



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

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# World Health Organization Worldwide Reproductive Statistics\*

## The Magnitude of the Need for New Alternatives in Family Planning

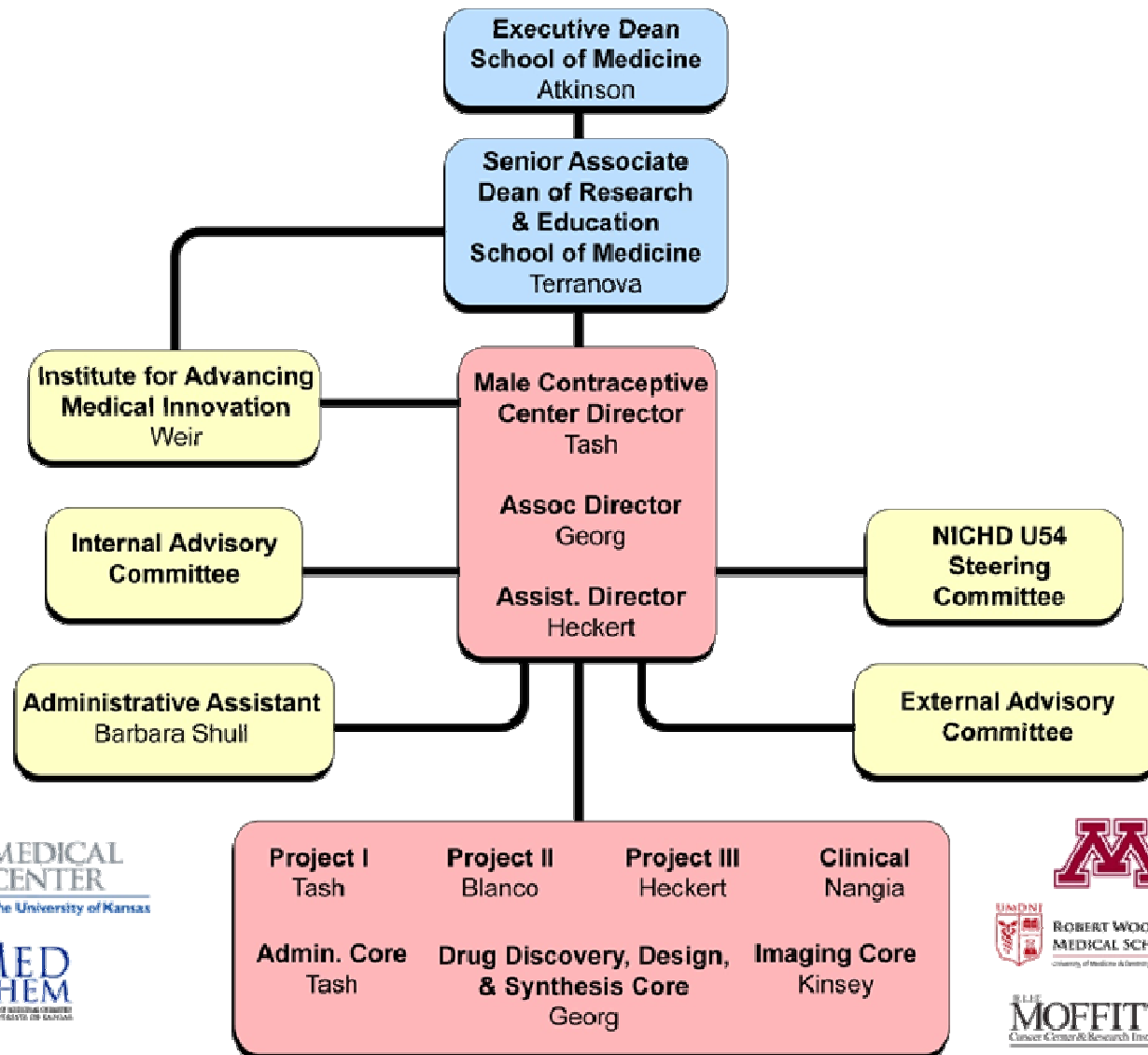
- 122 million planned pregnancies per year
- 87 million unintended pregnancies per year (42% of all pregnancies)
- 46 million pregnancies are terminated by abortion per year
- World Health Organization, National Institutes of Health, and Institute of Medicine have all stressed the need to develop new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

# Interdisciplinary and Multi-Institutional Components of Male Contraceptive Development

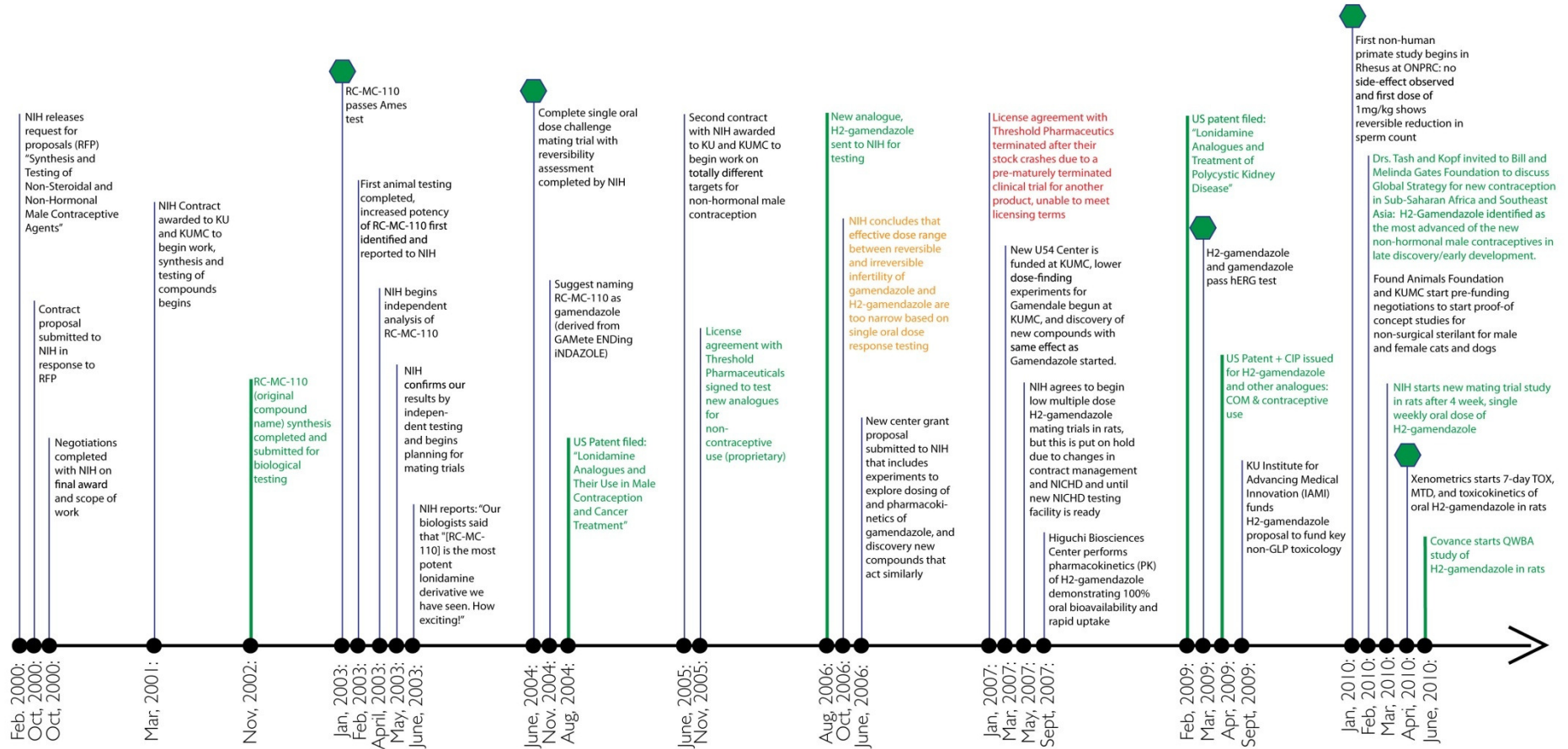
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- Reproductive biology (KUMC)
- Medicinal chemistry (U. Minn, KU)
- Molecular genetics (KUMC, Moffitt, UMDNJ)
- Proteomics (KU, KUMC)
- Structural biology/X-ray crystallography (Moffitt, UMDNJ)
- High throughput screening (HTS) (U. Minn, KU)
- Pharmacology/toxicology (KU, IAMI)
- Clinical/Urology (KUMC)

# KUMC NIH U54 Male Contraceptive Center Organization



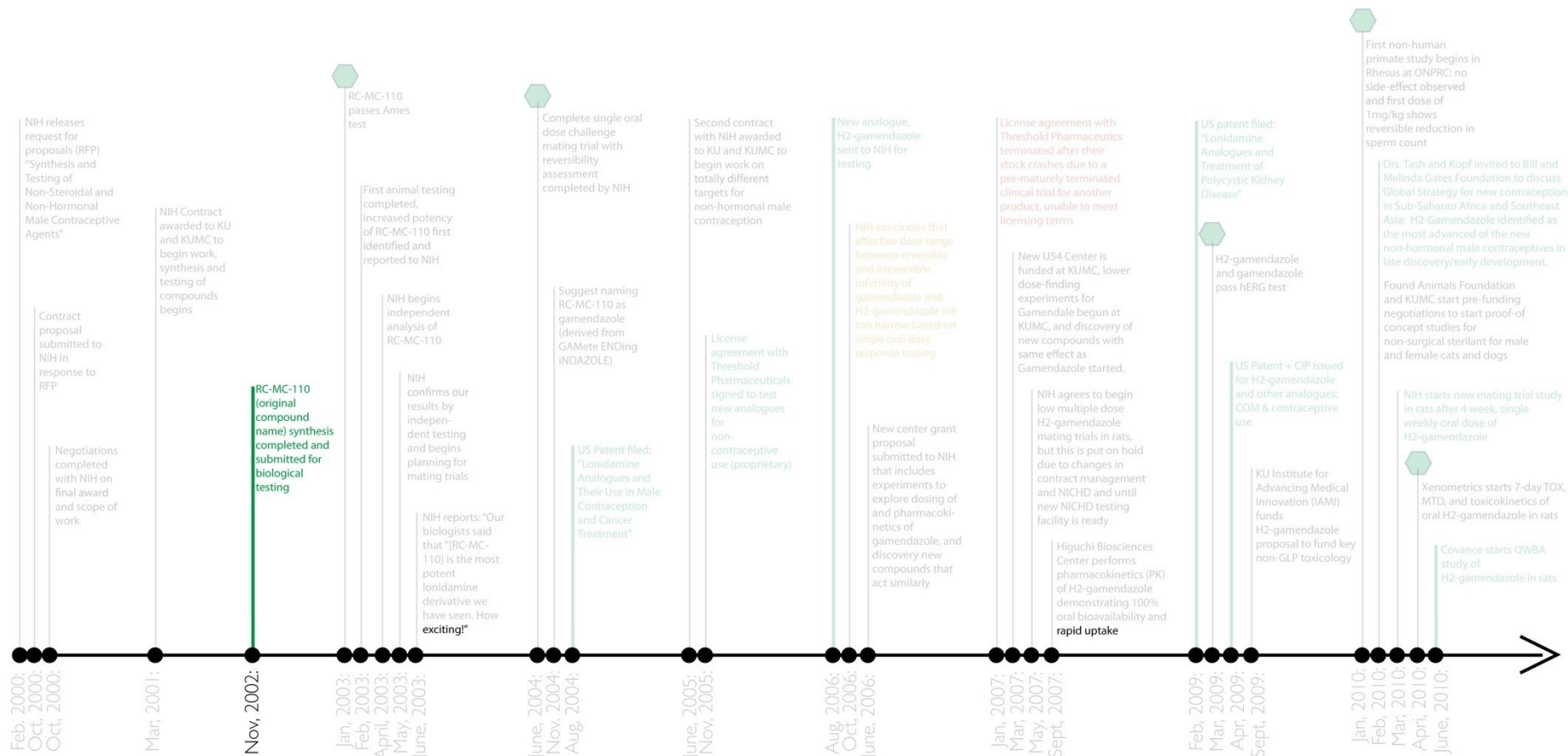
# Chronology of Gamendazole Discovery and Development



