Autoimmunity
Micro 204

Qizhi Tang, PhD

11/16/2018

Themes

1. **Overview:**

   Definition, epidemiology, classification

2. **Effector mechanisms autoimmune disease**
   a. Antibody-mediated and T cell-mediated
   b. Autoantigens
3. **Etiology of autoimmune diseases**
   a. Genetics
   b. Environment
4. **Therapeutic developments**

Autoimmunity & autoimmune diseases

Definition: immune response against self (auto-) antigen

- Most people have “autoimmunity” - immune recognition of self, but majority don’t have “autoimmune disease” – immune damage of self

General principles:

- Significant health burden, affect 5% of population and rising
- Multiple factors contribute to autoimmunity, including genetic predisposition, infections
- Fundamental problem is the failure of self-tolerance

Challenges:

- Many target antigens, heterogeneous disease manifestations, disease usually presents long after initiation

Examples of autoimmune diseases

Organ-specific

- Type 1 diabetes
- Goodpasture's syndrome
- Multiple sclerosis
- Graves disease
- Hashimoto's thyroiditis
- Autoimmune pernicious anemia
- Autoimmune Addison's disease
- Vitiligo
- Myasthenia gravis

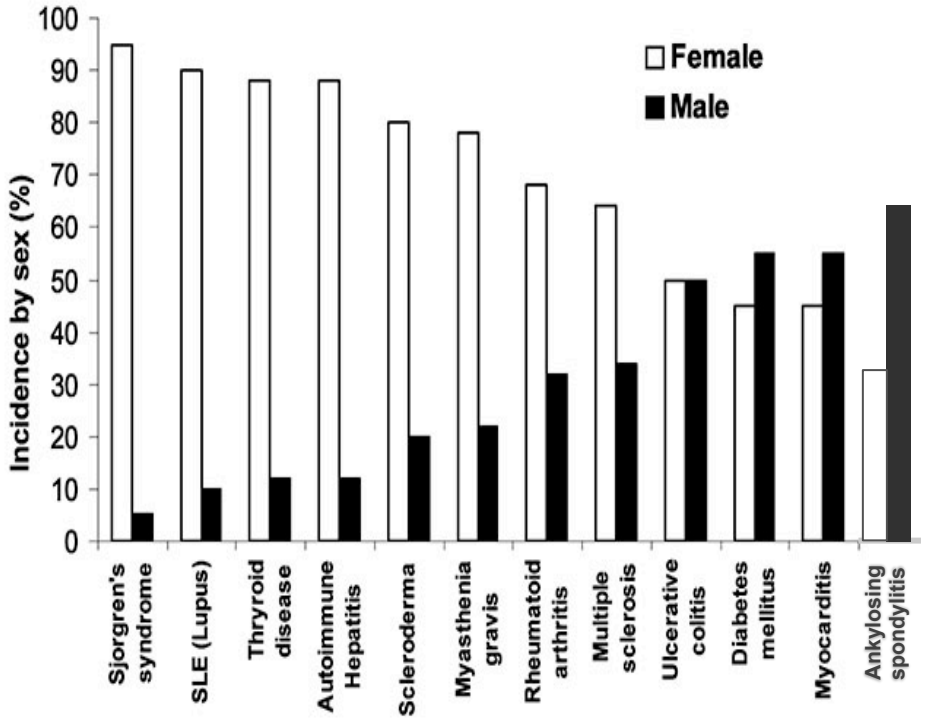
Systemic

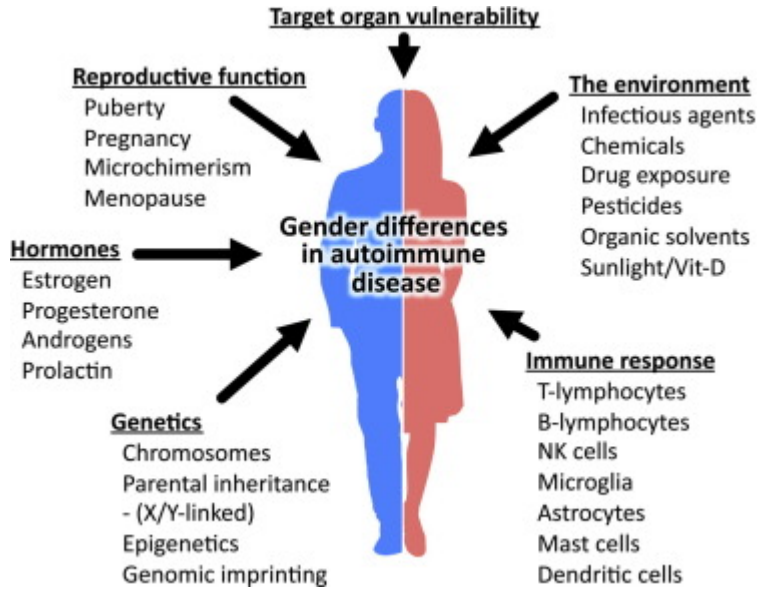
- Rheumatoid arthritis
- Scleroderma
- Systemic lupus erythematosis
- Sjogren's syndrome
- Hashimoto's thyroiditis
- Polymyositis

Diseases of hyperactive immune system (autoinflammatory diseases)

- Inflammatory bowel diseases
  - ✧ Crohn's disease
  - ✧ Ulcerative colitis
- Celiac disease
- Asthma
- Eczema

Prevalence by gender





Whitacre CC. Sex differences in autoimmune disease. Nature immunology. 2001 1;2(9):777-80.
Zandman-Goddard G, Peeva E, Shoenfeld Y. Gender and autoimmunity. Autoimmunity reviews. 2007 6(6): 366-72.
Ngo ST, Steyn FJ, McCombe PA. Gender differences in autoimmune disease. Frontiers in neuroendocrinology.

Inheritance and environment – twin studies

Disease	MZ twin concordance	DZ twin concordance
Type 1 diabetes	13-47.4% (30%)	3.8-11.6% (5.8%)
Multiple sclerosis	0-50% (16.7%)	0-16.7% (2.7%)
Celiac disease	60-75%	9.1-11%
Autoimmune thyroid disease	17-22%	0-1.9%
Psoriasis	35-64%	10-14%
SLE	11-40%	0-4%
Rheumatoid arthritis	0-21% (14%)	0-8.8% (3.5%)

- **Evidence of genetic influence:** concordance is uniformly higher between monozygotic twins than between dizygotic twins in all autoimmune diseases studied
- **Evidence of non-genetic influence:** risk of developing the same autoimmune disease by sibling with a diseases twin is never 100%
- **Relative contribution by genetics and environment differ** depending diseases : concordance rates between MZ twins differ for different diseases

Bogdanos, Dimitrios P., et al. "Twin studies in autoimmune disease: genetics, gender and environment." Journal of autoimmunity 38.2 (2012): J156-J169.

Classification of autoimmune diseases

- Broadly separated by the type of **effector** mechanism (similar to hypersensitivity classification scheme)
- Three classes:
  - **Type II:** Antibody against cell-surface antigen or matrix antigens
  - **Type III:** Immune-complex disease
  - **Type IV:** T cell-mediated disease

Mechanisms of autoimmune diseases

Type II: Antibody-mediated diseases

Autoimmune disease	Autoantigen	Consequence
Antibody against cell-surface or matrix antigens (type II)		
Autoimmune hemolytic anemia	Rh blood group antigens, I antigen	Destruction of red blood cells by complement and phagocytes anemia
Autoimmune thrombocytopenia purpura	Platelet integrin gpIIb:IIIa	Abnormal bleeding
Goodpasture's syndrome	Non-collagenous domain of basement membrane collagen type IV	Glomerulonephritis, pulmonary hemorrhage
Pemphigus vulgaris	Epidermal cadherin	Blistering of skin
Acute rheumatic fever	Streptococcal cell wall antigens. Antibodies cross-react with cardiac muscle	Arthritis, myocarditis, late scarring of heart valves
Graves' disease	Thyroid-stimulating hormone receptor	Hyperthyroidism
Myasthenia gravis	Acetylcholine receptor	Progressive weakness
Insulin-resistant diabetes	Insulin receptor (antagonist)	Hyperglycemia, ketoacidosis
Hypoglycemia	Insulin receptor (agonist)	Hypoglycemia

Antibody-dependent cytotoxicity

Complement deposition

Agonistic antibodies

Blocking antibodies

Figure 11-1 part 1 of 3 The Immune System, 2/e (© Garland Science 2005)

Graves' disease – effect of agonistic antibody

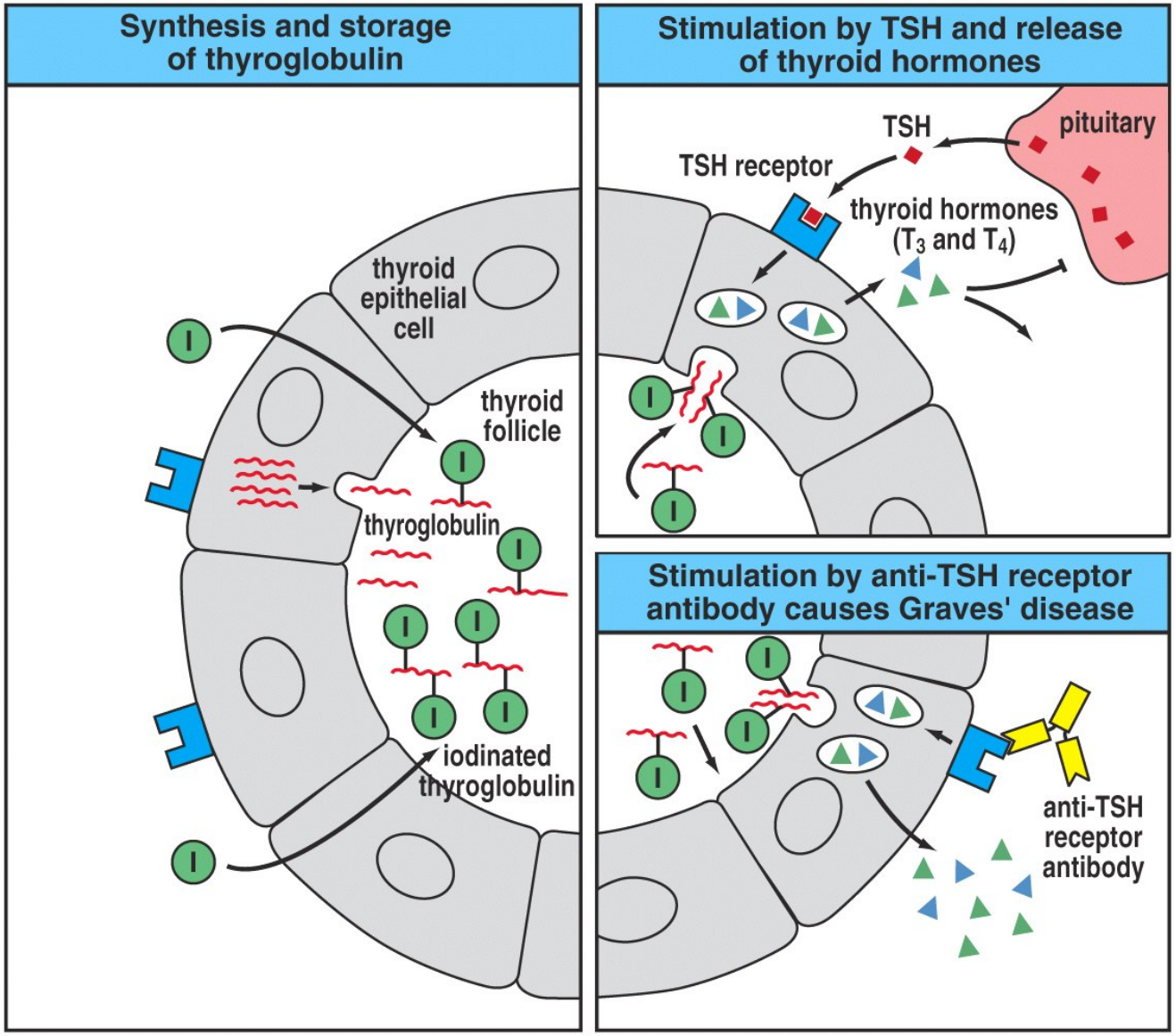


Figure 11-5 The Immune System, 2/e (© Garland Science 2005)

autoantibodies to TSH receptor mimic the action of TSH

Graves' disease:
Proof that it's antibody mediated

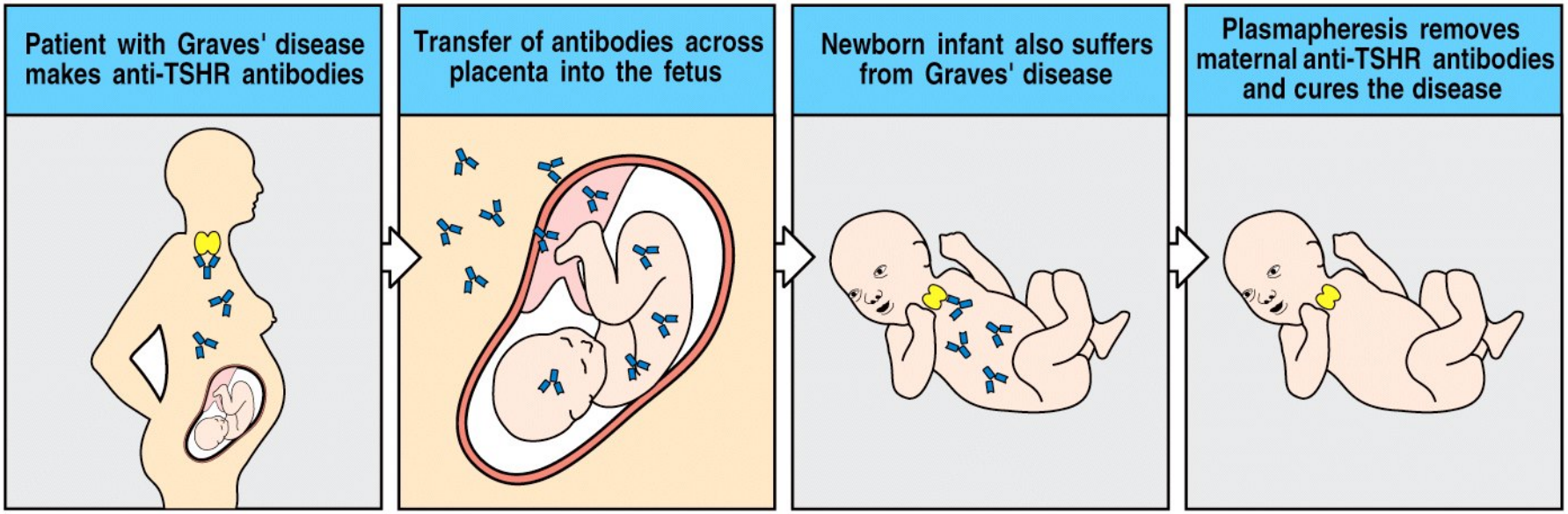
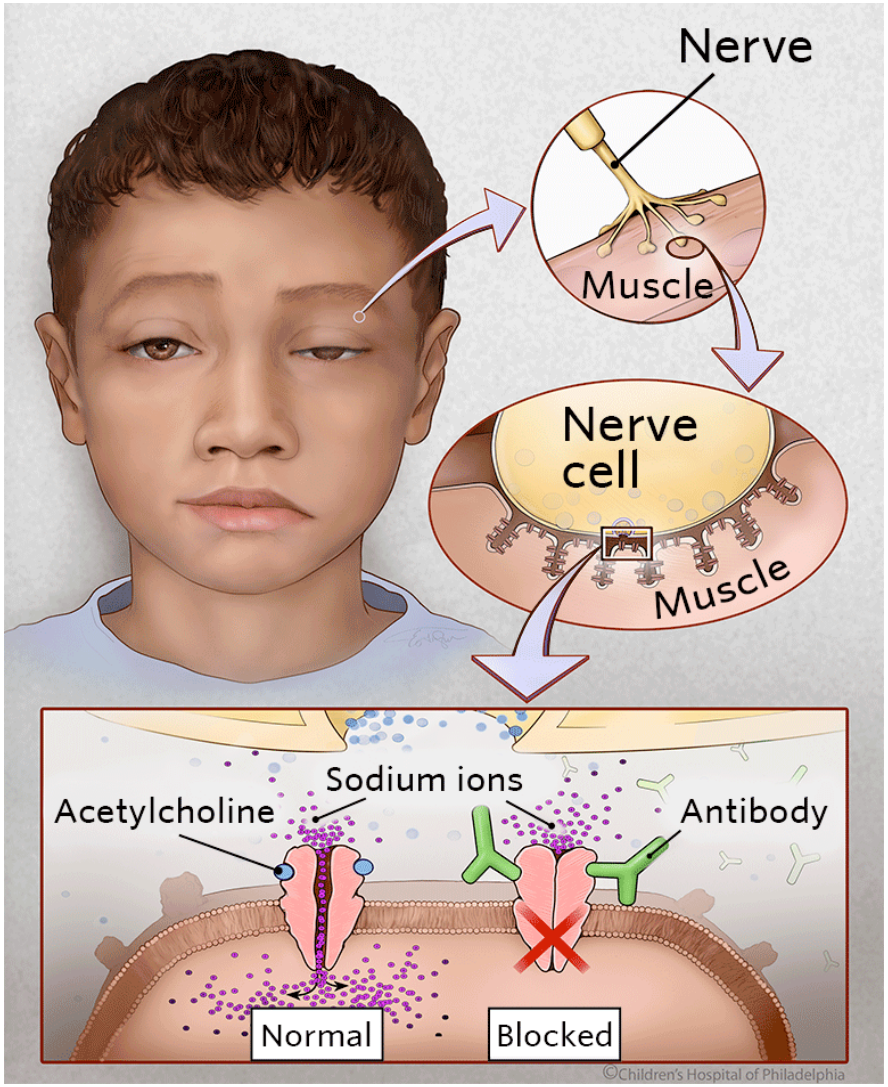


