

## HUNCH 1

### Preventing diaphragmatic and cardiac wasting to promote survival in metastatic breast cancer



DR. TERESA A. ZIMMERS

*The following hunch was proposed by Dr. Teresa A. Zimmers, PhD, who is an Associate Professor of Surgery and focuses on muscle preservation research at the IU Simon Cancer Center.*

Involuntary loss of muscle mass is a frequent complication of advanced cancers, including metastatic breast cancer. Muscle wasting (called cachexia) leads to impaired function and lower quality of life. Importantly, weight loss and the rate of weight loss are directly correlated with shorter survival across cancers and indeed, cachexia itself is thought to be responsible for up to a third of all cancer deaths. What has been less appreciated is that muscle wasting also occurs in the heart, the diaphragm and the muscles between the ribs of the chest.

We propose that the decline in heart and lung function seen in patients with advanced breast cancer results from the same factors responsible for muscle wasting in cancer cachexia. Furthermore, we propose that treatments directed at preserving heart and respiratory muscle mass and function will promote quality life and prolong survival in patients with metastatic breast cancer (and other cancers associated with cachexia including lung and pancreatic cancer). We will test our idea in a mouse model of metastatic breast cancer. Treatments known to increase whole body muscle mass in normal mice will be used. Treatments will be targeted to the heart and respiratory muscles using viruses to deliver the biological treatments. Heart function, respiratory rates, muscle loss and survival will be assessed.

When these pilot studies are complete, we will know whether blocking the activity of cachexia-inducing factors in the heart and respiratory muscles can reduce loss of cardiopulmonary function, slow declines in whole body function, preserve skeletal muscle mass and promote longer survival. Such proof of concept studies would provide powerful preliminary data to apply for NIH funding for pre-clinical and correlative studies that will 1) identify appropriate targets in patients with metastatic breast cancer, 2) define pre-clinical efficacy, and 3) investigate mechanisms.

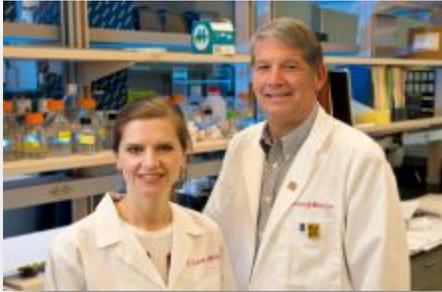
**BUDGET – \$100,000**

## HUNCH 2

### Enhancement of Avastin efficacy using E3330 in TNBC metastatic breast cancer animal model

---

*This project was submitted by Drs. Karen Pollok, Melissa Fishel and Mark R. Kelley. All serve as research professors at the IU School of Medicine and focus on pharmacology and toxicology for novel drug treatments in therapy resistant cancers.*



DR. MELISSA FISHEL (LEFT) AND DR.  
MARK R. KELLEY (RIGHT)

Tumors must develop a new, larger blood supply in order to grow and move to other parts of the body. Blocking the growth of these new blood vessels has been an effective therapy for many cancers. Avastin blocks blood vessel growth and is approved for the treatment of lung, colon, ovary, brain and other cancers. Avastin isn't currently approved in breast cancer treatment because adding Avastin to chemotherapy in breast cancer prolonged the time it took for tumors to grow (called progression free survival) but did not increase the overall time patients survived.

We have been studying a new drug E3330 that alters the function of several proteins, including some involved in blood vessel growth. We have compared Avastin, E3330 and the combination in two different models of abnormal blood vessel growth including; 1) macular degeneration (the leading cause of age-related blindness) and 2) glioblastoma (an aggressive brain cancer). In both models the combination of Avastin and E3330 was more effective than either drug alone. In this proposal we will test the combination in a mouse model of metastatic triple negative breast cancer. At the end of these studies, the data obtained in this proposal will determine if the combination of Avastin and E3330 could be a new combination treatment for TNBC. As E3330 is expected to enter clinical trials in 2015, we could translate our findings to the clinic quickly.



DR. KAREN POLLOK

**BUDGET – \$40,000**

# HUNCH 3

## Novel diagnostics and treatment of bone metastasis

---

*This hunch was proposed by a team including Drs. Hiroki Yokota, Likun Zhu, Mangilal Agarwal, Sungsoo Na and Jong Eun Ryu. Dr. Hiroki Yokota most recently worked on Hunch #8 with Dr. Hari Nakshatri. He and the rest of the team represent expertise in biomedical engineering, nanotechnology and mechanical engineering through Purdue University.*

In military combat, mechanical devices play a major role in removing enemy forces. Chemical and nuclear weapons are not primary resources because of their unwanted civilian casualties. In the fight against breast cancer and bone metastasis, we do not yet have the luxury to fight by mechanical means. Fortunately, scientists are reporting remarkable differences in mechanical properties of normal cells and cancer cells. Cancer cells are softer, which may allow them to more easily crawl, migrate and attach to bone. Using nanofabrication and microfluidics technologies, we propose to build a miniature device that detects and destroys soft, migratory cancer cells in blood. Two specific aims are:

- Design and make a micro device and prove that soft cancer cells can be detected and destroyed using mechanical forces (no side effects).
- Evaluate how the proposed device can select and specifically kill migrating cancer cells using many types of breast cancer cells, as well as chemical agents that make cancer cells rigid. Rigid cancer cells do not migrate freely, and they eventually die during blood circulation.

This is a pilot project that tests a proof-of-concept. Successful completion of this project may lead to new cancer therapies with no chemical or radiation-induced side effects, where blood becomes cancer free, and bone metastasis hardly happens. The scale-up device can be used like a dialysis machine for patients with chronic kidney disease. The device could also allow scientists to trap cancer cells for further testing, replacing more invasive biopsies.

**BUDGET – \$100,000**



FROM LEFT TO RIGHT, DRs. HIROKI YOKOTA, LIKUN ZHU, MANGILAL AGARWAL, SUNGSOO NA AND JONG EUN RYU.