Small Molecule Development
*From Inception to Market*

MacMillan Group Meeting
1-11-12
by
Anthony Casarez
Major Objectives

- Familiarize you with the process of drug discovery and development.

- Provide detail about optimization parameters.

- Frame the medicinal chemist’s role in the process.

- Relay opinions of leaders in the field regarding the future and direction of drug discovery.
Overview

The process can be divided into two major portions

- Preclinical

Overview

The process can be divided into two major portions

First Step

Target Discovery

Preclinical

Target Identification

Target Discovery

- Identification of a suitable target is the first step of any small molecule agonist/antagonist program.

Is the target the active site?

- Is the target the allosteric site?

What is known about the protein in question regarding the disease mechanism?

Classes of Disease mechanisms

- Genetic disorders
- Infection
- Immune/autoimmune disease
- Trauma from injury or organ failure
- Multicausal disease

Target Identification

Target Discovery

- Identification of a suitable target is the first step of any small molecule agonist/antagonist program.

  ![Diagram](image)

  (a) Competitive inhibition
  (b) Noncompetitive inhibition

- What is known about the protein in question regarding the disease mechanism?
- Is the target “druggable?”

### Druggability

- Access to cellular compartment
- Resistance susceptibility
- Transport mechanisms (cellular pumps)
- Side effects due to protein homology
- Toxicity from critical function inhibition

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
<th>Therapeutic Use</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agonist</strong></td>
<td>A ligand which increases the activity of a receptor, leading to increased receptor-mediated response.</td>
<td>To treat deficiency in endogenous agonist secretion or action (reduced receptor sensitivity)</td>
<td>Insulin: treatment of Type I diabetes. Epinephrine: b-adrenergic receptor agonist; smooth muscle relaxant for treatment of asthma and cardiac arrest</td>
</tr>
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<td><strong>Inverse agonist</strong></td>
<td>A ligand which decreases the constitutive activity of a receptor, leading to decreased receptor mediated response</td>
<td>To reduce excessive constitutive receptor activity.</td>
<td>None: Although many drugs are now known to have inverse agonist properties, there are no drugs marketed because of their inverse agonist properties.</td>
</tr>
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<td>A ligand which does not change the activity of a receptor but competes for residence time with the substrate in the active site</td>
<td>To block endogenous agonist action</td>
<td>Atenolol: b1-adrenergic antagonist used for treatment of hypertension, angina pectoris and acute myocardial infarction. Loratadine: H1 histamine receptor antagonist used for the treatment of allergic rhinitis</td>
</tr>
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<td><strong>Allosteric modulator</strong></td>
<td>A ligand that regulates receptor function by binding to a site distinct from that of the natural ligand.</td>
<td>To dampen or augment the activity of the endogenous agonist. Unlike the effect of antagonists, effects of allosteric modulators on endogenous agonist activity are saturable</td>
<td>Cinacalcet: positive allosteric modulator of the calcium-sensing receptor used for the treatment of secondary hyperparathyroidism</td>
</tr>
<tr>
<td><strong>Functionally-selective agonist</strong></td>
<td>A ligand that activates predominantly one of several responses coupled to a receptor</td>
<td>Improved therapeutic selectivity</td>
<td>None: Functionally selective ligands hold the promise of improved therapeutic efficacy with reduced adverse effects by targeting specific signaling pathways coupled to a single receptor subtype.</td>
</tr>
</tbody>
</table>

### Nomenclature

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*Loratadine*: H1 histamine receptor antagonist used for the treatment of allergic rhinitis |
| **Allosteric modulator**    |                                                                           |                                                      |                                                                          |
| **Functionally-selective agonist** |                                                                     |                                                      |                                                                          |

Target Validation

Knockout Mice

- Transgenic mice can be a useful tool to study the function of a particular protein
Target Validation

Knockout Mice

- Transgenic mice can be a useful tool to study the function of a particular protein

- Gene suppression is indicated by a phenotypic response like hair color

- Heterozygous mice can be bred to produce homozygous mice with the gene fully knocked-out
Target Validation

Knockout Mice
- Transgenic mice can be a useful tool to study the function of a particular protein

Clinical Data
- Has the target been validated from previously developed therapeutics?
- Is there a safety or efficacy profile?

