Turning ideas into medicines: early drug discovery in a global pharmaceutical company

Richard Myers, Ph.D.
Senior Scientist, Target ID & Validation
Takeda Pharmaceuticals

MC294 Biotechnology Seminar Series, UC Davis
AGENDA

• Introduction
• Job Search
• About Takeda
• Drug Discovery at Takeda
• Novel Target ID and Validation
• Qualities in new hires
• Ph.D. within the UC Davis MCIP Graduate Group
• PI: Nipavan Chiamvimonvat, M.D.
• Dissertation: Regulation of Cardiac Ion Channels
• HHMI Translational Research Training Fellowship and Designated Emphasis in Translational Research (DETR)

But, uncertain of long term goal and what to do after graduate school

• Post doc?
• Teaching?
• Industry?

Graduation Day!!!

Congratulations, Dr!

...now what?
The job search...

June 2013
Graduated with Ph.D.

July 2013
Interview at Celgene → rejected,
Post doc at Stanford fell through,
continued as a Post doc in Chiamvimonvat lab UCD

Feb 2014
Began teaching part time at Sacramento State while working full time at UCD

March 2014
First contacted by Randstad Pharma recruiter for Takeda job

Applications, Applications, Rejections, Applications

April 2014
1st phone interview with OHSU, Job offer

May 2014
2nd phone interview with OHSU, Declined first offer

June 2014
Phone interview with Takeda, Declined OHSU job offer

July 2014
Moved to San Diego, Began contractor position at Takeda

In-person interview at Takeda, offered and accepted Takeda job
Takeda Pharmaceuticals

- Founded in 1781 in Japan
- Came to the US in 1977
- Largest pharmaceutical company in Japan and in the top 15 in Asia
- Presence in 70 countries with 165 Takeda sites across the globe (18 devoted R&D sites)
- 31,328 employees worldwide
- San Diego company Syrrx acquired in 2005 to become Takeda California
Career highlights at Takeda (so far…)

So, how’s it been going?

2014
- Hired as contractor Staff Scientist in CVM

2015
- Hired as a full time employee in GI Group
- Target ID & Validation
- Moved to GI Biology group

2016
- Became a project leader
- Joined Takeda leadership program

2017
- Became a Functional Validation team manager
- Promoted to Senior Scientist
Career paths for Research Scientists at Takeda

**Scientist Track**

<table>
<thead>
<tr>
<th>RA/ SRA (BS)</th>
<th>Assoc. Scientist (MS)</th>
<th>Staff Scientist (PhD)</th>
<th>Senior Scientist (PhD+postdoc)</th>
<th>Princ. Scientist</th>
<th>Res. Fellow</th>
</tr>
</thead>
</table>

- Labwork
- Experimental design
- Meetings
- Presentations
- Project leadership
- Management of personnel
- Strategy
- Global interaction

**Management Track**

- Alternative track usually available after Senior Scientist level
- Titles: Associate Director / Director, etc
- Emphasizes leadership, communication, and strategic big picture thinking
An Overview of the Drug Discovery & Development Process

- It takes from 7 – 16 years to develop a drug (from target validation to NDA)
- The cost of this process can reach > $1 - 2 billion dollar
- **It is a world of failure** - The rate of success is poor (< 3% - from Idea to market)
  - “Needle in a haystack”. On average, in order for one medicine to be approved, research must screen about 10,000 compounds.
  - By the pre-clinical studies has been completed only 250 compounds have made it through the pipeline.
  - By the time clinical trial research in humans is done, only 5 compounds have survived, and out of these only 1 receives approval.

---

**Emphasis on the Drug Discovery Process**

- **Target selection process**
- **Target validation**
- **Lead ID**
- **Lead selection/optimization**
- **In vivo study/preclinical testing**

---

**Informatics data**

**Target validation**

**Compound screening**

**secondary assays**

**In vivo analysis**

**Candidate**

- Genetic, cellular and *in vivo* experimental models to identify and validate target
- HTS & selective library screens; structure based design
- Reiterative directed compound synthesis to improve compound properties
- *in vitro & ex vivo* secondary assays (mechanistic)
- Selectivity & liability assays
- Compound pharmacology
- Disease efficacy models
- Early safety & toxicity models
- Preclinical safety & toxicity package

---

**Early Human Translational Data is key!!**

---

Complex integrated process from in-vitro to in vivo studies

---

Source: Hughes et al, 2010, British Journal of Pharmacology
Keys for successful target ID & validation:

**Strong Rationale**

- **Frontload the biology**
  - Hypothesis driven
  - Well developed understanding of biology and proposed MOA
  - Preliminary data
  - Bioinformatics analysis

- **Human relevance**
  - Expression data
  - Disease relevance (SNPs, etc)

- **Early safety assessment**
  - Tissue expression, potential AEs
  - Modality
Keys for successful target ID & validation:
Alignment with Global DDU

• Is there a market?
  – Define target indication
  – Define patient need
  – Define patient population

• Competitive landscape
  – Competition from other companies
  – Therapeutic landscape (current and projected)

• Differentiation
  – vs standard of care
  – Novelty (MOA, delivery, etc.)
Keys for successful target ID & validation:

Build a clear path

- Validation plan
  - Define critical go/no-go experiments

- Risk mitigation strategy
  - Identify the risks and develop plan to minimize
  - Is there a therapeutic window?

