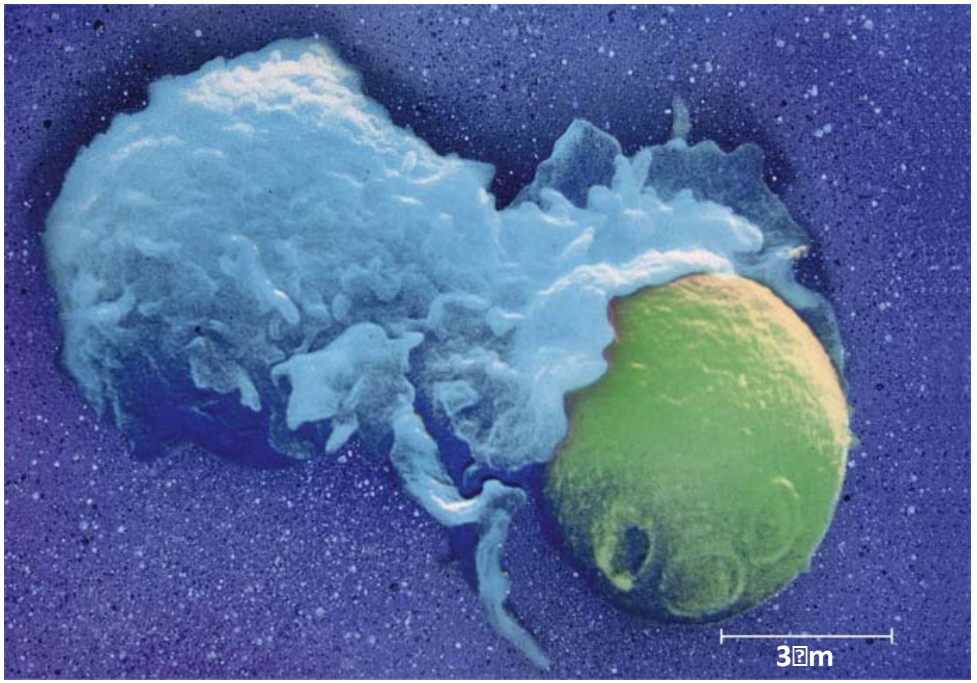
Molecular Mechanisms of Autoimmunity

By: Nadia Chanzu, PhD Student, UNITID

Infectious Minds Presentation

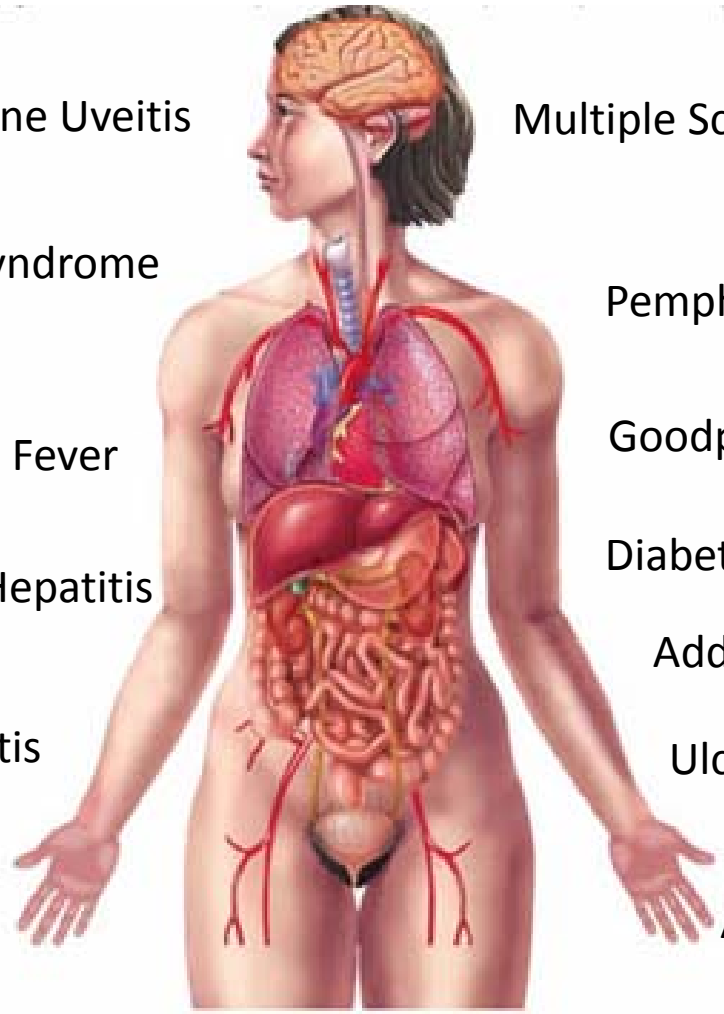
November 17, 2011

Introduction



Pick an organ, any organ . . .

Autoimmunity can affect ANY organ/organ system in the human body



Autoimmune Uveitis

Multiple Sclerosis

Sjogren's Syndrome

Pemphigus

Rheumatic Fever

Goodpasture's Syndrome

Diabetes

Autoimmune Hepatitis

Addison's Disease

Autoimmune Oophoritis

Ulcerative Colitis

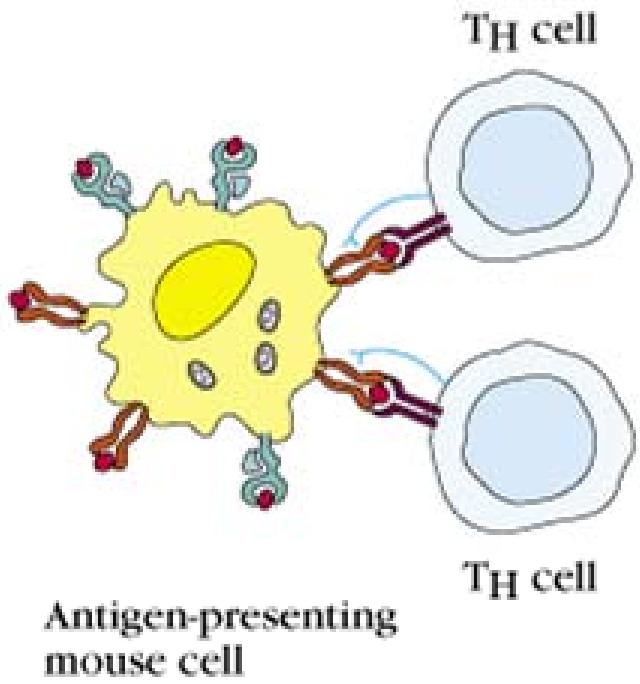
Rheumatoid Arthritis

Autoimmune hemolytic Anemia

Molecular Mechanisms of Autoimmunity

How is autoimmunity induced?

What could go wrong here?



Major factors in initiation and regulation of AI disease

1. MHC Control
2. Antigen Mimicry
3. Altered Proteins

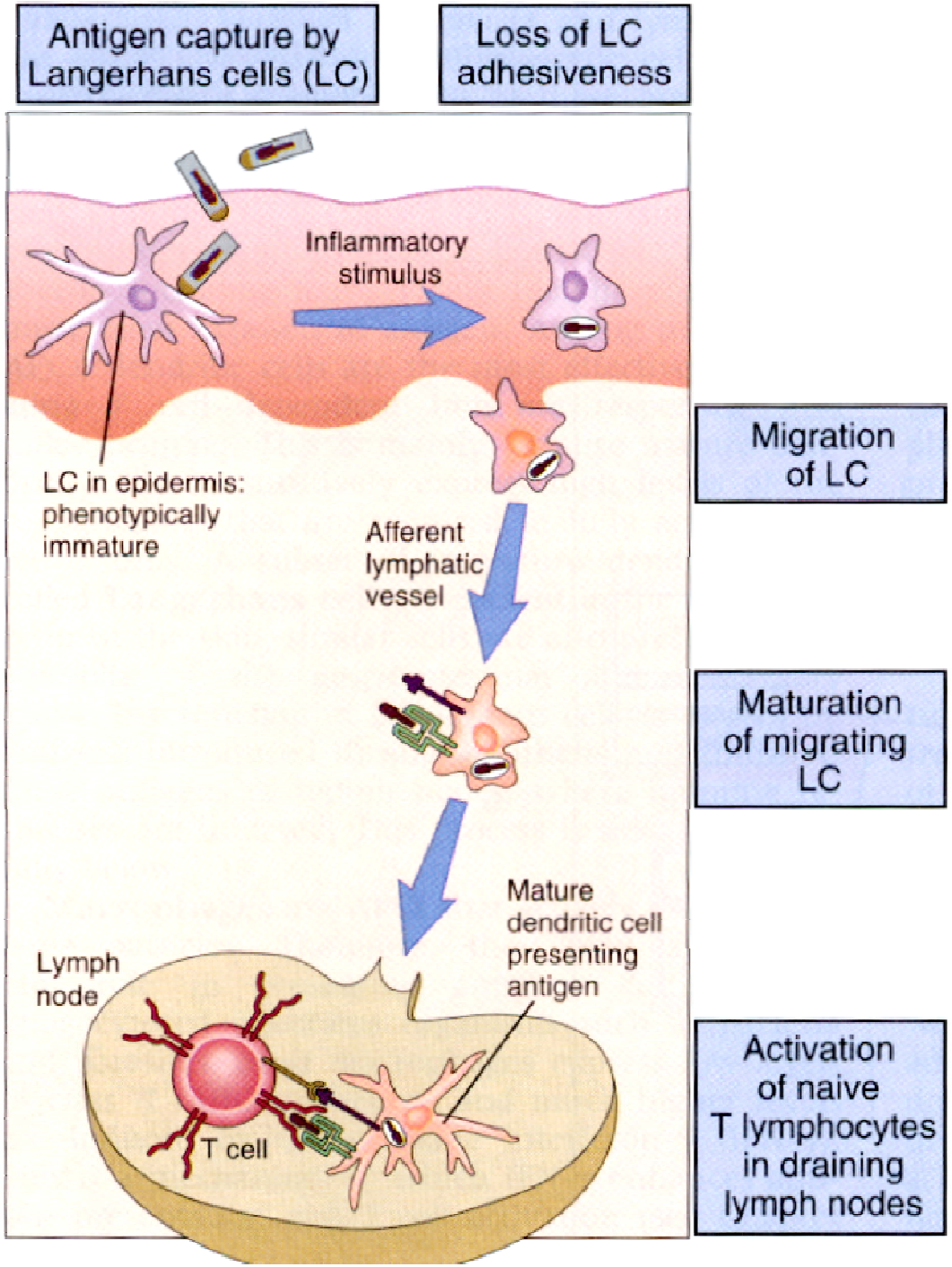
Major Histocompatibility Complex

- Human – A set of linked genes, located on chromosome 6

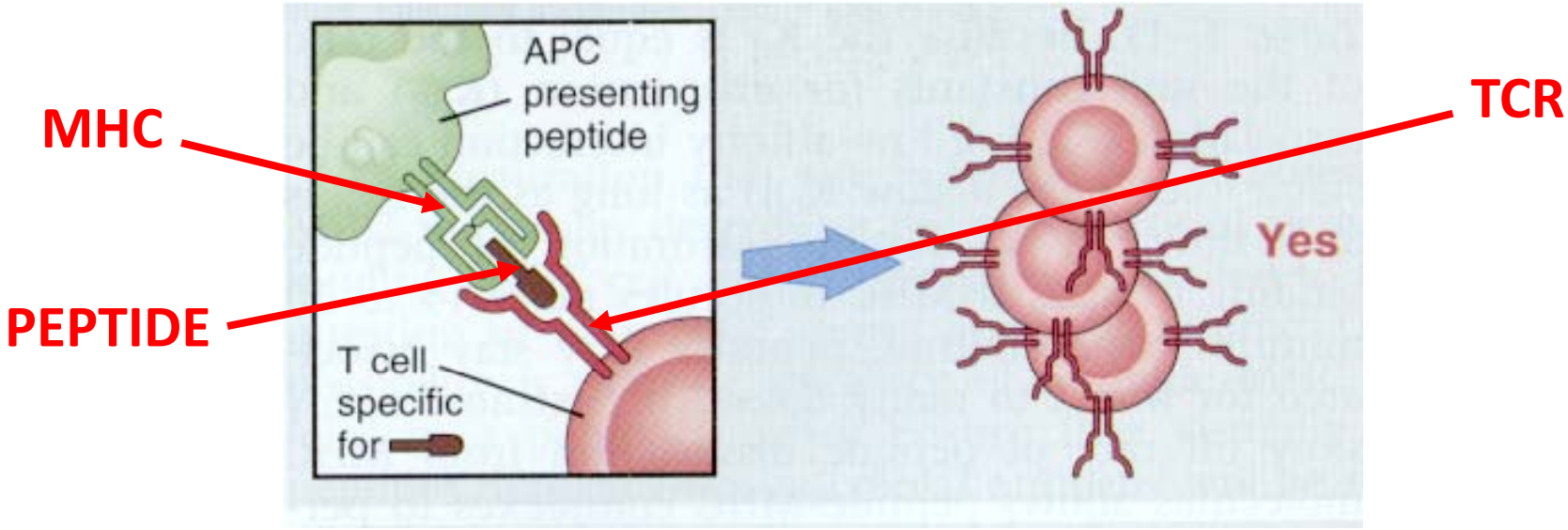
- Molecules encoded by the MHC:
  - Cell surface receptors
  - Bind unique antigen fragments
  - Display them for recognition by immune effectors; most importantly T – Cells

