

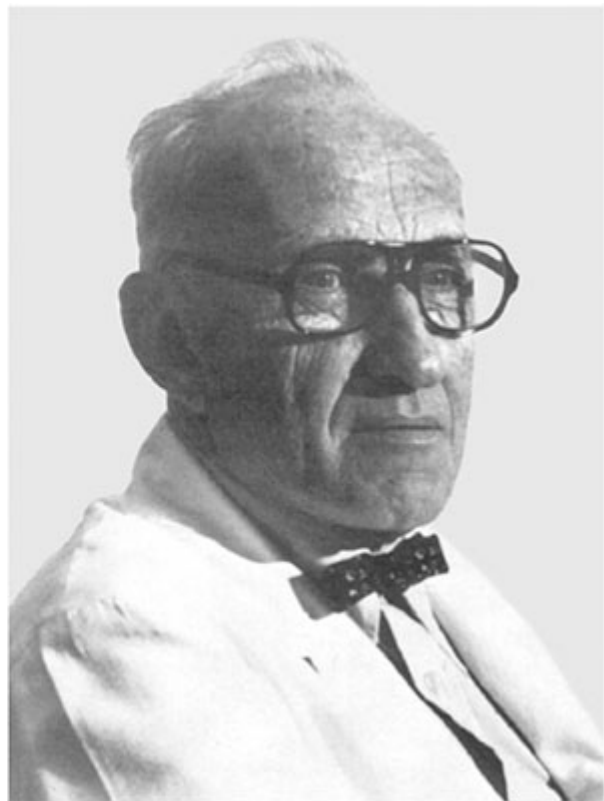
History of Immunoglobulin molecules

Snapshots in the history of Immunoglobulin molecules



1939

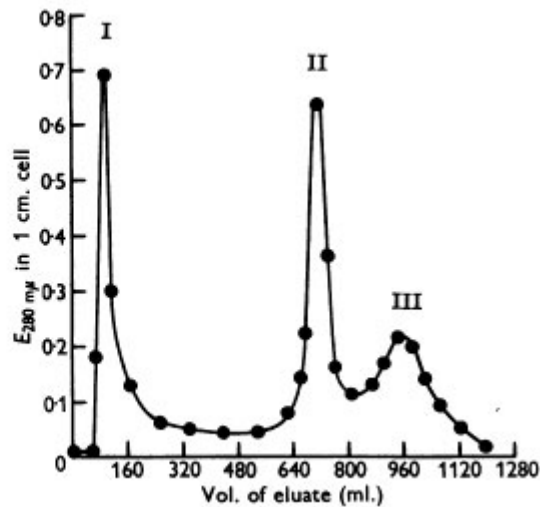
gamma-Globulin



Tiselius and Kabat in 1939 showed that antibodies belong to the γ -globulin fraction of serum proteins

1959

Three Fractions



Porter digested γ -globulins with papain, a proteolytic enzyme, and recovered 3 fractions: Fractions I and II of molecular weights between 50 and 55KDa retained the antigen binding capacity, whereas fraction III, of 80 KDa was crystalizable, and have a higher carbohydrate content ([Porter RR, Biochem J. 73:119-127, 1959](#)).

