Biosciences in the 21st Century

The Human Immunodeficiency Virus and AIDS
My Goals for Today’s Lecture!

- At the conclusion of today’s class, I hope that you will walk away (run away?) with an understanding of:
  
  - the impact of HIV on the developed and developing world.
  - strategies to prevent or treat HIV infection, including drugs, vaccines and topical microbicides.
  - the plight of women in the developing world and their struggle with HIV infection.
How Will I Accomplish These Goals?

- I will provide an overview of my experience with HIV and how HIV has defined scientific research in the past two decades.
- I will define means to fight HIV infection and why each method is important.
  - Therapeutic drug development: prolong survival
  - Vaccine development: can we prevent infection?
  - Topical microbicides: addressing the reality of AIDS in the world!
Who am I and What Do I Know?

- President and Chief Scientific Officer of ImQuest BioSciences, Inc.
- Executive Vice President and Chief Scientific Officer of ImQuest Pharmaceuticals, Inc.
- Co-founder of Arisyn Therapeutics, Inc.
- Have worked in the field of HIV therapeutic and microbicide development since 1992 but trained in the field of HIV virology since 1989.
- Have screened approximately 500,000 drug candidates for anti-HIV activity and participated in the development of dozens of these compounds.
- Currently developing HIV microbicides.
Acquired Immunodeficiency Syndrome (AIDS)

- The lentivirus HIV was discovered in 1982.

- The disease:
  - Primary viral infection, initial immune control but subsequent destruction of the immune system and the rise of opportunistic infections.

- Why is HIV unique and problematic?
  - Mutability; high error rate and lack of proofreading capability of the reverse transcriptase (RT) can generate mutation at every amino acid position in less than 24 hours
  - Infecst the hematopoietic cells that are supposed to fight the virus
  - Accessory and regulatory proteins control levels of virus production, immunologic effects, and other intricate means of control over HIV replication
  - Establishment of reservoirs or sanctuary sites; latency; resistance; integration of the provirus
The Epidemiology of HIV

Estimated number of people living with HIV globally, 1990–2007

This bar indicates the range
Estimated number of adult and child deaths due to AIDS globally, 1990–2007

This bar indicates the range
Estimated number of people newly infected with HIV globally, 1990–2007

Number of people newly infected with HIV

Millions

Year

A Global View of HIV Infection
Adults and children estimated to be living with HIV, 2007

Total: 33.2 (30.6 – 36.1) million
Estimated number of adults and children newly infected with HIV, 2007

- **Western & Central Europe & Central Asia**: 150,000 (70,000 – 290,000)
- **Middle East & North Africa**: 35,000 (16,000 – 65,000)
- **Sub-Saharan Africa**: 1.7 million (1.4 – 2.4 million)
- **East Asia & Central Asia**: 150,000 (70,000 – 290,000)
- **South & South-East Asia**: 340,000 (180,000 – 720,000)
- **Caribbean**: 17,000 (15,000 – 23,000)
- **North America**: 46,000 (38,000 – 68,000)
- **Latin America**: 100,000 (47,000 – 220,000)
- **South & South-East Asia**: 340,000 (180,000 – 720,000)
- **Oceania**: 14,000 (11,000 – 26,000)

**Total**: 2.5 (1.8 – 4.1) million
Estimated adult and child deaths from AIDS, 2007

Total: 2.1 (1.9 – 2.4) million
Children (<15 years) estimated to be living with HIV, 2007

Total: 2.5 (2.2 – 2.6) million
Estimated number of children (<15 years) newly infected with HIV, 2007

Total: 420,000 (350,000 – 540,000)
Estimated deaths in children (<15 years) from AIDS, 2007

Total: 330 000 (310 000 – 380 000)
Human Immunodeficiency Virus
Virion structure and function

• Structural proteins
  • Envelope (SU and TM)
  • Core (CA, MA, NC)

