

First clinical experience using a 'pathotropic' injectable retroviral vector (Rexin-G) as intervention for stage IV pancreatic cancer

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Abstract. Metastatic or non-resectable (stage IV) pancreatic cancer has a rapidly fatal outcome (median survival: 3-6 months), thus making gene therapy a viable therapeutic option. The objectives of the clinical studies are to evaluate the safety/toxicity and potential anti-tumor response/efficacy of intravenous (i.v.) infusions of a 'pathotropic' retroviral vector bearing a cytotoxic gene construct (Rexin-G) as a gene transfer intervention for stage IV pancreatic cancer. An intra-patient dose escalation regimen was used wherein increasing doses of Rexin-G were given i.v. daily for 8-10 days. Completion of this regimen was followed by a one-week evaluation period for toxicity, after which, the maximum tolerated dose of Rexin-G was administered for another 8-10 days. In a second protocol, i.v. Rexin-G was administered frontline for 6 days followed by 8 doses of weekly gemcitabine. The NIH Common Toxicity Criteria Vs.2 was used to assess toxicity, and the NCI-RECIST criteria and tumor volume measurements were used to evaluate potential anti-tumor responses. We report the results of the first 3 patients that participated in the studies. Rexin-G arrested tumor growth in 3 of 3 patients without experiencing dose-limiting toxicity. No bone marrow suppression, significant alterations in liver and kidney function, nausea and vomiting, mucositis or hair loss were observed. Two patients are alive with stable disease ~5 and 14 months from diagnosis, and 1 patient is alive with progressive disease 20 months from diagnosis. The encouraging results of this first clinical experience will guide the design and planning of phase I/II clinical trials to establish the safety and efficacy of Rexin-G as the first targeted injectable gene therapy vector for stage IV pancreatic cancer.

Introduction

Conceptually, the targeted delivery system (TDS) employed here targets retroviral vectors selectively to areas of pathology (i.e., pathotropic targeting), which enables preferential *in vivo* gene delivery to vascular lesions in balloon-injured rat arteries (1,2), and to areas of active angiogenesis, remote tumors and/or metastatic sites (3,4) in tumor-bearing mice. These pathotropic vectors incorporate a physiological surveillance function derived from von Willebrand (blood coagulation) factor by molecular engineering of the retroviral envelope protein without loss of viral infectivity (2). The desired gain-of-function (i.e., tumor-targeting) facilitates vector accumulation in cancerous lesions wherein collagenous proteins are exposed and/or deposited as a result of tumor invasion and tumor-associated angiogenesis (3-7). When injected intravenously, pathotropic vectors traverse the heart and lungs, and withstand formidable obstacles of turbulence and flow, to accumulate in tumor nodules in minutes (4) and enable efficient gene delivery to remote tumors and metastatic sites in animal models of cancer (3,4). Thus, a pathotropic retroviral vector bearing a cytotoxic dominant negative cyclin G1 construct (8), designated Rexin-G, induced tumor regression (3,4) without appreciable toxicity in short- and long-term efficacy studies in mice (4,9).

Further, toxicology studies showed that vector doses equivalent to 2-10 times the highest dose proposed for a phase I clinical trial did not cause bone marrow suppression or any significant alterations in liver or kidney function in mice, rats and pigs (transcript from the NIH/Recombinant Advisory Committee meeting, 2000). Biodistribution studies using a Taqman PCR-based assay for vector integration showed that low-level positive PCR signals were detected only in the liver and spleen one week after i.v. Rexin-G infusions, which represent the major sites of viral clearance. No pathology attributable to the vector was observed in non-target organs of vector-treated animals (10). These preclinical data indicate that Rexin-G may be administered systemically with a wide margin of safety, providing the basis for an FDA-approved phase I clinical trial for metastatic colon cancer in the United States (10) and Bureau of Food and Drugs (BFAD)-approved protocols for stage IV pancreatic cancer and other solid tumors in Manila, Philippines. Here, we report on the first clinical experience and the results of safety

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and efficacy studies using i.v. Rexin-G as a gene transfer intervention for stage IV pancreatic cancer.

Materials and methods

Clinical vector production and characterization. Rexin-G (also known as Mx-dnG1) is a non-replicative 'pathotropic' retroviral vector encoding an N-terminal deletion mutant construct (8) of human cyclin G1 (11) under the control of the Moloney murine leukemia virus long terminal repeat promoter (12). The expression vector also contains the neomycin phosphotransferase gene driven by the Sv40 early promoter. The clinical vector was produced by transient transfection of human embryonic kidney, 293T cells taken from a certified master cell bank in compliance with the Code of Federal Regulations on current good manufacturing practices (cGMP). The clinical vector was stored in volumes of 150 ml in 500 ml cryobags at -80°C . The fully validated product exhibits a viral titer of 3×10^7 colony forming units (units) per milliliter (4), a biologic potency of 65-70% growth inhibitory activity in human breast, colon and pancreatic cancer cells, a uniform particle size of ~ 100 nm with no viral aggregation, <550 bp residual DNA indicating absence of intact oncogenes, no detectable E1A or SV40 large T antigen, and no detectable replication competent retrovirus (RCR) in 5 passages on mus Dunni and human 293 cells. The product is sterile with an endotoxin level of <0.3 EU/ml, and the end of production cells are free of mycoplasma and other adventitious viruses.

Vector preparation and infusion. Preparation of the Rexin-G vector for patient administration consisted of rapid thawing of the vector in the cryobag in a 37°C 80% ethanol bath. The vector was thawed 15-30 min prior to infusion into the patient, and infused intravenously over 1-3 h.

