A View from Inside Pharmaceutical Development: Perspective on Career Paths
The views, comments and thoughts in today’s presentation about working in pharmaceutical industry do not represent Merck: *Merck Research Laboratories (MRL)* or *Merck Sharpe & Dohme (MSD)*. They are the opinions of each speaker.
Outline

• Welcome

• Introduction of Speakers / Careers they represent

• Split into 2 group: half tour bioprocess plan, half tour the Neuroscience assay labs

• Switch activities: tour bioprocess / tour labs

• Conclusions
Practical Information

- Bathrooms are down the hall behind us
  - Women’s room to the right
  - Men’s room to the left

- In case of emergency, proceed left down hallway to exit building

- **Photography is strictly prohibited**; please be mindful of cell phone use, particularly during the tours
Future Jobs in Academics?

Where will a biology PhD take you?

A faculty job is an “alternative” career.

At this rate, <8% of entering PhD students will become tenure-track faculty. Yet, 53% of PhD students say research professorships are their most desired career.

- 86,000 current US biology PhD students
- 9,000 receive PhDs
- 720 leave the US
- ? years average time to degree
- 37-68,000 current postdocs
- 15% of postdocs get tenure-track faculty jobs within 6 years post PhD
- 29,000 current tenured and tenure-track faculty
- 20% get non-tenure track academic jobs within 6 years post PhD
- 17,000 current bio PhDs doing non-science jobs
- 22,500 current industry researchers
- 24,000 current non-research, science related jobs
- 7,000 current gov’t researchers

10% of former postdocs (up from 2% in 2010) consider themselves unemployed.

Sources:

Unless otherwise noted, NH: Biomedical Workforce Working Group (2012)
• Carrie Markgraf
• Discovery Program Lead and Compound Leader
Carrie Markgraf: Background

Middlebury College
Biology / Psychology majors

University of Vermont
MD, PhD—Exp’t Psych

University of Miami
Post Doc—Neurology

University of Miami
Post Doc-Psych

UT Houston
Brain Injury In Vivo Models

Marion Merrell Dow
Discovery-Stroke & Brain Injury In Vivo Models

Merck
Toxicology

Schering-Plough
Safety NeuroPharmacology

Lab Association

Internet Search

Personal Networking

Proximity

Lab Association

Middlebury College

Public

Be well
Positions in Drug Discovery

- High School / College education: Lab technician
  - $27-35K

- B.S. / B.A.: Scientists / Biologist
  - $40-71K

- PhD: Principal Scientist, Senior Principal Scientist
  - $75-95K starting + annual bonus $5000-$10,000
  - Average $138K + annual bonus ~20% salary + stocks
  - Head of laboratory
  - Responsible for running compounds in your assay / model
  - Analyzing / reporting results
  - Participating in teams to represent your area of expertise
  - Keeping management informed of progress, issues, upcoming milestones
  - Attend scientific meetings, publish papers when approved

*a: American Association of Pharmaceutical Scientists, 2013 report*
Positions in Preclinical Development

**Laboratory positions**
- PhD, DVM: Lab Head, Principal Scientist, Sr. Principal Sci.
- Starting salary 75-95K starting + annual bonus $5000-$10,000\(^a\)
- Average $150K + annual bonus \(\sim\)20% salary + stocks\(^a\)
- Oversee assays run in your lab, develop new assays to address issues, keep current with literature and competitors’ technologies
- Manage colleagues in lab

**Non-laboratory scientific positions**
- PhD, DVM: Study Director, Compound Leader
- Starting salary 75-95K starting\(^a\) + annual bonus; Average $150K + bonus \(\sim\)20%
- Design and oversee studies (SD) or a compound’s program (CL)
- Requires knowledge of GLP regulations and of broad nonclinical development
- Develop study design, analyze & interpret data for standard and investigative studies
- Write sections of documents for FDA, EMA etc. that will support clinical trials
- Keep management apprised of issues and upcoming milestones, presentations

\(^a\): American Association of Pharmaceutical Scientists, 2013 report
Other Positions

• **Project Management**
  – Co-leads project team
  – Tracks all activities and keeps all parts moving on time
  – BA/BS, MA, PhD.  PMP certification preferred
  – $91-165K, average $126K + bonus\(^a\)

• **Regulatory Affairs**
  – Interacts with regulatory authorities in all countries
  – Knowledge of regulations, sets strategies for advancing a compound
  – $75-85K starting salary\(^a\)

• **Scientific Writer**
  – Works with Study Director or Research Physician to write sections of regulatory documents (IND, IMPD, NDA, study protocol)
  – Scientific Writing certificate

