History & Overview of the Pharmaceutical/Biotechnology Industry

How were and how are drugs derived?

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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

[Image of Digitalis flower]

"Digoxigen acsv" by Calvero - Own work. Licensed under Public domain via Wikimedia Commons.
# Some Plant-Derived Pharmaceuticals

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

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

"Morphin - Morphine" by NEUROtiker0 - Own work. Licensed under Public domain via Wikimedia Commons.
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.

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.

Image is in the public domain.
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

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.

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

http://www.nobel.se/medicine/laureates/1908/ehrhlich-bio.html
http://www.chemheritage.org/EducationalServices/chemach/ppb/pe.html
http://casweb.ou.edu/pbell/Histology/Outline/contents.html
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 Salvarsan and compound 606 – Arsphenamine was introduced in the 1910s as the first effective treatment for syphilis.
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*

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

Convergence of Disciplines

Organic synthesis for making compounds

Analytical chemistry for isolating and purifying compounds from biological sources

Pharmacology and physiology for establishing models to test the efficacy of new compounds

Pharmaceutical Industry
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.
- 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-20\textsuperscript{th} century: drugs via molecular manipulation
- 1963, Destin Chemical, maker of OTC brands: BenGay, etc.
- 1981, first billion dollar drug Feldene
- 1999, 150\textsuperscript{th} anniversary and Forbes company of the year
- 2000, Warner-Lambert acquired
- 2002, Pharmacia-Upjohn acquired
- 2005, Lipitor sales reach $12.2 \times 10^9
- 2009, Purchased Wyeth

Alexander Fleming: Discoverer of penicillin and its antibacterial properties

Image removed due to copyright restrictions.
Photo of Feldene bottle & capsules.
Pfizer announces new commercial structure

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 transmembrane 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

Celecoxib

Structure from Wikimedia Commons. Image is in the public domain.
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.
## Improvements in Research Methodology from Integration of Combinatorial Chemistry

<table>
<thead>
<tr>
<th>Traditional</th>
<th>Today</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Libraries of molecules</td>
<td>Libraries of molecules</td>
<td>More Starting Compounds</td>
</tr>
<tr>
<td>Sequential Screening</td>
<td>Automated Parallel Screening</td>
<td>Increased Screening Capacity</td>
</tr>
<tr>
<td>Lead</td>
<td>Lead</td>
<td>More Lead Substances</td>
</tr>
</tbody>
</table>

Adapted from *In Quest of Tomorrow's Medicines* by Jürgen Drews
Therapeutic Classification of Approved Drug Therapy Targets

- Neurological: 29%
- Infections: 14%
- Hematopoiesis: 11%
- Endocrine: 11%
- Inflammation: 10%
- Cardiovascular: 10%
- Cancer: 8%
- Gastrointestinal: 3%
- Other: 4%
Biochemical Classification of Approved Drug Therapy Targets

- Membrane Receptors: 52%
- Enzymes: 22%
- Hormones/Growth Factors: 13%
- Other: 5%
- Ion Channels: 5%
- Nuclear Receptors: 2%
- DNA: 1%

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)

• **Results:**
  - Effective MAb therapies for several diverse indications
  - > 70 MAb therapies in clinical trials in 2000
Monoclonal Antibody Therapies

**Technological Innovations**

- Köhler & Milstein
  - Monoclonal antibodies
  - 1975

  - Mouse-Human Chimeric Antibodies
  - 1984
  - 1986

- Antibody Engineering techniques for creating humanized Abs
  - 1991-1996
  - 1997
  - 1998
  - 2001
  - ➤ 2009

**FDA-approved clinical application**

- OrthoClone/OKT3
- ReoPro
- Zenapax, Rituxan
- Simulect, Synagis, Remicade, Herceptin
- Campath
- ➤ Several NCE

FDA approved antibody-based therapeutics

Image removed due to copyright restrictions. FDA Approved Antibody-based Therapeutics
FDA approved antibody-based therapeutics (continued)

Image removed due to copyright restrictions. FDA Approved Antibody-based Therapeutics
FDA approved antibody-based therapeutics (continued)

Image removed due to copyright restrictions. FDA Approved Antibody-based Therapeutics

http://www.immunologylink.com/FDA-APP-Abs.html
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
FDA approved antibody-based therapeutics (continued)

Image removed due to copyright restrictions. FDA Approved Antibody-based Therapeutics
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

- 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)
- 1996, Sandoz and Ciba-Geigy merge to form Novartis
Amount ($) invested in R&D by pharmaceutical and biotech companies worldwide has been steadily increasing.

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.
Figure 1: Pharmaceutical and Biotech R&D expenditure ($ bn) v/s Number of NME/BLA Approvals, the US, 1995-2010. In: Pharmaceutical Research and Development (R&D) - Increasing Efficiency through Information Technology and Externalization. GBI Research, May 14, 2010.

## NMEs approved by the FDA: Jan-June 2013

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

*Approved as a biologics license application

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Revenues from global generics and biogenerics market

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

- Petabytes of Data
- Combinatorial Chemistry
- ESTs
- HTS
- Human Genome
- SNPs
- Pharmacogenomics
- Proteins
- Metabolic Pathways
- Medical Data Growth
- Mergers & Acquisitions
- External Research Partnerships
- Growth in Clinical Trials
- The Internet

1990
2000
2010
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?