Integrations of Different Technology Platforms (Enabling Technologies) in Solving Complex Clinical Problems:

The Road to Better Disease Managements

Shaker A. Mousa, PhD, MBA, FACC, FACB

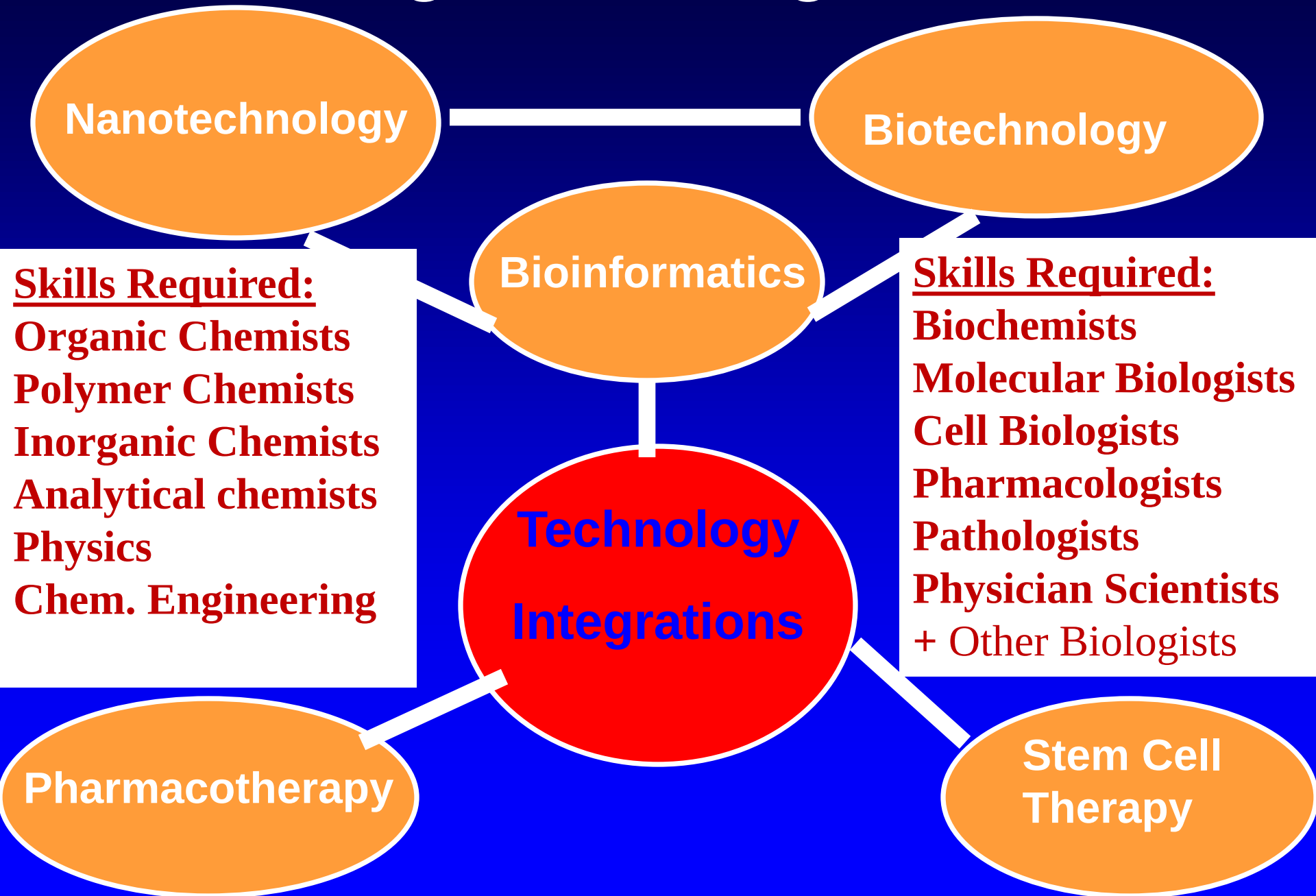
Pharmaceutical Research Institute (PRI)

Albany College of Pharmacy and Health Sciences

State University of New York at Albany (UAlbany) &

Rensselaer Polytechnic Institute (RPI)

Enabling Technologies: R & D



The Pharmaceutical Research Institute

(1 Discovery Drive, Rensselaer, NY)

PRI - Development

CFG

PRI Discovery

UAlbany College of Nanoscale Science & Engineering

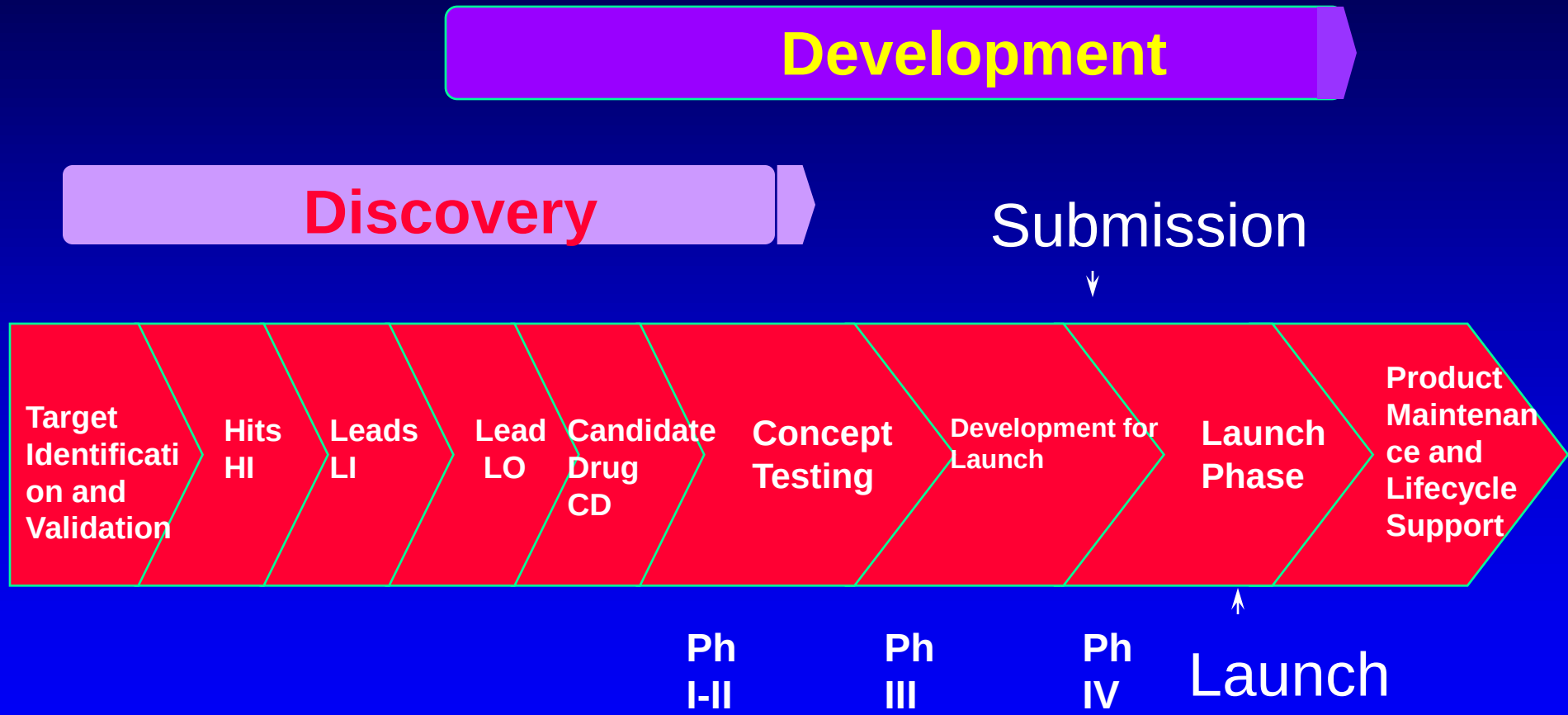
UAlbany CNSE: *At-a-glance*

- Founded 2004
- Faculty: ~50 and growing
- Degree Programs:
  - PhD in Nanoscale Science
  - PhD in Nanoscale Engineering
  - MS in Nanoscale Science
  - MS in Nanoscale Engineering
  - MS/MBA (Nano + Business)
  - BS Nanoscience (new!)

UAlbany CNSE: *Infrastructure*

- 800,000 sq ft in facilities
  - 80,000 sq ft of 300mm wafer clean rooms
- Shared-use, co-location model
  - Partners include SEMATECH, IBM, AMD, Global Foundries, Tokyo Electron, ASML, Applied Materials, among more than 250 international companies
- Over $5B in assets, Over 2,500 employees within the complex

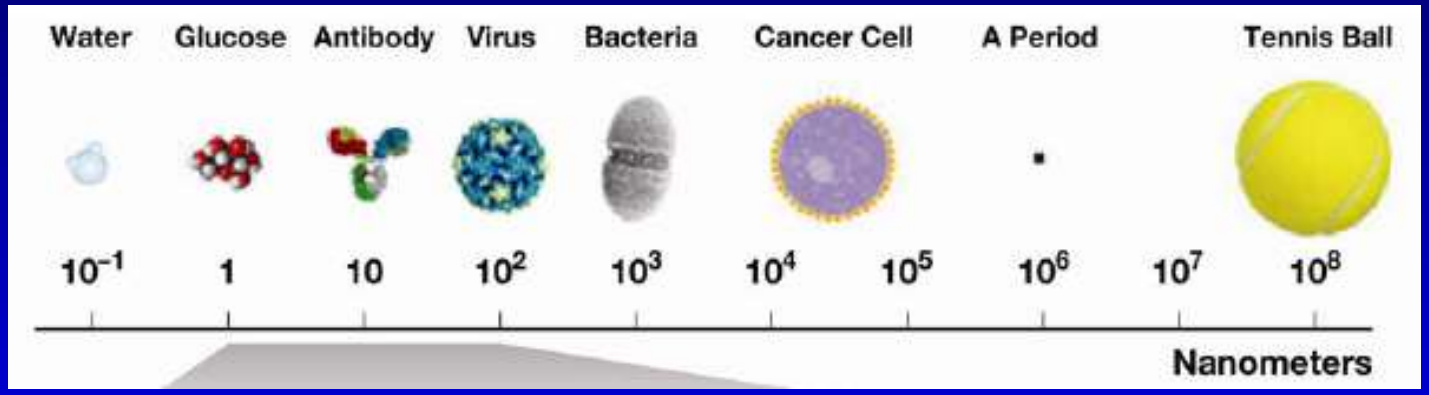
Drug Discovery and Development



Can Nanobiotechnology Shorten Time to Development ?

"Nano" – From the Greek word for "dwarf" and means for 10^{-9}, or one billionth. In this case it refers to 10^{-9} meters, or 1 nanometer (nm). 1 nm is about 3 atoms long.

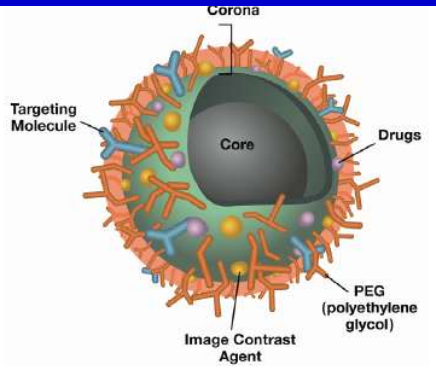
"Nanotechnology" – The science of manufacturing materials and machines at the nanometer, or atomic/molecular, scale.



Why Nano?

Therapeutic Benefits

- Solubility
  - Carrier for hydrophobic entities
- Multifunctional capability
- Active and passive targeting
  - Ligands; size exclusion
- Reduced toxicity

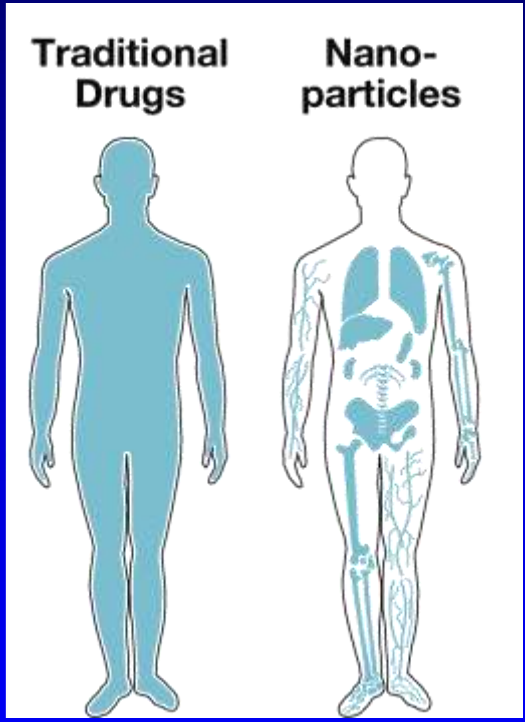


McNeil, (2005), J. Leuk. Biol., 78:585-594

↑Solubility ↑Stability ↑Specificity = ↓Toxicity ↑Efficacy

Why Nano?

