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Molecularly Targeted Nanomedicine: Role of HSP90 Inhibitor and Sophorolipids

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MOLECULARLY TARGETED NANOMEDICINE: ROLE OF HSP90 INHIBITOR AND SOPHOROLIPIDS

Shuguftha Naz

Apr'6th, 2017

Outline

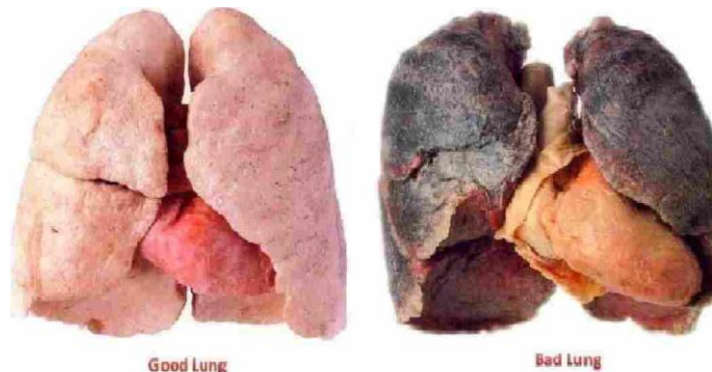
- Introduction and Background
 - Lung cancer and statistics
 - Cancer and Nanotechnology
- Nano-Medicine Approach
 - Nanoparticle-based drug delivery system
 - Synthesis of nanoparticles
 - Characterizations
 - Microscopic studies
 - Assays
- Conclusions
 - What we have accomplished
 - What comes next

Lung Cancer Statistics

- Lung cancer is currently the leading cause of cancer-related mortality due to its poor prognosis and low survival rate.

The American Cancer Society's estimates for lung cancer in the United States for 2017 are:

- About 222,500 new cases of lung cancer (116,990 in men and 105,510 in women)
- About 155,870 deaths from lung cancer (84,590 in men and 71,280 in women)

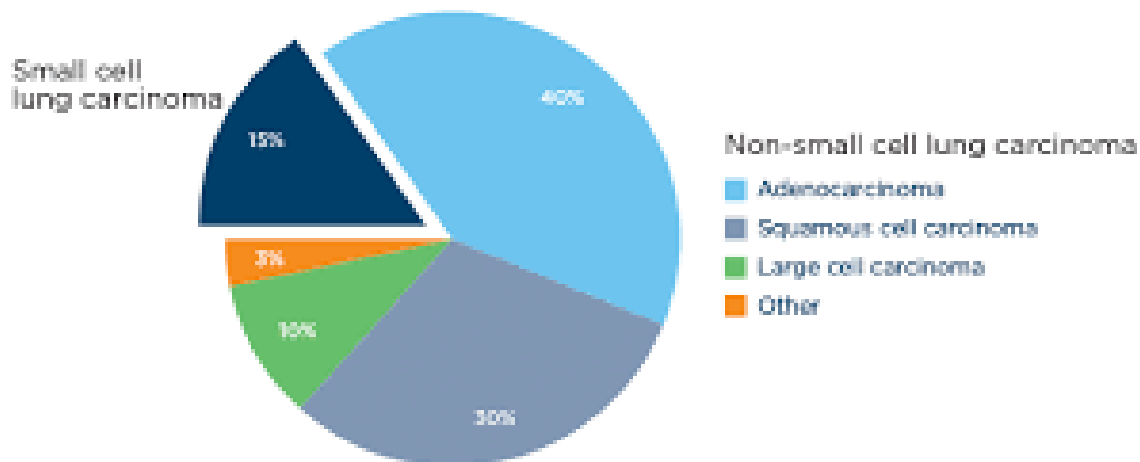


Types of Lung Cancer

Small-cell lung cancer – a less common type. Occurs in 10-15% of population.

Non-small-cell lung cancer – the most common type, accounting for more than 85-90% of cases; can be either squamous cell carcinoma, adenocarcinoma or large-cell carcinoma.

Types of Lung Cancer by Histology

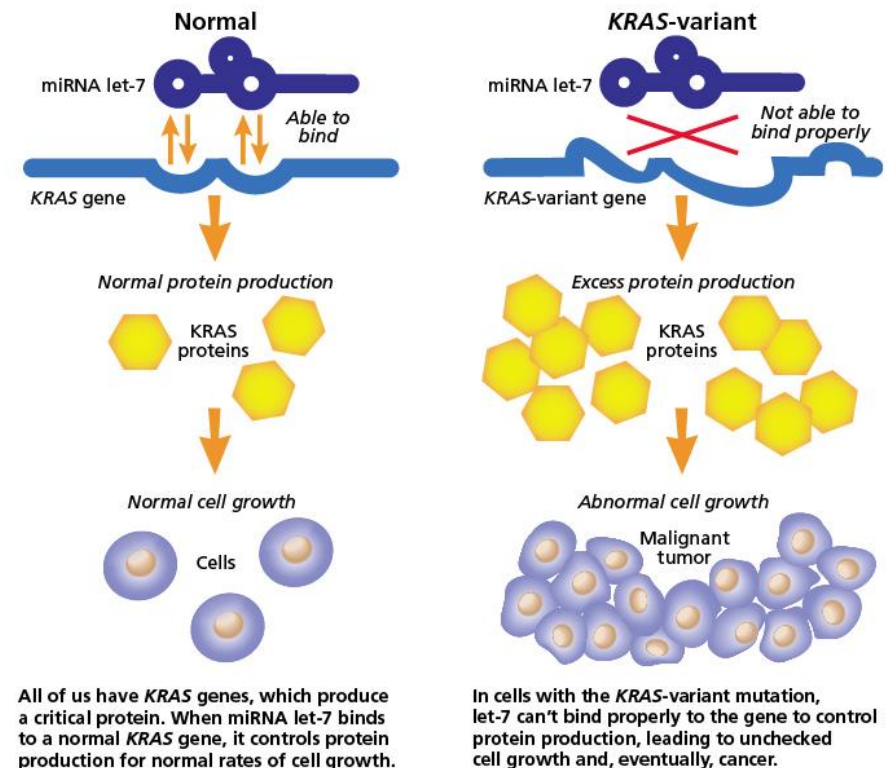


What is K-RAS mutant NSCLC?

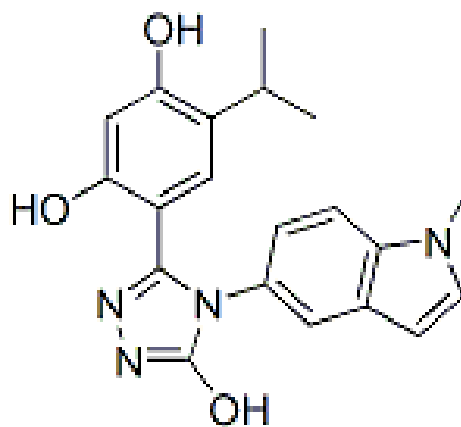
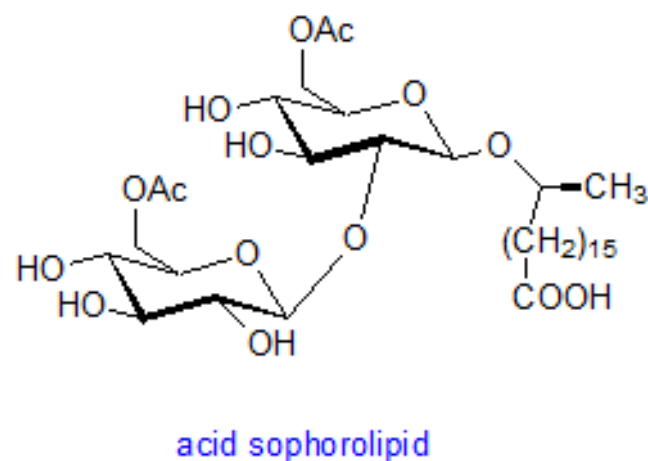
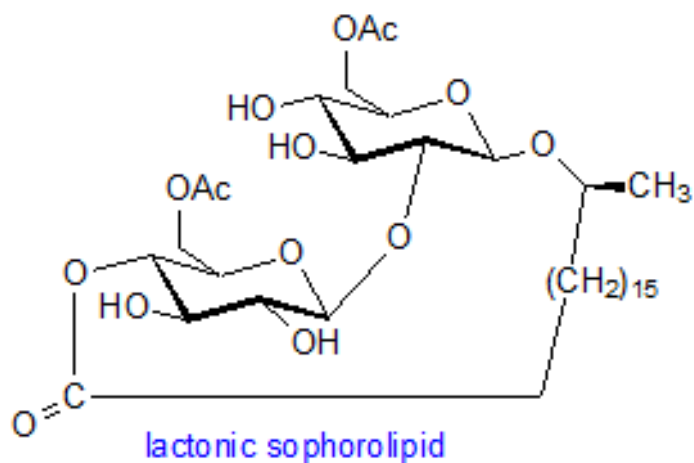
- Oncogenic mutations in Kirsten rat sarcoma oncogene homolog (KRAS) occur in 15%–30% of non-small cell lung cancer (NSCLC).
- For K-RAS NSCLC, the 5-year survival rate is less than 50% in phase I, followed by 73% in phase II and 58% in phase III, which is less than 15% in overall.
- Undruggable!!

KRAS at Work

Though the entire process of cellular protein production is complex and not entirely understood, Weidhaas and Slack made a breakthrough by focusing on one small piece of that puzzle: how a mutation in the *KRAS* gene can prevent the microRNA (miRNA) let-7 from binding to it well enough to control how much protein it produces.



Potential anti-tumor drugs: GT and LSL



Ganetespib

Why nanoparticle-based drug delivery system?

- Higher surface area to volume ratio
- High intracellular uptake.
- Reduced toxicity to normal cells.
- Targeted specific cells and tissues.
- Higher bioavailability.

