GSK
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# Transplant Immunology

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Cancer Center™

# Introduction to transplantation

**Graft:** Cells, tissues, or organs for implantation or transplantation.

**Transplantation:** The transfer of a graft from donor to host/recipient.

**Autologous/Syngeneic:** A procedure in which cells are removed, stored, and later given back to the same person (or genetically identical person).

From Greek: *auto* (self) + *logos* (study)

**Xenogeneic:** Graft derived from an animal of a different species than the recipient (e.g. animal into human).

# Allogeneic transplantation

**Allogeneic:** Graft derived from a genetically non-identical donor of the same species.

From Greek: *allogenes*; *allos* (other, another different) + *genes* (born)

**Alloresponse:** immune response to antigens from another individual or species (alloantigens or xenoantigens).

**Graft rejection (host-versus-graft):** Immune cells from the host/recipient cause destruction of the graft.

**Graft-versus-host-disease:** Immune cells in the donor graft cause inflammation and destruction of the host/recipient tissues.

# Alexis Carrel (1873-1944)

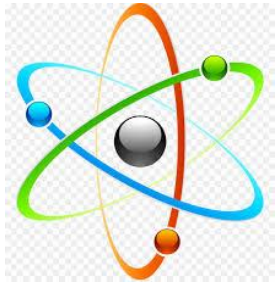
**Nobel Prize in Physiology or Medicine 1912**

"in recognition of his work on vascular suture and the transplantation of blood vessels and organs"

"Having grown up watching his mother, a professional embroiderer, Dr. Carrel realized the method of suture might be made vastly more precise through the use of tiny needles and very fine thread, and after studying with one of the finest embroiderers in Lyons, France, in the mid 1890s, Dr. Carrel was skilled in creating stitches so small that they were invisible on both sides of a sheet of paper."

*http://www.nobelprize.org/nobel_prizes/medicine/laureates*

# Bone marrow transplant history – don't quote me




1922: shielding legs protects guinea pigs against TBI (J Fabricius-Moller, Denmark)
1949: shielding spleen or femoral head protects mice against TBI (Leon Jacobson, U of C)
1951: IP injection of spleen cells (L Jacobson) and IV injection of marrow (Egon Lorenz, NCI) protects against TBI
1955: van Bekkum and colleagues report on "secondary" syndrome after transfer of allo marrow
1957: First allogeneic BMT reported – leukemia (ED Thomas, Cooperstown, NY)
1958: First successful allogeneic BMT, radiation accident (Georges Mathé, France*)
1959: Twin transplants for leukemia – engrafted, but failed (Thomas)
1968: First matched related donor transplant, immunodeficiency (Good, Minnesota)
1971: Post-transplant cyclophosphamide, studied in rejection, can prevent GVHD (Santos, Hopkins)
1973: First unrelated donor transplant for SCID (O'Reilly, MSKCC)
1974: Mitigation of secondary disease of allogeneic mouse radiation chimeras by modification of the intestinal microflora (van Bekkum)
1977: First large trial (100 patients) (ED Thomas)
1988: First cord blood transplant – Fanconi anemia (Gluckman, France and Broxmeyer, USA)
1995: Post-transplant cyclophosphamide can prevent graft rejection
2002: Successful transplantation of mismatched allografts using PT-Cy (Fuchs and Luznik, Hopkins)

# Immune cells in transplantation

- T cells: CD4 and CD8
- B cells
- Natural Killer (NK) cells
- Antigen presenting cells: dendritic cells, monocytes, macrophages, B cells, or host tissues
- Other cells: gamma-delta T cells, Innate lymphoid cells, others?

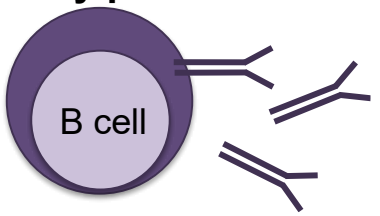
*BMT: A clinical therapy and an experimental model.*

# The most common form of transplant

**Blood transfusion** is required every 2 seconds in the US, with a total of 21 million blood components transfused per year. (2016)

"During the 20th century, knowledge of blood groups grew …to nearly 300 discrete antigens." *Reid, ME. Hematology Am Soc Hematol Educ Program. 2009.*

Transfusion of blood cells expressing antigens foreign to the host/recipient leads to **graft rejection** via **Antibody production**



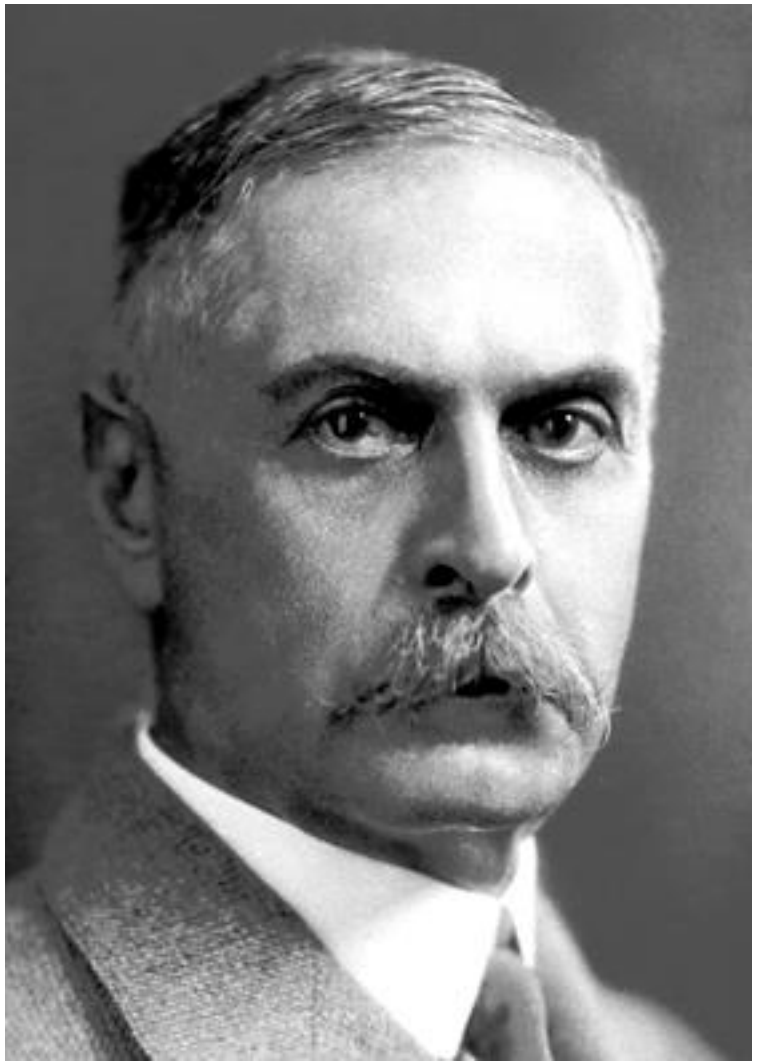

*http://www.redcrossblood.org/learn-about-blood/blood-facts-and-statistics*

# Karl Landsteiner (1868-1943)

**The Nobel Prize in Physiology or Medicine 1930**

"for his discovery of human blood groups"
- Discovery of the ABO system

"…Landsteiner observed that when…blood serum of a human was added to normal blood of another human the red corpuscles in some cases coalesced into larger or smaller clusters."



# Transplantation antigens

**ABO antigens** - carbohydrate antigens; allelic differences in glycosyltransferase, which modify the H antigen; IgM

**Rh antigens** - hemolytic disease of newborn; IgG

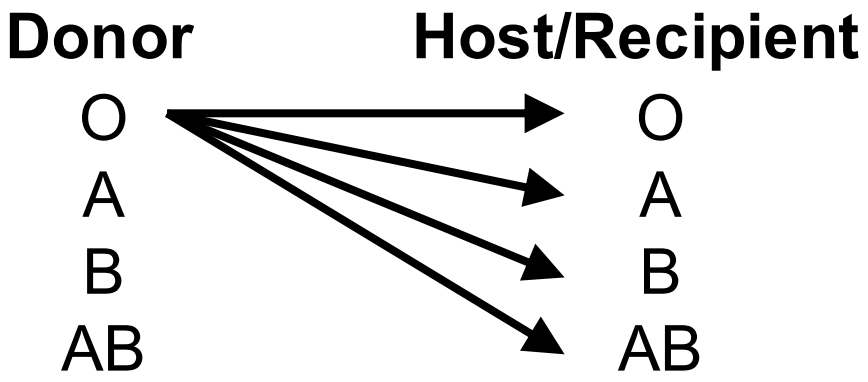
**Major histocompatibility complex** (MHC) - human leukocyte antigens (HLA) in humans

**Minor histocompatibility antigens** - polymorphic peptides derived from non-MHC proteins that can be presented by MHC to activate T cells and drive graft rejection

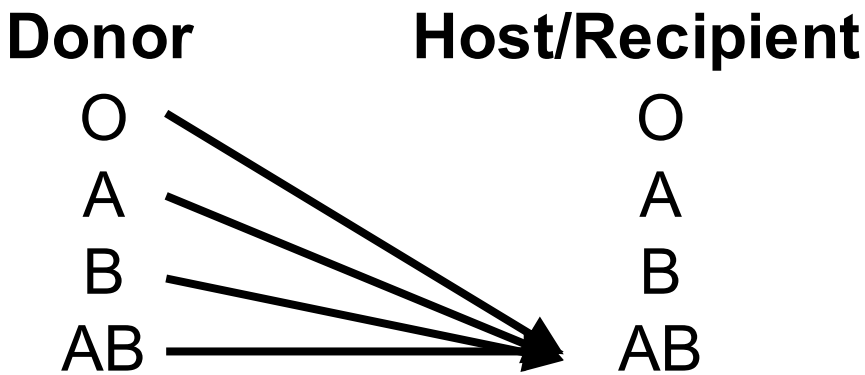
# Preventing graft rejection: ABO antigen matching in blood transfusion

**Group A** – has only the A antigen on red cells
**Group B** – has only the B antigen on red cells
**Group AB** – has both A and B antigens on red cells
**Group O** – has neither A nor B antigens on red cells

