Late-gestation heat stress: programming effects on three generations

Jimena Laporta
Assistant Professor
Mammary Gland Physiology

ANIMAL & DAIRY SCIENCES
University of Wisconsin-Madison

Section Environmental stress:

Mitigating the adverse effects on animal physiology

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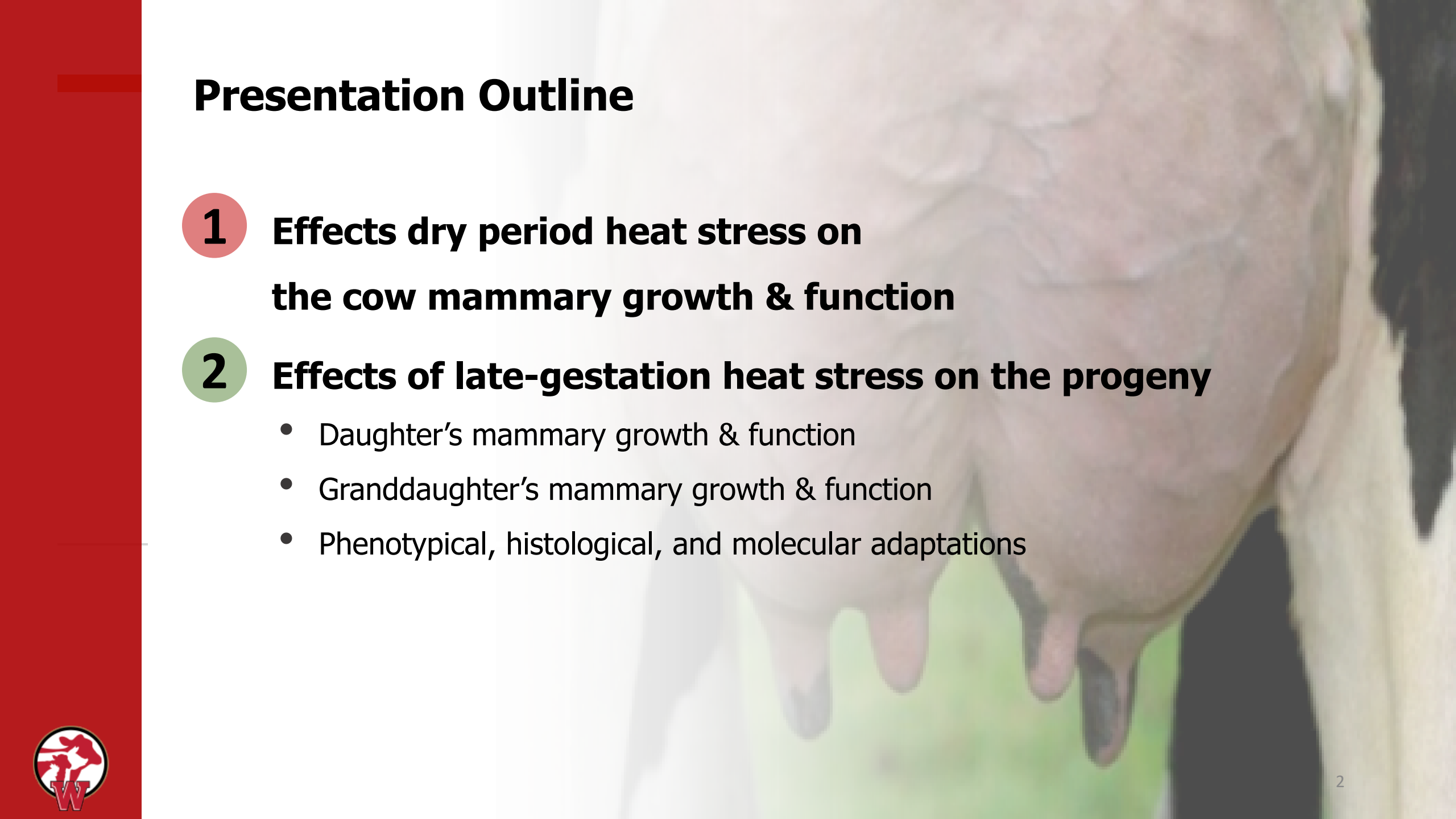
Lyon, France

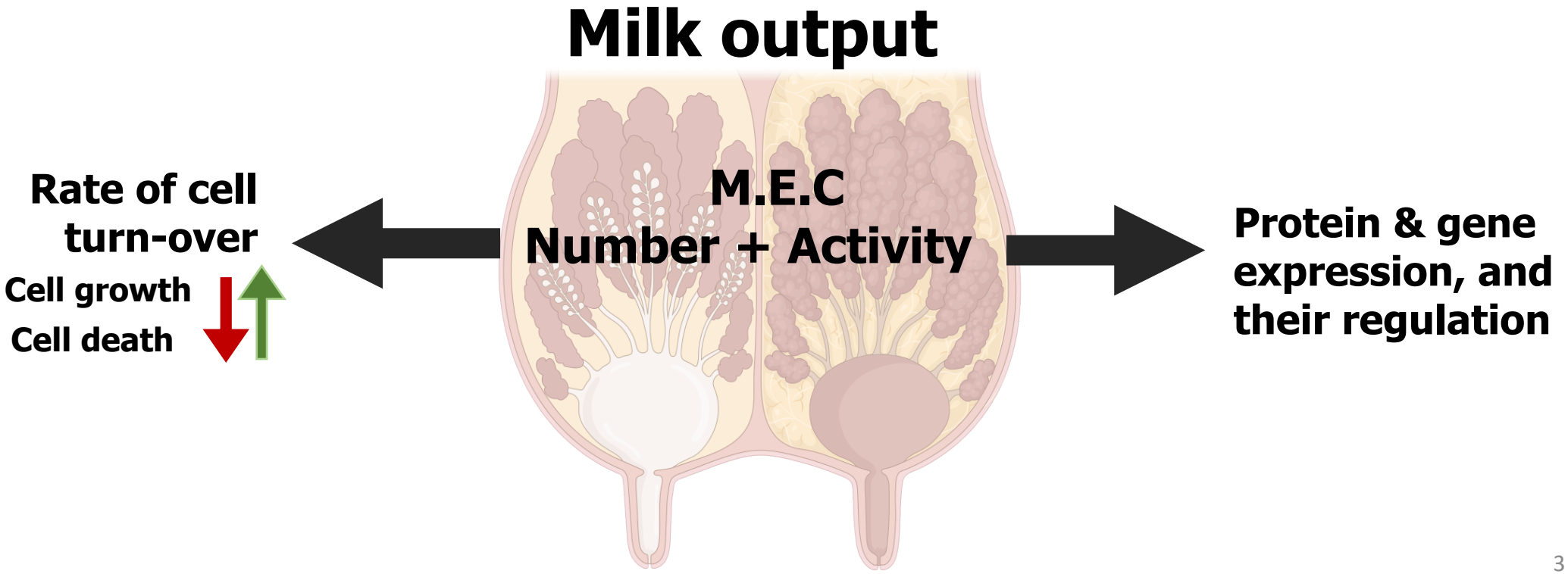
Presentation Outline

1. **Effects dry period heat stress on the cow mammary growth & function**
2. **Effects of late-gestation heat stress on the progeny**
   - Daughter's mammary growth & function
   - Granddaughter's mammary growth & function
   - Phenotypical, histological, and molecular adaptations



Bovine Mammary Gland

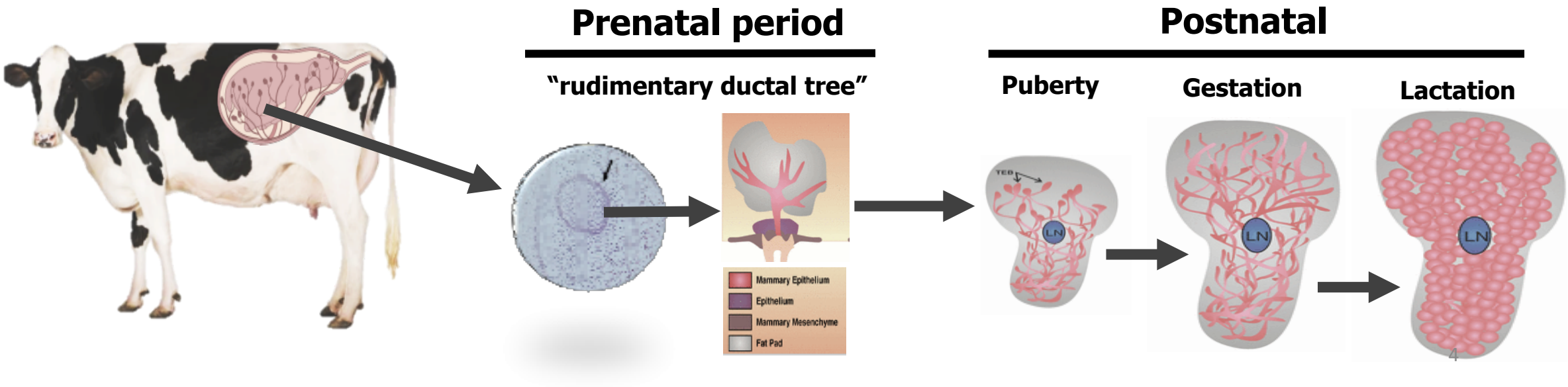
- Unique and fascinating organ!
- Undergoes repeated cycles of functional differentiation and regression over the lifetime.
- Most of its functional growth and development occur under the influence of hormones and **environmental factors that can influence its developmental trajectory**.



Mammary Early-life Development

- Begins before the heifer is born (prenatally, in utero)
- Highly regulated, sensitive, and dynamic processes lead to a **"rudimentary" ductal/epithelial system that gives rise to the mammary parenchyma during later developmental stages** (i.e. lactation)

- **Hypothesis: the degree of development in early life can dictate future potential**
- **Maternal stressors can derail key developmental processes of the fetal mammary gland**



Heat Stress in Dairy Cattle

- Largest challenge affecting the dairy industry worldwide
- Modern high-producing dairy cows are becoming more susceptible!
- The focus of heat stress research and mitigating strategies: lactating cow

- **Heat stress does not discriminate**
  - Impact physiology & productivity at all ages & physiological status
  - Not a priority when it comes to heat abatement on farm

