Contraceptive Development
Challenges and Barriers to Innovation and Contraception Research

Diana Blithe, PhD, Senior Scientist and Chief,
Contraceptive Development Program, DiPHR, NICHD

Typical Effectiveness of Contraceptive Methods

Long-Acting Reversible Contraceptive (LARC) Methods

More effective

>99%

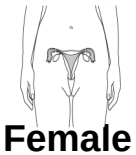
Implant

Copper IUD

Hormonal IUD

~ 1% Failure rate

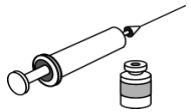
Vasectomy



Female Sterilization

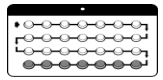
NOT REVERSIBLE

Combined Hormonal Contraceptives (containing EE)



Injectable

~4% Failure rate

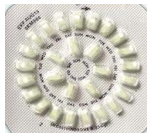


COC Pills

Ring

Patch

~ 8% Failure rate



POPs

~ 9% Failure rate

User-controlled

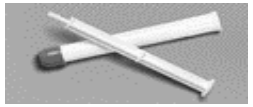
Non-Hormonal Contraceptive Products

Male Condom

Female Condom

Diaphragm

~ 13% Failure rate



Buffering Gel

~14 Failure rate

Spermicides

Sponge

> 20% Failure rate

User-controlled -- Coitally-Dependent

Develop Better Products for Women - Fill Unmet Needs

Long-Acting Reversible Contraceptive (LARC) Methods

More effective

>99%

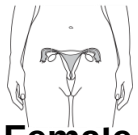
Implant

Copper IUD

Hormonal IUD

< 1% Failure rate

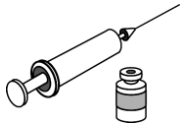
Vasectomy



Female Sterilization

NOT REVERSIBLE

LARC-ish



Injectable

4% Failure rate

Hormonal Contraceptives (containing Estradiol)

Ring

~ 8% Failure rate

Improve on mid-Tier Methods

User-controlled

Safer and Better

Less effective

Existing Male Methods

More effective

Less effective

>99%

Effective Reversible Male Method

<88%

Male Condom

~ 13% Failure rate

Men need and want more options!

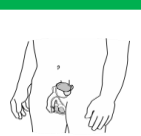
Long-Acting Reversible Contraceptive (LARC) Methods

Implant

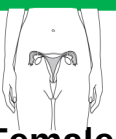
Copper IUD

Hormonal IUD

< 1% Failure rate



Vasectomy



Female Sterilization

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Combined Hormonal Contraceptives (containing EE)

Injectable

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COC Pills

Ring

Patch

~ 8% Failure rate

POPs

> 9% Failure rate

User-controlled

Non-Hormonal Contraceptive Products

Female Condom

Diaphragm

Buffering Gel

~14 Failure rate

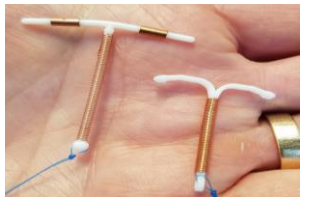
Spermicides

Sponge

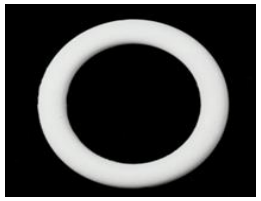
> 20% Failure rate

In development for Women:

- Mona Lisa **Mini** (**smaller Copper IUD**) compared with Paragard in nulliparous women.
  Status: Phase III data analysis and manuscript preparation.



- **Nestorone/Estradiol Vaginal Ring** - Estradiol (E2) replaces Ethinyl Estradiol (EE).
  Safer for obese women. Status: Phase IIb data analysis.



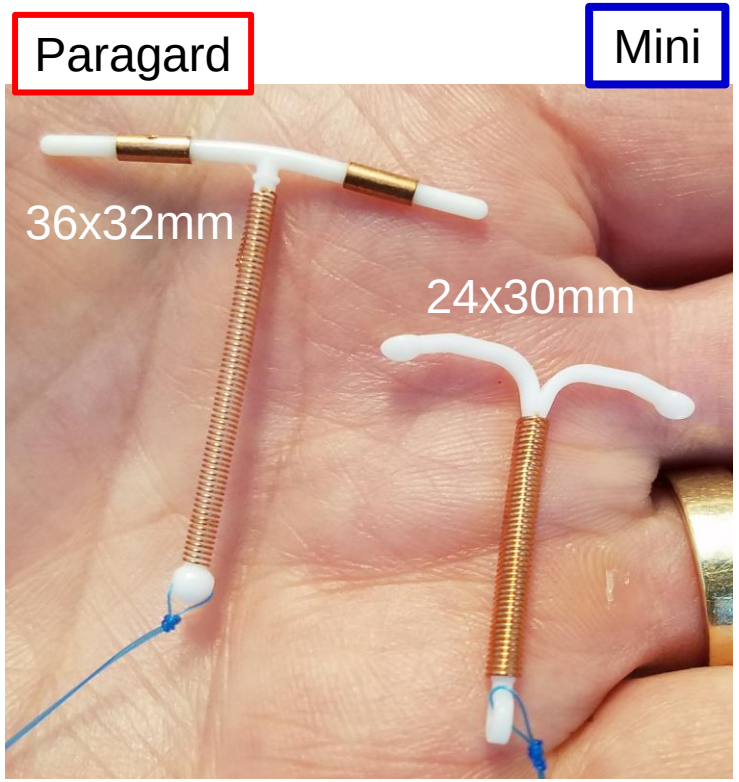
- **Levonorgestrel Butanoate –** safe, acceptable, **user-controlled injectable** method.
  Status: Phase IIa – dose-finding is ongoing.

- **MPT (Dapivirine and Levonorgestrel)** for **protection against HIV and Pregnancy –**
  Status: repeating Phase I with redesigned ring material.

- **Ulipristal Acetate – low dose continuous pill** - safe, acceptable, **user-controlled** method.
  Status: Phase IIa – dose-finding on **clinical hold**.