Group O: Universal donor




Group AB: Universal recipient

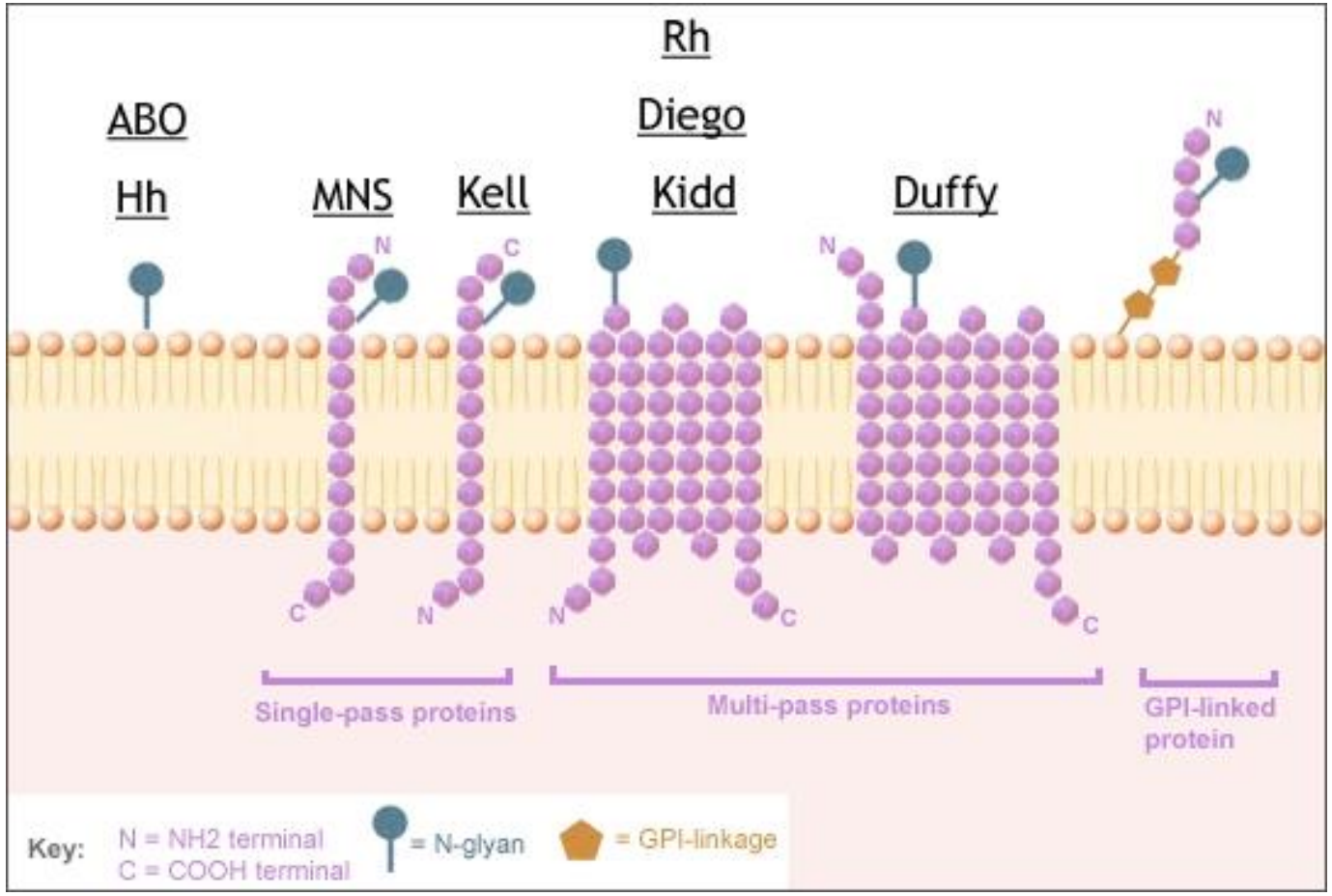



*As a practical consequence, every hospital has type O blood on hand.*

*http://www.redcrossblood.org/learn-about-blood/blood-types*

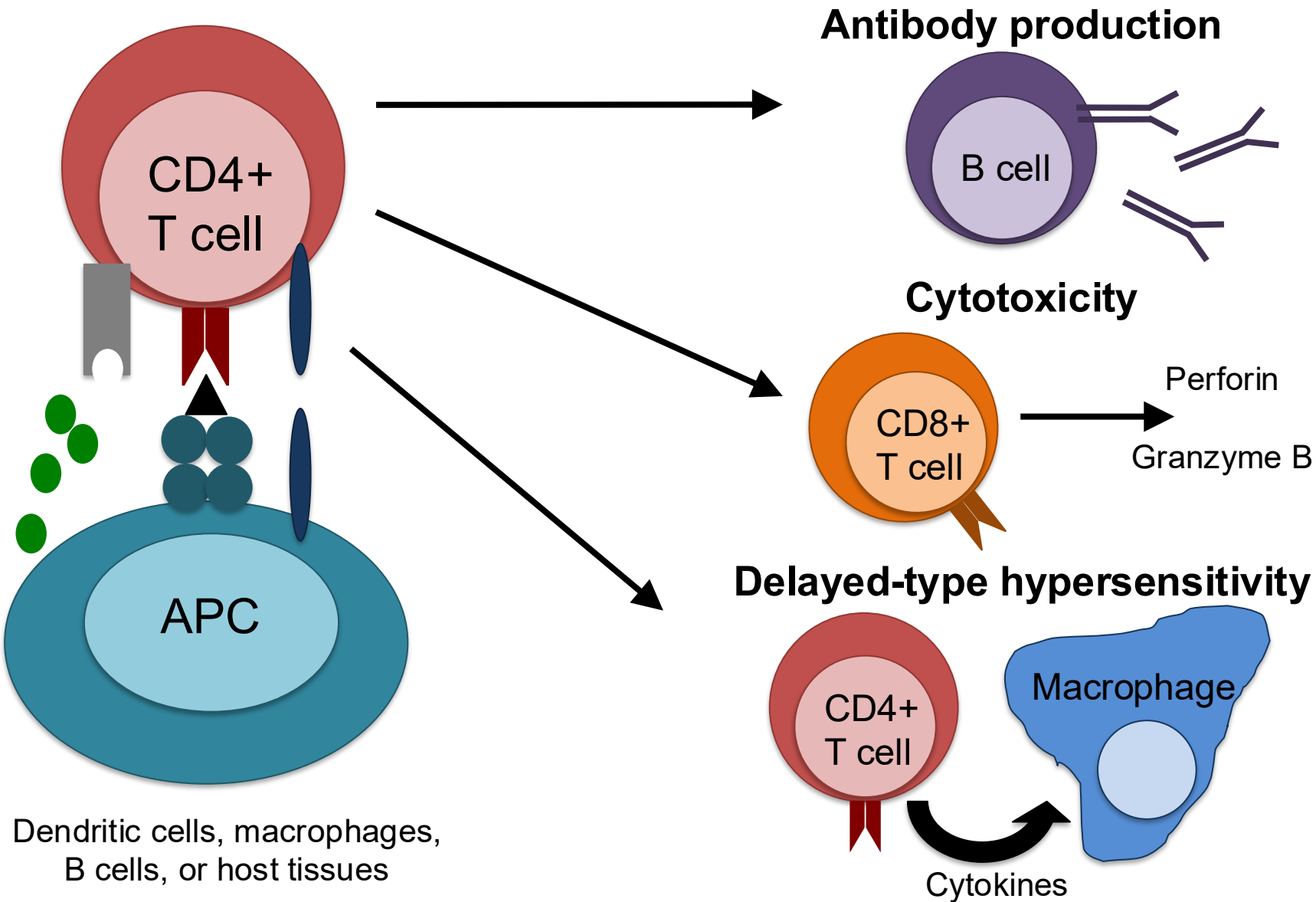
# Beyond ABO matching

30 known human blood group system genes




*1) International Society of Blood Transfusion (ISBT); 2016.*
*2) Dean L. Blood Groups and Red Cell Antigens [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2005. Chapter 2, Blood group antigens are surface markers on the red blood cell membrane.*

# Alloreactivity leading to graft rejection



# Hyperacute rejection of solid organs

- graft loss in the first 48h
- preformed Abs in recipient's serum against graft's endothelial cells
- low affinity IgM against ABO blood group antigens or galactose-α-1-3-galactose (xenotransplantation)
- high affinity IgG antibodies against HLA class I antigens:

  - 1% of population and 30% renal transplant patients

  - due to blood transfusions, pregnancies, failed allografts and unknown factors

  - pre-transplant cross match of patient's serum and donor lymphocytes

# Acute rejection

- Graft loss between 5-90 days after transplantation
- Effector cells: CD4 and CD8 T cells, macrophages
- Increased expression of chemokines, adhesion molecules, and cytokines (IL-2, IFN$\gamma$, TGF$\beta$)
- Poor graft survival is associated with anti-MHC class II antibodies

# Chronic rejection

- Multifactorial etiology, including antibody-mediated rejection, TGF$\beta$ causing fibrosis

# T Cells are Essential for Organ Rejection

- In mice and humans, no T cells = no rejection*
- Conversely, very few T cells are sufficient for rejection
- Agents that block T cell activation prevent rejection
- Generation of IgG (which is responsible for antibody-mediated rejection) is dependent on T cell help
- *Exception: Pre-formed antibodies (ABO, HLA)

Acknowledgments: Fadi Lakkis, M.D.

# T Cells and NK cells contribute to hematopoietic (marrow) graft rejection

- MHC-mismatched marrow/HSCs: Both T and NK cells contribute to graft rejection in experimental models
  - missing self
  - hybrid resistance
- MHC-matched marrow/HSCs: T cells mediate rejection, NK cells do not
- In humans, donor-specific anti-HLA antibodies can lead to graft rejection
- Donor T cells contribute to overcoming host rejection

# T-cell-mediated graft rejection

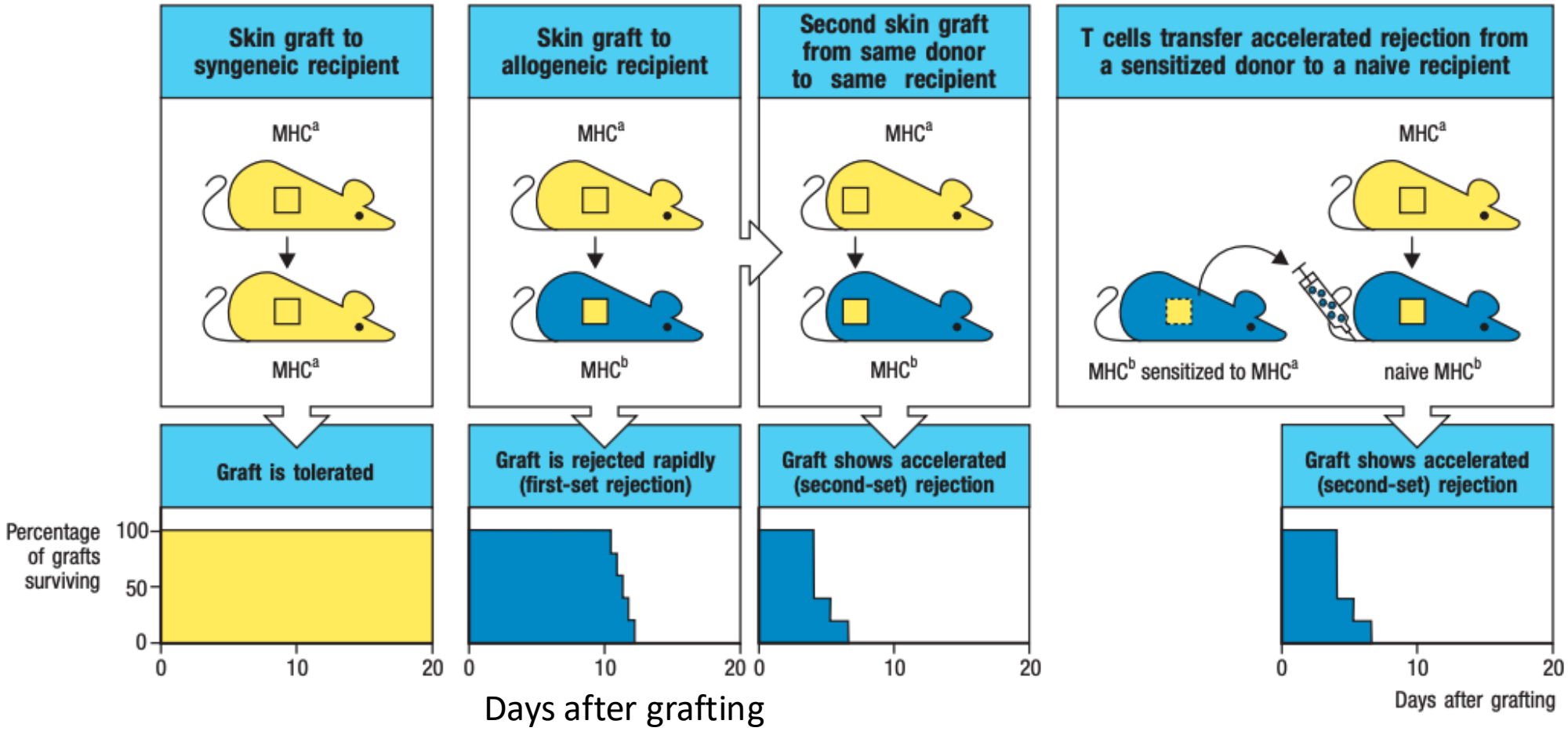
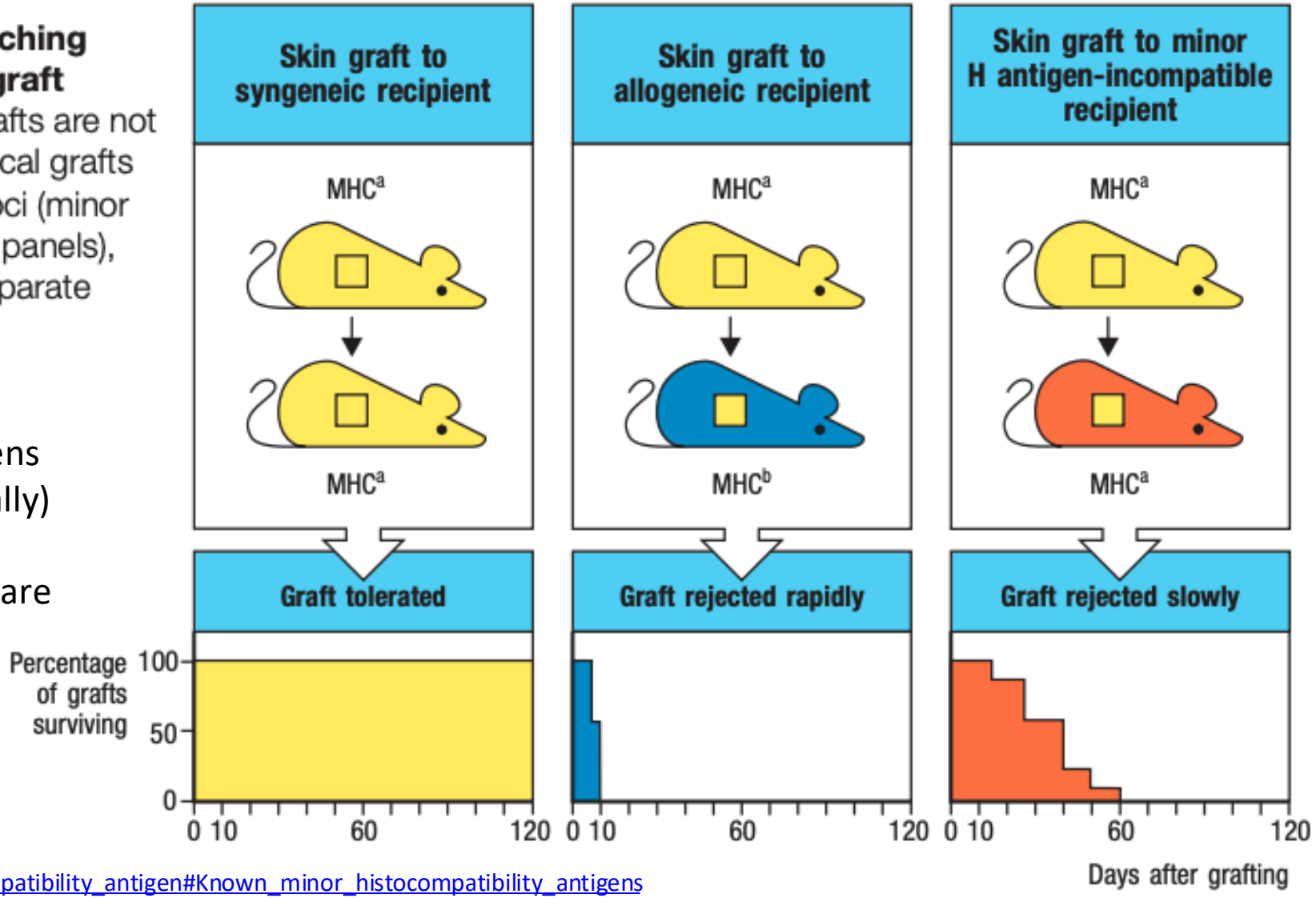



**Fig. 15.45 Skin graft rejection is the result of a T-cell-mediated anti-graft response.** Grafts that are syngeneic are permanently accepted (first panels), but grafts differing at the MHC are rejected about 10–13 days after grafting (first-set rejection, second panels). When a mouse is grafted for a second time with skin from the same donor, it rejects the second graft faster (third panels). This is called a second-set rejection, and the accelerated response is MHC-specific; skin from a second donor of the same MHC type is rejected equally fast, whereas skin from an MHC-different donor is rejected in a first-set pattern (not shown). Naive mice that are given T cells from a sensitized donor behave as if they had already been grafted (final panels).

# Major and minor antigens can lead to rejection

**Fig. 15.46 Even complete matching at the MHC does not ensure graft survival.** Although syngeneic grafts are not rejected (left panels), MHC-identical grafts from donors that differ at other loci (minor H antigen loci) are rejected (right panels), albeit more slowly than MHC-disparate grafts (center panels).