Chemical Biology
- What is known about the biological pathways of the disease?
- Has a small molecule chemical knockout produced a phenotypic response?

In Vitro

- Outside of the organism; isolated enzyme or cell based assays

- Monitors a surrogate readout (reporter)

- More cost effective than animal studies

- Can usually be performed in a High Throughput (HTS) Manor

- Does it correspond to the target directly?

**Assay Development**

In Vitro

- Outside of the organism; isolated enzyme or cell based assays
- Monitors a surrogate readout (reporter)
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- Can usually be performed in a High Throughput (HTS) Manor
- Does it correspond to the target directly?

*The key to successful assay is accurate target readout*

Assay Development

In Vivo

- Inside the living organism
- Monitors biological efficacy and pharmacology in tandem
- The inadequacy of animal models is believed to be the major roadblock in pharmaceutical development

Hit to Lead

Preclinical Compound/Library Synthesis

Preclinical studies
- Research team formed and objectives set
- Novel chemicals synthesized
- Chemicals tested for efficacy and safety in test tubes and animals. Results used to choose drug candidate.
- Formulation, stability scale-up synthesis, chronic safety in animals
- Company files Investigational New Drug (IND) application with FDA

Clinical studies
- FDA reviews NDA
- Company files New Drug Application (NDA)
- Phase III: large clinical trials in many patients
- Phase II: studies in patients (efficacy)
- Phase I: studies in healthy human volunteers

Drug is approved for marketing

Hit Generation

High Throughput Screening

- Once a reliable in vitro assay is developed
- Aimed at rapidly screening a large compound collection(s)
- Can run 96, 384, or 1536 well plates

A large number of “hits” were coming from HTS screens that were not indicative of aqueous solubility (because they were dissolved in DMSO) which in turn possessed abysmal pharmacological properties.

The proceeding guidelines aimed to avoid producing further “hits” but more “leads”

**Lipinski’s 5**

- Not more than 5 hydrogen bond doners (–NH_n, or –OH)
- Not more than 10 hydrogen bond acceptors
- Molecular mass ≤ 500 daltons
- Partition coefficient (log P) ≤ 5

*substrates for biological transporters are exceptions*

As these rules only address absorption, revisions have been made regarding truly successful development.
Guidelines Revised

- Following **Lipinski’s rules** for drug design has **significant limitations**
- **Rotatable bonds and polar surface** area are now commonly **included** in the guidelines
- Collection analysis showed that 65% of compounds with 7 or fewer rotatable bonds possessed ≥ 20% oral bioavailability and < 25% of compounds with > 10 rotatable bonds had ≥ 20% bioavailability. **Flexibility affects absorption**

![Graph showing optimal drug-like space](image)

**Churcher et al.**
- logP ≤ 3
- PSA > 75 Å,
- MW = 100-250 Da
- Aromatic rings ≤ 3
- Few sp² centers

**Hit to Lead**

**Prevailing Strategies**

- **Target oriented synthesis (TOS)** – Accesses a precise region of chemical space usually based on a preexisting “privileged structure”

- **Combinatorial Chemistry** – Uses a common core structure with points of diversity e.g. $R_1$, $R_2$, and $R_3$ can generate $N_{R_1} \times N_{R_2} \times N_{R_3}$ possible structures

- **Diversity oriented synthesis (DOS)** – Aims to drastically explore chemical space utilizing complexity (3-dimensional) and diversity (appendage, stereochemical, skeletal) generating reactions.


