

**Response to reviewers' comments**

**Re: Atopic eczema treatment now and in the future: Targeting the skin barrier and key immune mechanisms in human skin**

**Reviewer 00646537:** *Interesting review and quite well written - The author seems to be essentially talking about atopic dermatitis, but in some sections seems to be alluding to 'eczema' as a general concept. This probably needs to be clarified better as 'eczema' per se has a large number of types and the points mentioned may not be applicable to many of these types - Would suggest focusing more on what is new related to the immunopathology (the second half of the paper – dealing in detail with the skin barrier/ filaggrin mutation and immune dysfunction). The first part could probably be made more concise. - A table could summarize the therapeutic implications of the newer concepts – summarizing the drug groups and mechanism of action.*

Thank you for your encouraging comments and valid points. We have clarified the nomenclature as you have advised by referring to the disease throughout as “atopic eczema”. We have maintained the focus on immunopathology and in response to your helpful suggestion we have added a table to summarise the therapeutic implications (please see Table 1).

**Reviewer 00646494:** *an interesting and well written review.*

Thank you for your confidence in our work.

**Reviewer 00646503:** *A good and comprehensive review, very clear to readers and with a full bibliography. In order to increase the comprehensiveness of the paper, I suggest to add a figure relative to the paragraph "Immune dysfunction plays a key role in eczema pathogenesis".*

Thank you for your positive comments and helpful advice. We have added another figure to illustrate key aspects of the immune dysfunction in atopic eczema (please see Figure 3).

**Reviewer 00646519:** *In general the manuscript represents an interesting review, authors should include a couple of phrases stating the diseases associated with filaggrin mutations and add a table with the current treatments.*

Thank you for your informative comment. In response to your advice, we have added a couple of phrases and a reference describing the other diseases associated with filaggrin mutations (please see page 8). We have created a table (Table 1) listing current and novel treatments, as you advised, to complement the treatments listed in Figure 1.

**Reviewer 00646561:** *This a basic and very elementary review regarding the pathogenetic mechanism of atopic eczema and possible target treatments. It's clear and well-written. THE following paragraph should be remove as includes trade mark products and adds poor value: "The knowledge of a central role for dry skin in eczema has stimulated interest in the development of bespoke*

*emollients as treatment for xerosis.70 In one study a standard emollient, Aquamol? cream (the control) was compared to Balneum? cream, an emollient containing 5% urea, a skin ceramide N-stearoyl phytosphingosine (NP) and lactate.70 When skin that had previously been treated with Balneum? was changed to Aquamol? there was an increase in TEWL from 11.58 to 11.94 g/m2/h; this suggested that skin barrier function was improved more by using Balneum? than Aquamol?.70 However this improvement between the creams may be due to the sodium lauryl sulfate in Aquamol? having an emulsifying effect and increasing barrier damage.70 When hydration was also considered, the application of Balneum? showed greater hydration compared to the Aquamol?, suggesting improvement of the stratum corneum barrier.70 There is the possibility of damage if Balneum? is used with eczema as it increases pH slightly and further work is needed to define the optimal emollient treatment for eczema."*

Thank you for your comment and pointing out the problem with trademarks. We have removed all reference to trade-marked products, both in the text (please see pages 12-13) and also in Figure 4.