Angela M.H. Brodie, PhD, FAACR: In Memoriam (1934–2017)
V. Craig Jordan

On June 7, 2017, the cancer research community lost Professor Angela MH Brodie, PhD, FAACR, the "Mother of Aromatase Inhibitors." The discovery of specific aromatase inhibitors (AI) is a major advance in targeted therapeutics. Three cheap orally active agents, anastrozole, letrozole, and exemestane, are now available worldwide. These medicines are used ubiquitously for the treatment of estrogen receptor (ER)-positive breast cancer in postmenopausal women. Breast cancer that is ER positive is so prevalent, it can be argued that hundreds of thousands of patients have benefited, with recurrences prevented or delayed, primarily breast cancer prevented and lives extended.

She was born September 28, 1934, in Oldham, Lancashire, England, and attended Ackworth Quaker boarding school where she learned to consider "others before self and to look for the good in people." World War II broke out when Angela was 5 years old, and she experienced nightly bombing raids. She witnessed the destruction of war and the suffering of families. As a result, she had a lifelong abhorrence of war and violence.

Her father, Herbert Hartley, an industrial chemist, encouraged Angela to pursue a career in science at a time when women were not welcome in the pursuit of scientific discovery. She earned her Bachelor of Science degree (hons) in Biochemistry (1956), followed by her Master of Science degree (1959) at the University of Sheffield. For her PhD in Chemical Pathology, she traveled to the University of Manchester (1961). She was supported by a prestigious Medical Research Council scholarship. There at the Christie Hospital, she witnessed the consequences of radical mastectomy in demolishing a woman’s sense of identity. To Angela, it was simple: Women deserved better.

Interest in steroid endocrinology took her to the Worcester Foundation for Experimental Biology (WFEB) in Shrewsbury, MA. It was the "swinging 60s" and the era of "make love and not war." Angela was accepted into the prestigious NIH-sponsored steroid biochemistry training program. However, this was not to study cancer but the latest knowledge about steroid hormone synthesis in the body and the applications of that knowledge. The WFEB was founded in 1944 by Gregory Pincus and Hudson Hoagland. Theirs was a singular goal, to devise a clinically useful oral contraceptive and they (Drs. Pincus, Chang, and Rock) succeeded. During the 1960s, the WFEB was acknowledged worldwide as 'the home of the oral contraceptive.' This was the place to be for those interested in science in the service of society.

After her training, Angela did not return to England, but instead stayed on at the WFEB, working with the world famous British husband and wife team of Drs. James and Sylvia Tait, who had earlier discovered aldosterone. Both were Fellows of the Royal Society and only the second married couple after Queen Victoria and Prince Albert to be elected as Fellows. Naturally, the focus of their research was on the steroid aldosterone, a salt-retaining steroid hormone. Angela contributed to four articles while working with the world class Tait Team. Nevertheless, cancer research remained elusive for Angela. At this time, Angela met Harry Brodie, PhD, who was working on the biosynthesis of the sex steroids estrogen and androgen. Estrogen is created from androgen by aromatization, and this was key to their future research in anticancer agents. This moment created a team and they married in 1964. Their two sons, Mark and John, were born in 1968 and 1969. Returning to work in 1971, the world of government-supported medicine had shifted from contraception to cancer research. In 1971, President Richard Nixon signed the National Cancer Act. The new goal was to advance knowledge of cancer research rapidly from the laboratory to aid and cure patients. The war on cancer had been declared. Here was the chance Angela had sought and the Brodies were ready, Harry the chemist and Angela the pharmacologist.

In 1972, Dr. Elwood V. Jensen, Director of the Ben May Laboratories for Cancer Research at the University of Chicago (Chicago, IL), was a new member of the WFEB external advisory board. Elwood was a world leader in the ER signal transduction pathway that drives breast cancer growth. The strategic goal with Elwood’s appointment was to enhance the exploitation of the rich resources in endocrinology at the WFEB to aid discovery in cancer. Anticancer studies with ICI46,474 (not yet tamoxifen) were started at the WFEB in 1973 using the dimethylbenzamidracene (DMBA)-induced rat mammary carcinoma model. Studies on the value of tamoxifen to block estrogen binding to the breast tumor...
ER were also completed at that time. All techniques were imported to the WFEB through the good offices of Elwood Jensen. Tamoxifen was a start, but Angela took a different view. She reasoned "there is no available anti-estrogen as good as no estrogen at all: that should be our goal."

