The “Male Pill”: The Learning Curve from Basic Science to the Drug Development Pipeline and the Strength of Interdisciplinary Collaboration

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University of Kansas Medical Center
World Health Organization Worldwide Reproductive Statistics*

The Magnitude of the Need for New Alternatives in Family Planning

- 122 million planned pregnancies per year
- 87 million unintended pregnancies per year (42% of all pregnancies)
- 46 million pregnancies are terminated by abortion per year
- World Health Organization, National Institutes of Health, and Institute of Medicine have all stressed the need to develop new male contraceptive methods

Interdisciplinary and Multi-Institutional Components of Male Contraceptive Development

- Reproductive biology (KUMC)
- Medicinal chemistry (U. Minn, KU)
- Molecular genetics (KUMC, Moffitt, UMDNJ)
- Proteomics (KU, KUMC)
- Structural biology/X-ray crystallography (Moffitt, UMDNJ)
- High throughput screening (HTS) (U. Minn, KU)
- Pharmacology/toxicology (KU, IAMI)
- Clinical/Urology (KUMC)
1969: I decided to devote my career towards developing a male contraceptive that is non-hormonal and reversible.

1970: Research basic biology of male reproduction.


2000: Developed a contraceptive delivery system that could be used to develop a male contraceptive.
2002: RC-MC-110 (gamendazole) synthesized after several dozen SAR (structure-activity relationship) synthesis rounds
Chronology of Gamendazole Discovery and Development

2004: US Patent filed to protect IP soon after gaining proof of concept (POC)
Chronology of Gamendazole Discovery and Development

2005: License agreement signed
(too early in process, later disclosures from licensee were disturbing)
2007: Licensee pulls a product that was not disclosed to be in clinical trials, their stock values plummet preventing their meeting milestones, license is terminated.
Chronology of Gamendazole Discovery and Development

2009: US patent issued for Gamendazole and analogues issued: composition of matter, synthesis, use as contraceptives
2010: First non-human primate POC study started: So far proven safe and reversible inhibition of spermatogenesis observed. Additional dose finding planned.
ONPRC Pilot Project: Reversible Inhibition of Spermatogenesis in Nonhuman Primates by Novel Non-hormonal Contraceptive Agent, H2-Gamendazole

Joseph Tash, Ph.D. Principal Investigator, KUMC Contraception & Reproductive Health Branch, NICHD, NIH U54 HD-055763 (JST)

Mary B. Zelinski, Co-Investigator, ONPRC

Gunda Georg, Ph.D. Institute for Therapeutics Discovery & Development, University of Minnesota

Scott Weir, Pharm. D., Ph.D.
Melinda Broward, M.S.
Cancer Center, University of Kansas
Reversible Inhibition of Sperm Production in First Non-Human Primate* by Single Oral Dose of H2-Gamendazole

*Study will last 12 weeks in each of 3 monkeys at 2 different oral doses
2010: Bill and Melinda Gates Foundation convenes “Experts in Contraception” meeting to define strategies to get contraceptive in use SSA & SA H2-gamendazole placed on the map.
Contraceptive technology landscape
Product Profiles for Review and Feedback

February 12th, 2010
## Highly-discussed Discovery opportunities

<table>
<thead>
<tr>
<th>Target</th>
<th>High-level description / quotes</th>
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| GnRH II receptor antagonist | - Female hormonal target; contraceptive efficacy shown in monkey and dog models  
                              - Unique isoforms of GnRH have been found to have activity in reproductive tissue (GnRH I, II, and III)  
                              - Contraceptive action of GnRHAIL believed to be via down-regulation of GnRH II receptor                                              |
| PC6-inhibitor               | - Inhibition of PC6 was found to prevent embryo implantation in the mouse uterus   
                              - "Promising [female] product considering that it is non-hormonal and could be used for addressing contraception as well as HIV infection" |
| Eppin                       | - Eppin protein secreted by Sertoli cells and epididymal epithelial cells  
                              - Critical for the enzymatic degradation of semen coagulate which frees the spermatozoa for motility and capacitation  
                              - Anti-Eppin antibodies from male monkeys shown to inhibit human sperm motility (in vitro)                                      |
| Catsper                     | - CatSper critical in sperm motility required to penetrate outer coat of egg for fertilization  
                              - Inhibition prevents Ca²⁺ entry needed for forceful asymmetric motion required to penetrate  
                              - "Highly selective; non-hormonal; potential lack of side effects; could be developed for males/females"  
                              - "Very specific target, actually 4 targets, blocking any one of which will affect sperm function"  
                              - However some concerns related to toxicology issues                                                                 |
| a-adrenoreceptor            | - Selective blockade of a-adrenoreceptors causes inhibition of longitudinal muscular contractions of the vas deferens  
                              - Causes infertility by causing failure of ejaculation, even though orgasm is normal                                                                 |
| **H2-Gamendazole**          | - Non-hormonal male contraceptive agent "likely most potent reversible single oral dose anti-spermatogenic agent in the pipeline"  
                              - "Furthest along"  
                              - Pilot trials currently underway in non-human primates                                                                                             |
Male Contraceptive Drug Development Program: From Target Validation through Identification of Development Candidate
IND Pre-Clinical and First in Human Trials: POC in Males Undergoing Elective Vasectomy
KU-AS-272 As a Single Dose Non-Surgical Sterilant for Male and Female Dogs and Cats and Feral Animals

