History & Overview of the Pharmaceutical/Biotechnology Industry

How were and how are drugs derived?

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September 19, 2013

Therapeutics in the 19th Century

- Scurvy – Lind 1763
- Infectious diseases
  - Vaccination - Jenner 1798
  - Cholera - turning off Broad Street pump 1854
  - Antiseptic techniques - Lister 1867
- Nonexistent until end of 19th century

Digitalis

- **The first medicines were plants**
- **The first prescribed botanical therapeutic was *Digitalis purpurea*, a known herbal remedy studied for dose range and toxicities by William Withering**
- **Withering officially described his foxglove prescription in 1785**
- **Digitalis, the active ingredient from the purple foxglove, is still often used for controlling heart rate**

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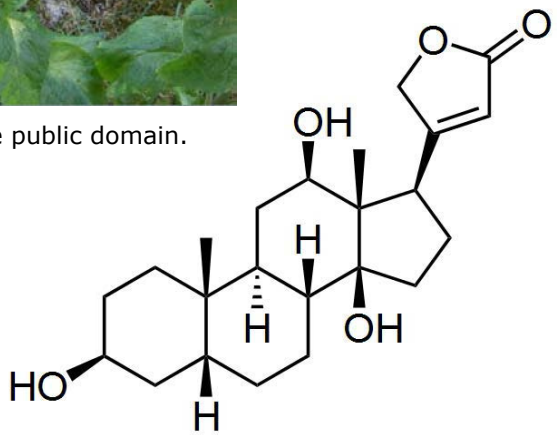


"Digoxigen acsv" by Calvero - Own work. Licensed under Public domain via Wikimedia Commons.

http://www.bris.ac.uk/Depts/Chemistry/MOTM/digitalis/digtalis.htm

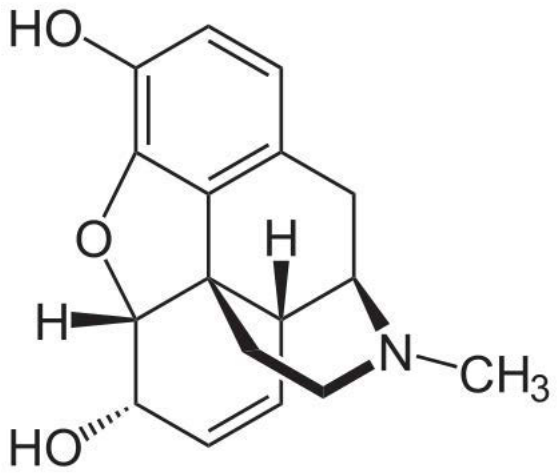
Some Plant-Derived Pharmaceuticals

Drug	Chemical	Indication	Plant producer
Aspirin	Salicylate	Analgesic, anti-inflammatory	*Salix alba* (white willow tree) *Filipendula ulmaria* (meadowsweet)
Caffeine	Xanthine	Increases mental alertness	*Camellia sinensis*
Cocaine	Alkaloid	Ophthalmic anesthetic	*Erythoxylum coca* (coca leaves)
Codeine	Alkaloid	Analgesic, cough suppressor	*Papaver somniferum* (opium poppy)
Dicoumarol	Coumarin	Anticoagulant	*Melilotus officinalis*
Digoxin	Steroid	Increases heart muscle contraction	*Digitalis purpurea* (purple foxglove)
Ipecac	Alkaloid	Induces vomiting	*Psychotria ipecacuanha*
Morphine	Alkaloid	Analgesic	*Papaver somniferum* (opium poppy)
Pseudoephedrine	Alkaloid	Clears nasal congestion	*Ephedra sinica*
Quinine	Alkaloid	Malaria	*Cinchona pubescens* (fever tree)
Reserpine	Alkaloid	Antihypertensive	*Rauvolfia serpentina* (Indian snakeroot)
Scopalamine	Alkaloid	Motion sickness	*Datura stramonium* (Jimson weed)
Paclitaxel	Terpenoid	Ovarian, lung, breast cancer	*Taxus brevifolia* (western yew tree)
Theophylline	Xanthine	Anti-asthmatic, diuretic	*Camellia sinensis*
Vincristine	Alkaloid	Leukaemia	*Catharanthus roseus* (rosy periwinkle)

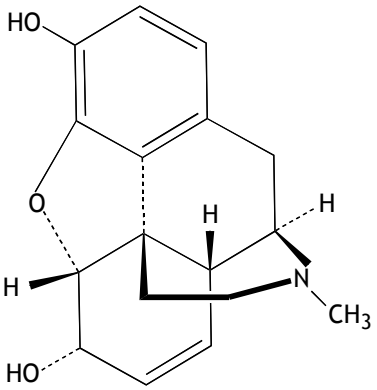
An Industry Begins to Emerge

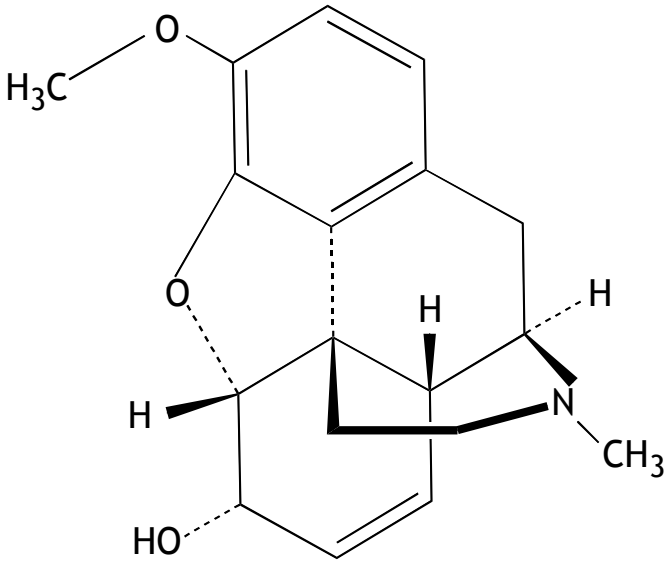
Morphine

- **Alkaloid derived from an organic acid extracted from poppy juice**
- **Friedrich Wilhelm Sertürner in 1815**

