

Recognizing and Treating Adverse Effects of Vaccines in Animals

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Overview

- Peracute
- Acute
- Reproductive
- Episodic- Veterinary Version of “Autism and Vaccination”



Adverse Events-Cats

- Between 2002-2005 more than 1.25 million doses of various vaccines administered to 0.5 million cats (Banfield Study).
- Adverse reactions within 30 days of vaccination of 51.6/10,000 cats vaccinated (0.52%), with 92% of these reactions occurring within the first 3 days.
- Clinical signs with vaccination-associated adverse events
 - lethargy (\pm pyrexia) in 54%,
 - local pain or swelling at the vaccine site (25%)
 - vomiting (10%)
 - facial or periorbital edema (6%)
 - generalized pruritus (2%).
- Death was reported in four cats
- At least two of these it was attributed to anaphylaxis.



Adverse Events-Small Dogs

- Adverse events in 1.2 million dogs that received 3.4 million doses of vaccine. 38.2/10,000 vaccinations (AE 0.38%)
- administration of multiple vaccine doses to small breed dogs at the same appointment.
- Young adult small-breed neutered dogs at highest risk
- History of a vaccine AE in a small breed dog is not predictive of future risk. Any dog, regardless of size, breed, gender, or age, can experience a vaccine AE.
- Mitigating risk in small dogs (puppies and small breeds) by reducing the volume of vaccine is not recommended. Doing so may result in a suboptimal response to the vaccine and may not eliminate risk associated with hypersensitivity to one or more vaccine constituents.



Vaccine Example: Rabies

- Rabies vaccine causes adverse reactions in 1 out of 60,000 dogs.
- In the United States, rabies in domestic animals (like dogs, cats, and cattle) has declined dramatically since the 1950s. This decrease is mainly due to rabies vaccinations.
- The benefits of giving rabies vaccines for protection against disease far outweigh the risks of occurrence of adverse reactions.



Peracetic Reactions



Adverse Reactions to Vaccines

- Peracute vaccine reactions are uncommon, but they are important to watch out for because some of these rare reactions can be fatal. It is recommended that animals be monitored for vaccine reactions for 24 hours following vaccinations.



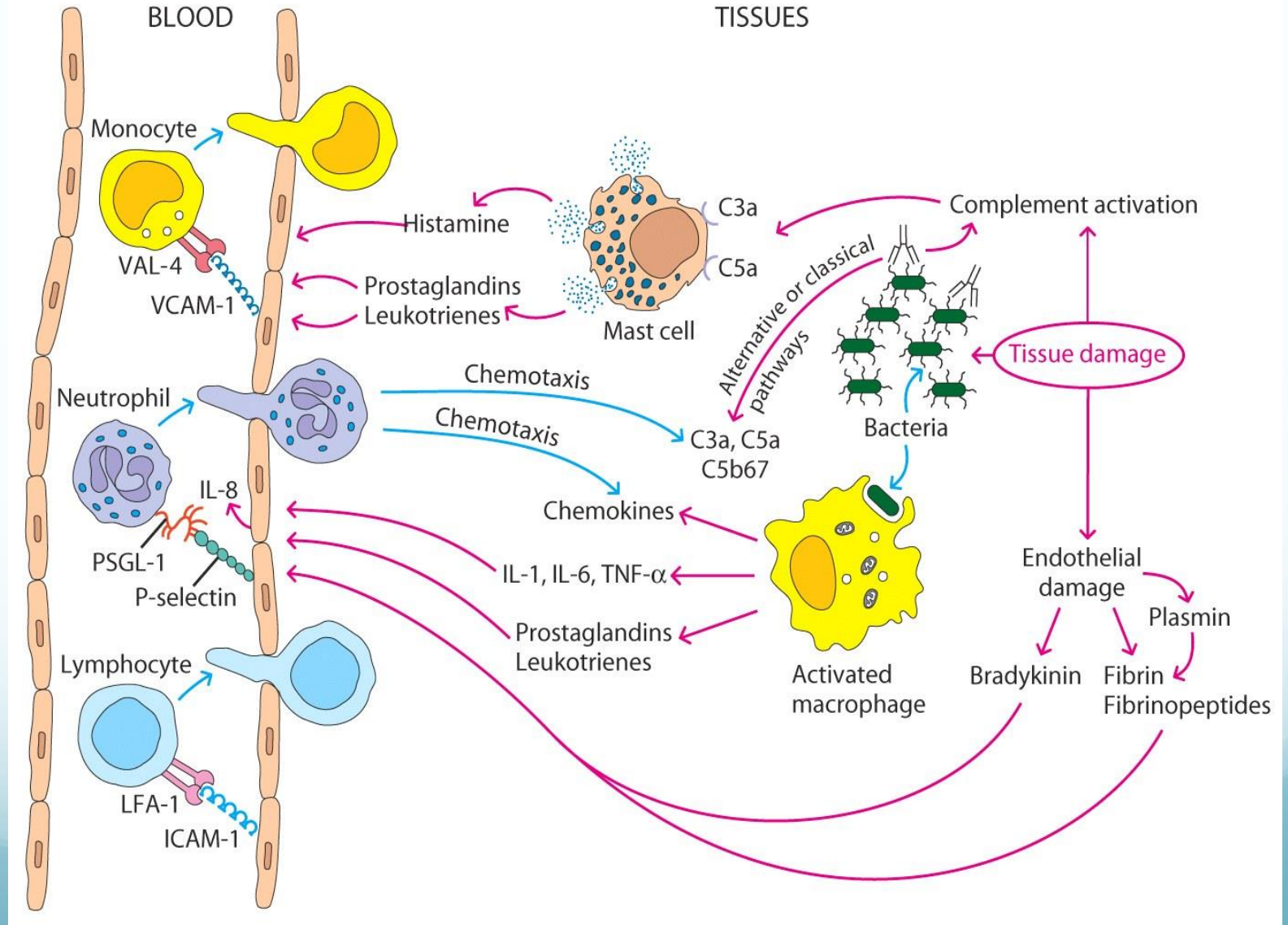
Anaphylaxis

- **Anaphylaxis** is a rare, life-threatening, immediate allergic reaction. The most common symptoms are the sudden onset of diarrhea, vomiting, seizures, coma, and shock. The animals' gums will be very pale, and the limbs will feel cold.
- Immune-mediated hypersensitivity (type I) reaction to vaccination, but it is rare (approximately 1–5/10,000 vaccines).

