New Biological and Immunological Therapies for Cancer

Sant P. Chawla, M.D., FRACP

The Sarcoma Oncology Center,
Santa Monica CA 90403

7th International Conference on Drug Discovery &Therapy

Promising Developments:
Immunotherapy and Gene Therapy

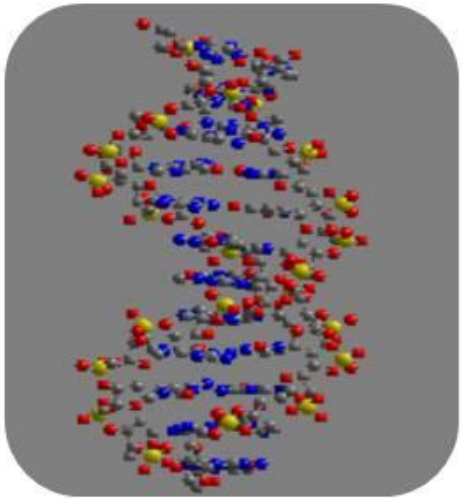
US FDA Approved Therapies	In Clinical Development
❑ Dendritic Cell Therapy ❑ Cancer Vaccines ❑ Oncolytic Viruses ❑ Immune Checkpoint Inhibitors (mAbs)	❑ Targeted Retrovectors: Targeting the tumor microenvironment ➢ **Rexin-G** (Cytocidal Gene) ➢ **Reximmune-C** (GM-CSF) ❑ Targeted Lentivectors: Dendritic Cell Targeting ➢ **LV305** (NY-ESO1 Gene)

Rexin-G Retroviral Vector:
First Targeted, Injectable Gene Delivery

SARCOMA oncology center

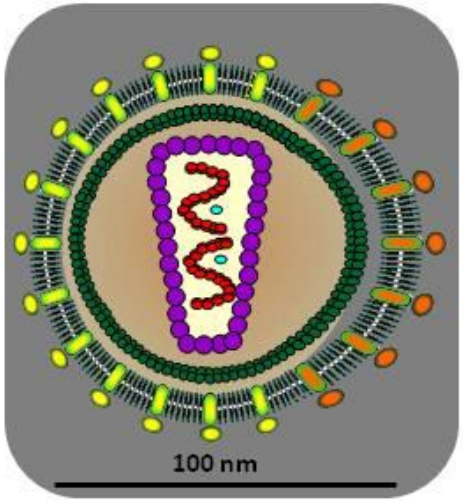
Molecular Components of Tumor-Targeted Rexin-G

Therapeutic Payload
(Bioactive Construct)



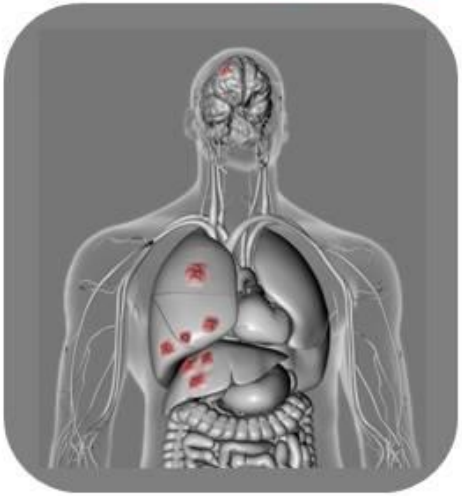
Killer gene provides broad-spectrum activity

