

# **Obesity and Breast Inflammation: Implications for Carcinogenesis**

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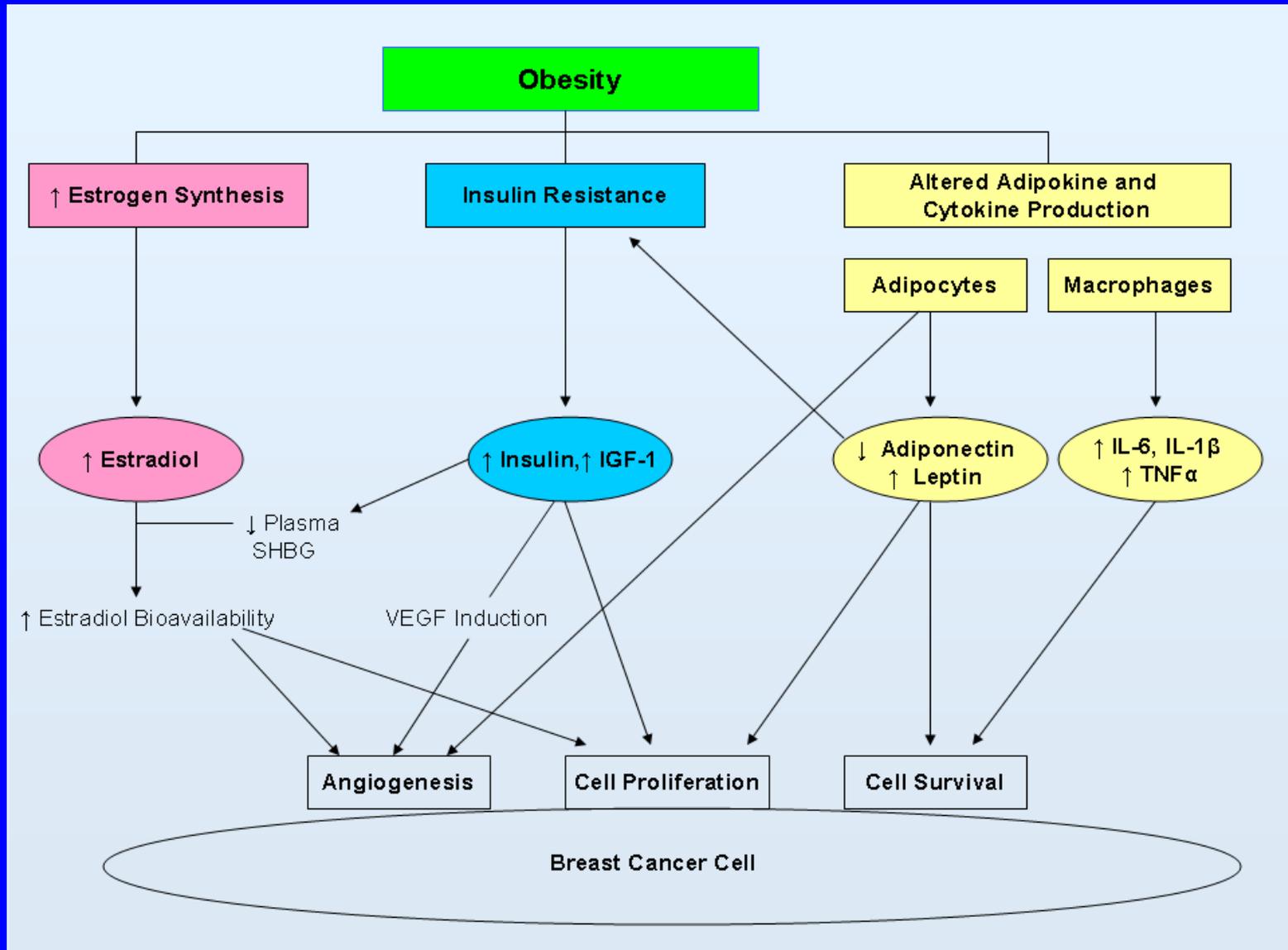
**Weill Cornell Cancer Center**

**Weill Cornell Medical College**

# Obesity and Breast Cancer

- Risk factor for development of hormone receptor-positive breast cancer in postmenopausal women.
- Poor prognostic factor for breast cancer patients regardless of menopause or hormone receptor status.
- Altered levels of hormones (estrogen, insulin, IGF-1), adipokines (leptin, adiponectin) and pro-inflammatory mediators (TNF $\alpha$ , IL-1 $\beta$ , PGE $_2$ ) contribute to obesity-related breast carcinogenesis.

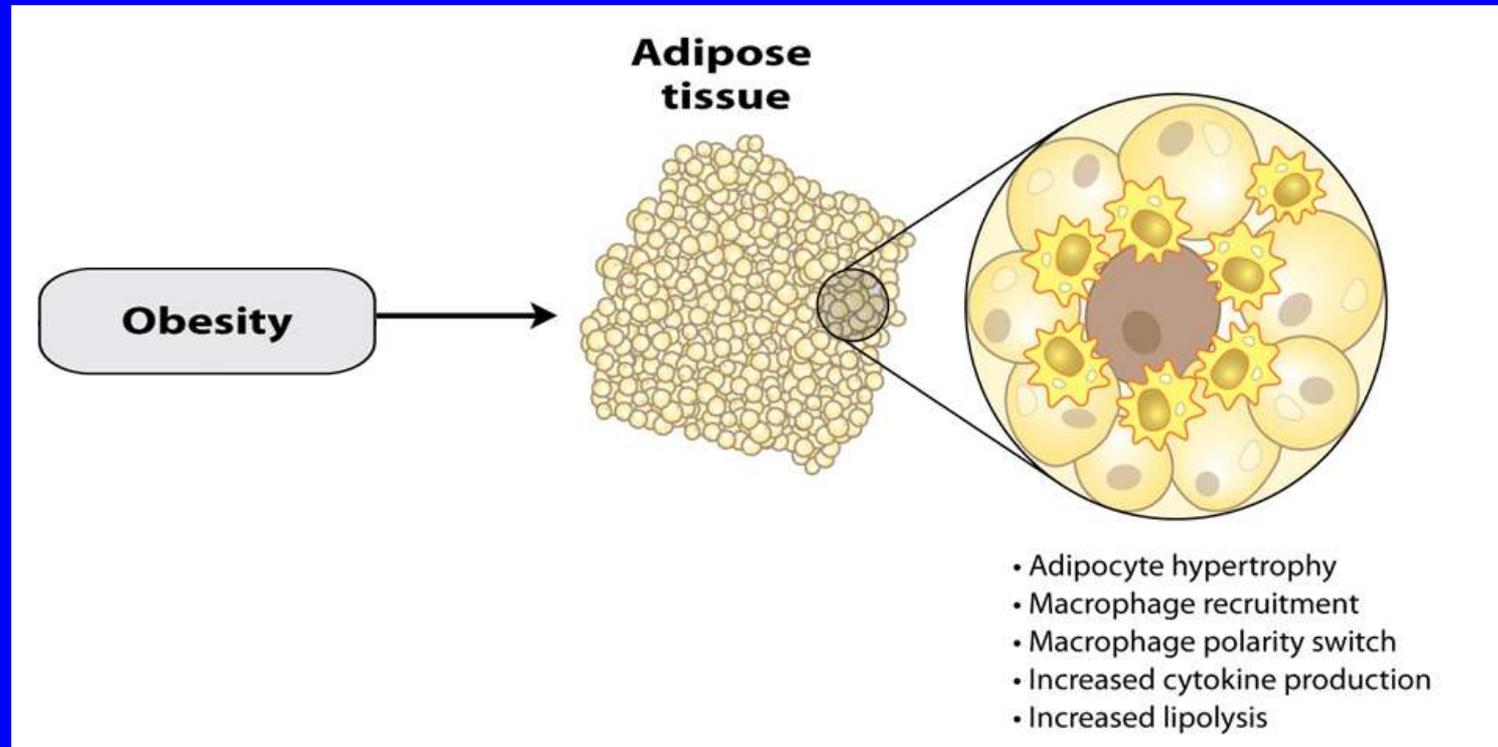
# Pathways Linking Obesity with Breast Cancer



# Obesity, Estrogen and Increased Risk of Postmenopausal Breast Cancer

- After menopause, peripheral aromatization of androgen precursors in adipose tissue is largely responsible for estrogen synthesis.
- Obesity causes inflammation in visceral and subcutaneous fat.
- Inflammatory mediators induce aromatase, the rate-limiting enzyme for estrogen biosynthesis.
- Direct link between obesity→breast inflammation→aromatase expression was previously unknown.

