- 九州大学　片山研究室より、資料をDLして下さい。

  リンク⇒講義資料より

- 小テストは以下のメアドに提出

  moriken37yuta@gmail.com
  件名：小テスト

Why we'd better think based on evolution?

なぜ進化で考えると良いのか？

Evolutionary medicine-based therapy and diagnosis (進化医学に基づいて治療・診断を考える)

Content:

1. Darwinian medicine　ダーウィン医学、進化医学
2. Diabetes 糖尿病
3. Defense for pathogens vs. autoimmunity/allergy
   病原体からの防御 vs. アレルギー、自己免疫疾患

1. Darwinian medicine (evolutionary medicine)
ダーウイン医学（進化医学）

- How people get sick => Why people get sick
- Why evolution has shaped these mechanisms in ways that may leave us susceptible to disease.
- It works well to explain diseases including cancer, infection, autoimmunity, anatomy, mental illness (がん、感染症、自己免疫疾患、解剖学、精神疾患）

1962
James Neel

How to make question based on Darwinian medicine

Q1: Why scurvy occurs?

壊血病という病気はなぜ起こるのか？

A1: Lack of vitamin C causes scurvy

Vitamin Cが欠乏すると壊血病になる。

Q2: Why lack of vitamin C causes scurvy?

vitamin Cが欠乏するとなぜ壊血病になるのか？

A2: vitamin C is needed for blood coagulation.

血液凝固にvitamin Cが必要だから

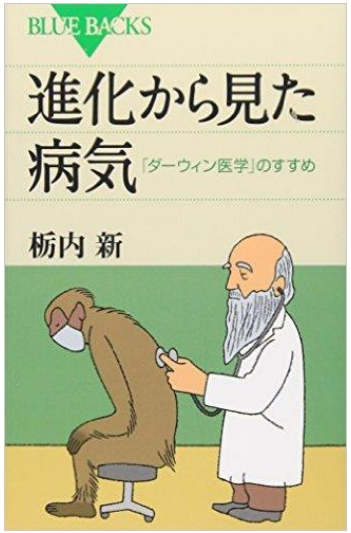
Q3: Why human does not biosynthesize important vitamin C? (Darwinian)

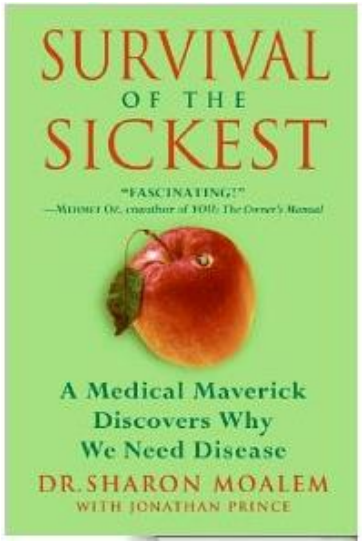
なぜ大事なvitamin Cを生合成しないのか？

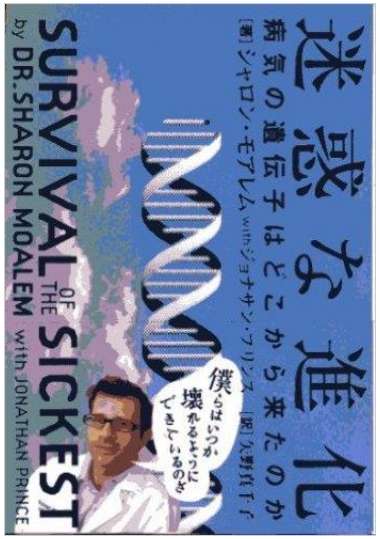
A3: Up to rodent synthesize vitamin C. Change in metabolism and food.

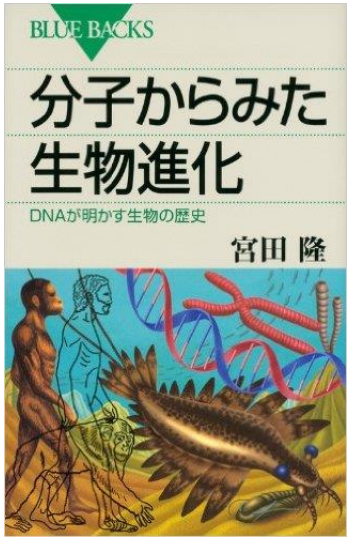
げっ歯類までは生合成する。代謝系における変化。食物の変化。

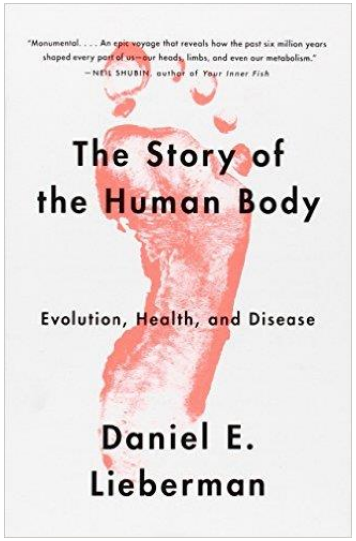
References

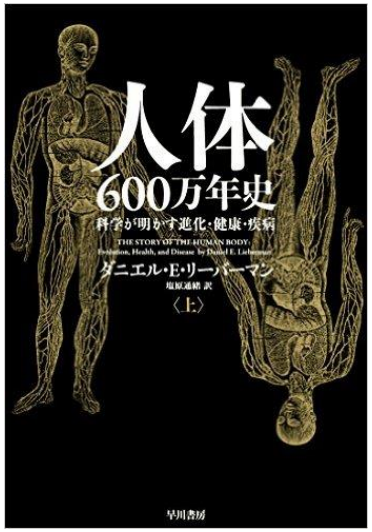

BLUE BACKS
進化から見た病気
「ダーウィン医学」のすすめ
栃内 新


SURVIVAL OF THE SICKEST
"FASCINATING!"
A Medical Maverick Discovers Why We Need Disease
DR. SHARON MOALEM
WITH JONATHAN PRINCE

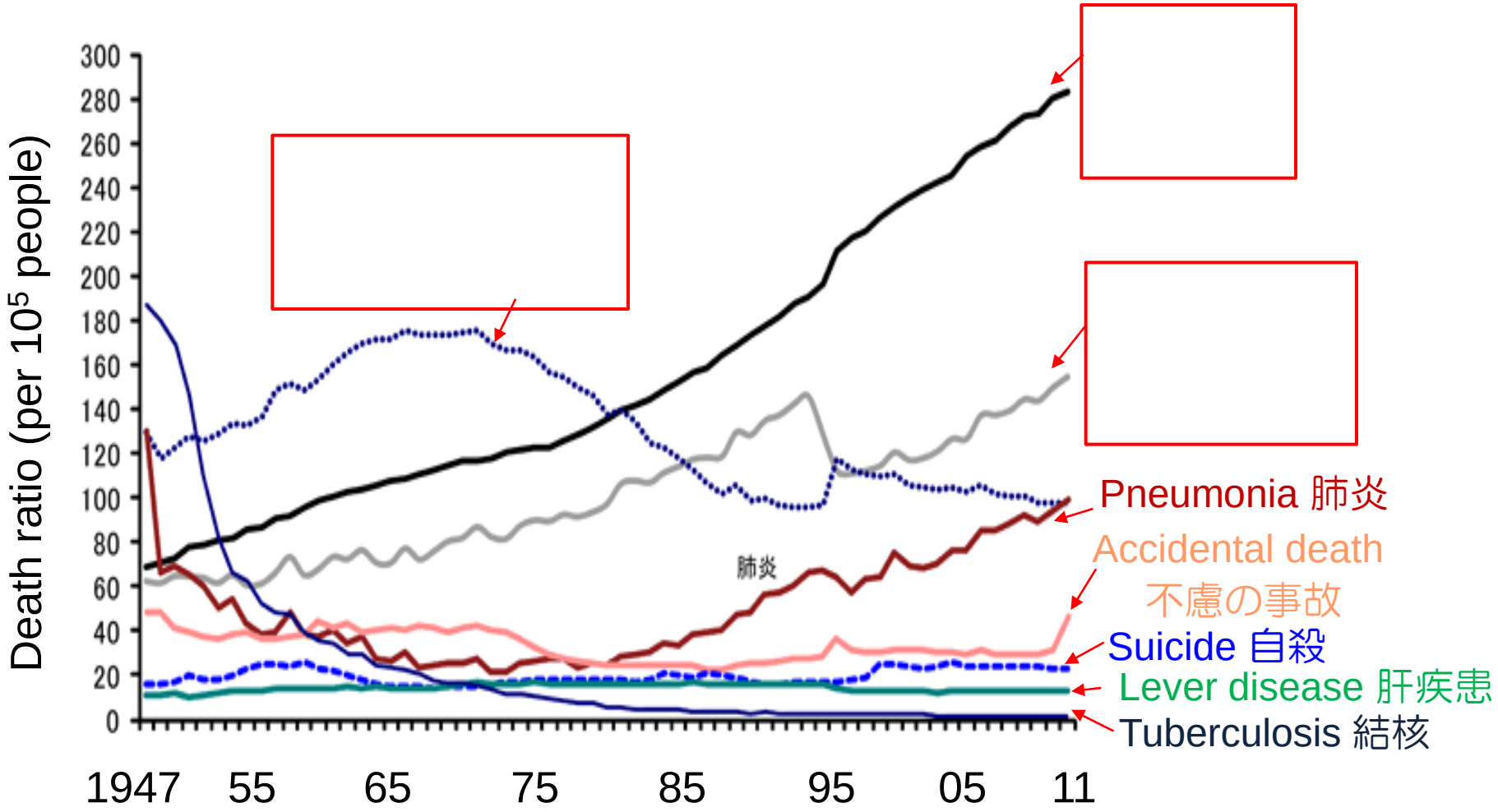

迷惑な進化
病気の遺伝子はどこから来たのか
SURVIVAL OF THE SICKEST
by DR. SHARON MOALEM with JONATHAN PRINCE


BLUE BACKS
分子からみた生物進化
DNAが明かす生物の歴史
宮田 隆


The Story of the Human Body
Evolution, Health, and Disease
Daniel E. Lieberman


人体
600万年史
科学が明かす進化・健康・疾病
ダニエル・E・リーバーマン
〈上〉
早川書房

Cause of death in Japan



ストレプトマイシン発見
1944

Natural selection (Darwin, 1858)

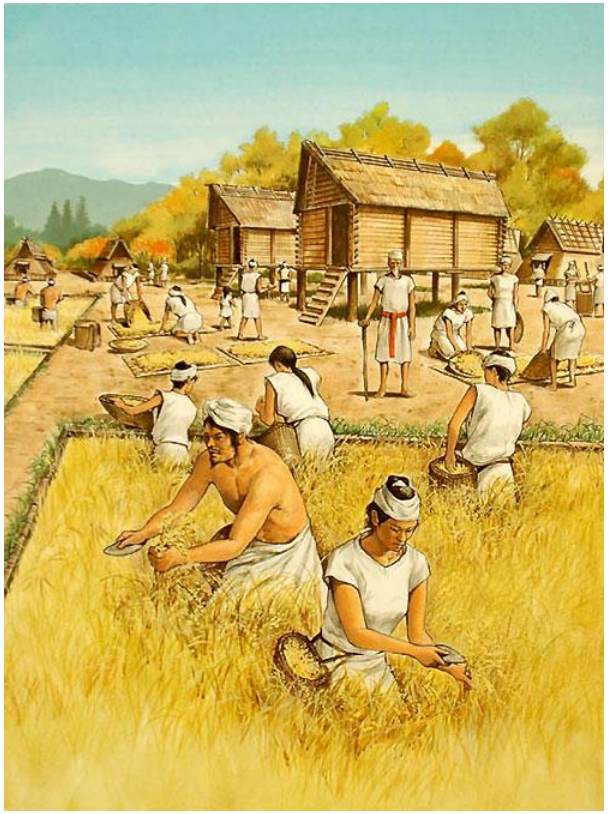
The giraffe ancestor who has longer neck (the fittest) survives, then long necks become common in population.

Change in life style

200k years ago
(hunting, sampling)

Much exercise
Efficient energy absorption
Miscellaneous food
Small group

10k years ago
(farming)



grain (carbohydrate)
Livestock (milk)

present

satisfaction (fat, carbohydrate, salt), lack of exercise
work at midnight
longevity, stressful, hygiene, reading

Mismatch diseases

Acid reflux　胃酸逆流	Flat foot偏平足
Alzheimer's disease アルハイマー病	Hemorrhoid痔
Apnea無呼吸	Hypertension高血圧
	Insomnia不眠症
	Irritable bowel syndrome 過敏性腸症候群
Cancer が	Lactose intolerance 糖不耐性
Cirrhosis of the liver肝硬変	Metabolic syndrome メタボリックシンドローム
	Multiple sclerosis多発性硬症
Coronary heart disease冠状動脈性心疾患	
Crohn’s disease クローン病	Osteoporosis骨粗しょう症
Depression うつ病	Scurvy壊血病
Diabetes type 2二型糖尿病	

Ref: “The story of the human body”

Person who overcomes mismatch diseases will appear by genetic mutation. Is this genotype spread in homo sapience?

今後、Mismatch diseasesを進化で克服した個人が出てきたとして、その子孫がやがて人類のマジョリティーを占めるようになるか？

2. Diabetes

血糖値が高いと何が問題か？

Which one does include more glucose?

Total amount of blood　5L

Coke　350 mL

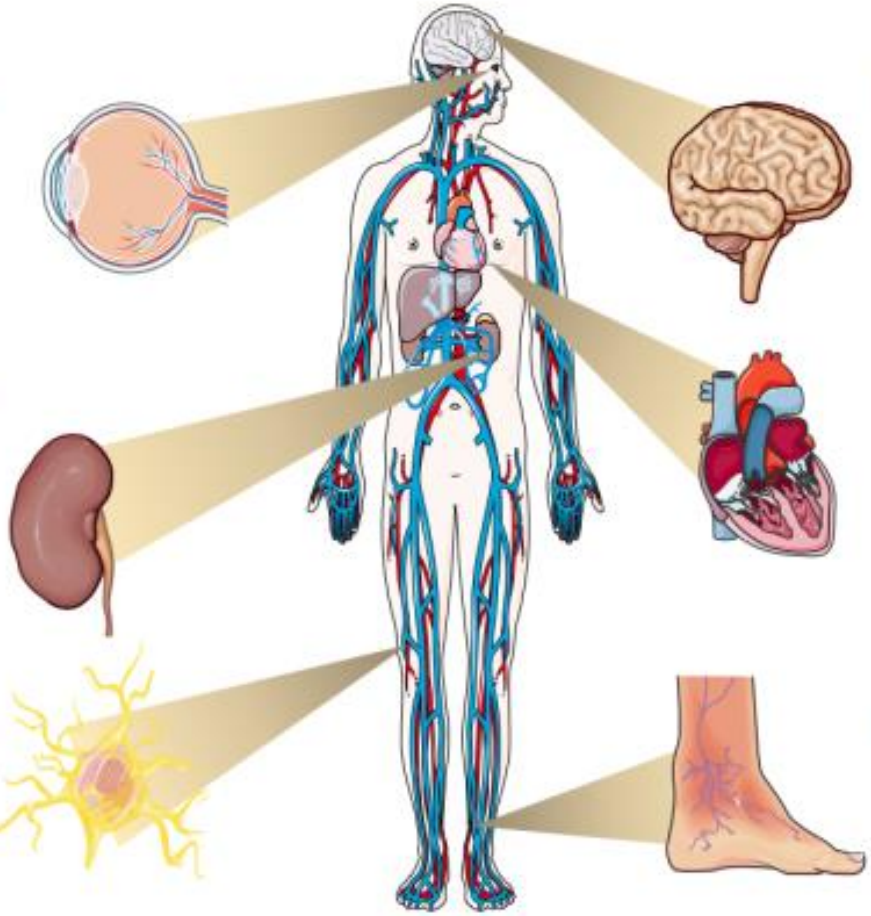
Diabetic complications 糖尿病合併症

Microvascular

Eye
High blood glucose and high blood pressure can damage eye blood vessels, causing retinopathy, cataracts and glaucoma

Kidney
High blood pressure damages small blood vessels and excess blood glucose overworks the kidneys, resulting in nephropathy.

