



Immune Checkpoints & Counterpoints:

Toward a More Precise, Pro-Active Approach to Immune Modulation in Solid Tumors

Sant P. Chawla, MD

Counterpoint Biomedica LLC &
The Sarcoma Oncology Center
Santa Monica CA 90403

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XC-Targeting, an Enabling Platform

Validation of Clinical Utility and Effectiveness



Counterpoint's founders previously developed Rexin-G and Reximmune-C, the first and only tumor-targeted gene expression vectors to be fully validated in the clinic.

➤ Targeted Clinical Retrovectors:

- ❖ Over 270 patients treated, >3,000 total infusions
- ❖ Demonstrated to be safe and well tolerated
- ❖ Cancers treated: Pancreas, soft tissue sarcoma, osteosarcoma, breast, lung, liver, kidney, prostate, larynx, colon, melanoma

➤ Targeted Onco-Aptamers (mAb-Tropins):

- ✓ mAb-Tropin Design and Selection
- ✓ Preclinical Validation in Animals
- ✓ GMP Production and Formulation
- ❖ IND Development and FDA Approval
- ❖ Phase I/II Clinical Trials (Checkpoint mAbs)



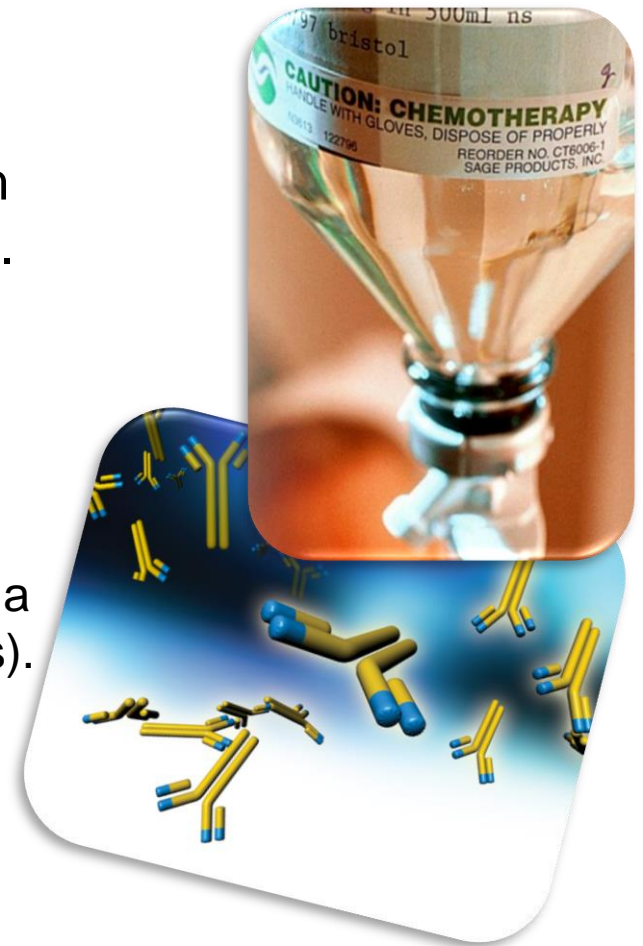
The Clinical Problem:

Systemic Biodistribution and Dose-Limiting Toxicities



The clinical toxicities of many biologic and chemotherapeutic agents is a result of the non-specific nature of drug distribution, which affects / damages normal tissues and organs.

- Chemotherapies and Biologics are distributed widely to both target and non-target organs, requiring high plasma levels to be effective.
- Immune Checkpoint Inhibitors (mAbs) produce a range of immune-related adverse events (irAEs).
- Systemic Delivery of Immune-stimulating Cytokines (GM-CSF, IL-2, and INF-alpha) is associated with significant systemic toxicities.



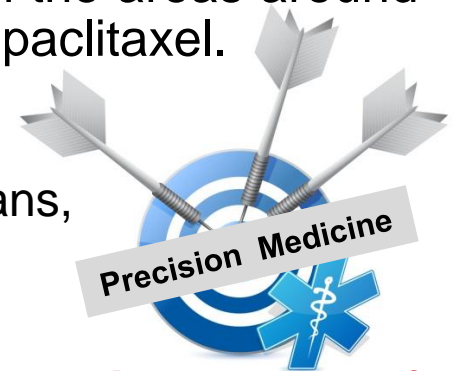
The Clinical Solution:

More “Active” and Efficient Targeting of Drug Delivery



❑ **Passive Delivery Systems**—drug accumulations in the areas around tumors with leaky vasculature (EPR effects)—e.g. Nab-paclitaxel.

- The majority (>95%) of passively administered cancer Drugs are known to accumulate primarily in other organs, in particular the liver, spleen, and lungs.



❑ **Active (or “Targeted”) Delivery** — provides the advantages of higher concentrations in tumors and lower systemic exposures, resulting in less systemic side effects and irAEs.

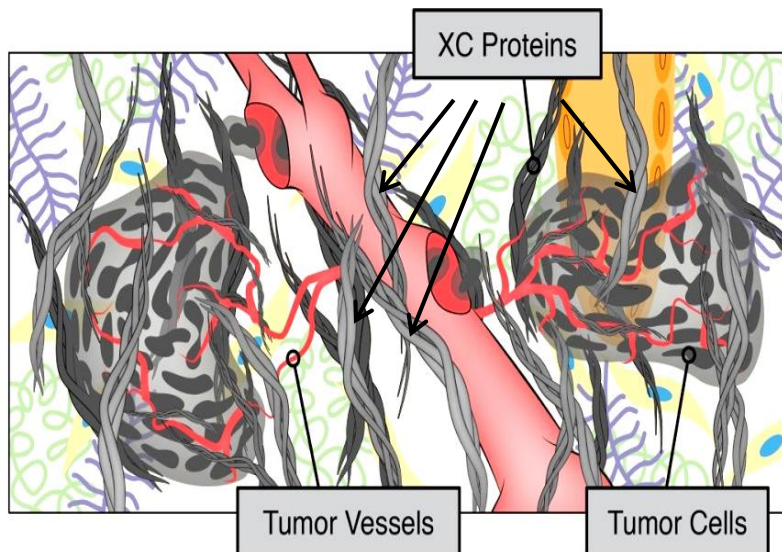
- Active drug delivery is orders of magnitude more efficient than passive EPR effects, overcoming vast dilutions in the circulation while seeking-out and accumulating to high levels in tumor compartments.
- Lower drug doses avoid the issues of dose-limiting toxicities and treatment-limiting toxicities — thus enhancing the treatment duration, natural immune responses, and ultimately tumor control.