Mona Lisa (ML) NT Cu380 Mini

- ML Mini is 20% smaller than Paragard
- Currently marketed in Europe (clinical data are not required for marketing copper IUDs in the EU)
- Not approved in US



CCN016: Enrolled 1088 women - **>80% Nulliparous**
Evaluated Safety, Efficacy and Acceptability over 36 Months

Collaboration with FHI360 and the Bill & Melinda Gates Foundation

Results and Challenges:

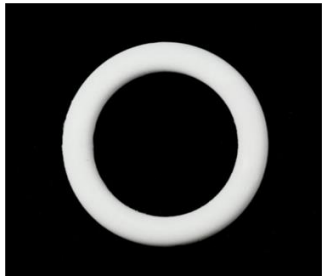
Nulliparous women had higher continuation rate and were more likely to recommend it.

Fewer removals due to bleeding or pain adverse events.

Need a commercial partner to take the package to FDA for US approval.

NEW VAGINAL RING

Nestorone® / E2 (17-β-Estradiol) vaginal ring
(collaboration with Population Council)



Nestorone® – potent progestin but not orally active (safe for breast-feeding women)

Advantage of Nes/E2 Ring–

Estradiol (**E2**) replaces Ethinyl Estradiol (**EE**) synthetic hormone used in most COC pills, rings, patches

(EE is a potent endocrine disrupter; EE can increase risk of blood clots in susceptible women)

The **Nes/E2** ring is safer for women (including for obese women)

One ring is used for 3 months

CCN012B – Contraceptive Efficacy of Nes/E2 Ring (Phase IIb)

Participants use rings for **1 year** for contraception (4 rings/year)

Randomized:

Group 1 – **Continuous Use** - Use each ring continuously (90 days per ring)

Group 2 – **Cyclic Use -** Remove ring for short interval at the end of each month

Results: Highly Effective - Pregnancy failure rate ~1% - (LARC-ish)

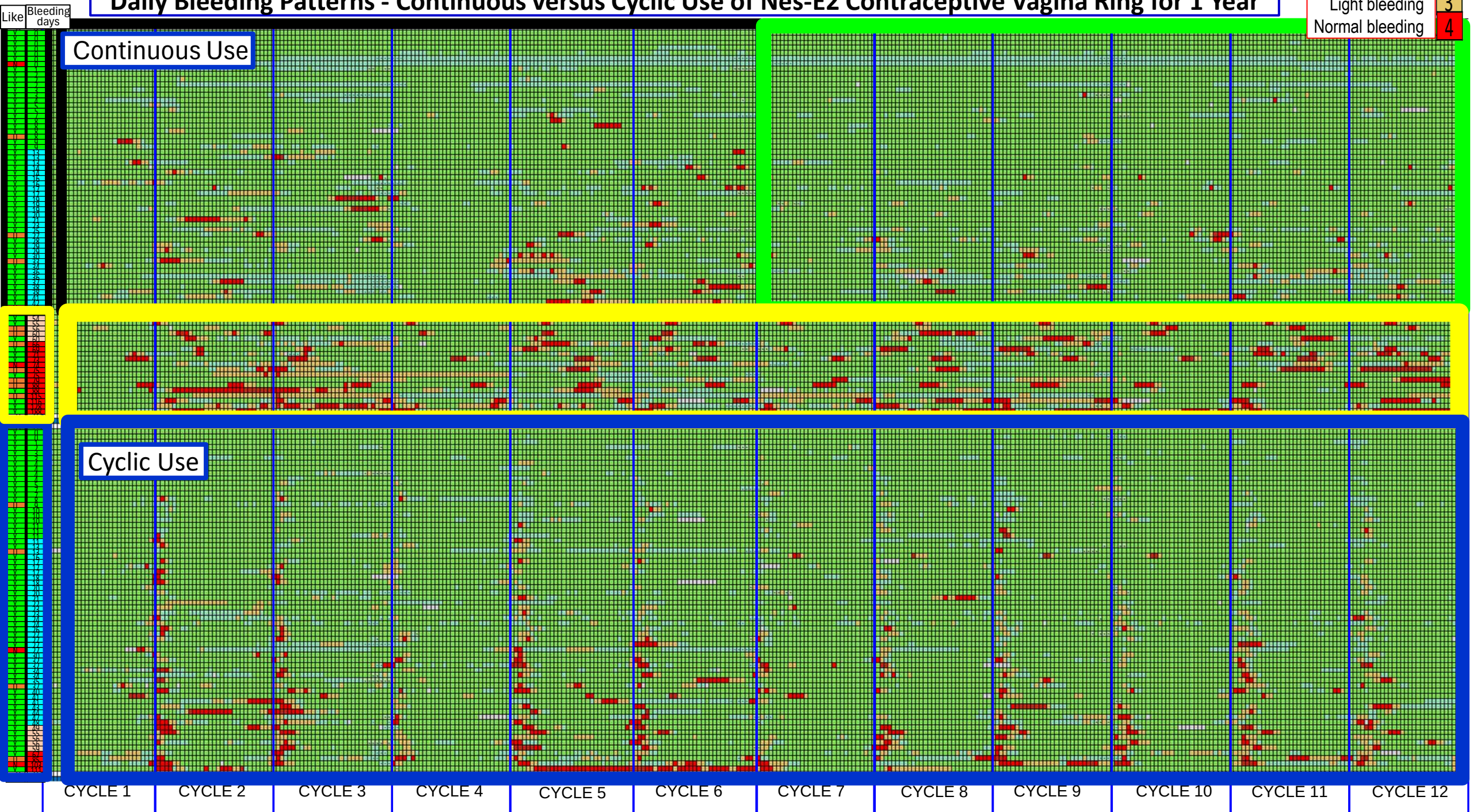
Much better compared to typical use failure rates (~8%) with other user-controlled methods.