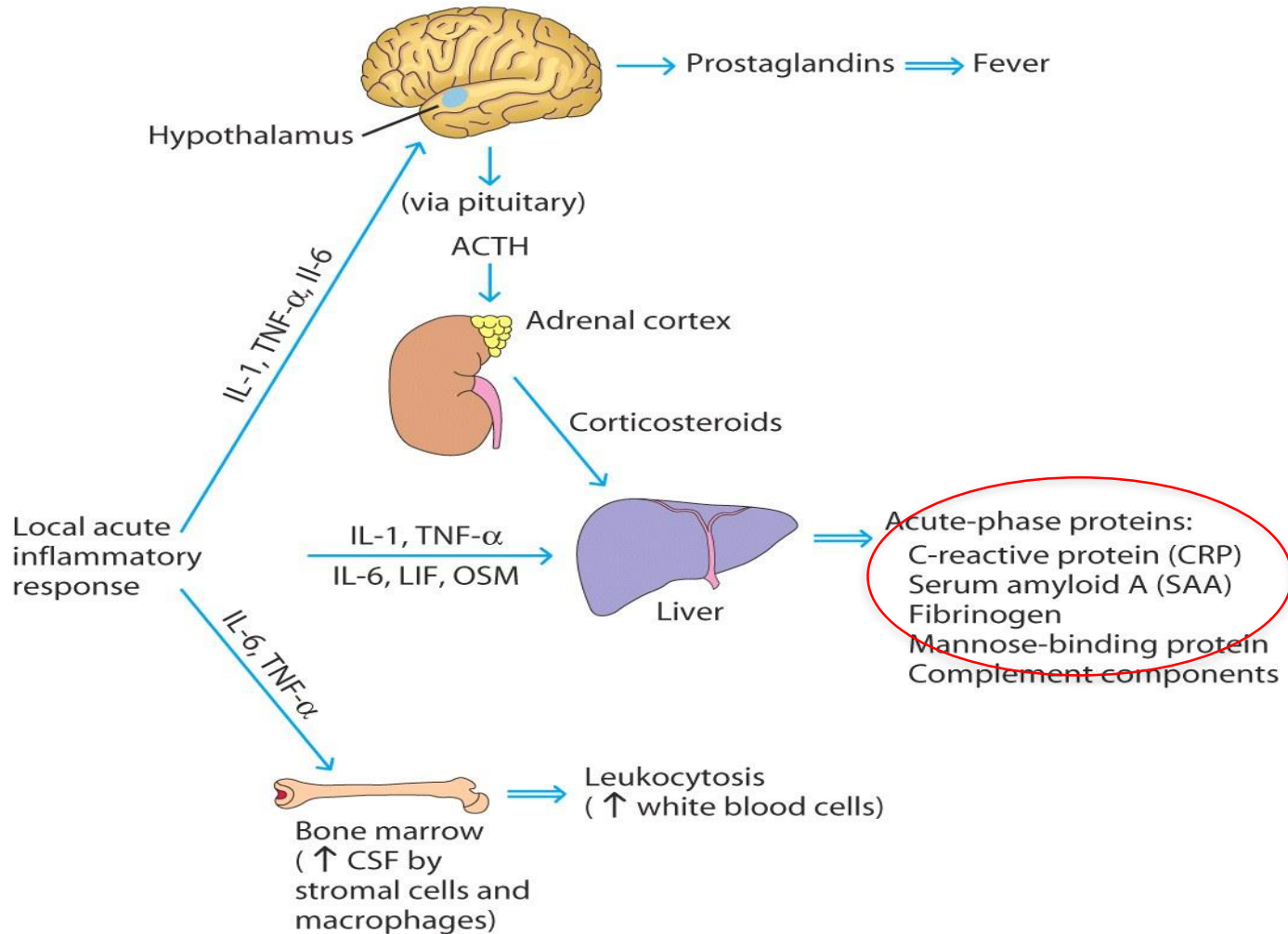
Acute Reactions



Inflammatory Response



Inflammatory Response



Systemic response

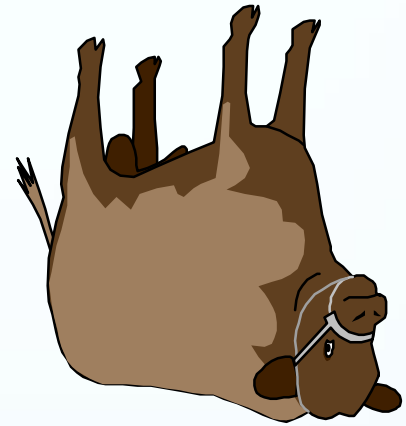
Primary Immune Response- Animal Doesn't Lie

- Immune response
 - Proinflammatory response necessary
 - Expect Some Side effects
 - No side effects- **no response**
 - Without response-Higher disease
 - Poorer immunity (active response)



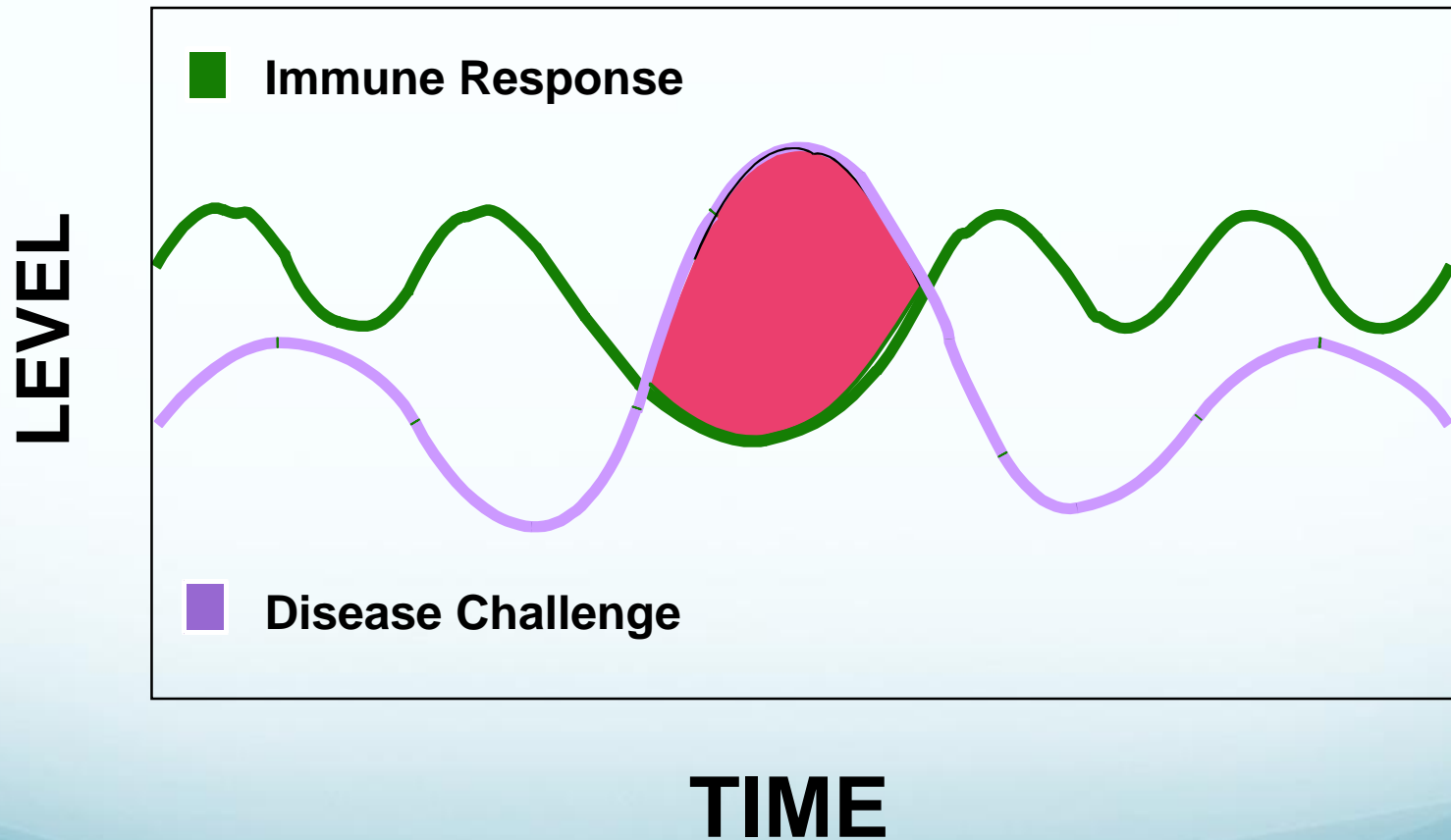
When you Vaccinate, if Nothing Happens, Nothing Happened

