Tumor Growth Control with IDO-Silencing Salmonella—Reply

Edwin R. Manuel1, Bruce R. Blazar2, and Don J. Diamond3

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-silenced S. typhimurium VNP20009 strain... and S. typhimurium A1-R would be enlightening," yet will it provide any further insight into 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 cytosine deaminase gene, investigators observed significant conversion of the antifungal agent 5-fluorocytosine to the extremely cytotoxic anticancer agent 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. IDO expression in melanoma could also be interpreted as a possible barrier to VNP20009 efficacy as IDO is known to have antimicrobial activity (9, 10).

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.

Grant Support
This work was partially supported by R01 CA72669 (B.R. Blazar), the Tim Neving Lymphoma Research Fund, CIT-COH Biomedical Initiative Grant, and R21 CA174306 (D.J. Diamond). The COH cancer center is supported by P30-CA033572-28.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Received May 2, 2013; accepted May 8, 2013; published OnlineFirst July 5, 2013.

References


Tumor Growth Control with IDO-Silencing Salmonella—Reply

Edwin R. Manuel, Bruce R. Blazar and Don J. Diamond


Updated version
Access the most recent version of this article at:
doi:10.1158/0008-5472.CAN-13-1274

Cited articles
This article cites 10 articles, 6 of which you can access for free at:
http://cancerres.aacrjournals.org/content/73/14/4592.full.html#ref-list-1

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.