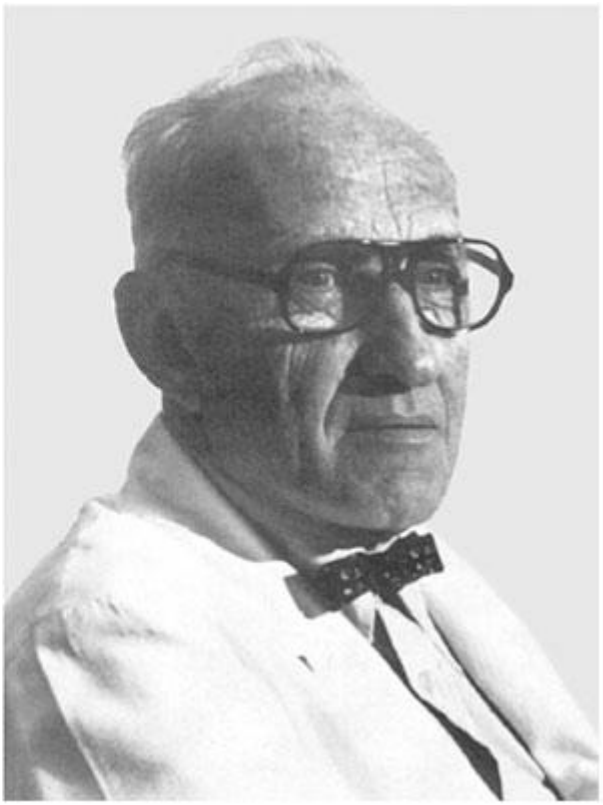
History of Immunoglobulin molecules

Snapshots in the history of Immunoglobulin molecules

1939

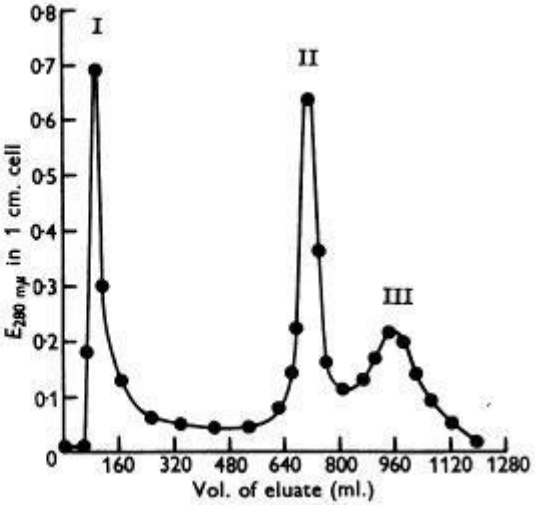
gamma-Globulin



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 crystallizable, and had 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

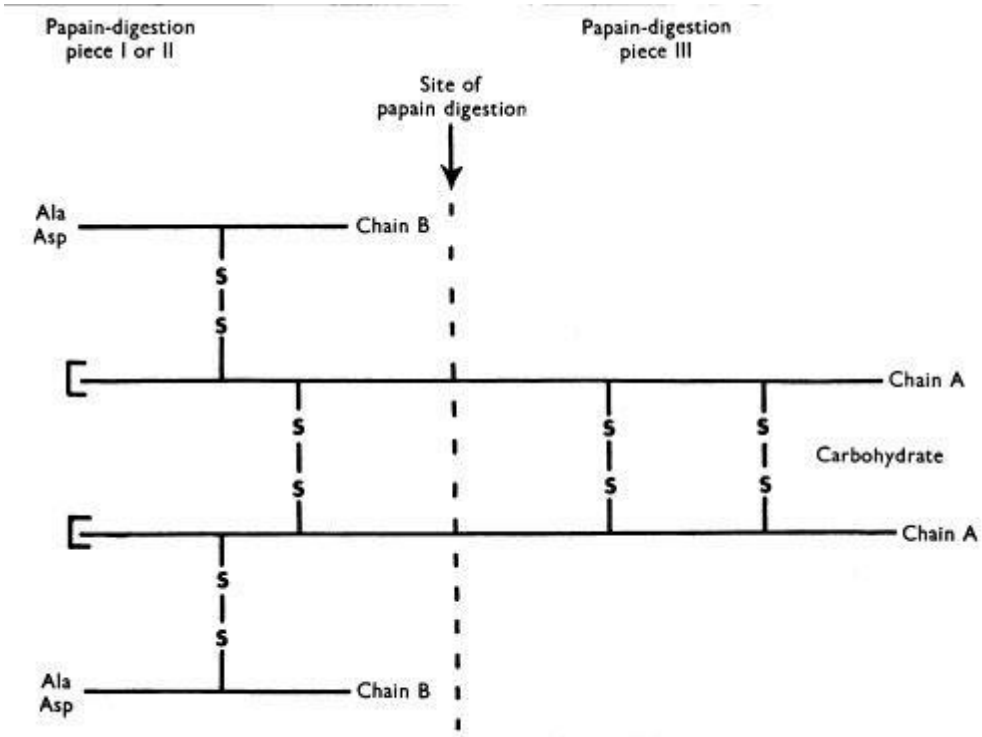
γ-Globulin class		Type and number of chains	Properties assigned to H chains	Properties assigned to L chains
Ultra-centrifugal	Immuno-electrophoretic			
7S	γ_2 γ_{1A}	Small number of L and H* chains	Complement fixation, Skin fixation Placental passage (? Immunologic specificity)	Antibody specificity. 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

