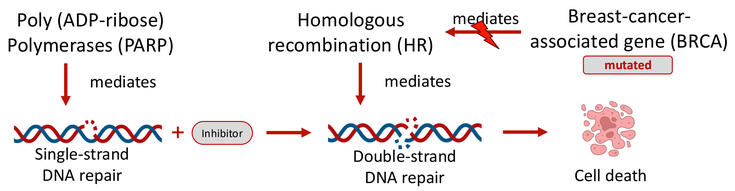
Evaluation and Optimization of STING Agonist Implants for Ovarian and Breast Cancers

Yulei Xu[a], *Xiaoheng Lyu*[a], *Khadijah Zai*[b], *Shicheng Yang*[b,c], *Needa Brown*[b,d], *Srinivas Sridhar*[a,b,c]

a. Department of Bioengineering, Northeastern University, Boston, MA
b. Department of Physics, Northeastern University, Boston, MA
c. Department of Chemical Engineering, Northeastern University, Boston, MA
d. Department of Materials Science and Engineering, University of Central Florida, Orlando, FL

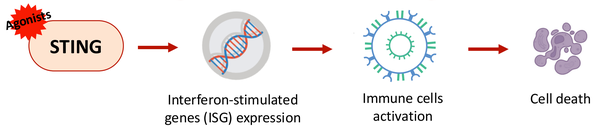
Background and Objectives



Problem
The PARPi therapy is not durable, and resistance develops with drug delivery barriers in BRCA-deficient ovarian and breast cancers

PARPi induce innate immune responses via **cGAS/STING pathway**

Solution
Combined treatment with STING agonist **ADU-S100** can enhance the efficacy by triggering tumor-specific immune activation



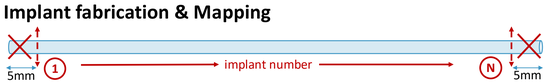
- Current clinical trials require multiple rounds of intratumoral injections to reach a high-dose delivery of STING agonist
- We innovatively formulated PLGA-based ADU-S100 implants for sustained and localized drug delivery

  Trials conducted under pH6 and pH7.4 to mimic tumoral and physiologic pH, respectively

PLGA-based Implants Fabrication and Drug Quantification

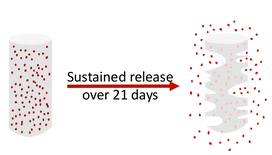
***In vitro* bio-mimicking drug release model**

Implant fabrication & Mapping



Poly (lactic-co-glycolic) acid (PLGA) is a biodegradable and biocompatible polymer
8mg (high dose) of free ADU-S100 drug is encapsulated in 180mg PLGA-based implants

Drug release & quantification



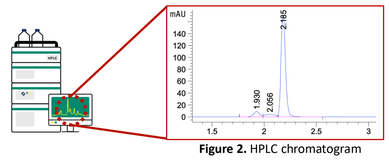
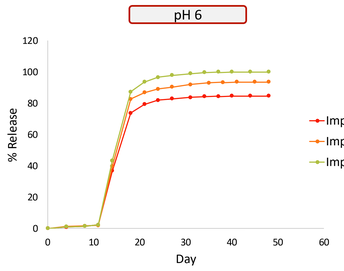
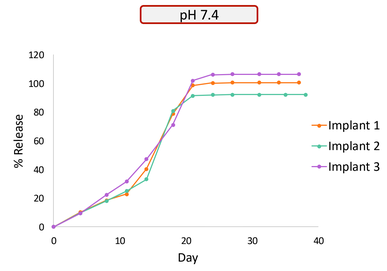


