Mouse models of food allergy: how well do they simulate the human disorder?

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Outline

• Food allergy epidemiology and pathophysiology

• Mouse models of food allergies.
  To what extent do they simulate the human disorder?
  What are the strengths and limitations of these models?

• «Fiber and Bacterial SCFA Enhance Oral Tolerance and Protect against Food Allergy through Diverse Cellular Pathways». Tan et al., 2016, Cell Reports 15, 2809–2824

• “Anti-hIgE gene therapy of peanut-induced anaphylaxis in a humanized murine model of peanut allergy» Pagovich et al., J Allergy Clin Immunology 2016 Dec;138(6):1652-1662.e7
Food allergy

- Food allergy is a significant public health problem not only because it afflicts millions of people but also because of the life threatening nature of allergic reactions.

- The prevalence of food allergies has significantly increased during the past decade especially among the children with nearly 8% under the age of 18 years afflicted the prevalence among adults is also significant (~4%)

- Although food allergies afflict both sexes, among children younger than 18 years, it is relatively more common among males; among adults (more than 18 years), an opposite trend was reported.

- Not only the prevalence but also the severity of food induced allergic reactions has increased during the past several years

- It is important that rapid progress is made not only in advancing the knowledge on causes and mechanisms but also, in developing effective prevention/therapeutic strategies to facilitate control and management of this escalating epidemic.

- Food allergy mouse model that simulates the human disorder will be highly valuable as a research and development tool.
Why are Food Allergies on the Rise? Hypotheses

• Although genetics might play an important role in disease susceptibility, the rising trend of food allergies over few decades implicates a critical role for environmental factors.

• “Hygiene Hypothesis” attributes improved personal hygiene and elimination of major childhood infectious diseases to explaining the general rise of immune mediated disorders – both autoimmune and allergies.

• Other critical environmental factors related to the food allergy epidemic might be changes in food production (e.g., food processing methods) and consumption (e.g., changes in food matrix, exposure doses, age at first exposure to solid food, etc.

• Use of antibiotics and change in gut microbiota
Nearly ∼40% of food allergic children suffered from a severe type of reaction characterized by shortness of breath and/or shock reactions which are potentially fatal.

Classification of food allergies

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Type-I (Immediate) HSR</th>
<th>Type-IV (Delayed) HSR</th>
<th>Type-I+ Type-IV (Mixed) HRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Examples*</td>
<td>IgE antibody and mast cell/basophil mediated</td>
<td>Cell (lymphocyte and monocyte)-mediated tissue damage</td>
<td>IgE, mast cell, basophil + eosinophil-mediated tissue damage</td>
</tr>
<tr>
<td></td>
<td>Most food allergies (peanut, tree nut, most milk, most wheat, soy, fish, shellfish, egg, and sesame allergy)</td>
<td>Celiac disease, contact dermatitis to sesame oil, food (milk, soy, rice, and oat), protein-induced enterocolitis syndrome</td>
<td>Eosinophilic gastro enterenteritis; eosinophilic esophagitis (often associated with food allergy)</td>
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</tbody>
</table>

- **Immediate vs. delayed hypersensitivity reactions (HSRs):** this classification is based on kinetics of clinical reaction upon oral exposure to food;

- **Transient vs. persistent food allergies:** this classification is based on whether they are outgrown (therefore, called transient) or not (therefore, called persistent);

- **Type-1 vs. Type-2 food allergies:** former type caused directly by the food itself and the latter due to cross-reactivity of antibodies against aeroallergens with other proteins from food; The IgE binding activity to airborne allergens is primarily due to conformational epitopes; by contrast, IgE binding to peanut allergens specifically, and food allergens in general, has been ascribed to linear epitopes

- **Exercise induced food allergy:** this is based on whether physical exercise is required after food ingestion for clinical reactions to occur.
Peanut allergy

- Food proteins are taken up by specialised epithelial cells, M cells, transferred to antigen-presenting cells such as dendritic cells, and processed into peptide fragments presented on the cell surface by class II MHC molecules;

- Peptides are then presented to naive T helper (Th) cells via MHC/T cell receptor interaction, resulting in Th cell priming and activation;

- T helper cells secrete cytokines that stimulate B cells to synthesise IgE antibodies specific for peanut in the sensitisation phase of the immune response;

- In the effector phase of the immune response, the IgE antibodies made specifically to peanut are bound primarily on mast cells and basophils by the high affinity surface IgE receptors (FcεRI).
Antigen uptake in the mouse small intestine

To elicit anaphylaxis after oral ingestion, allergen must first breach the epithelial barrier to reach either local or distal effector cells such as mast cells or basophils.

