AGA:
Pancreatic ductal adenocarcinoma (PDA) is innately resistant to treatment with a wide variety of chemotherapy. Using a clinically predictive genetically engineered mouse model of pancreatic cancer (KPC mice), we recently demonstrated that pancreatic tumors are poorly perfused, resulting in limited drug delivery and low drug concentrations within tumor tissues. We were able to augment drug delivery to KPC tumors by treating the mice with an inhibitor of the Hh pathway, resulting in prolonged survival when combined with chemotherapy. An incidental finding of this study was that mice treated with Hh inhibitor + chemotherapy had fewer liver metastases than controls, despite living longer with primary tumors. The goal of this proposal is to determine whether this treatment prevents the formation of new metastases, destroys existing metastases, or both.

We will address the possibility of metastasis prevention by using KPC mice harboring bioluminescent and fluorescent reporters. Mice with very small primary tumors will be treated with Hh inhibitor + chemotherapy prior to the dissemination of tumors cells. The hematogenous circulation, seeding and expansion of metastatic cells will each be monitored, allowing for a precise determination of whether Hh inhibition prevents metastasis and, if so, at what state. Conversely, the effects of Hh inhibition on established metastases will be assessed by treating mice with ultrasound-verified macroscopic metastases. Using ultrasound, we will be able to quantify tumor responses over time within each animal. Following necropsy, delivery of two drugs, doxorubicin and gemcitabine, will be assessed in metastases using confocal microscopy and mass spectrometry, respectively.

We anticipate that Hh pathway inhibitors will augment drug delivery in pancreatic tumor metastases similar to our earlier results in primary tumors, leading to partial responses in the metastatic lesions. However, it is our opinion that complete regression of the metastatic lesions are unlikely and therefore insufficient to fully explain our earlier observations. Therefore, it is likely that the Hh inhibitor + chemotherapy regiment also has plays a role in preventing the establishment of new metastatic lesions. This distinction is very relevant to decisions about what disease stages should be included in potential clinical trials of Hh pathway inhibitors.