Neuropathy
Hyperglycemia damages nerves in the peripheral nervous system. This may result in pain and/or numbness. Feet wounds may go undetected, get infected and lead to gangrene.



Macrovascular

Brain
Increased risk of stroke and cerebrovascular disease, including transient ischemic attack, cognitive impairment, etc.

Heart
High blood pressure and insulin resistance increase risk of coronary heart disease

Extremities
Peripheral vascular disease results from narrowing of blood vessels increasing the risk for reduced or lack of blood flow in legs. Feet wounds are likely to heal slowly contributing to gangrene and other complications.

How dose high BGL cause these diseases?

Diabetes mellitus

- High glucose conc. in blood. (≥ 126 mg/dL, HbA1c ≥ 6.5%)
- Type I: destruction of pancreatic β cell, leading to depletion of insulin. Then become high glucose conc. 膵臓β細胞が破壊され、インシュリンが枯渇し、その結果、高血糖になる。
- Type II: decrease in secretion of and response to insulin. 90% of diabetes patients.
- 5% of the world's adult population. 7.4 million in Japan.
- Causing diabetic complications （合併症）：

  diabetic neuropathy 糖尿病性神経障害
  diabetic retinopathy 糖尿病性網膜症
  diabetic nephropathy 糖尿病性腎症

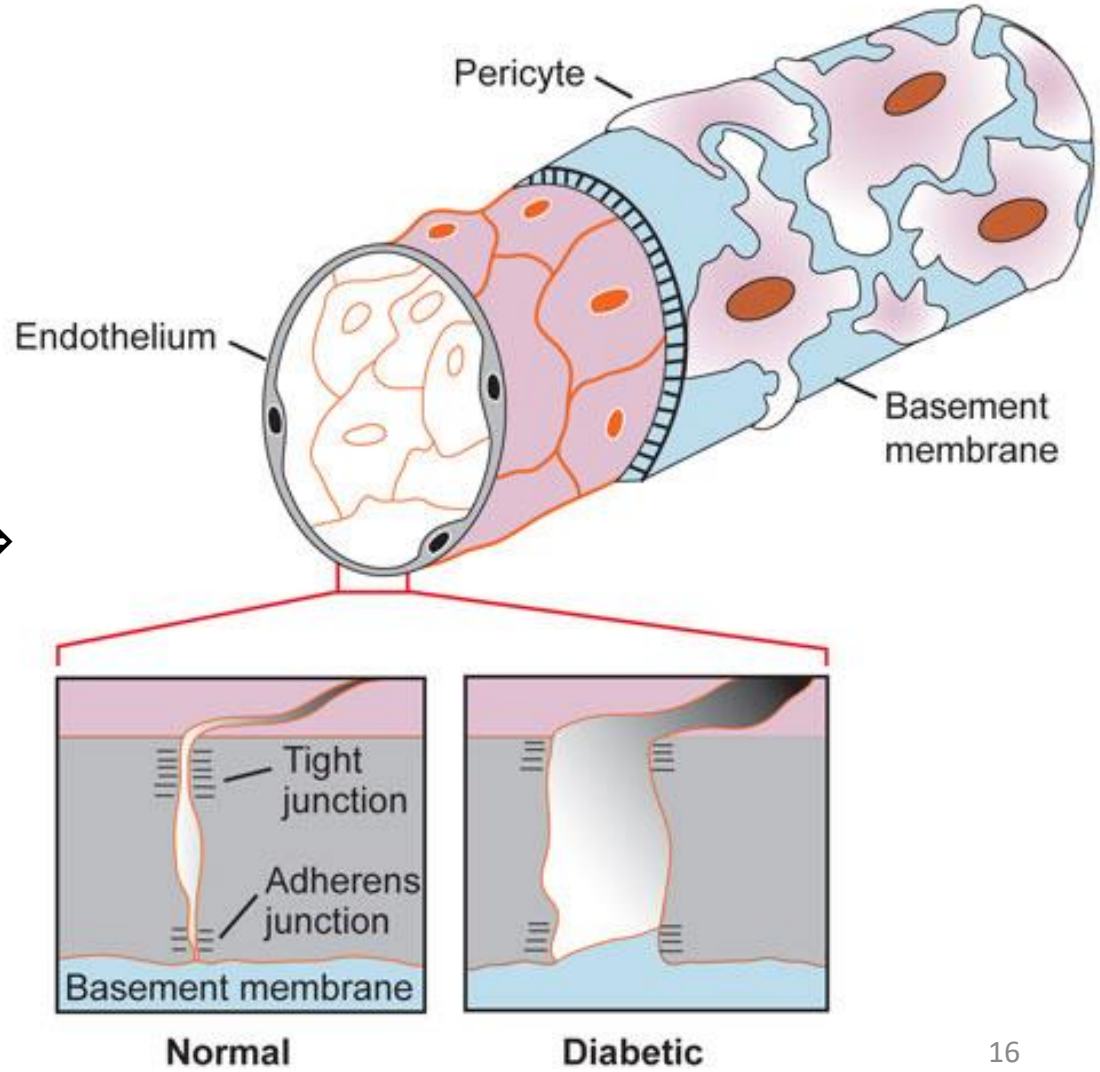
  } Microvascular disease 微小血管障害

  myocardial infarction 心筋梗塞
  peripheral vascular disease 末梢血管障害

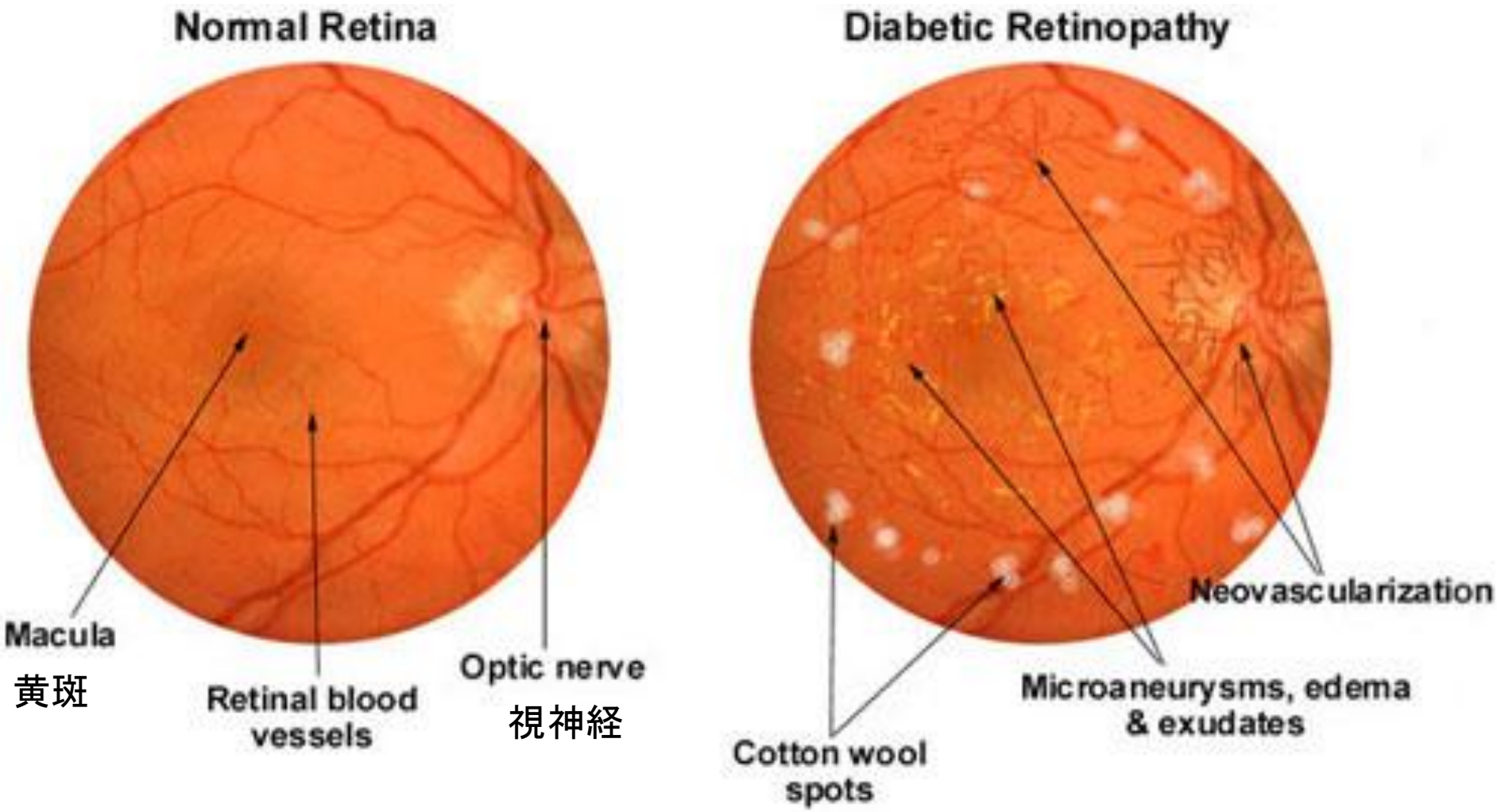
  } Macrovascular disease 大血管障害

Mechanism of diabetic retinopathy

1. Endothelial cell (血管內皮細胞) and basement membrane (基底膜) exposed to high blood glucose conc.
2. Glycation of endothelial membrane protein and basement membrane protein.
3. Thickening and weakening of basement membrane.
4. Loss of pericyte (周皮細胞)
5. Leakage of plasma ⇒ Retinal edema （浮腫）、exudate （滲出）
6. microaneurysm（微小動脈瘤）⇒ hemorrhage（出血）

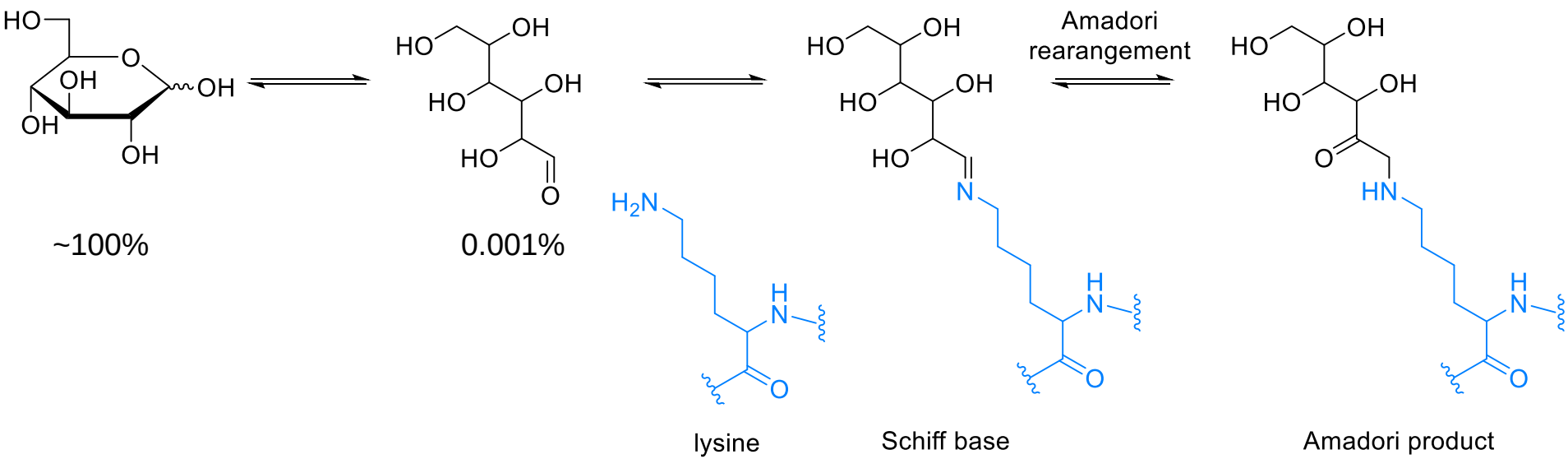


Diabetic retinopathy 糖尿病性網膜症

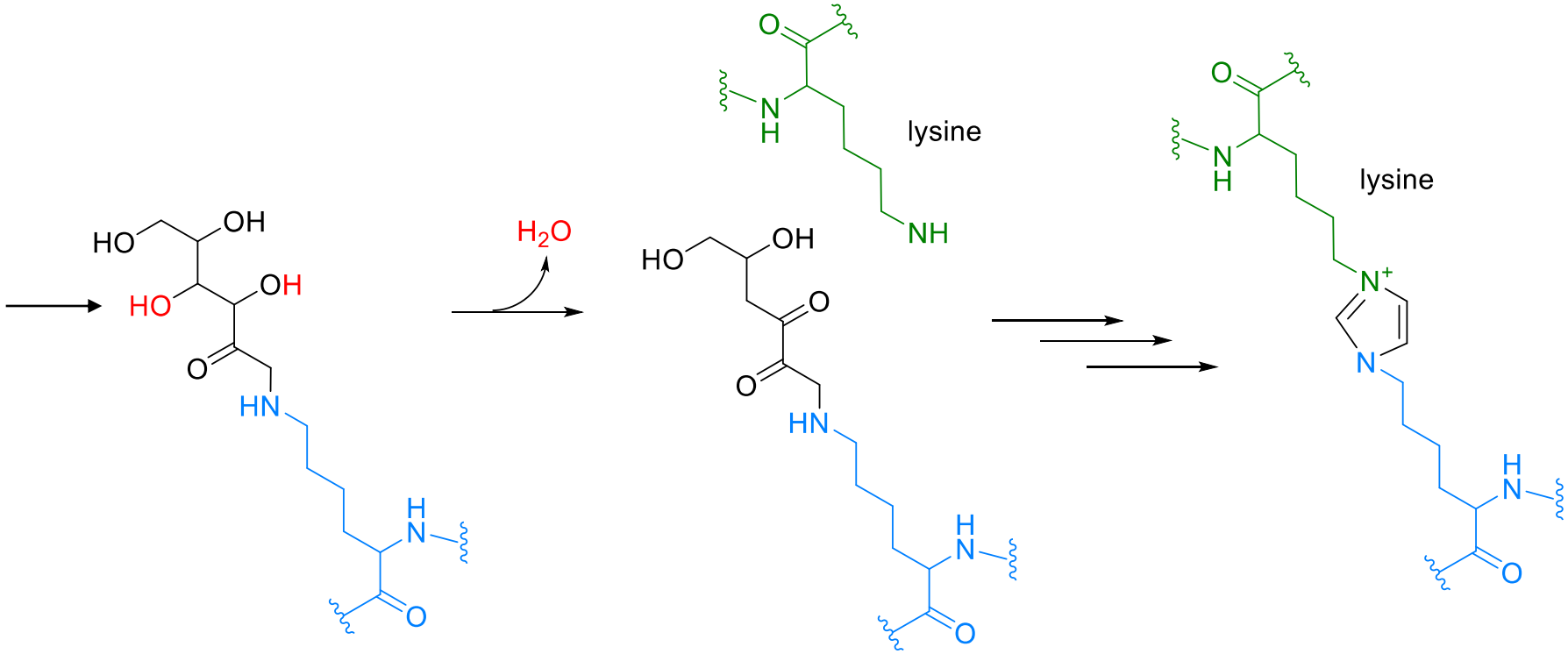


AGE (advanced glycation end product) 終末糖化産物

- Obtained by glycation of protein (Mailard reaction)
- Inducing protein denaturation leading to diabetic complications