1961

Heavy and Light chains

HYPOTHETICAL RELATIONS BETWEEN TYPES OF POLYPEPTIDE CHAINS AND PROPERTIES OF γ -GLOBULINS

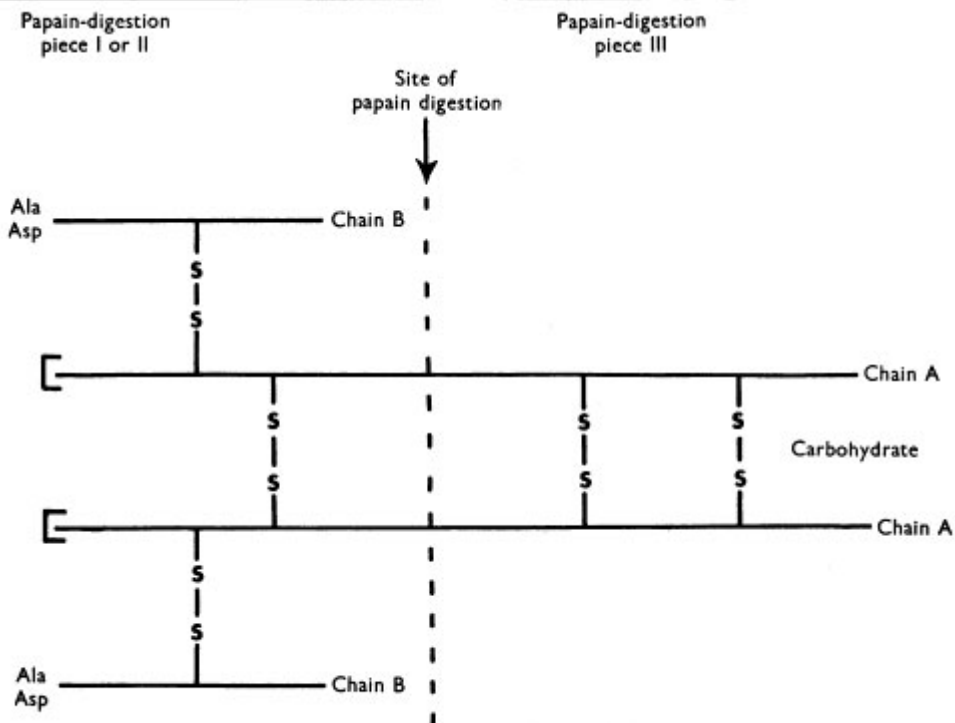
γ -Globulin class		Type and number of chains	Properties assigned to H chains	Properties assigned to L chains
Ultra-centrifugal	Immuno-electrophoretic			
7S	γ_2 γ_{1A}	Small number of L and H* chains	Complement fixation, Skin fixation Placental passage (? Immunologic specificity)	Antibody specificity. Heterogeneity. Antigenic cross-reactivity with other γ -globulins.
19S	γ_{1M}	Large number of L and H* chains	Complement fixation (? Immunologic specificity)	Antibody specificity. Heterogeneity. Antigenic cross-reactivity with other γ -globulins.
3.4S	Bence-Jones	L chains†	...	Antigenic cross-reactivity with other γ -globulins. Reversible temperature dependent solubility properties.

* γ_2 -globulins, γ_{1A} -globulins, and γ_{1M} -globulins appear to possess different kinds of H chains (see text).
† Most Bence-Jones proteins have molecular weights consistent with the presence of two L chains.

Edelman and Poulik reported that rabbit 7S γ -globulins and human myeloma proteins reduced in strong urea solutions and alkylated, separated into heavy (H) and light (L) chains bound by disulfide bonds ([Edelman GM and Poulik MD, J Exp Med. 113:861-884, 1961](#))

1963

Y Structure



Scheme 1. Diagrammatic structure of rabbit γ -globulin (Porter, 1962).

Porter and colleagues proposed the basic Y structure of four polypeptide chains and 5 interchain disulfide bonds ([Fleischman JB et al., Biochem J. 88:220-228, 1963](#))

