



## ASO Author Reflections: An Optimal Biological Model for Successful Drug Discovery

V. Craig Jordan, OBE, PhD, DSc, FMedSci, FAACR<sup>1</sup>

University of Texas MD Anderson Cancer Center, Houston, TX

### PAST

Over 100 years ago, Professor Paul Ehrlich created the model of drug discovery based on synthetic chemical candidates being tested in appropriate animal models of human disease. Following toxicology, a promising candidate was tested in a clinical trial.<sup>1</sup> Today, the marriage of molecular biology and medicine employs massive molecular screens of chemical libraries to identify candidates for study. Models are molecules in the computer. However, discovery in pharmacology and therapeutics requires an interlocking appreciation of the whole cell, the whole body, metabolism, and attention to decipher the unexpected. What is a discovery?<sup>2</sup> A discovery is an unanticipated result that does not give you the answer you seek. If you have the ‘wrong answer’ but your controls are all correct, it is your ideas that are incorrect. Your results become a discovery. Comprehensive cancer centers were created in the 1970s to accelerate laboratory discoveries to aid patient survival. The plan worked at Wisconsin.

### PRESENT

The discovery of selective estrogen receptor modulators (SERMs) is an unanticipated success story.<sup>3</sup> Medicines that failed in their primary indication of fertility control (tamoxifen) or breast cancer (raloxifene) were initially

discarded by industry, but re-invented in the focused environment of the Wisconsin Comprehensive Cancer Center. A single laboratory studied the molecular mechanisms of anti-estrogens; metabolism in animals, patients and acquired drug resistance; structure function relationships; breast cancer cell growth in culture; and drug effects on different human tumors that were estrogen target tissues.<sup>4</sup> These results were used immediately for clinical trials at Wisconsin that were advanced to national clinical trials. The goal was to investigate ‘the good, bad, and the ugly of tamoxifen’.<sup>5</sup> The result, decades later, was that millions of women lived longer, with improved health, and billions of dollars were accrued annually for both tamoxifen and raloxifene. A new scientific concept was confirmed—it was now possible to treat multiple disease in a patient using one medicine.

### FUTURE

There are now five US FDA-approved SERMs in clinical use.<sup>6</sup> A bold step needs to be taken in an enriched environment to expand the model and create selective nuclear receptor modulators for all members of the nuclear receptor super family. Success will allow diseases to be treated, never before considered to be possible. The correct mix of professionals in the right environment, dedicated to resolving biology through models and mechanisms, could replicate SERM discovery at the Wisconsin Clinical Cancer Center in the 1980s. However, this is a cautionary tale. Education in the pharmacological/cancer research sciences has moved from biological models towards big data. Scientists with training in translational research to address disease treatment are becoming scarce. Without an investment in innovators in drug discovery, then the plan for the National Cancer Act will fail. It is people who affect change through discovery. Invest in the young.

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V. C. Jordan, OBE, PhD, DSc, FMedSci, FAACR  
e-mail: VCJordan@mdanderson.org

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