Nanotechnology in Cancer Diagnosis and Therapy

Steven. A. Curley, M.D., F.A.C.S.

The University of Texas
M.D. Anderson Cancer Center
and Rice University

THE UNIVERSITY OF TEXAS
MD ANDERSON
CANCER CENTER
Making Cancer History™

MACRO

PERSON (~6ft tall)
2 billion nm

APPLE (~8cm)
80 million nm

ANT (~5mm)
5 million nm

100,000 nm (.1 mm)

MICRO

diameter of
a HUMAN
HAIR
75,000 nm

smallest the
EYE CAN SEE
10,000 nm

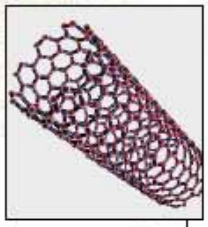
e. coli
BACTERIA
2,000 nm

100 nm (.001 mm)

NANO

BUCKYBALL
1 nm

DNA
2 nm

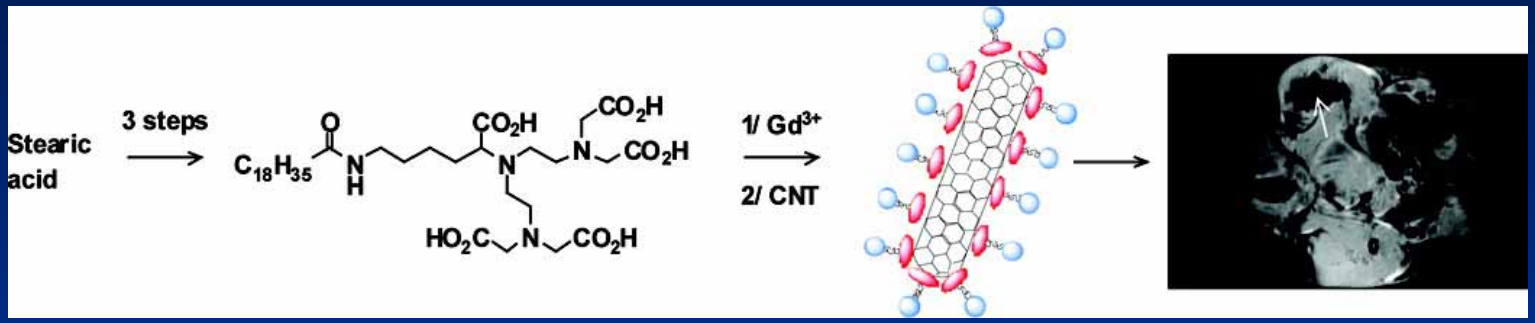


diameter of a
CARBON
NANOTUBE
1.3 nm

Nanotechnology Cancer Research

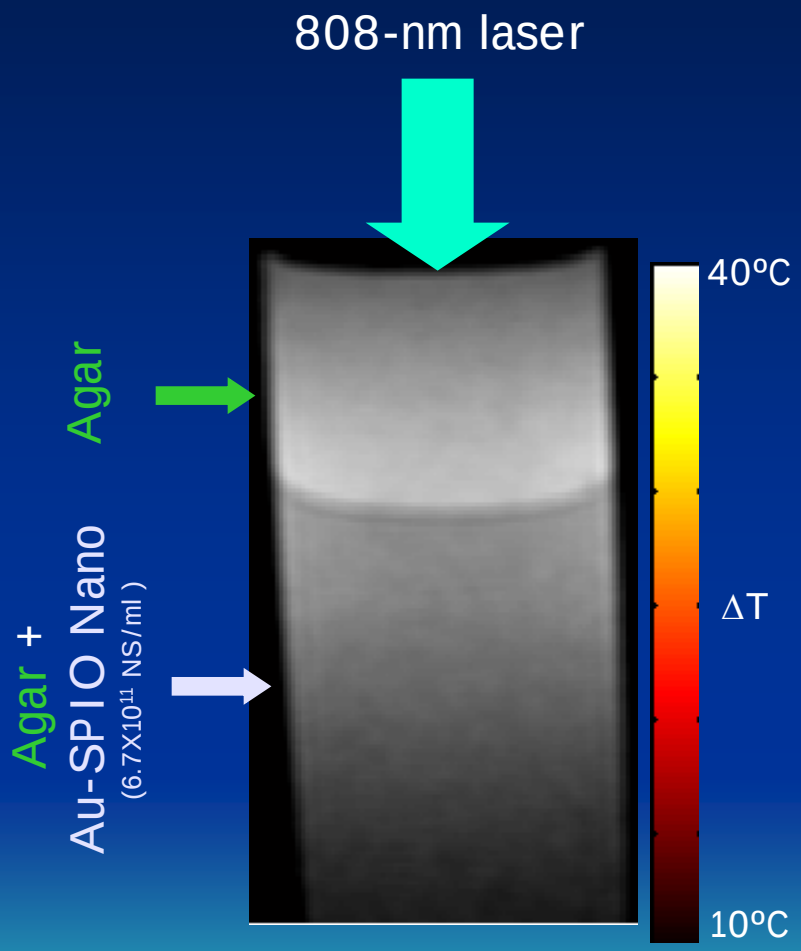
- Improved cancer diagnosis
  - Imaging
  - Blood and tumor-specific tests
- Tissue engineering
- Drug and biologic agent delivery
- Nanoparticles as therapeutic agents

Cancer Diagnosis

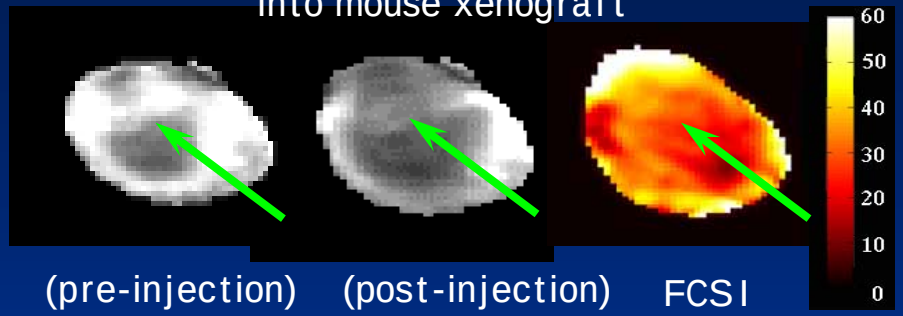


Carbon nanotubes with Gadolinium

Gold-SPIO nanoshells for MR visibility



Direct injection of 1cc Au-SPIO into mouse xenograft

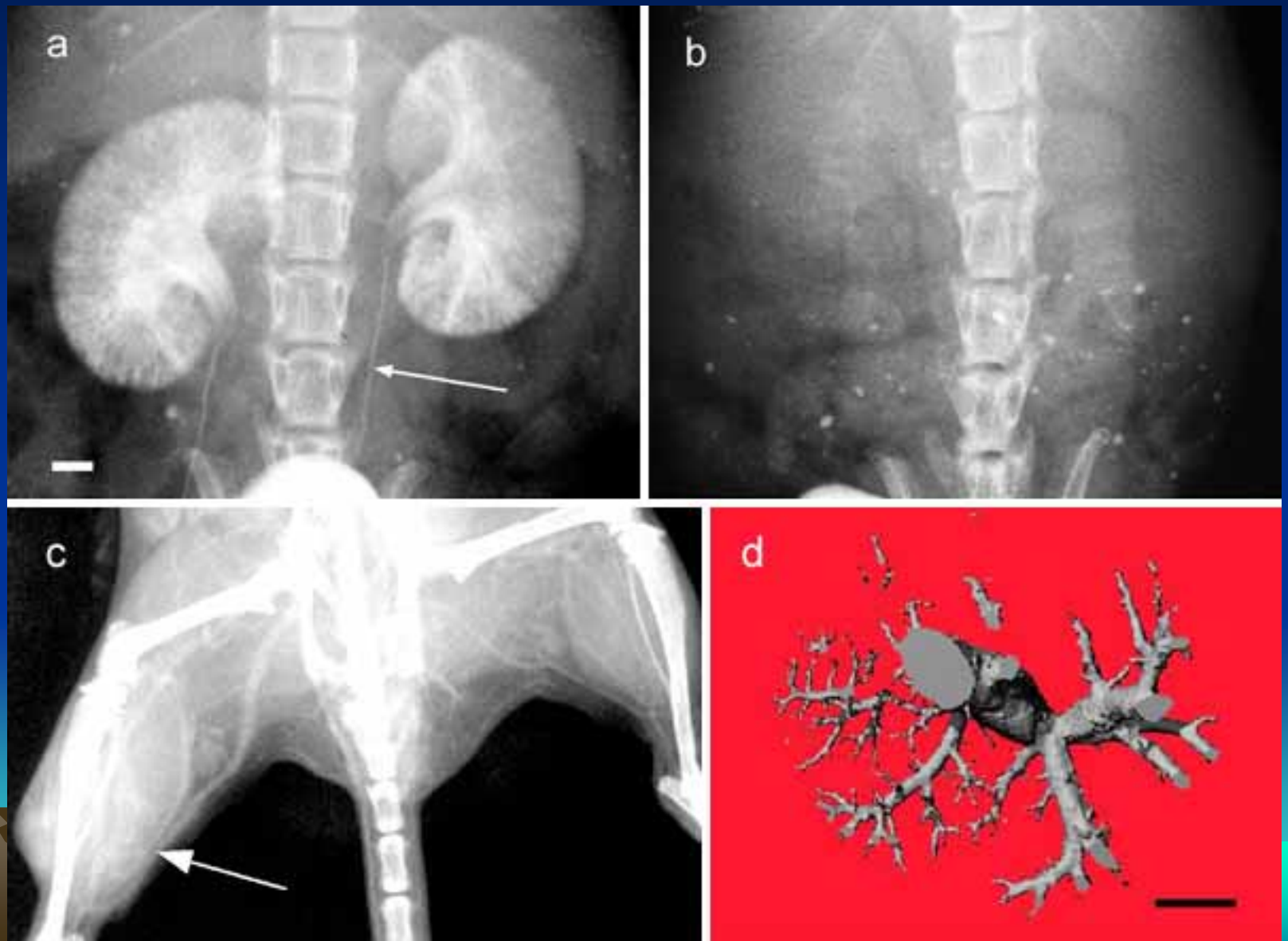


(pre-injection) (post-injection) FCSI MRTI

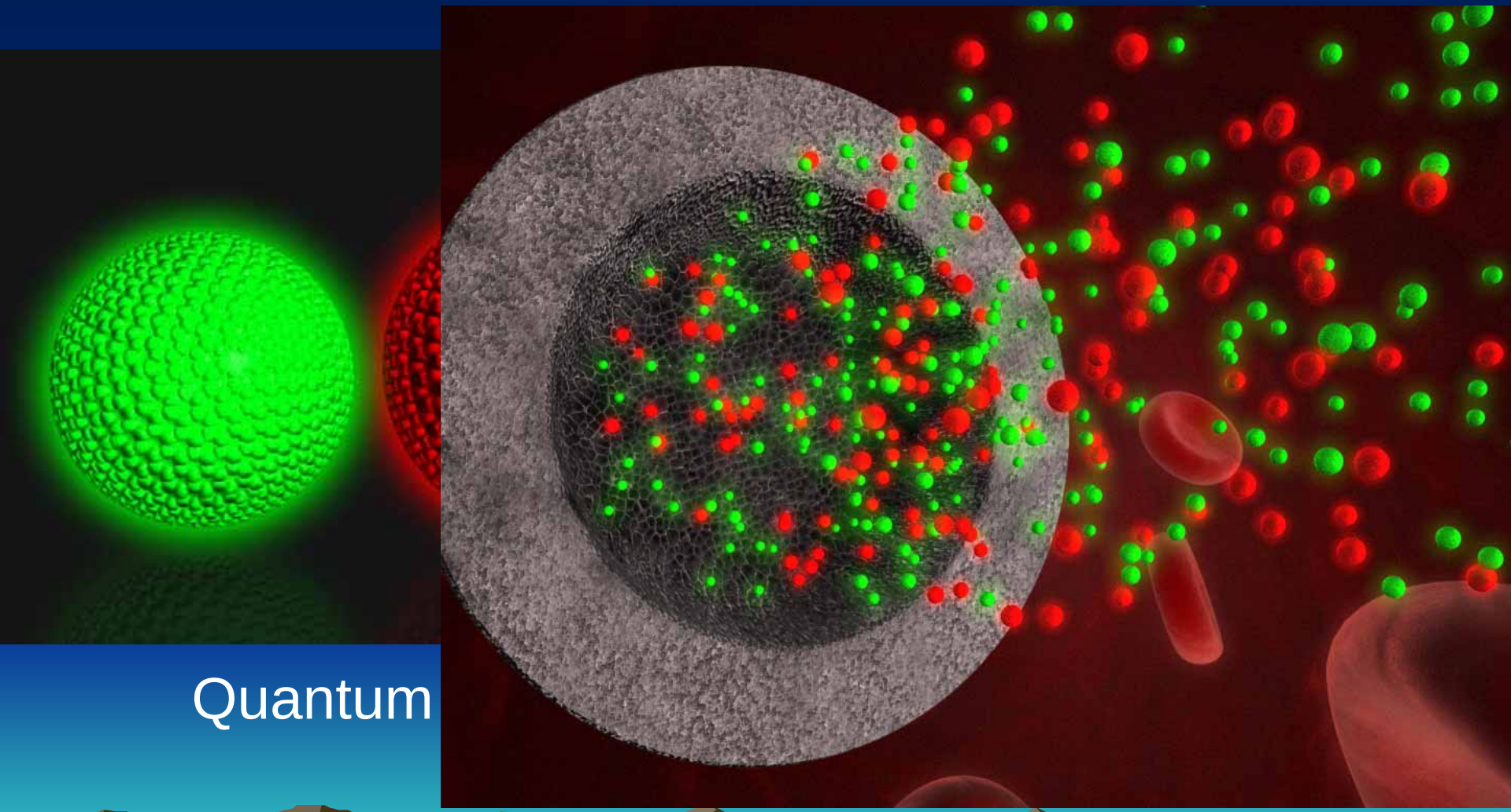
FCSI T2* (ΔT2* = 11.7 ± 3.0 ms)

FCSI can potentially be used to more effectively guide emerging therapies, such as light activated nanoshells. Here, in addition to temperature monitoring, the T2* can be related to concentration of nanoparticles and used for treatment planning.

