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## Activated Innate Immunity in Childhood: A Novel Treatment Target

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# Activated Innate Immunity in Childhood: A Novel Treatment Target

Olga T. Hardy, M.D.

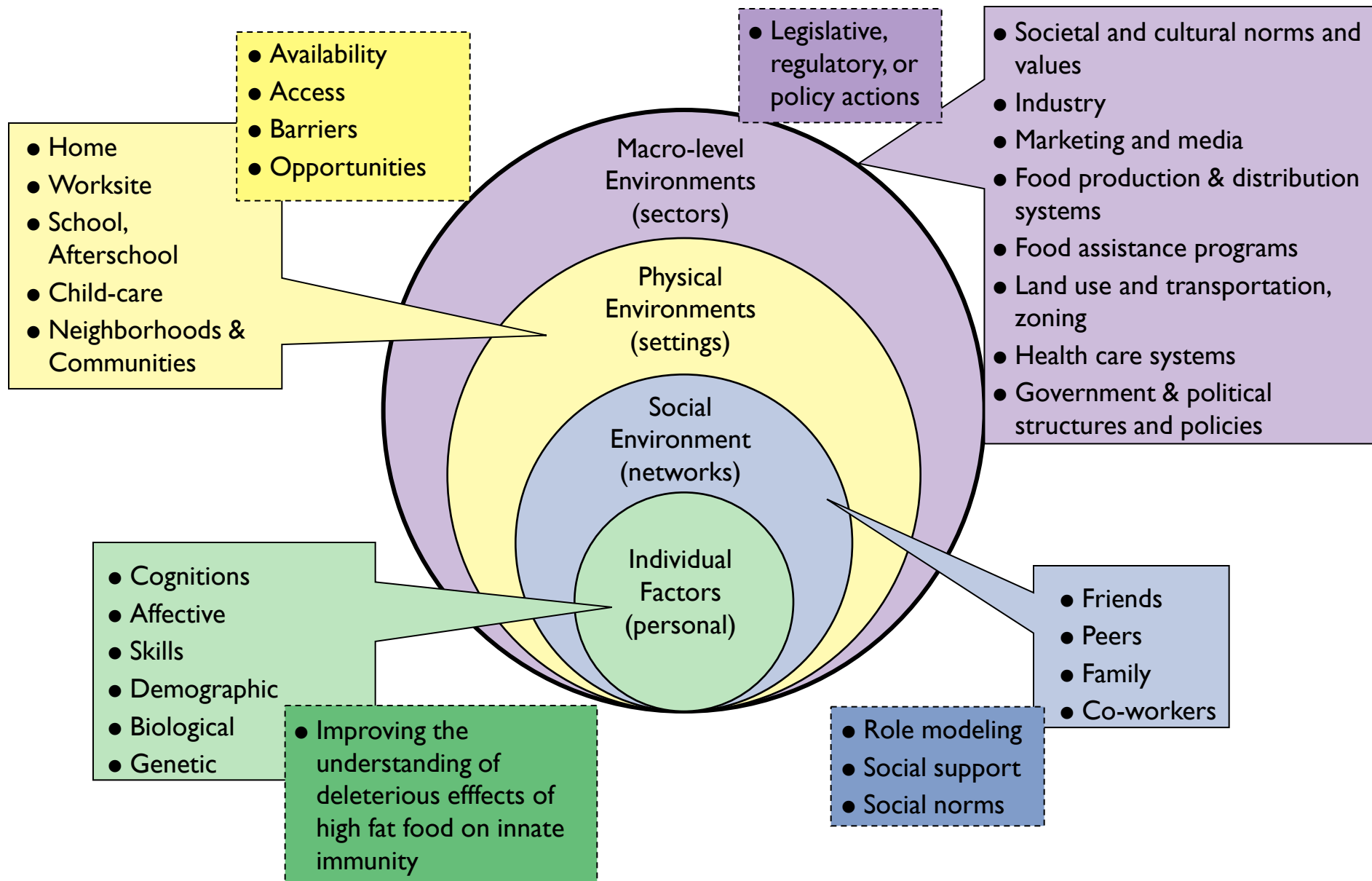
University of Massachusetts Medical School  
Division of Pediatric Endocrinology and Diabetes

