The Most-Cited 1988 Life-Sciences Papers Highlight the Polymerase Chain Reaction, Cell Signaling, AIDs and HIV Infection, and Oncogenes and the Molecular Basis of Cancer. Reviews Were Very Strongly Represented

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The list of 102 most-cited 1988 papers is remarkable for the extraordinarily high impact (823 citations) achieved by a primordial paper on the polymerase chain reaction, a method of amplifying tiny amounts of deoxyribonucleic acid (DNA) that has already found countless applications in diagnosis and research. Thirteen papers were devoted to various aspects of acquired immunodeficiency syndrome (AIDS) and human immunodeficiency virus (HIV) infection. Another theme strongly represented was communication within and between cells. For the second year running, the US tally of papers declined, while the UK share increased.

There is a well-worn old saw according to which papers devoted to experimental techniques always register frequencies in citation studies that are totally disproportionate to their real significance. If this cliché were to be reflected in reality, then a listing of the publications most cited in the literature during a particular year might well be expected to include a large number of methods papers. The 1988 listing of life-sciences papers does not confirm this prediction. Of the top 102 publications, only 3 are centered on investigational techniques.

Yet this year's compilation does include the exception that proves the rule. While one of the three methods papers (by William R. Pearson, University of Virginia, Charlottesville, and David J. Lipman, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Maryland) describes new ways of comparing sequences carrying biological information, the other two are devoted to a technique that has revolutionized many sectors of experimental biology in very recent years—the polymerase chain reaction. One of these reports (by

BIBLIOGRAPHY

The 1988 life-sciences articles most cited in the *SCI*®, 1988-1989. Articles are listed in alphabetic order by first author. Numbers following the bibliographic entry indicate the 1988 and 1989 *SCI/SSCI*® research-front specialties for which these are core papers.

Citations			Bibliographic Data
Total '88-'89	'88	'89	
87	16	71	**Akbar A N, Terry L, Timms A, Beverley P C L & Janossy G.** Loss of CD45R and gain of UCHL1 reactivity is a feature of primed T-cells. *J. Immunol.* 140:2171-8, 1988. 89-0415
157	55	102	**Angel P, Allegretto E A, Okino S T, Hattori K, Boyle W J, Hunter T & Karin M.** Oncogene *jun* encodes a sequence-specific *trans*-activator similar to AP-1. *Nature* 332:166-71, 1988. 89-0060
110	25	85	**Brand N, Petkovich M, Krust A, Chambon P, de Thé H, Marchio A, Tiollais P & Dejean A.** Identification of a second human retinoic acid receptor. *Nature* 332:850-3, 1988. 89-2234
130	22	108	**Brandt S J, Peters W P, Atwater S K, Kurtzberg J, Borowitz M J, Jones R B, Shpall E J, Bast R C, Gilbert C J & Oette D H.** Effect of recombinant human granulocyte-macrophage colony-stimulating factor on hematopoietic reconstitution after high-dose chemotherapy and autologous bone marrow transplantation. *N. Engl. J. Med.* 318:869-76, 1988. 89-1051
165	27	138	**Brown J H, Jardetzky T, Saper M A, Samraoui B, Bjorkman P J & Wiley D C.** A hypothetical model of the foreign antigen binding site of class-II histocompatibility molecules. *Nature* 332:845-50, 1988. 88-0556, 89-0627
133	27	106	**Casey P J & Gilman A G.** G protein involvement in receptor-effector coupling. *J. Biol. Chem.* 263:2577-80, 1988.
78	13	65	**Cedar H.** DNA methylation and gene activity. *Cell* 53:3-4, 1988. 89-2118
156	37	119	**Chirico W J, Waters M G & Blobel G.** 70K heat shock related proteins stimulate protein translocation into microsomes. *Nature* 332:805-10, 1988.
116	14	102	**Chiu R, Boyle W J, Meek J, Smeal T, Hunter T & Karin M.** The c-Fos protein interacts with c-Jun/AP-1 to stimulate transcription of AP-1 responsive genes. *Cell* 54:541-52, 1988. 89-1013
103	29	74	**Chodosh L A, Baldwin A S, Carthew R W & Sharp P A.** Human CCAAT-binding proteins have heterologous subunits. *Cell* 53:11-24, 1988.
105	40	65	**Curran J W, Jaffe H W, Hardy A M, Morgan W M, Selik R M & Dondero T J.** Epidemiology of HIV infection and AIDS in the United States. *Science* 239:610-6, 1988. 88-4452, 89-2115
139	12	127	**Davis M M & Bjorkman P J.** T-cell antigen receptor genes and T-cell recognition. *Nature* 334:395-402, 1988.
117	33	84	**de Vos A M, Tong L, Milburn M V, Matias P M, Jancarik J, Noguchi S, Nishimura S, Miura K, Ohtsuka E & Kim S-H.** Three-dimensional structure of an oncogene protein: catalytic domain of human c-H-*ras* p21. *Science* 239:888-93, 1988. 89-0240
83	5	78	**DeCaprio J A, Ludlow J W, Figge J, Shew J-Y, Huang C-M, Lee W-H, Marsilio E, Paucha E & Livingston D M.** SV40 large tumor antigen forms a specific complex with the product of the retinoblastoma susceptibility gene. *Cell* 54:275-83, 1988. 89-0573
89	34	55	**Deen K C, McDougal J S, Inacker R, Folena-Wasserman G, Arthos J, Rosenberg J, Maddon P J, Axell R & Sweet R W.** A soluble form of CD4 (T4) protein inhibits AIDS virus infection. *Nature* 331:82-4, 1988. 89-0580
173	40	133	**Deshaies R J, Koch B D, Werner-Washburne M, Craig E A & Schekman R.** A subfamily of stress proteins facilitates translocation of secretory and mitochondrial precursor polypeptides. *Nature* 332:800-5, 1988. 89-1275
174	31	143	**Dinarello C A.** Biology of interleukin 1. *FASEB J.* 2:108-15, 1988.
88	13	75	**Dunphy W G, Brizuela L, Beach D & Newport J.** The Xenopus *cdc*2 protein is a component of MPF, a cytoplasmic regulator of mitosis. *Cell* 54:423-31, 1988. 89-1138
82	35	47	**Elliott J F, Rock E P, Patten P A, Davis M M & Chien Y-h.** The adult T-cell receptor δ-chain is diverse and distinct from that of fetal thymocytes. *Nature* 331:627-31, 1988. 89-1708
246	43	203	**Evans R M.** The steroid and thyroid hormone receptor superfamily. *Science* 240:889-95, 1988. 89-0418
188	75	113	**Evans R M & Hollenberg S M.** Zinc fingers: gilt by association. *Cell* 52:1-3, 1988. 88-1259, 89-2332
201	48	153	**Fauci A S.** The human immunodeficiency virus: infectivity and mechanisms of pathogenesis. *Science* 239:617-22, 1988. 88-5253
108	18	90	**Ferguson M A J & Williams A F.** Cell-surface anchoring of proteins via glycosyl-phosphatidylinositol structures. *Annu. Rev. Biochem.* 57:285-320, 1988. 89-4419

