Author's response to reviews

Title: Topical Rapamycin Inhibits Tuberous Sclerosis Tumor Growth in a Nude Mouse Model

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Author's response to reviews: see over
Re: MS: 1091820409167852
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Dear BMC Dermatology Editors,

Thank you for your response regarding our manuscript entitled “Topical Rapamycin Inhibits Tuberous Sclerosis Tumor Growth in a Nude Mouse Model”. We appreciate the thorough evaluation and constructive comments from the reviewers. We have addressed all issues noted by reviewers and now submit a revised manuscript.

Point-by-point response to reviewers’ comments:
Reviewer 1
In response to the comment in the second paragraph of the reviewer’s report that oral ingestion could still contribute to blood levels: on page 10 (discussion) we have changed “grooming does not increase drug levels” to “it is unlikely that drug ingestion during grooming increases drug levels”. Further studies on this would be useful but we have made reasonable attempts to address this issue and described the details of our methods and findings so that other investigators can pursue this issue further if they are interested.

Discretionary revisions
We have made the corrections suggested in the introduction section.

Reviewer 2
Discretionary revisions
1. We are aware of only one published report on topical rapamycin in humans that addresses the issue of systemic drug levels after topical administration of rapamycin (Ormerod et al., 2005, reference 35). We mention this study in the first paragraph of the discussion section: “In a randomized, double-blind clinical trial, 8% topical rapamycin was effective for the treatment of psoriasis and there was evidence of skin penetration without measurable rapamycin in blood [35].”

2. We evaluated phospho-S6 levels (by immunoblotting) in tumors from pilot dose finding studies of topical rapamycin and CCI-779 and we found that phospho-S6 levels were reduced with topical mTOR inhibitor treatment (6 of 6 samples) compared to vehicle controls (2 samples). Because this was an expected finding and not novel, we did not pursue these studies in the tumors from the preclinical trial described in this paper. It is not appropriate to include the pilot phospho-S6 immunoblot data in our paper because the studies were limited.
3. We have pursued correlative studies of proliferation, apoptosis, and cell cycle regulation in a previous relevant study (Lee et al., 2006, reference 19). In our prior work we encountered some problems because of tumor heterogeneity due to variable amounts of necrosis in most of these Tsc2/- tumors. We therefore made the decision not to pursue such correlative studies this time.

Thank you for considering publishing this revised version of our manuscript in *BMC Dermatology*.

Sincerely,

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