May 20, 2011

# **DISCLOSURE**

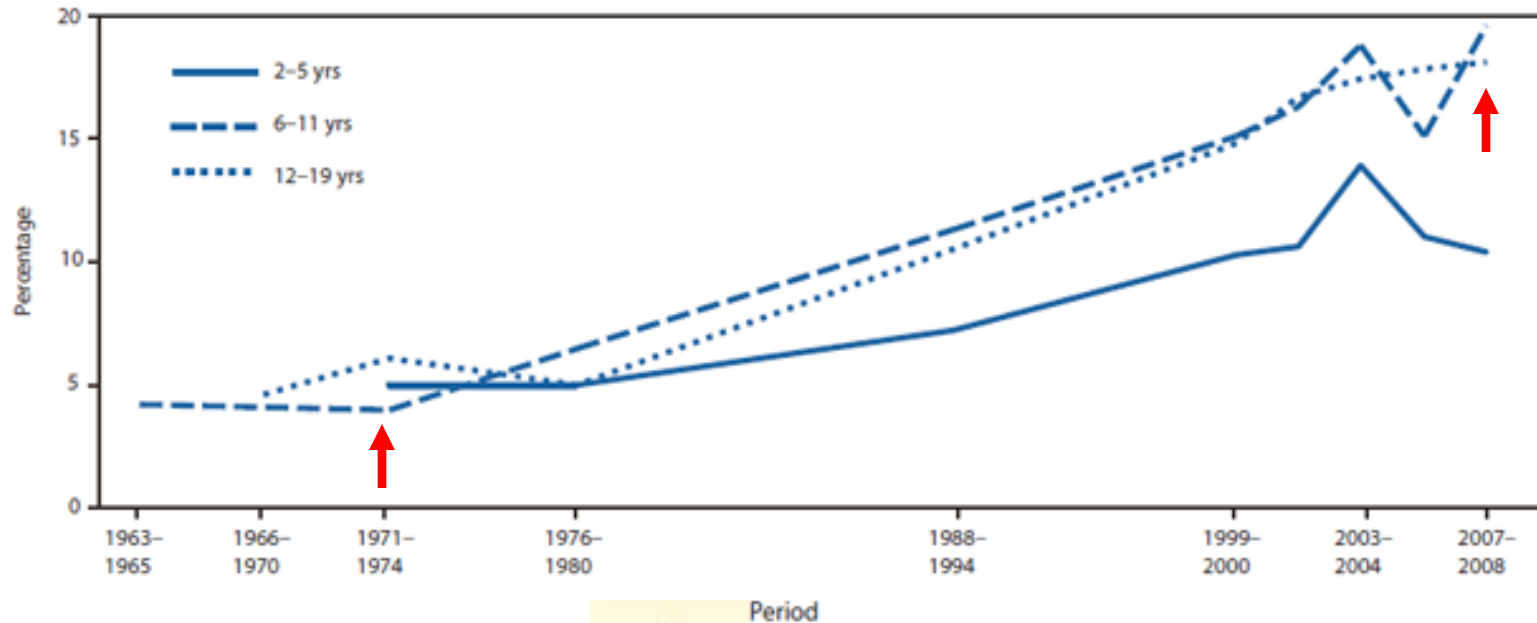
**I have no actual or potential conflict of interest  
in relation to this program or presentation.**

# An Ecological Framework: Multiple Influences on Physical Activity and Eating Behaviors



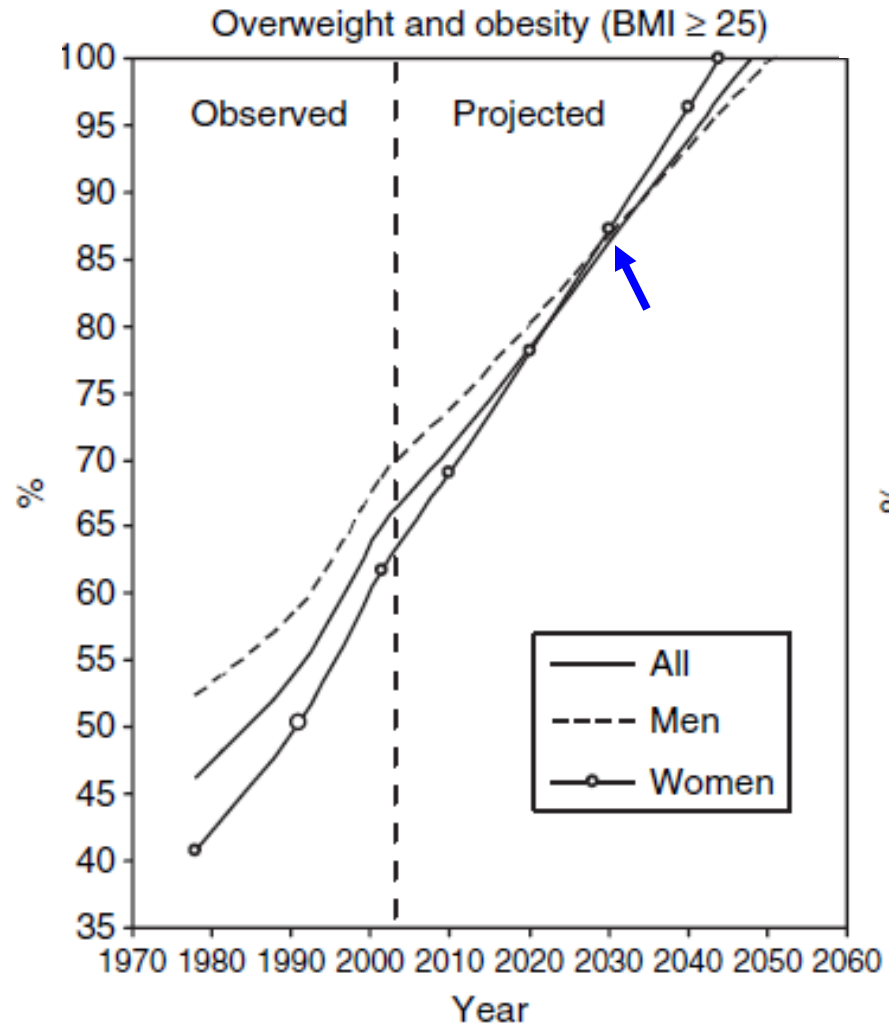
# Childhood obesity is an epidemic

Prevalence of obesity among children and adolescents, by age group --- United States, 1963-2008