- Droopy ear- OK
- Listless- OK
- Down and out- Not OK

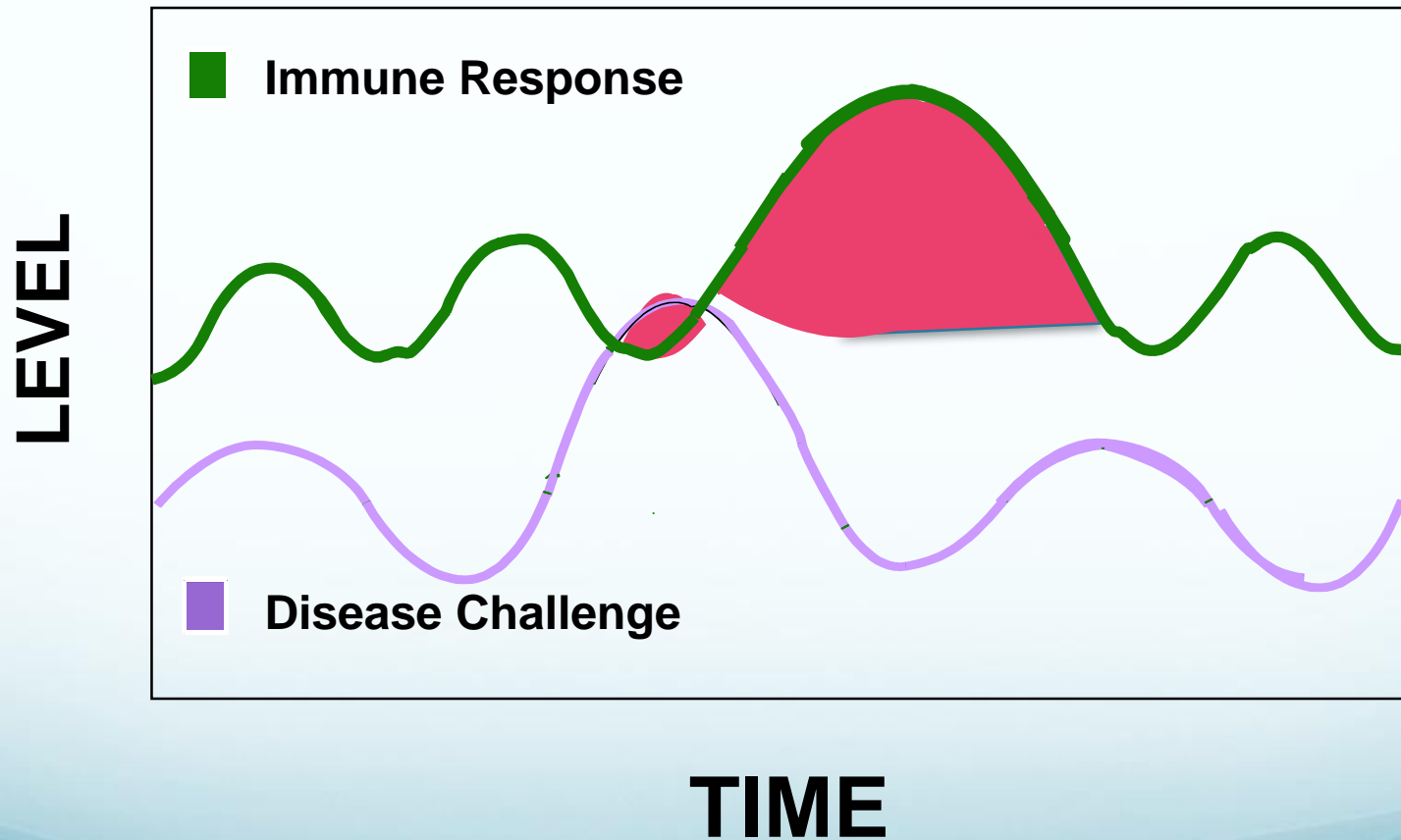


- Lactating Cow- drop test and/or production

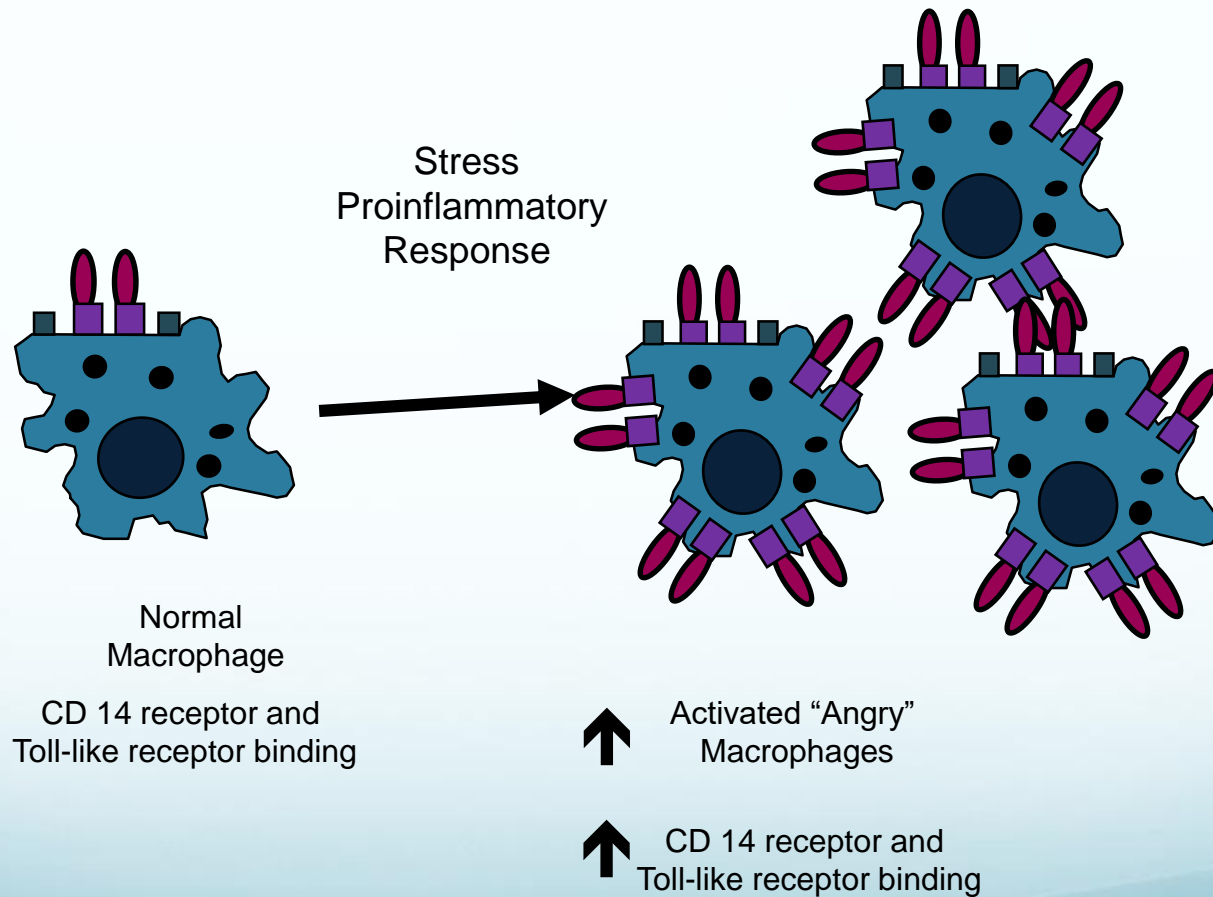
Not Enough of A Good Thing



Too Much of A Good Thing



Macrophages are the Immune System's Eyes and First Responder



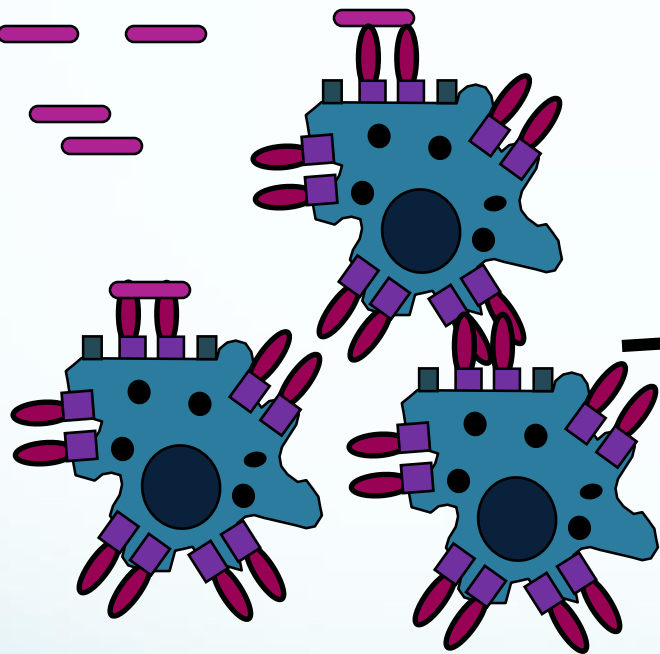
Activated Macrophages Recruit and Activate Neutrophils as First Responder in Response to Pathogens

