

Effects of Matrix Metalloproteinase 9 Inhibition on Uterine Contraction and Birth Timing

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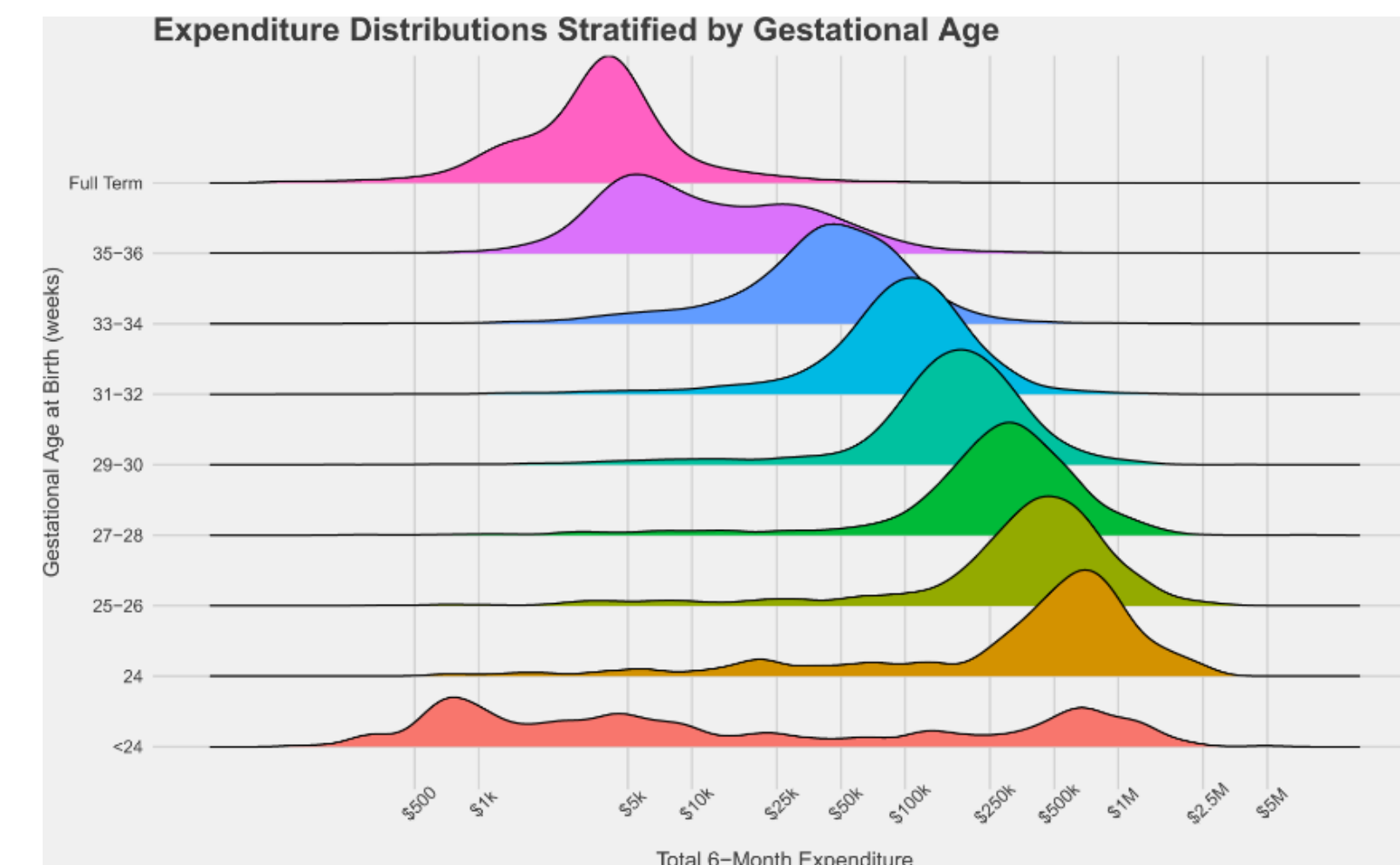


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PRETERM BIRTH

- ❖ Birth Prior to 37 weeks gestation
- ❖ 15 million babies annually
- ❖ Leading cause of mortality for children ages 5 and under
- ❖ Survivors face increased lifetime risk of disabilities
- ❖ Economic Impact: \$26 billion annually