Antigen Presentation

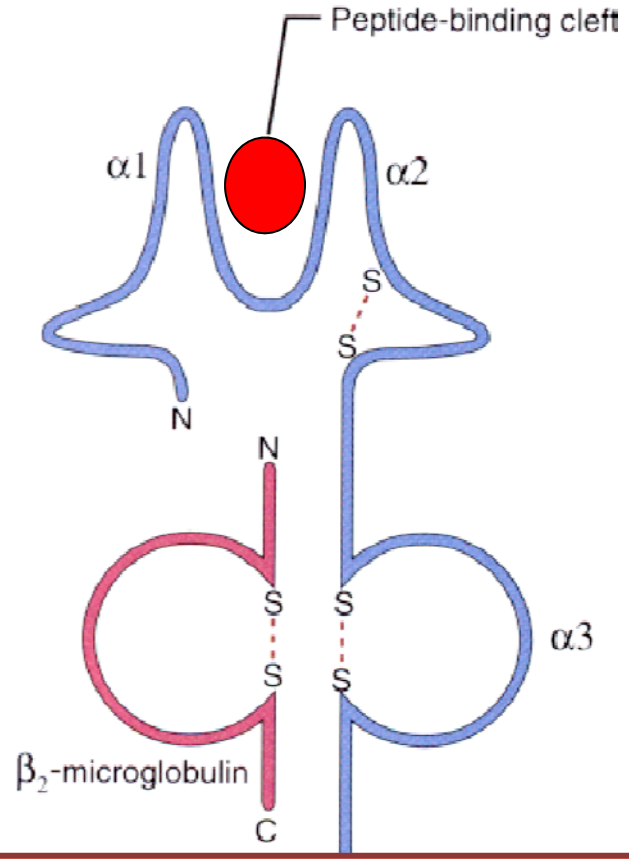
APC to T-cell



- The MHC accomplishes its major role in immune recognition by satisfying two distinct molecular functions:
  - Binding of peptides (or in some cases non-peptidic molecules)
  - Interaction with T cells, usually via the αβ T-cell receptor (TCR).

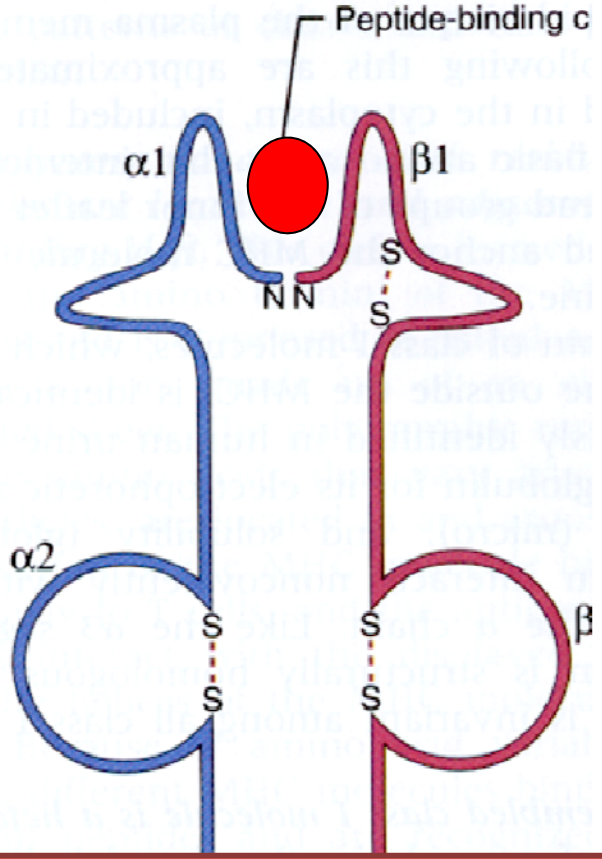


MHC CLASS I



Three MHC Class I alpha chain genes:
HLA – A, B and C

MHC CLASS II



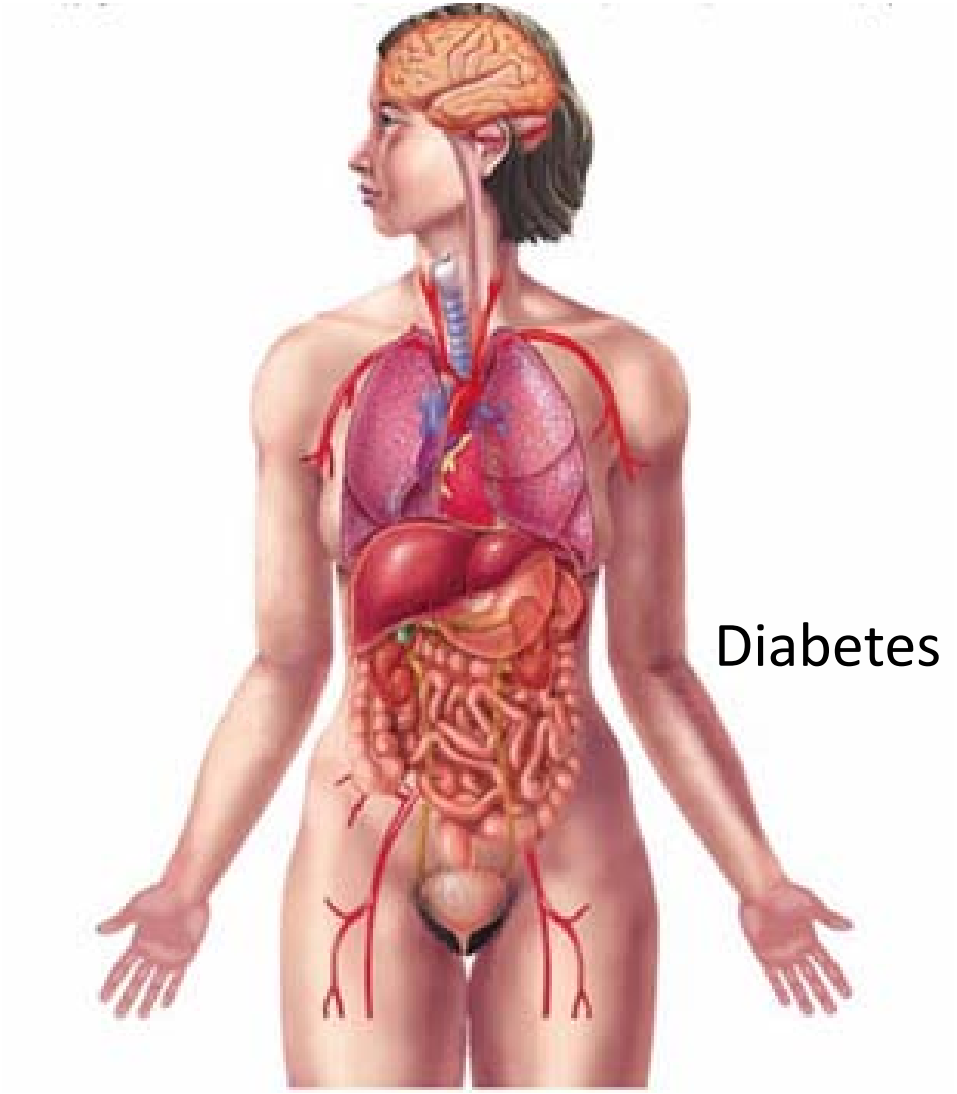
Three MHC Class II alpha chain genes:
HLA – DR, DP and DQ

MHC & Autoimmunity

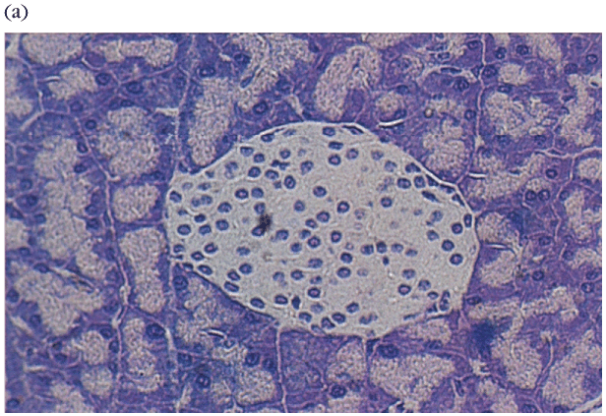
- Regardless of the underlying cause of autoimmunity, predisposition to a given autoimmune response is associated with certain HLA allele(s)

- Involvement of the requisite HLA allele is at the level of antigen presentation by the APCs for T Cell recognition

