DRUG DISCOVERY

# Fundamental science behind today's important medicines

**Jonathan M. Spector,[1] Rosemary S. Harrison,[1] Mark C. Fishman[2]***



**Today's most transformative medicines exist because of fundamental discoveries that were made without regard to practical outcome and with their relevance to therapeutics only appearing decades later.**

There is much debate about the value to society of fundamental research. In a time of constrained resources, does such work need justification according to its practical outcomes? Should we be shifting funding from discovery for its own sake to projects more definably linked to human health, particularly when it comes to the discovery of new pharmaceuticals? Would such a shift over the long run enhance the number of better long-term therapies? One way to address these questions would be to determine the importance of fundamental research, unrelated to drug discovery per se, to the ultimate generation of new medicines. Thus, we undertook to elucidate the scientific origins of some of today's most important drugs.

The first drugs, recorded in the Ebers Papyrus (1500 BC) (*1*), were complex mixtures of plants noted to have therapeutic effects. By the late 1800s, the active ingredients of several such natural products were isolated and themselves became medicines. Following Paul Ehrlich's work in 1909, drugs began to be generated by the screening of chemicals, natural and synthetic, for effects on biological systems. In all of these cases, the molecular target of the drug was isolated, if at all, only long after the drug was in use. Today, drug discovery generally begins with a known molecular target. This would suggest that it rests upon fundamental biological discovery.

For our analysis, we focused upon a compendium of the 28 "most transformative" medicines approved for clinical use by the U.S. Food and Drug Administration (FDA) between 1985 and 2009 (*2*). For each medicine, we asked whether it began with a basic discovery, meaning an observation about biology or pathophysiology of disease. We also queried whether it was apparent at the time that this discovery held the promise of a new therapeutic and, if not, how long it took for this to be appreciated.

To achieve consensus on the key discoveries, we used the "Delphi method," asking a set of experts in each field (table S1) about potentially relevant scientific discoveries. Then, in an iterative fashion, we sent them the timelines we constructed for revision until we ultimately reached general agreement. When drug classes were cited as transformative, we studied the first medicine in that class to be approved by the FDA. The literature was reviewed to identify individuals who were personally involved in discovery or development efforts, had themselves studied the topic for a specific drug, or were senior physicians or researchers who could provide a historical perspective (table S1). Two exemplary timelines of drug discovery are shown in Figs. 1 and 2 (the remainder are displayed in appendix S1).

We found that approximately 80% of the medicines on this list (table S2) could be traced back to one or several basic discoveries (Figs. 1 and 2 and appendix S1). The average time period from first basic discovery to FDA approval was 31 years (median, 32 years), with essentially no differences for small molecules versus biologics. When the list of medicines was divided in half according to the year of FDA approval, there was a trend toward shorter timelines for newer medicines (on average, 26 years versus 36 years; $P = 0.054$, unpaired $t$ test).

Often, the seminal insights into a new drug were made decades before FDA approval and before subsequent stepwise discoveries revealed the target to be "druggable" (*3*). For example, some of the most important antihypertensive medicines are inhibitors of the angiotensin-converting enzyme (ACE) (Fig. 1 and appendix S1). They reduce blood pressure by blocking ACE, and hence the conversion of the decapeptide angiotensin I to the active hypertensive peptide angiotensin II. Obviously, the elucidation of ACE's biological action in 1956 (*4*) made feasible the generation of the first ACE inhibitor, captopril, but ACE would not even have been sought had angiotensin not been discovered in 1939 (*5*) (Fig. 1). One could argue that the field began in 1898 with the discoveries by Tigerstedt and Bergman of renin (the renal extract that raises arterial pressure) (*6*), which was subsequently found to liberate angiotensin I from its precursor angiotensinogen.

Another example is imatinib, the first small-molecule tyrosine kinase inhibitor approved for treating cancer, specifically chronic myelogenous leukemia (CML) (Fig. 2 and appendix S1). Imatinib was generated in 1992 following the discovery that abnormal kinase activity of the *Bcr-Abl* fusion gene was the cause of CML (*7*–*9*). That finding rested upon the 1960 discovery of an abnormal chromosome (the so-called Philadelphia chromosome) in white blood cells from patients with CML (*10*), the subsequent recognition that this karyotypic change derived from a translocation (*11*), and the elucidation of the *Abl* gene at the site of the translocation (*12*).

In other cases, drugs were built upon convergence of disparate scientific lines of evidence. For example, the statins, used to reduce low-density lipoproteins (LDL) that transport cholesterol in the blood, are inhibitors of the enzyme 3-hydroxy-3-methyl-glutaryl–coenzyme A (HMG-CoA) reductase (appendix S1). The development of lovastatin, the first drug in this class, directly rested upon the understanding of the cholesterol biosynthetic pathway that came from fundamental research in the 1950s, and particularly the observation that HMG-CoA reductase controls the rate-limiting step in cholesterol synthesis (*13*–*15*). However, the understanding of how inhibition of HMG-CoA reductase actually lowers LDL cholesterol (by raising LDL receptor number) depended on a different line of investigation, namely, the elucidation of the LDL receptor by Brown and Goldstein in 1974 (*16*).

In the case of AIDS, the first effective drug, zidovudine, was generated as an anti-cancer agent 20 years before it was found to be

[1]Novartis Institutes for BioMedical Research, Cambridge, MA 02139, USA. [2]Harvard Department of Stem Cell and Regenerative Biology, Harvard University, Cambridge, MA 02138, USA.
*Corresponding author. Email: mark_fishman@harvard.edu

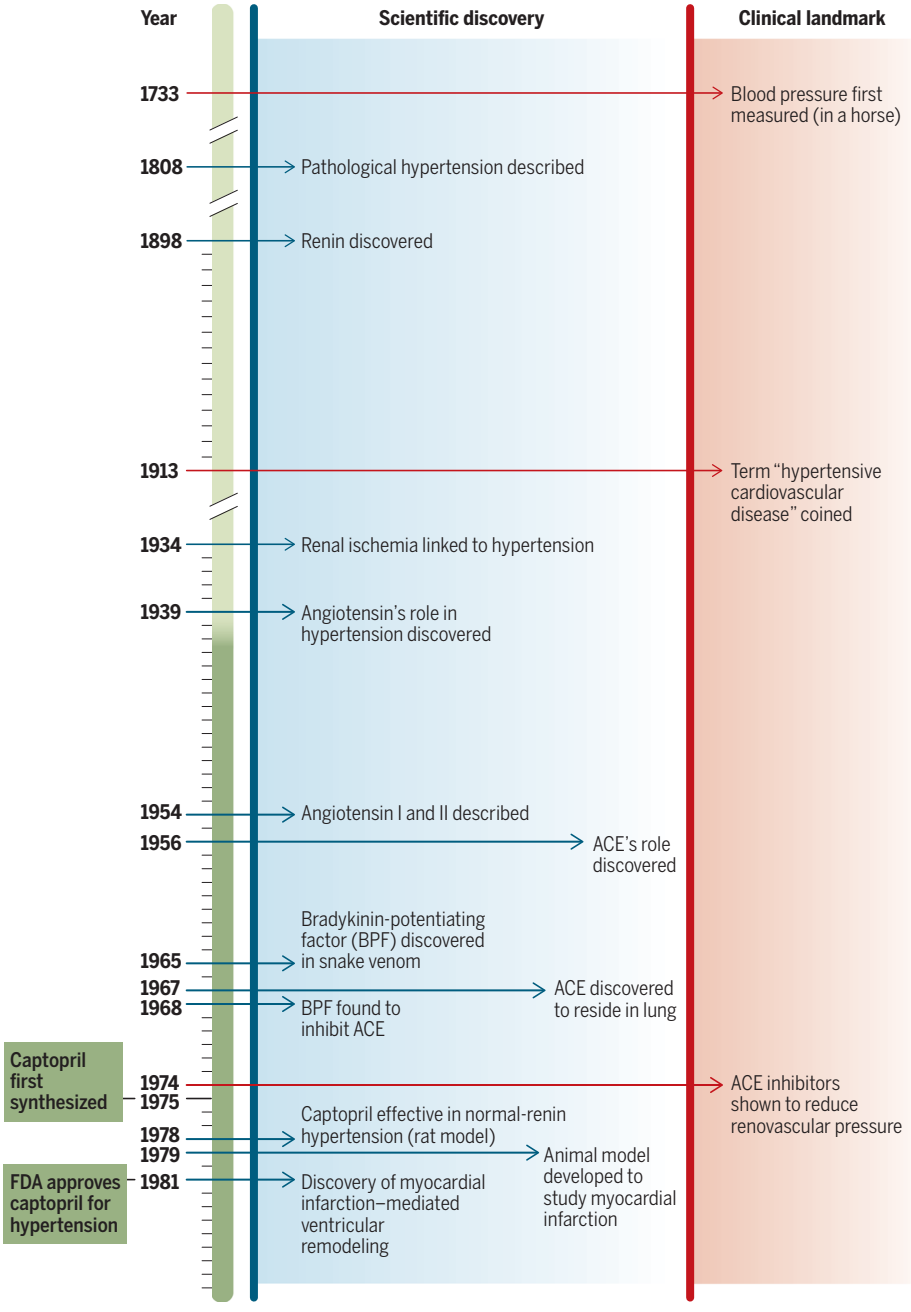


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**Fig. 1. A timeline of basic discoveries leading to FDA approval of the ACE inhibitor captopril.** The role of the renin-angiotensin system in regulating blood pressure was discovered in 1898 by Tigerstedt and Bergman, who identified renin activity in kidney extracts. This discovery set the stage for the elucidation of the renin substrate, angiotensinogen (start of dark green shading), eventually leading to the development of captopril and other ACE inhibitors.

effective in a screen of molecules that blocked HIV-1 replication (appendix S1). It was only later that its target was found to be the reverse transcriptase of HIV. That recognition, of course, rested upon the fundamental discovery of viral reverse transcriptase (*17*, *18*) and of techniques enabling the culture of primary human T cells (*19*, *20*).

Some drugs depended not only on elucidation of the appropriate target but also on the invention of a new technology, such as the method for generating monoclonal antibodies (*21*–*23*). Such drugs are exemplified by rituximab, an anti-CD20 antibody for treating B cell lymphoma; trastuzumab, an anti-HER2 antibody for treating metastatic breast cancer; antibody inhibitors of tumor necrosis factor for various indications; and aptamers (*24*) such as pegaptanib, which blocks vascular endothelial growth factor (VEGF), for the treatment of wet age-related macular degeneration.

In a few cases, stepwise advances were clearly part of a drug discovery effort, for example, the drugs clozapine, propofol, omeprazole, and remifentanil. In two cases, sildenafil and metformin, the key events included both a series of fundamental findings and serendipitous observations of physiological effects when the drugs were used to treat other diseases in human patients.

We conclude that most of the drugs on our list (table S2) originated in basic discoveries made by scientists seeking to understand a biological process or disease, often over decades. This is in agreement with observations made 40 years ago by Comroe and Dripps, who investigated important clinical advances in various fields in response to concerns by President Johnson that the fruits of basic research not remain "locked up in the laboratory" (*25*). Others have similarly reported that the time from seminal target identification to compound synthesis could take 40 to 50 years (*26*, *27*). We cannot know precisely when pharmaceutical companies begin most new drug projects, but many analyses suggest that it is about 10 to 12 years (*28*) before a New Drug Application is filed with the FDA. Thus, for many transformative drugs, there appears to be a 20-year "incubation" period (typically in academia) before formal projects begin in pharmaceutical companies. Some of the time delay may be due to strategic decisions by pharmaceutical companies (*29*, *30*), for example, hesitancy to take on risky programs or those devoted to rare diseases. It also seems likely, however, that it takes time and accumulation of insights to provide a convincing enough portrait of a potential drug target to render it appropriate to launch a pharmaceutical drug discovery project.

We understand that these charts cannot be exact or complete, given the impossibility of knowing precisely what drove individual scientists, or teams of scientists, to pursue specific lines of investigation. In addition, this analysis is about scientific advancement and not about patentability or lack thereof for any of these developments. Finally, we are also aware that the experts consulted may have their own biases, that assignment of credit is controversial, and that some decisions about key discoveries that we present here are debatable. Most of our experts did have strong opinions, and we suspect that others might

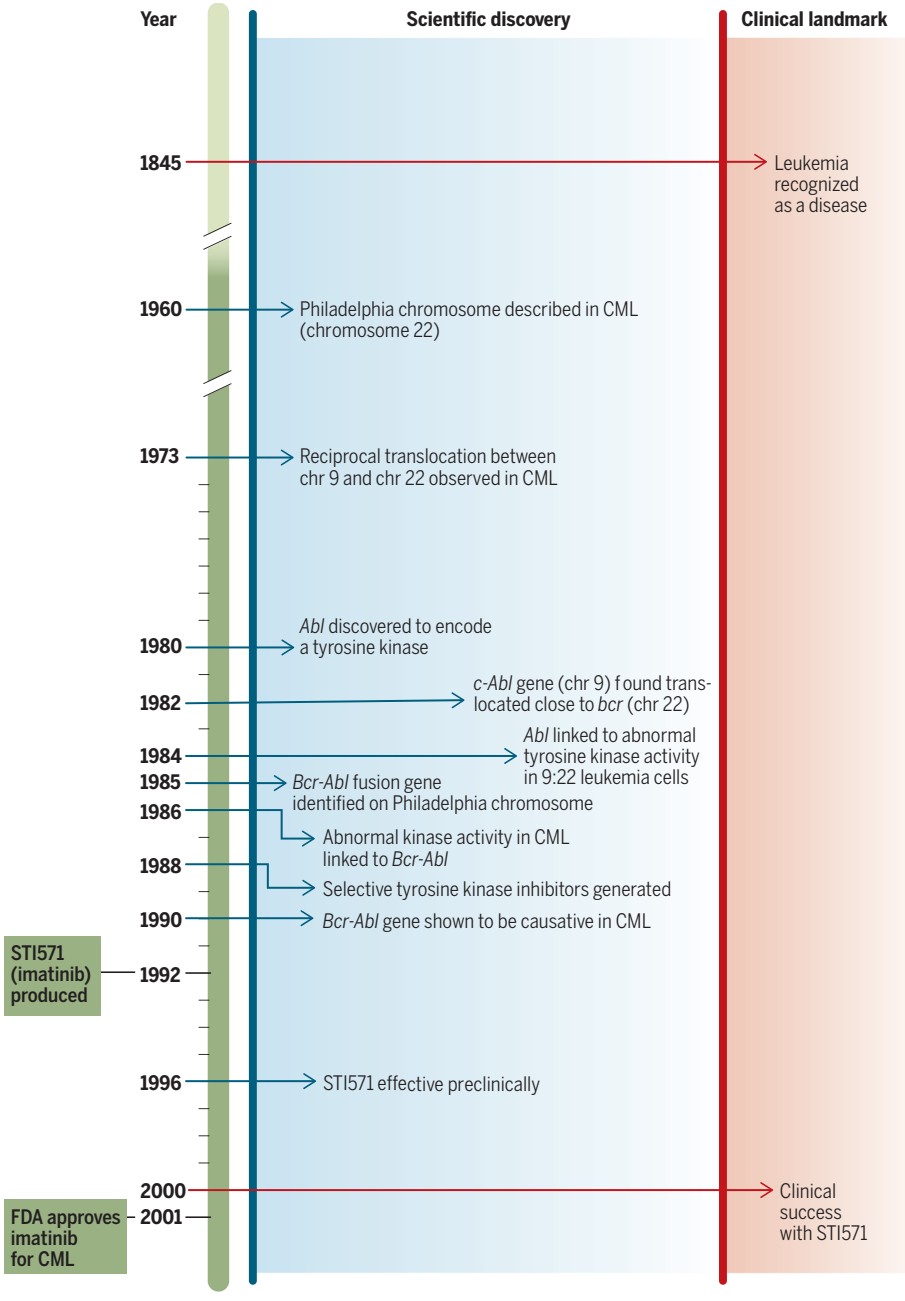


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**Fig. 2. A timeline of basic discoveries leading to FDA approval of imatinib.** The discovery by Nowell and Hungerford in 1960 of the chromosomal translocation characteristic of CML, termed the Philadelphia chromosome, led to subsequent identification of the *Bcr* and *Abl* genes at the translocation junction. Next followed the demonstration that this translocation led to production of a fusion protein with constitutive Abl kinase activity. These discoveries ultimately informed the development of imatinib, which received FDA approval in 2001.

suggest modifications or point to key discoveries made even earlier. For all medicines that we examined, however, we did have agreement among several experts, and discussion usually revealed additional discoveries that pushed timelines back even further.

There has been much debate about how best to allocate limited resources in pursuit of improvements in human health. In particular, there is debate about whether the balance of funding should shift from fundamental discovery toward using such discovery more directly in the generation of new therapeutics. As our analysis makes clear, many important new drugs rest upon one or a set of fundamental discoveries, and many years of ongoing fundamental work may have elapsed before the realization that such work holds the key to a medical breakthrough. Thus, the more we know, the more we can do. It would seem prudent in a society dedicated to the health of its citizens, and with incredible opportunities on the horizon for cures of previously intractable illnesses, that we boost support for basic scientific discovery, knowing that this is the best route to the generation of powerful new medicines.

## SUPPLEMENTARY MATERIALS

www.sciencetranslationalmedicine.org/cgi/content/full/10/438/eaaq1787/DC1
Table S1. List of medicines and Delphi participants.
Table S2. Analyses of medicines studied.
Appendix S1. Discovery and drug development timelines for 28 transformative medicines.

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# Supplementary Materials for

## Fundamental science behind today's important medicines

Jonathan M. Spector, Rosemary S. Harrison, Mark C. Fishman*

*Corresponding author. Email: mark_fishman@harvard.edu

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**Table S1. List of medicines and Delphi participants.** The list of drugs or drug classes was obtained from Kesselheim and Avorn's "transformative drugs" study *(2)*. Where a drug class was described, the first medicine approved in that class by the US Food and Drug Administration (FDA) was studied. The single combination therapy on the list (fluticasone and salmeterol for pulmonary disease) was excluded.

| **Specialty** | **Drug or drug class** | **Delphi participants** |
|---|---|---|
| Anesthesiology | Propofol | Stefan Bushuven, Institute for Anesthesiology, Intensive Care, Emergency Medicine and Pain Therapy, Hegau-Bodensee-Hospital Singen, Germany |
| | | John (Iain) B Glen, Director, Research Department, Glen Pharma, UK |
| | | Michael Todd, Professor Emeritus, Department of Anesthesia, University of Iowa |
| | Remifentanil | Paul Feldman, Head of Discovery and Translational Medicine, Intarcia Therapeutics, USA |
| | | Donald Stanski, Emeritus Faculty, Department of Anesthesia, Stanford University, USA |
| Cardiology | Lovastatin | Joseph L Goldstein, Professor and Chairman, Department of Molecular Genetics, UT Southwestern Medical Center, USA |
| | | Scott Grundy, Distinguished Professor, Internal Medicine, UT Southwestern Medical School, USA |
| | | Jonathan Tobert, Academic Visitor, Nuffield Department of Population Health, University of Oxford, UK |
| | ACE inhibitors | Y.S. (Mick) Bakhle, Honorary Senior Research Fellow, National Heart and Lung Institute, Imperial College London, UK |
| | | Marc Pfeffer, Victor J. Dzau Professor of Medicine, Department of Medicine, Brigham and Women's Hospital, USA |
| | Alteplase | Roger Lijnen, Professor, Faculty of Medicine, Centre for Molecular and Vascular Biology, Belgium |
| | | DC Rijken, Department of Hematology, Erasmus University Medical Center, Rotterdam, the Netherlands |
| | | Frans Van de Werf, Emeritus Professor of Cardiology, University of Leuven, Belgium |
| Dermatology | TNF blockers | Bruce Beutler, Regental Professor and Director of the Center for Genetics of Host Defense, UT Southwestern Medical Center, USA |
| | | Jean-Michel Dayer, Emeritus Professor of Medicine, University of Geneva, Switzerland |
| | | Sir Marc Feldmann, Emeritus Professor, University of Oxford, UK |
| | | David Goeddel, Managing Partner, The Column Group, USA |
| | | Georges Kollias, Professor and Director, Immunology Division, Biomedical Sciences Research Center "Alexander Fleming", Greece |
| | | Sir Ravinder N Maini, Professor of Rheumatology, Kennedy Institute, Imperial College of London, UK |

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|---|---|---|
| | | David Wallach, Professor, Department of Biological Chemistry, Weizmann Institute of Science, Israel |
| | Onabotulinumtoxin A | Bahman Jabbari, Professor Emeritus of Neurology, Yale School of Medicine, USA |
| | | Alan B Scott, Director and Senior Scientist, Strabismus Research Foundation, USA |
| Endocrinology | Bisphosphonates | Frank H (Hal) Ebetino, Professor (Research), Department of Chemistry, University of Rochester, USA |
| | | Graham Russell, Emeritus Professor of Musculoskeletal Pharmacology, University of Oxford, UK |
| | Metformin | Clifford J Bailey, Professor of Clinical Science and Director of Biomedical Sciences Research Life and Health Sciences, Aston University, UK |
| | | Vivian Fonseca, Professor of Medicine and Pharmacology, Tullis Tulane Alumni Chair in Diabetes<br>Chief, Section of Endocrinology, Tulane University Health Sciences Center, USA |
| Gastroenterology | Omeprazole | George Sachs, Distinguished Professor in Medicine and Physiology, UCLA, USA |
| | | Hiroshi Satoh, Professor, Department of Pharmacology and Experimental Therapeutics, Kyoto Pharmaceutical University, Japan |
| | TNF blockers | See above |
| Infectious diseases | HIV protease inhibitors | Sir Tom Blundell, Professor, Department of Biochemistry, University of Cambridge, UK |
| | | Charles W Flexner, Professor, Department of Pharmacology and Molecular Sciences, Johns Hopkins University, USA |
| | | Laurence Pearl, Professor of Structural Biology (Life Sciences), University of Sussex, UK |
| | | Alexander Wlodawer, Chief, Macromolecular Crystallography Laboratory, National Cancer Institute, National Institutes for Health, USA |
| | Zidovudine | Dani Paul Bolognesi, Professor Emeritus of Surgery, Duke University School of Medicine, USA |
| | | Robert Gallo, Director, Institute of Human Virology, University of Maryland School of Medicine, USA |
| | | Robert Yarchoan, Chief, HIV and AIDS Malignancy Branch, National Cancer Institute, National Institutes for Health, USA |
| Genetics | Alglucerase | Gary Murray, Program Director, National Institute on Alcohol Abuse and Alcoholism, National Institutes for Health, USA |
| | | Raphael Schiffmann, Medical Director, Institute of Metabolic Disease, Baylor Scott & White Research Institute |
| | Nitisinone | Bengt Lindblad, Reader, University of Gothenburg, Sweden |
| | | Ted Lock, Industrial Professor of Toxicology, Liverpool John Moores University, UK |
| | | Lakshminarayan Ranganath, Honorary Professor, University of Liverpool, UK |
| Nephrology | ACE inhibitors | See above |

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|---|---|---|
| | Epoetin alfa | John Adamson, Professor of Clinical Medicine, University of California, USA |
| | | Wolfgang Jelkmann, Direktor des Instituts für Physiologie der Medizinischen Universität Lübeck, Germany |
| | | Stephen Schuster, Robert and Margarita Louis-Dreyfus Professor in Chronic Lymphocytic Leukemia and Lymphoma Clinical Care and Research, University of Pennsylvania, USA |
| Neurology | Sumatriptan | Hans-Christoph Diener MD, PhD<br>Senior Professor for Clinical Neurosciences, Department of Neurology, University Hospital Essen, University Duisburg-Essen, UK |
| | Interferons | Lawrence M. Pfeffer, Muirhead Professor and Vice-Chair, Department of Pathology, University of Tennessee Health Science Center, USA |
| Oncology | Imatinib | David Baltimore, President Emeritus, Robert Andrews Millikan Professor of Biology, Caltech, USA |
| | | Renaud Capdeville, Global Program Head for Hematologic Malignancies, Global Drug Development, Novartis, Switzerland |
| | | George Q Daley, Professor of Hematology/Oncology, Director of Stem Cell Transplantation Program, Boston Children's Hospital, USA |
| | | Brian J Druker, Director, Knight Cancer Institute, Oregon Health & Science University, USA |
| | | Juerg Zimmermann, Global Head of Medicinal Chemistry, Novartis, Switzerland |
| | Rituximab | Edward A Clark, Professor, Microbiology and Immunology, Department of Microbiology, University of Washington, USA |
| | | Antonio Grillo-Lopez, Former Chief Medical Officer, Biogen Idec, USA |
| | | Ronald Levy, Professor and Chief, Division of Oncology, Stanford School of Medicine, USA |
| | | Jeffrey Ledbetter, Herndon and Esther Maury Endowed Professor in Rheumatoid Arthritis, Division of Rheumatology, University of Washington, USA |
| | | Lee Marshall Nadler, Virginia and D.K. Ludwig Professor of Medicine, Harvard Medical School, USA |
| | Trastuzumab | Paul Carter, Senior Director and Staff Scientist, Antibody Engineering, Genentech, USA |
| | | H Michael Shepard, Vice President and Chief Scientific Officer, Halozyme, USA |
| | | Robert A Weinberg, Daniel K. Ludwig Professor for Cancer Research, Massachusetts Institute of Technology, USA |
| Ophthalmology | Anti-VEGF agents | Lloyd Paul Aiello, Professor of Ophthalmology, Harvard Medical School, USA |
| | | George L King, Professor of Medicine, Joslin Diabetes Center, USA |
| | | Joan W Miller, Chief and Chair, Department of |

| | | |
|---|---|---|
| | | Ophthalmology, Massachusetts Eye and Ear, USA |
| | Latanoprost | Thomas Hejkal, Professor of Ophthalmology and Chair Emeritus, Department of Ophthalmology and Visual Sciences, University of Nebraska Medical Center |
| | | Carol Toris, Professor, Department of Ophthalmology and Visual Sciences, University of Nebraska Medical Center |
| Psychiatry | Fluoxetine | Arvid Carlsson, Carlsson Research, Sweden |
| | | Tomas Hokfelt, Professor, Department of Neuroscience, Karolinska Institutet, Sweden |
| | | Peter Kramer, Clinical Professor Emeritus of Psychiatry and Human Behavior, Brown University, USA |
| | | Richard Wurtman, Cecil H. Green Distinguished Professor, Massachusetts Institute of Technology, USA |
| | Clozapine | Alan Green, Chair and Professor of Psychiatry, Dartmouth Geisel School of Medicine, USA |
| | | Herbert Meltzer, Professor of Psychiatry and Physiology, Northwestern University, USA |
| Pulmonary medicine | Epoprostenol | Sir Salvador Moncada, Research Domain Director, Cancer, University of Manchester, UK |
| | | Brendan Whittle, Professor of Applied Pharmacology, William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London |
| Rheumatology | TNF blockers | See above |
| | Bisphosphonates | See above |
| Urology | Sildenafil | Andy Bell, Head of Medicinal Chemistry, ex Scientia Ltd, UK |
| | | David Brown, Medical Researcher, UK |
| | | Nick Terrett, Scientific Associate Vice President, European Chemistry Lead, Merck Sharp & Dohme, UK |
| | Tamsulosin | Christopher Chapple, Professor, University of Sheffield, UK |
| | | Debra Schwinn, Professor, University of Iowa, USA |
| | Finasteride | Julianne Imperato-McGinley, Abby Rockefeller Mauze Distinguished Professor of Endocrinology in Medicine, Department of Medicine, Weill Cornell Medical College, USA |
| | | Patrick C Walsh, University Distinguished Service Professor of Urology, Johns Hopkins Medical Institutions, USA |

**Table S2. Analyses of medicines studied.**

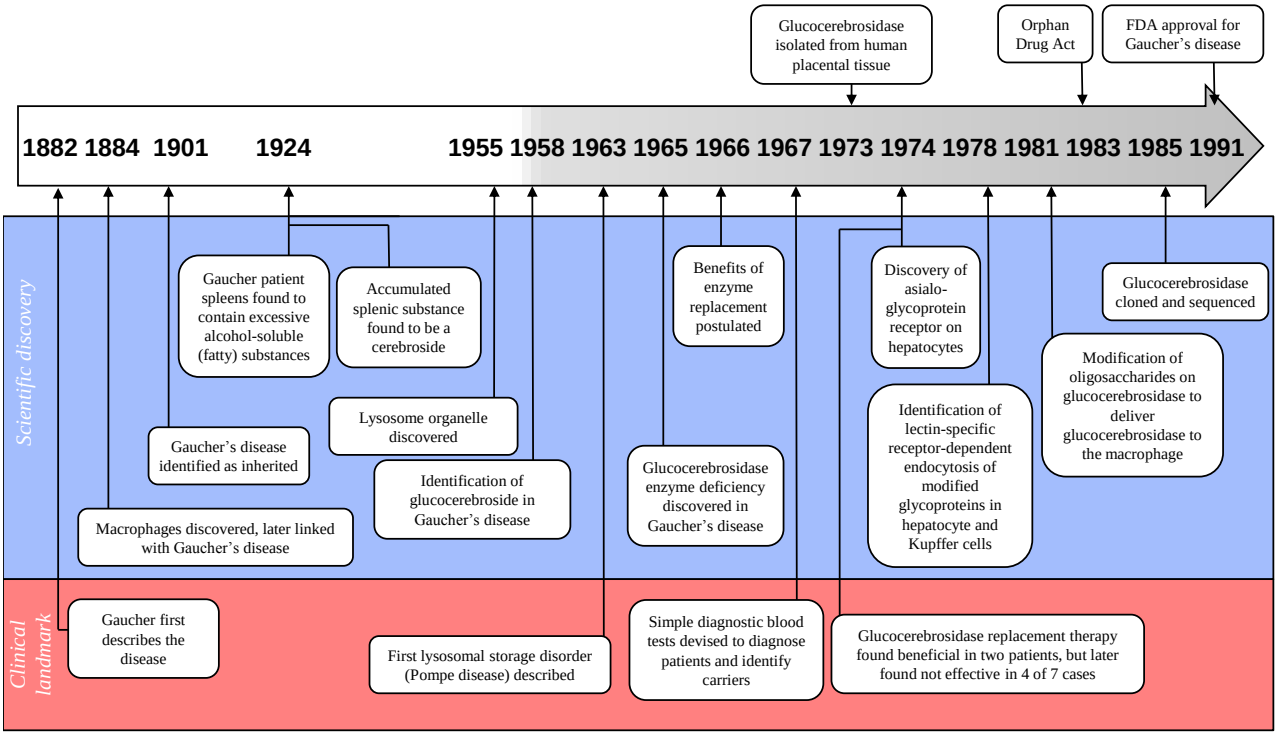
| Drug or drug class | Origins in basic discoveries? | If origins were in basic discoveries, were the discoveries disease-oriented? | Were the early discoveries made as part of a drug discovery program? | Year the first key basic discovery was made | Year of FDA approval | Drug disovery and development period, starting at earliest relevant basic discoveries |
|---|---|---|---|---|---|---|
| Alglucerase | Yes | Yes | No | 1958 | 1991 | 33 |
| Alteplase | Yes | No | No | 1947 | 1987 | 40 |
| ACE inhibitors | Yes | No | No | 1939 | 1981 | 42 |
| Clozapine | No | | | | | |
| Epoetin alfa | Yes | No | No | 1950 | 1989 | 39 |
| Epoprostenol | Yes | No | No | 1957 | 1995 | 38 |
| Bisphosphonates | Yes | No | No | 1961 | 1978 | 17 |
| Finasteride | Yes | Yes | No | 1951 | 1992 | 41 |
| Fluoxetine | Yes | No | No | 1953 | 1987 | 34 |
| Imatinib | Yes | Yes | No | 1960 | 2001 | 41 |
| TNF blockers | Yes | No | No | 1967 | 1998 | 31 |
| Interferons | Yes | No | No | 1957 | 1993 | 36 |
| Latanoprost | Yes | No | No | 1976 | 1996 | 20 |
| Lovastatin | Yes | No | No | 1954 | 1987 | 33 |
| Metformin | No | | | | | |
| Nitisinone | Yes | Yes | No | 1977 | 2002 | 25 |
| Omeprazole | Yes | Yes | Yes | 1969 | 1989 | 20 |
| Onabotulinum-toxinA | Yes | No | No | 1922 | 1989 | 67 |
| Anti-VEGF agents | Yes | No | No | 1983 | 2004 | 21 |
| Propofol | No | | Yes | | | |
| Remifentanil | No | | Yes | | | |
| Rituxan | Yes | Yes | No | 1975 | 1993 | 18 |
| HIV protease inhibitors | Yes | No | No | 1978 | 1995 | 17 |
| Sildenafil | No | No | No | 1976 | 1998 | 22 |
| Sumatriptan | Yes | Yes | No | 1938 | 1992 | 54 |
| Tamsulosin | Yes | No | No | 1972 | 1997 | 25 |
| Trastuzumab | Yes | Yes | No | 1975 | 1998 | 23 |
| Zidovudine | Yes | No | No | 1970 | 1987 | 17 |

**Appendix S1. Discovery and drug development timelines for 28 transformative medicines.**

Shaded areas in timelines represent discoveries linked with eventual drug discovery and development. The list of drugs or drug classes was derived from Kesselheim and Avorn's "transformative drugs" study *(2)*. Where a drug class was described, the first medicine approved in that class by the United States Food and Drug Administration was studied.

