



Stanford - South Africa

Biomedical Informatics Program



Drug discovery and validation

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How have we discovered drugs?

- Average time from project inception to drug launch: 13-14 years
- Average total investment per LAUNCHED drug = \$1 billion
- Average chance of project success:
 - 1-3% at inception
 - 7-8% if drug reaches preclinical testing



1. Basic science

- Generate hypotheses about potential drug targets based on basic research.
- E.g. A studied gene is mutated in some HIV-infected patients who never progress to AIDS.
- Can I develop a drug that “mimics” this mutation in other people, so that they also will not progress?



1. Basic science

OR

- E.g. I have elucidated a series of genes involved in the development of cancer.
- Can I interrupt the development by blocking one (or more) of the genes?



2. Identify a “lead” compound

- Given the target, attempt to find a compound that binds it (binding assay) or interferes with its function (functional assay)
- Usually identified through screening:
 - Using the target, develop an (ideally inexpensive) assay for binding/function
 - Create (or purchase) a large library of compounds
 - Test them in the assay, pull out the “positives” for further study.



2. Identify a “lead” compound

- Usually, the lead compound(s) will not be ideal drug candidates
 - Do not fit Lipinski rules
 - High chance of toxicity (or demonstrated in animal studies)
 - Does not have desired effect
 - Myriad other problems.



Lipinski's Rules

Christopher Lipinski created rules to predict which drugs would fail because of poor pharmacokinetics.

- Molecular mass > 500 Da
- High lipophilicity
- More than 5 hydrogen bond donors
- More than 10 hydrogen bond acceptors



3. Optimize the lead

- Organic chemists create variations of lead (using Lipinski rules, e.g.) to eliminate problems.
 - Can use “combinatorial chemistry” in which many variations of a backbone molecule are generated by systematically adding/removing different chemical groups
- Develop more focused assays
 - Test the desired characteristics more accurately
 - Can be more expensive, since not used for screening



4. Test optimized leads in animals

[NOTE: Rats are not just “small humans”]

Nevertheless, must establish safety in animals (mice, rats, pigs, dogs, etc...)

Check for metabolism of drug

Check for toxicity, adverse reactions

Perhaps, check for signs of efficacy.

Get indication of dosage ranges (mg/kg)



5. Phase I clinical trial

- < 100 healthy people (usually paid)
- Start low dose, increase
- Check safety
 - Liver, kidney blood tests
 - Other, as indicated
- Evaluate pharmacokinetics (blood levels as a function of dose)
- Establish maximum tolerated dose (from below!)
- In parallel, work on formulation (purity, reproducibility)



6. Phase II clinical trial

- < 1000 patients with disease
- Continue to evaluate safety
- Establish optimal dosing
- Preliminary test of efficacy



7. Phase III clinical trial

- < 10,000 patients with disease
- Use formal statistical hypothesis test to evaluate the efficacy and safety of new drug compared to “current best”
- Needs to at least match current best
- Fully documented trial data submitted to the government agency that authorizes marketing of drug.



8. Phase IV clinical study

- Post-marketing surveillance
- After the drug is released, company must continue to monitor for safety.
- Especially important for rare ($< 1/10,000$) side effects



Phase IV withdrawals

VERY expensive to pull drug this late:

- Chloramphenicol--antibiotic with rare bone marrow failure
- Grepafloxacin--antibiotic causes increased cardiac arrhythmia
- Vioxx -- arthritis medicine with increased rate of heart attacks
- Troglitazone--diabetes medicine with rare liver failure
- Viagra--erectile dysfunction medicine with rare heart attacks (NOT WITHDRAWN, TOO POPULAR?)



Notes on drug development

- Cost of canceling a drug project increases exponentially as it progresses through steps.
- Thus, better to cancel a project early with any indication of problems, than to “hope” it all works out.
- These decisions currently made based on incomplete information. Valuable drugs may be cancelled that could be “saved.”



Notes on drug development

- Drug companies are generally looking for reasons to cancel a drug, and the pipeline of targets is generally thought to be adequate.
- Adverse events that are 1/10,000 are not seen until post-market, and are therefore very expensive.
- More common adverse events (1/100–1/1000) will lead to cancellation in phase I or II.
- What about pharmacogenomics to save these?



Can PGx save drugs?

In principle, YES, but issues:

Need pharmacogenomic information early in development, so studies can be focused:

- Choose subset of patients who will tolerate drug in phase I studies.
- Avoid lengthy additional studies (patents = last only 17 years)
- May need to co-develop a genetic test (e.g. Herceptin)



Can PGx save drugs?

- Companies prefer “one size fits all” drugs
- Unclear economic model for fractured markets with “one size fits some”
- Orphan drug regulations exist currently to make it attractive for companies to develop drugs for small populations
 - E.g. life-saving drug for very rare disease
- Will orphan drug laws apply to fractured markets?



Off patent drugs

- After 17 years (in US) a drug goes off the patent, and other companies can begin producing it.
- Who is responsible for post-marketing surveillance then?
- Who should followup on pharmacogenomic opportunities?



Cost/Benefit Concerns for PGx

- If cost of the test > cost of adverse reaction, then why do it?
 - E.g. Codeine & CYP2D6, 7% of whites do not metabolize into active metabolite
- Cost of information systems to support PGx data storage and decision support
- Cost of industrial processes to create multiple drugs vs. “one size fits all”



Ethical Issues

- Will pharmaceutical companies focus on particular genetic polymorphisms for drug development and ignore others?
- What if these polymorphisms are associated with groups that are more/less economically advantaged?

More on this later...