Active Tumor Targeting: Targeting the Tumor Microenvironment



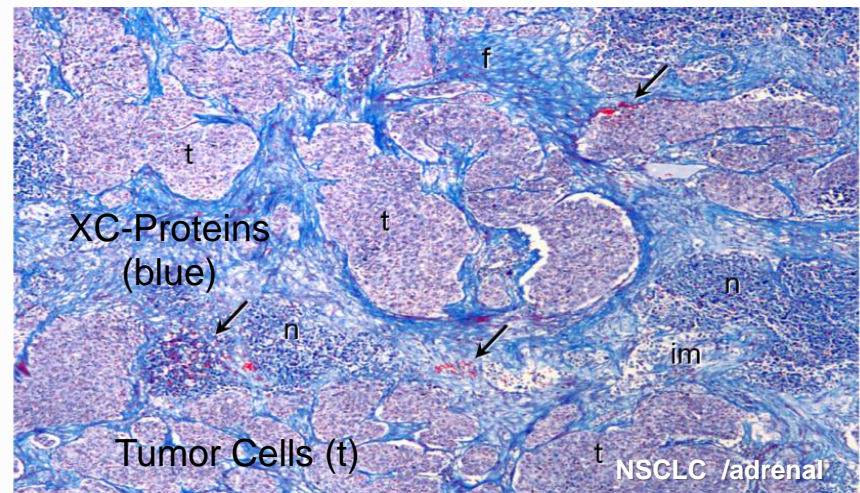
Exposure of Collagenous (XC-) Proteins is a HistoPathological Feature of all Invasive Cancers

Abnormal Tumor Microenvironment:



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:



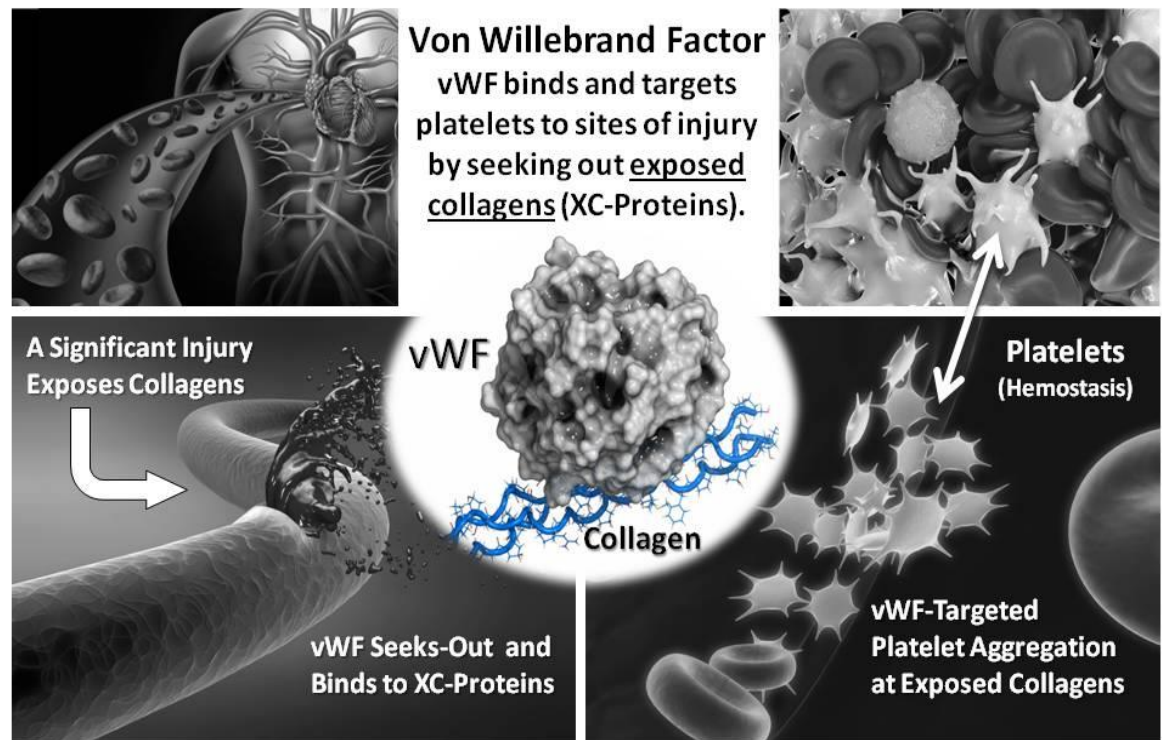
XC-Proteins exposed by tumor invasion, stroma formation, & angiogenesis.

(XC)Tumor-Targeting: A Physiological Surveillance Function within von Willebrand Factor



- **von Willebrand Factor** (vWF) is an important “targeting” protein involved in blood clotting and wound healing.
- Naturally guides circulating platelets to injured and diseased tissues by seeking-out abnormal XC-proteins.
- **XC-Targeting:** the surveillance function provides a molecular mechanism for the development of tumor-targeted drug delivery.

Molecular Engineering the XC-Binding Domain of vWF Provides the Basis for Tumor-Targeted Drug Delivery

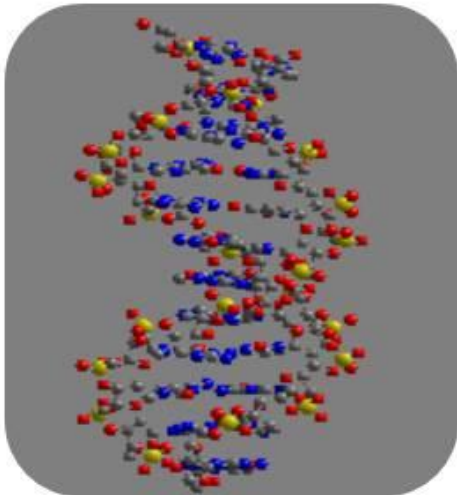


Rexin-G, XC-Targeted Retroviral Vector: First Targeted, Injectable Gene Delivery



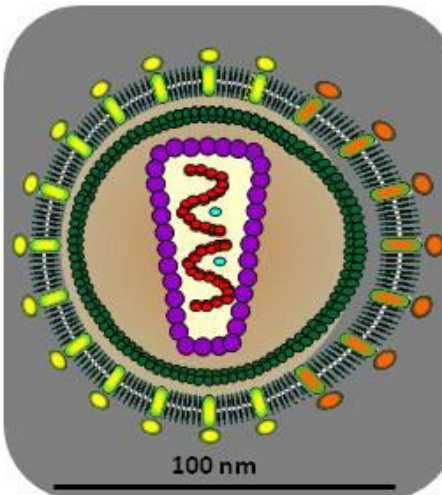
Molecular Components of Tumor-Targeted Rexin-G