Gram Negative bacteria

M. Haemolytica

H. Somni

P. multocida



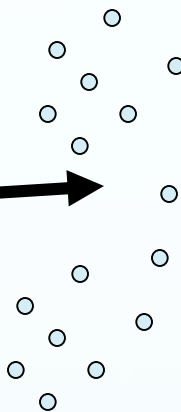
Activated "Angry"
Macrophages

Innate Cytokines

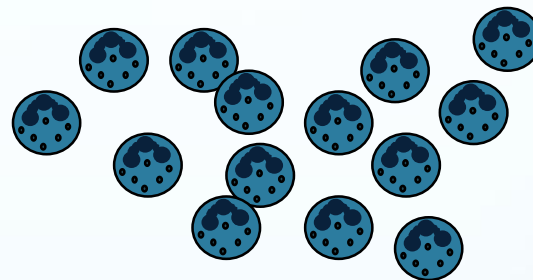
IL-1 β

IL-6

IL-8



Produce
Proinflammatory
Cytokines



Recruits Neutrophils

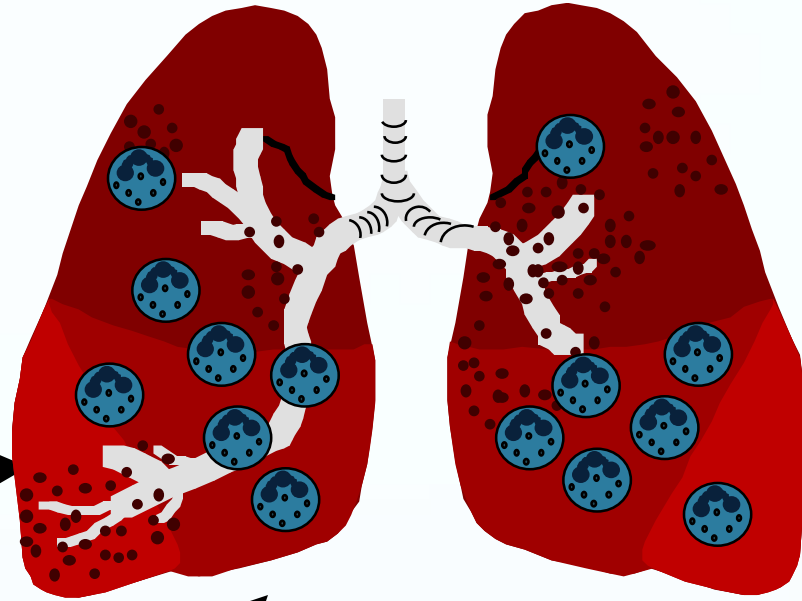
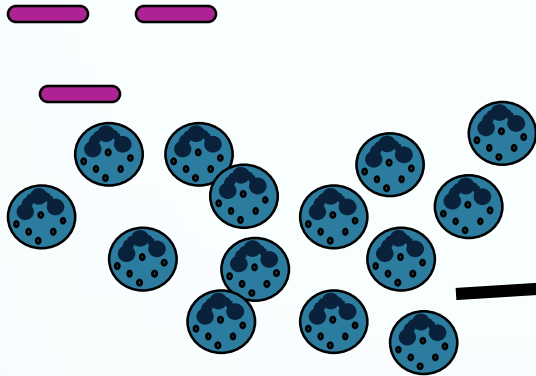
Macrophage effector mechanisms against extracellular pathogens

Gram Negative bacteria

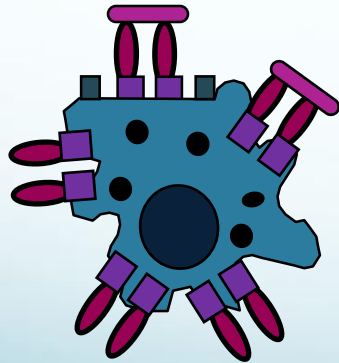
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Recruits Neutrophils



Activated "Angry"
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Innate Cytokines

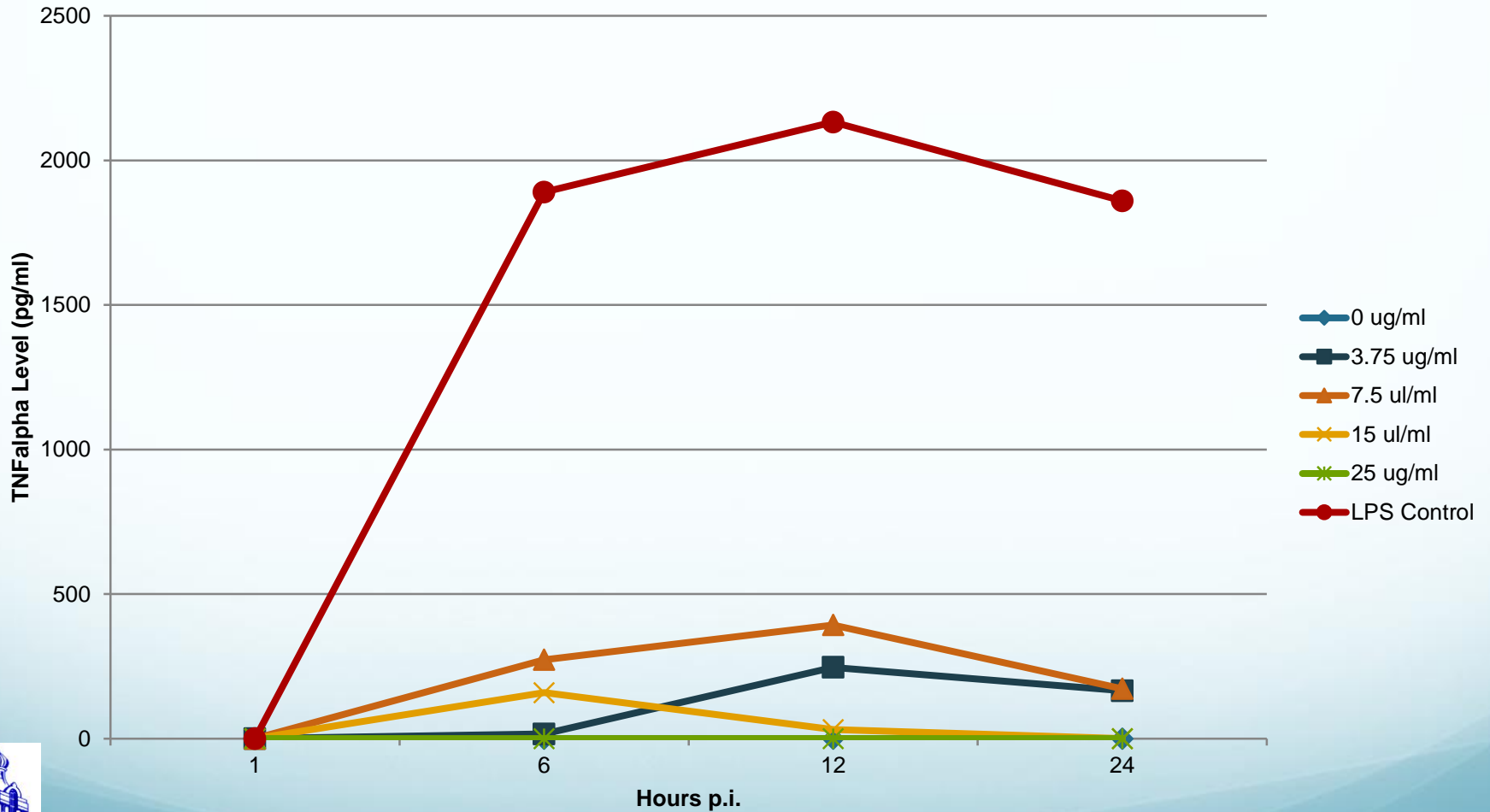
IL-1 β

IL-6

IL-8

Controlled Response

TNFalpha ELISA



Endotoxin- Reactions-Swine

Table 1 Vaccines used in the experiments and their endotoxin content

Vaccine	No. of vaccines being tested	Range of endotoxin concentration IU × 10 ⁶ /dose	No. of vaccinated animals (no. of controls)
<i>Escherichia coli</i>	4	0.24–2.4	23 (3)
Actinobacillosis	4	0.12–4.8	14 (5)
Multi-component	3	0.48–4.8	10 (4)
Live	2	0.30–3.0	7 (3)

Krug, M., Cussler, K., 1998. Endotoxin in porcine vaccines: clinical signs and safety aspects, in: Presented at the 1998 International Conference on Humane Endpoints in Animal Experiments for Biomedical Research, Netherlands, pp. 114–117.