Minor histocompatibility antigens (originally defined experimentally)

They are SNPs whose proteins are presented on MHC.

https://en.wikipedia.org/wiki/Minor_histocompatibility_antigen#Known_minor_histocompatibility_antigens

# Peter Medawar (1915-1987)

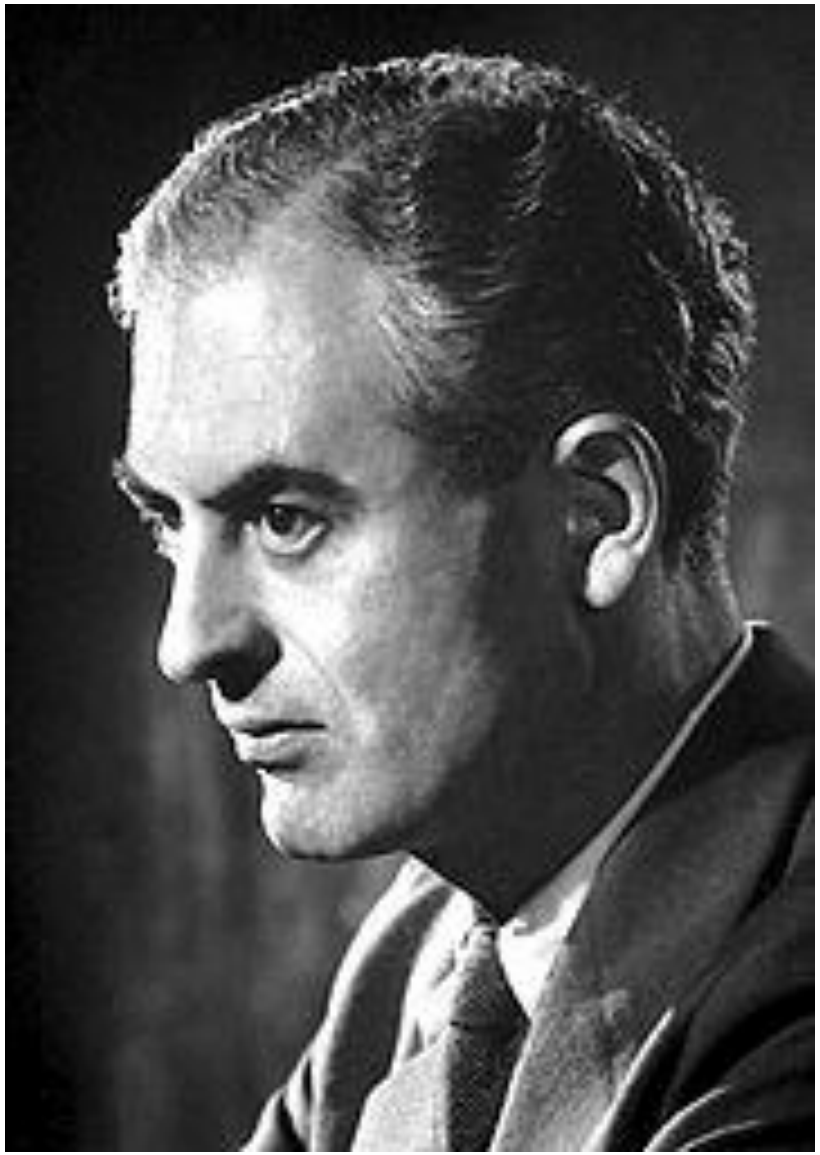
**Nobel Prize in Physiology or Medicine 1960 with Sir Frank Macfarlane Burnet**

*assist to Rupert Billingham and Leslie Brent

“for discovery of acquired immunological tolerance"

“Grafting of normal tissue was systematically studied by Medawar who was able to show among other things that the graft reaction is an immunity phenomenon … and that the cellular immunological pattern is an expression of the individual genetic constitution”

- Fetal development of immunologic tolerance



# Quantitative studies on tissue transplantation immunity. II. The origin, strength and duration of actively and adoptively acquired immunity

By R. E. Billingham,* L. Brent,† and P. B. Medawar, F.R.S.

*Department of Zoology, University College, University of London*

(*Received* 7 *April* 1954)

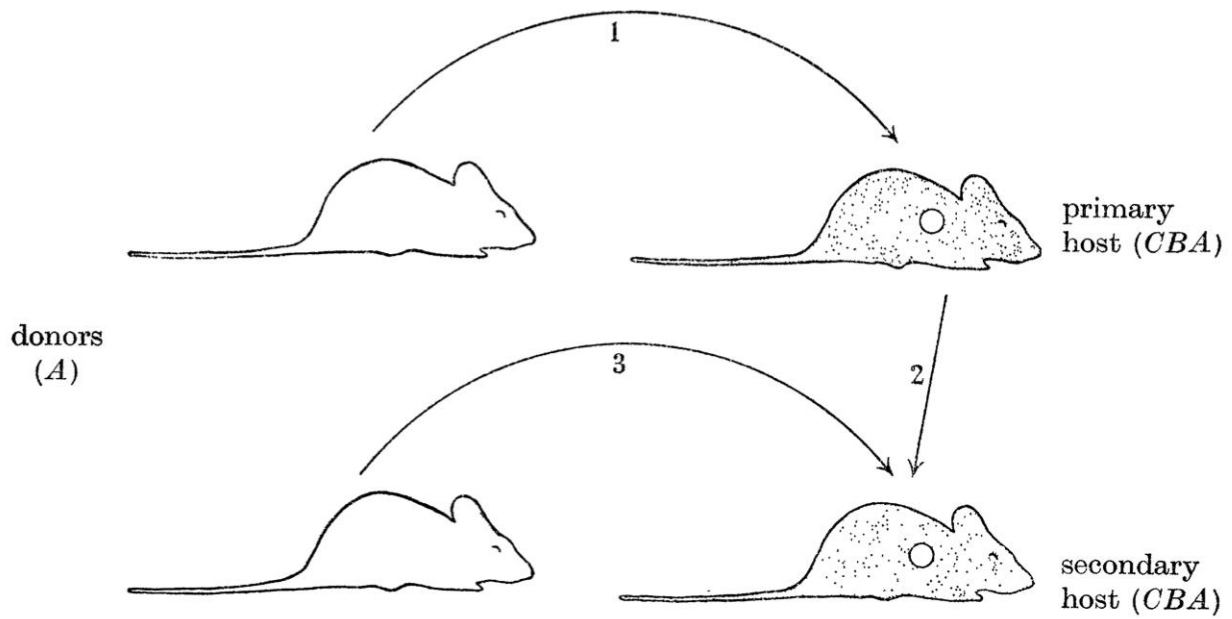



Figure 1. Illustrating the conduct of an experiment on transferred immunity. The primary host (*CBA* strain) is actively immunized to a skin graft (or other tissues) from an *A*-line donor (1). When immunity has developed, lymph nodes (or body fluids, etc.) are transferred from primary to secondary host (also of *CBA* strain) (2). The secondary host is then challenged with a graft of *A*-line skin (3). If immunity has been transferred, the secondary host behaves as if it had itself been actively immunized.

# QUANTITATIVE STUDIES ON TISSUE TRANSPLANTATION IMMUNITY

## III. ACTIVELY ACQUIRED TOLERANCE

By R. E. BILLINGHAM,* L. BRENT and P. B. MEDAWAR, F.R.S.

*Department of Zoology, University College London*

(*Received* 2 *May* 1955)

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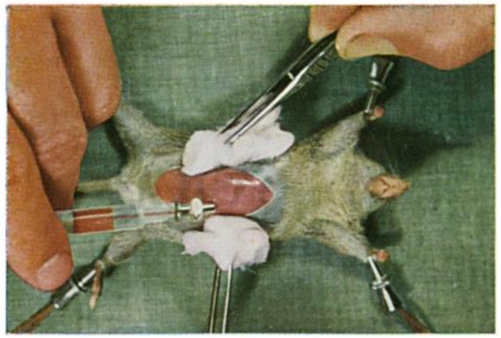

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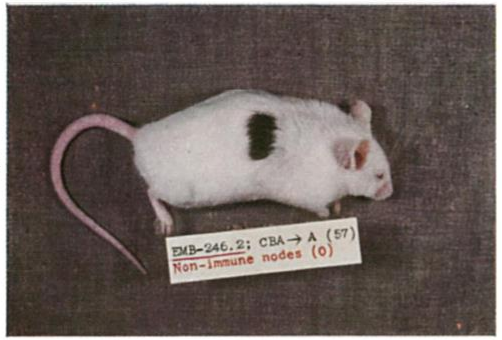


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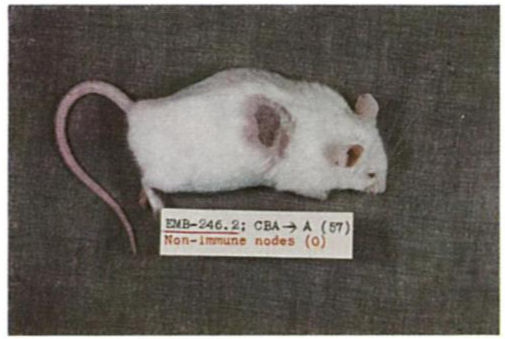


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FIGURE 1. The technique of injecting mouse embryos through the body wall without laparotomy. The skin has been opened down the ventral midline and gently parted; 17-day embryos have been brought into view and are being injected with a suspension of adult tissues through a fine needle attached to a micrometer-controlled syringe (§3·2.)

FIGURE 2. The appearance of an *A*-line skin homograft 11 days after transplantation to a normal adult *CBA* mouse. Breakdown is complete, and the graft is drying in air to form a scab. Contrast figures 3 to 6. (§3·2.)

FIGURE 3. *A*-line skin homografts on a group of tolerant adult *CBA* mice belonging to a single litter, the members of which had been injected *in utero* with an adult *A*-line tissue suspension. Each mouse bears two homografts, that on the right transplanted 83 days beforehand, that on the left 50 days later. The grafts are perfectly normal. Contrast figure 2. (§3·2.)

FIGURES 4, 5. A *CBA* skin homograft 57 days after transplantation to a tolerant adult *A*-line mouse which had been injected during uterine life with an adult *CBA* tissue suspension. The graft is shown before (figure 4) and after (figure 5) clipping away its pelt of normal agouti hairs: it has been fully incorporated into the skin of its host. (For the later history of this graft, refer to figure 15.) (§3·2.)

FIGURE 6. An *AU* (black-haired) skin homograft 52 days after transplantation to an *A*-line mouse which had been injected *in utero* with whole blood from an adult *AU* donor. (§3·2.)

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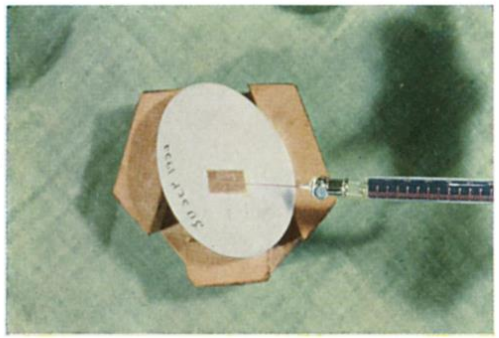

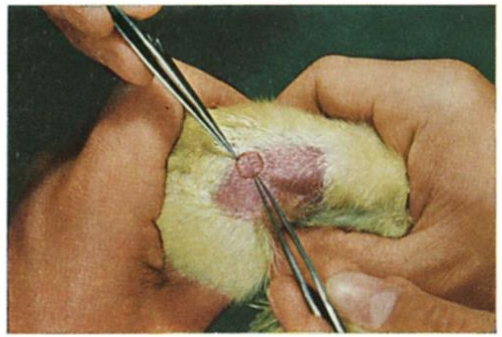

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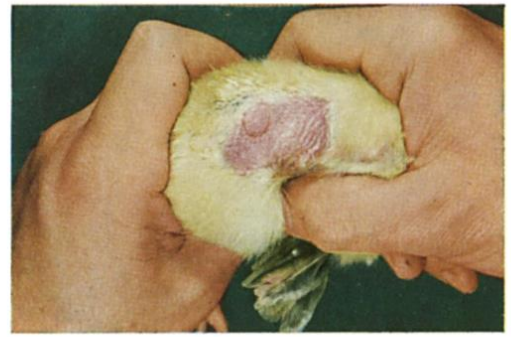

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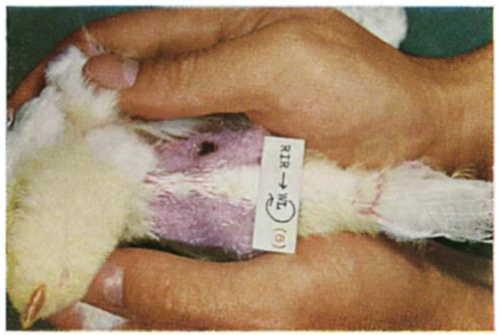

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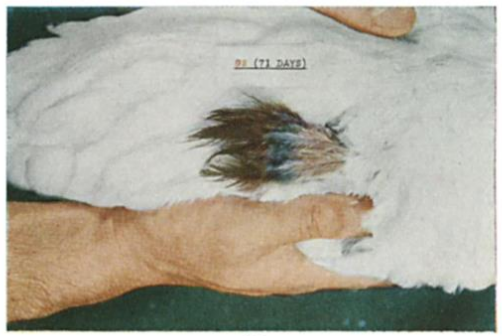

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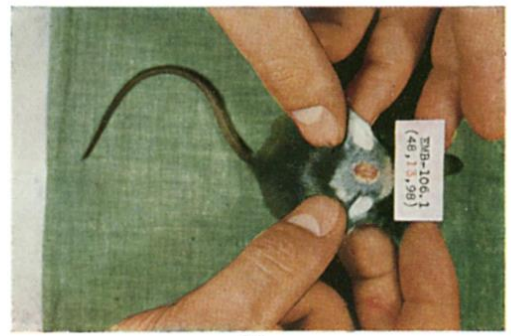

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FIGURE 7. The technique of intravenous injection of chicken embryos. A rectangle of shell lying over a prominent chorio-allantoic vein has been removed and the shell membranes have been made transparent by the application of paraffin oil. A fine needle mounted on a tuberculin syringe has been inserted coaxially with the vein and in the direction of blood flow. For the tolerance induced by this procedure, see figure 11. (§3·3.)

FIGURES 8, 9. The 'test operation' in two-week-old chicks: a skin graft is being put into place on a muscular bed lying dorso-laterally and anteriorly to the sacrum (figure 8); it is then held in place by a film of plasticized collodion applied in solution and allowed to dry (Cannon & Longmire 1952). (§3·3.)

FIGURE 10. The appearance of a skin autograft, and of a skin homograft from a 2-week-old Rhode Island Red chick, 8 days after transplantation to a normal 2-week-old White Leghorn chick. The autograft on the animal's left side has healed soundly, and its outline is difficult to discern. The homograft, on the right side, has broken down and formed a scab. Contrast figure 11. (§3·3.)

FIGURE 11. A skin homograft 71 days after transplantation from a 2-week-old Rhode Island Red chick to a 2-week-old White Leghorn chick which had been injected with 0·2 ml. of its future skin donor's blood on the 11th day of embryonic life. The graft has differentiated normally. (§3·3.)

FIGURE 12. The specificity of acquired tolerance. A *CBA* mouse, tolerant of *A*-line tissues, carries two *A*-line homografts, of 48 and of 98 days' standing respectively. Thirteen days before this photograph was taken, a skin homograft from an *AU* donor had been transplanted between the two grafts already in place. The *AU* homograft is totally destroyed. (§4·2.)