The clinical protocol. The objectives were: i) to determine the potential toxicity (safety) of successive intravenous infusions of Rexin-G, and ii) to assess a potential anti-tumor response (efficacy). The protocol was designed for end-stage cancer patients with an estimated survival time of at least 3 months (13). Two patients with stage IV pancreatic cancer who were considered refractory to standard chemotherapy by their medical oncologists were invited to participate in the clinical study using Rexin-G as approved by the Philippine BFAD. After determining that the patients met the eligibility criteria for the study, and after signing an informed consent approved by the Makati Medical Center Hospital Ethics Committee, an intra-patient dose escalation regimen by intravenous infusion of Rexin-G was given daily for 8-10 days. Completion of this regimen was followed by a one-week rest period for assessment of toxicity; after which, the maximum tolerated dose of Rexin-G was administered i.v. for another 8-10 days. If the patient did not develop a grade 3 or 4 adverse event related to Rexin-G during the treatment periods (15), the dose of Rexin-G was escalated as follows: i) dose escalation (induction) regimen (treatment day/dose level/vector dose per day): day 1-6/I/ 4.5×10^9 units; day 7-8/II/ 9.0×10^9 units; day 9-10/III/ 1.4×10^{10} units, ii) high dose (intensification) regimen (treatment day/dose level/vector dose per day): day 18-27/III/ 1.4×10^{10} units.

Based on the observed safety in the first 2 patients, a third patient with stage IVB pancreatic cancer with numerous liver metastases was given a frontline treatment with intravenous Rexin-G for 6 days, followed by 8 weekly doses of gemcitabine at 1000 mg/m^2 in a second clinical protocol approved by the Philippine BFAD.

Evaluation of overall tumor response (efficacy). Tumor response was evaluated by two methods: i) determination of the tumor volume using the formula: $\text{width}^2 \times \text{length} \times 0.52$ (16) as measured by calipers, or by radiologic imaging (MRI or CT scan), and ii) the NCI-RECIST criteria (14). Evaluations of overall tumor responses using both criteria were conducted by the principal investigators/medical oncologists of the clinical trial (G.H.C., and C.L.).

Evaluation of toxicity (safety). Patients were evaluated for toxicity by the principal investigators of the study (G.H.C. and C.L.) using the NIH Common Toxicity Criteria Vs.2 (15). Serial complete blood counts with differential and platelet counts, liver and kidney function tests were obtained pursuant to the protocols' Study Calendar.

Protection of patient confidentiality. The patients' demographic information and the toxicity and tumor response data were entered in individual case report forms with patients' initials and designated PIN numbers and the files were kept in a fire-safe locked cabinet together with the signed informed consents.

Results

Clinical reports. Patient #1, a 47-year-old Filipino female was diagnosed, by histologic examination of biopsied tumor tissue and staging studies, to have localized adenocarcinoma of the pancreatic head. She underwent a Whipples surgical procedure which included complete resection of the primary tumor. This was followed by single agent gemcitabine weekly for 7 doses, but chemotherapy was discontinued due to unacceptable toxicity. Several months later, a follow-up MRI showed recurrence of the primary tumor with metastatic spread to both the supraclavicular and abdominal lymph nodes. In compliance with the clinical protocol, the patient received two 10-day treatment cycles of Rexin-G for a cumulative dose of 2.1×10^{11} units over 28 days, with an interim rest period of one week. In the absence of systemic toxicity, the patient received an additional 10-day treatment cycle for a total cumulative dose of 3×10^{11} units. Results: the sizes of two superficial supraclavicular lymph nodes were measured manually using calipers. A progressive decrease in the tumor volumes (16) of the supraclavicular lymph nodes was observed, reaching 33% and 62% reductions in tumor size, respectively, by the end of treatment cycle #2 on day 28 (Table I). Follow-up abdominal MRI revealed: i) no new areas of tumor metastasis, ii) discernable areas of central necrosis, involving 40-50% of the primary tumor, and iii) a significant decrease in the size of the para-aortic abdominal lymph node (Fig. 1A and B). On day 54, a follow-up MRI showed no interval change in the size of the primary tumor. Consistent with these findings, a progressive decrease in CA19-9 serum levels (from a peak of 1200 to a low of 584 U/

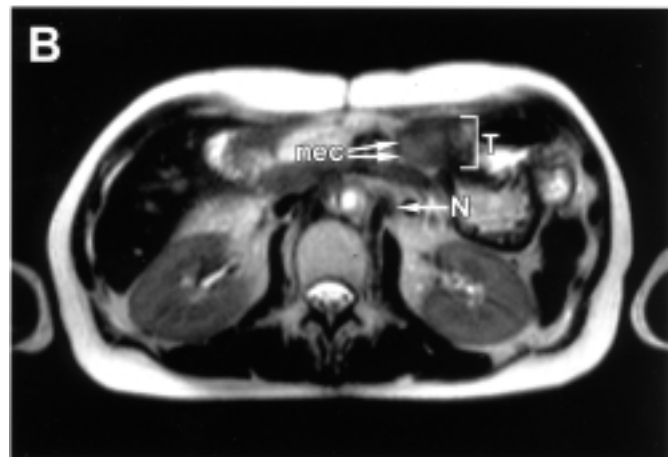
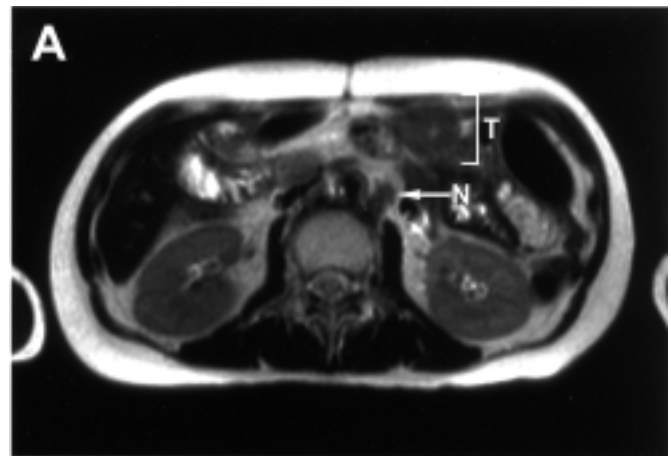
Table I. Patient #1 caliper measurements of supraclavicular lymph nodes.

