A Novel Self-Reporting Paclitaxel Prodrug without Systemic Neurotoxicity: Preclinical Assessment for Targeted Treatment of Metastatic Breast Cancer
James McIntyre, PhD, Research Professor of Radiology and Radiological Science
Barbara Fingleton, PhD, Assistant Professor of Cancer Biology
Vanderbilt University

Our overall goal is to complete pre-clinical assessment of our new prodrug version of the widely used taxane, paclitaxel. Paclitaxel has efficacy against primary breast cancer and advanced (metastatic) breast cancer and is currently a “standard-of-care” for patients with advanced hormone-refractory or triple-negative breast cancer. Paclitaxel has dose-limiting and potentially life-threatening toxicities, including: (1) blood toxicity (myelotoxicity) that reduces the numbers of white blood cells available to help protect the body from infection; and (2) neurotoxicity that results in “neuropathy”, i.e., the loss of feeling in the feet, legs, hands or arms, etc. A major benefit of our nanoparticulate paclitaxel, NDPXL, is that this version delivers the drug to the tumor itself and thus reduces or eliminates off-target toxic side-effects. These toxic and debilitating side-effects not only limit the dose and duration of treatment with paclitaxel or other chemo drugs, but also seriously impacts the quality of life for many women being treated with this otherwise effective chemotherapy.

Our approach is to use a molecular scaffold called a nanodendron or ND that holds the paclitaxel away from cells. Thus, paclitaxel is formulated as a prodrug called ND-paclitaxel, abbreviated as NDPXL. To free the drug from NDPXL, the activity of an enzyme called matrix metalloproteinase (MMP)-9 is needed. Levels of MMP9 are normally very low in the body, but it is present in large amounts around many breast primary and metastatic cancers (tumors). The tumor-associated MMP9 provides a way to selectively release the active drug paclitaxel from NDPXL primarily in the vicinity of tumor cells where it can act to kill them. Both human and mouse MMP9 can work to release the drug from NDPXL. MMP9 is particularly high in BC patients with the poorest prognosis. Importantly, nerve cells have almost no MMP9 so the NDPXL does not affect them. In a pilot study, we showed that NDPXL achieves the same effects as the FDA-approved formulation of paclitaxel, Abraxane®, in mouse models of primary breast cancer, i.e., it reduces tumor growth at similar dose. However, mice treated with Abraxane® developed peripheral neuropathy, measured by loss of response to various touch stimulations, e.g., to the paws, as well as liver toxicity. By contrast, mice treated with NDPXL did not develop peripheral neuropathy, i.e., no change in response to various touch stimulations, or any evidence of liver damage. In this proposed work, we will perform efficacy testing of NDPXL in the clinically relevant setting of metastasis. We will first do experiments to find the best dose of NDPXL to use, that is, the amount that will cause the most tumor killing with minimal side effects. Because of the way NDPXL is made, we expect that we can use much higher doses than nab-paclitaxel, Abraxane®, and so have better efficacy. We will test NDPXL in mouse models of established lung and liver metastases, organ sites that account for the majority of deaths due to metastatic breast cancer. Follow-up studies on bone metastases are envisaged.

In addition to the drug nanodendron NDPXL, we have a similar molecule called NDPB that functions as a light-emitting beacon to show sites of high MMP9 activity as found in many cancers including many breast cancers. The current version of this beacon, NDPB, either alone or linked to the drug molecule making a dual or bifunctional agent NDPXL-NDPB, can be detected in mice using a research imaging instrument, i.e., we can take a picture of MMP9 activity from outside of the animals to show where the drug is being delivered and where it is being released to kill tumor cells. This will help us know that we are getting drug delivered and appropriately activated only where we want it – that is, around tumor foci. In the future, we plan to develop a version of our beacon that can be imaged with a PET scan; this might be useful, in patients, for finding out if they may have small and/or early stage metastatic lesions with high MMP9 activity that could be targeted using NDPXL treatment.

With the studies outlined in this application, we expect to show efficacy of NDPXL for treating metastatic disease in mouse models of metastatic breast cancer, without the usual nerve and/or blood toxicity of paclitaxel. If so, we also would expect NDPXL to work in patients as it is readily activated by human MMP9. NDPXL, formulated under Good Manufacturing Practice (GMP), could then, after Investigational New Drug (IND)-enabling safety, pharmacology and
toxicology tests, be tested in people. If NDPXL is shown to be superior to other formulations, we would then plan a first in human Phase I clinical trial with NDPXL, e.g., in breast cancer patients unresponsive to first-line therapy for metastatic breast cancer; this would be overseen by Dr. Ingrid Mayer (Consultant), a medical oncologist and our clinician collaborator. We expect that NDPXL will work better than current chemotherapy for treating breast cancer patients with either clinically evident or occult metastatic disease, and may even cure some patients, but would have much less toxicity than untargeted formulations of paclitaxel, with less nasty debilitating side-effects, such as neuropathy. If we find that NDPXL works to treat breast cancer metastases, we would also expect it to have efficacy versus metastatic disease developed from other cancers, including pancreatic cancer.