Letter to the Editor

Tumor Growth Control with IDO-Silencing *Salmonella* —Reply

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The letter by Hoffman states that *Salmonella typhimurium* (S. *typhimurium*) A1-R alone could be equally, or more, efficient in colonizing tumors compared with the VNP20009 strain transformed with short hairpin RNA against indoleamine 2,3-dioxygenase (IDO) described in our recent report in Cancer Research (1). Published evidence highlights the colonizing properties of the A1-R strain that was the result of the unique method for its isolation from mouse tumors (2). As Hoffman states, the A1-R strain has "high tumor colonization efficacy and antitumor efficacy" in a number of xenograft models using immunodeficient mice. These concepts are equally applicable to the VNP20009 strain, as it was also highly regarded for its ability to colonize and eradicate tumors in murine models when administered as a single agent (3). Paradoxically, VNP20009 failed to adequately colonize or control human tumors to the same degree in clinical trials and has since called into question the clinical translation of observations made in syngeneic and xenograft murine models using any *S. typhimurium* strain (4).

Hoffman states that a "direct comparison of tumor-targeting of the IDO-transformed *S. typhimurium* VNP20009 strain … and *S. typhimurium* A1-R would be enlightening," yet will it provide any further insight to mechanisms to attain clinical efficacy? Earlier studies using VNP20009 in patients with metastatic melanoma, even those with evidence of VNP20009 intratumoral colonization, failed to show any signs of regression (4). Thus, while *S. typhimurium* tumor colonization in murine models correlates with regression, colonization in patient tumors does not. In that sense, the ability of A1-R to efficiently colonize murine tumors may not predict its clinical outcome. In a more recent pilot trial using VNP20009 to express the E. coli cytotoxic deaminase gene, investigators observed significant conversion of the antifungal agent 5-flucytosine to the extremely cytotoxic antitumor 5-fluorouracil specifically within patient tumor tissue (5). It is becoming more apparent that *S. typhimurium* shows more promise as a tumor-specific delivery vehicle than it does as a treatment by itself (6–8). In our study, enhanced colonization of VNP20009 was seen as an additional benefit to silencing IDO. However, the unique ability to attract and activate polymorphonuclear cells strictly within tumor tissue using the combination of VNP20009 and IDO silencing is a novel improvement to *S. typhimurium* and applicable to many human tumors that express IDO.

If a comparison should be made, we feel the more relevant one would be to compare colonization of AR-1 and shIDO-ST in tumors of patients with cancer, and determine whether the property of colonization *per se* without IDO modulation by shIDO expression correlates with tumor regression. Would AR-1 overcome the barriers that prevented VNP20009 from succeeding as an antitumor therapy? This is a difficult question to answer because it is perplexing why VNP20009 was clinically unsuccessful. It will likely require more than additional observations in murine models showing greater tumor colonization and control by *S. typhimurium*. More in-depth mechanistic studies of how these *S. typhimurium* strains achieve tumor growth control would provide a firmer platform for improvement and translation.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed by the authors.

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References


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