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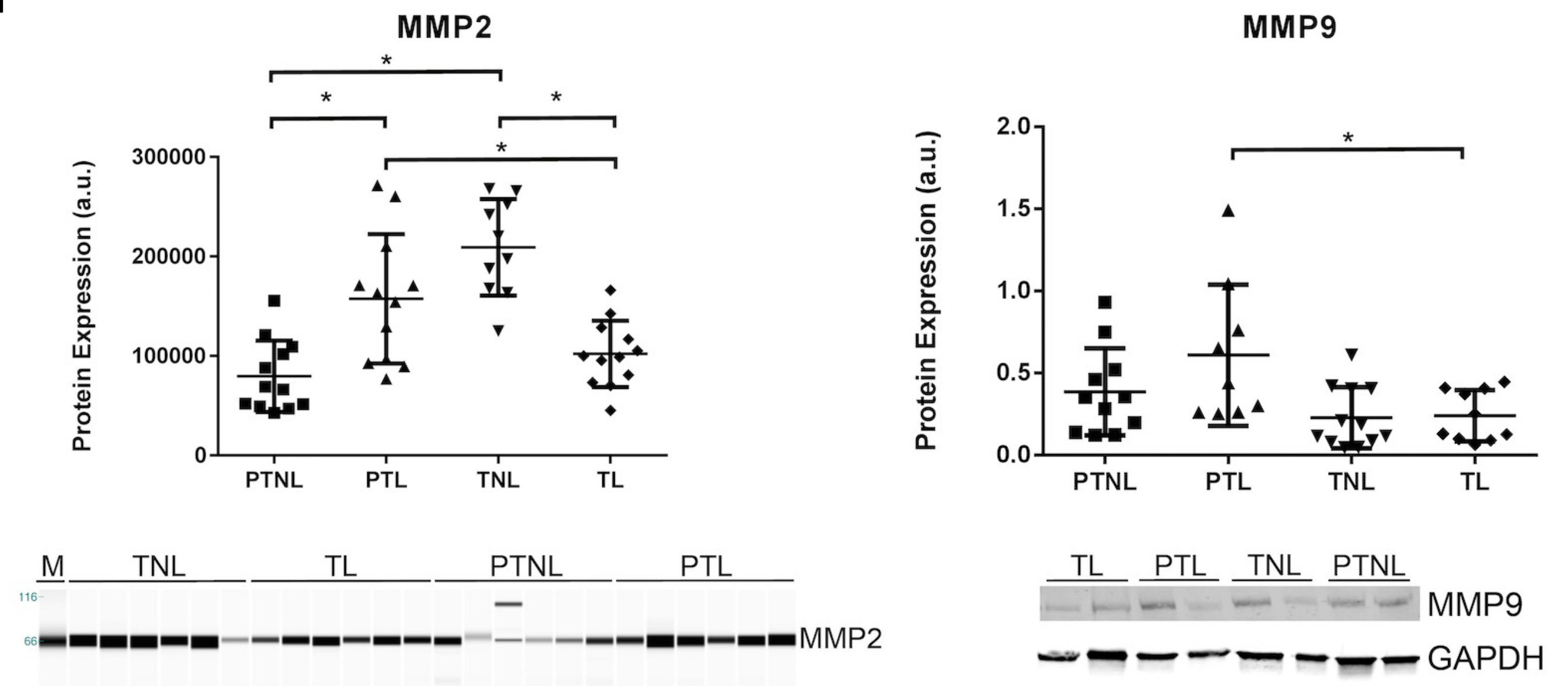
- ❖ World Health Organization Preterm Birth Fact Sheet February 2018
- ❖ Beam et al (2020) *J Perinatol* 40:1091



Christian Copley-Salem

MMP2/9 Expression in Preterm Myometrium

- ❖ MMP9 increased in the amniotic fluid during term and preterm parturition
- ❖ MMPs play a major role in tissue remodeling (cervix)
