INDO-DUTCH WORKSHOP

NANO-PHOTOMEDICINES FOR MOLECULAR IMAGING GUIDED TARGETED PHOTODYNAMIC THERAPY

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Theme

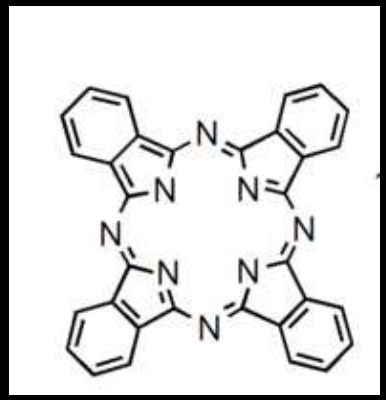
An INDO-DUTCH story of how NANOTECHNOLOGY can enable us to develop Advanced biomedical technologies to improve Cancer Treatment

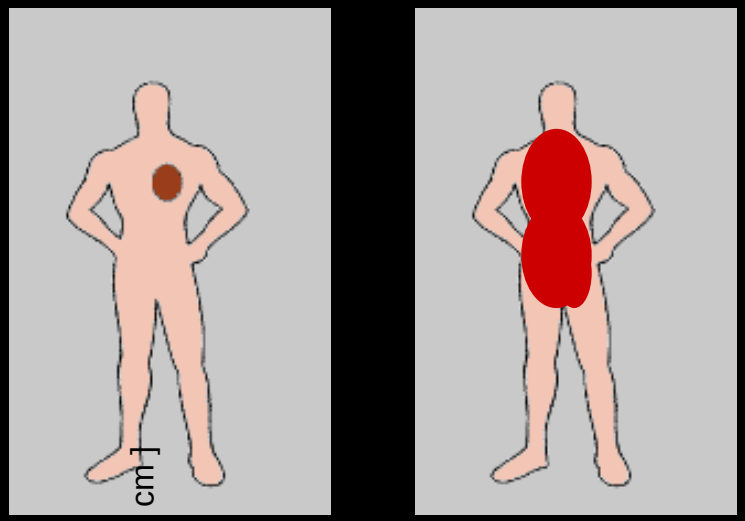
Nanotechnology enabled Photodynamic Therapy of Cancer

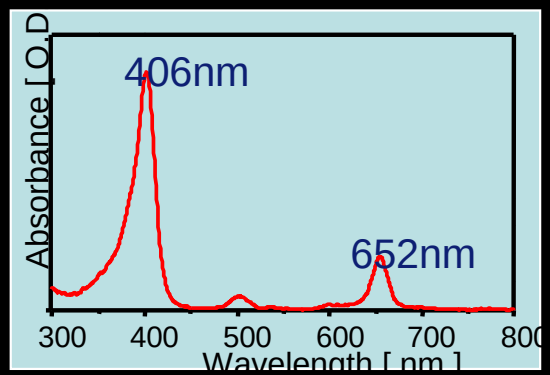
Limitations of current PDT

PDT = Photosensitizer + Oxygen + Light = kill Cancer

PS molecule







1. Most of the PS drugs are hydrophobic hetrocyclic molecules that is insoluble in physiological system (Blood). This leads to:

   Low $^1O_2$ efficiency

   Non-specific accumulation in the body resulting whole-body photo-toxicity

2. Uncontrolled Tissue selectivity of PS due to its chemical nature: Photofrin goes to connective tissue and blood vessels, ALA concentrates in mucosal layers, mTHPC accumulate on vasculature

   No control on pharmacokinetics of diff. molecules

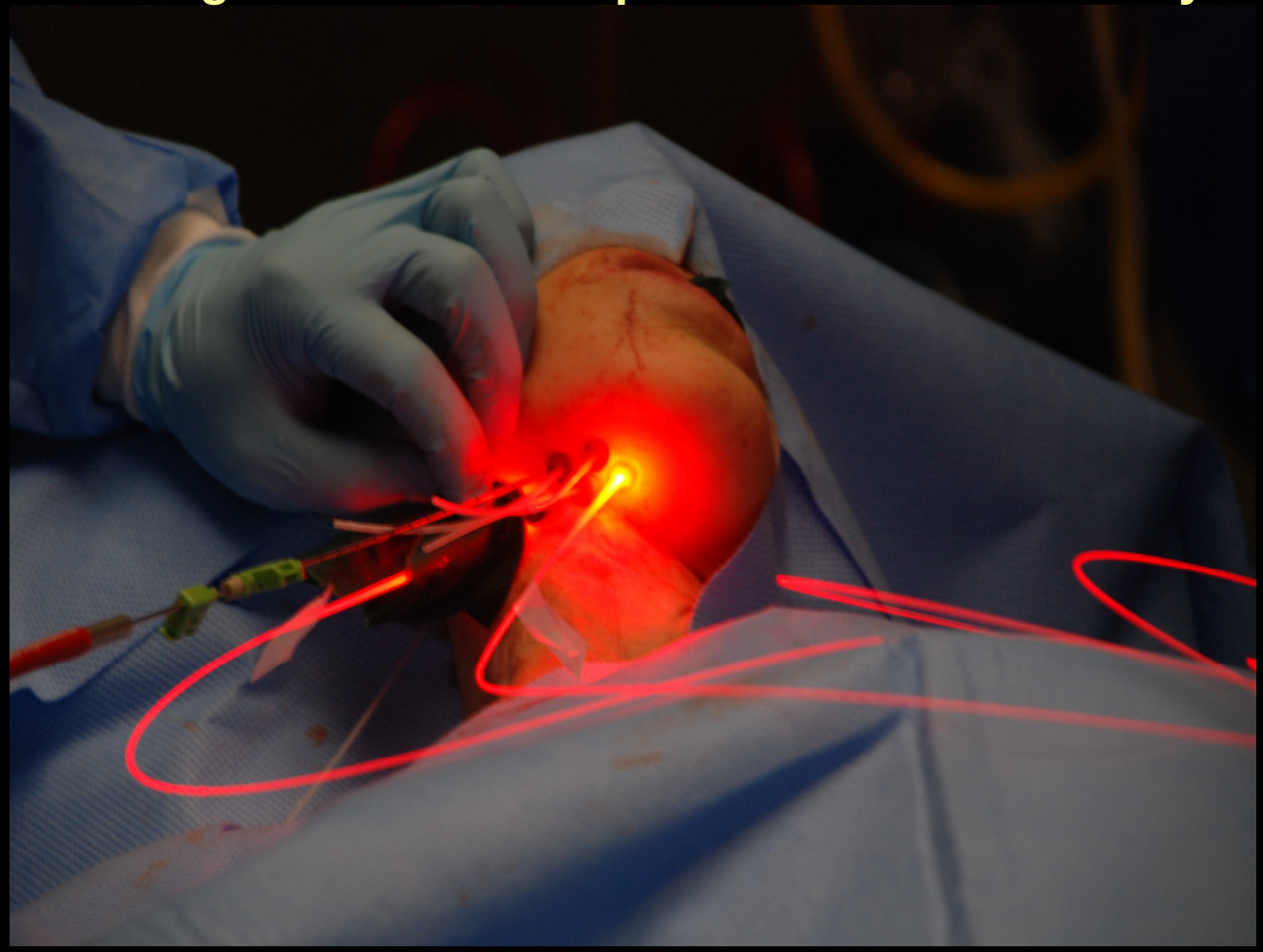
3. Low absorption of PS in the RED region where the tissue penetration of light is better. This makes PDT less effective for treating solid tumors

4. Fast photobleaching of PS molecules

Complicated dose matrics : Drug, light and oxygen dosimetry is very critical for successful PDT

Presently, highly invasive optical methods are used for dosimetry

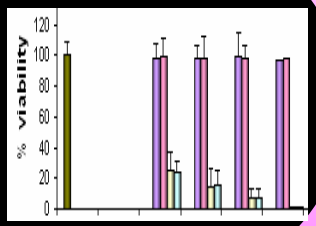
It’s a high time to develop noninvasive dosimetry



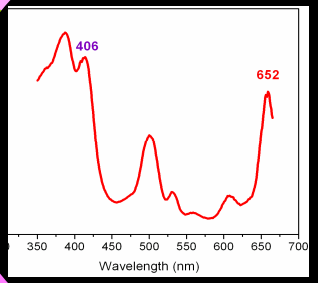
The Nano-solutions

Multifunctional Nano-photomedicines *for* future PDT

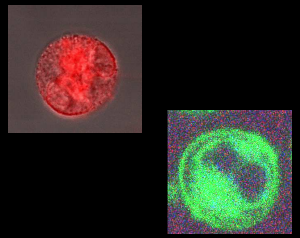
Enhanced PDT effect



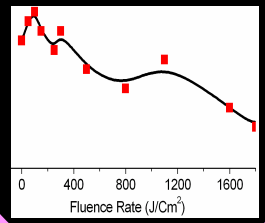
Water soluble Nano-PS with Higher Q-band absorption