Cancer Diagnosis

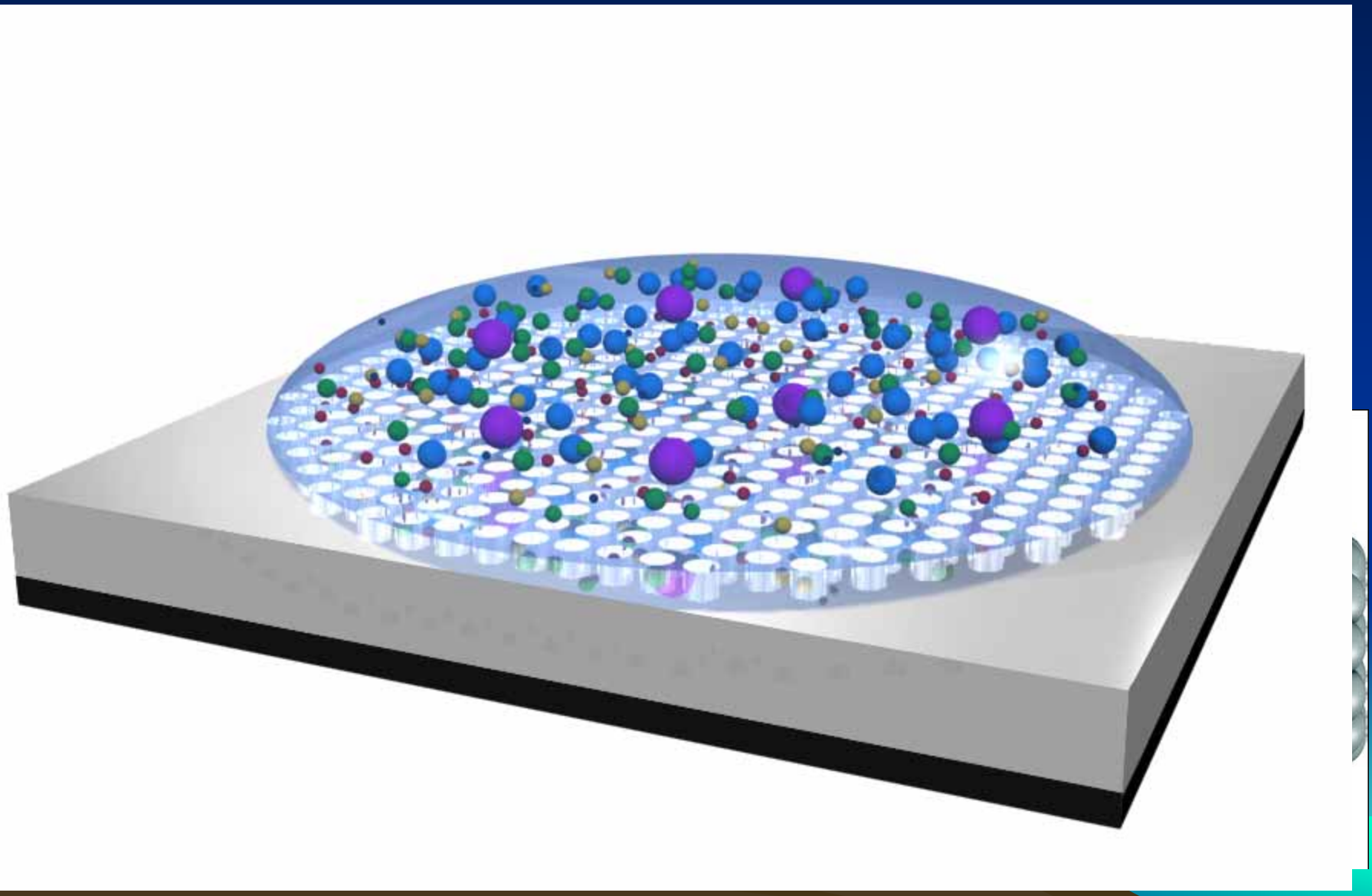


Cancer Diagnosis

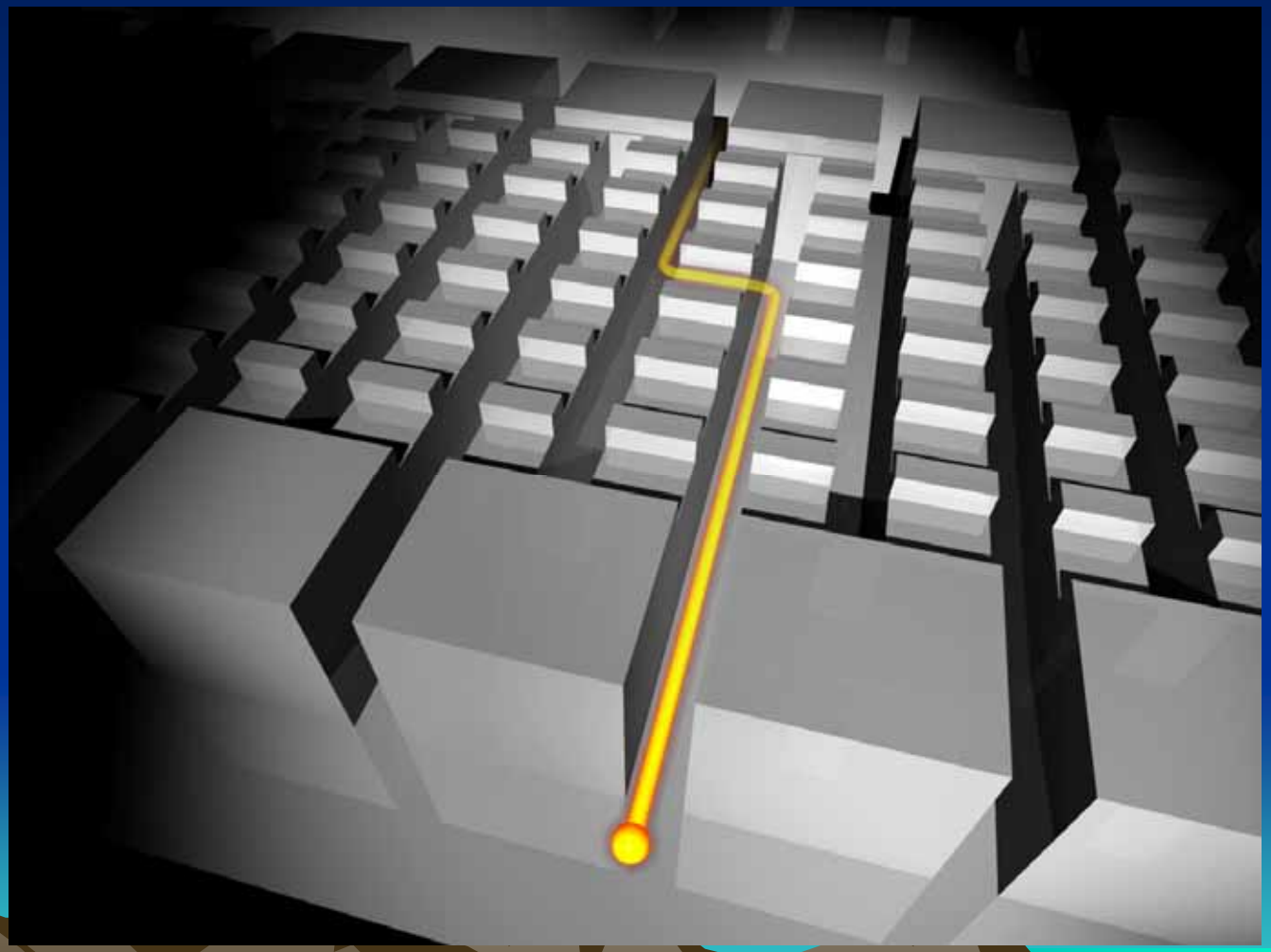


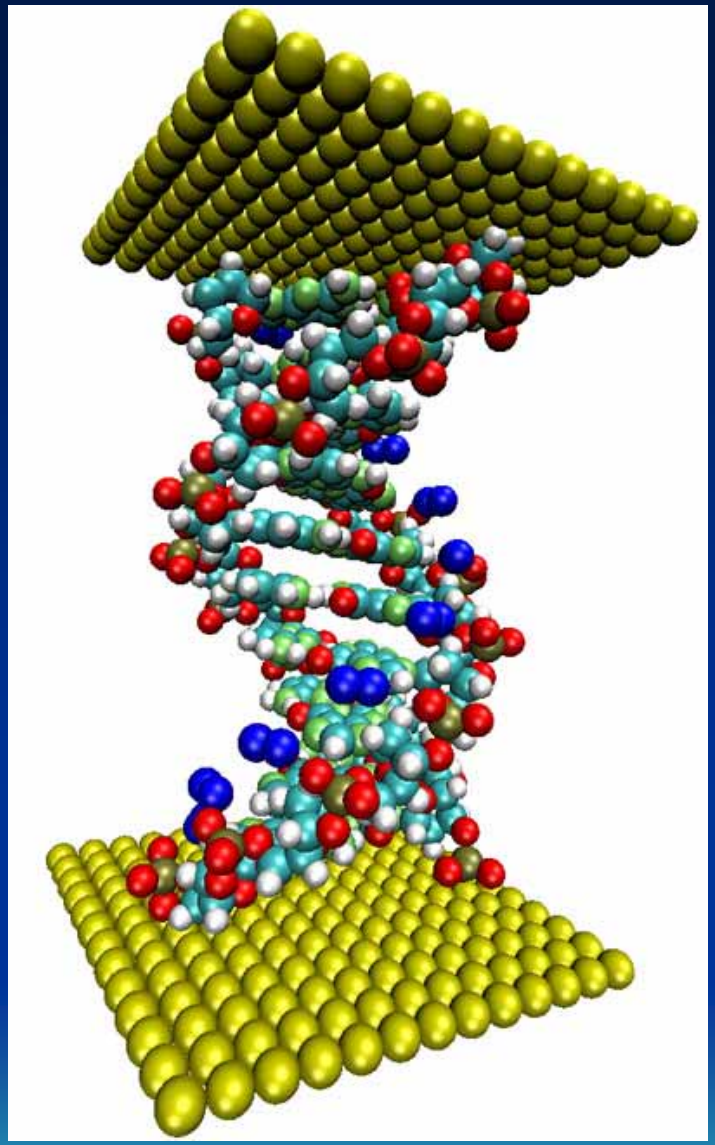
Quantum

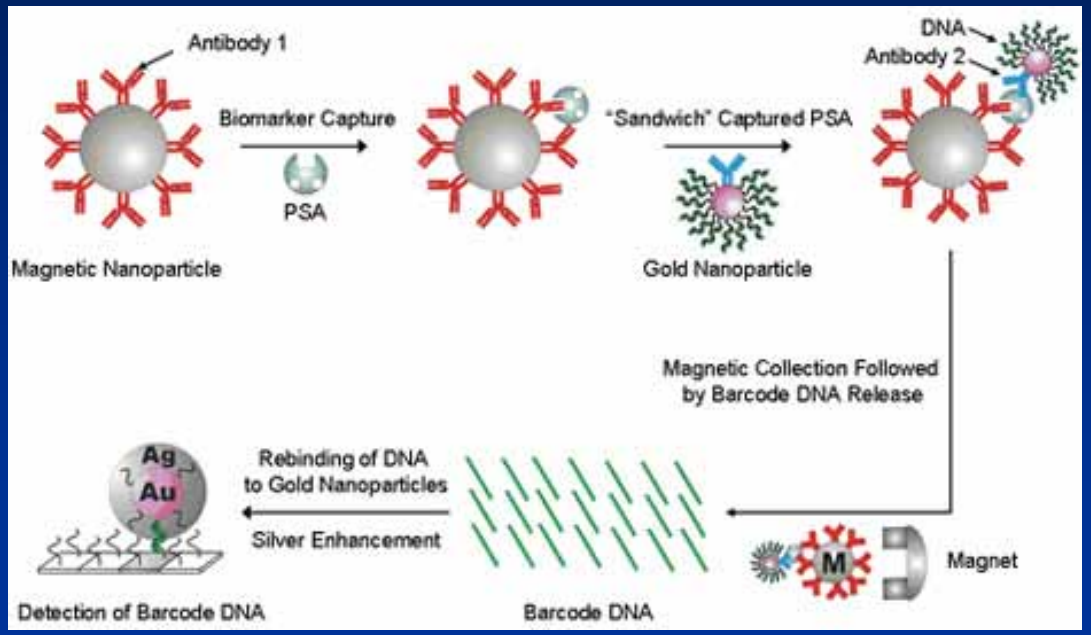
Cancer Diagnosis



Cancer Diagnosis

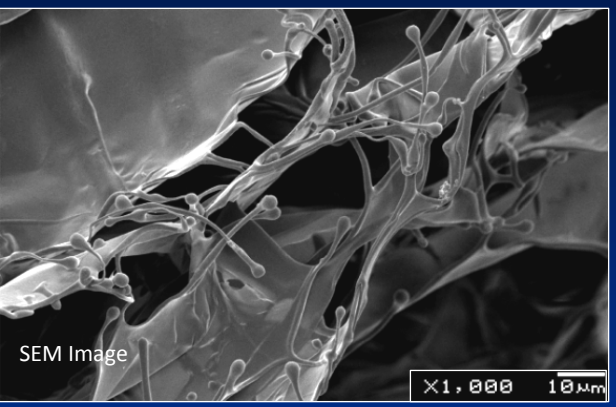





Antibody 1
Biomarker Capture
PSA
DNA
Antibody 2
"Sandwich" Captured PSA
Magnetic Nanoparticle
Gold Nanoparticle
Magnetic Collection Followed
by Barcode DNA Release
Ag
Au
Rebinding of DNA
to Gold Nanoparticles
Silver Enhancement
M
Magnet
Detection of Barcode DNA
Barcode DNA

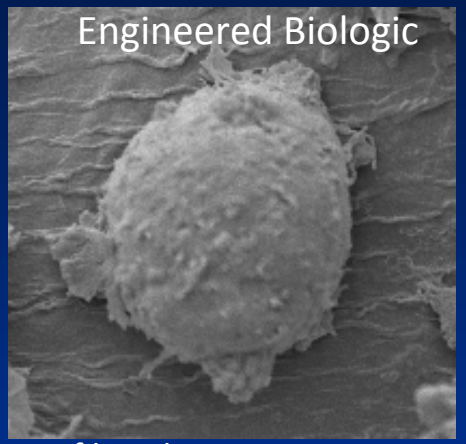
Tissue Bioengineering

Design of Engineered Biologics



Nano-chemistry, structure, and mechanics of the biologically derived material can be designed per complex patient-specific clinical need, architecture, and design

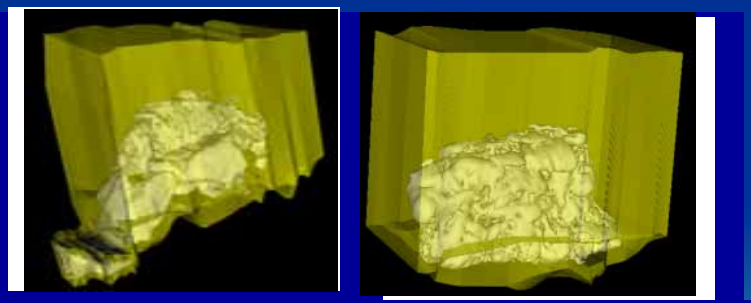
Endothelial Cell Anchored to Engineered Biologic



Nano-fiber diameter: 97.2±2.7 nm

In Vivo Regeneration of Tissues

Engineered Biologic **Bone Graft: Clinical Control**

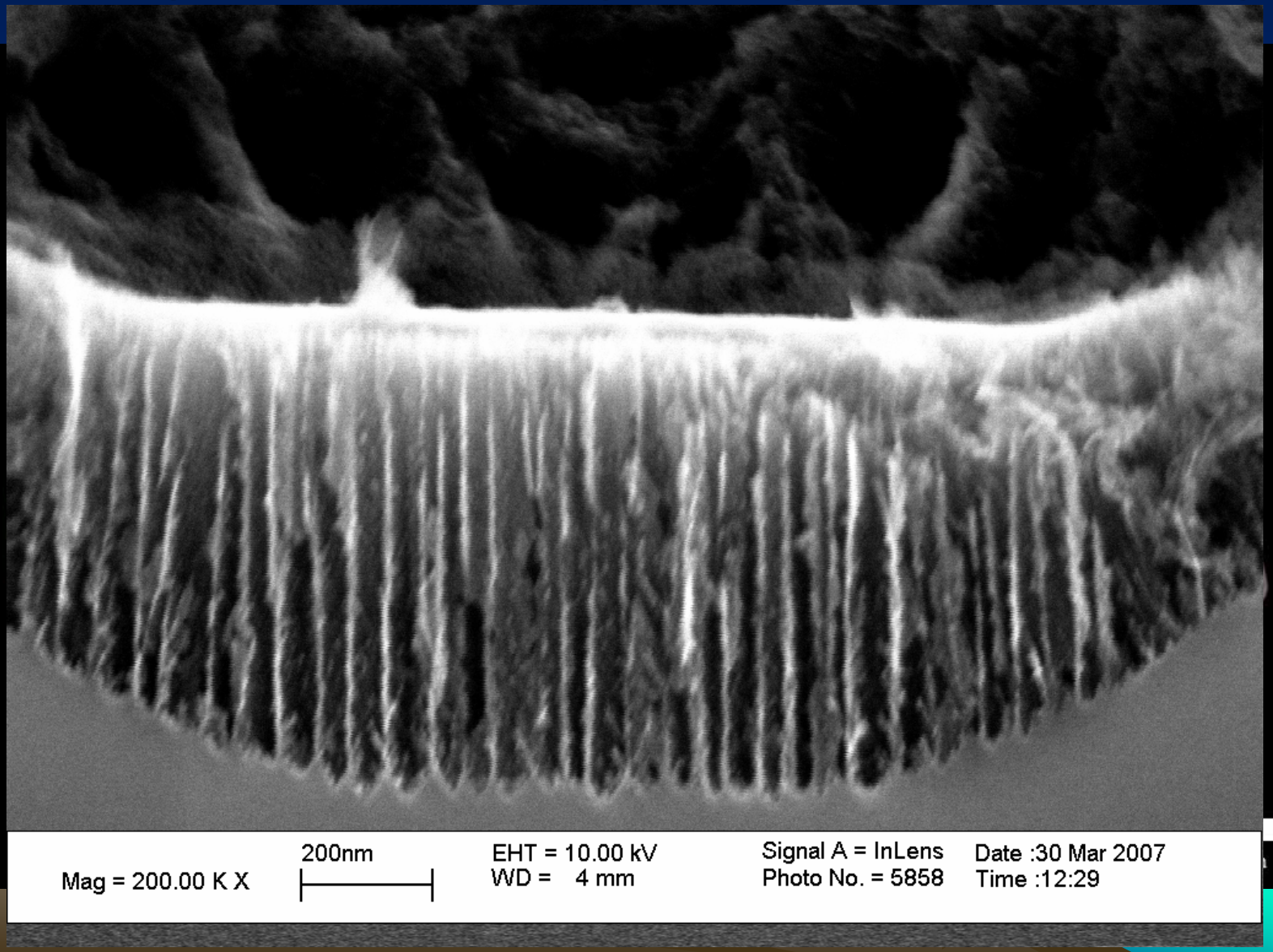


Regeneration of Critical–Sized Bone via Engineered Biologics in an *in vivo* sheep model similar to the clinically used bone graft by 84 days. (Rios et al 2009)

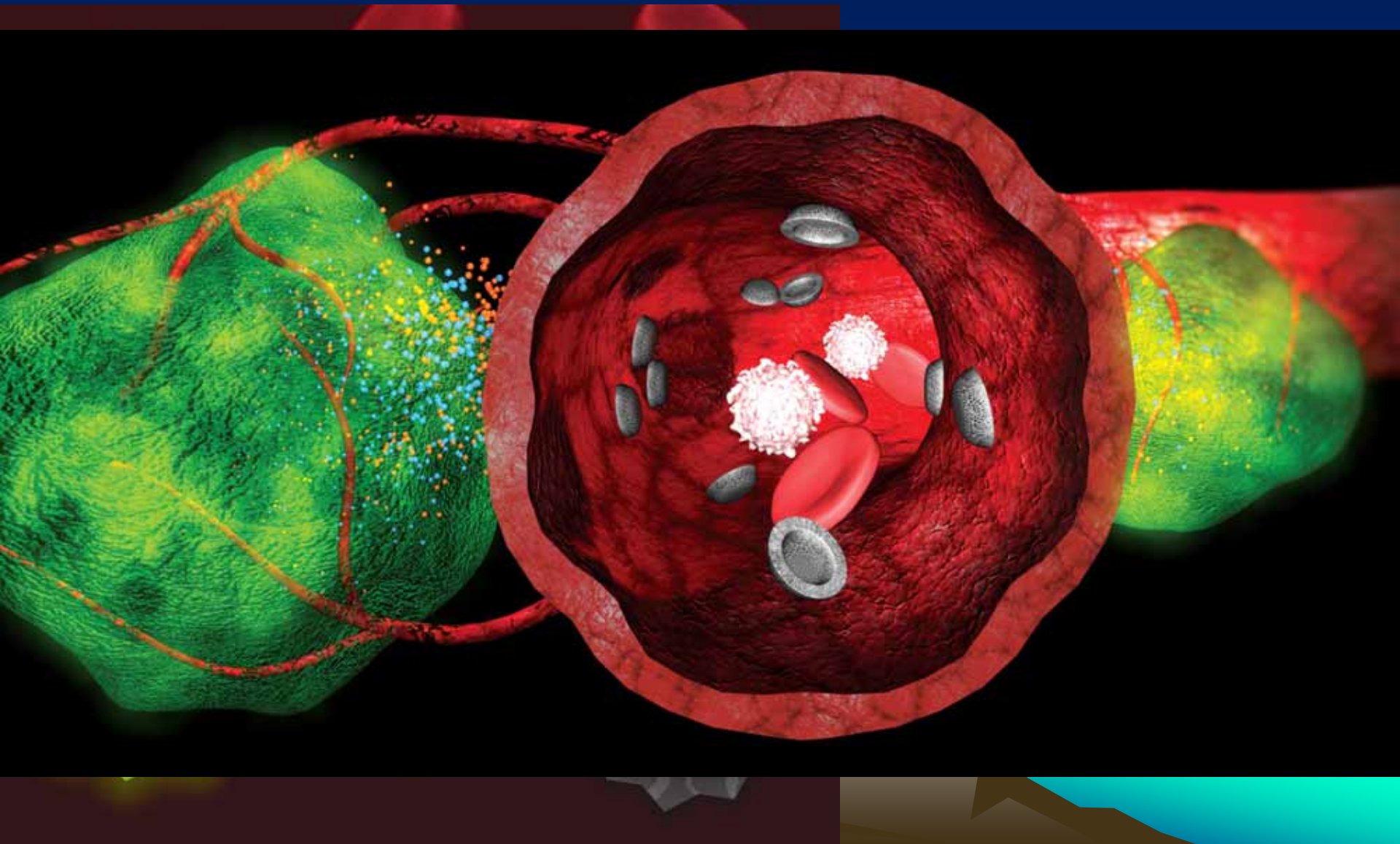
Engineered Biologic **Normal Abdominal Wall**

