Biomedical Sciences Working Group (BSWG)

Formerly known as the Biomedical Sciences Committee (BSC)

MTN
microbicide trials network

Who are we?

- Jeanne Marrazzo, MD (BSWG Chairperson) – U. Washington, Seattle, WA
- Charlene Dezzutti, PhD (MTN NL director) – Magee-Womens Research Institute, Pittsburgh, PA
- Craig Hendrix, MD – Johns Hopkins University, Baltimore, MD
- Betsy Herold, MD – Albert Einstein College of Medicine, New York, NY
- Florian Hladik, MD – U. Washington, Seattle, WA
- Yunda Huang, PhD – SCHARP, Seattle, WA
- John Mellors, MD – U. Pittsburgh, Pittsburgh, PA
- Urvi Parikh, PhD – U. Pittsburgh, Pittsburgh, PA

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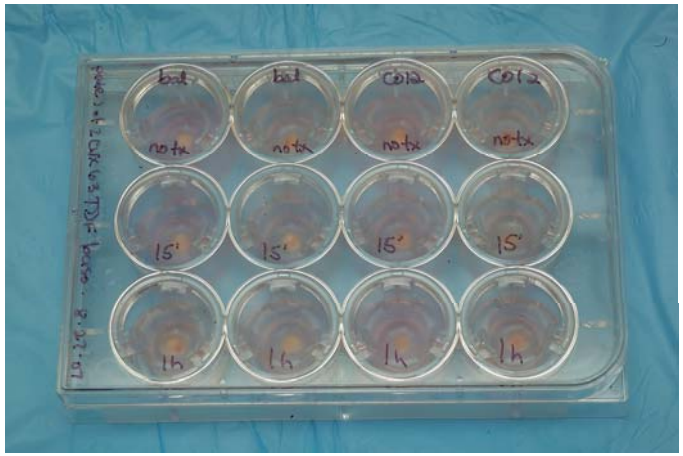
What do we do?

- Provide scientific advice on protocol design and implementation
  - Translate laboratory results to protocol design
  - Interpret clinical trial results back to the laboratory
  - Recommend and implement protocol sub-studies



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Lessons learned on why trials failed

- Efficacy
  - Adherence
  - Low potency
  - Ineffective against relevant HIV-1 subtypes
  - Activity decreased in the genital tract (acidic pH, vaginal secretions, semen, etc.)
  - Distribution: not reaching target cells/tissue
- Safety
  - Disrupt epithelial barrier allowing entry of HIV-1
    - Recruit/activate target cells
    - Increase HIV-1 replication
  - Interfere with innate defenses
    - Endogenous antimicrobial activity (flora, defensins, SLPI, etc.)

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Important things to remember…

- None of our pre-clinical assays are currently predictive of clinical success
- For HIV-1 clinical trials, our only endpoint is HIV-1 infection
  - We have **no** surrogate marker or endpoint

Our approach – HPTN 035

- BSWG obtained funding from the Gates Fdn to collect an additional vaginal swab
  - Our goal is to evaluate the swabs from the women who seroconvert to a subset of women who don't to compare biomarkers
    - Markers of inflammation (cytokines & innate factors)
    - Anti-microbial activity
    - Analysis of vaginal bacteria
  - To date 88% (n=2049) of the women approached so far have consented to participate and 96% of the swabs (n=3355) have been collected.

Our approach – MTN 001

- Highly intensive PK study of topical/oral tenofovir in women
  - Cross-over study design comparing topical, oral, and both for PK analysis
  - The main goal is to determine where tenofovir is located in the female genital tract (lumen or cells) and how long it stays there

Our approach – MTN 006/007

- MTN 007 will evaluate the effect of short-term exposure of PMPA gel on the rectal mucosa
  - Up to 12 biopsies will be taken for histology, cell phenotyping, RT-PCR, ex vivo challenge with HIV-1
  - Swabs will be taken for inflammatory measurements
  - Rectal lavage will be taken to determine epithelial sloughing and inflammatory measurements
- MTN 006 will be a topical/oral comparison of tenofovir in women and men
  - Similar to the MTN 001 study design
  - Main objective is PK analysis

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Our approach – MTN 015

- The current hypothesis is to determine if topical gel arms change any parameters as compared to the no gel arm
- Parameters include:
  - Vaginal swab – quantitative bacterium-specific PCR and markers of inflammation
  - CVL – HIV-1 RNA levels, infectious HIV-1 shedding, analysis of vaginal flora, anti-microbial activity, anti-HIV-1 immunoglobin (IgG/IgA)
  - Plasma – HIV-1 DRV, allele specific mutations
  - PBMCs – anti-HIV-1 specific cell-mediated immunity

Our approach – BSWG study

- Candidate Biomarker Measurements in Cervicovaginal Fluid Samples: Comparative Analysis of Collection Methodologies
  - The goal is to optimize the way to collect and analyze specimens
    - 40 women (10 with BV) will be recruited at JHU for CVL and swab collection
    - CVL will be collected using Normisol-R, saline, and water
    - Swabs (Dacron swab, cytobrush, and flocked swabs) will be collected on the endocervical canal or vaginal wall
    - We will be testing for cytokines, anti-microbial activity, recovery of spiked HIV-1, quantitative bacterium-specific PCR

Summary

- The BSWG's goal is to determine how to better interpret laboratory data prior to and during clinical trials to attempt to validate the pre-clinical microbicide evaluation
- Our results should help to better predict which microbicide products would be more likely to succeed

Questions

"Mr. Osborne, may I be excused? My brain is full."