Date	Caliper measurement cm	Tumor volume cm ³	% reduction in size from start of Regin-G Rx
Day 1	LN1 1.9x2.1	3.9	
	LN2 1.5x1.8	2.1	
Day 26	LN1 1.8x1.8	3.0	23
	LN2 1.3x1.3	1.1	48
Day 27	LN1 1.7x1.7	2.6	33
	LN2 1.15x1.15	0.8	62

ml) were noted, amounting to a 50% reduction in CA19-9 levels on day 54 (Fig. 1C). However, a follow-up CT scan on day 101 showed a significant increase in the size of the primary tumor and the supraclavicular lymph nodes. The patient refused further chemotherapy until day 175 when the patient agreed to receive weekly gemcitabine, 1000 mg/m². By RECIST criteria, patient #1 is alive with progressive disease on day 189 follow-up, 6.75 months from the start of Regin-G infusions, 11 months from the time of tumor recurrence, and 20 months from the time of initial diagnosis.

Patient #2, a 56-year-old Filipino female was diagnosed to have stage IVA locally advanced and non-resectable carcinoma of the pancreatic head, by cytologic examination of biliary brushings. Exploratory laparotomy revealed that the tumor was wrapped around the portal vein and encroached in close proximity to the superior mesenteric artery and vein. She had received external beam radiation therapy with 5-fluorouracil, and further received single agent gemcitabine weekly for 8 doses, followed by monthly maintenance doses. However, a progressive rise in CA19-9 serum levels was noted and a follow-up CT scan revealed that the tumor had increased in size (Fig. 2A). The patient received two treatment cycles of Regin-G as daily intravenous infusions for a total cumulative dose of 1.8×10^{11} units. Results: serial abdominal CT scans showed a significant decrease in tumor volume from 6.0 cm³ at the beginning of Regin-G infusions to 3.2 cm³, at the end of the treatment, amounting to a 47% decrease in tumor size on day 28 (Fig. 2). Follow-up CT scan on day 103 showed no interval change in the size of the tumor, after which the patient was maintained on monthly gemcitabine. By RECIST criteria, patient #2 is alive, asymptomatic with stable disease on day 154 follow-up, 5.5 months from the start of Regin-G infusions, and 14 months after initial diagnosis.

Patient #3, a 47-year-old Chinese diabetic male was diagnosed to have stage IVB adenocarcinoma of the body and tail of the pancreas, with numerous metastases to the liver and portal lymph node, confirmed by CT guided liver biopsy. Based on the rapid fatal outcome of stage IVB adenocarcinoma of the pancreas, the patient was invited to participate in a second clinical protocol using Regin-G frontline followed by gemcitabine weekly. The guiding hypothesis was that a priming dose of Regin-G would sensitize the tumor to chemo-



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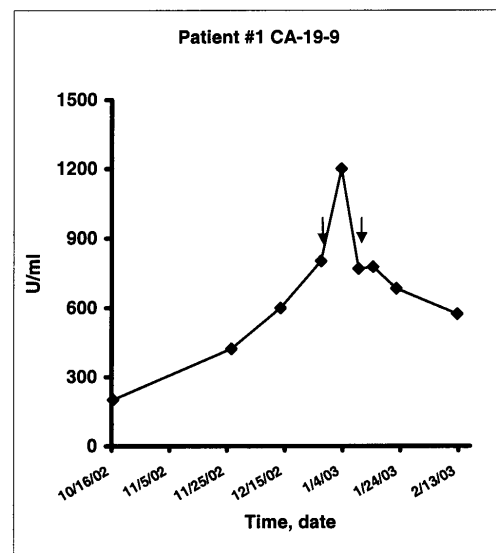


Figure 1. (A), Representative MRI from patient #1 one day after completion of treatment cycle #1 showing a large round recurrent tumor (T; bracketed area) in the region of the pancreas within the area of the surgical bed and an enlarged para-aortic lymph node (N) indicating metastasis. (B), Follow-up MRI from patient #1 four days after completion of treatment cycle #2 showing an irregularity in the shape of the recurrent tumor (T; bracketed area) with a large area of central necrosis (nec) involving 40-50% of the tumor mass and a significant decrease in the size of the para-aortic lymph node metastasis (N). (C), Regin-G induces a reduction in CA19-9 serum level in patient #1. Serum CA19-9 levels (U/ml), plotted on the vertical axis, are expressed as a function of time (date), plotted on the horizontal axis. The start of each treatment cycle is indicated by arrows.

