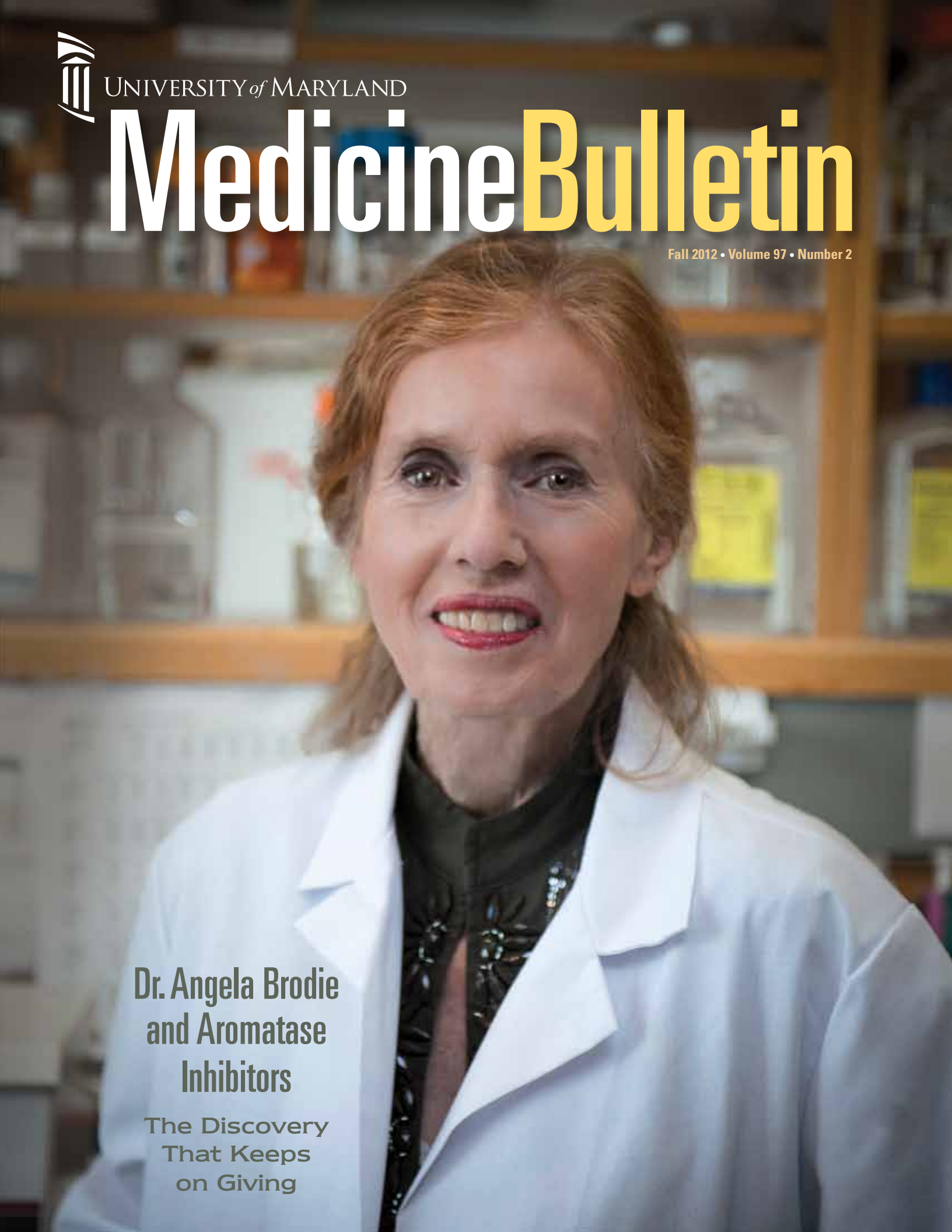

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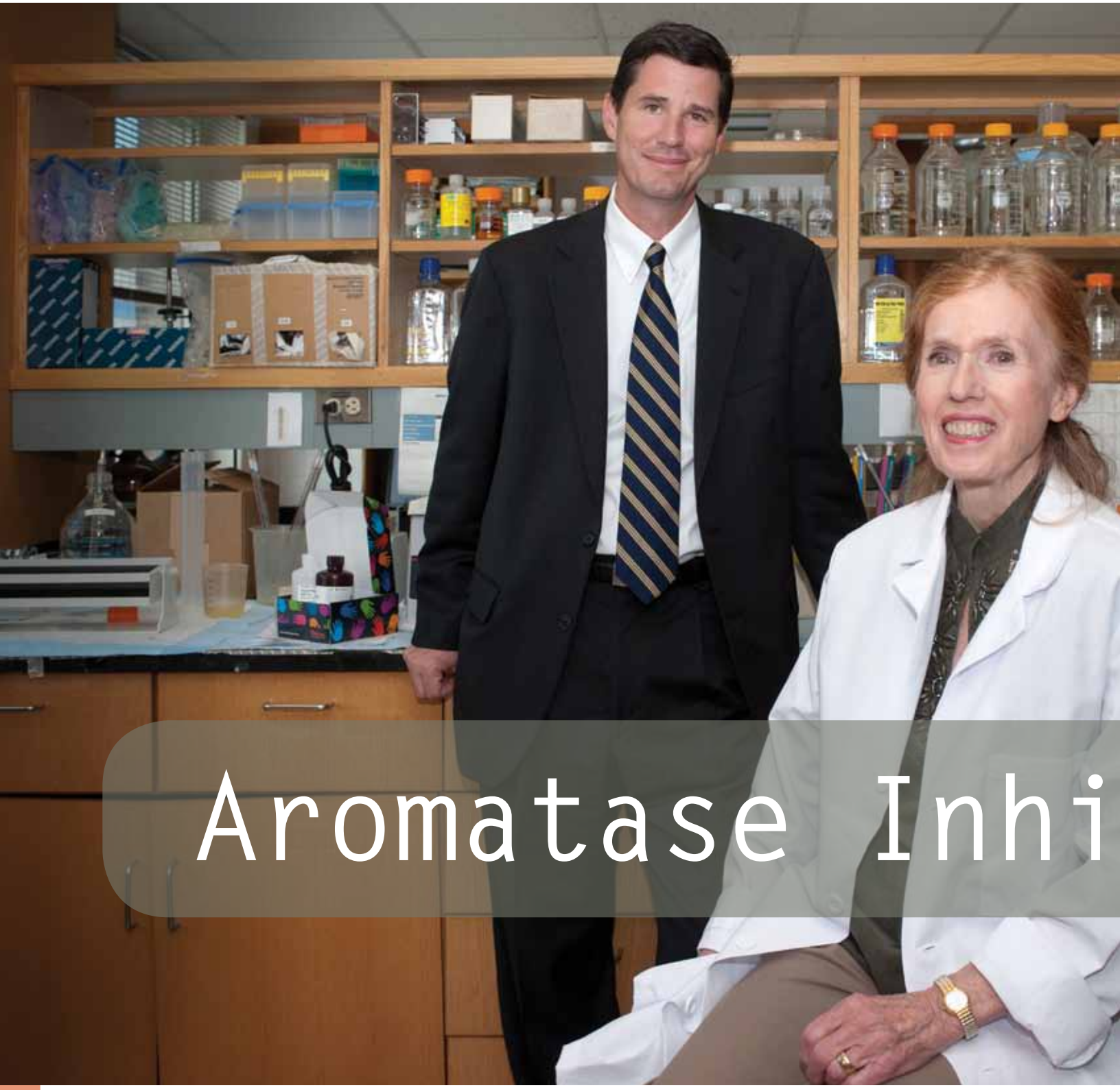
## Dr. Angela Brodie and Aromatase Inhibitors

### The Discovery That Keeps on Giving



# Aromatase Inhi

By Rita M. Rooney

*Photos by Richard Lippenholz*

*Angela Brodie, PhD and John A. Olson Jr., MD, PhD*

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## The Discovery That Keeps on Giving

Admitting to the inevitable roadblocks within scientific discovery, Angela Brodie, PhD, professor of pharmacology, counters with a smile that scientists don't expect overnight success.

"Identifying inhibitors that work well in the test tube is a long way from seeing their effective use in the clinic," Brodie says.

She should know. Brodie's major scientific awards recognize her development of aromatase inhibitors in the treatment of breast cancer as among the most important contributions to cancer cure. She has received the Kettering Prize from the General Motors Cancer Research Foundation, awarded for the most important recent basic science cancer research. In addition, she is recipient of the Dorothy P. Landon ACCR Prize for groundbreaking translational cancer research. Most recently, she received the prestigious Pharmacia Award of the American Society for Experimental Therapy.

Brodie's development of aromatase inhibitors took place during the 1970s and early 1980s, but the aromatase story has a sequel—one that chronicles continuing new achievement. Brodie has teamed with a physician–scientist who is accelerating the impact of inhibitors on breast cancer surgery, and she is further collaborating with a researcher and together they are applying a similar strategy to prostate cancer therapy.

