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Combination Therapy of Prostate Cancer Utilizing Functionalized Iron Oxide Nanoparticles carrying TNF-α and Lactonic Sophorolipids

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Outline

- Introduction
  - What are nanoparticles?
  - Tumor Necrosis Factor-alpha (TNF-α) and Lactonic sophorolipids (LSLs)
- Experimental
  - Synthesis of IONPs & Surface Ligand Modification
- Results
  - Characterizations
  - Microscopy Images
  - Biological Assays
- Conclusion
Introduction: What are Nanoparticles?

- Nanoparticles are tiny (1-100 nm) particles that exhibit unique properties and characteristics at nano-scale.
- Many uses in the field of biomedicine and therapeutics
  - Targeted drug delivery
    - Encapsulation of small molecules (drugs, optical dyes)
    - Dosage control and imaging
  - Surface ligand modification (folic acid) for receptor specificity
    - Only treat cells of interest
  - MRI Contrast Imaging (Iron Oxide nanoparticles)
- Our Aim: Treat LNCaP strain prostate cancer with a combination therapy of soluble TNF-α and LSLs with folate-functionalized iron oxide nanoparticles (IONPs)
Introduction: Why use TNF-α and LSLs?

- **TNF-α**
  - Cytokine important in many cellular pathways
    - Apoptosis and proliferation pathways
  - In cancer cells, TNF-α and associated proteins behave aberrantly
    - Nuclear factor kappa B (NF-κB) initiates proliferation unchecked
    - Binding to its receptor, TNFR-1, does not occur in tumor cells
  - Solution: Introduction of exogenous soluble TNF-α may help initiate cell death in tumors
    - Inspired by Aurimune* (gold nanoparticle)

- **LSLs**
  - Glycolipids extracted from non-pathogenic yeast
  - Enhance immune response and reduce inflammation
    - Associated with large decreases in cytokine mRNA
    - Suspected inhibition of NF-κB
  - Implementation inspired by Dr. Richard Gross’ research
  - Hypothesis: Synergy between these two compounds?

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Experimental: Nanoparticle Synthesis

Iron salts

IONP-Synthesis

FeCl₂ + FeCl₃ + PAA

HCl/H₂O

NH₄OH/H₂O

IONP-COOH

Fe

HOOC

COOH

DMF/H₂O

Solvent diffusion

(i) HOOC-PEG-NH₂ (EDC/NHS)
(ii) Propargyl amine (EDC/NHS)

Click chemistry

Folate – N₃

TNF-α & LSLs

Dil

DMF/H₂O

IONP-Dil-TNFα-LSL-FOL

PAA-IONP-Dil

IONP-Dil-FOL

IONP-NH₂

Click chemistry

Folate – N₃

Dil

DMF/H₂O

TFN-α

Dil dye

LSL

PEG
Results: IONP Characterization

Dynamic Light Scattering

FT-IR

100% D = 58.77 nm

1680 cm⁻¹
Results: Fluorescence Microscopy – Dye Internalization
Results: Fluorescence Microscopy – Dye and Combination Therapy
Results: MTT Assay

![MTT Assay Graph]

- Control
- LSL
- TNF-alpha
- Comb

Cell Viability %

3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT)
(Mitochondrial Reduction)

(E,2Z)-6-(4,5-dimethylthiazol-2-yl)-1,3-diphenylformazan (Formazan)
Results: Apoptosis/Necrosis Assay (TNF-α)

Annexin-V/Fluorescein
Hoescht
Ethidium homodimer
Results: Apoptosis/Necrosis Assay (Combination)

Annexin-V/Fluorescein
Hoescht
Ethidium homodimer
Results: Apoptosis/Necrosis Assay Results

Fluorescence unit

- Control
- TNF-alpha
- Comb
- Staurosp
- Inhibitor
Results: Migration Assay

[Graph showing wavelength (nm) on the x-axis and intensity x 10^4 on the y-axis. Two lines represent IONP and IONP-TNF/LSL.]

[Diagram showing a schematic of a cell migration assay with chambers and a channel.]
Conclusions

- Successful synthesis of folate-conjugated IONPs and encapsulation of TNF-α and LSLs
- Results of cytotoxicity assays show up to 80% cell death with combined treatment after 24 hrs
- Significant increase in apoptotic initiation following 24 hr. incubation with TNF-α and combination treatment
- Our results support our hypothesis the synergistic combined therapy
- Next step: Look to in-vivo mouse models for treatment
Thank You!
References