AGE (advanced glycation end product) 終末糖化産物



Amadori product

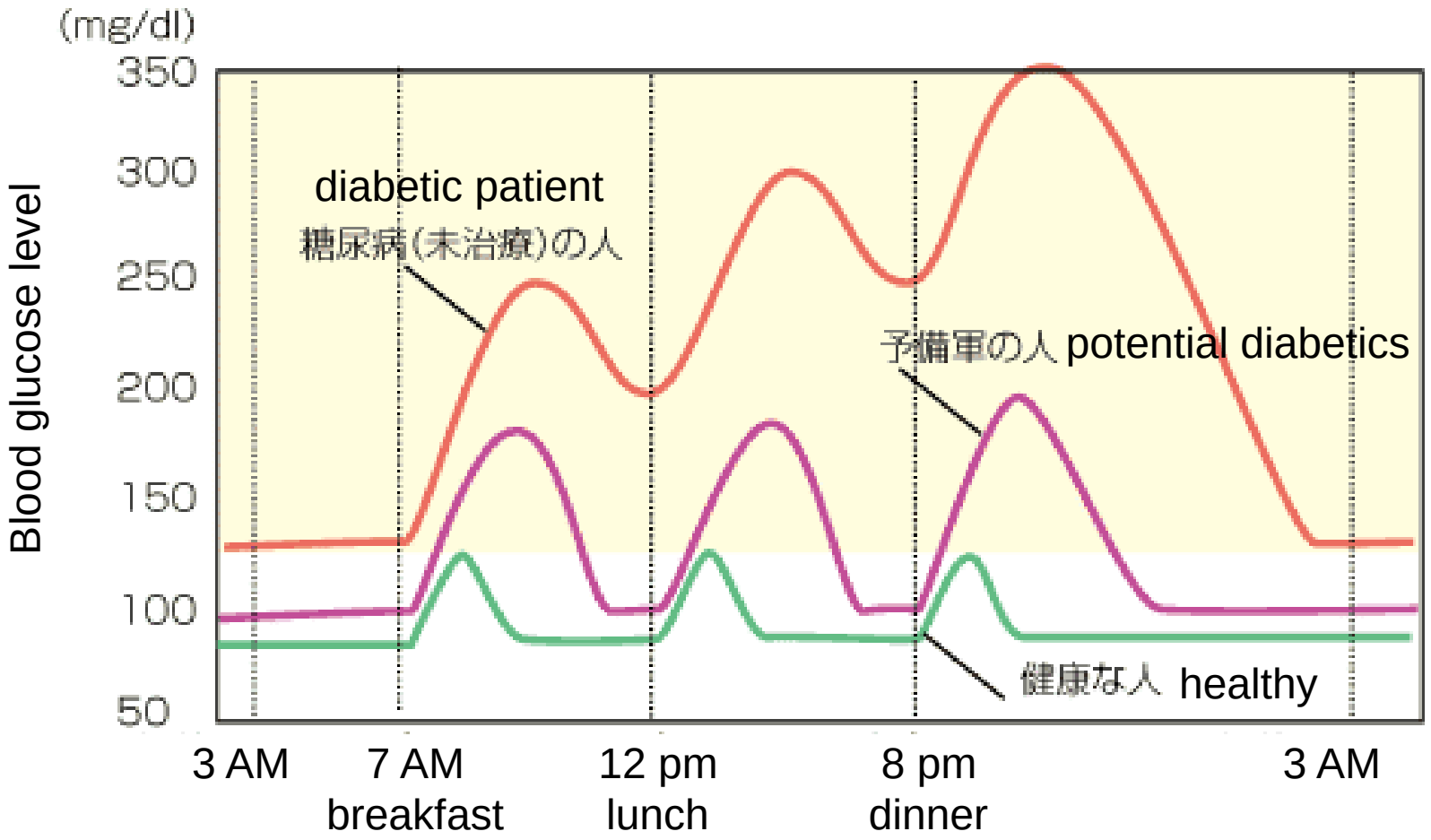
Amadori dione

GOLD

weeks, months, years (Mailard reaction)

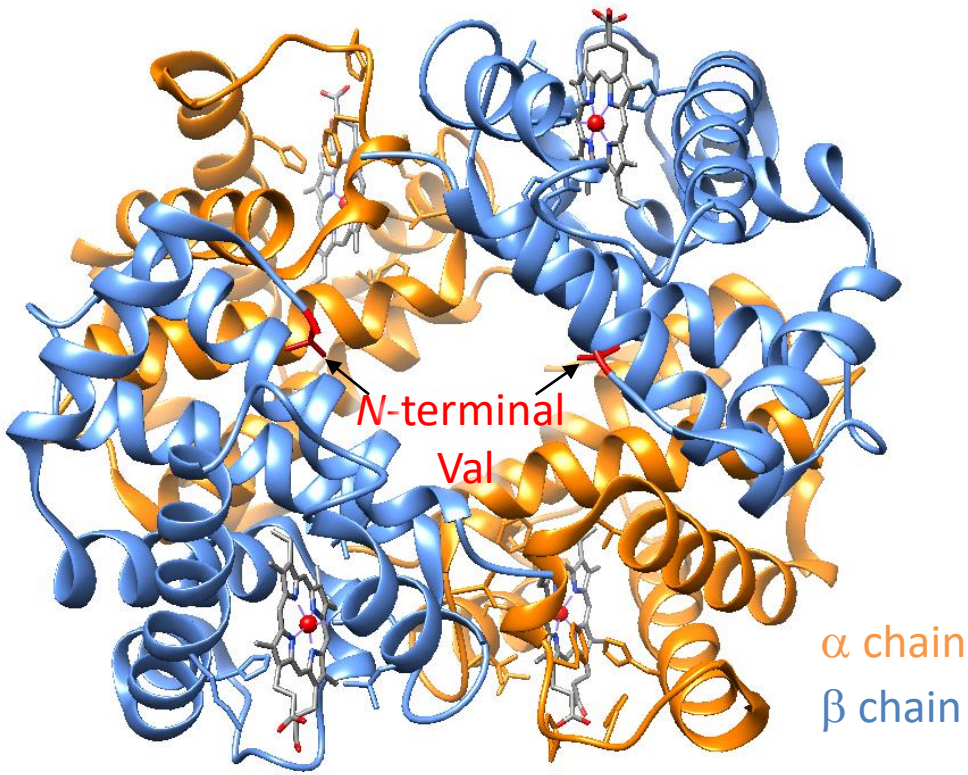
BGL is not constant

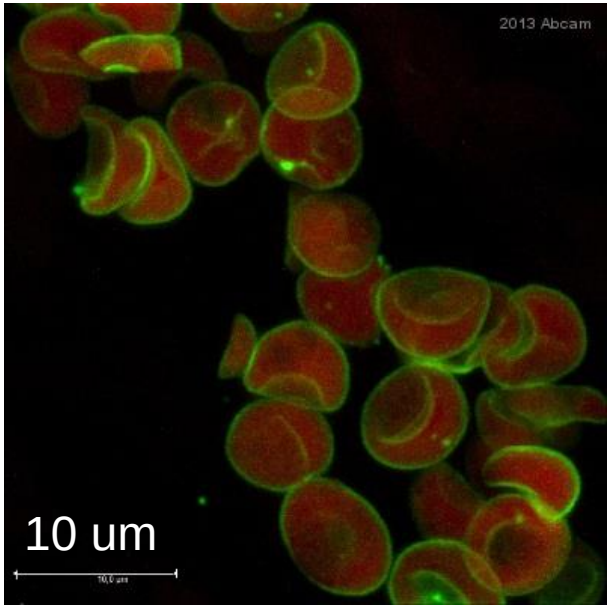
Affected by meal taking and daily stress. How can we remove such short-term effects?



Monitoring blood glucose conc. by using hemoglobin (Hb)

- Half-life of red blood cell (RBC) is 2 months.
- Easy to sample enough amount of Hbs (20×10^{12} RBCs/person, 2.7×10^{8} Hbs/RBC)
- Blood glucose conc. of more than a months can be monitored by checking Hb's glycation incorporated in RBC.
- HbA1c (one of β chains' N-terminus is glycated) is used.
- Diabetes: HbA1c ≥ 6.5%





Green: RBC's GLUT1

Project by Google x

Detecting disease early with nanoparticles

Nanoparticles are really small: more than 2000 nanoparticles could fit inside a red blood cell.

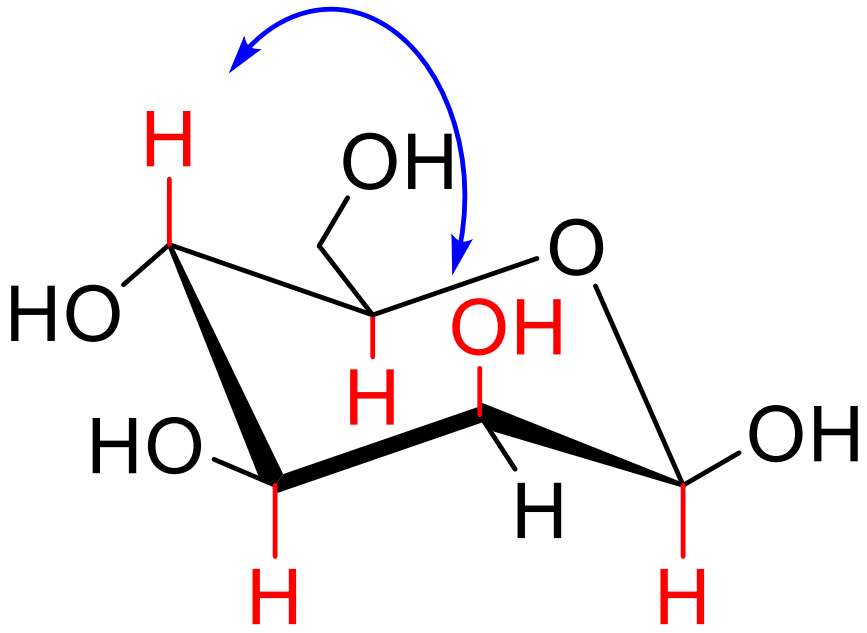
Nanoparticles circulate in the blood and can be built to attach to particular types of cells, such as circulating cancer cells.

A device worn on the outside of the body can detect the nanoparticles and provide useful information to physicians.

Why do we choose troublesome glucose as energy source?

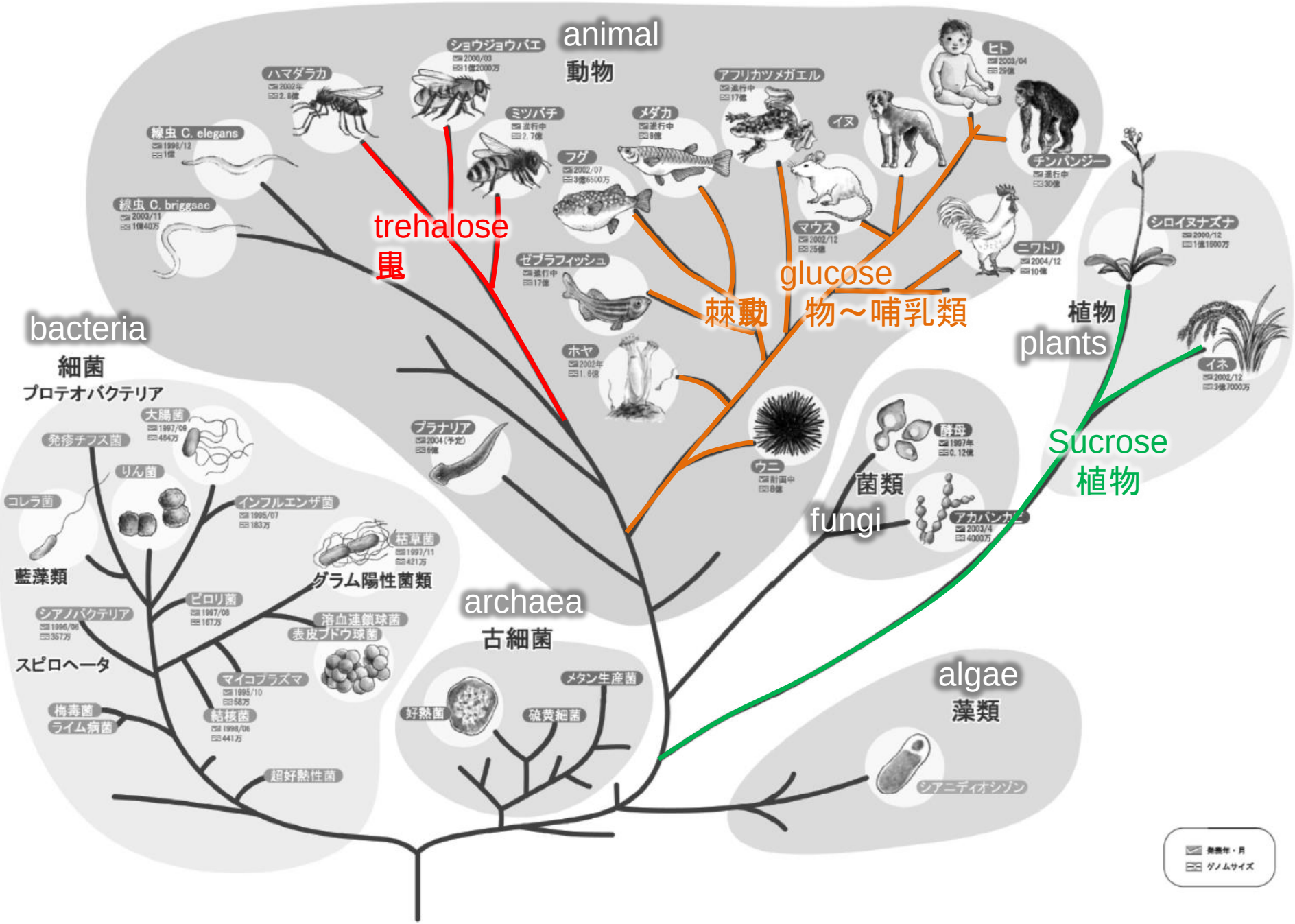
なぜ厄介なグルコースを栄養に選んだのか？

There’s no repulsion in glucose
グルコースは安定



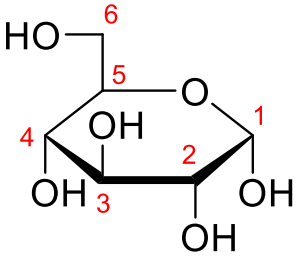
D-glucose

D-mannose

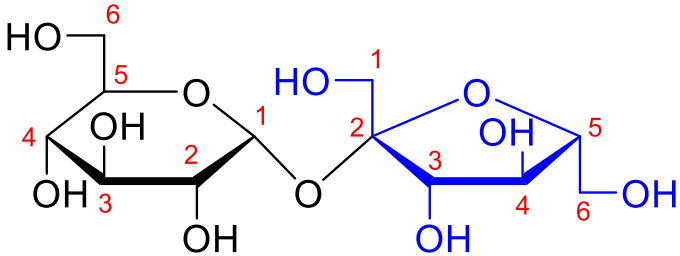

animal
動物
trehalose
昆
棘皮動物～哺乳類
glucose
bacteria
細菌
プロテオバクテリア
植物
plants
Sucrose
植物
fungi
菌類
archaea
古細菌
algae
藻類
藍藻類
スピロヘータ
グラム陽性菌類
ハマダラカ
ショウジョウバエ
線虫 C. elegans
線虫 C. briggsae
ミツバチ
メダカ
フグ
アフリカツメガエル
イヌ
ヒト
チンパンジー
マウス
ニワトリ
シロイヌナズナ
イネ
ゼブラフィッシュ
ホヤ
ウニ
酵母
プラナリア
大腸菌
発疹チフス菌
りん菌
コレラ菌
インフルエンザ菌
枯草菌
ピロリ菌
シアノバクテリア
溶血連鎖球菌
表皮ブドウ球菌
マイコプラズマ
結核菌
梅毒菌
ライム病菌
超好熱性菌
好熱菌
硫黄細菌
メタン生産菌
シアニディオシゾン
発表年・月
ゲノムサイズ

Energy media in vessels of multicellular organisms
多細胞生物のエネルギーメディア

Non-reducing sugars were chosen !