1965

V and C Regions

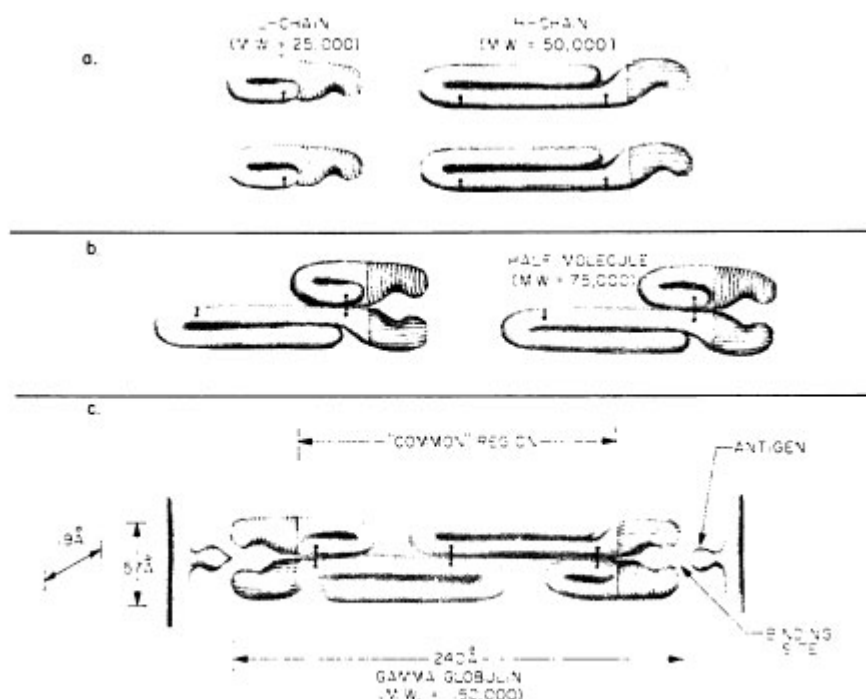


FIG. 1.—Diagrammatic representation of the multiple chain structure of rabbit gamma globulin (see text). Covalent, interchain disulfide linkages (●—●) serve to stabilize the complex structure after formation.

Dreyer and Bennett proposed that the V and C regions must be the products of different genes ([Proc Nat Acad Sci USA 54: 864-869, 1965](#))

IgA

TABLE II
Effect on Anti-B Agglutinins after Absorption with Specific Antisera

Sample	Saline control	Prior absorption with		
		Anti- γ_1 A	Anti- γ_2 S	Anti- γ_1 M
L. T. saliva.....	3+	0	2+	3+
J. C. saliva.....	3	Tr.	3	3
D. D. saliva.....	4	0	1+	4
L. C. saliva.....	4	0	1+	4
S. Z. colostrum.....	3+	0	3+	3+
L. D. colostrum.....	4	0	3	4
L. H. serum*.....	3	2	2+	0

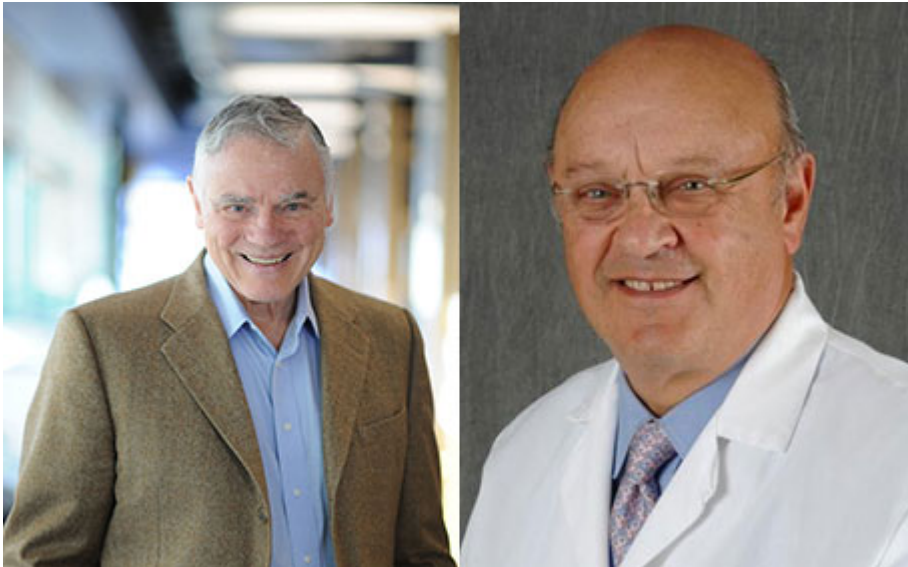
* Serum completely lacked γ_1 A; agglutinins found only in 19S region on density gradient ultracentrifugation.

Tomasi and coworkers demonstrated that IgA present in saliva and colostrum is produced locally and secreted as a dimer or trimer by ([Tomasi TB et al., J Exp Med 121:101-124, 1965](#)) and Newcomb and coworkers demonstrated the existence of the secretory piece ([Newcomb RW et al., J Immunol](#)

[101:905-913, 1968](#)).