Citations			Bibliographic Data
Total '88-'89	'88	'89	
87	37	50	**Fisher R A, Bertonis J M, Meier W, Johnson V A, Costopoulos D S, Liu T, Tizard R, Walker B D, Hirsch M S, Schooley R T & Flavell R A.** HIV infection is blocked *in vitro* by recombinant soluble CD4. *Nature* 331:76-8, 1988. 89-0580
117	40	77	**Franza B R, Rauscher F J, Josephs S F & Curran T.** The Fos complex and Fos-related antigens recognize sequence elements that contain AP-1 binding sites. *Science* 239:1150-3, 1988. 89-1013
89	8	81	**Gabrilove J L, Jakubowski A, Scher H, Sternberg C, Wong G, Grous J, Yagoda A, Fain K, Moore M A S, Clarkson B, Oettgen H F, Alton K, Welte K & Souza L.** Effect of granulocyte colony-stimulating factor on neutropenia and associated morbidity due to chemotherapy for transitional-cell carcinoma of the urothelium. *N. Engl. J. Med.* 318:1414-22, 1988. 89-1051
93	13	80	**Gautier J, Norbury C, Lohka M, Nurse P & Maller J.** Purified maturation-promoting factor contains the product of a Xenopus homolog of the fission yeast cell cycle control gene *cdc2*$^+$. *Cell* 54:433-9, 1988. 89-1138
80	21	59	**Gonzalez F J, Skoda R C, Kimura S, Umeno M, Zanger U M, Nebert D W, Gelboin H V, Hardwick J P & Meyer U A.** Characterization of the common genetic defect in humans deficient in debrisoquine metabolism. *Nature* 331:442-6, 1988. 89-0640
162	17	145	**Hanks S K, Quinn A M & Hunter T.** The protein kinase family: conserved features and deduced phylogeny of the catalytic domains. *Science* 241:42-52, 1988.
84	10	74	**Harbour J W, Lai S-L, Whang-Peng J, Gazdar A F, Minna J D & Kaye F J.** Abnormalities in structure and expression of the human retinoblastoma gene in SCLC. *Science* 241:353-7, 1988. 89-0573
77	9	68	**Hemler M E.** Adhesive protein receptors on hematopoietic cells. *Immunol. Today* 9:109-13, 1988. 89-3405
82	16	66	**Hemmingsen S M, Woolford C, van der Vies S M, Tilly K, Dennis D T, Georgopoulos C P, Hendrix R W & Ellis R J.** Homologous plant and bacterial proteins chaperone oligomeric protein assembly. *Nature* 333:330-4, 1988. 89-1275
113	2	111	**Hirata Y, Yoshimi H, Takata S, Watanabe T X, Kumagai S, Nakajima K & Sakakibara S.** Cellular mechanism of action by a novel vasoconstrictor endothelin in cultured rat vascular smooth muscle cells. *Biochem. Biophys. Res. Commun.* 154:868-75, 1988. 89-1398
80	21	59	**Hirning L D, Fox A P, McCleskey E W, Olivera B M, Thayer S A, Miller R J & Tsien R W.** Dominant role of N-type Ca^{2+} channels in evoked release of norepinephrine from sympathetic neurons. *Science* 239:57-61, 1988. 89-2063
86	33	53	**Hoey T & Levine M.** Divergent homeo box proteins recognize similar DNA sequences in *Drosophila*. *Nature* 332:858-61, 1988.
93	17	76	**Hoffman E P, Fischbeck K H, Brown R H, Johnson M, Medori R, Loike J D, Harris J B, Waterston R, Brooke M, Specht L, Kupsky W, Chamberlain J, Caskey C T, Shapiro F & Kunkel L M.** Characterization of dystrophin in muscle-biopsy specimens from patients with Duchenne's or Becker's muscular dystrophy. *N. Engl. J. Med.* 318:1363-8, 1988. 89-1095
81	17	64	**Holt I J, Harding A E & Morgan-Hughes J A.** Deletions of muscle mitochrondrial DNA in patients with mitochondrial myopathies. *Nature* 331:717-9, 1988. 88-0946, 89-0938
77	9	68	**Honoré T, Davies S N, Drejer J, Fletcher E J, Jacobsen P, Lodge D & Nielsen F E.** Quinoxalinediones: potent competitive non-NMDA glutamate receptor antagonists. *Science* 241:701-3, 1988. 89-1028
96	38	58	**Hussey R E, Richardson N E, Kowalski M, Brown N R, Chang H-C, Siliciano R F, Dorfman T, Walker B, Sodroski J & Reinherz E L.** A soluble CD4 protein selectively inhibits HIV replication and syncytium formation. *Nature* 331:78-81, 1988. 89-0580
105	9	96	**Ingham P W.** The molecular genetics of embryonic pattern formation in *Drosophila*. *Nature* 335:25-34, 1988. 89-0413
92	10	82	**Itoh Y, Yanagisawa M, Ohkubo S, Kimura C, Kosaka T, Inoue A, Ishida N, Mitsui Y, Onda H, Fujino M & Masaki T.** Cloning and sequence analysis of cDNA encoding the precursor of a human endothelium-derived vascoconstrictor peptide, endothelin: identity of human and porcine endothelin. *FEBS Lett.* 231:440-4, 1988. 89-1398
165	40	125	**Jones N C, Rigby P W J & Ziff E B.** *Trans*-acting protein factors and the regulation of eukaryotic transcription: lessons from studies on DNA tumour viruses. *Gene. Develop.* 2:267-81, 1988.
78	35	43	**Kakidani H & Ptashne M.** GAL4 activates gene expression in mammalian cells. *Cell* 52:161-7, 1988.
223	60	163	**Kappler J W, Staerz U, White J & Marrack P C.** Self-tolerance eliminates T cells specific for Mls-modified products of the major histocompatibility complex. *Nature* 332:35-40, 1988. 88-0256, 89-5495