Endotoxin- Reactions-Swine

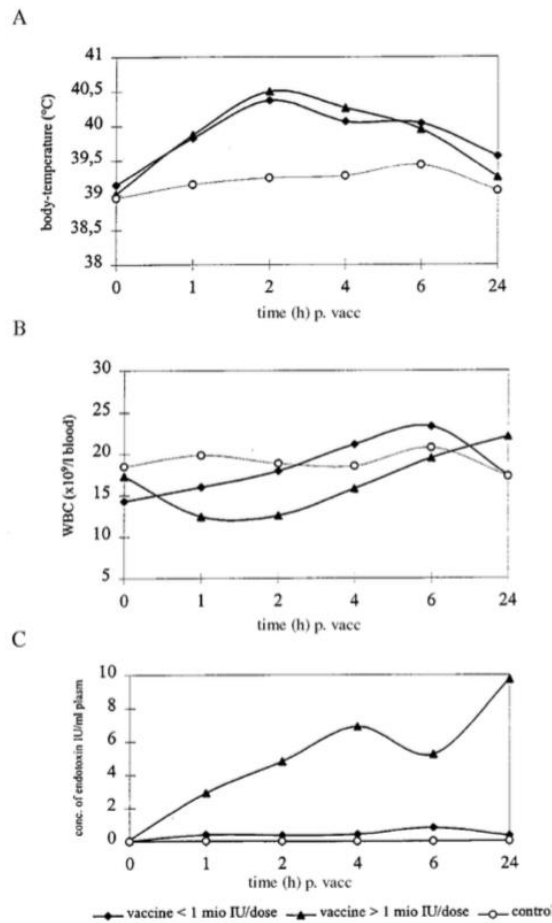


Fig 1 Body temperature (A), white blood cell count (B) and concentration of plasma endotoxin (C) after injection of vaccines containing less ($n = 44$) or more ($n = 25$) than 1×10^6 IU/dose endotoxin

Endotoxin- Reactions-Swine

Table 2 Clinical signs after injection of vaccines containing endotoxin less ($n=44$) or more ($n=25$) than 1×10^6 IU/dose

Clinical signs	Criteria	Vaccine endotoxin conc. IU/dose	% showing signs after					
			15 min	1 h	2 h	4 h	6 h	24 h
Behaviour	Restless, trembling	$< 1 \times 10^6$	6.8	22.7	11.3	11.4	18.2	0
		$> 1 \times 10^6$	36	60	52	28	24	12
Activity	Reluctant to move, recumbent	$< 1 \times 10^6$	2.3	15.9	22.7	18.2	2.3	2.3
		$> 1 \times 10^6$	12	44	52	48	12	8
Food intake	Refused	$< 1 \times 10^6$	4.6	18	22.7	22.7	25	2.3
		$> 1 \times 10^6$	16	60	60	60	48	16
Respiratory system	Accelerated respiratory rate	$< 1 \times 10^6$	2.3	11.4	15.9	11.4	2.3	0
		$> 1 \times 10^6$	32	40	36	8	12	0
Cardiovascular system	Pale mucous membranes, blue ears	$< 1 \times 10^6$	6.8	13.6	13.6	6.8	13.6	4.5
		$> 1 \times 10^6$	16	40	24	16	16	8

What About Bacterins in Cattle?- Endotoxin Stacking

- Endotoxin Stacking and Vaccines (ranked most reactive to least reactive)
 - E.coli Mastitis vaccines
 - Pinkeye (Moraxella bovis)- Whole cell LOS very reactive
 - Histophilus somnus Whole cell LOS very reactive
 - Salmonella-Whole cell LPS
 - Scour vaccines E.coli-Whole cell LPS
 - Mannheimia hemolytica- Whole cell LPS
 - Pasteurella multocida
- Subunit vaccines- no issues, leukotoxin, fimbriae, OMP
- **Leptospira DOES NOT contribute to ENDOTOXIN STACKING- leptospiral LPS does not have potent endotoxigenic properties**
- If need to use more than one- administer on other side of the neck



Inflammatory Response

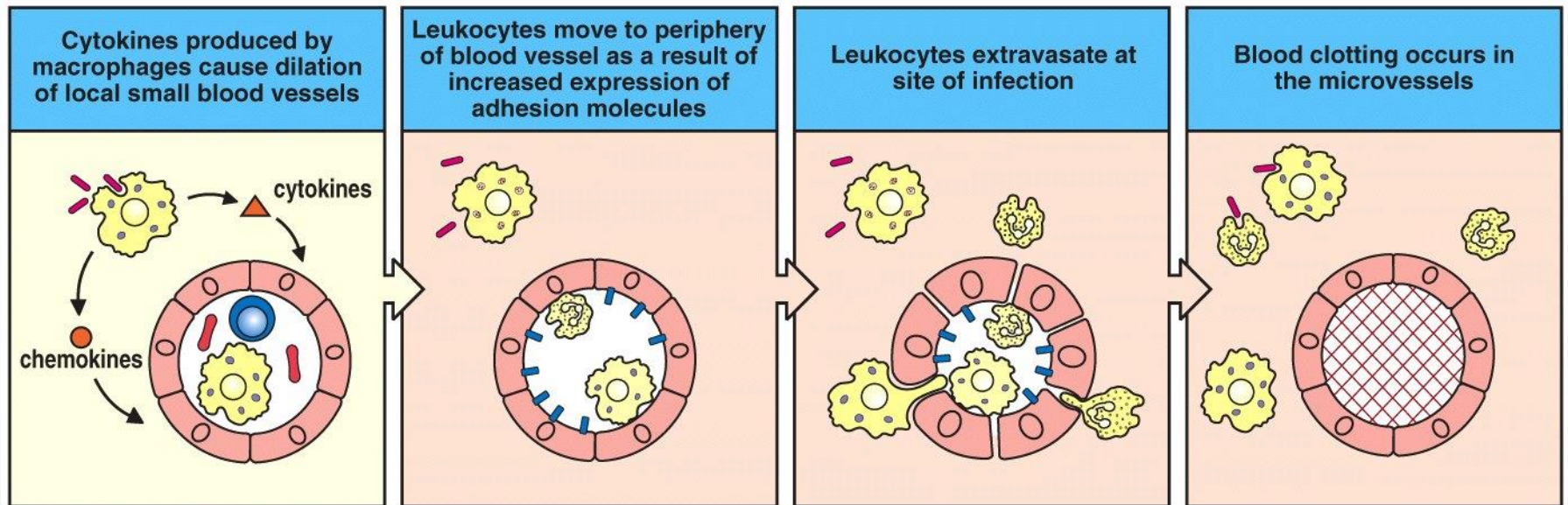


Figure 2-8 Immunobiology, 6/e. (© Garland Science 2005)