# Alglucerase

*Recombinant beta-glucocerebrosidase*




**1882-Gaucher first describes the disease**
P.C.E. Gaucher, De l'epithelioma primitif de la rate. (1882).

**1884-Macrophages discovered – they are later linked to Gaucher's disease**
E. Metschnikoff, Zool. Inst. Univ. wien. u. *Zool. Stat. Triest* **5**, 141–168 (1884).

**1901-Gaucher's disease identified as inherited**
N.E. Brill, Primary splenomegaly with a report of three cases occurring in one family. *Am. J. Med. Sci.* **121**, 377-92 (1901).

**1924-Gaucher patient spleens found to contain excessive alcohol-soluble (fatty) substances**
E. Epstein, Beitrag zurchemie der Gaucherschen krankeit. *Biochem Z.* 1**45**, 398–402 (1924).

**1924-Accumulated splenic substance found to be cerebrosidase**
H. Lieb, Cerebrosidespeicherung bei Splenomegalie Typus Gaucher. *Ztchr Physiol Chem.* **140**, 305 (1924).

**1955-Lysosome organelle discovered**
C. De Duve, B.C. Pressman, R. Gianetto, R. Wattiaux, F. Applemans, Tissue fractionation studies. 6. Intracellular distribution patterns of enzymes in rat-liver tissue. *Biochem J.* **60**, 604–17 (1955).

**1958-Identification of glucocerebroside in Gaucher's disease**

A. Roseberg, E. Chargaff, A reinvestigation of the cerebroside deposited in Gaucher's disease. *J Biol Chem*. **233**, 1323–1326 (1958).

**1963-First lysosomal storage disorder (Pompe disease) described**
H.G. Hers, Alpha-Glucosidase deficiency in generalized glycogen storage disease (Pompe's disease). *Biochem. J*. **86**, 11–6 (1963).

**1965-Glucocerebrosidase enzyme deficiency discovered in Gaucher's disease**
R.O. Brady, J.N. Kanfer, D. Shapiro, Metabolism of Glucocerebrosides. II. Evidence Of An Enzymatic Deficiency In Gaucher's Disease. *Biochem. Biophys, Res, Commun*, **18**, 221–5 (1965).

**1966-Benefits of enzyme replacement postulated**
R.O. Brady, The sphingolipidoses. *N. Engl. J. Med.* **275**, 312–8 (1966).

**1967-Simple diagnostic blood tests devised to diagnose patients and identify carriers**
J.P. Kampine, R.O. Brady, J.N. Kanfer, M. Feld, D. Shapiro, Diagnosis of gaucher's disease and niemann-pick disease with small samples of venous blood. *Science*. **155**, 86-8 (1967).

**1973-Glucocerebrosidase isolated from human placental tissue**
P.G. Pentchev, R.O. Brady, S.R. Hibbert, A.E. Gal, D. Shapiro, Isolation and characterization of glucocerebrosidase from human placental tissue. *J. Biol. Chem.* **248**, 5256–61 (1973).

**1974-Discovery of asialoglycoprotein receptor on hepatocytes**
G. Ashwell, A.G. Morell, The role of surface carbohydrates in the hepatic recognition and transport of circulating glycoproteins. *Biochem. Soc. Symp.* **41**, 99-128 (1974).
G. Ashwell, A.G. Morell, The dual role of sialic acid in the hepatic recognition and catabolism of serum glycoproteins. *Biochem. Soc. Symp.* **40**, 117-24 (1974).

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R.O. Brady, P.G. Pentchev, A.E. Gal, S.R. Hibbert, A.S. Dekaban, Replacement therapy for inherited enzyme deficiency. Use of purified glucocerebrosidase in Gaucher's disease. *N. Engl. J. Med.* **291**, 989–93 (1974).

**1978-Identification of lectin-specific receptor-dependent endocytosis of modified glycoproteins in hepatocyte and Kupffer cells**
H. Kolb, V. Kolb-Bachofen, A lectin-like receptor on mammalian macrophages. *Biochem. Biophys. Res. Commun.* **85**, 678-683 (1978).
H. Kolb, C. Schudt, V. Kolb-BachofenV, H. Kolb H. Cellular recognition by rat liver cells of neuraminidase-treated erythrocytes: Demonstration and analysis of cell contacts. *Exp. Cell Res*. **113**, 319-325 (1978).

**1981-Modification of oligosaccharides on glucocerebrosidase to deliver glucocerebrosidase to the macrophage**
F.S. Furbish, C.J. Steer, N.L. Krett, J.A. Barranger, Uptake and distribution of placental glucocerebrosidase in rat hepatic cells and effects of sequential deglycosylation. *Biochim. Biophys. Acta.* **673**, 425-34 (1981).

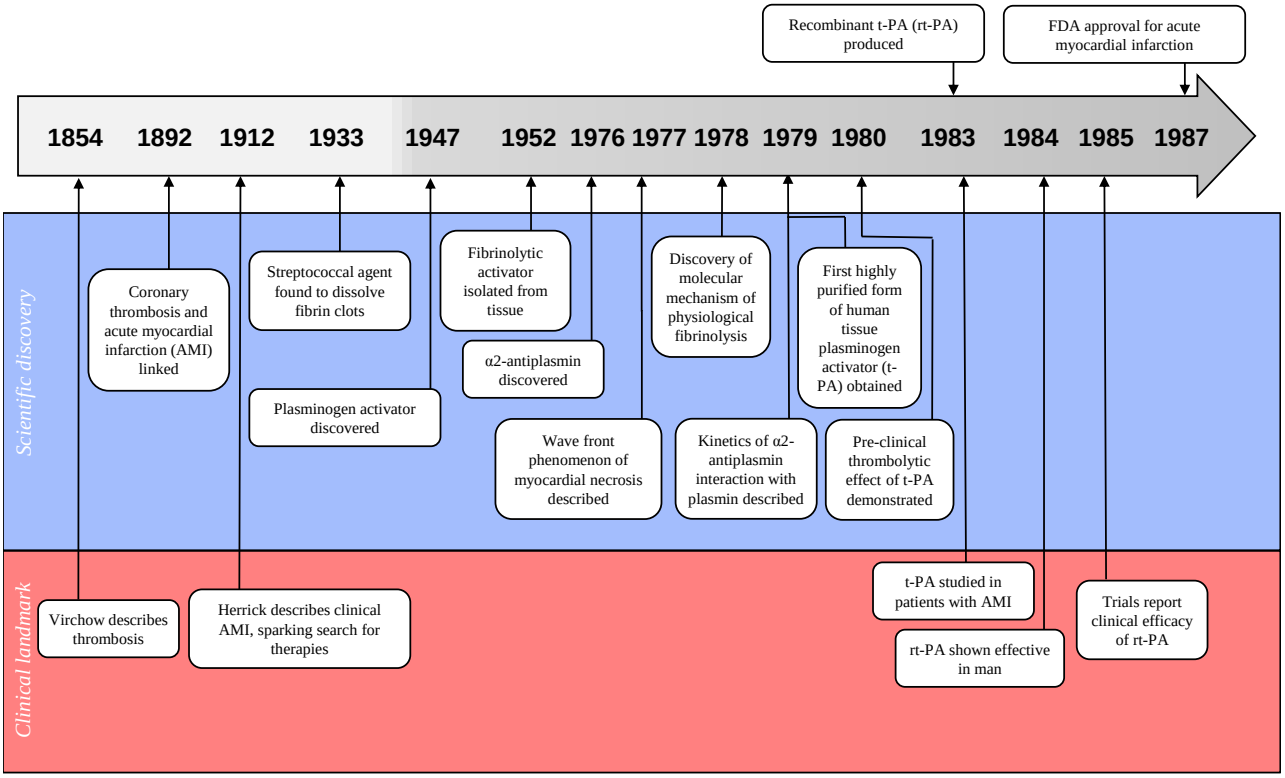
**1985-Glucocerebrosidase cloned and sequenced**
E.I. Ginns, P.V. Choudary, B.M. Martin, S. Winfield, B. Stubblefield, J. Mayor, D. Merkle-Lehman, G.J. Murray, L.A. Bowers, J.A. Barranger, Isolation of cDNA clones for human beta-glucocerebrosidase using

the lambda gt11 expression system. *Biochem. Biophys. Res. Commun.* **123**, 574–580 (1984).

J. Sorge, C. West, B. Westwood, E. Beutler, Molecular cloning and nucleotide sequence of human glucocerebrosidase cDNA. *Proc. Natl. Acad. Sci. U.S.A.* **82**, 7289-93 (1985).

# Alteplase

*Recombinant tissue plasminogen activator*




**1854-Virchow describes thrombosis**
R. Virchow, Ortliche Storungen des Kreislaufes. In: Virchow R, Vogel J, Stiebel, SF, eds. *Handbuch der speciellen pathologie und therapie.* Vol 1. Erlangen: Ferdinand Enke **95** (1854).

**1892-Coronary thrombosis and acute myocardial infarction (AMI) linked**
W. Osler, The Principle and Practice of Medicine. New York: D. Appleton. (1892).

**1912-Herrick describes clinical AMI, sparking search for therapies**
J.B. Herrick, Clinical features of sudden obstruction of the coronary arteries. *JAMA.* **59**, 2015 (1912).

**1933-Streptococcal agent found to dissolve fibrin clots**
W.S. Tillett, R.L. Garner, The fibrinolytic activity of hemolytic streptococci. *J. Exp. Med.* **58**, 485–502 (1933).

**1947-Plasminogen activator discovered**
T. Astrup, P.M. Permin, Fibrinolysis in the animal organism. *Nature* **159**, 681 (1947).

**1952-Fibrinolytic activator isolated from tissue**
T. Astrup, A. Stage, Isolation of a soluble fibrinolytic activator from animal tissue. *Nature*. **170**, 929 (1952).

**1976-α2-antiplasmin discovered (serendipitously leads to study of melanoma cell line producing plasminogen activator)**

D. Collen, Identification and some properties of a new fast-reacting plasmin inhibitor in human plasma. *Eur. J. Biochem*. **69**, 209–16 (1976).

**1977- Wave front phenomenon of myocardial necrosis described**

K.A. Reimer, J.E. Lowe, M.M. Rasmussen, R.B. Jennings, The wavefront phenomenon of ischemic cell death. 1. Myocardial infarct size vs duration of coronary occlusion in dogs. *Circulation* **56**, 786-94 (1977).

**1978- Discovery of molecular mechanism of physiological fibrinolysis**

B. Wiman, D. Collen, Molecular mechanism of physiological fibrinolysis. *Nature* **272**, 549-550 (1978).

**1979-First highly purified form of tissue plasminogen activator (t-PA) obtained**

D. Rijken, G. Wijngaards, M. Zaal-de Jong, *et al*, Purification and partial characterization of plasminogen activator from human uterine tissue. *Biochim Biophys Acta.* **580**, 140 (1979).

**1979-Kinetics of α2-antiplasmin interaction with plasmin described**

B. Wiman, H.R. Lijnen, D. Collen, On the specific interaction between the lysine-binding sites in plasmin and complementary sites in alpha2-antiplasmin and in fibrinogen. *Biochim Biophys Acta.* **579**, 142-54 (1979).

**1980-Pre-clinical thrombolytic effect of t-PA demonstrated**

O. Matsuo, D.C. Rijken, D. Collen, Thrombolysis by human tissue plasminogen activator and urokinase in rabbits with experimental pulmonary embolus. *Nature* **291**, 590 –1 (1980).

**1983-t-PA studied in patients with AMI**

F. Van de Werf, P.A. Ludbrook, S.R. Bergmann SR, *et al*, Coronary thrombolysis with tissue-type plasminogen activator in patients with evolving myocardial infarction. *N. Engl. J. Med.* **310**, 609–13 (1984).

**1983-Recombinant t-PA (rt-PA) produced**

D. Pennica, W.E. Holmes, W.J. Kohr, R.N. Harkins, G.A. Vehar, C.A. Ward, W. Bennett, E. Yelverton, P.H. Seeburg, H.L. Heyneker, D.V. Goeddel, D. Collen, Cloning and expression of human tissue-type plasminogen activator cDNA in *E. coli. Nature* **301**, 214-221 (1983).

F. Van de Werf, S.R. Bergmann, K.A. Fox, *et al*, Coronary thrombolysis with intravenously administered human tissue-type plasminogen activator produced by recombinant DNA technology. *Circulation* **69**, 605–10 (1984).

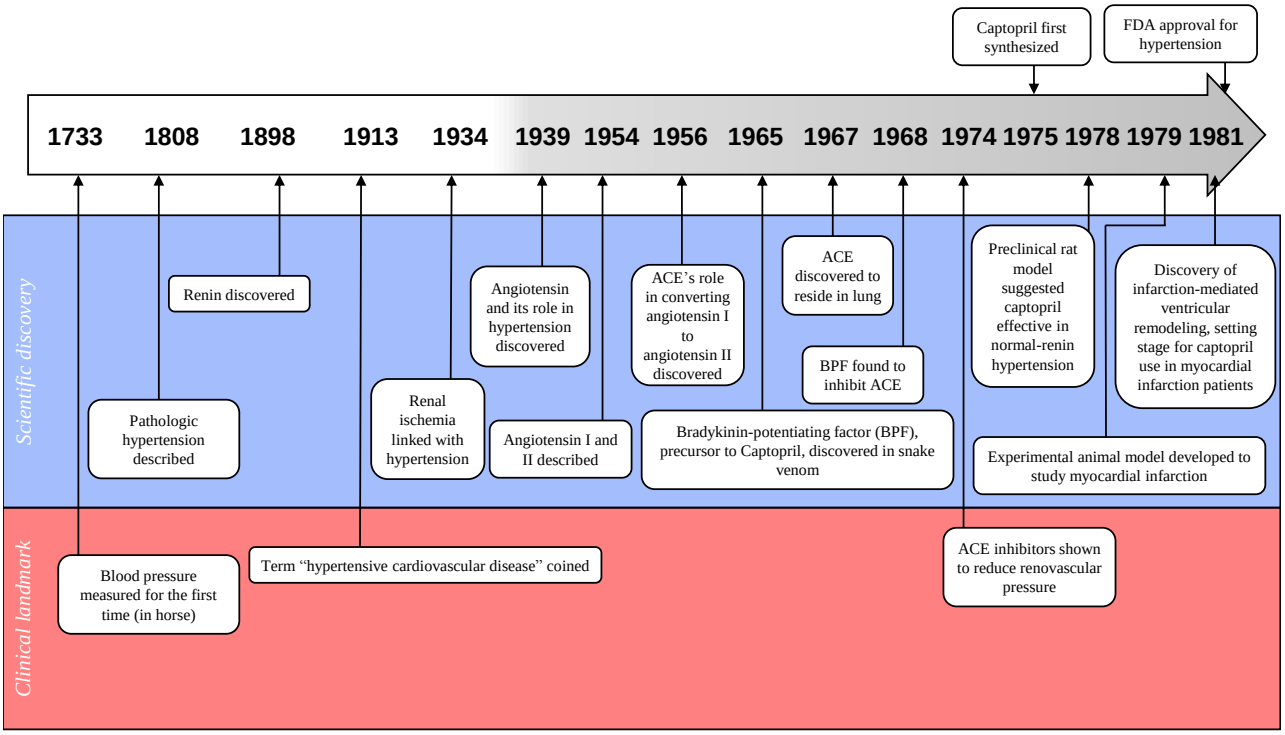
**1984-rt-PA shown effective in man**

D. Collen, E.J. Topol, A.J. Tiefenbrunn, *et al*, Coronary thrombolysis with recombinant tissue-type plasminogen activator: a prospective, randomized, placebo-controlled trial. *Circulation* **70**, 1012–1017 (1984).

**1985-Trials report clinical efficacy of rt-PA**

Verstraete *et al*., 1985; Chesebro *et al*., 1987 (TIMI); GUSTO 1993

# ACE inhibitors




**1733-Blood pressure measured for the first time (in horse)**
S. Hales, Statistical essays containing haemostaticks; or an account of some hydraulic and hydrostatical experiments made on the blood and blood pressure of animals. London: Innys and Manby (1733).

**1808-Pathologic hypertension described**
T.I. Young, The Croonian lecture. On the functions of the heart and arteries. *Phil. Trans. R. Soc. Lond.* **1**, 1-31 (1809).

**1898-Renin discovered**
R. Tigerstedt, P. Bergman, Niere und kreislauf. *Scand. Arch. Physiol.* **8**, 223 (1898).

**1913-Term "hypertensive cardiovascular disease" coined**
T. Janeway, A clinical study of hypertensive cardiovascular disease. *Arch. Intern. Med.* **12**, 752-786 (1913).

**1934-Renal ischemia linked with hypertension**
H. Goldblatt, J. Lynch, R.F. Hanzal, *et al*, Studies on experimental hypertension: I. The production of persistent elevation of systolic blood pressure by means of renal ischemia. *J. Exp. Med.* **59**, 347-9 (1934).

**1939-Angiotensin and its role in hypertension discovered**

E. Braun-Menendez, J.C. Fasciolo, L.F. Leloir, J.M. Munoz, La sustancia hipertensora de la sangre del rinon isquemido. *Rev Soc Arg Biol.* **15**, 420–5 (1939).
I.H. Page, O.H. Helmer, A crystalline pressor substance (angiotonin) resulting from the reaction between renin and renin-activator. *J. Exp. Med.* **71**, 29-42 (1940).

**1954-Angiotensin I and II described**
L.T. Skeggs, W.H. Marsh, J.R. Kahn JR, *et al*, The existence of two forms of hypertensin. *J. Exp. Med.* **99**, 275-82 (1954).

**1954-ACE's role in converting angiotensin I to angiotensin II discovered**
L.T. Skeggs, J.R. Khan, N.P. Shumway. Preparation and function of the hypertensin-converting enzyme. *J. Exp. Med.* **103**, 295–9 (1956).

**1956-Bradykinin-potentiating factor (BPF), precursor to Captopril, discovered in snake venom**
S.H. Ferreira, A bradykinin-potentiating factor (BPF) present in the venom of Bothrops Jararca. *Br. J. Pharmacol. Chemother.* **24**, 163–9 (1965).

**1967-ACE discovered to reside in lung**
K.K.F. Ng, J.R. Vane, Conversion of angiotensin I to angiotensin II. *Nature* **216**, 762-6 (1967).

**1968-BPF found to inhibit ACE**
Y.S. Bakhle, Conversion of angiotensin I to angiotensin II by cell-free extracts of dog lung. *Nature* **220**, 919–21 (1968).

**1974-ACE inhibitors shown to reduce blood pressure in man**
J.G. Collier, B.F. Robinson, J.R. Vane, Reduction of the pressor effects of angiotensin in man by a synthetic nonapeptide ($BPP_{9A}$ or SQ 20,881) which inhibits converting enzyme. *Lancet* **301**, 72-4 (1973).
H. Gavras, H.R. Brunner, J.H. Laragh, *et al*, An angiotensin converting-enzyme inhibitor to identify and treat vasoconstrictor and volume factors in hypertensive patients. *N. Eng. J. Med.* **291**, 817-21 (1974).

**1975-Captopril first synthesized**
M.A. Ondetti, B. Rubin, D.W. Cushman, Design of specific inhibitors of angiotensin-converting enzyme: new class of orally active antihypertensive agents. *Science* **196**, 441–4 (1977).

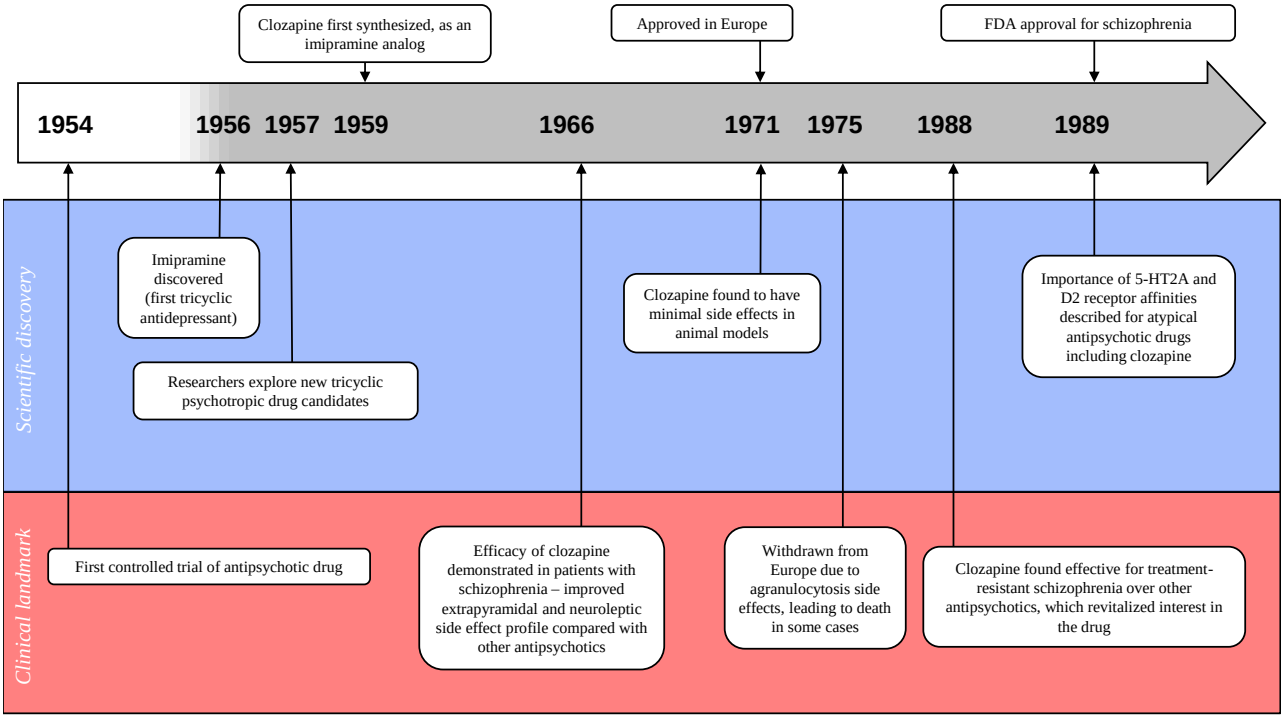
**1978-Preclinical rat model suggested captopril effective in normal-renin hypertension**
R.J. Laffan, M.E. Goldberg, J.P. High, T.R. Schaeffer, M.H. Waugh, B. Rubin, Antihypertensive activity in rats for SQ 14,225, an oral active inhibitor of angiotensin I-converting enzyme. *J. Pharmacol. Exp. Ther.* **204**, 281-8 (1978).

**1979-Experimental animal model developed to study myocardial infarction**
M.A. Pfeffer, J.M. Pfeffer, M.C. Fishbein, P.J. Fletcher, J. Spadaro, R.A. Kloner, E. Braunwald, Myocardial infarct size and ventricular function in rats. *Circ Res.* **44**, 503-12 (1979).

**1981-Discovery of infarction-mediated ventricular remodeling, setting stage for captopril use in myocardial infarction patients**
P.J. Fletcher, J.M. Pfeffer, M.A. Pfeffer, E. Braunwald, Left ventricular diastolic pressure-volume relations in rats with healed myocardial infarction: effects on systolic function. *Circ. Res.* **49,** 618-26 (1981).

# Clozapine

*Mechanism unknown*




**1954-First controlled trial of antipsychotic drug**
J. Elkes, C. Elkes, Effect of chlorpromazine on the behaviour of chronically overactive psychotic patients. *Brit. Med. J.* **2**, 560-5 (1954).

**1956-Imipramine discovered**
R. Kuhn, The treatment of depressive states with G 22355 (imipramine hydrochloride). *Am. J. Psychiatry* 115, 459-64 (1958).

**1957-Researchers explore new tricyclic psychotropic drug candidates – i.e. an exploratory, non-focused approach**
H. Hippius, The history of clozapine. *Psychopharmacology* **99**, S3-S5 (1989) - refers to 1957 on timeline

**1959-Clozapine first synthesized, as an imipramine analog**
D. Bente, M.P. Engelmeier, K. Heinrich, H. Hippius, W. Schmitt, On the place of a new type of dibenzodiazepine derivative in the drug therapy of depressive illnesses. *Arzneimittelforschung* **14(suppl)**, 538-40 (1964).

**1966-Efficacy of clozapine demonstrated in schizophrenia – lacks extrapyramidal and (drug induced movement disorder) and neuroleptic (depressive or sedative) side effects typical of antipsychotics**
H. Gross, E. Langner, Effect profile of a chemically new broad spectrum neuroleptic of the dibenzo-diazepine group. *Wien. Med. Wochenscher* **116**, 814-6 (1966).

D. Bente, M.P. Engelmeier, K. Heinrich, H. Hippius, W. Schmitt. Clinical studies with a neuroleptically active dibenzothiazepine derivative. *Arzneimittelforschung* **16**, 314-6 (1966).

**1971-Clozapine found to have minimal side effects in animal models**
G. Stille, H. Lauener, E. Eichenberger, The pharmacology of 8-chloro-1 1-(4-methyl-1-piperazinyl)-5H-dibenzo [b,e][1,4] diazepine (clozapine). *Il Farmaco* **26**, 603-625 (1971).

