Donald McDonnell, Ph.D.
2020 Susan G. Komen®
Brinker Award for Scientific Distinction in Basic Science

Donald McDonnell, Ph.D., is being honored for his significant contributions to breast cancer research, which have been instrumental in advancing our understanding of estrogen receptor (ER) signaling in normal physiology and breast cancer progression. His translational research has resulted in critical insights into the structure, function and regulation of nuclear hormone receptors and is helping to lay the foundation for the development and clinical use of novel endocrine therapies to treat ER+ breast cancer and prevent recurrence.

With a career spanning over 30 years in both industry and academia, Dr. McDonnell's research has focused on defining the mechanisms of action of the estrogen receptor and other nuclear hormone receptors in breast cancer and exploiting this fundamental knowledge to develop new breast cancer therapies. As a graduate student in the 1980s, he cloned the vitamin D receptor and identified it as a member of the nuclear hormone receptor family of proteins that function as nuclear transcription factors to control the expression of specific genes that regulate cell growth. Dr. McDonnell went on to probe the relationship between ER structure(s) and the receptor's transcriptional activity and developed model systems to further dissect the signaling pathways that regulate nuclear hormone receptor action. He demonstrated how the binding of estrogen or other agents to the estrogen receptor differentially alter the receptor's structure, and exploited this information to develop drugs whose relative agonist/antagonist activity can be tuned in a cell selective manner. His laboratory demonstrated that resistance to tamoxifen can be ascribed to changes in cancer cells that allow them to recognize an "inactive receptor" as an "active receptor". This work led to the discovery of several new subclasses of drugs, known as selective estrogen receptor downregulators (SERDs), that bind to and induce a conformational change in ER that targets it for proteasomal degradation. Currently there are 12 SERDs in clinical trials for endocrine therapy-resistant, ER+ metastatic breast cancer.

More recently, Dr. McDonnell and his team have focused on identifying new molecular targets, such as AGR2 and LYPD3, that emerge as tumors become resistant to tamoxifen or aromatase inhibitors and exploiting these differences between resistant and non-resistant cells to develop new approaches to treat endocrine therapy-resistant breast cancers. They have also defined the role of the nuclear receptor Estrogen Receptor Related Receptor alpha (ERRα) in TNBC and are now developing small molecule ERRα antagonists for use in the treatment of TNBC and other cancers. His group's more recent work also includes important contributions to our understanding of the biological links between obesity, elevated cholesterol, and breast cancer. They demonstrated that elevated cholesterol, specifically its metabolite 27-hydroxycholesterol, acts as an estrogen and promotes the growth and progression of ER+ breast cancer. Recently, he has assembled a large, multi-investigator effort, to explore the impact of endocrine therapies on tumor immunity in multiple cancer types and these efforts have led to the development of three new clinical trials that are expected to open by years end.

Dr. McDonnell earned his PhD from the Baylor College of Medicine, Houston, TX, under the mentorship of Dr. Bert O'Malley. He completed postdoctoral fellowship training at Smith, Kline, and Beckman before taking a faculty position at Baylor. He spent a few years as Director of drug discovery at Ligand Pharmaceuticals, and then joined the faculty at Duke University in 1994. Dr. McDonnell is a Professor in the Department of Pharmacology and Cancer Biology and the Co-Director of the Women's Cancer Program at the Duke Cancer Institute. He is also an influential mentor and educator, training over 40 post-doctoral fellows and over 35 graduate students.

Dr. McDonnell's pioneering work has shed light into the biology and pharmacology of the estrogen receptor and led to the development of new drugs for the treatment of hormone dependent breast cancer. His leadership in the field, translational approach to studying nuclear hormone receptors and ingenuity in advancing laboratory successes into new cancer drugs will have a lasting impact on breast cancer research and breast cancer care for years to come.