

# 現代病としてのアレルギー疾患と、その治療法の提案

## Allergic diseases as modern diseases and our proposed formulations for their treatment

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工学研究院 応用化学部門

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森 健

Takeshi MORI

## Self-introduction

森 健 (MORI Takeshi) 50

**Major :** Chemistry for Medicine

**Publication :** > 200 (**h-index :** 35)

**1974:** Born in Isahaya, Nagasaki Prefecture (eldest of three siblings)

**1993:** Graduated from Nagasaki Prefectural Isahaya High School

**2001:** Completed doctoral course at Kyushu University Graduate School of Engineering

**2001:** Assistant at Tokushima University, Department of Applied Chemistry and Engineering

**2005:** Assistant Professor at Kyushu University, Department of Applied Chemistry

**2013:** Associate Professor

**2008-2009:** Visiting Researcher at Duke University, Department of Biomedical Engineering

**2025:** Professor

**Family :** Wife, son (20), daughter (12)

**Motto :** 大器晩成 Late bloomers (子供や孫に誇れる仕事をする)

**Hobby :** Mountain climbing, rock music



30 year  
→



2023/7/17@八ヶ岳

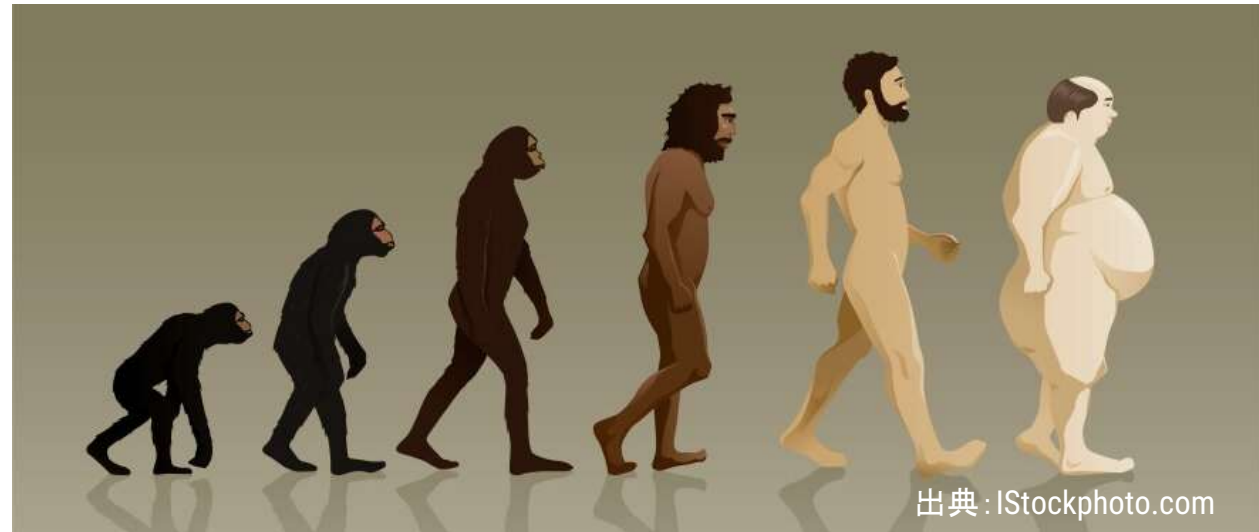
# My research philosophy

## Chemistry



X

## Evolutionary medicine



分子の目、定量性、分子運動性  
Molecular perspective, quantitative

なぜ淘汰圧を生き抜くことができたヒトが  
いまだに病気になるのか？  
Why do humans who have survived the  
selective pressure still get sick?

**30年後に役立つ治療法や診断法を提案する**

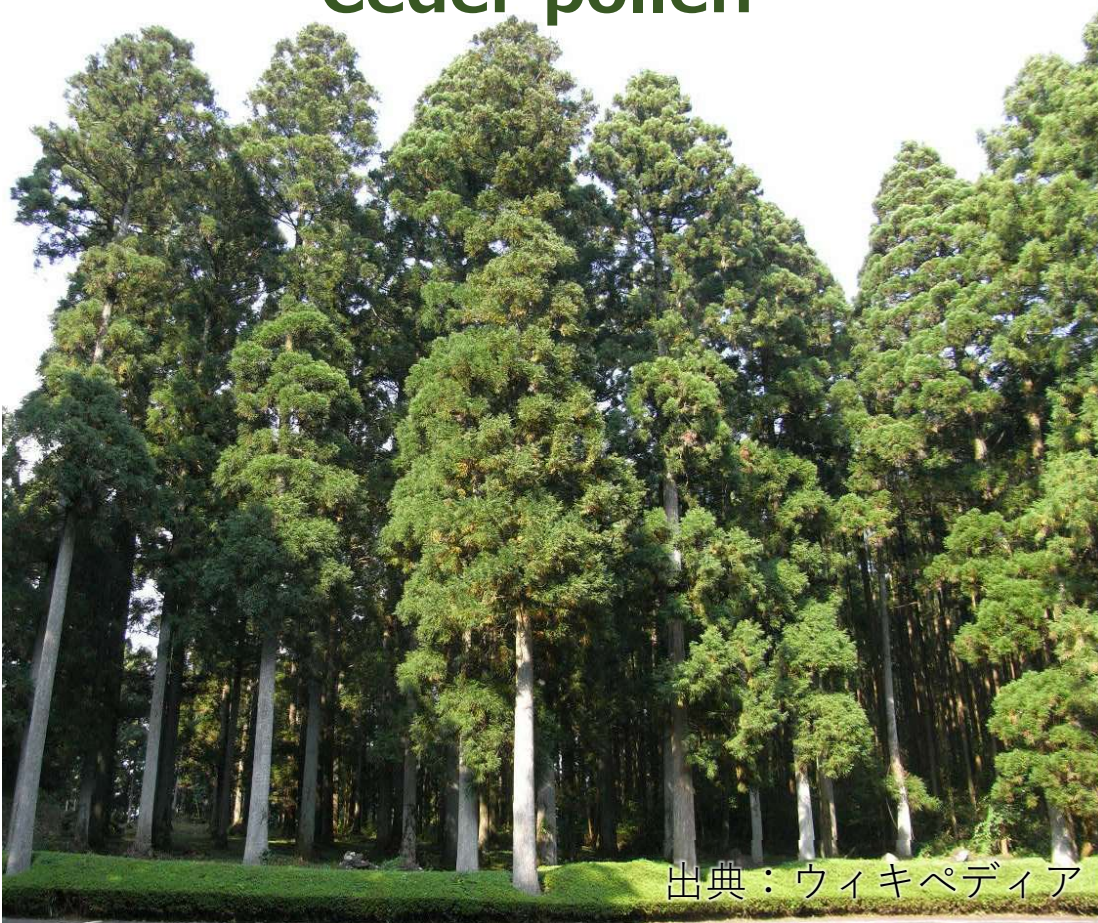
Proposing treatments and diagnostic methods that will be useful 30 years from now

# 国内で患者の多いアレルゲン

Allergens with the highest number of patients in Japan

スギ

Ceder pollen



チリダニ

Houst dust mite



- 布団やじゅうたんをすみかとして、ヒトのアカやフケを餌にする。
- 死骸とフンがアレルゲン
- They live in futons and carpets and feed on human burrs and dandruff.
- Their carcasses and droppings are allergens.

# 花粉症を引き起こす植物 Plants that cause hay fever

共通の性質は？  
What is the common property?



スギ  
ceder

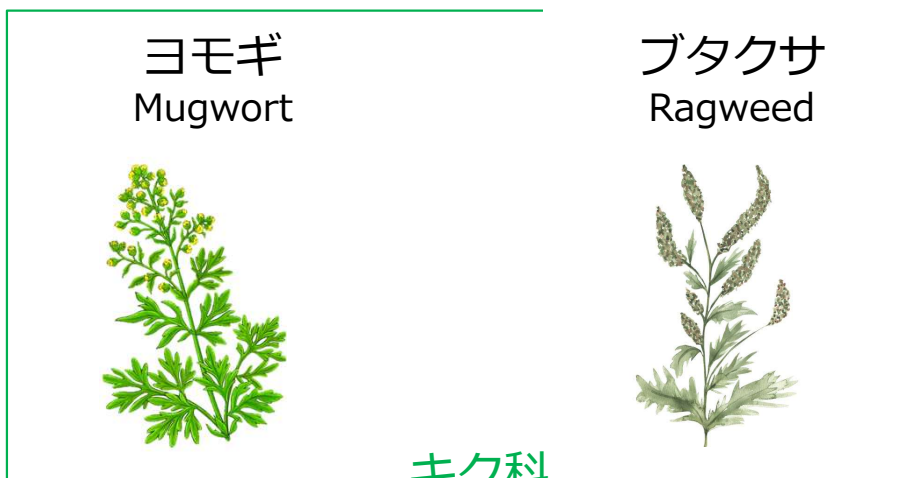
ヒノキ  
Cypress

ヒノキ科  
Cupressaceae



シラカバ  
Birch

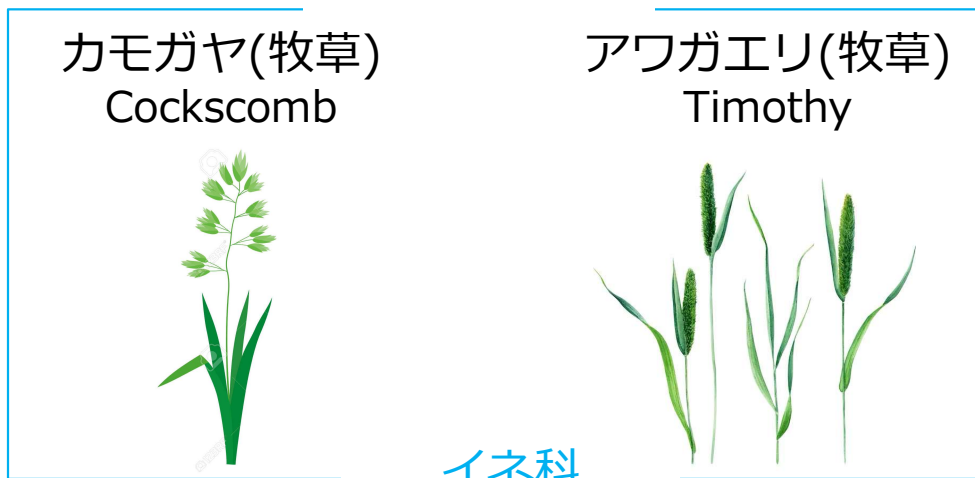
カバノキ科  
Birch family



ヨモギ  
Mugwort

ブタクサ  
Ragweed

キク科  
Asteraceae



カモガヤ(牧草)  
Cockscomb

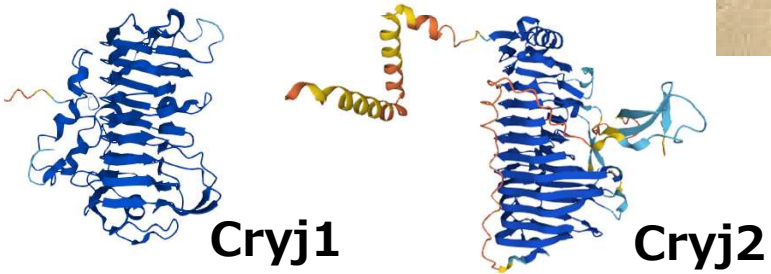
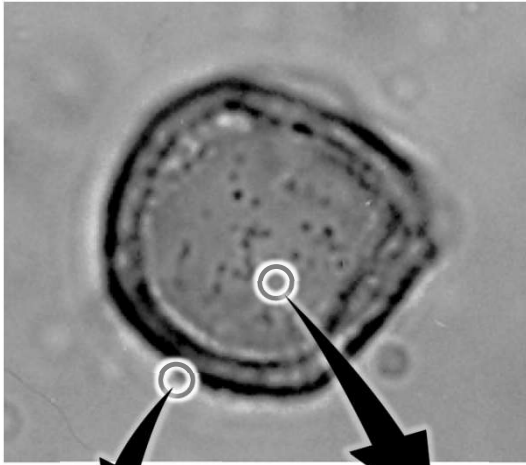
アワガエリ(牧草)  
Timothy