*Figure 1. Comparison of TOS (A), medicinal and combinatorial chemistry (B), and DOS (C). Each three-dimensional plot is meant to represent the chemical product or collection of products derived from a single synthesis pathway. Each axis plots a calculable or measurable property of a small molecule (for example, molecular weight, solubility). A) The aim in TOS is to synthesize a single target structure having known or predicted properties (red sphere). B) The goal in medicinal and combinatorial chemistry is to synthesize a collection of analogues (blue spheres) of a target structure having known or predicted properties (red sphere). C) The aim in DOS is to populate chemistry space broadly with complex and diverse structures having unknown properties (blue spheres) as a first step in the small molecule discovery process. In some ways, these three approaches to synthesizing small-molecules represent points along a continuum.*
Hit to Lead

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**TOS**

**Target oriented synthesis (TOS)** – Accesses a precise region of chemical space usually based on a preexisting “privileged structure”

- A “privileged structure” refers to a core, comprising of a significant portion of the molecule’s size, that generally possess biological activity.
- Most privileged structures also possess 2 or more rings

![Indole Leads](image)

NPY₃, 0.8 nM  
NK₁, 0.8 nM  
5HT₆, 0.7 nM

**Hit to Lead**

**Target oriented synthesis (TOS)** – Accesses a precise region of chemical space usually based on a preexisting “privileged structure”

**Combinatorial Chemistry** – Uses a common core structure with points of diversity e.g. $R^1$, $R^2$, and $R^3$ can generate $N_{R1} \times N_{R2} \times N_{R3}$ possible structures

Rational Design

Target oriented synthesis (TOS) – Accesses a precise region of chemical space usually based on a preexisting “privileged structure”

Combinatorial Chemistry – Uses a common core structure with points of diversity e.g. $R^1$, $R^2$, and $R^3$ can generate $N_{R1} \times N_{R2} \times N_{R3}$ possible structures

- Both can also implement rational design which is the design of a molecule or core structure based on key interactions predicted within a binding pocket
- Rational design requires X-ray or NMR structural data

Agouron’s AIDS drug nelfinavir (Viracept) was based on a rational design model
Hit to Lead

Preclinical

Testing/Optimization

Lead Optimization

**ADMET**

**Absorption** – The process by which a drug proceeds from the site of administration to the systemic circulation

**Distribution** – Movement of drug molecules from systemic circulation to the various tissue and organs of the body

**Metabolism** – Mechanism by which a drug is chemically converted to another substance, usually more polar and easily excreted

**Excretion** – Clearance of the unchanged drug (and possible metabolites) through the kidneys (urination), liver (fecal), or lungs (gas)

**Toxicity** – Drug or drug metabolites leading to organ/system failure and eventually permanent damage or death

Absorption

Passive

- Involves dissolution and uptake through intestinal cell membranes through **passive diffusion**.
- Since most target administrations are oral (to maximize patient compliance) this is thought to be the **main mechanism** from which drugs enter the body.

Carrier Mediated

- Involves active transport of a drug into the cell via membrane proteins. Authors of the below paper assert that **active transport** is actually predominant.

Absorption
In Vitro Models

Caco-2 cell line
- Derived from human colorectal carcinoma; widely used due to expression of tight junctions, mirovilli, and a number of enzymes (peptidases, esterases, p-glycoprotein, uptake transporters), and bile acids that are characteristic intestinal absorptive cells
- Expression of P-glycoprotein (PgP) or MDR1 (multidrug resistance protein 1) provides information about active drug efflux
- In vivo correlation with passive drug uptake has been well established though requires 21 day incubation period

MDCK cell line
- Similar to Caco-2 but derived from dog kidney; only requires 3 day incubation
- Can be transfected with human MDR1, providing useful data

Lack of CYP3A4, a metabolizing enzyme, limits predictive power
Best when used in combination with metabolic stability (hepatocyte) assays

Absorption

In Vivo

Bioavailability (F)

