

# Contraception by blocking soluble adenylyl cyclase (sAC; ADCY10)

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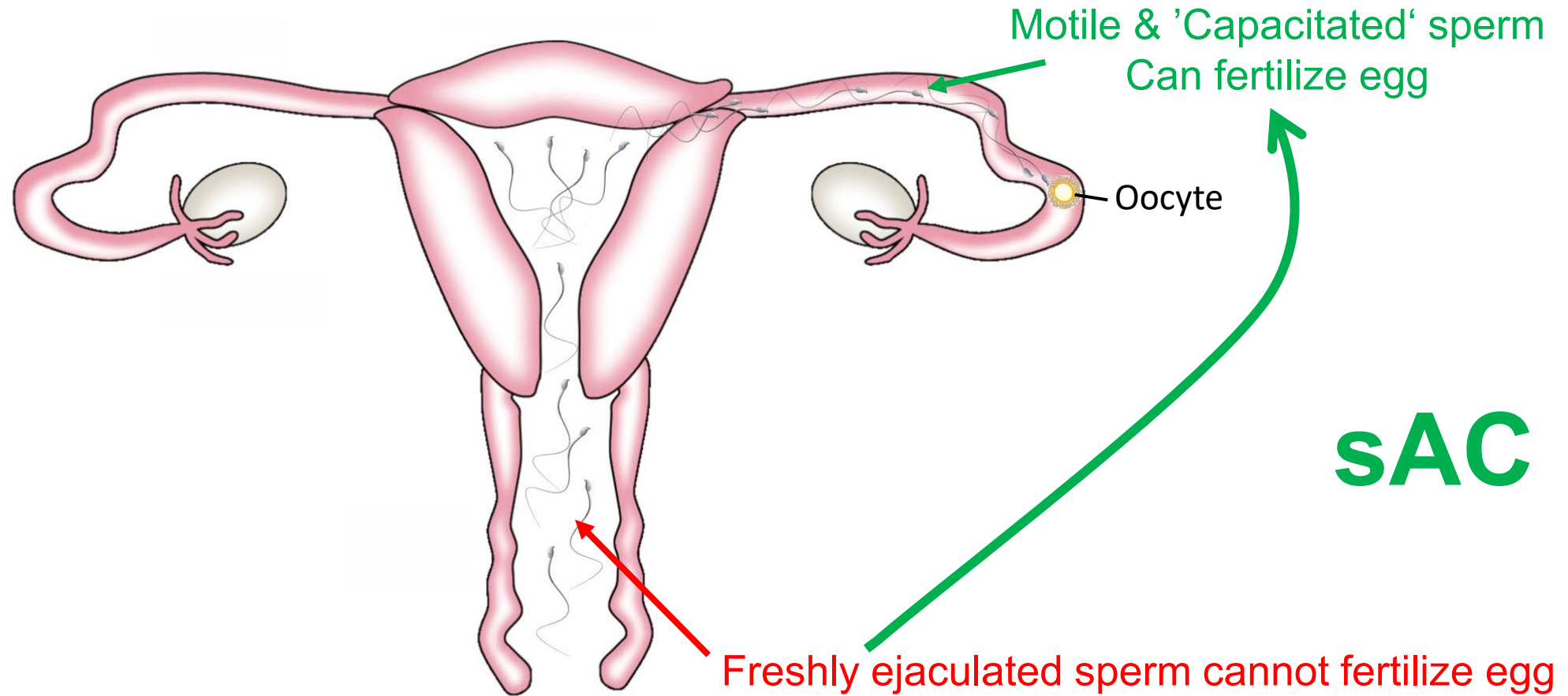
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**Conflict of Interest Disclosure:**  
Drs. Levin & Buck are co-founders of Sacyl Pharmaceuticals, Inc. established to develop sAC inhibitors for contraception