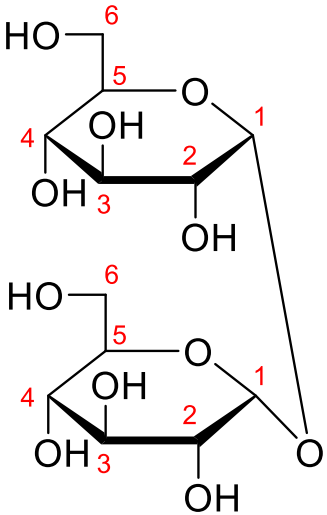


glucose



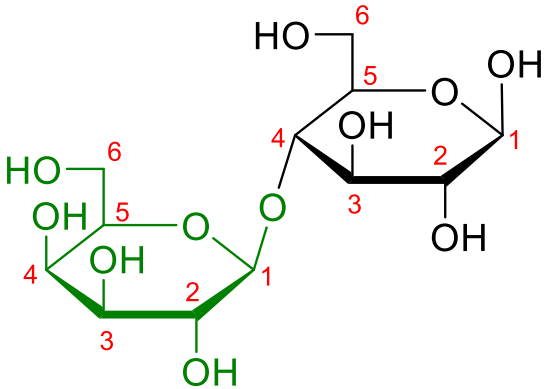
sucrose

α-D-glucopyranosyl-(1->2)-β-D-fructofuranoside



trehalose

α-D-glucopyranosyl-(1->1)-α-D-glucopyranoside



lactose

β-D-galactopyranosyl-(1->4)-D-glucose

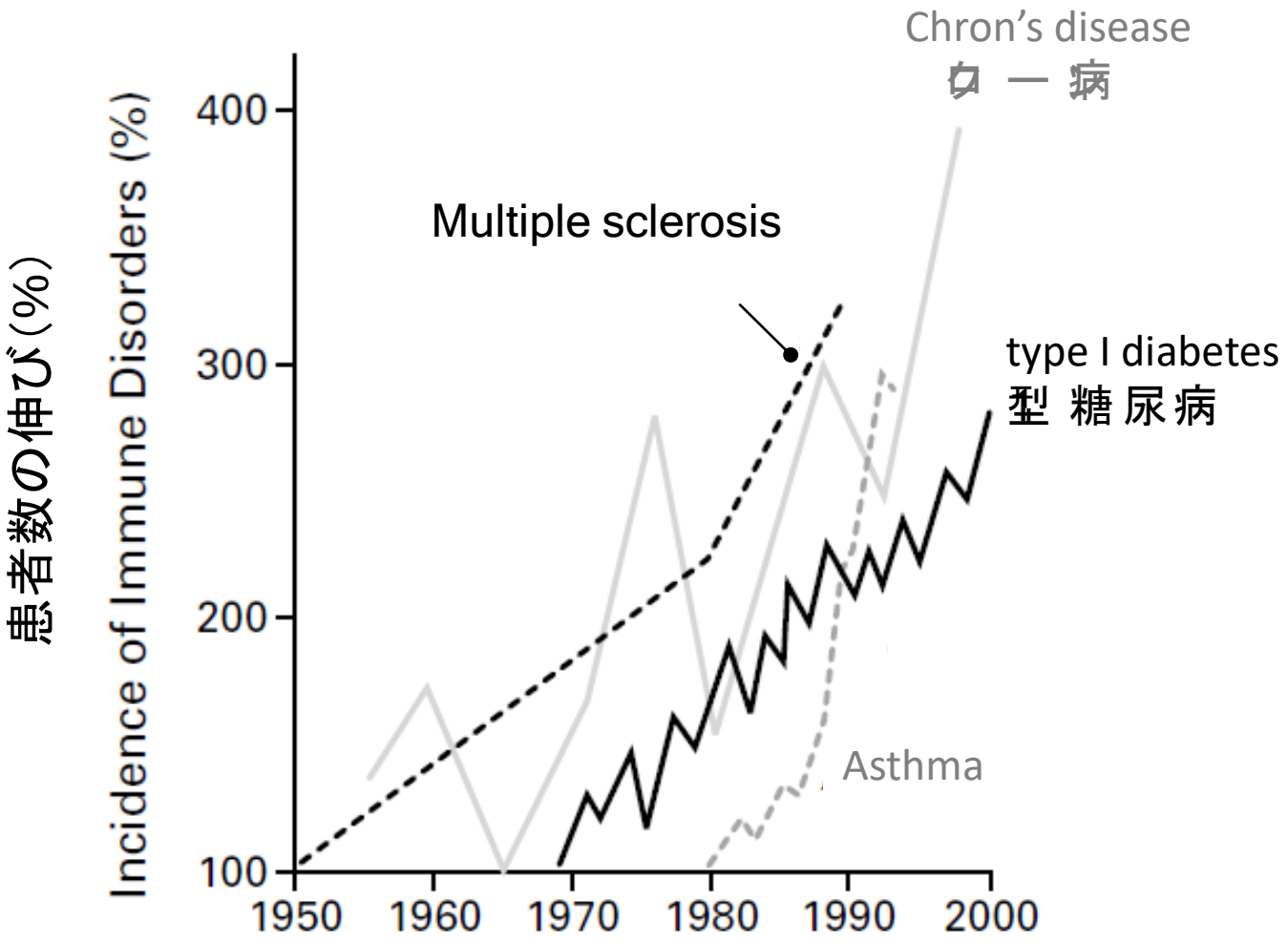
Please propose therapeutic method to treat diabetes

Q：糖尿病の治し方を提案せよ。

3. Defense for pathogens vs. autoimmunity/allergy

なぜ免疫は間違えるのか？

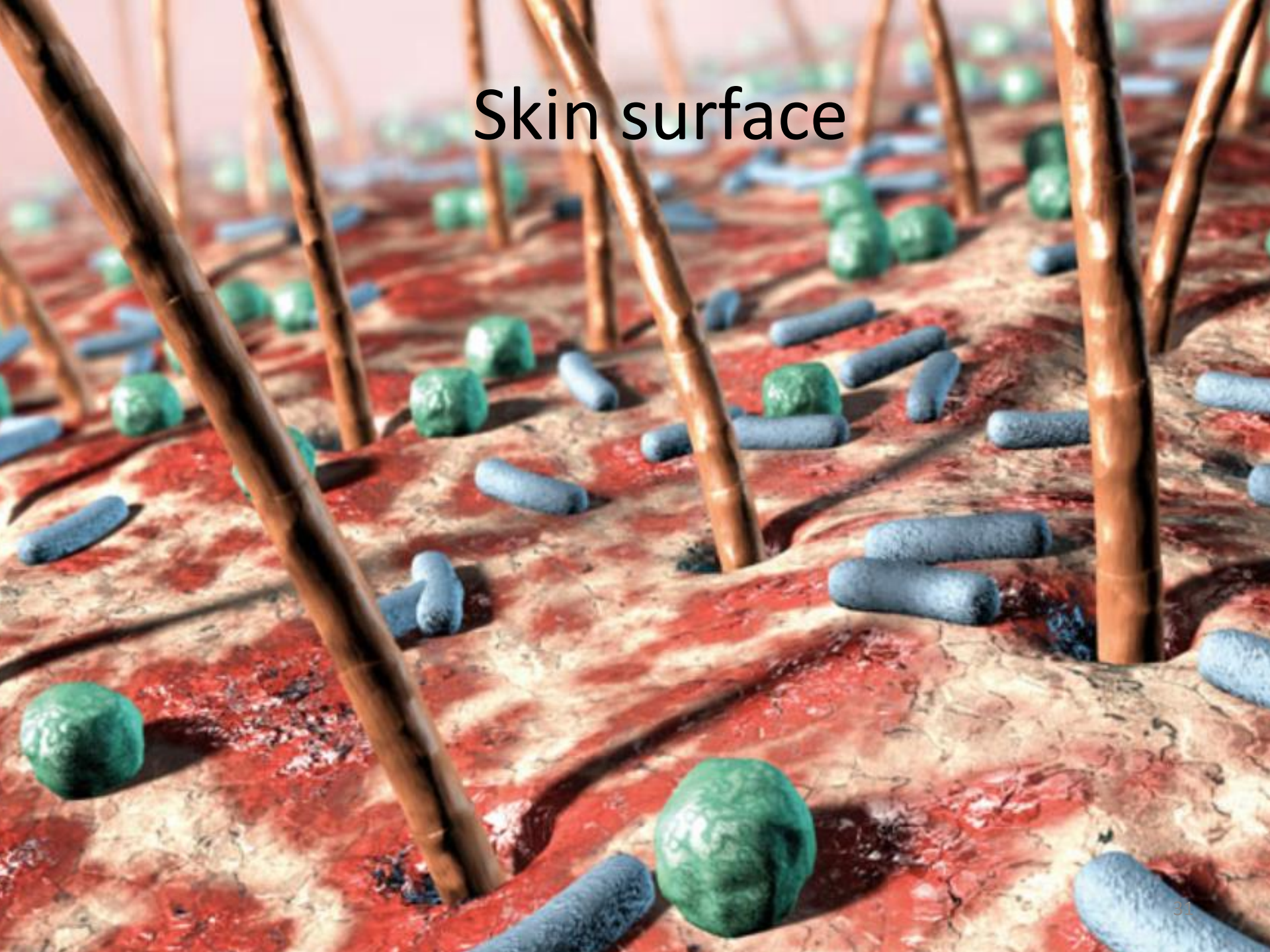
Rapid increase of autoimmune disease & allergy
自己免疫疾患、アレルギーが急増中



