Bases de l'auto-immunité
Panorama et physiopathologie des maladies auto-immunes

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76e Journées pharmaceutiques internationales de Paris - Immuno JPIP 2025

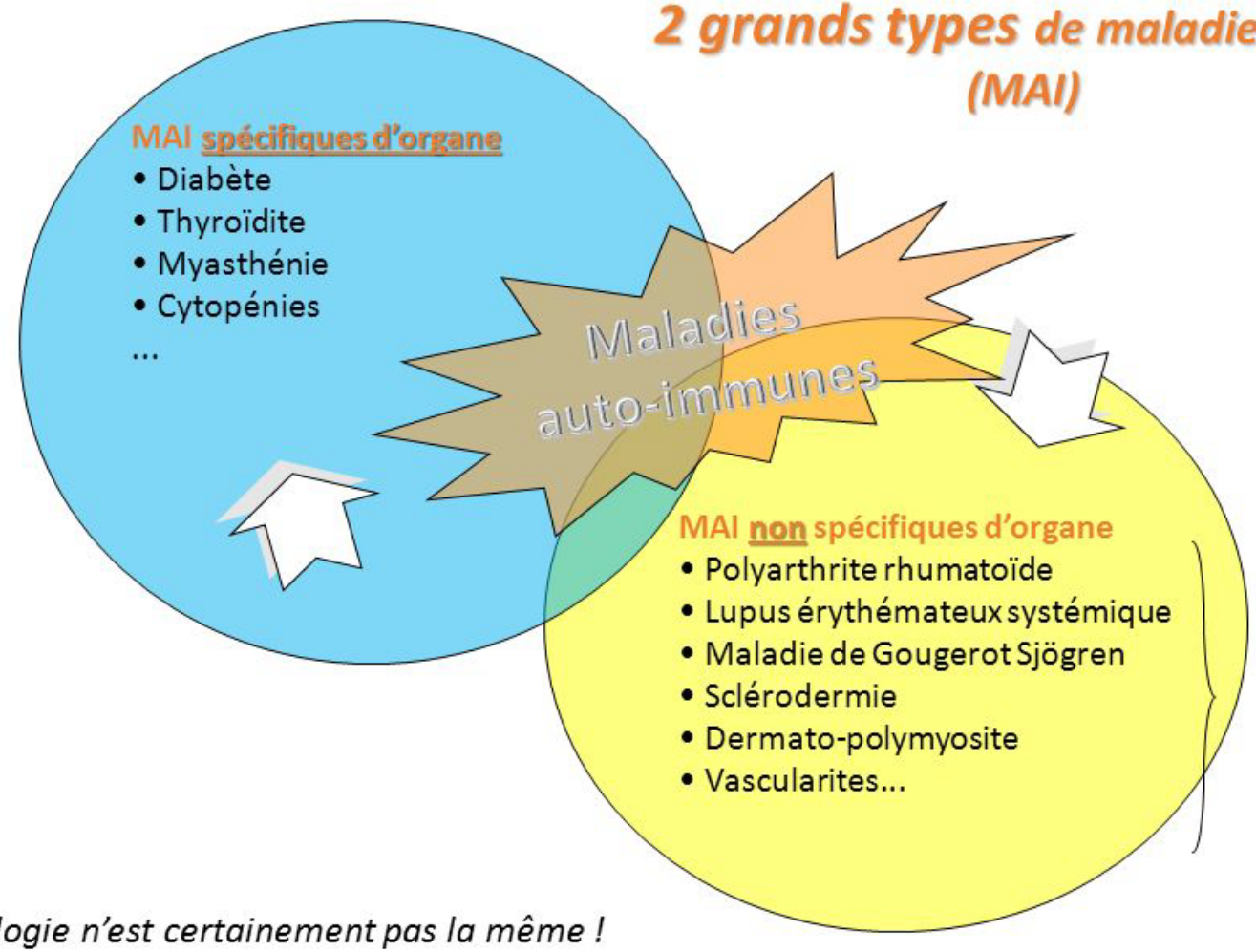
Conflicts of interest

- **Consultant:** Boehringer, LFB Biotechnologies
- **Investigator:** Abbvie, Boehringer
- **Financial support (grants):** CSL Behring, LFB Biotechnologies

Maladie auto-immune: définition

- Les **maladies auto-immunes** sont dues à une hyperactivité du système immunitaire à l'encontre de substances ou de tissus qui sont normalement présents dans l'organisme.
- Parmi ces maladies on trouve **la sclérose en plaques, le diabète de type 1** (jadis appelé « diabète juvénile » ou « diabète insulino-dépendant »), le **lupus** systémique, les thyroïdites auto-immunes, la **polyarthrite rhumatoïde**, etc….

2 grands types de maladies auto-immunes (MAI)

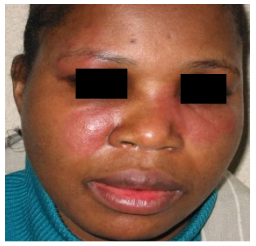
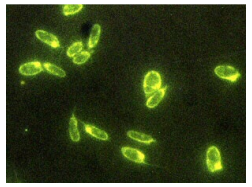


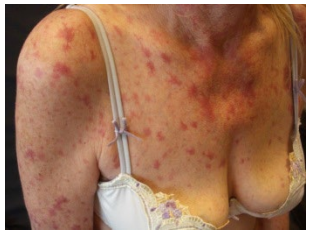
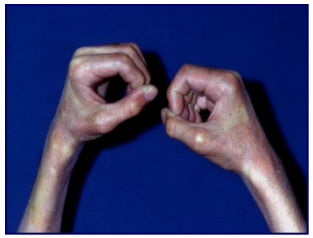
Souvent atteintes de
- la peau
- les articulations
- les reins
- les vaisseaux

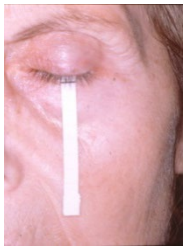
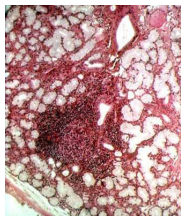
La physiopathologie n'est certainement pas la même !

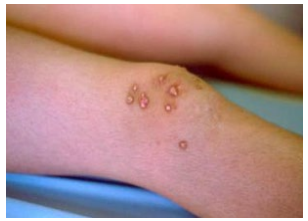
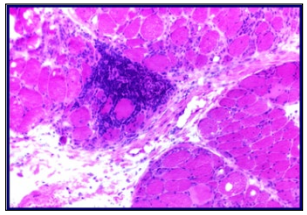
Maladies-vedettes: maladies systémiques

- Connectivites

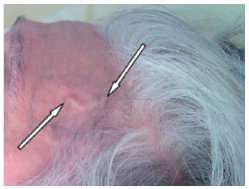
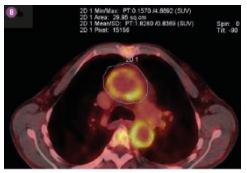


Lupus systémique

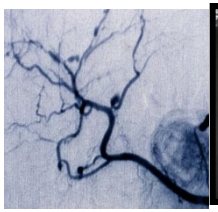
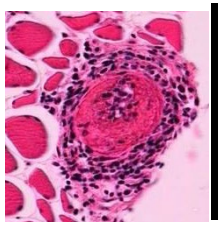


Sclérodermie systémique

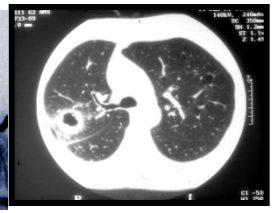
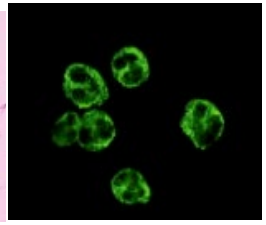


Sjögren

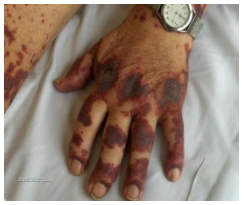
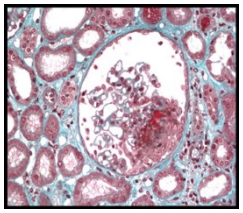


Myosites

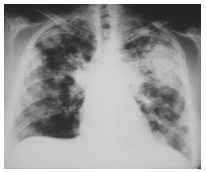
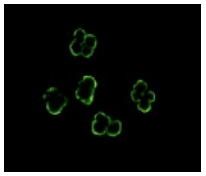
- Vascularites



Horton

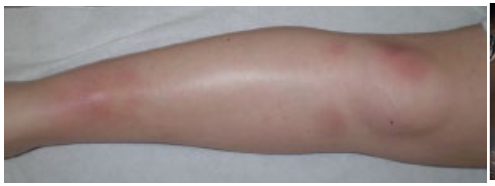
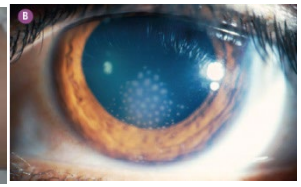
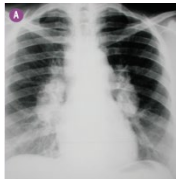


Périartérite noueuse



Wegener



Polyangéite microscopique



Churg Strauss

- Granulomatoses




Sarcoïdose

Criteria for the definition of autoimmune diseases

➢**Direct evidence**

Direct transfert of the disease from human to human or from a human to an animal (the recipient's immune system must be functional).

➢**Indirect evidence**

Animal models identical or very close to disease manifestations observed in humans.

➢**Circumstantial evidence**

Clinical or experimental data underlying the autoimmune nature of a disease in the absence of definite proof (characterization of an antigen specific autoimmune reaction, activation of T lymphocytes in culture in the presence of an autoantigen).

Rose NR, Bona C. Immunol Today 1993;14(9):426-30

Immune thrombocytopenic purpura: the proof!

ANNALS OF INTERNAL MEDICINE

VOLUME 38 MARCH, 1953 NUMBER 3

IMMUNOLOGIC MECHANISMS IN IDIOPATHIC AND NEONATAL THROMBOCYTOPENIC PURPURA*

By WILLIAM J. HARRINGTON, M.D.,† *St. Louis, Missouri,* CHARLES C. SPRAGUE, M.D., *New Orleans, Louisiana,* VIRGINIA MINNICH, M.S., CARL V. MOORE, M.D., F.A.C.P., ROBERT C. AULVIN, B.S., and REUBENIA DUBACH, Ph.D., *St. Louis, Missouri*

Effect of the patient's total blood FC on a healthy subject

Date	Patient F. C.		Recipient W. H. Platelets × 10^3 per mm.^{3}										
	Platelets × 10^3 per mm.^{3}	Agglutinin Titer	Before Transfusion	After Transfusion of 500 c.c. of Patient's Whole Blood									
				15 Min.	1 Hr.	2 Hrs.	1 Day	2 Days	3 Days	4 Days	5 Days	6 Days	7 Days	8 Days
10–22–50	0	1:16	800	400	125	25	. 0 .	15	35	117	260	320	675	1,100

