# DART
# Drugs in Human Semen

**HESI Annual Meeting**
**Alexandria, VA**

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**Bristol-Myers Squibb**

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ILSI Health and
Environmental Sciences
Institute

# Drugs in Human Semen

- **Goal**: To address recent MHRA and FDA requests for data demonstrating safety of pharmaceuticals regarding male-mediated conceptus exposure, and arrive at an appropriate and data-based use of contraception in clinical trials.

- **Steering Team**

| | | | |
|---|---|---|---|
| Graham Bailey | Johnson & Johnson | Jim Kim | HESI |
| Kimberly Benson | U.S. FDA | Larry Leshin | U.S. FDA |
| Bruce Beyer | sanofi-aventis | Jimmy McBlane | MHRA |
| Bill Breslin | Lilly | Graeme Moffat | Amgen |
| Gary Chellman | Charles River Labs | Christine Nguyen | U.S. FDA |
| Ruediger Cordts | Boehringer-Ingelheim | Anthony Scialli | Tetra Tech Sciences |
| Liz Davidson | Consultant (MHRA) | George Scott | Amgen |
| Tony DeLise | sanofi-aventis | Jane Stewart | AstraZeneca |
| Wafa Harrouk | U.S. FDA | Kary Thompson | Bristol-Myers Squibb |
| Kok Wah Hew | Takeda | Ulla Wandel-Liminga | Sweden Medical Products Agency |
| Julia Hui | Celgene | | |

# Drugs in Human Semen

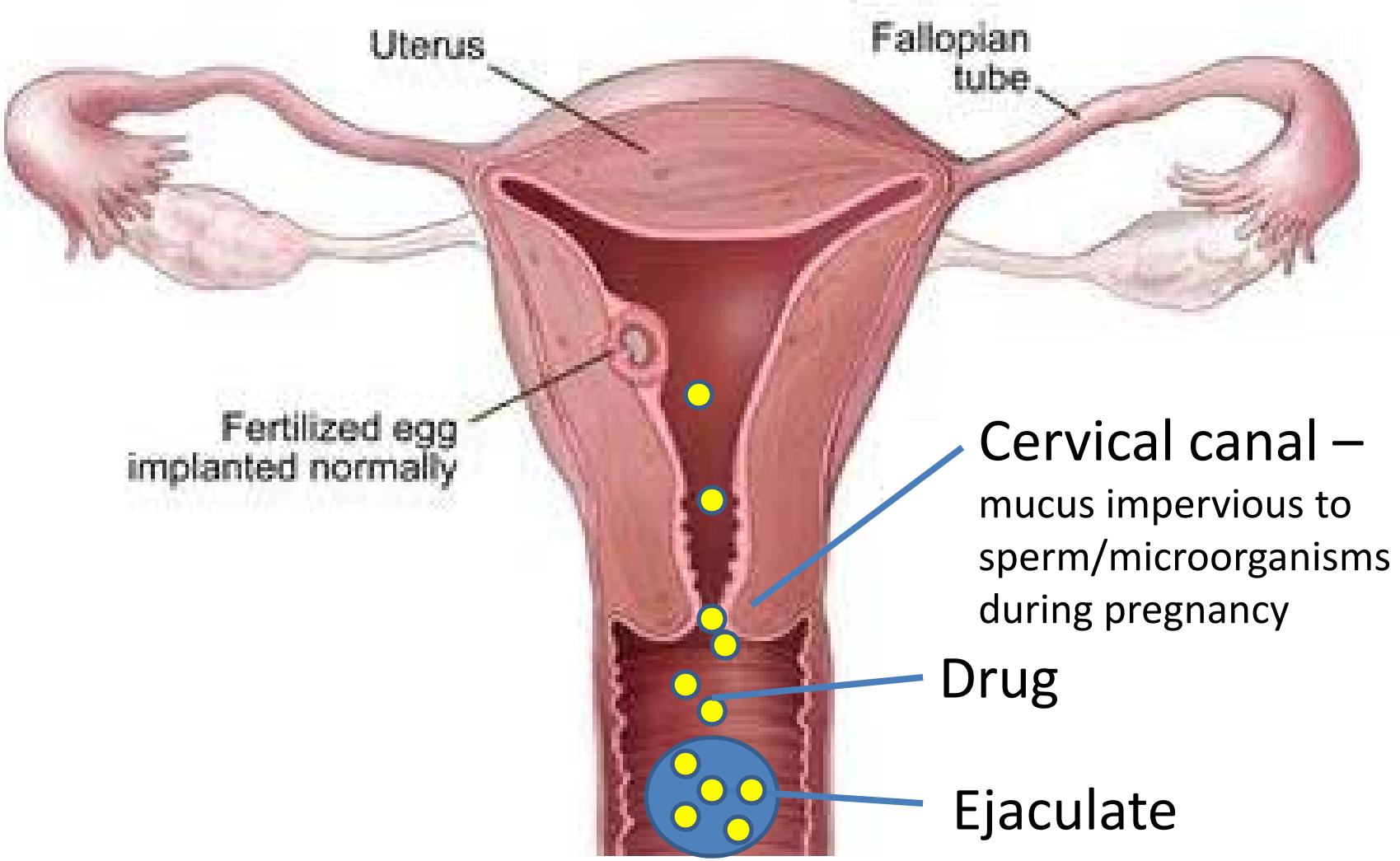
- Regional health authority concern for male-mediated embryo/fetal harm following indirect exposure to drugs has lead to requirement for use of barrier protection for men enrolled in clinical trials with pregnant partners.
- Most companies do not routinely assess for semen concentrations of drug.

