

## Author Response: Does the Time of Inactivation of pRb Determine the Cell of Origin of Retinoblastoma?

Madhavan and Khetan<sup>1</sup> raise questions about our paper that were largely addressed in the original publication.<sup>2</sup> First, we reiterate that it is not possible to draw direct conclusions about the cell of origin of human retinoblastoma on the basis of data in the TAg-RB mouse model; unfortunately, we lack the unambiguous marker of the tumor lineage in human retinoblastoma that TAg provides in the mouse. Second, the timing of *RBI* loss in humans does not coincide with the developmental period in which TAg is activated in TAg-RB. Human retinoblastoma tumors have frequently been detected prenatally.<sup>3</sup>

TAg-RB arises from the inner nuclear layer after postnatal day 8,<sup>2</sup> and so it is unlikely to display a cone phenotype, as Madhavan and Khetan postulate, since the cones have already matured by that point.<sup>4</sup> Moreover, we have never observed overlap between TAg and cone opsin or RXR $\gamma$  staining (Pajovic S, unpublished data, 2010), but have shown overlap with multiple cell markers that clearly demonstrated that the cell of origin in this model possesses features of differentiated Müller glia with progenitor properties.<sup>2</sup> Although timing of pRB inactivation in our model makes it “not surprising that the cells stain for maturing progenitors,” what is interesting is that inactivation of pRB at this time and in this unique cell type produces a tumor with significant similarity to human retinoblastoma, regardless of whether it originates from the same cell type.

We agree with Madhavan and Khetan<sup>1</sup> that the genetic changes after *Rb1* loss should be evaluated in other mouse models of retinoblastoma, and we would welcome such studies. Indeed, we regard our original paper as an invitation to our colleagues to molecularly and histologically define other mouse models and to interpret mouse data with caution in regard to human retinoblastoma. However, the assertion that the TAg-RB model cannot be considered to be a “good” model for human disease without such studies<sup>1</sup> is flawed. It has been said that there are no good models, only useful ones.<sup>5</sup> Despite a different initiating mechanism and cell of origin, our data indicate histologic and (post-*Rb1* loss) molecular similarities between TAg-RB and human retinoblastoma. These similarities, plus the recent successful translation of therapies tested in TAg-RB to the clinic,<sup>6,7</sup> validate TAg-RB as a useful model.

After more than 30 years of research, the identity of the retinoblastoma cell of origin remains complex and invites dis-

ussion; but most of all, it requires far more research in both mouse models and human disease.

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