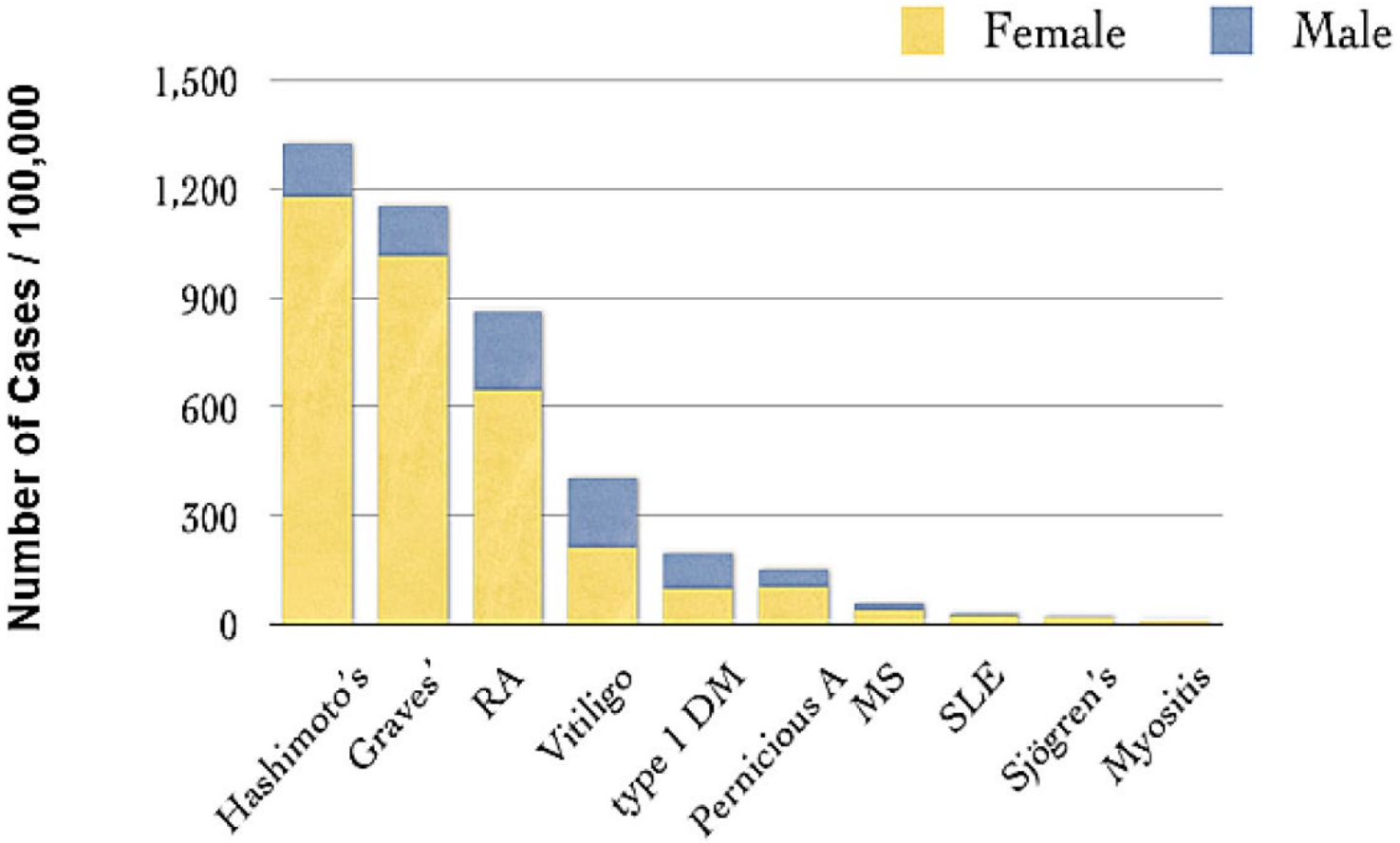
The plasma of patient FC contained *in vitro* agglutinins against all tested platelets. Decrease in the platelet count of a healthy subject after transfusion of 500 cc of blood from patient FC whose plasma contained platelet agglutinins.

Harrington WJ et al. Annals of Internal Medicine, 1953

Autoimmune diseases transferred from one individual to another

Disease	Mechanisms involved	Donnor	Receipient	Transfert
Idiopathic thrombocytopenic purpura (ITP)	Autoantibodies	Human	Human	Serum
Graves disease Myasthenia gravis Microscopic polyangiitis	Autoantibodies	Mother	Fetus	Trans-Placental
Pemphigus vulgaris Bullous pemphigoid	Autoantibodies	Human	Animal	Serum infusion
Type 1 diabetes mellitus ITP Hashimoto's thyroiditis Myasthenia gravis	Autoreactive lymphocytes	Human	Human	Bone marrow allograft

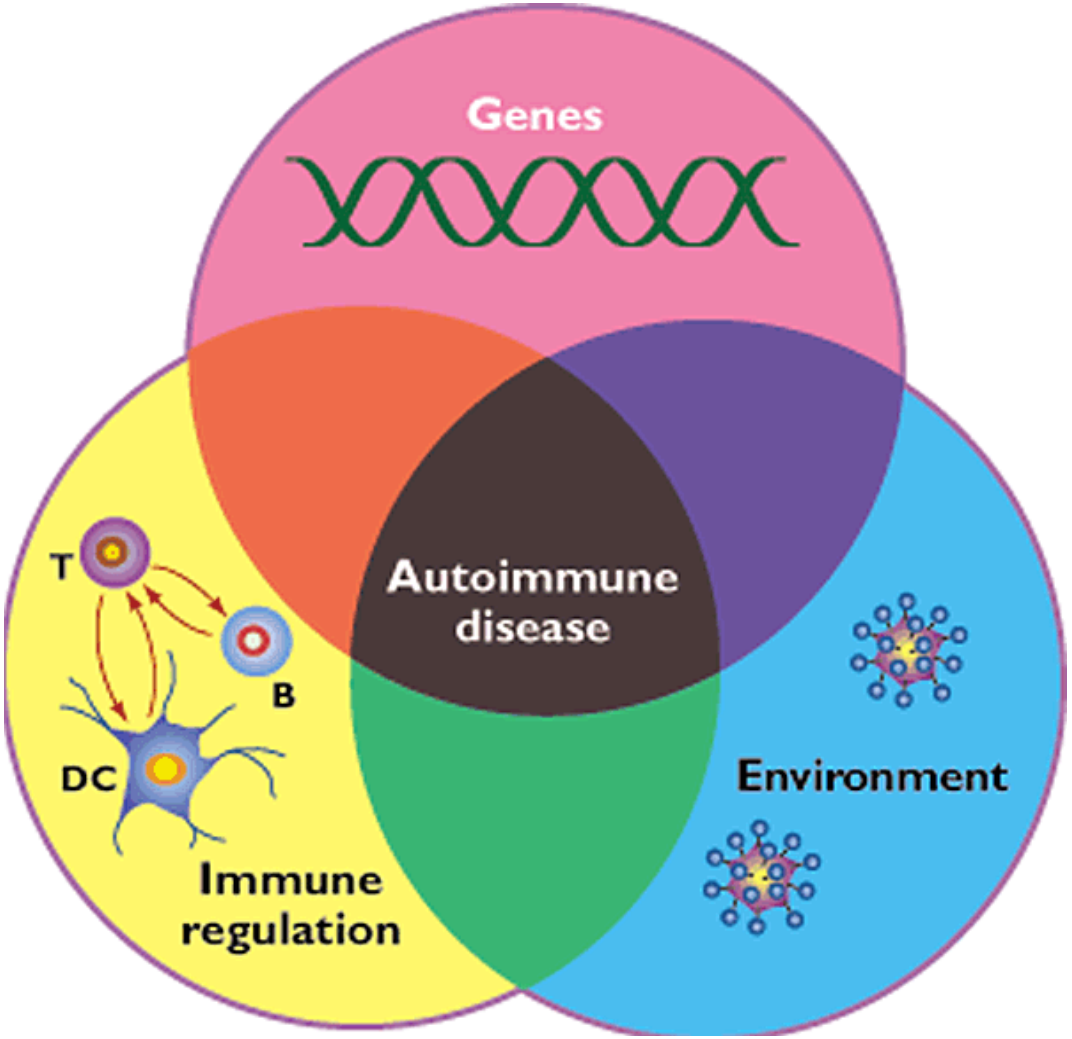
Prévalence des maladies autoimmunes



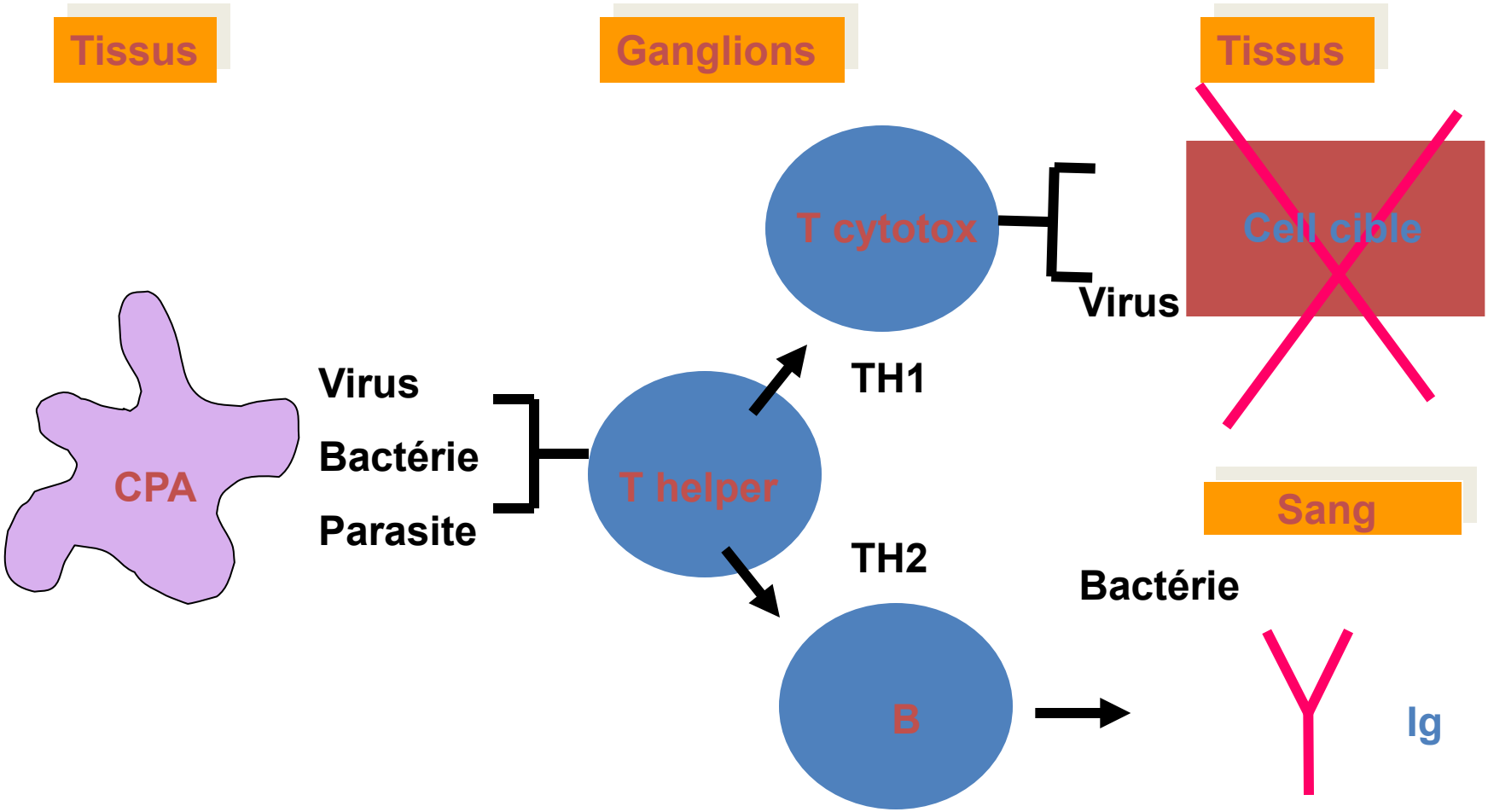
- 10 most common autoimmune diseases in the US
- all autoimmune diseases combined affect about 3% of the US population