# Obesity Causes An Inflammatory State

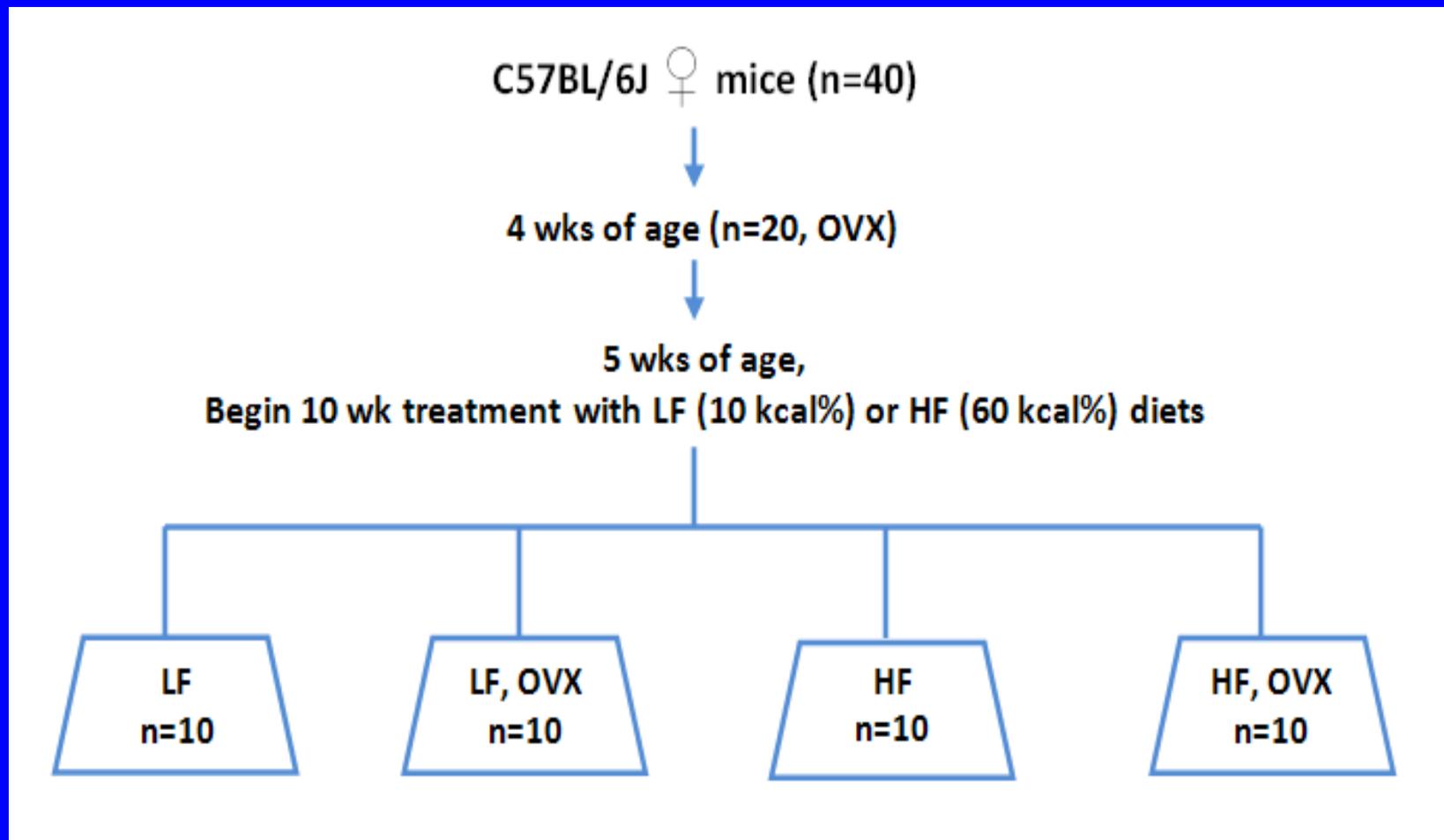


Adapted from Olefsky & Glass. *Annu. Rev. Physiol.* 2010;72:219-246.