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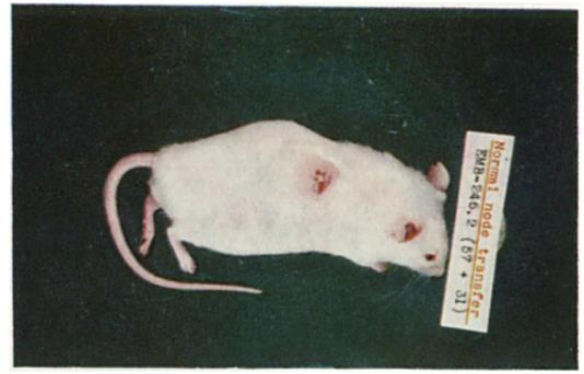


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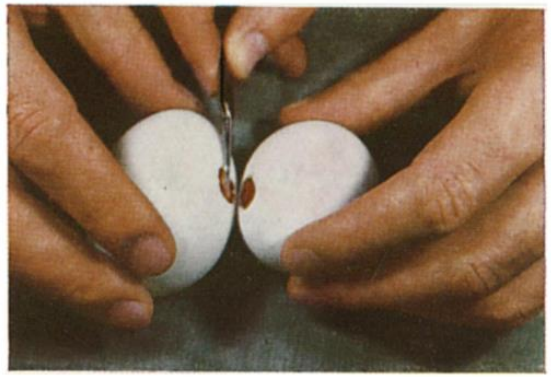

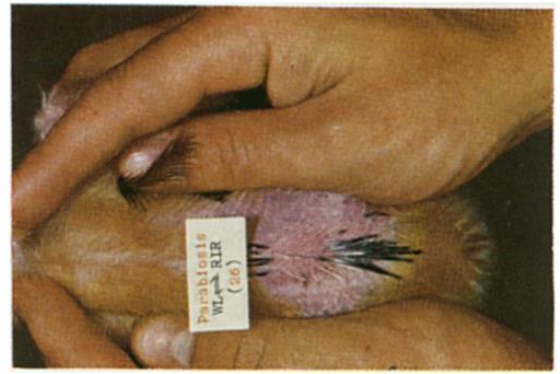


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FIGURES 13, 14. Abolition of tolerance by the implantation of 'immune' node cells. Seventy-seven days after the transplantation of an *A*-line skin homograft to a fully tolerant *CBA* host, the host was injected intraperitoneally with cells expressed from the regional lymph nodes of normal *CBA* mice which had been actively immunized against *A*-line skin. The hitherto tolerated *A*-line homograft became grossly inflamed within 8 days of the inoculation (figure 13) and its breakdown was complete in 12 days (figure 14). Contrast figure 15. (Table 8*A* and §6).

FIGURE 15. Abolition of tolerance by the implantation of normal nodes (contrast figures 13, 14). The tolerant *A*-line mouse illustrated in figures 4 and 5, carrying a *CBA* homograft of 57 days' standing, was inoculated with cells expressed from the lymph nodes of normal *A*-line mice. The present photograph illustrates the appearance of the homograft 31 days later: total breakdown. (Table 8*B* and §6.)

FIGURE 16. The technique of artificial synchorial twinning ('parabiosis') in 10- to 11-day-old chicken embryos. The shell and shell membranes have been removed over a circular area in both eggs to expose the chorio-allantoic membranes. The bared areas are being brought face to face, and a plasma bridge is being inserted between them to make a vascular connexion. (§7.)

FIGURE 17. Illustrating the perfectly normal differentiation of a White Leghorn skin homograft 26 days after transplantation to a Rhode Island Red host with which the graft donor had been in parabiotic union. The graft has healed soundly and White Leghorn feathers are beginning to grow. Contrast the heterograft illustrated by figure 20. (§7.)

FIGURES 18, 19. Homografts on birds which had been synchorially united to their future donors during embryonic life. Figure 18 shows a Rhode Island Red graft 282 days after transplantation to its 6-day-old White Leghorn parabiotic partner; figure 19 shows a White Leghorn graft 240 days after transplantation to its newly hatched Rhode Island Red parabiotic partner. (Table 9, §7.)

FIGURE 20. A chicken skin heterograft 26 days after transplantation to a newly hatched duck with which it had been in synchorial union during the latter half of embryonic life. Contrast figure 17. The heterograft survives, but it is swollen and inflamed, and imperfectly differentiated. (§8).

# Immune tolerance

**Tolerance** is the failure to respond to an antigen. *Janeway, Immunobiology.*

Inoculation of mice and chickens during the fetal life created lifelong specific tolerance, but preserves acquired immunity against other antigens. *Billingham, Brent and Medawar, (1953), p.1409.*

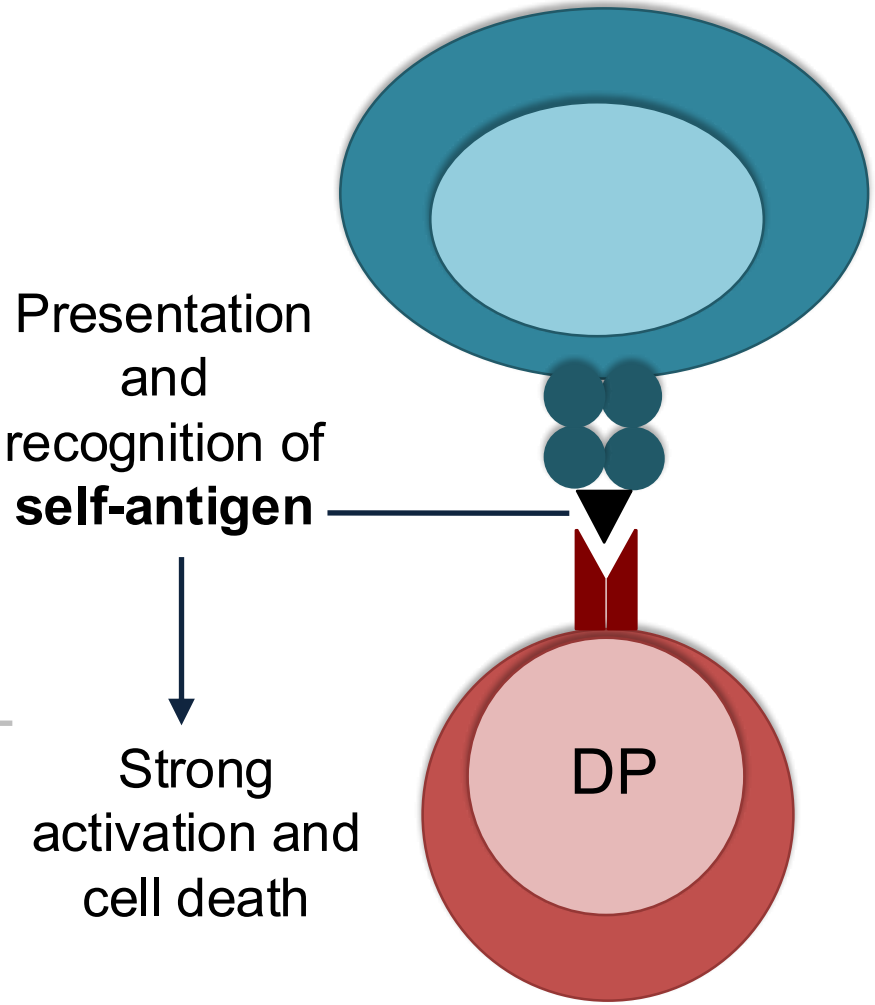
Mechanisms of tolerance:

- Central, thymic negative selection
- Peripheral

- apoptosis post-activation (Fas/FasL), exhaustion?
- Anergy
- Suppression: regulatory T cells
- Ignorance

# Mechanisms of tolerance

1. Central tolerance: deletion of autoreactive T cells in the thymus
2. Peripheral: apoptosis post-activation; T cell exhaustion
3. Anergy induced by TCR recognition in the absence of costimulation
4. Suppression by regulatory T cells/myeloid suppressor cells/Bregs
5. Ignorance or physical separation from antigen



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2. Peripheral: apoptosis post-activation; T cell exhaustion
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4. Suppression by regulatory T cells
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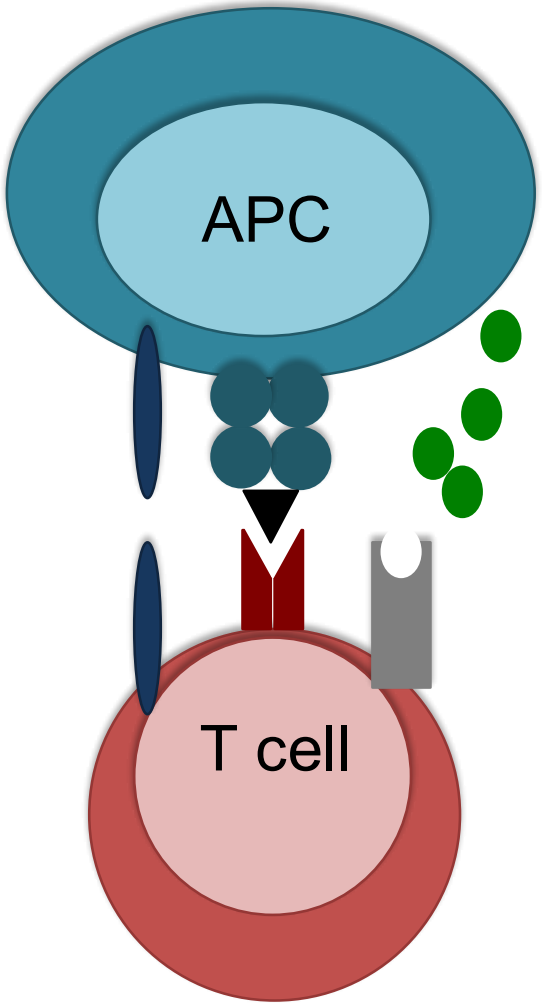
TCR ligation and costimulation

Apoptosis



# Mechanisms of tolerance

1. Central tolerance: deletion of autoreactive T cells in the thymus
2. Peripheral: apoptosis post-activation
3. Anergy induced by TCR recognition in the absence of costimulation
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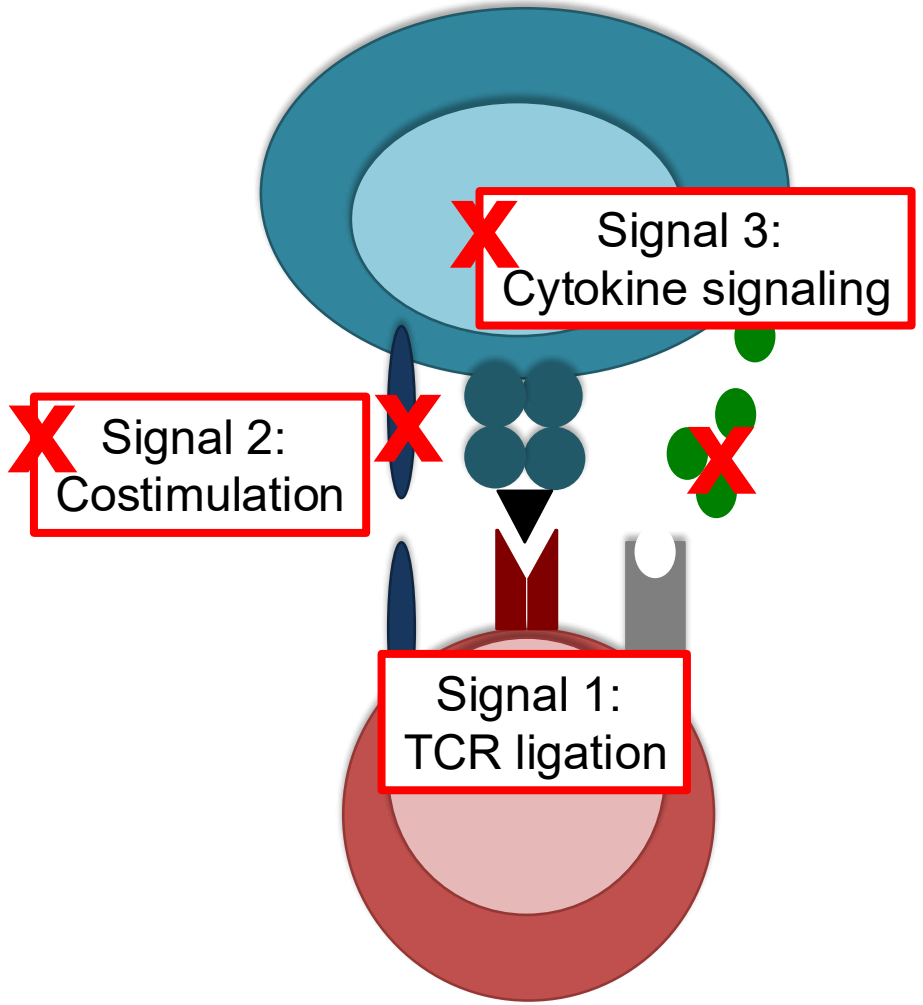
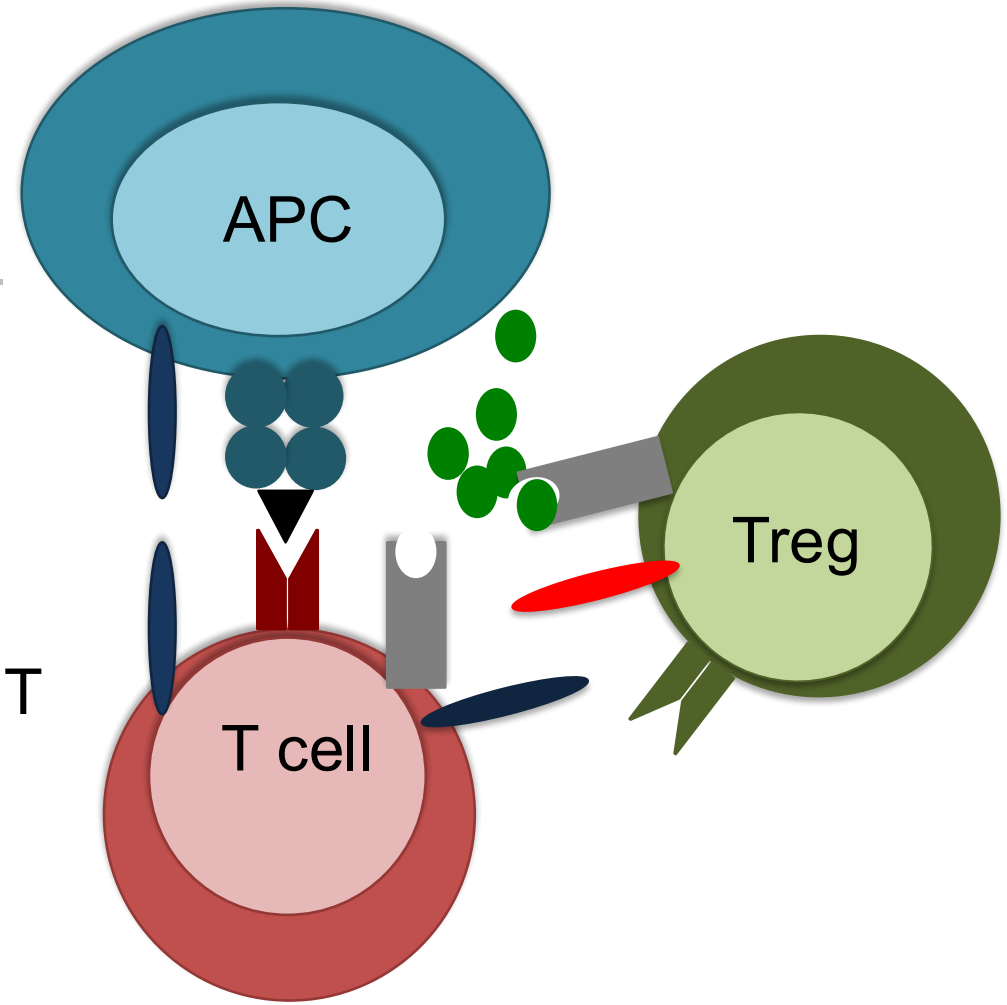
5. Ignorance or physical separation from antigen



