1.25	1.2	1.4	1.4	1.5	1.5	1.3	1.3	1.25	1.5	1.3	1.3	1.2	1.2	1.36	1.36	1.2	1.2	1	1
5	SCV-07 20 mg/kg	1.29	1.2	1.2	1.2	1.2	1.1	1.2	1.2	1	1	1.1	1.1	1.1	1.1	1.3	1.3	1.5	1.5	1.25	1.3
6	SCV-07 10 mg/kg+ CDDP 2 mg/kg	1	1	0.9	0.9	1	1	1.2	1.2	1.1	1.1	1.2	1.2	1.1	1.1	1.2	1.2	1.07	1	1.1	1.1
7	SCV-07 20 mg/kg+ CDDP 2 mg/kg	1.1	1.2	1.1	1	1.3	1.3	1.2	1.2	0.9	1	1	1	1.1	1.1	1	1	1.1	1.1	1	1

Appendix 3.12: Tumor volumes* (cm³) on Day 12

Group	Treatment	F1	F2	F3	F4	F5	M1	M2	M3	M4	M5
1	Vehicle Control	1.372	1.183	1.47	2.048	1.6875	1.6875	1.6875	2.048	1.0985	1.372
2	CDDP 2 mg/kg	0.5	0.5	0.5	0.5	0.3645	0.3645	0.3645	0.5	0.55	0.6655
3	CDDP 6 mg/kg	0.1715	0.0135	0.1715	0.108	0.0005	0.256	0.256	0.256	0.256	0.3645
4	SCV-07 10 mg/kg	0.9	1.372	1.6875	1.0985	1.171875	1.0985	0.864	1.257728	0.864	0.5
5	SCV-07 20 mg/kg	0.9288	0.864	0.726	0.864	0.5	0.6655	0.6655	1.0985	1.6875	1.015625
6	SCV-07 10 mg/kg+ CDDP 2 mg/kg	0.5	0.3645	0.5	0.864	0.6655	0.864	0.6655	0.864	0.535	0.6655
7	SCV-07 20 mg/kg+ CDDP 2 mg/kg	0.726	0.55	1.10019	0.8712	0.405	0.5	0.6655	0.5	0.6655	0.5

* Tumor volumes were calculated using the formula "Tumor Volume=LengthxWidthxWidth/2" based on the data listed in Appendix 11.

Appendix 3.13: Tumor measurements (cm) on Day 14

Group	Treatment	F1		F2		F3		F4		F5		M1		M2		M3		M4		M5	
		L	W	L	W	L	W	L	W	L	W	L	W	L	W	L	W	L	W	L	W
1	Vehicle Control	1.7	1.7	1.6	1.6	1.6	1.7	1.9	1.9	1.9	1.8	1.6	1.6	1.7	1.7	1.6	1.6	1.5	1.5	1.7	1.7
2	CDDP 2 mg/kg	1.2	1.2	1.2	1.2	1.1	1.1	1.18	1.2	1.1	1.1	1.2	1.2	1.1	1.2	1.2	1.2	1.1	1.3	1.21	1.21
3	CDDP 6 mg/kg	0.8	0.8	0.6	0.6	0.8	0.8	0.8	0.8	0.4	0.4	1.1	1.1	1.1	1.1	1.1	1	1	1	1	1
4	SCV-07 10 mg/kg	1.4	1.4	1.5	1.5	1.6	1.7	1.5	1.5	1.38	1.4	1.55	1.5	1.36	1.36	1.4	1.4	1.33	1.33	1.2	1.2
5	SCV-07 20 mg/kg	1.3	1.3	1.4	1.4	1.3	1.3	1.4	1.4	1.2	1.2	1.3	1.3	1.3	1.3	1.5	1.5	1.5	1.6	1.3	1.3
6	SCV-07 10 mg/kg+ CDDP 2 mg/kg	1.2	1.2	1	1	1.2	1.2	1.4	1.4	1.3	1.3	1.4	1.4	1.3	1.3	1.4	1.4	1.2	1.2	1.2	1.2
7	SCV-07 20 mg/kg+ CDDP 2 mg/kg	1.3	1.4	1.2	1.2	1.4	1.4	1.3	1.4	1	1.1	1.1	1.2	1.2	1.2	1.2	1	1.2	1.2	1.2	1.2

Appendix 3.14: Tumor volumes* (cm³) on Day 14

Group	Treatment	F1	F2	F3	F4	F5	M1	M2	M3	M4	M5
		1	Vehicle Control	2.4565	2.048	2.176	3.4295	3.078	2.048	2.4565	2.048
2	CDDP 2 mg/kg	0.864	0.864	0.6655	0.83544	0.6655	0.859685 ₄	0.726	0.864	0.7865	0.885780 ₅
3	CDDP 6 mg/kg	0.256	0.108	0.256	0.256	0.032	0.6655	0.6655	0.5	0.5	0.5
4	SCV-07 10 mg/kg	1.372	1.6875	2.176	1.6875	1.33308	1.74375	1.257728	1.372	1.176318 ₅	0.864
5	SCV-07 20 mg/kg	1.0985	1.372	1.0985	1.372	0.864	1.0985	1.0985	1.6875	1.8	1.0985
6	SCV-07 10 mg/kg+ CDDP 2 mg/kg	0.864	0.5	0.864	1.372	1.0985	1.372	1.0985	1.372	0.864	0.864
7	SCV-07 20 mg/kg+ CDDP 2 mg/kg	1.193	0.864	1.372	1.183	0.55	0.726	0.864	0.6	0.864	0.864

* Tumor volumes were calculated using the formula "Tumor Volume=Length×Width×Width/2" based on the data listed in Appendix 3.13.

Appendix 3.15: Tumor weights (g) on Day 16

Group	Treatment	F1	F2	F3	F4	F5	M1	M2	M3	M4	M5
1	Vehicle Control	4.75	5.1	3.9	4.3	2.98	3.83	4.6	3.68	3.73	4
2	CDDP 2 mg/kg	1.56	0.7	1.3	1.9	1.68	1.89	1.6	2	2.3	1.82
3	CDDP 6 mg/kg	0.3	0.5	0.9	0.4	0.78	1.1	1.2	1.9	1.2	0.9
4	SCV-07 10 mg/kg	3.38	4.1	4.4	3.9	3	3.4	3.02	3.27	3	2.49
5	SCV-07 20 mg/kg	2.54	3.3	2	3.2	2.49	2.55	2.46	1.85	3	2.18
6	SCV-07 10 mg/kg+ CDDP 2 mg/kg	2	3.2	1.8	2.5	2	3.14	2.32	2.11	2.85	2.21
7	SCV-07 20 mg/kg+ CDDP 2 mg/kg	1.62	2.4	2.7	2.7	1.48	1.59	1.32	1.23	1.47	1.42

Appendix 3.16: Body weights (g) on Day 0

Group	Treatment	F1	F2	F3	F4	F5	M1	M2	M3	M4	M5
1	Vehicle Control	17.4	18.2	16	16.7	16.8	18.2	18	18.5	17.2	17
2	CDDP 2 mg/kg	17.6	17.2	17.5	16.3	15.7	17.5	18.2	18.5	18.7	18
3	CDDP 6 mg/kg	17.9	16.2	17.5	17	16	18.1	18	18.7	18.3	18
4	SCV-07 10 mg/kg	17	16.7	17	17.3	16.3	18.4	17.9	18	17	18.3
5	SCV-07 20 mg/kg	16	17.2	17.3	17.5	16.7	17.8	16.8	17.1	17.3	17.8
6	SCV-07 10 mg/kg+ CDDP 2 mg/kg	17.5	16.5	16	16	16.6	18.5	18	17.3	18.2	16.4
7	SCV-07 20 mg/kg+ CDDP 2 mg/kg	16	17.2	16.4	16.5	16.8	16.7	17.2	17.6	18	17.3