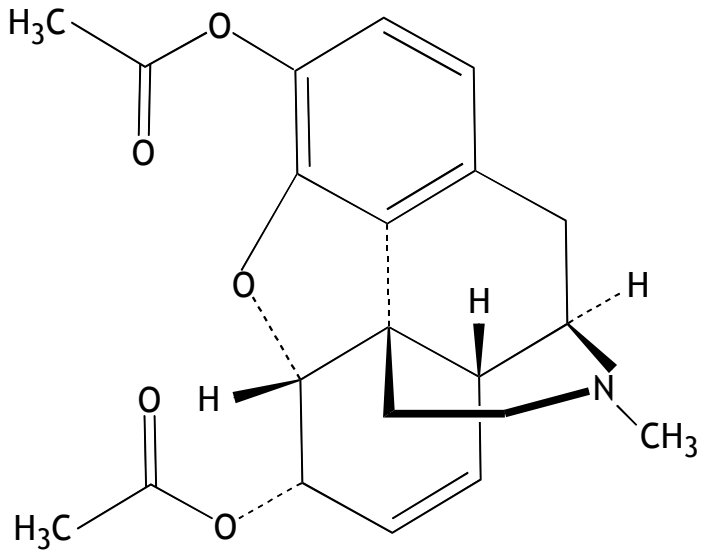


Morphine Derivatives





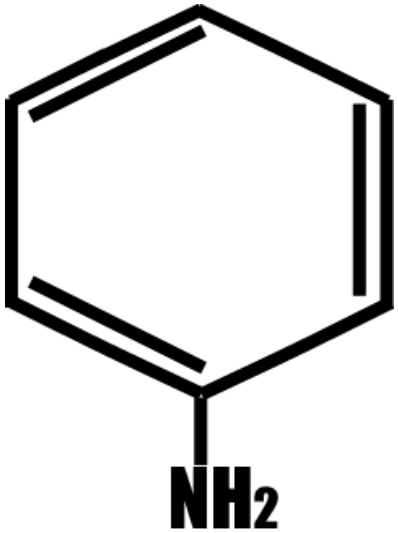
CODEINE
(methyl-ether morphine)

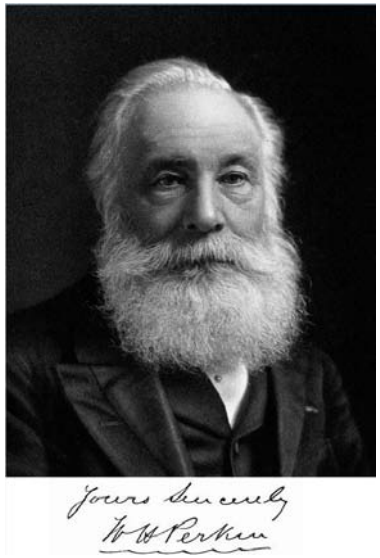


HEROIN
(diacetyl morphine)

Late 19th Century

Nascent pharmaceutical industry grew from established dye-producing industry where organic synthesis to create new molecules and production processes for making them matured.





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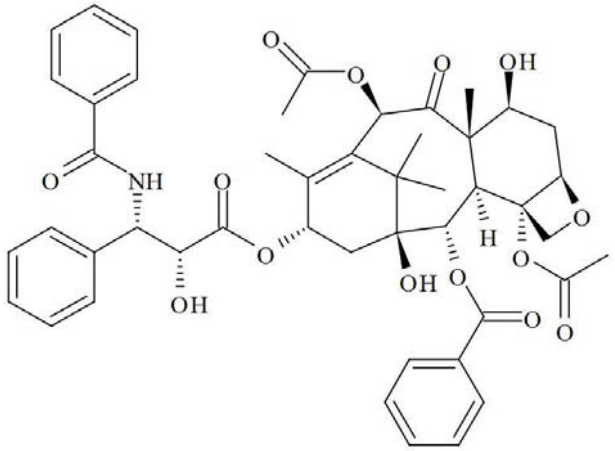
Aniline purple (mauve), the first synthetic dye, was discovered in 1856 by Sir William Henry Perkin as he worked with coal tar derivatives trying to synthesize quinine.

Perkin commercialized mauve, creating the industrial-scale fine chemical production industry.

Paclitaxel

- **Extracted from yew trees**
- **Discovered in the 1960s by National Cancer Institute**
- **1983 – antitumor trials in humans began**
- **1991 – Bristol-Myers Squibb obtained rights to produce Taxol**



Courtesy of R. Terrett on Wikimedia Commons.
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Natural Pharmaceuticals, Inc. – harvesting plantation grown yew trees.

Image removed due to copyright restrictions. Plantation-grown yew trees.
Natural Pharmaceuticals Photo.
See: http://pubs.acs.org/email/cen/html/090804094313.html.

http://pubs.acs.org/email/cen/html/090804094313.html

Dyes and Medicine

- **Differential staining of tissues and cells led Paul Ehrlich to speculate that "chemoreceptors" on cells affected how cells responded to chemicals.**
- **Later, Ehrlich extended this idea to pathogens noting that chemical structures should differentially affect host and pathogen tissues, providing a basis for "chemotherapy", or using chemicals to treat disease.**

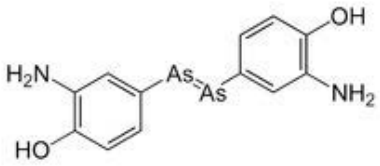
Image removed due to copyright restrictions. Slide showing skull tissue stained with Mallory triple stain. See: https://casweb.ou.edu/pbell/histology/Captions/Cellmethods/16.Mallory.html

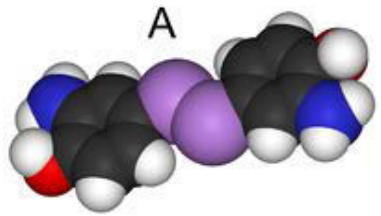
- **Major therapeutic success was Salvarsan, first drug for syphilis, marketed in 1910.**

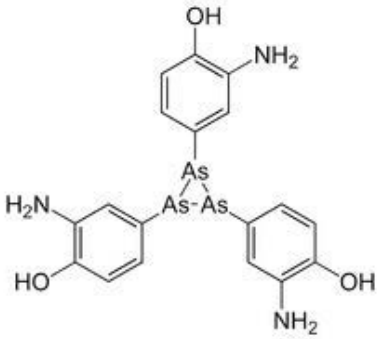
http://www.nobel.se/medicine/laureates/1908/ehrlich-bio.html
http://www.chemheritage.org/EducationalServices/chemach/ppb/pe.html
http://casweb.ou.edu/pbell/Histology/Outline/contents.html

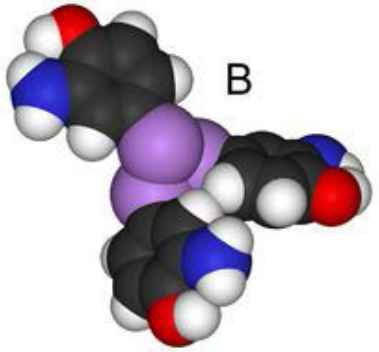
Arsphenamine

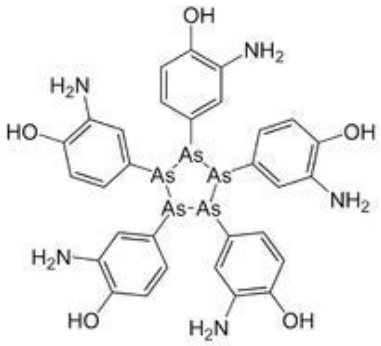
The structure of Arsphenamine has been proposed to be akin to the azobenzene (**A**), but mass spectral studies published in 2005 suggest it is actually a mixture of the trimer **B** and the pentamer **C**. Also known as Salvarasan and compound 606 – Arsphenamine was introduced in the 1910s as the first effective treatment for syphilis.

