



Dr. Honn, who was recently named distinguished professor, holds 13 patents for various compounds and methods.

# WSU'S MOST CITED RESEARCHER KEEPS PUSHING LIMITS

Dr. Kenneth Honn continues to develop novel cancer research

WHEN IT COMES TO HIS RESEARCH FINDINGS, Kenneth Honn, Ph.D., is stubborn. "I've been fighting dogma forever, but I absolutely will not give up," said this internationally known cancer researcher. "The things we're working on just turn out to be controversial, so what are you going to do?"

In his 20-plus years at Wayne State, Dr. Honn has become the most-cited researcher at the university according to the last study done, and frequently receives more external funding in a single year than many faculty members receive in their entire careers. This professor of radiation oncology and pathology, and adjunct professor of chemistry has also introduced and helped develop what has become one of the hottest areas in cancer research today. It all derives from a simple philosophy, he said. "Like I tell my students, you just have to follow your instincts."

Dr. Honn is perhaps best known as the man who put the cancer-research spotlight on eicosanoids, a large and diverse group of 20-carbon fatty acids, including several that are active in preventing the spread of cancer. His research group is also heavily invested in the study of a number of transmembrane proteins known as integrins. The group found that some integrins serve as receptors in tumor cells and facilitate their movement to other parts of the body. One of Dr. Honn's latest interests - and one that is sure to spur some new arguments - is his assertion that low-dose radiation may actually do more harm than good in treating cancer by enhancing the spread of cancer known as metastasis.

His work has always turned heads and sometimes turned up noses, he said. But, Dr. Honn's choice for a research field paid off early on in his career. By 1979, just a year after earning his doctorate from the WSU biological sciences department and joining the WSU faculty, he had already found that some eicosanoids were active against the spread of cancer, or metastasis. "The whole thing with eicosanoids, cancer and metastasis really took off," Dr. Honn recalled. His first projects centered on the roles of two eicosanoids, thromboxane and prostacyclin, in fighting tumor-cell progression. Thromboxane regulates the activity of platelets, which veer from their normal function in blood clotting to one of promoting metastasis in tumor cells. Prostacyclin, on the other hand, inhibits platelet function and tumor cell adhesion to the endothelial lining of the blood vessels, and therefore hinders metastasis.

By Leslie Mertz

In 1981, Dr. Honn published his results in two papers- one of them with cancer researcher Dr. Bonnie Sloane – in the journal *Science*. In the same year, he also received two grants from the National Institutes of Health (NIH) and another from the American Cancer Society. In 2003 alone, for example, Dr. Honn had a staggering 10 active research grants totaling \$1.4 million. He typically has two NIH and several other grants in any given year. His funding has remained reliable.

thinking about translational research, but that’s what we were doing.”

The thromboxane work is still continuing. Dr. Honn’s research group recently found that cancer cells express the enzyme that makes thromboxane. “In a paper that was just accepted in the *American Journal of Pathology*, we report that we cloned thromboxane synthase from prostate cancer, and it plays a role in motility. We found that the highest expression of the enzyme is in cells that are undergoing perineural invasion, which is how the cancer cells

proliferation were actually prevention of apoptosis and stimulation of angiogenesis,” he said. Both are critical for metastasis. Normal cells undergo apoptosis, or programmed cell death, but tumor cells are adept at avoiding it. In addition, tumor cells require an entire network of new blood vessels, which occur via angiogenesis.

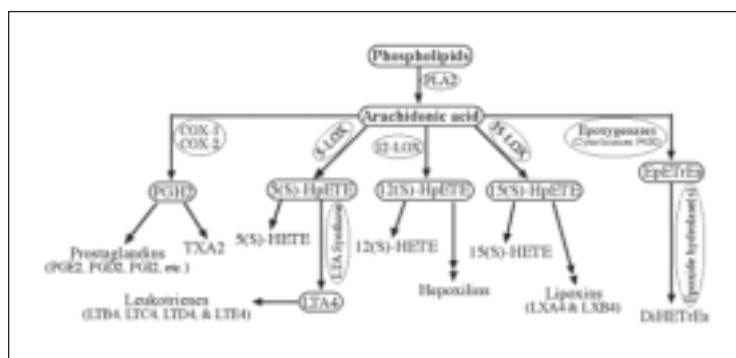
Dr. Honn began working with WSU chemists Larry Marnett and Carl Johnson, and the three men collaborated with another pharmaceutical company on developing drugs to shut down 12-lipoxygenase. Marnett left the university and now heads a research institute at Vanderbilt University and Johnson just retired from Wayne State, but Dr. Honn has continued to study 12-lipoxygenase, currently working with a local biotech company to test newly designed compounds. He commented, “We’re hoping that within a year, we’ll be in a phase I clinical trial with these 12-lipoxygenase inhibitors.”