# Three Potential Mechanisms of Embryo/Fetal Exposure Considered

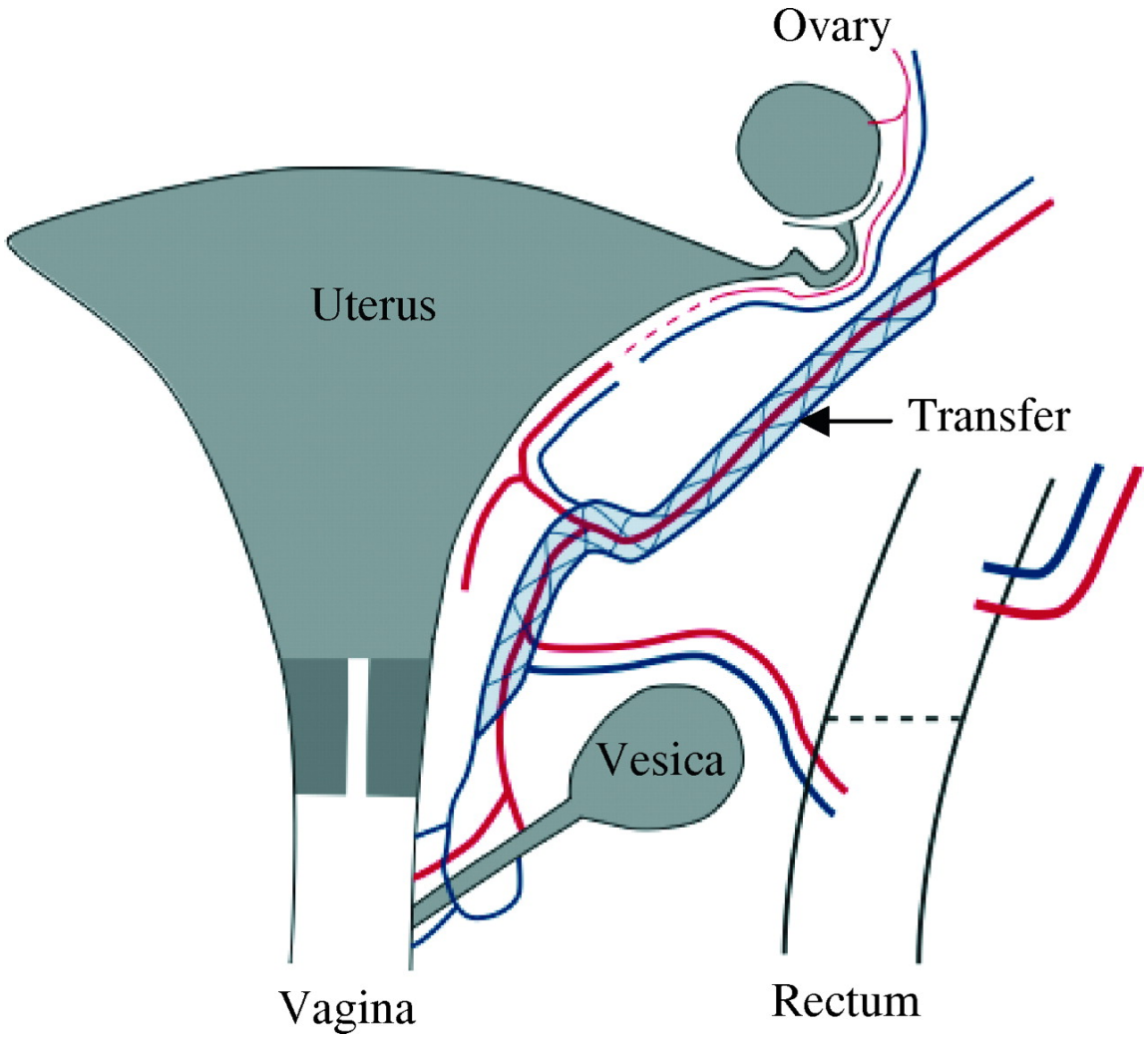
- Vaginal absorption of drug into maternal circulation and subsequent distribution to conceptus – likely most relevant