Figure 2. HPLC chromatogram

Drug release profile

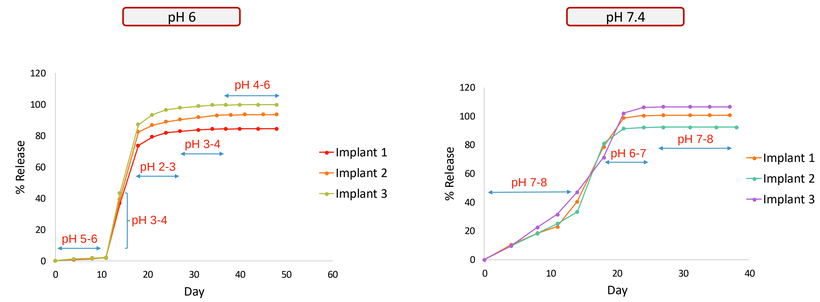


Delay release profile



Sustained-release profile

Local pH change



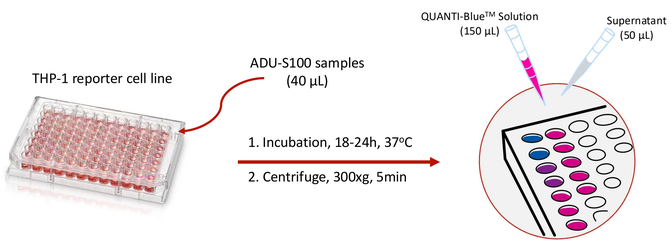
- Both of the groups showed sustained release over 21 days.
- The local pH drops as the PLGA-based implants hydrolyze and slowly release the drug, echoing the release pattern shown in the graph.

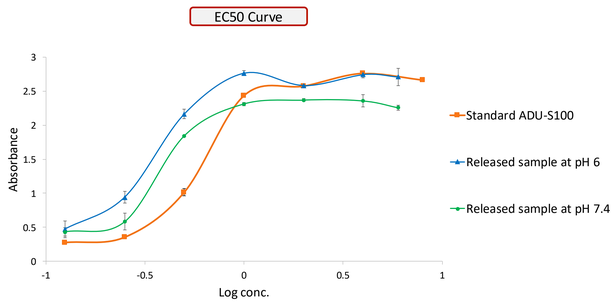
Discussions

- Both of the implant groups reached sustained release of drug over 21 days, and the profiles follow the same pattern within each batch group
- Compared to pH7.4 release profile, pH6 has a delayed release, which may be due to the interaction between ADU-S100 and the PLGA matrix
- Local pH change may be another factor causing the delayed release since PLGA undergoes hydrolysis to break down, and the rate of hydrolysis is influenced by the environmental pH
- PLGA hydrolysis will generate acidic monomers including lactic acid and glycolic acid
- The bio-mimicking buffer system may not be strong enough to compensate for the pH changes

THP-1 Reporter Cell Bioactivity Assay

Bioactivity test





- Optical density (OD) measured by microplate reader.
- Interestingly, in both of the pH groups, the released samples showed lower EC50, which means they have higher sensitivity than the standards.

Discussions

- The bioactivity tests showed inspiring results that the drug released from the implant triggered the STING pathway as we hypothesized
- Due to the higher sensitivities of the released samples, we suggested that PLGA material may also contribute to the STING activation enhancing our therapy

PLGA blank control assay

Figure 2. Plate image of blank PLGA only bioactivity test

- Bioactivity test conducted on blank PLGA-only samples
- We still see color changes in different concentration gradients of PLGA, which means, PLGA can also trigger the STING pathway, enhance our therapy

Future Work

Created in BioRender.com

- To better mimic the actual biological system, a continuous stirred tank reactor may be introduced to avoid local pH change impact on drug release
- Translate the implants into *in vivo* models to evaluate the efficacy as well as build the actual drug release profile
- Preliminary in vivo study shows that mice are active with the ADU-S100 treatment regardless of tumor burden
- Also, compared to PARPi treated only group, the groups combined with ADU-S100 showed a significant extended life

Acknowledgements

This work is supported by USAMRAA/CDMRP HT9425-23-1-0274 & USMRAA/CDMRP HT9425-23-2-0813.