UMDNJ - GSBS  PATH N5209

The Business of Science

“From Molecules to Medicines”

Course Organizers:
Nick Ponzio
Steve Ritland
Shanon Hunt
Holly Hilton
Today’s Agenda

• Welcome and Introduction (Nick)
• Business meets Science: The Drug Innovation Industry (Steve)
• A whirlwind tour of drug discovery and development (Shanon)
• Course structure (Shanon)
• A *very* short course in pharmacology (Steve)
• Project team activity: Select your therapeutic area for semester project
This course is about how new drugs get created

This course will provide...

• An introduction to the Big Picture of *How Things Are Actually Done* in Biotech/Pharma

• Insight into the day-to-day activities of scientists / clinicians working in industry

• Practical experience in how molecules move through the drug development cycle (semester project)

• Examples of areas where industry and academia collaborate to solve healthcare problems

Whether you pursue a career in industry or academics, it’s an advantage to understand how the biotech/pharma industry works
Research funding for biomedical research:

What does it take to begin a research project?

Good Idea(s)

Talent and Expertise

Location & Resources

Money (the fossil fuel that powers research)
Research funding for biomedical research

How do you get $$$ to begin a research project?

• Idea
• Proposal (key Q: who is interested and able to fund?)
• Peer Review
• Prioritization and modification
• Check’s in the mail!
• Begin your research
Research funding for biomedical research

**Where** is biomedical research done?

- *Academic Institutions*
- Research Institutes (Public and Private)
- Industry
- Private Foundations
- Consortia and alliances
- Backyard
Survey of most frequently cited papers in clinical research: Author Affiliation
Research funding for biomedical research

Who funds biomedical research?

- Government (NIH)
- Private organizations/foundations/individuals
- Industry
- Professional Societies
- Universities
- Rich Aunt or Uncle (p.s.: don’t count on this one to drive your career)
Research funding trends: Cyclical

Percentage of NIH R01* Applications Funded, Fiscal Years 1995-2005

*RO1 Equivalents: R01, R29, R37
Source: National Institutes of Health

Similar trends for money from private sources
## Success rates for NIH RO1 Proposals

### Challenging Times for All Researchers

<table>
<thead>
<tr>
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<th>1999</th>
<th>2007</th>
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<tr>
<td>Overall success rate for NIH RO1* Proposals</td>
<td>32%</td>
<td>24%</td>
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<tr>
<td>Success rate on first submission</td>
<td>29%</td>
<td>12%</td>
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### Especially for Young Investigators

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<tr>
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<th>Then 1990</th>
<th>Now 2007</th>
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<tr>
<td>Age at first Ro1* grant</td>
<td>39</td>
<td>43</td>
</tr>
<tr>
<td>% of Ro1s* that go to first-time investigators</td>
<td>29%</td>
<td>25%</td>
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Most frequently cited papers in clinical research: Funding source

![Graph showing percentage of studies funded by different sources over the years. The x-axis represents the years from 1994 to 2002, and the y-axis represents the percentage with funding. The sources include University, Government or public, Private organisation or foundation, Industry, Professional society, and Other/unknown.]
Data from papers reporting clinical trials

Authorship:
86% had one or more authors with university or hospital affiliations; 47% had authors with industry affiliations.
No change over the period surveyed

Funding:
A majority of trials have always been funded by industry, but have increased significantly over the period surveyed.
After 1999, 31 of the 32 most frequently cited trials (97%) were funded exclusively by industry.
What do the current trend lines tell us about funding of biomedical research?

- **Funding levels** are cyclical
  - You can anticipate major swings over the course of your career and will likely need to access multiple sources of funding

- **Funding priorities** can change rapidly
  - Politically popular topics, basic versus applied research, career development programs --- you need to be prepared to adapt

- **Source** of funding can introduce bias
  - May be explicit (where the sponsor directly influences the research design, conduct, or interpretation)
  - May be implicit (where the researcher is biased to produce results that are favorable to continued funding)
  - As a researcher in either an academic or industrial setting you need to actively manage conflict of interest

Source of funding can introduce bias

- May be explicit (where the sponsor directly influences the research design, conduct, or interpretation)
- May be implicit (where the researcher is biased to produce results that are favorable to continued funding)
- As a researcher in either an academic or industrial setting you need to actively manage conflict of interest
Pros & Cons of Industry-sponsored clinical research

Potential advantages:

• Research is generally applied to practical problems
• Opportunity to integrate your research expertise with a larger resource network directed at producing a useful product or invention
• Many career development options @ the science / business interface

Potential disadvantages:

• May limit your academic freedom
• Projects can be terminated or redirected for commercial reasons
Increasing focus on conflicts of interest
- Codes of conduct have been strengthened for university, government, and industry employees
- Increasing transparency on sources of funding
- Chain of enforcement that connects sources of funding → researchers → peer-reviewed publications

Public / Private partnerships
- Playing an increasingly important role in biomedical research
- Driving greater visibility and mutual accountability

Whether you pursue a career in industry or academics, it’s an advantage to understand how the biotech/pharma industry works.
Where Business Meets Science: A Quick Look at the Drug Innovation Industry
Breakdown of the Life Sciences Landscape
(a job-hunter’s map of the industry)

Adapted from: Mapping the Healthcare Landscape, Datamonitor Nov 2009
First: The Good News About the Pharma/Biotech Industry

The industry remains one of the most reliably profitable sectors of the US economy...

The industry continues to create jobs for scientists...

Left panel adapted from: Mapping the healthcare landscape, Datamonitor Nov 2009
Right panel adapted from: Battelle/Bio Outlook 2010
And for scientists, the industry tends to pay pretty well...

Table E5-2. Average Annual Wages in the Biosciences and Other Major Industries, 2008

<table>
<thead>
<tr>
<th>Industry</th>
<th>Average Annual Wages per Employee, 2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs &amp; Pharmaceuticals</td>
<td>$93,378</td>
</tr>
<tr>
<td>Finance and Insurance</td>
<td>$85,274</td>
</tr>
<tr>
<td>Research, Testing, &amp; Medical Laboratories</td>
<td>$80,785</td>
</tr>
<tr>
<td>Total Biosciences</td>
<td>$77,595</td>
</tr>
<tr>
<td>Professional, Scientific, and Technical Services</td>
<td>$74,354</td>
</tr>
<tr>
<td>Agricultural Feedstock &amp; Chemicals</td>
<td>$72,279</td>
</tr>
<tr>
<td>Information</td>
<td>$70,780</td>
</tr>
<tr>
<td>Medical Devices &amp; Equipment</td>
<td>$63,606</td>
</tr>
<tr>
<td>Manufacturing</td>
<td>$54,392</td>
</tr>
<tr>
<td>Construction</td>
<td>$49,014</td>
</tr>
<tr>
<td>U.S. Total Private Sector</td>
<td>$45,229</td>
</tr>
<tr>
<td>Real Estate and Rental and Leasing</td>
<td>$43,239</td>
</tr>
<tr>
<td>Transportation and Warehousing</td>
<td>$42,969</td>
</tr>
<tr>
<td>Health Care and Social Assistance</td>
<td>$42,150</td>
</tr>
<tr>
<td>Retail Trade</td>
<td>$26,181</td>
</tr>
</tbody>
</table>

Source: Battelle analysis of BLS, QCEW data from the Minnesota IMPLAN Group
And to provide other forms of professional satisfaction…
But…There are Some Storm Clouds on the Horizon

<table>
<thead>
<tr>
<th>By The Numbers</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>139 million</td>
<td>Current number of US employees (jobs lost since the start of the current recession) (Source: U.S. Bureau of Labor Statistics Sept 2010)</td>
</tr>
<tr>
<td>1.4 million</td>
<td>Current number of US bioscience employees (jobs lost from the US bioscience sector since 2007) (Source: CNBC EconWatch May 2010)</td>
</tr>
<tr>
<td>8.6% → 0.2%</td>
<td>Historical CAGR for the pharma / biotech industry (forecast through 2014) (ref: DM Healthcare Landscape Nov 2009)</td>
</tr>
</tbody>
</table>
So What’s a Scientist to do?