Regeneration of Critical–Sized Abdominal Wall Musculofascia via Engineered Biologics in an *in vivo* guinea pig model results in similar gross appearance as the Normal Native Abdominal Wall after 4 weeks. (Gobin, Butler, Mathur 2006)

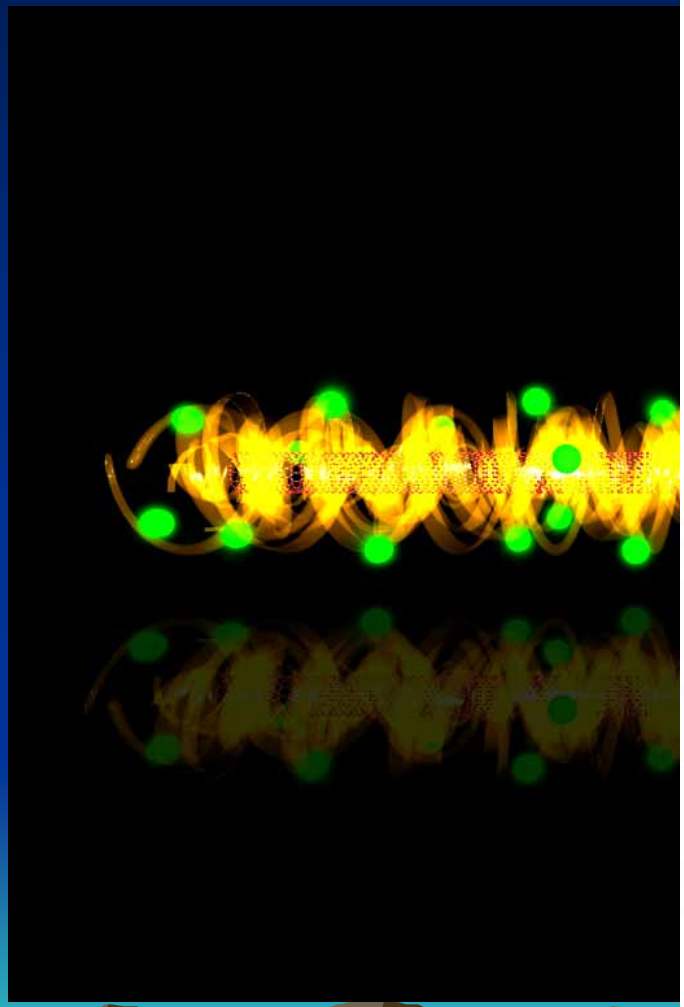
Drug and Biologic Agent Delivery

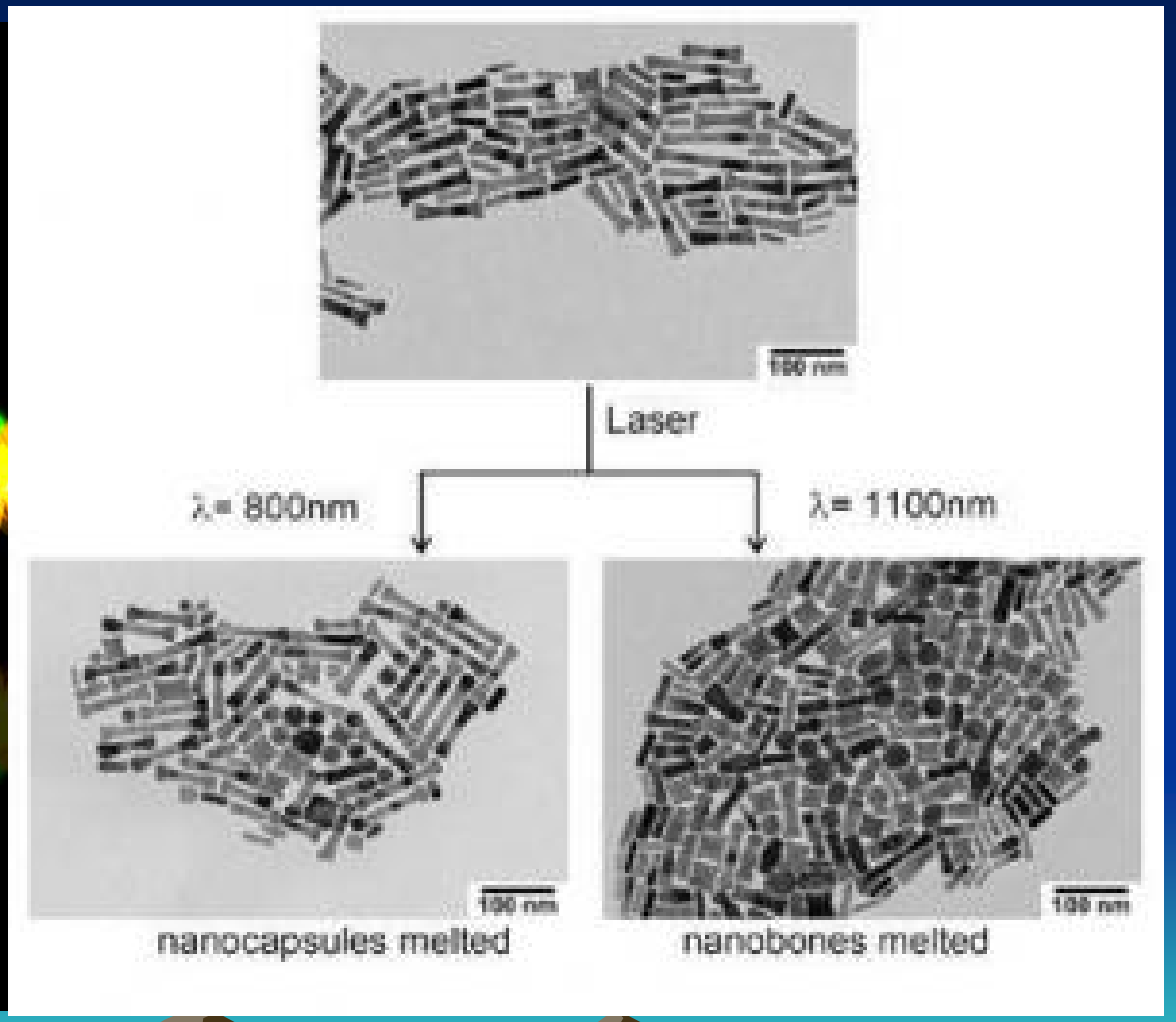


Drug and Biologic Agent Delivery



Drug and Biologic Agent Delivery





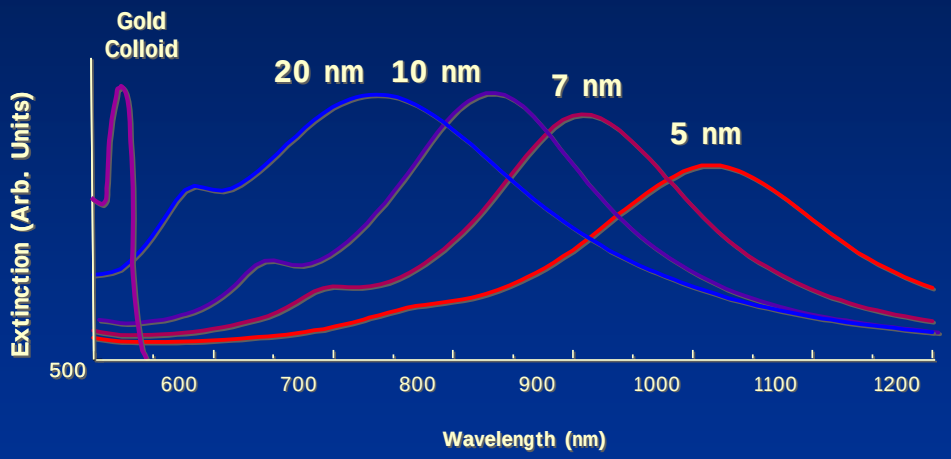
Carbon

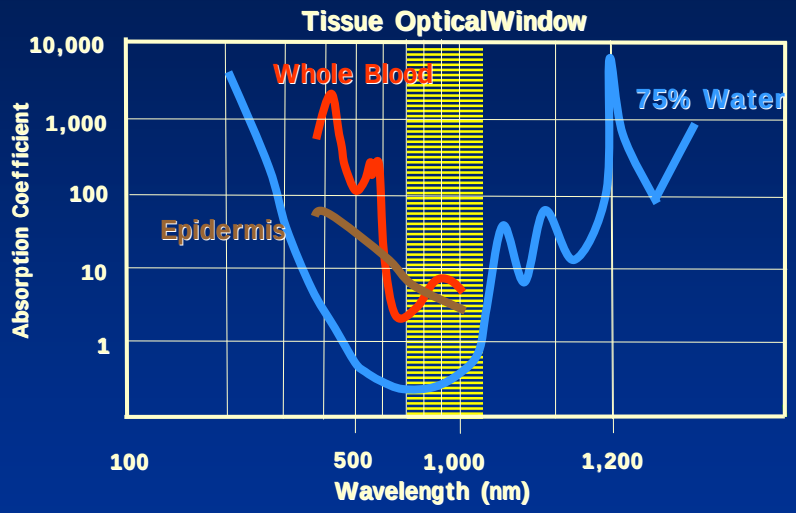
Gold

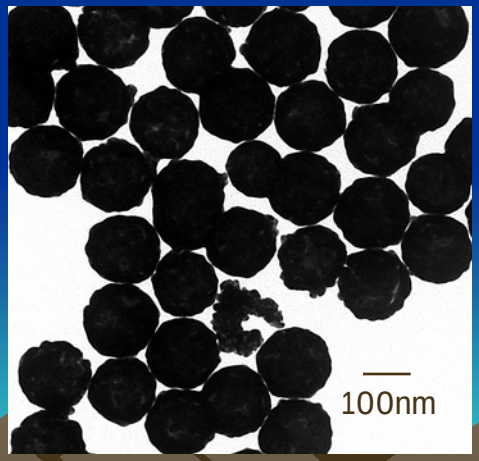
Nanoparticles in Clinical Trials

- 30 nm Au nanoparticles for drug delivery/reduction of toxicity- TNF arrayed on surface, phase I
- 150 nm Au nanoshells, non-targeted delivery- near infrared laser stimulation (plasmon resonance) to treat oropharyngeal cancer, phase I
- Nanoparticles in Cancer Therapy

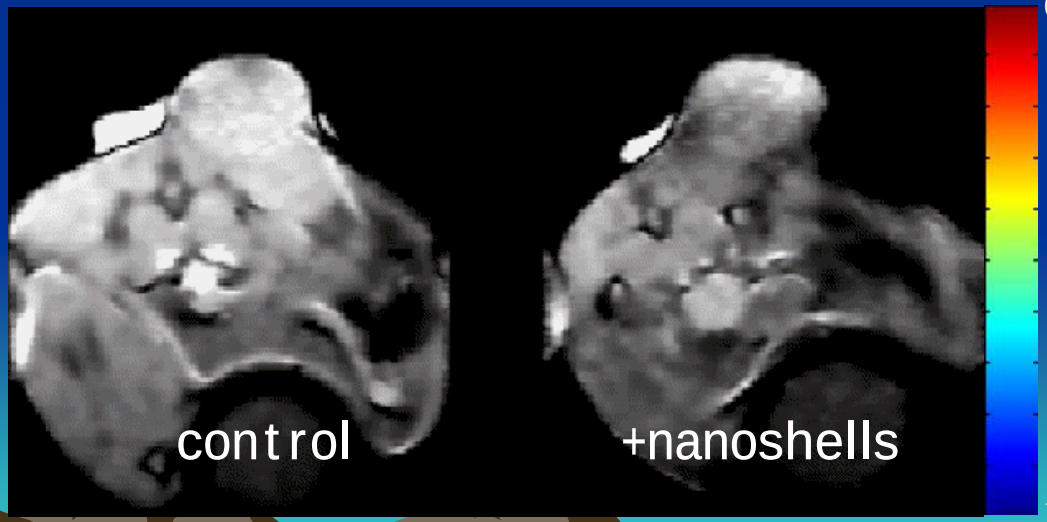
Tunable gold nanoshells for photothermal therapy





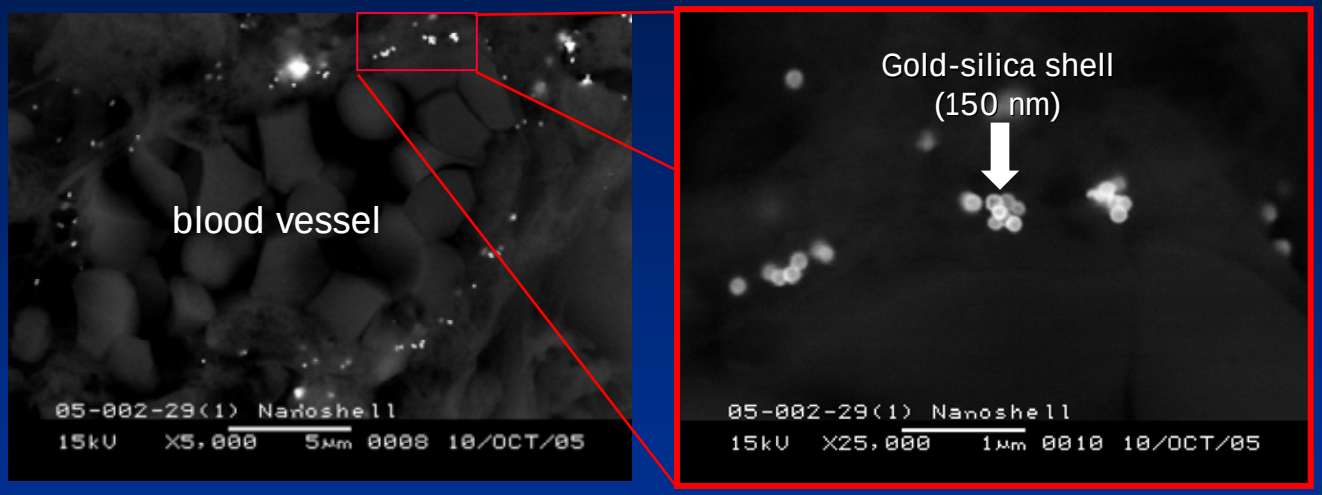


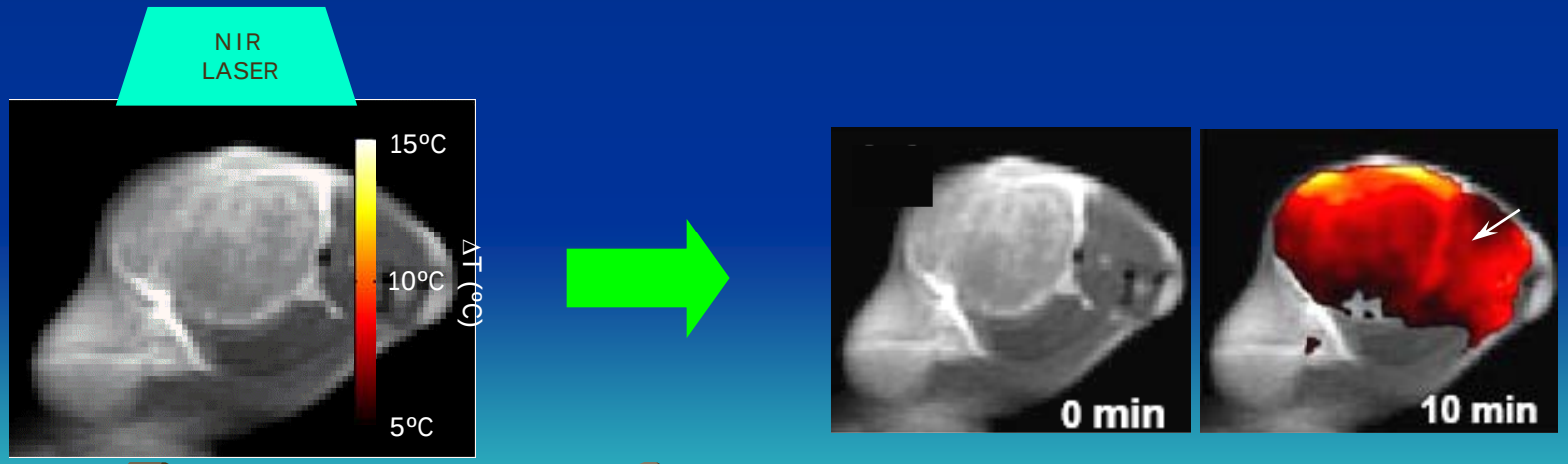
TEM of nanoshells



Mouse: Balb/c with CT26 xenograft
Laser: 808 nm, 3 min. @ 4W/cm^2

Passive extravasation of gold nanoshells



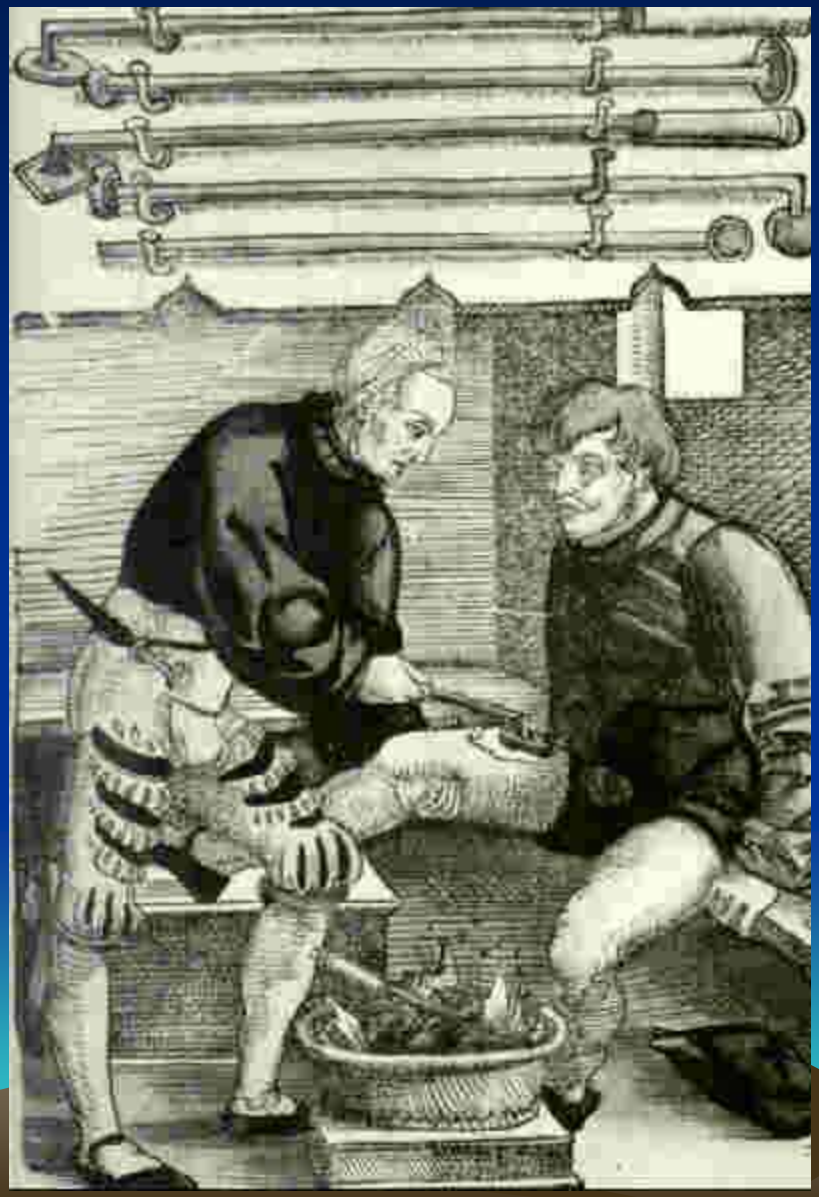


(0.6 W/cm2 for 20 min at 808-nm)

