Vaccine Development against HSV Past, Current and Future

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Two Types of HSV Vaccines

**Prophylactic Vaccines**
For the uninfected patient, intended to protect against (genital) infection or disease

**Therapeutic Vaccines**
For the infected patient, intended to reduce the frequency and/or severity of recurrent infections and transmission to susceptible partners
HSV Vaccine Strategies

1. Inactivated virus preparations
2. Live, cell culture-attenuated vaccines
3. Live, genetically-attenuated vaccines
4. Live, replication-impaired vaccines
5. Vectored vaccines
6. Nucleic acid-based vaccines
7. Subunit (recombinant) vaccines
8. Peptide vaccines
1. Inactivated Virus Preparations

- Checkered history
- Limited safety concerns
- Broadly immunogenic but predominantly induces antibody responses
- Adjuvants enhance CMI responses
- Most clinical trials have been seriously flawed
- No inactivated vaccine has been proven effective
- No inactivated virus vaccine currently in commercial development
1. Inactivated (Whole) Virus Preparations

**Skinner HSV-1 Vaccine - Developer: Porton International**

- **Prophylaxis study (open trial)**
  - used consorts of patients with genital herpes
  - 1/60 vaccine recipients developed genital herpes; no control group; historic attack rate reported at 40%/ per year
  - no pre-immunization serology
  - vaccine poorly immunogenic

- **Therapeutic study (randomized, double-blind, placebo-controlled)**
  - treatment of patients with > 6 recurrences per year
  - vaccination schedule: 0,1,2 months - f/u to 12 months
  - reduced mean recurrences per month from 0.7 to 0.5 in females, no effect in males
1. Inactivated (Subunit) Virus Preparations

HSV-2 GS Vaccine - Developer: Merck & Co

- Inactivated HSV-2 virion- lectin column purified vaccine
- Prophylaxis study (randomized, double-blind, placebo-controlled)
  - used consorts of patients with genital herpes
  - vaccine was poorly immunogenic inducing antibody titers substantially less than those seen following infection
- Status: Development discontinued
2. Live, Cell Culture Attenuated Vaccines

- Multiple cell culture passages have failed to produce a vaccine that does not revert to a pathogenic virus
- Capable of establishing latency
- Broadly immunogenic and capable of inducing both humoral and cellular immune responses and with reversion capable of causing disease
3. Live, Genetically Engineered Vaccines

- Multiple mutations and genetically stable thus limited safety concerns
- If not over-attenuated should be broadly immunogenic and capable of inducing both humoral and cellular immune responses
3. Live, Genetically Engineered Vaccines

**R7020 Vaccine - Developer: Pasteur-Merieux**

- Safety and immunogenicity study (open trial)
  - well tolerated but poorly immunogenic after two doses
  - thought to be overly attenuated
- Status: Development discontinued
3. Live, Genetically Engineered Vaccines

RAV 9395 Vaccine - Developer: Aviron (MedImmune)

- Animal studies
  - protected guinea pigs against disease and latency
  - did not prevent mucosal infection at any dose tested
- Status: Development discontinued
4. Live, Replication-Impaired Vaccines

- Genetically-engineered to undergo only a single replication cycle - progeny virions are non-infectious or no progeny are generated
- Safety concerns regarding possibility of recombination resulting in production of virulent virus
- Broadly immunogenic inducing antibody and CMI responses
- Could be issues regarding ability to use antibody assays to detect vaccine failure (i.e., infection)
4. Live, Replication-Impaired Vaccines

Knipe HSV-2 Vaccines - Developer: Sanofi-Pasteur

- HSV-2 mutants lacking two important genes
- Induces humoral and cellular immune responses and protects animals against disease resulting from intravaginal HSV-2 challenge
- Further development planned
4. Live, Replication-Impaired Vaccines

**TA-HSV-2 Vaccine** – Developers: Cantab/Glaxo-Wellcome

- Single deletion -gH
- Animal studies
  - Prophylactic vaccination protected animals against genital disease and reduced latency but did not prevent mucosal infection
  - Therapeutic vaccination reduced frequency of recurrent infections in guinea pigs
4. Live, Replication-Impaired Vaccines

TA-HSV-2 Vaccine Developers: Cantab/Glaxo-Wellcome

- Single deletion -gH gene
- Human safety/immunogenicity phase I studies
  - dose-ranging study in HSV seropositive and seronegative subjects, subcutaneous immunization
  - vaccine well tolerated, minimal reactogenicity
  - in seronegative subjects vaccination induced T and B cell responses
4. Live, Replication-Impaired Vaccines

TA-HSV-2 Vaccine Developers: Cantab/Glaxo-Wellcome

- Phase II safety/immunogenicity/therapeutic efficacy trial
  - subjects are patients with frequently recurring genital herpes, > 6 recurrences per year
  - primary outcome measure is reduction in the frequency of symptomatic recurrent infections
  - Results showed no effect on symptomatic or asymptomatic recurrences
- Status: Development discontinued
5. Vectored Vaccines