The case for entrepreneurship in R&D in the pharmaceutical industry

Frank L. Douglas, V. K. Narayanan, Lesa Mitchell and Robert E. Litan
Nature Reviews Drug Discovery | AOR, published online 20 August 2010;

The Basic Value Proposition for Pharma
Profits Are a Key Driver of Innovation
(the Incentive -> Innovation -> Commercialization cycle)

A Capitalist’s view of the US pharmaceutical industry:

High Prices / High Profit Potential
(Proprietary Medicines)

Incentive for R&D
New Medicines

Incentive for substitutes
Generics, Me-Toos (Price Competition)

Net Result: Faster Pace of Advancement of Healthcare (*hypothetically)
A Key Challenge for Scientists in the Next 20 Years

(meaning: You)

- Fact: Healthcare is an increasingly important part of our global economy (in the US: 17.3% of our GDP and growing)

- Fact: Global healthcare costs are growing at an unsustainable rate (in the US: 9.8% average annual increase versus 3.3% for the GDP)

- Opinion: Healthcare innovation is a critical product of the US economy over the next 50 years

- Opinion: Those individuals who are able to apply true scientific innovation to the process of drug discovery and development will create value (in all senses)
Attrition During Discovery and Development

Many players, few winners

Average cost to bring a successful new drug to market: 1.7B
Average probability of success from Ph1 to registration: 11.5%

Source: Nature Reviews in Drug Discovery March 2010 How to improve R&D productivity: the pharmaceutical industry’s grand challenge
Overview of Drug Discovery and Development Process

(Shanon)
Overview of Drug Discovery and Development
The fairy-tale version

Discovery

2-6 years
Target identification, lead identification, lead optimization, clinical candidate selection

Phase 0

Starts after a lead molecule (clinical candidate) is found
Lab testing, animal studies for safety (tox studies) and efficacy

Phase 1

20-80 Healthy Volunteers
Purpose: determine safety and dosage

Health Authority
End of Ph 1 Meeting

Phase 2

100-300 Patients
Purpose: demonstrate efficacy

Health Authority
End of Ph 2 Meeting

Phase 3

1000-5000 Patients
Purpose: monitor adverse reactions to long term use

Health Authority
End of Ph 3 Meeting

NDA

Launch!

Years
It is not, in fact, a nice, clear linear process.
- The compound could be sent backward to further explore a safety issue
- It’s an imperfect science. Something always slows down the development.

There is considerable overlap of activities between Phases.
- Toxicology animal studies continue to the NDA
- Phase 1 or Phase 2 clinical trials can be running concurrently with Phase 3 trials
- Phase 2 and 3 can be combined

There are other aspects to consider
- Regulatory interactions and requirements in other countries (Global Regulatory Affairs)
- The process of developing and manufacturing drug supply changes (CMC teams)
- New competitor activities or changes in market demand could change the development strategy (Business teams)
Overview of Drug Discovery and Development

**Discovery/Phase 0**

- **Target Identification and Validation**
  - Target Assessment (TA)
  - Lead Series Identified (LSI)
  - Clinical Lead(s) Selected (CLS)
  - Clinical Candidate(s) Selected (CCS)
  - Entry Into Human (EIH)

- **Lead Identification**
  - Identify one or more leads (biological or chemical compounds) that interact with the target to get the desired therapeutic effect.
  - Optimize the physicochemical characteristics of the compound to make it more druggable.

- **Lead Optimization**
  - Demonstrate safety in animals prior to human trials, show therapeutic advantages

- **Phase 0 Preclinical Testing**
  - Identify a biological pathway and molecular structure of interest

**Genomics**

**Proteomics**

**Bioinformatics**

**High Throughput Screening**

**In silico modeling**

**GLP Tox**

**IND Package**
Overview of Drug Discovery and Development

Exploratory Development

- **Entry Into Human (EIH)**
- **Start of Phase 2**
- **Start of Phase 3**

**Phase 1**

- Evaluate safety in healthy human volunteers
- Establish **PK and PD profile** for better characterized drugs.

**Biomarkers**

**Modeling and Simulation**

**Dosage**

**Treatment Duration**

- Evaluate efficacy and side effects in patients
- Establish **PK and PD profile** for better characterized drugs.
Overview of Drug Discovery and Development
Confirmatory Development

Demonstrate/confirm the compound is **as effective as existing drugs**, if not more so

Refine safety profile
(long-term toxicity, undesirable side effects)
across a large number of patients

Evaluate use of the drug in different patient groups
Identify **new therapeutic opportunities**
Develop **new formulations**

**Market Preparation**

**Brand Management**

**Post Approval Commitments**

Phase 3
NDA
Phase 4

Filing Decision
Approval and Launch
In Summary

- 12-15 years of discovery and development
- R&D investment of $1,000,000,000 to bring ONE drug to market
- 20 years of patent protection from patent filing date
- Seemingly insurmountable biology and regulatory hurdles

