

**What New Pediatric
Vaccines Will We Be Using
in the Next 10 Years?**

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**“It’s tough to make predictions,
especially about the future.”**

Yogi Berra



Dd

"This stuff worked pretty well on me."

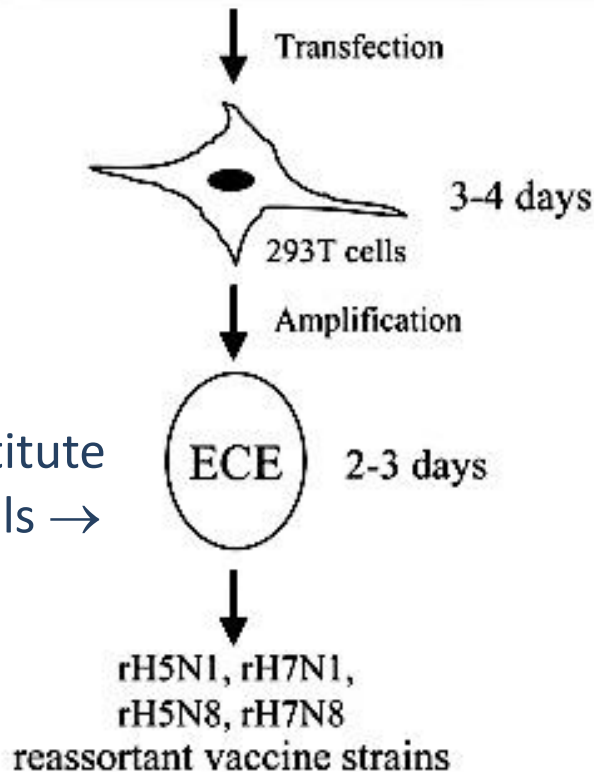
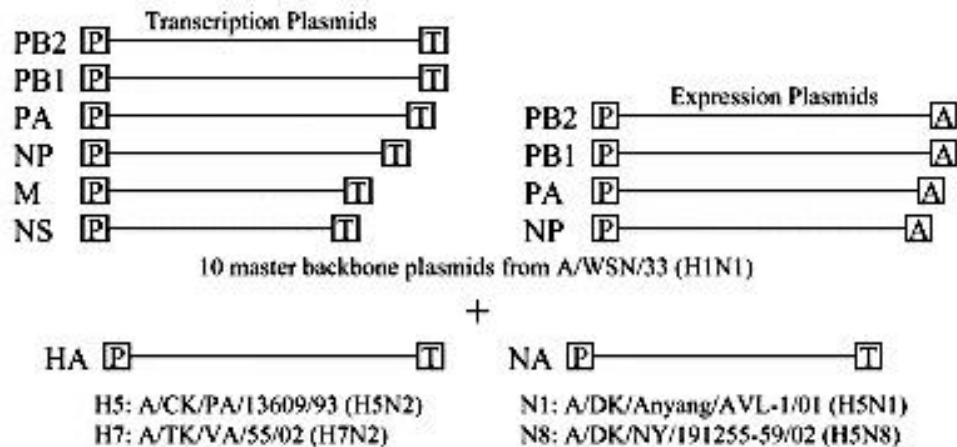
Selected Vaccine Candidates for Discussion

- Influenza
- Tuberculosis
- Malaria
- Dendritic Cell-based HIV
- Parainfluenza-3
- Respiratory Syncytial Virus

New Influenza Vaccines

- Reverse genetics & Cell-culture based propagation
- Prospects for a Universal Vaccine?