- HSV gene(s) expressed by a replicating vector
- Safety concerns are based on profile of the vector
- Limited HSV antigen expression provides narrow immunogenicity but responses are both humoral and cellular
- Vector examples:
  - Canarypox virus
  - Varicella-zoster virus
  - Salmonella
- Status: Sindbis virus vectored HSV-2 gD vaccine had limited preclinical development by Chiron (Novartis) but development appears to have been discontinued
6. Nucleic Acid-Based Vaccines

- Plasmid expression vectors containing one or two HSV genes and may also encode cytokine genes
- Theoretical safety concerns
- Limited HSV antigen expression therefore narrow immunogenicity (similar to recombinant subunit vaccines)
- Can induce CMI responses
- PowderMed (Pfizer) – DNA vaccines on gold beads; phase 1 study completed but results not released; development appears to have been discontinued
- Merck - HSV-2 gD vaccine; development appears to have been discontinued
- Vical - Vaccine encoding HSV-2 antigens formulated with cationic lipid; no mention of clinical trials at ClinicalTrials.gov.
6. Nucleic Acid-Based Vaccines

HSV-2 (gD) DNA Vaccine: Developer: Wyeth Lederle (Pfizer)

- Vaccine included bupivacaine and was delivered using a Biojector needle-free injection system.
- A phase 1 clinical trial using doses up to 3,000 ug showed the vaccine was well tolerated but poorly immunogenic.
- Status: Development appears to have been discontinued.
7. Subunit (Recombinant) Vaccines

- Produced by recombinant DNA technology
- No safety concerns except as regards adjuvants
- Limited number of antigens and therefore narrow immunogenicity
- Predominantly induces antibody responses but inclusion of adjuvants enhances CMI responses (and reactogenicity)
7. Subunit Vaccines

gD2/alum Vaccine - Developer: Chiron (Novartis)

- Therapeutic study - (randomized, double-blind, placebo-controlled)
  - patients with 4-14 recurrences per year
  - vaccination schedule: 0 and 2 months; f/u 12 months
  - vaccine (100ug dose) boosted neutralizing titers
  - Vaccinated subjects had fewer recurrences
- Subsequent therapeutic trial with gD2/gB2/MF59 showed no benefit.
- Status: Development discontinued
7. Subunit Vaccines

gD2/gB2/MF59 Vaccine - Developer: Chiron

- Prophylaxis studies - (randomized, double-blind, placebo-controlled)
  - consorts of patients with genital herpes and subjects with multiple sexual partners or history of an STD
  - the vaccine induced high neutralizing titers
  - primary outcome measure: protection against infection as measured by seroconversion or HSV isolation
  - vaccination afforded 50% protection during the initial 5 months of the trial, however the overall efficacy was only 9% (26% for females and -4% for males)
  - Vaccine may have had different effects in the two study populations
7. Subunit Vaccines

gD2/Alum/MPL Vaccine - Developer: GlaxoSmithKline

- Clinical trials
  - 1\textsuperscript{st} outcome measure - prevention of genital HSV disease
  - Three phase III studies: vaccine immunogenic and well tolerated
  - 007 study: double seronegative consorts; vaccine protected women but not men
  - 017 study: ± HSV-1 positive consorts; vaccine protected only double seronegative women
  - Herpevac study: double seronegative women; vaccine did not protect against HSV-2 genital herpes but did protect against HSV-1 genital herpes

- Status: Development discontinued
8. Peptide Vaccines

- Synthetic peptides that are known antigenic epitopes
- Limited safety concerns
- Single peptides are narrowly immunogenic, hence this strategy will require pools of peptides
- Capable of stimulating both B and T cell responses
- Responses can be enhanced with adjuvants
- Genocea, using a clever methodology to identify T-cell epitopes, is in the preclinical development of both therapeutic and prophylactic vaccines. Currently there is no listing on ClinicalTrials.gov
HerpV Vaccine: Developer: Agenus

- Vaccine consists 32 synthetic 35mer HSV-2 peptides non-covalently complexed with recombinant human Hsc70 protein with QS21 adjuvant
- A phase 1 clinical trial in HSV-2 seropositive subjects showed the vaccine was reactogenic and produced variable T cell responses
- Status: The company reports plans to advance to phase 2 trial in 2012
Herpes Simplex Virus Vaccines: Summary

- A variety of strategies have been exploited in pursuit of an effective HSV vaccine
- Subunit HSV vaccine studies have established that it is feasible to make prophylactic and therapeutic vaccines but a broadly useful product remains elusive
- In the short run the most promising two strategies are live, replication incompetent mutants (Knipe/Sanofi-Pasteur) and T-cell peptide vaccines (Genocea)
- In the longer term a greater focus on induction of local mucosal responses and prevention of latency may be the key to a broadly effective vaccine.
Colleagues/Collaborators

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