Bacterial Toxin Repression of Nuclear Hormone Receptors: Host-Pathogen-Hormone Interactions and Implications for Therapy

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Host Hormone-Immune-Bacterial Interactions: Implications for Susceptiblity to Inflammatory Sequelae of Bacterial Infections

- Do hormones affect host inflammatory/immune responses?
  - Glucocorticoids
  - Estrogen
  - Progesterone
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  - *B. anthracis* LeTx
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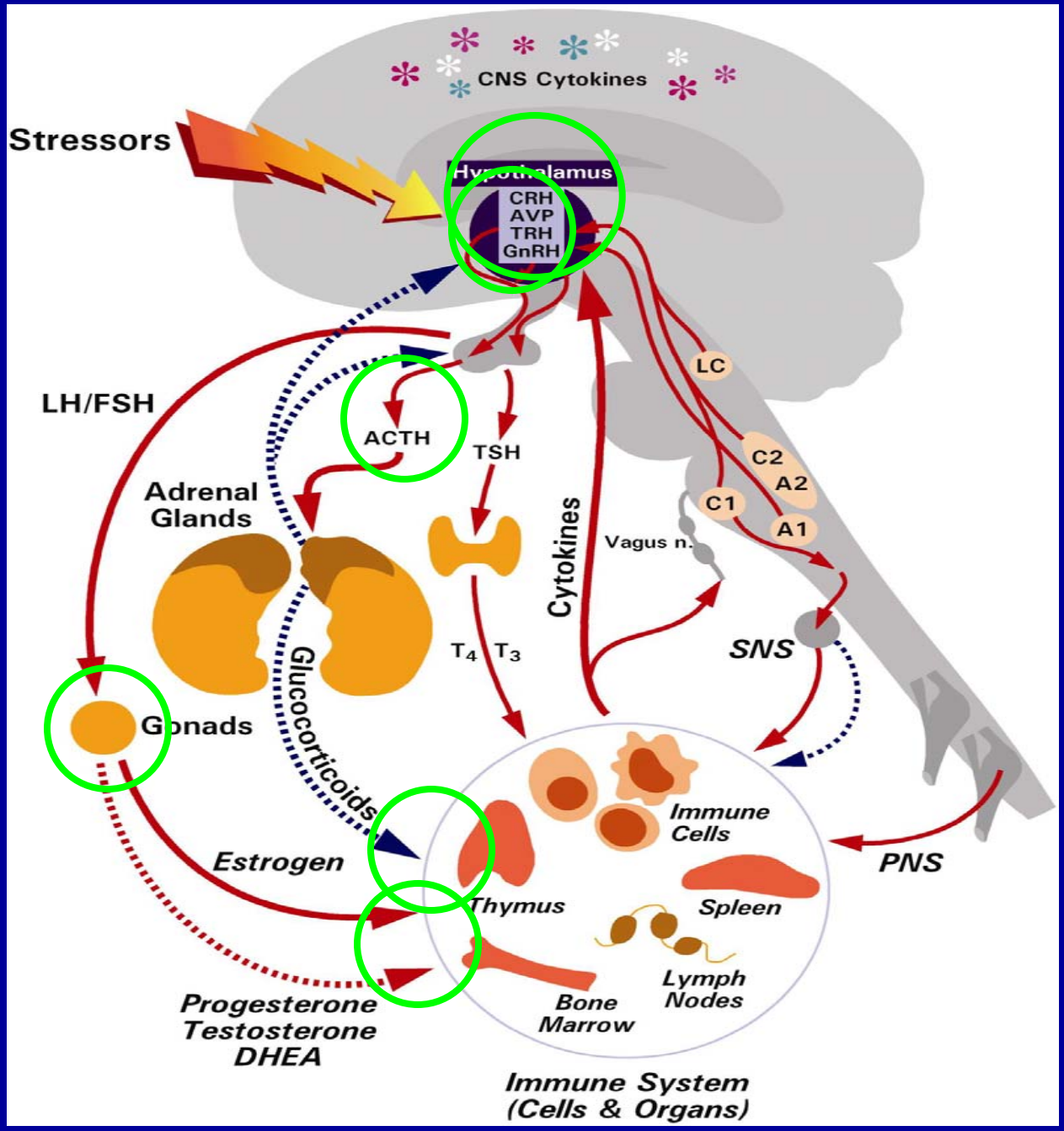
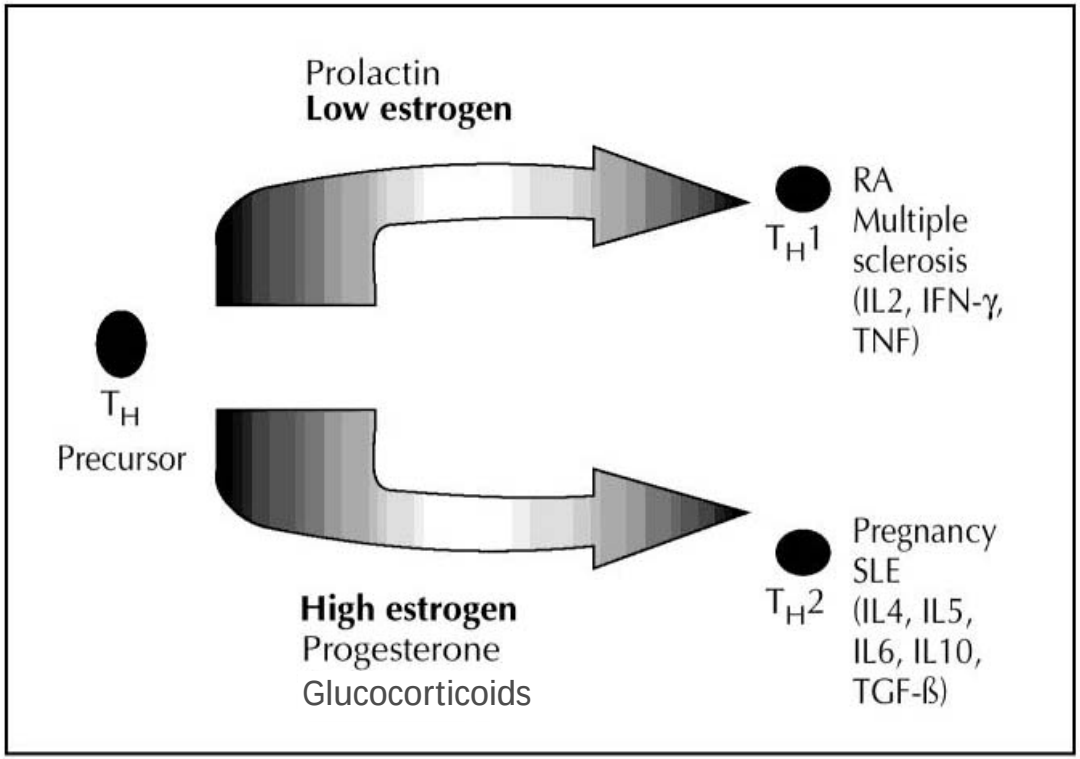