- Translational plan
  - POC study in human
  - PD biomarkers
  - Assessing target engagement
**How do we run a drug discovery program?**

1. Primarily internal
   - Traditional approach for big pharma
   - Pros: full control over program and work quality
   - Cons: significant investment in FTEs and management, potentially less innovative

2. Primarily external
   - Provide funds to a trusted partner
   - New model for some pharma companies
   - Usually a small Biotech company with a new technology or Academic lab with a novel drug idea
   - Pros: innovative, less internal FTE and management resources needed
   - Cons: less control over pace and quality, requires constant due diligence and oversight

3. Mixed internal/external
   - Flexes strengths of both, limits weakness for either approach
   - Pros: flexible, still innovative, collaborative
   - Cons: complex relationship with many partners can be difficult to manage
Project Leaders at the center of drug discovery

Internal

- Biology
- Medicinal Chemistry
- DMPK
- Safety
- Bioinformatics
- CMC

External

- Global DDU
- Academic Partners
- CROs
- Biotech Company
- Translational Medicine

Takeda California
High Functioning Leaders are Catalysts for Building a Best-In-Class Pipeline

**Helping Patients**

**Best Pipeline**

**High Performing Project Teams**

**High Functioning Project Leaders**

### Research Project Teams
1. Make rapid data driven decisions
2. Function as a cohesive team
3. Effectively engage with global organization
4. Leverage internal and external resources

### Research Project Leaders
1. Provide vision with clear expectations and accountability
2. Apply innovative and strategic thinking
3. Communicate effectively
4. Adhere to highest scientific standards
5. Excel at navigating technical and institutional complexity
6. Courage!
Qualities we look for in new research scientists

“Hard” Skills

Scientific Rigor
• Technical expertise
• Depth and breadth of scientific knowledge
• Proven scientific track record

Prior Industry Experience
• Prior industry experience, particularly in drug discovery is a big bonus

“Soft” Skills

Communication
• Presentations skills
• Interpersonal skills
• Collaborative

Leadership
• Record of or willingness to lead/manage teams
• Drive for results

Enthusiasm
• Passion for science and helping patients
• Innovative, creative thinking
• Team fit
Target ID and Validation: the earliest stages of drug discovery
- Searching for novel mechanisms for a future generation of medicines
bacTRAP: Bacterial Artificial Chromosome – Translating Ribosome Affinity Purification

Neuronal heterogeneity in the brain

BAC-TRAP Technology

BAC design

Cell-specific driver [egfp L10a ribosomal protein]

Pronuclear injection

BAC-TRAP mouse

Cell-type specific gene expression data

eGFP tagged ribosome allows immunoprecipitation of *translating* RNA

Collect whole tissue lysate

Immunoprecipitation

Anti-EGFP bead

Translating ribosome affinity purification (TRAP)

RNA purification and RNA seq

A Novel target!

…now validate!

BacTRAP Technology:
- GFP-labeled ribosome expressed in specific cell type based on driver gene
- Homogenize target tissue and IP of translating RNA in cell type of interest
- Purify RNA and run RNA seq
- Enrichment of genes expressed determined by relative change between Pre- and Post-IP values
- Animals can be subjected to disease models, pharmacology, or other perturbations to assess cell-specific and disease-relevant changes in gene expression

Heiman et al., Cell 2008
External Collaborations in Drug Discovery

External collaborations are becoming increasingly important

- **Academic Partners**
  - Disease/biology/technical expertise
- **Specialty Biotech**
  - Pioneer new drugs, capabilities, and/or technologies
  - Partnerships $\rightarrow$ acquisitions
- **Contract Research Organizations (CROs)**
  - Fee for service or long term partnerships
  - Option for outsourcing labor/time intensive work
  - Specialty applications
- **Clinical Partners**
  - Disease expertise, access to patient samples
- **Research Consortia**
  - Expert partnerships with multiple partners including big pharma to tackle big diseases
  - Access to big data
- **Patient groups**
  - Connect to the needs of patients and the human impact of disease
Some Current Trends in Drug Discovery

- Patient-centered drug discovery
  - Approach disease from patient needs
- Translational medicine from the start
  - Must establish human translatability of animal/cell data early
- Big data
  - Patient-tailored medicine
  - Novel target ID
- Novel targets, novel MOAs
  - High competition, low market need for well-worn targets
  - New ways to target a disease
- Targeted delivery, novel modalities
  - Cell/tissue/organ-specific drug delivery
  - Biologics
  - Nucleotide-based drugs
- New opportunities for rare diseases where treatment options are few
  - Making a big impact for a small population of patients as opposed to a mild impact on a large number of patients
- External partnerships for drug discovery