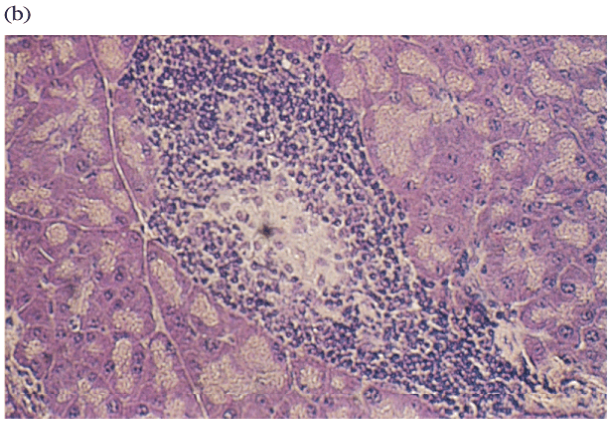
MHC Control gone wrong? DR3, DR4



Diabetes



Normal Pancreas



Pancreas with Insulitis

Associations of HLA serotype with susceptibility to autoimmune disease

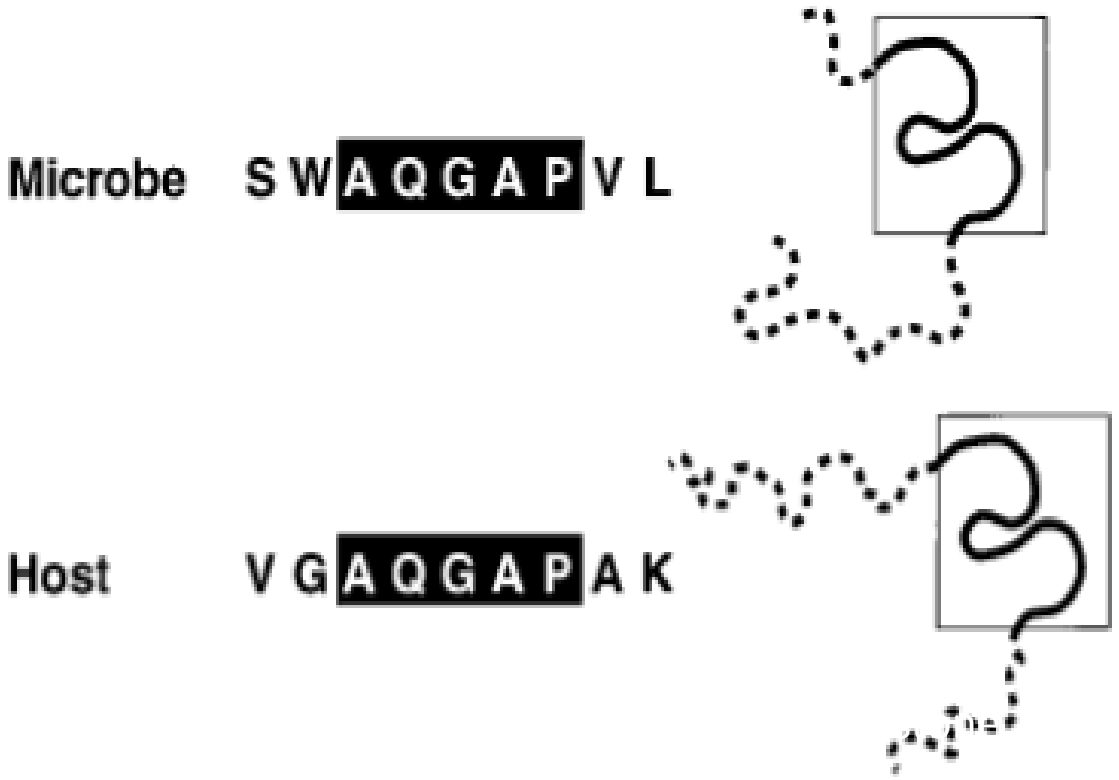
Disease	HLA allele	Relative risk	Sex ratio (♀:♂)
Ankylosing spondylitis	B27	87.4	0.3
Acute anterior uveitis	B27	10	< 0.5
Goodpasture's syndrome	DR2	15.9	~1
Multiple sclerosis	DR2	4.8	10
Graves' disease	DR3	3.7	4–5
Myasthenia gravis	DR3	2.5	~1
Systemic lupus erythematosus	DR3	5.8	10–20
Type I insulin-dependent diabetes mellitus	DR3/DR4 heterozygote	~ 25	~1
Rheumatoid arthritis	DR4	4.2	3
Pemphigus vulgaris	DR4	14.4	~1
Hashimoto's thyroiditis	DR5	3.2	4–5

Figure 13-20 Immunobiology, 6/e. (© Garland Science 2005)

Major factors in initiation and regulation of AI disease

1. MHC Control
2. Antigen Mimicry
3. Altered Proteins

Molecular Mimicry

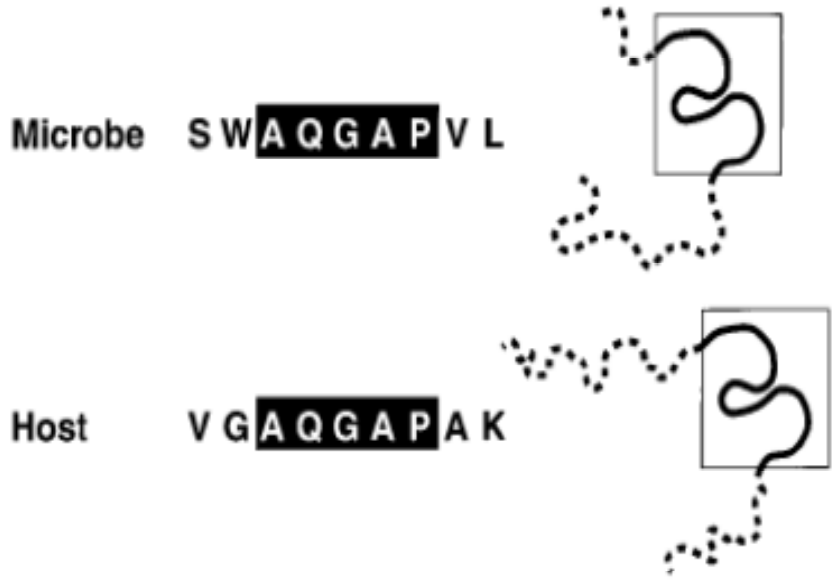


Molecular Mimicry

- Microbe and Host Cell:
  - Share of a linear amino acid sequence
  - Share of conformation fit

- Host immune response against the microbe reacts if the host sequence comprises a biologically important domain

- Autoimmunity may occur



Rheumatic fever is a classic example of molecular mimicry

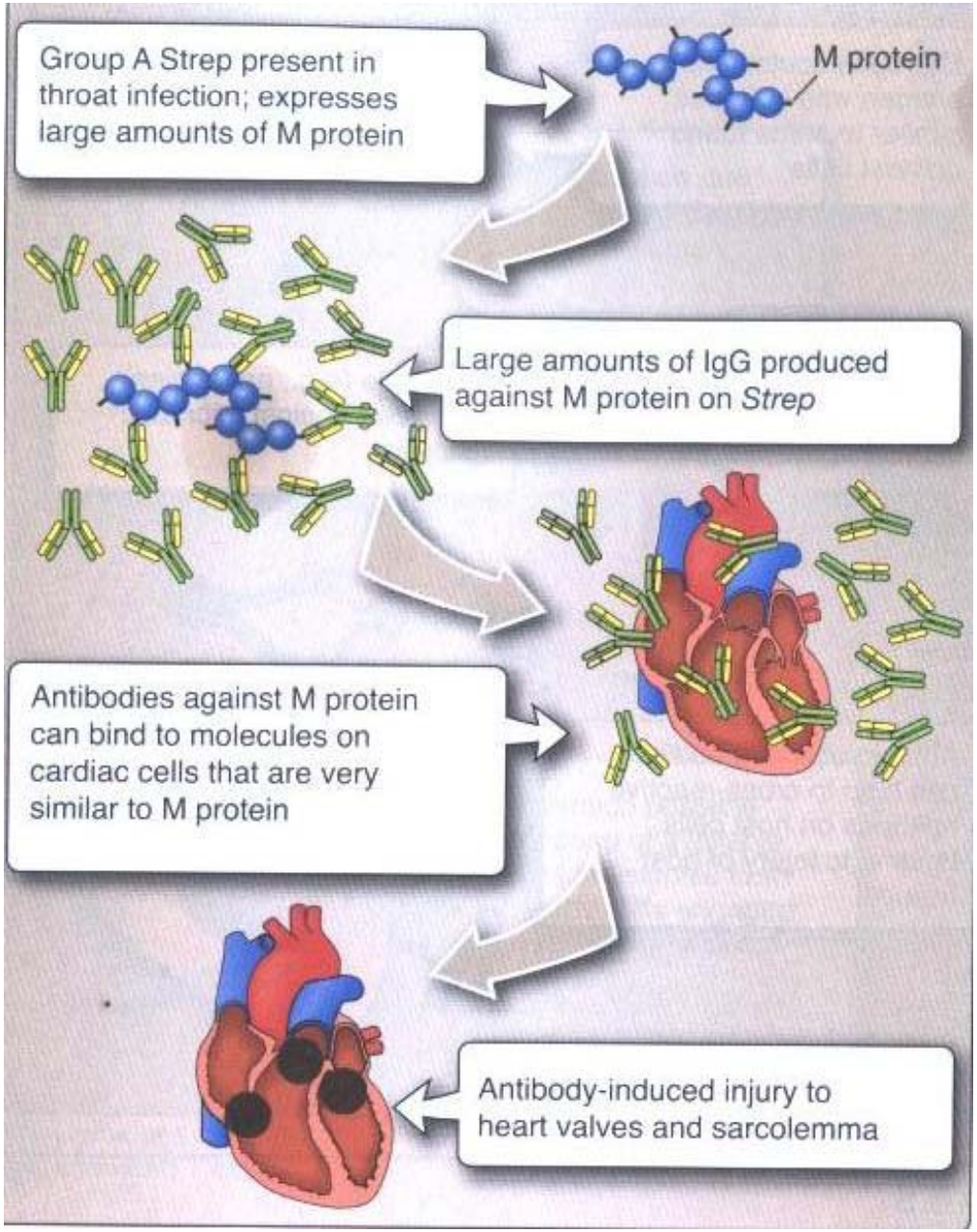


TABLE 20-3 Molecular mimicry between proteins of infectious organisms and human host proteins

Protein*	Residue†	Sequence‡
Human cytomegalovirus IE2	79	P D P L G R P D E D
HLA-DR molecule	60	V T E L G R P D A E
Poliovirus VP2	70	S T T K E S R G T T
Acetylcholine receptor	176	T V I K E S R G T K
Papilloma virus E2	76	S L H L E S L K D S
Insulin receptor	66	V Y G L E S L K D L
Rabies virus glycoprotein	147	T K E S L V I I S
Insulin receptor	764	N K E S L V I S E
Klebsiella pneumoniae nitrogenase	186	S R Q T D R E D E
HLA-B27 molecule	70	K A Q T D R E D L
Adenovirus 12 E1B	384	L R R G M F R P S Q C N
α-Gliadin	206	L G Q G S F R P S Q Q N
Human immunodeficiency virus p24	160	G V E T T T P S
Human IgG constant region	466	G V E T T T P S
Measles virus P3	13	L E C I R A L K
Corticotropin	18	L E C I R A C K
Measles virus P3	31	E I S D N L G Q E
Myelin basic protein	61	E I S F K L G Q E

*In each pair, the human protein is listed second. The proteins in each pair have been shown to exhibit immunologic cross-reactivity.

†Each number indicates the position on the intact protein of the amino-terminal amino acid in the listed sequence.

‡Amino acid residues are indicated by single-letter code. Identical residues are shown in blue.

SOURCE: Adapted from M. B. A. Oldstone, 1987, *Cell* **50:**819.

