Help Us Start a BioPharmaceutical Company

Rutgers iJOBS
Princeton, 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. (Neuropharmacology) – Univ Chicago; Postdocs – Cornell, Yale
- 1 wife, 2 grown children, 1 grand-dog, 1 granddaughter
- **Bridgewater NJ (1991-2012):**
  - 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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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

Background

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."

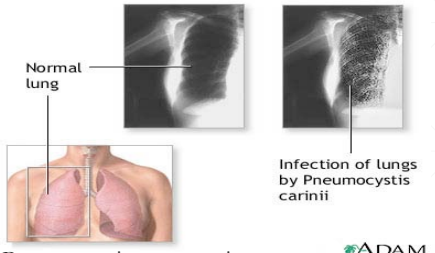
CDC *MMWR*
June 5, 1981 / 30(21);1-3

Background

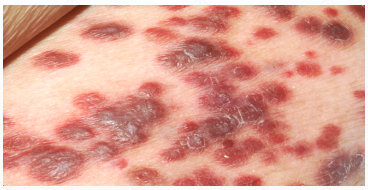
AIDS patients die of opportunistic infections

Infections	
Parasites	*Toxoplasma* species *Cryptosporidium* species *Leishmania* species *Microsporidium* species
Bacteria	*Mycobacterium tuberculosis* *Mycobacterium avium intracellulare* *Salmonella* species
Fungi	*Pneumocystis carinii* *Cryptococcus neoformans* *Candida* species *Histoplasma capsulatum* *Coccidioides immitis*
Viruses	Herpes simplex Cytomegalovirus Varicella-zoster

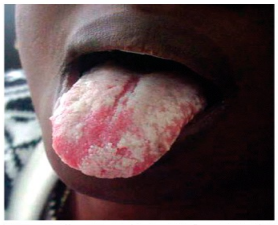
Malignancies
Kaposi's sarcoma (associated with herpesvirus HHV8) Non-Hodgkin's lymphoma, including EBV-positive Burkitt's lymphoma Primary lymphoma of the brain



Pneumocystis pneumonia



Kaposi's Sarcoma



Slonczewski Figure 26.14

Parham Figure 13.31

Background

AIDS results from a loss of CD4 T cells

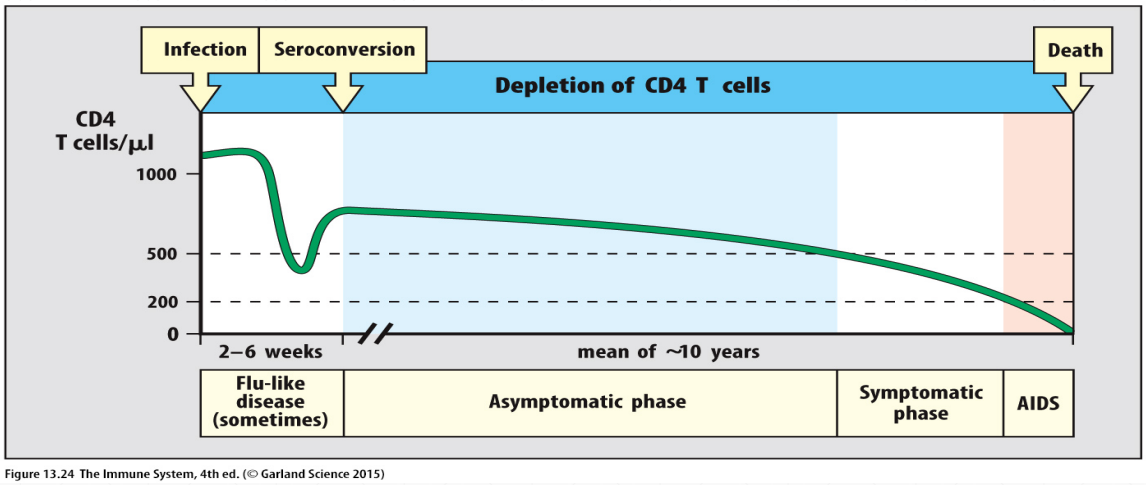
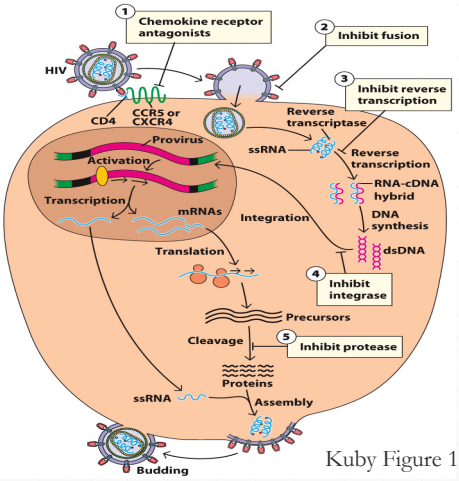