- ❖ MMP9 regulates contraction in other cell types
- ❖ MMP2/9 inhibitors rapidly affect contractile response in rat myometrium



* $p < 0.05$

- ❖ Ulrich et al.(2020) *Biol Reprod* 100:1597



OBJECTIVES

Determine effects of MMP2/9 on uterine contraction in human myometrium

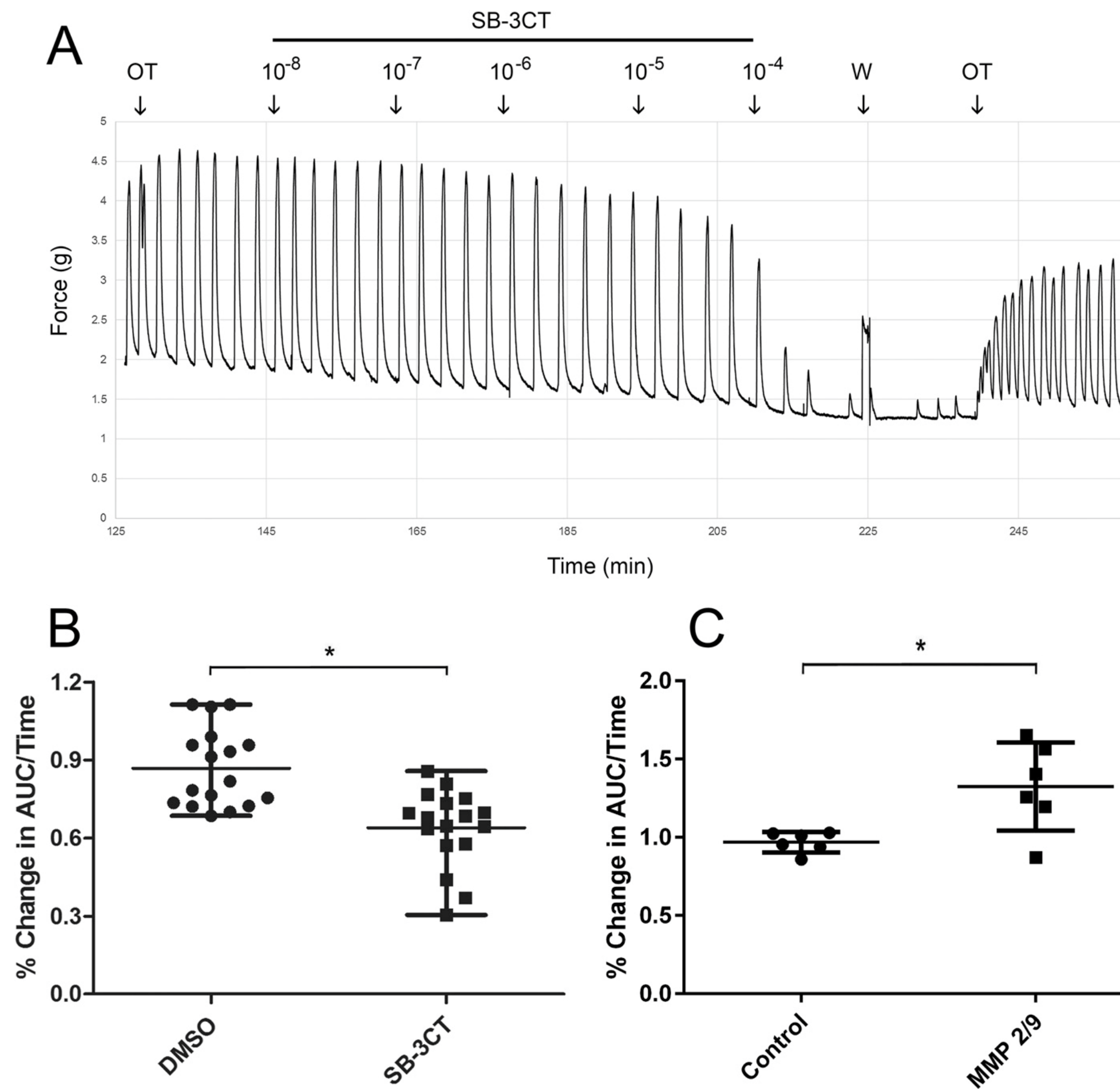
Determine if inhibition of MMP2/9 could delay parturition in mice





