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A Phase I/II Study of Intravenous Rexin-G and Reximmune-C for Cancer Immunotherapy:

The GeneVieve Protocol

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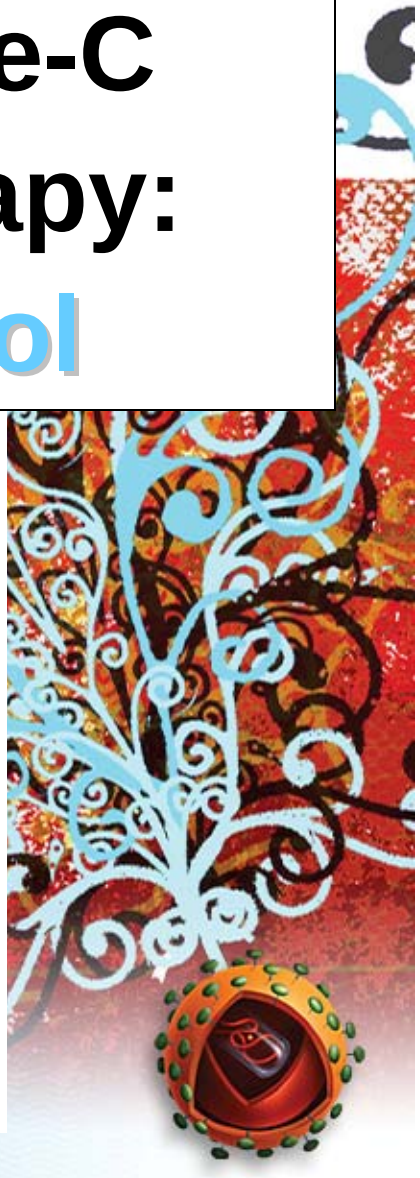


ABSTRACT

PURPOSE: To evaluate the safety and potential anti-tumor activity of intravenous infusions of Rexin-G followed by Reximmune-C pulses for cancer immunotherapy.

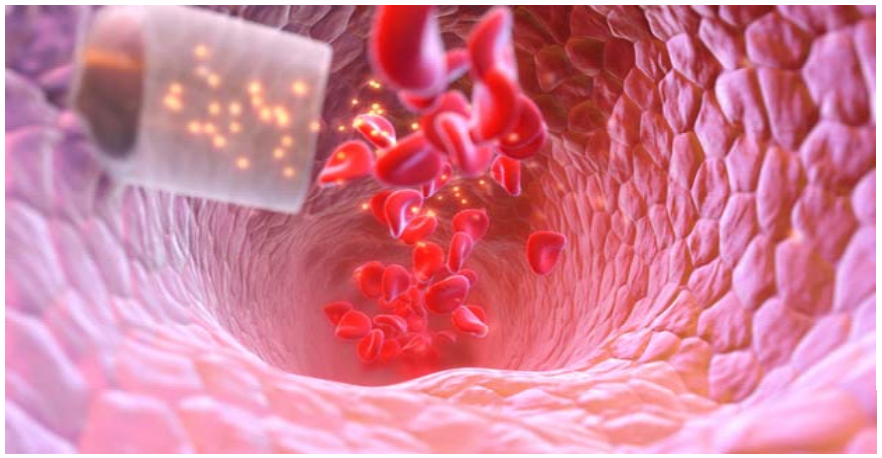
PATIENTS AND METHODS: Seven patients with chemo-resistant solid malignancies, and 2 chemo-naïve patients received Rexin-G, 2 x 10e11 cfu on Days 1, 3, and 5, plus Reximmune-C, 0.5 or 1.0 x 10e10 cfu on Day 3, and valacyclovir at 3 gms/day p.o. on Days 6-19, comprising one cycle. Treatment cycles were repeated up to 6 cycles if there was ≤ Grade 1 toxicity.