Figure 11-7 The Immune System, 2/e (© Garland Science 2005)

Myasthenia Gravis – antagonistic antibodies



autoantibodies to the acetylcholine receptor block neuromuscular transmission from cholinergic neurons to skeletal muscles

Type III: Immune-complex mediated diseases

Autoimmune disease	Autoantigen	Consequence
Immune-complex disease (type III)		
Subacute bacterial endocarditis	Bacterial antigen	Glomerulonephritis
Mixed essential cryoglobulinemia	Rheumatoid factor IgG complexes (with or without hepatitis C antigens)	Systemic vasculitis
Systemic lupus erythematosus	DNA, histones, ribosomes, snRNP, scRNP	Glomerulonephritis, vasculitis, arthritis

Figure 11-1 part 2 of 3 The Immune System, 2/e (© Garland Science 2005)

Review: Immune complex formation

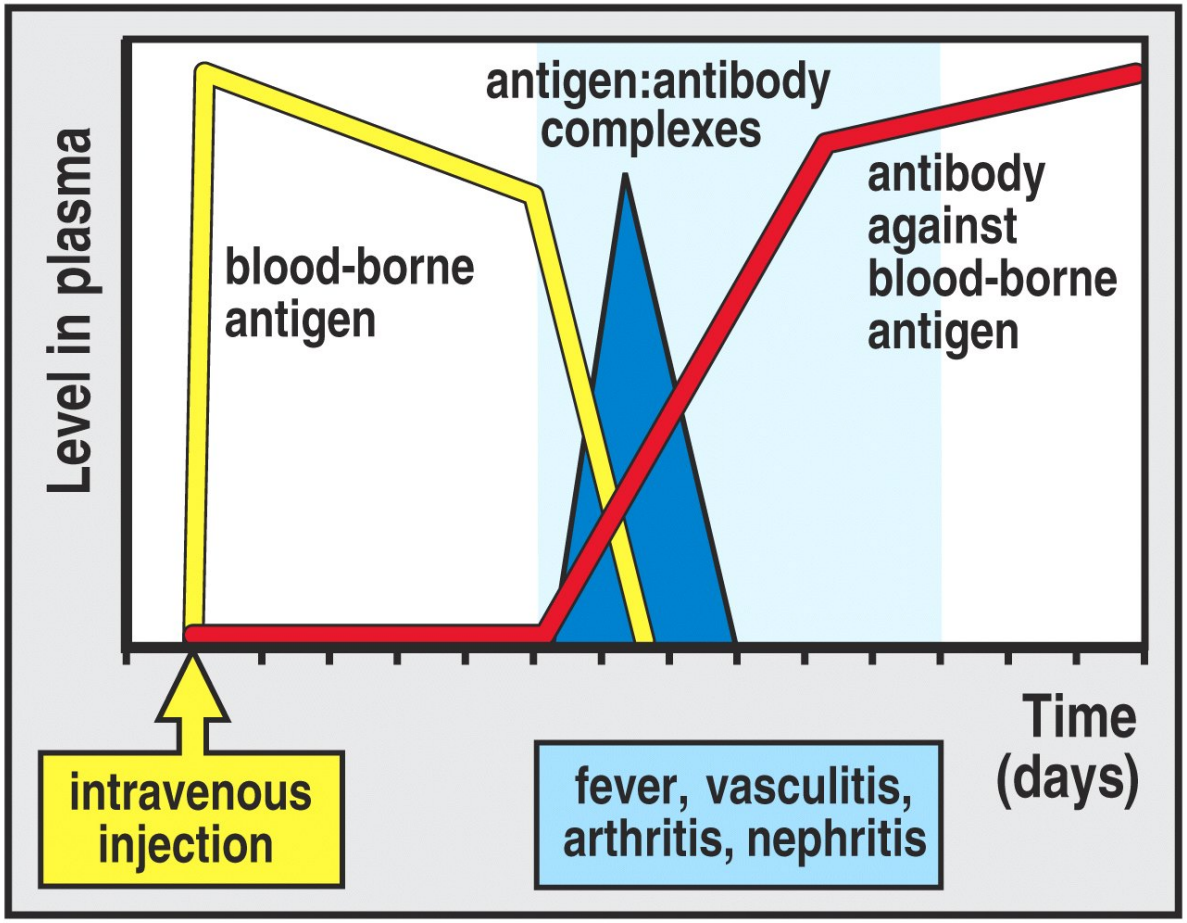


Figure 10-32 The Immune System, 2/e (© Garland Science 2005)

A model for the pathogenesis of SLE

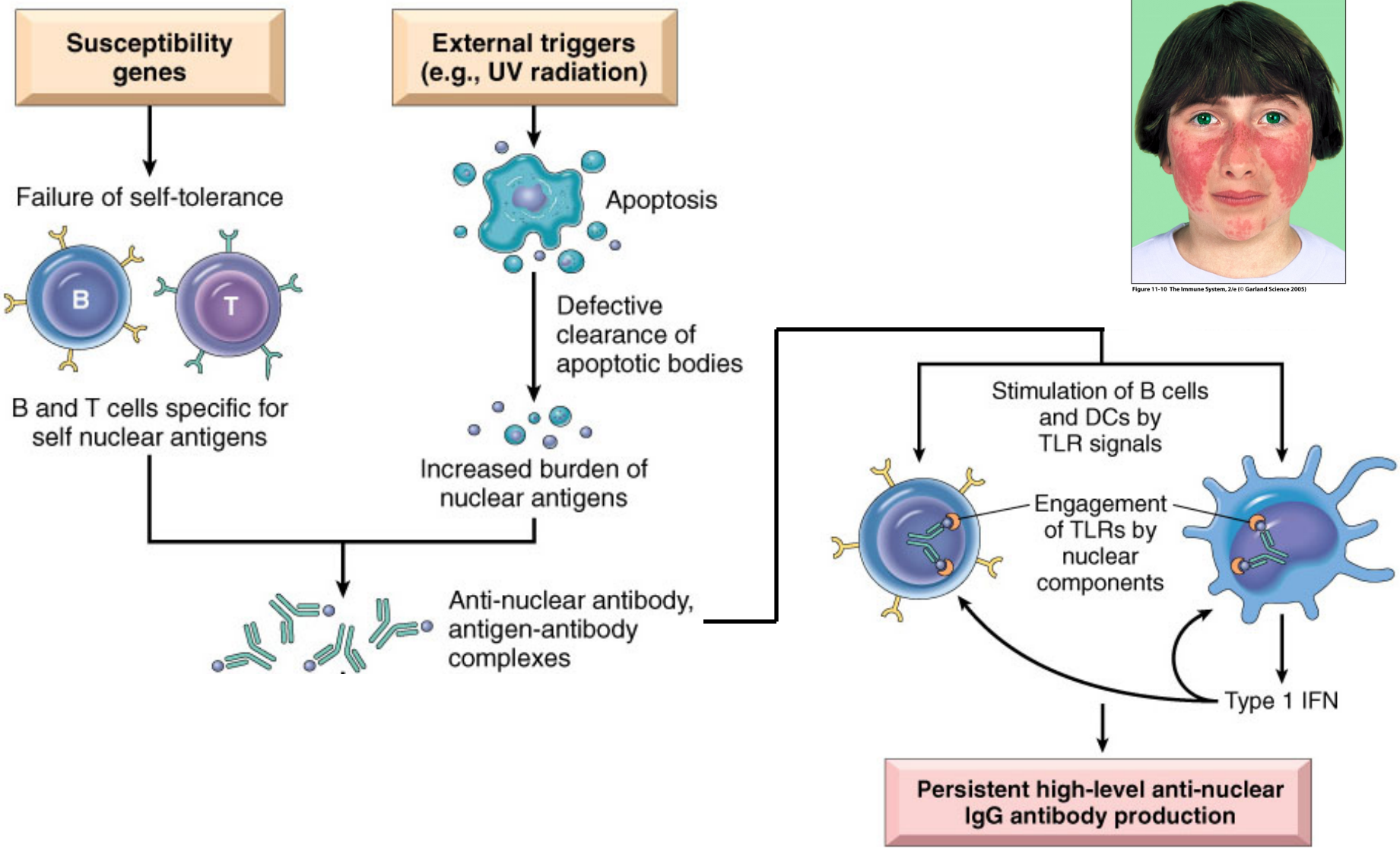


Figure 11-10 The Immune System, 2/e (© Garland Science 2005)

SLE: immune complexes in the kidney

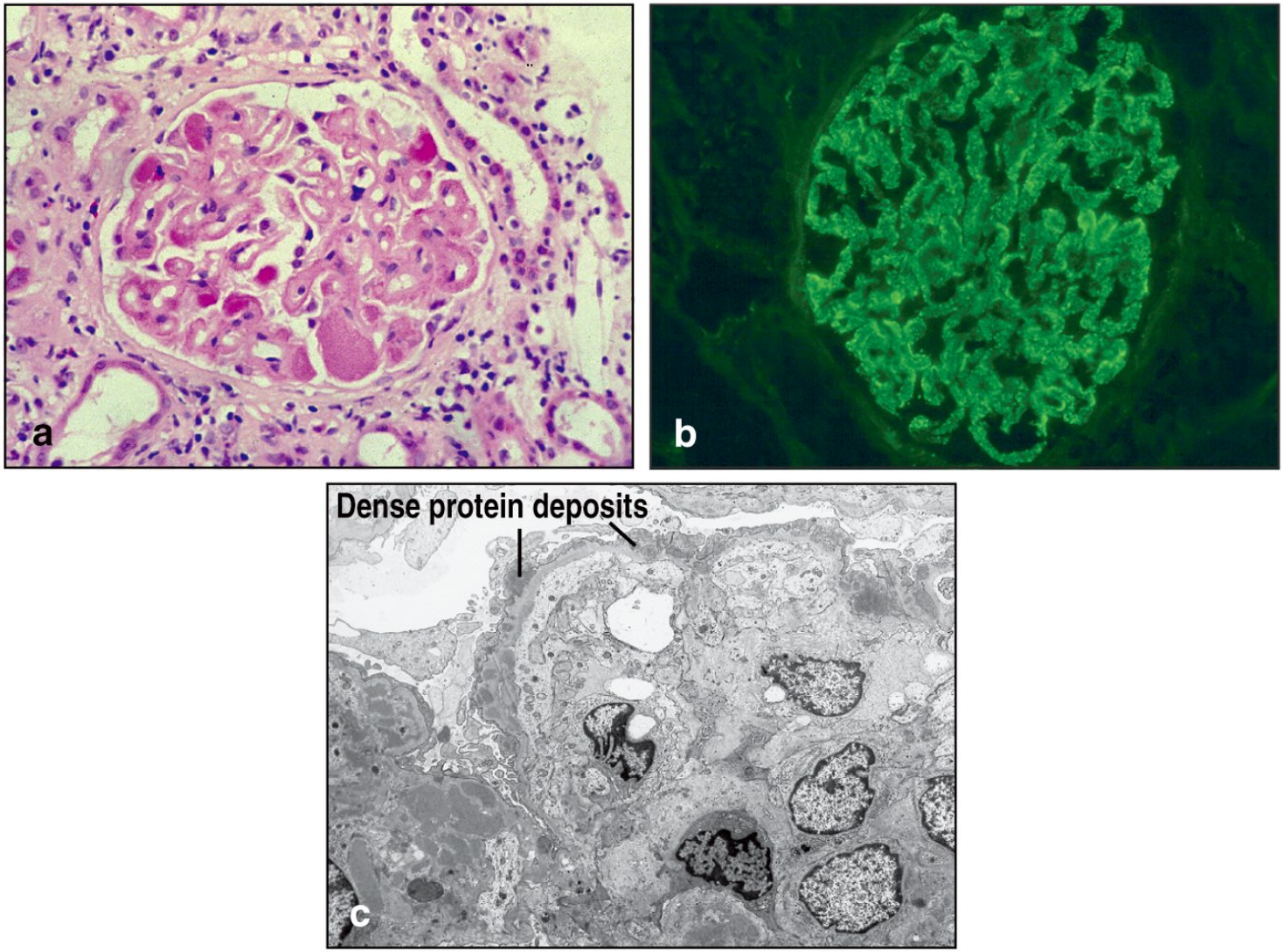
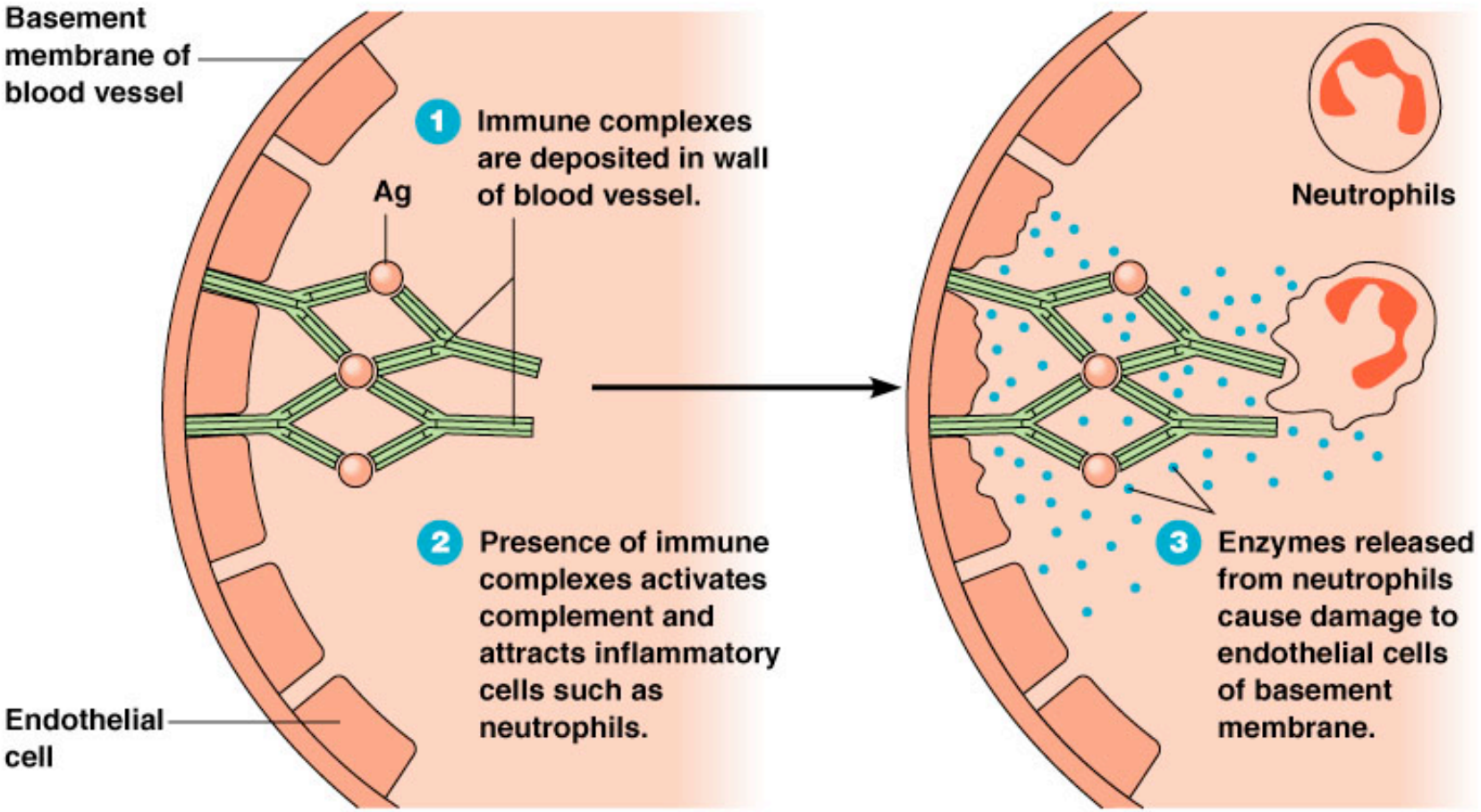
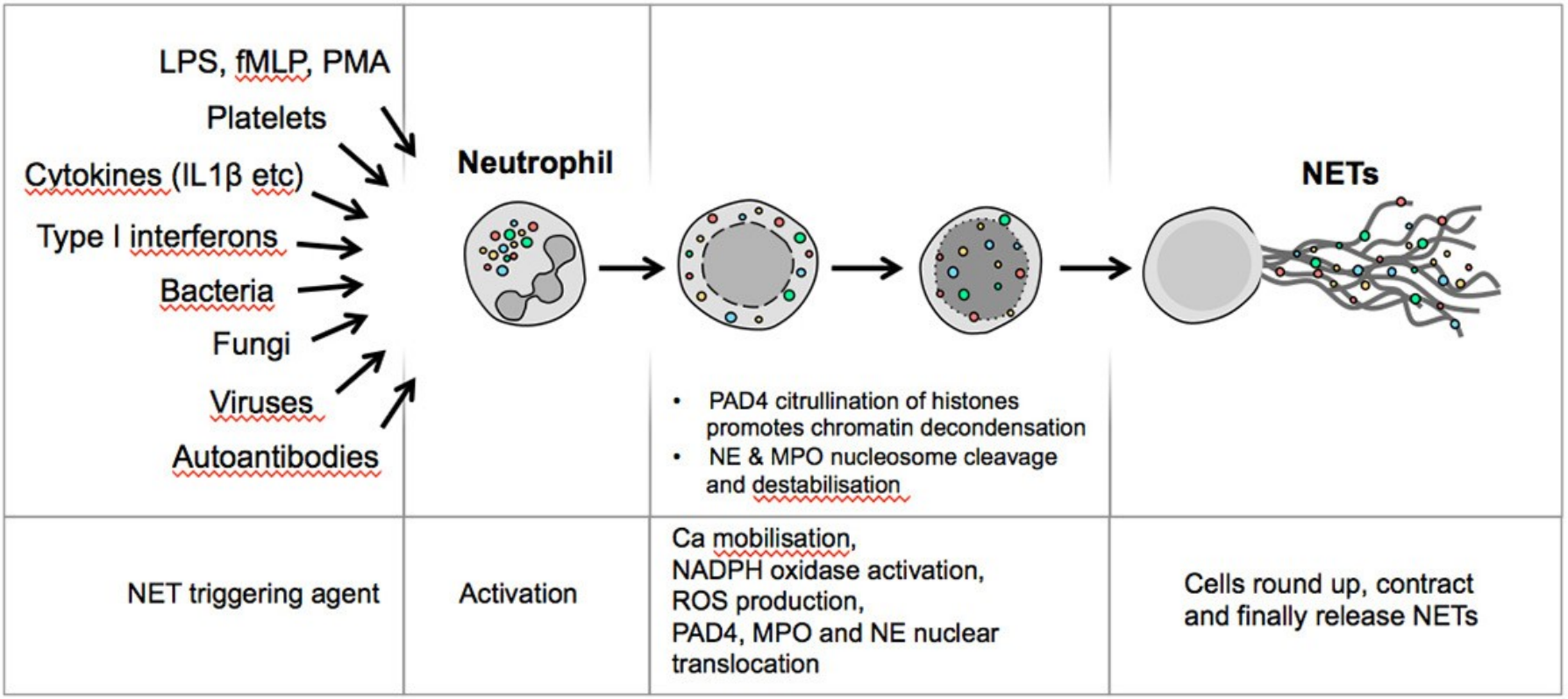