1969-2000: Researched basic biology of male reproduction including sperm function and testis function. search for targets and mechanism that could be used to develop a male contraceptive

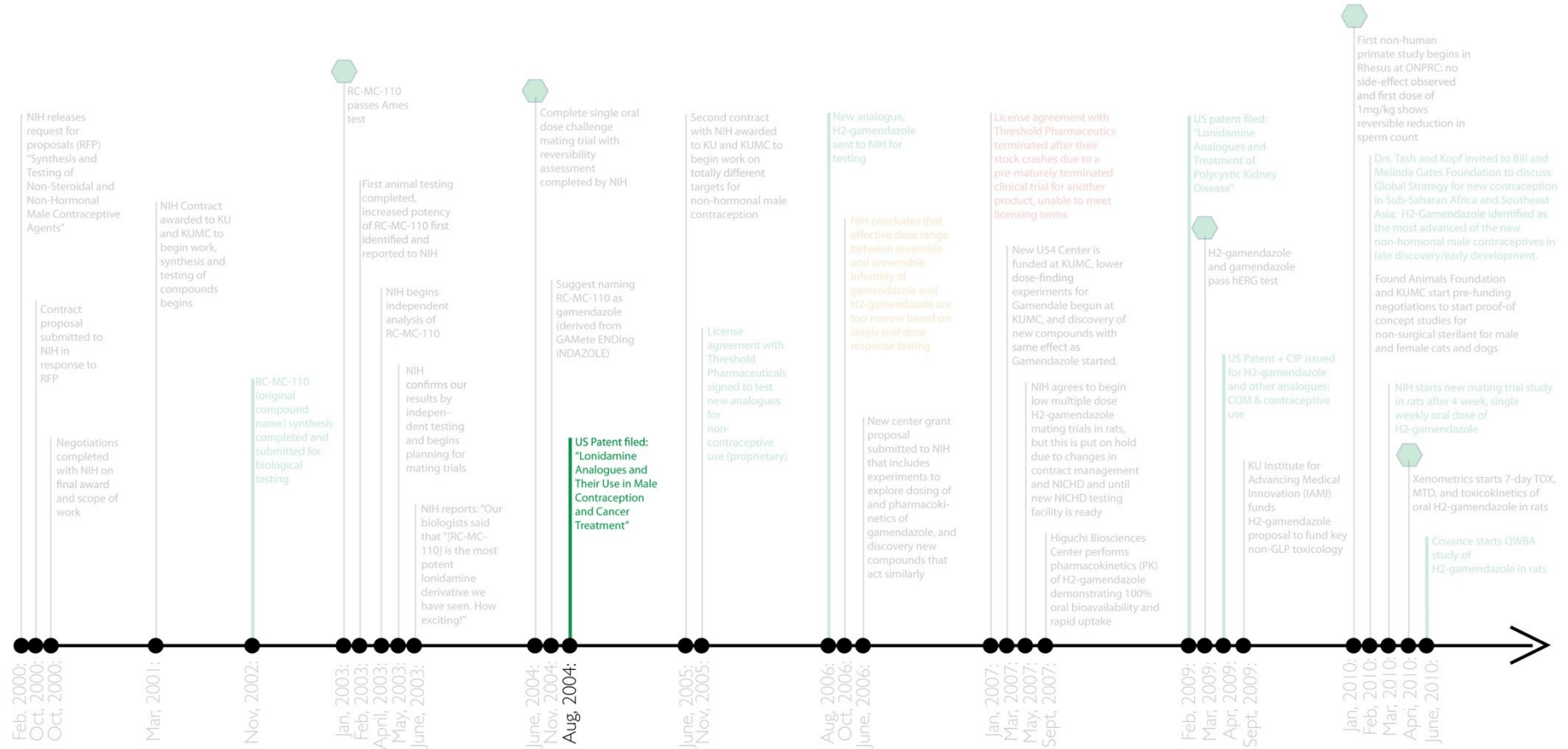
1990-2000: identified a variety of early drug candidates, developed novel male contraceptive Reversible Male Contraceptive Agents

# Chronology of Gamendazole Discovery and Development



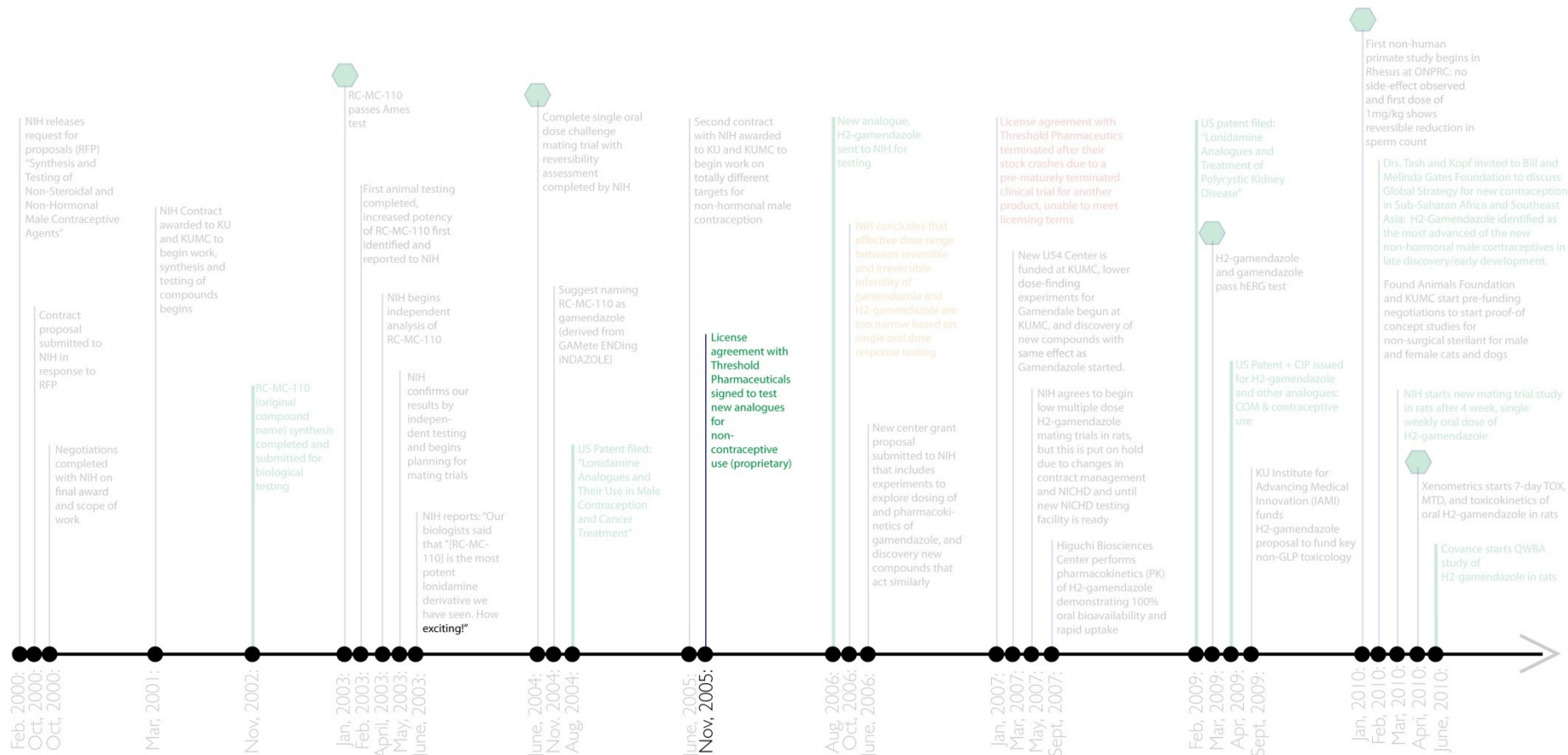
2002: RC-MC-110 (gamendazole) synthesized after several dozen SAR (structure-activity relationship) synthesis rounds

# 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

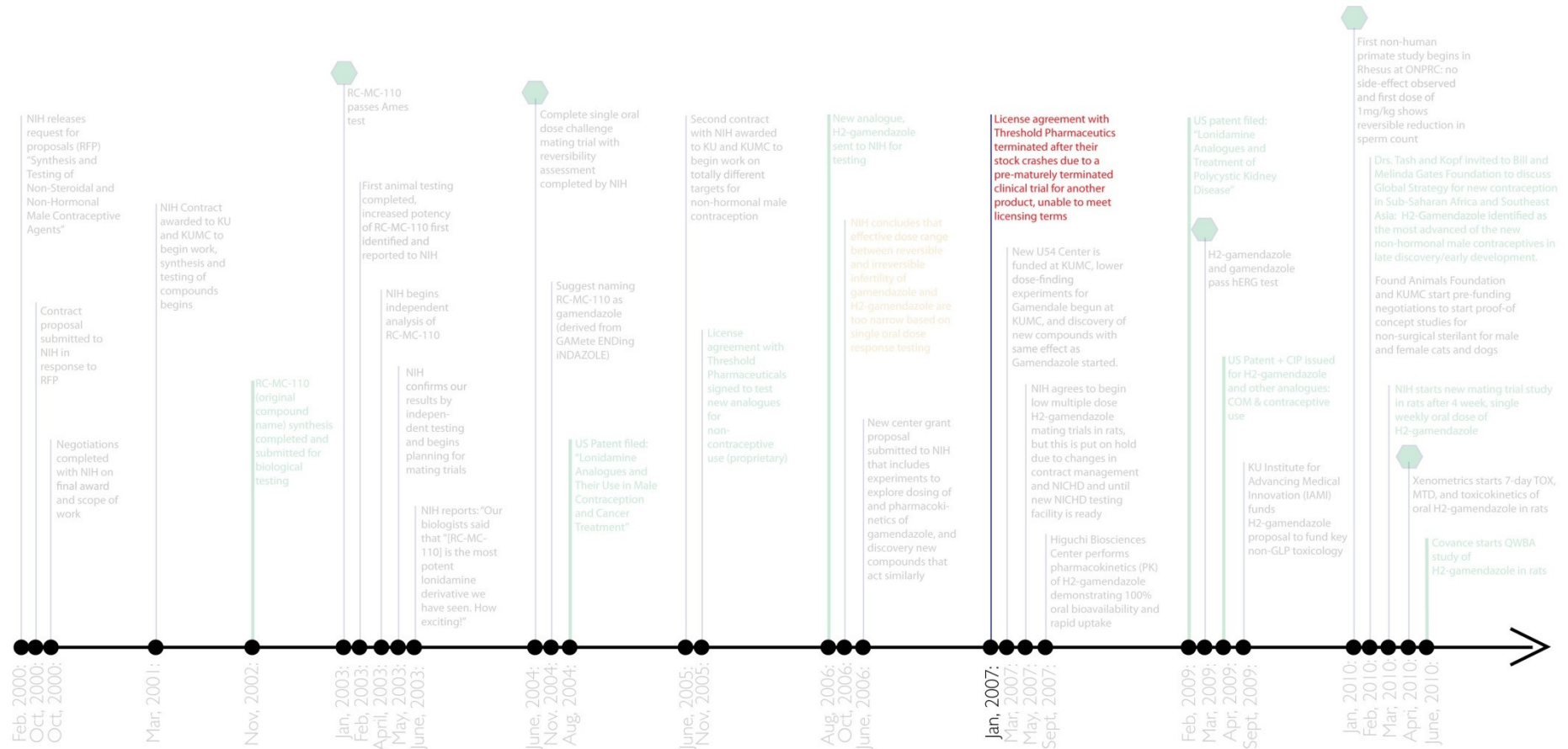


2005: License agreement signed

(too early in process, later disclosures from licensee were disturbing)

