# Changing the Way We Treat Cancer with CYT-6091 (Aurimune®): A Model Cancer Nanomedicine

*International Symposium on*
*Assessing the Economic Impact of Nanotechnology*

Washington, D.C.
27 March 2012

# The Opportunity

Problem: For many cancers, response rates of patients treated surgically first, followed by chemotherapy and/or radiation are poor

- Surgery alone does not cure most patients of cancer
- Following surgery, many patients present with metastatic disease

Need: Improve efficacy and safety, and minimize recurrent disease

- Targeting tumors
- Limit exposure of healthy tissues and organs to cytotoxics

Solution: Use nanotechnology-based therapeutics, first

- First treat patients medically to reduce tumors, use surgery only if needed
  - May lead to improved tumor regression, reduced side effects, and reduced recurrent disease

# Benchmarks for a Cancer Nanomedicine

Needs to Avoid Uptake by Mononuclear Phagocyte System (MPS)

- Primarily the liver and spleen

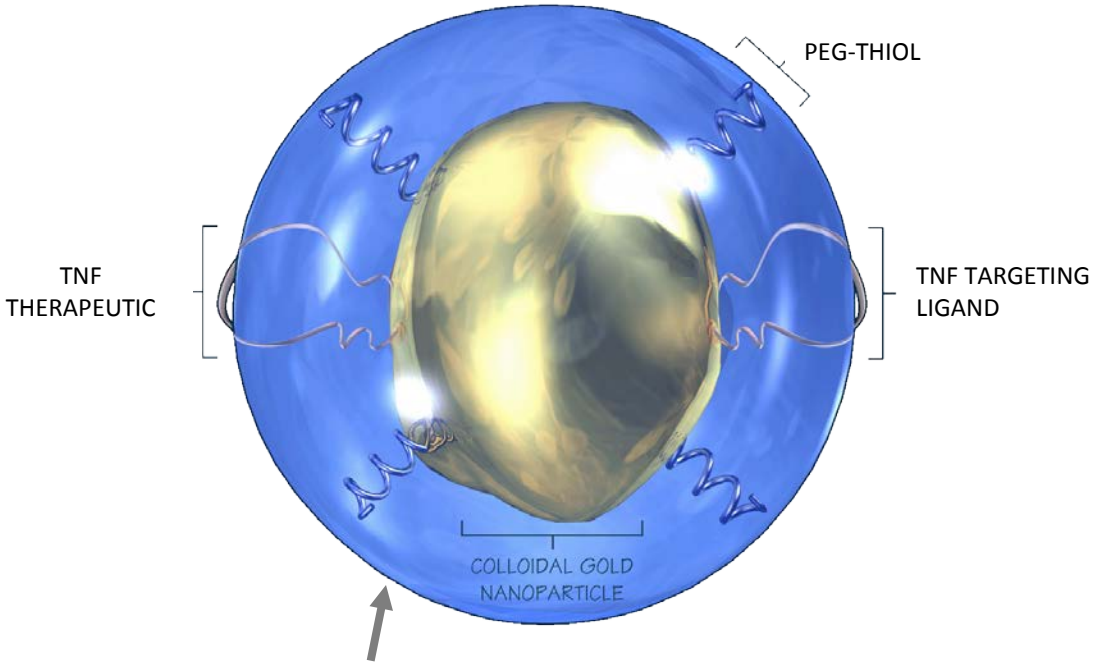
Needs to Target Tumors (Passive and Active)

- Corollary
  - Less severity/frequency of side-effects compared to unformulated API

Needs to Be Manufactured to Defined Specifications

- Robust
- Reproducible
- Cost Effective

# Design of CYT-6091 (Aurimune®):




Water absorbed by PEG-Thiol shields nanoparticle from immune detection



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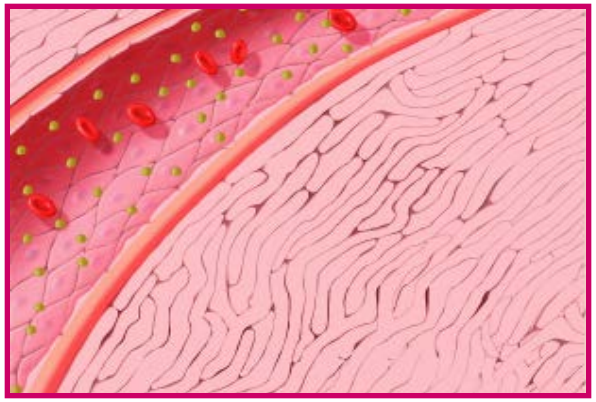
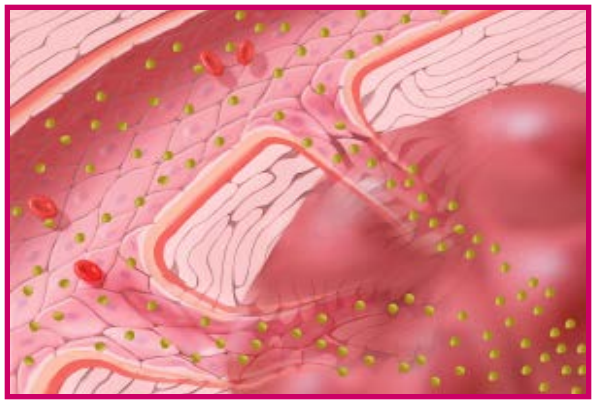
# Safe, Targeted Delivery: Size Matters



Too Large for Toxic Side Effects. CYT-6091 is small enough to safely travel through healthy blood vessels, but too large to pass through blood vessel walls into healthy tissues and organs, resulting in reduced toxicity.



Small Enough to Exit Tumor Vessels. All solid tumors are fueled by new, "leaky" blood vessels that have gaps in their walls. When CYT-6091 reaches these "leaky" vessels, the nanoparticles are small enough to pass through these walls into their target, the tumor.