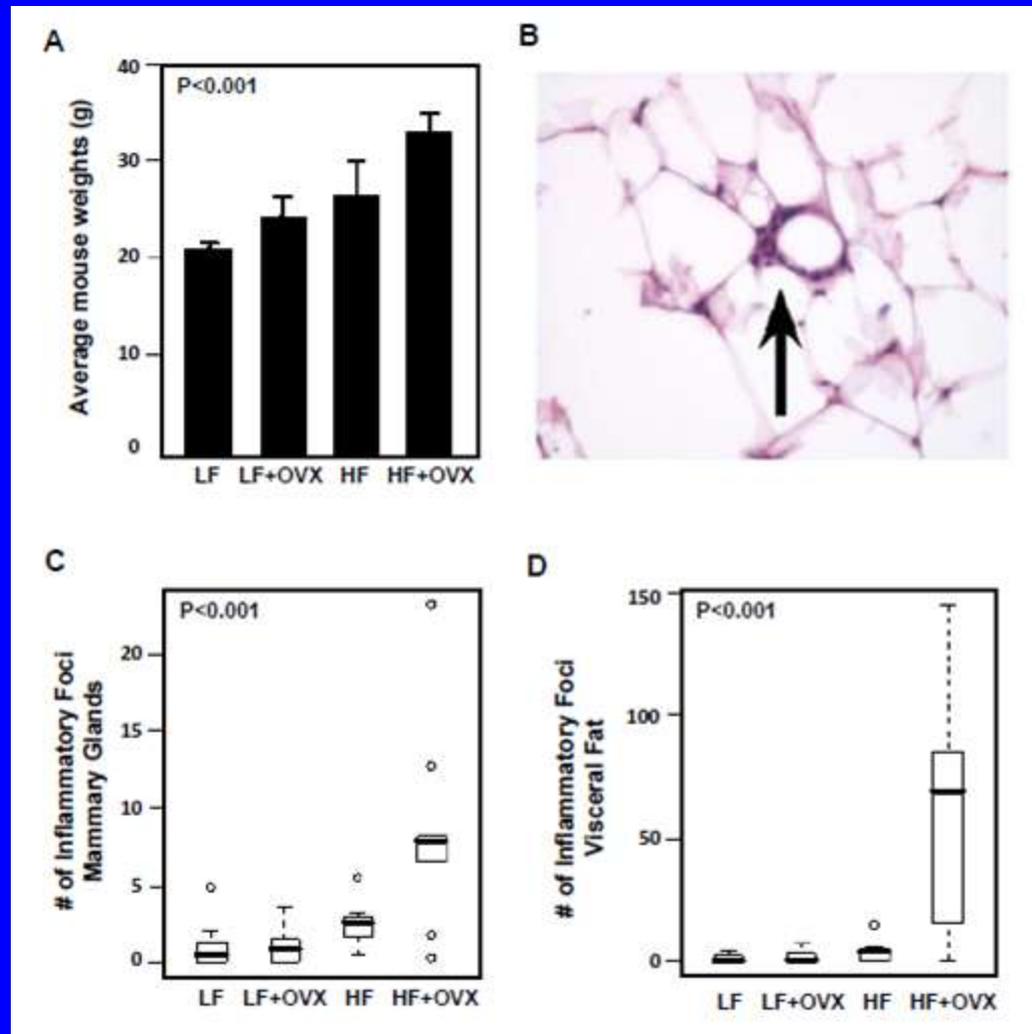
# Hypothesis

Obesity induced inflammation will be a/w increased levels of pro-inflammatory mediators (PGE<sub>2</sub>, TNF- $\alpha$ , IL-1 $\beta$ ) leading, in turn, to elevated aromatase expression in breast tissue and visceral fat.

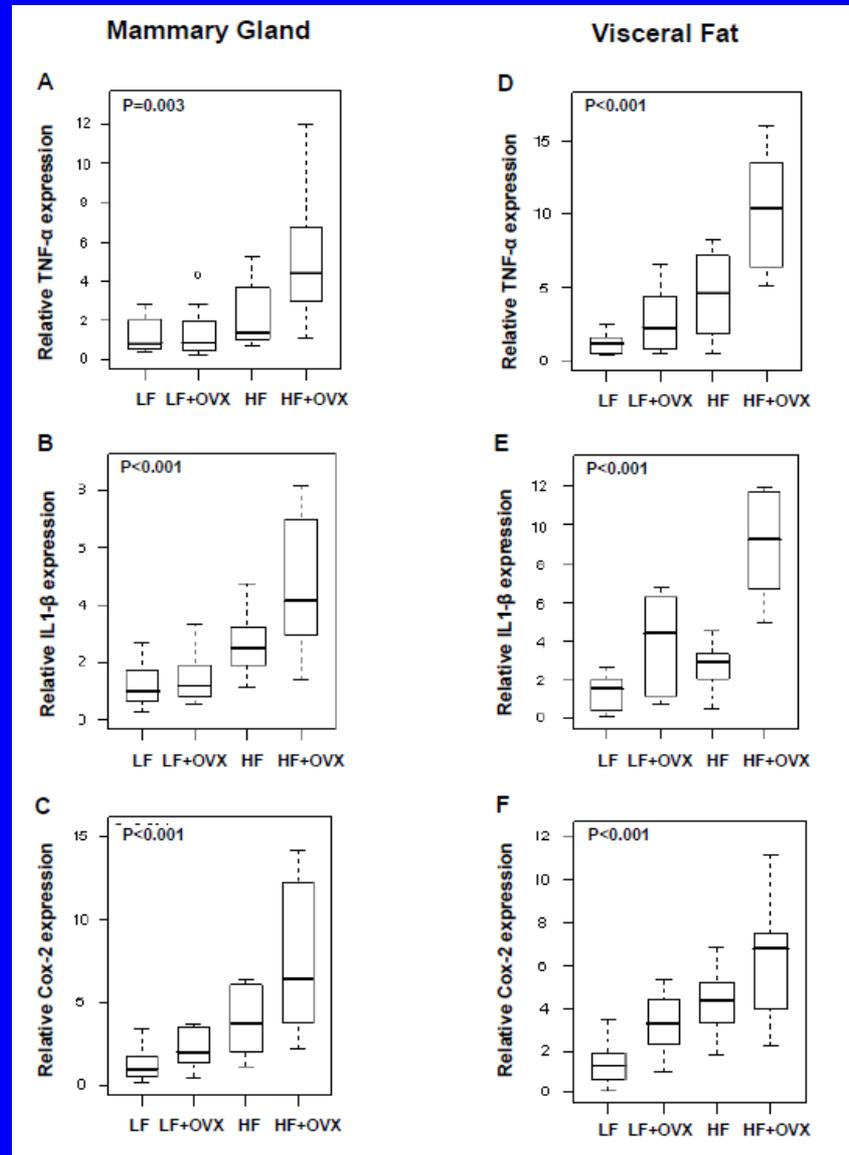
# Diet Induced Obesity: Experimental Design



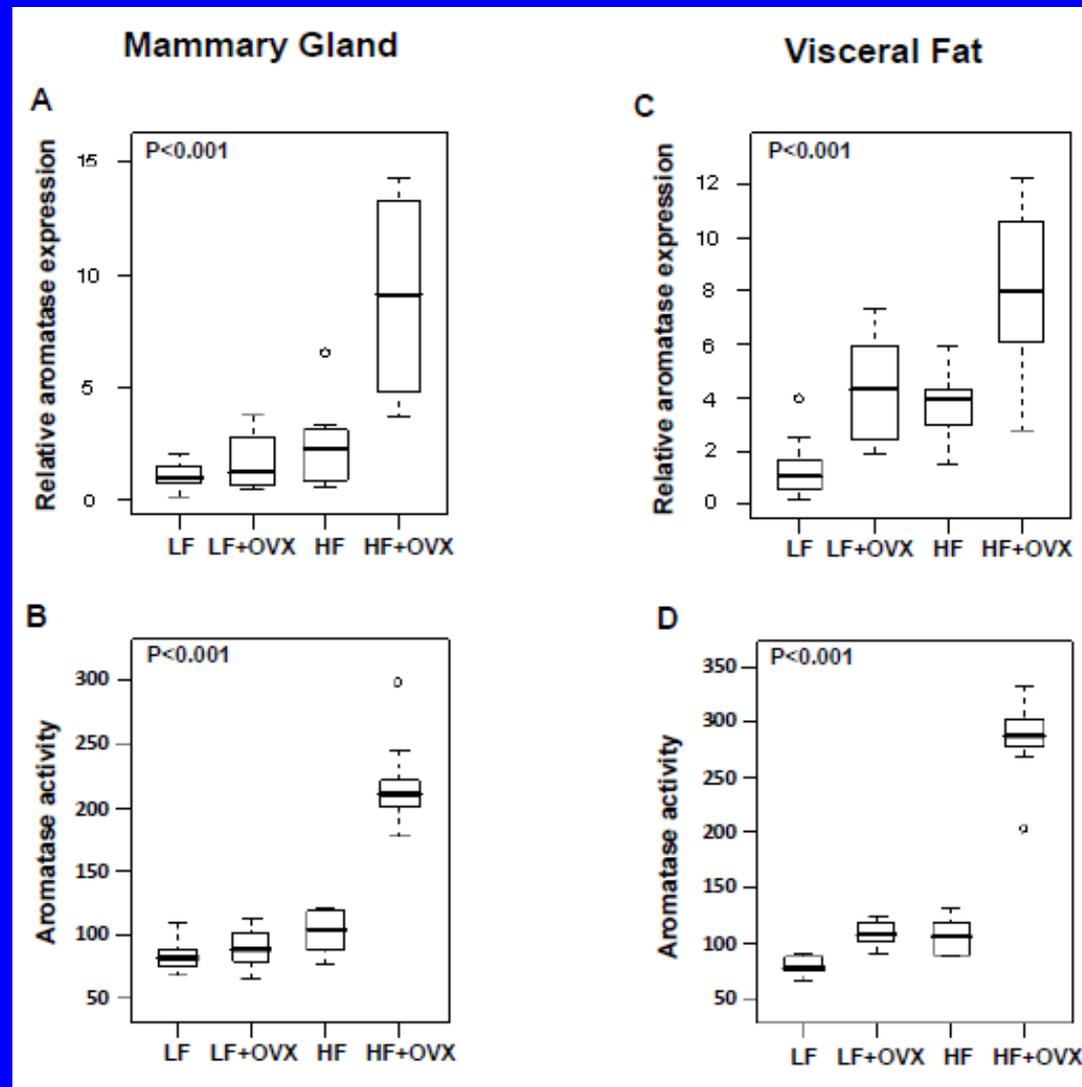
# Diet Induced Obesity Causes Inflammation in the Mammary Gland and Visceral Fat