Naive C3H/HeJ mice were fed fluorescein isothyocyanate (FITC)-labeled milk proteins, and 10 min after feeding the intestine was removed, frozen, and cryosections prepared. Sections were counterstained with Texas Red-phalloidin, or DAPI. (a) Intestine from unfed mice, showing absence of endogenous green fluorescence. (b–d) At 10 min after feeding, FITC-BLG was clearly present within cells running along the lacteals of the small intestine (b–c). Antigen was cell associated (d) in the lamina propria (LP), and below the level of the epithelium (Ep). Pasteurization of milk protein (-lactalbumin, e) rendered the soluble milk proteins insoluble, and the particulate proteins were preferentially taken up the Peyer’s patch.
foods can trigger allergic immune response and disease in many species (mice, rats, pigs, and dogs) as they do in humans used to study both the inductive phase (mechanisms of sensitization) and the effector phase (pathophysiological mechanisms) of food allergic disease.

(i) immune response plus disease models
(ii) Immune response models

(a) adjuvant based models and
(b) adjuvant-free mouse models
One major challenge to this goal is that the normal immune response to antigens encountered via the gastrointestinal tract is a response of active immune tolerance.

Oral exposure results in the generation of food antigen-specific T lymphocytes with regulatory activity that suppress the generation of antigen-specific effector lymphocyte responses, including pro-allergic Th2 responses and IgE production.

- **Transdermal exposure** to food antigens to bypass the innate “oral tolerance: food antigen is repeatedly applied on the clipped skin of mice and then covered with a bandage. After several weeks mice develop robust systemic dose-dependent allergic immune responses as well as systemic anaphylaxis upon oral exposure to the same food.
- **Four oral sensitization mouse models** for rice, shrimp tropomyosin, soybean, and peanut. Single intragastric exposure to a large dose of peanut followed by intraperitoneal challenge to induce disease symptoms such as vascular leakage, hypothermia, decrease in breathing rate, and mast cell release of protease.

**Advantage**: readouts of food allergy are completely food allergen dependent.

**Limitations**: use of parenteral administration to induce disease; and (iii) less robust readouts such as modest IgE responses and clinical scores.
Innate default “oral tolerance” to food antigens can be breached if food antigens are co-administered with mucosal adjuvant such as cholera toxin (CT) or superantigen (SEB).

Pathogenesis of human food allergy may also involve natural co-exposure to food derived toxins such as bacterial enterotoxins.

- Enhanced IgE antibody responses and
- more pronounced tissue damage including systemic anaphylaxis.

**Advantage**: oral route is used to induce sensitization but also for elicitation of allergic reactions.

**Limitations**: (i) it is challenging to evaluate natural response to food proteins alone in the absence of coexposure to adjuvant; (ii) it is difficult to distinguish the effects of food allergen from those of adjuvant effects; and (iii) may give false positive responses.
Are Mechanisms of Sensitization to Foods Similar in Mice and Humans?

- Dose and frequency of food exposure and timing of food exposure required for sensitization in humans is largely unknown and whether early-life exposure to allergenic foods is protective or pathogenic is debated.

- In mouse models, there is clear evidence for dose-response effects for sensitization.

- Many human food allergies start in early infancy and childhood, mouse models have generally used adult mice (more than four weeks age).

- Use of Raw Food Extracts, Purified Proteins, or Recombinant Protein Allergen for Sensitization

- Use of Adjuvant in Mouse Models and Relevance to Human Food Allergies
Induction of specific IgE antibody responses to foods in humans and mouse models.

Most oral food-induced systemic anaphylaxis in humans is mediated by IgE antibody, mast cell, and/or basophil pathway. In mice systemic anaphylaxis may be mediated by IgE or IgG1 antibodies; involvement of mast cells and macrophages has been well demonstrated in basic studies.