When requested by regional healthy authorities, using “worst case” assumptions, potential embryo/fetal risk based on known male systemic exposures is modeled. In this approach, only extremely potent teratogens could be a concern.

# Diffusion of drug from semen and across cervical barrier



# Model of counter-current transfer of heat or a substance between vaginal vein blood and uterine arterial blood






Einer-Jensen N , Hunter R 2005;129:9-18
Published by BioScientifica

# Drugs in Semen

**Experimental Approaches:**

1) Vaginal dosing of pregnant **cynomolgus monkeys** with assessment of drug in maternal and fetal plasma.
2) Thalidomide experiments in pregnant **rabbits** comparing intra-vaginal and oral routes.
3) Use of vital dyes (e.g. trypan blue) placed into vagina of pregnant **rats** followed by time course evaluation of dye migration in dams.
4) Imaging studies in pregnant **mice**

# Cynomolgus Monkey Study

- Bristol-Myers Squibb
- Amgen
- Charles River Labs
- Objectives:
  - Determine if traditional assumptions and calculations presently used are sufficient to predict potential male-mediated embryo/fetal harm

# Cynomolgus Monkey Study

- Study Design
  - 3 pregnant cynomolgus monkeys (GD 60/70)
  - Given 1 mL of 0.75% metronidazole gel vaginally and monitored for leakage (minimal to none)
  - Timed cesarean-section 7 hours after dose for collection of maternal and fetal blood samples and amniotic fluid
  - Plasma and amniotic fluid samples analyzed for parent and metabolite (MS/MS)

# Cynomolgus Monkey Study: Metronidazole Concentrations

| Dam ID | Gestation Day | Maternal Plasma (ng/mL) | Fetal Plasma (ng/mL) | Amniotic Fluid (ng/mL) |
|---|---|---|---|---|
| 1501 | GD 70 | 94.4 | 105 | 145 |
| Maternal/fetal ratio | | 0.9x | | |
| 1502 | GD 60 | 756 | 735 | 649 |
| Maternal/fetal ratio | | 1.0x | | |
| 1503 | GD 70 | 494 | 539 | 817 |
| Maternal/fetal ratio | | 0.9x | | |

# Cynomolgus Monkey Study: [Hydroxymetronidazole]

| Dam ID | Gestation Day | Maternal Plasma (ng/mL) | Fetal Plasma (ng/mL) | Amniotic Fluid (ng/mL) |
|---|---|---|---|---|
| 1501 | GD 70 | 3.66 | 4.17 | 2.01 |
| Parent/metabolite ratio | | 26x | 25x | 72x |
| 1502 | GD 60 | 26.5 | 21.1 | 8.69 |
| Parent/metabolite ratio | | 29x | 31x | 75x |
| 1503 | GD 70 | 19.6 | 21.3 | 13.4 |
| Parent/metabolite ratio | | 25x | 26x | 61x |

# Cynomolgus Monkey Study: Conclusions

- Maternal systemic exposure to metronidazole is variable following vaginal dosing
- Fetal exposure was equivalent to maternal systemic exposure for parent and metabolite on GD 60 and 70
- Supports that traditional modeling of fetal exposure to drug in semen would be sufficiently conservative to predict potential fetal risk

# PK Pregnant Rabbit Study Thalidomide

- Celgene Corp.
- Objective –
  - To compare embryonic concentrations of thalidomide following maternal oral or vaginal administration in rabbits

