



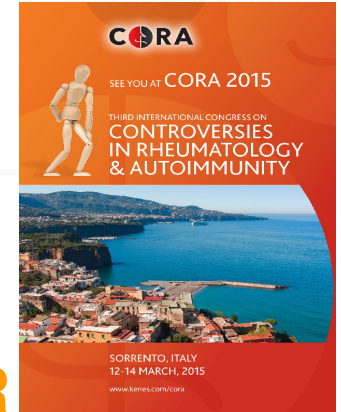
**From basic immune understanding  
to clinical breakthrough**



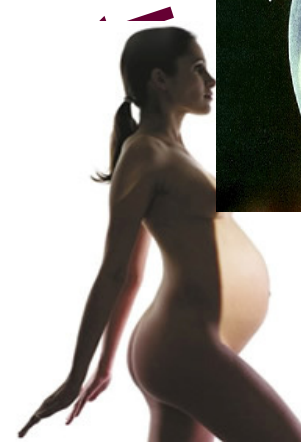
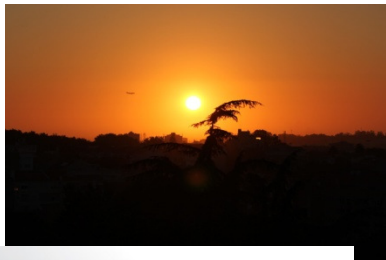
# Prediction and prevention of autoimmunity

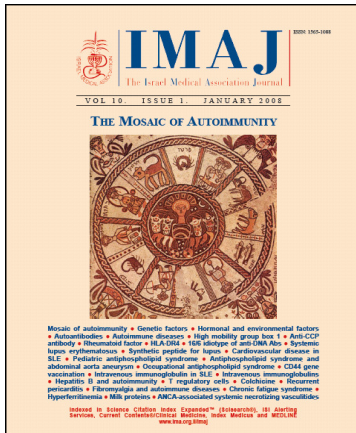


**Yehuda Shoenfeld MD, FRCP, MaACR**



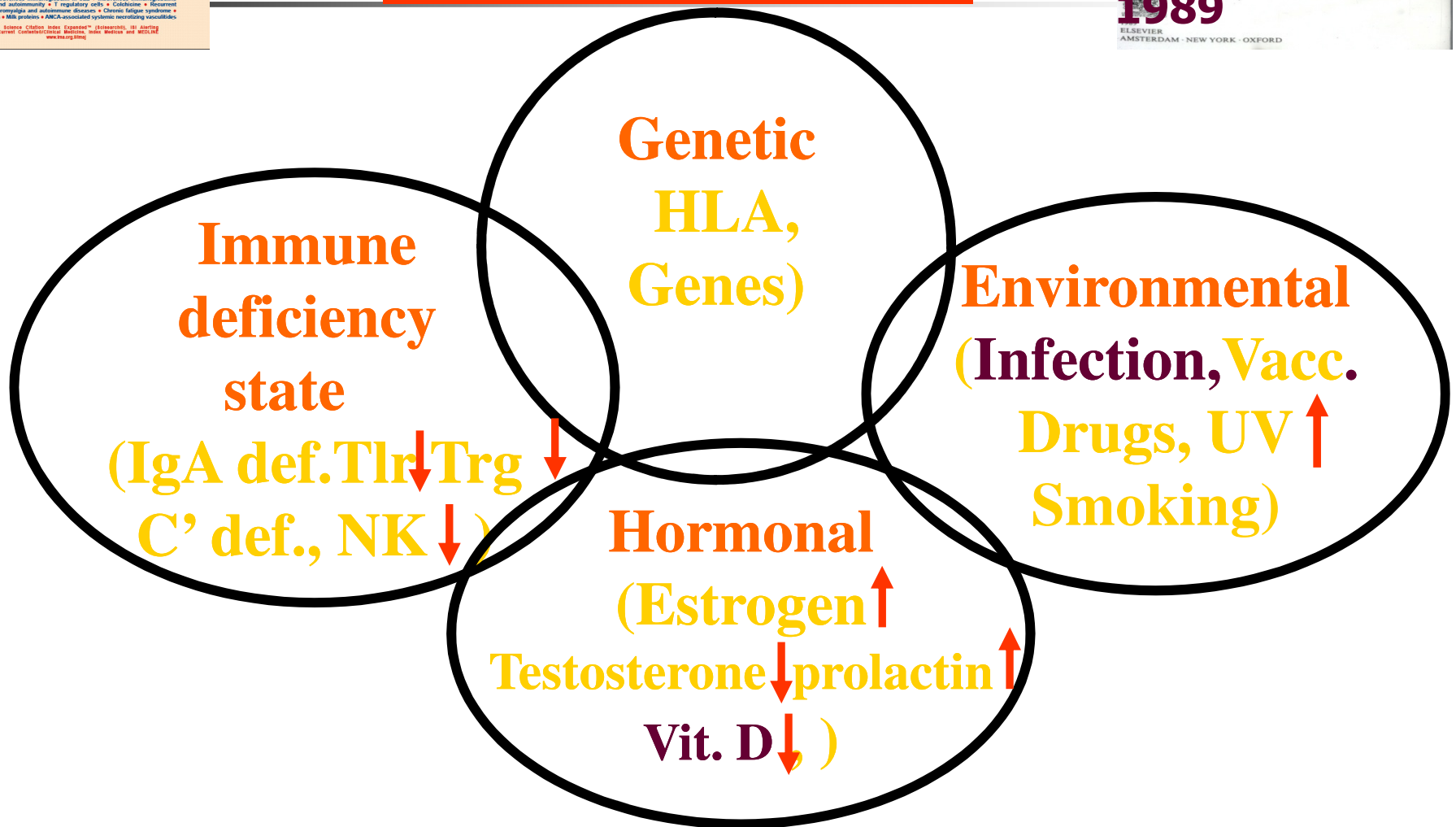
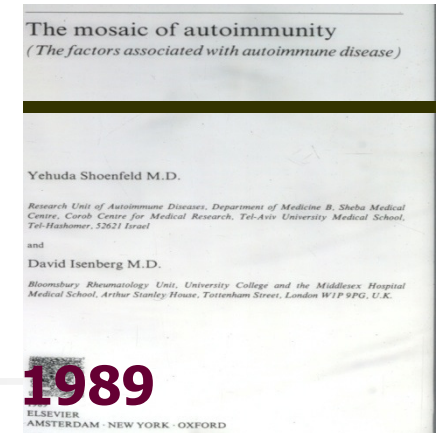
**09 2014  
Baltimore**