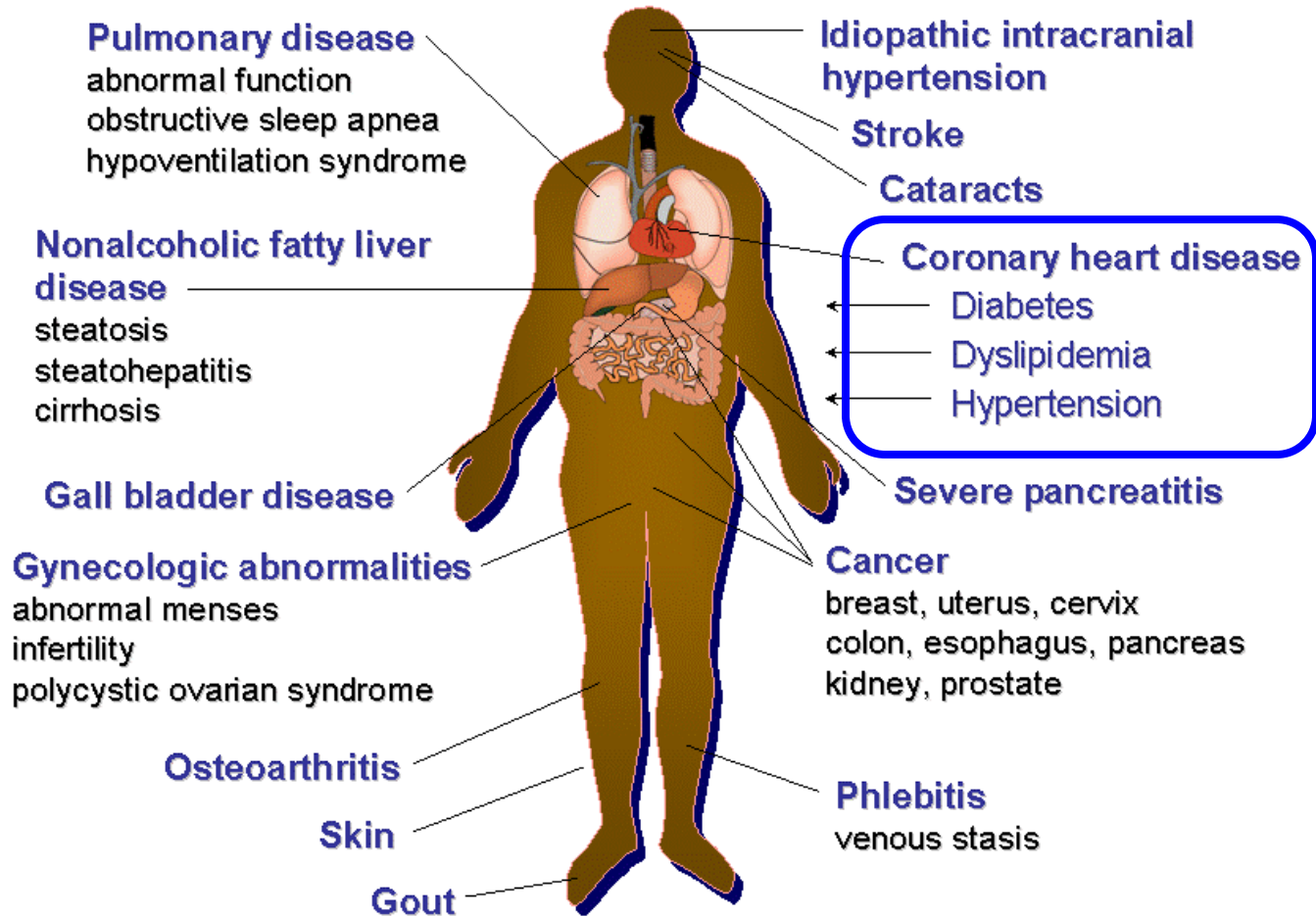
“CDC Grand Rounds: Childhood Obesity in the United States.” MMWR: Morbidity and Mortality Weekly Report. January 21 2011. 60(2):42-46.

# Based on current trends 86% of U.S. adults will be overweight by 2030



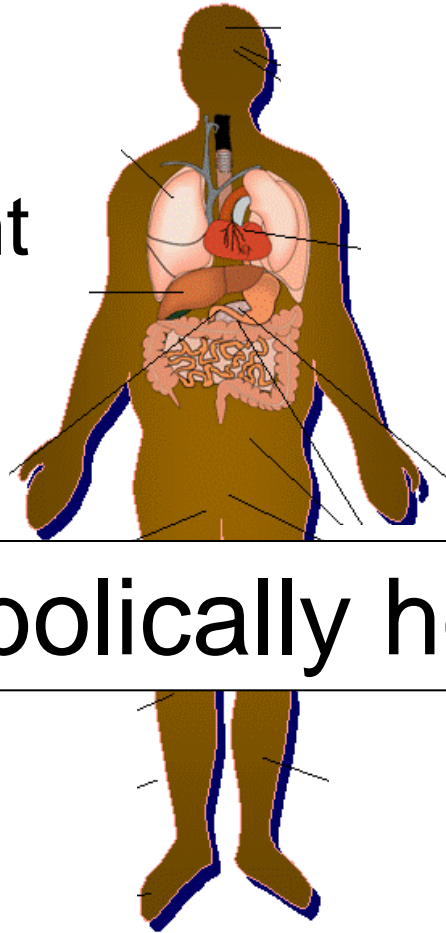
Wang Y, et al. Will all Americans become overweight or obese? estimating the progression and cost of the US obesity epidemic. Obesity. 2008.

