Advances in Diabetes Care and Prevention

Camillo Ricordi, MD

Director, Diabetes Research Institute and Cell Transplant Center
University of Miami, Florida, USA
www.DiabetesReseaerch.org

Founding President, The Cure Alliance
www.TheCureAlliance.org
www.CellR4.org

MILLER SCHOOL OF MEDICINE
UNIVERSITY OF MIAMI

DIABETES RESEARCH INSTITUTE
UNIVERSITY OF MIAMI

- Center of Excellence of the University of Miami
- MISSION: To Cure Diabetes in the Fastest, Most Efficient and Safest Way Possible
- Home of the UM Cell Transplant Program and the Division of Cellular Transplantation, Dept . Of Surgery
- First cGMP Human Cell Processing Facility in the USA FDA approved to deliver therapeutic cell products across state barriers
- NIH Cell Distribution Center
- FDA approved, FACT and AABB Certified
- Over 160 Physicians, Scientists and Staff
- Coordinating Center of the DRI Federation

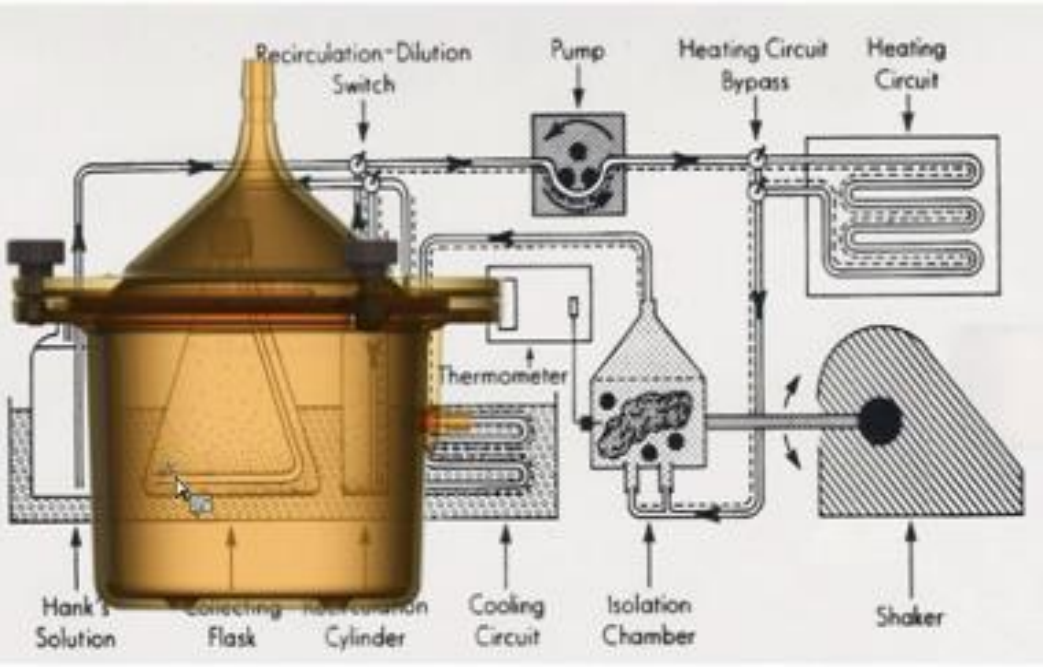
1988 – 2018

