Understanding the Drug Discovery and Development Pathway - Utilizing CTDD resources and expertise

Karen Lackey
October 2016
Effective Drug
benefit/risk and feasibility

Pharmacology
- Known intervention point in disease pathology
- Selectivity within disease pathology pathways
- Off-target and on-target effects - efficacy and therapeutic index
- Biomarkers of drug action
- Patient stratification
- Duration of action and drug levels needed
- Comparison with SoC

Physical form
- Distribution, Metabolism, Pharmacokinetics (DMPK) in multiple species
- Toxicity in multiple species
- Solubility/formulations
- Metabolic stability - metabolite identification
- Generation of API
- Commercial assessment
Important Aspects for an effective drug that will not be covered...

- Intellectual property
  - Time of exclusivity
  - Breadth of global coverage
- Clinical trial design
- Product profiles with expected, up- and downsides of drug
- Funding
- Regulatory requirements
- Molecular Design and optimization strategies
Discussion Outline

- Essential components of discovering an effective drug
- Value of translational medicine and the impact in drug development
- Resources and opportunities to advance drug discovery ideas from academic research
Current Views of the Drug Discovery Industry

Essential components of discovering an effective drug

- Successful, profitable, and creates patient benefit
- Expensive with high failure rate
- Advances in genetics have not solved unmet medical needs at the expected rate
- Large pharmaceutical companies are “outsourcing” their R&D innovation
- High need for appropriately priced, effective medicines
Investment in time, resources and funding exponentially increase along the drug discovery continuum.

A therapeutic modality identified in early research must overcome many scientific and business hurdles over the lifetime of the project often requiring optimization and improvements.

De-risking projects with data to demonstrate drug intervention feasibility is key at every step in the process.
Hit Discovery

Target → Assay → Chemical Starting Point

Understanding

Pre-Screen

Post-Screen

Hit

Lead

Candidate

IND

Drug

Disease Intervention

Target/Pathway ID

Investigator Target Proposal

Investigator Project Proposal

Preliminary Product Profile

Research Plan

Consult (Data & Protocol)

Literature Search

Informatics Xray Analysis Homology Database Mining

Assay Validation, Standards & Hit Threshold

Complexity, Cost, Robustness, Practicality Assessment

Protocol Upload to Database

Pilot Screen

Funding

Give RS/RSL Plates

Vault Data Upload

Re-assay

Deconvolution

Wells of Interest Identification

Similarity Search

QA of WOI

Bench Screen

Virtual Screen

Primary Screen
The easiest & cheapest component of drug discovery: hit identification

- Associating a biological target or pathway with a small molecule, biological or novel modality is fairly straightforward in both academia and industrial settings.
- Rigor in the data is the most important part of this step and includes replicate testing, QC of the hits to confirm structure, and preliminary SAR.
Lead Discovery
Well of Interest → Validated Hit → Lead w Functional Activity

Primary Validation
- Create Cmpds of Interest Plates
- QC or Characterize COI plates
- Data Integrity
- Dose Response

Lead
- Outsourcing Options
- Resynthesis or Repurchase
- Secondary Assay
- Selectivity

Candidate
- Computational SAR Expansion
- Analog Synthesis
- SAR Validation
- Preliminary MedChem Plan

IND
- Cellular Mechanism of Action Studies
- Target Mode of Action Studies
- Cellular Efficacy & Selectivity Studies
- Chemical Series Prioritization
- in vitro Toxicity
- PhysChem Measurements
- Internal & External Cmpd Profile

Drug
- Chemical Probe
- Preliminary Novelty Search
- Revisit Literature Search
- Publication Strategy?
- Lead(s) Identified

Preliminary Characterization
Establishing requirements for an effective drug: Lead Discovery

- Assay systems for Potency, Mechanism of Action, and Selectivity
- Establishing Structure Activity Relationships (SAR) require that assay systems can distinguish compounds with reproducibility
- Novelty or the ability to build in novelty are often important, but not necessary
- SAR within each lead series allows a project team to prioritize investments for further work: critical to know where molecules can be changed as new information is generated (e.g. solubility, PK, tox, etc)
Candidate Selection → IND Enablement

**Candidate Optimization**
- Product Profile
- Prelim. PoC in Human Design
- Clinical Candidate Criteria
- Bioevaluation Cascade Funnel

**Candidate Development**
- Animal Models of Disease
- in vivo Mechanism of Action Studies
- in vitro Mode of Action Studies
- Route of Administration, Frequency, & Duration of Exposure
- in vitro DMPK

**IND Enablement**
- Target ID (if needed)
- (Bio)Analytical Methods Development & Validation
- Synthetic Route Optimization
- Alternate Indications
- Novelty Search
- IP Plan
- Broader Cmpd Profiling
- Licensing
- Clinical Candidate Nomination

**Additional Topics**
- Surrogate Biomarkers
- Clinical Material Manufacturing
- Surrogate Toxicity/Storage
- Reproductive Toxicity Studies
- Toxikokinetics
- Target Product Profile
- GLP Tox: 2 Species
- Therapeutic Index Determination
- Advanced PoC
- Clinical Protocol
- GLP Tox: 2 Species
- Clinical Trial Design
The valley of death in most academic setting: Clinical Candidate selection

- Many Contract Research Organizations are set up with cost effective and timely fee-for-service access to many of these project components with high degrees of data integrity.
- Focus is on creating the “product” and ensuring that it can be manufactured.
- Establishing risk/benefit to intended patient population is essential.
Clinical Trials → FDA Approval → Therapeutic

Clinical Trials
- IRB/Bioethics
- Trial Recruitment
- Orphan Diseases
- Repurpose
- Novel Meds: PoC

IND
- Phase 0
- Phase I
- Phase II
- Phase III
- FDA Review

NDA Therapy

Drug
- Marketing
- Foreign Markets
- Liability
- Phase IV FDA Continuing Review
- Adverse Event Reporting
- Patent/Product Life Cycle
- Reformulations
- Biosimilars

Post-Approval

Hit
Lead
Candidate

The most critical and expensive phase of drug discovery: human clinical trials

- A target or pathway is not truly validated until target engagement, efficacy and safety are demonstrated in the intended patient population.
- The greatest failure rate in developing novel medicines occurs in this phase due to lack of efficacy within the therapeutic window tested.
- Medical University research clinicians can significantly impact the success rate of novel medicines by having a thorough understanding of patient populations, establishing biomarkers/symptoms/signs of disease severity, progression and improvement, and adverse event reporting/understanding.
Making the whole greater than the sum of its parts...

