2b. Where Drugs Come From: SBDD versus Phenotype
## Targets Which Have Yielded Clinical Candidates With the Help of Structure-Based Drug Design

### Therapeutic Area

<table>
<thead>
<tr>
<th>Therapeutic Area</th>
<th>Targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>ACE, Renin, Thrombin, Factor VII, Factor Xa</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>Carbonic anhydrase <em>(1st approved drug, Dorzolamide, 1995)</em></td>
</tr>
<tr>
<td>Inflam / immun</td>
<td>Human neutrophil elastase, P38, IMPDH, ICE, COX2, MMP-X, JAK3</td>
</tr>
<tr>
<td>Cancer</td>
<td>Purine nucleoside phosphorylase, Thymidylate synthase, VEGF kinase (KDR), Aurora-2, CDK2, EGF kinase (erbB), Glycinamide ribonucleotide formyltransferase, HSP90, BTK, ......</td>
</tr>
<tr>
<td>Antivirals</td>
<td>HIV protease, Influenza sialidase (neuraminidase), HCV protease, HCV polymerase, rhinovirus 3C protease, rhinovirus coat proteins</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Caspases (broad), secretory PLA2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>PPAR-gamma, DPP-IV, Aldose reductase</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Cathepsin K</td>
</tr>
<tr>
<td>Various CNS</td>
<td>GSK3 kinase, Acetylcholinesterase, BACE</td>
</tr>
</tbody>
</table>
Fragment Based Design: A Specialized Form of SBDD

X-ray or NMR

Yields weakly potent starting points -- *but often with excellent physical properties*

Linking is challenging

Fragment Based Design of BACE Inhibitors

Figure 1. Fragment-based NMR screening 10000 compounds from a custom database and identified novel micro-molar and milli-molar leads for novel BACE-1 inhibitors_modern

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Phenotypic Screening’s Track Record

First-in-class

Followers


Probes entire pathway(s) - can be multiple classes of hits

Hits are excellent tools for interrogating disease biology

Encourages clear thinking about screening collection & assays

Focuses chemistry on phenotype, pharmacology, tox

Courtesy of Nature. Used with permission.
Phenotype-Driven Science Requires Different Thinking

Biology:
- Probes entire pathway(s) - can be multiple classes of hits doing different things
- Target ID challenging (but cmpds are good tools)
- Ineffective without clear link between assay & disease
- Puts a huge emphasis on the quality of the assays

Chemistry
- Encourages clear thinking about screening collection
- May serendipitously find cmpds that hit multiple targets
- Provides a huge jump-start for chemistry teams
- Focuses chemistry on phenotype, pharmacology, tox
- Good starting molecules may be elusive
- SAR may never make sense

Development
- May be harder to explain tox findings
- There will be internal skeptics
- Regulatory agencies may be nervous
3. How We Find Drugs: A Bit About Process & Philosophy
High-Level View of R&D Process

Of course reality isn’t quite this clean and linear...
Idealized Drug R&D Process: A Little More Detail

Thx to Scott Garman

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Lead optimization: modifying the structure of a confirmed hit to improve its characteristics.

*Goal is to produce a preclinical drug candidate.*

Confirmed hits are evaluated in secondary assays, and a set of related compounds, called analogs, are synthesized and screened.

The testing of analog series results in structure-activity relationships (SAR): quantitative information that correlates changes in chemical structure to biological & pharmacological data.
“Lead opt” is highly iterative.

Leads are assessed in a range of assays. Med chemists modify cmpds to optimize pharmacological properties e.g. bioavailability or stability. These new analogs are then tested to determine potency, selectivity, and MOA.

Biomarkers are essential to show cmpds are working as intended & get to the site of action in required amounts.

New information of all kinds comes in constantly, often changing the design parameters.

The “lead opt” process continues until a defined drug profile is achieved that warrants clinical testing.
Formulation & delivery are closely linked. i.v. delivery of a novel drug might require a different formulation than oral, b/c metabolic stability or solubility can differ significantly.

Formulation can dramatically affect absorption, e.g. through their interaction with cell membrane of the GI tract.

Formulation and delivery are highly specialized fields of research, and formulation scientists are now involved in drug discovery and development programs from the early stages.

Much effort is centered around new ways of formulating known drugs to increase their efficacy or safety profiles.
The decision to take a new drug candidate into development entails a significant commitment in terms of money, resources, and time.

90% failure, huge cost, average time 12 years.

Drug development requires rigorous attention to standards; it is a highly regulated process.

Careful attention to development issues should begin at the start of discovery! (Systems perspective.)

Details of development covered later in the course.
4. Serendipity and Avoiding Micro-Management
Leo Sternbach reasoned that his old dyes, which reminded him of the chemical structure of thorazine, might make a decent starting point for his investigations. His idea was to add a basic amine to his old molecules since this was often necessary for biological activity.

