1. The Mission & Its Challenges
I don't like standing near the edge of a platform when an express train is passing through. I like to stand right back and if possible get a pillar between me and the train. I don't like to stand by the side of a ship and look down into the water. A second's action would end everything. A few drops of desperation.”

-- WINSTON CHURCHILL (1874-1965)
In the 2\textsuperscript{nd} century AD, Soranus of Ephesus treated melancholia and mania patients with alkaline waters which we now know contain very high levels of Li.
Hippocrates, Galen, Pliny the Elder and others knew that willow bark could ease aches and pains and reduce fevers. It has long been used in Europe and China to treat these conditions and is also mentioned in texts from ancient Egypt, Sumer, and Assyria.

The active extract of the bark, called **salicin** was isolated to its crystalline form in 1828. Soon thereafter, **salicylic acid** was separated in its pure state, and **aspirin** was discovered 40 years later.
What is a Drug?

A substance used as a medication or in the preparation of medication – it is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease.

For our purposes: a drug must be approved by a regulatory body and be recognized in an official pharmacopoeia or formulary.
Diverse Ways to Contribute to Discovering New Medicines

- Discovering therapeutics: many scientific disciplines
- Inventing new technologies that are used in R&D
- Clinical – POC; safety; defining medical needs; Dx; patient stratification
- Basic biology: understanding pathways, targets, etc.
- Scale up / manufacturing
- Drug delivery – formulations, nanoparticles, nano-factories, …
- Funding & Policy: NIH, FDA, CDC, insurance companies, congress, …
- Systems / process engineering, decision theory, etc.
- The human element - org structure, leadership, risk-taking, motivation
- Science journalism
What is Medicine?

Medicine is the applied science or practice of the diagnosis, treatment, and prevention of disease.

What is “Therapy”?

Therapy refers to the whole collection of interlinked components used in medicine to treat a particular situation – drugs, devices, diagnostics, surgery, support services, and everything else.

Photograph courtesy of Richard Mortel on flickr. License: CC-BY-NC-SA.
The Fundamental Biochemical Hypothesis

If you create a molecule that can intervene in a disease-relevant biochemical process in the body – for example, by blocking or activating the function of a receptor or enzyme – this may translate into clinical benefit.

If it works – great! You’ve confirmed the biochemical hypothesis and you are on the way to a drug.

If it fails –
- Maybe your biochemical hypothesis was wrong
- Maybe the body compensated for your drug somehow
- Maybe you didn’t deliver enough of the drug to the right place for long enough
The Current Environment

Many acute diseases are now well treated

Chronic diseases, generally, are not:

- Management vs. cure
- Side effects
- Lack of knowledge to identify patients early, track the progress of their disease, and to “customize” their treatment
What Problem Are We Solving?

For diseases with no treatment, or poor treatments, we seek true breakthroughs.

For diseases that are already well served by existing medicines (e.g. hypertension) we seek more incremental advantages in safety, cost, convenience, or effectiveness.

In the real world these improvements can be quite useful but are often belittled as “me-too”
The principal challenge: converting a chemical with interesting biological properties into a drug by solving multiple complex issues “simultaneously” (in a single molecule).
ADME: You’ll Hear This a Lot …

**Absorption** - the process of a substance entering the blood circulation.

**Distribution** - the dispersion of substances throughout the fluids and tissues of the body.

**Metabolism** (or Biotransformation) - the irreversible chemical transformation of parent compounds into daughter metabolites.

**Excretion** - the removal of the substances from the body. In rare cases, some drugs irreversibly accumulate in body tissue.
Downward Trends in New Drug Approvals

NME = New Medical Entities. BLA = Biologics License Applications.
Nature Biotechnology (2012), 30, pp 41-49

Courtesy of Macmillan Publishers Limited. Used with permission.
Sharper Declines in Some Disease Areas

DECLINING ANTIBACTERIAL APPROVALS
(PAST 25 YEARS)