Appendix 3.17: Body weights (g) on Day 3

Group	Treatment	F1	F2	F3	F4	F5	M1	M2	M3	M4	M5
1	Vehicle Control	17.6	18.4	16	16.9	17	18.4	18	18.8	17.4	17.2
2	CDDP 2 mg/kg	15	16.2	16.6	14	15.2	17.1	18.4	18.3	17.6	17.2
3	CDDP 6 mg/kg	14	14.1	15.5	15	14	17.2	16.9	17.5	17.9	17.2
4	SCV-07 10 mg/kg	17.6	16.8	16.8	18	16.7	18.6	18.2	18.3	17.2	18.5
5	SCV-07 20 mg/kg	17.4	17.6	17.5	17.9	17	18	17	17.3	17.5	18
6	SCV-07 10 mg/kg+ CDDP 2 mg/kg	17.1	15	16.3	15	14.7	18.3	17.5	17.6	18	17
7	SCV-07 20 mg/kg+ CDDP 2 mg/kg	15	17.1	15.2	15.4	16	15.1	16.4	16.4	17.4	17.1

Appendix 3.18: Body weights (g) on Day 6

Group	Treatment	F1	F2	F3	F4	F5	M1	M2	M3	M4	M5
1	Vehicle Control	18.3	19	16.5	17.8	18.5	18.6	18.2	19	17.6	17.4
2	CDDP 2 mg/kg	16.4	16.8	17.7	15.3	16.4	18.7	19	19	18.3	17.6
3	CDDP 6 mg/kg	15	15.2	16	16.4	15	17.9	15.3	17.4	16	17.8
4	SCV-07 10 mg/kg	18	17.4	18.2	18.4	17.1	18.8	18.4	18.7	17.4	18.8
5	SCV-07 20 mg/kg	17.9	18.5	17.7	18.3	17.4	18.3	17.2	17.5	17.7	18.3
6	SCV-07 10 mg/kg+ CDDP 2 mg/kg	18	16	17.3	16.1	16.3	19	19	18.6	18.5	16.3
7	SCV-07 20 mg/kg+ CDDP 2 mg/kg	16.4	18.4	16.6	16.6	17.1	16	17	16	18.9	16

Appendix 3.19: Body weights (g) on Day 9

Group	Treatment	F1	F2	F3	F4	F5	M1	M2	M3	M4	M5
1	Vehicle Control	19.1	19.2	16.7	17.8	18.2	19.2	18.5	19.3	18.4	17.6
2	CDDP 2 mg/kg	16.8	16.8	18	16	17	18.9	19.1	19	18.4	17.4
3	CDDP 6 mg/kg	15	15	15.5	16.2	15	16.4	15.2	17.3	16	15.7
4	SCV-07 10 mg/kg	19	18.5	18.6	18.8	17.1	19.1	18.8	19	18	19
5	SCV-07 20 mg/kg	18	18.5	17.1	18.9	18.7	18.7	17.7	18.1	18.1	18.6
6	SCV-07 10 mg/kg+ CDDP 2 mg/kg	18.2	16.5	17.3	16.3	16.8	19	18.9	15	15	15
7	SCV-07 20 mg/kg+ CDDP 2 mg/kg	16	17.1	16.4	16	17.4	15.7	17	15.8	15	16.6

Appendix 3.20: Body weights (g) on Day 12

Group	Treatment	F1	F2	F3	F4	F5	M1	M2	M3	M4	M5
1	Vehicle Control	19.4	20	17	19.2	16.7	20.4	20.5	21.2	18.4	19.6
2	CDDP 2 mg/kg	17.1	15.1	17.5	16.3	18	18.3	20	20	21	19
3	CDDP 6 mg/kg	13.1	17	17	16	16	18.9	16	16.1	18.3	17.8
4	SCV-07 10 mg/kg	19.5	19	19.8	18.8	16.6	20	19	17.7	19.7	18.8
5	SCV-07 20 mg/kg	18.5	18.6	17.8	19.2	20	18	20	19.7	19.3	20.1
6	SCV-07 10 mg/kg+ CDDP 2 mg/kg	18.3	16.7	17.5	16.9	19.8	21.4	20	16.8	20	15.5
7	SCV-07 20 mg/kg+ CDDP 2 mg/kg	16.1	17.4	17.6	17.2	19	17.9	20.6	17.9	18.2	17.7

Appendix 3.21: Body weights (g) on Day 15

Group	Treatment	F1	F2	F3	F4	F5	M1	M2	M3	M4	M5
1	Vehicle Control	19.8	21	18.3	20.5	18.3	21.2	21.2	21.4	18.9	20
2	CDDP 2 mg/kg	15.2	15	17.6	16.8	17.5	17.1	19.3	18.5	20	18.5
3	CDDP 6 mg/kg	11.1	16.3	14.4	16.3	13.6	18.4	14.6	14.7	15.8	16.5
4	SCV-07 10 mg/kg	20.3	18.6	19.1	18.9	16	20.2	19.4	16.7	20	19.6
5	SCV-07 20 mg/kg	19	18.8	19.1	18.1	19.8	18.3	20.5	18.9	20	20.6
6	SCV-07 10 mg/kg+ CDDP 2 mg/kg	18.1	16.4	17	15.8	19.1	21.4	20.1	16.8	19.4	15.6
7	SCV-07 20 mg/kg+ CDDP 2 mg/kg	15.8	16.4	17.6	17.4	18.8	16.3	17.9	15.7	18.8	16.7

Example 4

In Vitro Effects of SCV-07 on Proliferation of B16, LLC, and RenCa Cell Lines

Abbreviations

5-Fu	5-Fluorouracil
CV	Coefficient of Variation
DMEM	Dulbecco's modified Eagle's medium
DMF	N, N-dimethyl formamide
DTIC	5-(3,3-Dimethyl-1-triazenyl)imidazole-4-carboxamide
FBS	Fetal bovine serum
LLC	Lewis lung carcinoma
MTT	Methylthiazolyldiphenyl-tetrazolium bromide
NA	Not applicable
OD	Optical density
PBS	Phosphate buffered saline
RPMI	Roswell Park Memorial Institute
SD	Standard Deviation
SDS	Sodium dodecyl sulphate
SOP	Standard operation procedure
VBI	Vital Bridge (China), Inc.
Vs	Versus

Summary

[0011] The study was undertaken to evaluate the *in vitro* cytotoxic effect of SCV-07 on B16, LLC, and RenCa cells.

[00112] B16, LLC, or RenCa cells were cultured in 96-well plates in the presence of SCV-07 or a positive control drug (i.e., DTIC, 5-Fu, and Cisplatin) at 12 different concentrations including the blank control. The concentrations of SCV-07 were chosen based on the plasma concentration approximated from the efficacious dose of the previous *in vivo* studies. The concentrations of 5-Fu and Cisplatin were selected per their respective IC₅₀ values reported in the literature. The incubation time of SCV-07 and positive control drugs varied from 24 to 72 hours. The inhibitory effects of the drugs on cell proliferation were determined by the MTT method.

[00113] The treatment of 5-Fu and Cisplatin resulted in significant cytotoxic effects in the corresponding cell lines. The IC₅₀ values for 5-Fu to inhibit B16 cell proliferation were estimated to be 0.26, 0.38, and 0.26 µg/mL in three assays. In RenCa cells, the IC₅₀ values for 5-Fu were estimated to be 0.03, 0.04, and 0.04 µg/mL in three assays. The IC₅₀ values for Cisplatin to inhibit LLC cell proliferation were estimated to be 3.26, 3.07, and 3.10 µg/mL in three assays. SCV-07 at all test concentrations (0.05 to 100 µg/mL) did not inhibit cell proliferation in the cultured B16, LLC, and RenCa cells. The IC₅₀ values for SCV-07 were not obtained due to the lack of fit of its concentration-inhibition curves.

