

# Immunity

Robbins and Cotran  
Chapter 6 pp. 193-240

## Tysabri Recall Batters Biotechs

Peter Kang, 03.04.05

The outlook for the biotech sector suddenly became very bleak this week as shares of **Biogen Idec** tanked after the company halted sales of its Tysabri multiple sclerosis drug, which was deemed by a bevy of Street pundits as a blockbuster drug. The American Stock Exchange Pharmaceutical Index (DRG) logged another modest gain of 1.2% this week, while the Nasdaq Biotechnology Index (NBI) plunged 6.2%.

# Innate immunity

- Present before infection
- Evolved to recognize microbes
- Epithelial barriers, phagocytes, natural killer (NK) cells, and plasma proteins (including complement)

Figure removed for copyright reasons.

Source: Box 6-1 B in [RC]  
Kumar, V., A. K. Abbas,  
and N. Fausto. *Robbins and  
Cotran Pathologic Basis of  
Disease*, 7th ed.  
Philadelphia PA: Elsevier,  
2005. ISBN: 0721601871.

# Adaptive immunity

Figure removed for copyright reasons.

Source: Figure 6-2 in [RC]

# T cells

- T cell receptor (TCR) rearrangement allows for antigen binding
- 95%  $\alpha\beta$  TCR
  - 60% CD4+
  - 30% CD8+
- 2 signals for activation
  - TCR + CD28

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Source: Figure 6-4 B in [RC]