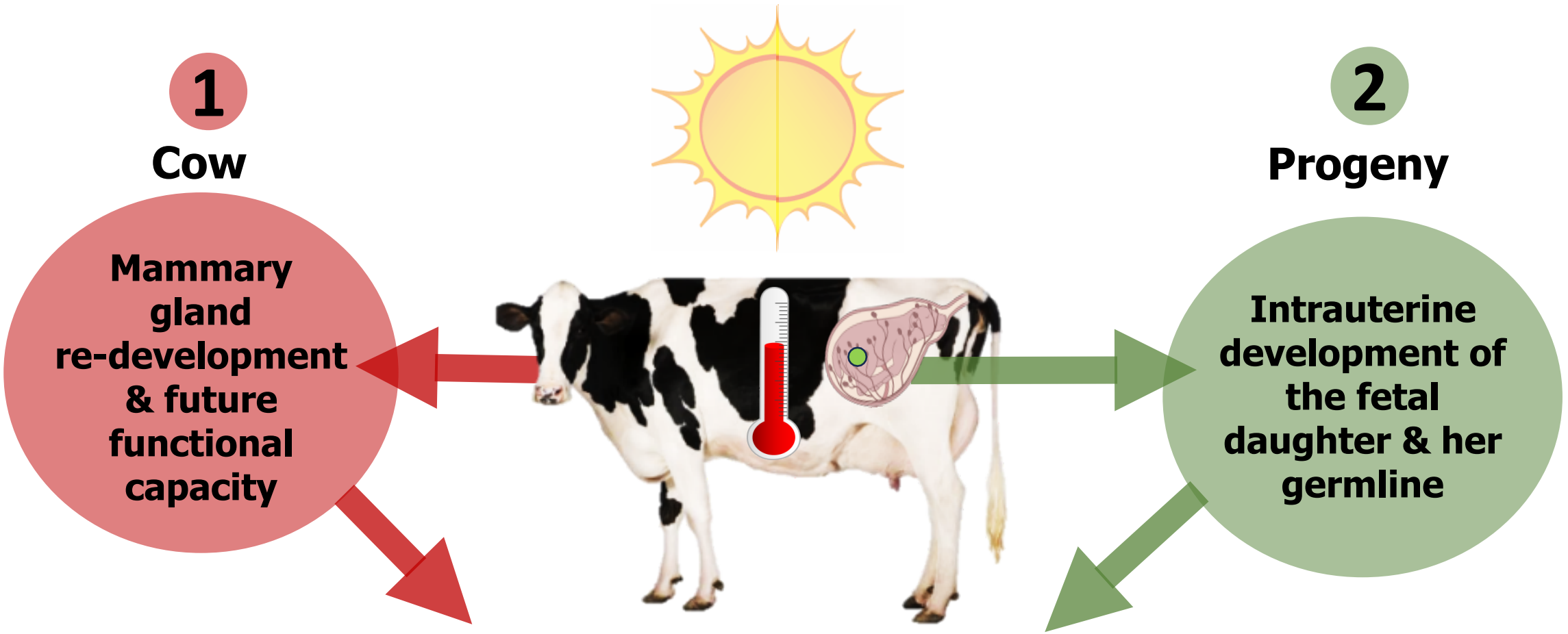
Calf

Heifer

Dry cow

Lactating cow

Three programming events in a dry-pregnant cow



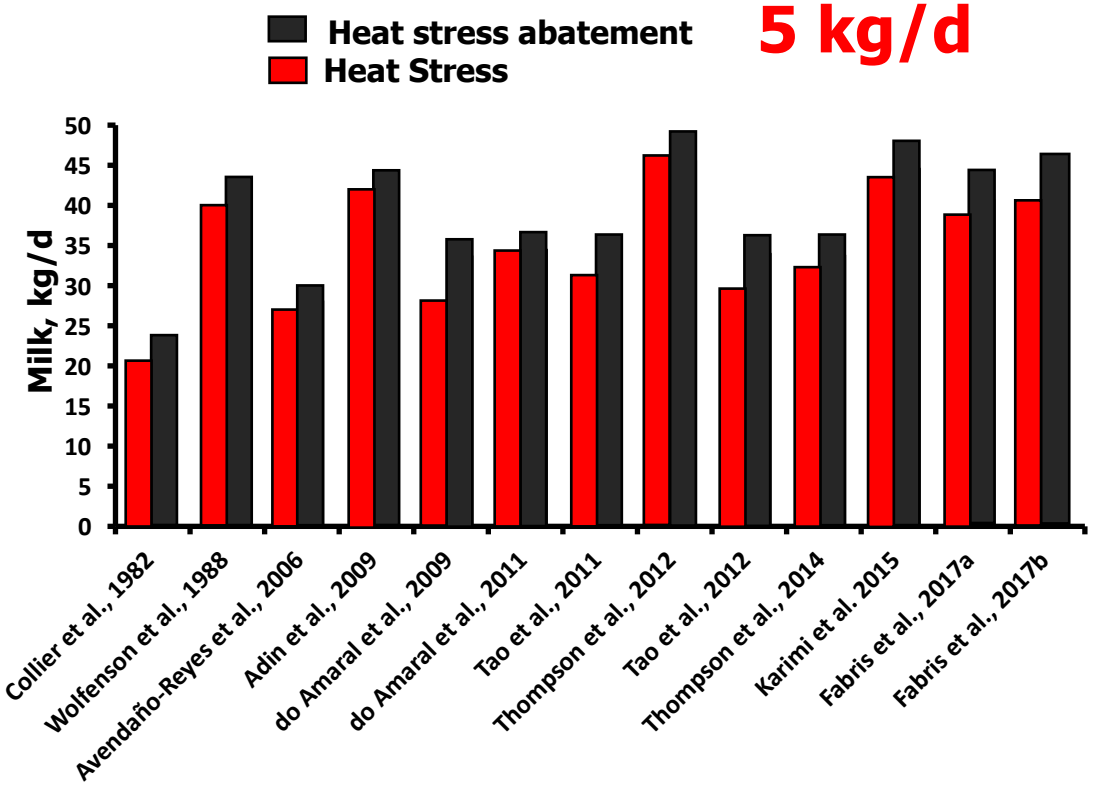
Heat stress compromises the dam's productivity in her upcoming lactation & lifetime productivity of her progeny

1 Effects on the Cow

Dry cow

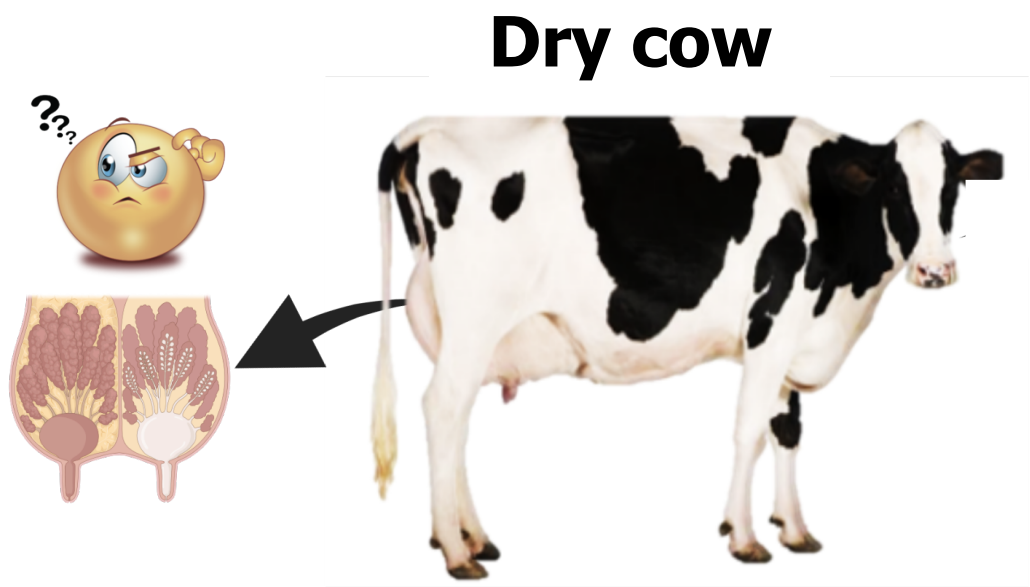
Don’t need or benefit from cooling
They are more thermotolerant
It is not profitable to cool them
There is a lack of space or infrastructure

Avg. milk loss in the next lactation

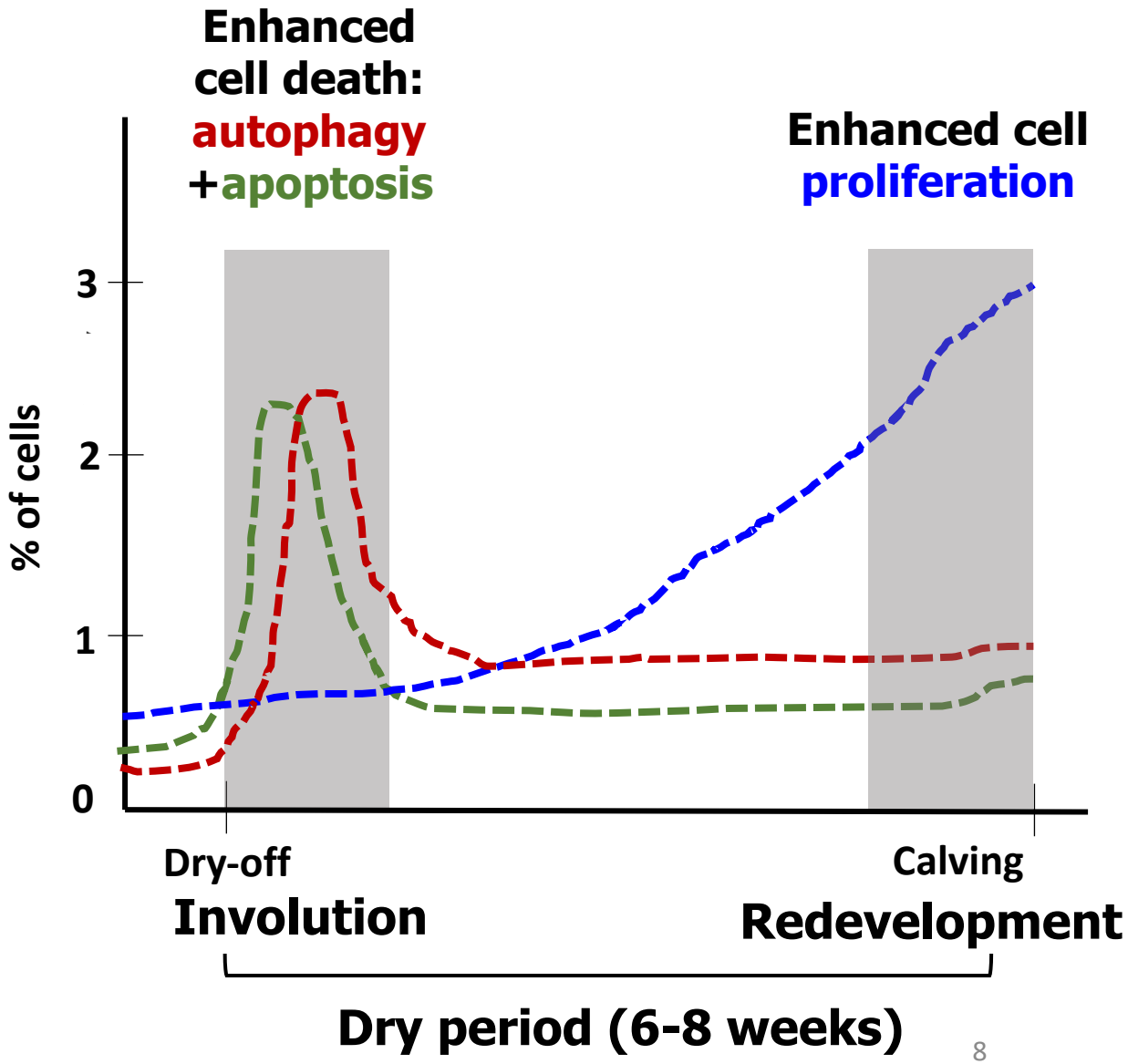


Adapted from: Dahl, Tao & Laporta (2019)