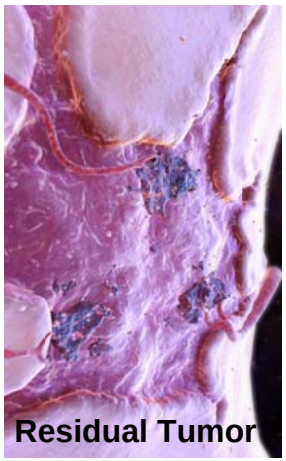
RESULTS: *Safety Analysis*: Grade 2 tumor pain at Dose 2 (n=2); no dose limiting toxicity, and no detectable GM-CSF in patients' serum. *Efficacy Analysis*: 3/9 PR, 5/9 SD, 1/9 PD at Dose I-II; Median PFS of >11 mos.; Median OS >13 mos; 78% one-year survival from treatment initiation. Three patients underwent tumor resection or biopsy. Histopathologic examination revealed: (1) vector localization in residual tumor, (2) GM-CSF transgene expression in necrotic tumors, and (3) eradication of tumor in the indicator cervical lymph node and tumor infiltration primarily by CD8+ killer T cells, respectively.

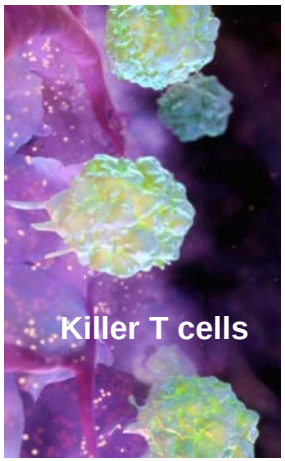
CONCLUSIONS: These findings indicate that the targeted gene delivery system, represented by Rexin-G and Reximmune-C, is precise, and (2) the strategic combination of Rexin-G plus Reximmune-C is safe and well-tolerated, may control tumor growth, evoke anti-tumor immunity, and prolong overall survival time—advancing personalized cancer vaccination as a realistic goal.

Targeted Injectable Genetic Medicine

Pathotropic Targeting of Rexin-G & Reximmune-C







Rexin-G is a pathotropic nanoparticle bearing a cytocidal anti-Cyclin G1 construct that is injected directly into a vein to deliver its genetic payload selectively to cancerous lesions that have spread throughout the body without eliciting systemic side effects or organ damage.

Tumor-targeted **Reximmune-C** nanoparticles bearing a GM-CSF gene accumulate within residual tumors, recruiting and stimulating anti-tumor immunity.

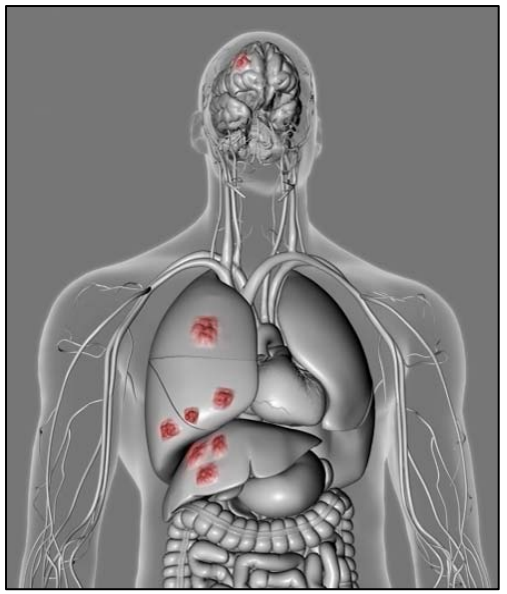
Rexin-G has gained commercial approval in the Philippines for all solid tumors, and Orphan Drug and Fast Track Status in the U.S. for (1) pancreas cancer, (2) soft tissue sarcoma and (3) osteosarcoma, based on plausible demonstrations of clinical safety and efficacy in these types of solid tumors.

BACKGROUND & RATIONALE

- Metastatic cancer has an invariably fatal outcome. Therefore, innovative therapies are urgently needed.
- Rexin-G and Reximmune-C are tumor-targeted retrovectors bearing a cytocidal anti-cyclin G1 construct and a controllable GM-CSF expression construct, respectively.
- A two-tier approach, aimed at evoking a personalized vaccination against a patient's own specific cancer, combines (1) a targeted vector bearing a tumoricidal payload, i.e. Rexin-G, with (2) a targeted vector bearing a potent immuno-stimulatory GM-CSF gene, i.e. Reximmune-C (U.S. FDA-CDER, 2010).
- Rexin-G is administered to control tumor growth and expose neoantigens within the tumor microenvironment, followed by defined pulses of Reximmune-C to recruit the patient's immune cells into the lesions. The goal is to induce immunologic activation, recognition of tumor neoantigens, and induction of long lasting anti-tumor immunity.

