스테로이드 호르몬계 신약개발

이 재 운 (Ligand-Pharmaceuticals)

Discovery of New Steroid Hormonal Drugs

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Most drug discovery has focused in recent years on the development of molecules that either interact with or block receptors, proteins that act as on-off switches for genetic activity, on the surfaces of human cells. Now, we have developed a technology that targets "receptors inside the cell" (intracellular receptors), opening a new and compelling avenue for drug discovery. Our receptor-based small molecule drugs can be catagorized in two ways: 1) receptor agonists, or molecules that activate a receptor; and 2) receptor antagonists, or drugs that inactivate a receptor.

Intracellular Receptors: A superfamily of intracellular receptors are found inside of the cell and have a common mechanism of action. When the naturally occurring molecules, also called ligands, that interact with these receptors enter the cell and bind a specific receptor, this complex interacts directly with DNA sequences near appropriate target genes. This complex can then either "turn on" or "turn off" transcription of the target genes. There have been over 35 distinct intracellular receptors identified to date, the first of which was the glucocorticoid receptor identified in 1985. Examples of intracellular receptors include: the retinoic acid receptors, the sex steroid receptors (estrogen, progesterone, androgen receptors), thyroid hormone receptors and receptors involved in cholesterol biosynthesis. These small molecular ligands modulate a surprisingly large number of biological activities in aminal cells by influencing numerous target genes. Thus, the list of diseases that involve the intracellular receptors is extensive and includes cancer, gynecological disorders, cardiovascular disorders, inflammatory disorders and skin diseases.

Proof of Principle: The activation or inactivation of intracellular receptors has already proven to be therapeutically useful. A number of existing drugs act as intracellular receptor agonists or antagonists. Hoffmann-La Roche's "Accutane" and Johnson & Johnson's "Retin-A", approved as treatments for severe acne, are agonists for the retinoic acid receptors. Imperial Chemical Industries' "Nolvadex" (tamoxifen) is an estrogen antagonist used to

delay the recurrence of breast cancer post-mastectomy. G.D. Searle's "Aldactone", approved for congestive heart failure and hypertension, is an aldosterone or mineralocorticoid antagonists. "Cortisone" and dexamethasone, both anti-inflammatory agents, are glucocorticoid receptor agonists. However, the existing drugs are not perfect and, in fact, many cross-react with different, but related receptors, resulting in unintended and unwanted effects. The reason is that the intracellular receptors have such similar structures and act in a similar manner. Thus, our goal is to develop more specific antagonists and agonists, allowing increased potency and reduced side effects. This is greatly enhanced by recent advances on the understanding of the molecular interactions of these drugs with intracellular receptors.

Technology: Our technology centers around the characterization of this "super family" of intracellular receptors and the use of this knowledge base to more intelligently create receptor agonists and antagonists. This include: (1) the identification of receptor subtypes; (2) the localization of specific subtypes to certain tissues; (3) the correlation of specific subtypes to different physiological activities; and (4) the discovery of orphan receptors, or receptors for which the molecules that naturally interact with them are not known.

Orphan receptors; More than two dozen of the 35 intracellular receptors identified to date are considered orphan receptors. Characterization of these receptors and identification of the naturally occurring molecules that activate them could provide information on completely new physiological pathways or provide new clues on how to control known physiological pathways. Some of these receptors include: Estrogen Receptor-related (ERR1, ERR2); Nerve Growth Factor Inducible receptor (NGF1-B); a subfamily of urinary tract-related receptors (hTR2); erb A-related receptors (EAR1, EAR2) believed to be involved in lipid metabolism; apolipoprotein regulating protein receptor (ARP-1) involved in the synthesis of HDL; hepatic nuclear factor receptor (HNF-4), which may be involved in the regulation of apolipoproteins; and the peroxisome proliferation-activated receptors (PPAR) involved in fatty acid oxidation. In addition to creating a better tamoxifen or a better "Accutane", one can develop brand-new proprietary drugs with powerful therapeutic activities never seen before.

