Drug Discovery and Development: From Bench to Patients

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Lehigh University, Bioscience in the 21st Century Lecture
Presentation Outline

• Overview drug discovery and development
• Merck’s investment in Infectious Disease
• Case study: Towards HIV eradication
Innovation Timelines

- Discovery to approval phases
- For every 10K molecules entering pipeline, 1 approved
- Process takes ~10 – 15 years
- Average cost is $800M - $1B
An Unexpected Journey

TARGET VALIDATION

START

ROP (lead finding)

HTS (hit finding)

FIH

PRECLINICAL

PHASE I - III

TEAMS, TIME, DATA, DECISIONS

ROP (lead optimization)

FILING

APPROVAL
Drug discovery is hard; must combine rigorous science and quality tools to support decision making.

Safe and well-tolerated drugs
\textit{with no benefit to patients}

Inadequate differentiation
Safety findings, including \textit{insufficient therapeutic index}

Nature Reviews Drug Discovery (2013); 12:569
Where Do Ideas Originate?

THE AHA MOMENTS
HOW PEOPLE REALIZE WHAT TO DO IN LIFE
by Anna Vital

BRAD PITT
actor
saw that graduating matters less than being an actor (2 weeks before graduation)

BEN SILBERMANN
Pinterest founder
made 50 versions of the same picture grid

NICK WOODMAN
GoPro founder
went surfing and could not take pictures of himself

BRIAN CHESKY
Airbnb founder
rented his air mattress and made cash

SARA BLAKELY
Spanx founder
while selling fax machines discovered slimming underwear

SAMUEL MORSE
telegraph inventor
found his wife dead because her letter reached him too late

INGVAR KAMPARD
IKEA founder
couldn’t fit a table in his car so he took the legs off

BILL GATES
Microsoft founder
realized he needed to sell his product before he made it

STEVE JOBS
Apple founder
wanted a computer interface as pretty as the calligraphy on his college campus posters

CARESSE CROSBY
Inventor of bra
could not fit her bust into a corset

MOMOFUKU ANDO
Instant noodle inventor
saw people lining up for soup on a cold day

CHIP WILSON
Lululemon founder
noticed many women do yoga, but have no special pants to wear

DONALD FISHER
Gap founder
could not find a store selling jeans that fit well

JAN KOUIM
WhatsApp founder
could not afford to call his father in Ukraine

DIETRICH MATESCHITZ
Red Bull founder
tried a local drink in Thailand to help with jetlag
Therapeutic Concept: How do we decide what to work on?

**SCIENTIFIC AND TECHNICAL**
- Scientific opportunity:
  - Strength of hypothesis
  - Availability of targets
  - Availability of assays
  - Animal models
  - Chemical starting points
- Patent situation and freedom to operate
- Competition
- Development hurdles:
  - Formulation and routes of administration
  - Toxicology
  - Clinical development
  - Regulatory hurdles
  - Production

**STRATEGIC**
- Unmet medical need
- Market predictions
- Company strategy & franchise
- Company pipeline

**OPERATIONAL**
- Resource needs:
  - Staff and expertise
  - Facilities
  - Cost
  - Timescale

Drug Discovery / Development: The basic steps

- Understand the disease (level of genes, proteins, and cells)
- Select & validate targets
- Discover right molecule (potential drug)
- Test in lab and clinic for safety & efficacy
- Gain approval and get in hands of doctors & patients
Where Do Our Ideas for Drug Targets Come From?

• Scientific literature
• Conferences, seminars
• Our basic research
• Human genetics
• In-house target identification screens
• Business development & licensing opportunities
• Collaborations with internal and external world
• Serendipity
Improving Probability of Success (POS) by Emphasizing Human Target Validation

Ideal Drug Candidate

Function Phenotype

Clinical Outcome

Target Validation
Building a convincing case

• Expression studies
  – Genomics
  – Proteomics
• Genetic approaches
  – Antisense oligonucleotides
  – RNAi
  – CRISPR
  – Transgenic animals
• Pharmacological approaches (biochemical, cellular, animal models)
  – Phenotypic screening
  – Antibodies
  – Tool compounds

Phenotypic screen workflow:

Lentivirus shRNAs → Cells with Specific Phenotype → Gene Candidates → Target Validation

Transduction, Treatment (opt'l), Selection → Hit identification

Genomic studies → Pharmacological studies → Animal models
### Modality Selection: What are the options?