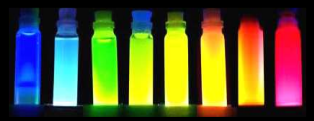
Target specific delivery



Stable photo physical Properties

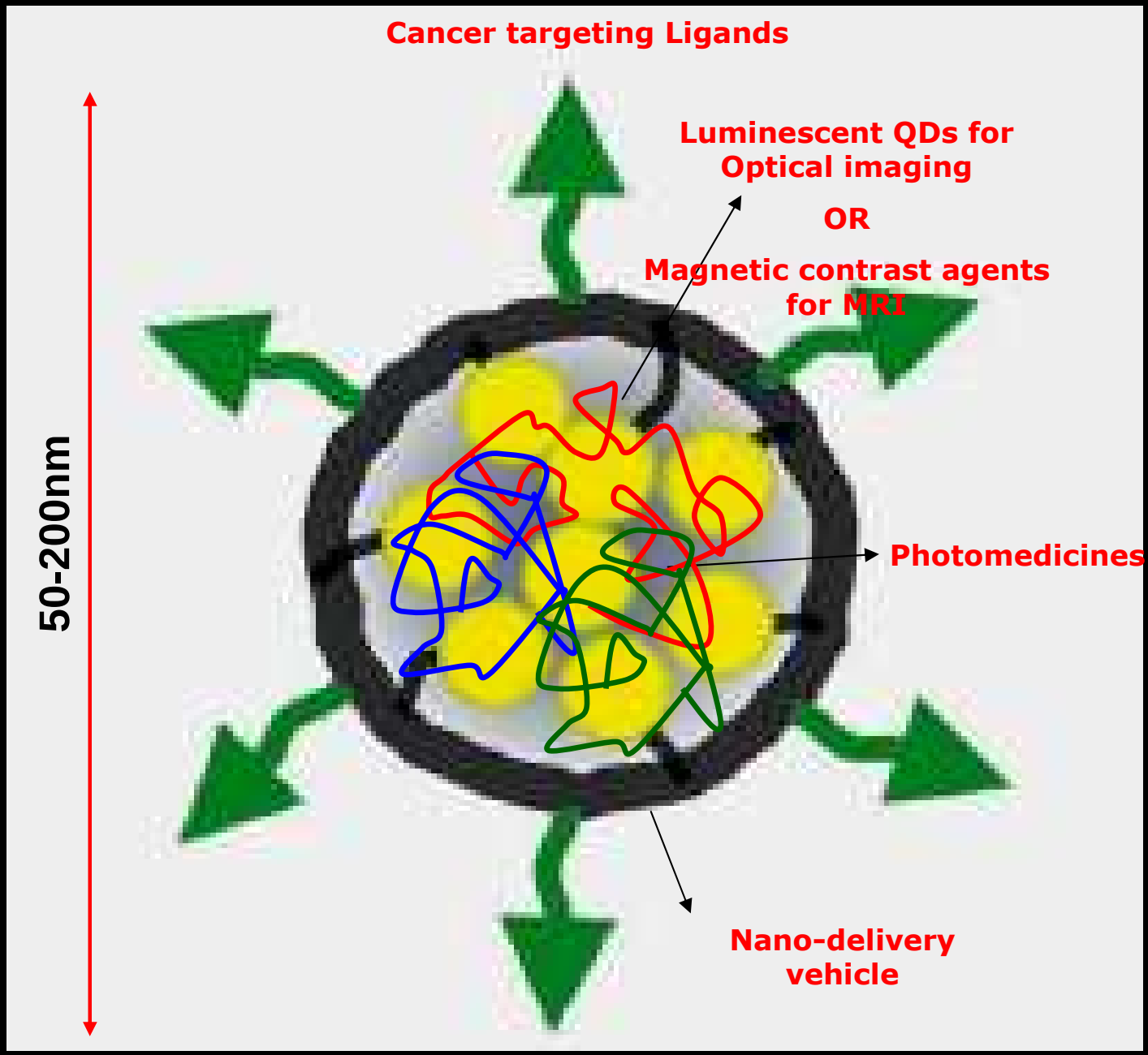


Molecular imaging – Optical

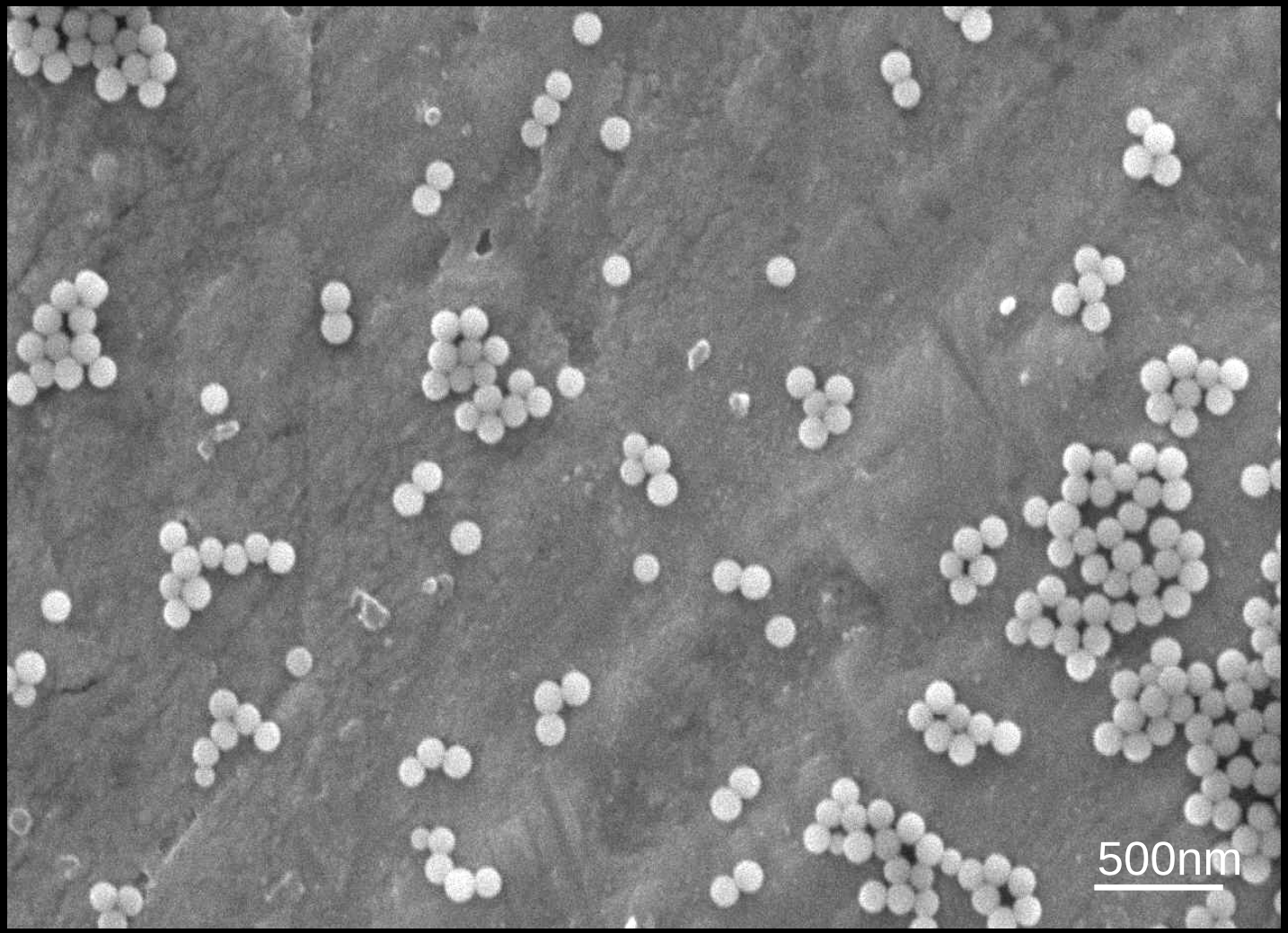


Molecular Imaging :MRI

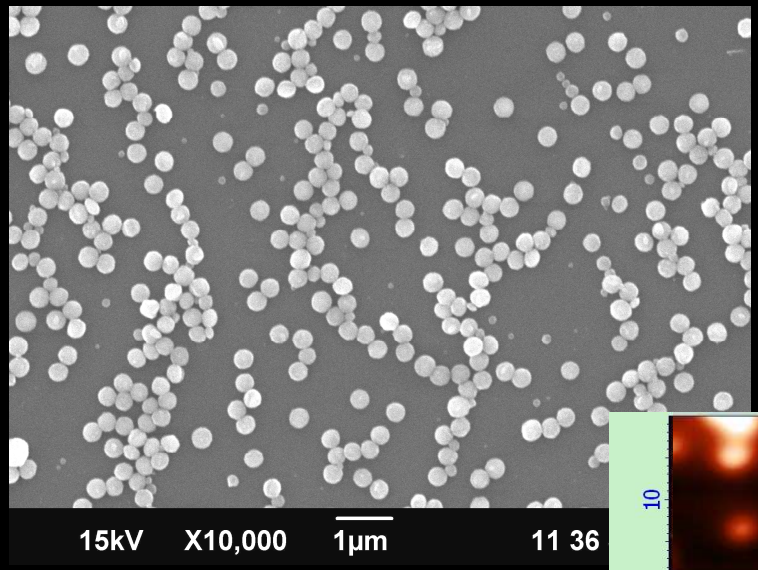
Nano-Photomedicine Design



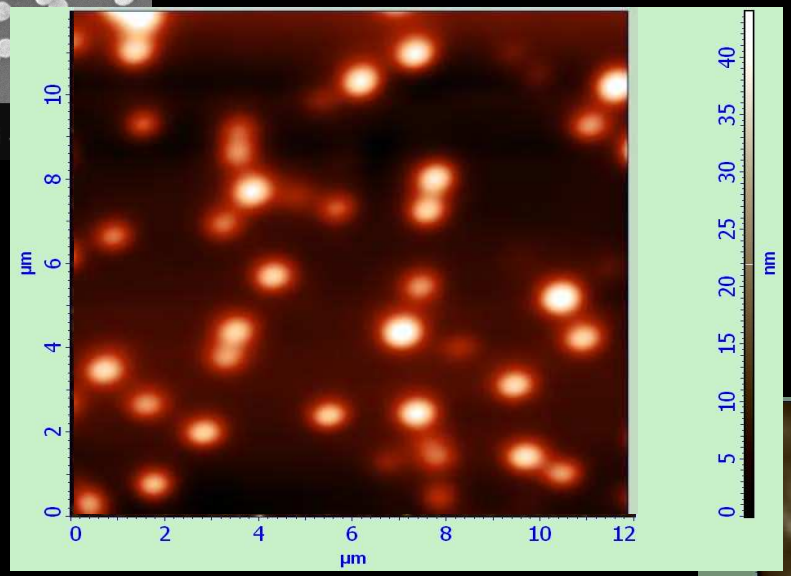
Electron microscopic image of based nanophotomedicine