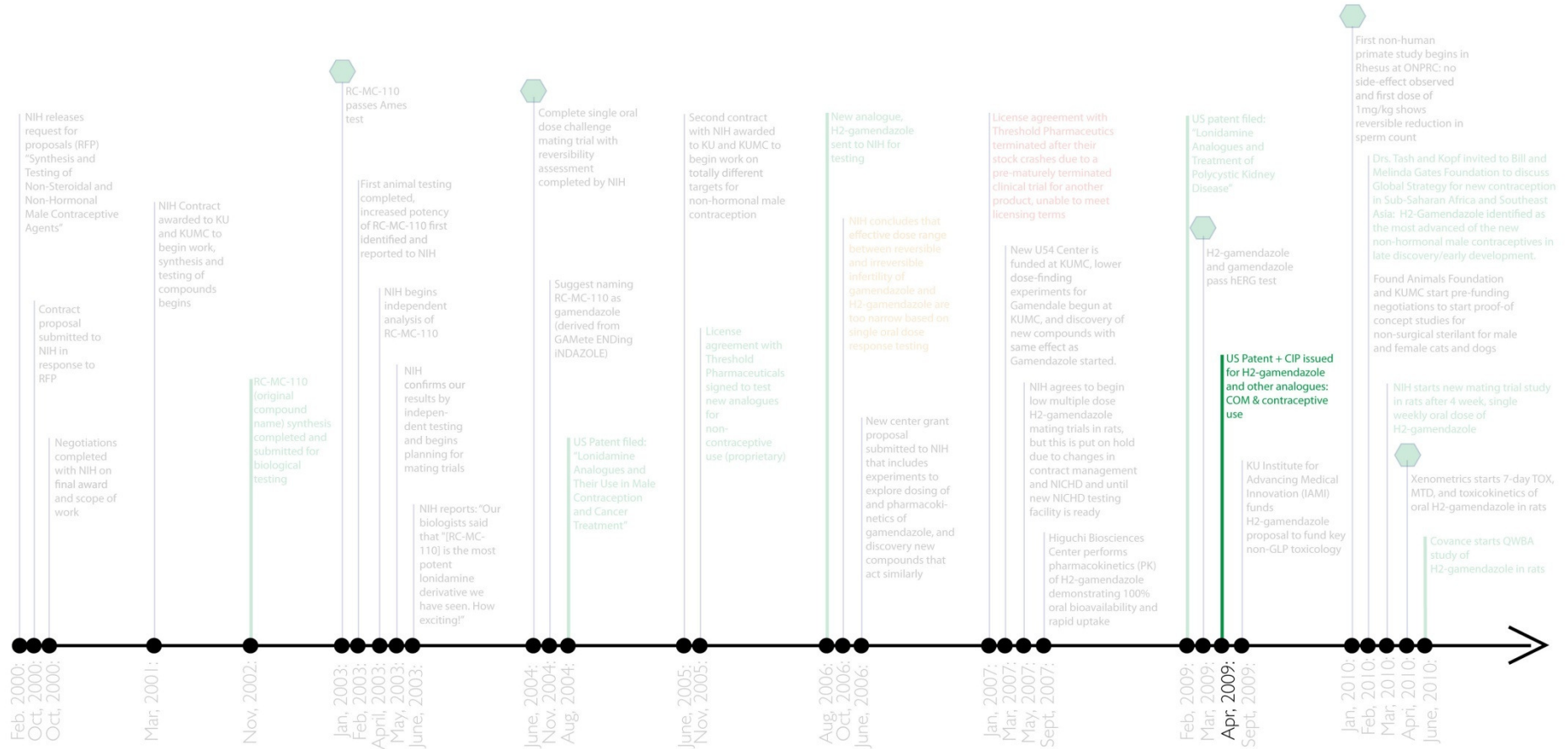


# Chronology of Gamendazole Discovery and Development



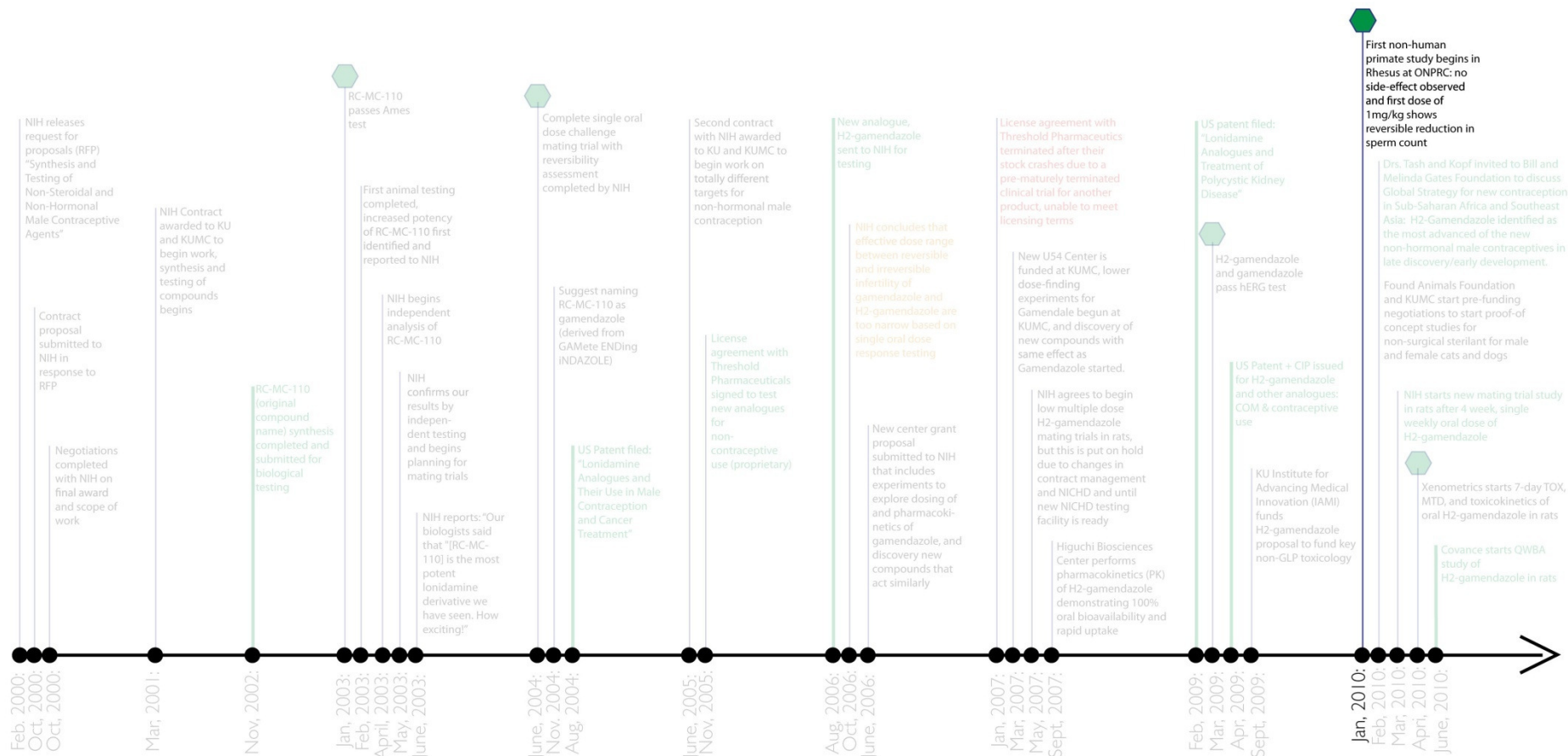
2007: Licensee pulls a product that was not disclosed to be in clinical trials, their stock values plummet preventing their meeting milestones, license is terminated.

# Chronology of Gamendazole Discovery and Development



2009: US patent issued for Gamendazole and analogues issued:  
composition of matter, synthesis, use as contraceptives

# Chronology of Gamendazole Discovery and Development



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

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Contraception & Reproductive Health Branch,  
NICHD, NIH U54 HD-055763 (JST)



Mary B. Zelinski, Co-Investigator, ONPRC

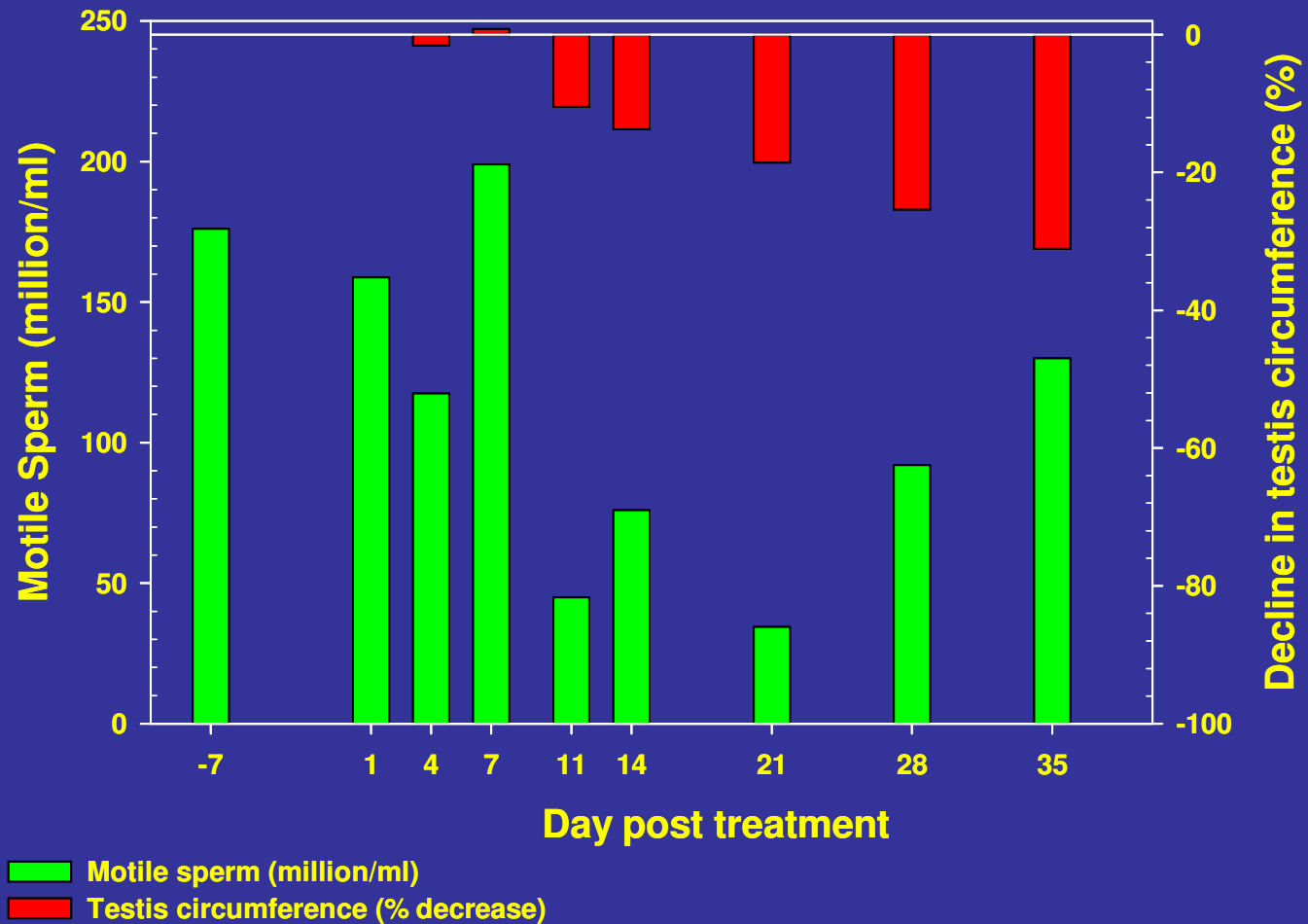


Gunda Georg, Ph.D.  
Institute for Therapeutics Discovery & Development, University of Minnesota