<table>
<thead>
<tr>
<th>Modality</th>
<th>MW</th>
<th>Peptides</th>
<th>Proteins</th>
<th>mAbs</th>
<th>Virus like particle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small Molecules</td>
<td>400</td>
<td>2000</td>
<td>20000</td>
<td>150000</td>
<td>20000000</td>
</tr>
</tbody>
</table>

*GARDASIL® Human Papillomavirus Vaccine Types 6,11,16,18*
### Modality Selection: How do we choose?

<table>
<thead>
<tr>
<th>Modality</th>
<th>Dosing Route/Convenience</th>
<th>Where is the Target?</th>
<th>No, really, where is the Target? (subcellular)</th>
<th>Why?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small Molecule</td>
<td>QD oral</td>
<td>Central/Periphery</td>
<td>All targets</td>
<td>Convenience and Biodistribution</td>
</tr>
<tr>
<td>Peptide</td>
<td>QD/QW injectable</td>
<td>Periphery</td>
<td>Extracellular, cell surface</td>
<td>Selectivity and larger binding sites than small molecules</td>
</tr>
<tr>
<td>Protein</td>
<td>QW/QM injectable</td>
<td>Periphery</td>
<td>Extracellular, cell surface</td>
<td>Selectivity and Safety</td>
</tr>
<tr>
<td>Antibody</td>
<td>QW/QM injectable</td>
<td>Periphery</td>
<td>Extracellular, cell surface</td>
<td>Selectivity and Safety</td>
</tr>
<tr>
<td>Vaccine</td>
<td>Injectable (sometimes multiple)</td>
<td>Immune System</td>
<td>Pathogens</td>
<td>Disease prevention</td>
</tr>
</tbody>
</table>
Lead Identification: Where do we start?

- Build assays
- Screen for hits (libraries, compound collections)
- Collaborate with many scientific functions to collect information
- Identify lead classes: fall short of ideal drug characteristics but show the potential to deliver a drug with optimization
Lead Identification: What makes a good lead?

- Potent and Selective for Target
- Good Physicochemical Properties
- Evidence of SAR
- Pharmacokinetics / Oral Absorption
- IP / Competition

Lead Series

Analog
Lead Optimization: Turning a lead into a drug

- Compound Designed and Synthesized
  - Biochemical Assay on Target
  - Selectivity Assay off Target
- Functional Cellular Assay
- Physicochemical Property Assessment
- Safety & PK Assays
- PK Study in Rodents
- Formulation and additional PK/PD
- Efficacy Study in Preclinical Model
- Toxicology Studies
- Drug Candidate

1000s
100s
10s
<5
1
Pharmacokinetics and Pharmacodynamics

Pharmacokinetics (PK) — Describes what the body does to the drug
Pharmacodynamics (PD) — Describes what the drug does to the body

Dosage Regimen → Plasma Concentration → Site of Action → Effects

Adapted from Rowland and Tozer, Clinical Pharmacokinetics: Concepts and Applications 3rd ed 1995
Pharmacokinetics/ADME

What does the body do to the medicine?