Size controlled synthesis of nanodelivery vehicle

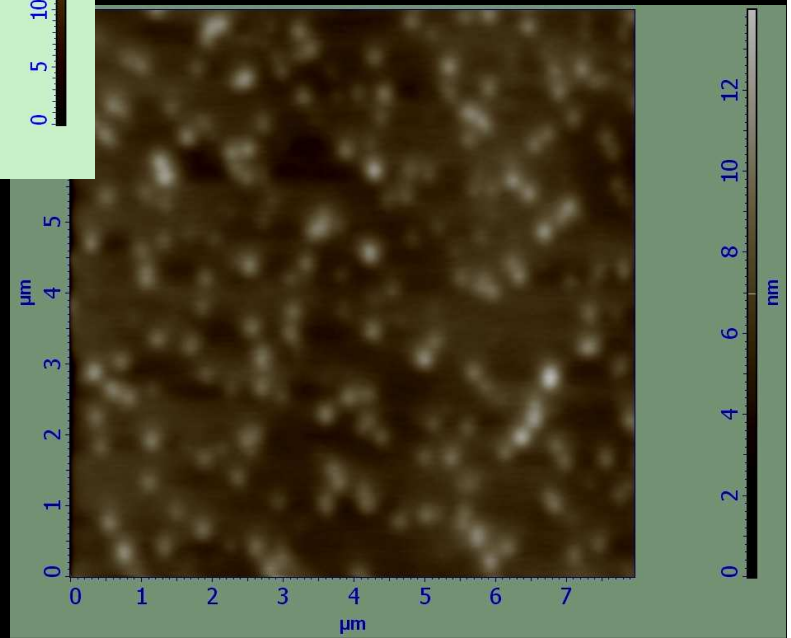


200nm, ZnO/PEG

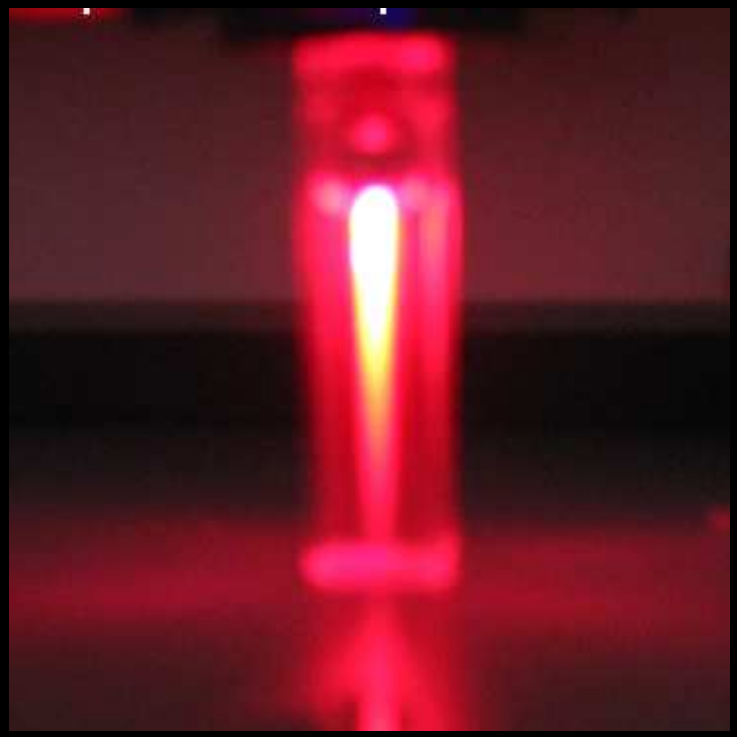


40nm-Chitosan

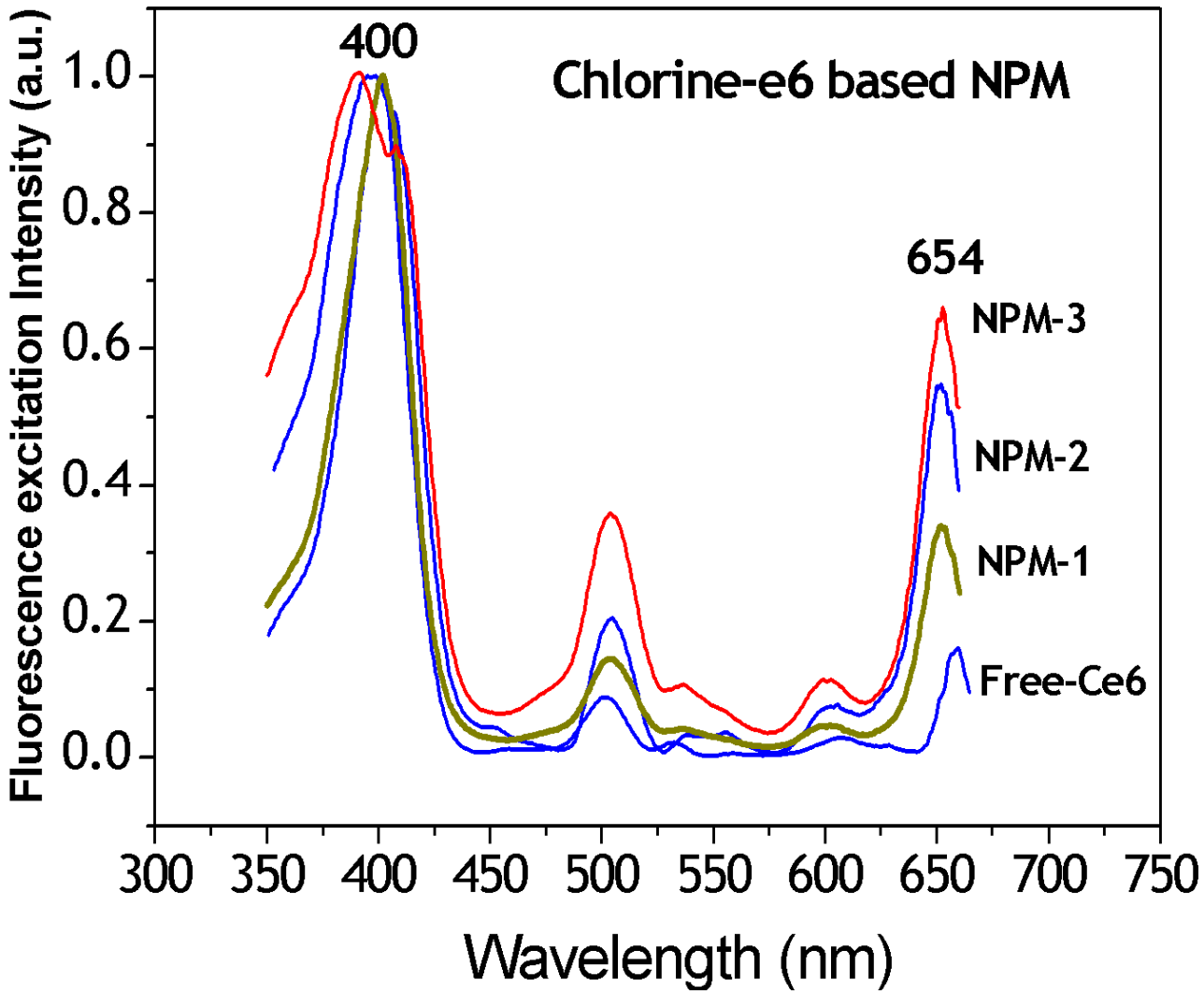
12nm-PLGA



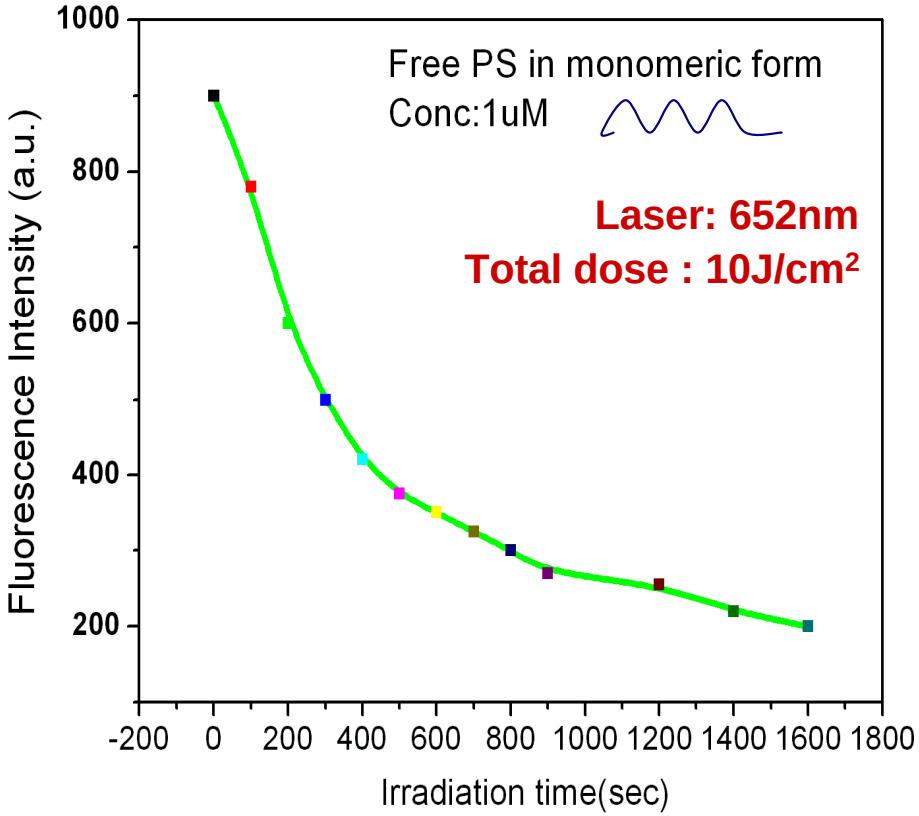
Remain Fluorescent and Photodynamically active in Water / PBS