High acceptability

User Control - a woman can control bleeding and number of cycles

(based on her response to the method and her preferences)

Daily Bleeding Patterns - Continuous versus Cyclic Use of Nes-E2 Contraceptive Vagina Ring for 1 Year



Levonorgestrel Butanoate (LB)

A new injectable progestin

- **Easy access**: no need for highly skilled provider
- **Concealable**: Not detectable after injection
- **Higher effectiveness** than pills, patches, rings – **(lasts 3 months)**

Advantages of LB:

- **Safe**: LNG (active component of LB) is very safe for contraception
- **Estrogen free**: important when risk factors contraindicate use of estrogen
  - LB will not increase risk of blood clots – safe for obese women

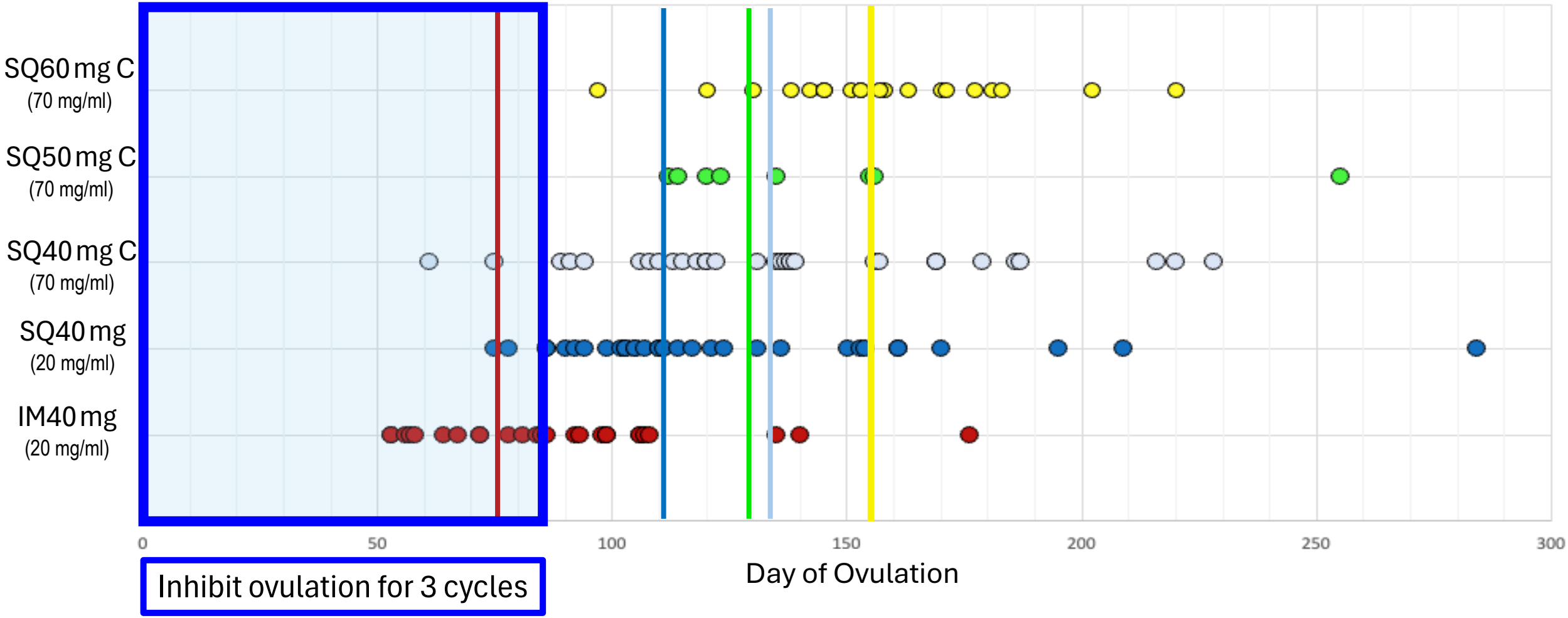
❖ **Potential for self-injection**

❖ *Results to date* **- High acceptability**, especially in previous DepoProvera users

–Unlike Depo - LB has no glucocorticoid activity - **No mood changes! No weight gain!**

–Few side effects reported.

Dose Finding Study – Intramuscular (IM) versus Subcutaneous (SQ) Injections



Time to Ovulation depends on Route of Delivery and Concentration

Next Step: Evaluate for contraceptive efficacy.

Challenge: Need a commercial partner. LNG is very safe! How many cycles of efficacy will be required for approval? The more cycles required, the more expensive and longer the study will be.

MPT – Dapivirine and Levonorgestrel in a Vaginal Ring - Protect against HIV and Pregnancy

Collaboration with the International Partnership for Microbicides (IPM) / Population Council

Advantage over existing methods:

Dapivirine-only ring - success in preventing HIV infection

Levonorgestrel:

- Safe: LNG is safe for contraception
- Estrogen free: important when risk factors contraindicate use of estrogen
- LNG will not increase risk of blood clots – safe for obese women

Status: Completed Phase I study – 3-month ring assessed for PK, Safety and Acceptability

Challenge: Two components makes regulatory approval more burdensome.

Ulipristal Acetate – Selective Progesterone Receptor Modulator (SPRM)

UPA - single dose (30 mg) approved worldwide for Emergency Contraception (ella®)

UPA – chronic dose (5 mg/d for 90 days) - approved in Europe and Canada for treatment of uterine fibroids (Esmya or Fibristal).

CCN013 - Low dose Ulipristal Acetate (UPA) – daily pill for contraception

Advantage over existing methods:

- **No Ethinyl Estradiol or Estradiol**
- **Safe for women with obesity, diabetes, other health issues?**
- **May have protective properties against breast cancer?**

CCN013A - Study Design

- **Randomized double blind comparative study**
  - **10 mg UPA dose**
  - **5 mg UPA dose**
- **Treatment for 84 days (3 “cycles”)**

Results: 10 mg UPA inhibits ovulation and stops bleeding

Westhoff CL *et al*, Contraception. 2022 112:54-60.