Clin Immunol Immunopathol, 1997

Physiopathologie des maladies auto-immunes



LA REACTION IMMUNITAIRE ADAPTATIVE ANTI-INFECTIEUSE



Human organ-specific autoimmune diseases with its microbial trigger

Disease	Organism	Immunologic Factor
Rheumatic heart disease	Streptococci	T cell response to strep M5 protein
Guillain-Barre	Campylobacter	Cross reacting Ab to gangliosides
Polyarteritis nodosa	Hepatitis B	Immune complexes
Lyme arthritis	Borrelia bergdorferi	LFA-1 mimicry of OspA; T cell response to OspA
Chronic autoimmune hepatitis	Hepatitis C	Epitopes differ from autoimmune hepatitis
Myocarditis	Coxsackie virus B3	Response to cardiac myosin

Paget SA et al. TRANSACTIONS OF THE AMERICAN CLINICAL AND CLIMATOLOGICAL ASSOCIATION, VOL. 123, 2012

Facteurs liés à l'environnement

- Inhomogénéité dans la prévalence des maladies autoimmunes
  =>Gradient Nord-Sud pour la SEP et le diabète de type I
- Incidence croissante ces 40 dernières années

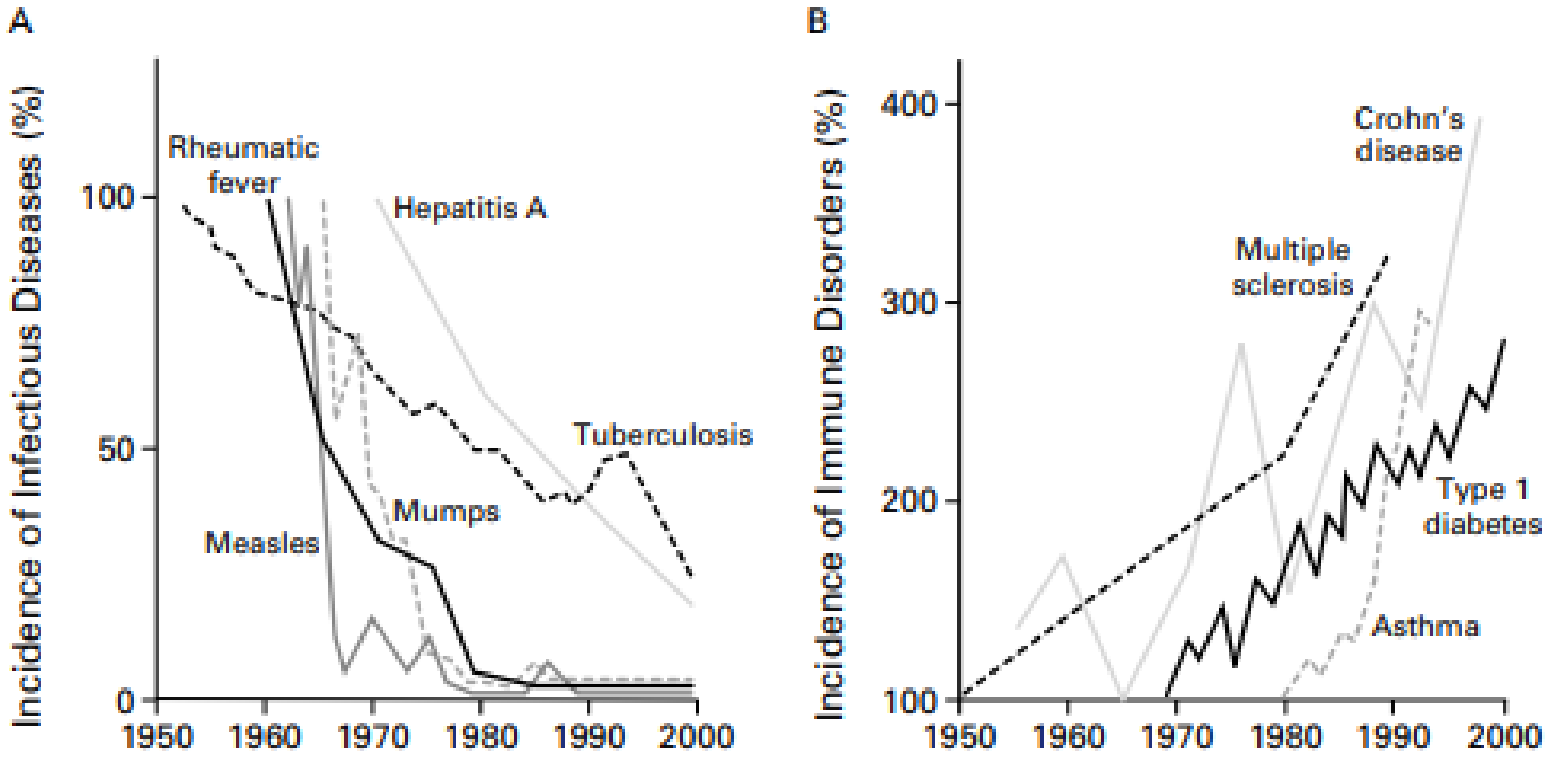


Figure 1. Inverse Relation between the Incidence of Prototypical Infectious Diseases (Panel A) and the Incidence of Immune Disorders (Panel B) from 1950 to 2000.

In Panel A, data concerning infectious diseases are derived from reports of the Centers for Disease Control and Prevention, except for the data on hepatitis A, which are derived from Joussemet et al.[12] In Panel B, data on immune disorders are derived from Swarbrick et al.,[10] Dubois et al.,[13] Tuomilehto et al.,[14] and Pugliatti et al.[15]

Bach JF 2002. N Engl J Med, Vol. 347, No. 12 · September 19, 2002

Gut microbiota alterations in specific autoimmune diseases

Autoimmune Disease	Key Gut Microbiota Alterations Observed	Proposed Functional Impact
Systemic Lupus Erythematosus (SLE) [11,35]	Decreased gut microbiota diversity; Increased Ruminococcus gnavus; Decreased Firmicutes/Bacteroidetes (F/B) ratio; Enriched: Rhodococcus, Eggerthella, Klebsiella, Prevotella, Actinomyces, Flavonifractor; Reduced: Dialister, Pseudobutyrivibrio	Correlated with disease activity; May promote Th17 cell development; Contributes to disease exacerbation; Potential for altered IgA production
Rheumatoid Arthritis (RA) [31]	Reduction in beneficial microbial populations (e.g., Bifidobacterium, Lactobacillus); Increase in potential pathogenic microbes	Linked to elevated AID risk; May influence immune system regulation
Multiple Sclerosis (MS) [12]	Reduction in beneficial microbial populations (e.g., Bifidobacterium, Lactobacillus); Increase in potential pathogenic microbes	Linked to elevated AID risk; May influence immune system regulation
Autoimmune Thyroid Diseases (AITDs: Graves' Disease, Hashimoto's Thyroiditis) [32]	Significant changes in diversity and composition; Simpson index lower in GD; Other diversity indices greater in HT	May enhance intestinal permeability (↑ zonulin); Promotes autoantibody synthesis; Reshapes Th1 helper lymphocyte pool
Type 1 Diabetes Mellitus (T1DM) [6]	Reduction in beneficial microbial populations (e.g., Bifidobacterium, Lactobacillus); Increase in potential pathogenic microbes	Linked to elevated AID risk; May influence immune system regulation
General Autoimmune Diseases [5,8]	Depletion of commensal microbes; Presence of potentially pathogenic microbes	Influences pathogenic processes; Strong interaction with the immune system; May affect host metabolism

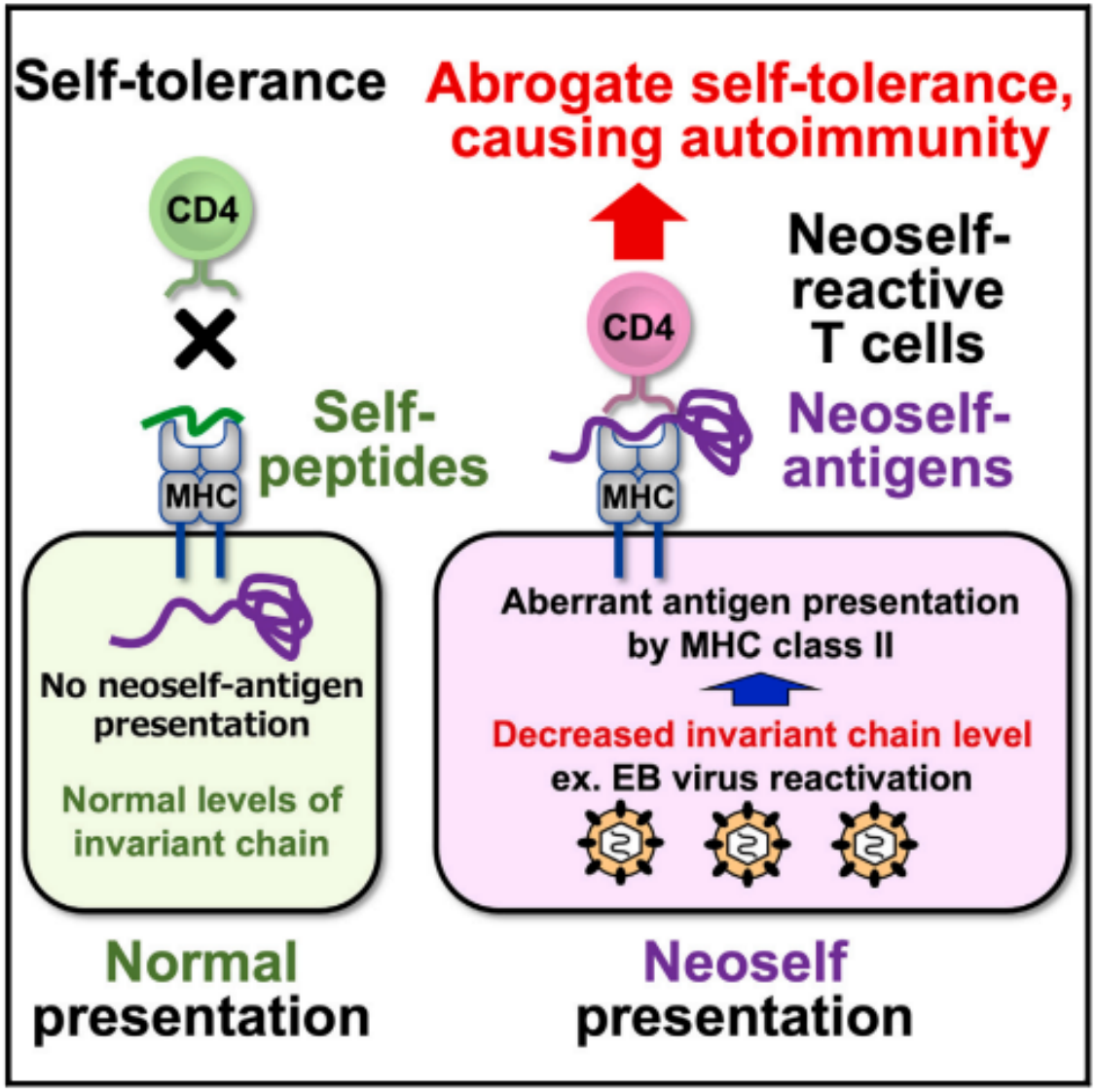
Vineesh A, et al. Cureus 2025

Neoself-antigens are the primary target for autoreactive T cells in human lupus

- Development of lupus-like autoimmunity upon loss of the invariant chain in adult mice
- Self-antigens presented on MHC-II in the presence or absence of the invariant
- B cell activation profile in invariant-chain-deleted mice similar to SLE patients
- Clonal expansion of neoself-reactive TFH cells in invariant-chain-deleted mice
- Neoself-reactive T cells in CD4+ T cells from SLE patients
- Clonal expansion of the neoself-reactive T cell repertoire in SLE patients