History: Thermal Cancer Therapy

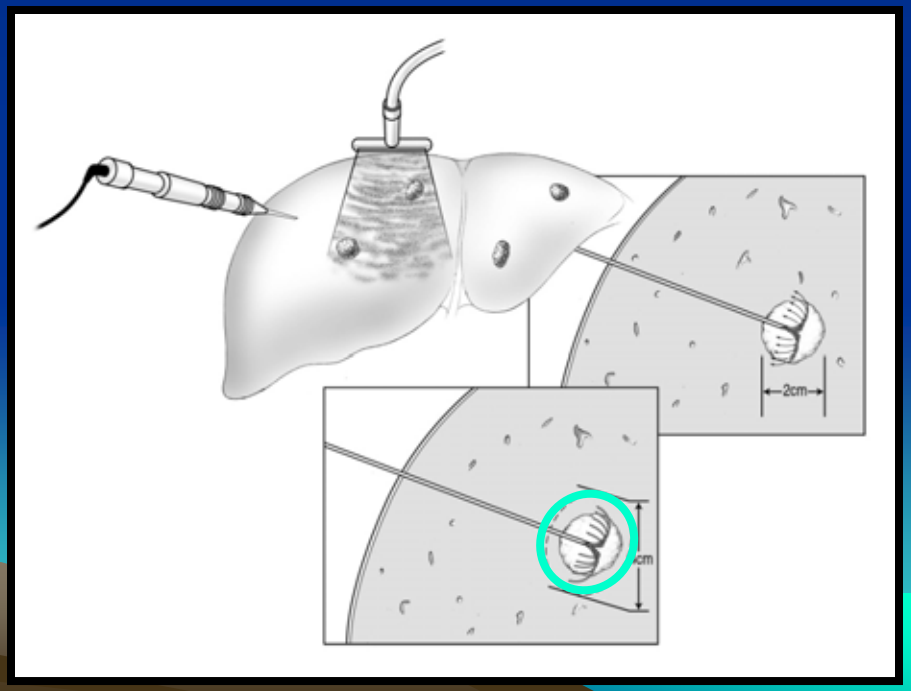
- Hot oil treatment of tumors described in 5000 year old Egyptian papyrus
- Tumor “cautery” used for numerous cancer types over past 400 years
- Electrocautery destruction of superficial and endothelial malignancies over past 120 years
- More recently, cryoablation, laser photocoagulation, radiofrequency ablation, and microwave coagulation

Cancer Cautery



Radiofrequency Ablation

- New treatment first pioneered at M.D. Anderson beginning in 1995: based on our clinical research RFA was approved by the FDA in 2001
- Radiofrequency ablation (RFA) is a thermal (heat) treatment technique which produces localized tumor destruction
- RFA kills cancer cells around the needle placed directly into the tumor



Radiofrequency Ablation
Status in 2010

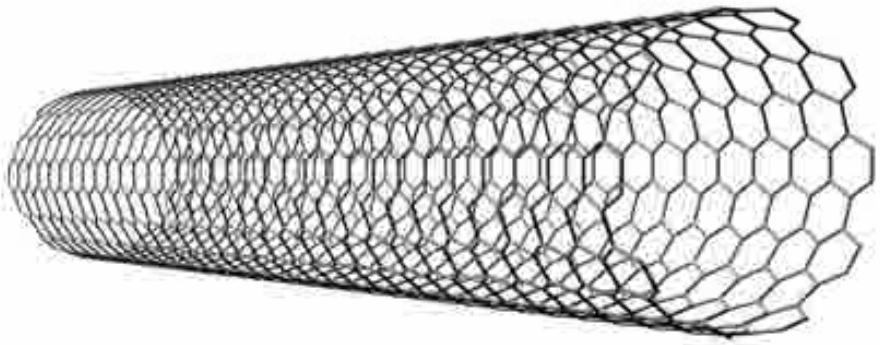
- Can treat cancers in the:
  - liver
  - kidneys
  - lungs
  - prostate
  - bone
  - breast???
- Problems with current types of RFA:
  - Can only treat a few tumors
  - Invasive
  - Damages normal tissue
  - Incomplete killing of cancer cells

External RF Treatment

- The idea: Non-invasive, no needles placed into tumors
- Could be used to treat many kinds of cancer: liver, lung, prostate, kidney, thyroid, lymphoma, brain, melanoma, sarcoma, adrenal, bone, etc.
- Collaboration between the M.D. Anderson Cancer Center and Rice University

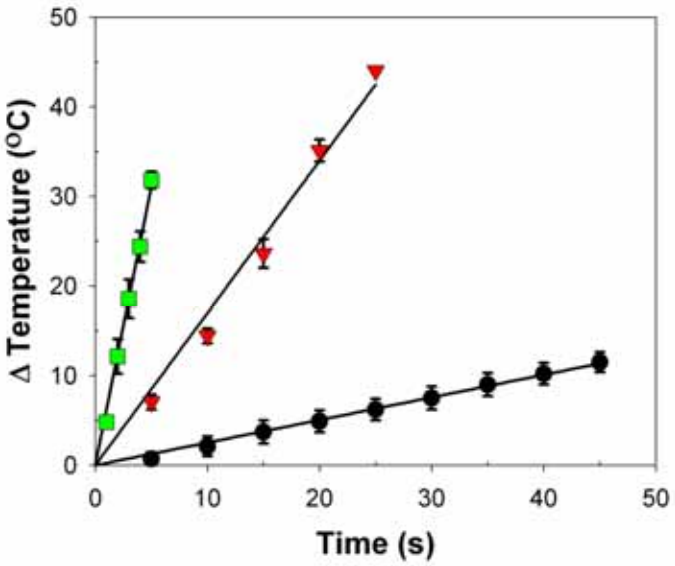
Noninvasive Radiofrequency (RF) Field Generator

Therapeutic Agents

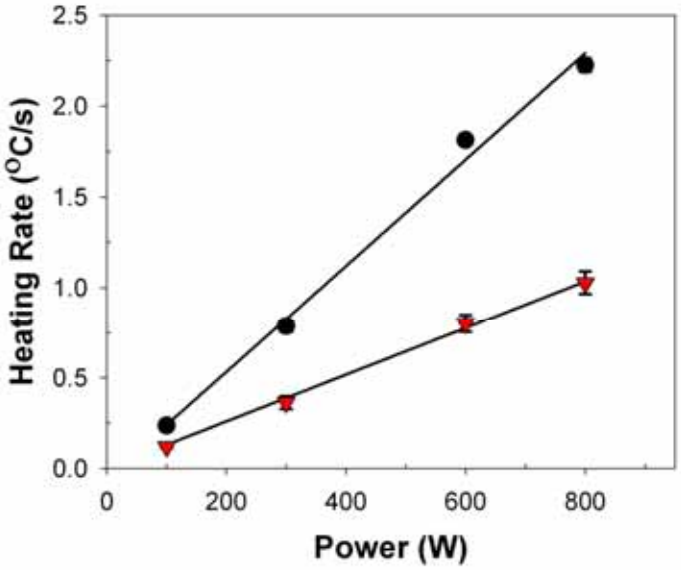


SWNTs are 1 nm in diameter, 50-1000 nm long

RF-induced heating of soluble SWNTs

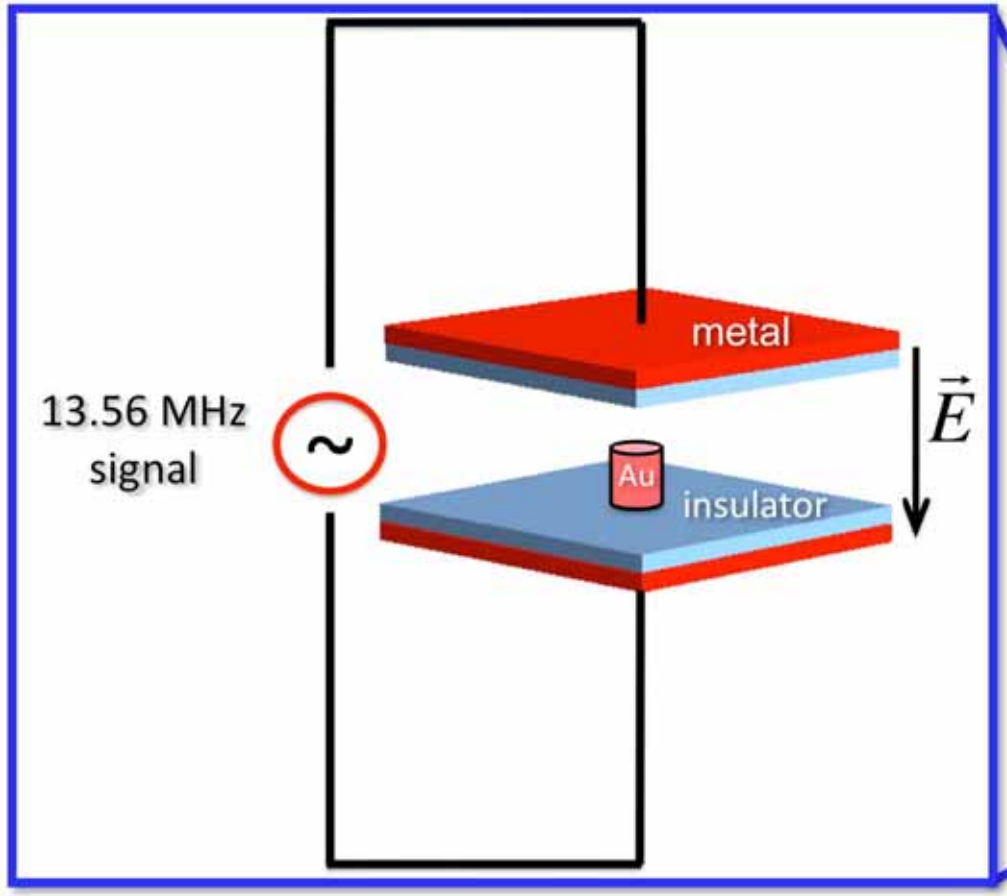


RF-induced heating of soluble SWNTs

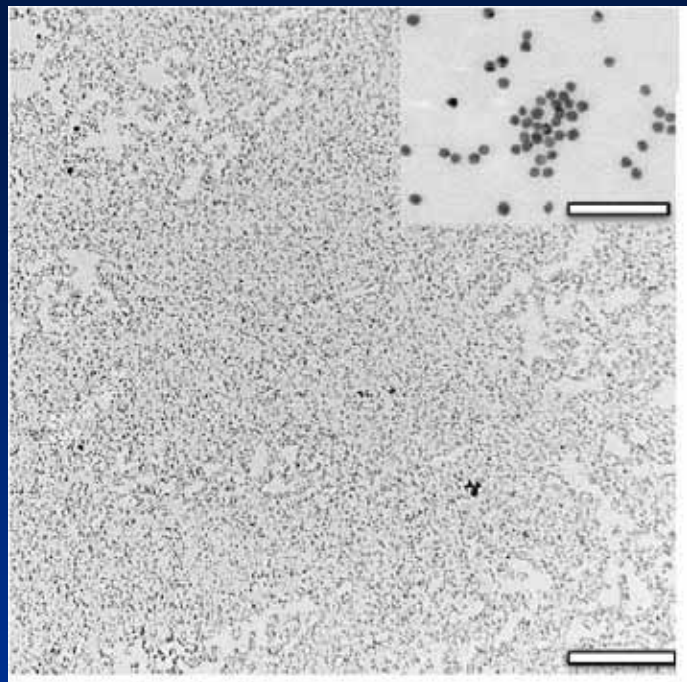


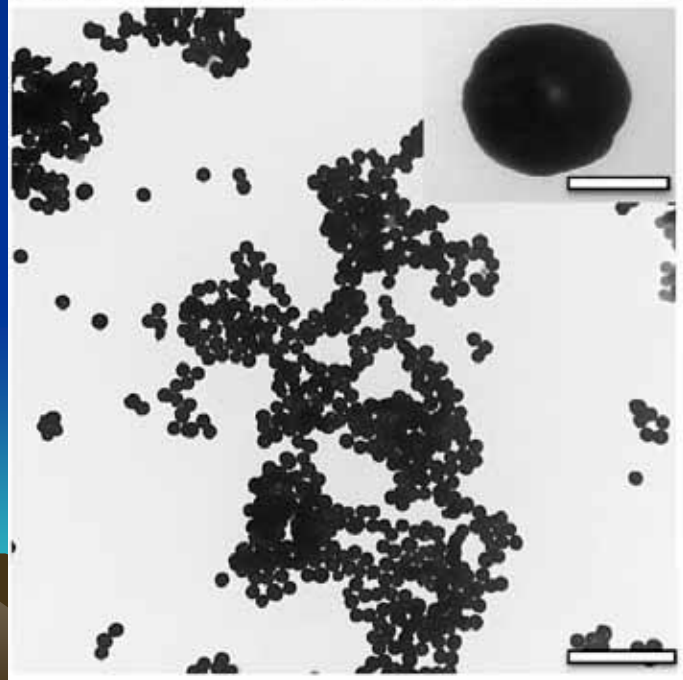
Gold Nanoparticles (GNPs)

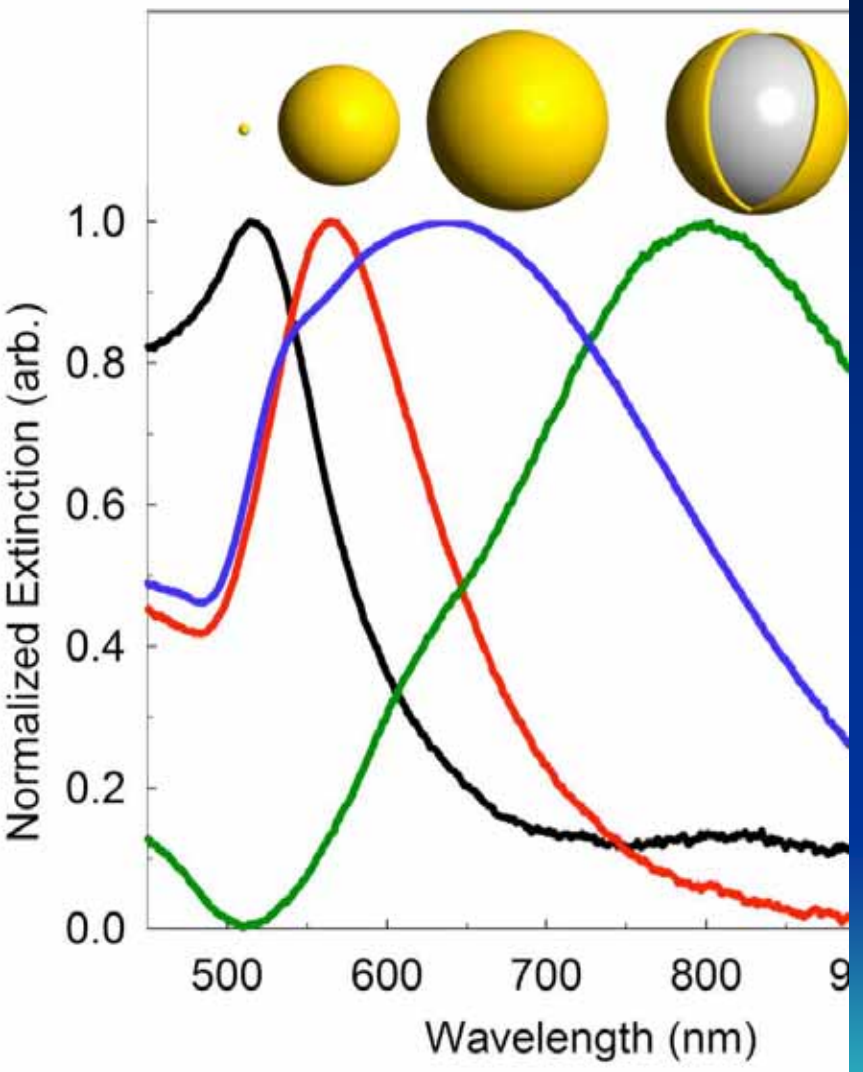
- 5 nm in diameter
- Excellent metallic conductor
- Known to be nontoxic to mammalian cells
- Gold is already FDA-approved in humans
- Possible to modify and add chemical side groups that may be used to target cancer cells


