Retrovirus replication
HIV Entry and Fusion

• viral protein gp120 binds to cell surface protein CD4
  • viral protein gp41 fuses viral membrane with cell membrane
• gp120 and gp41 are products of the viral env gene
Host Cell Proteins & HIV Infection

- HIV gp120 - CD4 interactions are important for infection
- Genetically engineered mouse cells expressing CD4 CAN NOT be infected with HIV
- Therefore, there must be other receptor(s) required for HIV infection
Molecular Biological Screen for HIV Co-receptor

human cell expressing HIV env

Human T-cell

cells fuse (syncytia)
Molecular Biological Screen for HIV Co-receptor

mouse cell expressing HIV env

mouse cells expressing CD4

cells won’t fuse
Molecular Biological Screen for HIV Co-receptor

Mouse cell expressing T7 and env + mouse cells expressing CD4 with a cDNA insert from HeLa and a T7-driven reporter gene

Only in the presence of co-receptor will cells fuse

T7-driven reporter now “switched on” in presence of T7 from env+ cell.
Chemokines Inhibit HIV-CD4+ Cell fusion

Chemokines are peptides/proteins produced by many different cells to attract macrophages, T cells, eosinophils, basophils, and neutrophils to sites of inflammation.

RANTES, MIP-1α, MIP-1β, IL-8, NAP-2, etc.
Chemokines Inhibit HIV-CD4+ Cell fusion

Chemokine receptors are 7-TM, G-protein-coupled receptors

A search for CKRs that allowed CD4+ cells to fuse with env-expressing vectors revealed that CCKR5 is an HIV co-receptor
HIV Binding and Fusion Require Both CD4 and Specific Chemokine Receptor (either CCKR5 or CXCR4)

Gp120 interaction with both CD4 and chemokine receptor is necessary in order for gp41 to Fold-back upon itself, the first, critical step in fusion.
Chemokines Inhibit HIV-CD4+ Cell fusion

CD4 & CCKR5 (R5 viruses) - the primary transmitted viruses

CD4 & CXCR4 (X4 viruses) - develop later in infection

Dual-tropic (Can use either CXCR4 or CCKR5)
Genetic defects in CCKR5 render individuals resistant to HIV infection and AIDS.

Between 7-11% of Caucasians have this (heterozygous) defect.
Recently Approved (March 2003) Fusion Inhibitor

IV dosing required - twice daily.
Blocks fusion by interfering with gp41
Marketing slowed by difficulty in manufacturing drug.
In phase 3 clinical trial: ~2-fold increase in HIV RNA <400 copies/mL in patients receiving T-20 + ART vs ART alone.

Side effects: injection site reactions, hypersensitivity, increased risk of pneumonia
Resistance: In treated patients, between 4–422-fold decrease in viral susceptibility to T-20 compared to before treatment.
Mutations in gp41 (positions 36-38)
In Clinical Trials

T-1249: “Second generation” T-20 analog:
Decreased incidence of resistance vs. T-20 once-a-day dosing (but still by injection)

PRO-140: CCKR5 Receptor antagonist antibody directed against CCK55 -
block binding of HIV, especially in macrophages
Phase I

PRO-542: rCD4-IgG2 fusion protein
block HIV binding, label HIV virion for destruction
Phase II

AMD-3100: Aza-crown ether
Blocks fusion by binding to CXCR4 and preventing CXCR4-gp120 interactions.
Phase I/II
HIV Vaccine Development

Issues related to Goals:
Prevention vs. Treatment
Neutralizing antibodies vs. cell-based (CD4/CD8)
Mucosal vs. Intravenous immunity

Issues related to Means:
Protein(s) - which one(s) and how presented
Whole virus - attenuated* / killed
*trials appear to have led to HIV infection
Vectors - viral, DNA
Prime and Boost
Treatment Trials

REMUNE: gp120-depleted killed whole HIV-1 virus

Phase III in US - was disappointing,
Focused on HAART patients with low/undetectable HIV-1 RNA

Increased CD4+ counts, some decreased HIV-1 RNA, but not as promising as hoped

Sponsor company Immune Response underwent Restructuring, now plans on testing a reformulated vaccine for prevention
Vaccines in Clinical Trials

AIDSVAX - gp120-based vaccine for prevention

originally co-sponsored by NIH, since pulled support due to lack cell-based response.

Phase III clinical trial showed no effect in patient population as a whole; however, certain minority groups showed a modest effect - not statistically/biologically relevant

Sponsor Company VaxGen is being sued by investors for not being up-front with preliminary clinical trial data
Vaccines in Clinical Trials

Aventis: ALVAC

canarypox vector expressing HIV-1 env-gag-pol

Merck: Ad5
adenovirus vector expressing gag

Phase I trial scheduled for:
Ad5 “prime” then ALVAC “Boost”
Vaccines in Clinical Trials

Epimmune: EP HIV-1090

DNA-based vaccine includes 21 key elements HIV-1 epitopes plus a Universal Helper T-cell epitope (to enhance magnitude and duration of response)

Phase I trials just began with Nat’l Inst. Of Health (NIH)
Opportunistic Viral Infections

Cytomegalovirus (CMV)

Recently Approved:
- Vistide (cidofovir)
- Vitravene (fomivirsen)
- Foscavir (foscarnet)
- Cytovene (gangcylovir)

Hepres Simplex Virus (HSV)

Recently Approved:
- Valacyclovir (Valtrex)
Opportunistic Infections

Pneumocystis carinii pneumonia (PCP)

Recently Approved:
- Bactrim
- Septra
- NebuPant (pentamidine)
- Pentam (pentamidine)
- Neutrexin (trimetrexate)
- Mepron (atovaquinone)

In Trials:
- dapsone
Opportunistic Mycobacterial Infections

Tuberculosis
Recently Approved:
- Rifapentine

Mycobacterium avium complex /
Mycobacterium avium intracellulare (MAC/MAI)

Recently Approved:
- Zithromax (azithromycin)
- Mycobutin (rifabutin)
- Biaxin (clarithromycin)
Kaposi Sarcoma (KS)

Recently Approved:
- DaunoXome
- Doxil
- Intron A (interferon alpha-2b)
- Roferon (interferon alpha 2a)
- Taxol
- Panretin (alitretinoin)

In Trials:
- Thalidomide
- Virulizin
Other Agents

Recently Approved:
- Marinol (THC) (Nausea / wasting syndrome)

In Trials:
- Memantine (for dementia / neuropathic pain)
  Also subject of an NDA for Alzheimer's