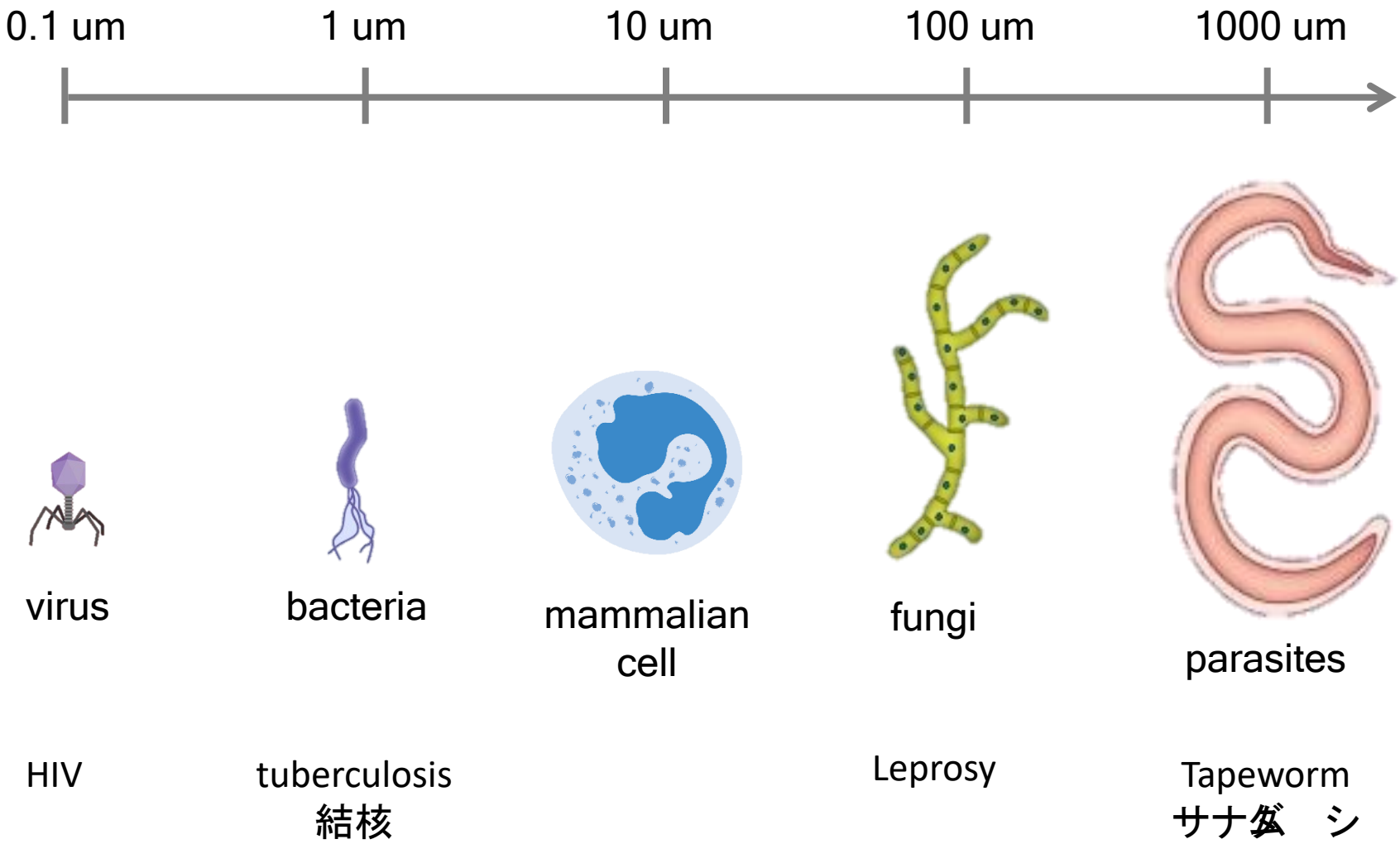
2002 New England J Med 911

ヒトは死ぬと、微生物の苗床になる

Skin surface



Pathogens 病原体



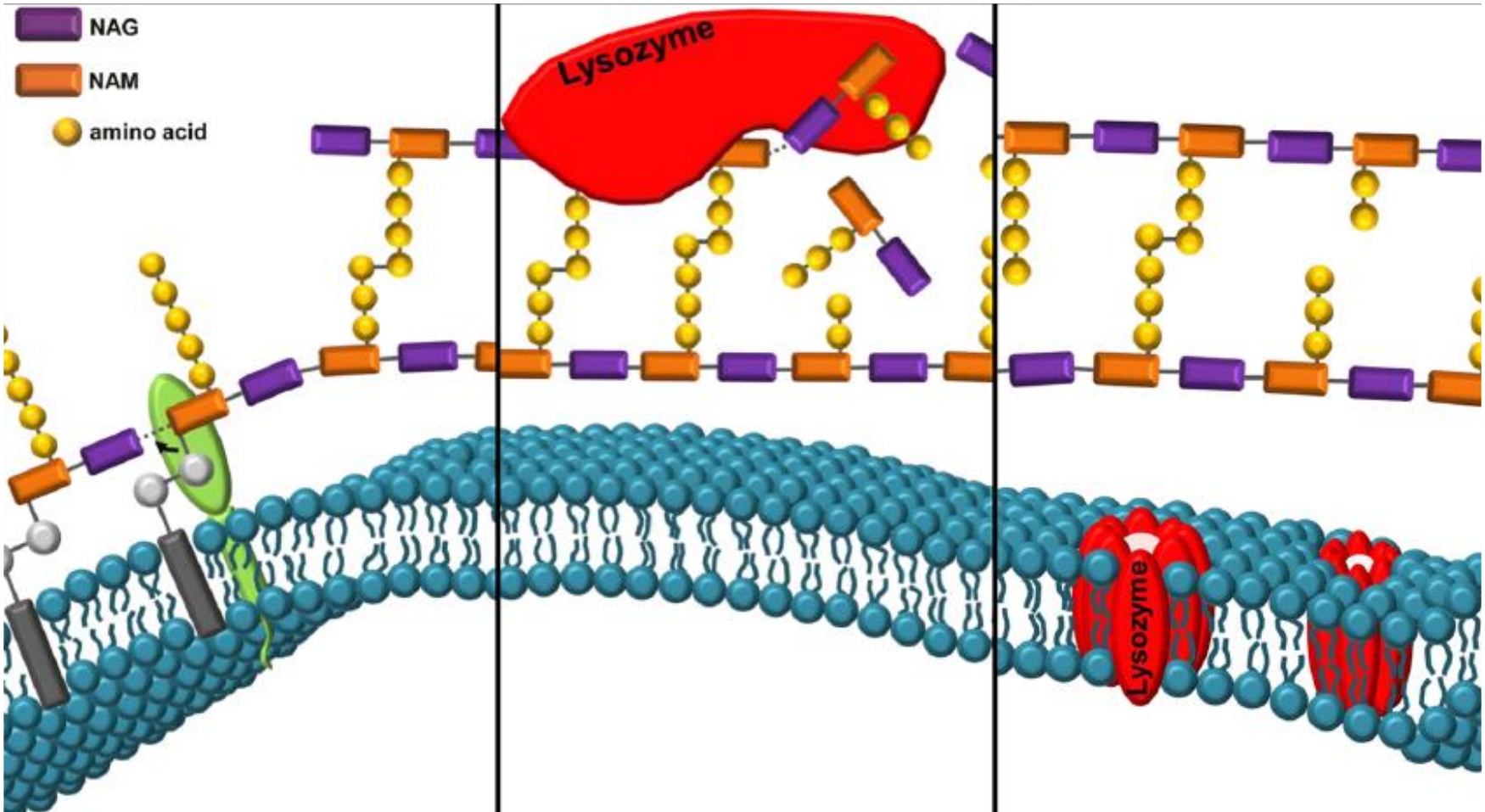
How to fight with pathogens
病原体に抗う方法

Immune system: 3 lines of defense

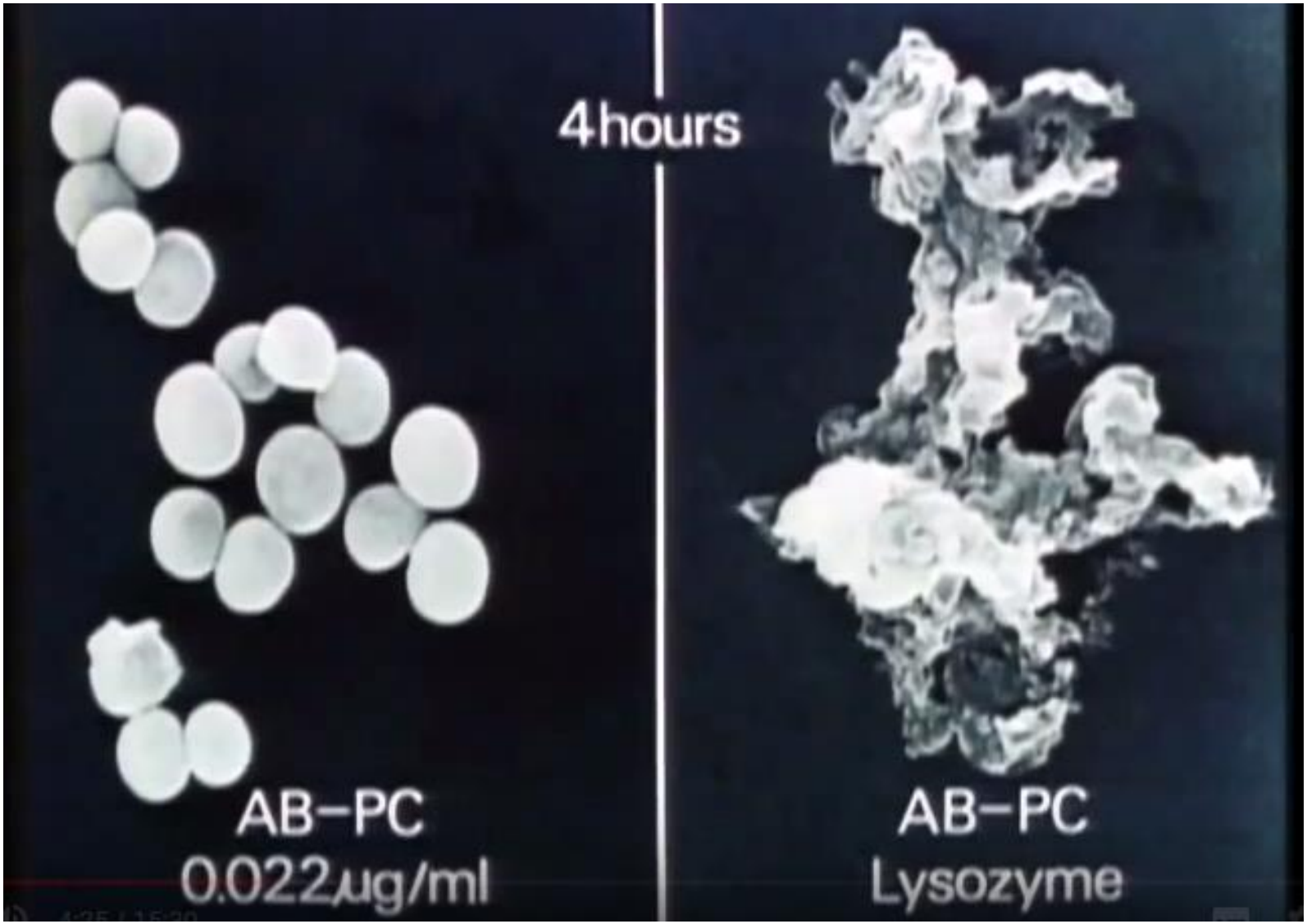
Innate Immunity (Non-specific Defense Mechanisms)		Adaptive Immunity (Specific Defense Mechanisms)
Timeline: 0 to 12 hours		Timeline: 1 to 7 Days
1st Line of Defense	**2nd Line of Defense**	**3rd Line of Defense**
• Skin • Mucous membranes • Secretions of skin • Secretions of mucous membranes	• Macrophages • Other Phagocytes (i.e. neutrophils, NK cells) • Antimicrobial proteins • The Inflammatory response (e.g. redness, fever)	• Lymphocytes (B & T Cells) • Antigen-specific • Antibodies • Memory

Killing by anti-microbial molecules

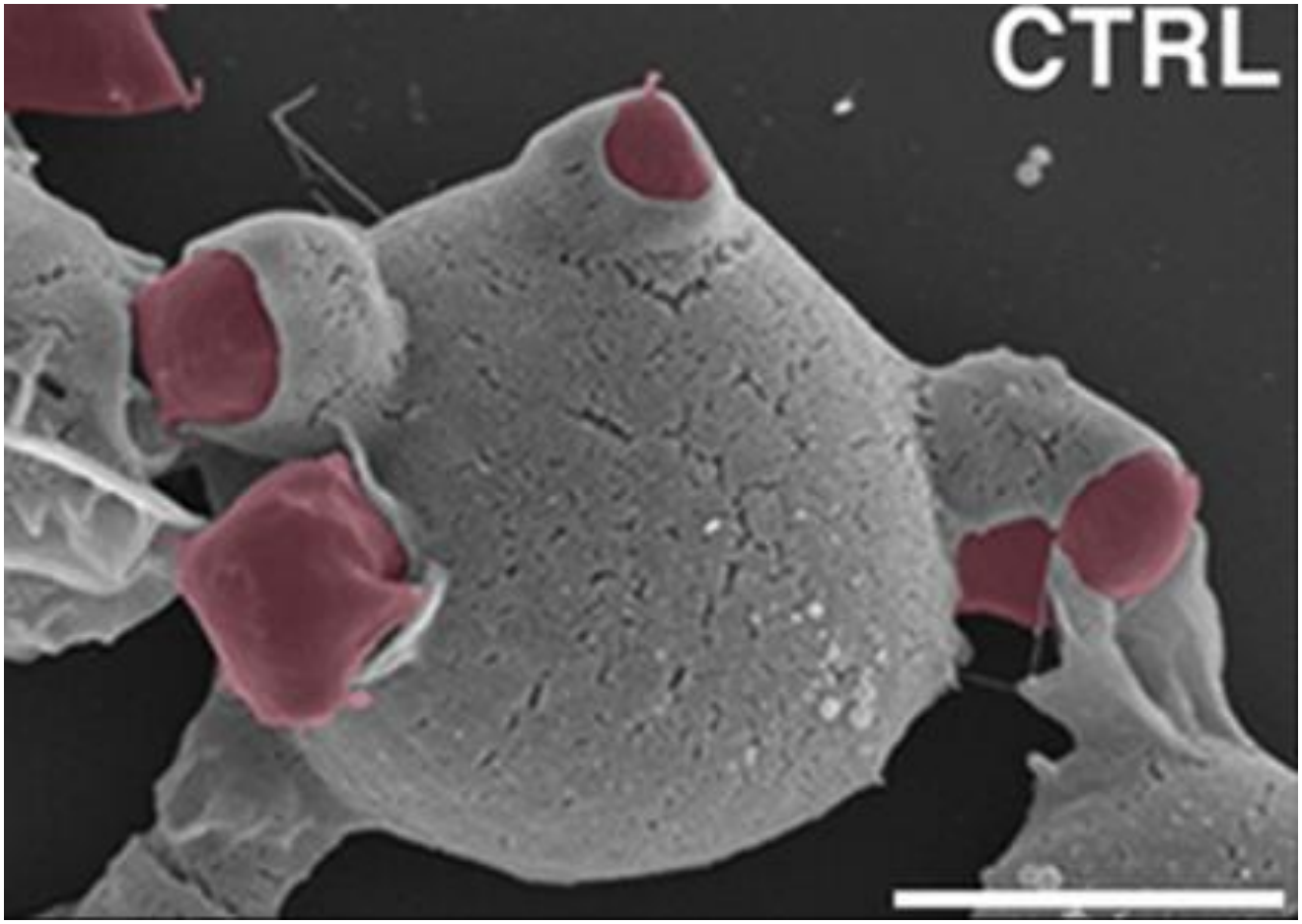
- Lysozyme
- Anti-microbial peptides



Effect of lysozyme on s.aureus (黄色ブドウ球菌)



Killing by phagocytosis



Recognizing microbial unique molecules with receptors to eat.
バクテリアに固有の分子を受容体で認識して食べる

How to recognize pathogen
病原体をどうやって認識する

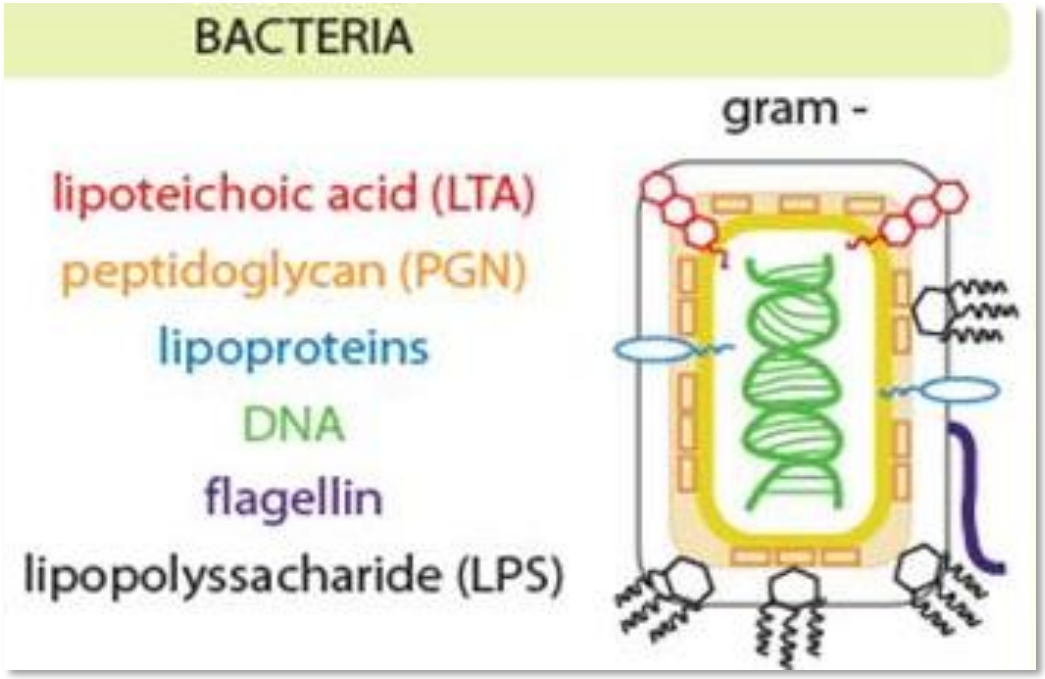
Case 1: pathogens exist outside of cells

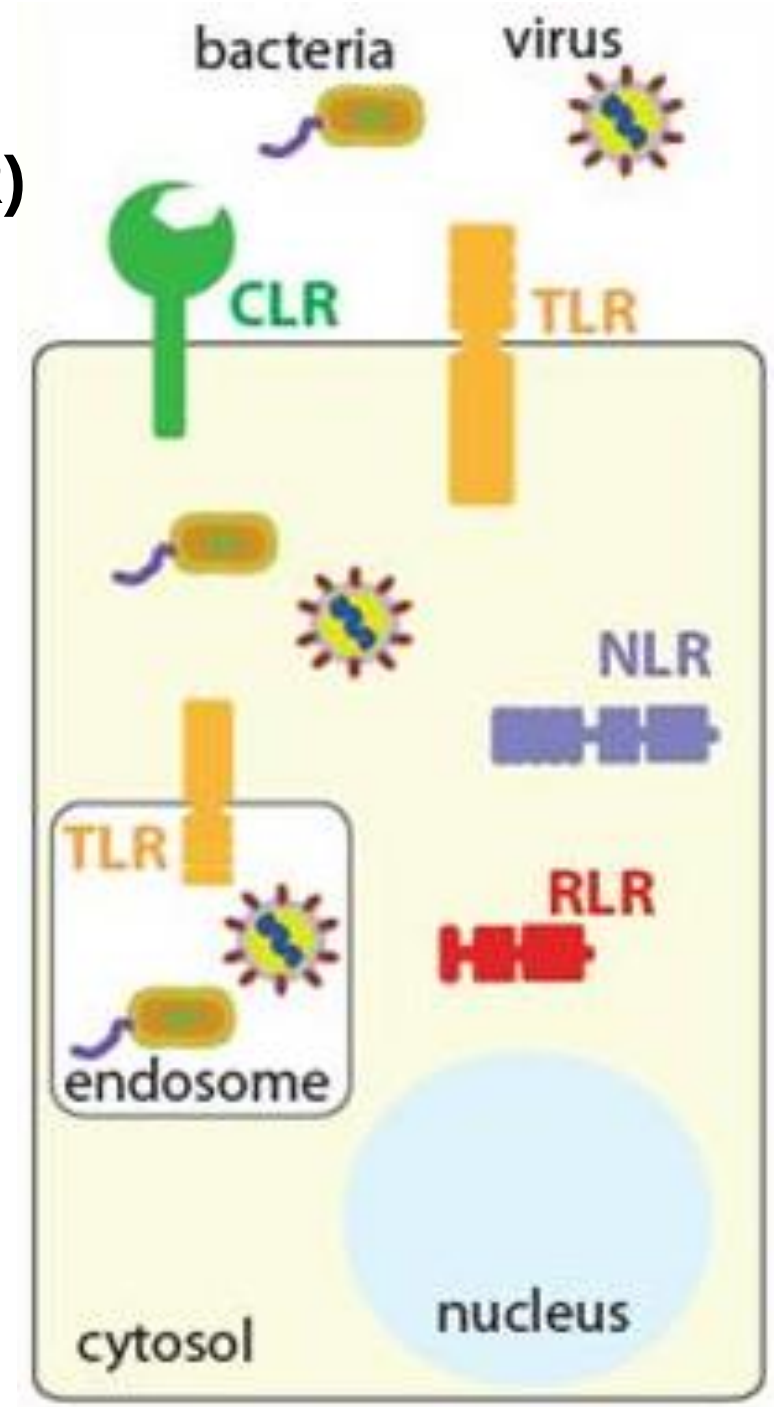
病原体が細胞の外にいる場合

Case 2: pathogens exist inside of cells (infection)