1983-1987: 16
1988-1992: 14
1993-1997: 10
1998-2002: 7
2003-2007: 4
2008-2009: 1

Image by MIT OpenCourseWare.
The Truly Staggering Cost of Inventing New Drugs

<table>
<thead>
<tr>
<th>Company</th>
<th># Drugs Approved</th>
<th>R&amp;D Spending Per Drug ($Mil)</th>
<th>Total R&amp;D Spending 1997-2011 ($Mil)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AstraZeneca</td>
<td>5</td>
<td>11,791</td>
<td>58,955</td>
</tr>
<tr>
<td>GlaxoSmithKline</td>
<td>10</td>
<td>8,171</td>
<td>81,708</td>
</tr>
<tr>
<td>Sanofi</td>
<td>8</td>
<td>7,909</td>
<td>63,274</td>
</tr>
<tr>
<td>Roche Holding AG</td>
<td>11</td>
<td>7,804</td>
<td>85,841</td>
</tr>
<tr>
<td>Pfizer Inc.</td>
<td>14</td>
<td>7,727</td>
<td>108,178</td>
</tr>
<tr>
<td>Johnson &amp; Johnson</td>
<td>15</td>
<td>5,886</td>
<td>88,285</td>
</tr>
<tr>
<td>Eli Lilly &amp; Co.</td>
<td>11</td>
<td>4,577</td>
<td>50,347</td>
</tr>
<tr>
<td>Abbott Laboratories</td>
<td>8</td>
<td>4,496</td>
<td>35,970</td>
</tr>
<tr>
<td>Merck &amp; Co Inc</td>
<td>16</td>
<td>4,210</td>
<td>67,360</td>
</tr>
<tr>
<td>Bristol-Myers Squibb</td>
<td>11</td>
<td>4,152</td>
<td>45,675</td>
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<tr>
<td>Novartis AG</td>
<td>21</td>
<td>3,983</td>
<td>83,646</td>
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<tr>
<td>Amgen Inc.</td>
<td>9</td>
<td>3,692</td>
<td>33,229</td>
</tr>
</tbody>
</table>

Sources: (1) InnoThink Center For Research In Biomedical Innovation; (2) Thomson Reuters Fundamentals via FactSet Research Systems. Taken from Matthew Herper, Forbes Magazine, “The Medicine Show,” 10 Feb 2012.
Omeprazole (Prilosec)
Racemate
Approved in 1989

Proton pump blocker - specific inhibition of H+/K+-ATPase in gastric parietal cells

Generally well tolerated drug
Both isomers get converted to active form of the drug
Going off patent in 2001

Esomeprazole (Nexium)
S-isomer of omeprazole
Approved in 2000

Onset of Symptom Relief: Esomeprazole Versus Omeprazole

© John Wiley & Sons. All rights reserved. This content is excluded from our Creative Commons license. For more information, see http://ocw.mit.edu/help/faq-fair-use/.
Laboratory studies have shown Sucrosa (placebo) to be occasionally effective in the treatment of pain and discomfort associated with chronic rhinitis, allergies, hives, sinusitis, arthritis conditions, ankylosing spondylitis, fibromyalgia, gout, lupus, osteoarthritis, psoriatic arthritis, reactive arthritis, rheumatoid arthritis, asthma, acute and chronic pain, low back pain, inflammatory bowel disease (IBD), abdominal pain, ulcerative colitis, constipation, diarrhea, dyspepsia (indigestion), intestinal gas, heartburn, hemorrhoids, irritable bowel syndrome (IBS), lactose intolerance, constipation, motion sickness, ankle pain, tendinitis, bursitis, heel spurs, knee pain, lower back pain, muscle cramps, tinnitus, vertigo, asthma, erectile dysfunction, migraine headaches, attention deficit disorder (ADD), bedwetting, lactose intolerance, rheumatoid arthritis, sleep disturbance, rosacea, scleroderma, shingles, insomnia, jet lag, narcolepsy, sleep apnea, somnolence, urinary incontinence, urinary tract infections, premenstrual syndrome, and yeast infections.

Side effects associated with the use of a placebo include alterations in heartbeat; increased blood pressure and cold extremities; muscle weakness, stiffness, and spasms; muscle and bone pain; nervousness; decreased mental sharpness; tremor; headache; abnormal sensation; vertigo; sleep disturbance; mood and personality changes; alterations in speech and movement; memory impairment; confusion and depression; abnormality; stomach upset; diarrhea; dry mouth; constipation; gas; thirst; acid reflux; difficulty swallowing; changes in appetite; burping and inability of the tongue to move; flushing; hot flashes; sweating; itching; rash; acne; skin reaction to sunlight; difficult or rapid breathing; dryness or discomfort of the throat or nose; nose bleed; yawning and sinus disorder; cold-like symptoms; cough; hiccup; visual disturbances; ringing in the ears; ear pain; eye discomfort; swelling or tearing; alterations in hearing and smelling; visual intolerance to light; and bad taste; allergic reactions including swelling of face, lips, tongue, and/or throat, which may cause difficulty in breathing and/or swallowing; wheezing; hives; rash; severe sloughing of the skin; chills; heat sensitivity; swelling; bloating; hangover effect; fever; fainting; dizziness on standing up; warm/cold sensations; dehydration; and changes in urination and menstruation.
FDA NEWS RELEASE