Vector Design Engineering



Stealth vector enables repeated i.v. infusions

Active (XC-) Tumor-Targeting

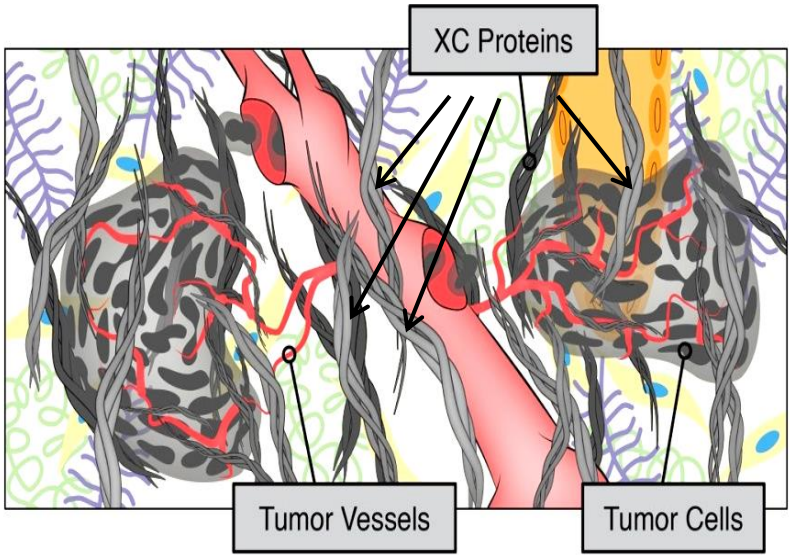


Tumor-targeting seeks out cancerous lesions

Active Vector Targeting:
Targeting the Tumor Microenvironment

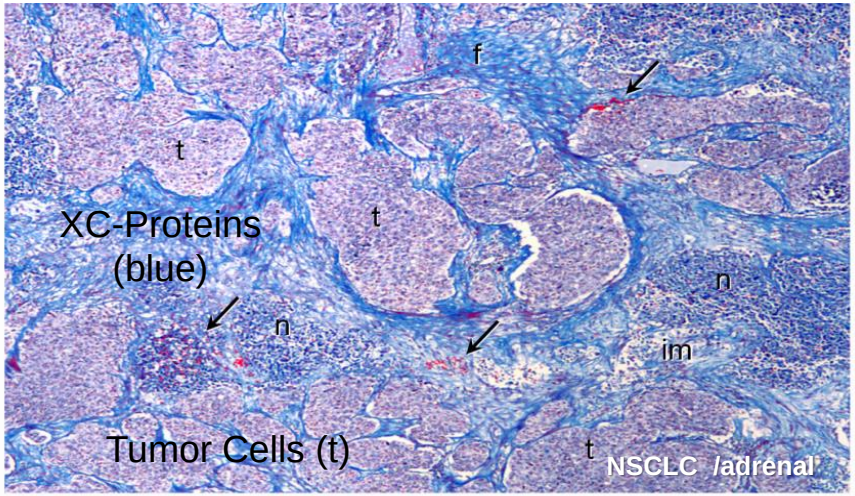
Exposure of Collagenous (XC-) Proteins is a HistoPathological Feature of all Invasive Cancers

Abnormal Tumor Microenvironment:



The Collagenous XC-Proteins in a Human Tumor Biopsy are Stained Bright Blue by the Trichrome-stain

Tumor cells (t) immersed in a sea of exposed collagenous (XC-) proteins:



XC-Proteins exposed by tumor invasion, stroma formation, & angiogenesis.

Advanced, Adaptive Phase I/II Trials
FDA-Approved Trials

Advanced:
Each clinical study included a Phase II efficacy component.

Adaptive:
Used comprehensive analysis of clinical response criteria for this targeted biologic.

Across-the-board Dose Escalation:
FDA allowance upon aggregate analysis.

Chemotherapy-resistant Cancers

Phase I/II Study – all types of sarcoma*

Phase I/II Study – pancreatic cancer*

Phase II Study – osteosarcoma*

RESULTS: Rexin-G® exhibits an outstanding safety record (with no DLT); dose-dependent single-agent efficacy; gains in tumor control, progression-free survival (PFS), and overall survival (OS).

- **FDA grants Orphan Drug***:

Osteosarcoma, STS, and Pancreatic Cancer

Advanced Phase I/II Evaluation of Tumor-Targeted Gene Delivery: Intravenous Infusions of Rexin-G as Stand-alone Therapy for Chemotherapy- Resistant Bone and Soft tissue Sarcoma

- **Primary Endpoint:** Evaluation of clinical toxicity / safety
- Secondary Endpoint # 1: Evaluation of vector-related safety
- Secondary Endpoint # 2: Identify potential tumor responses

Patients:

Bone and Soft Tissue Sarcoma, chemotherapy-resistant (n = 36)

Dosing Schedule:

Dose Escalation, Doses I-V [1-4 x 10e11 cfu i.v. BIW or TIW x 4 wks]

Note: Intra-patient dose-escalation was allowed up to Dose Level II;
Additional treatment cycles were given if patient had $\leq$ Grade 1 toxicity

Enrollment:

n = 33 evaluable patients (completed one cycle with follow-up PET-CT)

Rexin-G Safety & Efficacy is Affirmed

US FDA Grants Orphan Drug: Osteosarcoma & STS

Wide Range of Sarcomas Treated

 # Previous Chemotherapy Regimens

Median ……..…. 4

Range ……..…. (1-10)

Many Types of Sarcomas Treated

Leiomyosarcoma ……	10 (27%)
Liposarcoma ……	6 (16%)
Synovial cell sarcoma ……..	4 (11%)
Osteosarcoma …….. …..….	3 (8%)
MMMT ovary …….....	2 (6%)
Ewing's sarcoma ……...	2 (6%)
Angiosarcoma …….....	2 (6%)
Malignant fibrous histiocytoma ...	2 (6%)
Chondrosarcoma ……..….	1 (3%)
Malignant spindle cell sarcoma....	1 (3%)
Fibrosarcoma …….....	1 (3%)
Amelanotic schwannoma ….....	1 (3%)
Alveolar Soft Parts Sarcoma	1 (3%)

Results to Date: (33 evaluable patients)

✓ **Primary Endpoint:**

No dose limiting toxicity (DLT) was observed;
Grade1 chills (n = 1), Grade 1 fatigue (n = 2);
Grade 2 tumor pain (n = 2)

✓ **Secondary Endpoint # 1:**

No vector-neutralizing antibodies; No vector integration and no RCR detected in peripheral blood lymphocytes (No Long-term Concerns)

✓ **Secondary Endpoint # 2:**

Dose-dependent improvements in tumor control rates, progression-free survival (PFS) and overall survival (OS) times were improved

RESULTS of the Phase I / II Study

Chemo-Resistant Bone and Soft Tissue Sarcomas

SARCOMA oncology center

Evaluation of Anti-tumor Activity of Intravenous Infusions of Rexin-G as Stand-alone Therapy

Dose Level	Tumor Response By RECIST Criteria	Tumor Response By PET Criteria	Tumor Response By CHOI Criteria	Median PFS By RECIST, Months	Median OS, Months	One-Year Survival
I (n=6)	3SD, 3PD	1PR, 4SD, 1PD	2PR, 4SD	1.2	3.2	0%
II, III (n=14)	10SD, 4PD	4PR, 9SD, 1PD	7PR, 7SD	3.8	7.8	28.6% 2 yr = 0%
IV, V (n=13)	9SD, 4PD	3PR, 8SD, 2PD	1PR, 10SD, 2PD	4.1	11.5	38.5% 2 yr = 31.0%