Scott Weir, Pharm. D., Ph.D.  
Melinda Broward, M.S.  
Cancer Center, University of Kansas

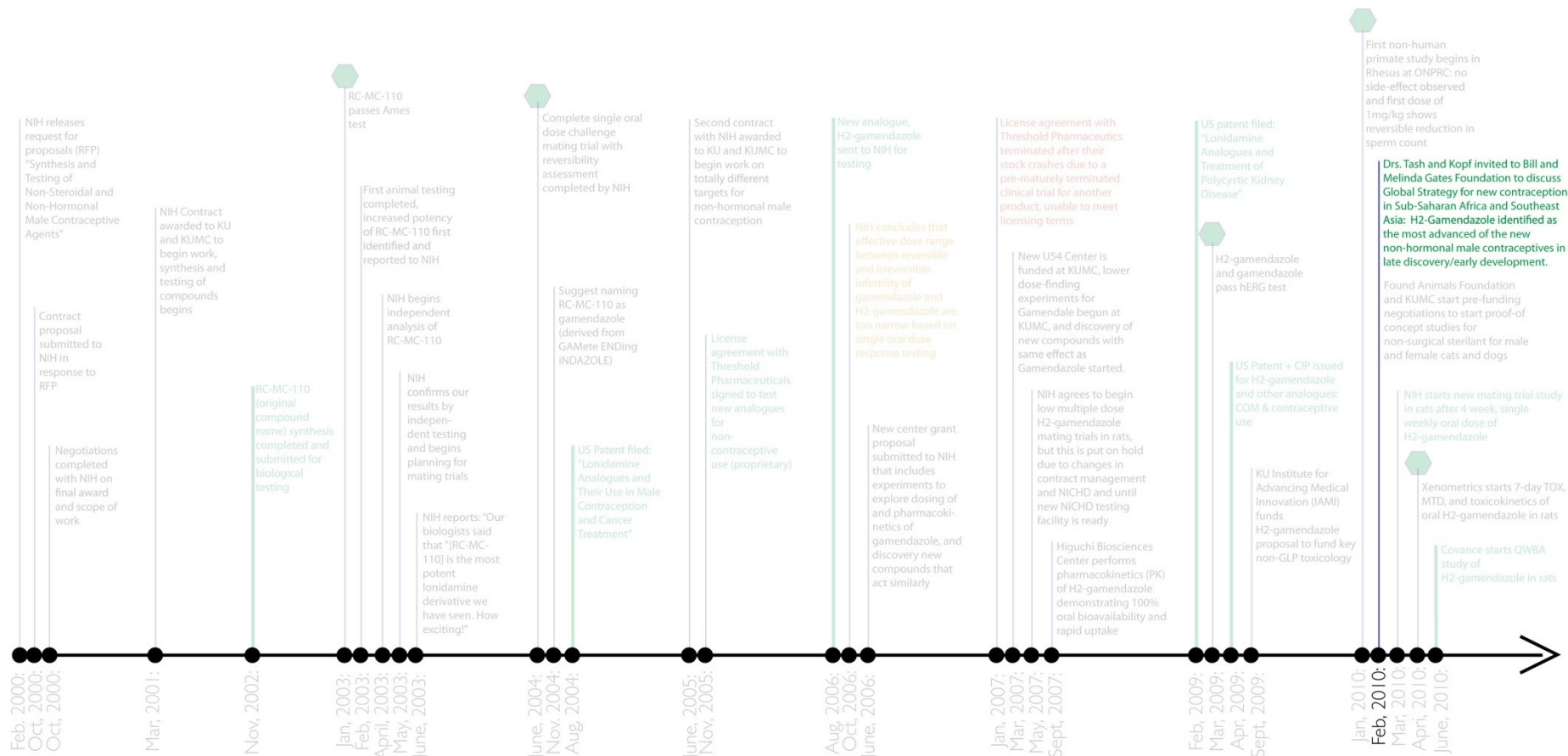


# Reversible Inhibition of Sperm Production in First Non-Human Primate\* by Single Oral Dose of H2-Gamendazole



\*Study will last 12 weeks in each of 3 monkeys at 2 different oral doses

# Chronology of Gamendazole Discovery and Development



**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 12<sup>th</sup>, 2010

BILL & MELINDA  
GATES *foundation*

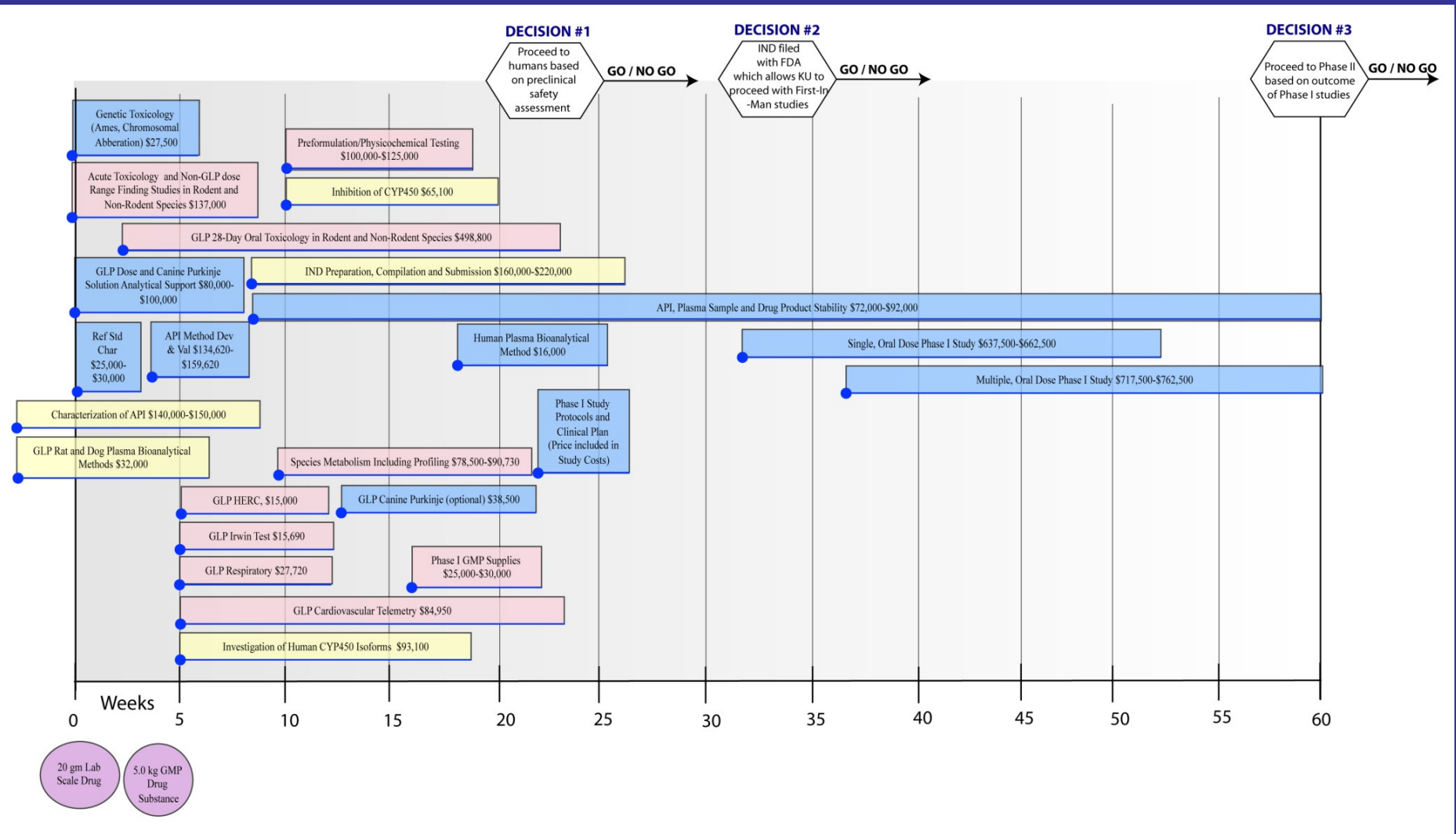
## Highly-discussed Discovery opportunities

Target	High-level description / quotes
GnRH II receptor ant	<ul style="list-style-type: none"> <li>Female hormonal target; contraceptive efficacy shown in monkey and dog models</li> <li>Unique isoforms of GnRH have been found to have activity in reproductive tissue (GnRH I, II, and III)</li> <li>Contraceptive action of GnRH AIIA believed to be via down-regulation of GnRH II receptor</li> </ul>
PC6-inhibitor	<ul style="list-style-type: none"> <li>Inhibition of PC6 was found to prevent embryo implantation in the mouse uterus</li> <li><i>"Promising [female] product considering that it is non-hormonal and could be used for addressing contraception as well as HIV infection"</i></li> </ul>
Eppin	<ul style="list-style-type: none"> <li>Eppin protein secreted by Sertoli cells and epididymal epithelial cells</li> <li>Critical for the enzymatic degradation of semen coagulate which frees the spermatozoa for motility and capacitation</li> <li>Anti-Eppin antibodies from male monkeys shown to inhibit human sperm motility (in vitro)</li> </ul>
Catsper	<ul style="list-style-type: none"> <li>CatSper critical in sperm motility required to penetrate outer coat of egg for fertilization</li> <li>Inhibition prevents Ca<sup>2+</sup> entry needed for forceful asymmetric motion required to penetrate</li> <li><i>"Highly selective; non-hormonal; potential lack of side effects; could be developed for males/females"</i></li> <li><i>"Very specific target, actually 4 targets, blocking any one of which will affect sperm function"</i></li> <li>However some concerns related to toxicology issues</li> </ul>
α-adrenoreceptor	<ul style="list-style-type: none"> <li>Selective blockade of α-adrenoreceptors causes inhibition of longitudinal muscular contractions of the vas deferens</li> <li>Causes infertility by causing failure of ejaculation, even though orgasm is normal</li> </ul>
H2-Gamendazole	<ul style="list-style-type: none"> <li>Non-hormonal male contraceptive agent <i>"likely most potent reversible single oral dose anti-spermatogenic agent in the pipeline"</i></li> <li><i>"Furthest along"</i></li> <li>Pilot trials currently underway in non-human primates</li> </ul>