OBJECTIVES of PHASE I/II STUDY

To evaluate the over-all safety and anti-tumor potential of intravenous infusions of Rexin-G, followed by Reximmune-C pulses for cancer immunotherapy.



Endpoints of the Study

- **Primary Endpoint:** Clinical toxicity/safety
- **Secondary Endpoint # 1:** Vector-related safety
- **Secondary Endpoint # 2:** Anti-tumor activity (Efficacy)

Patients:
All solid malignancies (n = 9)

Dosing Schedule: Seven patients with chemo-resistant solid malignancies, and 2 chemo-naïve patients received Rexin-G, 2 x 10e11 cfu on Days 1, 3, and 5, plus Reximmune-C, 0.5 or 1.0 x 10e10 cfu on Day 3, and valacyclovir at 3 gms/day p.o. on Days 6-19, comprising one cycle. Phase II component by adaptive design: Treatment cycles were repeated up to 6 cycles if there was ≤ Grade 1 toxicity.

Adaptive Design enables optimization of patient dosing and evaluation parameters, thus expediting clinical development.

Patient Characteristics

(n = 9)

Age (years)	
Median	56
Range	(34-91)
Gender	
Female	6 (66%)
Male	3 (34%)
Race	
White	3 (34%)
African-American	1 (11%)
Asian	5 (55%)
Disease Stage	
Metastatic	9 (100%)
Performance Score	
0-1	9 (100%)
Type of Cancer	
Colon Cancer	2 (22%)
Pancreas Cancer	2 (22%)
Prostate Cancer	2 (22%)
Ovarian Cancer	1 (11%)
Breast Cancer	1 (11%)
Ewing's sarcoma	1 (11%)

RESULTS of Phase I/II Study

Primary Endpoint: No dose limiting toxicity (DLT)
Grade 2 tumor pain (n = 2)

Secondary Endpoint # 1: No detectable GM-CSF in patients' serum; No vector-neutralizing antibodies; No vector integration and no RCR detected in peripheral blood lymphocytes