1 Effects on the Cow

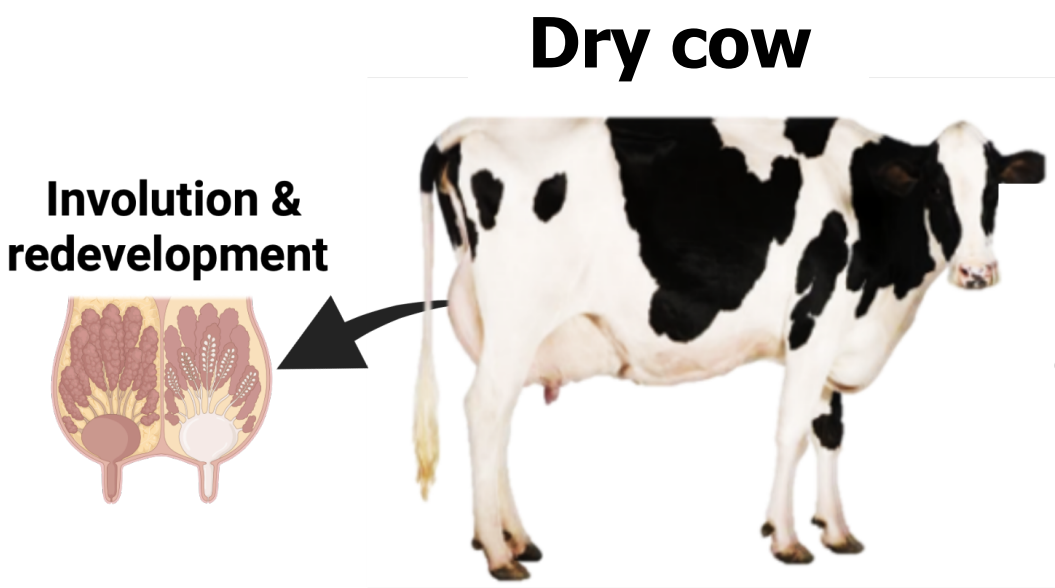


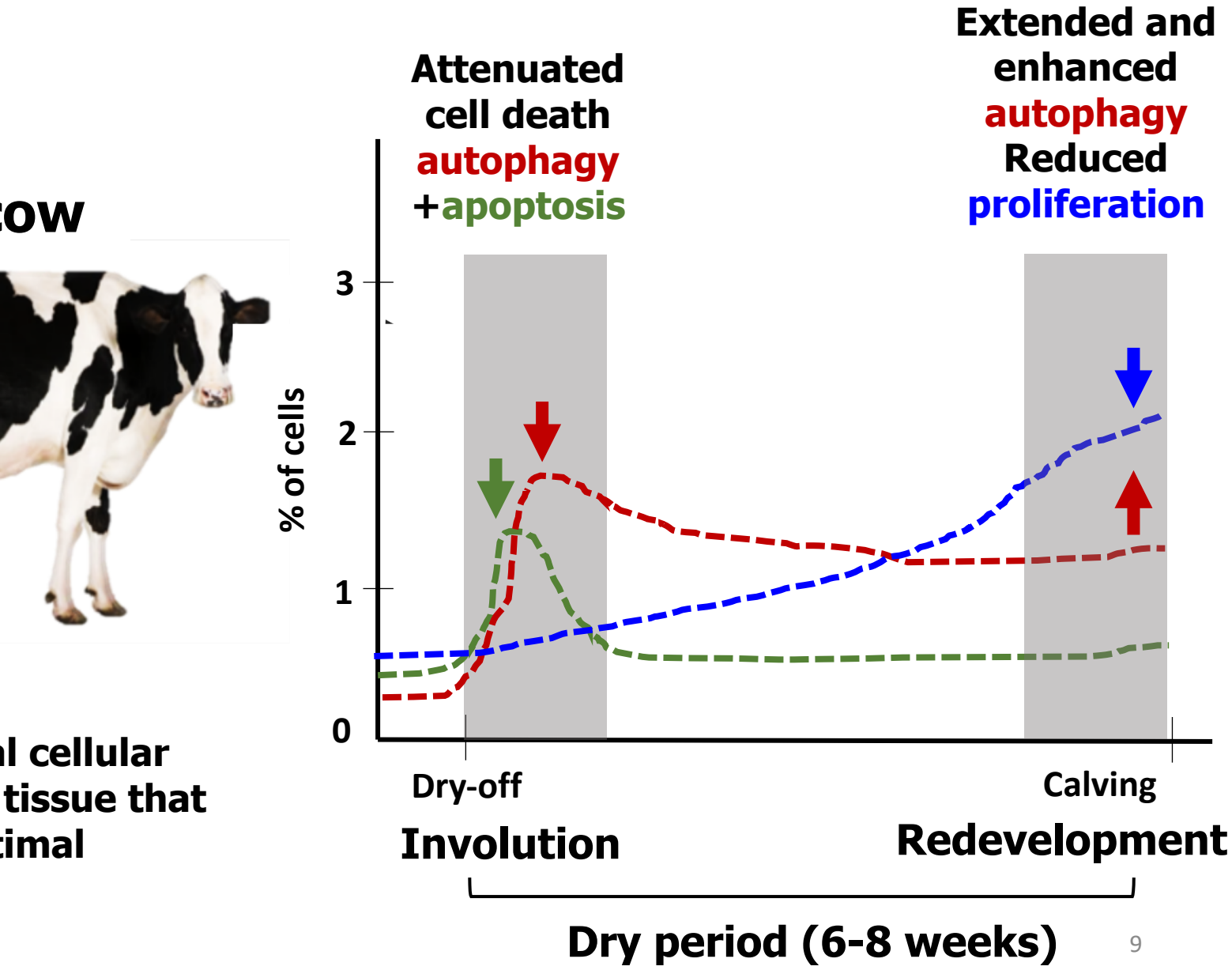
The mammary gland undergoes drastic microstructural, cellular & molecular changes during the dry period.



Adapted from Tao et al. (2013)

1 Effects on the Cow

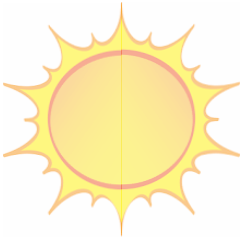




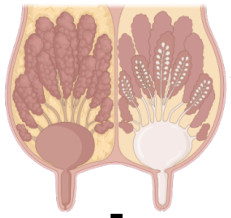
Heat stress derails normal cellular processes in the mammary tissue that are necessary for optimal regeneration

Tao et al. (2013); Wohlgemuth et al. (2016)

1 Effects on the Cow



Involution & redevelopment



Biopsy
3, 7, 14, 35

Dry cow

Changes the transcriptomic profile

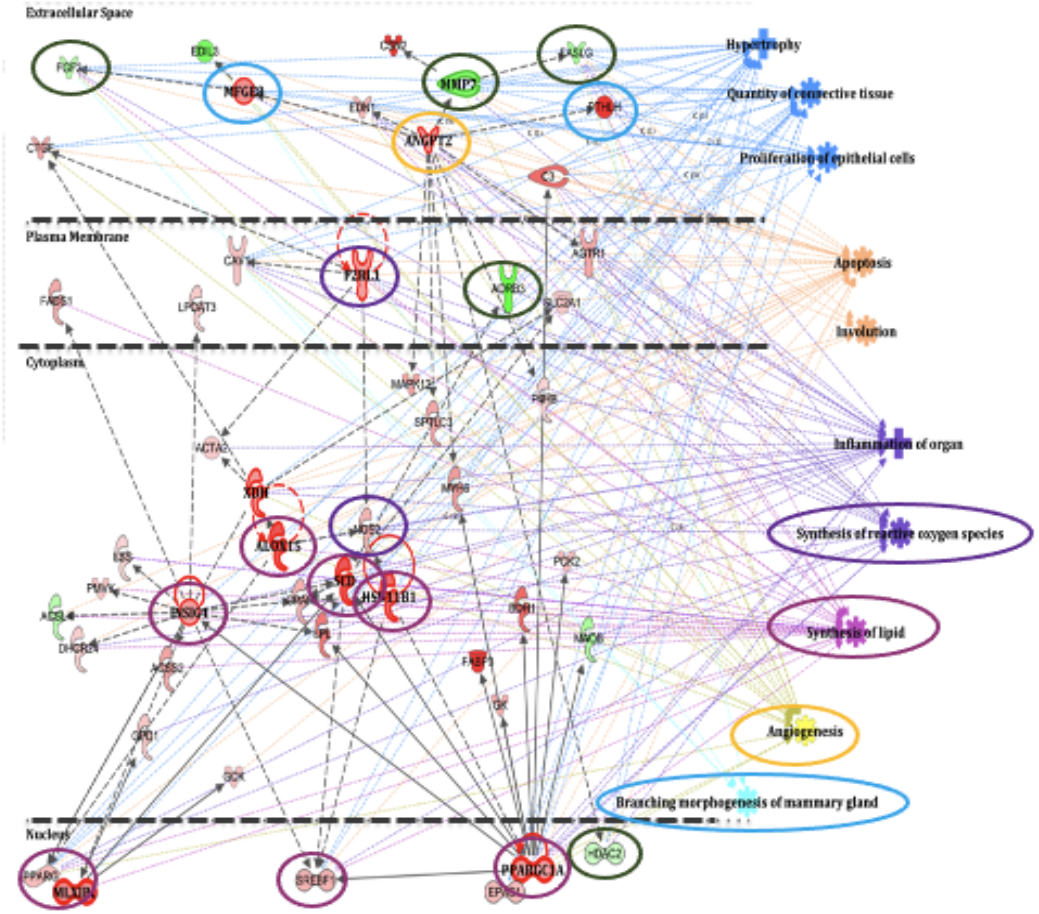
- Quantity of connective tissue
- Cell proliferation and apoptosis
- Angiogenesis
- Inflammation & synthesis of ROS
- Branching morphogenesis

SCIENTIFIC REPORTS

RNA-Seq reveals novel genes and pathways involved in bovine mammary involution during the dry period and under environmental heat stress

Bethany Dado-Senn[1], Amy L. Skibiel[1], Thiago F. Fabris[1], Y. Zhang[2], Geoffrey E. Dahl[1], Francisco Peñagaricano[1,3] & Jimena Laporta[1]

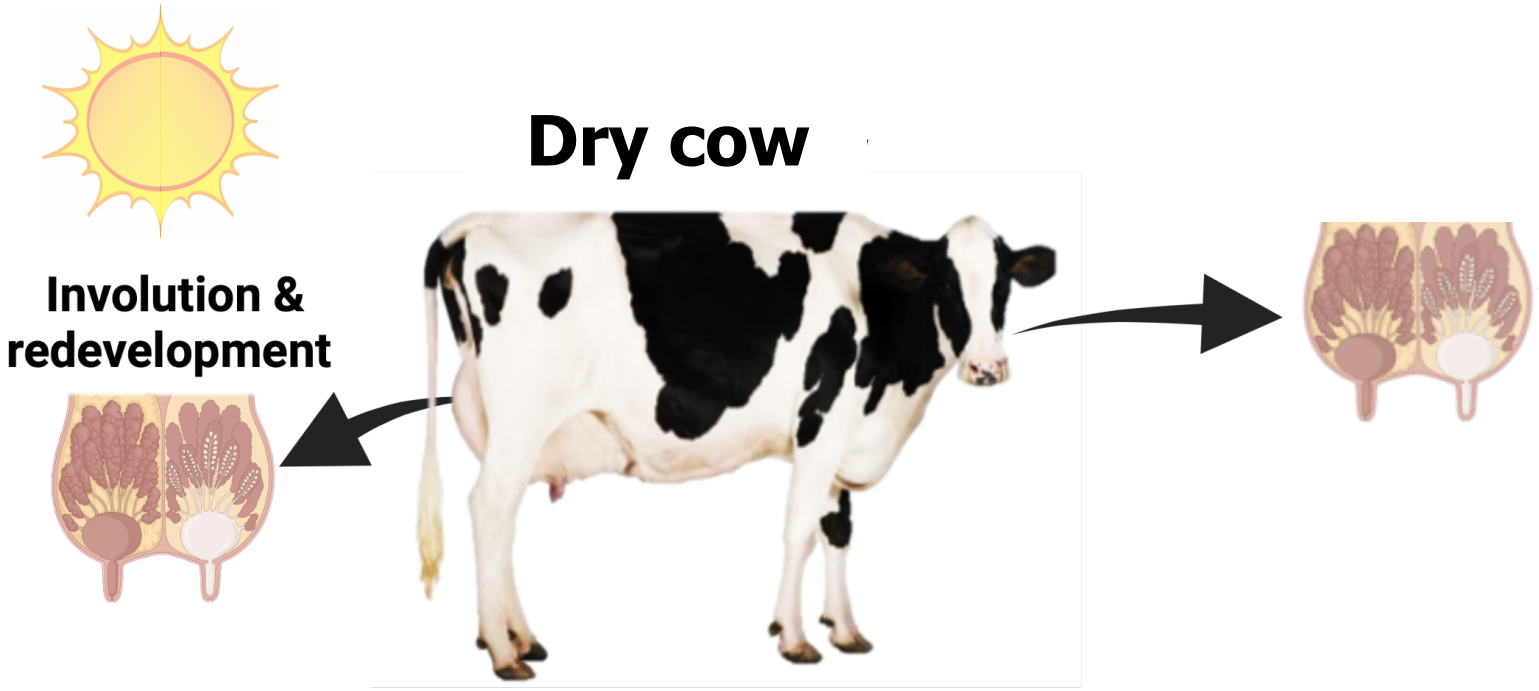
Interactions between upstream regulators, downstream genes, and physiological functions impacted by heat stress



upstream regulators and summary network HT relative to CL cows [Red=up; Green=down]

Dado-Senn et al., (2018a)

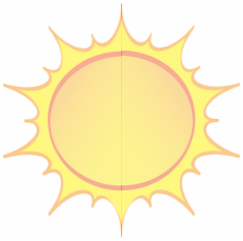
1 Effects on the Cow



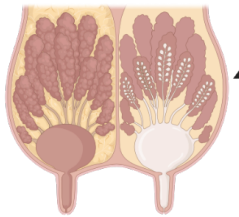
Carry-over effects on the mammary gland microstructure, cellular & processes in the subsequent lactation?