# IND Pre-Clinical and First in Human Trials: POC in Males Undergoing Elective Vasectomy

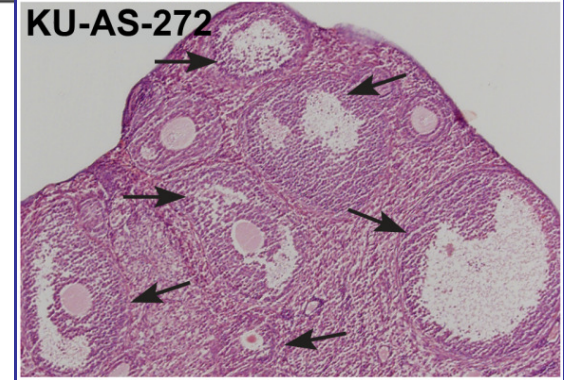
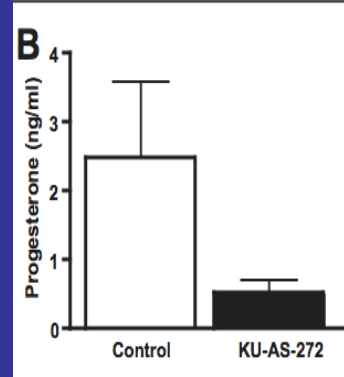
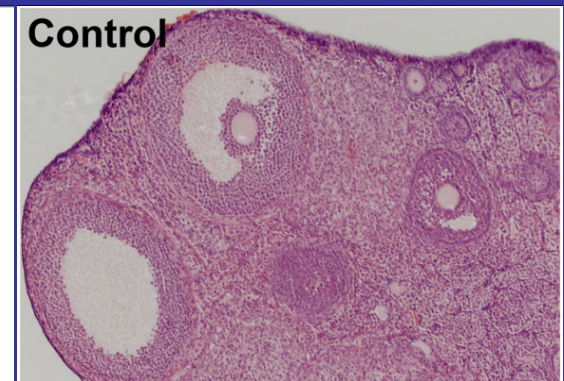
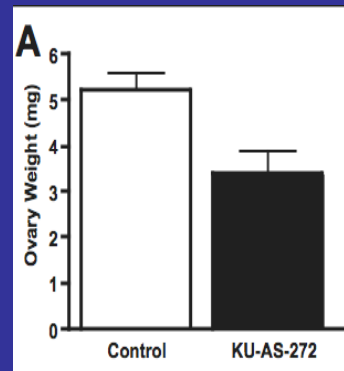
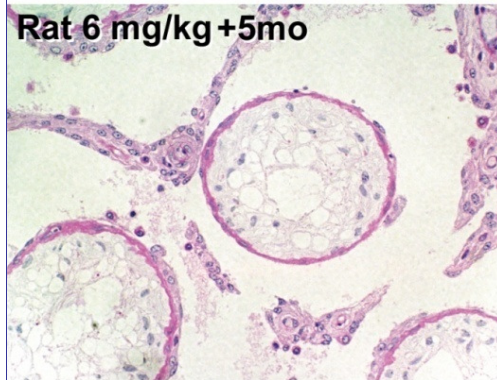
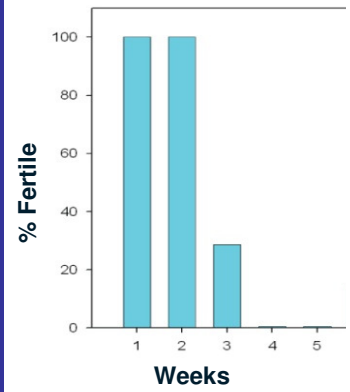
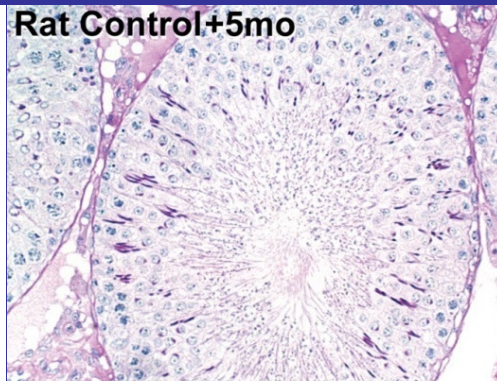
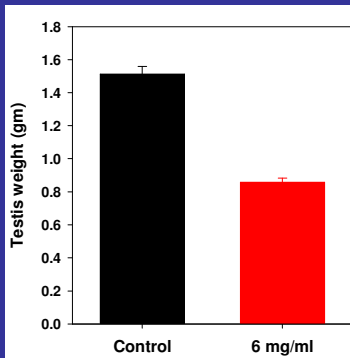


# KU-AS-272 As a Single Dose Non-Surgical Sterilant for Male and Female Dogs and Cats and Feral Animals

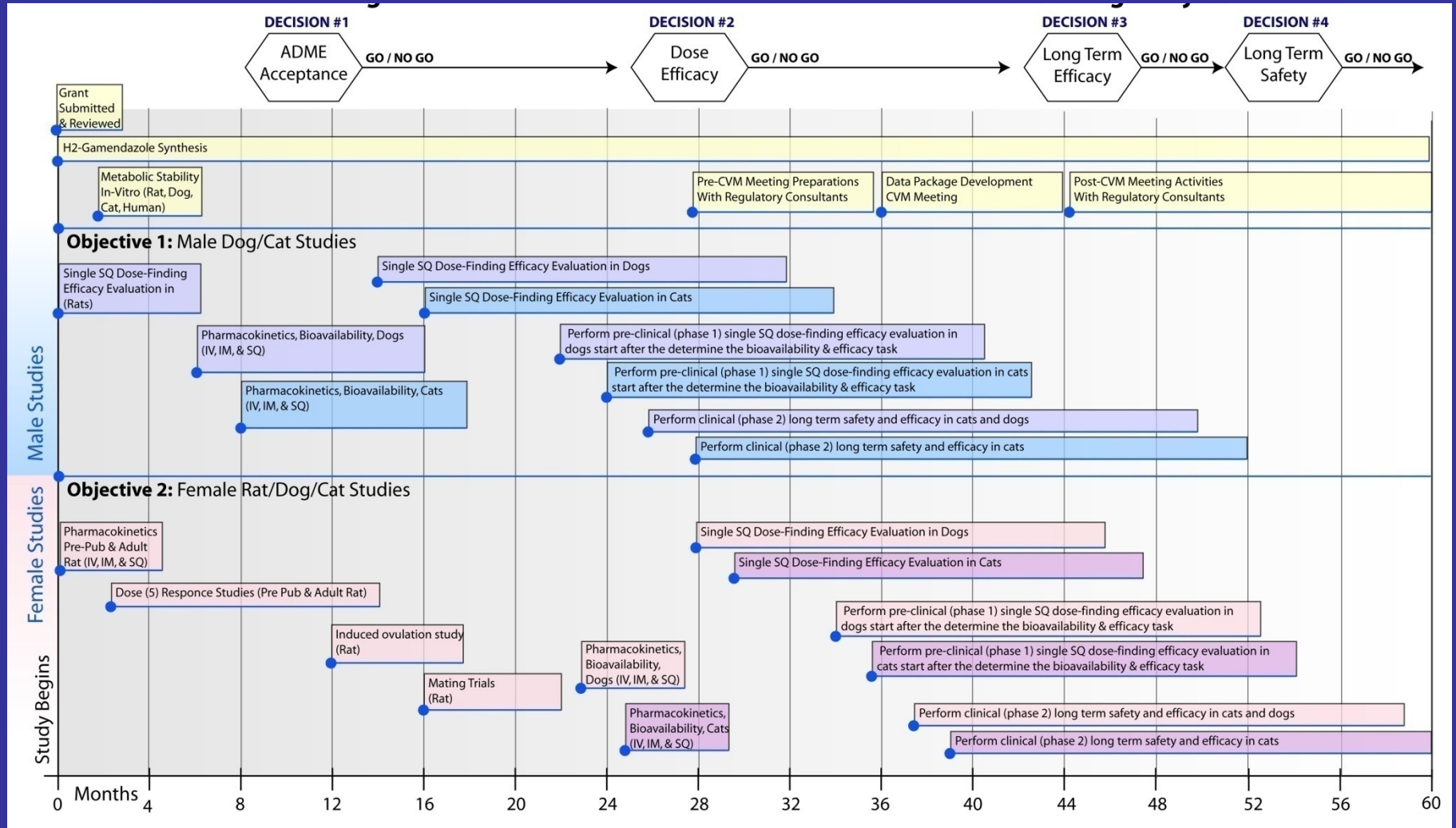


## Male Rats

## Female Mice



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





# Conclusions

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- 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

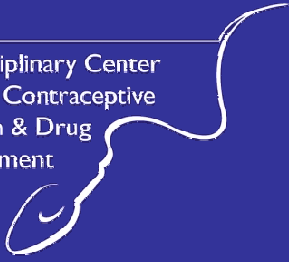
# Male Contraceptive Collaborators (1)

- 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.)

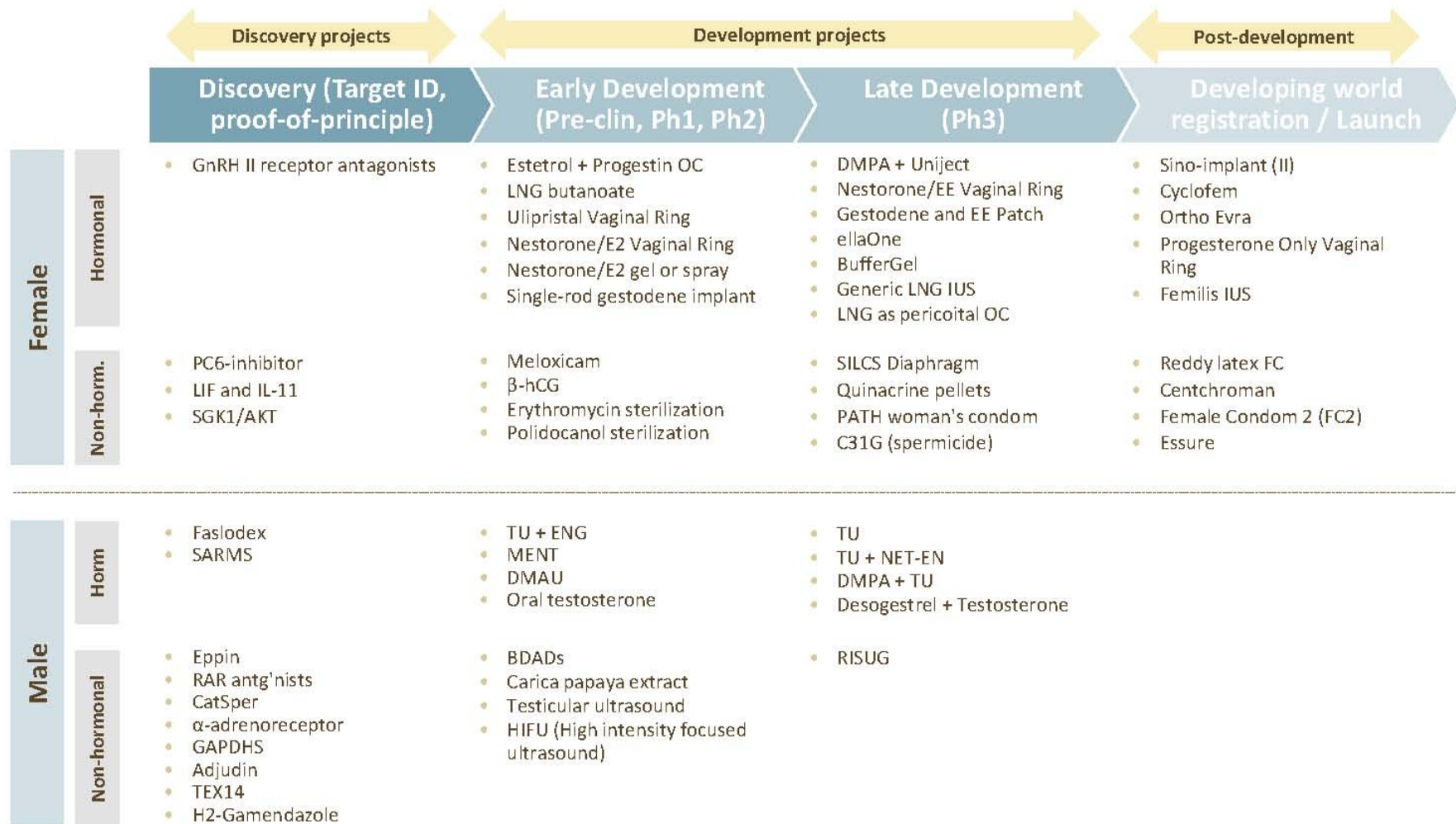
Interdisciplinary Center  
for Male Contraceptive  
Research & Drug  
Development



Thanks!

