

# BIONANOTECHNOLOGY AS A NOVEL TREATMENT FOR BRAIN TUMORS

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# How Cancer Develops

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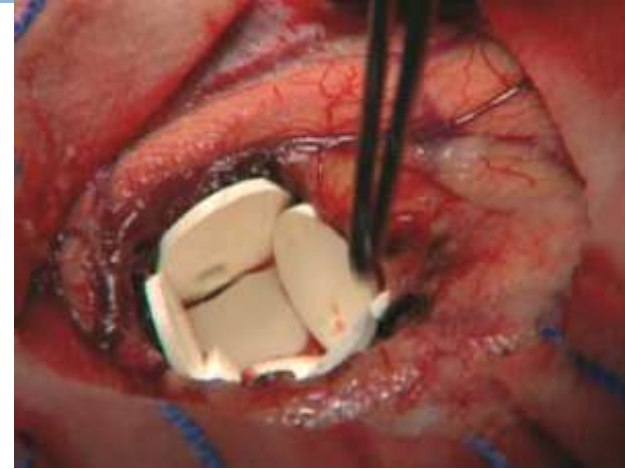
- Three general mechanism
  - Viral genetics
  - Epigenetics
  - Genetic Mutations

# Glioblastoma Multiforme

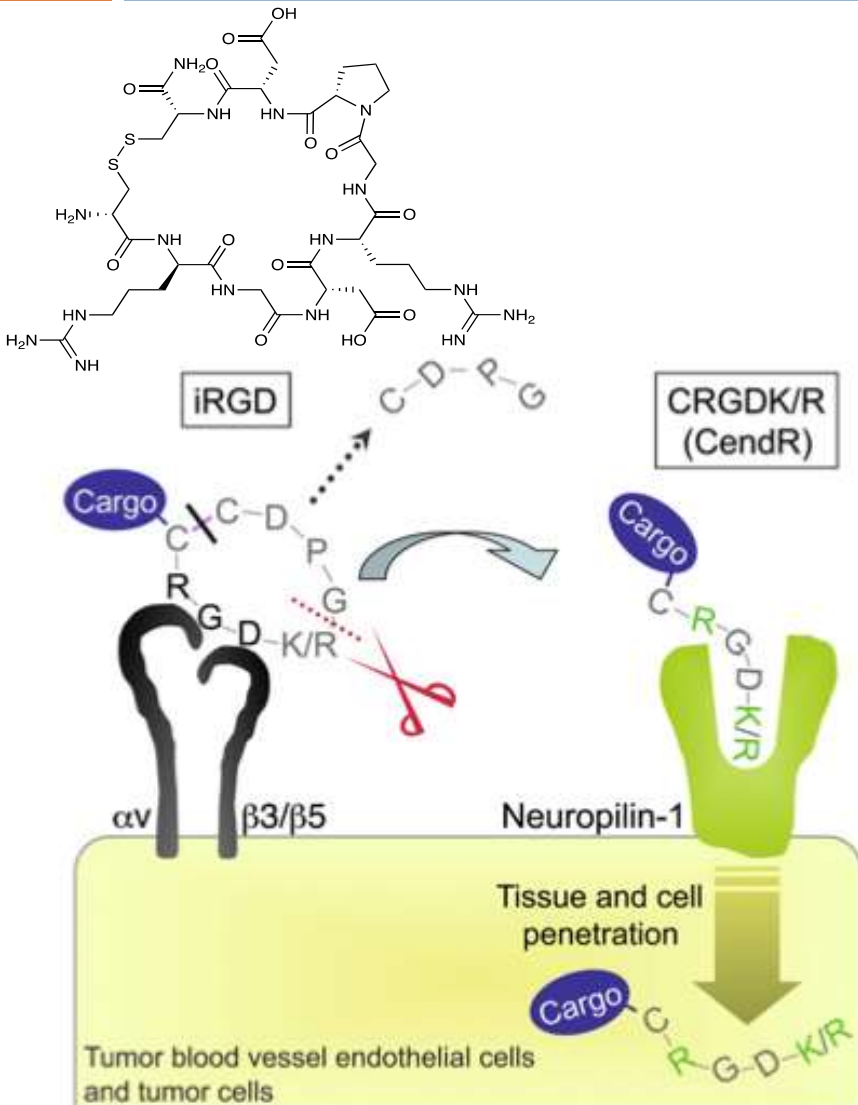
- ❑ Gliomas: 49% of all primary brain tumors and 2% of all newly diagnosed tumors in the US every year
- ❑ Greater than 60% of all gliomas diagnosed in the US every year are GBM
- ❑ 4 month survival without treatment and 15 months with treatment
- ❑ After recurrence, the survival period is only 3-5 months

# Treatment Options

- ❑ Surgery
  - ❑ Partial or total resection of the tumor
- ❑ Radiation
  - ❑ Ionizing radiation
- ❑ Chemotherapy
  - ❑ Difficult for systemic drugs to penetrate the BBB
  - ❑ Gliadel Wafers extends survival length by 2 months and increases survivors at 6 months after diagnosis by 50%



