Autoimmune diseases

•Fundamental abnormality: the adaptive immune system is triggered by self antigens to initiate a sustained immune response against self molecules that results in tissue injury

•Specificity for self antigens occurs because the T cell repertoire of the adaptive immune system is generated by selection of T cells on self-peptides presented by self-MHC molecules: the adaptive immune system is based on self-recognition

First element: inappropriate activation of adaptive immune response

•Sustained adaptive immune response to self antigens may or may not result in tissue injury according to particular host genetics

Second element: effector mechanism enabled to mediate injury

Autoimmune diseases

• 200+ distinct diseases that affect ~10% of the population, but vary according to the target tissue, cell or molecule that is the target of the autoimmune response and in the immunologic mechanisms that mediate target tissue injury

• Often serious and chronic, although they often fluctuate in intensity with spontaneous or therapy-induced remissions and exacerbations

• Most have delayed onset in teen age through early adulthood, emphasizing role of non-germline encoded events in pathogenesis

• Genetic predisposition is clear from high identical twin concordance and substantial familial aggregation

Autoimmune diseases relatively common

Diseases	Approximate Prevalence in USA
Psoriasis and psoriatic arthritis	2-3%
Hashimoto's thyroiditis	1-2%
Celiac disease	1-2%
Rheumatoid arthritis	0.8%
Myasthenia gravis	0.1%
Pemphigus vulgaris	0.1%
Type 1 diabetes mellitus	0.1%
Multiple sclerosis	0.1%
Systemic lupus erythematosus	0.1%

Autoantibodies

• Identified in the 1950s and led to the recognition of the autoimmune nature of rheumatoid arthritis and systemic lupus erythematosus,

•Autoimmune diseases were previously considered "collagen" diseases and the term "collagen vascular" or "connective tissue disease" is still heard

• Usually IgG class and somatically diversified, reflecting T cell help in the germinal center

• Occur in sets specific for different epitopes on a given autoantigen molecule or supermolecular complex, implying disease is driven by a response to distinct autoantigenic structures

Central abnormality in nearly all autoimmune diseases is inappropriate and sustained activation of T cells

- Initiates autoimmune response
- Directly mediates tissue injury via T cellular immune mechanisms
- Provides help to B cells to produce autoantibodies

For disease to occur the activated T or B cells via autoantibodies must be able to mediate tissue injury in target organs

Effector processes mediating tissue injury in autoimmune diseases are those found in many other immune responses

- Autoantibodies to target antigens (Type II)
- Immune complexes of autoantigen and autoantibody (Type III)
- T cell mediated cellular immune injury (Type IV)
  - CD4 T cell-macrophage
  - CD8 T cell cytolysis

(No evidence of allergic / IgE-mediated injury)

Injury Mechanism- CD4 and/or CD8 T cells

Examples:

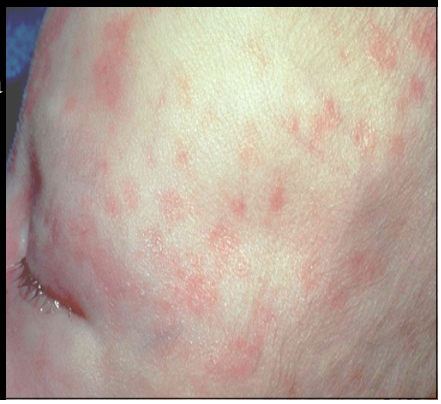
- Type I diabetes mellitus *
- Anterior uveitis
- Multiple sclerosis
- Psoriasis / psoriatic arthritis
- Celiac disease*

*Antibodies are present and diagnostically/prognostically useful, but do not appear to be pathogenic

Injury Mechanism- Antibodies

Direct evidence for the pathogenic role of autoantibodies comes from transplacental transfer of maternal autoantibodies to the fetus that <u>may</u> cause a <u>transient</u> and passive, but sometimes devastating, autoimmune syndrome in the neonate

- Autoimmune thrombocytopenia
- Coombs positive hemolytic anemia
- Systemic lupus erythematosus-complete congenital heartblock
- Myasthenia gravis
- Pemphigus vulgaris
- Grave's disease