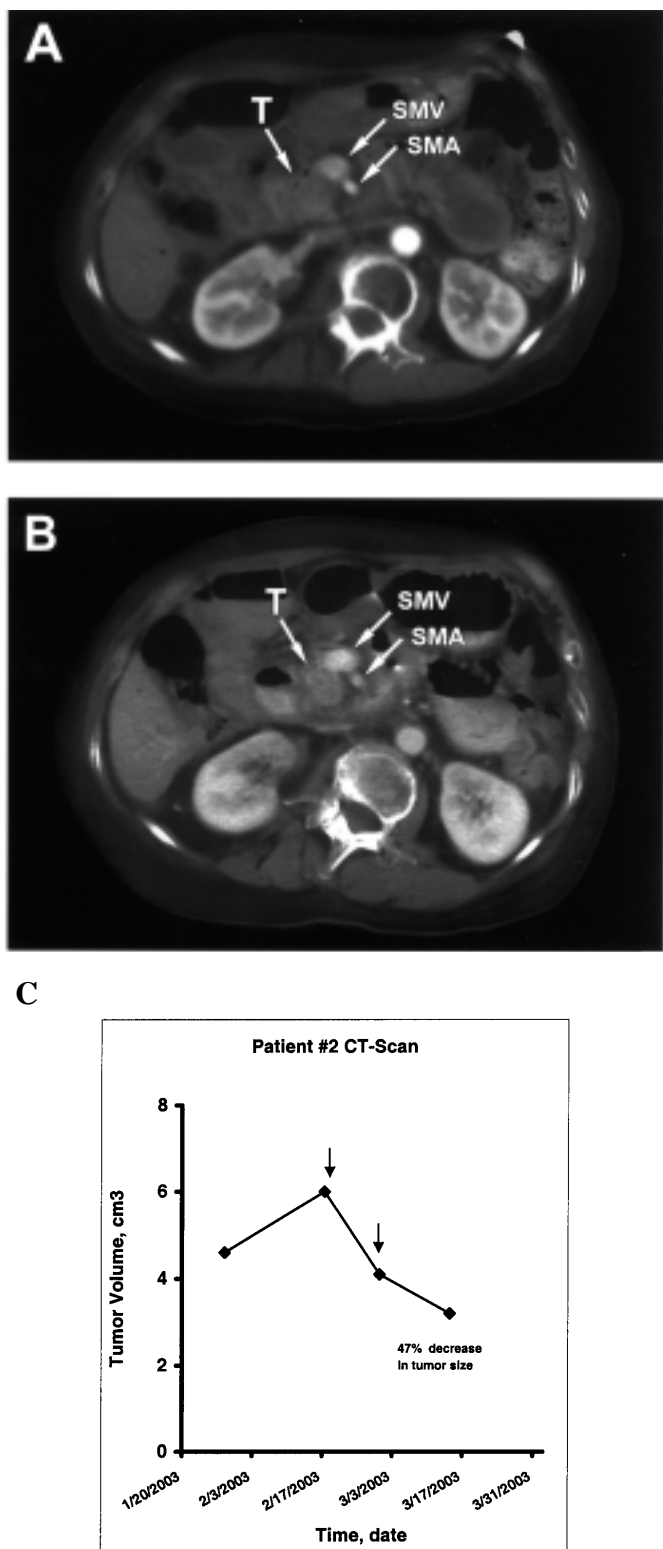


Figure 2. (A), Representative abdominal CT scan from patient #2 obtained at the beginning of treatment cycle #1 revealing a 6.0 cm³ mass in the region of the pancreatic head (T) encroaching on the superior mesenteric vein (SMV) and the superior mesenteric artery (SMA). (B), Follow-up abdominal CT scan from patient #2 two days after completion of treatment cycle #2, revealing that the pancreatic tumor mass (T) has decreased in size and regressed away from the superior mesenteric vessels (SMV and SMA). The start of each treatment cycle is indicated by arrows. (C), Regin-G arrests primary tumor growth in patient #2. A progressive decrease in tumor size was noted with successive treatment with Regin-G. Tumor volume (cm³) derived by using the formula: width² x length x 0.52 (16) and plotted on the vertical axis, is expressed as a function of time, plotted on the horizontal axis. The start of each treatment cycle is indicated by arrows.

therapy with gemcitabine for better cytotoxic efficacy (unpublished data). After determining that he met the eligibility criteria for the study, the patient received daily i.v. infusions of Regin-G at a dose of 4.5x10⁹ units/dose for 6 days for a total cumulative dose of 2.7x10¹⁰ units, followed by 8 weekly doses of gemcitabine (1000 mg/m²). On day 62, follow-up abdominal CT scan showed that the primary tumor had decreased in size from 7.0x4.2 cm (tumor volume: 64.2 cm³) baseline measurement to 6.0x3.8 cm (tumor volume: 45 cm³) (Fig. 3A). Further, there was a dramatic reduction in the number of liver nodules from 18 nodules (baseline) to 5 nodules (Fig. 3C) with regression of the largest liver nodule from baseline 2.2x2 cm (tumor volume: 4.6 cm³) to 1x1 cm (tumor volume: 0.52 cm³) on day 62 (Fig. 3B). By the RECIST criteria, patient #3 is alive with stable disease on day 133 follow-up, 4.7 months from the start of Regin-G infusions and ~5 months from the time of diagnosis.

Evaluation of overall tumor responses by the NCI-RECIST criteria. Table II illustrates the comparative evaluation of overall tumor responses in the 3 patients. Using the RECIST criteria, Regin-G induced tumor growth stabilization in all 3 patients. The time to disease progression was 3.4 months for patient #1. Patients #2 and #3 continue to have stable disease 5.5 and 4.7 months from the start of Regin-G treatment respectively. Evaluation of survival shows that patient #1 is alive with progressive disease 20 months from the time of diagnosis, and 2 patients are alive with stable disease ~5 and 14 months from diagnosis.

Adverse events. All 3 patients tolerated the vector infusions well with no associated nausea or vomiting, diarrhea, mucositis or hair loss. Figs. 4 and 6 illustrate patient #1 and #2's vital signs during the vector infusions. No significant alteration in patients' hemodynamic functions were noted during the vector infusions, nor at any other time immediately after the infusions and during the interim evaluation periods. Figs. 5, 7 and 8 depict the complete blood counts, liver and kidney function tests obtained during the period of vector infusions for patient #1 (Fig. 5), patient #2 (Fig. 7) and patient #3 (Fig. 8). There were no clinically significant alterations in hemoglobin, white count, platelet count, AST, ALT, total bilirubin, BUN, creatinine and K levels noted during the vector infusions and the interim evaluation periods.