For Immediate Release: May 23, 2011
Media Inquiries: Erica Jefferson, 301-796-4988, erica.jefferson@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA

FDA approves Incivek for hepatitis C

The U.S. Food and Drug Administration today approved Incivek (telaprevir) to treat certain adults with chronic hepatitis C infection. Incivek is used for patients who have either not received interferon-based drug therapy for their infection or who have not responded adequately to prior therapies. Incivek is approved for use with interferon therapy made up of peginterferon alfa and ribavirin.

The current standard of care for patients with chronic hepatitis C infection is peginterferon alfa and ribavirin taken for 48 weeks. Less than 50 percent of patients respond to this therapy.

The safety and effectiveness of Incivek was evaluated in three phase 3 clinical trials with about 2,250 adult patients who were previously untreated, or who had received prior therapy. In all studies patients also received the drug with standard of care. In previously untreated patients, 79 percent of those receiving Incivek experienced a sustained virologic response (i.e. the infection was no longer detected in the blood 24 weeks after stopping treatment) compared to standard treatment alone.

The sustained virologic response for patients treated with Incivek across all studies, and across all patient groups, was between 20 and 45 percent higher than current standard of care.

The studies indicate that treatment with Incivek can be shortened from 48 weeks to 24 weeks in most patients. Sixty percent of previously untreated patients achieved an early response and received only 24 weeks of treatment (compared to the standard of care of 48 weeks). The sustained virologic response for these patients was 90 percent.

When a person achieves a sustained virologic response after completing treatment, this suggests that the hepatitis C infection has been cured.

Sustained virologic response can result in decreased cirrhosis and complications of liver disease, decreased rates of liver cancer (hepatocellular carcinoma), and decreased mortality.
F.D.A. Approves New Cystic Fibrosis Drug

By ANDREW POLLACK
Published: January 31, 2012

The first drug that treats an underlying cause of cystic fibrosis, rather than just the symptoms, was approved by the Food and Drug Administration on Tuesday, more than 22 years after the gene responsible for the disease was first identified.

The drug, called Kalydeco and developed by Vertex Pharmaceuticals, counters the effect of one specific mutation in the gene that accounts for 4 percent — or about 1,200 — cystic fibrosis cases in the United States.

“This is a breakthrough therapy for the cystic fibrosis community because current therapies only treat the symptoms of this genetic disease,” Dr. Janet Woodcock, the director of the Center for Drug Evaluation and Research at the F.D.A., said in a statement issued by the agency.
F.D.A. Approves a Drug for Cystic Fibrosis

By ANDREW POLLACK
Published: January 31, 2012

The first drug that targets the underlying disease process, rather than just the symptoms, has been approved by the Food and Drug Administration on Thursday. Kalydeco, manufactured by Vertex Pharmaceuticals, is expected to be more expensive than any other drug on the market, with patients expected to pay around $300,000 per year per patient.

The Lung Function Scale...

FRIDAY, JULY 20, 2012

80%!!!!!!!

I can’t believe it! I’ve gone from 67% to 80% in 5 weeks and I’ve also gained 3KG!!!!! AMAZING!

As I mentioned in my previous post I have had a cold and I went to the hospital to do blood tests, get antibiotics and do a sputum culture earlier in the week. I called the CF coordinator at the hospital yesterday to get the results from the tests and mentioned that I have still had a cold. I decided to go into the hospital yesterday to see my doctor to see if I could prevent my cold from getting worse. I was so nervous to do the lung function- I think I’ve secretly been avoiding doing it because I was so worried that it wouldn’t be what I wanted it to be. Mum bought me a little home lung function monitor a couple of days ago and I refused to try it out of fear!! I bit the bullet and decided I needed to face reality whether I liked it or not. I did my first test and it was 78%! I was amazed but suddenly 80% was within reach and I was determined to make it. On my second try and I made it and I’d compare the feeling to winning Tattslotto!! I had not been at 80% since August 2009. After, my doctor and I looked at a graph that showed all my lung functions from 09 to present- I wish I had of got a copy to put on my blog. If I can get one I’ll post it on here because it’s a very good visual representation of my decline in health over the past 2-3 years and my rapid increase in the past 5 weeks on KALYDECO!!! :-D
2. Where Drugs Come From: An Introduction
Sources of Drugs