Major factors in initiation and regulation of AI disease

1. MHC Control
2. Antigen Mimicry
3. Altered Proteins

The development of T cells:

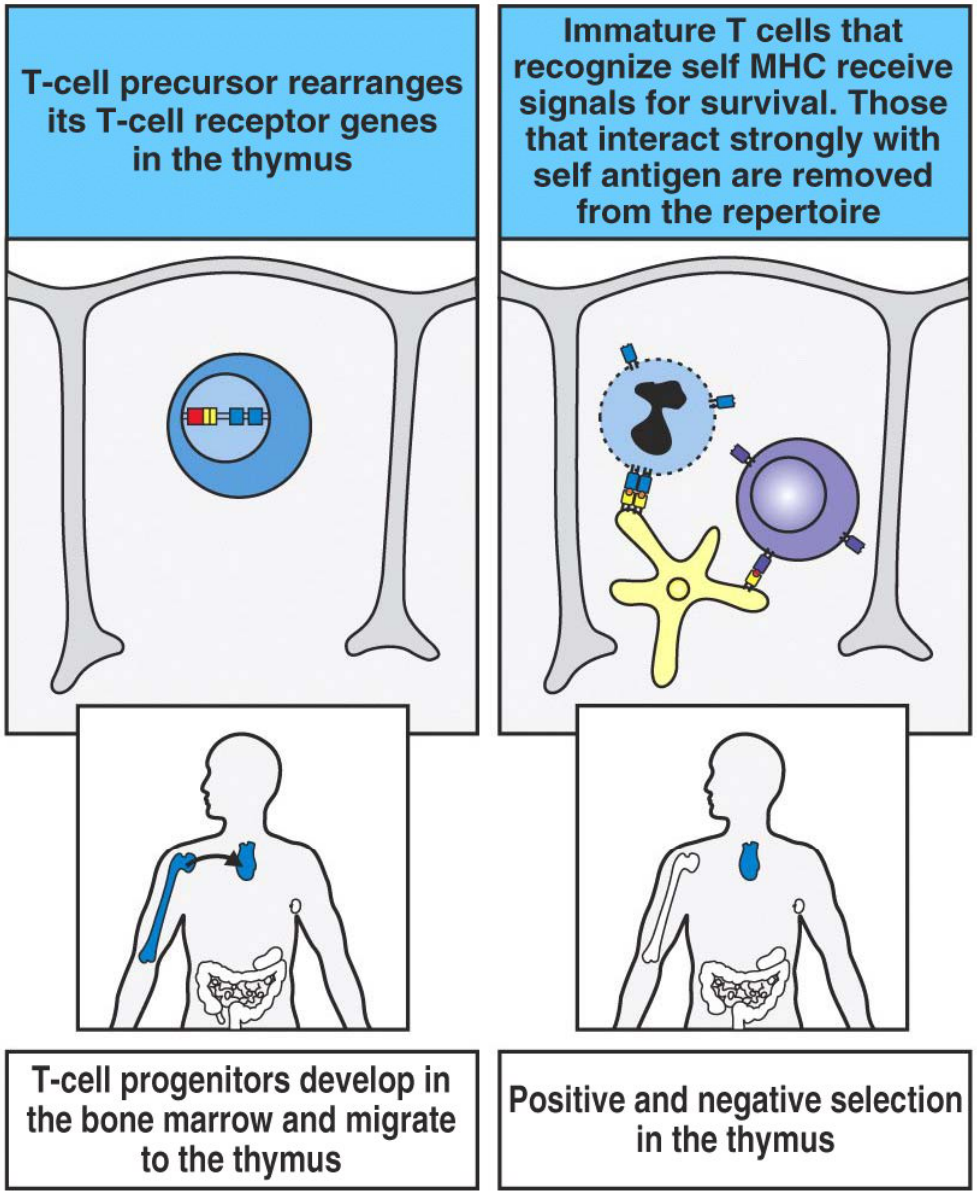


Figure 7-2 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

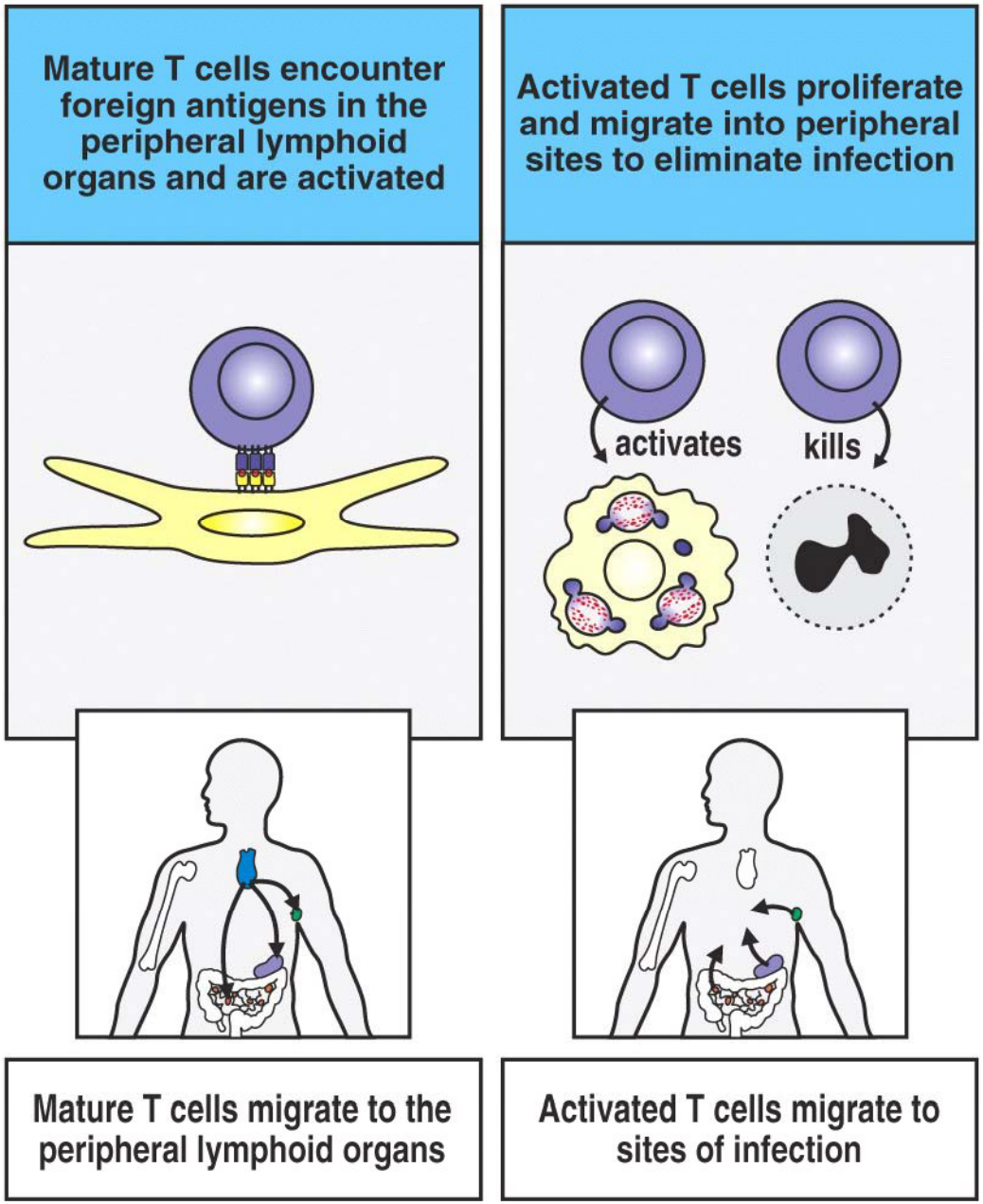


Figure 7-2 part 2 of 2 Immunobiology, 6/e. (© Garland Science 2005)

Protein Mutation & Altered Expression

Expression of Autoimmune Regulator Gene (AIRE) in the thymus shape the immune repertoire:

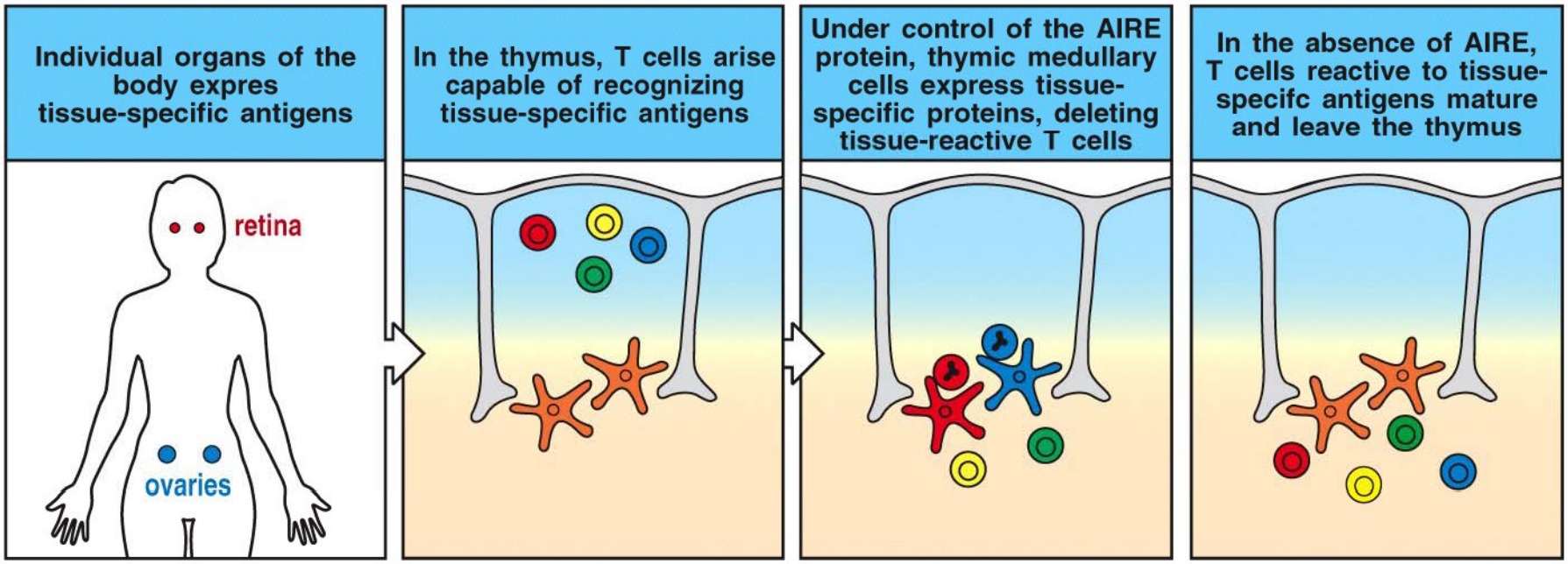


Figure 13-9 Immunobiology, 6/e. (© Garland Science 2005)

Exceptions to the Rule – Simple Genetic Autoimmune Illnesses

Disease	Gene	Mechanism
APS-1 (Autoimmune polyglandular syndrome type 1)	*AIRE*	Decreased expression of self-antigens in the thymus, resulting is a defect in negative selection
IPEX (Immunodysregulation, polyendocrinopathy, enteropathy, X-linked)	*FOXP3*	Decreased generation of Tregs
ALPS (autoimmune lymphoproliferative syndrome)	*FAS, FASL*	Failure of apoptotic death of self reactive T or B cells

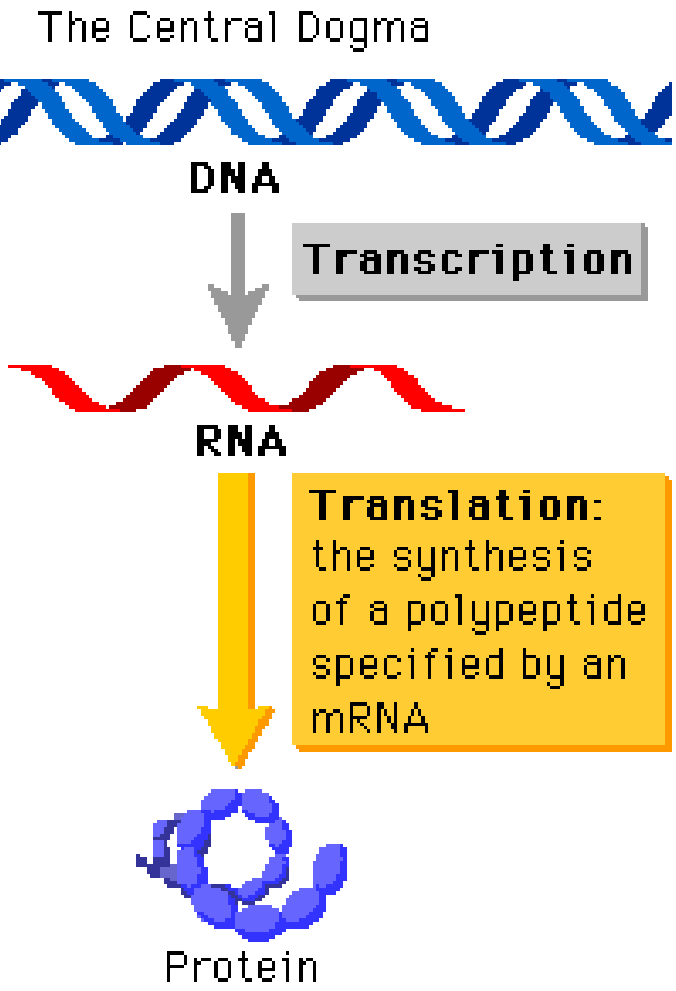
Major factors in initiation and regulation of AI disease

