What is immunosuppression and how is it involved in transition cow problems?

Barry Bradford

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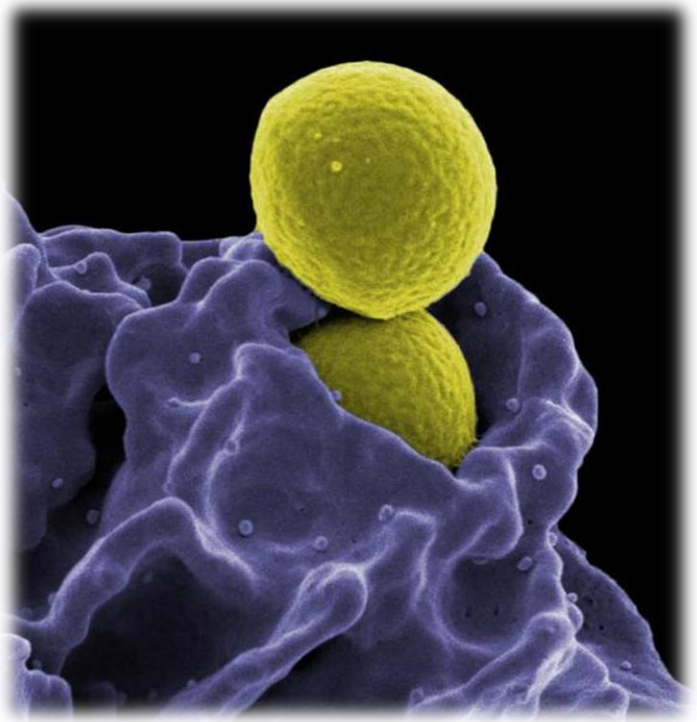
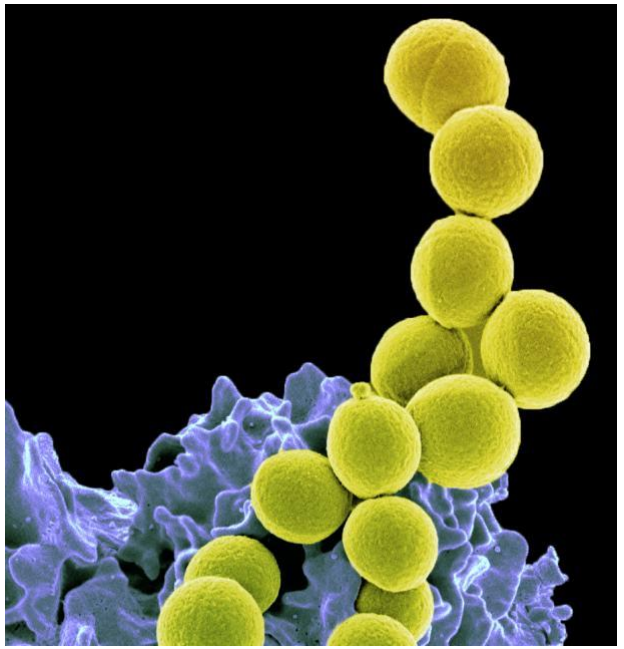
Overview

1. Basics of the immune system and what we are re-learning
2. The evidence for an altered immune state in the transition to lactation
3. Nutritional immunology
   - Immunometabolism



Roles of the immune system

- Monitors and manages the normal and pathogenic microflora found in and around the body
  - Bacteria
  - Viruses
  - Fungi
  - Multicellular parasites
- Detects and clears rogue and compromised cells, tissue debris
- Many emerging regulatory roles



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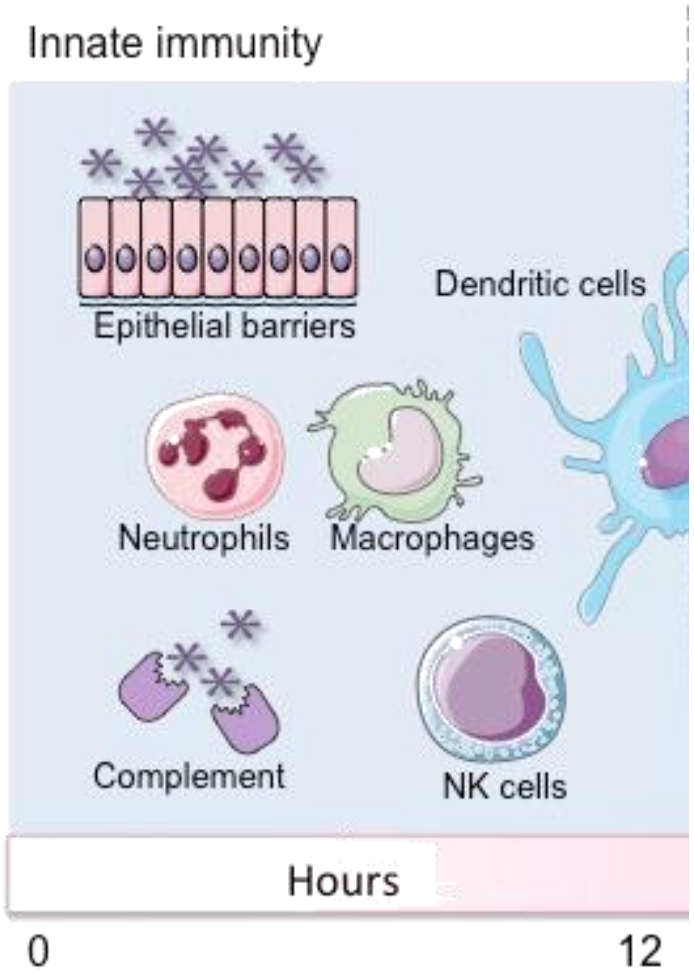
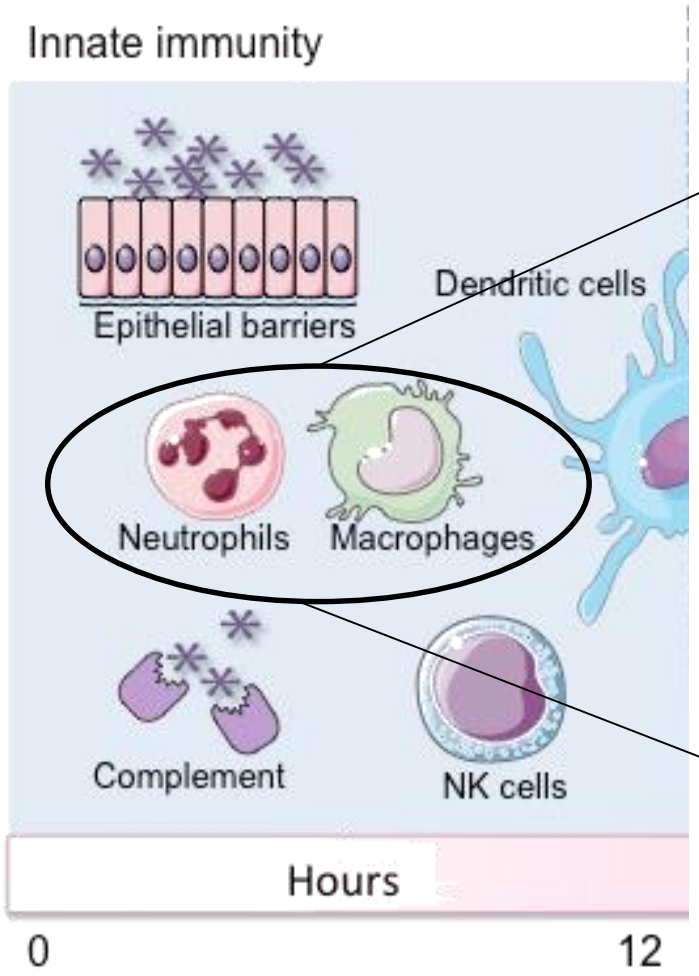
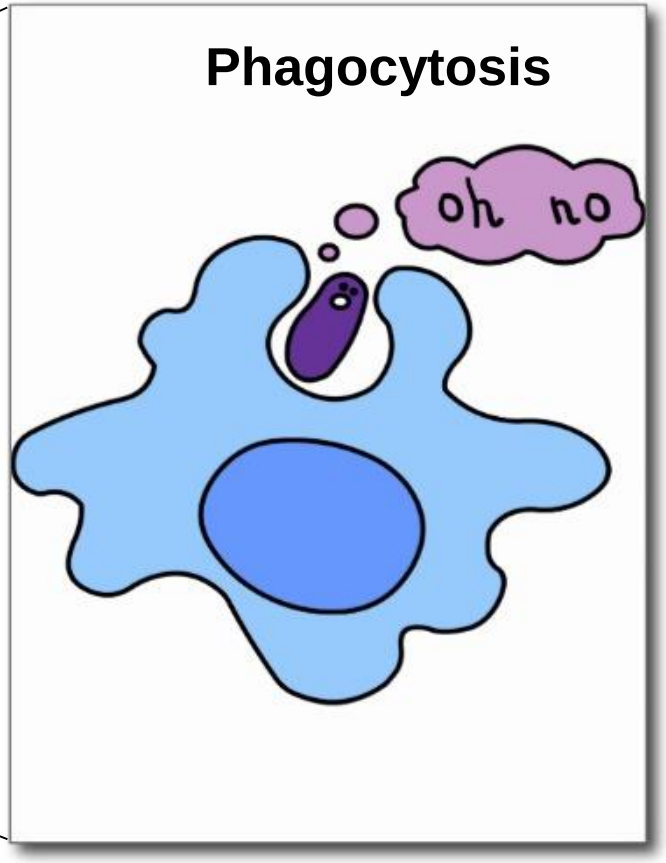


Think of the immune system like the armed forces

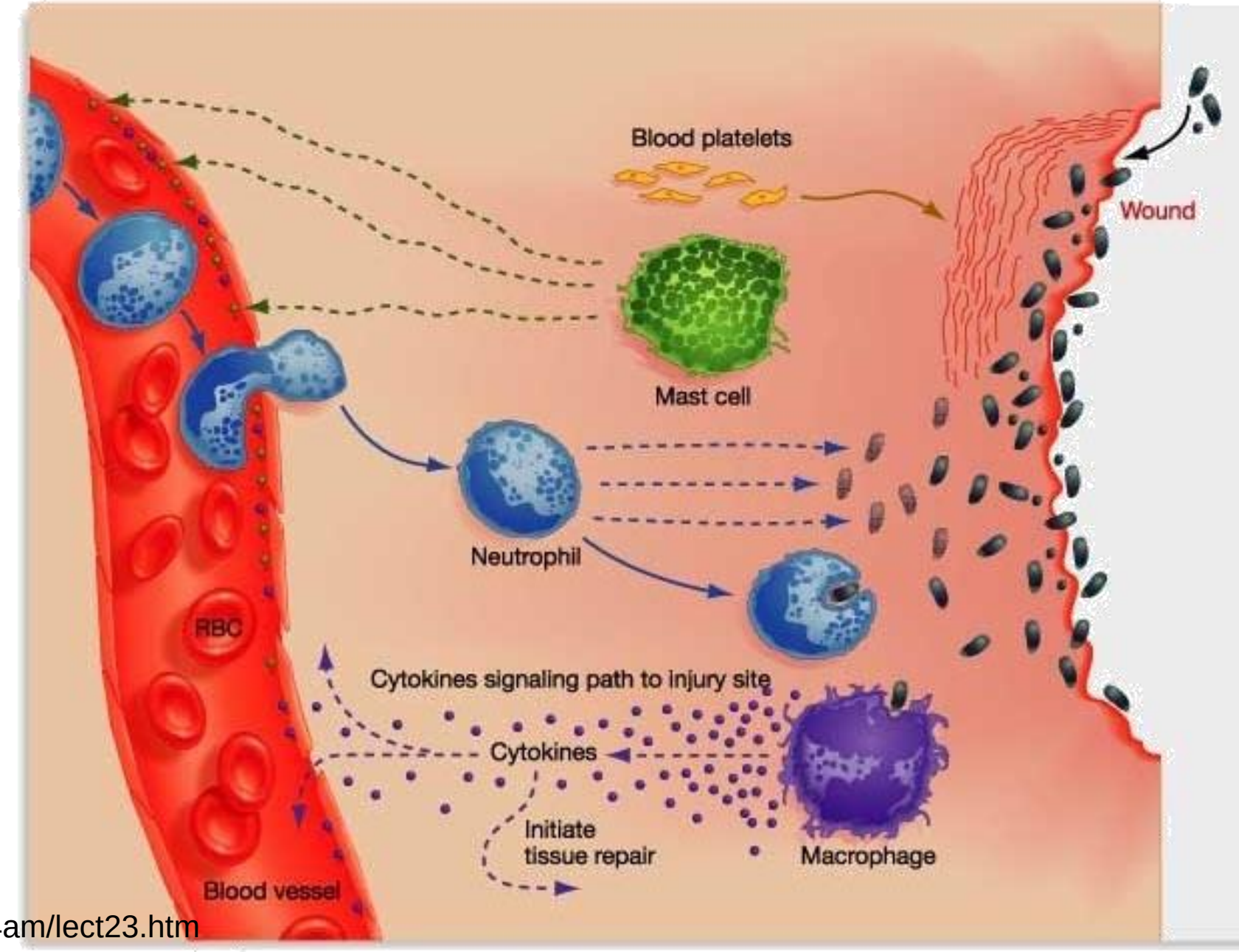




laraslittlebcells.wordpress.com

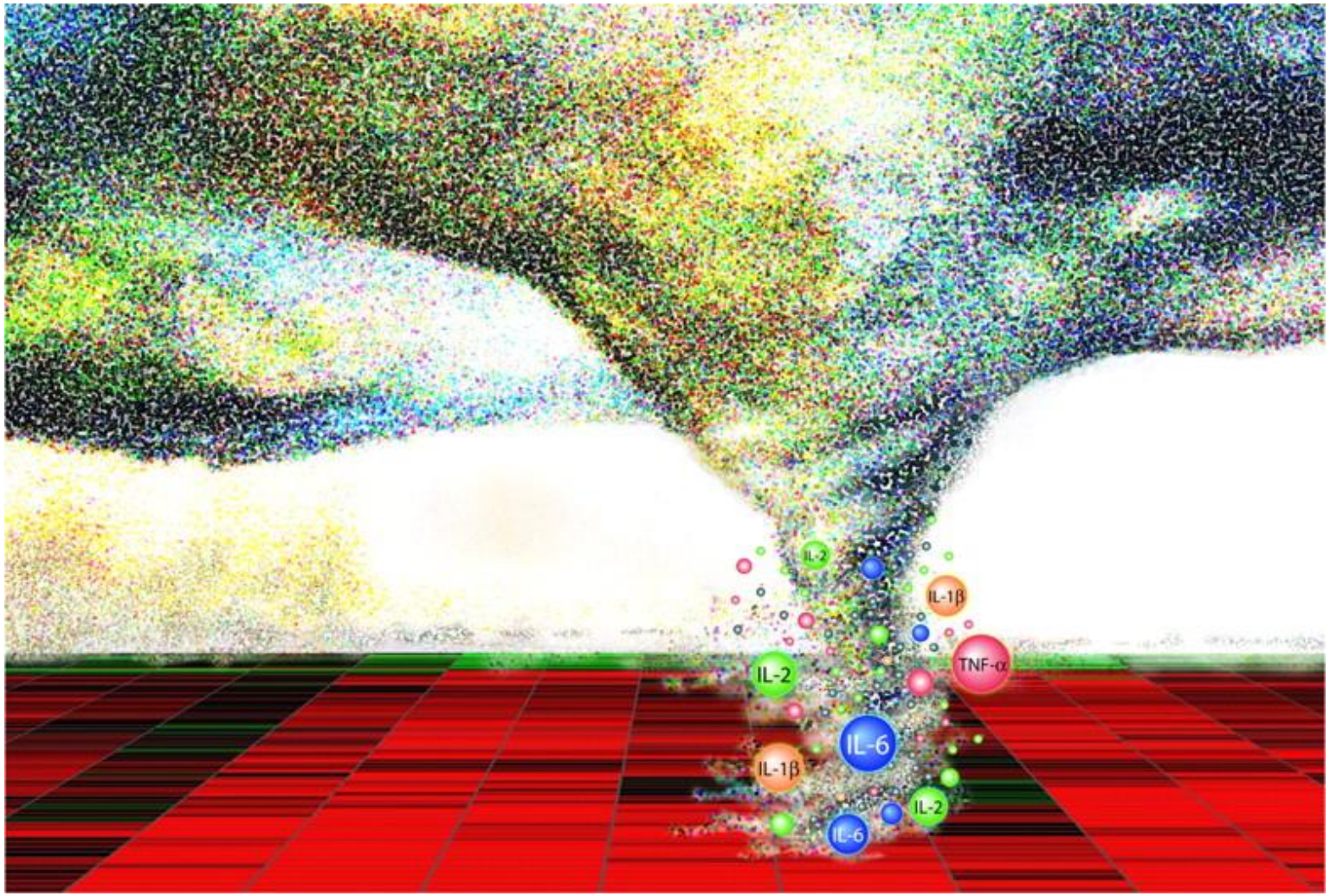
Innate immunity: the rapid response team

