



**Pharma
Summit 25**

Evolving through change



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Prof Kingston Mills
Professor of Experimental
Immunology and Director
of Trinity Biomedical
Sciences Institute



Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

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 **uniphar**

How immunology is central to the design of new therapeutics and vaccines for inflammatory disease, cancer and infection

Kingston Mills

*Trinity Biomedical Sciences Institute
Trinity College Dublin, Ireland*



'Immunology is super-interesting'

Lunch with the FT: Gideon Rachman buys Bill Gates a cheeseburger and discusses true fanaticism, death, philanthropy, China and who'll pay the bill

I am sitting on a bar stool. On the other side of a round metal table, the world's second richest man is signing a Diet Coke, eating French fries with his fingers and explaining the history of the polio vaccine. Bill Gates would still be the richest man in the world, if he hadn't been giving his money away. Now, after donating \$15 billion to the Bill & Melinda Gates Foundation — which funds health, development and educational causes — he is down to his 19th.

For a man who has made such an impact on the world, Gates seems to have a simple life. We meet at his office in Kirkland, a suburb of Seattle, and walk across the road to the Blue Cafe in the Woodlands, a small local hotel. It is a pleasant enough spot, overlooking Lake Washington, but I am guessing it has been chosen for convenience rather than taste. We are seated in the bar area, away from the other diners. Gates is wearing a brilliant white, slip-up espadrille over a plain green shirt and khaki trousers. Now in his mid-fifties, he still looks youthful, with just a hint of grey in his sandy hair.

A waitress comes into view and Gates orders a cheeseburger and a chocolate milkshake. He also goes for a cheeseburger, with a crab dip, and we get talking about life in Seattle. He tells me that he still drives himself around the city, intrigued by his lack of attention. I ask whether he has expensive tastes for meals. His gaze is steady and "will you need for that is a deck of cards?" So he is an avid poker player. "Yes, I have a nice office. I have a nice house. I'm not doing it for money, money, money. I just don't happen to have expensive tastes." Once a couple of miles away, however, like the launch of the Microsoft Store on the online, complete with a library with a question from The Great Gatsby on the online.

Gates's account of the origins of Microsoft also has little to do with money. He founded the firm in 1975, after dropping out from Harvard to develop his passion for computers. "When I decided to go and start Microsoft, it wasn't because it was some lucrative career. That's what this qualified friend and co-founder of Microsoft) and I



forable for some people. There's all sorts of reasons to put off doing it, because once you make your money, you were supposed to do it, you know what you are doing... So putting up something new is very difficult and also it's kind of forces you to think about your death."

In Gates's case, there is a strong Christian faith, rooted in the family. His late mother Mary (short of the Seattle branch of the United Way, International, a charity). His father Bill senior, now 84, is also an energetic philanthropist, and is reportedly managing his billion-dollar net worth in Washington state. Above all, Gates's wife, Melinda, whom he met at Microsoft and married in 1994, (the couple has three children) is passionately engaged in the foundation's work. The couple are the founders of the Bill & Melinda Gates Foundation.

In 2008, Gates became non-executive chairman of Microsoft and he now devotes most of his time to the foundation. But, he says, "I'm working as much as ever. I did it all in my twenties and early thirties, when I took no vacations and didn't go home most nights. That was true fanaticism. In those years, when Warren Buffett, the billionaire investor who is now a close friend, bridge partner and a major donor to the Gates Foundation, would meet the man from Microsoft, Gates would usually find time in his diary. "I've got to see you, I don't do things like that." So, I imagine, you had no social life. Gates puts his right hand on his chest. "No, I associated with my parents on a Sunday night, but I just didn't go out with people who were involved in investments."

Gates says he has no regrets about his fanaticism, but he is clearly utterly proud by the medical challenges that his foundation is taking on — in particular the effort to develop new vaccines for malaria and HIV and to eradicate polio through vaccination. The next step, he says, is to meet enjoying himself now when he gets into the action, and as he talks, he folds his arms across his chest and rocks gently back-

THE NEW YORKER

MEDICAL DISPATCH | NOVEMBER 30, 2015 ISSUE

INFLAMED

The debate over the latest cure-all craze.

BY JEROME GROOPMAN

As a result, understanding and controlling inflammation has become a central goal of modern medical investigation. The internal research arm of the National Institutes of Health recently designated inflammation a priority, mobilizing several hundred scientists and hundreds of millions of dollars to better define its role in health and disease; in 2013, the journal *Science* devoted an entire issue to



'Cancer, atherosclerosis, diabetes, neurological diseases and autoimmune diseases all have inflammation at their core. This places the study of **inflammation** at the heart of modern medicine.'

David Baltimore, Nobel laureate



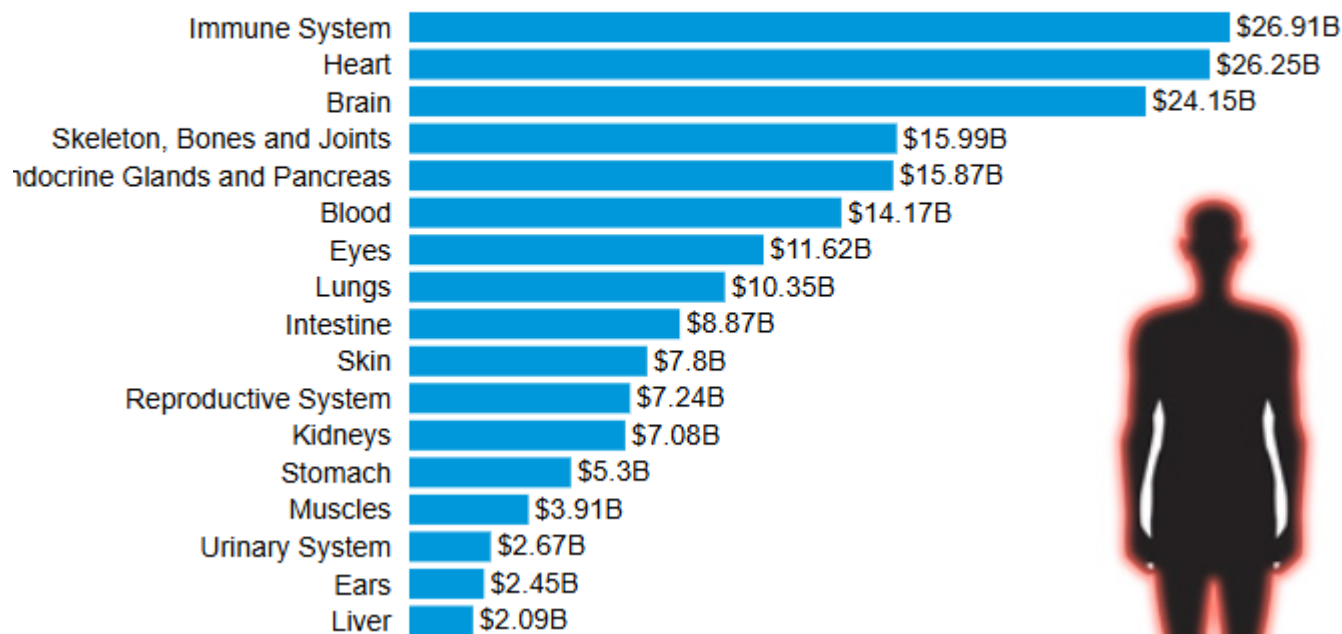
The Human Body, According to Venture Capitalists

The investors who support emerging medical technologies play an important role in determining which new therapies reach the public. A WSJ Pro analysis of venture investment trends since 1999 reveals which body systems stand to benefit most from their decisions.

By: [Renee Lightner](#), [Christopher Zinsli](#) and [Alberto Cervantes](#)

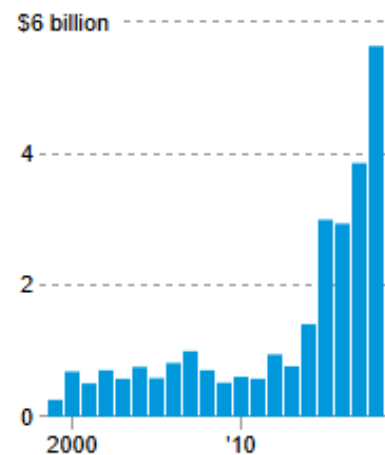
Last updated Feb. 14, 2019 | Published Sept. 14, 2014

