Inflammation Status (as estimated by plasma biomarkers) is Associated with CVD Risk in middle aged and older men and women

These markers represent:

- The "general inflammatory status"
- Both innate and adaptive immune status
- The specific pathway in which they participate

What do we mean by "general inflammatory status?

Represent:

- Immune Response, Coagulation
- Plasmin generation for fibrinolysis, collagenase activation
- Cellular activation/migration/proliferation
- Opsonization
- Complement Activation
- Oxidative Damage and Repair
- RAS (angiotensinogen is an APR, and Angiotensin II activates NFkB)
- ????

Inflammation Status is Associated with CVD Risk and other diseases of older age

However, the strength of the association (i.e., the RR) appears to decline with age(or with increased disease burden?)

Also

Although data are limited, the association appears at least as strong in middle aged women as in middle aged men, but may be less strong in elderly women compared to elderly men

Gender differences in inflammation and mortality

In distinction to what occurs in middle age, it appears that inflammation is associated with mortality in the elderly in a time-dependent manner:

Inflammation markers predict mortality that occurs within 3 years of the blood collection much more strongly than mortality after 3 years from blood collection.

This is true for both CVD mortality and non-CVD mortality

There is also a gender interaction: this effect is seen much more strongly in men than women

Data from the Cardiovascular Health Study, presented by N. Jenny, ___ National meeting of the Epidemiology and Disease Prevention Council of the AHA, 2002

Given the many activities associated with the term “inflammation”, could these markers of inflammation be specific for heart attacks ?

No

Association of Markers of Inflammation With CVD Risk

Other outcomes associated with higher inflammation markers:

Type 2 diabetes
CHF
Some cancers
Cognitive decline
Frailty
All-cause mortality
All chronic diseases of old age ?

The "Inflammation Hypothesis" of Chronic Diseases of Aging

1. In providing a necessary "interface" to the environment, "inflammation" can result in damage.

2. The better our responses and/or the more environmental stress to which we respond, the more damage we do.

3. We trade short-term benefit for long-term damage; a good trade from an evolutionary standpoint

Association of Markers of Inflammation With Aging

$$[(G \times P) \times C]_t = D_t$$

$$\frac{[(\text{Genes} \times \text{Programming}) \times \text{Challenge}]_{\text{time}} = \text{Damage}_{\text{time}}}{\text{Capacity}}$$

Markers of Inflammation are Associated with CVD Risk

CRP is both a general marker of inflammation and an important component of the innate immune system

Strong correlation to components of Metabolic Syndrome especially adiposity

Inflammation, Thrombosis and Metabolic Syndrome

TABLE 2 7-11 year old obese girls and boys

Correlations between plasma hemostatic factors, adiposity measures, and insulin[1]

Variable	Fibrinogen	PAI-1	D-Dimer	%BF
%BF	0.42[2]	0.08	0.40[2]	—
VAT	0.21	0.49[2]	0.16	0.40[2]
SAAT	0.40[2]	0.32[4]	0.37[4]	0.78[2, 3]
TFM	0.42[2]	0.28	0.40[2]	0.85[2, 3]
FFM	0.23	0.50[2]	0.27	0.25
BMI	0.41[2]	0.24	0.43[2]	0.78[2, 3]
Insulin	0.11	0.61[2, 3]	0.13	0.42[2, 3]

dren. Even early in childhood, adiposity is associated with unfavorable concentrations of hemostatic factors that are in turn implicated in cardiovascular morbidity and mortality later in life. *Am J Clin Nutr* 1998;67:1136–40.

Ferguson MA, Gutin B, Tracy RP, et al. *Am J Clin Nutr*. 1998;67:1136-40.

