



## SR13668: Novel Drug to Treat Cancer

Orally Active Inhibitor of Akt Pathway  
Available for Partnering

U.S. Patent 6,800,655, October 5, 2004  
Patent pending in Canada, Europe, and Japan

### Executive Summary

- Therapeutic Indication: Cancer (Breast, Prostate, Ovarian)
- Target: Akt Inhibition
- Mechanism of Action: Antiangiogenic, proapoptotic
- Route of Administration: Oral
- In Vitro Efficacy: G1 cell cycle arrest  
Inhibition of Akt phosphorylation
- In Vivo Efficacy: Xenograft tumor suppression with 10–50 mg/kg daily dose  
Suppression of growth of established tumors  
Combination effect with taxol in ovarian cancer xenografts  
Decreased tumor vasculature
- Safety: No in vivo toxicity in single dose rats (1000 mg/kg) or in chronic dose nude mouse (100 mg/kg daily, 32 days)  
No adverse effects on fasting glucose level  
No genotoxicity (Ames assay, CHO chromosomal aberration assay, mouse bone marrow micronucleus assay)

### Rationale

SRI applied lead-based rational drug design to develop a novel small-molecule inhibitor of the Akt pathway. This compound, designated SR13668, is based on a naturally occurring anticancer agent indole-3-carbinol (I3C) found in cruciferous vegetables. SR13668 differs from currently available cancer therapeutics and nonspecific cytotoxic agents because it targets the cell-survival-promoting oncoprotein Akt in a unique way.

### Computer-Aided Rational Drug Design

I3C is a dietary component found exclusively in cruciferous vegetables, such as broccoli, cauliflower, and cabbage. This naturally occurring anticancer agent is effective against a variety of cancers, including breast, lung, prostate, cervical, colon, ovarian, and liver. I3C apparently inhibits phosphorylation and activation of Akt and decreases NF- $\kappa$ B DNA binding in the tumor-derived breast cancer cell line MDA-MB-468, but not in the immortalized nontumorigenic breast line HBL100. I3C abrogates epidermal growth factor (EGF)-induced activation of Akt in aggressive PC-3 prostate cancer cells and decreases expression of the known downstream modulators of the Akt cell survival pathway.



Yet I3C also has drawbacks as a potential anticancer agent. I3C is a prodrug and is highly unstable in acidic media. When I3C is exposed to an acidic medium such as stomach acid, at least 20 acid condensation products (oligomers) are formed. The oligomers that are formed, and the quantities of each oligomer, depend on pH, as well as on what else is present in the stomach at the time (e.g., Vitamin C). Because this reaction is so highly variable, the ratios of metabolites formed vary among individuals, and the anticancer effects vary as well.

Of the more than 20 oligomers formed, four are known to have anticancer activity. SRI used these four active I3C oligomers as lead compounds for the development of a novel indole analog that would maintain I3C's unique and safe biological profile while optimizing its anticancer activity. Our lead compound, SR13668, shows promising anticancer activity in both in vitro and in vivo models of breast, prostate, and ovarian cancer.

## **Contact Information**

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