# Obesity is a risk factor for numerous medical conditions



# However ... not all obese individuals develop complications

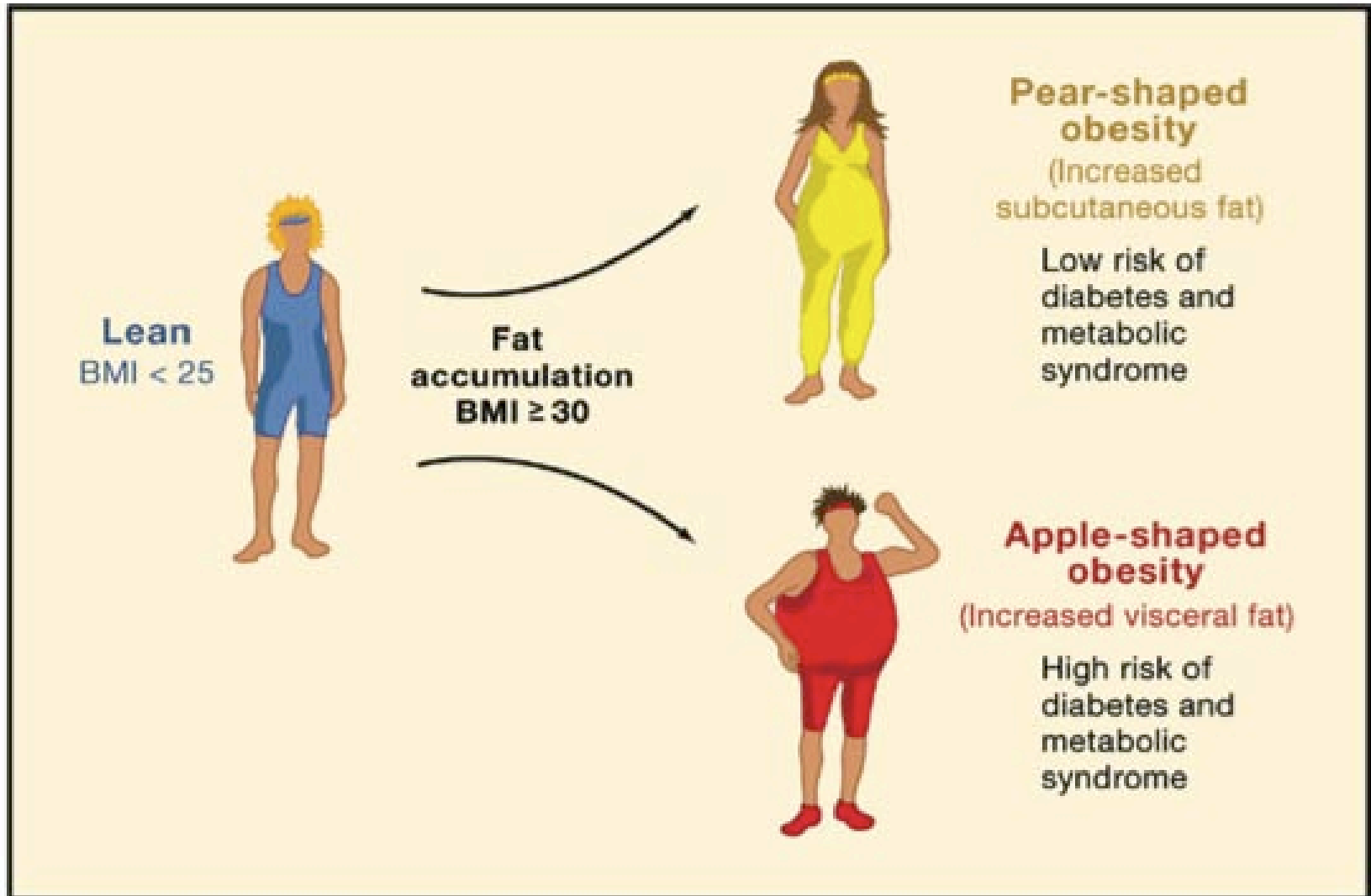
51% of overweight adults



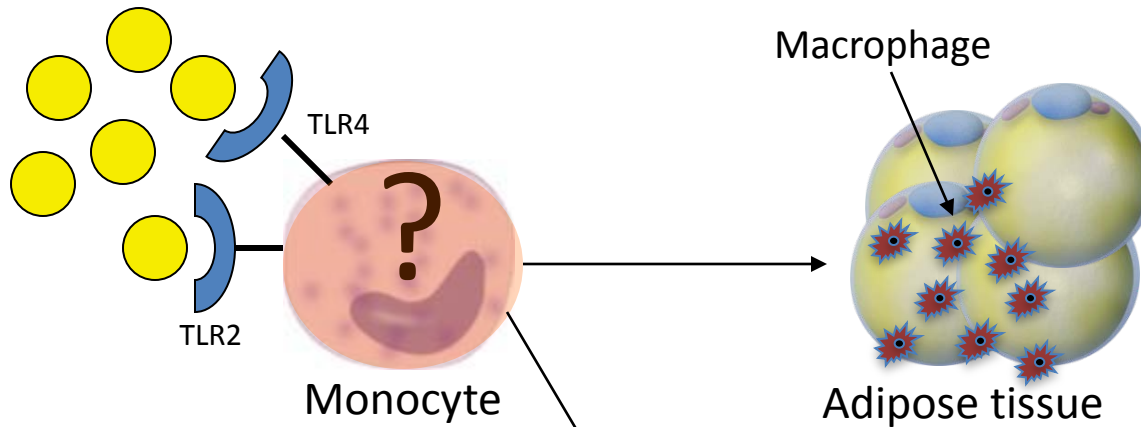
31% of obese adults

Metabolically healthy

# Increased visceral fat is associated with a high risk of diabetes



# Monocytes may be a modifiable source of proinflammatory cytokines



Mononuclear cells from adults with T1DM and T2DM have increased expression of TLR2, TLR4, CCL2 and increased secretion of IL6 and Tnf $\alpha$