Dado-Senn et al., (2018b)

1 Effects on the Cow



Involution & redevelopment



Dry cow

RESEARCH ARTICLE

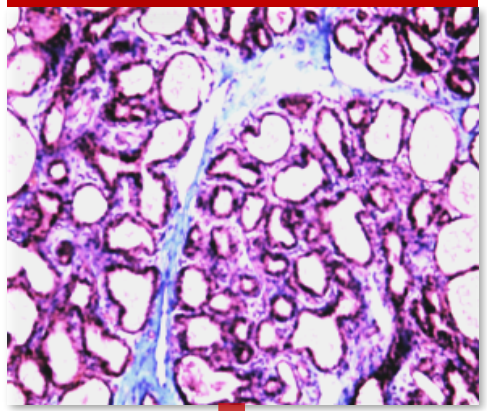
Dry period heat stress induces microstructural changes in the lactating mammary gland

Bethany Dado-Senn, Amy L. Skibiel*, Thiago F. Fabris, Geoffrey E. Dahl, Jimena Laporta*

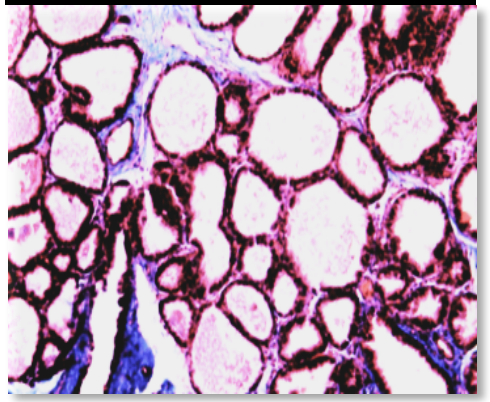
PLOS ONE

Lactation days 14, 42, 84

HS while dry



CL while dry



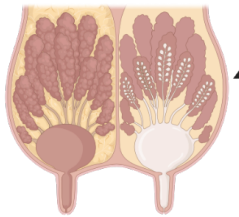
Alveoli: milk producing structures
MEC: milk secretory units

- Fewer alveoli & fewer MEC
- Lower rate of proliferation
- More connective tissue
- Less efficient mammary glands
- Less milk synthetic & storage capacity

Dado-Senn et al., (2018b)

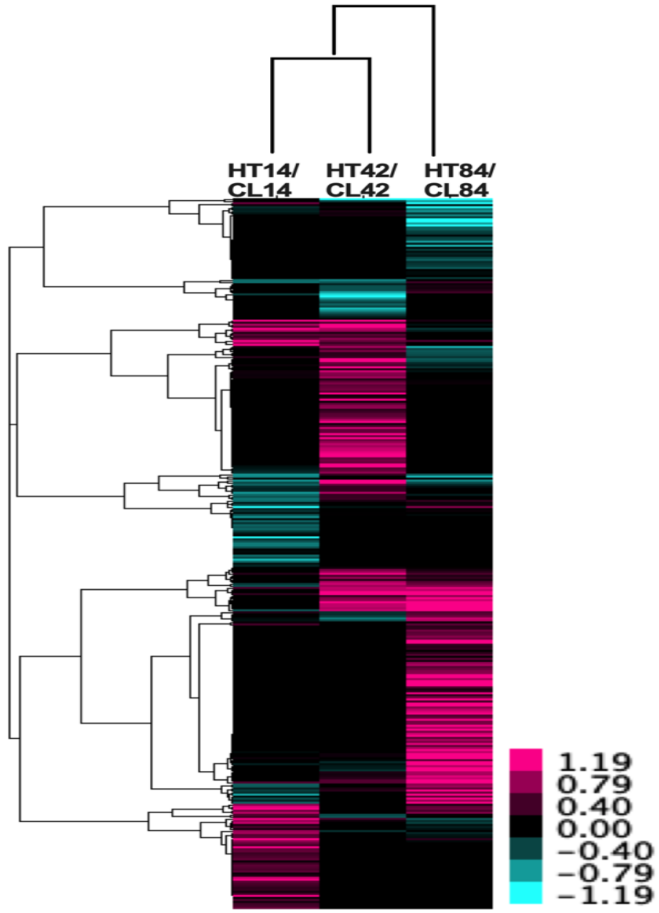
1 Effects on the Cow

Involution & redevelopment



Dry cow

- Immune function
- Cell structure
- Cell organization
- Cell apoptosis



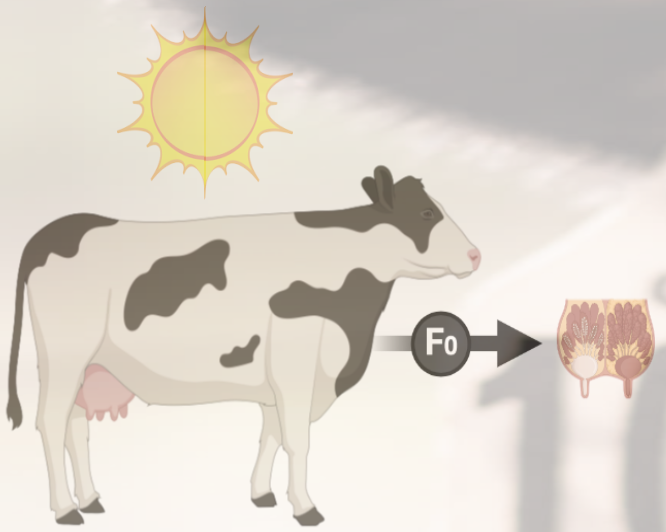
increased or decreased proteins in HS relative to CL

250 differentially abundant proteins reflecting long-lasting changes in the mammary gland of heat-stressed cows

Skibiel et al (2022)

Summary 1 → effects on the cow

Exposure to heat stress during the dry period F_0



Derails mammary gland involution

- Cell turn over & branching morphogenesis

Carry-over effects on the mammary gland in the subsequent lactation

- **Histological**
  - Fewer, smaller alveoli with fewer MECs
  - Less synthetic capacity
- **Molecular**
  - dysregulation of immune function
  - tissue remodeling
  - impaired protein synthesis and metabolism

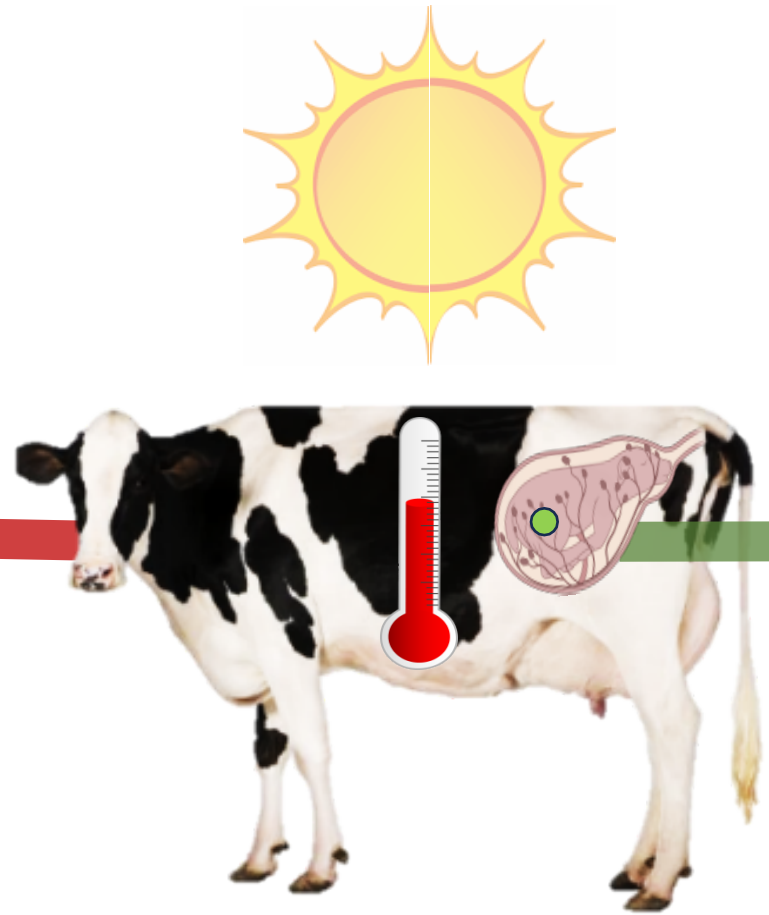
Lower yields due to prior exposure to heat stress during the dry period

Three programming events in a dry-pregnant cow

1

Cow

Mammary re-development & future functional capacity



2

Progeny

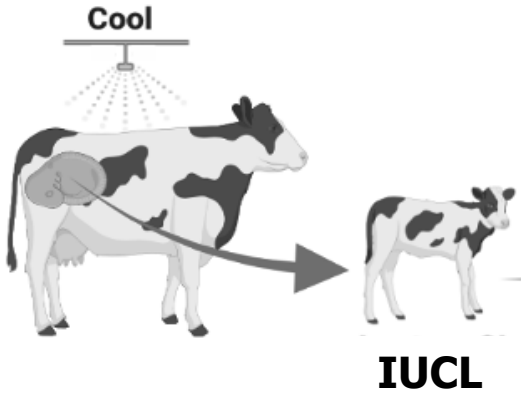
Suboptimal intrauterine environment **for the developing daughter & her germline**

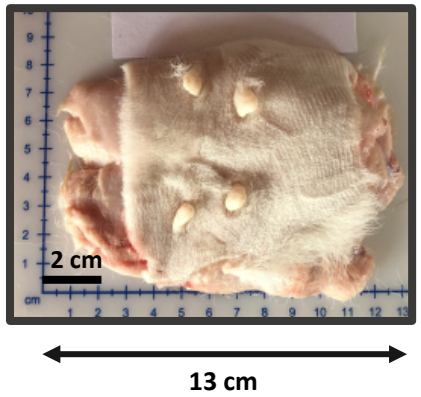
Daughters [F_1]

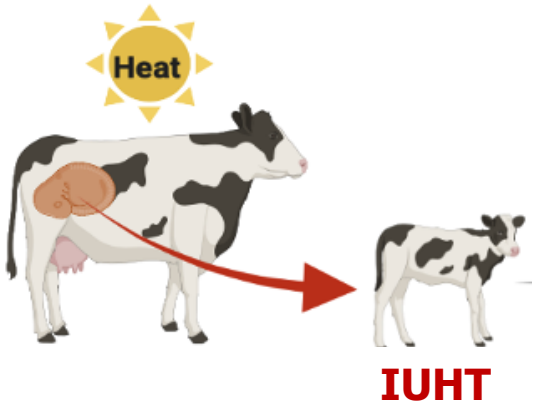
Granddaughters [F_2]

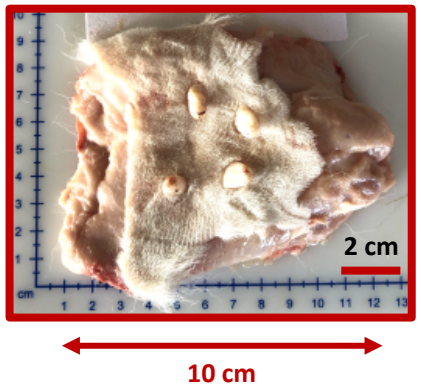
2 Effects on the progeny: Daughters [F_1]

Whole udder harvest @ birth









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Board Invited Reviews

In utero hyperthermia in late gestation derails dairy calf early-life mammary development

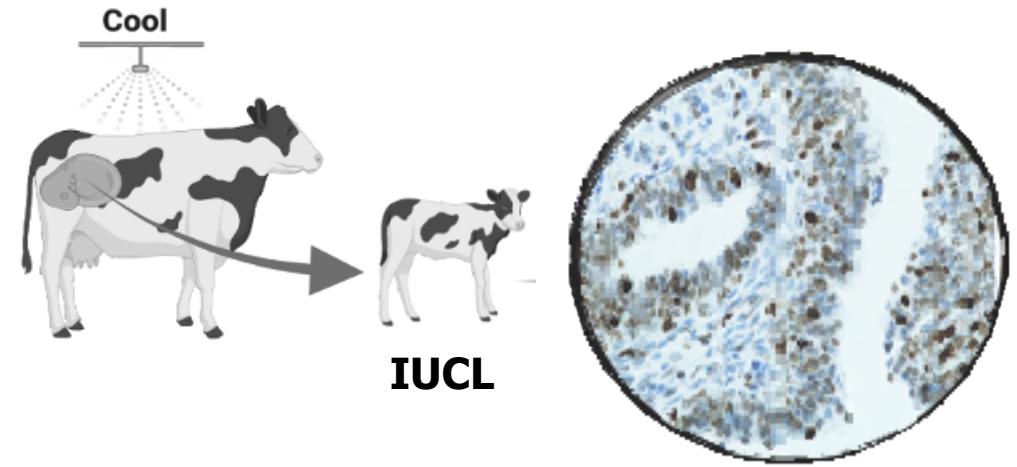
Bethany M. Dado-Senn,[†] Sena L. Field,[†] Brittney D. Davidson,[†] Geoffrey E. Dahl,[‡] and Jimena Laporta[†]