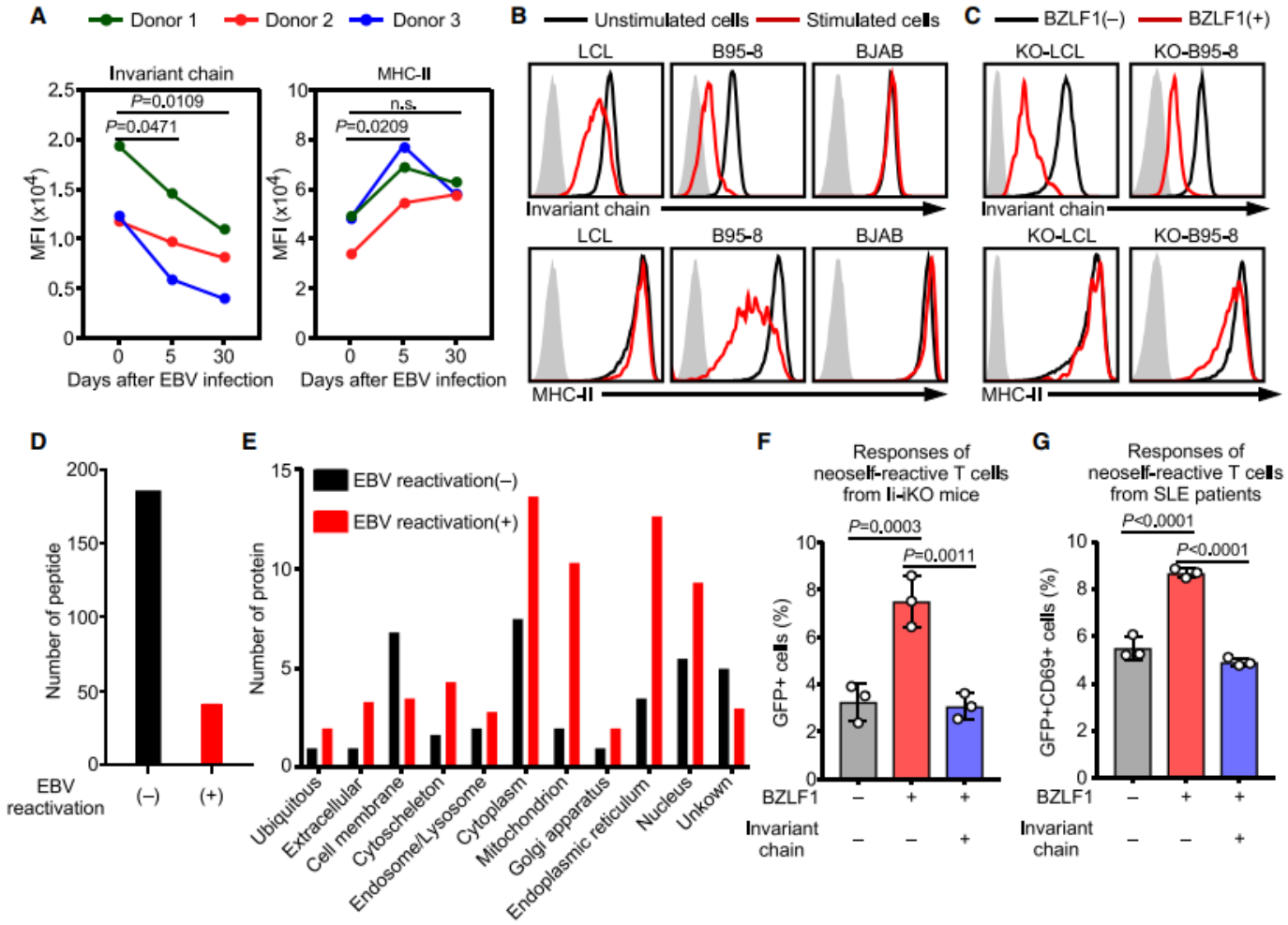
Mori S et al. Cell 187, 1–17, October 17, 2024

Neoself-antigens are the primary target for autoreactive T cells in human lupus



Mori S et al. Cell 187, 1–17, October 17, 2024

Neoself-antigens are the primary target for autoreactive T cells in human lupus



Enhanced activation of neoself-reactive T cells upon EBV reactivation

Mori S et al. Cell 187, 1–17, October 17, 2024

Autoimmunité: historique

Autoréactivité physiologique

- **1901. P. Ehrlich : Horror autotoxicus.**
- **1957. M. Burnet : théorie de la sélection clonale.**
- **1975. S. Avrameas : caractérisation des autoanticorps naturels.**
- **1990. Les lymphocytes T et B autoréactifs constituent une part importante des répertoires immunitaires exprimés dans les conditions physiologiques.**

Autoréactivité pathologique

- **1956: Witebski et Rose: Thyroïdite autoimmune induite chez le lapin.**
- **1957: Anticorps anti-nucléaires, anti-DNA**
- **1973: Réponse autoimmune à l 'acétylcholine**
- **1998: anticorps anti-protéase du facteur Willebrand**

Nobel Prize in Physiology or Medicine 2025

Ill. Niklas Elmehed © Nobel Prize Outreach

Mary E. Brunkow

Prize share: 1/3

Ill. Niklas Elmehed © Nobel Prize Outreach

Frederick J. Ramsdell

Prize share: 1/3

Ill. Niklas Elmehed © Nobel Prize Outreach

Shimon Sakaguchi

Prize share: 1/3

Mary E. Brunkow, Fred Ramsdell and Shimon Sakaguchi shared the Nobel prize **for their work on peripheral immune tolerance, a process that is key to organ transplants and treatment of autoimmune diseases**

Immunologic self-tolerance maintained by activated T cells expressing IL-2 receptor alpha-chains (CD25). Breakdown of a single mechanism of self-tolerance causes various autoimmune diseases

CD4+CD25+ cells contribute to maintaining self-tolerance by down-regulating immune response to self and non-self Ags in an Ag-nonspecific manner, presumably at the T cell activation stage; **elimination/reduction of CD4+CD25+ cells relieves this general suppression, thereby not only enhancing immune responses to non-self Ags, but also eliciting autoimmune responses to certain self-Ags. Abnormality of this T cell-mediated mechanism of peripheral tolerance can be a possible cause of various autoimmune diseases.**

Sakagushi S et al. J Immunol 1995

The regulation and differentiation of regulatory T cells and their dysfunction in autoimmune diseases

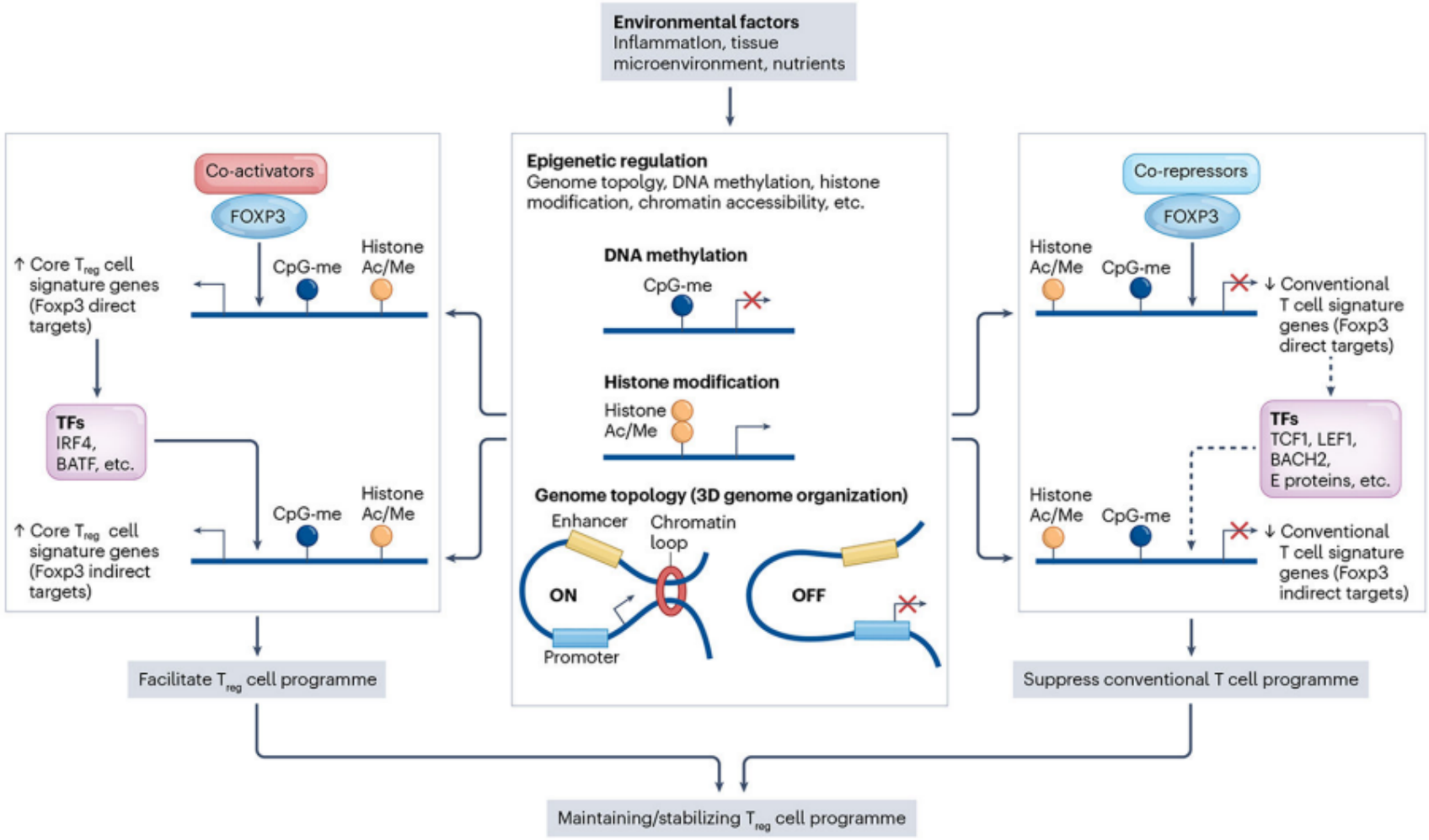


Fig. 1 |. FOXP3-centred gene regulatory network: epigenetic modulation of T_{reg} cell function and stability.