[00114] In conclusion, this study demonstrated that SCV-07 did not have *in vitro* cytotoxic effects on cultured B16, LLC, and RenCa tumor cells.

Introduction

[00115] The objective of the study was to evaluate *in vitro* cytotoxic effects of SCV-07 on B16, LLC, and RenCa cells.

[00116] SCV-07 is an immunomodulator. It has been demonstrated in the previous *in vivo* studies to inhibit the growth of tumor cells (B16, LLC, or RenCa) subcutaneously implanted in mice⁽¹⁻³⁾. In this study, the *in vitro* cytotoxic effects of SCV-07 on these tumor cell lines were evaluated.

[00117] B16, LLC, and RenCa cells were cultured in 96-well plates in the presence of SCV-07 or a positive control drug (DTIC, 5-Fu, or Cisplatin). The incubation time of the drugs in different cell lines varied from 24 to 72 hours. The MTT assay was used for the assessment of the inhibition of cell proliferation.

Materials and Methods

Materials

SCV-07

[00118] SCV-07 (Lot # RR002101) was provided by the Sponsor. A stock solution of SCV-07 at the concentration of 0.5 mg/mL was prepared by dissolving 4.2 mg SCV-07 in 8.4 mL of sterile Dulbecco's PBS (Invitrogen, Cat# 14190-144). The stock solution was then sterile filtered, stored at 2-8°C, and protected from light with tin foil. Prior to use, the stock solution was further diluted to various concentrations with culture media.

DTIC

[00119] DTIC was purchased from Sigma (Cat. # D2390, Lot # 026K1363). A stock solution of 10 mg/mL was prepared by dissolving 8.8 mg of DTIC in 500 μ L of 0.1 N HCl, followed by the addition of 380 μ L of Milli-Q water. Once prepared, the stock solution was sterile filtered, stored at 2-8°C, and protected from light with tin foil. Prior to use, the stock solution was further diluted to various concentrations with culture media.

5-FU

[00120] 5-Fu was purchased from Sigma (Cat. # F6627, Lot # 125K1499). A stock solution of 0.5 mg/mL was prepared by dissolving 4.8 mg of 5-Fu in 9.6 mL of sterile Dulbecco's PBS (Invitrogen, Cat. # 14190-144). Once prepared, the stock solution was sterile filtered, stored at 2-8°C, and protected from light with tin foil. Prior to use, the stock solution was further diluted to various concentrations with culture media.

Cisplatin

[00121] Cisplatin was purchased from Qilu Pharmaceutical Co. LTD. A stock solution of 1 mg/mL was prepared by dissolving 10 mg of cisplatin in 10 mL of sterile Dulbecco's PBS (Invitrogen, Cat. # 14190-144). Once prepared, the stock solution was sterile filtered and stored at 2-8°C. Prior to use, the stock solution was further diluted to various concentrations with culture media.

Other Materials

[00122] MTT was purchased from Sigma (Cat. # M2128). FBS, Penicillin-Streptomycin, DMEM and RPMI-1640 media were purchased from Invitrogen. Falcon[®] 96-well flat-bottom plates (BD, Cat. # 353072) were purchased from Fisher Scientific.

Test Systems

B16 Cell Culture

[00123] B16 melanoma cell line was obtained from Shanghai Cell Bank, Chinese Academy of Sciences. The cells were cultured in RPMI-1640 medium supplemented with 10% FBS, 100 units/mL Penicillin, and 100 µg/mL Streptomycin.

LLC Cell Culture

[00124] LLC cell line was obtained from Shanghai Cell Bank, Chinese Academy of Sciences. The cells were cultured in DMEM supplemented with 10% FBS, 100 units/mL Penicillin, and 100 µg/mL Streptomycin.

RenCa Cell Culture

[00125] RenCa cell line was obtained from Chinese Military Academy of Sciences. The cells were cultured in RPMI-1640 medium supplemented with 10% FBS, 100 units/mL Penicillin, and 100 µg/mL Streptomycin.

MTT Assay

[00126] MTT assay was conducted according to VBI SOP 65.026. Briefly, the suspensions of B16, LLC, or RenCa cells were prepared with the corresponding culture media described above. One hundred µL of the cell suspensions were seeded into each well of Falcon[®] 96-well flat-bottom plates. The seeding density was 10000 cells per well (for B16 and LLC cell lines) or 7000 cells per well (for RenCa cell line). Drug treatment was performed by adding 25 µL of drugs to the plates and then incubating the plates at 37°C

with 5% CO₂ for a pre-defined period of time (see Table 4.1 for details on the drug treatment). The drugs were treated with 12 concentrations including the blank control, with each concentration tested in quadruplicates. The concentrations of SCV-07 were chosen based on the plasma concentrations approximated from the efficacious dose of the previous *in vivo* studies. The concentrations of 5-Fu and Cisplatin were selected per their respective IC₅₀ values reported in the literature for the corresponding cell lines. After the drug treatment, MTT was added to each well at a final concentration of 1 mg/mL, and the cell incubation was continued for 4 hours. At the end of MTT incubation, the extraction buffer consisting of SDS and DMF was added to the plates to solubilize formazan converted from MTT by viable cells. OD of each well was then measured with Tecan Infinite M200 plate reader at 570 nm.

Table 4.1. Drug Treatment Design

Cell Line	Drug	Duration (hours)	Final Drug Concentration (µg/mL)											
			0	0.05	0.1	0.2	0.5	1	2	5	10	20	50	100
B16	SCV-07	24	0	0.05	0.1	0.2	0.5	1	2	5	10	20	50	100
	DTIC	24	0	0.25	0.5	1	2.5	5	10	25	50	100	250	500
	5-Fu	24	0	0.05	0.1	0.2	0.5	1	2	5	10	20	50	100
LLC	SCV-07	48	0	0.05	0.1	0.2	0.5	1	2	5	10	20	50	100
	Cisplatin	48	0	0.1	0.2	0.5	1	2	5	10	20	50	100	200
RenCa	SCV-07	72	0	0.05	0.1	0.2	0.5	1	2	5	10	20	50	100
	5-Fu	72	0	0.05	0.1	0.2	0.5	1	2	5	10	20	50	100

Data Analyses

Calculation of Mean and SD

[00127] Raw OD data were imported into Microsoft Excel for the calculation of mean and SD.

Calculation of IC₅₀

[00128] The IC₅₀ for inhibiting cell proliferation was calculated with Prism 5.01 (GraphPad Software, Inc.). The concentrations of a drug that resulted in cell killing were excluded from determination of the IC₅₀. The IC₅₀ was estimated by using the formula below:

$$Y = \text{Bottom} + \frac{\text{Top} - \text{Bottom}}{1 + 10^{(X - \text{LogIC}_{50})}}$$

Herein, X stands for concentration of a drug, and Y for corresponding OD. Bottom stands for theoretically lowest OD (corresponding to the maximal inhibition of cell growth), while Top represents the theoretical highest OD. The IC₅₀ represents the concentration of the drug producing 50% response. Upon entering all X and Y values, the values of Bottom, Top, and IC₅₀ were automatically determined via the program by fitting to the built-in inhibition model (i.e., Log [Inhibitor] vs Response model).

Results

Effects of SCV-07 on B16 Cells

[00129] The effects of SCV-07 and positive control drugs on B16 cell proliferation were measured. The calculated IC₅₀ values are listed in Table 4.2. Raw data and the calculated mean and SD are tabulated in Appendices 4.1-4.4. The concentration-inhibition curve of SCV-07 was essentially flat, indicating the absence of a cytotoxic effect (i.e., inhibition of cell proliferation) of SCV-07 on B16 cells. DTIC was initially used as the positive control. However, the cytotoxic effect was noted only at higher concentrations (i.e., 250 and 500 µg/mL), and IC₅₀ was not established due to the failure of the curve to converge. This is probably due to the lack of hepatocyte-dependent activation of DTIC. The inhibition of cell growth was observed for 5-Fu at a range of concentrations from 0.2 to 20 µg/mL. Cell killing was induced at 50 and 100 µg/mL. The two concentrations were thereby excluded from the IC₅₀ analysis. The IC₅₀ values were determined to be 0.26, 0.38, and 0.26 µg/mL for 5-Fu in three assays. On the contrary, IC₅₀ values were not obtained for SCV-07 due to the lack of fit of its concentration-inhibition curves.