Figure 13.24 The Immune System, 4th ed. (© Garland Science 2015)

Parham Figure 13.24 (See Kuby Table 18-4)

Background

1985-now: Science took on the challenge: ART (Anti-retroviral therapy) Targets



Kuby Figure 18-17

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

Category	FDA approval date*
Nucleoside/nucleotide analogues	1987
Nonnucleoside reverse transcriptase inhibitors	1996
Protease inhibitors	1995
Fusion/attachment inhibitors	2003
Chemokine coreceptor antagonists	2007
Integrase inhibitors	2007

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

Kuby Table 18-6

Background

Impact of anti-HIV drugs

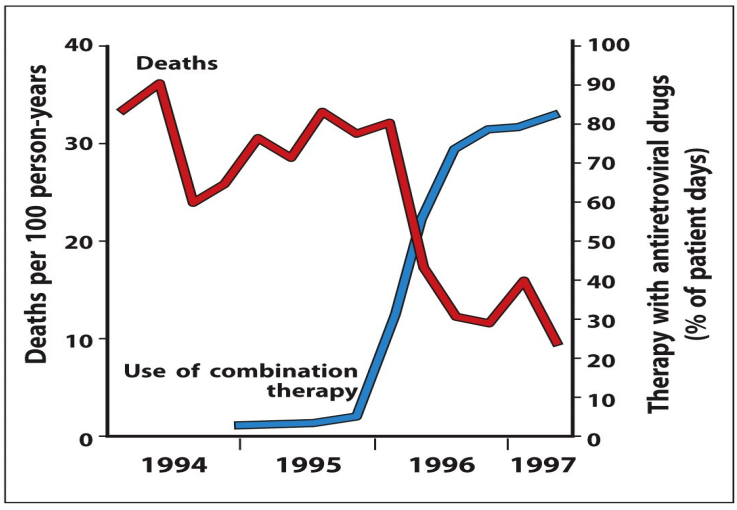
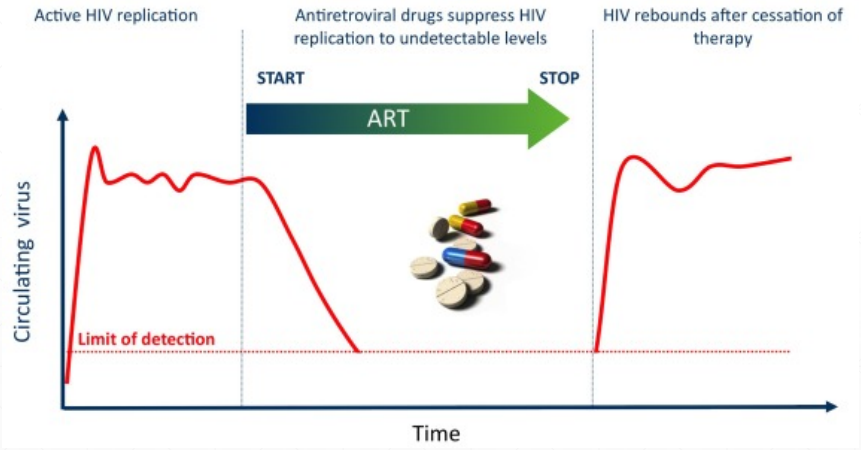


Figure 13.29 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Janeway Figure 13.29