metal
13.56 MHz
signal
Au
insulator
$\vec{E}$

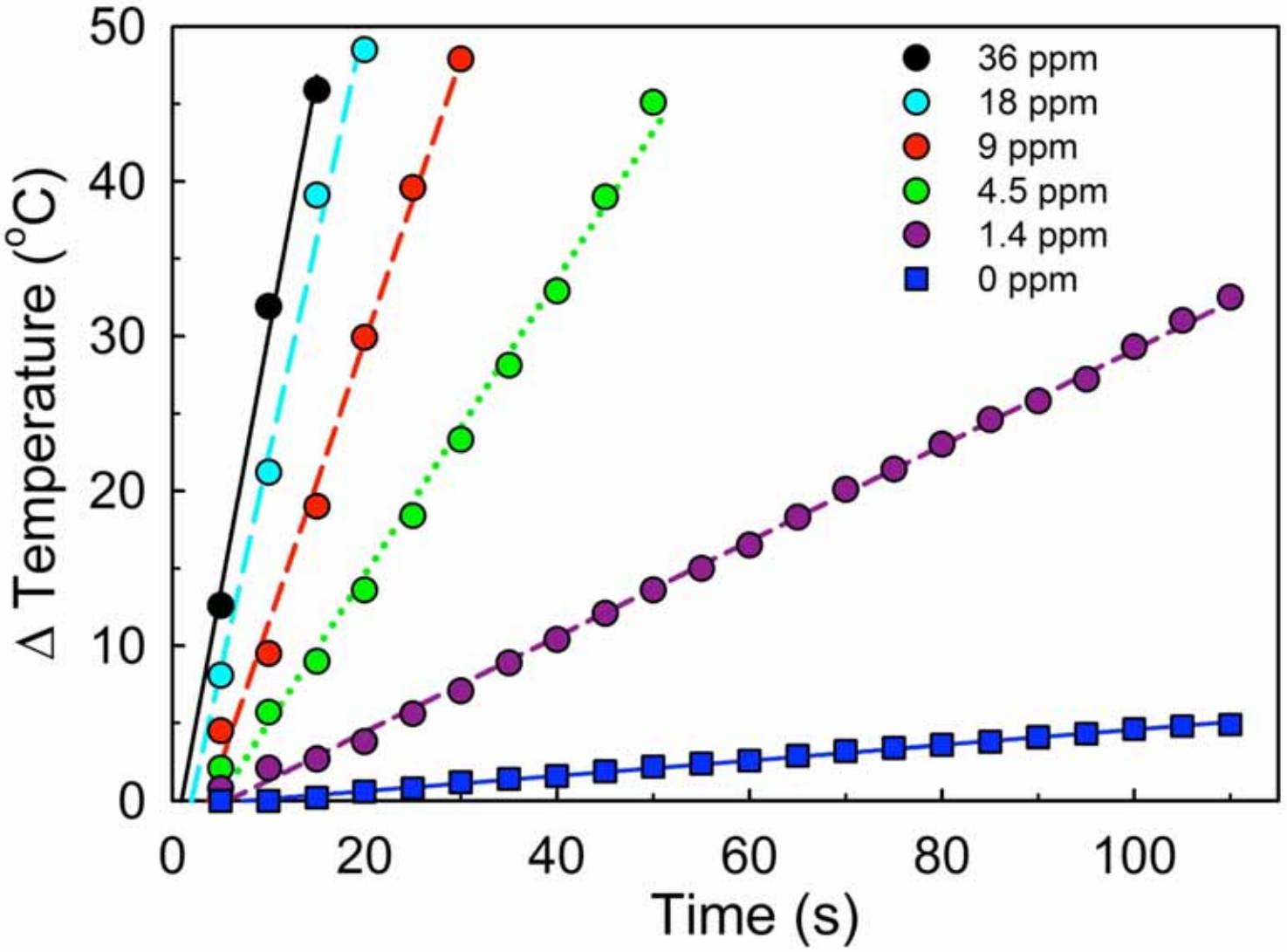

DANGER
HIGH
VOLTAGE
DANGER
HIGH
VOLTAGE



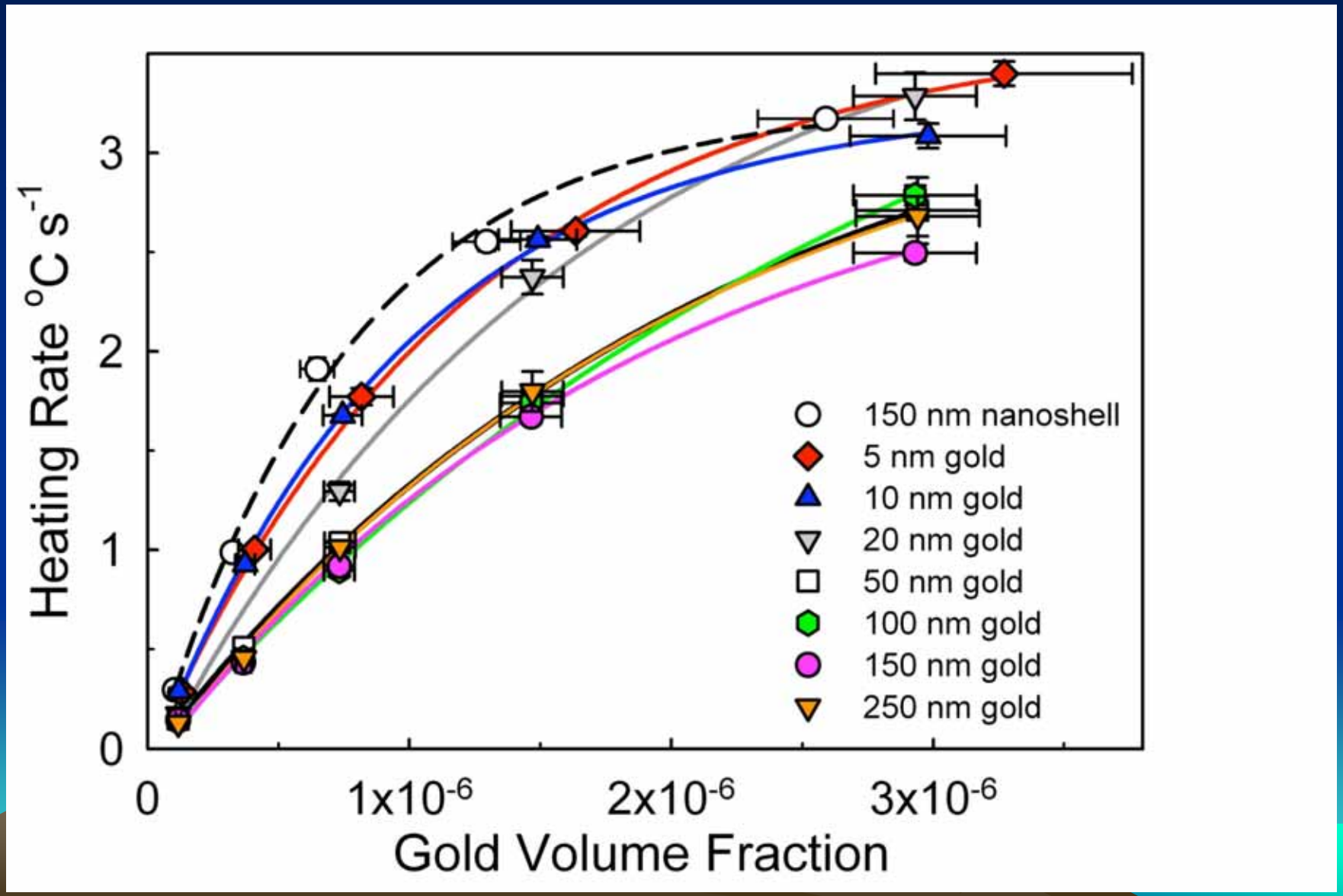



Normalized Extinction (arb.)
1.0
0.8
0.6
0.4
0.2
0.0
500
600
700
800
Wavelength (nm)

Heating rates of Au nanoparticles in a 13.56 MHz RF Field



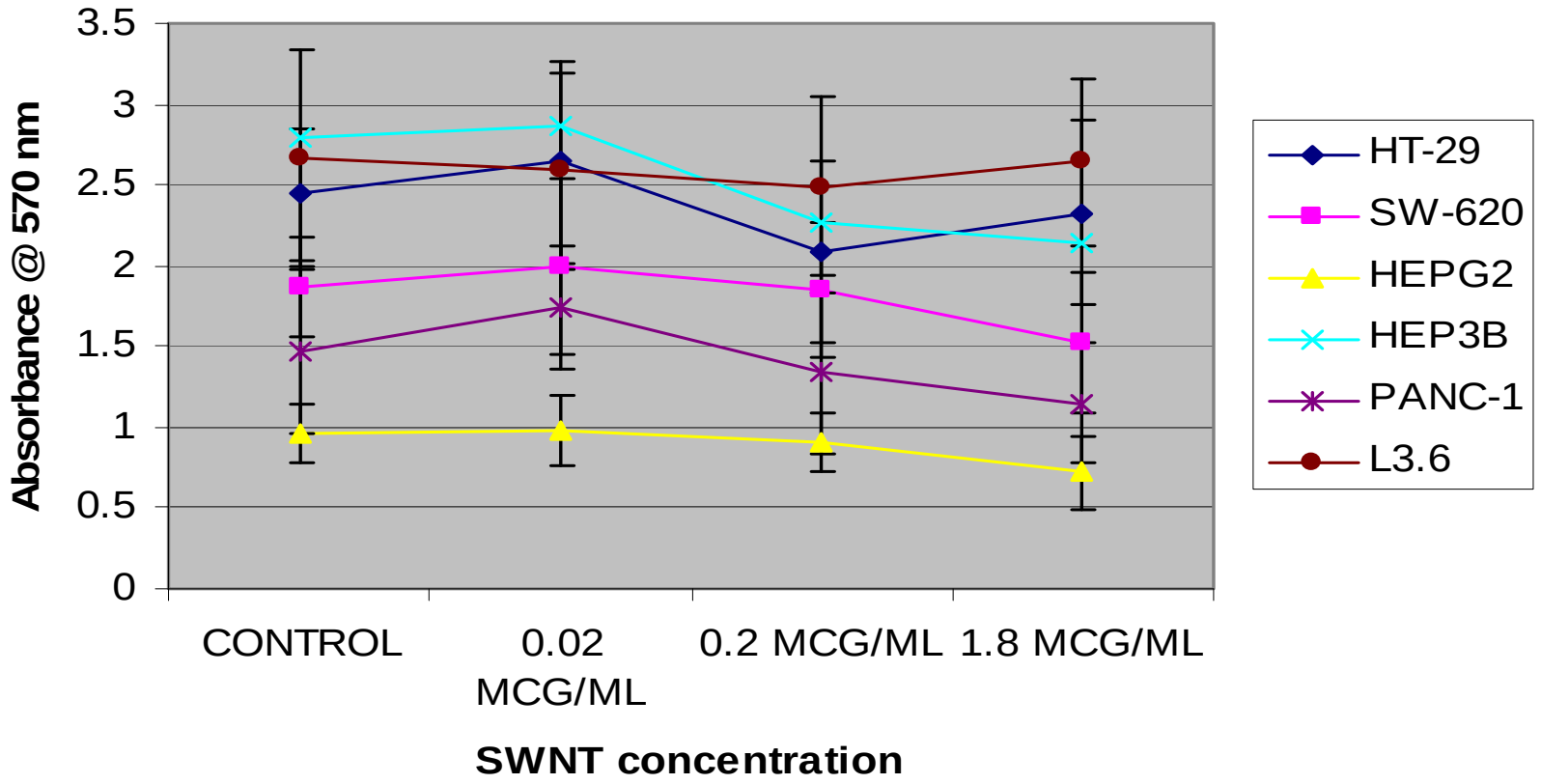
Heating rates of Au nanoparticles in a 13.56 MHz RF Field



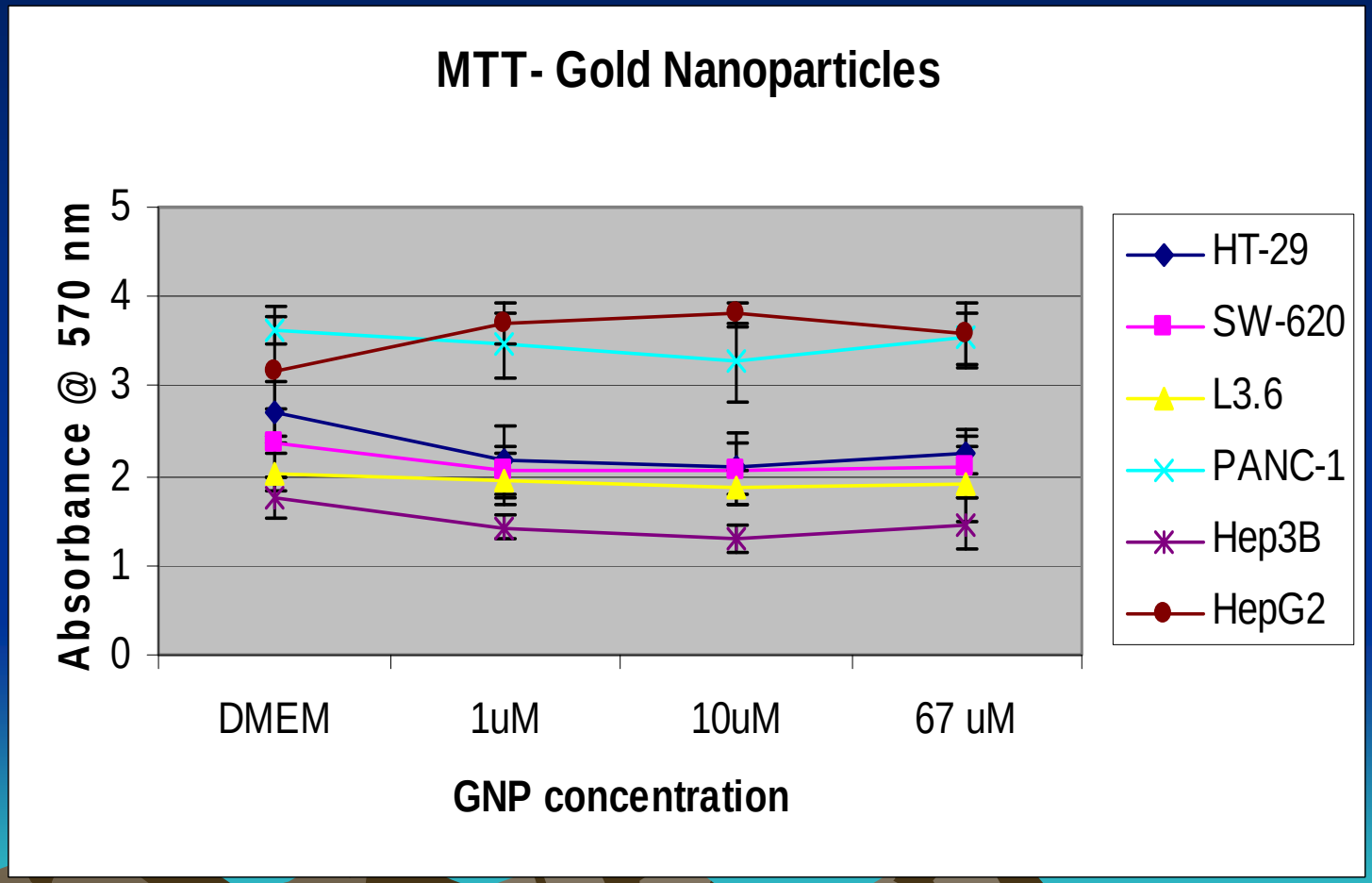
Human Cancer Cell Lines

- Hepatocellular cancer: Hep3B and HepG2
- Pancreatic adenocarcinoma: Panc-1 and L3.6
- Colorectal adenocarcinoma: HT-29 and SW-620

Cell Proliferation Data



Cell Proliferation Data



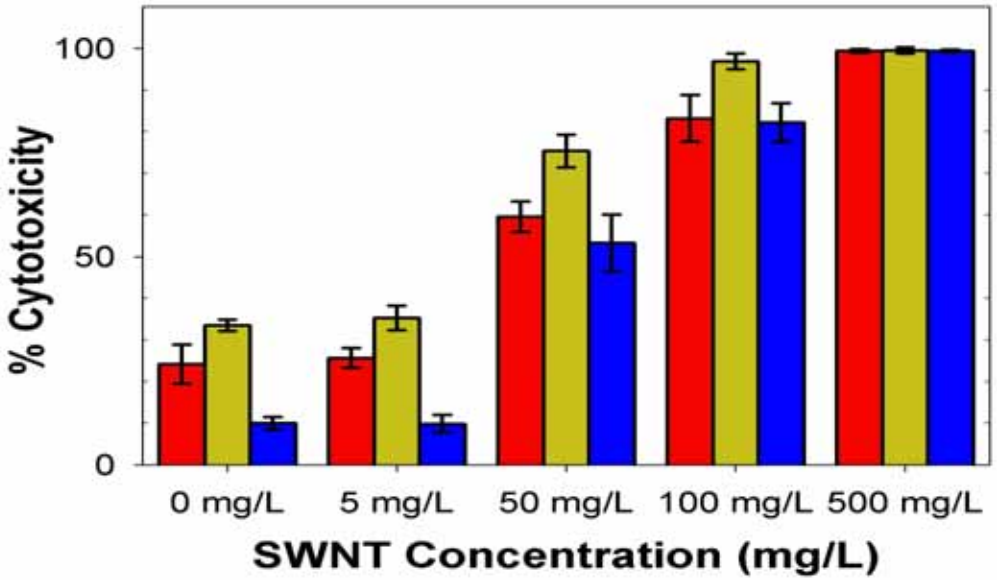
SWNT or GNP Containing Cell Culture-RF Exposure

- SWNTs or GNPs added 24 hours prior to RF exposure
- Other cell cultures were treated with media alone
- Parameters:
  - 13.56 MHz
  - spacing 10 cm
  - continuous RF field
  - variable exposure time
- Cells returned to incubator for 24 hours
- PI FACS to assess cell viability

Shortwave RF Field Generator

- Totally noninvasive
- No wires or capacitor plates required for sample

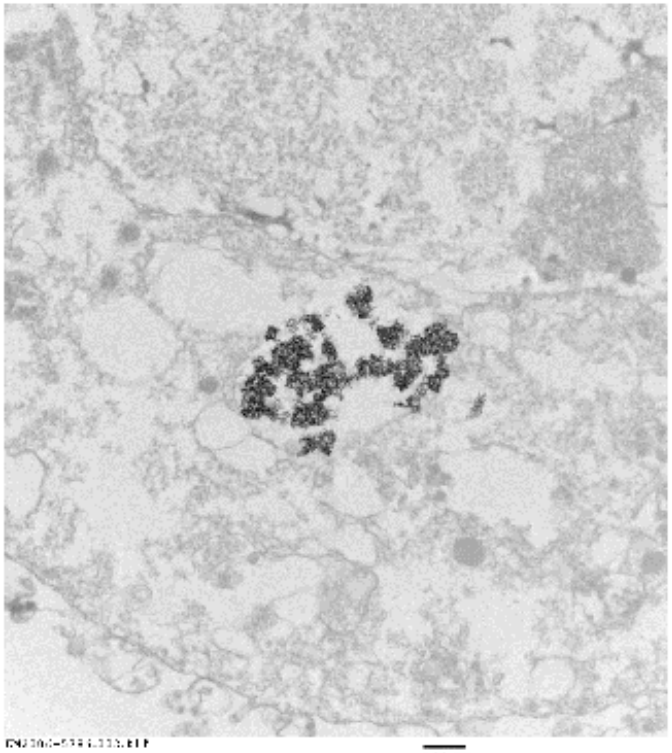
SWNT Dose-Related Cytotoxicity With RF Field Treatment