30 Years of the Ricordi Chamber

Reprinted from DIABETES, VOL. 37, NO. 4, APRIL 1988

Automated Method for Isolation of Human Pancreatic Islets

CAMILLO RICORDI, PAUL E. LACY, EDWARD H. FINKE, BARBARA J. OLACK, AND DAVID W. SCHARP

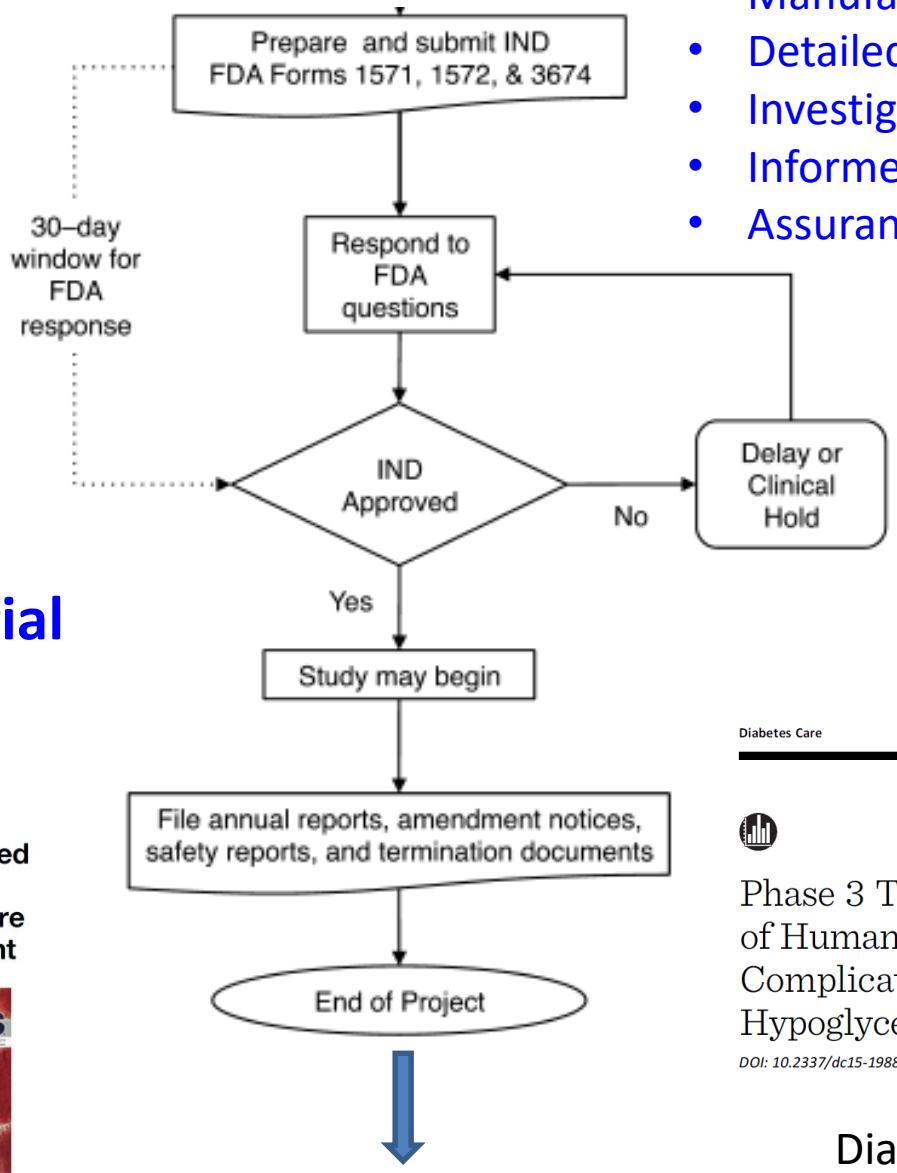


Clinical Islet Transplantation Consortium

- Preclinical data
- Manufacturing information
- Detailed Clinical protocols
- Investigator information
- Informed consents
- Assurances: IRB, IND

IND 9336

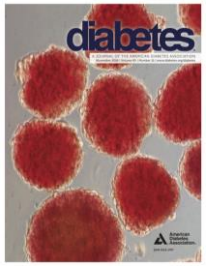
Phase III Clinical Trial (2004-2016)



Biologic License Application

National Institutes of Health–Sponsored Clinical Islet Transplantation Consortium Phase 3 Trial: Manufacture of a Complex Cellular Product at Eight Processing Facilities

Diabetes 2016;65:3418–3428 | DOI: 10.2337/db16-0234



Diabetes Care

Phase 3 Trial of Transplantation of Human Islets in Type 1 Diabetes Complicated by Severe Hypoglycemia

