# In vitro evaluation of the immune-skewing potential of different candidate building blocks for nanoparticle-based allergen immunotherapy for treatment of allergy*

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Allergen immunotherapy (AIT) is currently performed with aluminum hydroxide-adsorbed allergen extracts. This approach is effective, but requires a long burdensome treatment protocol with a relatively high frequency of allergic side-effects. There is...

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| **Ethical review** | Approved WMO |
| **Status** | Recruiting |
| **Health condition type** | Allergic conditions |
| **Study type** | Observational invasive |

## Summary

### ID

NL-OMON54501

**Source**
ToetsingOnline

**Brief title**
Screening potential allergy vaccine components

### Condition

- Allergic conditions

**Synonym**
Allergy, Hypersensitivity

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Academisch Medisch Centrum
**Source(s) of monetary or material Support:** Health Holland TKI-PPP ,Canadian biotech company from Quebec City, ANGANY Inc,Canadian biotech company from Quebec City;ANGANY Inc

## Intervention

**Keyword:** Allergen immunotherapy, Allergy, Nanoparticles

## Outcome measures

### Primary outcome

not applicable

### Secondary outcome

Not applicable

# Study description

### Background summary

AIT is the only causal treatment for allergy that targets the immunological basis of the disease. All other treatments are symptomatic treatments, either typical pharma treatments such as antihistamines or corticosteroids or biologicals such as anti-IgE. Upon cessation of administration of such symptom medication, symptoms return rapidly. AIT is the only treatment with documented sustained reduction of symptoms after stopping the treatment. However, to achieve this state of prolonged tolerance, a very long treatment protocol of 3 to 5 years is required. For subcutaneous AIT this means that patients have to visit an outpatient clinic for their monthly injection for years. This burden is one of the reasons that the majority of patients resort to symptom medication. In addition, current AIT frequently gives allergic side-effects because allergen is administered essentially in its native (symptom-triggering) conformation. To increase acceptance of AIT it is clear that significant reduction of the burden of treatment duration and frequency and of side-effects would be a major step forward.
Immunologically, successful AIT transforms an allergen-specific IgE/Th2-dominated inflammatory immune response into an allergen-specific anti-inflammatory response dominated by regulatory T-cells, regulatory B-cells and IgG4 antibodies. During current AIT protocols, allergen extracts, usually

adsorbed to aluminum hydroxide, are subcutaneously administered. To induce the desired persistent anti-inflammatory response dominated by IgG4, this treatment is given for 3 to 5 years. Besides the duration of the treatment, chronic exposure to aluminum hydroxide is increasingly considered as undesirable. In recent years it has become clear that AIT is likely to be more effective at younger age when the immune system may still be more receptive to immune modulation. In addition, it has been shown that AIT in young patients with allergic rhinitis prevents the development of allergic asthma. Although there is not really convincing evidence that chronic exposure to aluminum hydroxide is detrimental, there is a demand for alternatives, in particular when AIT will increasingly be used at younger age.

In summary, there is a need to develop alternatives for current generation AIT products that 1) require less injections to achieve an effective reduction of symptoms and 2) are not dependent on addition of aluminum hydroxide. There are essentially four potential building blocks for the design of an improved AIT vaccine:

a. The allergen, either as a complete extract or as purified major allergens. The allergen can be modified to a) decrease allergenicity (hypo-allergenicity: less side-effects) and b) target it more effectively to (receptors on) antigen presenting cells.
b. Adjuvants, to more effectively induce allergen-specific anti-inflammatory immune responses, both with respect to kinetics (quicker) and persistence (memory that can be triggered ideally by natural exposure or by occasional booster injections) than is currently achieved with aluminum hydroxide.
c. A vehicle for formulation and administration of allergen, to replace aluminum hydroxide as a depot for allergen that helps shielding off IgE-binding sites
d. Antibody approaches to more effectively target the allergen to the appropriate antigen-presenting cells in the skin such as dendritic cells (DCs) and Langerhans cells (LCs).