Background

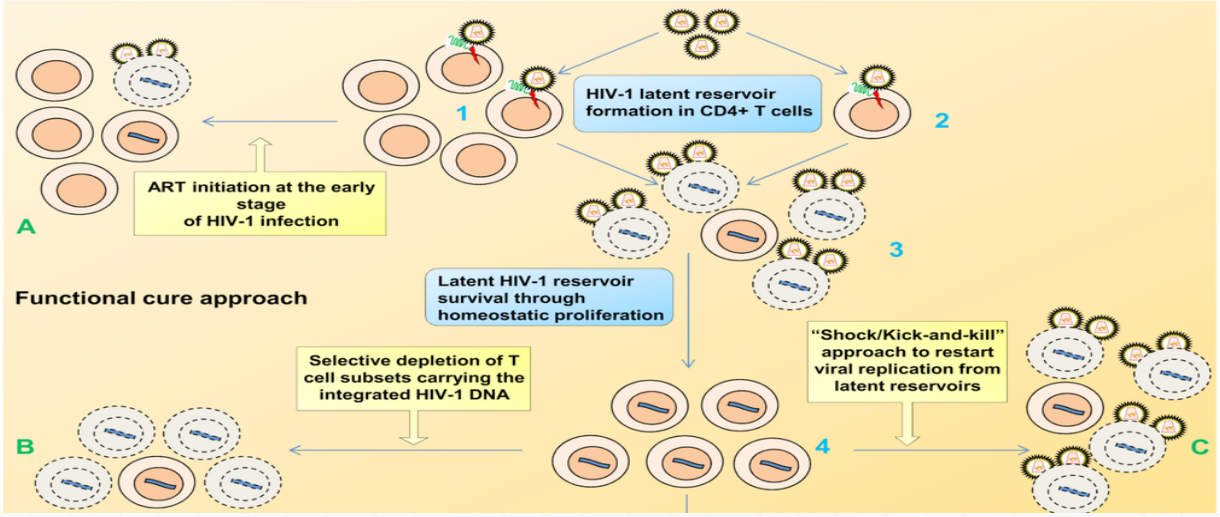
Latency and ART



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

Background

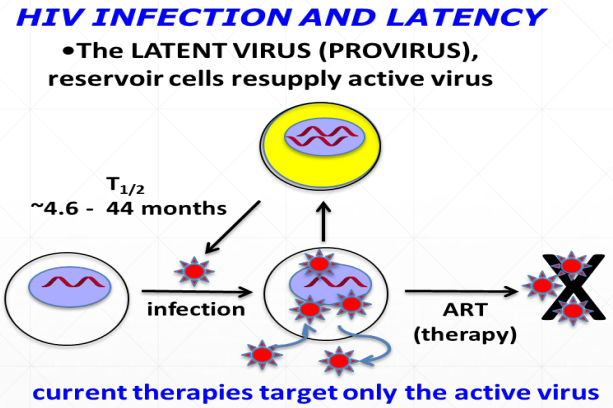
How to Deal with the Latent Reservoir

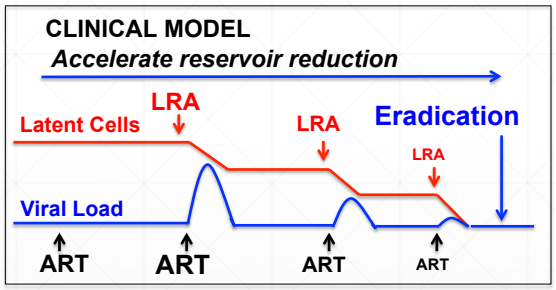


Battistini and Sgarbanti *Viruses* 2014, *6*(4), 1715-1758;

