HIV vaccines

- We don't know how to make one that would work.
- We do know that a product of the correct design could probably be manufactured and distributed.
- We do know that an effective product would be used.

HIV microbicides

- We do know how to make one that would work (I think).
- We don't (yet) know that a product of the correct design could be manufactured and distributed.
- We don't know for sure that an effective product would actually be used by real women in the real world.

The third generation of microbicides (specific inhibitors, topical ARVs) is the one we have to get right! (Or there may be no "Next Generation")

- **We need** …. Active ingredients, compounds that might actually prevent HIV-1 transmission.
- …. Formulation expertise, particularly for co-formulating inhibitor combinations.
- …. Product development expertise - industrial input into the overall process would be desirable.
- …. A better regulatory process, flexibility from the FDA - an easier path to testing combination formulations.
- …. Trial sites and volunteers, focused on concepts that have a real chance of proving effective.

Primate models can help microbicide development ("low" and "high" dose models can be used)

- Priority in clinical development should be given to compounds with proven efficacy in primates.
- Monkey availability is limited.
  - access issues for non-NIH funded projects at primate centers
- ARVs or compounds similar to those in clinical testing are generally likely to be reasonably safe (non-toxic).
  - some will probably be affordable;
  - can be gel-formulated (HMC).
- Entry inhibitors conferring protection in the macaque model include PSC-RANTES, CMPD 167, BMS-378806, T-1249, C52L, CV-N, CD4-IgG2, b12, CAP, etc.
- RT-inhibitors include Tenofovir (UC-781 has not been successfully tested in the macaque model).

The case for combination microbicides

The arguments for using inhibitor combinations are as strong for prevention as for treatment.

- **Increased breadth of coverage against divergent HIV-1 strains.**
- **Reduced probability of transmitting viruses resistant to any single inhibitor.**
- **Possible synergy, creating dose-sparing effects.**
- **Supportive data from animal models.**

Industry plays a critical role in microbicide development

- The Pharmaceutical Industry tends to protect its clinical candidates but is sometimes willing to make available alternative compounds that are similar to the 'crown jewels' and "just as good".

- Models for industry involvement include:
  - Direct corporate funding, by share-holders and the private sector.
  - Involvement of NIH or an NGO as direct funding partners.
  - Agreement by an NGO to develop a company's products collaboratively (e.g., IPM with Tibotech/J&J, Merck, Bristol-Myers).

The best model will vary from company to company.

Microbicides, oral prophylaxis and vaccines are complementary, not competitive ways to prevent HIV-1 sexual transmission

Why not try to combine technologies?

- Deliver entry inhibitors/ARVs both orally and vaginally.
- Use a microbicide formulation to deliver vaccine antigens vaginally or rectally, directly to mucosal sites.
- Can oral prophylaxis boost the protective effects of a sub-optimal vaccine?
- See if a partially protective microbicide can help a partially effective vaccine confer better protection (a monkey study is now being planned, with Dan Barouch).

Basic/pre-clinical microbicide research
A summary of where we are

- The pipeline is open. Many compounds suitable for human trials are available but not yet tested.
- A major research question:
  - Can we develop the combination microbicide & microbicide/PREP/vaccine concepts?
- What are the major choke-points?
  - Better access to animal models (including appropriate viruses and viral load assays).
  - Creating feasible public-private sector models.
  - More flexible regulatory processes.

The Forum for Collaborative Research

- Prevention science needs such a forum.

- Over the past decade, prevention science has followed not this approach but has instead become:

The Forum for Competitive Research

- NGO wars.
- Inter- and intra-foundation politics.
- Fights over trial sites and volunteers.
- Battles for funding in a competitive world.
- Everyone knows the stories…….. It's time to stop!