- A measure of the amount of drug that is actually absorbed from a given dose.
- Limited by dissolution, permeability, gut motility, ionization, and first pass (loss of drug as it passes through sites of elimination before entering circulation) effects.
- When metabolism is mainly hepatic (liver) then F can be represented as: 
  \[ F = F_a(1-E_h) \]
  where \( F_a \) = intestinal fraction absorption, \( E_h \) = metabolic hepatic extraction ratio

Area Under the Curve (AUC)

- Directly derived from concentration of drug in systemic circulation from either oral or intravenous doses
- Comparison of \( AUC_{oral} \) to \( AUC_{iv} \) allows for the calculation of F where
  \[ F = \frac{AUC_{oral}/Dose_{oral}}{AUC_{iv}/Dose_{iv}} \]

Formulation can matter

- Vitamin C absorption from powdered form
- Vitamin C absorption from liposomal encapsulation

(data from Azantis Inc.)

Distribution

Volume of Distribution

- Apparent volume of distribution (Vdss), inferred from system exposure or by actual tissue measurement, is a theoretical volume to estimate drug distribution.
- Defined by the steady state of drug entry and exit from the central compartment to the tissue compartment.
- In units of L/kg of body weight and allows for the calculation of drug half-life ($T_{1/2}$) from $T_{1/2} = \frac{0.693 \times Vdss}{Cl}$ where Cl is clearance.

Predictive Methods

Allometry scaling: Human Vdss is extrapolated as the responding body weight compared to anatomical, physiological, and biochemical similarities in mammals.

Distribution

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Predictive Methods

**Allometry scaling**: Human Vdss is extrapolated as the responding body weight compared to anatomical, physiological, and biochemical similarities in mammals

**Proportionality method**: Compares free fraction \( (f_P) \) of drug in plasma of dog to that of human to estimate Vdss

**Average Fraction Unbound in Tissue Method**: After \( (f_{ND}) \) of tissue is calculated from the Oie-Tozer equation for each preclinical species, the average value is assumed for humans which can then be used to calculate Vdss

Distribution

Drug-Protein Binding

- Called free fraction ($f$) which is the extent that a drug binds to tissue ($f_{ND}$) or serum ($f_{P}$) proteins
- In serum the two major proteins of concern are $\alpha_1$-acid glycoprotein (44,000 D) and serum albumin (65,000 D); macromolecular complex formation restricts distribution to tissue
- Equilibrium dialysis and ultracentrifugation are methods used to assess ($f$)

Serum albumin with simultaneous (unrealistic) molecules of known transport

Rendering shows actual location of binding for various biomolecules (some fatty acids) but in reality would only bind one at a time

Rendered by Prof. Stephen Curry Imperial College, London

Distribution

Brain Penetration

- The brain is separated from the circulatory system by the **blood-brain barrier (BBB)**, preventing the uptake of many drugs.
- Physiochemical properties such as **charge**, **molecular weight**, and **lipophilicity** are of utmost importance when designing CNS drugs.
- Along with Caco-2 and MDCK cell lines, **models** to study uptake include **brain-blood partitioning**, **brain perfusion**, the **indicator dilution technique**, **brain uptake index**, the **capillary depletion technique**, and **intracerebral microdialysis**.

Metabolism

Phase I

- Often in the form of direct **hydrolysis, reduction, or oxidation** performed in the **liver** (though metabolism does happen in other tissues)
- Commonly performed **hydrolases, reductases, the cytochrome P450 enzyme family, monoamine oxidases (MAO’s), and flavin-containing monooxygenases (FMO’s)**

Excessive alcohol consumption = compromised liver function

Metabolism

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\[
\begin{align*}
\text{Hydrolysis} & : R = X = O, S, \text{or NH} \\
\text{Oxidation} & : R^3 N R^4 \xrightarrow{\text{MAO}} \text{R}^1 R^2 \\
\text{Oxidation/Hydrolysis} & : P450 \xrightarrow{\text{mEH}} \text{OH} \xrightarrow{\text{mEH}} \text{OH}
\end{align*}
\]

\[mEH = \text{microsomal epoxide hydrolase}\]