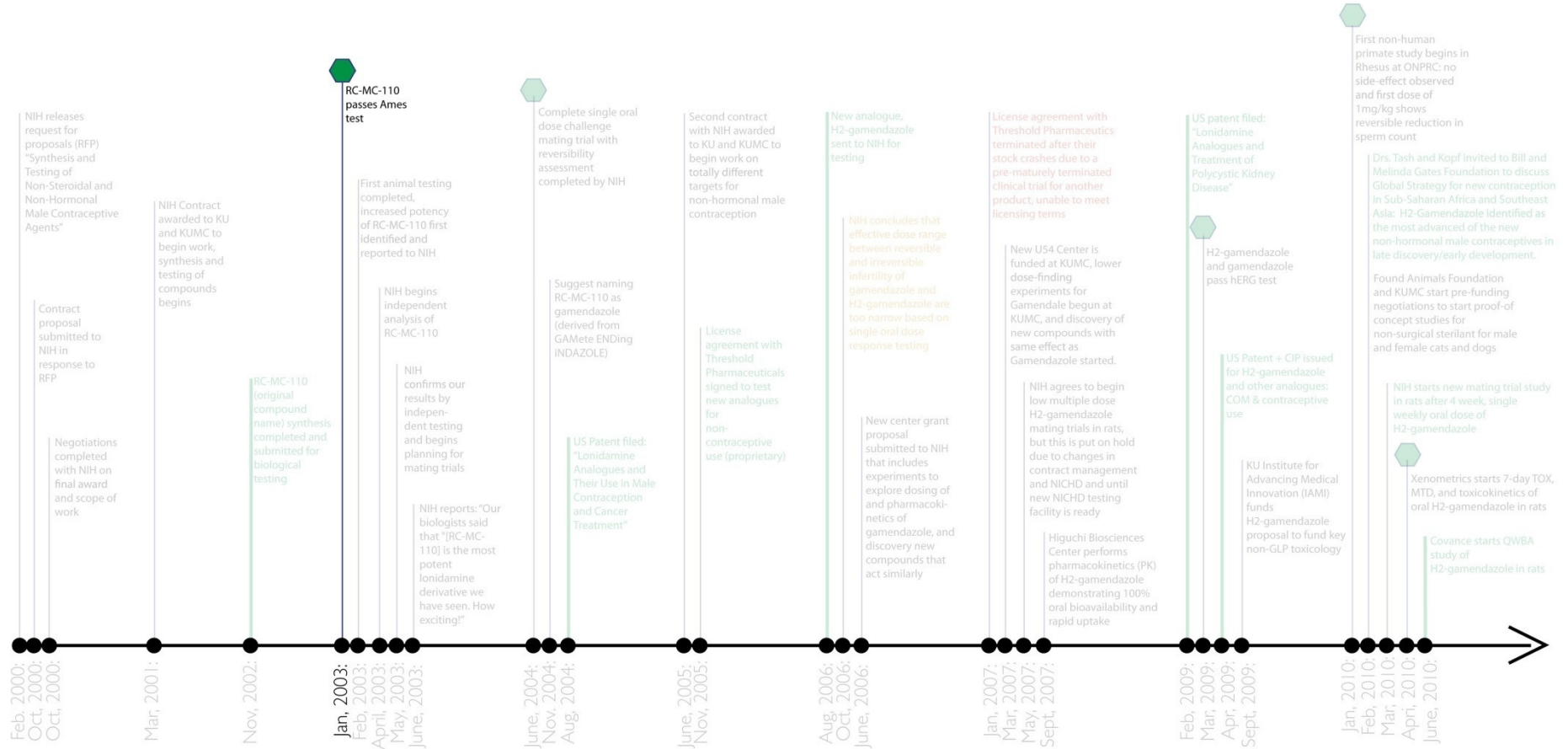


# At least 55 near-, mid-, and long-term options exist in global contraceptive pipeline



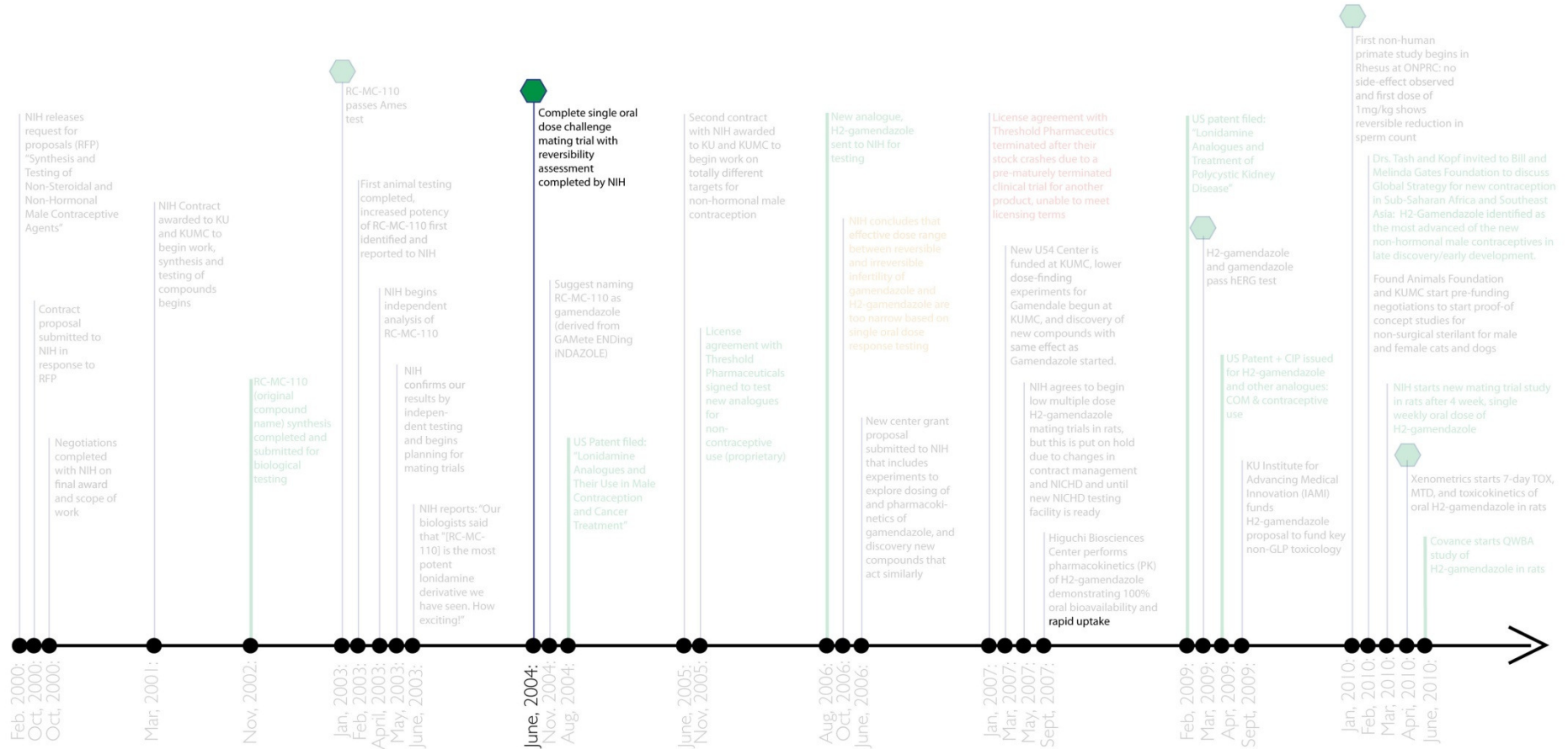
Note: LNG (levonorgestrel); TU (testosterone undecanoate); NET-EN (norethisterone oenanthate); RISUG (reversible inhibition of sperm under guidance); EE (ethinyl estradiol); MENT (7 alpha-methyl-nortestosterone); PC (proprotein convertases); GAPDHS (Glyceraldehyde-3-phosphate dehydrogenase, testis-specific); HIFU (High intensity focused ultrasound); SARMS (selective androgen receptor modulators); DMAU (Dimethandrolone 17β-Undecanoate); E2 (estrogen estradiol); BDAD (bis-dichloroacetyl-diamines)

# Chronology of Gamendazole Discovery and Development



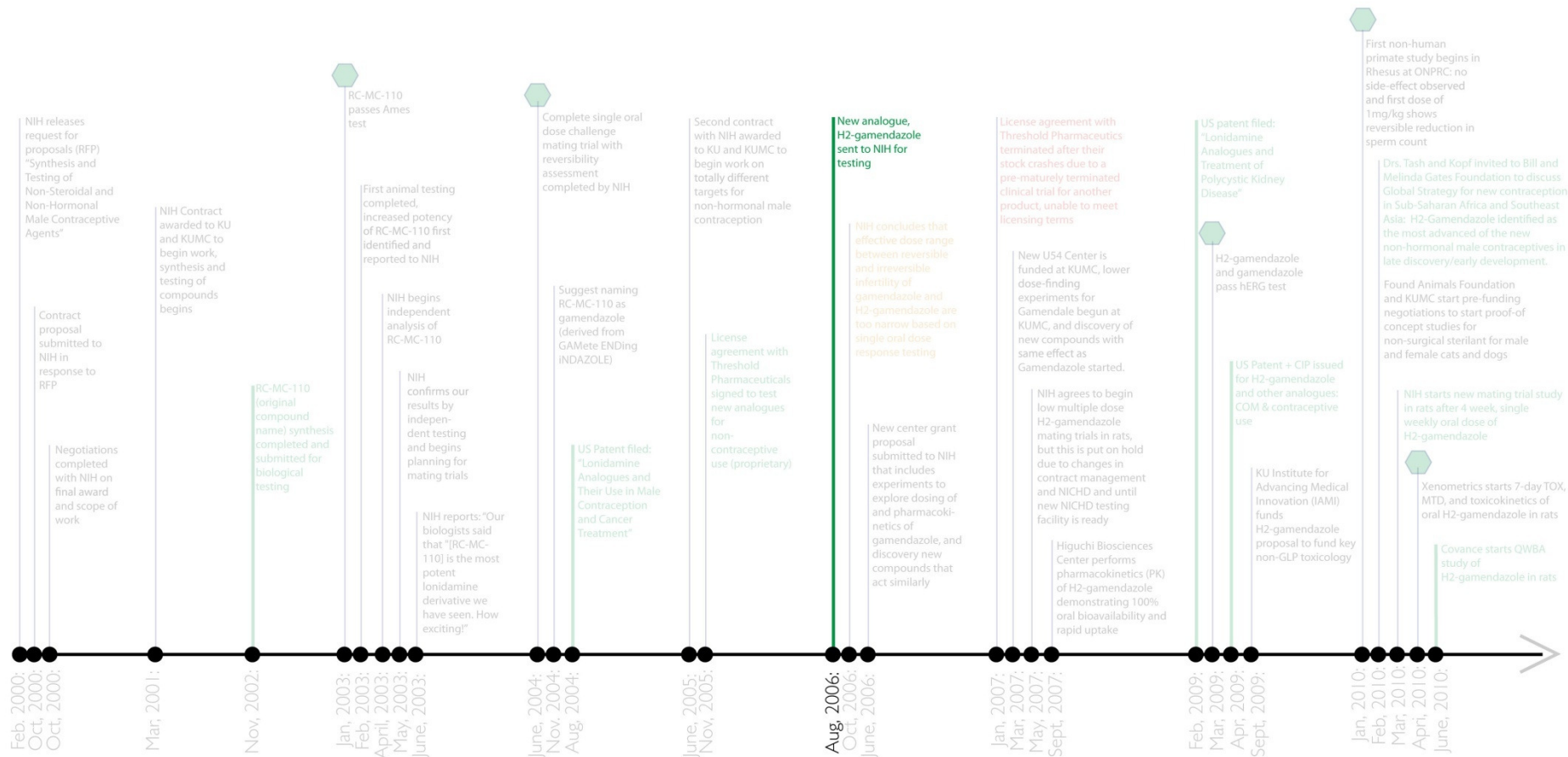
RC-MC-110 passes Ames test, first animal testing begins