# The mosaic of autoimmunity

## Yehuda Shoenfeld MD,FRCP

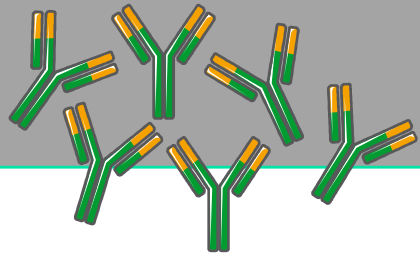


# Natural history of autoimmune diseases (AIDs)

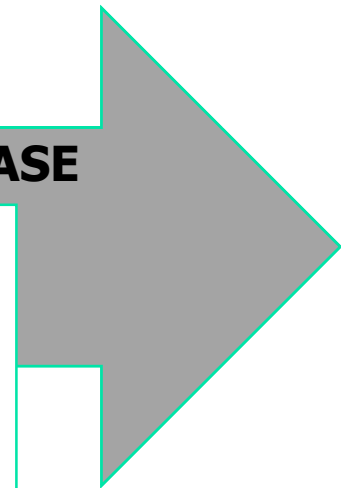
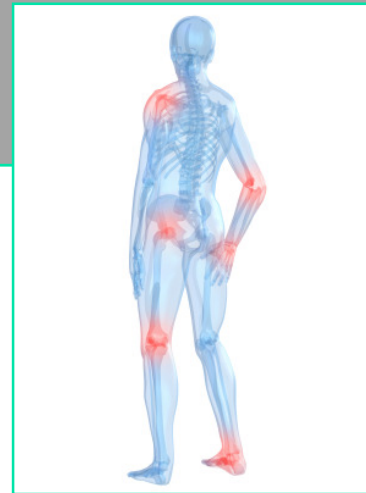
**SCREENING / PREVENTION ?**



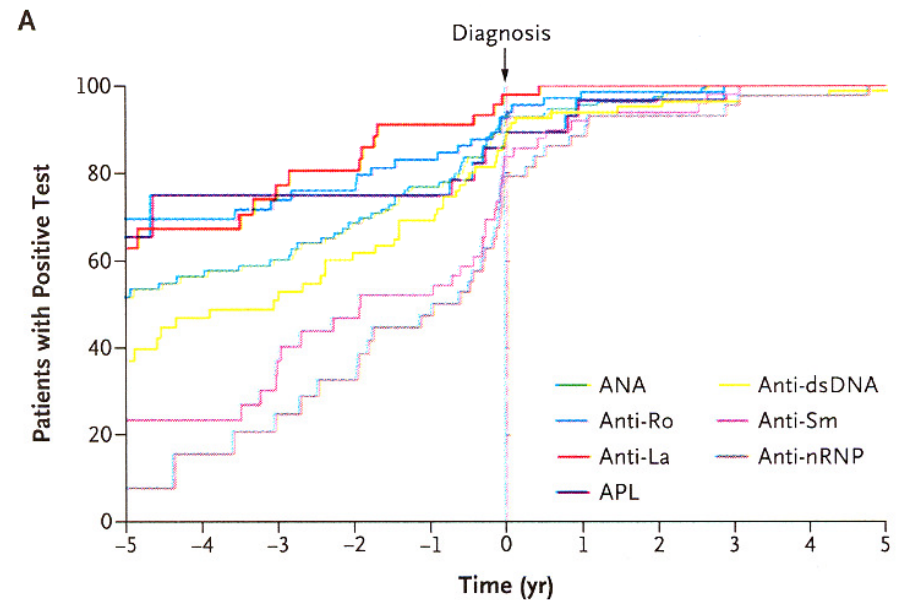
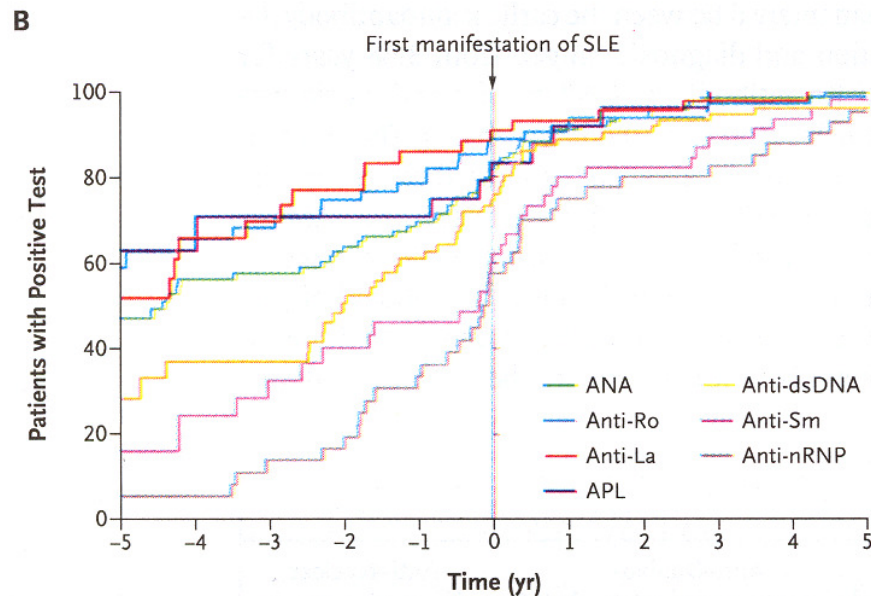
**PRECLINICAL PHASE**



**CLINICAL DISEASE**



# Arbuckle MR, et al. Development of autoantibodies before the clinical onset of systemic lupus erythematosus. N Engl J Med 2003; 349:1526-33.