**Due to its engineered nanometer size and targeted capabilities, CYT-6091 is able to reduce toxicity and increase efficacy.**

# CYT-6091: Avoids Immune Recognition and Uptake

PEG bound to gold nanoparticles prevents uptake by the liver and spleen, major organs of the MPS, (black color is aggregated gold particles)

- Uncoated nanoparticles may be safe, but do not reach tumor target

Untreated

cAu-TNF

CYT-6091

cAu-TNF

PEG-THIOL Bound to cAu-TNF



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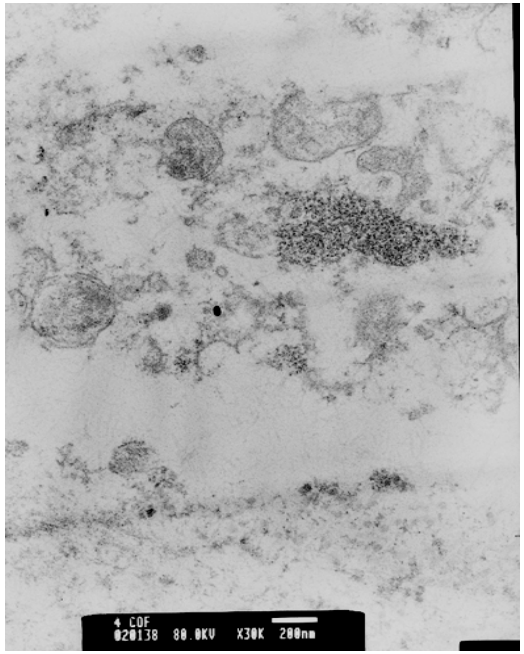
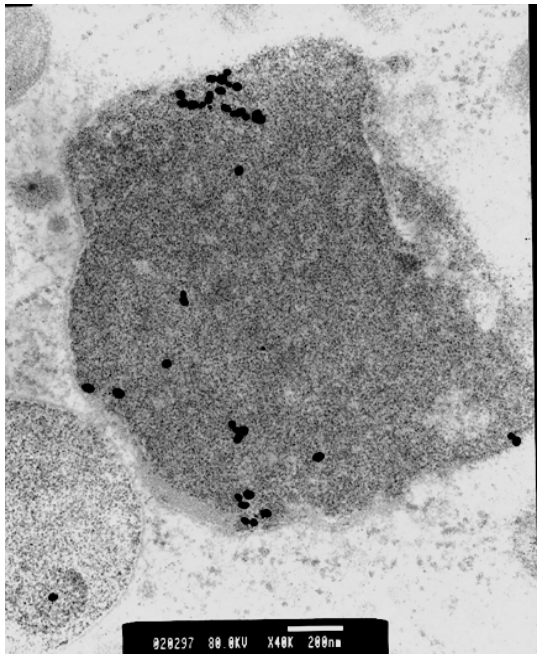
# Differential Uptake of CYT-6091 in Mouse Model

Electron micrographs comparing tumor and healthy tissue

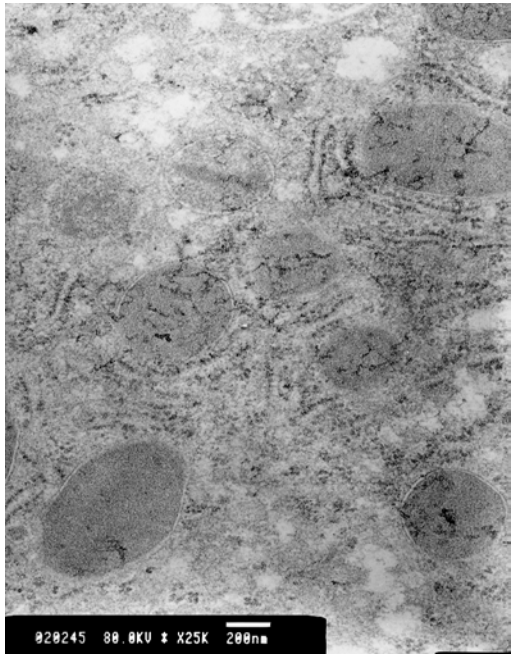
Spleen




Tumor




Liver




Bar at bottom = 200 nm



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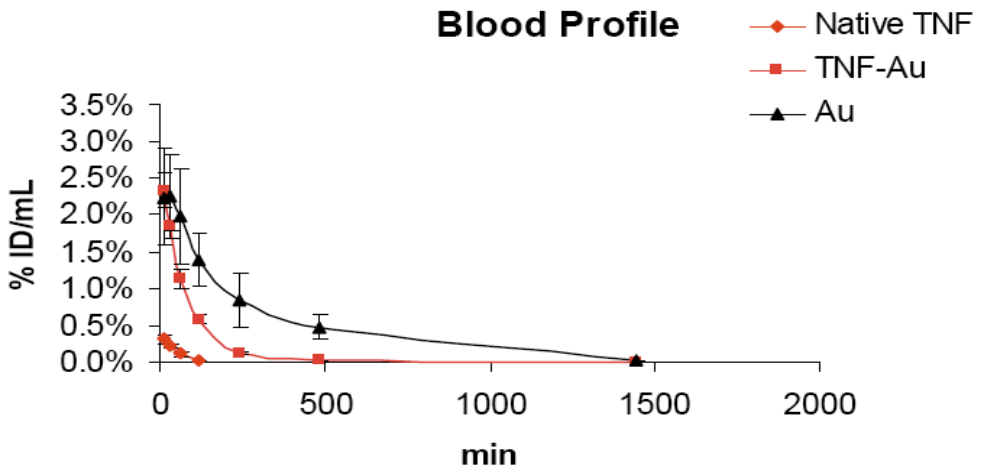
# Pharmacokinetic Modeling of CYT-6091 in the Rat*




| PK Parameter | Native TNF | CYT-6091 | |
|---|---|---|---|
| | | TNF | Gold |
| $V_d$ (mL) | 326 | 36 | 47 |
| Clearance (mL/min) | 5.08 | 0.43 | 0.14 |
| Elimination Rate | 0.027 | 0.004 | 0.003 |
| Terminal Half Life (min) | 26 | 182 | 217 |