CNS Cytokines
Stressors
Hypothalamus
CRH
AVP
TRH
GnRH
LH/FSH
ACTH
TSH
LC
C2
A2
C1
A1
Adrenal Glands
Cytokines
Vagus n.
SNS
T4 T3
Glucocorticoids
Gonads
Immune Cells
PNS
Estrogen
Thymus
Spleen
Lymph Nodes
Bone Marrow
Progesterone
Testosterone
DHEA
Immune System
(Cells & Organs)

Effects of Estrogen & Progesterone on T Helper Phenotypes:

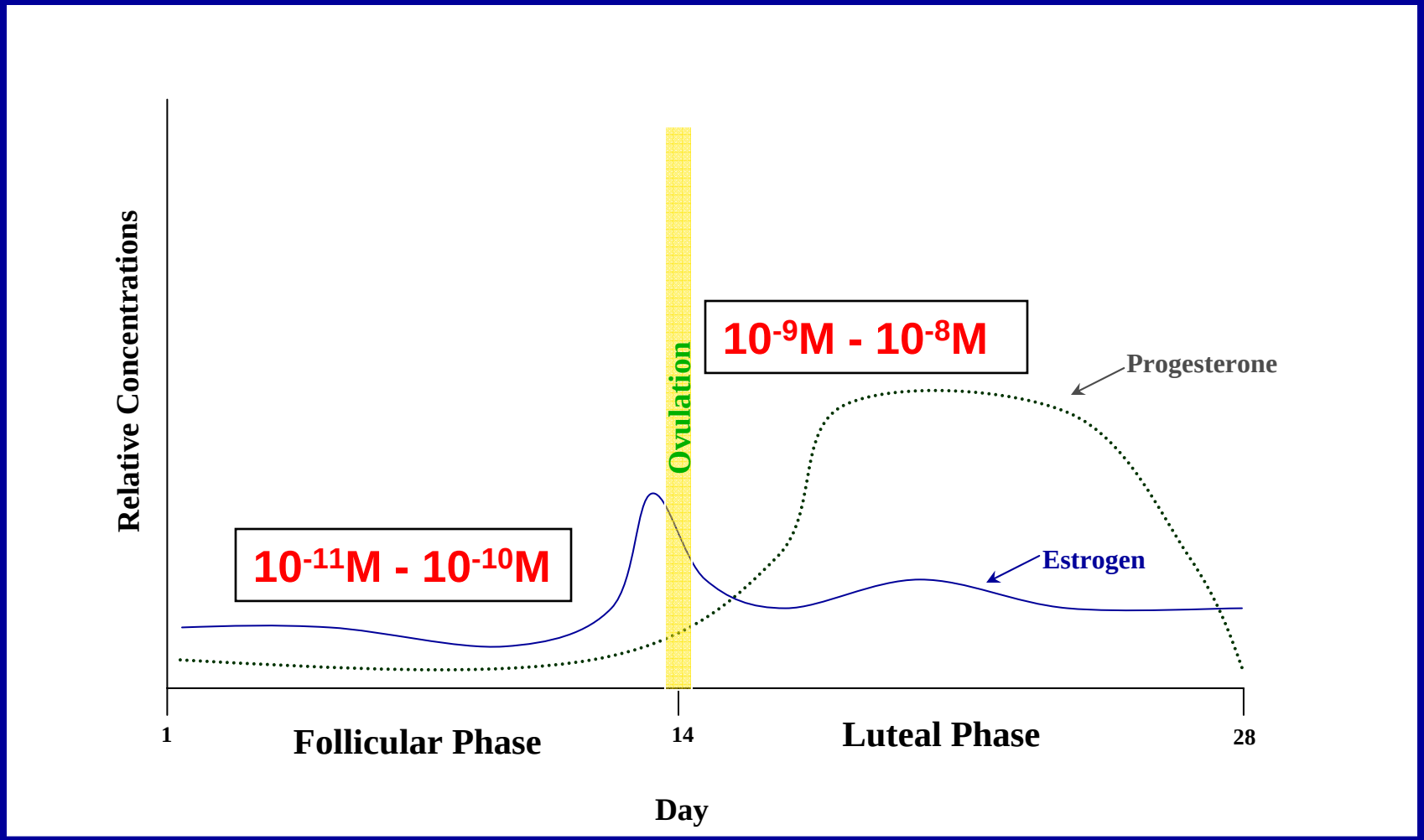


Cellular

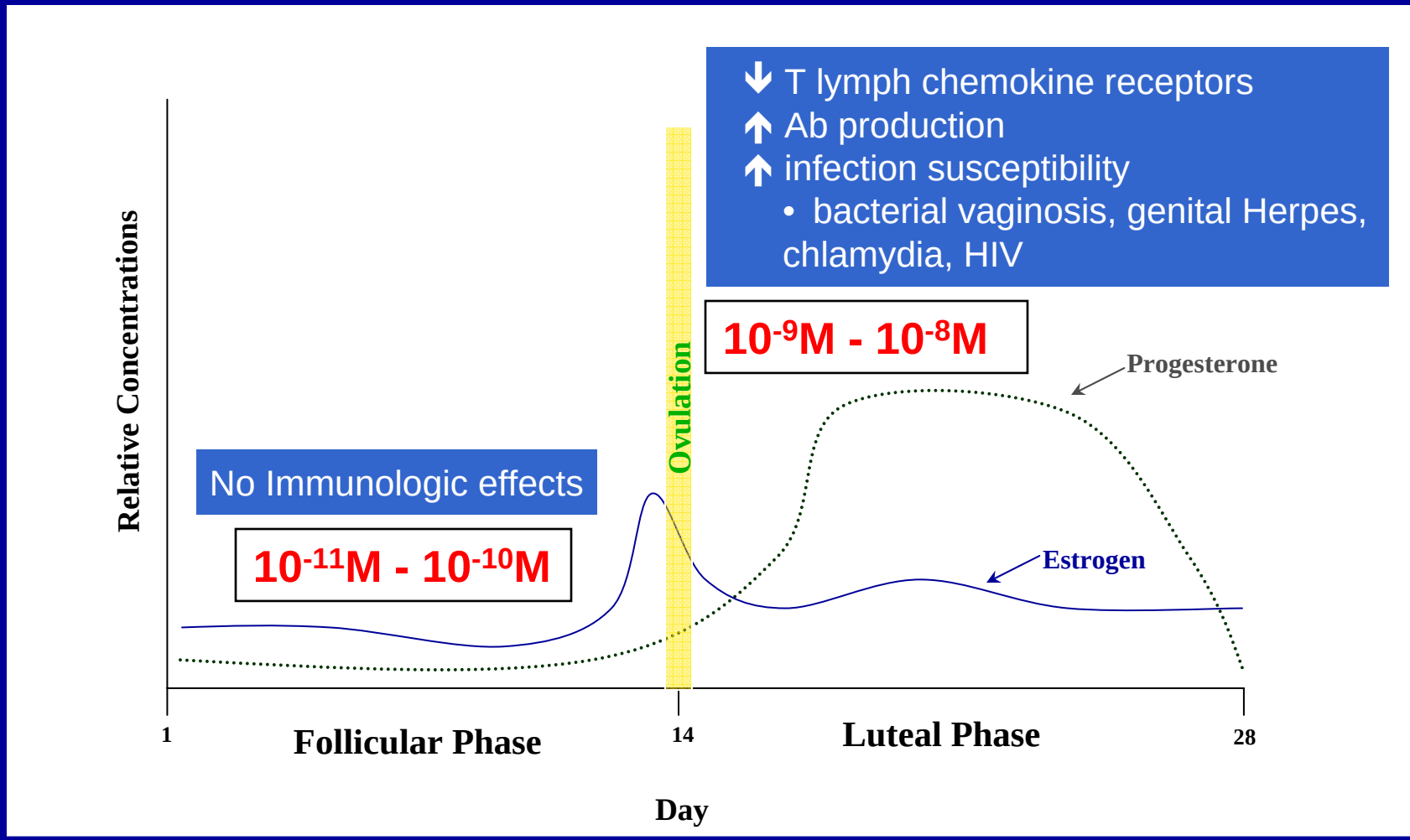
Humoral

Lahita, 1999

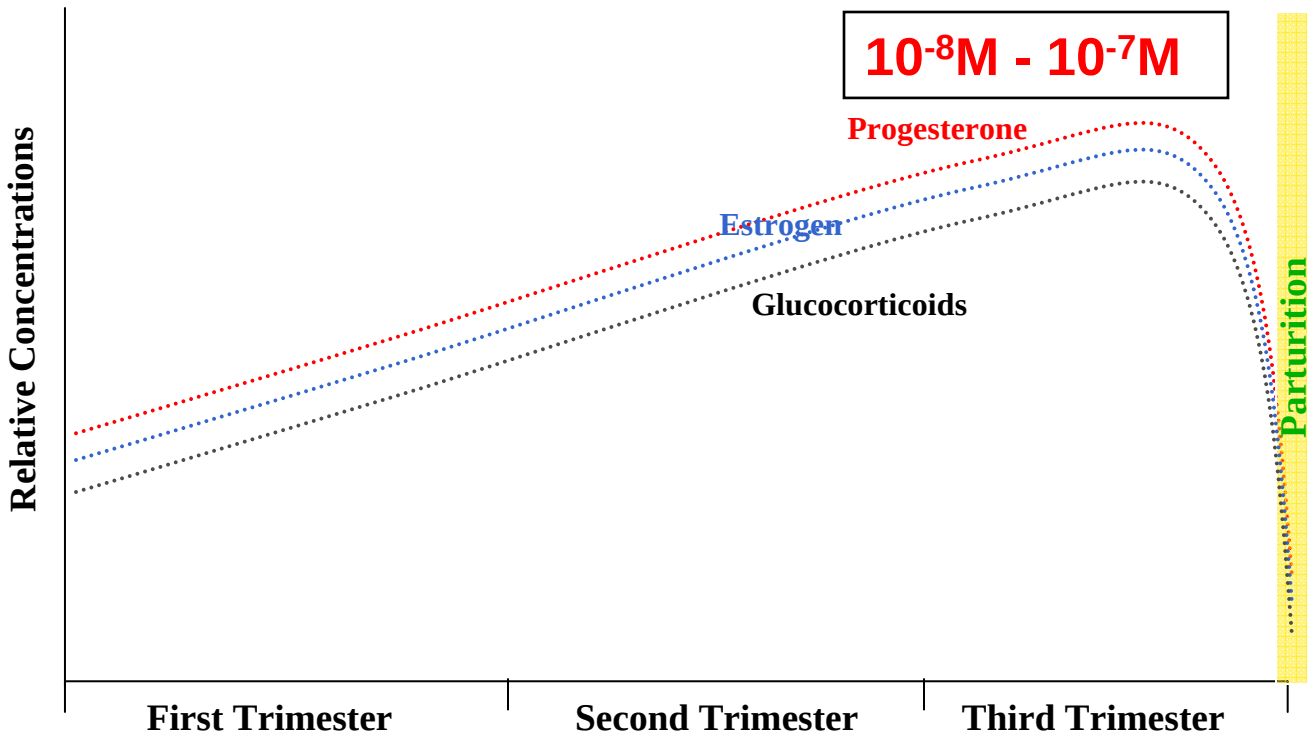
Estrogen & Progesterone Vary during the Menstrual Cycle