Citations			Bibliographic Data
Total '88-'89	'88	'89	
112	21	91	**Kawano M, Hirano T, Matsuda T, Taga T, Horii Y, Iwato K, Asaoku H, Tang B, Tanabe O, Tanaka H, Kuramoto A & Kishimoto T.** Autocrine generation and requirement of BSF-2/IL-6 for human multiple myelomas. *Nature* 332:83-5, 1988. 89-0007
83	22	61	**Kishimoto T & Hirano T.** Molecular regulation of B lymphocyte response. *Annu. Rev. Immunol.* 6:485-512, 1988. 89-0007
142	24	118	**Kisielow P, Blüthmann H, Staerz U D, Steinmetz M & von Boehmer H.** Tolerance in T-cell-receptor transgenic mice involves deletion of nonmature $CD4^+8^+$ thymocytes. *Nature* 333:742-6, 1988. 88-0256, 89-5495
117	25	92	**Kitaguchi N, Takahashi Y, Tokushima Y, Shiojiri S & Ito H.** Novel precursor of Alzheimer's disease amyloid protein shows protease inhibitory activity. *Nature* 331:530-2, 1988. 89-0090
110	19	91	**Koenig M, Monaco A P & Kunkel L M.** The complete sequence of dystrophin predicts a rod-shaped cytoskeletal protein. *Cell* 53:219-28, 1988. 89-1095
111	35	76	**Lai F A, Erickson H P, Rousseau E, Liu Q-Y & Meissner G.** Purification and reconstitution of the calcium release channel from skeletal muscle. *Nature* 331:315-9, 1988. 88-0913, 89-1771
184	31	153	**Landschulz W H, Johnson P F & McKnight S L.** The leucine zipper: a hypothetical structure common to a new class of DNA binding proteins. *Science* 240:1759-64, 1988. 89-1013
96	16	80	**Leaf A & Weber P C.** Cardiovascular effects of n-3 fatty acids. *N. Engl. J. Med.* 318:549-57, 1988. 88-7111, 89-1721
77	15	62	**Lotz M, Jirik F, Kabouridis P, Tsoukas C, Hirano T, Kishimoto T & Carson D A.** B cell stimulating factor 2/interleukin 6 is a costimulant for human thymocytes and T lymphocytes. *J. Exp. Med.* 167:1253-8, 1988. 89-0007
188	67	121	**Low M G & Saltiel A R.** Structural and functional roles of glycosyl-phosphatidylinositol in membranes. *Science* 239:268-75, 1988. 88-2516, 89-4419
203	53	150	**MacDonald H R, Schneider R, Lees R K, Howe R C, Acha-Orbea H, Festenstein H, Zinkernagel R M & Hengartner H.** T-cell receptor V_β use predicts reactivity and tolerance to *Mls* ^{a}-encoded antigens. *Nature* 332:40-5, 1988. 89-0289
84	22	62	**Majerus P W, Connolly T M, Bansal V S, Inhorn R C, Ross T S & Lips D L.** Inositol phosphates: synthesis and degradation. *J. Biol. Chem.* 263:3051-4, 1988. 88-0256, 89-1985
79	15	64	**Marrack P & Kappler J.** T cells can distinguish between allogeneic major histocompatibility complex products on different cell types. *Nature* 332:840-3, 1988. 89-5495
103	11	92	**Michie H R, Manogue K R, Spriggs D R, Revhaug A, O'Dwyer S, Dinarello C A, Cerami A, Wolff S M & Wilmore D W.** Detection of circulating tumor necrosis factor after endotoxin administration. *N. Engl. J. Med.* 318:1481-6, 1988. 89-2468
80	10	70	**Morstyn G, Campbell L, Souza L M, Alton N K, Keech J, Green M, Sheridan W, Metcalf D & Fox R.** Effect of granulocyte colony stimulating factor on neutropenia induced by cytotoxic chemotherapy. *Lancet* 1:667-72, 1988. 89-1051
96	15	81	**Moss A R, Bacchetti P, Osmond D, Krampf W, Chaisson R E, Stites D, Wilber J, Allain J-P & Carlson J.** Seropositivity for HIV and the development of AIDS or AIDS related condition: three year follow up of the San Francisco General Hospital cohort. *Brit. Med. J.* 296:745-50, 1988. 89-0584
148	25	123	**Neer E J & Clapham D E.** Roles of G protein subunits in transmembrane signalling. *Nature* 333:129-34, 1988. 89-2063
212	4	208	**Nishizuka Y.** The molecular heterogeneity of protein kinase C and its implications for cellular regulation. *Nature* 334:661-5, 1988. 89-1985
100	22	78	**O'Garra A, Umland S, De France T & Christiansen J.** 'B-cell factors' are pleiotropic. *Immunol. Today* 9:45-54, 1988.
168	37	131	**Ou C-Y, Kwok S, Mitchell S W, Mack D H, Sninsky J J, Krebs J W, Feorino P, Warfield D & Schochetman G.** DNA amplification for direct detection of HIV-1 in DNA of peripheral blood mononuclear cells. *Science* 239:295-7, 1988. 88-3875, 89-0584
92	10	82	**Palmer R M J, Ashton D S & Moncada S.** Vascular endothelial cells synthesize nitric oxide from L-arginine. *Nature* 333:664-6, 1988. 89-4383
129	3	126	**Pearson W R & Lipman D J.** Improved tools for biological sequence comparison. *Proc. Nat. Acad. Sci. USA* 85:2444-8, 1988.
82	27	55	**Piot P, Plummer F A, Mhalu F S, Lamboray J-L, Chin J & Mann J M.** AIDS: an international perspective. *Science* 239:573-9, 1988. 88-4452, 89-2115

Citations			Bibliographic Data
Totals '88-'89	'88	'89	
119	28	91	**Ponte P, Gonzalez-DeWhitt P, Schilling J, Miller J, Hsu D, Greenberg B, Davis K, Wallace W, Lieberburg I, Fuller F & Cordell B.** A new A4 amyloid mRNA contains a domain homologous to serine proteinase inhibitors. *Nature* 331:525-7, 1988. 88-0963, 89-0090
96	26	70	**Price R W, Brew B, Sidtis J, Rosenblum M, Scheck A C & Cleary P.** The brain in AIDS: central nervous system HIV-1 infection and AIDS dementia complex. *Science* 239:586-92, 1988. 88-5253, 89-0822
158	4	154	**Ptashne M.** How eukaryotic transcriptional activators work. *Nature* 335:683-9, 1988.
169	45	124	**Rauscher F J, Cohen D R, Curran T, Bos T J, Vogt P K, Bohmann D, Tijian R & Franza B R.** Fos-associated protein p39 is the product of the *jun* proto-oncogene. *Science* 240:1010-6, 1988. 89-1013
137	55	82	**Rauscher F J, Sambucetti L C, Curran T, Distel R J & Spiegelman B M.** Common DNA binding site for Fos protein complexes and transcription factor AP-1. *Cell* 52:471-80, 1988. 89-1013
102	22	80	**Rauws E A J, Langenberg W, Houthoff H J, Zanen H C & Tytgat G N J.** *Campylobacter pyloridis*-associated chronic active antral gastritis. *Gastroenterology* 94:33-40, 1988. 88-3801, 89-1247
83	4	79	**Roesler W J, Vandenbark G R & Hanson R W.** Cyclic AMP and the induction of eukaryotic gene transcription. *J. Biol. Chem.* 263:9063-6, 1988. 89-1013
93	25	68	**Rosa F, Roberts A B, Danielpour D, Dart L L, Sporn M B & Dawid I B.** Mesoderm induction in amphibians: the role of TGF-β2-like factors. *Science* 239:783-5, 1988.
119	39	80	**Rothbard J B & Taylor W R.** A sequence pattern common to T cell epitopes. *EMBO J.* 7:93-100, 1988. 89-0627
107	34	73	**Ryder K, Lau L F & Nathans D.** A gene activated by growth factors is related to the oncogene v-*jun*. *Proc. Nat. Acad. Sci. USA* 85:1487-91, 1988. 89-1013
129	34	95	**Sackmann M, Delius M, Sauerbruch T, Holl J, Weber W, Ippisch E, Hagelauer U, Wess O, Hepp W, Brendel W & Paumgartner G.** Shock-wave lithotripsy of gallbladder stones: the first 175 patients. *N. Engl. J. Med.* 318:393-7, 1988. 88-0175, 89-0623
823	126	697	**Saiki R K, Gelfand D H, Stoffel S, Scharf S J, Higuchi R, Horn G T, Mullis K B & Erlich H A.** Primer-directed enzymatic amplification of DNA with a thermostable DNA polymerase. *Science* 239:487-91, 1988. 88-3875, 89-3817
81	11	70	**Sanders M E, Makgoba M W, Sharrow S O, Stephany D, Springer T A, Young H A & Shaw S.** Human memory T lymphocytes express increased levels of three cell adhesion molecules (LFA-3, CD2, and LFA-1) and three other molecules (UCHL1, CDw29, and Pgp-1) and have enhanced IFN-γ production. *J. Immunol.* 140:1401-7, 1988.
92	17	75	**Santoro C, Mermod N, Andrews P C & Tijian R.** A family of human CCAAT-box-binding proteins active in transcription and DNA replication: cloning and expression of multiple cDNAs. *Nature* 334:218-24, 1988. 89-3178
82	11	71	**Sassone-Corsi P, Lamph W W, Kamps M & Verma I M.** *fos*-Associated cellular p39 is related to nuclear transcription factor AP-1. *Cell* 54:553-60, 1988. 89-1013
85	34	51	**Schwarz T L, Tempel B L, Papazian D M, Jan Y N & Jan L Y.** Multiple potassium-channel components are produced by alternative splicing at the *Shaker* locus in *Drosophila*. *Nature* 331:137-42, 1988. 89-1771
81	20	61	**Silverberg E & Lubera J A.** Cancer statistics, 1988. *CA—A Cancer J. Clin.* 38:5-22, 1988.
108	47	61	**Simoons M L, Arnold A E R, Betriu A, de Bono D P, Col J, Dougherty F C, von Essen R, Lambertz H, Lubsen J, Meier B, Michel P L, Raynaud P, Rutsch W, Sanz G A, Schmidt W, Serruys P W, Thery C, Uebis R, Vahanian A, Van de Werf F, Willems G M, Wood D & Verstraete M.** Thrombolysis with tissue plasminogen activator in acute myocardial infarction: no additional benefit from immediate percutaneous coronary angioplasty. *Lancet* 1:197-203, 1988. 88-0900, 89-0756
84	5	79	**Smith K A.** Interleukin-2: inception, impact, and implications. *Science* 240:1169-76, 1988.
117	22	95	**Sporn M B & Roberts A B.** Peptide growth factors are multifunctional. *Nature* 332:217-9, 1988.
94	32	62	**Stahl M L, Ferenz C R, Kelleher K L, Kriz R W & Knopf J L.** Sequence similarity of phospholipase C with the non-catalytic region of src. *Nature* 332:269-72, 1988. 89-7970
116	25	91	**Tanzi R E, McClatchey A I, Lamperti E D, Villa-Komaroff L, Gusella J F & Neve R L.** Protease inhibitor domain encoded by an amyloid protein precursor mRNA associated with Alzheimer's disease. *Nature* 331:528-30, 1988. 89-0090
94	38	56	**Traunecker A, Lüke W & Karjalainen K.** Soluble CD4 molecules neutralize human immunodeficiency virus type 1. *Nature* 331:84-6, 1988. 89-0580