How can it possibly be worth it?
Course Structure and Organization

Shanon
When and where you need to be

- **Session Dates**
  - Wednesday evenings
  - Sept 7 - Dec 14 (see syllabus)

- **Session Times**
  - 6:00 PM - 9:00 PM (with one break, if you’re really, really lucky)

- **Classroom Location**
  - UMDNJ Newark Campus
  - Medical Sciences Building (MSB) in the Department of Pathology
  - Room C-555 (main lecture); breakout rooms for team activities

- **Critical Due Dates**
  - Date of your assigned Debate Session
  - MC Presentation #1: October 12th
  - MC Presentation #2: November 9th
  - Final Project Portfolios: December 14th (last day of class)
How the class is organized

- **Practical application** of the drug discovery/development process
- **Modular approach** & lecturers who do this for a living
How you’ll spend your class time

Lecture (first ~1 hour of each class)
- Each session will begin with a high level introduction of the topic and its context for your semester project

Activities Section (~2 hours for each class)
- Activities will apply concepts from that day’s lecture
- The activities conducted in class will be part of your Project Portfolio, due at the end of the course.

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
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<tbody>
<tr>
<td>6 pm ~ 7:00</td>
<td>Lecture</td>
</tr>
<tr>
<td>7:15 ~ 9 pm</td>
<td>Activities</td>
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<tr>
<td>15 mins</td>
<td>Break</td>
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What you will deliver over the semester

- Semester Group Project – Project Portfolios
- Group Presentations
- Case Study Debates
The Project Portfolio is a collection of deliverables that you will prepare over the course of the semester.

Each group will be required to submit a project portfolio at the end of the semester.

PPs will make up 30% of your semester grade.

**Due Date: December 14th**

**Project Portfolios include the following:**
1. Introduction/Executive Summary
2. Target Rationale
3. Experimental Strategy
4. Target Product Profile (TPP)
5. Project Gantt Chart (Timeline for drug development)
6. Phase 1 Program Strategy
7. Phase 2 Trial Design/Schedule of Assessments
8. Decision Criteria for Entry into Confirmatory Development (Lifecycle Investment Point)
9. Unique Selling Points
10. Lifecycle Strategic Plan
The good news:

**Exams:** There are *no exams* in this course!

**Project portfolio:** You will build your final project portfolio *one step at a time* as we proceed through the individual class sessions.

The bad news:

**Teams:** Your team members and therapeutic areas are *assigned*

**Team grading:** You will be graded *as a team* on your project portfolio including a component of *peer feedback*.
Each group will develop and deliver two Management Committee Presentations (20 min. each)

This is a “decision point” presentation, with a request to management

Teams must select 2-3 presenters for each of the presentations (and the presenters must be different between MC1 and MC2)

**Week 6: MC Presentation #1 – Entry into Development Portfolio**
- Therapeutic Area
- Target, MoA, Scientific Rationale
- Pharmacology
- Development Plan/Next Steps
- 20% of your final grade

**Week 10: MC Presentation #2 – Lifecycle Investment Decision/Entry into Confirmatory Trials**
- Opportunity assessment, market potential
- Clinical Proof of Concept (Ph1 & 2 data, efficacy & safety)
- Phase 3 & registration strategy
- 25% of your final grade
Class Debates

- 6-8 people will be assigned to each debate, assignments to follow
- Students will need to prepare for their role ahead of class
- More details on the debates will be provided as we get closer
- Debates will count for 10% of your final grade

Week 7

*Ethics of Ph1 studies, safeguards, policies, oversight, accountabilities (case study: TeGenero)*

Week 9

*Personalized Healthcare: Are biomarkers helping or hurting pharmaceutical productivity?*

Week 13

*Mock FDA Advisory Committee Meeting (TBD)*

*Process, stakeholders, and risk:benefit issues*
1. Please come to class on time.
   • Our lectures are industry professionals who volunteer their time to teach this class.

2. Please do not use your computers, phones, iPads, etc. during lectures.
   • They will be very useful during project time (the second half of class), so please bring them.