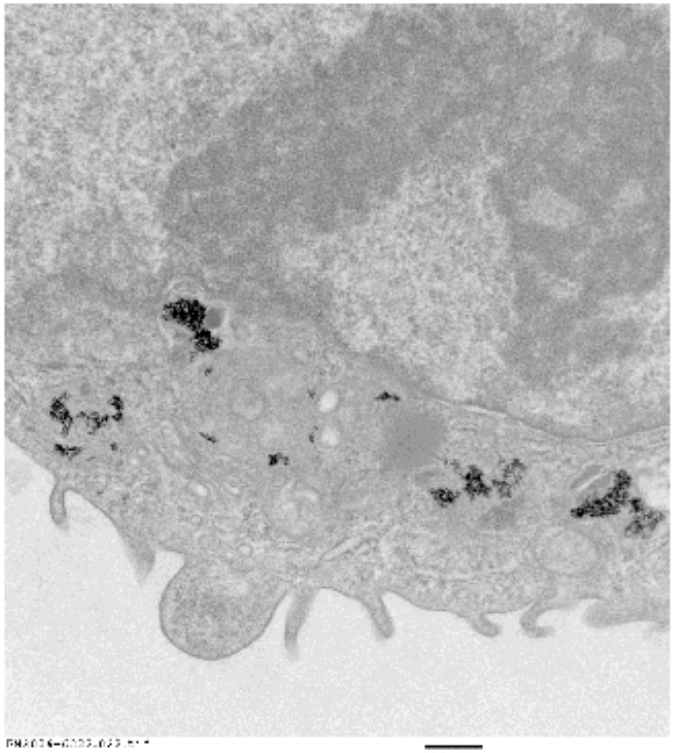
Hep 3B cells
Hep G2 cells
Panc-1 cells

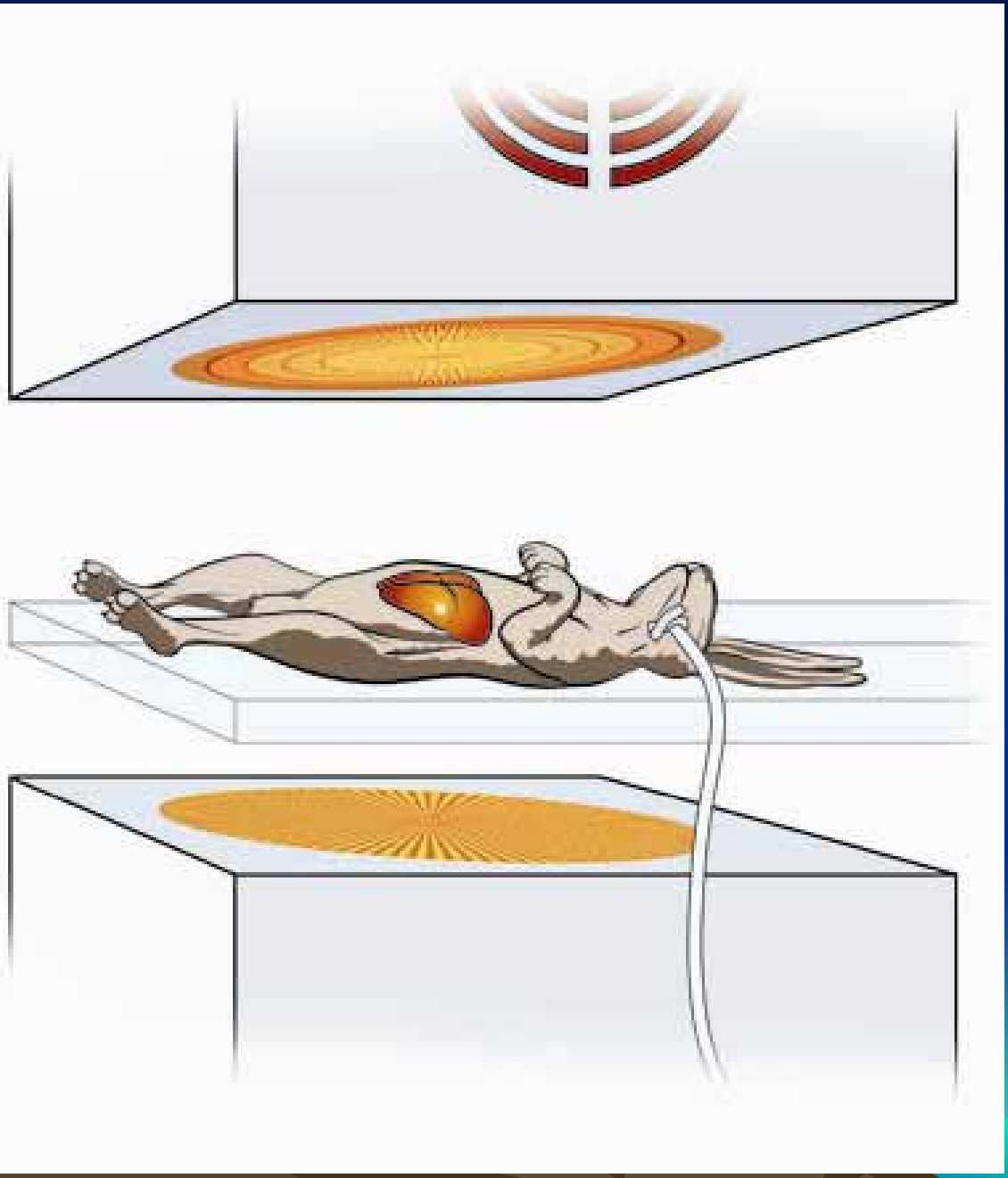
Human Pancreatic Cancer Cell Line with GNPs

RF



No RF





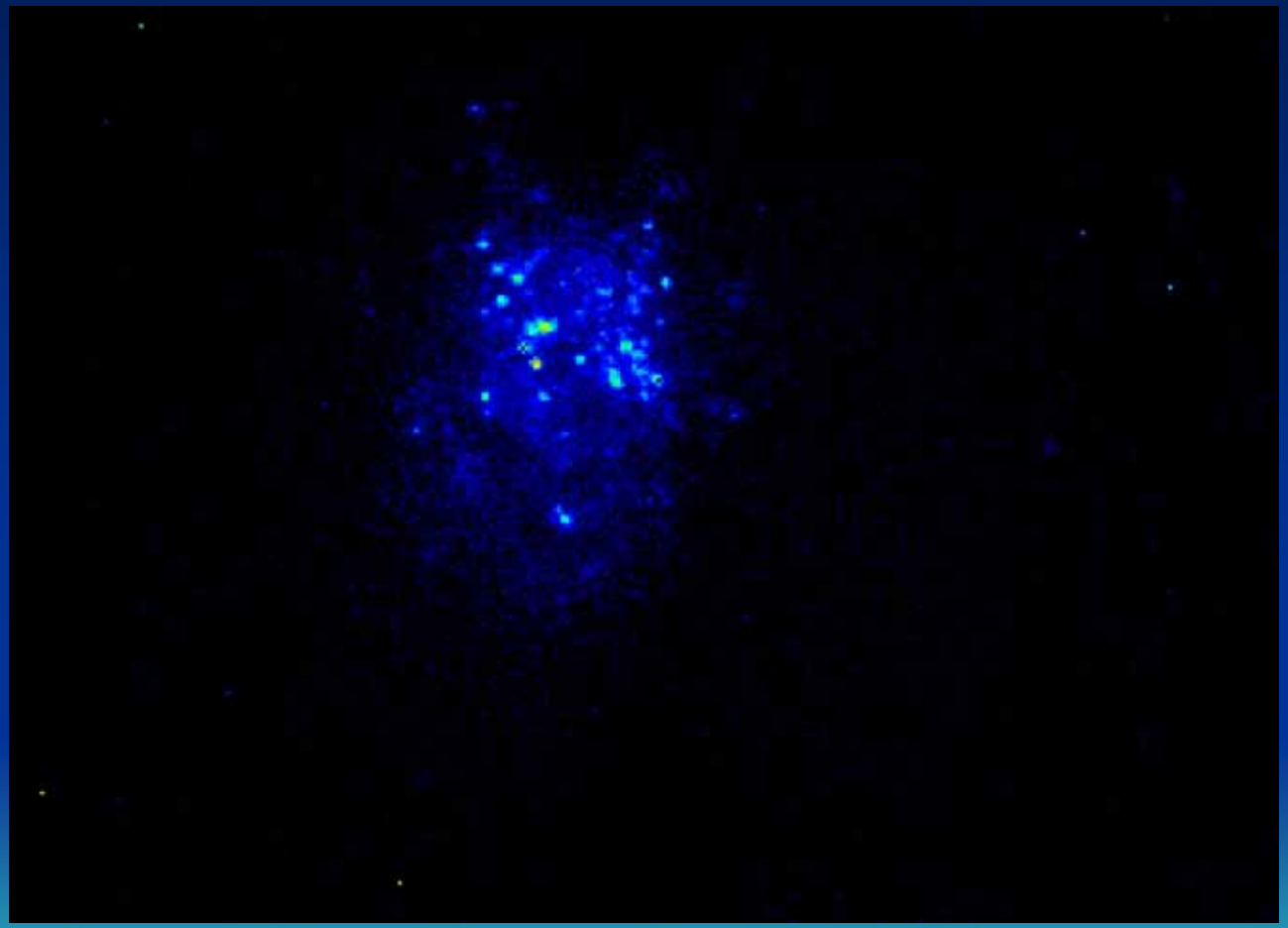
RF and SWNTs in vivo

- NZW rabbits bearing 1-1.5 cm hepatic VX2 tumors
- Tumors directly injected with 1.0 ml of functionalized SWNTs or with control solutions (no SWNTs)
- Animal treated with external RF 400W for 2 minutes
- Tissue temperatures were monitored during the RF treatment
- Tumors harvested 48 hours later

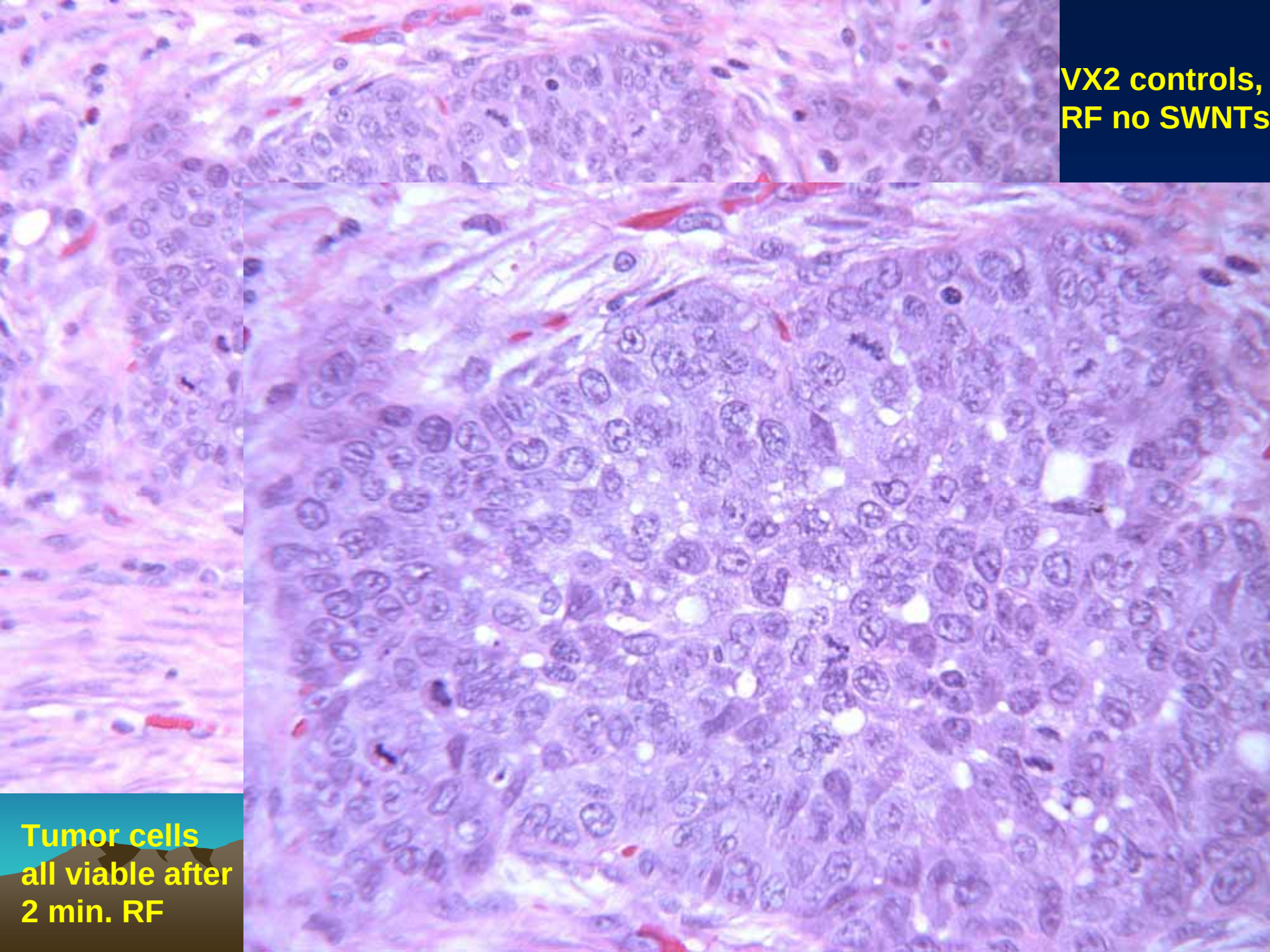
RF and SWNTs in vivo

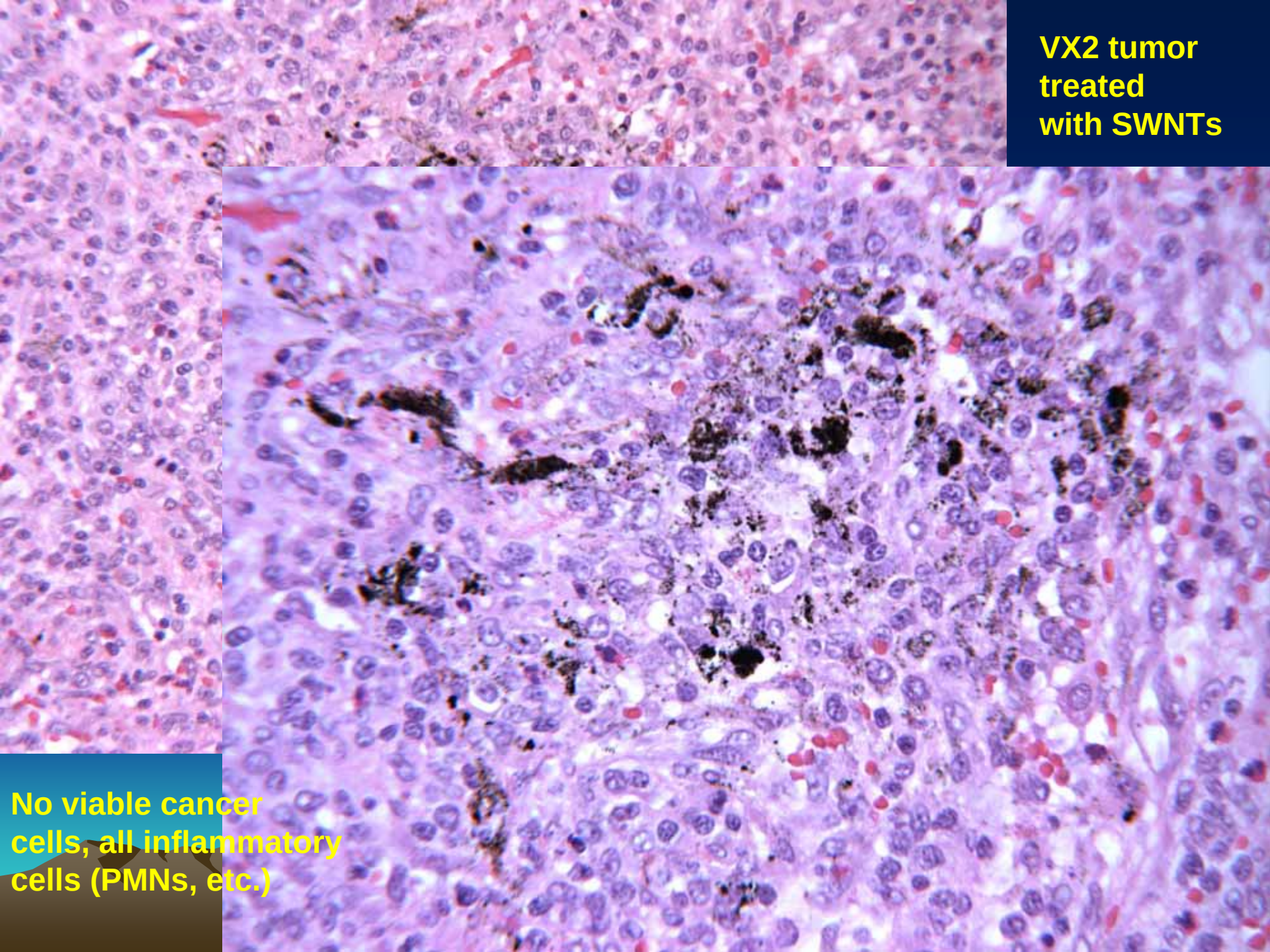
- During RF, thermistors adjacent to tumor showed temperature increase
- Thermistor in liver 2 cm away showed no temperature increase
- Tumors injected with functionalized SWNTs were necrotic at 48 hours by H&E and NADH staining
- Tumors injected with control solutions were completely viable