Table 4.2 IC₅₀ for Growth Inhibition of B16 Cells

Assay ID	IC ₅₀ (μg/mL)		
	SCV-07	DTIC	5-Fu
11280701	-	-	NT
12050701	-	NT	0.26
12050702	-	NT	0.38
12050703	-	NT	0.26

"-" indicates that IC₅₀ value was not obtained due to lack of fit. NT: not tested.

Effects of SCV-07 on LLC Cells

[00130] The effects of SCV-07 and Cisplatin (positive control drug) on LLC cell proliferation were measured. The calculated values of IC₅₀ are listed in Table 4.3. Raw data and the calculated mean and SD are tabulated in Appendices 4.5-4.7. The concentration-inhibition curve of SCV-07 was essentially flat, indicating the absence of the cytotoxicity in LLC cells. On the contrary, the cytotoxic effect was observed for Cisplatin at concentrations of 1.0 μg/mL and above. The IC₅₀ values for Cisplatin were 3.26, 3.07, and 3.10 μg/mL in three assays, while IC₅₀ values could not be established for SCV-07 due to the lack of fit of its concentration-inhibition curves.

Table 4.3. IC₅₀ for Growth Inhibition of LLC Cells

Assay ID	IC ₅₀ (μg/mL)	
	SCV-07	Cisplatin
12060704	-	3.26
12060705	-	3.07
12060706	-	3.10

"-" indicates that IC₅₀ value was not obtained due to lack of fit.

Effects of SCV-07 on RenCa Cells

[00131] The effects of SCV-07 and 5-Fu (positive control drug) on RenCa cell proliferation were measured. The calculated IC₅₀ values are listed in Table 4.4. Raw data and the calculated mean and SD are tabulated in Appendices 4.8-4.10. The concentration-inhibition curve of SCV-07 was essentially flat, indicating the absence of the cytotoxicity in RenCa cells. On the contrary, the cytotoxic effects were observed for 5-Fu at a range of concentrations from 0.05 to 10 µg/mL. Cell killing was induced at 20, 50, and 100 µg/mL. The three concentrations were thereby excluded from the IC₅₀ analysis. The IC₅₀ values for 5-Fu were 0.03, 0.04, and 0.04 µg/mL in three assays. By contrast, the IC₅₀ values were not obtained for SCV-07 due to the lack of fit of its concentration-inhibition curves.

Table 4.4. IC₅₀ for Growth Inhibition of RenCa Cells

Assay ID	IC ₅₀ (µg/mL)	
	SCV-07	5-Fu
12070704	-	0.03
12070705	-	0.04
12070706	-	0.04

"-" indicates that IC₅₀ value was not obtained due to lack of fit.

Conclusion and Discussion

[00132] The treatment of 5-Fu and Cisplatin resulted in significant inhibition of cell proliferation in the corresponding cell lines, validating this assay for use in determining the potential cytotoxicity of the test compounds. The IC₅₀ values for 5-Fu to inhibit B16 cell proliferation were estimated to be 0.26, 0.38, and 0.26 µg/mL in three assays. In RenCa cells, the IC₅₀ values for 5-Fu were estimated to be 0.03, 0.04, and 0.04 µg/mL in three assays. The IC₅₀ values for Cisplatin to inhibit LLC cell proliferation were estimated to be 3.26, 3.07, and 3.10 µg/mL in three assays. The cytotoxicity was noted for DTIC at higher concentrations (i.e., 250 and 500 µg/mL). The lack of appreciable cytotoxicity at lower concentrations of DTIC is consistent with the requirement of metabolic conversion of DTIC to more toxic metabolites by hepatocytes, which were not included in the assay.

DTIC							
Conc. (ug/mL)	OD1	OD2	OD3	OD4	Mean	SD	CV
0	1.1309	1.2231	1.2149	1.0987	1.17	0.062	5.28%
0.25	1.1613	1.1378	1.0642	1.0816	1.11	0.046	4.12%
0.5	1.2172	1.1962	1.0476	1.0961	1.14	0.081	7.09%
1	1.1808	1.2467	1.1306	1.1605	1.18	0.049	4.17%
2.5	1.1187	1.1669	1.2015	0.9904	1.12	0.092	8.26%
5	1.2193	1.2789	1.2814	1.1601	1.23	0.058	4.66%
10	1.1866	1.163	1.2257	1.1542	1.18	0.032	2.70%
25	1.1756	1.138	1.2473	1.1683	1.18	0.046	3.92%
50	1.1646	1.1502	1.204	1.0905	1.15	0.047	4.09%
100	1.1285	1.04	1.1651	1.0657	1.10	0.057	5.20%
250	0.9685	0.9461	0.8378	0.8835	0.91	0.060	6.55%
500	0.6193	0.5894	0.615	0.6246	0.61	0.016	2.55%

Appendix 4.2: Raw Data and Calculated Mean and SD of MTT Assay 12050701

Cell line B16(10000 cell/well) Drug treatment (SCV-07 vs 5-Fu)
 Drug treatment time 24 hours

SCV-07							
Conc. (ug/mL)	OD1	OD2	OD3	OD4	Mean	SD	CV
0	0.6845	0.6673	0.6631	0.708	0.6807	0.0204	3.00%
0.05	0.6626	0.6924	0.7006	0.7459	0.7004	0.0345	4.92%
0.2	0.7661	0.7629	0.7463	0.755	0.7576	0.0088	1.17%
0.5	0.744	0.7374	0.7929	0.6887	0.7408	0.0426	5.75%
1	0.7415	0.7574	0.7718	0.7476	0.7546	0.0132	1.75%
1	0.7591	0.6618	0.7503	0.739	0.7276	0.0446	6.13%
2	0.7616	0.7472	0.7613	0.7359	0.7515	0.0124	1.65%
5	0.7604	0.7323	0.7637	0.7508	0.7518	0.0141	1.88%
10	0.7405	0.7439	0.7174	0.6915	0.7233	0.0243	3.35%
20	0.7291	0.6819	0.7529	0.7262	0.7225	0.0296	4.10%
50	0.5887	0.6665	0.7022	0.677	0.6586	0.0489	7.43%
100	0.6107	0.5747	0.6334	0.6176	0.6091	0.0248	4.08%

5-Fu							
Conc. (ug/mL)	OD1	OD2	OD3	OD4	Mean	SD	CV
0	0.6025	0.6102	0.5967	0.5826	0.5980	0.0117	1.95%
0.05	0.6949	0.6641	0.6086	0.5543	0.6305	0.0621	9.85%
0.1	0.6278	0.6051	0.6123	0.6158	0.6153	0.0095	1.54%
0.2	0.5906	0.5763	0.55	0.5112	0.5570	0.0349	6.26%
0.5	0.4997	0.4868	0.4703	0.466	0.4807	0.0155	3.23%
1	0.4645	0.4544	0.4483	0.4631	0.4576	0.0076	1.67%
2	0.4425	0.4342	0.4424	0.4546	0.4434	0.0084	1.90%
5	0.4366	0.4313	0.4241	0.4194	0.4279	0.0076	1.78%
10	0.4033	0.4083	0.401	0.4063	0.4047	0.0032	0.80%
20	0.3805	0.3811	0.3807	0.3761	0.3796	0.0023	0.62%
50	0.3363	0.3357	0.3322	0.3286	0.3332	0.0036	1.07%
100	0.2875	0.2919	0.2906	0.2729	0.2857	0.0087	3.06%

