New Frontiers in Contraceptive Discovery

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Research for a Lifetime: A Scientific Colloquium to Commemorate the NICHD’s 50th Anniversary

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World Population Growth
Unintended Pregnancies (US, 2006)

~50% of US pregnancies are unintended ( > 3 million per year)

- 52/1,000 women 15-44 yrs
  - 80/1,000 women < HS education
  - 78/1,000 Hispanic women
  - 91/1,000 Black women
  - 132/1,000 women < 100% FPL
  - 17/1,000 higher income white women
Maternal Mortality and Morbidity (US, 2007)

• 4.2 million births
• 600 maternal deaths
• 34,000 near misses
• >1,000,000 hospitalizations for complications
• Maternal deaths worldwide ~360,000 annually
Preventing Pregnancy = Preventing Death

Estimated annual deaths per 100,000 women

- OC (also deaths from use)
- Condom
- No method/abortion
- No method/birth

Contraceptive Methods by effectiveness (WHO)

<table>
<thead>
<tr>
<th>Effective Level</th>
<th>Method</th>
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</thead>
<tbody>
<tr>
<td>Most Effective</td>
<td>Sterilization</td>
</tr>
<tr>
<td></td>
<td>IUDs</td>
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<tr>
<td></td>
<td>Implants</td>
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<tr>
<td>Effective</td>
<td>Pill</td>
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<td></td>
<td>Patch/Ring</td>
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<td></td>
<td>Injection</td>
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<tr>
<td>Less Effective</td>
<td>Diaphragms, Caps</td>
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<tr>
<td></td>
<td>Spermicidies</td>
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<tr>
<td></td>
<td>Condoms</td>
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<td>Withdrawal</td>
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# Contraception Methods

<table>
<thead>
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</tr>
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<tbody>
<tr>
<td>Sterilization</td>
<td>Laparotomy</td>
<td>Ø</td>
<td>Diaphragm</td>
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<tr>
<td>IUDs</td>
<td>Inert</td>
<td>Ø</td>
<td>Spermicides</td>
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<tr>
<td>Implants</td>
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<td>Ø</td>
<td>Male Barriers</td>
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<td></td>
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<td></td>
<td>Withdrawal</td>
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<tr>
<td>Pill</td>
<td>2 pills</td>
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<tr>
<td>Patch/Ring</td>
<td></td>
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1962
# Contraceptive Methods

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<td></td>
<td></td>
</tr>
<tr>
<td>Sterilization</td>
<td>Laparotomy</td>
<td>Laparoscopic</td>
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<tr>
<td></td>
<td></td>
<td>Hysteroscopic</td>
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<tr>
<td></td>
<td></td>
<td>Vasectomy</td>
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<tr>
<td><strong>Effective</strong></td>
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<td></td>
</tr>
<tr>
<td>IUDs</td>
<td>Inert</td>
<td>Copper</td>
</tr>
<tr>
<td></td>
<td>Ø</td>
<td>Hormonal</td>
</tr>
<tr>
<td>Implants</td>
<td>Ø</td>
<td>Capsules</td>
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<tr>
<td></td>
<td></td>
<td>Rods</td>
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<tr>
<td><strong>Less Effective</strong></td>
<td></td>
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<tr>
<td>Sterilization</td>
<td></td>
<td>Laparotomy</td>
<td>Laparoscopic Hysteroscopic Vasectomy</td>
<td>Transvaginal</td>
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<tr>
<td>IUDs</td>
<td></td>
<td>Inert</td>
<td>Copper Hormonal</td>
<td>Phase 2, 3</td>
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<tr>
<td>Implants</td>
<td></td>
<td>Ø</td>
<td>Capsules Rods</td>
<td>Phase 1, 2</td>
</tr>
<tr>
<td>Effective</td>
<td></td>
<td></td>
<td>~40 pills &quot;EC&quot; Patch Ring</td>
<td>Many</td>
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<tr>
<td>Pill</td>
<td></td>
<td>2 pills</td>
<td>DMPA Net-En Cyclofem</td>
<td>Phase 1, 2, 3</td>
</tr>
<tr>
<td>Patch/Ring</td>
<td></td>
<td>Ø</td>
<td></td>
<td>Phase 2</td>
</tr>
<tr>
<td>Injection</td>
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<td>Ø</td>
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<td>PATH Condom Microbicides</td>
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<tr>
<td>Less Effective</td>
<td></td>
<td>Diaphragm</td>
<td>Condoms Diaphragm Sponge</td>
<td>Hormonal Contraceptives Novel targets</td>
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Contraceptive Research and Development

Cooperative Agreements
- Contraceptive Centers Program (U54)
- Male Contraceptive Development Program (U01)

Support Contracts
- Biological Testing Facility
- Chemical Synthesis Facility
- Peptide Synthesis Facility
- Medicinal Chemistry Facility