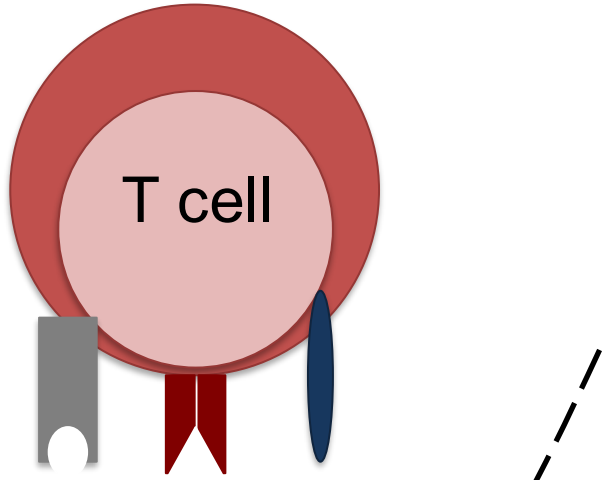
# Mechanisms of tolerance

1. Central tolerance: deletion of autoreactive T cells in the thymus
2. Peripheral: apoptosis post-activation
3. Anergy induced by TCR recognition in the absence of costimulation
4. Suppression by regulatory T cells (or other suppressor cells)
5. Ignorance or physical separation from antigen



# Mechanisms of tolerance

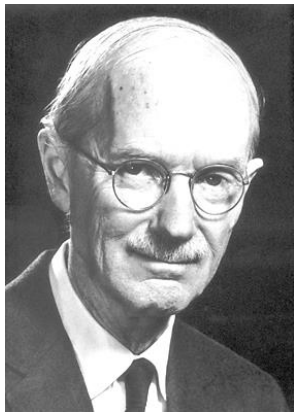
1. Central tolerance: deletion of autoreactive T cells in the thymus
2. Peripheral: apoptosis post-activation
3. Anergy induced by TCR recognition in the absence of costimulation
4. Suppression by regulatory T cells
5. Ignorance or physical separation from antigen




Exclusion from immune privileged sites such as eyes and testes

# The Nobel Prize in Physiology or Medicine 1980

"for their discoveries concerning genetically determined structures on the cell surface that regulate immunological reactions"

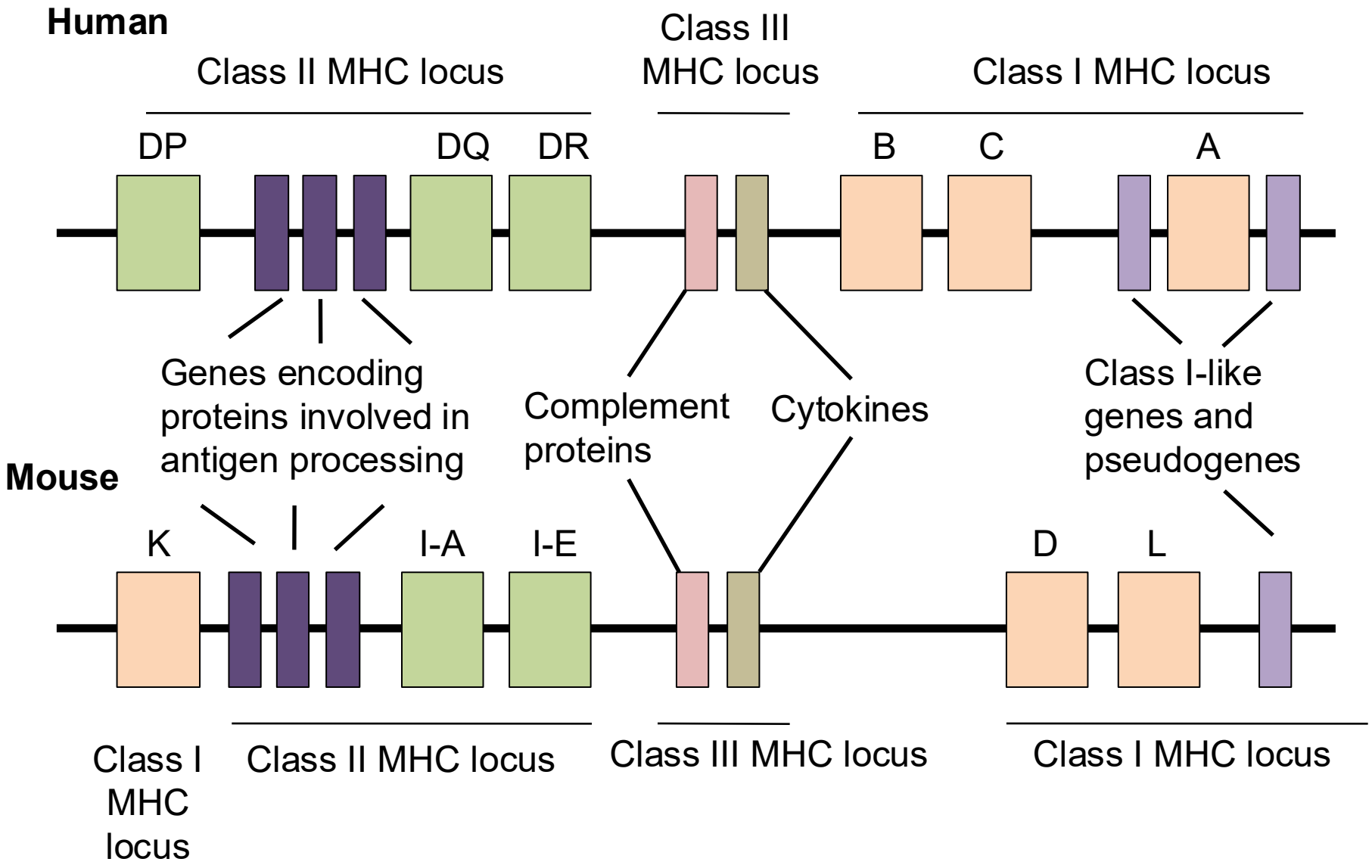


**George Snell** (1903-1996) discovered the genetic factors that determine the possibilities of transplanting tissue from one individual to another. It was Snell who introduced the concept of H antigens.

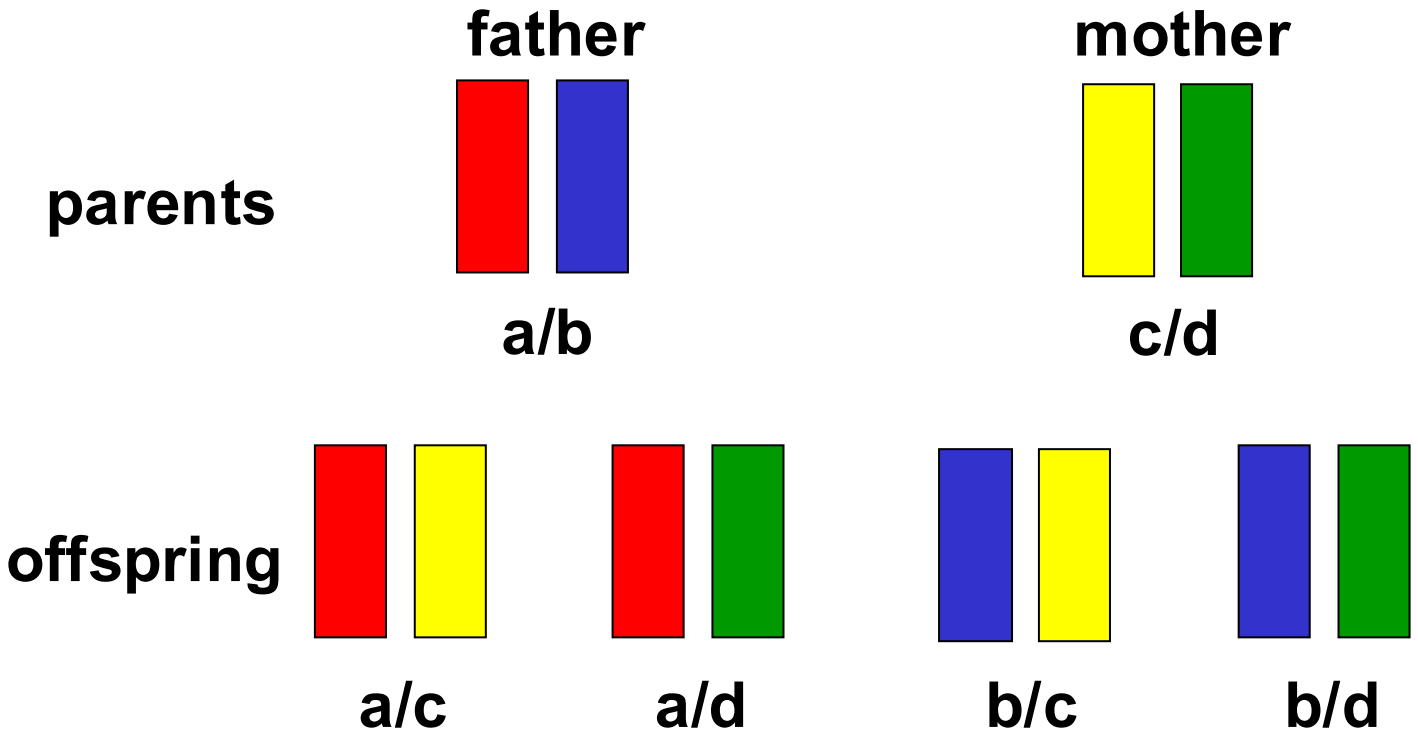
**Jean Dausset** (1916-2009) demonstrated the existence of H antigens in man and elucidated the genetic factors regulating their formation.

**Baruj Benacerraf** (1920-2011) showed that genetic factors intimately related to the genes that determine an individual's unique constitution of H antigens actually regulate the interaction among the various cells belonging to the immunological system…

# Schematics of human and mouse MHC loci



# Inheritance patterns of codominant HLA alleles




| Probability of matching | # matched haplotypes 0 | 1 | 2 |
|---|---|---|---|
| Parent → child | 0 | 100 | 0 |
| Sib → sib | 25 | 50 | 25 |

# Donors for Allogeneic Bone Marrow Transplantation

- Only 1/3 of patients have an HLA-identical sibling
- 50-80% have a matched unrelated donor
- Mean interval from search to transplant: 4 months
- <20% of donor searches result in a transplant

The NEW ENGLAND JOURNAL of MEDICINE

Special Article

# HLA Match Likelihoods for Hematopoietic Stem-Cell Grafts in the U.S. Registry

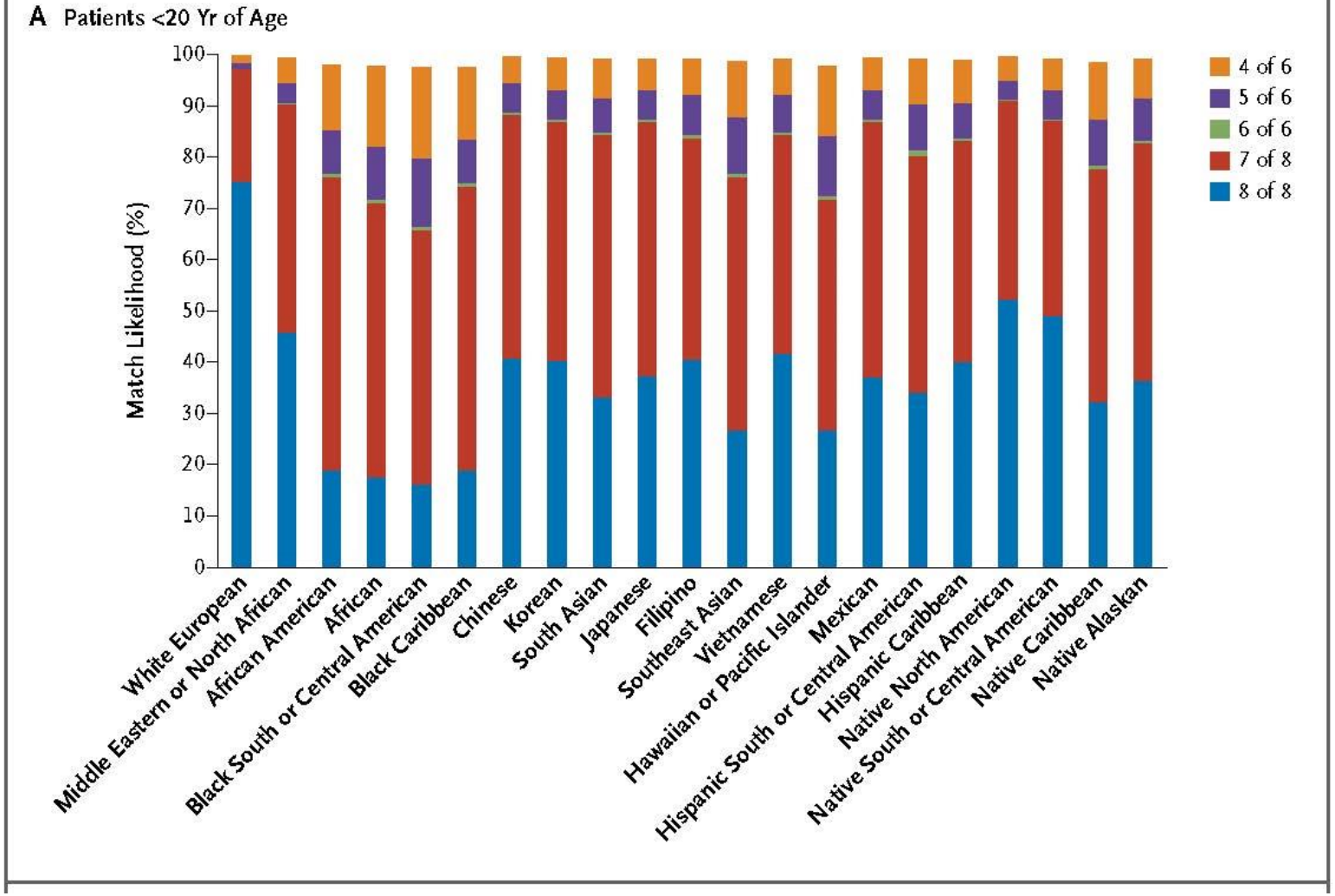
Loren Gragert, B.S., B.A., Mary Eapen, M.B., B.S., Eric Williams, Ph.D., John Freeman, B.S., Stephen Spellman, M.B.S., Robert Baitty, M.P.P., Robert Hartzman, M.D., J. Douglas Rizzo, M.D., Mary Horowitz, M.D., Dennis Confer, M.D., and Martin Maiers, B.A.