Male Rats

Female Mice

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<tr>
<th>Testis weight (gm)</th>
<th>1.2</th>
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<tr>
<td>Weeks</td>
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<td>2</td>
<td>3</td>
<td>4</td>
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Rat Control + 5mo

Rat 6 mg/kg + 5mo

A 5

Ovary Weight (mg)

Control  KU-AS-272

Progestosterone (mg/ml)

Control  KU-AS-272
Project Timeline for KU-AS-272 as Single Dose Non-Hormonal Sterilant for Male & Female Dogs & Cats

Objective 1: Male Dog/Cat Studies
- Single SQ Dose-Finding Efficacy Evaluation in Rats
- Pharmacokinetics, Bioavailability, Dogs (IV, IM, & SQ)
- Pharmacokinetics, Bioavailability, Cats (IV, IM, & SQ)
- Perform pre-clinical (phase 1) single SQ dose-finding efficacy evaluation in dogs after the determine the bioavailability & efficacy task
- Perform clinical (phase 2) long term safety and efficacy in cats and dogs

Objective 2: Female Rat/Dog/Cat Studies
- Dose (5) Response Studies (Pre Pub & Adult Rat (IV, IM, & SQ))
- Induced ovulation study (Rat)
- Mating Trials (Rat)
- Pharmacokinetics, Bioavailability, Dogs (IV, IM, & SQ)
- Pharmacokinetics, Bioavailability, Cat (IV, IM, & SQ)
- Perform pre-clinical (phase 1) single SQ dose-finding efficacy evaluation in cats after the determine the bioavailability & efficacy task
- Perform clinical (phase 2) long term safety and efficacy in cats and dogs

Timeline:
- 0 Months: Study Begins
- 4 Months: ADME Acceptance
- 8 Months: Go/No Go Decision 1
- 12 Months: Go/No Go Decision 2
- 16 Months: Go/No Go Decision 3
- 20 Months: Go/No Go Decision 4
- 24 Months: Pre-CVM Meeting Preparations With Regulatory Consultants
- 28 Months: Data Package Development CVM Meeting
- 32 Months: Post-CVM Meeting Activities With Regulatory Consultants
Conclusions

- Collaboration is essential
- Employ the knowledge of experts outside your own comfort zone or knowledge base
- Find alternatives, most leads fail along the way
- Protect IP early, be as broad as possible
- Don’t license too early, later is more attractive
- Accept that as things move along the pipeline they seem to move slower
- Constantly strive towards your goal, but be flexible along the way
Male Contraceptive Collaborators (1)

- **Tash lab**: Lesya Holets, Ph.D., Julie Cotitta, Vijayalaxmi Gupta, Ph.D., Anne Grissell, Brian Kern, S. Kendall Smith, Jennifer Hughes, Jackie Huff, Aneesha Garry, Stacy Wolfe, Brady Timmerberg, Michael J. Wulser, Sotirios-E. Macheras, Adam Gregg, Melissa K. Emerson, Brent Burroughs, Kimberly Pickens (*post doc, medical students, and technicians*)

- **Georg lab (U.Minn)**: Gunda Georg, Derek Hook, Ramappa Chakrasali, Sudhakar R. Jakkaraj, Subhashree Rangarajan, Dinah Dutta, Xingxian Gu (*U54, NIH contract, medicinal chemistry*)