Figure 13-33 Immunobiology, 6/e. (© Garland Science 2005)

Tissue destruction initiated by immune complexes



NETs and Ets – role in autoimmunity?



Lee, KH, et al. "Neutrophil extracellular traps (NETs) in autoimmune diseases: A comprehensive review." Autoimmunity Reviews (2017).

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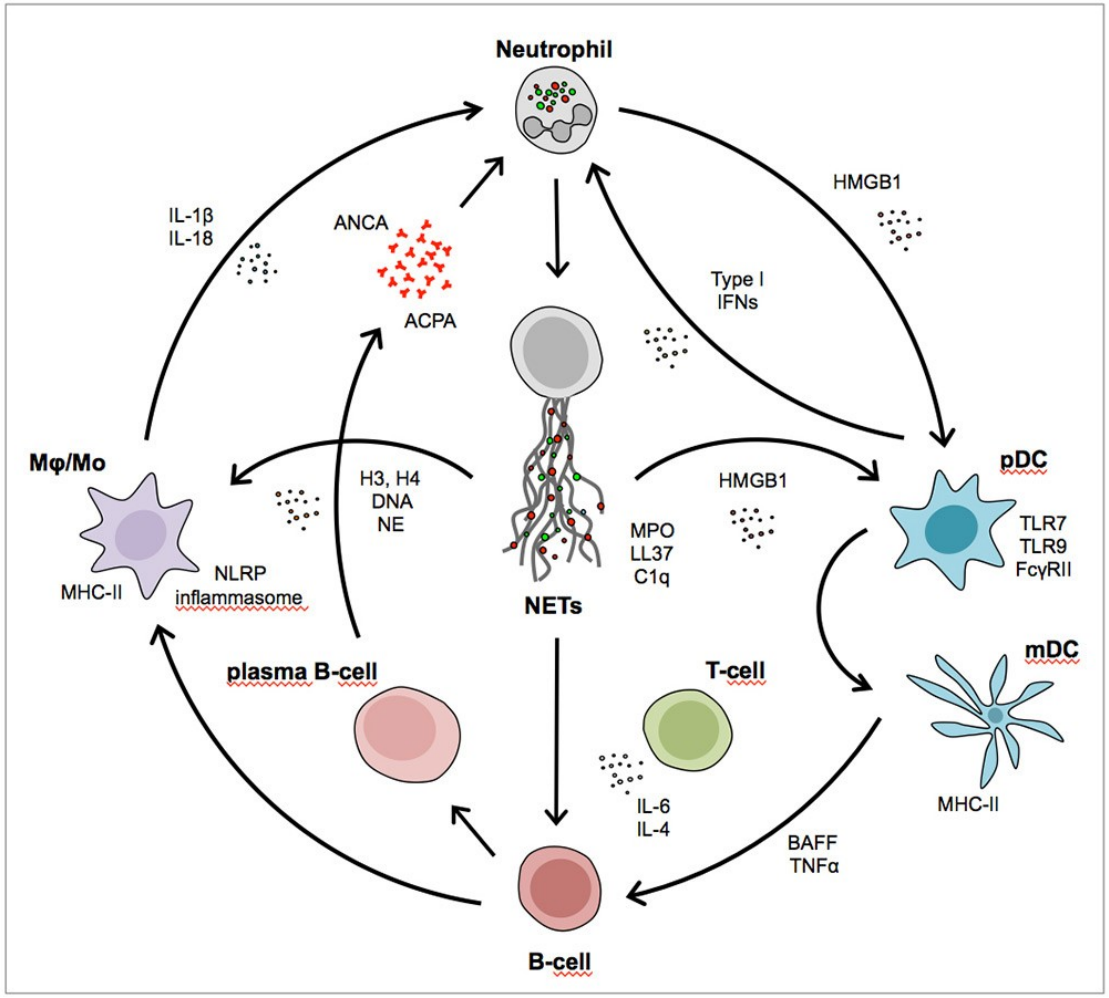


Lee, KH, et al. "Neutrophil extracellular traps (NETs) in autoimmune diseases: A comprehensive review." Autoimmunity Reviews (2017).

Type IV: T cell-mediated diseases

Autoimmune disease	Autoantigen	Consequence
T cell-mediated disease (type IV)		
Insulin-dependent diabetes mellitus	Pancreatic β-cell antigen	β-cell destruction
Rheumatoid arthritis	Unknown synovial joint antigen	Joint inflammation and destruction
Multiple sclerosis	Myelin basic protein, proteolipid protein	Brain degeneration. Paralysis
Celiac disease	Gluten modified by tissue transglutaminase	Malabsorption of nutrients Atrophy of intestinal villi

Figure 11-1 part 3 of 3 The Immune System, 2/e (© Garland Science 2005)

T cell-mediated tissue destruction

- Direct T cell cytotoxicity via $CD8^+$ CTL
- Self-destruction of tissue cells induced by cytokines, eg, TNFa
- Recruitment and activation of macrophages leading to bystander tissue destruction
- Induction of target tissue apoptosis by the T cell membrane protein FasL

Type I diabetes:
T cell-directed attack of pancreatic islet β-cells

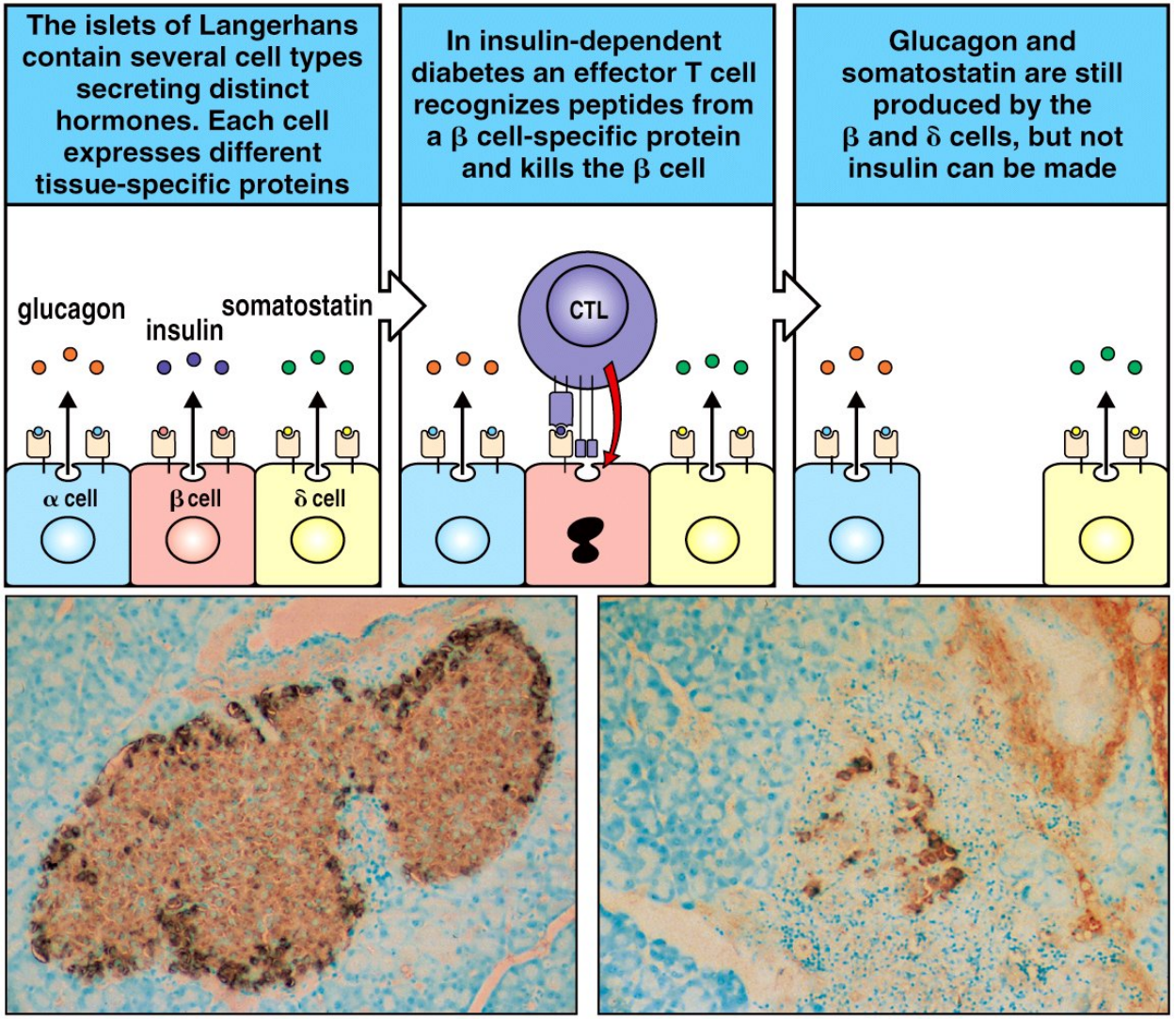
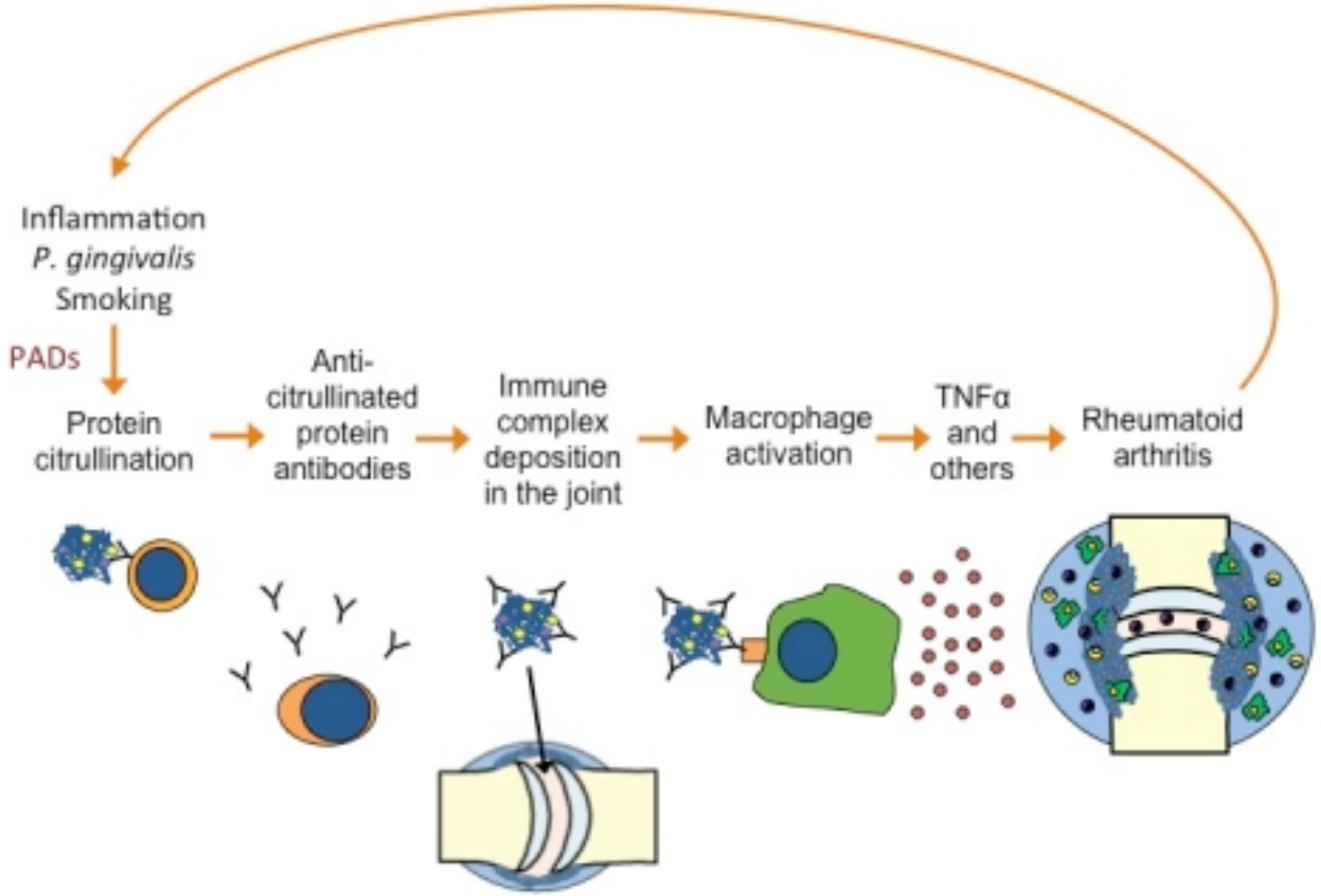


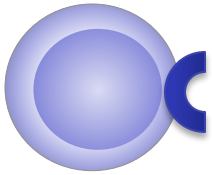
Figure 13-34 Immunobiology, 6/e. (© Garland Science 2005)

Neoantigens from post-translational modification



Identifying targeted self antigens
T cell autoantigens

Clone T cell

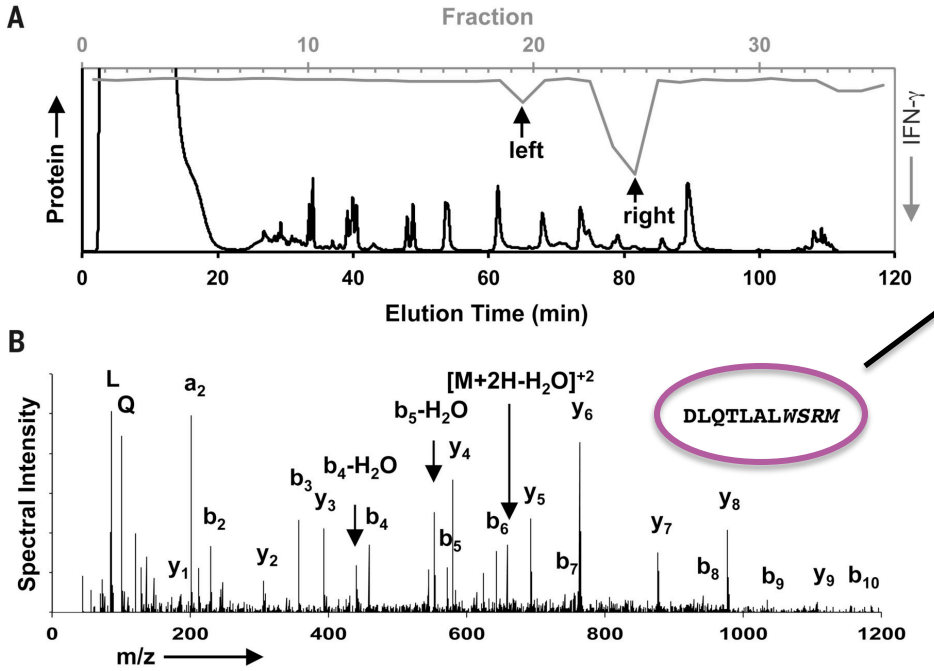


Stimulate with APC+

Fractions of target tissue lysate

Determine fraction that stimulate

Determine the sequence of the fraction



DLQTLALWSRM

Insulin Chromogranin A

Delong, Thomas, et al. "Pathogenic CD4 T cells in type 1 diabetes recognize epitopes formed by peptide fusion." Science 351.6274 (2016): 711-714.