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

XC-Targeted Rexin-G: Seeks-out & Accumulates-in Human Tumors



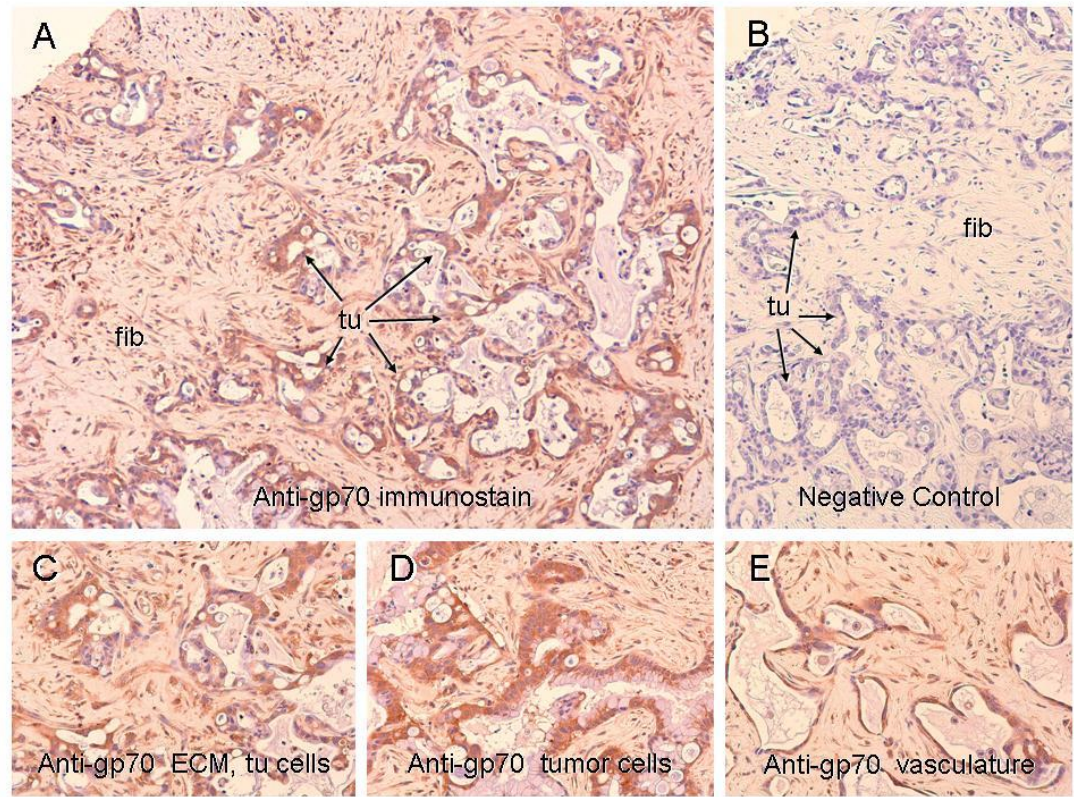
Accumulation of Rexin-G vector particles seen in a metastatic liver lesion

Treatment preceding surgery enabled direct visualization of histology

Immunohistochemical staining for Rexin-G^{env} protein shows the XC-targeting-dependent accumulation of vector in:

- Tumor ECM (**A**)
- Tumor cells (**C,D**), and
- Tumor vasculature (**E**)
- Versus IHC Control (**B**)

Immunohistochemical Staining for the Retrovector in a Bx Liver Tumor Following Treatment w Rexin-G



Studies of XC-Targeted Rixin-G: Safety and Efficacy Proven in Clinical Trials



Clinical: Rixin-G as Monotherapy in Chemotherapy-resistant Cancers:

Phase I/II Study – all sarcomas*

Phase I/II Study – pancreas cancers*

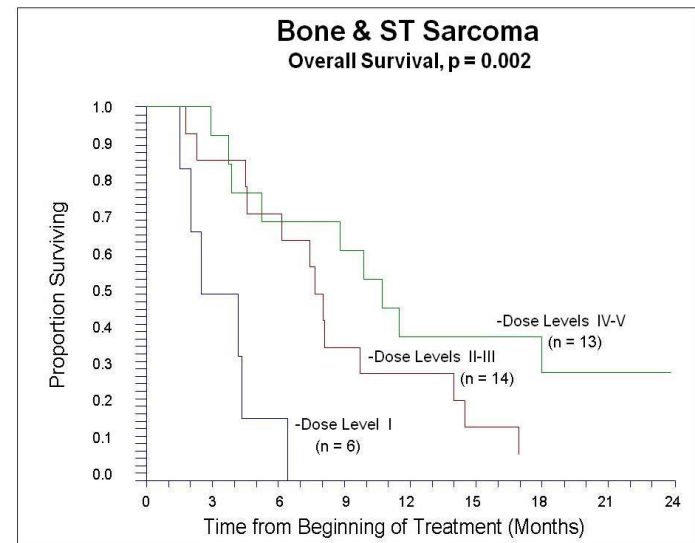
Phase II Study – osteosarcoma*

RESULTS: Rixin-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

Rixin-G Improves Survival



Dose-Dependent Survival Benefits:
The Gold Standard for Objective Responses



XC-Targeted Reximmune-C: Tumor-Targeted GM-CSF Expression Vector

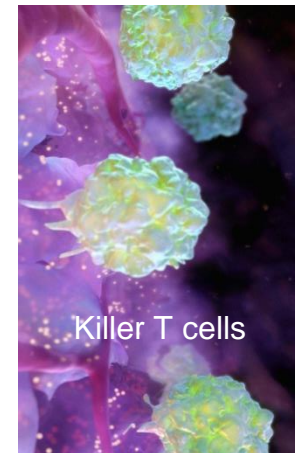
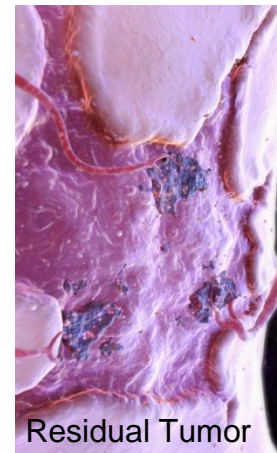


The GeneVieve Protocol:

Two-Stage Cancer Immunotherapy

Rexin-G (Cytocidal Gene) followed by **Reximmune-C** (Cytokine GM-CSF Gene provides vaccination in situ).

- **Rexin-G** is a tumor-targeted retroviral vector bearing a cytocidal Cyclin G1 construct, utilized to kill the tumor cells and expose neoantigens.
- **Reximmune-C** is a tumor-targeted retroviral expression vector bearing a GM-CSF gene, utilized to recruit the patient's immune cells into the tumor microenvironment and to evoke tumor recognition and anti-tumor immunity.

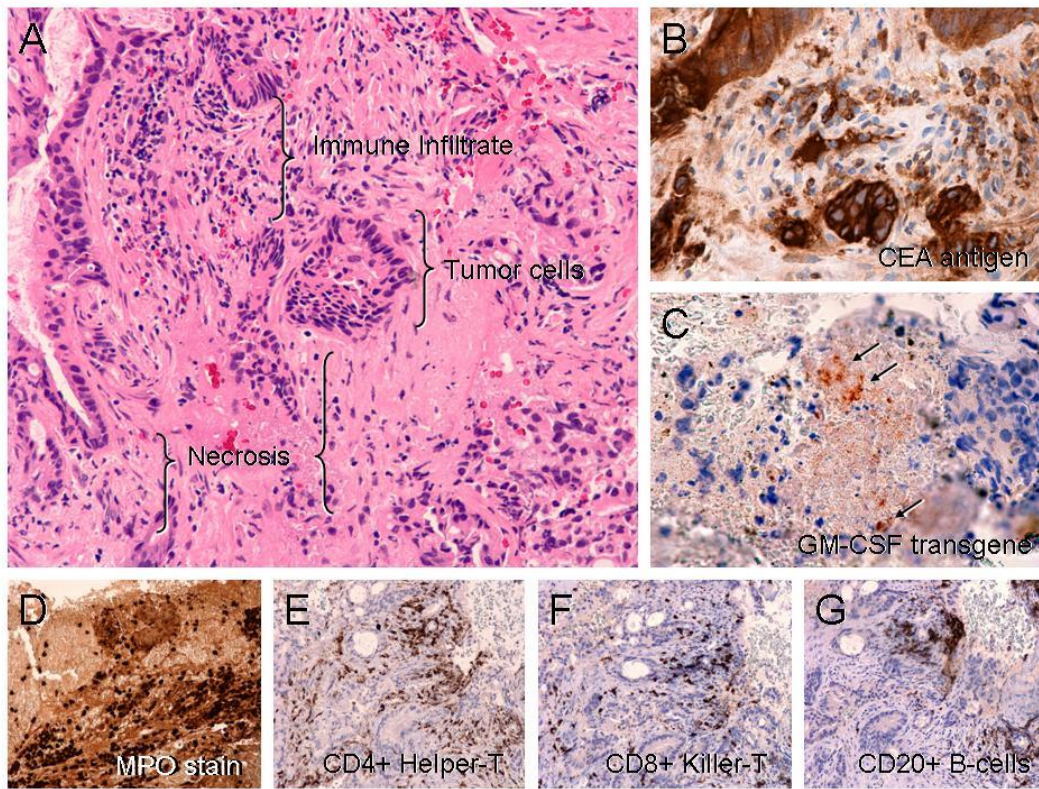


The GeneVieve Protocol: Mechanism-of-Action

Histology and Transgene (**GM-CSF**) Expression in a Residual Tumor from a Colon Cancer Patient following 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.

