

P013 Impact of selective inhibitors of the p110 δ isoform of PI-3kinase in the proliferation, survival and differentiation of acute leukaemia

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Phosphoinositide 3-kinases (PI3Ks) are a group of intracellular enzymes linked to the pathogenesis of Acute Leukaemia (AL). PI3Ks drive essential cellular processes including cell proliferation, survival and migration. Mammals have 8 distinct isoforms of PI3K. Broad-spectrum inhibitors non-specifically target all PI3K isoforms, and given the risk that non-selective inhibitors will be deleterious to the organism, new therapies will have to be targeted at specific PI3K isoforms. Class IA PI3Ks signal downstream of tyrosine kinases and Ras (often deregulated in AL) and are comprised of p110 α , p110 β and p110 δ isoforms. The successful treatment of AL with cytotoxic agents is frequently limited by resistance. We previously reported that pharmacological inactivation of p110 δ in primary Acute Myeloid Leukaemia (AML) samples strongly potentiates currently available therapeutic agents without adverse effects on the biology of normal haematopoietic progenitors (*Billottet et al., Oncogene advance online publication 15 May 2006*). There is now increasing evidence that therapies aimed at overcoming the block in AL differentiation are needed. We therefore investigated the impact of pharmacological inhibition on the differentiation of acute leukaemic cells using various biochemical and bioinformatic approaches. Our results indicate that p110 δ inhibitors do not affect the differentiation of myeloid cells but rather **target the proliferation and survival of AML in conjunction with current clinical therapies.**