Side Effects of Chemotherapy & Radiation

Usually Not Serious

- Fatigue
- Hair Loss
- Loss of appetite
- Mouth sores
- Nausea
- Vomiting
- Diarrhea
- Skin Changes

Potentially Serious

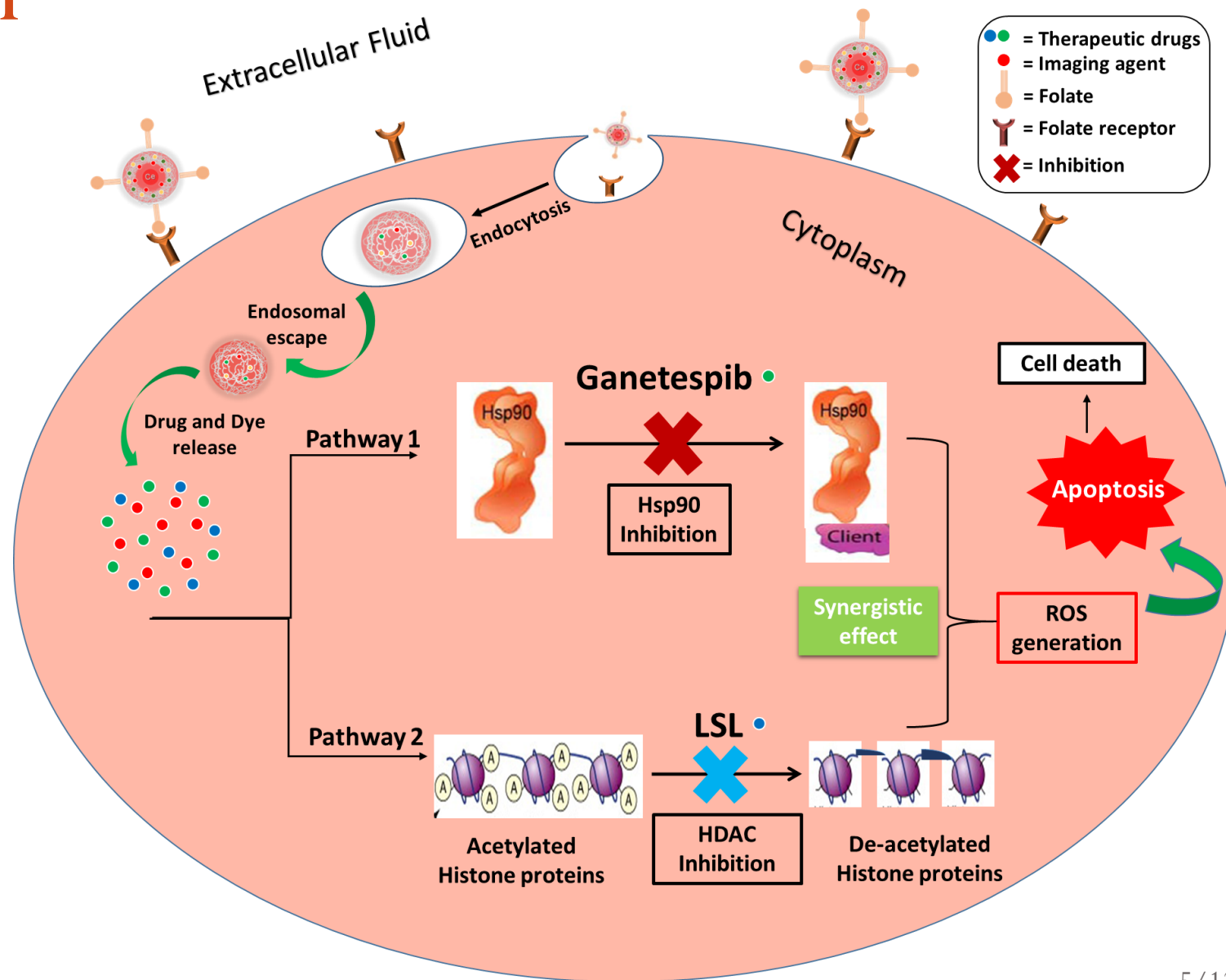
- Bleeding or bruising
- Low blood cell counts
- Infection



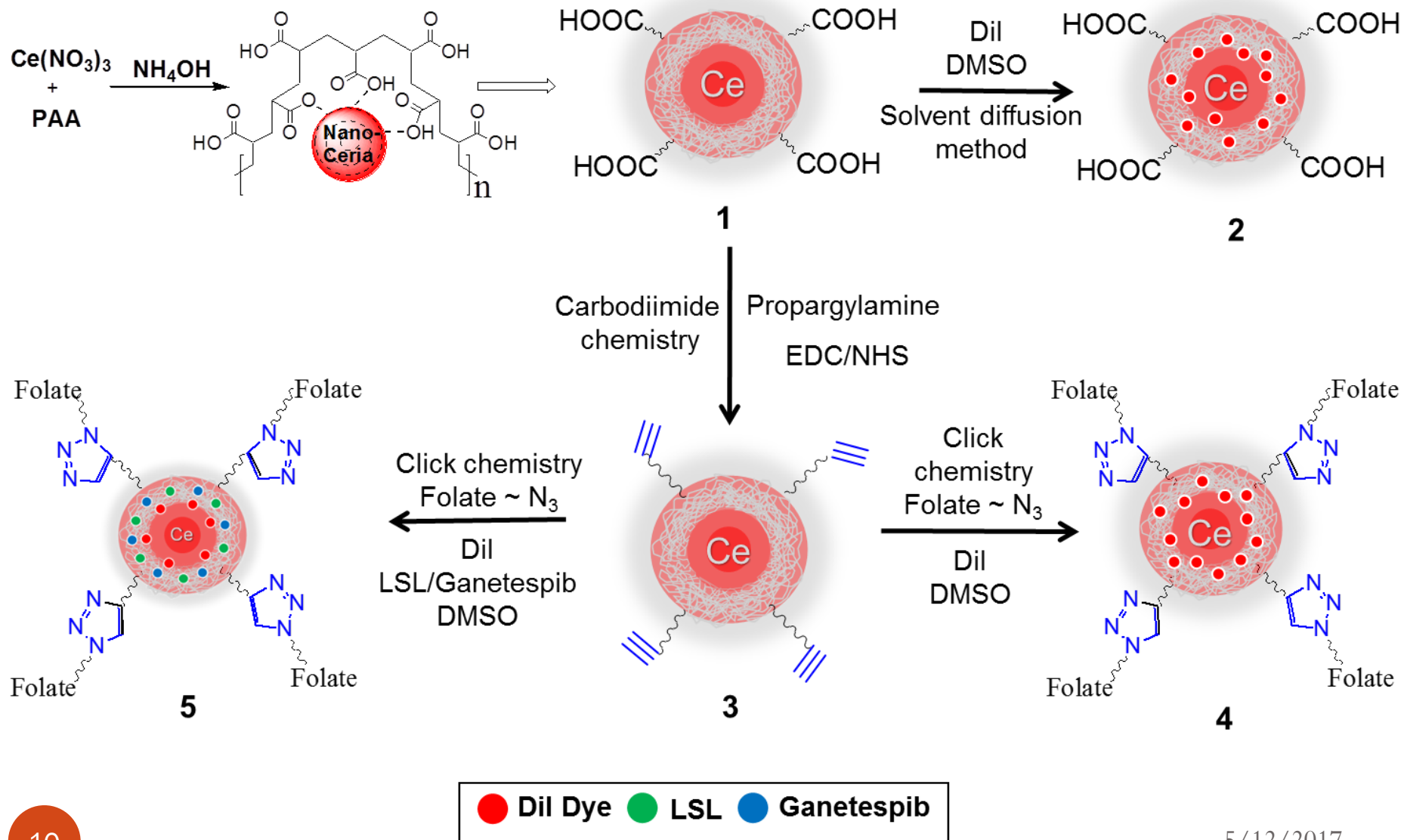
Various nanoparticle-based drug delivery systems

1. Polymeric nanoparticles
2. Metallic nanoparticles:
 - ✓ Iron oxide nanoparticles (IONP)
 - ✓ Cerium oxide nanoparticles (NC)
 - ✓ Gold Nanoparticles
 - ✓ Silver Nanoparticles