イネ科  
Grass family

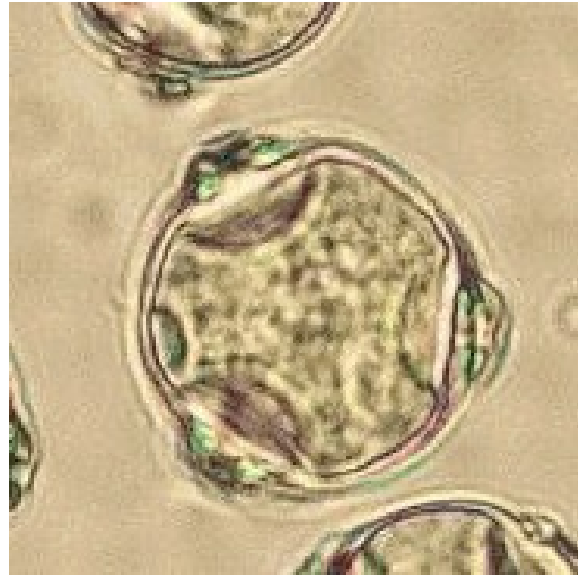
# アレルギーの原因 = 微粒子 (10-30 $\mu\text{m}$ )

Allergy Causes = Fine Particles (10-30  $\mu\text{m}$ )

スギ花粉  
Cyder pollen  
( $\sim 30 \mu\text{m}$ )



シラカバ花粉  
Birch pollen  
( $\sim 30 \mu\text{m}$ )

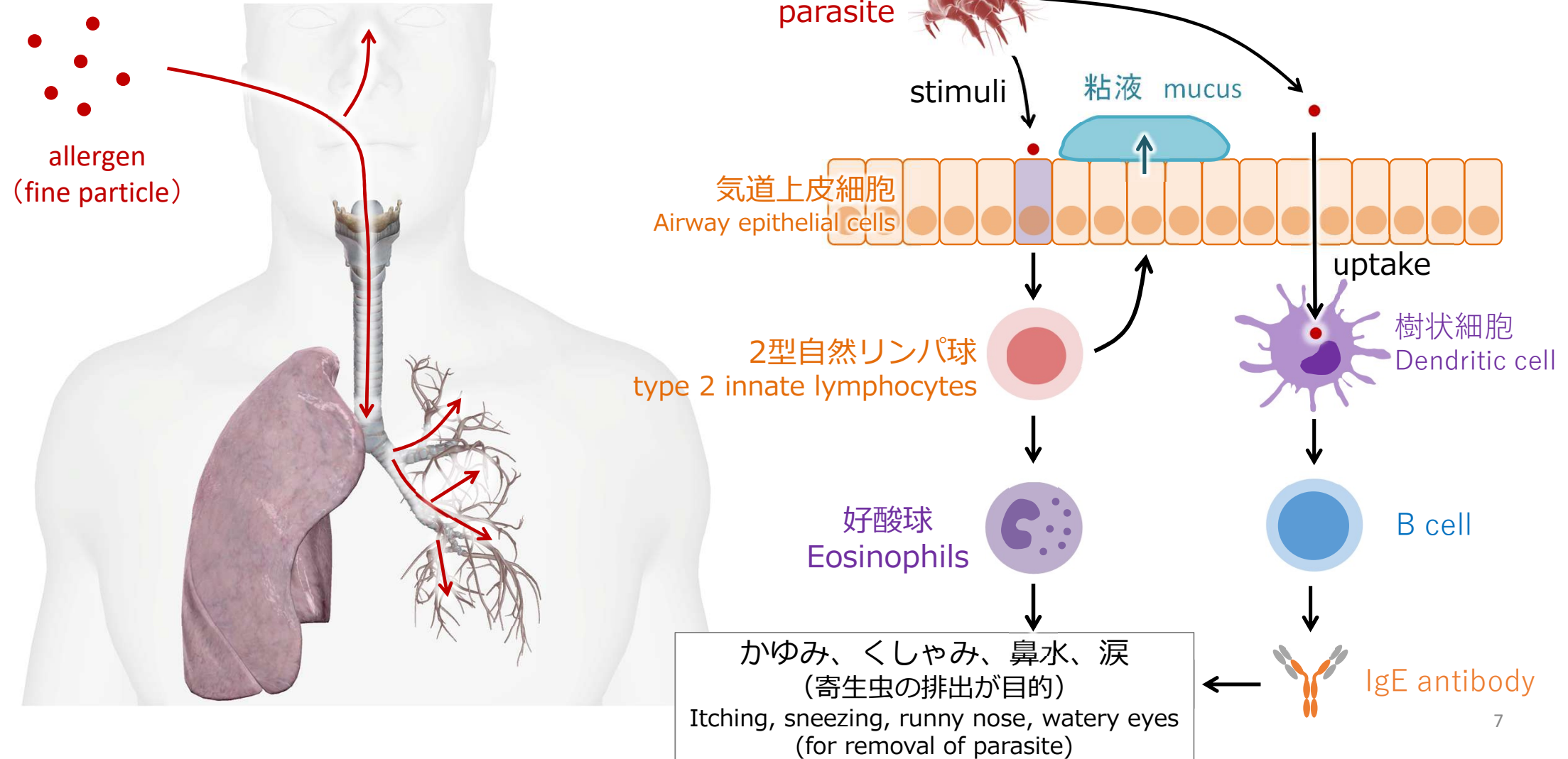


チリダニのフン  
Dust mite droppings  
( $\sim 10 \mu\text{m}$ )



# アレルギー発症のメカニズム

## Mechanism of allergy development



# 寄生虫：アレルギー反応の本来の標的

## Parasites: the natural target of allergic reactions



ダニ, Tick  
(1 mm)



シラミ, Lice  
(2 mm)



ノミ, Flea  
(2 mm)



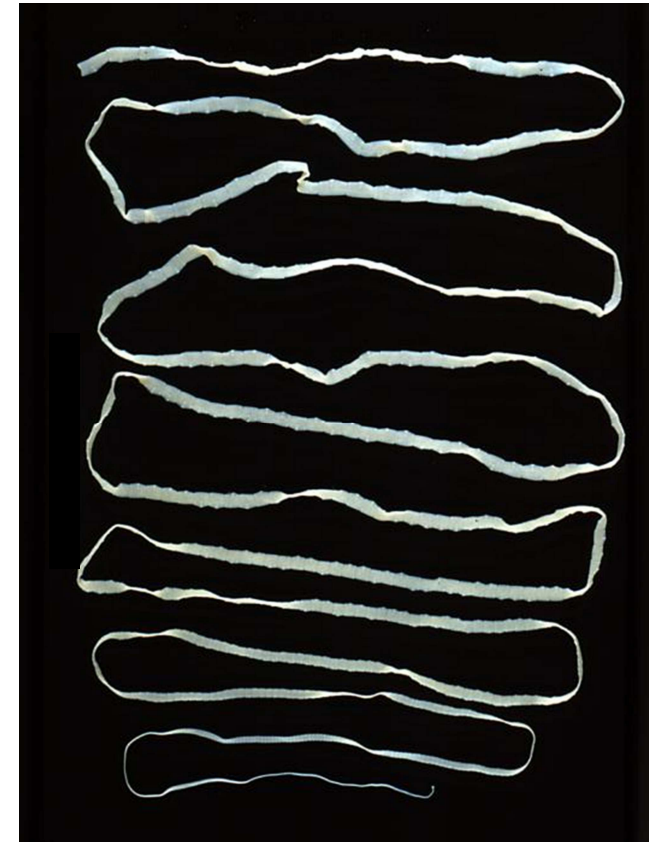
鞭虫  
Whipworm  
(4-7 cm)



十二指腸虫(鉤虫)  
Hookworm  
(4-5 cm)



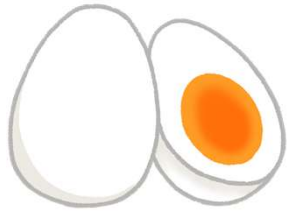
回虫  
Roundworm  
(20 cm)



サナダムシ  
Tapeworm  
(10 m)

# アレルギーを引き起こす食物 Foods that cause allergies

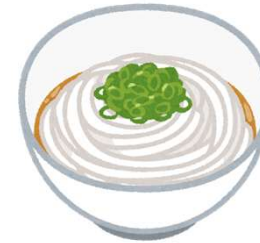
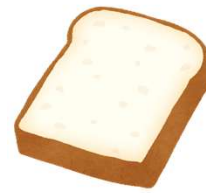
共通の性質は？  
What is the common property?



Egg



Milk



Wheat



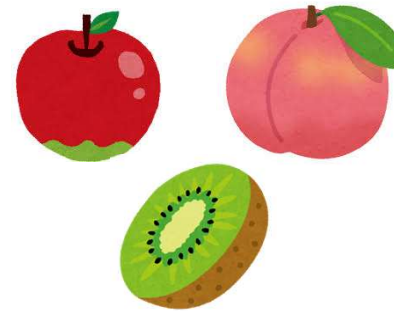
Peanut



甲殻類  
(Shrimp, crab)



そば  
buckwheat



Fruits  
(リンゴ、モモ、キウイ)

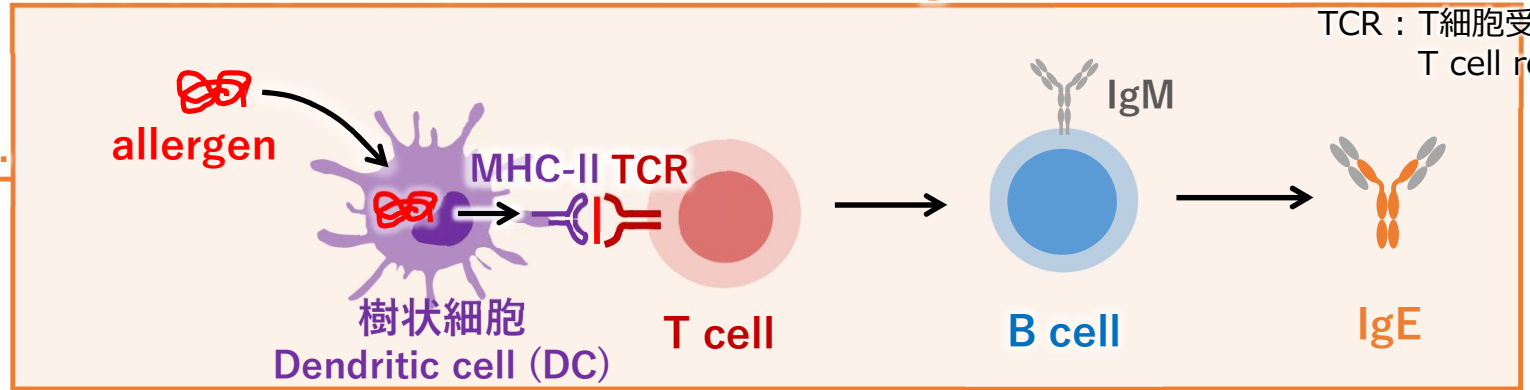


Nuts  
(くるみなど)