Craig Ulrich
Veronica Arinze

MMP2/9 Inhibition Reduces the Contractile Response



*p<0.05



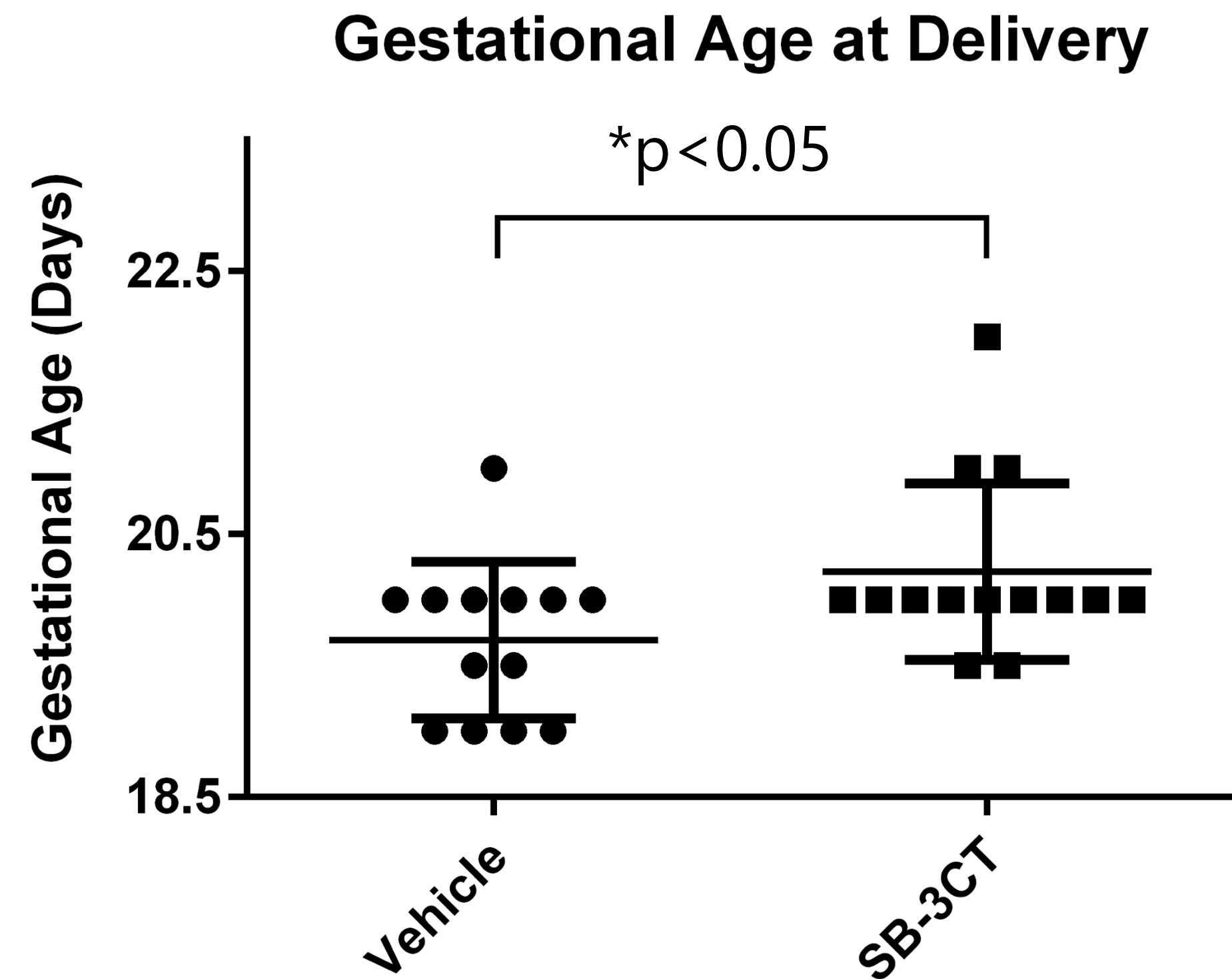
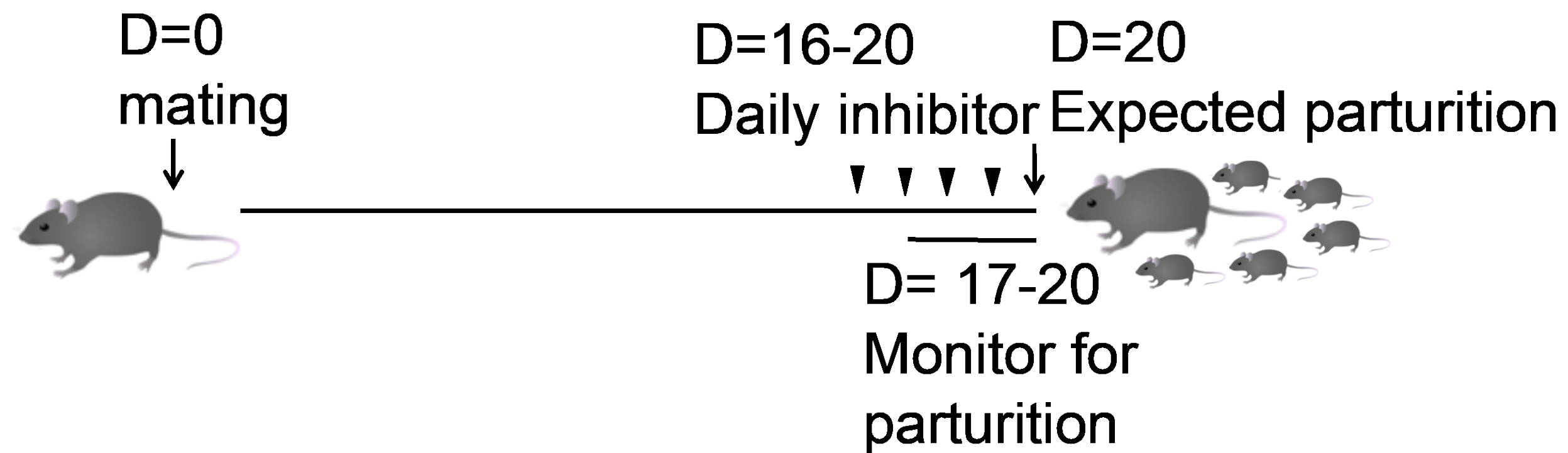
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❖ Ulrich et al.(2020) *Biol Reprod* 100:1597