Sumida TS et al. Nat Rev Immunol. 2024 July ; 24(7): 503–517

Females are more susceptible to autoimmune diseases than males

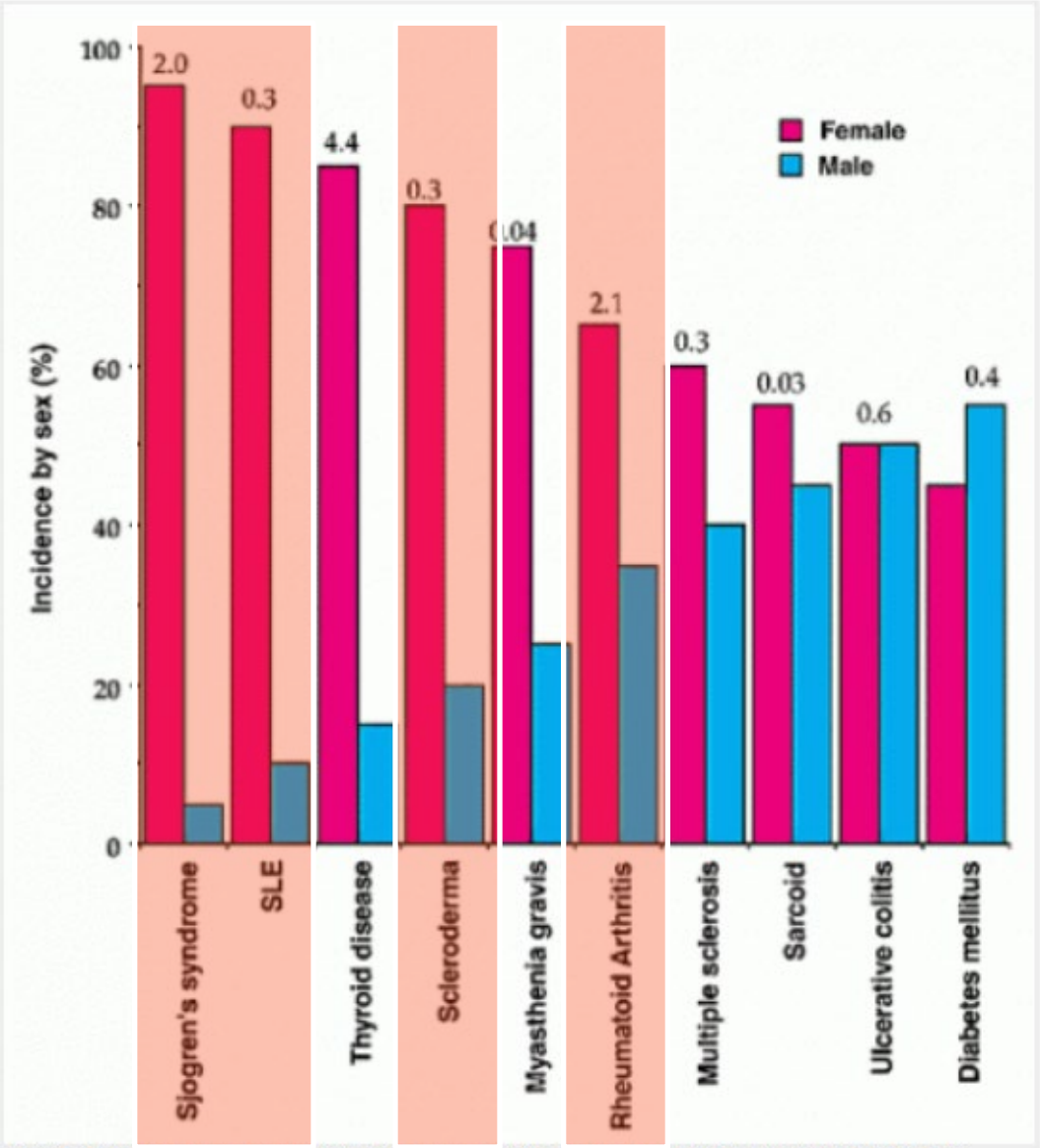
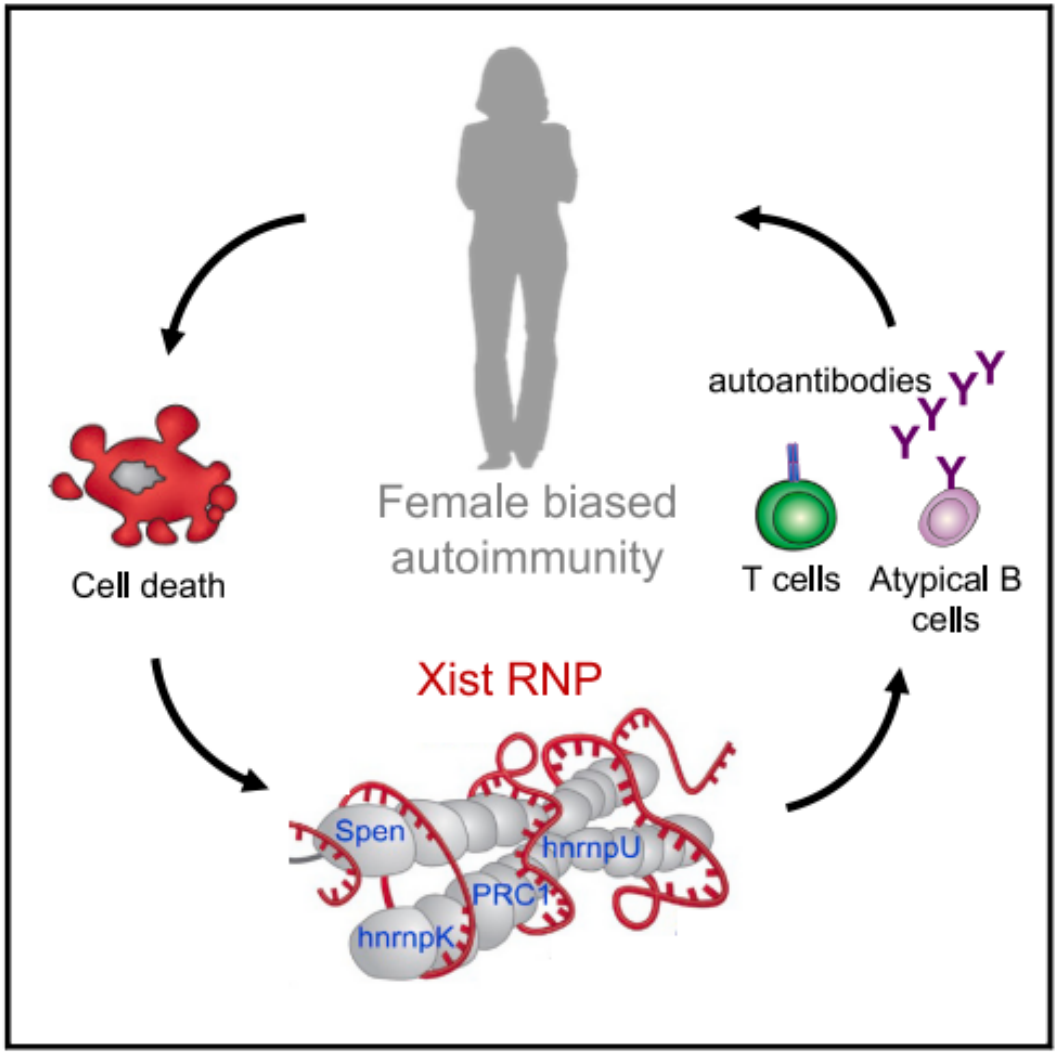


Fig. 1. Gender and autoimmune disease. Numbers refer to total number of cases (x 1,000,000) in the US.

Xist ribonucleoproteins promote female sex-biased autoimmunity



Dou DR et al. Cell 2024: 187, 733–749

Xist ribonucleoproteins promote female sex-biased autoimmunity

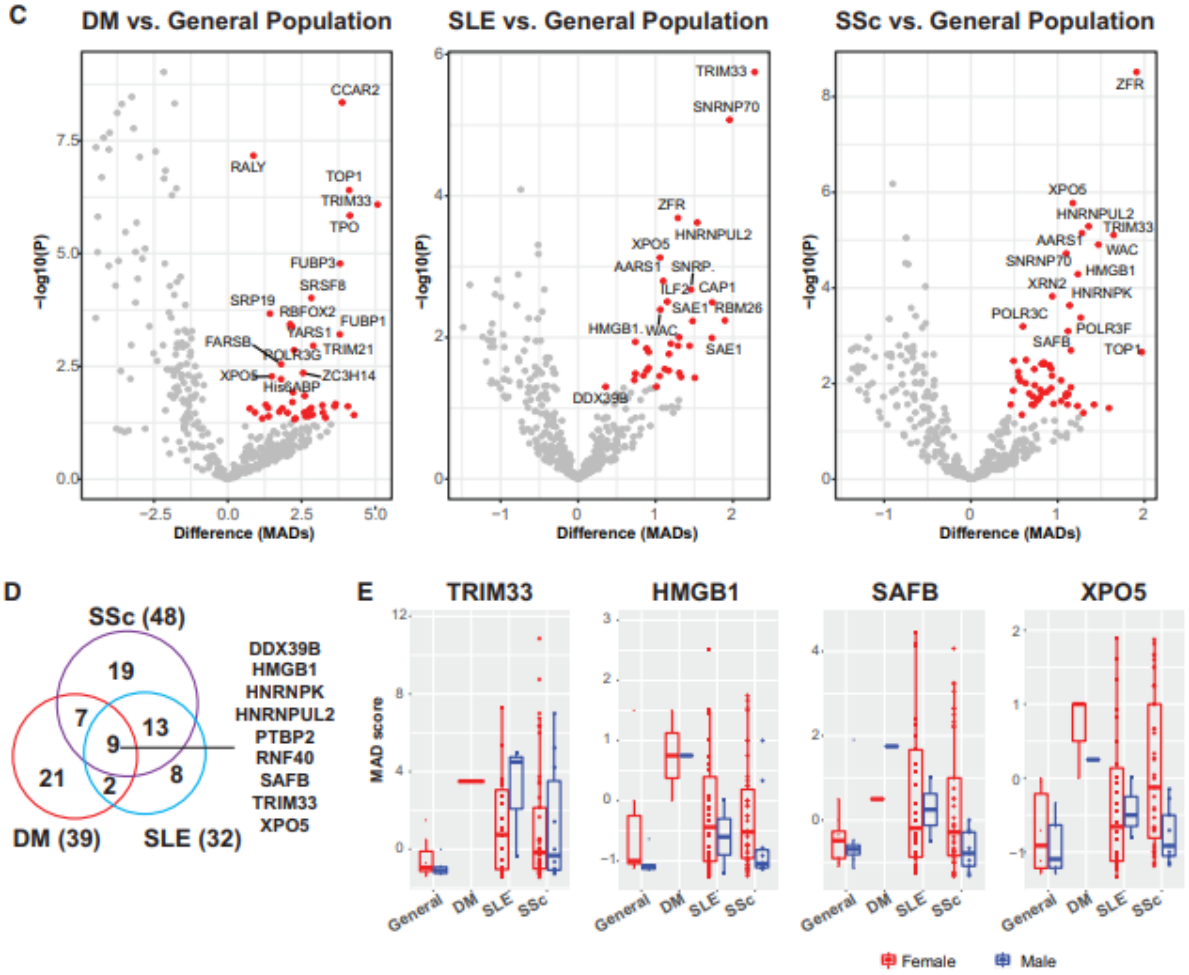
- Autoimmune diseases disproportionately affect females.
- Xist long non-coding RNA (lncRNA) is expressed only in females to randomly inactivate one of the two X chromosomes to achieve gene dosage compensation.
- The Xist ribonucleoprotein (RNP) complex is an important driver of sex-biased autoimmunity.
- Inducible transgenic expression of a non-silencing form of Xist in male mice introduced Xist RNP complexes and sufficed to produce autoantibodies.
- Male SJL/J mice expressing transgenic Xist developed more severe multi-organ pathology in a pristane-induced lupus model than wild-type males.
- Xist expression in males reprogrammed T and B cell populations and chromatin states to more resemble wild-type females.
- Human patients with autoimmune diseases displayed significant autoantibodies to multiple components of XIST RNP.
- Thus, a sex-specific lncRNA scaffolds ubiquitous RNP components to drive sex-biased immunity.