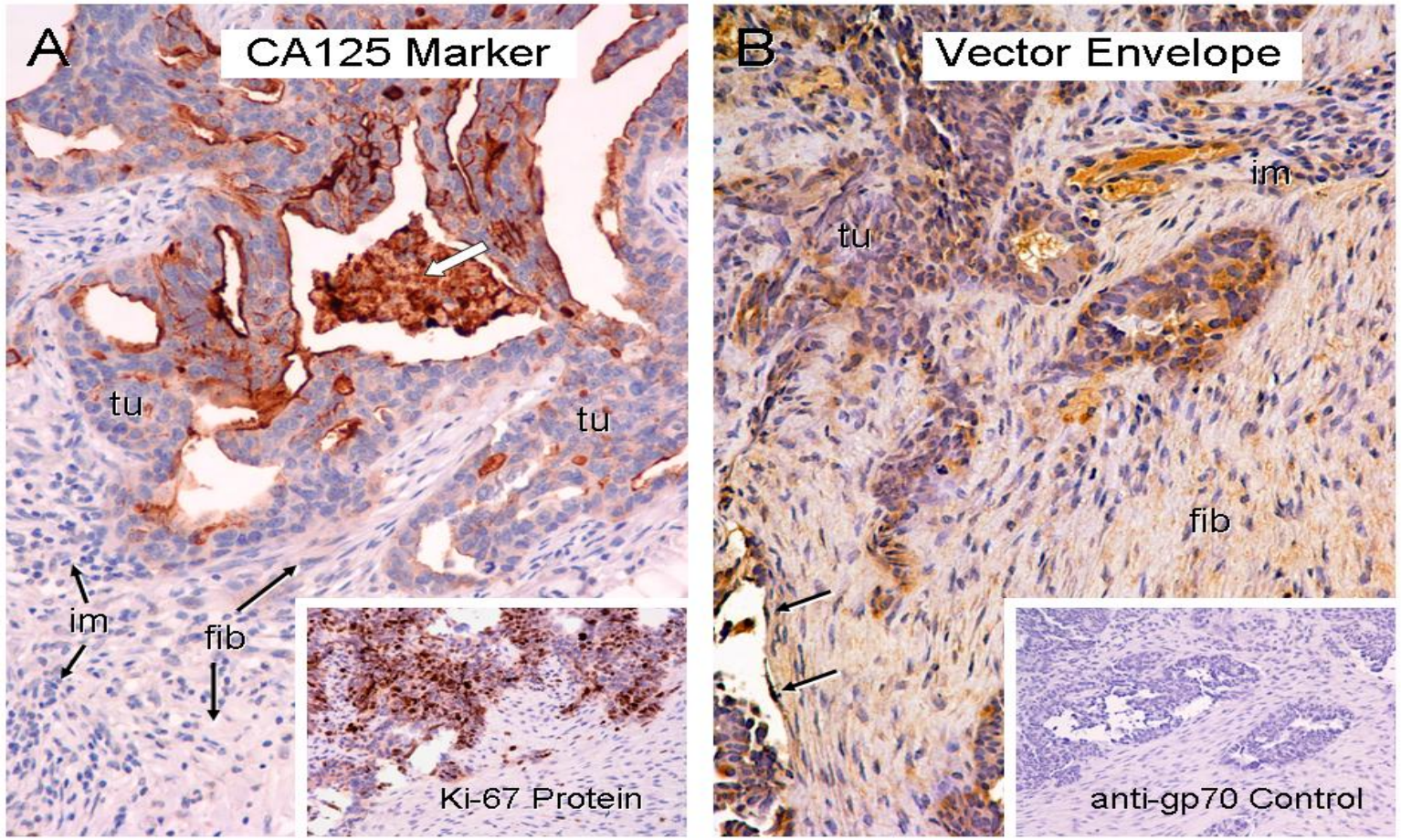
Secondary Endpoint # 2: See Table below

Reximmune-C Dose Level	Best Tumor Response By RECIST	Median PFS By RECIST, Months	Median OS, Months From Start of Rexin-G Treatment
I (n=5)	2PR, 2SD, 1PD	> 12	> 14
II (n=4)	1PR, 3SD	> 10.5	> 12