Citations			Bibliographic Data
Total '88-'89	'88	'89	
80	21	59	**van Eden W, Thole J E R, van der Zee R, Noordzij A, van Embden J D A, Hensen E J & Cohen I R.** Cloning of the mycobacterial epitope recognized by T lymphocytes in adjuvant arthritis. *Nature* 331:171-3, 1988. 88-1488, 89-3650
111	8	103	**Vogelstein B, Fearon E R, Hamilton S T, Kern S E, Preisinger A C, Leppert M, Nakamura Y, White R, Smits A M M & Bos J L.** Genetic alterations during colorectal-tumor development. *N. Engl. J. Med.* 319:525-32, 1988. 89-0573
128	29	99	**Volpe P, Krause K-H, Hashimoto S, Zorzato F, Pozzan T, Meldolesi J & Lew D P.** "Calciosome," a cytoplasmic organelle: the inositol 1,4,5-trisphosphate-sensitive Ca^{2+} store of nonmuscle cells? *Proc. Nat. Acad. Sci. USA* 85:1091-5, 1988. 89-1771
87	24	63	**Ward J W, Holmberg S D, Allen J R, Cohn D L, Critchley S E, Kleinman S H, Lenes B A, Ravenholt O, Davis J R, Quinn M G & Jaffe H W.** Transmission of human immunodeficiency virus (HIV) by blood transfusions screened as negative for HIV antibody. *N. Engl. J. Med.* 318:473-8, 1988. 88-3007, 89-2978
88	42	46	**Webster N, Jin J R, Green S, Hollis M & Chambon P.** The yeast UAS_G is a transcriptional enhancer in human HeLa cells in the presence of the GAL4 *trans*-activator. *Cell* 52:169-78, 1988.
117	19	98	**Whyte P, Buchkovich K J, Horowitz J M, Friend S H, Raybuck M, Weinberg R A & Harlow E.** Association between an oncogene and an anti-oncogene: the adenovirus E1A proteins bind to the retinoblastoma gene product. *Nature* 334:124-9, 1988. 89- 0573
89	16	73	**Williams A F & Barclay A N.** The immunoglobulin superfamily—domains for cell surface recognition. *Annu. Rev. Immunol.* 6:381-405, 1988. 89-4451
78	11	67	**Wong G G & Clark S C.** Multiple actions of interleukin 6 within a cytokine network. *Immunol. Today* 9:137-9, 1988. 89-0007
95	6	89	**Yamamoto K K, Gonzalez G A, Biggs W H & Montminy M R.** Phosphorylation-induced binding and transcriptional efficacy of nuclear factor CREB. *Nature* 334:494-8, 1988. 89-1013
105	0	105	**Yanagisawa M, Inoue A, Ishikawa T, Kasuya Y, Kimura S, Kumagaye S-i, Nakajima K, Watanabe T X, Sakakibara S, Goto K & Masaki T.** Primary structure, synthesis, and biological activity of rat endothelin, an endothelium-derived vasoconstrictor peptide. *Proc. Nat. Acad. Sci. USA* 85:6964-7, 1988. 89-1398
478	64	414	**Yanagisawa M, Kurihara H, Kimura S, Tomobe Y, Kobayashi M, Mitsui Y, Yazaki Y, Goto K & Masaki T.** A novel potent vasoconstrictor peptide produced by vascular endothelial cells. *Nature* 332:411-5, 1988. 89-1398
105	7	98	**Yarden Y & Ullrich A.** Growth factor receptor tyrosine kinases. *Annu. Rev. Biochem.* 57:443-78, 1988.

Randall K. Saiki, Cetus Corporation, Emeryville, California, and colleagues) holds top place in the entire list with a remarkably high 823 citations in 1988 and 1989.

The Polymerase Chain Reaction

The central maneuvers of genetic engineering—fragmenting a piece of DNA, inserting it into a vector, and then inserting that into a bacterium to clone the gene—can take several days. For many purposes, such as identifying a microorganism from a vanishingly tiny amount of DNA, a quicker method of gene copying is highly desirable. Such a technique is now available in the form of the *polymerase chain reaction* (PCR). Devised by Kary B. Mullis, Saiki, and others at the Cetus Corporation, the PCR is a method of copying DNA chemically in a test tube in just a few hours. Although it does not use living cells, the process can make DNA grow exponentially because it takes place in successive steps, each doubling the amount of DNA.

The key to the technique is that one must know the sequences of short stretches of DNA on either side of the gene to be copied. A gene machine is used to make two "primers"—single strands of DNA, one complementary to one of the flanking sequences and the other to the other. The DNA double helix containing the gene is then untwisted. When the two primers are added, each binds to its complementary flanking sequence. The enzyme DNA polymerase is then added, and immediately extends not only the primers, but also the target gene, too. This series of three steps, each requiring a different temperature, comprises one cycle of the PCR. With an appropriate succession

of temperature changes, as few as 20 cycles can generate approximately a million times the amount of the original target sequence.

