We are hereby submitting a manuscript entitled “Decreased transcription-coupled nucleotide excision repair capacity is associated with increased p53- and MLH1-independent apoptosis in response to cisplatin” for consideration in BMC Cancer. This manuscript contains highly novel unpublished results that are not under consideration for publication elsewhere.

One of the most commonly used classes of anti-cancer drugs presently in clinical practice are the platinum-based drugs. Cisplatin and related drugs induce DNA lesions that are substrates for nucleotide excision repair. Some of my previous work, using primary human fibroblasts as a model system, has indicated that defects in a specific pathway of nucleotide excision repair, transcription-coupled nucleotide excision repair (TC-NER), lead to hypersensitivity to this DNA damaging therapeutic.

One of the challenges in cisplatin therapy is the emergence of a resistant population of cells. This is often associated with increased DNA repair, loss of p53 and/or loss of DNA mismatch repair capacity. These latter genetic alterations are very common in cancer and lead to decreased death signaling. The contribution of TC-NER to cisplatin sensitivity in the context of these common tumour-association genetic changes was not known. Therefore, we sought to examine the role of TC-NER in the cisplatin response of prostate and colorectal cancer cell lines with various combinations of p53 and MMR defects, including an isogenic panel of cell lines derived from HCT116 cells.

To summarize, RNA interference was used to decrease the expression of the Cockayne syndrome group B protein (CSB) in several prostate and colon cancer cell lines. This protein was selected because it is required in an early rate limiting step in TC-NER but similar results were obtained by targeting the xeroderma pigmentosum group A protein required at a later step in this repair process. We found that the tumour cells were initially TC-NER proficient and that RNAi against
CSB significantly decreased the capacity of tumour cells to repair transcription-blocking DNA lesions. Most importantly, this RNA interference strategy increased the responsiveness of tumour cells to cisplatin-induced apoptosis, even in the p53 null and MMR-deficient tumour cell lines. Collectively, this compelling data suggests that strategies to target CSB and more generally TC-NER represent a novel therapeutic strategy to overcome resistance to platinum-based drugs.

I trust that you will agree that the present manuscript is topical and represents a significant advance that deserves publication in BMC Cancer. I look forward to a favorable decision in the near future.

Sincerely

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