In the frame of three projects at Amsterdam UMC, we are exploring possibilities to improve AIT for both respiratory and food allergy. The three projects largely overlap with respect to timelines. We have combined these three projects in a single protocol because experiments to be carried out with moDCs generated from voluntary blood donations will be used in identical experiments. In fact, candidate vaccine components from the three different projects can and will be compared in single experiments to establish which (combination of) approaches is most promising to improve AIT. The three projects are:

1) Dendritic cell targeting for resetting immune balance (DC4BALANCE).
This is a 4 years* project with a start date on January 1, 2019, ending December 31, 2022. Due to Covid-19 restrictions in 2020/21, the end date may move up to one year to December 31 2023. Pilot experiments have been carried out with blood donations from subjects with unknown demographic and clinical

background (buffy coats from Sanquin / volunteers through BACON). Since it is known that DCs from allergic and from non-allergic donors possess different immune-skewing properties, it is difficult to draw firm conclusions from the experiments. There is a need to perform these experiments with blood from donors with known clinical background.

The project is funded by Health Holland under the TKI-PPP and focuses on several diseases, one being house dust mite allergy. The candidate vaccine building blocks to study immune modulatory characteristics in this project are:

• Purified house dust mite allergens Der p 1 and Der p 2 and house dust mite extract
• Vitamin D3, retinoic acid and a TGFb mimetic peptide as candidate anti-inflammatory adjuvants
• Nanoparticles: liposomes of various composition and PLGA nanoparticles as alternative for aluminum hydroxide. By loading the liposomes/nanoparticles with allergen, it is shielded off from contact with mast cells when injected, decreasing the risk of side-effects.
• Antibodies against receptors on DCs, for more effective targeting to the right antigen-presenting cells.

2) Sialylation van allergens - mode of action for improved immunotherapy using novel immune tolerizing pathways (SIALLERGEN). This is a 4 years* project starting November 1, 2019, ending by December 31, 2023. Due to Covid-19 restrictions in 2020/21, the end date may move up to June 30, 2024. Based on previous findings this project is continued, funded by Eurostars, starting January 2025, ending December 2027.

The project is also funded by Health Holland under TKI-PPP and focuses on house dust mite allergy and peanut allergy. The central hypothesis of the project is that sialylated antigens/allergens effectively induce a regulatory anti-inflammatory immune response. This effect is thought to be mediated by Siglec receptors on DCs. The candidate vaccine building blocks to study immune modulatory characteristics in this project therefore are:

• For house dust mite: purified Der p 1 and Der p 2, and sialylated versions thereof
• For peanut: purified Ara h 1, Ara h 2, Ara h 3 en Ara h 6 and sialylated versions thereof
• Sialylated liposomes loaded with house dust mite allergens Der p 1 and/or Der p 2 or with peanut allergens Ara h 1 and/or Ara h 2. The advantage of this approach may again be that the allergen is shielded off from contact with mast cells when injected, decreasing the risk of side-effects.

3) Evaluation of plant-based bioparticles surface-expressing (ANGANY).This project is a 3-year project starting in October 2019 and ending by September

2022. Based on previous findings an additional plant-based bioparticle project is funded by Amsterdam UMC under TKI-PPP starting in August 2024 and ending in July 2026.