Many similarities and differences in clinical presentation of food allergy in humans vs. mice. In most models, clinical reactivity to foods is measured with a scoring scale for systemic anaphylaxis: this method is highly subjective. In mouse models, hives or rashes are not reported. In one case, atopic dermatitis was reported. Vomiting is absent in mice.

Both sexes are afflicted with food allergies in humans, although there are relative differences based on age; among adults, most afflicted are females; among children, most afflicted are males. Most mouse models have used females. In mice, females tend to exhibit more robust IgE antibody responses in general.

In humans genetics plays an important role in food allergy susceptibility. Both HLA and non-HLA genes have been studied. In mice also role of genetics is critical for food allergy. Role of genetics in cholera toxin based peanut and milk allergy was shown to operate at the TH1/TH2 responses with C3H/Hej being susceptible and BALB/c mice being resistant. C3H/HeJ mice are susceptible to oral challenge, whereas Balb/c mice and C57BL/6 mice, although they can be readily sensitized to antigens, require systemic allergen challenge to elicit systemic anaphylaxis.
Dietary Fiber and Bacterial SCFA Enhance Oral Tolerance and Protect against Food Allergy through Diverse Cellular Pathways

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Roles of dietary fiber and vitamin A in mouse model of allergy

- Alterations in gut microflora composition have been suggested as an alternative explanation for increased allergy incidence.

- The gut microbiota promotes epithelial integrity and regulatory T (Treg) cells, both critical for mucosal homeostasis.

- Consumption of dietary fiber, appears to be a critical determinant for gut bacterial ecology, diversity, and function

- Dietary-fiber-derived metabolites, short-chain fatty acids (SCFAs), have been implicated in gut homeostasis and Treg cell biology.

- Western diets, typically high in fat but also low in fiber, may therefore be associated with changes in gut bacterial ecology, epithelial integrity, and Treg cell development, and this may compromise oral tolerance and allow for the development of food allergies
HF Feeding Enhances oral tolerance via CD103+ DCs Activity

CD103-expressing dendritic cells (DCs) (CD103+ DCs) are present at high frequency in the small intestine and migrate to the mesenteric lymph node (MLN) to initiate oral tolerance.

Mucosal CD103+ DCs are described as master regulators of immune tolerance through their capacity to promote the differentiation of naive T cells into Treg cells in the MLN.
Tolerogenic genes Aldh1a2

CD103+ DCs express the enzyme retinaldehyde dehydrogenase-2 (RALDH2) (encoded by Aldh1a2) which converts vitamin A to retinoic acid. This promotes the differentiation of naive T cells into Treg cells and imprints the gut homing receptor CCR9 on them.

Alteration of RALDH activity is associated with impaired oral tolerance

CD103+ DC analyzed from the MLN of HF-fed mice exhibited greater enzymatic RALDH activity compared to ZF-fed mice as determined by ALDEFLUOR assay.

flow cytometry plot of ALDEFLUOR expression in CD103+ DCs in the MLN and corresponding graph between ZF- and HF-fed mice as determined by ALDEFLUOR assay kit
Study of the tolerogenic properties of CD103+ DCs in HF-fed mice by Treg conversion assay

CD103+ DCs from mice fed on a ZF or HF diet were sorted and co-cultured with CD4+ CD25 CD62L+ naive T cells derived from OT-II mice in the presence of ovalbumin (OVA) peptide.

OT-II mice express the mouse α-chain and β-chain T cell receptor that pairs with the CD4 co-receptor and is specific for chicken ovalbumin peptide. This results in CD4+ T cells that primarily recognize ovalbumin peptide residues when presented by the MHC class II molecule.
In vitro, HF diet feeding enhances the tolerogenic activity of CD103+ DCs, which is dependent on the retinoic acid signaling pathway.

CD103+ DCs derived from HF-diet-fed mice were more potent in converting naive T cells to FoxP3+ Treg cells, as well as inducing greater expression of the gut homing receptor CCR9, and these phenotypes were abrogated in the presence of retinoic acid receptor (RAR) signaling inhibitor LE540.
Antigen-specific tolerogenic phenotype in vivo

Carboxyfluorescein succinimidyl ester (CFSE)-labeled OT-II CD4+ T cells were adoptively transferred into mice fed on either a ZF or HF diet and then orally challenged them with OVA. T cell proliferation was analyzed by flow cytometry 72 hr later.