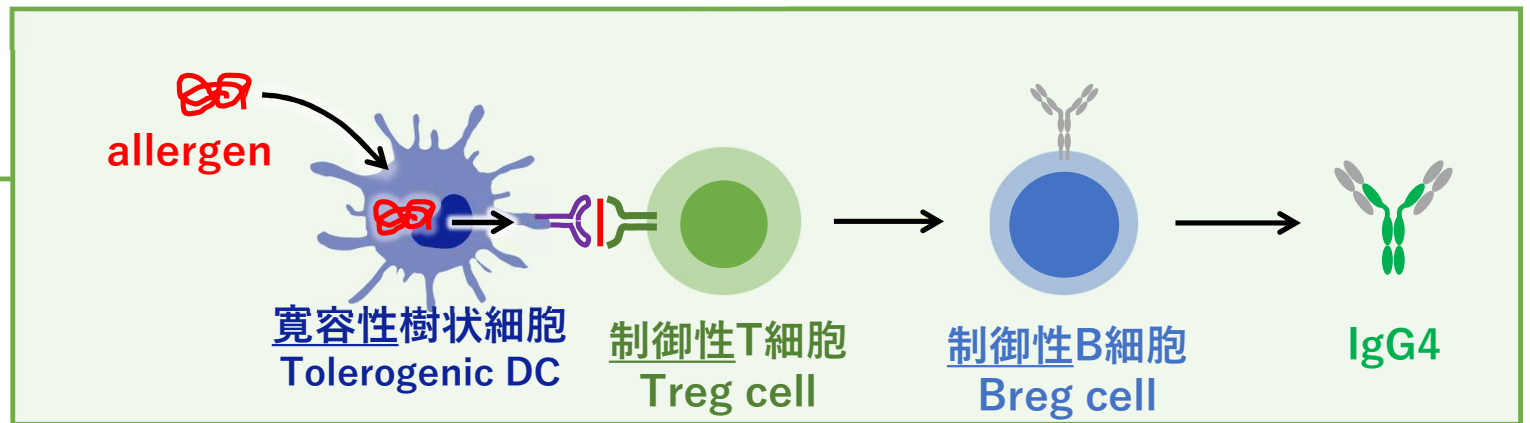
# 食物アレルギーへの感作は皮膚から起こる

## Sensitization to food allergens begins through the skin

### 食物アレルギーの発症 Onset of food allergies

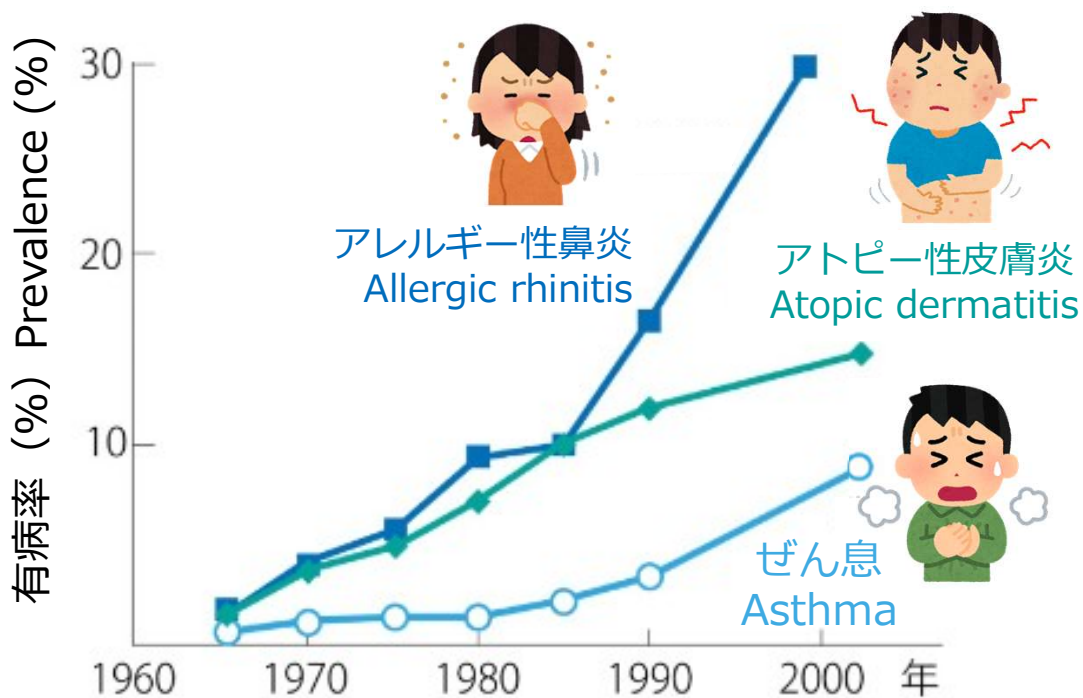


### 経口免疫療法 Oral immunotherapy



# アレルギーの現状 Current status of allergies

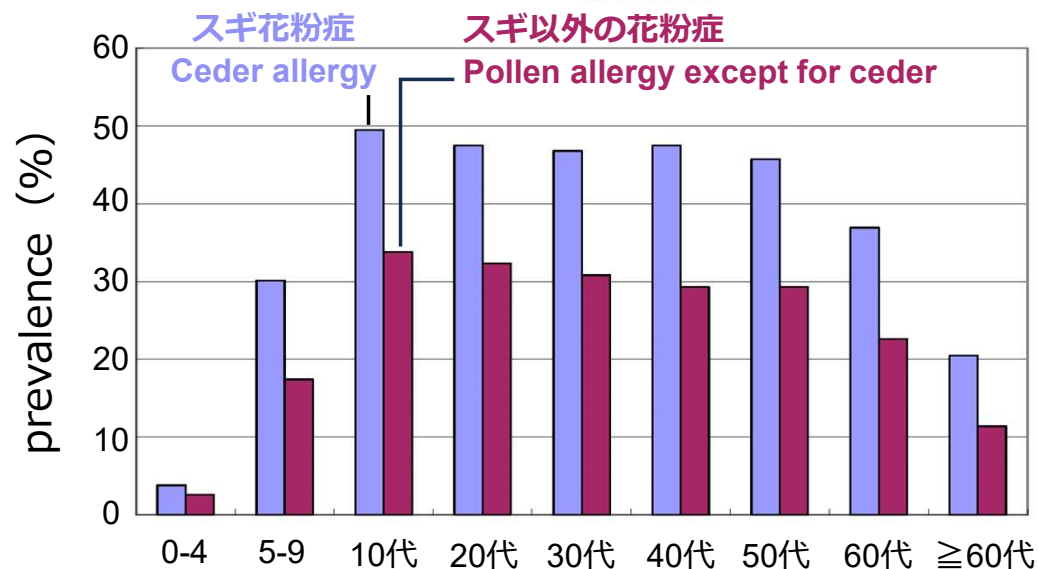
## 日本のアレルギー有病率 Prevalence of allergies in Japan



出典：日本健康増進支援機構

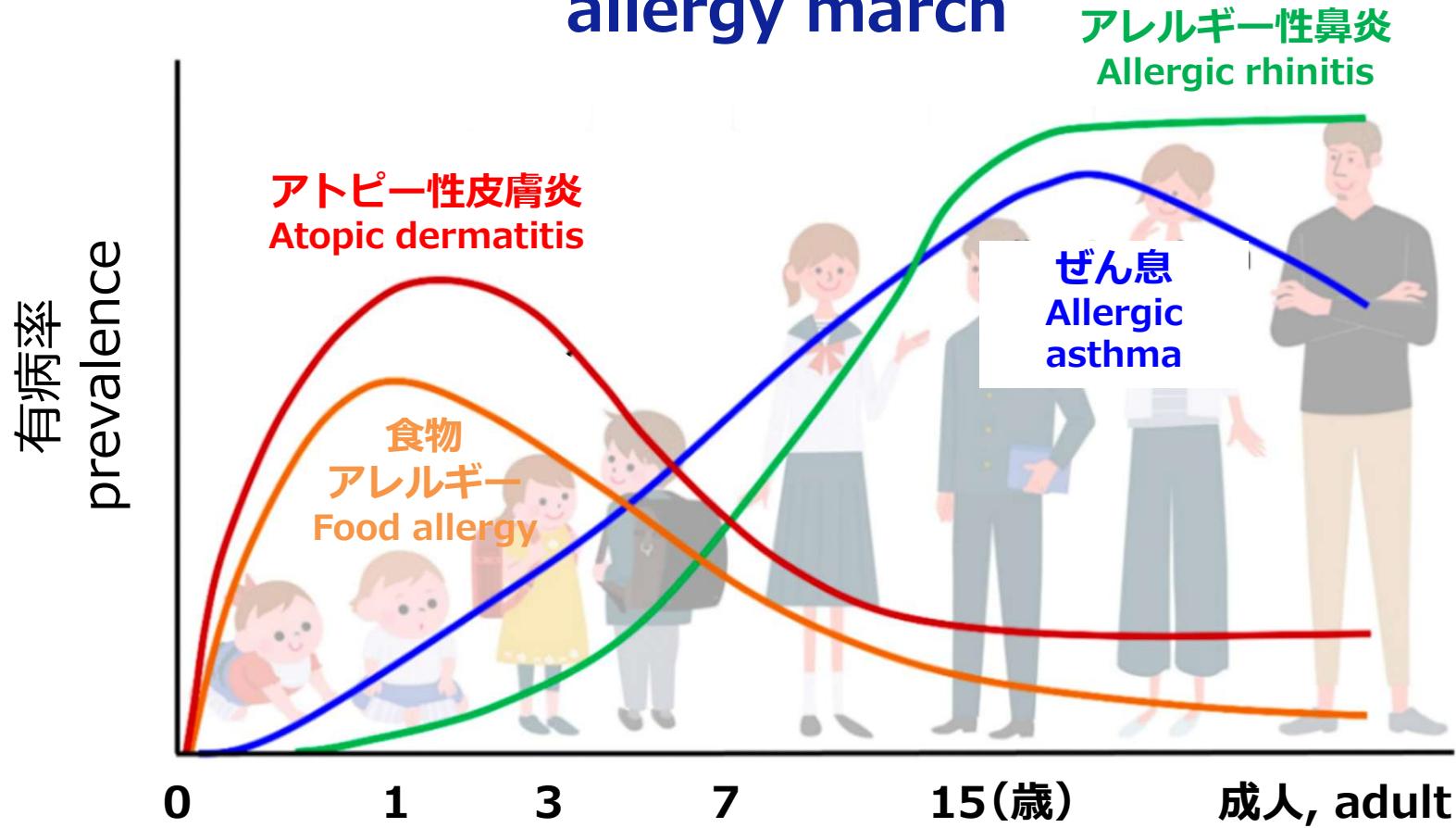
## スギ花粉症, cedar pollen allergy

- 全国民の**39%**が罹患 2019年時
- 労働生産性の低下等による経済損失：  
**2,200億円(1日あたり)**
- 39% of the population is affected.
- Economic losses due to reduced labor productivity, etc.: **220 billion yen (per day)**



出典：松原篤 他 日本耳鼻咽喉科学会会報 1 2 3 - 4 8 7

# アレルギー・マーチ allergy march



一旦アレルギーに罹患して「アレルギー体質」になると、その後、他のアレルギーに罹患しやすくなる。  
Once you have suffered from an allergy and become "allergic," you become more susceptible to other allergies.