Gragert L, Eapen M, Williams E, Freeman J, Spellman S, Baitty R, Hartzman R, Rizzo JD, Horowitz M, Confer D, Maiers M. HLA match likelihoods for hematopoietic stem-cell grafts in the U.S. registry. N Engl J Med. 2014 Jul 24;371(4):339-48. PMID: 25054717

# Match Likelihoods According to Racial and Ethnic Group and Age

**Figure 1.** Match Likelihoods According to Racial and Ethnic Group and Age.

The likelihood of finding a match with the use of a search strategy in which an 8/8 HLA-matched donor is sought first, then a 7/8 HLA-matched donor, and thereafter a cord-blood unit with an adequate cell dose is shown.

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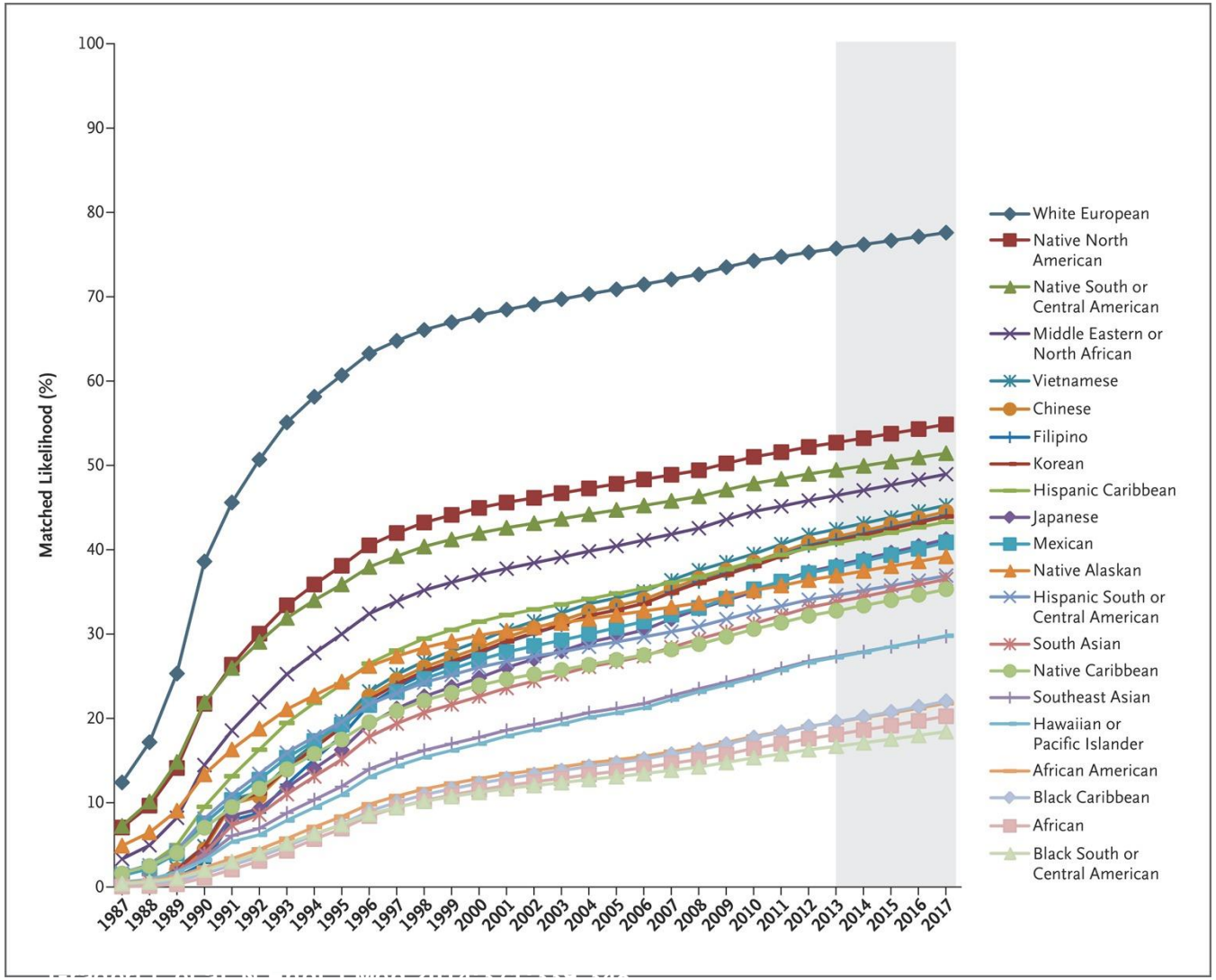
Gragert L, Eapen M, Williams E, Freeman J, Spellman S, Baitty R, Hartzman R, Rizzo JD, Horowitz M, Confer D, Maiers M. HLA match likelihoods for hematopoietic stem-cell grafts in the U.S. registry. **N Engl J Med.** 2014 Jul 24;371(4):339-48. PMID: 25054717

# Likelihood of Finding an 8/8 HLA Match by Year End, Based on Current Donor Availability and with Recruitment Trends Extended to 2017

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# The degree of antigen matching required varies by transplant type

| Organ | HLA-A,-B,-DR,-DQ | HLA-C, DP | Anti-HLA class I Ab | Anti-HLA class II Ab | ABO blood group |
|---|---|---|---|---|---|
| BMT, related | ++ | | + | | - |
| BMT, unrelated | ++ | + | + | | - |
| Kidney | + | | ++ | +/- | ++ |
| Heart/Lung | retro | | ++ | +/- | ++ |
| Liver | retro | | +/- | - | +/- |
| Cornea | + | | | | |
| Pancreas | | | ++ | | ++ |
| Platelet | + | | + | | |

++ : Essential
+ : Typically peformed
+/- : Controversial or varies between centers
- : Not required or typically performed
Retro : Used retrospectively to determine treatment

# Niels K. Jerne 1911-1994

**The Nobel Prize in Physiology or Medicine 1984 with Georges J.F. Köhler, César Milstein**

"for theories concerning the specificity in development and control of the immune system and the discovery of the principle for production of monoclonal antibodies“

**“Niels K. Jerne** is the great theoretician in immunology …His second theory explains how the *cells of the immune system which mature in the thymus gland* develop under the influence of the transplantation antigens of the host.”

# Peter Doherty and Rolf Zinkernagel

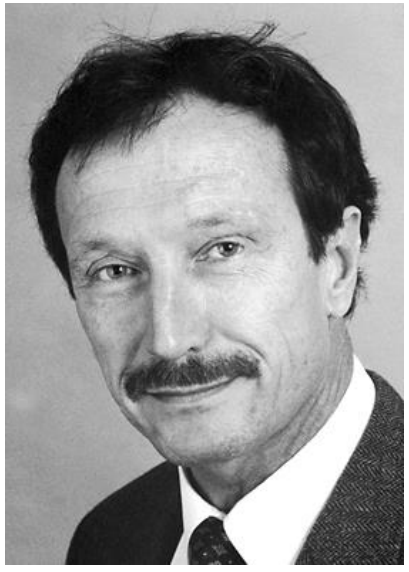
**The Nobel Prize in Physiology or Medicine 1996**

"for their discoveries concerning the specificity of the cell mediated immune defense"

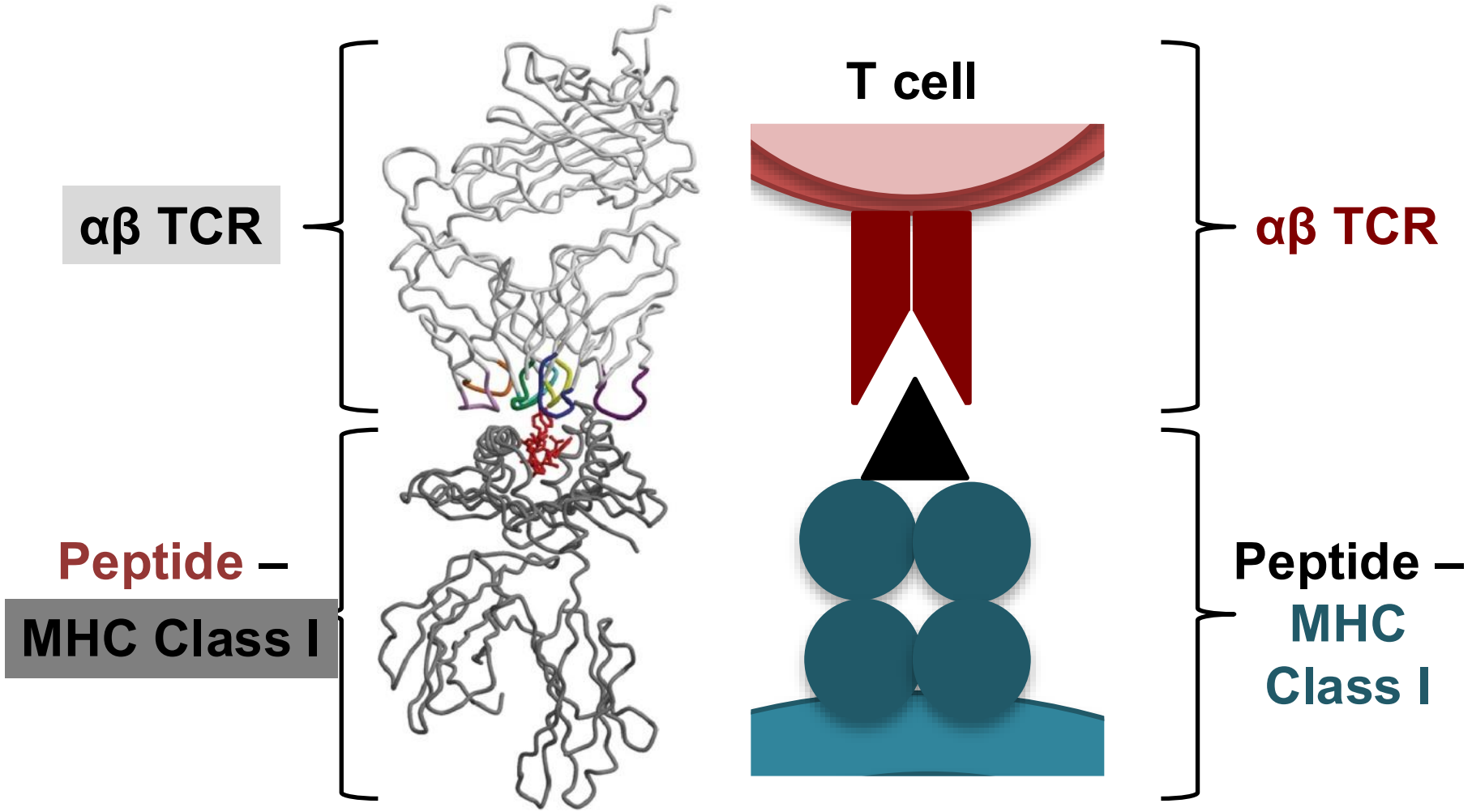
“Zinkernagel's and Doherty's findings …demonstrated conclusively the requirement for the cellular immune system to recognize simultaneously both 'foreign' molecules (in the present case from a virus) and self molecules (major histocompatibility antigens). What also became obvious was the important function of the major histocompatibility antigens (in man called HLA-antigens) in the individual´s normal immune response and not only in conjunction with transplantation.”

Peter C. Doherty (b. 1940)

Rolf M. Zinkernagel (b.1944)



# T cells recognize short peptides presented on the cell surface by MHC molecules



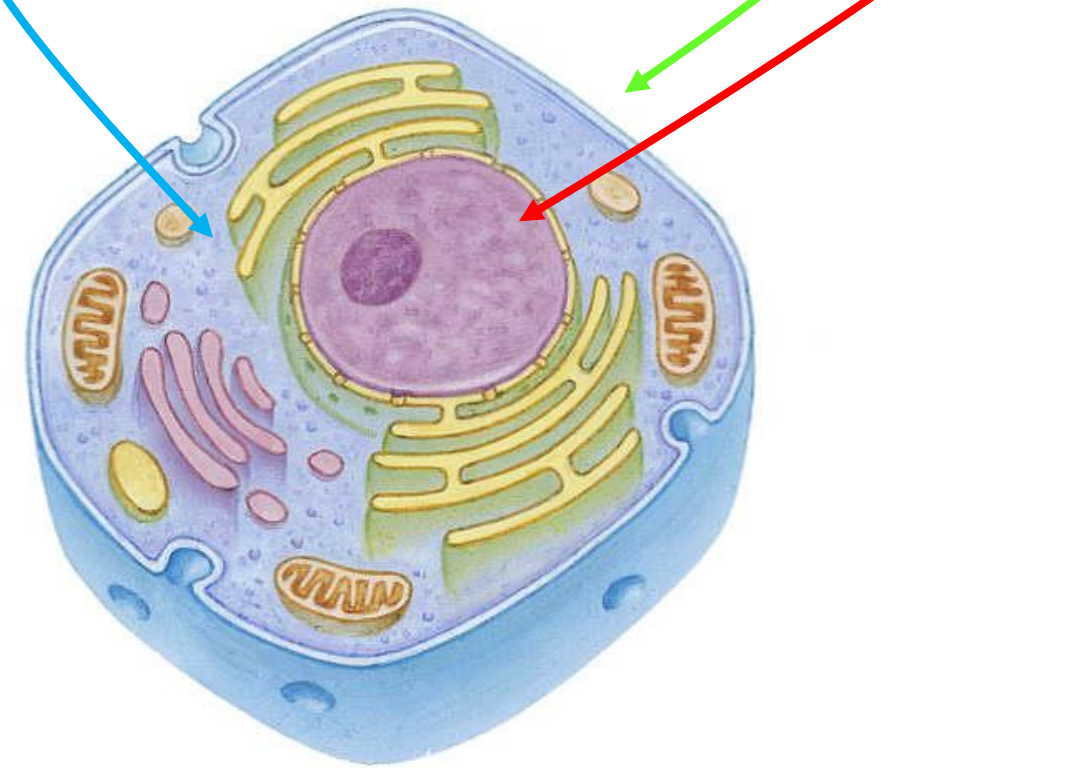
# MHC-associated “peptidome”