# iRGD Interaction with Tumor Cells



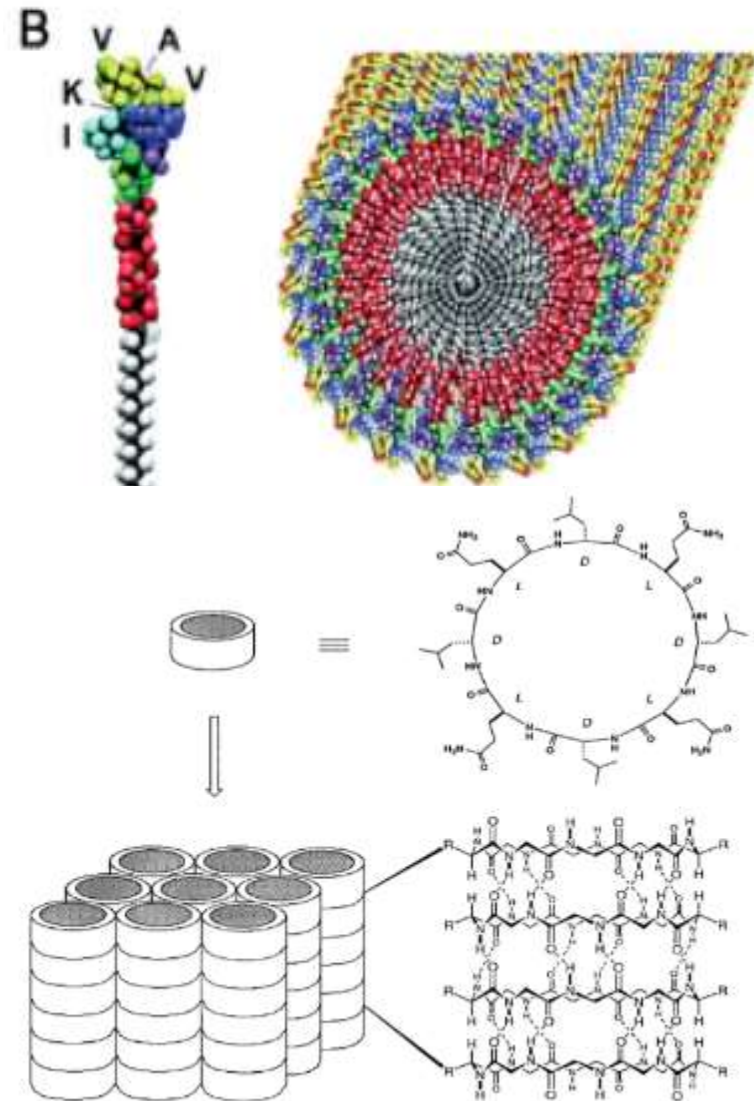
- ❑ Identification of iRGD peptide that can become internalized
- ❑ The  $\alpha_v$  and  $\beta_3/\beta_5$  integrin-dependent binding of iRGD
- ❑ Neuropilin-1 regulates internalization of iRGD
- ❑ Selective entry of cargo

# Application in Brain Tumors

- ❑ Integrins are vital in the survival and growth of glioma cancer cells
- ❑  $\alpha_v$  and  $\beta_5$  integrin overexpression in malignant gliomas
- ❑ neuropilin-1 overexpression in glioblastoma

# Nanotube Self-Assembly

- Three factors that drive peptide self-assembly
  - Molecules must reach a critical aggregation concentration
  - Hydrophobicity of peptide sequence and assembly media
  - Hydrogen bonds between peptide sequences

