Editorial

Nuclear receptor (NR) proteins are ligand-dependent transcription factors that belong to the superfamily of steroid/thyroid/retinoid/vitamin D receptors. NR family members play important roles in cell growth, differentiation, homeostasis, metabolism and development. NRs are modular proteins that contain three distinct functional domains. An N-terminal domain containing a ligand-independent activation function, AF-1, a middle zinc-finger containing DNA binding domain (DBD) and C-terminal ligand binding domain (LBD) that also harbors a ligand-dependent transactivation function, AF-2. The activity of NR proteins is modulated by ligand binding to their LBDs that results in a conformational change leading to either transactivation or transrepression of target gene expression in a cell/tissue and promoter/gene-context dependent manner. NRs are one of the best therapeutic targets since their activities could be modulated by small molecules, leading to subtle changes in gene expression in the desired direction and normalization of the altered physiological/pathological phenotype.

In the past decade, a number of molecular, genetic, structural and pharmacological studies have contributed to increased understanding of the molecular pathways involved in NR action. These studies have identified not only novel mechanisms of NR action but also provided new disease targets for small molecule ligands. These studies in addition have yielded novel molecular assays for the rapid identification of compounds with the desired pharmacological profile and have helped set a stage for the rational design of the next generation of pharmaceuticals. There are 48 members of the NR superfamily in the human genome. Interestingly, all the NRs (except LXR), whose ligands are known, are successful therapeutic targets. Therefore, synthetic and/or natural ligands of steroid hormone receptors (AR, MR, PR and GR), RAR, RXR, VDR, TR and PPAR, are currently marketed drugs (Table **I**).

Table I. Nuclear Receptor Ligand Drugs

Nuclear Receptor	Drug	Indication
ER	Estrogens (e.g. Premarin)	HRT, Osteoporosis
	Evista	Osteoporosis
PR	Progestins	Menstrual cycle disorders, Endometriosis
ER+PR	Estrogens + Progestins (oral)	Contraception
GR	Glucocorticoids (Steroids)	Inflammation
MR	Spironolactone	Congestive heart failure
	Eplerenone	Congestive heart failure, Hypertension
AR	Testosterone	Hypogonadism
	Androgel	Hypogonadism
	Casodex (Bicalutamide)	Prostate cancer
	Flutamide	Prostate cancer
TR	Thyroid hormone (e.g., Synthroid)	Hypothyroidism, Goiter, Thyroid cancer
RAR	Retinoic acid	wrinkle effacement
	Tazarotene	Acne, Psoriasis
	Tazarotene	wrinkle effacement
	Adaplene	Acne
	Acitretin	Psoriasis
	13 cis-retinoic acid	Acne
	9 cis-retinoic acid	KS
RXR	Bexarotene	CTCL
VDR	1α, 25 dihydroxyvitamin D3 (Calcitriol)	Psoriasis, Renal osteodystrophy, Osteoporosis, Rickets
	1α-hydroxyvitamin D3	Osteoporosis
	Zemplar	Renal osteodystrophy
	Calcipotriol (Dovonex)	Psoriasis
	Tacalcitol	Psoriasis
PPARα	Gemfibrozil (Lopid)	Dyslipidemia
	Fenofibrate (Tricor)	Dyslipidemia
PPARγ	Actos	Type II diabetes
	Avandia	Type II diabetes

ER, Estrogen receptor; PR, Progesterone receptor; GR, glucocorticoid receptor; MR, Mineralocorticoid receptor; AR, Androgen receptor; RAR, Retinoic acid receptor; RXR, Retinoid X receptor; VDR, Vitamin D receptor; PPAR, Peroxisome proliferator activated receptor.

Further, the involvement of even orphan NRs whose ligands have not been identified, and LXRs, in important physiological or metabolic processes provides the rest of NRs with a high level of validation as potential therapeutic targets. NR based drugs account for approximately 10-15% of the total worldwide pharmaceutical market. Most of these drugs are best currently available options for the treatment of conditions associated with significant morbidity and mortality. A number of these treatments are currently in vogue even though their use is accompanied by unwanted side effects. For example, although glucocorticoids (GR agonists), one of the most successful classes of pharmaceuticals, are widely used for the treatment of inflammatory diseases (rheumatoid arthritis, systemic lupus erythematosus, ulcerative colitis, Crohn's disease, etc.), their use is associated with osteoporosis, hyperglycemia, hypertension, sleep disturbances and psychosis. Similarly, topical corticosteroids cause skin thinning and tachyphylaxis and thus cannot be applied for generally more than two weeks. Therefore, there is an urgent need for the development of safer oral and topical glucocorticoids without the above-mentioned side effects. PPARγ ligands, Actos and Avandia, are medicines of choice for the treatment of type II diabetes but their use is accompanied by unwanted side effects of weight gain and edema. Further, widespread use and development of VDR ligands for osteoporosis and inflammatory indications is hampered by their undesired side effect of hypercalcemia/hypercalciuria. Increased biology of NR action has resulted in the elucidation of the mechanisms underlying therapeutic actions and side effects. Recently, considerable pharmaceutical research has been directed towards identifying efficacious NR ligands devoid of their classical side effects. While it is not possible to cover all the NRs in a single issue, here a number of leading drug hunters provide a glimpse in the drug discovery efforts on selected members of this superfamily (MR, PR, Retinoid Receptors, FXR, VDR, PPARs and LXRs). In this decade, we hope to see the emergence of novel drugs from some of these efforts.

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