**Basic Science**
- Pathway & Mechanism
  - Genetics
  - Epigenetics
  - Lipidomics
  - Phosphoproteomics
  - 2nd Messengers
  - Cell Biology
  - Animal Model

**Clinical Science**
- Clinical Practice
  - Standard of Care
  - Disease Progression
  - Patient Population
  - Clinical Outcomes
  - Unmet Clinical Need

**CTDD**
- Target or Pathway Screen
- *in vitro* Cellular Assays
- Compounds, biologicals, probes
- *in vivo* Disease Model
- *ex vivo* Patient
- PK ADME/TOX Formulation
- Patient Stratification
- Clinical Trial Design

**Define Product Profile**
**Target Engagement & Relevance**
**Disease Specific Biomarkers**
**Clinical Response Proof of Concept**
**Achieve Product Profile**

**Therapeutic Development**
Discussion Outline

- Essential components of discovering an effective drug
- Value of translational medicine and the impact in drug development
- Resources and opportunities to advance drug discovery ideas from academic research
...more than 75% of protein research still focuses on the 10% of proteins that were known before the genome was mapped — even though many more have been genetically linked to disease.
Largest Attrition For Pioneer Targets: Clinical PoC

Value of Translational Medicine

Generating effective and safe molecules in animals

Sufficient efficacy and/or safety in the chosen patient group

>90% failure rate for pioneer drugs due to lack of efficacy
“Non-Industry” essentials to achieve effective medicines

- Biomarkers for guiding patient selection, dose and duration of treatment
- Ex-vivo patient assay systems (e.g. PDX models, biorepositories)
- Deep understanding of disease pathology
- Understanding the patient needs, current standard of care, and how current treatments behave in pre-clinical models
- Co-morbidities
Discussion Outline

- Essential components of discovering an effective drug
- Value of translational medicine and the impact in drug development
- Resources and opportunities to advance drug discovery ideas from academic research
Center for Therapeutic Discovery and Development (CTDD) - Mission

- Pursue a new paradigm for partnerships in drug discovery specifically designed to increase the success rate of translating a key scientific finding into patient benefit
Partnership opportunities

Industry
- Host on-site visits of therapeutically focused divisions of pharmaceutical companies
- Make connections for specific project requests

Faculty
- Create research agreements on your behalf (e.g. ImmunArray)
- Grant applications
- Spin out companies
- Concept Huddle creation
BMS-MUSC Collaboration: Fibrosis

How it works

Master Agreement
Data management, funding, JSC

Joint Steering Com.

Disease Area Portfolio Committees

Immunology
3 projects
Biology
Chemistry
Clinical Sci

Fibrosis
4 projects
Biology
Chemistry
Clinical Sci

Biomarkers
2 Projects
Clinical Sci
Biostat

Scleroderma
3 PI’s
-pt samples
-ex vivo studies
-animal model

IPF
1 PI
-pt samples

DKD
1-3 PI’s
-pt samples
-pt data
-bioinformatics
Aeterna Zentaris (biotech company: AEZS)
Compound Collection Donation & Strategic Alliance

AEZS donated ~100,000 proprietary compounds to MUSC
AEZS areas of focus: Oncology, Endocrinology, Women’s Health, Neuroscience

1. AEZS can develop one clinical candidate discovered at MUSC per year for 10 years beginning in 2018.
2. AEZS does not receive royalties in therapeutic areas outside their key therapeutic areas of interest.

MUSC-AEZS Strategic Alliance Announcement
The South Carolina Compound Collection (SC$^3$)  
*MUSC Lead Discovery Strategy*

- High quality, annotated collection of >125,000 compounds valued at $5M - $15M
- Smaller, diverse screening set based on cluster analyses
- Objective is to support >24 faculty projects in the first year
Drug Discovery Concept Huddle - future resource
virtual platform to enhance project opportunities

Self-assembly, collaborative,
Interactive use of the platform

“reverse” Huddle
- Suggestion from biotech VP, head of Drug Discovery and Development
- Company pitches specific project need or therapeutic area
- Faculty add their platform, technology or expertise to the established categories (firewalled)
- CTDD prioritizes and showcases (under CDA) the most promising ideas/projects

CTDD will...
- Facilitate a concept huddle to generate a virtual project portfolio
- Provide drug discovery expertise and infrastructure support for projects
- Serve as a bridge between MUSC Investigators and industry scientists
Currently available resources

- Assay development consultation
- Computational Chemistry for virtual screening and modeling
- Representative Set - 10,000 small molecule compound set
- Representative Set Lite - 1000 small molecule compound set
- Hit analysis, QC and preliminary SAR analysis
- SAR compound sets
- Vault/database
- Consultation for screening cascade
- Vetted contract research organizations for DMPK, synthesis, IND enabling studies
- Lead series analyses, medicinal chemistry strategies
- Negotiating research agreements with industry
- Alliance management