DESIGN AND SCREENING OF NEW CONTRACEPTIVES FOR SAFETY, EFFICACY AND ADDITIONAL HEALTH BENEFITS

Patricia L. Morris
Center for Biomedical Research
Population Council

2011 International Conference on Family Planning: Research and Best Practices, Dakar, Senegal
Partnerships to increase uptake and acceptability of new Family Planning Methods

Bench to Bedside to Bench
Bench to Bedside to Bedroom

Kenya, 2010
A NEW or EXISTING CONTRACEPTIVE which offers an additional benefit of promoting BREAST HEALTH while remaining safe for the endometrium would likely -

✓ enhance client satisfaction,
✓ improve acceptability and,
✓ increase use

of the contraceptive product.
Challenges in testing and safety evaluations for new contraceptive technologies

**Tissue & Gene** expression changes are usually monitored by toxicology and tissue histology using a small number of biological characteristics [“bio”markers] to establish safety and validate efficacy.

**Biopsy specimens** are usually restricted to 1 or 2 tissues before study start as a baseline and after contraceptive use to ensure reversibility (or not if desired) and a recovery return to baseline; small samples are usually reserved for histology with limited biomarker assessment.
Clinical Trial Assessment of Endometrial Tissue Safety for a New Contraceptive Vaginal Ring (CVR)*

<table>
<thead>
<tr>
<th>Baseline biopsy</th>
<th>Final biopsy after a 3mo. CVR clinical trial*</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1 Proliferation Biomarker: Ki67 labeled</td>
<td></td>
</tr>
<tr>
<td>#2 Proliferation Biomarker: pH3 labeled</td>
<td></td>
</tr>
<tr>
<td>#3 Viability Biomarker: Bcl2 labeled</td>
<td></td>
</tr>
</tbody>
</table>

* Representative histology data kindly provided by Drs. Alistair Williams, Univ. Edinburgh Scotland and Regine Sitruk-Ware, Population Council
A Need and a Challenge:

If a sensitive, high throughput biological assay tool for human cells in small biopsy samples could be designed & validated to quantitatively measure multiple physiologically meaningful biomarkers, it would facilitate priority selection of the lead contraceptive candidates for safety and potential health benefits.

Effective, safe contraception + added health benefit = increased acceptability and client use for family planning and birth spacing.
Projections indicate a worsening cancer epidemiology for the developing nations of the world in incidence and mortality*.

Choices for contraception promoting breast and/or endometrial health in young healthy women or those at risk of disease could have significant impact on choice and disease emergence.

In the developing world, breast cancer is characterized by

- lower incidence -- for example in Sub-Saharan Africa than in developed countries
  
  *but*

- earlier occurrence at relatively young ages, in mainly multiparous, premenopausal patients

- later stage disease presentation

- more aggressive tumors, worse prognosis and women are more likely to die from disease
In a study of breast cancer tissue from 378 women in Nigeria and Senegal*, researchers studied a *limited number of biomarkers* to detect a *pattern*, i.e., genes were turned on and active in the African tumors.

Researchers concluded that:

1. *specific breast cell type found* to be growing abnormally in breast cancers in African women was different from the cell source most commonly found in cancers in the developed world;
2. tumors arising from these cells have a *worse prognosis*, regardless of race;
3. *changes in breast gene expression* were correlated with abnormal growth promoting “biomarkers”

Together with extensive data from investigators world-wide, such findings indicate that complex molecular signatures should be established to use to predict healthy vs. disease gene patterns.

* Compared with breast cancer tissue from 930 Canadian women; Perou *et al.*
Resource limited settings:

In many sub-Saharan countries for the foreseeable future, there will be a great unmet need for breast health and breast cancer screening; e.g. in Uganda, mammograms are few.*

How to address scarce human resources for detection of breast cancer?

- Provide breast health awareness (education and self-exam)
- Enlist involvement of non-physician health workers; task shifting

✓ Link breast health with family planning options and services

Can we design, screen and select a new contraceptive with a dual benefit promoting breast health and increase client acceptability?

Our studies show that a new female contraceptive can safely slow the growth rate of normal human breast cells: Contraception with potential breast health benefits

Flow cytometry analyses using Propidium Iodide

G₀ G₁ (Red), G₂M (Blue), S (Green)

* DNA synthesis for cell proliferation
At the Bench:
New key GENE and PROTEIN molecular signatures follows the treatment of human breast cells

Control
Normal Human Breast cells
(hTERT-HMEC)

+ Vaginal Contraceptive
Normal Human Breast cells
(Ulipristal+ hTERT-HMEC)

Signal read outs are fluorescence of the same biomarkers and their intensity in both panels, shown with individual cell DNA (blue)
Bench to Bedside, then Bedside to Bench

High Complexity Analysis
Human biopsy samples from clinical trial studies
Human Endometrium: Molecular Signature

- endometrium
- complex tissue
  - epithelial
  - stroma
  - stem cells

Barcode labeling

Laser sorting
- read labels:
  - type of cell
  - stage of cell cycle
  - cell size & complexity
  - biomarkers (14)

Morris Laboratory:
Mechanisms in Reproductive Biomedicine
Example of complex molecular profiling analyses in human cells

Legend: A1 – normal cells, then estrogen responses examined: unique set of genes

A2 – normal cells exposed to the new contraceptive for 6 months; unique genes
Our studies demonstrate that development of new, highly effective and safe contraceptives for women could also include a high throughput screening tool for potential beneficial effects on specific cell types as well as standard safety studies on target tissue.

Improvements in existing or next-generation contraceptives could be configured based on a wider array of human genome-based gene expression patterns.
CAPACITY BUILDING PARTNERSHIPS

Brazil
Cameroon
India
Korea
Puerto Rico
Japan

Dominican Republic
Equador

K. Hwang, L. Mitchell, C. Rapelje, R. Sitruk-Ware, J.W. Townsend and P. L. Morris
These translational research studies are supported by the Population Council and the *Eunice Kennedy Shriver* National Institute of Child Health and Development, National Institutes of Health, USA.