Author's response to reviews

Title: TNF-alpha blockade is ineffective in animal models of established polycystic kidney disease

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Author's response to reviews: see over
Dear Editors:

Thank you for your recent communications and guidance to submit revisions for our recent manuscript. We thank the reviewers for their productive comments, and provide a revised manuscript for your consideration. We have provided a detailed set of responses to most every reviewer request, with changes tracked carefully—we additionally highlight below several significant issues emphasized in your editorial response. We hope the accuracy and comprehensiveness of our revisions now make this manuscript acceptable for publication and communication to the readership of BMC Nephrology.

1. Histology methods

As requested, we have improved our materials and methods sections regarding cyst enumeration. Additionally, we would respond to the referees that as we considered various methodologies, we noted a strong correlation between cyst number and cyst involvement as a fraction of tissue area. We feel the single measure is most simple and direct method to communicate the lack of response.

2. Inflammation markers:

In the interest of the editorial request for prompt resubmission, we would not conduct additional analyses for inflammatory or pharmacodynamic (cAMP) markers, either by whole-tissue lysate interrogation or by focused immunohistology studies.

We do note, however, that our pathology team did not note significant changes in across or within PCK rat cohorts (excerpted below) during histology work-up. In light of this data, we had not considered the additional analyses suggested by the referees. Additionally, we are somewhat reluctant to collect more nuanced, cellular measures of disease response, as other major anatomic and physiologic factors indicative of tissue and whole animal response are not changed by Enbrel treatment.

Our pathologist commented:

“... Some sections of kidney also displayed minimal to mild, multifocal, cortical, interstitial inflammatory cell infiltration consisting of lymphocytes. This type of minimal subacute, interstitial inflammation is
often observed in normal rat kidneys and was considered an incidental finding, not related to cyst formation. There was no indication of glomerular sclerosis or periglomerular fibrosis occurring within any of the glomerular structures in any kidney section evaluated.

As mentioned above, we have included clean and edited documents versions with track changes, as well as a point-by-point response document. We appreciate your consideration of our manuscript, and look forward to receiving your input and further guidance regarding its suitability for publication.

Regards,

Jeffrey Roix