Hypothesis

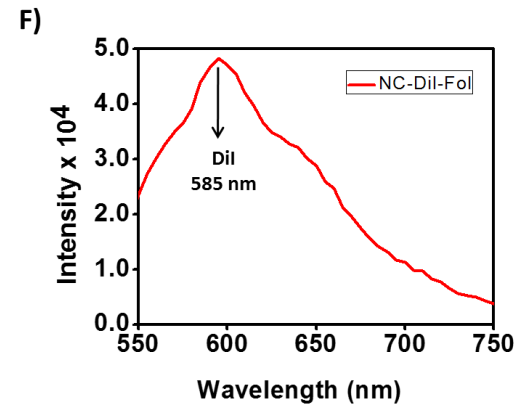
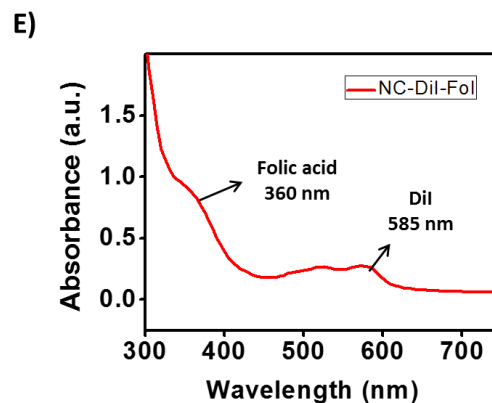
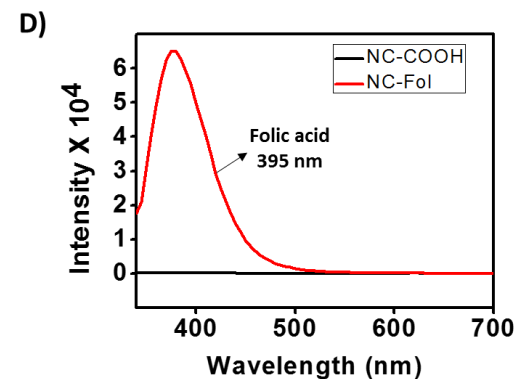
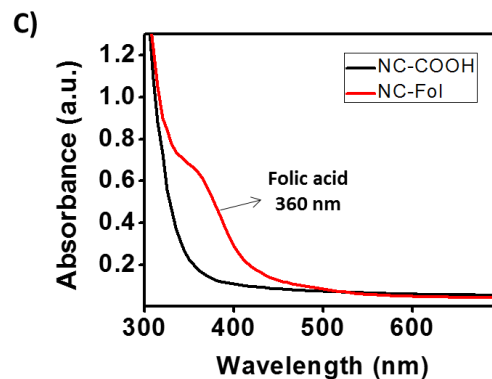
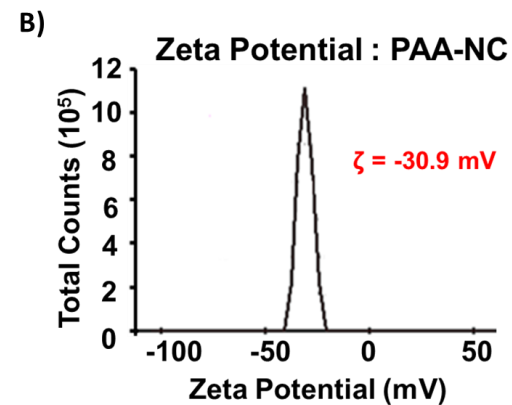
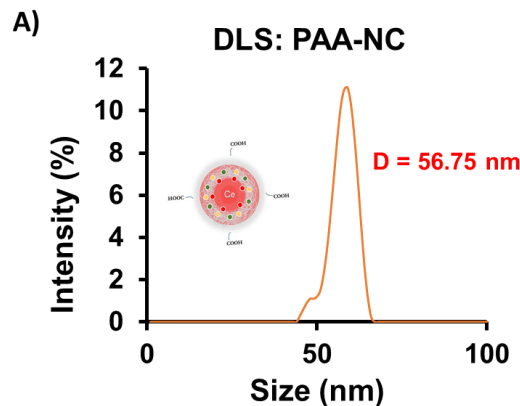
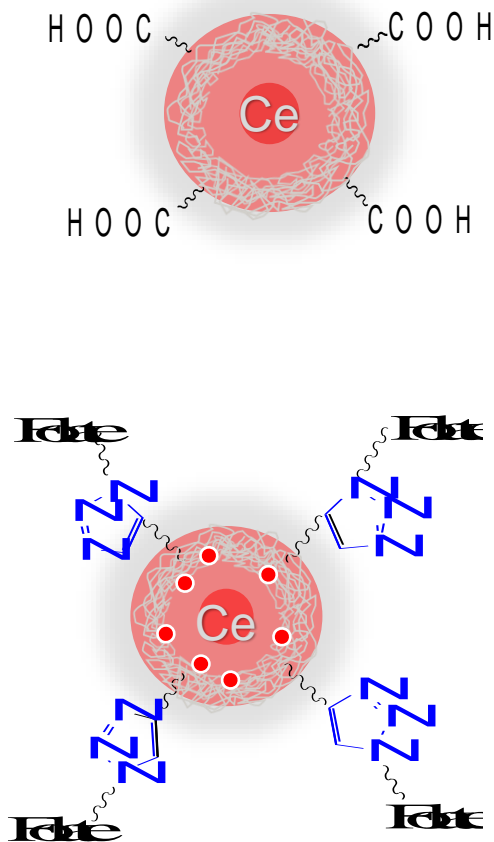


Synthesis of NC:

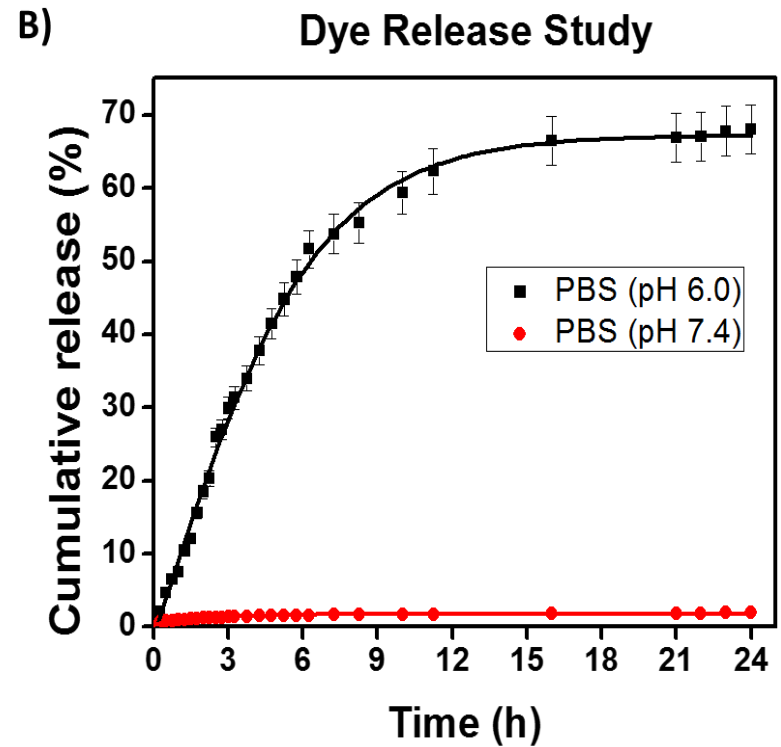
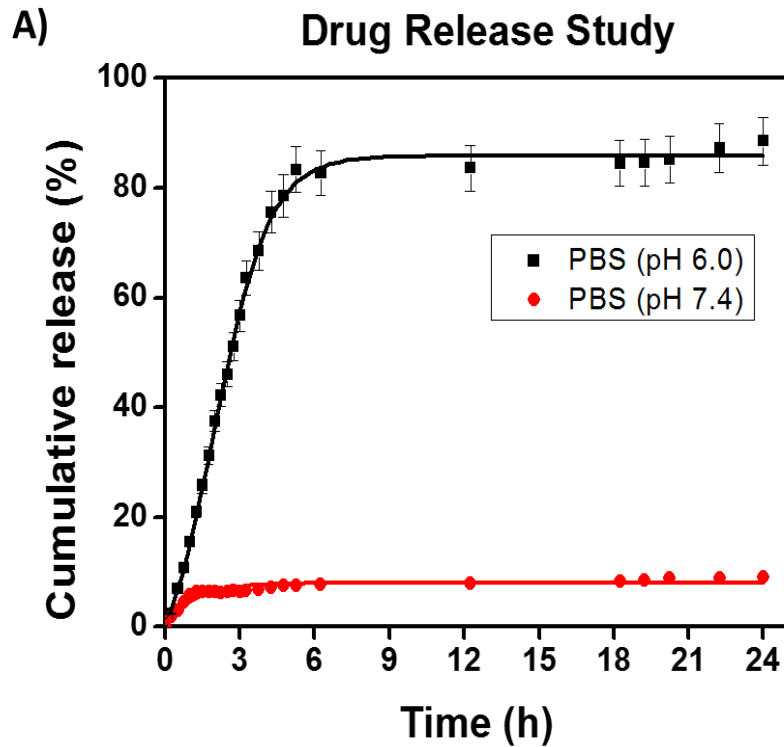
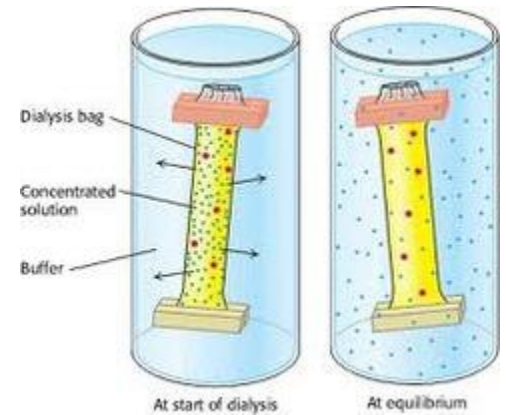


Characterizations

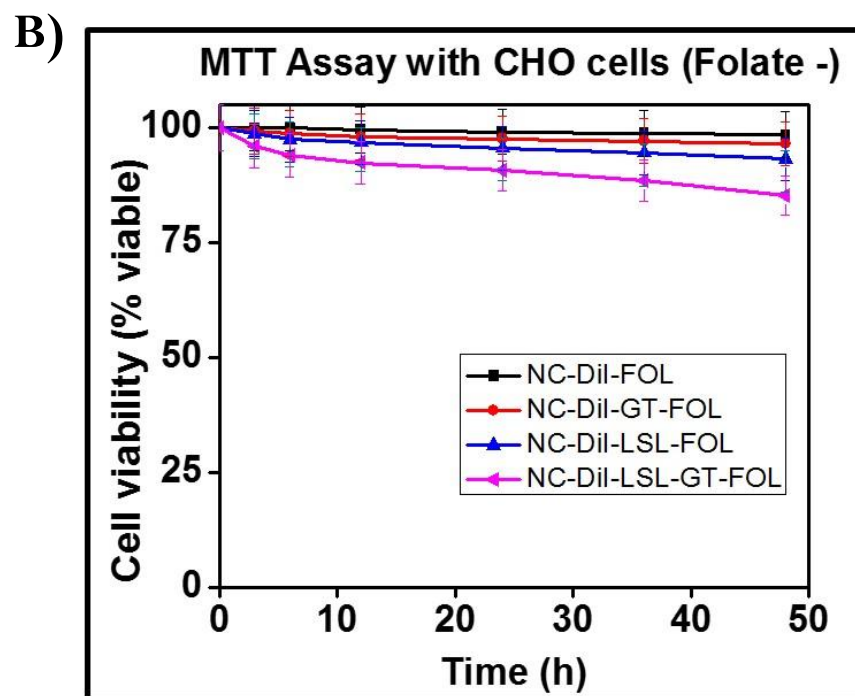
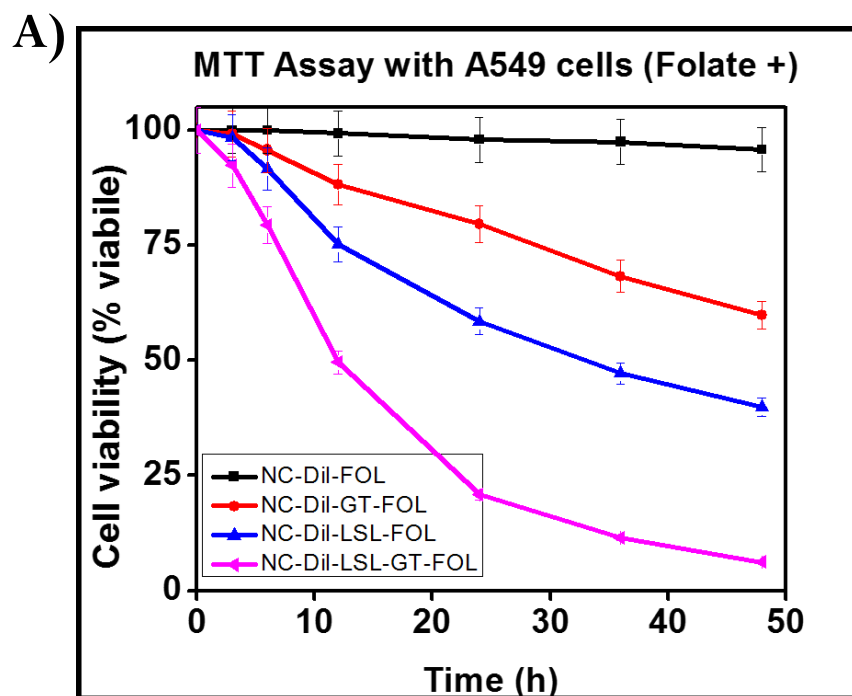
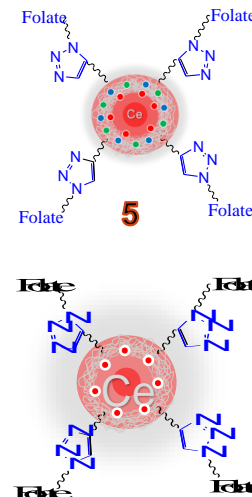
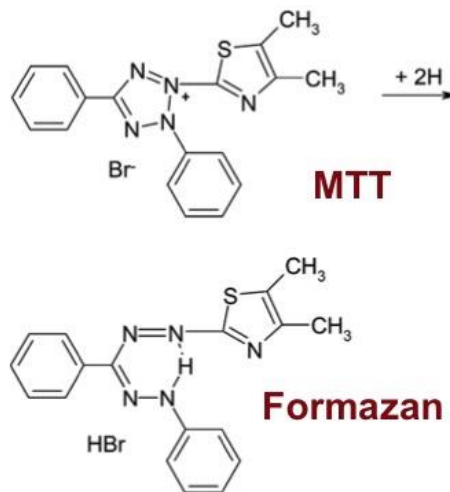
– UV Studies