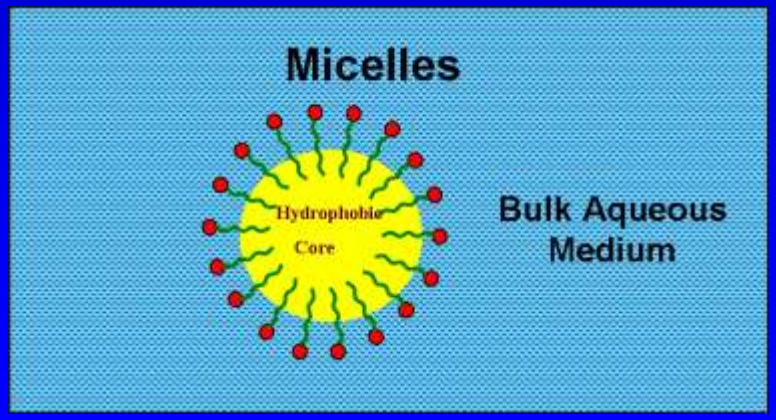
- Multi-functionality: targeting delivery
- Improve therapeutic effects
- Lower toxic side effects
- Ability to delivers multiple drugs directly
- Enables gene delivery
- Enables non-drug therapies (photo-thermal, photodynamic etc.)

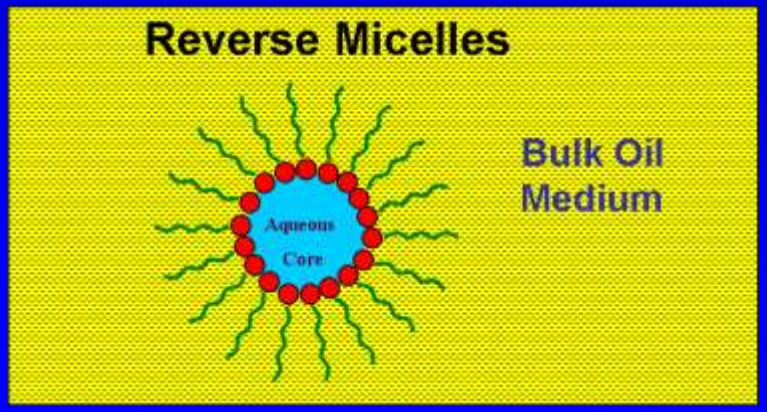


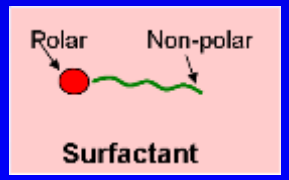
Nanoparticles & Applications

- Drug Delivery
- Gene Therapy
- Imaging

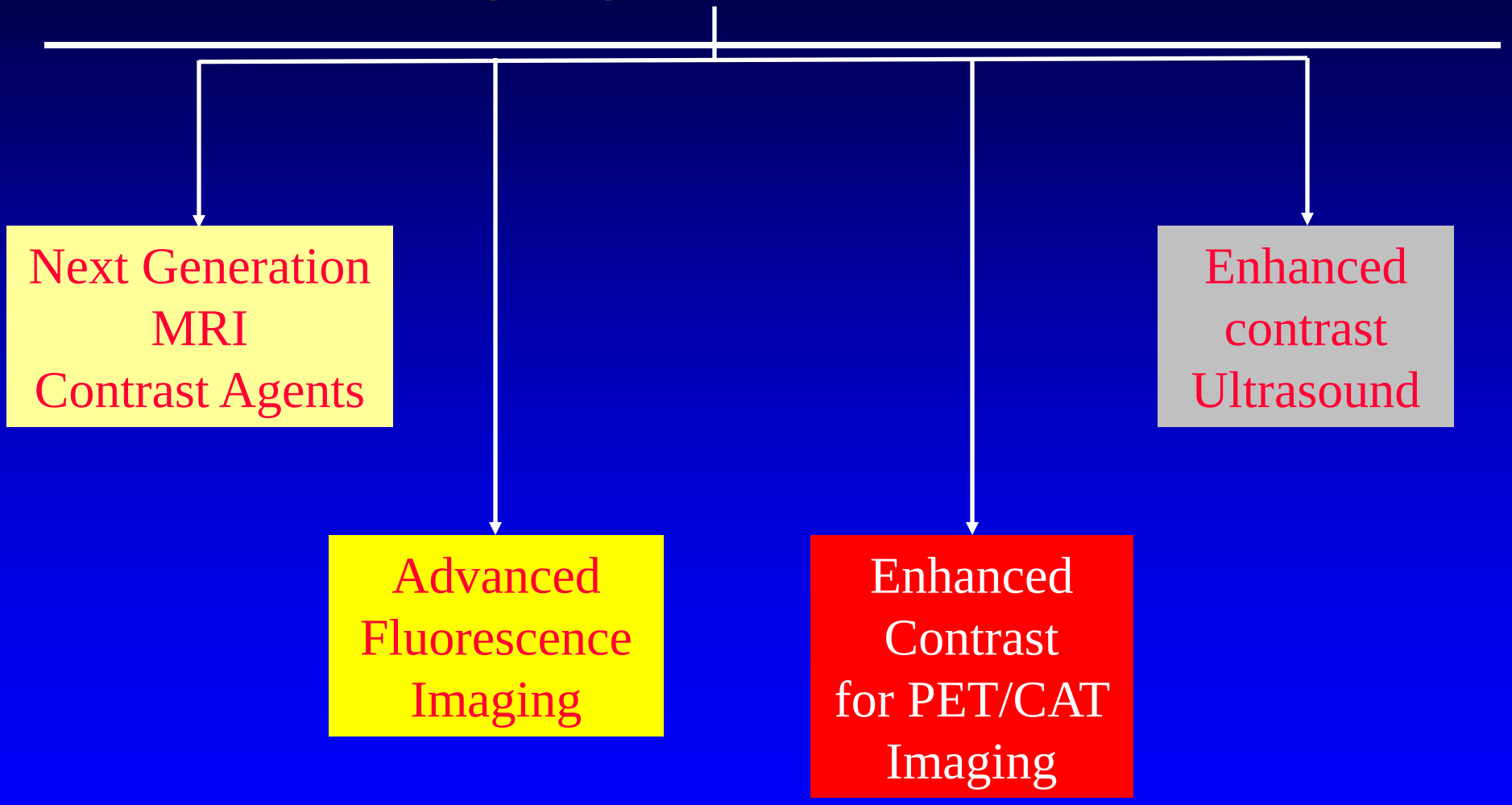
Synthesis of the nanoparticles





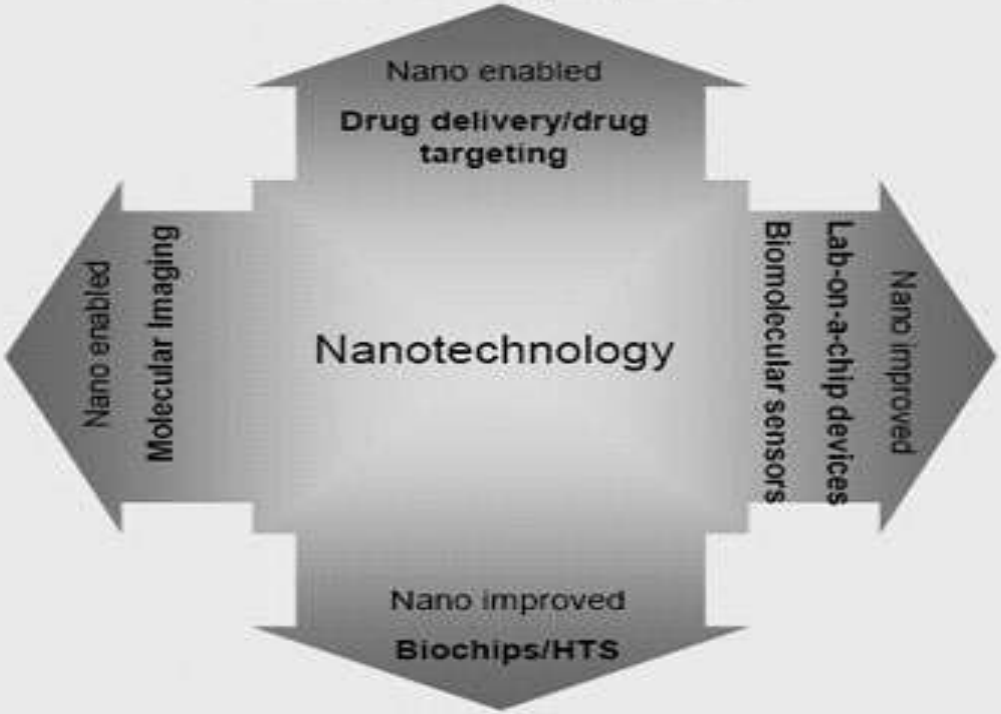


Nanoparticles / Nanoprobes for Medical Imaging and Biosensors



Improving Health Outcomes

- Less side effects
- Specific and more efficient therapies
- Shortened therapy duration
- "Solubilisation" of insoluble agents
- Diminished drug degradation



- Early state diagnostics
- New imaging technologies (e.g. online monitoring)
- Drug distribution monitoring/ drug effect control
- Less side effects
- Enhanced specificity

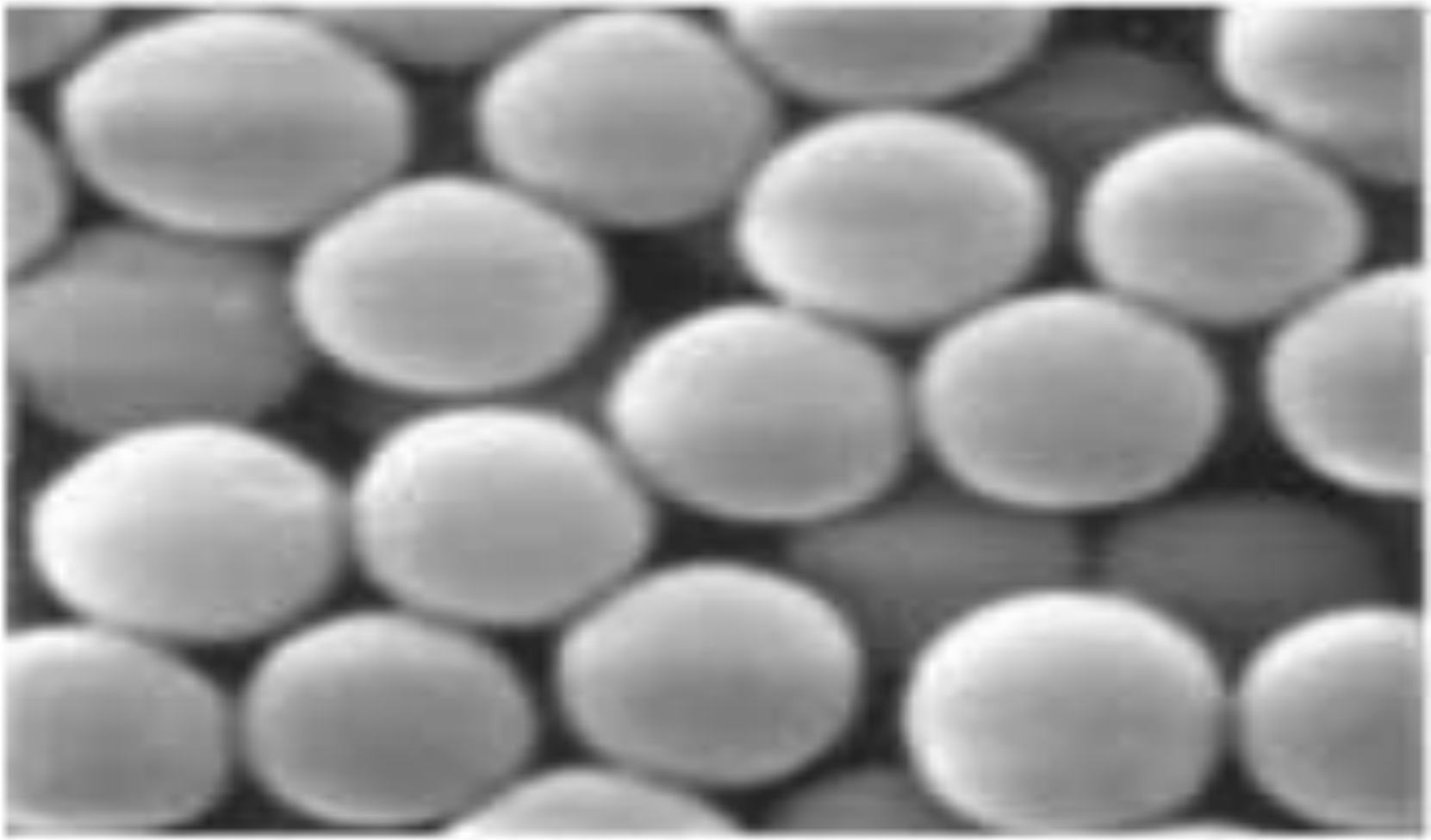
- Early state diagnostics
- More efficient therapies
- Shortened therapy duration
- Theranostics
- Enabled biocompatibility
- More specific diagnostics