Appendix 4.3: Raw Data and Calculated Mean and SD of MTT Assay 12050702

Cell line B16(10000 cell/well) Drug treatment (SCV-07 vs 5-Fu)
 Drug treatment time 24 hours

SCV-07							
Conc. (ug/mL)	OD1	OD2	OD3	OD4	Mean	SD	CV
0	0.695	0.5837	0.6308	0.5974	0.6267	0.0496	7.92%
0.05	0.6386	0.6994	0.7424	0.7349	0.7038	0.0474	6.73%
0.1	0.6938	0.7456	0.7138	0.6847	0.7095	0.0270	3.80%
0.2	0.711	0.7734	0.6973	0.6892	0.7177	0.0382	5.32%
0.5	0.7112	0.7642	0.7546	0.7006	0.7327	0.0314	4.29%
1	0.7452	0.7924	0.7406	0.7118	0.7475	0.0334	4.47%
2	0.7075	0.7205	0.7687	0.6784	0.7188	0.0377	5.24%
5	0.6359	0.7209	0.7446	0.6954	0.6992	0.0467	6.68%
10	0.6511	0.7422	0.7219	0.7425	0.7144	0.0433	6.06%
20	0.694	0.6401	0.6941	0.7006	0.6822	0.0282	4.14%
50	0.6777	0.6159	0.5761	0.5922	0.6155	0.0446	7.24%
100	0.5076	0.5969	0.5342	0.5324	0.5428	0.0381	7.01%

5-Fu							
Conc. (ug/mL)	OD1	OD2	OD3	OD4	Mean	SD	CV
0	0.6183	0.6048	0.6115	0.4979	0.5831	0.0571	9.79%
0.05	0.6181	0.6008	0.5703	0.5218	0.5778	0.0422	7.31%
0.1	0.6282	0.6158	0.5688	0.5398	0.5882	0.0412	7.00%
0.2	0.5831	0.5388	0.526	0.5072	0.5388	0.0323	5.99%
0.5	0.4926	0.4553	0.4541	0.4382	0.4601	0.0231	5.01%
1	0.4534	0.4464	0.4319	0.4357	0.4419	0.0098	2.23%
2	0.4307	0.4249	0.4251	0.3913	0.4180	0.0180	4.31%
5	0.4054	0.4086	0.4028	0.3941	0.4027	0.0062	1.54%
10	0.3888	0.367	0.3859	0.3523	0.3735	0.0171	4.58%
20	0.3756	0.3672	0.3688	0.3629	0.3686	0.0053	1.43%
50	0.3154	0.3314	0.3323	0.309	0.3220	0.0116	3.62%
100	0.2735	0.2699	0.2734	0.2604	0.2693	0.0062	2.29%

Appendix 4.4: Raw Data and Calculated Mean and SD of MTT Assay 12050703

Cell line B16(10000 cell/well) Drug treatment (SCV-07 vs 5-Fu)
 Drug treatment time 24 hours

SCV-07							
Conc. (ug/mL)	OD1	OD2	OD3	OD4	Mean	SD	CV
0	0.5745	0.6092	0.5949	0.6477	0.6066	0.0309	5.09%
0.05	0.6809	0.675	0.6089	0.6452	0.6525	0.0330	5.06%

0.2	0.6696	0.7292	0.6947	0.6956	0.6973	0.0245	3.51%
0.5	0.7292	0.7111	0.7482	0.7192	0.7269	0.0160	2.20%
1	0.6555	0.6848	0.711	0.6885	0.6850	0.0228	3.33%
1	0.6734	0.7213	0.6829	0.6622	0.6850	0.0257	3.75%
2	0.7587	0.7358	0.7332	0.7322	0.7400	0.0126	1.70%
5	0.7289	0.7114	0.7598	0.7487	0.7372	0.0214	2.91%
10	0.7394	0.7117	0.6772	0.7079	0.7091	0.0255	3.59%
20	0.6577	0.6828	0.6062	0.6144	0.6403	0.0363	5.66%
50	0.629	0.6333	0.6409	0.708	0.6528	0.0371	5.69%
100	0.5753	0.5682	0.5656	0.6062	0.5788	0.0187	3.23%

5-Fu							
Conc. (ug/mL)	OD1	OD2	OD3	OD4	Mean	SD	CV
0	0.6025	0.5566	0.5621	0.5446	0.5665	0.0251	4.43%
0.05	0.6739	0.5901	0.5928	0.5259	0.5957	0.0606	10.18%
0.2	0.569	0.5109	0.5079	0.4717	0.5149	0.0402	7.82%
0.5	0.4684	0.4738	0.4973	0.4692	0.4772	0.0136	2.86%
1	0.4535	0.4405	0.4448	0.435	0.4435	0.0078	1.76%
1	0.5876	0.5856	0.6025	0.5704	0.5865	0.0131	2.24%
2	0.435	0.4246	0.4211	0.4037	0.4211	0.0130	3.09%
5	0.4194	0.4031	0.4156	0.3885	0.4067	0.0140	3.43%
10	0.4113	0.394	0.3915	0.3873	0.3960	0.0106	2.66%
20	0.3864	0.3903	0.3819	0.3743	0.3832	0.0069	1.79%
50	0.3367	0.3291	0.3243	0.3047	0.3237	0.0137	4.22%
100	0.2669	0.2823	0.2876	0.272	0.2772	0.0094	3.41%

Appendix 4.5: Raw Data and Calculated Mean and SD of MTT Assay 12060704

Cell line LLC (10000 cells/well) Drug treatment (SCV-07 vs Cisplatin)
Drug treatment time 48 hours

SCV-07							
Conc. (ug/mL)	OD1	OD2	OD3	OD4	Mean	SD	CV
0	1.4131	1.3671	1.4141	1.4641	1.4146	0.0396	2.80%
0.05	1.4385	1.4471	1.3818	1.4299	1.4243	0.0292	2.05%
0.1	1.4923	1.5682	1.4111	1.3321	1.4509	0.1019	7.03%
0.2	1.5528	1.5654	1.4445	1.3831	1.4865	0.0877	5.90%
0.5	1.4889	1.5723	1.4563	1.4307	1.4871	0.0616	4.14%
1	1.4774	1.6092	1.4985	1.4398	1.5062	0.0728	4.83%

2	1.4785	1.5705	1.4299	1.4039	1.4707	0.0734	4.99%
5	1.4811	1.5539	1.4662	1.4039	1.4763	0.0616	4.17%
10	1.4506	1.5419	1.4917	1.4419	1.4815	0.0457	3.09%
20	1.4742	1.5821	1.4846	1.4122	1.4883	0.0702	4.72%
50	1.4266	1.5641	1.6047	1.5048	1.5251	0.0774	5.08%
100	1.3986	1.4666	1.4381	1.4162	1.4299	0.0293	2.05%

Cisplatin							
Conc. (ug/mL)	OD1	OD2	OD3	OD4	Mean	SD	CV
0	1.4438	1.3406	1.4	1.4602	1.4112	0.0535	3.79%
0.1	1.2981	1.2868	1.4543	1.4465	1.3714	0.0914	6.66%
0.2	1.2665	1.2446	1.351	1.3193	1.2954	0.0486	3.75%
0.5	1.2295	1.1064	1.2561	1.2975	1.2224	0.0822	6.73%
1	1.1076	1.0239	1.0597	1.151	1.0856	0.0555	5.11%
2	0.9158	0.8338	0.8627	0.8629	0.8688	0.0342	3.93%
5	0.6476	0.6367	0.654	0.6724	0.6527	0.0150	2.29%
10	0.4029	0.4246	0.4569	0.4347	0.4298	0.0224	5.22%
20	0.2586	0.2343	0.257	0.2308	0.2452	0.0147	5.98%
50	0.19	0.1874	0.1826	0.1887	0.1872	0.0032	1.73%
100	0.1641	0.1489	0.159	0.1593	0.1578	0.0064	4.05%
200	0.1241	0.1219	0.1218	0.1242	0.1230	0.0013	1.08%

