Carl G. Hartman Award. The 2007 recipient of the Carl G. Hartman Award is Dr. Bert W. O'Malley. Dr. O'Malley is a highly original, creative scientist, never afraid to take risks. He has had a major impact on reproductive endocrinology and has been an outstanding mentor of young scientists. Although in many ways a larger than life character, Dr. O'Malley always has been generous and considerate in his dealing with colleagues.

It had been understood since the 1950s that estrogen and progesterone were primary epigenetic factors associated with the development of human female tissue, but their intracellular molecular mechanisms of action were unknown. Following the identification of the estrogen receptor by Jensen, Bert O'Malley's discoveries revealed the mechanism of steroid action to be at the level of nuclear DNA transcription. Dr. O'Malley went on to demonstrate the critical importance of a previously undiscovered superfamily of mediators for their actions—namely, the nuclear receptor coregulators. These discoveries provided a coherent foundation for understanding epigenetic promotion of reproductive tissue growth and development by steroid hormones, and provided the foundation for all future regulatory studies of the impact of estrogen and progesterone on implantation of a fertilized egg, pregnancy maintenance, and prenatal embryonic development, and for the hormone mediated embryonic and pubertal development of breast, uterine, ovarian, prostate, and brain tissue.

Devising the best early animal model for studying the molecular endocrinology of steroid sex hormone control of reproductive tissue development, the chick oviduct, Dr. O'Malley was first to show (1972) that estrogen and progesterone act primarily by inducing synthesis of the cellular mRNAs for specific target proteins (ovalbumin and avidin). He correctly calculated and predicted that the primary response to a steroid hormone (and its nuclear receptor) was at the level of gene transcription, thus substantiating that the steroid receptors were transcription factors. Dr. O'Malley's pioneering work provided a coherent foundation for the field of epigenetic endocrine-mediated early development of reproductive tissues in all animals and humans. His work on the ovalbumin gene was among the first to recognize that genes have intervening, noncoding sequences, now known as introns.

In 1992, the O'Malley lab used proteolytic enzyme and antibody epitope mapping to demonstrate specific distinct receptor structures for pure agonists, pure antagonists, and mixed antagonists/agonists of estrogen receptors (ER) and progesterone receptors (PR). An initial structural model was postulated in which the C-terminal tail (later defined as helix 12) of the receptor flips over and covers the LBD of the molecule in a ligand-dependent manner; anti-hormones (Tamoxifen and RU486) were shown to prevent this conformational change in PR and ER, respectively. Some years later, this key model was confirmed by X-ray crystallography in other labs. This early work of the O'Malley lab

contributed the first substantiated understanding of the mechanism of action of how agonists and antagonists of female hormones structurally activate or inactivate a receptor's ligand binding domain for eventual transcriptional regulation.

In the first proof-of-principle experiments using human receptors, the O'Malley lab reported that ER and PR can interact with specific repressor proteins in yeast (SSN6); this specific interaction repressed the transcriptional activity of the TAF1 activation domain of steroid receptors. In this pioneering study, Dr. O'Malley and colleagues proposed that "estrogen induces an allosteric change in the receptor to displace a repressor," and that anti-estrogens were not effective in displacing this repressor. Encouraged, they predicted the existence of such repressor proteins in mammals, and then were first to demonstrate biochemically the existence of such repressor protein(s) for the human thyroid hormone receptor (TAF2) in mammalian cells. This work elucidated the mechanism by which the two activation domains of nuclear receptors (TAFs) work, and in that publication they correctly predicted that corepressor exchange occurred with a yet to be discovered coactivator. The O'Malley lab next cloned the first authentic steroid receptor coactivator (SRC-1) and proved its in vivo role by mouse knockout experiments, which revealed an inherited resistance to steroid hormone stimulated development in the absence of the SRC-1 gene. They also were first to delete the SRC-3 (AIB1) coactivator in mice, showing it to have a profound effect in cancer development; SRC-3 later was shown to be necessary for efficient estrogen induction of pubertal growth and breast tumors in mice. Dr. O'Malley also recently discovered a new type of tumor suppressor protein (REGy) that works by degrading growth stimulatory coactivators. The great importance of coactivators to normal reproductive development and pathology is now generally accepted. Over 250 coregulators (coactivators/corepressors) in animals and humans have been reported. In fact, coactivators are master genes for all of human metabolism/growth, and defects in coactivators predispose individuals to inherited disorders of uterine implantation, reproductive organ development, metabolism, sexual differentiation (androgen insensitivity), and brain development.

