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# UNLOCKING NICOTINIC SELECTIVITY: DIRECT C–H FUNCTIONALISATION OF (–) CYTISINE

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**This talk will cover the synthesis of new ligands that are specific for key neuronal nicotinic acetylcholine receptor (nAChR) subtypes. This, in turn, links to an ability to target, for example, the high affinity nicotine receptor in brain (the 4, 2 nAChR) and that has implications for treating tobacco addiction and smoking cessation. It is important to understand the society and health challenge that tobacco addiction presents, so there will be some coverage of this and current therapeutic approaches and that touches on the business drivers that are also (inevitably) involved. The talk will also discuss the synthetic chemistry explored and developed around cytisine, a naturally occurring nicotinic partial agonist that was the inspiration for a current smoking cessation agent (varencline) but that is also used widely in its own right. Total synthesis had been used to access a number of interesting ligands but this has been superseded by an approach based on direct and highly effective C-H activation of cytisine itself. The outcomes of that chemistry will be described as well as the associated pharmacology that characterised the selectivity profiles observed. Computational studies have also played a central role both to elucidate the mode of action of a ligand's interaction with the receptor protein associated with the immediate region of the binding site but also at a full receptor scale, to understand how ligand binding and subsequent protein perturbation leads to activation (opening) of ion channel. This, in turn, has led to development of a general mechanism for signal transduction within the therapeutically-important Cys-loop family of receptors.**

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