130 SLE subjects US Army

→ 115 (88%) Ab positive before diagnosis

520 controls

→ 0

US Army Serum Repository (sera stored up to 30 yrs)

Arbuckle MR, et al. Development of autoantibodies before the clinical onset of systemic lupus erythematosus.  
N Engl J Med 2003; 349:1526-33.



**Table 1.** Detection of Autoantibodies before Diagnosis and before the Onset of Symptoms in 130 Patients with Systemic Lupus Erythematosus.\*

Autoantibody	Positive Test before Diagnosis <i>no. (%)</i>	Time from First Detection to Diagnosis <i>yr</i>	Positive Test in First Serum Sample <i>%</i>	Total Patients with Positive Test <i>no. (%)</i>	Interval between Positive Test and Diagnosis <i>yr</i>	Positive Test before Onset of Symptoms† <i>no. (%)</i>	Interval between Positive Test and Onset of Symptoms <i>yr</i>
Antinuclear antibodies	101 (78)	9.2	50	109 (84)	3.01±0.25	89 (77)	2.25±0.27
Anti-Ro antibodies	61 (47)	9.4	64	64 (49)	3.68±0.34	55 (48)	2.97±0.39
Anti-La antibodies	44 (34)	8.1	62	45 (35)	3.61±0.38	39 (34)	2.83±0.43
Antiphospholipid antibodies	24 (18)	7.6	67	27 (21)	2.94±0.50	19 (17)	2.29±0.56
Anti-double-stranded DNA antibodies	72 (55)	9.3	48	80 (62)	2.24±0.31	54 (47)	1.24±0.31
Anti-Sm antibodies	41 (32)	8.1	31	49 (38)	1.47±0.34	28 (24)	0.47±0.44
Anti-nuclear ribonucleo-protein antibodies	34 (26)	7.2	23	43 (33)	0.88±0.32	23 (20)	0.20±0.47

PPV ranged from 95% (dsDNA) to 100% (Sm)  
(mean for all antibodies, 96%)

# Specific autoantibodies precede the symptoms of Rheumatoid Arthritis

(Nielen M, et al. Arthritis Rheum 2004; 80:380-6)

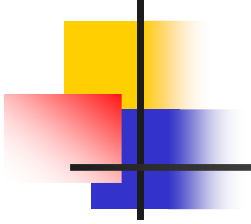


**Table 2.** Diagnostic value of IgM-RF and anti-CCP for RA\*

	Blood donor population 0–5 years before symptom onset				Risk of developing RA within 5 years (PPV, %)	
	Sensitivity, %	Specificity, %	PPV, %	NPV, %	General population	High-risk population†
IgM-RF	20.5	98.6	88.2	71.1	1.5	37.7
Anti-CCP	28.9	99.5	96.6	73.5	5.3	69.4
IgM-RF or anti-CCP	36.5	98.1	90.6	75.4	1.9	43.8
IgM-RF and anti-CCP	13.0	100	100	75.4	100	100

\* IgM-RF = IgM rheumatoid factor; anti-CCP = anti-cyclic citrullinated peptide; PPV = positive predictive value; NPV = negative predictive value.

† Defined as individuals who have  $\geq 2$  first-degree relatives with rheumatoid arthritis (RA) (5-year incidence of RA among such individuals has been reported to be 3.9% [10]).



# **Multiple autoantibodies as predictors**



# **Autoantibody explosion in systemic lupus erythematosus: more than 100 different antibodies found in SLE patients**



**Sherer Y, Gorstein A, Fritzler MJ,  
Shoenfeld Y.**

**Sem Arth Rheum 34: 501-537, 2004.**

**Sherer-Shoenfeld; Volcano of autoantibodies-187**

**Yehuda Shoenfeld, MD,FRCP.**

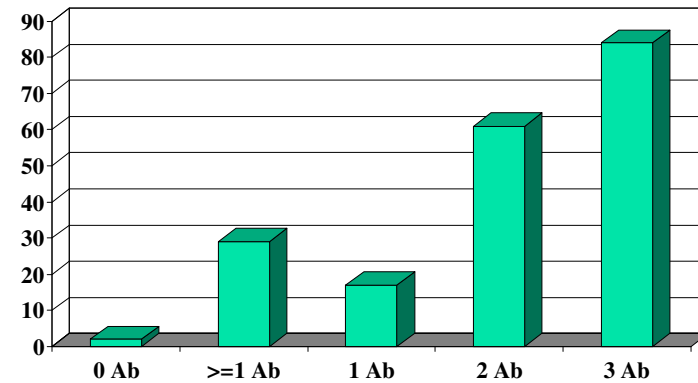
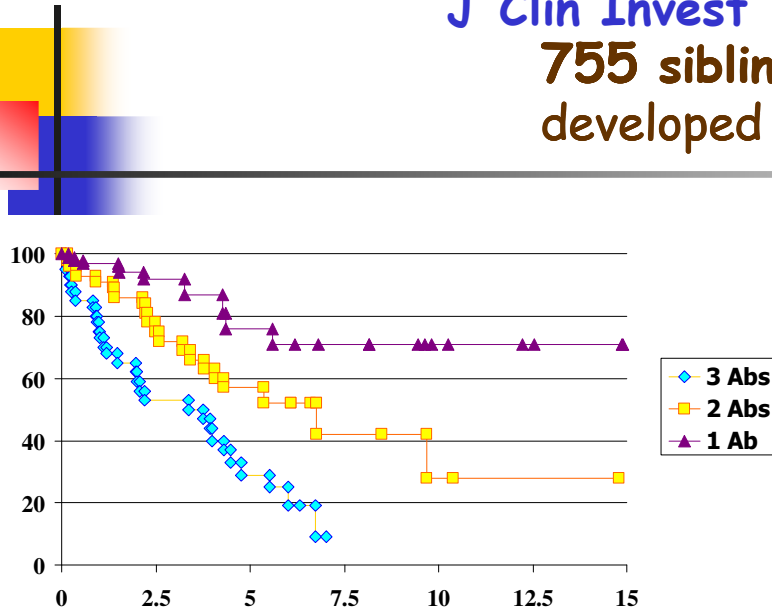


Kulmala P, et al.

Prediction of insulin-dependent diabetes mellitus in siblings of children with diabetes. A population-based study.