*Study Conducted by the Nanotechnology Characterization Laboratory (NCL), NCI



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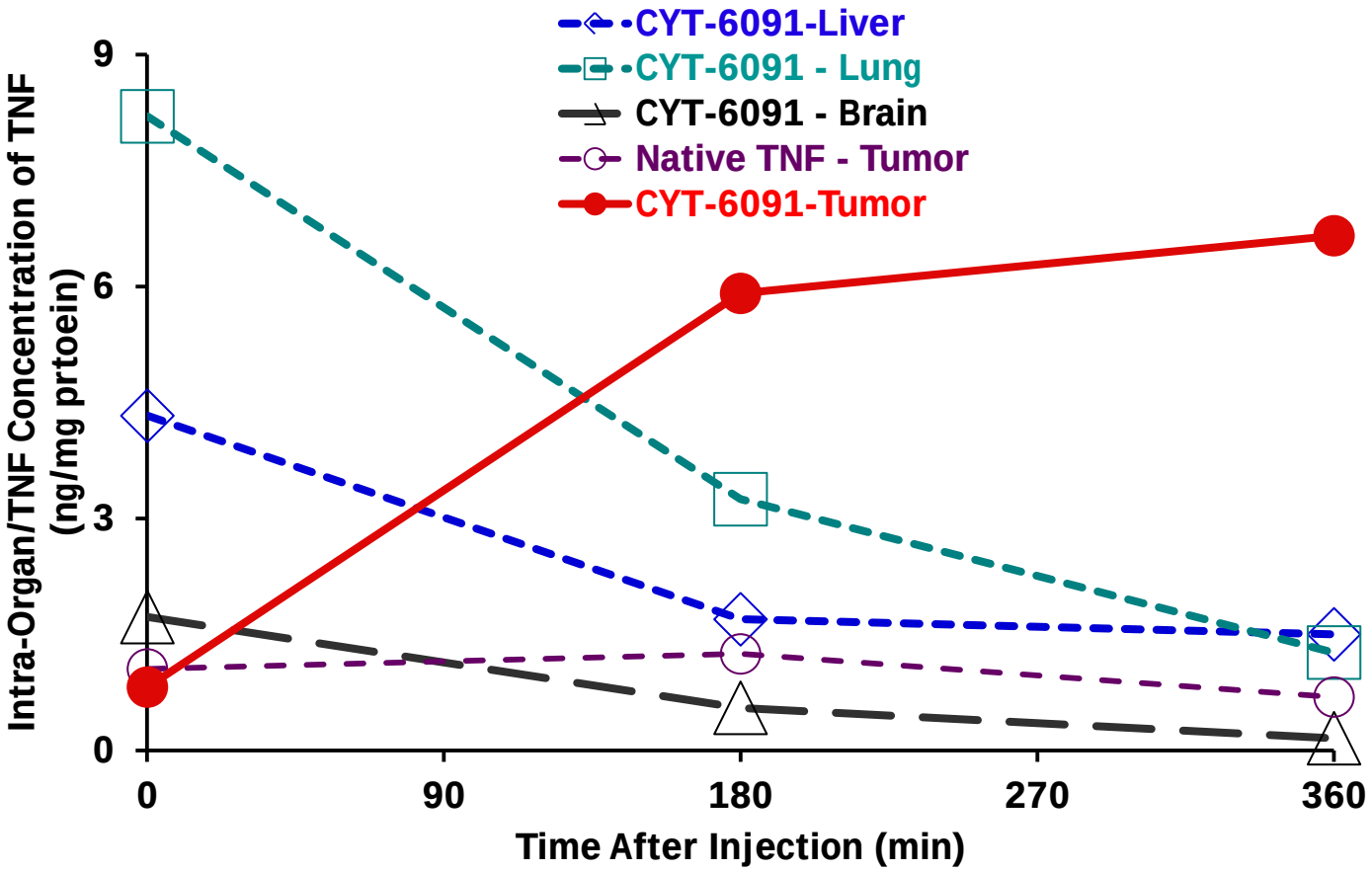
# Biodistribution of TNF Following CYT-6091 Rx

Tumor concentrations of TNF increase after dosing of mice with CYT-6091

- TNF levels in all major organs, including liver, decrease over same time period



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# CYT-6091's Active Agent: Tumor Necrosis Factor (TNF)

Previous systemic clinical testing with TNF shows

- No clinical effect at maximum tolerated dose of 0.4 mg
- At 1 mg patients experience severe hypotension, leading to complete organ failure and possibly death
- Not approved by FDA or EMA (European agency)

Isolated Limb Perfusion (ILP) procedure (EMA approved)

- Temporary surgical isolation of tumor-burdened limb -- maintain limb viability with heart-lung machine
- 1 mg TNF administered followed 30 minutes later by chemotherapy results in complete response rates = 85%

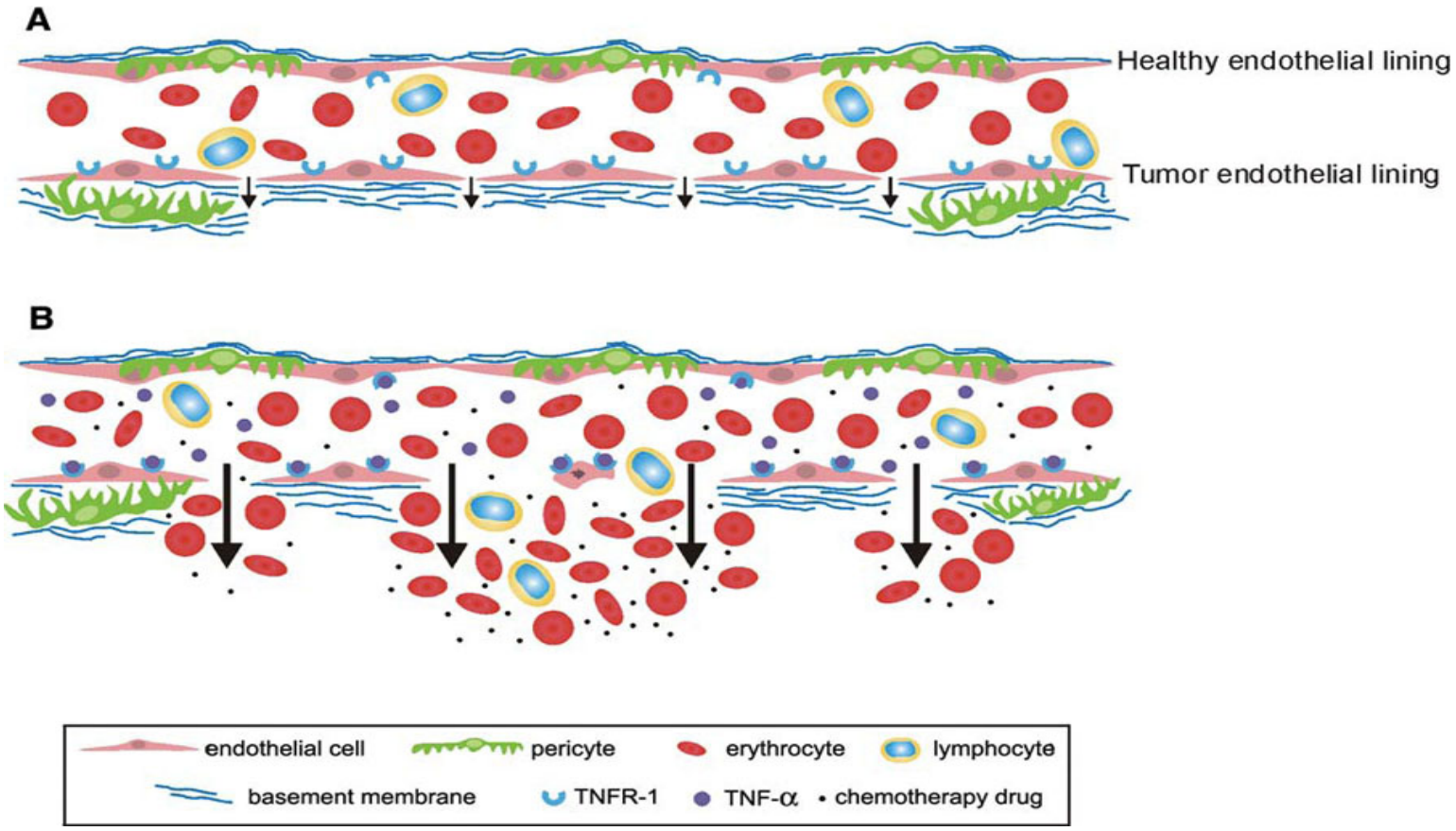
CYT-6091 systemic clinical testing

- Succeeded in rescuing TNF therapeutic potential with CytImmune platform
- CYT-6091's targeting capability has potential to significantly improve typical chemotherapy response rates