The technique was first reported in 1987.[1] Mullis has written about its unlikely origins during a moonlit drive through the mountains of California.[2] A major advance came with the 1988 paper in which Saiki and colleagues introduced a heat-stable DNA polymerase from the bacterium *Thermus aquaticus*. This obviated the need to add fresh polymerase during each of the 30 or so cycles in a typical run. In December 1989, *Science* selected DNA polymerase as its first "molecule of the year."[3,4]

AIDS and Human Immunodeficiency Virus

Thirteen papers were specifically devoted to AIDS, various aspects of HIV infection, and their immunology, as compared with nine in the previous year.[5] In one of these, Chin-Yih Ou, the Centers for Disease Control (CDC), in Atlanta, Georgia, and colleagues used the PCR to identify proviral sequences of HIV directly from DNA in blood samples. The process took three days, rather than the three to four weeks required when diagnosis is based on isolation of the virus.

An important group of four papers indicated a possible approach to the prevention of AIDS through the CD4 antigen, an essential receptor on the cell surface for HIV infection. The papers were by Richard A. Fisher, Biogen Research Corporation, Cambridge, Massachusetts, and colleagues; Rebecca E. Hussey, Dana-Farber Cancer Institute, Boston, Massachusetts, and colleagues; André Traunecker, Basel Institute for Immunology, Switzerland, and colleagues; and Keith C. Deen, Smith Kline and French Laboratories, King of Prussia, Pennsylvania, and colleagues. They showed that a soluble form of the CD4 antigen was capable of blocking HIV infection, providing a possible prophylactic tool. The frequent co-citation of these papers together as a group is reflected in their similar scores of 87, 96, 94, and 89, respectively.

Four of the HIV papers were reviews. James W. Curran and colleagues, CDC, surveyed the epidemiology of the infection in the US. Anthony S. Fauci, National Institutes of Health (NIH), Bethesda, reviewed the mechanisms of infection and the disease itself. Peter Piot, Institute of Tropical Medicine, Antwerp, Belgium, and colleagues from several countries provided an international perspective, while Richard W. Price, Memorial Hospital, New York, and colleagues reviewed the effects of HIV on the brain and nervous system.

The paper by John W. Ward, CDC, and colleagues showed that, although screening of blood had been introduced in the US during the previous three years, and despite the voluntary deferral of blood donation by at-risk individuals, there was still a small but significant risk of HIV being transmitted to patients receiving blood transfusions. The authors called for greater emphasis on deferral and for the evaluation of assays to detect HIV infection earlier.

The Immune System

Three of the most-cited papers of 1988 reported progress in solving one of the central problems of immunology—why an animal is tolerant to its own "self" tissues, although its immune system is capable of recognizing and eliminating any one of a limitless number of "foreign" antigens that may enter the body as infectious agents. One was the fourth-placed paper (223 citations) by John W. Kappler, Howard Hughes Medical Institute, National Jewish Center for Immunology and Respiratory Medicine, Denver, Colorado, and colleagues.

Another paper was authored by H. Robson MacDonald at the Lausanne Branch of the Ludwig Institute for Cancer Research, Epalinges, Switzerland, and coworkers. The third was by Pawel Kisielow, Basel Institute for Immunology, and colleagues. Taken together, these two reports provided further evidence that tolerance to self antigens is achieved by the early deletion of certain clones of lymphocytes that would otherwise attack these antigens. Potentially self-de-

structive clones, in other words, are eliminated, leaving only those comprising the defensive machinery against invading antigens.

Cancer and Its Genetic Basis

Six papers were devoted to oncogenes, mutated versions of normal genes called proto-oncogenes that occur in animal cells and can turn them into malignant cells. Abraham M. de Vos, University of California (UC), Berkeley, and colleagues described the three-dimensional structure of a protein of the *ras* gene family, which includes many of the commonly found oncogenes isolated from human tumors and transformed cell lines. They discovered regions of the molecule that may well participate in other functions in the cell.

In one of the most-cited papers of 1987,[5] Johannes L. Bos, State University of Leiden, The Netherlands, and coworkers showed that mutations of *ras* genes were present in more than a third of human colorectal tumors, usually occurring before the appearance of cancer.[6] In 1988, a further paper by Bert Vogelstein, Johns Hopkins University School of Medicine, Baltimore, Maryland, Bos, and others reported changes during the development of colorectal tumors. Study of these changes suggests that the steps needed for the appearance of cancer often involve activation of an oncogene by mutation, together with the loss of several genes that normally suppress tumor development.

The first positive demonstration of a physical link between an oncogene and an anti- or negative oncogene was the subject of a paper by Peter Whyte, Cold Spring Harbor Laboratory, New York, and colleagues. They discovered that the protein of a virus oncogene, E1A, interacts with an anti-oncogene that inhibits the function of the protein produced by the retinoblastoma gene.

Retinoblastoma, a condition in which tumors grow in the eyes of children, featured in the listing of 1987 most-cited life-sciences papers,[5] when Wen-Hwa Lee, University of California, San Diego (UCSD), and collaborators described the identification, cloning, and sequencing of the putative gene for this form of cancer.[7] In their 1988 paper, J. William Harbour and coworkers at NIH found abnormalities of the retinoblastoma gene in two neuroendocrine tumors (small cell lung cancer and pulmonary carcinoids). Their finding indicates that the retinoblastoma gene is involved not only in the development of this condition, but also in malignant diseases in other tissues in adults.

Frank J. Rauscher, Roche Institute for Molecular Biology, Nutley, New Jersey, and colleagues published two papers that strengthen the links between the *fos* oncogene, which is associated with osteosarcoma in the mouse, and the *jun* proto-oncogene. B. Robert Franza, Cold Spring Harbor Laboratory, first-named author of a third Rauscher paper, commented in *The Scientist*®[8] on the most cited of this trio of papers. This confirmed that in mammalian cells a genetically defined control element was the target not of one protein, but of many proteins, and indicated that the combinations thereof at any one time represent a fine-tunable way of mediating or modulating expression of the functionally linked genes. The paper "certainly caught the attention of a lot of people, who all of a sudden decided that *fos* and *jun* were important to work on," Franza commented.[8]

Three papers described the use of recombinant DNA products to ameliorate the damage to bone marrow that accompanies chemotherapy for cancer. Paralleling the highly cited[5] 1987 paper by Jerome E. Groopman, New England Deaconess Hospital, Boston, and colleagues on the use of genetically engineered human granulocyte-macrophage colony-stimulating factor to restore white blood cell counts in AIDS patients,[9] Stephen J. Brandt, Duke University Medical Center, Durham, North Carolina, and colleagues gave the same agent to patients with breast cancer or melanoma. Their paper showed that it can accelerate the recovery of the bone marrow after high dosage chemotherapy and bone marrow transplantation.

Similar benefits of granulocyte colony-stimulating factor were demonstrated in two papers. One was by Janice L. Gabrilove, Memorial Sloan-Kettering Cancer Center, New York, and colleagues who treated patients with carcinoma of the urothelium. The other was authored by G. Morstyn, Ludwig Institute for Cancer Research, Melbourne, Australia, and colleagues. They treated patients suffering from various advanced malignancies.