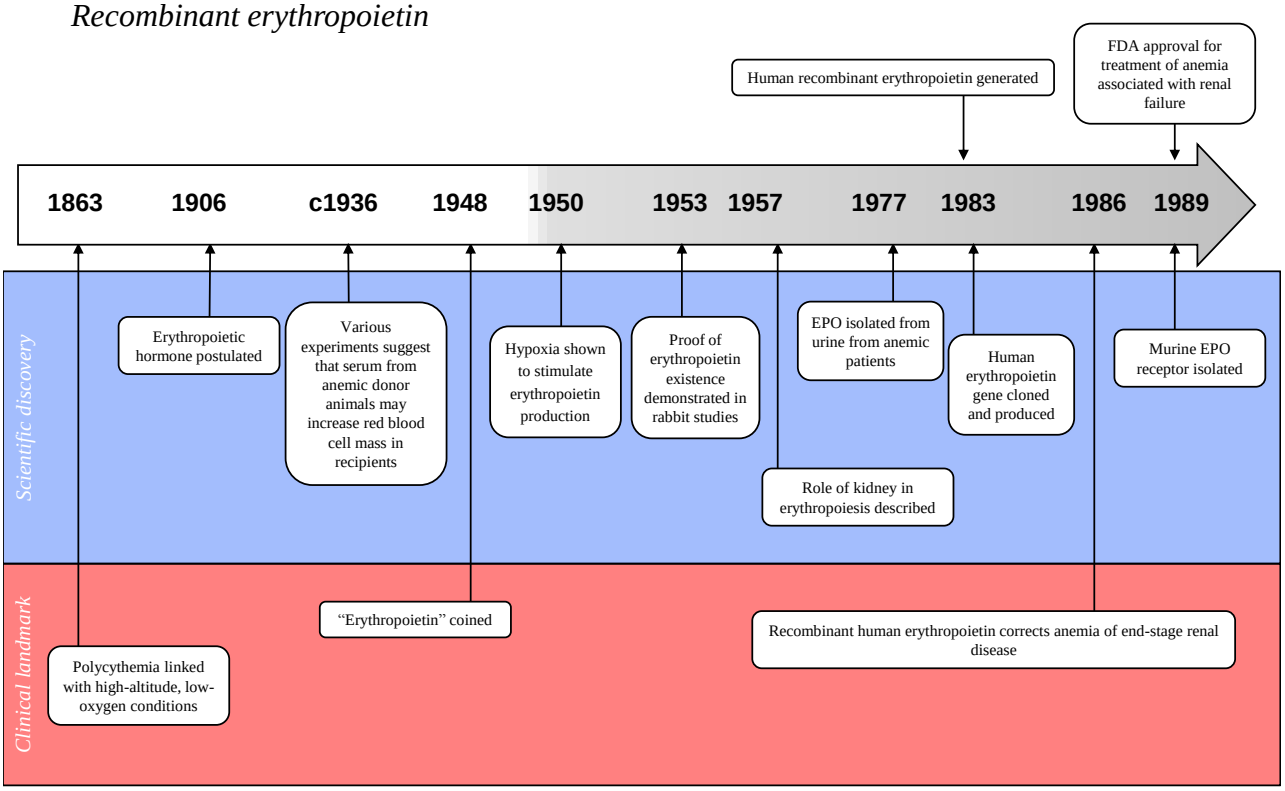
**1975-Withdrawn from Europe due to agranulocytosis, leading to death in some cases**
J. Idänpään-Heikkilä, E. Alhava, M. Olkinuora, I. Palva, Clozapine and agranulocytosis. *Lancet* **306**, 611 (1975).

**1988-Clozapine found effective for treatment-resistant schizophrenia over other antipsychotics**
J. Kane, G. Honigfeld, J. Singer, H. Meltzer, Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. *Arch. Gen. Psychiatry* **45**, 789-96. (1988).

**1989-Importance of 5-HT2A and D2 receptor affinities described for atypical antipsychotic drugs including clozapine**
H.Y. Meltzer, S. Matsubara, J.C. Lee, Classification of typical and atypical antipsychotic drugs on the basis of dopamine D-1, D-2 and serotonin2 pKi values. *J. Pharmacol. Exp. Ther.* **251**, 238-46 (1989).

# Epoetin alfa

*Recombinant erythropoietin*




**1863-Polycythemia linked with high-altitude, low-oxygen conditions**
D. Jourdanet, De l'anemie des altitudes et de l'anemie en general dans ses rapports avec la pression de l'atmosphere. Paris (1863).

**1906-Erythropoietic hormone postulated**
C. Carnot, C. DeFlandre Sur l' activité hémopoiétique du sérum au cours de la régénération du sang. *CR. Acad. Sci. Paris* **143**. 432–5 (1906).

**c1936- Various experiments demonstrated that serum from anemic donor animals increases red blood cell mass in recipients**
E. Hjort, Reticulocyte increase after injection of anemic serum. *Mor. Mag. Laegevidensk.* **97** (1936).

N. Krumdieck, Erythropoietic substance in the serum of anemic animals. *Proc. Soc. Exp. Biol. Med.* **54**, 14–7 (1943).

**1948-"Erythropoietin" coined**
E. Bonsdorf, E. Jalavisto, A humoral mechanism in anoxic erythrocytosis. *Acta Physiol. Scand.* **16** (1948).

**1950-Hypoxia shown to stimulate erythropoietin production**
K.R. Reissmann, Studies on the mechanism of erythropoietic stimulation in parabiotic rats during hypoxia. *Blood* **5**, 372–80 (1950).

**1953- Proof of erythropoietin existence demonstrated in rabbit studies**
A. Erslev, Humoral regulation of red cell production. *Blood* **8**, 349-57 (1953).

**1957-Role of kidney in erythropoiesis described**
L.O. Jacobson, E. Goldwasser, W. Fried, L. Plzak, Role of the kidney in erythropoiesis. *Nature* **179**, 633–4 (1957).

**1977-EPO isolated from urine of anemic patients**
T. Miyake, C.K. Kung, E. Goldwasser, Purification of human erythropoietin. *J. Biol. Chem.* **252**, 5558–64 (1977).

**1983-Human erythropoietin gene cloned and produced**
F.K. Lin, S. Suggs, C.H. Lin, *et al*, Cloning and expression of the human erythropoietin gene. *Proc. Natl. Acad. Sci. U.S.A.* **82**, 7580–4 (1985).

K. Jacobs, C. Shoemaker, R. Rudersdorf, *et al*, Isolation and characterization of genomic and cDNA clones of human erythropoietin. *Nature* **313**, 806–10 (1985).

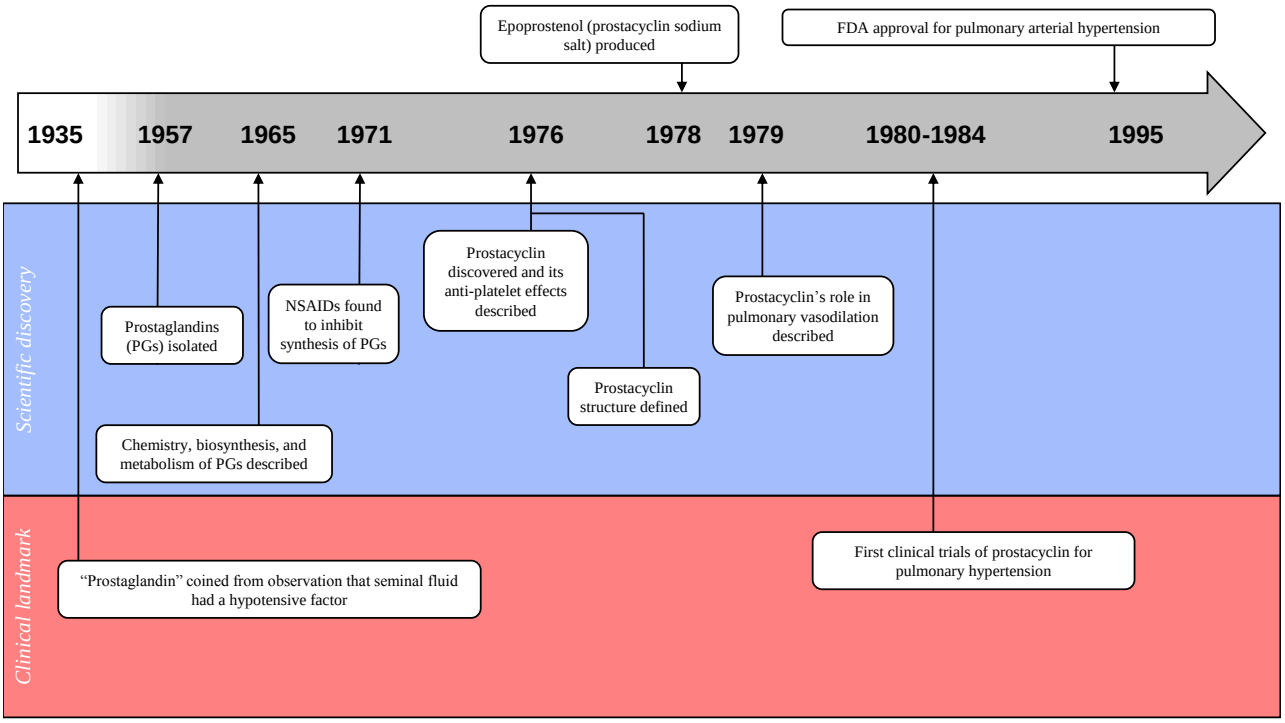
**1986-Recombinant human erythropoietin corrects anemia of end-stage renal disease**
C.G. Winearls, D.O. Oliver, M.J. Pippard, C. Reid, M.R. Downing, P.M. Cotes, Effect of human erythropoietin derived from recombinant DNA on the anaemia of patients maintained by chronic haemodialysis. *Lancet* **328**, 1175-1178 (1986).

J.W. Eschbach, J.C. Egrie, M.R. Downing, J.K. Browne, J.W. Adamson, Correction of the anemia of end-stage renal disease with recombinant human erythropoietin. Results of a combined phase I and II clinical trial. *N. Engl. J. Med.* **316**, 73–8 (1987).

**1989-Murine EPO receptor isolated**
A.D. Dandrea, H.F. Lodish, G.W. Wong, Expression cloning of the murine erythropoietin receptor. *Cell* **57**: 277 (1989).

# Epoprostenol

*Synthetic prostacyclin*




**1935-"Prostaglandin" coined from observation that seminal fluid had a hypotensive factor**
U.S. Von Euler, Über die spezifische blutdrucksenkende Substanz des menschlichen Prostataund Samenblasensekrets. *Wein. Klin. Wochenscher* **14**, 1182-3 (1935).

**1957-Prostaglandins (PGs) isolated**
S. Bergström, J. Sjövall, The isolation of prostaglandin. *Acta Chem. Scand.* **11**, 1086 (1957).

**1965-Chemistry, biosynthesis, and metabolism of PGs described**
B. Samuelsson, The Prostaglandins. *Angew. Chem. Internat. Edit.* **4**, 410-416 (1965).

**1971-NSAIDs found to inhibit synthesis of PGs**
J.R. Vane, Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nat. New. Biol.* **231**, 232-5 (1971).

**1976-Prostacyclin discovered and it's anti-platelet effects described**
S. Moncada, R. Gryglewski, S. Bunting, J.R. Vane, An enzyme isolated from arteries transforms prostaglandin endoperoxides to an unstable substance that inhibits platelet aggregation. *Nature* **263**, 663-5 (1976).

R.J. Gryglewski, S. Bunting, S. Moncada, R.J. Flower, J.R. Vane, Arterial walls are protected against deposition of platelet thrombi by a substance (prostaglandin X) which they make from prostaglandin endoperoxides. *Prostaglandins* **12**, 685–713 (1976).

**1976-Prostacyclin structure defined**
N. Whittaker, S. Bunting, J. Salmon, S. Moncada, J.R. Vane, R.A. Johnson, D.R. Morton, J.H. Kinner, R.R. Gorman, J.C. McGuire, F.F. Sun, The chemical structure of prostaglandin X (prostacyclin). *Prostaglandins* **12**, 915-28 (1976).

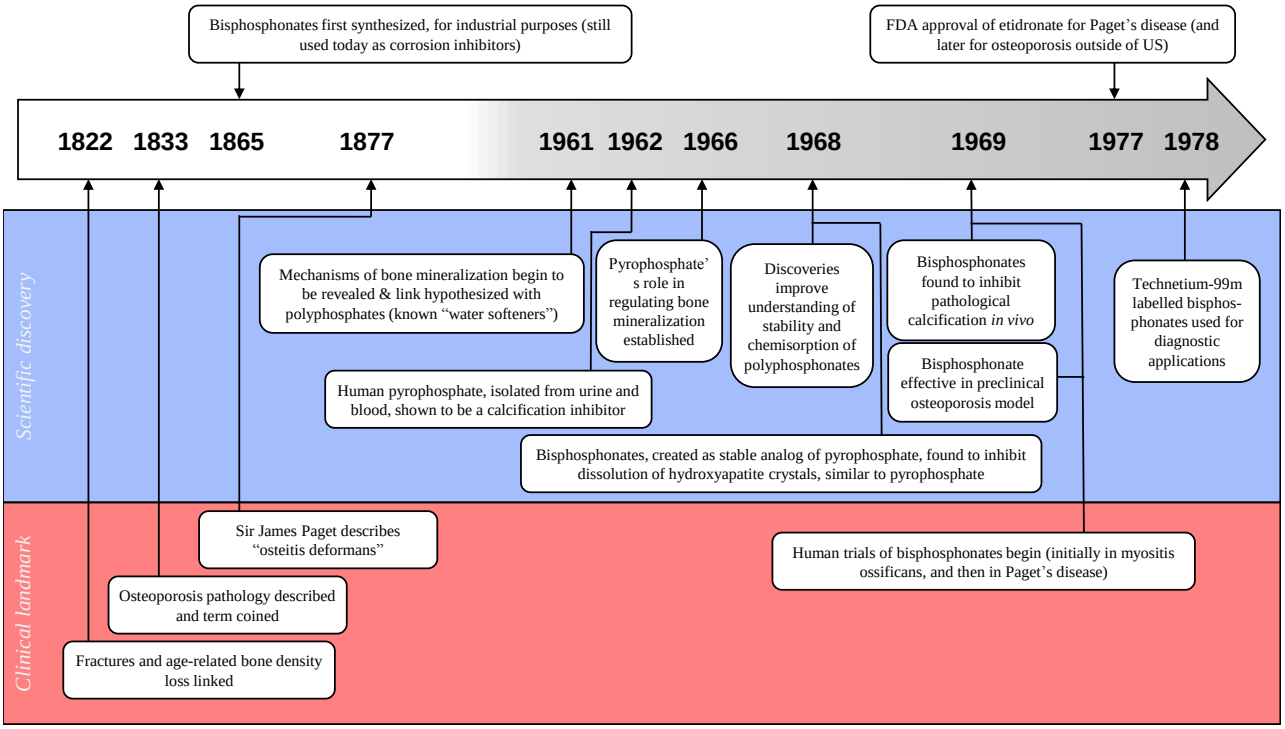
**1979-Prostacyclin's role in pulmonary vasodilation described**
S. Moncada, J.R. Vane, Arachidonic acid metabolites and the interactions between platelets and blood-vessel walls. *N. Engl. J. Med.* **300**, 1142-7 (1979).

**1980-1984-First clinical trials of prostacyclin for pulmonary hypertension**
J. Szczeklik, A. Szczeklik, R. Nizankowski, Prostacyclin for pulmonary hypertension. *Lance*t **316**, 1076 (1980).

L.J. Rubin, B.M. Groves, J.T. Reeves, M. Frosolono, F. Handel, A.E. Cato, Prostcyclin-induced acute pulmonary vasodilation in primary pulmonary hypertension. *Circulation* **66**, 334-8 (1982).

T. Higenbottam, D. Wheeldon, F. Wells, J. Wallwork, Long-term treatment of primary pulmonary hypertension with continuous intravenous epoprostenol (prostacyclin). *Lancet* **323**, 1046-7 (1984).

# Bisphosphonates




**1822-Fractures and age-related bone density loss linked**
A. Cooper, B.B. Cooper, A treatise on dislocations, and on fractures of the joints. London, United Kingdom: Churchill. 425 (1822).

**1833-Osteoporosis pathology described and term coined**
J.F. Lobstein, Traite d'anatomie Pathologique. Paris: Chez F. G. Levrault (1833).

**1865-Bisphosphonates first synthesized, for industrial purposes**
N. Menschutkin, Ueber die Einwirkung des Chloracetyls auf phosphorige Saure. Ann Chem Pharmacol **133** (1865).

**1877-Sir James Paget describes "osteitis deformans"**
J. Paget, On a form of chronic inflammation of bones (osteitis deformans). *Medico-chirurgical transactions* **60**, 37-63 (1877)

**1961-Mechanisms of bone mineralization begin to be revealed & link hypothesized with polyphosphates (known "water softeners")**
H. Fleish, W.F. Neuman, Mechanisms of calcification: role of collagen, polyphosphates, and phosphatase. *Am. J. Physiol*. **200**, 1296–300 (1961).

**1962-Human pyrophosphate, isolated from urine and blood, shown to be a calcification inhibitor**
H. Fleisch, S. Bisaz, Isolation from urine of pyrophosphate, a calcification inhibitor. *Am. J. Physiology.* **203**, 671-5 (1962).

H. Fleisch, S. Bisaz, Mechanism of calcification: inhibitory role of pyrophosphate. *Nature* **195**, 911 (1962).

**1966-Pyrophosphate's role in regulating bone mineralization established (prompting search for analogs)**
H. Fleisch, R.G. Russell, F. Straumann, Effect of pyrophosphate on hydroxyapatite and its implications in calcium homeostasis. *Nature* **212**, 901–3 (1966).

**1968-Bisphosphonates, created as stable analog of pyrophosphate, found to inhibit dissolution of hydroxyapatite crystals, similar to pyrophosphate**
H. Fleisch, R.G. Russell, S. Bisaz, P.A. Casey, R.C. Mühlbauer, The influence of pyrophosphate analogues (diphosphonates) on the precipitation and dissolution. *Calcif. Tissue Res.* **Suppl:10–10a** (1968).

**1968-Discoveries that improve understanding of stability and chemisorption of polyphosphonates**
M.D. Francis, The inhibition of Calcium Hydroxyapatite Crystal Growth by Polyphosphonates and Polyphosphates. *Calc. Tiss. Res.* **3**, 151-162 (1969).

**1969-Bisphosphonates found to inhibit pathological calcification in vivo**
H. Fleisch, R.G.G. Russell, M.D. Francis, Diphosphonates inhibit hydroxyapatite dissolution in vitro and bone resorption in tissue culture and in vivo. *Science* **165**, 1262–1264 (1969).

M.D. Francis, R.G. Russell, H. Fleisch, Diphosphonates inhibit formation of calcium phosphate crystals in vitro and pathological calcification in vivo. *Science* **165**, 1264–6 (1969).

**1969-Human trials of bisphosphonates begin (initially in myositis ossificans, and then in Paget's disease)**
C.A. Bassett, A. Donath, F. Macagno, R. Preisig, H. Fleisch, M.D. Francis, Diphosphonates in the treatment of myositis ossificans. *Lancet* **294**, 845 (1969).

R.G.G. Smith, M.B. Russell, Diphosphonates and Paget's Disease of bone. *Lancet* **297**, 945-947 (1971).

**1969-Bisphosphonate effective in preclinical osteoporosis model**
H. Fleisch, R.G.G. Russell, B. Simpson, R.C. Muhlbauer, Prevention by a diphosphonate of immobilisation 'osteoporosis' in rats. *Nature* **223**, 211–2 (1969).

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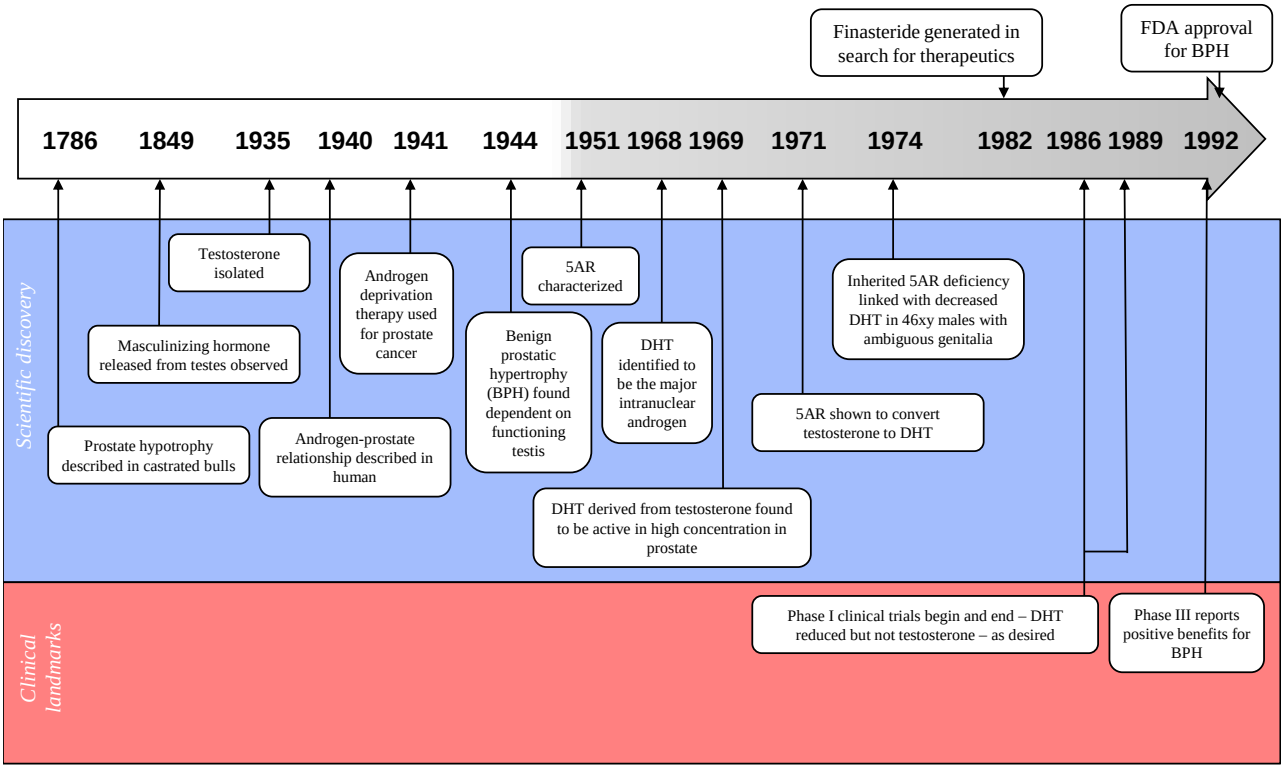
I. Fogelman, R.G. Bessent, J.G. Turner, D.L. Citrin, I.T. Boyle, W.R. Greig, The use of whole-body retention of Tc-99m diphosphonate in the diagnosis of metabolic bone disease. *J. Nucl. Med.* **19**, 270-5 (1978).

# Finasteride

*5-α-reductase (5AR) inhibitor*




**1786-Prostate hypotrophy described in castrated bulls**
J. Hunter, Observations on Certain Parts of the Animal Oeconomy. London, England. (1786).

**1849-Masculinizing hormone released from testes observed**
A.A. Berthold, Transplantation der Hoden. *Arch. Anat. Physiol. Wissenscher. Med.* 42-46 (1849).

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A. Butenandt, G. Hanisch, The transformation of dehydroandrosterone into androstendiol and testosterone; a method for producing testosterone from cholesterin. *Hoppe-Seyler's Z Physiol Chem*. **237**, 89-98 (1935).

L. Ruzicka, A. Wettstein, Synthesis of the testicular hormone (testosterone) (androstene 3-on-17-ol). *Helv. chim. Acta.* 18, 1264-75 (1935).

**1940-Androgen-prostate relationship described in humans**
C. Huggins, R. Steven, The effect of castration on benign hypertrophy of the prostate in man. *J Urol.* **43**, 705 (1940).

**1941-Androgen deprivation therapy used for prostate cancer**

C. Huggins, C.U. Hodges, Studies on prostate cancer. I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. *Cancer Res.* **1,** 293 (1941)

**1944-Benign prostate hypertrophy (BPH) found dependent on functioning testes**
R.A. Moore, Benign hypertrophy and carcinoma of the prostate. *Surgery* **16**, 152 (1944)

**1951-5-alpha-reductase characterized**
J.J. Schneider, P.M. Horstmann, Effects of incubating desoxycorticosterone with various rat tissues. *The Journal of Biological Chemistry* **191**, 327-38 (1951).

**1968-DHT identified to be the major intranuclear androgen**
N. Bruchovsky, J.D. Wilson, The conversion of testosterone to 5-alpha-androstan-17-beta-ol-3-one by rat prostate in vivo and in vitro. *J. Biol. Chem*. **243**, 2012-21 (1968).

N. Bruchovsky, J.D. Wilson, The intranuclear binding of testosterone and 5-alpha-androstan-17-beta-ol-3-one by rat prostate. *J. Biol. Chem.* **243**, 5953-60 (1968).

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N. Bruchovsky, J.D. Wilson, The intranuclear binding of testosterone 5α-androstan-17β-ol-3-one by rat prostate. *J. Biol. Chem*. 243, 5953-60 (1968).

J.D. Wilson, J.D. Walker, The conversion of testosterone to 5α-androstan-17β-ol-3-one (dihydrotestosterone) by skin slices of man. *J. Clin. Invest*. **48**, 317-79 (1969).

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J.D. Wilson, Recent studies on the mechanism of action in testosterone. *N. Engl. J. Med.* **287**, 1284-91 (1972).

J.D. Wilson, I. Lasnitzki, Dihydrotestosterone formation in fetal tissues of the rabbit and rat. *Endocrinology* **89**, 659-68 (1971).

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J. Imperato-McGinley, L. Guerrero, T. Gautier, *et al*, Steroid 5-α-reductase deficiency in man: an inherited form of male pseudohermaphroditism. *Science* **186**, 1213-5 (1974).

P.C. Walsh, J.D. Madden, M.J. Harrod, J.L. Goldstein, P.C. MacDonald, J.D. Wilson, Familial incomplete male pseudohermaphroditism, type 2. Decreased dihydrotestosterone formation in pseudovaginal perineoscrotal hypospadias. *N. Engl. J. Med.* **291**, 944-949 (1974).

**1982-Finasteride generated**
J.R. Brooks, D. Berman, M.S. Glitzer, *et al*, Effect of a new 5-alpha-reductase inhibitor on size, histologic characteristics and androgen concentrations of the canine prostate. *Prostate* **3**, 35-44 (1982).

**1986-1989-Phase I clinical trials begin and end – DHT reduced but not testosterone**
G.J. Gormley, E. Stoner, R.S. Rittmaster, *et al*, Effects of finasteride (MK-906), a 5_-reductase inhibitor, on circulating androgens in male volunteers. *J. Clin. Endocrinol. Metab*. **70**, 1136-1141 (1990).

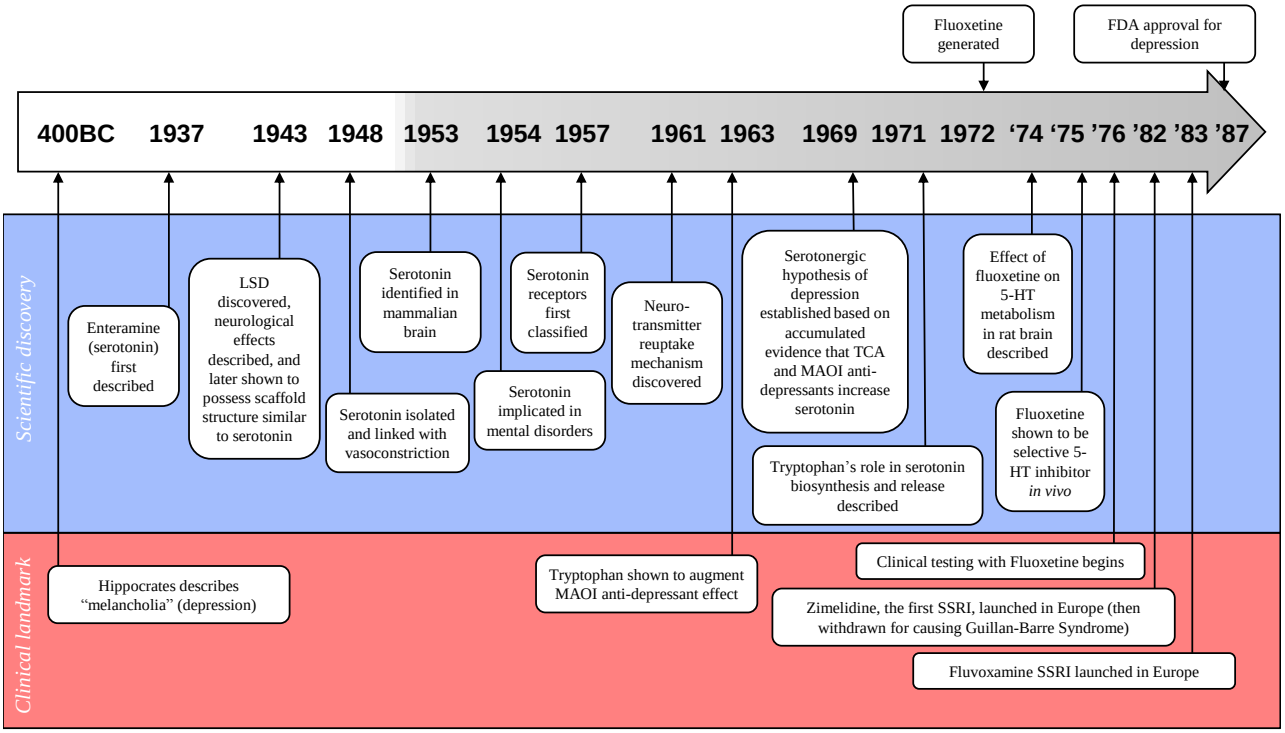
R.S. Rittmaster, E. Stoner, D.L. Thompson, *et al*, Effects of MK-906, a specific 5_-reductase inhibitor, on serum androgens and androgen conjugates in normal men. *J, Androl.* **10**, 259-262 (1989).

**1992-Phase III reports positive benefits for BPH**

G.J. Gormley, E. Stoner, R.C. Bruskewitz, *et al*, The effect of finasteride in men with benign prostatic hyperplasia. The Finasteride Study Group. *N. Engl. J. Med.* **327**, 1185-1191 (1992).