Total amount invested by venture capital deals, 1999-2018

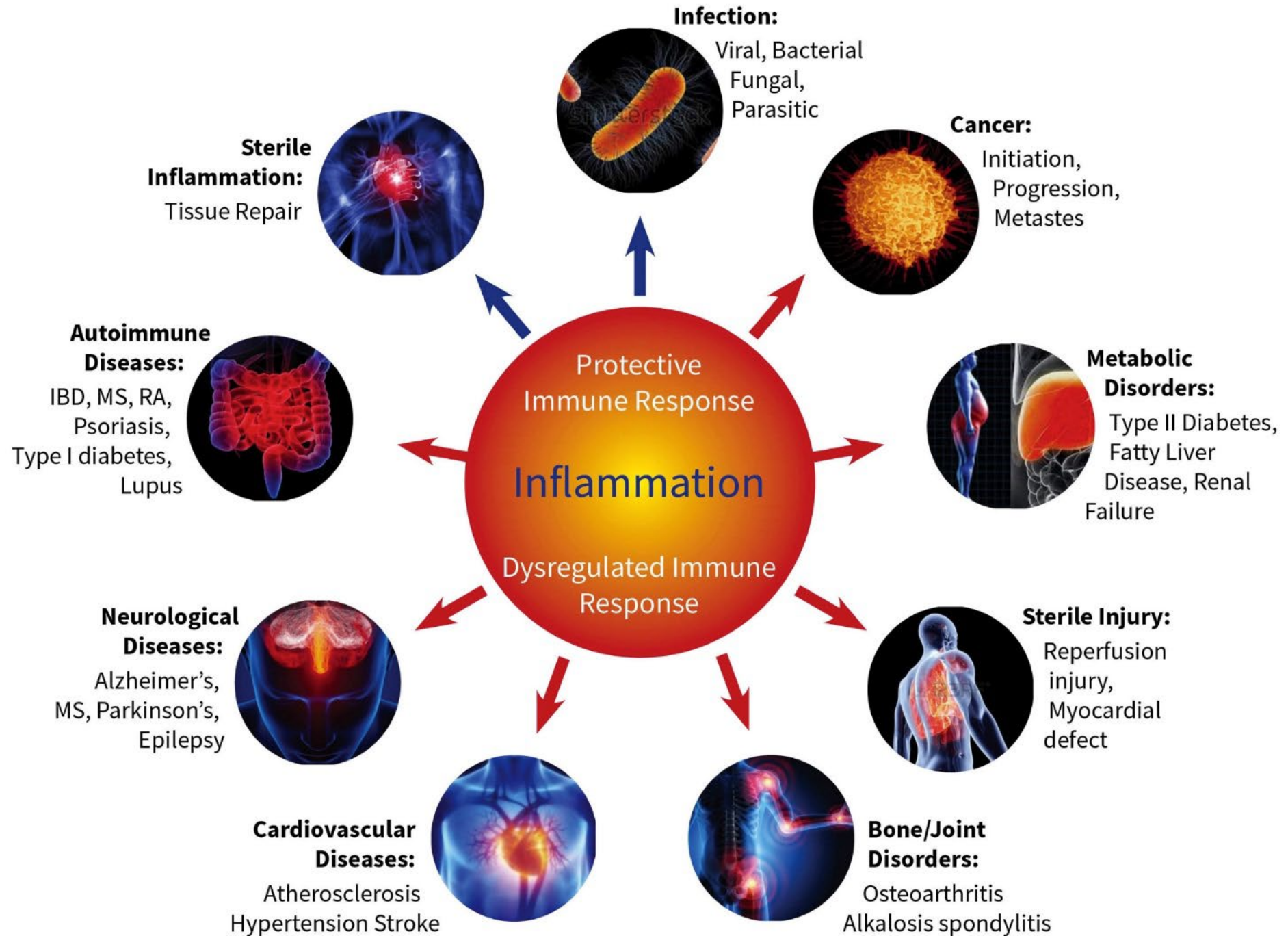


Immune System

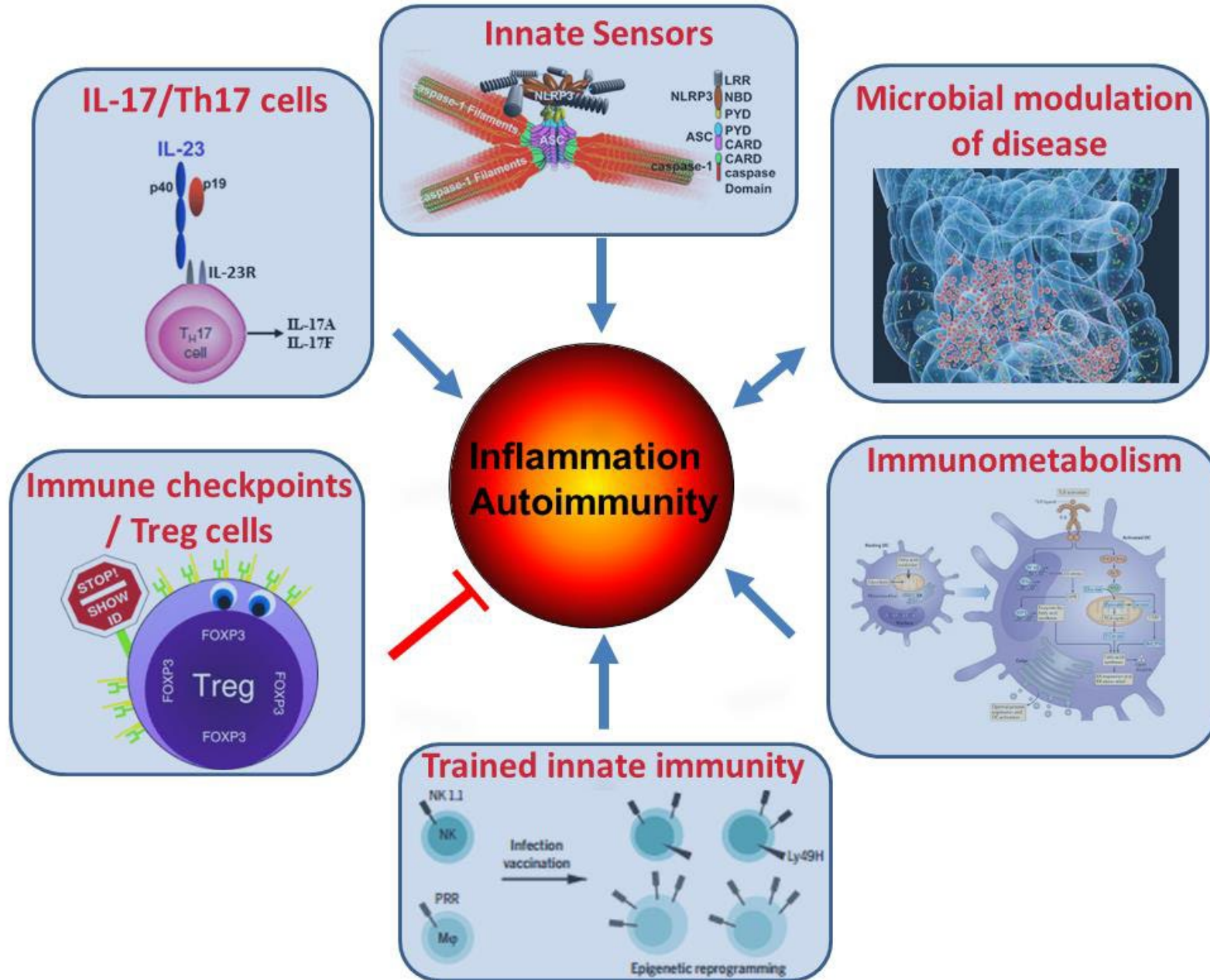
The emerging field of immuno-oncology is driving considerable interest in this sector. The amount of capital invested in immunological startups last year surpassed the amount committed to any medical field in any year on record.



Total 1999-2018:
\$26.91 billion



Frontier areas of immunology



Precipitating factors in human diseases: Genetic versus environmental

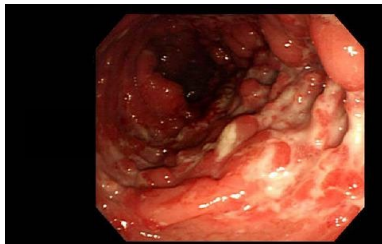
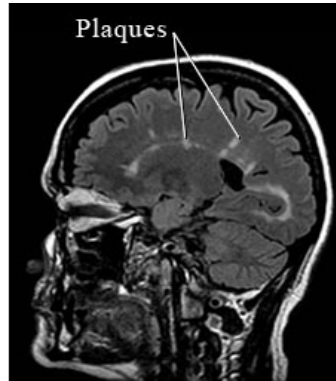
Variation in the Human Immune System Is Largely Driven by Non-Heritable Influences

Petter Brodin,^{1,2,3,11} Vladimir Jojic,^{4,11} Tianxiang Gao,⁴ Sanchita Bhattacharya,³ Cesar J. Lopez Angel,^{2,3} David Furman,^{2,3} Shai Shen-Orr,⁵ Cornelia L. Dekker,⁶ Gary E. Swan,⁷ Atul J. Butte,^{6,8} Holden T. Maecker,^{3,9} and Mark M. Davis^{2,3,10,*}



Measured 204 different parameters, including cell population frequencies, cytokine responses, and serum proteins, and found that 77% of these are dominated and 58% almost completely determined by nonheritable influences.

Autoimmune / chronic inflammatory diseases

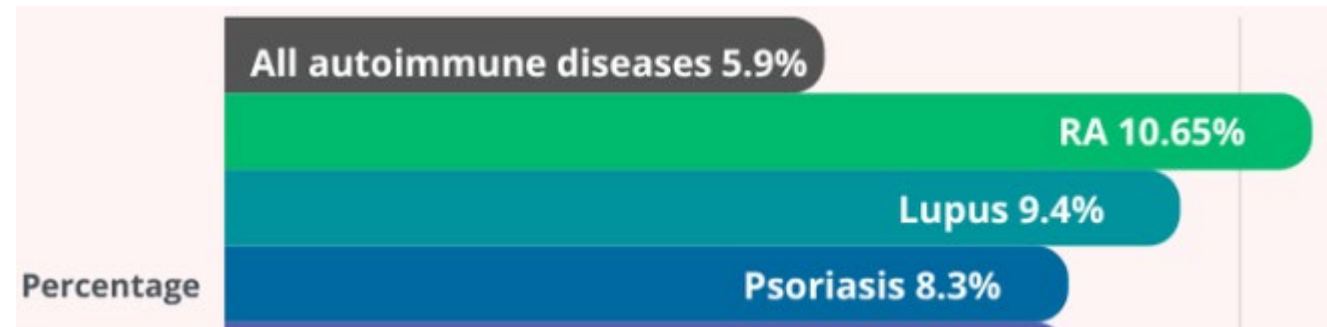


- Affect over 300 million people worldwide and increasing

- **Rheumatoid arthritis** (RA): 1/100, 20m people in US
- **Psoriasis** 1/50-1/1000; 5.5m in US
- **Multiple sclerosis** (MS): 1/700,
- **Crohn's disease and Ulcerative colitis**: 1/500-1/2000
- **Type 1 Diabetes**: 1/100,000 – 1/2000

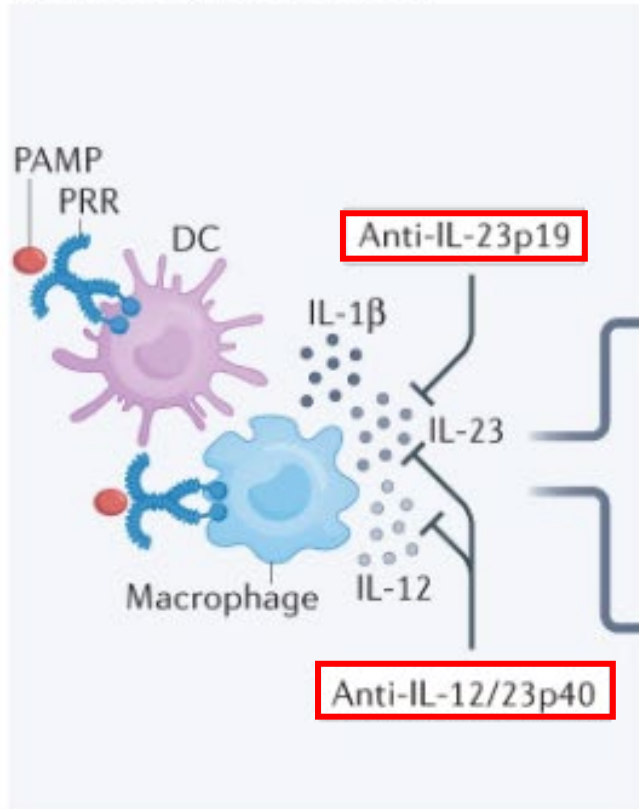
- Pharmacological drugs, including traditional chemotherapy, still major first line treatment, but biologics increasing use and market share

% patients prescribed Biologics at time of diagnosis

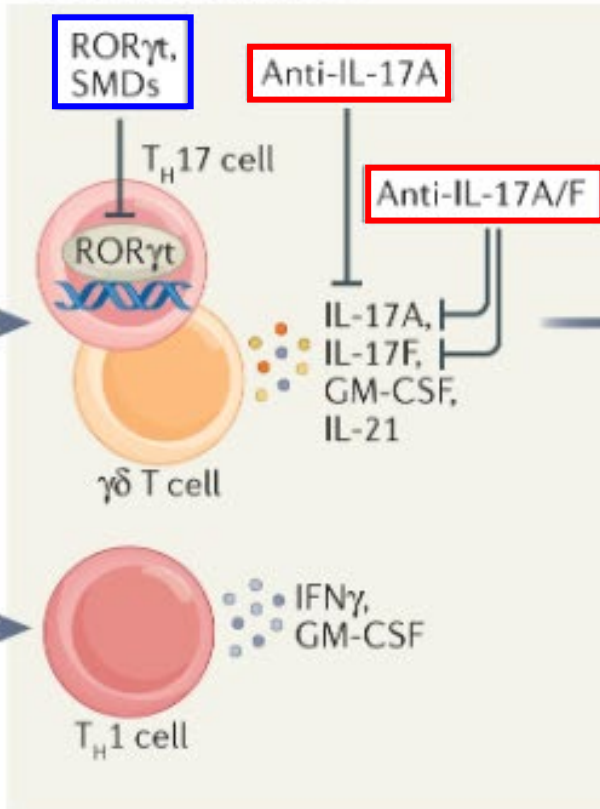


Drug targets in IL-23-IL-17 pathway

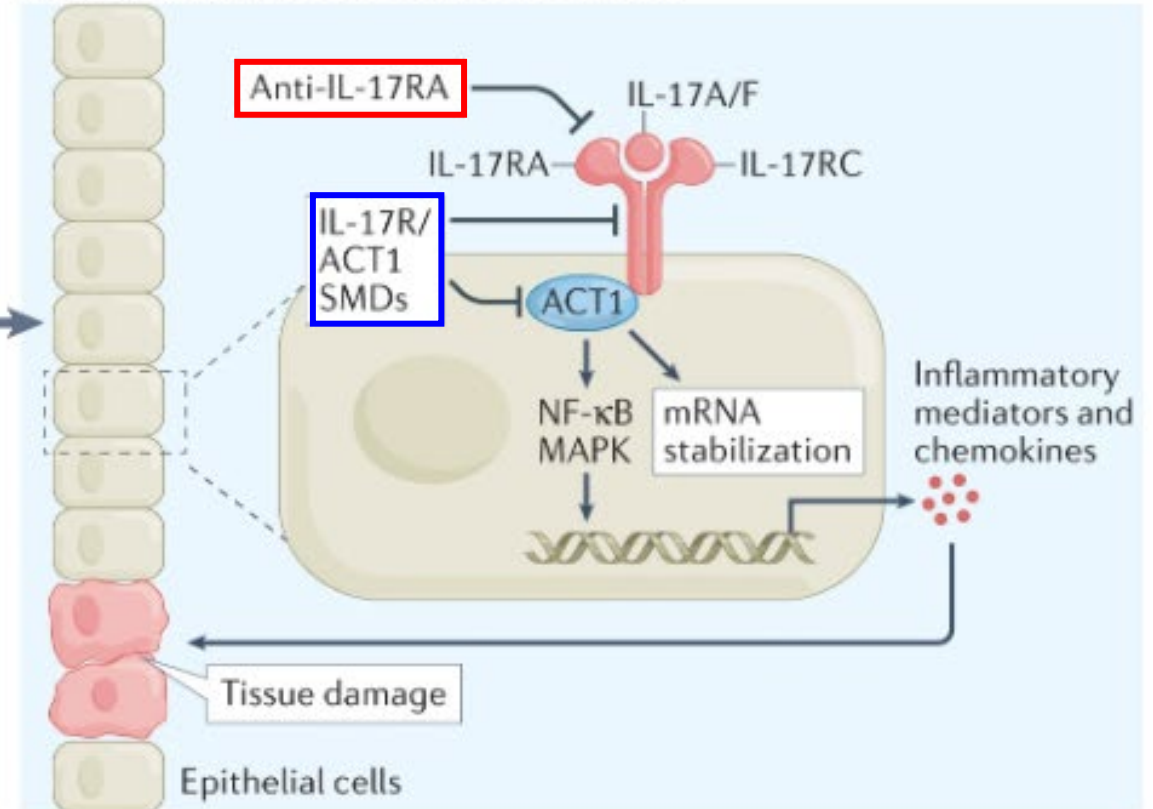
Production of T cell-polarizing cytokines by myeloid cells