A potentially far-reaching discovery of 1988, whose implications are still being worked out, is that of the "leucine zipper," described in the paper by William H. Landschulz and colleagues, Carnegie Institution of Washington, Baltimore. They have found a particular feature of certain proteins in eukaryotes, characterized by regions of the molecule with repetitions of the amino acid leucine. This permits the molecules to bind to DNA. One feature of the leucine zipper that is still unclear is why these regions have sequences similar to those of oncogenes such as *fos* and *jun*.

Cell Signaling

Peter Angel, UCSD School of Medicine, another author in the 1987 listing,[5] appears with colleagues in the 1988 compilation for a paper with 157 citations. They provided more evidence on how proto-oncogenes are involved in the transduction of signals between cells.

As highlighted last year,[5] identification of the messengers and mechanisms involved in communication between and within cells has become a burgeoning research field during the last decade. This chain of events begins when a "first messenger" (hormone or neurotransmitter) acts on a receptor on the cell surface and thereby triggers the generation of a "second messenger" (often diacylglycerol or inositol triphosphate) that initiates the cell's response. The signal is amplified in the production of the second messenger, sometimes through proteins called signal transducers. In other cases, the first messenger opens up an "ion channel," and the degree of amplification depends on the number of ions that flow into the cell while each channel is open.

One of the highly cited 1987 papers[5] was that in which Shigeo Ohno, Tokyo Metropolitan Institute of Medical Science, Japan, and colleagues, working with protein kinase C (which can be activated in the cell by diacylglycerol), indicated how a limited portfolio of signaling substances is able to generate a wide diversity of messages.[10] The fifth most-cited paper of 1988 (212 citations) is that in which Yasutomi Nishizuka, Kobe University School of Medicine, Japan, reviews the many different subspecies in the family of proteins comprising protein kinase C. It also indicates ways in which different kinase play distinct roles in processing and modulating cellular responses to external signals. An earlier review on protein kinase C by Nishizuka[11] was the most highly cited life-sciences paper of 1986, with 296 citations.[12]

There were five other high impact reviews of various aspects of signaling. Steven K. Hanks, Salk Institute for Biological Studies, La Jolla, California, surveyed the molecular biology of the protein kinase. Ronald M. Evans, Howard Hughes Medical Institute, Salk Institute for Biological Studies, was in third place overall with 246 citations to his review of the steroid/thyroid hormone receptor family, which includes receptors for thyroid hormone and several other substances. Mark Ptashne, Harvard University, Cambridge, Massachusetts, reviewed transcriptional activators in eukaryotic cells. Eva J. Neer, Harvard Medical School, Boston, and David E. Clapham, Mayo Foundation, Rochester, Minnesota, reviewed the proteins that couple cell surface receptors with various ion channels and enzymes. And Michael B. Sporn and Anita B. Roberts, National Cancer Institute, Bethesda, discussed the eclectic roles of peptide growth factors.

A paper in the 1987 listing[5] focused on retinoic-acid—which, like its parent substance vitamin A, is required for the control of endothelial cell growth and for cellular differentiation. In this publication, Martin Petkovich, Nigel J. Brand, and colleagues at

Table 1: The 1988 and 1989 ISI® research fronts that include at least three of the most-cited 1988 life-sciences papers as core documents. A=number of Bibliography papers that are core to each research front. B=total number of core documents. C=total number of citing papers published for the year designated by the prefix.

Number	Name	A	B	C
88-0256	γ δ T-cell receptor genes in human T-cell precursors, somatic generation of immune diversity, and surface expression	3	51	1,007
89-0007	Interleukin-6 receptor expression, human endothelial cells, acute phase response, and differentiation factor	4	28	761
89-0090	Alzheimer's disease amyloid precursor protein, differential brain expression, and reactive astrocytes following neuronal damage	3	48	800
89-0573	Tumor suppressor genes, human breast cancer, medullary thyroid carcinoma, molecular mechanisms, and biology of disease	4	58	871
89-0580	Human immunodeficiency virus, HIV infection, recombinant soluble CD4 receptor, and protein expression via a *cis*-acting sequence	4	44	1,079
89-1013	Sequence specific DNA interaction of the Fos *jun* protein complex, early gene induction, transcription factor AP-1, and leucine zipper domain	9	56	1,692
89-1051	Recombinant human granulocyte macrophage colony-stimulating-factor, and hematopoietic reconstitution following autologous bone marrow transplantation	3	29	739
89-1398	Endothelin stimulates release, rat cardiac membranes, vascular smooth muscle and systemic vasoconstrictor peptide	4	37	587
89-1771	Ryanodine receptor Ca^{2+} release channel complex of skeletal muscule sarcoplasmic reticulum, calcium regulation, and mammalian cardiac ventricular cells	3	55	1,140
89-5495	T cell receptor V_β expression, positive selection, and transgenic mice	3	20	573

INSERM's Molecular Biology and Genetic Engineering Group in Strasbourg, France, reported their identification of the retinoic acid receptor as a member of the steroid/thyroid receptor family.[13] Petkovich is now among the coauthors of a highly cited 1988 paper, of which Brand is the first author. The paper reports the identification of a second human retinoic acid receptor.

Alzheimer's Disease

The 1987 listing[5] included a clutch of reports by Rudolph E. Tanzi, Harvard Medical School, and colleagues.[14] They described the isolation, cloning, and characterization of the DNA that codes for amyloid, which is found in the brains of Alzheimer's disease patients. They then used the DNA as a probe to determine where the amyloid gene was expressed in the brains of patients with either Alzheimer's disease or Down's syndrome and to map the gene on chromosome 21. Before the end of 1987, however, Tanzi and others had shown that the disease did not seem to segregate together with the supposed amyloid gene in affected families. Although amyloid was certainly involved in the condition, the amyloid gene was not *the* Alzheimer's disease gene.

Of three high impact 1988 papers on Alzheimer's disease, two threw light on the condition from a rather different perspective, that of the protease inhibitor enzymes that are now being found to play several different roles in metabolism. They were authored by Tanzi and colleagues, and by Nobuya Kitaguchi and coworkers, Asahi Chemical Industry Company, Limited, Shizuoka, Japan. Working independently, they located, within the precursor of the amyloid beta-protein, a domain containing a sequence for a protease inhibitor. The reason for this relationship is still unclear.

Other Highlights

The list included two highly cited papers on so-called stress proteins. This is a group of proteins, including heat shock proteins, which are rapidly synthesized when cells undergo physicochemical stress—of which heat is one variety. There are three families of stress proteins. They can be distinguished according to their molecular weights, but while some have been isolated and cloned, their functions are not well understood.

Table 2: The number of authors per paper for the 1988 life-sciences articles most cited in the *SCI®*, 1988-1989.

Number of Authors per Paper	Number of Papers
23	1
15	1
14	1
12	1
11	6
10	4
9	8
8	5
7	9
6	9
5	12
4	8
3	10
2	18
1	9

The papers by Raymond J. Deshaies, UC, Berkeley, and colleagues, and by William J. Chirico and colleagues, Howard Hughes Medical Institute, The Rockefeller University, New York, together provided the first biochemical assay for the major heat shock protein, hsp 70, whose physiological significance is known with certainty. It is involved in the translocation of proteins across membranes and thus into mitochondria and the endoplasmic reticulum in the cell. The group of proteins to which it belongs is remarkable in having been conserved during evolution so that it occurs in organisms as diverse as humans, the fruit fly *Drosophila*, and the bacterium *Escherichia coli*.