# Effect of Systemically Administered CYT-6091 on Tumor Vasculature

By delivering TNF to the tumor vasculature CYT-6091 causes vascular breakdown

- Massive vascular leak destroys high intra-tumor pressure




From: R. van Horssen el al, The Oncologist 2006;11:397-408



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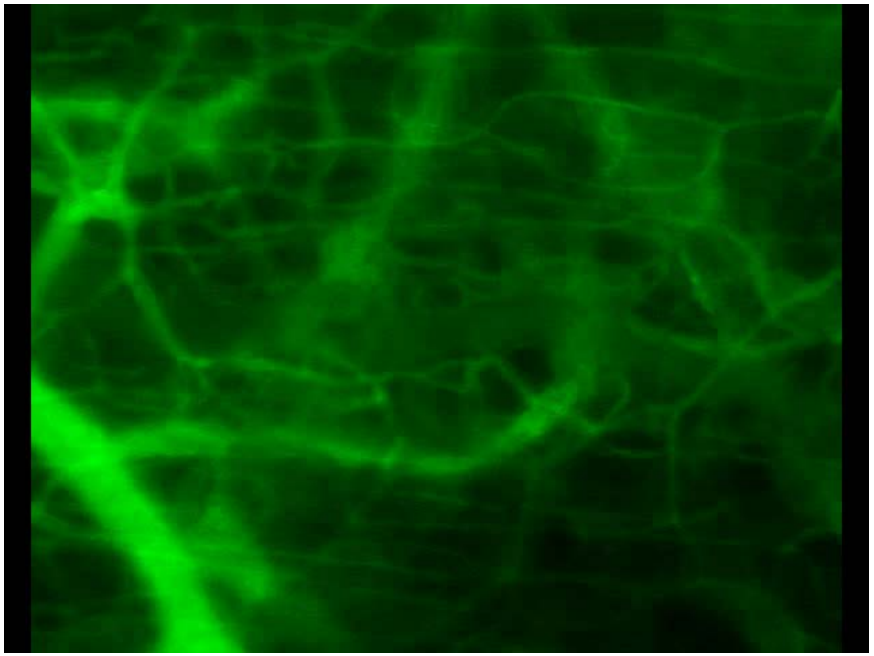
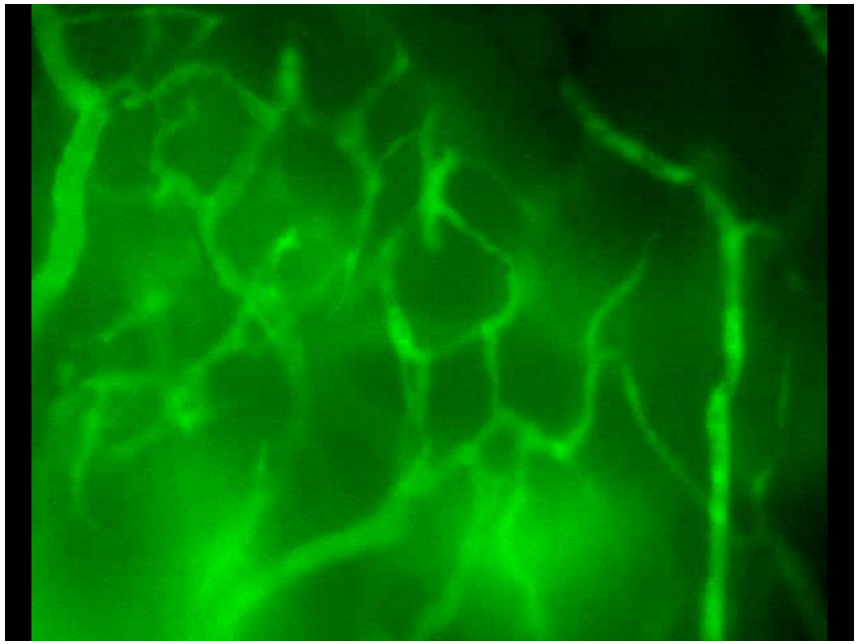
# Selective Induction of Vascular Leak by CYT-6091



Normal Vasculature
No Vascular Leak



Tumor Neovasculature
Vascular Leak

# Killing Tumors: CYT-6091 Pre-Clinical Mouse Data

Stealthy. PEG-Thiol bound to colloidal gold nanoparticles avoids immune detection by the MPS

Targeted. CYT-6091 delivers TNF to solid tumors:

- *Passively* by extravasating from the tumor vasculature
- *Actively* by binding to TNF receptors on tumor endothelial cells

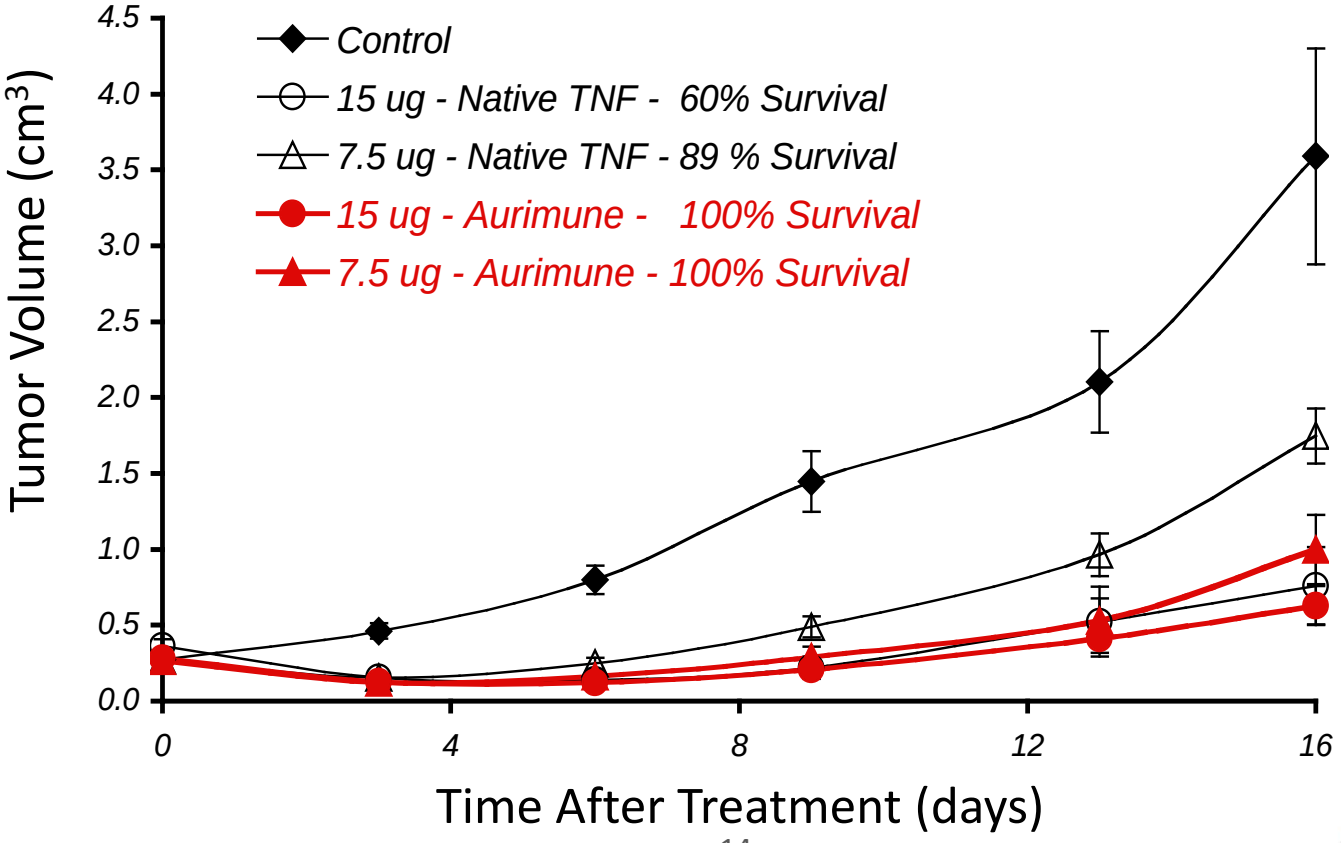
Accumulation. CYT-6091 accumulates TNF in TNF sensitive and insensitive tumors