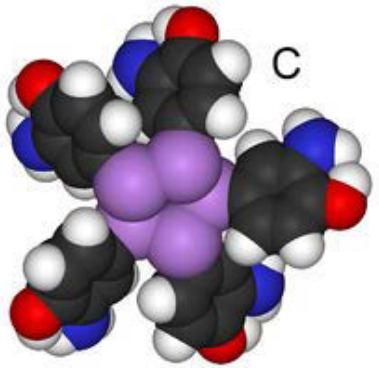












Wikipedia.org

Salvarsan treatment kit for syphilis

Germany, 1909-1912: The kit included tools to help prepare injections for treatment of syphilis.

Pharmaceuticals Extracted from Biological Source
(some protein-based examples produced using genetic engineering)

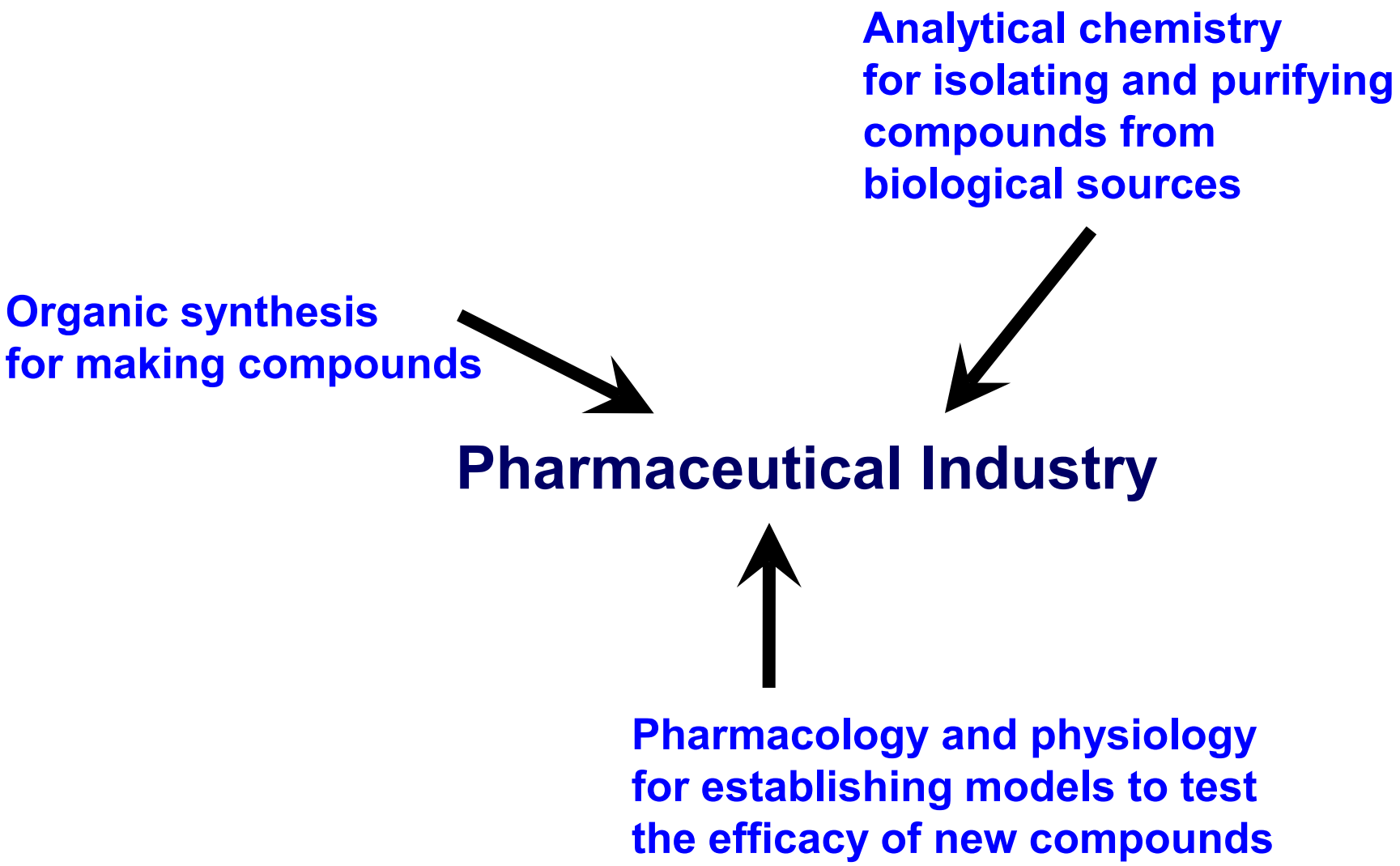
Substance	Medical application
Blood products (e.g. coagulation factors	Treatment of blood disorders such as hemophilia A or B
Vaccines	Vaccination against various diseases
Antibodies	Passive immunization against various diseases
Insulin	Treatment of diabetes mellitus
Enzymes	Thrombolytic agents, digestive aids, debriding agents (i.e. cleansing of wounds)
Antibiotics	Treatment against various infectious agents
Plant extractives (e.g. alkaloids)	Various, including pain relief

Eli Lilly & Company

- Founded in May, 1876 by Colonel Eli Lilly, a pharmaceutical chemist
- 1886, chemist Ernest Eberhard joined Lilly from Purdue
- 1923, introduced Iletin, world's first insulin product
- 1940s, became active in antibiotics; helped develop method to mass produce penicillin
- 1950s, develops vancomycin followed by erythromycin
- 1980s, issues with Darvon, a painkiller alleged to be addictive – deaths associated with overdoses; launches Humulin® insulin (rDNA production of insulin) and Prozac®
- 1982, Oraflex, an arthritis drug, taken off market after it's linked to 50+ deaths - pleads guilty to 25 misdemeanor criminal counts
- 2013, filed $500 million international lawsuit with NAFTA against Canada, alleging they invalidated patents for its drugs Straterra and Zyprexa

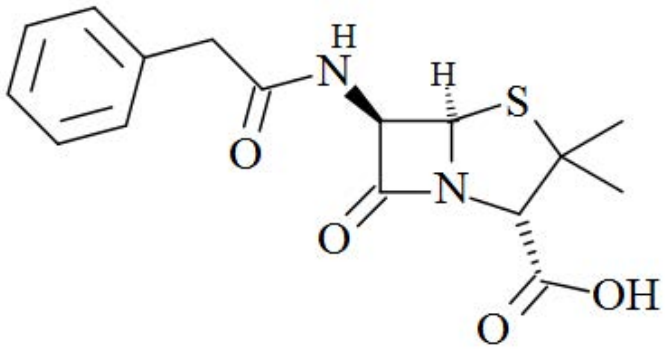
Image removed due to copyright restrictions.
Illustration of the pure active form of insulin.
See: http://customers.hbci.com/~wenonah/gif/aminose2.jpg.

