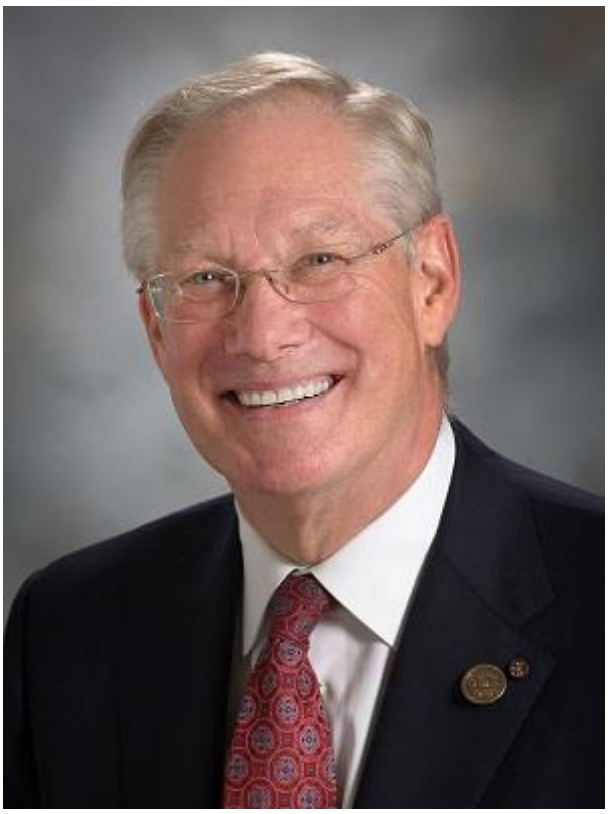
V. Craig Jordan (1947-2024)

V. Craig Jordan was a clinical pharmacologist whose finding that non-steroidal anti-oestrogens can act as oestrogen receptor (ER) agonists or antagonists at the body's different tissue ERs, revolutionized women's health, from breast cancer treatment to osteoporosis prevention.



V. Craig Jordan, discoverer of Selective ER Modulators (SERMs), was the founding father of targeted therapy in cancer. Today, there are 5 FDA-approved SERMs (tamoxifen, raloxifene, toremifene, basedoxifene, ospemiphene) used to treat and/or prevent major conditions in women: from the treatment of all stages of breast cancer, to breast cancer risk reduction, osteoporosis treatment, and menopause symptoms' alleviation. Yet, when Jordan began his research in the early 1970s, with combination chemotherapy being perceived as the cure to all cancers, his concept of a targeted and gentle cancer therapy was deeply resisted. Worldwide, breast cancer is the second most common cancer, osteoporosis affects at least 200 million women, and menopause symptoms impact roughly 85% of women. Jordan's SERM discovery has had an enormous influence on the lives of women around the world, as well as, the discovery of other selective nuclear receptor modulators and aromatase inhibitors.

Jordan was born in New Braunfels, Texas in 1947 and educated at Moseley Hall Grammar School, Cheadle. There, he met Charles Bescoby, a biology teacher, who tutored him to get A-level grades, allowed him to use the laboratory to teach university-level biochemistry to other boys, and supported his application to the University of Leeds in West Yorkshire, UK, where he completed a PhD in

pharmacology on the three dimensional structure of the ER. In parallel with Moseley Hall, Jordan secured a technician position at ICI Pharmaceuticals (later AstraZeneca), Alderley Park, UK. ICI would later support his laboratory at Leeds.

While being at Leeds, Jordan was awarded a commission and sent to the Regular Army training course in Nuclear, Biological, and Chemical Warfare Defense. His maternal grandfather was the musketry training officer for the Cheshire Regiment and his mother's family, the Mottrams, were elite horse archers who protected the Black Prince at the Battle of Poitiers. Jordan was later recruited to the British Army's Intelligence Corps, becoming the youngest captain in the service. Eventually, he joined the British Special Air Service (SAS) with a personal recommendation by General Sir Michael Rose.

In 1972, ICI Pharmaceuticals lost interest in ICI 46,474 (later tamoxifen) as a contraceptive or advanced breast cancer drug. At the Worcester Foundation for Experimental Biology (WFEB), Massachusetts (1972-74), Jordan established the DMBA rat mammary carcinoma model to evaluate the anti-cancer properties of ICI 46,474. He discovered that tamoxifen worked only on ER-positive breast cancer.

British American Jordan and British Angela Brodie crossed paths and discoveries at the WFEB. Jordan's findings that tamoxifen blocks the growth of ER-positive breast cancer, as the first targeted anti-oestrogenic therapy, inspired Angela Brodie to pursue the second targeted anti-oestrogenic therapy, which is blocking the oestrogen synthesis enzyme. Brodie became the discoverer of selective aromatase inhibitors, which are now used worldwide for the treatment of breast cancer in postmenopausal women.