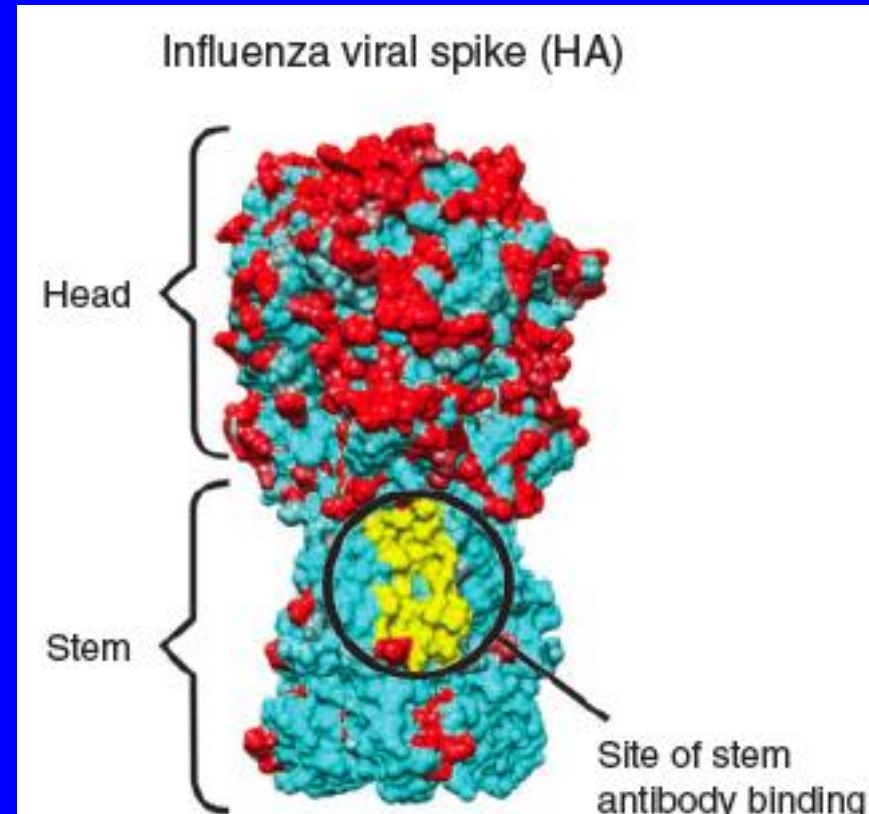
Reverse Genetics Technique



- **Extract RNA** from master vaccine strain & candidate wild-type strains
- **Amplify** HA & NA genes from wild-type strains & “backbone” genes from master vaccine strain
- **Clone** each in plasmids & transfect 293T cells
- **Collect** only reassortant viruses containing wild-type HA/ NA genes & master vaccine strain backbone genes
- **Infect** ECE (embryonated chick eggs) or cell lines (Marcus Darby Canine kidney cells, MDCK)
- **Disrupt** cells, collect, inactivate vaccine virus or modify to make cold-adapted live attenuated vaccines

Universal Influenza Vaccine Wish List

- Common conserved antigen(s) not subject to drift or shift
- Uniform across all Influenza A strains & B strains if possible
- Stimulate neutralizing antibody & CTL responses
 - Neutralizing Ab to HA
 - Nabel & Fauci, Nature Medicine, 2010, 16 (12): 1389
 - CTL responses are HLA-restricted
 - Staneková and Varečková Virology Journal 2010, 7:351



Universal Influenza Vaccine

- **Whole virion-gamma irradiation inactivated**
 - cytotoxic T-cell immunity vs. different influenza A strains
- **Single epitope M2e ectodomain**
 - 24 amino acid in length
 - antibodies to broad spectrum of influenza A strains
 - not effective vs. B strains
- **Multi-epitope vaccines**
 - **M2e epitope + highly conserved *Nucleoprotein (NP)* + proprietary **TLR9 agonist ISS** (Immuno Stimulating Sequence)**
 - NP provides cytotoxic T-cell immunity
 - M2e stimulates protective antibodies
 - **Nine conserved epitopes from HA, NP and M122** combined into a recombinant protein expressed in *E. coli*
 - induces both humoral and cellular immunity vs. both Type A and Type B strains

Why Do We Need a New TB Vaccine?