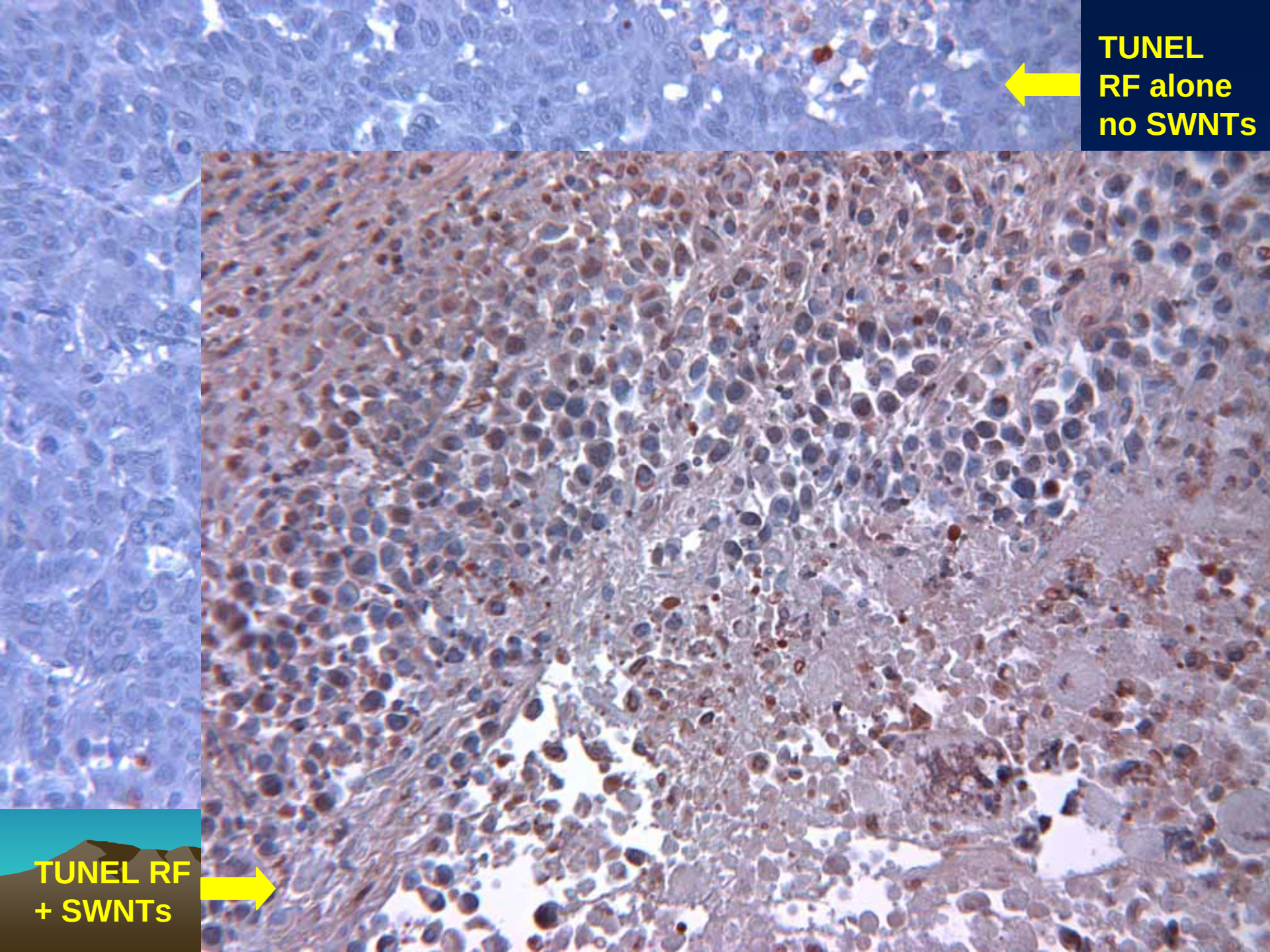
Near Infrared Microscopy



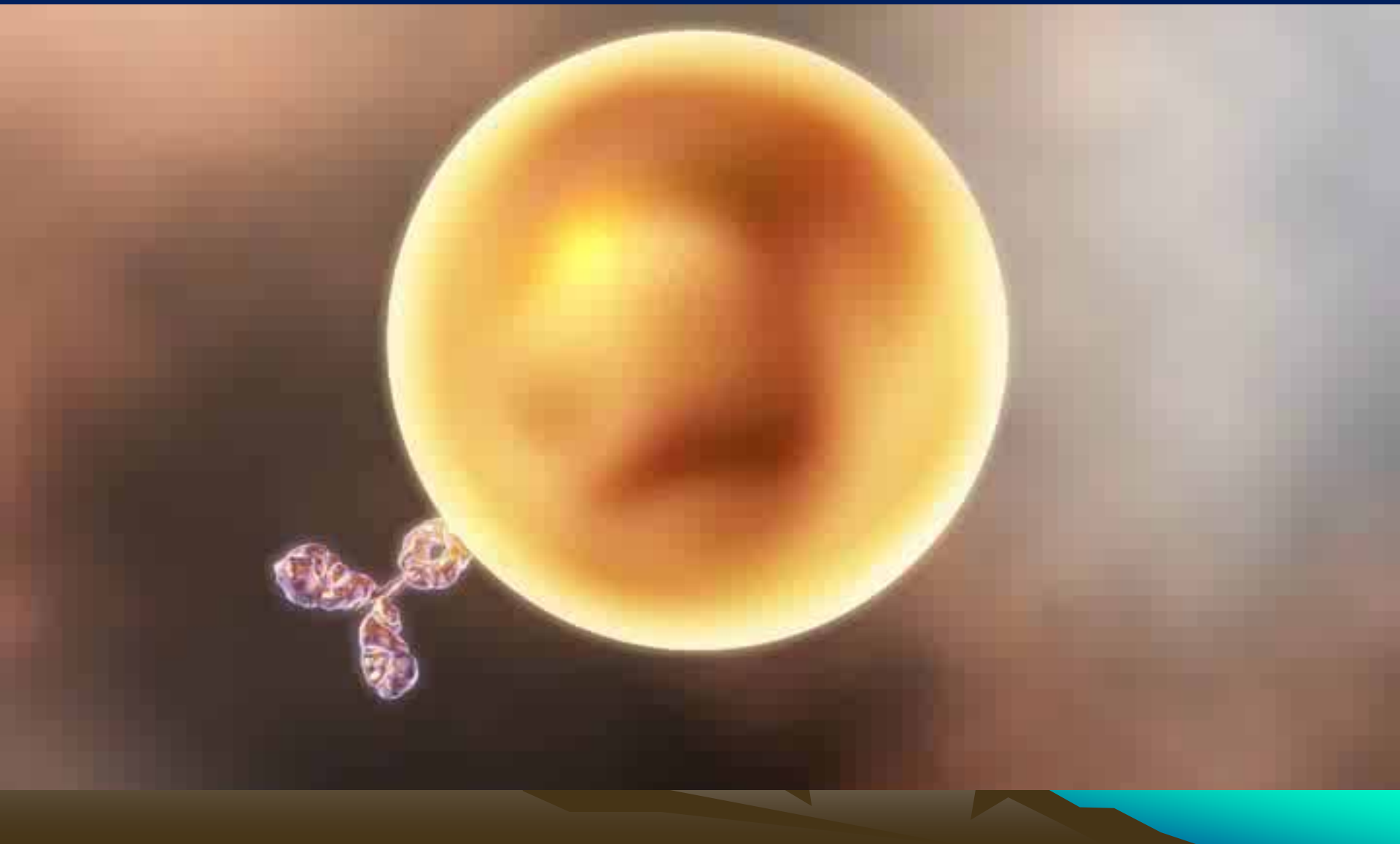
Multiple SWNTs in Rabbit Liver


VX2 controls,
RF no SWNTs
Tumor cells
all viable after
2 min. RF

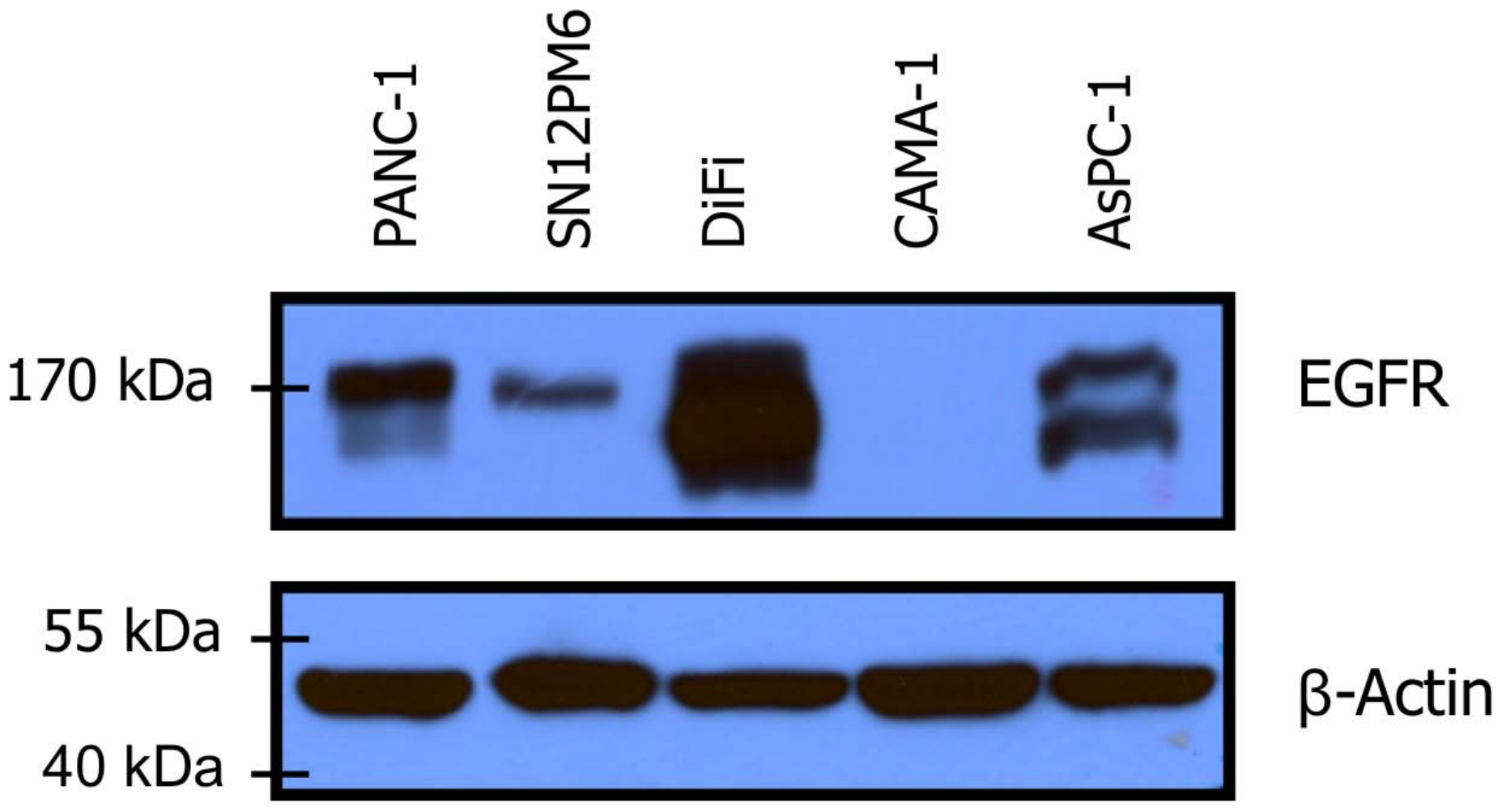

VX2 tumor
treated
with SWNTs
No viable cancer
cells, all inflammatory
cells (PMNs, etc.)