During the treatment period, patient #2 developed two brief episodes of low-grade (37.7°C) fever that were not associated with neutropenia near the end of treatment cycle #2. However, interpretation of this grade 1 adverse event was confounded by the growth of acinetobacter from the patient's blood culture while culture of the Regin-G vector was negative for bacterial growth. Patient #3 developed one febrile episode (37.6°C-39.5°C) on day 6 that lasted for 24 h. Blood culture and culture of the vector were negative for bacterial growth.

In summary, as predicted by preclinical studies (10), the vector infusions were not associated with nausea or vomiting, diarrhea, mucositis, hair loss, hemodynamic instability, bone marrow suppression or organ dysfunction. Therefore, no dose limiting toxicity was noted in any patient that received Regin-G, indicating that more vector infusions may be given to achieve greater therapeutic efficacy. In contrast to the

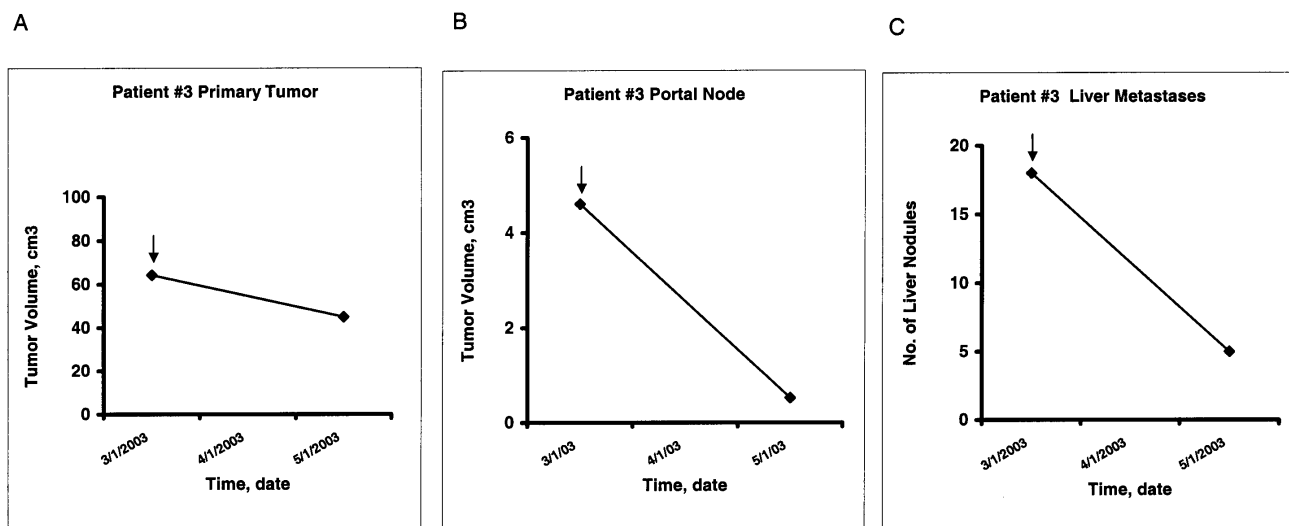


Figure 3. Rixin-G plus gemcitabine induces tumor regression in patient #3 with metastatic pancreatic cancer. Tumor volumes (cm³) of primary tumor (A) and portal node (B) and (C) number of liver nodules, plotted on the Y axis, are expressed as a function of time, date. The start of Rixin-G infusions is indicated by arrows.

Table II. Evaluation of overall tumor responses by RECIST.

Patient no.	1	2	3
Stage of disease	Recurrent IVB	IVA	IVB
Previous Rx	Whipples procedure Ext. beam radiation Gemcitabine	Ext. beam radiation 5-Fluorouracil Gemcitabine	None
Karnofsky score before treatment	0	0	0
Treatment/s and dose	Rixin-G IV (3.0x10 ¹¹ U)	Rixin-G IV (1.8x10 ¹¹ U)	Rixin-G IV (2.7x10 ¹⁰ U) Gemcitabine IV (1000 mg/m ² x 8)
Response	Tumor growth stabilization	Tumor growth stabilization	Tumor growth stabilization
Duration of response	3.4 months	>5.5 months	>4.7 months
Survival status	Alive, with progressive disease, 20 months from diagnosis	Alive, with stable disease, 14 months from diagnosis	Alive, with stable disease, 5 months from diagnosis

deleterious sides effects of chemotherapy, the patients' reported a general feeling of well-being during the vector infusion periods.

Discussion

Pancreatic cancer is the fourth leading cause of cancer death in the United States, and is the deadliest of all cancers (13). Complete surgical resection of the pancreatic tumor offers

the only effective treatment for this disease (17). Unfortunately, such 'curative' operations are only possible in 10-15% of patients with pancreatic cancer, typically those individuals in whom jaundice is the presenting symptom. The median survival time for patients with non-resectable pancreatic cancer is 3-6 months (13). Hence, the management of advanced pancreatic cancer is generally directed at palliation of symptoms. External beam radiation does not appear to prolong survival, although sufficient reduction in tumor size