- Bacillus Calmette–Guerin (BCG) formulated a century ago
 - Overall efficacy of BCG is controversial
 - Prevent disseminated disease and mortality in newborns and children
 - Not able to prevent chronic infection nor pulmonary TB in adults
 - Do not know how BCG induces protection, why it does not prevent persistent infection, what immune response would be needed to achieve sterile immunity or to prevent reactivation of latent infection

Approaches to Developing New TB Vaccines

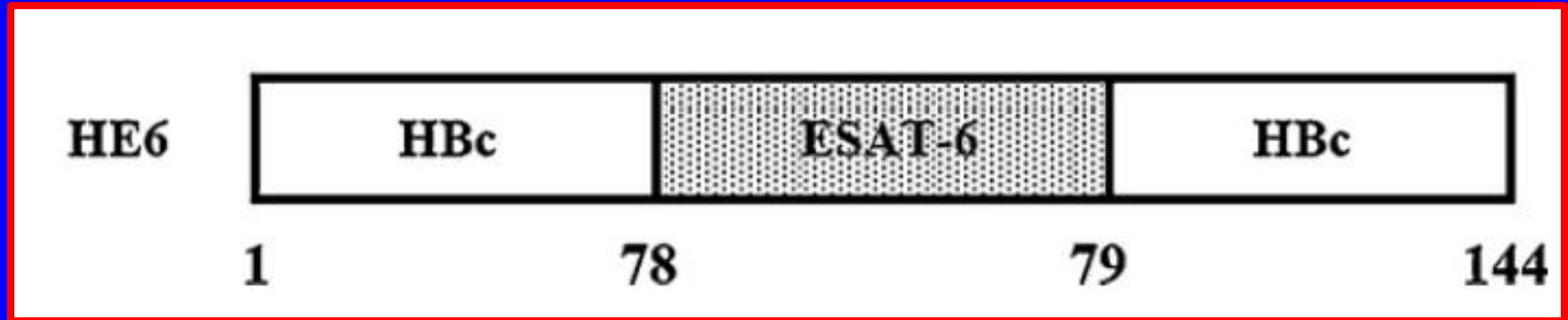
- **Improved BCG vaccine: rBCG30**
 - Extra copy of a major secretory protein (Ag85b) essential for cell wall synthesis → improved immunogenicity & protection in animal models
 - Phase I clinical trials in humans completed
- **Prime-Boost strategy:**
 - Prime with BCG or Super BCG
 - Boost with MVA(Modified Vaccinia Ankara) vector containing the gene for TB antigen 85A or a subunit vaccine containing 85A.....
 - More robust CD4 response than either vaccine alone

New Tuberculosis Vaccines in Clinical Trials

	Description	Developmental stage	Sponsor or funder
MVA85A ?	Attenuated strain of vaccinia expressing Ag85A	Phase 1 completed and phase 2 continuing; phase 2b in infants started	Wellcome Trust, Aeras, Emergent BioSolutions
rBCG30 ?	BCG overexpressing Ag85B	Phase 1 completed	University of California, Los Angeles; Aeras
AERAS-402	Non-replicating Ad35 expressing Ag85A, Ag85B, and TB10.4	Phases 1 and 2 continuing	Aeras
AdAg85A	Non-replicating Ad5 expressing Ag85A	Phase 1	McMaster University
M72	Recombinant fusion (Mtb39 and Mtb32) in AS02 and AS01 adjuvant systems	Phases 1 and 2 completed; additional trials continuing	GlaxoSmithKline, Aeras, Tuberculosis Vaccine Initiative
H1-IC31 ?	Recombinant fusion of Ag85B-ESAT-6 in IC31 adjuvant	Phase 1 completed	Statens Serum Institut, Tuberculosis Vaccine Initiative
H1-CAF01	Recombinant fusion of Ag85B-ESAT-6 in CAF01 adjuvant	Phase 1 continuing	Statens Serum Institut, Tuberculosis Vaccine Initiative
H4-IC31 (AERAS-404)	Recombinant fusion of Ag85B-TB10.4 in IC31 adjuvant	Phase 1 completed	Statens Serum Institut, Aeras
rBCGΔUreC:Hly (VPM1002)	BCG with an endosome escape mechanism	Phase 1 completed	Vakzine Projekt Management, Tuberculosis Vaccine Initiative, Max Planck Institut
RUTI	Detoxified <i>M tuberculosis</i> in liposomes	Phase 1 completed	Archivel Farma
<i>M vaccae</i>	Inactivated <i>M vaccae</i>	Phase 3 completed	National Institutes of Health