# Diet Induced Obesity is Associated with Increased Levels of Pro-inflammatory Mediators



# Levels of Aromatase are Increased in Diet Induced Obesity

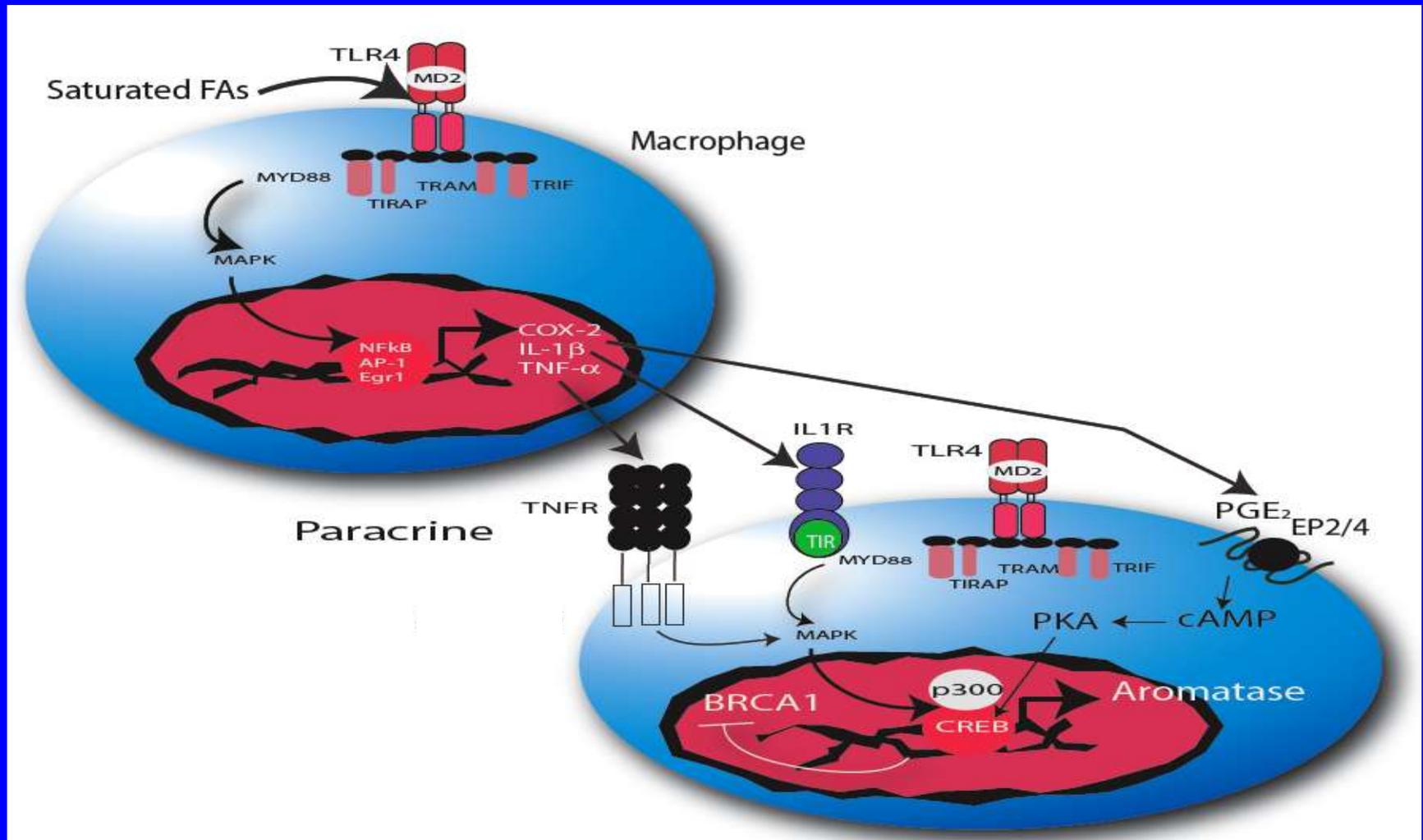


# Obesity Causes Inflammation and Increased Aromatase Levels in the MG and VF of *ob/ob* Mice

Endpoint	MG			VF		
	Wild-type	<i>ob/ob</i>	<i>P</i>	Wild-type	<i>ob/ob</i>	<i>P</i>
Inflammatory foci	0.8 (0.0, 2.6)	13.8 (8.5, 20.4)	<0.001	0 (0.0,10.6)	64.5 (25.5, 202)	<0.001
Relative TNF- $\alpha$ expression	0.9 (0.6, 4.9)	4.9 (0.7, 9.7)	0.007	1.0 (0.5, 2.8)	5.3 (0.6, 8.7)	0.02
Relative IL-1 $\beta$ expression	1.0 (0.4, 2.3)	2.9 (0.3, 9.7)	0.02	1.1 (0.03, 6.0)	5.7 (1.1, 7.9)	0.005
Relative Cox-2 expression	1.0 (0.4, 2.5)	3.8 (1.2, 5.7)	0.001	1.0 (0.4, 3.7)	2.2 (0.6, 4.8)	0.02
Relative aromatase expression	1.2 (0.2, 5.6)	6.1 (0.04, 7.6)	0.007	0.9 (0.4, 2.7)	1.8 (0.8, 6.8)	0.009
Aromatase activity	90 (68,112)	210 (146, 278)	<0.001	98 (67, 154)	272 (177, 355)	<0.001

NOTE: Inflammatory foci, number of inflammatory foci per cm<sup>2</sup> of tissue; real-time PCR was used to quantify relative TNF- $\alpha$ , IL-1 $\beta$ , Cox-2, and aromatase transcript levels; aromatase activity, femtomoles/ $\mu$ g protein/hour. Values are summarized in median (range), *P* values are based on Wilcoxon rank-sum test, *n* = 10/gp.