Dou DR et al. Cell 2024: 187, 733–749

Autoimmune disease patients experience increased serum reactivity toward antigens of the XIST RNP

(C) Volcano plot of serum reactivity of sera grouped by DM, SSc, and SLE patients, compared with general population

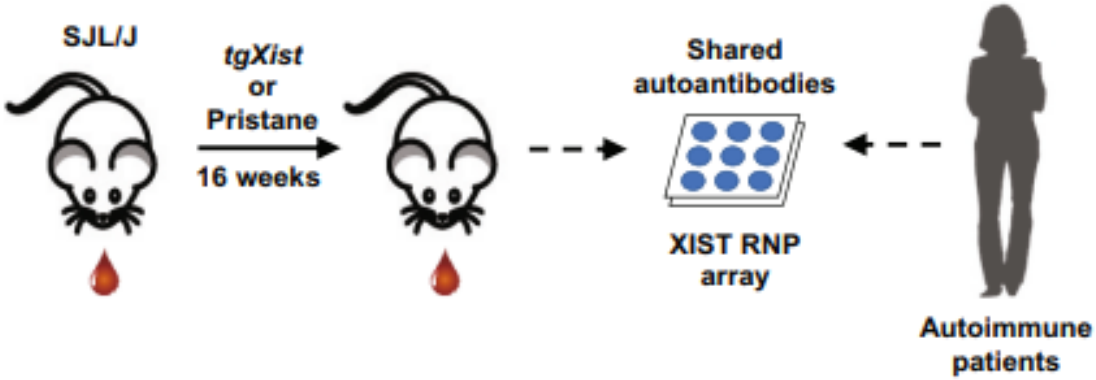
(D) Metrics of unique antigens from the array with significant elevated serum activity in autoimmune patients, compared with the general population.

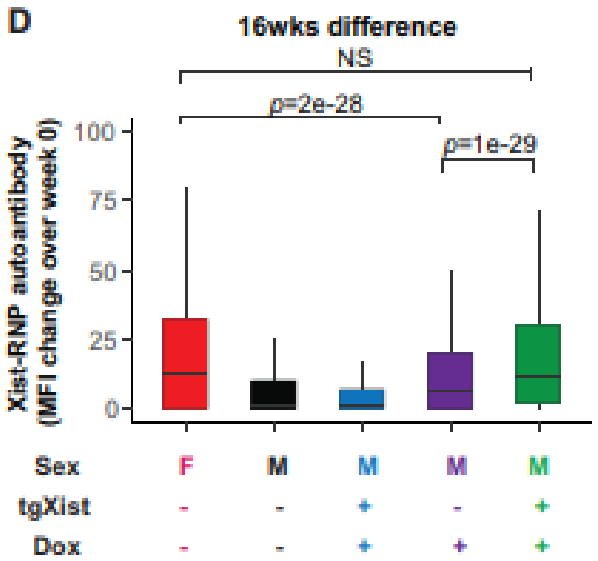


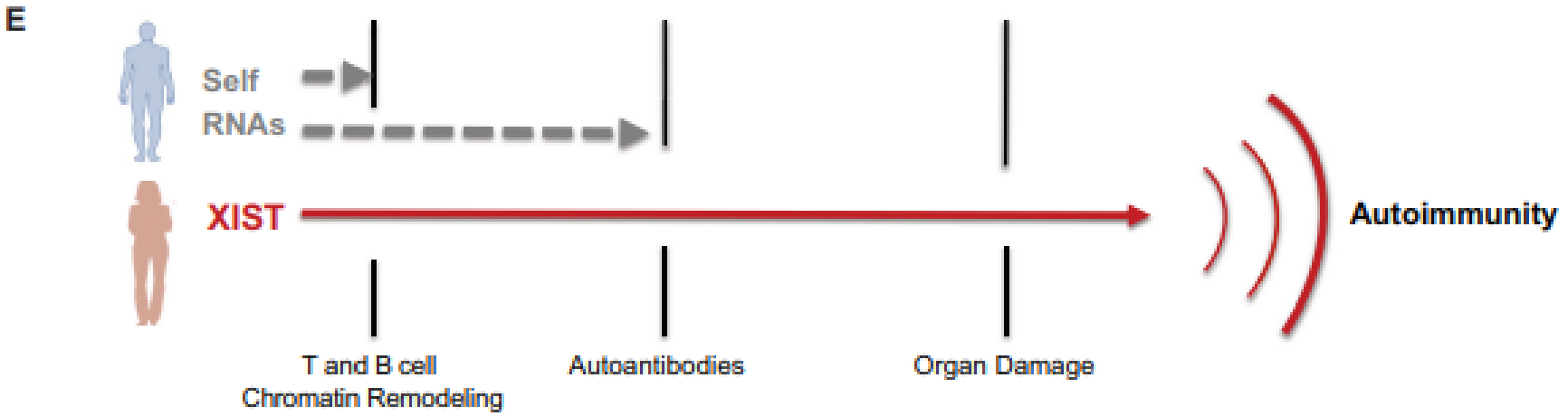
(E) Serum reactivity (MAD) plots of representative antigens significantly reactive in all three autoimmune patient cohorts grouped by disease type and colored by sex (red, female; blue, male).