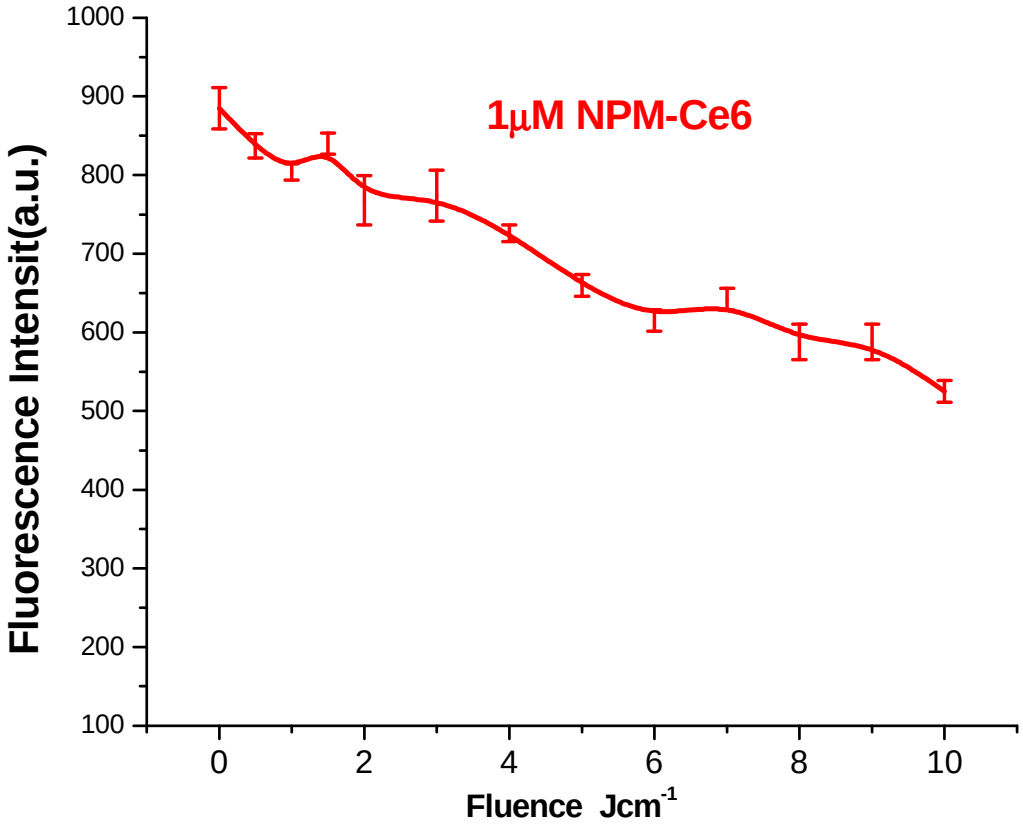


Better Absorption in Q-band

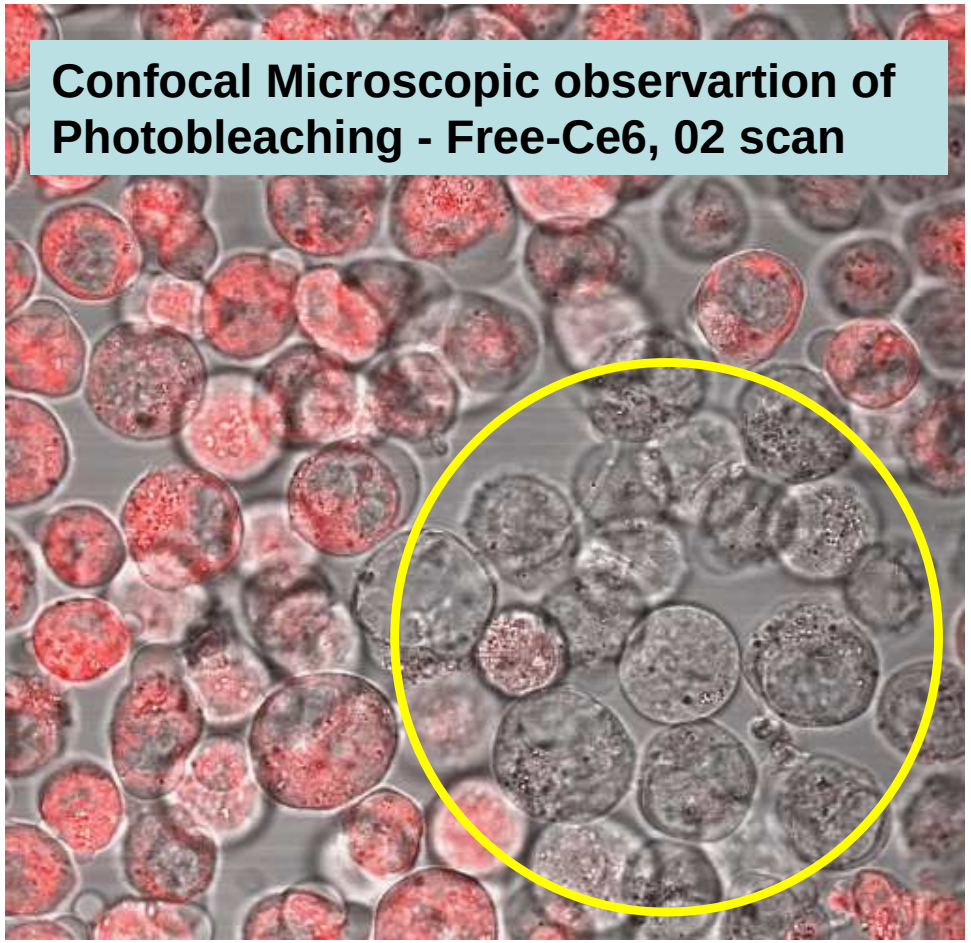


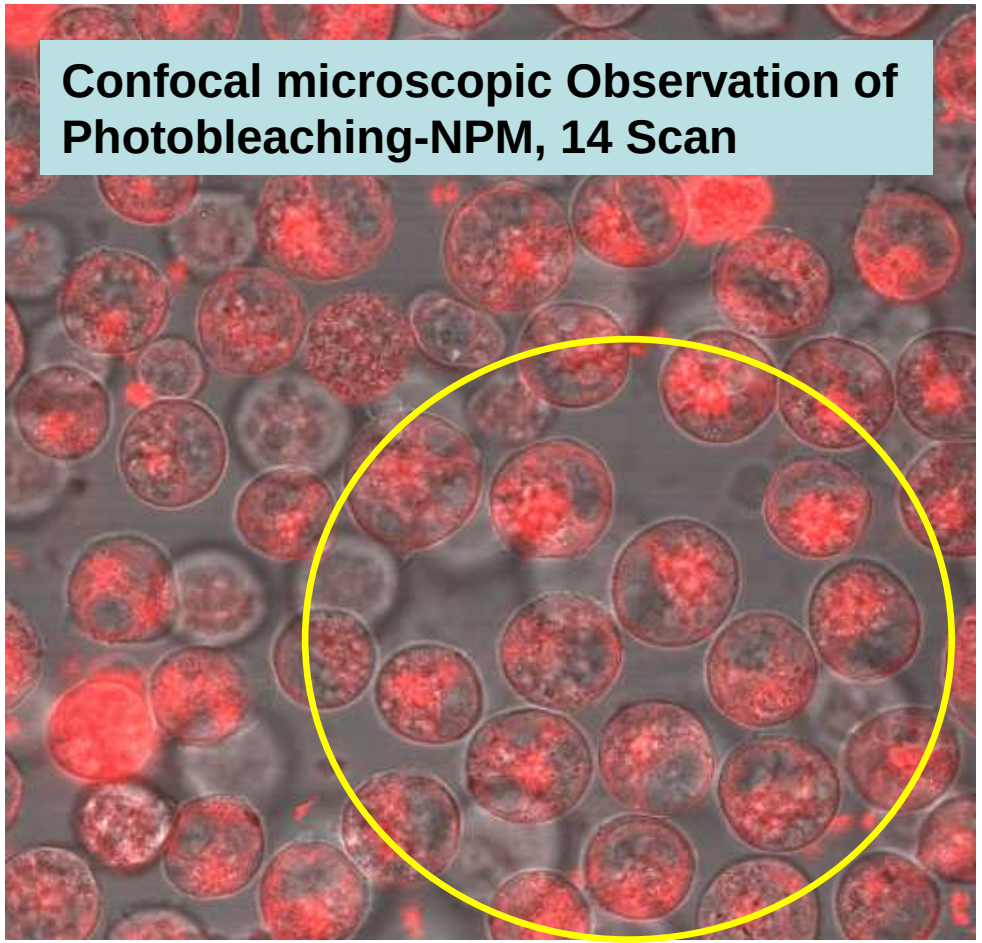
No fast Photobleaching



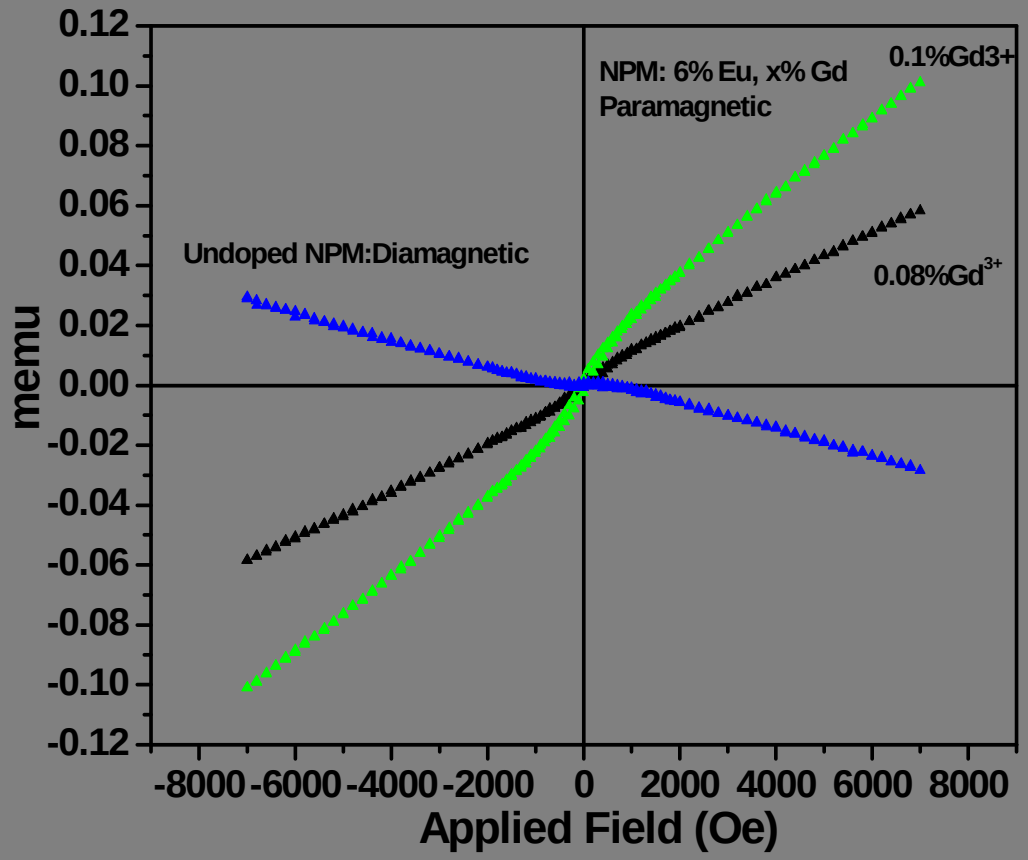


No fast Photobleaching

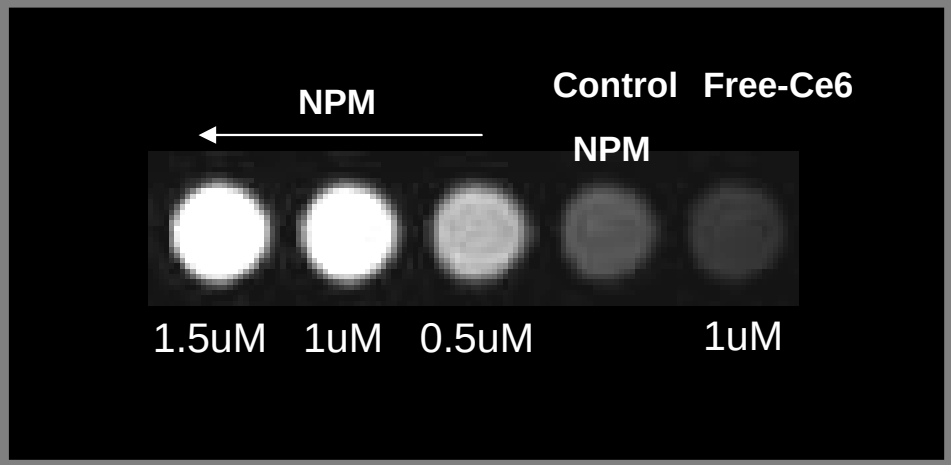




NANOMED can be detected by Molecular Imaging - MRI



T1 weighed contrast



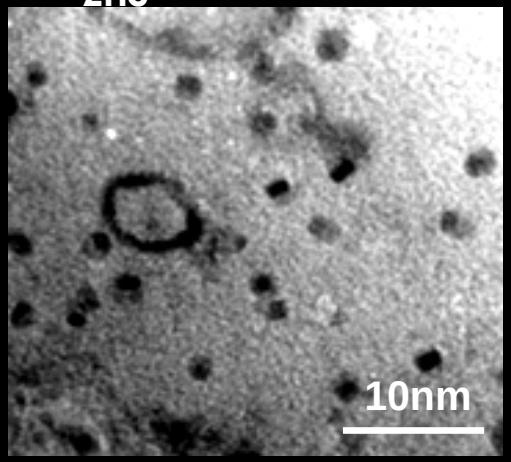
MRI imaging conditions

- 1.5 T (GE)
- T1 contrast image
- TR/TE= 200ms/9ms
- FOV 19 by 19 cm^2
- 256*256 points
- 4 acquisitions
- Band width 41.67KHz
- Pulse sequence spin echo technique
- Each well consists of 250uL of sample Vol.
- ~ 100K KB cells

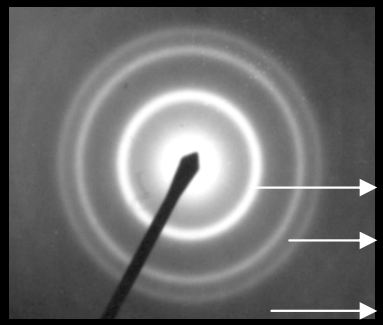
Optical dosimetry without affecting PS

Doping Nanomed with Luminescent QDs

TEM-ZnS

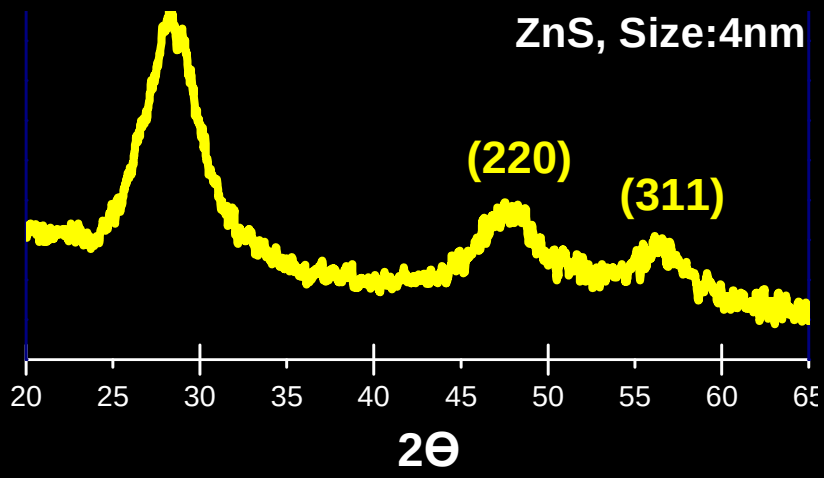


SAED



β-ZnS

XRD



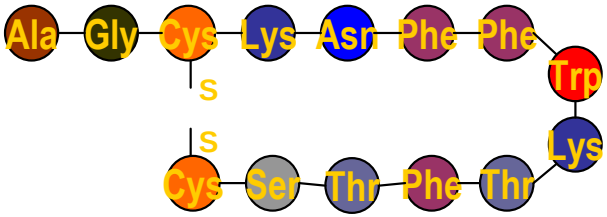
Luminescent QDs: Doped ZnS

Cancer Targeting by Bioconjugation

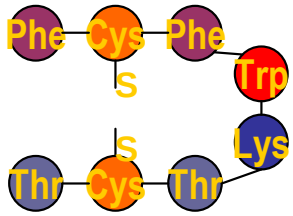
Peptide Receptor target: Somatostatin

Somatostatin is a peptide hormone that regulates the endocrine system and affects neurotransmission and cell proliferation via interaction with G-protein-coupled somatostatin receptors

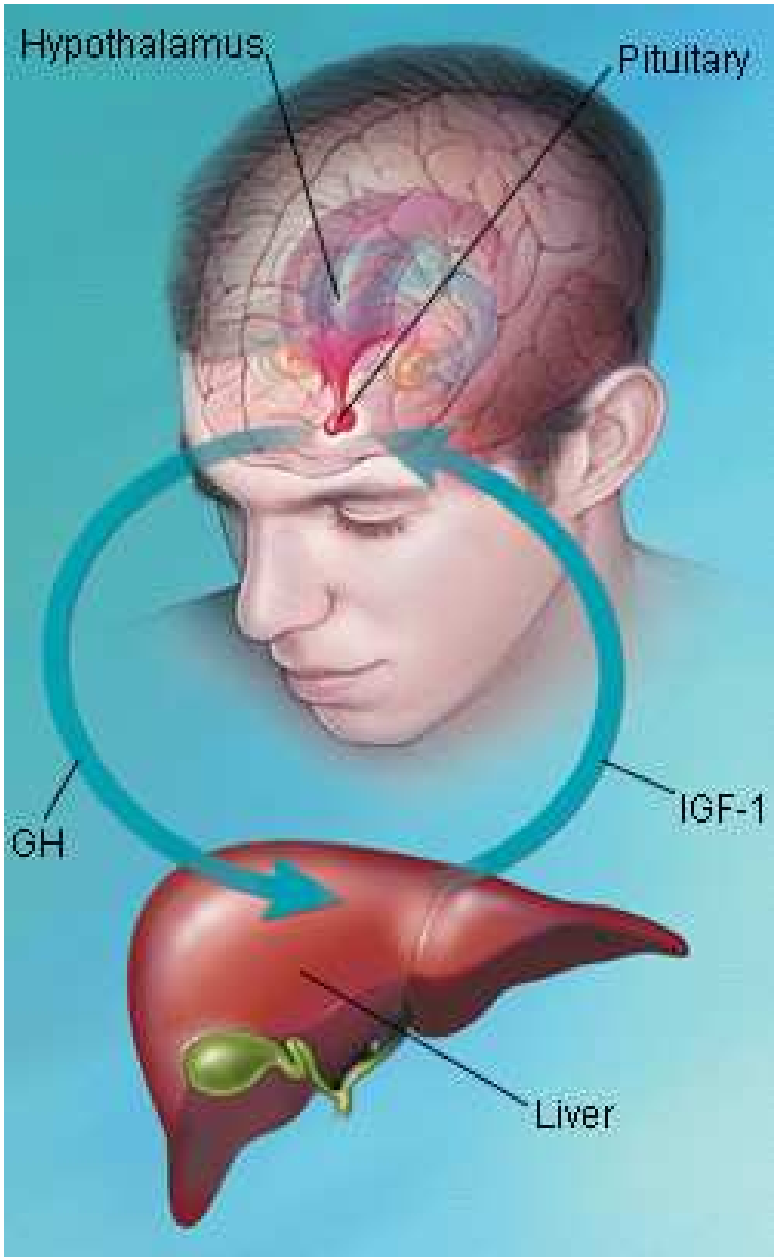
Features : sst2 is highly over expressed in Nueroendocrine Tumors