Inflammation, Thrombosis and Metabolic Syndrome

12-week caloric restriction; ave weight loss 7.9 kg

TABLE 2. Biochemical Characteristics Before and After Weight Loss

	Week 0	Week 12
Total cholesterol, mmol/L	5.69±0.08	5.11±0.09*
LDL-C, mmol/L	3.79±0.08	3.38±0.08*
HDL-C, mmol/L	1.15±0.03	1.08±0.03*
Triglyceride, mmol/L	1.67±0.06	1.44±0.06*
Glucose, mmol/L	4.90±0.07	4.79±0.05
CRP, mg/L	5.56±0.36	4.12±0.36*

Values are mean±SEM.
*$P<0.001$ vs week 0.

Heilbronn LK. *Arterioscler Thromb Vasc Biol*. 2001;21:968-70

Association of Markers of Hemostasis/Inflammation With CVD Risk:

Findings Related to Medications:

Estrogen Replacement

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Biochemical Effects of HRT

Increases	Reduces
– HDLc	– LDLc
– Triglyceride	– Fibrinogen
– Factor VIIc	– PAI-1
– Prothrombin F1.2	– Antithrombin
– Protein C	

Composite Clinical Effect Unknown

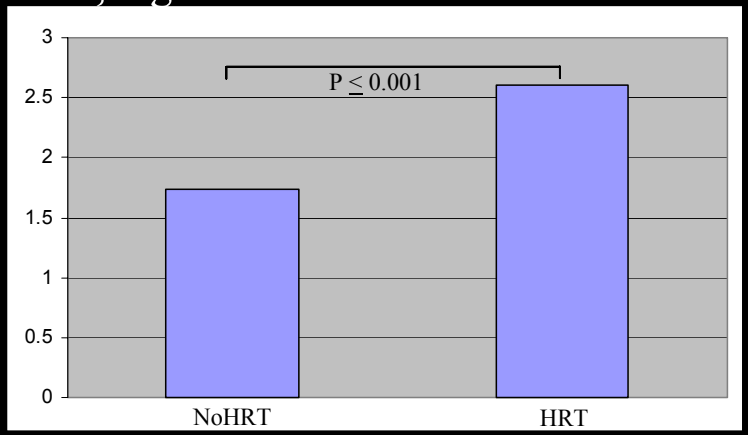
- Observational studies: ~ 50% risk reduction

