Lung cancer is the leading cause of cancer mortality (causing 1 in 4 of all cancer deaths) in US and worldwide. Radiation remains the cornerstone of lung cancer treatment and over 60% of lung cancer patients will undergo radiation therapy, with majority receiving concurrent chemotherapy. However, despite advances in radiation technology and medicine, the 5 year survival rate of lung cancer patients remains just 17%. Molecularly targeted therapies, which can improve the therapeutic ratio of radiation, have enormous potential to benefit the millions of lung cancer patients who rely on radiation therapy.

We have developed a novel molecularly targeted therapy based on a mesoporous silica nanoparticle (MSNPs) construct with tumor targeting ability to enhance the effects of radiation for lung cancer. The nanoparticle is conjugated to antibody to home to cancer cells and delivers siRNA against a mitotic gene (pole-like kinase 1, PLK1) to initiate G2/M cell cycle arrest and apoptosis. We show that the nanoparticle construct is not only an effective single agent therapeutic for lung cancer but also renders cancer cells more susceptible to radiation damage.

**Hypothesis:** Due to EGFR’s role in DNA repair and PLK1’s role in mitosis, cetuximab-MSNPs delivery of siPLK1 (C-siPLK1-NP) can target EGFR+ cancer and enhance the efficacy of radiation

*Cetuximab – EGFR monoclonal antibody

**Abstract**

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**Nanoparticle Design**

![Figure 1](image1.png)

**Figure 1.** (A) TEM image of mesoporous silica nanoparticle core. Bar: 50 nm. (B) Schematic of surface coating of mesoporous silica nanoparticles with (layer by layer) cross-linked PEI, PEG, Antibody, and siRNA. (C) Hydrodynamic size of final nanoconstruct with and without siRNA.

**Table 1.** Functionalized NP. Size distribution and charge determined by Malvern Nano ZS.

<table>
<thead>
<tr>
<th>Particle size (nm)</th>
<th>PDI</th>
<th>Zeta Potential (mV) in 10 mM NaCl</th>
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<tr>
<td>104 ± 1.7</td>
<td>0.19</td>
<td>8.10 ± 0.3</td>
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</table>

**Nanoparticle Blood Compatibility**

![Figure 2](image2.png)

**Figure 2.** NP protects siRNA for up to 24 hr contact time with 50% human serum.

**Cetuximab-NP specifically targets EGFR+ lung cancer over low EGFR normal lung cells**

![Figure 3](image3.png)

**Figure 3.** Effects of nanoparticle construct on blood were evaluated and benchmarked against FDA approved nanoparticle drugs, Abraxane and Feraheme (B-D).

**Table 3.** Effects of nanoparticle construct on blood were evaluated and benchmarked against FDA approved nanoparticle drugs, Abraxane and Feraheme (B-D).

**Figure 4.** Cetuximab conjugated nanoparticles loaded with dye tagged siRNA were incubated with EGFR+ NSCLC or normal lung cells (NL20) for 1 hr.

**Conclusions and Future Directions**

- We have developed a targeted siRNA nanoparticle platform based on mesoporous silica that demonstrates effective siRNA delivery both in vitro and in vivo.
- When conjugated to EGFR-antibody and delivering siRNA against PLK1, the material is effective as both a monotherapy and as a radiation sensitizer in NSCLC cells.
- The targeted nanoparticle can be applied to other cancer types with high EGFR and PLK1 expression (e.g., TNBC, CRC).
- Future work will evaluate the radiation sensitization in NSCLC lung tumor models, with the ultimate goal of clinical translation.

**Acknowledgements**

- Prospect Creek Foundation
- NCI SBIR R44 CA217234
- Joe Gray, KCI, OHSU
- Charles Thomas & Jerry Jaboin, Radiation Medicine, OHSU
- "OHSU, W.N., J.M., and W.Y. have a significant financial interest in PDX Pharmaceuticals, LLC, a company that may have a commercial interest in the results of this research. This potential conflict of interest has been reviewed and managed by OHSU."