Q: To Philipp Starkl
What are the factors that determines the fate of immune response i.e., whether the antigen will induce type1/2 response?

A: This is an interesting and complex question. It presumably depends on the combination and type of immune signals. As for a type 2 response, tissue damage seems to be a critical signal that can be, for instance, initiated by a disrupted epithelium or cell death. On the other hand, classical bacterial components, such as LPS or other TLR ligands induce the production of immune mediators that favour the development of a type 1 response. *S. aureus* seems to be a rich source of factors that trigger both branches (and also type 17). In our study we also observed that infection with *S. aureus* deficient in several cytolytic toxins leads to less severe skin lesions and lower IgE levels, indicative of the importance of toxins for the *S. aureus*-induced type 2 response.

Q: To Philipp Starkl
How is the FceRI on Langerhans cell?

A: In mice, FceRI seems to be specifically expressed in basophils and mast cells while in humans, the receptor is also (in addition to basophils and mast cells) expressed on monocytes, Langerhans cells, eosinophils, neutrophils and platelets (and intestinal epithelial cells under certain circumstances); however, the configuration and function on these cell types is different from mast cells and basophils: while the latter express a tetrameric receptor setup (1 alpha chain, 1 beta chain, 2 gamma chains) IgE/antigen binding leads to cell activation, the former express a trimeric receptor setup (1 alpha chain, 1 beta chain, 2 gamma chains), associated with antigen presentation in antigen presenting cells

Q: To Philipp Starkl
If allergic reactions are protective against staph infection and venom exposure is it a mistake to use antihistamines in atopic dermatitis, bee stings and spider bites?

A: thanks for this interesting question; I think it is difficult to give generalized treatment recommendations; at this point, beneficial (detoxification) functions for mast cell-derived proteases (for different reptile and scorpion venoms as well as against *S. aureus*) and heparin (for honey bee venom) have been reported; I am not aware of studies showing or addressing, a
potential function of histamine in this context, therefore, I think it is not a mistake to use antihistamines in the situations described in the question;

**Q: To Philipp Starkl**
I wonder if allergic reactions are protective against S aureus, is it not a contradiction that you often see S aureus colonization/infection in allergic atopic dermatitis - that would rather indicate a less efficient immune response against S aureus?

**Why do atopic dermatitis patients show high IgE and increased S. aureus colonization and a susceptibility towards S. aureus infections? Moreover, CTCL patients with type 2 inflammation show elevated IgE and a susceptibility towards S. aureus sepsis?**

Thanks for these important questions. It is true that the observations from atopic dermatitis and CTCL patients seem to contradict our findings at first. However, I think that there are important difference to the experimental model in our study that might account for these differences to human patients. For instance, atopic dermatitis patients suffer from a chronic condition which is often caused (at least in part) by genetic factors. Such factors influence, for instance, skin barrier integrity and therefore favour the colonization (and chronic infection) with *S. aureus*. It is true that such patients often have high levels of *S. aureus* (toxin)-specific IgE antibodies but I think that due to the constant infection/inflammation and genetic driving factors, normally favourable aspects of adaptive immunity (e.g. TH17 cells, mast cells IgE and IgG antibodies) are not sufficient to mediate protection but further enhance inflammation and worsen disease. On the other hand, CTCL have a dysregulated immune system with predominant TH2 immunity. This disbalance, especially the malfunctional T cell response in the skin, is likely an important factor favouring *S. aureus* colonization and infection.

In our experimental model, the animals are healthy without genetic abnormalities and only *transiently infected* with *S. aureus* (they can efficiently clear the infection) and are then (after development of type 1/2/3 immunity and IgE) challenged with a more severe secondary infection. Therefore, our model rather reflects the situation of a healthy (non-atopic, without pre-disposing genetic factors, impaired skin barrier or dysregulated immunity, such as in atopic dermatitis or CTCL) person, transiently exposed to *S. aureus* (and developing an immune response). In this context, it’s an interesting observation that 30-40% of healthy controls of atopic dermatitis and asthma studies have detectable levels of *S. aureus* toxin-specific IgE. This indicates that type 2 immunity and IgE antibodies are part of the anti-*S. aureus* immune response in healthy, non-atopic individuals. It would be interesting to know whether such healthy people with *S. aureus* toxin-specific IgE have a changed frequency of severe *S. aureus* infections as this would reflect a situation comparable to our experimental models. However, even if that would be the case, it would be very challenging to proof the importance of IgE antibodies as they coincide with numerous other aspects of adaptive immunity (e.g. antigen-specific T cells and specific antibodies of other subclasses).

**Q: To Francesca Capon**
How many further genes with two mutations were identified apart from MPO and what were they?
Q: To Francesca Capon and Stefan Haskamp?
Do you think that the role of MPO in regulation of the vasculature or NO may be relevant in pustular psoriasis?
Stefan: Thank you for the question. MPO derived oxidants may contribute to the tissue damage in cardiovascular disease. Therefore, MPO may be a good therapeutic target. In contrast, we showed and Francesca’s group confirmed that MPO deficiency and the lack of MPO derived oxidants contributes to inflammation in generalized pustular psoriasis. Therefore, I think that MPO may have pro and anti-inflammatory features depending on its location and/or abundancy. However, I am not an expert in vascular biology.