Activation of pathogenic T cells in lymph nodes

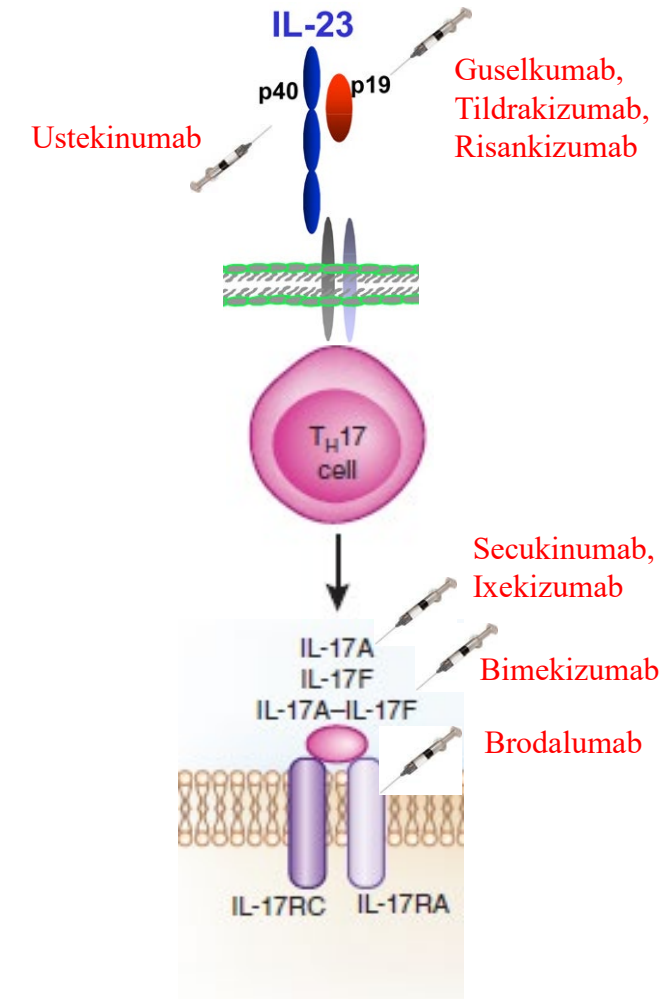


Effector function of IL-17 in target issue



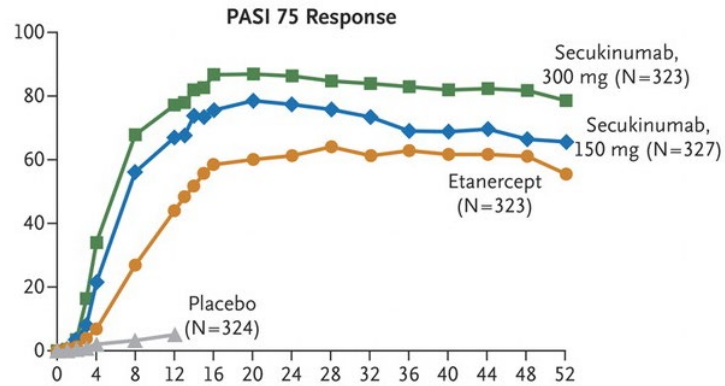
IL-17/IL-23 therapies for autoimmune/inflammatory diseases

Indication	Evidence of role for IL-17 pathway	MoAb to IL-17 pathway in clinical trials / human use
Psoriasis	IL-17RA SNP association. Th17 and $\gamma\delta$ T17 in skin lesions	ustekinumab, secukinumab, ixekizumab, bimekizumab, brodalumab guselkumab, tildrakizumab, risankizumab approved
Psoriatic arthritis	Th17, Tc17, $\gamma\delta$ T17 and ILC3 in skin lesions and synovial fluid	ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab, risankizumab, approved
Ankylosing spondylitis	IL-23R, STAT3 & CARD9 SNP association	secukinumab, ixekizumab, brodalumab approved
Rheumatoid arthritis	IL-17 in synovial fluid.	ustekinumab or guselkumab no efficacy secukinumab low efficacy
Multiple sclerosis	Th17 and $\gamma\delta$ T17 in brain lesions	secukinumab some efficacy phase 2
Inflammatory bowel disease	IL-23R SNPs association. Th17 enhanced in CD and UC	ustekinumab approved, secukinumab, brodalumab \uparrow disease
Type 1 diabetes	Th17 expanded in blood in T1D	ustekinumab and ixekizumab phase 2/3 recruiting
Uveitis	Elevated IL-17 and IL-23 in blood	secukinumab phase did not meet primary endpoint.
Atopic dermatitis	IL-17A \uparrow in skin lesions, \uparrow Th17 in blood	secukinumab phase 2 completed
Neutrophilic asthma	IL-17A SNPs association, Th17 cells \uparrow in blood	secukinumab and brodalumab phase 2 trials terminated
Graft versus host disease	\uparrow Th17 in blood of GVHD patients	Ustekinumab Phase 2 completed, some benefit
Hidradenitis suppurativa	Substantial skin infiltrating CD161 ⁺ Th17 cells	bimekizumab, secukinumab phase 3 ongoing
Alzheimer's disease (AD)	\uparrow Th17 in blood in mild cognitive impairment	ustekinumab in pre-clinical Alzheimer's diagnosis.
Fatty liver disease	IL-17 \uparrow in obesity / liver disease.	Secukinumab completed



IL-23/IL-17 pathway biologics – a ‘cure’ for psoriasis

Secukinumab (anti-IL-17A)



Langley, N Engl J Med. 2014; 371:326-38



*Before treatment
GLDEMAN457A/O549



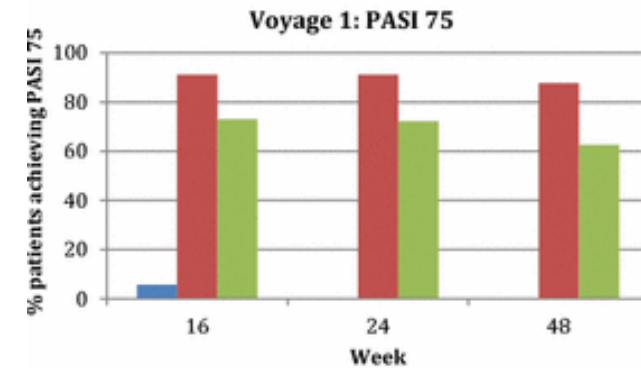
NOVARTIS

- 89% PASI 75 response rates at Year 5.
- 44% of psoriasis patients completely clear skin (PASI 100) at Year 1, maintained to Year 5 (41%).
- 21% of psoriasis patients - skin clearance for up to one year without treatment

(Step in Trial; P2223 26th EADV Congress 2017)

Guselkumab (anti-IL-23)

- Placebo
- Guselkumab Anti-IL-23
- Adalimumab Anti-IL-17R



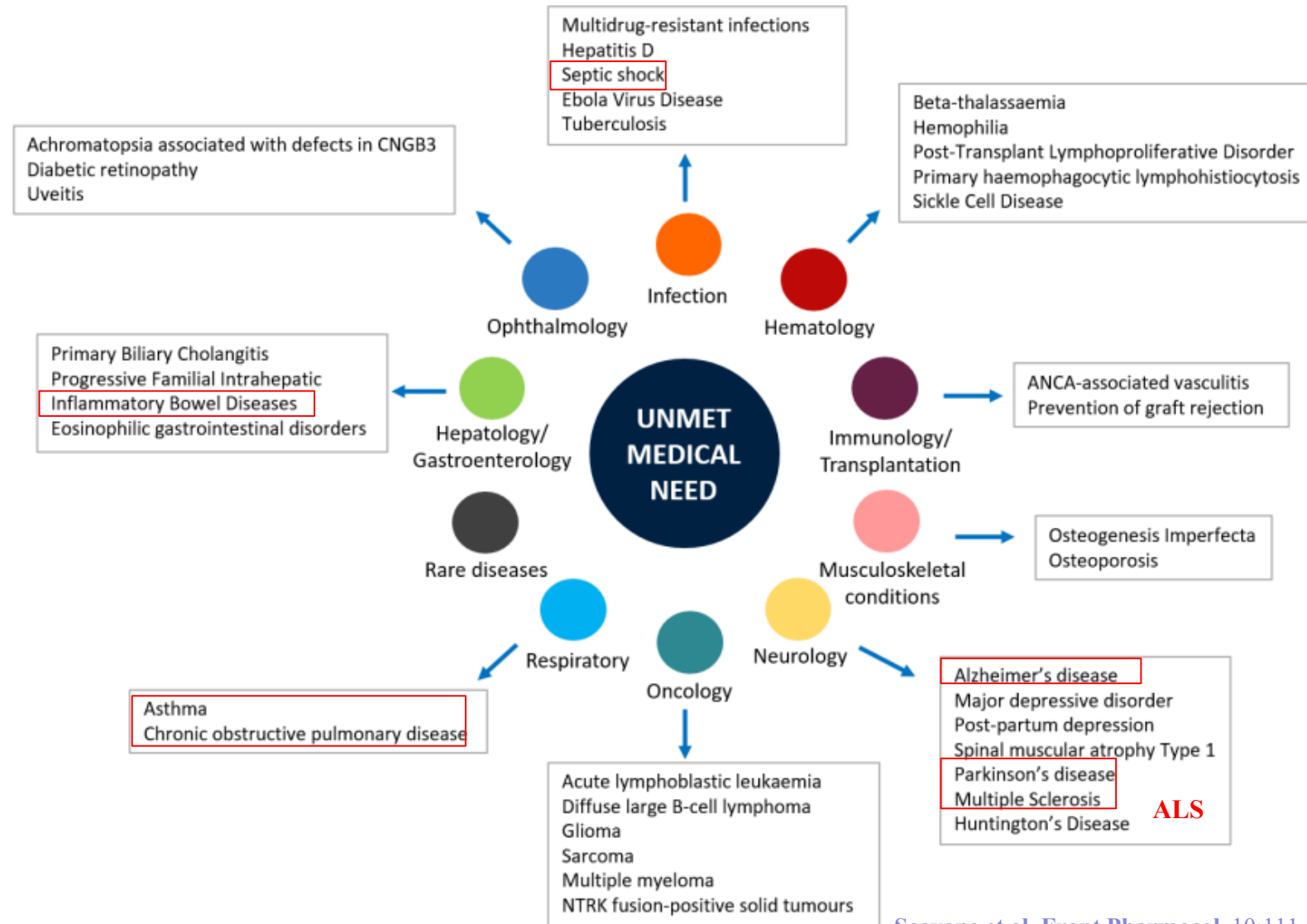
Nakamura et al Dermatol Ther. 2017, 7 (3) 281.