Mononuclear cells from obese adults have increased NF $\kappa$ B binding and increased expression of IL6 and Tnf $\alpha$

IL6, Tnf $\alpha$   $\longrightarrow$  Metabolic disease



Mice lacking TLR2 or TLR4 are protected from high fat diet induced insulin resistance

# Objectives



Monocyte

1

## Assess inflammatory state

### *Gene expression*

- Toll-like receptors (TLR2, TLR4)
- Cytokines (Tnf $\alpha$ , IL6)

2

## Correlate monocyte inflammation with anthropometric measurements and serum markers

- BMI, Waist circumference
- Glucose, Insulin, Lipid profile
- Tnf $\alpha$ , IL6

## Adolescents

- Overweight with metabolic syndrome (Overwt-MetSyn)
- Overweight without metabolic syndrome (Overwt-Healthy)
- Lean

## **Hypotheses:**

1. Monocytes from Overwt-MetSyn subjects will have increased gene expression of TLRs and cytokines when compared to Overwt-Healthy and Lean subjects
2. TLR and cytokine expression will show a positive correlation with anthropometric and serum markers of metabolic disease

# Twenty four adolescents were recruited to participate in this pilot study



UMMS clinics

- Pediatric endocrinology
- Adolescent medicine
- Nutrition

Dorchester Academy – inner city high school



- Lean – BMI < 85% age and gender
- Overweight – BMI > 85% age and gender
- Metabolic syndrome – 3 of the 5 components
  - \*Waist circumference > 75% age, gender, ethnicity
  - \*Triglycerides > 100
  - \*HDL < 50 (girls) and < 40 (boys)
  - \*Systolic blood pressure > 95% age, gender
  - \*Fasting glucose >100 mg/dl

# 3 groups are similar in age, gender, ethnicity

	Overwt MetSyn (n=6)	Overwt Healthy (n=9)	Lean (n=9)
Female, No. (%)	6 (100)	6 (67)	6 (67)
Age (yr)	16.5 (15.4-17.2)	16.8 (15.9-19.8)	16.6 (15.6-18)
Ethnic group, No. (%)			
African American	4 (67)	6 (67)	7 (78)
Caucasian	0	2 (22)	1 (11)
Hispanic	2 (33)	1 (11)	1 (11)
BMI (kg/m <sup>2</sup> )	39 (30-52)*	32 (26-40)*	21 (18-25)^
BMI %	98 (96-99)*	94 (85-99)*	50 (36-84)^
<b>Waist circumference</b>	<b>117 (98-142)**</b>	<b>95 (80-112)*</b>	<b>74 (61-83)^</b>
Systolic BP (mm Hg)	122 (102-139)	117 (108-141)	114 (104-129)
Diastolic BP (mm Hg)	75 (61-84)	71 (53-85)	73 (63-81)
White blood cell counts (k/uL)	8 (5-12)*	6 (4-9)	6 (4-7)
Monocytes (%)	8 (4-12)	9 (6-14)	8 (5-11)
Cholesterol (mg/dL)	119 (72-162)	113 (83-155)	109 (73-145)
Triglyceride (mg/dL)	61 (23-125)	48 (24-97)	51 (34-90)
HDL (mg/dL)	40 (32-47)	41 (24-56)	42 (29-56)
LDL (mg/dL)	67 (27-90)	62 (49-100)	57 (32-81)
CRP (pg/mL)	3.5 (1-11)	3.1 (1-16)	1 (1-1)
Fasting glucose (mg/dL)	98 (82-119)	89 (66-109)	95 (84-110)
Fasting insulin (uIU/mL)	13 (2-31)*	6 (2-14)	3 (2-6)^
HOMA-IR	2.9 (0.8-7.1)*	1.3 (0.3-3.3)	0.7 (0.4-1.4)^
<b>TNF-<math>\alpha</math> (pg/mL)</b>	<b>2.14 (0.75-4.66)**</b>	<b>0.86 (0-2.5)</b>	<b>0.95 (0.3-1.84)</b>
<b>IL6 (pg/mL)</b>	<b>2.75 (0.49-3.89)**</b>	<b>1.46 (0-2.74)*</b>	<b>0.61 (0-2.2)^</b>