Sternbach prepared ~40 new cmpds and screened them for muscle relaxant, sedative, and anticonvulsant properties. Nothing worked... until the last compound!

He investigated the chemistry and found that a key intermediate was entirely different -- this compound had undergone an unexpected molecular rearrangement to produce a different ring system called a **benzodiazepine**. This molecule eventually became a drug called *Librium*.

He then came up with a better molecule: **Valium**.
By 1970, in the USA 20% of women and 7% of men were using “minor tranquilizers and sedatives” – mostly benzodiazepines.

“Kids are different today” I hear every mother say
Mother needs something today to calm her down
And though she's not really ill
There's a little yellow pill
She goes running for the shelter of a mother's little helper
And it helps her on her way, gets her through her busy day...

“Mother’s Little Helper,” The Rolling Stones, 1966
“I construe my function as a director of research as mainly to create the kind of environment which is conducive to the advancement of learning. That sounds pompous, but this is all a director can do. You cannot direct people to have ideas, and no one can have a big enough grasp of the whole of biological science to be able to say which lines of research are certainly going to be fruitful and which are certainly going to be a waste of time. So what one has to do is simply create an environment and an atmosphere in which science flourishes.”

— Peter Medawar

Nobel Prize in Physiology or Medicine, 1960
5. Why This is So Hard: Some Specific Challenges
5.1 Natural Products
“The Dose Makes the Poison”

Atropa belladonna
(Belladonna, Deadly Nightshade)

Agrippina the Younger
Sister of Caligula
Mother of Nero

Muscarinic antagonists – parasympathetic system blockers

Atropine
Scopolamine (Hyoscine)
Hyoscyamine
Natural Products

Source of MANY drugs

However, the “rules” governing “drug-likeness” are mysterious

If you need to chemically modify the drug – horrific synthetic & design challenges

And, if you can’t make it in bulk by fermentation – nightmare!

Product of the bacterium Streptomyces hygroscopicus

Discovered in soil sample on Easter Island (Rapa Nui)

First developed as antifungal agent; later discovered to be immunosuppressive

In 2010 shown to prolong the life of middle-aged mice

Antiproliferative; being studied in various cancers

Product of the bacterium Streptomyces hygroscopicus

Discovered in soil sample on Easter Island (Rapa Nui)

First developed as antifungal agent; later discovered to be immunosuppressive

In 2010 shown to prolong the life of middle-aged mice

Antiproliferative; being studied in various cancers

Sirolimus (rapamycin)

Rapamune™ (1999)

Inhibits response to IL-2; approved for use in organ transplant rejection
5.2 Pharmacoeconomics
Is the Drug Worth the Cost?

Dronedarone for the Treatment of Atrial Fibrillation: A NICE Single Technology Appraisal

McKenna, Claire¹; Maund, Emma²; Sarowar, Muhammad¹; Fox, David²; Stevenson, Matt³; Pepper, Chris⁴; Woolacott, Nersys²; Palmer, Stephen¹

From the evidence presented by the manufacturer, dronedarone appeared highly cost effective in each of the population groups examined compared with using standard baseline therapy alone as first-line treatment, or compared with sotalol or amiodarone as first-line AAD, with incremental cost-effectiveness ratios (ICERs) well below £20 000 per QALY gained. The ICER for dronedarone relative to class 1c agents was around £19 000 per QALY. Although the evidence presented by the manufacturer indicated that dronedarone was cost effective, the estimates of treatment effect relative to other AADs and safety in the longer term were highly uncertain. The NICE Appraisal Committee in its preliminary guidance did not recommend the use of dronedarone for AF. However, following the response from a large number of consultees and commentators, NICE revised its preliminary guidance to allow the use of the drug in a specific subgroup of AF patients with additional cardiovascular risk factors.

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5.3 Polypharmacy
“Polypharmacology”

Prozac is used for major depression, obsessive-compulsive disorder, panic disorder, and other indications.

Mechanism: selective serotonin reuptake inhibitor (SSRI) – block the serotonin transporter (SERT)

However, also a potent $5\text{-HT}_{2C}$ receptor antagonist, and an agonist of the $\sigma_1$-receptor... unclear exactly how these activities contribute!
Threading a Needle

A French army doctor was seeking drugs to relax surgical patients – “sedation without narcosis”

Rats became tolerant of aversive stimuli

The drug was superior in calming and reducing shock; patients reported improved well being.

It was taken into manic patients: spectacular!

Chlorpromazine (Thorazine) - 1954

Antipsychotic

“The single greatest advance in psychiatric care”

What chlorpromazine blocks (A PARTIAL LIST): Dopamine receptors (subtypes D1 – D5); Serotonin receptors (5-HT1 and 5-HT2); Histamine receptor H1; α1- and α2-adrenergic receptors; M1 and M2 muscarinic acetylcholine receptors; ....
Threaded a Needle

Sorafenib is quite “dirty” but is nonetheless useful for some cancers (RCC, HCC). Its effectiveness is definitely related to its polypharmacy (VEGF, PDGF, raf).