- More specific acting drugs
- Increased knowledge about the cellular machinery

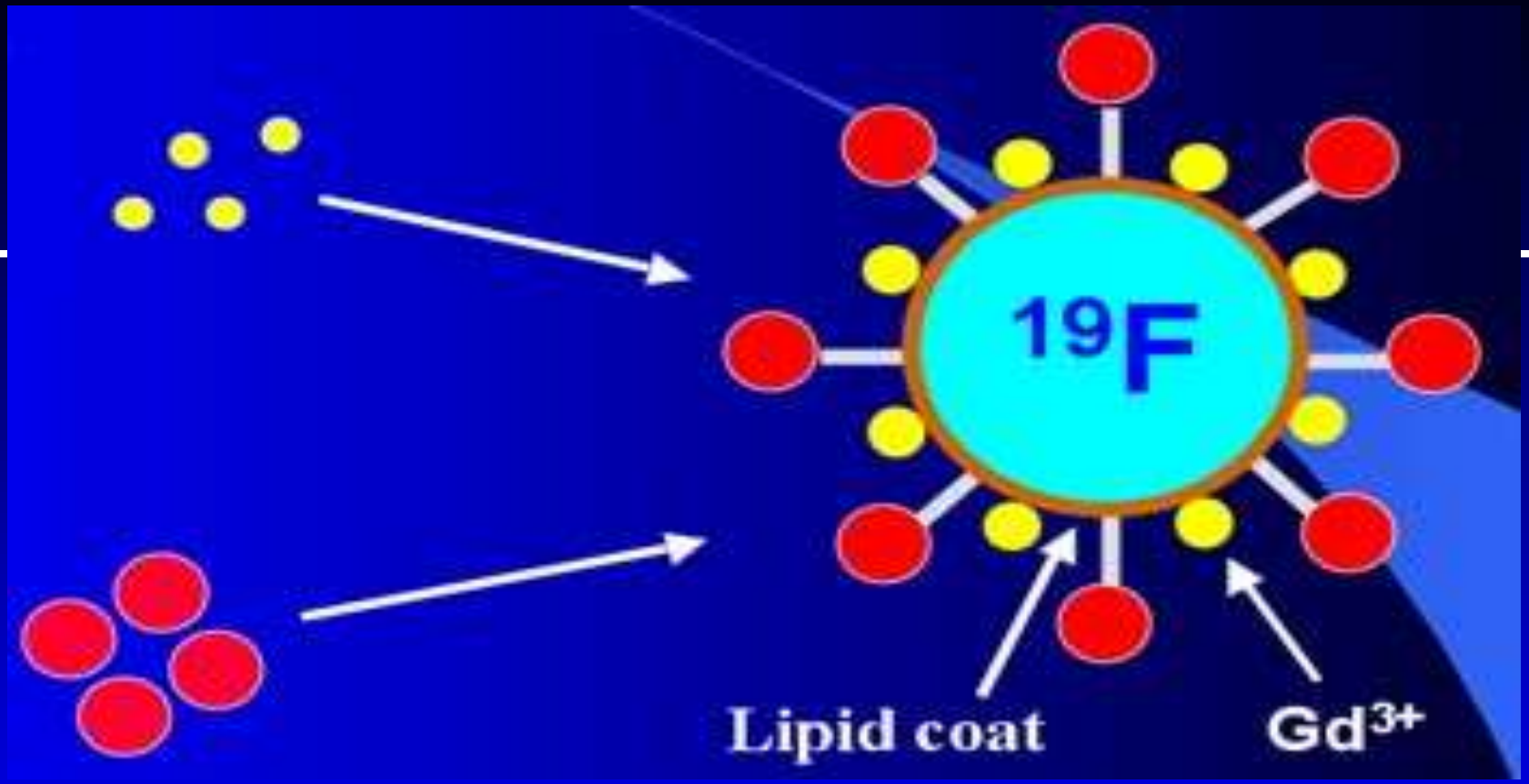
Current ongoing Project at PRI in Nanobiotechnology

Early Detection, Prevention, and Treatment

1. Development of Oral vaccine formulation for Hepatitis B and C.
2. Targeted delivery to the Liver (fibrosis, cirrhosis, hepatic carcinoma, and hepatitis C virus)
3. Targeted delivery of Chemotherapy loaded Nano for pancreatic, breast, and prostate cancer for early detection and therapeutics
4. Site Directed delivery of novel targets in Osteoporosis and Bone disorders



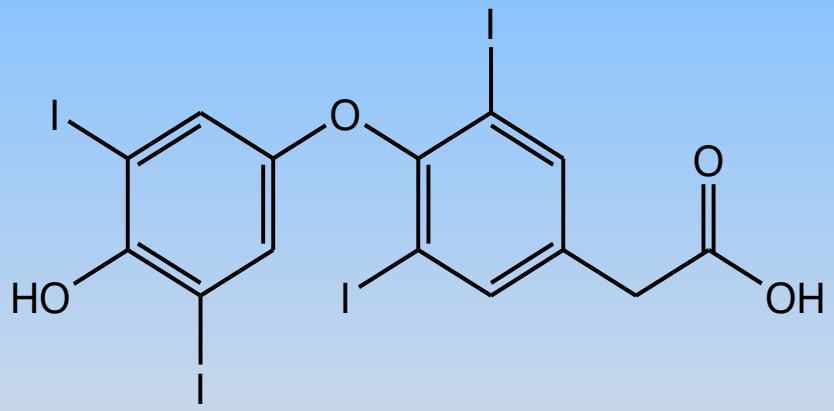
Could nanoparticles provide promising treatment of Hepatitis C and Its complications (fibrosis, Cirrhosis and hepatic carcinoma ?



Nanoparticles can be loaded with a variety of molecules, including imaging agents and drugs. By also attaching molecules that serve as "zip codes", these nanoparticles can be programmed to find particular cells

Re-formulation of an Old Hormone
Thyroid Hormone agonists and antagonists

T-4



Tetrac

Pro-angiogenesis Effect of T4, T4-Agarose, VEGF, and FGF2 in the CAM model (Mousa et al Circulation Research 2005)

PBS Control

T4 (0.1 μM)

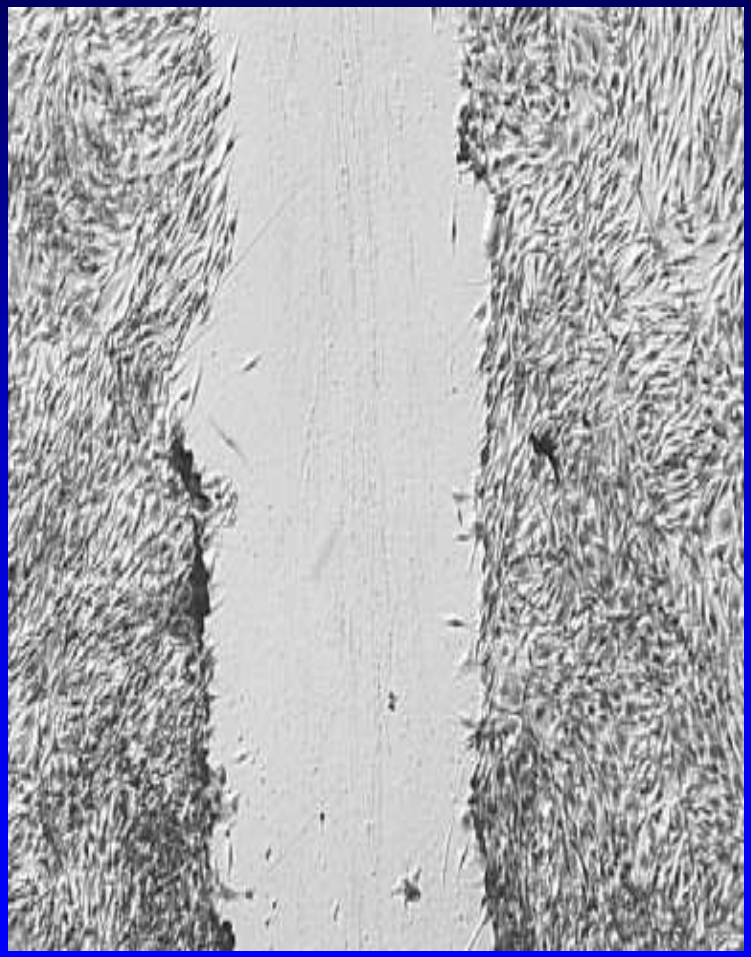
T4-Agarose (0.1 μM)

GC-1 (0.01 μM)

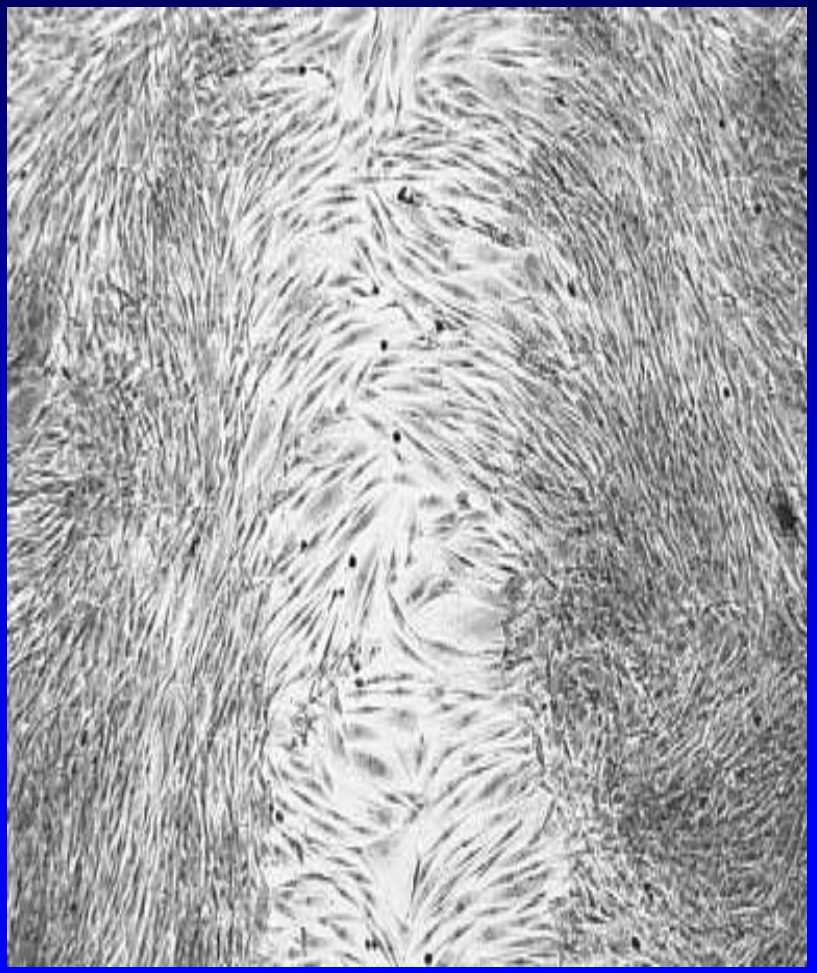
VEGF165 (2 μg)

FGF2 (1 μg)