[†]Department of Animal and Dairy Sciences, University of Wisconsin-Madison, Madison, WI 53706, USA
[‡]Department of Animal Sciences, University of Florida, Gainesville, FL 32611, USA

Adapted from: Dado-Senn et al., (2022)

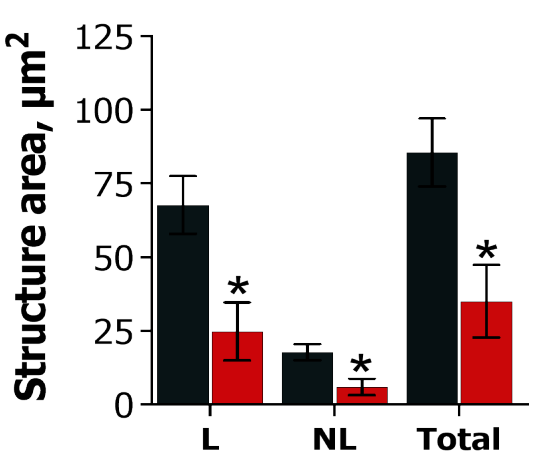
2 Effects on the progeny: Daughters [F_1]

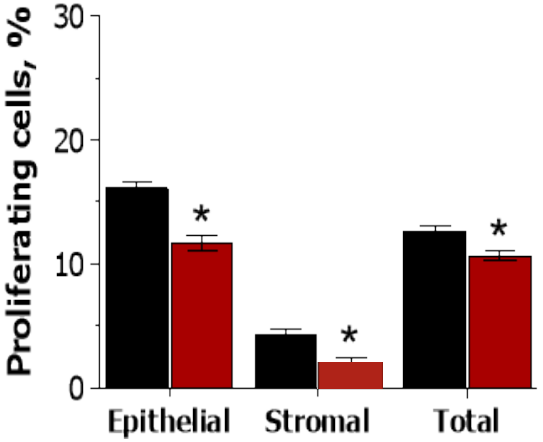
Parenchyma microstructure & cell proliferation @ birth



In utero heat-stressed heifers had:

- Less ductal-epithelial structures
- Underdeveloped ductal structures
- Fewer cells proliferating in all compartments

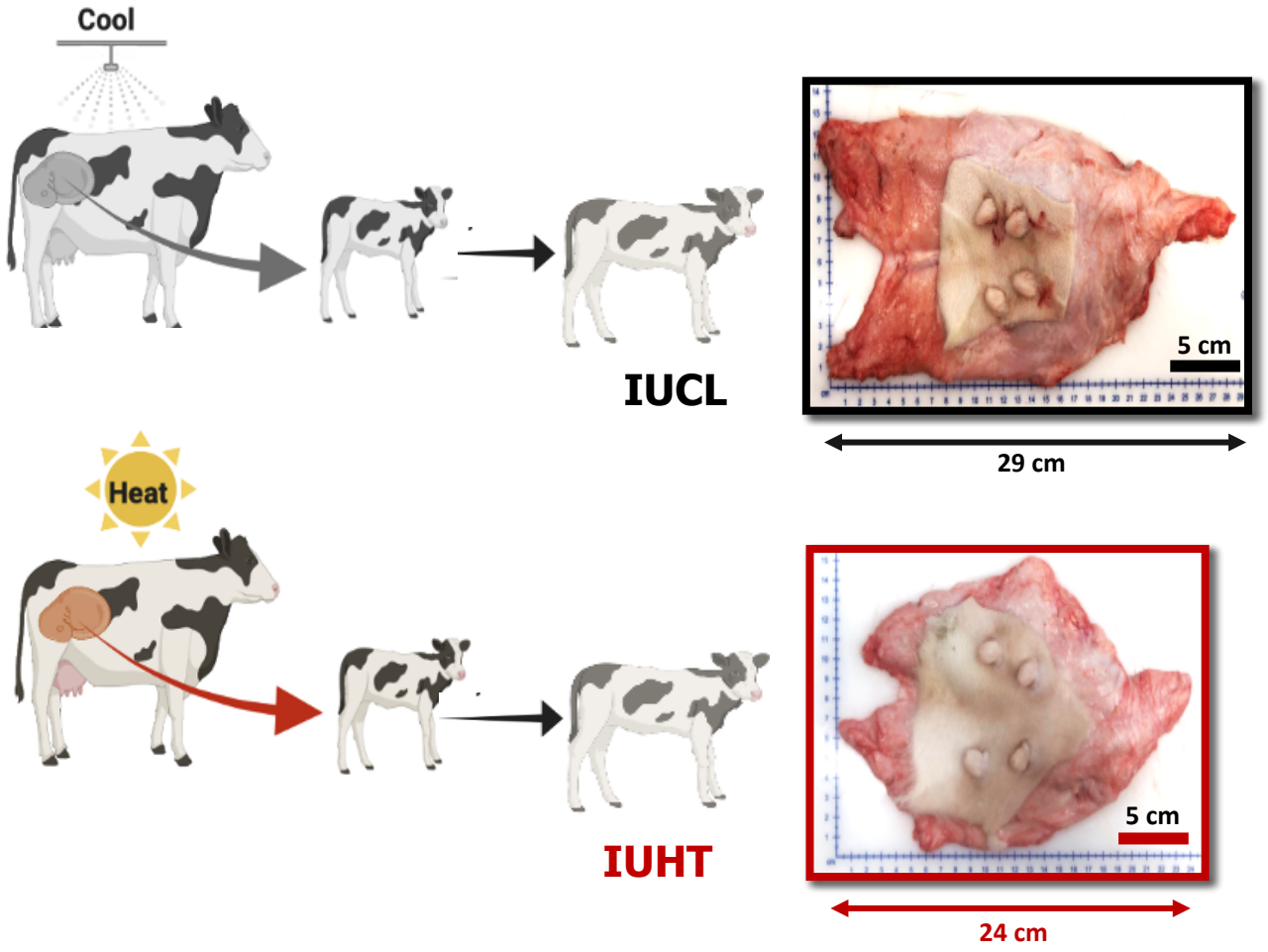


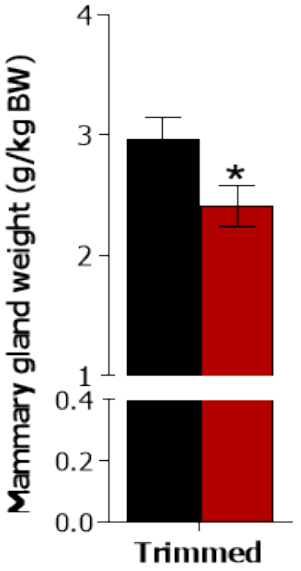


Adapted from: Dado-Senn et al., (2022)

2 Effects on the progeny: Daughters [F_1]

Whole udder harvest @ weaning





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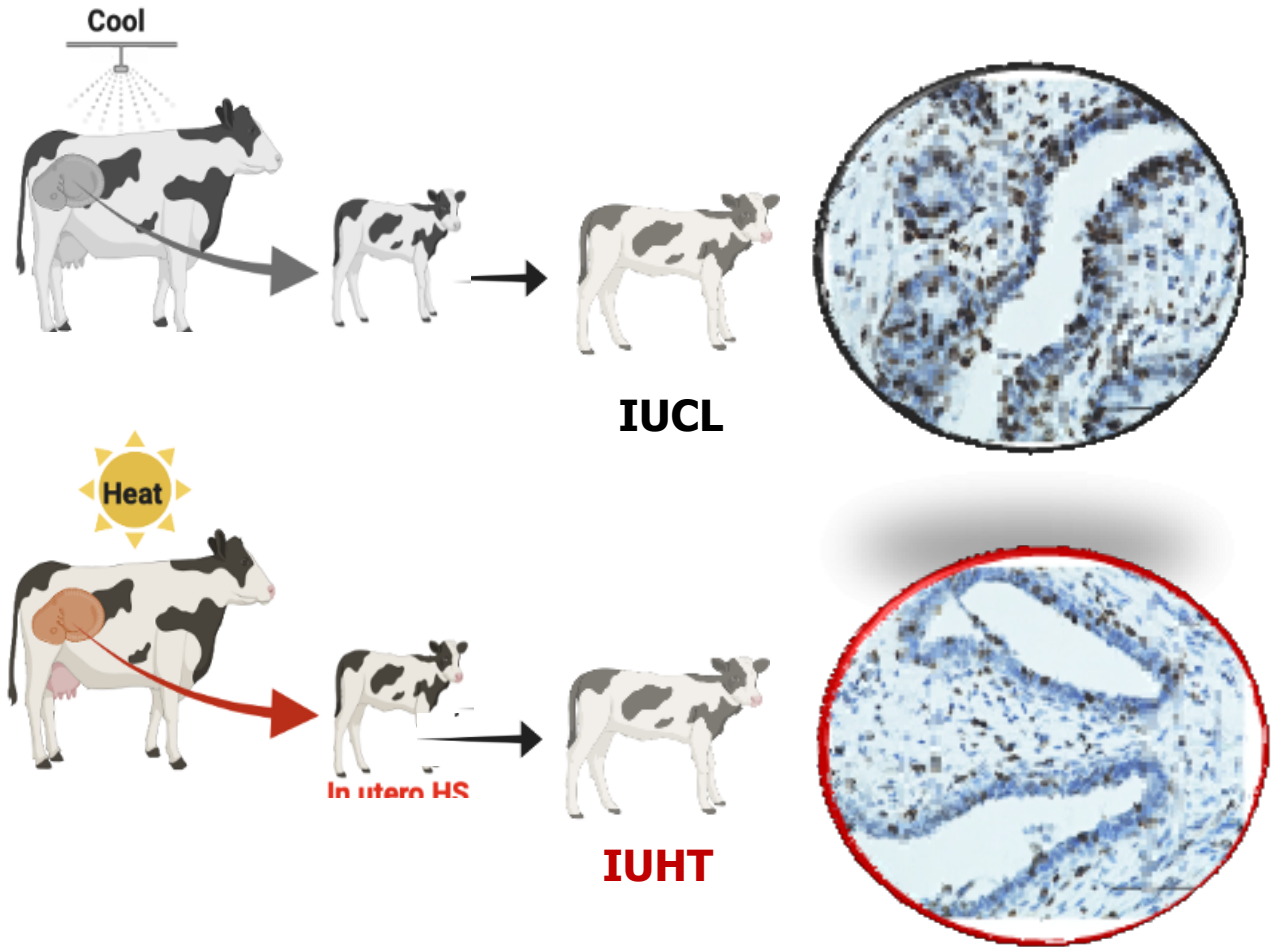
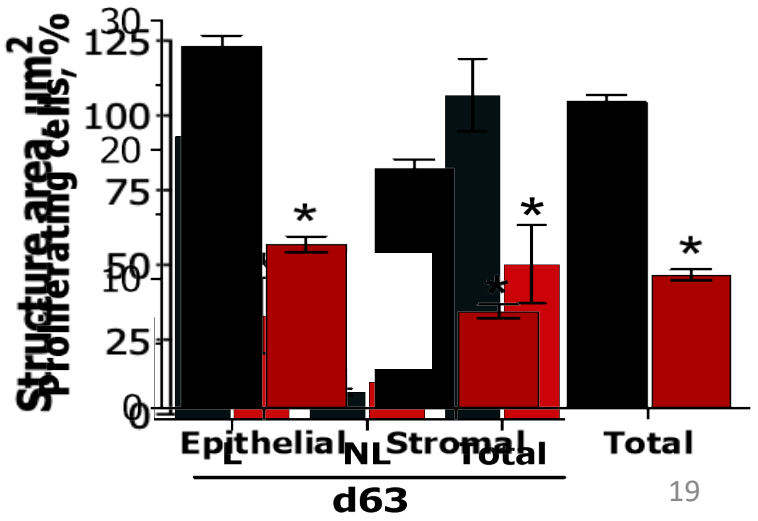
2 Effects on the progeny: Daughters [F_1]