# Saturated Fatty Acids Activate the TLR4→NF-κB Axis in Macrophages Leading to Induction of Aromatase



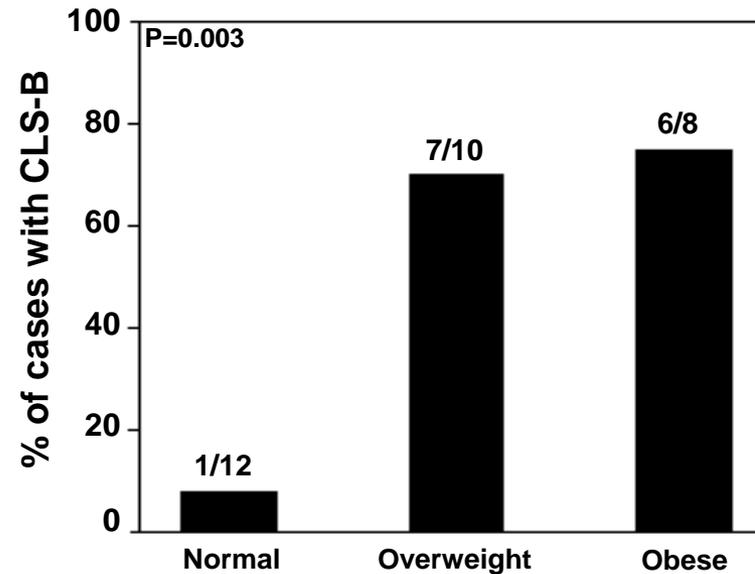
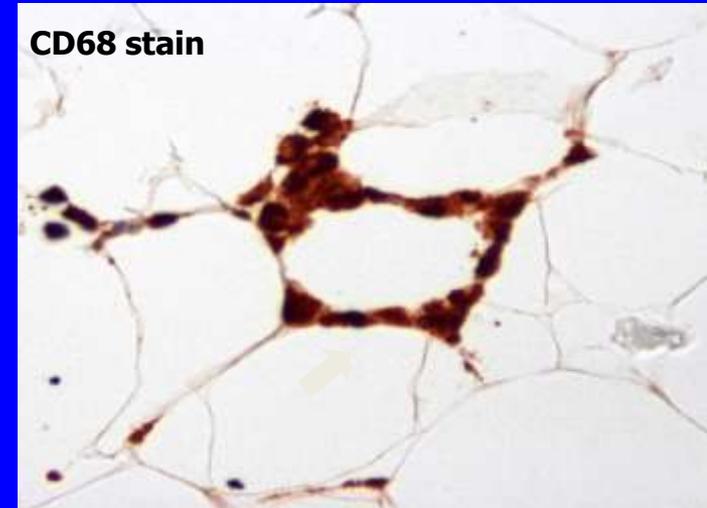
# Objectives

- To determine if CLS of the breast (CLS-B) exist in women and correlate with BMI.
- To investigate if increased levels of pro-inflammatory mediators and aromatase are present in the breast tissue of obese women.

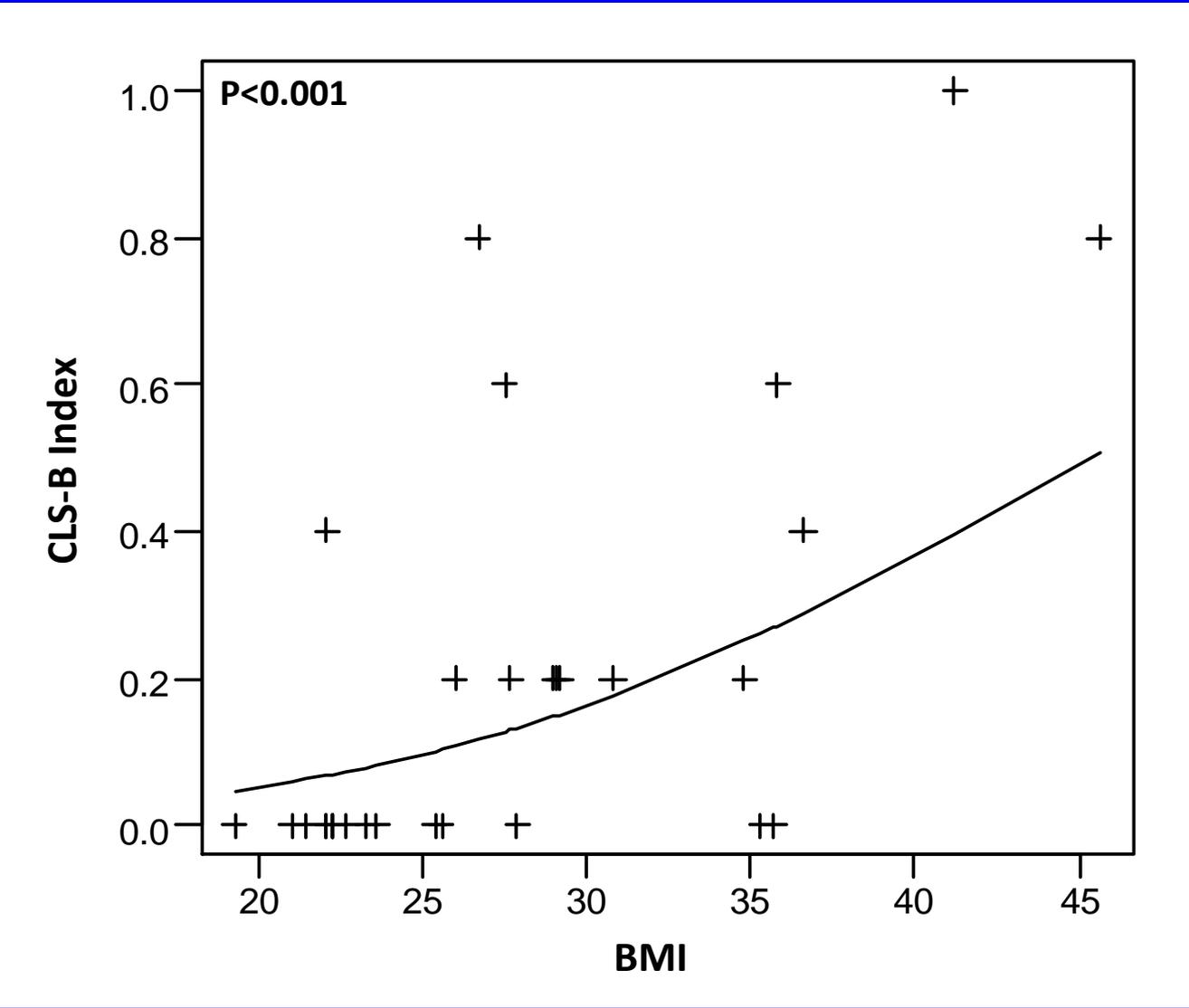
# Study Design

- Normal breast white adipose tissue was obtained from 30 women who underwent surgery.
- Routine H&E staining and CD68 IHC was performed.

