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CORRESPONDENCE

Comment in reply to Chen et al. Journal of Neuro-Oncology (2023) 165:535–545 "Focused ultrasound combined with radiotherapy for malignant brain tumor: a preclinical and clinical study"

Gregory J. Czarnota[1]

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Dear Sir/Madam,

We write in regards to Chen et al. [1] in which preclinical and clinical work were undertaken with focussed ultrasound (FUS) in the presence of microbubbles for blood brain barrier opening and radiotherapy (XRT). The authors state that the mechanism for the synergistic effect between FUS and XRT observed remains unclear and efforts should be made to identify a potential mechanism.

We call attention to work now over a decade in progress from initial discovery [2], to mechanistic studies [3], and to recent applications to central nervous system (CNS) malignancies [4] which address exactly that.

It has been demonstrated that exposure of endothelial cells to focussed ultrasound-stimulated intravascular microbubbles, such as that done during blood-brain barrier opening, stimulate the acid-sphingomyelinase (ASMase) pathway [2]. Mechanistic studies further have demonstrated that this can be inhibited chemically or genetically in animal models [3]. When combined with radiation (also known to stimulate that pathway - see references in [2 and 3] - exposure to ultrasound-stimulated microbubbles causes an enhancement of ASMase pathway activity leading to even greater ceramide production. Ceramide, toxic to endothelial cells, leads to endothelial cell apoptosis, vascular collapse, and anoxia in a targeted tumour, leading to a significant enhancement in cell death compared to treatment with either modality alone [4 and 5]. This has recently been demonstrated in the CNS in regards to correlative immuno-histochemical studies in a glioblastoma-multiforme (GBM) model [6]. That work demonstrated through histological analyses of tumors 72 hours after FUS + XRT (4 Gy) showed 93% and 396% increases in apoptosis, and 320% and 336% increases in vessel-associated ceramide, compared to FUS and XRT only [6].

We of course encourage continued exciting research such as that by Chen et al., but also encourage concurrent mechanistic studies looking at established biomarkers (ceramide) which are at the core of an underlying mechanism for the synergy seen between focussed ultrasound-stimulated intravascular microbubbles and radiotherapy. This is important especially as work progresses to first in human clinical trials of what is an unprecedented enhancement of radiation effect through an acoustic-bio-mechanical mechanism.

Author contributions GJC authored this comment.

Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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✉ Gregory J. Czarnota
gregory.czarnota@sunnybrook.ca

[1] University of Toronto, Toronto, Canada

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