Help Us Start a BioPharmaceutical Company

Rutgers University
Piscataway, New Jersey

Larry Wennogle, Ph.D.
Overview of the Pharmaceutical Industry

- Introductory statements and setting the stage for the symposium
- My career in brief
- 30,000 foot view of the Pharmaceutical Industry
  - Markets/revenues/employees
- The challenges
- The changing landscape
  - Historical perspective
- A few words about the legal aspects and patent law
Sam Kongsamut, Ph.D. background

- Diplomatic upbringing (Saigon, Bangkok, Ottawa, The Hague, Chicago, NYC, CT, NJ)
- Ph.D. (Neuropsychopharmacology) – Univ Chicago; Postdocs – Cornell, Yale
- 1 wife, 2 grown children, 1 grand-dog, 1 granddaughter
  - R&D: Discovery → Clinical Development → 2 Marketed Products
  - Psychiatry, neurology, age-related illnesses
  - Management (portfolio, people)
  - External (open) Innovation / Business Development

- Rudder Serendip LLC (2012-present):
  - Consulting: universities, foundations, small companies
  - Exec Dir, Entrepreneur Ctr, Institute for Life Science Entrepreneurship

- Entrepreneurial Activity:
  - Biochron Therapeutics [circadian rhythm modulation]
  - Neurotrope BioScience [Alzheimer's disease]
  - Co-founder, BryoLogyx Inc. [oncology immunotherapy; HIV/AIDS]

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973-937-8115

Today’s session - 1

Learning goals:
1. How to plan for pharmaceutical R&D
2. The importance of multidisciplinary collaboration
3. What functions are necessary to create a startup biopharma company
Today’s session - 2

Scenario:
- Your task is to put together a company to search for agents to cure HIV
- You have received seed funding sufficient for a year of operations
- During the next hour, you will form mock Research and Development teams and define essential directions needed
  - What preliminary data can you generate in the first year to support further fundraising?
  - What is your R&D plan? What are the risks?
  - How will different disciplines work together?
- At the end of the hour, we will debrief and discuss

1981: First reports of AIDS

“In the period October 1980-May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus (CMV) infection and candidal mucosal infection.”

CDC MMWR
June 5, 1981 / 30(21):1-3
### AIDS patients die of opportunistic infections

**Infections**

<table>
<thead>
<tr>
<th>Parasites</th>
<th>Bacteria</th>
<th>Fungi</th>
<th>Viruses</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Toxoplasma species</em></td>
<td><em>Mycobacterium tuberculosis</em></td>
<td><em>Pneumocystis carinii</em></td>
<td><em>Herpes simplex</em></td>
</tr>
<tr>
<td><em>Cryptosporidium species</em></td>
<td><em>Mycobacterium avium</em></td>
<td><em>Cryptococcus neoformans</em></td>
<td><em>Cytomegalovirus</em></td>
</tr>
<tr>
<td><em>Leishmania species</em></td>
<td><em>Mycoplasma avium intracellular</em></td>
<td><em>Candida species</em></td>
<td><em>Varicella-zoster</em></td>
</tr>
<tr>
<td><em>Microsporidium species</em></td>
<td><em>Salmonella species</em></td>
<td><em>Histoplasma capsulatum</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Coccidioides immitis</em></td>
<td></td>
</tr>
</tbody>
</table>

**Malignancies**

- Kaposi’s sarcoma (associated with herpesvirus HHV8)
- Non-Hodgkin’s lymphoma, including EBV-positive Burkitt’s lymphoma
- Primary lymphoma of the brain

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### AIDS results from a loss of CD4 T cells

**Figure 13.24** The Immune System, 4th ed. © Garland Science 2015

- **Infection**
- **Seroconversion**
- **Depletion of CD4 T cells**
- **Death**

- **CD4 T cells/μL**
  - 1000
  - 500
  - 200
  - 0

**Flu-like disease (sometimes)**

**Asymptomatic phase**

**Symptomatic phase**

**AIDS**

**Mean of ~40 years**

**2–6 weeks**

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Parham Figure 13.24 (See Kuby Table 18-4)
1985-now: Science took on the challenge: ART (Anti-retroviral therapy) Targets

TABLE 18-6 Categories of HIV-1 drugs in clinical use

<table>
<thead>
<tr>
<th>Category</th>
<th>FDA approval date*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleoside/nucleotide analogues</td>
<td>1987</td>
</tr>
<tr>
<td>Nonnucleoside reverse transcriptase inhibitors</td>
<td>1996</td>
</tr>
<tr>
<td>Protease inhibitors</td>
<td>1995</td>
</tr>
<tr>
<td>Fusion/attachment inhibitors</td>
<td>2003</td>
</tr>
<tr>
<td>Chemokine coreceptor antagonists</td>
<td>2007</td>
</tr>
<tr>
<td>Integrate inhibitors</td>
<td>2007</td>
</tr>
</tbody>
</table>

*Year of first FDA approval for a drug to treat HIV-1 infection in that drug category.