# Chronology of Gamendazole Discovery and Development



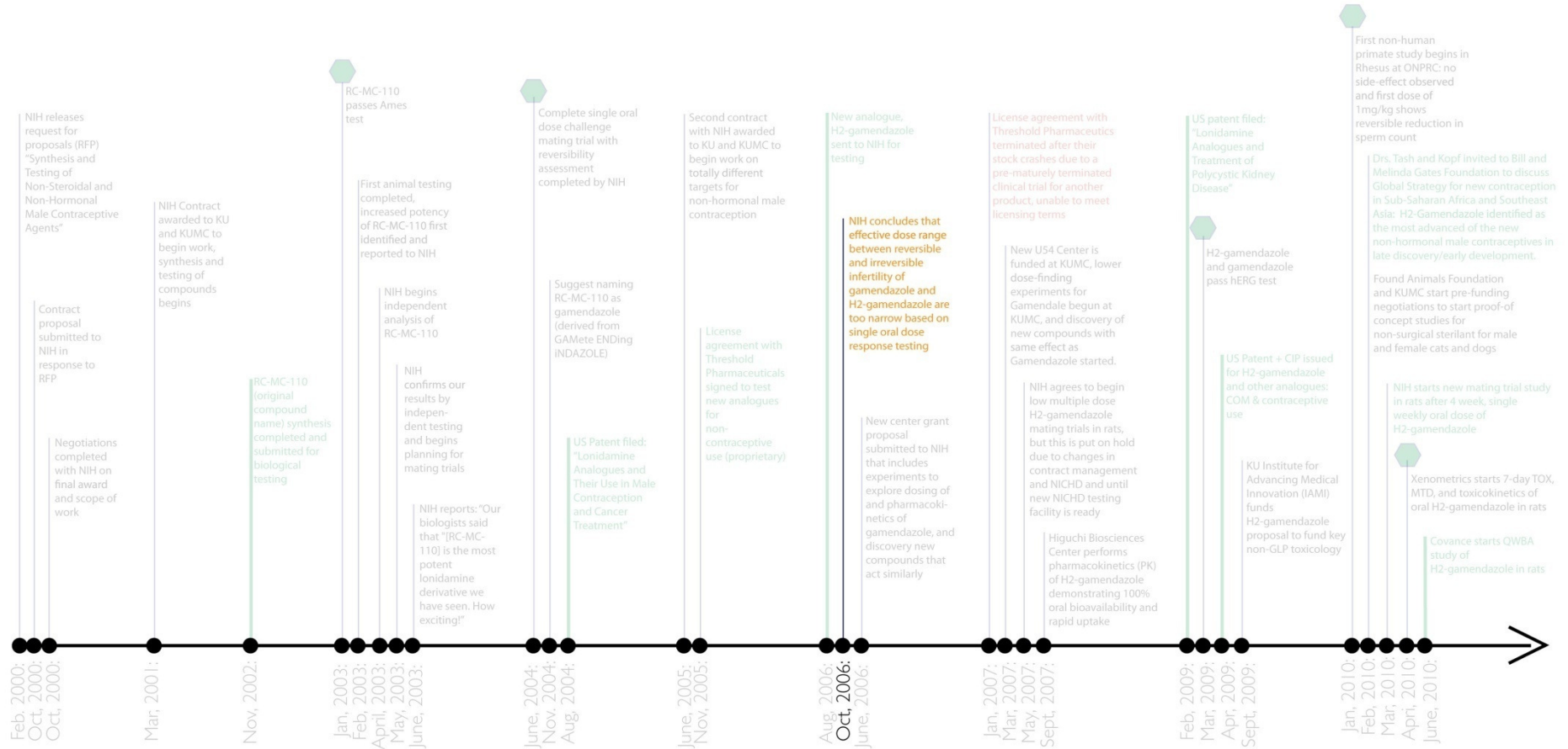
Proof of concept (POC) as reversible male contraceptive achieved

# Chronology of Gamendazole Discovery and Development



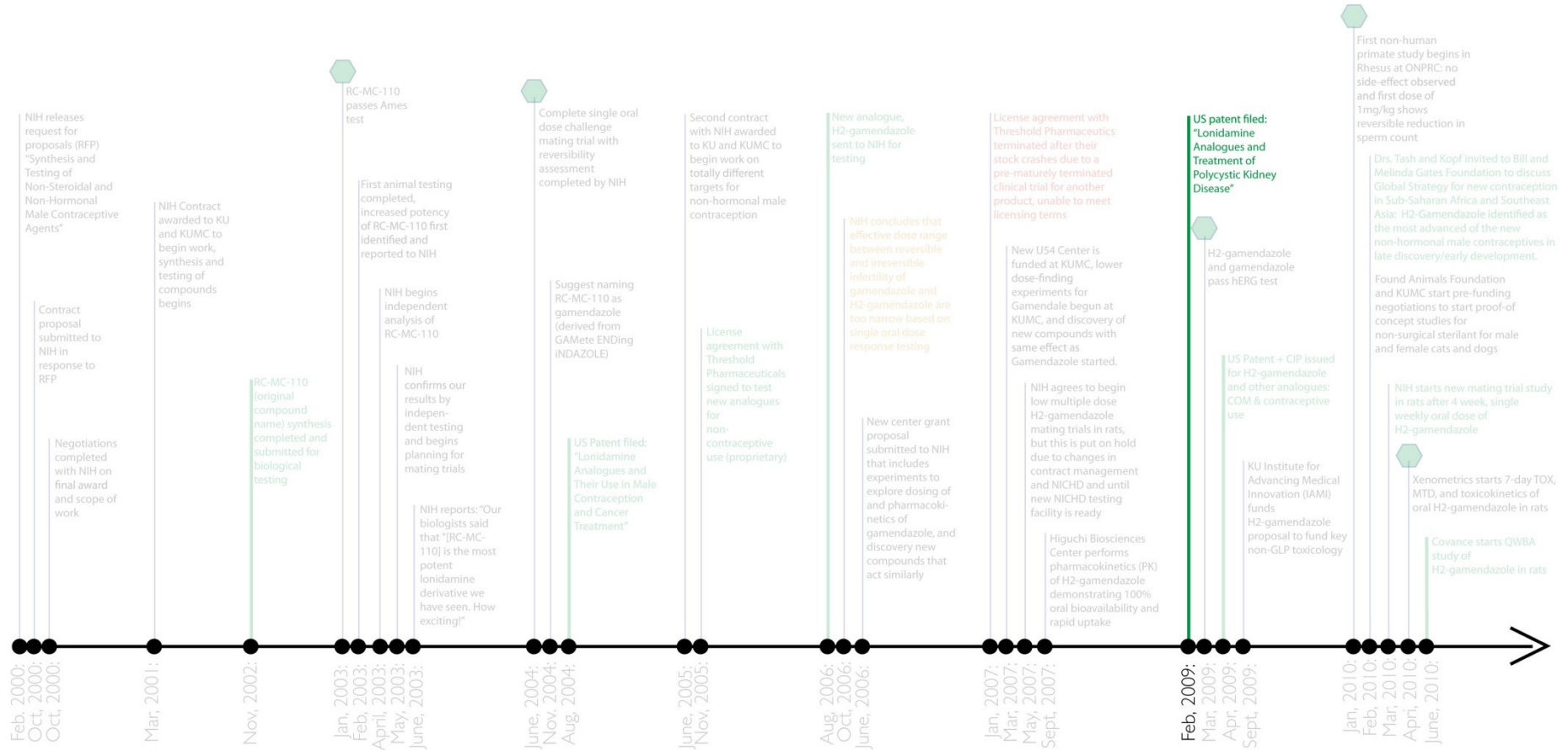
H2-gamendazole synthesized and testing started

# Chronology of Gamendazole Discovery and Development



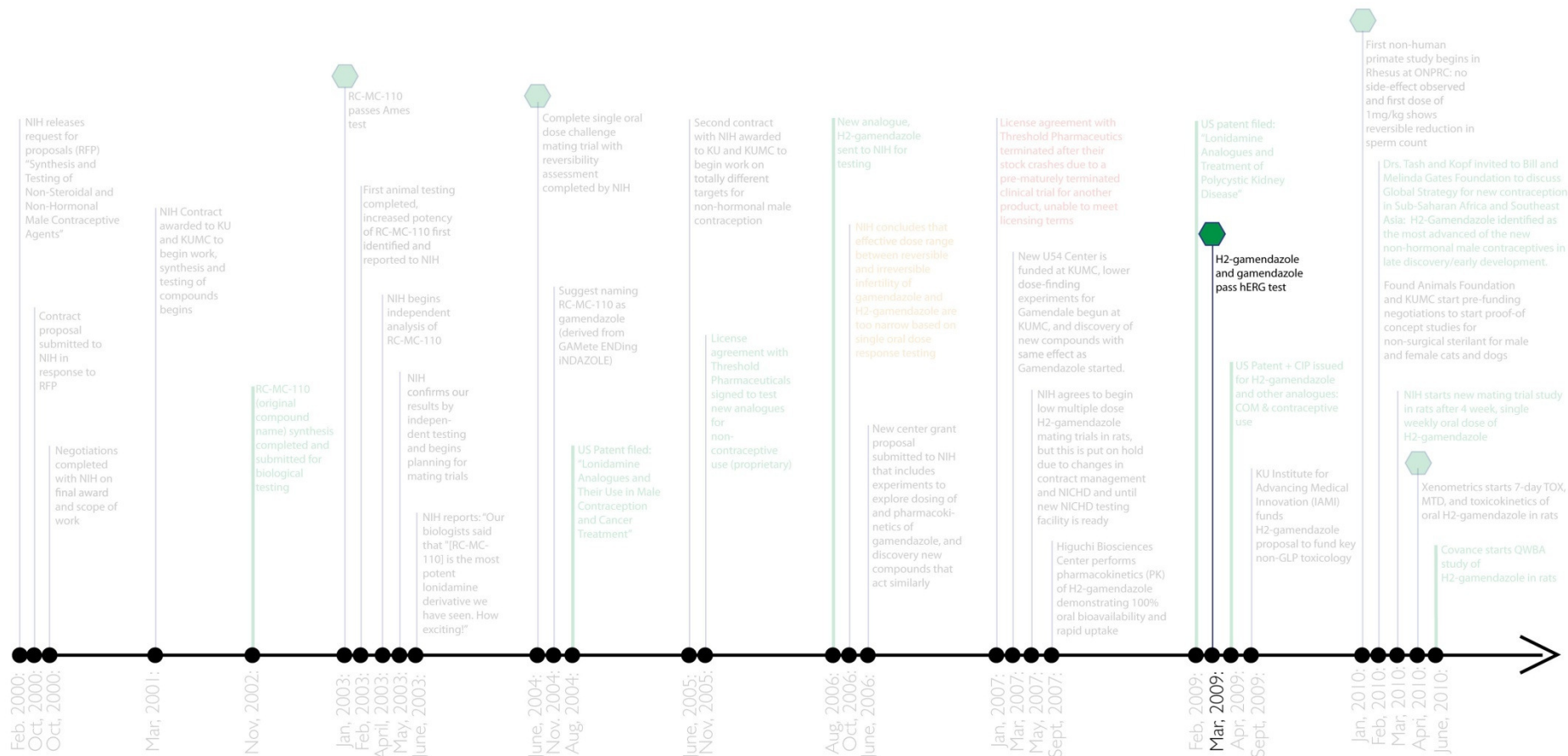
Based on goal of single dose 100% efficacy AND 100% reversibility  
NIH and we agree that observed 100% efficacy with 67% reversibility isn't good enough.  
We start multiple testing low dose range finding studies.