The project is funded by a Canadian biotech company from Quebec City, ANGANY Inc. The concept is a plant-based nanoparticle approach. The plant bioparticles are exposing allergens on the surface and are rich in glucosylceramide which is thought to induce anti-inflammatory responses. Surprisingly, in pilot experiments the multivalent surface expression showed decreased capacity to induce basophil activation, possibly explained by sterically unfavorable presentation to achieve IgE cross-linking. In mice, the bioparticles induced a more vigorous IgG response than aluminum hydroxide adsorbed allergens. The candidate vaccine building blocks to study immune modulatory characteri

## Study objective

Allergen immunotherapy (AIT) is currently performed with aluminum hydroxide-adsorbed allergen extracts. This approach is effective, but requires a long burdensome treatment protocol with a relatively high frequency of allergic side-effects. There is a need to increase safety and to reduce the duration and frequency of administration during treatment protocols. Modification of allergens, application of novel adjuvants, nanoparticles and cell-targeting strategies are amongst the possible strategies to reach improved safety and efficacy. Pre-clinical evaluation of such innovations requires blood samples from allergic patients and appropriate controls. The aim is to enroll volunteers for donation of blood samples for the isolation of PBMCs and collection of serum. This will allow to make steps towards:

1. Safer AIT: shielding off allergen from interaction with mast cells by application of nanoparticles, high-density presentation on nanoparticles, sialylation of allergens altering their IgE-binding surface.
2. More effective induction of an anti-inflammatory regulatory response (Tregs/Bregs/IgG4): addition of adjuvants, modification by sialylation, presentation in context of glycosylceramide containing plant bioparticles.
3. Replacement of aluminum hydroxide: liposomes, PLGA, plant bioparticles.

## Study design

The study aims at recruiting healthy subjects (n=20) and subjects with allergic rhinitis (n=40), or peanut allergy (n=20) that are prepared to give 50-200 ml of blood on multiple occasions (up to maximally 20 times in 4 years) for pre-clinical evaluation of novel approaches for AIT. Between subsequent blood donations a period of at least 2 months is required. Patients with allergic (caused by house dust mite, cat or [grass] pollen sensitization) and non-allergic rhinitis and patients with peanut allergy will be approached either retrospectively or prospectively. Retrospective recruitment will take

place via the ENT department at the AMC. The database kept at the ENT department, containing a subgroup of patients that have consented to be approached for future allergy-associated research projects, will be used. To comply with GDPR legislation, CTcue will be used to select patients that have consented without jeopardizing the privacy of those that have not provided such consent. For prospective recruitment, allergic subjects will be recruited via the allergy outpatient clinic of the ENT department of Amsterdam UMC or the Internal Medicine department of the Amsterdam UMC and Huid Medisch Centrum Paasheuvelweg, where they will be asked whether they are interested to participate in the study when they come for their normal consultation visits. Likewise, prospective recruitment of allergic subjects also occurs via advertisements (e.g. on notification boards) in the AMC, Amsterdam UMC intranet and social media of the student association of the medical faculty at the AMC (MFAS). Healthy subjects not having chronic inflammatory diseases will be approached via www.link2trials.com, MFAS social media, the Amsterdam UMC intranet and via advertisements on notification boards of outpatient clinic departments not primarily seeing patients with inflammatory diseases (e.g. orthopedic surgery). Advertisements for allergic and healthy subjects will contain contact details from the laboratory of Experimental Immunology. Prospectively recruited subjects do not need to go through the ENT department, which will save them time and effort. All subject that enter the study via the ENT department will receive a skin prick test (SPT). While subject that enter the study via the Department of Experimental Immunology will be characterized via the measurement of allergen-specific IgE serum levels. Subjects that enter via the Internal Medicine-Allergy outpatient clinic at Amsterdam UMC or Huid Medisch Centrum Paasheuvelweg already have a doctor-diagnosed allergy based on history, confirmed with skin prick test and/or IgE levels and/or a provocation test. The choice of methods depends on the material and expertise available at the clinical and laboratory departments, making inclusion into the study highly efficient for both the subjects and the clinicians/researchers. However, these different methods provide us with the same information regarding the allergic background of the patients. Subjects that enter the study via the Department of Experimental Immunology could still be invited for a SPT to confirm previous IgE serum level results. For mass-spectometry experiments, 500 ml of blood is required. Subjects will be recruited via similar routes as mentioned above. After a 500 ml blood donation, a subsequent donation can only take place after a period of at least 4 months. During the study, subjects may at each moment withdraw from participation, without giving a reason for their withdrawal. Upon withdrawal of subjects, new candidate subjects may be approached for replacement. Subjects will be provided with a patient information sheet and will be asked to sign informed consent. Subjects will be given 50 euro reimbursement for the blood donation and reimbursement of their travel costs.