Effect of T4-agarose on Wound healing in Human Dermal Fibroblast

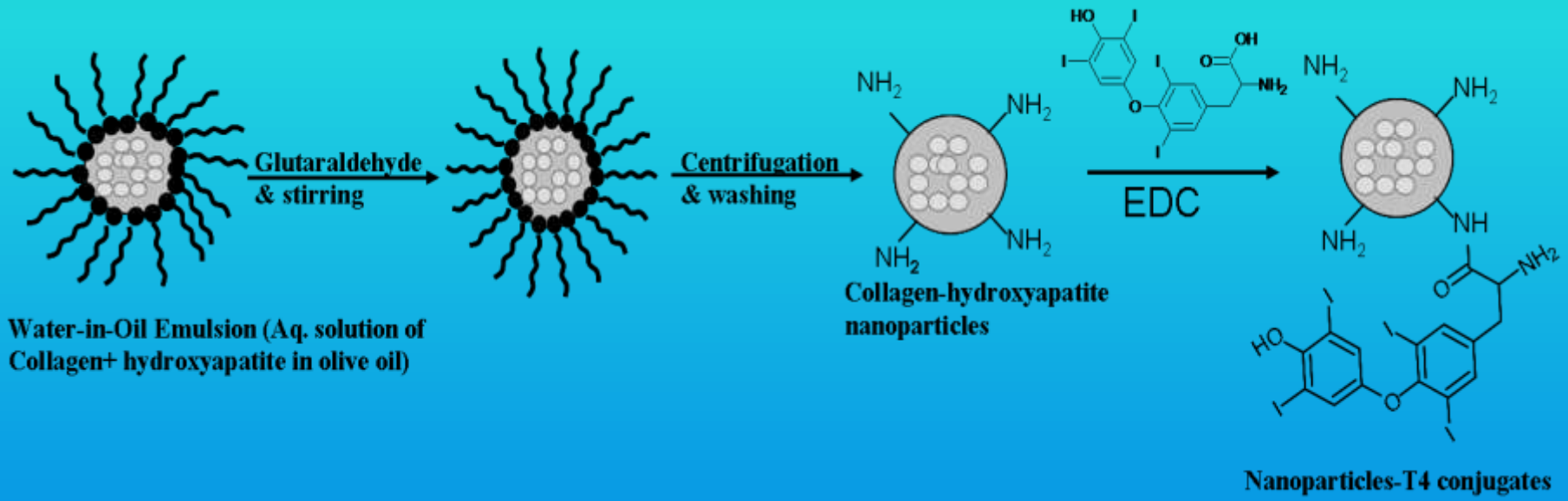


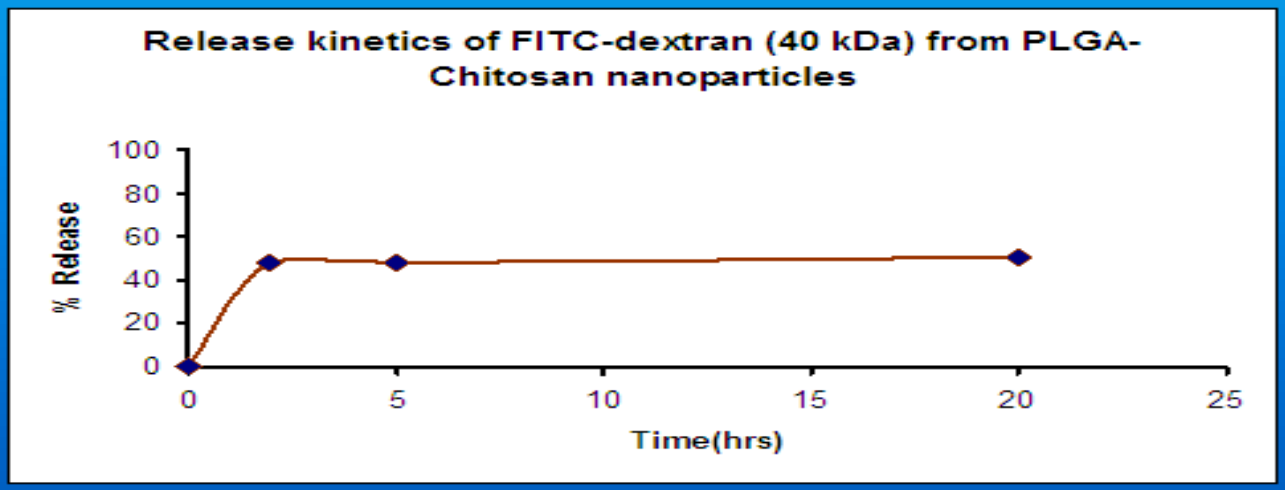
Control

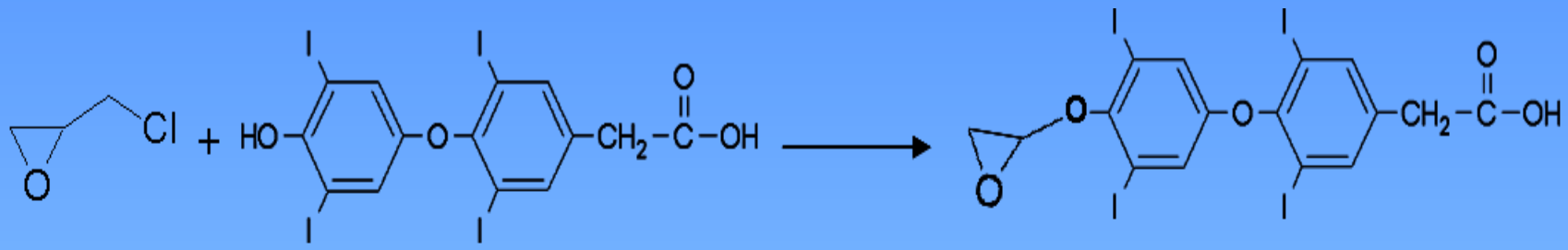


T4-agarose 0.01 μM

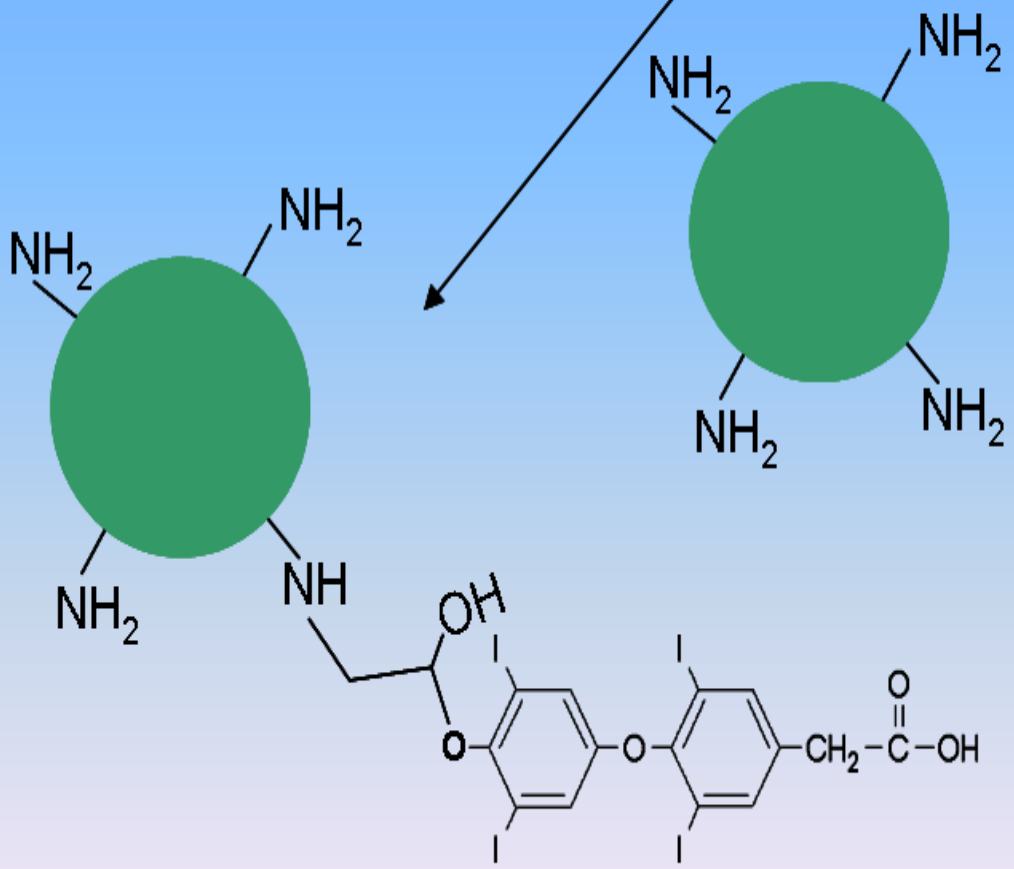
Collagen-hydroxyapatite and Chitosan nnanosphere conjugated to Thyroxine (L-T4) using carbidiimide chemistry