病原体が細胞内にいる場合（感染した場合）

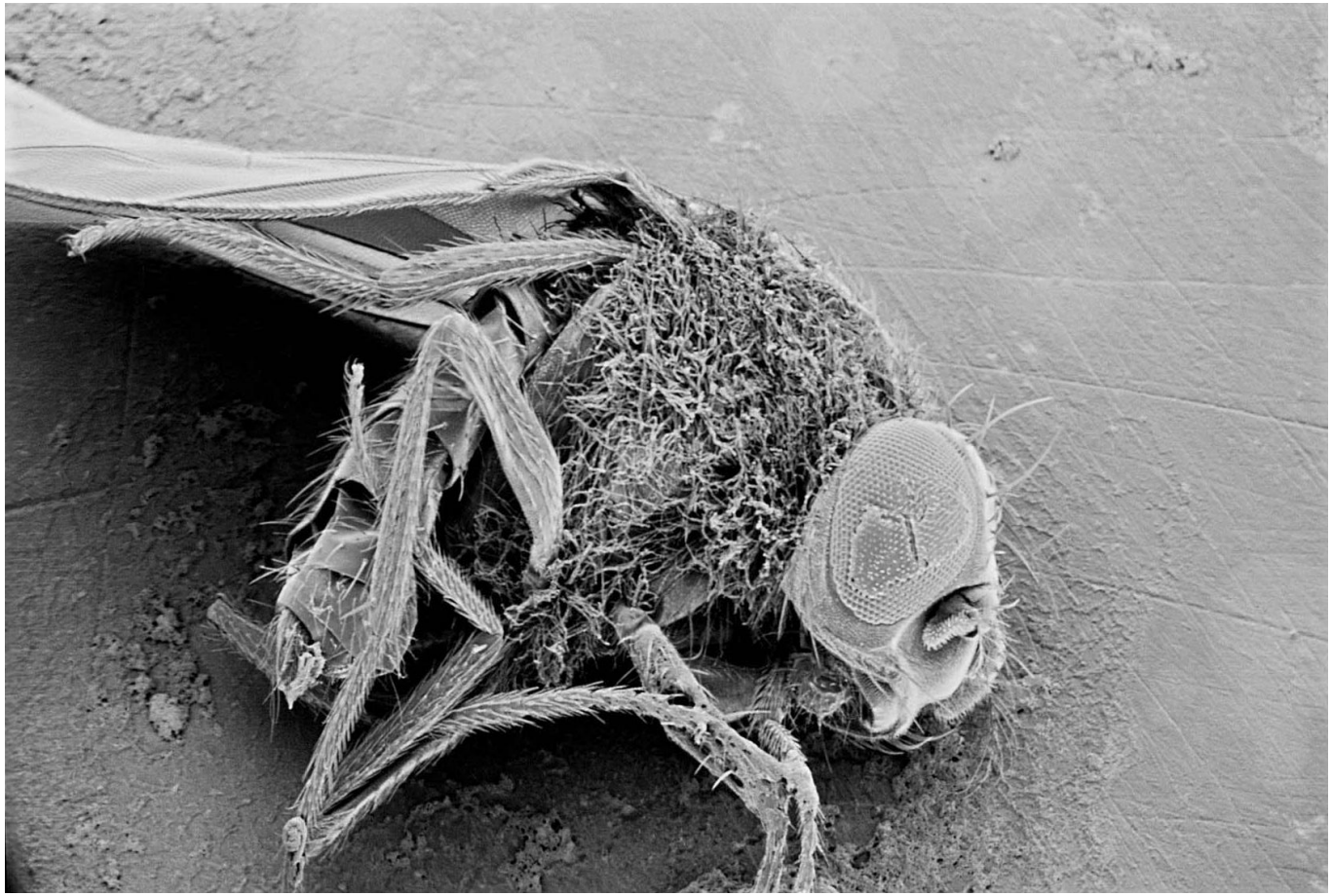
Recognizing microbial unique molecules:
pattern recognition receptors (PRR)





Plants have more PRRs because they do not have acquired immunity.
植物はPRRの種類がもっと豊富。獲得免疫を持たないから。

PRR-deficient fly dies by fungi infection



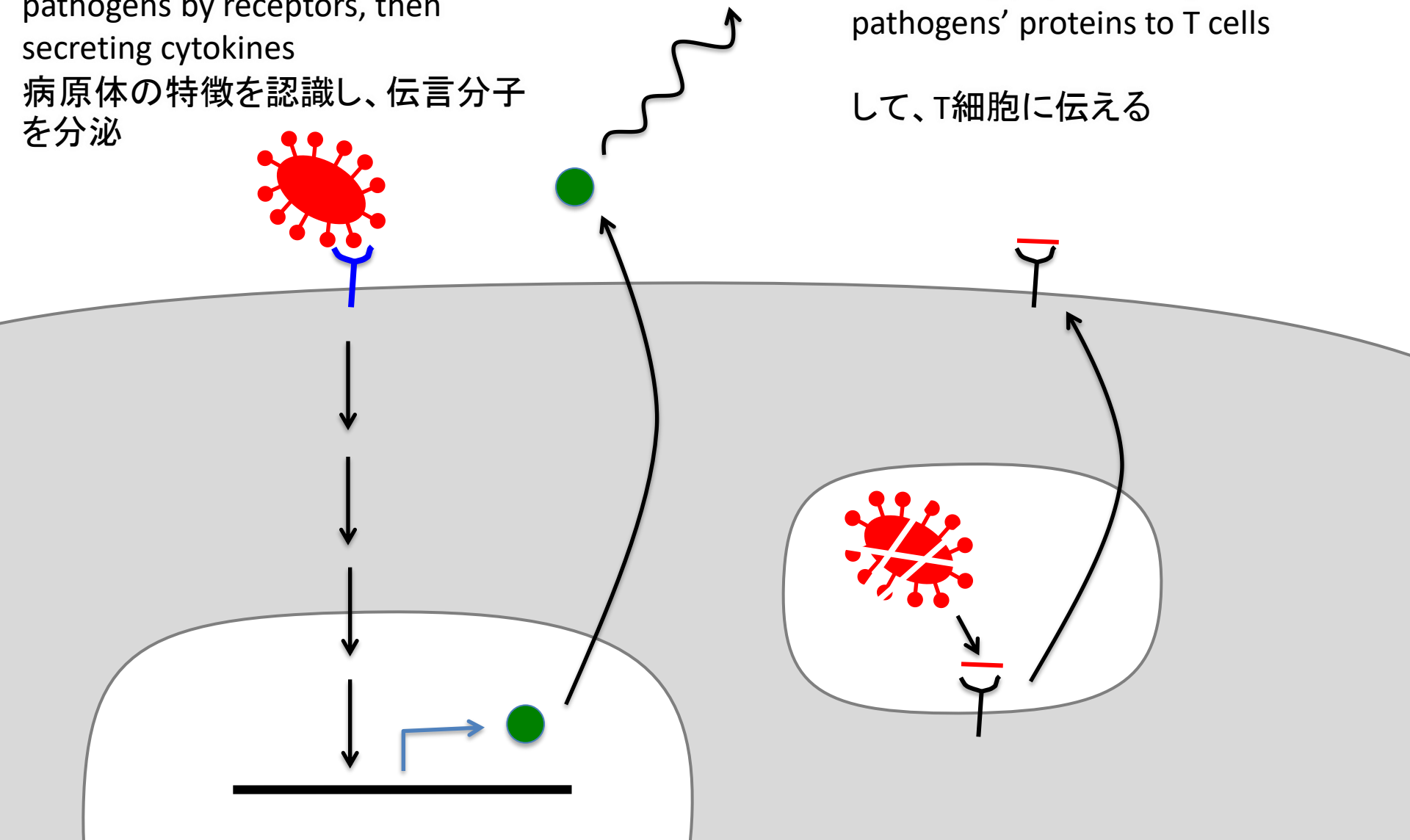
1996 Cell 978

How to call helping cells

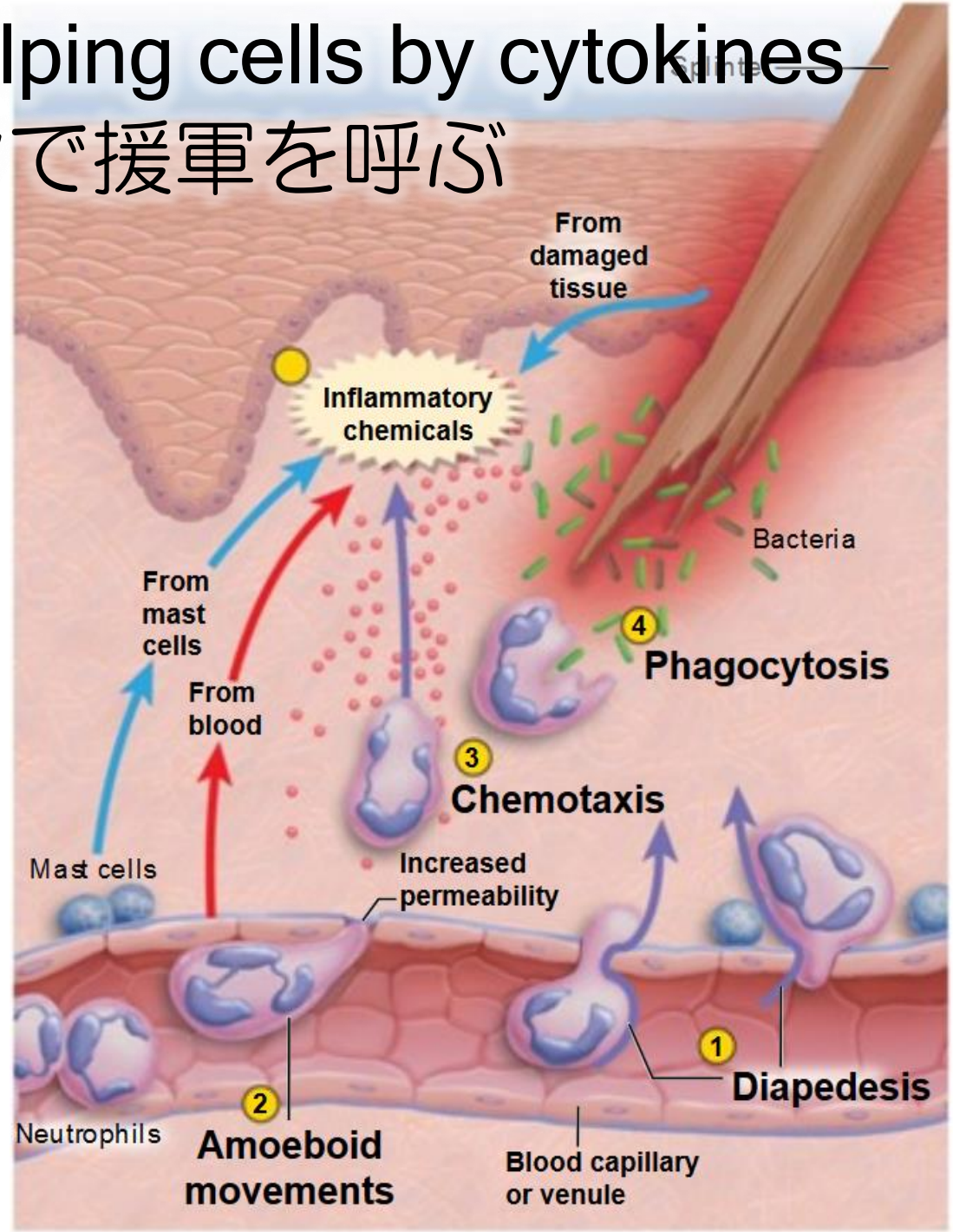
Sensing unique molecules of pathogens by receptors, then secreting cytokines
病原体の特徴を認識し、伝言分子を分泌

Presenting peptides originated from pathogens' proteins to T cells

して、T細胞に伝える



Calling for helping cells by cytokines
サイトカインで援軍を呼ぶ



Without adaptive immunity, we cannot alive
適応免疫がなければヒトは生存できない

Genetics Home Reference

Your Guide to Understanding Genetic Conditions

Omenn syndrome　Omenn症候群

Omenn syndrome is an inherited disorder of the immune system (immunodeficiency). Omenn syndrome is one of several forms of severe combined immunodeficiency (SCID), a group of disorders that cause individuals to have virtually no immune protection from bacteria, viruses, and fungi. Individuals with SCID are prone to repeated and persistent infections that can be very serious or life-threatening. Infants with Omenn syndrome typically experience pneumonia and chronic diarrhea. Often the organisms that cause infection in people with this disorder are described as opportunistic because they ordinarily do not cause illness in healthy people.

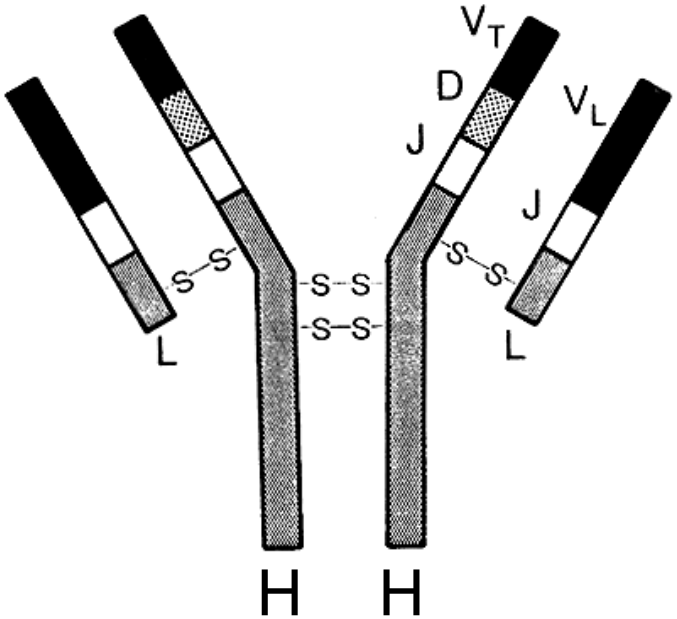
In addition to immunodeficiency, children with Omenn syndrome develop autoimmunity, in which the immune system attacks the body's own tissues and organs. This abnormal immune reaction can cause very red skin (erythroderma), hair loss (alopecia), and an enlarged liver and spleen (hepatosplenomegaly). In addition, affected individuals have enlargement of tissues that produce infection-fighting white blood cells called lymphocytes. These include the thymus, which is a gland located behind the breastbone, and lymph nodes, which are found throughout the body.

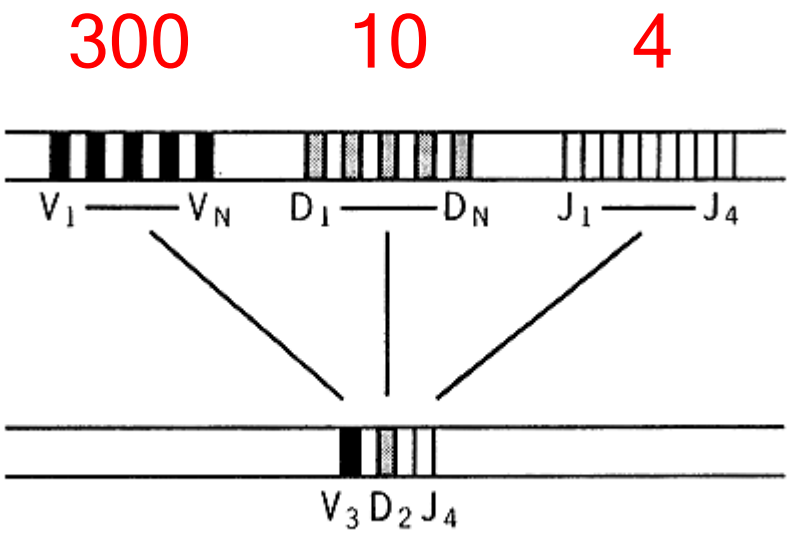
If not treated in a way that restores immune function, children with Omenn syndrome usually survive only until age 1 or 2.