Innate immune response



www.uic.edu/classes/bios/bios100/lecturesf04am/lect23.htm

Inflammatory signals: a positive feedback loop

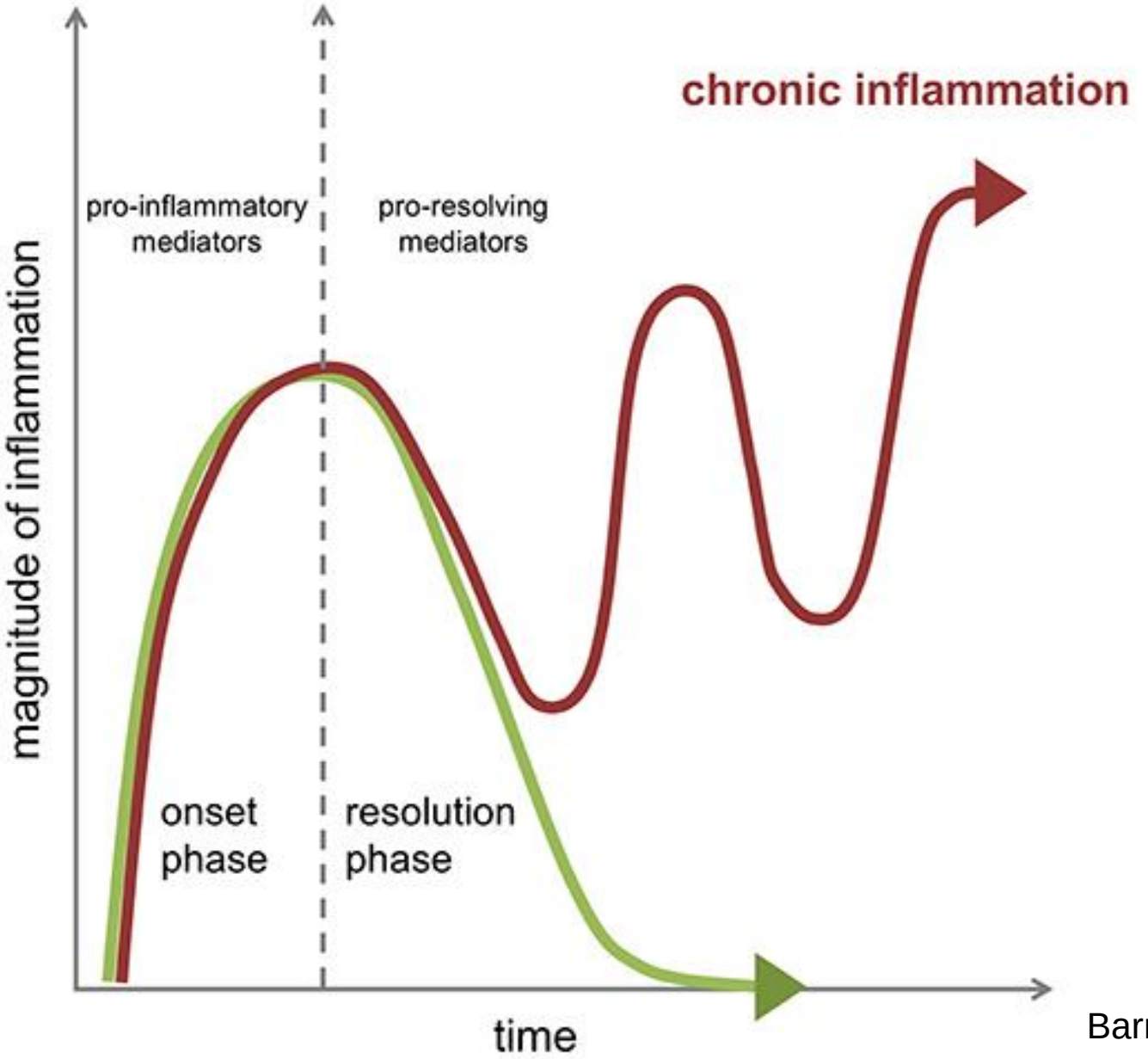


Tisoncik J R et al. Microbiol. Mol. Biol. Rev. 2012;76:16-32

Inflammation

- Cytokines
- Oxylipids
- Acute phase proteins

- All classes include both inflammatory and resolving signals

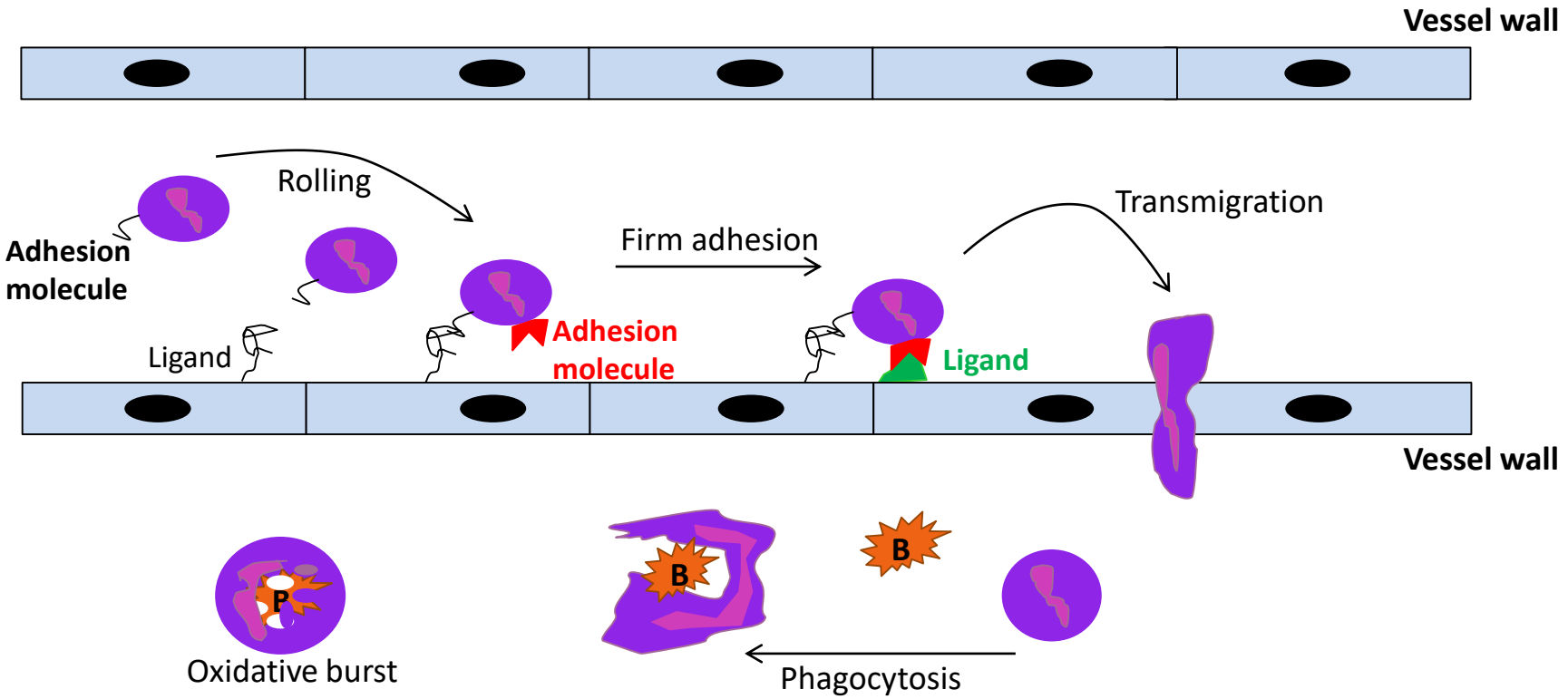


Barnig et al., 2019

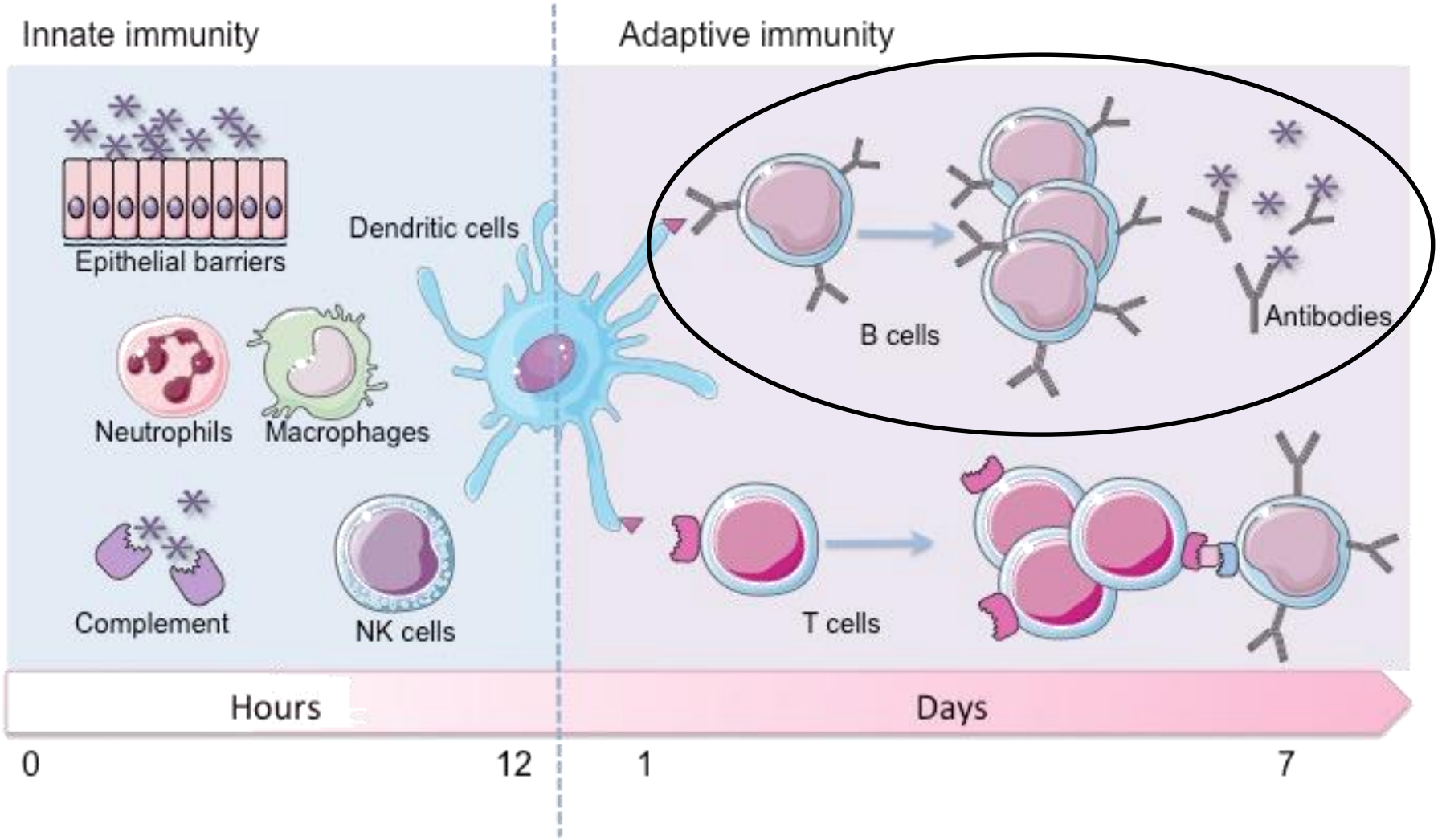
Chemotaxis

- The pipette is releasing a cytokine
- Watch the neutrophil..

Neutrophil migration



Courtesy of Dr. Luís Mendonça



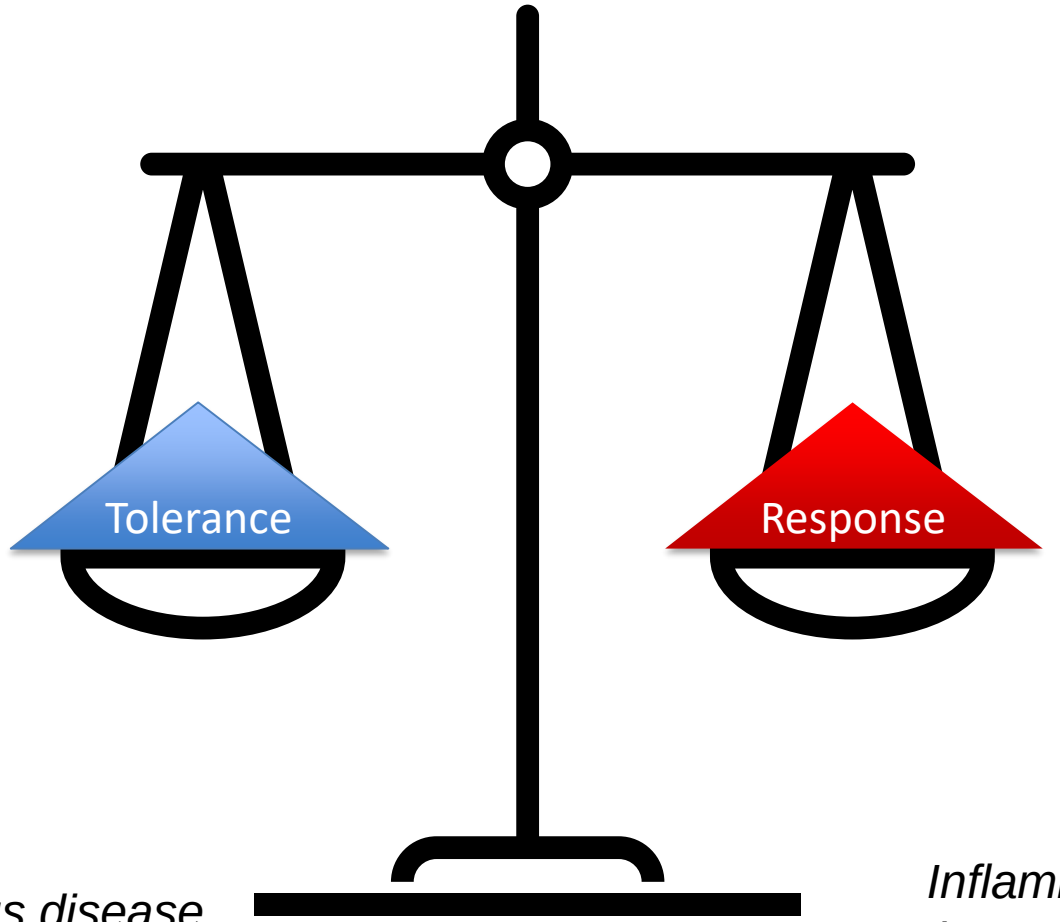
Adaptive immunity: in it for the long haul

Animals can respond to health challenges in 2 ways

- TOLERANCE

- RESISTANCE (IMMUNE RESPONSE)