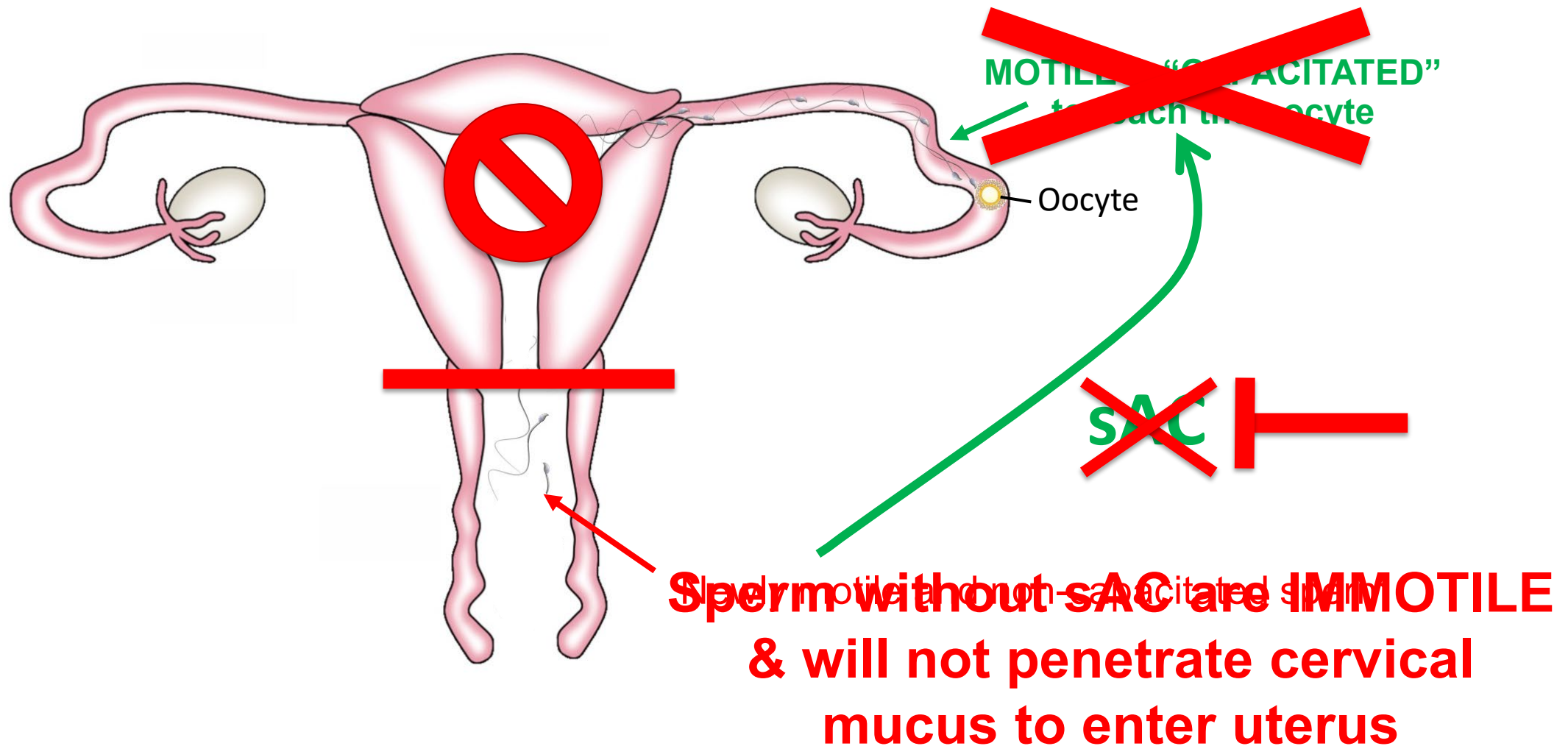
# sAC is the “ON” switch for motility and capacitation which are essential for Fertilization



Epididymal sperm are immotile

\*Capacitation is defined as the ability to fertilize an egg.

# Contraceptive effects of a sAC inhibitor



# Can inhibiting sAC cause infertility?

## **sAC is essential for male fertility in mice**

- sAC KO mice are male-specific sterile
  - *Sperm do not capacitate*
  - *Sperm are immotile*

## **sAC is essential for male fertility in humans**

- 2 sAC KO men are **STERILE**, but otherwise **HEALTHY**
  - *Sperm are immotile*