# Fluoxetine

*selective serotonin reuptake inhibitor*




**400BC-Hippocrates describes "melancholia" (depression)**
S.W. Jackson, Melancholia and depression: from Hippocratic times to modern times. Yale University Press (1990).

**1937-Enteramine (serotonin) first described**
V. Erspamer, M. Vialli, Ricerche sul secreto delle cellule enterocromaffini. *Boll. D. Soc. Med-chir. Pavia* **51**, 357-63 (1937).

**1943-LSD discovered and neurological effects described[3] (later, shown to possess scaffold structure similar to serotonin)**
A. Hofmann, *LSD: My problem child*; Tarcher: Los Angeles, CA (1979).

**1948-Serotonin isolated**
M.M. Rapport, A.A. Green, I.H. Page, Partial purification of the vasoconstrictor in beef serum. *J. Biol. Chem.* **174**, 735 (1948).

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M.M. Rapport, A.A. Green, I.H. Page, Serum vasoconstrictor, serotonin; isolation and characterization. *J. Biol. Chem.* **176**, 1243 (1948).

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B.M. Twarog, I.H. Page, Serotonin content of some mammalian tissues and urine and a method for its determination. *Am. J. Physiol.* **175**, 157-61 (1953).

**1954-Serotonin implicated in mental disorders**
D.W. Woolley, E. Shaw, A biochemical and pharmacological suggestion about certain mental disorders. *Proc. Natl. Acad. Sci. U.S.A.* **40**, 228-31 (1954).

**1957-Serotonin receptors first classified**
J.H. Gaddum, Z.P. Picarelli, Two kinds of tryptamine receptor. *Br. J. Pharmacol.* **12**, 134–139 (1957).

**1961-Neuro-transmitter reuptake mechanism discovered**
G. Hertting, J. Axelrod, I.J. Kopin, L.G. Whitby, Lack of uptake of catecholamines after chronic denervation of sympathetic nerves. *Nature* **189**, 66 (1961).

G. Hertting, J. Axelrod, Fate of tritiated noradrenaline at the sympathetic nerve-endings. *Nature* **192**, 172-3 (1961).

**1963-Tryptophan shown to augment MAOI anti-depressant effect**
A. Coppen, D.M. Shaw, J.P. Farrell, Potentiation of the antidepressive effect of a monoamine-oxidase inhibitor by tryptophan. *Lancet* **281**, 79-81 (1963).

**1969-Serotonergic hypothesis of depression established (based on accumulated evidence that TCA and MAOI anti-depressants increase serotonin)**
A. Carlsson, H. Corrodi, K. Fuxe, T. Hökfelt, Effects of antidepressant drugs on the depletion of intraneuronal brain 5-hydroxytryptamine stores caused by 4-methyl-α-ethylmetatyramine. *Eur. J. Pharmacol.* **5**, 357-66 (1969).

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J.D. Fernstrom, R.J. Wurtman, Brain Serotonin Content: Physiological Dependence on Plasma Tryptophan levels. *Science* **173**, 149-152 (1971).

J.D. Fernstrom, R.J. Wurtman, Brain Serotonin Content: Increase Following Ingestions of Carbohydrate Diet. *Science* **174**, 1023-1025 (1971).

J.D. Fernstrom, R.J. Wurtman, Brain Serotonin Content: Physiological Regulation by Plasma Neutral Amino Acids. *Science* **178**, 414-416 (1972).

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D.T. Wong, J.S. Horng, F.P. Bymaster, K.L. Hauser, B.B. Molloy, A selective inhibitor of serotonin uptake: Lilly 110140, 3-(p-trifluoromethylphenoxy)-N-methyl-3-phenylpropylamine. *Life Sci.* **15**, 471-9 (1974).

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R.W. Fuller, K.W. Perry, B.B. Molloy, Effect of an uptake inhibitor on serotonin metabolism in rat brain: studies with 3-(*p*-trifluoromethylphenoxy)-*N*-methyl-3-phenylpropylamine. *Life Sci.* **15**, 1161–1171 (1974).

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R.W. Fuller, K.W. Perry, B.B. Molloy, Effect of 3-(*p*-trifluoromethylphenoxy). *N.N*.methyl-3-phenylpropylamine on the depletion of brain serotonin by 4-chloroamphetamine. *J. Pharmacol. Exp. Ther*. **193**, 793–803 (1975).

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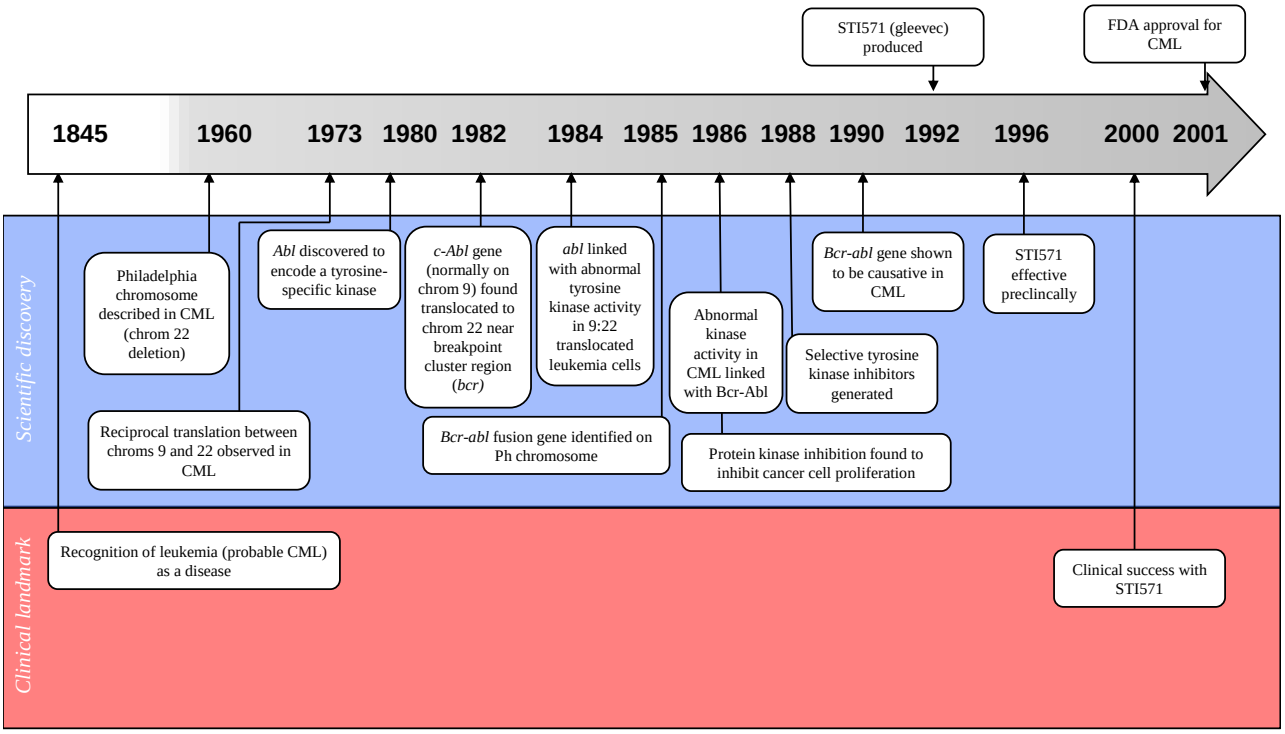
L. Lemberger, H. Rowe, R. Carmichael, S. Oldham, J.S. Horng, F.P. Bymaster, D.T. Wong, Pharmacologic effects in a man of a specific serotonin-reuptake inhibitor. *Science* **199**, 436-7 (1978).

**1982-Zimelidine, the first SSRI, launched in Europe (then withdrawn for causing Guillan-Barre Syndrome)**

R.C. Heel, P.A. Morley, R.N. Brogden, A.A. Carmine, T.M. Speight, G.S. Avery, Zimelidine: a review of its pharmacological proerties and therapeutic efficacy in depressive illness. *Drugs* **24**, 169-206 (1982).

# Imatinib

*tyrosine kinase inhibitor*




**1845-Recognition of leukemia (probable CML) as a disease**
J.H. Bennett, Case of hypertrophy of the spleen and liver in which death took place from the suppuration of the blood. *Edinburgh Med. Surg. J.* **64**, 413-23 (1845).

**1960-Philadelphia chromosome described in CML (chrom 22 deletion)**
P.C. Nowell, D.A. Hungerford, A minute chromosome in human chronic granulocytic leukemia. *Science* **132**:1497 (1960)

**1973-Reciprocal translation between chroms 9 and 22 observed in CML**
J.D. Rowley, A new consistent chromosomal abnormality in chronic myelogenous leukemia identified by quinacrine flourescence and Giemsa staining. *Nature* **243**, 290-3 (1973).

**1980 - *Abl* discovered to encode a tyrosine-specific kinase**
O.N. Witte, A. Dasgupta, D. Baltimore, Abelson murine leukaemia virus protein is phosphorylated *in vitro* to form phosphotyrosine. *Nature* **283**, 826-831 (1980)

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A. de Klein, A. Geurts van Kessel, G. Grosveld, *et al*, A cellular oncogene is translocated to the Philadelphia chromosome in chronic myelocytic leukemia. *Nature* **200**, 765-7 (1982).

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J.B. Konopka, S.M. Watanabe, O.N. Witte, An alteration of the human c-abl protein in K562 leukemia cells unmasks associated tyrosine kinase activity. *Cell* 37, 1035-42 (1984).

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E. Shtivelman, B. Lifshitz, R.P. Gale, E. Canaani E, Fused transcript of abl and bcr genes in chronic myelogenous leukemia. *Nature* **315**, 550-4 (1985).

R.L. Davis, J.B. Konopka, O.N. Witte, Activation of the c-abl oncogene by viral transduction or chromosomal translocation generates altered c-abl proteins with similar in vitro kinase properties. *Mol Cell Biol.* **5**, 204-213 (1985).

**1986-Abnormal kinase activity in CML linked with Bcr-Abl**
Y. Ben-Neriah, G.Q. Daley, A.M. Mes-Masson, O.N. Witte, D. Baltimore, The chronic myelogenous leukemia-specific P210 protein is the product of the bcr/abl hybrid gene. *Science* **233**, 212-214 (1986).

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T. Tamaoki, H. Nomoto, I. Takahashi, Y. Kato, M. Morimoto, F. Tomita, Staurosporine, a potent inhibitor of phospholipid/Ca++ dependent protein kinase. *Biochem Biophy Res Comm*. **135**, 397-402 (1986).

**1988-Selective tyrosine kinase inhibitors generated**
P. Yaish, A. Gazit, C. Gilon, A. Levitzki, Blocking of EGF-dependent cell proliferation by EGF receptor kinase inhibitors. *Science* **242**, 933-35 (1989).

A. Gazit, P. Yaish, C. Gilon, A. Levitzki, Tryrphostins I: synthesis and biological activity of protein tyrosine kinase inhibitors. *J. Med. Chem.* **32**, 2344-52 (1989).

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G.Q. Daley, R.A. Van Etten, D. Baltimore, Induction of chronic myelogenous leukemia in mice by the P210bcr/abl gene of the Philadelphia chromosome. *Science* **247**, 824-30 (1990).

M.A. Kelliher, K. McLaughlin, O.N. Witte, N. Rosenberg, Induction of a chronic myelogenous leukemia-like syndrome in mice with v-abl and BCR/ABL. *Proc. Natl. Acad. Sci. U.S.A.* **87**, 6649-53 (1990).

N. Heisterkamp, G. Jenster, J. ten Hoeve, D. Zovich, P.K. Pattengale, J. Groffen, Acute leukemia in bcr/abl transgenic mice. *Nature*, **344**, 251-3 (1990).

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R. Capdeville, E. Buchdunger, J. Zimmerman, A. Matter, Glivec (STI571, imatinib), a rationally developed, targeted anticancer drug. *Nat. Rev. Drug Discov*. **1**, 493-502 (2002).

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B.J. Druker, S. Tamura, E. Buchdunger, *et al*, Effects of a selective inhibitor of the Abl tyrosine kinase on growth of Bcr-Abl positive cells. *Nat. Med.* **2**, 561-6 (1996).

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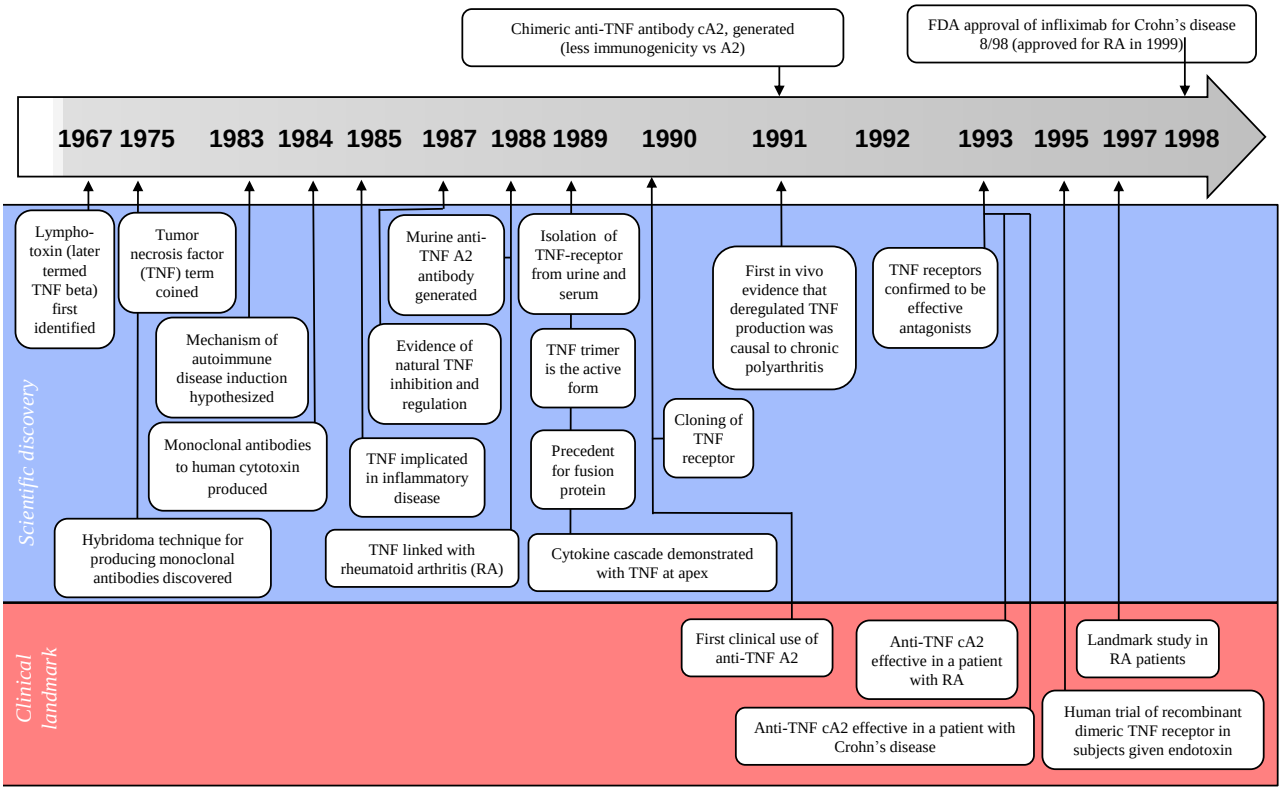
B.J. Druker, M. Talpaz, D.J. Resta, B. Peng, E. Buchdunger, J.M. Ford, N.B. Lydon, H. Kantarjian, R. Capdeville, S. Ohno-Jones, C.L. Sawyers, Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *N. Engl. J. Med*. **344**, 1031-7 (2001).

# TNF blockers




**1967-Lymphotoxin (later termed TNF beta) first identified**
N.H. Ruddle, B.H. Waksman, Cytotoxic effect of lymphocyte-antigen interaction in delayed hypersensitivity. *Science* **157**, 1060-1062 (1967).

G.A. Granger, T.W. Williams, Lymphocyte cytotoxicity in vitro: activation and release of a cytotoxic factor. *Nature* **218**, 1253-4 (1968).

**1975-Tumor necrosis factor (TNF) term coined**
E.A. Carswell, L.J. Old, R.L. Kassel, *et al.*, An endotoxin-induced serum factor that causes necrosis of tumors. *Proc. Natl. Acad. Sci. U.S.A.* **72**, 3666–70 (1975).

**1975-Hybridoma technique for producing monoclonal antibodies discovered**
G. Kohler, C. Milstein, Continuous cultures of fused cells secreting antibody of predefined specificity. *Nature* **256**, 495-7 (1975).

**1983-Mechanism of autoimmune disease induction hypothesized**
G.F. Bottazzo, R. Pujol Borrell, T. Hanafusa, M. Feldmann, Role of aberrant HLA-DR expression and antigen presentation in induction of endocrine autoimmunity. *Lancet* 184, 1115-1118 (1983).

**1984-TNF isolated**

B. Beutler, J. Mahoney, N. Le Trang, P. Pekala, A. Cerami, Purification of cachectin, a lipoprotein lipase-suppressing hormone secreted by endotoxin-induced RAW 264.7 cells. *J. Exp. Med.* **161**, 984-95 (1985).

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D. Pennica, G.E. Nedwin, J.S. Hayflick, *et al.*, Human tumour necrosis factor: precursor structure, expression and homology to lymphotoxin. *Nature* **312**, 724–9 (1984).

**1985-Monoclonal antibodies to human cytotoxin produced**

T. Hahn, L. Toker, S. Budilovsky, D. Aderka, Z. Eshhar, D. Wallach, Use of monoclonal antibodies to a human cytotoxin for its isolation and for examining the self-induction of resistance to this protein. *Proc Natl Acad Sci.* **82**, 3814-3818 (1985).

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B. Beutler, I.W. Milsark, A.C. Cerami, Passive immunization against cachectin/tumor necrosis factor protects mice from lethal effect of endotoxin. *Science* **229**, 869-71 (1985).

J.M. Dayer, B. Beutler, A. Cerami, Cachectin/tumor necrosis factor stimulates collagenase and prostaglandin E2 production by human synovial cells and dermal fibroblasts. *J. Exp. Med.* **162**, 2163–8 (1985).

**1987-Evidence of natural TNF inhibition and regulation**

P. Seckinger, S. Isaaz, J.M. Dayer, A human inhibitor of tumor necrosis factor alpha. *J. Exp. Med.* **167**, 1511-6 (1988).

**1988-Murine anti-TNF A2 antibody generated**

D.M. Knight, H. Trinh, J. Le, S. Siegel, D. Shealy, M. McDonough, B. Scallon, M.A. Moore, J. Vilcek, P. Daddona, *et al*., Construction and initial characterization of a mouse-human chimeric anti-TNF antibody. *Mol. Immunol*. **30**, 1443-53 (1993).

J. Le, J. Vilcek, unpublished; J. Vilcek, M. Feldmann, Historical review: cytokines as therapeutic targets of therapeutics. *Trends in Phys. Sci.* **25**, 201-9 (2004).

**1988-TNF linked with rheumatoid arthritis**

G. Buchan, K. Barrett, M. Turner, *et al.*, IL-1 and TNF mRNA expression in rheumatoid arthritis: prolonged production of IL-1 alpha. *Clin. Exp. Imm.* 73, 449–55 (1988).

T. Saxne, M.A. Palladino, D. Heinegra˚d, *et al.*, Detection of TNF alpha but not TNF beta in rheumatoid arthritis synovial fluid and serum. *Arthritis Rheum.* **31**, 1041–5 (1988).

F.S. Di Giovine, G. Nuki, G.W. Duff, TNF in synovial exudates. *Ann. Rheum. Dis.* **47**, 768–72 (1988).

F.M. Brennan, D. Chantry, A. Jackson, R.N. Maini, M. Feldmann, Inhibitory effect of TNF alpha antibodies on synovial cell interleukin-1 production in rheumatoid arthritis. *Lancet* **334**, 244-247 (1989).

**1989-Isolation of TNF receptor from urine and serum**

H. Engelmann, D. Aderka, M. Rubinstein, D. Rotman, D. Wallach, A tumor necrosis factor (TNF)-binding protein purified to homogeneity from human urine protects cells from TNF toxicity. *J. Biol. Chem*. **264**, 11974-11980 (1989)

P. Seckinger, S. Isaaz, J.M. Dayer, Purification and biologic characterization of a specific tumor necrosis factor alpha inhibitor. *J. Biol. Chem.* **264**, 11966-73 (1989)

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R.A. Smith, C. Baglioni, Multimeric structure of the tumor necrosis factor receptor of HeLa cells. *Biol. Chem.* **264**, 14646 (1989).

**1989-Cytokine cascade demonstrated with TNF at apex**
F.M. Brennan, D. Chantry, A. Jackson, R. Maini, M. Feldmann, Inhibitory effect of TNF alpha antibodies on synovial cell interleukin-1 production in rheumatoid arthritis. *Lancet* **300**, 244-245 (1989).

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D.J. Capon, S.M. Chamow, J. Mordenti, S.A. Marsters, T. Gregory, H. Mitsuya, R.A. Byrn, C. Lucas, F.M. Wurm, J.E. Groopman, *et al.,* Designing CD4 immunoadhesins for AIDS therapy. *Nature* **337**, 525 (1989).

A. Trannecker, J. Schneider, H. Kiefer, K. Karjalainen, Highly efficient neutralization of HIV with recombinant CD4-immunoglobulin molecules. *Nature* **339**, 68 (1989).

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A.R. Exley, J. Cohen, W. Buurman, *et al.,* Monoclonal antibody to TNF in severe septic shock. *Lancet* **335**, 1275-7 (1990).

**1990-Cloning of the TNF Receptor**
H. Loetscher, Y.-C.E. Pan, R. Gentz, M. Brockhaus, H.Tabuchi, W. Lesslauer, Molecular cloning and expression of the human 55 kd tumor necrosis factor receptor. *Cell* **61**, 351 (1990).

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**1991 First in vivo evidence that deregulated TNF production was causal to chronic polyarthritis**
J. Keffer, L. Probert, H. Cazlaris, S. Georgopoulos, E. Kaslaris, D. Kioussis, G. Kollias, Transgenic mice expressing human tumour necrosis factor: a predictive genetic model of arthritis. *EMBO J.* **10**, 4025–4031 (1991).

**1991-Chimeric anti-TNF antibody cA2 generated (less immunogenicity vs anti-TNF A2)**
D.M. Knight, H. Trinh, J. Le, *et al*,. Construction and initial characterization of a mouse-human chimeric anti-TNF antibody. *Mol. Immunol.* **30**, 1443–53 (1993).

Albert Lasker Clinical Medical Research Award to Marc Feldmann and Ravinder N Maini for 'Discovery of anti-TNF therapy as an effective treatment for rheumatoid arthritis and other autoimmune disorders (2003).

M. Feldmann, R.N. Maini, TNF defined as a therapeutic target for rheumatoid arthritis and other autoimmune diseases. *Nature Med.* **9**, 1245-1250 (2003).

**1992-Anti-TNF cA2 effective in a patient with RA**
M.J. Elliott, R.N. Maini, M. Feldmann, *et al.*, Treatment of rheumatoid arthritis with chimeric monoclonal antibodies to tumor necrosis factor alpha. *Arthritis Rheum.* **36**, 1681-1690 (1993).

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B. Derkx, J. Taminiau, S. Radema, *et al.*, Tumour-necrosis-factor antibody treatment in Crohn's disease. *Lancet* **342**, 173–4 (1993).

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K.M. Mohler, D.S. Torrance, C.A. Smith, *et al*., Soluble tumor necrosis factor (TNF) receptors are effective therapeutic agents in lethal endotoxemia and function simultaneously as both TNF carriers and TNF antagonists. *J. Immunol.* **151**, 1548-156 (1993).

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A.F. Suffredini, D. Reda, S.M. Banks, M. Tropea, J.M. Agosti, R. Miller, Effects of recombinant dimeric TNF receptor on human inflammatory responses following intravenous endotoxin administration. *J. Immunol.* **155**, 5038-45 (1995).

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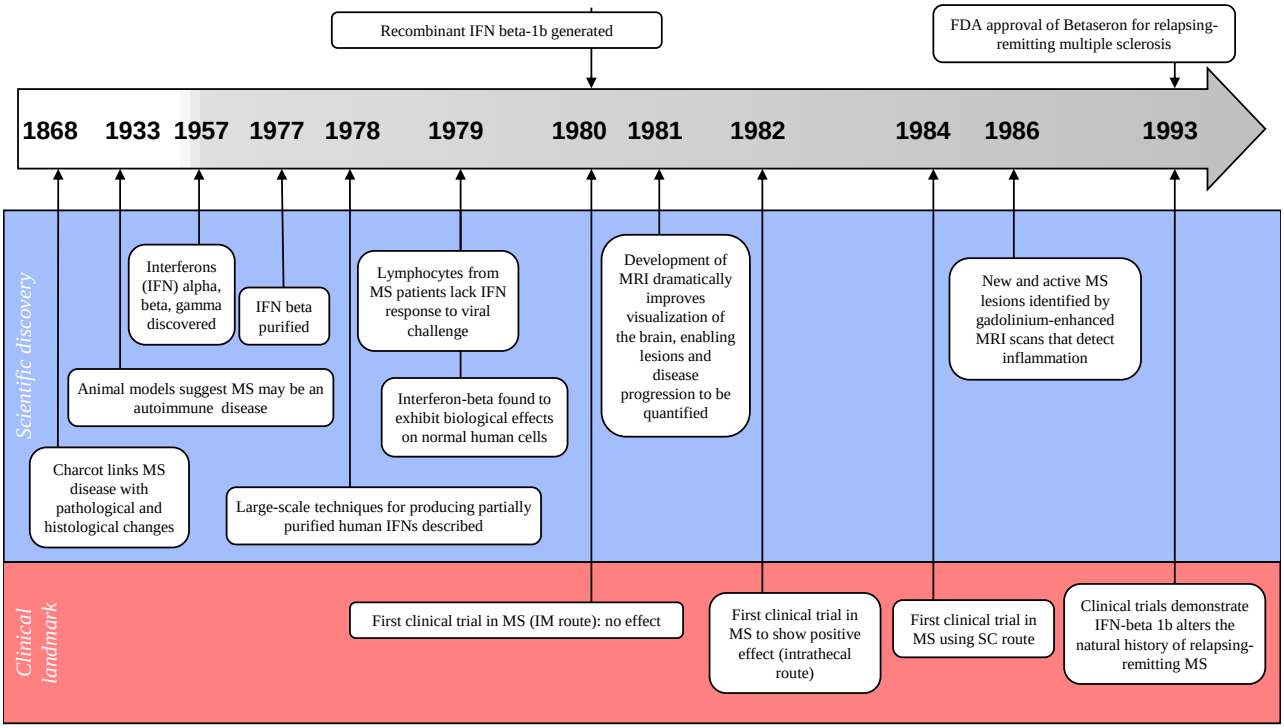
L.W. Moreland, S.W. Baumgartner, M.H. Schiff, E.A. Tindall, R.M. Fleischmann, A. Weaver, R.E. Ettlinger, S. Cohen, W.J. Koopman, K. Mohler, M.B. Widmer, C.M. Blosch. *N. Engl. J. Med.* **337**, 141-7 (1997).

# Interferons




**1868-Charcot links MS disease with pathological and histological changes**
J.M. Charcot, Lectures on the diseases of the nervous system delivered at the Salpêtrière. London (1877).

**1933-Animal models suggest MS may be an autoimmune disease**
T.M. Rivers, D.H. Sprunt, G.P. Berry, Observations on attempts to produce acute disseminated encephalomyelitis in monkeys. *J. Exp. Med*. **58**, 39–56 (1933).

F.F. Schwentker, T.M. Rivers, The antibody response of rabbits to injections of emulsions and extracts of homologous brain. *J. Exp. Med.* **60**, 559–574 (1934).

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A. Isaacs, J. Lindenmann, Virus interference. 1. The interferon. *Proc. R. Soc. Lond. B. Biol. Sci*. **147**, 258-67 (1957).

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W. Berthold, C. Tan, Y.H. Tan, Purification and in vitro labelling of interferon from a human fibroblastoid cell line. *J. Biol. Chem.* **253**, 5206-12 (1978).

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K. Cantell, S. Hirvonen, Large-scale production of human leukocyte interferon containing $10^8$ units per ml. *J. Gen. Virol.* **39**, 541-3 (1978).

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P.A. Neighbour, B.R. Bloom, Absence of virus-induced lymphocyte suppression and interferon production in multiple sclerosis. *Proc. Natl. Acad. Sci. U.S.A.* **76**, 476-80 (1979).

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L.M. Pfeffer, J.S. Murphy, I. Tamm, Interferon effects on the growth and division of human fibroblasts. *Exp Cell Res* **121**, 111-120 (1979).

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T. Fog, Interferon treatment of multiple sclerosis patients: a pilot study. In: Boese A (ed) Search for the cause of multiple sclerosis and other chronic diseases of the nervous system. *Verlag Chemie, Weinheim*. 491-3 (1980).

S.D. Cook, P.C. Dowling, Multiple sclerosis and viruses: an overview. *Neurology* **30**, 80-91 (1980).

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S. Nagata, H. Taira, A. Hall, *et al*., Synthesis in E. coli of a polypeptide with human leukocyte activity. *Nature* **284**, 316-20 (1980).

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I.R. Young, A.S. Hall, C.A. Pallis, N.J. Legg, G.M. Bydder, R.E. Steiner, Nuclear magnetic resonance imaging of the brain in multiple sclerosis. Lancet **318**, 1063–1066 (1981).

**1982-First clinical trial in MS to show positive effect (intrathecal route)**
L. Jacobs, *et al*., Intrathecal interferon in multiple sclerosis. *Arch. Neurol.* **39**, 609-15 (1982).