“Nature”
- “Natural Products” – plants, minerals
- Animals – e.g. insulin, liver extracts
- Microbiological sources – e.g. penicillin

Synthetic / medicinal chemistry
- Often copied in some fashion from nature

Recombinant DNA -- biologicals (proteins, Ab)
Where Hits and Leads Come From

Random Screening
- In-house collections
- Purchased compounds
- Known drugs/drug candidates
- Combinatorial libraries (focused / diverse)
- Fragment libraries
- Natural products

Directed Methods
- Endogenous ligands / substrates
- Known compounds
- Active metabolites
- Target families (chemogenomics)
- Virtual screening / “structure-based design”
- De novo design

Rydzewski, p240
Many Drugs Copy From Nature

MVT-101 (NCI) – 1st gen HIV-PR inhibitor
Broad Mechanisms

“Antagonists” / “inhibitors” – turn things down

“Agonists” / “potentiators” – turn things up

Orthosteric vs allosteric

Competitive, uncompetitive, noncompetitive

Fast on/off vs. slow on/off

Covalent vs. noncovalent

If covalent - reversible vs irreversible
High-Throughput Screening

Testing large libraries of compounds in multi-well plates in an automated, industrialized (robotic) way

96 wells per plate $\rightarrow$ 384 $\rightarrow$ 1,536 and even higher

Biochemical (binding, function) or cellular

Tiny quantities of material (by historical standards)

Became popular in the 1990s

Required completely different mindset ...
High-Throughput Screening Techniques

- Absorbance
- Fluorescence Intensity
- Fluorometric Imaging Plate Reader (FLIPR)
- Fluorescence Polarization (FP)
- Fluorescence Resonance Energy Transfer (FRET)
- Radioligand Displacement
- Scintillation Proximity Assay (SPA)
- Amplified Luminescent Proximity Assay (AlphaScreen)
- Surface Plasmon Resonance (SPR)

Rydzewski, p228
High-Throughput Screening Challenges

- Trade-offs: complexity, reagent availability, material requirements, equipment & reagent cost, data quality, ...

- What to screen!?“Diversity” … “drug-space” … “drug-likeness”

- Artifacts:
  - Compound fluorescence / quenching
  - Light scattering b/c of insolubility
  - Cytotoxicity
  - Reactive or aggregating compounds
  - Edge effects
  - Mechanical problems e.g. evaporation, sticking to plastic

Now largely understood & controllable
“The solution to pharma’s productivity problems” (?!)

Based on a simplistic belief in sheer numbers

But, there were a few problems:

\[ \frac{10^6}{10^{60}} = 0 \]

No clear definition of “diversity”

No clear idea of what “drug space” is, even for the targets we already know about

The chemistry was less robust than we all hoped; this led to boring cmpds with poor physical properties

Hard / expensive to intelligently screen \(10^6\) compounds

“Natural product-like” libraries that really weren’t
## Combi-Chem Then & Now

<table>
<thead>
<tr>
<th>Circa 1995</th>
<th>Circa 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large Libraries (~ $10^5$)</td>
<td>Smaller libraries, typically &lt; $10^3$</td>
</tr>
<tr>
<td>Many “Rule of 5” violations</td>
<td>Mostly “rule of 5” compliant</td>
</tr>
<tr>
<td>Many solid phase syntheses</td>
<td>Many solution phase syntheses</td>
</tr>
<tr>
<td>Often multiple cmpds per well</td>
<td>Usually one cmpd per well</td>
</tr>
<tr>
<td>Minimal purification</td>
<td>Extensive purification typical</td>
</tr>
<tr>
<td>Primarily used for diversity screening</td>
<td>Primarily used for property optimization</td>
</tr>
</tbody>
</table>

*Rydzewski, p246*
Diversity-Oriented Synthesis: Blending Natural Products With Combinatorial Design