MVA=modified vaccinia Ankara. Ag=antigen. Ad=adenovirus. AS=adjuvant system. ESAT-6=early secretory antigenic target 6. CAF=cationic adjuvant formulation. Hly=haemolysin. *11 new tuberculosis vaccines that have gone into clinical trials. Two of them, MVA85A and AERAS-402 *Mycobacterium vaccae*, have gone into phase 2 trials and one, *M vaccae*, has completed a phase 3 trial.

New MTB Vaccine Candidates: HBc-ESAT-6



- ESAT absent from all BCG but present in MTB strains
 - Poorly immunogenic \square unstable tertiary structure
- ESAT-6 sequence inserted in assembly domain of HBc
- Higher ESAT-6-specific IgG, & IFN- γ T cell responses (increased Th1-biased CD4+ T cell responses)
- Booster for BCG or Super-BCG vaccinated individuals?
- Effect of pre-existing anti-HBc antibodies on ESAT immune response?

MVA85A Vaccine

- **Recombinant, replication-deficient vaccinia virus expressing MTB Ag85A**
- **85A contains CD4 & CD8-T-cell epitopes**
 - protective in mice and guinea pigs
 - CD4- & CD8-T-cell responses in humans
 - Strong primary Th1 responses & boosts previous immunity
 - Prior vaccinia vaccination might reduce response to 85A
- **Trials in children in Capetown, South Africa:**
 - Dose finding in BCG-vaccinated infants: Scriba, Journal of Infectious Diseases 2011;203:1832–43
 - Safety in children & adolescents: Scriba, Eur. J. Immunol. 2010. 40: 279–290

RTS,S Malaria Vaccines

- 25% fusion protein RTS (B cell Repeats + T cell epitopes + HBsAg (S) antigen) & 75% wild-type HBsAg (S) antigen
- Proprietary GSK Adjuvant systems (AS) used with RTS,S