Appendix 4. 6: Raw Data and Calculated Mean and SD of MTT Assay 12060705

Cell line LLC (10000 cells/well) Drug treatment (SCV-07 vs Cisplatin)
 Drug treatment time 48 hours

SCV-07							
Conc. (ug/mL)	OD1	OD2	OD3	OD4	Mean	SD	CV
0	1.4272	1.3239	1.4266	1.4842	1.4155	0.0668	4.72%
0.05	1.456	1.3736	1.4003	1.4518	1.4204	0.0402	2.83%
0.1	1.4119	1.3813	1.4015	1.3273	1.3805	0.0377	2.73%
0.2	1.3869	1.3807	1.4118	1.3288	1.3771	0.0349	2.53%
0.5	1.3689	1.3883	1.3435	1.312	1.3532	0.0330	2.44%
1	1.3774	1.4727	1.3709	1.3566	1.3944	0.0529	3.80%
2	1.3888	1.3787	1.3023	1.3347	1.3511	0.0401	2.97%
5	1.3882	1.4287	1.3784	1.3639	1.3898	0.0278	2.00%
10	1.3838	1.3646	1.4306	1.3676	1.3867	0.0305	2.20%
20	1.3617	1.4192	1.4016	1.3575	1.3850	0.0302	2.18%
50	1.3541	1.4293	1.4801	1.4914	1.4387	0.0625	4.35%
100	1.3945	1.3994	1.411	1.4409	1.4115	0.0208	1.47%

Cisplatin							
Conc. (ug/mL)	OD1	OD2	OD3	OD4	Mean	SD	CV
0	1.339	1.3719	1.4185	1.4699	1.3998	0.0570	4.07%
0.1	1.3265	1.2827	1.4548	1.4766	1.3852	0.0951	6.87%
0.2	1.1914	1.2543	1.3664	1.3314	1.2859	0.0785	6.10%
0.5	1.2099	1.072	1.2569	1.2888	1.2069	0.0956	7.92%
1	1.0624	0.9971	1.0372	1.1493	1.0615	0.0644	6.07%
2	0.857	0.8196	0.858	0.8878	0.8556	0.0279	3.26%
5	0.6211	0.6123	0.6541	0.6823	0.6425	0.0321	4.99%
10	0.3884	0.4067	0.4585	0.4381	0.4229	0.0314	7.42%
20	0.2526	0.2307	0.258	0.233	0.2436	0.0137	5.64%
50	0.186	0.1812	0.1837	0.1882	0.1848	0.0030	1.63%
100	0.1609	0.1473	0.159	0.1601	0.1568	0.0064	4.08%
200	0.1228	0.1226	0.1224	0.1237	0.1229	0.0006	0.47%

Appendix 4.7: Raw Data and Calculated Mean and SD of MTT Assay 12060706

Drug treatment (SCV-07 vs Cisplatin)

Cell line LLC (10000 cells/well) Drug treatment time 48 hours

SCV-07							
Conc. (ug/mL)	OD1	OD2	OD3	OD4	Mean	SD	CV
0	1.4351	1.3309	1.4312	1.4827	1.4200	0.0638	4.50%
0.05	1.4728	1.3554	1.4340	1.4665	1.4322	0.0539	3.77%
0.1	1.4237	1.3684	1.3839	1.3602	1.3841	0.0282	2.04%
0.2	1.3918	1.3477	1.4257	1.3061	1.3678	0.0521	3.81%
0.5	1.3643	1.3710	1.3840	1.2949	1.3536	0.0399	2.95%
1	1.3714	1.4547	1.4033	1.3810	1.4026	0.0372	2.65%
2	1.3762	1.3586	1.3582	1.3631	1.3640	0.0084	0.62%
5	1.3890	1.3812	1.3867	1.3997	1.3892	0.0078	0.56%
10	1.3536	1.3438	1.4203	1.3918	1.3774	0.0353	2.56%
20	1.3870	1.3834	1.4179	1.3917	1.3950	0.0156	1.12%
50	1.3991	1.4275	1.4750	1.5036	1.4513	0.0469	3.23%
100	1.4015	1.3835	1.4165	1.4369	1.4096	0.0227	1.61%

Cisplatin							
Conc. (ug/mL)	OD1	OD2	OD3	OD4	Mean	SD	CV
0	1.3262	1.3668	1.4249	1.4716	1.3974	0.0639	4.58%
0.1	1.3274	1.3206	1.4551	1.4797	1.3957	0.0834	5.98%
0.2	1.2235	1.2814	1.3661	1.3362	1.3018	0.0629	4.83%
0.5	1.2338	1.1176	1.2645	1.2875	1.2259	0.0754	6.15%
1	1.0775	1.0392	1.0629	1.1371	1.0792	0.0417	3.87%
2	0.8508	0.8616	0.8627	0.8901	0.8663	0.0168	1.93%
5	0.6228	0.6287	0.6673	0.6841	0.6507	0.0297	4.57%
10	0.3873	0.4067	0.4589	0.4376	0.4226	0.0318	7.53%
20	0.2473	0.2358	0.2583	0.2328	0.2436	0.0117	4.78%
50	0.1833	0.1825	0.1841	0.1885	0.1846	0.0027	1.45%
100	0.1612	0.1493	0.1591	0.1599	0.1574	0.0055	3.46%
200	0.1238	0.1223	0.1222	0.1239	0.1231	0.0009	0.75%

Appendix 4.8: Raw Data and Calculated Mean and SD of MTT Assay 12070704

Cell line RenCa (7000 cells/well) Drug treatment (SCV-07 vs 5-Fu)
 Drug treatment time 72 hours

SCV-07

Conc. (ug/mL)	OD1	OD2	OD3	OD4	Mean	SD	CV
0	1.1512	1.0942	1.1050	1.0829	1.1083	0.0300	2.70%
0.05	1.0374	1.0135	1.0011	0.9291	0.9953	0.0466	4.68%
0.1	1.0565	1.0203	1.0421	1.0147	1.0334	0.0194	1.88%
0.2	1.0777	1.0217	0.9710	1.0184	1.0222	0.0437	4.27%
0.5	1.0957	1.0963	1.0017	1.0202	1.0535	0.0497	4.72%
1	1.0492	1.0211	0.9666	1.0728	1.0274	0.0457	4.45%
2	1.0209	1.0683	1.0650	1.0673	1.0554	0.0230	2.18%
5	1.0664	1.1032	0.9598	1.0856	1.0538	0.0644	6.11%
10	0.9690	1.0370	1.0541	1.0158	1.0190	0.0368	3.61%
20	1.1018	1.1023	0.9306	1.0288	1.0409	0.0812	7.80%
50	1.0275	1.0561	0.9939	0.9547	1.0081	0.0437	4.34%
100	0.9803	0.9369	1.0102	0.9290	0.9641	0.0381	3.95%

5-Fu							
Conc. (ug/mL)	OD1	OD2	OD3	OD4	Mean	SD	CV
0	1.0886	1.0952	1.0514	1.0915	1.0817	0.0204	1.88%
0.05	0.6485	0.6341	0.6411	0.6063	0.6325	0.0184	2.91%
0.1	0.4897	0.4751	0.5134	0.5262	0.5011	0.0230	4.59%
0.2	0.4176	0.3867	0.3894	0.3800	0.3934	0.0166	4.22%
0.5	0.3363	0.3221	0.3346	0.3203	0.3283	0.0083	2.52%
1	0.3088	0.2917	0.2998	0.3067	0.3018	0.0077	2.56%
2	0.2875	0.2766	0.2880	0.3072	0.2898	0.0127	4.39%
5	0.3027	0.2948	0.2819	0.2933	0.2932	0.0086	2.92%
10	0.2745	0.2829	0.2743	0.2925	0.2811	0.0086	3.07%
20	0.2639	0.2577	0.2471	0.2730	0.2604	0.0109	4.18%
50	0.2221	0.2255	0.2151	0.2263	0.2223	0.0051	2.30%
100	0.2036	0.1959	0.1882	0.2070	0.1987	0.0084	4.22%