Background

Latency Reversing Agents (LRA): Shock and Kill



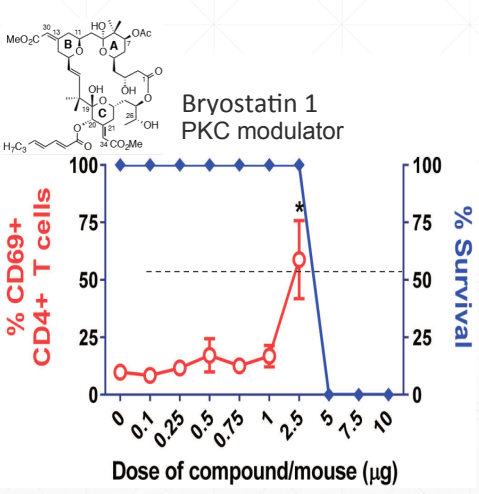


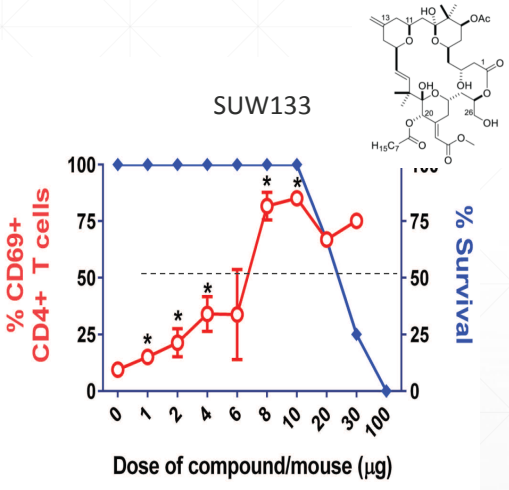
LRA = latency reversing agent (Bryostatin-1)
ART = anti-retroviral therapy

https://www.youtube.com/watch?v=A6g_JRHcOsU

Background

The Therapeutic Index of Bryostatin and Analog in Mice

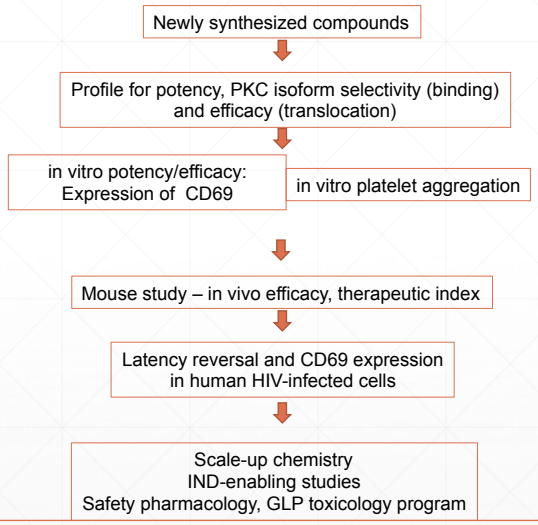




Marsden et al. (2017) PLOS Pathogens

Possible compound selection flowchart

Background



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
  - http://www.psychogenics.com/
  - https://www.criver.com/insights/acquisition-brains-line-expands-neuroscience-services-portfolio

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

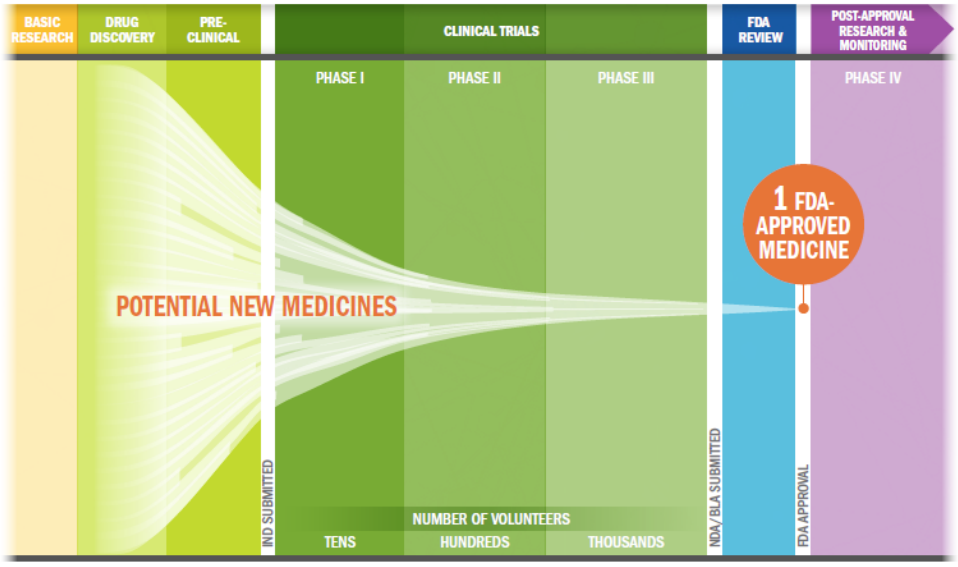
Some cost background

- 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

THE BIOPHARMACEUTICAL RESEARCH AND DEVELOPMENT PROCESS



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Key: IND: Investigational New Drug Application, NDA: New Drug Application, BLA: Biologics License Application