Key concepts

- **Effector mechanisms:** much like those for allergic reactions and immune response to pathogens.
- **Autoantigens:** targeted by autoantibodies and autoreactive T cells overlap, but not identical
- **Neoantigens:** some autoantigens are formed by post-translatinal modifications triggered by inflammation, thus may not be present in primary lymphoid organ during central tolerance induction

Etiology of autoimmune diseases

Failure of self tolerance

Why and how?

Mechanisms of immune tolerance

Layers of self-tolerance		
Type of tolerance	**Mechanism**	**Site of action**
Central tolerance	Deletion Editing	Thymus Bone marrow
Antigen segregation	Physical barrier to self-antigen access to lymphoid system	Peripheral organs (eg, thyroid, pancreas)
Peripheral anergy	Cellular inactivation by weak signaling without co-stimulus	Secondary lymphoid tissue
Regulatory cells	Suppression by cytokines, intercellular signals	Secondary lymphoid tissue and sites of inflammation
Cytokine deviation	Differentiation to T_H2 cells, limiting inflammatory cytokine secretion	Secondary lymphoid tissue and sites of inflammation
Clonal exhaustion	Apoptosis post-activation	Secondary lymphoid tissue and sites of inflammation

Figure 13-16 Immunobiology, 6/e. (© Garland Science 2005)

Autoimmune diseases caused by single-gene mutations

	Hereditary C1q deficiency	SPENCDI	AGS	ALPS	IPEX	APS1
Gene(s)	C1qA, C1qB, C1qC	TRAP (ACP5)	TREX1, RNaseH2 H2 (A, B, C), SAMHD1	FAS, FASLG, CASP10	FOXP3	AIRE
Inheritance	Autosomal recessive	Autosomal recessive	Autosomal recessive	Autosomal dominant, recessive, variable penetrance	X-linked	Autosomal recessive*
Autoimmune features	SLE, glomerulonephritis, angioedema, +ANAs, +RNP Abs	SLE, thrombocytopenia, hemolytic anemia	SLE, chilblains, hemolytic anemia, +ANAs	Autoimmune cytopenia	Enteropathy Type 1 diabetes	Multi-organ disease +Organ-specific autoAbs anti-IFN Abs, NALP5 Abs
Tolerance defect	Impaired clearance of apoptotic material	Activation of Type 1 interferon signaling	Activation of type 1 interferon signaling	Defective lymphocyte apoptosis	Loss of Tregs	Defective deletional tolerance
Immune defect	Innate	Innate	Innate	Adaptive	Adaptive	Adaptive

not the basis of most autoimmune diseases

Forward genetics to find causal genes of autoimmune diseases

nature Vol 435|26 May 2005|doi:10.1038/nature03555

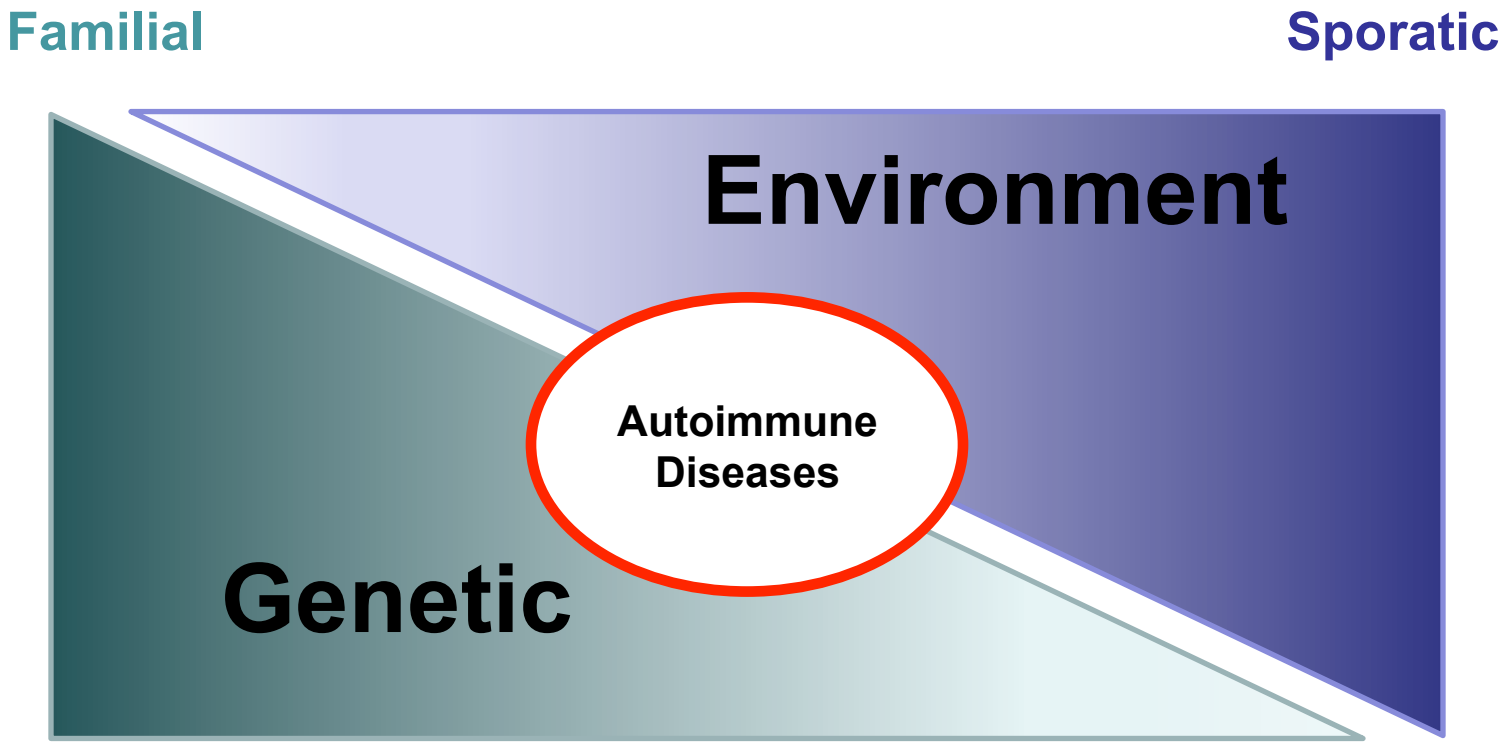
ARTICLES

A RING-type ubiquitin ligase family member required to repress follicular helper T cells and autoimmunity

Carola G. Vinuesa[1], Matthew C. Cook[2], Constanza Angelucci[1], Vicki Athanasopoulos[1], Lixin Rui[1], Kim M. Hill[1], Di Yu[1], Heather Domaschenz[1], Belinda Whittle[1,3], Teresa Lambe[4], Ian S. Roberts[5], Richard R. Copley[6], John I. Bell[4], Richard J. Cornall[4] & Christopher C. Goodnow[1,3]

Reading list

Searching for the causes of autoimmune diseases

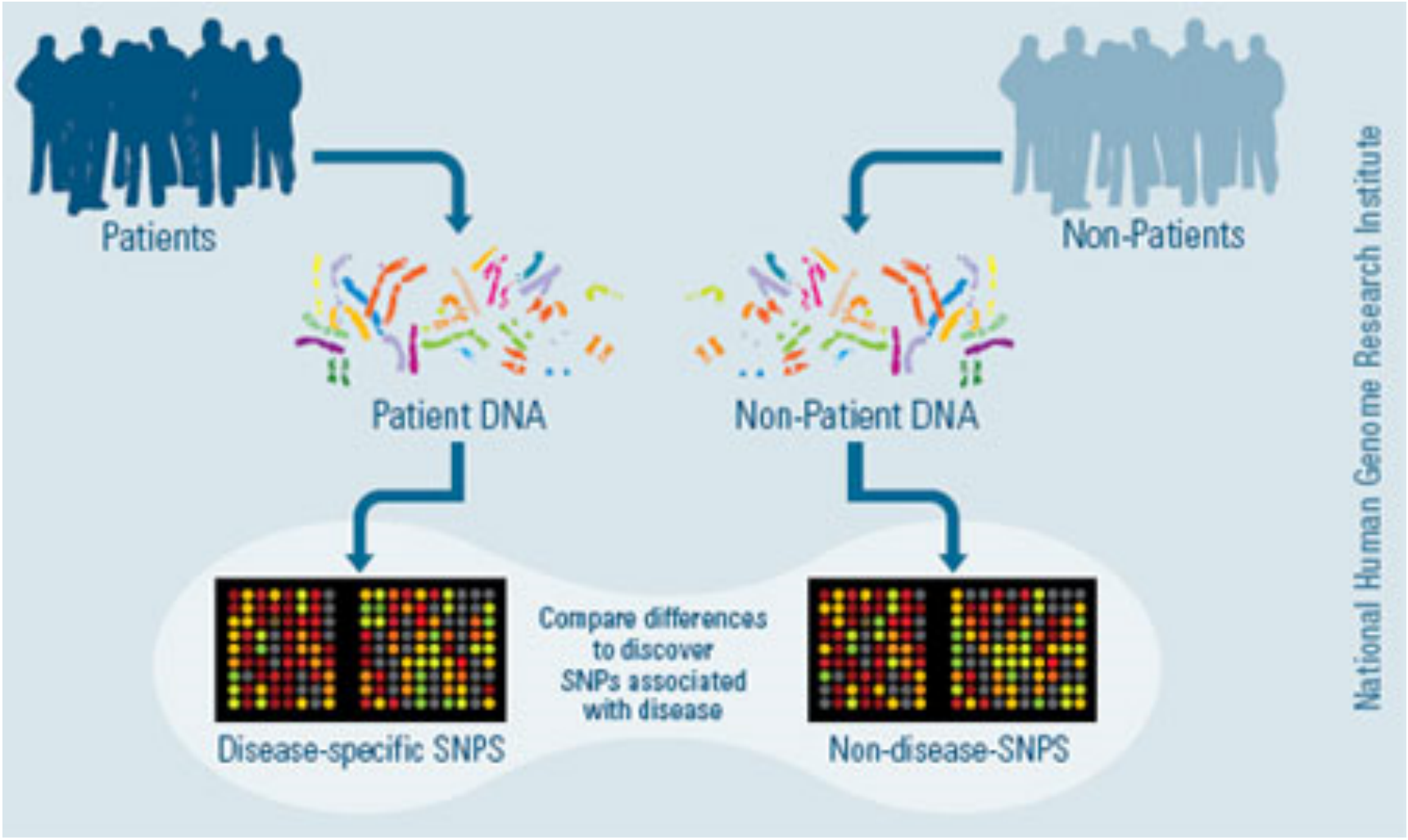


Genetic basis of autoimmune diseases

- Genetic predisposition of autoimmune diseases
  - Increased incidence in twins
  - Familial patterns
- Multiple genes are associated with autoimmunity
  - Most autoimmune diseases are not caused by single-gene mutations
- MHC genes
  - Major risk factor of autoimmune diseases
  - Disease-associated alleles may be found in normal individuals
- Non-MHC genes
  - Many loci identified by genomic methods, animal studies
  - Some genes are associated with multiple autoimmune diseases

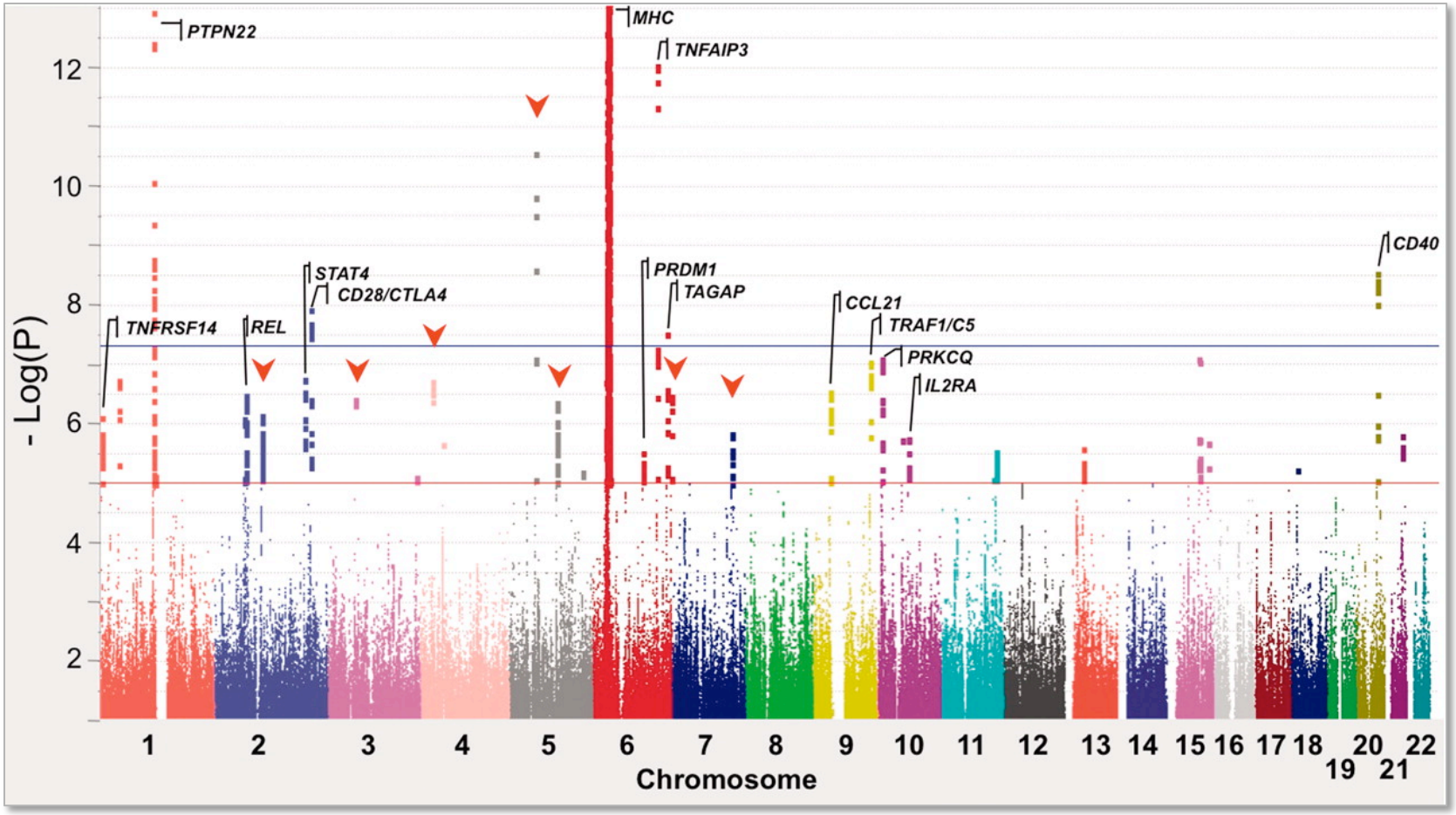
Search for genes linked to autoimmune diseases - GWAS

GWAS=Genome Wide Association Study



Single nucleotide polymorphism (SNP)-Chip with an array of over500,000 SNP's

An example of GWAS of RA



HLA is the strongest genetic factor for susceptibility for many autoimmune diseases

HLA-associated risk factors for autoimmune disease

Disease	HLA allotype	Frequency (%)		Relative risk
		Patients	Control	
Ankylosing spondylitis	B27	> 95	9	> 150
Narcolepsy	DQ6	> 95	33	> 40
Celiac disease	DQ2 and DQ8	95	28	30
IDDM	DQ8 and DQ2	81	23	14
Subacute thyroiditis	B35	70	14	14
Multiple sclerosis	DQ6	86	33	12
Rheumatoid arthritis	DR4	81	33	9
Juvenile rheumatoid arthritis	DR8	38	7	8
Psoriasis vulgaris	Cw6	87	33	7
Addison's disease	DR3	69	27	5
Graves' disease	DR3	65	27	4
Myasthenia gravis	DR3	50	27	2
IDDM	DQ6	< 0.1	33	0.02

Figure 11-23 The Immune System, 2/e (© Garland Science 2005)