Absorption
Distribution

Predict human PK
Identify elimination routes
Understand bioactivation risks
Identify enzymes/transporters involved

Conc (µM)

Metabolism
Elimination

Metabolism: enzymatic conversion into polar products
Excretion: Removal of intact drug

Time (hr)
Biomarkers

- Characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.
- Physical, chemical, molecular
- Single analyte or multiplex (e.g., signature)

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>Function or indicator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target Engagement</td>
<td>Does drug interact with intended target</td>
</tr>
<tr>
<td>Pharmacodynamic</td>
<td>Proximal/Pathway marker; how target, cell, organ, system responds to drug</td>
</tr>
<tr>
<td>Disease-related</td>
<td>Diagnostic – Measures risk or presence of disease</td>
</tr>
<tr>
<td></td>
<td>Prognostic – Informs on whether patient is likely to respond to a therapy</td>
</tr>
<tr>
<td></td>
<td>Progression – Informs on status of disease over time</td>
</tr>
<tr>
<td></td>
<td>Efficacy - Distal marker; informs whether a drug has a therapeutic effect</td>
</tr>
<tr>
<td>Safety/Toxicity</td>
<td>Informs on unintended, potentially toxic effects of a therapy (can be target-related or off-target activity)</td>
</tr>
<tr>
<td>Selection/Stratification</td>
<td>Helps identify patient population least or most likely to respond to a particular therapy</td>
</tr>
</tbody>
</table>
Biomarker Research Leverages Multiple Platforms and Technologies

Technology integration enables biomarker discovery, development, qualification & application

- **Immunoassays**
  - ELISA
  - Mesoscale
  - Luminex
  - Western Blotting
  - Singulex

- **Pharmaco-analytics**
  - Clinical chemistry
  - Immunoassay
  - Biochemical analysis
  - Hematology
  - Microbiology

- **Pharmaco-histology**
  - Histology
  - IHC
  - Digital Imaging/Image analysis
  - EM

- **Proteomics**
  - LC/MS
  - GC/MS
  - Lipid profiling
  - Phospho-PTx

- **Metabolomics**
  - LC/MS
  - GC/MS
  - Lipid profiling

- **Lipidomics**
  - LC/MS
  - GC/MS
  - Lipid profiling

- **In Vitro & Cellular Assays**
  - Binding assays
  - Flow cytometry
  - In situ hybridization
  - Drug response
    - RNAi

- **Genomics**
  - Sequencing
  - Gene expression analysis
  - Circulating nucleic acids
Safety Assessment

- Addressed at all stages in life history of drug
- In vitro and in vivo tests used to predict adverse and toxic effects in human

**Exploratory (non-GLP) toxicology**
- In vitro screens, e.g.,
  - In silico screens
  - Mutagenicity
  - Cytotoxicity
  - Immunotoxicity
  - Hepatotoxicity
  - Embryotoxicity
- Single and repeat dose range-finding studies in 2 species

**Regulatory (GLP) toxicology**
- Safety pharmacology
- Genotoxicity (in vitro and in vivo)
- 28-day repeat dose toxicity and recovery in 2 species
- 3-12 month chronic toxicity in 2 species
- Reproductive toxicology in 1 species, covering:
  - Fertility and implantation
  - Fetal development
  - Pre- and postnatal effects
- 24 month carcinogenicity in 2 species

- Ultimate test - post-marketing surveillance; drug can be removed from market after several years
Clinical Development Timelines

- Phase I – healthy individuals, PK/TE/safety
- Phase IIa/b – patients; PK/PD/efficacy (Proof of concept) & safety
- Phase III -- Expansion of Ph II, different populations, possible combinations, compare to commonly used treatments

**Diagram Notes:**
- Discovery
- Pre-Clinical
- Clinical Trials
- FDA Review
- Lg-scale Manufacture
- Number of Volunteers:
  - Ph I: 20 – 100
  - Ph II: 100 – 500
  - Ph III: 1000-5000
- IND Submitted: 3 – 6 years
- NDA Submitted: 6 – 7 years
- 1 FDA Drug: 0.5 - 2 years

**Abbreviations:**
- CIM: Confidence in Mechanism
- CIS: Confidence in Safety
- IND: Investigational New Drug
- NDA: New Drug Application
Merck has been strongly committed to the treatment & prevention of infectious diseases since introducing penicillin in 1942.
• Single strand, enveloped RNA virus
• Infects immune cells such as CD4+ T cells, macrophages, and dendritic cells
• Leads to decline in CD4+ T cells, loss of cell-mediated immunity, and increased susceptibility to opportunistic infection
• Life cycle and therapeutic targets:
Pneumocystis Pneumonia --- Los Angeles

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. Case reports of these patients follow.
• “We hope to have such a vaccine [against HIV] ready for testing in approximately two years.”