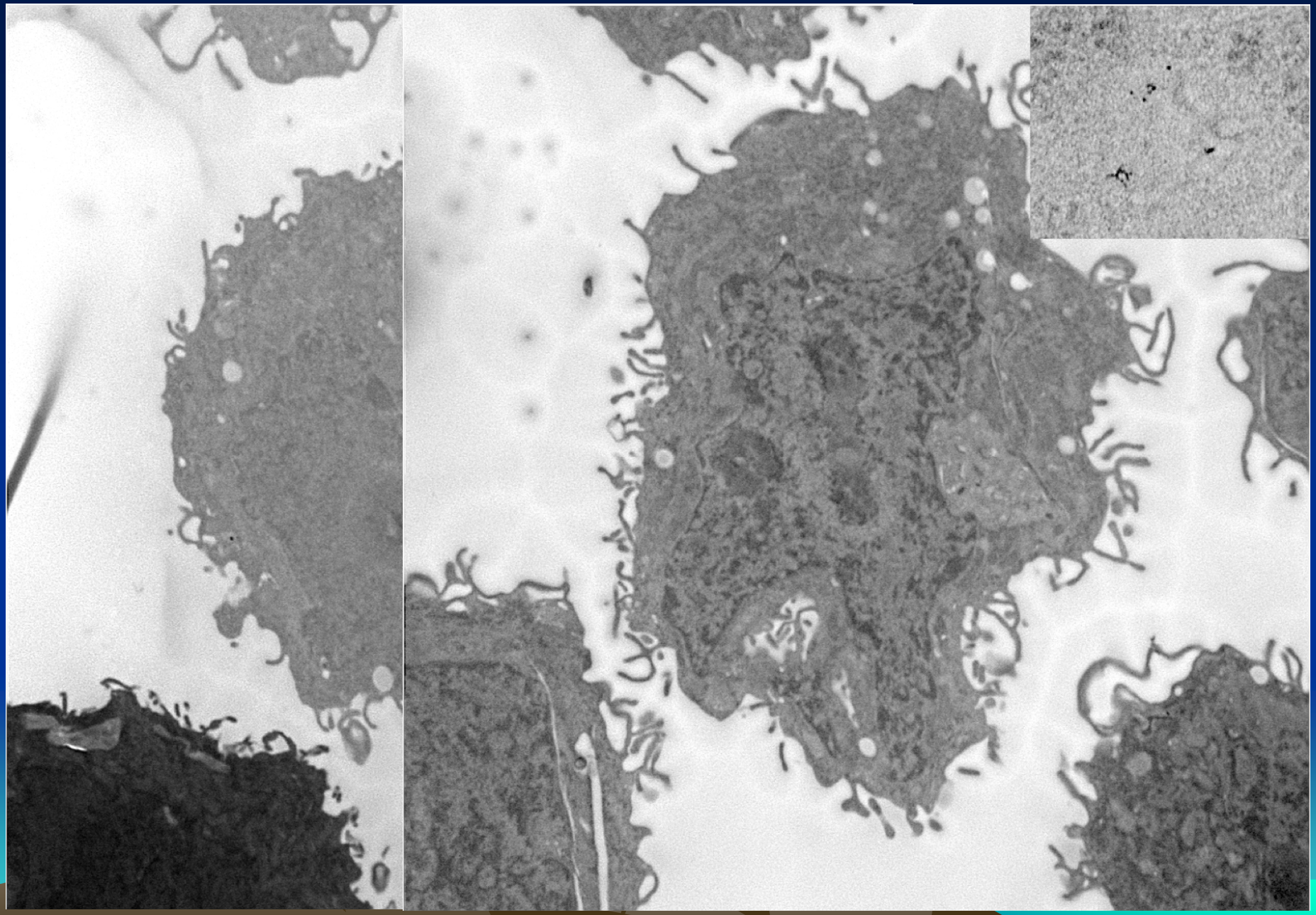

TUNEL
RF alone
no SWNTs
TUNEL RF
+ SWNTs

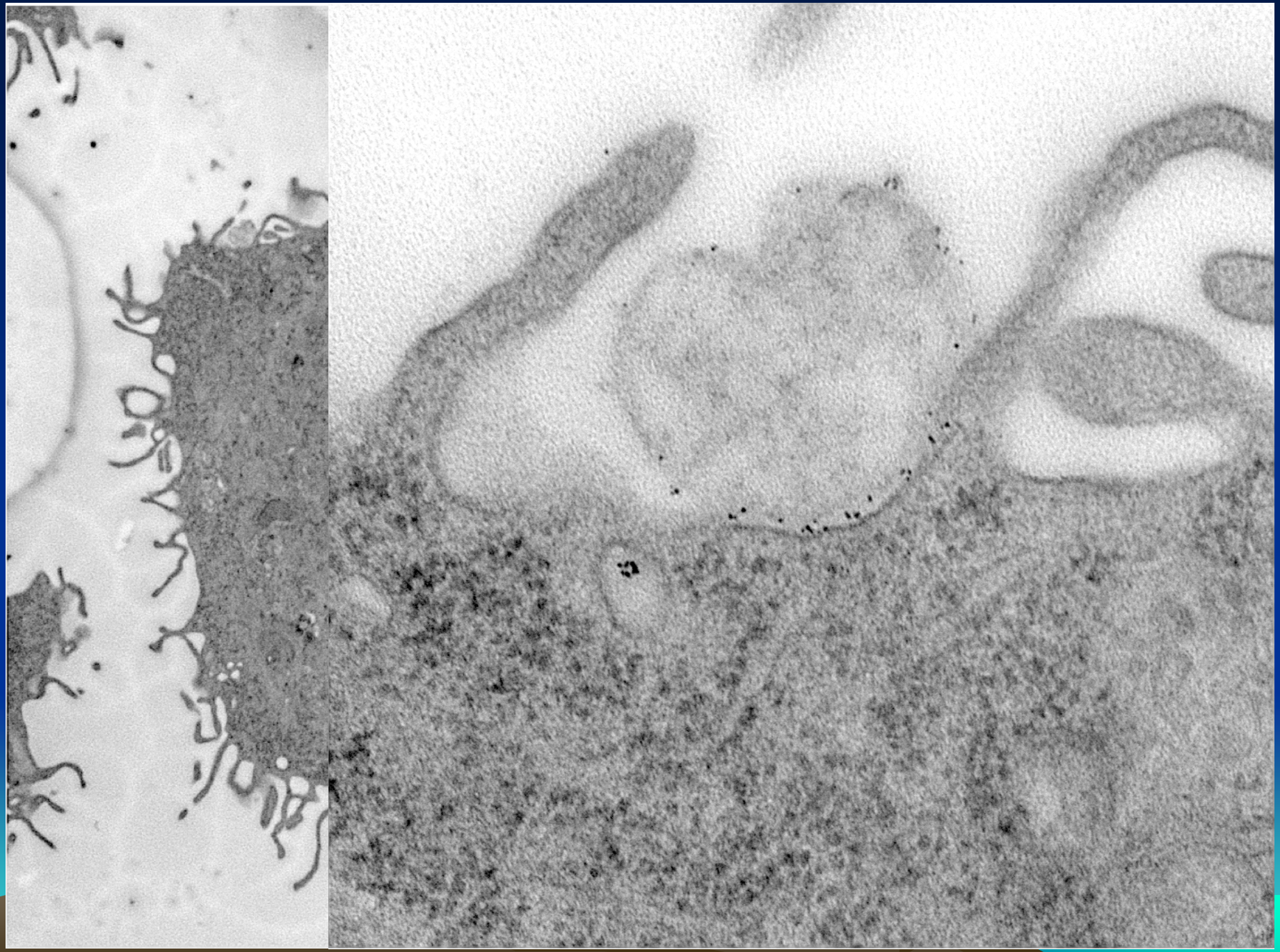
Targeted Gold Nanoparticles

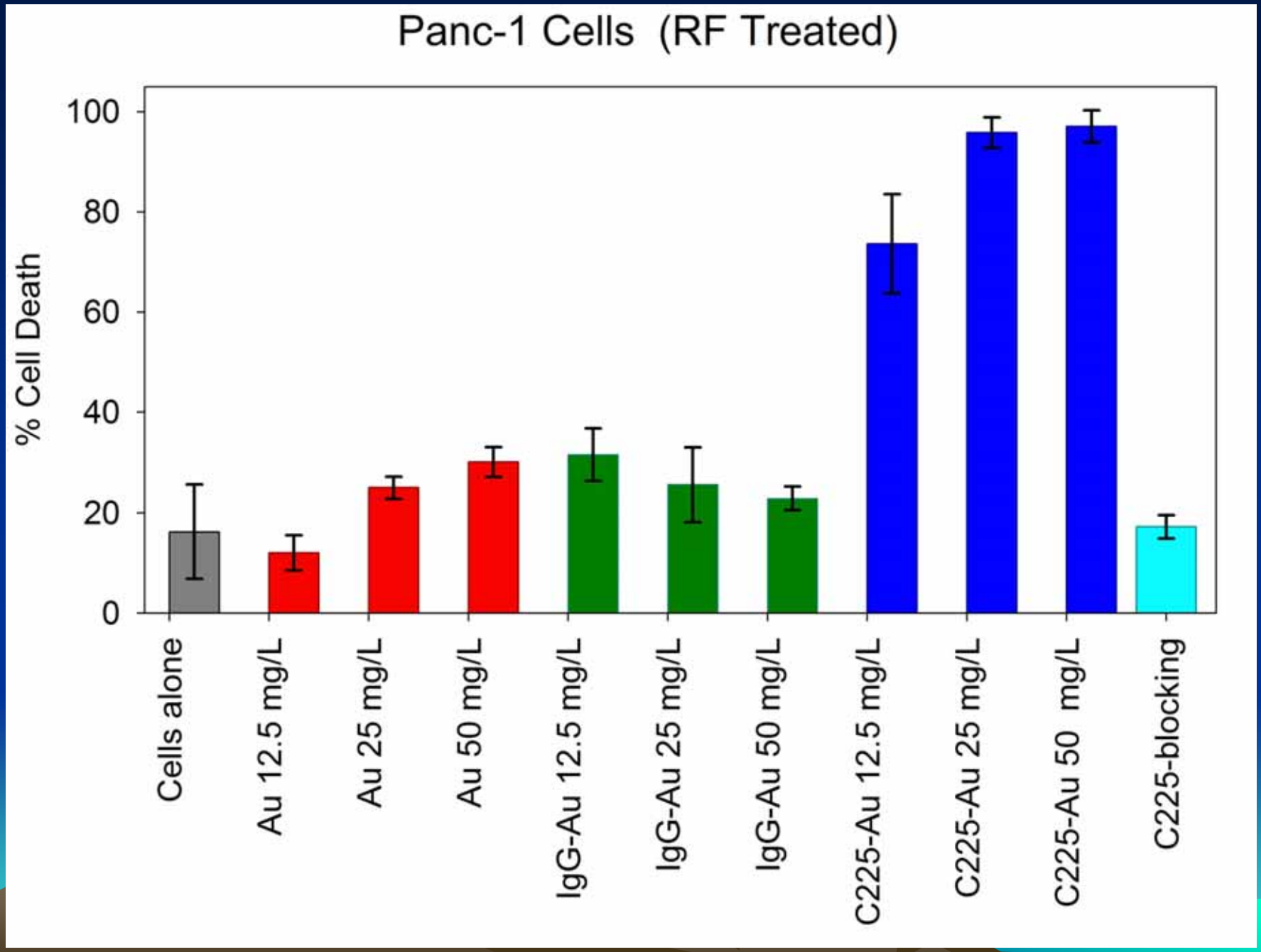


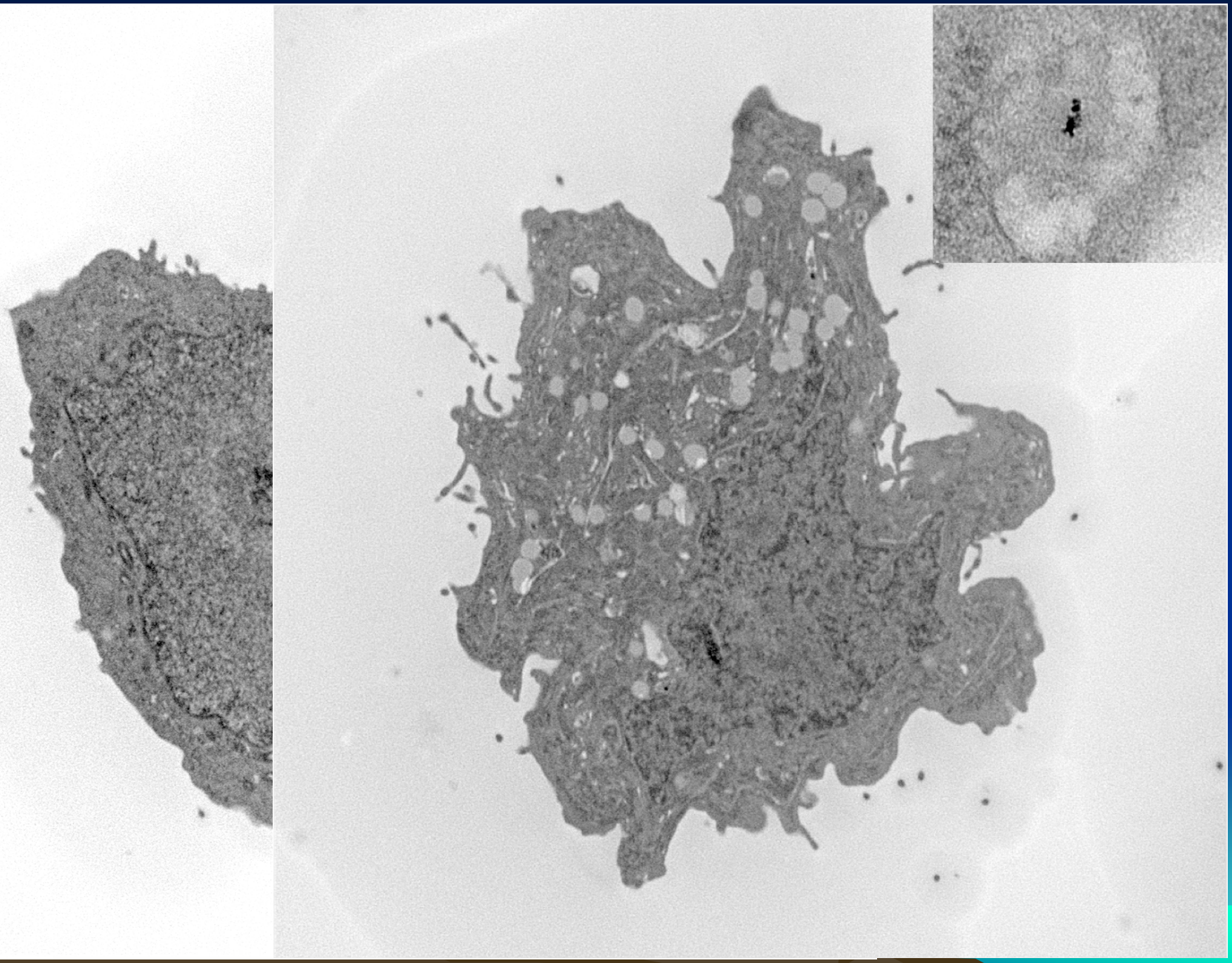
Western Blot for EGFR

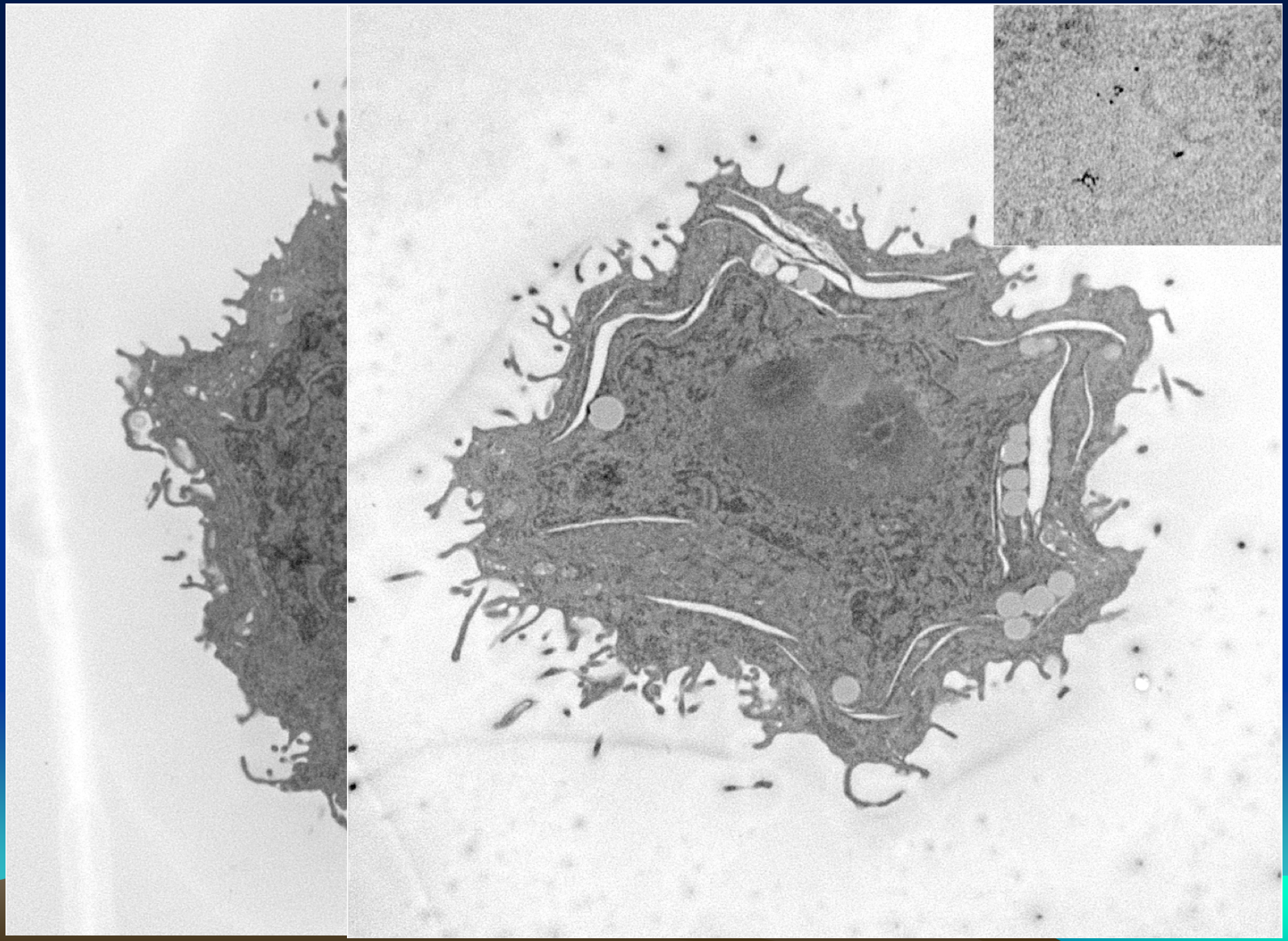


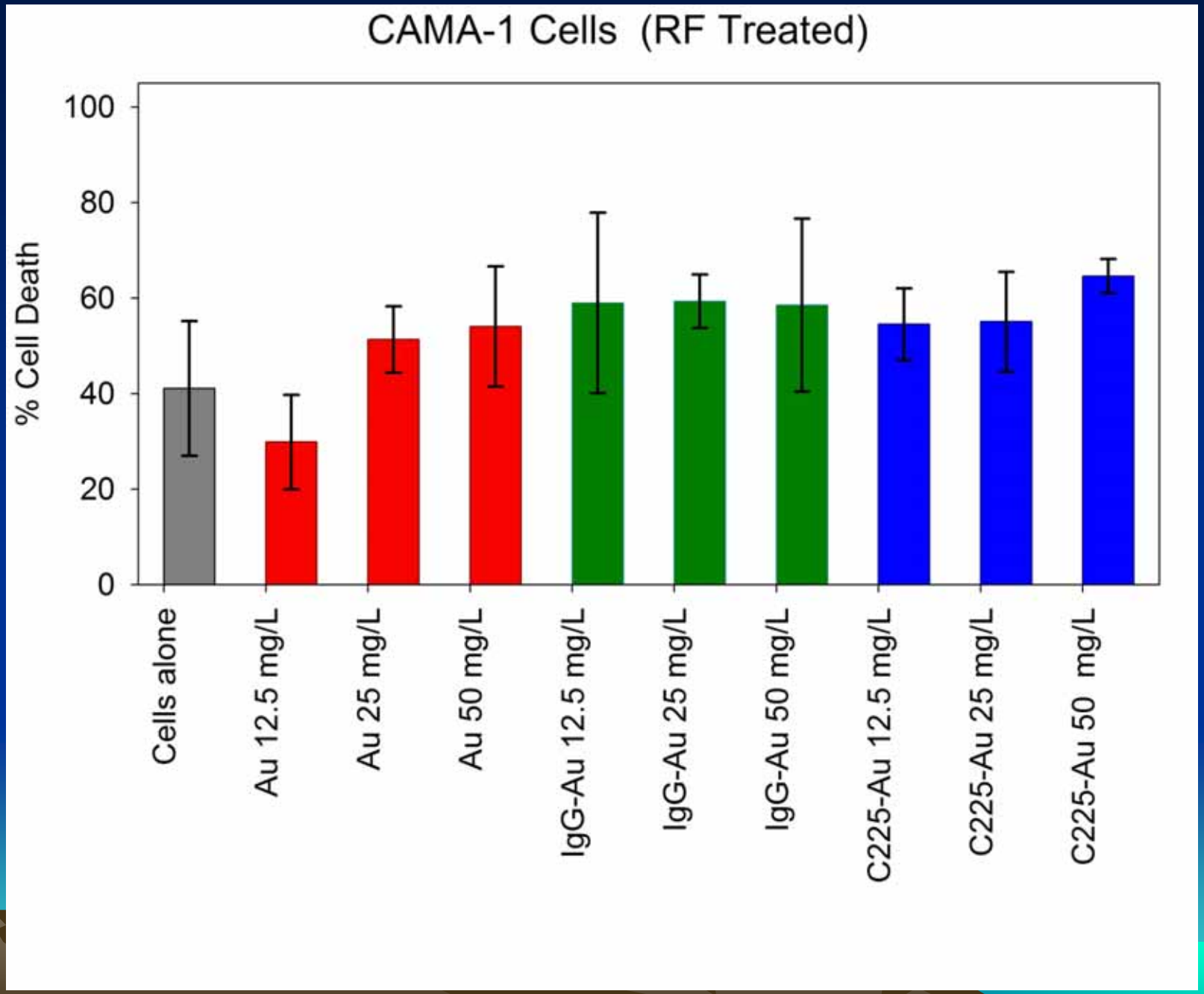





Panc-1 Cells (RF Treated)
% Cell Death
100
80
60
40
20
0
Cells alone
Au 12.5 mg/L
Au 25 mg/L
Au 50 mg/L
IgG-Au 12.5 mg/L
IgG-Au 25 mg/L
IgG-Au 50 mg/L
C225-Au 12.5 mg/L
C225-Au 25 mg/L
C225-Au 50 mg/L
C225-blocking

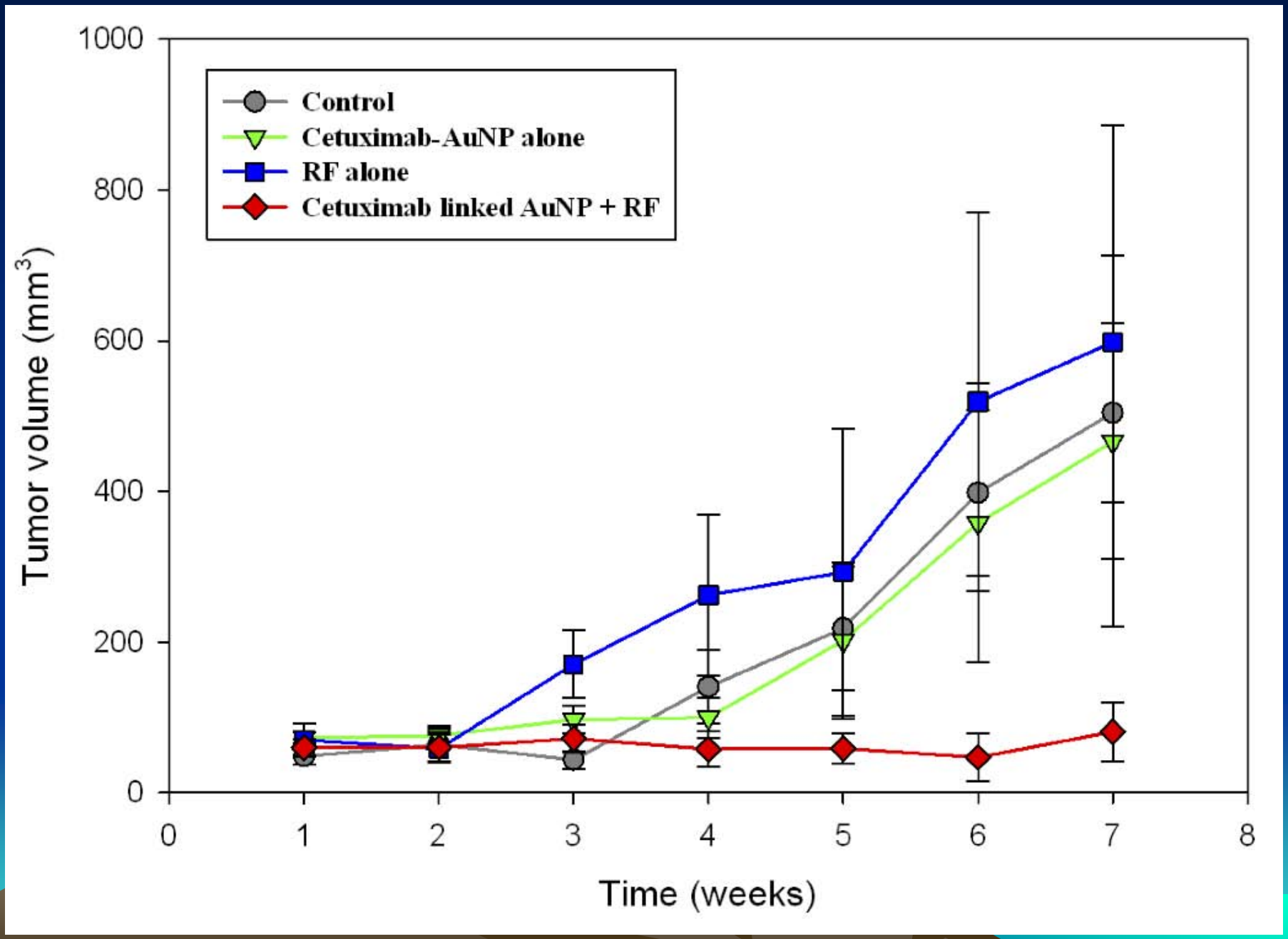





CAMA-1 Cells (RF Treated)
% Cell Death
100
80
60
40
20
0
Cells alone
Au 12.5 mg/L
Au 25 mg/L
Au 50 mg/L
IgG-Au 12.5 mg/L
IgG-Au 25 mg/L
IgG-Au 50 mg/L
C225-Au 12.5 mg/L
C225-Au 25 mg/L
C225-Au 50 mg/L

The So What Questions

- Are there long-term toxicities associated with nanoparticles?
- Can we reliably attach cancer-targeting molecules to the nanoparticles?
- Can we specifically target a variety of different cancer types, in a variety of individual patients?
- Will nanotechnology approve our ability to diagnose and treat cancer patients?


Control
Cetuximab-AuNP alone
RF alone
Cetuximab linked AuNP + RF
Tumor volume (mm3)
Time (weeks)
0
200
400
600
800
1000
0
1
2
3
4
5
6
7
8

Thank You!