Convergence of Disciplines



Penicillin

- Discovered in 1928 by Alexander Fleming: a mold on his culture plates was apparently responsible for the bacterial lysis he observed
- In 1939, Howard Flory, Ernst Chain, and Norman Heatley began work to isolate and purify the active compound from the fungus

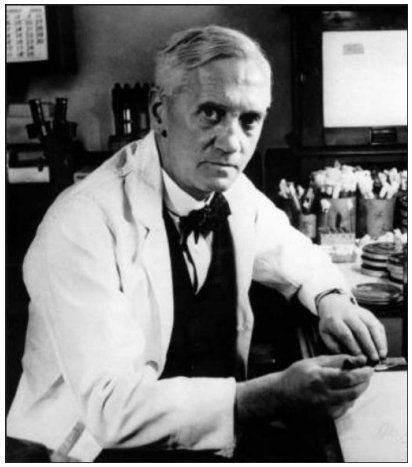


Penicillin structure, from Wikimedia Commons. Image is in the public domain.

- Their successful isolation allowed clinical tests of the antibiotic
- Large-scale production of penicillin, spurred by war efforts, led pharmaceutical companies to establish microbiology and fermentation departments, drawing research scientists from academia to staff them

Brief History of Pfizer

- Charles Pfizer & Charles Erhart (1840) & 1849 formed Charles Pfizer & Co.
  - Bulk chemicals, tartaric acid and citric acid via fermentation technology
- 1928, penicillin production by Pfizer during and after WW II lead to additional antibiotics: tetracycline, direct marketing, FDA and Henry Welch
- Mid-20th century: drugs via molecular manipulation
- 1963, Destin Chemical, maker of OTC brands: BenGay, etc.
- 1981, first billion dollar drug Feldene
- 1999, 150th anniversary and Forbes company of the year
- 2000, Warner-Lambert acquired
- 2002, Pharmacia-Upjohn acquired
- 2005, Lipitor sales reach \$12.2 x10^{9}
- 2009, Purchased Wyeth



Alexander Fleming from Wikimedia Commons.
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Alexander Fleming: Discoverer of penicillin and its antibacterial properties

Image removed due to copyright restrictions.
Photo of Feldene bottle & capsules.
See: http://labeling.pfizer.com/ShowLabeling.aspx?id=569.

Pfizer announces new commercial structure

Image removed due to copyright restrictions. Second Quarter 2013 Earnings Teleconference, Pfizer, July 30, 2013. Page 6.
See: http://www.pfizer.com/files/investors/presentations/q2charts_073013.pdf

http://www.pfizer.com/files/investors/presentations/q2charts_073013.pdf

Major Families of Antibiotics

- β-Lactams
- Tetracyclines
- Aminoglycoside antibiotic
- Macrolides
- Ansamycins
- Peptide/glycopeptide antibiotics
- Miscellaneous antibiotics

Therapeutic Index

- 100s of compounds with antibiotic activity isolated from microorganisms
- Only a few are clinically useful
- Must exhibit differential toxicity: toxic to pathogen, not (or at least less) toxic to humans
- Therapeutic Index = toxic dose / therapeutic dose (the bigger, the better)

Microbiology and Fermentation:
Looking for Other Therapeutic Properties

- **Ivermectin**: an antiparasitic drug isolated from a soil fungus
- **Lovastatin**: a cholesterol synthesis inhibitor isolated from an Aspergillus species
- **FK 506**: immunosuppressant isolated from a Streptomyces species

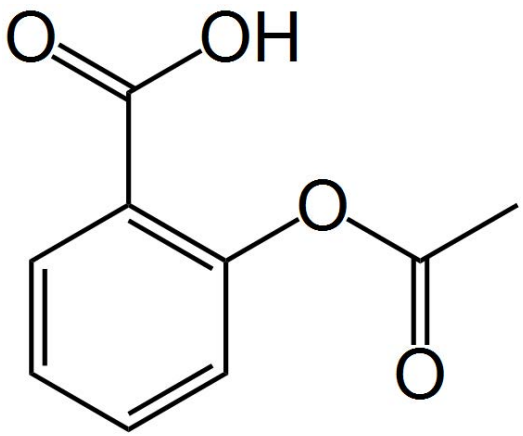
More about Drug Action

- "Receptor," in this case, is defined as a component of the cell that reacts with a chemical to produce a measurable response
- Many receptor molecules are proteins
- Some drugs exert trans-membrane effects from outside the cell
- Some drugs are transported into the cell to affect endogenous receptors

Types of drugs include:

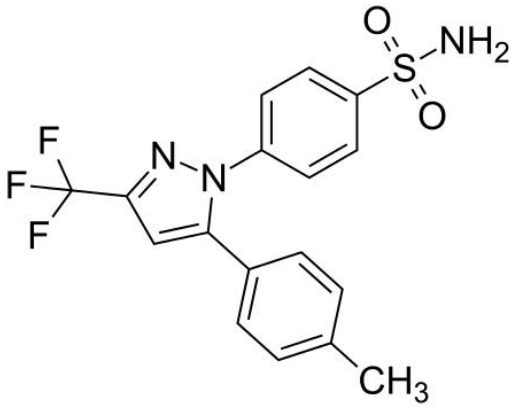
- Antimicrobials
- Vaccines & antisera
- Cardiovascular drugs
- Drugs affecting the nervous system
- Hormones
- Chemotherapeutics
- Immunosuppressives

NSAIDs: all inhibit cyclooxygenase enzymes



Inhibits prostaglandin production via the cyclooxygenase I enzyme, blocking the inflammation response

Aspirin structure from Wikimedia Commons.
Image is in the public domain.



Inhibits prostaglandin production by the isoenzyme cyclooxygenase II, which is an induced enzyme

Structure from Wikimedia Commons.
Image is in the public domain.

