Author's response to reviews

Title: Spatial morphological and molecular differences within solid tumors contribute to the failure of vascular disruptive agent treatments.

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Dear Editor,

Please find attached the manuscript entitled: “Spatial Morphological and Molecular Differences Within Solid Tumors Contribute to the Failure of Vascular Disruptive Agent Treatments” by Ms Linh Nguyen, Dr Theodora Fifis, Mrs Cathy Malcontenti-Wilson, Dr Lie Sam Chan, Dr Mehrdad Nikfarjam, Dr Vijayaragavan Muralidharan and Professor Christopher Christophi for consideration for publication in BMC Cancer.

Solid tumor metastases are difficult to treat and current treatment options for colorectal liver metastases are limited. Vascular disruptive agents (VDAs), effectively target large solid tumors and reduce their mass by more than 90%. However VDAs are not effective as monotherapies because a thin rim of viable tumor persists in the periphery, invariably giving rise to recurrence. Systemic therapies are based on the assumption that tumor cells are equally susceptible to the drugs regardless of their location within the tumor or their stromal associations.

There are several proffered explanations for therapy failures. One theory claims solid tumors are not completely destroyed due to inability of the drug to penetrate deep into the tumor mass. We did a literature review on this claim and we could not find histological evidence to support it. Even if there is such evidence, it would not account for the results we and others reported using VDAs. In all published reports VDA treatment kills cells in the centre and only cells in the periphery survive. Another theory claims that cancer cells that survive treatment are the cancer stem cells or cancer initiating cells and these are naturally resistant to treatments. A third theory claims certain cancer cells have a
mesenchymal morphology or adopt it by an Epithelial to Mesenchymal Transition (EMT) upon drug treatment enabling them to resist drug therapy and acquire invasive metastatic properties. Recently it has been shown that tumor cells induced to undergo EMT also acquire stem cell characteristics.

In this manuscript we demonstrate the surviving tumor cells in the periphery have a significantly different microenvironment to the central tumor. We present evidence that the tumor periphery is a niche of natural resistance and as such it has important implications not only in VDA treatments but also in other systemic therapy treatments. A better understanding of the tumor microenvironment and the mechanisms that provide protection to drug treatments would identify new targets for combination therapies and better clinical outcomes.

Our findings will be of particular interest to both researchers and clinicians in the cancer field and we believe publishing the results in BMC cancer will reach this audience.

Best regards,

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