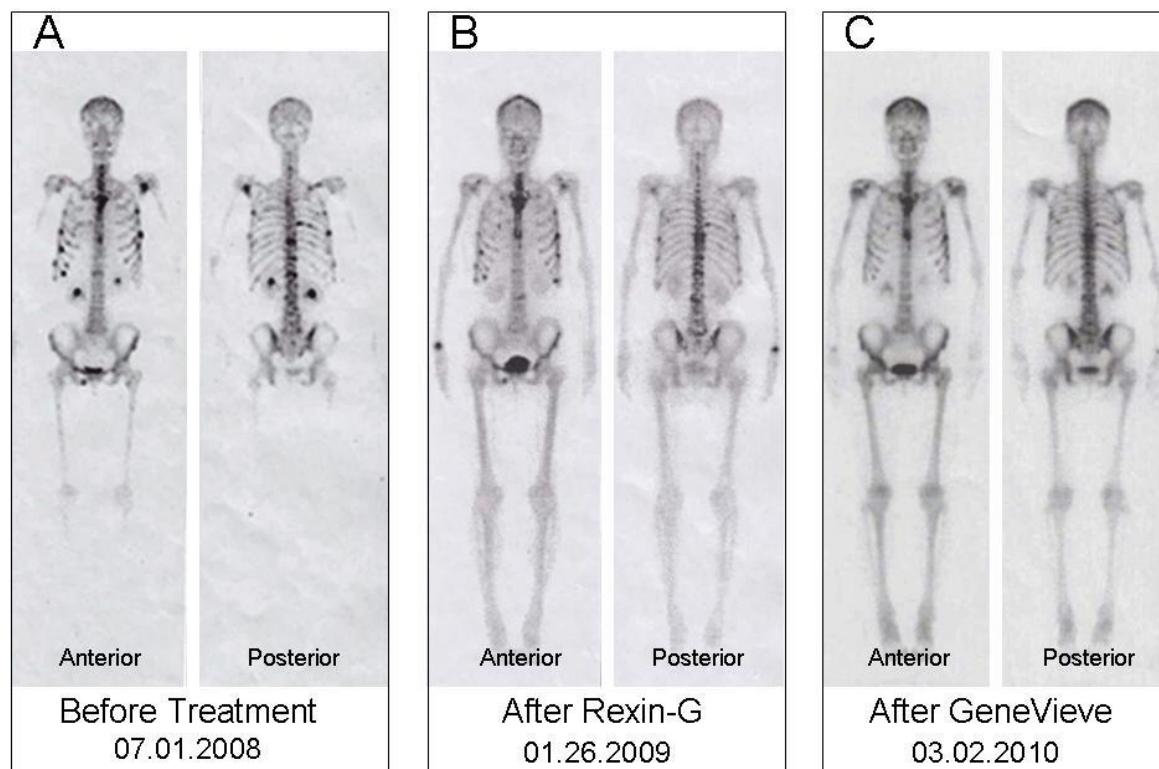
The Genevieve Protocol: Rexin-G Treatment followed by Tumor-Targeted Reximmune-C (i.v.)



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



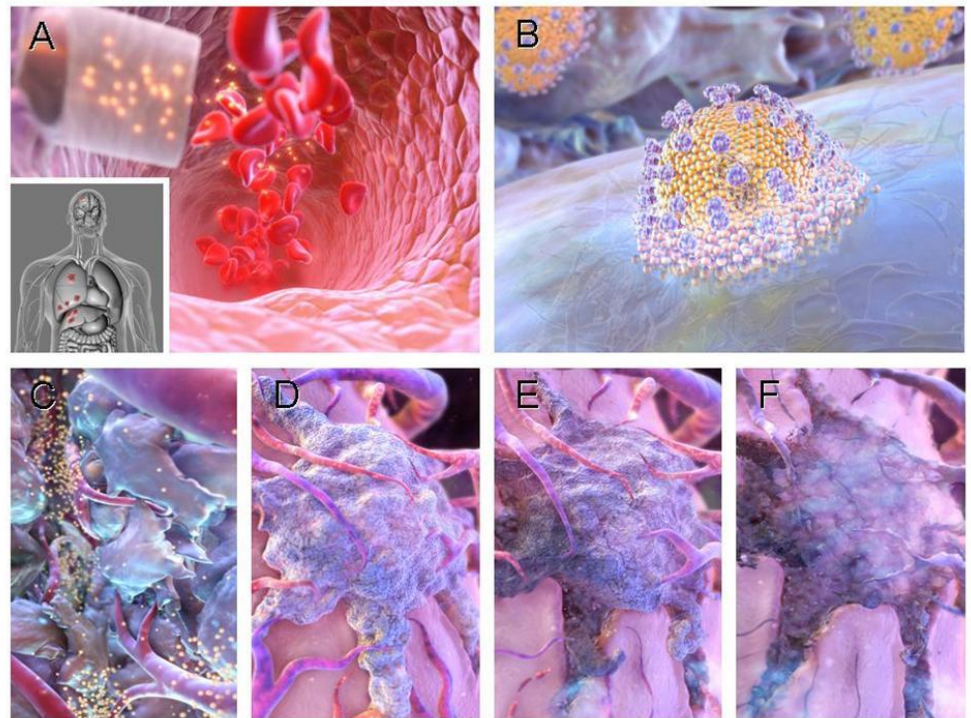
Clinical Validation of XC-Targeting: Phase I & II Evaluations of Targeted Immunotherapy



CONCLUSIONS:

- ✓ 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 (**86% one year survival rate**).
- ✓ **Reximmune-C** provides an opportunity for local stimulation of tumor immune responses.