1968

Lambda chain



Hood and Ein confirmed that the Lambda chain is encoded by two separate genes that are expressed as a single polypeptide chain ([Nature 220:764-767, 1968](#))

1969

Variable and Constant Regions

EU C _L (RESIDUES 109-214)	THR VAL ALA ALA PRO SER VAL PHE ILE PHE PRO PRO SER	110	120
EU C _{H1} (RESIDUES 119-220)	SER THR LYS GLY PRO SER VAL PHE PRO LEU ALA PRO SER		
EU C _{H2} (RESIDUES 234-341)	LEU LEU GLY GLY PRO SER VAL PHE LEU PHE PRO PRO LYS		
EU C _{H3} (RESIDUES 342-446)	GLN PRO ARG GLU PRO GLN VAL TYR THR LEU PRO PRO SER		
ASP GLU GLN - - LEU LYS SER GLY THR ALA SER VAL VAL CYS LEU LEU ASN ASN PHE		130	
SER LYS SER - - THR SER GLY GLY THR ALA ALA LEU GLY CYS LEU VAL LYS ASP TYR			
PRO LYS ASP THR LEU MET ILE SER ARG THR PRO GLU VAL THR CYS VAL VAL VAL ASP VAL			
ARG GLU GLU - - MET THR LYS ASN GLN VAL SER LEU THR CYS LEU VAL LYS GLY PHE			
TYR PRO ARG GLU ALA LYS VAL - - GLN TRP LYS VAL ASP ASN ALA LEU GLN SER GLY		140	150
PHE PRO GLU PRO VAL THR VAL - - SER TRP ASN SER - GLY ALA LEU THR SER GLY			
SER HIS GLU ASP PRO GLN VAL LYS PHE ASN TRP TYR VAL ASP GLY - VAL GLN VAL HIS			
TYR PRO SER ASP ILE ALA VAL - - GLU TRP GLU SER ASN ASP - GLY GLU PRO GLU			
ASN SER GLN GLU SER VAL THR GLU GLN ASP SER LYS ASP SER THR TYR SER LEU SER SER		160	170
- VAL HIS THR PHE PRO ALA VAL LEU GLN SER - SER GLY LEU TYR SER LEU SER SER			
ASN ALA LYS THR LYS PRO ARG GLU GLN GLN TYR - ASP SER THR TYR ARG VAL VAL SER			
ASN TYR LYS THR THR PRO PRO VAL LEU ASP SER - ASP GLY SER PHE PHE LEU TYR SER			
THR LEU THR LEU SER LYS ALA ASP TYR GLU LYS HIS LYS VAL TYR ALA CYS GLU VAL THR		180	190
VAL VAL THR VAL PRO SER SER SER LEU GLY THR GLN - THR TYR ILE CYS ASN VAL ASN			
VAL LEU THR VAL LEU HIS GLN ASN TRP LEU ASP GLY LYS GLU TYR LYS CYS LYS VAL SER			
LYS LEU THR VAL ASP LYS SER ARG TRP GLN GLU GLY ASN VAL PHE SER CYS SER VAL MET			
HIS GLN GLY LEU SER SER PRO VAL THR - LYS SER PHE - - ASN ARG GLY GLU CYS		200	210
HIS LYS PRO SER ASN THR LYS VAL - ASP LYS ARG VAL - - GLU PRO LYS SER CYS			
ASN LYS ALA LEU PRO ALA PRO ILE - GLU LYS THR ILE SER LYS ALA LYS GLY			
HIS GLU ALA LEU HIS ASN HIS TYR THR GLN LYS SER LEU SER LEU SER PRO GLY			

Edelman and coworkers reported the first complete sequence of a γ G immunoglobulin molecule and demonstrated the existence of variable (V) and constant (C) regions in the H and L chains ([Edelman GM et al., Proc Nat Acad Sci USA 63:78-85, 1969](#))

1972

Nobel Prize - 1972



Edelman and Porter shared the Nobel Prize in Medicine in 1972 “for their discoveries concerning the chemical structure of antibodies”

[Gerald M. Edelman - Facts](#). *Nobelprize.org*. Nobel Media AB 2014.

[Rodney R. Porter - Facts](#). *Nobelprize.org*. Nobel Media AB 2014.

