RISE:2018
RESEARCH, INNOVATION AND SCHOLARSHIP EXPO

Graduate
Interdisciplinary Topics
PhD in Chemical Engineering
Abstract ID# 2123

Northeastern University

Development of Scale-up Manufacturing of 'INCeRT' Implants for Localized Tumor Delivery of Chemotherapeutics

Sanahan Vijayakumar[1], Neha Shankar[2], Bijay Singh[3], Srinivas Sridhar[1,3]

[1]Department of Chemical Engineering, Northeastern University, Boston, MA 02115, [2]Department of Health Sciences, Northeastern University, Boston, MA, [3]Department of Physics, Northeastern University, Boston, MA

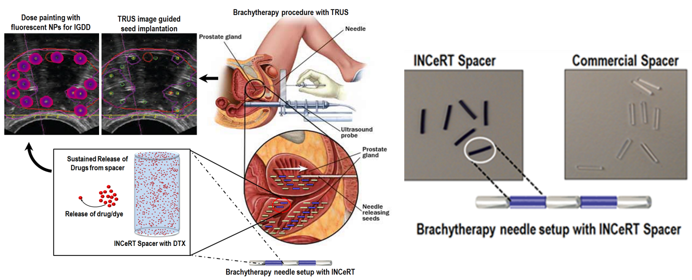
OPPORTUNITY

ABSTRACT

Prostate cancer (PCa) is the second leading cause of cancer-related deaths in men, with 26,730 deaths in the US in 2017, requiring new treatment options[1]. One approach for PCa treatment is brachytherapy, which uses radioactive seeds deposited in the prostate gland to release controlled and localized radiation. The current form of brachytherapy utilizes plastic inert spacers to place radioactive seeds in the prostate[1]. We have earlier synthesized biocompatible and biodegradable polymer-based "smart" Implantable Nanoplatform for Chemo-radiation Therapy (INCeRT) spacers that combine radiation therapy and targeted drug delivery. These spacers are fabricated as a chemo-toxic agent, Docetaxel (DTX), loaded Poly(lactic-co-glycolic) acid (PLGA) cylindrical implant usable in brachytherapy procedures[2]. Previous research has demonstrated the success of spacers fabricated from a mixture of PLGA, DTX and a solvent[1]. However, the development of solvent-free, DTX-loaded, PLGA spacers is considered a significant improvement for pharmaceutical grade manufacturing, that is critically needed for translation to the clinic. The mechanistic effects of hot melt extrusion, a pharmaceutical process used to develop polymer-based drugs of uniform shape and density, is analyzed through rheology and calorimetry for successful extrusion of biocompatible spacers by taking advantage of the low glass transition temperature of PLGA[3]. In-vitro and in-vivo experiments of rodent models will help determine the efficacy of solvent-free spacers. This novel PCa therapeutic strategy would benefit patients by substantially yielding higher survival rates, improved targeted drug delivery while avoiding systemic toxicity.

BRACHYTHERAPY

- Insertion of radioactive seeds in prostate tissue that release radiation over time
- Uses inert spacers for spatial guidance to place and separate radioactive seeds



INNOVATION

- INCeRT spacers loaded with DTX for combined chemo-radiation therapy
- Localized and sustained drug delivery with inhibition of tumor growth

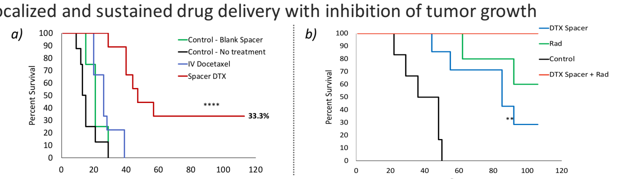


Figure 1: a) Mouse survival of INCeRT Spacers as a monotherapy and b) combined with radiation therapy

GOAL

Effectively Translate and Scale-Up Spacers to the Clinic

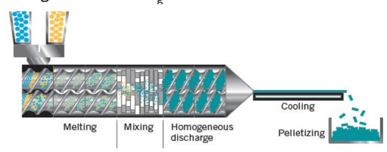
CHALLENGES

1. Increased production
   - Need for continuous or semi-batch process
2. Only use FDA approved materials
   - No solvents or nanoparticles
3. Maintain same In-Vitro/In-Vivo effectiveness
   - DTX-Spacers should successfully inhibit tumor growth