• Enzymes
  • Reverse transcriptase
  • Protease
  • Integrase

• Regulatory and accessory proteins
HIV Replication

1. Free Virus
2. Binding and Fusion: Virus binds to cell at two receptor sites.
3. Infection: Virus penetrates cell. Contents emptied into cell.
4. Reverse Transcription: Single strands of viral RNA are converted into double-stranded DNA by the reverse transcriptase enzyme.
5. Integration: Viral DNA is combined with the cell’s own DNA by the integrase enzyme.
6. Transcription: When the infected cell divides, the viral DNA is ‘read’ and long chains of proteins are made.
8. Budding: Immature virus pushes out of the cell, taking some cell membrane with it.
9. Immature virus breaks free of the infected cell.
10. Maturation: Protein chains in the new viral particle are cut by the protease enzyme into individual proteins that combine to make a working virus.
Virus Attachment

- Viral attachment: gp120 interaction with CD4
- Chemokine receptor engagement: gp41 interaction with CCR5 or CXCR4
- Maraviroc acts as a CCR5 antagonist to inhibit entry
Viral Penetration and Fusion

- Engagement of gp41 with the beta-chemokine receptors induces conformational rearrangements that result in the fusion of the cellular and viral membranes.
- T-20 (enfuvirtide, Fuseon) mimics the fusion domain and prevents fusion.
Upon fusion of the membranes, the viral core is released into the cellular cytoplasm and uncoats to expose the viral RNA, initiating reverse transcription.

Is core entry and uncoating an antiviral target?
Reverse Transcription

- The HIV RNA genome is converted into a double stranded DNA copy through the action of the virus-encoded RT.
- Nucleoside and nucleotide analogs mimic natural bases and become incorporated into the nascent DNA strand, terminating strand elongation by RT.
- Nonnucleoside RT inhibitors bind to the HIV-1 RT and allosterically inhibit polymerase function.
Nuclear Entry and Pre-Integration

- HIV integrase catalyzes the incorporation of the HIV DNA into the host cell genome, creating the HIV provirus.
- Viral protein R (Vpr) facilitates the movement of HIV into the nucleus.
- Integration makes HIV a component of the human genome and yields latently and chronically infected cells.
Viral RNA and protein are produced in infected cells using the host cell metabolic machinery.

Viral accessory and regulatory proteins regulate the timing and degree of replication.

Cellular activation also plays a critical role in regulating the level of expression of HIV.

Integrase inhibitors.
Protein Synthesis and Protease

- Assembly of the virus particle occurs at defined (polarized) locations in the infected cell.
- Virus production requires assembly of viral genetic material and structural polyproteins at the cell membrane.
- Virus is released from the cell by budding and requires the action of the virus-encoded protease.
- Maturation inhibitors.
- Protease inhibitors.
Treating and Preventing HIV Infection

- Education and Abstinence
- Therapeutic agents
- Vaccines
- Topical microbicides
- The Food and Drug Administration (FDA) and the testing and approval process for HIV treatments
The Evolution of Highly Active Anti-Retroviral Therapies (HAART)

- The early years of monotherapy: the age of drug resistance
- The development of combination therapies: shifting treatment paradigms
- Managing the treatment of a chronic life-long infection: the age of long term toxicity
- The future: the age of personalized therapy?
Anti-Retroviral Agents

- Nucleoside reverse transcriptase inhibitors
- Nonnucleoside reverse transcriptase inhibitors
- Protease inhibitors
- Entry inhibitors
- Fusion inhibitors
- Integrase inhibitors
Problems With Anti-Retroviral Therapy

- Resistance (development of multi-drug resistant virus strains: super-bugs?)
- Toxicity
- Drug interactions
- Adherence
- Co-infections
Why Does it Take So Long to Approve New Drugs?

- Developing a new drug can take 10 years or more.

- Most HIV drugs are identified by testing existing drugs for anti-HIV activity (screening). A newer method is rational drug design. In this process, scientists "build" drug molecules to fight HIV in specific ways.

- When a promising drug is identified, it goes through pre-clinical testing. This involves laboratory and animal studies. These show whether the drug works against HIV and how it works. They also show how it can be manufactured, and make sure it is not too toxic (poisonous).

- If pre-clinical results are good enough, the drug company files an Investigational New Drug (IND) application. Then it starts testing the drug in humans (clinical trials). Only about 1 candidate drug in 1,000 makes it into clinical trials.