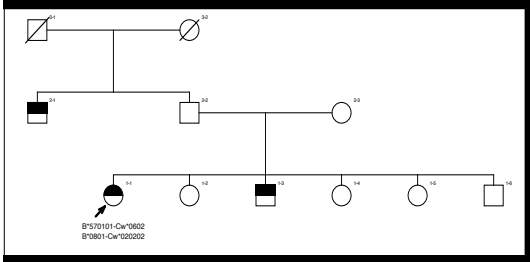


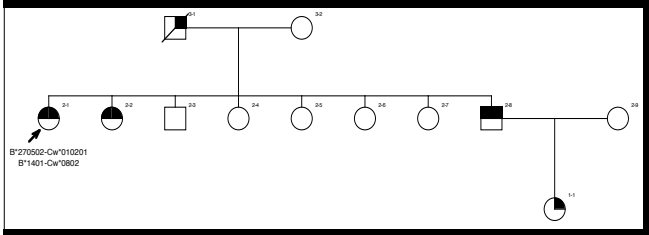
Who develops an autoimmune disease?

Inherited susceptibility- a major clue

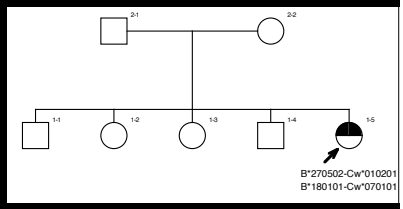
Psoriatic Arthritis inheritance

Multiplex





Sporadic or Simplex



Mixed multifactorial pattern, partially dominant mode of inheritance, incompletely penetrant

Who develops an autoimmune disease?

Inherited susceptibility- a major clue

Identical twin concordance- 25-50%

Familial aggregation- (family history)

$$\text{Recurrence rate } \lambda_S = \frac{\text{Frequency in sibs}}{\text{Frequency in population}}$$

Disease	Frequency in sibs	Frequency in population	λ_S
SLE	10-25%	0.1%	100-250
RA	5%	0.8%	6

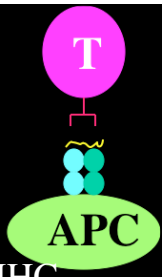
What genes are responsible for the development of an autoimmune disease?

Inherited susceptibility associated with particular MHC alleles for virtually *all autoimmune diseases*

$$\text{Relative Risk (Odds ratio)} = \frac{\text{Probability of finding allele in disease group}}{\text{Probability of finding allele in control group}}$$

Diseases	HLA specificities associated with susceptibility	Relative Risk
Multiple sclerosis	HLA-DR2 (DR15, DR16)	4.8
Ankylosing spondylitis	HLA-B27	20.0
Pemphigus vulgaris	HLA-DR4	14.2
Rheumatoid arthritis	HLA-DR4	4.2

This returns us to the processes involved in the determination of immunologic self



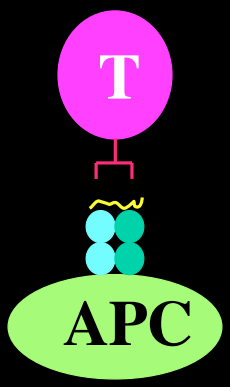
T cells

- Recognition of self-peptides presented by self-MHC
- Mechanisms of T cell repertoire selection, tolerization and the development of immunologic self

MHC

- Binding and presentation of a particular self peptide is a "necessary" condition for development of autoimmunity
- The HLA alleles that present self peptides in autoimmune diseasest are not mutant, "abnormal" genes

Autoimmune diseases: classification according to the class of the susceptibility MHC allotype and lineage of autoantigen specific T-cells mediating injury



	Class I	Class II
	CD8	CD4
	HLA-A,B, or C	HLA-DR, DQ, or DP
	Psoriasis	Multiple sclerosis
	Psoriatic arthritis	Rheumatoid arthritis
	Reiter's syndrome	Lupus erythematosus
	Ankylosing spondylitis	Pemphigus vulgaris

Events in the development of an autoimmune disease

Autoimmune diseases develop in previously healthy individuals many years after birth and the disease "appears" to be acquired

Pre-teen	Adolescence Young adulthood	Midlife	≥6th Decade
Type 1 diabetes mellitus		Rheumatoid arthritis Hashimoto's throiditis	
	Autoimmune thrombocytopenia Coombs + hemolytic anemia Myasthenia gravis Grave's disease Celiac disease Pemphigus vulgaris Multiple sclerosis Psoriasis and psoriatic arthritis Systemic lupus erythematosus		Polymyalgia rheumatica Giant cell arteritis

Autoimmune diseases develop in previously healthy individuals many years after birth and the disease "appears" to be acquired

Germline encoded susceptibility gene

What is going on in the intervening period???