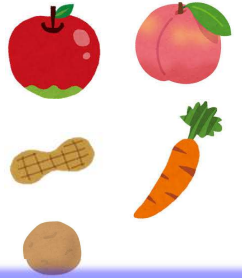
# 花粉症が引き起こす食物アレルギー (PFAS)

## Pollen allergy-related food allergies (PFAS)



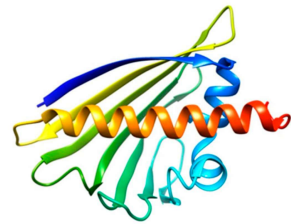
- 口内のかゆみ
- 鼻、目、皮膚の症状
- Itchy mouth
- nose, eyes and skin symptoms

花粉, pollen	食物, food
シラカバ Birch (カバノキ科)	Apple, peach (バラ科) Soybean, peanut (マメ科) carrot (セリ科) potato (ナス科)

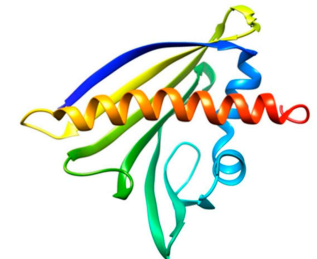
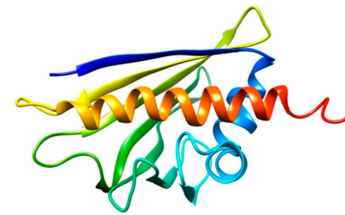


### アレルゲンの構造の類似

#### Similarities in the structure of allergens



類似



シラカバ Birch  
(Bet v 1)

りんご Apple  
(Mal d 1)

ピーナッツ peanut  
(Ara h 8)

# ライフスタイルの変化 Lifestyle changes

1960年代まで  
Until the 1960s



- 大家族(家畜の飼育)
- 便への暴露
- 回虫の寄生
- 腸内細菌叢の変動
- 抗生物質の不使用
- Large family (raising livestock)
- Exposure to feces
- Infestation with roundworms
- Changes in the intestinal flora
- No use of antibiotics

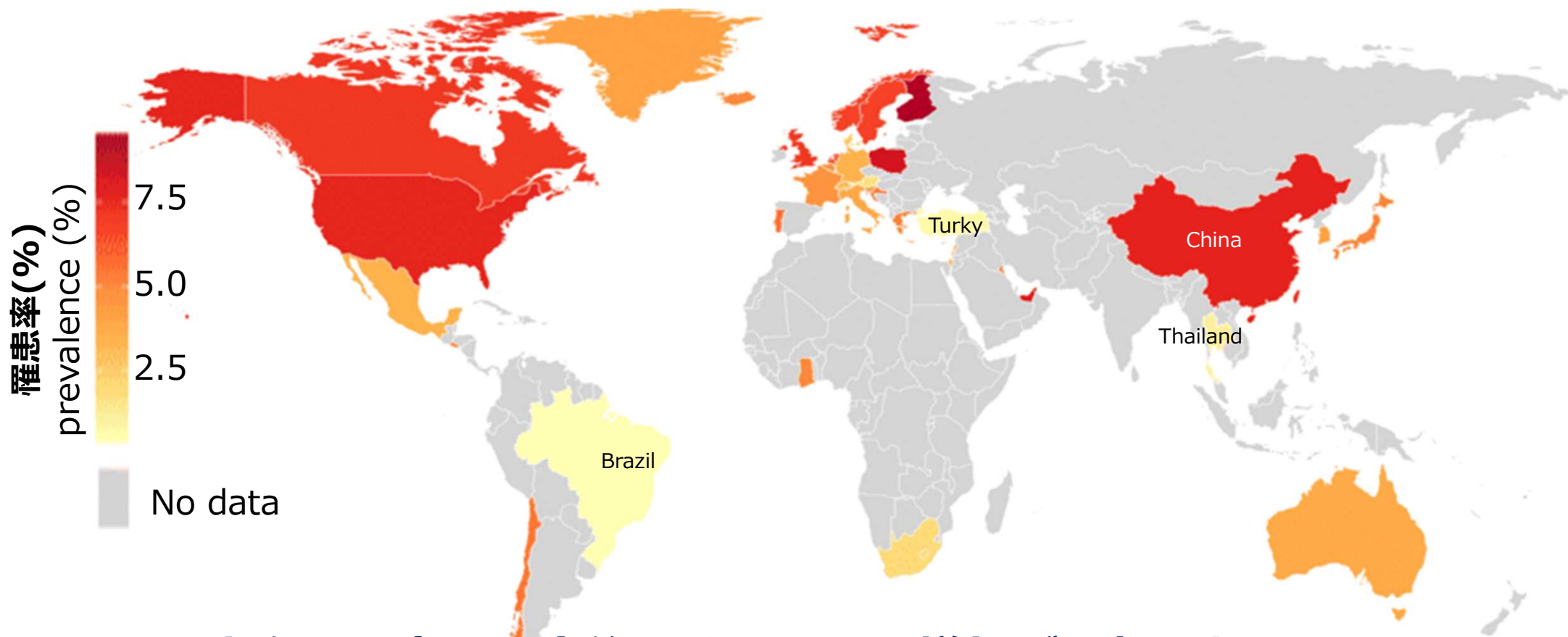
現在  
present



- 核家族
- 便への暴露低下
- 回虫の寄生低下
- 腸内細菌叢の安定化
- 抗生物質の使用
- 外出しない(コロナ、スマホ、異常な暑さ)
- Nuclear family
- Reduced exposure to feces
- Reduced infestation with roundworms
- Stabilization of intestinal flora
- Use of antibiotics
- Not going out (COVID, smartphones, extreme heat)

# 世界のアレルギー罹患率 例：小児の食物アレルギー(2018年)

Global prevalence of allergies Example: Food allergies in children (2018)



**先進国で高い。今後、途上国でも増加が予想される。**

It is high in developed countries, and is expected to increase in developing countries in the future.

# アレルギー免疫療法 Allergen immunotherapy

アレルギーを投与して免疫寛容を誘導する**唯一の根治療法**

The **only definitive treatment** is to administer allergens and induce immune tolerance

## 皮下製剤

Subcutaneous formulation



- シーズン前に月1回投与
- 医師が投与
- Administered once a month before the season
- Administered by a doctor



液剤 liquid

## 舌下製剤

Sublingual formulation



- 毎日投与
- 患者自身が投与
- Administered daily
- Administered by patient



液剤 liquid

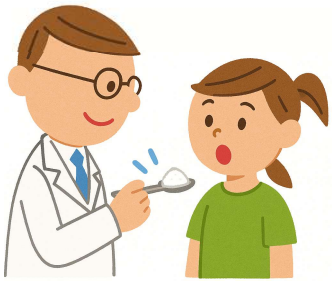


錠剤 tablet

# 食物アレルギーの治療：経口免疫療法

## Treating food allergies: oral immunotherapy

経口投与  
oral admin.



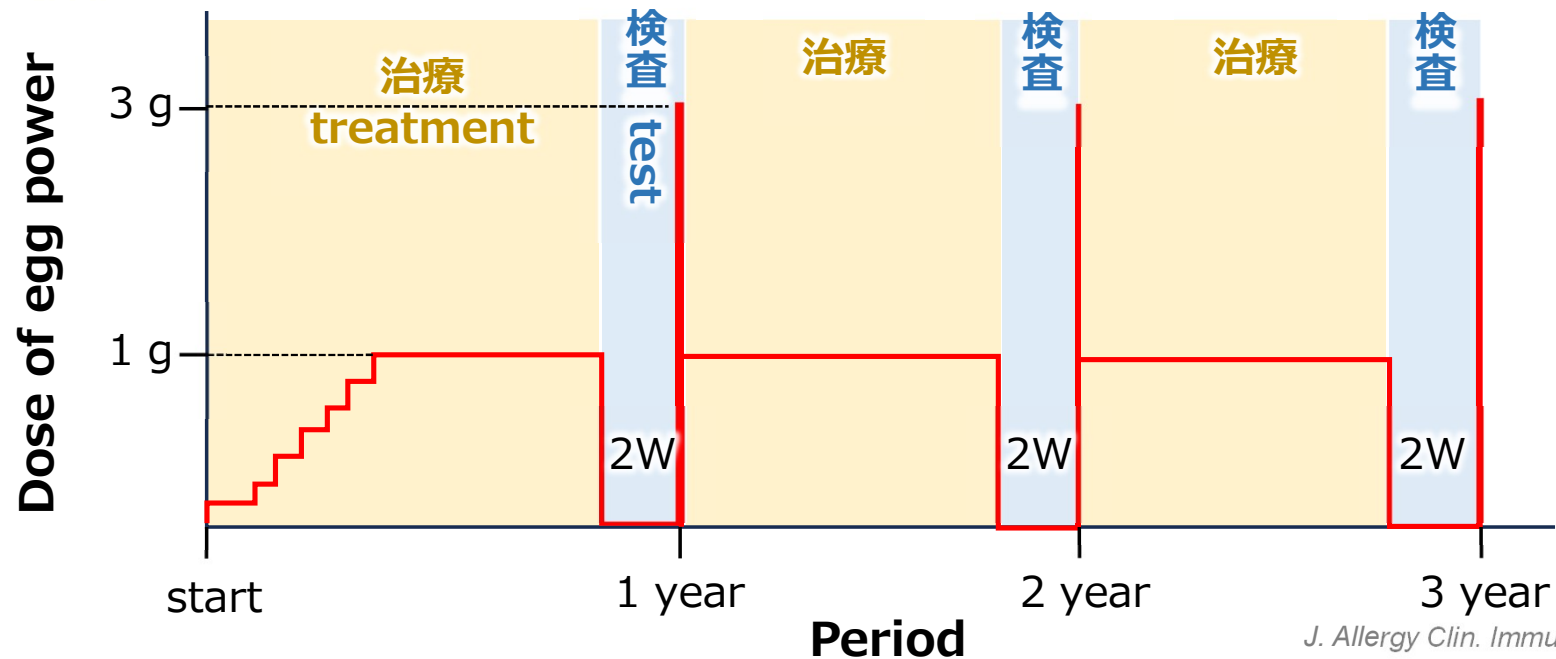
- 毎日投与
- 最初は入院、その後自宅で投与
- Administered daily
- First hospitalized, then administered by patient