Appendix 4. 9: Raw Data and Calculated Mean and SD of MTT Assay 12070705

Cell line RenCa (7000 cells/well) Drug treatment (SCV-07 vs 5-Fu)
 Drug treatment time 72 hours

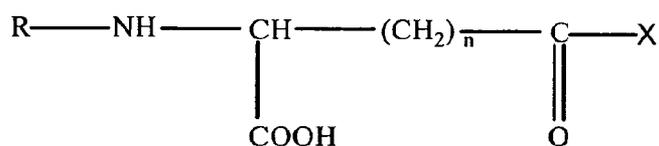
SCV-07							
Conc. (ug/mL)	OD1	OD2	OD3	OD4	Mean	SD	CV
0	1.1302	1.0936	1.1067	1.0937	1.1061	0.0172	1.56%
0.05	1.0943	1.0399	0.9717	1.0023	1.0271	0.0528	5.14%

0.1	1.0329	1.0464	0.9478	1.0264	1.0134	0.0445	4.39%
0.2	1.0809	1.0599	1.0848	0.9881	1.0534	0.0449	4.26%
0.5	1.0460	1.0517	0.9973	1.0159	1.0277	0.0257	2.50%
1	1.0780	1.1082	1.0618	0.9667	1.0537	0.0611	5.80%
2	1.0990	1.1076	1.1703	1.0328	1.1024	0.0563	5.10%
5	1.0603	1.0883	1.1130	1.0614	1.0808	0.0251	2.32%
10	1.0470	1.1484	1.1144	1.0625	1.0931	0.0468	4.28%
20	1.1738	1.1348	1.0721	1.0460	1.1067	0.0582	5.26%
50	1.0781	1.1069	1.0368	1.0795	1.0753	0.0289	2.69%
100	1.0145	1.0008	1.0017	0.9641	0.9953	0.0217	2.18%

5-Fu							
Conc. (ug/mL)	OD1	OD2	OD3	OD4	Mean	SD	CV
0	1.1518	1.1850	1.1659	1.2038	1.1766	0.0227	1.93%
0.05	0.6016	0.6238	0.5999	0.6511	0.6191	0.0240	3.87%
0.1	0.4858	0.4996	0.5300	0.5037	0.5048	0.0185	3.66%
0.2	0.3779	0.4014	0.3843	0.4218	0.3964	0.0197	4.96%
0.5	0.3096	0.2969	0.3027	0.3181	0.3068	0.0091	2.98%
1	0.3073	0.2830	0.2847	0.2981	0.2933	0.0115	3.93%
2	0.2980	0.2903	0.2744	0.2933	0.2890	0.0102	3.54%
5	0.3027	0.2859	0.2876	0.2945	0.2927	0.0076	2.61%
10	0.2929	0.2816	0.2719	0.2777	0.2810	0.0089	3.15%
20	0.2585	0.2576	0.2555	0.2560	0.2569	0.0014	0.54%
50	0.2216	0.2162	0.2188	0.2141	0.2177	0.0032	1.49%
100	0.1911	0.1943	0.1915	0.2014	0.1946	0.0048	2.45%

CLAIMS

1. A method of treatment for treating, at least partly preventing, inhibiting or reducing lung cancer, a metastasis thereof, or a metastasis in a lung from a cancer outside the lung, or for treating, at least partly preventing, inhibiting or reducing growth of lung cancer cells, a metastasis thereof, or a metastasis of cancer cells in a lung from cancer cells outside the lung, in a subject, comprising administering to the subject an effective amount of an immunomodulator compound of formula A



(A)

- wherein, n is 1 or 2, R is hydrogen, acyl, alkyl or a peptide fragment, and X is an aromatic or heterocyclic amino acid or a derivative thereof, so as to treat, at least partly prevent, inhibit or reduce said lung cancer, said metastasis thereof, or said metastasis in a lung from a cancer outside the lung in the subject, or so as to treat, at least partly prevent, inhibit or reduce growth of said lung cancer cells, said metastasis thereof, or said metastasis of cancer cells in said lung from cancer cells outside the lung, in the subject.
2. The method of claim 1, wherein X is L-tryptophan or D-tryptophan.
 3. The method of claim 1 wherein said compound is SCV-07.
 4. The method of claim 1 wherein said compound is administered at a dosage within a range of about 0.001-1000 mg.
 5. The method of claim 1 wherein said compound is administered at a dosage within a range of about 0.01-100 mg.

6. The method of claim 1 wherein said compound is administered at a dosage within a range of about 0.00001-1000 mg/kg subject body weight.
7. The method of claim 1 wherein said compound is administered at a dosage within a range of about 0.01-100 mg/kg subject body weight.
8. The method of claim 1 wherein said compound is SCV-07, and is administered at a dosage within a range of about 0.001-1000 mg.
9. The method of claim 1 wherein said compound is SCV-07, and administered at a dosage within a range of about 0.00001-1000 mg/kg subject body weight.
10. The method of claim 3 wherein said treatment is for primary lung cancer.
11. The method of claim 10 wherein said compound is administered at a dosage within a range of about 0.001-1000 mg.
12. The method of claim 10 wherein said compound is administered at a dosage within a range of about 0.1-100 mg.
13. The method of claim 10 wherein said compound is administered at a dosage within a range of about 0.00001-1000 mg/kg subject body weight.
14. The method of claim 10 wherein said compound is administered at a dosage within a range of about 0.01-100 mg/kg subject body weight.
15. The method of claim 3 wherein said treatment is for a lung cancer metastasis.
16. The method of claim 15 wherein said compound is administered at a dosage within a range of about 0.001-1000 mg.
17. The method of claim 15 wherein said compound is administered at a dosage within a range of about 0.1-100 mg.
18. The method of claim 15 wherein said compound is administered at a dosage within a range of about 0.00001-1000 mg/kg subject body weight.

19. The method of claim 15 wherein said compound is administered at a dosage within a range of about 0.01-100 mg/kg subject body weight.
20. The method of claim 12 wherein said dosage is about 10 mg.
21. The method of claim 17 wherein said dosage is about 10 mg.
22. The method of claim 1 wherein said compound of formula A is administered in a treatment regimen additionally including administration of at least one of radiation or a chemotherapy agent.
23. The method of claim 22 wherein said chemotherapy agent comprises at least one of cisplatin, 5-Fu or DTIC.