Future immune-based drugs for inflammatory diseases

Key target to block inflammation

- IL-23/IL-17
- Inflammasome / IL-1 β
- Endogenous anti-inflammatories
- Autoantigen-specific Treg cells
- Multiple undiscovered

Indications



Inhibition of IL-11 signalling extends mammalian healthspan and lifespan

<https://doi.org/10.1038/s41586-024-07701-9>

Received: 18 April 2023

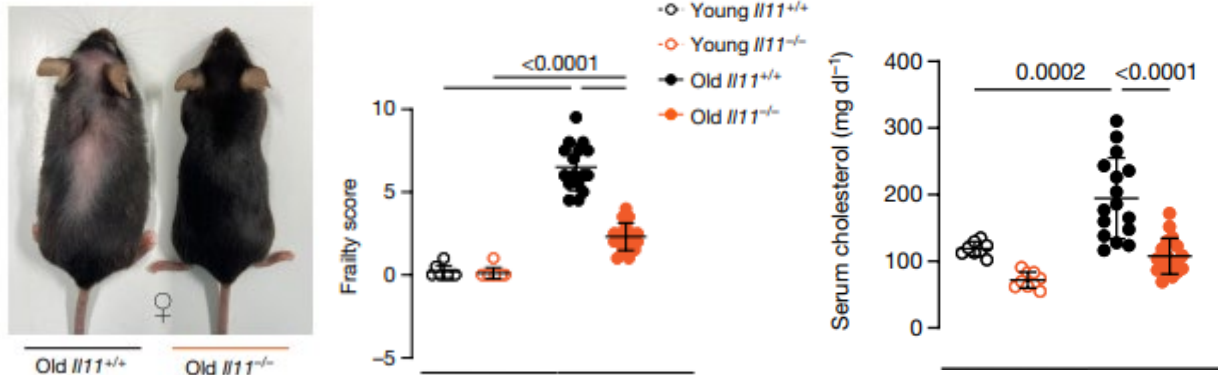
Accepted: 11 June 2024

Published online: 17 July 2024

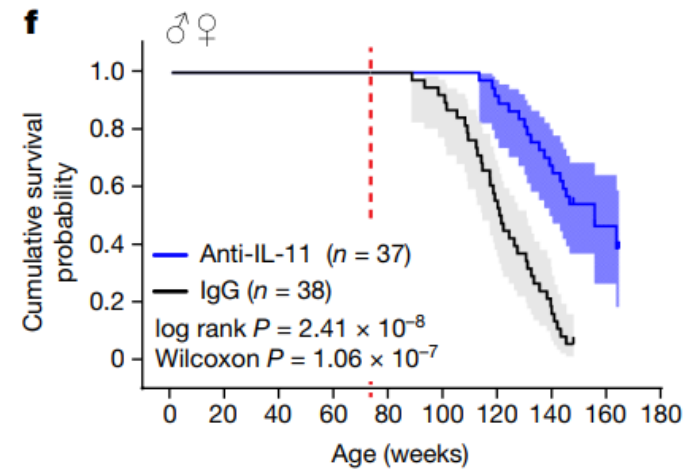
Anissa A. Widjaja^{1,2,13,14}, Wei-Wen Lim^{1,2,12}, Sivakumar Viswanathan¹, Sonia Chothani¹, Ben Corden^{2,3}, Cibi Mary Dasan¹, Joyce Wei Ting Goh¹, Radiance Lim¹, Brijesh K. Singh¹, Jessie Tan², Chee Jian Pua², Sze Yun Lim¹, Eleonora Adami⁴, Sebastian Schafer¹, Benjamin L. George¹, Mark Sweeney⁵, Chen Xie², Madhulika Tripathi¹, Natalie A. Sims^{6,7}, Norbert Hübner^{4,8,9}, Enrico Petretto^{1,10}, Dominic J. Withers^{5,11}, Lena Ho¹, Jesus Gil^{5,11}, David Carling^{5,11} & Stuart A. Cook^{1,2,5,13,14}

Nature | Vol 632 | 1 August 2024 |

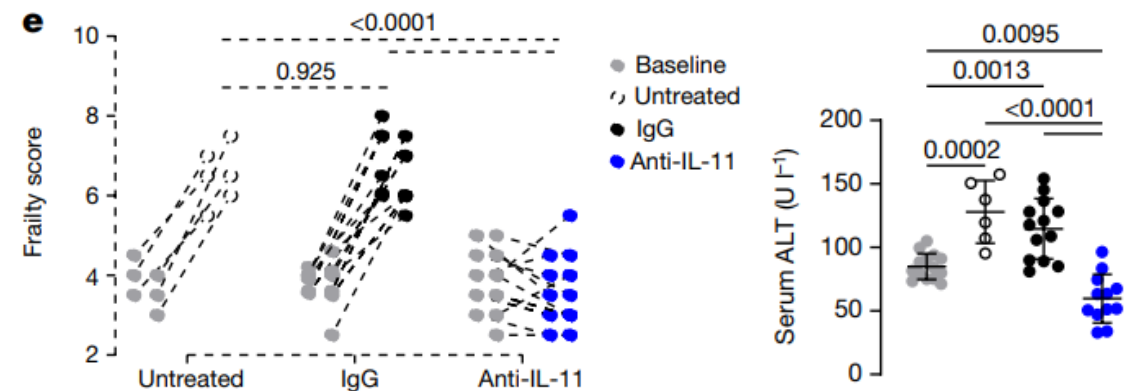
Female IL-11-deleted mice are protected from age-associated obesity, frailty, and metabolic decline.



Inhibition of IL-11 extends life expectancy of male and female mice.



Therapeutic inhibition of IL-11 reduces age-associated metabolic dysfunction, pathogenic signalling and sarcopenia in male mice.



Anti-IL-11 currently in early-stage clinical trials for fibroinflammatory diseases

Certain cancer can now be cured in certain patients - exploiting fundamental discoveries in Immunology

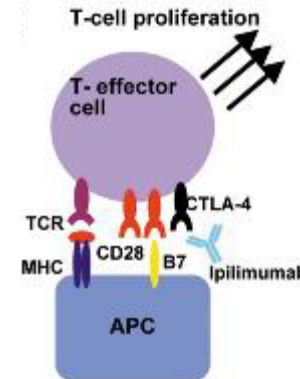


Jim Allison

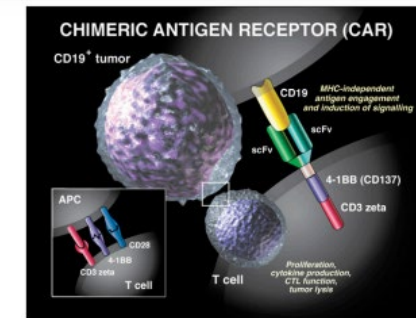


Tasuku Honjo

Nobel Prize in Medicine, 2018



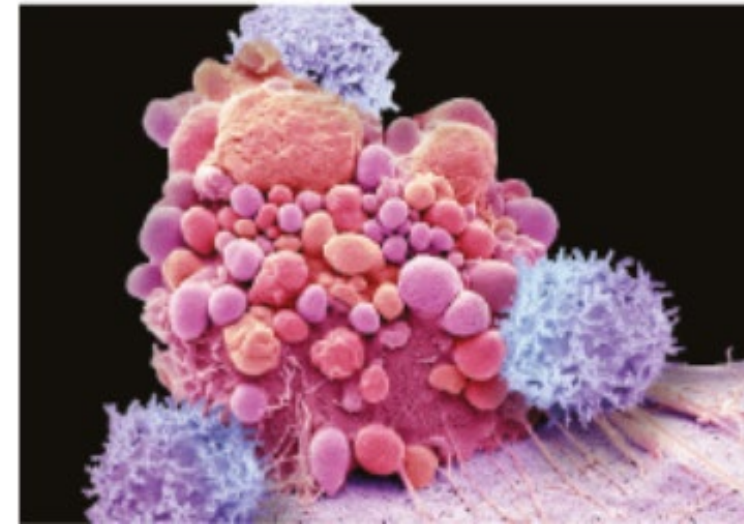
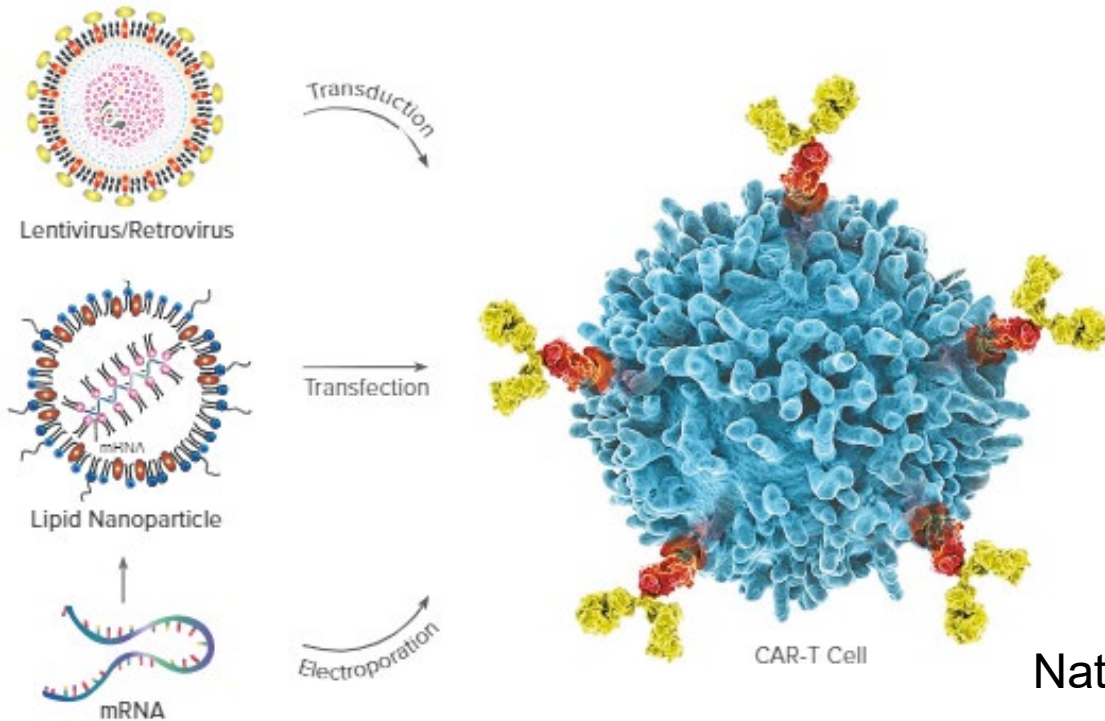
Immune checkpoint inhibitors
Removing the block on T cell activation and survival



Chimeric antigen receptors (CAR) T cells
A living drug – re-infused genetically engineered T cells from cancer patients

CAR-T cells

approaches for modifying T cells to recognize & attack cancer cells



T cells attacking a cancer cell

Nature, Feb 2022

Developed for use in treatment of acute lymphoblastic leukaemia (B cells lymphoma, CD19⁺)

Complete remission (CR) rates as high as 90% have been reported in children and adults with relapsed and refractory ALL treated with CAR-modified T cells

Safety issues: Cytokine release syndrome. Cytokine storm after T cells blast. 3 people died in trial by JUNO (reported 2015)

Switch to turn on/off CAR-T cells?