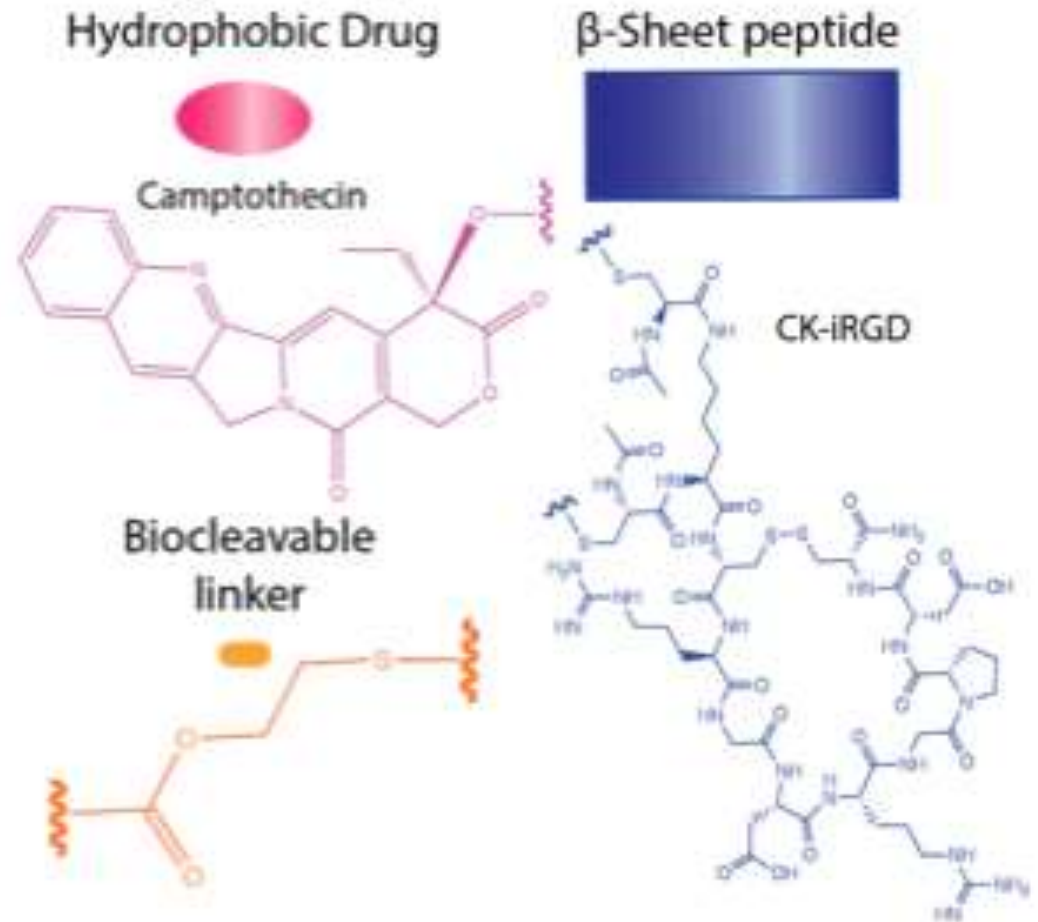




# Drug Design and Synthesis

- Drug Amphiphile
  - iRGD peptide
  - Camptothecin drug

## b. Drug amphiphile components



# Assembly

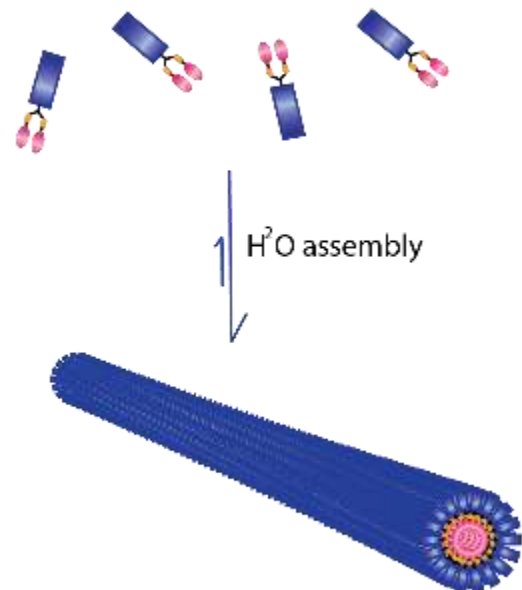
## Self-Assembly

- Form toroid structures and nanotubes in an aqueous environment

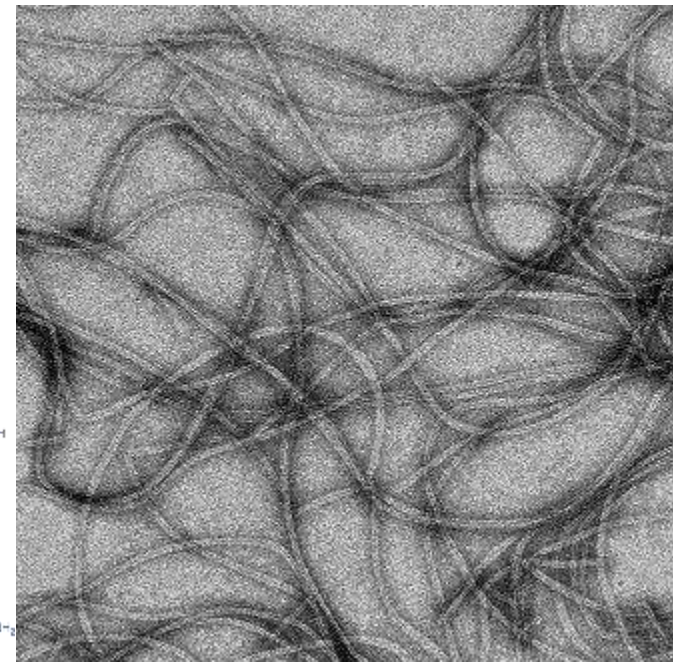
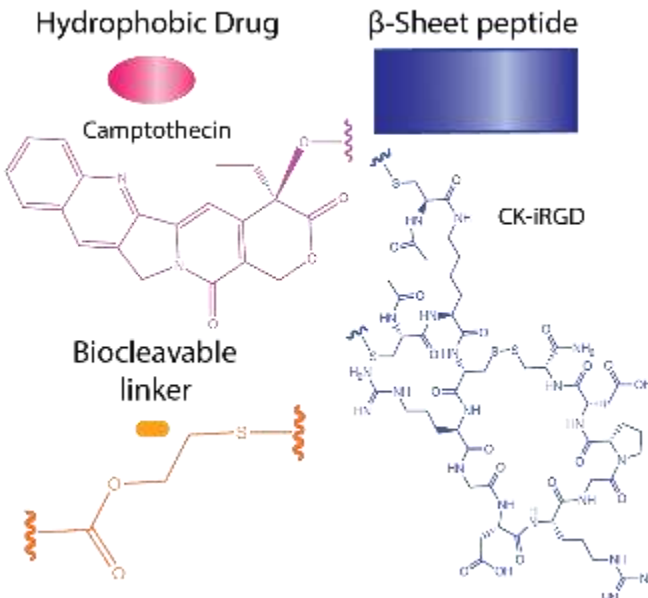
## Formation of the Hydrogel