Dose-dependent survival benefits, p = 0.002

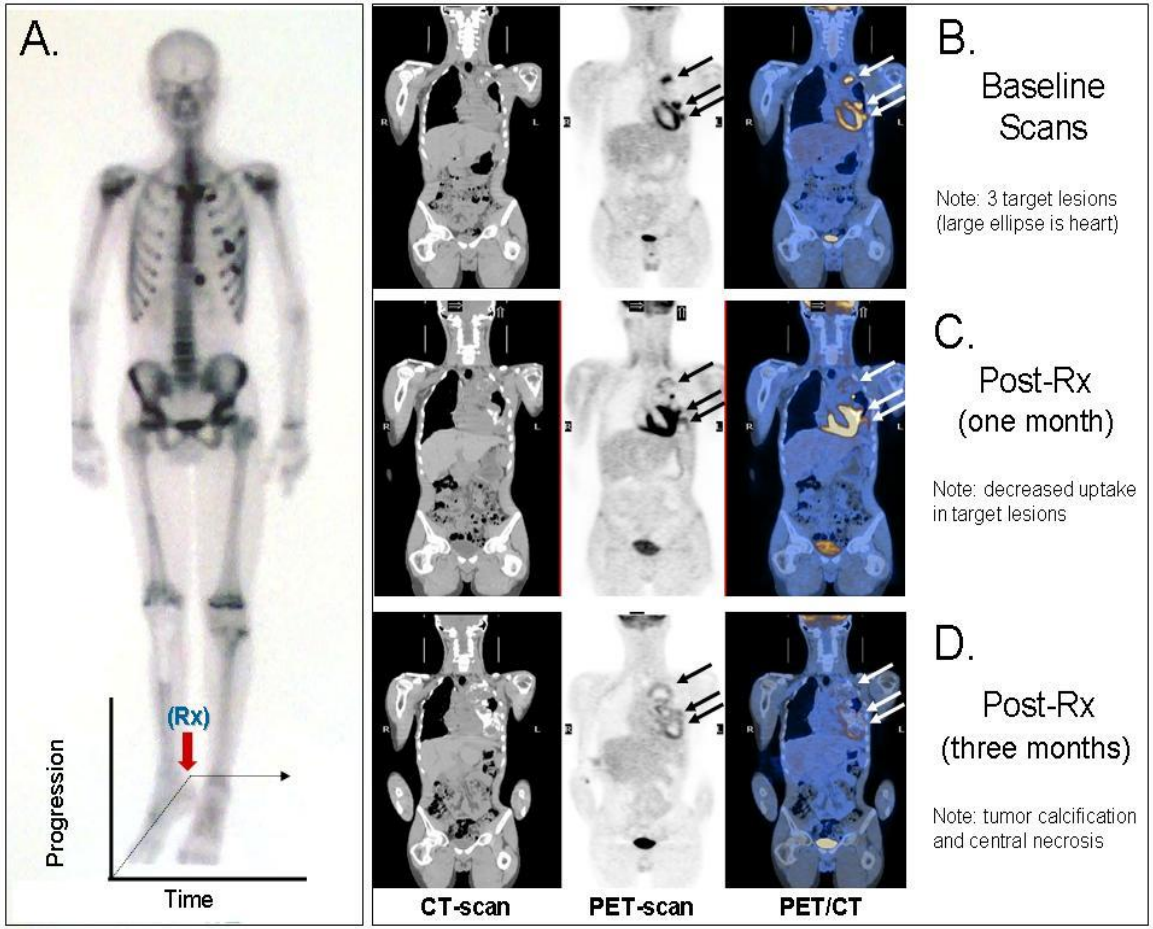
A Case Study:

Single–Agent Efficacy in Osteosarcoma

Osteosarcoma

Note: life-threatening metastatic lesions in lungs and ~heart (A)

- Evidence of Rexin-G efficacy as seen in a 17-year old male
- Tumor responses by PET and CHOI. are noteworthy (B vs C,D)
- Rapid progression of disease is halted (inset)
- Gains in expected survival (PFS, OS)