Acceptability

Question: "Do you like the study pill?"				
End of Study Visit	**10 mg/d**	**5 mg/d**	**5mg 24/4**	**All subjects**
	N = 50	**N = 51**	**N = 49**	**N = 150**
Yes	45 (90.0%)	47 (92.2%)	46 (93.3%)	138 (92.0%)
No	5 (10.0%)	4 (7.8%)	3 (6.1%)	12 (8.0%)

"What did you like most about the study pill?"	**10 mg/d**	**5 mg/d**	**5mg 24/4**	**All subjects**
End of Study Visit	**N=49**	**N=48**	**N=50**	**N=147**
Stopped/Lightened Menses	33	30	26	89
No side effects	9	8	10	27
Simple/Easy to Take	2	11	4	17
Positive affect on mood/PMS symptoms	2	3	1	6
Decreased cramps	0	3	2	5
Other positive side effects	4	1	4	9
Other – related to study participation	3	0	8	11

More than one response from some individuals

Status: All studies of chronic use of Ulipristal Acetate are on Indefinite Clinical Hold due to rare instances (1/100,000 women being treated for fibroids) of Severe Liver Injury.

Evaluation of Nestorone/Testosterone Gel for Male Contraception – CCN017

Couples use the method for contraception

Screen & Suppression Phase : Efficacy Phase : Recovery Phase

4 - 24 weeks | 1 year (52 weeks) | 8 - 24 weeks

Time commitment ~ 2 years

Target – 200 couples completing one year of efficacy

Primary Endpoint: Prevention of pregnancy

Secondary Endpoints:

- Safety, side effects
- Acceptability to both partners

Combined Nes and T Gel
~ ½ teaspoon per shoulder

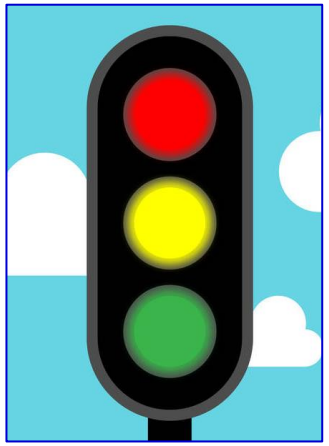
CCN017 - Contraceptive Efficacy Study

Study has ended. Data analysis is ongoing.

Efficacy??	**Better than expected**
Reversibility??	**Fully Reversible**
Acceptability??	**Highly acceptable. Some subjects asked if they could re-enroll.**

Nes T Gel for Male Contraception

- ✓ **Effective!**
- ✓ **Reversible!**
- ✓ **Safe!** **(but need more data)**
- ✓ **Acceptable!**
- ✓ **User-controlled** (aka accessible)



NEXT STEP!
What will FDA want?

Contraceptive Research Collaborators

Contraceptive Development Program

- Min Lee
- Jeffrey Kroopnick
- Jill Long
- Genevieve Depke
- Danielle Gross
- Ahnyah Phillips
- Tamar Jacobsohn
- Frances Fernando

CCTN Coordinating Center

Premier/Health Decisions International - PI: Clint Dart

Population Council

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- Narendar Kumar
- Jim Sailor
- Lisa Haddad
- Ruth Merkatz
- Dan Loeven
- John Townsend

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- Tabitha Sripipatana
- Kevin Peine

Daré Bioscience

- Sabrina Johnson
- Christine Mauck

FHI360

- David Hubacher
- Laneta Dorflinger
- Kavita Nanda

Bill & Melinda Gates Foundation

- Kirsten Vogelsong
- Mark Barone
- Stephen Ward
- Trisha Wood-Santos

- International Partnership for Microbicides
- Office of AIDS Research
- National Institute of Child Health and Human Development
- National Institute for Allergies and Infectious Diseases

CCTN Sites – Female Methods

- David Archer, Andrea Thurman, Eastern Virginia Medical School
- Kurt Barnhart, Courtney Schreiber, University of Pennsylvania
- Anne Burke, Johns Hopkins University
- Beatrice Chen, Sharon Achilles, University of Pittsburgh-Magee
- Mitch Creinin, Melissa Chen, University of California, Davis
- Phil Darney, Jennifer Kerns, University of California, San Francisco
- Jeff Jensen, Alison Edelman, Oregon Health and Sciences University
- Bliss Kaneshiro, University of Hawaii
- Anita Nelson, Essential Access Health
- Nancy Fang, Aaron Lazorwitz, University of Colorado
- Michael Thomas, University of Cincinnati
- David Turok, Lori Gawron, University of Utah
- Carolyn Westhoff, Paula Castano, Columbia University
- Katherine White, Boston Medical Center
- Carrie Cwiak, Emory University
- Jessica Atria, Albert Einstein School of Medicine

University of Washington

- Stephanie Page
- William Bremner
- John Amory
- Brad Anawalt
- Arthi Thirumalai

The Lundquist Institute

- Christina Wang
- Ronald Swerdloff
- Peter Liu
- Fiona Yuen
- Brian Nguyen

CCTN Sites – Male Methods

CCTN Partner Investigators & Institutions

- Richard Anderson, University of Edinburgh, Scotland, UK
- Cheryl Fitzgerald, University of Manchester, UK
- Kristina Gemzell Danielsson, Karolinska Inst, Sweden
- John Kinuthia, University of Nairobi, Kenya
- Cristina Meriggiola, University of Bologna, Italy
- Ajay Nangia, University of Kansas, USA
- Gabriela Noe, ICMER, Chile
- Jose Vinay, University of Chile, Chile
- Felix Mhlanga, University of Zimbabwe, Zimbabwe