Efficacy of the RTS,S Vaccine

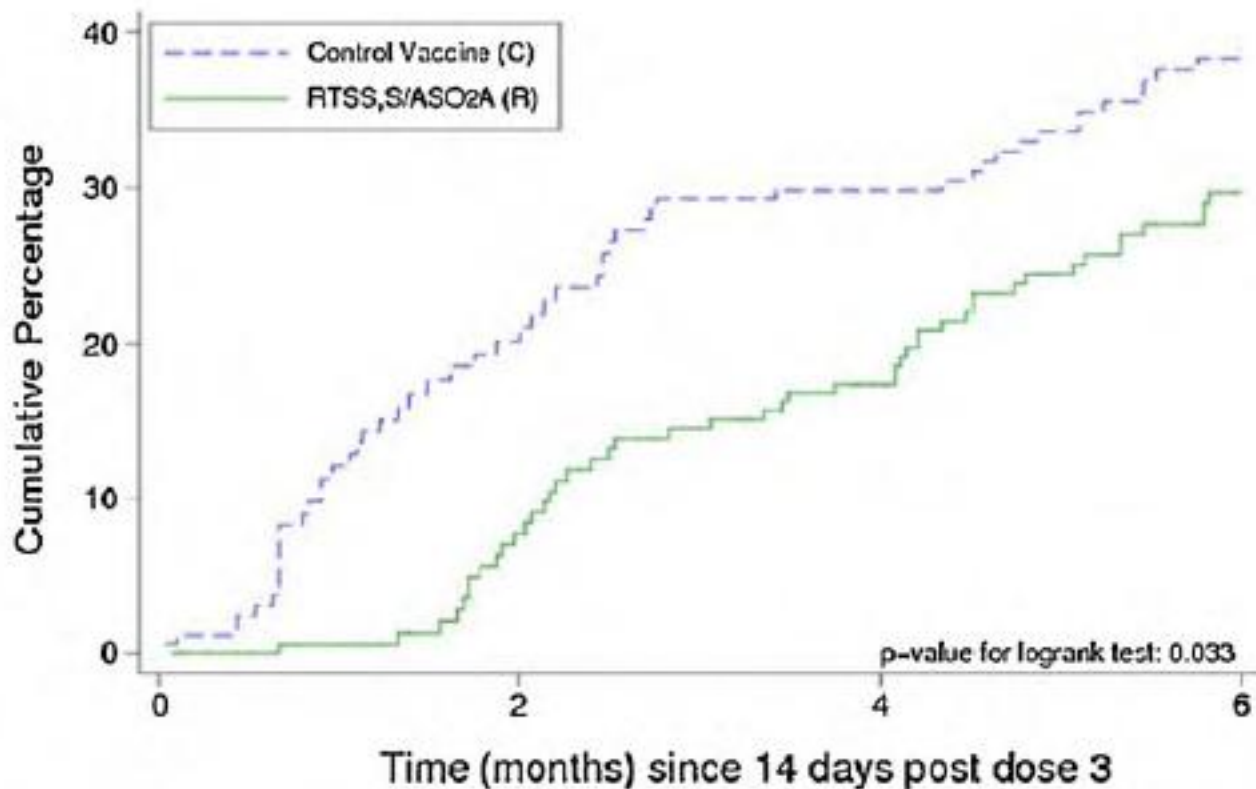
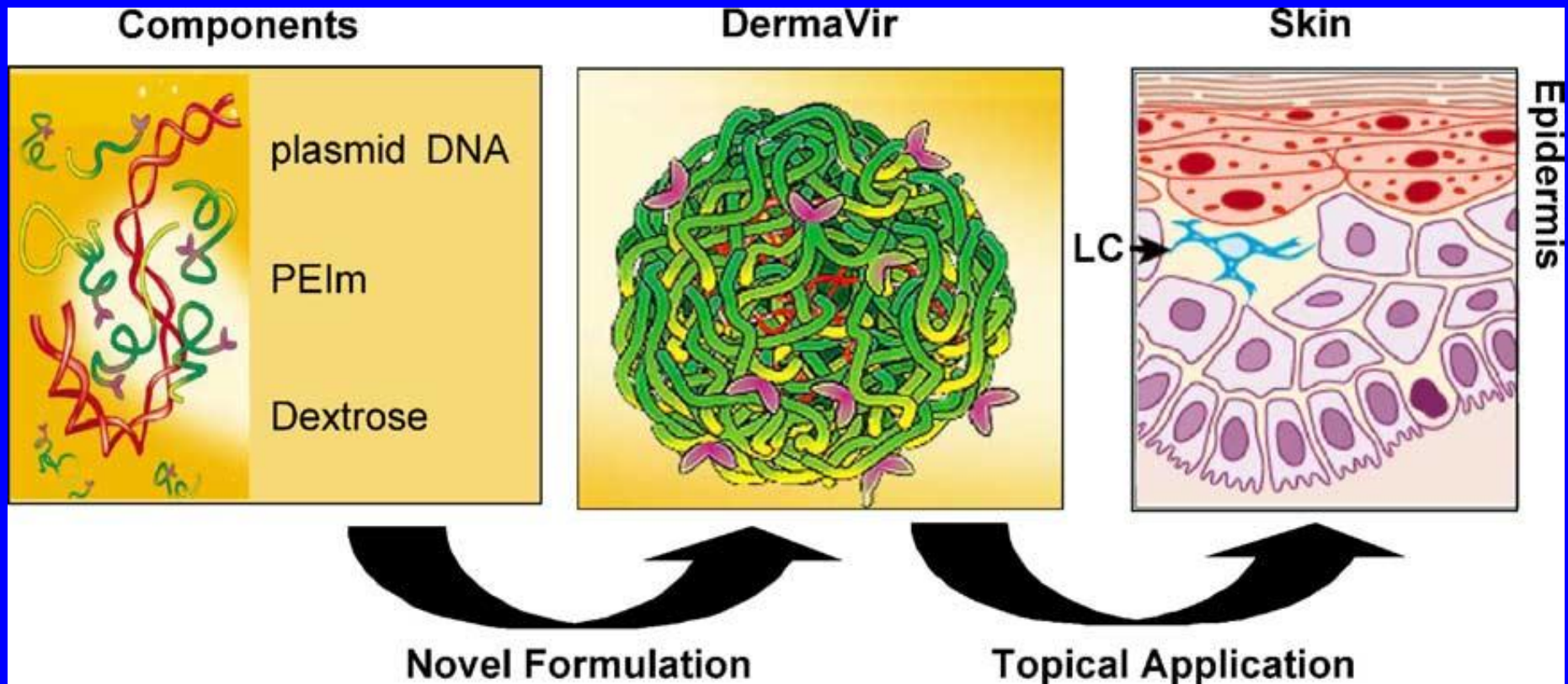


