Angela M. Hartley Brodie

(1934–2017)

Discoverer of selective aromatase inhibitors for breast-cancer treatment.

Angela Brodie was a giant in the world of breast-cancer therapy. She discovered and developed the first selective aromatase inhibitor — a drug that blocks the synthesis of oestrogen, which fuels the growth of breast-cancer cells. Such treatments have saved the lives of hundreds of thousands of women; a third generation of the compounds are now the drugs of choice in postmenopausal women.

Brodie died aged 82 on 7 June in Fulton, Maryland, from complications arising from Parkinson's disease. She was born in Oldham, UK, on 28 September 1934. Unusually for the time, her father, an organic chemist, encouraged her interest in science. After gaining a BSc and MSc in biochemistry from the University of Sheffield, she completed a PhD in chemical pathology in 1961 at the University of Manchester.

In Manchester, working as a research assistant at the Christie Cancer Hospital, she saw how traumatic radical mastectomy procedures were for women. She vowed to develop a better treatment for breast cancer that would, as she put it, avoid sending women to the “butcher's shop”.

In 1962, she went for postdoctoral training in steroid biochemistry on a fellowship at the Worcester Foundation for Experimental Biology in Shrewsbury, Massachusetts. Here she met and married the organic chemist Harry Brodie, and raised a family. On her return to work in 1971, they became collaborators — Harry the chemist and Angela the pharmacologist — working together for the next decade.

Her strategy was to rid people with breast cancer of oestrogen. This, she thought, was more thorough than simply blocking oestrogen receptors, as drugs such as tamoxifen did. Hers was a niche area of research; most of the community was focused on chemotherapy rather than on targeting hormones. Together, the Brodies spent the 1970s optimizing aromatase inhibitors and their method of administration, using synthetic compounds and testing them *in vivo* and *in vitro* to block oestrogen synthesis. In 1979, they moved to Maryland — Angela went to the University of Maryland School of Medicine in Baltimore, where she continued the aromatase inhibitor work with an eye to moving it into clinical testing. (Harry became a study-section administrator at the National Institutes of Health in Bethesda.)

The Brodies' systematic research gave rise to their best compound, 4-hydroxyandrostenedione (4-OHA), in 1977 (A. M. H. Brodie *et al.* *Endocrinology* **100**, 1684–1695; 1977). This was the first molecule able to inhibit the synthesis of oestrogen alone in breast-cancer cells, without interfering with other physiologically important processes or causing toxic side effects. But when the Brodies tried to pursue drug development, they faced scepticism. The pharmaceutical industry at the time, particularly in the United States, was uninterested in drugs that did not kill off cancer cells.

In 1981, Angela met medical oncologist Charles Coombes (now at Imperial College London). As a British physician, Coombes was easier to persuade of the possible benefits of targeting therapies towards oestrogen. He organized the first clinical trial in 1981. At that point, 4-OHA had no patent protection, because Brodie had made the decision to put her patients before profit. Initial results were promising enough to spur further clinical testing and marketing of 4-OHA through the Swiss pharmaceutical company Ciba-Geigy, under the name formestane. The drug was heralded as a way to help postmenopausal women — the group that is most susceptible to breast cancer and whose tumours are most responsive to anti-oestrogen therapy.

The early successes of 4-OHA spurred the development of better anti-oestrogen therapies. By the late 1990s, work by Brodie and others helped to develop aromatase inhibitors that could be taken orally. Brodie also spent much time studying some patients' resistance to the drugs. Resistance arose because of selective pressure from the drugs — over time, tumour cells that could grow in an oestrogen-free environment were able to proliferate. Today, three aromatase inhibitors (anastrozole, exemestane and letrozole) are commonly used worldwide.

From the mid-1990s, Brodie broadened her work to prostate-cancer treatment. With chemist Vincent Njar of the University of Maryland, Brodie developed a drug (VN/124-1, or galeterone) to block the synthesis of androgens such as testosterone, which fuel the growth of prostate cancer. In 2012, the US Food and Drug Administration gave fast-track approval to conduct clinical trials of the drug, and the results of phase II trials were promising.

In her 48-year career, Brodie published more than 200 peer-reviewed research articles. She won numerous awards, and in 2005 became the only woman to win the Charles F. Kettering Prize, the highest recognition for improvements to clinical cancer care. Brodie fought bias against women throughout her career, serving on committees for female cancer researchers to shape a more-inclusive community. Her quiet, almost frail demeanour belied a will of steel. She mentored more than 40 graduate students and postdoctoral fellows. She was part of the team, following the data wherever the results led.

Despite her success, Angela remained grounded. She found relief from the stresses of work in the support of her husband, her two children, her grandchildren and in sky diving and mountain climbing. And for 30 years she rode and cared for her horse, Blue. The University of Maryland's School of Medicine plans an endowed professorship to honour both Brodies. ■

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