- For TNF sensitive tumors:
  - One treatment induces potent anti-tumor responses at lower doses
- For TNF insensitive tumors:
  - One treatment induces transient anti-tumor response
  - Multiple doses causes cytostasis
  - Combination with doxorubicin is additive

# Effect of CYT-6091 and TNF on Tumor Growth

Single treatment of C57BL/6 mice with TNF-sensitive MC-38 tumors

- High dose TNF effective, but causes 40% mortality
- High dose CYT-6091 equally effective with no mortalities
- Low dose CYT-6091 just as effective as high dose, shows potential of tumor targeting



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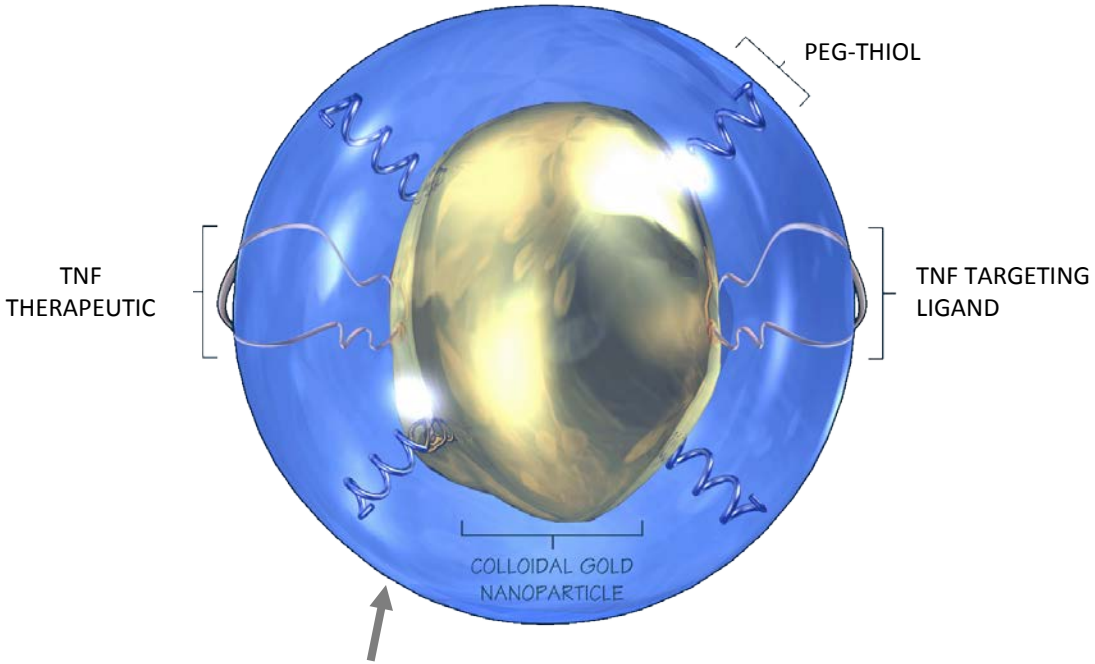
# CYT-6091 Clinical Trial in Cancer Patients




Water absorbed by PEG-Thiol shields nanoparticle from immune detection



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# Clinical Grade CYT-6091

Current production capacity scaled 10-fold from Phase I to Phase II

- Solved manufacturing challenge for a nanomedicine
- Process is robust, reproducible and cost effective
- 3-year shelf life as a freeze-dried product




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# Goal of CYT-6091 (Aurimune) Clinical Trial

Safely administer 1 mg of TNF formulated as CYT-6091 to cancer patients without inducing hypotension

# CYT-6091 Phase I Trial: Clinical Observations

Safe, systemic delivery. Delivered 1.2 mg of TNF with no dose limiting toxicity

- No Hypotension, the dose-limiting toxicity associated with TNF use in man
- No Serious Adverse Events that were unexpected and related to treatment

Tumor targeted. Drug accumulation at tumor sites

- Gold particles seen in tumors but few if any in healthy tissues

Not Antigenic. No antibody response

- Titer checks after CYT-6091 treatments show no anti-TNF antibodies

# CYT-6091 Phase I Patient Population

| Patient ID and Dose | Histology |
|---|---|
| 01 (50 µg/m2) | Cutaneous Melanoma |
| 02 (50 µg/m2) | Colon Adenocarcinoma |
| 03 (50 µg/m2) | Ocular Melanoma |
| 04 (100 µg/m2) | Colon Adenocarcinoma |
| 05 (100 µg/m2) | Colon Adenocarcinoma |
| 06 (100 µg/m2) | Ocular Melanoma |
| 07 (150 µg/m2) | Lung Adenocarcinoma |
| 08 (150 µg/m2) | Pancreatic Adenocarcinoma |
| 09 (150 µg/m2) | Pancreatic Adenocarcinoma |
| 10 (200 µg/m2) | Invasive Ductal Carcinoma |
| 11 (200 µg/m2) | Leiomyosarcoma |
| 12 (200 µg/m2) | Ocular Melanoma |
| 13 (250 µg/m2) | Ocular Melanoma |
| 14 | Pancreatic Adenocarcinoma |
| 15 (250 µg/m2) | Pancreatic Adenocarcinoma |