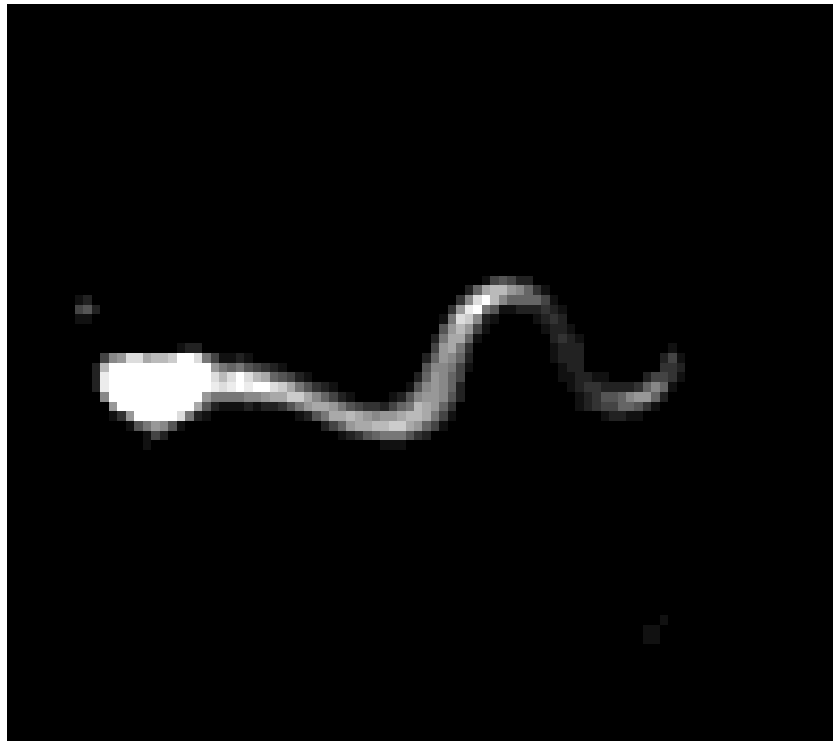
*Thus, sAC is genetically validated in **MICE** and **MEN** to be a contraception target*

# Workflow to build a sAC inhibitor contraceptive

- 1. Need = nonhormonal contraception for men &/or women*
- 2. Target = sAC (ADCY10)*
  - Knockouts in male mice and men are infertile*
- 3. We developed inhibitors suitable for “proof-of-concept studies.”*

# sAC inhibitor blocks human sperm motility

**+ sAC Inhibitor**



Latest generations of sAC inhibitors turn enzyme completely OFF



# Workflow to build a sAC inhibitor contraceptive



**ONE RING**  
Dual-Purpose Ring to Prevent HIV and Pregnancy

**MATRIX**

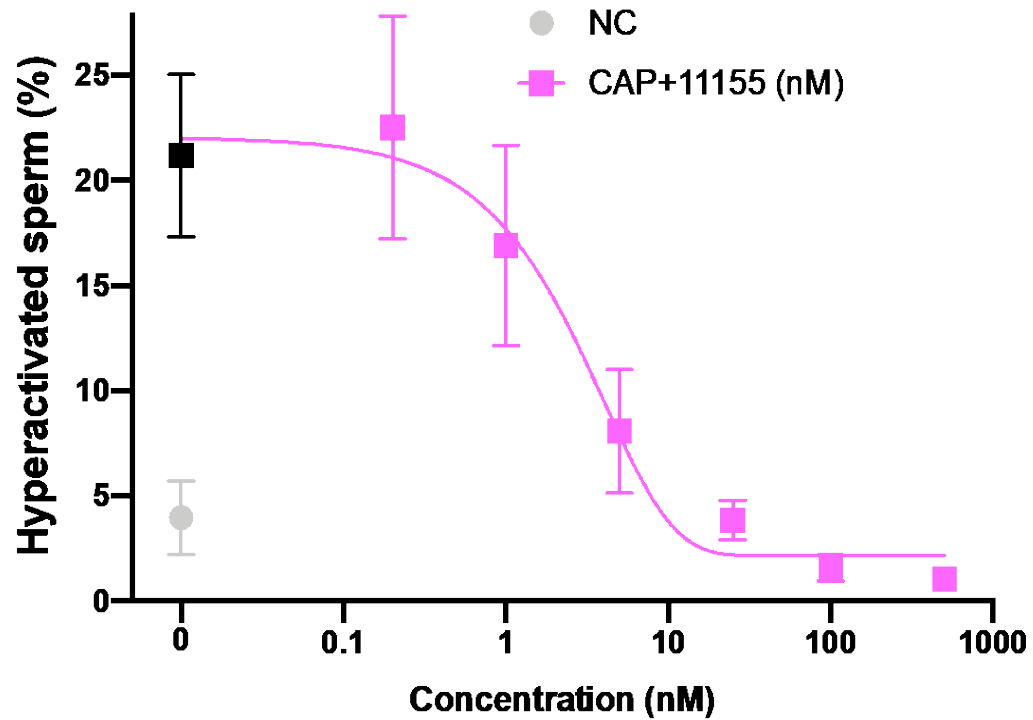
## Female nonhormonal intravaginal contraceptive