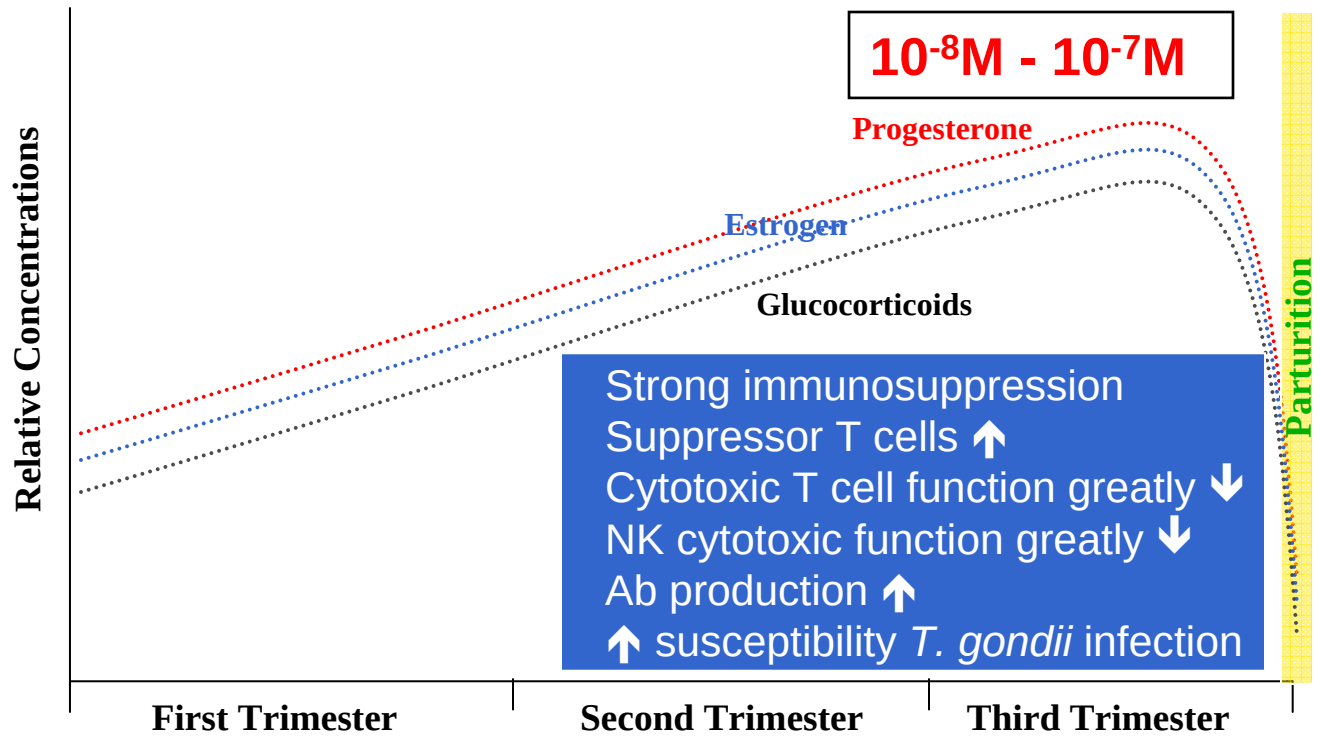
Changes in Immune Function during Menstrual Cycle



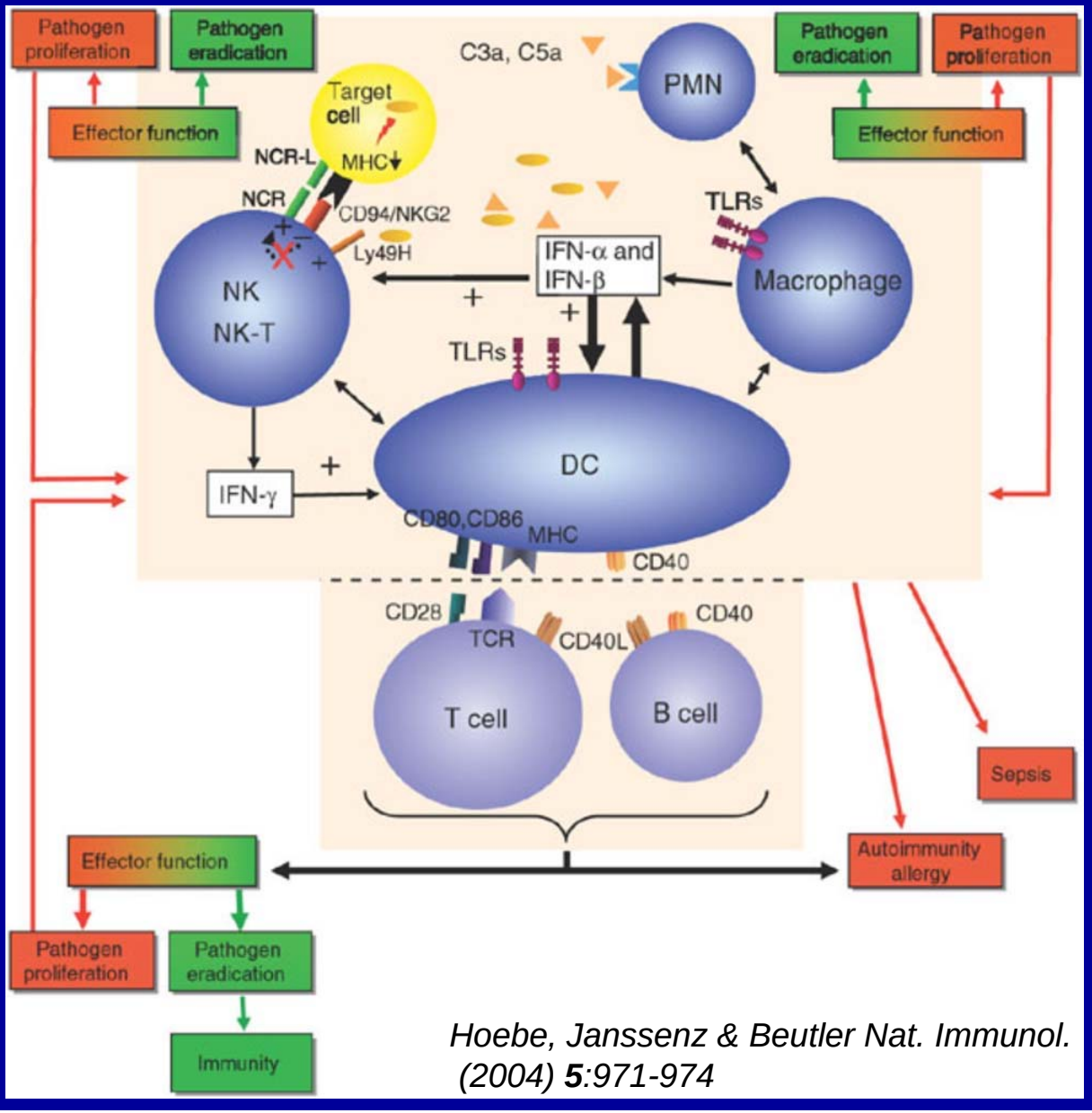
Progesterone, Estrogen, Glucocortcoids during Pregnancy