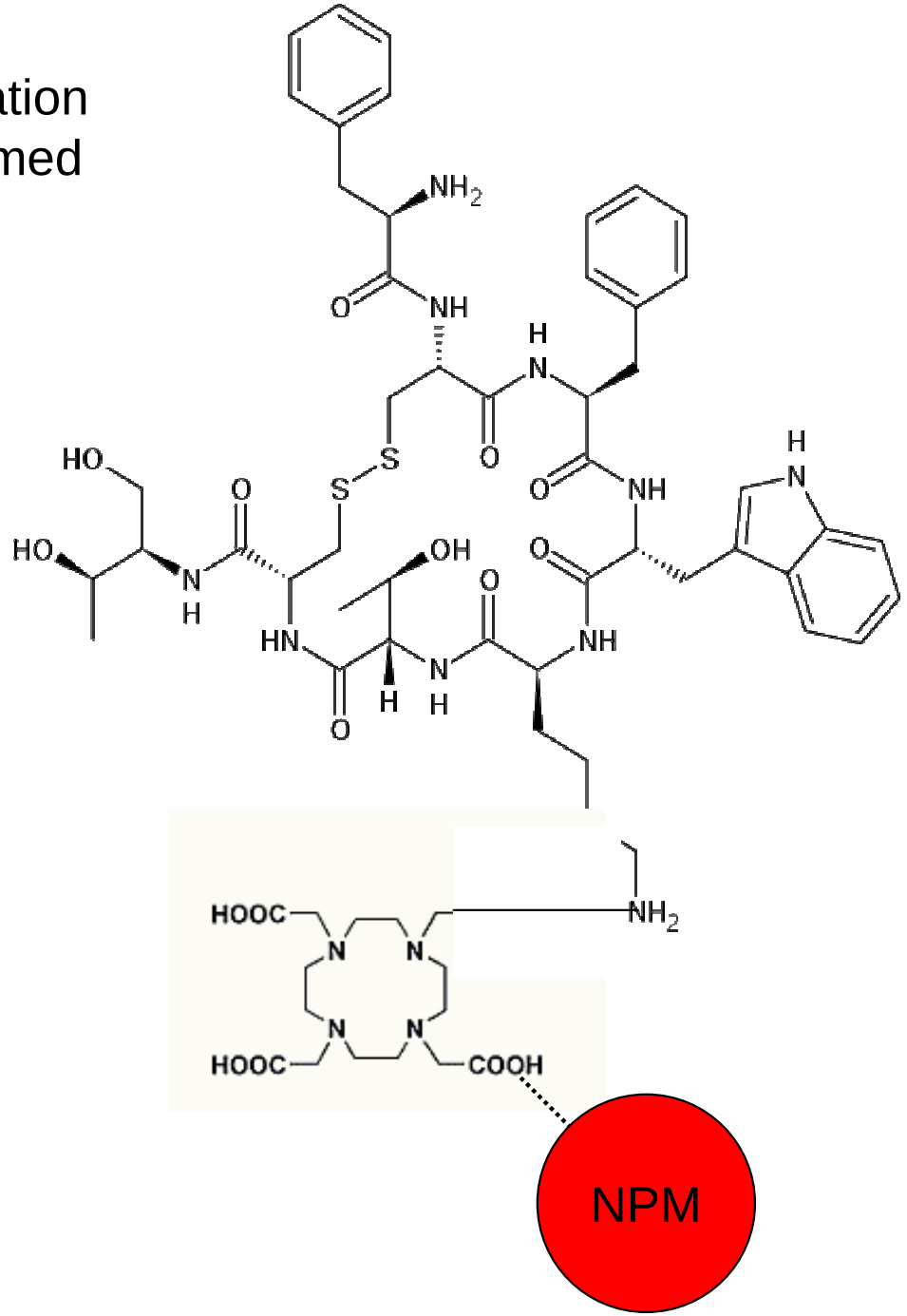
Somatostatin



Octreotide

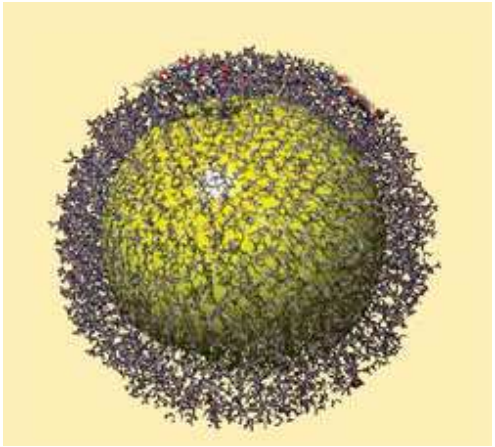


Peptide Conjugation
with Nanophotomed

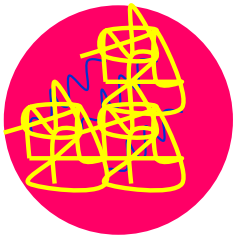


Bio Conjugation

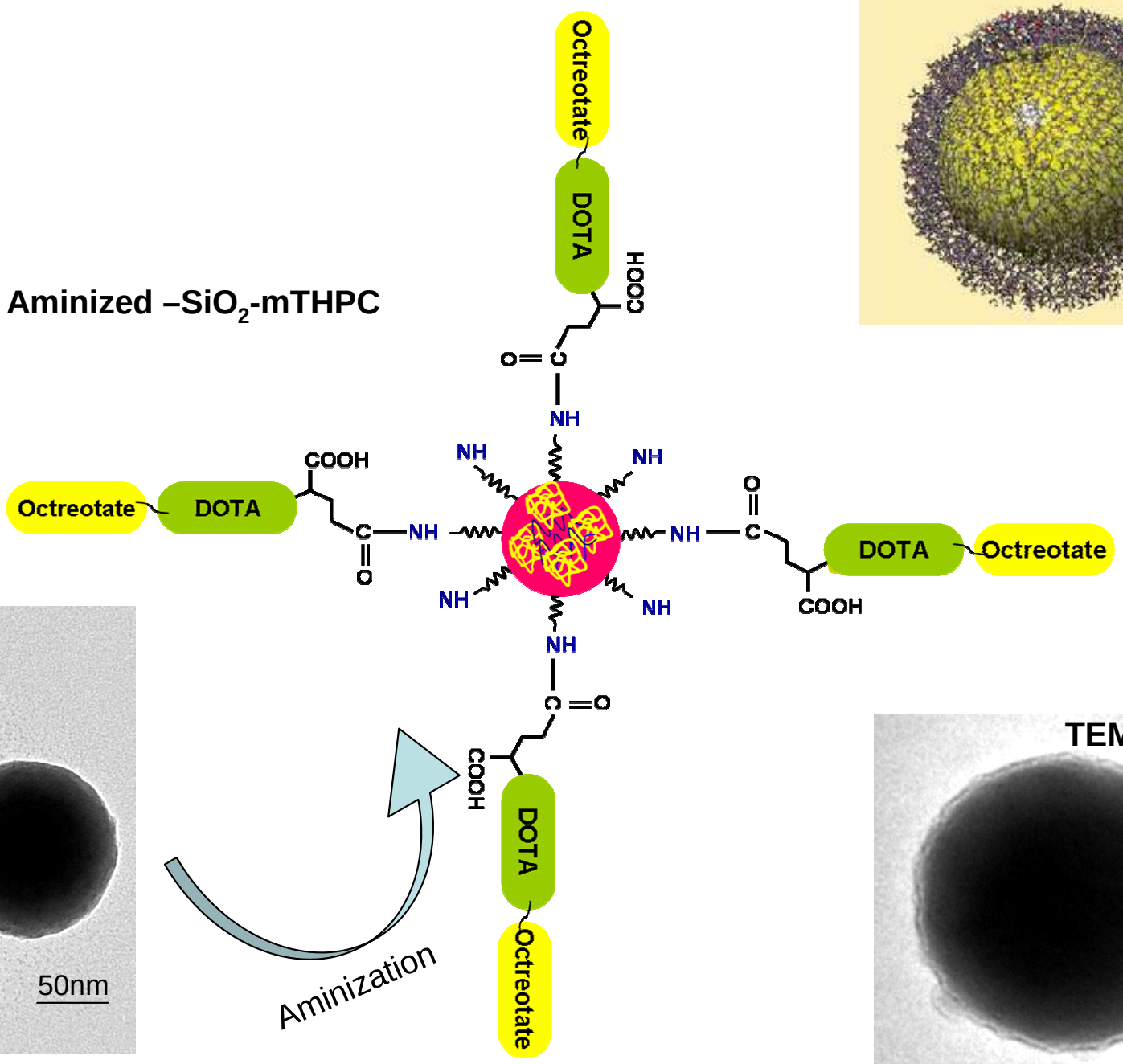
mTHPC@SiO_2--[DOTA-Tyr^3 –Octreotate]