Aurora Inhibitors Exhibit Variable Cell Activity Despite Consistent Enzyme Activity

<table>
<thead>
<tr>
<th></th>
<th>MK-0457</th>
<th>VRT-426</th>
<th>VRT-960</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aur-A Ki (nM)</strong></td>
<td>0.6</td>
<td>1.3</td>
<td>1.3</td>
</tr>
<tr>
<td><strong>Aur-B Ki (nM)</strong></td>
<td>18</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td><strong>Anti-Proliferation IC50 (nM)</strong></td>
<td>19</td>
<td>4</td>
<td>250</td>
</tr>
<tr>
<td><strong>Aur-A inhibition biomarker IC50 (nM)</strong></td>
<td>43</td>
<td>9</td>
<td>29</td>
</tr>
</tbody>
</table>

Anti-proliferation: $^3$H-thymidine incorporation at 96h in colo-205 cells
Aur inhibition biomarker: Auto-Pi of Aur-A at 2h in Hela cells

James Westcott, Philip Reaper, Mark Anderton, Peter Weber, Graham Cheetham, Peter Charlton, and John Pollard, Vertex UK, Presented at AACR annual meeting, 14 April 2007
Kinetics Are Consistent With Structural Hypothesis

$$EI + k_{on} \xrightarrow{k_{off}} EI$$

Open / active

$$EI + k^{*}_{on} \xrightarrow{k^{*}_{off}} EI^*$$

Closed / inactive

STEP 1: Moderate affinity

$$K_i = 11 \text{ nM}$$

VRT-426

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Source: Peter Charlton & John Pollard, Vertex Pharmaceuticals Ltd, UK
Kinetics Are Consistent With Structural Hypothesis