Celecoxib

For most of the 20th century, new drugs came from synthesis of new molecules

How it works:

- **Serendipitous findings of therapeutic effects of chemicals**
- **Using those chemicals as prototypes, medicinal chemists made derivatives**
- **Derivatives were tested for improved effects or novel effects**

For most of the 20th century, new drugs came from synthesis of new molecules

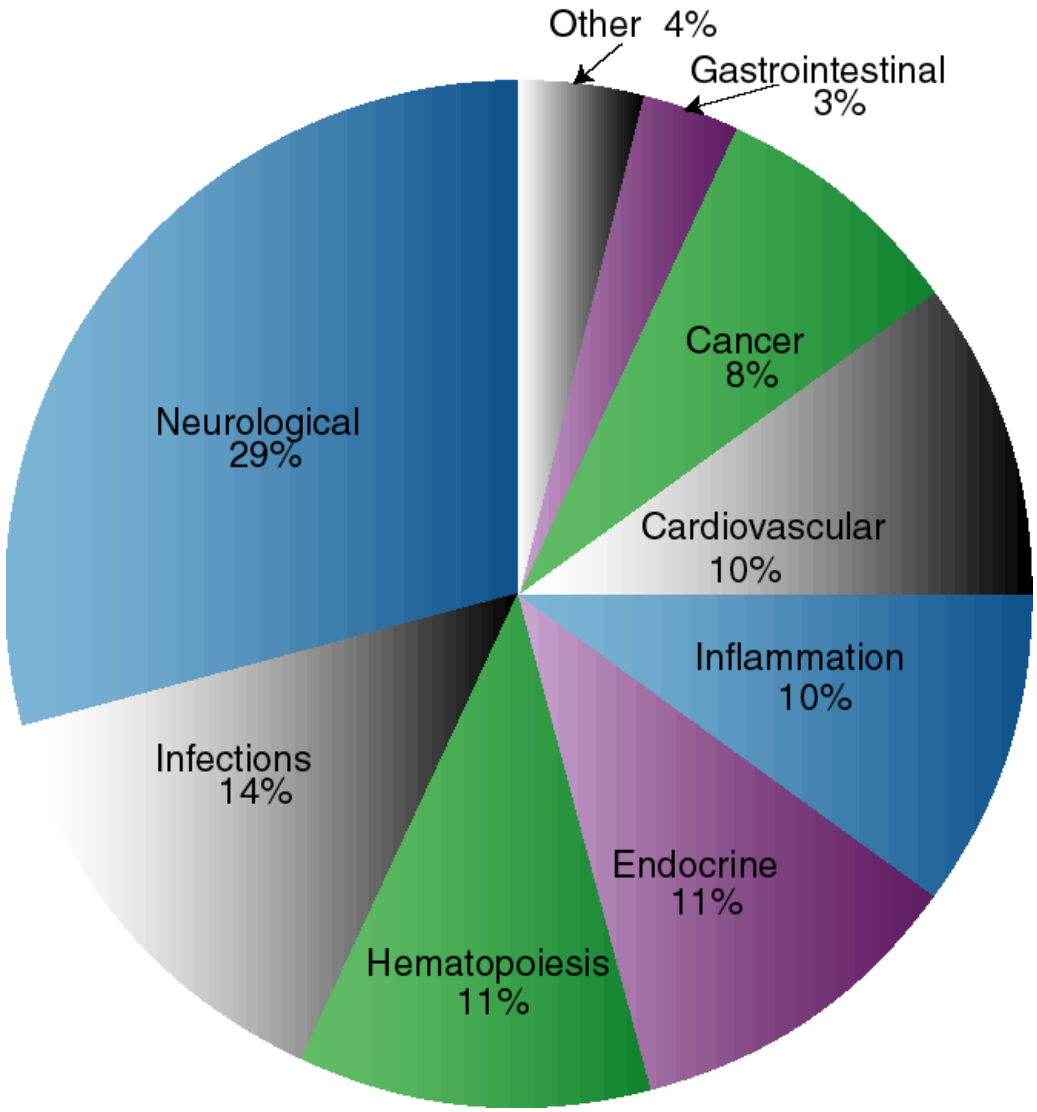
Image removed due to copyright restrictions. Figure 2: Sons of sulfanilamide. A schematic representation of drugs that originated from sulfanilamide.
Source: Drews, J. "Drug Discovery: A Historical Perspective." *Science* 287, no. 5460 (2000): 1960-64.
See: http://www.sciencemag.org/content/287/5460/1960.

Improvements in Research Methodology from Integration of Combinatorial Chemistry

Traditional	Today	Difference
Libraries of molecules	Combinatorial Chemistry → Libraries of molecules	More Starting Compounds
Sequential Screening	Automated Parallel Screening	Increased Screening Capacity
Lead	Lead	More Lead Substances