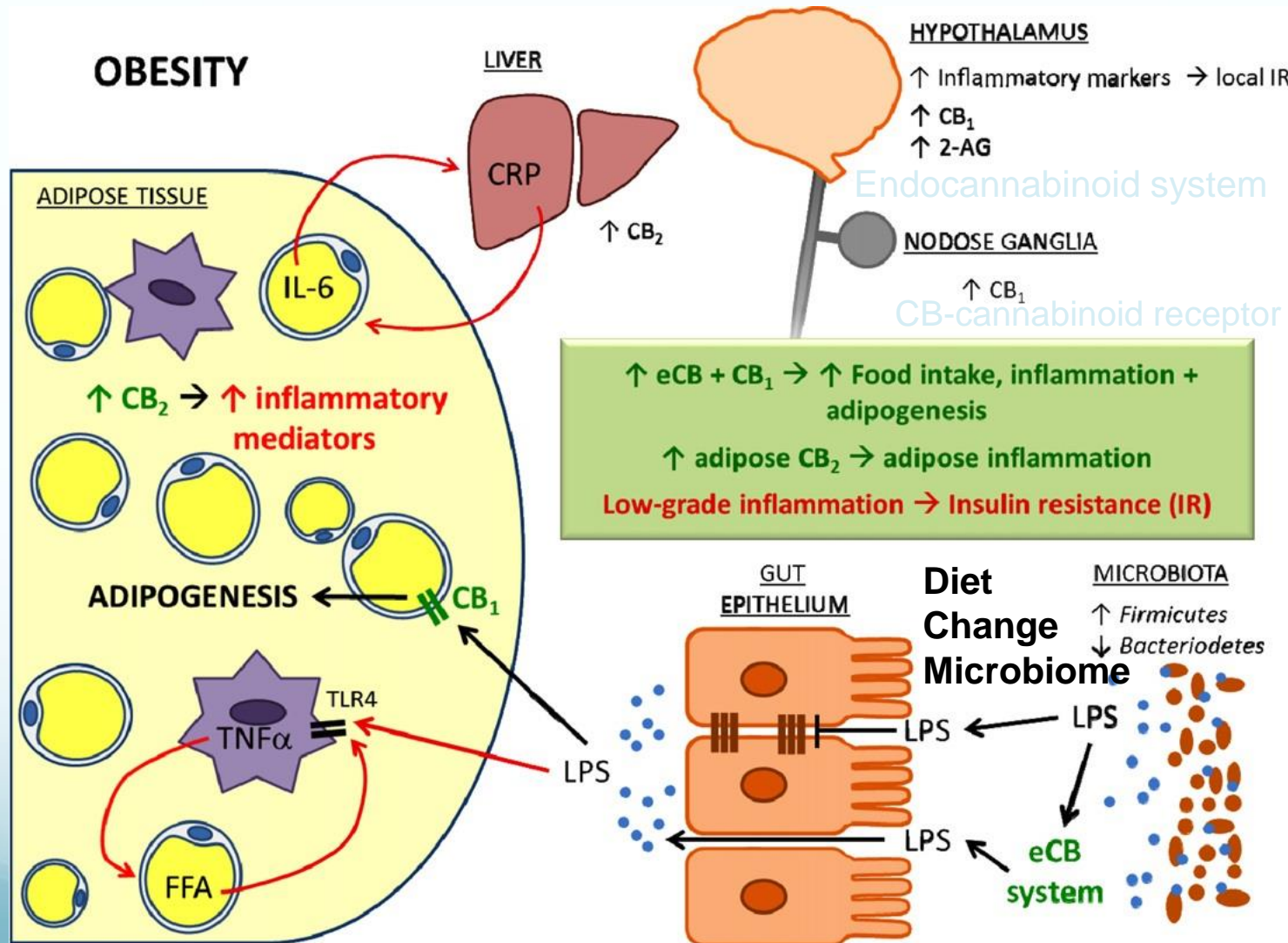
Tissue Damage

Tissue Damage- Overactive Immune System



Brain-Gut-Microbiota axis

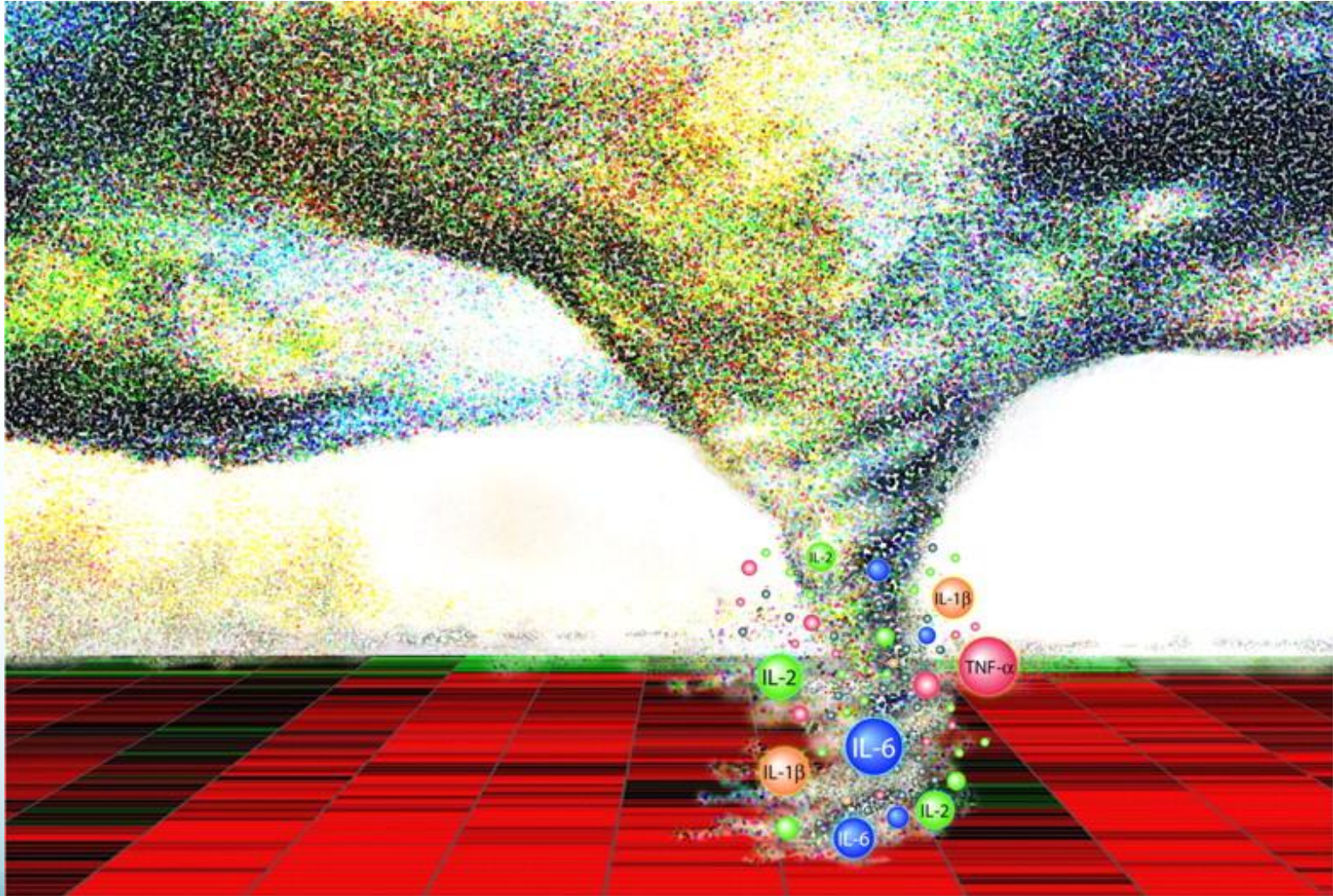
Inflammation and Obesity- Overconditioned Weaned Calves, Fat Cattle, Transition Cow



Cytokine Storm

- High Temps- 104°-106°F
- Respiratory Disease-
 - Acute Lung Injury
 - Acute Respiratory Disease Syndrome
- Is BRSV???
- Is Vaccination or Aspirin the Answer?

Cytokine Storm



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

Controlling Inflammation During Times of Stress

- Avoid practices that increase inflammation
 - Vaccination- with gram negatives
 - Too hot a ration too fast
 - Animals properly hydrated



Reproductive Interactions



Vaccine Induced Abortions

- Endotoxin-Systemic response
- Virus- MLV- Naive
 - Classic Swine Fever Virus
 - PRRSV-swine
 - Pseudorabies virus-Swine herpesvirus
 - Equine Herpesvirus-horses
 - Bovine herpesvirus 1

Pregnant Cows and MLV Vaccination



Misuse- Opening Pandora's Box

- Safe in pregnant animals vaccinated with the same product prior to breeding (within 12

- **NOT without recent vaccination**

New Label-MLV Pregnant Animals

Duration of Safety Claim is now called an EXEMPTION

New Label

However, if an exemption is granted, the label must include the following statement concerning residual risk: “Fetal health risks associated with the vaccination of pregnant animals with this vaccine cannot be unequivocally determined during clinical trials conducted for licensure. Appropriate strategies to address the risks associated with vaccine use in pregnant animals should be discussed with a veterinarian.”



31 IBR Vaccine Cases

- From 9 states- CO, IN, MN, MT, NE ND, SD, WI, WY
- From 2009-2016
- Not all histories are complete
- Most were given during pregnancy. Some were properly vaccinated.
- An additional two cases occurred following the administration of an oil adjuvanted vaccine during pregnancy



Year Case Received and Case #	State of affected herd	Number of animals affected	Number of animals in affected group	Prior Herd Vaccinated On label with MLV	Vaccination during Pregnancy with MLV	When did the first abortion occur following vaccination	Results of Genomic analysis
2009	SD	2	70		Yes		Group 3
2009	SD	10	250				Group 3
2009	SD	6	60				Group 2
2010	SD						Group 3
2010	SD	4	60				Group 3
2010	SD						Group 3
2010	SD	6			No, Killed Vaccine		Group 2
2010	WY	4 abortions, 5 stillbirths, 1 weak calf		Yes	Yes	20-30 days	Group 3
2010	WY	17	208	No	Yes	32-122 days	Group 3
2010	WY	12	165	Yes	Yes	32-55 days	Group 3
2011	SD	3					Group 3
2011	WY			No	Yes	31-38 days	Group 3
2012	SD	3	435				Group 3
2012	SD	2					Group 1
2013	WY			No	Yes		Group 3
2013	WY				Yes		Group 3
2013	NE				Yes		Group 3
2014 #1	ND	44	106	Yes	No, Vaccinated with Adjuvanted Scours Vaccine	6 days	Group 2
2014	MN	1					Group 3
2014	SD	16					Group 2
2014	WY				Yes		Group 3
2014	WY	25	300		Yes		Group 3
2014	MT	15	30		Yes	~30 days	Group 3
2015 #2	MN	15-20	220	No	Yes, (Group 2 & Group 3)	~90 days	Group 3
2015 #3	ND	13	48	No	No, calves vaccinated with MLV		Group 3
2015 #4	IN	3 heifers, 1 cow	71 heifers, 35 cows	Yes	Yes	20-30 days	Group 3
2015	ND	25	75	No	Yes		Group 3
2015	WI			Yes	Yes		Group 3
2016	CO	3	200	Yes	Yes	~80 days	Group 3
2016	CO	9	500	Yes	No, Vaccinated with Adjuvanted Scours Vaccine	~70 days	Group 3
2016	WI			No	Yes		Group 3



Take Aways-Case Studies

- Heifers were most susceptible in all 4 cases
- Calves can shed vaccine virus that can cause abortion
- MLV BHV-1 vaccines must be used judiciously following label directions. In spite of the following the label, reproductive issues can still occur.