Note: Patients at Dose II were enrolled later and have a shorter follow-up period.

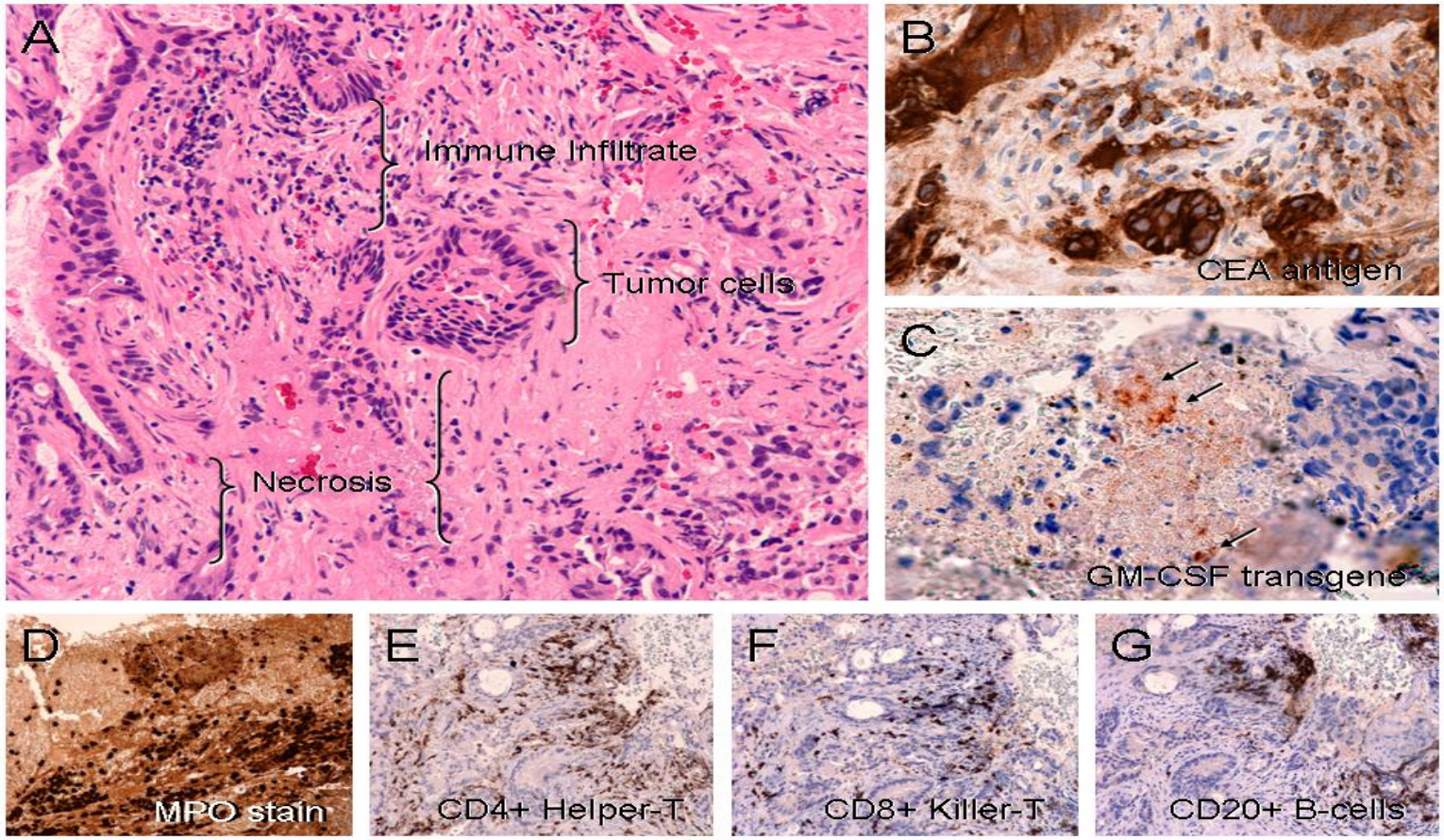
The GeneVieve Protocol (Rexin-G + Reximmune-C) is safe and well-tolerated, controls tumor growth and may prolong progression-free survival and overall survival in patients with solid malignancies.