Dou DR et al. Cell 2024: 187, 733–749

Model of XIST RNP in autoimmune progression

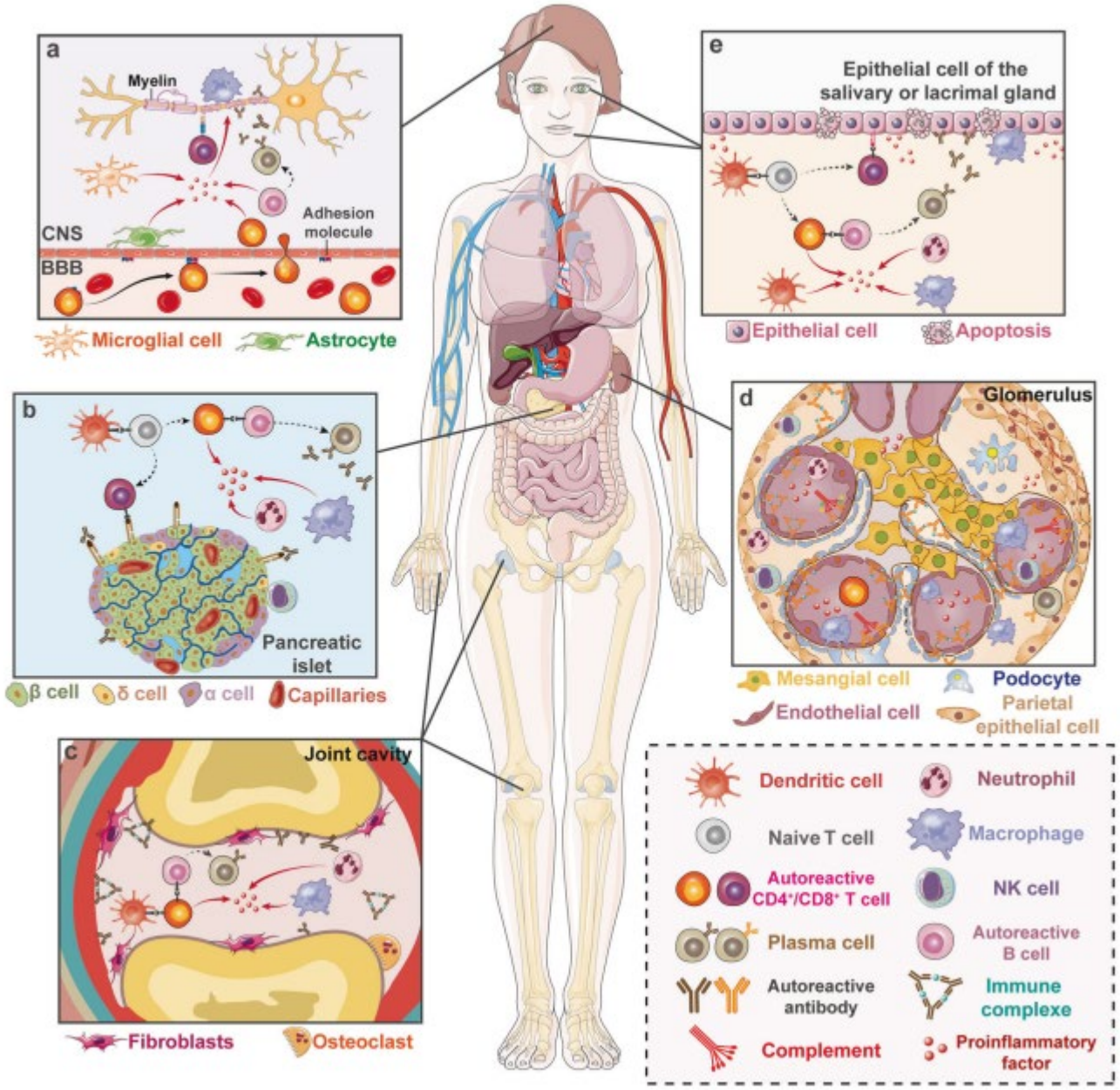




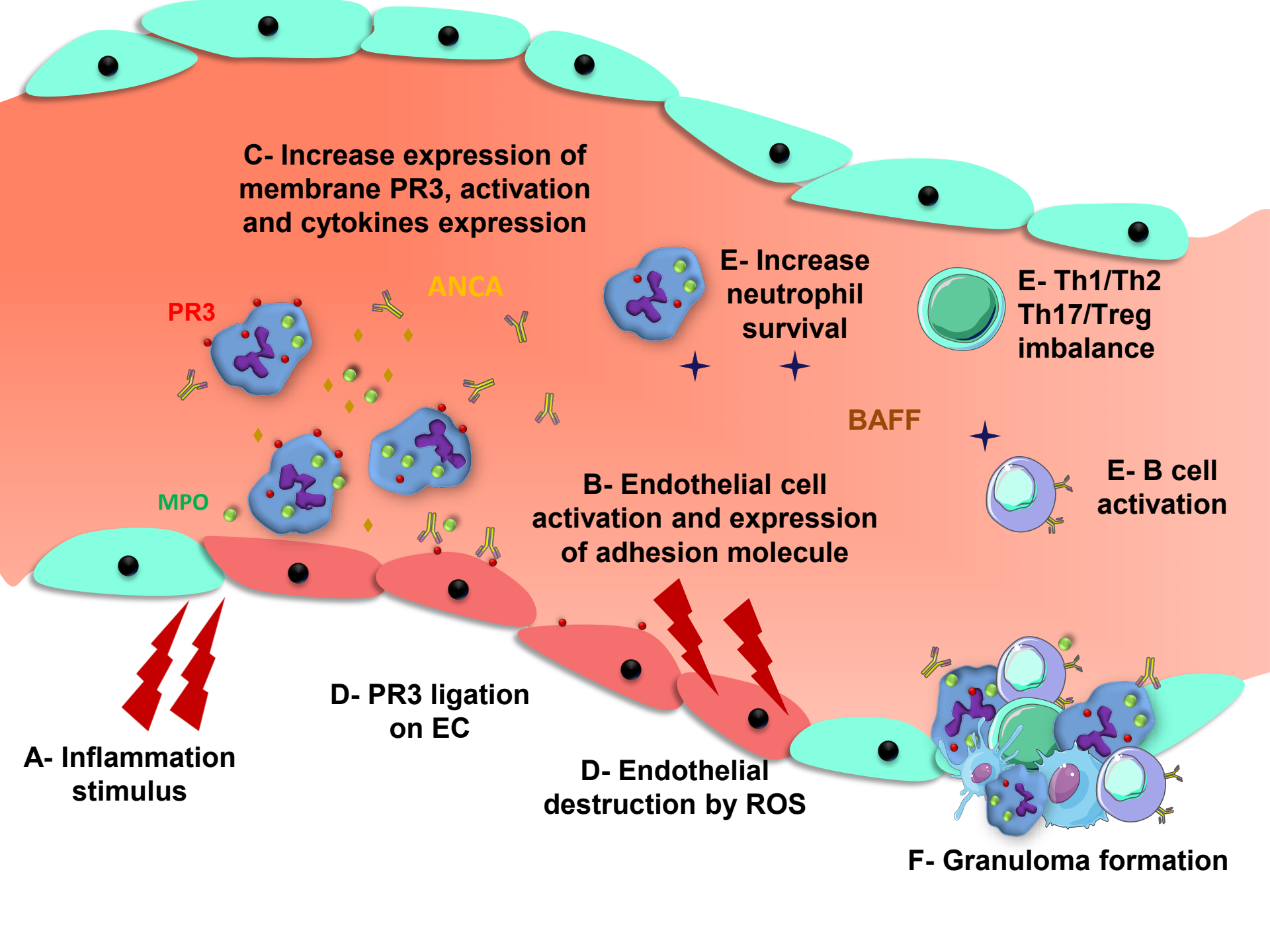


Dou DR et al. Cell 2024: 187, 733–749

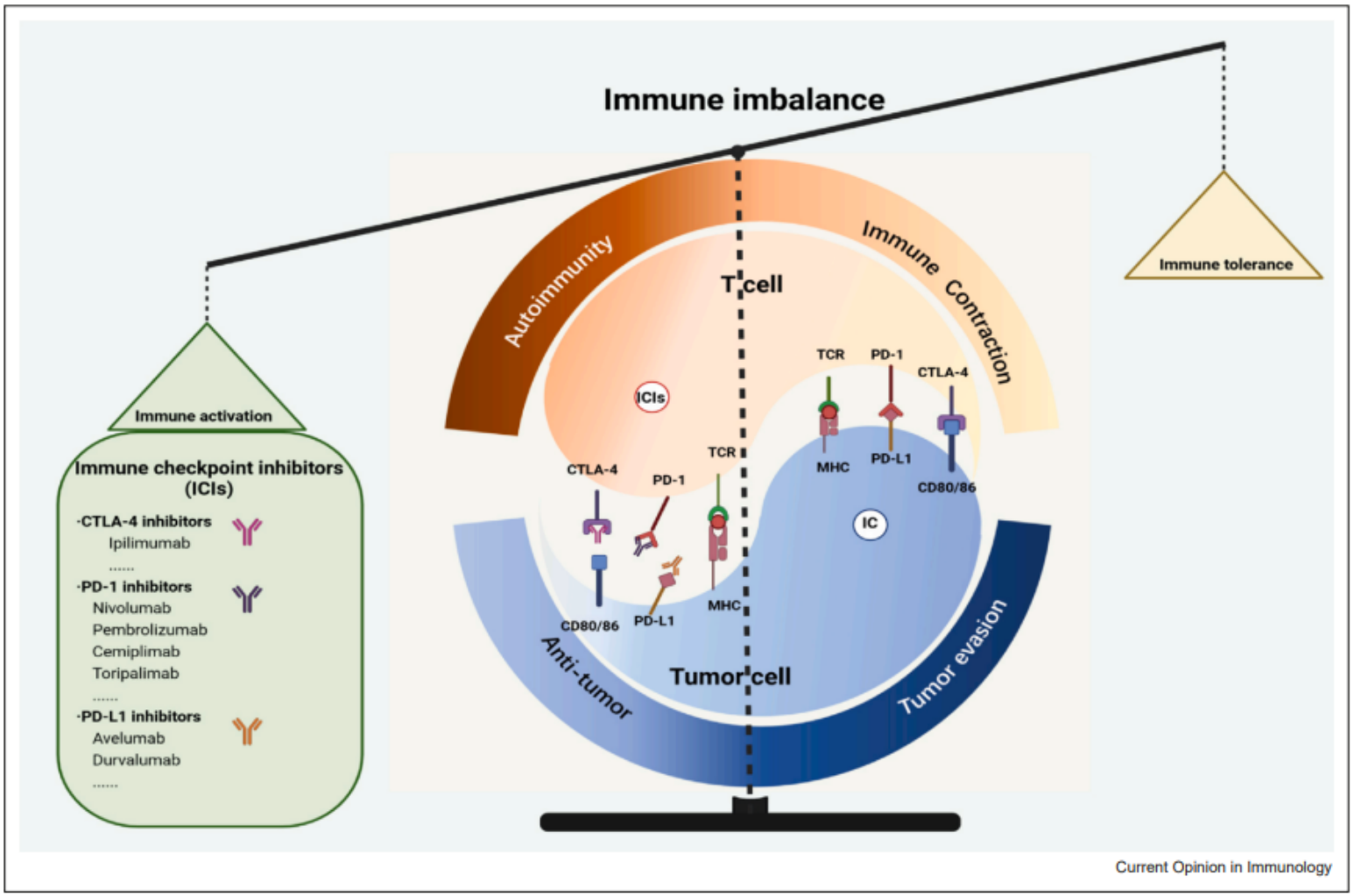
Pattern diagram of some typical autoimmune diseases



Signal Transduction and Targeted Therapy (2024) 9:263


C- Increase expression of membrane PR3, activation and cytokines expression
ANCA
PR3
MPO
E- Increase neutrophil survival
E- Th1/Th2 Th17/Treg imbalance
BAFF
E- B cell activation
B- Endothelial cell activation and expression of adhesion molecule
A- Inflammation stimulus
D- PR3 ligation on EC
D- Endothelial destruction by ROS
F- Granuloma formation

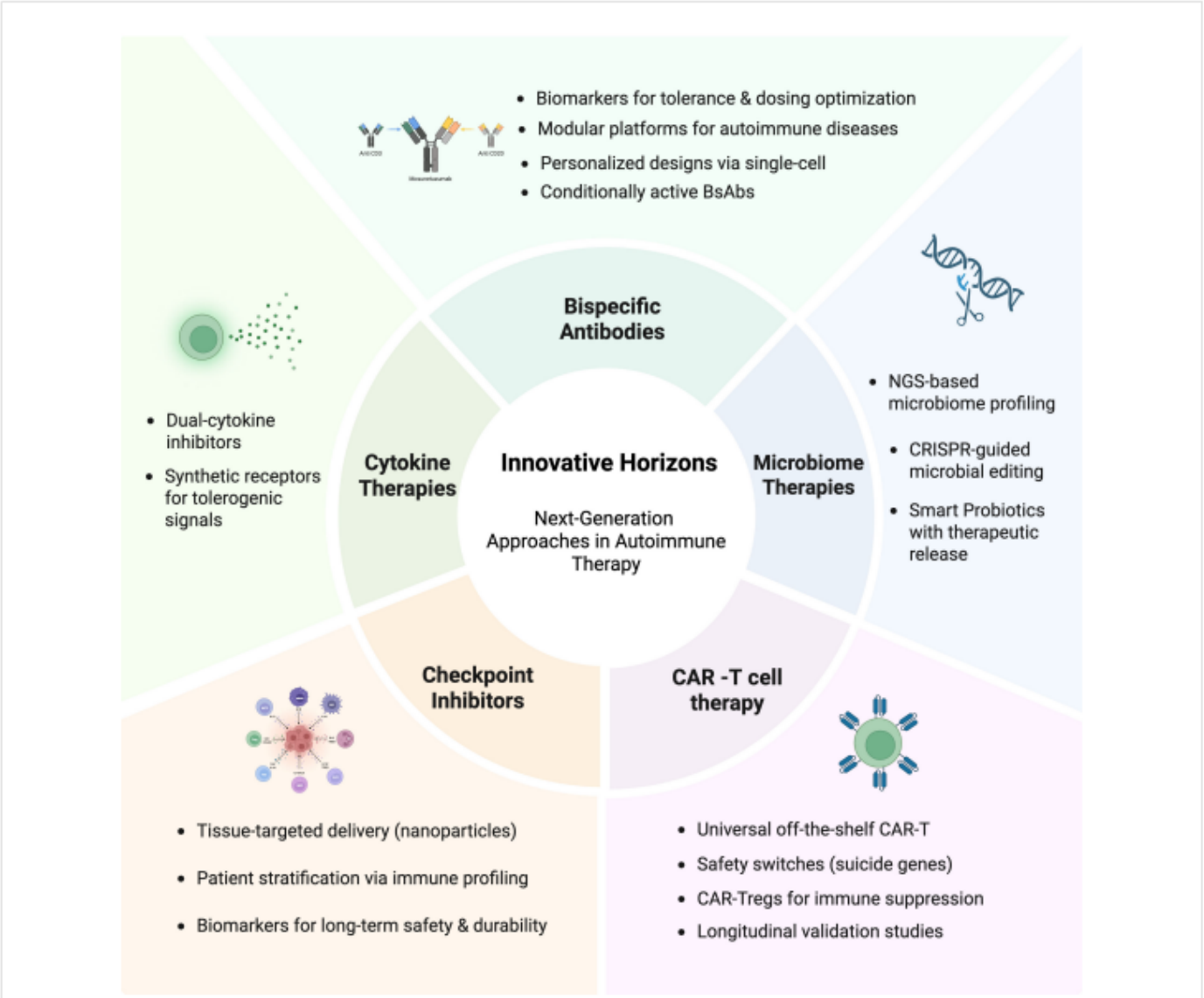
Autoimmune-related adverse events induced by immune checkpoint inhibitors



The Yin and Yang indicate the immune balance between immune activation and tolerance, which could be disrupted by ICIs. Immune checkpoints maintain the immune tolerance by negatively regulating T cell activity, while also enabling tumor evasion. The administration of ICIs shifts the immune landscape toward immune activation, enhancing the antitumor immune response, but also potentially leading to irAEs. Figure designed using Biorender.com. IC: immune checkpoint; MHC: major histocompatibility complex.