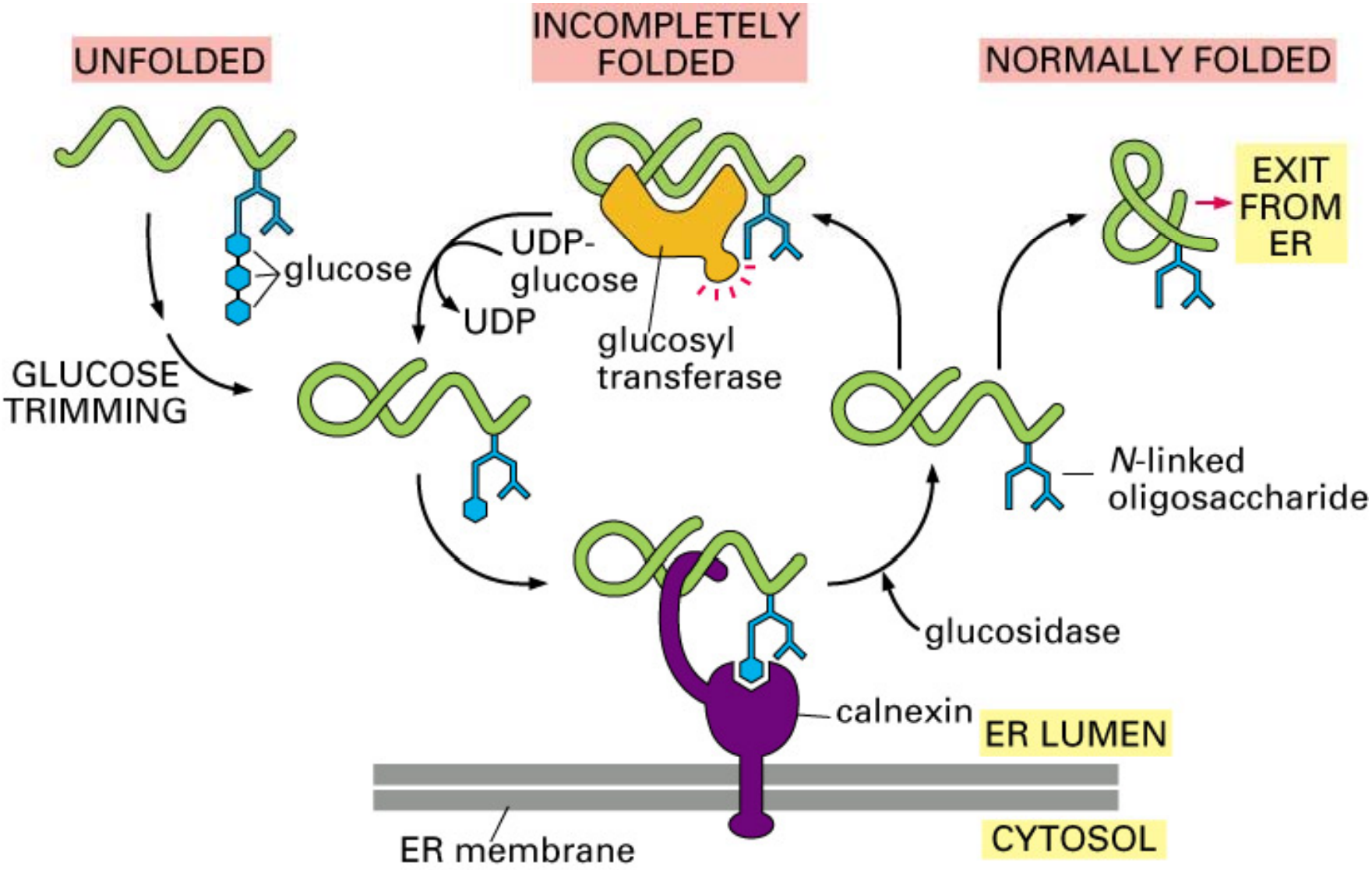
1. MHC Control
2. Antigen Mimicry
3. Altered Proteins

Posttranslational Modification

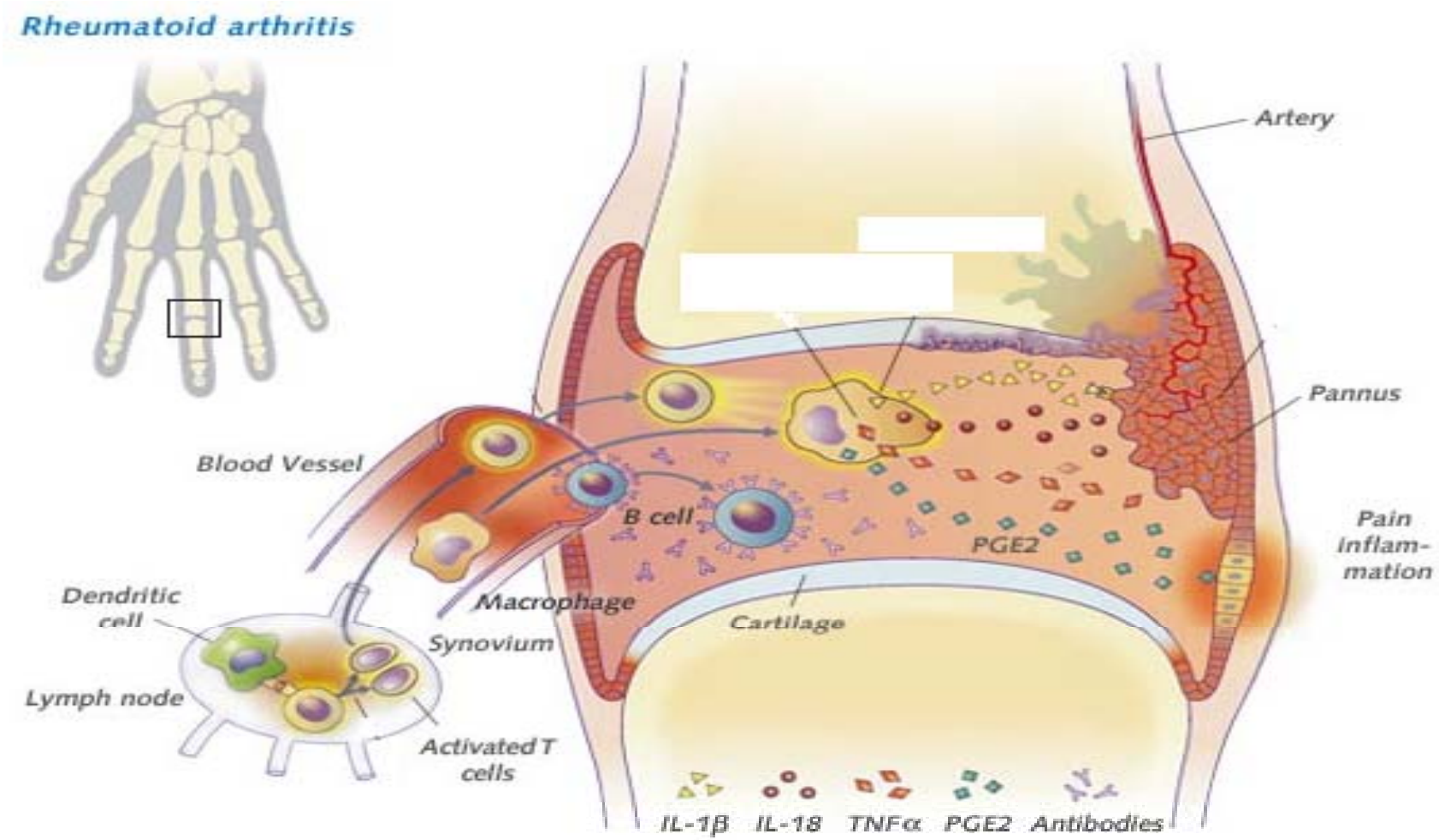
- Translation: Process of synthesizing the peptide chain of amino acids specified by the nucleotide sequence on the mRNA

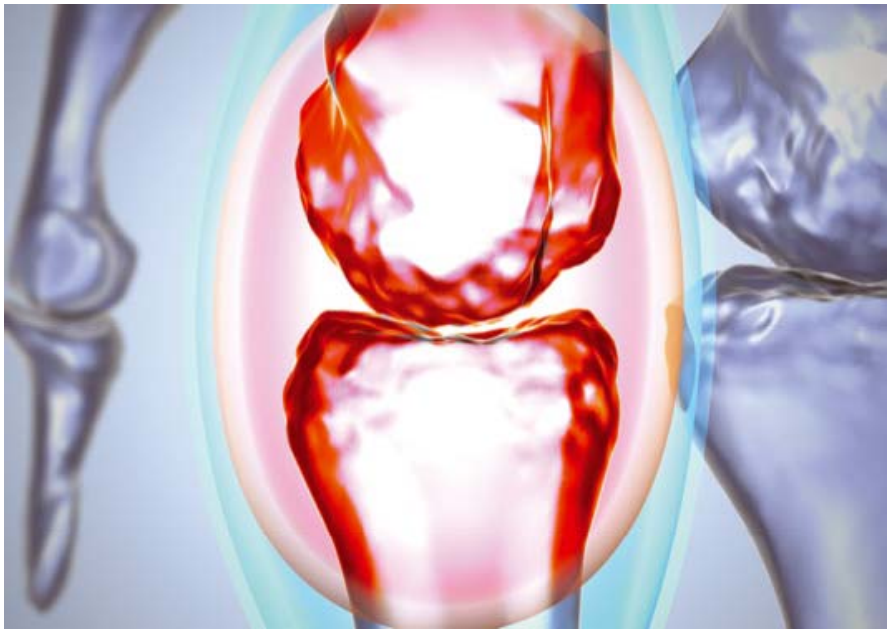
- Post-translational modification: The chemical modification of a protein after its translation




UNFOLDED
INCOMPLETELY FOLDED
NORMALLY FOLDED
glucose
UDP-glucose
UDP
glucosyl transferase
EXIT FROM ER
GLUCOSE TRIMMING
N-linked oligosaccharide
glucosidase
calnexin
ER LUMEN
ER membrane
CYTOSOL