Egg powder



Milk powder

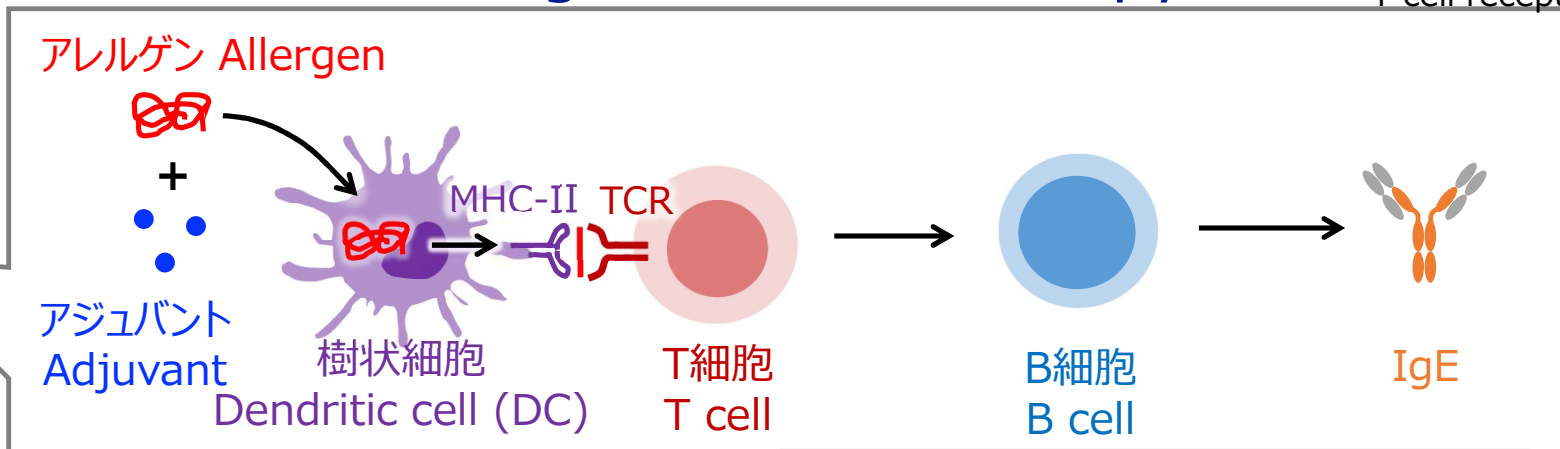


# アレルギー免疫療法の機序

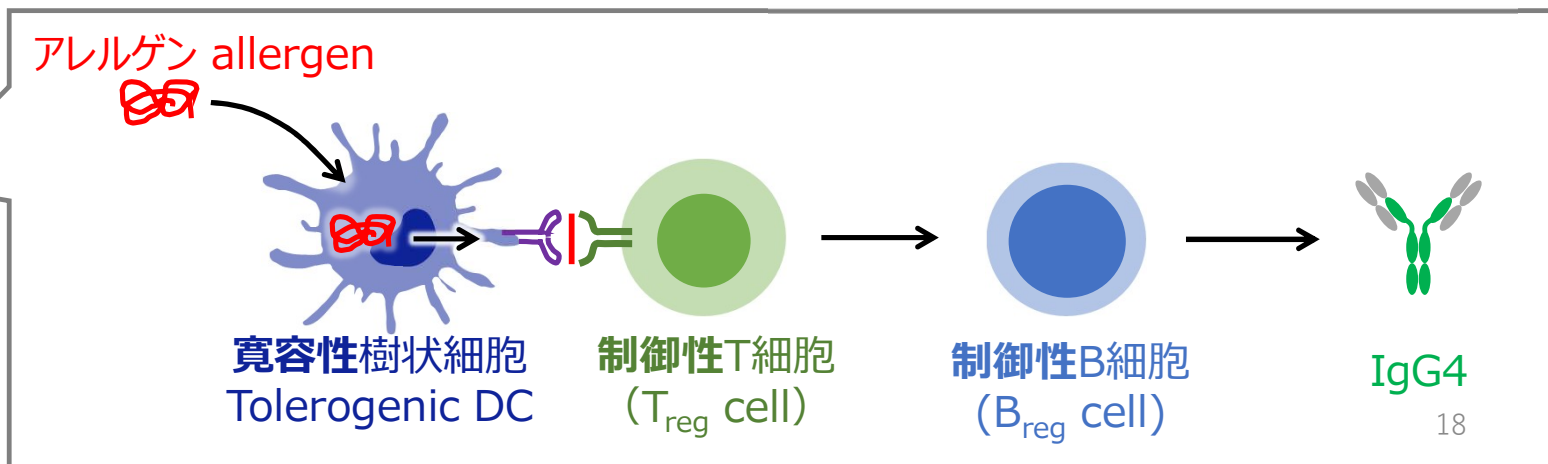
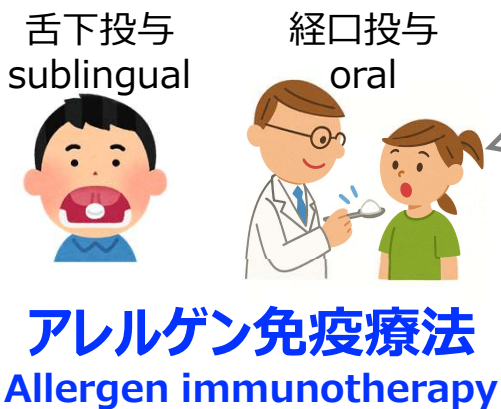
## Mechanism of allergen immunotherapy

| : T細胞エピトープ  
 T cell epitope  
 TCR : T細胞受容体  
 T cell receptor

### アレルギーの発症 Onset of allergies



### 免疫記憶の上書き Overwriting immune memory



# アレルギー免疫療法

## Allergen immunotherapy

### アレルギーの種類 Types of allergens

#### Pollen

Cedar  
Cypress  
Birch  
Alder  
Ragweed  
Mugwort  
Duckweed  
Weed grass  
.  
.  
.

#### Environmental

Dust mites  
Mold and bacteria  
Cat dander  
Dog dander  
Bee venom  
.  
.  
.

#### Food

Eggs  
Milk  
Wheat  
Peanuts  
Tree nuts  
Soybeans  
Sesame  
Buckwheat  
Shellfish  
Fish  
Fruits



**欧米には多数の花粉・環境アレルギー製剤あり**

There are many pollen and environmental allergen preparations available in Europe and the United States

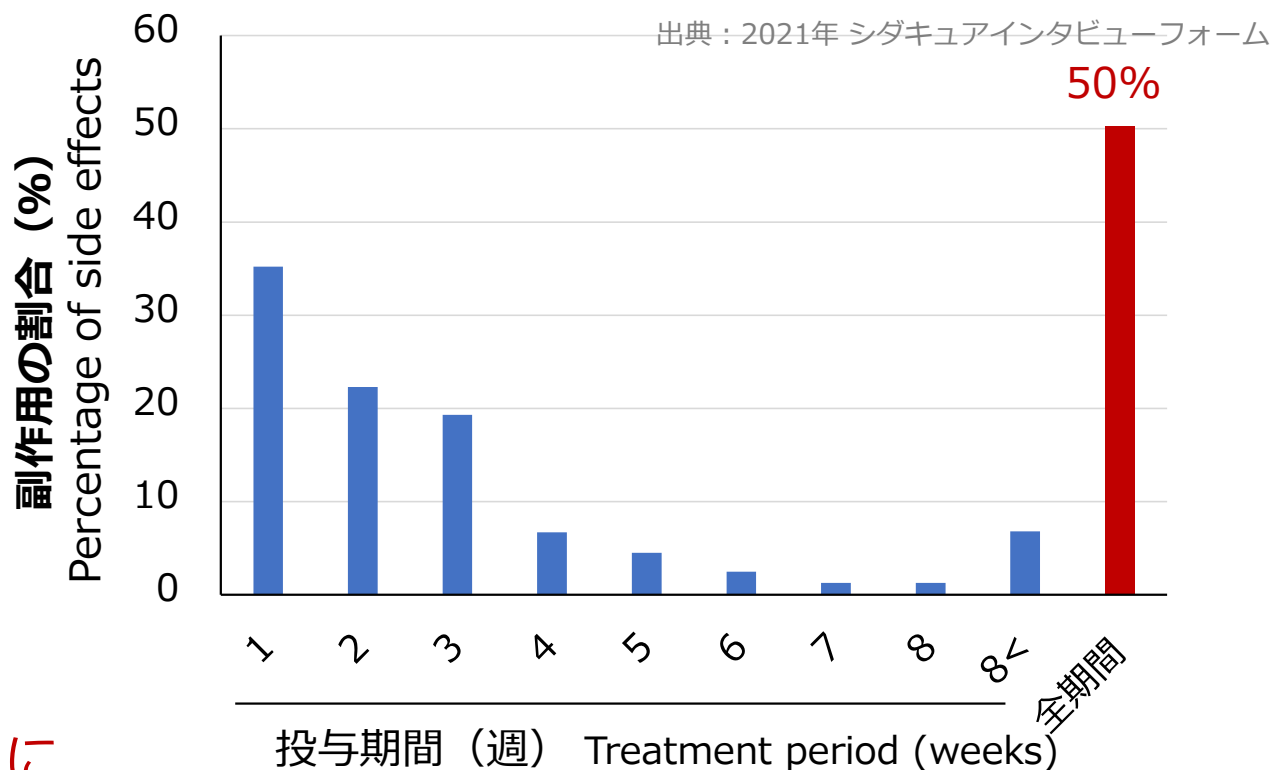
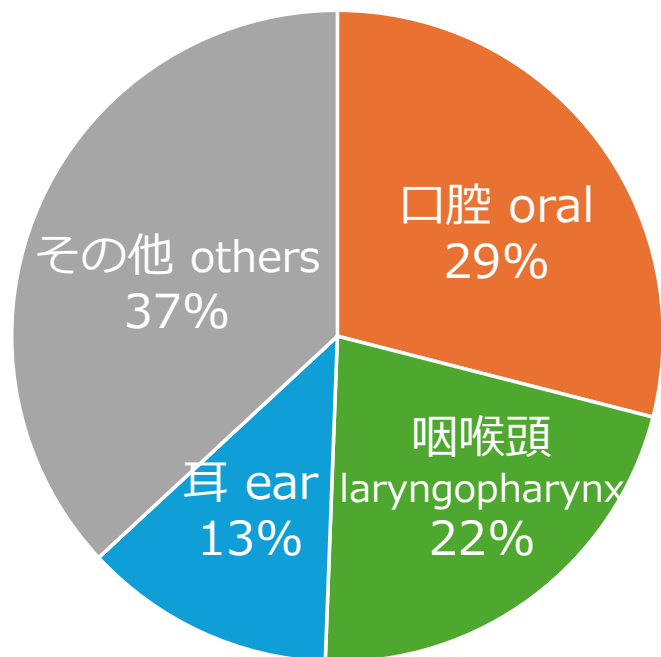
**国内の承認製剤は2種類のみ**

Only two types of drugs are approved in Japan

# アレルギー免疫療法の課題（１）副作用の発症率が高い

## Challenges of allergen immunotherapy (1) High incidence of side effects

スギの舌下薬（シダキュア）の場合 In the case of cedar sublingual medication



副作用の半数以上は口腔と咽喉頭に  
起こる浮腫、掻痒、刺激感

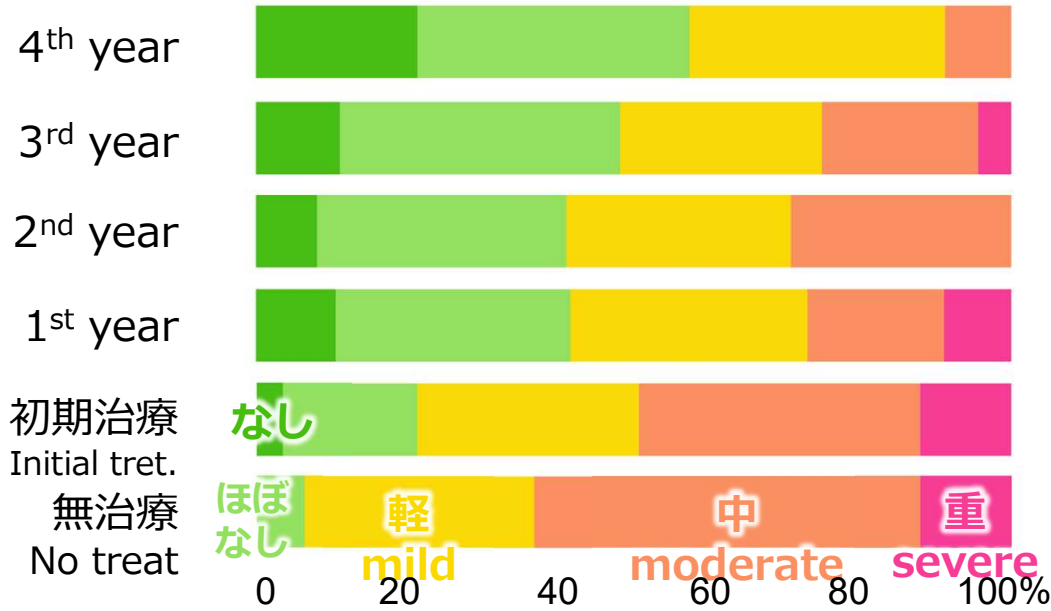
More than half of the side effects were swelling, itching, and irritation in the oral cavity and larynx.