Balancing tolerance and response

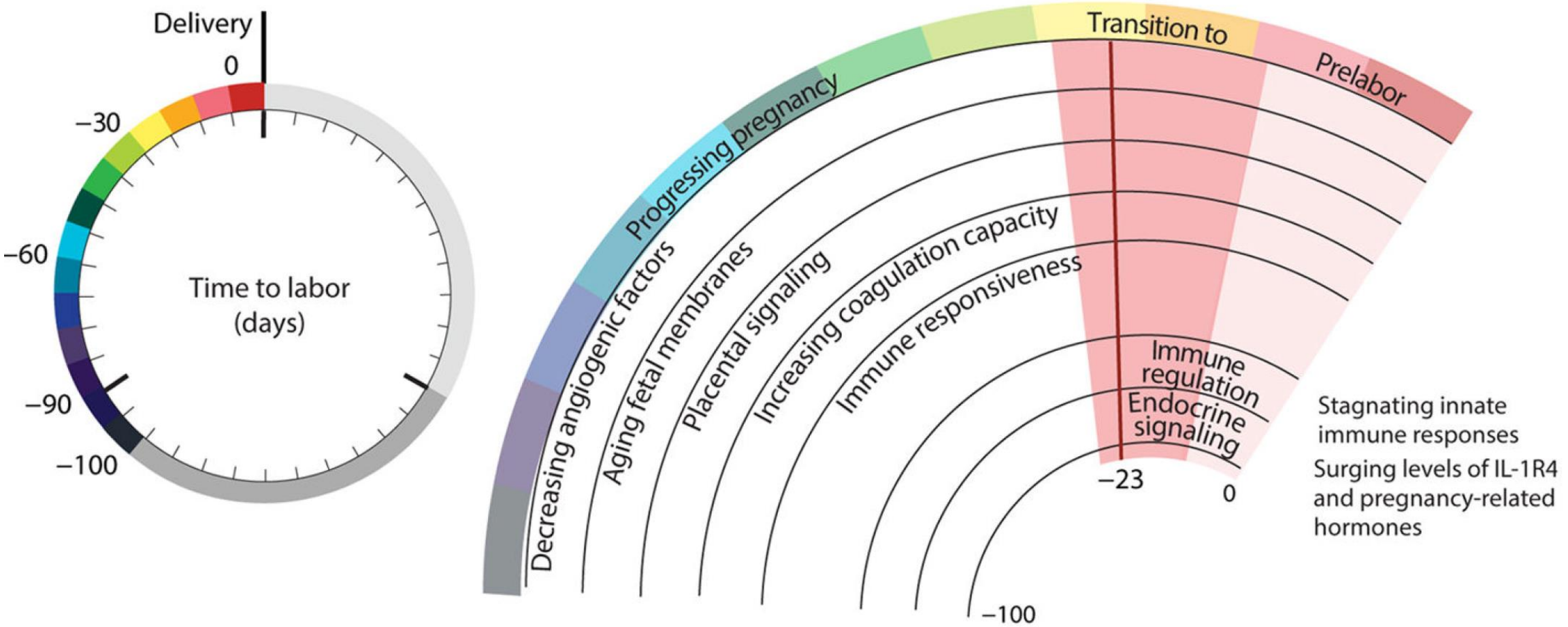


There is a gradient between tolerance and response, under continuous regulation

Infectious disease

Inflammatory / autoimmune disorders

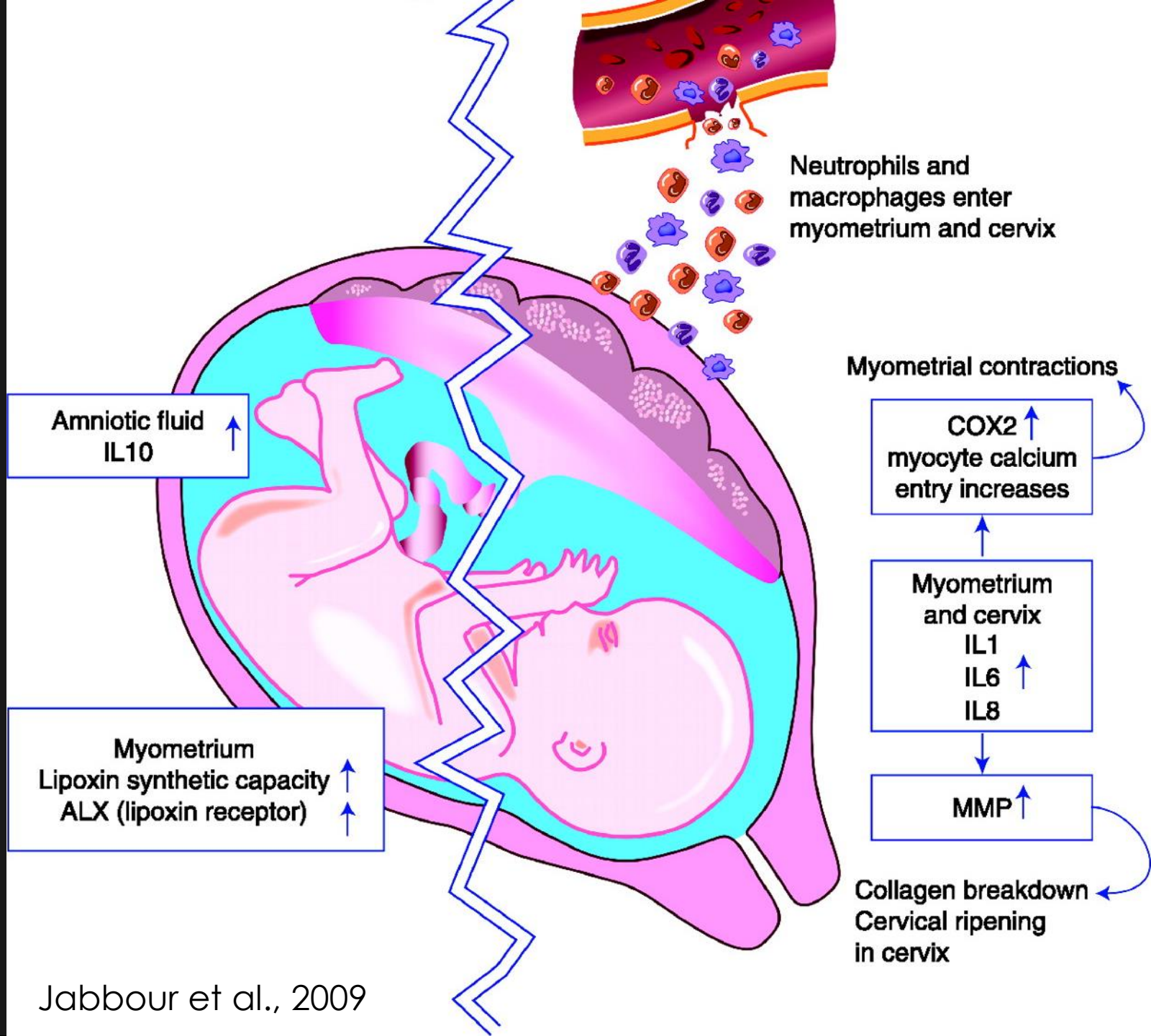
Pregnancy and parturition involves immune shifts



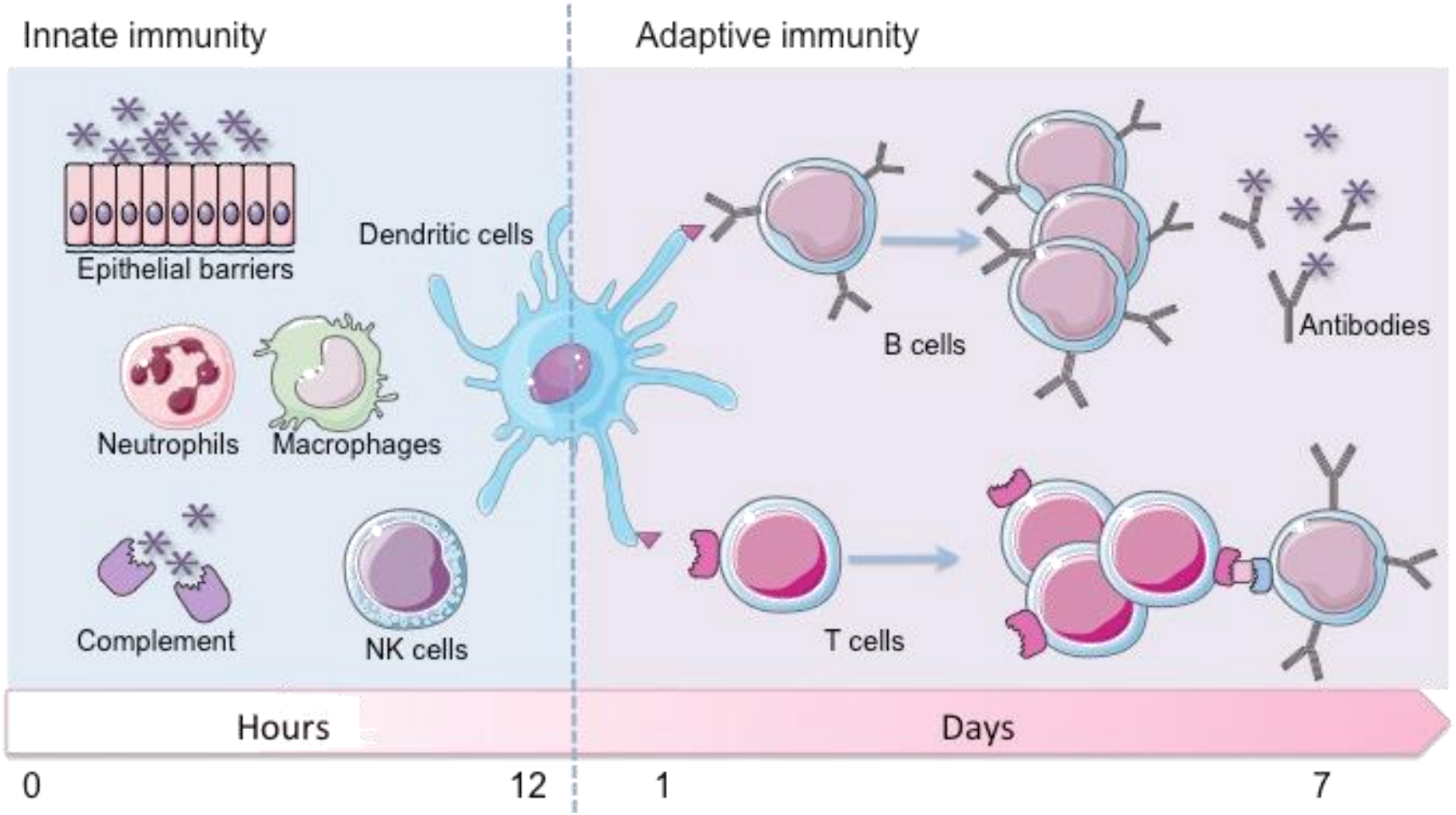
Stelzer et al., 2021

Inflammatory signals are essential for parturition

1. Stimulate release of proteases
2. Promote contractions
3. Interact with prostaglandin synthesis pathways

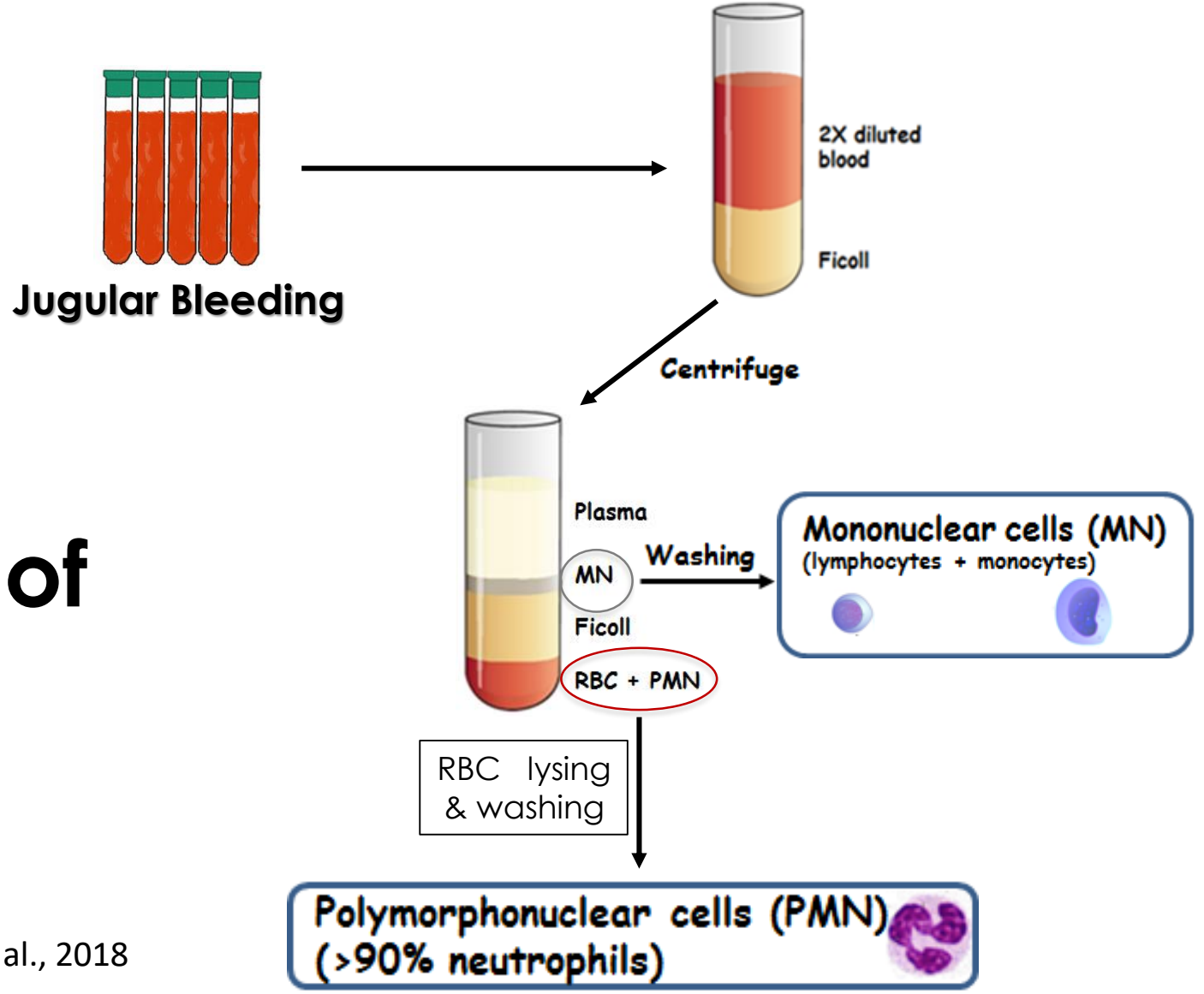


Jabbour et al., 2009



Does this system function normally in the period around calving?

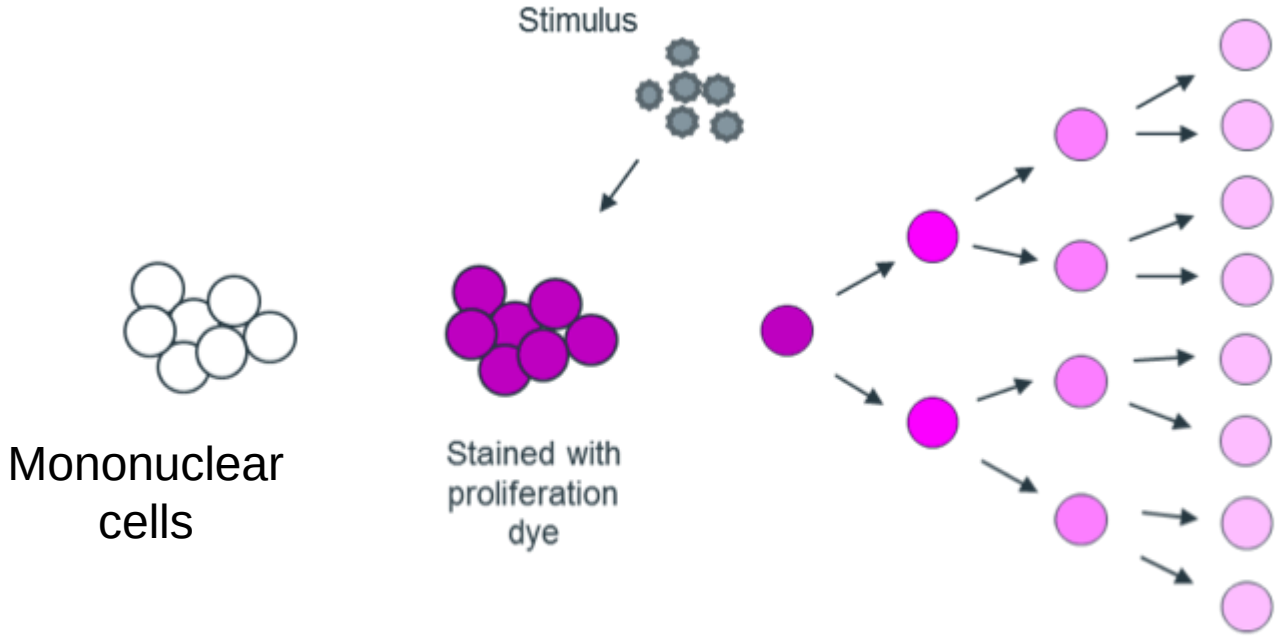
Ex vivo evaluation of immune cell responses



