TARGET VALIDATION

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Drug Discovery & Development

Source: http://dlab.cl/molecular-design/drug-discovery-phases/
How do you identify a target?

- Target: the naturally existing cellular or molecular structure involved in the disease that the drug-in-development is meant to act on

- So: you need to:
  - Understand the molecular mechanism of the disease of interest
  - Identify a therapeutic target in this mechanism (enzyme, gene, receptor, channel, etc)

- Comes out of basic research
Target Validation: a Bottleneck

- Compound libraries
- Target identification
- Target validation
- Assay development
- High throughput screening
- Lead optimization
- ADMET
- Clinical trials

Bottlenecks in drug discovery
Non-problematic steps in drug discovery
Success Rate in Clinic

NME Success Rates By Phase And Overall
2007-2011 Industry Portrait, Pure

Success Rate For Each Phase
- Preclinical: 64%
- Phase 1: 44%
- Phase 2: 22%
- Phase 3: 65%
- Registration: 83%

Percent Calculated To Achieve 1 Approval
- Preclinical: 3%
- Phase 1: 5%
- Phase 2: 12%
- Phase 3: 54%
- Registration: 83%
Typical Large Pharma Numbers

- Start 100 new screening programs/assays
  - New targets
- About 50 find acceptable leads or chemotypes to pursue
- 20-25 advance into late stage lead optimization
- 10 programs advance into phase I

- Why the attrition?
Why Compounds Fail

- PK
  - Human ADME
  - Rodent vs dog vs monkey vs human
- Tox not predicted by animal studies
- Commercial reasons
- Lack of efficacy
  - Biological rationale is incorrect
  - Relevance of animal models
    - Oncology
    - Alzheimer’s
Validating molecular targets in preclinical drug discovery

A recent analysis of failures in Phase II and III trials in the past two years confirmed earlier reports that more than half of the drugs fail due to insufficient efficacy. In other words, the clinical target validation fails for about 50 per cent of therapeutic approaches. A retrospective analysis of drug development programs at Pfizer revealed some opportunities for optimisation of the drug development process. Three knowledge pillars have been identified, which increase the likelihood of candidate survival in Phase II trials: deep understanding of the drug exposure at the site of action, target binding of the drug, and clear expression of functional pharmacological activity. The latest reached highest significance for prediction of success in clinical trials. Hence, an in-depth biological understanding of a molecular target as one of the very early steps in the entire drug discovery and development process which can determine later success or failure of the emerging drug candidate is required.
Lessons learned from the fate of AstraZeneca’s drug pipeline: a five-dimensional framework

- The 5 R’s
  - Right Target
  - Right Patient
  - Right Tissue
  - Right Safety
  - Right Commercial Potential
Common Rationale Academics

- Target in the literature for 15 years
- Multiple publications: looks like there is validation
- No one has found a drug...

- Let’s start a program!
Things to Think About

- What type of modulator do you need?
  - Agonist? Antagonist? Partial agonist?
- Where is the target?
- How will you screen? What is your readout?
- What are your secondary assays?
- Are there species differences?
- What animal models are available?
  - Are there standards/known compounds as a control?
  - Predictability?
  - Biomarker?
How many targets are there?

- Human genome: ~30,000
- Druggable genome: ~3,000
- Disease modifying genes: ~3,000
- Drug targets: ~600-1,500

Targets with an FDA approved drug: 324 (1357 drugs)

Hopkins and Groom 2002
Overington et al 2006
Examples of Targets

- Receptors and enzymes
- Either intracellular or on membrane surface
  - Examples: GPCRs, kinases, proteases, phosphatases
- Transcription factors
- Nuclear receptors
- Ion channels, transporters
- Protein-protein interactions

- Phenotypic screens can be difficult: what is the target?
What do current drugs target?
Where Do Targets Come from?

- Historically: natural products
  - Herbal medicine, snake venom
- Clinical observations
  - Side-effects known drugs: could be useful in other indication
- Rational approaches based on biochemistry/biology
- Understanding genetic mutations in people
- Screening/systems biology
-Omics

- New platform technologies
  - Genomics, proteomics, pharmacogenomics
  - RNAi screening
  - Pathway analysis
  - Transgenic animals

- Key question always remains: how to validate?
Validated Target Examples (?)

- Genetic mutations associated with disease
  - Alzheimer’s: amyloid precursor protein (APP) and secretase
  - HER2 in breast cancer
- Kinases
- Upregulation in disease process
  - Inflammation and COX2
COX2: Validated?