**1984-First clinical trial in MS using SC route**
R.L. Knobler, H.S. Panitch, S.L. Braheny, *et al.*, Systemic alpha interferon therapy in multiple sclerosis. *Neurology* **34**, 1273-9 (1984).

**1986-Gadolinium-enhanced MRI scans – detecting inflammation - identify new and active lesions. MRI becomes an established method of monitoring disease progression in clinical trials.**
R.I. Grossman, F. Gonzalez-Scarano, S.W. Atlas, S. Galetta, D.H. Silberberg, Multiple sclerosis: gadolinium enhancement in MR imaging. *Radiology* 161, 721–725 (1986).

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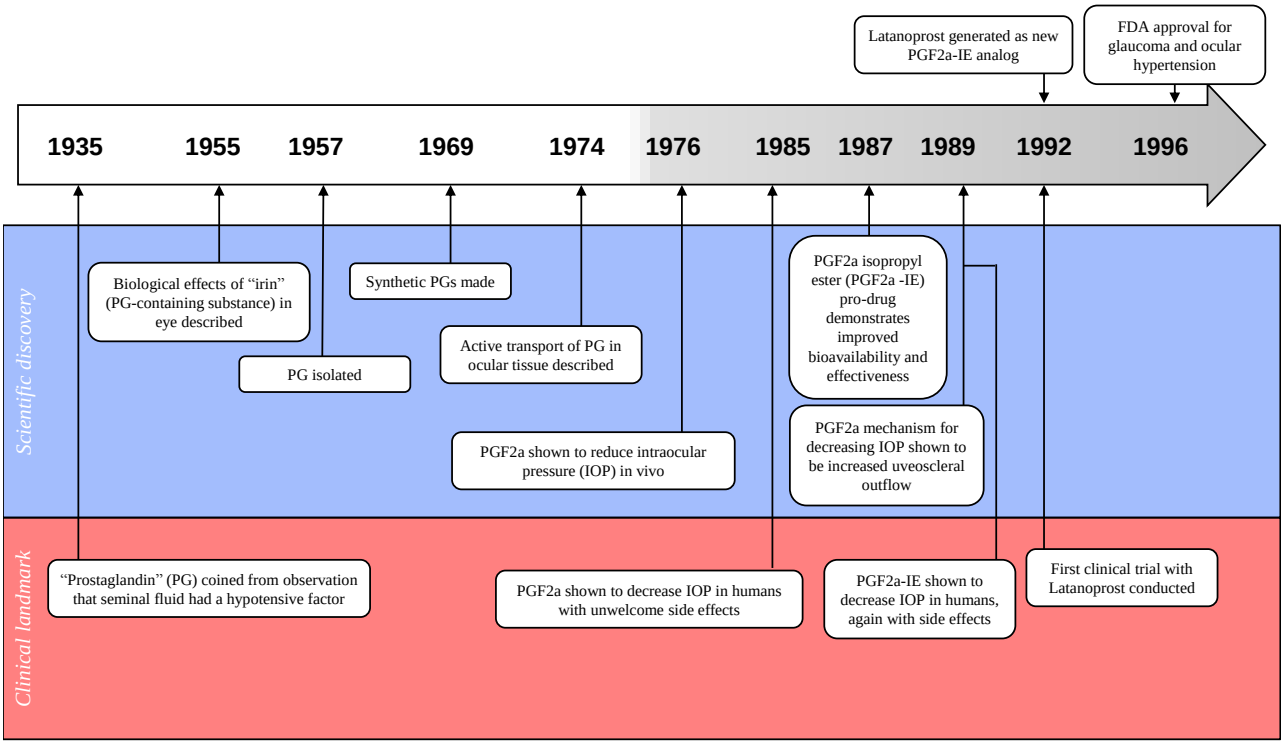
The IFNB Multiple Sclerosis Study Group, Interferon beta-1b is effective in relapsing-remitting multiple sclerosis, Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. *Neurology* **43**, 655–661 (1993).

# Latanoprost

*prostaglandin agonist*




**1935-"Prostaglandin" (PG) coined from observation that seminal fluid had a hypotensive factor**
U.S. Von Euler, Über die spezifische blutdrucksenkende Substanz des menschlichen Prostataund Samenblasensekrets. *Wien. Klin. Wochenschr.* **14**, 1182-3 (1935).

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N. Ambache, Irin, a smooth-muscle contracting substance present in rabbit iris. *J. Physiol*. **129**, 65-6 (1955).

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S. Bergström, J. Sjövall, The isolation of prostaglandin. *Acta Chem. Scand.* **11**, 1086 (1957).

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E.J. Corey, N.M. Weinshenker, T.K. Schaaf, W. Huber, Stereo-controlled synthesis of dl-prostaglandins F2.alpha. and E2. *J. Am. Chem. Soc*. **91**, 5675-7 (1969).

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L.Z. Bito, The effects of experimental uveitis on anterior uveal prostaglandin transport and aqueous humor composition. *Invest. Ophthalmol.* **13**, 959-66 (1974).

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C.B. Camras, L.Z. Bito, K.E. Eakins, Reduction of intraocular pressure by prostaglandins applied topically to the eyes of conscious rabbits. *Invest. Ophthalmol. Vis. Sci*. **16**, 1125-34 (1977).

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G. Giuffré, The effects of prostaglandin F2 alpha in the human eye. *Graefes Arch. Clin. Exp. Ophthalmol.* **222**, 139-41 (1985).

**1987-PGF2**a **isopropyl ester (PGF2**a**-IE) pro-drug demonstrates improved bioavailability and effectiveness**
L.Z. Bito, R.A. Baroody, The ocular pharmacokinetics of eicosanoids and their derivatives, 1: comparison of ocular eicosanoid penetration and distribution following the topical application of PGF , PGF -1-methyl ester, and PGF -1-isopropyl ester. *Exp. Eye Res.* **44**, 217–226 (1987).

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M.C. Groeneboer, P.F.J. Hoyng, A. Kuizenga, Prostaglandin F isopropyl ester versus iloprost phenacyl ester in rabbit and beagle eyes. *Curr. Eye Res.* **8**, 131–138 (1989).

**1989-PGF2**a **mechanism for decreasing IOP shown to be increased uveoscleral outflow**
S.F.E. Nilsson, M. Samuelsson, A. Bill, J. Stjernschantz, Increased uveoscleral outflow as a possible mechanism of ocular hypotension caused by prostaglandin F2a-1-isopropylester in the cynomolgus monkey. *Exp. Eye Res.* **48**, 707-16 (1989).

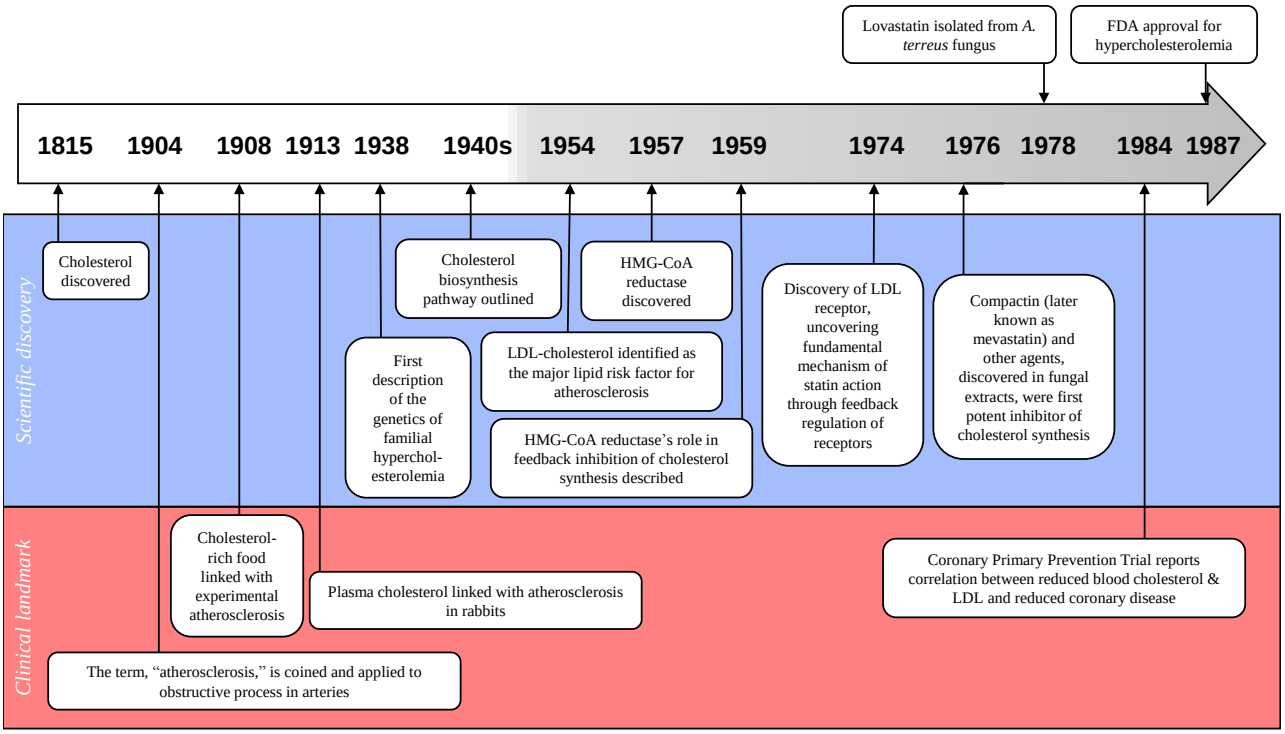
**1989-PGF2**a**-IE shown to decrease IOP in humans, again with side effects**
J. Villumsen, A. Alm, Prostaglandin F -isopropylester eye drops: effects in normal human eyes. *Br. J. Ophthalmol.* **73**, 419–426 (1989).

**1992-Latanoprost generated as a new PGF2**a**-IE analog, eliminating most side effects plaguing its precursors**
J. Stjernschantz, B. Resul, Phenyl-substituted prostaglandin analogs for glaucoma treatment. *Drugs Future* **17**, 691-701 (1992).

**1992-First clinical trial with Latanoprost conducted**
A. Alm, J. Villumsen, P. Tornquist, *et al.*, Intraocular pressure reducing effect of PhXA41 in ocular hypertensive patients: a placebo controlled double masked dose finding study. *Invest. Ophthalmol. Vis. Sci*. **33(suppl)**, 1247 (1992).

# Lovastatin

*HMG-CoA reductase inhibitor*




**1815-Cholesterol discovered**
M.E. Chevreul, Recherches chimiques sur les corps gras d'origine animale. *Paris, FG Levrault, In-8°, XVI-484* (1823).

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F. Marchand, Ueber Atherosclerosis. *Verhandlungen der Kongresse fuer Innere Medizin. 21 Kongresse* (1904).

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A.I. Ignatowski, Ueber die Wirkung der tierschen Einweisse auf der Aorta. *Virchow's Arch. Pathol. Anat.* **198**, 248 (1909).

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N. Anitschkow, S. Chalatow, Ueber experimentelle Cholester-insteatose und ihre Bedeutung fuer die Entstehung einiger pathologischer Prozesse. *Zentrbl. Allg. Pathol. Anat.* **24**, 1–9 (1913).

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C. Muller, Xanthomata, hypercholesterolemia, angina pectoris. *Acta Med. Scand.* **89**, 75–84 (1938).

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K. Bloch, D. Rittenberg, On the utilization of acetic acid for cholesterol formation. *J. Biol. Chem.* **145**, 625-636 (1942).

K. Bloch, The biological conversion of cholesterol to pregnanediol. *J. Biol. Chem.* **145**, 661-666 (1945).

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J.W. Gofman, F. Lindgren, H. Elliot, W. Mantz, J. Hewitt, V. Herring, The role of lipids and lipoproteins in atherosclerosis. *Science* **111**, 66-171 (1950).

J.W. Gofman, O. Delalla, F. Glazier, N.K. Freeman, F.T. Lindgren, A.V. Nichols, B. Strisower, A.R. Tamplin, The serum lipoprotein transport system in health, metabolic disorders, atherosclerosis and coronary heart disease. *Plasma* **2**, 413-484 (1954).

J.W. Gofman, L. Rubin, J.P. McGinley, H.B. Jones, Hyperlipoproteinemia. *Am. J. Med.* **17**, 514-520 (1954).

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Lynen F. In: Wolstenholrne GE, O'Connor CM, eds. *Ciba Foundation Symposium o Bio-synthesis of Terpenes and Sterols.* London; J and A Churchill, **95** (1958).

J.J. Ferguson, I.F. Durr, H. Rudney, The biosynthesis of mevalonic acid. *Proc. Natl. Acad. Sci. U.S.A.* **45**, 499–504 (1959).

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M.D. Siperstein, M.J. Guest, Studies on the homeostatic control of cholesterol synthesis (abstract). *J. Clin. Invest.* **38**, 1043 (1959).

**1974-Goldstein and Brown discover LDL receptor (uncovering fundamental mechanism of statin action through feedback regulation of receptors)**
M.S. Brown, J.L. Goldstein, Familial hypercholesterolemia: defective binding of lipoproteins to cultured fibroblasts associated with impaired regulation of 3-hydroxy-3-methylglutaryl coenzyme A reductase activity. *Proc. Natl. Acad. Sci. U.S.A.* **71**, 788-92 (1974).

J.L. Goldstein, M.S. Brown, Familial hypercholesterolemia: Identification of a defect in the regulation of 3-hydroxy-3-methylglutaryl coenzyme A reductase activity associated with overproduction of cholesterol. *Proc. Natl. Acad. Sci. U.S.A.* **70**, 2804-8 (1973).

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A. Endo, A. Kuroda, K. Tanzanwa, Competitive inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase by ML-236A and ML-236B fungal metabolites, having hypercholesterolemic activity. *FEBS Letter* **72**, 323-326 (1976).

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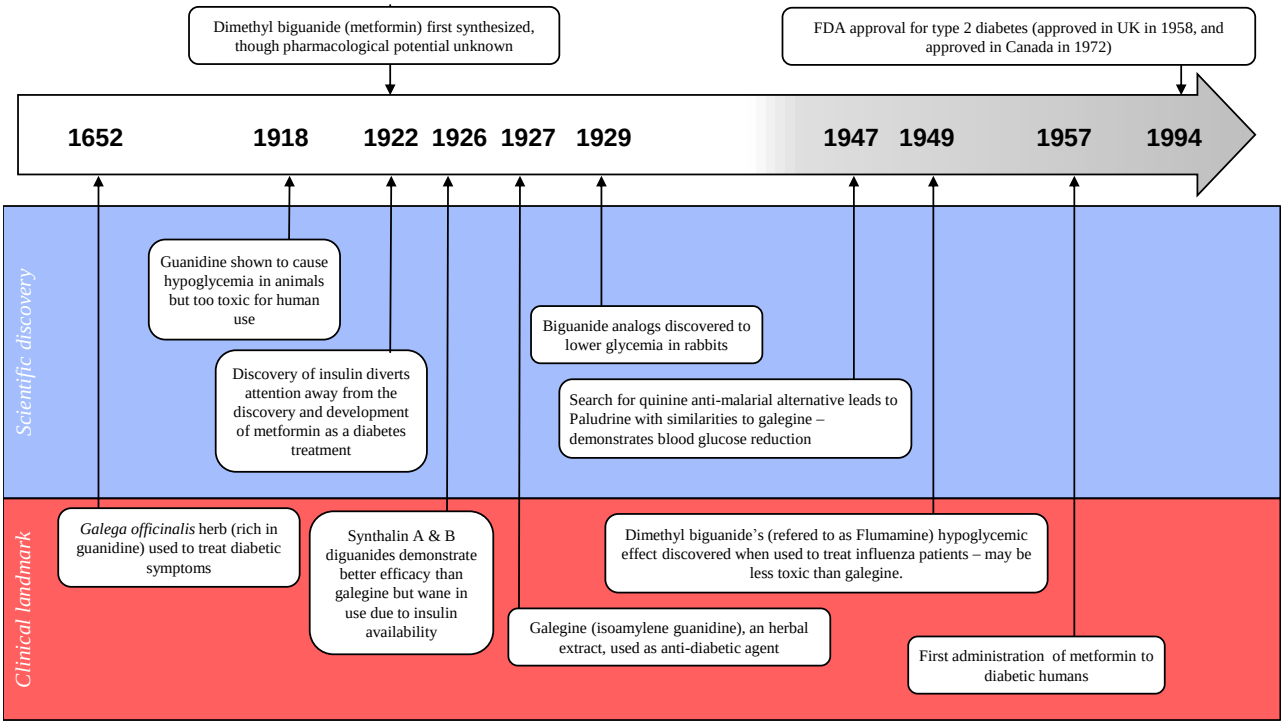
A.W. Alberts, J. Chen, G. Kuron, *et al*., Mevinolin: a highly potent competitive inhibitor of hydroxymethylglutaryl-coenzyme A reductase and a cholesterol-lowering agent. *Proc. Natl. Acad. Sci.* **77**, 3957–61 (1980).

**1984-Coronary Primary Prevention Trial reports correlation between reduced blood cholesterol & LDL and reduced coronary disease**

The Lipid Research Clinics Coronary Primary Prevention Trial results I. Reduction in incidence of coronary heart disease. *JAMA* 251, 351-64 (1984).

# Metformin

*suppresses hepatic gluconeogenesis*




**1652-Galega officinalis herb (rich in guanidine) used to treat diabetic symptoms**
N. Culpeper, The English Physitian or an astrologo-physical discourse on the vulgar herbs of this nation. London: Peter Cole (1652).

**1918-Guanidine shown to cause hypoglycemia in animals – but too toxic for human use**
C.K. Watanabe, Studies in the metabolic changes induced by administration of guanidine bases. *J. Biol. Chem.* **33**, 253–265 (1918).

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E. Werner, J. Bell, The Preparation of Methylguanidine, and of Pp-Dimethylguanidine by the Interaction of Di-cyanodiamide,and Methylammonium and Dimethyl-ammonium Chlorides Respectively. *J. Chem. Soc. Trans.* **121**, 1790–4 (1922).

**1922-Discovery of insulin diverts attention away from the discovery and development of metformin as a diabetes treatment**
E.P. Joslin, Pancreatic extract in the treatment of diabetes. *Boston Med. Surg. J.* **186**, 654 (1922).

F.G. Banting, C.H. Best, J.B. Collip, W.R. Campbell, A.A. Fletcher, J.J.R. Macleod, E.C. Noble, The effect produced on diabetes by extracts of pancreas. *Trans. Assoc. Am. Physicians* **37**, 337-347 (1922).

**1926-Synthalin A and B diquanides demonstrate better efficacy and safety than galegine, but wane in use compared to insulin**
E. Frank, M. Nothmann, A. Wagner, Uber synthetisch dargestellte Korper mit insulinartiger Wirkung auf dennormalen und den diabetischen Organismus. *Klin. Wschr.* **5**, 100–2107 (1926).

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H. Muller, H. Rheinwein, Pharmacology of galegin. *Arch. Exp. Path. Pharmacol.* **125**, 212–228 (1927).

H. Simonnet, G. Tanret, Sur les propietes hypoglycemiantes du sulfate de galegine. *Bull Soc Chim Biol Paris* (1927).

**1929-Biguanide analogs discovered to lower glycemia in rabbits**
K.H. Slotta, R. Tschesche, Uber biguanide. II. Die blutzuckersenkende wirkung der biguanides. *Berichte der Dtsch Chem Gesellschaft B Abhandlungen* **62**, 1398–405 (1929).

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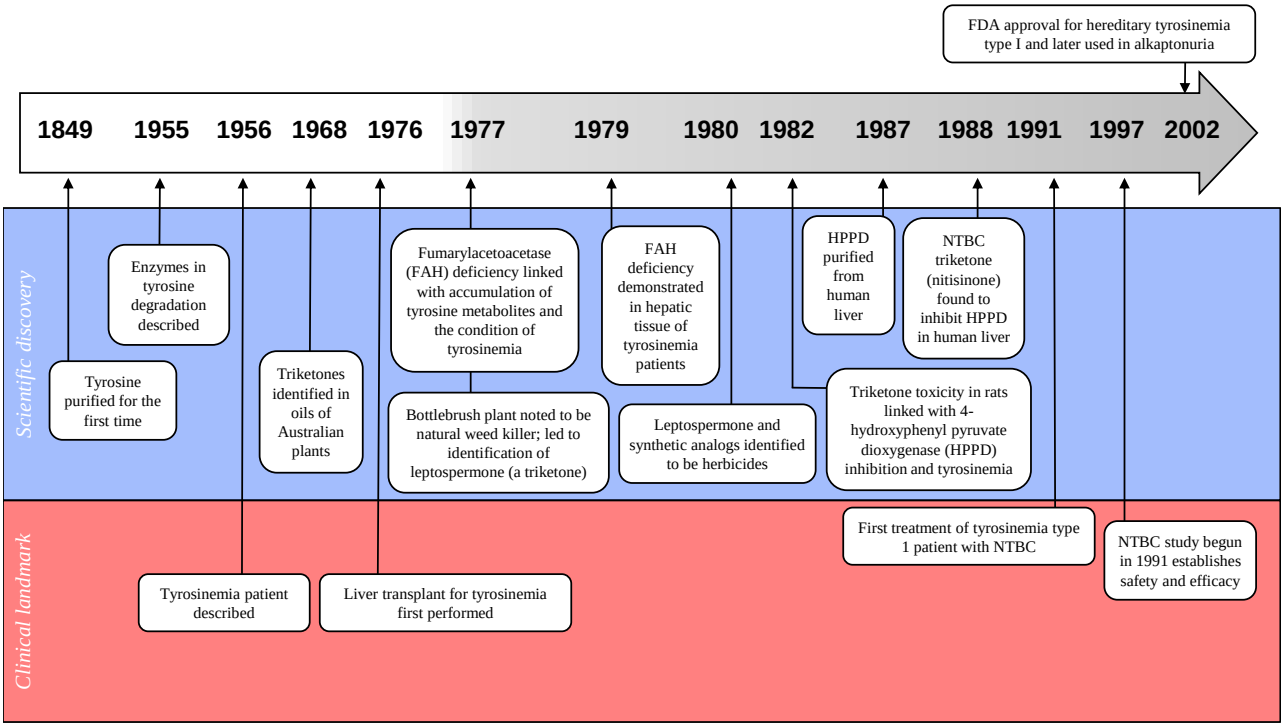
K.K. Chen, R.C. Anderson, The toxicity and general pharmacology of N1-p-chlorophenyl-N5-isopropyl biguanide. *J. Pharmacol. Exp. Ther.* **91**, 157–160 (1947).

**1949-Dimethyl biguanide's (flumamine) hypoglycemic effect discovered when used to treat influenza patients – may be less toxic than galegine**
E.Y. Garcia, Flumamine, a new synthetic analgesic and antiflu drug. *J. Phillippine Med. Assoc.* **26**, 287 (1950).

**1957-First administration of metformin to diabetic humans – authors apparently unaware of 1929 German studies**
J. Sterne, Du Nouveau dans les antidiabetiques. la NN dimethylamino guanyl guanidine (NNDG). *Maroc. Med.* **36**, 1295–6 (1957).

# Nitisinone

*reversible inhibition of 4-hyroxyphenylpyruvate dioxygenase (HPPD)*

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F. Bopp, Einiges uber albumin, casein, und fibrin. *Ann Chem Pharm* **69** (1849).

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W.E. Knox, Enzymes Involved in Conversion of Tyrosine to Acetoacetate. *Methods Enzymol.* 287–300 (1955).

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M.D. Baber, A case of congenital cirrhosis of the liver with renal tubular defects akin to those in the Fanconi syndrome. *Arch. Dis. Child.* **31**, 335–9 (1956)

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R.O. Hellyer, The occurrence of beta-triketones in the steam-volatile oils of some myrtaceous Australian plans. *Australian Journal of Chemistry* **21**, 2825 (1968).

**1976-Liver transplant for tyrosinemia first performed**
R.O. Fisch, E.R.B. McCabe, D. Doeden, U. Koep, B.A. Kohloff, A. Silverman, T.E. Starzl, Homotransplantation of the liver in a patient with hepatoma and hereditary tyrosinemia. *J. Pediatr.* **93**, 542-546 (1978).

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**leptospermone**
No primary reference identified

**1977-Fumarylacetoacetase (FAH) deficiency linked with accumulation of tyrosine metabolites and the condition of tyrosinemia**
B. Lindblad, S. Lindstedt, G. Steen, On the enzymic defects in hereditary tyrosinemia. *Proc. Natl. Acad. Sci. U.S.A.* **74**, 4641–5 (1977).

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S.P. Fallstrom, B. Lindblad, S. Lindstedt, G. Steen, Hereditary tyrosinemia - fumarylacetoacetase deficiency. *Pediatr. Res.* **13**; 78 (1979).

**1980-Leptospermone and synthetic analogs identified to be herbicides**
C.G. Knudsen, D.L. Lee, W.J. Michaely, H.L. Chin, N.H. Nguyen, R.J. Rusay, T.H. Cromartie, R. Gray, B.H. Lake, T.E. Fraser, D. Cartwright, Discovery of the Triketone Class of HPPD Inhibiting Herbicides and their Relationship to Naturally Occurring β-Triketones. In Narwal SS, Hoagland RE, Dilday RH, Reigosa MJ. *Allelopathy in Ecological Agriculture and Forestry* Springer. 101–11 (2000).

**1982-Triketone herbicides toxicity in rats linked to inhibition of 4-hydroxyphenyl pyruvate dioxygenase (HPPD)**
E.A. Lock, M.K. Ellis, P. Gaskin, M. Robinson, T.R. Auton, W.M. Provan, L.L. Smith, M.P. Prisbylla, L.C. Mutter, D.L. Lee, From toxicological problem to therapeutic use: The discovery of the mode of action of 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC), its toxicology and development as a drug. *J. Inher. Metab. Dis.* **21**, 498-506 (1998).

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S. Lindstedt, B. Odelhög, 4-Hydroxyphenylpyruvate dioxygenase from human liver. *Methods Enzymol.* **142**, 139–42 (1987).

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Personal communication, Edward Lock.

**1991-First treatment of tyrosinemia patients with NTBC**
S. Lindstedt, E. Holme, E.A. Lock, O. Hjalmarson, B. Strandvik B, Treatment of hereditary tyrosinaemia type I by inhibition of 4-hydroxyphenylpyruvate dioxygenase. *Lancet* **340**, 813–7 (1992).

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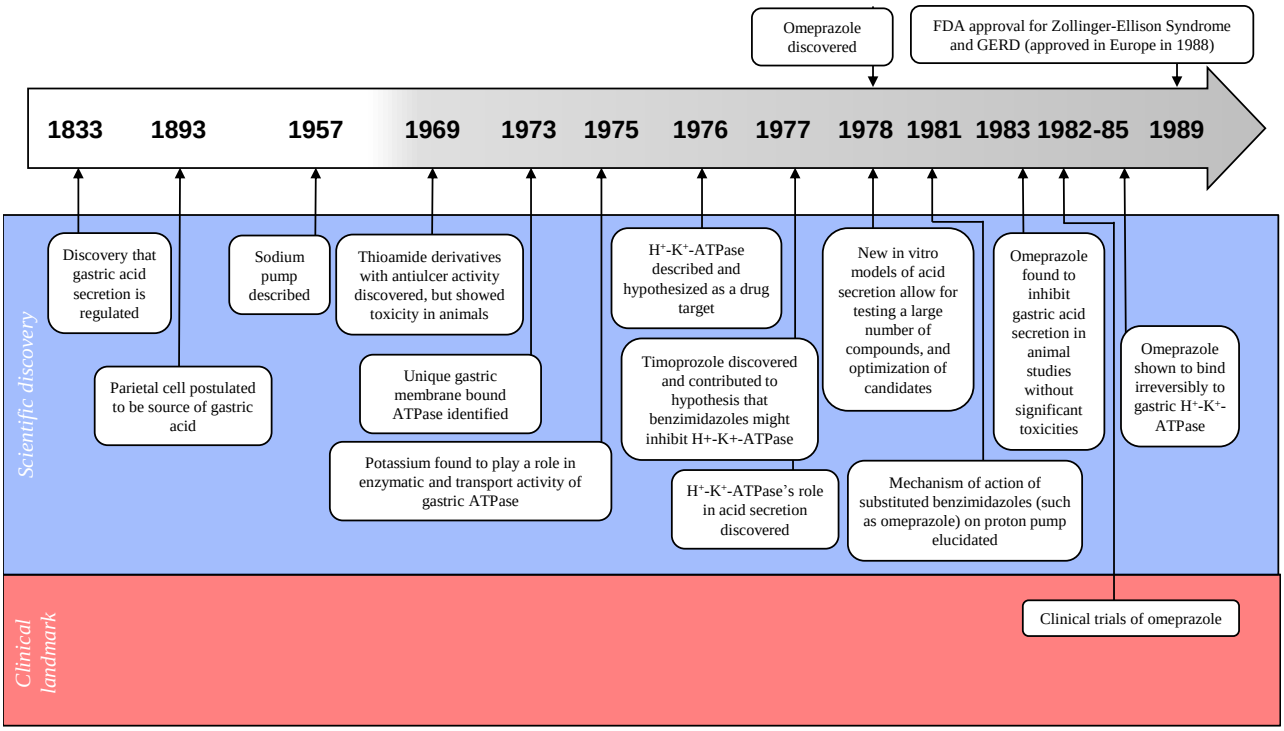
E. Holme, S. Lindstedt S, Nontransplant treatment of tyrosinemia. *Clin Liver Dis* 4, 805-814 (2000).

# Omeprazole

*proton pump inhibitor*




**1833-Discovery that gastric acid secretion is regulated**
W. Beaumont, Experiments and observations on the gastric juice and the physiology of digestion. Plattsburgh, NY (1833).

