

Executive Summary

The nuclear receptor drug targets are part of a superfamily of intracellular receptors, present in most animal species, that mediate transcriptional responses triggered by metabolic ligands. In humans, 48 nuclear receptors have been identified and include those binding hormonal ligands such as glucocorticoids, mineralocorticoids, sex steroids, and thyroid hormones. Whereas others, labeled orphan receptors, bind with ligands as yet unknown. Nuclear receptors act as transcription factors, transducing the ligand associated signals to regulate gene expression involved in a large spectrum of physiological phenomena.

In humans, nuclear receptors are important regulators of homeostatic and metabolic processes essential for survival. Because of their role in a wide variety of biological processes, including the immune response, vascular and cardiac function, tumor formation, carbohydrate and lipid metabolism, and toxin clearance, they have become recognized as one of the more valuable drug target classes. In fact, they have been the focus of drug discovery efforts since the early years of the 20th century when a series of findings that certain natural steroid and thyroid hormones could be used to treat diseases. A thorough knowledge of their biological function did not come until much later.

Nuclear receptors have so far earned their place among the dominant biological drivers of pharmaceutical development. Virtually all the receptors for which ligands have been identified are successful therapeutic targets, with either natural or synthetic forms of the ligands having been converted to marketed drug products. This holds particularly true for the steroid hormone receptors—estrogen (ER), glucocorticoid (GR), mineralocorticoid (MR), progesterone (PR), and androgen (AR)—as well as for thyroid hormone receptor (TR), retinoic acid receptor (RAR), peroxisome proliferator-activated receptor (PPAR), vitamin D receptor (VDR), and retinoid X receptor (RXR). Collectively, these agents account for approximately 13% of all drugs approved in the United States and an appreciable portion of global pharmaceutical sales.

The cognate ligands of nuclear receptors provide a logical entry point to the design of synthetic modulators. However, attempts to use these ligands—which are generally vitamins and dietary lipids as well as hormones—or their synthetic mimics as drugs have often resulted in side effects. This is because although the receptors are present in multiple tissue types, the specific coactivators they recruit in response to ligand binding may be tissue dependent. Thus, in addition to the usual assortment of agonists (full, partial, and inverse) and antagonists, a major goal in drug development is to design compounds that selectively modulate the functional activity of nuclear receptors based on cellular context. Much of the cutting-edge work in the field revolves around these selective agents, spawning a slew of acronyms including SERMs,

SARMs, SEGRAs, and SPPARMs (targeting ERs, ARs, GRs, and PPARs, respectively). Further progress in this area will come from rational design of superior compounds, which will be dependent on an improved understanding of receptor structure, receptor-protein interactions, and coactivator and corepressor function.

The success of the existing nuclear receptor-based drugs lends credence to the potential value of the less-studied members of the receptor family. Some, like liver X receptor (LXR) and farnesoid X receptor (FXR), are already the basis for clinical development programs, and there is reason for optimism that the orphan receptors, because of their involvement in important physiological processes, will yield dividends. This is the second of the two key areas of future promise in the study of nuclear receptors: the exploitation of orphan receptors by identifying their cognate ligands and using them to create novel therapies. Thus, the growth of the field will depend on improving the characteristics of drugs directed at the established, familiar receptors and designing new classes of agents that tap into the potential of the relatively unexplored members of the family.

The material for this report is organized into five chapters. Chapter 1 provides an introduction to the nuclear receptor family by providing a discussion of the classification and associated terminology of these receptors. Chapter 2 reviews the natural ligand(s) if known as well as the pathway biology and/or pathology associated indications related to each receptor. Chapter 3 is a detailed presentation of drug development activity organized by nuclear receptor type and reviews company drug candidate development pipelines. Chapter 4 reviews the likely directions of drug development over the next five years as indicated by preclinical and clinical trial activity. Chapter 5 looks at the worldwide sales of the top nuclear receptor-targeted drugs, the prominent companies in this area, the indications and pipelines. This analysis identifies changes in these markets while pointing to the innovators in the nuclear receptor space.