Early AIs had been used successfully to treat metastatic breast cancer (MBC) in postmenopausal women. Prominent clinical publications in the New England Journal of Medicine, most notably by Richard Santen, MD, defined treatment practice. However, these studies illustrated the nonspecific nature of the standard medicine aminoglutethimide. This inhibitor of aromatase was not specific for the CYP19 aromatase enzyme, but interfered with other steroid regulatory processes.

Harry, Angela's strongest academic supporter, wanted to give her the chance to run her own laboratory and to obtain NIH grants. The plan was. Harry would create compounds to be tested and he would substitute Angela as the principal investigator (PI) on his RO1 NIH grant once she had demonstrated academic leadership with first authored articles. She succeeded with eight first authored-referred publications between 1976 and 1980. Harry tells the story that upon their grant application with Angela as the PI, the work was well received, with a fundable score. However, if the PI could trim the budget by getting rid of the chemist, then this would ensure funding. Harry agreed for Angela to do just that.

Angela and Harry identified 4-hydroxyandrostenedione (4-OHA) as a potent and specific inhibitor, but there was no synthetic patent protection, as it was a known compound. They did, however, patent ester derivatives in 1980. Nevertheless, 4-OHA was their best compound. The animal system used to evaluate the antitumor properties of their compounds was the DMBA-induced rat mammary carcinoma model. Harry and I administered the DMBA to all the rats to initiate carcinogenesis, which would take 6 months. Angela was not even allowed in the laboratory that day. We were taking no chances with Angela's health! Comparisons of 4-OHA with tamoxifen demonstrated the superiority of 4-OHA. She was correct in her strategic goal. This prediction was proven in clinical trials decades later. I returned to England from the WFEB in September 1974, and the Brodies gave me a farewell party in their home. In recent years, I thanked Harry, who is of Scottish ancestry, but he claims to have no recollection of the event. I call that a really good party!

Despite interesting anticancer findings with antihormones in the laboratory, the reality of research in the war on cancer was to save lives. The clinical goal in the 1970s was to use cytotoxic chemotherapy to cure cancer. This laudable goal was based upon the success of combination chemotherapy to cure childhood leukemia and to MOPP up Hodgkin disease. All that was necessary was to find the right combination of cancer-killing chemotherapies. There was little or no hope that Brodie could advance 4-OHA from the laboratory to treat patients. Antiestrogenic strategies were only palliative in the late stages of breast cancer, so clinicians, particularly in America, favored cytotoxic chemotherapy. By chance, Angela and Harry met a British medical oncologist Dr. Charles Coombs who was easily persuaded to undertake a clinical trial in London. Despite the fact that patent protection was secured on ester derivatives of 4-OHA, Angela was firm "we will only give him our best compound." Coombs declared that he would give it to MBC patients if they sent him their compound. That AI was 4-OHA with no patent protection, but the path to this clinical trial was not as it is today. There was no pharmaceutical company to provide the formulated test drug. The 4-OHA was synthesized in Brodie's laboratory at the University of Maryland (College Park, MD), where she moved from the WFEB in 1979. Harry was working at the NIH in Bethesda, MD. The refrigerated drug was shipped over to London to be administered to patients. The results were positive for the treatment of MBC using injections of 4-OHA. The Swiss pharmaceutical company CIBA subsequently marketed 4-OHA as formestane. Her extraordinary commitment and faith in her laboratory findings underscores her total commitment to advancing a medicine to aid women's health. She was unwavering and overcame enormous administrative obstacles. Now, women had something better!