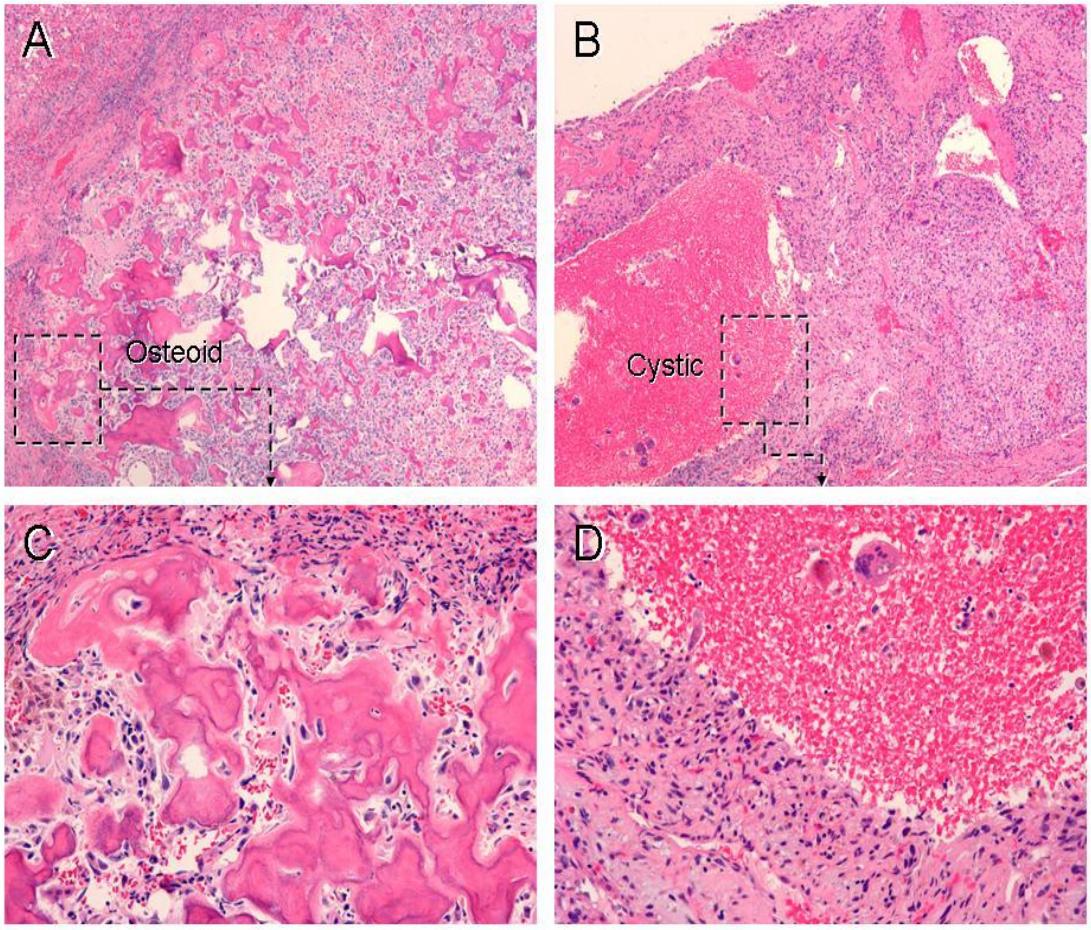
A Case of Surgical Remission in Chemo-Resistant Osteosarcoma

Rexin-G plus Surgery: A Lasting Remission

- Rexin-G Treatment Halts Progression of the Metastatic Disease

- Surgical excision of two remaining lesions shows:
  - A,C: Ossification
  - C,D: Cystic Conversion

- Neoadjuvant / Adjuvant Treatment produces a Sustained Remission with no evidence of residual disease (>7 Yrs)



Long-Term Follow Up
Dose-Dependent Survival Benefits

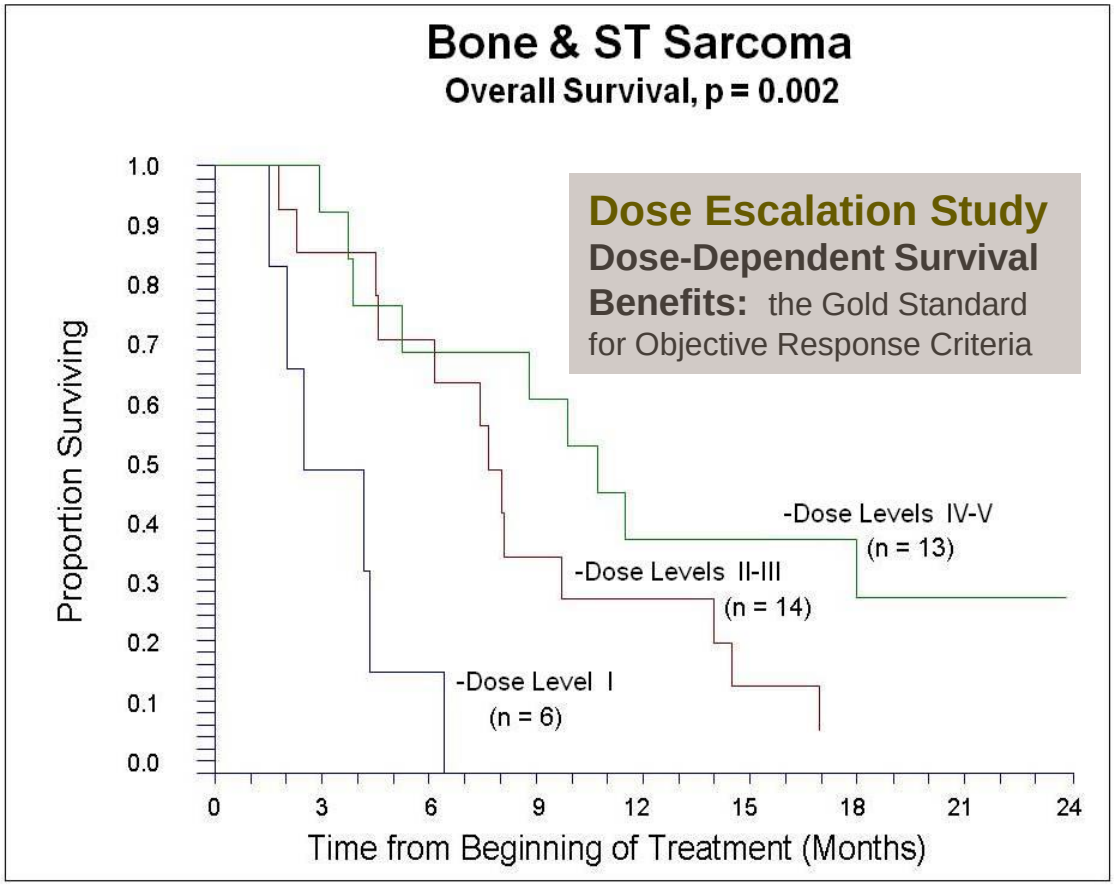
Advanced Phase I/II Study using Rexin-G, an XC-Targeted Gene Therapy Vector for Chemotherapy Resistant Sarcoma
(Chawla et al., 2016)