Garcia et al., 2018

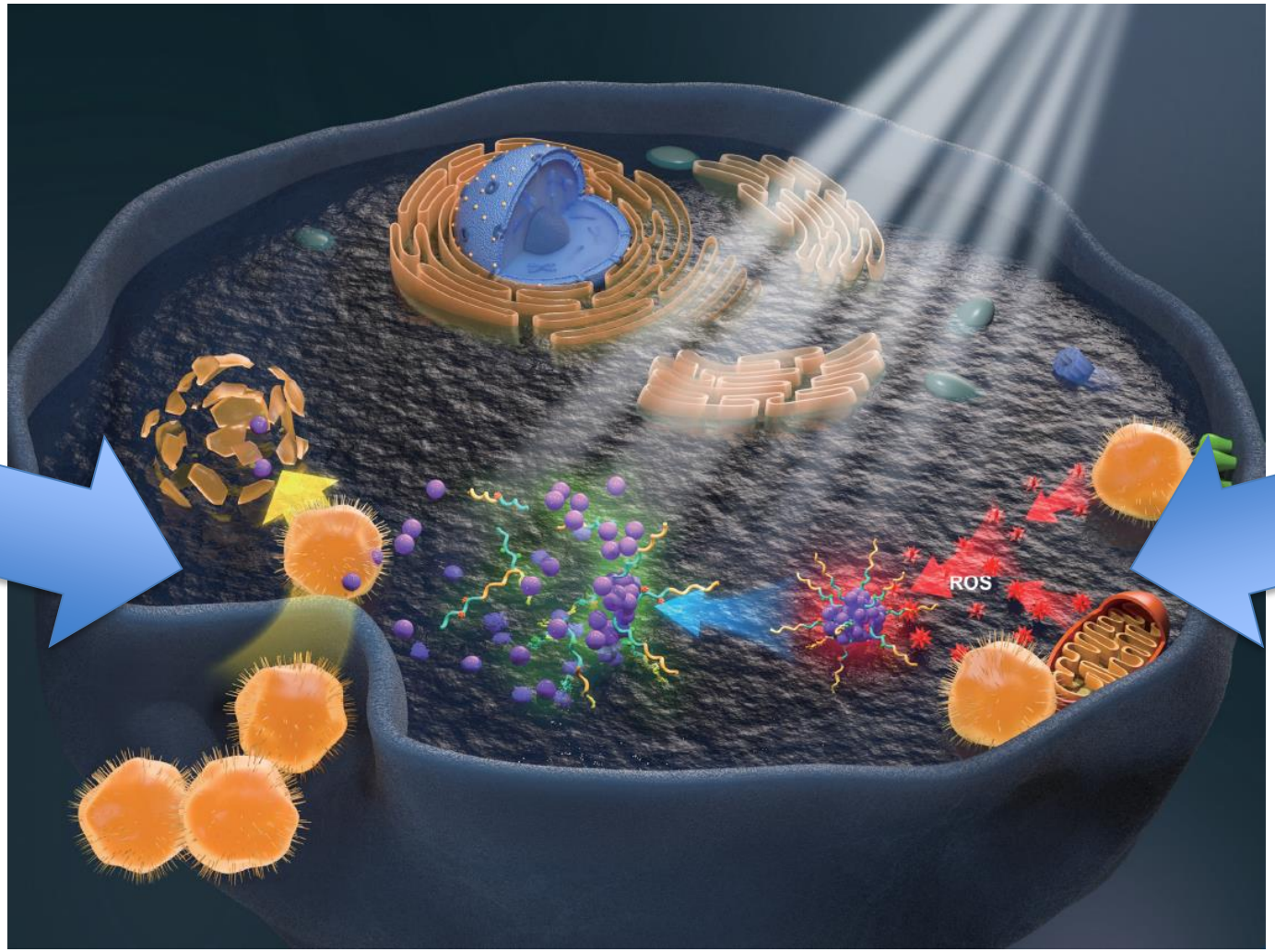
Assessing lymphocyte functionality (adaptive)

- Lymphocytes can be separated because they don't adhere to culture plates
- Lymphocytes should proliferate (mitosis) when given an appropriate stimulus
- Relative cell expansion in response to a stimulus in a test tube is used as a proxy for lymphocyte functionality



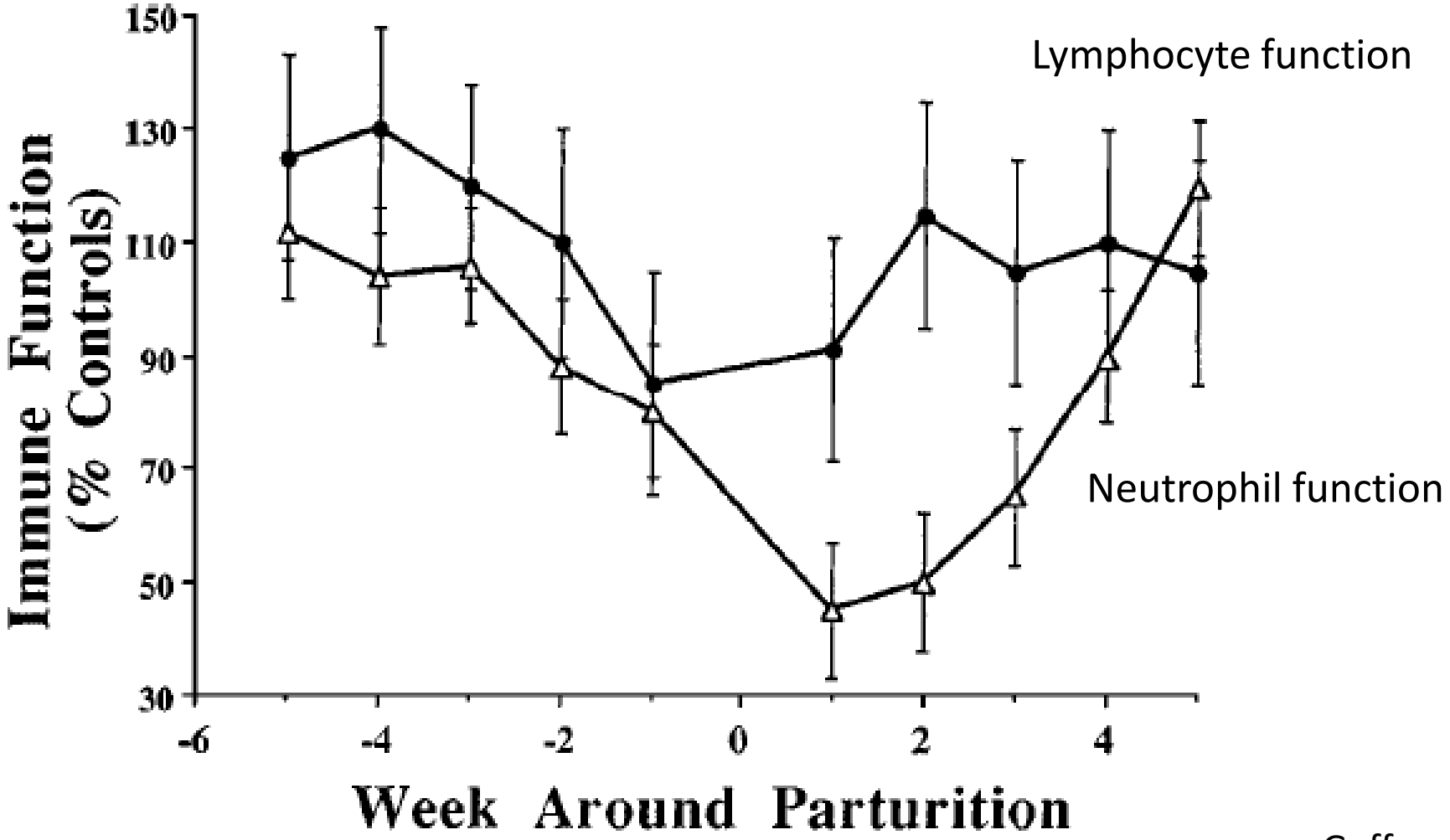
Assessing neutrophil functionality (innate)

Phagocytosis can be measured by labeling particles (like bacteria) and tracking movement into the neutrophils



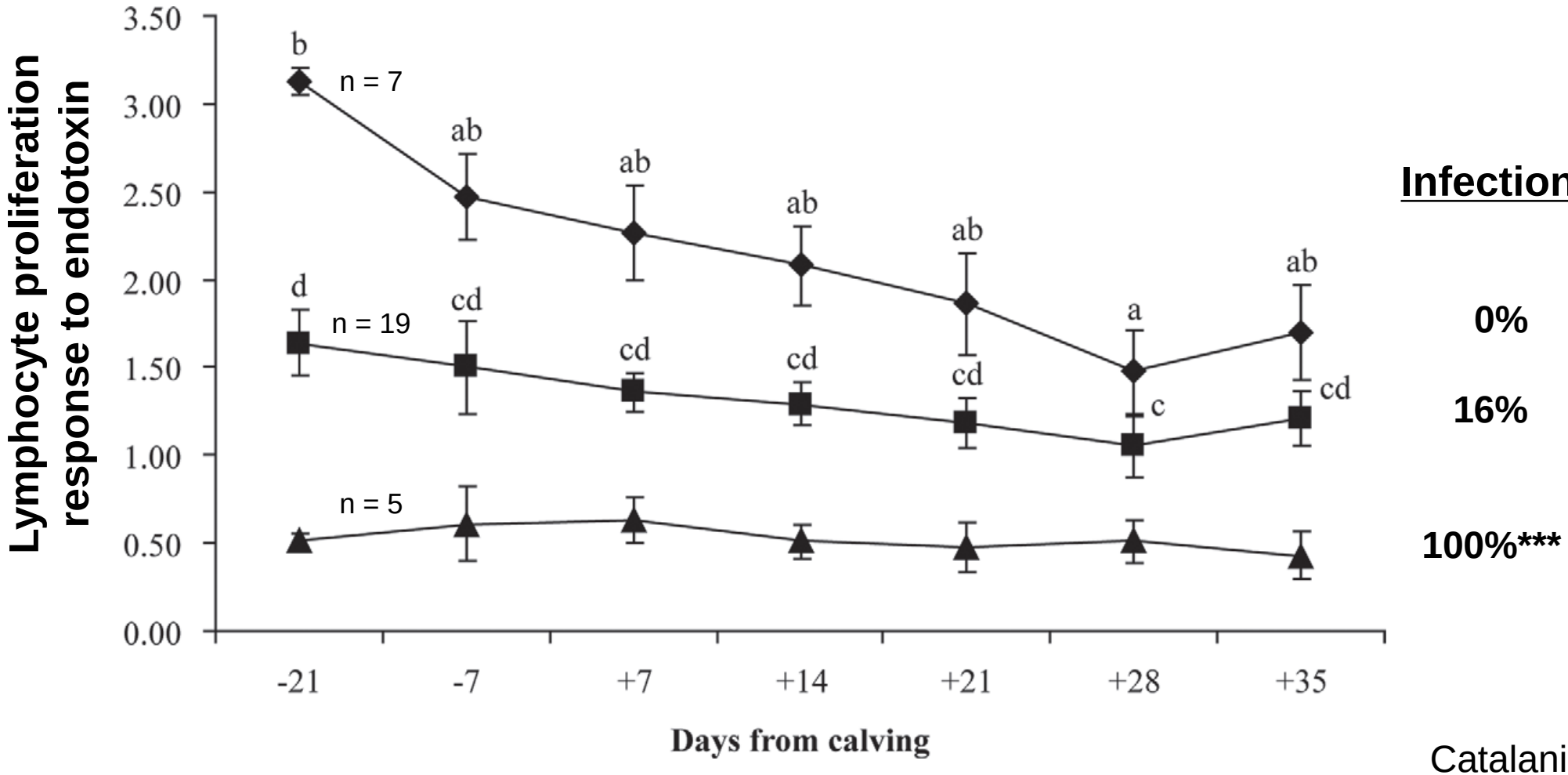
Oxidative burst is the production of reactive oxygen species by neutrophils as a killing tool.

Transition leukocytes have decreased functionality



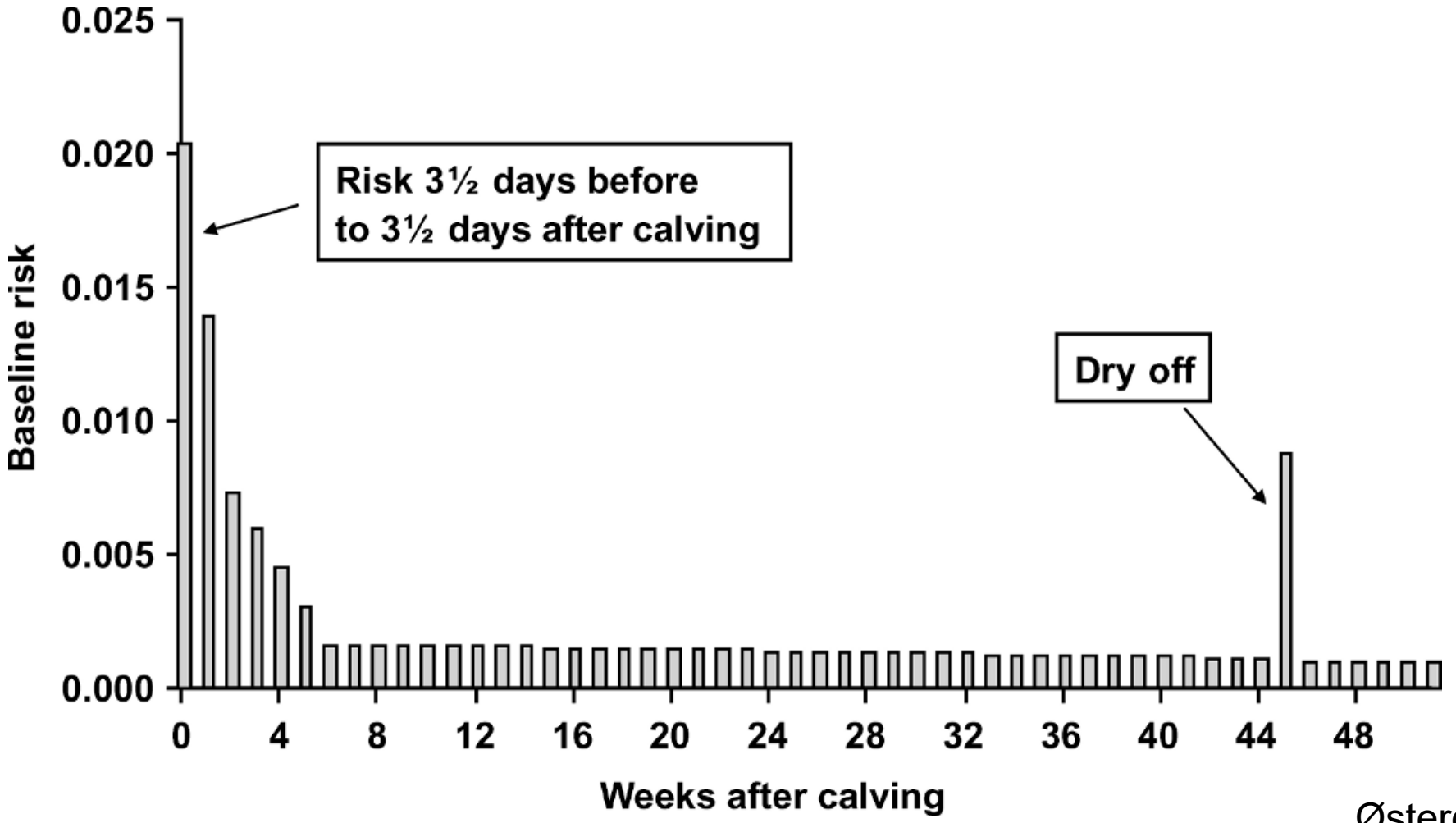
Goff and Horst, 1997

Immune function predicts infection risk (small study)



