Introduction: A Refresher on Why Drug Discovery is Hard
Mt. Katahdin, Maine, “the knife edge trail” 3’ wide with 800’ drop on either side

Courtesy of Patrick Spinney on flickr. License: CC-BY.
LACK OF INFORMATION

Wrong molecule
Wrong delivery approach
Wrong target
Wrong indication

“It can blow at any seam”

- Harder problems
- Higher hurdles
- Poor processes / mgmt
- FUD (M&A; Wall Street)
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 spur, 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, somnolality, 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 spasm; 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 anddream 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 andsmelling; 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.
6. Deciding: Data Overload, Fear, Uncertainty, Bias, the whole mess
The principal challenge: converting a chemical with interesting biological properties into a drug by solving multiple complex issues in a single molecule.
But .. Data ≠ Knowledge … All these measurements approximate the human condition
“Every design balances--connects--dozens of values, like a conceptual mobile, and the weights of those values, their relative utility or attractiveness, are changing constantly.”

Fred Hapgood, *Up the Infinite Corridor: MIT and the Technical Imagination*
# It’s Not All Chance: **Behaviors** of Great Teams

<table>
<thead>
<tr>
<th><strong>DOING WHAT MATTERS</strong></th>
<th><strong>MINDSET</strong></th>
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<tbody>
<tr>
<td>Focus on patient needs</td>
<td>Challenge assumptions &amp; be open to surprises</td>
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<tr>
<td>Relentlessly solve high-value problems</td>
<td>Urgency</td>
</tr>
<tr>
<td>Curate the world’s relevant knowledge</td>
<td>Demonstrate resilience and ignore clues to quit</td>
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<tr>
<td>Learn how to interpret complex data</td>
<td>Communicate in all directions</td>
</tr>
<tr>
<td>Pay attention to details</td>
<td>Have a champion at senior levels</td>
</tr>
<tr>
<td>Develop appropriate validated readouts and use wisely</td>
<td>Take chances</td>
</tr>
<tr>
<td>Generate PK data early &amp; often</td>
<td>Be practical</td>
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Most oral drugs follow certain “rules” – MW <500, logP <5, and so forth.

But there are many drugs that break these rules ...

... and many molecules that follow the rules are not drugs.

We don’t understand the exceptions (in either direction).

Conclusion: there are some trends and patterns, dimly understood at best -- not actually “rules” at all ...

Cyclosporine
Cyclic undecapeptide
MW = 1203
7. Picking & Validating Targets
Rate-limiting step in R&D is usually confusion about basic biology

Drug Target Network Disease Patient
Target validation requires:
1. Demonstration critical involvement in a disease process;
2. Modulating the target is likely to have a therapeutic effect.

Validating a molecular target in vitro usually precedes the validation of the therapeutic concept in vivo; together this defines its clinical potential.

Validation involves studies in intact animals or cell-based models that can provide information about the integrative response of an organism to a pharmacological intervention.
Target Discovery & Validation (2 of 2)


Includes: large-scale exploration of gene function including the analysis of regulatory networks, biochemical pathways, protein-protein interactions, and the effects of gene or functional knockouts or up-regulation/gain-of-function.

Goal: to determine disease mechanisms & identify disease genes / markers. These results will indicate therapeutic strategies for the development of novel therapeutics.

Requires model systems (animal and cell) as well as high-throughput data of various kinds (well covered in this dep’t).
Classes of Biomarkers

Class 1 – Target occupancy
- Gives evidence the drug occupies the target
- Example – PET radioligand to measure $D_2$ receptor occupancy in schizophrenia

Class 2 – Target-Based
- Changes downstream from target occupancy specific to target
- Example – Elevated norepinephrine (NE) metabolite levels in the presence of an NE uptake (NET) inhibitor

Class 3 – Disease-Based
- Linked to biomarkers found previously in patients w. disease
- Example – Proteins expressed in plasma in schizophrenia patients vs. controls
PET Ligand for the CB-1 Receptor

Class 1 Biomarker

- Pre-clinical study in rhesus shows CB-1 receptor occupancy & displacement by candidate CB-1 antagonist
- Results of clinical study confirmed CB-1 receptor occupancy in humans
- PET ligand preparation and validation is resource-intensive

Courtesy of American College of Neuropsychopharmacology. Used with permission.
Schizophrenia as an Example

Class 3 Biomarker

Several disease-based (class 3) biomarkers available:

- Prepulse inhibition – responds to clozapine
- P50 gating – linked to DA, 5HT, NMDA challenges
- Auditory P300 – also abnormal in AD, BPD, ADHD
- Mismatch negativity – no response to clozapine
- Smooth eye pursuits – clozapine worsens

Both EEG and fMRI / BOLD monitoring

Cortical response variability is increased in schizophrenic patients relative to controls and clinically unaffected siblings – by EEG, BOLD

Courtesy of Macmillan Publishers Limited. Used with permission.

