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Development of selective mechanism-based inhibitors for human semicarbazide-sensitive amine oxidase (SSAO)

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Human membrane primary amine oxidase (hAOC3, also known as vascular adhesion protein-1, VAP-1) is a member of the copper dependent amine oxidase family. The enzymatic function of this protein is commonly known as Semicarbazide Sensitive Amine Oxidase (SSAO), and has been shown to play a crucial role in leukocyte rolling, adhesion and migration in various disease models. The binding site of this enzyme contains a topaquinone co-factor, derived from a modified tyrosine residue, that catalyses the oxidative deamination of primary amines to aldehydes with co-committal release ammonia and hydrogen peroxide. As part of our ongoing research into inflammatory lung diseases, we decided to target this enzyme using a mechanism-based inhibitor approach. Here we present the various challenges we have had to address during development including design, selectivity over related amine oxidases, *in vitro* cell health considerations and most significantly, optimisation of our molecules to be true mechanism-based inhibitors with no substrate turnover. The influence of *in vitro* SAR profiling and computer aided drug design will be discussed.

Biography

Jonathan S Foot completed his PhD at the University of York in 2005 and has held Postdoctoral positions at the University of Toronto (2009) and the Australian National University (2006). He is a Senior Research Scientist at Pharmaxis Ltd., in Sydney Australia where he works in the Drug Discovery department with roles in medicinal chemistry, computer-aided drug design and project managment.

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