APPROACH

HOT MELT EXTRUSION (HME)

- Heat and pressure to melt PLGA and force it through an orifice
- Pharmaceutical grade process
- Products display uniform shape, density and DTX mixing
- Take advantage of the low T_g of PLGA



MECHANICAL TESTS

1. Differential Scanning Calorimetry: Thermal transitions
   - Effect of DTX on T_g & T_m of PLGA
2. Rheology: Flow and viscoelastic behavior
   - Determine viscoelastic range
   - Determine viscous properties around T_g

DATA

RHEOLOGY

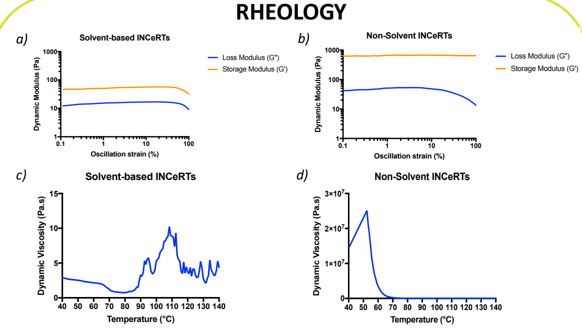


Figure 2: a) and b) Amplitude sweep of solvent and non-solvent INCeRTs. c) and d) are temperature sweeps of solvent and non-solvent INCeRTs.

DIFFERENTIAL SCANNING CALORIMETRY

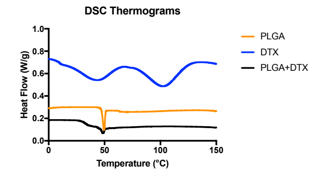


Figure 3: DSC thermograms for PLGA, DTX & PLGA+DTX. DTX does not change the T_g of PLGA

QUANTIFICATION OF DTX RELEASE

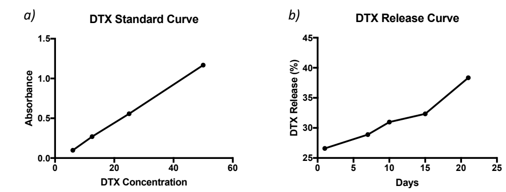
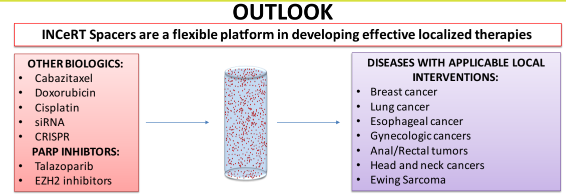


Figure 4: a) DTX Standard curve (@ 272 nm) and b) DTX Release curve of INCeRT spacers. Five pieces of spacers (2 mm) dissolved in 0.5 ml PBS (pH 7.2) and incubated at 37°C

RESULTS

OUTLOOK



CONCLUSION & PERSPECTIVES

- Improve brachytherapy by making smart 'INCeRT' spacers
- HME for pharmaceutical-grade up-scale
- Mechanical understanding of PLGA with rheology & DSC
- In-Vitro & In-Vivo comparative studies will be conducted
- Solvent-based vs Non-solvent INCeRTs
- Flexible platform for addition of various biologics

ACKNOWLEDGEMENTS

Sridhar Lab: Dr. Rajiv Kumar, Dr. Jodi Belz, Paige Baldwin
DFCI/BWH: Dr. Robert Cormack, Dr. Mike Makrigiorgos

REFERENCES

1. R. Kumar, J. Belz, S. Markovic, T. Jadhav, W. Fowle, M. Niedre, R. Cormack, M. G. Makrigiorgos and S. Sridhar, International journal of radiation oncology, biology, physics **91** (2), 393-400 (2015).
2. R. Kumar, J. Belz, H. Korideck, R. Cormack, M. Makrigiorgos and S. Sridhar, Cancer Research **75** (15 Supplement), 1806-1806 (2015).
3. C. McConville, P. Tawari and W. Wang, International Journal of Pharmaceutics **494** (1), 73-82 (2015).

Partially supported by 1R41CA224646-0