From the literature

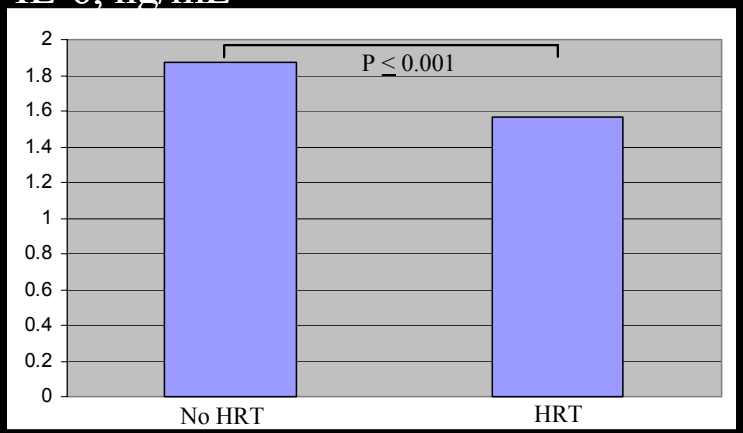
HRT Use and Inflammation Markers

R. Tracy, unpublished cross-sectional data on current or previous HRT use from CHS

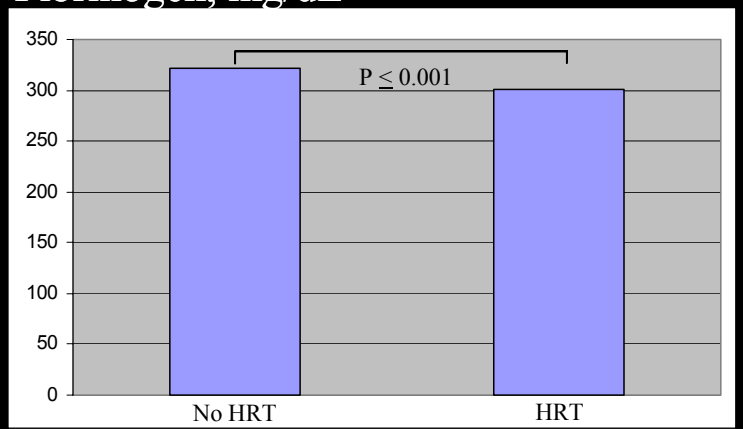
CRP, mg/L



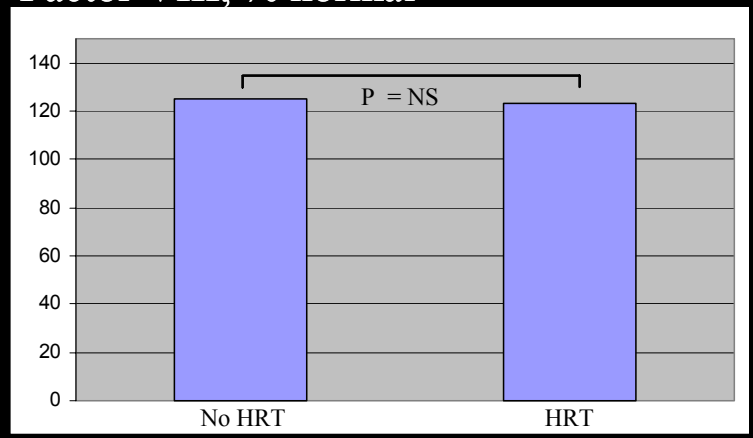
IL-6, ng/mL



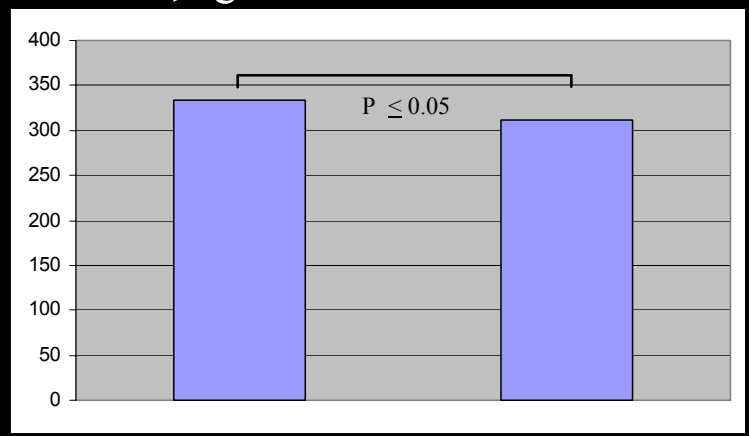
Fibrinogen, mg/dL



Factor VIII, % normal



ICAM-1, ng/mL



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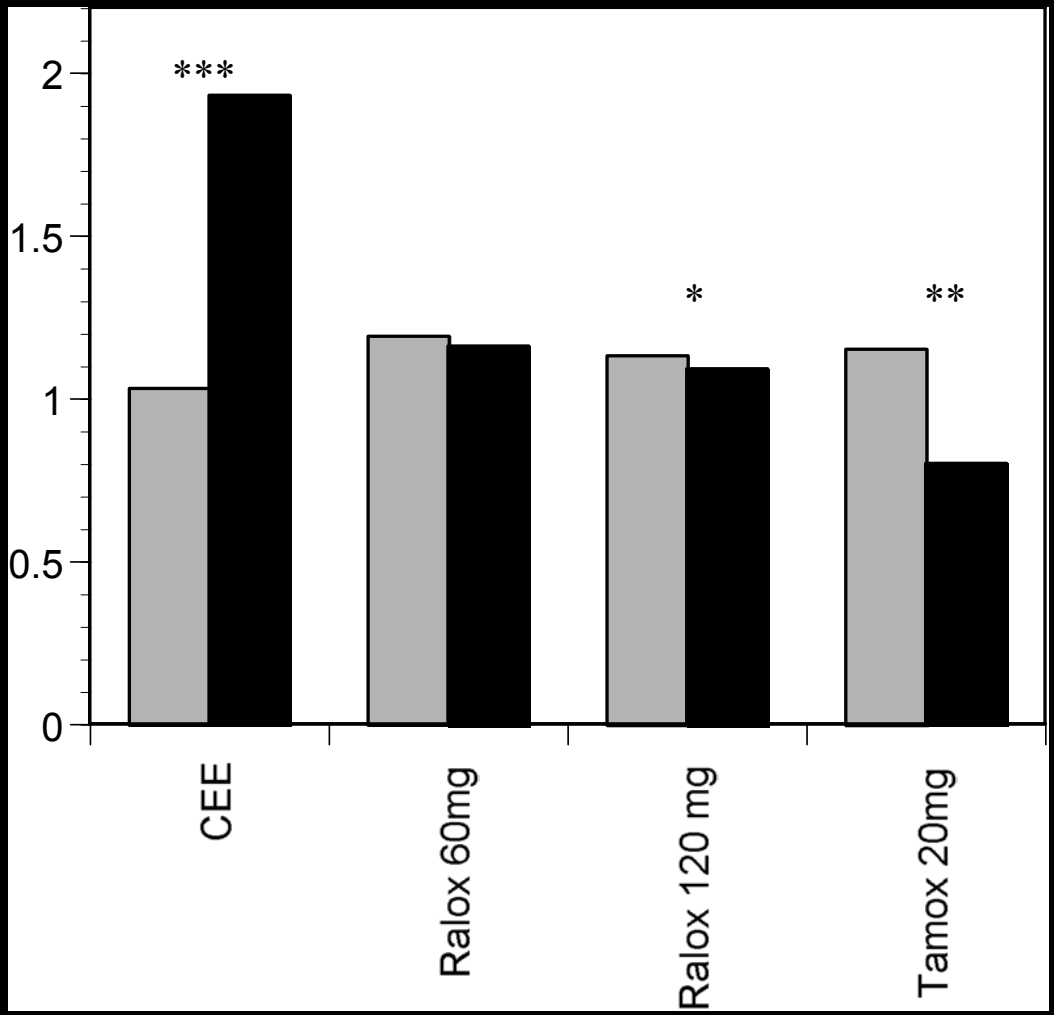
Comparative Effects of Different HRT on CRP



CEE (0.625 mg + 2.5 mg MPA): Cushman, M., et al., *Circulation*, 1999. **100**(7): p. 717-22

Raloxifene: Walsh, B.W., et al., *J Clin Endocrinol Metab*, 2000. **85**(1): p. 214-8

Tamoxifen: Cushman, M., et al., *Arterioscler Thromb Vasc Biol*, 2001. **21**: p. 255-261.

Also:
Low-dose and/or patch-deliveral Estrogen does not appear to raise CRP levels

Association of Markers of Inflammation With CVD Risk:

The Many Dimensions of Inflammation One Dimension – Immune Response

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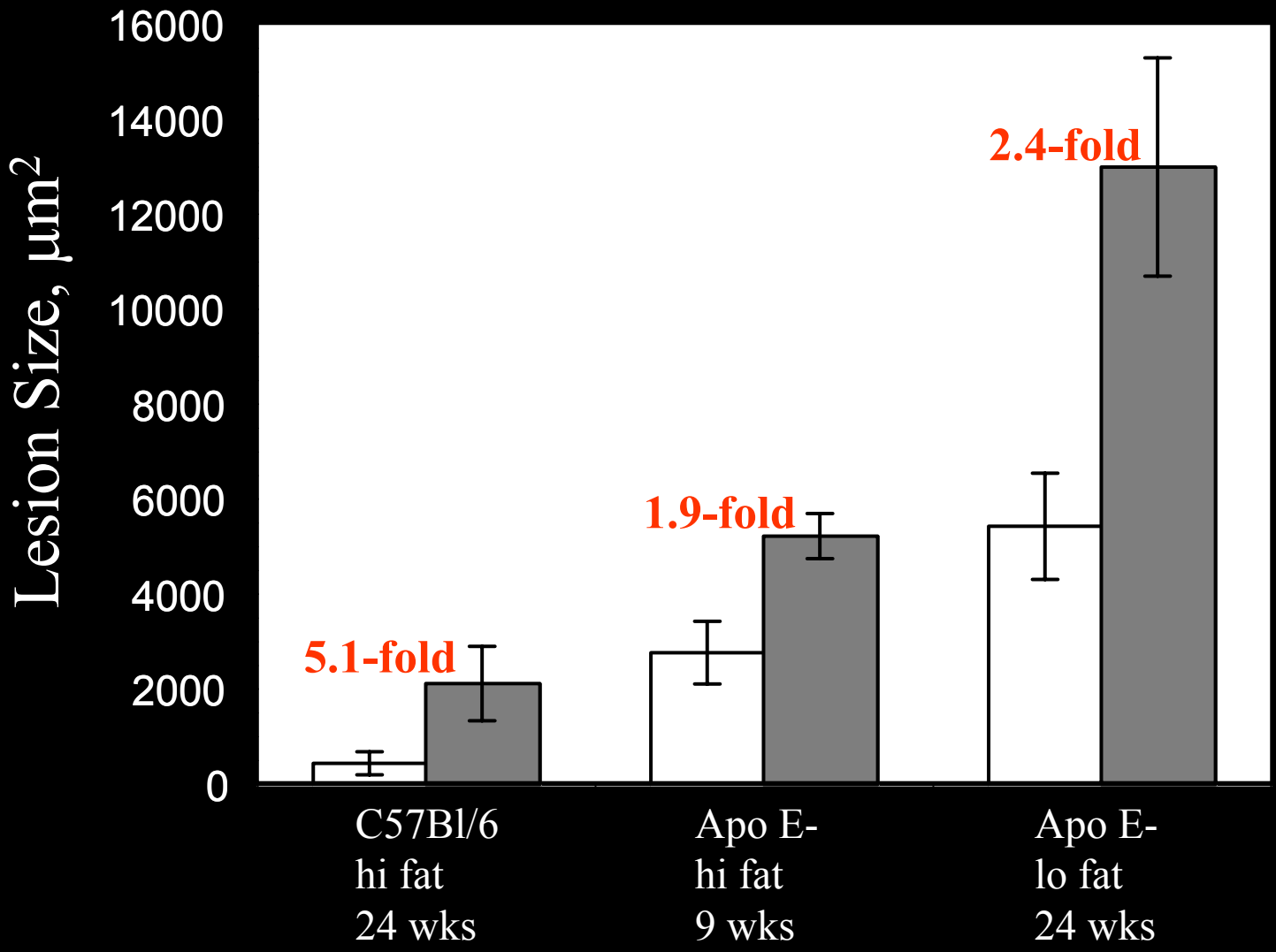
Effect of weekly injections of IL-6 on Murine Atherosclerosis