CFSE- OT-II CD4+ cells isolated from HF-challenged mice proliferated significantly less compared to ZF-fed mice.

This decreased proliferation was associated with an increased proportion of antigen-specific Treg cells in the MLN.
HF Feeding Enhances Oral Tolerance

ZF- or HF-diet-fed mice were subjected to a model of oral tolerance involving multiple challenges with peanut extract to examine whether the effects of dietary fiber on CD103+ DC activity and their capacity to induce Treg cells could enhance tolerance in vivo.

HF-diet-fed mice contained a greater proportion of CD103+ DCs in the MLN, as well as an increased proportion of Treg cells that expressed higher levels of CCR9.
HF diet Protects against Food Allergy

Mice were subjected to an established model of peanut allergy. Mice fed on HF diet showed significantly reduced clinical symptoms of anaphylaxis, which correlated with lower levels of serum IgE, higher CD103+ and Treg and lower total cells in MLN.
Treg cells are necessary for protection against food allergy:
Treg depletion by anti-CD25 in HF mice

Low fiber diet impairs epithelial homeostasis and promote Th2 skewing

qPCR analysis of small intestinal jejunum revealed that ZF-fed mice exhibited greater gene expression of pro-inflammatory cytokines Tslp and Il33 compared to HF-diet-fed mice

Gut epithelial permeability is increased under ZF-fed conditions

Greater infiltration of bacteria to the MLN in ZF-diet-fed mice

No morphological changes in the small intestine in CT-induced inflammation
HF-Mediated Protection against Food Allergy Relies on Vitamin A Metabolism

RALDH activity is dependent on the availability of vitamin A, and thus determines the tolerogenic capability of CD103+ DCs.

To test if the tolerogenic effects of HF feeding relied on vitamin A, mice were placed on either a control (AIN93G) or vitamin-A-deficient diet (VAD) for 12 weeks and then switched to a HF diet or a vitamin-A-deficient HF diet (VAD-HF), respectively, for 2 weeks prior to experimentations.

- Mice fed on a VAD-HF diet (and also control and VAD diet) showed exacerbated clinical symptoms of anaphylaxis as well as increased, but not significant, total serum IgE levels.

- VAD-HF fed mice showed a reduced proportion of CD103+ DCs when compared to HF-fed mice.

- VAD-HF and HF had similarly greater proportions of Treg cells than mice fed on a control or VAD diet, suggesting a proportion of Treg cell induction by HF occurred independently of CD103+ DCs. Despite similar numbers of MLN Treg cells in VAD-HF- and HF-fed groups, total cell numbers were significantly decreased in MLN of HF-fed mice.

- In vivo proliferation assay utilizing OT-II T cells to determine whether the Treg cells were functional in VAD-HF mice. Adoptively transferred CD4+ T cells from OT-II mice proliferated significantly more in VAD-HF compared to HF diet feeding, suggesting that Treg cells from VAD-HF-fed mice might be defective.
Microbiota composition in HF fed mice

Analysis of microbiota composition of mice indicated that bacterial composition was largely dependent on the dietary fiber content rather than on vitamin A.

Fecal microbiota composition was analyzed by 16S rRNA metagenomic sequencing from feces of mice fed on either a control (AIN93G), VAD, HF, VAD-HF, or ZF diet.

Relative abundance of bacteria is presented at the family level (left), and comparison of microbial community diversity is presented as unweighted PCoA plots (right).
HF Feeding Promotes IgA Responses

• The increase of IgA-coated bacteria represents an effort by the host immune system to exclude unfavorable bacteria.

• ZF fed mice showed a greater percentage of IgA-coated bacteria in feces isolated from ZF compared to HF-fed mice, suggesting the occurrence of dysbiosis in ZF-fed mice.

• In accordance with beneficial effects of HF diet feeding on gut homeostasis, mice fed on a HF diet had greater levels of serum IgA compared to ZF-fed mice.
Increased IgA in HF-fed mice was associated with a significantly higher proportion of TFH cells, as defined by CXCR5 and PD-1 expression on CD4+ FoxP3 cells compared to ZF-diet-fed mice.

Mice fed on a HF diet had a greater germinal center response, with a greater proportion of B220+GL7+CD95+ germinal center B cells in the Peyer's patches (PPs).