1. Validated *in vitro* (Balbach et al., Mol Hum Repro 2021)
  - sAC inhibitor **INTERRUPTS** Capacitation and **STOPS** Motility
2. Working with Marc Baum and John Moss (Oak Crest) to develop IVR
  1. “Multipurpose Protection Technology” (MPT) Ring
  2. sAC inhibitor **CONTRACEPTIVE** delivered w/anti-HIV peptide
3. Lead candidate undergoing preclinical validation

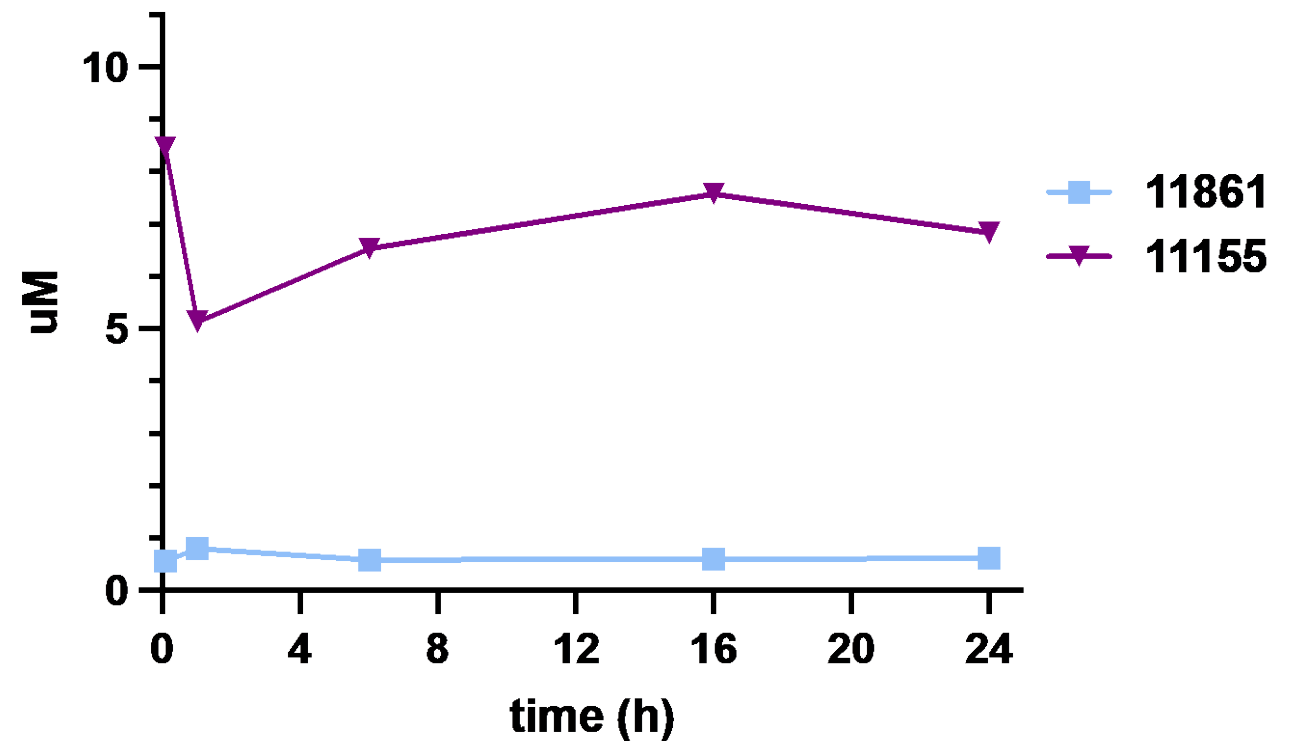


