

PUBLIC/LAY ABSTRACT:

Progress has been made in understanding metastasis but no therapeutic pharmacological agent has been identified that directly targets metastatic breast cancers. Combining inhibition of at least two potential metastasis targets with dual targeting cocktails has the potential to decrease breast cancer metastasis. This proposed work is centered on targeted therapies for dual inhibition of the newly discovered MDM4-CXCR4 axis using experimental models of both triple negative breast cancer metastasis and estrogen receptor positive breast cancer metastasis. Amplification and overexpression of the *MDM4* gene (also known as *MDMX*), and mutations to the *TP53* gene, drive metastatic breast cancers. Both the *TP53* and *MDM4* genes express stable proteins in metastatic breast cancers. Pharmacological targeting of the MDM4 protein in cancer with *TP53* mutations is possible and as such inhibition of MDM4 as a target should be explored as a method to block breast cancer metastasis. An additional metastasis driving pathway that shows great promise for inhibition, and already has clinically approved pharmacological inhibitors, is called the CXCR4/CXCL12 pathway. The Bargonetti team uncovered a novel link between the CXCR4/CXCL12 and MDM4 pathways (which they call the MDM4-CXCR4 axis). The agents that block CXCR4/CXCL12 are proven safe for applications to harvest blood stem cells. This project uses an experimental system to test a cocktail of the clinically available CXCR4 antagonist molecule and a novel MDM4 inhibitor, together these pharmacological agents have the potential to both block the breast cancer metastases and potentially kill existing metastatic lesions. The focus is on testing if inhibiting the signaling between the two pathways, either alone or in combination, block breast cancer metastasis in experimental models of triple negative and estrogen receptor positive breast cancers. As such, the project has the potential to extend the lives of people living with metastatic breast cancer.