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**Pilot toxicology study of a novel sirtuin inhibitor as a potential therapeutic candidate in colorectal cancer**

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**ABSTRACT**

Colorectal cancer (CRC) is third most common malignancy in world. 5-fluorouracil (5-FU) is the standard first line treatment for colon cancer. However, many patients acquire resistance to the drug hence the need to find an adjuvant therapeutic agent to improve therapeutic outcome. Sirtuins are class III histone deacetylases (HDACs) which play a key role in cancer. Over-expression of SIRT1 and SIRT2 provides a tumor cell survival advantage and resistance to therapy by inhibiting apoptosis and allowing unchecked cell division. We have synthesised a patent pending novel sirtuin inhibitor (BZD9L1) with demonstrated anti-cancer activities in colorectal cancer. This project aims to expand on the current findings to determine the dose threshold and to evaluate acute toxicity profile of BZD9L1 in BALB/c mice. HCT 116 colorectal cancer cells were treated with BZD9L1 and/or 5-FU to assess the effect of combination treatment on cell viability and survival using CyQuant and clonogenic assay. In vivo acute toxicity study were performed in female BALB/c mice treated with 2000 mg/kg of BZD9L1 and screened for signs of toxicity for two weeks after administration via intraperitoneal injection. Combination treatment with BZD9L1 and 5-FU resulted in synergistic reduction of HCT 116 cell viability and survival compared to single treatment of either one. Mice exhibited no behavioural distress and no observable toxicity symptoms or death. In addition, no pathological changes in major organs was observed in mice treated with BZD9L1 at 2000 mg/kg. The median lethal dose (LD50) of the BZD9L1 was greater than 2000 mg/kg. BZD9L1 demonstrated anti-cancer effect by reducing the cell viability and survival in vitro without causing any apparent acute toxicity effect in vivo. The results suggested that BZD9L1 was non-toxic even at high dose highlighting its potential as a novel anti-cancer agent. On-going work includes sub-chronic toxicity and colorectal tumour xenograft studies in vivo.