**Study burden and risks**

Patients will contribute to increasing the knowledge in the field of innovation of AIT for the treatment of allergic diseases, In the future this may provide

new safer and more effective treatments that benefit the allergic patient. Disadvantage of volunteering is minimal. Blood drawing can cause a low level of pain and may occasionally results in a hematoma. Skin tests are safe and adverse events are uncommon. Vasovagal reactions (pallor, sweating, faintness) may appear in up to 4 out of 10,000 patients. Systemic allergic reactions (such as e.g. an asthma episode) are even less common and may be seen in 1.5-2.2 out of 10,000 patients. No fatalities have been reported. As this test is performed under the observation of the study personnel, adequate treatment of those reactions can be effectively initiated.

## Contacts

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## Trial sites

### Listed location countries

Netherlands

## Eligibility criteria

**Age**
Adults (18-64 years)

### Inclusion criteria

-Subjects with doctor-diagnosed allergic rhinitis or convincing history of allergic rhinitis and a positive SPT and/or serum IgE levels for HDM, cat or

pollen allergens
-Subjects with a doctor-diagnosed peanut allergy or a convincing history of peanut allergy and positive SPT and/or serum IgE levels for peanut allergens
-Healthy subjects, defined as not having allergic or non-allergic rhinitis, peanut allergy or other inflammatory non-communicable diseases such as rheumatoid arthritis, type 2 diabetes, celiac disease, colitis ulcerosa, Crohn*s disease, and multiple sclerosis.
-Age between 18-65
-Signed informed consent

### Exclusion criteria

• History of AIT (SCIT or SLIT) with any allergen within the past year of the time of blood donation.
• Ongoing AIT (SCIT or SLIT) with any allergen at the time of blood donation.
• Vaccination within one week before blood donation.
• Immunosuppressive or biological medication (e.g. IL-5, anti-IgE therapy) within the last six months prior to blood donation.
• Severe immune disorders (including auto-immune diseases) and/or diseases requiring immunosuppressive drugs.
• Active malignancies or any malignant disease during the previous 5 years.
• Active inflammation or infection at the time of blood donation.
• Use of systemic steroids within 4 weeks before the blood donation.
• Treatment with systemic and local β-blockers.
• Volunteers who are students or employees ofone of the participating research groups or 1st grade relatives or partners of the investigators

## Study design

### Design

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| Study type: | Observational invasive |
| Intervention model: | Other |
| Allocation: | Non-randomized controlled trial |
| Masking: | Open (masking not used) |
| Control: | Active |
| Primary purpose: | Treatment |

## Recruitment

NL

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| Recruitment status: | Recruiting |
| Start date (anticipated): | 09-05-2022 |
| Enrollment: | 80 |
| Type: | Actual |

# Ethics review

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| Approved WMO Date: | 29-10-2019 |
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 16-12-2020 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 05-10-2021 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 19-09-2023 |
| Application type: | Amendment |
| Review commission: | MEC Academisch Medisch Centrum (Amsterdam)<br>Kamer G4-214<br>Postbus 22660<br>1100 DD Amsterdam<br>020 566 7389<br>mecamc@amsterdamumc.nl |
| Approved WMO Date: | 11-12-2024 |

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|---|---|
| Application type: | Amendment |
| Review commission: | MEC Academisch Medisch Centrum (Amsterdam)<br>Kamer G4-214<br>Postbus 22660<br>1100 DD Amsterdam<br>020 566 7389<br>mecamc@amsterdamumc.nl |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| CCMO | NL71330.018.19 |