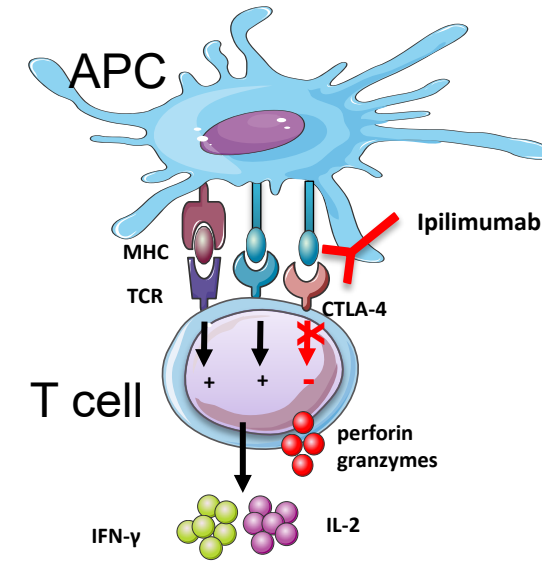
Immune checkpoint inhibitors: Anti-CTLA4 (ipilimumab + others)

Cancer regression and autoimmunity induced by cytotoxic T lymphocyte-associated antigen 4 blockade in patients with metastatic melanoma

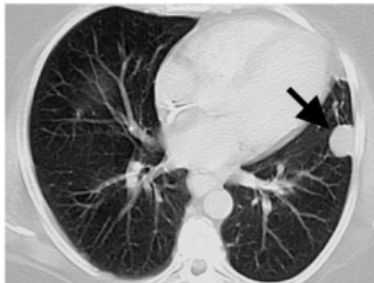
Giao Q. Phan¹, James C. Yang¹, Richard M. Sherry¹, Patrick Hwu¹, Suzanne L. Topalian¹, Douglas J. Schwartzentruber¹, Nicholas P. Restifo¹, Leah R. Haworth¹, Claudia A. Seipp¹, Linda J. Freezer¹, Kathleen E. Morton¹, Sharon A. Mavroukakis¹, Paul H. Duray¹, Seth M. Steinberg², James P. Allison³, Thomas A. Davis¹, and Steven A. Rosenberg^{1,††}

PNAS | July 8, 2003 | vol. 100 | no. 14 | 8375

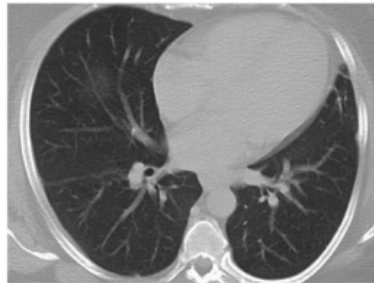
- Removes CTLA4 blockade on T cell activation
- Advanced melanoma – 22% survival after 3 yrs
- Approved in 2011 for melanoma
- Efficacy in other indications
- A significant proportion of recipients develop immune-associated adverse reactions



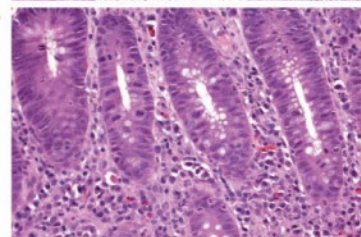
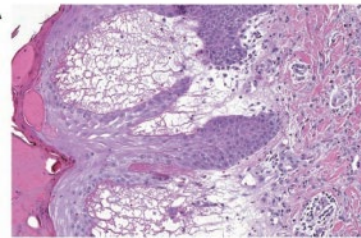
Pre-



Post-treatment



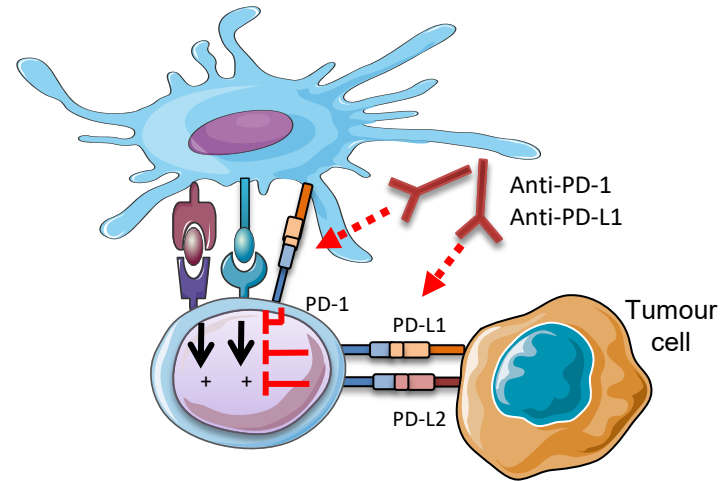
Dermatitis and colitis



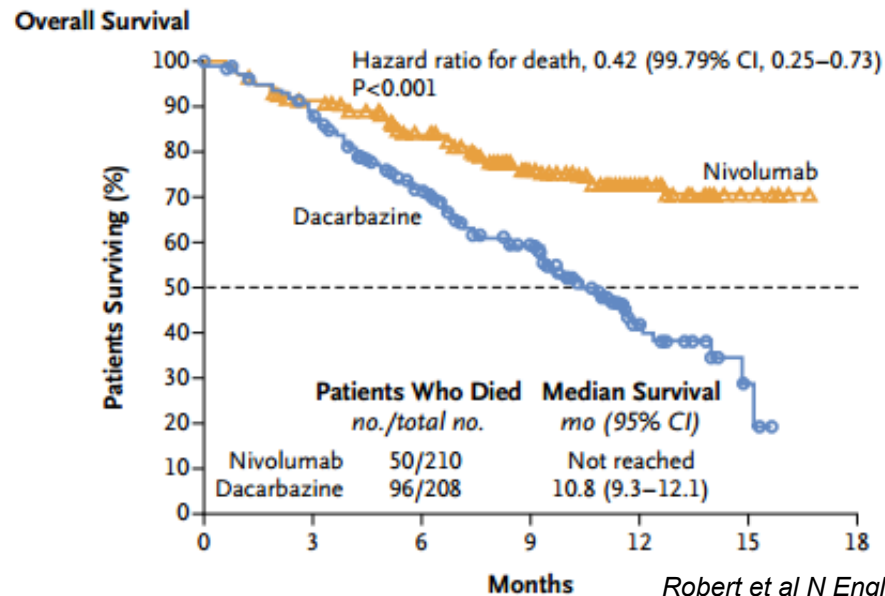
Immune checkpoint inhibitors: Anti-PD-1/anti-PD-L1 and combinations

Nivolumab/ Pembrolizumab + others

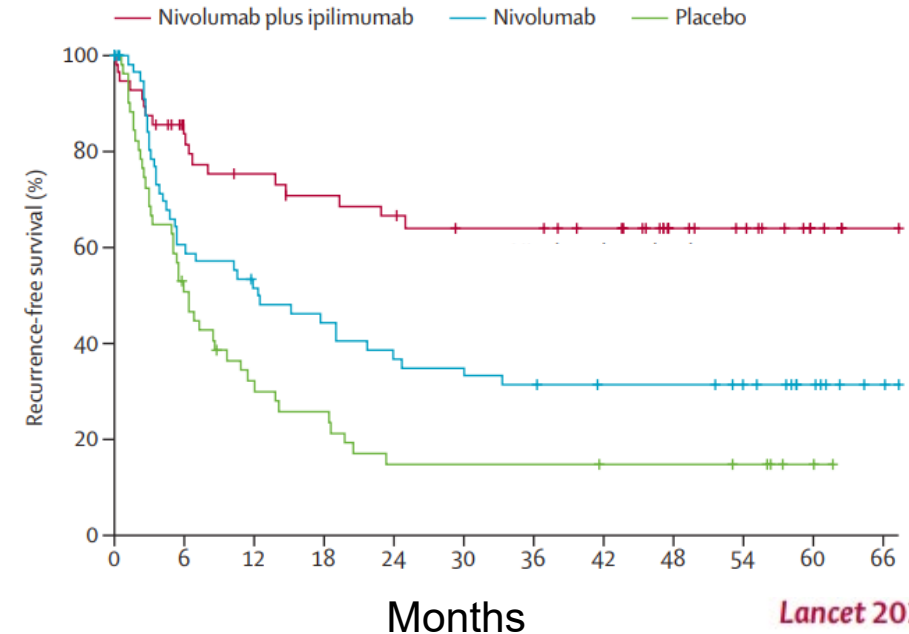
- Anti-PD-1 antibody
- Negative signal to T cell
- Blocking PD-1 enhances effector T cells
- Increases CTL and reduces Tregs
- 200 trials anti-PD-1 or anti-PDL-1 completed or underway in a variety of cancer indications



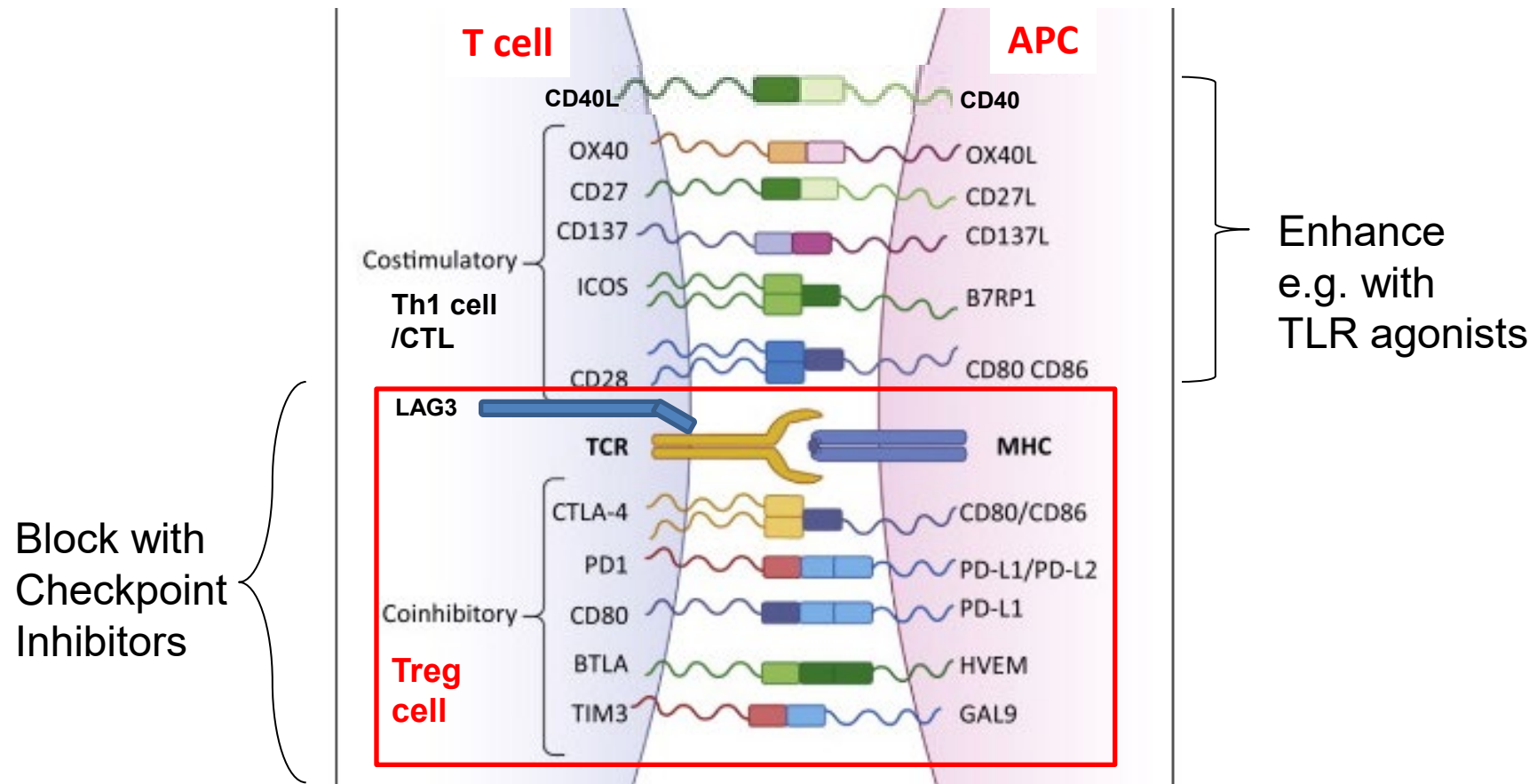
Previously untreated Melanoma
without *BRAF* mutation



Combination of CTLA4 + PD-1 inhibition in stage 4 melanoma



Multiple new targets in the immunology Synapse – enhancing T cell responses to tumours