John A. Olson Jr., MD, PhD, Campbell and Jeanette Plugge Professor of Surgery, was recently recruited to Maryland as vice chair, department of surgery and chief of the division of general and oncologic surgery. He reports that he was attracted to Maryland because of its impressive level of research as well as the presence of Brodie. Shortly after his arrival, the two began a collaboration exploring the merits of using inhibitors in conjunction with surgery.

Vincent C.O. Njar, PhD, professor of medicinal chemistry and pharmacology, and head of the medicinal chemistry section of the center for biomolecular therapeutics, has been collaborating with Brodie for several years on developing androgen synthesis inhibitors to treat prostate cancer. Their work, which is meeting with considerable success, has been predicated on the premise that, if aromatase drugs are effective for breast cancer, the same concept might well apply to the development of inhibitors for prostate cancer. Their lead inhibitor (VN/124–1) is now in clinical trials.

Aromatase is an enzyme that makes estrogen, a hormone that is a growth factor in most breast cancers. Brodie began with the idea of developing inhibitors to the enzyme which in turn would reduce the production of estrogen. Initially, she and her husband, now a retired

Angela Brodie, PhD, can be contacted at abrodie@umaryland.edu

organic chemist and National Institutes of Health (NIH) administrator, were working on estrogen synthesis inhibitors as related to women's reproductive issues. She saw the possibilities for these inhibitors of estrogen synthesis as treatment for breast cancer, however, and changed the direction of her work.

"When I first started research, little was known about estrogen production or how it acted, she says. "The only course of treatment for breast cancer was surgery to remove the sources of estrogen, and it seemed to me there just had to be a better way."

Receptors that classify a patient's sensitivity or resistance to aromatase inhibitors can be identified from biopsy tissue. If the tumor has estrogen receptors, the treatment is recommended. If it doesn't, chemotherapy is given. However, among the majority of those who will benefit from inhibitors, some will later become resistant.

While the Brodie laboratory was developing aromatase inhibitors, pharmaceutical companies were conducting clinical trials of tamoxifen, the drug that became the first in the non–surgical arsenal against breast cancer. While it is responsible for significant strides in the treatment of the disease, tamoxifen is slightly estrogenic and binds to the receptor, blocking its action. It also can lead to stroke and endometrial cancer. Brodie believed that inhibiting the estrogen would not have the same side effects. Today, aromatase inhibitors are the first line of defense against breast cancer, due to their effectiveness and the absence of serious complications associated with chemotherapy and the earlier tamoxifen.

During the early years of her research, Brodie served a fellowship at Worcester Foundation for Experimental Biology sponsored by the NIH. A few years later, Njar was at the same foundation for post-doctoral work. While they worked at Worcester during different times and never met there, Njar was aware of Brodie's research. In 1994, while working on a fellowship sponsored by the Alexander von Humboldt Foundation in Germany, he began looking for a target for prostate cancer and decided that if aromatase drugs were effective for breast cancer, the same approach might be used to target the androgen involved in prostate cancer. He contacted Brodie who was already working on developing androgen synthesis inhibitors for prostate cancer. Brodie invited him to join her team. Njar came to Maryland on a grant secured by her laboratory. He joined the faculty in 1999, and formed his own lab, with the purpose of developing compounds that would inhibit the androgen synthesis and block the receptor. He and Brodie have since pooled their respective expertise toward this aim.

Brodie adds that the androgens are produced not only by the testes, but in other tissue in the body including the adrenals and prostate tumor itself. Earlier treatment did not block all pathways, and so their purpose was to develop a compound that would block both the androgen receptor and androgen synthesis.

"The whole idea was developed from aromatase inhibitors," Njar says. "The same rationale applies if you consider the targets—aromatase and the various prostate targets. While not the same enzyme, the mechanism of how they work is the same."

In collaboration, Njar and Brodie developed several compounds they believed to be as effective as prostate surgery. In surgery, removing the testes cuts down the production of androgens. Animal studies indicated comparable results with several of the compounds. But the colleagues weren't satisfied with an "as good as" determination. They began to explore whether compounds could be developed that would exceed the limitations of the radical surgical procedure then prescribed for prostate cancer.