similar

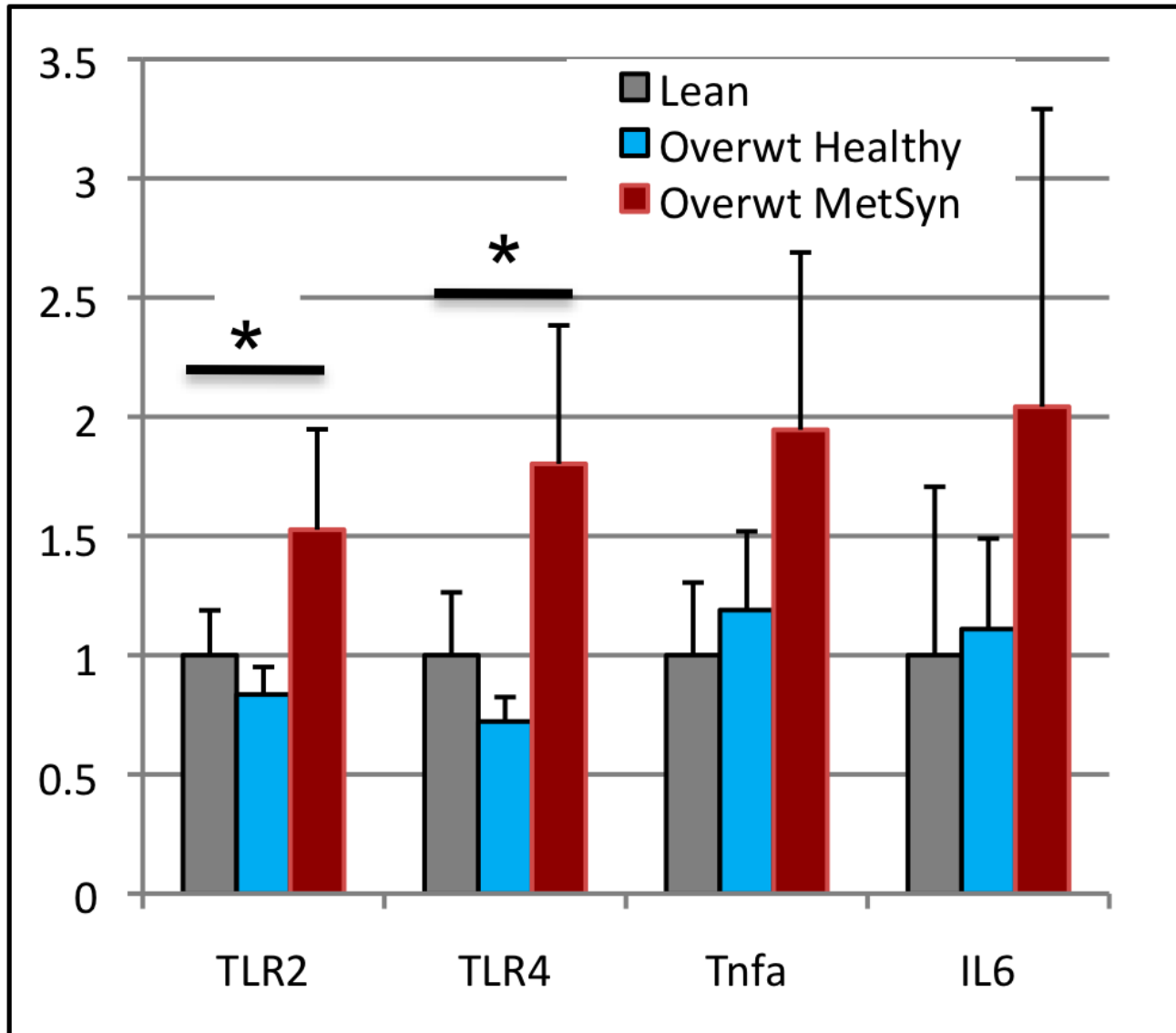
Data presented as mean (range)

\* P < 0.05 compared with lean

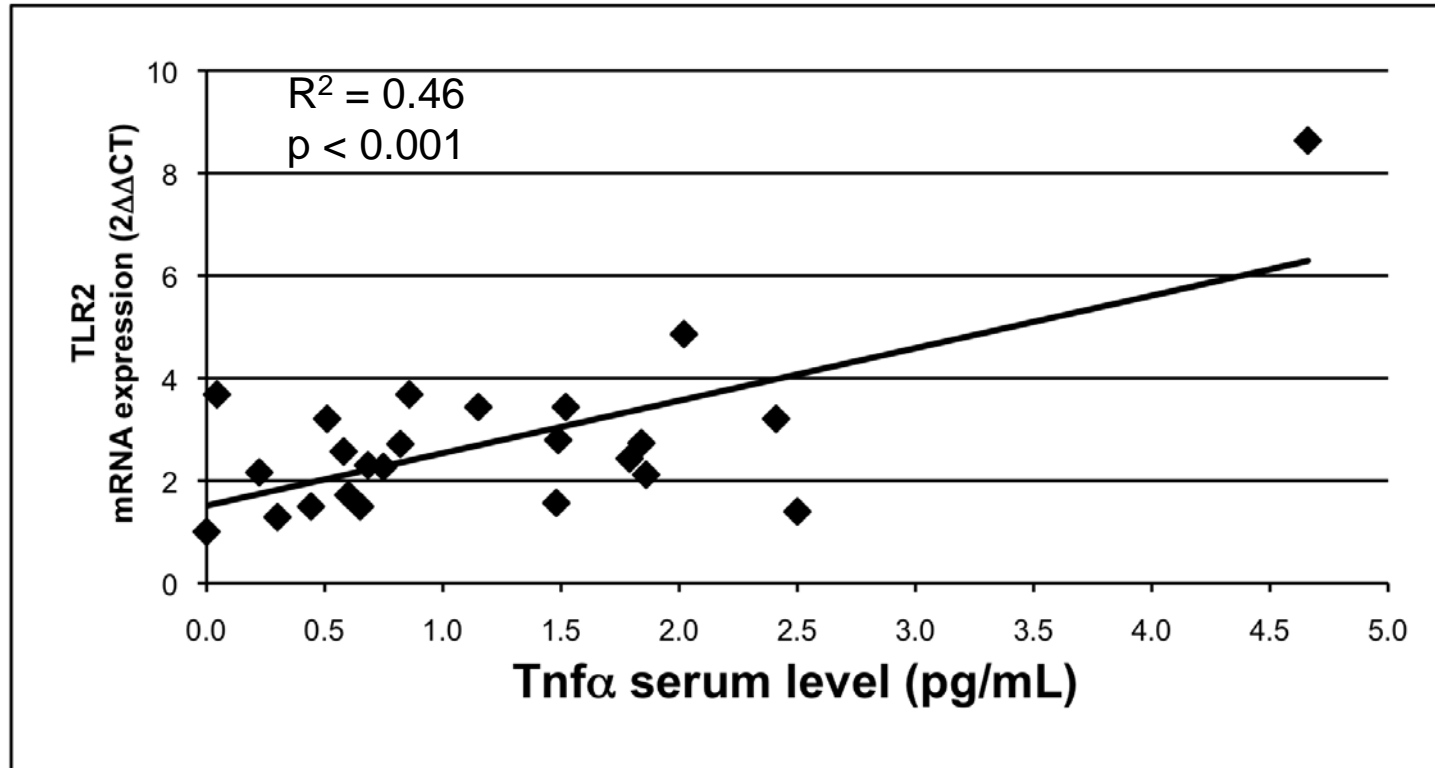
\*\* P < 0.05 compared with overweight healthy

