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## DOCTOR OF PHILOSOPHY

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

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<b>Degree:</b>	Doctor of Philosophy
<b>Full Name:</b>	Katie Jayne Stott
<b>Thesis title:</b>	Pre-Clinical Evaluation of Inhibitors of Apoptosis Protein (IAP) Antagonists in Colorectal Cancer
<b>Summary:</b> (max. 300 words)	<p>CRC is frequently associated with a pro-inflammatory tumour microenvironment in which TNF<math>\alpha</math> signalling plays an important role. Inhibitor of apoptosis proteins (IAPs) are capable of converting TNF<math>\alpha</math> 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.</p> <p>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 TNF<math>\alpha</math>, was also overcome through the use of a novel small molecule FLIP inhibitor that targets the FLIP: FADD protein-protein interaction.</p> <p>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 <i>Fusobacterium nucleatum</i> infection as a predictive biomarker for clinical positioning of these agents was investigated. <i>F. nucleatum</i> infection was shown to promote an upregulation of CIAP2 and TNF<math>\alpha</math> and there was evidence to suggest that FLIP expression was also downregulated by the infection. Importantly, co-culture of <i>F. nucleatum</i> infected monocytic cells significantly enhanced the efficacy of IAP antagonism in a manner dependent on bacterial induction of TNF<math>\alpha</math> secretion in the immune cells. Collectively, this work suggests that the presence of <i>F. nucleatum</i> bacteria promotes a tumour microenvironment rich in TNF<math>\alpha</math> and may 'prime' tumours to become sensitive to IAP antagonists with elevated CIAP2 and lower FLIP expression.</p>

*To be completed by Examiner*

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I hereby certify that this is the final accepted copy of the submitted work and that all required amendments have been completed and submitted within the required deadline.

**Name of Examiner:** Richard Turkington

**Signature of Examiner:** 

**Date:** 9/4/2021

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