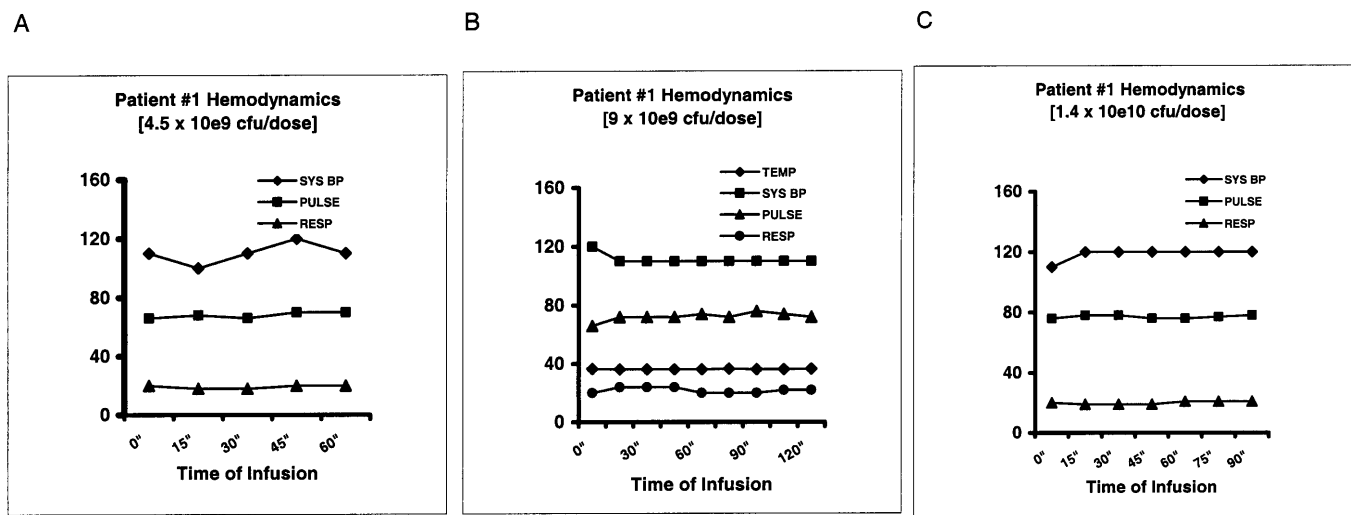


Figure 4. Dose escalation of REXIN-G has no adverse effects on patient #1's hemodynamic functions. For each dose level, the systolic blood pressure, expressed as mm Hg, pulse rate per min and respiratory rate per min are plotted on the vertical axis, while time of infusion is plotted on the horizontal axis.

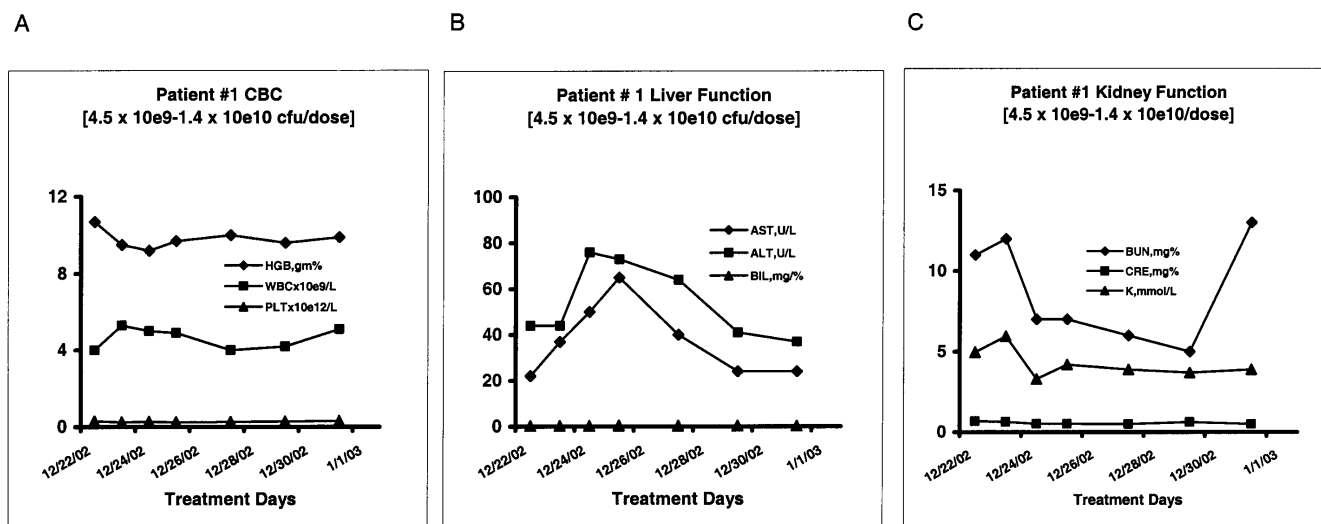


Figure 5. Dose escalation of REXIN-G has no adverse effects on patient #1's blood counts, liver and kidney function. (A), Hemoglobin (gms %), white blood count and platelet count are plotted on the Y axis and expressed as a function of treatment days, plotted on the X axis. (B), AST (U/l) ALT (U/l) and bilirubin (mg %), plotted on the Y axis, are expressed as a function of treatment days, plotted on the X axis. (C), Blood urea nitrogen (mg %), creatinine (mg %) and potassium (mmol/l) levels, plotted on the Y axis, are expressed as a function of treatment days, plotted on the X axis. Dose level I (4.5×10^9 cfu/dose) was given for 6 consecutive days, rest period for 2 days, followed by dose level II (9×10^9 cfu/dose) for 2 days and then dose level III (1.4×10^{10} cfu/dose) for 2 days.

may lead to alleviation of pain (13). The addition of chemotherapy with fluorouracil (5-FU) to external beam radiation has increased the survival time for these patients (18). Recently, gemcitabine, a deoxycytidine analogue, has been shown to improve the quality of life of patients with advanced pancreatic cancer (18), although the duration of survival is extended by only 8-10 weeks. Due to the characteristically poor prognosis of pancreatic cancer, a variety of experimental approaches, including cancer immunotherapy and gene therapy strategies are under current clinical investigation (19-21).