3. Please do feel free to ask questions/interact with lecturers.
   • This is a good opportunity for you to get to know experts in their fields who do drug development every day.
Team Peer Feedback Form

Evaluator: ___________
Team member being evaluated: _______________________

1. This team member contributed substantially to developing the project strategy
   Yes ___   No ___
   Comments:

2. This team member contributed substantially to management committee presentations
   Yes ___   No ___
   Comments:

3. This team member contributed substantially to the final project portfolio
   Yes ___   No ___
   Comments:

Overall peer review rating: ____ (score 5% for each “Yes” answer to a maximum of 15%)
# Student Feedback Form

Session Date: ___________
Session Topic: ________________

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<td>Low</td>
<td>Medium</td>
<td>High</td>
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My satisfaction level with the *overall course* thus far is: (circle one)

My satisfaction with this *particular session* is: (circle one)

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**Specific** comments and suggestions (What worked well? Do you have any constructive feedback?):
Course Website

Resources for Students

http://www.umdnj.edu/gsbsnweb/olc/fmtm/index.htm

Course Syllabus
Schedule of Classes and Topics
Course logistics
Project information
Background Reading

Course Files
Organized by session date
Reference articles/pre-read material
Lecture presentations
Examples and templates for exercises

Relevant websites

Faculty contact info
Pixelated Pharmacology 101® and Definition of a few key terms used in this Course (Steve)
What’s a *molecular target*?
What’s a *hit*?
What’s a *lead*?
What’s a *drug*?
What’s a *ligand*?
What’s a *receptor*?
What’s *ADME*?

Why should we *care* about all this *jargon*?
Receptor Function – Normal Response

Response

Receptors

Ligands
Receptor Function – Pathological Response

Normal

Disease

Response

Receptors

Ligands
Antagonists (♦) Block Agonist (♣) Function
Finding Drug Candidates: Its About Affinity, Selectivity and Distribution

- **Affinity**
  - Ligand must have sufficient affinity at the receptor to occupy it at a reasonable concentration and cause the desired response (efficacy)

- **Selectivity**
  - The ligand needs to achieve the desired occupancy at target receptor without significantly affecting the function of other essential receptors.

- **Distribution**
  - The ligand must distribute to the site of the receptor
  - It needs to achieve sufficient “effective” concentration at the site to occupy receptor
  - It must maintain this concentration between dosing intervals
Occupancy $\theta$ is the % of Receptors that have Bound Ligand

3 of 9 (33%) receptors are occupied at this ligand concentration

$\theta = 0.33$
Competing Equilibria

Receptors  Ligands  Serum Protein
Metabolism Reduces Ligand Conc. & Receptor Occupancy

Occupancy = 60%

Metabolizing enzymes

Elimination
Barriers to turning a potent molecule into a drug: ADME

- Absorption
- Distribution
- Metabolism
- Excretion

Diagram:
- Drug enters through GI tract.
- Liver processes the drug.
- Portal vein takes the drug to the liver.
- Drug is sent to the heart, lung, and target tissue.
- Oral (po) delivery versus iv delivery.
**Drug:** A drug is any chemically defined, non-dietary substance that will produce clinical effects or alter some bodily functions such as relieving symptoms, curing diseases or used as preventive medicine.

**Molecular Target:** A molecular structure that will undergo a specific interaction with drugs that are administered to treat or diagnose a disease. The resulting interaction has a connection with the clinical effect(s) of the drug. Good drugs are potent and specific; that is, they must have strong effects on a specific biological pathway and minimal effects on all other pathways. Confirmation that a compound inhibits the intended target (drug target validation) and the identification of undesirable secondary effects are among the main challenges in developing new drug candidates.

**Some Examples:**
- Phosphodiesterase-5 is the molecular target of Viagra (sildenafil)
- HMG-CoA reductase is the molecular target of Lipitor (atorvastatin)
- ??? is the molecular target of aspirin
- ??? Is the molecular target of Avandia (rosiglitazone)
- ??? Is the molecular target of Avastin (bevacizumab)

Definitions adapted from: Imming et al, NRD Oct 2006
Drug Potency: Potency is the dose of drug required to produce a specific effect of given intensity. Drug potency depends on both affinity and efficacy.

Drug Selectivity: Describes a drug's ability to affect a particular molecular target or cell population in preference to others.

Drugability: Describes the overall physicochemical profile of a compound including potency, selectivity, solubility, permeability, stability, toxicity, and metabolism in vitro and in vivo.