Metabolism

Phase II

- Usually **conjugating reactions**, appending a polar moiety to either the parent substrate or that after Phase I metabolism

- The two most prominent forms of conjugation are **sulfation** and **glucuronidation**

**Sulfation**

Sulfation reaction diagram

**Glucuronidation**

Glucuronidation reaction diagram

**Metabolism**

**Phase I**
- Often in the form of direct **hydrolysis, reduction, or oxidation** performed in the liver (though metabolism does happen in other tissues)
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- The two most prominent forms of conjugation are **sulfation** and **glucuronidation**

**Predictive Methods**
- **LCMS, LCMS/MS, and NMR** can all be used to identify metabolites
- Hepatocytes (**liver cells**), microsomes (**endoplasmic reticulum fragments**), and the **cytosol** can all be used in vitro to determine metabolites
- Intrinsic metabolic clearance (**CL_{int}**) can be calculated from microsome and hepatocyte scaling factors

Excretion

Renal (Kidney)

- Filters xenobiotics directly from the blood stream via passive diffusion or active transport by three processes: glomular filtration, tubular secretion, and tubular reabsorption
- The kidney directs filtrates into the bladder which allows for urinary excretion
- Renal excretion is the sum of the rate of filtration plus secretion minus rate of reabsorption and can be calculated by: $C_{IR} = \frac{\text{excreted amount/time interval}}{\text{mean plasma}}$

Fig. (13). Drug transporters located in the renal tubule cells showing both uptake transporters (yellow arrows) and efflux transporters (green arrows). Only transporters that have been shown to transport drugs are shown; there are additional transporters that transport endogenous compounds, but these are outside of the scope of this review. OAT, organic anion transporter; OCT, organic cation transporter; MRP, multidrug resistance related protein; MDR, multidrug resistance protein.

**Excretion**

**Hepatic (Liver)**

- Excretion can happen prior to or after metabolism of a xenobiotic (foreign substance) via passive diffusion or active transport into the bile duct.
- The bile duct leads to the duodenum (small intestine) which allows for **fecal excretion**.
- **Biliary clearance** can be calculated by measuring bile flow and drug concentration in plasma and bile: \[ CL_B = \frac{[\text{bile}] \times [\text{bile flow}]}{[\text{plasma}]} \]

Fig. (12). Drug transporters located in the hepatocytes showing both uptake transporters (yellow arrows) and efflux transporters (green arrows). Only transporters that have been shown to transport drugs are shown; there are additional transporters that transport endogenous compounds, but these are outside of the scope of this review. NTCP, sodium taurocholate cotransporting polypeptide; OATP, organic anion transporting polypeptide; OCT, organic cation transporter; MRP, multidrug resistance related protein; MDR, multidrug resistance protein; BSEP, bile salt export pump; BCRP, breast cancer related protein.

Excretion

Summary of Excretion Pathways

Toxicology

Organ Toxicity

- Function of three main determinants: **Intrinsic toxic** property of a chemical, **local concentration** within an **organ**, capability of **host defense** to **detoxify** and **cope** with **chemical injury**
- Medicinal chemists should be aware of **traditional toxic functionalities** but those liabilities are not always severe depending on ADME for that particular compound
- All measures should be taken to **assess toxicity** in vitro before administration to a mammal


Toxicity

Genetic Toxicity

- **Carcinogens** can be mutagenic or non-mutagenic.
- Mutagenic carcinogens induce **DNA sequence mutations**
- The **Ames test** and **VITOTOX® assay** both test for mutagenic toxicity base on a bacterial genotoxic response.