半数の患者で治療の初期(1ヶ月)に  
副作用が起こる。Half of patients experience  
side effects early in treatment (first month).

# アレルギー免疫療法の課題 (2) 治療期間が長く、効果が持続しにくい。

## Challenges with allergen immunotherapy (2) The treatment period is long and the effects are not sustained.

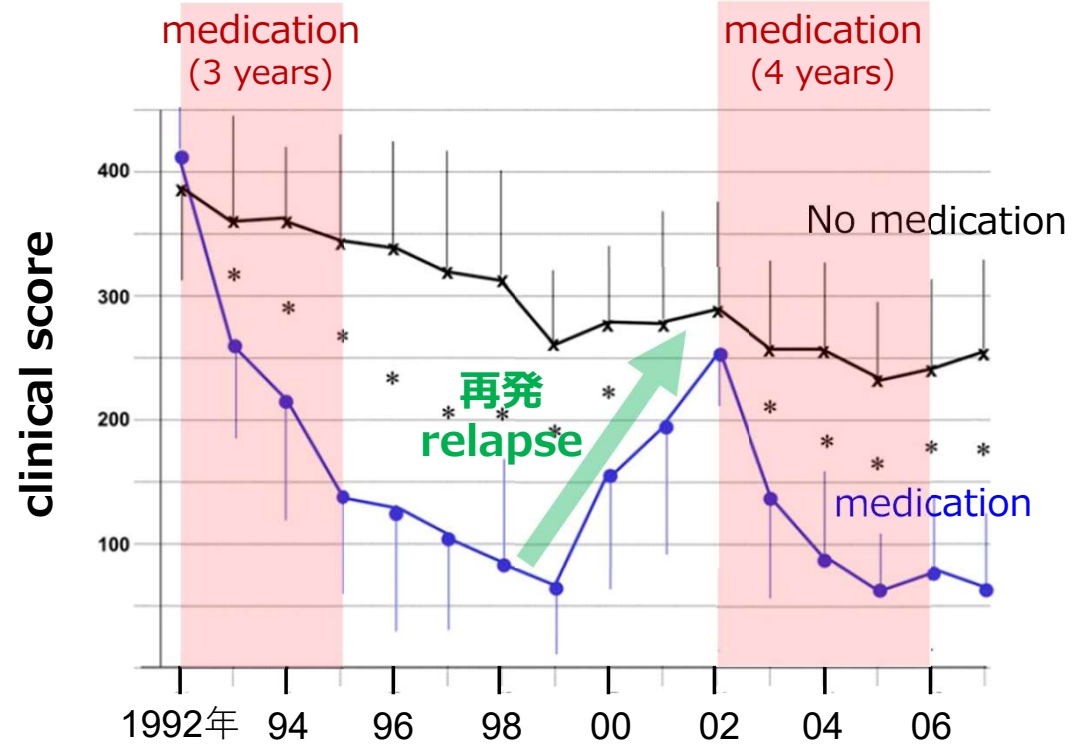
スギの舌下薬 (シダトレン) の場合  
In the case of cedar sublingual medication



**年単位の投薬が必要**  
Yearly medication required

アレルギー 67, 1011 (2018)

ダニの舌下薬の場合  
In the case of sublingual medication for mites



**投薬を休止すると再発する**

Relapse occurs when medication is discontinued

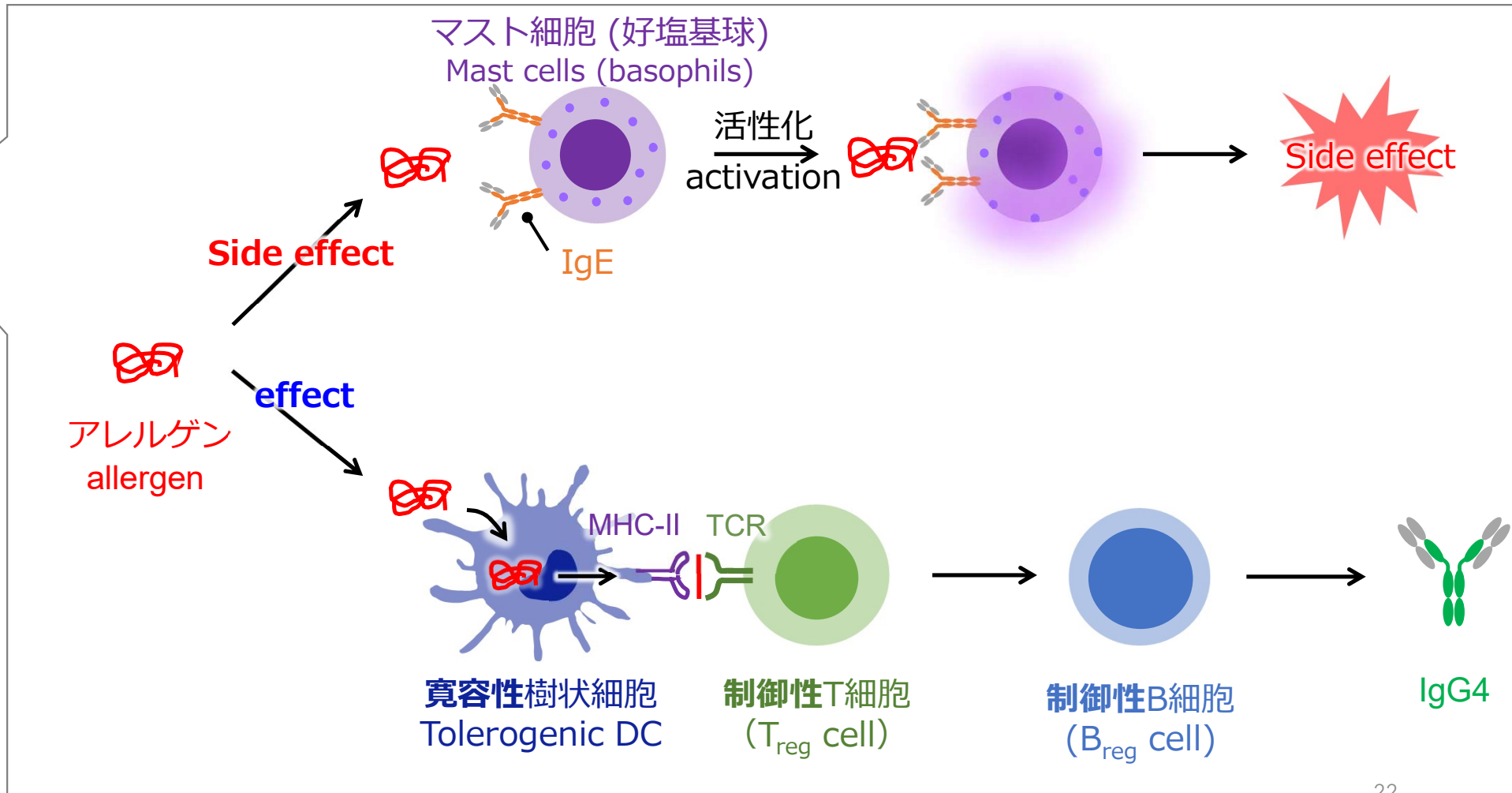
J. Allergy Clin. Immunol. 126, 969 (2010)