Reproductive development is a combination of genetic inheritance, early fertilization, pregnancy maintenance, epigenetic regulation of embryo development, and puberty. In the latter four processes, no epigenetic factors play more important roles than the steroid hormones, specifically estrogen and progesterone. It is hard to imagine that, in the early 1960s, we didn't know whether these hormones acted on the cell membrane, on intracellular organs via translational protein synthesis, or at the level of nuclear transcription. By virtue of Dr. O'Malley's pioneering work, we now understand that the primary actions of sex steroid hormones and nuclear receptors occur at the level of gene transcription. He proved the pathway of action from hormone to gene to protein, then went on to discover the "missing link" intermediary factors that implement the transcriptional instructions in the receptors—the coregulators. Coactivators are master genes that have an immense regulatory influence on tissue development and physiology because they activate subfamilies of genes in a manner designed to coordinately regulate major growth and metabolic gene sets. Dysfunction in the coactivators (or corepressors) leads to serious consequences. Such inherited dysfunction has been demonstrated to be causal in diverse instances of fertility regulation, reproductive tissue differentiation,

embryonic lethality and growth retardation, mental retardation, and predispositions to reproductive malignancies. Dr. O'Malley's many and sustained scientific contributions afford him a valid claim to the title of father of the field of molecular reproductive biology.

The O'Malley laboratory has contributed much to the concept of "team science." He has trained more than 250 students and postdoctoral fellows, many of whom now serve as professors, CEOs, or deans. He initiated the NICHD Reproductive Centers Program as the first PI of such a Center at Vanderbilt in the mid-1960s He also heads one of the longest-running NIH Reproductive Training Grants and Programs in the U.S. He established the first Cell Biology Department and Reproductive Center at Baylor College of Medicine (BCM) and spearheaded it into the top-ranking department of its type in the country. He is a Distinguished Professor and Scholar at BCM, where he is valued for his administrative skills, and continues to participate as an award-winning teacher.

Among the awards and honors that Dr. O'Malley has received are the Ernst Oppenheimer Award, Gregory Pincus Memorial Medal, Distinguished Achievement in Modern Medicine Award, Axel Munthe Award in Reproductive Biology, British Endocrine Society Medal, Fred Conrad Koch Medal, Pasarow Award in Cancer Research, Endocrine Transatlantic Medal, George W. Beadle Award, Rodbell Award (NIH/NIEHS), and the Feltrinelli International Prize for Biology, as well as election by his peers to membership in the Royal Academy of Medicine of Ireland, National Academy of Sciences, Institute of Medicine, American Academy of Arts and Sciences, and the Academy of Medicine, Engineering and Sciences of Texas. Dr. O'Malley has also served as president of the Endocrine Society. Dr. O'Malley received honorary degrees from the New York Medical College (D.Sc., in 1979); the Karolinska Institutet in Stockholm, Sweden (M.D., in 1984); the National University of Ireland (D.Sc. in 1985); and the University of Maryland (D.Sc., in 2001).

Dr. O'Malley received his B.S. degree from the University of Pittsburgh in 1959, his M.D. from the University of Pittsburgh School of Medicine in 1963, and completed his Internship and Residency at Duke University Department of Medicine in 1965. He was a Clinical Associate at NCI, NIH, Bethesda, Maryland, from 1965 to 1967; and served as Head, Molecular Biology Section, Endocrine Branch, NCI, NIH, from 1967 to 1969. In 1969, he moved to Vanderbilt University School of Medicine where he was Professor and Occupant of the Lucius Birch Chair and Director of the Reproductive Biology Center. In 1973, Dr. O'Malley moved to his current professional home at Baylor College of Medicine, where he serves as Tomas C. Thompson Professor and Chairman, Department of Molecular and Cellular Biology, and Director of the Baylor Center for Reproductive Biology.