- Margaret Heckler, U.S. Secretary of Health and Human Services, press conference announcing Gallo’s discovery of HIV, 1984
The Heckler Prediction was Wrong but:

- Blood donation guidelines established within months
- Test for contaminated blood available within 2 years
- First therapies available within 4 years
- Comprehensive US government advice on prevention available within 5 years (Koop’s Surgeon General’s Report…)
- First highly effective combination therapies available within 13 years
- More than 15 drugs available within 20 years
- **Today:** Many well-tolerated and convenient drugs, including multiple one-pill once-daily regimens, available, making HIV a manageable chronic disease for many
The Efficacy of Azidothymidine (AZT) in the Treatment of Patients with AIDS and AIDS-Related Complex

Margaret A. Fischl, M.D., Douglas D. Richman, M.D., Michael H. Grieco, M.D., J.D., Michael S. Gottlieb, M.D., Paul A. Volberding, M.D., Oscar L. Laskin, M.D., John M. Leedom, M.D., Jerome E. Groopman, M.D., Donna Mildvan, M.D., Robert T. Schooley, M.D., George G. Jackson, M.D., David T. Durack, M.B., D.Phil., Dannie King, Ph.D., and The AZT Collaborative Working Group


• 250 mg q4h → now 300mg bid
Dose-dependent viral load decrease observed with L-697,661 monotherapy

HOWEVER, viral load rapidly rebounded in all patients

Rebounding virus displayed mutations that conferred resistance to the antiviral drug

Similar experience with other antiretroviral drugs tested as monotherapy (e.g., AZT, 3TC)
The emergence of combination therapy, aka HAART (Highly Active Anti-Retroviral Therapy)

- Hypothesis in early 90s: Using antiretroviral drugs in combination would minimize emergence of drug resistance
  - Treatment failure would require viruses to have resistance to more than one drug
  - Use of 3 drugs or more in combination would minimize emergence of drug resistance and treatment failure
Combination Therapy Made a Difference

• It is estimated that HIV protease inhibitors, taken in combination with other antiretroviral drugs, cut the US death rate from AIDS by 70 percent.

Figure 1. Mortality and Frequency of Use of Combination Antiretroviral Therapy Including a Protease Inhibitor among HIV-Infected Patients with Fewer Than 100 CD4+ Cells per Cubic Millimeter, According to Calendar Quarter, from January 1994 through June 1997.

Timelines: Integrase Strand Transfer Inhibitors

1 Hazuda DH, et al., 2000, Science 287:646
2 Hazuda DH, et al., 2004, Science 305:528
3 Little S, et al., 2005, CROI, Abstract #161

Raltegravir FDA approved OCT2007
Elvitegravir FDA approved (as part of Stribild) – AUG2012
Dolutegravir FDA approved – AUG2013
Triumeq FDA approved – AUG2014
Elvitegravir FDA approved (standalone) – SEP2014
Raltegravir Ph. 2 PN004: HIV RNA <50 Copies/mL (95% CI) [Non-Completer=Failure]

- Raltegravir 100 mg b.i.d. (n=39)
- Raltegravir 200 mg b.i.d. (n=40)
- Raltegravir 400 mg b.i.d. (n=41)
- Raltegravir 600 mg b.i.d. (n=40)
- Efavirenz 600 mg q.d. (n=38)
Patients in the HAART Era Have a 10-Year Shorter Expected Survival than Age- and Gender-Matched Controls