Non-HLA autoimmune disease genes

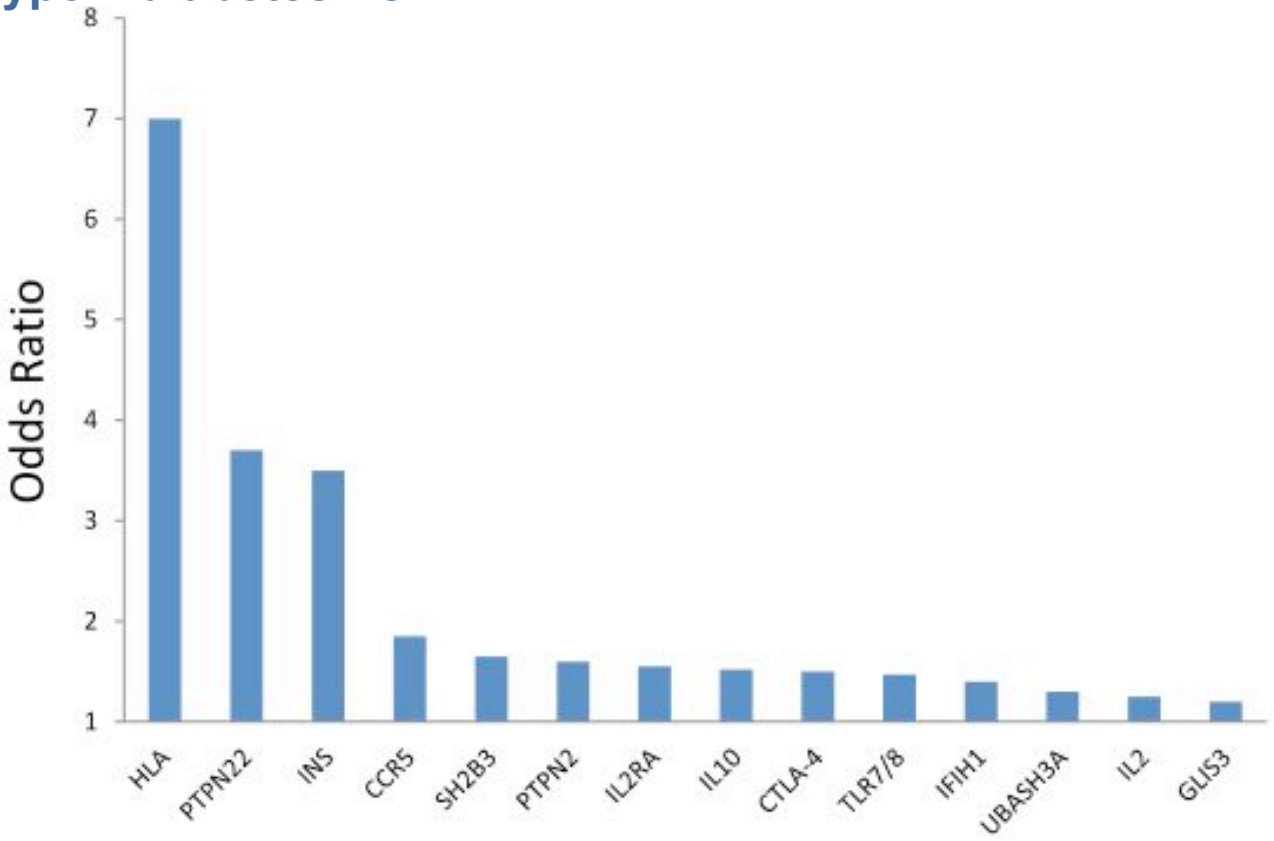
Genes	Function	Diseases
PTPN22	T and B cell receptor signaling	RA, T1D, CD
CTLA4	Transmits inhibitory signals to T cells	T1D, RA
CD2/CD58	Activation of T lymphocytes	RA, MS
IL23R	Unique component of the heterodimeric IL-23 receptor	IBD, PS, AS
IL10	Down regulates immune responses, including cytokines, MHC class II and costimulatory molecules	IBD, SLE, T1D
IL2/IL21	T cell trophic growth factors	CeD, IBD, RA, T1D
IL12B	p40 subunit common to IL-12 and IL-23	IBD, PS
IL2RA	IL-2 receptor α chain	MS, T1D
TNFAIP3	Induced by TNF and pattern recognition receptor activation; inhibits NF-κB signaling	RA, SLE, PS
TNIP1	Interacts with TNFAIP3	SLE, PS
PRDM1	Transcriptional repressor of IFN-β; induces B cell maturation	RA, SLE
BLK	B lymphoid tyrosine kinase	SLE, RA
PTPN2	T cell protein tyrosine phosphatase	IBD, T1D
NOD2	Microbial sensor in intestinal epithelial cells	Crohn's disease

Zenewicz, Lauren A., et al. "Unraveling the genetics of autoimmunity." Cell 140.6 (2010): 791-797.

Beyond GWAS

- Establish causality
- Identify mechanisms of pathogenesis

type 1 diabetes risk



Beyond GWAS

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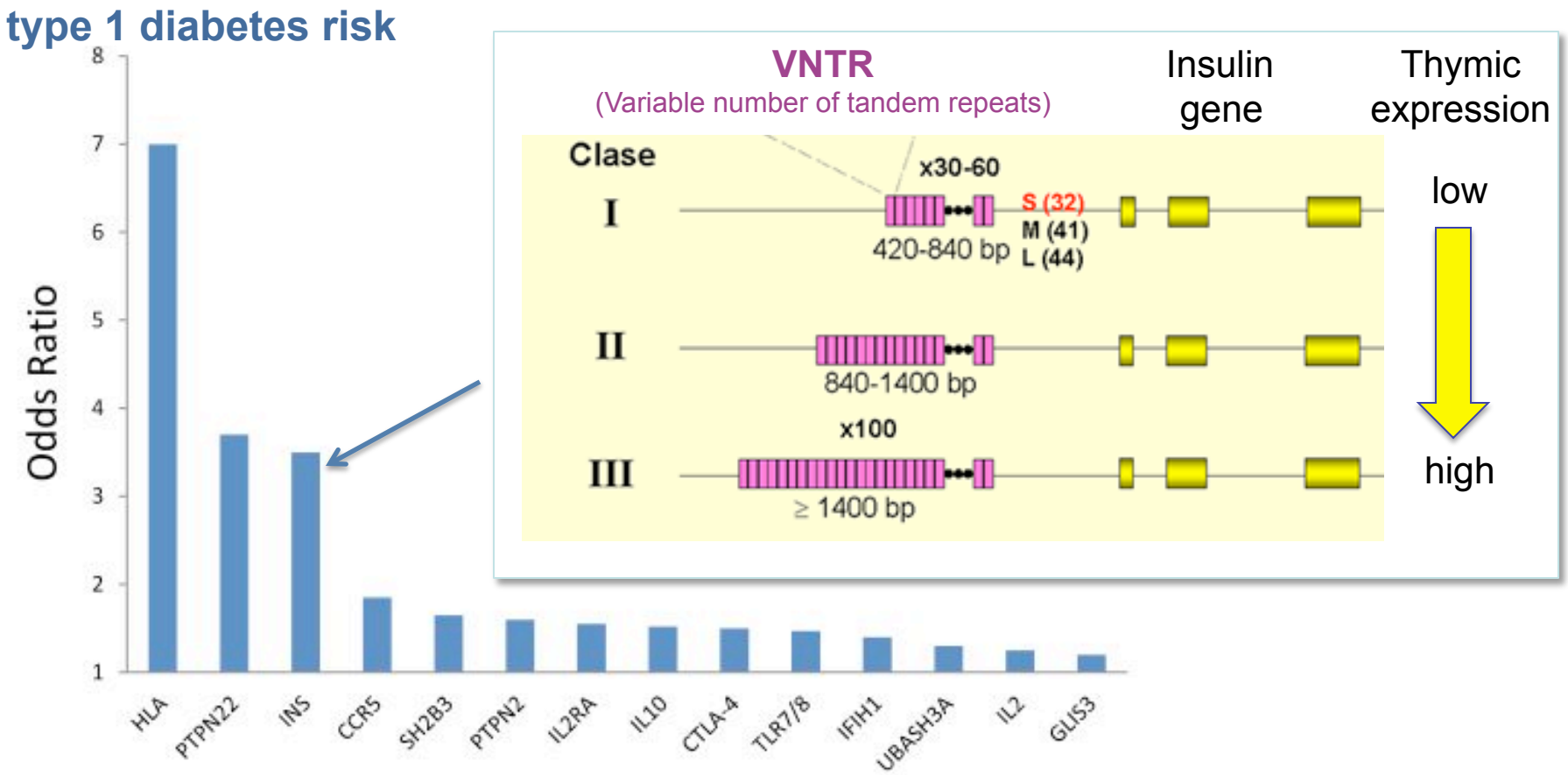

Pugliese, A, et al. Nature genetics 15.3 (1997) 293-297
Vafiadis, P. et al Nature genetics 15.3 (1997) 289-293

Modeling autoimmune diseases in mice

Spontaneous models

- Non-obese diabetic (NOD) mouse – model of type 1 diabetes
- NZBxNZW - model of lupus
- KBxN - model of rheumatoid arthritis

Induced models

- Experimental autoimmune encephalopathy (EAE) - model of multiple sclerosis by immunizing mice with proteins of the myelin sheath and adjuvant
- Collagen-induced arthritis
- Colitis

Genetic models

- Modeling human risk alleles
- Forward genetics

How PTPN22 control autoimmune diseases

How PTPN22 control autoimmune diseases

Approach	Findings	reference
Human T cell in vitro	• Diseases associated PTPN22 has enhanced ability to terminate TCR signaling • Decreased T cell and B cell responses	Vang et al. *Nat genet* 37.12 (2005): 1317 Rieck et al. *JI* 179.7 (2007): 4704

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Knock-out mice	• Normal activation of naïve cells, enhanced memory/effector T cell reactivity, more GC formation • Increased Tregs • Enhanced Treg function	Hasegawa et al Science, 303 (2004): 685 Brownlie et al. *Sci. Signal.* 5.252 (2012): ra87 Maineet al *JI* 188.11 (2012): 5267

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Transgenic in NOD	• Hyporesponsiveness of T and B cells, diabetes protection	Yeh *et al.* JI, 191.2 (2013): 594

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Knock-down in NOD mice	• Enhanced Tregs, diabetes protection	Zheng et Diabetes, 62.3 (2013): 896

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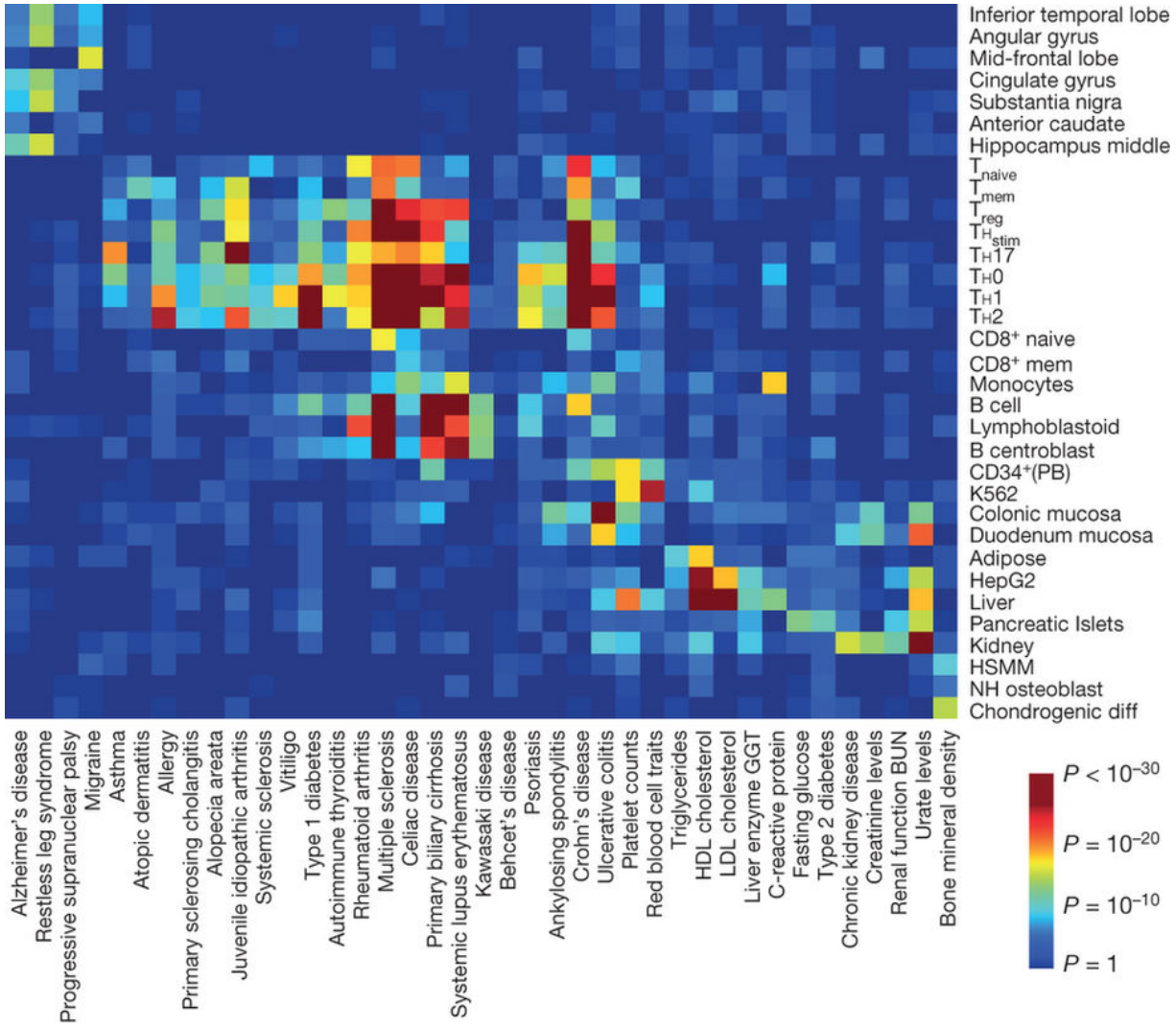
Knock-down in NOD mice	• Enhanced Tregs, diabetes protection	Zheng et Diabetes, 62.3 (2013): 896
Knock-in disease allele	• Disease allele is a hypomorph • Spontaneous autoimmune diseases	Zhang et al. *Nat genet* 43.9 (2011): 902. *Dai et al. *JCI* 123.5 (2013): 2024.

* Reading list

Study of non-protein coding SNPs

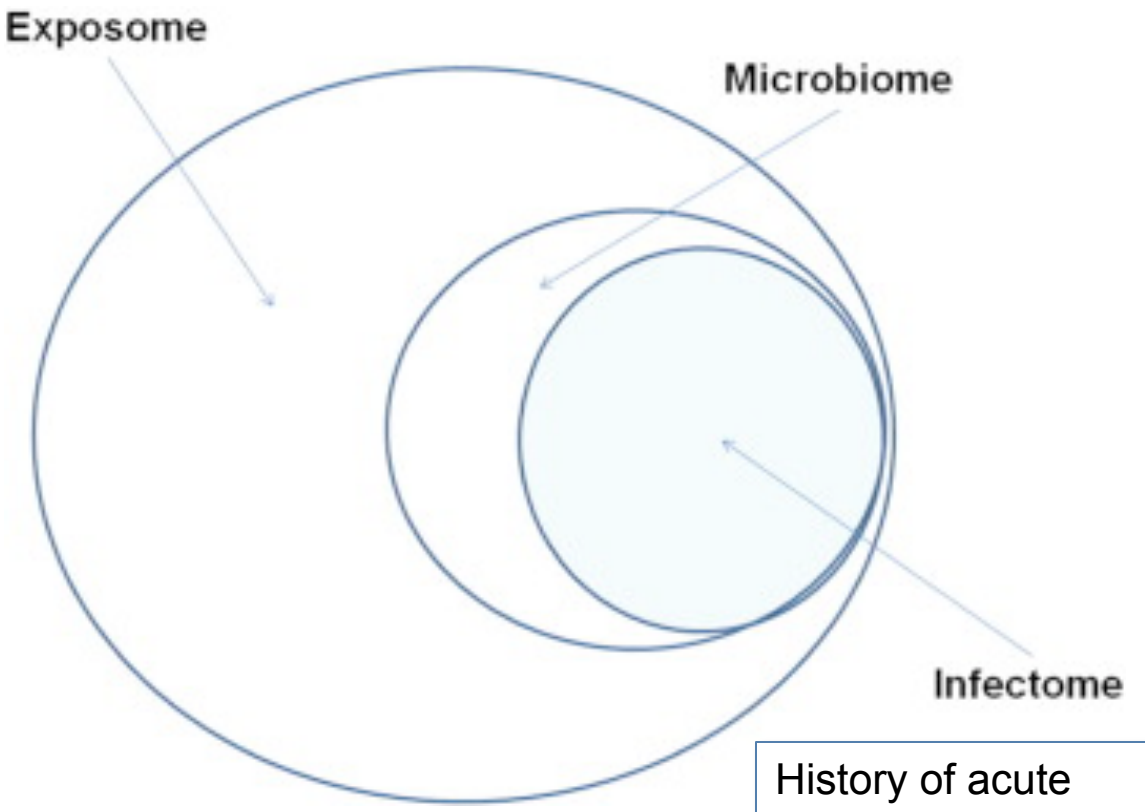


Reading list: *Farh, KK et al. Nature 518.7539 (2015): 337-343.*

What trigger autoimmune diseases?