1974

Monomers

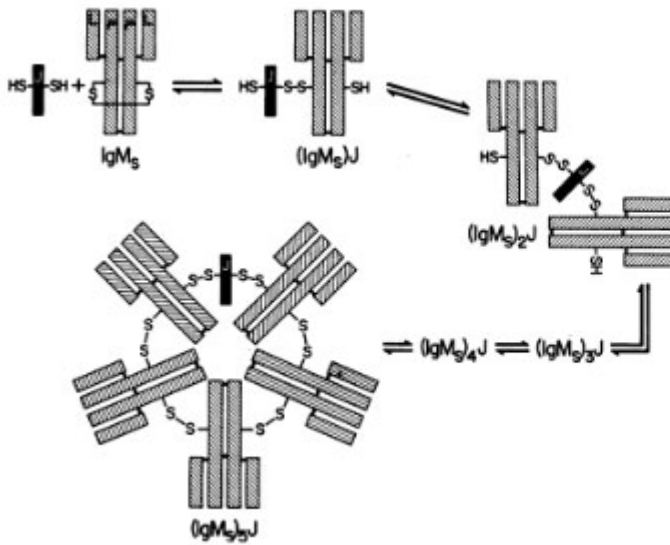
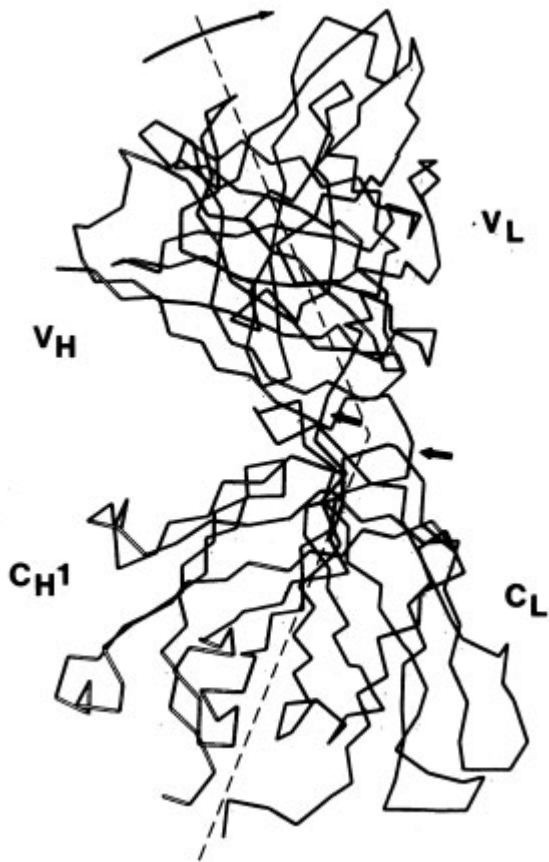


FIG. 5. The clasp model of J linkage in pentamer IgM and the postulated disulfide exchanges leading to its formation. IgM₅ = monomer of pentameric IgM.

Koshland and coworkers demonstrated that the monomers of the polymeric IgM and IgA are linked by the J chain in a clasp way ([Halpern MS and Koshland ME, Nature 228:1276-1278, 1970](#); [Chapuis RM, Koshland ME, Proc Nat Acad Sci 71:657-661, 1974](#))

3D Structure



Poljak and colleagues described the three-dimensional structure of IgG(I) myeloma protein ([Poljak et al., Proc Nat Acad Sci 71. 3440-3444, 1974](#)).