T-CELL MEDIATED DISEASE





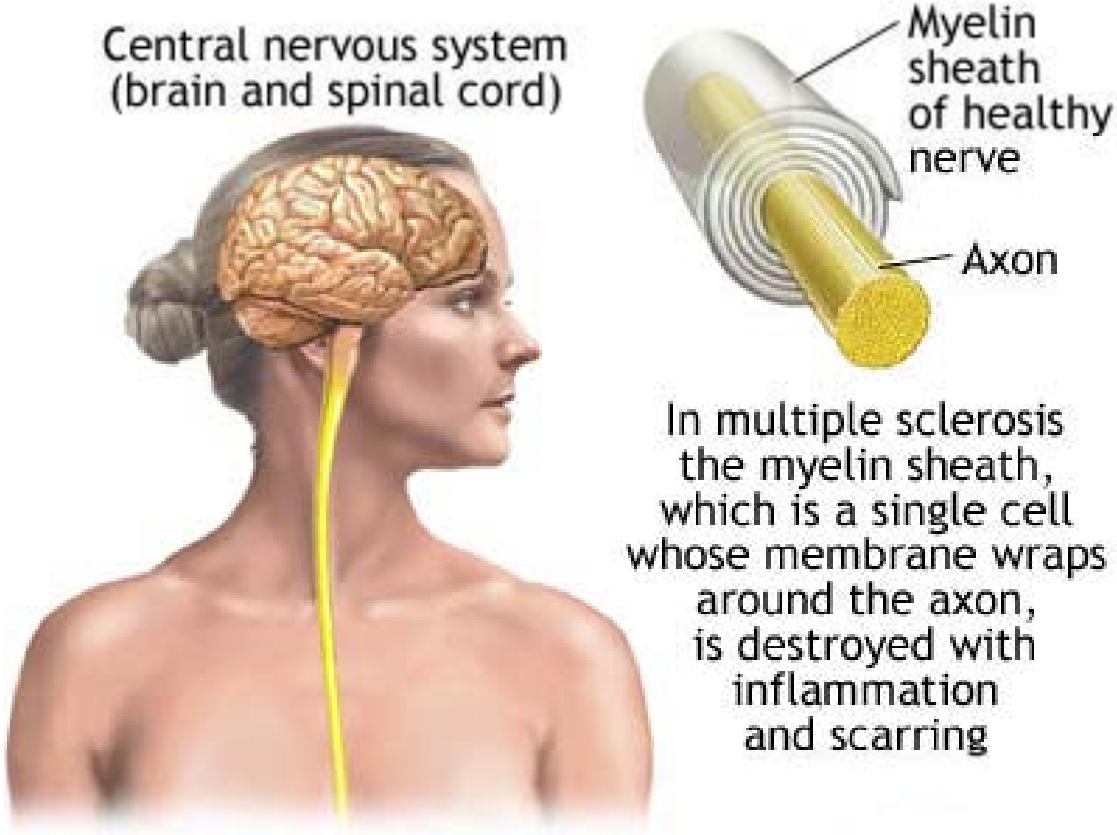
Autoimmunity to Sequestered Proteins

- Sequestered proteins are normally sheltered from immune recognition

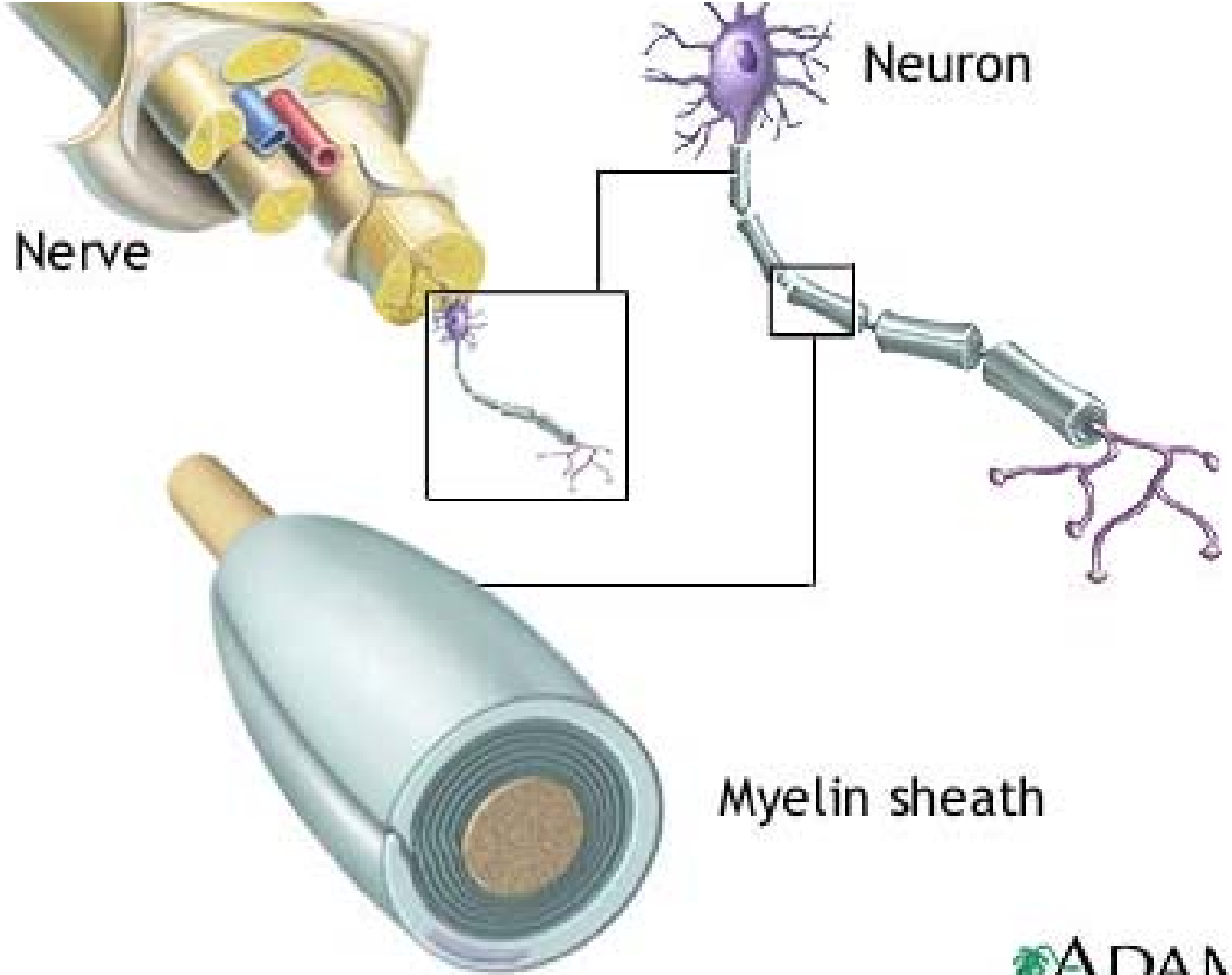
- However, they can become immunogenic once exposed to recognition by immune cells and induce efficient immune responses

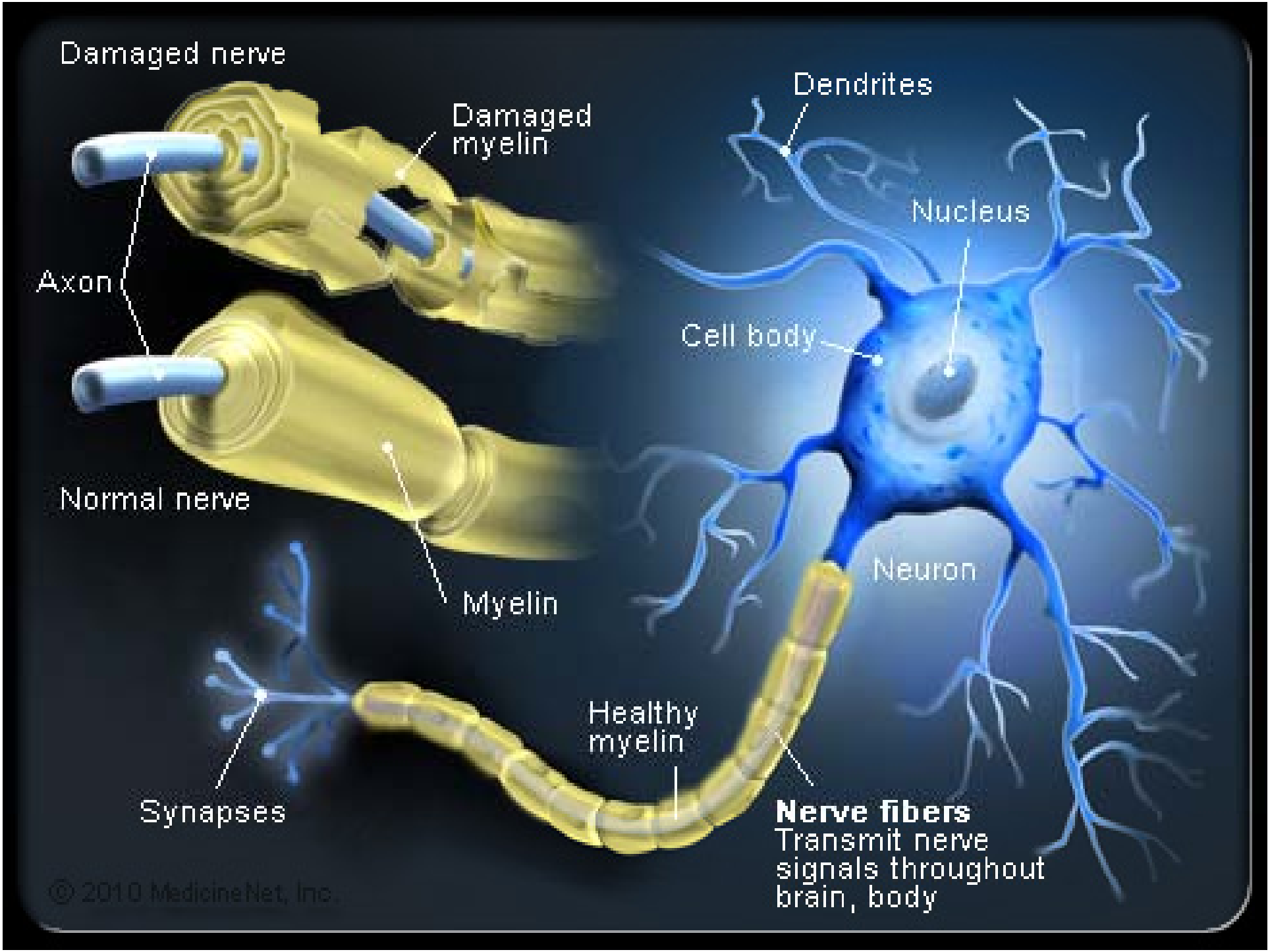
- A good example: *Antibodies in blood can attack Myelin Basic Protein if Blood-Brain barrier is breached*

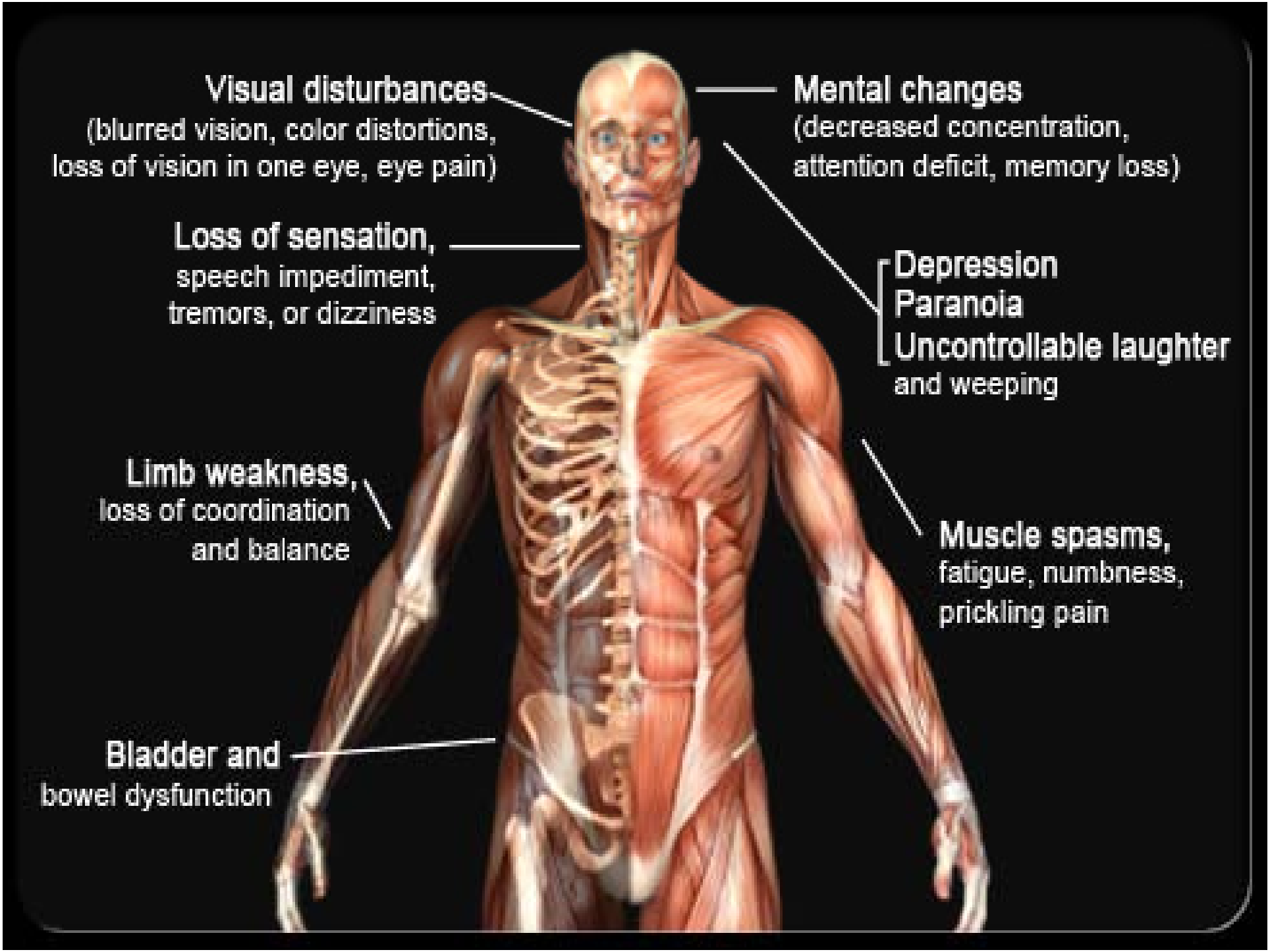
Multiple Sclerosis



MS patients can have autoantibodies and/or self reactive T cells which are responsible for the demyelination


Neuron
Nerve
Myelin sheath
A.D.A.M.