# Chronology of Gamendazole Discovery and Development



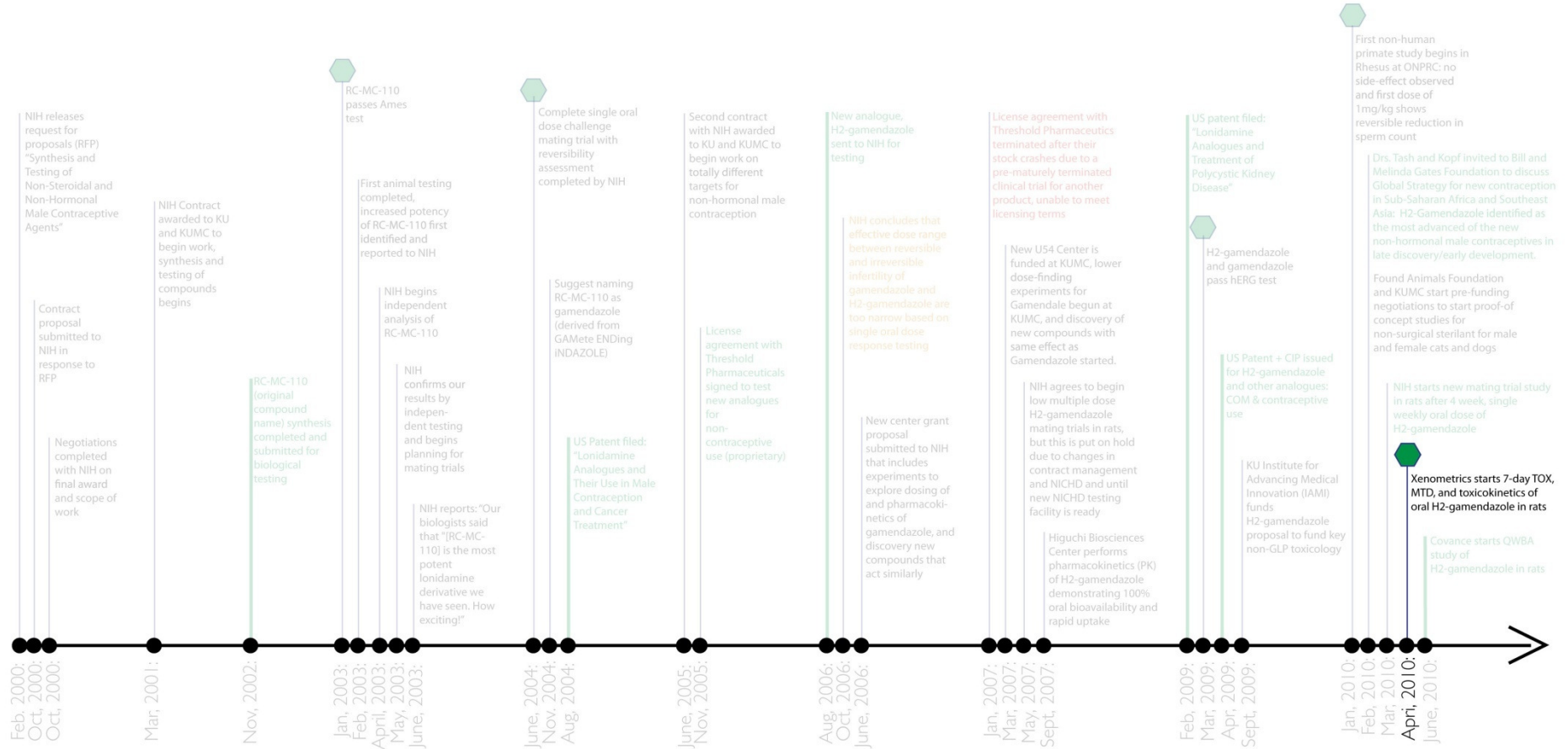
Collaboration with Kidney Institute yields POC gamendazole analogues as treatment for Polycystic Kidney Disease, Divisional patent filed, divisional patent for female contraceptive agents added

# Chronology of Gamendazole Discovery and Development



H2-gamendazole and gamendazole pass hERG test

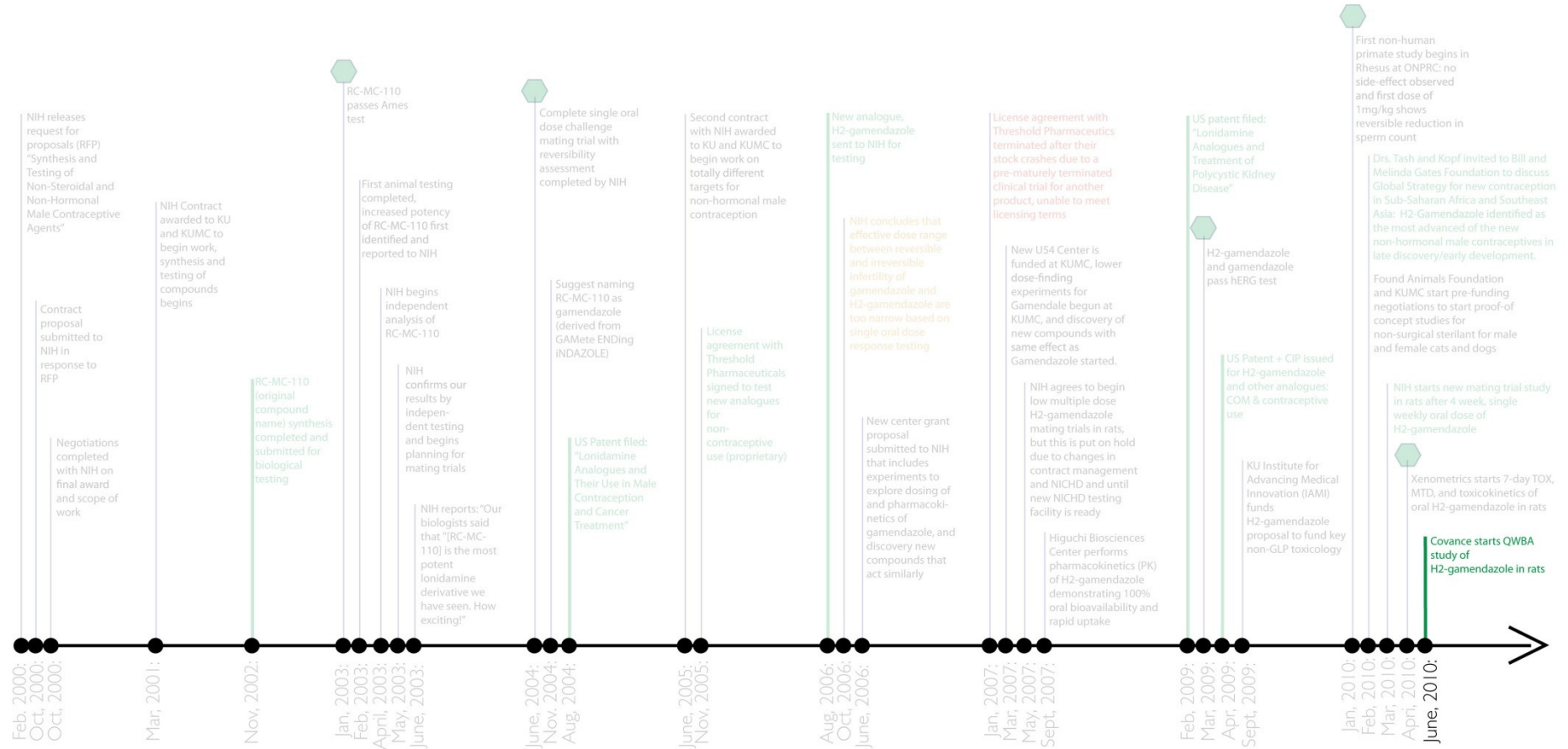
# Chronology of Gamendazole Discovery and Development



Critical POC toxicology will start at CRO (IAMI funded)

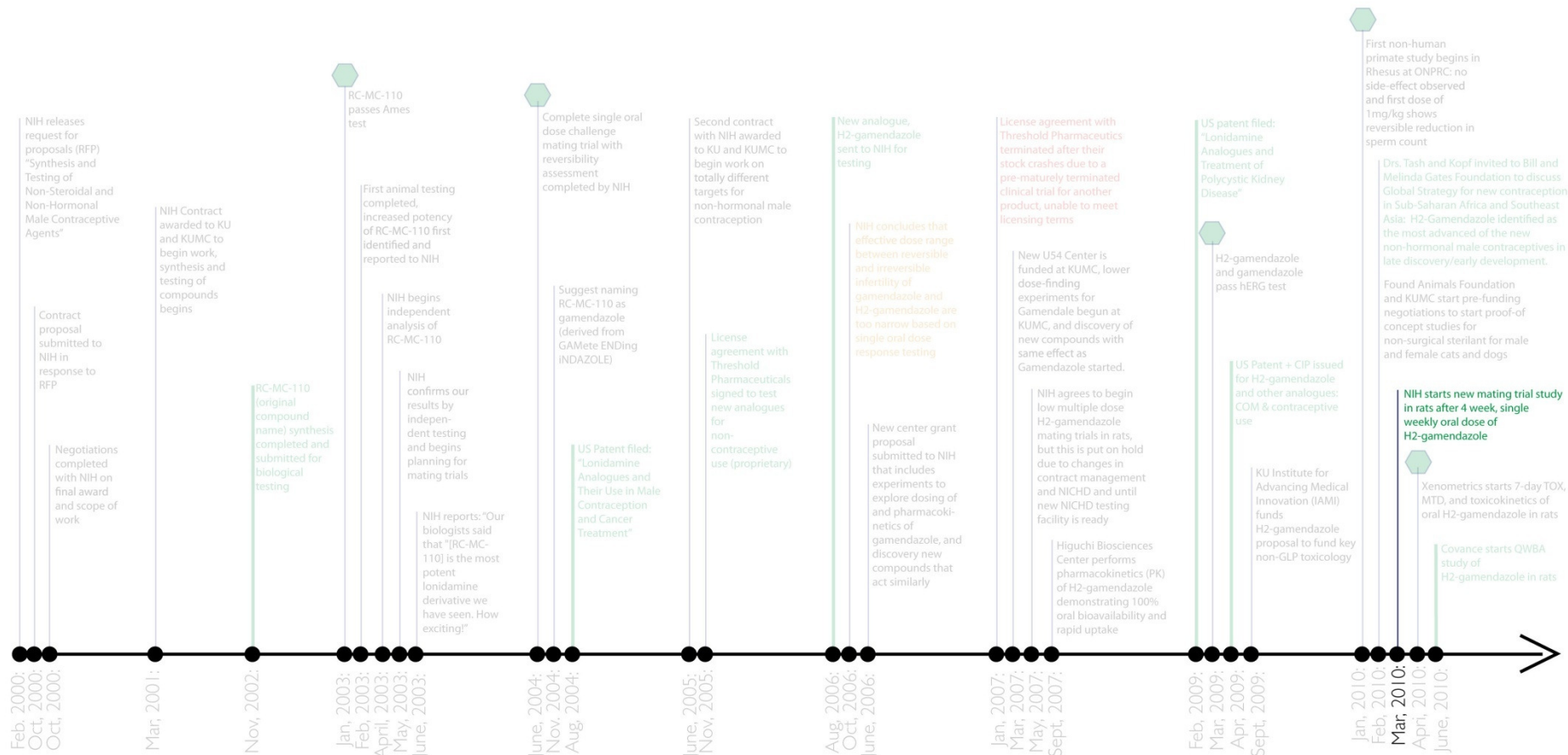


# Chronology of Gamendazole Discovery and Development



QWBA will start at CRO (IAM) funded)

# Chronology of Gamendazole Discovery and Development



2010: NIH to start new mating trials with single weekly 4 week dosing regimen