- Crosslinking of nanotubes

a. Drug amphiphile self-assembly



b. Drug amphiphile components



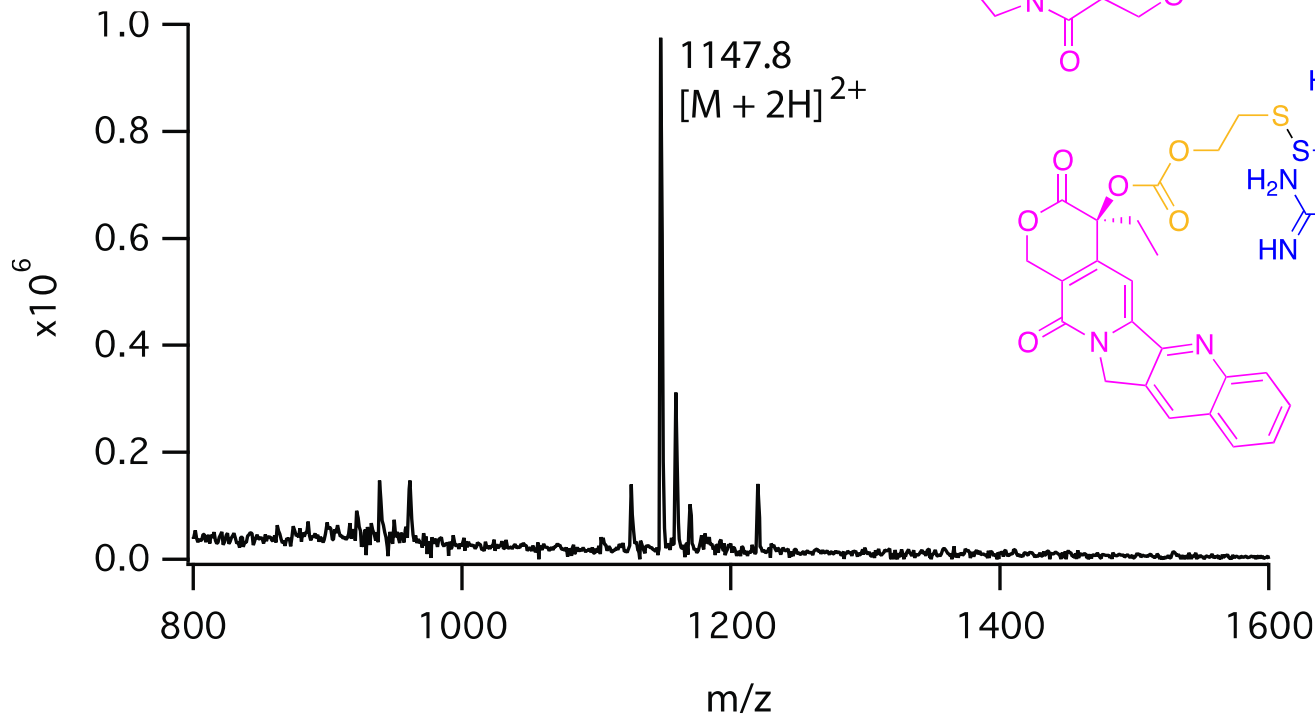
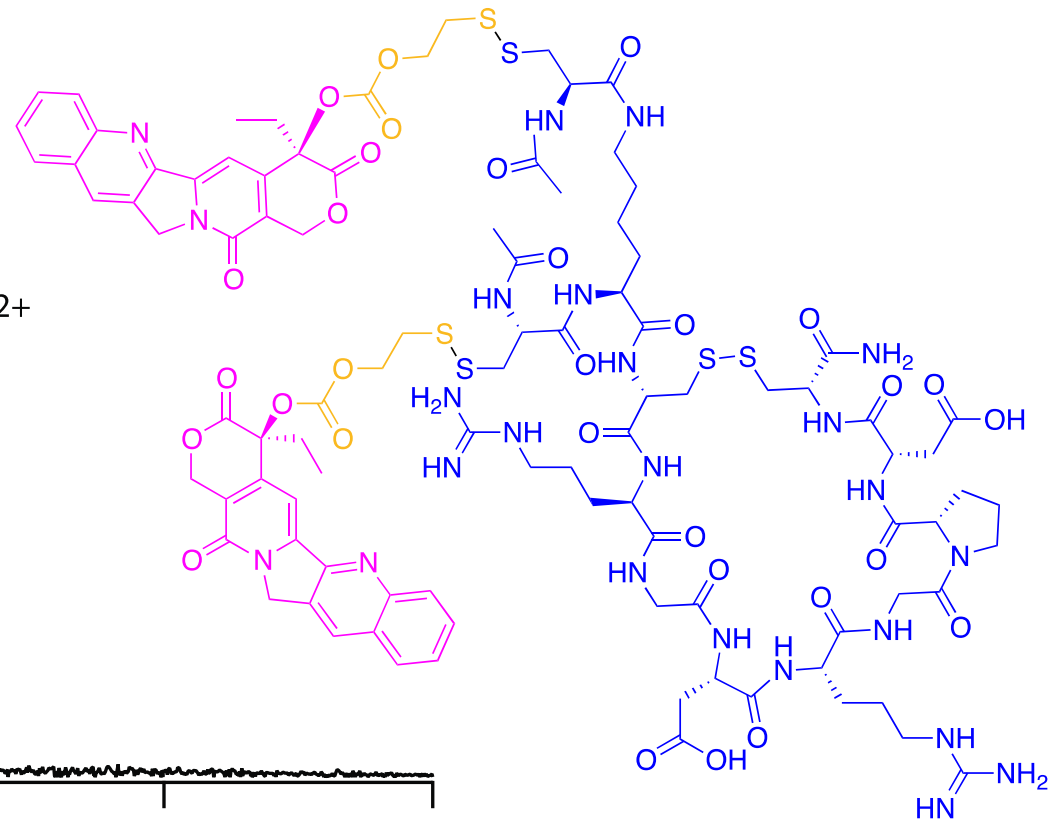
# Impact of the Research