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



XC-Targeting, an Enabling Platform

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➤ **Targeting Onco-Aptamers (mAb-Tropins):**

- ✓ **mAb-Tropin Design and Selection**
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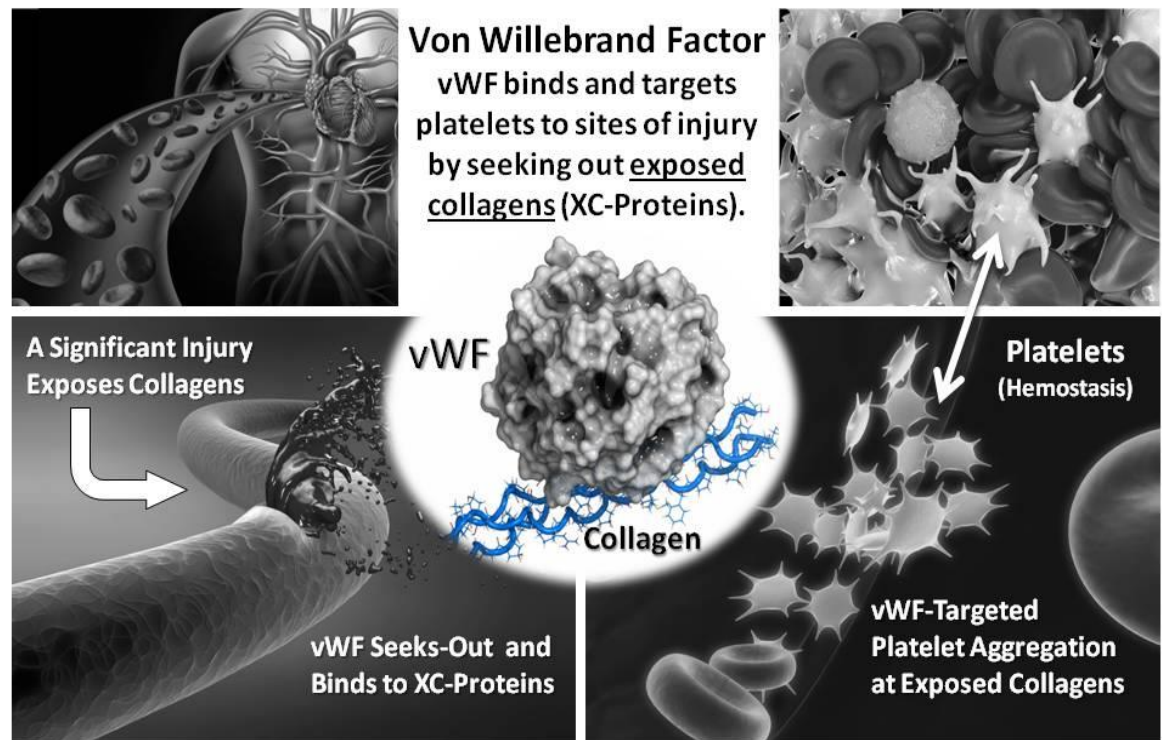


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- **XC-Targeting:** the surveillance function provides a molecular mechanism for the development of tumor-targeted drug delivery.

Molecular Engineering the XC-Binding Domain of vWF Provides the Basis for Tumor-Targeted Drug Delivery



The Counterpoint Approach: Onco-Aptamers

Bifunctional Polypeptides Provide “Active” Drug Delivery



XC-Targeted Drug Cargos:

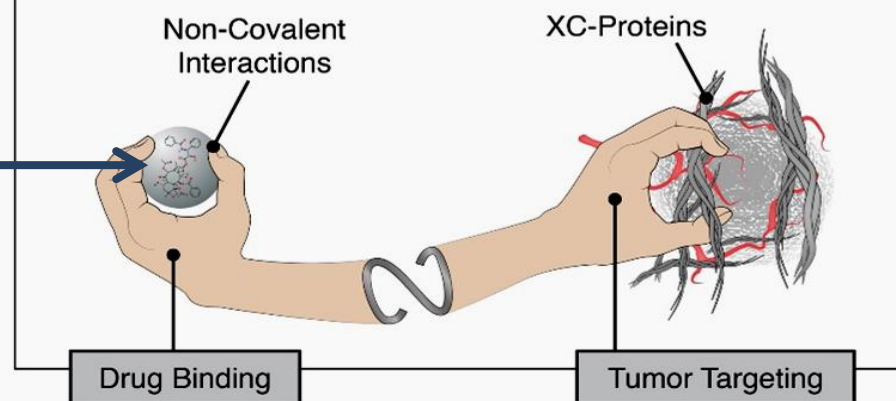
Chemotherapeutic Drugs,
Small Molecules, mAbs,
siRNAs, Nanoparticles.

Drug Binding:

High-affinity drug binding
domains provide for strong
non-covalent drug /
aptamer interactions.

Note: the tumor-targeting
platform does not require
alterations in either the
chemical composition or
manufacturing of FDA-
approved drug cargos.

TWO-HANDED STRUCTURE OF ONCO-APTAMER



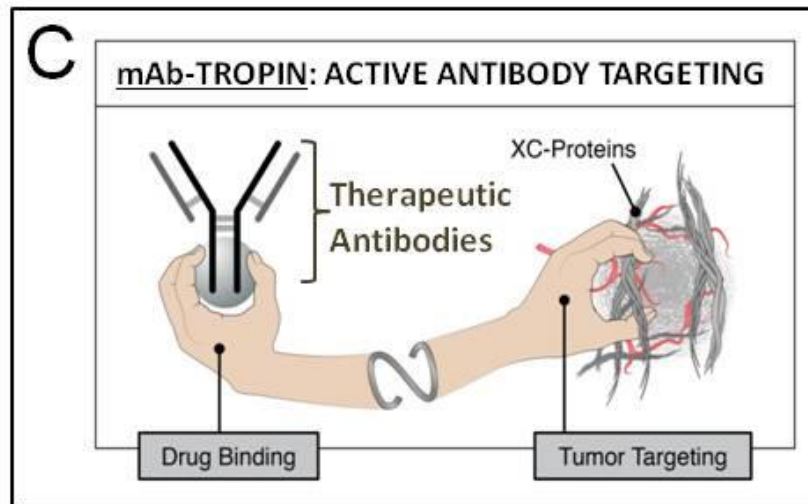
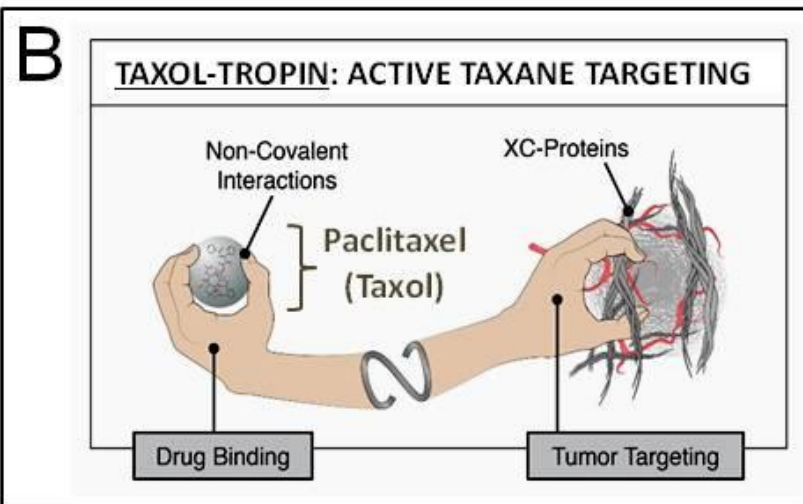
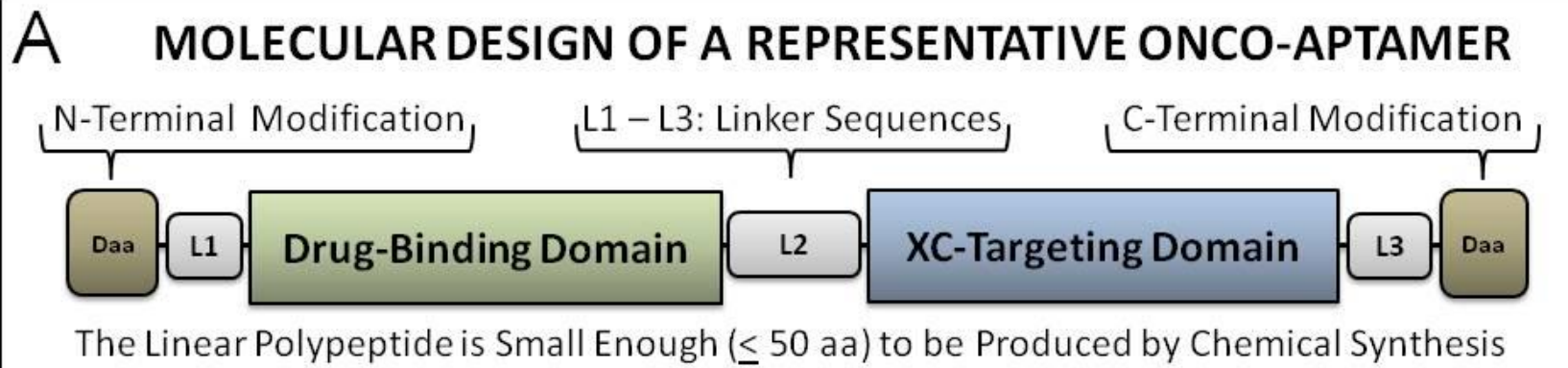
Primary Binding Domains of the Bifunctional Polypeptides