Figure 1: Tumor growth curves in all treatment groups

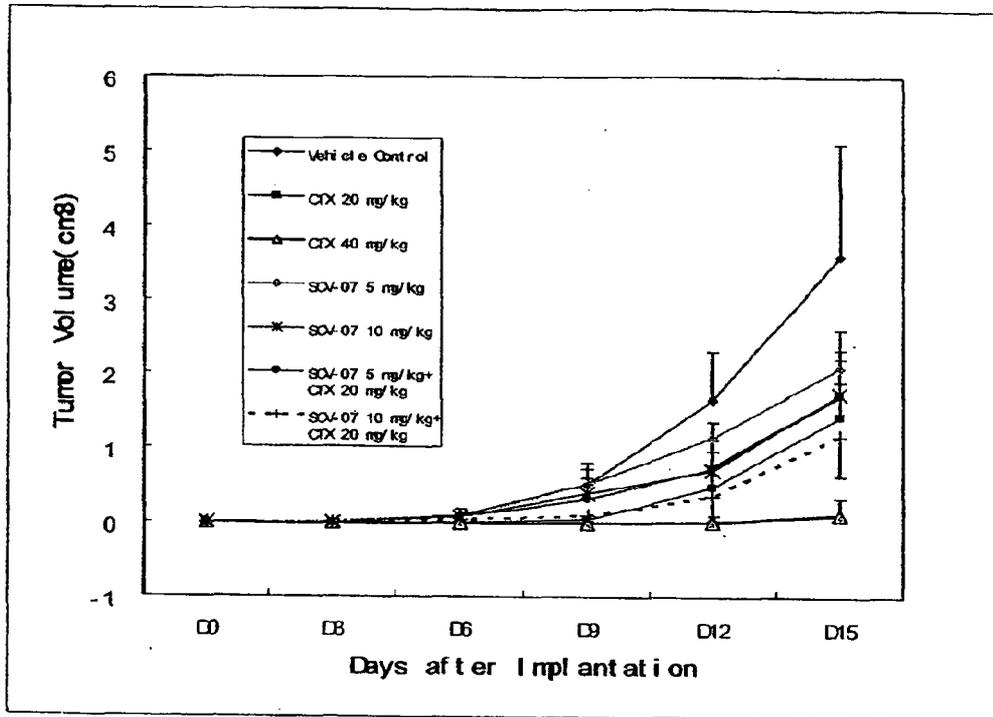
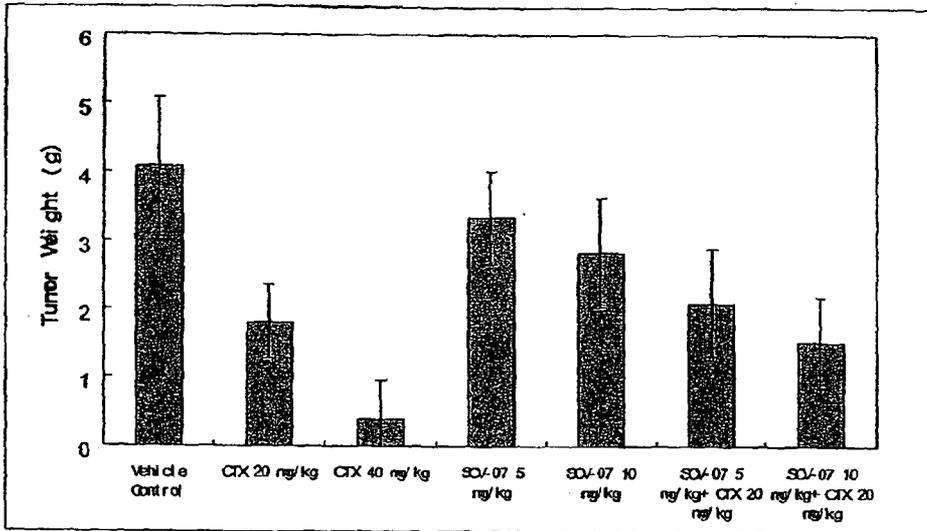
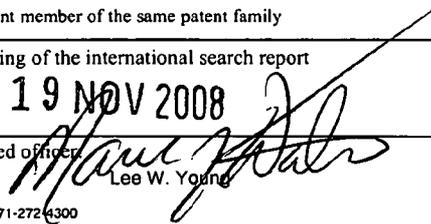


Figure 2: Tumor weights measured on Day 16



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/09932

<p>A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - A01N 43/38; A61K 31/40, 38/00 (2008.04) USPC - 514/19, 419 According to International Patent Classification (IPC) or to both national classification and IPC</p>														
<p>B. FIELDS SEARCHED</p> <p>Minimum documentation searched (classification system followed by classification symbols) USPC-514/19, 419</p> <p>Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched USPC-435/108 (see search terms below)</p> <p>Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) PubWest: DB = PGPB, USPT, EPAB, JPAB: terms- immunomodulator, immunostimulatory, tryptophan, glutamyl, lung, cancer, cisplatin, SCV-07, respiratory, metastasis, radiation, chemotherapy; Google Scholar: terms- SCV-07, lung cancer, immunomodulator, cisplatin, gamma glutamyl tryptophan</p>														
<p>C. DOCUMENTS CONSIDERED TO BE RELEVANT</p> <table border="1"> <thead> <tr> <th>Category*</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>Y</td> <td>SMITH et al. Natural Killer Cell Cytolytic Activity Is Necessary For In Vivo Antitumor Activity of the Dipeptide L-Glutamyl-L-Tryptophan. Int. J. Cancer, 2003, Vol 106, pp 528-533, especially p 532, Fig 5</td> <td>1-23</td> </tr> <tr> <td>Y</td> <td>US 5,916,878 A (KOLOBOV et al.) 29 Jun 1999 (29.06.1999) col 4, ln 21-22, ln 35-37, ln 67; col 5, ln 48; col 12, ln 20-21, ln 24</td> <td>1-23</td> </tr> <tr> <td>Y</td> <td>AKHMATOVA et al. Immunovac-VP-4, immunomodulator decreases immunosuppression and enhances the cytotoxic activity induced by the cytostatic Cisplatin. Zh Mikrobiol Epidemiol Immunobiol. 2005, Abstract only, downloaded from http://www.ncbi.nlm.nih.gov/pubmed/15881938 on 5 Nov 2008</td> <td>22-23</td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	Y	SMITH et al. Natural Killer Cell Cytolytic Activity Is Necessary For In Vivo Antitumor Activity of the Dipeptide L-Glutamyl-L-Tryptophan. Int. J. Cancer, 2003, Vol 106, pp 528-533, especially p 532, Fig 5	1-23	Y	US 5,916,878 A (KOLOBOV et al.) 29 Jun 1999 (29.06.1999) col 4, ln 21-22, ln 35-37, ln 67; col 5, ln 48; col 12, ln 20-21, ln 24	1-23	Y	AKHMATOVA et al. Immunovac-VP-4, immunomodulator decreases immunosuppression and enhances the cytotoxic activity induced by the cytostatic Cisplatin. Zh Mikrobiol Epidemiol Immunobiol. 2005, Abstract only, downloaded from http://www.ncbi.nlm.nih.gov/pubmed/15881938 on 5 Nov 2008	22-23
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.												
Y	SMITH et al. Natural Killer Cell Cytolytic Activity Is Necessary For In Vivo Antitumor Activity of the Dipeptide L-Glutamyl-L-Tryptophan. Int. J. Cancer, 2003, Vol 106, pp 528-533, especially p 532, Fig 5	1-23												
Y	US 5,916,878 A (KOLOBOV et al.) 29 Jun 1999 (29.06.1999) col 4, ln 21-22, ln 35-37, ln 67; col 5, ln 48; col 12, ln 20-21, ln 24	1-23												
Y	AKHMATOVA et al. Immunovac-VP-4, immunomodulator decreases immunosuppression and enhances the cytotoxic activity induced by the cytostatic Cisplatin. Zh Mikrobiol Epidemiol Immunobiol. 2005, Abstract only, downloaded from http://www.ncbi.nlm.nih.gov/pubmed/15881938 on 5 Nov 2008	22-23												
<p><input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/></p>														
<p>* Special categories of cited documents:</p> <table border="0"> <tr> <td>"A" document defining the general state of the art which is not considered to be of particular relevance</td> <td>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</td> </tr> <tr> <td>"E" earlier application or patent but published on or after the international filing date</td> <td>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</td> </tr> <tr> <td>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</td> <td>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</td> </tr> <tr> <td>"O" document referring to an oral disclosure, use, exhibition or other means</td> <td>"&" document member of the same patent family</td> </tr> <tr> <td>"P" document published prior to the international filing date but later than the priority date claimed</td> <td></td> </tr> </table>			"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention	"E" earlier application or patent but published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone	"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art	"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family	"P" document published prior to the international filing date but later than the priority date claimed			
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention													
"E" earlier application or patent but published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone													
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art													
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family													
"P" document published prior to the international filing date but later than the priority date claimed														
<p>Date of the actual completion of the international search 09 November 2008 (09.11.2008)</p>		<p>Date of mailing of the international search report 19 NOV 2008</p>												
<p>Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201</p>		<p>Authorized officer  Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774</p>												