- Tumor Penetrating Hydrogel:
  - Shorter tubes can diffuse easily
  - Treat hard to target tumors
  - High weight percentage delivery
  - Slowly release the drug over long periods of time
  - Destroy residual cancer cells and prevent metastasis
  - Injected into the tumor instead of surgery

# Synthesis of Drug Amphiphile

- Synthesize diCPT-iRGD with 30.4% drug loading

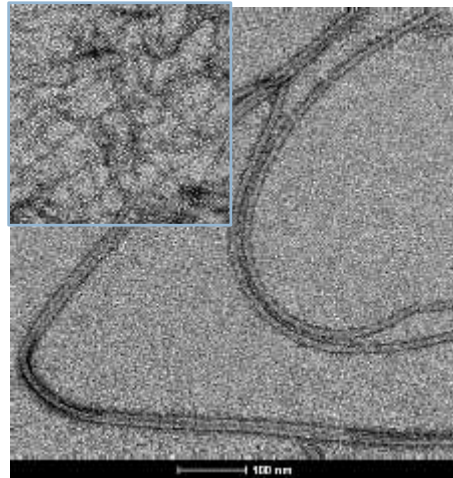


# Self-Assembly Study

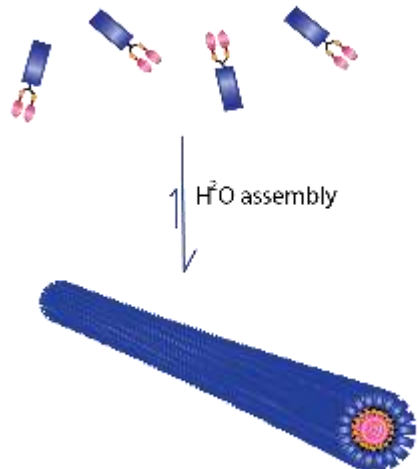
5mM Hydrogel



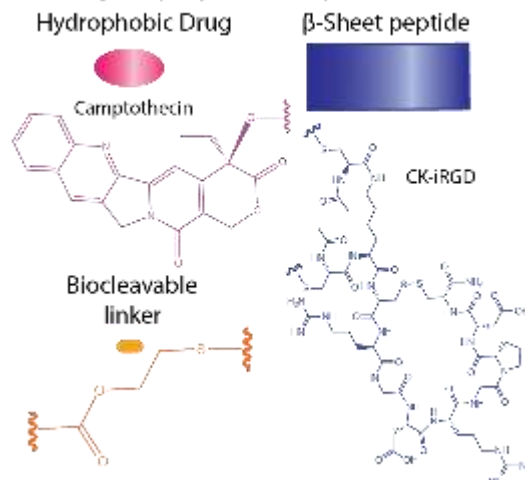
$9.87 \pm 0.57$  nm



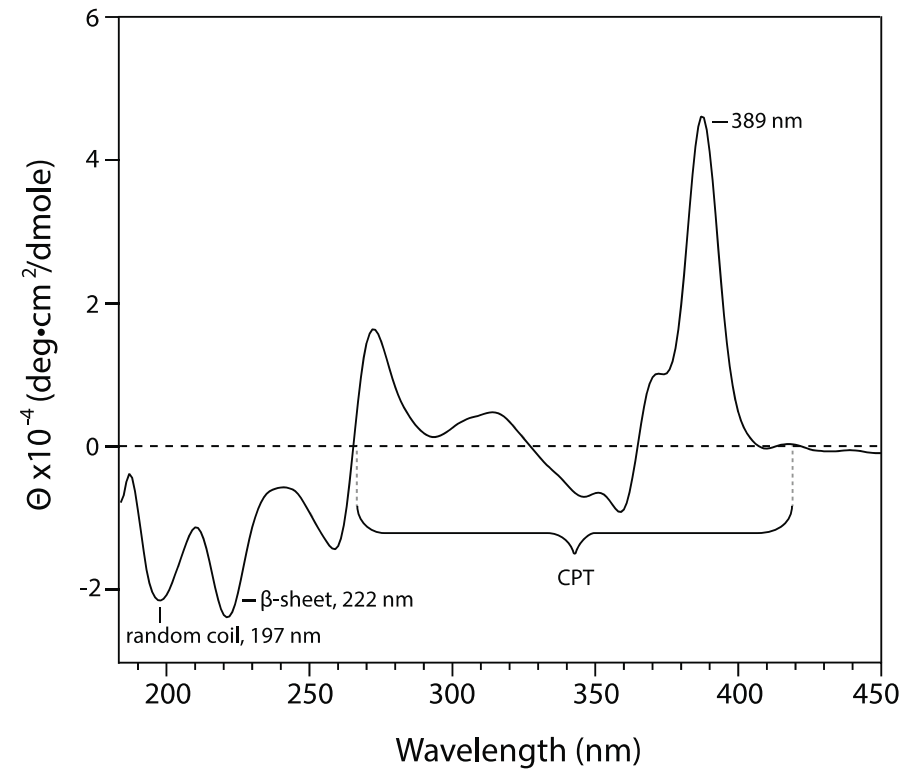
a. Drug amphiphile self-assembly



b. Drug amphiphile components

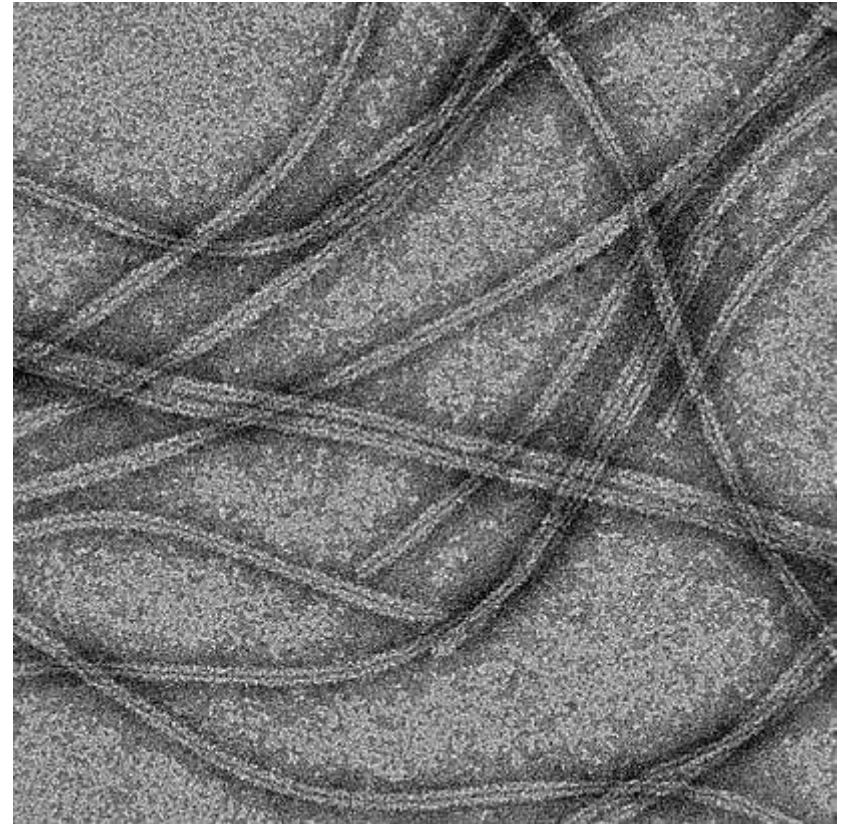
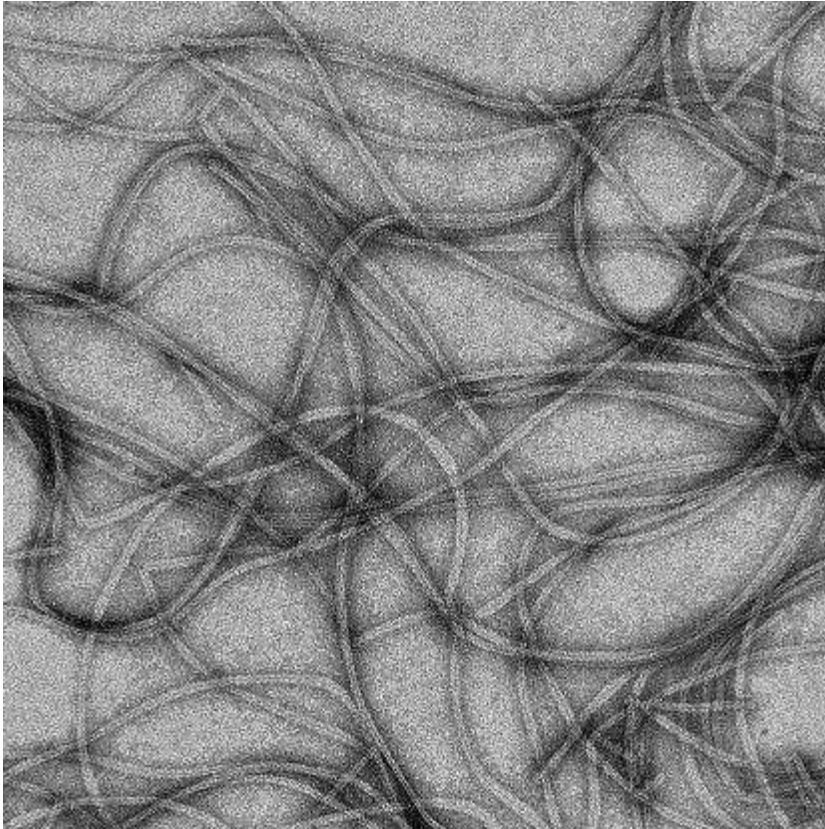