1. Sequences that bind non-covalently to approved anti-cancer drugs (the cargo).
2. Proven tumor-targeting sequences that seek out and bind tightly to XC-proteins.



Lead XC-Targeted Onco-Aptamer Designs

Custom Engineered for Specific Classes of Drugs

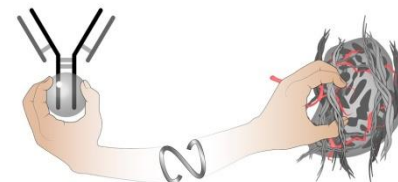


(XC-)Tumor-Targeted Onco-Aptamers

Summary of Structural & Functional Properties



- ❑ Bifunctional tumor-targeting polypeptides
 - XC-binding domain concentrates drug at the tumor sites
 - XC-targeting is based on a clinically proven technology
- ❑ Non-covalent drug-binding characteristics
 - No modifications of the approved drug manufacturing required
- ❑ Protease-resistant designs
 - Terminal D-amino acids or PEGylation prevent degradation
- ❑ Onco-aptamers are typically less than 50 amino acids
 - Chemical synthesis of onco-aptamers is feasible – with predictable economies-of-scale
- ❑ Applicable to a broad range of therapeutic modalities
 - Taxanes, small molecules, mAbs, RNAis, nanoparticles

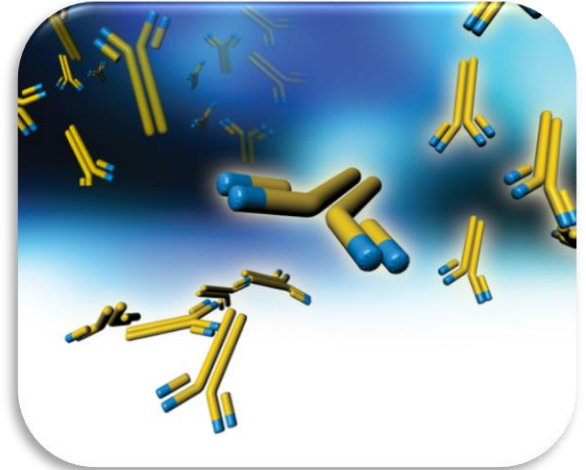


Checkpoints and Counterpoints:

Mitigating “irAEs” with Pro-active Tumor Targeting



- ❑ **Monoclonal antibodies** (mAbs) are now well established as “targeted therapies” for a wide variety of malignancies; however, there are still problems with systemic biodistribution, target selectivity, poor tumor penetration, and untoward toxicities, which limit clinical utility.
- ❑ **Monoclonal antibodies** are typically considered to be safer than cytotoxic agents, but Immune Checkpoint Inhibitors bring a new toxicity profile.
- ❑ **Immune Checkpoint Inhibitors**, designed to activate anti-tumor T cell responses, offer a promising avenue for immunotherapy; however the systemic biodistribution of these potent mAbs introduces autoimmune disorders and serious immune-related Adverse Events (irAEs).
- ❑ **Tumor targeted onco-aptamers** are designed to compartmentalize the T cell response to enhance efficacy and reduce immune-related reactions.



Preclinical Validation *In Vitro* and *In Vivo*

Stringent Aptamer Binding Studies—Confirmed in Animals

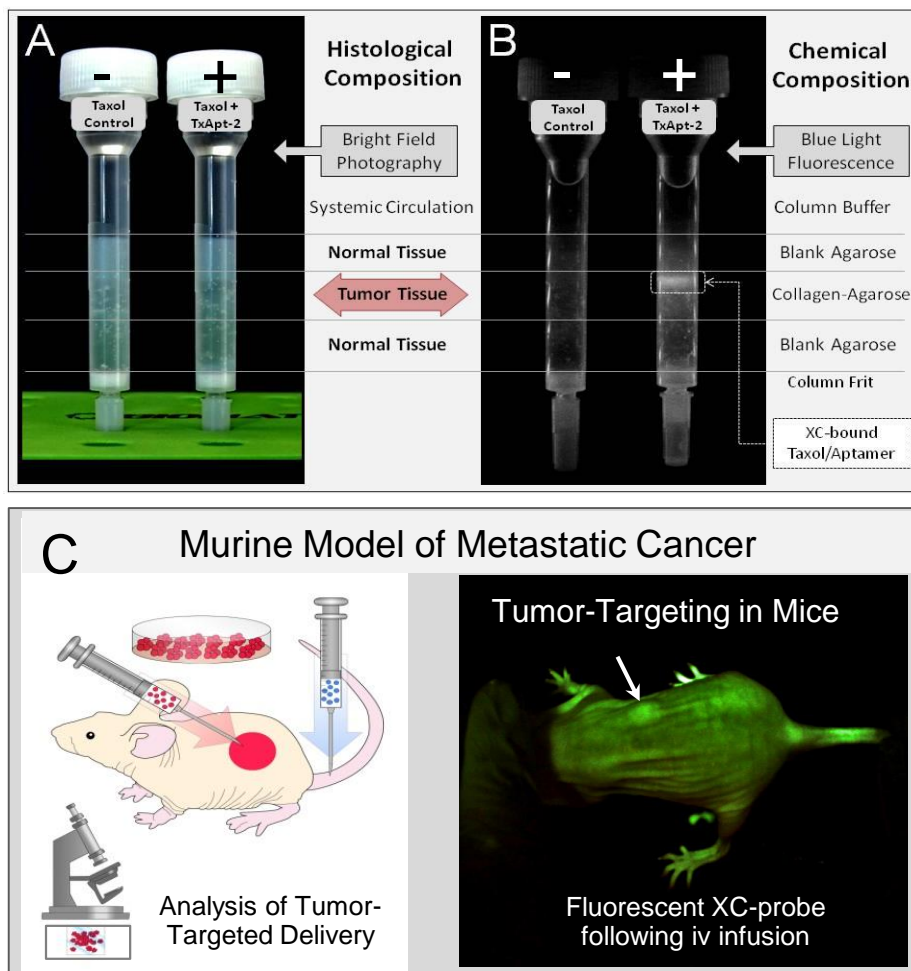


In Vitro Binding / Targeting: Agarose Affinity Chromatography (in layers) Model Tumor Tissues

High-affinity binding of onco-aptamers to the **Fluorescent Cargo** and to **XC-Proteins** is demonstrated in this in vitro simulation of tumor targeting (**A**, bright field), using layers of blank-agarose & collagen-agarose (as a model for tumors). Note: the aptamer-dependent band of intense fluorescence (**B**) shows XC-targeted drug delivery.