Veronica Arinze

MMP2/9 Inhibition Delays Parturition

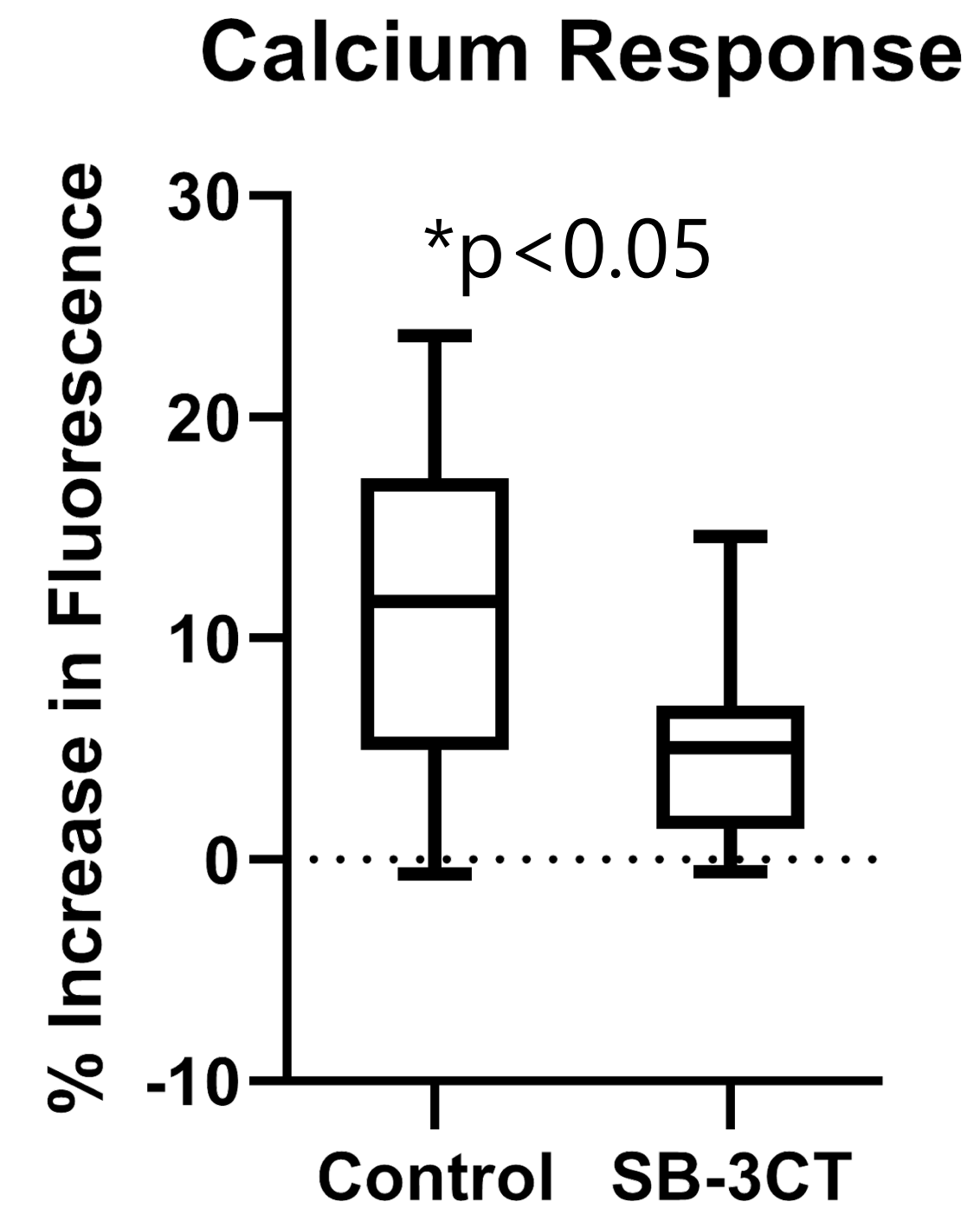
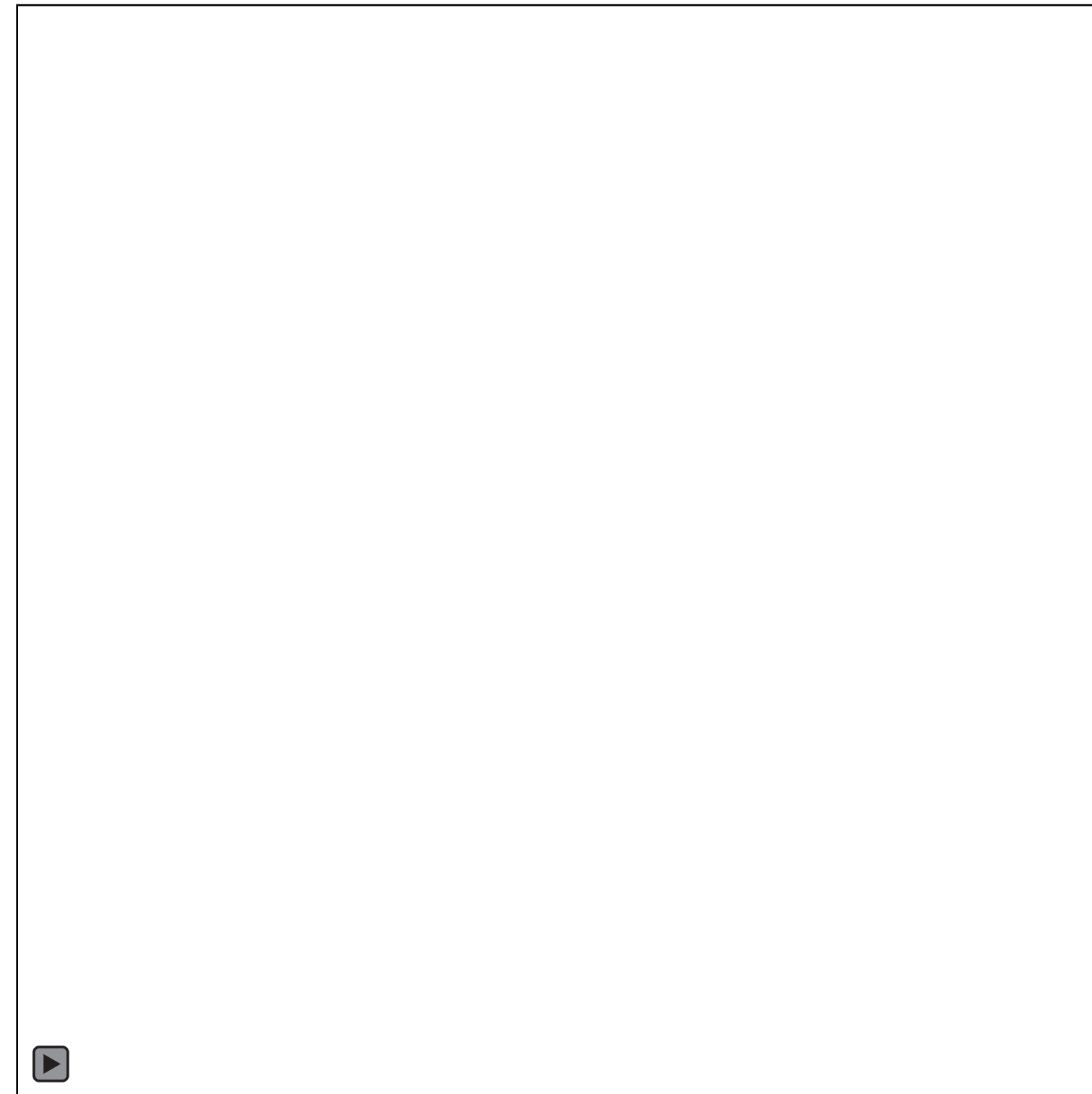