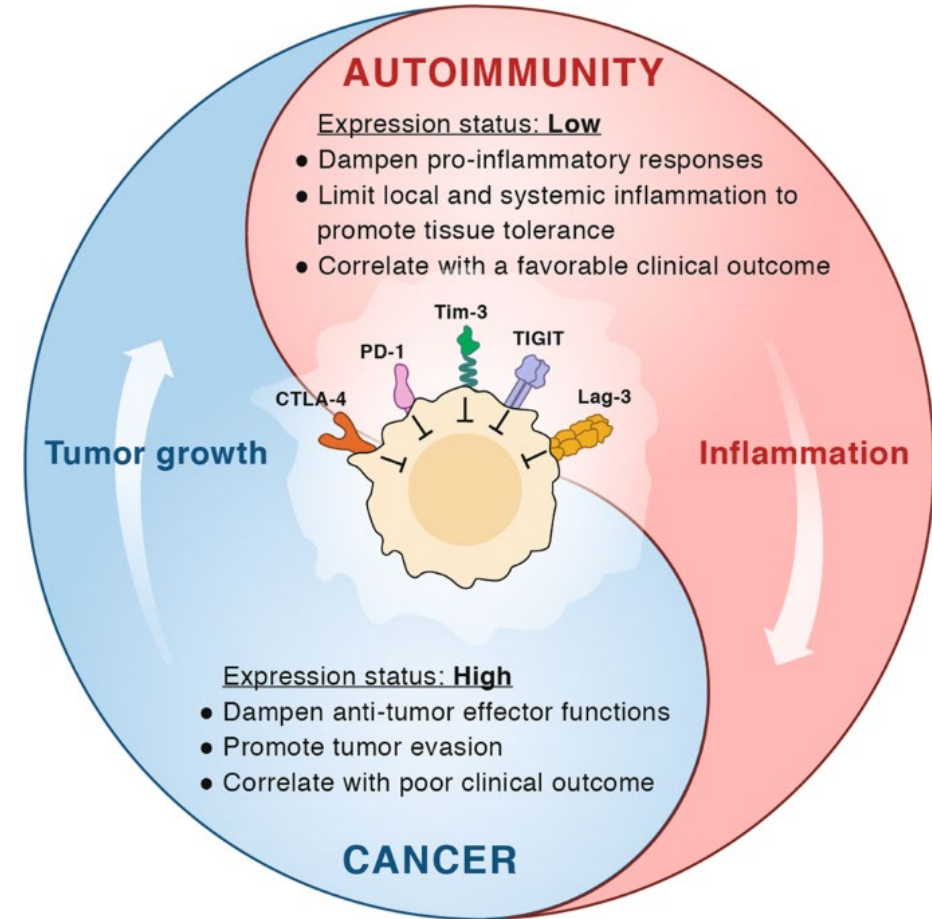
Clinical trials

IMP321	Dimer of LAG3, APC activator	I/II	Breast, prostate
IMP701	Monoclonal antibody to LAG3	I	Cancer
M7824	Bi-functional anti-PDI + TGFβ trap	I/II	Prostate
Dacetuzumab/ Lucatumumab	Anti-CD40 agonist MoAb	I	CLL, NHL, MM
TLR agonists	TLR9, TLR7/8	III	NSCLC, various

Immune checkpoints prevent autoimmune diseases

Immune checkpoints

- Natural brakes on the immune system
- Prevent development of autoimmunity
- But also suppress immunity to tumors
- Immune checkpoint inhibitor (anti-PD-1/PDL-1 & anti-CTLA4 highly effective in treating cancer
- Responders develop autoimmune diseases



PD-1 agonistic MoAbs in clinical development for autoimmune diseases

- Expression of PD-1 increased in synovium of RA patients
- Strong expression on T cells correlates with disease activity

nature reviews drug discovery

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NEWS IN BRIEF | 02 June 2023

PD1 agonist antibody passes first phase II trial for autoimmune disease

- Lilly running another Phase II in RA and options for other autoimmune disease
- BMS/Celgene CC-90006 (Moab) licensed from AnaptysBio was in phase I for psoriasis

Features | March 4, 2021

Merck-Pandion acquisition: re-balancing immune response to treat autoimmune disease \$1.85bn

Gilead Bets \$405M on MiroBio's Checkpoint Agonists for Autoimmune Disease

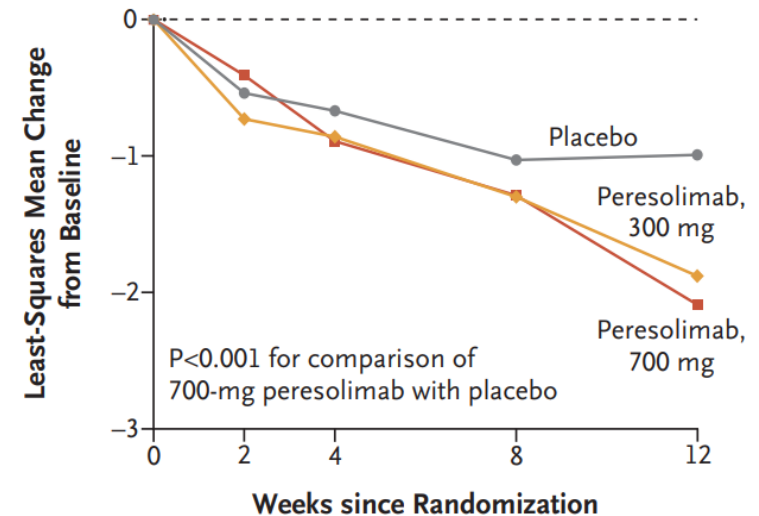
Published: Aug 05, 2022 | By Alex Keown

The NEW ENGLAND JOURNAL of MEDICINE

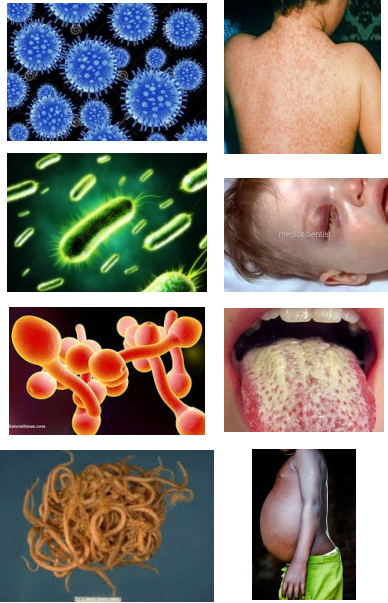
ORIGINAL ARTICLE

A Phase 2 Trial of Peresolimab for Adults with Rheumatoid Arthritis

Jay Tuttle, Ph.D., Edit Drescher, M.D., Jesus Abraham Simón-Campos, M.D.,



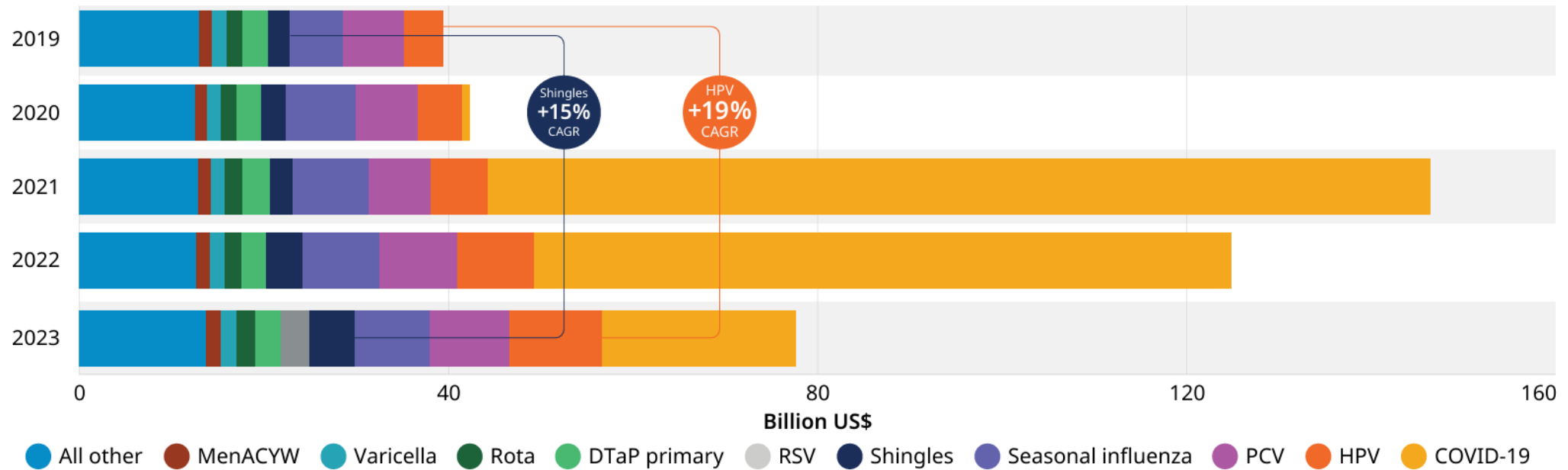
Vaccines for Infectious Diseases



- Infectious diseases: >15m global death annually (150,000 in US)
- Vaccination: one of the greatest achievements of modern medicine
- Vaccination: one the most cost-effective ways of saving lives
- Many infectious disease without an effective vaccine
- The COVID-19 vaccineS changed the business case - vaccines are now big business



Vaccine value (US\$) from 2019–2023 showing the top 10 vaccines by value (WHO data)

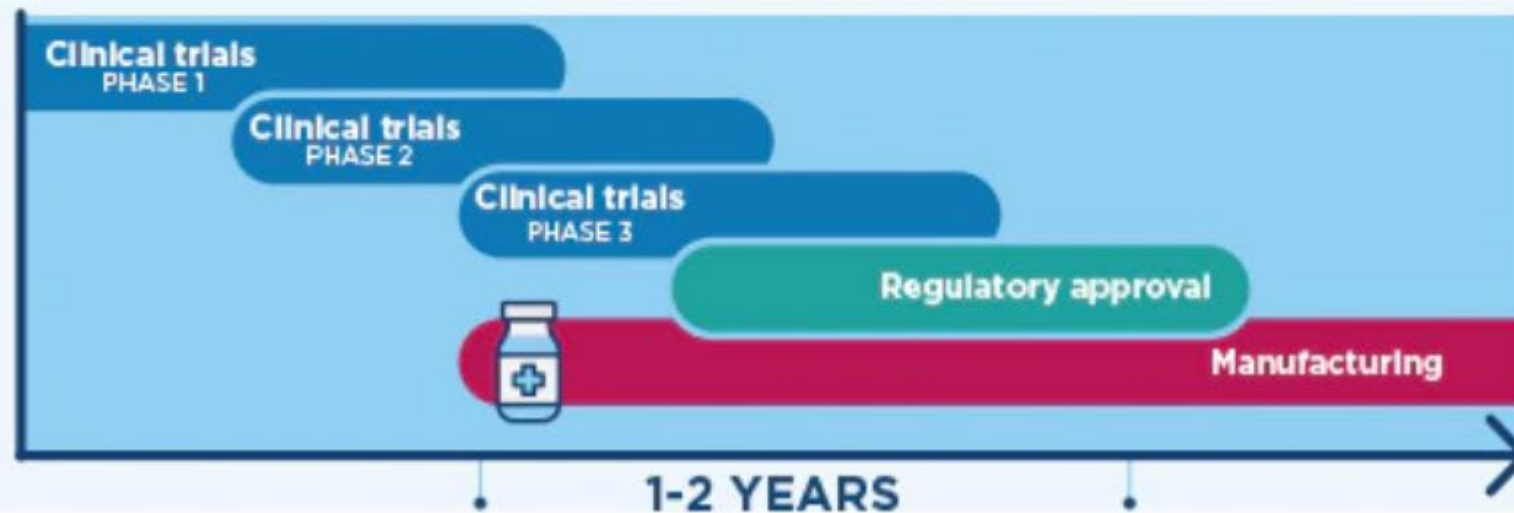


COVID-19 vaccines developed in 1/10 time of a typical vaccine

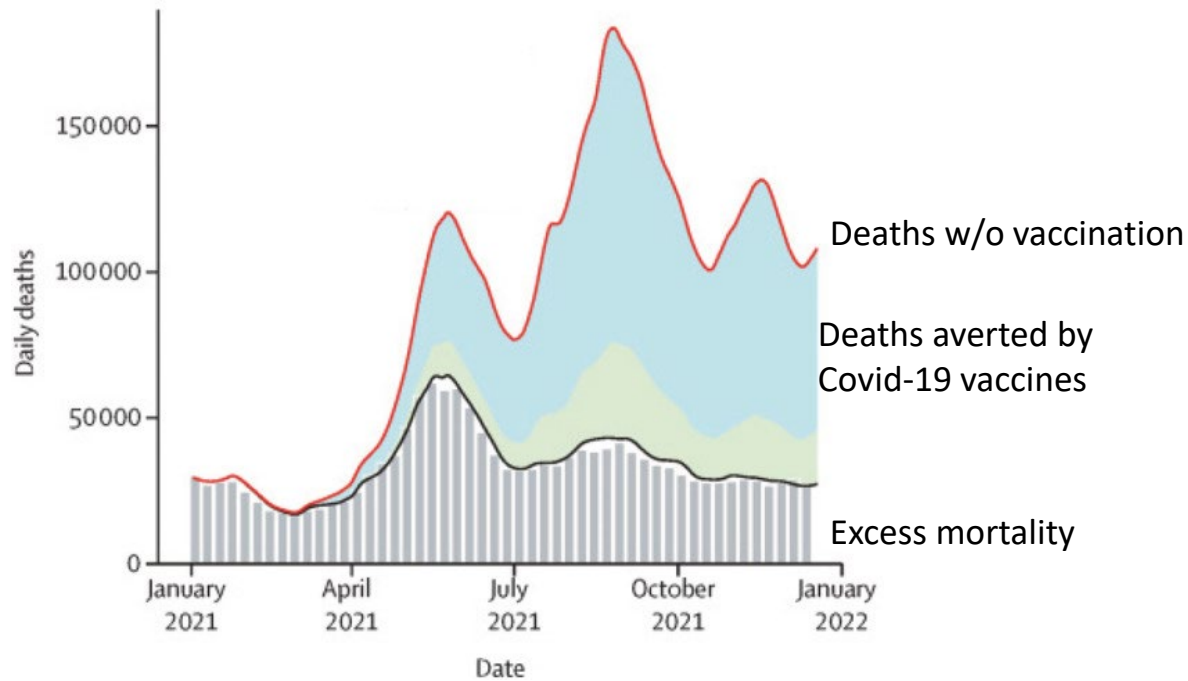
Traditional vaccine development: One step at a time



COVID-19 vaccine development: Multiple steps happening at once



COVID-19 vaccines prevented an estimated 14.4 million deaths from COVID-19 (19m including excess deaths) in first year of use.