Air
Water
Soil
Food
Hormone
Tobacco
Pharmaceuticals,
- Medicine
- Supplements
- Silica solvents,
- Dental materials,
- Vaccines,
- Implants

Ultraviolet radiation
- Vit D

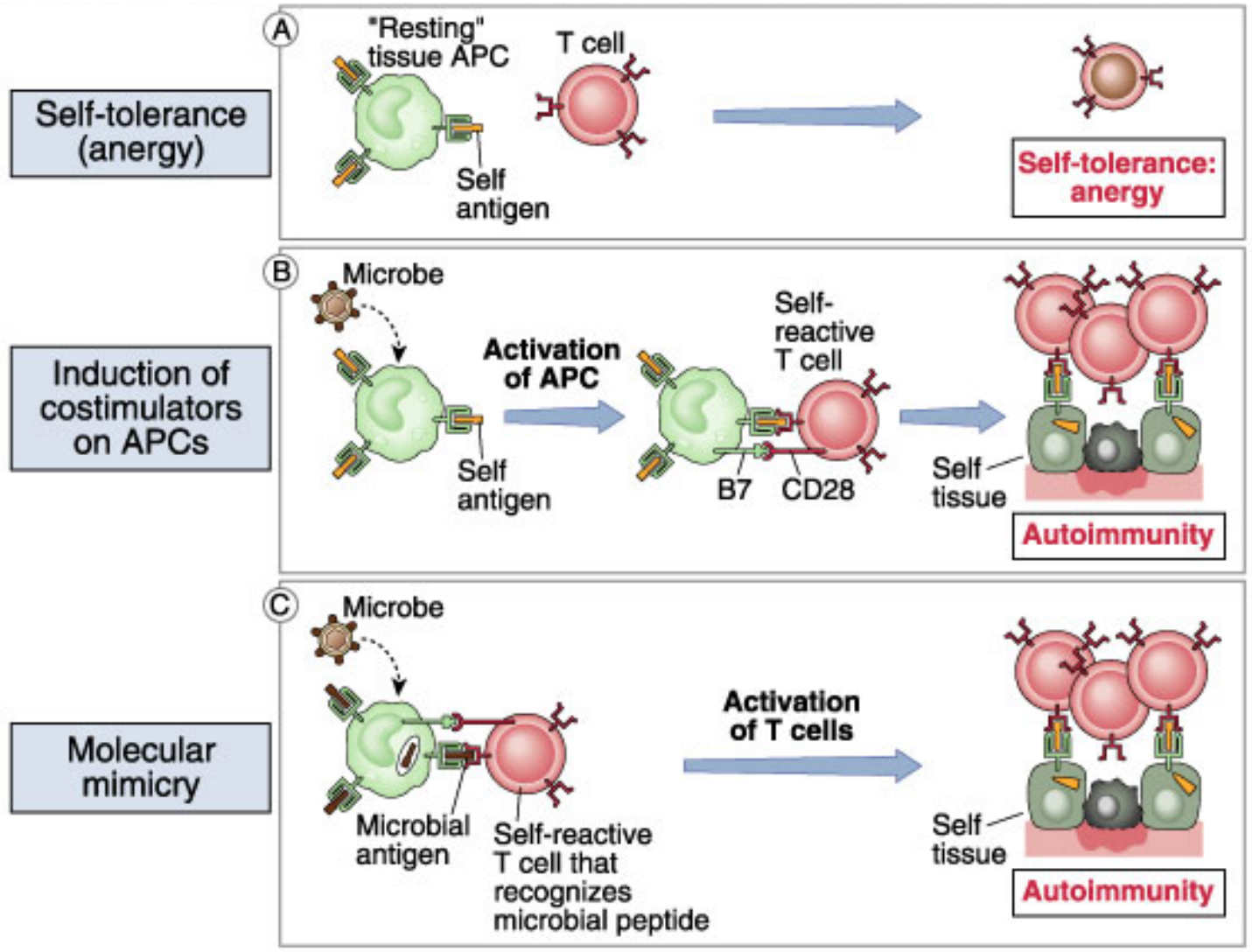


History of acute and chronic infections

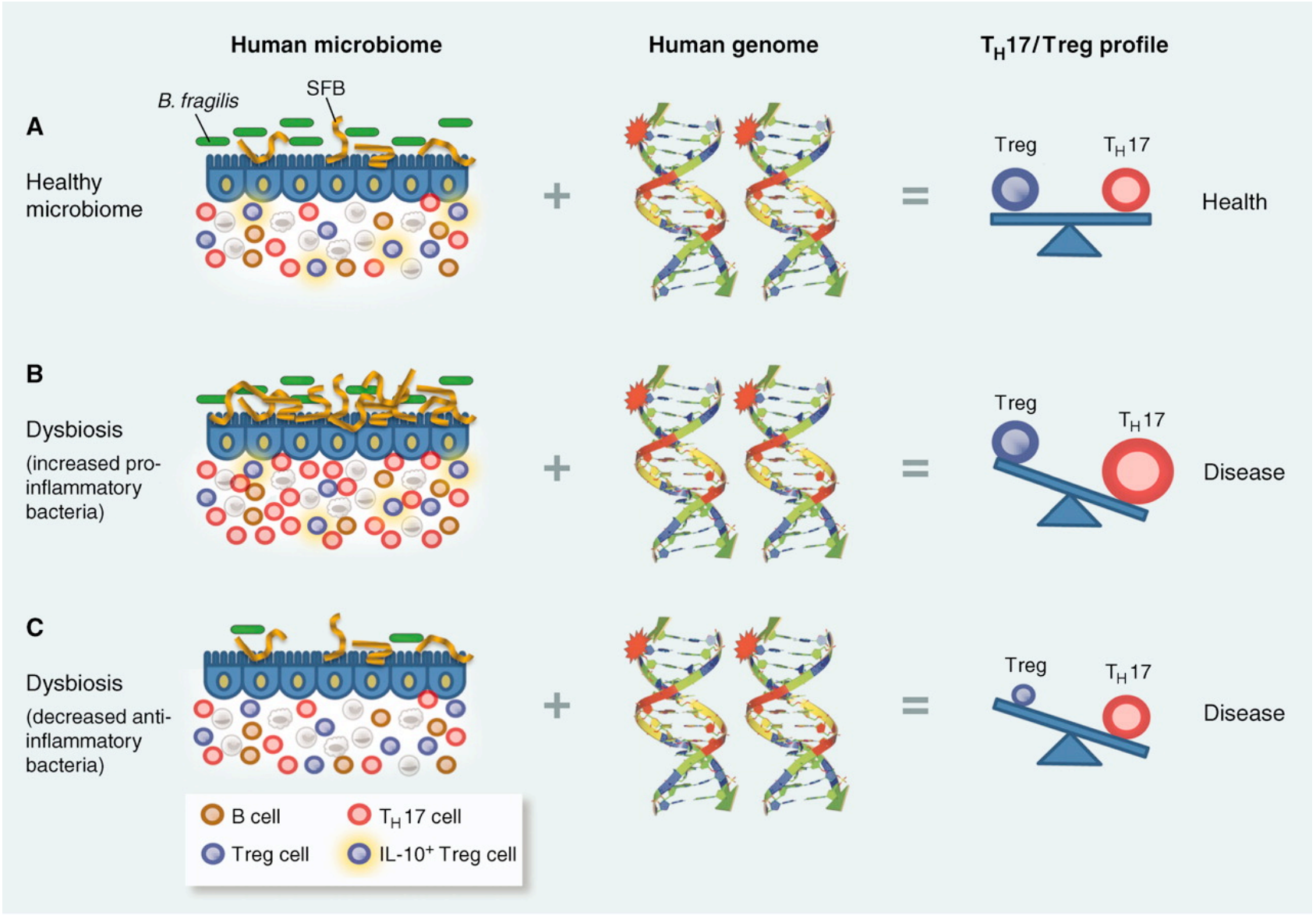
Infections and autoimmunity

- **Infections trigger autoimmune reactions**
  - Clinical prodromes, animal models
  - Autoimmunity develops after infection is eradicated (i.e. the autoimmune disease is precipitated by infection but is not directly caused by the infection)
- **Some autoimmune diseases are reduced or prevented by infections**
  - Increasing incidence of type 1 diabetes, multiple sclerosis in developed countries; experimental - NOD mice: mechanism unknown
  - The “hygiene hypothesis” (originally proposed to describe effects of infections on asthma)

Mechanisms of infectious trigger of autoimmune diseases



Microbes and autoimmunity?



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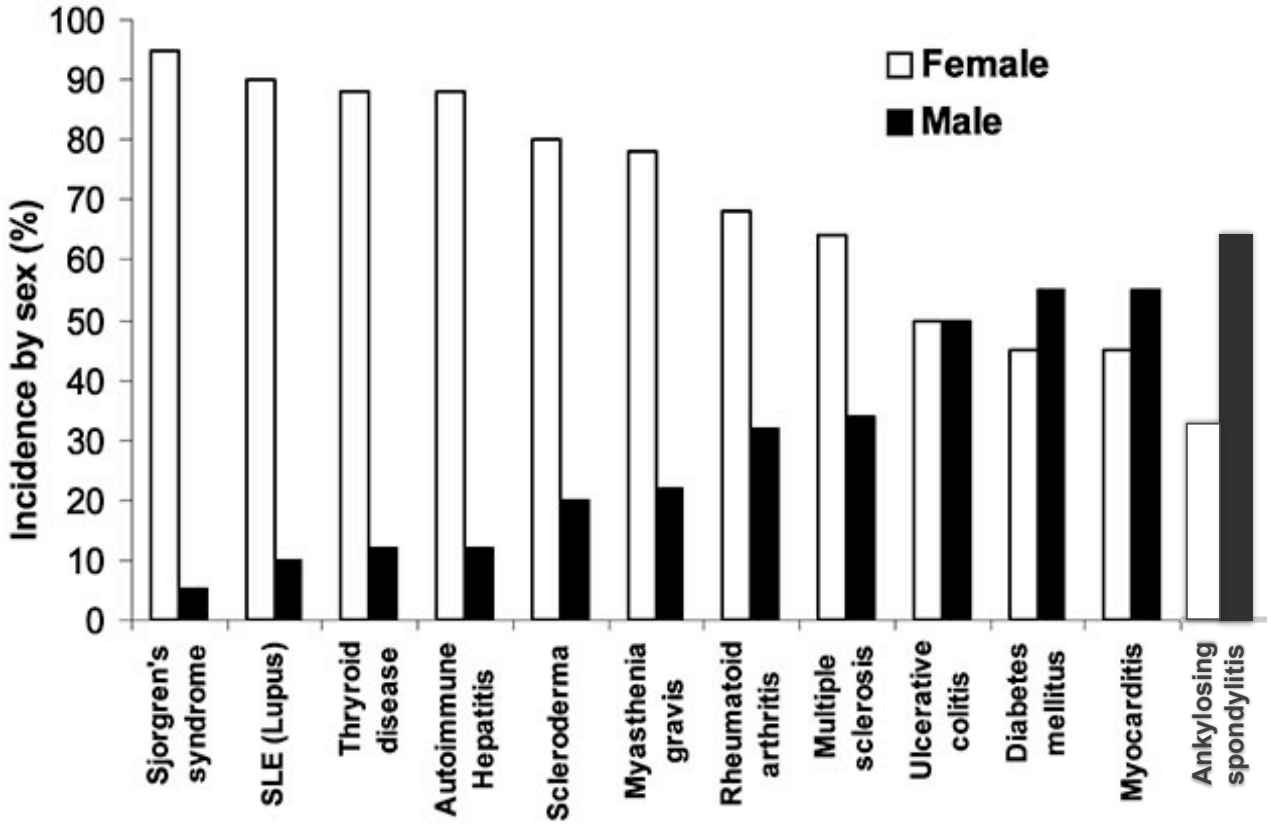
Hormonal impacts of autoimmune diseases



marked reduction in disease severity in many autoimmune conditions during **pregnancy**. Rheumatoid arthritis is perhaps the classic example of this effect. In some cases there is also a rapid exacerbation (rebound) after giving birth.

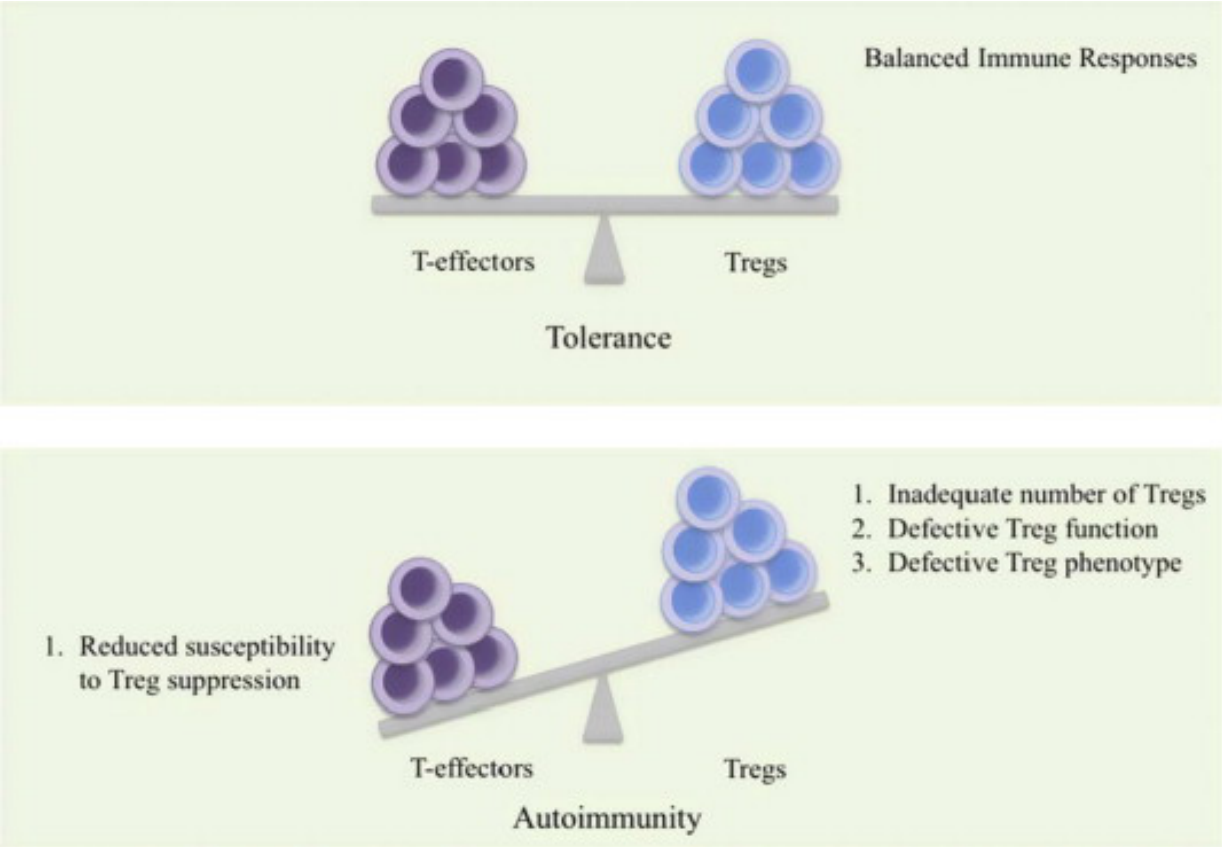
Key concepts and unresolved issues

- Most autoimmune diseases have complex genetic traits
  - HLA is a most influencing gene for autoimmune disease susceptibility
  - Many loci are identified for multiple diseases, eg PTPN22, CD25
  - Most genetic alterations individually confer small increase in disease risks
  - Multiple genetic alterations compound to increase risks
- Contributions of genetics to autoimmune disease vary by diseases, but almost never 100%
- How of most disease-associated alleles contribute to disease development is not known
- More than half of GWAS hit are non-coding
- “Environmental” impact on autoimmune diseases is well established, but poorly defined for most diseases