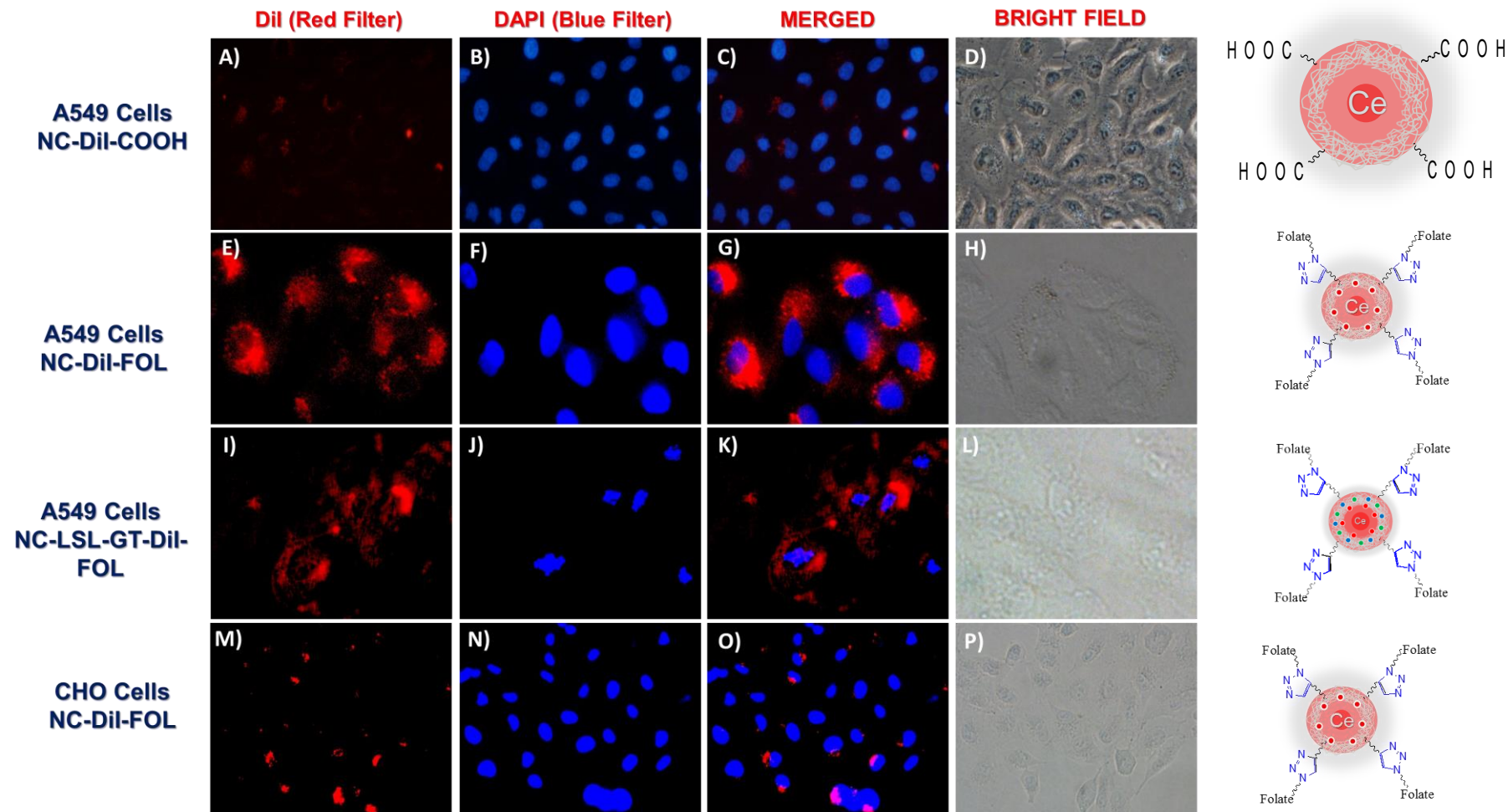
Drug Release Study



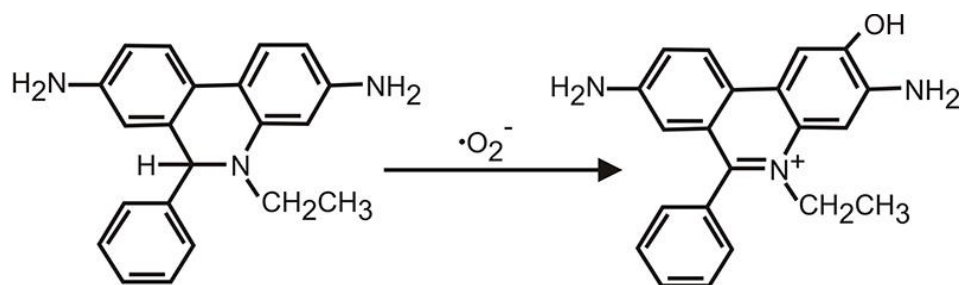
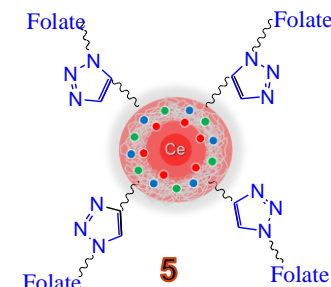
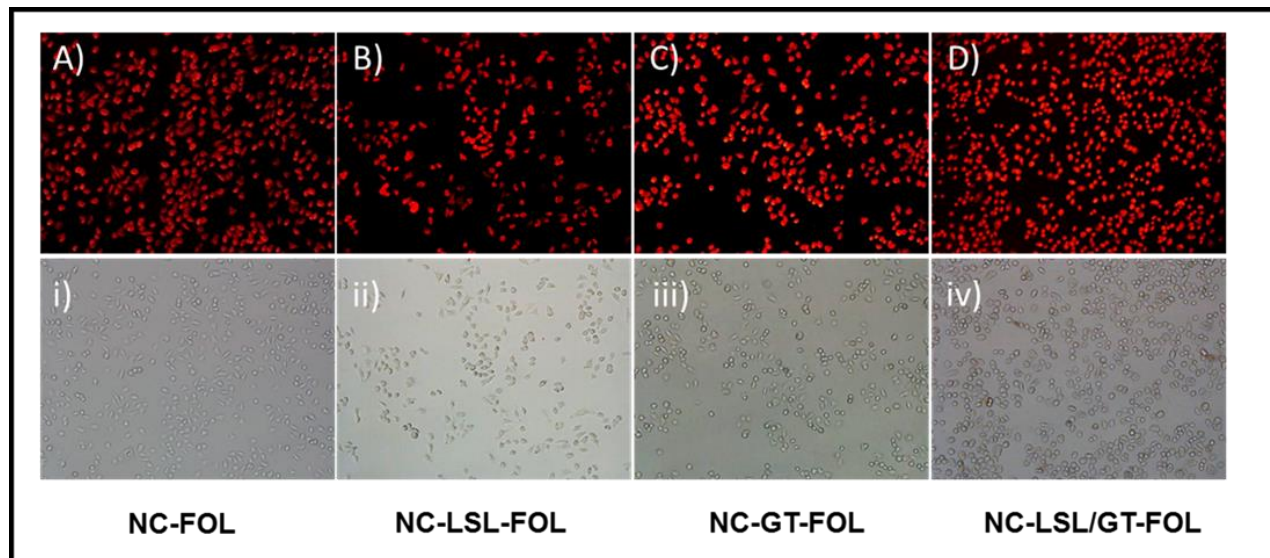
Cytotoxic Study (MTT Assay)