# PK Pregnant Rabbit Study
# Study Design

- Oral dosages:
  - 20 mg/kg/day (NOAEL in previous rabbit EFD study)
  - 180 mg/kg/day (malformations seen in previous study)
- Intravaginal (IVg) dosages:
  - 2, 20, and 180 mg/kg/day
- 8 mated rabbits/group (N=2/time point) dosed from GD 7-11
- Sample collection at 1, 3, 6, and 24 hours postdose on GD11 for assay of thalidomide concentration in:
  - Maternal plasma samples
  - Yolk sac cavity (YSC) fluid from each implant (analyzed individually)
  - Embryos (pooled by litter prior to analysis)

# PK Pregnant Rabbit Study - Preliminary Outcomes

- Exposures were more variable following intravaginal dosing as compared to oral dosing
- Maternal plasma, YSC fluid, and embryonic exposures (AUC) were lower following IVg administration as compared to oral administration
- No meaningful difference in YSC fluid/maternal plasma AUC ratio between these routes

- Conclusion: There was no difference in uptake of thalidomide into the intrauterine compartment following oral and intravaginal routes of administration.

# Pregnant Rat Study using Vital Dyes

- Johnson & Johnson
- Objective: Visually evaluate dye distribution when administered intravaginally to pregnant rats
- Study Design
  - Dye to be administered on GD12
    - Use dyes with various sizes and polarity
  - Animals to be sacrifice at 0.25, 0.5, 1, 2, and 4 h
- Study in progress

# Transgenic Pregnant Mouse Imaging Study

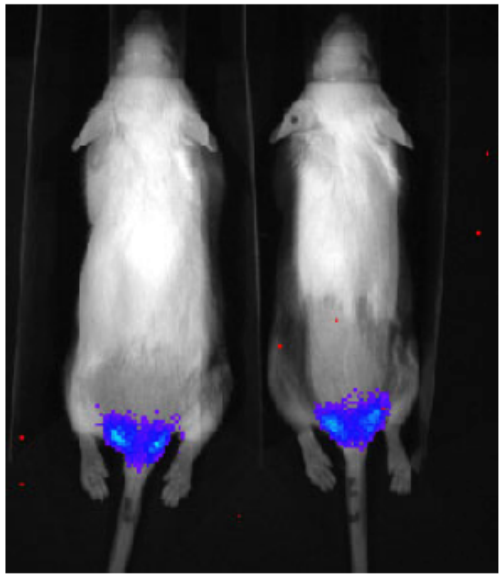
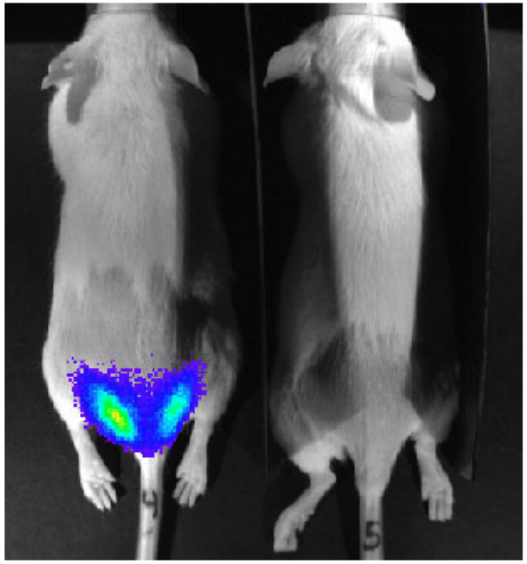
- sanofi aventis
- Objective:
  - Visualize potential embryo/fetus exposure to compounds via intravaginal route using optical imaging model

