Drug Discovery and Development for HIV and Opportunistic Infections

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Drug Discovery and Development for HIV and Opportunistic Infections

Anti-HIV Drugs

- Overview of the Drug Discovery and Development Process
- HIV Life Cycle and Targets of Opportunity
- Current HIV Therapies
  - RT Inhibitors
  - Protease Inhibitors
- Resistance Mechanisms
- In the Pipeline
  - Integrase Inhibitors
  - Cytokine/gp40 inhibitors
  - Nucleocapsid-Interactive Agents
- Vaccines
Drug Discovery and Development for HIV and Opportunistic Infections

Drugs Against Opportunistic Infections

- Opportunistic Viral Infections
- Opportunistic Fungal Infections
- Opportunistic Parasites
- Opportunistic Bacterial Infections
- AIDS-Associated Neoplasms
Overview of the Drug Discovery and Development Process

- Market
  - Phase 4
- Development
  - Phase 3
  - Phase 2
  - Phase 1
- Discovery
  - >10,000 Compounds
  - ~5 Compounds
  - 2010
  - 2011
  - 2012
  - 2017
  - 2018
  - 1 Compound

2003
How HIV/AIDS has Changed the FDA Approval Process

<table>
<thead>
<tr>
<th>Pre-clinical</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>screening</td>
<td>Phase 1</td>
</tr>
<tr>
<td>synthesis &amp; purification</td>
<td>Phase 2</td>
</tr>
<tr>
<td>animal testing</td>
<td>Phase 3</td>
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- Short-term Tox
- Long-term Tox
- Accelerated Development/Review
- Treatment IND
- Parallel Track

IND
NDA
Approval
Where do the 10,000+ Compounds Come From?

“Lead Compound”

Observation
Screening
Rational Design

10-10,000 Compounds

“Lead Compound”

Lead Optimization
100-1,000 Compounds
Where do “Lead Compounds” Come From?

• Existing Drugs!

- Side effects: antihistamine promethazine (sedative)
  chlopromazine - antipsychotic
  β-blockers for angina (hypotensive)
- Improvements: β-lactams (oral availability, resistance, and specificity)
- Me-too Drugs: ACE inhibitors
Where do “Lead Compounds” Come From?

• Screening
  - Extensive Screening: New types of compounds screened for ANY activity (benzodiazepines)
  - Random Screening: Focus on one activity, screen many compounds (antibiotics)
  - High-Throughput Screening: Variation of Random Screening in which $10^4 - 10^7$ compounds are screened in months-years
  (Combinatorial Chemistry - making $10^2-10^5$ compounds at once)
Where do “Lead Compounds” Come From?

• Observation
  - Ethnopharmacology
    Ancient medicines (morphine, cocaine)
    Ancient poisons (digitalis, reserpine)
    Contemporary medicines (green tea, Compound Q)
  - Serendipity
    penicillin
    vinca alkaloids
    many more!!
  - Analogy
    renin - HIV protease
Where do “Lead Compounds” Come From?

• Rational Approaches
  • Substrate/Natural Ligand Analogs
    Tagamet - Histidine : H2-receptor
    6-mercaptopurine - purines : purine metabolism
    AZT - thymidine : HIV Reverse Transcriptase
  • Structure-Based Design
    ? Too soon to tell?
    Very useful in optimization of Leads

• Genomics
  - Antisense Agents
  - Biological Agents
  - Gene Therapy
The Money Game

“$500M in R&D for each new drug”

R&D INVESTMENTS BY RESEARCH-BASED PHARMACEUTICAL COMPANIES

Expenditures ($ billions)

Source: PhRMA Annual Survey, 1999
*Estimated

Cost per Drug (millions)

Average Cost per Drug over ten years ~$450M
Status of Anti-HIV/Opportunistic Disease Drug Development Pipeline - 2001

As of 2003: 33 Antivirals, 14 vaccines: 83 total drugs in development
Drug Discovery for HIV

Existing Drugs - Improvements

Screening

Observation - RESISTANCE!

Rational Approaches

Require TARGETS
HIV Life Cycle - In Search of Drug Targets

Diagram of a Retrovirus

- lipid envelope
- Receptor binding proteins
- viral RNA
- capsid: core proteins
- Reverse transcriptase

25 nm
Protease