- Classical COX inhibitors (NSAIDs): not selective: side effects
  - Irritation GI mucosa based on mechanism, drug properties
- ‘90s: discovery of isoforms
  - COX1: present in most tissues, incl GI tract, protective
  - COX2: upregulated in inflammation
  - Concept: inhibit COX2 but not COX2
- COX2 inhibitors: Celecoxib (Celebrex, Pfizer), Rofecoxib (Vioxx, Merck)
  - Rofecoxib voluntarily withdrawn 2004: increased chance of heart attack
  - 2005: advisory panels: it’s OK. Merck did not put it back on market
  - 2017: possible return? Tremeau Pharmaceuticals: joint pain in hemophilia; single phase III study
Surprise! Arthritis Drug Celebrex Shown As Safe As Ibuprofen And Naproxen
When do you consider a target validated?

- Mechanistic studies?
- Analysis in cell culture?
- Analysis in animal models?
- Clinical data (protein or gene expression)?
- Therapeutic intervention: phase II studies?
- FDA approval?
IN THE PIPELINE

Derek Lowe's commentary on drug discovery and the pharma industry. An editorially independent blog from the publishers of Science Translational Medicine. All content is Derek's own, and he does not in any way speak for his employer.

Target (In)validation

By Derek Lowe | June 1, 2015
Target (In)Validation: A Critical, Sometimes Unheralded, Role of Modern Medicinal Chemistry

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Excerpts and blog commentary:

Too often, medicinal chemistry teams blindly accept the biological underpinnings of a new program as sound and are unaware that their ensuing efforts at compound optimization may confirm or debunk the link between the biological target and the disease. In many instances, this event occurs very early in the discovery process, at the level of preclinical interrogation.

The number of targets that you can be sure are good ones, before anyone’s actually made a drug to hit them, is not large. You rarely get signals like PCSK9, where you can point at a human population with exactly the phenotype you’re trying to cause (and even then, there’s always the worry that your therapy might not recapitulate that “human knockout” mutation in every respect). There are a few targets kicking around out there that have never really been “drugged” but that everyone’s still pretty sure would be great things to affect (p53 and/or cMyc in cancer, for example), but the list is short. Otherwise, unless someone else has already blazed that trail, you’re going to be finding out not only “Is this compound going to hit the target”, but “Is this target worth hitting in the first place”.
Excerpts and blog commentary:

The infrastructure behind any drug discovery program should be stress-tested at a very early stage. Fear of obtaining suboptimal results from a suboptimal compound should not be a reason to defer such system testing. It is not uncommon for medicinal chemists to challenge their primary assay and note when occasional aberrations in output are observed. This feedback to biologists is quite helpful in establishing the durability of the primary assay. Accordingly, this philosophy should extend to downstream assays as well.

That fear is a very real one. “Oh, if you try to test using just the chemical matter we have now, you’ll probably kill the project for no good reason”. That’s not a silly argument; it really is possible to go in too early with something that’s too nonselective or too non-potent. But it can also be used to delay the day of reckoning, to avoid getting an answer that no one wants to get. You have to be honest with yourself and be ready to hear the bad news, and not keep telling yourself that you’re waiting for a better compound before asking the hard questions. Otherwise, you’ll have a compound that’s been optimized in every direction and is ready for the clinic before you know if you should have been doing all that work in the first place. Some readers may just possibly have had such an experience in their careers.
Excerpts and blog commentary:

But as this paper goes on to say, even trying out your compound *in vivo* and seeing the effect you wanted may not be enough. That’s a big step, for sure, but you’ll be a lot more confident if you can hit the system with more than one chemical series. (This, in my experience, is a rare luxury). It’s a rare project that won’t charge ahead at this point (and a rare management team that won’t complain if they don’t).

*The certainty of target validation/invalidation is far from absolute. It is akin to a lawyer’s task of establishing judgment beyond a reasonable doubt to a jury. A highly effective medicinal chemistry team is commonly lauded for intense focus. However, this focus should not preclude a critical assessment, from the broader perspective of drug discovery, of the compounds being used to make project go/no-go decisions.*

If you don’t have that wonderful situation of multiple chemotypes, the paper suggests, then you should make the most of what you have – take some structurally similar compounds into the *in vivo* model, but ones that don’t have activity in the primary assay. These negative controls might surprise you. That’s also good advice, but can be a tough sell with some biologists. But from what I’ve seen, and from a look over the history of drug research in general, I’d say that skimping on the negative controls is both one of the most common shortcuts and one of the ones you’ll be most likely to wish you hadn’t taken.
Target Evaluation Criteria

- Druggable?
  - What evidence is there to support a drug discovery program?
  - Are there small molecule inhibitors for this class of targets?
  - Availability and predictive value of animal models?
  - Are there species differences?
  - Biomarker available?

- Structural Information?
  - Protein crystal structure, NMR

- IP
  - Competition?
ADDA examples

- Phenotypic screens
  - HO-1, 14-3-3 theta, TXNIP, NMI
  - What is the target?
  - Will not be accepted in the ADDA program anymore

- Defined target examples
  - CD38
  - DPY30
  - LRRK2
  - Tau-Fyn
Next Lecture’s Topic: Pharmacokinetics and ADME

$Ed$ $Acosta$ – $April$ $6$ ($next$ $week$)