We are grateful that Drs. Grando and Pittelkow have chosen Durham, North Carolina where they argue that mouse models of desmoglein 3 (Dsg3) to highlight our recent paper in their Letter to the Editor.

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Authors’ Reply

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We are grateful that Drs. Grando and Pittelkow have chosen to highlight our recent paper in their Letter to the Editor, where they argue that mouse models of desmoglein 3 (Dsg3) deficiency lack the phenotype of human pemphigus, thereby providing support for a multifogenic theory of pemphigus. Our studies focused exclusively on the genetic mapping and phenotype of a spontaneous mouse mutation within the Dsg3 gene that resulted in a unique squeaky phenotype characterized by immunodeficiency and a wasting disease. Squeaky mice share phenotypic similarities with Dsg3-deficient mice, but they also exhibit unique characteristics due to their hypomorphic expression of a truncated Dsg3 protein. Nonetheless, pemphigus results from autoantibodies, not congenital genetic alterations in their target molecules.

We appreciate this opportunity to reiterate several key points of our paper to diminish any possible over- or misinterpretation of the data presented. Squeaky mice have a dramatic phenotype that includes severe immunodeficiency and inspiratory stridor (squeaking) due to primary pathological changes within the larynx and airway obstruction. Hallmarks of pathology include significant hyperplasia of the epiglottis that results in its thickening and deformation. This pathology extends to lesions on the back of the tongue as described for Dsg3-deficient mice. There is no evidence of acantholysis in the tongue or other sites. Thereby, hypomorphic Dsg3 protein expression may support intercellular adhesion and prevent spontaneous acantholysis in Dsg3-sqk/sqk mice, but it appears insufficient to prevent epithelial sloughing and lesions resulting from mechanical damage or stresses, such as chewing on solid food or snout abrasions. The histology of these oral lesions and snout erosions was substantiated in Figure 6. We acknowledge that we incorrectly stated that alopecia is frequently observed in pemphigus patients in our manuscript, which should have read infrequently, as indicated in the cited reference. These mice have been made available to the research community through the Mutant Mouse Resource and Research Center at the University of North Carolina, Chapel Hill (http://www.mmrrc.org).

In their letter, Drs. Grando and Pittelkow claim that our results, in conjunction with previous animal studies, failed to substantiate that Dsg3 is the principal desmosomal cadherin that holds keratinocytes together. Even though this issue was not investigated in our studies, and we made no claim that Dsg3 is the principal cadherin that holds keratinocytes together, it is accepted that the underlying intraepithelial blister formation of pemphigus is caused by IgG autoantibodies against the desmosomal adhesion proteins expressed on epidermal keratinocytes, Dsg3, and/or Dsg1. A pathogenic role for anti-Dsg IgG has also been established by the injection of patients’ sera or affinity-purified IgG from pemphigus sera into neonatal mice, which reproduces the immune pathology and clinical symptoms of pemphigus. Disease activity in most patients is also closely correlated with serum levels of Dsg reactive antibodies. Although anti-Dsg1 and/or Dsg3 autoantibodies are found in more than 90% of pemphigus patients, autoantibodies reactive with desmocollins, envoplakin, periplakin, A2ML1, desmoplakin I and II, and plectin may also be present in some rare forms of the disease. Given the strong association between Dsg3 and pemphigus, it is to be expected that we would highlight the

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importance of Dsg3 autoantibodies and pemphigus in our publication.

We agree that the development of animal models of pemphigus is an important area of research. However, the pathology of pemphigus is strongly, if not exclusively, associated with the development of anti-cadherin autoantibodies that block keratinocyte intercellular adhesions. Thus, it should be expected that mice genetically deficient in cadherins would not faithfully recapitulate the manifestations of pemphigus autoimmune disease in the absence of pathogenic autoantibody formation, as this is not the root cause of the disease in humans. Instead, genetic alterations in cadherin structure, expression, and function will likely result in diverse manifestations as is documented in our publication and within the published literature. Therefore, the development of animal models of pemphigus must unquestionably require the study of pathogenic autoantibodies, not the study of congenital genetic alterations of their target adhesion molecules. The future study of autoantibodies of differing target molecule specificities in mouse pemphigus models will determine whether antibody binding to cadherins other than Dsg3 alone or in combination can induce pathology that echoes the manifestations of pemphigus in patients as hypothesized by Grando and Pittelkow. 3

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