May I Have the Envelope, Please...
the Award Goes to...

J. Kelly Wright, Jr, MD
U of Va Surgery Grand Rounds
September 20, 2017
Conflicts

• I am known to have plenty of biases
• History is a pack of lies about events ...told by people who weren't there.
  George Santayana
• Nothing to gain financially from my opinions
• Industry sponsored PI with OctaPharma
Nobel Prize
Medicine/Physiology
Nobel Prize
Medicine/Physiology

• An arbitrary measure of greatness
• Impact should stand test of time
• A HISTORICAL CONTEXT TO GAUGE PROGRESS
• Transplantation
Alfred Bernhard Nobel

- B 1833, Stockholm, son of engineer/inventor
- Russian education as engineer
- Invention of dynamite (TNG with diatomaceous earth)-allowing for controlled detonation
- D 1896
Dynamit-Actien-Gesellschaft
vormals Alfred Nobel & Co., Hamburg
Älteste Sprengstoff-Fabrik der Welt
Gegründet 1865

Fabriken:
Krummel bei Hamburg, Schlebusch (Rheinland), Saarwellingen (Saarrevier)

Alfred Nobel
Established in 1895 in Alfred Nobel’s Last Will

• “Capital shall be invested…the interest on which shall annually distributed [as] prizes to those…[who] shall have conferred the greatest benefit to mankind.”

• Recognition of the most important discovery in the 5 fields: chemistry, physics, literature, fraternity between nations (peace) and medicine/physiology

• Prize in economics added in 1968
Nobel Foundation

- 1901-1977- Karolinska Institutet faculty chose Med/phys prize

- 1977- present- Nobel Assembly, 50 member committee (3yr term), with associations to KI but separate legally & financially
Nobel Prize for Medicine/Physiology

- 211 Nobel Laureates in Medicine/Physiology named
- 18 Laureates with direct ties to field of transplantation
  - 11 immunology/ID
  - 4 pharmacology/immunosuppression
  - 1 clinical hematology/oncology
  - 2 clinical surgery
1912- Alexis Carrel

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

- B 1873, Lyon FR
- MD 1900, U Lyons
- Rockefeller Inst for Med Research 1906
- Vascular suture technique, hypothermic storage, artificial oxygenator, whole organ transplant techniques
- D 1944
1960

Medawar & Burnet

"for discovery of acquired immunological tolerance"
Sir Frank MacFarlane Burnet

- B 1899, Traralgon, Victoria, Australia
- MD 1923, U Melbourne
- Rejection of grafts akin to viral infection, “self vs non-self”
- Ideas led to expansion by Medawar
- D 1985
Sir Peter Brian Medawar

- B 1915, Rio De Janiero, BR
- Biology degrees, Magdalen College, Oxford
- Medical Research Council Labs — why skin allografts lacked permanence
- U Birmingham, Acquired Tolerance
- D 1987
‘ACTIVELY ACQUIRED TOLERANCE’ OF FOREIGN CELLS

By Dr. R. E. BILLINGHAM*, L. BRENT and Prof. P. B. MEDAWAR, F.R.S.
Department of Zoology, University College, University of London

The experiments to be described in this article provide a solution—at present only a ‘laboratory’ solution—of the problem of how to make tissue homografts immunologically acceptable to hosts which would normally react against them. The principle on which the procedures are based is that of the in vivo transplantation of F1 hybrid tissue antigens, as exemplified by the CBA F1 strain, into syngenic or even strain-matched recipients.

1. Mice and chickens never develop, or develop to only a limited degree, the power to react immunologically against foreign homologous tissue cells with which they have been inoculated in foetal life. Animals so treated are tolerant not only of the foreign cells of the original inoculum, but also of skin grafts freshly transplanted in adult life from the original donor or from a donor of the same antigenic constitution.

2. Acquired tolerance is immunologically specific: mice and chickens made tolerant of homografts from one donor retain the power to react against grafts transplanted from donors of different antigenic constitutions.
Snell, Dausset & Benacerraf

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

- B 1903 Bradford MA
- PhD 1930 Bussey Institute
- Jackson Lab inbred murine strains, concept of MHC in acceptance or rejection of cancer and transplants
- D 1996
Jean Dausset

- B 1916, Toulouse, FR
- MD 1939, U Paris
- St Antoine Hosp
- Leukocyte antigens-Hu1---HLA
- D 2009
Baruj Benacerraf

- B 1920 Caracas, Venezuela
- MD 1945, MedCollVirginia
- NYU, NIAID – studying MHC and immune responsiveness

THE ROLE OF MHC GENE PRODUCTS IN IMMUNE REGULATION AND ITS RELEVANCE TO ALLOREACTIVITY

Nobel Lecture, 8 December, 1980
by
BARUJ BENACERRAF
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

- B 1911 London
- MD 1951, U Copenhagen
- Basel Institute of Immunology
- Clonal selection, B-cell proliferation, self-nonself MHC recognition in thymus
- D 1994
Human Immune System = $10^{12}$ Lymphocytes

T-cells

B-cells

$2000$ Ab. Molecules per s

ANTIGEN
Cesar Milstein

- B 1927 Bahia Blanca ARG
- PhD Biochem 1960, U Cambridge
- Medical Research Council Lab for Molecular Biology
- Monoclonal antibody development
- D 2002
Georges K.F. Kohler

- Born 1946 in Munich
- PhD in Immunology, University of Freiburg, 1974
- Early career collaboration with Cesar Milstein
- Developed fused cell (hybridoma) technology for producing clonally specific antibodies
- Died 1995
Immunized mouse → Fusion → Cell culture

Spleen cells →  → Myeloma cells

Sparse seeding of cells in a medium allowing selection of hybrid cells

Expansion of clones with a predetermined antibody specificity

Collection of antibodies from the tissue culture medium
Elion and Hitchings

"for their discoveries of important principles for drug treatment"
George H. Hitchings

- B 1908 coastal Washington
- PhD Chem 1933, Harvard
- Burroughs- Wellcome
- Purine/pyrimidine chemistry
- Collaboration with Elion
- Allopurinol, 6MP, AZA, trimethoprim
- D 1998
Gertrude B. Elion

- B 1918 NYC
- MS Chem 1941, NYU
- Burroughs- Wellcome
- Purine synthesis and metabolism
- Pathways leading to chemotherapy and immunosuppressive drugs
- D 1999
Table II. Clinical use of drugs developed by Elion and Hitchings.

