LETTER

REPLY TO SPAN ET AL.:

Rational design of oxygen microparticles for radiation therapy

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In their letter, Span et al. (1) suggest that our oxygen-loaded polymer hollow microparticles (PHMs) may be used to radiosensitize hypoxic tumors. It has been long appreciated that tumor sensitivity to radiotherapy is oxygen-dependent (2), and that this is mediated at least in part through mitochondrial reactive oxygen species (3). Span et al. (1) highlight that current clinical approaches for the resensitization of tumors have failed to improve the efficacy of radiotherapy, including attempts to augment oxygen delivery in anemic patients. They (1) and others (4) posit that failure of these clinical approaches is related to an inability to effectively raise tumor oxygen tension, a problem that may be addressed by administering PHMs.

We agree that circulating, gas-filled microparticles have the potential to raise tissue oxygen tensions within metabolically hyperactive tumors. However, it should be noted that the PHMs we describe (5) have been specifically designed to address acute hypoxemic emergencies, and that alternative applications, such as radiosensitization, are likely to impose unique design requirements. We propose for consideration the following design modifications to augment tumor oxygen tension in the setting of radiotherapy.

First, it will be important that PHMs retain the majority of their oxygen payload until they reach the tumor microenvironment. The PHMs described in our work (5) release their oxygen payload within minutes of contact with hypoxic plasma because of the extensive nanocapillary network embedded within the thin polymer shell. It is possible that current iterations would release their payload too quickly, an aspect that could be easily addressed by engineering a nonporous, ultrathin, oxygen-permeable shell. Because the mass of oxygen release from PHMs is dictated by the diffusion gradient (i.e., more oxygen is off-loaded to more hypoxic tissues), it is likely that more oxygen gas would be offloaded to a hypoxic tumor site than healthy, respiring tissues. A shell whose oxygen permeability is pH-triggered may augment regional oxygen delivery further, as tumor regions are likely to be acidotic. Second, it may be possible to design a shell that is disrupted by ultrasound to enable sonographically triggered oxygen release to solid tumors, minimizing the total dose of microparticles needed to achieve a given increase in tumor oxygen tension. Third, it is important that PHMs have sufficient resonance time in the circulation to reach the capillary network of the solid tumor, an important limitation of lipid-based microbubbles used for this purpose (6). Relatedly, it is important for any injectable microparticle to not release gas in the absence of an oxygen sink (e.g., when injected under normal or hyperoxic conditions), which could cause a gas embolism. Finally, the inclusion of cytotoxic gases into the gas core or chemotherapeutic agents into the particle shell material may enhance the efficacy of this technique further.

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3 Diehn M, et al. (2009) Association of reactive oxygen species levels and radioresistance in cancer stem cells. *Nature* 458(7239): 780–783.
4 Lagerlöf JH, Kindblom J, Bernhardt P (2014) Oxygen distribution in tumors: A qualitative analysis and modeling study providing a novel Monte Carlo approach. *Med Phys* 41(9):094101.
5 Seekell RP, et al. (2016) Oxygen delivery using engineered microparticles. *Proc Natl Acad Sci USA* 113(44):12380–12385.
6 Kwan JJ, Kaya M, Borden MA, Dayton PA (2012) Theranostic oxygen delivery using ultrasound and microbubbles. *Theranostics* 2(12): 1174–1184.

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