Optical Imaging

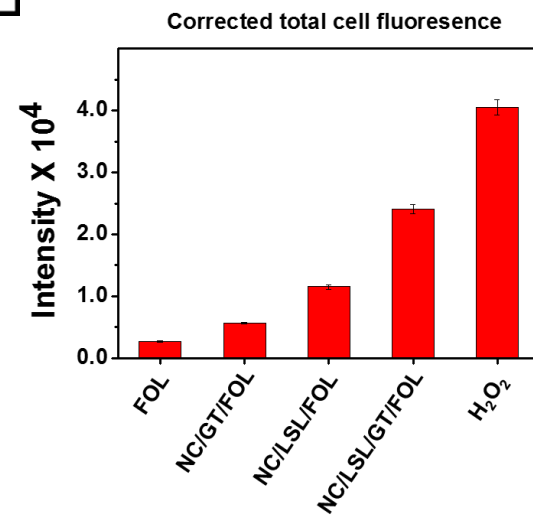


ROS Experiment



Dihydroethidium

2-Hydroxyethidium



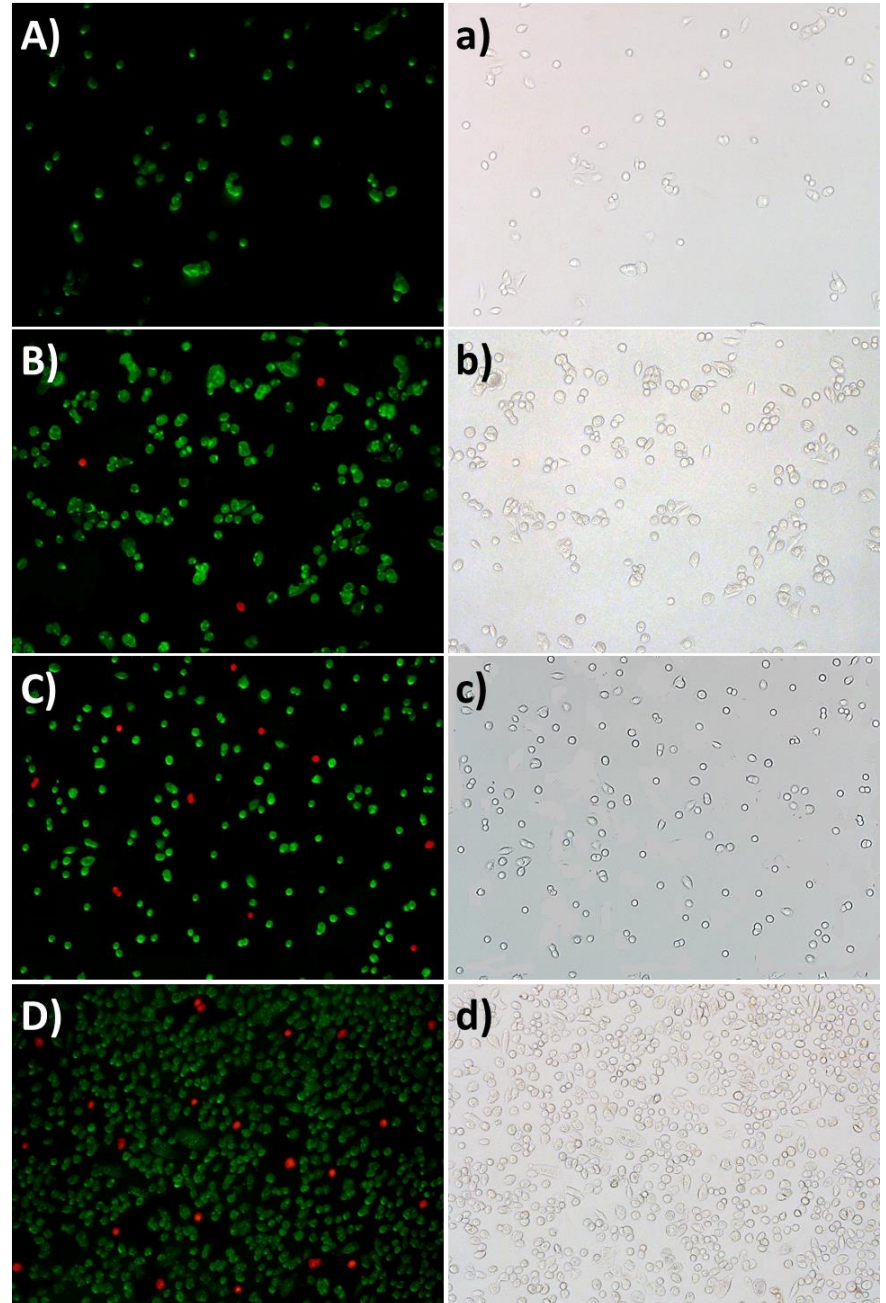
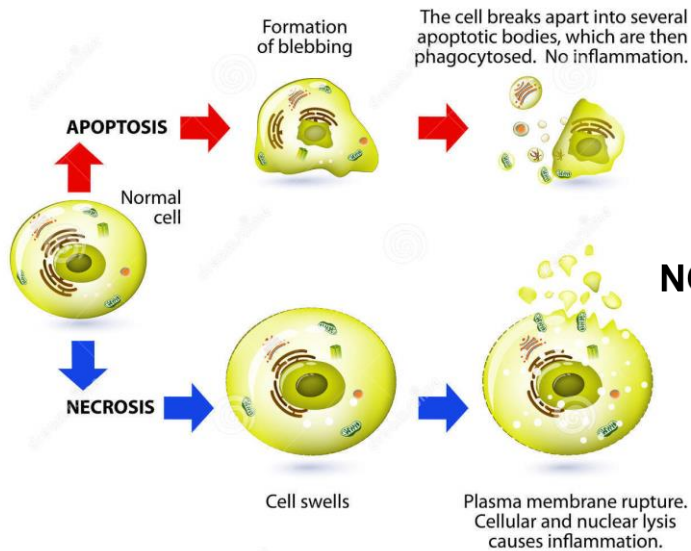
Apoptosis & Necrosis

NC-FOL

NC-GT-FOL

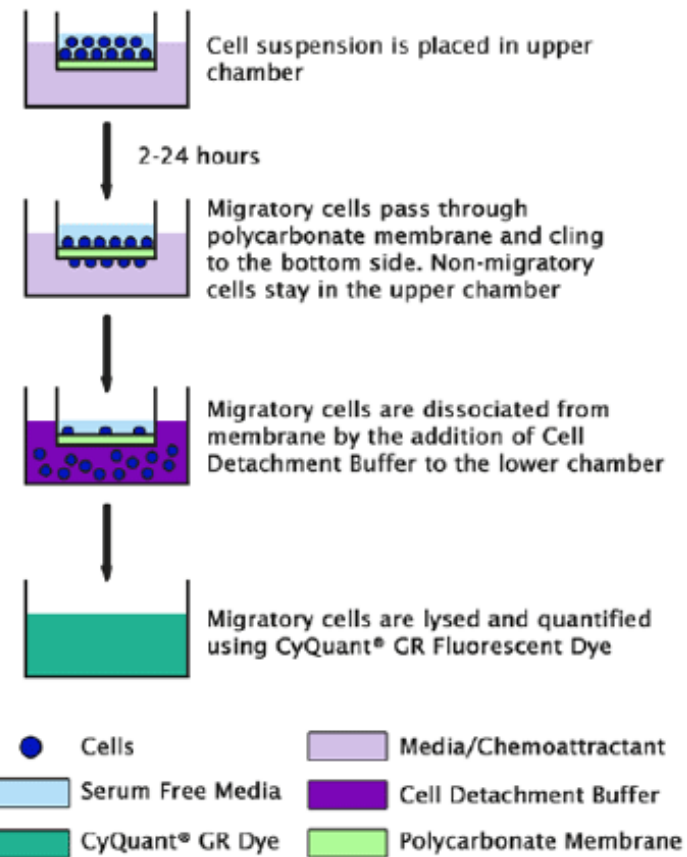
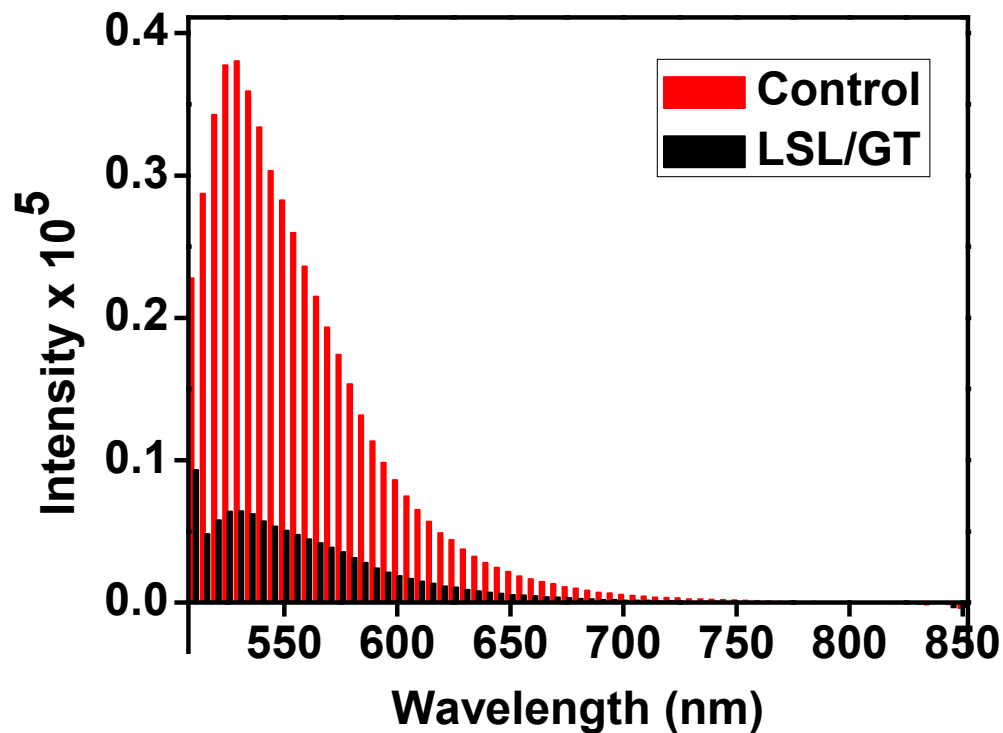
NC-LSL-FOL