Jordan went back to Leeds (1974-79), where he discovered tamoxifen's role as an adjuvant therapy for the treatment of early-stage breast cancer after surgery, and chemoprevention agent for the reduction of breast cancer risk in high-risk women. Clinicians Trevor Powles and Bernard Fisher used Jordan's chemoprevention data to initiate the Royal Marsden and NSABP trials. In 1977, Jordan presented tamoxifen's long-term adjuvant therapy data, at a meeting in King's College, Cambridge, which encouraged the attendees Michael Baum and Helen Stewart to initiate the NATO and Scottish trials.

In 1977, Jordan discovered tamoxifen's most potent metabolite, 4-hydroxytamoxifen, due to its hydroxyl. This opened the door for the synthesis of new hydroxyl-containing SERMS: raloxifene, bazedoxifene, and lasofoxifene. In 1979, Jordan presented his data on tamoxifen being the gentle, long-term adjuvant therapy at the Adjuvant Therapy of Cancer meeting in Tuscon, Arizona. His presentation was sandwiched between two greats of chemotherapy: Vince DeVita and Bernard Fisher. The ATLAS and aTTom trials later showed that 10 years of adjuvant tamoxifen therapy reduces breast cancer mortality by 50%.

At the University of Wisconsin, Jordan discovered that tamoxifen can encourage the growth of endometrial cancer in certain women. He alerted the clinicians to implement gynaecological monitoring in postmenopausal women, and sought tamoxifen derivatives that carried no risk of endometrial cancer (e.g., lasofoxifene). Lasofoxifene demonstrates many qualities of an ideal SERM: high potency for the prevention of osteoporosis (the daily dose is 1/100th the daily dose of raloxifene), a reduction of ER-positive breast cancer, reduction in strokes and coronary heart disease, but unlike tamoxifen – no increase in endometrial cancer.

In 1987, Jordan discovered that keoxifene maintained bone density in ovariectomized rats. Jordan's research was rejected by all osteoporosis journals with the premises that "anti-oestrogens cannot build bone, only oestrogens can". In 1994, keoxifene was renamed raloxifene by the pharmaceutical industry. In 1999, raloxifene was proven to maintain bone density in the MORE trial. Jordan then Chaired the breast cancer committee evaluating raloxifene for osteoporosis treatment.

Other advancements followed: the world's only successful transfection of ER into ER-negative breast cancer, pioneering structural and pharmacological studies into ER mutations in tamoxifen-resistant breast cancer, the discovery that ER's Asp351-to-H12 interaction dictates the co-activator recruitment to the ER:SERM complex and thus the SERM's oestrogenic or anti-oestrogenic behavior, and establishing the world's premier collection of patient-representative breast cancer cell lines, which Jordan freely shared with other scientists.

At the Robert Lurie Comprehensive Cancer Center of Northwestern University; Chicago, the Fox Chase Cancer Center; Philadelphia, the Lombardi Comprehensive Cancer Center of Georgetown University; Washington, and the University of Texas MD Anderson Cancer Center; Texas, the mechanisms underpinning oestrogen-induced apoptosis were deciphered -that oestrogen can not only fuel breast cancer cells, but also kill them in women who failed multiple therapies and might not have other treatment options. This simultaneously solved a 70-year-old mystery by David Karnofsky and birthed a new group of cancer therapeutics, Selective oEstrogen Mimics (SEMs).

Jordan received many honours. He joined the British Pharmacological Society (BPS) in 1976 and was elected to Fellowship in 2004. Jordan was awarded the Gaddum Memorial Award for research contributions to pharmacology (1993), the Sir James Black Award for contributions to drug discovery (2015), and Sir Henry Wellcome Gold Medal for discovery of SERMs (2022) by BPS. Other recognitions include: the Cameron Prize (1993) (other recipients are the Nobel laureates: Alexander Fleming, Marie Curie, and Louis Pasteur), her Majesty Queen Elizabeth II appointing Jordan Companion of the Most Distinguished Order of St. Michael and St. George (CMG) (2019) "for international services to women's health", and election to the National Academy of Sciences (2009) (USA); National Academy of Medicine (2018) (USA); Academy of Medical Sciences (2009) (UK equivalent of NAM), and an Honorary Fellowship of the Royal Society of Medicine (2008) (UK).

77-year old Jordan with a 55-year old career: it all started with his mother, Cynthia Mottram, allowing him to turn his bedroom into a chemistry laboratory. Now, his legacy lives on as the ultimate alchemist when it came to potential, failure, and contradiction: he turned all of his mentees from humble beginnings into rock stars in academia and the pharmaceutical industry, the failed contraceptive tamoxifen into a blockbuster breast cancer drug, the failed breast cancer drug raloxfiene into a blockbuster osteoporosis drug, and oestrogen from the fuel of breast cancer into its killer (SEMs).

Craig, you dared -as cancer researcher and patient-, you won, and women's health is in your debt for life.

Contribution by Jordan's last PhD student, Balkees Abderrahman, MD, PhD.