DOCTOR OF PHILOSOPHY

Pre-clinical evaluation of inhibitors of apoptosis protein (IAP) antagonists in colorectal cancer

Stott, Katie

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Awarding institution:
Queen's University Belfast

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Thesis Deposit Form

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Degree:	Doctor of Philosophy
Full Name:	Katie Jayne Stott

Thesis title:

Pre-Clinical Evaluation of Inhibitors of Apoptosis Protein (IAP) Antagonists in Colorectal Cancer

Summary: (max. 300 words)

CRC is frequently associated with a pro-inflammatory tumour microenvironment in which TNFa signalling plays an important role. Inhibitor of apoptosis proteins (IAPs) are capable of converting TNFa signalling from a pro-apoptotic to a pro-survival and pro-inflammatory signal. Overexpression of IAPs is associated with chemoresistance and poor prognosis in CRC. Consequently, IAPs are an attractive target for therapeutic intervention and IAP antagonists, such as ASTX660, have recently been developed.

In vitro results indicated that the CRC cell line models investigated harboured intrinsic resistance to IAP antagonist-mediated cell death and revealed FLIP, a pseudo-caspase, is a major mediator of this resistance mechanism. Moreover, Entinostat, a clinically relevant Class I HDAC inhibitor, was found to downregulate FLIP expression and sensitise the CRC cell line models to ASTX660, in a caspase-8 dependent manner. Furthermore, this FLIP-mediated resistance, to ASTX660 and TNFa, was also overcome through the use of a novel small molecule FLIP inhibitor that targets the FLIP: FADD protein-protein interaction.

Clinical approval of IAP antagonists is not only hampered by intrinsic resistance, but also by a lack of clinical biomarkers. Herein, the potential of using the presence of a Fusobacterium nucleatum infection as a predictive biomarker for clinical positioning of these agents was investigated. F. nucleatum infection was shown to promote an upregulation of CIAP2 and TNFa and there was evidence to suggest that FLIP expression was also downregulated by the infection. Importantly, co-culture of F. nucleatum infected monocytic cells significantly enhanced the efficacy of IAP antagonism in a manner dependent on bacterial induction of TNFa secretion in the immune cells. Collectively, this work suggests that the presence of F. nucleatum bacteria promotes a tumour microenvironment rich in TNFa and may 'prime' tumours to become sensitive to IAP antagonists with elevated CIAP2 and lower FLIP expression.

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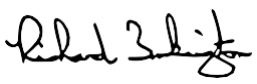
Signature of Examiner: 

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