Long-term, Localized Delivery of a Chemotherapeutic from Cell Degradable Polymeric Films

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Hypothesis

We hypothesize that prolonged, localized drug delivery at the site of tumor resection margins will prevent cancer cells proliferation and tumor recurrence.

Objective

Here, we propose to incorporate a hydrophobic, anti-neoplasmic drug into a hydrophobic, acidically-inert, polymeric film to achieve prolonged drug release and sustained inhibition of cancer cell proliferation in the harsh environment of the stomach.

Background

Cancer - *Gastric tumor resection*

Cancer is the second leading cause of death worldwide. In gastric cancer, most patients are treated by tumor resection in the early progression stages. However, recurrence of cancer at the margin of resection can occur in 50% of cases. Secondary, more systemic treatments like chemotherapy and external radiation are the current gold-standard treatments for inhibiting cancer recurrence but produce systematic totoxicities that can severely limit the long term survival of the patient.

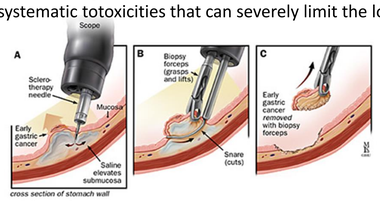


Figure # 1. Gastric Cancer Tumor Resection Procedure (*Johns Hopkins Medicine: Gastroenterology & Hepatology, Gastric Cancer Therapy*.). Margins are 50% susceptible to the cancer recurrence.

How to localize Therapies? - *PTK-UR films*

- PTK-based scaffold technology is specifically degraded by cell-generated ROS. ROS is natural produced in the body in inflammatory responses **(1)**.

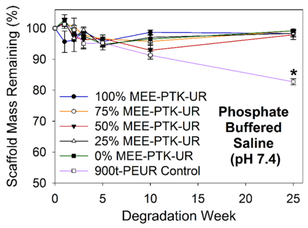


Figure #2. PTK-UR scaffolds are not degraded by water, while polyester-based materials are sensitive to hydrolysis **(1).**

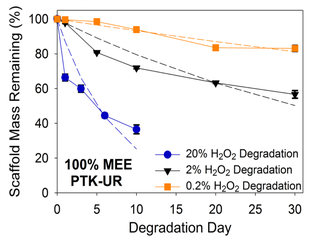


Figure # 3. PTK-UR in degradation-response due to different concentrations of ROS producing mediums **(1).**

- These polymers are acidically-inert and stable in aqueous environment. Most commonly used biodegradable materials employ polyesters which are sensitive to acidic environments. Thus, PTK-UR materials represent an ideal material that is both biodegradable and can withstand the harsh acidic environment of the stomach.

How to achieve prolonged drug release?

HCPT profile

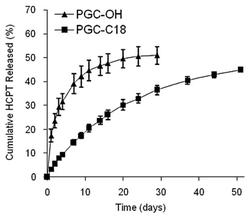


Figure # 4 Release profile of the drug 10-hydroxycamptothecin from polymers based in an aqueous environment **(2)**. The hydrophobicity interaction between the film and the drug increase the long period of drug release.

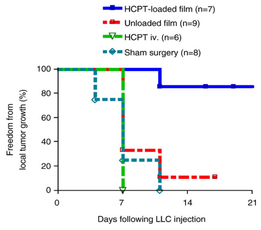


Figure #5 *In vivo* prevention of tumor recurrence by 10-hydroxycamptothecin using polymeric films **(2).** HCPT retains its anti-neoplasmic activity after being released from the films.

Experimental Approach

Polymer Synthesis

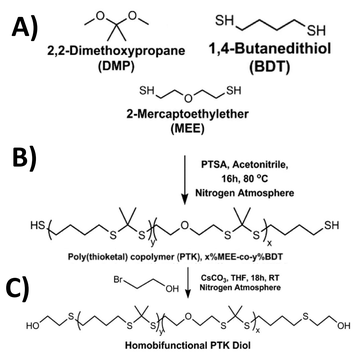
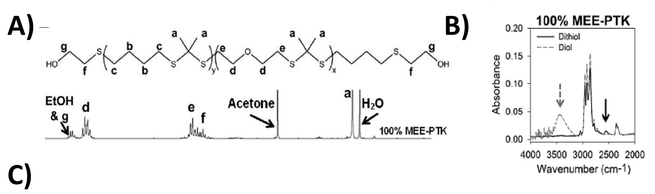


Figure # 6. Synthesis of PTK-diol polymers. **(A)** PTK polymers were synthetized from biocompatible 2-mercaptoethylether (MEE) monomers. **(B)** Thiolated PTK polymers were functionalized by the addition of hydroxyl groups at the polymer terminals. **(C)** Homobifunctional PTK diol synthetized.