diCPT-iRGD 1mM



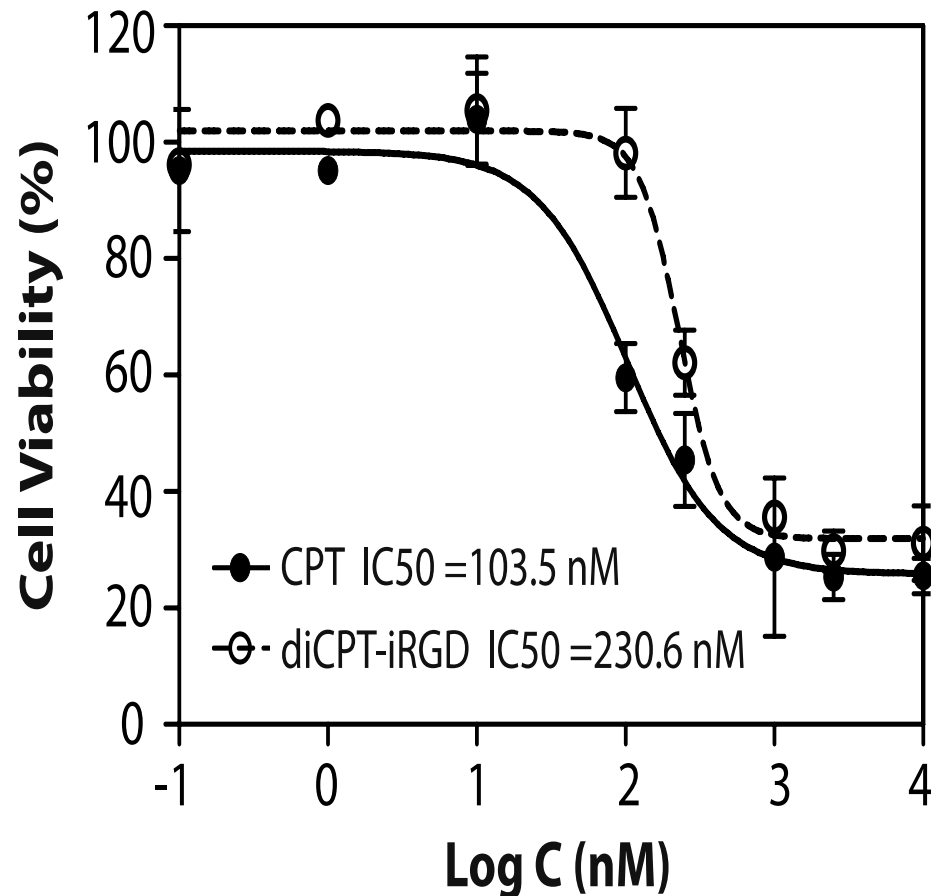
# DiCPT-iRGD Nanostructures

- diCPT-iRGD conjugate formed long nanotubes that crosslink to form a hydrogel



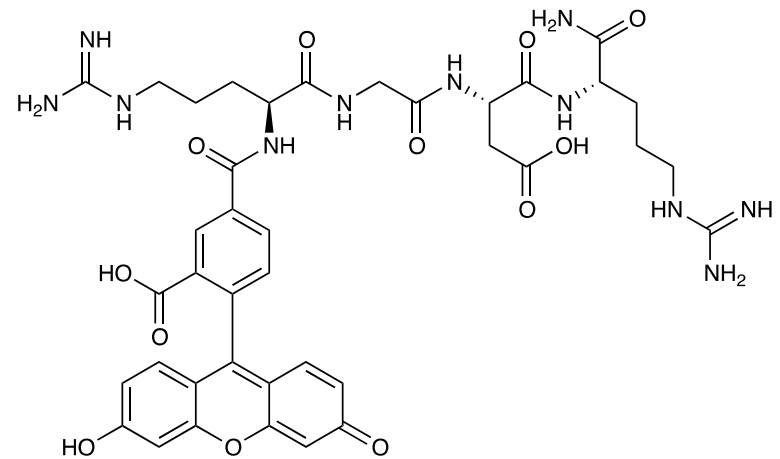
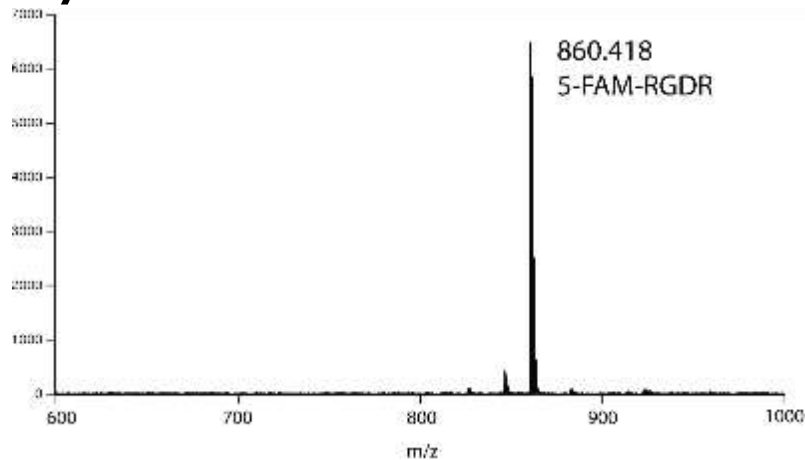
# Toxicity Assay

- *In vitro* dose-response relationship study of diCPT-iRGD on U87 human brain tumor line

