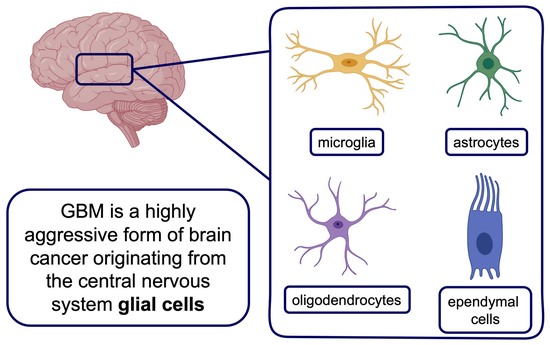
Design and Characterization of Cationic Nanoparticles for miRNA Delivery in the Treatment of Glioblastoma Multiforme

Deidra M Ward and Nicholas A Peppas

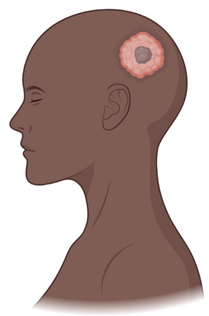
The McKetta Department of Chemical Engineering, The University of Texas at Austin, Austin, TX

INTRODUCTION

Glioblastoma Multiforme (GBM)



GBM is a highly aggressive form of brain cancer originating from the central nervous system **glial cells**



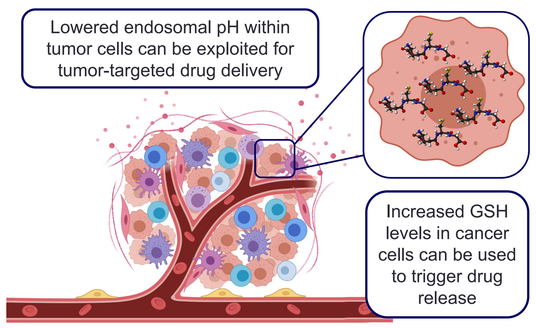
Current Treatment Options

- Surgery
- Irradiation
- Chemotherapy

Current Patient Outcomes

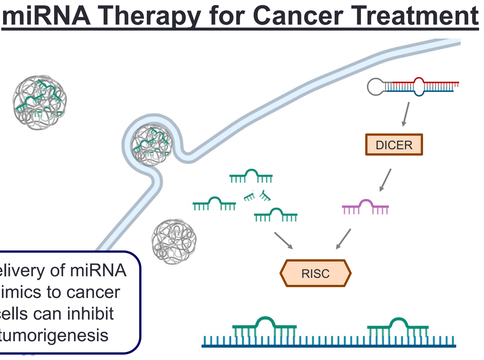
Tumor Microenvironment

Lowered endosomal pH within tumor cells can be exploited for tumor-targeted drug delivery



Increased GSH levels in cancer cells can be used to trigger drug release

miRNA Therapy for Cancer Treatment



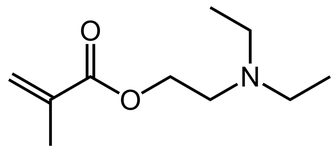
Delivery of miRNA mimics to cancer cells can inhibit tumorigenesis

Hypothesis

Sufficiently small, polycationic nanoparticles with advanced, pH-tunable characteristics can be used for the controlled release of miRNA mimics

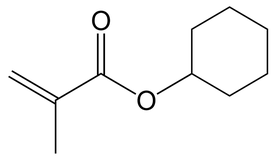
MATERIALS

Cationic Monomer



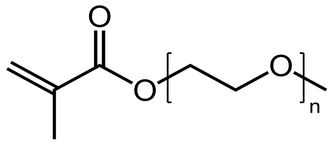
2-(diethylamino) ethyl methacrylate (DEAEMA)

Hydrophobic Monomer



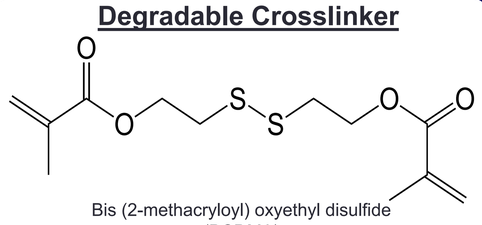
cyclohexyl methacrylate (cHMA)

Stealth Agent



Poly(ethylene glycol) methyl ether methacrylate (PEGMA)

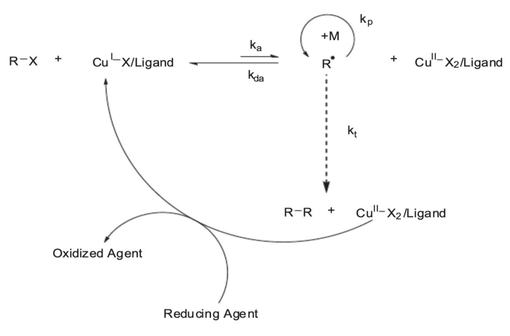
Degradable Crosslinker



Bis (2-methacryloyl) oxyethyl disulfide (DSDMA)