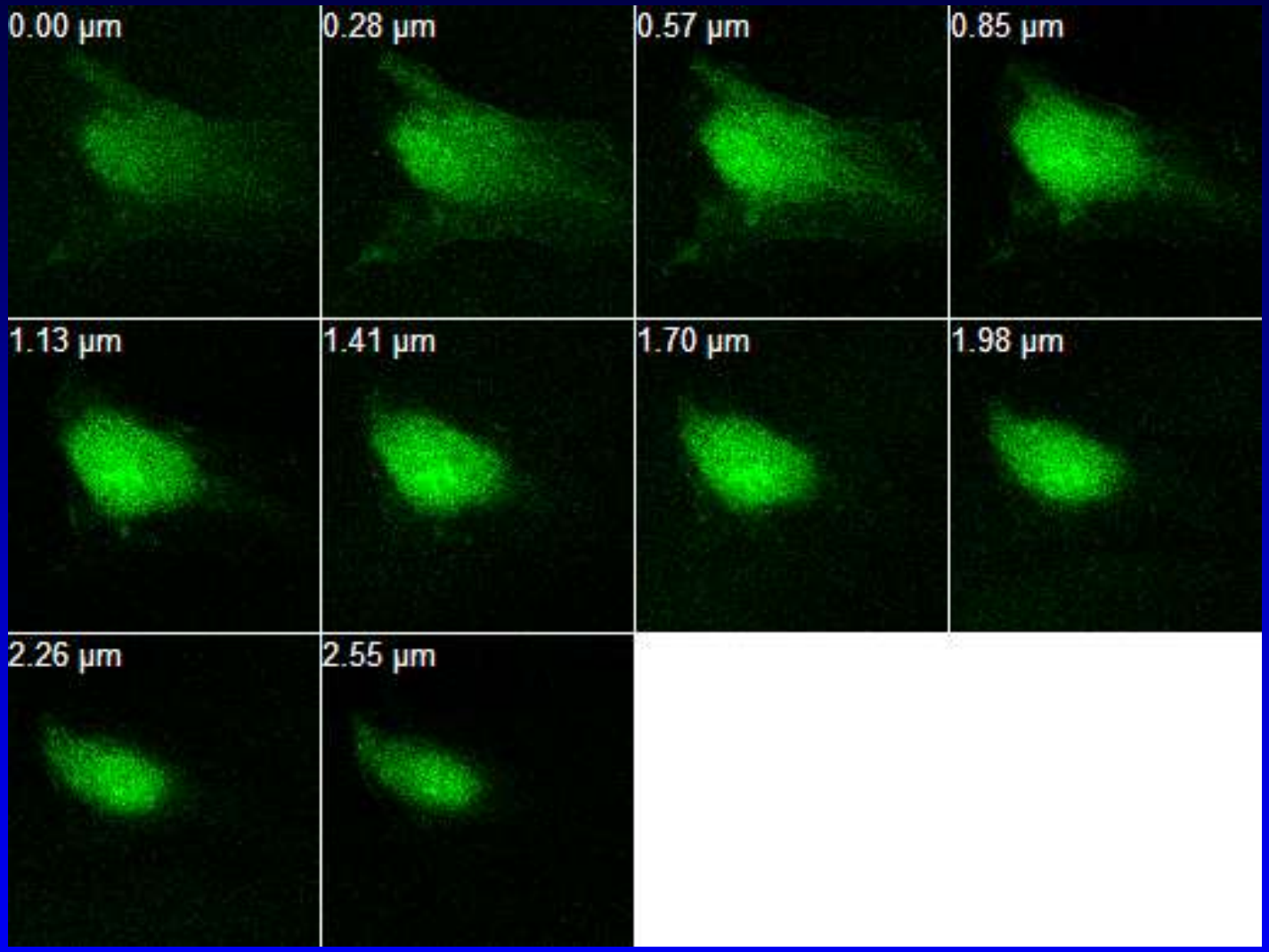




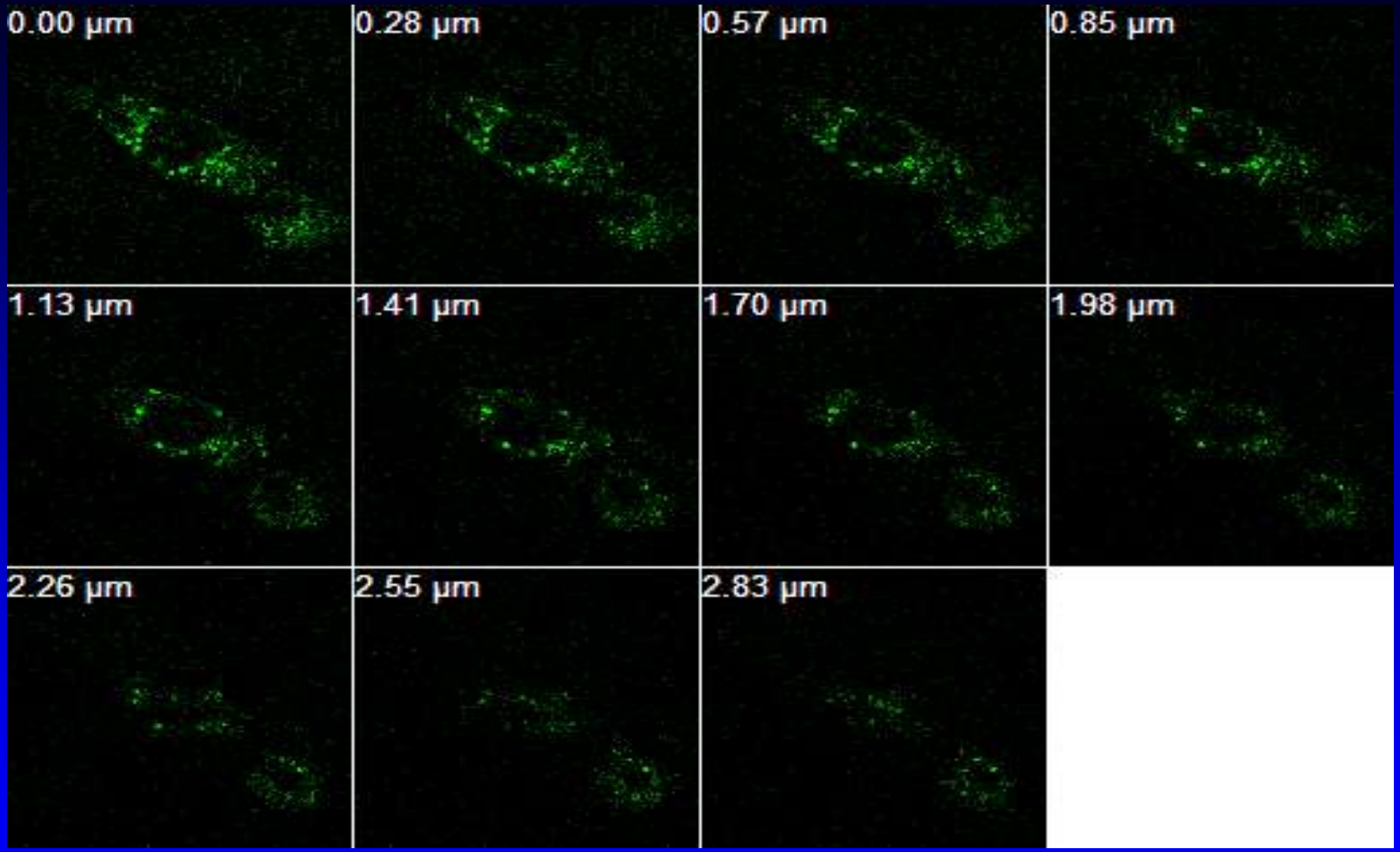
Epichlorohydrin **Tetrac** **Epoxy activated Tetrac**



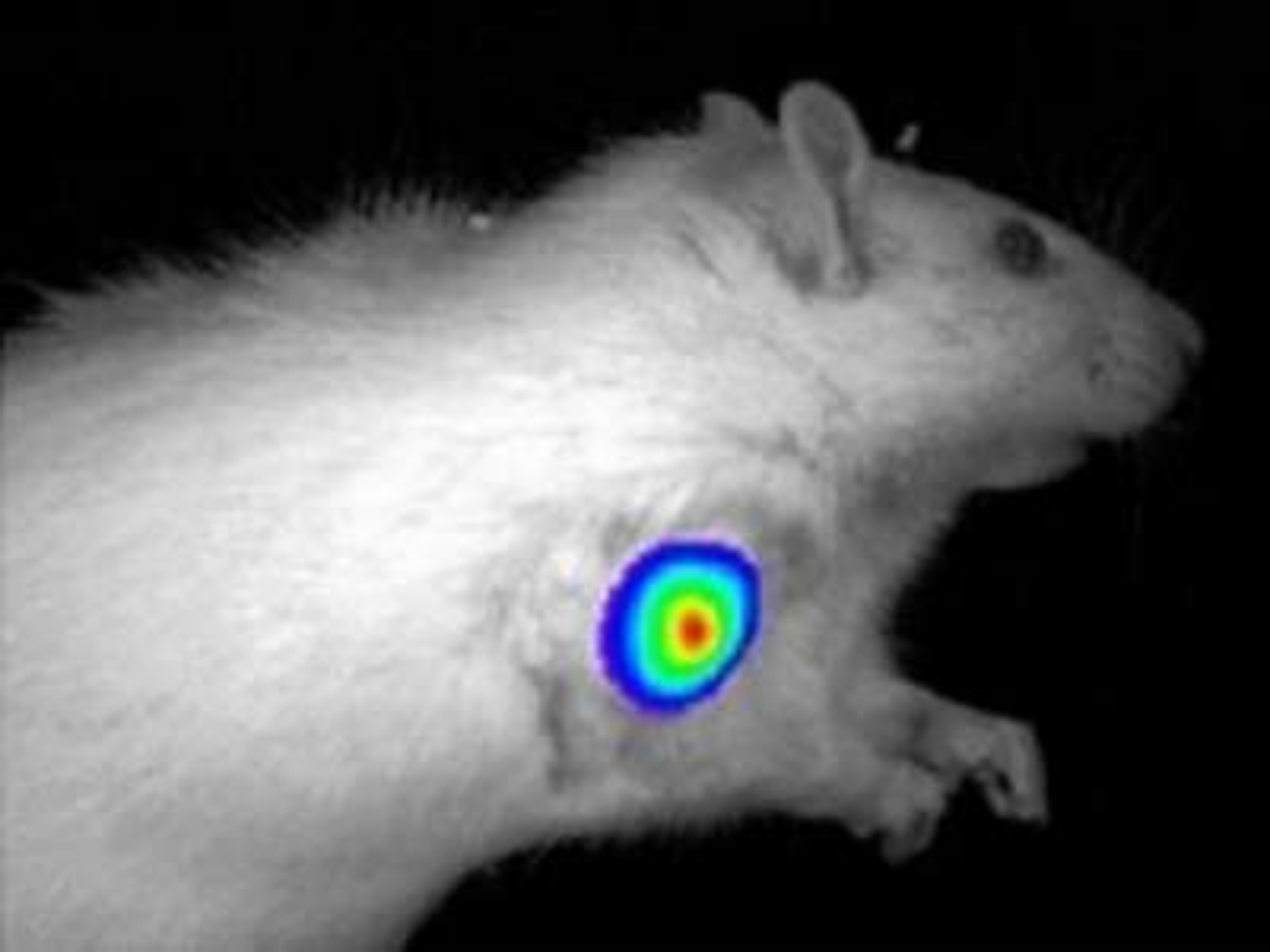
Tetrac conjugated PEG-PLGA nanoparticles



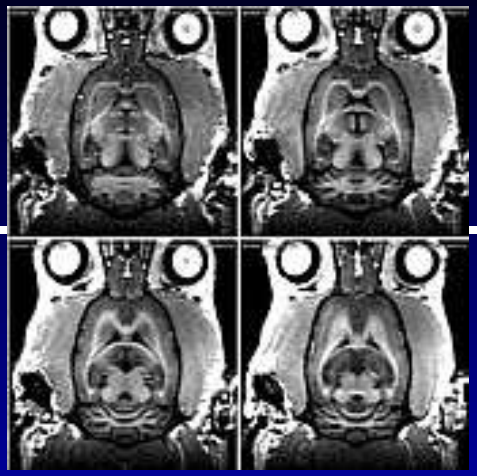
Z-stack image of Alexa flour labeled T4



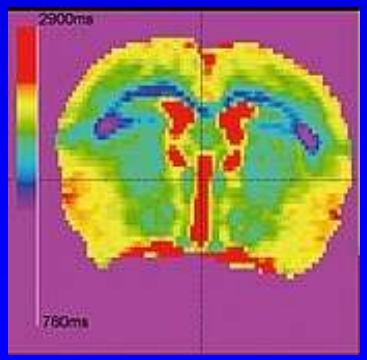
Z-stack Images of Alexa flour labeled T4Nanoparticles



Bio-Imaging



- 16cm 7T Pharmascan Horizontal MRI / MRS system

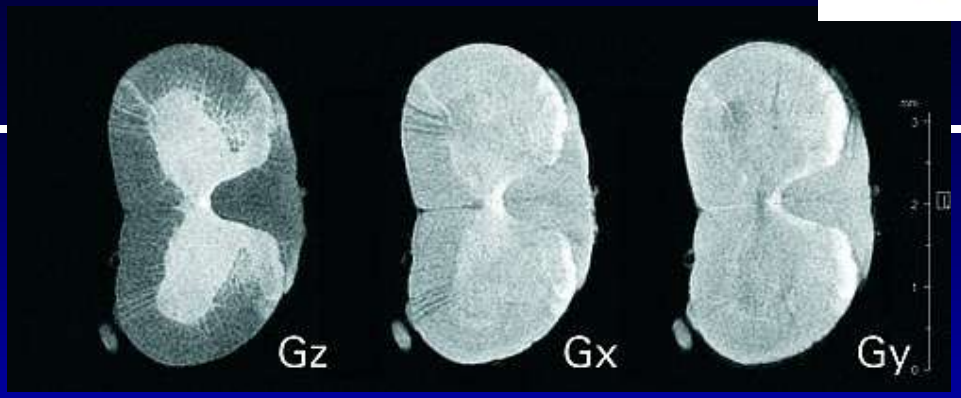


BTT-TIC

NMR: Microimaging / MRS

BTT-TIC

SS-NMR probe head



Diffusion Imaging: direction diffusion anisotropy experiment along three main axes. **Rat spinal cord**.

14T (600MHz) Wide-bore Solid-State NMR and Multichannel Heteronuclear Microimaging Spectrometer (Bruker)

- **exceptional sensitivity for imaging and MRS (spatially resolved NMR spectroscopy) studies of small animals, tissue samples and materials approaching µm range resolution.**

Whole body image of a Zebra fish.