Changes in Immune Function during Pregnancy

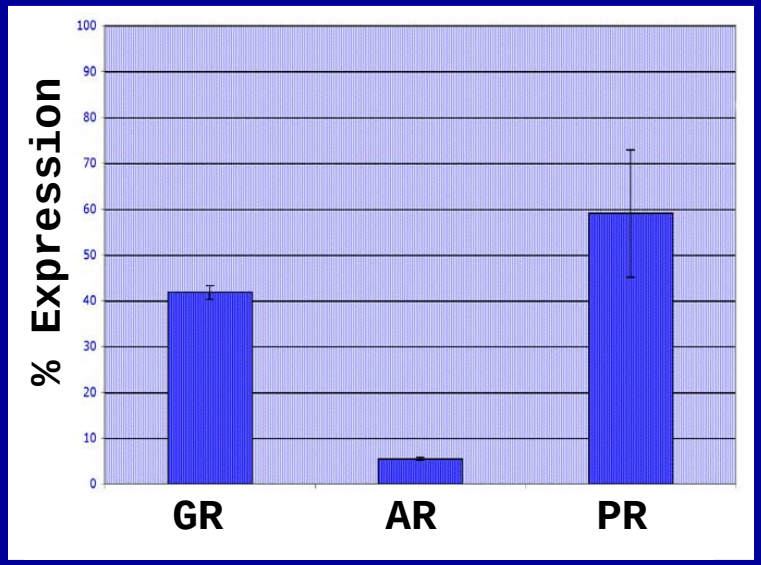


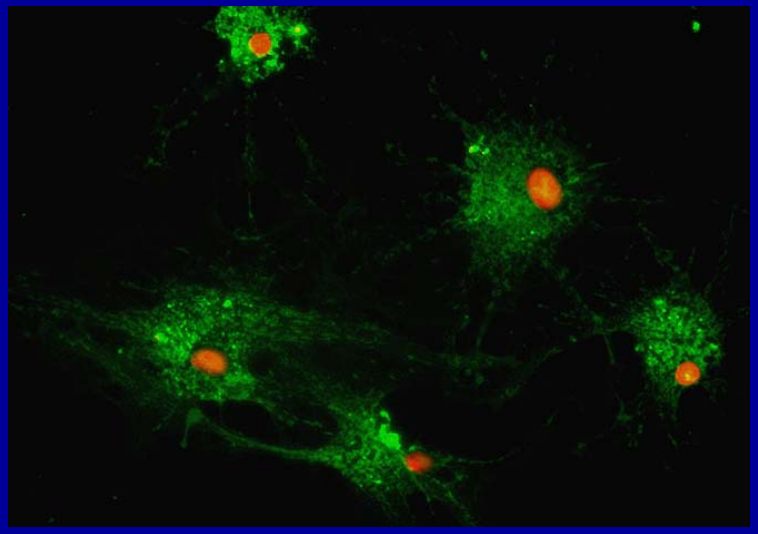
Dendritic Cells: bridge between innate inflammation and adaptive immune responses



Hoebe, Janssenz & Beutler Nat. Immunol. (2004) ***5****:971-974*

Steroid Hormone Receptor Expression in Cultured Dendritic Cells (CD11c+)





FACS Analysis:
% DCs expressing steroid hormone receptors (female rats).

Fluorescent micrograph
cultured DC cells expressing PR in cytoplasm

Progesterone Receptor
Nucleus

Butts et al. unpublished data not for dissemination

Progesterone Effects on DC Cell Function:

(C. Butts et al., submitted 2006)

Progesterone has functional effects on mature but not immature DCs:

- **Does not affect Ag uptake by immature DCs**
- **Suppresses pro-inflammatory (TNFα) but not anti-inflammatory (IL-10) cytokine production**
- **Down-regulates co-stimulatory molecule expression (MHCII & CD80)**

Overall effect of progesterone on DCs is anti-inflammatory

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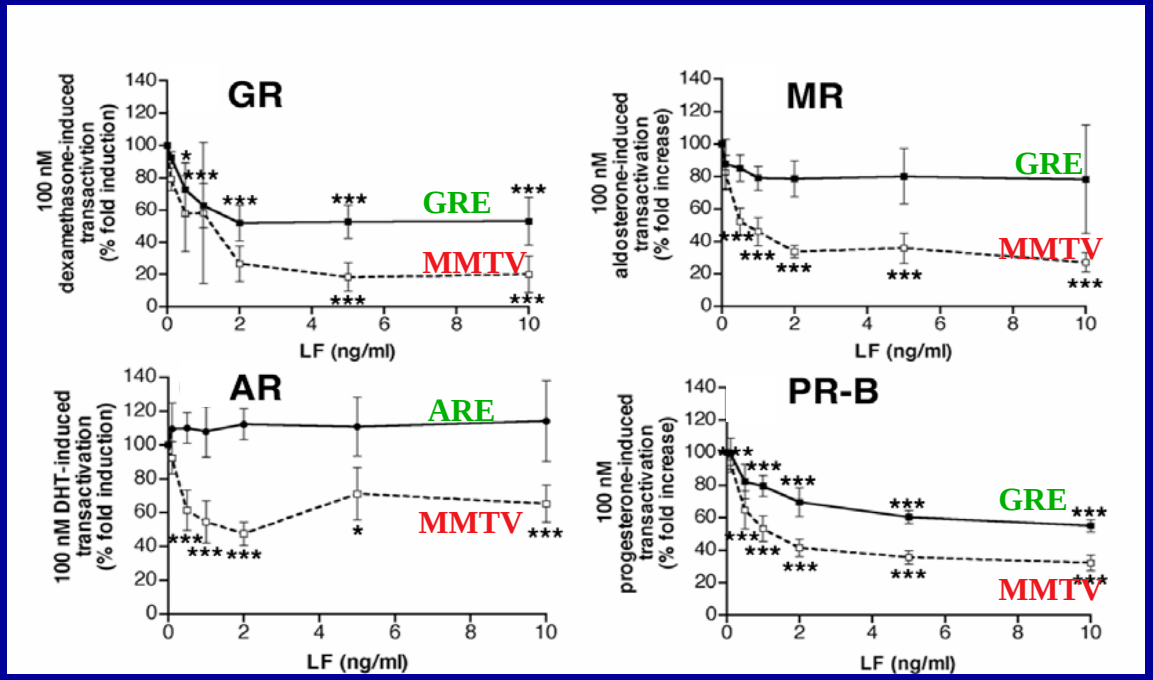
Selective *B. anthracis* LeTx repression of nuclear hormone receptors is both receptor and promoter dependent