Impact of anti-HIV drugs

Figure 13.29. Janeway’s Immunobiology, 6th ed. (© Garland Science 2012)
Latency and ART

Active HIV replication
Antiretroviral drugs suppress HIV replication to undetectable levels
HIV rebounds after cessation of therapy

Circulating virus
Limit of detection
Time

Background

Kulpa & Chomont J Virus Erad 2015, 1(2), 59-68

How to Deal with the Latent Reservoir

HIV-1 latent reservoir formation in CD4+ T cells
Latent HIV-1 reservoir survival through homeostatic proliferation
"Shock/Kick-and-kill" approach to restart viral replication from latent reservoirs

Functional cure approach

Selective depletion of T cell subsets carrying the integrated HIV-1 DNA

Background

Battistini and Sgarbanti Viruses 2014, 6(4), 1715-1758
Latency Reversing Agents (LRA): Shock and Kill

**HIV INFECTION AND LATENCY**

- The LATENT VIRUS (PROVIRUS), reservoir cells resupply active virus

\[ T_{1/2} \approx 4.6 - 44 \text{ months} \]

Current therapies target only the active virus

**CLINICAL MODEL**

*Accelerate reservoir reduction*

<table>
<thead>
<tr>
<th>Latent Cells</th>
<th>LRA</th>
<th>LRA</th>
<th>Eradication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral Load</td>
<td>ART</td>
<td>ART</td>
<td>ART</td>
</tr>
</tbody>
</table>

LRA = latency reversing agent (Bryostatin-1)
ART = anti-retroviral therapy

Background

L. Wennogle - Help us start a new Biopharmaceutical company

https://www.youtube.com/watch?v=A6g_1RHeOzU

The Therapeutic Index of Bryostatin and Analog in Mice

**Bryostatin 1**
PKC modulator

**SUW133**

Mansden et al. (2017) PLOS Pathogens
Possible compound selection flowchart

Newly synthesized compounds

Profile for potency, PKC isoform selectivity (binding) and efficacy (translocation)

in vitro potency/efficacy: Expression of CD69

in vitro platelet aggregation

Mouse study – in vivo efficacy, therapeutic index

Latency reversal and CD69 expression in human HIV-infected cells

Scale-up chemistry
IND-enabling studies
Safety pharmacology, GLP toxicology program

Criteria for progression

IC50 < 10 nM
Stimulates cytosol to membrane translocation at 100 nM

EC50 < 100 nM
Stim CD69 (T-cell activation)
>100x separation vs. platelet aggr EC50

Dose to stimulate CD69 expression vs. lethal dose (better than SUW133)

PK – analytical chemistry

EC50 < 100 nM

Teams

1. Medicinal Chemistry
2. Screening and assay development
3. Pharmacology
4. Pharmacokinetics/Analytical Laboratory
5. Legal – Patents, material transfer agreements, Confidentiality agreements
6. Business Development and Finance – Grant writing, funding, Website
The Challenge: build a company

- Different areas of expertise: throughout
  - How long will it take? How much will it cost?
  - Medicinal chemistry: What analogs will you synthesize? How will you know if you are making good/better compounds?
  - Assay Development and Screening: What assays do you need to develop? How robust are they? What throughput do you need (how many compounds will medicinal chemists make?)?
  - Pharmacology: What animal models do you need? What translational biomarkers do you need?
  - Pharmacokinetics/analytical: What are the ideal pharmacokinetic properties of desired compounds? What needs to be optimized?
  - Legal: Can you make patentable compounds? What patents need to be filed? When? What legal agreements need to be put in place?
  - Business Development: Planning for the future: How much money will the company need? What information do you need from your colleagues to draft a plan and calculate $ needs? What funding sources will you go to? How will you convince funders to invest?