Tumor-Targeting in Mice:

The stringent binding studies translate into demonstrations of active tumor-targeting in vivo (**C**).



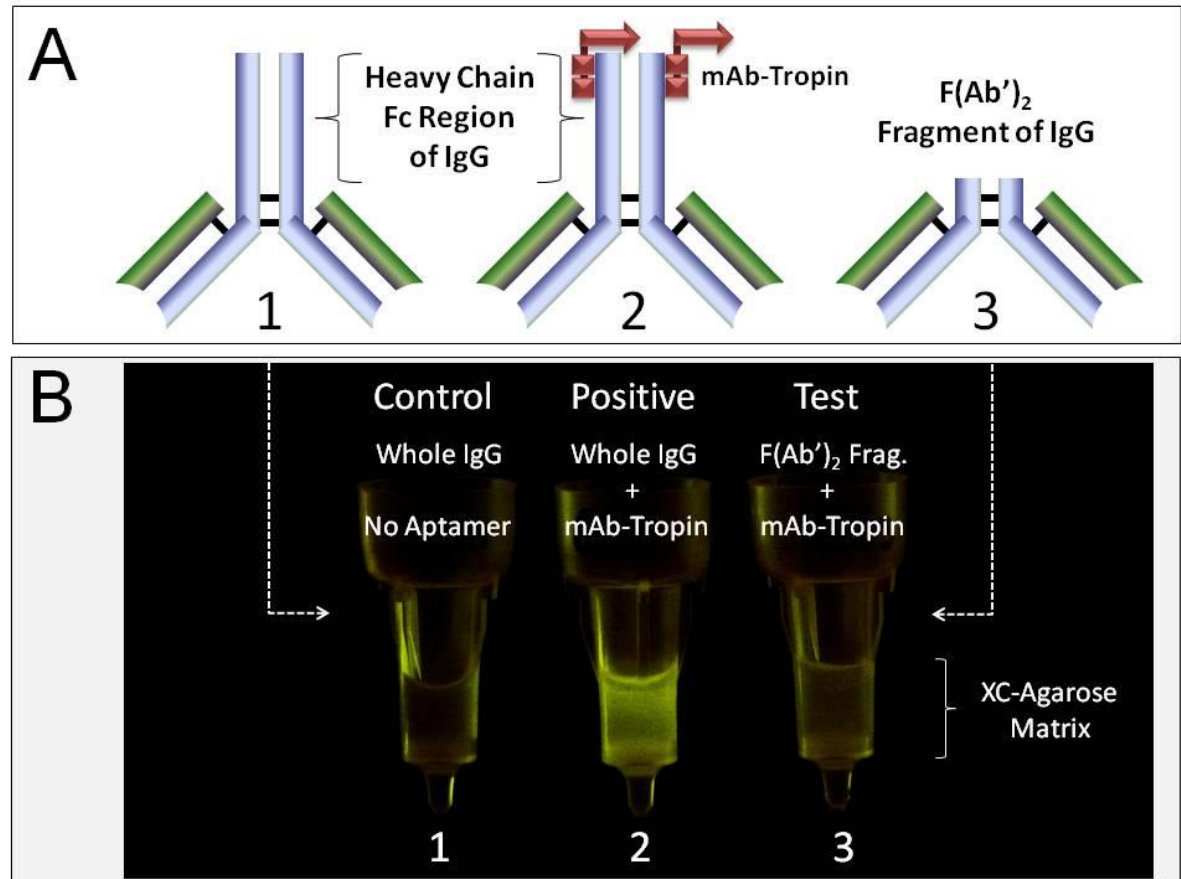
mAb-Tropins Bind the Fc Region of IgGs

Binding of Whole IgGs versus F(Ab')₂ Fragments



XC-Agarose Binding Studies

- **FITC-labeled IgGs vs F(Ab')₂ fragments** confirm the mAb-Tropin binding sites are in the Fc region of the IgG molecule.
- The deduced Fc binding site is far removed from IgG antigen-binding domains & receptor-mediated functions.