✓**SAFETY:**

- No dose-limiting toxicity
- No vector related toxicity

✓**EFFICACY:**

- Controls tumor growth
- Improves Progression-Free Survival (PFS);
- Improves Overall Survival (dose-dependent OS)



Note: 2 Long-term (>7 Yr) Cancer-free Survivors

A Phase II Evaluation of Tumor-Targeted Gene Delivery: Intravenous Infusions of Rexin-G as Stand-alone Therapy for Chemotherapy- Resistant Metastatic Osteosarcoma

- **Primary Endpoint:** Evaluation of efficacy
- Secondary Endpoint # 1: Evaluation of safety

Patients:

Osteosarcoma, chemotherapy-resistant (n = 22)

Dosing Schedule:

Dose Escalation, Doses I-II [1-3 x 10e11 cfu i.v. BIW or TIW x 4 wks]

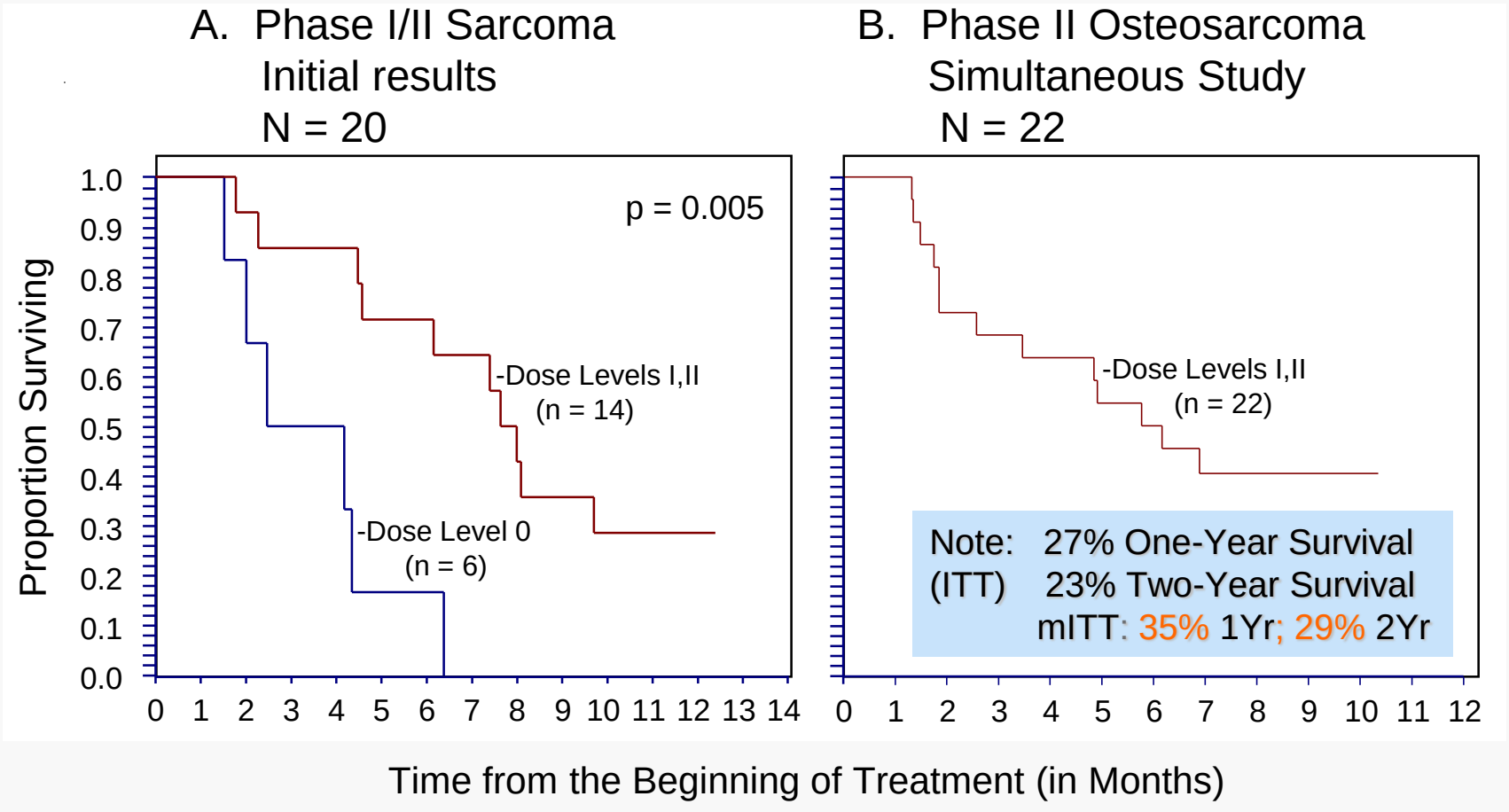
Note: Intra-patient dose-escalation was allowed up to Dose Level II; Additional treatment cycles were given if patient had ≤ Grade 1 toxicity

Enrollment:

n = 17 evaluable patients (completed one cycle with follow-up PET-CT)

Confirmatory Phase II Study

Efficacy in Chemo-resistant Osteosarcoma



Advanced Phase I/II Evaluation of Tumor-Targeted Gene Delivery: Intravenous Infusions of Rexin-G as Stand-alone Therapy for Chemotherapy- Resistant Pancreatic Cancer