• **Medical Science Liaison**
  – Liaison with outside experts in academics, hospitals
  – Develop relationships with Key Opinion Leaders (KOL) in disease area
  – $100-$150K + bonus/stocks\(^a\)

\(^a\): American Association of Pharmaceutical Scientists, 2013 report
Conclusions

• Variety of positions within pharmaceutical industry, both laboratory-based and non-lab based

• Industry offers opportunity to work in multi-disciplinary teams and have real impact on bringing new human medicines to market
  – Good scientific support with resources necessary to do the job
  – Typically, regular hours (8-4) with additional effort for important regulatory interactions, for example with FDA
  – Well-paid, good benefits, smart and interactive colleagues

• Challenges include finding company with compatible style of management
  – Attend a lot of meetings
  – Mergers, change of management or disease area are out of your control
Training, Courses and Certifications

- Review guidances on ICH and FDA websites
- Review Scientific Reviews for approved drugs (FDA website)
- [http://www.amwa.org/certification](http://www.amwa.org/certification)
<table>
<thead>
<tr>
<th>Society</th>
<th>Annual Meeting</th>
<th>Website</th>
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<tr>
<td>American College of Toxicology (ACT)</td>
<td>US November</td>
<td><a href="http://www.actox.org/">http://www.actox.org/</a></td>
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<tr>
<td>American Heart Assoc. (AHA)</td>
<td>US October</td>
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- Krupali Prevete
- Program Coordinator
**Therapeutic Area Lead (TAL)**

- Responsible for a particular Therapeutic Area (e.g. Cardiovascular, Infectious Disease, Biologics/Vaccines, Woman's Health, Neuro)
- Oversee/advise CL on their programs
- Responsible for all regulatory and internal documents within assigned area.
- Requires an advanced degree (e.g. Ph.D. in relevant field, D.V.M. (or equivalent Veterinary Medicine degree) with highly advanced level of knowledge and understanding of the drug discovery process.

**Compound Leader (CL/DPL)**

- Safety representative on the Early Development Teams and EDT and Product Development Teams
- Responsible for preclinical development strategy and risk
- Oversee design and timely reporting of SA studies to support clinical trials and marketing application
- Contribute to Regulatory/Internal documents
- Requires a Ph. D. in relevant field with advanced level of knowledge and understanding of the drug discovery process

**Program Coordinator (PC)**

- PC’s are considered operational experts in non-clinical drug development
- Coordinate all non-clinical studies and Regulatory submissions in SALAR
- Determine drug requirements for studies
- Provide monthly tracking in a pipeline management tool for the status, issues, and resolution plans on all active programs
- BS/BA degree in relevant area with commensurate experience
Program Coordinator (PC)

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My Career Path

1977-1987
UNC-Chapel Hill
B.S. Pharmacy, 1982
Ph.D. Pharmacology, 1987
Dr. Luigi Cubeddu

1987-1991
Post-doc, UT-Southwestern
Dr. Elliott Ross
My Career Path – Part 2

1991-1996
Neuroscience

1996-2009
Neuroscience, Obesity, Diabetes, CV

2009-present
Neuroscience Site Lead
Distinguished Scientist, Pharmacology
Drug Discovery Projects are Complex
A team approach is required

Diversity of knowledge & scientific viewpoints

Managing this complexity is one of the key jobs of a manager in a biology group like Pharmacology/SPS
The Drug Discovery Process
A 10-15 year effort for projects that succeed

ID proteins appropriate for drug intervention in medically-relevant pathways

Find non-optimized compounds, antibodies, etc. that modulate target activity

Chemistry & mechanistic studies: Can the lead be converted to a drug?

Optimize the lead for efficacy & safety sufficient to test in humans

Does the molecule have desired human PK? What types of side-effects are observed and at what dose? Is there evidence of efficacy in small studies?

Is the molecule safe and effective in larger clinical trials?

Are there opportunities to expand the drug’s indications? Are there new safety signals that emerge post-approval?
Pharmacology/SPS at Merck Research Labs

- Characterize drug mechanism of action & enable chemical optimization
- Generate protein reagents to fuel studies across MRL, from structural studies to assays
- Assess safety & efficacy of lead compounds in animal models of disease
- Convert in vitro assays to high-throughput, automated platforms & screen millions of compounds

In vitro Pharm
In vivo Pharm
Protein Sciences
High-Throughput Screening
What Does a Scientific Manager Do?

• Set overall strategic direction for projects
  – Is this a tractable target? What resources (people/money) do we need to prosecute a drug discovery program on this target? How long will it take? Etc.
  – Need a sufficiently broad and detailed scientific background to understand the science involved in projects under his/her direction.