<table>
<thead>
<tr>
<th>Purine and pyrimidine analogues</th>
<th>Indications</th>
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<tbody>
<tr>
<td>6-Mercaptopurine, thioguanine</td>
<td>Leukemia</td>
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<tr>
<td>Azathioprine</td>
<td>To prevent rejection after organ transplantation</td>
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<td></td>
<td>Autoimmune diseases</td>
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<tr>
<td>Allopurinol</td>
<td>Gout</td>
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<td></td>
<td>Uric acid accumulation after treatment with cytostatic drugs</td>
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<td>Acyclovir</td>
<td>Herpes virus infections</td>
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<tr>
<td>Pyrimethamine</td>
<td>Malaria</td>
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<tr>
<td>Trimethoprim (often combined with sulfa)</td>
<td>Bacterial infections, mainly urinary tract infection</td>
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<tr>
<td></td>
<td>Pulmonary infections caused by e.g. Pneumocystis carinii (complication to decreased immune defence at transplantation and AIDS)</td>
</tr>
</tbody>
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1990

Murray and Thomas

"for their discoveries concerning organ and cell transplantation in the treatment of human disease"
Joseph E. Murray

- Born 1919 Milford MA
- Harvard MD 1943
- Plastic Surgery interests
- 1950 PBBH to work on kidney Tx project
- 1954 1st successful human L ident KT
- 1959 LRKT + TBI
Twin’s Life May Hang on Fingerprint Today

A fingerprinting at 4 p.m. today at Roxbury Crossing police station may save the life of a 23-year-old Marlboro man seriously ill in Peter Bent Brigham Hospital.

The fingerprinting is to determine whether Ronald Lorraine of Fort Main Street, Marlboro, is the identical twin of a patient named Ronald in the Brigham Hospital.

So far the graft has stuck, as Peter Bent Brigham, last week, said last week, when the identical twin was identified. Only the skin from the arm has been attempted

If the fingerprints are not identical, the twin will stick after identical twins.

If the fingerprints do not match, it still is not definite that the two boys are only four.

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E. Donnall Thomas

- Born rural TX 1920
- Harvard MD 1946
- Career in Oncology at UWash
- Bone marrow transplants in dogs and humans
- Overcoming issues of GVHD
Marrow Transplantation for Malignant Disease

BY E. DONNALL THOMAS, MD

ABSTRACT: The results of high-dose chemotherapy and marrow transplantation from an HLA-identical sibling for various stages and types of leukemia and lymphoma are summarized. It has been shown that marrow transplantation can be carried out successfully using partially matched family members or matched unrelated donors. Some of the complications of marrow transplantation are discussed. KEY INDEXING TERMS: Marrow Transplantation; Malignant Disease. [Am J Med Sci 1987; 294(3): 75-79.]
"for their discoveries concerning the specificity of the cell mediated immune defense"
Peter C. Doherty

- B 1940 Brisbane, Aus
- PhD 1970, U Edinburgh
- Slow virus infection
- 1973-75 John Curtin School of Medical Research, Canberra
- Currently at St Jude’s Memphis
Rolf M. Zinkernagel

- B 1944 Basel, Switz
- 1970 MD, U Basel
- 1975 PhD, Australian National Uni, Canberra
- 76-79 Scripps
- 79- Zurich
T-cell immunity defined by HLA restriction
For their discovery concerning the activation of innate immunity and of the dendritic cell and its role in adaptive immunity
Bruce A. Beutler

- B 1957 Chicago
- 1981 MD, U Chicago
- 81-85 Rockelfeller (cachectin)
- 85- UT Southwestern, Dallas (TNF regulation, LPS receptor-Toll like receptor family)
Jules A. Hoffman

- B 1941 Echternach, LUX
- 1969 PhD, U Strasbourg
- 1974- CNRS (National Center of Scientific Research), Strasbourg, (Toll gene in drosophila)
Ralph M. Steinman

- B 1943 Montreal
- D 9/30 2011 (3 days prior to Nobel announcement)
- 1968 MD, Harvard
- 1972-2011 Rockefeller
- Dendritic cells (APC’s)
Aspergillus infection

The gatekeepers of the immune system

Two lines of defence are activated when an infection threatens the human body

1. Innate immunity
   - Defends the body, destroying most microorganisms
2. Adaptive immunity
   - Maintains a memory of microorganisms enabling faster reaction next time

If microorganisms break through, a second line of defence comes into operation

Discoveries have led to new methods of preventing and treating disease

Figure 12.
Nobel Prize
Medicine/Physiology

- Impact should stand test of time
- A HISTORICAL CONTEXT reflects significant PROGRESS
Multidisciplinary Team
Our Multidisciplinary Team

Surg, hep, anesth, consults, nursing, sw, psych, pharm, finan, admin, med ctr, etc