**1893-Parietal cell postulated to be source of gastric acid**
C. Golgi, Sur la fine organisation des glandes peptiques des mamiferes. *Arch. Ital. Biol.* (1893).

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J.C. Skou, The influence of some cations on an adenosine triphosphatase from peripheral nerves. *Biochim. Biophys. Acta* **23**, 394–401 (1957).

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M. Kanno, S. Narumi, T. Hirata, K. Gomaibashi, Y. Kanai, A. Nohara, Y. Sanno, Inhibition of the gastric secretion in the rat by thioacetamide derivatives. *J Takeda Res Labs* **32**, 181-187 (1973).

C.E. Malen, B.H. Danree, New thiocarboxamides derivatives with specific gastric antisecretory properties. *J. Med. Chem.* **14**, 244-246 (1971).

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A.L. Ganser, J.G. Forte, K + -stimulated ATPase in purified microsomes of bullfrog oxyntic cells.

*Biochim. Biophys. Acta* **307**, 169–80 (1973).

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J.G. Forte, A. Ganser, R. Beesley, T.M. Forte, Unique enzymes of purified microsomes from pig fundic mucosa. K+-stimulated adenosine triphosphatase and K+-stimulated pNPPase. *Gastroenterology* **69**, 175–89 (1975).

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G. Sachs, H.H. Chang, E. Rabon, R. Schackman, M. Lewin, G. Saccomani, A nonelectrogenic H+ pump in plasma membranes of hog stomach. *J. Biol. Chem.* **251**, 7690–8 (1976).

G. Sachs, $H^+$ transport by a non-electrogenic gastric ATPase as a model for acid secretion. *Rev. Physiol. Biochem. Pharmacol.* **79**, 133-162 (1977).

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J.G. Forte, H.C. Lee, Gastric adenosine triphosphatases: a review of their possible role in HCl secretion. *Gastroenterology* **73**, 921-26 (1977).

G. Sachs, Metabolic and membrane aspects of gastric $H^+$ transport. *Gastroenterology* **73**, 931-940 (1977).

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G. Sundell, S.E. Sjostrand, L. Olbe, Gastric antisecretory effects of H83f/69, a benzimidazolyl-pyridyl-methyl-sulfoxide. *Acta Pharm. Tox. Suppl.* 77 (1977).

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S.E. Sjostrand, B. Ryberg, L. Olbe, Stimulation and inhibition of acid secretion by the isolated guinea pig gastric mucosa. *Acta Physiol. Scand.* Spec. Suppl. 181–185 (1978).

E. Fellenius, B. Elander, B. Wallmark, H.F. Helander, T. Berglindh, Inhibition of acid secretion in isolated gastric glands by substituted benzimidazoles. *Am. J. Physiol.* **243**, G505–G510 (1982).

E. Fellenius, *et al*. A micromethod for the study of secretory function in isolated human oxyntic glands from gastroscopic biopsies. *Clin. Sci.* **64**, 423–431 (1983).

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B.A. Berkowitz, G. Sachs, Life cycle of a blockbuster drug: discovery and development of omeprazole (prilosec). *Mol. Interventions* **2**, 6-11 (2002).

**1981-Mechanism of action of substituted benzimidazoles (such as omeprazole) on proton pump elucidated**
E. Fellenius, T. Berglindh, G. Sachs, *et al.*, Substituted benzimidazoles inhibit gastric acid secretion by blocking ($H^+$+$K^+$) ATPase. *Nature* **290**, 159-61 (1981).

**1983-Omeparazole found to inhibit gastric acid secretion in animal studies without significant toxicities**
H. Larsson, *et al.*, Inhibition of gastric acid secretion by omeprazole in the dog and rat. *Gastroenterology* **85**, 900–907 (1983).

**1982-1985-Clinical trials of omeprazole**

T. Lind, C. Cederberg, G. Ekenved, U. Haglund, L. Olbe, Effect of omeprazole – a gastric proton pump inhibitor – on pentagastrin stimulated acid secretion in man. *Gut* **24**, 270–276 (1983).

O. Bonnevie, *et al.*, Gastric acid secretion and duodenal ulcer healing during treatment with omeprazole. Scand. J. *Gastroenterology* **19**, 882–884 (1984).

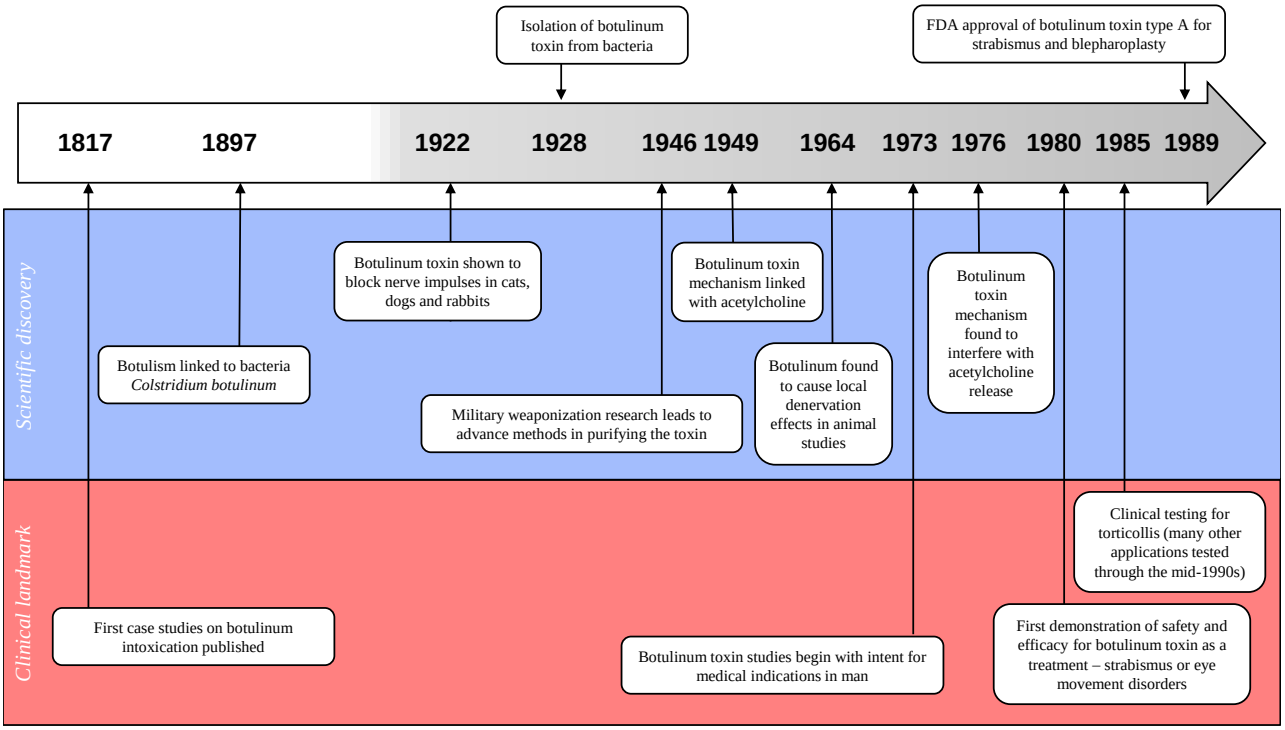
K. Lauritsen, *et al*., Effect of omeprazole and cimetidine on duodenal ulcer. A double blind comparative trial. *N. Engl. J. Med.* **312**, 958–961 (1985).

**1985 – Omeprazole shown to bind irreversibly to gastric $H^+$-$K^+$-ATPase**
W.B. Im, D.P., Blakeman, J.P. Davis, Irreversible inactivation of rat gastric (H+-K+)-ATPase in vivo by omeprazole. *Biochem. Biophys. Res. Commun.* **126**, 78–82 (1985).

W.B. Im, J.C. Sih, D.P. Blakeman, J.P. McGrath, Omeprazole, a specific inhibition of gastric (H+/K+)-ATPase, is a H+-activated oxidizing agent of sulfhydryl groups. *J. Bio. Chem.* **260**, 4591-4597 (1985).

# OnabotulinumtoxinA

*acetylcholine receptor blocker*




**1817-First case studies on botulinum intoxication published**
J. Kerner, Vergiftung durch verdorbene Wu¨rste. *Tu¨binger Bla¨tter fu¨r Naturwissenschaften und Arzneykunde* **3**, 1-25 (1817).

J. Kerner, Neue Beobachtungen über die in Württemberg so häufig vorfallenden tödlichen Vergiftungen durch den Genuss geräucherter Würste. Tübingen: Osiander. (1820)

**1897-Botulism linked to bacteria *Clostridium botulinum***
E. Van Ermengem, Ueber einen neuen anaeroben Bacillus und seine Beziehungen zum Botulismus'. *Zeitschrift fur Hygeien und Infekt* **26**, 1–56 (1897).

**1922-Botulinum toxin known to block nerve impulses in cats, dogs and rabbits**
E.C. Dickson, R. Shevky, Botulism. Studies on the manner in which the toxin of clostridium botulinum acts upon the body: I. The effect upon the autonomic nervous system. *J. Exp. Med.* **37**, 711–31 (1923).

E.C. Dickson, E. Shevky, Botulism. Studies on the manner in which the toxin of clostridium botulinum acts upon the body: II. The effect upon the voluntary nervous system. *J. Exp. Med.* **38**, 327–46 (1923).

**1928-Isolation of botulinum toxin from bacteria**
P. Snipe, H. Tessmer, H. Sommer, Studies on Botulinus Toxin: 3. Acid Precipitation of Botulinus Toxin. *The Journal of Infectious Diseases* **43**, 152–160 (1928).

**1946-Military weaponization research leads to advanced methods in purifying the toxin – which is later used for clinical research**
C. Lamanna, O.E. McElroy, H.W. Eklund, The purification and crystallization of Clostridium botulinum type A toxin. *Science* **103**, 613 (1946).

**1949-Botulinum toxin mechanism linked with acetylcholine**
S.V. Burgen, F. Dickens, L.J. Zatman, The action of botulinum toxin on the neuro-muscular junction. *The Journal of Physiology* **109**, 10–24 (1949).

**1964-Botulinum found to cause local denervation effects in animal studies**
D.B. Drachman, Atrophy of skeletal muscle in chick embryos treated with botulinum toxin. *Science* **145**, 719–21 (1964).

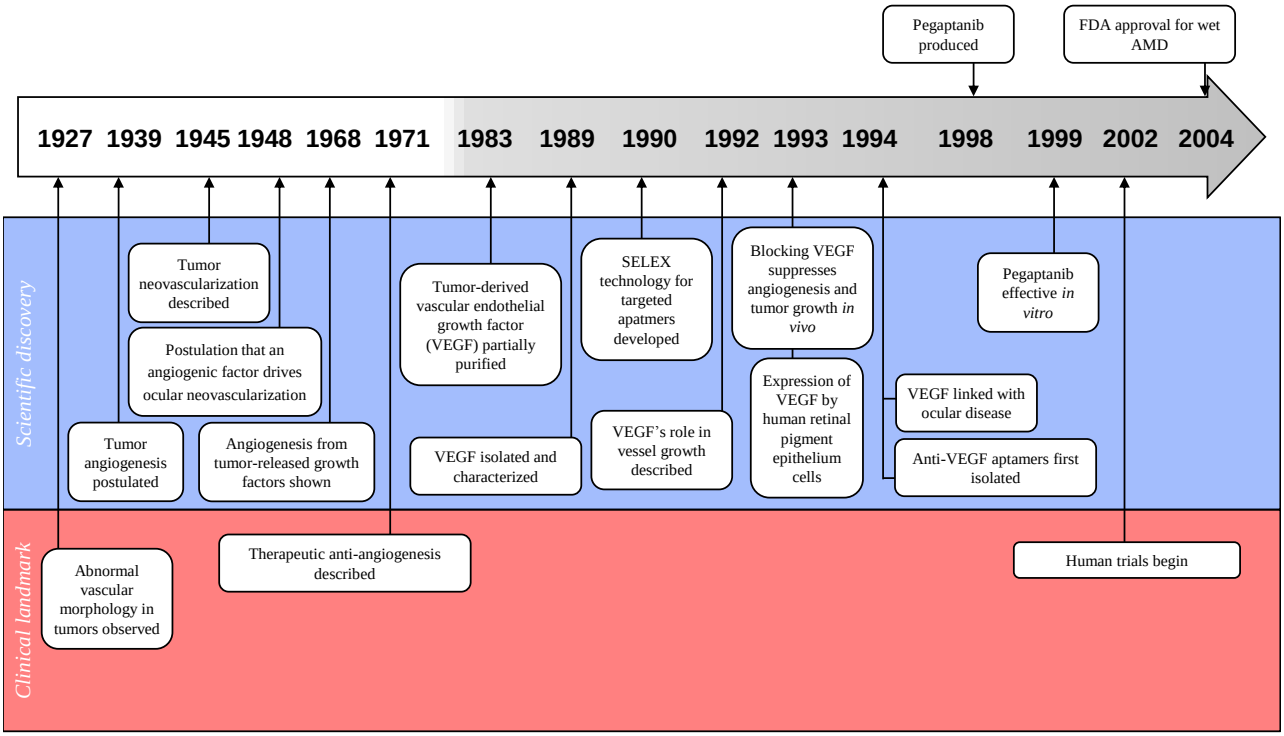
**1973-Botulinum toxin studies begin with intent for medical indications in man**
A.B. Scott, A. Rosenbaum, C.C. Collins, Pharmacologic weakening of extraocular muscles. *Invest. Ophthalmol.* **12**, 924–7 (1973).

**1976-Botulinum toxin mechanism found to interfere with acetylcholine release**
I. Kao, D.B. Drachman, D.L. Price, Botulinum toxin: mechanism of presynaptic blockade. *Science* 193, 1256-8 (1976).

**1980-First demonstration of safety and efficacy for botulinum toxin as a treatment – strabismus or eye movement disorders**
A.B. Scott, Botulinum toxin injection into extraocular muscles as an alternative to strabismus surgery. *Ophthalmology* **87,** 1044-1049 (1980).

**1985-Clinical testing for torticollis**
J.K. Tsui, A. Eisen, E. Mak, J. Carruthers, A. Scott, D.B. Calne, A pilot study on the use of botulinum toxin in spasmodic torticollis. *The Canadian Journal of Neurological Sciences. Le Journal Canadien Des Sciences Neurologiques* **12**, 314–316 (1985).

# Anti-VEGF agents




**1927-Abnormal vascular morphology in tumors observed**
W. H. Lewis. *Bulletin of the John Hopkins Hospital.* **41**, 156-62 (1927).

**1939-Tumor angiogenesis postulated**
A. G. Ide, N. H. Baker, S. L. Warren. Vascularization of the Brown Pearce rabbit epithelioma transplant as seen in the transparent ear chamber. *Am. J. Roentgenol.* **42**, 891-99 (1939).

**1945-Tumor neovascularization described**
G. H. Algire, H. W. Chalkey, F. Y. Legallis, H. D. Park. Vascular reactions of normal and malignant tissues in vivo. III. Vascular reactions of mice to fibroblasts treated in vitro with methylcholanthrene. *J Natl Cancer Inst.* **6**, 73-85 (1945).

**1948-Postulation that an angiogenic factor drives ocular neovascularization**
I. Michaelson. The mode of development of the vascular system of the retina with some observations on its significance for certain retinal diseases. *Trans Ophthalmol Soc UK*. **68**, 137–180 (1948).

**1968-Angiogenesis from tumor-released growth factors shown**
M. Greenblatt, P. Shubi. Tumor angiogenesis: transfilter diffusion studies in the hamster by the transparent chamber technique. *J Natl Cancer Inst.* **41**, 111-24 (1968).

R. L. Ehrmann, M. Knoth. Choriocarcinoma. Transfilter stimulation of vasoproliferation in the hamster cheek pouch. Studied by light and electron microscopy. *J Natl Cancer Inst.***41**, 1329-41 (1968).

**1971-Therapeutic anti-angiogenesis described**
J. Folkman. Tumor angiogenesis: therapeutic implications. *N Engl J Med.* **285** (21), 1182-6 (1971).

**1983-Tumor-derived vascular endothelial growth factor (VEGF) partially purified**
D. R. Senger, S. J. Galli, A. M. Dvorak, C. A. Perruzzi, V.S. Harvey, H. F. Dvorak. Tumor cells secrete a vascular permeability factor that promotes accumulation of ascites fluid. *Science* **219** (4587), 983-5 (1983).

**1989-VEGF isolated and characterized**
N. Ferrara, W. J. Henzel. Pituitary follicular cells secrete a novel heparin-binding growth factor specific for vascular endothelial cells. *Biochem Biophys Res Commun.* **161**, 851-8 (1989).

D. W. Leung, G. Cachianes, W. J. Kuang, D. V. Goeddel, N. Ferrara. Vascular endothelial growth factor is a secreted angiogenic mitogen. *Science* **246**, 1306-9 (1989).

P. J. Keck, S. D. Hauser, G. Krivi, K. Sanzo, T. Warren, J. Feder, D. T, Connolly. Vascular permeability factor, an endothelial cell mitogen related to PDGF. *Science* 246, 1309-12 (1989).

**1990-SELEX technology for targeted apatmers developed**
C. Tuerk, L. Gold. Systematic evolution of ligands by exponential enrichment: RNA ligands to bacteriophage T4 DNA polymerase. *Science* **249**, 505-10 (1990).

**1992-VEGF's role in vessel growth described**
K. H. Plate, G. Breier, H. A. Weich, W. Risau. Vascular endothelial growth factor is a potential tumor angiogenesis factor in human gliomas in vivo. *Nature* **359**, 845-8 (1992).

D. Shweiki, A. Itin, D. Soffer, E. Keshet. Vascular endothelial growth factor induced by hypoxia may mediate hypoxia-initiated angiogenesis. *Nature* **359**, 843-5 (1992).

**1993-Blocking VEGF suppresses angiogenesis and tumor growth *in vivo***
K. J. Kim et al. Inhibition of vascular endothelial growth factor-induced angiogenesis suppresses tumor growth in vivo. *Nature* **362**, 841-4 (1993).

**1993 - Expression of VEGF by human RPE cells**
A. P. Adamis, D. T. Shima, K. T. Yeo, T. K. Yeo, L. F. Brown, B. Berse, P. A. D'Amore, J. Folkman. Synthesis and secretion of vascular permeability factor/ vascular endothelial growth factor by human retinal pigment epithelial cells. *Biochem Biophys Res Commun*. **193**, 631-638 (1993).

**1994-VEGF linked with ocular disease**
J. W. Miller, A. P. Adamis, D. T. Shima, P. A. D'Amore, R. S. Moulton, M. S. O'Reilly, J. Folkman, H. F. Dvorak, L. F. Brown, B. Berse, T. K. Yeo, K. T. Yeo. Vascular endothelial growth factor/vascular permeability factor is temporally and spatially correlated with ocular angiogenesis in a primate model. *Am J Pathol.* **145**, 574-84 (1994).

A. P. Adamis, J. W. Miller, M. T. Bernal, D. J. D'Amico, J. Folkman, T. K. Yeo, K. T. Yeo. Increased vascular growth factor levels in the vitreous of eyes with proliferative diabetic retinopathy. *Am J Ophthalmol.* **118**, 445-50 (1994).

L. P. Aiello, R. L. Avery, P. G. Arrigg, B. A. Keyt, H. D. Jampel, S. T. Shah, L. R, Pasquale, H. Thieme, M. A. Iwamoto, J. E. Park, H. V. Nguyen, L. M. Aiello, N. Ferrara , G. L. King. Vascular endothelial

growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. *N Engl J Med.* **331**, 1480-7 (1994).

**1994-Anti-VEGF aptamers first isolated**
D. Jellinek, L. S. Green, C. Bell, N. Janjic. Inhibition of receptor binding by high-affinity RNA ligands to vascular endothelial growth factor. *Biochemistry.* **33**, 10450-56 (1994).

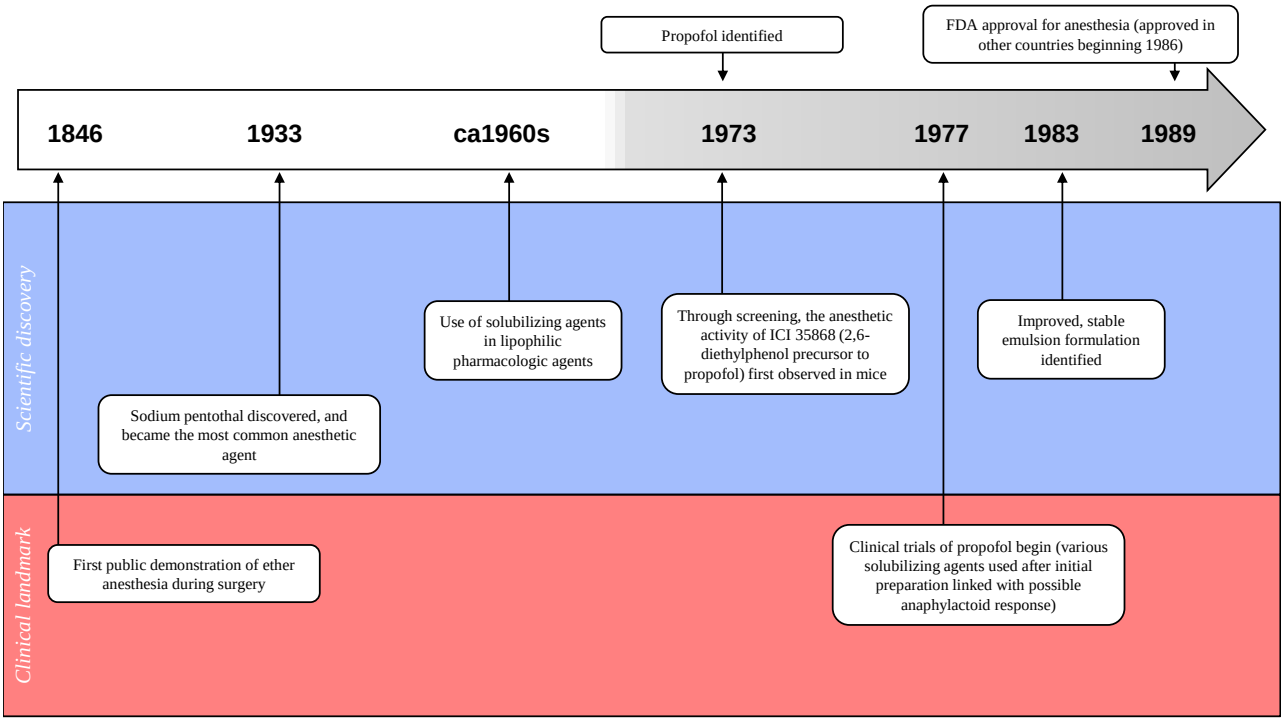
**1998-Pegaptanib produced**
J. Ruckman, et al. 2'-Fluotopyrimidine RNA-based aptamers to the 165-amino acid form of vascular endothelial growth factor (VEGF 165). Inhibition of receptor binding and VEGF-induced vascular permeability through interactions requiring the exon 7-encoded domain. *J Biol Chem.* **273**, 20556-67 (1998).

**1999-Pegaptanib effective *in vitro***
C. Bell, E. Lynam, D. J. Landfair, N. Janjic, M. E. Wiles. Oligonucleotide NX1838 inhibits VEGF165-mediated cellular responses in vitro. *In Vitro Cell Dev Biol Anim.* **35**, 533-42 (1999).

**2002-Human trials begin**
Eyetech Study Group. Preclinical and phase 1A clinical evaluation of an anti-VEGF pegylated aptamer (EYE001) for the treatment of exudative age-related macular degeneration. *Retina.* **22**, 143-52 (2002)

# Propofol

*Gamma-aminobutyric acid A ($GABA_A$) modulator*




**1846-First public demonstration of ether anesthesia during surgery**

H. J. Bigelow. Insensibility during surgical operations produced by inhalation. *Boston Med and Surg J* **35**, 309-317 (1846).

**1933-Sodium pentothal discovered, and became the most common anesthetic agent**

Discovered by Ernest Vowliler & Donalee Tabern, Abbott Laboratories. (1933).

J. S. Lundy, R. M. Tovell. Annual report for 1934 of the Section on Anesthesia: including data on blood transfusion. *Proc. Staff Meetings, Mayo Clinic* **10**, 257 (1935).

T. W. Pratt, A. L. Tatum, H. R. Hathaway, R. M. Waters. Sodium ethyl (1-methyl butyl) thiobarbiturate: preliminary experimental and Hiniral study. *Am. J. Surg.* **31**, 464 (1936).

**1960s-Use of solubilizing agents in lipophilic pharmacologic agents**

J. B. Glen. The discovery and development of Propofol. In: The wondrous story of anesthesia. Eds: Eger EI, Saidman L, Westhorpe R. Springer (2014).

**1973-Through screening, anesthetic activity of ICI 35868 (2,6-diethylphenol precursor to propofol) first observed in mice**

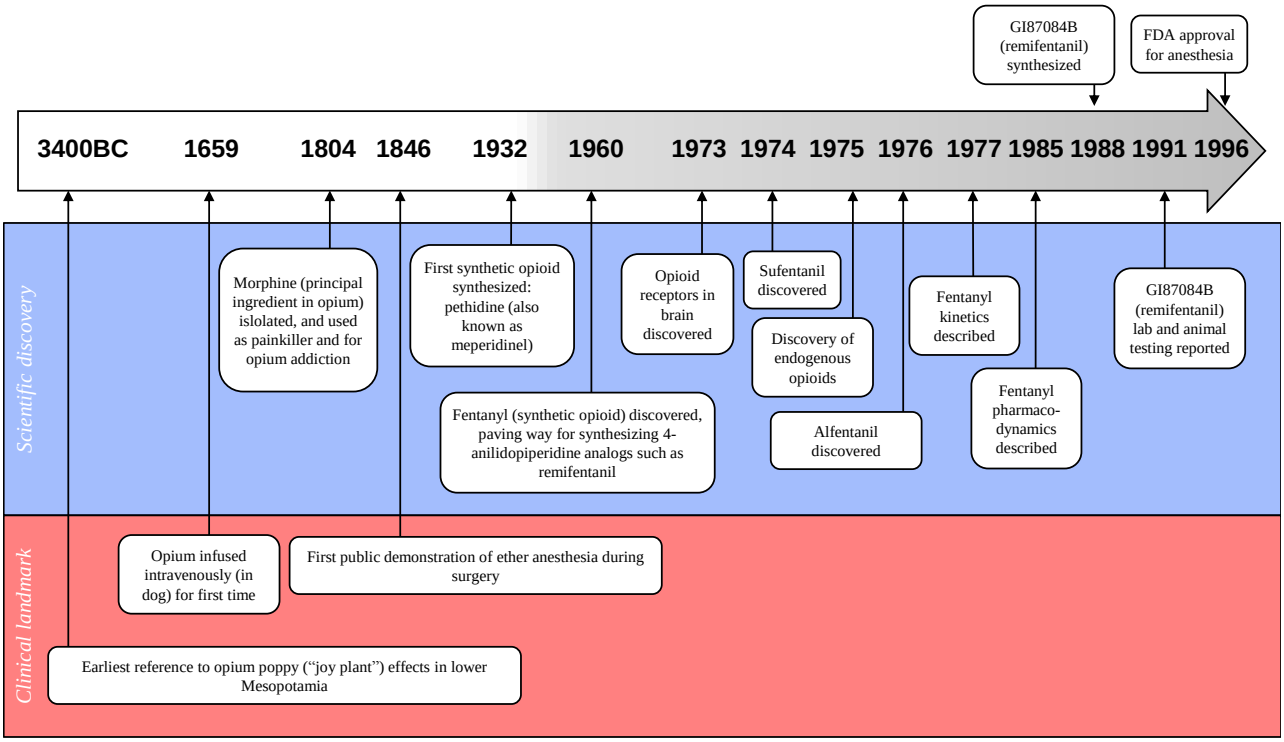
R. James, J. B. Glen. Synthesis, biological evaluation, and preliminary structure-activity considerations of a series of alkylphenols as intravenous anesthetic agents. *J Med Chem* **23**, 1350-7 (1980).

**1977-Clinical trials of propofol begin (various solubilizing agents used after initial preparation linked with possible anaphylactoid response)**
B. Kay, G. Rolly. ICI 35868 a new intravenous induction agent. *Acta Anaes Belgica*. **28**, 303–16 (1980).

**1983-Improved, stable emulsion formulation identified**
J. B. Glen, S. C. Hunter. Pharmacology of an emulsion formulation of ICI 35 868. *Br J Anaesth* **56**, 617-26 (1984).

# Remifentanil

*μ opioid agonist*




**3400BC-Earliest reference to opium poppy ("joy plant") effects in lower Mesopotamia**

**1659-Opium infused intravenously (in dog) for first time**
M. Hunter, E. B. Davis, eds. The Works of Robert Boyle, Volume 13, Unpublished Writings. London: Pickering & Chatto Ltd. 252–7 (1645–c1670).

**1804-Morphine (principal ingredient in opium) islolated, and used as painkiller and for opium addiction**
Sertuerner F. Ueber das Morphium, eine neue salzfähige Grundlage, und die Mekonsäure, als Hauptbestandtheile des Opiums. *Annalen der Physik* **55**, 56-89 (1817)

**1846-First public demonstration of ether anesthesia during surgery**
H. J. Bigelow. Insensibility during surgical operations produced by inhalation. *Boston Med and Surg J* **35**, 309-317 (1846)

**1932-First synthetic opioid synthesized: pethidine (i.e., meperidine, Demerol)**
O. Eisleb, O. Schaumann. Dolantin, ein neuartiges Spasmolytikum und Analgetikum (Chemisches und Pharmakologisches), *Deutsche med. Wchnschr* **67**: 967 (1939).

