Development of Novel Anti-Angiogenic SRPK1 Inhibitors

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Tumour angiogenesis occurs when the balance between pro-angiogenic and anti-angiogenic VEGF-A isoforms is switched by differential splicing of VEGF-A to the proangiogenic form. Current anti-VEGF therapies non-specifically target both pro-angiogenic and anti-angiogenic VEGF signalling. VEGF-A splicing is regulated by serine-rich protein kinase-1 (SRPK1), and inhibition of SRPK1 changes splicing towards the anti-angiogenic $VEGF_{165b}$ form, leading to potent inhibition of new blood vessel growth. SRPK1 is overexpressed in advanced prostate cancer and is required for prostate and melanoma cancer growth and tumour angiogenesis in vivo. Here we show generation of novel small molecule inhibitors (SPHINXs) that target SRPK1. Topical administration of SPHINX compounds inhibits choroidal neovascularization and SRPK1 inhibition inhibits tumour growth in cancer xenografts. To develop inhibitors with improved pharmacokinetic and biodistribution properties, we generated hydrochloric acid salt conjugates of SPHINXs that retain potent activity against SRPK1 with improved solubility profiles. We analysed SRPK1 inhibition in kidney, prostate and breast cancer cells, hERG inhibition in vitro, and pharmacokinetic and distribution profiles following SPHINX administration to ensure safety characteristics of the compounds and develop formulations that can be applied systemically. We analysed expression of SRPK1 in large tumour tissue microarrays from patients with breast cancer and prostate cancer combined with follow up clinicopathological data. We tested compound specificity against a whole kinome screen and by SILAC-based proteomic analysis of phosphorylation changes after SPHINX treatment. Potent compounds that selectively inhibit pro-angiogenic $VEGF\text{-}A_{165a}$ without inhibiting anti-angiogenic, cytoprotective $VEGF\text{-}A_{165b}$ promise safer and more specific and efficacious therapeutics for angiogenic related disorders.

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