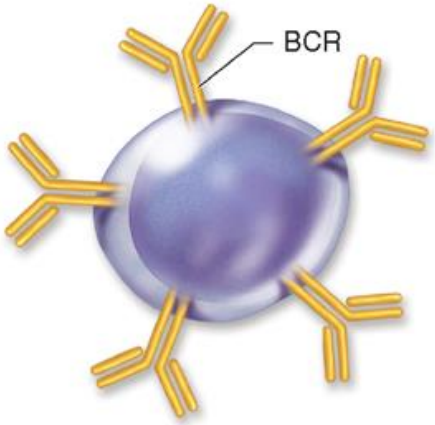

S. Tonegawa
利根川 進

Adaptive immunity: B cell receptor

適応免疫:B細胞受容体







H-chain:

300x10x4 = 10^4

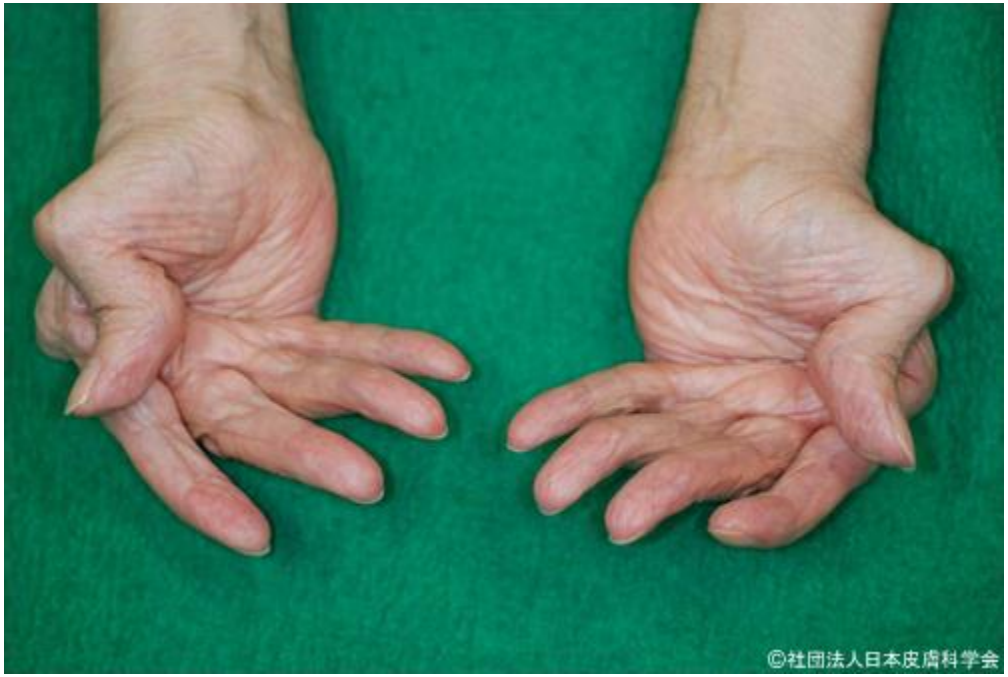
H x L > 10^9

Adaptive immunity is risky
適応免疫は危険な選択

Neonatal jaundice
新生児黄疸

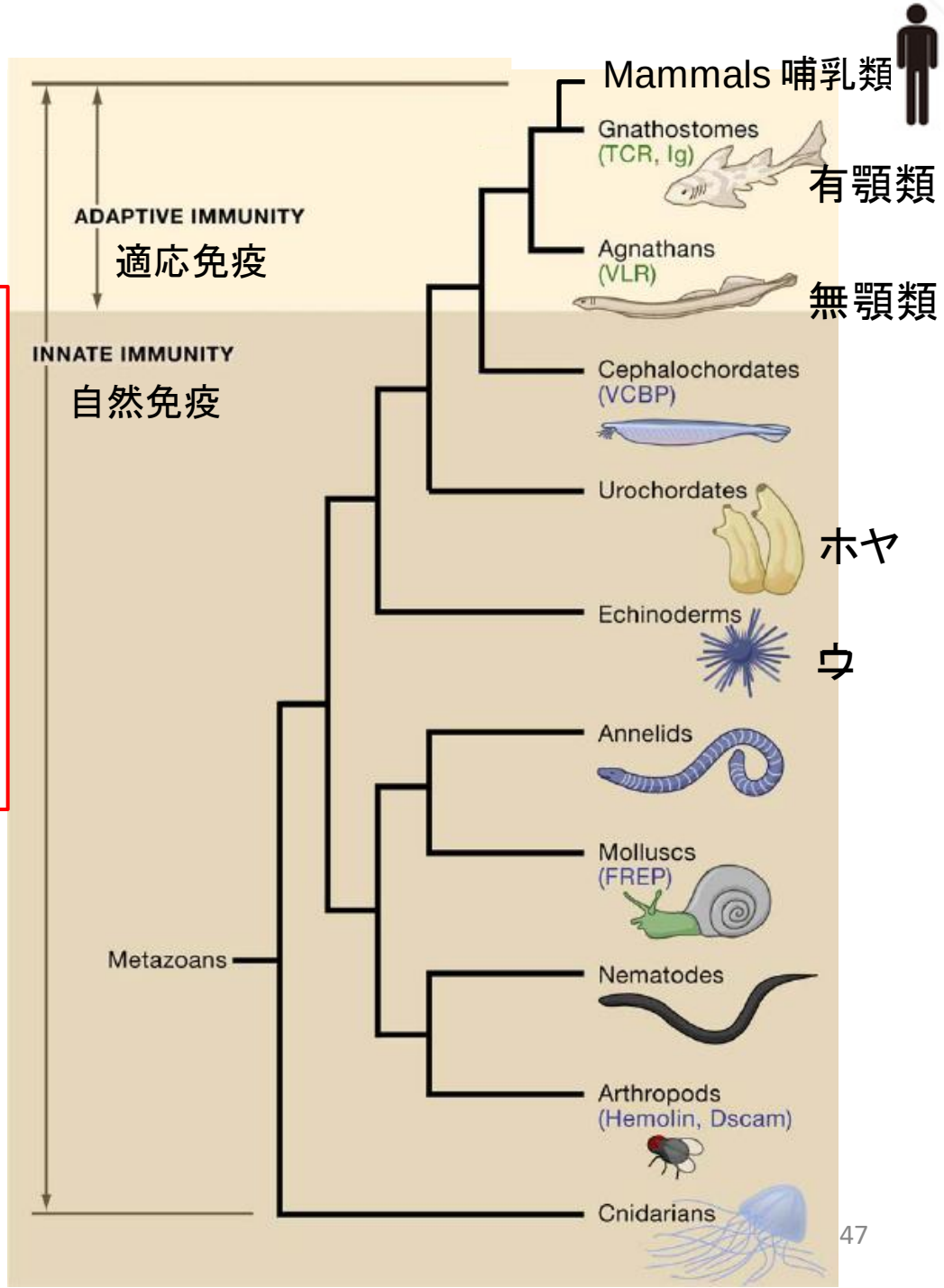
Attacking neonatal RBC
by mother's antibody

Autoimmune disease
自己免疫疾患



Attacking self proteins
by self-immune system

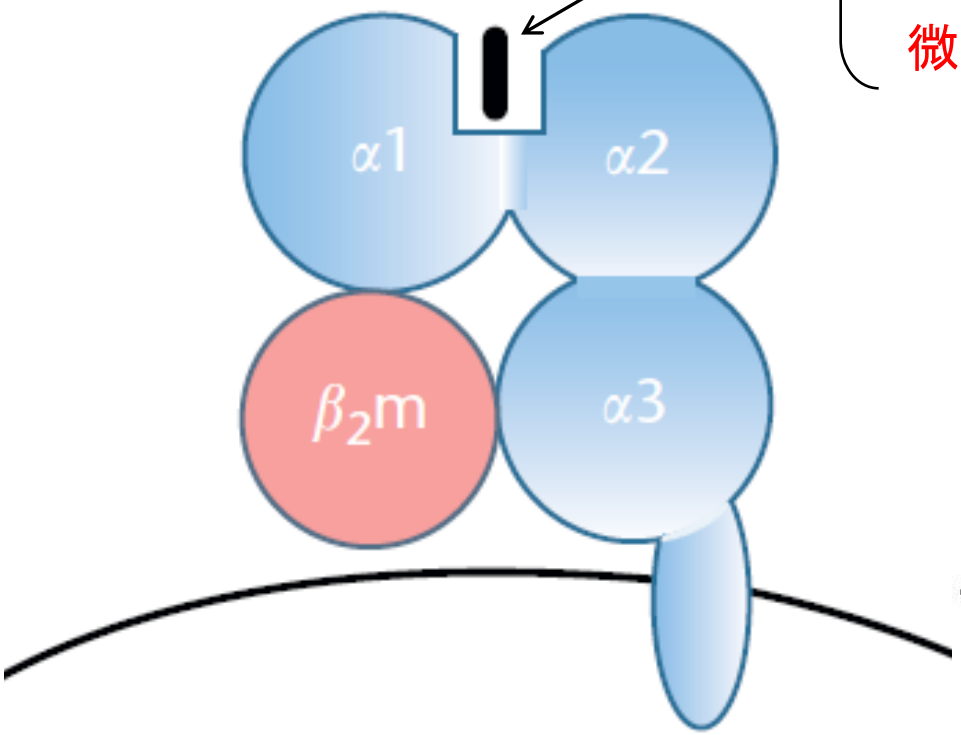
Reason why adaptive immunity was necessary

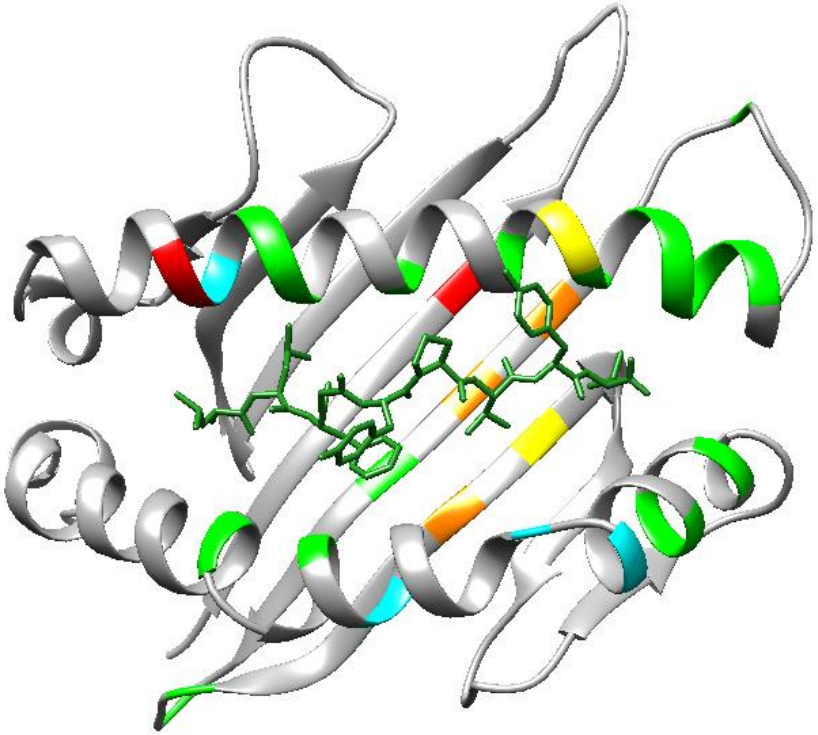


2010 Nat Rev Genet 47; 2006 Cell 815

MHC presents microbial unique molecules on the cell surface
細胞内感染を外部に伝えるMHC

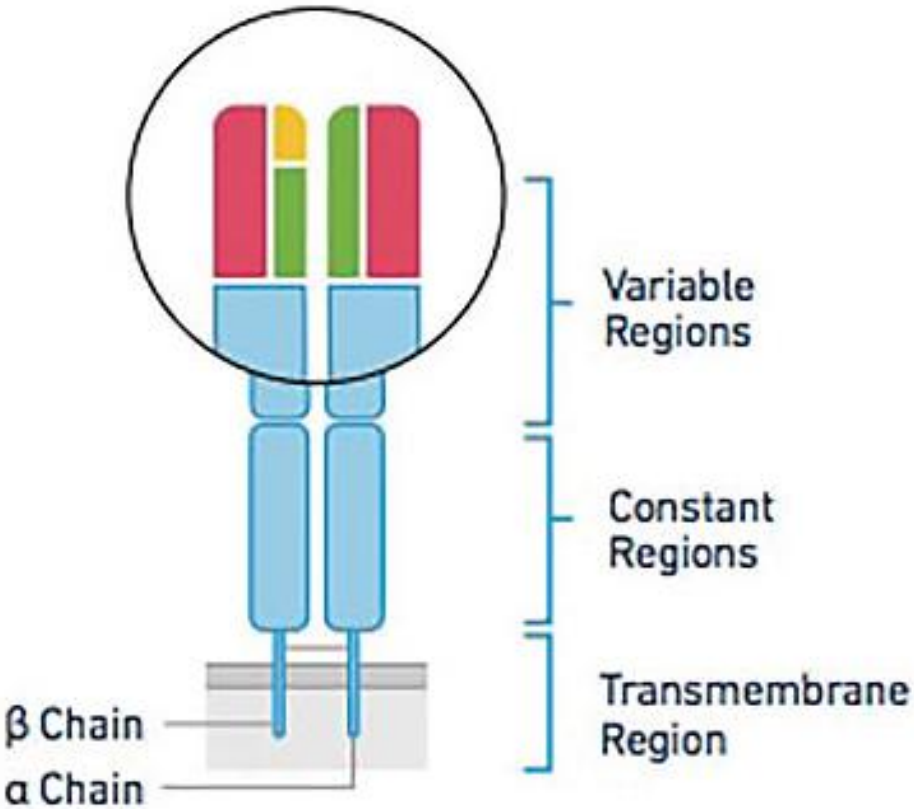
・Microbial glycolipids
微生物由来の糖脂質
・Bacterial vitamin B derivatives
バクテリア由来のVitamin B誘導体
・Microbial peptides (~10 mer)
微生物由来のペプチド（10量体）

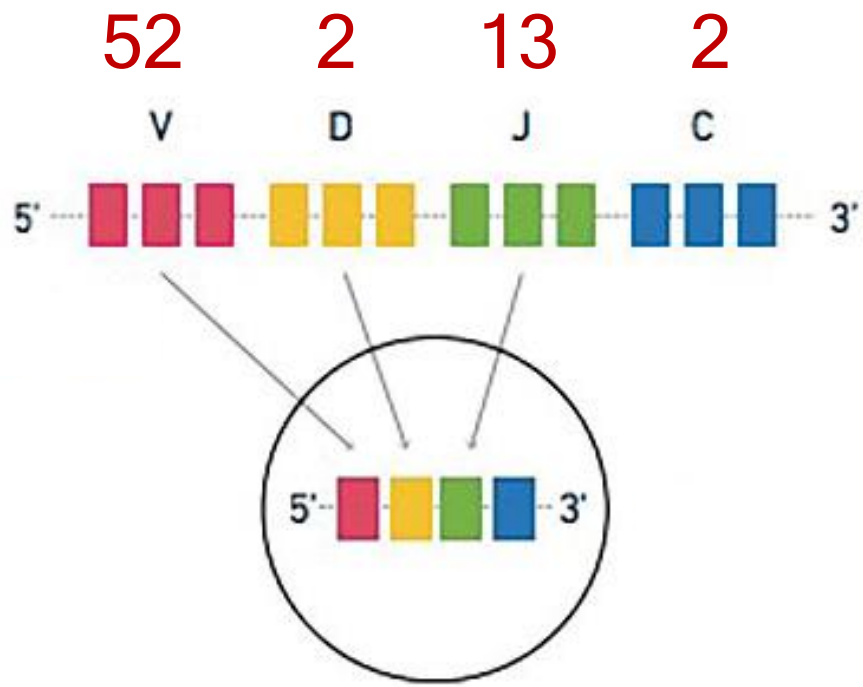




What is the advantage of peptides to recognize microbes?