NC-LSL/GT-FOL

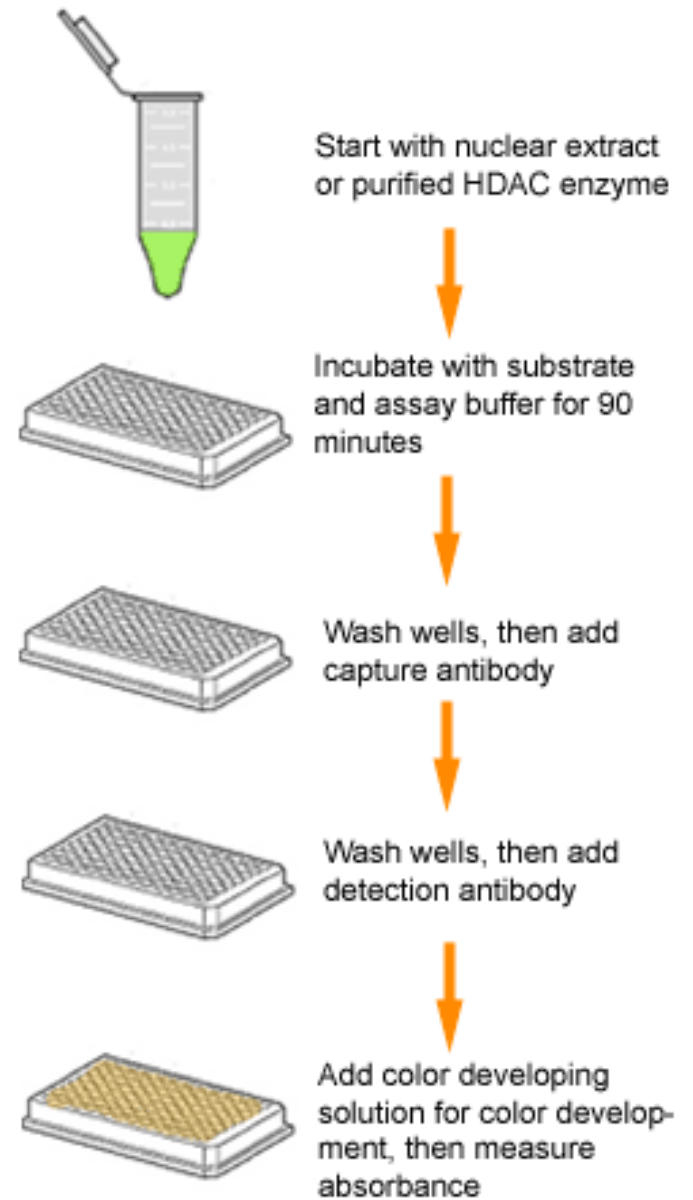
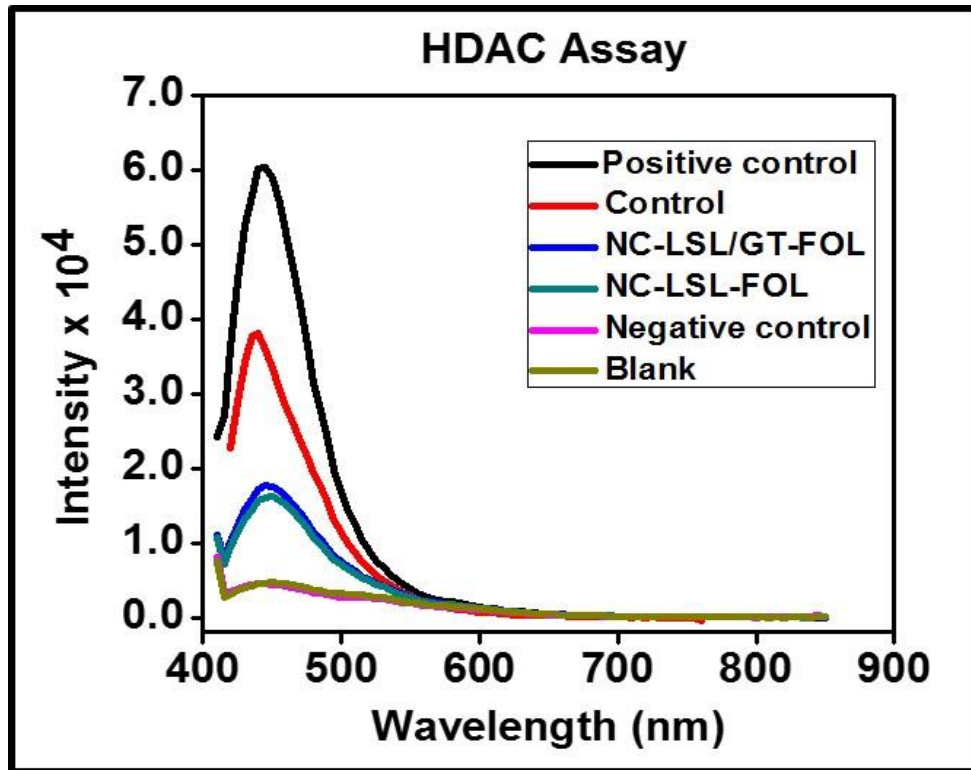


Migration Assay

Migration Assay



HDAC Inhibition Assay



Conclusions

- On a final note, we have successfully designed and synthesized nanoceria as a delivery vehicle carrying unique drug cocktail for the targeted treatment of NSCLC.
- We have achieved significant synergistic effect of the combinational drugs.

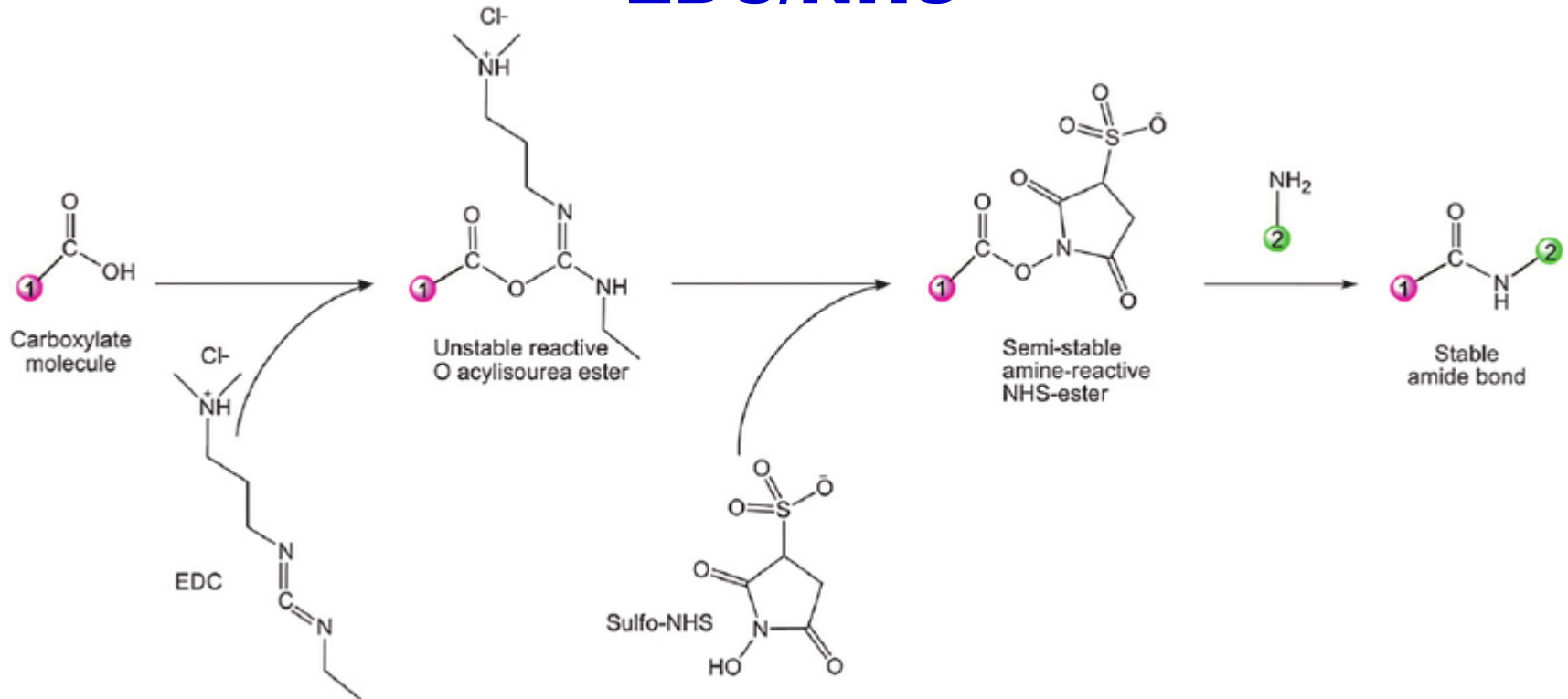
- **What Comes Next**

- Pre-clinical studies
- We would like to continue experimenting with drug combinations and also target other cancer cell lines.

A golden scroll with a metallic sheen, held by two golden rods with silver conical tips. The words "Thank You" are written in a black, elegant cursive script on the scroll's surface. The background is a light blue gradient.

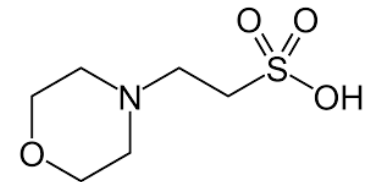
*Thank
You*

EDC/NHS



1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide • HCl
MW 191.70

Sulfo-N hydroxysuccinimide

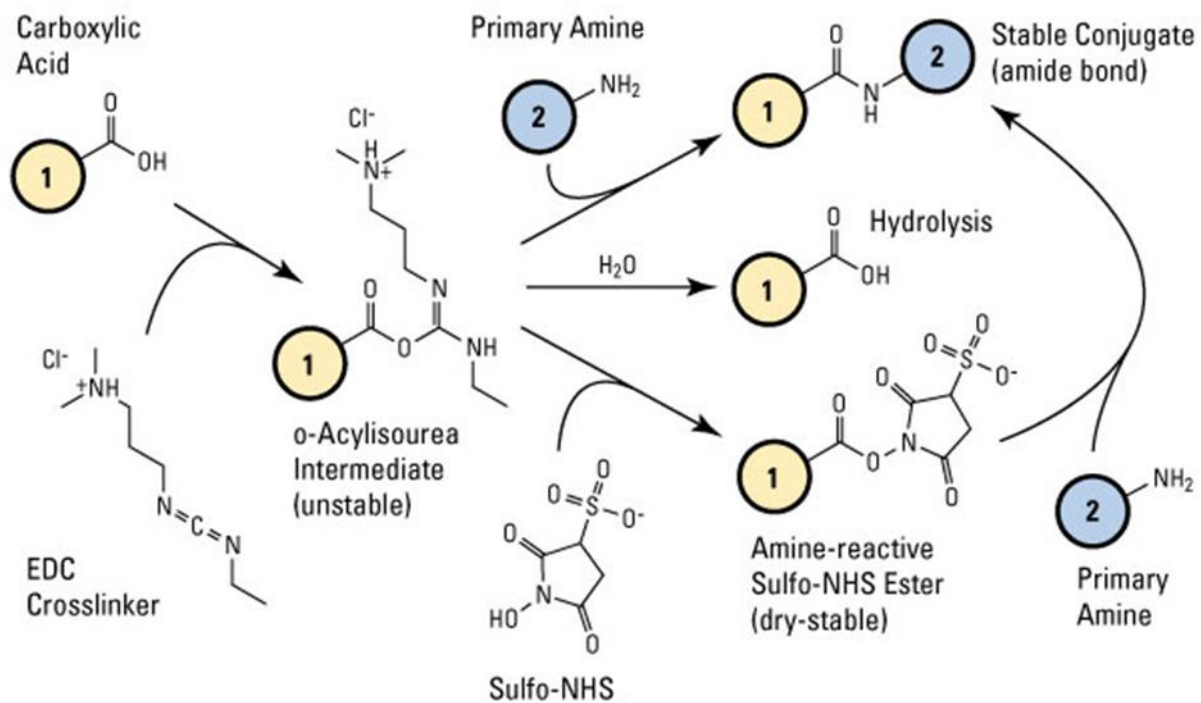


MES buffer (4-morpholinoethanesulfonic acid)