Some Examples:
- Staurosporin is a potent but non-selective kinase inhibitor (a research tool, not a drug)
- Erlotinib (Tarceva) is a potent and relatively specific inhibitor of EGFR that also has good solubility, permeability, stability, toxicity, and metabolism (i.e. it is a drug)

Definitions adapted from: Fabian et al, NBT March 2005
**Drug Metabolism:** Enzymatic biotransformation of a drug by the body, usually for the purpose of elimination/excretion. The major players here are the Phase 1 cytochrome P450 (CYP) enzymes and the Ph2 conjugating enzymes (glucuronidation, sulfation, etc.)

**Pharmacokinetics (PK):** What the body does to the drug. Specifically: bodily absorption, distribution, metabolism, and excretion of drugs (ADME). Commonly used PK terms include T1/2, CMax, Tmax, Ctrough, AUC, %F, and Vss

**Pharmacodynamics (PD):** What the drug does to the body, including biochemical and physiological effects of drugs and the mechanisms of their actions

**Drug-Drug Interaction (DDI):** An interaction between a drug and another substance that prevents the drug from performing as expected

**Some Examples:**
- Measuring whether a particular biochemical activity is inhibited in tissues?
- Measuring whether a particular drug inhibits CYP3A4?
- Measuring how long it takes to achieve peak plasma concentrations?

Definitions adapted from: Imming et al, NRD Oct 2006
**Compound Library:** A large, chemically diverse collection of synthetic molecules or natural products having defined composition

**High Throughput / Screening Assays:** Initial preclinical testing of compounds using enzymatic, cell based, or animal models to characterize their biological and toxic effects for potential clinical applications

**Hits:** Compounds scoring as positive in the initial screening assay. Hits undergo subsequent counterscreening and characterization assays

**Leads:** Molecules showing expected efficacy in relevant in vitro pharmacological models, often also passed the preliminary in vitro toxicological and ADME screening, is ready to be taken into lead optimization

**Medicinal chemistry:** Manipulation of functional groups to determine Structure-Activity Relationships (SAR) and improve initial lead structures

**Some Examples:**
- Pharmacopeia has a 7.5 million member compound collection
- Measuring whether a particular drug inhibits CYP3A4?
- Measuring how long it takes to achieve peak plasma concentrations?
A Whole Genome of Potential Drug Targets

Future Drug Target Space

- Human Genome
  - 24000

- Genetic association
  - 6465
  - ~2400

- Mouse K/O
  - ~320

- Predicted druggable genome
  - ~3505

- Lead/chemical tools
  - ~145
  - 160
  - 170

- Drugs
  - 578

-N5209


**Genetic association linkage data estimated by text-mining from entity co-occurrence within Medline abstracts. Data produced by Anna Gaulton and Andrew Hopkins, using a modified version of Lucene, by Lee Hadland, to text-mine Medline.
Some useful debabbleizers as the course goes on:

CMC: http://www.chemsuppliers.org/glossary.html
Toxicology: http://www.atsdr.cdc.gov/glossary.html
Development: http://www.drugdevelopment-technology.com/glossary/
Project Teams: 4 Therapeutic Areas

- Oncology
- Viral Diseases
- Fibrotic Diseases
- Inflammation & Autoimmune Diseases
Oncology
Cancer: Impact on Patients

2009 Estimated US Cancer Deaths*

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esophagus</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>3%</td>
<td></td>
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<tr>
<td>All other sites</td>
<td>25%</td>
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<tr>
<th>Tumor Type</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>Ovary</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Uterine corpus</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Liver &amp; intrahepatic</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Brain/ONS</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>All other sites</td>
<td>25%</td>
<td></td>
</tr>
</tbody>
</table>

*ONS=Other nervous system.
Source: American Cancer Society, 2009.
Hallmarks of Cancer: Opportunities for Therapeutic Intervention
Cancer Pathways: Opportunities for Therapeutic Intervention
Virology
## Top Opportunities in Virology

“*Virus*” is a Latin word used by doctors to mean, "Your guess is as good as mine”

- Bob Hope

<table>
<thead>
<tr>
<th></th>
<th>Unmet need</th>
<th>Competitive environment</th>
<th>PHC potential</th>
<th>Target Risk</th>
<th>Dev/Reg Risk</th>
<th>Time to market</th>
<th>Opportunity size</th>
<th>Potential peak sales ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV cure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.8 – 5.5 B</td>
</tr>
<tr>
<td>HBV clinical cure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.9 B</td>
</tr>
<tr>
<td>Severe influenza</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>425 - 850 M</td>
</tr>
<tr>
<td>Severe pediatric RSV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>650 – 800 M</td>
</tr>
<tr>
<td>Congenital CMV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>740 - 780M</td>
</tr>
<tr>
<td>HPV related AIN</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>630 M – 1.26 B</td>
</tr>
<tr>
<td>HIV clinical cure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 – 2+ B</td>
</tr>
<tr>
<td>Virus related CFS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>500 – 750 M</td>
</tr>
</tbody>
</table>

