Published in final edited form as:

Int J Radiat Oncol Biol Phys. 2018 June 01; 101(2): 495–496. doi:10.1016/j.ijrobp.2018.02.018.

In Reply to Pratz and Kapp

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To the Editor:

We thank Drs. Pratz and Kapp for their interest in the RECA approach (Radiotherapy Enhanced by Cherenkov photo-Activation) and for raising valuable questions (1, 2).

We agree that Cherenkov light production is inefficient in tissue compared with radiolysis (3, 4). However, it has been noted that only free radicals generated within approximately 4 nm of the DNA helix contribute clinical damage, and then when relatively efficient repair mechanisms have failed (5). In contrast, in a typical non-skin tissue, the Cherenkov ultra-violet (UV) photo-activating photon (with wavelength ~315 nm) travels much further (6), and psoralen photo-activated damage is harder to repair (7). Integral Cherenkov light must therefore be considered, together with the multifaceted biological effects of photo-activated psoralen not just to DNA but also to intra-cellular proteins and lipids (respective binding rates 17%, 57% and 26%) (8). In RECA, psoralen photo-activation occurs simultaneously with radiation therapy, raising a driving hypothesis of our research that synergistic multi-component damage amplification will occur.

The possibility of non-Cherenkov amplification of light from solid water (an epoxy-based Plastic Water, CIRS, Virginia, USA [9]) was investigated through imaging studies directly comparing radiation induced light output (potentially both Cherenkov and any scintillation contamination) from solid water with that of tissue (chicken, beef, and pork). Ultraviolet A (UVA) intensity in the range 315–380 nm (the region of interest for psoralen activation) was measured using a back-thinned, deep-cooled, charge-coupled device camera (iKon-M934, Andor, Belfast, UK; with 10%–40% quantum efficiency) with a UVA band-pass filter (60–95% transmission FF01-390, Semrock, Rochester, New York) coupled to a UV-compatible lens. The results showed the cumulative intensity of 315–380 nm light between

the solid water and the tissue samples was similar (within approximately 15% for 15 MV and 30% for 6 MV). The reported effects are therefore considered relevant and representative of those expected in the in vivo condition.

The authors also raise concerns regarding possible complications of RECA due to normal tissue psoralen uptake and carcinogenicity, as reported with PUVA (psoralen UVA therapy) superficial treatment techniques. Psoralen is biologically inert until photo-activated (8). The RECA approach is a method to enhance conformal radiation therapy, whereby the conformity of radiation dose ensures photo-activation is strongly localized within the high-dose region. In addition, Cherenkov UV light intensity in RECA is substantially lower than that in PUVA, which is a sole treatment delivered externally with a high-intensity UV lamp. These concerns are thus not considered to be significant limitations. Regarding the cell medium transparency to Cherenkov light, the suggested DNA-filled medium would have created overly unfavorable experimental conditions.

This article presented our first investigations into the feasibility of RECA and was necessarily focused on in vitro work. The promising results that were observed warrant further investigation in an in vivo setting where these, and other questions, can be effectively addressed.

Acknowledgments

Conflict of interest: This work was funded by the Duke Brainspore P50 CA190991. Additional support was received from Immunolight Llc. X.Z. receives funding support from Duke Department of Radiology Putman Seed Fund 2016-01 and Duke Cancer Institute C3O Pilot 2017. MO, PY, JA, and MD are inventors on a patent for the RECA approach. Patent # WO 2017075057 A1.

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