^ P < 0.05 compared with all overweight (Overweight healthy and Metabolic syndrome)

# Monocytes from Overwt-MetSyn subjects display increased expression of inflammatory genes



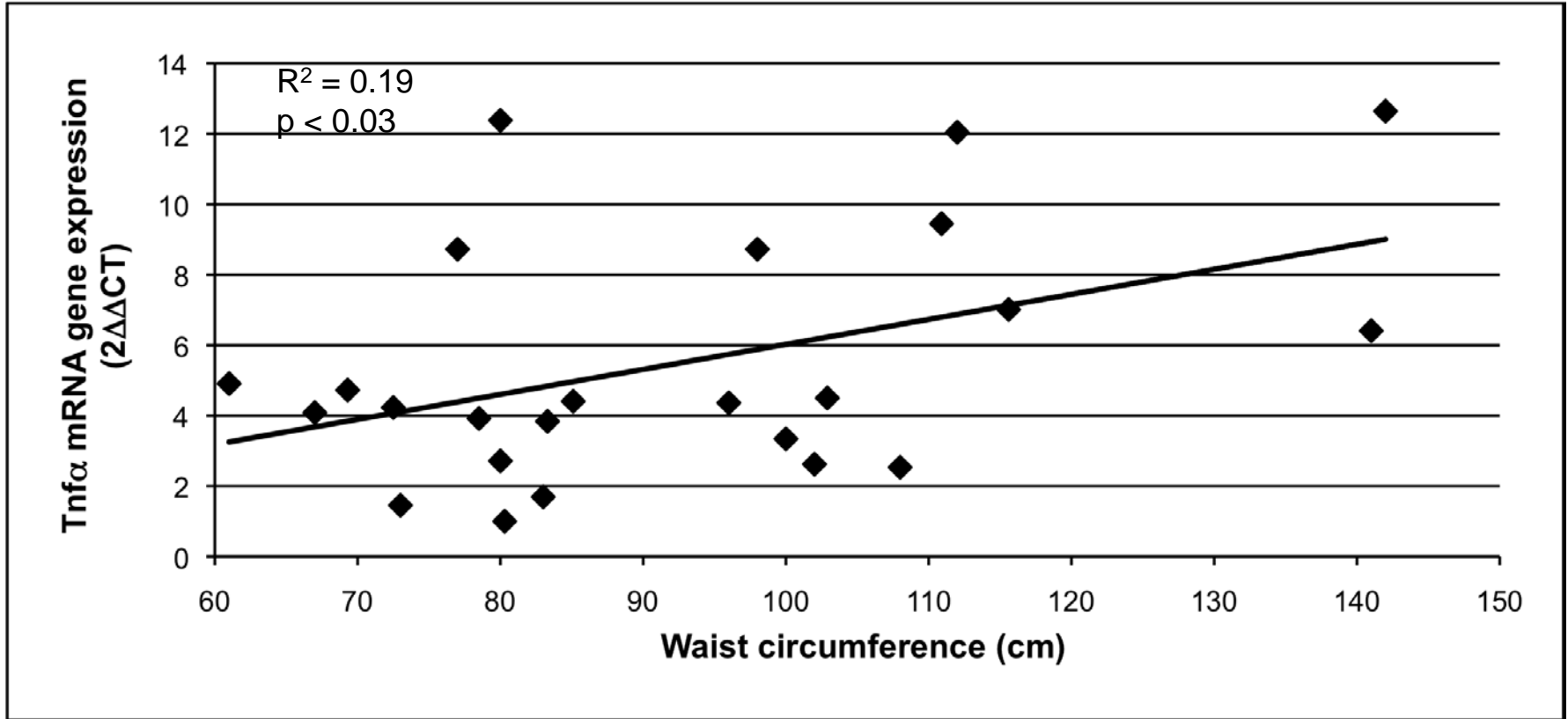
# TLR expression in monocytes correlates with circulating cytokines