STEP 1: Moderate affinity
Ki 11nM

STEP 2: Isomerization and generation of tighter binding complex Ki* = 0.75 nM

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## Covalent Inhibitors

### Table 2. Targets, Indications, and Mechanism of Action of Covalently Interacting Small Molecules

<table>
<thead>
<tr>
<th>mechanism</th>
<th>target</th>
<th>indication</th>
<th>name of drug or representative drug</th>
<th>reacting functionality</th>
<th>reversibility</th>
<th>dose (mg)</th>
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</thead>
<tbody>
<tr>
<td>acylation</td>
<td>serine-type D-Ala-D-Ala carboxypeptidase</td>
<td>bacterial infection</td>
<td>amoxicillin*</td>
<td>β-lactam</td>
<td>irreversible</td>
<td>100–500</td>
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<tr>
<td></td>
<td>triacylglycerol lipase</td>
<td>obesity</td>
<td>orlistat</td>
<td>lactone</td>
<td>reversible</td>
<td>360</td>
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<td>acetylolefinesterase</td>
<td>Alzheimer’s disease</td>
<td>rivastigmine</td>
<td>carbamate</td>
<td>reversible</td>
<td>6–12</td>
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<td>β-lactamase</td>
<td>bacterial infection</td>
<td>clavulanate*</td>
<td>β-lactam</td>
<td>irreversible</td>
<td>500</td>
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<tr>
<td></td>
<td>prostaglandin epoxide synthase</td>
<td>pain</td>
<td>aspirin</td>
<td>ester</td>
<td>reversible</td>
<td>1000</td>
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<td></td>
<td>vitamin K epoxide reductase</td>
<td>anticoagulant</td>
<td>warfarin</td>
<td>coumarin</td>
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<tr>
<td></td>
<td>(warfarin-sensitive)</td>
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<td></td>
<td>enol–acyl carrier</td>
<td>bacterial infection</td>
<td>isoniazid</td>
<td>hydrazide</td>
<td>irreversible</td>
<td>300</td>
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<tr>
<td></td>
<td>protein reductase</td>
<td>(tuberculosis)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>aldehyde</td>
<td>alcoholism</td>
<td>disulfiram</td>
<td>disulfide</td>
<td>irreversible</td>
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<td></td>
<td>dehydrogenase</td>
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<td></td>
<td>UDP-N-acetylglucosamine-1-carboxyvinyltransferase alanine racemase</td>
<td>bacterial infection</td>
<td>fosfomycin</td>
<td>epoxide</td>
<td>3000</td>
<td></td>
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<tr>
<td>alkylation</td>
<td>(tuberculosis)</td>
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<td></td>
<td>GABA-ATPase</td>
<td>epilepsy</td>
<td>vigabatrin</td>
<td>amine</td>
<td>irreversible</td>
<td>3000</td>
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<td>aromatase</td>
<td>breast cancer</td>
<td>exemestane</td>
<td>methyl</td>
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<td></td>
<td>protacine</td>
<td>gastric epithelial hyperplasia</td>
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<td>H/K^+ ATPase</td>
<td>platelet aggregation inhibitor</td>
<td>clonazolam</td>
<td>thiol</td>
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<td>75</td>
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<td>(seleno-enzyme)</td>
<td>hyperthyroidism</td>
<td>propylthioracil</td>
<td>thiouracil</td>
<td>450</td>
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<td>hemiketal formation</td>
<td>serine protease</td>
<td>viral infection</td>
<td>VX-950 (1q)</td>
<td>ketoamide</td>
<td>reversible</td>
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<td>hepatitis C virus</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>NS3*</td>
<td>cancer</td>
<td>gemcitabine*</td>
<td>vinyl carbonate</td>
<td>≥ 150–200</td>
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<tr>
<td></td>
<td>Michael addition</td>
<td></td>
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<tr>
<td></td>
<td>ribonucleoside diphosphate reductase</td>
<td>cancer</td>
<td>gemcitabine*</td>
<td>vinyl carbonate</td>
<td>≥ 150–200</td>
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<td>thymidylate synthase</td>
<td>cancer (NSCLC)</td>
<td>flouxuridine*</td>
<td>unsaturated amide</td>
<td>reversible</td>
<td>0.1–0.6 (mg/kg)/d</td>
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<tr>
<td></td>
<td>ErbB1/2*</td>
<td>hyperplasia</td>
<td>HIKI-272 (1t)</td>
<td>unsaturated amide</td>
<td>reversible</td>
<td>n/a</td>
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<td>5-α-reductase</td>
<td>prostate</td>
<td>finasteride*</td>
<td>unsaturated amide</td>
<td>reversible</td>
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<td>MAO-B</td>
<td>Parkinson’s disease</td>
<td>selegiline*</td>
<td>acetylenic amide*</td>
<td>reversible</td>
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<td></td>
<td>_validator</td>
<td>diabetes</td>
<td>vildagliptin</td>
<td>nitrite</td>
<td>reversible</td>
<td>100</td>
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<tr>
<td></td>
<td>cathepsin K^+</td>
<td>osteoporosis</td>
<td>vildagliptin</td>
<td>nitrite</td>
<td>reversible</td>
<td>10–30</td>
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</tbody>
</table>

* Prodrugs are indicated in italics. * As determined from the FDA label or other medical references. * Because of the large number of drugs developed for these targets, one representative drug is indicated in the table. * Indicates functionality covalently modified by the catalyst. * Estimated dose. * Approved in Canada, U.K., and Mexico. * Under clinical investigation. * Dose = 1000 mg/m² weekly. The average body surface area of a person is approximately 1.5–2 m². * Several irreversible MAO inhibitors are on the market for the treatment of depression. *Weekly dose used in the clinical trial “MK0822 (Odanacatib) Late Phase II Dose-Finding Study” described at www.clinicaltrials.gov.
Telaprevir (Incivek): An Insurmountable HCV-PR Inhibitor

Oxyanion hole


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Irreversibles Don’t Have to Use Catalytic Residues

Epidermal growth factor receptor (EGFR) kinase inhibitors

Acrylamide moiety reacts with conserved cysteine

Discovered by screening against mutants resistant to other EGFR inhibitors

The HIV protease inhibitor amprenavir was approved by the FDA in 1999 but its limited water solubility requires the use of softgel formulation for delivery and multiple pills for a single dose.

After screening 60 prodrugs in in vitro and in vivo assays, the phosphate prodrug, fosamprenavir calcium (GW-433908), was selected for its high water solubility, solution and solid-state stability, and rapid conversion to the parent drug on the apical side of epithelium.

The prodrug is delivered from a solid dosage form with a lower pill burden, two tablets replacing eight amprenavir softgels.
Current Events With Commentary

Four Blogs Worth Checking Out

Derek Lowe
“In the Pipeline”

Bruce Booth
“lifeSciVC”

John LaMattina
Forbes

Matthew Herper
“The Medicine Show”
END OF PART 1