Polymer Characterization



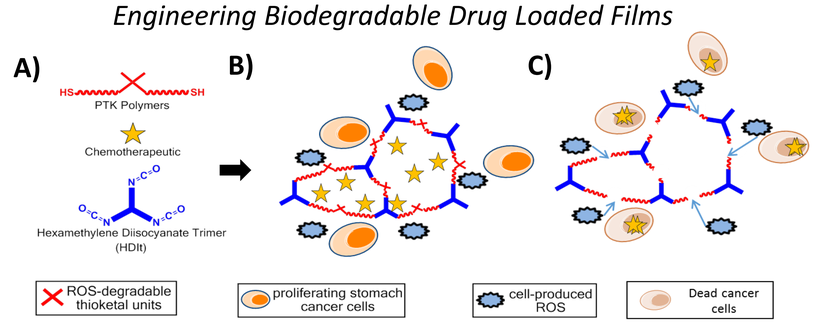
C)

Polymer	Feed MEE%	Actual MEE %	GPC M_n	PDI	Titration M_n
100% MEE-PTK	100%	100%	1500	1.52	1100

Figure # 7. Characterization of PTK 100%MEE-PTK diol polymers. **(A)** ^{1}H NMR spectra of the PTK 100%MEE-PTK diols. **(B)** ATR-FTIR spectra of thiol- and hydroxyl-terminated PTKs. These spectra demonstrate efficient conversion of PTK terminal thiols into hydroxyls. **(C)** Characterization summary showing percent of feed monomers, percent of monomers reacted by NMR (peaks at δ= 1.72 and δ= 3.64 ppm), gel permeation chromatography (GPC) analysis showed the M_n value and polydispersity index (PDI).

Drug Loading & PTK-UR Synthesis

Engineering Biodegradable Drug Loaded Films



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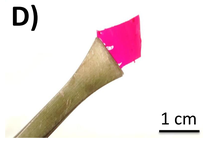
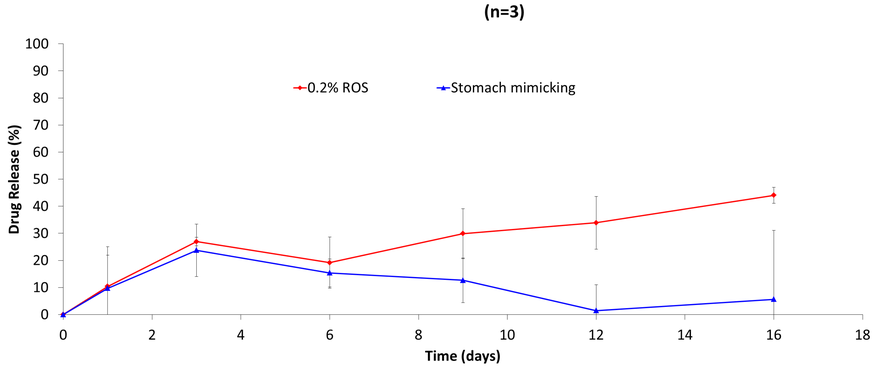


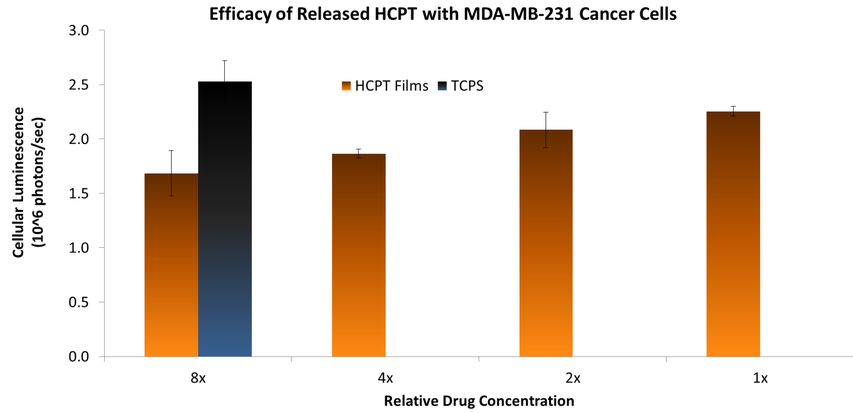
Figure # 8. **(A)** Components used to synthetize a drug loaded solvent cast films. **(B)** Films before degradation and drug release. **(C)** Thioketal degradation by ROS- producing cells to release the drug and promote antitumor activity. **(D)** Illustration of a drug loaded film, demonstrating a thin and flexible material.

Long Term Drug Release



- Nile Red-loaded PTK-UR films demonstrate gradual, sustained levels of drug release when incubated in an ROS-producing medium, while demonstrating minimal drug release when incubated in an acidic medium.

Cytotoxicity on Cancer cells



- Preliminary data show the growing cells affected by the drug released from films after 6 days in incubation.

Conclusion

- Thin and flexible material can be used as a tissue reinforcement material after tumor resection.
- Gradual and sustained drug release can be obtained from films in response to ROS, while an acidic environment promotes minimal release.
- Drug released from film still viable as a chemotherapeutic agent and can cause limit the growth of cancer cells.

Future studies

Futures studies will evaluate the sustained cytotoxic effect of released HCPT

- ***in vitro***
- ***in vivo*.**

VINSE Vanderbilt Institute of Nanoscale Science and Engineering

References

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(2) Jesse B. Wolinsky, Rong Liu, Joe Walpole, Lucian R. Chirieac, Yolonda L. Colson and Mark W. Grinstaff. (2010) **Prevention of in vivo lung tumor growth by prolonged local delivery of hydroxycamptothecin using poly(ester-carbonate)-collagen composites**. Journal of Controlled Release 144, 280–287

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