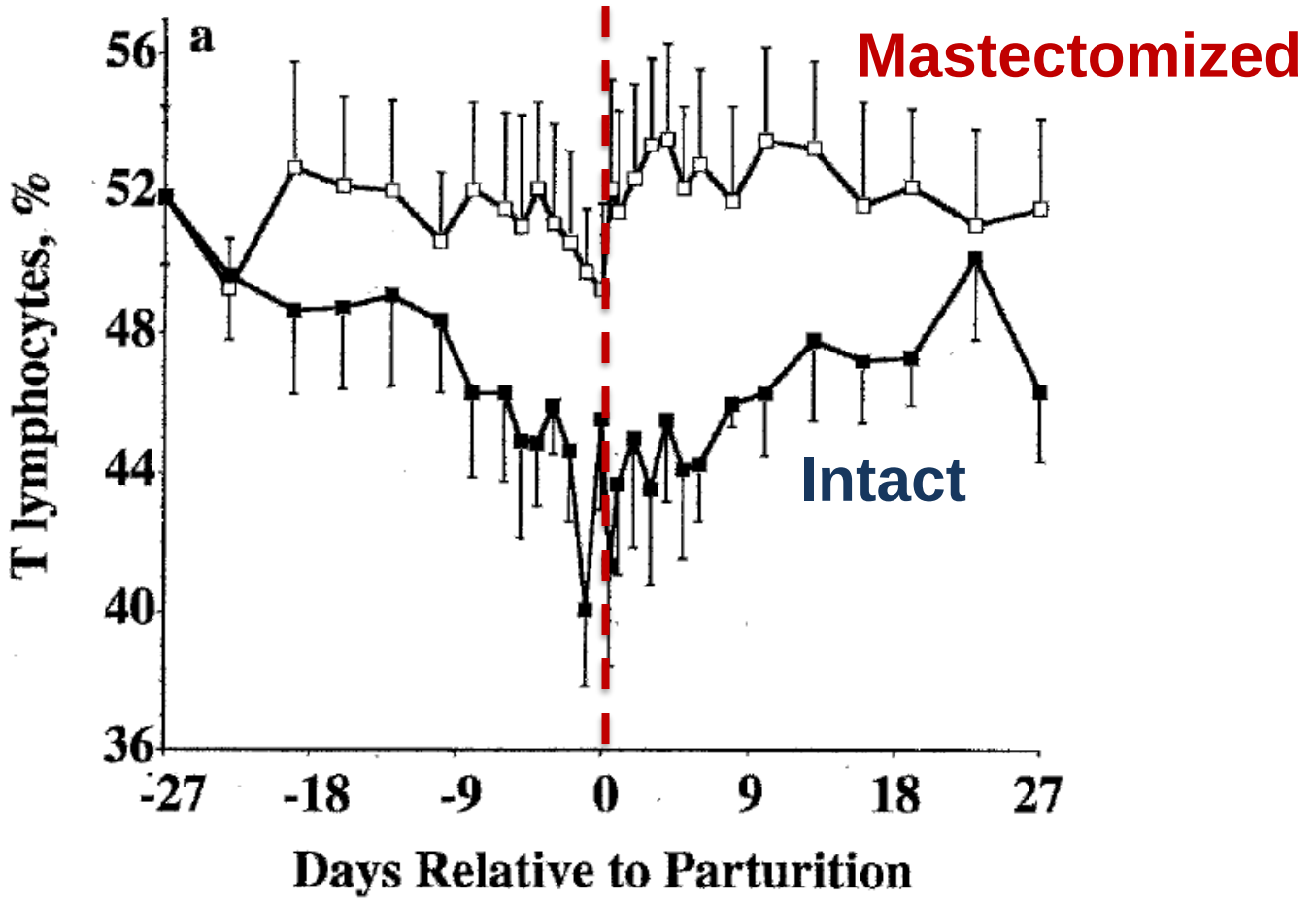
Catalani et al, 2013

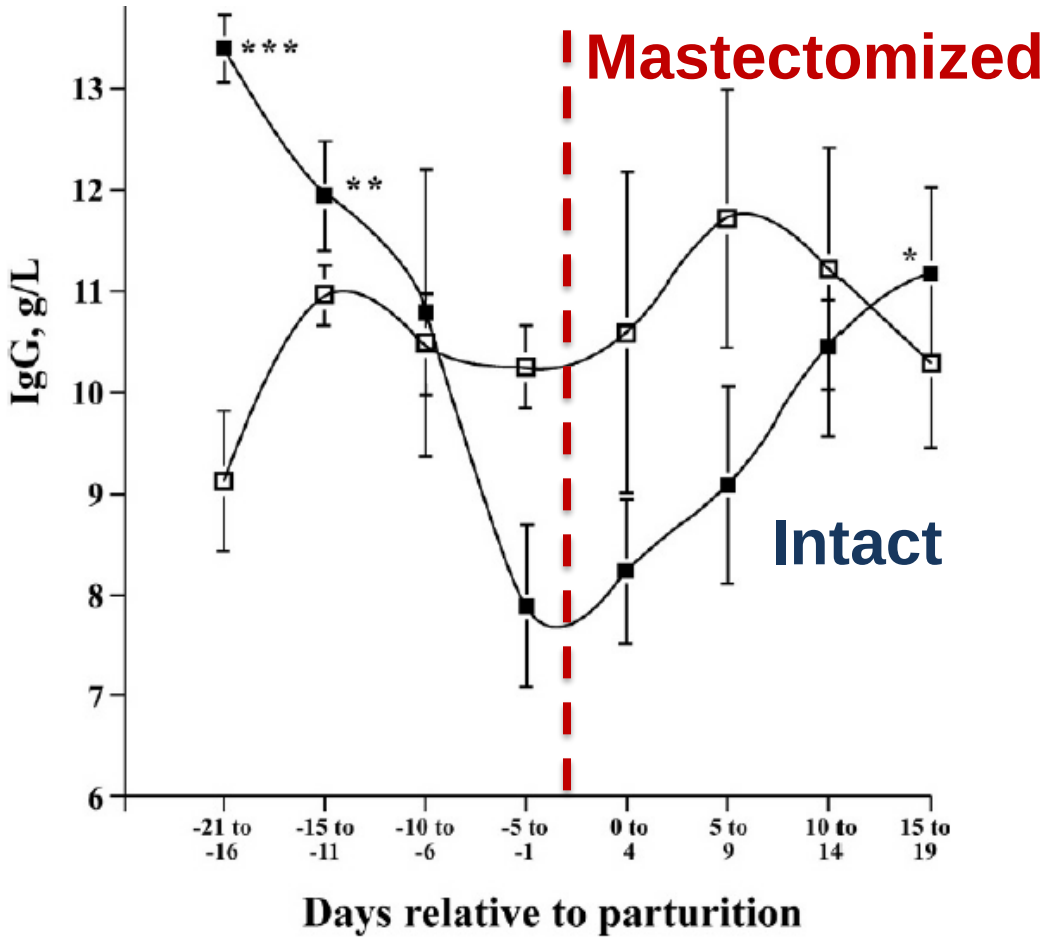
Immunosuppression coincides with greater infection risk



Østergaard et al, 2005

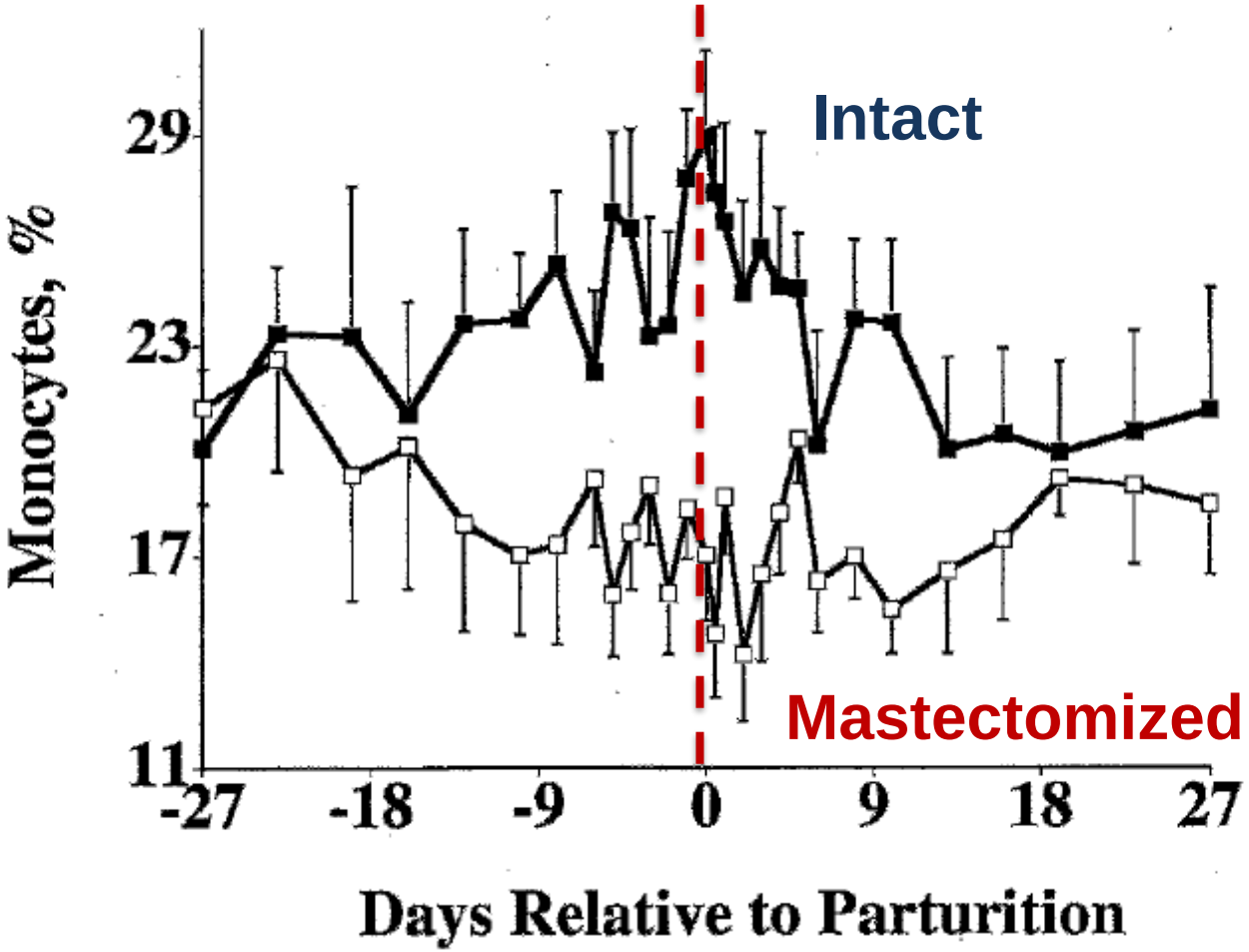
Is the mammary gland to blame?





Kimura et al., 2002; Nonnecke et al., 2003

Is the mammary gland to blame?

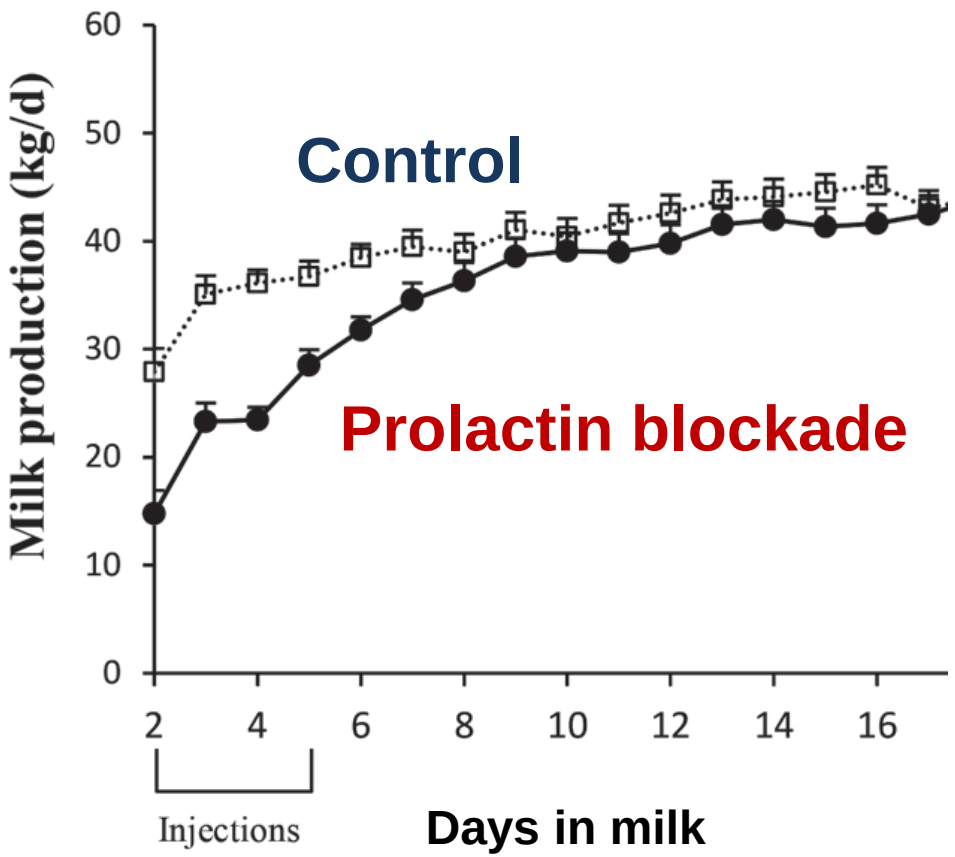


- Enhanced inflammatory response

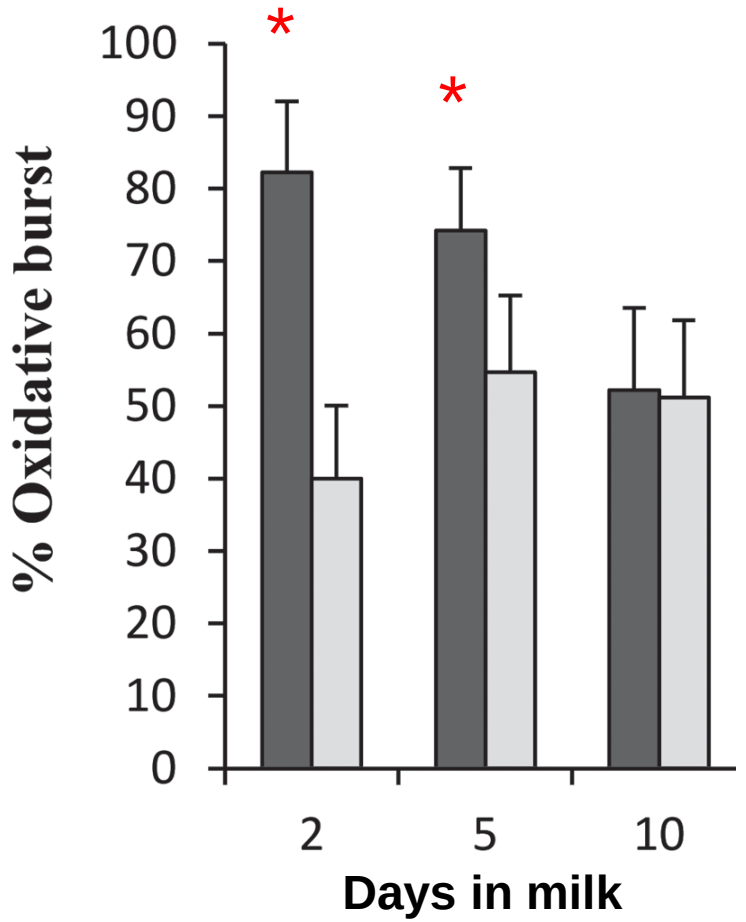
- Impaired chemotaxis
- Decreased phagocytosis
- Reduced killing ability

Kimura et al., 2002; Sordillo et al., 1995; Contreras et al., 2012; Kehrli et al., 1989; Nonnecke et al., 2003

Is the mammary gland to blame?