More than just "environment"

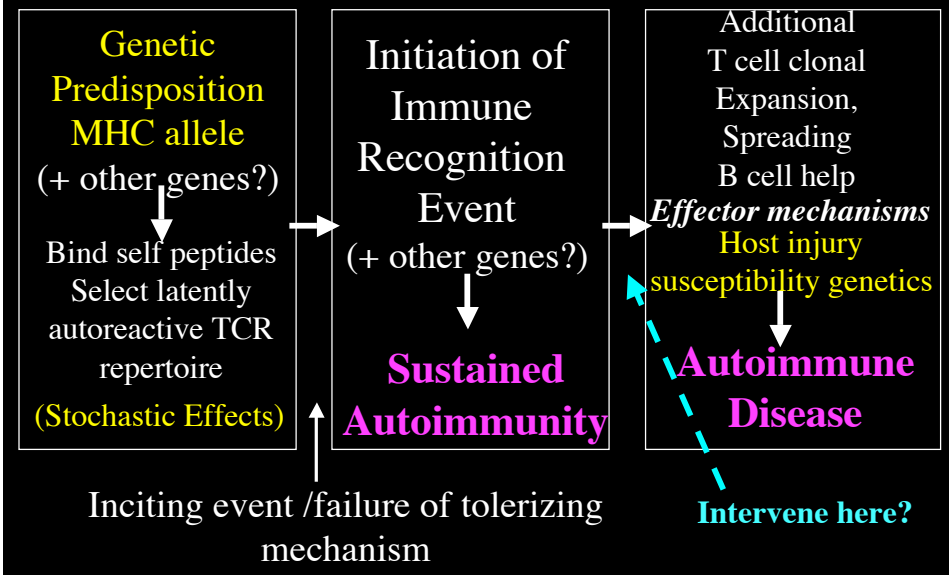
Expression and function of genes are stochastic

- •Alternative splicing of a immune regulatory gene
- •Selection of particular T (and B) cell clones in repertoire
- •Interaction of DC with T and B cells to generate clonal activation and expansion
- •Chance expansions of clones as "bystanders"

Becoming increasingly clear that there is a preclinical stage to most (all?) autoimmune diseases

- •State of clinically discordant identical twins
- •Presence of autoantibodies years before clinical disease in sporadic cases

Stages to progression of autoimmune disease



T cell repertoire: development of immune self

Central- thymic phase

- **Positive selection of the self reactive repertoire**
- **Negative selection / deletion of overtly self reactive T cells central " self tolerance"**

Requires expression of tolerizing self-molecules in thymic medullary cells

Requires expression of tolerizing self-molecules in thymic medullary cells

Large subset of genes are driven to be selectively expressed in the thymic medulla by AIRE, a transcription factor that binds to a promoter element found in these genes…"thymic homunculus"

Loss of expression of AIRE in medullary thymic cells results in autoimmune polyendocrinopathy syndrome Type I (APECED)

AIRE expression requires an intact T cell system, a normal thymocyte-microenvironment and NFκB signaling (RelB)
The appearance of autoimmunity in partial T cell immunodeficiencies can be due to a failure in AIRE expression and incomplete central tolerance of the few remaining T cells

T cell repertoire: development of immune self

Peripheral phase

Regulatory CD4 T cells (Tregs)

Express CD25 and Fox3P
Deficiency results in IPEX(overwhelming autoimmunity)

Immune dysregulation (Coombs+anemia, ITP
Polyendocrinopathy (T1DM)
Enteropathy (Epithelium is like celiac disease)
X-linked < 90% mutations in Fox3P

CTLA4 -Autoimmune syndromes from blocking
Mutations in CTLA4-CD28-ICOS region of 2q33-37

Failure of apoptosis - Fas deficiency

ALPS Autoimmune lymphoproliferative syndrome
Hemolytic anemia and thrombocytopenia

Peripheral phase

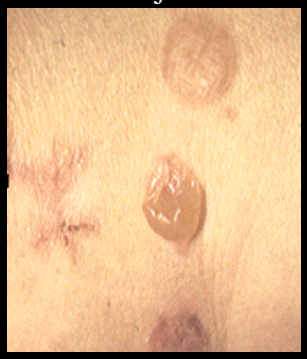
Facilitation of T cell activation (gain of function)