- **Primary Endpoint:** Evaluation of clinical toxicity / safety
- Secondary Endpoint # 1: Evaluation of vector-related safety
- Secondary Endpoint # 2: Identify potential tumor responses

Patients:

Pancreatic cancer, chemotherapy-resistant (n = 20)

Dosing Schedule:

Dose Escalation, Doses I-IV [1-3 x 10e11 cfu i.v. BIW or TIW x 4 wks]

Note: Intra-patient dose-escalation was allowed up to Dose Level II;
Additional treatment cycles were given if patient had ≤ Grade 1 toxicity

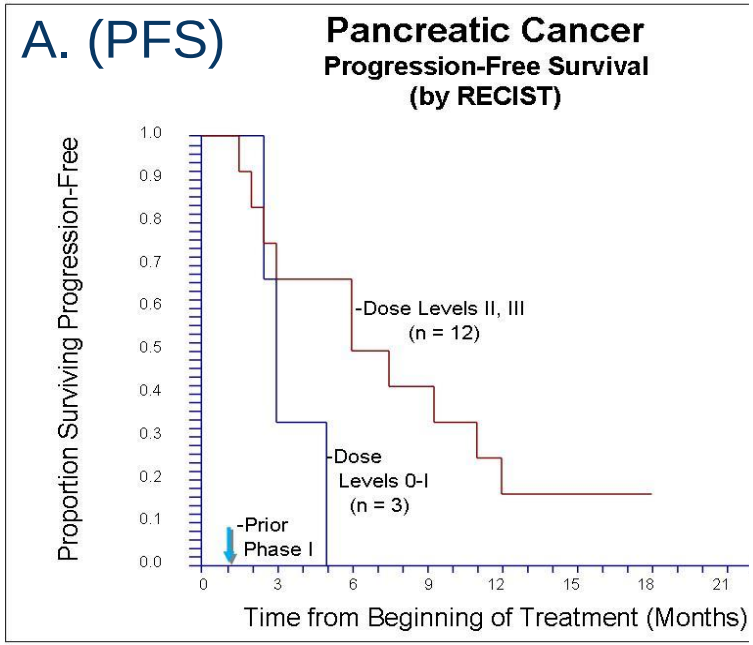
Enrollment:

n = 15 evaluable patients (completed one cycle with follow-up PET-CT)

Phase I/II Studies: Rexin-G Monotherapy

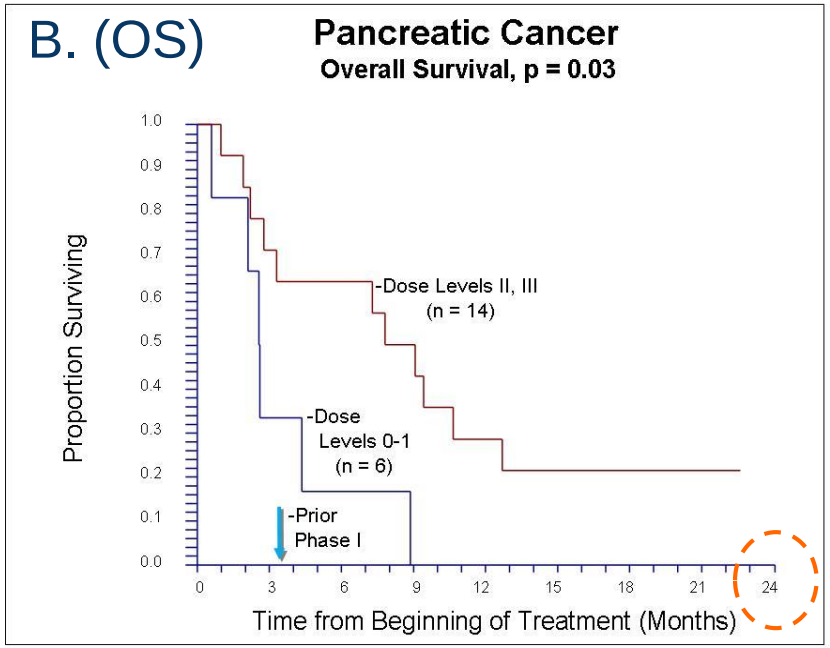
Stage IVB Gemcitabine-resistant Pancreatic Cancer

A. (PFS)



Kaplan Meier plot suggests a trend toward a dose-response relationship between progression-free survival and Rexin-G dosage (n = 15 evaluable)

B. (OS)



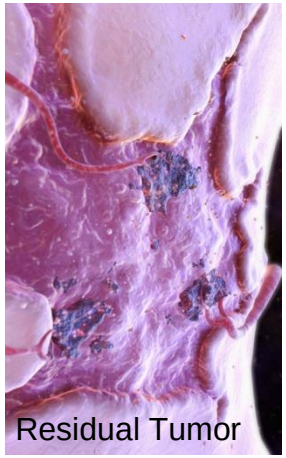
A significant dose-response relationship between overall survival and Rexin-G dosage in the Intention to Treat Patient Population (n = 20; 5% statistical level).

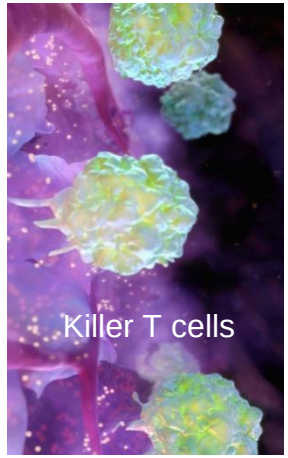
The GeneVieve Protocol for Cancer Immunotherapy

A Dual Targeted Approach:
Rexin-G (Tumor Control) followed by **Reximmune-C** (GM-CSF expression vector provides vaccination in situ).