“Peptidome” comprises ~10,000 distinct peptides derived from

nuclear proteins

cytoplasmic proteins

membrane proteins



# Antigen presentation

**DIRECT PRESENTATION**

**MHC class I**: peptides are processed by the endogenous pathway

**MHC class II**: peptides are processed through the exogenous pathway

**Host CD4+ T cells recognizing allopeptides bound to MHC class II dominate organ graft rejection.**

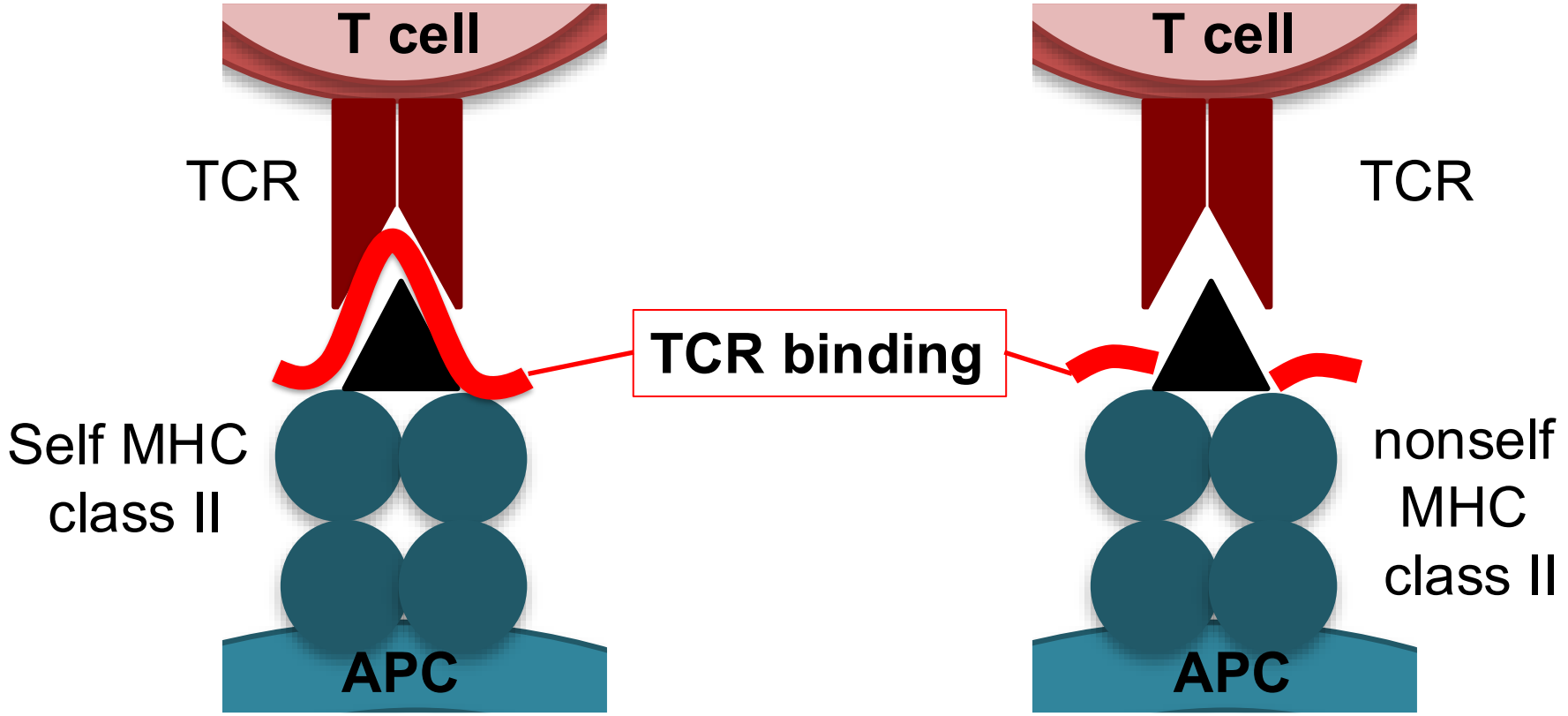
**INDIRECT PRESENTATION**

exogenous peptides from the donor presented by host APCs

# Recognition of non-self MHC

Foreign peptide:self MHC binding

MHC dominant binding




**Conventional response**

1 in 1.5-3.0x$10^5$ T cells

**Alloresponse to MHC Ags**

1 in $10^3$ T cells

# Alloreactive T cells

- Most cases: dependent on both allo MHC and bound peptide

- Polyspecificity: a single TCR can recognize multiple distinct (allo)peptide-(allo)MHC complexes (reason for high frequency?)

# Crossreactivity between T cell clones recognizing transplant and other Ags

- Alloreactive T cell clones react with ovalbumin (JI 136:389)
- Response to viral or parasitic antigens results in (cross)reactivity with alloantigens and rejection (JCI 111:1887)
- EBV-reactive clones react with three HLA-B molecules (JI 177:1427)

# Types of APCs

- **Bone marrow-derived:**
  - **Myeloid: DC, macrophages, other phagocytic cells (some migratory, some not)**
  - **Lymphoid: B cells**
- **Parenchymal cells:**
  - **Endothelial cells, epithelial cells**

Acknowledgments: Fadi Lakkis, M.D.

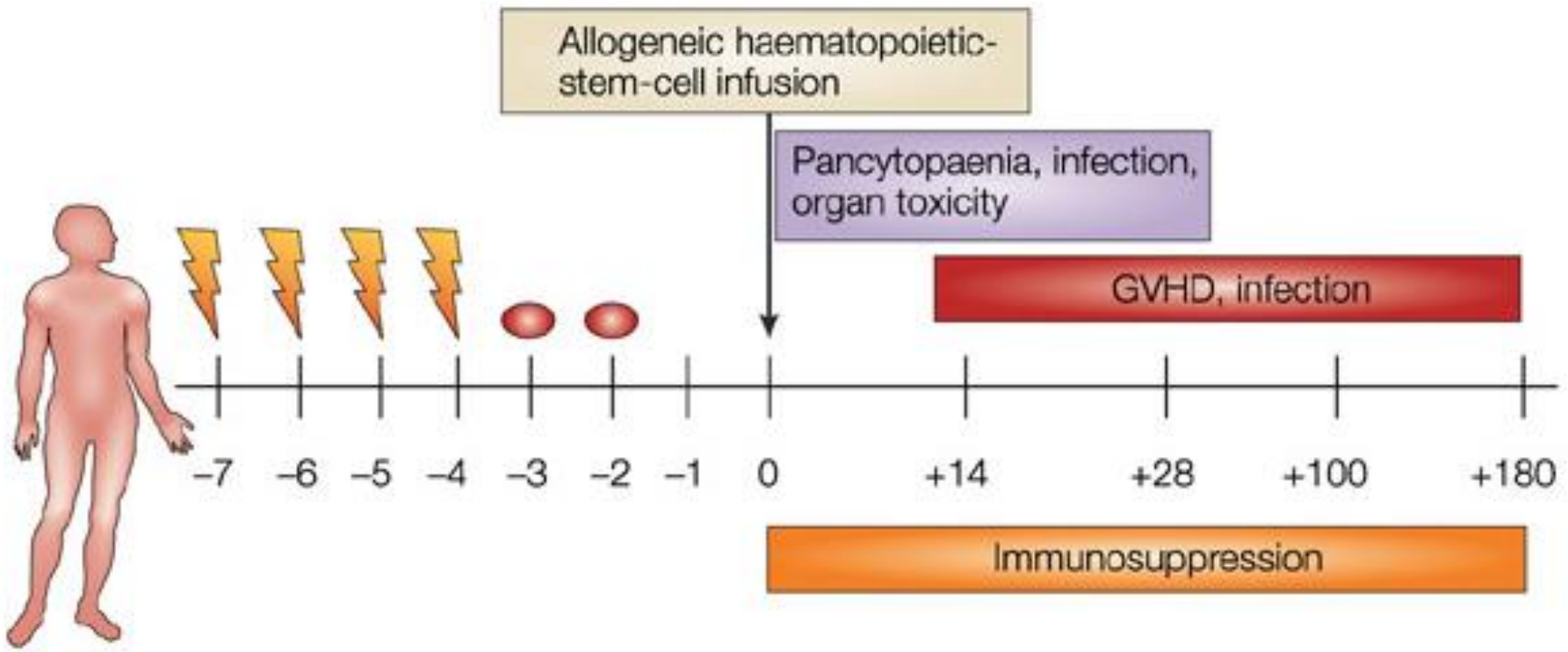
# Allogeneic hematopoietic stem cell transplantation (allo-HSCT)

- Rescue from high dose chemotherapy or radiation for malignancy
- BM failure or immune deficiency or genetic metabolic diseases
- Platform for immunotherapy: **graft-versus-tumor (GVT)** activity
- Experimental for autoimmune diseases
- By 2011, 1 million patients had undergone HSCT worldwide

# Critical functions of donor T cells post-BMT

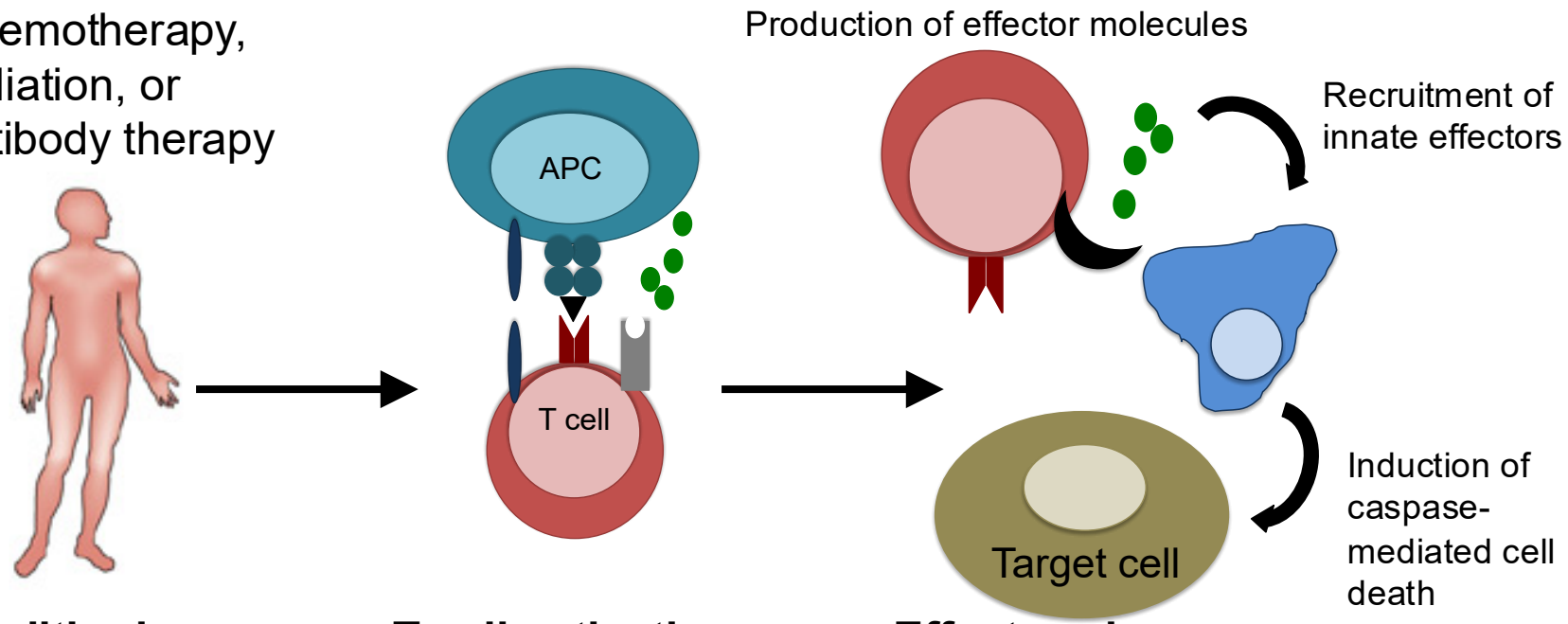
- Initial immune function post-BMT until new thymic T cell development occurs
- Promotion of donor HSC engraftment
- Anti-tumor immunity (GVT/GVL/GVM)

# Allo-HSCT regimen and risks




Bleakley & Riddell, Nat Rev Cancer. 2004.

# Pathophysiology of GVHD and GVT




**Graft-versus-host disease (GVHD)** against skin, liver, intestines, thymus, and hematopoietic system

**Graft-versus-tumor (GVT)** against MHC, minor histocompatibility antigens, and tumor-associated antigens

# Early demonstration of alloreactivity and GVH-like reaction



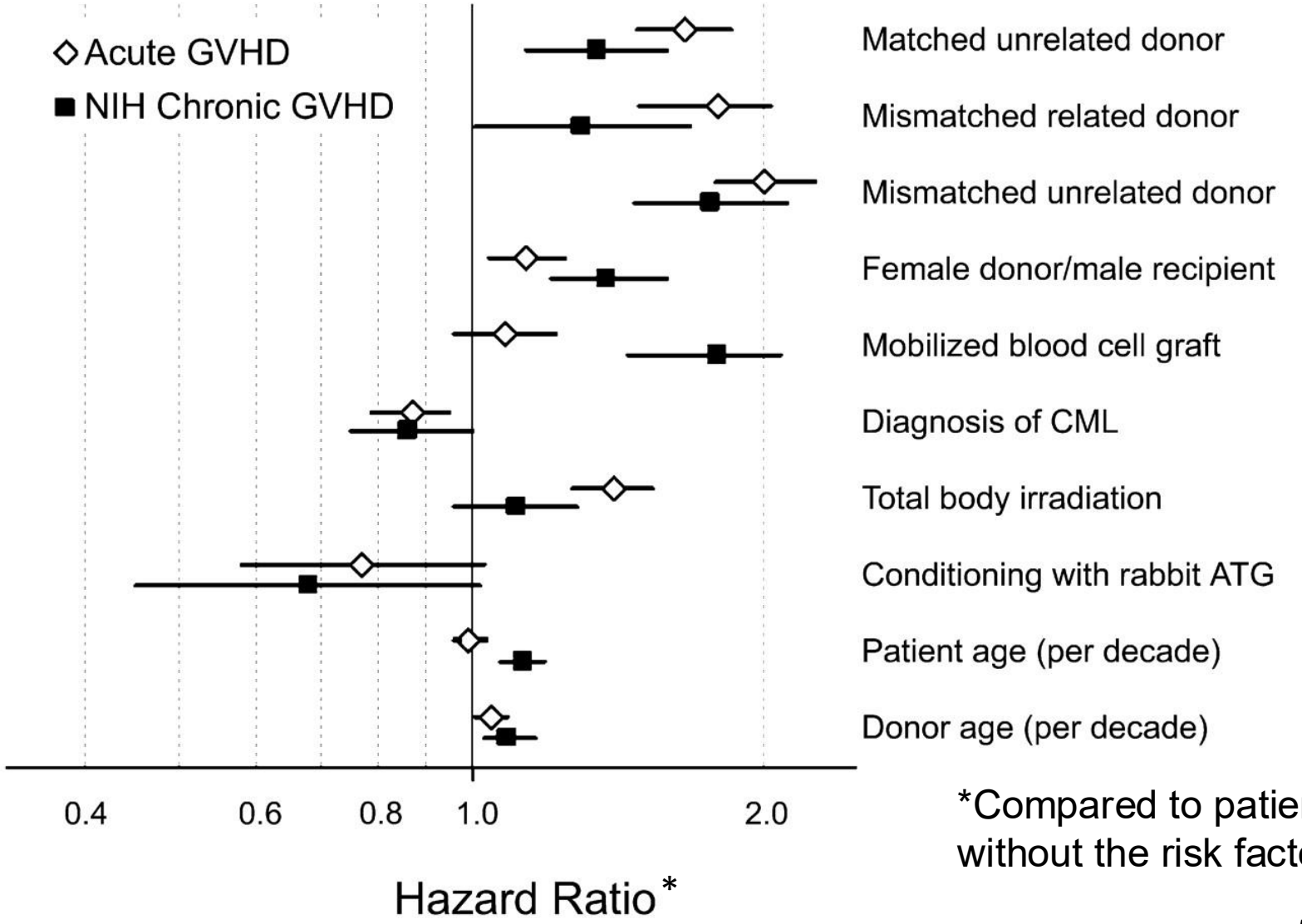
FIG. 1.

