Author’s response to reviews

Title: Adenoviral gene transfer of angiostatic ATF-BPTI inhibits tumour growth

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PDF covering letter
Answer to the reviewer Prof. Giampietro Gasparini over the paper: Adenoviral gene transfer of angiostatic ATF-BPTI inhibits tumour growth”

Comment: As far as in vivo studies are concerned, taking into account that antiangiogenic therapy interacts both with the stroma and parenchyma components of a tumour and that microenvironments characteristics may influence its efficacy, it is strongly suggested that also an orthotopic tumor model is used.

Answer: The interaction of the matrix with the tumour cells is indeed probably very important to assess the effect of an angiostatic. Therefore we presented in the paper data with lung carcinoma cells injected intravenously that induce tumours in the lungs. One might consider this model as orthotopic. Furthermore, orthotopic models for primary lung tumours are admittedly very interesting but our experience is that it is cumbersome to monitor their development accurately [1].

Comments: The effects of antiangiogenic therapy should be tested with treatments given at different times after tumour implantation, being tumour mass a critical variable for activity.

Answer: We had already performed such experiments with the L44 lung carcinoma and the CC531 colon adenocarcinoma. The results showed that the ATF-BPTI is no more effective when the tumour mass is too large. These results were expected. They are not the main subject of the article, however, we added these data’s in Fig 9 and commented on those in the results section. The material and methods are consequently updated.

Pharmacodynamics studies on the antiangiogenic and antitumor mechanisms of action of AFT-BPTI should be performed.

Answer: pharmacodynamic studies of the ATF-BPTI has been done in different arteriosclerosis en restenosis model by the group of P. Quax (TNO-PG, Leiden) [2-5]. Those showed the importance of the UPA Receptor for the inhibition of smooth muscle cells and endothelials cells migration. Concerning the mechanism of action of ATF-BPTI in cancer, the recombinant protein is needed and the experiments required are surpassing the purpose of the actual paper. Indeed we only aimed to establish the anti tumour activity of the ATF-BPTI and to correlate it with its intra tumoral concentration.
Comments: Was the endostatin source and schedule of administration similar to those published by the FolkmanaETMs group?

Answer: The protein sequence is identical to the one described by Folkman et al and used in the clinical trials initiated by EntrMed. Further they used recombinant protein in their preclinical experiments, and the peak blood concentrations were around 1 µg/mL (Herbst, R.S., et al., Curr Oncol Rep, 2001). These concentrations are similar to the one we obtained in our models.

Comments: The patterns of vascularisation mentioned on page 13 need to be referenced (Pezzella et al Am J Pathol 151: 1417-1423, 1997).

Answer: The reference was added to the manuscript.