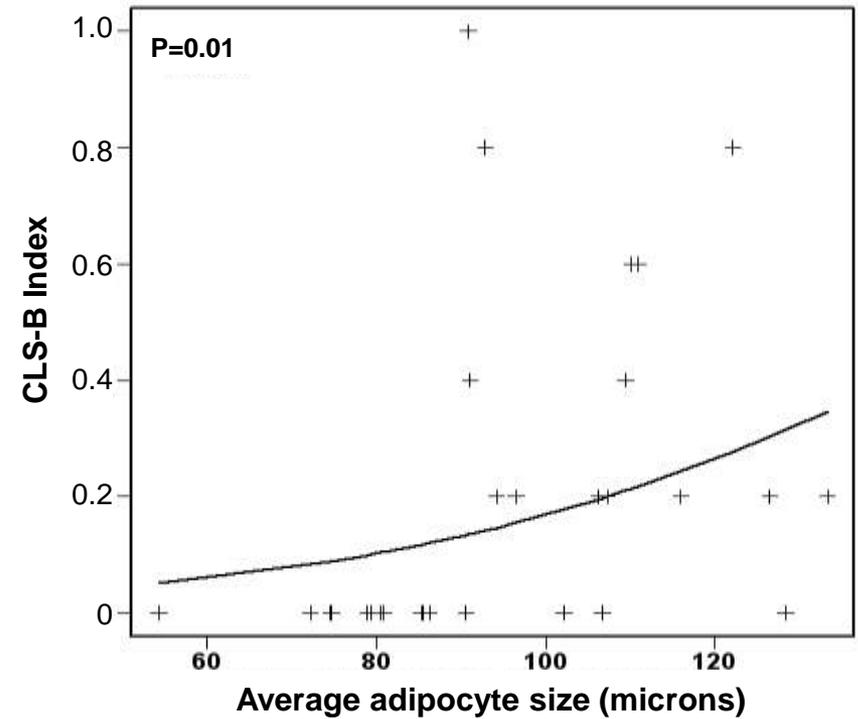
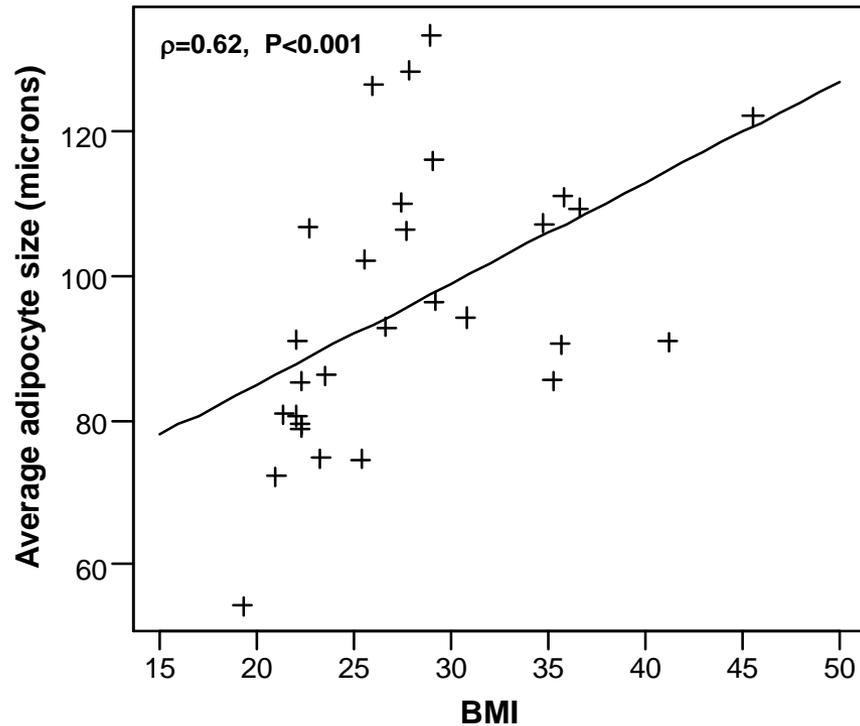
# CLS-B are Common in the Breasts of Overweight and Obese Women