❖ Ulrich et al.(2020) *Biol Reprod* 100:1597

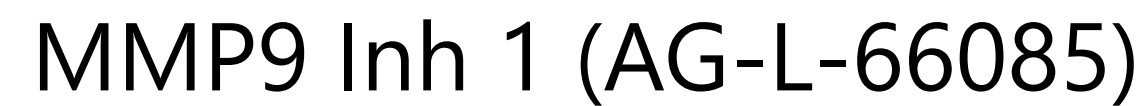


Craig Ulrich, Adrian Pena

MMP2/9 Inhibition Attenuates the Intracellular Ca^{+2} Response



Craig Ulrich



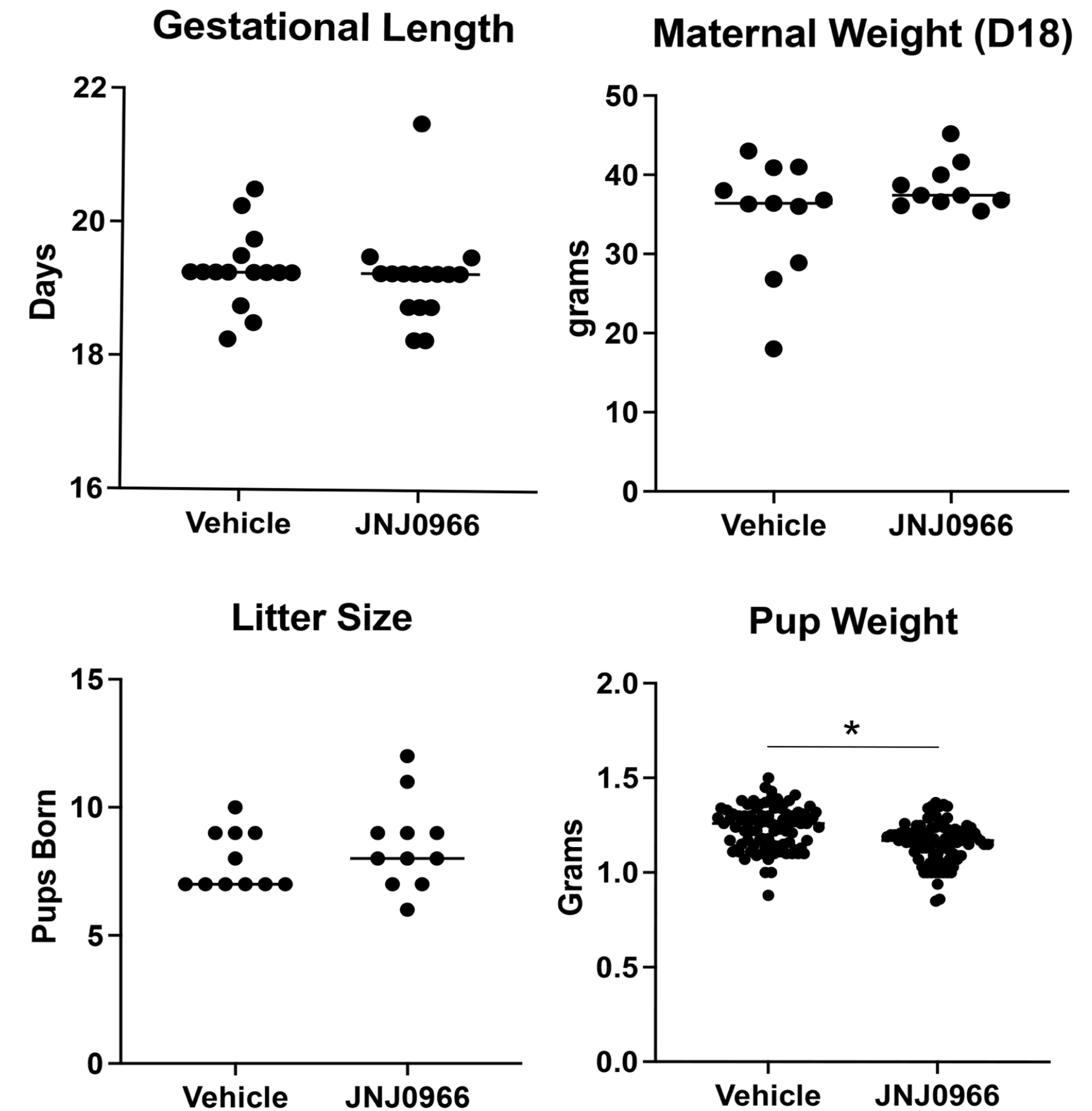
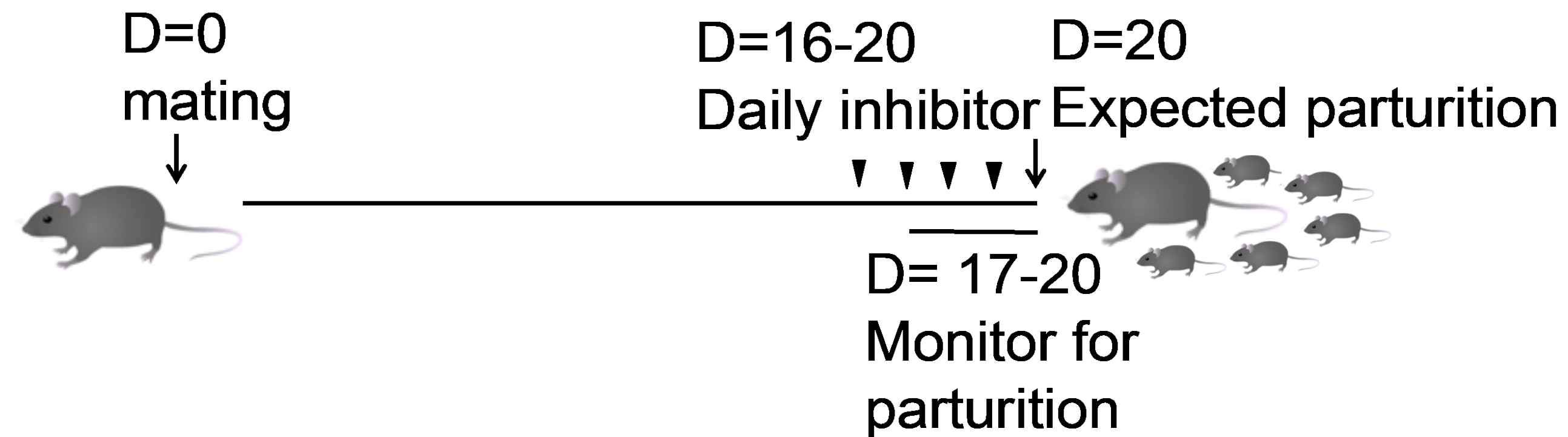
*p<0.01