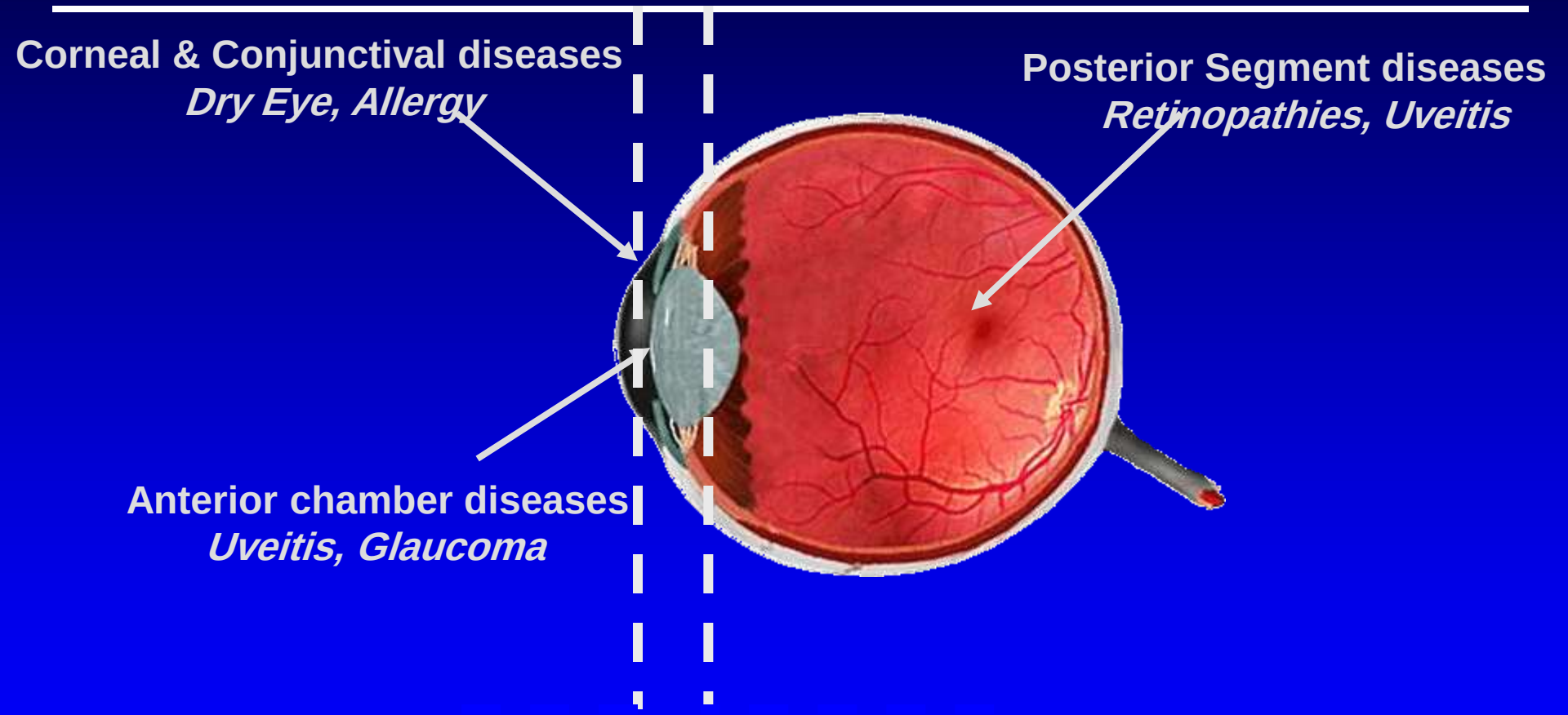
From Bench to Bedside: Innovation (2004 - Patents)-Spin Off's (2009)- Partnerships (2010)

- **Thyroid Agonists Nanoformulations Patents:**
  - Critical Limb Ischemia
  - Wound Healing
  - Foot Ulcer and other Ulcers
  - Coronary Artery Diseases (Coated Stent)
  - In Cardiac Arrest with Defibrillators
- **Thyroid Antagonists Nanoformulations Patents:**
  - Ocular Disorders (Diabetic Retinopathy, AMD)
  - Oncology (Solid tumors) – Under clinical Development for Glioma
  - Dermatology (Psoriasis, skin cancer, Varicose vein,..) – Clinical Trial
  - Osteoporosis

Spin Off's 2009 (Thyrotech INC)

Raised $150 millions 2010

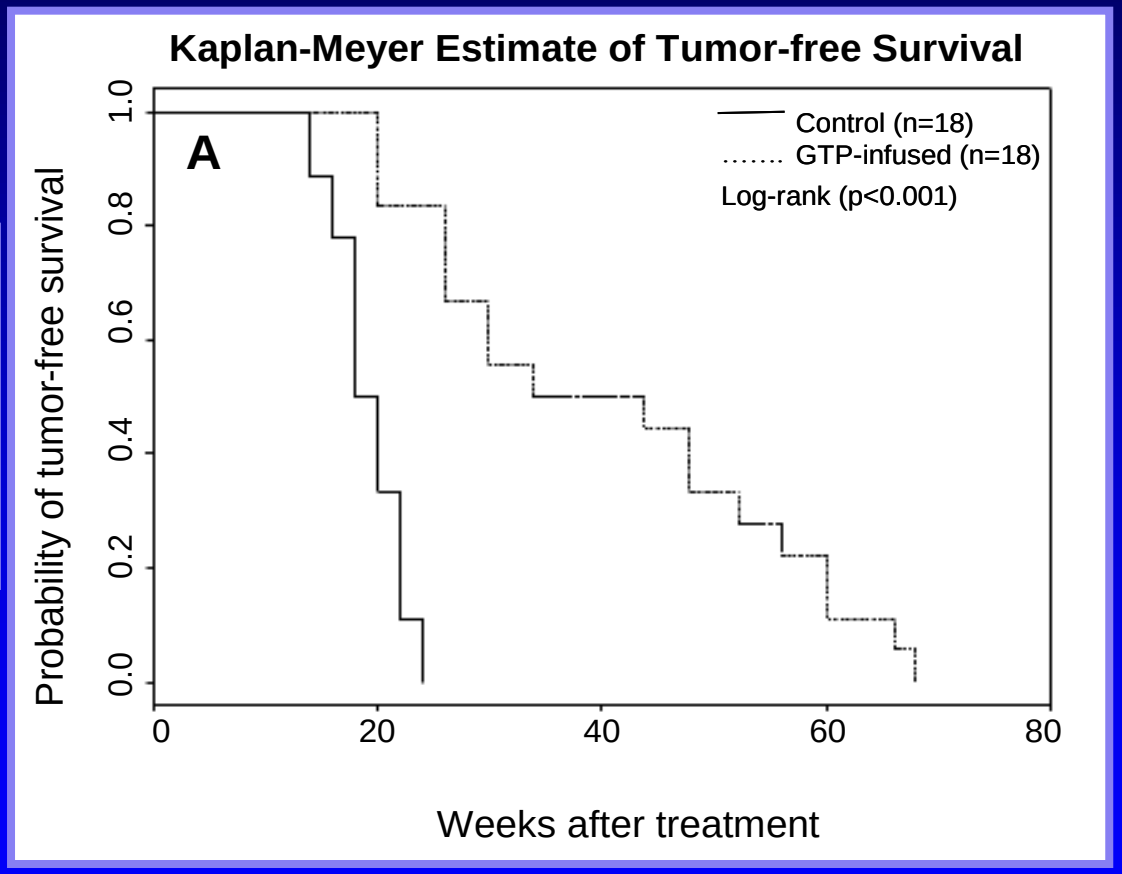
Cationic Nanoparticles reach all segments



PHYTOCOCKTAIL: A NEW MANTRA FOR PERSONALIZED CANCER PREVENTION

Effect of GTP on Tumor-free Survival

Water fed



GTP fed

Gupta et al: Proc. Natl. Acad. Sci. USA 98:10350-5, 2001

PEGylation (plyethelene glycol)

- Covalent attachment of Polyethylene Glycol polymer chains to a drug or therapeutic protein.
- Characteristics of PEG moieties:
  - Water solubility , High mobility in solution
  - Lack of toxicity and immunogenicity
  - Ready clearance from the body
  - Altered distribution in the body
- "mask" the agent from the host's immune system
- increasing the molecular weight of a molecule:
  - Improved solubility;
  - Reduced dosage frequency, Reduced toxicity;
  - Extended circulating life; Increased drug stability;
  - Enhanced protection from proteolytic degradation

PEG-ylated Drugs

- **PEGASYS:** PEGylated interferon alpha for use in the treatment of chronic hepatitis C and hepatitis B
- **Pegintron:** PEGylated interferon alpha for use in the treatment of chronic hepatitis C and hepatitis B
- **Oncaspar:** PEGylated L-asparaginase for the treatment of acute lymphoblastic leukemia in patients who are hypersensitive to the native unmodified form of L-asparaginase
- **Neulasta:** PEGylated recombinant methionyl human granulocyte colony-stimulating factor for severe cancer chemotherapy induced neutropenia
- **Doxil/Caelyx:** PEGylated liposome containing doxorubicin for the treatment of cancer

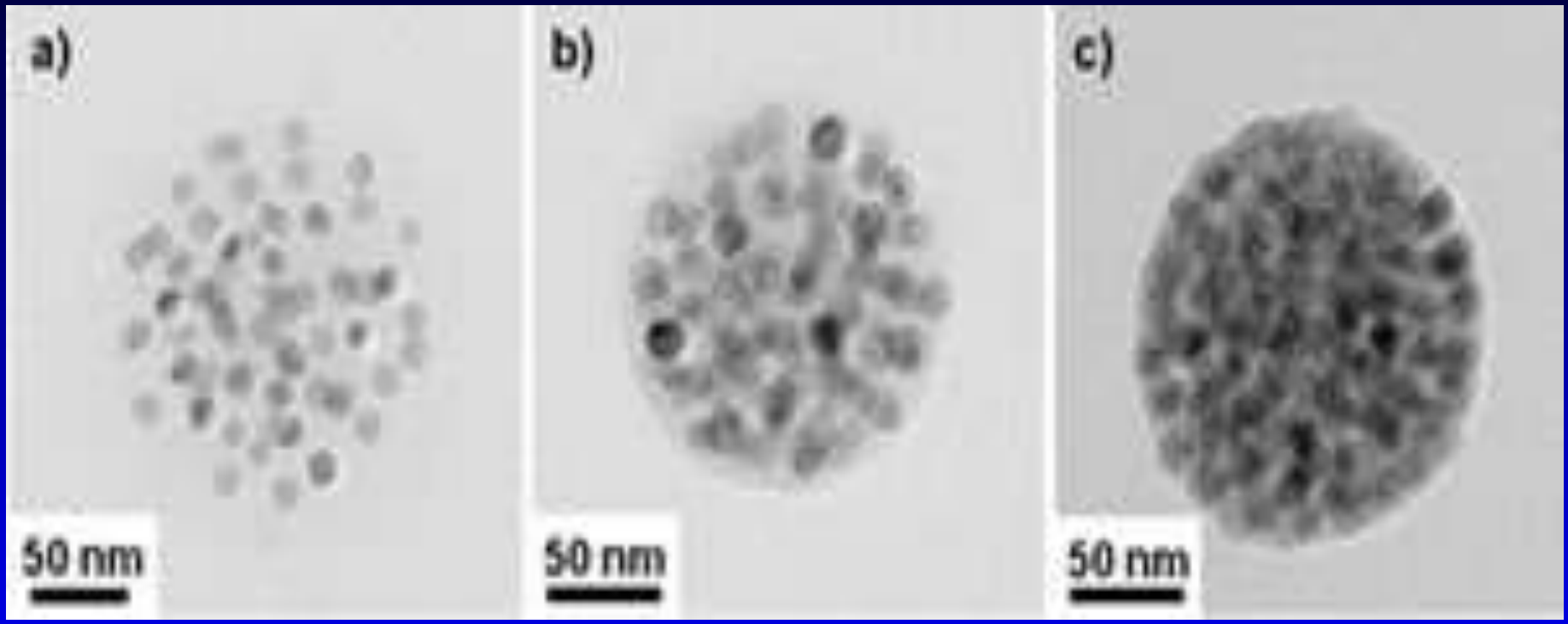
PLGA or poly (lactic-*co*-glycolic acid)

- Co-polymer
- Biodegradable, hydrolysis in the body
- Produce lactic acid and glycolic acid
- Minimal systemic toxicity using PLGA for drug delivery or biomaterial applications

PLGA in Clinical Use

- Grafts
- Sutures
- Implants
- Prosthetic devices
- Drugs
  - Lupron, depot injection

PLGA nanoparticles



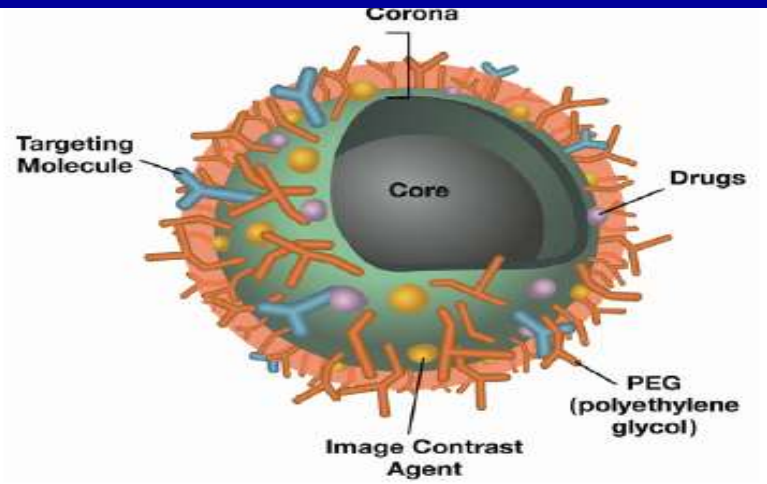
- Tunneling electron microscope images of PLGA nanoparticles-containing **different amounts** of magnetite nanocrystals
- Allow the PLGA nanoparticle to be viewed under MRI and guided towards cancer cells using a magnetic field.