Investigator Initiated Grants

Small Business, Academic Researchers

Contraceptive Clinical Trials Network
New Products for Women

**New Hormonal Products:**
- **Ella** (emergency contraception) - approved by FDA in 2010
- **Esmya** (fibroid treatment) – approved in Europe, NDA application pending in USA
- **Nestorone EE vaginal ring** - one ring for 1 year (13 cycles) - NDA application preparation
- **Levonorgestrel Patch** - weekly patch - safe for obese women
- **Levonorgestrel butanoate** - long acting injectable (4+ months) – long-acting & safe for obese women
- **Nestorone Estradiol vaginal ring** - continuous use for 3 months – long-acting & safe for obese women
- **Low dose ulipristal acetate** - estrogen independent contraception - safe for obese women & may have breast-protective properties.

**Non-hormonal products (dual protection):**
- **Path Woman’s Condom** - Phase III trial completed – Preparing Clinical Study Report for FDA review
- **C31G spermicidal gel** - Phase III trial – completed – pending commercial partner development
- **Buffer Gel** – Phase III trial – completed - pending commercial partner development
- **Silcs diaphragm with antimicrobicidal gel** – Phase I trial

**New initiative to identify targets for non-hormonal products for women:**
- Follicular development - potential preservation of fertility
- Oocyte maturation -WEE2, WEE1B, INSL3, LGR8, NALP
- Follicular rupture - Prostaglandin E2 Synthesis/Signaling Inhibitors, TRP1 Protease, Metalloproteinase, ADAMS, Endothelin
Ella® - Emergency Contraception

CDP – 3940
PATH - Female Condom
Agile Contraceptive Patch

AG 200-15  EE2 + LNG

AG 890  LNG only
Agile Combination Patch

Technology

The TCDS technology is composed of an inner, active matrix adhesive system that delivers both EE and LNG at unique, targeted levels through the skin.

The outer, peripheral adhesive system is responsible for patch adherence, stability, and patient comfort.

Soft, flexible fabric maximizes patient comfort

Provides reliable adhesion for 7 days

- Allows moisture to evaporate
- Minimizes irritation
- Increases drug stability
New Ring

Population Council

EE2/Nesterone for 12 months – 3 weeks in/ 1 week out.
  – 2,277 women, highly effective
  – Europe, Australia, Latin America, and the United States
  – 56 mm diameter
  – 8.4 mm cross-section

FDA review in progress.

Phase 2 – three month ring w E2 and NES
The Road to a Male Contraceptive Product

Basic research – supported by grants, contracts, Pharma
  – Identify and validate target
  – Identify drug(s)
  – Demonstrate efficacy in several species (reversible and safe)

Translational research – very difficult for academic investigators
  – Synthesis – GMP for clinical trials
  – Formulation and delivery
  – Toxicology – very high bar of safety for long-term use in healthy subjects

Clinical research
  – Investigational New Drug Application
  – Clinical trials in normal volunteers…
    • How many subjects? How long?
Hormonal Approach to Male Contraception

2-Step Process - Searching for the Best Regimen

Step 1 - Suppress gonadotropins using:

**Progestins** – commercially available as oral, injection, implant
  » --- but NOT labeled for use in men - not likely to be

*New progestins*:
  – Levonorgestrel butanoate – long-acting injection (~ 3-4 months)
  – Nestorone Gel - (daily) – Phase 1 trials in men are ongoing

Step 2 – Replace androgen to restore serum levels

- No oral **Testosterone** formulation yet

- **Testosterone** gel is commercially available
  - Combine with **Nestorone** Gel for effective contraceptive method
    - Phase 2 trials in men are ongoing
  - **Dual progestin and androgen activity (in animal models)**

- **DMAU** - oral (daily) – Phase 1 trials in men are ongoing
  - long acting injectable also possible
A Few Promising Leads for Men

**Adjudin [Adherens Junction Disruption] (Cheng)**

**CatSper: Cation channel Sperm (Clapham)**

**Epididymal Protease Inhibitor (EPPIN) (O’ Rand)**

**Glyceraldehyde 3-phosphate dehydrogenase-S (GAPDHS) (O’Brien)**

**Retinoic Acid Receptor Antagonists (Wolgemuth)**

*Antagonists to prevent sperm maturation, activation, motility.*
The Future of Contraceptive Development

Expand current program to emphasize development of non-hormonal male and female contraception.

Take advantage of advances in areas such as genomics, proteomics and bioinformatics.

- Target identification
- Target characterization (structural analysis of binding sites)
- Target validation (blocking = contraception)
- Target specificity (with sensitive expression assays)
- Lead identification (High Throughput Screening)
- Lead optimization (molecular modeling)
The Dream Pipeline

Effective and acceptable MALE contraceptives
Combination pills/patch/rings with NO VTE

Universal coverage for all contraceptives
OTC status for Pills
Unlimited refills
Self-administered DMPA injections
No more side effect mythology
Additional non-contraceptive benefits