| Patient ID and Dose | Histology |
|---|---|
| 16 (250 µg/m2) | Ocular Melanoma |
| 17 (300 µg/m2) | Colon Adenocarcinoma |
| 18 (300 µg/m2) | Ocular Melanoma |
| 19 (300 µg/m2) | Ocular Melanoma |
| 20 (300 µg/m2) | Ocular Melanoma |
| 21 (400 µg/m2) | Desmoplastic Small Round Cell |
| 22 (400 µg/m2) | Rectal Adenocarcinoma |
| 23 (400 µg/m2) | Colorectal Adenocarcinoma |
| 24 (500 µg/m2) | Ocular Melanoma |
| 25 (500 µg/m2) | Invasive Ductal Carcinoma |
| 26 (500 µg/m2) | Colorectal Adenocarcinoma |
| 27 (600 µg/m2) | Desmoplastic Small Round Cell |
| 28 (600 µg/m2) | Colorectal Adenocarcinoma |
| 29 (600 µg/m2) | Colorectal Adenocarcinoma |
| 30 (600 µg/m2) | Adrenocortical carcinoma |



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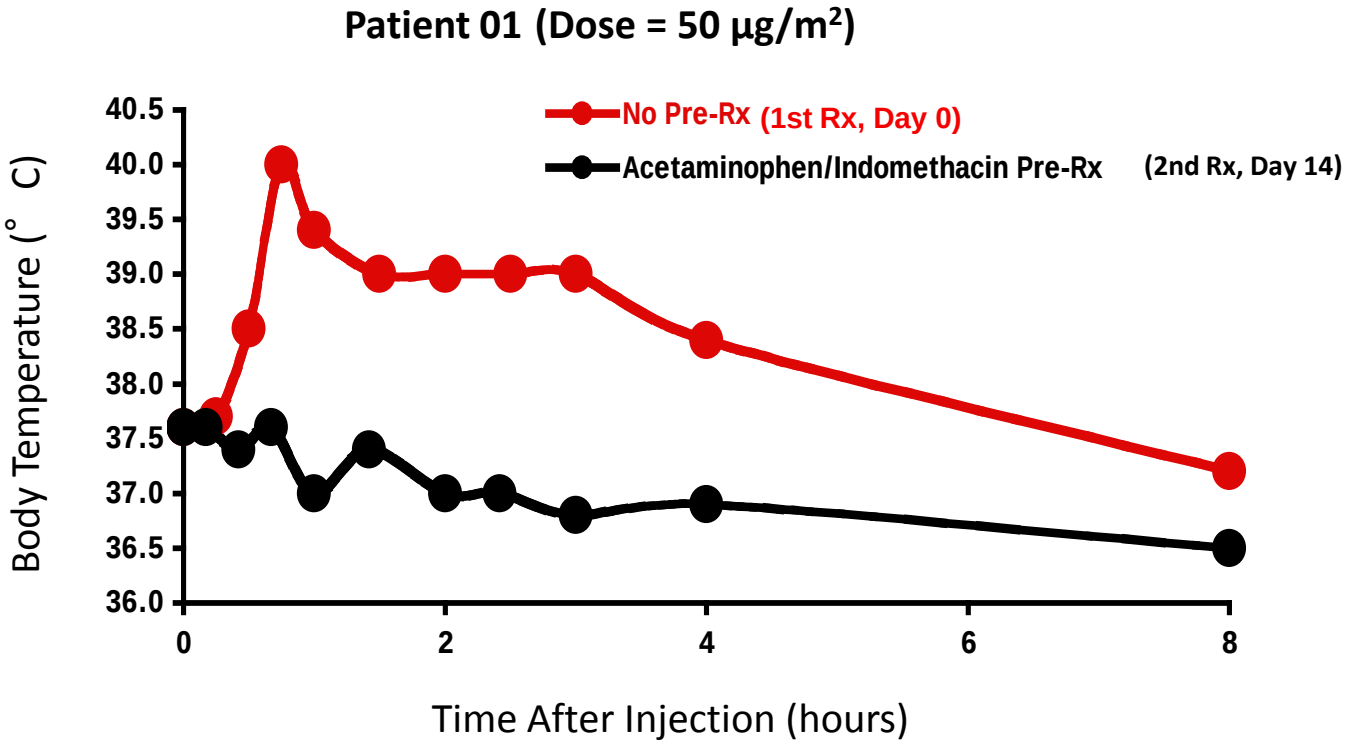
# Effect of Pre-Treatment on CYT-6091 Induced Fever




Acetaminophen/indomethacin/benadryl pretreatment used for all subsequent patient dosings



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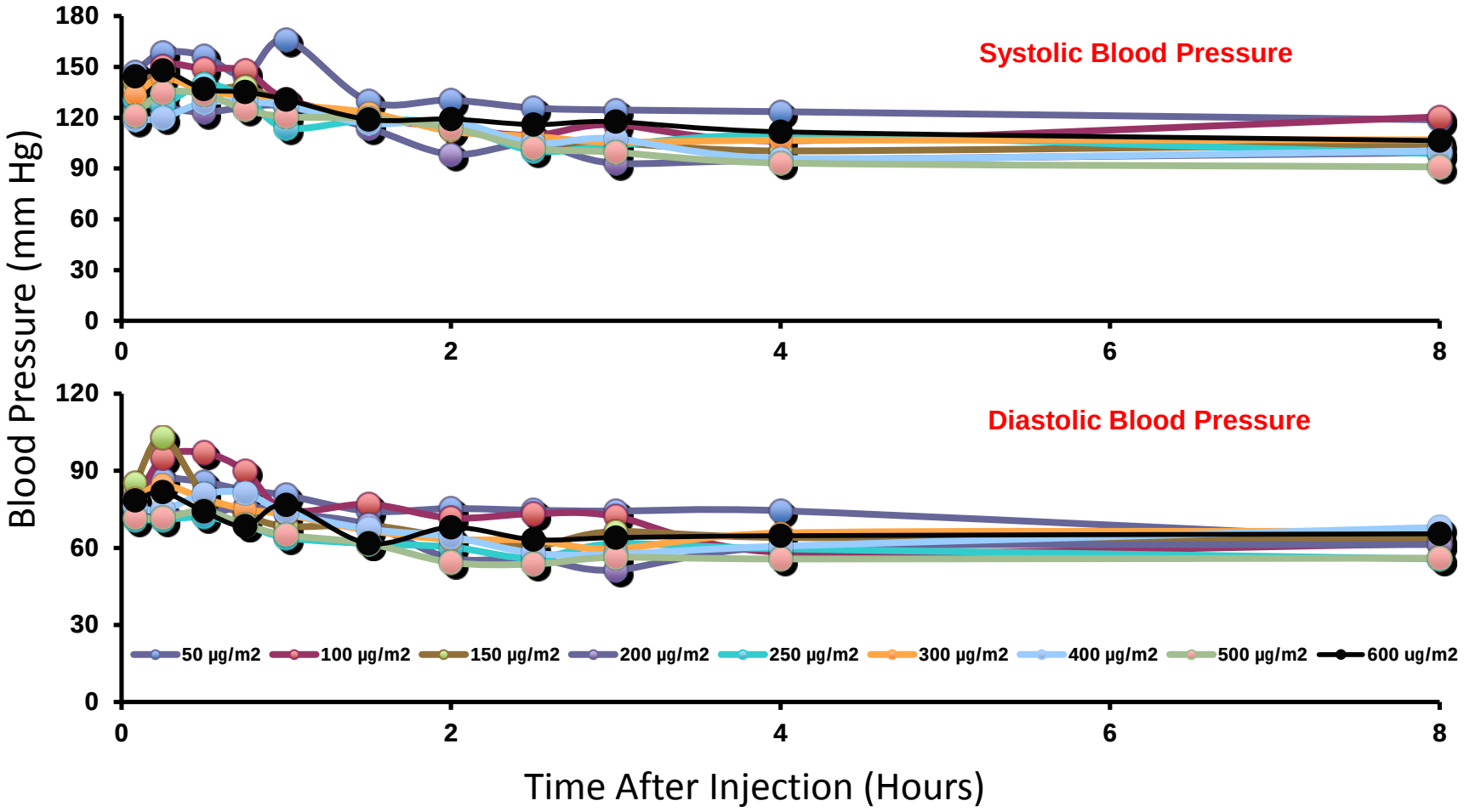
# Effect of CYT-6091 on Blood Pressure