Germinal center reactions are required for generating IgA+ plasmablasts, which mature into IgA-producing plasma cells that migrate to the small intestinal lamina propria. Increased germinal center reactions in HF-fed mice resulted in a significantly higher proportion of IgA+B220 IgA-producing plasma cells compared to ZF-fed mice.
Are changes to microbiota composition due to HF diet feeding responsible for the increase in IgA production?

Inoculation of germ-free mice with microbiota from ZF- versus HF-diet-fed mice

IgA levels in offspring, inheriting mother’s microbiota at birth, in mothers either fed on ZF or HF diets

(G) Germ-free mice were inoculated with fecal suspension from mice fed a ZF or HF diet, and total serum IgA was tracked for a total of 4 weeks determined by ELISA.

(H) Pregnant mother was fed on either a control or HF diet at estrous cycle 13 (E13), and serum IgA was measured in vaginally born offspring by ELISA.
Gut Microbiota Composition Protects against Food Allergy

Allergic reaction was studied in reconstituted germ-free mice with either a ZF or HFM diet. HFM mice had significantly better clinical anaphylaxis scores, a trend of decreases in total serum IgE levels and a greater proportion of Treg cells compared to ZFM mice.

However, no differences in proportion of CD103+ DCs or total cell numbers in the MLN were observed under allergic condition, suggesting that changes to microbiota were not fully capable of replicating the full effects of HF diet feeding.

feces from recipient mice 4 weeks post-reconstitution
SCFAs directly mediates the beneficial effects of fiber in food allergy model

- Dietary fiber is fermented by the gut microbiota into Short chain fatty acid SCFAs
- SCFA supplement in water reduced the allergic response in mice
- Direct signaling of bacterial products in the host via the adaptor protein MYD88 is required to have HF-dependent protection against food allergy by the gut microbiota
GPR43 and GPR109a Are Required for Dietary-Fiber-Mediated Protection against Food Allergy

SCFAs bind metabolite-sensing G-protein coupled receptors (GPCRs) GPR43, GPR109A, and GPR41 with varying affinities. These GPCRs are expressed on epithelial cells as well as immune cells.

A

B

C
GPR43 and GPR109a are required for epithelial integrity

- Expression of GPR43 on intestinal cells rather than on immune cells was important for HF-mediated protection against food allergy.

- Bone-marrow chimera experiments showed that GPR109A expression on immune cells was much more important for HF-mediated protection against food allergy than expression on non-immune cells.

- Deficiency in either GPR43 or GPR109A altered microbiota composition greatly.
Conclusion

Highlights

- Dietary fiber with vitamin A increases the potency of tolerogenic CD103+ DCs
- High-fiber diet protects mice against peanut allergy via gut microbiota and SCFA
- High-fiber effects rely on epithelial GPR43 and immune cell GPR109a
- Dietary fiber promotes TFH and IgA responses
Anti-hIgE gene therapy of peanut-induced anaphylaxis in a humanized murine model of peanut allergy

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New York and Ithaca, NY, Sichuan, China, and New Haven, Conn
NGS mice (NOD-scid IL2R gamma null mice) receiving with blood mononuclear cells from donors with peanut allergy and then sensitized with peanut extract

**NGS mice: NOD-scid IL2Rgamma\textsuperscript{null}**
These mice carry two mutations: severe combined immune deficiency (\textit{scid}) and a complete null allele of the IL2 receptor common gamma chain (\textit{IL2rgnull}).
The \textit{scid} mutation is in the DNA repair complex protein \textit{Prkdc} and renders the mice B and T cell deficient.
The \textit{IL2rgnull} mutation prevents cytokine signaling through multiple receptors, leading to a deficiency in functional NK cells.
The severe immunodeficiency allows the mice to be humanized by engraftment of human CD34+ hematopoietic stem cells (HSC), peripheral blood mononuclear cells (PBMC), patient derived xenografts (PDX), or adult stem cells and tissues.

only female mice were used in the allergy experiments
NSG mice reconstituted with human blood mononuclear cells from a donor with peanut (PN) allergy and a control donor

**A** Humanized mouse

Reconstitute mice with PBMC from peanut (PN) allergic or controls.