# Transgenic Pregnant Mouse Imaging Study

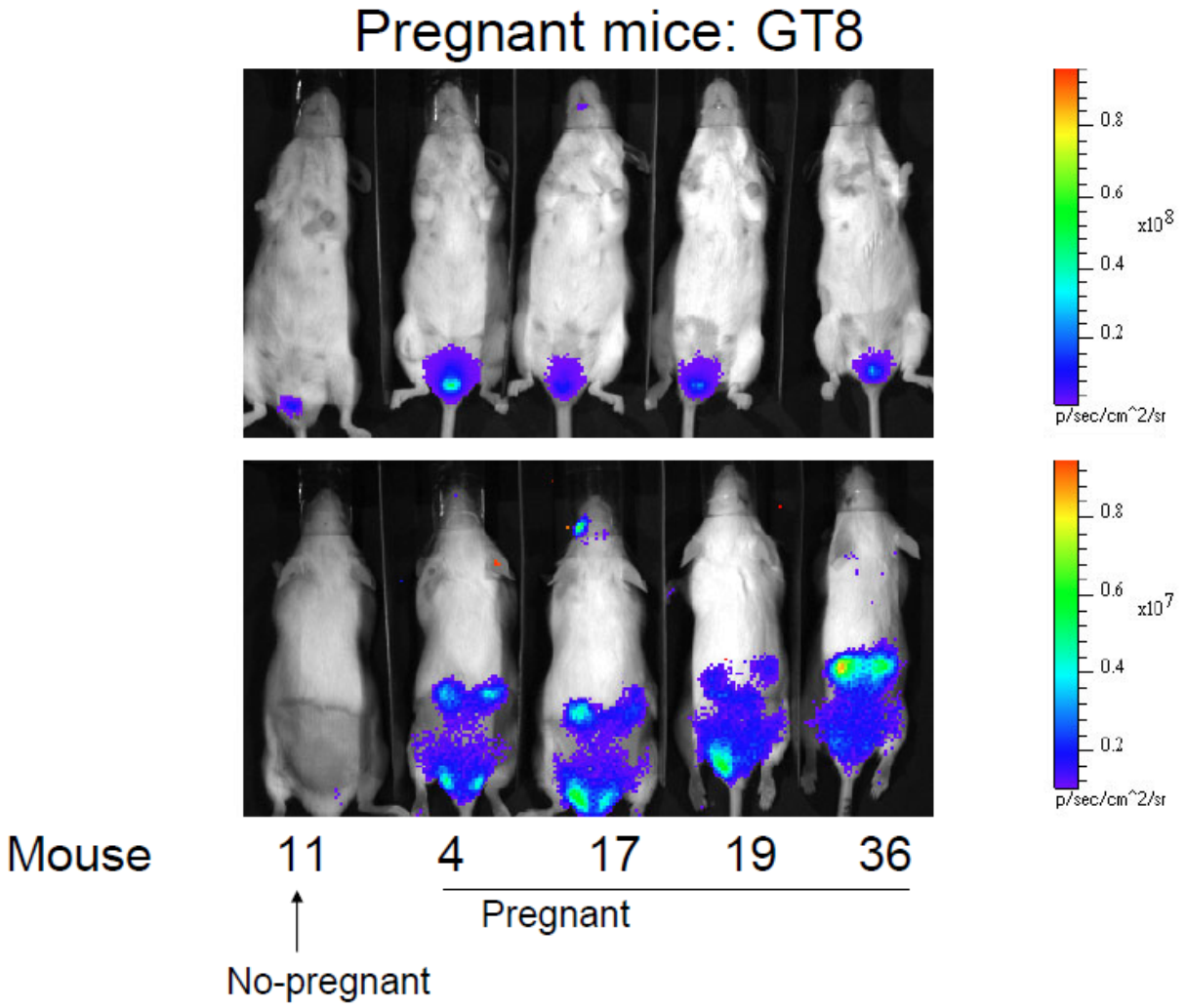
- Study Design
  - Exposure at different stages of estrus cycle and during pregnancy
  - Fluorescence imaging and *ex vivo* imaging
  - 13 β-actin-luciferase female transgenic mice
  - D-luciferin substrate dosed intravaginally (20 ul of 0.5 mg/kg)
  - Imaged with IVIS-100 between 1 to 10 min

# Imaging Study Results

**Mouse 10, 20 imaged at different estrus stage**

| | | | | |
|---|---|---|---|---|
| Time | 2/18 13:09PM | | 2/22 9:59AM | |
| Dorsal View |  | |  | |
| Mouse | 10 | 20 | 10 | 20 |
| Cycle | diestrus | diestrus | diestrus | estrus/metastrus |

# Imaging Study Results



# Transgenic Pregnant Mouse Imaging Study - Topline Results

1. Mice in diestrus and proestrus showed imaging signal
2. Mice in estrus/metestrus did not show any imaging signal
3. Pregnant mice indeed showed the imaging signal

# Drugs in Semen WG: Next Steps

- Complete vital dye study
- Define next steps for imaging study
- Symposium at Teratology Society June 29, 2011
- Publish Results

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