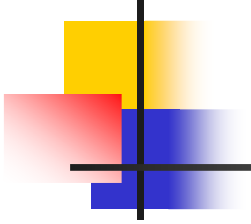
J Clin Invest 1998; 101:327-36.

**755 siblings of IDDM patients**  
**32 developed IDDM within 8 yrs**




Antibody	PPV
ICA	43%
IA-2	55%
GAD	42%
insulin	29%

Antibody	Risk
0	1%
1	2%
2	25%
3-4	70%



# Genetics and autoantibodies



**In Caucasian patients the  
HLA A1, B8, DR3 haplotype  
carries a relative risk of 8.3  
for the development of  
lupus**

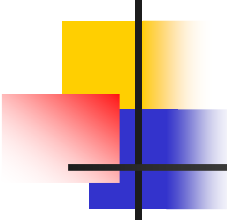
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***Worrall JG, et al.***

SLE: a rheumatological view. Analysis of the clinical features, serology and immunogenetics of 100 SLE patients during long-term follow-up.

***Q J Med 1990; 74: 319-30***





**A combination of autoantibodies to cyclic citrullinated peptide (CCP) and HLA-DRB1 locus antigens is strongly associated with future onset of rheumatoid arthritis**

*Berglin E, et al.*

*Arth Res Ther 2004; 6; R303-8*

---

- **SE (shared epitopes) (odds ratio [OR] = 2.35), anti-CCP antibodies (OR = 15.9), and IgA-RF (OR = 6.8) significantly predicted RA.**
- **Anti-CCP antibodies combined with SE had the highest OR (66.8, 95% confidence interval 8.3-539.4) in predicting RA.**



# **Prediction of autoimmune rheumatic diseases; myth or reality?**

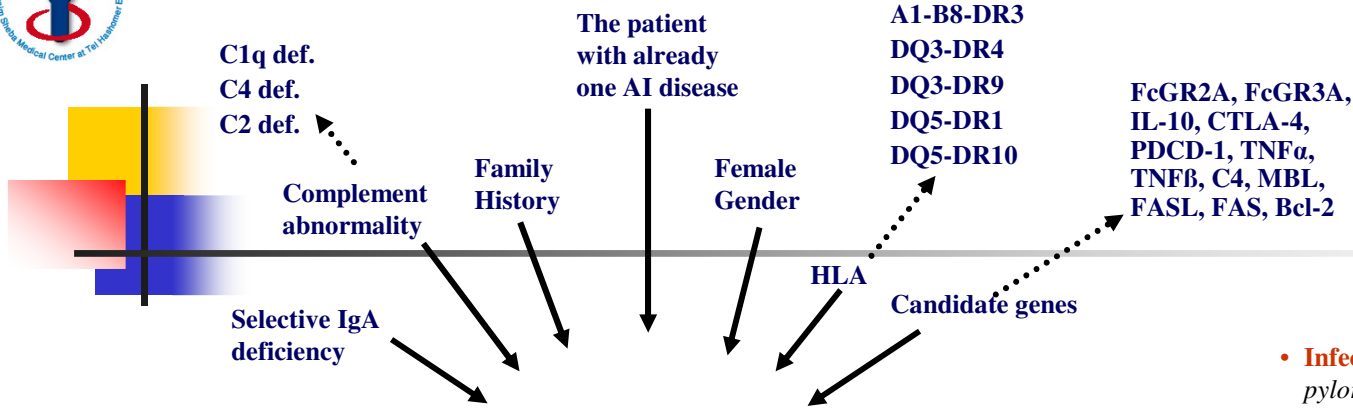
**N Bizzaro , Y Shoenfeld**

***Arthritis @Rheumatism 2007***



# Predicting and Preventing Autoimmunity

**Harel M, Shoenfeld Y**  
**Predicting and preventing**  
**autoimmunity,**  
**myth or reality?**  
*Ann. N.Y. Acad. Sci.*  
**1069: 322–345, 2006.**



**Autoimmune-prone individual**

**Environmental Factors**

**Appearance of Autoantibodies**

**Approximated time until clinical appearance of disease**

**Treatment/Prevention**

**Overt autoimmune disease**

- **Infections** (EBV, CMV, HCV, *Helicobacter pylori*, *Streptococcus pyogenes*)
- **UV light**
- **Vaccines** (Diphtheria, Tetanus toxoid, Polio and measles vaccines -> GBS, MMR vaccines -> ITP-like thrombocytopenia, Rubella vaccine -> Arthritis)
- **Drugs** (Hydralazine, Quinidine, Procainamide)
- **Toxins** (Silica dust, aromatic hydrocarbons, aliphatic chlorinated hydrocarbons, phthalate)
- **Silicone implants** (?)
- **Hormones** (pregnancy, ERT, OC, prolactin)
- **Smoking**
- **Stress**

- Disease Type**
- anti-Islet cell Abs -> DM
  - RF, anti-CCP -> RA
  - anti-PL, anti-Ro, anti-La, anti-dsDNA, anti-nuclear ribonucleoprotein, anti-HS, anti-nucleosome, anti-Histone, anti-rP protein -> SLE
  - anti-Ro, anti-La -> Sjorgren's
  - anti-gp120, anti-PDC -> PBC
  - ASCA -> crohn's disease