The Challenge: build a company (Process)

- **30-45 min**: Get into ‘functional’ teams
  1. Medicinal chemistry
  2. Assay Development and Screening
  3. Pharmacology
  4. Pharmacokinetics/analytical
  5. Legal
  6. Business Development
- Discuss the **key outputs** needed for company success within your teams
- Send representatives to other teams if you need information

- **15-30 min**: Your company will be made of ‘multifunctional’ teams: send a representative; coordinate across different functions

- **30 min**: Debrief as a group
Medicinal Chemistry Team

- Selected Strategy:
  - Shock and kill approach
  - PKC modulators – bryostatin-1
  - Competitors or collaborators
    - HDAC inhibitors
    - Broadly neutralizing antibodies
    - Vaccines
- Resources and equipment
  - Essential Hires, Consultants or contract arrangements

Checklist for Medicinal Chemistry Team

- Roughly estimate a timeline
- Roughly estimate a budget (1 person = $200K, "fully-loaded")
- Goals year one in house effort - # compounds made, purchased and scale required
- Potential external contracts, collaborators
- Licensing agreements required
- Efforts to establish intellectual property (patent applications)
- Equipment required
- Outline efforts to communicate with other teams
- What will you contribute to the grants to be written
- Anything else to plan for
Resources – Med Chem

- Contract laboratories – e.g. J-Star - J-Star Research, Inc. 3001 Hadley Road, Suites 1-4
  South Plainfield, New Jersey 07080

- Molecular Modeling consultants

- Libraries available such as via NIH

- Analytical companies – e.g. Robertson Microlit Laboratories Inc., 1705 US Highway 46 | Suite 1D |
  Ledgewood, NJ 07852 email: bperrotto@robertson-microlit.com

Screening and Assay Development Team

- Assays needed

- Throughput needed

- How to organize assays into a decision tree or screening tree

- Essential Hires, Consultants or contract arrangements
Checklist for Assay Development/Screening Team

- Roughly estimate a timeline
- Roughly estimate a budget (1 person = $200K, “fully-loaded”)
- Goals year one in house effort
- Potential external contracts, collaborators
- Licensing agreements required for cell lines or animal models
- Efforts to establish intellectual property (patent applications)
- Equipment required
- Outline efforts to communicate with other teams
- What will you contribute to the grants to be written
- Anything else necessary to plan for?

Resources – Assay Development Team

- CEREP Contract research organization. CRO performing numerous cellular, enzyme and binding assays
  - http://www.cerep.com
Pharmacology Team Checklist

- Flow chart of pharmacology efforts
- Animal models
- Translational biomarkers from animals to humans
- Essential hires, consultants or contract arrangements (1 person = $200K, “fully-loaded”)
- What will you plan to add to the grant application
- How essential will estimated toxicology information be to the grant application?
- Any other essential planning activities?

Resources for Pharmacology Team

- CROs such as Brains on line, Psychogenics, Charles River Laboratories, who have numerous animal models
Pharmacokinetics/Analytical Laboratory

• Analyze where the drug is going?
• Is it being metabolized?
• What route of administration is best? Oral? IV? Other?
• Formulations to evaluate
• Essential Hires, Consultants or contract arrangements

Checklist for Pharmacokinetic/Analytical Team

• Roughly estimate a timeline
• Roughly estimate a budget
• Goals year one in house effort
• Potential external contracts, collaborators
• Licensing agreements required
• Equipment required
• Outline efforts to communicate with other teams
• What will you contribute to the grants to be written
• Conference attendances, publications planned
Resources Analytical Team

- Contract organizations for animal models
- Academic experts
- CROs such as Absorption Systems
  - https://www.absorption.com/

Legal

- Intellectual property – do you own the patents?
- Can chemists make new compounds that are patentable?
- Who can you find that can help write/file patents?
- Consultants and/or engage law firm
Checklist – Legal Team

- Roughly estimate a timeline
- Roughly estimate a budget
- Goals year one in house effort
- Potential external contracts, collaborators
- Licensing agreements required
- Efforts to establish intellectual property (patent applications)
- Equipment required
- Outline efforts to communicate with other teams
- What special training will you oversee?
- How will you define and implement company policies?