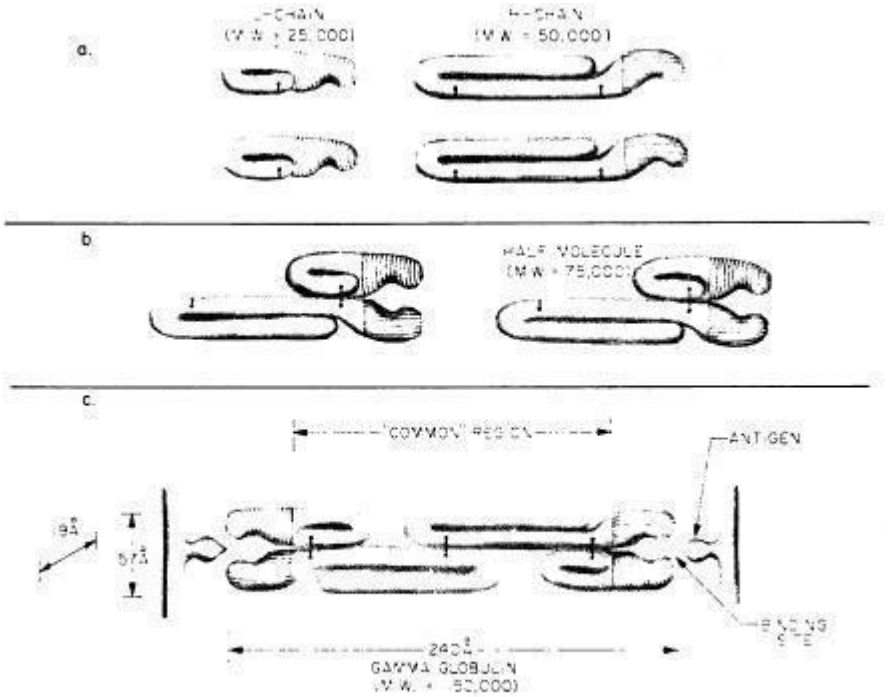


FIG. 1.—Diagrammatic representation of the multiple chain structure of rabbit gamma globulin (see text). Covalent, interchain disulfide linkages (●—●) serve to stabilize the complex structure after formation.

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-7S	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

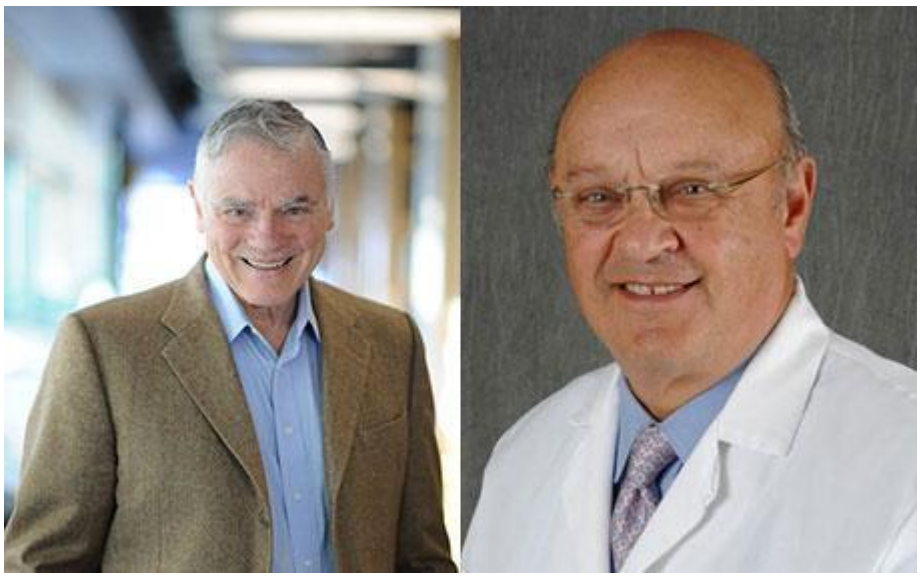
* Serum completely lacked γ_1A; agglutinins found only in 19S region on density gradient ultracentrifugation.