DOI: 10.2337/dc15-1988

Diabetes Care 2016 Jul; 39(7): 1230-1240

Clinical Study Report
June 23, 2017
Version 1.0

Allogeneic Purified Human Pancreatic Islets for Treatment of Type 1 Diabetes

Protocol #: CIT-07

US IND #: BB-IND 9336

Canadian CTA File Number: 9427-N1256-23C

Clinical Trial.gov Identifier: NCT00434811

Study Development Phase: Phase 3

IND Sponsor:
Division of Allergy, Immunology, and Transplantation (DAIT)
National Institute of Allergy and Infectious Diseases (NIAID)

Financial Sponsors:
National Institute of Allergy and Infectious Diseases (NIAID)
National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

Collaborators:
The following pharmaceutical companies provided study drugs or supplies; however, they had no role in the trial design, study conduct, data accrual, data analysis, the preparation of manuscripts, or of this report.

i. Sanofi/Genzyme: Thymoglobulin® (anti-thymocyte globulin, rabbit);
ii. Astellas Pharma, Inc.: Prograf®, (tacrolimus);
iii. Pfizer, Inc.: Rapamune® (sirolimus);
iv. LifeScan, Inc.: Glucometers and glucose strips.

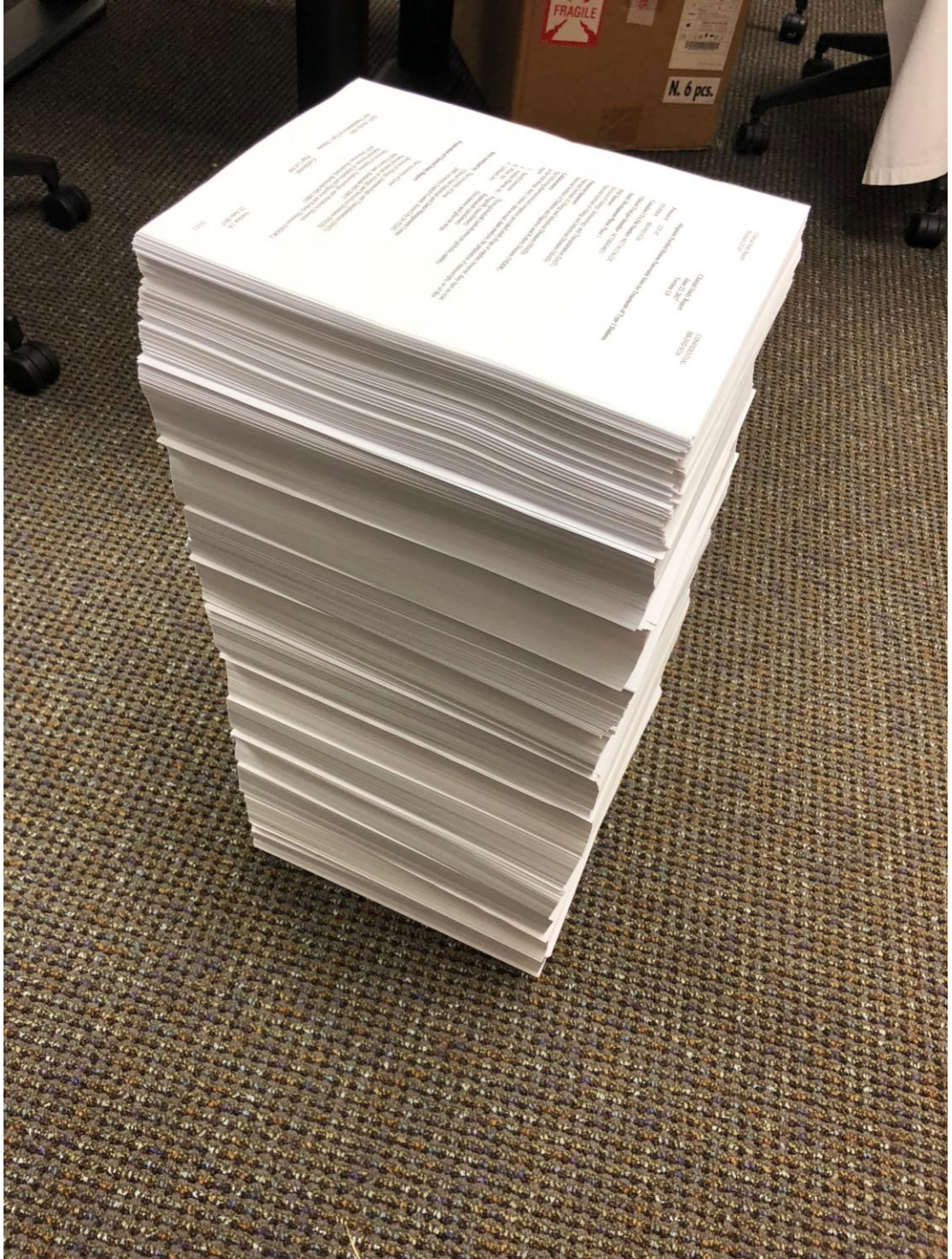
Data Analyzed by: The University of Iowa
Clinical Trials Statistical and Data Management Center
2400 University Capitol Centre, Iowa City IA 52242