Parenchyma microstructure & cell proliferation @ weaning



In utero heat-stressed heifers

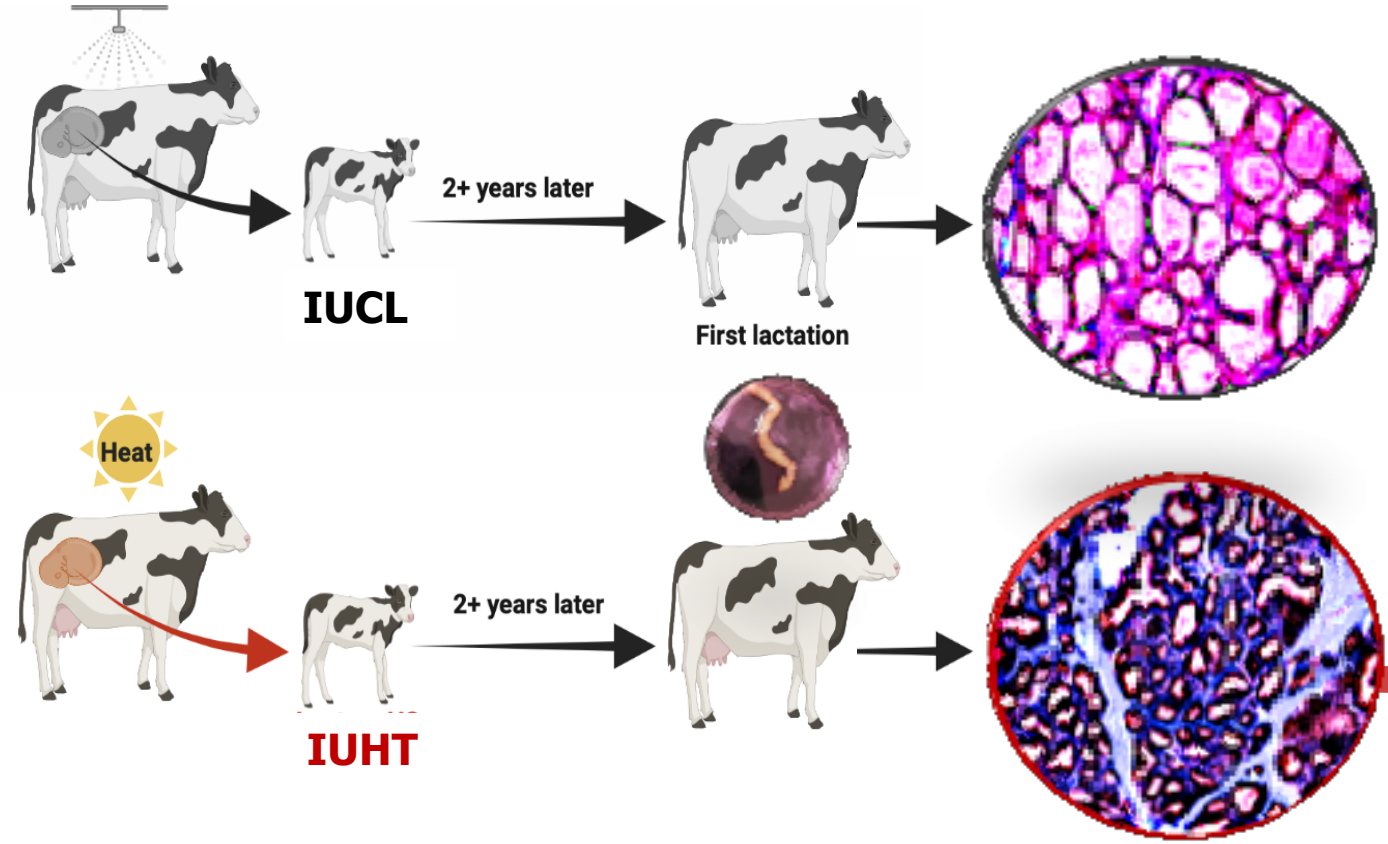
- Had a similar number of epithelial-ductal structures, but those were significantly underdeveloped
- 40% fewer proliferating cells in all three compartments!



Adapted from: Dado-Senn et al., (2022)

2 Effects on the progeny: Daughters [F_1]

Mammary biopsy @ first lactation



PLOS ONE

RESEARCH ARTICLE

In utero exposure to thermal stress has long-term effects on mammary gland microstructure and function in dairy cattle

Amy L. Skibiel, Bethany Dado-Senn, Thiago F. Fabris, Geoffrey E. Dahl, Jimena Laporta*

Department of Animal Sciences, University of Florida, Gainesville, FL, United States of America

In utero heat-stressed heifers

- Same number of alveoli
- Fewer epithelial cells
- 50% smaller luminal-alveolar area
- Lower % of proliferating cells

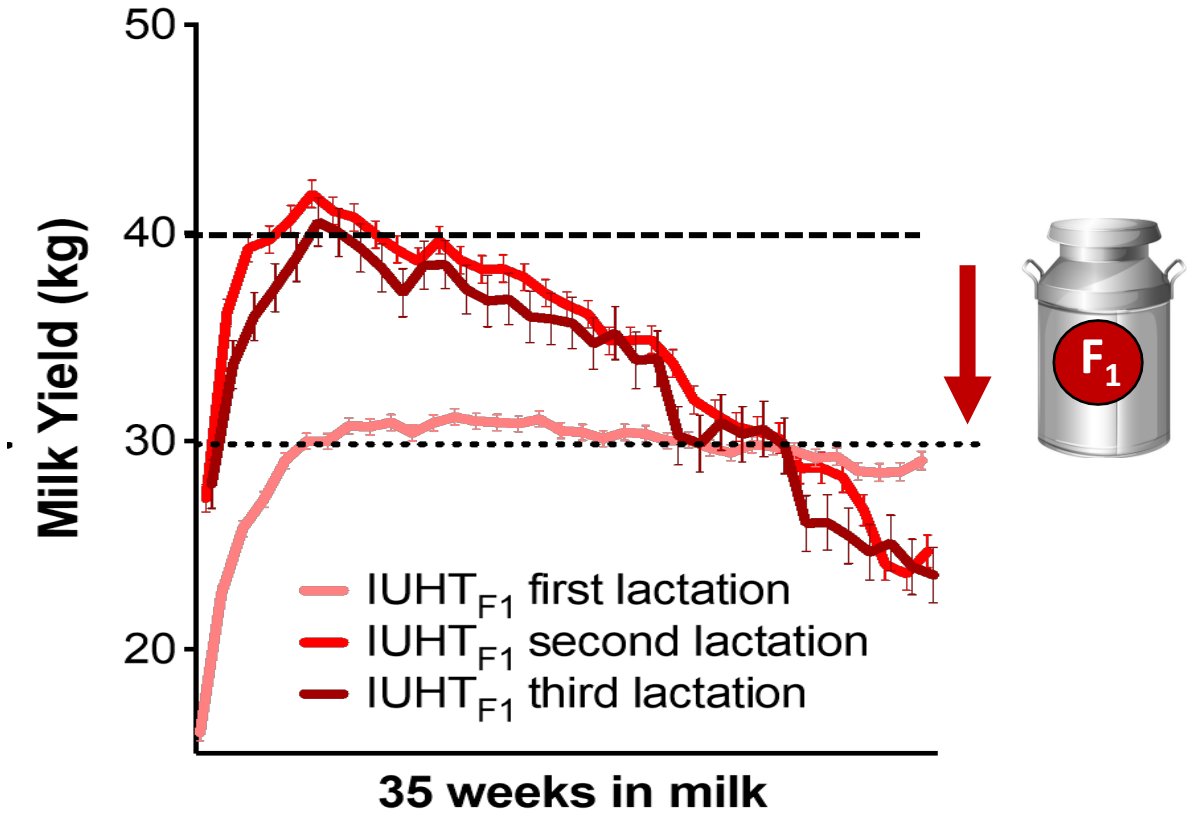
Alterations in mammary morphology & cell turnover arising in-utero compromise the future synthetic capacity of the daughters!

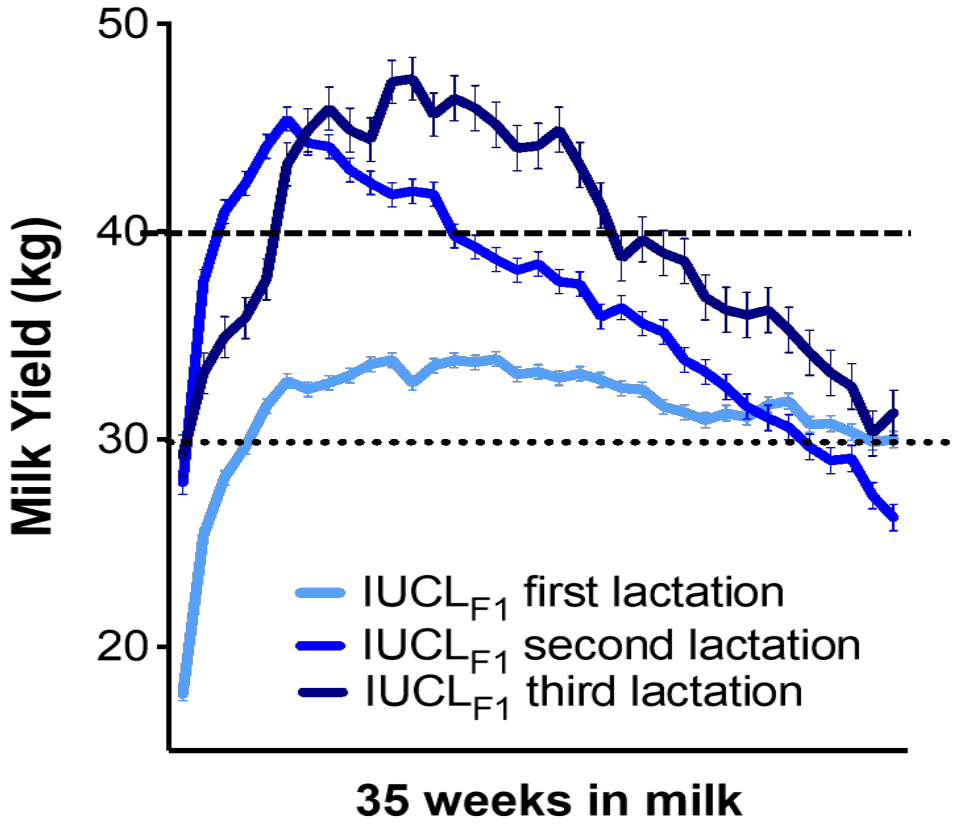
Adapted from: Dado-Senn et al., (2022)

2 Effects on the progeny: Daughters [F_1]

The effect is multi-lactational

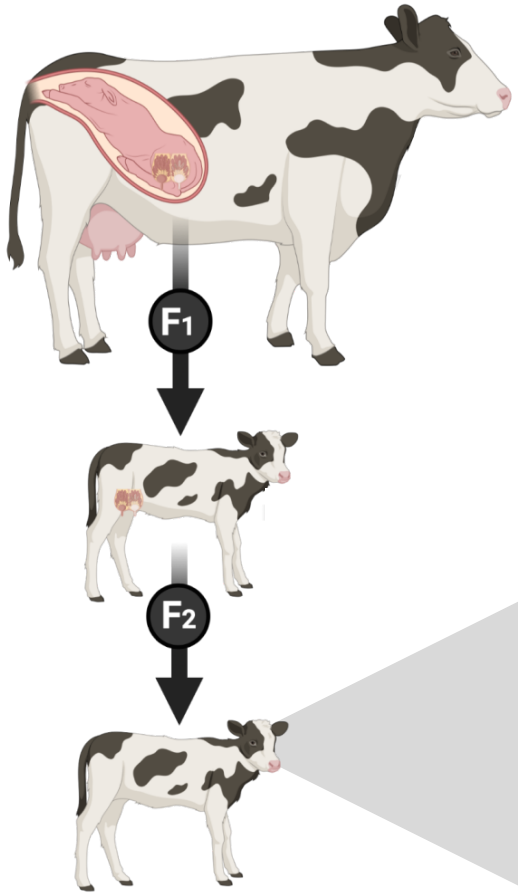
Long-lasting in utero programming effect of a less productive phenotype!