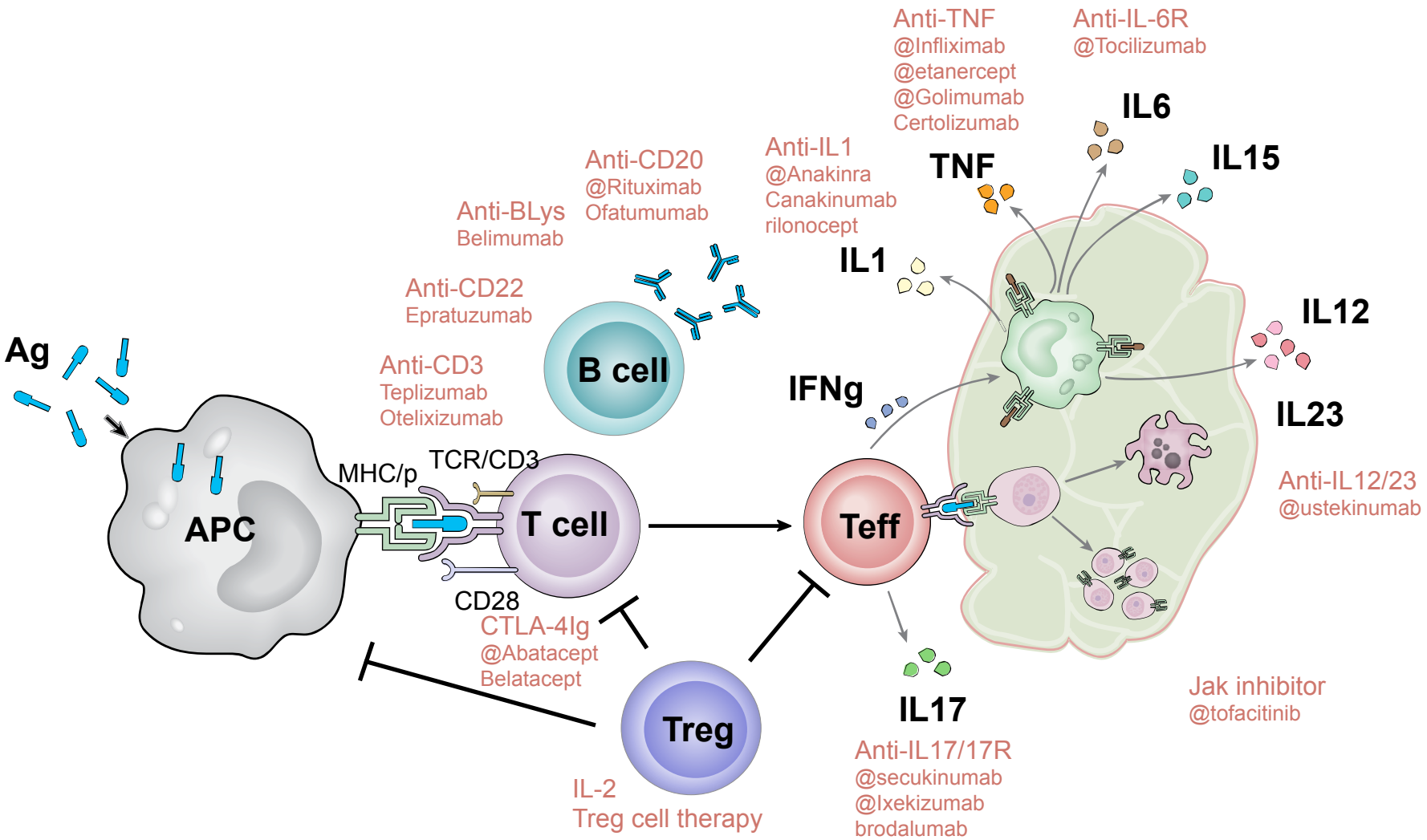
Treatment of autoimmune diseases

Therapies for autoimmune diseases

Goal:
restore **antigen-specific** tolerance by remove only the antigen-specific immune response

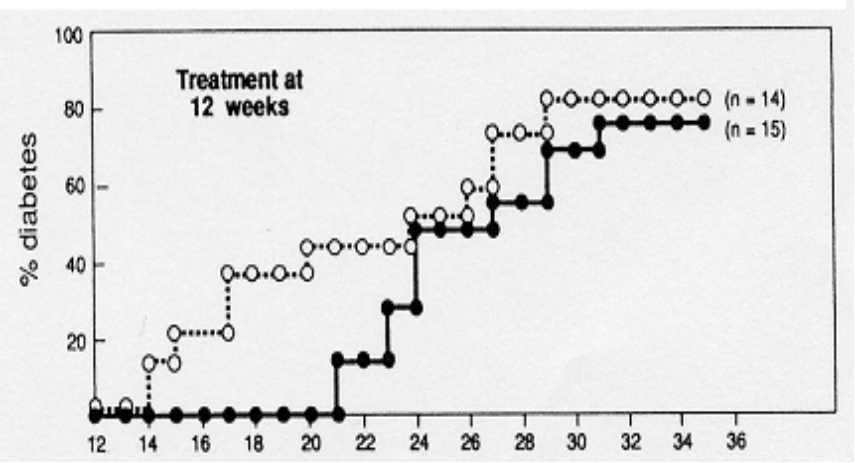


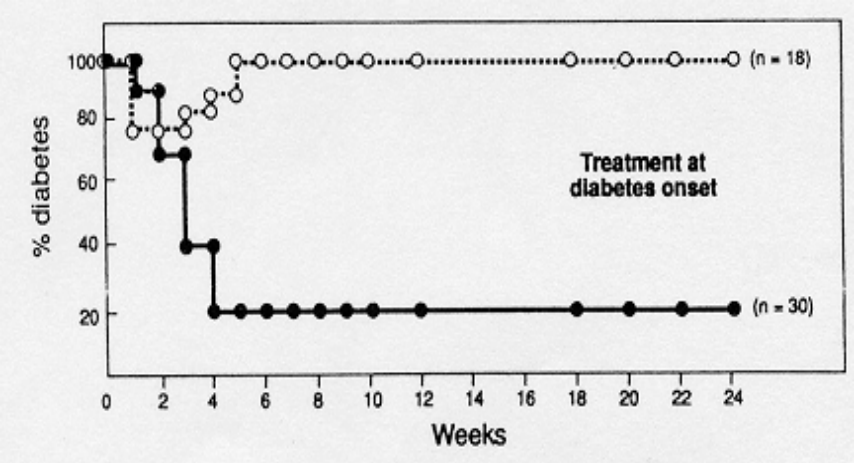
Targets for treating autoimmune diseases



@=FDA approval

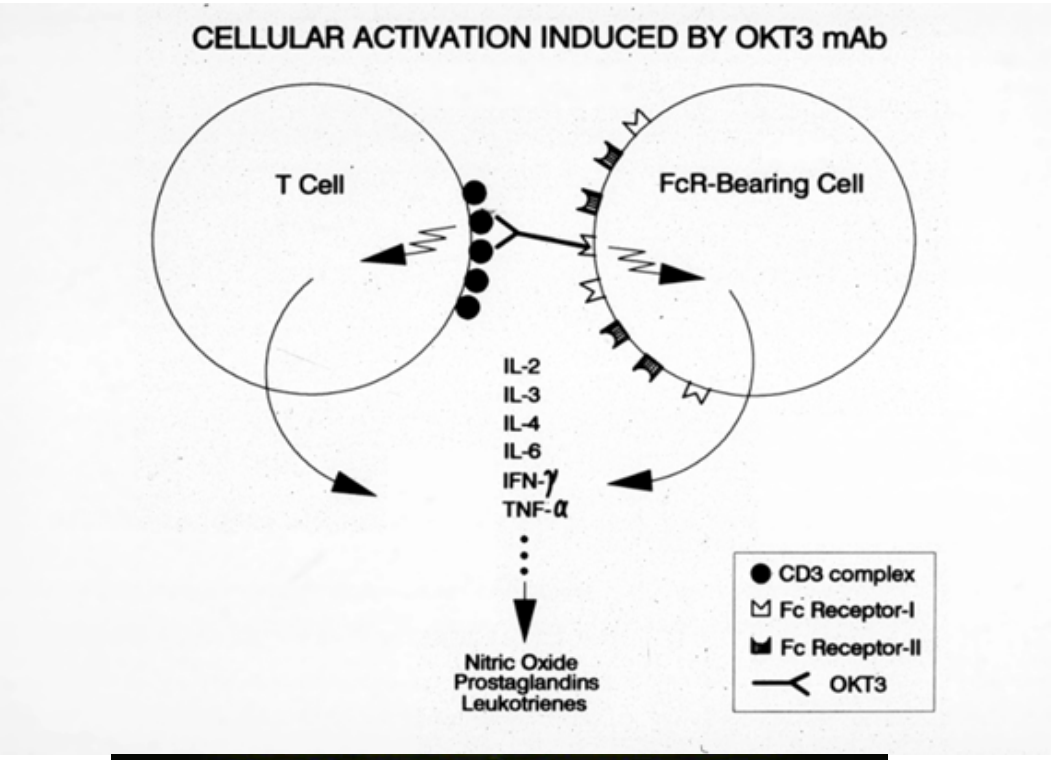
Treating type 1 diabetes with anti-CD3 in NOD mice





- Short term, low dose treatment had long lasting protection
- Better efficacy at time of disease onset

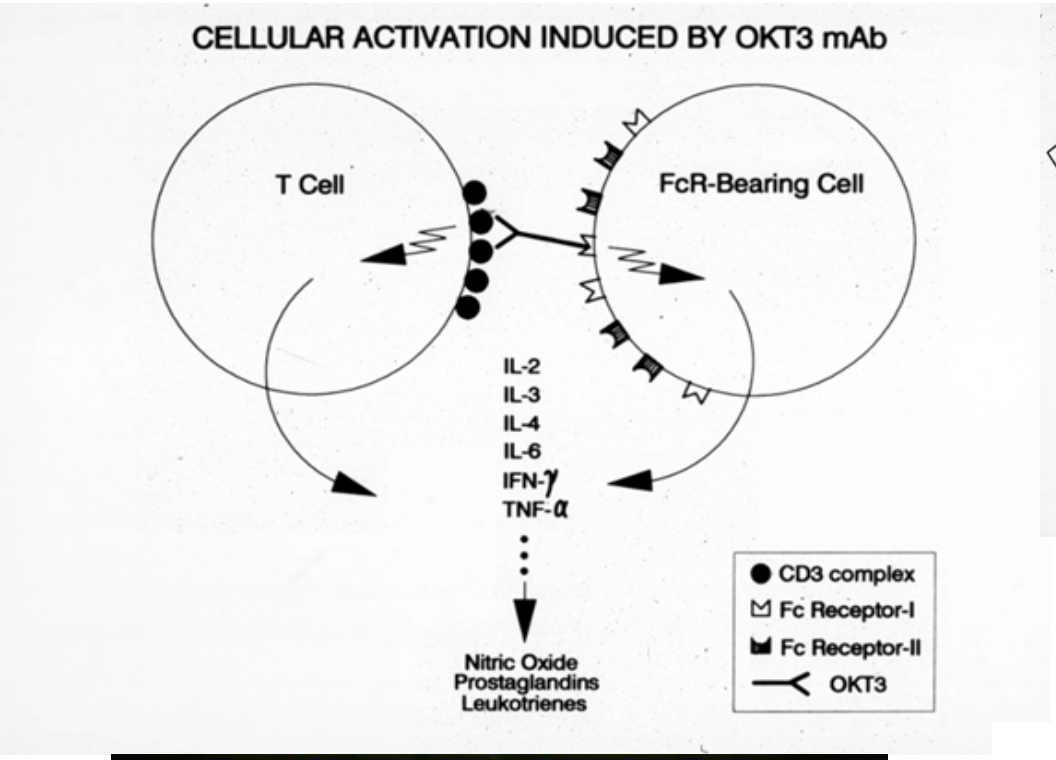
Minimizing toxicity of anti-CD3 mAb

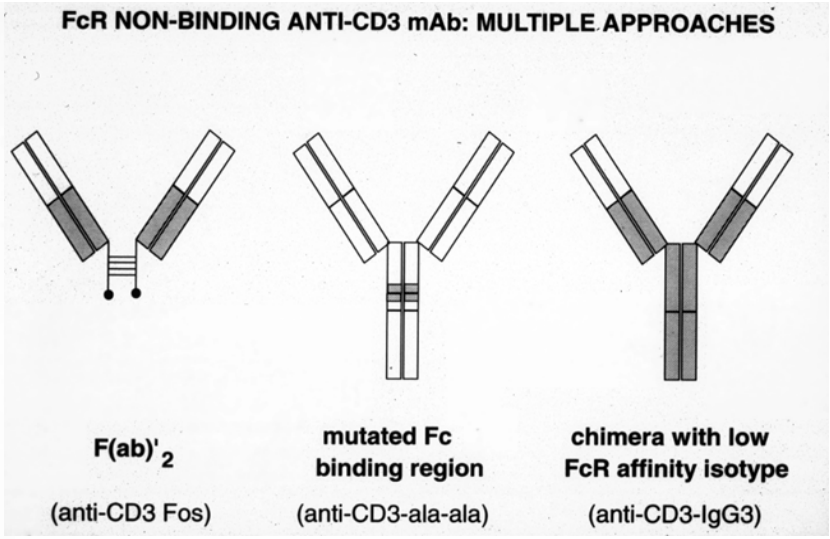


ORTHOCLONE OKT®3 CYTOKINE STUDY
TYPICAL FIRST-DOSE REACTIONS

	IL-2	TNFα	IFNγ
Chills	+	+	+
Headache	+		+
Pyrexia	+	+	+
Vomiting	+	+	+
Diarrhea	+	+	+
Tachycardia	+		+
Hypotension	+		+
Bronchospasm	+	+	
Arthralgia		+	

Minimizing toxicity of anti-CD3 mAb





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Tachycardia	+		+
Hypotension	+		+
Bronchospasm	+	+	
Arthralgia		+	

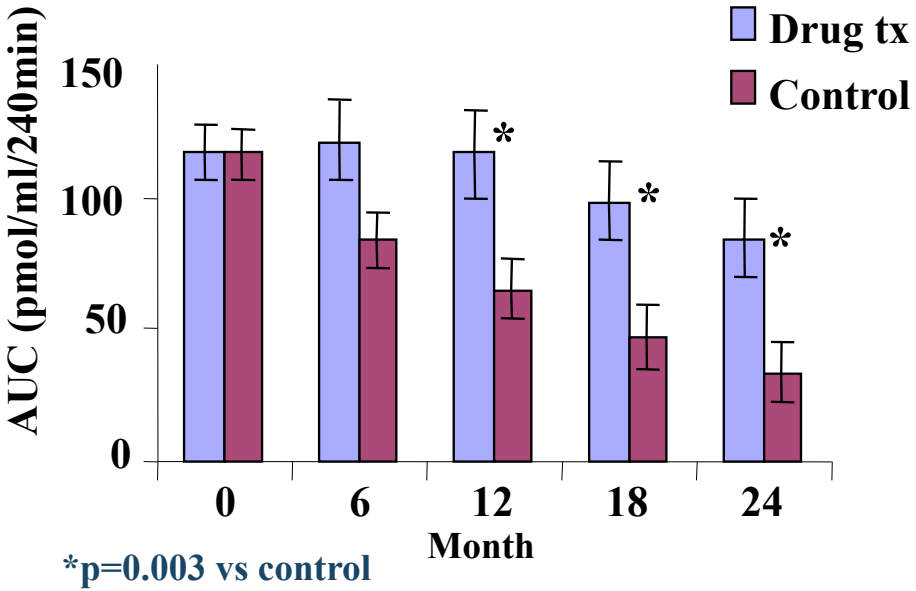
Rate of Depletion (%)

Endogenous Naive CD4 Cells	Transferred Th1 Cells
36.8	65.5
36.8	66.3
12.1	40.0
35.5	66.4

anti-CD3 Phase I/II trial in Type 1 diabetes

Study Protocol

- New onset Type 1 diabetes mellitus in stable metabolic condition, within the first 6 weeks since diagnosis
- Age 8 – 35
- Two week single treatment with increasing doses of anti-CD3 mAbs
  5 mg → 4 mg/dose.