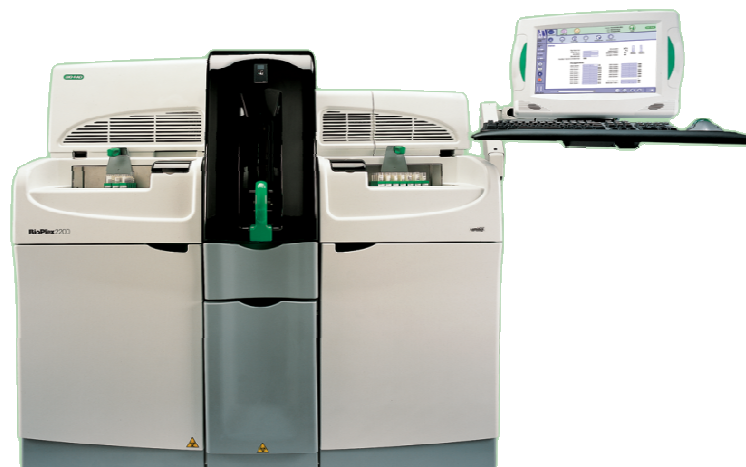
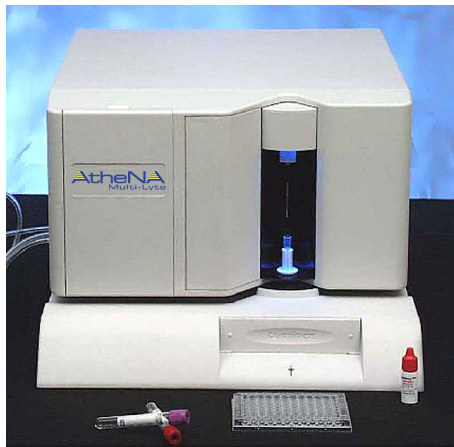
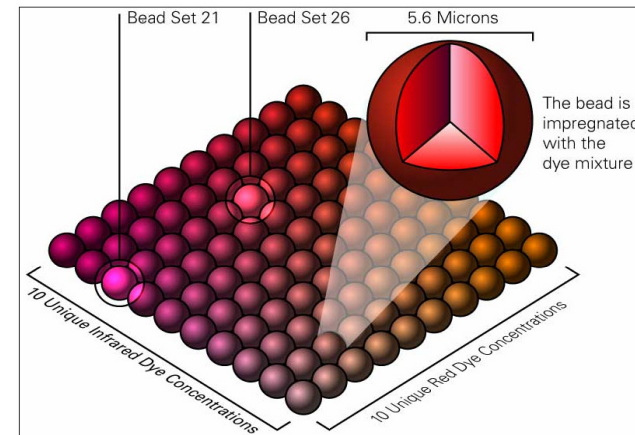
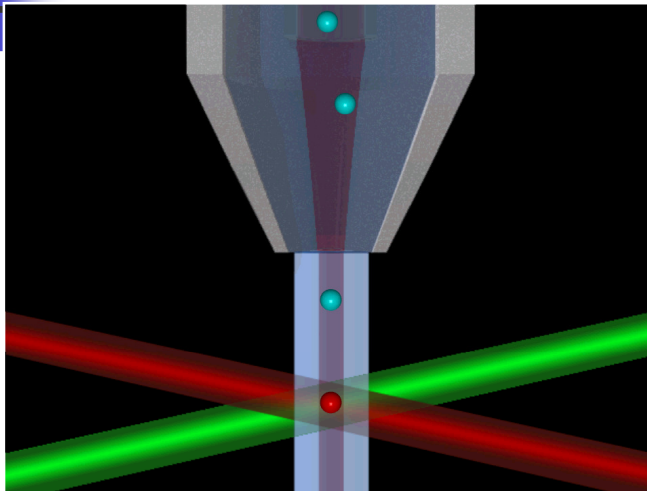
- anti-PL, anti-Ro, anti-La – 3.4 yrs prior to SLE
- anti-dsDNA – 2.2 yrs prior to SLE
- anti-Sm, anti-nuclear ribonucleoprotein – 1.2 yrs prior to SLE

- Ursodeoxycholic acid tx for PBC
- Dietary enrichment with PUFA for SLE
- Avoiding UV light and OC for SLE
- Aspirin tx for APS
- **Vitamin D receptor agonist**
- Synthetic peptides

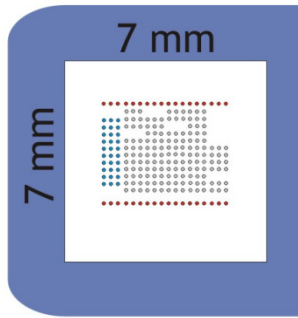


# THE PRESENT

# Multiplex bead array (MBA)

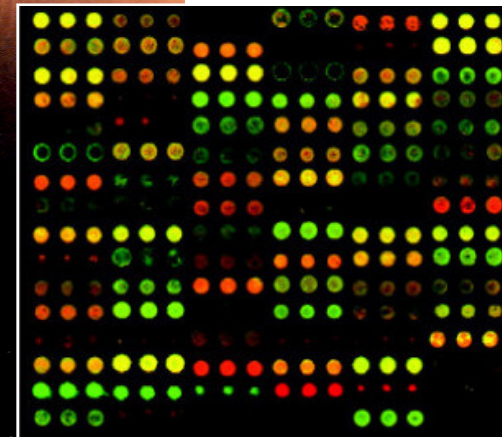
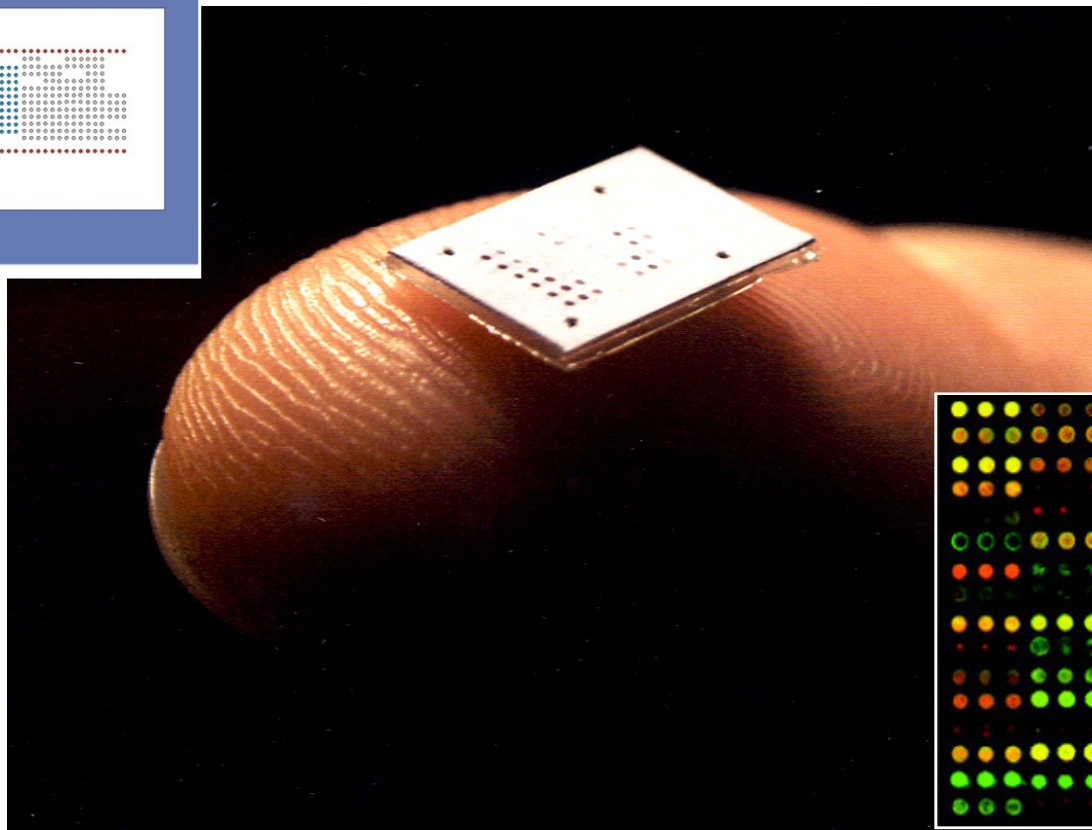
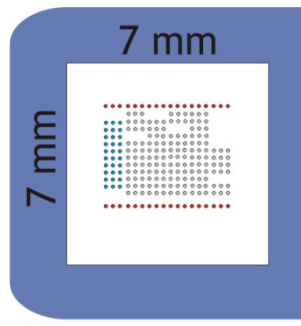