# Increasing BMI is a/w with Increased Breast Inflammation

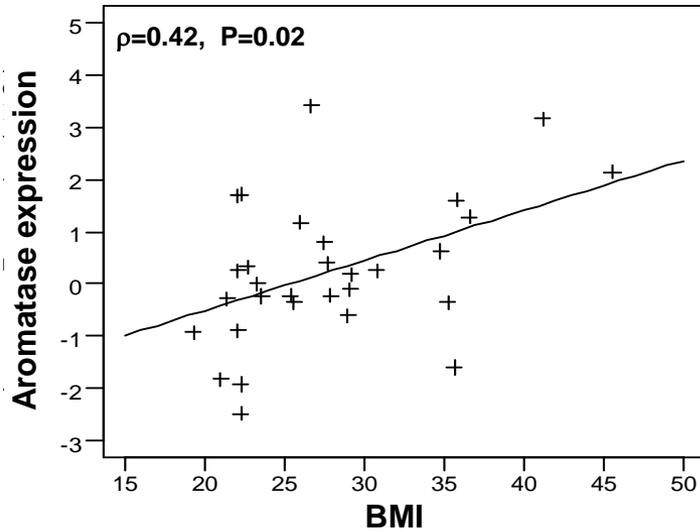


# Adipocyte Size Correlates with BMI and CLS-B Index

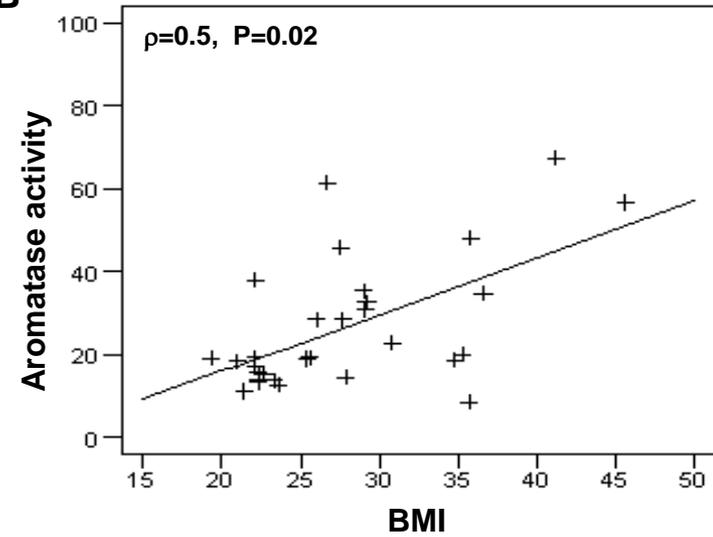


# Aromatase Expression and Activity Correlate Better with Breast Inflammation than BMI

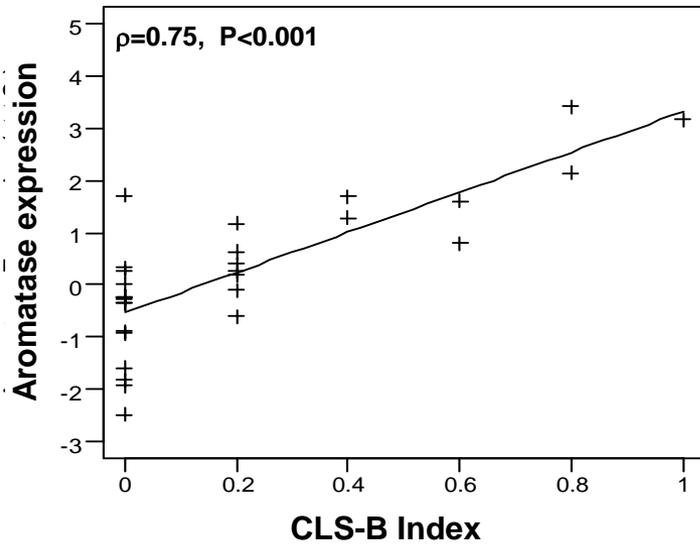
**A**



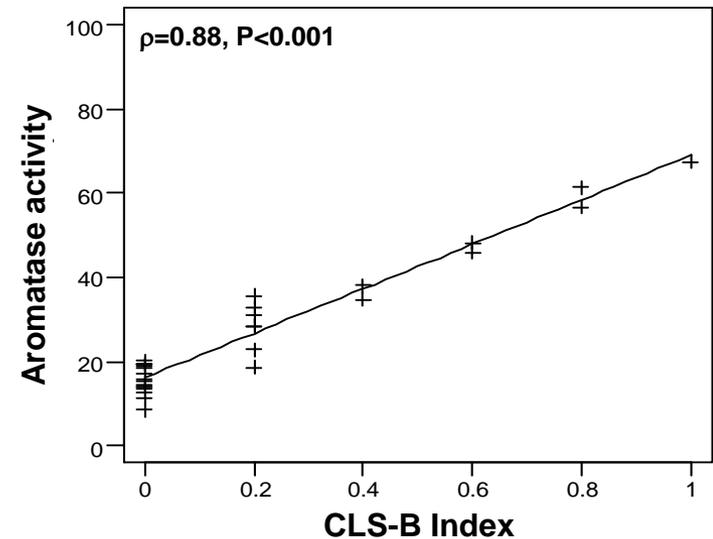
**B**



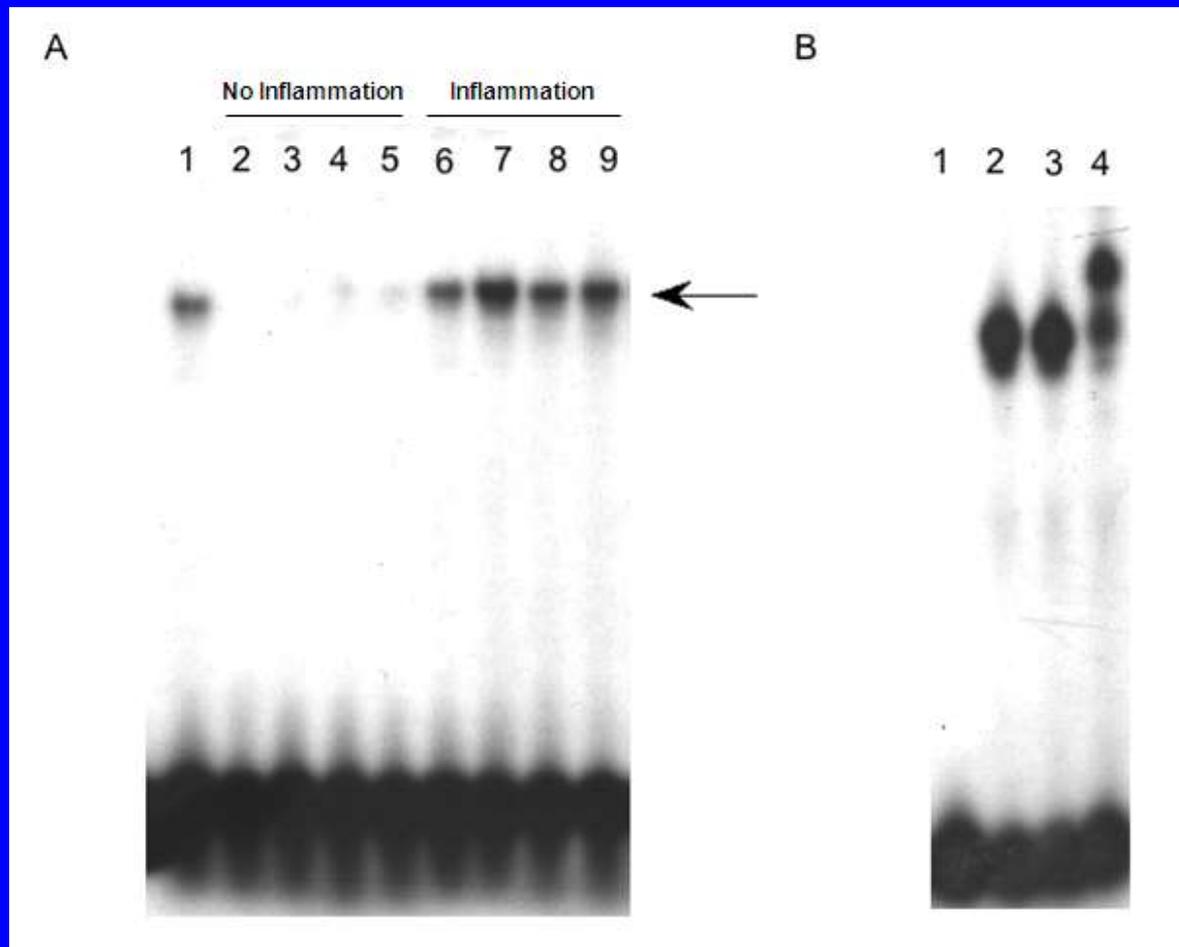
**C**



**D**

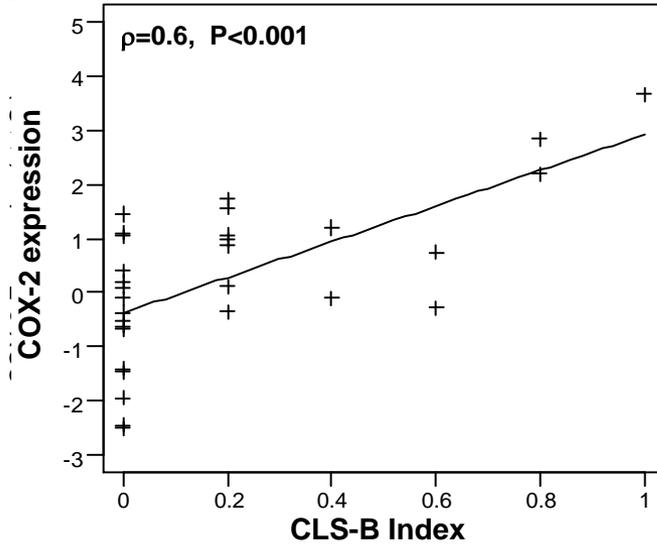


# NF- $\kappa$ B Binding Activity is Increased in a/w Breast Inflammation

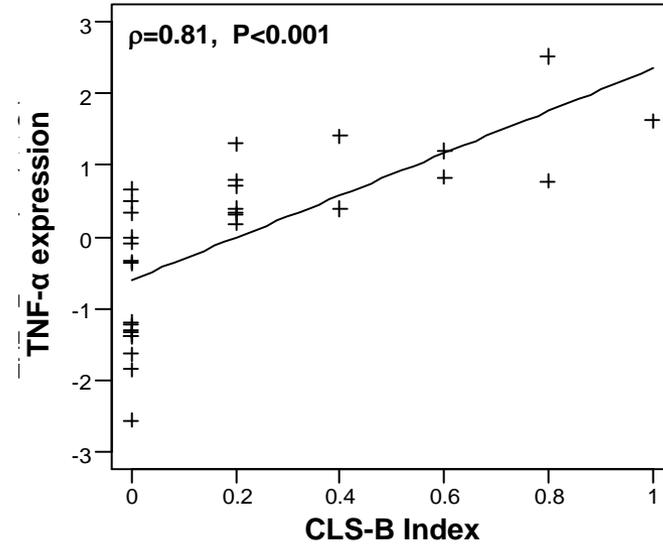


# Levels of Pro-inflammatory Mediators are Increased in Inflamed Breast Tissue

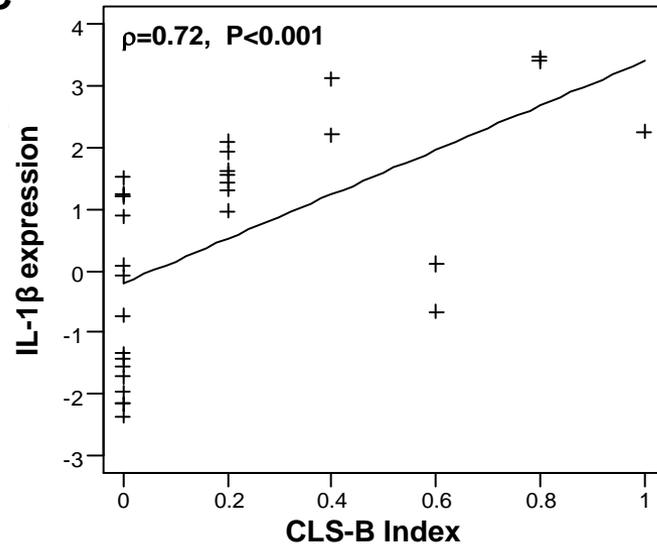
**A**



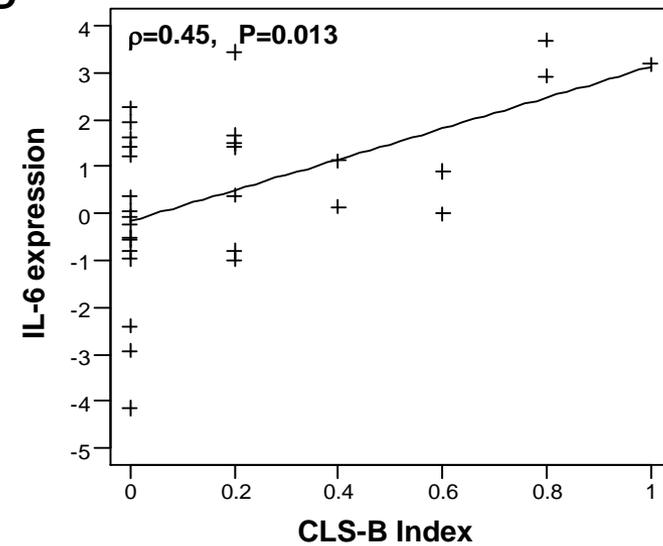
**B**



**C**



**D**



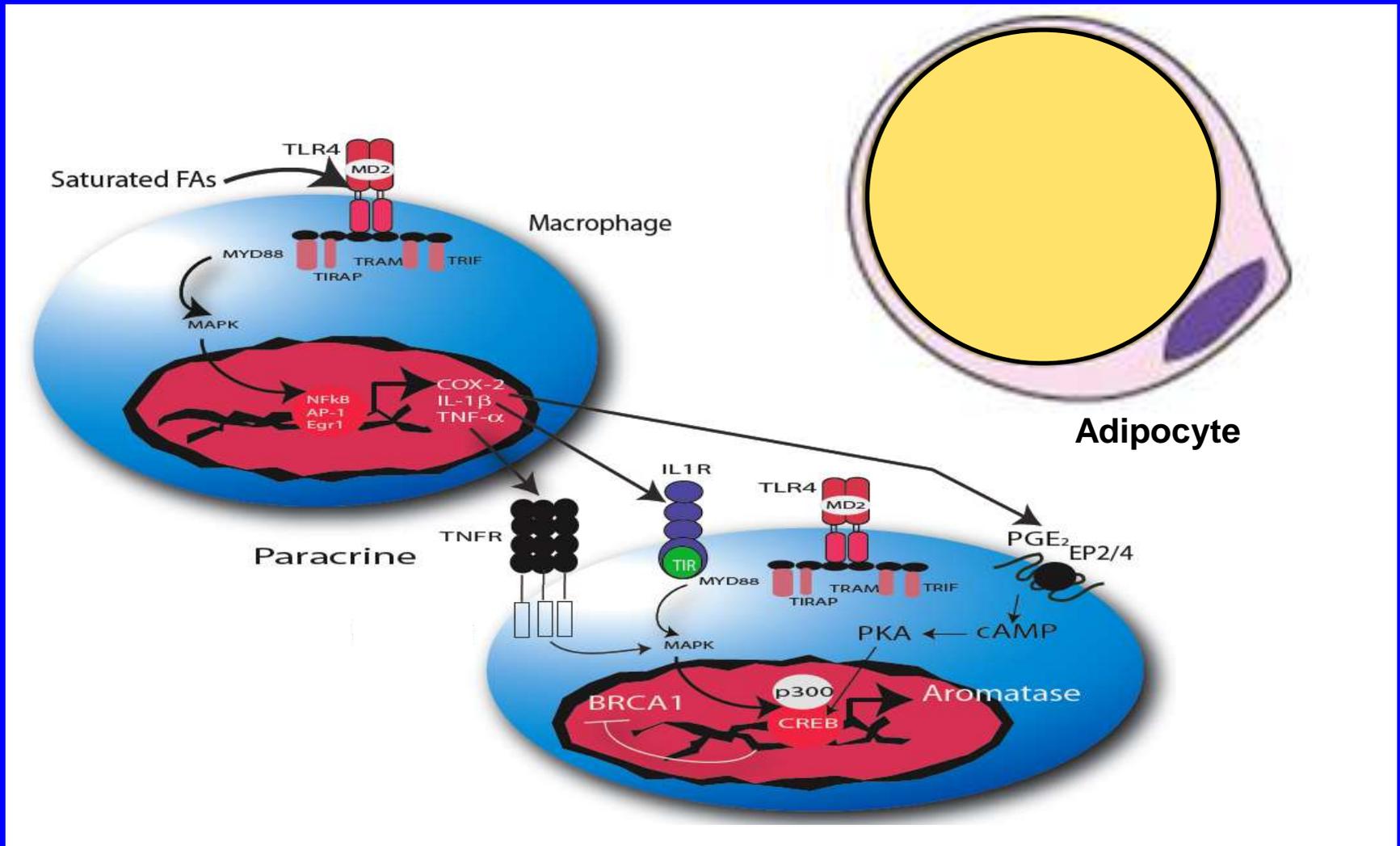
# Conclusions

- Inflammation (CLS-B) occurs in the breast tissue of most overweight and obese women.
- In both obese women and experimental models of obesity, breast inflammation was paralleled by elevated levels of pro-inflammatory mediators (TNF- $\alpha$ , IL-1 $\beta$ , COX-2, PGE<sub>2</sub>).
- In obesity, activation of the TLR4 $\rightarrow$ NF- $\kappa$ B pathway in macrophages is likely to be responsible for increased production of pro-inflammatory mediators leading, in turn, to elevated aromatase expression and estrogen synthesis.