## TLR4 expression

	$R^2$	$p$ -value
Tnfα serum	0.2	0.02
IL6 serum	0.2	0.02

# Cytokine expression in monocytes correlates with BMI and central obesity



## Tnfα expression

	$R^2$	$p$ -value
BMI	0.2	0.05

## IL6 expression

	$R^2$	$p$ -value
WBC count	0.2	0.01

# Conclusions



Monocyte

Yes

Yes

## Assess inflammatory state

### *Gene expression*

- TLR2, TLR4, Tnf $\alpha$ , IL6

## Correlate monocyte gene expression with anthropometric measurements and serum markers

- BMI, Waist circumference, Tnf $\alpha$ , IL6

## Adolescents

- Overwt-MetSyn, Overwt-Healthy, Lean

1. Monocytes from Overwt-MetSyn subjects display increased gene expression of TLRs and cytokines
2. TLR expression shows a positive correlation with circulating cytokines; cytokine expression correlates with BMI and waist circumference

## Ongoing research

1. Recruit more subjects
2. Assess TLR protein expression, surface markers
3. Measure secreted cytokines (Tnf $\alpha$ , IL6) from cultured monocytes at baseline and in response to TLR ligands and dietary lipids

# Innate immunity plays a key role in metabolic disease and may be a useful biomarker



Obese adolescent

↑Tnf $\alpha$ , IL6 serum levels



↑TLR2, TLR4 gene expression in MetSyn

↑Tnf $\alpha$ , IL6 gene expression (trend) in MetSyn



Obese adult

Type 2 diabetes mellitus



## Questions

1. Impact of dietary changes on monocyte
2. Improvement in monocyte inflammation loss and/or exercise?
3. Reversal of monocyte inflammation with pharmacotherapy or nutritional supplements?

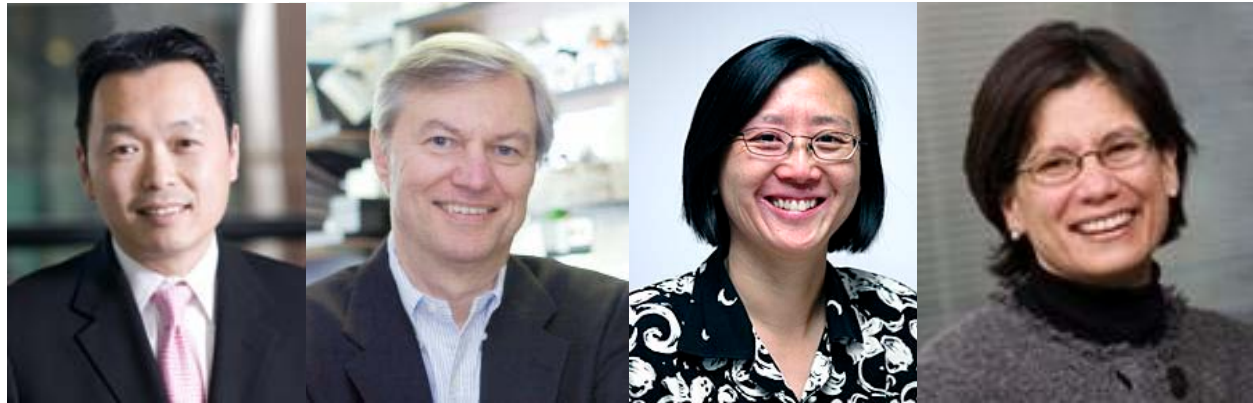
“It is unreasonable to expect that people will change their behavior so easily when so many forces in the social, cultural, and physical environment conspire against change”

*Institute of Medicine, 2000*

# Acknowledgments

- Mentorship Team

- Jason Kim, PhD
- Michael P. Czech, PhD
- Mary Lee, MD
- Katherine Luzuriaga, MD



- Collaborators

- Laura Hayman, PhD (UMass Boston)
- Jean Wiecha, PhD (UMass Boston)
- Albert Kim (UMass Boston)

- Study Nurse

- Carol Ciccarelli, Rn

- Czech Lab Members



- Funding Support

- CTSA K12 training grant
- CTSA Life Sciences Moment Fund
- Diabetes and Endocrinology Research Center Pilot and Feasibility grant



# Monocytes were isolated from whole blood with indirect magnetic labelling

- 25 ml whole blood collected in the fasting state

The only one-step, closed system for collection, cell separation and transport.

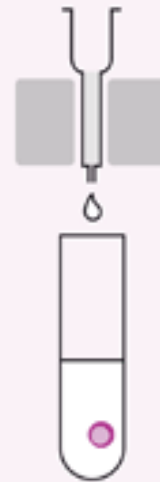
For the Separation of Mononuclear Cells from Whole Blood.



Plasma  
Lymphocyte and monocyte band  
Density gradient fluid  
Gel barrier  
Erythrocytes and neutrophils



Indirect magnetic labeling of non-monocytes using a cocktail of biotinylated antibodies and Anti-Biotin Microbeads

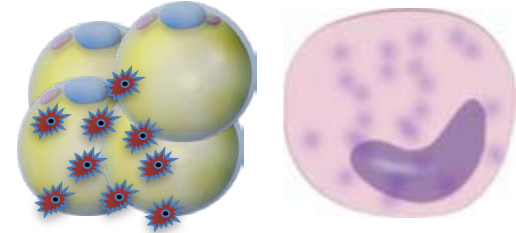


Non-monocytes are retained in a MACS Column placed in a MACS Separator. Monocytes pass through the column and are collected as the enriched, unlabeled cell fraction

# Topics to be covered in this presentation



Obesity and metabolic syndrome (MetSyn)



Immunologic pathways that may contribute to MetSyn



Potential impact on progression of metabolic disease