- **Heckert lab (KUMC)**: Leslie L. Heckert, Kaori Hornbaker (*U54, Sertoli cells, rt-PCR*)

- **Blanco lab (KUMC)**: Gustavo Blanco (*U54*)

- **Kinzy lab (UMDNJ)**: Terri Goss Kinzy, Jenna Hutton, Sedide B. Ozturk (*EEF1A1*)

- **Schönbrunn lab (Moffitt Cancer Center)**: Ernst Schönbrunn, Andreas Beckerman (*U54, NIH contract, HTS, protein cloning/expression, x-ray crystallography*)

- **Blagg lab (KU-Lawrence)**: Brian S. J. Blagg, M. Kyle Hadden (*Hsp90*)
Male Contraceptive Collaborators (2)

- **BIOQUAL**: Barbara Attardi, Sheri A. Hild, Janet Burgenson, David Gropp, Jessica Luke, Margaret Krol, Trung Pham, Bruce Till (*NIH Mating trials, Sertoli cells, endocrinology*)
- **KUMC**: Paul Terranova, Ajay Nangia, M.D., George Enders, Kathy Roby (*translational research support, pathology, ID8*)
- **KU/KUMC IAMi**: Scott Weir, Melinda Broward, Roger Rajewski (*drug development, pharmacokinetics, formulation*)
- **KU Biochemical Research Service Lab**: Michael Alterman, Todd Williams (*MALDI-TOF, MS, proteomics*)
- **KUMC Microarray Core**: Clark Bloomer, Stan Svojanovsky
- **Imaging Core**: William Kinsey, Stan Fernald (*U54, CRS*)
- **NIH**: Hyun K. Kim, Diana Blithe, June Lee, Contraception & Reproductive Health Branch, NICHD
- **Supported by**: NIH U54 HD-055763 (to JST), NIH N01 HD1-3313 (to GIG), U54 HD33994 Center for Reproductive Sciences (Specialized Cooperative Centers Program in Reproductive Research, SCCPRR), N01-HD-2-3338 (to BIOQUAL Inc.)
Thanks!
At least 55 near-, mid-, and long-term options exist in global contraceptive pipeline

<table>
<thead>
<tr>
<th>Discovery projects</th>
<th>Development projects</th>
<th>Late Development (Ph3)</th>
<th>Developing world registration / Launch</th>
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<tbody>
<tr>
<td><strong>Discovery (Target ID, proof-of-principle)</strong></td>
<td><strong>Early Development (Pre-clin, Ph1, Ph2)</strong></td>
<td><strong>Late Development (Ph3)</strong></td>
<td><strong>Developing world registration / Launch</strong></td>
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<tr>
<td>Female Hormonal</td>
<td>GnrH II receptor antagonists</td>
<td>Estetrol + Progestin OC</td>
<td>DMPA + Unjext</td>
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<tr>
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<td>LNG butanoate</td>
<td>LNG as perineal OC</td>
<td>Sino-implant (II)</td>
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<td>Ulipristal Vaginal Ring</td>
<td>Nestorone/EE Vaginal Ring</td>
<td>Cyclofen</td>
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<td>Nestorone/E2 Vaginal Ring</td>
<td>Gestodene and EE Patch</td>
<td>Ortho Evra</td>
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<td>Nestorone/E2 gel or spray</td>
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<td>Progesterone Only Vaginal Ring</td>
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<td>Single-rpd gestodene implant</td>
<td>BufferGel</td>
<td>Femilis IUS</td>
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<td>Female Non-hormonal</td>
<td>Meloxicam</td>
<td>Meloxicam</td>
<td>SILCS Diaphragm</td>
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<td>β-hCG</td>
<td>β-hCG</td>
<td>Quinacrine pellets</td>
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<td>Erythromycin sterilization</td>
<td>Erythromycin sterilization</td>
<td>PATH woman's condom</td>
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<td>Polidocanol sterilization</td>
<td>Polidocanol sterilization</td>
<td>C31G (spermicide)</td>
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<tr>
<td>Male Hormonal</td>
<td>Faslodex</td>
<td>TU + ENG</td>
<td>Reddy latex FC</td>
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<td>SARMS</td>
<td>MENT</td>
<td>Centchroman</td>
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<td>DMAU</td>
<td>Female Condom 2 (FC2)</td>
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<tr>
<td>Male Non-hormonal</td>
<td>Eppin</td>
<td>Oral testosterone</td>
<td>Essure</td>
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<td>RAR antg'nta</td>
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<td>α-adrenoreceptor</td>
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Note: LNG (levonorgestrel); TU (testosterone undecanoate); NET-EN (noretinolone enanthate); RISUG (reversible inhibition of sperm under guidance); EE (ethyln estradiol); MENT (7 α-methyl-testosterone); PC (proprotein convertases); GAPDH (Glyceraldehyde-3-phosphate dehydrogenase, testis-specific); HIFU (High intensity focused ultrasound); SARMS (selective androgen receptor modulators); DMAU (Dimethandrolone 17β-Undecanoate); E2 (estrogen estradiol); BDAZ (bis-dichloroacetyl-diamines)
Chronology of Gamendazole Discovery and Development

