# Taming food-induced immune disorders

Food-induced immune disorders are on the rise, affecting up to 10% of the worldwide population. The exact causes for this increase are unknown but better hygiene and changes in the human microbiome are among the suspected culprits. Food-induced immune disorders are not only inconvenient but can even be serious and life-threatening. For example, particular problems are caused by nut allergies which may lead to anaphylactic shock. Existing treatments for these diseases are insufficient and represent a major unmet medical need.

A novel approach to tackling the problem results from a better understanding of how the immune system handles the constant stream of antigens from food in the mouth. These antigens normally do not induce an immune response even though there is no central tolerance to them. Instead, the standard reaction to immunogenic proteins delivered through the mouth is a specific, peripheral unresponsiveness called oral tolerance.

The mechanisms of oral tolerance are not yet fully understood but today it is known that the tolerance induced in the oral mucosa differs from tolerance induced in the lower gastrointestinal tract. It is also known that food allergies, food intolerances and auto-immune diseases in general can originate in the mouth by some kind of malfunction of the oral immune system and its microbiome. It has been shown that food allergy and celiac disease patients suffer from an aberrant oral epithelium and micro flora, causing T cell responses against food proteins. Immunologists therefore have coined the term "mouth-gut" axis for this phenomenon, and thus the oral immune system and its microbiome is getting more and more attention in immunology.

## Oral tolerance and SLIT

Induction of antigen-specific immunotherapy and oral tolerance that leads to long-lasting, systemic and curative immune responses is the holy grail in immunology and has been demonstrated in allergen immunotherapy (AIT). Such an induction of antigen-specific tolerance is therefore a major goal also in the treatment of autoimmunity, and inflammatory disorders. It is known today that the oral mucosa is an immunoprivileged anatomical structure and e.g. sublingual administration of antigens or allergens in the form of drops or tablets, elicits tolerogenic immune responses. The sublingual route has already been established for inducing effective, antigen-specific tolerance in humans with respiratory allergies. Patients are being administered sub-threshold daily doses of an allergen and are desensitised by gradually escalating the dose level over time until a target maintenance dose is reached. Thereby, immunological reprogramming and long-term immune tolerance and clinical protection from allergic reactions may be achieved. However, the treatment regimen is long and complex, leading to a very low compliance: only 7% of patients complete the three-year therapy.

This so-called sublingual immunotherapy (SLIT) can elicit allergen-specific tolerance in individuals already sensitised against this allergen. However, the induction of oral tolerance depends on a lot of factors: e.g. type of antigen, dose and combination with other components, frequency of antigen contact, and immune status of the microenvironment. In particular, it is known that a limiting factor for efficacy is the amount of antigen that can be presented by SLIT to the tolerogenic oral mucosal immune system. In this context, a prolonged presence of the antigen in the oral cavity is difficult as this is an environment with the presence of enzymes and constant saliva production, resulting in poor absorption properties. All these factors negatively impact the amounts of antigen that can be presented to the oral immune system. Therefore, current SLIT approaches have significant limitations and no SLIT treatment has been approved for food allergies so far.

Based on previous experiences of its founders with AIT, SLIT and probiotics our company, Allero Therapeutics, has set out to overcome these difficulties with its Specific Oromucosal Immunotherapy (SOMIT) approach. SOMIT combines an antigen with tolerogenic bacterial particles (TBPs) and presents them with a mouth patch technology that provides for unidirectional and prolonged release to the inner cheek of the mouth. Probiotic bacteria are important for maintaining the immune-tolerant state in the mucosa. It is known that their presence can favour tolerogenic mechanisms by interacting with pattern recognition receptors at the surface of resident immune cells. Allero's TBPs are derived from probiotic bacteria and serve to condition the local oromucosal immune system to further stimulate the immune tolerance reprogramming by enhancing the antigen presentation and increasing the antigen uptake via tolerogenic antigen-presenting cells (APCs).

The APCs subsequently traffic to the draining lymph nodes where the expansion of antigen-specific T regulatory cells leads to a cell population that down-regulates pathological pro-inflammatory T effector cells in the tissues: Th2 in allergies and Th1/Th17 in autoimmune diseases such as coeliac disease.

Allero has already demonstrated that the concept works in animal models and patient-derived immune cells. For instance, in immune cells derived from patients with coeliac disease the proliferation of T effector cells is synergistically inhibited by TBPs in the presence of antigens, suggesting an antigen-specific inhibition of these T cells. In a pig model of food allergies, SOMIT-treated pigs did not present an allergic skin reaction when treated only a few times with a mouth patch containing the allergen mixed with TBPs.

Based on these observations, it is expected that administration of the patches with ascending doses of the antigens/allergens mixed with TBPs will lead to complete tolerance induction. One of the first target indications for our therapy will be prototypic immune-mediated disease indications such as celiac disease and food allergies such as peanut allergy.

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