Fig. 3. Kaplan-Meier survival curves for the cumulative proportion with at least one episode of clinical malaria during the double-blind and single-blind phases in cohort 2, respectively (ATP cohort)⁴⁰.

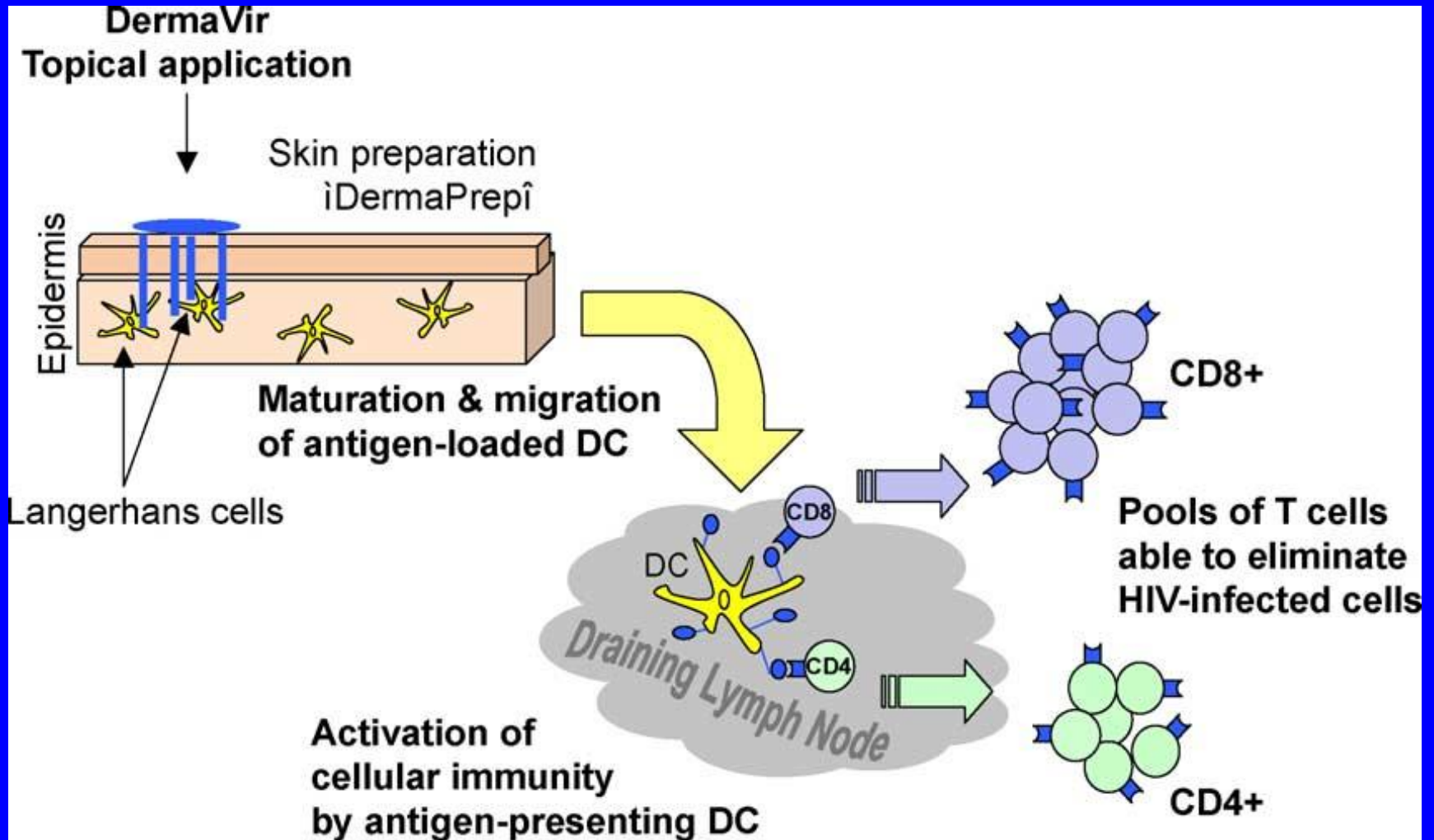
Dendritic Cell-based Vaccines



Components:

1. plasmid DNA, encoding entire HIV genome w/o integrase gene
2. polyethylenimine-mannose (PEIm)
3. glucose solution

Dendritic Cell-based Vaccines



Dendritic Cell-based Vaccines

- IMPAACT P1049:
 - *Phase I/II Safety, Tolerability and Immunogenicity Study of a Topical Therapeutic DNA Dendritic Cell Vaccine (DermaVir) in Children and Adolescents with HIV-1 Infection on HAART*
 - Waiting for immunologic data from the adult study (A5176):
 - IAS, 2011, Rome: safety & immunogenicity (IFN-gamma production & T cell proliferation)

Parainfluenza-3 Vaccine

- **HPIV3cp45 mutant** selected during serial passage of wild type HPIV3 in MK cells at 20°C and 22°C
 - cold adapted, temp. sensitive, attenuated by ≥ 5 mutations
 - Belshe, J Med Virol 1982; 10(4):235-242
- **Vaccine (rHPIV3cp45)** developed at the NIH:
 - Recovered from cDNA in Vero cells using a set of 5 plasmids:
 - 1 encoding full-length HPIV3cp45 cDNA under T7 polymerase control
 - 3 support plasmids encoding the N, P, and L proteins
 - 5th plasmid expressing T7 polymerase

Parainfluenza-3 Vaccine

- Phase I, II safety & dose finding studies in healthy seropositive & seronegative infants
- Phase I safety/ immunogenicity study in healthy seronegative infants 6-36 months of age
- Phase IIb safety, immunogenicity, efficacy study in the planning stage