Approximately 70% of all gene therapy protocols are aimed at treating metastatic cancer (21). The majority of active protocols involve some form of cancer immunotherapy via

cell-based gene transfer of cytokines or tumor antigens, while others involve the intratumoral delivery of oncolytic viruses or vectors bearing prodrugs, chemoprotective agents, antisense constructs, or tumor suppressor genes (21). However, the major unresolved problem that has hindered the development and deployment of effective cancer gene therapy is that of inefficient delivery to target cells *in vivo* (20,22-25), a problem that obviates and precludes many direct therapeutic approaches (20). In this regard, the advent of pathotropic targeting launches a new paradigm in cancer gene therapy. By targeting the histopathology of the lesion - rather than the cancer cells *per se* - to optimize the effective vector concentration at metastatic sites, the safety and the efficacy of the circulating

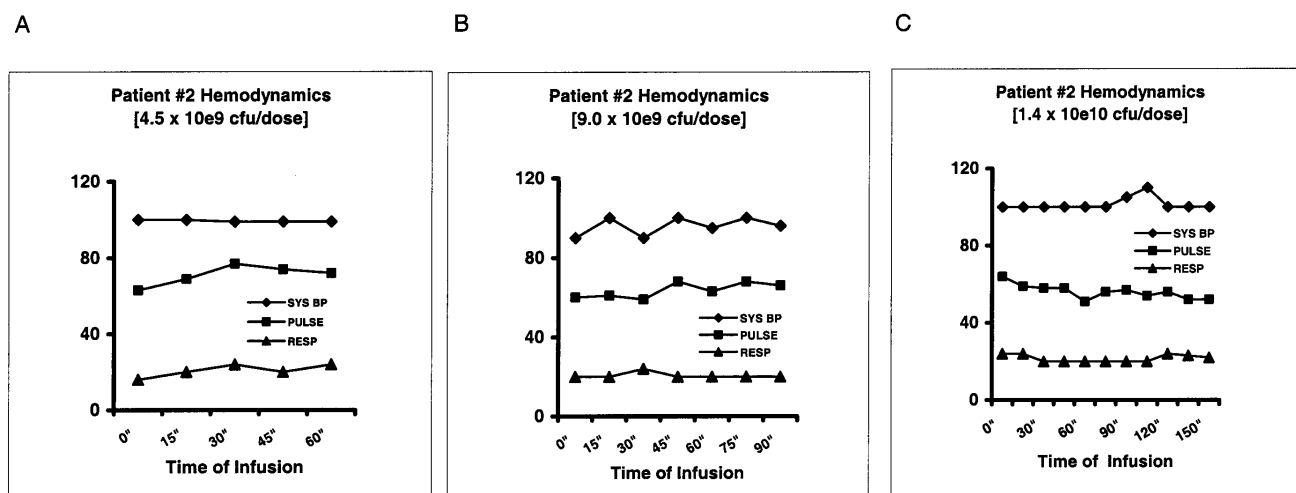


Figure 6. Dose escalation of Rexin-G has no adverse effects on patient #2's hemodynamic functions. For each dose level, the systolic blood pressure (mm Hg), pulse rate/min and respiratory rate/min are plotted on the vertical axis as a function of time of infusion, plotted on the horizontal axis.

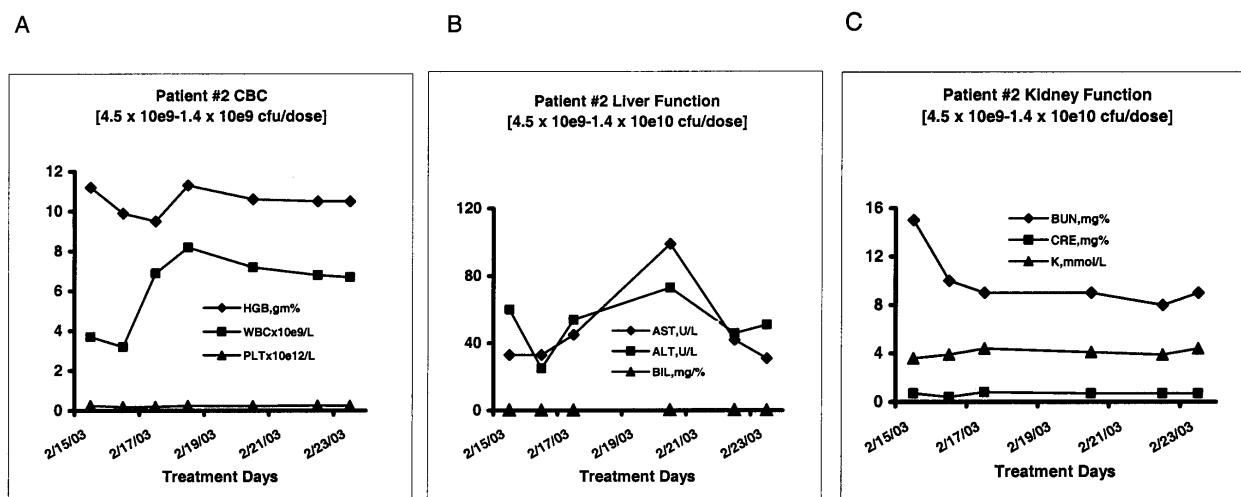


Figure 7. Dose escalation of Rexin-G has no adverse effects on patient #2's blood counts, liver and kidney functions. (A), Hemoglobin (gms %), white blood count and platelet count are plotted on the Y axis and expressed as a function of treatment days, plotted on the X axis. (B), AST (U/l) ALT (U/l) and bilirubin (mg %), plotted on the Y axis, are expressed as a function of treatment days, plotted on the X axis. (C), Blood urea nitrogen (mg %), creatinine (mg %) and potassium (mmol/l) levels, plotted on the Y axis, are expressed as a function of treatment days, plotted on the X axis. Dose level I (4.5×10^9 cfu/dose) was given for 5 consecutive days, followed by dose level II (9×10^9 cfu/dose) for 3 days and then dose level III (1.4×10^{10} cfu/dose) for 2 days.

gene therapy vector was increased dramatically in preclinical studies (3,4). Further enhanced by the inherent properties of the murine leukemia virus-based vector (which selectively transduces dividing cells) and the strategic specificity of a cell cycle control gene which exhibits tumoricidal and anti-angiogenic activities (4), the preclinical and clinical performance of this pathotropic vector establishes the potential for systemic delivery of genetic medicine for the physiologic surveillance and treatment of primary, remote, metastatic, and occult cancers.

