DEVELOPMENT OF NOVEL ANTI-ANGIOGENIC SRPK1 INHIBITORS

J. Batson[1], C. L. Allen[1], , J. Zhang,[2] S.F Wearmouth,[2] J.C. Morris[2], M.V.Gammons[3], D.O. Bates[1]
[1]Cancer Biology, Division of Cancer and Stem Cells, University of Nottingham, Queen's Medical Centre, Nottingham NG2 7UH, [2]School of Chemistry, University of New South Wales, Sydney.[3]Microvascular Research Laboratories, University of Bristol.
Jennifer.Batson@Nottingham.ac.uk

Pathological angiogenesis occurs when the balance between pro-angiogenic VEGF-A_{165}a and anti-angiogenic VEGF-A_{165}b is switched by differential splicing of VEGF mRNA to the proangiogenic form. VEGF-A_{165}b has been shown to inhibit pain, tumour growth and renal disease, identifying these as therapeutic areas for agents that switch splicing. Novel small molecule inhibitors (SPHINXs) have been identified that target SRPK1, the kinase promoting VEGF-A_{165}a splicing. Topical administration of SPHINX inhibits choroidal neovascularization[1] and local SRPK1 inhibition inhibits tumour growth in cancer xenografts. To develop these compounds for oncology, chronic pain or kidney disease, their pharmacokinetic and biodistribution properties need to be improved. We developed novel hydrochloric acid salt conjugates of SPHINXs that retain potent activity against SRPK1 with sub-100 nM IC50s and improved solubility profiles. We analysed SRPK1 inhibition in prostate cancer cells, hERG inhibition in vitro, pharmacokinetic and distribution profiles following SPHINX administration to ensure safety characteristics of the compounds and develop formulations that can be applied systemically. Potent compounds that selectively inhibit pro-angiogenic VEGF-A and can be administered systemically offer more specific, efficacious and safer therapeutics.

[1]Gammons (2013). IOVS 54:6052-662