



## SR16388: Novel Drug to Treat Cancer

Apoptosis Inducing, Antiangiogenic Steroid  
Available for Partnering

U.S. Patent 6,548,491 issued April 15, 2003  
Other U.S. Patent Applications Filed  
Patent pending in Canada, Europe, and Japan

### Executive Summary

- Therapeutic Indication: Cancer (Lung, Colon, Prostate)
- Target: Estrogen Receptor- $\beta$
- Mechanism of Action: Antiestrogen SERM, inhibitor of STAT3 and HIF-1
- Route of Administration: Oral
- In Vitro Efficacy: Inhibited growth of ER $\beta$ <sup>+</sup> A549 NSCLC cells in a dose-response manner (IC<sub>50</sub> = 0.10  $\mu$ M)  
Induced apoptosis in DU-145 androgen-independent prostate cells
- In Vivo Efficacy: NSCLC (A549) xenograft: suppression with 20 mg/kg daily potent suppression in combination (erlotinib or paclitaxel)  
Prostate (PC3) xenograft: suppression with 30 mg/kg daily synergistic suppression in combination with paclitaxel inhibits angiogenesis (microvessel density by CD31 stain)
- Safety: Bioavailability in rats is 41% at 10 mg/kg  
MTD is 250 mg/kg for male and female rats

### Rationale

The ligand-inducible transcription factors estrogen receptors- $\alpha$  (ER $\alpha$ ) and - $\beta$  (ER $\beta$ ) are differentially expressed in estrogen-responsive tissues. ER $\beta$  is highly expressed in lung, colon, and prostate epithelia, and in endothelial cells. The effects of estrogens in these tissues are predominantly mediated by ER $\beta$ . In addition to the genomic (DNA binding) actions of estrogens, estradiol rapidly activates signal transduction from plasma membrane estrogen receptors, including ER $\beta$ . These nongenomic effects are attributed to G-protein-associated estrogen receptors. The ensuing activation of multiple kinase cascades is reported to indirectly transactivate epidermal growth factor receptor (EGFR) or insulin-like growth factor-1 (IGF-1) receptor.

Compounds that bind estrogen receptors and act as agonists or antagonists are called selective estrogen receptor modulators (SERMs). The cellular response to SERMs is determined by differences in transcriptional co-regulator recruitment to the receptors. Each SERM has a unique profile of selective gene activation. The ligand-binding domains of the estrogen receptors differ by only two minor amino acid substitutions. Nevertheless, ligands that selectively bind ER $\alpha$  or ER $\beta$  have been successfully developed. Although ER $\alpha$ -selective SERMs have been



used for more than 20 years to treat patients with breast cancer, no ER $\beta$ -selective SERMs are currently available for clinical use.

To fill this gap, SRI applied drug design and screening criteria to select a novel steroid for efficacy in ER $\beta$  expressing tumors. Our lead candidate, 21-[2-(N,N-dimethylamino)ethyl]oxy-7 $\alpha$ -methyl-19-norpregna-1,3,5(10),17(20)-tetraen-3-ol citrate salt (SR16388), selectively binds ER $\beta$  with high affinity while acting as a low-affinity antagonist of ER $\alpha$ .

SR16388 is an orally active, small molecule SERM. It is unique because it not only binds ER $\beta$ , but also inhibits signal transducer and activator of transcription 3 (STAT3) and Hypoxia-inducible Factor-1 (HIF-1) transcription factor activation and expression, respectively, in metastatic tumor cells. Evidence indicates that the transcription factors ER $\beta$ , STAT3, and HIF-1 together regulate multiple genes critical for lung and prostate cancer cell survival, proliferation, vascularization, and metastasis.

SR16388 has shown outstanding promise for the treatment of non-small cell lung cancer (NSCLC), colon cancer, and androgen-independent prostate cancer (AI-PC) in pharmacological studies. It inhibits tumor growth and microvessel density in mouse xenograft models of ER $\beta$ -expressing AI-PC and NSCLC. It is synergistic in combination with paclitaxel and the EGFR inhibitor erlotinib (Tarceva™) in xenograft models. In addition, proliferation, tube formation, and migration assays showed that SR16388's antiangiogenic activity includes direct effects on microvascular endothelial cells.

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