[J Paediatr Child Health](#). 2022 Sep 20 : 10.1111/jpc.16213.

Nobel Prize goes to scientists behind mRNA Covid vaccines

🕒 2 days ago



| Professors Drew Weissman (left) and Katalin Kariko

By James Gallagher

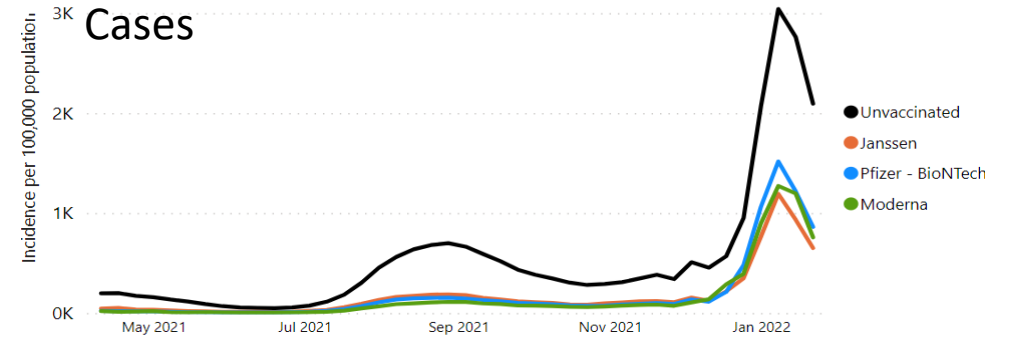
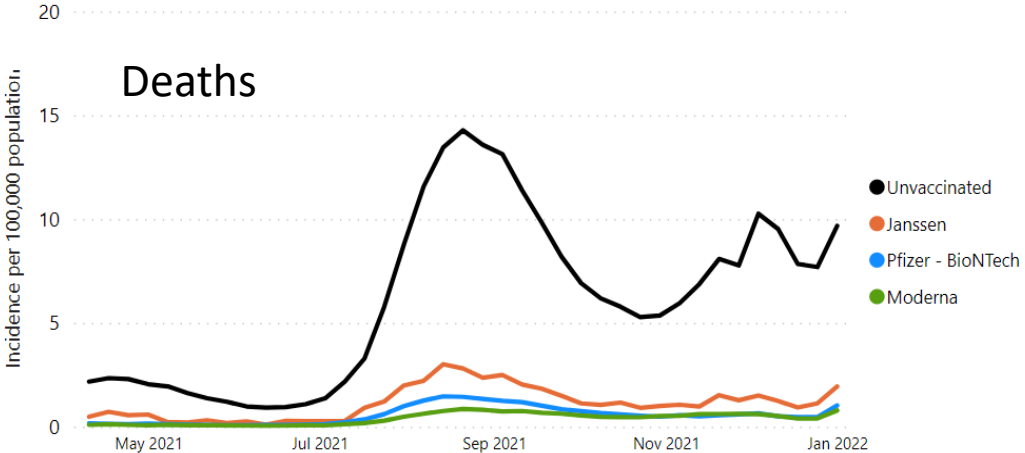
Health and science correspondent

The Nobel Prize in Physiology or Medicine has been awarded to a pair of scientists who developed the technology that led to the mRNA Covid vaccines.

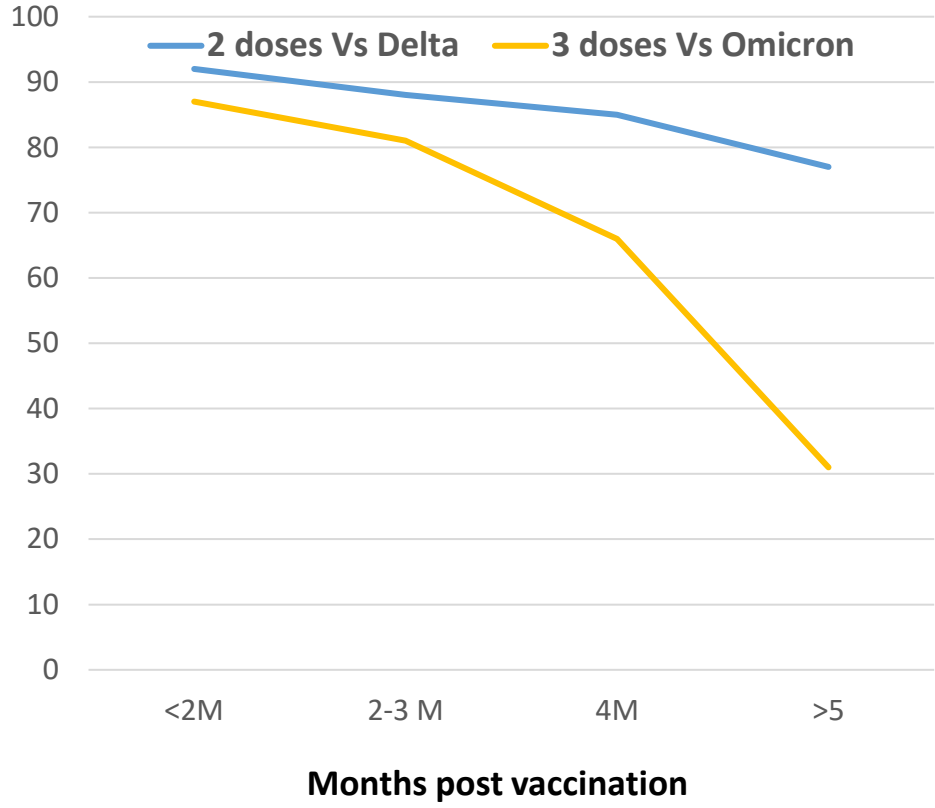
Professors Katalin Kariko and Drew Weissman will share the prize.

COVID-19 vaccines prevent severe disease but does not prevent SARS-CoV-2 infection or sustain protective immunity

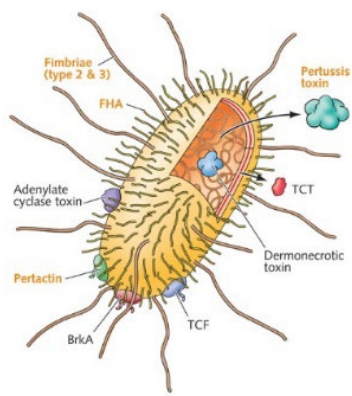
USA April 21 – Jan 22



Vaccine Efficacy (%) Versus Symptomatic Infection



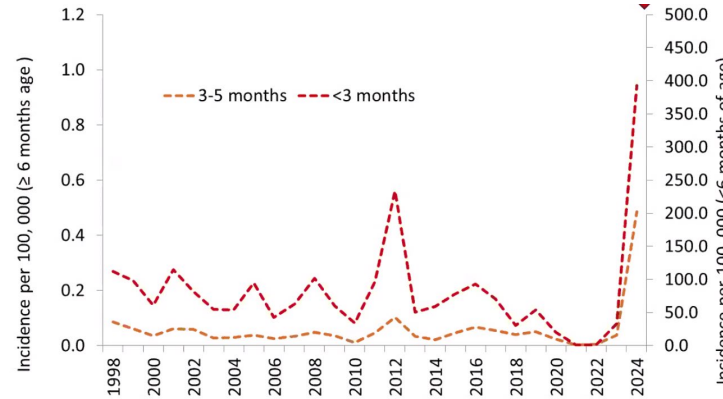
Qatar study NEJM Feb 2022



Bordetella pertussis

- Whooping cough (pertussis) - severe persistent respiratory infection especially in infants
- 24.1m cases, 160,700 infant deaths/yr
- Re-emerging pathogen - despite introduction of a new acellular pertussis (aP) vaccine in 1990s
- aP vaccines do not prevent infection and immunity wanes rapidly post vaccination

Pertussis cases in UK



Rising Whooping Cough Cases In The UK Lead To Tenth Child Death

The outbreak is part of a global resurgence of the disease, which has seen cases and deaths in countries like China, Philippines, and the Netherlands.

Edited by: Nikhil Pandey | World News | Aug 09, 2024 09:35 am IST

Read Time: 3 mins



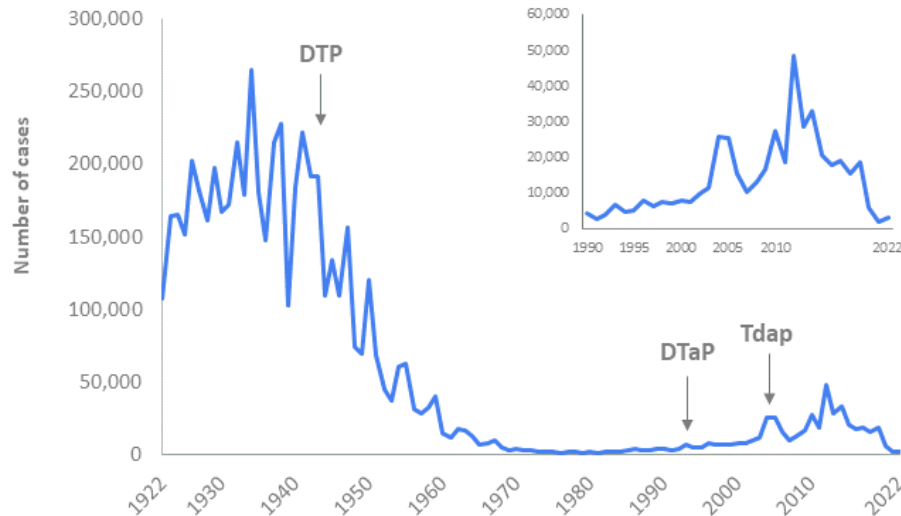
THE IRISH TIMES

Health

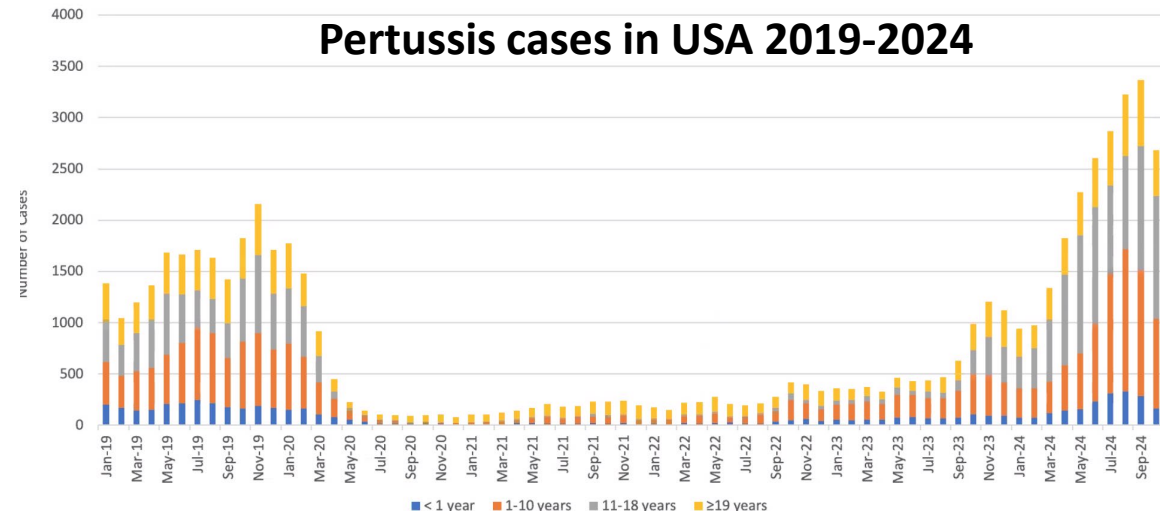
Whooping cough cases in country increase by 3,000% in a year