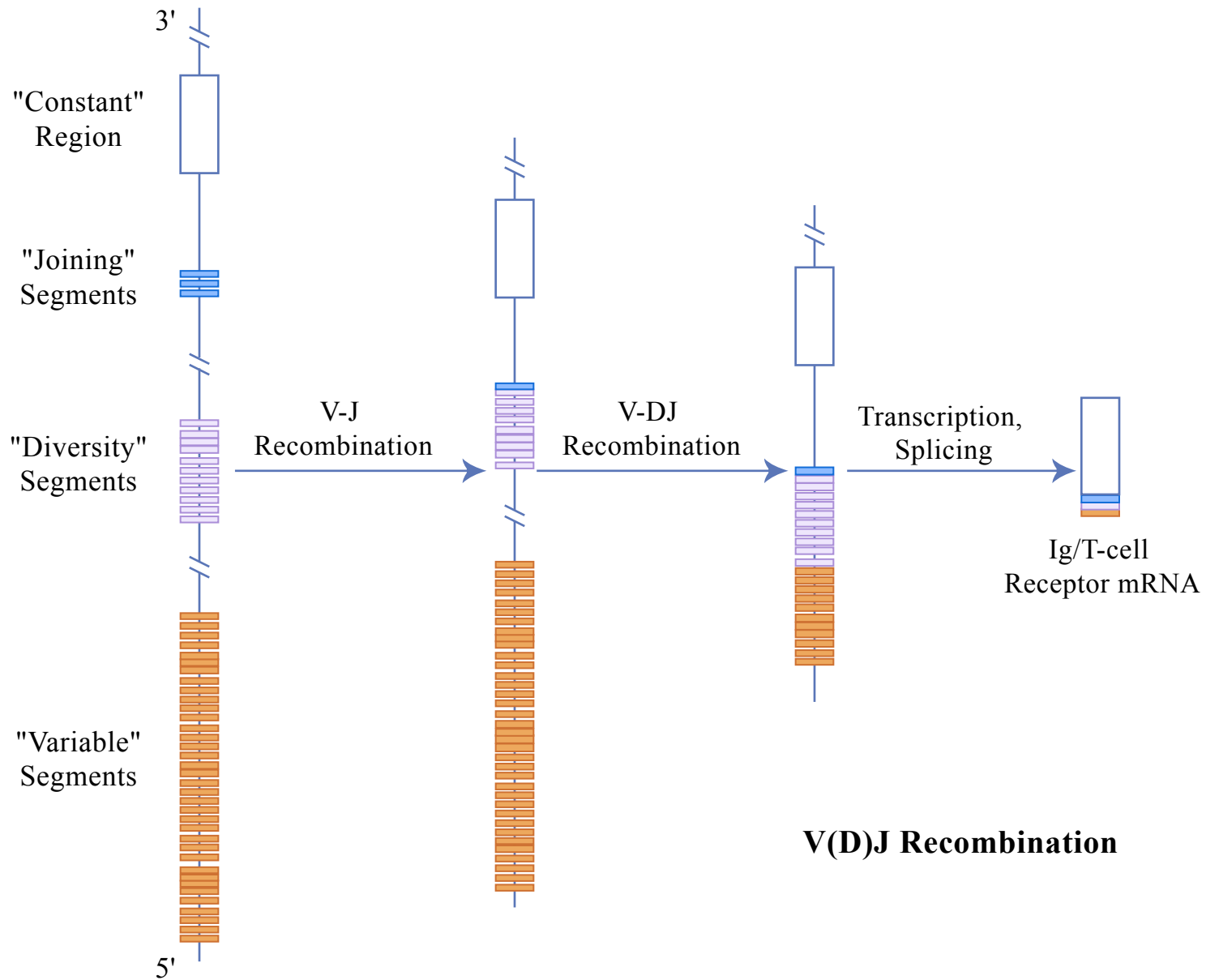


Figure by MIT OCW.

# B cells

- B cell receptor is surface-bound immunoglobulin M (IgM) and IgD
- Activated B cells differentiate into plasma cells and secrete soluble Ig

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Source: Figure 6-5 A, B in [RC]

# Dendritic cells (DC)

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Source: Figure 6-6 in [RC]



# Natural killer (NK) cells

- No TCR or BCR
- CD16+ CD56+
- Large granular lymphocytes
- Can kill tumor cells and viral-infected cells without prior exposure
- Target cells with decreased MHC Class I expression

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Source: Figure 6-8 in [RC]

# Major histocompatibility complex (MHC)

- Present peptide fragments to TCR
- Human leukocyte antigen (HLA)
- Highly polymorphic
- HLA-A, -B, and -C
- HLA-DP, -PQ, -DR

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Source: Figure 6-9 in [RC]

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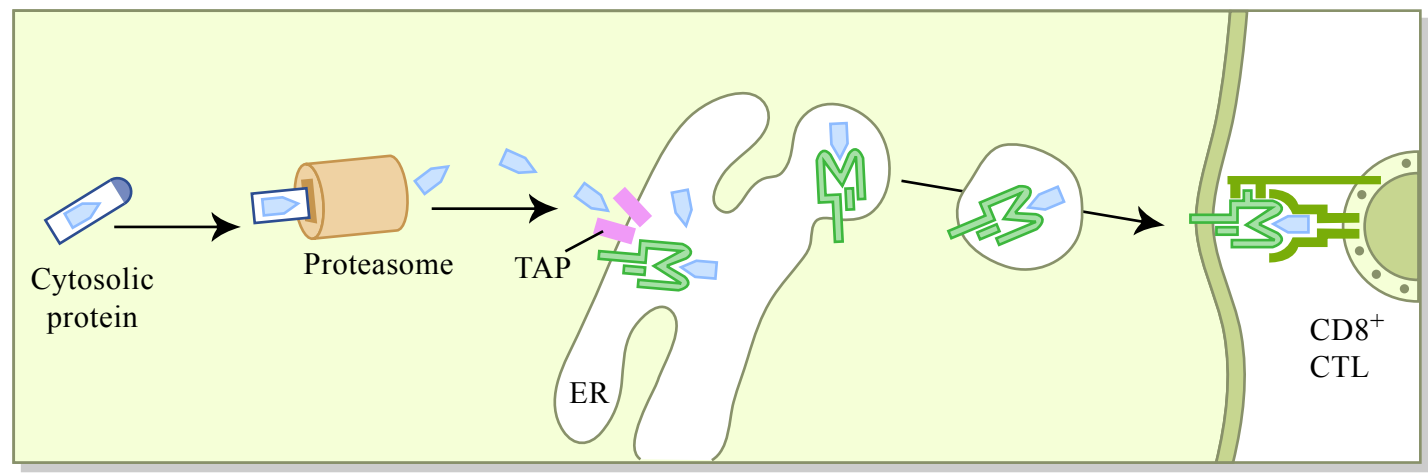
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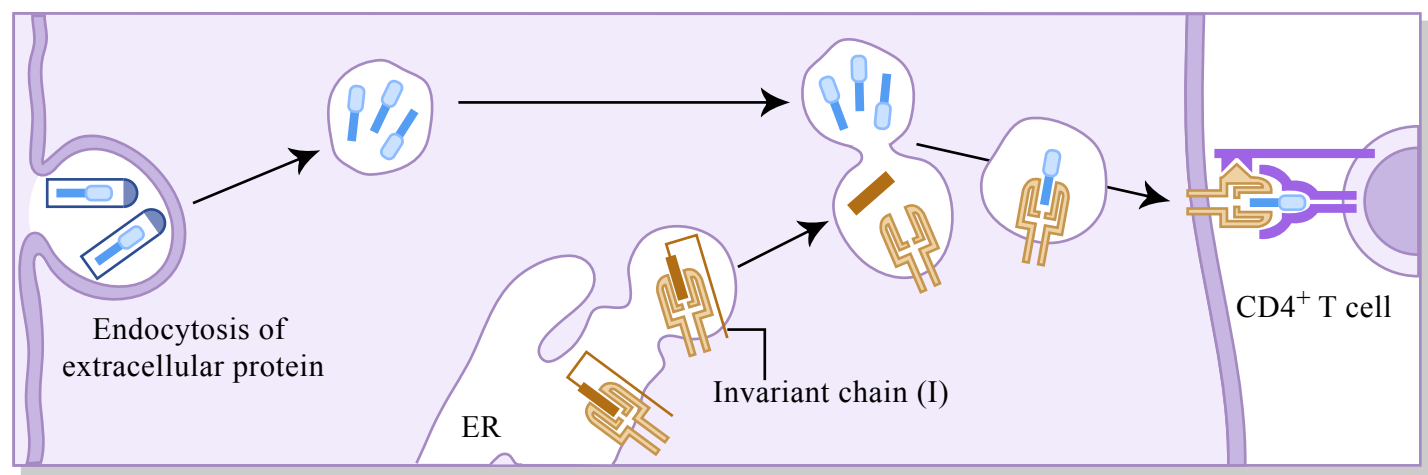
Source: Figure 6-10 in [RC]