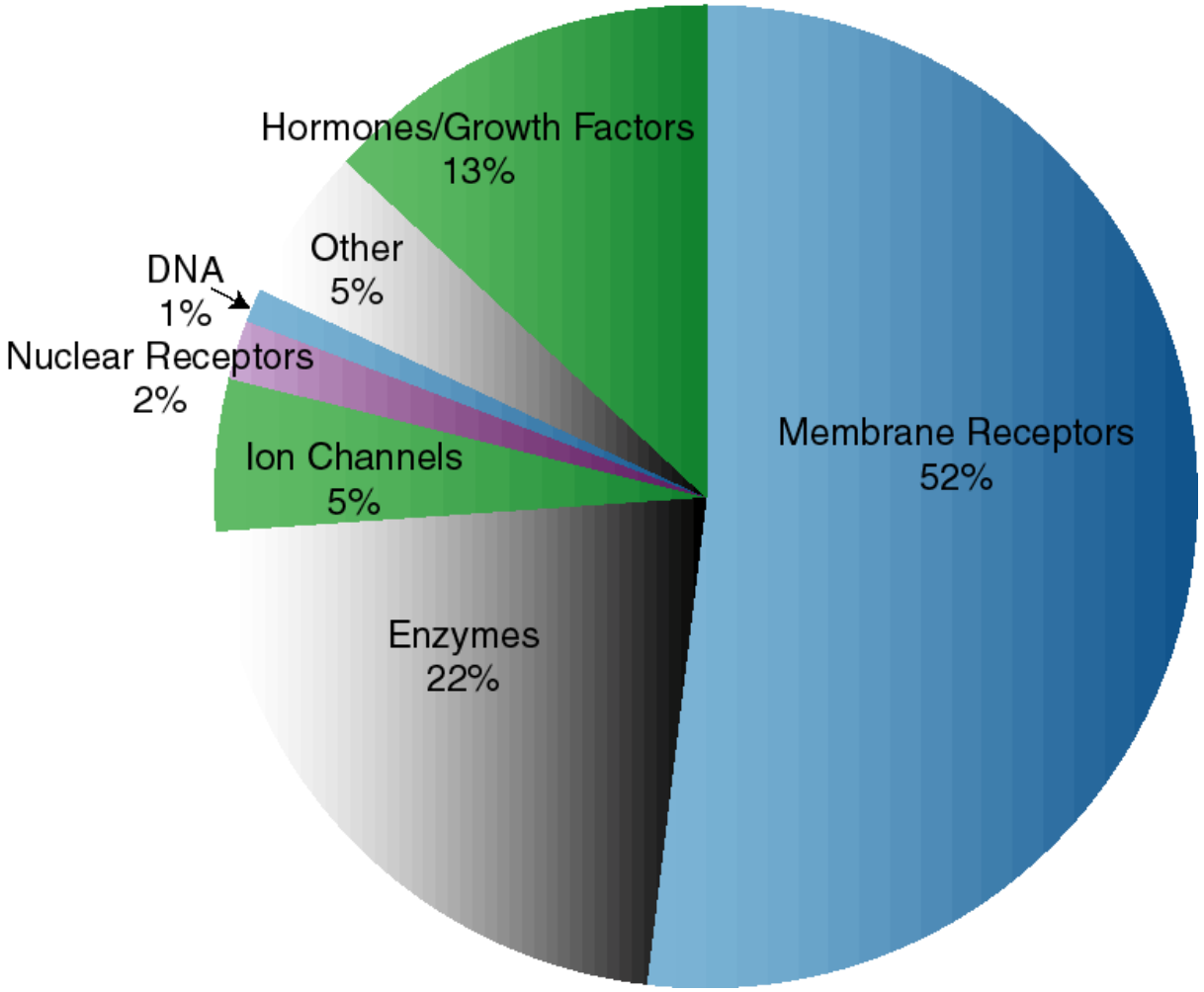
Adapted from In Quest of Tomorrow's Medicines by Jürgen Drews

Therapeutic Classification of Approved Drug Therapy Targets



Adapted from
In Quest of Tomorrow's Medicines
by Jürgen Drews

Biochemical Classification of Approved Drug Therapy Targets



Adapted from
In Quest of Tomorrow's Medicines
by Jürgen Drews

Recombinant DNA and Biotechnology

- Advances in Recombinant DNA and Molecular Genetics in the 1970s and 1980s
- Resulted in
  - Biopharmaceutical class of drugs
  - Improved discovery methods for finding interesting molecules

Recombinant DNA Technology and Drug Discovery

- **With advent of recombinant DNA and molecular biology technologies, scientists could predictably alter a protein's sequence and produce that altered protein in quantity**

- **Allowed rational approaches to structure – function relationships in drug design**

- **Allowed production of recombinant proteins for drugs themselves, *e.g.* insulin, antibody therapeutics like Herceptin, EPO,and β-glucocerebrosidase**

Monoclonal Antibody (MAb) Therapy: Technological Innovation Makes It Feasible

- **Problems:**
  - **Immunogenicity of MAbs made in mice**
  - **Murine MAbs not activating correct immune function in patients**
- **Technological Innovation:**
  - Antibody engineering, including techniques for humanized antibodies (replacing murine MAb sequences with human)

Image removed due to copyright restrictions. Illustration of mouse & human monoclonal antibodies. Source unknown.

- Results:
  - Effective MAb therapies for several diverse indications
  - > 70 MAb therapies in clinical trials in 2000

Monoclonal Antibody Therapies

Technological Innovations		FDA-approved clinical application
Köhler & Milstein Monoclonal antibodies	1975	
Boulianne, *et al.* & Morrison, *et al.* Mouse-Human Chimeric Antibodies	1984	
	1986	**OrthoClone/OKT3**
Antibody Engineering techniques for creating humanized Abs	1991-1996	**ReoPro**
	1997	**Zenapax, Rituxan**
	1998	**Simulect, Synagis, Remicade, Herceptin**
	2001	**Campath**
	➢2009	➢**Several NCE**

Source of data: Glennie and Johnson, *Clinical trials of antibody therapy*;Immunology Today (2000) 21(8): 403.

FDA approved antibody-based therapeutics

Image removed due to copyright restrictions. FDA Approved Antibody-based Therapeutics
See: http://www.immunologylink.com/FDA-APP-Abs.html.

http://www.immunologylink.com/FDA-APP-Abs.html

FDA approved antibody-based therapeutics (continued)

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See: http://www.immunologylink.com/FDA-APP-Abs.html.

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FDA approved antibody-based therapeutics (continued)

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FDA approved antibody-based therapeutics (continued)

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FDA approved antibody-based therapeutics (continued)

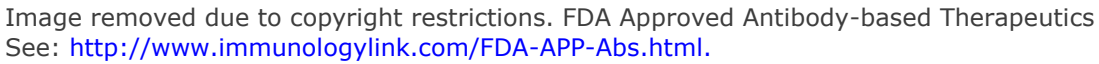


Image removed due to copyright restrictions. FDA Approved Antibody-based Therapeutics
See: http://www.immunologylink.com/FDA-APP-Abs.html.

http://www.immunologylink.com/FDA-APP-Abs.html

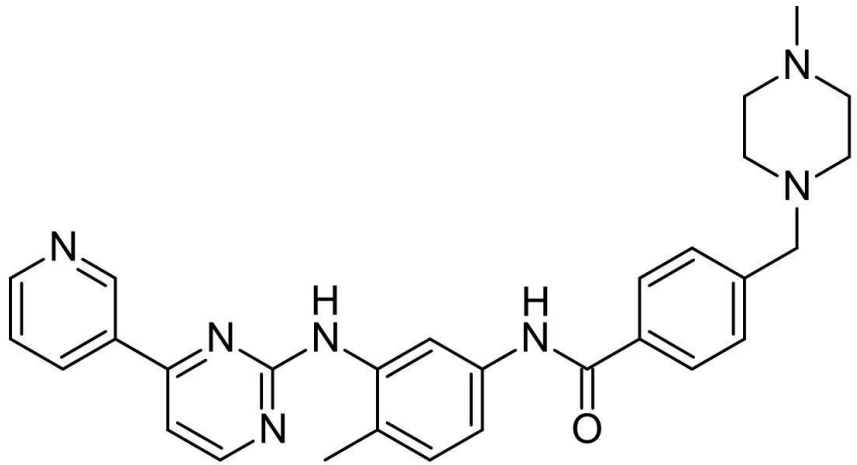
Things Are Changing

Drug Discovery Paradigms Shift with Advancing Technological Capabilities

- "Random" drug discovery: screening compounds using whole or partial animal screens
- Mechanism-Driven drug discovery: screening against a specific known or suspected mechanism
- Fundamental Science discovery