Damaged nerve
Damaged myelin
Axon
Normal nerve
Myelin
Dendrites
Nucleus
Cell body
Neuron
Synapses
Healthy myelin
Nerve fibers
Transmit nerve signals throughout brain, body
© 2010 MedicineNet, Inc.


Visual disturbances
(blurred vision, color distortions, loss of vision in one eye, eye pain)
Mental changes
(decreased concentration, attention deficit, memory loss)
Loss of sensation,
speech impediment, tremors, or dizziness
Depression
Paranoia
Uncontrollable laughter
and weeping
Limb weakness,
loss of coordination and balance
Muscle spasms,
fatigue, numbness, prickling pain
Bladder and
bowel dysfunction

Additional Factors!!

Pregnancy

- Antibody-mediated autoimmune diseases can appear in the infants of affected mothers as a consequence of trans-placental antibody transfer

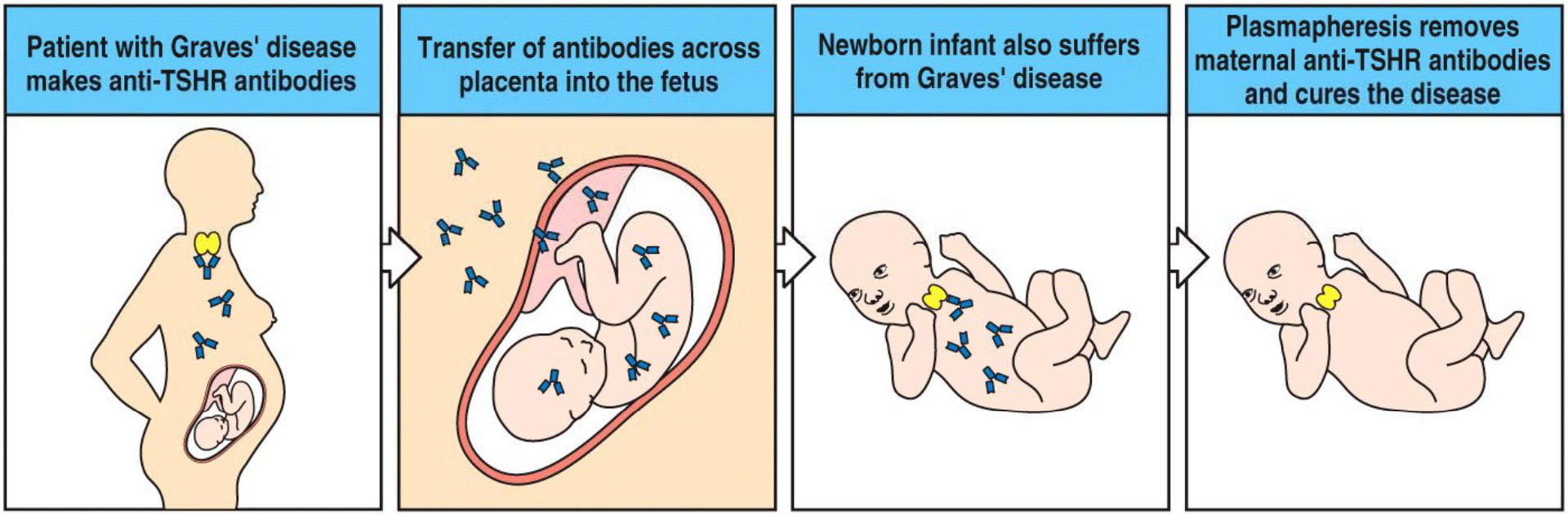


Figure 13-5 Immunobiology, 6/e. (© Garland Science 2005)

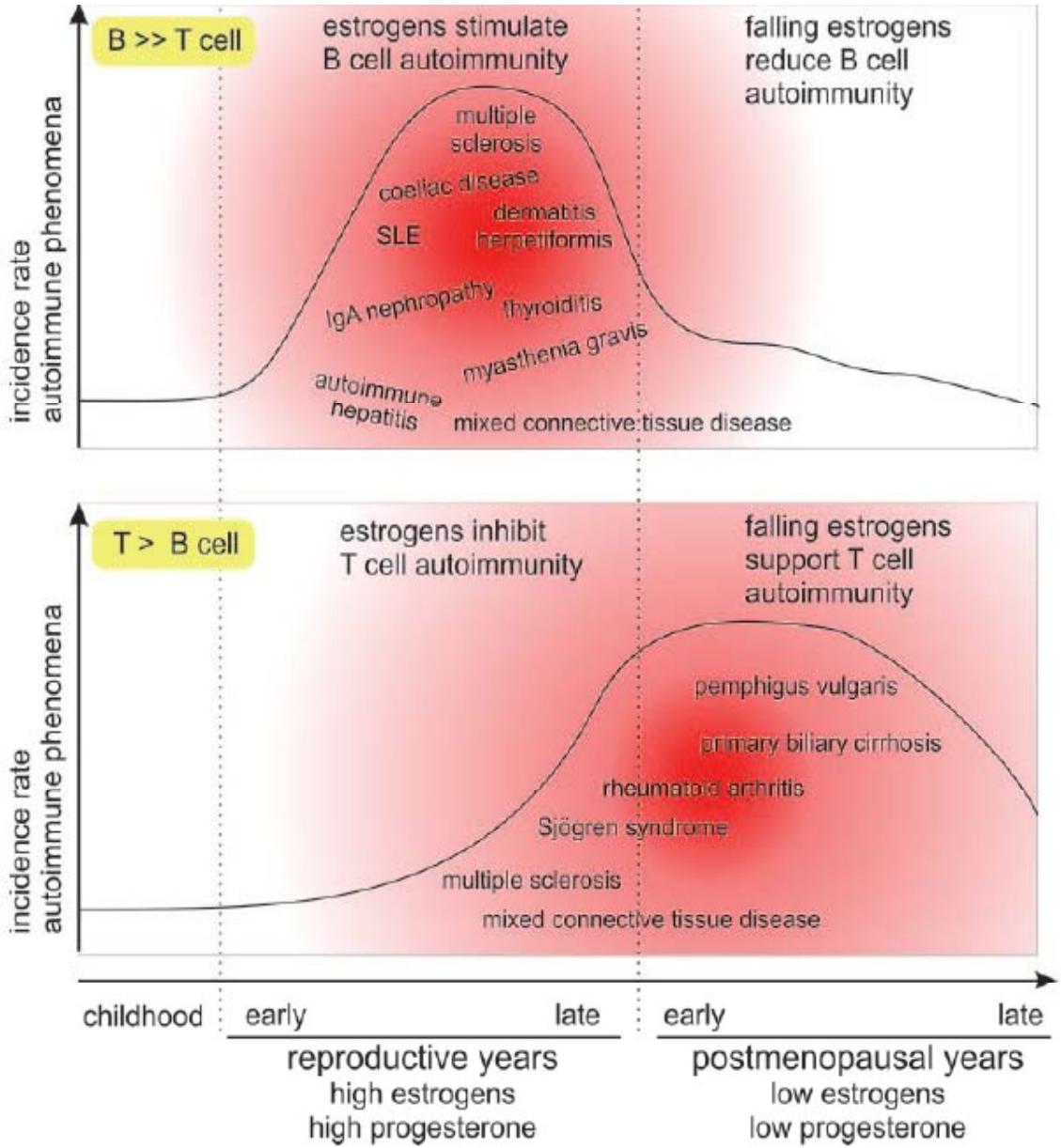
Hormones

- Some autoimmune diseases show a significant bias in gender suggesting that sex hormones are involved in pathogenesis

- Females are much more likely to develop autoimmune illness

Hypothesis: estrogen response elements (EREs) in several genes

Estrogens and Autoimmunity



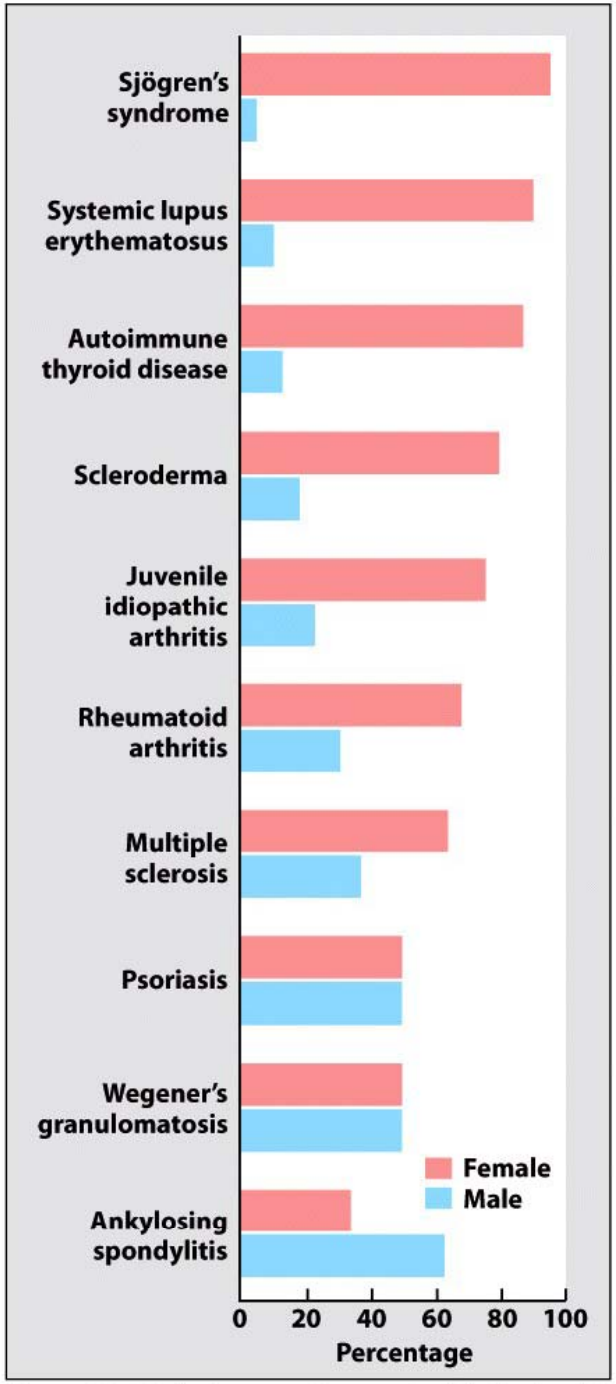


Figure 13.18 The Immune System, 3ed. (© Garland Science 2009)