DMSO Control
1 μ M MMP9 Inhibitor 1
1 μ M MMP9 Inhibitor 1
DMSO Control



Janet Lambert, Heather Burkin
& Craig Ulrich

MMP9-Specific Inhibition

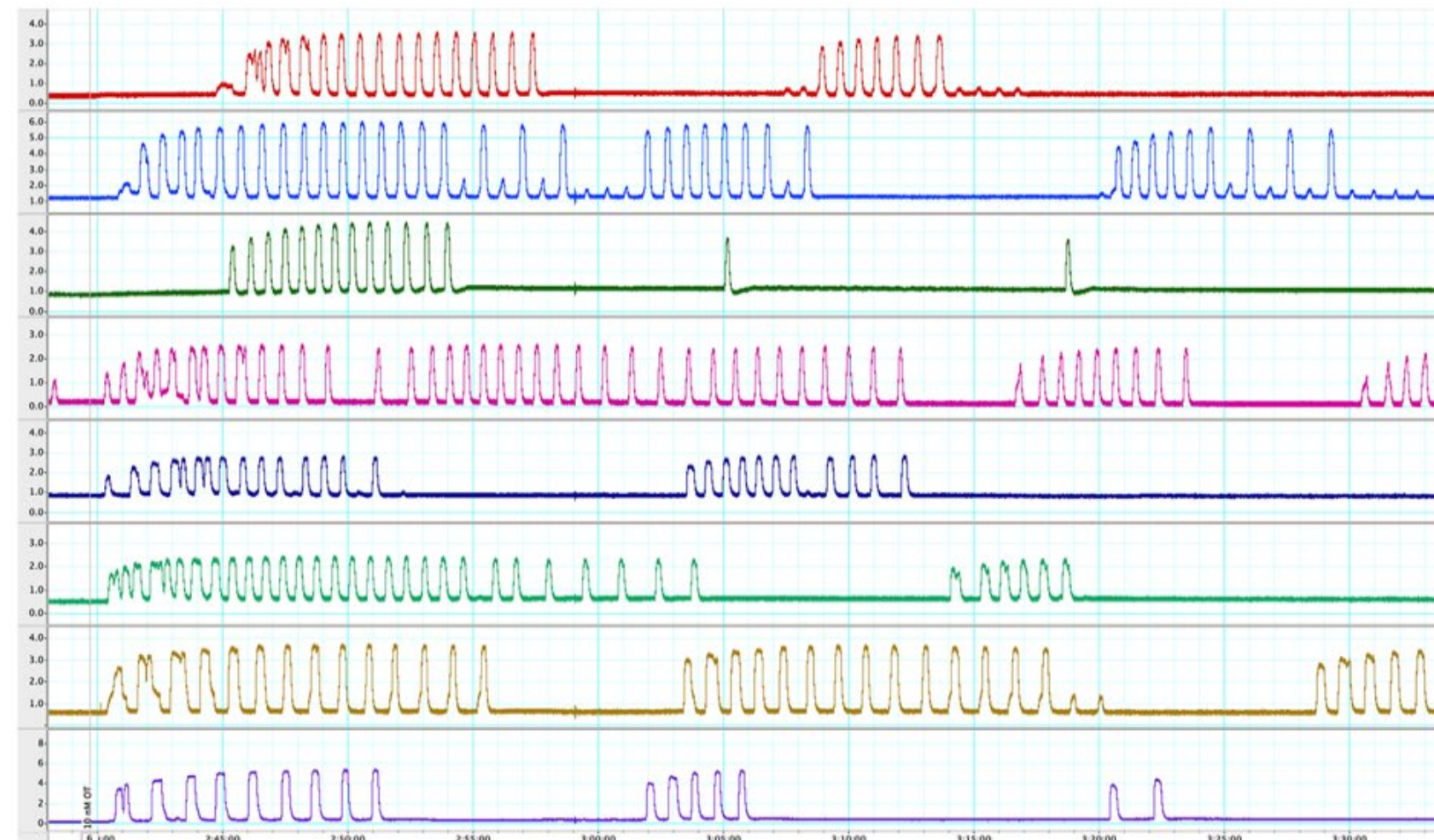


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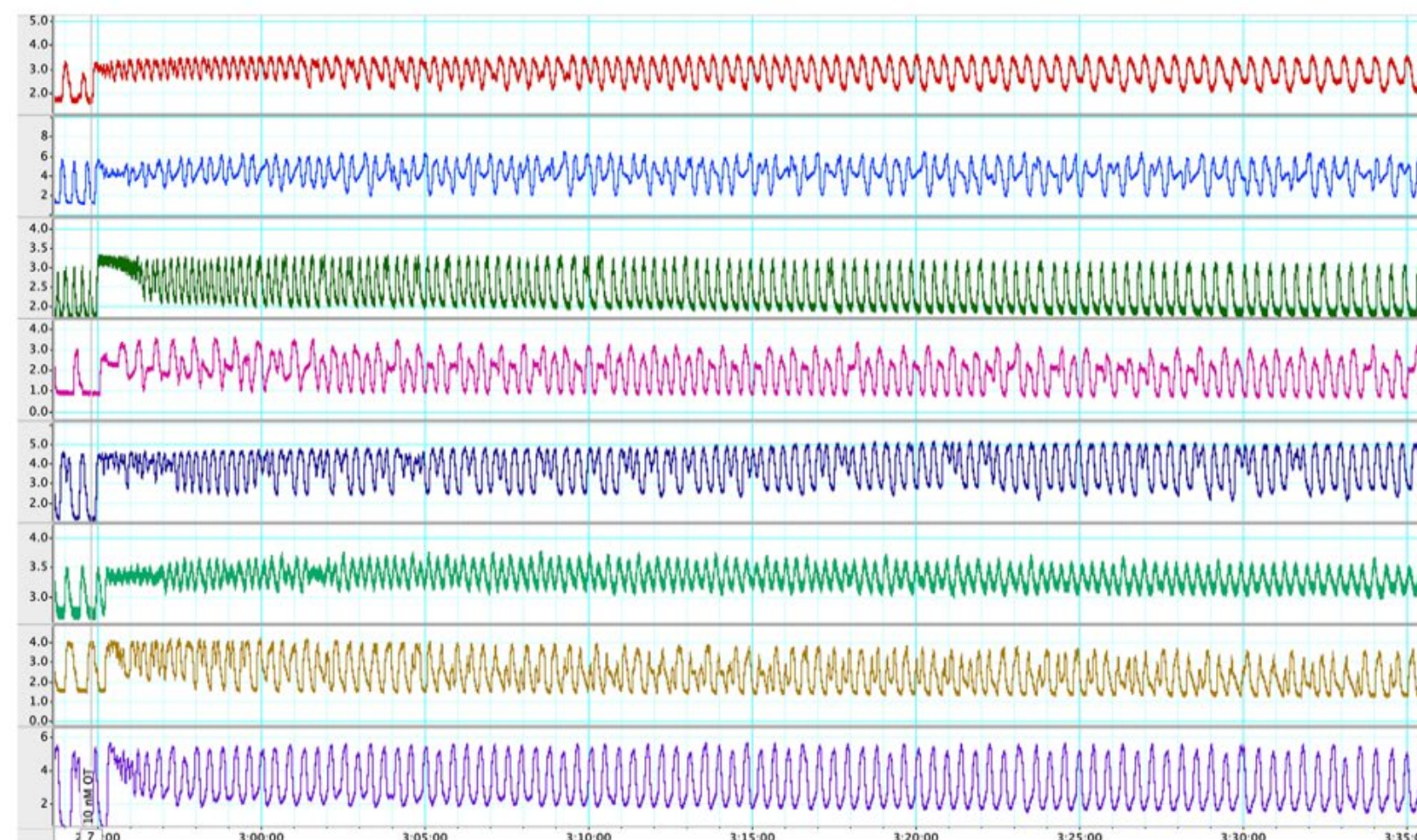
❖ Ulrich, Lambert and Burkin, *unpublished*