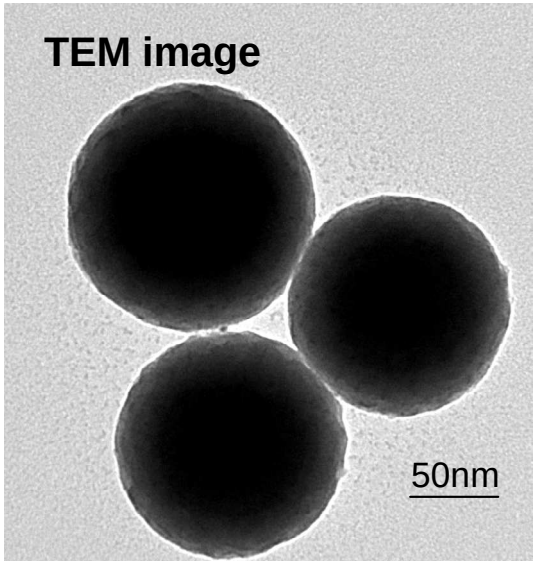
SiO_2-mTHPC



Aminized –SiO_2-mTHPC

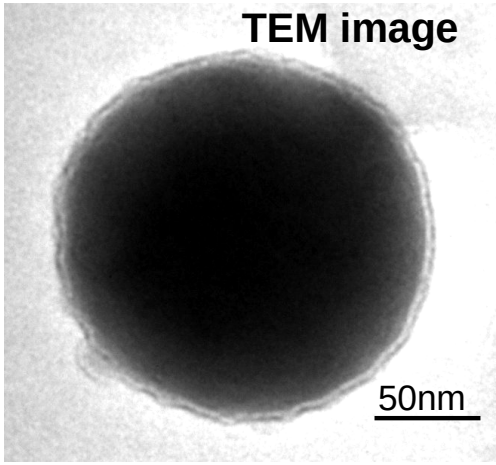


TEM image



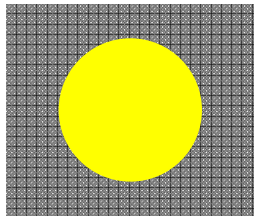
Aminization

TEM image

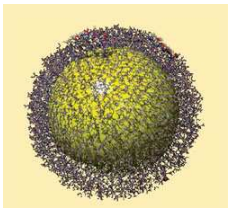


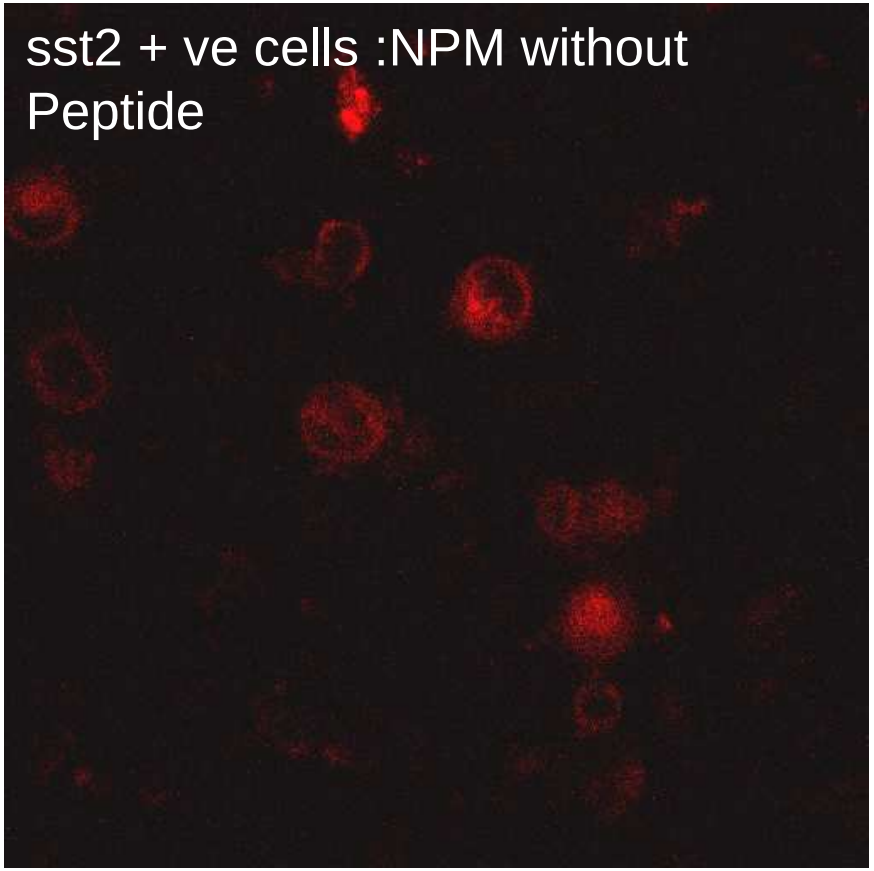
Taregeted delivery of Peptide conjugated NPMs with sst2 + ve K 562 Cells

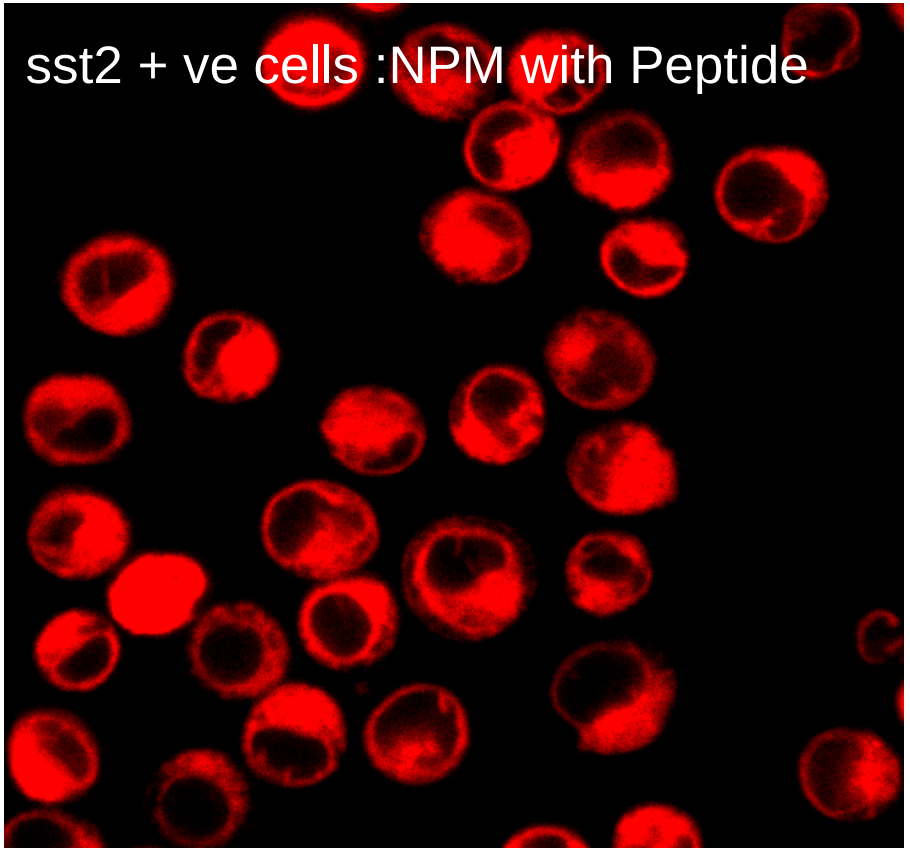
mTHPC@SiO_2



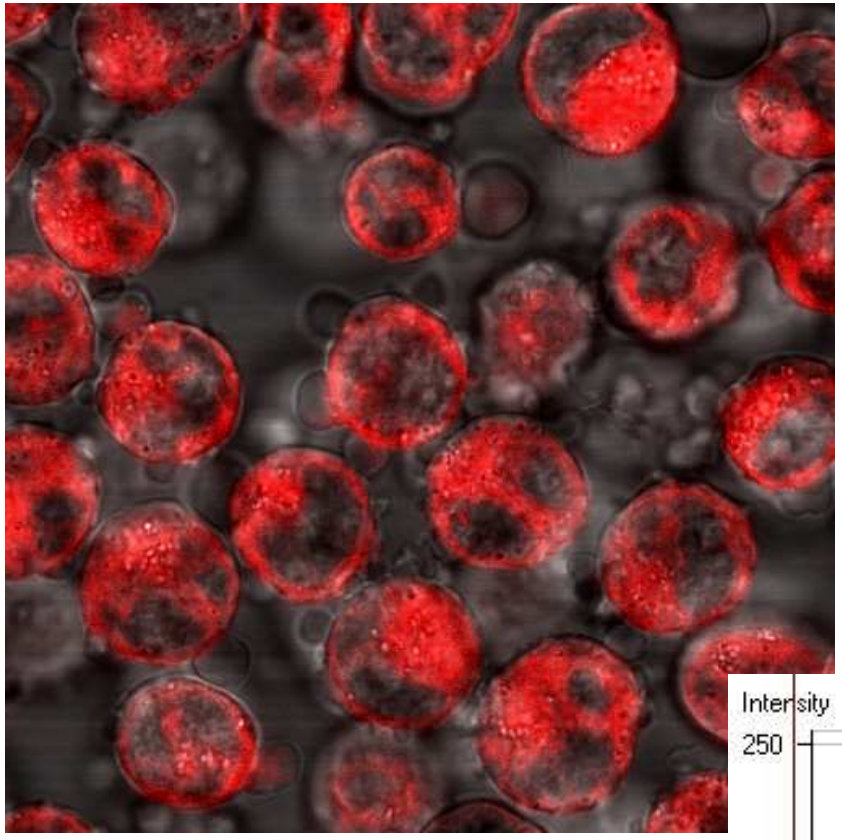
mTHPC@SiO_2--[DOTA-Tyr^3 –Octreotate]

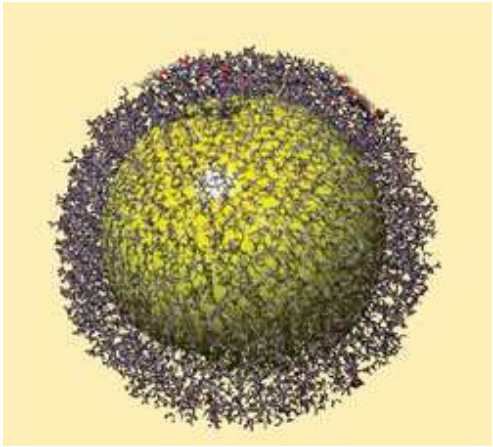


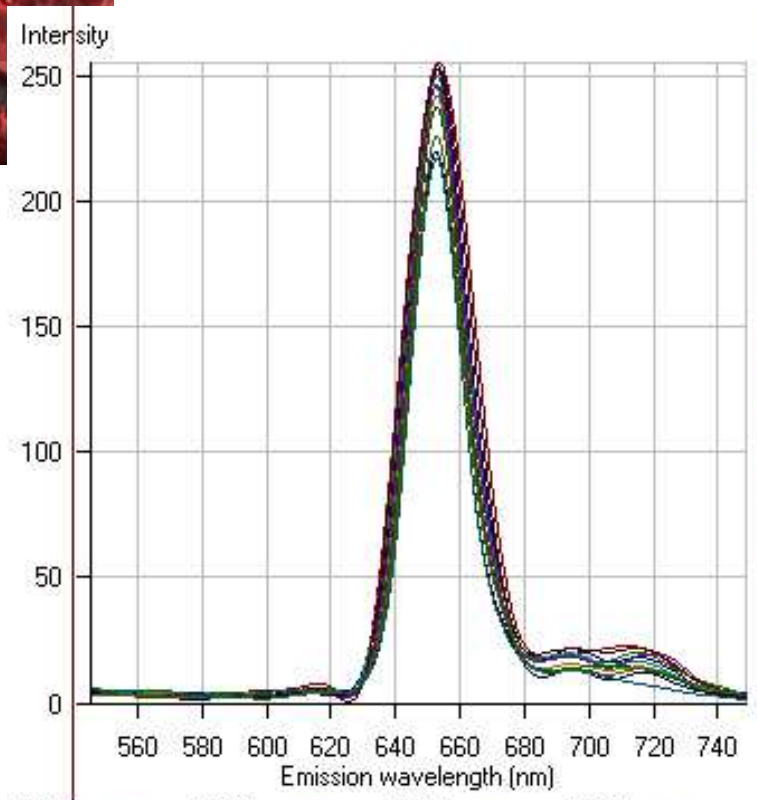


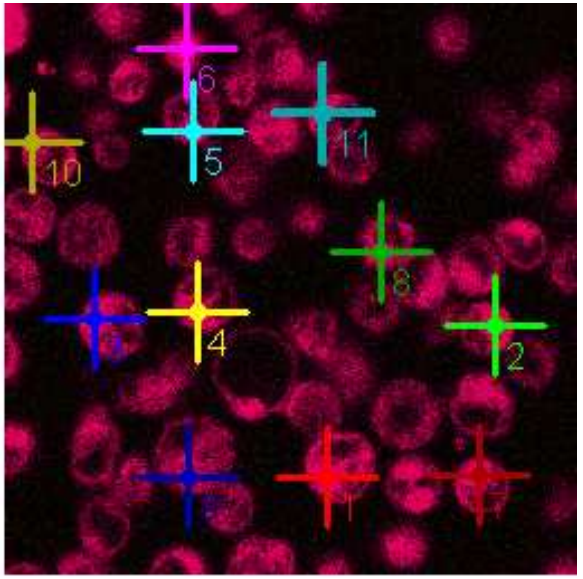


mTHPC@SiO_2--[DOTA-Tyr^3 –Octreotate]