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

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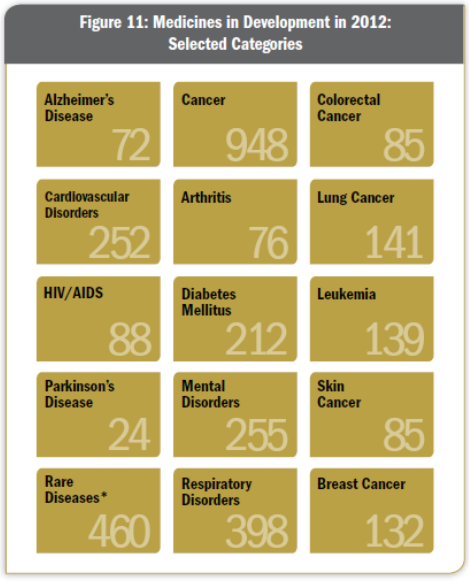
Data Sources

- 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

	Value (year)			*Health, United States, 2015* Table No.
Life Expectancy and Mortality				
Life expectancy, in years				Table 15
At birth	76.8 (2000)	78.8 (2013)	78.8 (2014)	
Infant deaths per 1,000 live births				Table 11
All infants	6.91 (2000)	5.96 (2013)	5.82 (2014)	
Deaths per 100,000 population, age-adjusted				Table 17
All causes	869.0 (2000)	731.9 (2013)	724.6 (2014)	
Heart disease	257.6 (2000)	169.8 (2013)	167.0 (2014)	
Cancer	199.6 (2000)	163.2 (2013)	161.2 (2014)	
Chronic lower respiratory diseases	44.2 (2000)	42.1 (2013)	40.5 (2014)	
Unintentional injuries	34.9 (2000)	39.4 (2013)	40.5 (2014)	
Stroke	60.9 (2000)	36.2 (2013)	36.5 (2014)	
Alzheimer's disease	18.1 (2000)	23.5 (2013)	25.4 (2014)	
Diabetes	25.0 (2000)	21.2 (2013)	20.9 (2014)	
Influenza and pneumonia	23.7 (2000)	15.9 (2013)	15.1 (2014)	
Nephritis, nephrotic syndrome and nephrosis	13.5 (2000)	13.2 (2013)	13.2 (2014)	
Suicide	10.4 (2000)	12.6 (2013)	13.0 (2014)	
Morbidity and Risk Factors				
Fair or poor health, percent				Table 45
All ages	8.9 (2000)	10.2 (2013)	9.8 (2014)	
65 years and over	26.9 (2000)	23.1 (2013)	21.7 (2014)	
Heart disease (ever told), percent				Table 38
18 years and over	11.3 (2000–2001)	11.4 (2011–2012)	11.5 (2013–2014)	
65 years and over	30.9 (2000–2001)	30.3 (2011–2012)	29.4 (2013–2014)	
Cancer (ever told), percent				Table 38
18 years and over	5.0 (2000–2001)	6.2 (2011–2012)	6.4 (2013–2014)	
65 years and over	15.2 (2000–2001)	18.5 (2011–2012)	18.2 (2013–2014)	
Hypertension,[1] percent				Table 54
20 years and over	30.2 (1999–2002)	32.2 (2007–2010)	33.0 (2011–2014)	

General

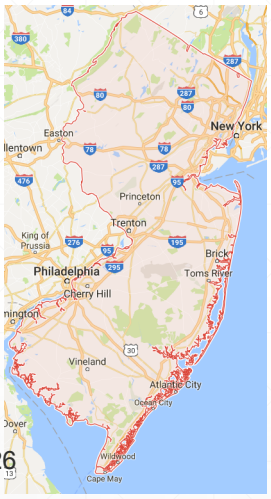
Etanercept binds specifically to tumor necrosis factor (TNF) and blocks its interaction with cell surface TNF receptors. TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. It plays an important role in the inflammatory processes of rheumatoid arthritis (RA), polyarticular-course juvenile rheumatoid arthritis (JRA), and the resulting joint pathology.[1, 2] 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.[3, 4]