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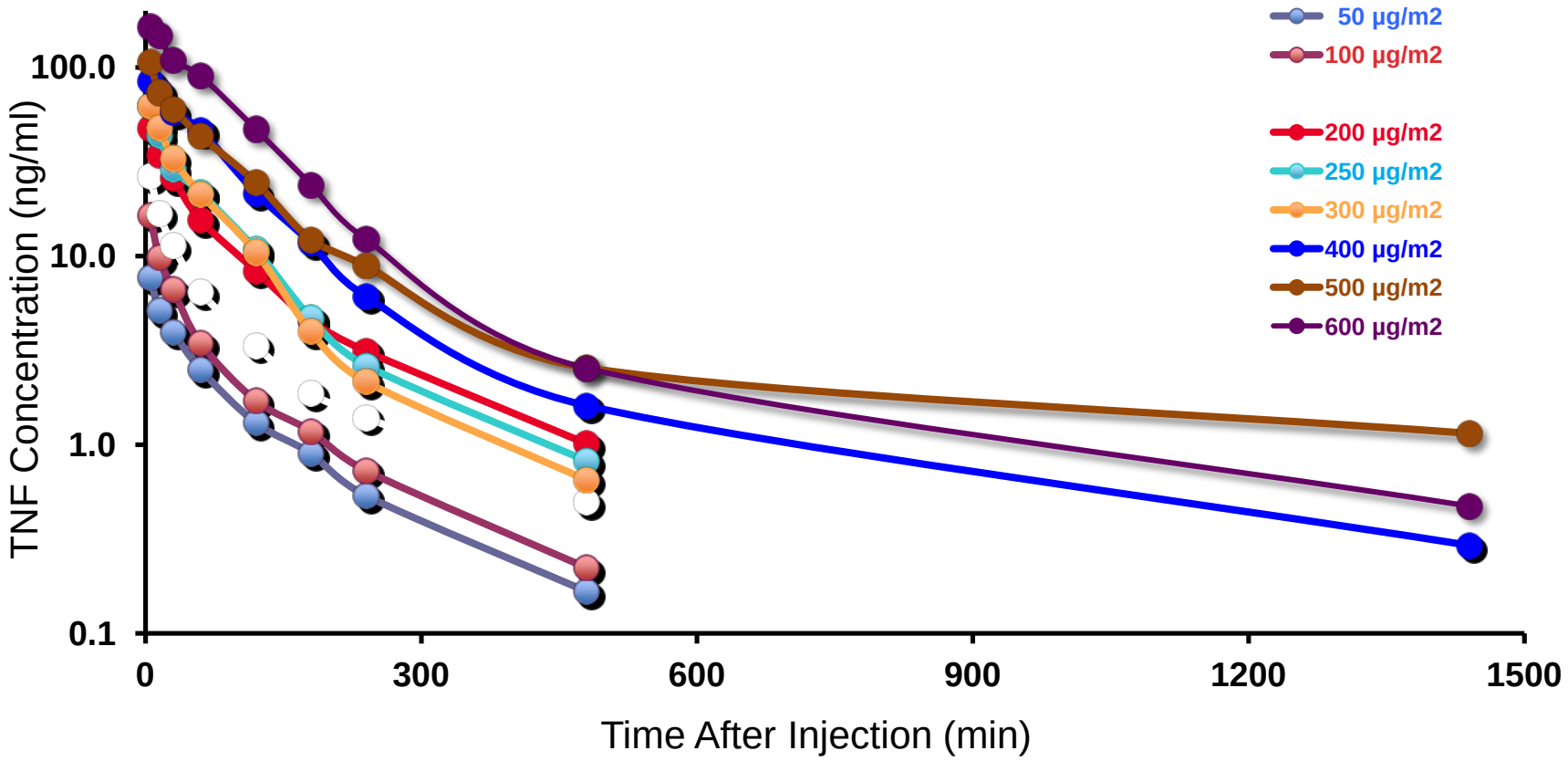
# Pharmacokinetics of CYT-6091 in Humans



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# Clinical Studies: Systemic TNF Vs. CYT-6091

Analysis of CYT-6091 Pharmacokinetic Data:
Comparison with the Historical Data on the Pharmacokinetics of rhTNF in Man
* Source: Gamm, et al., 1991. Eur. J. Cancer. 27: 856-863.
** Source: HR Alexander in *Biologic Therapy of Cancer*: Chapter 13 Page 331 Copyright 1995

| | Gamm et. al.* | | Alexander et. al.** | | CYT-6091 | |
|---|---|---|---|---|---|---|
| Dose Range (µg/m2) | $T_{1/2}$ (min) | AUC (ng-min/ml) | $T_{1/2}$ (min) | AUC (ng-min/ml) | $T_{1/2}$ (min) | AUC (ng-min/ml) |
| 150-170 | 27 | 542 | 27-32 | 543 | 173 | 1540 |
| 200 | -- | -- | 54-71 | Not Reported | 146 | 3434 |
| 250 | -- | -- | -- | -- | 112 | 3640 |
| 300 | -- | -- | -- | -- | 113 | 4461 |
| 400 | -- | -- | -- | -- | 265 | 9149 |
| 500-545 | -- | -- | 42 | 4571 | 371 | 10981 |
| 600 | -- | -- | -- | -- | 160 | 17501 |