Localization of Rexin-G Nanoparticles in Residual Tumor of a Patient with Metastatic Ovarian Cancer



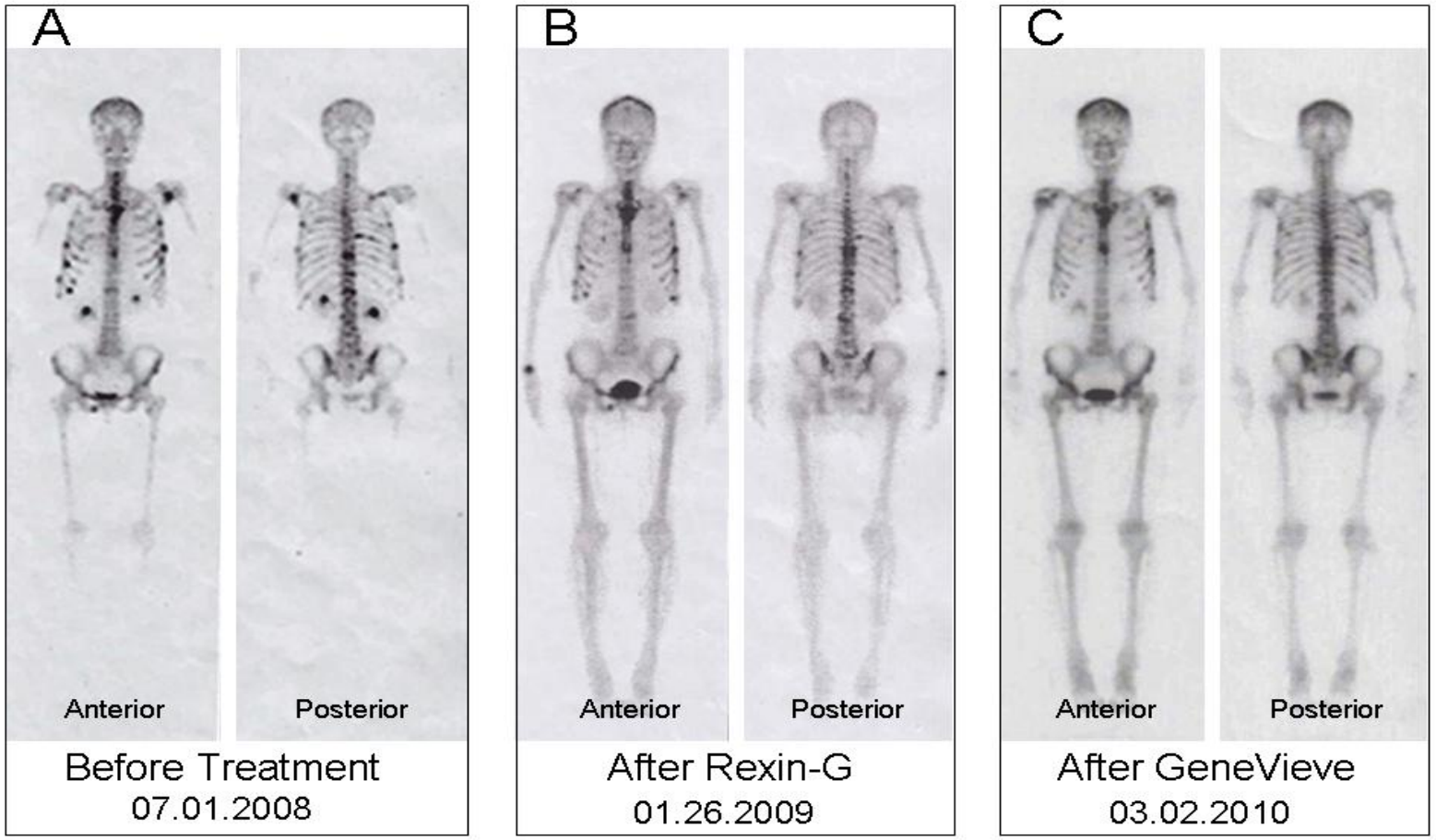
Note: The residual pelvic tumor was resected two hours after intravenous infusion of Rexin-G. (A) Residual tumor (tu) marked by CA-125 surrounded by tumor infiltrating lymphocytes (im) and fibrosis (fib); (B) Immunoreactive Rexin-G nanoparticles in tumor nests and tumor vasculature (brown staining material).

