CORRESPONDENCE

Noninvasive Imaging for Evaluation of the Systemic Delivery of Capsid-Modified Adenovirus in an Orthotopic Model of Advanced Lung Cancer

Sarkioja et al.[1] have evaluated efficacy of a capsid-modified adenovirus in an orthotopic model of lung cancer by using what they state is a novel animal model and imaging technology.

The authors state that they developed a novel orthotopic model of advanced lung cancer. However, the orthotopic lung cancer model that Sarkioja et al. claim to have developed was first developed by McLemore in the 1980s.[2] An improved orthotopic model of lung cancer that is more metastatic and patient-like was developed by our laboratory in the 1990s, including a model that expresses green fluorescent protein (GFP)[3] (please see below).

Sarkioja et al. state that they developed a model for longitudinal monitoring of tumor burden over time through monitoring GFP expression. The GFP whole-body imaging technology that Sarkioja et al. claim they developed was developed by our laboratory in 2000.[4] Our laboratory also was the first to use GFP imaging models to monitor drug efficacy in real time.[5] Although Sarkioja et al. claim to "take pictures" of images, the authors display only pseudo-color images. Sarkioja et al. do not present the original imaging data for reasons they do not explain. Examples of actual fluorescent protein images of drug response from our laboratory can be seen in our article, *The multiple uses of fluorescent proteins to visualize cancer in vivo*.[5]

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Author Reply

We would like to thank Dr. Hoffman for his interest in our work.[1] Indeed, as he states, lung tumors have been grown in mice previously. However, we are not aware of work that would have described direct intrapulmonary injection of green-fluorescent protein-positive tumor cells leading to an optically imaged model of metastatic lung cancer. The more we learn about the importance of the environment on tumor behavior, including treatment responsiveness, the more relevant orthotopic models seem. The articles referenced by Dr. Hoffman describe instillation of unlabeled lung cancer cells intrabronchially, labeled cells introduced via thoracotomy, or injection of melanoma or colon cancer cells. Although there certainly may be merit to these models (and to Dr Hoffman's corporation that provides them), we feel that direct injection may have some advantages. For example, thoracotomy or bronchoscopy requires specialized equipment and considerable procedural skill, whereas direct injection can be easily and safely performed in mice.

However, we would like to emphasize that the focus of our article was not the model but the data obtained with oncolytic viruses. Lung cancer is the most frequent cause of cancer mortality worldwide. Because few cases are detected when they are still local, cures are infrequent. Current treatment modalities for advanced disease include chemotherapy, radiation therapy, small molecular inhibitors, and monoclonal antibodies. However, none of these are curative and despite sometimes grueling side effects, survival is often only marginally improved. Therefore, novel treatment options are needed.

The antitumor mechanism and side-effect profile of oncolytic viruses is distinct from the therapeutics mentioned above. Therefore, it is possible that disease refractory to other modalities may be amenable to this novel approach.[2] Although still an adolescent technology, promising data have been obtained in nonrandomized and randomized trials.[3,4] Most importantly, the safety of the approach has been excellent, which facilitates the development of agents that are improved in efficacy, such as described in our article. After intravenous delivery, promising efficacy, safety, and biodistribution were seen, making clinical translation attractive. Nevertheless, the fact that few mice were completely cured suggests that much work remains.

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