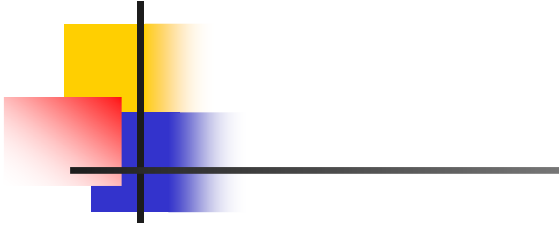
THE FUTURE  
(tomorrow...)

# Micro chips





## “Dream Day” - 1963



Martin Luther King, Jr. (January 15, 1929-April 4, 1968) directed the peaceful march on Washington, D.C. of 250,000 people to whom he delivered his address, “**I Have a Dream**”, he conferred with President John F. Kennedy and campaigned for President Lyndon B. Johnson; he was awarded five honorary degrees; was named Man of the Year by Time magazine in 1963; and became not only the symbolic leader of American blacks but also a world figure.

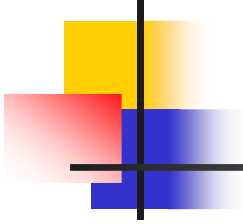
August 28, the anniversary of Dr. King’s 1963 I Have a Dream speech, is called “**Dream Day**”.



# I have a dream

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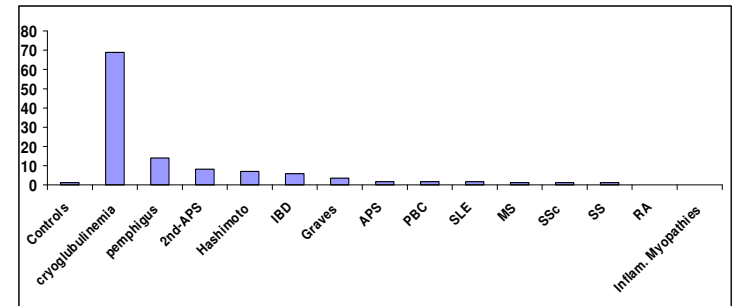
- 1) Multi autoantigenic chips
- 2) Multi genetic chips
- 3) Environmental ;infectious , silicone
- 4) Easy informatics



# Preventive therapy

# Hepatitis-C and Autoimmune Diseases

- 1) Mixed cryoglobulinemia.
- 2) Ch. Active hepatitis.
- 3) Polyarteritis nodosa.
- 4) Leukocytoclastic vasculitis.
- 5) Autoimmune thyroid disease.
- 6) Glomerulonephritis.
- 7) Polymyositis + anti-Jo-1 Ab.
- 8) Formation of autoantibodies and CIC (A@R. 3: 437, 1995).