Assays/Screening; A critical part of our technology is the creation of proprietary assays that make use of the knowledge learned about specific receptors. These assays can then be used to screen for new innovative drugs. In screening numerous molecules as drug candidates, we have chosen not to do animal testing, that is too costly and slow and sometimes misrepresentative of results in humans, or biochemical assays, that are fast but inconclusive. Instead, we rely on a proprietary cell-culture-based test, which is fast and uses the actual human receptors that are the drug targets. Using recombinant DNA technology, we replace the normal DNA in the cells used for its test with DNA that is encoded for the protein, also called luciferase, that makes fireflies produce light. The luciferase is engineered under the control of hormone receptor binding. When a test molecule binds with and activate an intracellular receptor and then prompts the DNA, sensitive instruments can then measure the amount of light produced. We have automated this process so that it can screen thousands of compounds per week. Promising candidates then undergo tests in cell culture and animals. These assays can accurately predict the therapeutic profile and side-effects of potential drugs. These assays can quickly detect cross-reactivity with other related receptors, a characteristic that can lead to unwanted side effects.

New Retinoids: Retinoids are synthetic analogs of retinoic acid, a naturally occurring non-peptide hormone. Retinoids have been shown to have a wide-range of biological activities, including an effect on cell growth, differentiation and embryonic development. Based on these activities, the possible therapeutic applications include treatment of psoriasis, severe acne, cancers (such as leukemia and squamous cell carcinomas), the ability to reverse certain precancerous changes in tissue, and as a preventive for certain epithelial malignancies, including skin, head and neck, bladder and prostate cancer. However, existing retinoids can cause side-effects, including birth defects, skin and mucosal irritation, the elevation of plasma lipids, thirst and skeletal effects. A family of six retinoic acid responsive intracellular receptors have been identified so far. These can be divided into two subfamilies, the retinoic acid receptors and the retinoid X receptors. Each subfamily has been shown to have a different distribution in the body. The currently marketed retinoid drugs interact with both receptor subfamilies. We are investigating the development of compounds that are selective for only one subfamily or

selective for specific members of one subfamily, in an attempt to produce more potent retinoids with fewer side effects.

LG1057 and analogs (9-cis-retinoic acid); LG1057 is a natural ligand for the retinoid X receptor subfamily. LG1057 was chosen as the first clinical candidate because it can induce differentiation of certain types of human leukemic cells in vitro. LG1057 has been shown to be more potent in its ability to induce the differentiation of leukemic cells in vitro than "Accutane" and Roche's all-trans retinoic acid. The latter is currently in clinical trials for the treatment of leukemia. LG1057 is currently completing Phase I/II clinical trials for acute promyelocyte leukemia, various solid tumors and Kaposi's sarcoma. Additional indications could include premalignant lesions such as oral leukoplakia and non-small cell lung cancer.

LG1069 and analogs; LG1069 has demonstrated selectivity for only the retinoid X receptor subfamily. In comparison, Roche's all-trans retinoic acid compound is selective for the retinoic acid receptor subfamily. In preclinical studies, LG1069 induced apoptosis or programmed cell death in human tumors in animal models. In cell lines derived from head and neck carcinomas as well as cervical carcinomas, LG1069 inhibited cell growth and modulated cell differentiation. In cervical carcinoma cell lines, LG1069 induced apoptosis. Oral form of LG1069 is completing Phase I/II clinical trials for head & neck tumor and Kaposi's sarcoma.

In conclusion, targeting intracellular receptors for new drug development poses some obvious benefits. They are key regulatory proteins inside cells that interact with hormones. Through our proprietary drug discovery and evaluation process, we can rapidly and accurately predict probable therapeutic and side-effect profiles of potential intracellular receptor-targeted drugs. The compounds promise enhanced therapeutic value with fewer, milder side effects than those of related drugs in clinical use. As small molecules, these drugs are expected to present fewer risks in discovery, manufacturing and development, and therefore fewer huddles for approval, than those faced by drugs which are complex molecules such as proteins, peptides or oligonucleotides.