# 従来の製剤の機序

## Mechanism of conventional formulations

| : T細胞エピトープ

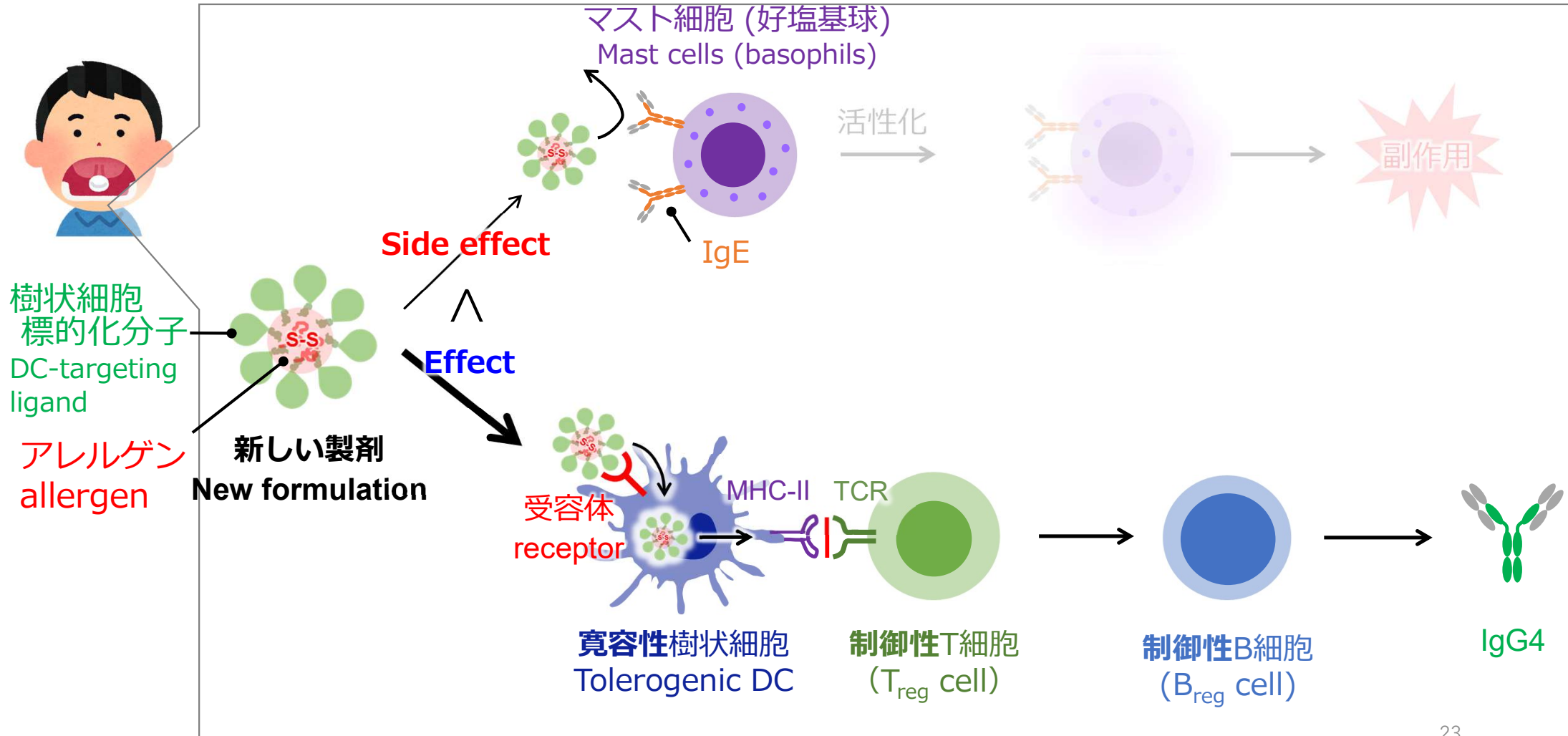
TCR : T細胞受容体



# 理想的な製剤の機序

## Mechanism of the ideal formulation

| : T細胞エピトープ  
TCR : T細胞受容体

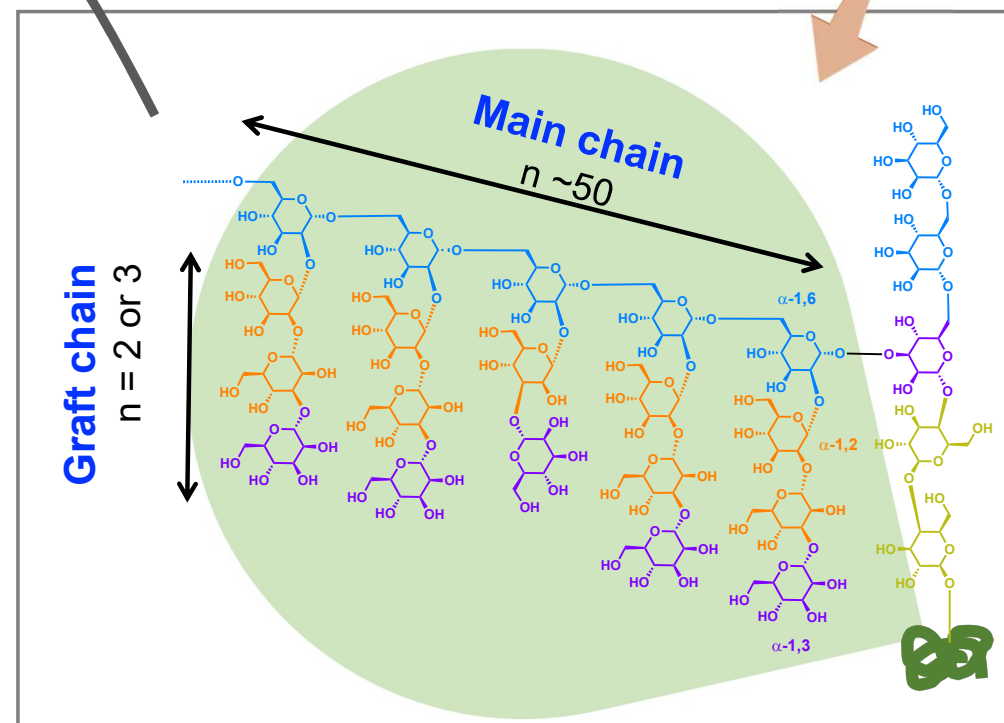
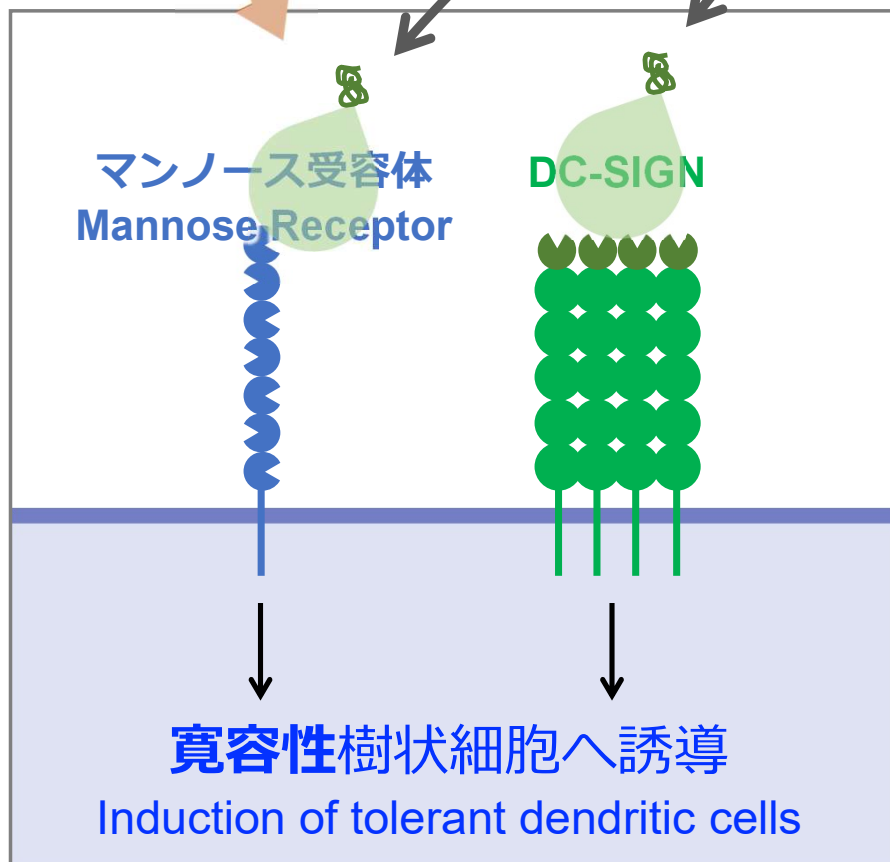
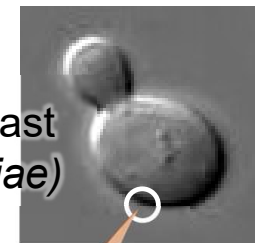


# 出芽酵母の細胞壁のマンナンは寛容性樹状細胞の誘導に好適

Mannan from the cell wall of budding yeast is suitable for inducing tolerant dendritic cells

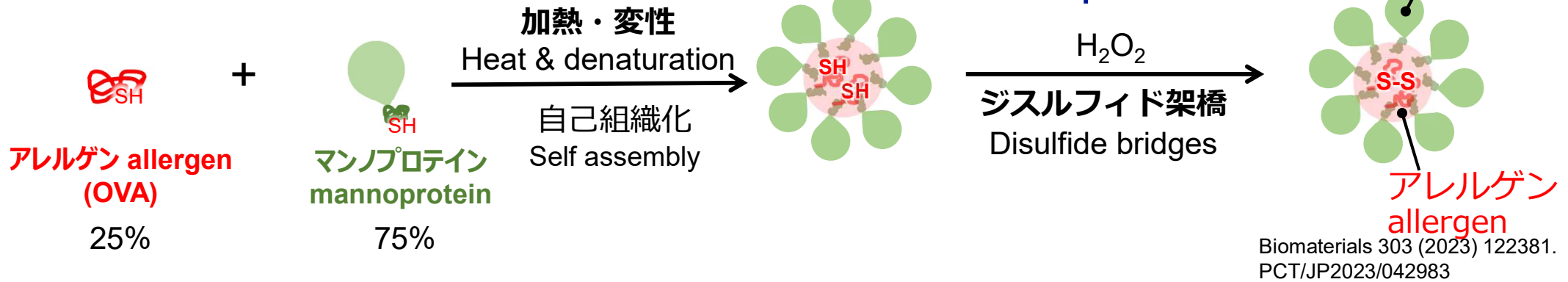


Budding yeast (*S. cerevisiae*)

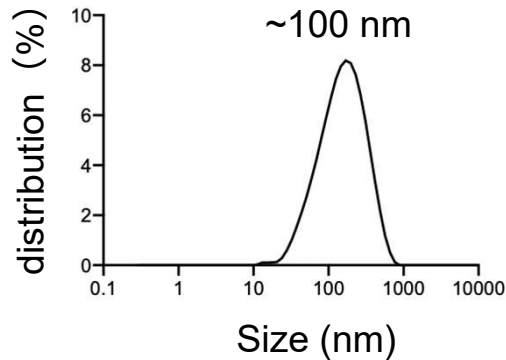


# 新製剤：マンナン被覆粒子

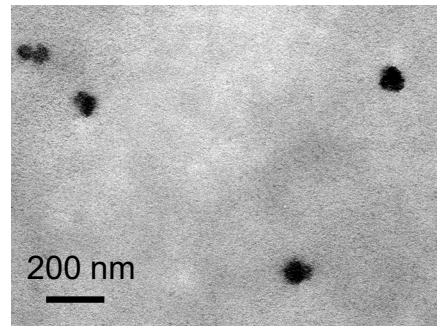
## New formulation: Mannan-coated particles



粒径分布 size



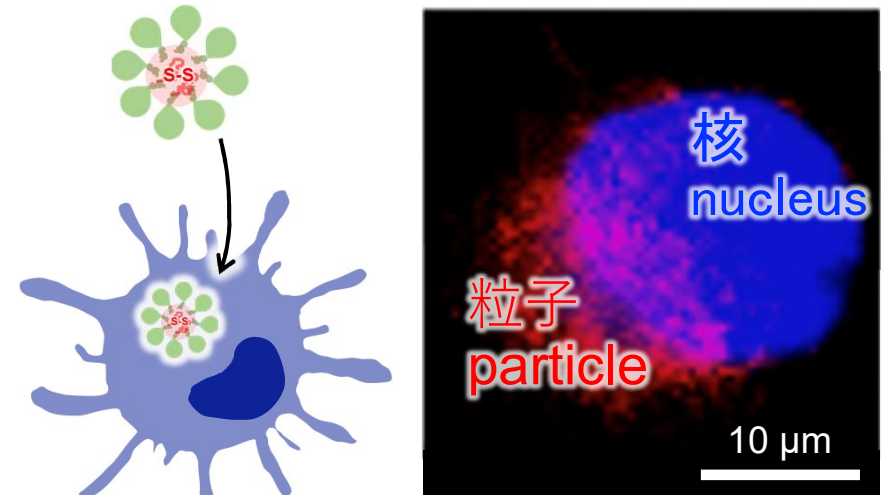
電子顕微鏡写真 micrograph



ワンポットで製造可能であり、大量生産に向く

It can be produced in one pot, making it suitable for mass production.

蛍光顕微鏡写真 micrograph



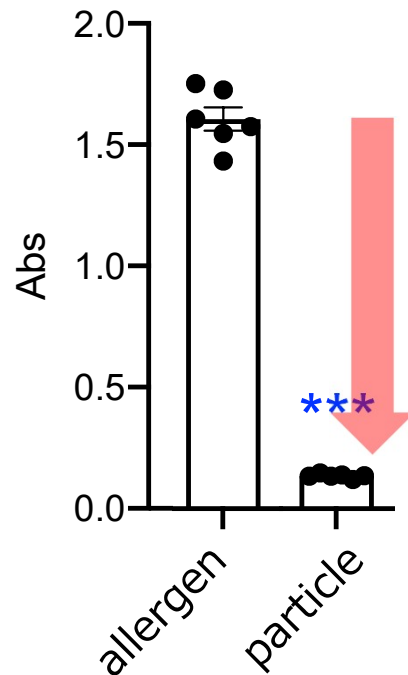
樹状細胞によく取り込まれる

Highly taken up by dendritic cells

# マンナン被覆粒子は高い安全性を有する

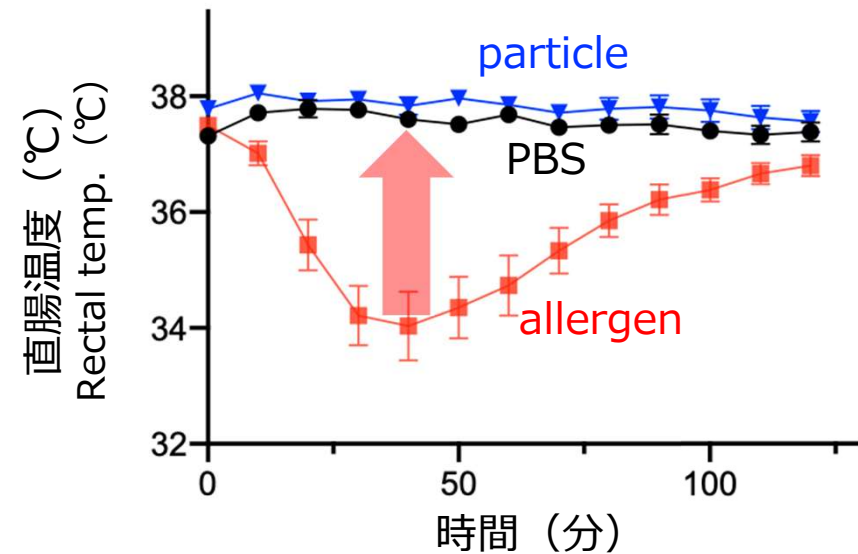
## Mannan-coated particles have high safety

抗アレルギーIgEの結合性  
Anti-allergen IgE binding



粒子にはIgE抗体が結合しにくい。  
IgE antibodies do not readily bind to the particles.