METHODS

ARGET ATRP Emulsion Polymerization



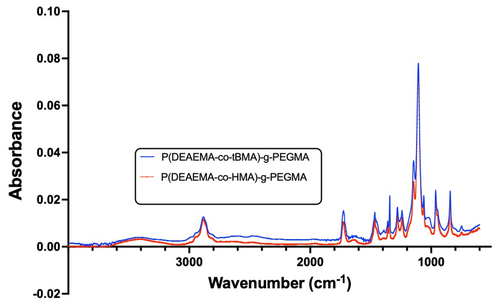
Allows for a highly controlled polymerization with the majority of polymer chains growing at the same rate

One-pot synthesis lends itself to industrial scale-up

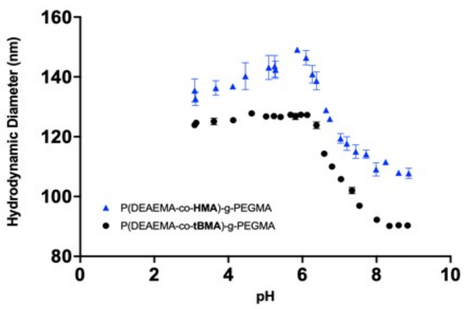
Nanoparticle Characterization

- **Composition**
  - FTIR
- **Swelling Behavior**
  - Dynamic Light Scattering
- **Surface Charge**
  - Zeta-Potential Analysis
- **Nanoparticle pKa**
  - Potentiometric Titration
- **Biocompatibility**
  - Incucyte Live-Cell Imaging

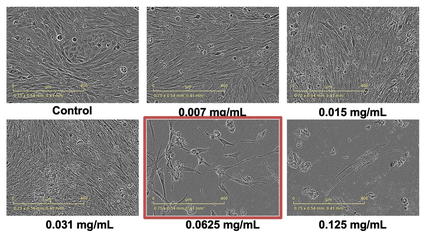
RESULTS AND DISCUSSION



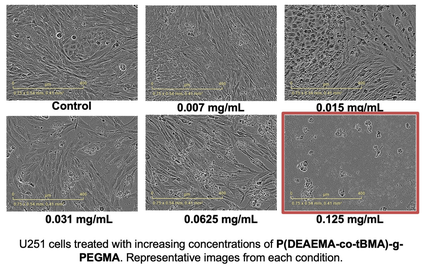
FTIR data for formulations of poly(2-(diethylamino) ethyl methacrylate-co-tert-butyl methacrylate)-g-poly(ethylene glycol) methyl ether methacrylate [**P(DEAEMA-co-tBMA)-g-PEGMA**] and poly(2-diethylamino) ethyl methacrylate-co-hexyl methacrylate)-g-poly(ethylene glycol) methyl ether methacrylate [**P(DEAEMA-co-HMA)-g-PEGMA**]



Hydrodynamic diameter as a function of pH for formulations of **P(DEAEMA-co-tBMA)-g-PEGMA** and **P(DEAEMA-co-HMA)-g-PEGMA**. Each point is the average of 3 runs. Error bars are present but may be too small to be seen.



U251 cells treated with increasing concentrations of **P(DEAEMA-co-HMA)-g-PEGMA**. Representative images from each condition.



U251 cells treated with increasing concentrations of **P(DEAEMA-co-tBMA)-g-PEGMA**. Representative images from each condition.

Discussion

FTIR data is consistent with the functional groups present in the nanoparticles, including a characteristic ether peak for PEGMA around 1100 cm^-1, a methacrylate ester peak at 1750 cm^-1, and an alkyl stretch around 2900 cm^-1.

Nanoparticles have favorable swelling behavior, remaining collapsed in basic conditions and beginning to swell in more acidic conditions. Further tuning is necessary to achieve swelling onset at endosomal pH.

Preliminary biocompatibility tests of nanoparticle formulations are promising, showing minimal impact on cell growth up to concentrations of 0.0625-0.125mg/mL

CONCLUSIONS

Overview

Initial pH-responsiveness of nanoparticles show great potential for tumor-targeted drug delivery. Further adjustments of cationic monomer and hydrophobic comonomer ratio may allow for lower swelling pH.

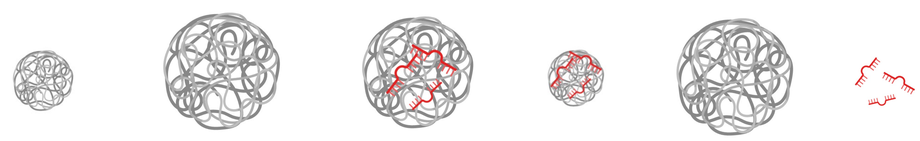
Preliminary biocompatibility tests of nanoparticle formulations are promising, showing minimal impact on cell growth after exposure to high dosages of blank nanoparticles.

Future Work

Loading of miRNA mimics by electrostatic complexation to nanoparticles will be assessed via Qubit RNA assays.

Uptake of miRNA mimics will be assessed by Incucyte live cell imaging and cell differentiation assays.

Nanoparticle surface modifications to enhance likelihood of blood-brain barrier transport.



ACKNOWLEDGEMENTS

Work supported by NIH Grant R01-EB022025.

REFERENCES

D.C. Forbes, N.A. Peppas. *Macromol. Biosci*. **2014**, 14, 1096-1105