T cell receptor



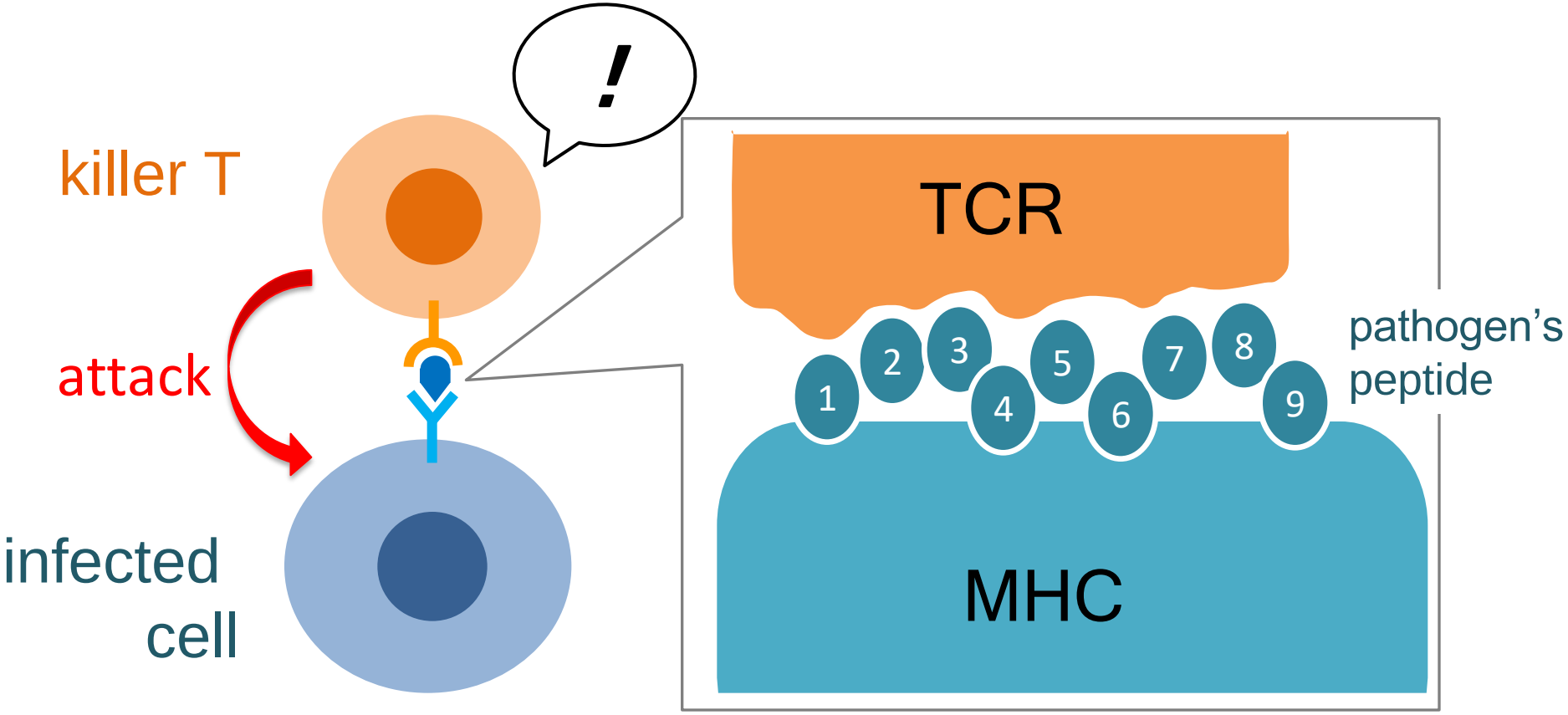


β-chain:

50x2x13x2 = 2704

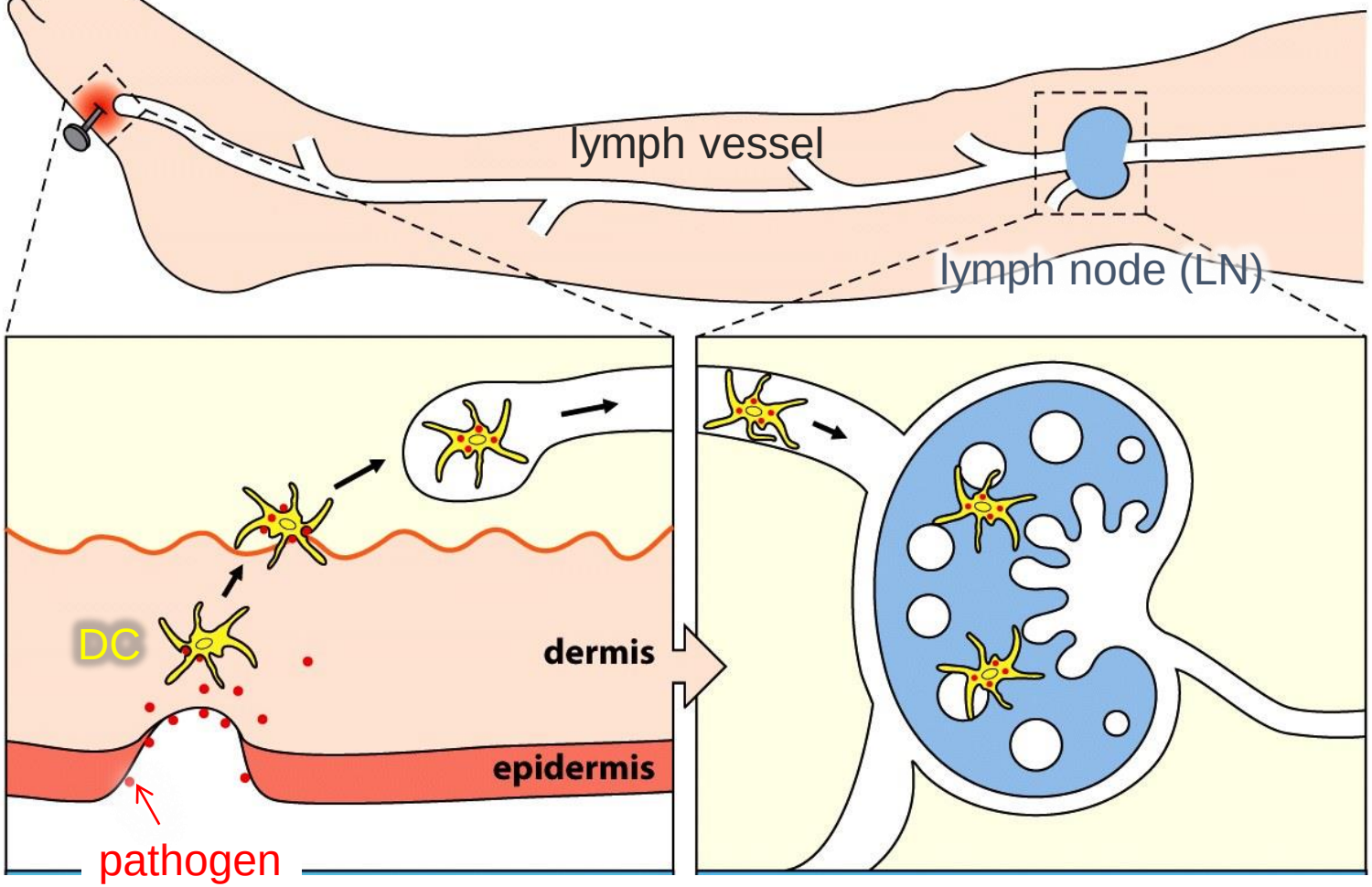
α x β ~ 10^16

Killer T cells find and kill infected cells via TCR
キラーＴ細胞は感染細胞をTCRで認識して殺す



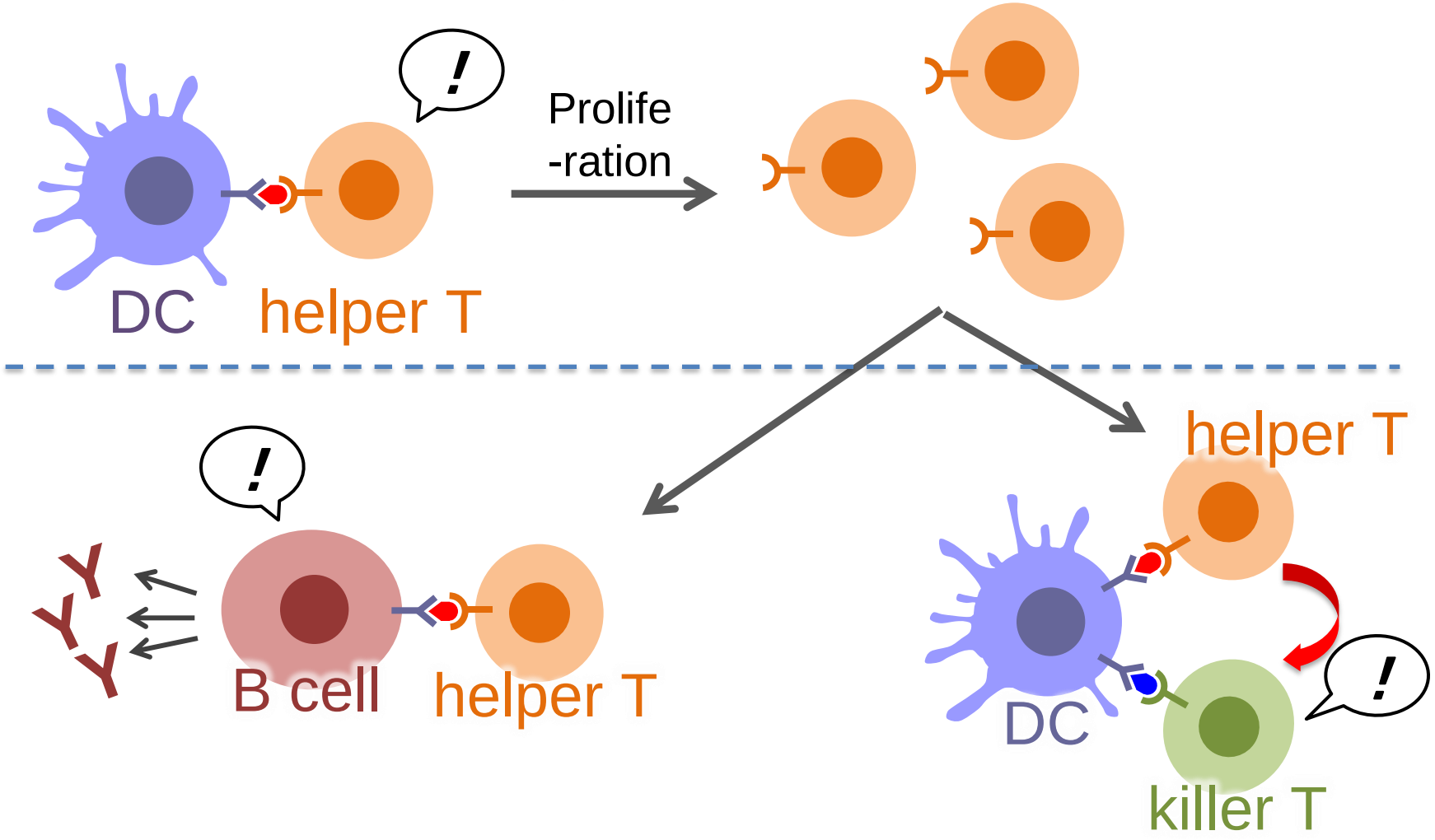
To avoid autoimmunity, killer T cells require activation by helper T cells.自己免疫を避けるために、キラーＴ細胞はヘルパーＴ細胞により活性化される必要がある。

Dendritic cell (DC) delivers pathogen's peptides to closest lymph node where T and B cells exist
樹状細胞は病原体のペプチドをリンパ節に運び、T、B細胞に見せる



The DC-mediated system is effective for large animals.

In lymph node



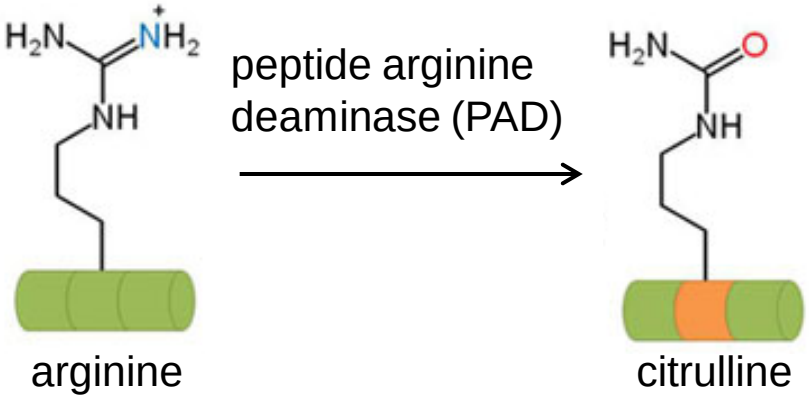
B cells and killer T cells can be activated only when approved by helper T cells.
ヘルパーT細胞に承認されたときのみ、B細胞とキラーT細胞は活性化できる。

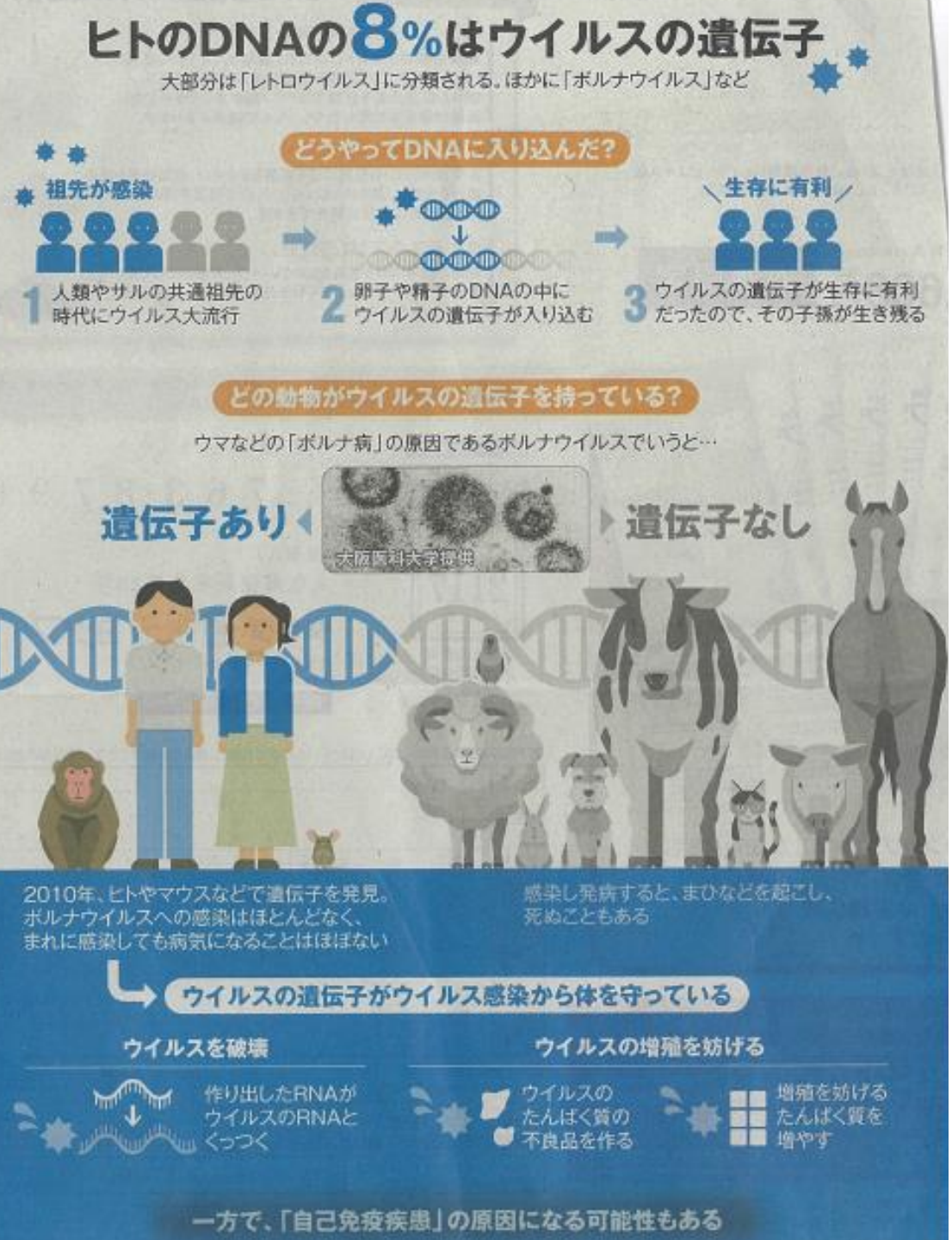
Why self-antigens are misidentified as foreign antigens?
なぜ自己抗原を敵と誤認するのか？

1. Molecular mimicry with foreign antigens
抗原と自己抗原の配列が似ているから。

2. Recognizing self-antigens in inflammatory condition
炎症の環境で自己抗原を認識したから。

3. Amino acid residues in self-antigens are changed
(eg. citrullinated peptide)
自己抗原の配列が変わったから
（例：シトルリン化ペプチド）





朝日新聞　19/1/14

- ウイルス由来DNAは、ウイルスタンパクの不良品を作ることで、ウイルス感染を阻害（例：ボルナ病）

- このタンパクが原因で、自己免疫疾患になる可能性

⇒molecular mimicry

Final report レポート課題

In addition to the diseases covered this time (diabetes, allergy, autoimmunity), choose what seems to be a mismatch disease and explain where the disease is caused by mismatching with the modern environment. (more than 120 words)
今回取り上げた疾患以外で、ミスマッチ病と思われるものを選び、どこが現代の環境とミスマッチしていて疾患が起るのか説明せよ。
（400字以上）

Deadline: May 28th
Submit via e-mail to me (moriken37yuta@gmail.com)
Title: final report

ネットの受け売りではなく、自分で調べたことをまとめたり、自分の考えを入れたりして、一工夫すること。