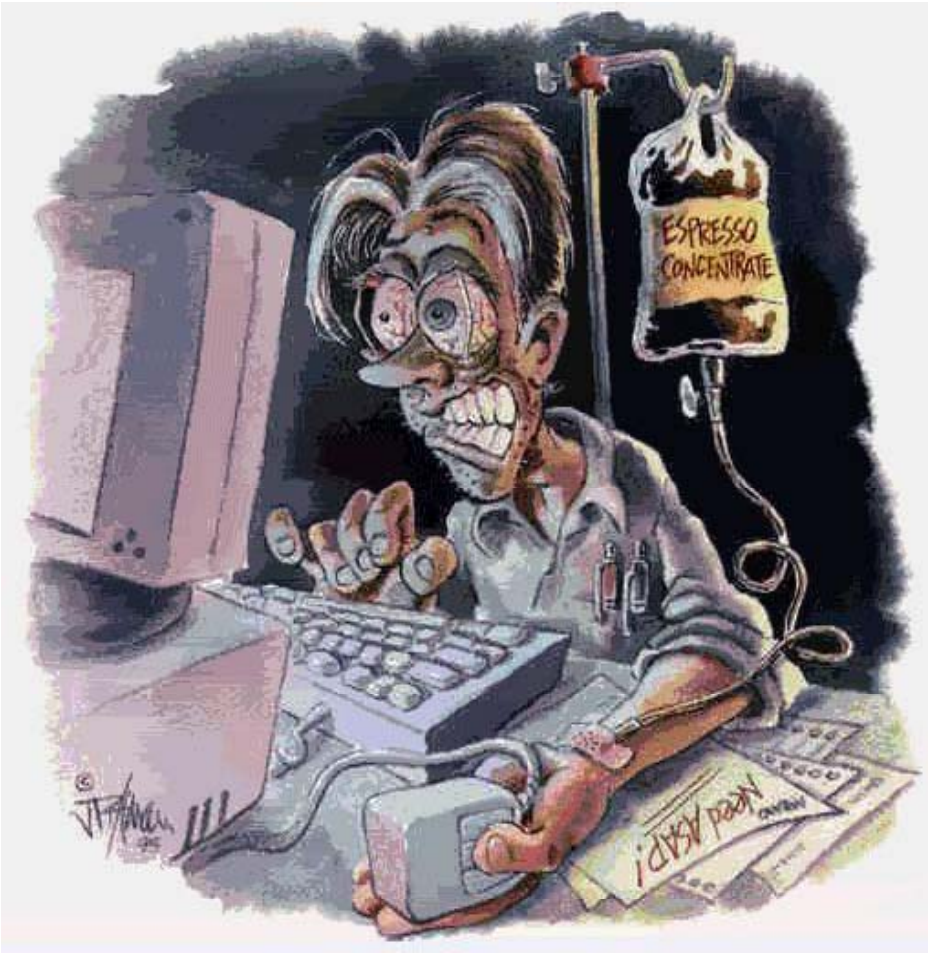
Stress

STRESS:

- Normal Stress (Exams!)
- Chronic Stress = Disease

Stress induces change for adaptation:

- Behavioral (e.g. Moods)
- Physiological (e.g. HBP)
- *Immunological (e.g. AI)*

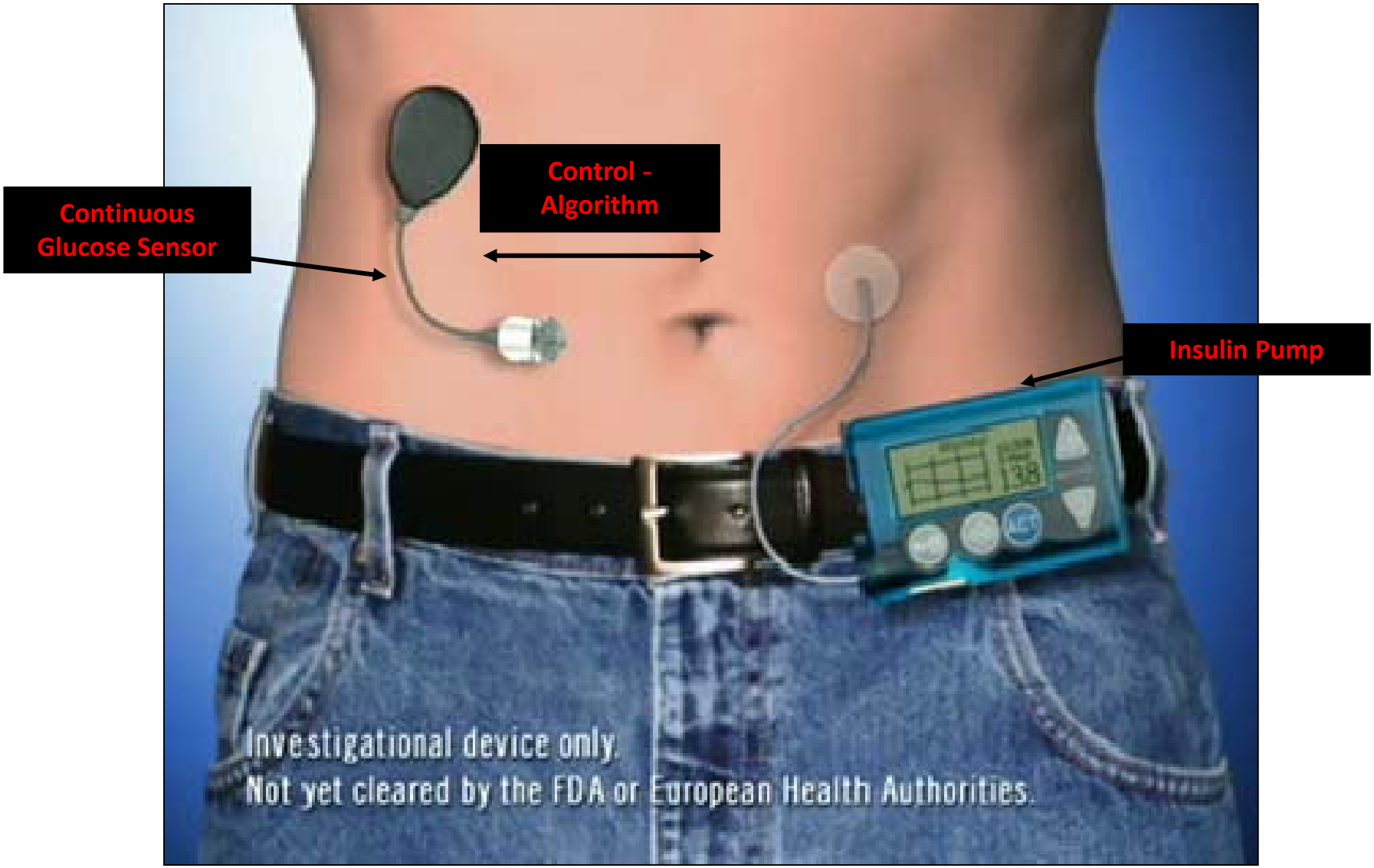


IF YOUR WORKLOAD GETS TOO MUCH...

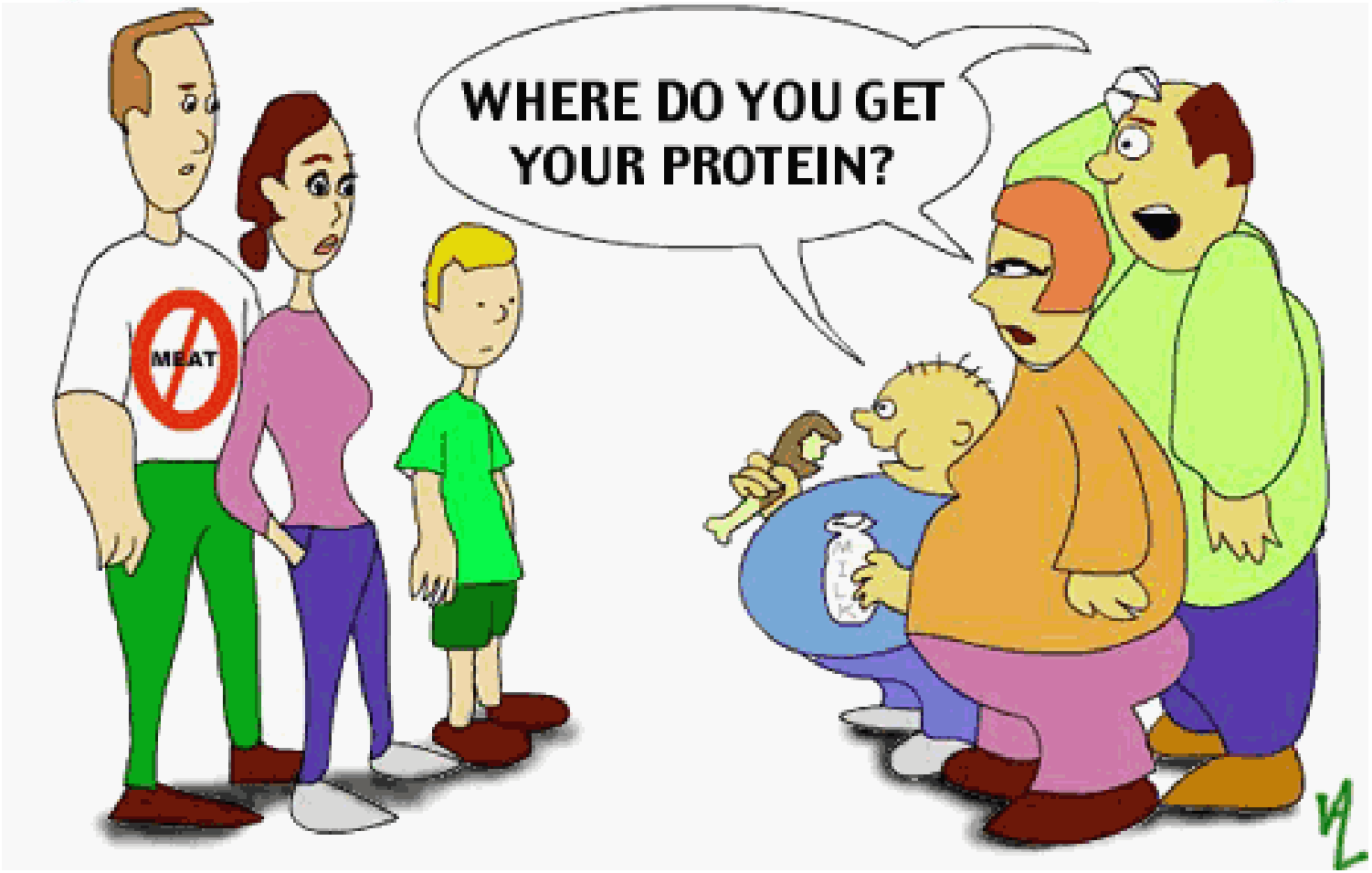
THINK OF HOW TO *BALANCE* YOUR LIFE!

Future

What is an Artificial Pancreas?



Questions



References

- Atassi MZ and Casali P. (2008). Molecular mechanisms of autoimmunity. Autoimmunity, **41** (2), p.123-132.
- Wiegers GJ, Kaufmann M, Tischner D and Villunger A. (2011). Shaping the T-cell repertoire: a matter of life and death. Immunology and Cell Biology, **89**, p.33-39.
- Waterfield M and Anderson MS. (2010). Clues to immune tolerance: the monogenic autoimmune sydromes. Annals of The New York Academy of Sciences Issue: The Year in Human and Medical Genetics, **1214** (2010), p.138 – 155
- Janeway CA, Travers P, Walport M and Shlomchik M. Immunobiology, Sixth Edition, Garland Science.