Histology and Transgene Expression in a Residual Tumor - Colon Cancer Patient after Infusion of Reximmune-C



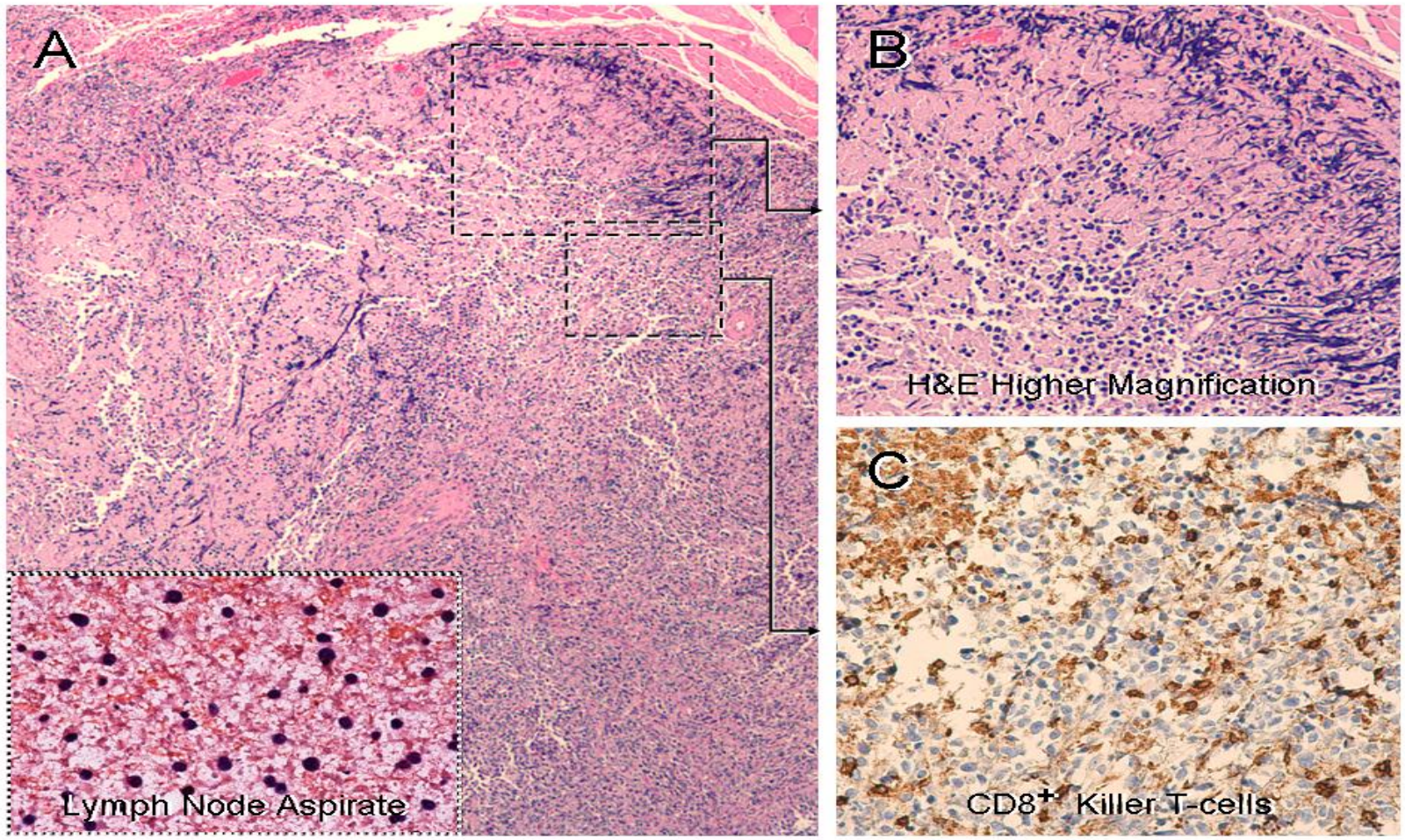
The residual tumor was resected two days after infusion of Rexin-G and Reximmune C. (A) H&E: areas of tumor necrosis with tumor infiltrating lymphocytes (TILs); (B) CEA+ tumor cells, (C) immunoreactive GM-CSF transgene (reddish-brown staining material) in a necrotic tumor, (D) MPO staining granulocytes; (E-G) CD4+, CD8+ and CD20+ TILs, indicating effective recruitment of patient's tumor infiltrating lymphocytes into the residual tumor.

Regression of Skeletal Metastases in a Patient with Chemo-Resistant Ductal Carcinoma of Breast



Note: Progressive tumor regression was seen in serial bone scans obtained over 20 months following treatment initiation with Rexin-G, followed by the GeneVieve Protocol: Rexin-G given in combination with Reximmune-C.

Histologic Evidence of Long Lasting Anti-tumor Immunity in a Patient with Metastatic Pancreas Cancer

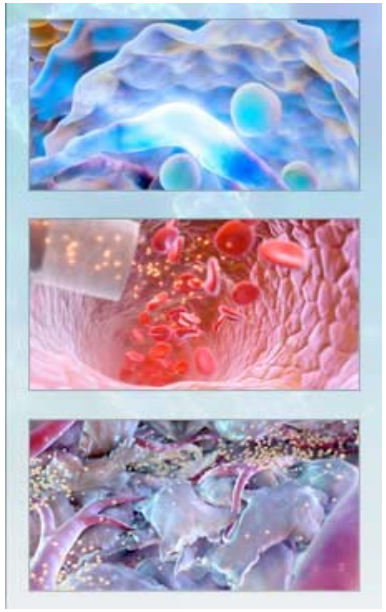


Note: An indicator cervical lymph node was resected 8 weeks and one year after treatment initiation. (A-B) H&E shows complete effacement of lymph node architecture and replacement with tumor infiltrating lymphocytes (TILs); (C, Boxed from A) CD8+ killer T cells; (A-left inset) Chronic inflammatory cells in lymph node aspirate with no malignant cells one year later.

CONCLUSIONS of Phase I/II Study

These findings indicate that:

- The targeted gene delivery platform—represented by Rexin-G and Reximmune-C—is precise, as shown by vector localization and GM-CSF transgene expression in metastatic tumors after intravenous administration of Rexin-G and Reximmune-C.



- The strategic combination of Rexin-G plus Reximmune-C is safe and well-tolerated; may control tumor growth, induce long lasting anti-tumor immunity, and prolong overall survival—thus, advancing personalized cancer vaccination as a realistic goal.