Why Nano?

Targeted Delivery

Therapeutic Benefits

- Solubility
  - Carrier for hydrophobic entities
- Multifunctional capability
- Active and passive targeting
  - Ligands; size exclusion
- Reduced toxicity



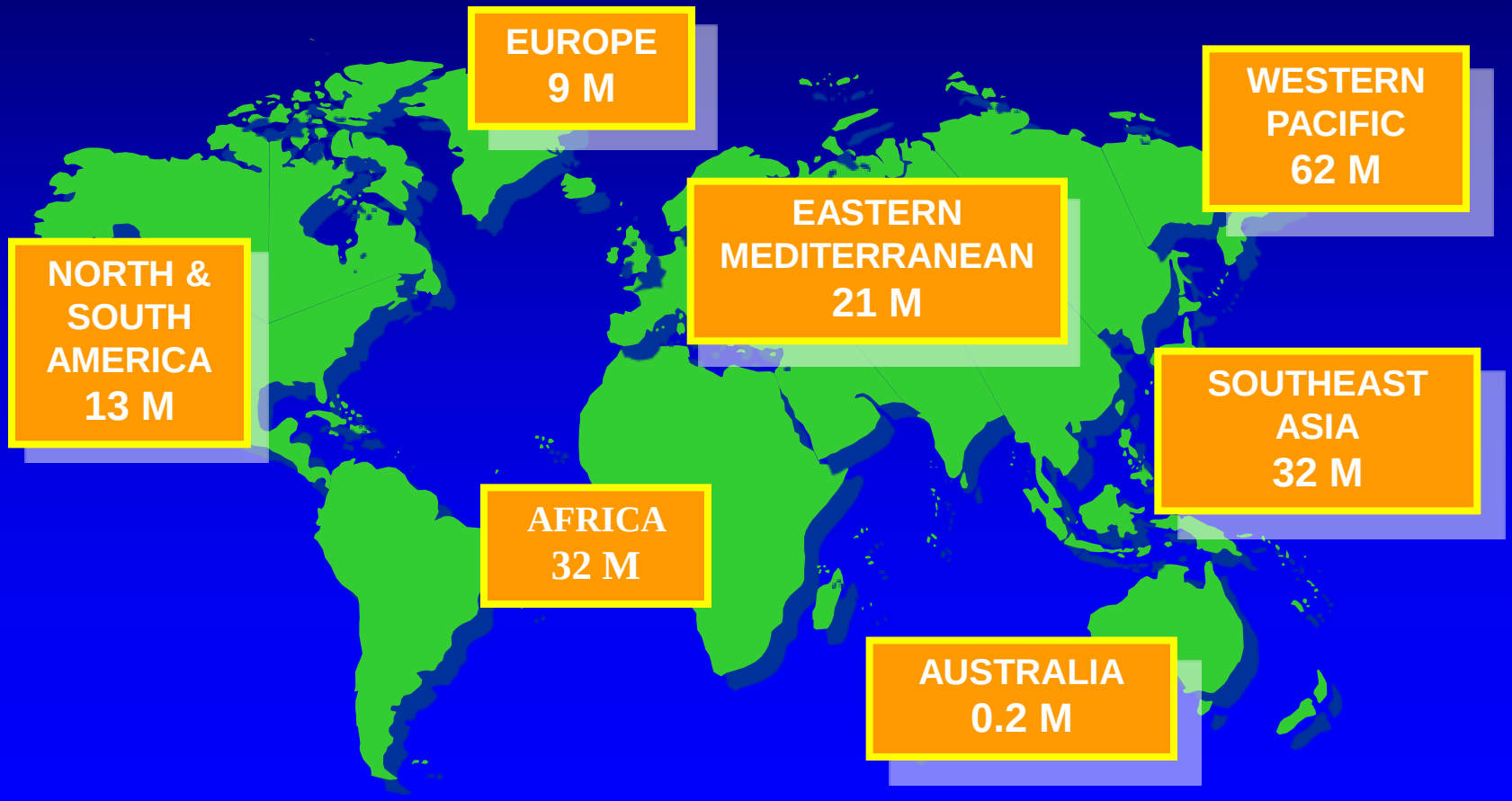
McNeil, (2005), J. Leuk. Biol., 78:585-594