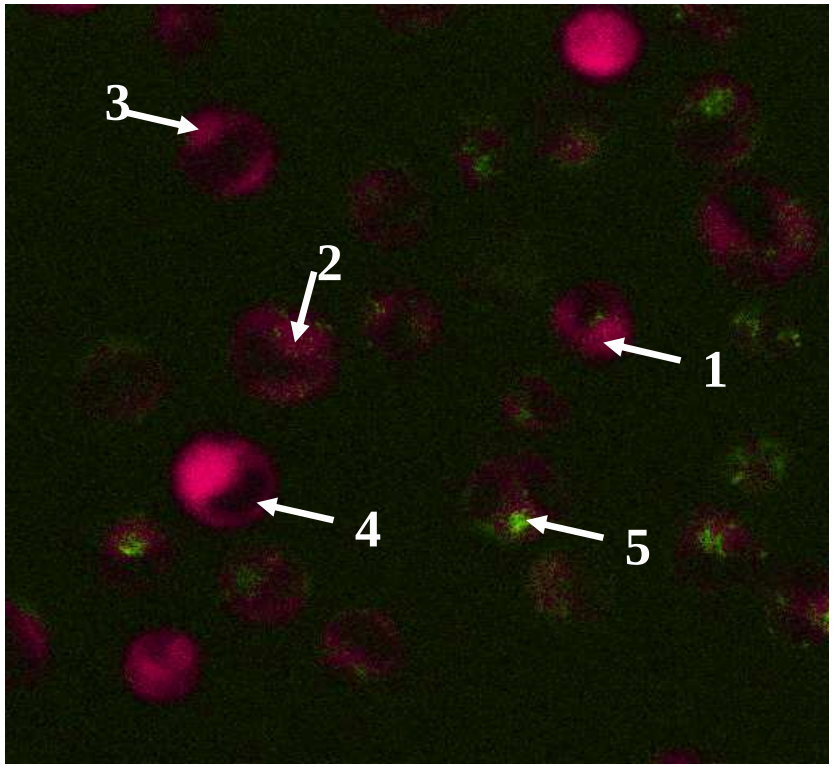




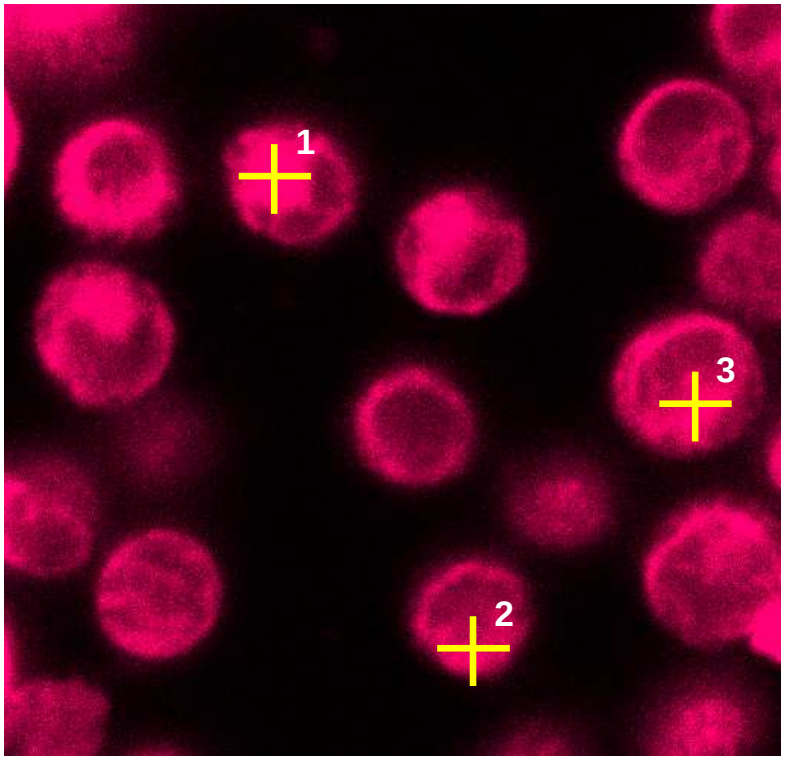


Control experiments with Receptor Blocking

Sst2 Receptor blocked Cells



Unblocked Cells



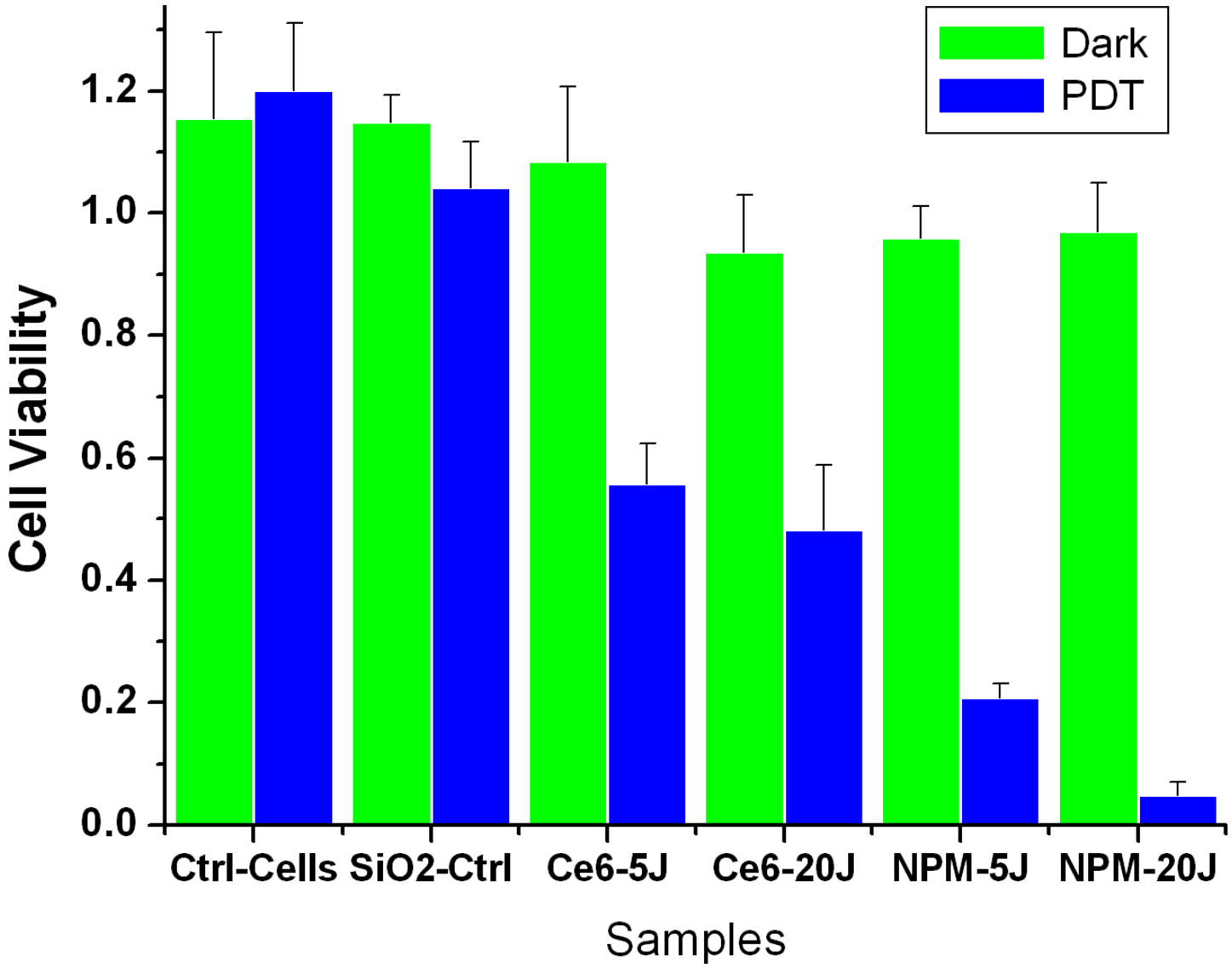
PDT Studies

Laser: 652nm (Biolitec, USA)

Light dose: 5 & 20Jcm $^{-1}$

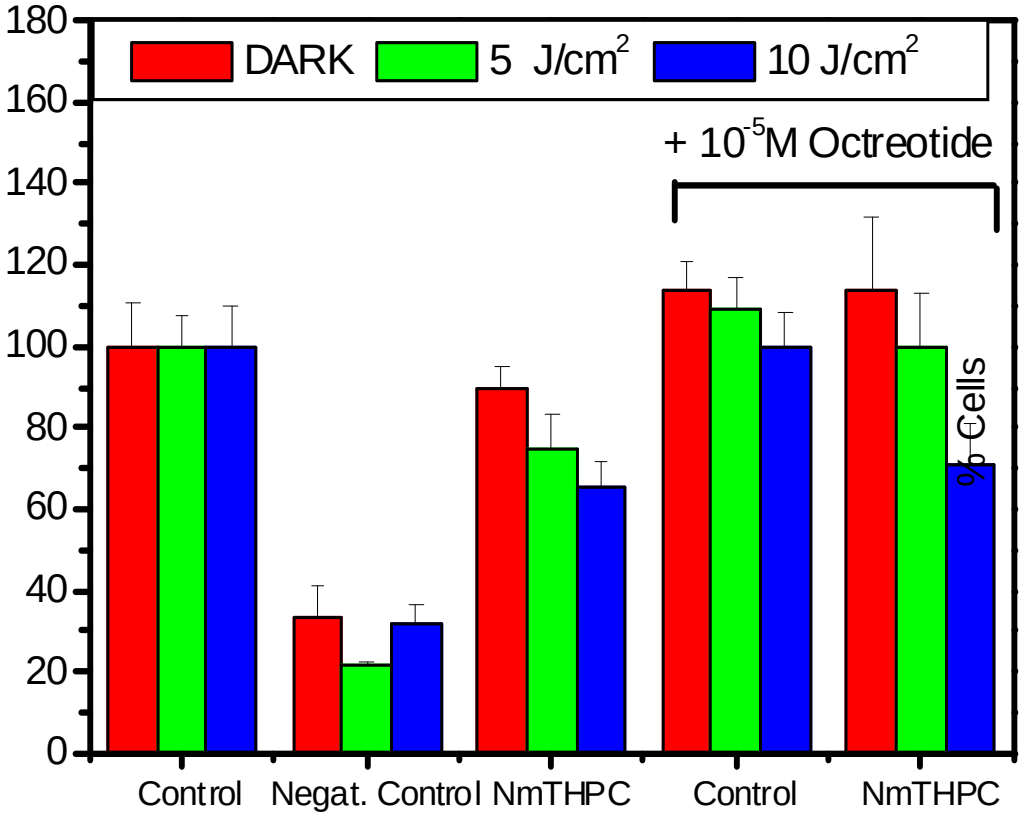
Ref Sample: Chlorin e6 (0.5uM)

Sample: NPM-Ce6 (~0.5uM)

