Author's response to reviews

Title: High-level inducible reexpression of Smad4 in the cervical cancer cell line C4-II and likewise Smad4 reexpression in pancreatic carcinoma cell lines BxPC3 and Capan 1 are associated with gene expression profiles that suggests a preferential role of Smad4 in extracellular matrix composition

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Author's response to reviews: see over
Dear editorial team,

Reviewer 4 suggests to accept the version 2.
With respect to the remaining criticism of reviewer 2 we have modified the last sentence of the background section in the abstract and we agree to alter the title to either
"High-level inducible reexpression of Smad4 in the cervical cancer cell line C4-II and likewise Smad4 reexpression in pancreatic carcinoma cell lines BxPC3 and Capan 1 are associated with gene expression profiles that suggests a preferential role of Smad4 in extracellular matrix composition"
or
"High-level inducible Smad4-reexpression in the cervical cancer cell line C4-II is associated with a gene expression profile that predicts a preferential role of Smad4 in extracellular matrix composition."

Comment on the comments:
The reviewer 2 still insists that we should show independence of Smad4 loss and loss of TGF-beta induced growth inhibition in further cervical carcinoma cell lines. This question has extensively been addressed previously by us and others; i.e. we have shown previously that the Smad4 status and expression level in a large panel of cervical cancer cell lines does not correlate either with TGF-beta sensitivity or with HPV status (Baldus et al., Oncogene 2005). He suggests to perform further experiments and to set up further approaches – which to our opinion would not shed new light on Smad4’s role in carcinogenesis – and/or which are either unaffordable (show loss of TGF-beta induced growth inhibition during the course from normal cells via CIN cells to cancer) or of unpredictable success (generate additional inducible Smad4 systems). Although Smad4 has been cloned in 1996 the single inducible Smad4 expression system published so far, to our knowledge, is the one published in JBC by the group of Massagué and does reach physiological Smad4 expression levels, only. (By the way, this study also concludes that reexpression of Smad4 is not sufficient to restore TGF-beta induced growth inhibition.)
In conclusion, in fact we are unwilling to perform the experiments suggested by this one reviewer. We believe that our data as presented in this manuscript provide a significant contribution to the field – as appreciated by the other reviewers – and will continue our work
to further decipher mechanisms of Smad4-mediated tumor suppression independent from direct and simple growth inhibition.

Sincerely Yours

S. Klein-Scory