Antigen uptake      Antigen processing      MHC biosynthesis      Peptide-MHC association

**Pathways of Antigen Processing & Presentation**



CLASS I MHC PATHWAY



CLASS II MHC PATHWAY

Figure by MIT OCW.

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Source: Figure 6-23 in [RC]

Figure removed for copyright reasons.

Source: Figure 6-27 in [RC]

# Biogen Idec and Elan announce update on TYSABRI ®

- Cambridge, MA and Dublin, Ireland -  
March 3, 2005 - Biogen Idec (NASDAQ:  
BIIB) and Elan Corporation, plc  
(NYSE:ELN) announced today an update on  
the voluntary suspension in the marketing  
of TYSABRI ® (natalizumab), a treatment  
for multiple sclerosis (MS).

# Multiple sclerosis

- Distinct episodes of neurologic deficits, separated in time, due to white matter lesions which are separated in space
  - Gradual progressive disease of the brain and spinal cord
  - Characterized by patches of demyelination of nerve fibers
  - Most common neurological disease of young adults in temperate climates
- Prevalence is 1 in 1,000 in USA
  - female:male around 2:1
  - Whites > Blacks > Asians



# Clinical picture

- Onset of symptoms occurs around age 30
- Often long periods of remission followed by relapses at intervals of months to years
- Early symptoms are mild, frequently affecting vision, but gradually involve the limbs, speech, emotion, sensation and bladder control...ultimately leading to paralysis
- Course of disease is highly variable, with average duration > 25 years

# Pathogenesis

- Loss of myelin (oligodendrocytes) from nerve fibers in the CNS
- Effect of demyelination is inability to transmit nerve impulses
- Demyelination occurs in foci or plaques
- Characterization by perivascular cuffing of mononuclear cells
- Acute lesions have CD4+ T cells and reactive microglial cells
  - Active plaques have myelin breakdown, PAS+ macrophages
  - Inactive plaques have few oligodendrocytes, increased astrocytes, with most axons intact

# Preventing immune homing

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Source: Figure 2-6 in [RC]

# Natalizumab (TYSABRI)

- Recombinant humanized MAb against  $\alpha_4$  integrin
- The  $\alpha_4$  subunit of  $\alpha_4\beta_1$  and  $\alpha_4\beta_7$  are expressed on all leukocytes except PMNs
- Bind to VCAM-1 (CNS) and MadCAM-1 (GI tract)
- Clinically shown to reduce relapses with or without recombinant IFN- $\beta$  (AVONEX)
- Indications include MS, Crohn's disease and rheumatoid arthritis

# Suspension of TYSABRI

- On February 28, 2005, the companies reported that they had suspended marketing of TYSABRI based on one confirmed case and one suspected case of progressive multifocal leukoencephalopathy (PML), a rare and frequently fatal, demyelinating disease of the central nervous system. The investigator has now changed the status of the second case from suspected to confirmed. The companies are continuing to examine these two cases. As indicated in the announcement on February 28, 2005, both patients received more than two years of TYSABRI therapy in combination with AVONEX<sup>®</sup> (Interferon beta-1a).