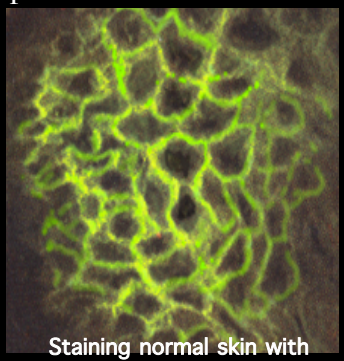
- PTPN22 tyrosine phoshpatase…
  - Initially described as a RA susceptibility gene, now seen in several systemic autoimmune diseases, small relative risk
- Memory effector T cells
  - Do not require costimulation via CD28 (CD28negative)
  - Acquire NK and other receptors that recognize "danger signals of inflammation, injury and stress and which if engaged lower threshold for T cell activation via TCR

Examples of MHC-T cell interactions in autoimmune disease

Identifying a probable inciting autoantigenic peptide recognized by CD4 T cells that provides help to autoantibody formation

Pemphigus vulgaris is a blistering disease of the skin and mucous membranes resulting from formation of high affinity IgG antibodies directed to a amino acids 200-229 of desmoglein 3 (DSG3) that forms the intercellular junctions of epidermal prickle cells





Staining normal skin with patient's serum

Susceptibility associated with DRB1*0402

The association of susceptibility to pemphigus with the DRB1*0402 allele suggests that CD4 T cells recognize a self peptide that provides help to B cells producing autoantibodies to desmoglein

- Knowing the autoantigen recognized by autoantibodies helped in the search for the peptide recognized by the T cell

The binding motif of the DRB1*0402 molecule was used to identify desmoglein peptides capable of binding to the MHC molecule

	P1	P4	P6
Peptide binding motif	I	R	S
	V	K	T
	L		V
	M		Y

Seven desmoglein peptides exhibit the DRB1*0402 binding motif

T cell proliferative response to desmoglein peptides by T cell lines (B cell help)

		Patient G	Patient R
78-93	ATQKITYRISGVGID		
97-111	FGIFVVDKNTGDINI		
190-204	LNSKIAFKIVSQEPA	++++	++++
206-220	TPMFLLSRNTGEVRT	++	
251-265	CECNIKVKDVNDNFP	++	
512-526	SARTLNNRYTGPYTF		
762-786	QSGTMRTRHYTGGTN		++

Wucherpfennig et al. (DRB1*0402 APC)

Why particular alleles encode susceptibility is not entirely clear

Obviously, peptide from target molecule must be bound by encoded susceptibility MHC molecule and p-MHC complex can be recognized by a T cell clone

Most evidence favors the view that the self peptide is not strongly bound by the MHC molecule and thus during thymic repertoire generation the presenting MHC molecule is allowed to select a T cell with very high affinity for the self-peptide (Fathman)

Rheumatoid arthritis is another example of an autoimmune disease where there is an exquisitely precise instance of MHC susceptibility that can be mapped to a single peptide-binding pocket, but the autoantigen is not as clearly understood

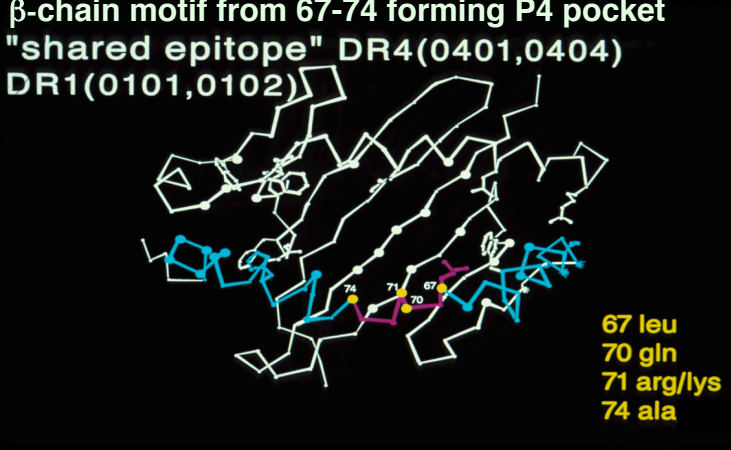
We usually think of one or two specific alleles as encoding a MHC molecule that regulates the peptide recognition underling an autoimmune disease

Rheumatoid arthritis is different because susceptibility is associated with a structural binding pocket motif shared by a group of alleles, *the shared epitope*

Susceptibility to develop RA is associated with:

Specificity	Allele
HLA-DR1	DRB1*0101 and DRB1*0102 not DRB1*0103
HLA-DR4	DRB1*0401 and DRB1*0404 not DRB1*0402
HLA-DR10	DRB1*1001
HLA-DR14	DRB1*1402 not DRB1*1401