**1960-Fentanyl (synthetic opioid) discovered, paving way for synthesizing 4-anilidopiperidine analogs such as remifentanil**

P. A. Janssen. A review of the chemical features associated with strong morphine-like activity. *Br J Anesth* **34**, 260-268 (1962).

**1973-Opioid receptors in brain discovered**

C. B. Pert, S. H. Snyder. Opiate receptor: demonstration in nervous tissue. *Science* **179**, 1011–4 (1973).

M. J. Kuhar, C. B. Pert, S. H. Snyder. Regional distribution of opiate receptor binding in monkey and human brain. *Nature* **245**, 447–50 (1973).

**1974-Sufentanil discovered**

C. J. Niemegeers, K. H. Schellekens, W. F. Van Bever, P. A. Janssen. Sufentanil, a very potent and extremely safe intravenous morphine-like compound in mice, rats and dogs. *Arzneimittelforschung* **26**, 1551–6 (1976).

**1975-Discovery of endogenous opioids**

J. Hughes, T. W. Smith, H. W. Kosterlitz, L. A. Fothergill, B. A. Morgan, H. R. Morris. Identification of two related pentapeptides from the brain with potent opiate agonist activity. *Nature* **18**, 577-580 (1975).

**1976-Alfentanil discovered**

J. Spierdijk, J. van Kleef, J. Nauta, *et al.* Alfentanil: a new narcotic induction agent. *Anesthesiology* **53**, S32 (1980).

**1977-Fentanyl kinetics described**

M. Michiels, R. Hendriks, J. Heykants. A sensitive radioimmunoassay for fentanyl: plasma level in dogs and man. *Eur J Clin Pharm.* **12**, 153-158 (1977).

D. A. McClain, C. C. Hug. Intravenous fentanyl kinetics. *Clin Pharm Therap.* **28**, 106-114 (1980).

**1985-Fentanyl pharmacodynamics described**

J. C. Scott, K. V. Ponganis, D. R. Stanski. EEG quantitation of narcotic effect: The comparative pharmacodynamics of fentanyl and alfentanil. *Anesthesiology* **62**, 234-241 (1985).

**1988-GI87084B (remifentanil) synthesized**

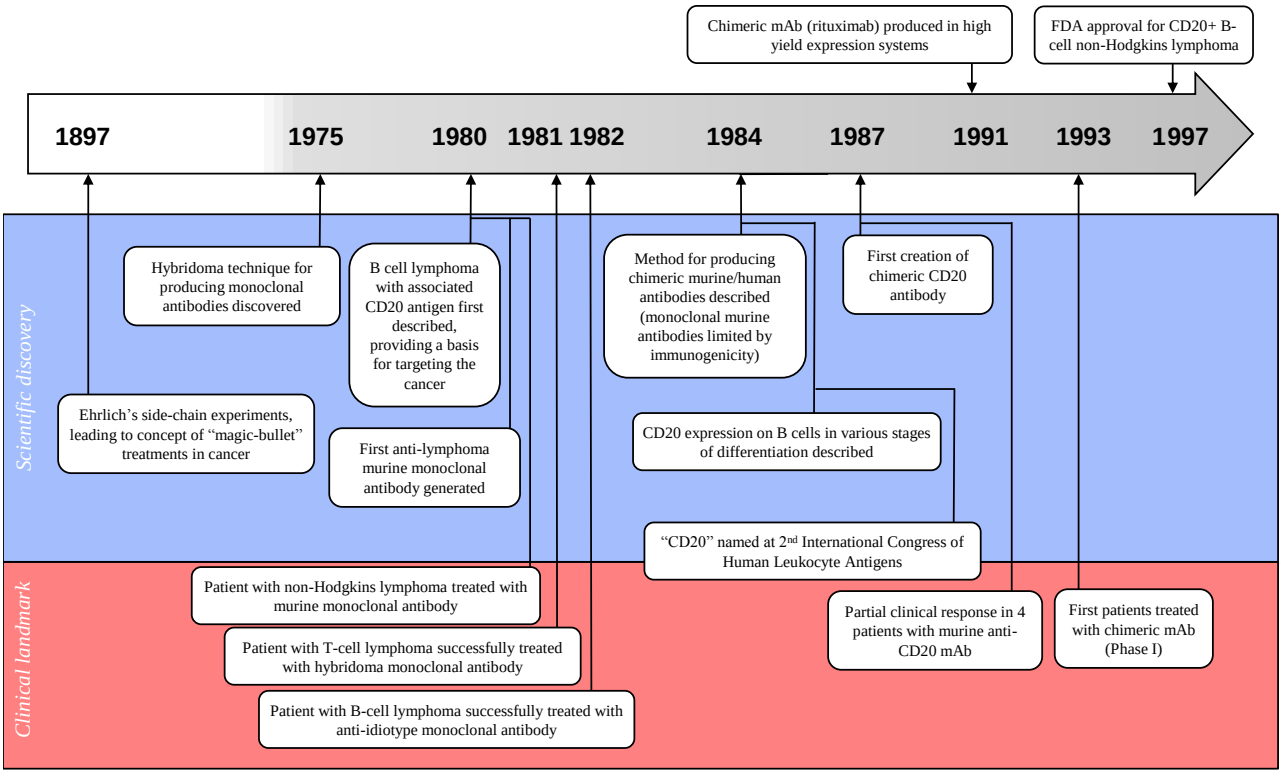
P. L. Feldman, M. K. James, M. F. Brackeen, *et al*. Design, synthesis, and pharmacological evaluation of ultrashort- to long-acting opioid analgetics. *J Med Chem* **34**, 2202-8 (1991).

**1991-GI87084B (remifentanil) lab and animal testing reported**

M. K. James, P. L. Feldman, S. V. Schuster, J. M. Bilotta, M. F. Brackeen, H. J. Leighton. Opioid receptor activity of GI 87084B, a novel ultra-short acting analgesic, in isolated tissues. *J Pharmacol Exp Ther* **259**, 712–8 (1991).

# Rituximab

*anti-CD20 mAb*




**1897-Ehrlich's side-chain experiments, leading to concept of "magic-bullet" treatments in cancer**
P. Ehrlich. Die Wertbemessung des Diphterie-heilserums und deren theoretische Grundlagen. *Klinisches Jahrbuch.* **6**, 299-326 **(**1987**).**

**1975-Hybridoma technique for producing monoclonal antibodies discovered**
G. Kohler, C. Milstein. Continuous cultures of fused cells secreting antibody of predefined specificity. *Nature* **256**, 495-7 (1975).

**1980-B cell lymphoma with associated CD20 antigen first described, providing a basis for targeting the cancer**
P. Stashenko, L. M. Nadler, R. Hardy, S. F. Schlossman. Characterization of a human B lymphocyte-specific antigen. *J Immunol.* **125** (4), 1678-85 (1980).

**1980-First anti-lymphoma murine monoclonal antibody generated**
L. M. Nadler, P. Stashenko, R. Hardy, S. F. Schlossman. A monoclonal antibody defining a lymphoma-associated antigen in man. *J Immunol*. **125** (2), 570-7 (1980).

**1980-Patient with non-Hodgkins lymphoma treated with murine monoclonal antibody (marginal response)**
L. M. Nadler, P. Stashenko, R. Hardy, et al. Serotherapy of a patient with a monoclonal antibody directed against a human lymphoma-associated antigen. *Cancer Res*. **40**, 3147-54 (1980).

**1981-Patient with T-cell lymphoma successfully treated with hybridoma monoclonal antibody**
R. A. Miller, R. Levy. Response of cutaneous T cell lymphoma to therapy with hybridoma monoclonal antibody. *Lancet* **2**, 226-30 (1981).

R. A. Miller, D. G. Maloney, J. McKillop, R. Levy. In vivo effects of murine hybridoma monoclonal antibody in a patient with T-cell leukemia. *Blood* **58**, 78-86 (1981).

**1982-Patient with B-cell lymphoma successfully treated with anti-idiotype monoclonal antibody**
R. A. Miller, D. G. Maloney, R. Warnke, R. Levy. Treatment of B-cell lymphoma with monoclonal anti-idiotype antibody. *New Eng J Med* **306**, 517-22 (1982).

**1984-CD20 expression on B cells in various stages of differentiation described. Stem cells lack CD20, allowing them to regenerate healthy B cells after treatment**
K. Anderson, M. Bates, B. Slaughenhoup, G. S. Pinkus, S. F. Schlossman, L. M. Nadler. Expression of human B cell-associated antigens on leukemias and lymphomas: a model of human B cell differentiation. *Blood* **63**, 1424-33 (1984).

**1984-Method for producing chimeric murine/human antibodies described**
S. L. Morrison, M. J. Johnson, L. A. Herzenberg, V. T. Oi. Chimeric human antibody molecules: mouse antigen-binding domains with human constant region domains. *Proc. Natl. Acad. Sci. U S A* **81**, 6851-6855 (1984).

G. L. Boulianne, N. Hozumi, M. J. Shulman. Production of functional chimeric mouse/human antibody. *Nature* **312**, 643-6 (1984).

**1987-Partial clinical response in 4 patients with murine anti-CD20 mAb**
O. W. Press, F. Appelbaum, J. A. Ledbetter, P. J. Martin, J. Zarling, P. Kidd, E. D. Thomas. Monoclonal antibody I F5 (anti-CD20) serotheraphy of human B-cell lymphomas. *Blood* **69**, 584 (1987).

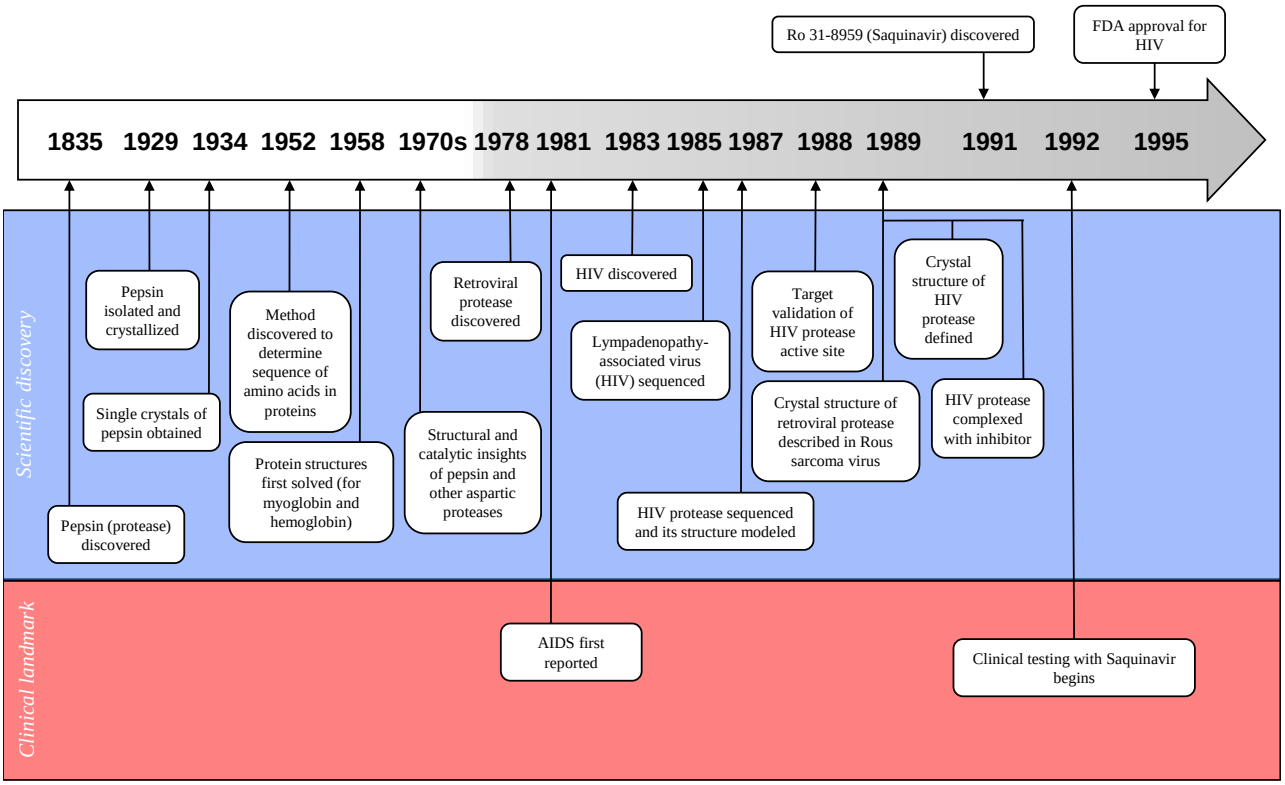
**1987-First creation of chimeric CD20 antibody**
A. Y. Liu, R. R. Robinson, E. D. Murray, J. A. Ledbetter, I. Hellstrom, K. E. Hellstrom. Production of a mouse-human chimeric monoclonal antibody to CD20 with potent Fc-dependent biologic activity. *J Immunol* **139**, 3521-6 (1987).

**1991-Chimeric mAb (rituximab) produced in high yield expression systems**
M. E. Reff, K. Carner, K. S. Chambers, P.C. Chinn, J. E. Leonard, R. Rabb, R. A. Newman, N. Hanna, D. R. Anderson. Depletion of B cells in vivo by a chimeric mouse numan monoclonal antibody to CD20. *Blood* **83**, 435 (1994).

**1993-First patients treated with chimeric mAb (Phase 1)**
D. G. Maloney, T. M. Liles, D. K. Czerwinski, C. Waldichuk, J. Rosenberg, A. Grillo-Lopez, R. Levy: Phase I clinical trial using escalating single-dose infusion of chimeric anti-CD20 monoclonal antibody (IDEC-C2B8) in patients with recurrent B-cell lymphoma. *Blood* **84**, 2457 (1994).

M. E. Reff, K. Carner, K. S. Chambers, P. C. Chinn, J. E. Leonard, R. Rabb, R. A. Newman, N. Hanna, D. R. Anderson DR: Depletion of B cells in vivo by a chimeric mouse human monoclonal antibody to CD20. *Blood* **83**, 435 (1994).

# HIV protease inhibitors




**1835-Pepsin (protease) discovered**
T. Schwann. Ueber das Wesen des Verdauungsprocesses. *Annalen der Physik.* **114**, 358-364 (1836).

**1929-Pepsin isolated and crystallized**
J. H. Northrop. Crystalline Pepsin. *Science* **69**, 580 (1929).

**1934- Single crystals of pepsin obtained**
J. D. Bernal, D. Crowfoot. X-ray Photographs of Crystalline Pepsin. *Nature* **794**, 133–134 (1934).

**1952-Method discovered to determine sequence of amino acids in proteins**
F. Sanger. The arrangements of amino acids in proteins. *Adv. Protein Chem.* **7**, 1-66 (1952).

**1958-Protein structures first solved (for myoglobin and hemoglobin)**
J. C. Kendrew, G. Bodo, H. M. Dintzis, R. G. Parrish, H. Wyckoff, D. C. Phillips. A three-dimensional model of the myoglobin molecule obtained by x-ray analysis. *Nature* **181**, 662-666 (1958).

M. F. Perutz, M. G. Rossmann, A. F. Cullis, H. Muirhead, G. Will, A. C. T North. Structure of haemoglobin: A three-dimensional Fourier synthesis at 5.5 A resolution, obtained by X-ray analysis. *Nature* **185**, 416-422 (1960).

**1970s Structural and catalytic insights of pepsin and other aspartic peptidases**

P. S. Sampath-Kumar, J. S. Fruton. Studies on the extended active sites of acid proteinases. *Proc. Natl. Acad. Sci. USA*. **71**, 1070–1072 (1974)

J. S. Fruton. Mechanism of the catalytic action of pepsin and related acid proteinases. *Adv Enzymol.* **44**, 1–33 **(**1976**).**

I. N. Hsu, L. T. J. Delbaere, M. N. G. James. Penicillopepsin from *Penicillum janthinellum* crystal structure at 2.8 A and sequence homology with porcine pepsin. *Nature* **266**, 140-145 (1977).

E. Subramanian, I. D. Swan, M. Liu, D. R. Davies, J. A. Jenkins, I. J. Tickle, T. L. Blundell. Homology among acid proteases: comparison of crystal structures at 3A resolution of acid proteases from Rhizopus chinensis and Endothia parasitica. *Proc. Natl. Acad. Sci. U S A* **74**, 556-559 (1977).

J. Tang, M. N. G. James, I-N. Hsu, J. A. Jenkins, T. L. Blundell. Structural evidence for gene duplication in the evolution of the acid proteinases. *Nature* **271**, 618–621 (1978).

**1978-Retroviral protease discovered**

K. J. Dittmar, K. Moelling K. Biochemical properties of p15-associated protease in an avian RNA tumor virus. *J Virol* **28**, 106–118 (1978).

K. Moelling, A. Scott, K. E. Dittmar, M. Owada. Effect of p15-associated protease from an avian RNA tumor virus on avian virus-specific polyprotein precursors. *J Virol.* **33**, 680–688 (1980).

Y. Yoshinaka, I. Katoh, T. D. Copeland, S. Oroszlan. Murine leukemia virus protease is encoded by the gag-pol gene and is synthesized through suppression of an amber termination codon. *Proc. Natl. Acad. Sci. USA.* **82**, 1618-22 (1985).

**1981-AIDS first reported**

Pneumocystis pneumonia--Los Angeles. *MMWR Morb Mortal Wkly Rep* **30**, 250–2 (1981).

**1983-HIV discovered**

M. Popovic, P. S. Sarin, M. Robert-Gurroff, *et al.* Isolation and transmission of human retrovirus (human t-cell leukemia virus). *Science* **219**, 856–9 (1983).

F. Barre-Sinoussi, J. C. Chermann, F. Rey, M. T. Nugeyre, S. Chamaret, J. Gruest, C. Dauguet, C. Axler-Blin, F. Vezinet-Brun, C. Rouzioux, W, Rozenbaum, L. Montagnier. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome. *Science* **220**, 868-71 (1983).

**1985-Lympadenopathy-associated virus (HIV) sequenced**

S. Wain-Hobson, P. Sonigo, O. Danos, S. Cole, M. Alizon. *Cell* **40**, 9-17 (1985).

**1987-HIV protease sequenced and its structure modeled**

L. H. Pearl, W. R. Taylor. Sequence specificity of retroviral proteases. *Nature* **328**, 482 (1987).

L. H. Pearl, W. R. Taylor. A structural model for the retroviral proteases. *Nature* **329**, 351-354 (1987).

**1988-Target validation of HIV protease active site**

N. E. Kohl, E. A. Emini, W. A. Schleif, L. J. Davis, J. C. Heimbach, R. A. Dixon, E. M. Scolnick, I. S Sigal. Active human immunodeficiency virus protease is required for viral infectivity. *Proc. Natl. Acad. Sci. U S A* **85**, 4686-4690 (1988).

**1989-Crystal structure of retroviral protease described in Rous sarcoma virus**
M. Miller, M. Jaskólski, J. K. Rao, J. Leis, A. Wlodawer. Crystal structure of a retroviral protease proves relationship to aspartic protease family. *Nature* **337**, 576–9 (1989).

**1989-Crystal structure of HIV protease defined**
A. Wlodawer, M. Miller, M. Jaskólski, B. K. Sathyanarayana, E. Baldwin, I. T. Weber, L. M. Selk, L. Clawson, J. Schneider, S. B. Kent. Conserved folding in retroviral proteases: crystal structure of a synthetic HIV-1 protease. *Science* **245**, 616–21 (1989).

R. Lapatto, T. Blundell, A. Hemmings, J. Overington, A. Wilderspin, S. Wood, J. R. Merson, P. J. Whittle, D. E. Danley, K. F. Geoghegan, S. J. Hawrylik, S. E. Lee, K. G. Scheld, P. M. Hobart. X-ray analysis of HIV-1 proteinase at 2.7A resolution confirms structural homology among retroviral enzymes. *Nature* **342**, 299-302 (1989).

**1989-HIV protease complexed with inhibitor**
M. Miller, J. Schneider, B. K. Sathyanarayana, M. V. Toth, G. R. Marshall, L. Clawson, L. Selk, S. B. H. Kent, A. Wlodawer. Structure of complex of synthetic HIV-1 protease with a substrate-based inhibitor at 2.3 A resolution. *Science* **246**, 1149-1152 (1989).

**1991-Ro 31-8959 (Saquinavir) discovered**
A. Krohn, S. Redshaw, J. C. Ritchie, B. J. Graves, M. H. Hatada. Novel binding mode of highly potent HIV- proteinase inhibitors incorporating the (R)-hydroxyethylamine isostere. *J Med Chem.* **34**, 3340–42 (1991)

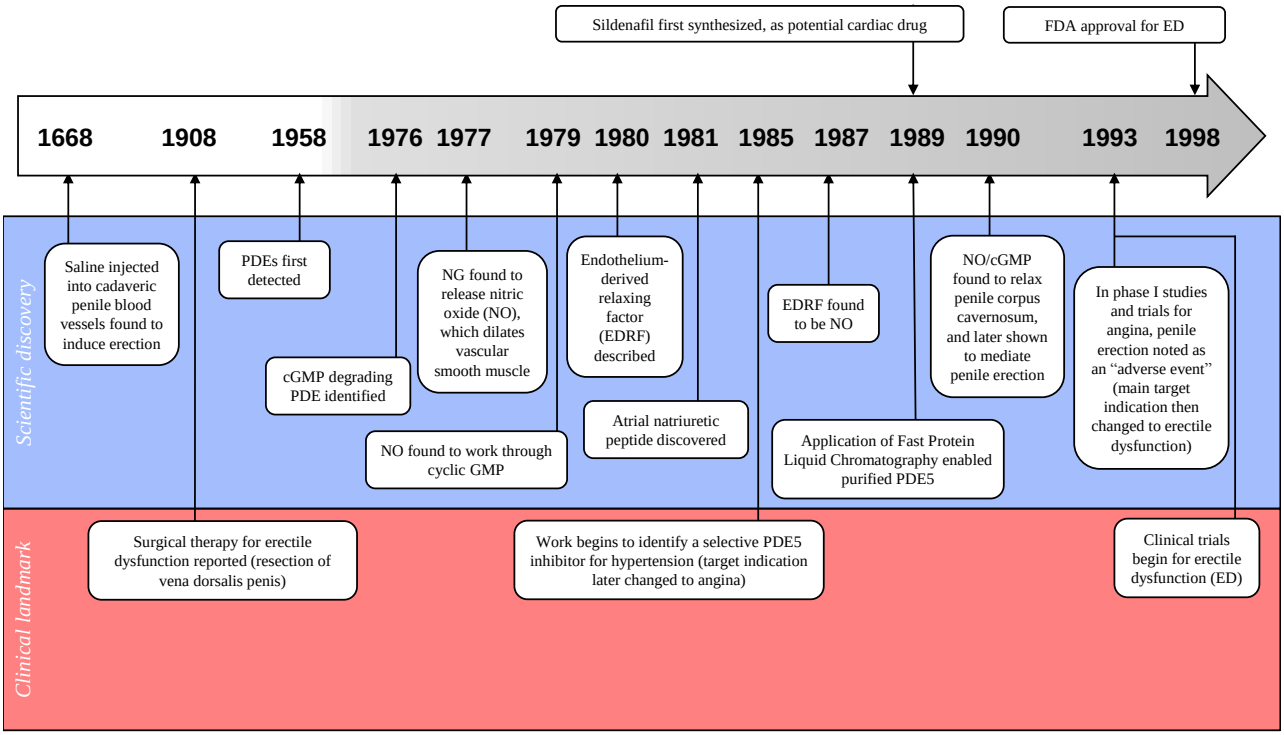
J. C. Craig, I. B. Duncan, D. Hockley, C. Greif, N. A. Roberts, J. S. Mills. Antiviral properties of RO 31-8959, an inhibitor of human immunodeficiency virus (HIV) proteinase. *Antiviral Res*. **16**, 295-305 (1991).

**1992-Clinical testing with Saquinavir begins**
Activity of the proteinase inhibitor RO 31-8959 on acute, chronic, and latent infection. *IXth International Conference on AIDS.* Berlin, June 1993 [abstract PO-A25-0601).

S. Vella. Update on a proteinase inhibitor. *AIDS*. **8** (3), S25-S29 (1994).

# Sildenafil

*PDE5 inhibitor*




**1668-Saline injected into cadaveric penile blood vessels found to induce erection**
H. D. Jocelyn, B. P. Setchell. Regnier de Graaf on the human reproductive organs: an annotated translation of Tractatus de virorum organis generationi inservientibus (1668). *J Reproduc Fertil* **17**, 97-99 (1972).

**1908-Surgical therapy for erectile dysfunction reported (resection of vena dorsalis penis)**
G. F. Lydston. The surgical treatment of impotency: further observations on the resection of the vena dorsalis penis in appropriate cases of impotence in the male, with a record of experiences. *Am J Clin Med* **15**, 1571-1573 (1908).

**1958-PDEs first detected**
T. W. Rall, E. W. Sutherland. Formation of a cyclical adenine ribonucleotide by tissue particles. *J Biol Chem*. **232** (2), 1065-79 (1958).

**1976-cGMP degrading PDE identified, and found to catalyze cyclic GMP**
T. M. Lincoln, C. L. Hall, C. R. Park, J. D. Corbin. Guanosine 3':5'-cyclic monophosphate binding proteins in rat tissues. *Proc. Natl. Acad. Sci. U.S.A.* **73** (8), 2559-63 (1976).

**1977-NG found to release nitric oxide (NO), which dilates vascular smooth muscle**
S. Katsuki , W. Arnold , C. Mittal, F. Murad. Stimulation of guanylate cyclase by sodium nitroprusside, nitroglycerin and nitric oxide in various tissue preparations and comparison to the effects of sodium azide and hydroxylamin. *J Cycl Nucl Prot Phosphoryl Res*. **3**, 23-5 (1977).

**1979-NO found to work through cyclic GMP**
C. A. Gruetter, B. K. Barry, D. B. McNamara, D. Y. Gruetter, P. J. Kadowitz, L. Ignarro L. Relaxation of bovine coronary artery and activation of coronary arterial guanylate cyclase by nitric oxide, nitroprusside and a carcinogenic nitrosoamine. *J Cyclic Nucleotide Res*. **5** (3), 211-24 (1979).

**1980-Endothelium-derived relaxing factor (EDRF) described**
R. F Furchgott, J. V. Zawadzki. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. *Nature* **288** (5789), 373-6 (1980).

**1981-Atrial natriuretic peptide discovered**
A. J. de Bold, H. B. Borenstein, A. T. Veress, H. Sonnenberg. A rapid and potent natriuretic response to intravenous injection of atrial myocardial extract in rats. *Life Sci* **28**, 89–94 (1981).
A. J. de Bold. Atrial natriuretic factor: a hormone produced by the heart. *Science* **230**, 767–770 (1985).

**1985-Work begins to identify a selective PDE5 inhibitor for hypertension (target indication later changed to angina)**
J. D. Fitzgerald. Trails of discovery: the discovery of the phosphodiesterase-5 inhibitor sildenafil (Viagra). *Dialogues in Cardiovasc Med* **21**, 55-59 (2015).

**1987-EDRF found to be NO**
L. J. Ignarro, G. M. Buga, K. S. Wood, R. E. Byrns, G. Chaudhuri. Endothelium-derived relaxing factor produced and released from artery and vein is nitric oxide. *Proc. Natl. Acad. Sci. U.S.A.* **84** (24), 9265-9 (1987).

R. M. Palmer, A. G. Ferrige, S. Moncada. Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. *Nature* **327** (6122), 524-6 (1987).

**1989-Sildenafil first synthesized, as potential cardiac drug**
N. K. Terrett, A. S. Bell, D. Brown, P. Ellis. Sildenafil (Viagra™), a potent and selective inhibitor of type 5 cGMP phosphodiesterase with utility for the treatment of male erectile dystfunction. *Bioorg Med Chem Lett*. **6**, 1819-24 (1996).

**1989-Application of Fast Protein Liquid Chromatography enabled purified PDE5**
J. D. Fitzgerald. Trails of discovery: the discovery of the phosphodiesterase-5 inhibitor sildenafil (Viagra). *Dialogues in Cardiovasc Med* **21**, 55-59 (2015).

**1990-NO/cGMP found to relax penile corpus cavernosum, and later shown to mediate penile erection**
L. J. Ignarro et al. Nitric Oxide and cyclic GMP formation upon electrical field stimulation cause relaxation of corpus cavernosum smooth muscle. *Biochem Biophys Res Commun*. **170**, 843-50 (1990).

J. Rejfer, W. J. Aronson, P. A. Bush, F. J. Dorey, L. J. Ignarro. Nitric oxide as a mediator of relaxation of the corpus cavernosum in response to nonadrenergic, noncholinergic neutotransmission. *N Engl J Med*. **326**, 90-94 (1992).

A. L. Burnett, C. J. Lowenstein, D. S. Bradt, T. S. K. Chang, S. H. Snyder. Nitric oxide: a physiologic mediator of penile erection. *Science* **257,** (5068), 401-3 (1992).