RC-MC-110 passes Ames test, first animal testing begins
Proof of concept (POC) as reversible male contraceptive achieved
Chronology of Gamendazole Discovery and Development

- 28
  - H2-gamendazole synthesized and testing started
Based on goal of single dose 100% efficacy AND 100% reversibility
NIH and we agree that observed 100% efficacy with 67% reversibility isn’t good enough.
We start multiple low dose range finding studies.
Collaboration with Kidney Institute yields POC gamendazole analogues as treatment for Polycystic Kidney Disease, Divisional patent filed, divisional patent for female contraceptive agents added
Chronology of Gamendazole Discovery and Development

- 31 H2-gamendazole and gamendazole pass hERG test

H2-gamendazole and gamendazole pass hERG test
Critical POC toxicology will start at CRO (IAMI funded)
Chronology of Gamendazole Discovery and Development

- **QWBA will start at CRO (IAMI funded)**

- **Discovery and Development**
  - **Contracts**
    - Contract proposal submitted to NIH in response to RFP
    - Negotiations completed with NIH on final award and scope of work
    - Contract awarded to RU and KUMC to begin work on synthesis and testing of compounds
  - **NIH**
    - NIH requests for proposals (RFP) “Synthesis and Testing of Non-steroidal and Non-Hormonal Male Contraceptive Agents”
    - NIH Contract awarded to RU and KUMC to begin work on synthesis and testing of compounds
  - **First animal testing completed**
    - Increased potency of RC-MC-110 first identified and reported to NIH
    - NIH begins independent analysis of RC-MC-110
    - NIH confirms our results by independent testing and begins planning for meeting trials
    - NIH requests: “Our biologists said that RC-MC-110 is the most potent nonsteroidal derivative we have seen. New exciting!”
  - **License agreement with Threshold Pharmaceuticals signed to test new analogues for non-contraceptive use (proprietary)**
  - **New analogue H2-gamendazole sent to NIH for testing**
  - **New center grant proposal submitted to NIH that includes experiments to explore dosing of and pharmacokinetics of gamendazole and discovery new compounds that act similarly
  - **New US4 Center is funded at KUMC, lower dose-feeding experiments for Gamendazole begin at KUMC, and discovery of new compounds with same effect as gamendazole started.**
  - **NIH agrees to begin low multiple dose H2-gamendazole meeting trials in rats, but this is put on hold due to changes in contract management and NIH and until new NIH testing facility is ready
  - **High-throughput screening (HTS) identifies 94 compounds that are lead candidates and begin preclinical development.**
  - **New analogue H2-gamendazole and other analogues pass NHG test**
    - US Patent: CIP issued for H2-gamendazole and other analogues
    - US Institute for Advancing Medical Innovation (IAMI) funds gamendazole development
  - **Gamendazole proposal to fund key non-IGF biology research**
    - Biometrics starts 7-day TK, MTD, and toxicokinetics of H2-gamendazole in rats
    - Covance starts QWBA study of H2-gamendazole in rats
    - NIH starts new meeting trial study in rats, after 4 week, single weekly oral dosages H2-gamendazole
    - Dan, Tish, and Knap invited to Bill and Melinda Gates Foundation to discuss Global Strategy for new contraceptives in Sub-Saharan Africa and Southeast Asia. H2-gamendazole identified as one of the most advanced of the new non-hormonal male contraceptives in late discovery/early development.
    - Found Ashland Foundation and KUMC start pre-funding negotiations to start small of concept studies for non-surgical deterrent for male and female cats and dogs
    - QWBA will start at CRO (IAMI funded)
2010: NIH to start new mating trials with single weekly 4 week dosing regimen