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

- **Discovery**: >10,000 Compounds
- **Market**: Phase 4
- **Phase 1**: ~5 Compounds
- **Phase 2**: 2009
- **Phase 3**: 2010
- **Phase 4**: 2011, 2016, 2017
- **NDA**: 1 Compound

Timeline:
- 2002: Discovery
- 2009: IND
- 2010: 2011: ~5 Compounds
- 2016: 2017: Market

Note: The image also includes a timeline with years ranging from 2002 to 2017, showing the progression from Discovery to Market.
How HIV/AIDS has Changed the FDA Approval Process

**Pre-clinical**
- screening
- synthesis & purification
- animal testing

**Clinical**
- Phase 1
- Phase 2
- Phase 3

**Approval**
- Accelerated Development/Review
- Treatment IND
- Parallel Track

**Steps**
- IND
- Short-term Tox
- Long-term Tox
- NDA
Where do the 10,000+ Compounds Come From?

Observation

Screening

Rational Design

10-10,000 Compounds

“Lead Compound”

100-1,000 Compounds

Lead Optimization
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

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

- Antivirals: 38
- Anticancer: 15
- Anti-infectives: 14
- Vaccines: 14
- Immunomodulators: 8
- Other: 14
- Antifungals: 6
- Antiviral: 38
Drug Discovery for HIV

Existing Drugs - Improvements

Screening

Observation - RESISTANCE!

Rational Approaches

Require TARGETS
Retrovirus replication