Gleevec is used in chronic myelogenous leukemia (CML), gastrointestinal stromal tumors (GIST), some myelodysplastic syndromes, and a range of other niche indications.

Reasonably selective, Gleevec still hits TK domains of abl (Abelson proto-oncogene), c-kit and PDGF-R (platelet-derived growth factor receptor).

Perspective

Published online: 19 March 2009 doi:10.1038/ni.1701

Selectivity and therapeutic inhibition of kinases: to be or not to be?

Kamran Ghoreschi¹, Arian Laurence¹ & John J O'Shea¹

Protein kinases, which serve critical functions in signaling pathways in all cells, are popular therapeutic targets. At present, eight kinase inhibitors have been approved in the United States, each of which shows nanomolar potency. Although the initial goal was to generate inhibitors with a high degree of selectivity, recent experience has revealed that many of these approved compounds target more than one kinase. Surprisingly, this promiscuity is less problematic than one would have imagined; indeed, it opens new therapeutic opportunities. In this Perspective, we discuss the present status of Janus kinase inhibitors—a new class of immunosuppressive drugs—and the advantages and disadvantages of selectively inhibiting this class of kinase.

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5.4 Late Failure
(Sometimes Even After Drug Launch)
Pfizer Pulls Torcetrapib

Loss leaves a gaping hole in company’s late-stage pipeline

Lisa M. Jarvis

**Pfizer** dropped a bombshell over the weekend by pulling the plug on what is considered in its new drug pipeline, the cholesterol agent torcetrapib. The company’s shares were down as much as 15% on Monday, the first day of trading following the news.

"This spells the death of what is arguably the most important development program at Pfizer," says Morgan Stanley stock analyst Jami Rubin, who notes that the scientific community was particularly shocked by the news.

Pfizer halted development of the drug after an independent data safety monitoring board found a significant rise in mortality rates among patients taking both torcetrapib and Pfizer’s Lipitor cholesterol drug. The board’s analysis of a Phase III study of 15,000 patients showed that 82 deaths occurred in torcetrapib/Lipitor patients, compared with 51 deaths in patients taking Lipitor alone.

Torcetrapib is part of an emerging class of drugs that aim to raise levels of high-density lipoprotein, or "good" cholesterol, by blocking cholesterol ester transfer protein (CETP). The drug was meant to be a companion to Lipitor, Pfizer’s top-selling product, which lowers low-density lipoprotein, or "bad" cholesterol.

Concerns over the safety of torcetrapib had been raised as early as last March, when Pfizer said it caused a rise in systolic blood pressure. But the company continued to display strong confidence in the drug, focusing on its blockbuster potential at a meeting with financial analysts just last week (C&EN, Dec. 4, page 14).

The loss of this critical product will undoubtedly push Pfizer to accelerate its plans to cut costs and improve operating efficiencies. Last week, Pfizer said it would trim its U.S. sales force by about 20%, eliminating roughly 2,000 jobs. The company will also ramp up its licensing efforts in order to maintain its goal of bringing six new drugs to the market annually starting in 2010.

The failure of torcetrapib puts a cloud over other CETP inhibitors in development, including products in the pipelines of **Merck** and **Roche**. "It’s the result nobody wanted to see and probably means no CETP inhibitors will reach the market until their benefits have been clearly demonstrated in large outcomes trials," says Deutsche Bank analyst Barbara Ryan.
Interim Review Alters Phase Three Studies of Novel Antithrombotic Therapy

By Duke Medicine News and Communications

Following review of interim data by the independent Data Safety Monitoring Board (DSMB) for two large-scale, global phase three trials evaluating vorapaxar, an investigational anti-clotting medication, researchers at Brigham and Women’s Hospital (BWH) and the Duke Clinical Research Institute (DCRI) announced today they are following the recommendations of the DSMB to discontinue study drug in one study among a subset of patients and discontinue study drug in the other trial in which the protocol target number of endpoint events had been reached.

Vorapaxar is a protease activated receptor-1 (PAR-1) inhibitor, which is a new class of anti-platelet heart medication that acts on a new target in heart disease, standard therapy, including aspirin and drugs such as clopidogrel.

The trials were designed to evaluate vorapaxar for the secondary prevention of cardiac events among patients with acute coronary syndromes and prior heart attack, stroke, or peripheral arterial disease.