Preparation of Clinical Study Report:

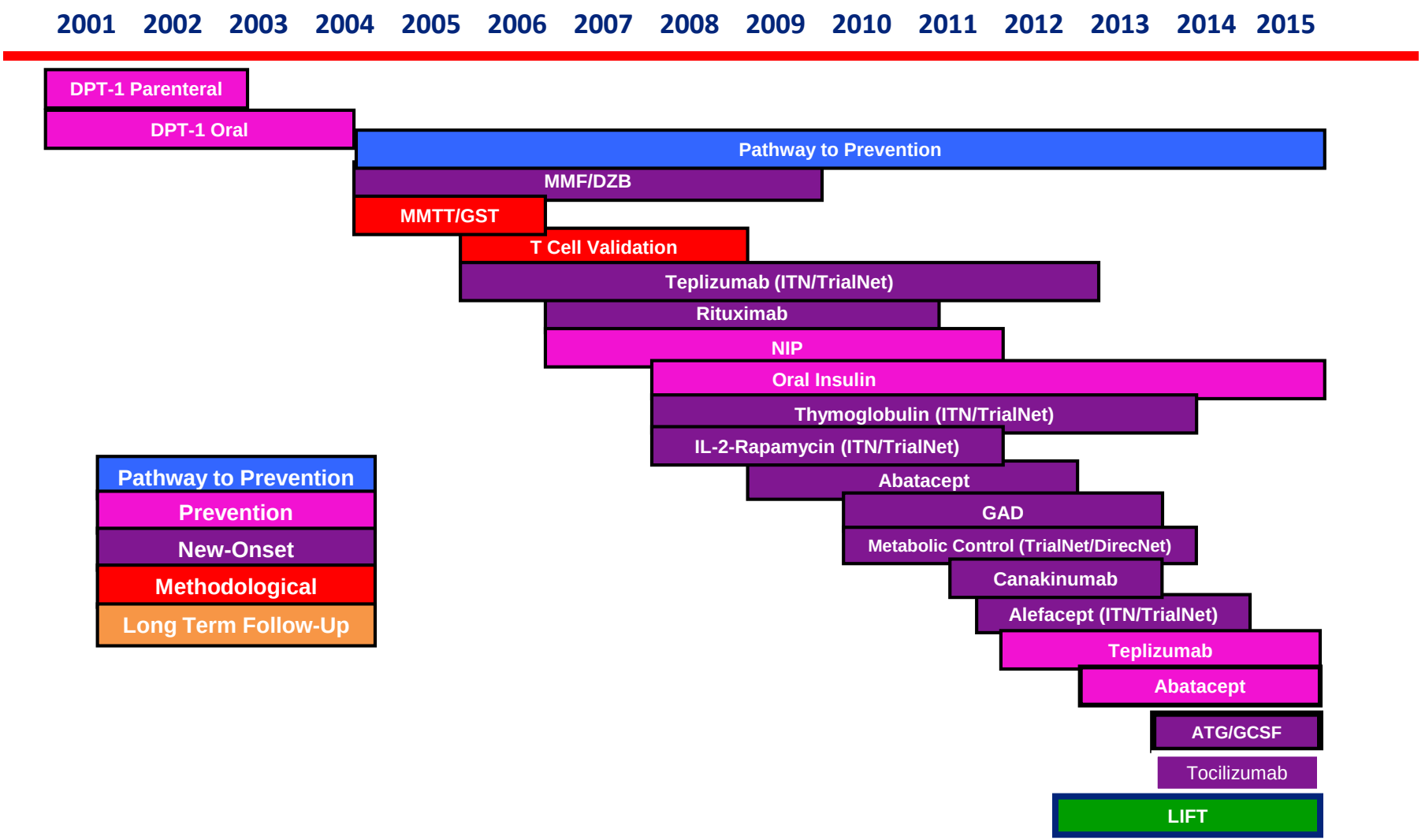
The University of Iowa

Division of Allergy, Immunology and Transplantation (DAIT)
National Institute of Allergy and Infectious Diseases (NIAID)
5601 Fishers Lane, Bethesda MD 20817

Division of Diabetes, Endocrinology and Metabolic Diseases
National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
6707 Democracy Boulevard, Bethesda MD 20892


FRAGILE
N. 6 pcs.

Two Decades of Disappointing Clinical Trials for T1D Prevention/Intervention



Antigen-Based Prevention Studies

- DPT-1 Parenteral Insulin — No effect
- Belgian Parenteral Insulin — No effect
- DPT-1 Oral Insulin — No effect
- TrialNet Oral Insulin — No effect in Primary Stratum
- DIPP Nasal Insulin — No effect
- INIT-II Nasal Insulin — Ongoing – finishing 2018??
- DIAPREV-IT GAD — No effect
- PRE-Point Oral Insulin — Immunologic hints

Immunomodulatory Secondary Prevention Studies

- ENDIT Nicotinamide — No effect
- DENIS Nicotinamide — No effect
- TrialNet Abatacept — Ongoing – finishing 2018
- TrialNet Teplizumab — Ongoing – finishing 2018

Antigen-Based New Onset Studies

- Oral Insulin France — No effect
- Oral Insulin Italy — No effect
- Oral Insulin US — No effect
- GAD Pilot — No effect (? subgroup)
- TrialNet GAD — No effect
- Diamyd EU GAD — No effect
- Diamyd US GAD — No effect
- Neurocrine Altered Peptide — No effect
