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Identifying novel epigenetically induced synthetic lethality therapeutic combinations for high risk MDS/AML

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High risk myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) are diseases of the aging; with many patients are unable to tolerate intensive therapies and an unmet need for novel therapeutic approaches. Epigenetic silencing of genes in MDS and AML can occur via the recruitment of histone deacetylases (HDACs) or by aberrant DNA hyper-methylation; these changes can be reversed making them prime targets for therapy. The development of agents that inhibit HDACs (HDACi) or the DNA methyl transferase activity (DNMTi) have proven successful in certain malignancies and have shown promise of increasing treatment tolerability. However, it is an over-simplification to assume that epigenetic based therapies simply allow the expression of tumor suppressor genes; so a greater understanding of their mode of action is required to develop more rationale combinations. Integrative analyses involving transcriptomics with methylation profiling or ChIP-seq of chromatin associated with histone acetylation modification marks has been undertaken to identify epigenetic primed induced synthetic lethal therapeutic combinations. The integrated analysis has identified novel primed gene and network targets specifically activated as a response to the epigenetic therapies. These studies not only provide further insight into the molecular mode of action of the epigenetic therapies but have identified agents that might work synergistically in combination thus providing potential novel therapies for MDS/AML patients.

Biography

Ken Mills is the Chair of Experimental Hematology in the Centre for Cancer Research and Cell Biology (CCRCB) in Queen's University Belfast. He coordinates the activities of the Blood Cancer Research Group with a focus on the molecular aspects of MDS and AML to identify novel therapies. He has published over 135 papers, several book chapters and he is on several Editorial Board and a regular Reviewer for high impact journals and national and international funding bodies.

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