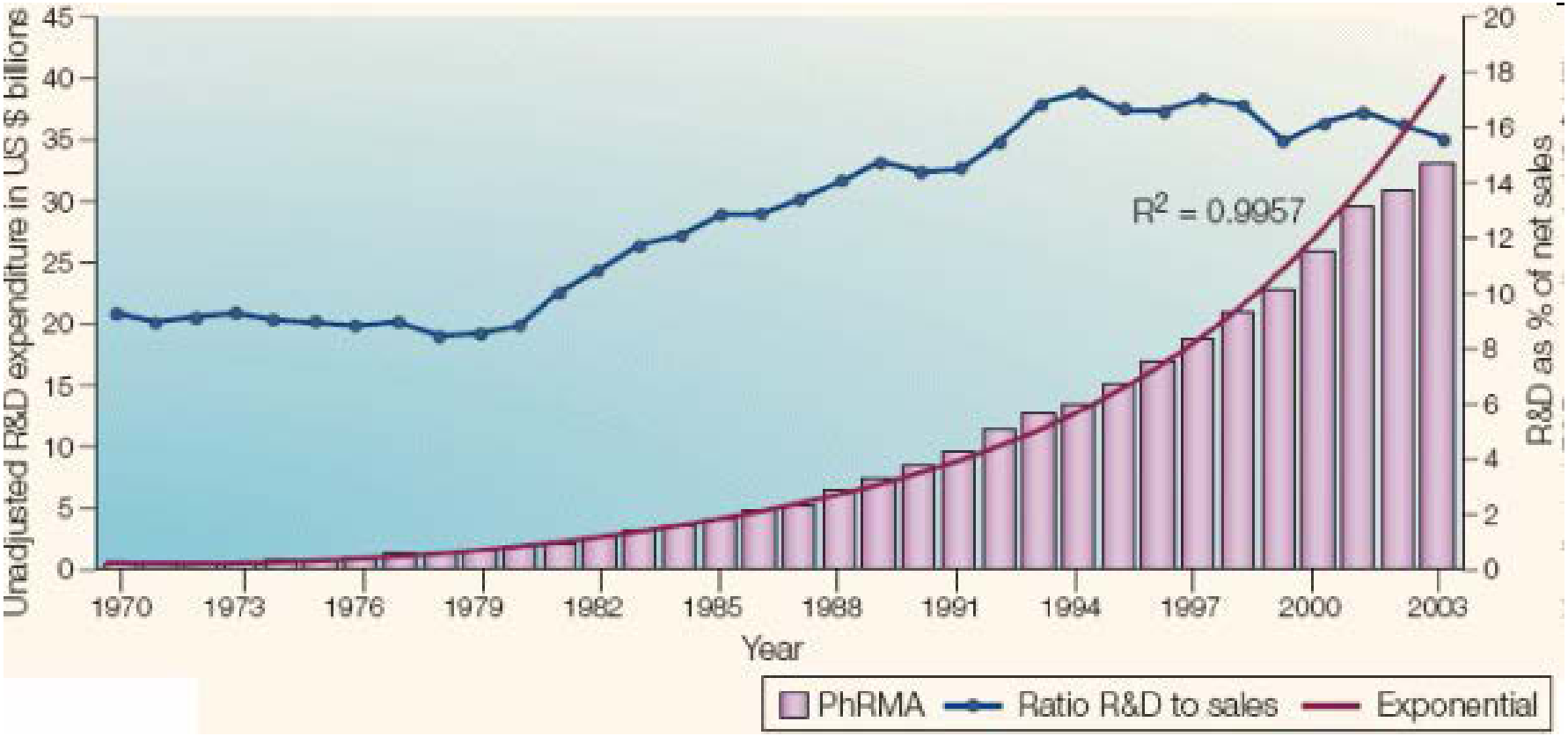
Novartis

- 1857, Johann Rudolf Geigy Merian and Johann Müller-Pack founded a dye extraction plant in Basel. Produces synthetic Fuchsine. Renamed Geigy Colour Company Ltd. in 1920.
- 1859, Alexander Clavel produces Fuchsine for dye factory, 1873 sells factory to Bindschedler & Busch. Renamed Company for Chemical Industry Basel in 1884 (Ciba adopted in 1945)
- 1970, Ciba and Geigy merge forming Ciba-Geigy Ltd. 1992, shortened to Ciba.
- 1886, Kern & Sandoz, chemical co. founded in Basel by Alfred Kern and Edouard Sandoz. Produced alizarin blue and auramine.
- 1996, Sandoz and Ciba-Geigy merge to form Novartis



Gleevec

Amount ($) invested in R&D by pharmaceutical and biotech companies worldwide has been steadily increasing



Reprinted by permission from Nature Publishing Group: *Nature Reviews Drug Discovery.*
Source: Cohen F. J. "Macro Trends in Pharmaceutical Innovation." *Nature Reviews Drug Discovery* (2005): 78-84.

Pharma spending has increased in proportion to sales - Source: Cohen F.J.(2005), Macro trends in pharmaceutical innovation, Nature Reviews Drug discovery, Vol 4 pp.78-84

Image removed due to copyright restrictions. Figure 1: Pharmaceutical and Biotech R&D expenditure ($ bn) v/s Number of NME/BLA Approvals, the US, 199a5-2010. In: Pharmaceutical Research and Development (R&D) - Increasing Efficiency through Information Technology and Externalization. GBI Research, May 14, 2010.

See: http://www.giiresearch.com/press/image/GBI214253.gif.

NMEs approved by the FDA: Jan-June 2013

Agent	Lead company	Indication
Alogliptin	Takeda	Type 2 diabetes
Mipomersen sodium	Genzyme	Homozygous familial hypercholesterolaemia
Pomalidomide	Celgene	Multiple myeloma
Ado-trastuzumab emtansine*	Genentech	HER2-positive metastatic breast cancer
Ospemifene	Shionogi	Moderate to severe dyspareunia
Technetium Tc-99m tilmanocept	Navidea	Lymphatic mapping in breast cancer/melanoma patients
Gadoterate meglumine	Guerbet	Contrast agent to visualize disruption of the blood-brain barrier
Dimethyl fumarate	Biogen Idec	Relapsing multiple sclerosis
Canagliflozin	Janssen	Type 2 diabetes
Fluticasone furoate plus vilanterol trifenatate	GSK	Chronic obstructive pulmonary disease
Radium Ra-223 dichloride	Bayer	Castration-resistant prostate cancer
Dabrafenib mesylate	GSK	*BRAF*^{V600E}-positive unresectable or metastatic melanoma
Trametinib dimethyl sulphoxide	GSK	*BRAF*^{V600E}- or *BRAF*^{V600K}-positive unresectable or metastatic melanoma

Source: "FDA Approvals for First Half of 2013." *Nature Reviews Drug Discovery* 12 (2013): 568.