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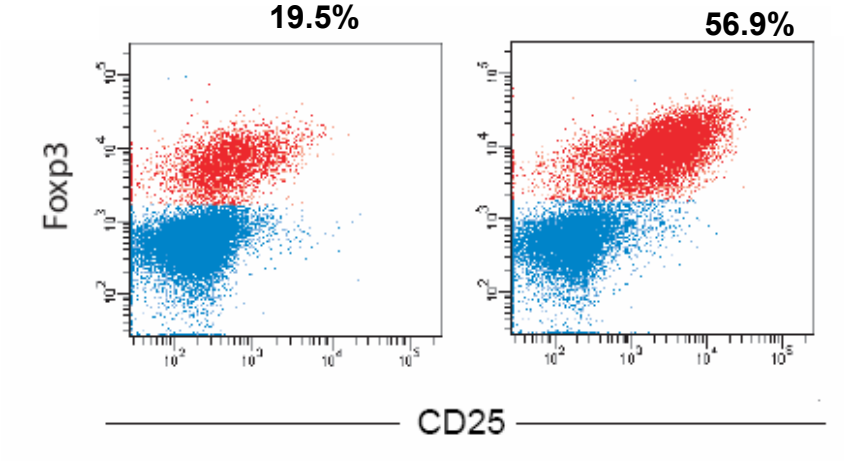
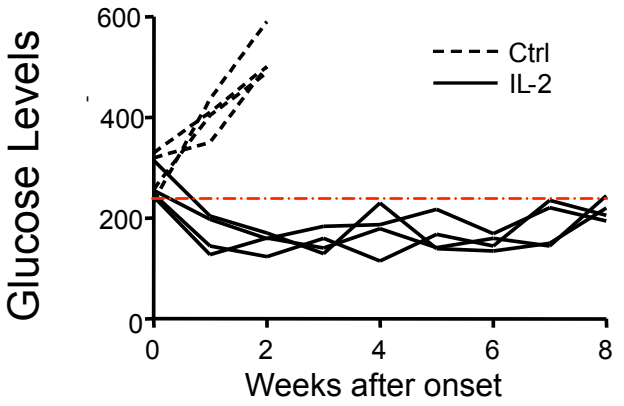
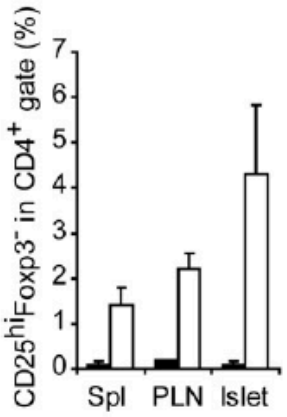
Promoting Tregs
Low-dose IL-2 in NOD mice

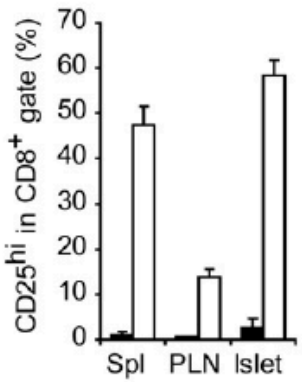
Low dose IL-2

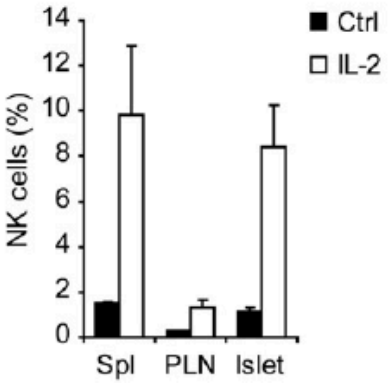


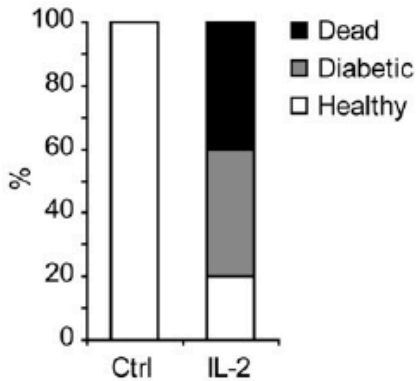


High dose IL-2







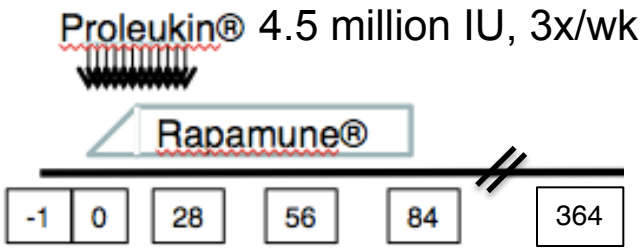


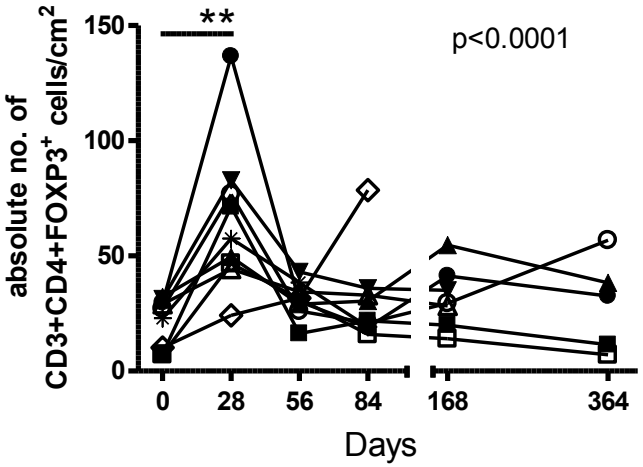
Tang Q et al. Immunity. 2008; 28(5):687-97Grinberg-Bleyer Y et al. J Exp Med, 2010; 207(9):1871-8.

Promoting Tregs

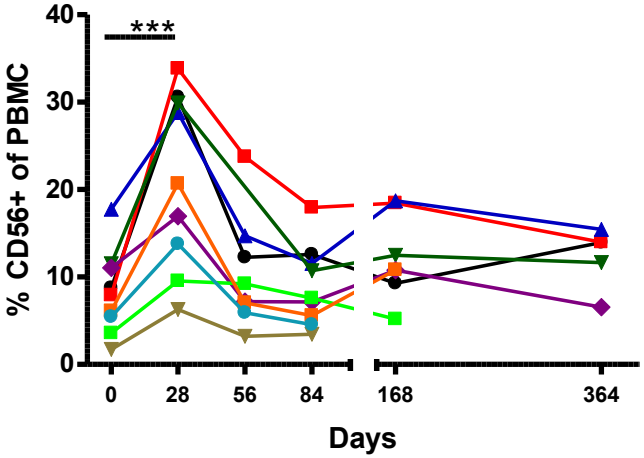
Low-dose IL-2 in humans with T1D

Trial design

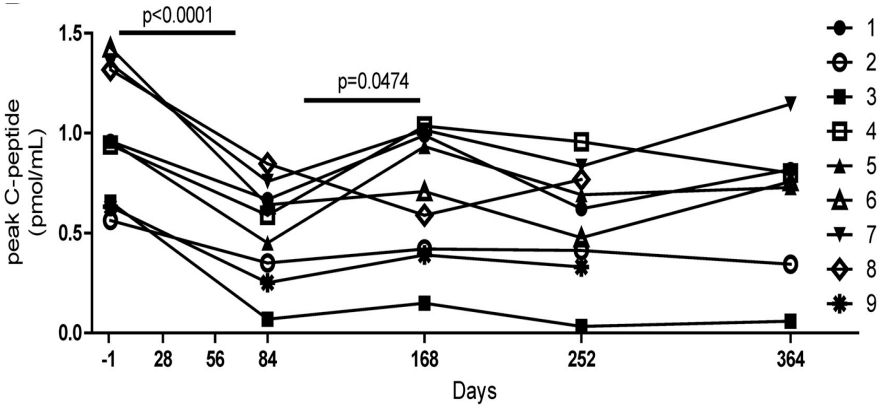




NK cells



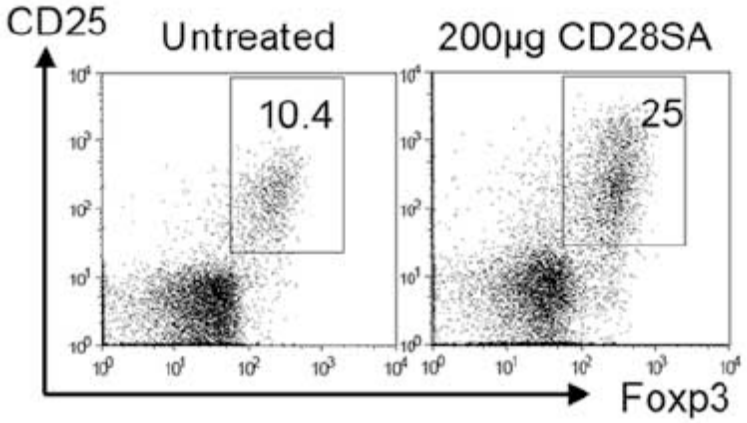
transient loss of c-peptide

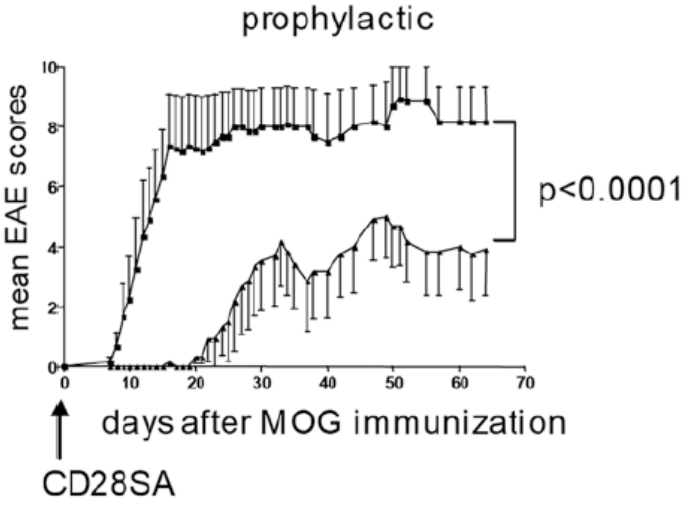


Long SA et al. Diabetes 2012 61:2340

Promoting Tregs

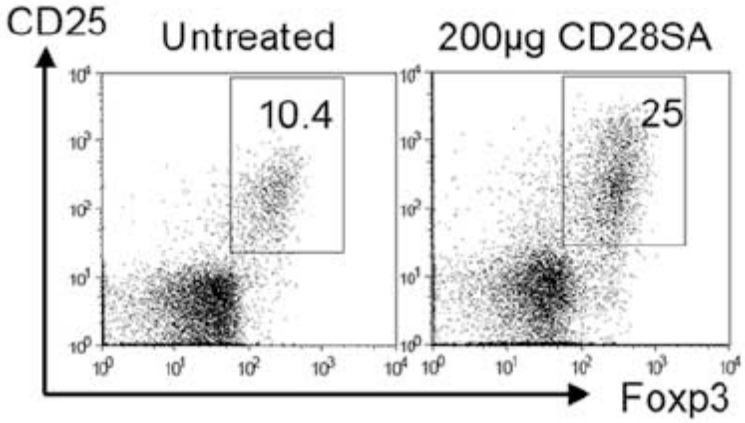
anti-CD28 super agonist

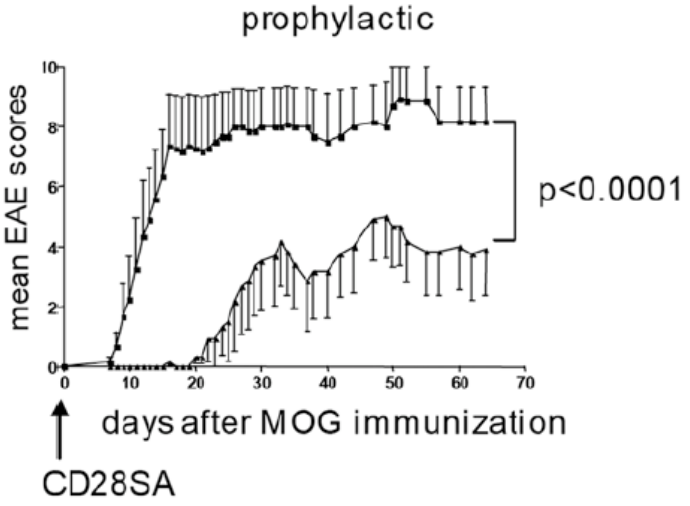




Ganesh Suntharalingam, F.R.C.A. et al. (2006) nejm 355;10; Gogishvili T, Langenhorst D, Lu¨ hder F, Elias F, Elflein K, et al. (2009) PLoS ONE 4(2): e4643; Eastwood D et al BJP 2010 161:512

Promoting Tregs
anti-CD28 super agonist





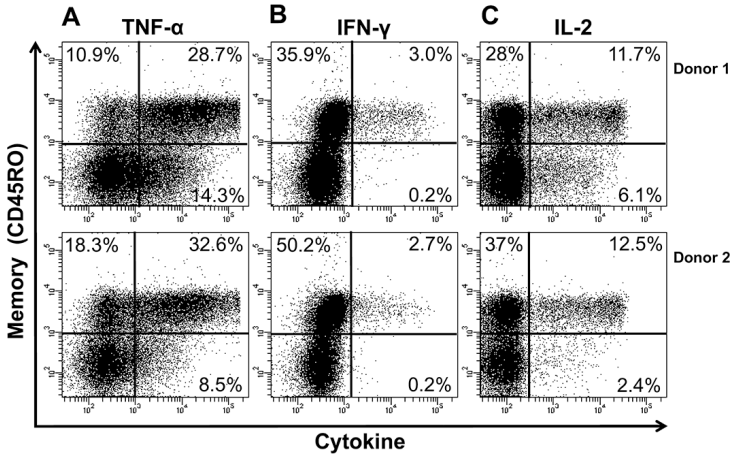
The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Cytokine Storm in a Phase 1 Trial of the Anti-CD28 Monoclonal Antibody TGN1412

Ganesh Suntharalingam, F.R.C.A., Meghan R. Perry, M.R.C.P., Stephen Ward, F.R.C.A., Stephen J. Brett, M.D., Andrew Castello-Cortes, F.R.C.A., Michael D. Brunner, F.R.C.A., and Nicki Panoskaltsis, M.D., Ph.D.

TGN1412 induces cyokine in human memory T cells



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Treg cell therapy – a living drug

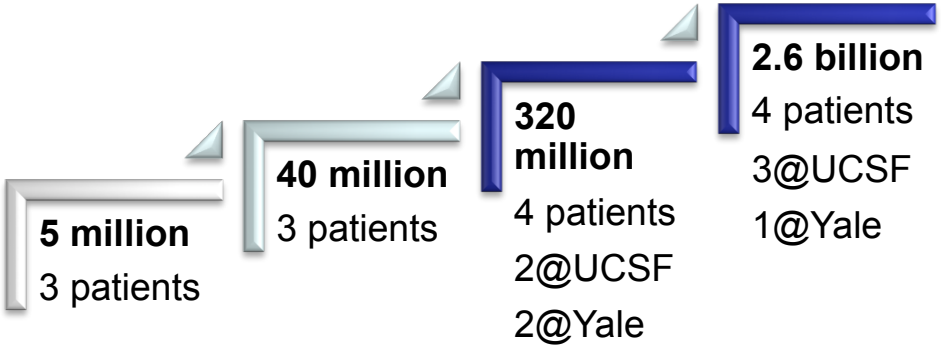
- Cells naturally perform therapeutic tasks.
- Cells are efficient delivery systems going to the right place at the right time.
- Cell behavior is intrinsically selective.
- Cells can handle human genetic variability can be autologous or generic.
- Cell behaviors can be engineered.

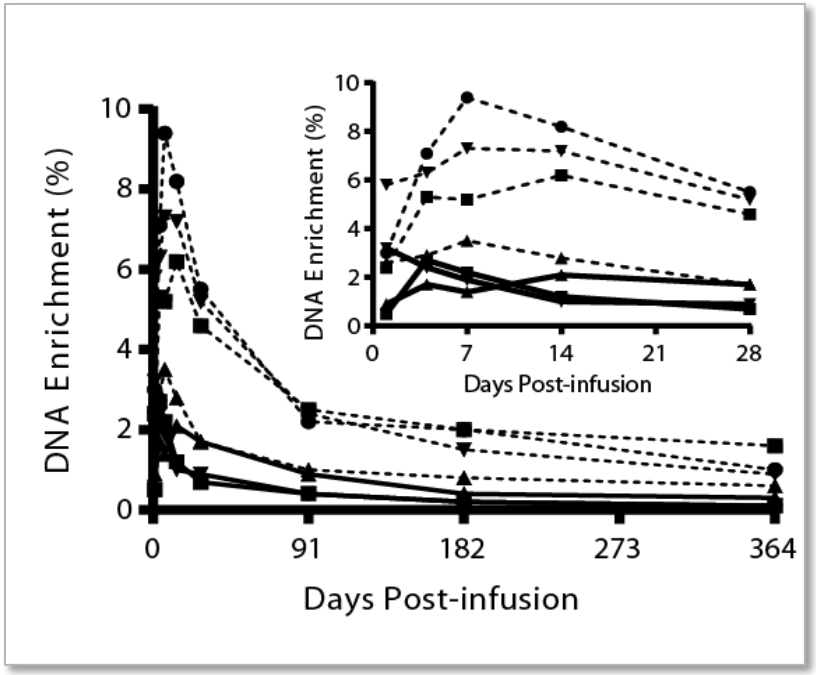
Phase I study of Treg cell therapy in T1D

Long-term persistence of infused Tregs

Inclusion Criteria:

- Between 18 and 45 years of age
- Meet ADA criteria for T1D
- Recent onset T1DM, 3 – 24 months
- Detectable C-peptide
- Absence of chronic infections
- No history of malignancy





Bluestone, Jeffrey A., et al. "Type 1 diabetes immunotherapy using polyclonal regulatory T cells." Science translational medicine 7.315 (2015): 315ra189-315ra189.

Key concepts and unresolved issues

- Therapies targeting effector mechanisms for various autoimmune diseases are being developed with success in recent years
  - Anti-TNF for RA
  - Anti-IL17 for psoriasis
  - Anti-IL-23 for ankylosing spondylitis
  - Anti-B cell therapies for T1D and MS
  - Anti-CD3 for T1D
- All of these therapies are non antigen specific and require maintenance treatments
- Inducing dominant regulation may restore tolerance
- Need to develop antigen-specific therapies so not to globally compromising patients' immune defense

Reading list

Delong, Thomas, et al. "Pathogenic CD4 T cells in type 1 diabetes recognize epitopes formed by peptide fusion." Science 351.6274 (2016): 711-714.

Dai, Xuezhi, et al. "A disease-associated PTPN22 variant promotes systemic autoimmunity in murine models." *The Journal of clinical investigation* 123.5 (2013): 2024-2036.

Bottini, Nunzio, and Erik J. Peterson. "Tyrosine phosphatase PTPN22: multifunctional regulator of immune signaling, development, and disease." *Annual review of immunology* 32 (2014): 83-119.

Vinuesa, Carola G., et al. "A RING-type ubiquitin ligase family member required to repress follicular helper T cells and autoimmunity." *Nature* 435.7041 (2005): 452-458.

Farh KK*, Marson A* et al Genetic and Epigenetic Fine Mapping of Causal Autoimmune Disease Variants. *Nature*. 518, 337-343 (2015).

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