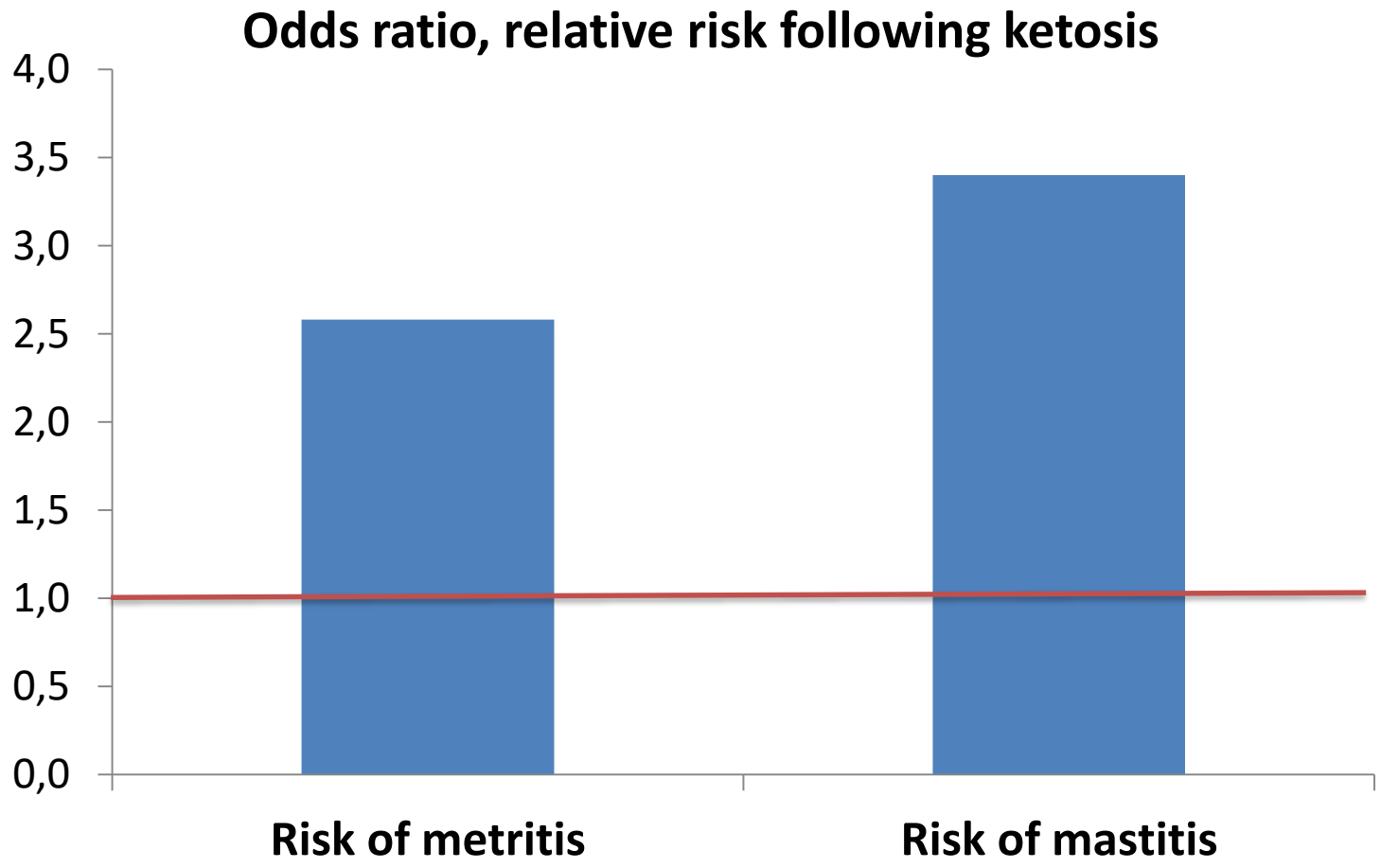


Lower prolactin, ketones; Higher glucose, calcium



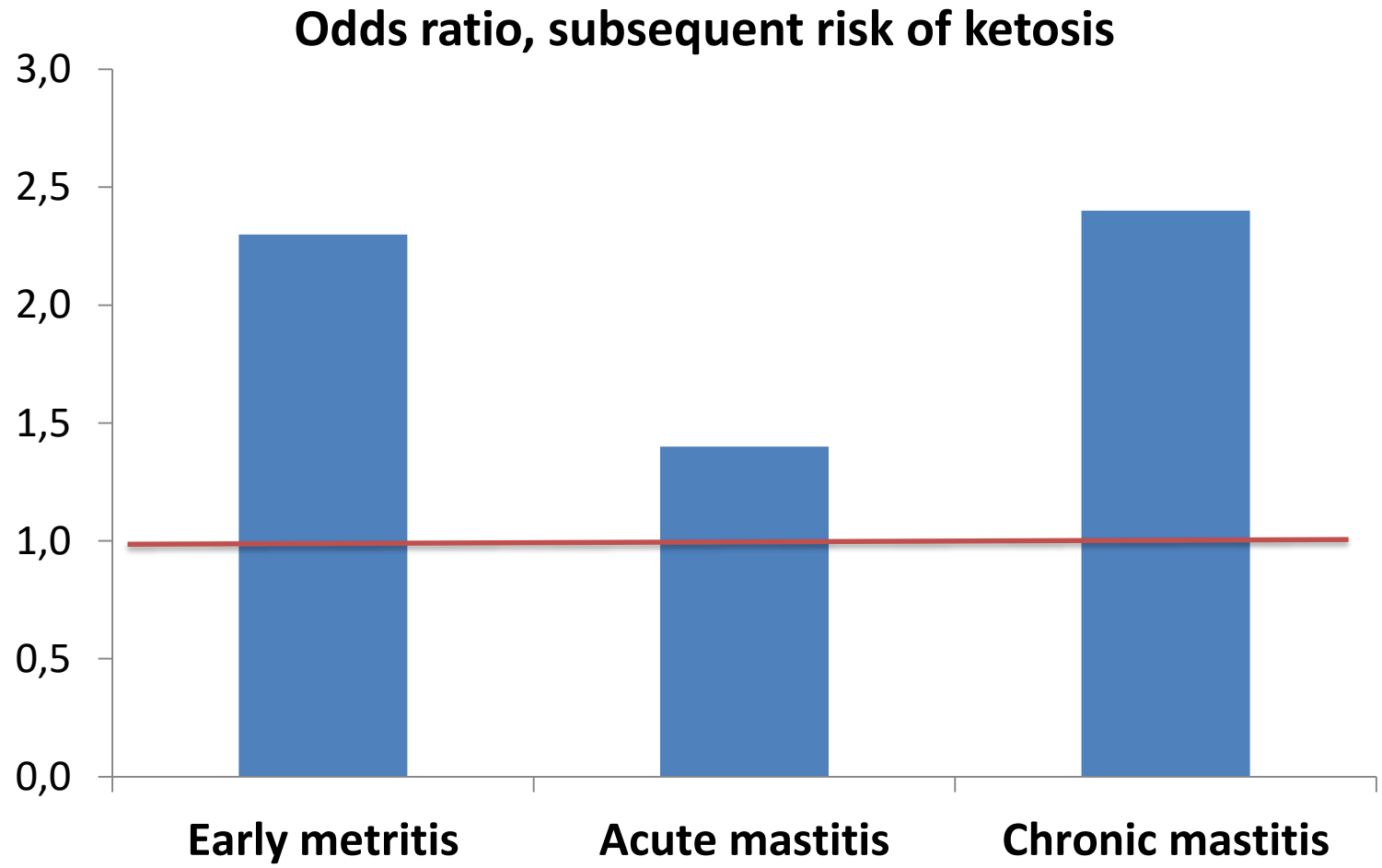
Vanacker et al., 2017

Ketosis associated with greater infection risk



Duffield et al., 2009; Doohoo and Martin, 1984

Infections associated with greater ketosis risk



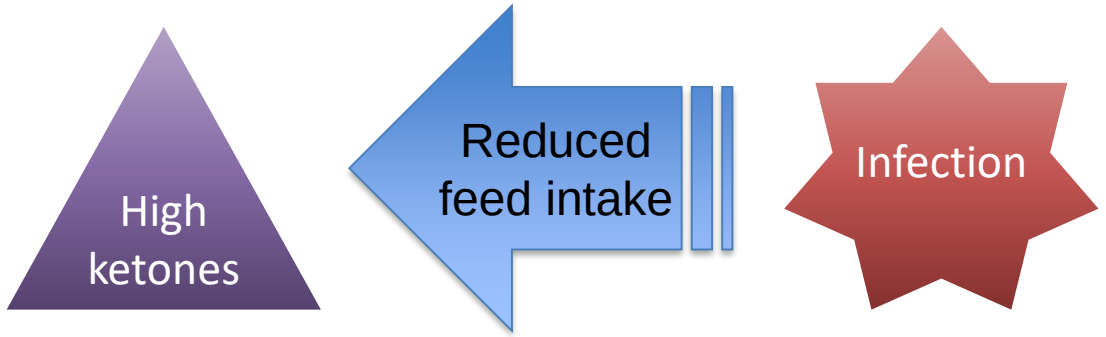
Gröhn et al., 1989

Transition cows: causal relationships are very hard

- **Example: ketosis and infectious disorders**

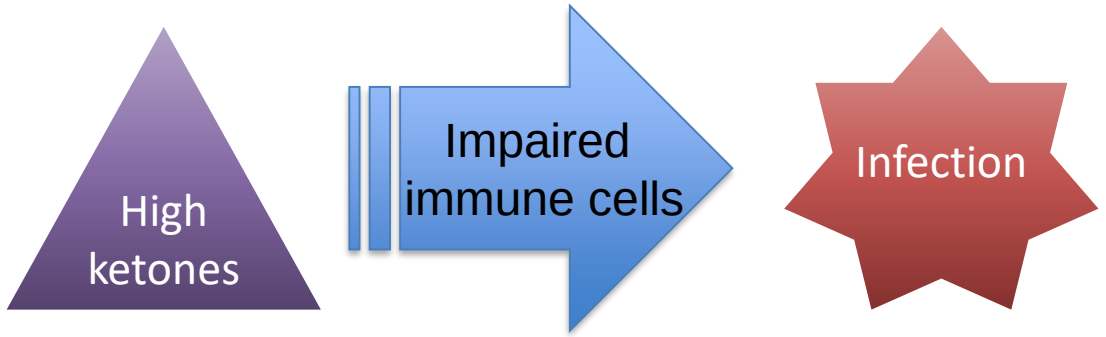
Transition cows: causal relationships are very hard

- **Example: ketosis and infectious disorders**
- **One view:**



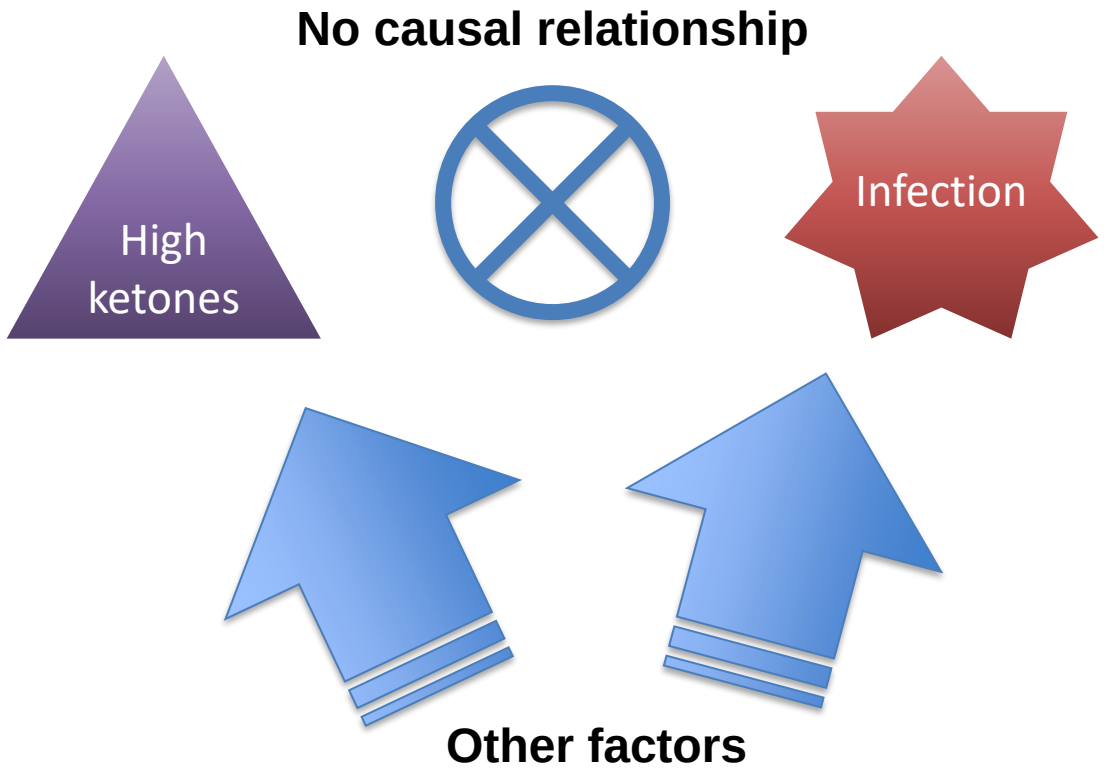
Transition cows: causal relationships are very hard

- **Example: ketosis and infectious disorders**
- **Another view:**

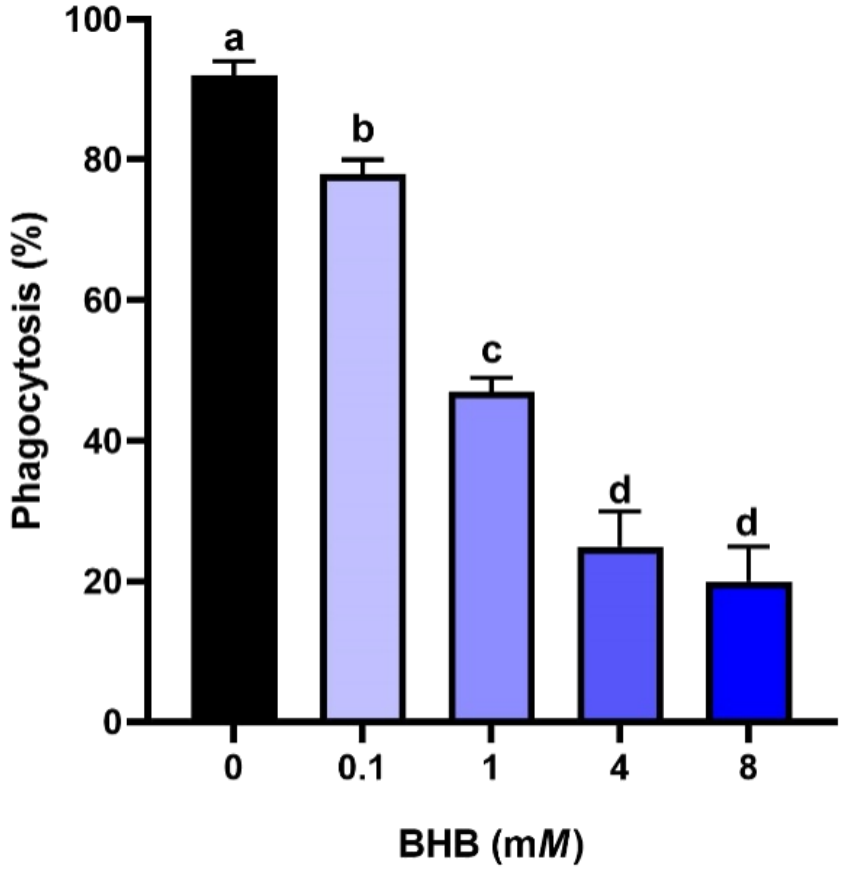


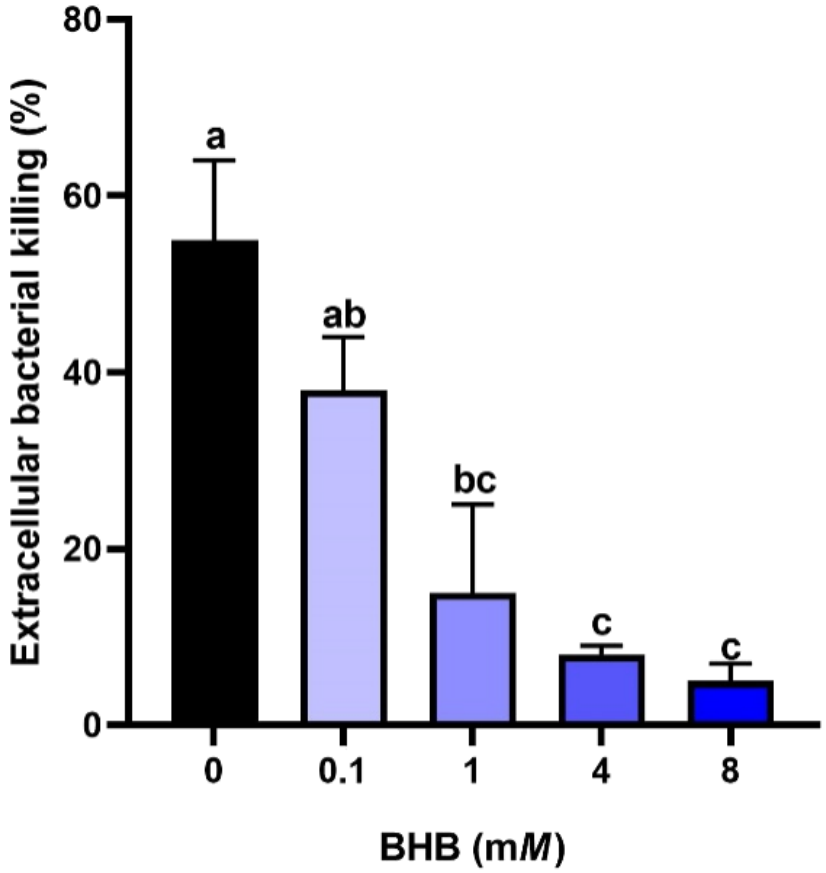
Transition cows: causal relationships are very hard

- **Example: ketosis and infectious disorders**
- **A third view:**



Ketone BHB impaired neutrophil bacterial killing





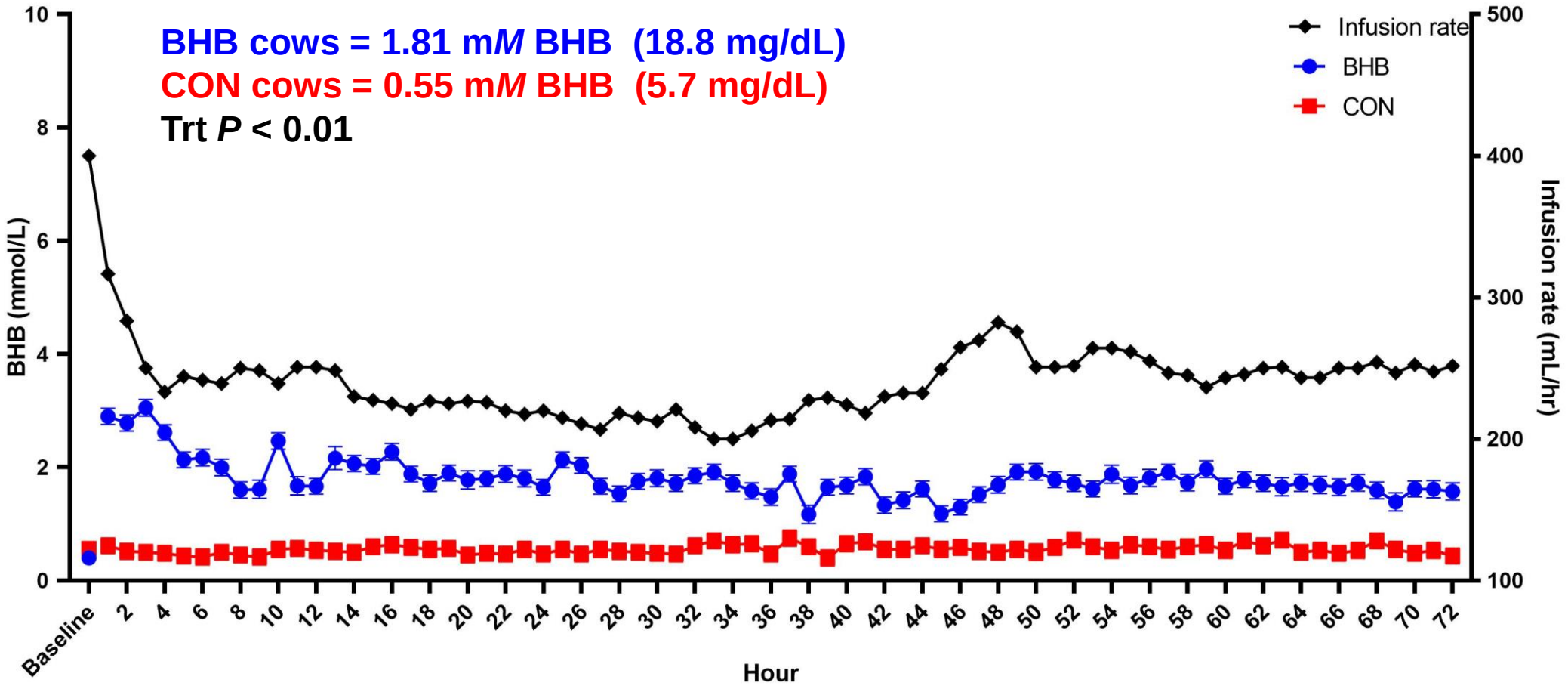
Different letters denote significance; Grinberg et al., 2008