- Even with optimal HAART, life expectancy is shorter than normal (in those with a low nadir CD4)
- T cell activation, proliferation defects, abnormal CD4/CD8 ratios and maturation defects persist during HAART (“immunosenescence”)
- Chronic inflammation persists during HAART and is associated with both immunologic failure and (perhaps) non-AIDS morbidity/mortality

Non-AIDS Events are more Common in HIV Disease, Even After Attempts are Made to Adjust for Age, HAART and Traditional Risk Factors

In treated patients who achieve durable suppression of the HIV virus, natural ageing, drug specific toxicity, lifestyle factors, persistent inflammation, and perhaps residual immunodeficiency are causally associated with premature development of many complications normally associated with ageing, including cardiovascular disease, cancer, and osteoporosis or osteopenia.
25,000,000 people have died from HIV and HIV-related causes in the past 30 years

32,200,000 – 38,800,000 currently living with HIV

~1,700,000 people die of HIV related diseases/yr
  – ~4,100 people died yesterday

~2,100,000 new infections/year
  – ~5,700 people infected yesterday
No Easy Cure for HIV Infection

- Despite continual improvements to highly active antiretroviral therapy (HAART), the presence and persistence of latent HIV-1 reservoirs precludes curing HIV infection.
Towards a Cure

- What is a reasonable goal?
  - Eradication
  - Remission: “VSOT” = Viral Suppression Off Therapy

- What are the barriers to cure?
  - Source of ongoing viremia?
  - Latent reservoir
  - Others?

- Possible approaches
  - Driving HIV out of hiding in latently infected cells
  - Restoring anti-HIV immune function to kill residual infected cells
  - Induce “permanent latency”, i.e., disable possibility of viral reactivation in latent cells
“Flush” and “Kill” Strategy for HIV Eradication

- DNA
- HIV genome
- Infected Memory
  - CD4+ T cell
- HIV RNA
- HIV proteins
- HIV Env
- Antibody Therapy
- Dying infected cell
Latency at the HIV Promoter: Epigenetic Silencing and Transcription
Searching for new latent HIV transcription activators

• Several mechanisms of action stimulate transcription of latent HIV genes, including:

  – Overt T cell activators (e.g., PHA, anti-CD3 + anti-CD28)
  – PKC agonists (e.g., prostratin, bryostatin, ingenol)
  – HDAC inhibitors (e.g., vorinostat, panobinostat, romidepsin)
Latency at the HIV Promoter: Epigenetic Silencing and Transcription

Chromatin Structure

Relaxation of chromatin

HDAC EZH2 → HIV TSS → HAT

Transcription Regulation

Phosphorylation

NFκB IκB

NFAT

P-TEFb

CDK9

HEXIM1

CyclinT1

7S RNA

Latency at the HIV Promoter: Epigenetic Silencing and Transcription
Clinical Proof of Concept for HDAC Inhibitor as Latent HIV Activator

- Patients with VL < 50 on ART
  - HIV gag RNA measured in resting T-cells isolated before and after patients were treated with 400mg vorinostat
  - Treatment with vorinostat (HDAC inhibitor) triggered significant increases in HIV RNA

• Archin et al., Nature (2012) 487,482–485
Oncology HDACi Being Explored Clinically for HIV Latency

Vorinostat (SAHA – Merck):
- Pan HDACi
- POC: increase in HIV RNA in latent T-cells titer on single 400 mg dose
- Multiple-dosing studies underway in HIV-infected patients
- Ames(+) = potential safety liabilities?

Panobinostat (Novartis):
- Potent pan-HDACi
- Oral, TIW, 20 mg dose
- Ames(+) = potential safety liabilities?

Romidepsin (Gilead):
- Potent Pan HDACi
- IV, reduced safety profile versus SAHA
- Significant drug-associated adverse events

Would an HDACi optimized for HIV latency offer an advantage over re-purposed HDACIs?
### An “Improved” HDACI for HIV Eradication?