- **Rexin-G** is a tumor-targeted retroviral vector bearing a cytocidal Cyclin G1 construct, utilized to bring the tumor burden under control.

- **Reximmune-C** is a tumor-targeted retroviral expression vector bearing a GM-CSF gene, utilized to provide localized expression within residual tumors, thereby recruiting TILs and stimulating anti-tumor immunity.





First Study Results (Genevieve Protocol):

A Phase I/II Study of Intravenous **Rexin-G** plus **Reximmune-C** for Chemotherapy-resistant Cancers

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 for positive indications of efficacy

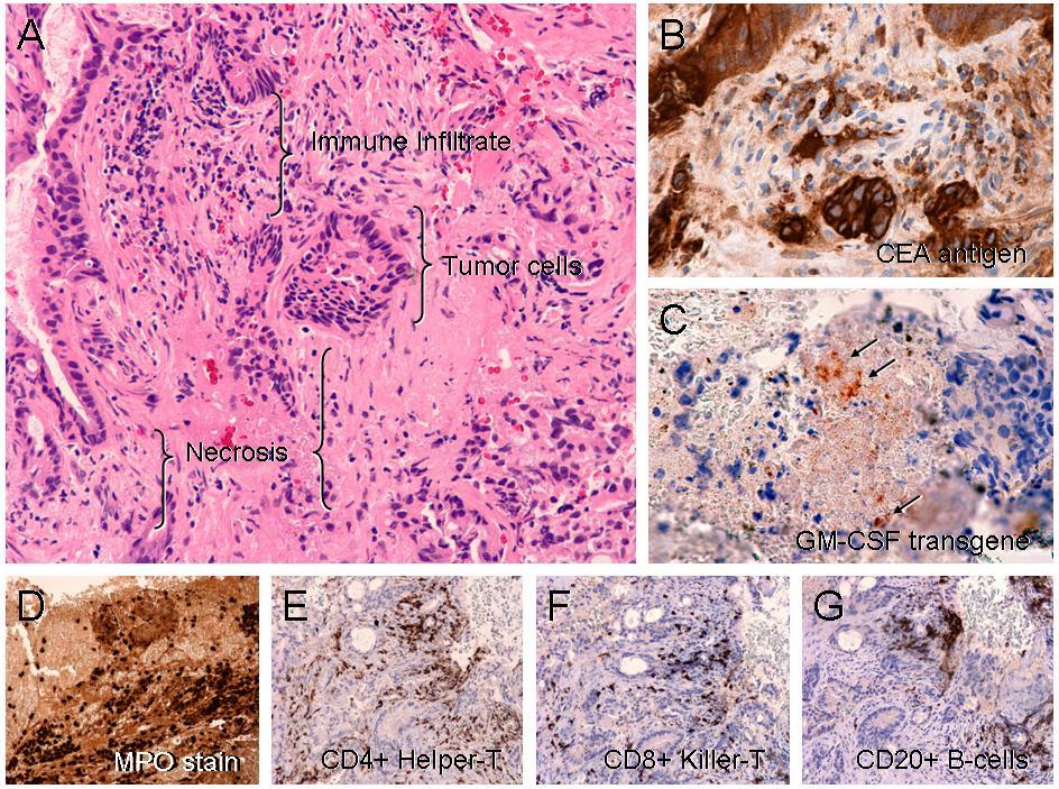
Reximmune-C Dose Level	Best Tumor Response RECIST, PET* or Bone Scan**	Median PFS RECIST, PET* or Bone Scan** Months	Median OS, (Months) From Start of Rexin-G Rx	Per Cent > One Year Survival
I (n = 5)	2PR**, 1SD, 2PD	4.5	21	80
II (n = 4)	1PR, 3SD	9	13	50
III (n = 7)	2PR*, 5SD	13	> 22	86

Note: One patient at Dose II, and one patient at Dose III had SD with extensive tumor necrosis.