Does BHB alter mastitis *in vivo*? Infusion study

- Late lactation cows (n = 12) continuously IV infused with either BHB (target: 1.8 m*M*) or isotonic saline for 72 h
- Challenged with *Strep uberis* in two quarters at the start of BHB infusion

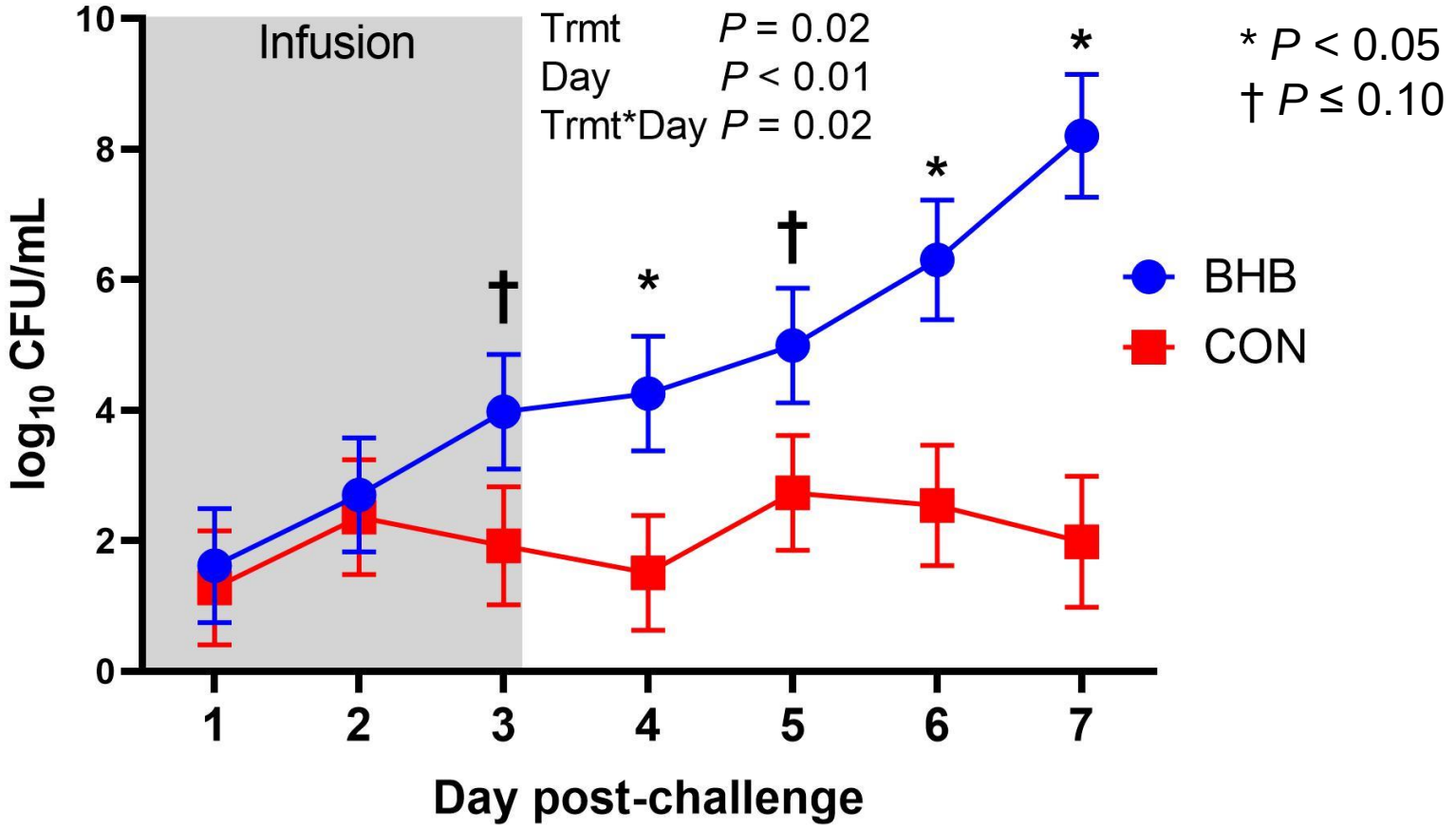
Swartz et al., 2021

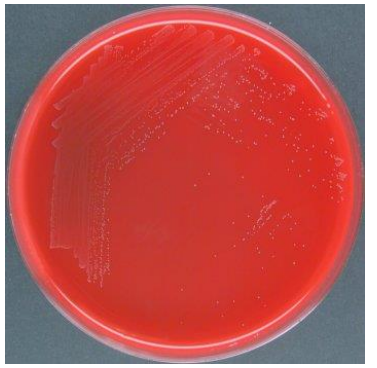
BHB clamp successful

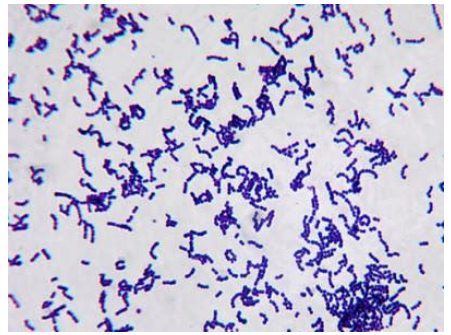


Swartz et al., 2021

S. uberis growth enhanced in BHB-infused cows

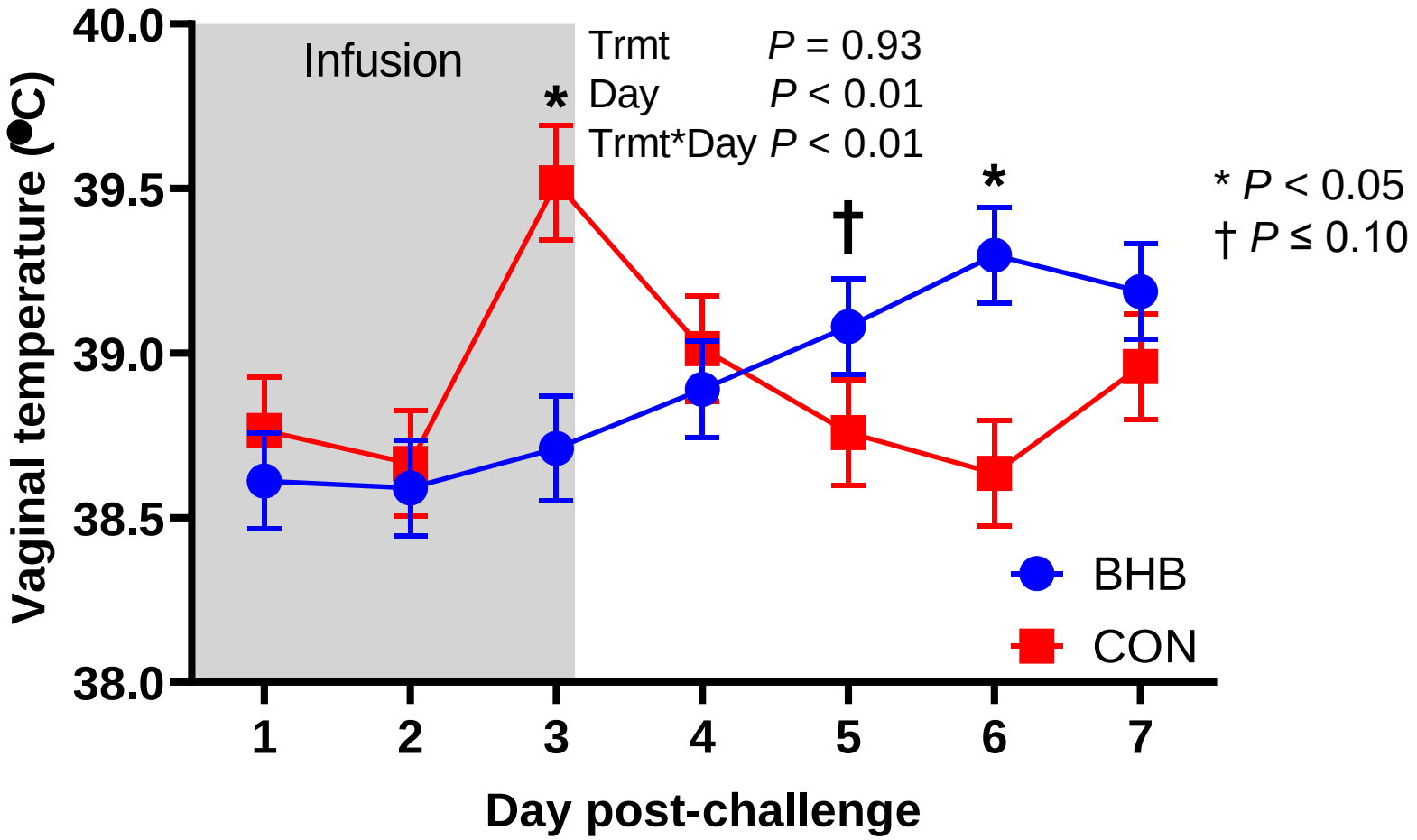






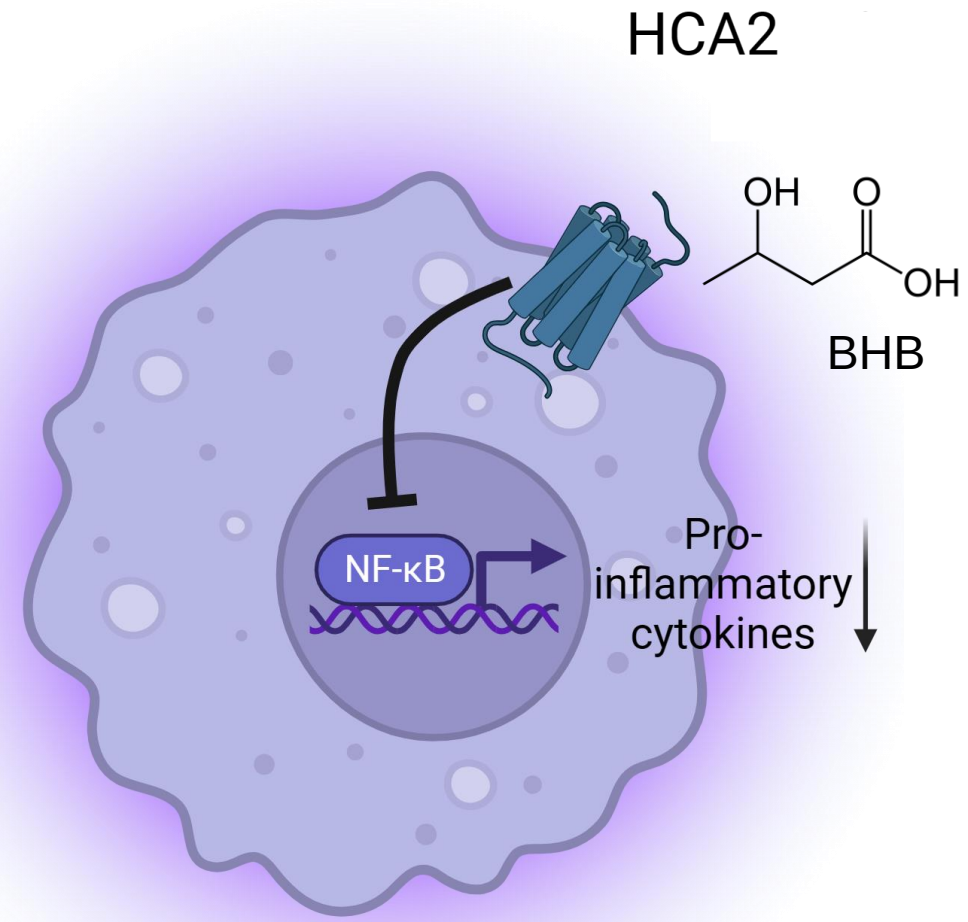
Swartz et al., 2021

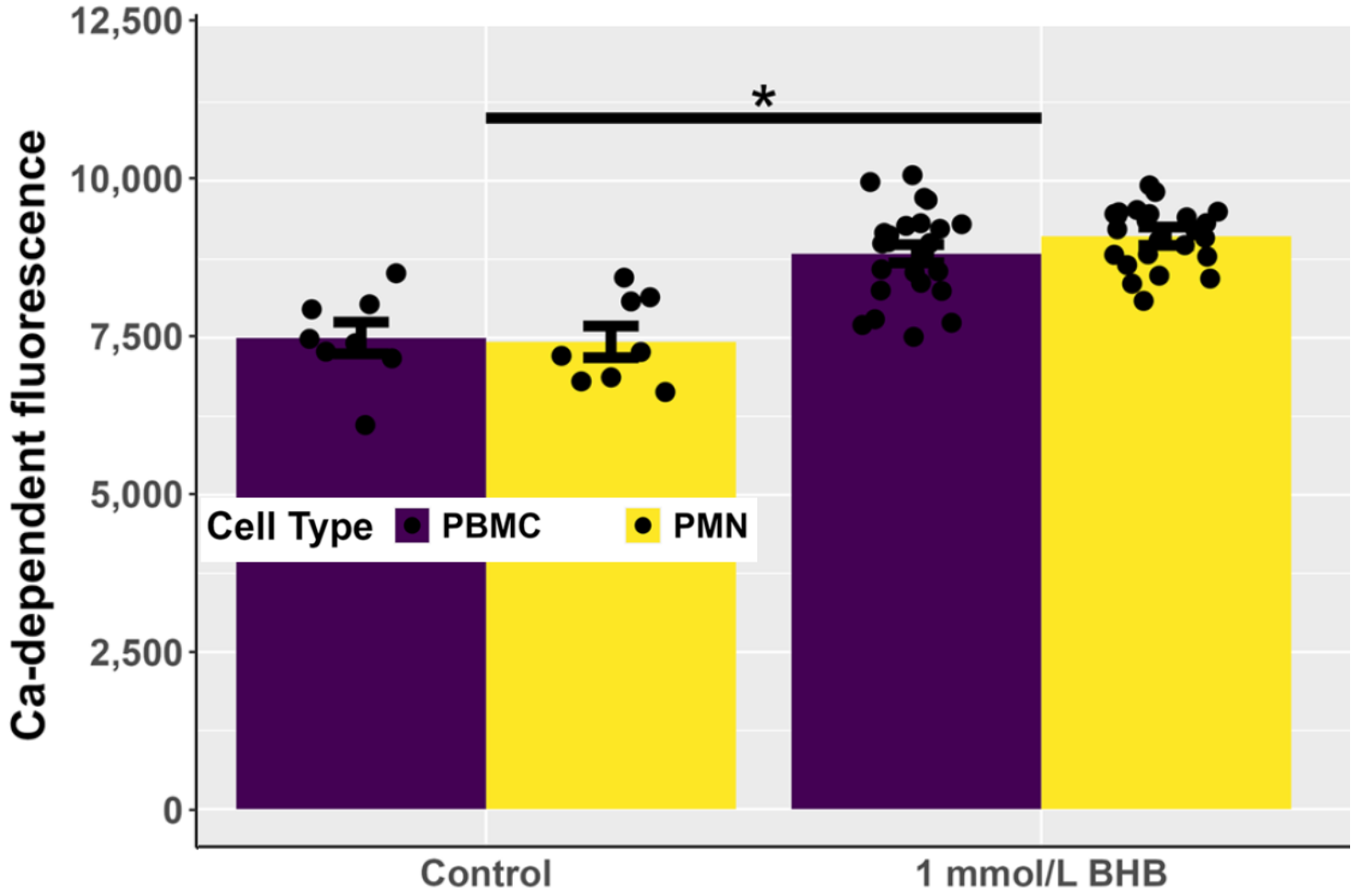
BHB delayed the febrile response to infection