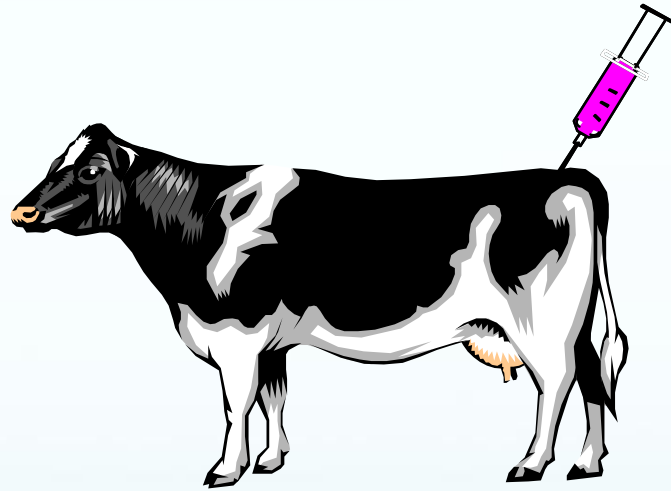


Summary

- Pregnant cow claim was not the original intent
- Safety- not efficacy
 - Definition of Safety never causes abortion- NOT
 - Definition of Safety rarely causes abortion- YES
 - Dependent on having a solid defense to stop the offense (MLV)
–Works in Football not in Cows
 - If defense stops MLV growth then no antigenic mass- vaccine efficacy??
- Pregnant cow is immunosuppressed
- Herpesvirus vaccines are abortifacient (non-temperature sensitive)



Vaccinating the Postpartum Cow



Postpartum Cow

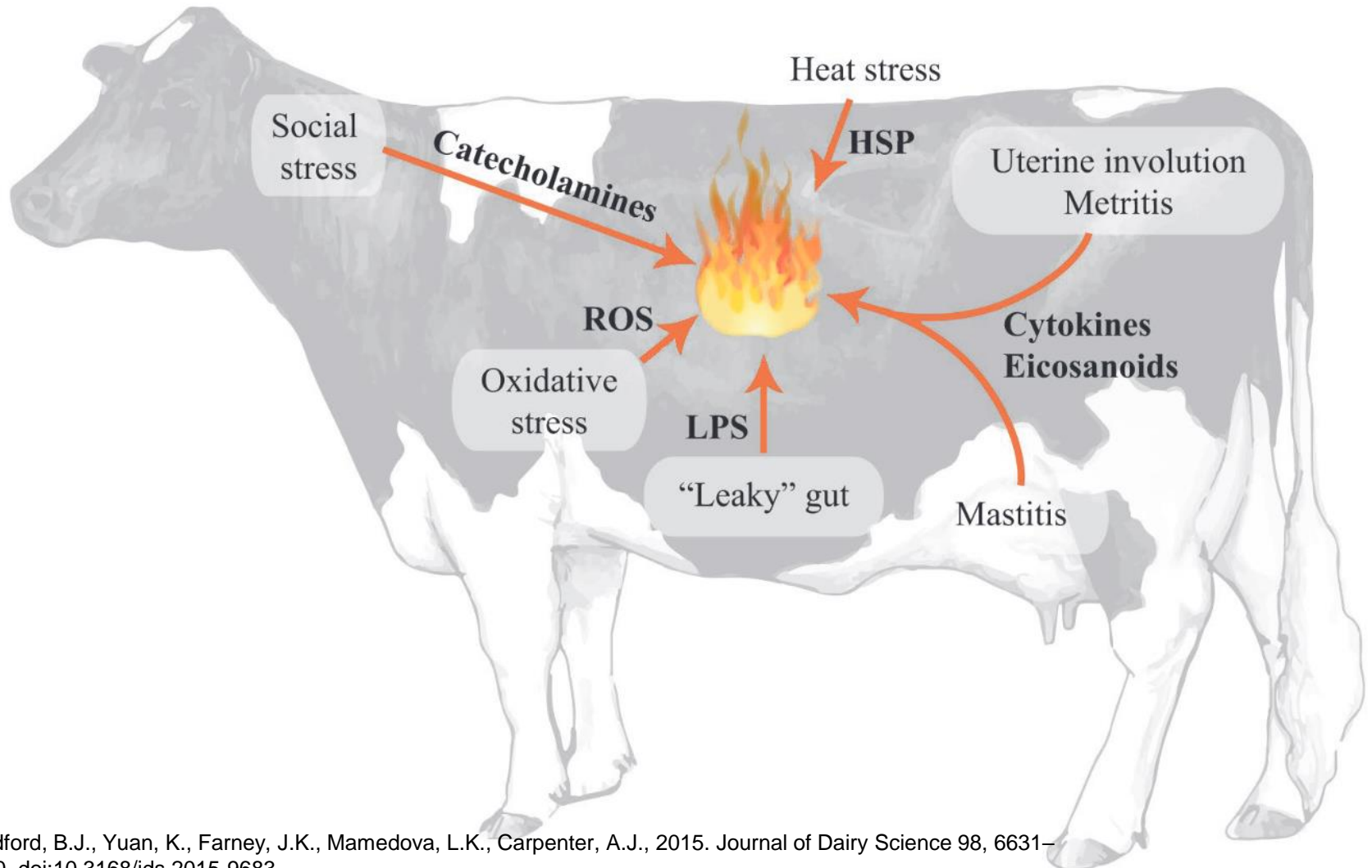
- Postpartum immunosuppression
- Energy Drain
- Ketosis immunosuppression
- Lose the opportunity to boost colostrum