Webster & Sternberg Mol. Cell Endocrinol. (2005) ***241****. 21-31*

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Mortality in Animal Models where HPA Axis is Interrupted

SCW Arthritis — *Sternberg et al. PNAS 89*

- **RU-486** — **100% mortality (F344 rats)**
- **cort** — **13% mortality**

EAE — *MacPhee et al. J Exp Med 89*

- **ADX** — **80% mortality**
- **cort** — **22% mortality**

Salmonella — *Edwards et al. PNAS 91*

- **hypophysect** — **100% mortality**
- **cort** — **5% mortality**

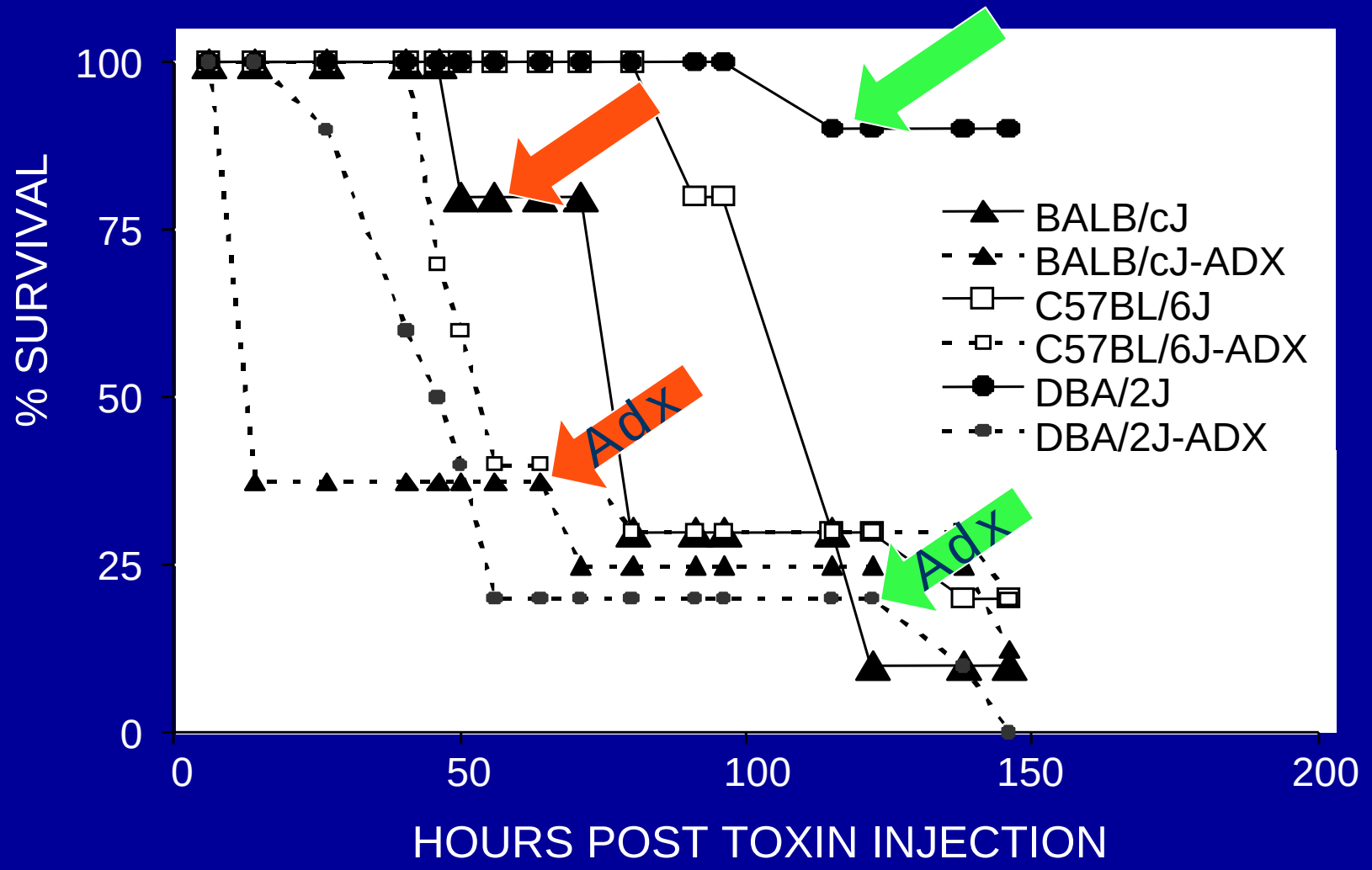