After developing several compounds, the researchers came up with a lead compound VN/124–1 and were able to publish results of their mouse studies to show more effective results than the ablative surgery usually performed. Soon after, Tokai Pharmaceuticals undertook drug development and clinical trials of the compound renamed TOK–001 or Galeterone began. Outcome from the Phase 1 trials were extremely positive. Normally Phase 1 defines safety only, and Phase 2 effectiveness. But this trial was used with patient volunteers, leading to exceptionally promising results in terms of effectiveness. In fact, on the basis of the results, Galeterone has received Fast Track Designation from the U.S. Food and Drug Administration for the potential treatment of metastatic castration-resistant prostate cancer (CRCP). A larger Phase 2B trial is expected to begin before the end of the year. While the researchers are highly encouraged by these results, it is the constant nature of the scientist to continue probing. Right now, Njar says he is focused on questioning what it is about this compound that makes it so much more effective than all the others developed by the research team.

The recent collaboration between Brodie and Olson might be called the perfect pairing of scientific interests. Her current primary study concerns those women who eventually develop a resistance to the inhibitors. Hormonal therapy is preferred for the 70 percent of women who respond positively. Patients can take it daily for a number of years in

John A. Olson Jr., MD, PhD, can be contacted at jolson@smail.umaryland.edu

contrast to chemotherapy in which the extent of treatments is limited.

"This makes it important to discover the mechanism by which some patients become resistant to the inhibitors," Brodie says. "When we know that, then we can work on finding a way to convert them back to becoming re–sensitized to the treatment."

She explains that receptors that classify a patient's sensitivity or resistance to aromatase inhibitors can be identified from biopsy tissue. If the tumor has estrogen receptors, the treatment is recommended. If it doesn't, chemotherapy is given. However, among the majority of those who will benefit from inhibitors, some will later become resistant.

"We're now looking at patients who would never respond to the treatment, as well as those who later become resistant to it," Brodie says.

*Vincent* C.O. Njar, PhD

Olson, who most recently held the position of chief of endocrine, breast and oncologic surgery at Duke University Medical Center, was familiar with tumor shrinkage through aromatase inhibitors prior to surgery, and was impressed with the results. At the time, it was more popular to use chemotherapy for pre-operative reduction of the tumor.

"To oncologists, it comes down to matching the right drug to the right tumor," Olson says. "Chemotherapy is a good option for women with certain kinds of tumors. However, it is well known that women with the estrogen receptor may respond much better to the hormonal treatment."

Brodie and Olson are now beginning to combine their considerable backgrounds in surgery and research. Olson has done extensive work in obtaining samples from tumors both during biopsy and tumor removal for the purpose of ensuring that the integrity of the sample is good, and therefore the molecular analysis is accurate

"Understanding why tumors respond to certain therapies begins with understanding the biology of the tumor from patient tumor samples," Olson says. "High quality samples are needed for research in order to determine why some tumors don't respond well to aromatase inhibitors." He has developed a device to assist with the proper collection of sampling during biopsy as well as surgery. He emphasizes that assumptions about tissue samples and how they are procured can lead to less than a strictly accurate molecular profile of the sample.

Brodie reports Olson's work will be enormously helpful to her studies in that until now, patients for aromatase treatment were selected on the sole basis of excised tissue.

"Now we can examine tissue following biopsy and diagnosis, after pre–operative treatment and following surgery," she says. "For many years, it was assumed that whatever was in the tumor at the start of growth would be the same during recurrence. We now believe it has probably changed considerably, but until recently, we haven't had the tissue to determine that."

Olson says he, like Brodie, is interested in knowing why women who are expected to respond to aromatase inhibitors don't.

"We're going to try to see if we can get those tumors that express a little of the estrogen receptor to express more so that it becomes increasingly responsive," he says.. "We also think that, depending on how a small tumor shrinks, we may be able to take less tissue, and thereby reduce the number of repeat surgeries. Prior treatment enhances the ability to get the entire tumor, even with small tumors."

Looking back, Brodie recalls that she wasn't ever discouraged in her pursuit of an effective non-surgical treatment for breast cancer. She was funded by the NIH throughout her studies, but there were times when she felt little encouragement either. Mostly, she remembers the difficulty in getting her research through clinical development. Then she delivered a paper in Rome describing her research. A British oncologist attending the meeting became interested and approached her regarding the potential for getting her discovery into the clinic. Brodie wound up synthesizing aromatase inhibitors at Maryland and shipping them to London where they were prescribed for a number of women with advanced breast cancer. Results were remarkable; so much so that, armed with clinical evidence, Novartis (then Ciba-Geigy) undertook clinical trials. That was only the start of the aromatase story. Continuing chapters report the drug's impact on the discovery of hormonal treatment for prostate cancer, and important collaboration between the Departments of Pharmacology and Surgery. And the words "the end" are far from being written.

Vincent C.O. Njar, PhD, can be contacted at vnjar@som.umaryland.edu