↑Solubility ↑Stability ↑Specificity = ↓Toxicity ↑Efficacy

Hepatitis C: A Global Health Problem

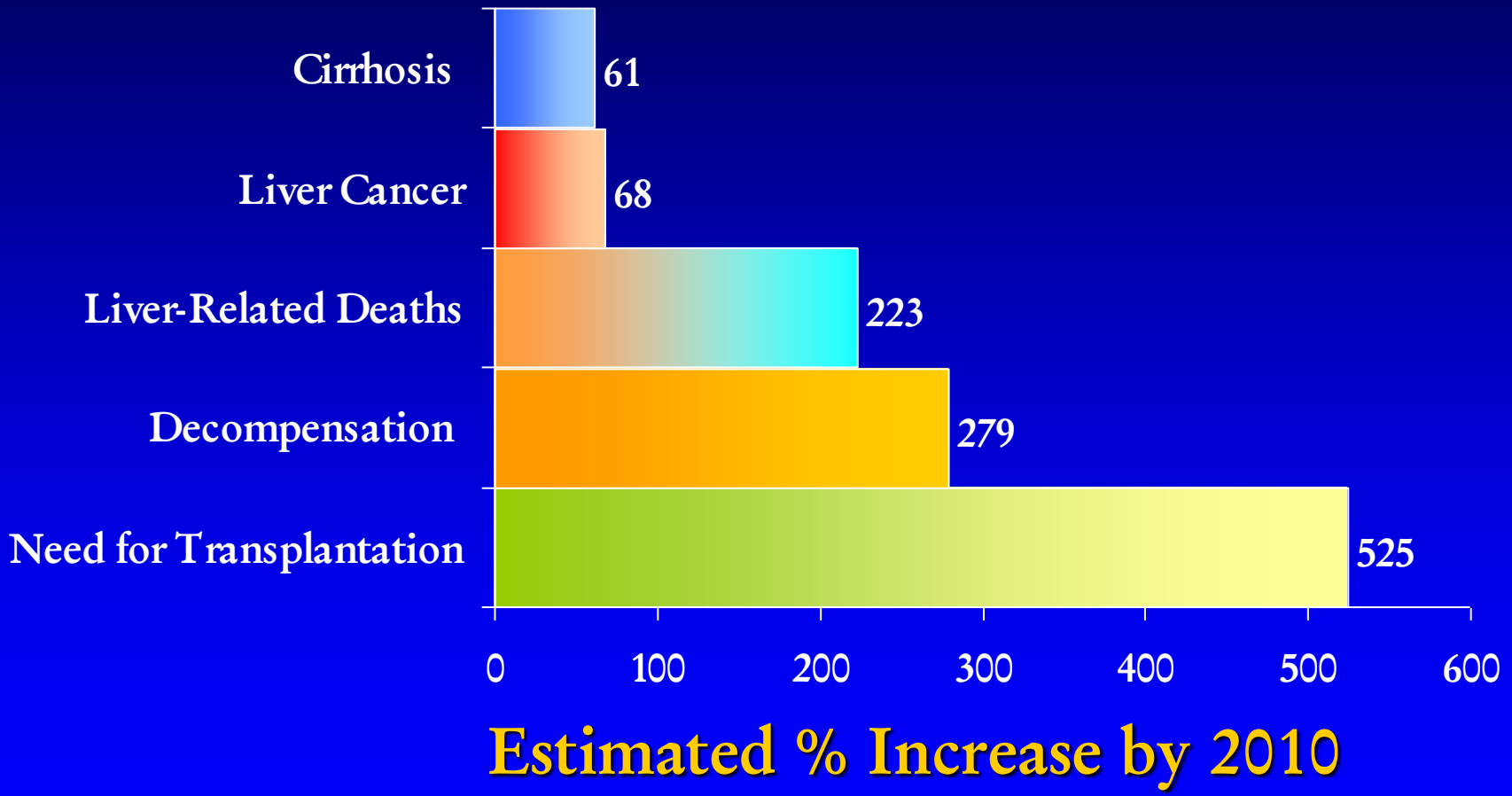
~170 Million Infected Worldwide

3-4 Million New Cases/Year

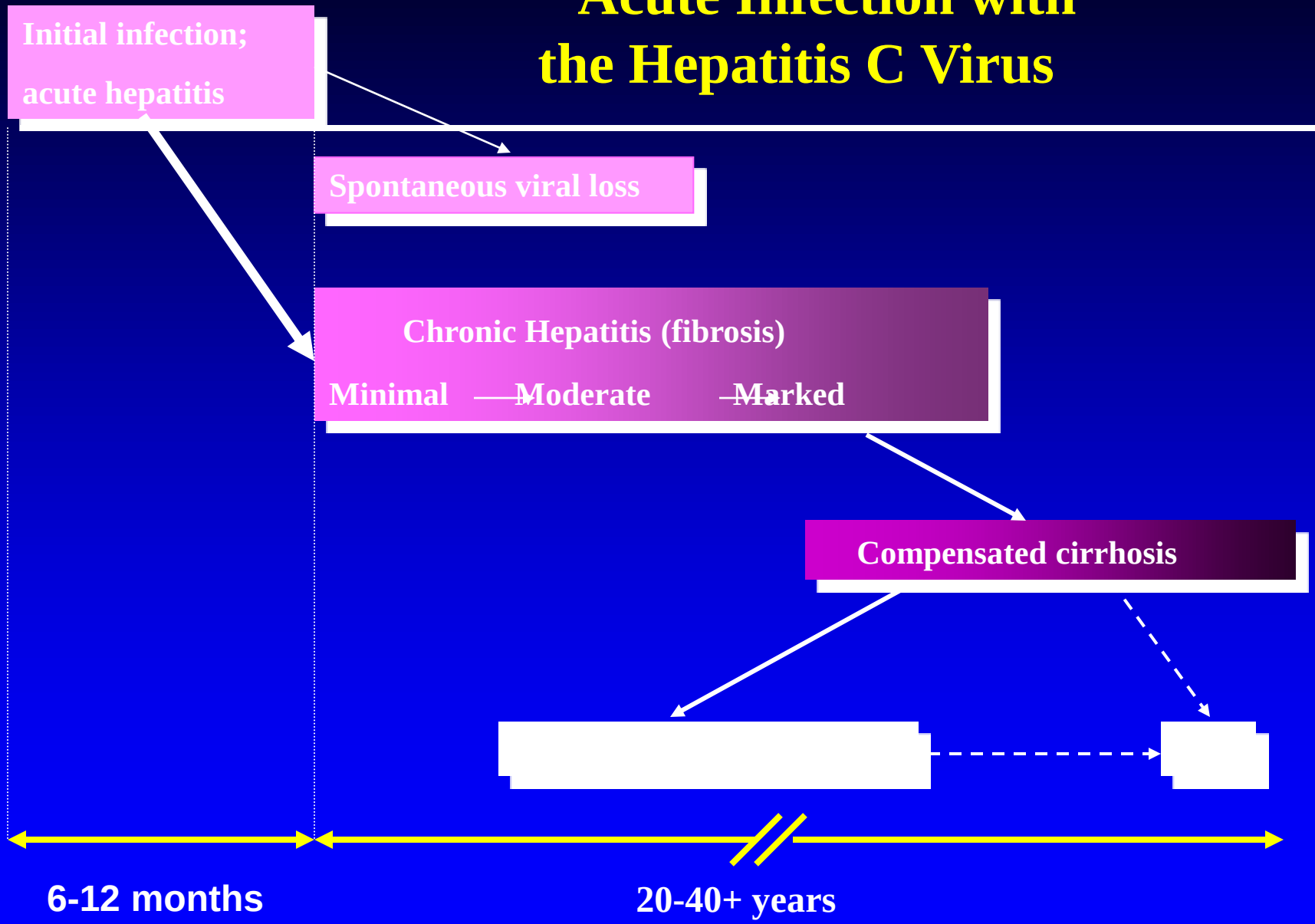


Weekly Epidemiological Record. N° 49, 10 December 1999, WHO

Future HCV Disease Burden



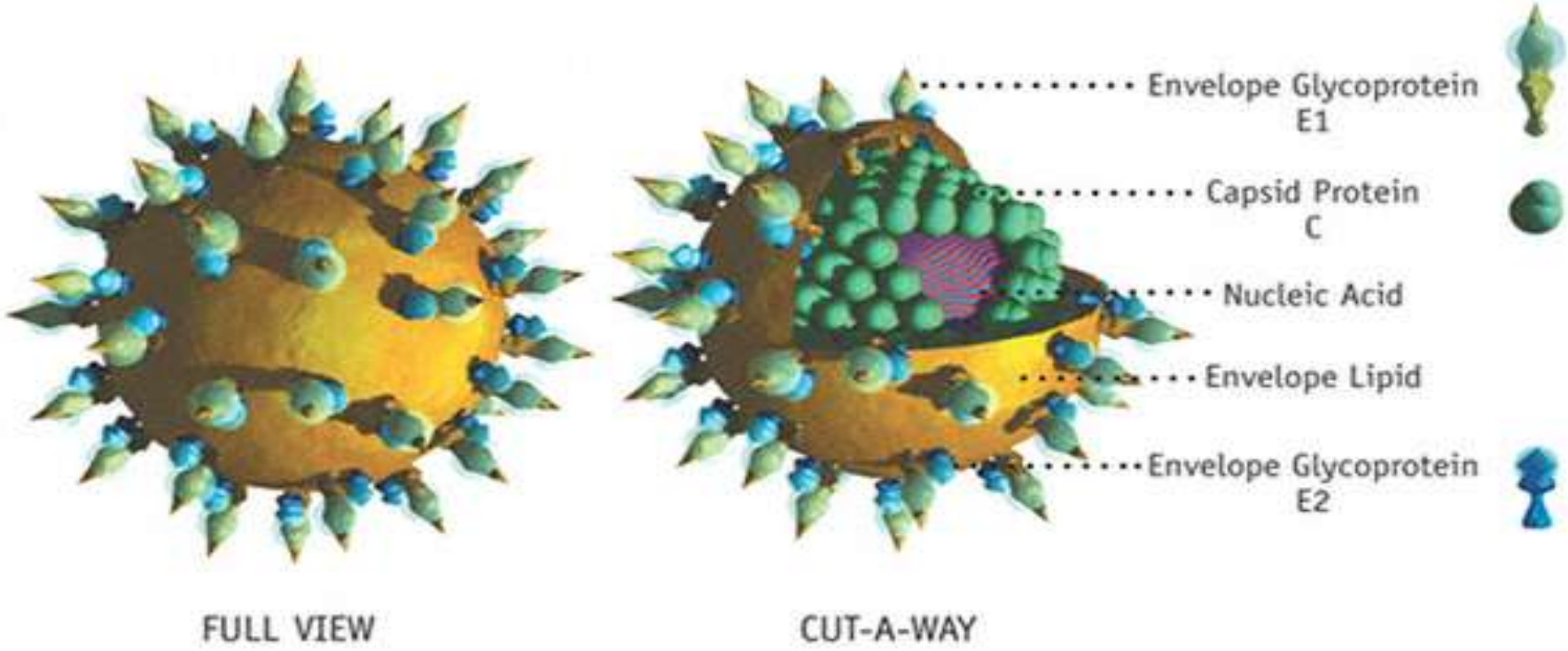
Sequence of Events After Acute Infection with the Hepatitis C Virus



Targeting Hepatitis C Virus

- **Interferon alpha and Ribavirin analogs**
- **HCV Polymerase Inhibitors (Thiobarbituric Acids)**
- **Micro-RNA Inhibition**

Model of the Human Hepatitis C Virus



Liver Targeting and Targeting Hepatitis C

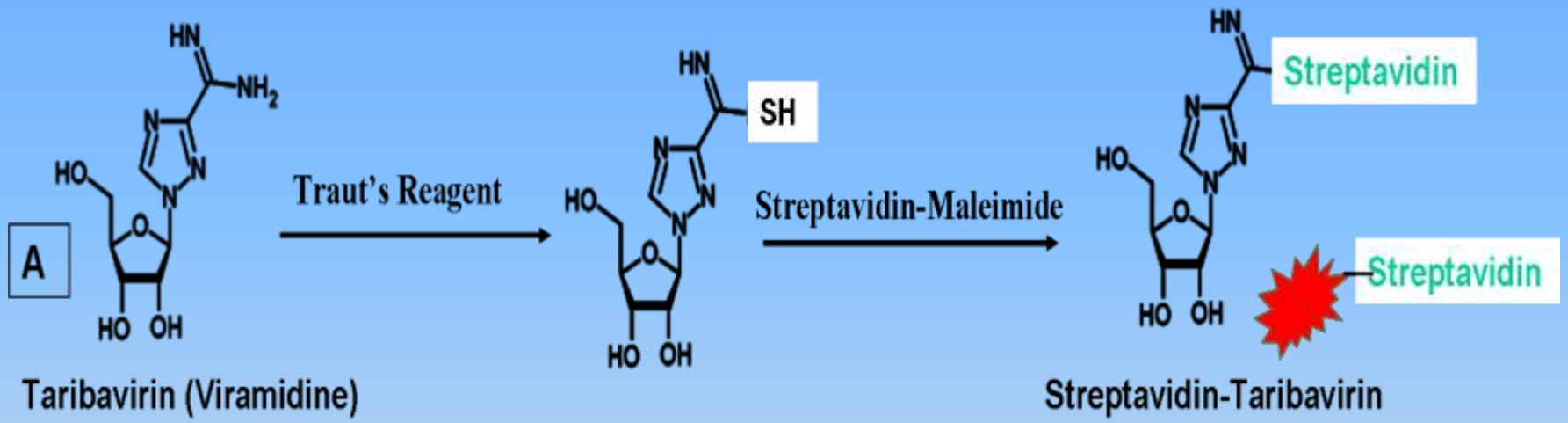
- **Targeting Stellate Cells**

- **Monoclonal Antibodies (Fab fragments) directed against epitopes conserved on HCV surface E2 Glycoprotein of genotypes 1a, 1b, 2a, 2b, and 4**

- **Anti-claudin 1 antibodies – For targeting and inhbition of HCV entry process**

- **TAT peptide (47-57) Targeting HCV**

Diagram showing conjugation strategy for linking taribavirin and p14 to nanoparticles



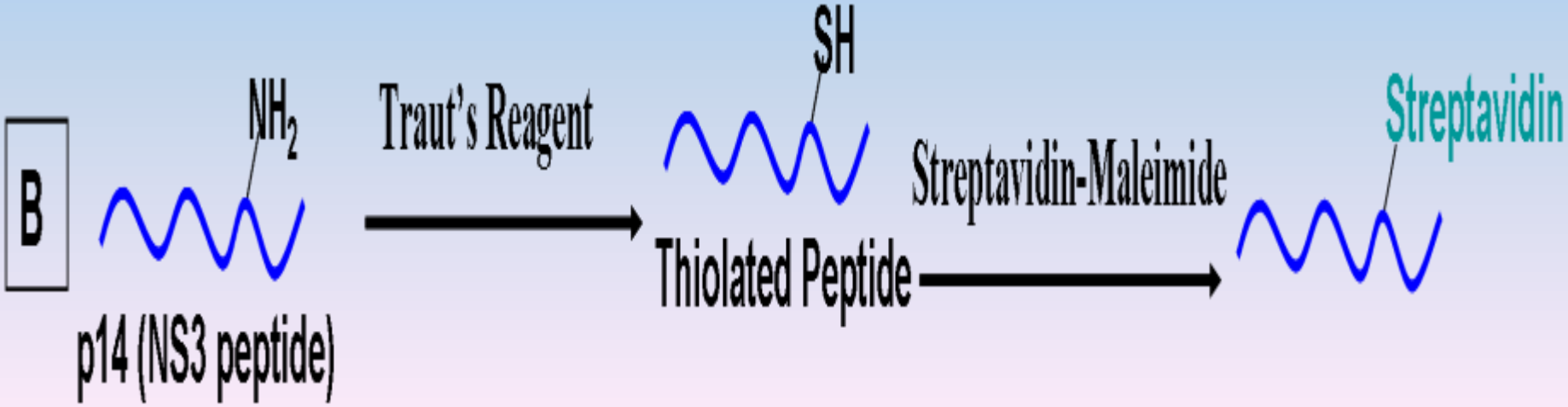
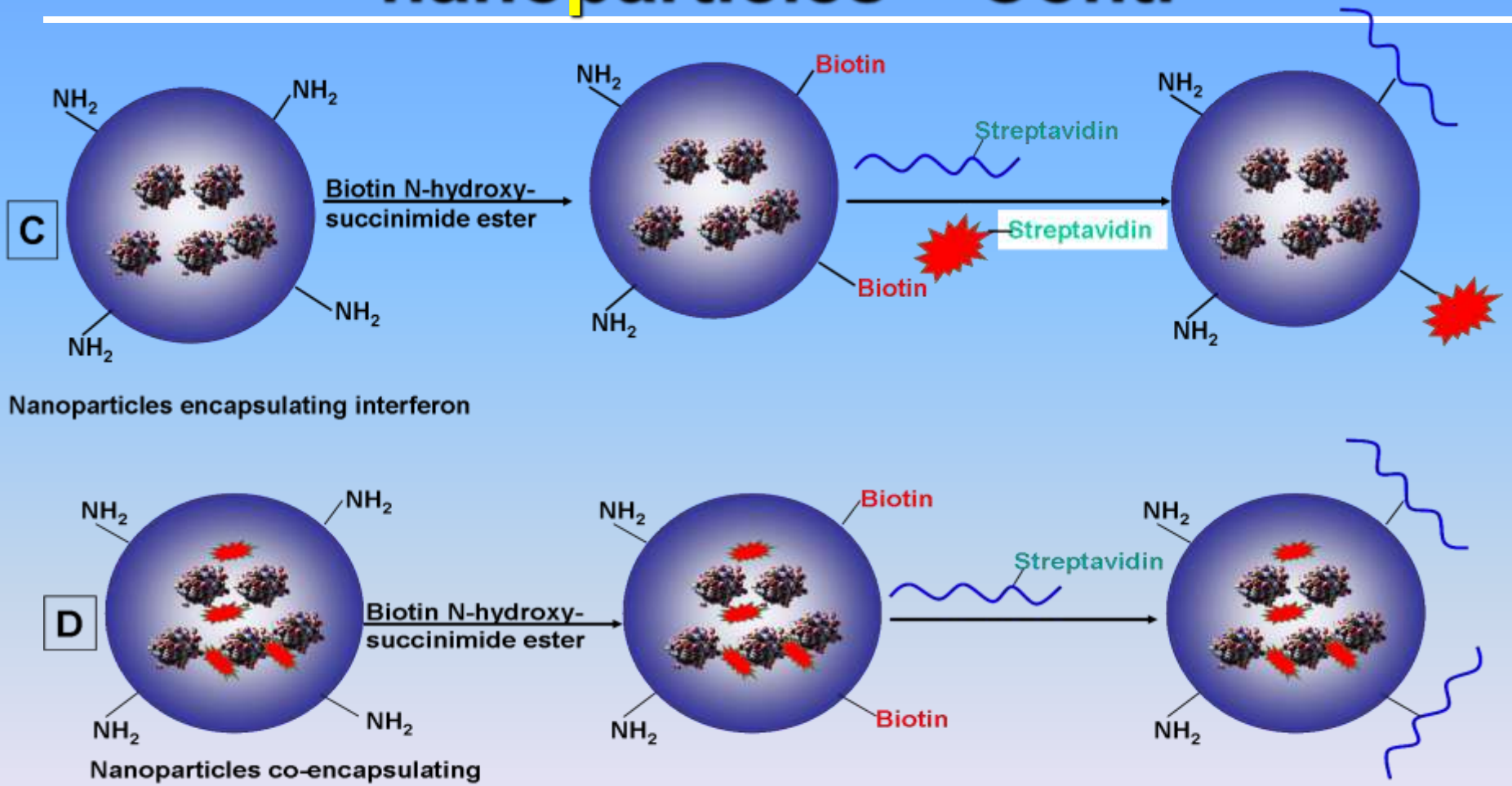


Diagram showing conjugation strategy for linking taribavirin and p14 to nanoparticles – Cont.



SUMMARY & CONCLUSIONS

Nanobiotechnology and Nanomedicine

- Nanomedicine has the potential in diagnosing, treating, curing, and preventing disease and traumatic injury, of relieving pain, and of preserving and improving human health, using molecular tools.
- Nanomedicine is not a substitute in most cases for current Medicine but rather complementary.
- It is about moving the technology up in the chain and solving bigger problems.

تستوجب إتخاذ قرارات تاريخية مفصلية لكي لا يفوت الأمة العربية قطار التطور كما فات العرب الأولى قطار الثورة الصناعية