Resources

- Legal.com
- Outside law firms
  - How will you identify best firms for this work?
  - Different areas of law: Corporate vs. intellectual property
Business Development

- How does the company create value?
- Where is the funding going to come from? Grants? How much?
- Venture capital? How much will you ask for? Why? How much money and how much time will you need to get to an ‘inflection point’?
- Partnerships with other companies?

Checklist – Business Development Team

- Roughly estimate a timeline
- Roughly estimate a budget
- Goals year one in house effort
- Potential external contracts, collaborators
- Licensing agreements required
- Outline efforts to communicate with other teams
- Develop plans to communicate externally to potential partners, investors, Societies
- How will you understand competition
- How will you coordinate the generation and submission of grant applications? To what agencies, foundations, entrepreneurs, etc.
Resources

▪ Grants.gov/SBIR
▪ Foundations
▪ BioNY+NJ
▪ Venture capital
▪ Strategic investors

supplemental
Additional information
Some cost background

- FTE cost $150-200K ‘fully loaded’
- Cost to synthesize a typical compound: $10K
- Typical

The Challenge: Odds are against you!

- 11-15 years to develop and win Food and Drug Administration (FDA) approval of a novel pharmaceutical agent
- Estimated costs range … Average cost of $2.6 Billion (PhRMA report) for New Drug Approval (NDA)
  - Central Nervous System drugs generally higher/longer/riskier
- Fewer than one in ten drugs that enter Phase I clinical development succeed to approval and marketing
- Fewer than one in two marketed drugs gain back the money used to win approval
- Estimates of how many small molecules are made/screened per novel pharmaceutical agent approved is difficult and depends on the field/prior art
Typical IND-enabling Pre-Clinical Toxicology and Safety Studies

Prior to studies in humans, an Investigational New Drug (IND) application must be filed with and approved by the FDA. The FDA has a specific set of in vivo/in vitro studies that must be conducted for IND approval.

- **In vitro**
  - Assay development and validation
  - Dose formulation analyses

- **Rat Toxicity**
  - Single dose
  - 7 day dose ranging
  - 14 and 28 day toxicity

- **Dog/Monkey**
  - Maximum tolerated dose
  - 7 day dose ranging
  - No effective dose level
  - 14 and 28 day toxicity

- **Genotoxicity**
  - Bacterial mutagenicity
  - Chromosome aberration
  - Rodent micronucleus

- **Safety Pharmacology**
  - hERG inhibition
  - CNS rodent
  - Cardiovascular (telemetry)
  - Respiratory
Data Sources

- Pharmaceutical Research and Manufacturing Association of America (PRMA)

Industry Overview

- Biopharmaceutical sector
Health, United States, 2015: At a Glance

National Center for Health Statistics' (NCHS) Office of Analysis and Epidemiology

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Help us start a new Biopharmaceutical company

### Life Expectancy and Mortality

<table>
<thead>
<tr>
<th>Age</th>
<th>Value (Year)</th>
<th>Table No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life expectancy, in years</td>
<td>76.8 (2000)</td>
<td>78.8 (2013)</td>
</tr>
<tr>
<td>Infant deaths per 1,000 live births</td>
<td>6.9 (2000)</td>
<td>5.9 (2013)</td>
</tr>
<tr>
<td>Deaths per 100,000 population, age-adjusted</td>
<td>869.0 (2000)</td>
<td>791.9 (2013)</td>
</tr>
</tbody>
</table>

### Morbidity and Risk Factors

<table>
<thead>
<tr>
<th>Condition</th>
<th>Value (Year)</th>
<th>Table No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fair or poor health, percent</td>
<td>8.9 (2000)</td>
<td>10.2 (2013)</td>
</tr>
</tbody>
</table>

### General

Etanercept binds specifically to tumor necrosis factor (TNF) and blocks its interaction with cell surface TNF receptors. TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. It plays an important role in the inflammatory processes of rheumatoid arthritis (RA), polyarticular-course juvenile rheumatoid arthritis (JRA), and the resulting joint pathology. Elevated levels of TNF are found in the synovial fluid of RA patients and in both the synovium and psoriatic plaques of patients with psoriatic arthritis. Two distinct receptors for TNF (TNFRs), a 55 kilodalton protein (p55) and a 75 kilodalton protein (p75), exist naturally as monomeric molecules on cell surfaces and in soluble forms. Biological activity of TNF is dependent upon binding to either cell surface TNFR.