Swartz et al., 2021

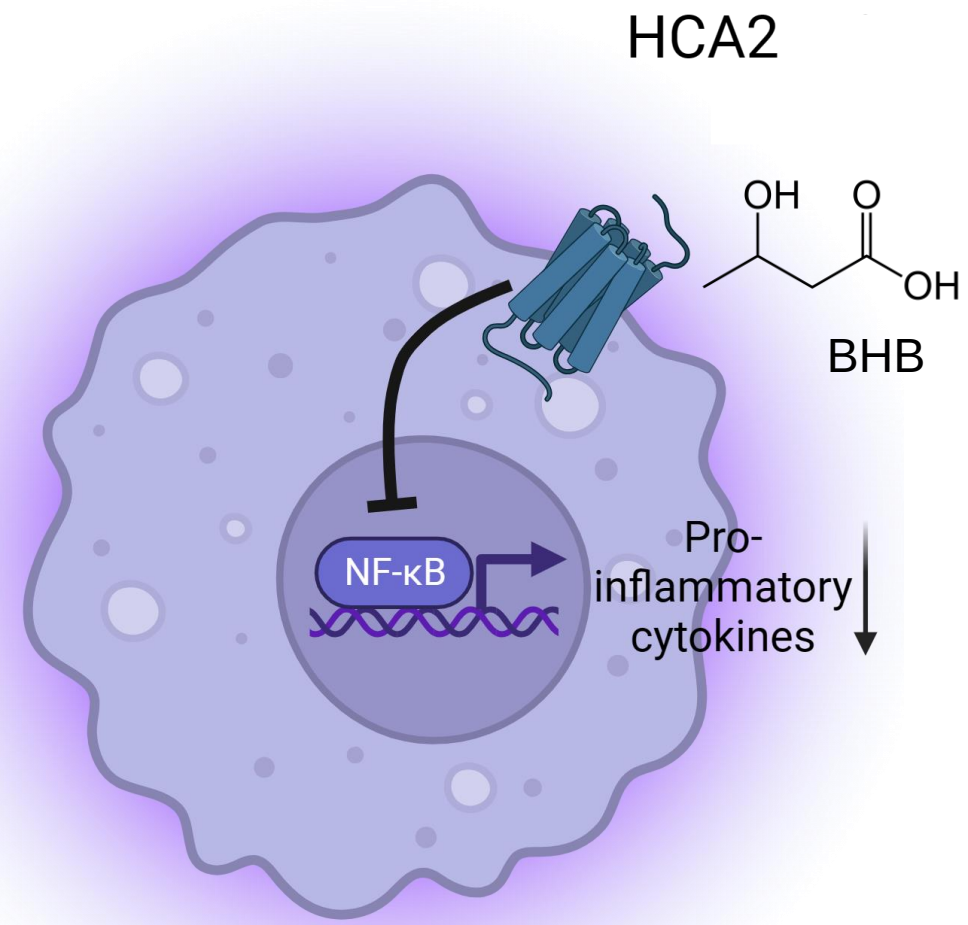
BHB reduces inflammation in multiple models / species

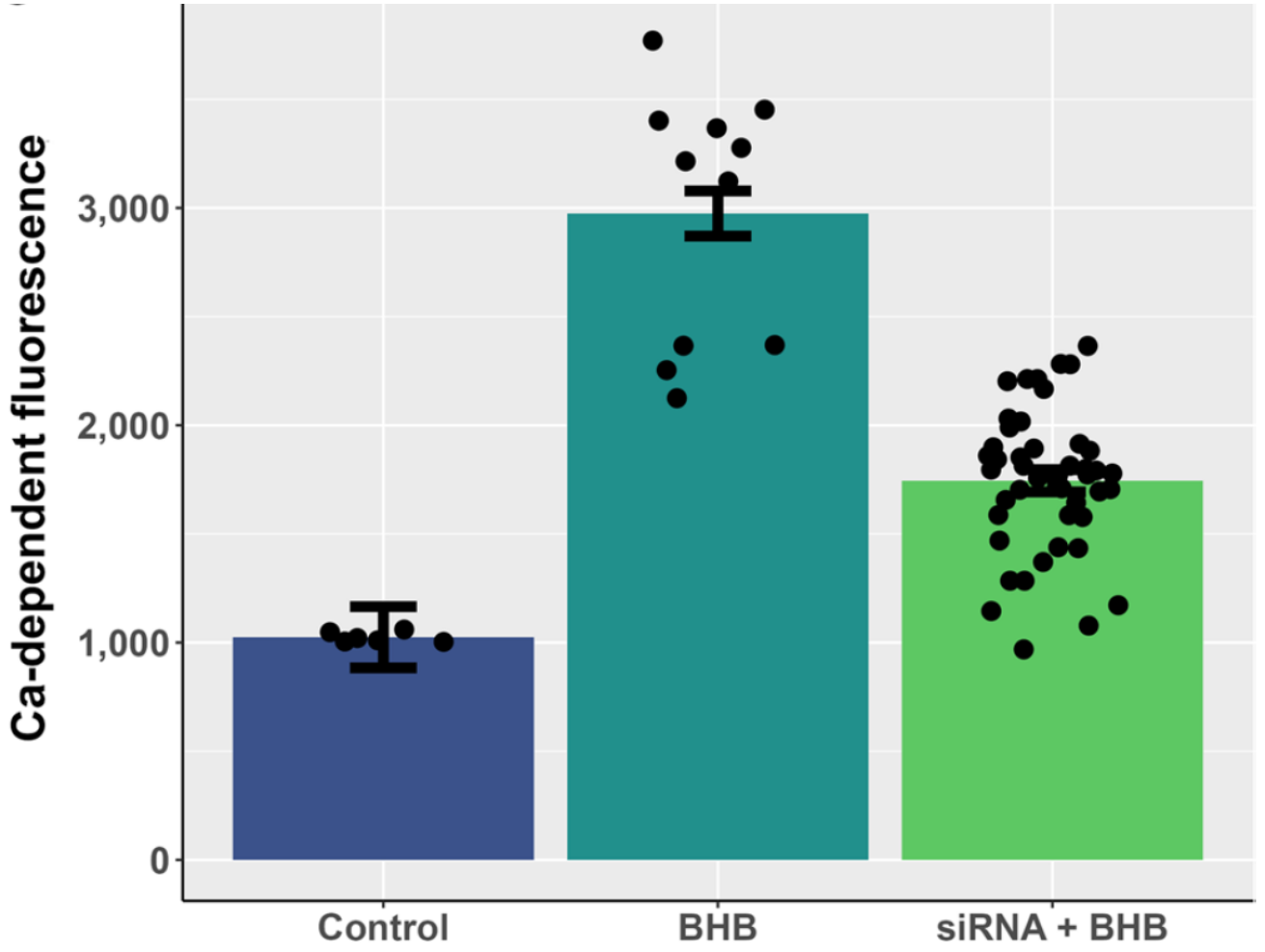




Mamedova et al., 2024

BHB acts at least partly through HCAR2 in bovine PBMC

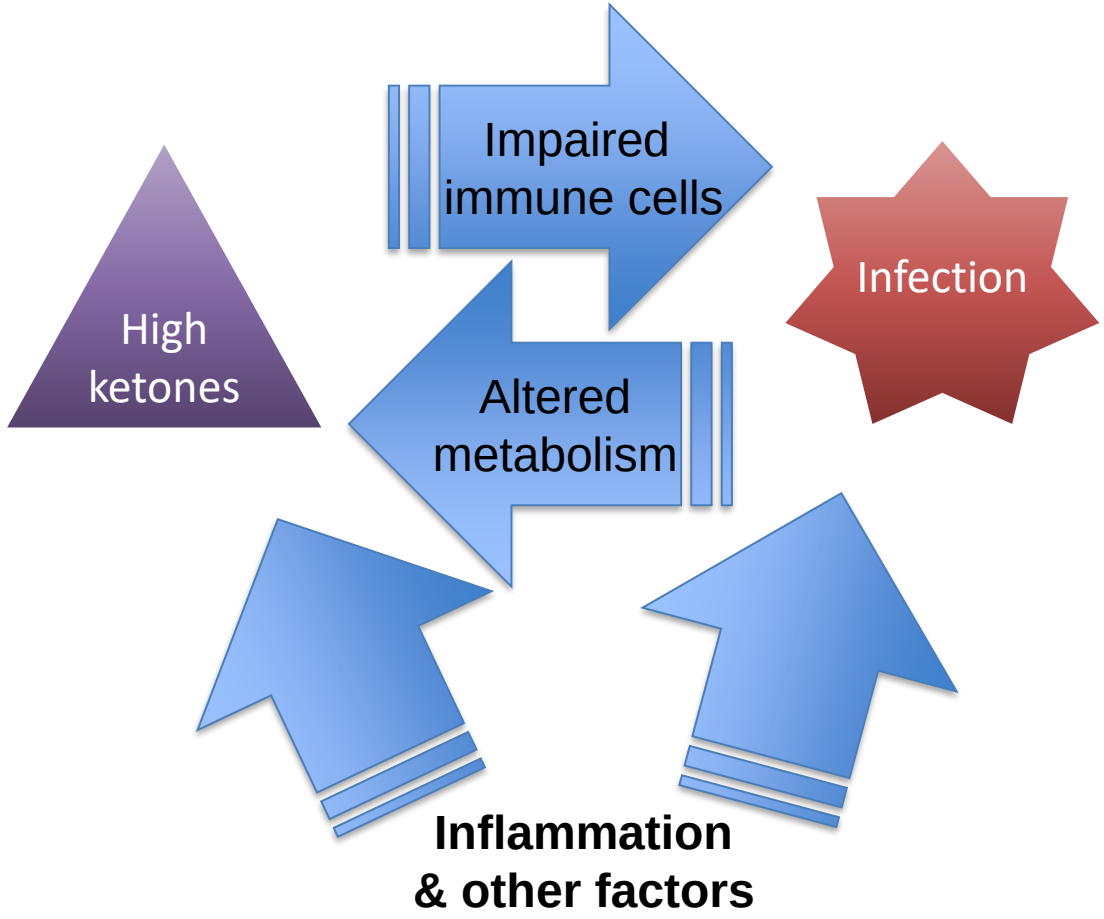




Mamedova et al., 2024

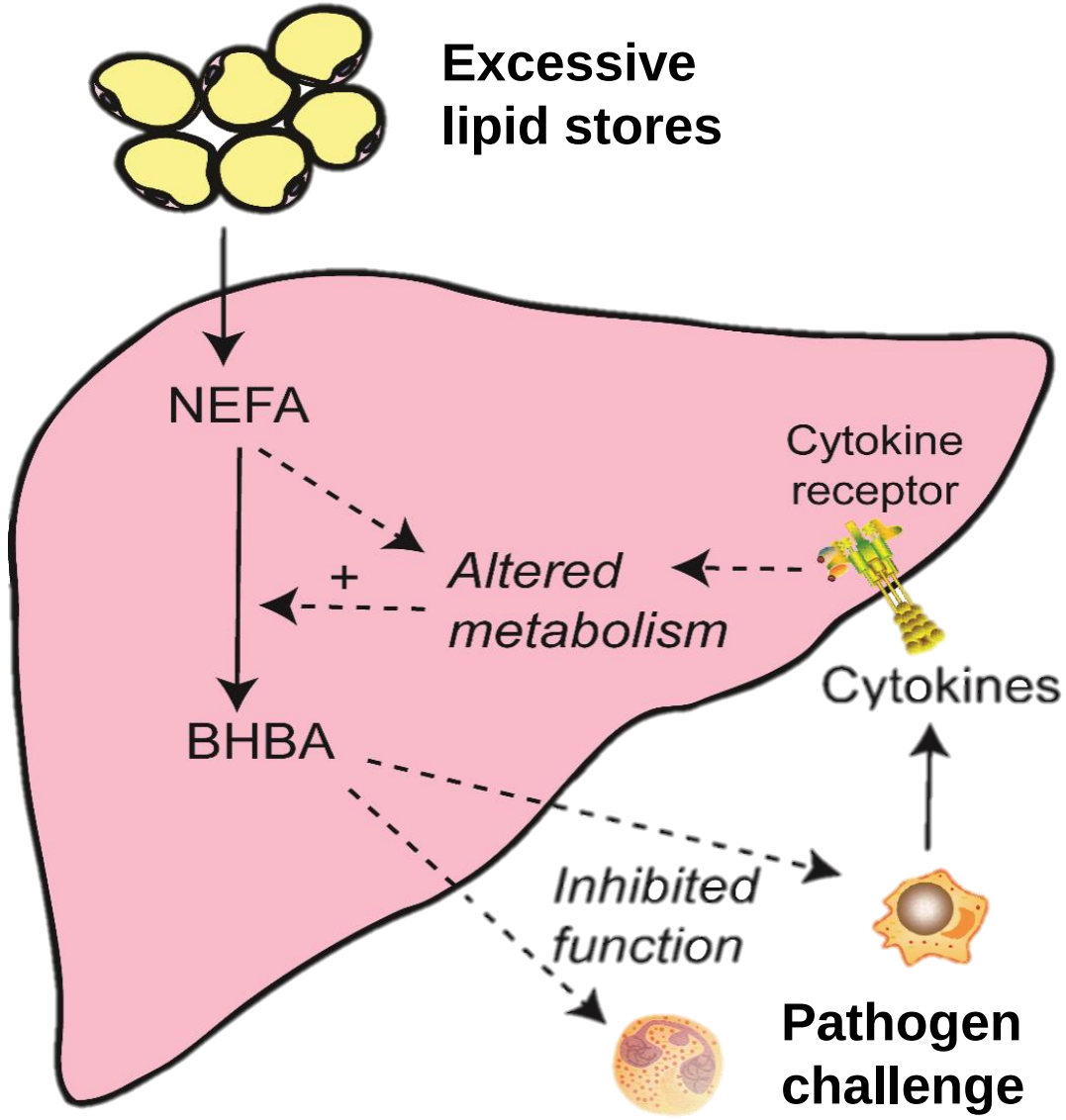
Transition cows: causal relationships are very hard

- **Example: ketosis and infectious disorders**
- **My view:**



A vicious cycle

Metabolic disorders
promote
Infections
promote
Metabolic disorders

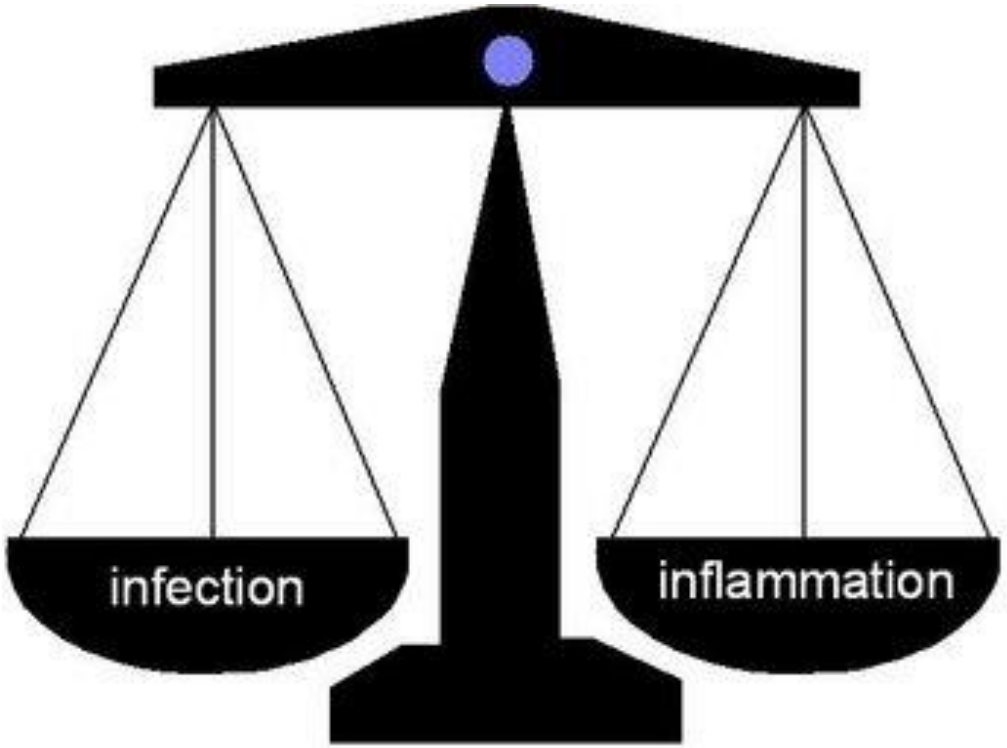


Balance is necessary….

Infections should draw
the focus
to immune support

Metabolic problems suggest an anti-inflammatory feeding strategies may help

But metabolic and infectious diseases are interwoven in transition cows!



Thank you!

Questions/comments:

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