Washington University in St. Louis
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CCR2-TARGETED CANCER NANOIMMUNOTHERAPY

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Disease indication –

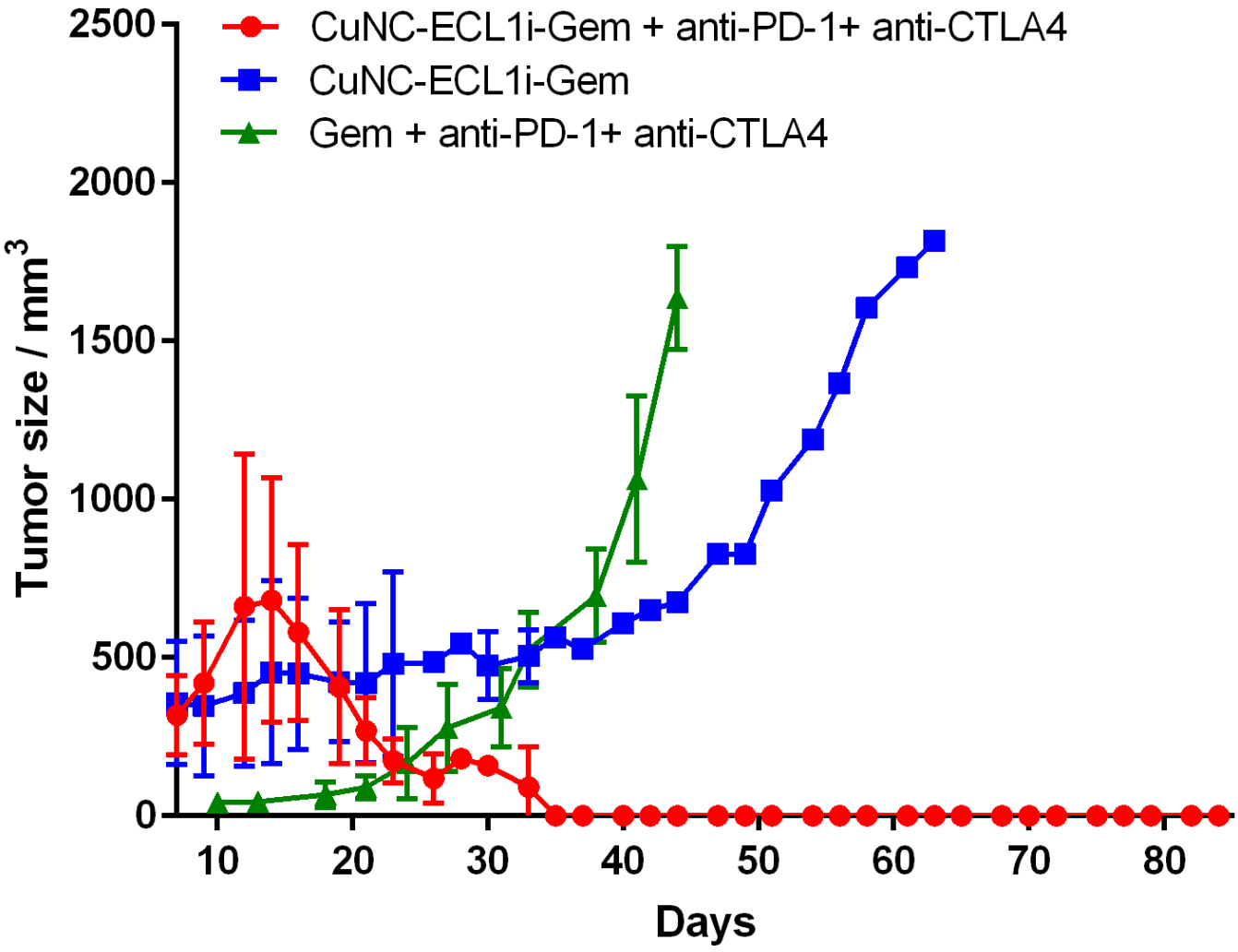
- Pancreatic ductal adenocarcinoma specifically
- More broadly, cancers treatable by immune checkpoint inhibitors

Drug format – Combination containing radiolabeled copper nanocluster, small molecule, and peptide

Drug class – First-in-class

Target – CCR2, the receptor for CCL2

Mode of action – The ECL1i peptide is conjugated to a copper nanocluster loaded with gemcitabine. ECL1i specifically binds CCR2, which is expressed by myeloid cells in the tumor microenvironment. Tumor-associated macrophages and other CCR2+ cells will internalize the targeted nanoclusters, releasing the gemcitabine to kill those cells. As those myeloid cells play a main role in promoting tumor development and creating an immunosuppressive tumor microenvironment to jeopardize drug treatment efficacy, their loss will assist anti-tumor immune activation by checkpoint inhibitors.



Research stage and Preliminary data – The inventors have completed and published *in vivo* toxicity and pharmacokinetics results for their ^{64}Cu-Cu@CuO$_x$-ECL1i-Gem drug in wild type mice. The non-loaded nanocluster with targeting peptide (^{64}Cu-Cu@CuO$_x$-ECL1i) is an effective PET imaging agent, so the researchers were able to perform extensive biodistribution analysis. Additionally, the team tested the efficacy of ^{64}Cu-Cu@CuO$_x$-ECL1i-Gem in combination with immune checkpoint inhibitor therapy in a mouse model of pancreatic ductal adenocarcinoma. In those proof-of-concept experiments, the nanocluster drug sensitized the mice to respond more completely to anti-CTLA4 therapy.

Background – Currently, immune checkpoint inhibitors see a positive response rate of only 20-30%, due to multiple mechanisms of resistance. One of those mechanisms is the development of an immunosuppressive tumor microenvironment by tumor-infiltrating myeloid cells. These cells can prevent the activation of normal or augmented anti-tumor immune responses.

Competitive edge – No approved drugs target the suppressive tumor microenvironment that promotes resistance to checkpoint inhibitors. By targeting and destroying these suppressive myeloid cells, treatment with the nanocluster drug can boost the efficacy of checkpoint inhibitor therapy.

Publication – Zhang X, Detering L, Sultan D, Luehmann H, Li L, Heo GS, … Liu Y. (2021). CC chemokine receptor 2-targeting copper nanoparticles for positron emission tomography-guided delivery of gemcitabine for pancreatic ductal adenocarcinoma. *ACS Nano*, 15(1):1186-1198.

Patent status – Pending

Web links – Lim Profile & Lab; Liu Profile