Murphy, James B. THE EFFECT OF ADULT CHICKEN ORGAN GRAFTS ON THE CHICK EMBRYO. J Exp Med. 1916;24(1):1-5.

# Graft-versus-host Disease

- T cell-mediated attack on epithelial tissues against MHC and minor histocompatibility antigens
- Managed by HLA matching, T cell depletion of the allograft, and immunosuppression
- Acute:
  < 100 days (usually 30-40)
  skin, liver, GI tract
- Chronic:
  100 days
  “autoimmune like” syndrome

# Multivariate risk factor profiles for grades 2-4 acute GVHD and NIH chronic GVHD




*Compared to patients without the risk factor.

*Flowers MED. Blood 2011.*

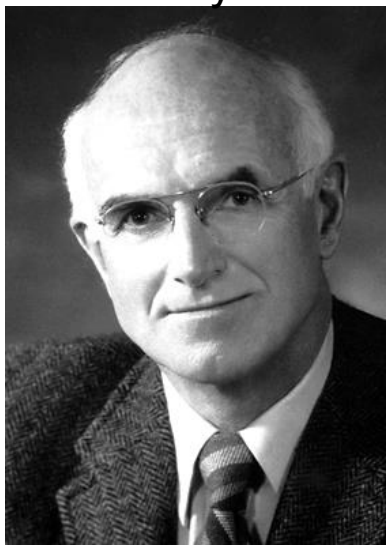
# Joseph E. Murray and E. Donnall Thomas

**The Nobel Prize in Physiology or Medicine 1990**

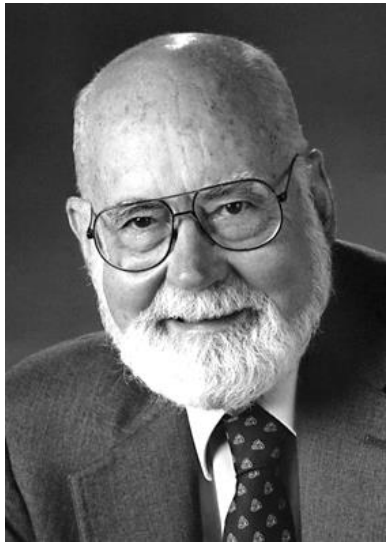
"for their discoveries concerning organ and cell transplantation in the treatment of human disease"

- Joseph E. Murray discovered how rejection following organ transplantation in man could be mastered
- E. Donnall Thomas managed to diminish the severe reaction that the graft can cause in the recipient, i.e. the so-called "graft-versus-host" reaction (GVH).
- In addition, Thomas could show that intraveneously infused bone marrow cells were able to repopulate the bone marrow and produce new blood cells.

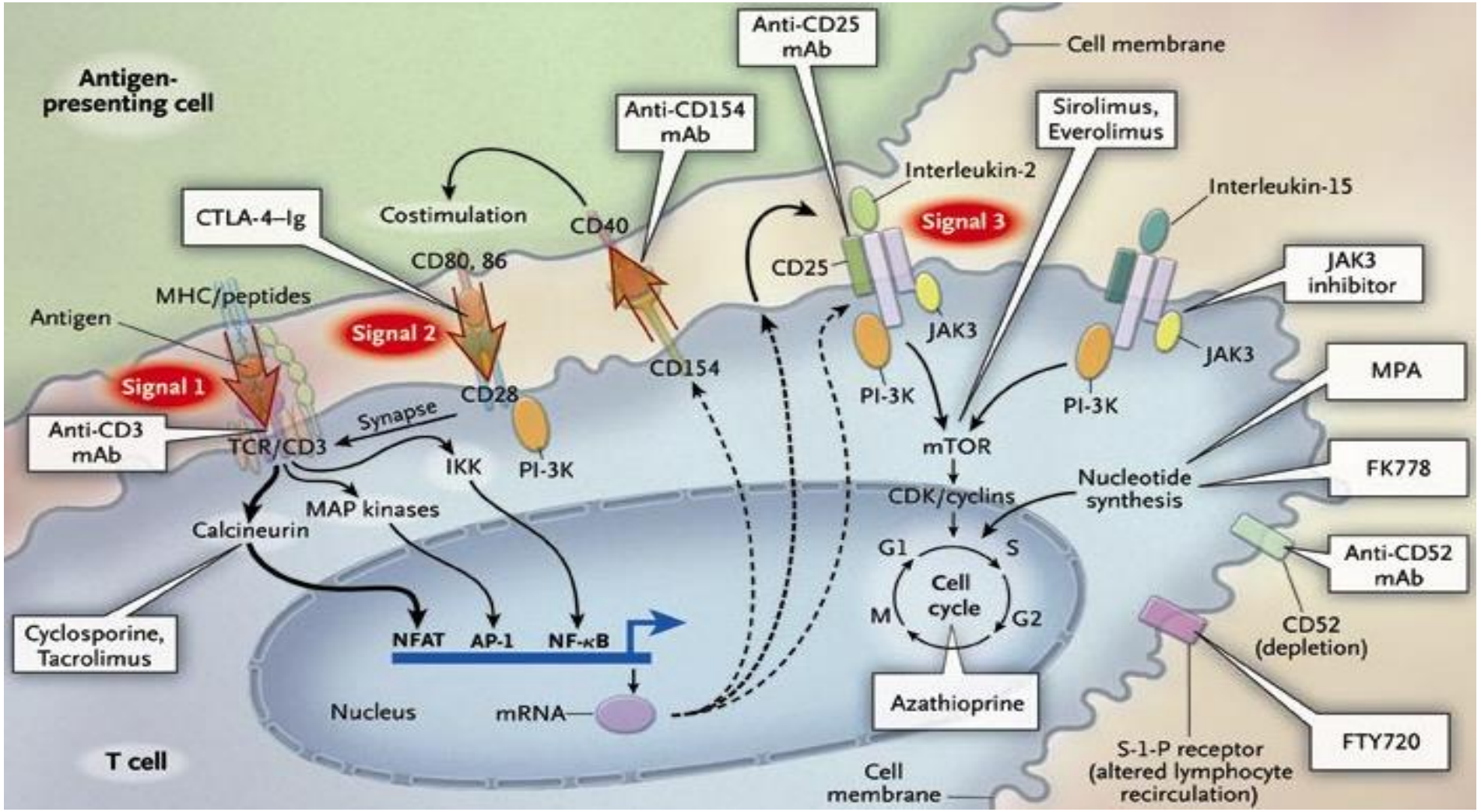
Joseph E. Murray 1919-2012



E. Donnall Thomas 1920-2012



# Individual Immunosuppressive Drugs and Sites of Action in the Three-Signal Model

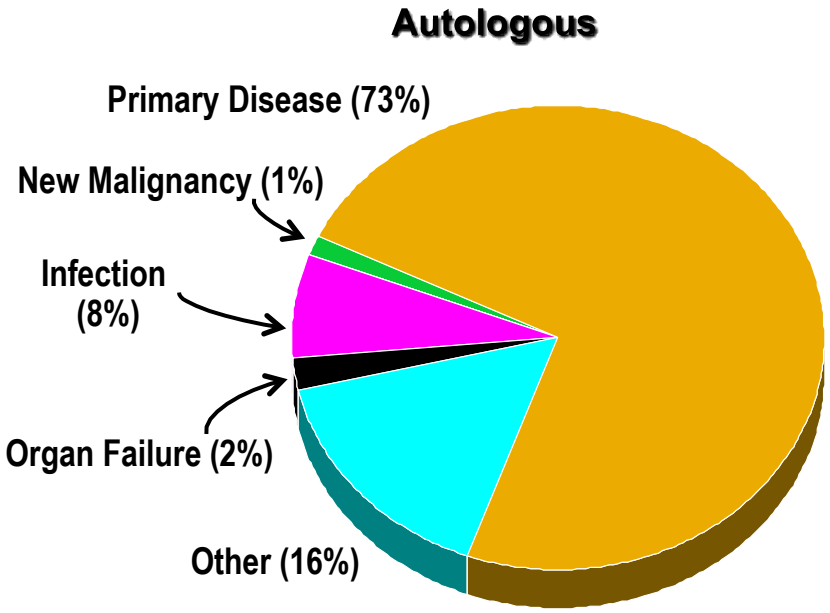



*Halloran, P.F., The New England Journal of Medicine; vol # 351; 2715*

# Graft-Versus-Leukemia or GVT

*Indirect Evidence*

- Abrupt withdrawal of immunosuppression, or flare of GVHD induces complete remission in some patients with relapse after allo-BMT
- Autologous BMT is associated with higher risk of relapse
- GVHD after BMT is associated with lower risk of relapse
- T cell depletion increases risk of relapse, esp CML

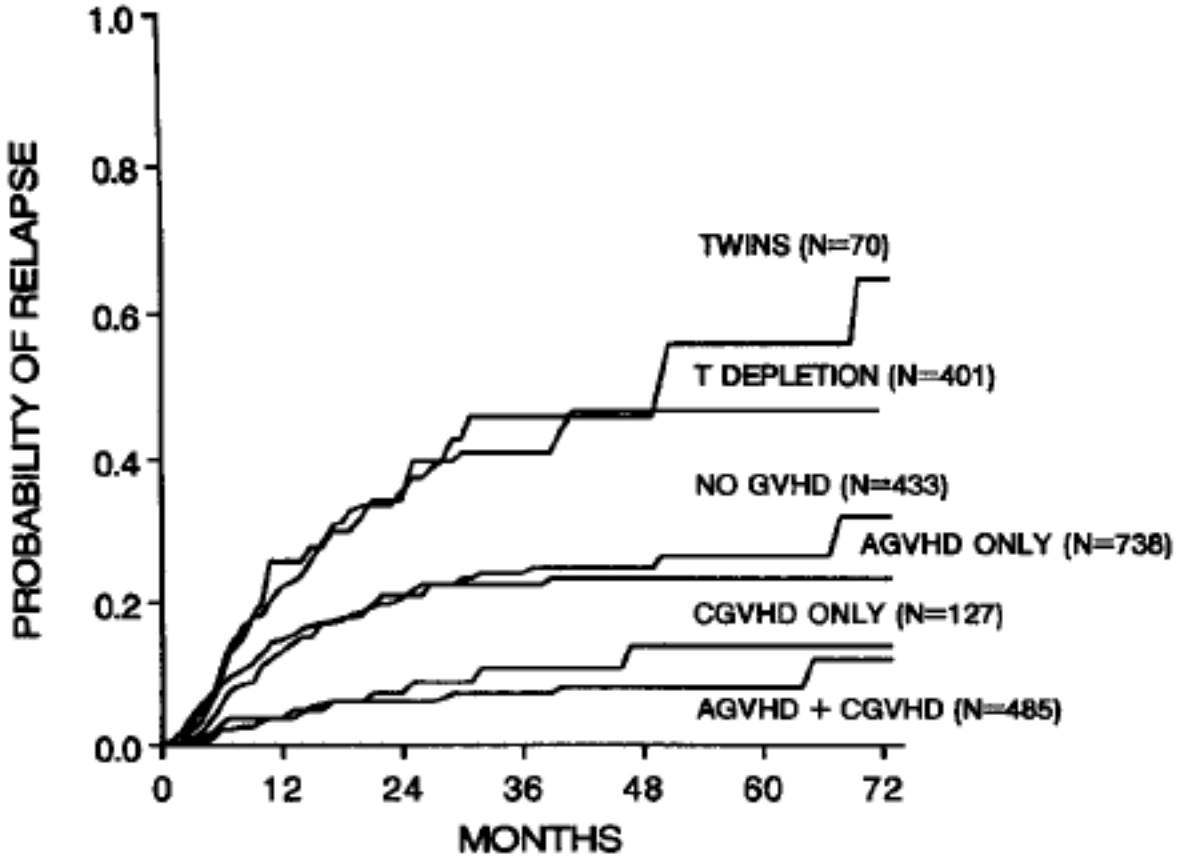



*Direct Evidence*

- Donor leukocyte infusion can induce complete remission after relapse

*CIBMTR 2011 Summary slides*

# Association between GVHD and GVT




*Horowitz MM. Blood. 1990.*

# “Re-emerging” concept in GI (gastrointestinal) GVHD

Reviews

MOLECULAR MEDICINE TODAY, MARCH 1996

## Does graft-versus-host disease attack epithelial stem cells?

George E. Sale

**Graft-versus-host disease (GvHD) is the opposite of graft rejection in that a transplant containing donor lymphocytes attacks the host's skin, liver and gut. This disease can usefully also attack host tumor cells. There is a peculiar distribution of normal tissue targets in epithelial stem cell sites, suggesting that GvHD may be the abnormal counterpart of a physiological growth control system. Efforts to understand how the graft-versus-tumor effect could be therapeutically separated from GvHD require further understanding**

***GE Sale. Mol Med Today 1996***

# Become a donor

https://bethematch.org