MCMV — *Ruzek et al. J. Immunol. 99*

- **ADX** — **100% mortality**
- **cort** — **20% mortality**

Shiga toxin — *Gomez et al. Clin. Exp. Immunol.*

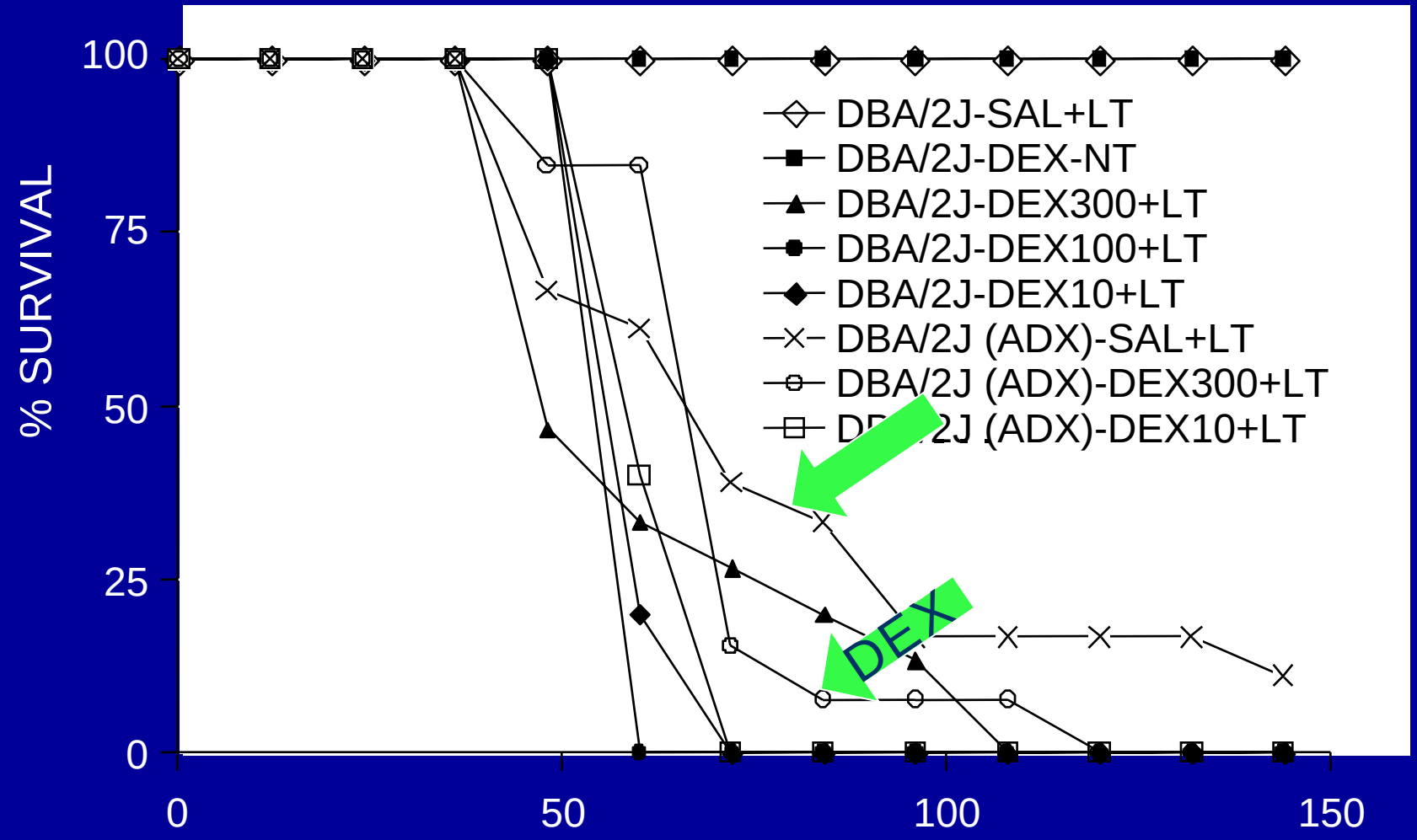
- **ADX** — **60% mortality**
- **cort** — **10% mortality**

Interruption of GC response affects LeTx mortality: Adx increases mortality in LeTx-resistant mice



M Moayeri et al, Infect. Immunity, 73 (7) 4238-4244, (2005)

Dexamethasone did not Rescue Adrenalectomized LeTx-Treated Mice



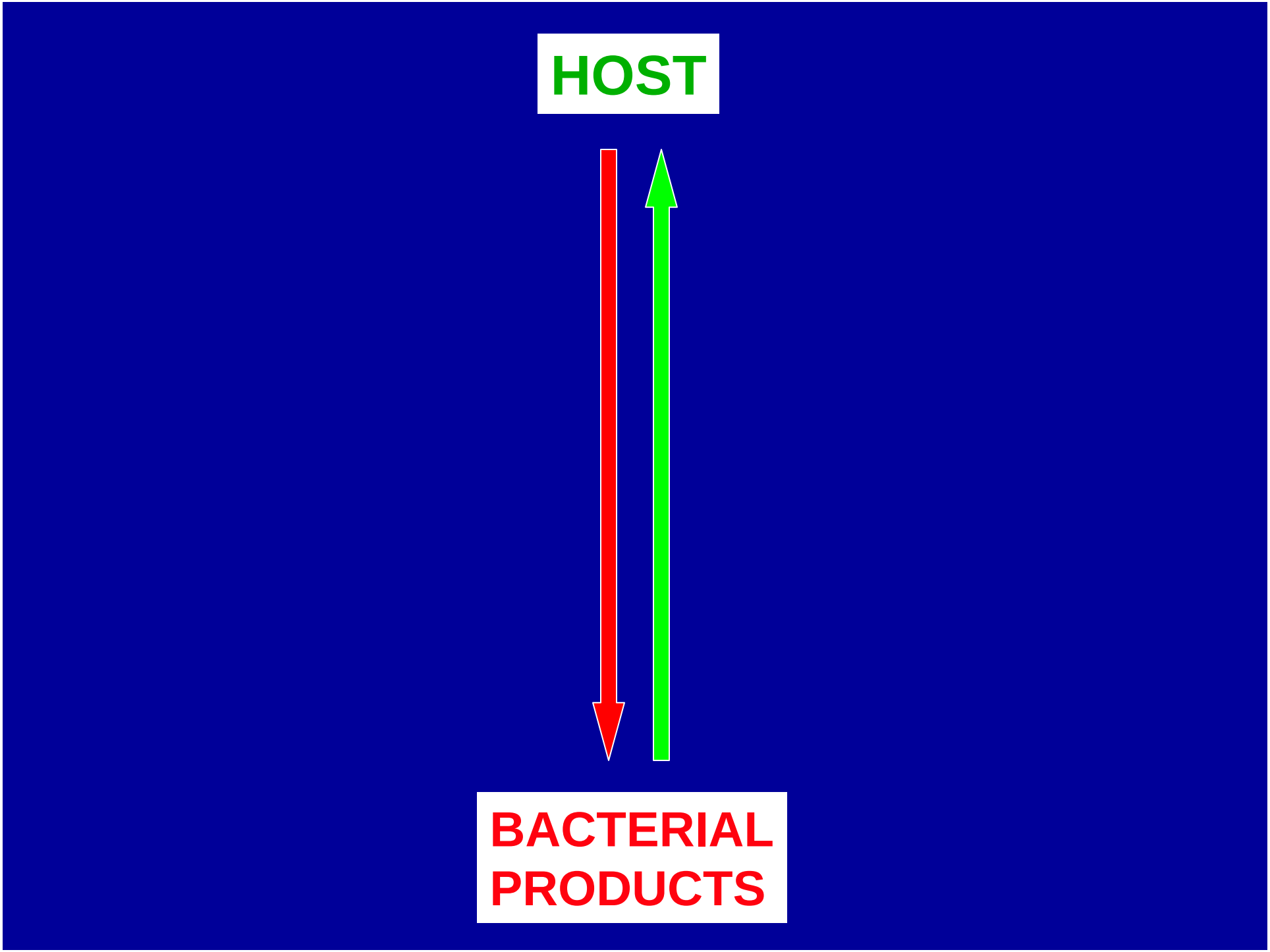
M Moayeri et al, Infect. Immunity, 73 (7) 4238-4244, (2005)