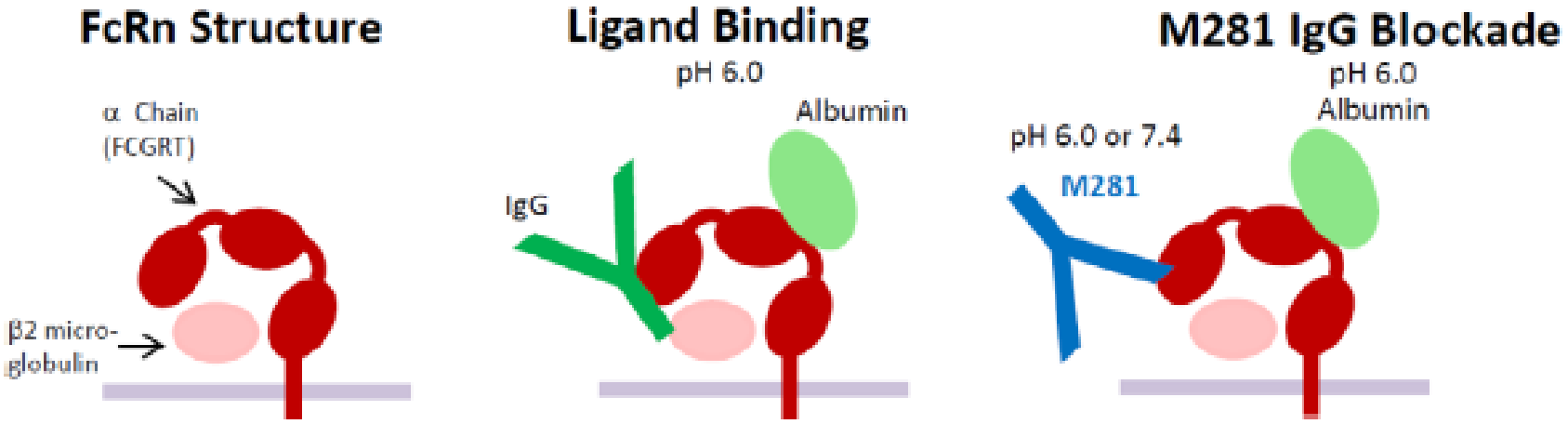
Current Opinion in Immunology 2025, 94:102556

Innovative Horizons in Next-Generation Therapeutic Approaches for Autoimmune Diseases.



Alsayb MA Front Immunol 2025

Mechanism of action of monoclonal antibodies targeting FcRn



M281, a fully human, effectorless IgG1 monoclonal antibody binds competitively and with high affinity at ph 6.0 or ph 7.4 to the IgG binding site of FcRn, a transmembrane endososomal receptor for IgG and albumin. M281 has no effect on IgM, IgA, IgE, or cellular response to immunisation.

British Journal of Haematology, 2021, 192, 425–432

CD19 CAR T-Cell Therapy in Autoimmune Disease — A Case Series with Follow-up

- 15 patients with severe SLE (8 patients), idiopathic inflammatory myositis (3 patients), or systemic sclerosis (4 patients) who received a single infusion of CD19 chimeric antigen receptor (CAR) T cells after preconditioning with fludarabine and cyclophosphamide
- In this case series, CD19 CAR T-cell transfer appeared to be feasible, safe, and efficacious in three different autoimmune diseases

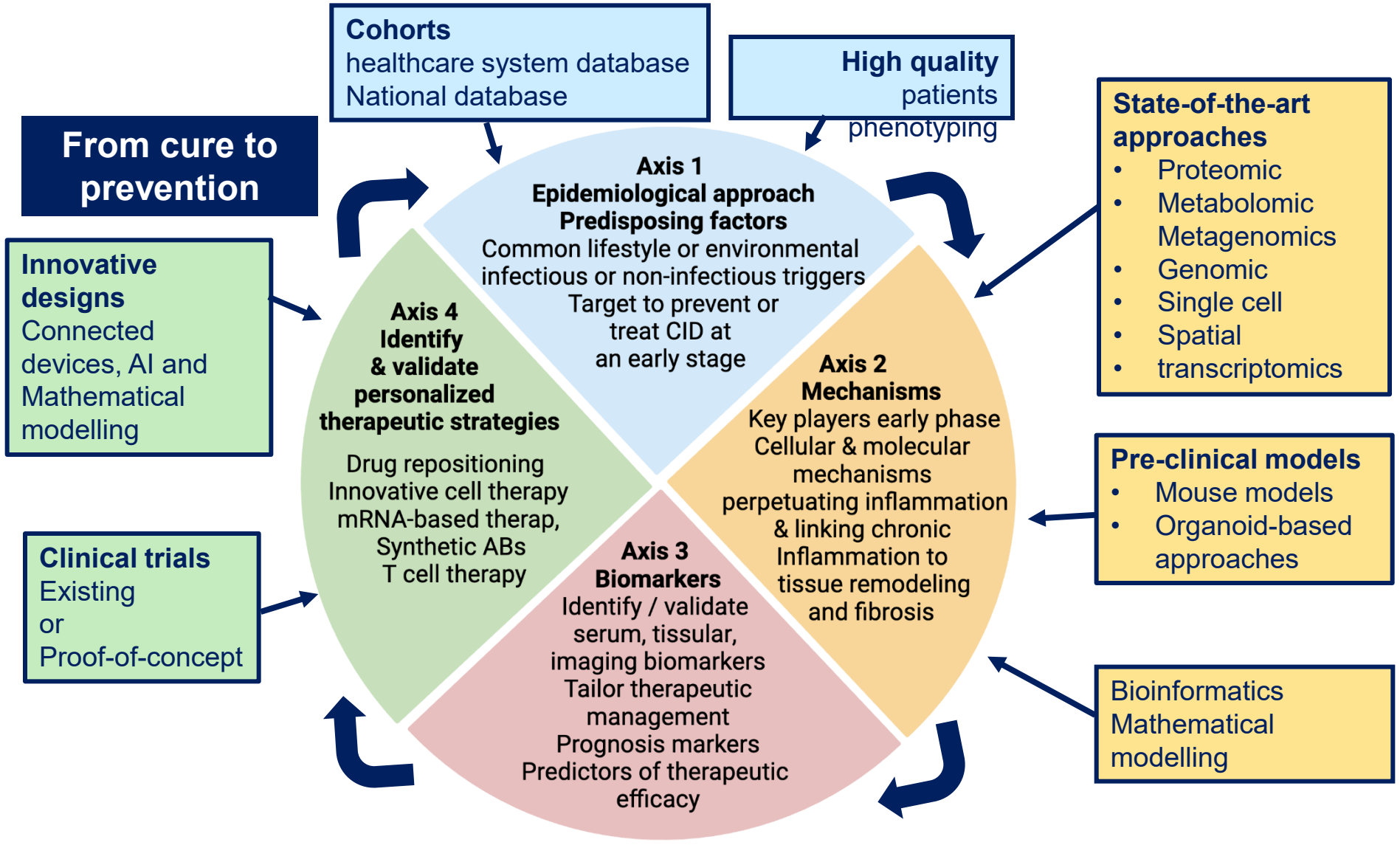
Table 3. Long-Term Safety of CD19 CAR T-Cell Therapy in Autoimmune Disease.*

Patient No.	Disease	<3 Months	3–6 Months	6–12 Months	>12 Months
1	SLE	UTI	0	0	URTI (nonspecified)
2	SLE	0	0	URTI (SARS-CoV-2†)	URTI (nonspecified)
3	SLE	URTI (SARS-CoV-2)	0	URTI (nonspecified)	URTI (SARS-CoV-2) and herpes zoster
4	SLE	0	0	0	Otitis
5	SLE	0	URTI (SARS-CoV-2†)	0	0
6	SLE	0	URTI (SARS-CoV-2† and RSV)	URTI (SARS-CoV-2†)	URTI (nonspecified)
7	SLE	0	0	0	
8	SLE	Pneumonia	0		
9	IIM	0	Enteritis (nonspecified)	0	0
10	IIM	0	Herpes simplex	0	0
11	IIM	URTI (nonspecified)	0		
12	SSc	0	URTI (*Haemophilus influenzae*)	0	0
13	SSc	0	Cellulitis	Herpes zoster	
14	SSc	URTI (SARS-CoV-2†)	0		
15	SSc	0			

* Shown is the infection profile of patients with autoimmune disease undergoing CD19 CAR T-cell therapy. Data are presented chronologically and according to site of infection. RSV denotes respiratory syncytial virus, SARS-CoV-2 severe acute respiratory syndrome coronavirus 2, URTI upper respiratory tract infection, and UTI urinary tract infection.
† The infection was treated with nirmatrelvir–ritonavir (Paxlovid).

Muller F et al. N Engl J Med 2024;390:687-700

Patients-centered bidirectional translational approach in Chronic inflammatory diseases



PEPR TRANSCEND-ID

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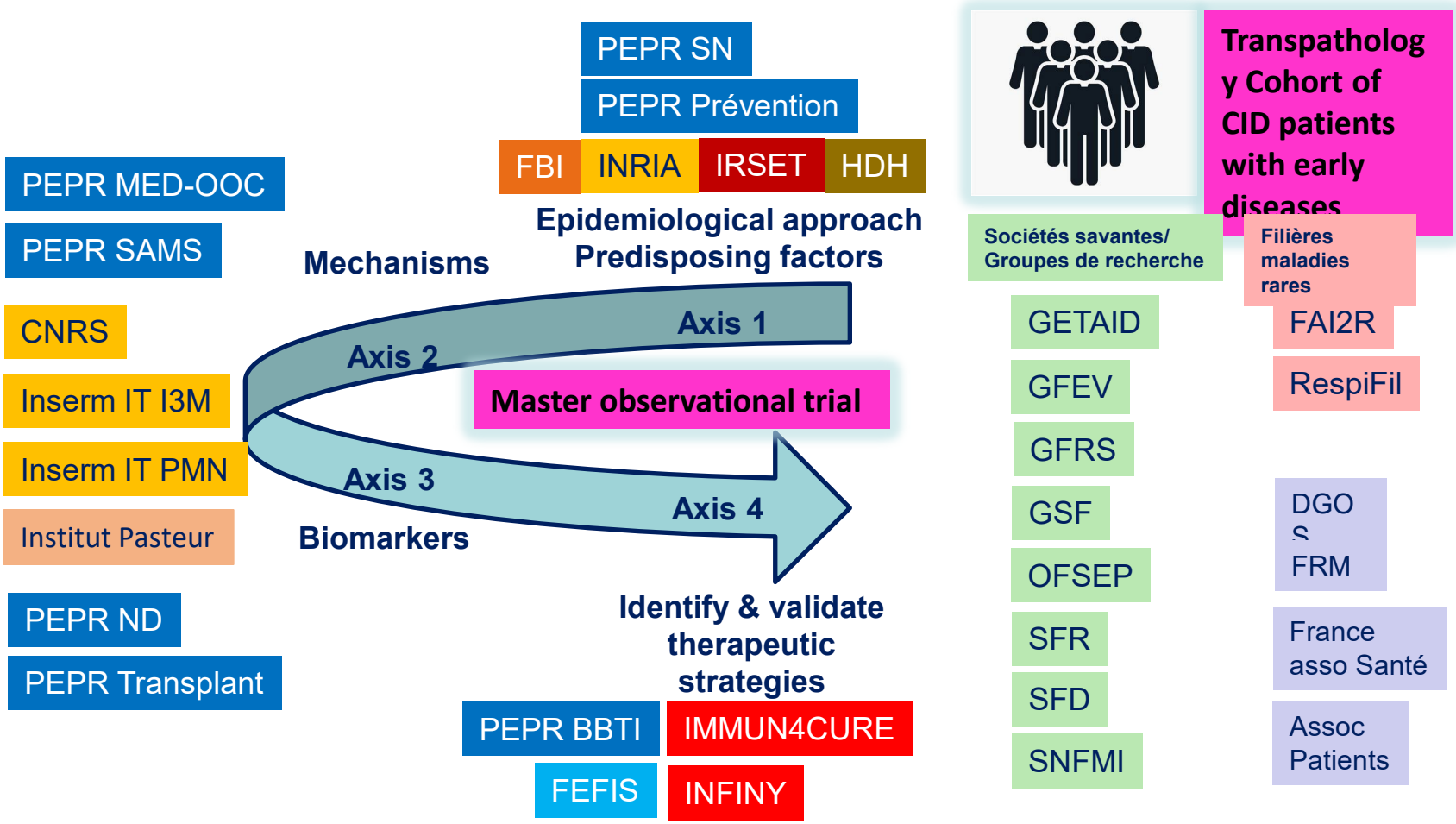

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