HIV Gene Therapy

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What is HIV?

- Human immunodeficiency virus (HIV), causes acquired immune deficiency syndrome (AIDS)
- AIDS — AIDS defining illnesses, CD4 count < 200.
- Retrovirus – RNA
- Killed more than 25 million people since 1981
- 1.1 million Americans among 33 million people with HIV
- 2.7 million new HIV infections and 2 million AIDS deaths in 2008
- More than half of those infected cannot get treatment
Background

• 1900’s – Monkeys to humans, West Central Africa
• 1981 – First HIV cases recognized, pneumocystosis, Kaposi’s Sarcoma
• 1985 – First HIV test licensed
• 1996-7 – HAART- highly active antiretroviral therapy
• 2001-2 – Leading C.O.D. worldwide, aged 15-59
• 2006-7 – Treatment extends life 24 years, $618,900
  • Berlin man cured of HIV
HIV Structure

- Retrovirus – RNA
- 9 genes (500 genes in a bacteria, 20,000-25,000 in human).
  - Three - structural proteins for new virus particles.
  - Six - proteins to control the ability to infect & copy
- Viral envelope, viral core, 3 enzymes
Mechanism of Infection
Current Treatment of HIV

- HAART - highly active antiretroviral therapy
  - Combination of inhibitors
  - Reduce mutation affects
- Fixed dose combinations
  - Increase adherence
- Mega-HAART / salvage therapy
- Drug Holidays
HAART side effects

- Abdominal pain
- Alopecia
- Anemia
- Asthenia
- Diarrhea
- Dizziness (Vertigo)
- Fanconi syndrome
- Flatulence
- Headache
- Hepatitis
- Hyperbilirubinemia
- Hypercholesterolemia (Dyslipidemia, Hyperlipidemia, high cholesterol)
- Hyperpigmentation (of nails, palms, or soles)
- Ingrown nails
- Insomnia
- Jaundice
- Lipodystrophy
- Liver failure
- Malaise
- Mental confusion
- Migraines
- Mitochondrial toxicity
- Mood swings
- Myalgia
- Myalgic Encephalomyelitis (chronic fatigue syndrome)
- Myopathy
- Nausea
- Neutropenia (low number of white blood cells)
- Nightmares
- Oral ulcers
- Pancreatitis
- Paresthesia (numbness)
- Peripheral neuropathy
- Rash
- Renal failure or insufficiency
- Somnolence (drowsiness)
- Stevens-Johnson syndrome
- Change in taste perception
- Vomiting
- Xeroderma (dry skin)
- Xerostomia (dry mouth)
Therapy

- Only one successful human case – Berlin man
- Focus usually placed on CD4 receptor and CCR5 coreceptor
- Types of therapy
  - Small-molecule approach to block CCR5
    - Maraviroc, mutations
  - Ribozymes
    - Blood stem cells infected with virus OZ₁, trials successful
  - Zinc-finger nucleases
    - Disable CCR5 gene, currently researching / successful preliminary trials
Berlin Man

- Only successful human cured of HIV
- 42 y/o male American in Germany, HIV+, leukemia
- Successful HAART
- Stem cell transplant – blood
- Rare genetic mutation - delta32 CCR5
  - Deletion
- 13 million → 232 → 1
Berlin Man Treatment

- Leukemia – white blood cells
- Destroy all blood-forming cells (stem, bone marrow)
  - Radiation, 2 immunosuppressive drugs, drugs to kill all immune cells
- Replaced with sample 61
- Lurking HIV not a problem
- 2.5 years since off all antiviral drugs and transplant, no detectable virus, active or latent.
- Tests
  - Most sensitive, extensive biopsies
  - Antibody tests positive, decreasing
Mutations like delta32 CCR5

- **Multicenter AIDS Cohort Study** [MACS].
  - Followed many gay men in six U.S. centers

- Many mutations must exist
  - 5% - delta32 CCR5
  - 95% - under research
Obstacles to Similar Treatments in U.S.

- Rarity of matches
  - Two in U.S. identical to Berlin man
  - 13 million, placentas
- No money
  - No universal health care
    - Insurance pays for 10, maybe 20 calls to matches, number 61
    - Can’t move to Germany
  - NIH, Academic study
- Only offered to those with leukemia, high mortality
- Real solution – changes in bone marrow registry
  - Current efforts on testing existing samples
Methods of Transmission

**Significant risk**
- Exchange of bodily fluids – blood, semen, vaginal fluid, breast milk
- Unprotected sex – vaginal and anal
- Mother to child
- Contaminated blood transfusions
- Needle sharing – intentional or accidental

**Low risk / no risk**
- Saliva, tears, sweat
- Insect bites
- Casual contact
- Airborne / environmental
- Kissing
- Tattoos / piercings
HIV prevention

- HIV vaccine
  - Envelope and protein coats
  - Only 1 success
- Post Exposure Prophylaxis
- Prevention
  - Condoms!
    - latex or polyurethane only
  - HIV testing
HIV – Still a Serious, Fatal Disease
References

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