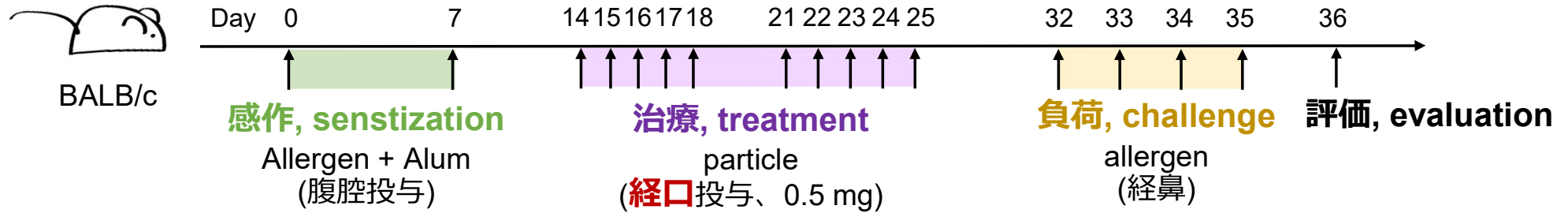
アナフィラキシー応答の評価  
Assessment of anaphylactic responses



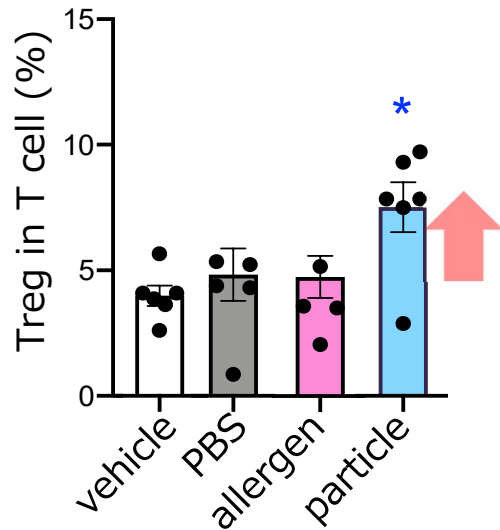
粒子はアナフィラキシー応答を誘導しない。  
The particles do not induce an anaphylactic response.

# マンナン被覆粒子は喘息モデルに高い治療効果を示す

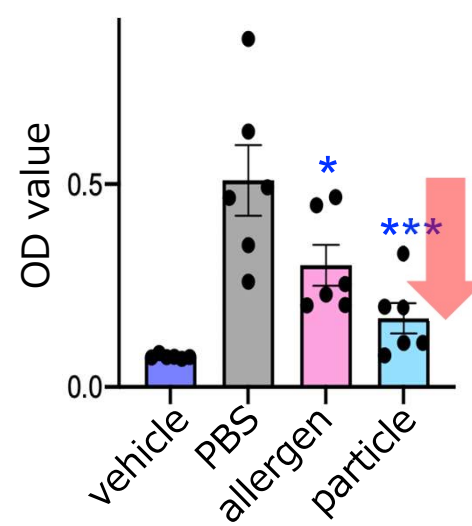
Mannan-coated particles show high therapeutic efficacy for asthma model



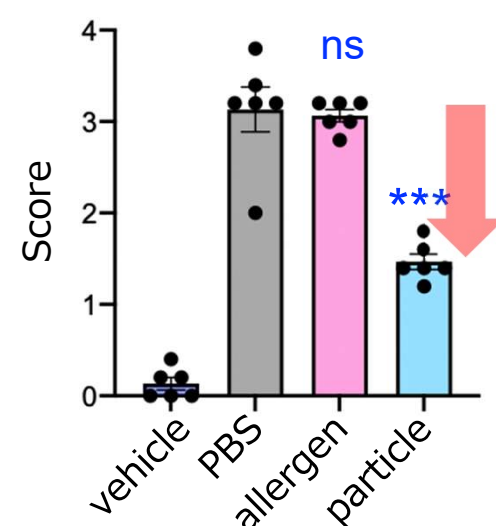
腸管のTreg細胞  
Intestinal Treg cells



血中の抗アレルギーIgE  
Anti-allergen IgE in the blood



肺の炎症スコア  
Lung Inflammation Score

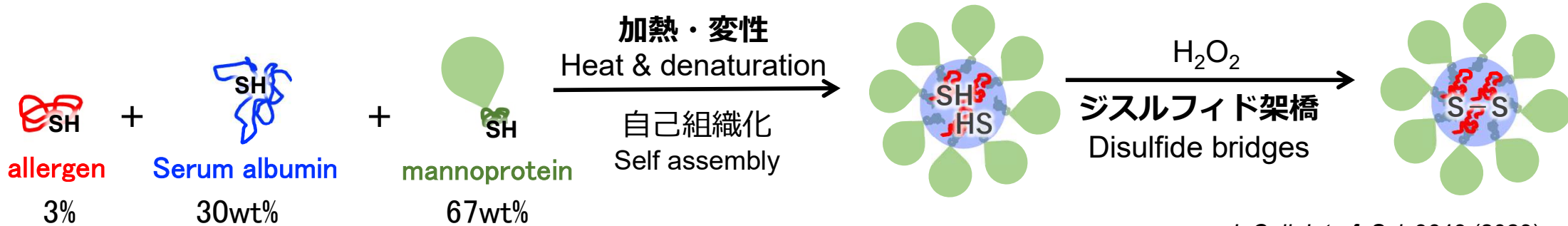


Treg細胞への分化を促進することで、IgE産生を抑え、肺の炎症（ぜん息）を抑制した。

By promoting differentiation into Treg cells, IgE production was suppressed, and asthma was suppressed.

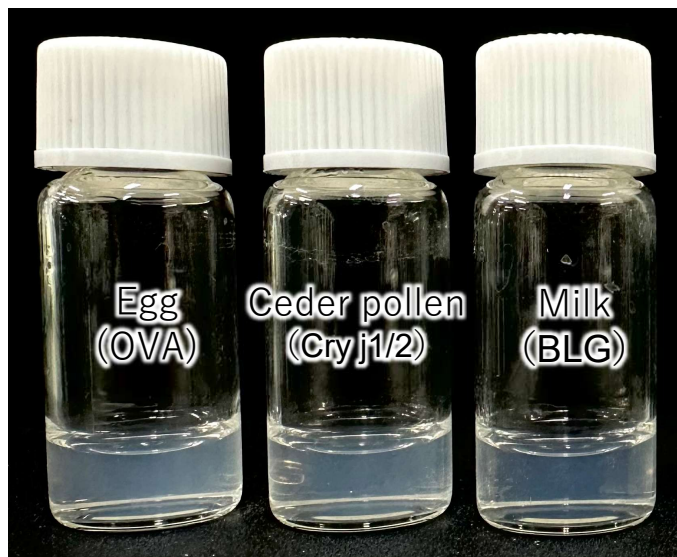
# 本法は実用的なアレルゲンに適用可能

## This method is applicable to practical allergens

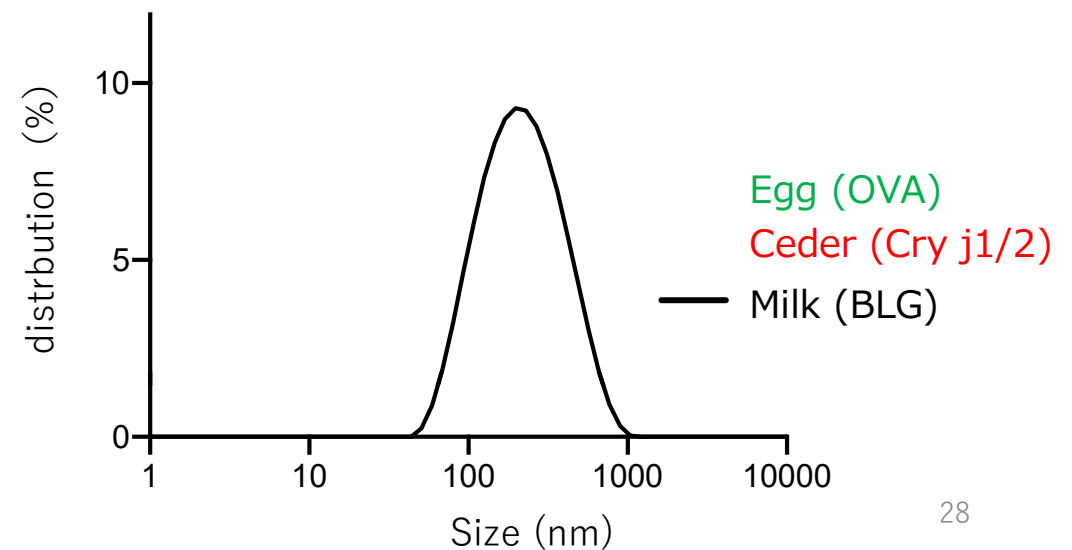


*J. Coll. Interf. Sci.* 3649 (2023).

Dispersion of particle



Size of particle



# TOLERO bio社の設立 (2024年2月)

## TOLERO bio Inc. has been established.



**田中義紀**

代表取締役CEO

多数のバイオ系スタートアップの社長を歴任



**長谷耕二**

アドバイザー

慶應義塾大学・薬学部・教授

粘膜免疫において顕著な業績 (Nature, Cell, Science、および姉妹誌多数)



**森健**

取締役CTO

九州大学・工学研究院・教授

複数のアレルギー免疫療法製剤を開発した実績



**村上大輔**

アドバイザー

九州大学病院・耳鼻咽喉・頭頸部外科・講師

・花粉症の臨床研究の豊富な実績

・スギ花粉症製剤の開発経験(第二相)



**Lee Gyeongwoo**

研究員

九州大学・工学研究院・特任助教

DDSの専門家

### Mission

安全で効率の高いアレルギー免疫療法の製剤を開発し、アレルギーの克服に寄与する。

Developing safe and effective allergen immunotherapy formulations to contribute to overcoming allergies.



**TOLERO bio**

# Perspective

1. 多様な花粉/環境アレルゲンに展開し、欧米並みの治療体制を実現。

Expanding to a variety of pollen/environmental allergens, we will realize a treatment system on par with Europe and the United States.

2. これまでにない食物アレルギーを自宅で治療する経口製剤を世界展開。

Globally launching an unprecedented oral formulation for treating food allergies at home.

3. アレルギーマーチを早期に断ち切り、世界の患者数を減少に転じる。

Early halting the allergic march and reducing the number of patients worldwide.