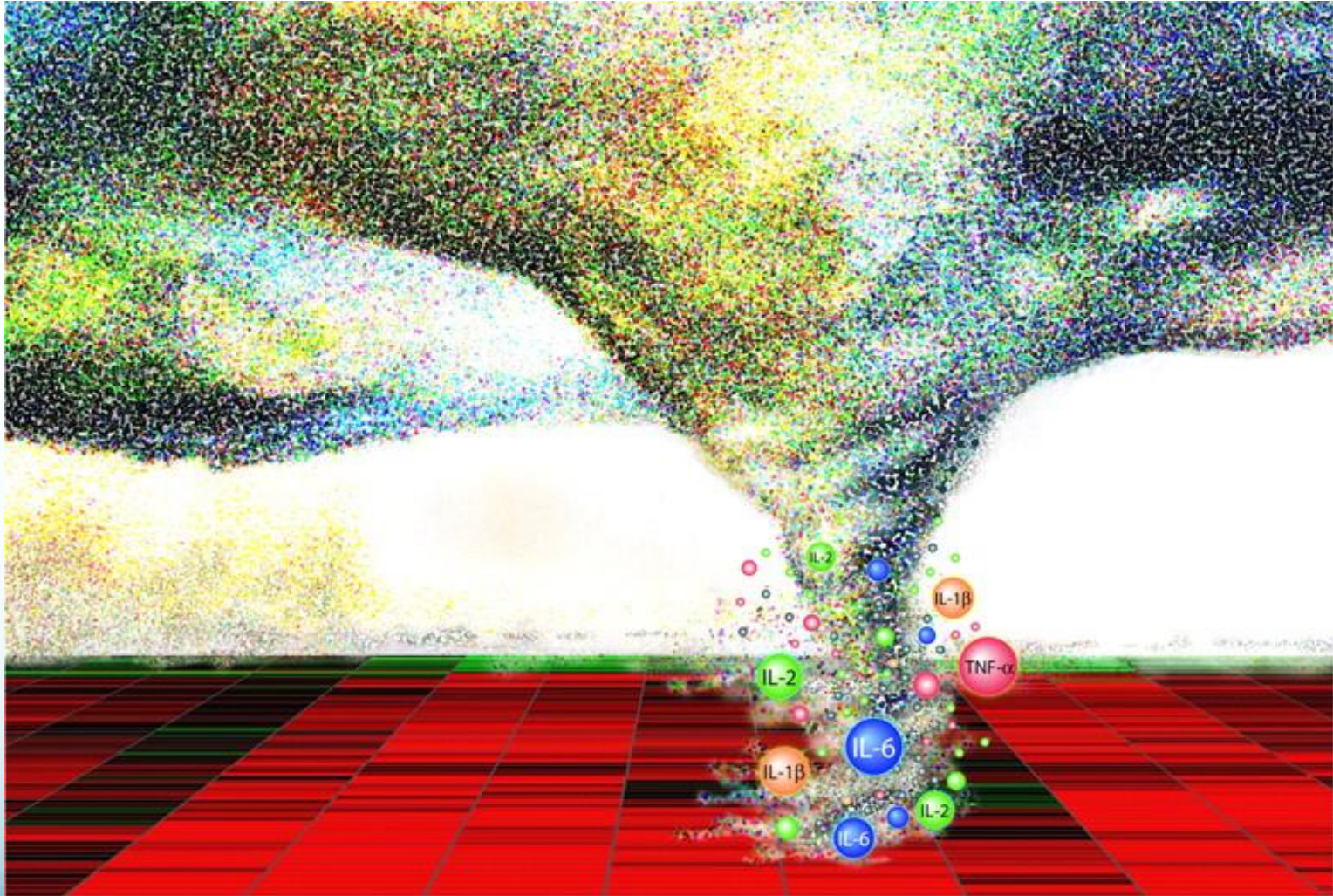
Immunosuppression

- Placenta and Uterine cytokines
- Progesterone
- Cortisol
- Bovine Pregnancy associated glycoprotein

Proinflammatory Response in Fresh Cow



Cytokine Storm



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

Fresh Cows-Cytokine Storm

- High Temps- 104°-106°F
- Respiratory Disease-
 - Acute Lung Injury
 - Acute Respiratory Disease Syndrome
- Is it Really BRSV in Cattle???
- Is Vaccination or Aspirin the Answer?

Periparturient Immunosuppression

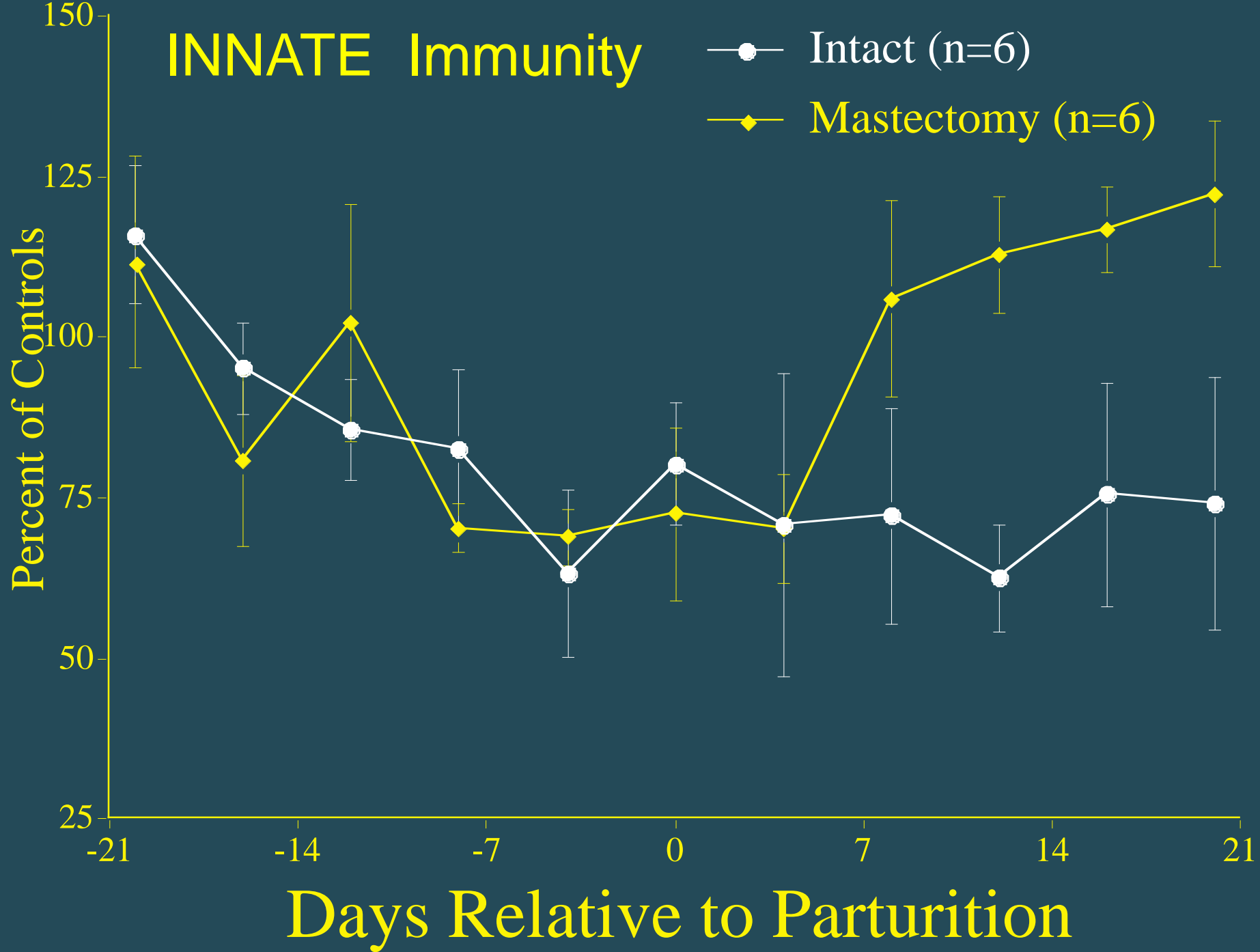
- Elevated incidence of new Inter-mammary infections 2 wk prepartum to 3 wk postpartum
- Elevated incidence of infectious disease postpartum Clinical Johne's, Salmonellosis
- Impaired native defenses around calving time

- Guidry, et al. 1976. *Am J Vet Res.* 37:1195
- Newbould. 1976. *Can J Comp Med.* 40:111
- Wells, et al. 1977. *Clin Exp Immunol.* 29:159
- Hill. 1981. *Res Vet Sci.* 31:107
- Manak. 1982. *J Reprod Immunol.* 4:263
- Kashiwazaki, et al. 1985. *Jpn J Vet Sci.* 47:337.
- Ishikawa. 1987. *Jpn J Vet Sci.* 49:469.





INNATE Immunity



“Episodic” Reactions



Feline Sarcomas and Vaccines

- Reports indicate that Sarcomas occur at a rate of about 1 case per 10,000 to 30,000 vaccinations.
- Vaccine-associated sarcoma was first recognized as an issue in cats in the early 1990s.



Feline Sarcomas and Vaccines

- While initial studies suggested a risk of sarcoma development in around 2/10,000 doses of vaccine administered which increased to 13–36/10,000 doses in other studies
- Current estimates based on larger epidemiologic studies (published between 2002 and 2007 suggest that the risk of sarcoma development following vaccination is actually very low (probably well below 1/10,000 doses of vaccine)
- Although initial reports linked development of sarcomas at vaccination sites with the use of inactivated rabies or Feline Leukemia Virus vaccines and aluminum-based adjuvants,
- Latest studies show no relationship between Feline vaccines and alums and Sarcomas



Feline Sarcomas and Vaccines



Figure 10 Regions indicated in green are recommended. Those in red are key sites that should be avoided. *Image ©iStockphoto.com/GlobalP*

Summary

- Anaphylaxis
- Acute Reactions- Endotoxin
- Reproductive issues
- Feline Sarcoma