• Be a conduit for communication – both up the management chain and back down to your team.

• Connect dots, identify opportunities

• Remove obstacles so your team can function at its best.
  – Compromise, yield, confront as necessary

• Recruit the best talent and then develop that talent to its fullest potential.

• Basically, roll up your sleeves and do whatever is necessary to help your team succeed.
Some Advice for Graduate Students and Postdocs

• Focus on research in a hot area, but be flexible. Your hot area will not always be hot.

• Get a broad scientific background. Don’t overspecialize.
  – Read, go to seminars, etc. outside of your immediate area of interest.

• Learn to communicate well!
  – Presentation skills are key – practice as much as possible!
  – Teaching is a great way to develop presentation skills.
  – Become a good writer – there are fewer and fewer good scientific writers.
  – Never stop publishing!!!!!!

• Learn to collaborate, function as part of a team, but also balance with a strong dose of self-motivation and independence.

• Develop a large and diverse network (internal and external)

• Balance in your life
  – Scientists (including me) tend to be workaholics.
  – Family, hobbies, etc. are important!
Merck Research Laboratories
Postdoctoral Research Fellow Program

- Academic focus in an industrial environment
- Focus on building your career & publication record
- Paired with an accomplished mentor
- Postdoctoral Fellows at Merck
  - Receive competitive salary & the same access and benefits as regular full-time employees
  - Have direct access to core capabilities, equipment, and expertise across MRL
  - Work exclusively on publishable topics
  - Obtain real experience in drug discovery and development
  - Participate in seminars, lectures and meetings, and interact with the local scientific community

Learn more at: www.merck.com/research/fellow
Questions?
High-Throughput Screening

- 7 robotic platforms capable of supporting a wide variety of screening modalities
  - 384-, 1536- and 3456-well plate formats
  - biochemical, cell-based and phenotypic screens
  - primary screening of millions of compounds completed in < 2 weeks

- Special technology platforms available that can support focused library screening
  - High-throughput mass spectrometry
  - Plate-based imaging assays
  - Electrophysiology
  - GPCR ligand bias
Pharmacology Goal: Identify, Characterize and Differentiate Lead Series

HTS Generates Thousands of Hit Compounds!!
- What is real?
- How do they work?
- What should we work on?

Biochemistry: characterize compound in vitro enzyme inhibition mechanism and potency

Biophysics: demonstrate in vitro target engagement

Cell Pharmacology: characterize ability of compound to modulate receptor or channel function

- Monitor ligand-induced changes in protein melting temperature
- Monitor binding kinetics to immobilized target
- Demonstrate subtype selectivity of Ca\textsuperscript{2+}-channel blocker

Potency improves as enzyme-inhibitor pre-incubation time is lengthened

Time-dependent inhibitors can have beneficial pharmacological properties
Pharmacology Goal: Deliver High Quality Preclinical Candidates

Build and Execute Assays to:
- Drive Structure-Activity Relationships
- Fully Characterize Biology of Compounds

Medicinal Chemistry

Biochemical Assays: intrinsic potency against target
- Selectivity!!

Cellular Assays: estimate potency in cellular milieu
- Selectivity
- Toxicity

Receptor Pharm Assays: intrinsic activity against target
- Agonist
- Antagonist
- Modulator
- Selectivity!!

Ion Channel Assays: intrinsic activity against target
- Blocker
- Use-dependence
- Selectivity!!

In vivo Assays
- Link in vitro and in vivo potency and efficacy
- Demonstrate target engagement
- Establish PK/PD relationships
In Vivo Pharmacology - Support Multiple Therapeutic Indications

- **Target Engagement** – receptor occupancy
- **Pharmacodynamic Effects** – e.g. neurochemistry, physiology, etc.
- **Efficacy** – e.g. behavior in a validated assay/model
- **Translation** – compound exposure → target engagement → efficacy

**Example: Neuroscience**

Receptor Occupancy → Electrophysiology

Pre compound → Post compound

Complex Behavior
Pharmacology Goal: Provide Data to Inform Clinical Trial Design

**MC38 tumors**

- 0/10 CR  - Isotype
- 2/10 CR  - Mechanism X
- 2/10 CR  - Anti-PD1
- 10/10 CR - Mechanism X + anti-PD-1

**Oncology**

- Tumor (fresh)

**Tissue Processing**
- IHC, ISH, LCM, Immuno-LCM

**Histoculture**
- ELISA (e.g. cytokines)

**Tissue Disassociation**
- FACs sorting/immunophenotyping
- In vitro functional assays

**Perform preclinical studies that can point to new indications for approved drugs**

**Gene Expression** (qPCR, Nanostring, NextGen sequencing)