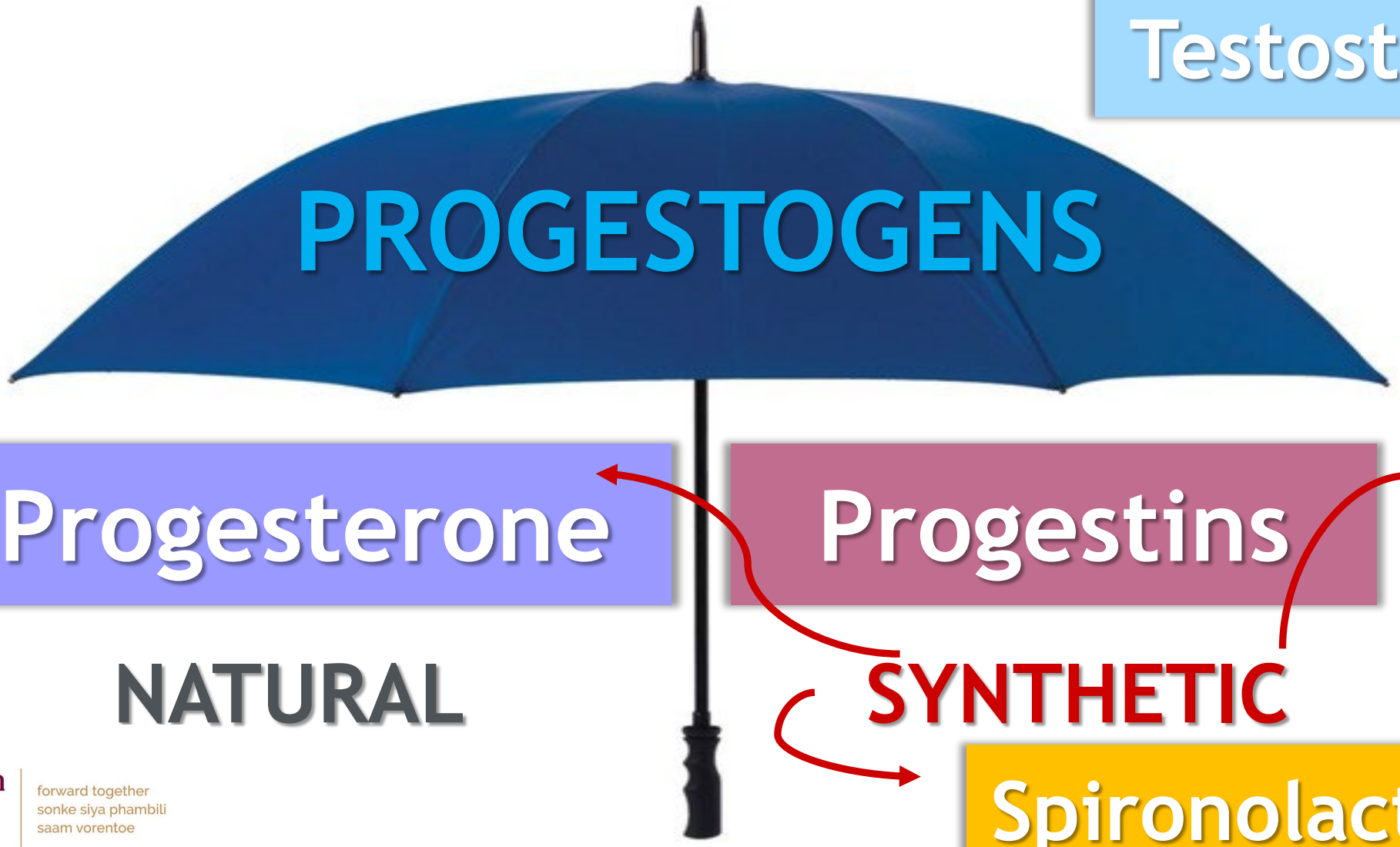
All progestins are NOT equal

Donita Africander

Stellenbosch
UNIVERSITY
IYUNIVESITHI
UNIVERSITEIT

forward together
sonke siya phambili
saam vorentoe

WHAT ARE PROGESTINS?



WHAT ARE PROGESTINS?

Many different progestins

Spironolactone

MENOPAUSAL HORMONE THERAPY

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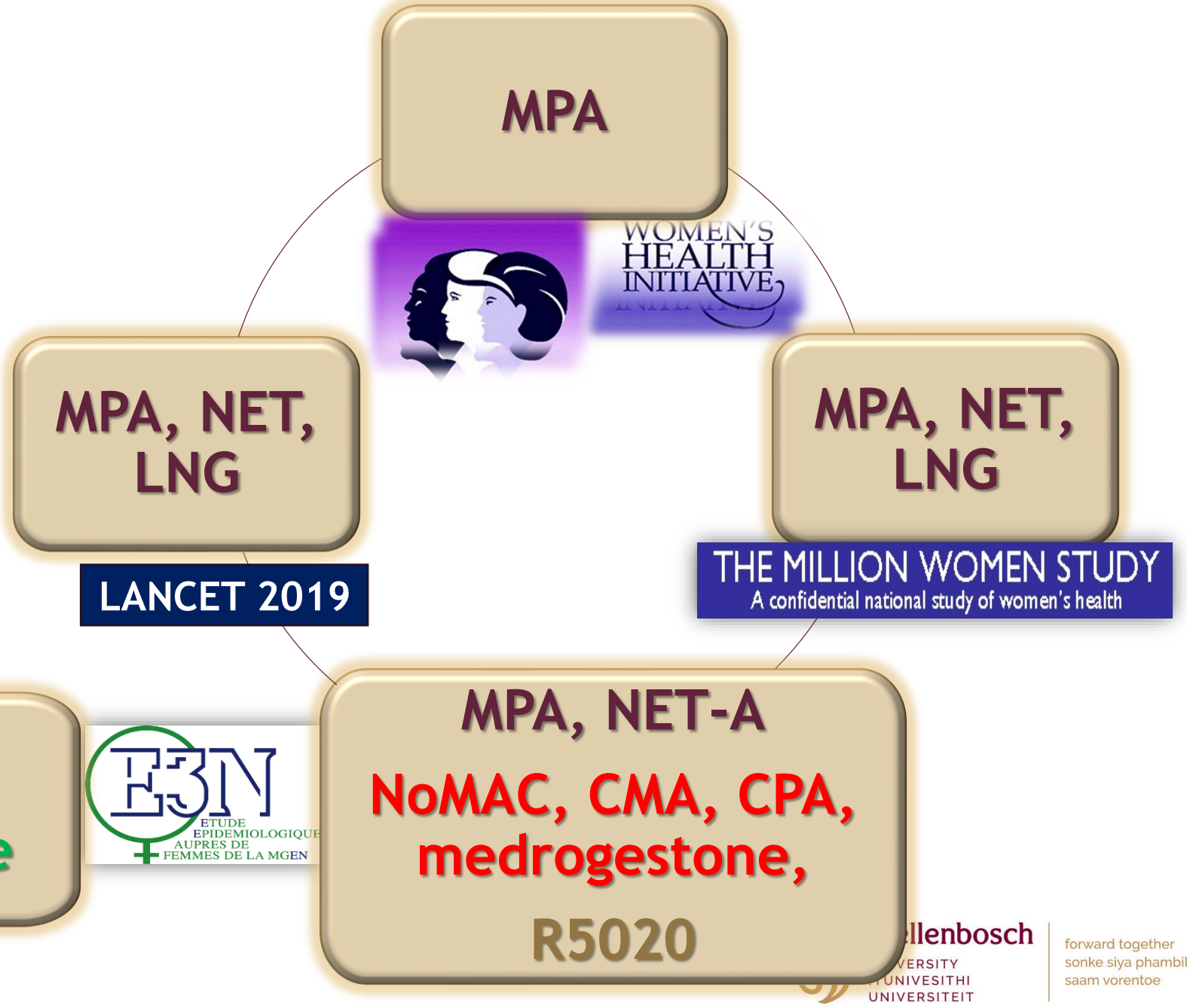
HORMONE REPLACEMENT THERAPY (HRT)