<table>
<thead>
<tr>
<th>Feature</th>
<th>VOR (SAHA)</th>
<th>“Next Gen” HDACIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Potent</td>
<td>No</td>
<td>????</td>
</tr>
<tr>
<td>Selective</td>
<td>No</td>
<td>????</td>
</tr>
<tr>
<td>Tolerable</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Non-toxic</td>
<td>Ames (+)</td>
<td>Ames (-)</td>
</tr>
<tr>
<td>DDIs?</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Optimal PK</td>
<td>Unlikely</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Latency at the HIV Promoter: Epigenetic Silencing and Transcription

Chromatin Structure

Transcription Regulation

HDAC EZH2

HIV TSS

nuc-0

nuc-1

HAT

NFκB

NFAT

P-TEFb

CDK9

HEXIM1

CyclinT1

IκB

Phosphorylation

7S RNA
Objective: To Identify Compounds that potentially synergize with HDACi’s

HIV Latency SAHA Synergy uHT Screen

2,900,000 Compounds

~4,500 Compounds

HIV LTR Induction With 250 nM SAHA

Screen

HIV LTR Induction With 250 nM SAHA

Confirmatory assays, n=3

Data analysis/Hit Selection

HIV LTR Induction With 250 nM SAHA

Toxicity @ 48 hours

CTG

NFκB BLA reporter counter screen

Follow-up Analysis

HIV LTR Induction Without SAHA

Initial Screen, n=3

Objective: To Identify Compounds that potentially synergize with HDACi’s
~4,500 HIV Latency Hits from uHTS

- Compounds with unknown mechanism: 66.5%
- HDAC Inhibitors: 16.1%
- Farnesyl Transferase Inhibitors: 17.4%
Positive Correlation Between Farnesyl Transferase Inhibition and HIV Latency Activation

- Correlation between FTi potency (IC$_{50}$ enzyme assay) and HIV latency activation (EC$_{50}$ in Jurkat T-cell model system)

![Graph showing correlation between Farnesyl-Transferase Enzymatic Assay IC$_{50}$ (µM) and Jurkat T-cell Induction (EC$_{50}$, µM).]
Will any uHTS latency hits synergize with compounds of known MOA?

• ~2000 HIV Latency uHTS hits (non-HDACi)
  • Complete Dose Response,
  • +/- EC_{20} of SAHA, HDACi (1,2,3), TNF\(\alpha\), JQ1, HMBA, Prostratin

- Jurkat HIV Latency T-cell Model (Luc reporter)

- Cytotoxicity of Compounds +/- EC_{20} of known HIV Activators

- Complete Dose Response of uHTS hits +/- EC_{20} of known HIV Activators

• N=3

• Re-test of compounds with decreased EC_{50} and/or increased Emax in the presence of known HIV activators

• N=3
Examples of uHTS Hit Synergy Profiles

Percent Activation (Normalized) to SAHA

Log Compound (M)

No PKC Synergy
Multiple Synergies
SAHA
Prostratin
TNF\(\alpha\)
No Enhancer
In Summary

- Drug discovery is lengthy, high cost, high risk….but very rewarding
- Must combine rigorous science and quality tools to support decision making
  - selecting/validating targets, finding hits/leads, developing preclinical model systems, discovering and validating translatable biomarkers, informing PK/PD/safety, designing & executing clinical trials
- Merck continues our 80 year+ commitment to preventing and treating infectious diseases
- HIV continues to be an unmet medical disease
- We’re investing in understanding HIV latency and developing novel therapeutics towards eradication
Acknowledgements

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**Case Western Reserve University**
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Jon Karn  
Curtis Dobrowolski
Thank you!