1975

Monoclonal antibodies

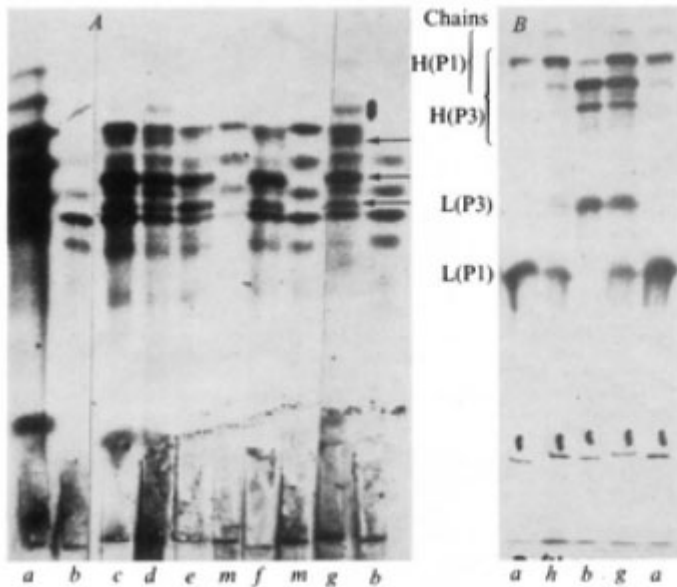
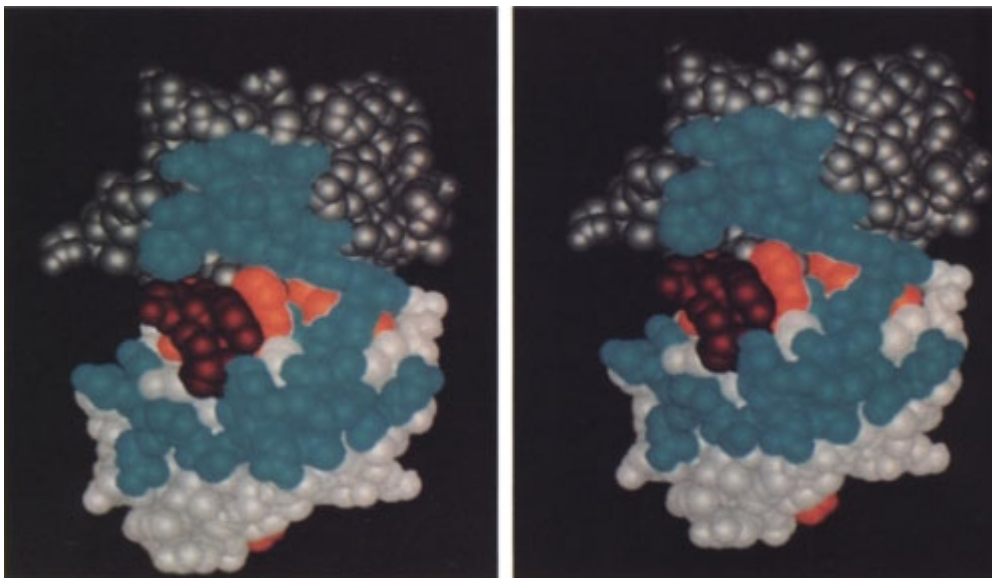


Fig. 1 Autoradiograph of labelled components secreted by the parental and hybrid cell lines analysed by IEF before (A) and after reduction (B). Cells were incubated in the presence of ^{14}C -lysine¹⁴ and the supernatant applied on polyacrylamide slabs. A, pH range 6.0 (bottom) to 8.0 (top) in 4 M urea. B, pH range 5.0 (bottom) to 9.0 (top) in 6 M urea; the supernatant was incubated for 20 min at 37 °C in the presence of 8 M urea, 1.5 M mercaptoethanol and 0.1 M potassium phosphate pH 8.0 before being applied to the right slab. Supernatants from parental cell lines in: a, P1Bu1; b, P3-X67Ag8; and m, mixture of equal number of P1Bu1 and P3-X67Ag8 cells. Supernatants from two independently derived hybrid lines are shown: e-f, four subclones from Hy-3; g and h, two subclones from Hy-B. Fusion was carried out¹⁴ using 10^6 cells of each parental line and 4,000 haemagglutination units inactivated Sendai virus (Searle). Cells were divided into ten equal samples and grown separately in selective medium (HAT medium, ref. 6). Medium was changed every 3 d. Successful hybrid lines were obtained in four of the cultures, and all gave similar IEF patterns. Hy-B and Hy-3 were further cloned in soft agar¹⁴. L, Light; H, heavy.

Kohler and Milstein ([Nature 256: 495-497, 1975](https://doi.org/10.1038/256495a0)) reported that the fusion of a myeloma cell with a spleen specific antibody-producing cell results in a hybridoma that produces monoclonal antibodies against the specific antigen. Continuous culture of cloned hybrid cells allows the production of large amounts of monoclonal antibodies against the desired antigen.