Huber SA, et al. *Arterioscler Thromb Vasc Biol*. 1999;19:2364-7

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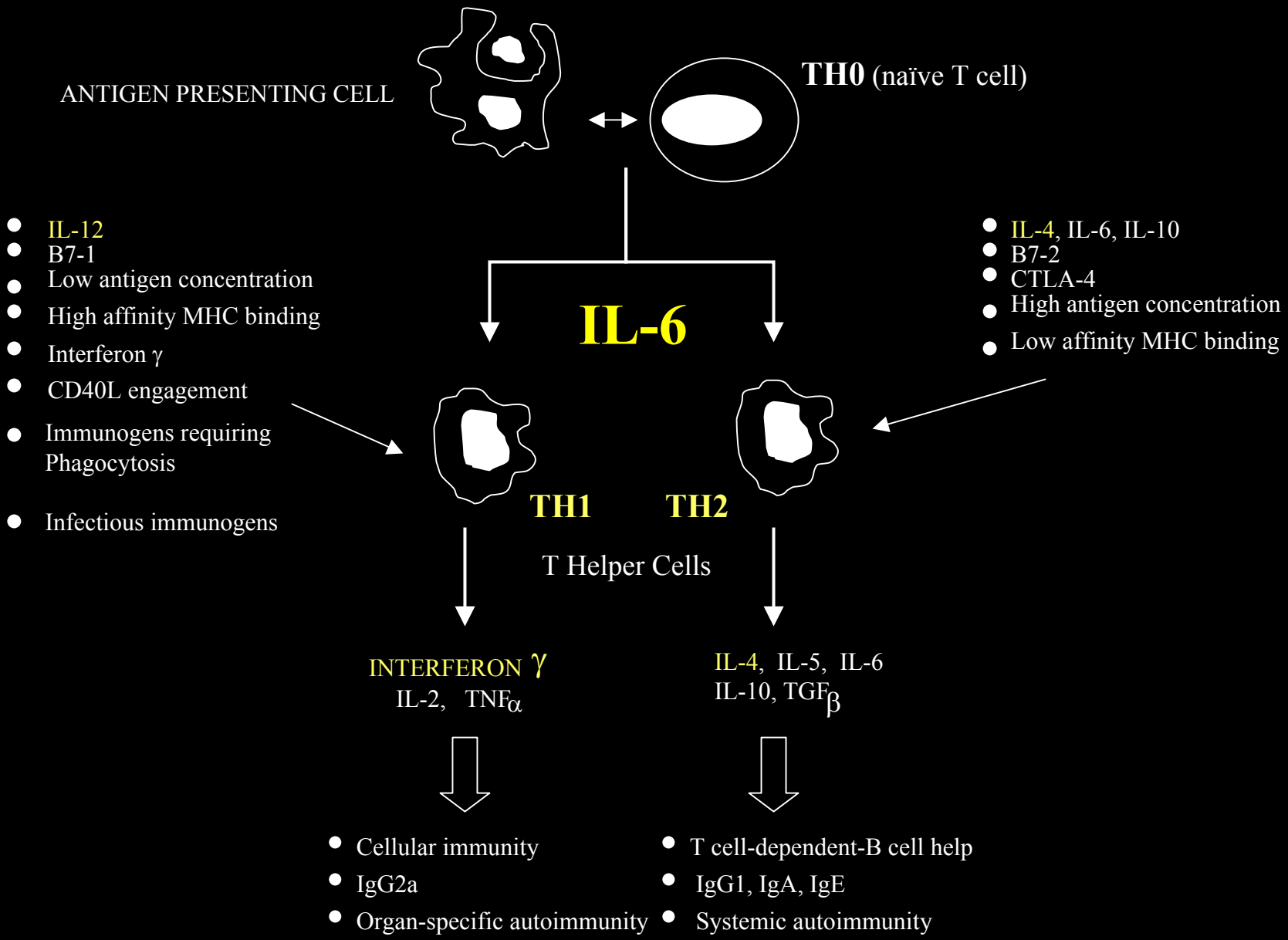
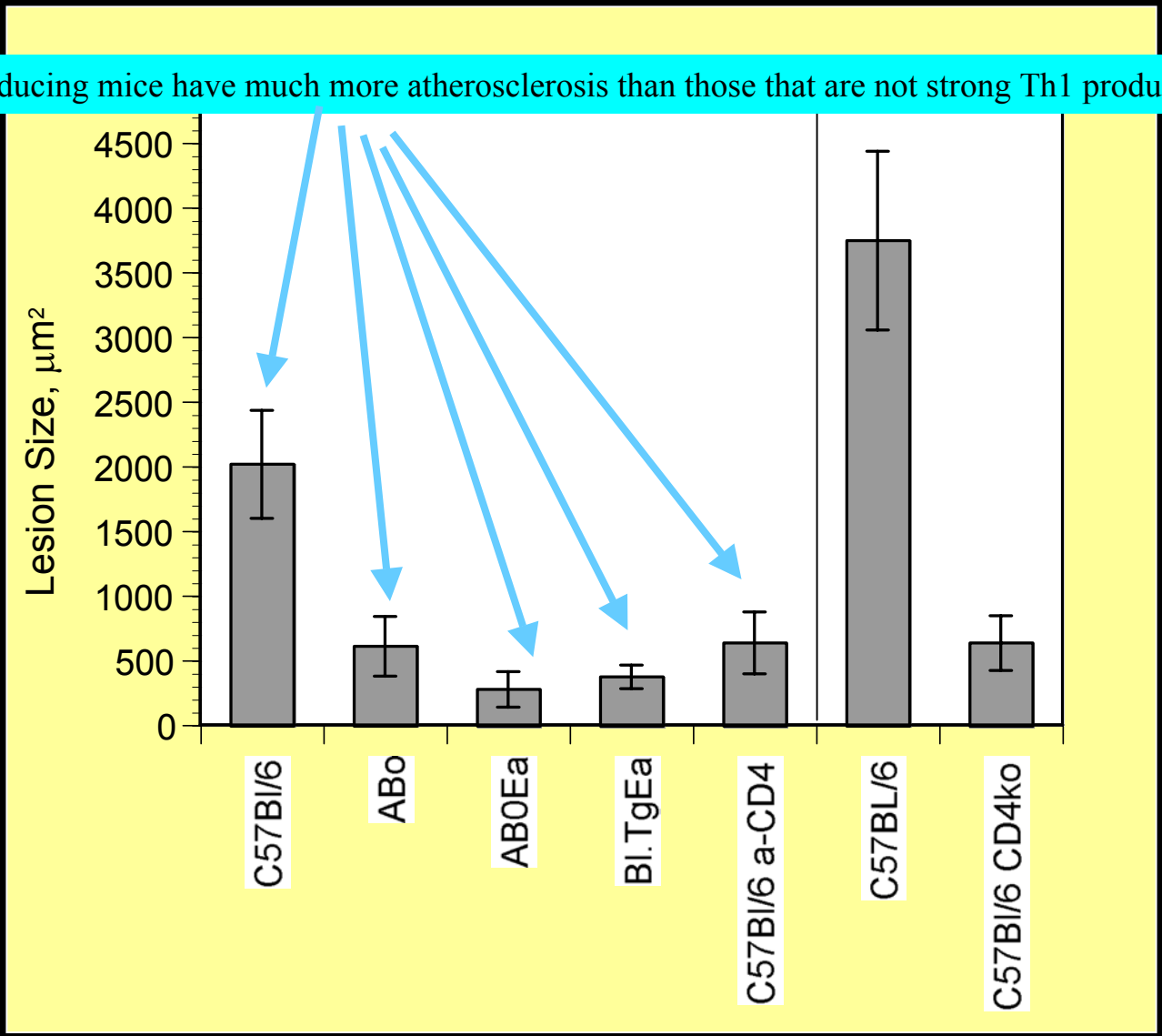
One Possible Role Of IL-6 In Atherosclerosis



Th1 Cells Promote Murine Atherosclerosis; Th2 Cells Inhibit It

Th1-producing mice have much more atherosclerosis than those that are not strong Th1 producers



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Huber SA, et al. *Circulation*. 2001;103:2610-6

Association of Immune Function With CVD Risk:

In preliminary studies, Th1 production in humans is a stable phenotype over time, and shows some degree of association with markers of inflammation and other variables

Hypothesis:

Th1 cell count, and/or % of lymphocytes, will be related to degree of atherosclerosis as estimated by carotid ultrasound, ankle-brachial blood pressure index or other measures