Adapted from: Laporta et al (2020)

2 Effects on the progeny: granddaughters [F_2]



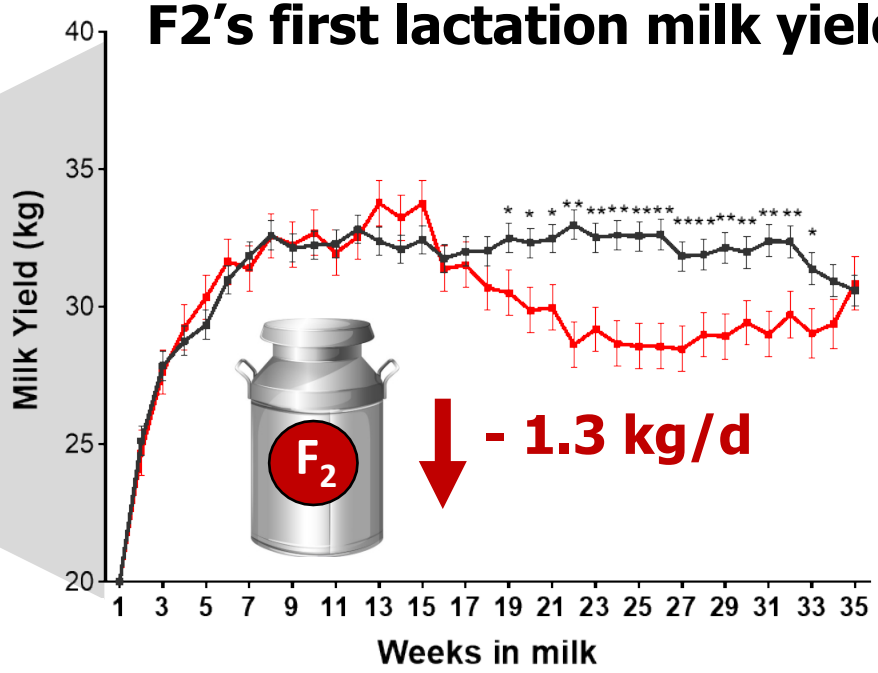
Granddaughters (born to IUCL vs. IUHT F_1 dams)

J. Dairy Sci. 103
https://doi.org/10.3168/jds.2020-18154

Late-gestation heat stress impairs daughter and granddaughter lifetime performance

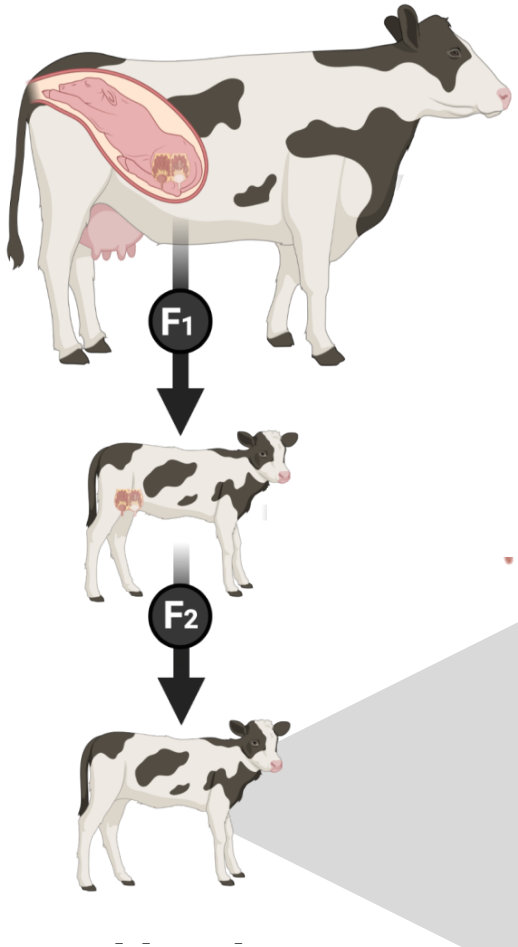
J. Laporta,[1]* F. C. Ferreira,[2] V. Ouellet,[1] B. Dado-Senn,[1] A. K. Almeida,[1] A. De Vries,[1] and G. E. Dahl[1]
[1]Department of Animal Sciences, University of Florida, Gainesville 32611
[2]Veterinary Medicine Teaching and Research Center, School of Veterinary Medicine, University of California, Davis, Tulare 93274

F2's first lactation milk yield



- **Granddaughters of heat-stressed dams produced less milk in their first lactation** (~4.5 years after the original heat-stress insult occurred!)

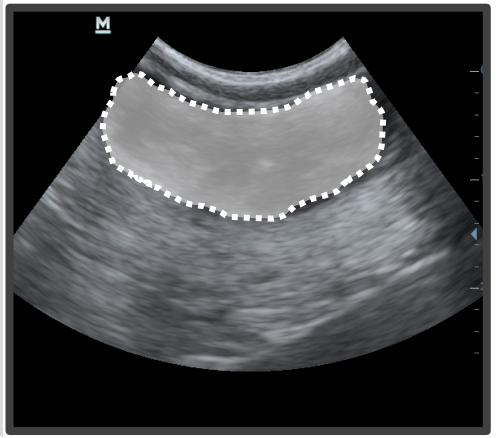
2 Effects on the progeny: granddaughters [F_2]



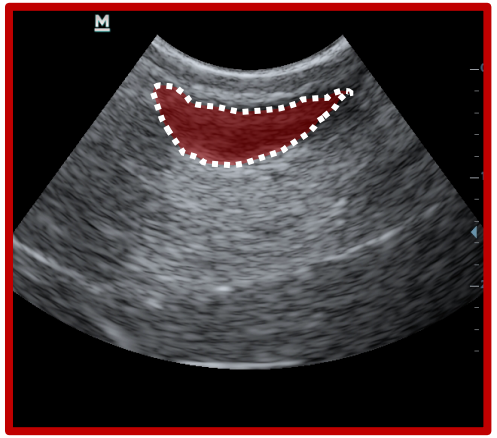
Granddaughters (born to IUCL vs. IUHT F_1 dams)

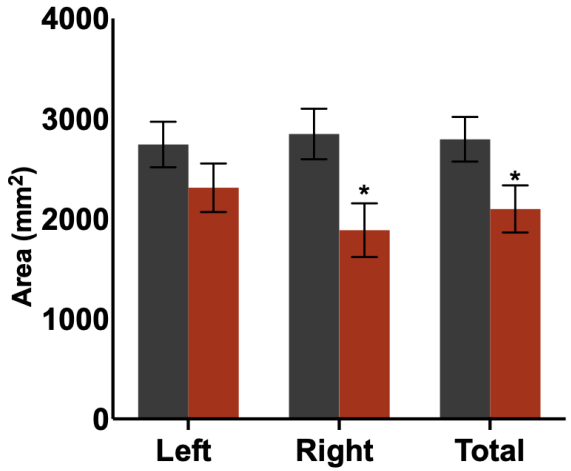
Mammary gland ultrasounds were performed on the rear left and right quarters at 70 days of age.

Granddaughters of F_0 cooled dams

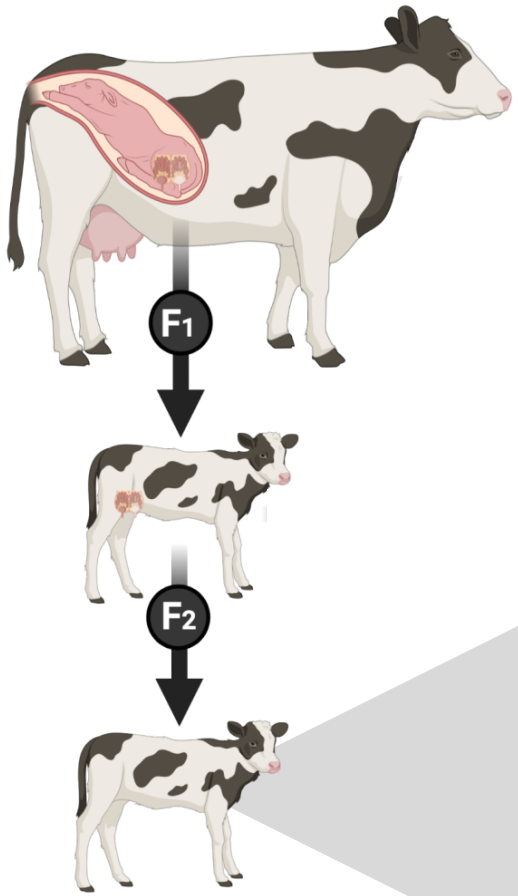


Granddaughters of F_0 heat-stressed dams





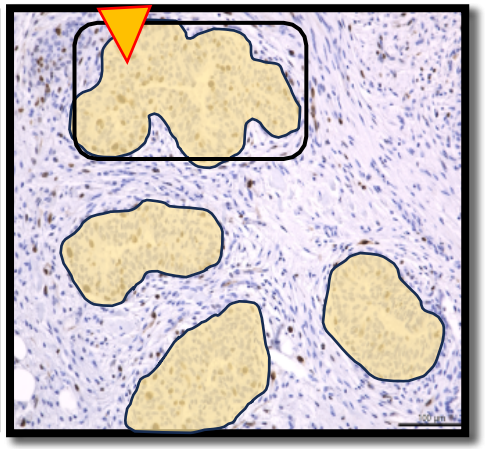
2 Effects on the progeny: granddaughters [F_2]



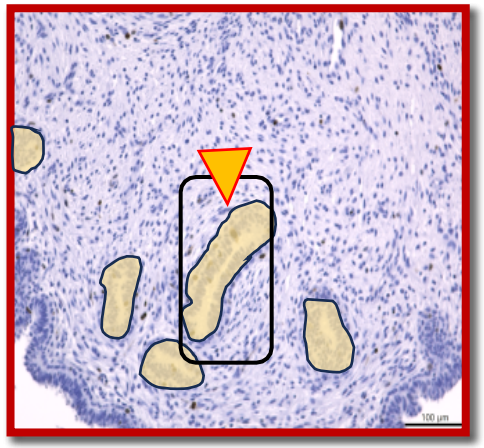
Granddaughters (born to IUCL vs. IUHT F_1 dams)

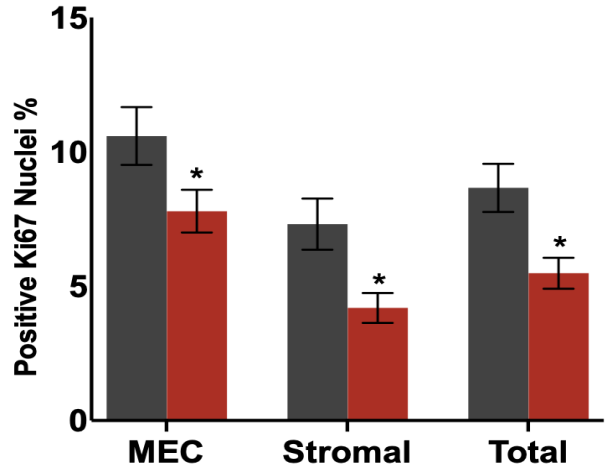
Mammary gland biopsies were performed on the rear quarters at 70 days of age to characterize tissue architecture (H&E) and cell proliferation (ki-67)