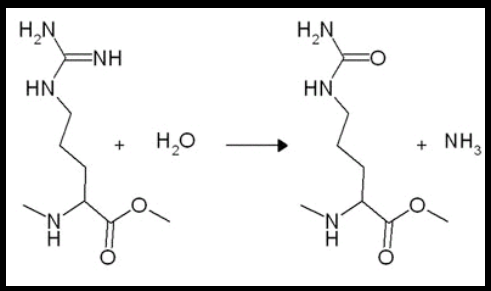
β-chain motif from 67-74 forming P4 pocket
"shared epitope" DR4(0401,0404)
DR1(0101,0102)



Central lesson from rheumatoid arthritis - genetic susceptibility is not the property of a single allotype, but a P4 peptide pocket encoded by several otherwise different allotypes that favors binding peptides with a neutral or negative amino acid

In RA several proteins (fibrinogen, vimentin, etc. become citrullinated and the presence of autoantibodies to citrullinated peptides is a key diagnostic test for RA

Post-translational modification of the amino acid arginine in a protein into the amino acid citrulline by peptidylarginine-deaminase (PAD) a susceptibility gene for RA in Asians



The inheritance of an allele encoding the shared epitope likely confers the property of making an adaptive immune response to various citrullinated peptides

Development of autoantibody precedes development of clinical disease!

Importance of MHC haplotypes

Brief review

Each ethnically distinct population is dominated by a relatively few MHC haplotypes, the alleles of which exhibit strong linkage disequilibrium

These reflect the selective effects of epidemics, local environment, founder effect, etc.

Through their strong effect on regulating adaptive immunity and the determination of self, certain combinations of alleles in linkage disequilibrium, determine susceptibility to autoimmune and other diseases

Maximum number of different types of HLA molecules expressed on the cell surface

	Nucleated cells	Antigen presenting cells
Class I (HLA-A)	2	2
Class I (HLA-B)	2	2
Class I (HLA-C)	2	2
Class II (HLA-DR)	0	2*
Class II (HLA-DQ)	0	4
Class II (HLA-DP)	0	4
Total	6	16

Each of these MHC molecules selects its *own T cell repertoire* that only recognizes peptides presented by that particular type of MHC molecule

A T cell positively selected by one MHC molecule may be eliminated by another MHC molecule during negative selection producing a "hole in TCR repertoire"

All the MHC alleles on a haplotype may influence disease susceptibility, either positively or negatively

Type I diabetes mellitus: <u>All</u> alleles of major DQ-DR haplotypes in linkage disequilibrium can influence susceptibility

DQB1	DQA1	DRB1	Specificity HLA-DR	T1DM
*0602	*0102	*1501	DR2	Dom. Protective
*0601	*0103	*1502	DR2	Neutral
*0201	*0501	*0301	DR3	**Strong Suscept.**
*0302	*0301	*0401	DR4	**Strong Suscept.**
*0302	*0301	*<u>0402</u>	DR4	**<u>Weak</u> Suscept.**
*0301	*0301	*0401	DR4	Neutral
*0303	*0301	*0401	DR4	Neutral
*0303	*0201	*0701	DR7	Dom. Protective

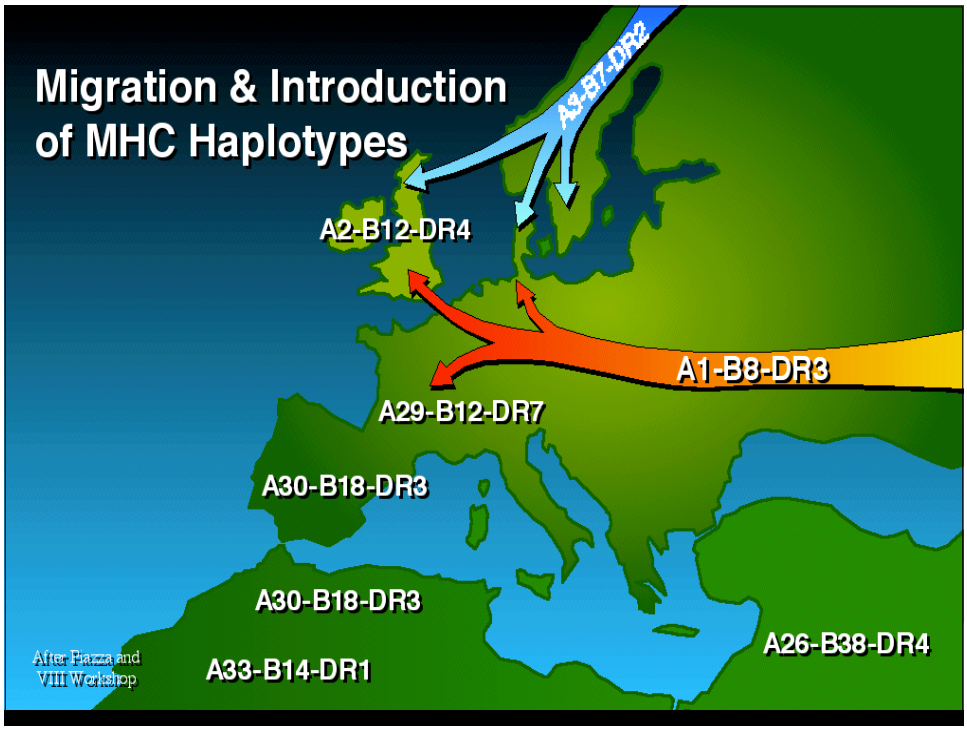
Likely interpretation of haplotype susceptibility to T1DM