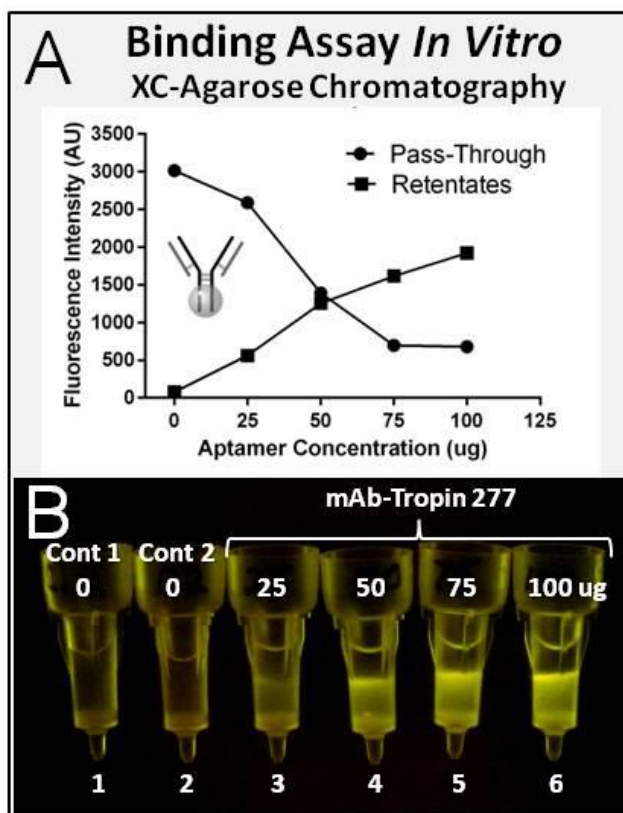


mAb-Tropin²⁷⁷: Proof-of-Concept *In Vivo*

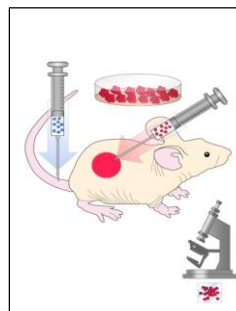
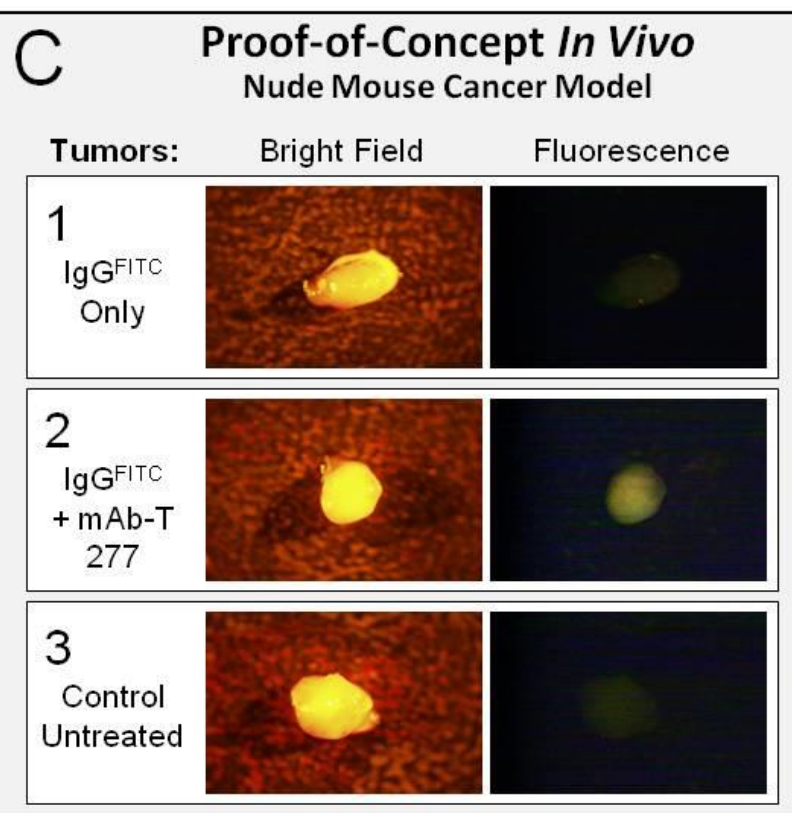
Targeted Delivery of FITC-IgGs to Tumors in Mice



Efficient Binding in Vitro



Active Targeting in Cancer Model



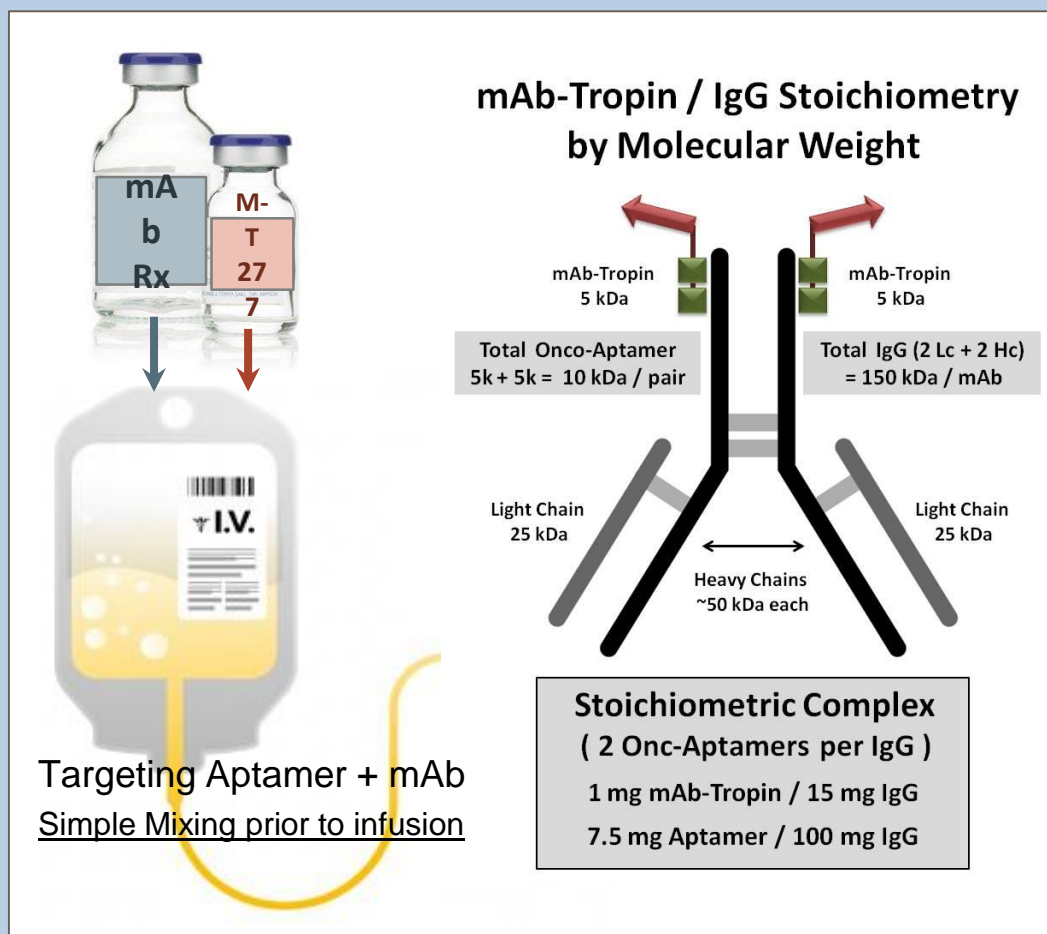
- Passive
Delivery

- Active
Delivery

- Background
Fluorescence

*mAb-Tropin*²⁷⁷: Clinical Development

“Pro-Active” Targeting of Immune Checkpoint Inhibitors



Planned Phase 1/2 Study tumor-targeted immune checkpoint inhibitor(s)

Clinical Indications: Advanced Sarcoma, Melanoma, and NSCLC

Aptamer Dose Escalation: 4
Dose Levels spanning a 1:1 molar ratio of mAb-Tropin to mAb/IgG.

Study Aims: Improved Safety & Efficacy of the lower dose mAb deployed with active targeting. (~1/2 the standard dose of mAb).

Expected Results: Confirmation of mAb-Tropin Safety, followed by Aptamer-dependent Efficacy with increasing Apt/ IgG ratios.

Executive Officers of the Company

Expertise in R&D, Clinical Trials, INDs, and IP Development



**Dr. Sant P. Chawla, M.D., Founder, President & Chief Medical Officer
— Diplomate, American Board of Medical Oncology**

A pioneering physician whose work in sarcoma oncology has brought him accolades and recognition as one of the world's foremost experts of sarcomas & sarcoma therapy, with extensive experience in clinical trials.



Dr. Frederick L. Hall, Ph.D., Founder & Chief Executive Officer

An established leader in the field of cell cycle control, oncogene discovery, and genetic medicine. Founder, Former President, CEO, and CSO of Epeius Biotechnologies Corp., Dr. Hall served for 12 years as a Research Director on the faculty of the USC Schools of Medicine and Pharmacy, where he was a co-inventor of the tumor-targeting technology.



**Dr. Erlinda M. Gordon, M.D., Founder & Chief Operating Officer
— Diplomate, American Board of Pediatric Hematology/Oncology**

Considered to be among the most accomplished physician-scientists in the field of cancer gene therapy. Founder, Former COO, CMO and Chairman of the Board of Epeius Biotechnologies Corp., Dr. Gordon served for 20 years on the faculty of the University of Southern California School of Medicine, and is co-inventor of the tumor-targeting technology.





Thank You

Sant P. Chawla, M.D., FRACP

COUNTERPOINT BIOMEDICA LLC

THE SARCOMA ONCOLOGY CENTER

2811 Wilshire Blvd, Suite 414

Santa Monica, CA 90403

santchawla@sarcomaoncology.com