# Conclusions

- The obesity→inflammation→aromatase axis may help to explain the link between obesity and the increased risk of breast cancer in postmenopausal women.
- CLS-B may represent a biomarker of breast cancer risk or poor prognosis.
- Strategies (lifestyle, diet, pharmacological) that disrupt the obesity→inflammation axis may be useful for reducing the risk of breast cancer or its progression.

# Therapeutic Opportunities to Suppress Obesity-related Breast Inflammation



# Chronic Inflammation and Cancer

Causal Mechanisms	Types of Cancer
Helicobacter pylori and chronic gastritis	Stomach cancer
Epstein-Barr virus	Lymphoma Nasopharyngeal carcinoma
Human papillomavirus	Anogenital carcinoma Oropharyngeal carcinoma
Hepatitis B or C virus	Hepatocellular carcinoma
HIV/AIDS	Non-Hodgkin's lymphoma Kaposi's sarcoma
Liver flukes (e.g., Clonorchis sinensis)	Cholangiocarcinoma
Schistosoma haematobium	Squamous carcinoma of urinary bladder
Gastroesophageal reflux	Adenocarcinoma of the distal esophagus
Inflammatory bowel disease	Colon cancer
Chronic obstructive lung disease	Lung cancer
Chronic diffuse infiltrative lung disease (e.g., asbestosis, silicosis)	Lung cancer
Chronic cholecystitis	Gallbladder cancer
Inflammatory atrophy of prostate	Prostate cancer
<b>Obesity</b>	<b>? Breast cancer</b>

# CONTRIBUTORS

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## NCI

- Levy Kopelovich, PhD

## MSKCC

- Clifford Hudis, MD
- Patrick Morris, MD
- Monica Morrow, MD
- Dilip Giri, MD

## **FUNDING**

- NIH/NCI
- BCRF