**Lay summary**

Many solid tumors, including breast cancer, establish an immune-suppressive microenvironment by engaging tumor-associated macrophages (TAMs). TAMs is a type of macrophage that promotes tumor growth and metastasis and inhibits cytotoxic T cells from killing cancer cells to suppress the efficiency of checkpoint blockade. However, macrophages can also be tumoricidal and T cell stimulatory. Thus, to eradicate metastatic breast cancer, we should both activate T cells (adaptive immune cells) and reprogram TAMs (innate immune cells) to alter the immune-suppressive microenvironment.

Here we show that monophosphoryl lipid A (MPLA) with IFNγ could polarize macrophages isolated from metastatic pleural effusions of breast cancer patients to kill cancer cells *in vitro*. *In vivo*, injection of MPLA with IFNγ not only controlled local tumor growth but also reduced metastasis in mouse models of luminal and triple negative breast cancers. Both macrophages and T cells were critical for the anti-metastatic effects of MPLA+IFNγ. Mechanistically, the combined MPLA+IFNγ treatment stimulated type I interferon signaling, reprogramed TAMs to tumoricidal macrophages, and activated cytotoxic T cells through macrophage-secreted cytokines.

Intraperitonal administration of MPLA+IFN has no toxicity to body weight, liver, lung, bone marrow and heart at the doses that induced dramatic anti-tumor immunity in mice. It is hopeful to identify a safe and effective dose of MPLA with IFN for neo-adjuvant, preoperative treatment in clinical trials. MPLA+IFN could be applied as a stand-alone treatment, could be used in conjunction with other therapies, or could be replaced by developing orally bioavailable approaches to activate the signaling pathways or molecules identified in this study. Most importantly, MPLA and IFN are already FDA-approved: MPLA as an adjuvant is used in vaccines against cervical cancer and shingles, and a variant of IFN (IFN 1b) is approved to treat chronic granulomatous disease and osteopetrosis. Thus, MPLA+IFN could be tested directly in human clinical trials for immediate patient impact.