-- = Not Tested



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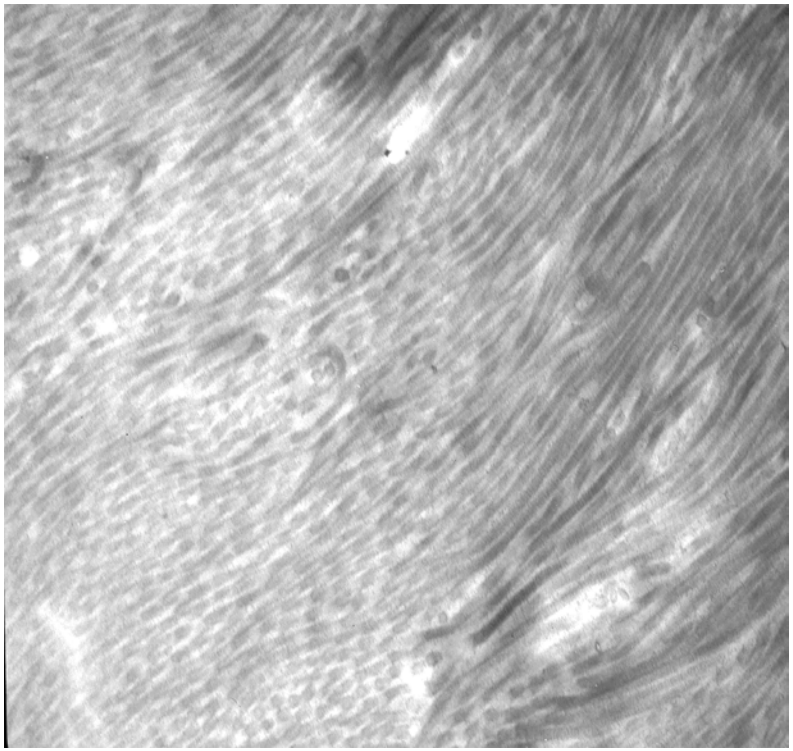
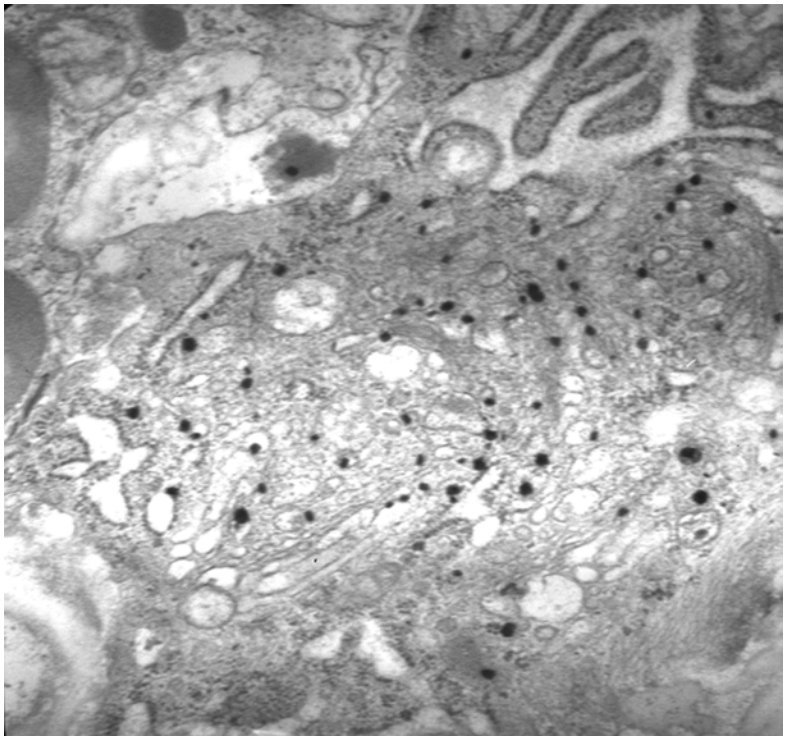
# Electron Micrographs* of a Patient's Biopsies

Patient diagnosed with inoperable breast cancer

- Patient had no prior treatment; samples taken 24h after treatment
- Drug accumulated in tumor, not in healthy breast tissue



**Healthy Breast**



**Tumor**

*Magnification = 20,000x



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# Strategy for Phase II Clinical Trial Design

Isolated Limb Perfusion (ILP) of TNF + chemotherapy is 85% effective

- Phase II protocol mimics ILP combination protocol

CYT-6091 Phase I Success + ILP Efficacy → Dramatic improvement in Overall Response Rates

# Potential CYT-6091 Phase II Clinical Trial Sites

| Cancer Indication | Chemotherapy | Principal Investigator |
|---|---|---|
| Non-small cell lung cancer/Ovarian | Taxotere® | Steven K. Libutti, M.D., FACS<br>Director, Montefiore-Einstein Center for Cancer Care<br>Montefiore Medical Center/Albert Einstein College of Medicine<br>Bronx, NY 10467 |
| Pancreatic | Gemcitabine | Professor John P Neoptolemos, FMedSci<br>Head of School of Cancer Studies<br>Head Division of Surgery and Oncology<br>The Duncan Building, The University of Liverpool<br>Liverpool L69 3GA, UK |
| Melanoma | DTIC | Prof. Alexander M.M. Eggermont, MD, PhD<br>Head Surgical Oncology<br>Erasmus MC - Daniel den Hoed Cancer Center<br>The Netherlands |
| Soft Tissue Sarcoma/Breast | Doxil® | Prof. Alberto A. Gabizon, M.D., Ph.D.<br>Head, Oncology Institute, Shaare Zedek MC<br>Hebrew University - School of Medicine,<br>Jerusalem, ISRAEL |

# The Promise of Cancer Nanomedicines

Deliver potent anti-cancer agents directly to the site of disease

- Reduced or no toxicity
- Improved efficacy

Treat cancer as a medical disease first

- Dose intravenously prior to surgery
- Limited biodistribution due to leaky tumor blood vessels
- Reduce tumor burden by tumor-targeted nanomedicines
- Reduce or eliminate sophisticated surgical procedures
- Improve patient outcome

Treat cancer as a chronic medical disease

- Treat periodically to destroy nascent tumor neovasculature
- Suppress metastatic disease

# CYT-6091: An Ideal Cancer Nanomedicine

Designed to meet critical requirements for tumor targeted therapy

- Not picked-up by liver and spleen
- Targets tumor endothelial cells
- Manufacturing process robust, reproducible and cost-effective

Avoids MPS Uptake

Targets Tumors

Manufactured to Defined Specifications



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