Estrogen + **PROGESTOGEN**

- **Progestins**
- **Bioidentical Progesterone**

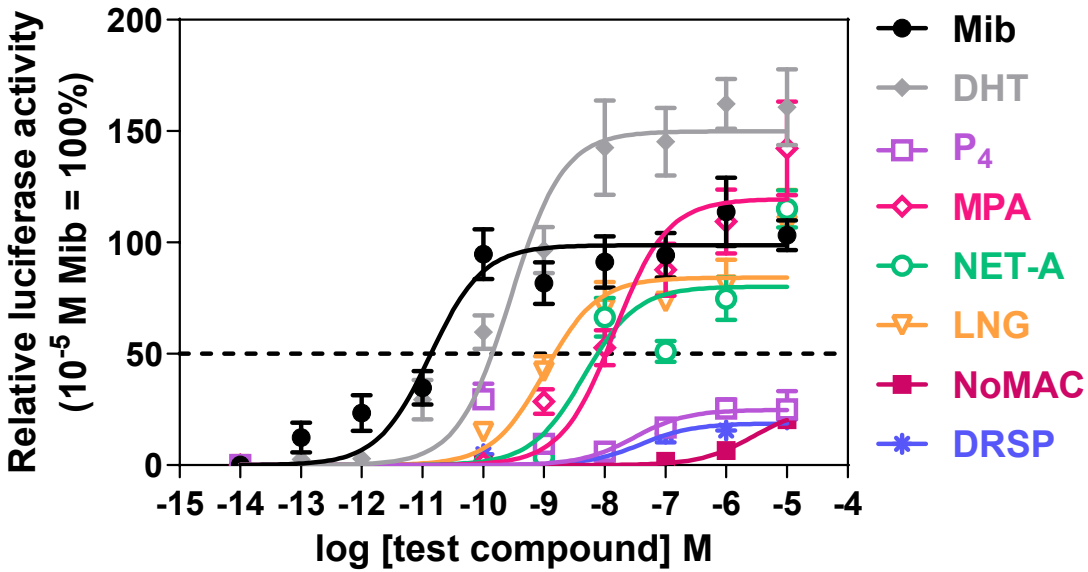
BREAST CANCER



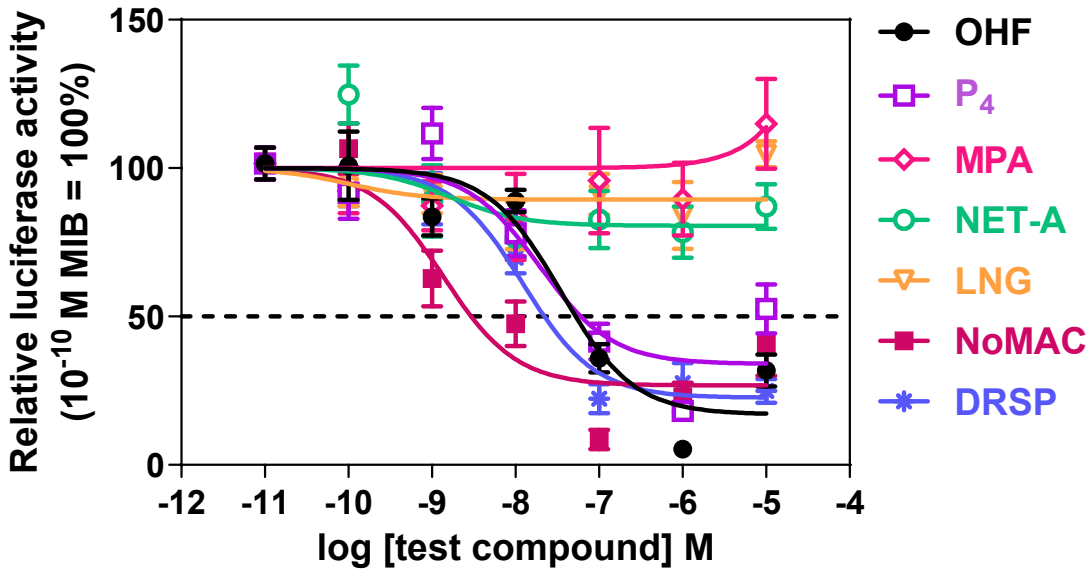

Mechanism
via
steroid receptors
Androgen Receptor
Mineralocorticoid receptor
Glucocorticoid receptor
Estrogen Receptor
Progesterone receptor
Journal of Steroid Biochemistry and Molecular Biology
Biochemical and Biophysical Research Communications
Comparing the androgenic and estrogenic properties of progestins used in contraception and hormone therapy
Contraception
Differential regulation of endogenous pro-inflammatory cytokine genes by medroxyprogesterone acetate and norethisterone acetate in cell lines of the female genital tract
Investigating the anti-mineralocorticoid properties of synthetic progestins used in hormone therapy
A direct comparison of the transcriptional activities of progestins used in contraception and menopausal hormone therapy via the mineralocorticoid receptor
The Journal of Biological Chemistry
AFFINITY SITES
Medroxyprogesterone Acetate Differentially Regulates Interleukin (IL)-12 and IL-10 in a Human Ectocervical Epithelial Cell Line in a Glucocorticoid Receptor (GR)-dependent Manner
Steroids
Differential off-target glucocorticoid activity of progestins used in endocrine therapy
The transcriptional activity of progestins used in contraception and menopausal hormone therapy via progesterone receptor A is dependent on the density of the receptor
frontiers Frontiers in Endocrinology
Upregulation of an estrogen receptor-regulated gene by first generation progestins requires both the progesterone receptor and estrogen receptor alpha
Characterisation of progestins used in hormonal contraception and progesterone via the progesterone receptor