**1993-In phase I studies and trials for angina, penile erection noted as an "adverse event"**

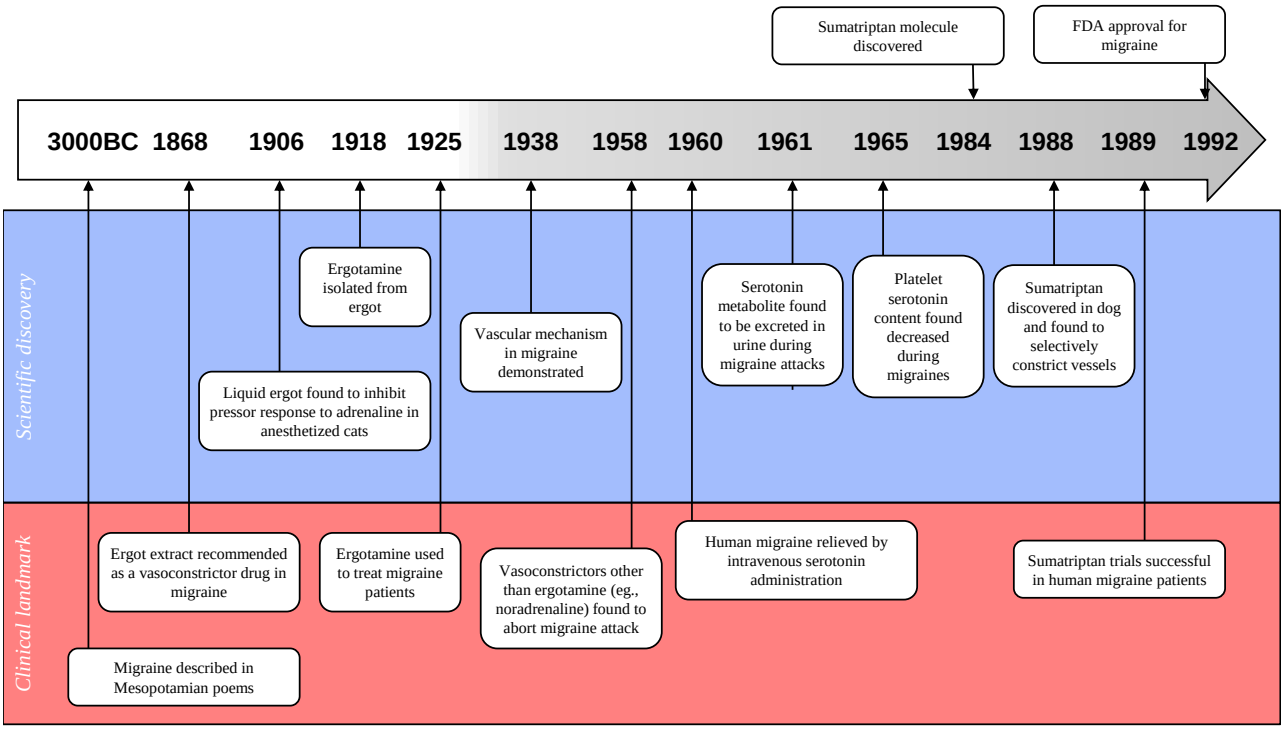
J. D. Fitzgerald. Trails of discovery: the discovery of the phosphodiesterase-5 inhibitor sildenafil (Viagra). *Dialogues in Cardiovasc Med* **21**, 55-59 (2015).
David Brown, personal communication.

**1993-Clinical trials begin for erectile dysfunction (ED)**

M. Boolell, M. J. Allen, S. A. Ballard et al. Sildenafil: an orally active type 5 cyclic GMP-specific phosphodiesterase inhibitor for the treatment of penile erectile dysfunction. *Int J Impot Res*. **8**, 47-52 (1996).

# Sumatriptan

*5-HT agonist*




**3000BC-Migraine described in Mesopotamian poems**
J. M. S. Pearce. Historical aspects of migraine. *J Neurol, Neurosurg, Psych* 49, 1097-1103 (1986).

**1868-Ergot extract recommended as a vasoconstrictor drug in migraine**
E. Woakes. On Ergot of Rye in the Treatment of Neuralgia. *Br Med J* 2, 360–1 (1868).

**1906-Liquid ergot found to inhibit pressor response to adrenaline in anesthetized cats**
H. H. Dale. On some physiological actions of ergot. *J Physiol* 34, 163–206 (1906).

**1918-Ergotamine isolated from ergot**
A. Stoll. Zur Kenntnis der Mutterkornalkaloide. *Verh Schweiz Naturf* 101, 190–1 (1918).

**1925-Ergotamine used to treat migraine patients**
H. W. Maier. L'ergotamine inhibitteur du sympathique etudie en clinique, comme moyen d'exploration et comme agent therapeutique. *Rev Neurol* 33, 1104–8 (1926).

**1938-Vascular mechanism in migraine discovered**
J. R. Graham, H. G. Wolff. Mechanisms of migraine headache and action of ergotamine tartrate. *Arch Neurol Psychiatry* 39, 737–63 (1938).

**1958-Vasoconstrictors other than ergotamine (eg., noradrenaline) found to abort migraine attack**

A. M. Ostfeld, H. G. Wolff. Studies on headache: Arterenol (norepinephrine) and vascular headache of the migraine type. *Arch Neurol Psychiatry* 74, 131-136 (1955).

**1960-Human migraine relieved by intravenous serotonin administration**
R. W. Kimball, A. P. Friedman, E. Vallejo. Effect of serotonin in migraine patients. *Neurology* 10, 107–11 (1960).

**1961-Serotonin metabolite found to be excreted in urine during migraine attacks**
F. Sicuteri, A. Testi, B. Anselmi. Biochemical Investigations in Headache: Increase in the Hydroxyindoleacetic Acid Excretion During Migraine Attacks. *Int Arch Allergy Immunol* **19**, 55–8 (1961).

**1965-Platelet serotonin content found decreased during migraines**
D. A. Curran, H. Hinterberger, J. W. Lance. Total plasma serotonin, 5-hydroxyindoleacetic acid and p-hydroxy-m-methoxymandelic acid excretion in normal and migrainous subjects. *Brain* **88**, 997–1010 (1965).

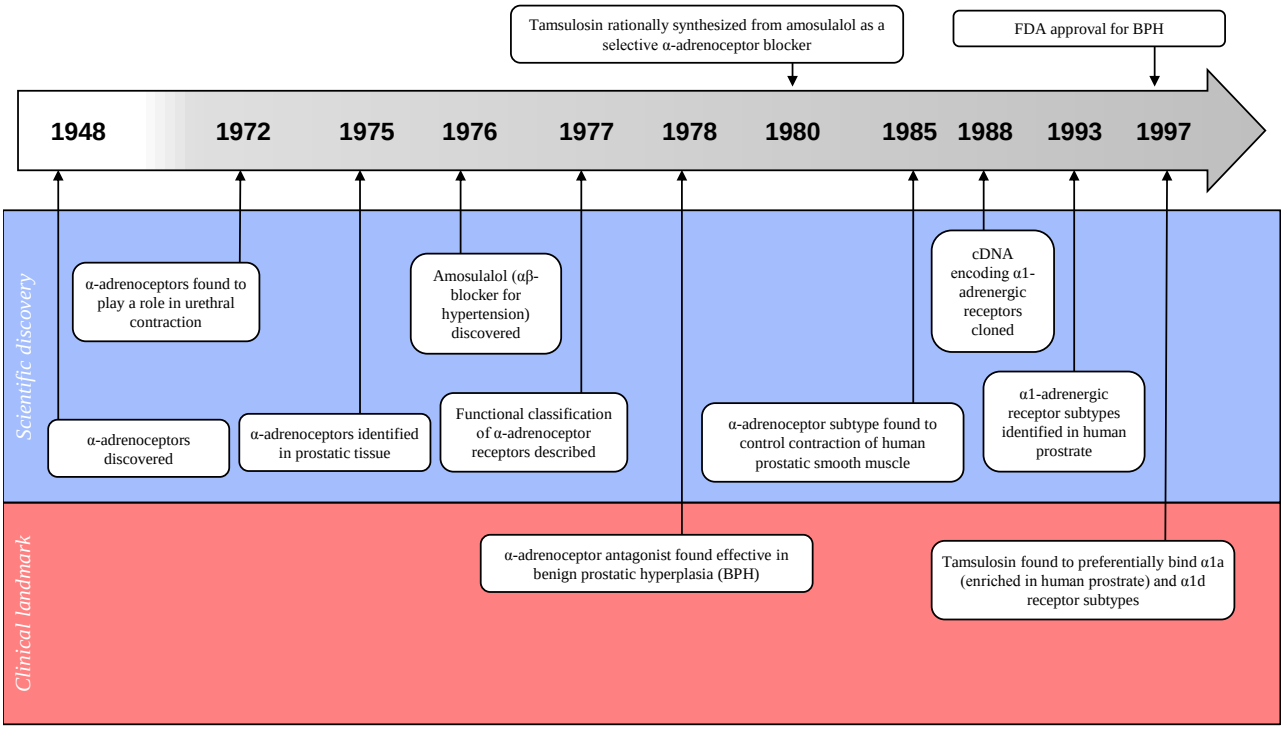
**1984-Sumatriptan molecule discovered**
P. P. A. Humphrey, W. Feniuk, M. Perren, *et al*. The pharmacology of the novel 5-HT1-like agonist, FR43175. *Cephalalgia* **9** (9), 23-33 (1989).

**1988-Sumatriptan discovered in dog and found to selectively constrict vessels**
P. P. Humphrey, W. Feniuk, M. J. Perren, *et al.* GR43175, a selective agonist for the 5-HT1-like receptor in dog isolated saphenous vein. *Br J Pharmacol* **94**, 1123–32 (1988).

**1989-Sumatriptan proves successful in human migraine patients**
V. L. Perrin, M. Färkkilä, J. Goasguen, A. Doenicke, J. Brand, P. Tfelt-Hansen. Overview of initial clinical studies with intravenous and oral GR43175 in acute migraine. *Cephalalgia* **9** (9), 63–72 (1989).

# Tamsulosin

*α-adrenoceptor antagonist*




**1948-α-adrenoceptors discovered**
R. P. Ahlquist. A study of the adrenotropic receptors. *Am J Physiol* **153** (3), 586-600 (1948).

**1972-α-adrenoceptors found to play a role in urethral contraction**
S. Raz, M. Caine. Adrenergic receptors in the female canine urethra. *Invest Urol.* **9** (4), 319-23 (1972).

**1975-α-adrenoceptors identified in prostatic tissue**
M. Caine, S. Raz, M. Zeigler. Adrenergic and cholinergic receptors in the human prostate, prostatic capsule and bladder neck. *Br J Urol.* **47** (2), 193-202 (1975).

**1976-Amosulalol (αβ-blocker for hypertension) discovered at the lab where tansulosin would be discovered**
Yamanouchi Co. Ltd. "Harnal" (in Japanese). *Yakushi-gaku Zassi.* **29** (2), 414-5 (1994).

**1977-Functional classification of α-adrenoceptor receptors described**
S. Berthelsen, W. A. Pettinger. A functional basis for classification of α-adrenergic receptors. *Life Sci.* **21**, 595-606 (1977).

**1978-α-adrenoceptor antagonist found effective in benign prostatic hyperplasia (BPH)**
M. Caine, S. Perlberg, S. Meretyk. A placebo-controlled double-blind study of the effect of phenoxybenzamine in benign prostatic obstruction. *Br J Urol.* **50** (7), 551-4 (1978).

**1980-Tamsulosin rationally synthesized from amosulalol as a selective α-andrenoceptor blocker (later applied to BPH)**
T. Takenaka, K. Honda, T. Fujikura, K. Niigata, S. Tachikawa, N. Inukai. New sulfamoylphenethylamines, potent alpha 1-adrenoceptor antagonists. *J Pharm Pharmacol.* **36** (8), 539-42 (1984).

**1985-α-adrenoceptor subtype found to control contraction of human prostatic smooth muscle**
Y. Kunisawa, K. Kawabe, T. Niijima, K. Honda, T. Takenaka. A pharmacological study of alpha adrenergic receptor subtypes in smooth muscle of human urinary bladder base and prostatic urethra. *J Urol.* **134** (2), 396-8 (1985).

**1988-cDNA encoding α1-adrenergic receptors cloned**
S. Cotecchia, D. A. Schwinn, R. R. Randall, R. J. Lefkowitz, M. G. Caron, B. K. Kobilka. Molecular cloning and expression of the cDNA for the hamster alpha 1-adrenergic receptor. *Proc. Natl. Acad. Sci. U S A* **85**, 7159-7163 (1988)

D.A. Schwinn, J. W. Lomasney, W. Lorenz, P. J. Szklut, R. T. Fremeau, T. L. Yang-Feng, M. G. Caron, R. J. Lefkowitz, S. Cotecchia. Molecular cloning and expression of the cDNA for a novel adrenergic receptor subtype. *J Biol Chem* **265**, 8183-8189 (1990).

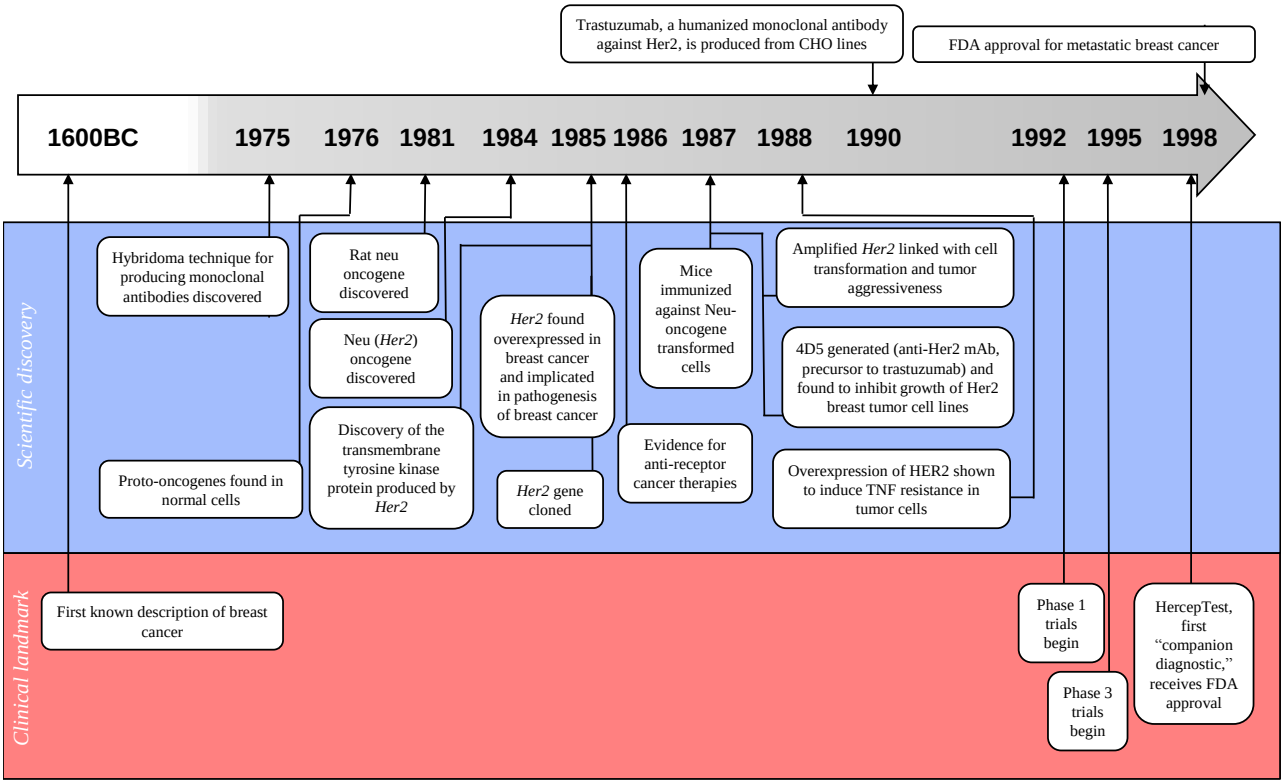
J. W. Lomasney, S. Cotecchia, W. Lorenz, W. Y. Leung, D. A. Schwinn, T. L. Yang-Feng, M. Brownstein, R. J. Lefkowitz, M. G. Caron. Molecular cloning and expression of the cDNA for the alpha 1A-adrenergic receptor. The gene for which is located on human chromosome 5. *J Biol Chem* **266**, 6365-6369 (1991).

**1993-α1-adrenergic receptor subtypes identified in human prostrate**
D. T. Price, D. A. Schwinn, J. W. Lomasney, L. F. Allen, M. G. Caron, R. J. Lefkowitz. Identification, quantification, and localization of mRNA for three distinct alpha 1 adrenergic receptor subtypes in human prostrate. *J Urol* **150**, 546-51 (1993).

**1997-Tamsulosin found to preferentially bind α1a and α1d receptor subtypes**
C. D. Richardson, C. F. Donatucci, S. O. Page, K. H. Wilson, D. A. Schwinn. Pharmacology of tamsulosin: saturation-binding isotherms and competition analysis using cloned alpha-1-adrenergic receptor subtypes. *Prostate* **33**, 55-59 (1997).

# Trastuzumab

*anti-HER2 tyrosine kinase receptor mAb*




**1600BC-First known description of breast cancer**
Edwin Smith papyrus; Egypt ~1600BC.

**1975-Hybridoma technique for producing monoclonal antibodies discovered**
G. Kohler, C. Milstein. Continuous cultures of fused cells secreting antibody of predefined specificity. *Nature* **256**, 495-7 (1975).

**1976-Proto-oncogenes found in normal cells**
D. Stehelin, H. E. Varmus, J. M. Bishop, P. K. Vogt. DNA related to the transforming gene(s) of avian sarcoma viruses is present in normal avian DNA. *Nature* **260**, 170-3 (1976).

**1981-Rat neu oncogene discovered**
C. Shih, L. C. Padhy, M. Murray, R. A. Weinberg. Transforming genes of carcinomas and neuroblastomas introduced into mouse fibroblasts. *Nature* **290**, 261–264 (1981).

L. C. Padhy, C. Shih, D. Cowing, R. Finkelstein, R. A. Weinberg. Identification of a phosphoprotein specifically induced by the transforming DNA of rat neuroblastomas. *Cell* **28**, 865-71 (1982).

**1984-Neu (*Her2*) oncogene discovered**

A. L. Schechter, D. F. Stern, L. Vaidyanathan, S. J. Decker, J. A. Drebin, M. I. Greene MI, R. A. Weinberg. The neu oncogene: an erb-B-related gene encoding a 185,000-Mr tumor antigen. *Nature* **312**, 513-6 (1984).

**1985-Discovery of the transmembrane tyrosine kinase protein produced by *Her2***
L. Coussens, T. L. Yang-Feng, Y. C. Liao, E. Chen, A. Gray, J. McGrath, P. H. Seeburg, T. A. Libermann, J. Schlessinger, U. Francke. Tyrosine kinase receptor with extensive homology to EGF receptor shares chromosomal location with neu oncogene. *Science* **230**, 1132-9 (1985).

**1985-*Her2* gene cloned**
A. Ullrich, L. Coussens, J. S. Hayflick, T. J. Dull, A. Gray, A. W. Tam, J. Lee, Y. Yarden, T. A. Libermann, J. Schlessinger, J. Downward, E. L. V. Mayes, N. Whittle, M. D. Waterfield & P. H. Seeburg. Human epidermal growth factor receptor cDNA sequence and aberrant expression of the amplified gene in A431 epidermoid carcinoma cell. *Nature* **309**, 418 – 425 (1984).

L. Coussens, T. L. Yang-Feng, Y. C. Liao, E. Chen, A. Gray, J. McGrath, P. H. Seeburg, T. A. Libermann, J. Schlessinger, U. Francke, A. Levinson, A. Ullrich. Tyrosine kinase receptor with extensive homology to EGF receptor shares chromosomal location with neu oncogene. *Science* **230,** 1132-1139 (1985).

C. R. King, M. H. Kraus, S. A. Aaronson. Amplification of a novel v-erbB-related gene in a human mammary carcinoma. *Science* **229**, 974-976 (1985).

K. Semba, N. Karnata, K. Toyoshima, T. Yamamoto. A v-erB-related protooncogene, c-erbB-2, is distinct from the c-erbB-1/epidermal growth-factor receptor gene and is amplified in a human salivary gland adenocarcinoma. *Proc. Natl. Acad. Sci. U.S.A* **82**, 6497-6501 (1985).

T. Yamamoto, S. Ikawa, T. Akiyama, K. Semba, N. Nomura, N. Miyajima, T. Saito, K. Toyoshima. Similarity of protein encoded by the human c-erb-B-2 gene to epidermal growth factor receptor. *Nature* **319**, 230-234 (1986).

**1985-*Her2* found overexpressed in breast cancer and implicated in pathogenesis of breast cancer**
C. R. King, M. H. Kraus, S. A. Aaronson. Amplification of a novel v-erbB-related gene in a human mammary carcinoma. *Science* **229**, 974-6 (1985).

**1986-Evidence for anti-receptor cancer therapies**
F. X. Real, W. J. Rettig, P. G. Chesa, M. R. Melamed, L. J. Old, J. Mendelsohn. Expression of epidermal growth factor receptor in human culture cells and tissues: relationship to cell lineage and stage of differentiation. *Cancer Research* **46**, 4726-4731 (1986).

R. E. Sobol, R. W. Astarita, C. Hofeditz, H. Masui, R. Fairshter, I. Royston, J. Mendelsohn. Epidermal growth factor expression in human lung carcinomas defined by a monoclonal antibody. *J Natl Cancer Research* **79**, 403-7 (1987).

**1987-Amplified *Her2* linked with cell transformation and tumor aggressiveness**
D. J. Slamon, G. M. Clark, S. G. Wong, W. J. Levin, A. Ullrich, W. L. McGuire. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science* **235** (4785), 117-82 (1987).

R. M. Hudziak, J. Schlessinger, A. Ullrich. Increased expression of the putative growth factor receptor p185HER2 causes transformation and tumorigenesis of NIH 3T3 cells. *Proc. Natl. Acad. Sci. U.S.A.* **84**, 7159-63 (1987).

**1987-4D5 generated (anti-Her2 mAb, precursor to trastuzumab) and found to inhibit growth of Her2 breast tumor cell lines**

R. M. Hudziak, G. D. Lewis, M. Winget, B. M. Fendly, H. M. Shepard, A. Ullrich. p185HER2 monoclonal antibody has antiproliferative effects in vitro and sensitizes human breast tumor cells to tumor necrosis factor. *Mol Cell Biol* **9**, 1165-1172 (1989).

**1987-Mice immunized against Neu-oncogene transformed cells**

R. Bernards, A. Destree, S. McKenzie, E. Gordon, R. A. Weinberg, D. Panicali. Effective tumor immunotherapy directed against an oncogene-encoded product using a vaccinia virus vector. *Proc Natl Acad Sci. U.S.A* **84**, 6854-6858 (1987).

**1988 - Overexpression of HER2 shown to induce TNF resistance in tumor cells**

B. J. Sugarman, G. D. Lewis, E. Eessalu, B. B. Aggarwal, H. M. Shepard. Effects of growth factors on the antiprofilerative activity of tumor necrosis factors. *Cancer Res* **47**, 780 (1987).
R. M. Hudziak, J. Schlessinger, A. Ullrich. Increased expression of the putative growth factor receptor p185HER2 causes transformation and tumorigenesis of NIH 3T3 cells. *Proc Natl Acad Sci. U.S.A* **84**, 7159 (1987)

R. M. Hudziak, G. D. Lewis, M. R. Shalaby, T. E. Eessaul, B. B. Aggarwal, A. Ullrich, H. M. Shepard. Amplified expression of the HER2/ ERBB2 oncogene induces resistance to tumor necrosis factor alpha in NIH 3T3 cells. *Proc Natl Acad Sci. U.S.A* **85**, 5102 (1988)

**1990-Trastuzumab, a humanized monoclonal antibody against Her2, is produced from CHO lines**

P. Carter, L. Presta, C. M. Gorman, J. B. Ridgway, D. Henner, W. L. Wong, A. M. Rowland, C. Kotts, M. E. Carver, H. M. Shepard. Humanization of an anti-p185HER2 antibody for human cancer therapy. *Proc. Natl. Acad. Sci. U.S.A.* **89** (10), 4285-9 (1992).

**1992-Phase 1 trials begin**

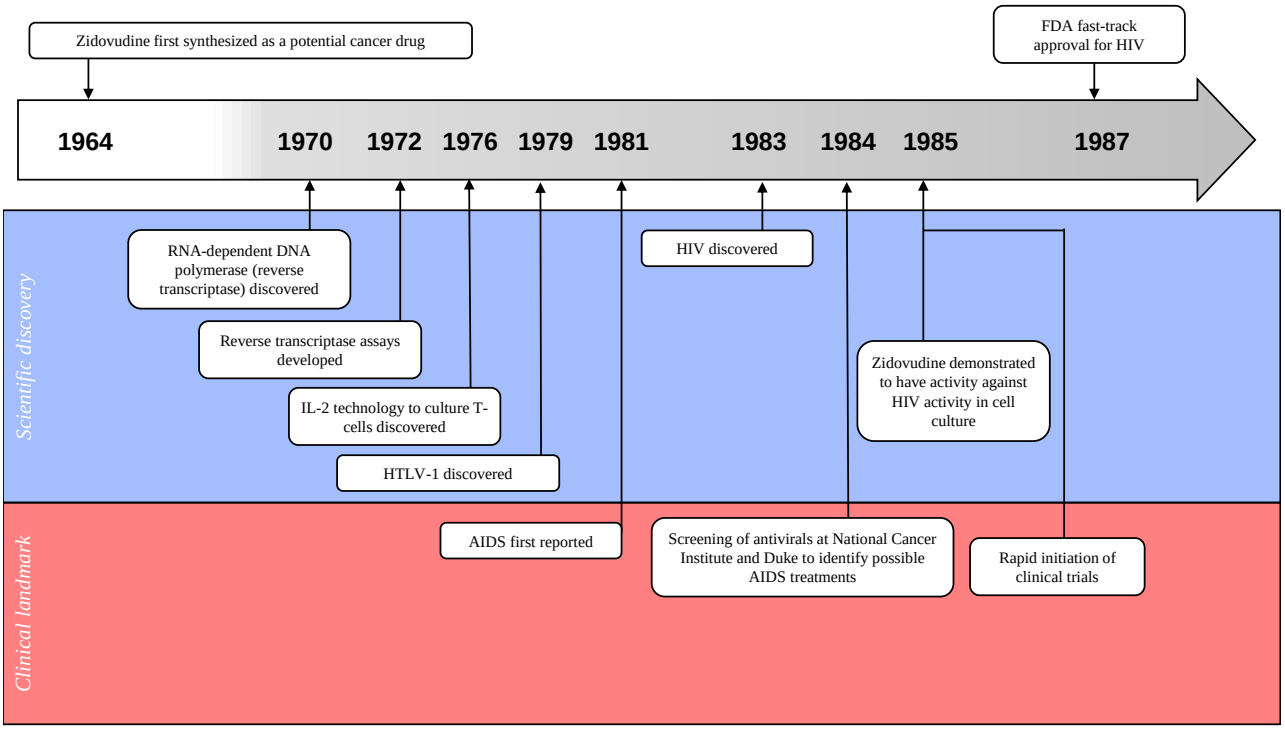
S. Shak, for the Herceptin Multinational Investigator Study Group. Overview of the trastuzumab (Herceptin) anti-HER2 monoclonal antibody clinical program in HER2-overexpressing metastatic breast cancer. *Semin Oncol* **26** (12), 71-7 (1999).

**1998-HercepTest, first "companion diagnostic," receives FDA approval**

T. W. Jacobs , A. M. Gown, H. Yaziji, M. J. Barnes, S. J. Schnitt. Specificity of HercepTest in determining HER-2/neu status of breast cancers using the United States Food and Drug Administration-approved scoring system. *J Clin Oncol* **17** (7), 1983-7 (1999).

# Zidovudine

Reverse transcriptase inhibitor




**1964-Zidovudine first synthesized as a potential cancer drug**

J. Zemlicka, J. V. Freisler, R. Gasser, J. P. Horwitz. Nucleosides. XVI. The synthesis of 2',3'-dideoxy-3',4'-didehydro nucleosides. *J Org Chem* **38**, 990–9 (1973).

**1970-RNA-dependent DNA polymerase (reverse transcriptase) discovered**

H. M. Temin, S. Mizutani. RNA-dependent DNA polymerase in virions of Rous sarcoma virus. *Nature* **226,** 1211–3 (1970).

D. Baltimore. RNA-dependent DNA polymerase in virions of RNA tumour viruses. *Nature* **226,** 1209–11 (1970).

**1972-Reverse transcriptase assays developed**

M. S. Robert, R. G. Smith, R. C. Gallo, P. S. Sarin, J. W. Abrell. Viral and cellular DNA polymerase: comparison of activities with synthetic and natural RNA templates. *Science* **176,** 798–800 (1972).

S. N. Bobrow, R. G. Smith, M. S. Reitz, R. C. Gallo. Stimulated normal human lymphocytes contain a ribonuclease-sensitive DNA polymerase distinct from viral RNA-directed DNA polymerase. *Proc Natl Acad Sci U S A* **69**, 3228–3232 (1972).

**1976-1977-IL-2 technology to culture T-cells discovered**

D. A. Morgan, F. W. Ruscetti, R. Gallo. Selective in vitro growth of T lymphocytes from normal human bone marrows. *Science* **193**, 1007–1008 (1976).

F.W. Ruscetti, D. A. Morgan, R. C. Gallo. Functional and morphologic characterization of human T cells continuously grown in vitro. *J Immunol* **119**, 131–138 (1977).

**1979-HTLV-1 discovered**
B. J. Poiesz, F. W. Ruscetti, M. S. Reitz, V. S. Kalyanaraman, R. C. Gallo. Isolation of a new type C retrovirus (HTLV) in primary uncultured cells of a patient with Sezary T-cell leukaemia. *Nature* **294**, 268–271 (1981)

**1981-AIDS first reported**
Pneumocystis pneumonia--Los Angeles. *MMWR Morb Mortal Wkly Rep* **30,** 250–2 (1981).

**1983-HIV discovered**
M. Popovic, P. S. Sarin, M. Robert-Gurroff, V. S. Kalyanaraman, D. Mann, J. Minowada, R. C. Gallo. Isolation and transmission of human retrovirus (human t-cell leukemia virus). *Science* **219**: 856–9 (1983).

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