

ORIGINAL ARTICLE

The future of specific immunotherapy: strategies and challenges for the next generation of allergy vaccines

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Abstract

The use of specific immunotherapy (SIT) for allergic disorders has recently been extended by introduction of a convenient, tablet-based, disease-modifying vaccine against grass pollen allergy. Allergy immunotherapy tablet (AIT) programmes targeting house dust mite and other allergies are currently in late-phase development. Next-generation allergy vaccines can have optimised potency and onset of action without compromising safety or convenience. Key to achieving these objectives is a combination of evidence-based mode-of-action studies and biomarker-centric translational research approaches. This will rely on using biobank and bioinformatics resources for multi-omic characterisations of the 'immunome' of allergic disease. Other important areas are ongoing paediatric trials and long-term studies in adults for further defining the potential role of SIT in allergic disease and primary prevention of asthma. Finally, combining cellular- and serological-based assays, and developments in targeted delivery platforms and component-resolved diagnostics will lead to increased ability to stratify patients, with more personalised diagnosis and treatment.

Specific immunotherapy (SIT) offers the only treatment for allergic patients whose disease cannot be controlled by symptomatic drugs. This is well documented, as indicated by the evidence described and presented at this symposium. SIT can have a disease-modifying effect and we can now demonstrate secondary prevention of asthma in patients with allergic rhinoconjunctivitis. In spite of this progress, SIT is still a niche treatment, with untapped potential for allergy management. Allergy-related diseases are clearly both undertreated and underdiagnosed. Specifically, we know that approximately 110 million Europeans suffer from allergy and 30% of these develop asthma, yet only a small percent – approximately 2% of allergy patients, receive SIT. Moreover, every year, \$20 billion are spent globally on allergic rhinoconjunctivitis, of which only 3% is used for SIT. So even with the recent entering of large pharma to this field and with geographical expansion into areas outside the United States and the European Union starting to take place we still must ask, how do we close the gap between those who could benefit from SIT, and those who actually receive it?

Optimising specific immunotherapy

The answer lies in finding the balance between improving clinical efficacy, decreasing the side effects, and keeping or improving convenience of delivery. Areas for improvement and innovation are based on gaining a better understanding of the mode of action and dose effects, which will lead to improved delivery and immunisation schedules. More effective and safer preparations, for example using adjuvants or combination therapies for faster onset and reduced dose, are likely to improve compliance. A longer-term goal is personalised and targeted treatment in which we can stratify patients and identify responders and non-responders. We can also expand the use of SIT to include the primary goal of asthma prevention.

What will drive this development is strong translational research with a pyramid approach that is based on better disease understanding, which supports biomarker development, and in turn validation of the principles in proof-of-concept trials (Fig. 1). This must proceed along the tradi-

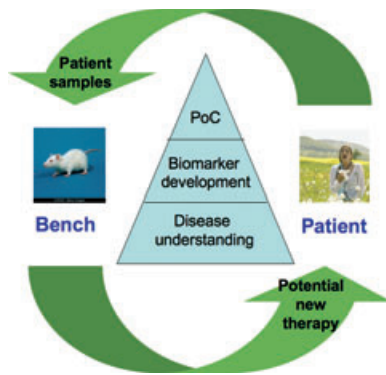


Figure 1 Strong Translational Research will drive the development of next generation vaccines.

tional hypothesis-driven approach to take potential new therapies from the bench to the patient. Equally important and interesting are more hypothesis-generating approaches that take successful vaccines as a starting point and go back to the bench to optimise them in experimental models. We need to look at translational research in this highly integrated fashion.

Regarding SIT biomarkers we are still only scratching the tip of the iceberg. Thus, we have a good understanding of serum antibody markers such as allergen-specific IgG₄ and IgE antibodies, and allergen-specific IgE blocking antibody assays. However, we still need good predictive markers for efficacy and safety. Some interesting opportunities are at hand through applying multivariate analysis of existing data and biobanks. At ALK over the last two decades we have collected approximately 20 000 samples in our biobanks that we believe represent a goldmine of information. Mining these in a smart and multivariate way may uncover new, previously unknown biomarker possibilities. Another approach is to use 'multi-omic' characterisation of clinical samples in order to find molecular signatures of allergic disease instead of looking for individual markers. As we have heard at this symposium, this could also involve epigenetic analysis.

Mining the 'immunome' network

We currently think of the SIT mode of action in a simplified linear fashion, but the nature of the underlying disease is actually more like a highly complicated network of interacting factors (1). A challenge is therefore to mine the so-called 'immunome' as a network. This calls for innovative approaches and considerable computing power. We have seen some first attempts at this approach, for example by Professor Patrick Holt's group (2). They defined an atopy module by subsetting peripheral blood mononuclear cells from aller-

gic patients and isolating CD4⁺ T-cells. These were used for gene expression profiling, which showed an enrichment of T-regulatory and Th2-associated expression signatures as expected, but also 25 novel genes. Now under investigation is how these signatures change under SIT. One hypothesis is that patients who respond positively to SIT will shut down the key genes in this module during the course of therapy and show a restricted or altered pattern of gene expression. More research is needed but this is a promising approach for the future.

As suggested by Professor Jörg Kleine-Tebbe, we can also integrate such 'omics-based approaches with cellular-based and serological-based marker assays. We have also seen advances in component-resolved diagnosis. These approaches will allow for more complete and precise diagnosis, and all these approaches are leading toward more personalized treatment. We already have some of the tools at hand now for assigning the right therapy to the right patients at the right time. Combining these methods with disease signatures and patient stratification are the future of allergy disease management.

Preventing the allergic march

Our main goal continues to be primary prevention, preventing the allergic march from allergic rhinoconjunctivitis to asthma. Allergic rhinoconjunctivitis is a known risk factor for asthma, and growing evidence suggests that prevention of allergic rhinoconjunctivitis can prevent asthma in high-risk children. Previous trials on using SIT for asthma prevention have had methodological limitations, so we look forward to future results from the randomised, double-blind placebo-controlled Grazax[®] Asthma Prevention (GAP) trial (3). With changes in grading of evidence and standardized methods of assessment, we can expect better studies in general in this area.

In summary, in the near future, we will have the opportunity to apply SIT to more than just treatment of patients who are not well controlled by symptomatic drugs. With better biomarkers we can stratify patients to optimise diagnosis, and monitor clinical response to optimise treatment. The disease-modifying effects could become a fundamental objective, as well as secondary prevention of asthma in patients with allergic rhinoconjunctivitis. Other possibilities are primary prevention of rhinoconjunctivitis and asthma in sensitised or at-risk infants. In conclusion, this symposium has documented some of the interesting developments in the field, and encouraged us that we will soon have even better therapies for our patients.

Conflict of interest

Poul Sørensen is an employee of ALK-Abelló.

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