*Approved as a biologics license application

Nat. Rev. Drug Discovery 2013, Vol. 12, pp. 568

Revenues from global generics and biogenerics market

Image removed due to copyright restrictions. Figure 3, Revenues from global generics and biogenerics market 2002-2007. In: Prabakar, S. "Widening Innovation-Productivity Gap in the Pharmaceutical Industry - New Challenges and Future Directions," Frost & Sullivan Market Insight, April 22, 2008.
See: http://www.frost.com/prod/servlet/market-insight-print.pag?docid=128394740.

Opportunities for Pharmaceutical Development

- **Unprecedented number of new chemical entities to investigate**

  Products of biotechnology revolution

- **New technologies for investigating complex biological systems**
- **New technologies for measuring drug effects**
- **New technologies for predicting outcomes**
- **Integrating New Technologies Effectively will be KEY**

Potential for Pharmaceutical Innovation from Current Scientific Advances

Improved Medicines to Address:

- **Unmet Medical Needs**
  - Treatments for known diseases that currently lack treatments
  - Treatments for diseases not yet recognized
- **Drug Efficacy**

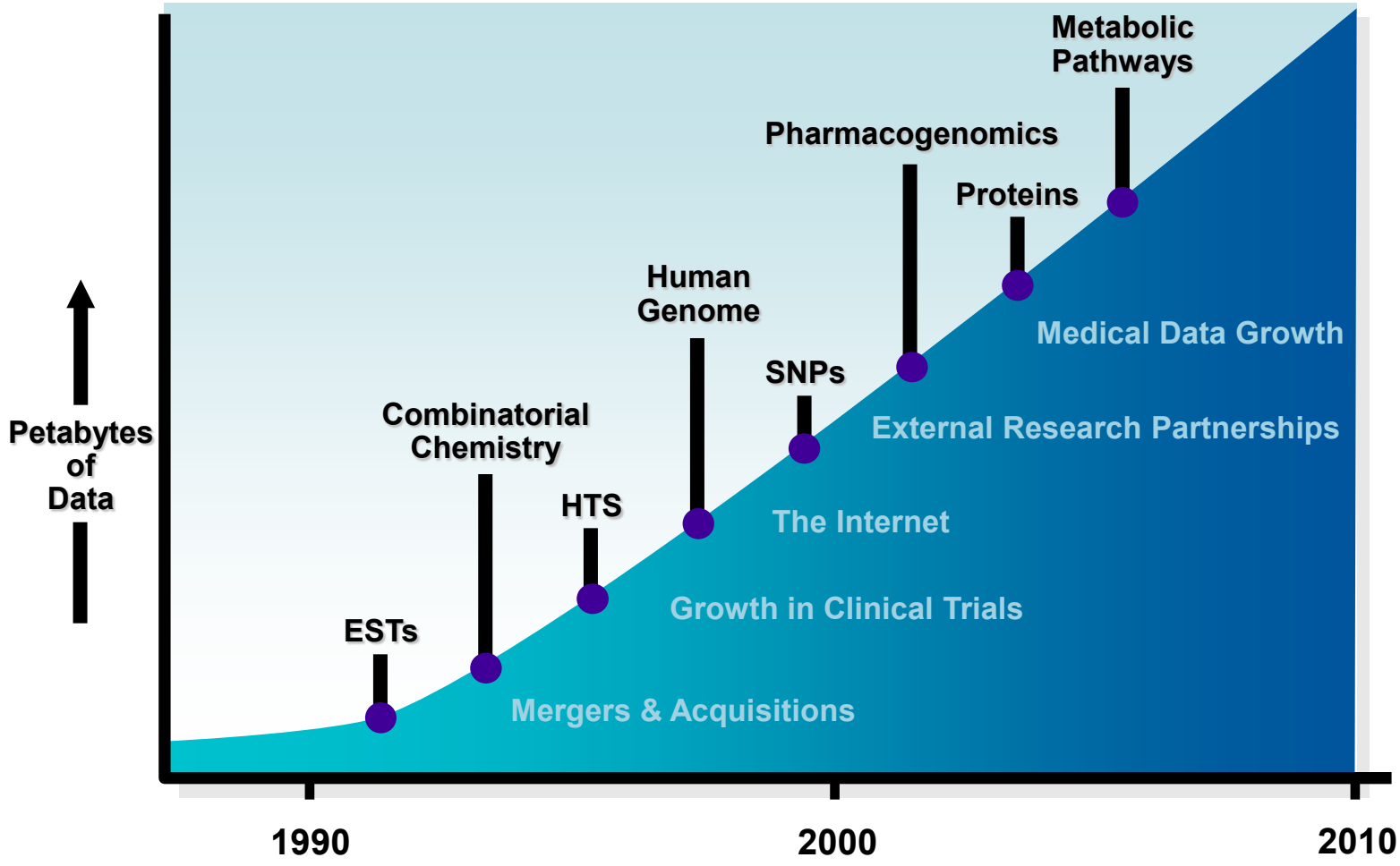
  More reliable patient response to therapies
- **Drug Safety**

  Fewer side effects

Challenges for Pharmaceutical Innovation from Current Advances

- Effective acquisition and integration of technological advances
- Conversion of data from genomics, proteomics and other high-throughput data-gathering technologies into medically relevant knowledge
- Successful application of that knowledge toward improved productivity in drug development

Explosion of Drug Discovery Data



Can Life Sciences Products Get To Patients?

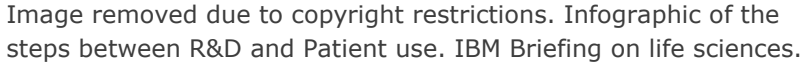


Image removed due to copyright restrictions. Infographic of the steps between R&D and Patient use. IBM Briefing on life sciences.

Conclusions

- Very rewarding industry
- Tremendous benefits (economic as well as quality of life)
- Storm clouds arising
  - Research deficit
  - Increasing regulatory pressures and cost containments
  - Global issues
  - Generics
  - Tremendous opportunities?

15.136J / 7.547J / 10.547J / 15.136J / ESD.691J / HST.920J / BCMP 230 Principles and Practice of Drug Development

Fall 2013