In this study, two methods were used to evaluate tumor responses to intravenous infusions of Rexin-G. Using the NCI-RECIST criteria that measures the sum of the longest diameters of target lesions that are greater than 2 cm, and the disappearance vs persistence of all non-target lesions as

points of comparison, 3 of 3 (100%) patients treated with Rexin-G had tumor growth stabilization for >100 days (3 months) (Table II). Evaluation of response by tumor volume measurement (formula: width² x length x 0.52) (16), revealed that Rexin-G induced tumor regression in 3 of 3 (100%) patients, i.e., a 33-62% regression of metastatic lymphadenopathy in patient #1 (Table I), a 47% regression of the primary tumor in patient #2 (Fig. 2C), and a 30% regression of the primary tumor, eradication of 72% (13/18) of metastatic liver foci, and an 89% regression of a metastatic portal node in patient #3 as documented by imaging studies (MRI or CT scan) and caliper measurements (Fig. 3). Further, evaluation of safety showed that no dose-limiting toxicity occurred up to a cumulative vector dose of 3×10^{11} units, indicating that more vector may be given to achieve greater therapeutic efficacy.

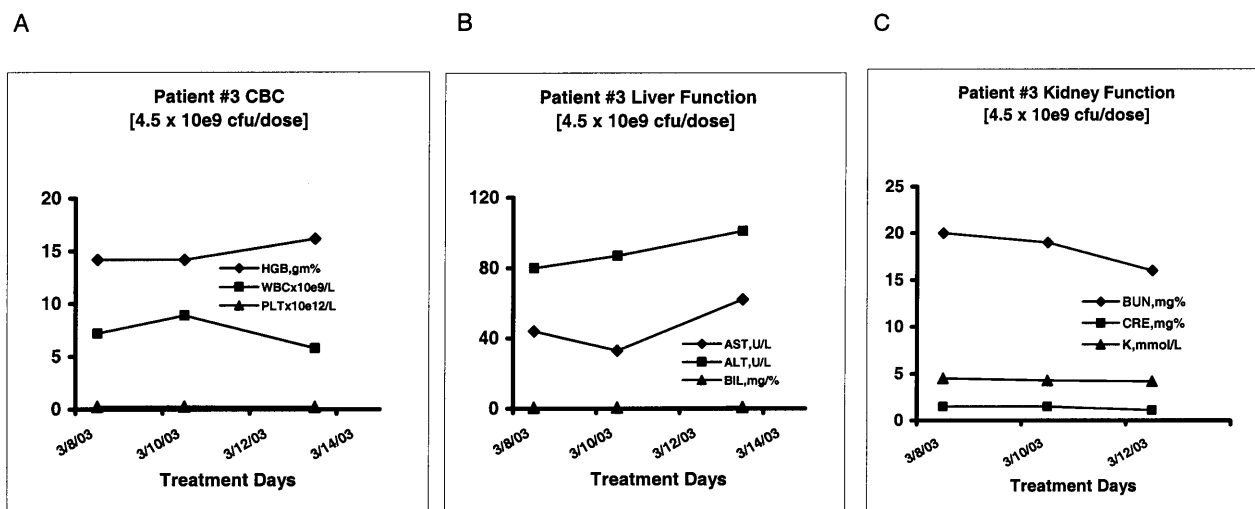


Figure 8. Rexin-G has no adverse effects on patient #3's blood counts, liver and kidney function. (A), Hemoglobin (gms %), white blood count and platelet count are plotted on the Y axis and expressed as a function of treatment days, plotted on the X axis. (B), REXIN-G has no adverse effects on patient's liver function. AST (U/l) ALT (U/l) and bilirubin (mg %), plotted on the Y axis, are expressed as a function of treatment days, plotted on the X axis. (C), REXIN-G has no adverse effects on patient's kidney function. Blood urea nitrogen (mg %), creatinine (mg %) and potassium (mmol/l) levels, plotted on the Y axis, are expressed as a function of treatment days, plotted on the X axis. Dose level I (4.5×10^9 cfu/dose) was given for 6 consecutive days. Normal values: hemoglobin (HGB), 12.5-16.0 gm %; WBC, $5.0-10.0 \times 10^9/l$; platelet count, $0.115-0.440 \times 10^{12}/l$; AST, 16-40 U/l; ALT, 9-72 U/l; bilirubin (BIL), 0.4-1.6 mg %; blood urea nitrogen (BUN), 7-10 mg %; creatinine (CRE), 0.6-1.3 mg %; potassium (K), 3.5-5.3 mmol/l.

The REXIN-G vector infusions were not associated with nausea or vomiting, diarrhea, neuropathy, hair loss, hemodynamic instability, bone marrow suppression, liver or kidney damage. Brief febrile episodes were the only adverse events associated with the vector infusions.

In summary, the REXIN-G infusions were not associated with the deleterious side effects of chemotherapy that could be life-threatening or even fatal. On the contrary, all 3 patients reported a notable feeling of well-being during the treatment periods. These findings suggest that REXIN-G may also improve the quality of life of patients with terminal cancer. Evaluation of survival revealed that 2 patients are alive with stable disease ~5 and 14 months after diagnosis, and 1 patient is alive with progressive disease 20 months after diagnosis. Although the number of patients studied is small, the results are encouraging as the median survival of patients with stage IV pancreatic cancer is only 3-6 months in spite of aggressive chemotherapy. Future phase I/II clinical trials are planned to establish the safety and efficacy of REXIN-G as the first effective tumor-targeted gene therapy vector that could impact overall survival of patients with stage IV pancreatic cancer.

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