The Return Of Vorapaxar, This Time For Post-MI Patients

The once highly-promising novel antiplatelet agent vorapaxar, widely thought to be dead on arrival after unacceptably high serious bleeding rates were found in two large clinical trials, has now returned to active duty. On Sunday the drug’s sponsor, Merck, announced that it would seek approval of the drug, with a narrower indication than originally planned, based on new data from a prespecified analysis of the TRA 2P-TIMI 50 trial presented at the ESC and published simultaneously in the Lancet.
### Post Marketing recalls

<table>
<thead>
<tr>
<th>Drug (Indication)</th>
<th>On market</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)</td>
<td>1985</td>
<td>1998</td>
<td>13</td>
<td>Reduced liver</td>
<td>Roche</td>
</tr>
<tr>
<td>Seldane (allergies)</td>
<td>1985</td>
<td>1997</td>
<td>12</td>
<td>Heart problems when taken with other drugs</td>
<td>Hoescht</td>
</tr>
<tr>
<td>Hismanal (allergies)</td>
<td>1988</td>
<td>1999</td>
<td>11</td>
<td>Heart arrhythmia</td>
<td>Janssen Pharmaceuticals</td>
</tr>
<tr>
<td>Propulsid (nocturnal heartbeat)</td>
<td>1993</td>
<td>2000</td>
<td>7</td>
<td>Cardiac arrhythmia</td>
<td>Janssen Pharmaceuticals</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>Razor (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>Lotoronex (IBD)</td>
<td>2000</td>
<td>2000</td>
<td>9 mos</td>
<td>Ischemic colitis, constipation</td>
<td>Glaxo</td>
</tr>
<tr>
<td>Lumiracoxib (pain)</td>
<td>2006</td>
<td>2007</td>
<td>1</td>
<td>Hepatitis, liver failure</td>
<td>Novartis</td>
</tr>
<tr>
<td>Zelnorm (constipation)</td>
<td>2004</td>
<td>2007</td>
<td>3</td>
<td>Cardiac events</td>
<td>Novartis</td>
</tr>
</tbody>
</table>

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The Saga of the Floxacin (fluoroquinolone) Antibiotics

Ciprofloxacin (Cipro)  
Approved 1987

Ofloxacin (Floxin)  
Approved 1990

Trovafloxacin (Trovan)  
Approved 1998, withdrawn 1999
Liver damage

Temafloxacin (Omniflox)  
Approved 1992, withdrawn 1992  
Allergic rxns, hemolytic anemia

Grepafloxacin (Raxar)  
Approved 1997, withdrawn 1999  
QT prolongation

Trovafoxacin (Trovan)  
Approved 1998, withdrawn 1999  
Liver damage
5.5 Generics: A Rising Bar
Past Successes → More Challenges Today

- Drugs with new mechanisms appear once in a while...
- Drugs with old mechanisms but better properties (e.g. once a day dosing, fewer side effects) come out regularly...
- Drugs become generic: cheaper, well understood

Hydrochlorothiazide
Diuretic

Amlodipine
Ca channel blocker

Valsartan
Angiotensin II Blocker

Enalapril
ACE inhibitor

Propranolol
Beta blocker

Aliskiren
Renin inhibitor
Going Generic

Table of projected annual sales figures for various drugs removed due to copyright restrictions.

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5.6 Getting Across Barriers
Oral Absorption: Balancing Many Factors

Factors contributing to poor oral bioavailability

- Low solubility/Slow dissolution
- GI tract instability
- Metabolic instability*
- Biliary excretion
- Limited passive diffusion
- Active efflux*
- Poor absorption
- First pass effect

*From enterocytes in small intestine
**In gut wall or liver for first pass effect
Microtubules (light blue), actin filaments (dark blue), ribosomes (yellow & purple), soluble proteins (light blue), kinesin (red), small molecules (white) and RNA (pink)
5.7 Metabolism & Tox
Cytochrome P450 ("CYPs")

- Family of enzymes that oxidize drugs
- CYP inhibition has important effects:
  - Some CYPs metabolize drugs into the bioactive form
  - Some CYPs help to eliminate drugs from the body by metabolizing them
- "Drug – drug interaction: Drug #1 blocks a CYP, which prevents the metabolism of Drug #2, causing Drug #2 to become toxic or fail to work.
- CYPs can also be induced, which can lead to the same issues.
Metabolic Transformations: Many Enzymes

**Phase I: oxidation or hydrolysis**

**Phase II: Conjugation**

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Please, Don’t Make This Molecule
5.8 “Drug-Likeness” & “Rules”
“Drug-Like” Compounds: Playing the Odds

Courtesy of Molinspiration Cheminformatics. Used with permission.
Have We Learned Anything?

What Do Medicinal Chemists Actually Make? A 50-Year Retrospective
W. Patrick Walters, Jeremy Green, Jonathan R. Weiss, and Mark A Murcko

J. Med. Chem., Just Accepted Manuscript • Publication Date (Web): 14 July 2011

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