Latest figures show 567 cases in Ireland up to November 9th, compared to 18 cases in 2023

Pertussis cases in US 1922-2022 (CDC)



Pertussis cases in USA 2019-2024



Current acellular pertussis vaccines prevent disease and reduce lung infection but do not prevent nasal infection with *B. pertussis*

Whole cell pertussis (wP) vaccines (1940-90s)

(killed whole bacteria, including LPS + other PAMPs)

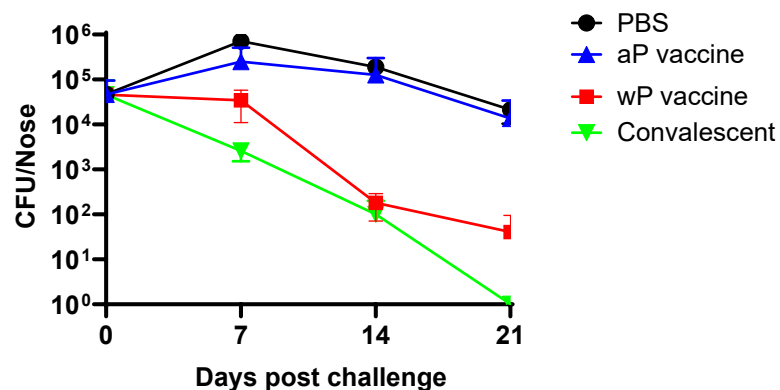
- Effective but had side effects

Acellular pertussis (aP) vaccines (2000s-)

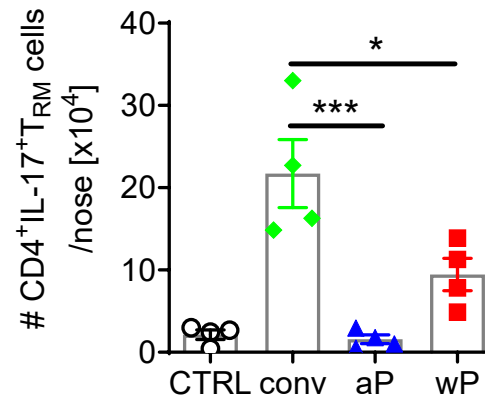
(3-5 antigens with alum)

- Safe, but do not prevent bacterial transmission
- Promote antibody and Th2 responses
- Does not induce respiratory T_{RM} cells

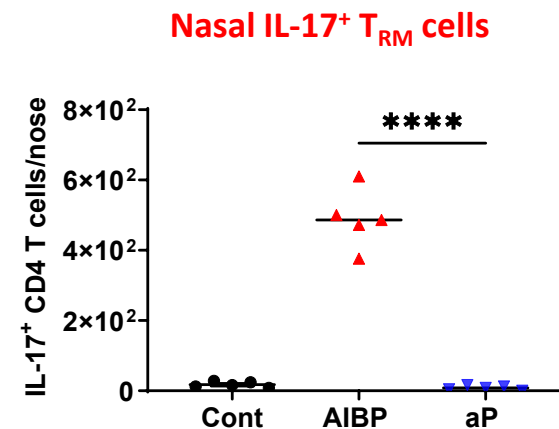
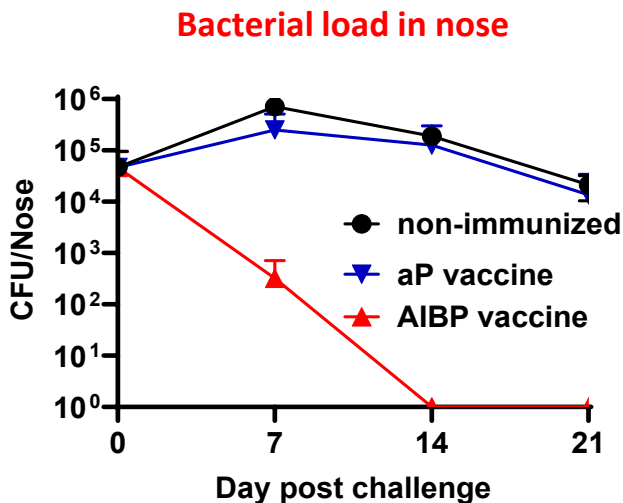
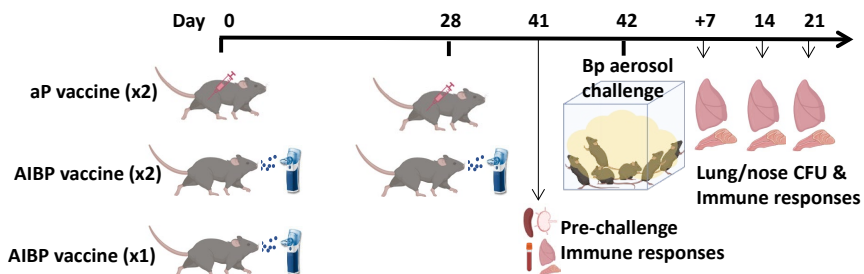
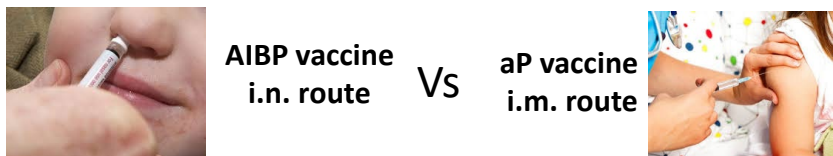
Bacterial load in nose



IL-17⁺ CD4⁺ T_{RM} in nasal tissue

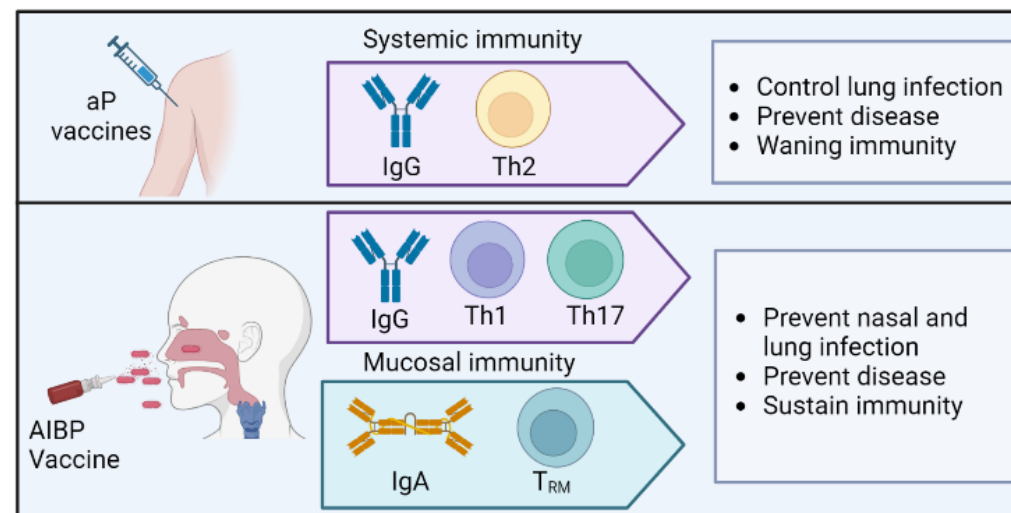
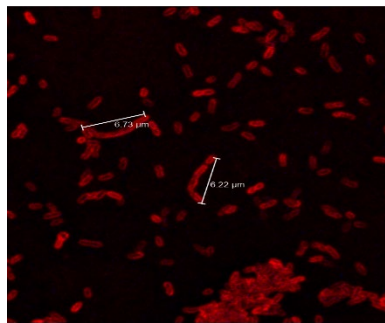
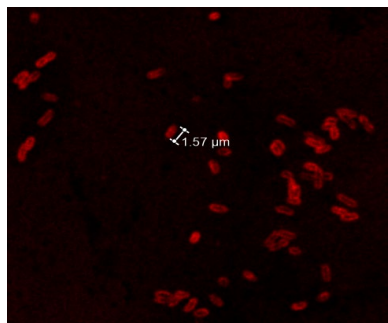


Aerosol-delivered antibiotic-inactivated *B. pertussis* vaccine (AIBP) induces potent respiratory IL-17⁺ T_{RM} cells and protects against nasal infection with *B. pertussis*



Un-treated *B. pertussis*

Ciprofloxacin-treated *B. pertussis*



Impact of mRNA technology on vaccine/treatments for other diseases

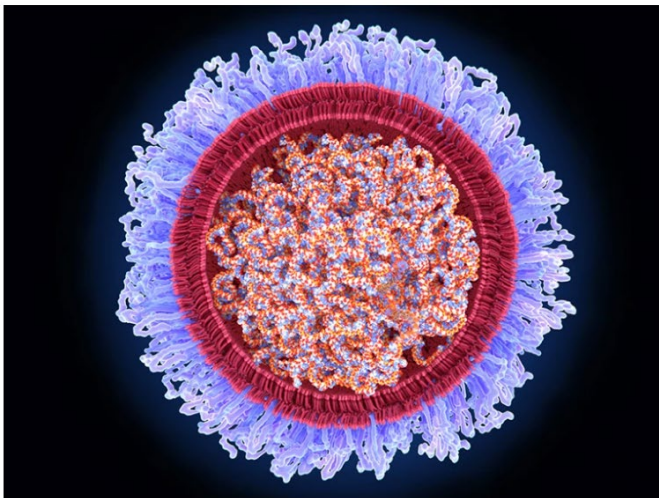
nature

NEWS EXPLAINER | 03 October 2023

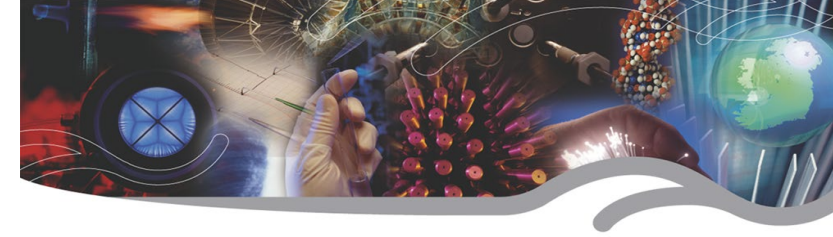
mRNA COVID vaccines saved lives and won a Nobel – what's next for the technology?

Nature talks to experts about how messenger RNA is transforming medicine.

[Elie Dolgin](#) & [Heidi Ledford](#)



- Rapid vaccine development against “new” pathogens
- Tackling tough pathogens
 - MRSA, HIV, CMV, TB, universal flu mRNA vaccines
- mRNA vaccine against cancer
- Genome editing: long lasting mRNA to correct rare diseases
 - Cystic fibrosis, Muscular dystrophy, Huntington’s disease, Haemophilia, Cancers



Mills lab present and recent past

Caroline Sutton	Sarah Edwards
Lisa Borkner	Aoife McGinley
Caitlín Ní Chasaide	Niamh McGuinness
Davoud Jazayeri	Aideen Allen
Sreeram Udayan	Roisin McManus
Lucy Curham	Lydia Dyck
Charlotte Leane	Sauna Quinn
Pauline Schmitt	Robert Walsh
Béré Diallo	Lara Dungan
Karen McCarthy	Stephen Lalor
Paula Kinsella	Sarah Higgins
Mieszko Wilk	Pádraig Ross
Kyle Cunningham	Patrick Kelly
Conor Finlay	Kevin Walsh
Mathilde Raverdeau	Anna Stefanska
Alicja Misiak	Sarah Jones
Martina Gogarty	Lisa Mielke
Mark Lynch	James Harris
Joseph DeCoursey	
William McCormack	
Barry Moran	

TCD collaborators
Rachael McLoughlin
Marina Lynch
Luke O'Neill
Ed Lavelle
Jean Fletcher
Aisling Dunne



Enterprise
Ireland



innovative
medicines
initiative



Collaborators

CNIO Madrid
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University of Lisbon
Julie Ribot
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Anthony Slavin
Jesus Paez-Cortez