• Questions?
Backups
30 years since isolating HIV

Timeline | Key moments in HIV research

- First clinical and epidemiological observations of AIDS
- CD4 identified as the main HIV receptor
- Efficacy trial for AZT
- Prevention of mother-to-child transmission with AZT
- Introduction of generic antiretrovirals
- Identification of tetherin
- Identification of TRIM5α
- Microbial translocation identified as a pathogenic process during HIV infection


- Isolation of HIV
- Nucleotide sequence of HIV genome determined
- HIV in blood plasma measured by PCR
- Identification of the two main co-receptors for HIV (CCR5 and CXCR4)
- Introduction of combination antiretroviral therapy
- Identification of APOBEC3G
- Characterization of patients that spontaneously control HIV
- First clinical trial demonstrating protective effect of male circumcision
- First person functionally cured from HIV (Berlin patient)

AZT, azidothymidine; TRIM5α, tripartite motif-containing 5α; CCR5, CC-chemokine receptor 5; CXCR4, CXC-chemokine receptor 4; iPrEx, initiative for pre-exposure prophylaxis.

* Microbicide trial (Caprisa 004)
* Pre-exposure prophylaxis trial (iPrEx)
* Characterization of post-treatment HIV controllers

2010 2011 2013

- Prevention by early treatment in serodiscordant couples (HPTN 052)
- Identification of SAMHD1

HIV/AIDS Timeline  1959 - 1985

- 1959: Man residing in Africa dies of an illness, later confirmed to be HIV.
- 1969: First weekly support group for people with KS begins at SF-based organization Shanti.
- 1979: Gay men in the US and Sweden begin showing signs of what will later be called AIDS.
- 1980: First cases of pneumocystis carinii and Kaposi's Sarcoma are reported in NY and CA.
- 1982: First AIDS case is reported in Africa.
- 1983: After being called Gay Related Immune Deficiency (GRID), the disease is renamed Acquired Immune Deficiency Syndrome (AIDS).
- 1984: First AIDS case is reported in San Francisco.
- 1985: The first International AIDS conference is held in Atlanta.

First AIDS case is reported in Africa.

Global Prevalence of HIV/AIDS

In 1980: ~15

In 1984: ~8,000

1987
- Ryan White, an Indiana teenager with AIDS, is barred from school, then speaks out publicly about HIV/AIDS stigma and discrimination.
- First panel of HIV/AIDS Memorial quilt created.
- Liberace dies of AIDS.

1986
- Rock Hudson dies of AIDS.
- First HIV case reported in China.
- First HIV cases reported in Russia and India.
- US shuts its doors to HIV-infected immigrants and travelers.
- AZT becomes first anti-HIV drug approved by FDA.

1990
- ACT Up is founded in New York.
- Americans with Disabilities Act enacted, protecting individuals with disabilities, including HIV/AIDS.
- CDC revises definition of AIDS to be more inclusive of women and IDUs.
- FDA licenses first rapid HIV test.

1991
- Ryan White dies at age 18. Ryan White Care Act enacted to provide services for HIV+ people.
- Red ribbon introduced as international symbol of AIDS awareness at Tony Awards.
- Magic Johnson announces he is HIV+ and retires from the NBA.

1993
- Tennis star Arthur Ashe dies of AIDS.

1993-1994
- Rapper Eric Wright, aka Eazy-E, dies of AIDS.
- FDA approves first oral test for HIV (OraSure).
- Housing Opportunities for People Living with HIV/AIDS (HOPWA) Act passed, providing housing assistance to people living with AIDS.
- Pedro Zamora, a young gay HIV+ man, appears on cast of MTV's The Real World.

Global Prevalence of HIV/AIDS
- In 1987: ~125,000
- In 1990: ~8 Million
- In 1994: ~16 Million
Immunology of HIV Latency

Establishment of Latency

- Activated CD4+ T-cell
- Resting Memory CD4+ T-cell
- Myeloid cell

Fate of Latently Infected Cells

- Activated CD4+ T-cell
- Apoptosis

Immune dysfunction Prevents Clearance of latently infected cells

- PD1
- PD1 and other inhibitory molecules contribute to T-cell dysfunction

Minority of cells become latently infected

Majority of cells die or are eliminated

Immune dysfunction reduces the clearance of infected cells