The GeneVieve Protocol: Mech-of-Action

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

Immune Infiltration Following Reximmune-C



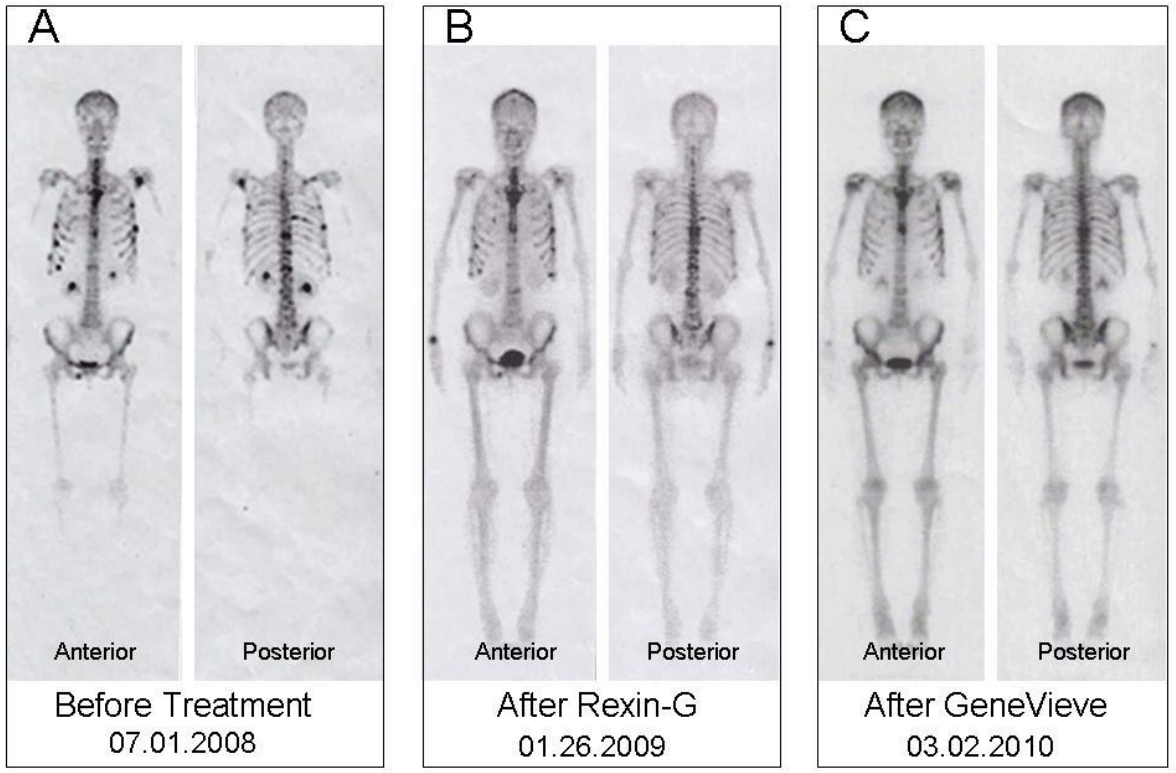
The residual tumor was resected two days after infusion of Rexin-G and Reximmune C. (**A**) H&E: areas of tumor necrosis with tumor infiltrating lymphocytes (TILs); (**B**) CEA+ tumor cells, (**C**) immunoreactive GM-CSF transgene (reddish-brown staining material) in a necrotic tumor, (**D**) MPO staining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

The Genevieve Protocol: Rexin-G Treatment Followed by Tumor-Targeted Reximmune-C (i.v.)

Combined Effects of Rexin-G plus Reximmune-C

Progressive tumor regression was observed in serial bone scans obtained over 20 months following treatment initiation with Rexin-G to control tumor growth, followed by the Reximmune-C to stimulate a local immune response.

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



Overall Conclusions:

Phase I & II Studies of Targeted Gene Delivery

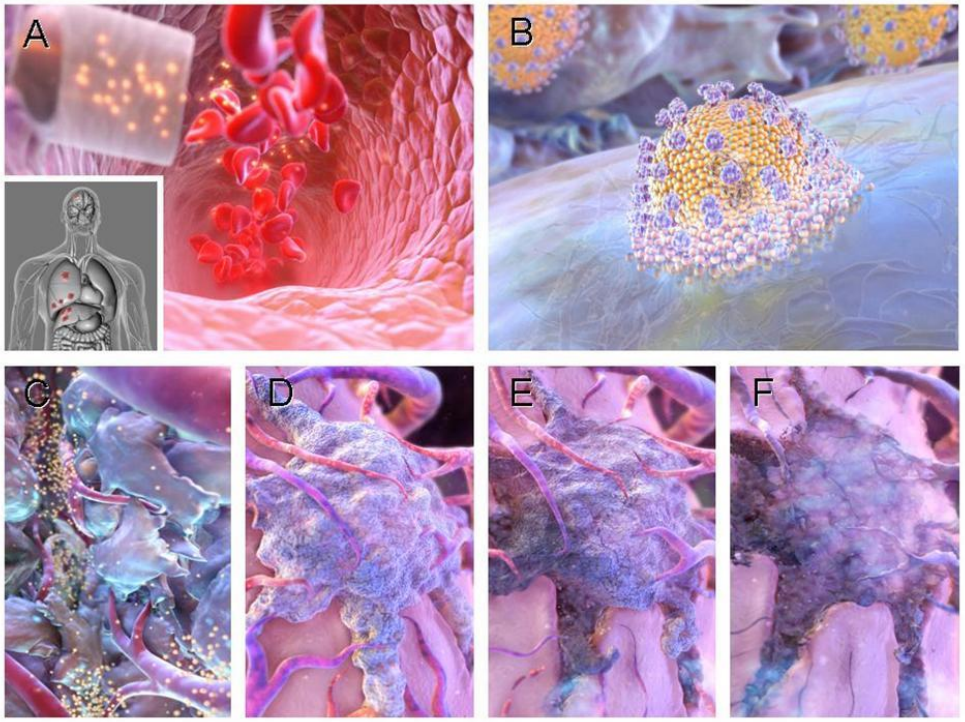
Taken together these studies Indicate that:

✓ Tumor-Targeted vectors (**Rexin-G** and **Reximmune-C**) are well-tolerated with no dose-limiting or organ-related toxicity.

✓ **Rexin-G** controls tumor growth and may improve progression-free survival (PFS) and overall survival (OS) in chemo-resistant cancers.

✓ **Reximmune-C** provides an opportunity for local stimulation of tumor immune responses.

Targeted, Injectable Retroviral Expression Vectors Deliver Therapeutic Genes for Tumor Control



Thank You

Sant P. Chawla, M.D., FRACP

SARCOMA ONCOLOGY CENTER

2811 Wilshire Blvd, Suite 414

Santa Monica, CA 90403