Alzheimer’s Disease: Example of Critical Need for Better Biomarkers

AD typically develops over many years, and clinical trials for a preventative agent would be prohibitively expensive.

Potential class 3 (disease progression) biomarkers include:
- CSF phospho-tau and b-amyloid (Ab\textsubscript{1-42})
- CSF, plasma and urine isoprostanes (inflammatory)

Figuring out new biomarkers for complex diseases like Alzheimer’s is just as great a contribution as discovering a new medicine – if not greater -- because it enables a whole field to progress far more rapidly.
8. Through a Glass, Darkly
Flying Blind

Medicine today is reactive (we treat sick people) & myopic (we have few tools to measure disease)

“The dirty little secret about medicine is that we physicians make decisions all the time based on woefully incomplete information.”

-- Paul Yock, MD, Stanford

“Flying Blind,” The Economist, 16 April 2009
The Need for Long-Term Thinking

From target discovery to the first approved drug against that target typically takes 30+ years.


A research project started now will not produce an approved drug until 2025-2030.

How should these incredibly long timelines influence our thinking?

Must consider many kinds of change -- demographics, novel therapies, technologies, basic science, etc.
“Everyone overestimates how much progress will be made in the next 2 years and underestimates how much will be made in the next 10.”

-- Bill Gates
“P4” Medicine

Medicine today is **reactive** (we treat sick people) & **myopic** (we have few tools to measure disease)...

... Medicine will gradually become **personalized, predictive, preventative, and participatory**.

- Diagnostics & omics → individualized care
- Risk factors understood
- Diseases eliminated before symptomatic
- Each of us bears greater responsibility for our health

Leroy Hood, inventor of protein sequencer, protein synthesizer, DNA synthesizer, ink-jet DNA synthesizer, & automated DNA sequencer
Some Coming Disruptions: Medicine circa 2030

- P4 medicine
- Widespread use of “regenerative” therapies
- Man - machine interface
- Therapy involves multiple diverse elements - not just “drugs”
- Far earlier and more accurate diagnosis; “ubiquitous self”
- Drugs against far more diverse targets (“undruggable”)
- Tests for disease progression and response to therapy
- Higher drug safety bar; better predictors of safety
- Reimbursement for results
- Routine & rational polypharmacy
- Preventative medicine; “neutraceuticals”
- Diverse, precisely targeted drug delivery mechanisms
- “Open source” pharmas
What Will “Therapy” Mean?

An *assembly of interlinked components* to manage the *entire disease life cycle*

- Drugs + regenerative approaches + devices + diagnostics + social network
- Participatory: at-home tests show benefits of therapy & motivate patients

**Focused R&D programs based on selected *subsets of patients* – therapy is personalized, predictive, and preventative**

- Each “disease” will be understood to be many related but distinct afflictions
- Biomarkers, diagnostics, and devices support patient selection & trial design
Regenerative Therapies:
Bioreactors and Skin Guns

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Far Earlier Diagnosis

Sarcosine levels predict severity of prostate cancer.


Troponin predicts MI.
Microscopic Needles: Painless Transdermal Delivery

University of Kentucky College of Pharmacy and the Georgia Institute of Technology

Transdermal drug delivery has proven successful in a number of applications, including pain management, congestive heart failure and hormone replacement ... but existing systems can only be used for a narrow range of compounds that easily pass through the skin.

New work: painlessly punch a series of microscopic holes in the outer layer of skin via pressing and removing a thumb-sized patch containing 50 stainless steel microneedles each about 620 microns -- about 1/40th of an inch -- in length. Next, gel containing naltrexone (a drug used for opiate and alcohol addiction) was applied to the prepared area, which was then covered by a protective dressing. Blood levels stayed constant for ~48 hours. Doses were 4X lower than oral administration and there were 10X lowered production of metabolites.