1979

Somatic Rearrangements

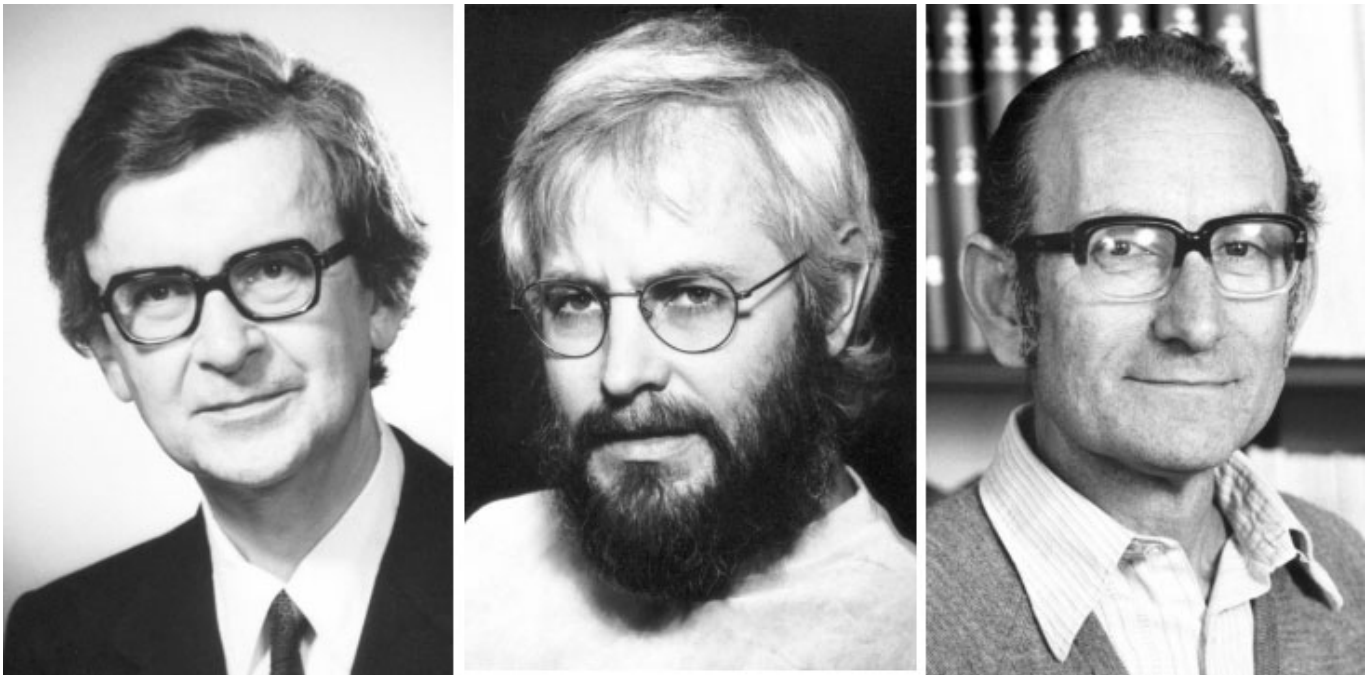


In the late 1970s, Tonegawa and colleagues in a series of elegant experiments demonstrated that

immunoglobulin V and C genes undergo somatic rearrangements to form the complete immunoglobulin gene ([Hozumi N, Tonegawa S, Proc Nat Acad Sci 73: 3628- 3632, 1976](#); [Brack C et al., Cell 15:1-14, 1978](#); [Sakano et al., Nature 277:627-633, 1979](#); [Sakano et al., Nature 280: 288-294, 1979](#); [Tonegawa S. Nature 302:575, 1983](#))

1984

Nobel Prize - 1984



In 1984, Niels Jerne, Georges Kohler and Cesar Milstein were awarded with the Nobel Prize for their discovery of the hybridomas technology for the production of large amounts of monoclonal antibodies for experimental, analytical, diagnostic and therapeutic purposes.

[Niels K. Jerne - Facts](#). *Nobelprize.org*. Nobel Media AB 2014.

[Georges J.F. Köhler - Facts](#). *Nobelprize.org*. Nobel Media AB 2014.

[César Milstein - Facts](#). *Nobelprize.org*. Nobel Media AB 2014.

1987

Nobel Prize - 1987



In 1987, Susumo Tonegawa was awarded with the Nobel Prize for his discoveries on the mechanisms of somatic rearrangement of the immunoglobulin genes.

[Susumo Tonegawa – Facts](#). *Nobelprize.org*. Nobel Media AB 2014.

Acknowledgement

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