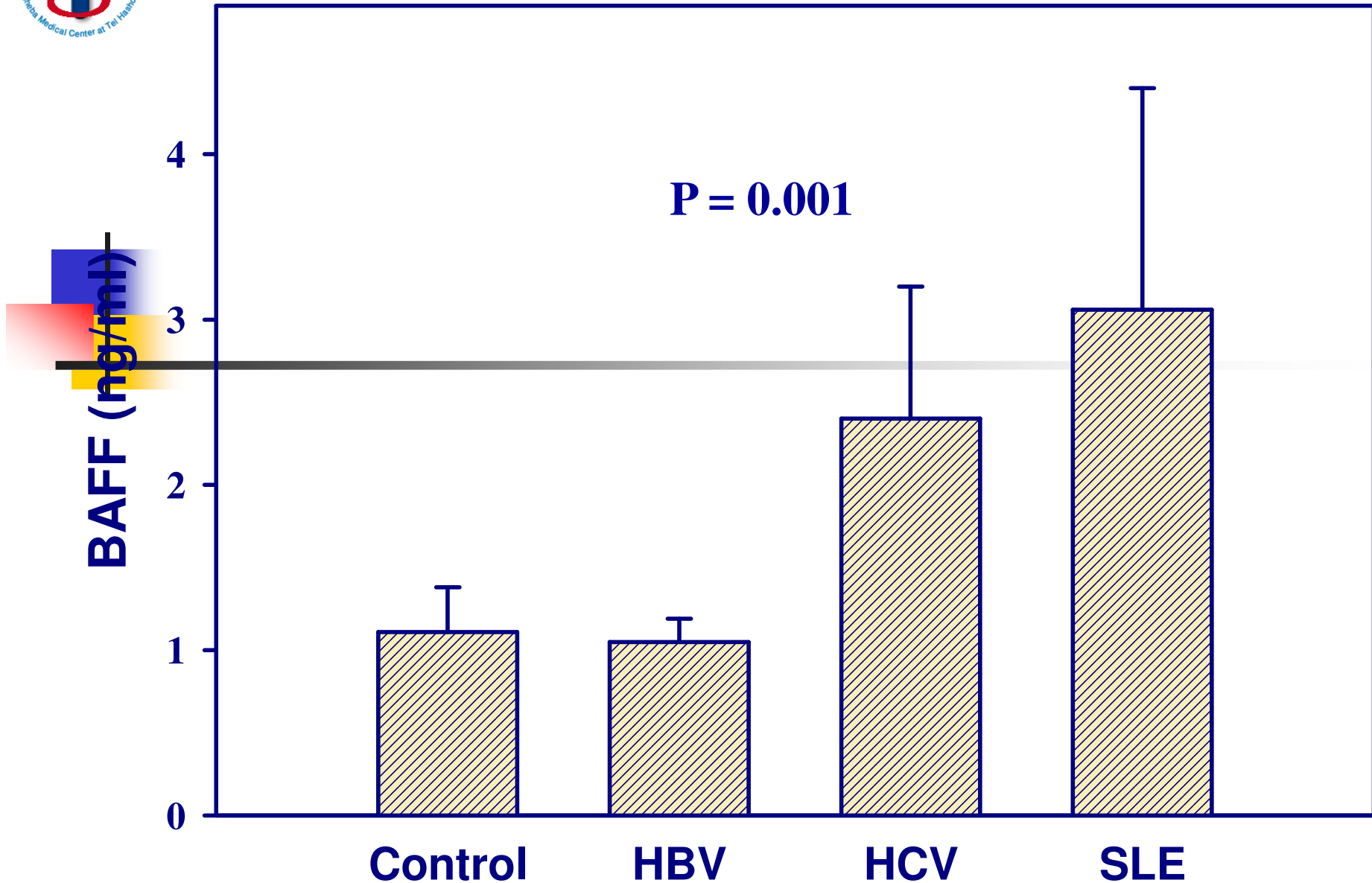


The prevalence of anti-HCV antibodies was 9.5% (116/1228) in our cohort:



## Soluble BAFF levels in HCV

Toubi et al *J Autoimmunity* 2006;27;134-9



# How to avoid autoimmune diseases



## Triggers of autoimmune diseases

ASIA syndrome (Brest implans ,Vaccines)

Infecions ;EBV vaccines, HCV eradication

Drugs ;avoid response to biologics

Stress

Sun exposure

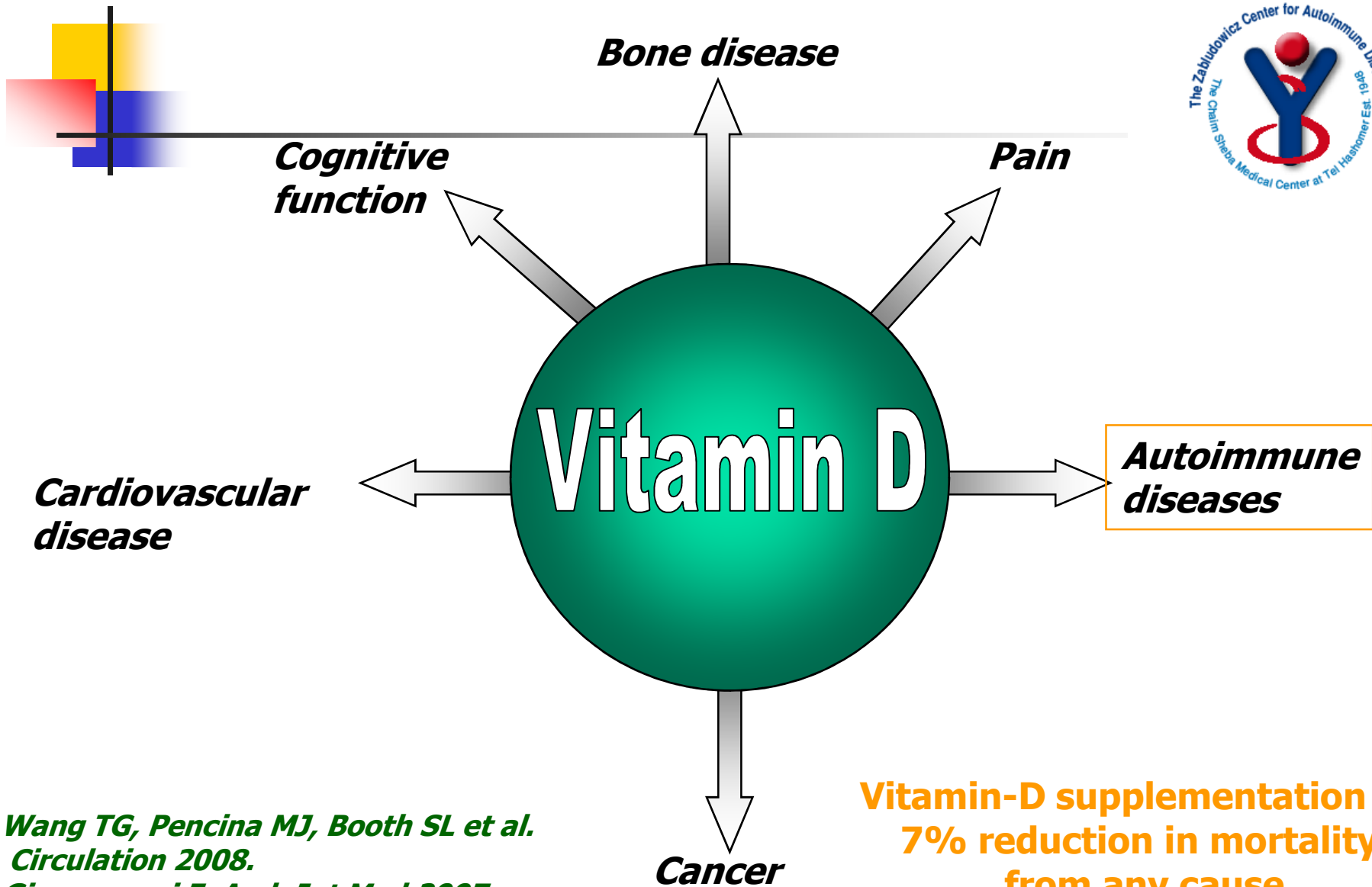
Dietunsaturated fatty acid

Address (Geoepidmeiology)