- When enough clinical trials are completed, the manufacturer submits an NDA, or New Drug Application. If the FDA approves the NDA, the drug can be sold to treat specific medical conditions.
The Development of an AIDS Vaccine

- Challenges: HIV is a wily opponent!
- Scientific progress.
- Latency. Immune responsiveness. Epitope masking.
- Will we ever have an HIV vaccine?
HIV Prevention Strategies

- Education
- Abstinence
- Condom distribution programs
- Needle exchange programs
- Issues for developed versus developing countries
- Vaccines
- Topical microbicides
Topical Microbicides

“The introduction of a microbicide with 60% efficacy introduced into 73 low-income countries could avert 2.5 million HIV infections over three years in women, men and infants.”

Watts et al., The London School of Hygiene and Tropical Medicine, 2002
What is a microbicide?

- A new class of products under development: none have been approved for use; three have failed
- Vaginal or rectal use by men and women
- Protection of an individual and their partner from HIV and possibly other sexually transmitted diseases
- Formulated as a gel, cream, sponge, or intra-vaginal ring
How will a microbicide work?

- Kill or immobilize the pathogen
- Create a barrier between the pathogen and the target cells or tissue in the vagina or the rectum
- Prevent infection from taking hold or spreading once the pathogen has initiated infection
For well over a decade, HIV has quietly but steadily claimed women’s lives. Today, over 50% of all people living with HIV/AIDS are women.

According to the United Nations, globally, young women and girls are more susceptible to HIV than men and boys, with studies showing they can be 2.5 times more likely to be HIV-infected as their male counterparts.

Their vulnerability is primarily due to inadequate knowledge about AIDS, insufficient access to HIV prevention services, inability to negotiate safer sex, and a need for more female-initiated prevention methods such as microbicides.
Percent of adults (15+) living with HIV who are female, 1990–2007
Median HIV prevalence among women (15-49 years) attending antenatal clinics in consistent sites in southern African countries, 1998–2006

Sources: Various antenatal clinic surveys.
Why do we need a microbicide?

- HIV infection in Africa, India, and southeast Asia
- The feminization of AIDS
- Empowering women to control their future
- Cultural issues
Characteristics of the Ideal Microbicide

- Colorless, tasteless, and odorless
- Inexpensive to manufacture and purchase
- Safe to use more than once a day and for long periods of time
- Effective against multiple STIs in addition to the prevention of HIV transmission
- Fast acting, long lasting and non-irritating
- Undetectable to either partner
- Available in contraceptive and non-contraceptive forms
- Available without a prescription
Economic Issues

- Cost of clinical trials required to develop drugs, vaccines and topical microbicides
- Cost of antiretroviral therapies and medical care
  - Lifetime cost of anti-HIV treatment estimated at more than $400,000, possibly as high as $648,000
  - Care to be provided for approximately 24.1 years
  - Costs: 68% for drugs; 16% outpatient care; 5% other medication and laboratory costs
  - 40,000 new infections in US = $12.8 Billion
- Loss of primary and future working generations which contribute to economic health of a country
Scientific Issues

- Future of HIV therapeutic strategies: need new drugs
- Viral latency and reservoir sites; genetic diversity
- Development of a successful HIV topical microbicide
- Development of a safe and effective HIV vaccine
- Long term HIV survivors
- ΔCCR5 Mutation
- Understanding how HIV causes disease
- Evolution of HIV
- Co-Infections: the effect of HIV on hepatitis and tuberculosis
ImQuest BioSciences

- IQP-0410 is being developed as an HIV therapeutic: will enter human clinical trials in 2008

- IQP-0528 is being developed as an HIV topical microbicide with support from the NIH, IPM and the USAID. We hope to have a clinical trial initiated in 2009.

- ImQuest is working with Duke University, The University of Utah, The University of Pittsburgh and Brown University to develop a long lasting microbicide product with support from the NIH. This project involves a three compound product.
More Information

- *Philadelphia* (with Tom Hanks)
- *And the Band Played On* (with Alan Alda)
- The Global Campaign for Microbicides (web site)
- NIH, FDA and CDC (websites)