A particularly fortuitous discovery, and one that surprised even Dr. Honn, came from Irma Grossi, a graduate student in his research group. “We were looking at the receptors on platelets that were responsible for the interaction between the platelet and the tumor cell, and the hot area of research at that time was integrins, some of which mediate platelet-platelet adhesion,” he explained. Grossi conducted some experiments and reported to Dr. Honn that she had found a particular form of an integrin on the tumor cells. No one had ever reported the occurrence, and Dr. Honn was highly skeptical until her repeated experiments and steadfastness convinced him.

Another fortuitous discovery was made by then postdoctoral student Dr. Mohit Trikha. He was following up on the project started by Dr. Grossi’s finding when he discovered that tumor cells produced truncated integrins, shorter versions of the full length receptors which were secreted by the tumor cell. He and Dr. Honn postulated that these truncated integrins were anti-adhesion molecules.

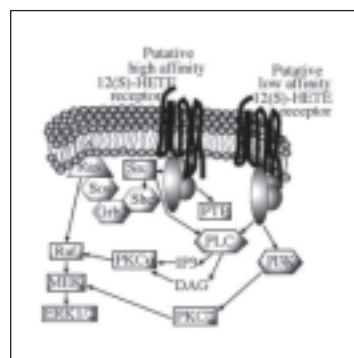
Once again, Dr. Honn faced opposition to his group’s findings, as well as an associated grant proposal on the topic. “Once dogma gets established, it’s just incredibly hard to break through. But we got more data, put the proposal back in, had to go back and get more data, put in the proposal again, and finally it got funded.” The extra effort was well worth it, he said. “We were right. We were absolutely right. And now, there are numerous researchers looking at integrins and discovering truncated forms.”

Besides the novelty of their discovery, Honn said truncated integrins are important because of their function. Through experiments conducted in collab-



FIGURES 1-2: Dr. Honn discovered in the 1970s that some eicosanoids were active against the spread of cancer, or metastasis. His first projects centered on the roles of two eicosanoids, thromboxane and prostacyclin, in fighting tumor-cell progression. Thromboxane regulates the activity of platelets, which veer from their normal function in blood clotting to one of promoting metastasis in tumor cells. Prostacyclin, on the other hand, inhibits platelet function and tumor cell adhesion to the endothelial lining of the blood vessels, and therefore hinders metastasis.

His 1981 findings led to a relationship with a German pharmaceutical company, which began making long-lived analogs of prostacyclin that it planned to test as anticancer agents. Although translational research is a buzzword now, relationships between academic and industry were few and far between in the early 1980s. “Think about it,” Dr. Honn said. “In ‘81 nobody was



escape from the prostate along a nerve path. We’re quite excited about this,” he said. He noted that WSU pathologists David Grignon and Mingxian Che collaborated on the paper.

By the late 1980s, Dr. Honn’s research turned toward 12-lipoxygenase, a member of another group of eicosanoids, that he suspected was “very important in terms of tumor-cell growth and metastasis. We later discovered the effects on

oration with WSU and Karmanos Cancer Institute professor Avraham Raz, Dr. Honn said, “We showed that the full-length integrin goes to the leading edge of the cell where attachment is important and the truncated integrin goes to the trailing edge of the cell where detachment is important. Consider that when the cell moves, it has to grab on at the leading edge, but detach at the trailing edge. That means that the truncated integrin functions as an anti-adhesion molecule to facilitate tumor-cell movement.”

He added, “This is a totally new mechanism for cell movement. Plus, we have found that there’s a correlation with the stage and the grade of prostate cancer and the production of the truncated integrin. Now we’re now looking to see if we can measure the truncated integrin in blood and see whether it can be used as some sort of a diagnostic feature not only in prostate cancer, but also in other types of cancer, specifically head, neck and lung cancers.” Dr. Honn and the university were awarded two patents on these discoveries and another for the use of specific antibodies to detect their presence in tumor tissue.