Hygiene theory;TPC from Helminthes



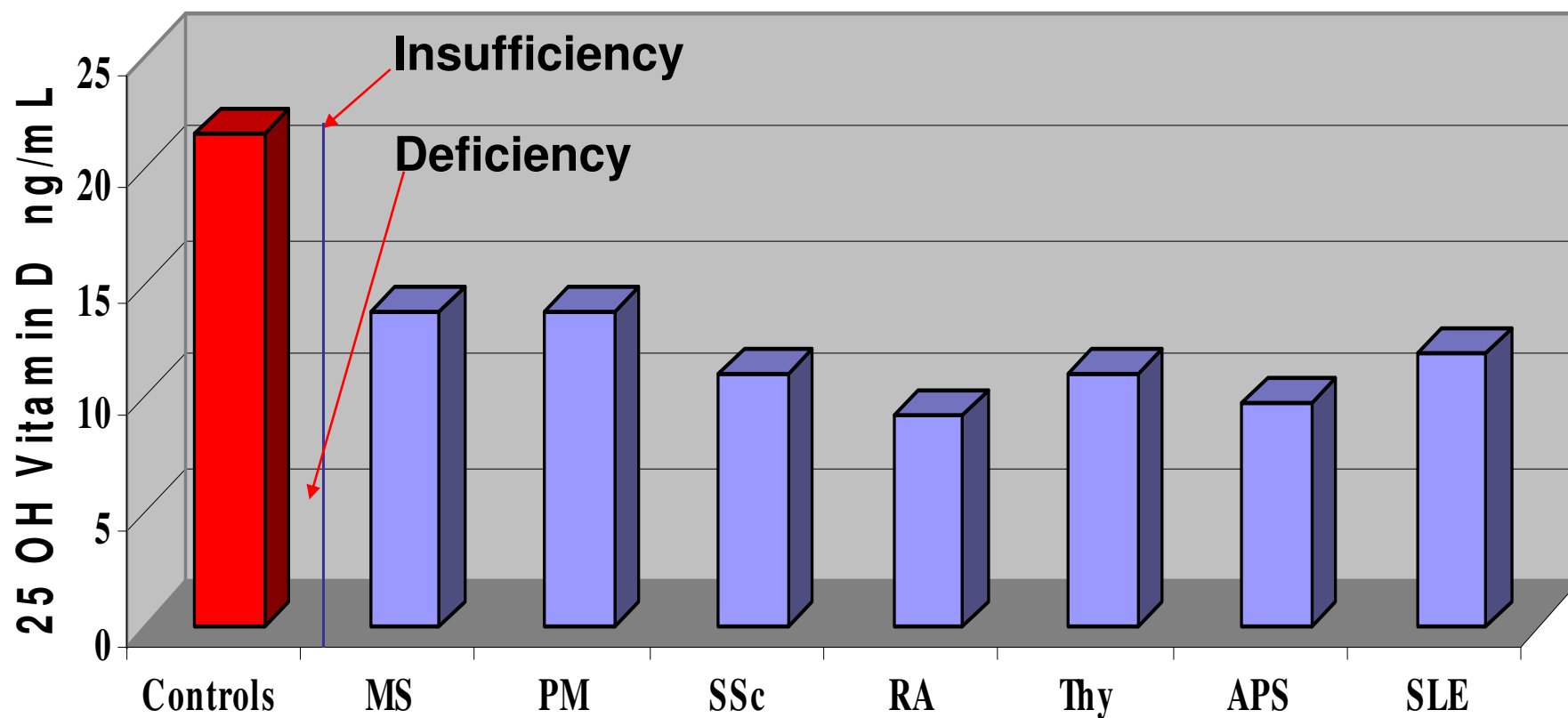
# Vitamin D: a pleiotropic molecule



*Wang TG, Pencina MJ, Booth SL et al. Circulation 2008.  
Giovannucci E. Arch Int Med 2007.*

**Vitamin-D supplementation =  
7% reduction in mortality  
from any cause**

## Average Vitamin D concentration



# Vitamin D prevention of autoimmune models



*Kamen DL et al. Autoimmunity Reviews 2006*

Proc. Natl. Acad. Sci. USA  
Vol. 93, pp. 7861-7864, July 1996  
Immunology

## 1,25-Dihydroxyvitamin D<sub>3</sub> reversibly blocks the progression of relapsing encephalomyelitis, a model of multiple sclerosis

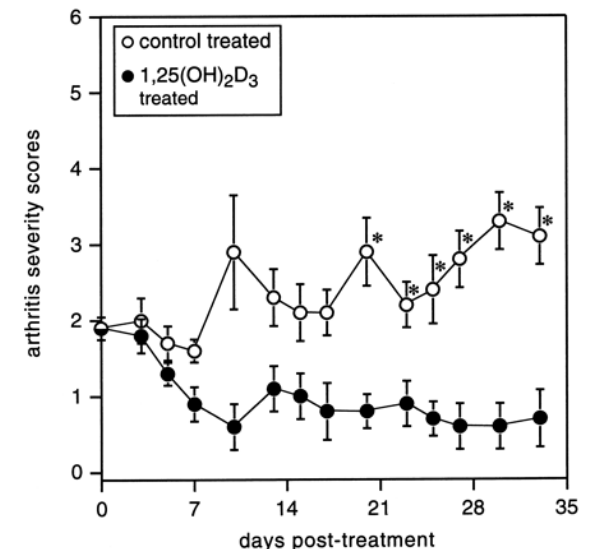
(vitamin D/vitamin D deficiency/myelin basic protein/autoimmunity)

MARGHERITA T. CANTORNA, COLLEEN E. HAYES, AND HECTOR F. DELUCA\*

## Collagen-induced arthritis

*1,25-Dihydroxycholecalciferol inhibits the progression of arthritis in murine models of human arthritis.*

*Cantorna MT, J Nutr. 1998*





U.V

Go for he sun



Thank  
You!