Attractiveness scale low to high: 🟠🟢🔵🟠
HCV Life Cycle – New Therapies & Targets

- Virus Binding and receptor mediated endocytosis
- Virus Binding and receptor mediated endocytosis
- Transport and release
- Entry inhibitors
- Immune modulators
- Core of the virus released
- Core of the virus released
- Core of the virus released
- Core of the virus released
- Core of the virus released
- RNA uncoating
- RNA uncoating
- RNA uncoating
- RNA uncoating
- RNA uncoating
- RNA uncoating
- Translation and polyprotein processing
- Translation and polyprotein processing
- Translation and polyprotein processing
- Translation and polyprotein processing
- Translation and polyprotein processing
- Translation and polyprotein processing
- RNA replication
- RNA replication
- RNA replication
- RNA replication
- RNA replication
- RNA replication
- RNA synthesis
- RNA synthesis
- RNA synthesis
- RNA synthesis
- RNA synthesis
- RNA synthesis
- Protease inhibitors
- Protease inhibitors
- Protease inhibitors
- Protease inhibitors
- Protease inhibitors
- Protease inhibitors
- NS5A inhibitors
- NS5A inhibitors
- NS5A inhibitors
- NS5A inhibitors
- NS5A inhibitors
- NS5A inhibitors
- Polymerase inhibitors
- Polymerase inhibitors
- Polymerase inhibitors
- Polymerase inhibitors
- Polymerase inhibitors
- Polymerase inhibitors
- New Therapies & Targets
- Life cycle Step
Inflammation and Fibrosis
Biological insult
- Pathogen, environmental, genetic, *unknown*

Inflammation
- Acute / chronic

Fibrosis
- Local / systemic

Organ Dysfunction
- Single / multiple

Death

“…the build-up of deadly scar tissue in a broad class of diseases that account for an estimated 45 percent of U.S. deaths each year.” [Science, Jan. 2007]
Healing Versus Fibrosis

**A**
- Proliferation, migration
  and matrix synthesis

**B**
- Increased proliferation,
  migration and matrix synthesis

**Physiological Wound Healing**

**Fibrosis**
Molecular Targets in Fibrosis
Potential Impact at Multiple Points

Anti-fibrotic mechanisms act on a number of cell types and processes:
- Activated epithelial cells
- Fibrogenic cytokines
- Activated fibroblasts
- Epithelial apoptosis
- ECM overproduction

Connective tissue synthesis

Fibroblast Foci

Transformation & Epithelial Apoptosis

Apoptosis resistant And cytokine over-responsive Phenotype

CTGF
TGF-β

Fibroblast Activation – Migration & Proliferation

Injury/Stress

“Activated” Epithelial cell

Alveolar Epithelial cell

CTGF
TGF-β

TGF-β
PDGF
TNF-α
IL-4
IL-13
bFGF

Fibroblast Foci
**Inflammation**: A pathologic process in response to physical, chemical, or autoimmune injury consisting of mediator release and inflammatory cell infiltration. Cardinal clinical signs of inflammation are redness; heat, swelling; and pain; and/or lost function

- Chronic inflammation: Prolonged and persistent inflammation marked chiefly by new connective tissue formation; examples include arthritis, lupus, inflammatory bowel disease

**Fibrosis**: A pathologic process involving the formation of excess fibrous connective tissue that can destroy the architecture and function of the underlying organ or tissue. Examples include pulmonary fibrosis, hepatic cirrhosis, scleroderma
Project Team and Debate Assignments
Assignment for Tonight

Team Introductions
- Collect your group into a breakout room
- Introduce yourselves and your background

Identify a disease for your semester project
- Review slides on your therapeutic area (on-line research is very helpful!)
- Select a disease of interest to the whole group
- Before you leave, please inform us of your choice

Post-class
- We will send your group some background information on your selected disease area.
- Please feel free to conduct your own research on the disease (including drugs currently available or in development)