Etanercept is a dimeric soluble form of the p75 TNF receptor that can bind to two TNF molecules. It inhibits the activity of TNF in vitro and has been shown to affect several animal models of inflammation, including murine collagen-induced arthritis. Etanercept inhibits...
State of New Jersey and Pharma

- GDP of New Jersey is 3.2% on the National GDP
- HealthCare Institute of New Jersey:
  - 78,447 employed in the Biopharmaceutical industry in NJ
- 2014: New Jersey Department of Labor and Workforce Development/Office of Research and Information estimated 115,000 workers in the Biopharmaceutical Life Sciences Cluster (Medical device manufacturing included)
  - 3.6% of the New Jersey private workforce; Nationally: 1.9%
  - $15B in wages or 8.1% of total state wages
- In 2013, there were 1,234 clinical trials ongoing in the state of New Jersey with 25,126 participants

Quick View on Patents in Pharma

- A patent (/ˈpætənt/ or /ˈpeɪtənt/) is a set of exclusive rights granted by a sovereign state to an inventor or assignee for a limited period of time in exchange for detailed public disclosure of an invention. An invention is a solution to a specific technological problem and is a product or a process.[1] Patents are a form of intellectual property.

- The procedure for granting patents, requirements placed on the patentee, and the extent of the exclusive rights vary widely between countries according to national laws and international agreements. Typically, however, a granted patent application must include one or more claims that define the invention. A patent may include many claims, each of which defines a specific property right. These claims must meet relevant patentability requirements, such as novelty, usefulness, and non-obviousness. The exclusive right granted to a patentee in most countries is the right to prevent others, or at least to try to prevent others, from commercially making, using, selling, importing, or distributing a patented invention without permission.[2][3][4]

- Under the World Trade Organization’s (WTO) Agreement on Trade-Related Aspects of Intellectual Property Rights, patents should be available in WTO member states for any invention, in all fields of technology, and the term of protection available should be a minimum of twenty years.[5] Nevertheless, there are variations on what is patentable subject matter from country to country.
Typical Big Pharma Composition of Matter, Small Molecule Patent

- ~750 compounds with complicated structure relationships
- Compounds never before made
- Dozens to hundreds of claims
- Prosecuted in multiple countries
- Generally prosecuted for 5-10 years with generation of multiple continuations, divisional patent applications
- Ex. Over 3000 patents include the structure of Lovastatin
- Major approved drugs have composition of matter, crystals, method of preparation, therapeutic applications, formulations, etc.
Summary and Conclusions

- Drug Development is risky
- Enormous investment with potential blockbuster payoffs
- Sizable fraction of personal/state/country/world economy
- Large workforce with multiple disciplines represented
- Incredible changes continue in the industry

Thank you!

My nearly 37 years in the Pharmaceuticals has been a wonderful experience. Consider a career in Pharma!
The Pharmaceutical Industry Has Had A Significant Impact on Human Health

- **Hepatitis C** – a once incurable disease that now has **cure rates above 90%**
- **HIV/AIDS** – once a death sentence, it’s now a chronic **manageable** condition
- **Cancer** – 83% of children with cancer now **survive**, compared to 58% in 1970
- **Vaccines** – more than 730,000 children’s lives have been **saved** in the last 20 years in the United States because of advances in vaccines.

https://youtu.be/-5X2kzlDroA
Comparing development of different product types

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Small molecule (pill)</th>
<th>Large Molecule (biologic)</th>
<th>Medical Device</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle time</td>
<td>10-15 yrs</td>
<td>10-12 yrs</td>
<td>3-7 yrs</td>
</tr>
<tr>
<td>Cost to develop</td>
<td>&gt;$2.5B including capital and failures</td>
<td>&gt;$2.5B including capital and failures</td>
<td>$31M</td>
</tr>
<tr>
<td>Regulatory Pathway</td>
<td>NDA (safe and efficacious)</td>
<td>BLA Safe and efficacious</td>
<td>510K (clinical benefit or substantial equivalence)</td>
</tr>
<tr>
<td>Price</td>
<td>++</td>
<td>+++</td>
<td>+</td>
</tr>
</tbody>
</table>

Superiority, cost effectiveness, health economic benefit
Shock and Kill

Background

Deeks et al., 2015 Nature Reviews Disease Primers

https://deathtaxesandviruses.com/2016/10/10/are-we-on-the-brink-of-a-hiv-cure/