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Cytochrome P450 enzymes as target for drug development

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The cytochrome P450 (CYP) enzymes belong to a superfamily of mixed function oxidases that are unique in their ability to oxidize xenobiotics, but under hypoxic conditions also can reduce certain chemical functionalities. There is now growing evidence that CYP1A1 and 2W1 are overexpressed in many human tumor types. The presence of certain CYPs may reflect a resistance mechanism by diminishing the pharmacological activity of anticancer drugs whilst specific CYPs can also modulate cell proliferation by the formation or conversion of endogenous signaling molecules. The potential for CYP-selective metabolism of xenobiotics coupled to their broad substrate specificity provides a unique opportunity to design drugs whose activity is dependent on a critical functional group that can be unmasked or restored by CYP metabolism selectively in tumor tissue. We have identified duocarmycin natural products which lend themselves to being great candidates for use in prodrug strategies. The electronic distribution and lipophilicity of the embedded chloromethylindoline trigger fragment is a key determinant in regioselective oxidation by specific CYP isoforms. We have synthesized and biologically evaluated several libraries of duocarmycins and have shown them to be bioactivated by CYP1A1 and 2W1 in cell-free and cell-based assays. At the meeting we will update on novel data from our drug discovery programme, which include single agent and combination treatment with standard of care drugs using colorectal cancer xenograft models.

Biography

Klaus Pors is an Associate Professor of Chemical Biology at The Institute of Cancer Therapeutics, University of Bradford, UK. His research group is involved with discovery of novel biological and chemical tools to explore the importance of enzymes in different disease states. Particular focus is on exploiting abnormal cytochrome P450 (CYP), aldehyde dehydrogenase (ALDH) or aldo-keto reductase (AKR) expression in the tumour microenvironment as target for biomarker and drug discovery; he has published 35 papers on these topics. He is a RSC Chemical Biology and Bioorganic Group committee member and the European Editor of Journal of Cancer Metastasis and Treatment.

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