Two Drugs in One Package

The Pharmacologic Basis for Antibody-Auristatin Conjugate Activity.
Nanoparticle - Aptamer Bioconjugates

Docetaxel-encapsulated nanoparticles formulated with biocompatible & bio-degradable copolymer; surface functionalized with fluoropyrimidine RNA aptamers that recognize extracellular domain of prostate-specific membrane antigen. These bioconjugates:

- Get taken up more effectively into prostate cancer cells
- Exhibit reduced toxicity in vivo as measured by mean body weight loss
- Exhibit significantly enhanced efficacy in vivo: tumor reduction & survival

Targeted nanoparticle-aptamer bioconjugates for cancer chemotherapy in vivo. PNAS 2006, 103, 6320.
<table>
<thead>
<tr>
<th>Route</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral (PO)</td>
<td>Swallowed by mouth</td>
</tr>
<tr>
<td>Intravenous (IV)</td>
<td>Injected directly into the bloodstream as bolus or infusion</td>
</tr>
<tr>
<td>Subcutaneous (SC)</td>
<td>Injected under the skin</td>
</tr>
<tr>
<td>Transdermal</td>
<td>Applied as a patch or other device and transported through the skin</td>
</tr>
<tr>
<td>Topical</td>
<td>Applied onto the skin</td>
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<tr>
<td>Intramuscular (IM)</td>
<td>Injected into the muscle</td>
</tr>
<tr>
<td>Epidural</td>
<td>Injected into the epidural (outermost) space in the spinal cord</td>
</tr>
<tr>
<td>Suppository</td>
<td>Placed in the rectum</td>
</tr>
<tr>
<td>Intranasal</td>
<td>Sprayed into the nose</td>
</tr>
<tr>
<td>Buccal</td>
<td>Held between cheek and gum until dissolved</td>
</tr>
<tr>
<td>Sublingual</td>
<td>Held under the tongue until dissolved</td>
</tr>
<tr>
<td>Intraperitoneal (IP)</td>
<td>Injected within the peritoneal cavity (abdomen)</td>
</tr>
<tr>
<td>Intra-arterial</td>
<td>Injected into an artery</td>
</tr>
<tr>
<td>Intracerebral</td>
<td>Injected directly into the brain</td>
</tr>
<tr>
<td>Intravitreal</td>
<td>Injected into the eye</td>
</tr>
<tr>
<td>Intrathecal</td>
<td>Injected into the spinal cord</td>
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</table>
9. The Age of Biological Engineering?
**Thermodynamic Decomposition of Ligand/Protein Binding**

- **Solvated Ligand**: \( \Delta G(1) \)
- **Solvated Apo Protein**: \( \Delta G(2) \)
- **Solvated Ligand in Bioactive Conformation**: \( \Delta G(3) \)
- **Solvated Protein in Ligand-Induced Conformation**: \( \Delta G(4) \)
- **Desolvated Ligand**: \( \Delta G(5) \)
- **Ligand-Induced Desolvated Protein Binding Site**:

\[ \Delta G_{\text{bind}} = \sum_{i=1}^{5} \Delta G(i) \]

**Source:** Schrödinger

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Atomic-Level Understanding of How to Optimize “Drug-likeness”? 

All of the challenges we have discussed – metabolism, interaction with transporters, cell permeability – can in principle be understood at the molecular level.

The first glimmers of success are starting to be seen, e.g. in the use of xray data for P450 enzymes to model both P450 inhibition and oxidative metabolism.

High-throughput assays are also getting better, leading to larger datasets from which to begin understanding the trends.
Network Medicine

Cellular function caused by network modules consisting of many interlinked factors.

Disease = breakdown of these complex functional modules.

Drugs can affect multiple cellular networks.

Surprising connections between diseases forces us to rethink the way in which we classify and separate them.

It’s Been Done Before

10 October 1902, Kill Devil Hills, NC

27 April 2005, Toulouse, France

Courtesy of Brianski on wikipedia. Photograph is in the public domain.
“High performance computing has fundamentally changed the way Boeing designs flight vehicles”

-- Michael Garrett, Director of Boeing’s Airplane Performance Division

1980: tested 77 wings for 767
2005: tested 11 wings for 787

“wind tunnel results matched CFD predictions”

Noise reducing chevrons designed entirely in silico

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20.201 Mechanisms of Drug Actions
Fall 2013

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