STEROID SULPHATASE INHIBITION: FROM CONCEPT TO CLINICAL TRIAL

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Breast carcinoma is the most common form of female cancer. Many tumours which are hormone-dependent are treated with anti-oestrogens or aromatase inhibitors. There is strong evidence to suggest that an inhibition of steroid sulphatase (STS), which converts oestrone (E1) sulphate to E1 and also dehydroepiandrostenedione (DHEA) sulphate to DHEA, will further attenuate oestrogenic stimulation in HDBC. E1-3-*O*-sulphamate (EMATE) was the first potent, orally active, irreversible STS inhibitor developed by us a decade ago. However, the unexpected high oestrogenicity of EMATE in rodents prompted us to develop non-oestrogenic agents. A series of bicyclic coumarin sulphamates was produced whose SARs led to the discovery of a series of tricyclic coumarin sulphamates of which STX64 (667COUMATE) was highly promising [1]. In a placental microsomes preparation, STX64 was found to be about 3-fold more potent than EMATE as an active site-directed inhibitor [1]. *In vivo*, STX64 inhibited rat liver STS activity by 93% (single dose, 10mg/kg, p.o.), inhibited E1S-stimulated uterine growth in ovariectomised (ovx) rats and caused regression of E1S-stimulated tumour growth in a NMU-induced mammary tumour model in a dose-dependent manner [2]. More importantly, in contrast to EMATE, STX64 is non-oestrogenic, as shown by its failure to stimulate uterine growth in ovx rats [2]. Toxicological studies in rats performed on STX64 showed no significant or irreversible toxicity. STX64 has an oral bioavailability of 95% in rats [3] which is attributed to its protection from metabolic degradation via sequestration into red blood cells as a result of binding to carbonic anhydrase II [3]. The crystal structure of hCAII bound with STX64 has recently been elucidated [4]. With these favourable toxico-pharmacological and pharmacokinetic parameters, STX64 became the first STS inhibitor to enter clinical trial for treating postmenopausal women with HDBC. Treatment consisted of a test dose of the drug followed by 3 two weekly cycles. Each cycle consisted of daily dosing for 5 days followed by 9 days off treatment. Patients were then followed up for 1 month. To date, 8 patients have been treated at the 5mg dose and 3 at the 20mg dose. For all subjects >90% of STS activity in PBLs was achieved 24h after the single dose was given or on Day 5 of cycle 1. In 3 tumor samples inhibition of STS activity ranged from 78-100%. Reductions in serum androstenediol concentrations of 44-90% were detected in 3/4 subjects studied. So far 4 subjects have shown clinical evidence of stable disease. No serious drug-related adverse effects have been detected to date. These preliminary Phase I trial results demonstrate that STX64 inhibits STS potently in humans. Thus, laboratory- and clinical results are encouraging, validating the concept that inhibiting STS constitutes a novel form of anti-endocrine therapy for the treatment of HDBC.

This work is supported by Sterix Ltd as a member of the Ipsen Group and clinical studies are coordinated by CRUK.

[1] Woo et.al. (2000) Chem. Biol., 7: 773; [2] Purohit et.al. (2000) Cancer Res., 60: 3394. [3] Ireson et. al. (2004) Br. J. Cancer 91: 1399. [4] Lloyd et. al. (2005) Biochem. J., 385: 715.