300 µg gastric gavage

PN extract sensitization 100 µg intraperitoneal

**B** Total human IgG

![Graph showing total human IgG over time after reconstitution](image)

**C** Total human IgE

![Graph showing total human IgE over time](image)

**D** PN-specific IgE

![Graph showing PN-specific IgE over time](image)
Characterization of allergic reaction in NSG mice reconstituted with human blood mononuclear cells from a donor with peanut (PN) allergy

E  Post-PN challenge clinical phenotype
Donor with no PN allergy (wk 5)  Donor with PN allergy (wk 5)

F  Anaphylaxis score (wk 5)

G  Histamine (wk 6)

H  Passive cutaneous anaphylaxis (wk 7.5)
extravasation of blue dye using human serum from a patient with peanut allergy and serum from a subject without peanut allergy
Treatment of peanut (PN) antigen–induced anaphylaxis with omalizumab after sensitization and peanut challenge

A  Free IgE

B  2 wk post-omalizumab

C  2 wk post-omalizumab

Mouse Serum: PBMC donor PN allergy + omalizumab

Mouse Serum: PBMC from non- PN allergic donor
Characterization of AAVrh.10anti-hlgE.

A  AAVrh.10anti-hlgE

Expression cassette

B  In vitro directed expression

C  NOD-scid IL2Rgamma\(^\text{null}\)
Prophylaxis of peanut (PN) antigen–induced anaphylaxis by treatment with AAVrh.10anti-hIgE before sensitization.
Prophylaxis of peanut (PN) antigen–induced anaphylaxis by prior treatment with AAVrh.10anti-hlgE.
Treatment of peanut (PN) antigen–induced anaphylaxis with AAVrh.10-anti-hIgE after mice exhibited peanut-specific allergic symptoms

A. Treatment after peanut (PN) sensitization

1. Reconstitute mice
2. PN extract 300 µg gastric gavage
3. wk 0-10

PN extract sensitization
100 µg intraperitoneal

B. Total human IgE

Time pre-/post-administration (wk)

C. Peanut-specific IgE (wk 4)

D. Free IgE
Treatment with AAVrh.10-anti-hIgE vs omalizumab

A Post-peanut (PN) challenge clinical phenotype

Donor with PN allergy + omalizumab
wk 10 (5 wk after therapy)

Donor with PN allergy + AAVrh.10-anti-hIgE
wk 10 (5 wk after therapy)

B Locomotor activity

Cumulative distance traveled (cm)

AAVrh.10-anti-hIgE vs Omalizumab

p=0.001

C Anaphylaxis score

Anaphylaxis score (1-5)

AAVrh.10-anti-hIgE vs Omalizumab

p=0.0008

p=0.00008

p=0.00003

D Histamine

Plasma histamine level (pg/ml)

AAVrh.10-anti-hIgE vs Omalizumab

p=0.0006

p=0.0003

p=0.001

p=0.0006

E Passive cutaneous anaphylaxis

wk 7 (2 wk after therapy)

wk 10 (5 wk after therapy)

Human serum: PN allergic donor

Human serum: non PN allergic donor

Mouse serum: PBMC donor PN allergy

Mouse serum: PBMC donor PN allergy + AAVrh.10-anti-hIgE

AAVrh.10-anti-hIgE vs Omalizumab

p=0.001

p=0.0001
Mouse survival after treatment with a single administration of AAVrh.10anti-hIgE, single administration of omalizumab alone, or control vector

Immunodeficient mice reconstituted with human mononuclear cells developed features of *graft-versus-host disease* (GVHD) including inflammatory and immune infiltrates of human cells in both the lungs and small intestines with mononuclear cells from both allergic and nonallergic donors.

As a consequence of GVHD, the model was limited to approximately 10 weeks after reconstitution with the human mononuclear cells
Key messages

• A novel humanized murine model of peanut allergy was created by reconstituting NSG mice with mononuclear cells derived from patients with peanut allergy, which reproduces the allergic phenotype at both the molecular and phenotypic levels.
• A single administration of a nonhuman primate serotype rh.10 AAV expressing omalizumab (AAVrh.10anti-hIgE) provides long-term protection from peanut allergen challenge in the mouse with peanut allergy.
• If this strategy can be translated to human subjects, it would represent a paradigm shift for the treatment of patients with clinically significant peanut allergy.
Thank you for the attention!