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

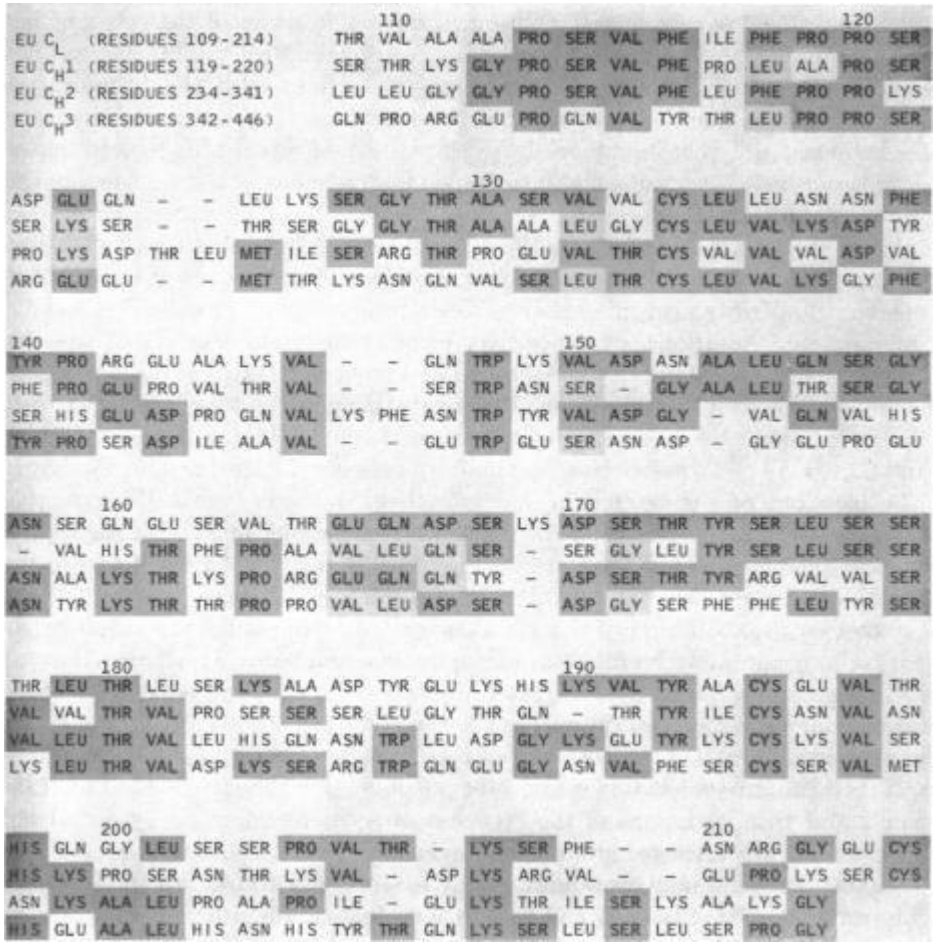
Lambda chain



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



Edelman and coworkers reported the first complete sequence of a γG 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