Another major research emphasis among Dr. Honn’s 13-member research group is a study that spans both eicosanoids and integrins. It began when graduate student Keqin Tang was working on her doctoral thesis on the proteins that interact with and may regulate 12-lipoxygenase. “With Russell Finley in the Center for Molecular Medicine and Genetics here at Wayne State, she discovered four proteins that specifically interacted with the 12-lipoxygenase, and one of them was the cytoplasmic tail of an integrin, so it brought our integrin work and our eicosanoid work together,” he said. The study is especially interesting because this particular truncated integrin, called beta 4, has been shown to be involved in neck-cancer metastasis.

The research group is now investigating the possibility that the association between 12-lipoxygenase and beta 4 integrin serves as a signal to produce another compound, called 12-HETE, that dissolves a structure (the hemidesmosome) anchoring the tumor cell to the extracellular matrix. Without the anchors, the cells can travel to new areas of the body.

While that work is continuing, Dr. Honn believes he now has evidence that deals a serious blow to the low-dose radiation treatment, called hyperfractionation, that is becoming popular among radiation oncologists. “I wondered whether radiation increases 12-lipoxygenase activity so we get more 12-HETE produced. If that’s the case, it could be that low-dose radiation actually increases the metastatic ability of tumor cells,” he said. “We looked through the literature and, lo and behold, there was anecdotal evidence that you

actually get a worse outcome in some cases with low-dose radiation, because you get more metastasis.” He said his group’s experiments now indicate radiation at low doses used in hyperfractionation stimulates protein synthesis for 12-lipoxygenase. “If you take those irradiated cells and inject them into the tail vein of a mouse, you see a great increase in metastasis.” Besides its potential effect on hyperfractionation, the work may have implications for new anti-cancer drugs, he said. “We actually just discovered that our 12-lipoxygenase inhibitors sensitize prostate tumor cells to radiation, and I’m talking about a two-fold sensitization, which is phenomenal. Plus, we have evidence that it will probably work in head and neck cancer, and in lung cancer, too.” Assistant Professor Daotai Nie, who is a member of Honn’s research group, is working under a grant from the Department of Defense to review a series of the inhibitors, and hopefully add one more cancer-treatment option to the growing drug arsenal.

With such an active research endeavor, several hundred publications, a long tally of grants, Dr. Honn’s vita is enormous. When asked if he’ll always remain busy in his scientific pursuits and adamant about his findings, Dr. Honn simply replied, “Sure. Why not?” ☺

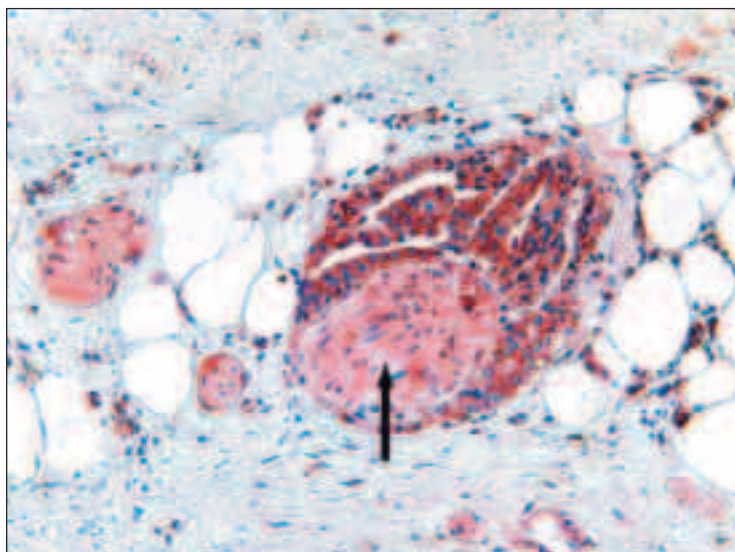


FIGURE 3: Cancer cells express the enzyme that makes thromboxane and thromboxane synthase plays a role in motility.

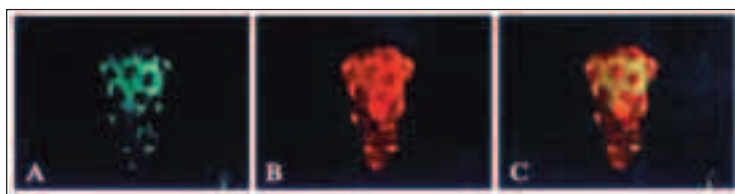


FIGURE 4: Collaborations among the research teams of Dr. Honn and Dr. Russell Finley forged the discovery of four proteins that specifically interacted with the 12-lipoxygenase, and one of them was the cytoplasmic tail of an integrin, bringing Dr. Honn’s integrin and eicosanoid work together. The truncated integrin, called beta 4, is involved in neck-cancer metastasis.