Hepatic Toxicity

- A **major cause** of post-market **withdrawal** of medications. Many conditions contribute to this withdrawal though four major ones are steatosis, cholestasis, phospholipidosis, and reactive intermediates
- **Steatosis is the accumulation of fatty acids** and is caused by the inhibition of β-oxidation of long-chain fatty acids which increases triglyceride concentration within the body
- **Cholestasis is the impairment of bile flow** and can lead to jaundice which hospitalizes 2-5% of cases and ~20% of the elderly
- **Reactive metabolites (electrophiles, free radicals)** can form covalent bonds with biomolecules leading to reduced function and genetic mutation
- **Phospholipidosis** involves the **accumulation of excess phospholipids** in cells accompanied by coincidental toxicities

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Toxicity

Cardio Toxicity

- **Interruption** of the *repolarization phase* of the ventricular cells due to interference of the drug with cardiac potassium channels (action potential repolarization)

- **Binding** of a number of drugs to the *hERG* (the human *Ether-à-go-go*-Related Gene) K+ channel has been shown to exhibit significant **cardio toxicity** and is now tested for in vitro via a competitive inhibition assay

Drug-Drug Interactions

- **Inhibition of CYP3A4** (a cytochrome P450 enzyme) confers potential inability to metabolize other ingested drugs

- **Inhibition of PgP** (multidrug resistance protein) inhibits cell efflux of potential toxins

Sanguinetti, M.; Ng, K. H. The Ion Channel lab, University of Utah http://www.cvrri.utah.edu/ms-lab/blockers.htm (accessed Jan 2012)
Medicinal Chemistry Feedback Loop

- Synthesis of New Compounds
- Rational Modifications
- ADMET Data
- 3-6 Years
Development

Process Optimization

Preclinical

Development

Pre-Clinical FDA Requirements
- Pharmacological profile of drug
- Perform acute toxicity in at least two animal species
- Short term toxicity studies based on duration of clinical trials

Process Chemistry
- Availability of cost-effective starting materials
- Minimization of synthetic and purification steps
- Scale-up validation
- Reduced cost of goods (COGS)

Chemistry, Manufacturing and Controls (CMC)
- Active Pharmaceutical Ingredients (API)
- Characterization
- Manufacturer and method of manufacture
- Process controls
- Specifications and purity profiles
- Container system for drug substance and storage
- Stability

New Drug Investigation Filing

Preclinical

IND filing

Clinical Trials

Clinical Trials

Phase I

- Healthy humans (20-80)
- Determine human ADMET values and side effects from increasing dose.
- Phase 1a is a shorter, safety assessment period
- Phase 1b is a longer evaluation which may include patients
- 40% failure rate

Phase II

- Tested in affected patients by randomized controlled trials (RCT)
- Determines efficacy along with short and long term side effects
- Phase 2a involves 100-300 patients, often hospitalized to determine dose response, patient type, frequency of dosing
- Phase 2b is more controlled and rigorously demonstrates efficacy
- 62% failure rate of successful phase I passes

Phase III

- Expanded with both controlled and uncontrolled trials meant to allow extrapolation to the general population
- Must be controlled and compared to standard of care
- Use double-blind study when practical and ethical
- Be randomized and of adequate size
- 40% failure of successful phase II passes
- 23% failure of successful phase III passes at registration

New Drug Application

Major Requirements

- Chemistry, manufacturing and control, samples
- ADMET data both clinical and non-clinical
- Clinical data (efficacy, safety, dosing, etc.)
- Safety update 120 days after NDA application
- Statistical analysis, case report tabulations and forms
- Patent information including certification

Review

- Assesses sponsor’s claims about drug safety and effectiveness.
- Reviewers can request reanalysis of drug performance in a patient subset or in the original population pool
- After a rigorous vetting process an action letter is sent of approval, approvable, or non-approvable with sufficient justification

Phase IV (overview)

- Monitors safety and long-term side effect after is it approved for prescription
- Evaluates effectiveness in larger population pools (general public)
- Retraction of an approved drug is common