# Clinical Lead (TDI-11155) Pharmacology

## Human Sperm Dose Response



## Human Vaginal Fluid Stability





# ON DEMAND male contraception

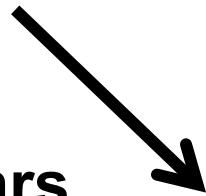


# Ex vivo motility assay

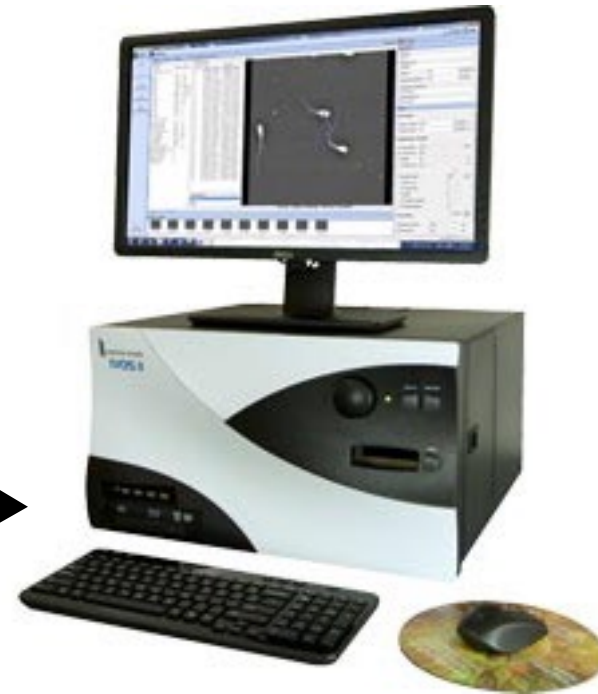
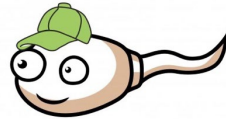
**Deliver sACi**  
(oral or *i.p.*)



**WAIT**  
**15' – 24 hrs**



**Collect sperm**



**Quantitate Motility**  
**CASA**

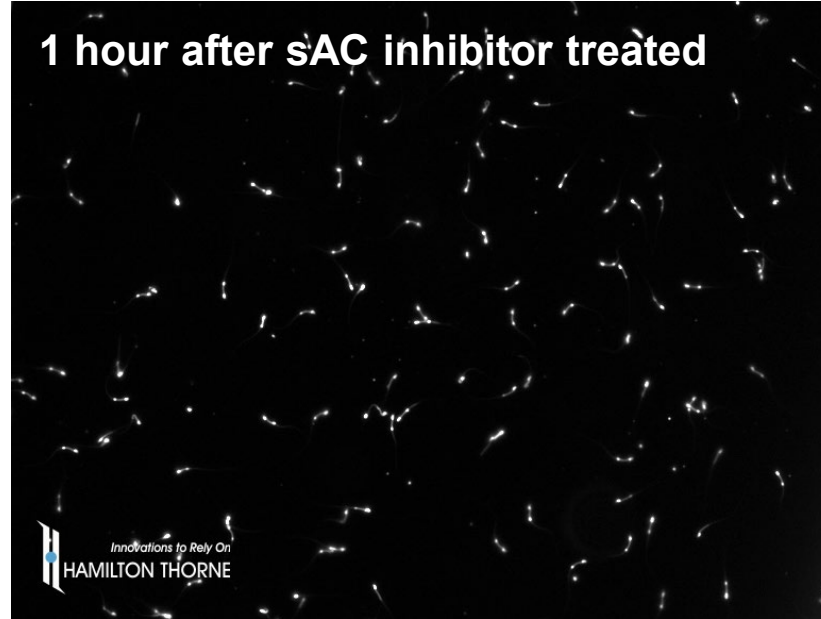
# *Ex vivo* motility

Sperm dissected from epididymis of sAC inhibitor-treated mice:

1 hour after vehicle treated

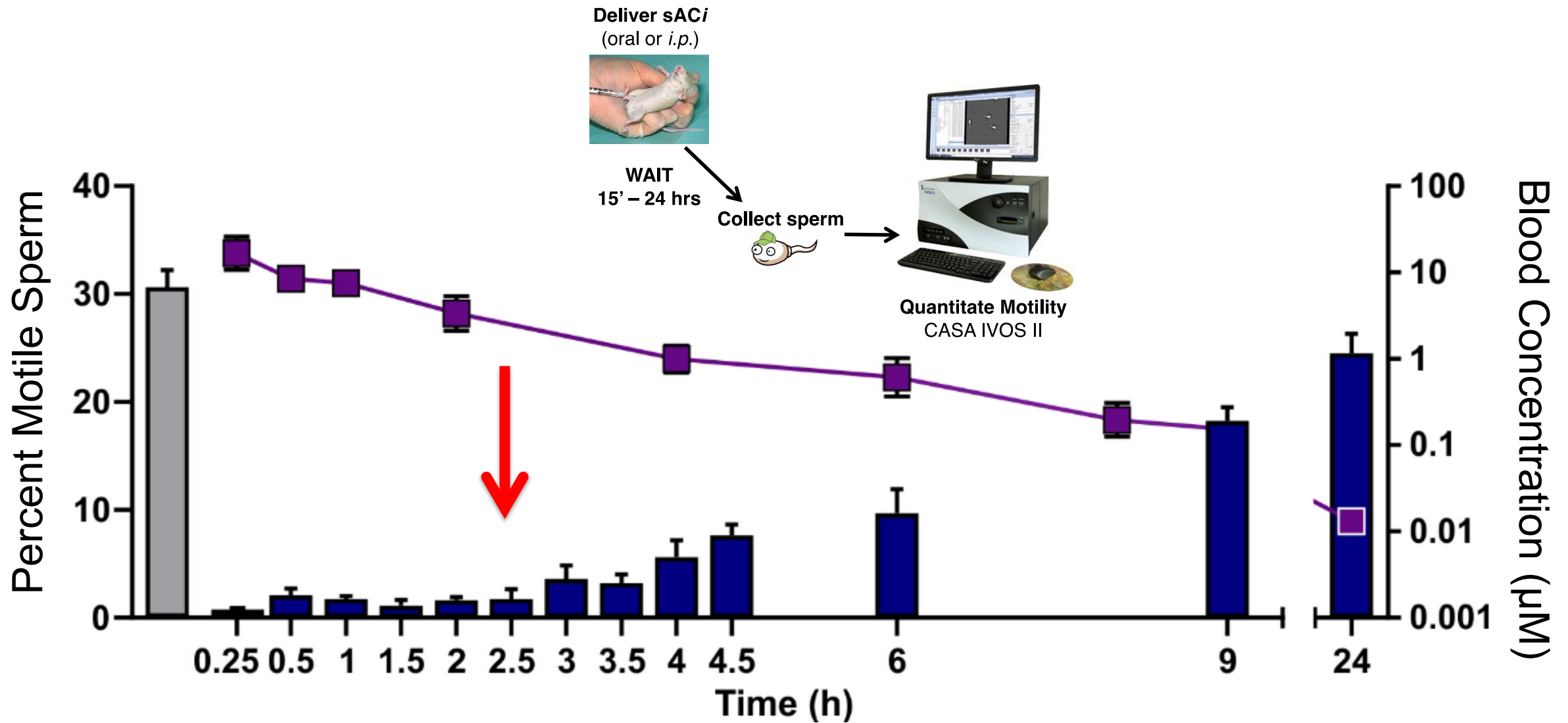
1 hour after sAC inhibitor treated

24 hours after sAC inhibitor treated

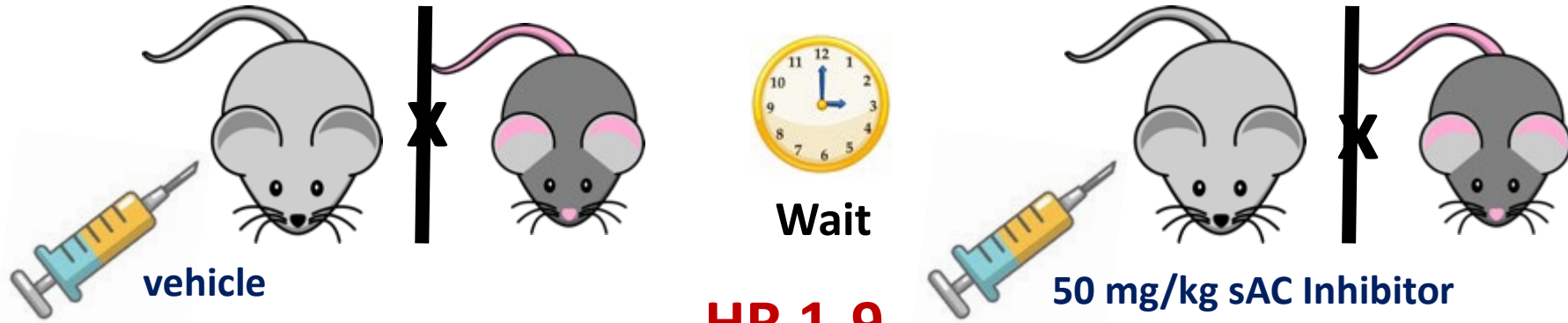


**A SINGLE DOSE of a sAC inhibitor blocks sperm motility**  
**Effect is reversible**

# Ex vivo Motility correlates with Pharmacokinetics

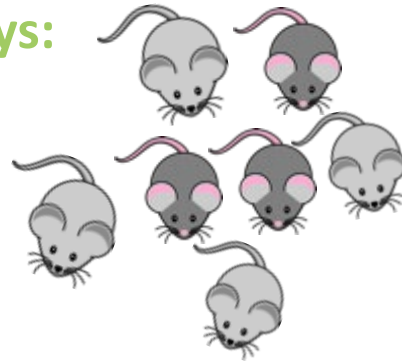


# Timed Mating

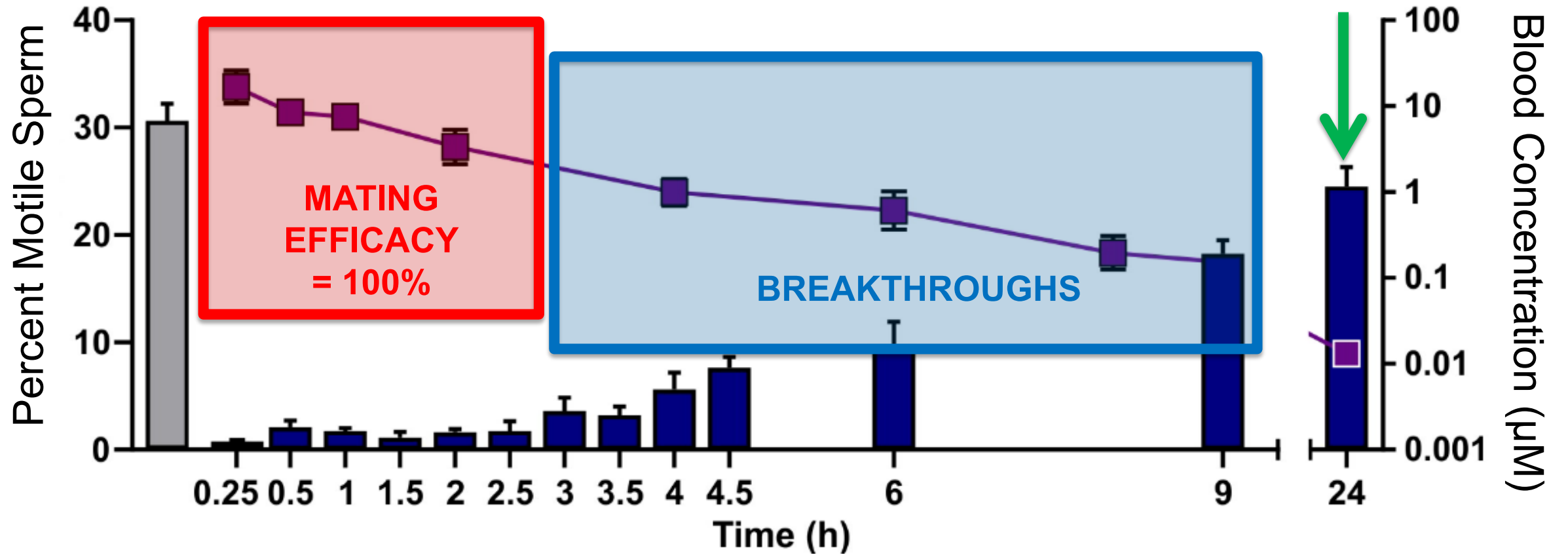


**HR 1-9**  
**HR 0.5-3.5**  
**HR 0.5-2.5**

21 days:



# MATING EFFICACY also correlates with PK



- **MATING BEHAVIORS are NORMAL**
- **Effect is NOT ABORTEFACIENT**
- **BREAKTHROUGHS are NORMAL** (progeny are fertile)
- **Effect is REVERSIBLE: One day after injection mice completely fertile**



# TWO Types of sAC inhibitor Contraceptives IN DEVELOPMENT

## 1. Female intravaginal contraceptive



**ONE RING**  
Dual-Purpose Ring to Prevent HIV and Pregnancy



**MATRIX**

## 2. On-demand birth control pill for men



# LevBuck Laboratory

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## Collaborators

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“sAC TEAM”



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