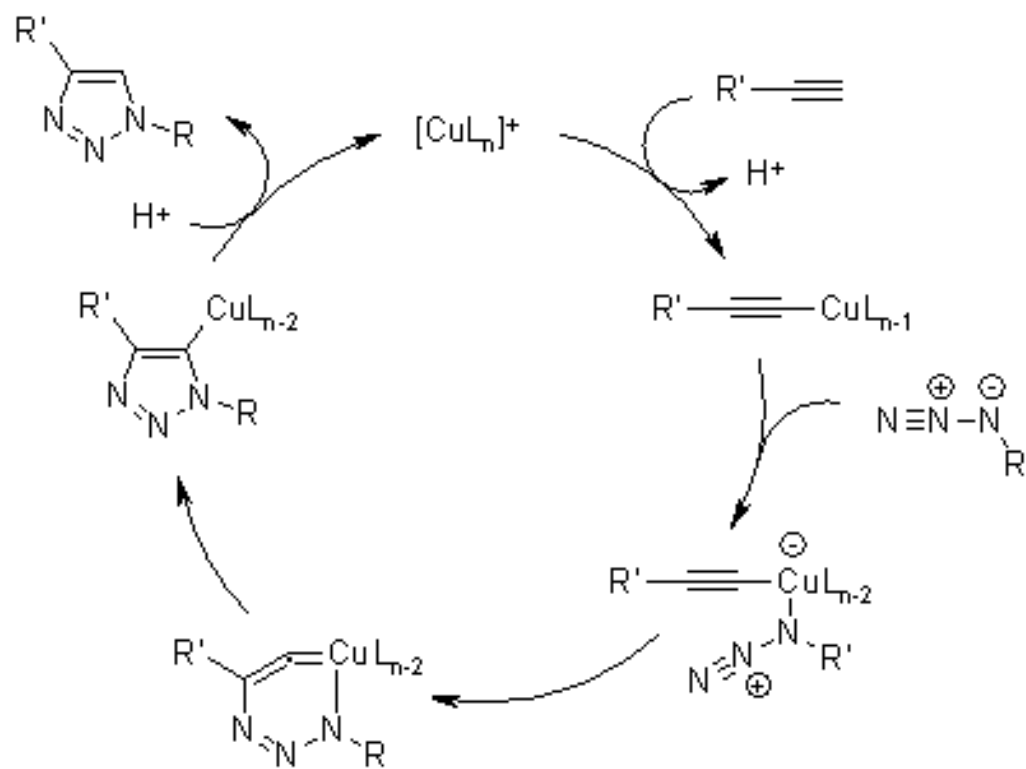
MES:

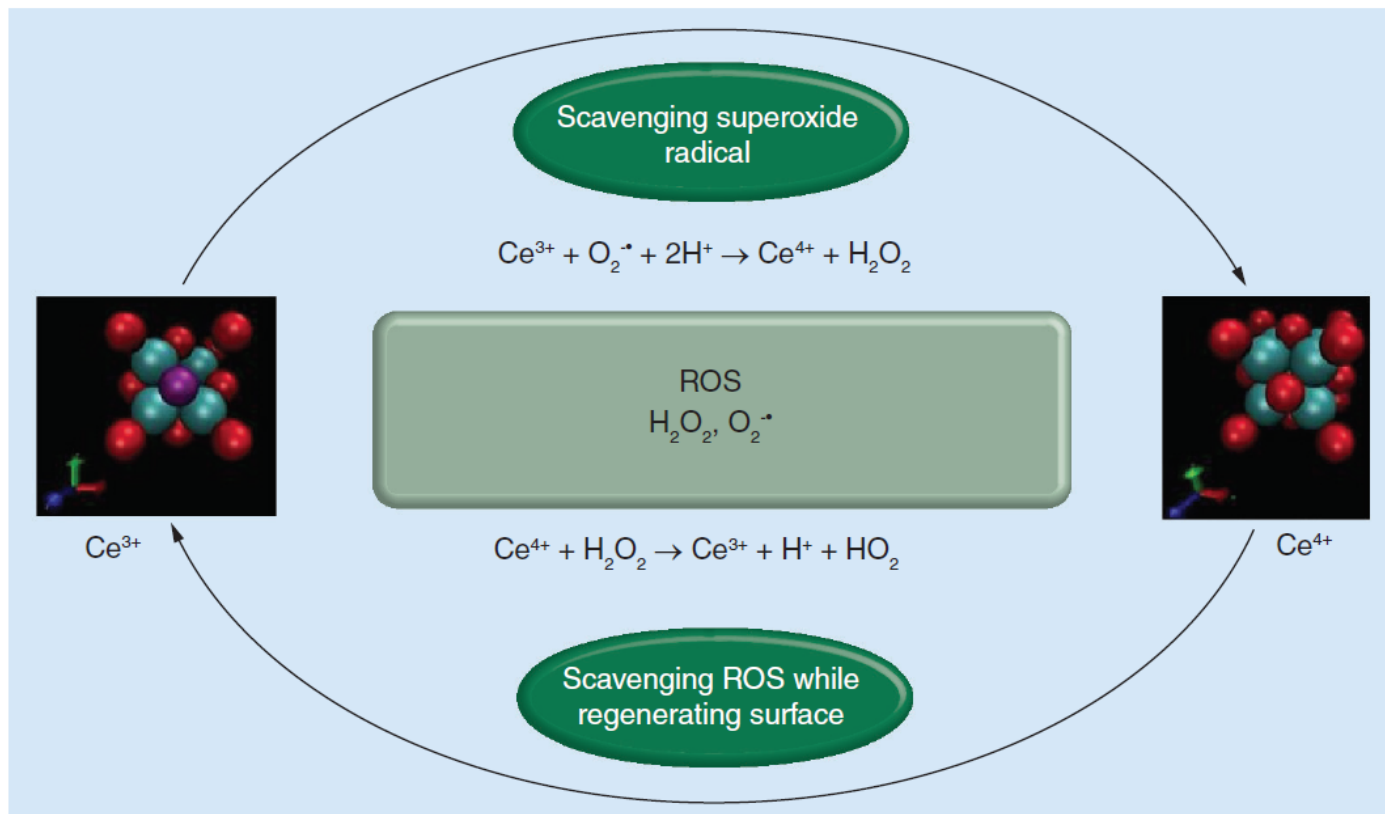
Acidic (pH 6) conditions- to increase efficiency.

Must be performed in buffers devoid of extraneous carboxyls and amines.