RSV Vaccine

- Background:
 - Severe RSV disease predominates in infants and children, it has also been identified as a cause of morbidity and mortality in the elderly, transplant & immunodeficient patients
 - 1960's formalin-inactivated RSV vaccine trial led to exacerbated disease upon natural infection of vaccinees, including two deaths compare to placebo recipients
 - New vaccine should be safe, & elicit immunity that is more durable than natural infection, a unique requirement for a vaccine

RSV Vaccine

- **Failed Candidates:**
 - Live attenuated, cold-passaged, w/ temp.-sensitive mutations
 - Recombinant virus with deletion mutations (SH, NS1 or NS2)
 - Such vaccines exhibited residual virulence, genetic instability, or insufficient immunogenicity in clinical testing
- **Current Candidates:**
 - Live attenuated molecular clone (MEDI-559):
 - Phase II trials in children (5–24 months) and infants (1–3 months)
 - Subunit purified F glycoprotein in alum
 - Recombinant chimeric F/G glycoprotein in related paramyxovirus (MEDI-534)
 - **Recombinant chimeric RSV-F/parainfluenza–HN glycoprotein**
 - Plasmid DNA encoding F and G glycoproteins
 - Recombinant G glycoprotein & G protein peptides

Comments

- Concerns about Vaccine Safety are the major threat to immunization programs in Developed countries
- Access to existing vaccines & development of vaccines for TB, Malaria, HIV, dengue are the major issues in resource poor areas of the world
- More sophisticated constructs that target and enhance specific protective responses will be the vaccines of the future