Granddaughters of F_0 cooled dams

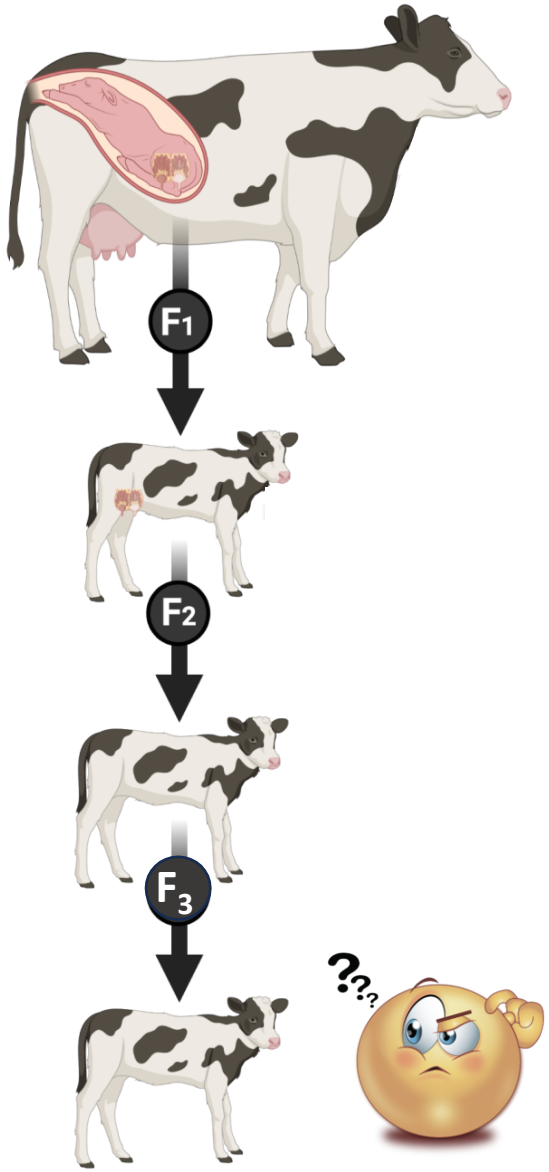


Granddaughters of F_0 heat-stressed dams

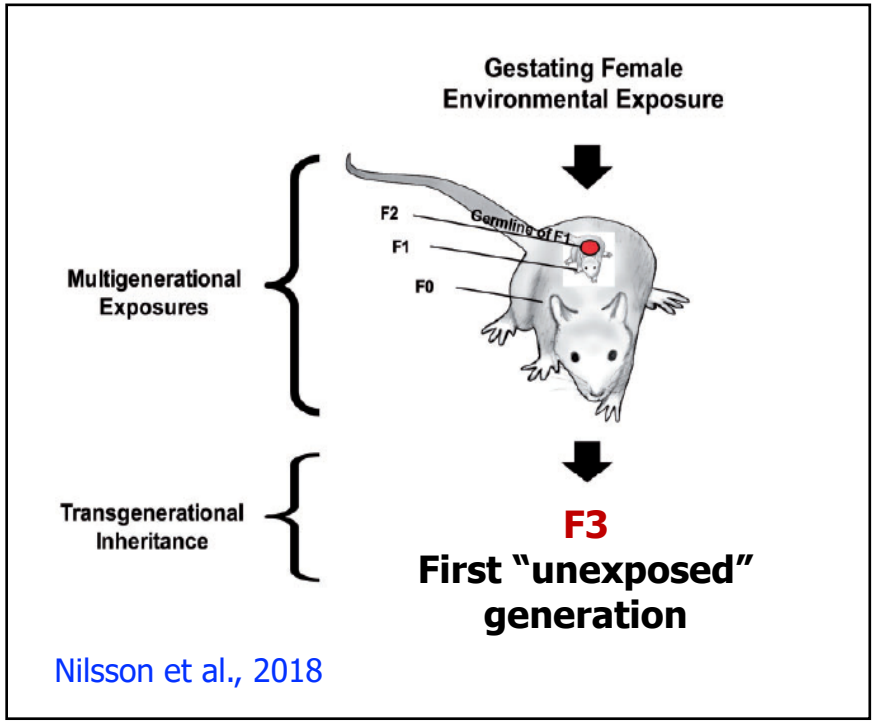




2 Effects on the progeny:



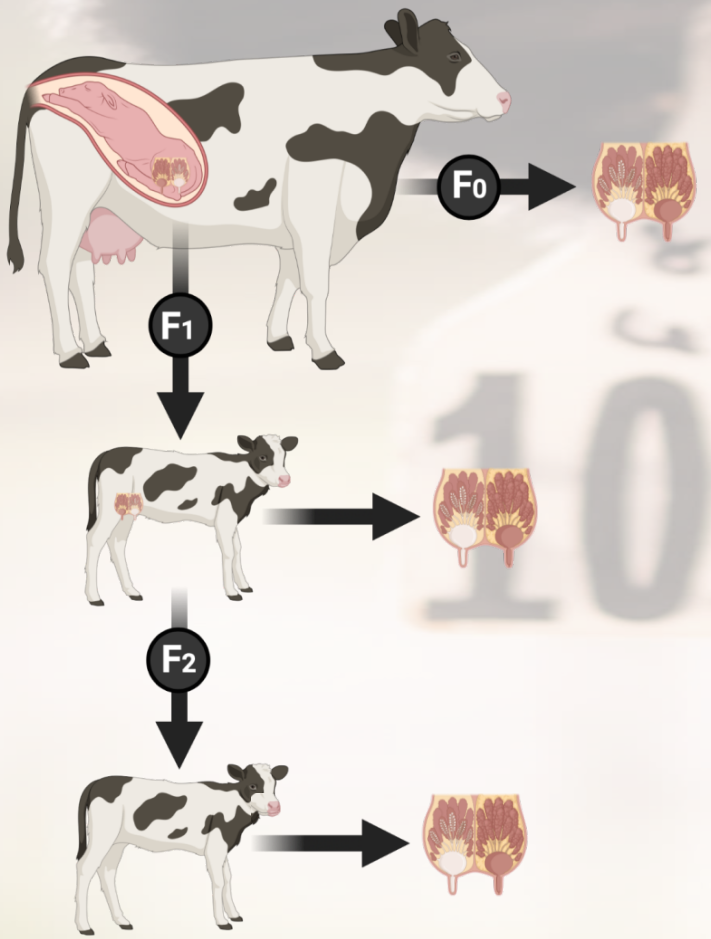
Is it trans (cross) generational?



Nilsson et al., 2018

Only F_3 individuals can be considered as a true transgenerational inheritance in the absence of exposure.

Summary: effect on the progeny



Late-gestation heat stress

Programming of the F_1

Derails normal mammary gland development

- Smaller alveoli with fewer & less proliferative MECs
- Less synthetic capacity

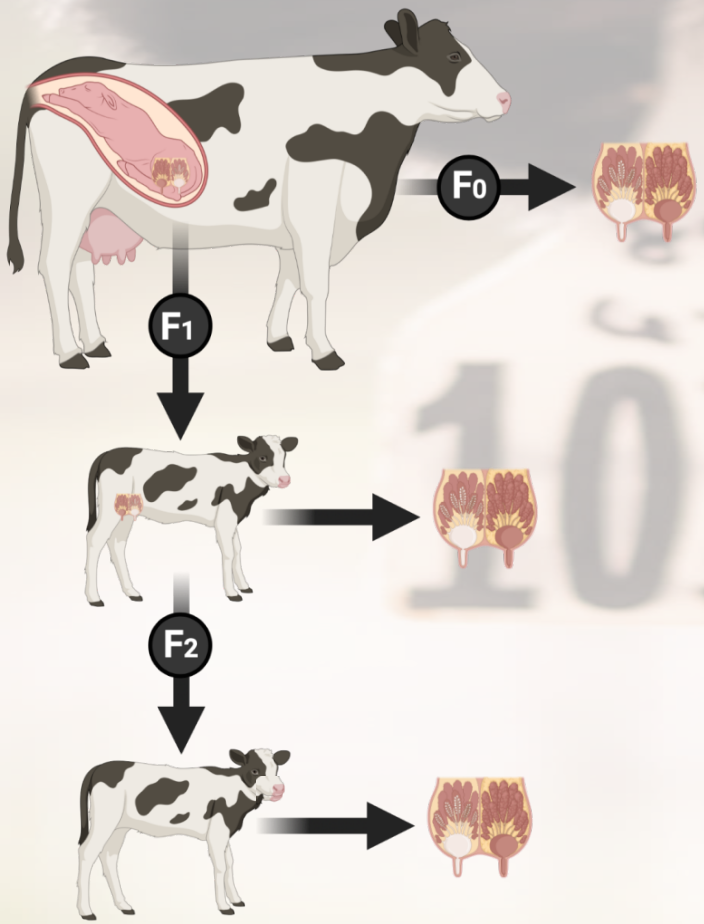
Triggers distinctive methylation patterns

- Environmentally induced epigenetic changes?

Phenotype persists until at least the F_2

- Multigenerational effect!
- F_2 survive less and produce less milk
- Mammary gland phenotypic differences!

Conclusions & Final Remarks



Biological importance of the dry period

Three programming effects

- Mammary development of the dam
- Fetal development daughter
- Gametes (future F_2 granddaughters)

Opportunity for the implementation of management interventions with long-lasting impacts on multiple generations

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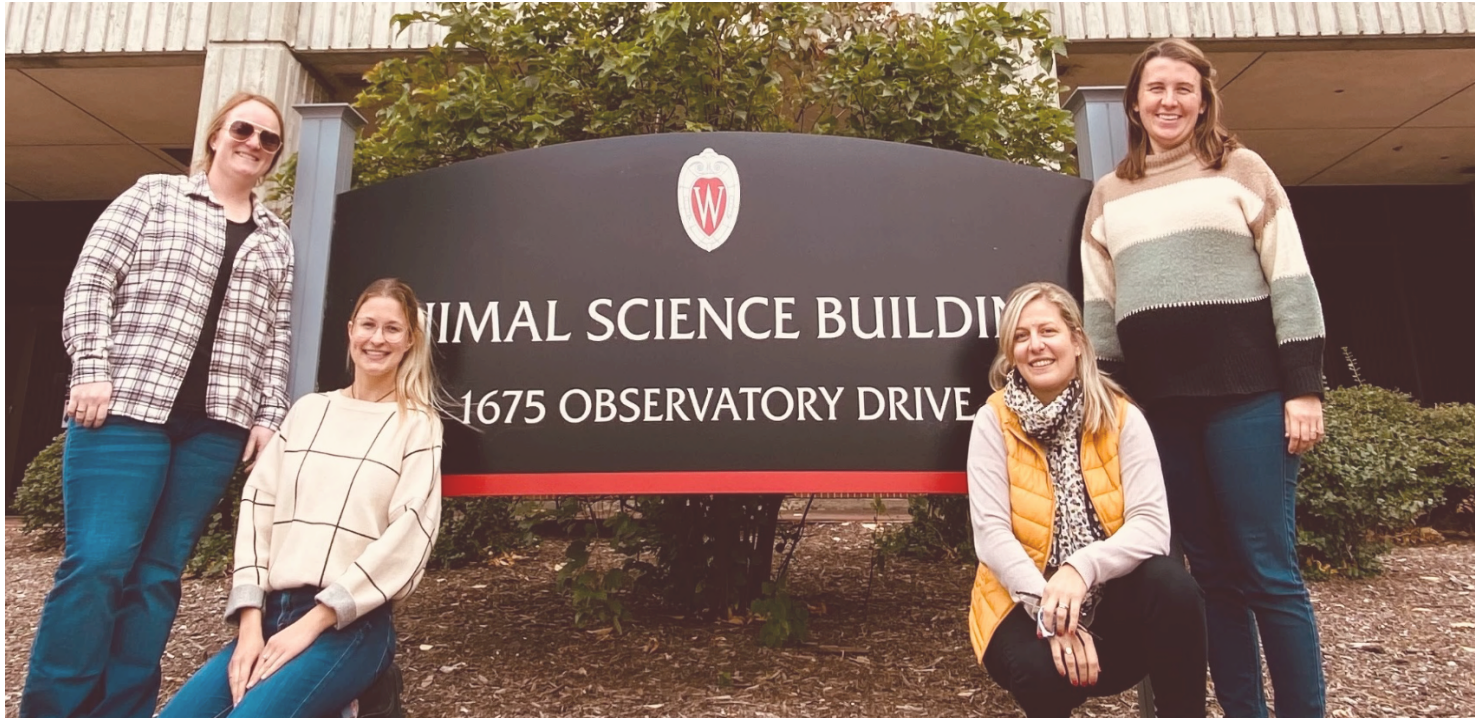

Jimena Laporta
Assistant Professor
Mammary Gland Physiology
jlaporta@wisc.edu

ANIMAL & DAIRY SCIENCES
University of Wisconsin-Madison

LAPORTA LABORATORY
@UW-MADISON