Click Chemistry



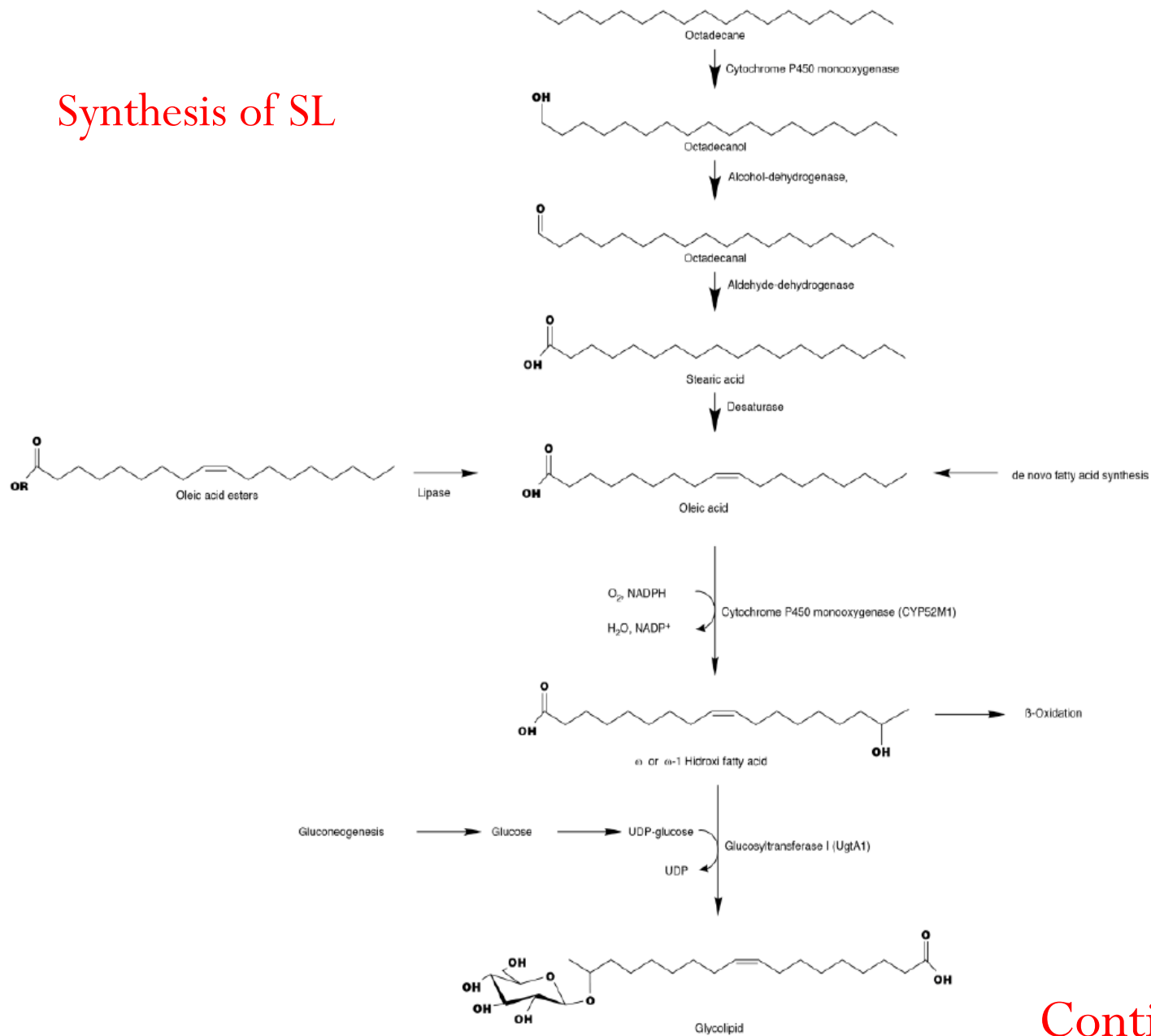


Tetrazolium dye, MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide

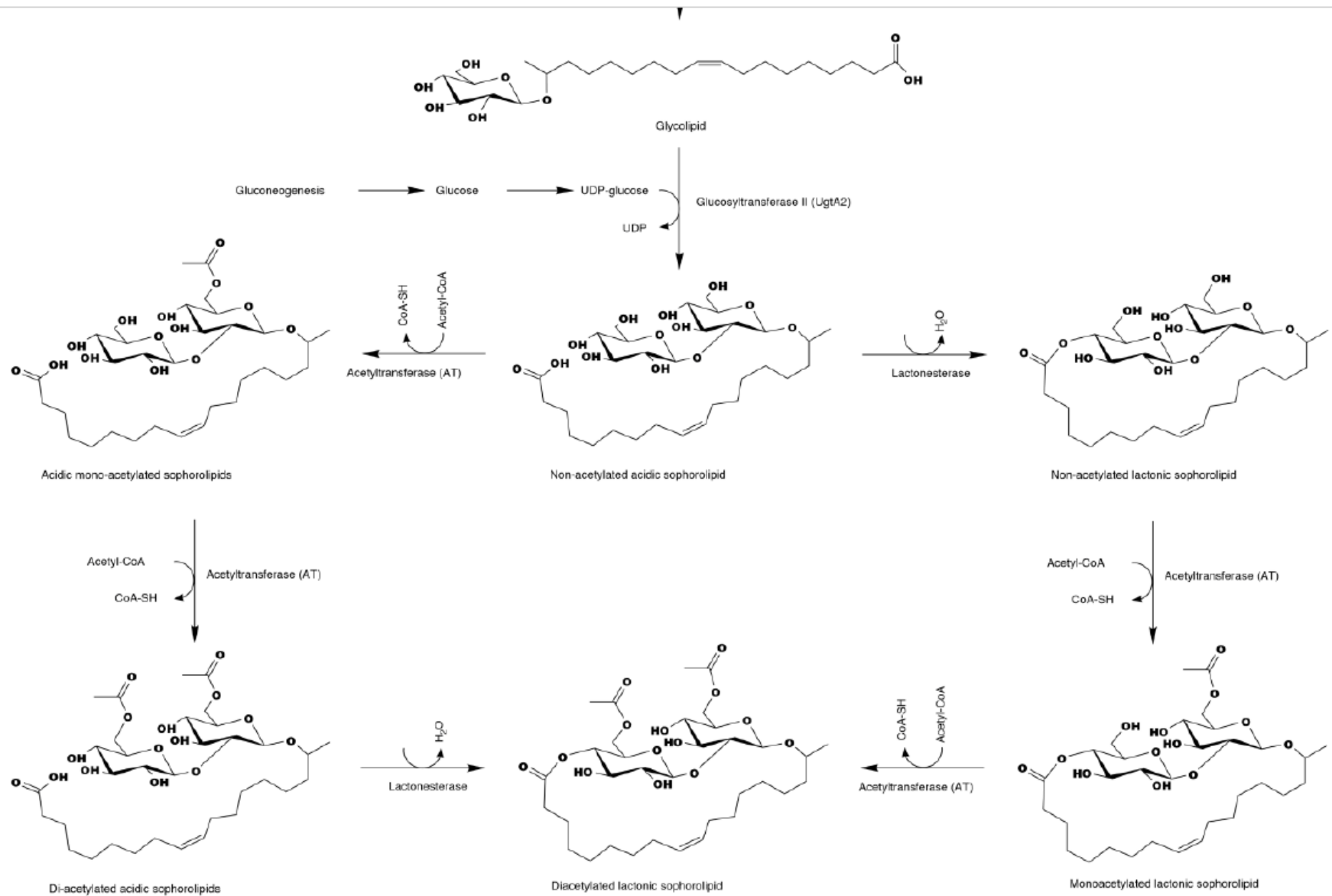
These survival rates include people who die from causes other than cancer.

- The 5-year survival rate for people with stage IA NSCLC is about 49%. For people with stage IB NSCLC, the 5-year survival rate is about 45%.
- For stage IIA cancer, the 5-year survival rate is about 30%. For stage IIB cancer, the survival rate is about 31%.
- The 5-year survival rate for stage IIIA NSCLC is about 14%. For stage IIIB cancers the survival rate is about 5%.
- NSCLC that has spread to other parts of the body is often hard to treat. Metastatic, or stage IV NSCLC, has a 5-year survival rate of about 1%. Still, there are often many treatment options available for people with this stage of cancer.

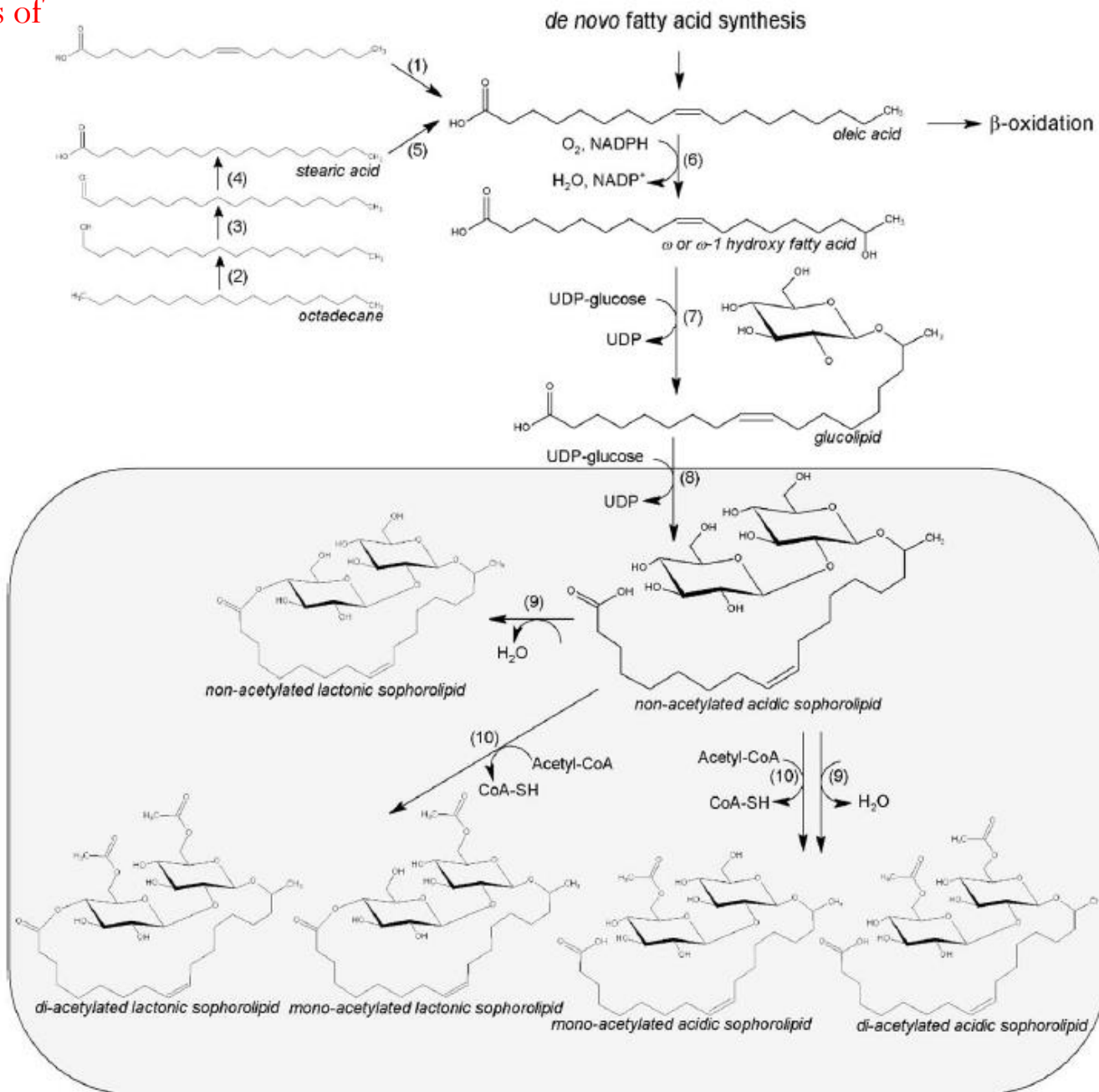
Synthesis of SL



Continued...



Simple synthesis of SL



Apoptosis

- ❖ Programmed cell death
- ❖ Disassembly of the cell organelles.
- ❖ Changes in phospholipid content present cytoplasmic membrane.
- ❖ Phosphatidyl Serine try to come out of the cell membrane.
- ❖ Annexin V (Natural anti coagulant) Ca^{2+} dependent phospholipid protein.



Hsp90 chaperone stabilizes client proteins; Hsp90 inhibition leads to client protein deactivation