ACTIVITY VIA THE ANDROGEN RECEPTOR

Androgenic



Anti-androgenic



Progesterone (P_4) ≠ MPA, NET & LNG

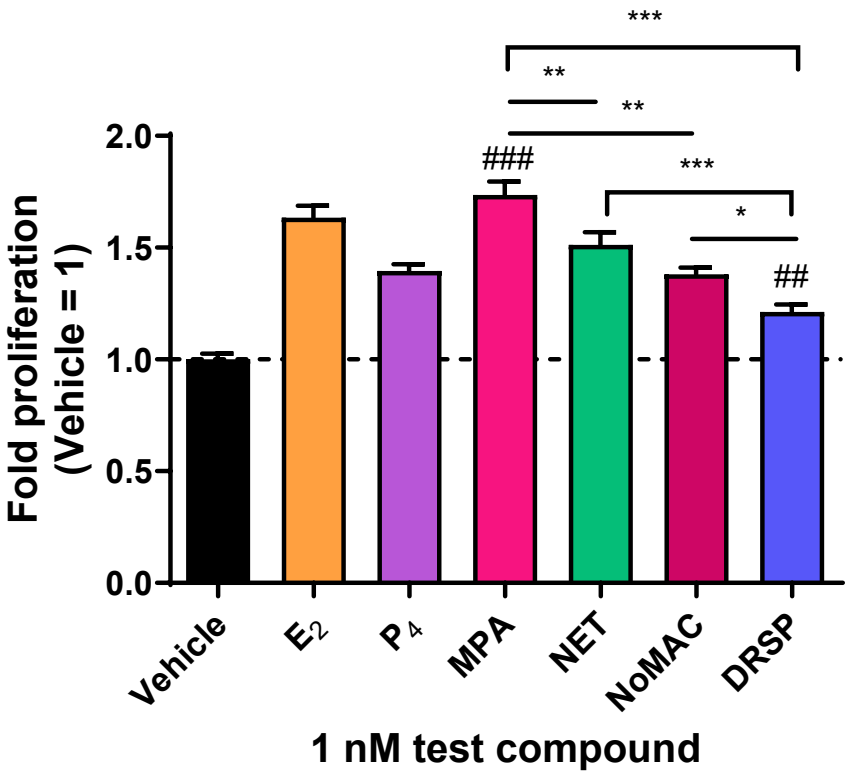
Progesterone (P_4) = NoMAC & DRSP

MPA, NET & LNG ≠ NoMAC & DRSP

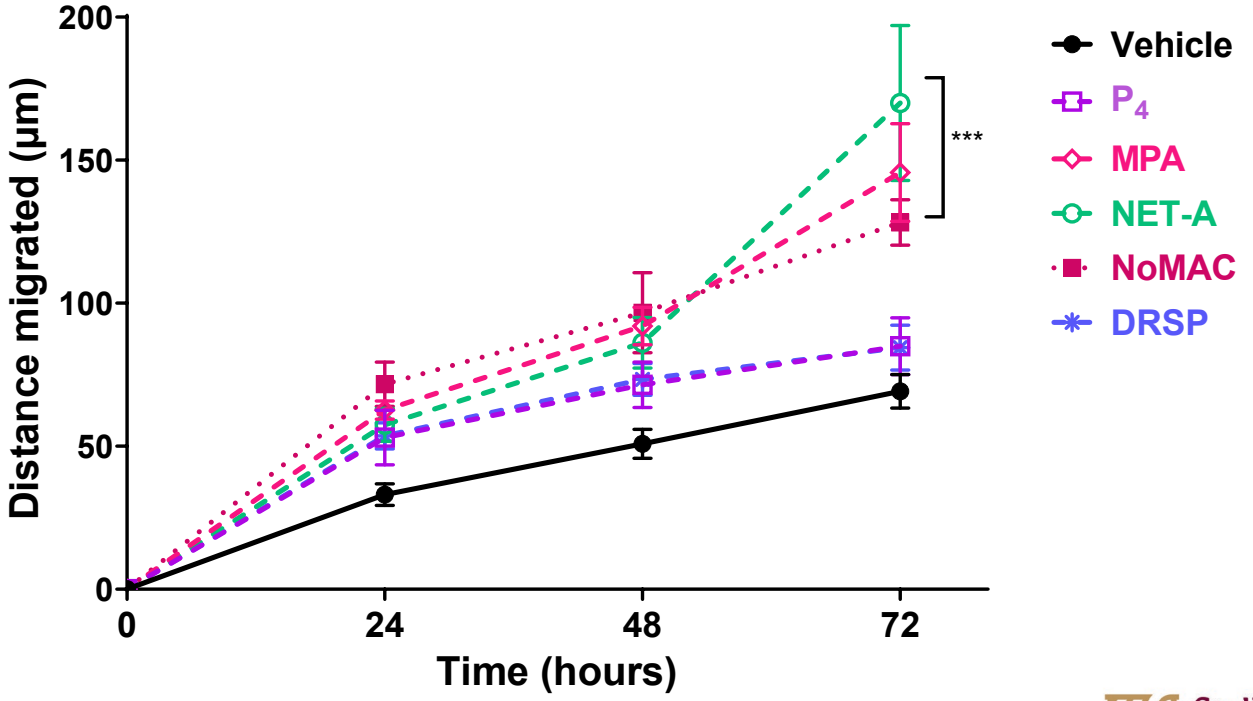
Africander et al. 2014; Louw du Toit et al. 2017