A high impact 1987 paper[5] by R.M.J. Palmer and colleagues at the Wellcome Research Laboratories, Beckenham, UK, helped to show how endothelial cells react to mechanical stress, and to various neurohormonal mediators, by releasing substances that either constrict or widen blood vessels.[15] They identified one of the most powerful of the vasodilators as nitric oxide. A 1988 paper from Palmer and coworkers (92 citations) demonstrated that nitric oxide can be synthesized from L-arginine by endothelial cells from the aorta of the pig when grown in tissue culture. This seems to be the route through which the nitric oxide is produced naturally. As the authors observed in *The Scientist*, deficiencies in the synthetic pathway may well contribute to a variety of diseases, including hypertension and atherosclerosis.[16] One of the coauthors, Salvador Moncada, has written two *Citation Classic®* commentaries[17,18] on earlier papers.

Complementing these studies on an agent that causes relaxation of smooth muscle cells, and thus the dilation of blood vessels, Masashi Yanagisawa, University of Tsukuba, Japan, and colleagues reported a peptide that causes blood vessels to constrict. Their paper is the second most cited of 1988, with 478 citations. It describes the isolation and cloning of a previously unknown vasoconstrictor peptide, endothelin, that is produced by endothelium from pig aorta cells. In a second paper, Yanagisawa and coworkers recorded the structure, synthesis, and biological activity of endothelin.

Nine US centers and one UK center were involved in the work reported in a paper on Duchenne's and Becker's muscular dystrophy, whose senior author was Eric P. Hoffman, Children's Hospital, Boston. Having earlier identified the muscular dystrophy gene and the corresponding protein, dystrophin,[19] in this paper, they described the precise basis of several forms of neuromuscular disease. Whereas an abnormal dystrophin was responsible for Becker's dystrophy, severe Duchenne's dystrophy was caused by an absence of dystrophin. M. Koenig and other colleagues of Hoffman at Children's Hospital reported the entire protein sequence of dystrophin in their *Cell* paper.

One of the most intriguing reports in the 1988 collection is that in which P.W. Ingham of the Imperial Cancer Research Fund Developmental Biology Unit, Oxford, UK, threw further light on the molecular biology underlying the development of *Drosophila*. American zoologist Thomas Hunt Morgan, winner of the 1933 Nobel Prize for physiology or medicine, introduced the fruit fly into genetics research in the early years of this century, because it has only four pairs of chromosomes and a life cycle of about 14 days. Only recently, however, largely

through Ingham's work, has it become clear that the molecular and cellular development of *Drosophila* is directly related to that of vertebrate animals.

Research Fronts

Table 1 shows the 10 ISI® research fronts for 1988 and 1989 whose core documents include at least three of the most-cited 1988 life-sciences papers. Particularly conspicuous, with nine of these papers in the core, is #89-1013, "Sequence specific DNA interaction of the Fos *jun* protein complex, early gene induction, transcription factor AP-1, and leucine zipper domain." This is a reflection of the growing importance of studies that are beginning to link cellular communication and recognition systems with gene action and carcinogenesis. Certain aspects of these relationships also are apparent to one degree or another in three of the four research fronts that have four papers in the core—#89-0007, "Interleukin-6 receptor expression, human endothelial cells, acute phase response, and differentiation factor"; #89-0573, "Tumor suppressor genes, human breast cancer, medullary thyroid carcinoma, molecular mechanisms, and biology of disease"; and #89-0580, "Human immunodeficiency virus, HIV infection, recombinant soluble CD4 receptor, and protein expression via a *cis*-acting sequence."

Authors

There is only one Nobel laureate in the list, Daniel Nathans, Johns Hopkins University School of Medicine, who in 1978 won the medicine prize with Werner Arber, University of Basel, Switzerland, and Hamilton O. Smith, also at Johns Hopkins, for work on enzymes used in producing recombinant DNA. The paper by Kevin Ryder, Lester F. Lau, and Nathans, Johns Hopkins University School of Medicine, related an oncogene to a gene activated by growth factors.

Seven scientists shared the honors as the most prolific authors of highly cited papers, with three papers each in the 1988 listing.

Table 3: The 20 journals that published the papers listed in the Bibliography. The numbers in parentheses are the 1989 impact factors for the journals. (The 1989 impact factor equals the number of 1989 citations received by the 1987-1988 articles in a journal divided by the number of articles published by the journal during that same period.) Data were taken from the 1989 *JCR* ®. The figures at the right indicate how many papers from each journal appear in the Bibliography.

Journal	Number of Papers
Nature (18.1)	37
Science (18.3)	18
Cell (25.2)	12
N. Engl. J. Med. (22.0)	8
Proc. Nat. Acad. Sci. USA (10.0)	4
Immunol. Today (18.3)	3
J. Biol. Chem. (6.6)	3
Annu. Rev. Biochem. (64.0)	2
Annu. Rev. Immunol. (25.1)	2
J. Immunol. (7.3)	2
Lancet (14.4)	2
Biochem. Biophys. Res. Commun. (3.2)	1
Brit. Med. J. (3.3)	1
Ca—A Cancer J. Clin. (4.7)	1
EMBO J. (11.9)	1
FASEB J. (18.3)	1
FEBS Lett. (3.7)	1
Gastroenterology (6.3)	1
Gene. Develop. (10.7)	1
J. Exp. Med. (11.8)	1

The authors included three oncogene investigators, Tony Hunter, Salk Institute for Biological Sciences, and Rauscher and Tom Curran, Roche Institute of Molecular Biology. Toshio Hirano and Tadamitsu Kishimoto, Osaka University, Japan, coauthored papers on the immune system. And Tomoh Masaki, University of Tsukaba, and Yanagisawa contributed three papers on various aspects of endothelin.

Last year's most prolific author, Robert Tjian, UC, Berkeley, who coauthored five papers on cell signaling and transcription factors, had two papers on this year's list. The average number of authors per paper (Table 2) was 5.5, down from 5.7 in 1987 and 6.0 in 1986.

Journals, Countries, and Institutions

Nature and *Science* again account for about half of the papers (Table 3). But both journals were more widely cited in the liter-

Table 4: National locations of the institutional affiliations listed by authors in the Bibliography, according to total papers (column A). B=number of papers coauthored with researchers affiliated with institutions in other countries. C=national locations of institutions listed by coauthors.