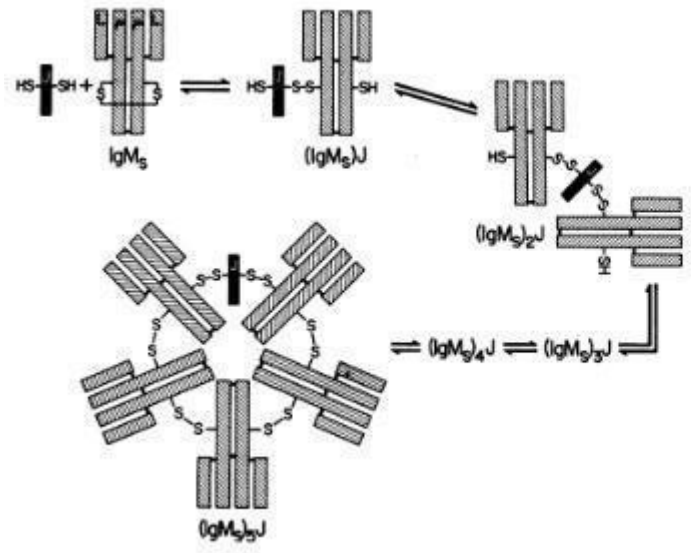
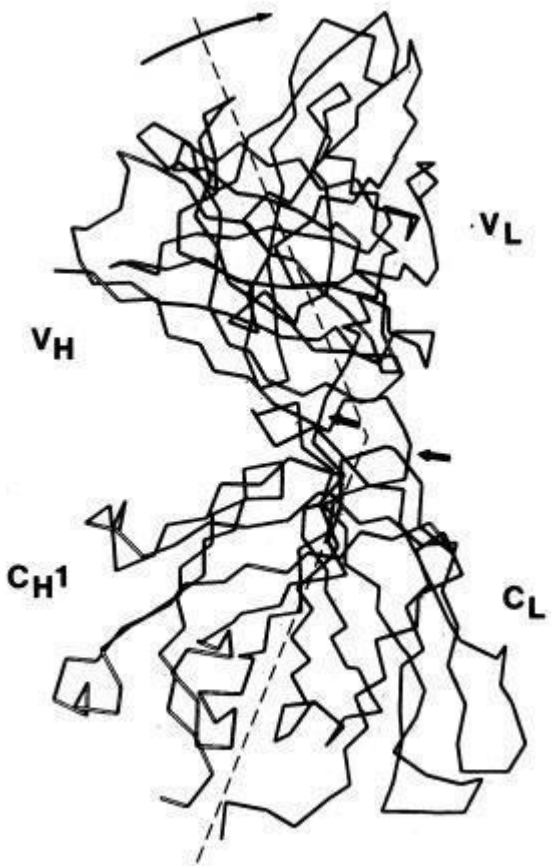


FIG. 5. The clasp model of J linkage in pentamer IgM and the postulated disulfide exchanges leading to its formation. IgM_s = monomer of pentameric IgM.

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(l) myeloma protein (Poljak et al., Proc Nat Acad Sci 71. 3440-3444, 1974).

1975

Monoclonal antibodies

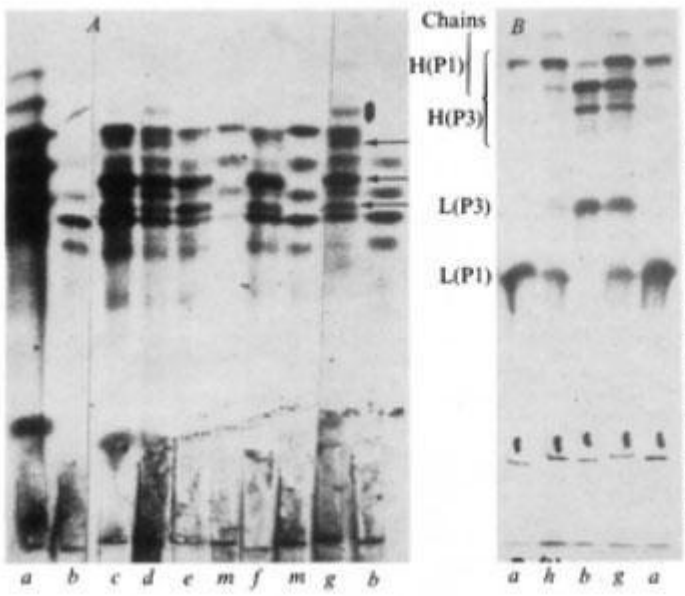
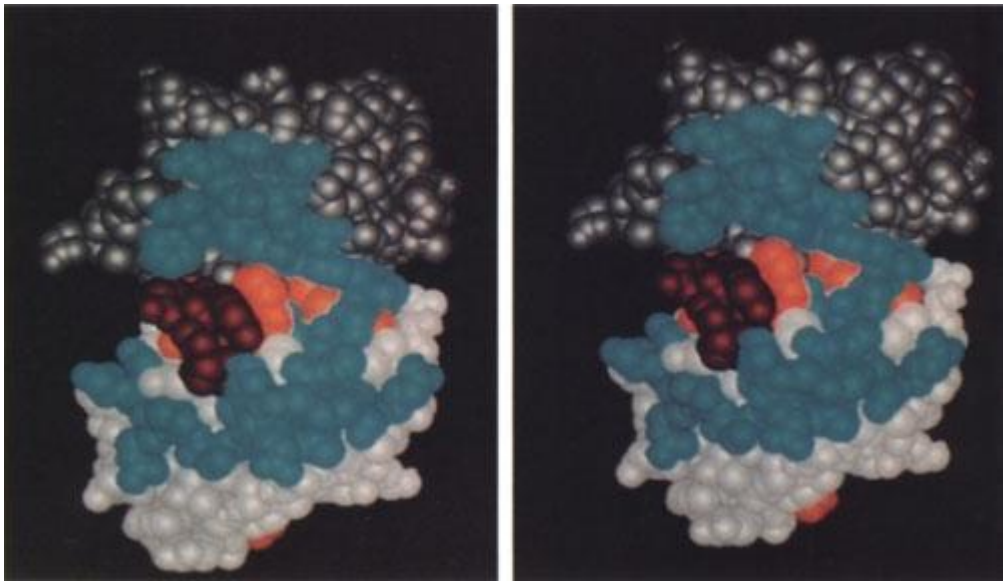