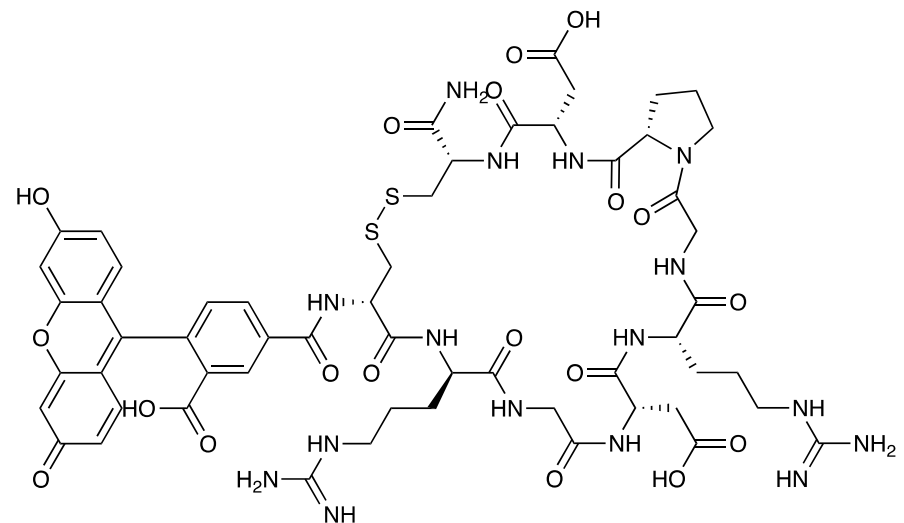
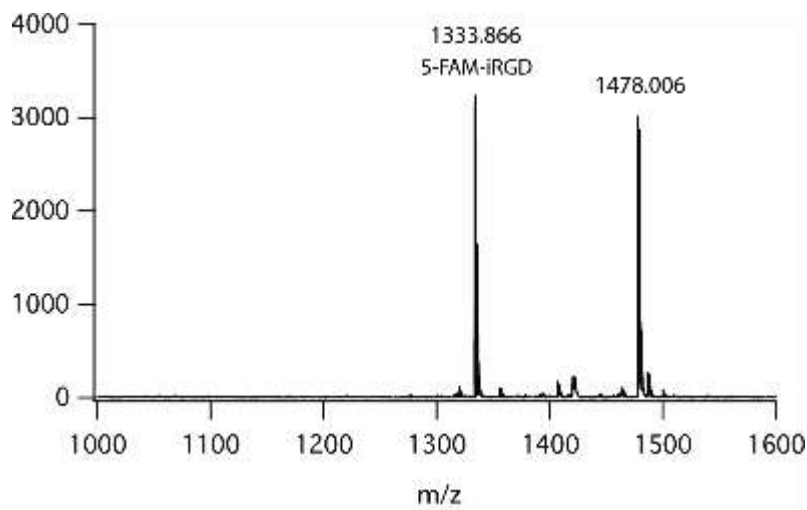


# Synthesis with 5-FAM Fluorophore

## Synthesis of the 5-FAM-RGDR

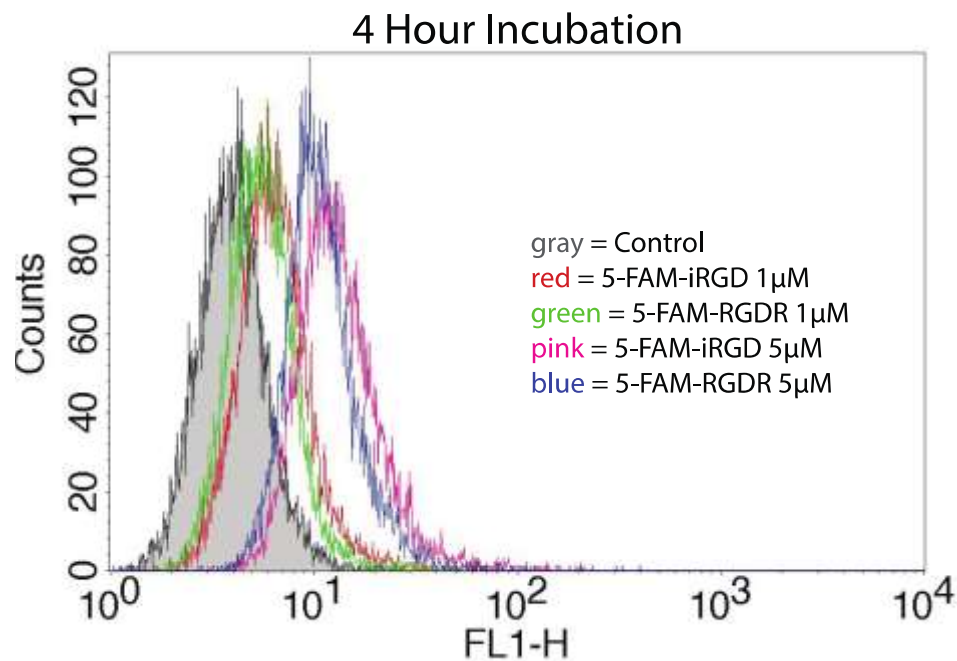


## Synthesis of 5-FAM-iRGD





# Cell Surface Homing Study



- ❑ Tumor target study using flowcytometry and fluorescence microscopy
  - ❑ Low ability to target to tumor cell line
  - ❑ No overexpression of  $\alpha_v$  and  $\beta_3/\beta_5$  integrins or neuropilin-1
  - ❑ Peptides targeted to cell surface but trypsinized

# Conclusion

- ❑ The diCPT-iRGD conjugate can:
  - ❑ Form complex nanostructures
  - ❑ Form an injectable hydrogel
  - ❑ Kill U87 human brain tumor cells with comparable toxicity to free CPT,
- ❑ Future research:
  - ❑ *In vitro* studies on the human brain tumor line U87: tumor homing studies, toxicity assays, drug release kinetics experiments, drug encapsulation studies
  - ❑ *In vivo* studies on toxicity in nude mice growing U87 human brain tumor cells

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