Country	A	B	C
US	76	14	Australia, Belgium, Canada, France, FRG, Japan, Kenya, The Netherlands, Switzerland, Tanzania, UK
UK	14	6	Belgium, Canada, Denmark, France, FRG, GDR, The Netherlands, Switzerland, US
Japan	10	2	US
Switzerland	7	6	Belgium, Canada, FRG, Italy, Kenya, Tanzania, UK, US
France	4	3	Belgium, FRG, GDR, The Netherlands, UK, US
FRG	4	3	Belgium, France, GDR, The Netherlands, Switzerland, UK, US
The Netherlands	4	3	Belgium, France, FRG, GDR, Israel, UK, US
Belgium	2	2	Canada, France, FRG, GDR, Kenya, The Netherlands, Switzerland, Tanzania, UK, US
Canada	2	2	Belgium, Kenya, Switzerland, Tanzania, US, UK
Israel	2	1	The Netherlands
Australia	1	1	US
Denmark	1	1	UK
GDR	1	1	Belgium, France, FRG, The Netherlands, UK
Italy	1	1	Switzerland
Kenya	1	1	Belgium, Canada, Switzerland, Tanzania, US
Tanzania	1	1	Belgium, Canada, Kenya, Switzerland, US

ature than in the previous year. *Nature*'s "impact factor" (an overall measure of the degree to which papers in a particular journal are cited) was 18.1, compared with 15.8 in the previous year. The figure for *Science* rose from 16.3 to 18.3. *Cell*, the *New England Journal of Medicine*, and the *Proceedings of the National Academy of Sciences* remain in third, fourth, and fifth places for the second year running. Next in order is *Immunology Today*—one of Elsevier's "Trends" stable—which did not appear at all in last year's listing but now shows an impact factor of 18.3, comparable with those of *Nature* and *Science*. Other periodicals not on last year's list include the *British Medical Journal* and the *Journal of Immunology*. *Genes and Development* and the *FASEB Journal* make their inaugural appearance. The *Biochemical Journal* fails to appear for the first time since 1982.

In last year's review,[5] we commented on the decline in the US national tally of papers, from 94 out of 103 to 82 out of 101, and the rise in the UK entries to 11 from 6.[5] This trend has continued (Table 4), with the US tally falling to 76 and that of the UK rising to 14. Japan has risen from fourth to third place with a score of 10, but in fourth position, with a score of 7, is Switzerland, which did not appear at all in the previous year. This reflects the major importance of immunological research being conducted at the Basel Institute for Immunology and other Swiss laboratories. Tanzania makes its first appearance in this annual review of life-sciences publications; Fred S. Mhalu, Muhimbili Medical Center, University of Dar es Salaam, Tanzania, is a coauthor of "AIDS: an international perspective" (first author Piot), published in *Science*.

Of the 123 institutions represented on the list, the most prolific were Harvard (Medical School and University) with 17 papers, the University of California (Berkeley, San Diego, San Francisco, and Davis) with 12 papers, and the National Institutes of Health with 11 papers. Sixteen papers were authored by departments with funding from the Howard Hughes Medical Institute.

Conclusion

The listing of most-cited life-sciences papers of 1988 provides a remarkably sharp snapshot of the prevailing paradigms of biological research, centered around the molecular biology of the immune system, cancer, and cell signaling. As with the previous

year's review, it contradicts the common view that methods papers emerge unduly strongly when publishing activity is examined by citation analysis. At the same time, the remarkably high score of 823 citations for the paper by Saiki and colleagues on the polymerase chain reaction reflects and highlights the far-reaching importance of a laboratory technique that certainly has transformed many different fields and activities within the life sciences.

Finally, another striking feature of this survey is that no less than 27 of the top 102 papers are reviews of one sort or another. These range widely, from AIDS to embryonic development, but the two largest groups were cell signaling (eight reviews) and immunology (seven reviews). Eugene Garfield has commented on the considerable importance of well-timed, insightful reviewing as a creative strand within the scientific enterprise.[20] The 1988 analysis confirms this view and suggests that pertinent reviewing may well be an activity of growing importance.

* * * * *

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REFERENCES

1. **Mullis K B & Faloona F.** Specific synthesis of DNA *in vitro* via a polymerase catalysed chain reaction. *Methods Enzymol.* 155:335-50, 1987.
2. **Mullis K B.** The unusual origin of the polymerase chain reaction. *Sci. Amer.* 262(4):56-65, April 1990.
3. **Koshland D E.** The molecule of the year. *Science* 246:1541, 1989.
4. **Guyer R L & Koshland D E.** The molecule of the year. *Science* 246:1543-6, 1989.
5. **Garfield E.** The 1987 life-sciences articles most cited in 1987 and 1988. *Current Contents* (17):3-18, 23 April 1990.
6. **Bos J L, Fearon E R, Hamilton S R, Verlaan-De Vries M, Van Boom J H, Van der Eb A J & Vogelstein B.** Prevalence of *ras* gene mutations in human colorectal cancers. *Nature* 327:293-7, 1987.
7. **Lee W-H, Bookstein R, Hong F, Young L-J, Shew J-Y & Lee E Y-H P.** Human retinoblastoma susceptibility gene: cloning, identification, and sequence. *Science* 235:1394-9, 1987.
8. **Franza R.** Hot papers. *The Scientist* 3(4):13, 20 March 1989.
9. **Groopman J E, Mitsuyasu R T, DeLeo M J, Oette D H & Golde D W.** Effects of recombinant human granulocyte-macrophage colony-stimulating factor on myelopoiesis in the acquired immunodeficiency syndrome. *N. Engl. J. Med.* 317:593-8, 1987.
10. **Ohno S, Kawasaki H, Imajoh S, Suzuki K, Inagaki M, Yokokura H, Sakoh T & Hidaka H.** Tissue-specific expression of three distinct types of rabbit protein kinase C. *Nature* 325:161-6, 1987.
11. **Nishizuka Y.** Studies and perspectives of protein kinase C. *Science* 233:305-12, 1986.
12. **Garfield E.** The most-cited 1986 life-sciences articles highlight cell-surface receptors, tumor necrosis factor, and AIDS research. *Current Contents* (50):3-16, 12 December 1988.
13. **Petkovich M, Brand N J, Krust A & Chambon P.** A human retinoic acid receptor which belongs to the family of nuclear receptors. *Nature* 330:444-50, 1987.
14. **Tanzi R E, Gusella J F, Watkins P C, Bruns G A P, St. George-Hyslop P H, Van Keuren M L, Patterson D, Pagan S, Kurnit D M & Neve R L.** Amyloid protein gene: cDNA, mRNA distribution and genetic linkage near the Alzheimer locus. *Science* 235:880-4, 1987.
15. **Palmer R M J, Ferrige A G & Moncada S.** Nitric oxide release accounts for the biological activity of endothelium-deriving relaxing factor. *Nature* 327:524-6, 1987.
16. **Palmer R M J & Moncada S.** Hot papers. *The Scientist* 3(9):13, 1 May 1989.
17. **Moncada S.** Citation classic. Commentary on *Lancet* 1:18-21, 1977. (Barrett J T, ed.) *Contemporary classics in the life sciences. Volume 2: the molecules of life.* Philadelphia: ISI Press, 1986. p. 54.
18. - - - - - - - -. Citation Classic. Commentary on *Nature* 263:663-5, 1976. (Barrett J T, ed.) *Contemporary classics in the life sciences. Volume 2: the molecules of life.* Philadelphia: ISI Press, 1986. p. 186.
19. **Hoffman E P, Brown B H & Kunkel L M.** Dystrophin: the protein product of the Duchenne muscular dystrophy gene. *Cell* 51:919-28, 1987.
20. **Garfield E.** Reviewing review literature. Parts 1 & 2. *Current Contents* (18):3-6, 4 May 1987; (19):3-8, 11 May 1987. (Reprinted in: *Essays of an information scientist: peer review, refereeing, fraud, and other essays.* Philadelphia: ISI Press, 1989. Vol. 10. p. 113-22.)