Do MMPs Affect Calcium Reuptake?

JNJ0966-Treated



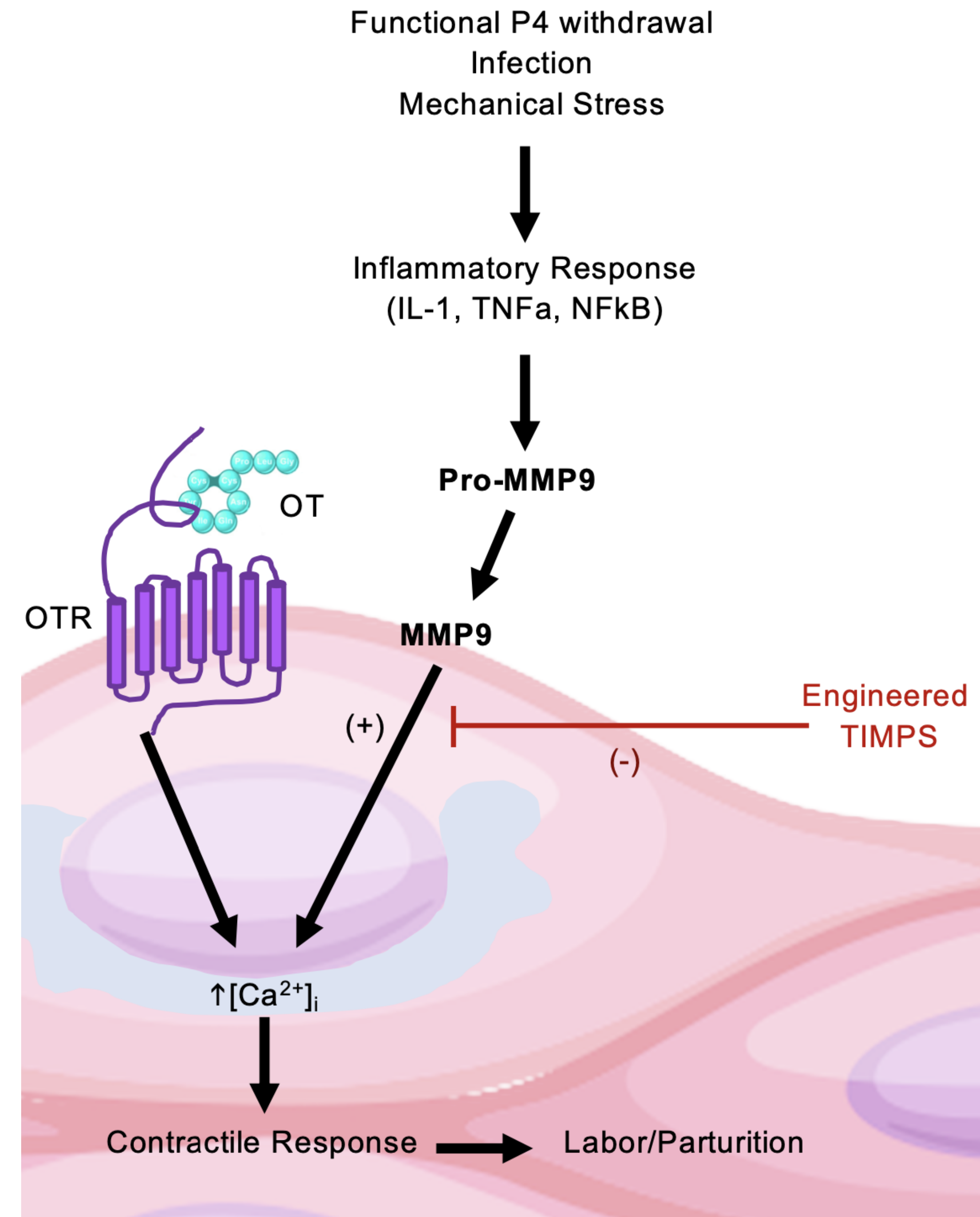
Vehicle-Treated



- ❖ SERCA2a pumps cytosolic Ca^{2+} into the SR to facilitate relaxation.
- ❖ SERCA2a is proteolyzed by MMP-2 in cardiomyocytes.
- ❖ MMP inhibition may prevent SERCA2a degradation.
- ❖ (Roczowsky et al., (2020) *Cardiovasc Res* 116:1021)

FUTURE DIRECTIONS

- ❖ Does MMP inhibition “rescue” preterm birth in mouse models? (Lambert & Burkin)
- ❖ Can TIMPS or engineered TIMP variants inhibit contraction and/or delay parturition? (Samazdeh & Burkin)
- ❖ How does MMP2/9 inhibition affect intracellular Ca^{2+} responses to oxytocin? (Leblanc & Burkin)



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Burkin Lab

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