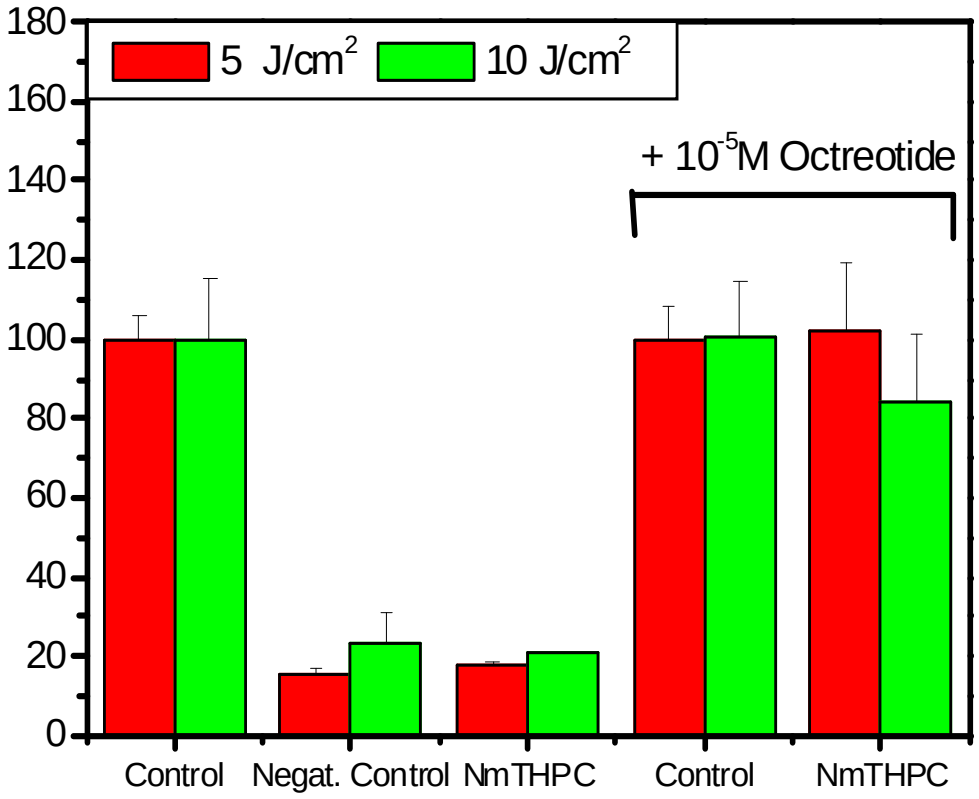


Photodynamic Therapy Results with Receptor Blocking

Unconjugated NP

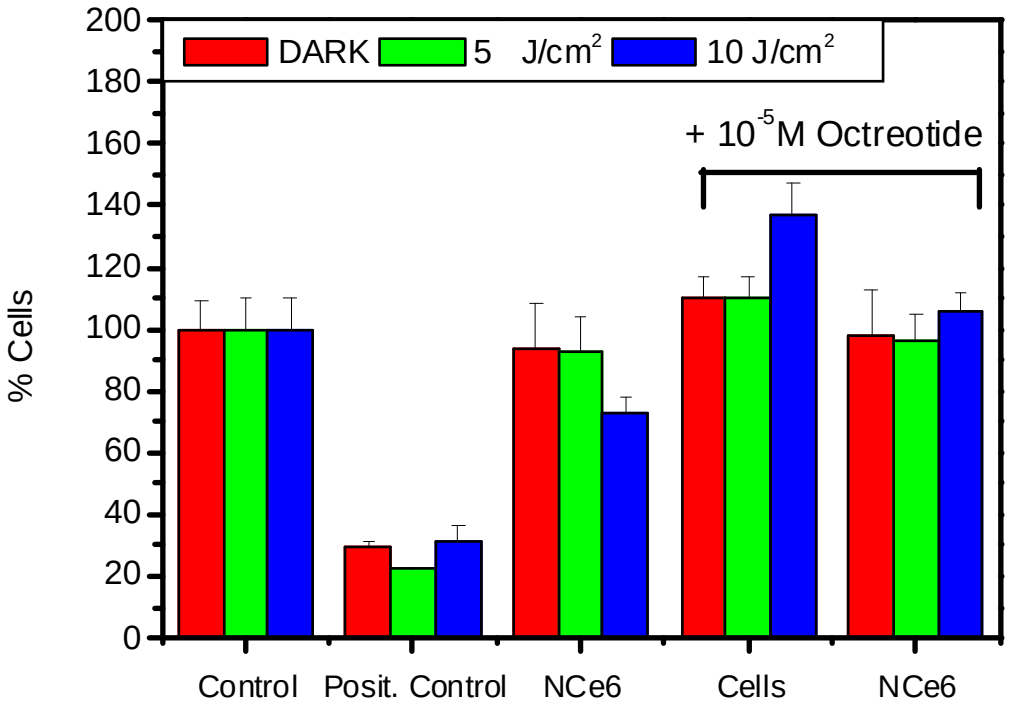


Conjugated NP

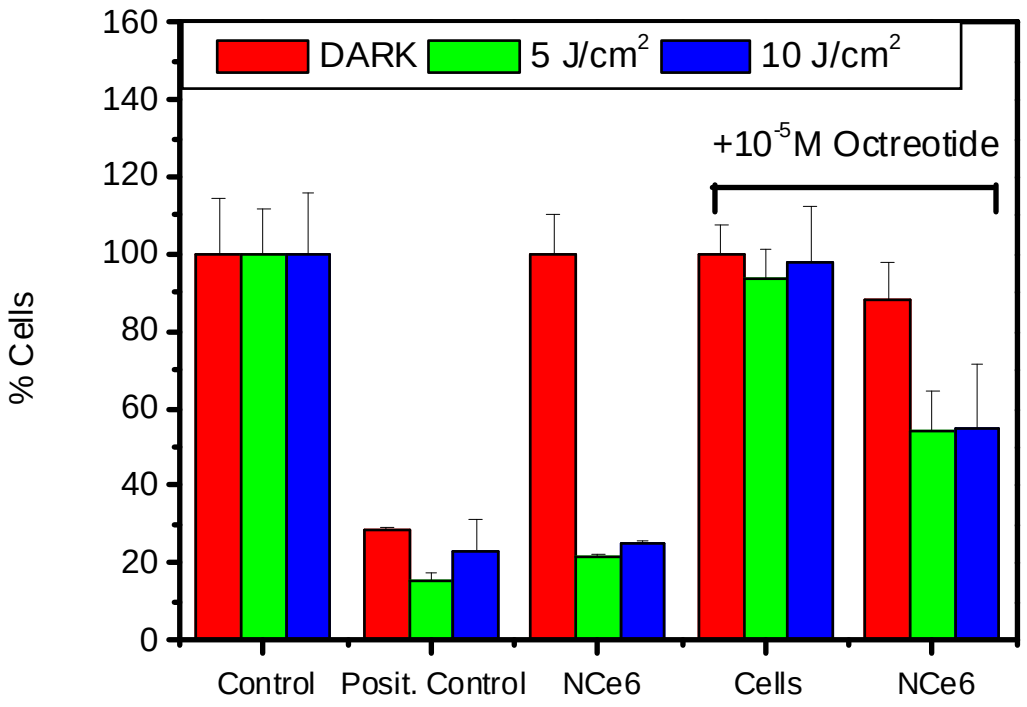


When PS is amphiphilic Ce6

NPM -Peptide un-conjugated

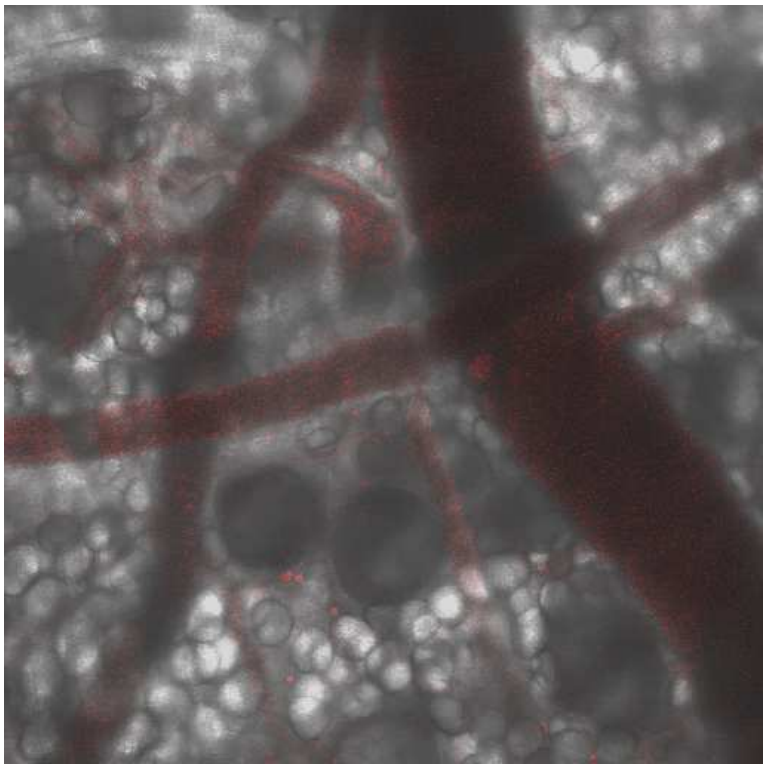


NPM -Peptide conjugated

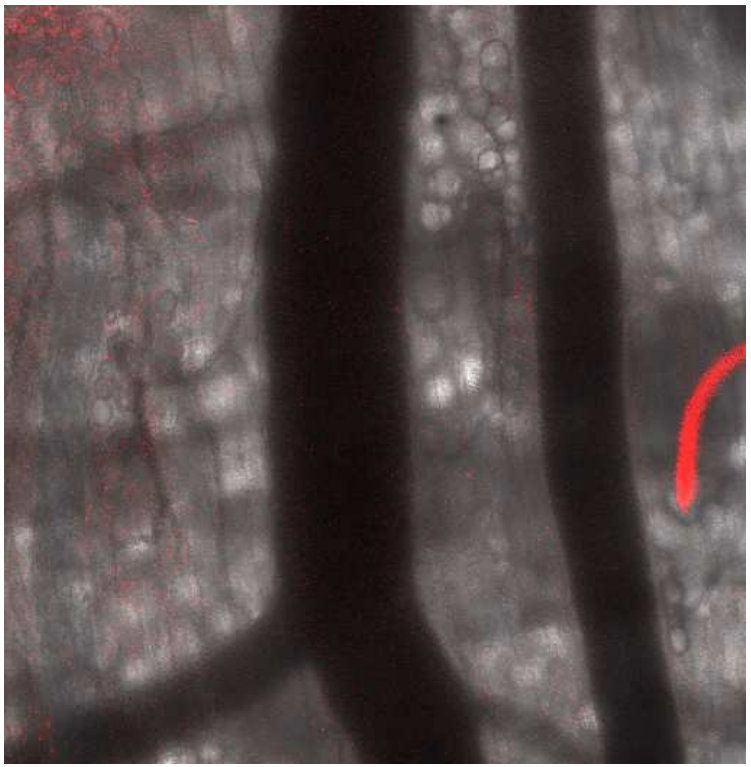


In vivo pharmacokinetcs-

5min



24 Hrs



PCT Patent Applied : Targeted Nanophotomedine, PCT/NL2009/050337

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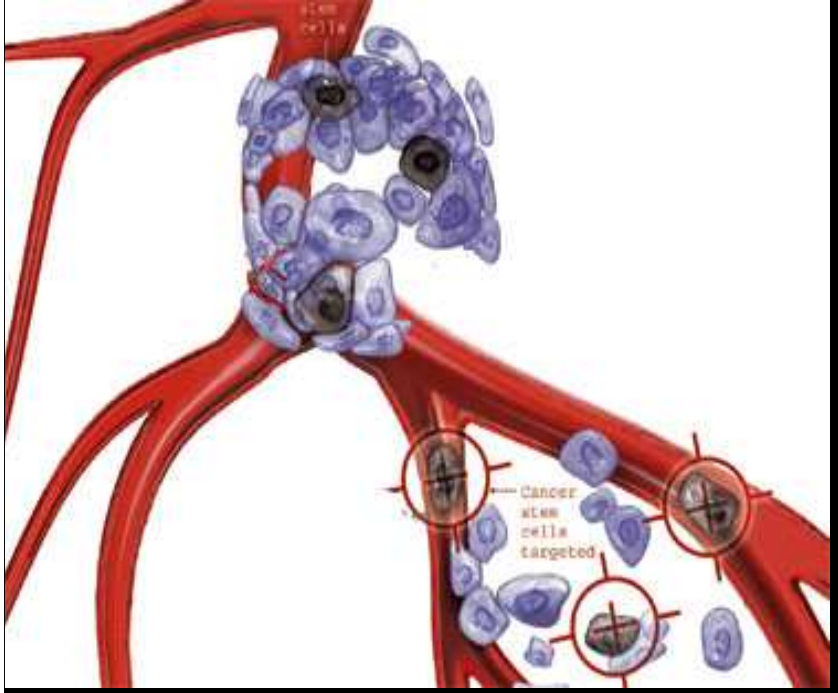
Anusha Ashokan and Manzoor K, Biomaterials (2010)

Manzoor K and Dominic Robinson, et al, Nanomedicine (To be submitted)

Proposed future Plan

Preclinical Trials in tumor models: At Erasmus MC and Amrita Nanocentre, Cochin

Phase – I Clinical study : FR receptor positive Nasopharangal Carcinoma

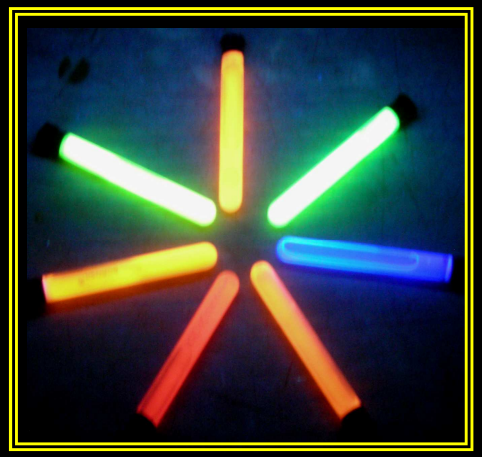


Other Research Focus at Amrita Centre for Nanoscience

- Molecular receptor Targeted nano-chemotherapeutics
- Cancer Stem cell targeted nano-chemotherapeutics
- Radio-Wave therapy using plasmonic nanocrystals
- iPSC based Cardiovascuar tissue engineering
- Nanotoxicology
- Raman Spectroscopic Finger printing of Oncogenes
- Nanomedicines targeted to autoimmune disease (MS)

Thanks to

Marie-Curie IIF Program, EC



Erasmus MC, Rotterdam

Amrita Nanocentre, India