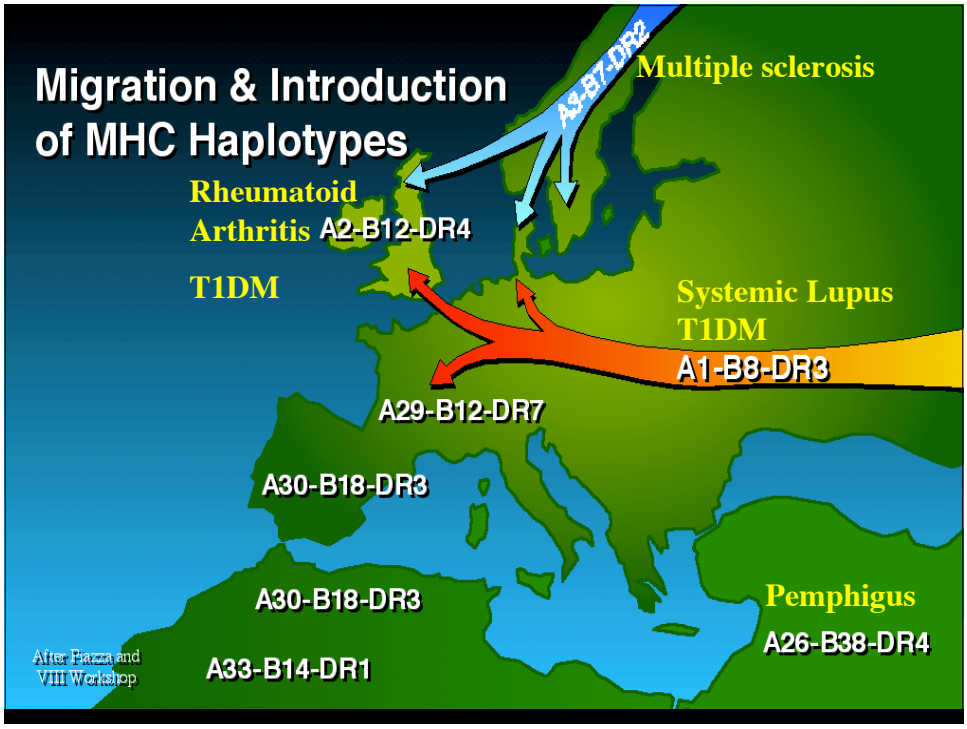
Neutral= MHC molecules are not able to present autoantigenic peptides, or no T cell in their selected repertoire exists to recognize it

Strong susceptibility= MHC molecules encoded by these alleles bind autoantigenic peptides with moderate affinity and select high affinity autoreactive T cell clones

Weak susceptibility= MHC molecules encoded by these alleles bind autoantigenic peptides with high affinity and select low affinity autoreactive T cell clones

Dominant protection= central elimination in negative selection of T cell clones capable of reacting with autoantigenic peptide




Migration & Introduction
of MHC Haplotypes
A3-B7-DR2
Multiple sclerosis
Rheumatoid
Arthritis A2-B12-DR4
T1DM
Systemic Lupus
T1DM
A1-B8-DR3
A29-B12-DR7
A30-B18-DR3
A30-B18-DR3
Pemphigus
A26-B38-DR4
A33-B14-DR1
After Piazza and
VIII Workshop