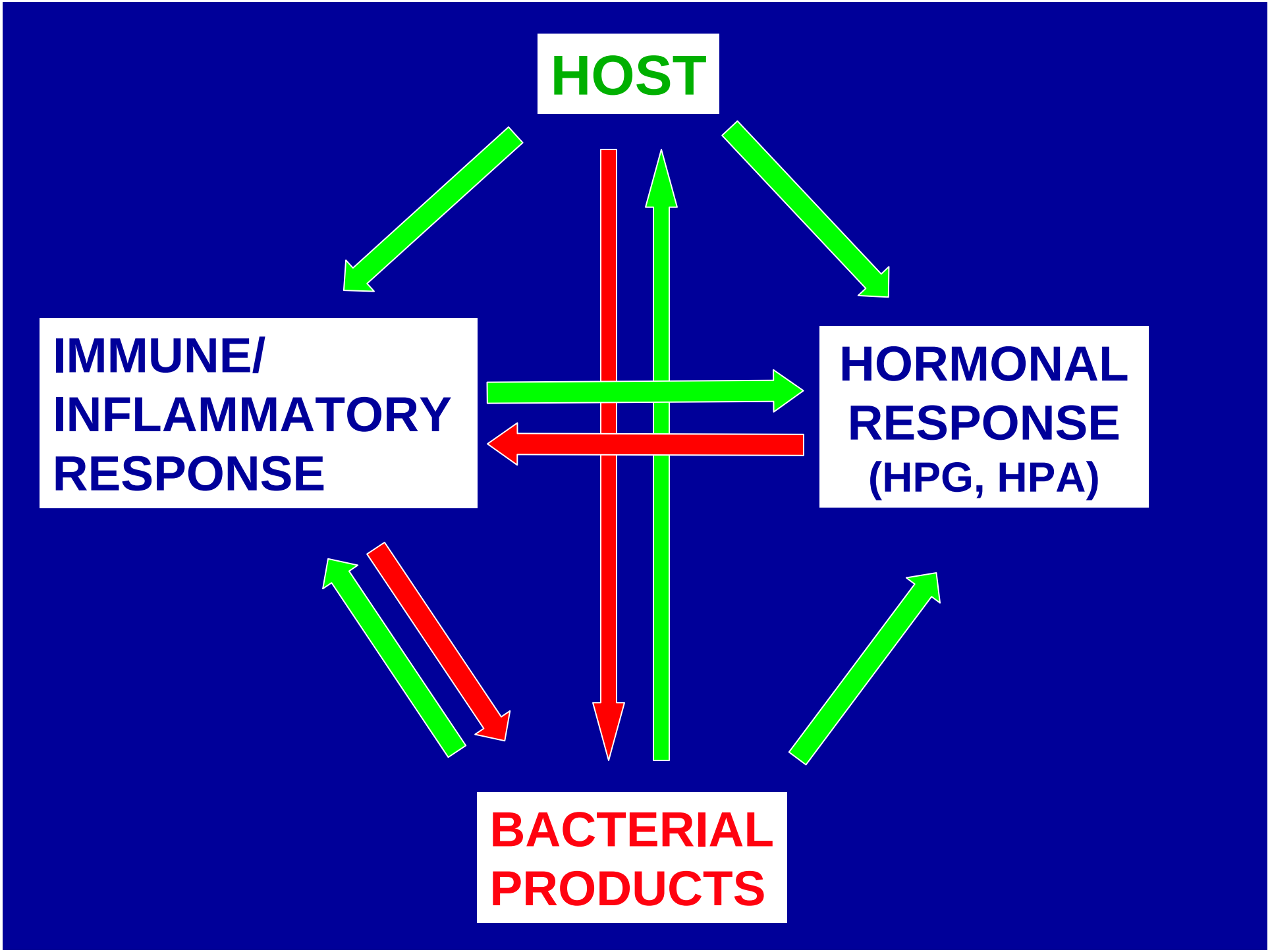
RU-486 had variable effects on *B. anthracis* LeTx mortality, suggesting that adrenal factors other than GC may play a role.

M Moayeri et al, Infect. Immunity, 73 (7) 4238-4244, (2005)

Summary

- **Glucocorticoids & progesterone suppress inflammatory responses.**
- ***Clostridia* bacterial toxins partially repress GR transactivation.**
- ***Clostridia* bacterial toxins partially reverse Dex suppression of TNFα production.**


HOST
BACTERIAL
PRODUCTS


HOST
IMMUNE/
INFLAMMATORY
RESPONSE
HORMONAL
RESPONSE
(HPG, HPA)
BACTERIAL
PRODUCTS

Future Directions

- What happens when these factors interact *in vivo*?

- Do GR/PR antagonists (e.g. RU-486) prevent GC/P suppression of inflammatory responses *in vivo?*
  - Time-course after exposure to bacterial products?
  - Dose response?
  - Interactions with other drugs (prostaglandin)?

- Are there host factors predisposing to susceptibility to infection/shock?
  - Hormone levels (pregnancy, menstrual cycle phase)
  - GR and PR resistance (receptor polymorphisms, mutations)

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