

OPEN SESSION

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VRBPAC MEETING, MAY 16-17 2001
"DESIGNER CELL SUBSTRATES"

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NEW HIV VACCINES AND ADJUVANTS
UNDER DEVELOPMENT

- Inactivated HIV
- Recombinant plasmid DNA vaccines
- Purified proteins, peptides, lipopeptides
- **Bacterial vectors:**
 - Attenuated *Salmonella* delivering DNA vaccine
 - Attenuated *Shigella* delivering DNA vaccine
 - Recombinant BCG vectors
- Novel adjuvants, cytokines, co-stimulatory proteins.

'AIDS Vaccines Show Promise After Years of
Frustration'

Science, March 5 2001. 291: 1686-1688

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New HIV Vaccines may Require Novel Cell
Substrates

- Complementing cell lines for @m-replicating viral vectored vaccines
- Optimal production of recombinant live attenuated viruses
- Production of inactivated HIV vaccines.

NEW HIV VACCINES UNDER
DEVELOPMENT

- **Viral Vectors:**
 - Pox viruses: **Canarypox**; MVA (modified vaccinia Ankara); NYVAC, Recombinant vaccinia.
 - **Adenovirus 5**: replication competent; non-replicating vectors
 - Adeno-associated virus: non-replicating vectors
 - Venezuelan equine encephalitis: non-replicating vectors
 - **Semliki forest virus**: non-replicating vectors
 - Herpes virus: non-replicating vectors

DESIGNER CELL SUBSTRATES:
ADVANTAGES

- Derived from primary cells or from well-characterized diploid cell lines.
- Cellular immortalization is achieved with known transforming genes (either viral or cellular)
- Absence of immortalizing genes and/or their products can be closely monitored during vaccine production and final product characterization

Adenovirus 5 El-transformed Designer Cell Substrates: Advantages

- Adenovirus 5 is non-oncogenic in humans.
- Adenovirus (or Ad5 Ela/lb)-transformed cells are not tumorigenic in immunocompetent animal models:
- Ad5 El-expressing cells are killed by cytotoxic T cells and by natural killer (NK) cells
- Ad5 El-expressing cells are highly sensitive to mediators of apoptosis (i.e., TNF α)

Designer Cell Substrates for Vaccine Development: OVRRA Approach

- Extensive safety testing should be conducted on the new Master Cell Banks (MCB) independently of the vaccine vector. Rationale:
- The same MCB can be used for production of multiple products.
- If an adventitious agent is detected in the MCB, it is important to document its removal during product processing/purification and its absence in the final product.
- Some viral vaccine vectors may interfere or reduce the sensitivity of certain safety assays.

Adenovirus 5 El-Transformed Designer Cell Substrates: Advantages

- Ad5-transformed cells are only weakly tumorigenic in immunodeficient (athymic) nude mice:
TPD, : 6.5×10^6 cells
- Ad5-transformed- HEK cells (293) have been used in the production of adenovirus-based-vectors for gene therapy.

Designer Cell Substrates for Vaccine Development: OVRRA Approach

- Sponsors should be encouraged to place the results of the MCB studies in the public domain in order to increase public confidence in the safety of the new cell substrate

Designer Cell Substrates for Vaccine Development: Potential Safety Concerns

- Incomplete medical history of the original tissue and/or incomplete documentation of the tissue culture ingredients used in the propagation of the cell substrate
- Long passage history of immortalized cells may result in exposure to adventitious agents, and potentially to TSE/BSE agents due to undocumented bovine ingredients in the culture medium

Proposed Testing of Novel Designer Cell Substrates for Vaccine Development

- MCB Tumorigenicity/ oncogenicity studies:
- Intact cells: Use several cell doses, observe nude mice for 5-6 months
- DNA (high MW): To establish the inability of oncogenic sequences (viral or cellular-derived) to cause tumors in animal models

Proposed Testing of Designer Cell Substrates for Vaccine Development

Adventitious agent testing:

- In addition to the standard assays, incorporate new state-of-the-art assays for detection of agents that can infect human cells (as needed).
- Cell lysates: *To detect occult oncogenic viruses; Inoculate two animal species (i.e., newborn hamsters and rats); Observe for 5-6 months*
- Sequence the PrP gene of the MCB.
- Test for the presence of protease-resistant PrP protein by sensitive Western Blots.

Designer Cell Substrates for Vaccine Development

Residual DNA:

- A concerted effort should be made to reduce the amount of cell-substrate-derived DNA in the final product to ≤ 10 ng per human dose.
- For vaccine administration via the oral route : higher levels of residual cellular DNA may be allowed, especially if studies demonstrated no oncogenic potential.

Designer Cell Substrates for Vaccine Development: Discussion Points for VRBPAC

- Please discuss the adequacy of OVRP approach to the evaluation of "Designer Cell Substrates" for use in the manufacturing of viral vaccines:
 - Tumorigenicity/ oncogenicity studies
 - Residual cell substrate DNA
 - Potential contamination with adventitious agents including occult oncogenic viruses and TSE/BSE agents..
- Please discuss any additional safety concerns.