Brodie continued to investigate new AIs over the next 25 years. The pharmaceutical industry created many new compounds, as the AIs were becoming the medicines of choice for adjuvant therapy of postmenopausal patients with ER-positive breast cancer. Her focus, once AIs were used clinically, was to understand acquired resistance to AI therapy. Her prediction that AIs would be superior to tamoxifen was confirmed.

What is not widely known is that Brodie broadened her work at the University of Maryland to create new ways to treat androgen-dependent prostate cancer. She was the leader of the prostate program (1983–2006) of the Marlene and Stewart Greenbaum Cancer Center at the University of Maryland. In collaboration with Vincent Njar, Professor of Pharmacology at the University of Maryland, they developed a drug galaterone (VN/124). Galaterone has a unique mechanism of action, as it blocks both the androgen receptor and androgen synthesis in prostate cancer. In 2011, the FDA announced that they would fast track approval for clinical trials.

The academic community has recognized Brodie's discoveries and determination. She would tell her students "to do something that is going to benefit mankind." That she did. Her recognition includes the Brinker International Award for Breast Cancer Research (2000), Dorothy P. Landon/AACR Award for Translational Research (2006), The Pincus Medal WFEB (2007), the Robert and Claire Passarow Award, and the ASPET Award (2012). Brodies and I shared the 24th Gregory Pincus Memorial Award (June 14, 2007) from the Worcester Foundations for Biomedical Research, which was formally the WFEB. Our relationship over 45 years is best summed up by Dr. Thoru Pederson, President of the Worcester Foundation, who stated at our ceremony "Drs. Brodie and Jordan first met at the Foundation in 1972. Although their subsequent career paths and extraordinary discoveries were totally independent of one another, they have shared a lifelong spirit of collegiality and open communication, never considering themselves as competitors. We honor them today for their epochal contributions to medical science, and we applaud them for their selfless style of science they have practiced, serving not themselves but the world in the tradition of Gregory Pincus."

Two accolades stand out that are the hallmark of success for this pioneering woman scientist. The Kettering Prize from the General Motors Foundation and Fellow of the AACR Academy. The Kettering Prize was for the most outstanding recent contribution to the treatment of cancer and was considered the top international award for clinical cancer research (1979–2005). Brodie received the Kettering Prize in 2005. Not only was she a clinician receiving the last Kettering Prize, but also she is the only woman to receive the Kettering Prize.
The 110 Fellows of the AACR Academy represent the achievements and advances in cancer research worldwide. Brodie was inducted into the inaugural class in April 2013 for her landmark achievements in establishing that a specific AI that blocks estrogen biosynthesis would benefit womankind. She helped mankind with the later discovery of galaterone for the treatment of prostate cancer. Brodie was unable to attend the celebrations in 2015, but in 2016, Angela and Harry’s seats were again empty at our table. Suddenly, there they were, coming into the room and friendships were renewed. I was aware that Angela had been ill with Parkinson disease, but I was unaware of just how seriously ill Angela now was. Nevertheless, she insisted on attending the celebrations for the AACR Academy. Harry made her attendance possible. As exemplified by her life’s work, her philosophy was to remain calm and never to create a fuss. She just got on with the job, to accomplish it. She did just that.

Angela M. Hartley Brodie is survived by her husband Harry of Fulton, MD, a son, Mark Brodie, a drama teacher in San Fernando, CA, and wife Amy; a brother Emeritus Professor Laurence Hartley of Western Australia and his wife Jeanie; and two grandchildren, Jackson and Ryland. She was preceded in death by a son Dr. J.H. Brodie, a talented mathematician. Brodie found horseback riding, skydiving, and mountain climbing calming from her high stress and performance-based career in cancer research!

The University of Maryland has announced the creation of the Angela and Harry Brodie Distinguished Professorship in Translational Cancer Research. They previously honored Dr. Angela Brodie when she received the Kettering Prize, the world’s top clinical cancer award, in 2006. She received the University of Maryland Gold Medal for Research and their Research Lecturer of the Year award.
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