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.[5] 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.[6, 7] Etanercept inhibits

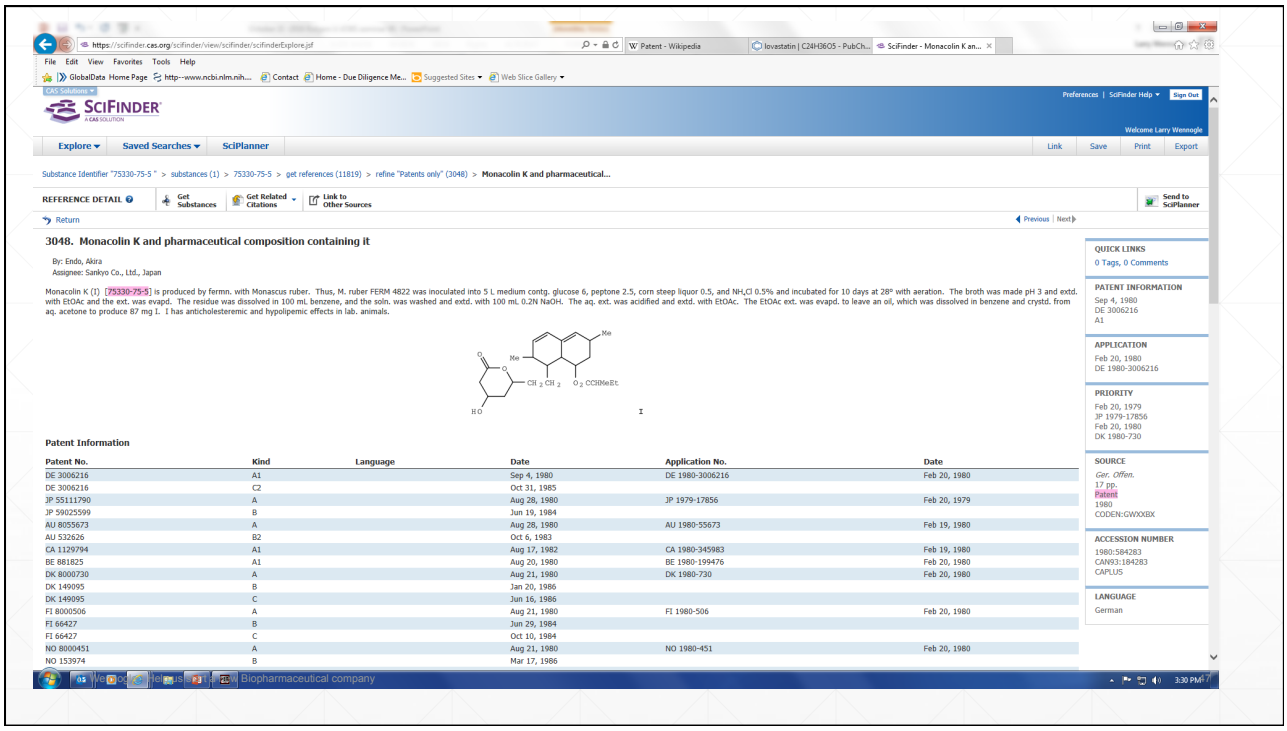
State of New Jersey and Pharma

- 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]:17 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]
- 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,[4] 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!