## Phase IV Withdrawals

<table>
<thead>
<tr>
<th>Drug (Indication)</th>
<th>Approved</th>
<th>Withdrawn</th>
<th>Years Delay</th>
<th>Reason Drug Is Pulled</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fenfluramine (weight loss)</td>
<td>1973</td>
<td>1997</td>
<td>24</td>
<td>Pulmonary hypertension, heart valve disease</td>
<td>Wyeth-Ayerst</td>
</tr>
<tr>
<td>Posicor (hypertension, angina)</td>
<td>1985</td>
<td>1998</td>
<td>13</td>
<td>Reduced liver enzymes</td>
<td>Roche</td>
</tr>
<tr>
<td>Seldane (allergies)</td>
<td>1985</td>
<td>1997</td>
<td>12</td>
<td>Heart problem when taken with other drugs</td>
<td>Hoescht Marion Roussel</td>
</tr>
<tr>
<td>Hismanal (allergies)</td>
<td>1988</td>
<td>1999</td>
<td>11</td>
<td>Heart arrhythmia</td>
<td>Janssen Pharmaceutica</td>
</tr>
<tr>
<td>Propulsid (nocturnal heartbeat)</td>
<td>1993</td>
<td>2000</td>
<td>7</td>
<td>Cardiac arrhythmia</td>
<td>Janssen Pharmaceutica</td>
</tr>
<tr>
<td>Vioxx (pain)</td>
<td>1999</td>
<td>2004</td>
<td>5</td>
<td>Heart attack, stroke</td>
<td>Merck</td>
</tr>
<tr>
<td>Baycol (anti-cholesterol)</td>
<td>1997</td>
<td>2001</td>
<td>4</td>
<td>Muscle deterioration</td>
<td>Bayer</td>
</tr>
<tr>
<td>Rezulin (anti-diabetes)</td>
<td>1997</td>
<td>2000</td>
<td>3</td>
<td>Liver toxicity</td>
<td>Pfizer</td>
</tr>
<tr>
<td>Razar (antibiotic)</td>
<td>1997</td>
<td>1999</td>
<td>2</td>
<td>Severe cardiovascular problems</td>
<td>Glaxo</td>
</tr>
<tr>
<td>Raplon (airway muscle relaxant)</td>
<td>1999</td>
<td>2001</td>
<td>2</td>
<td>Bronchospasm</td>
<td>Organon</td>
</tr>
<tr>
<td>Duract (pain)</td>
<td>1997</td>
<td>1998</td>
<td>1</td>
<td>Hepatitis, liver failure</td>
<td>Wyeth-Ayerst</td>
</tr>
<tr>
<td>Lotronex (IBD)</td>
<td>2000</td>
<td>2000</td>
<td>9 months</td>
<td>Ischemic colitis, constipation</td>
<td>Glaxo</td>
</tr>
</tbody>
</table>

It requires between **800 million and 1.4 billion dollars** of investment for **one** approved drug.

Of all of the **millions upon millions** of compounds screened, only **one** FDA approved drug (**sunitinib**, Pfizer, renal carcinoma) came from a **combinatorial library**.

**Natural product** derived structures (parent compounds, derivatives, analogues, and mimics) still comprise of **57.7%** of all FDA **approved drugs**.

“**People who say natural product research has had its day are being arbitrary and are limiting their options for no good reason**” —Barry Trost

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The Future

Drug Targets

- At present day ~3,000 human proteins are “druggable” but only a fraction of these will be safe and efficacious drug targets with ~200 targeted by current therapies
- Many new protein targets should be identified with high throughput crystallography and functional genomics
- Proteomics will always be a source of target production

New Drugs

- A modification of Lipinski’s rules will allow chemists to produce more lead-like molecules
- New methodologies that tolerate polar functional groups will help to reduce the synthesis of more lipophilic (poor solubility) libraries
- Structure based drug design will increase as more crystallography data is produced
- Pharmaceutical companies and synthetic chemists will need to better collaborate in order to define and address the biggest challenges plaguing drug discovery
- The Grand Challenge (proposed by Schreiber): Building a comprehensive database of bioactive compounds and screening data, finding a small molecule modulator of each function of every human protein
- Pharmaceutical companies will gladly take, but will they share?