Fig. 1 Autoradiograph of labelled components secreted by the parental and hybrid cell lines analysed by IEF before (*A*) and after reduction (*B*). Cells were incubated in the presence of ^{14}C-lysine[24] and the supernatant applied on polyacrylamide slabs. *A*, pH range 6.0 (bottom) to 8.0 (top) in 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*, P1Bul; *b*, P3-X67Ag8; and *m*, mixture of equal number of P1Bul 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 out[4,5] using 10^8 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 agar[14]. L, Light; H, heavy.

Kohler and Milstein (Nature 256: 495-497, 1975) 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

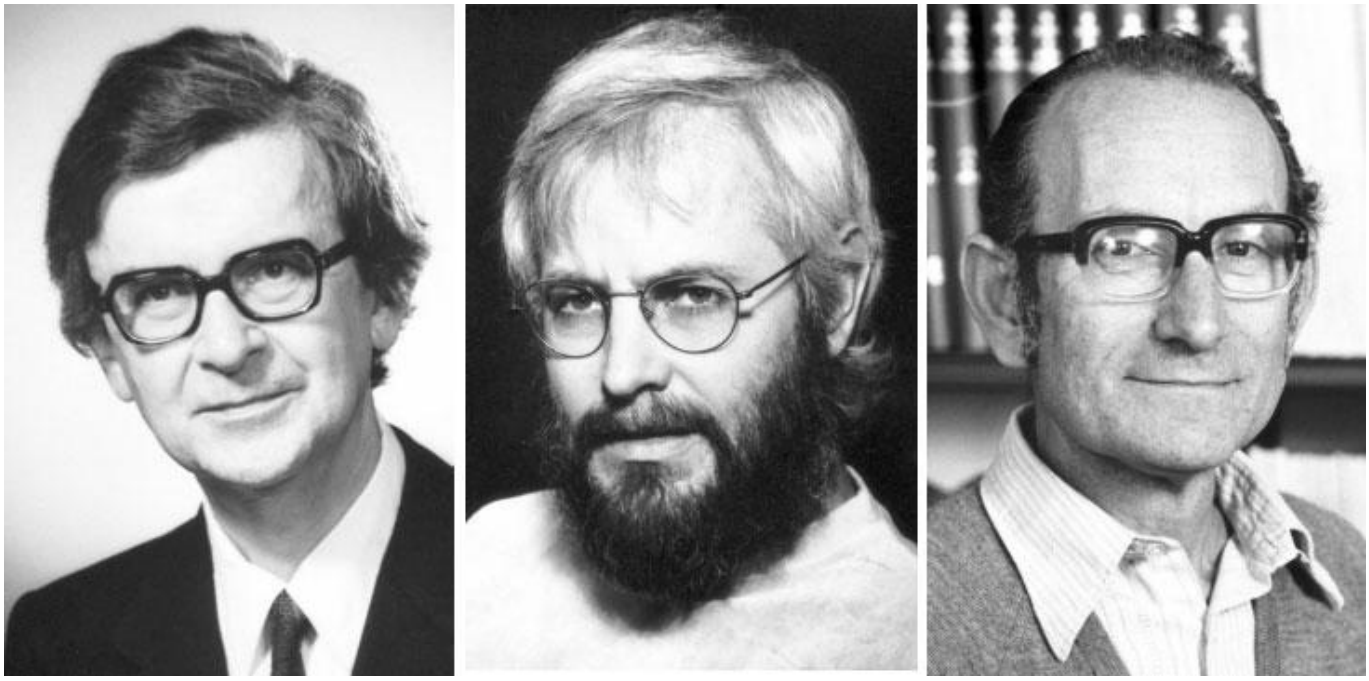


In the late 1970s, Tonegawa and colleagues in a series of elegant experiments demonstrated that

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
History kindly supplied by Dr Luis Garcia – Immunopaedia Steering Committee

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