Progestins do not always elicit similar effects to progesterone or each other

Cell proliferation



Cell migration



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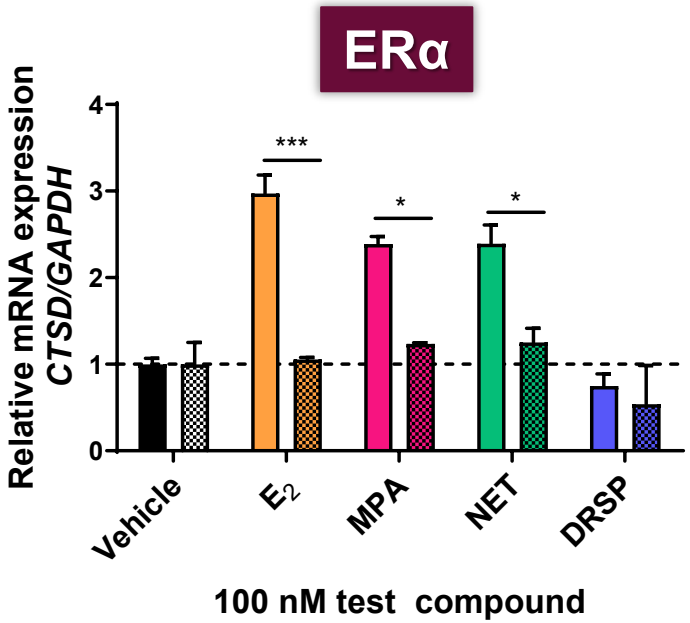
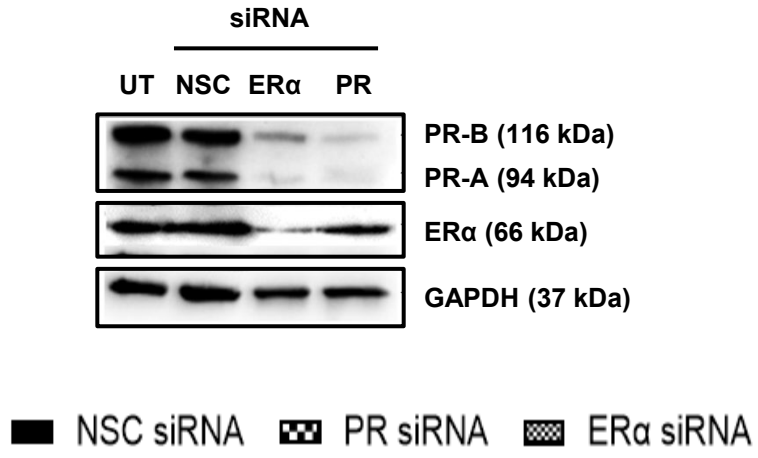
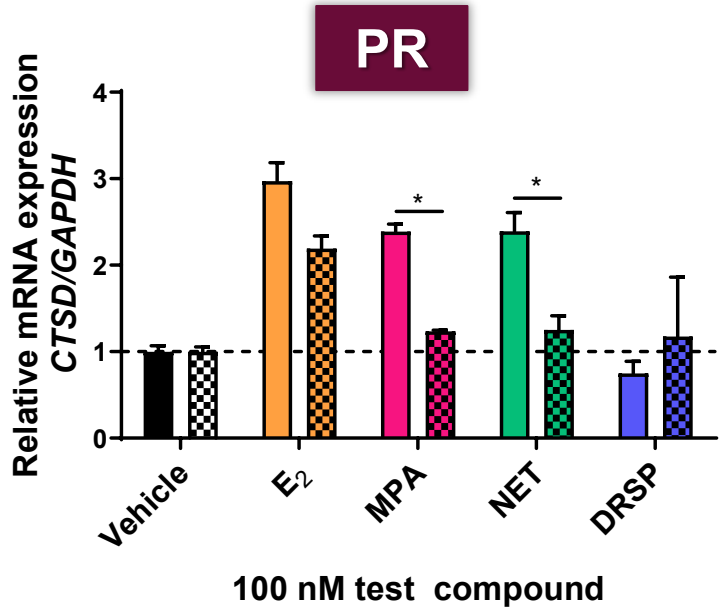
Louw du Toit et al. 2024; Louw-du Toit unpublished

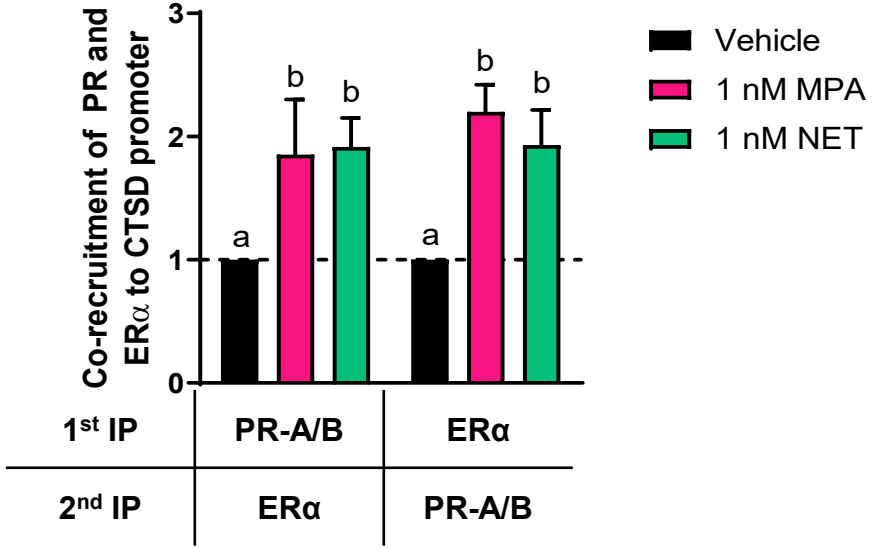
ERα-PR interaction







PR and ERα co-recruitment



Perkins et al. 2022

TAKE HOME MESSAGE

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Progesterone ≠ **Progestins**

Progestogens - not a generic term

TAKE HOME MESSAGE

Progestins used in MHT is not a "one-size-fits-all"

BEST PROGESTIN FOR YOU!!