Backup Slides

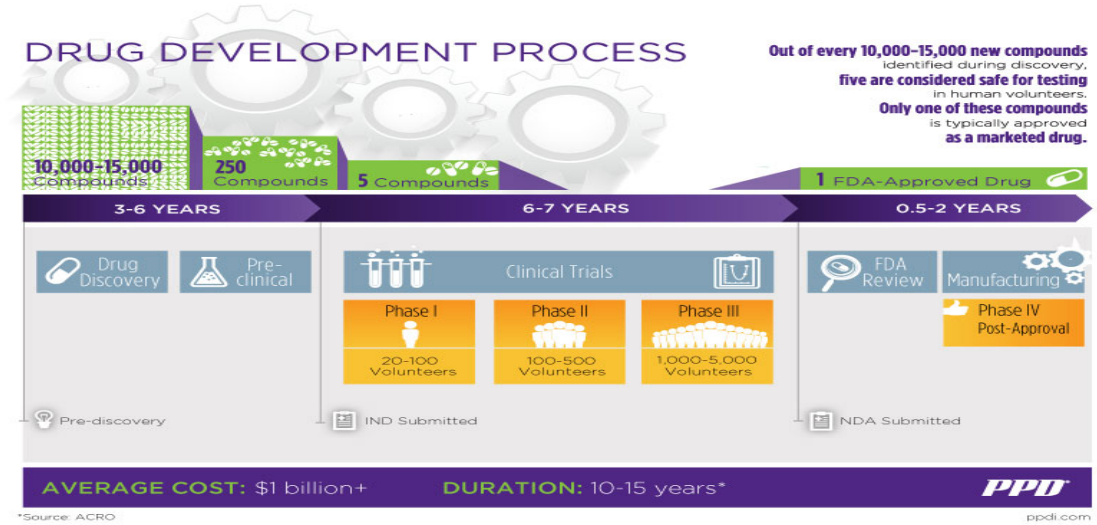
The Pharmaceutical Industry Has Had A Significant Impact on Human Health

- **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/-5X2kzIDroA

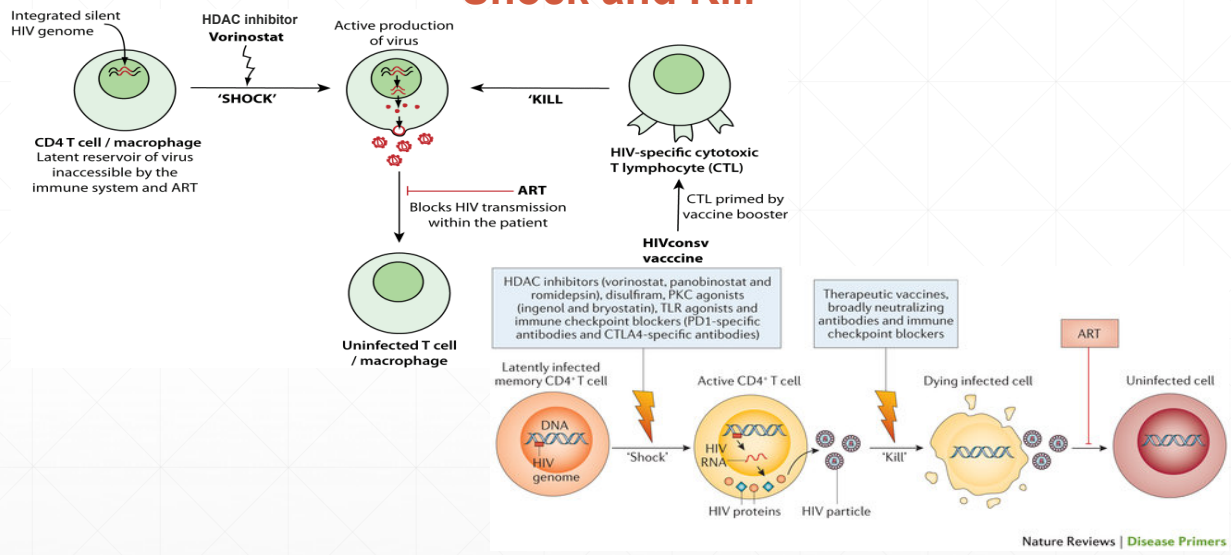
Comparing development of different product types

Attribute	Small molecule (pill)	Large Molecule (biologic)	Medical Device
Cycle time	10-15 yrs	10-12 yrs	3-7 yrs
Cost to develop	>$2.5B including capital and failures	>$2.5B including capital and failures	$31M
Regulatory Pathway	NDA (safe and efficacious)	BLA Safe and efficacious)	510K (clinical benefit or substantial equivalence)
Price	++	+++	+
Superiority, cost effectiveness, health economic benefit			



Background

Shock and Kill



Deeks et al., 2015 *Nature Reviews Disease Primers*

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