- Proinsulin-Plasmid — No effect
- Proinsulin Peptide — Safe
- DiaPep-277 Heat Shock Protein — No effect (papers retracted for fraud)

Ongoing and Planned Antigen-Based Studies

- GPPAD Oral Insulin for Primary Prevention
- DIAPERV-IT 2 – GAD + Vit D for Prevention
- Alpha-methyl-dopa for Prevention
- Proinsulin Plasmid in New Onset
- Proinsulin Peptide in New Onset
- Lactococcus lactis with hProins + IL-10 and anti-CD3 in New Onset

Immunomodulatory Primary Prevention Studies

- FINISH Casein hydrolysate — Modest effect on abs
- TRIGR Casein hydrolysate — No effect
- FINDIA Hydrolysate free of bovine insulin — Modest effect on abs
- NIP Docosahexaenoic Acid — No effect

Immunomodulatory New Onset Studies

- Cyclosporin France — Transient effect
- Cyclosporin Canada/EU — Transient effect
- Teplizumab Anti-CD3 Pilot — Transient effect
- Otelixizumab Anti-CD3 Pilot — Transient effect
- Abate Teplizumab — Transient effect
- Protégé Teplizumab (2°endpoint) — Transient effect
- DEFEND Otelixizumab (2 trials) — No effect
- Etanercept — ? Effect
- Mycophenylate±Anti-CD25 — No effect
- Rituximab Anti-CD20 — Transient effect
- Abatacept CTLA4-Ig — Transient effect
- Canakinumab Anti-IL1-β — No effect
- Anakinra IL-1 trap — No effect
- Thymoglobulin — No effect
- Alefacept CTLA4-Ig (2°endpoint) — Potential effect

JAMA | Original Investigation

JAMA 2017; 318:1891-1902

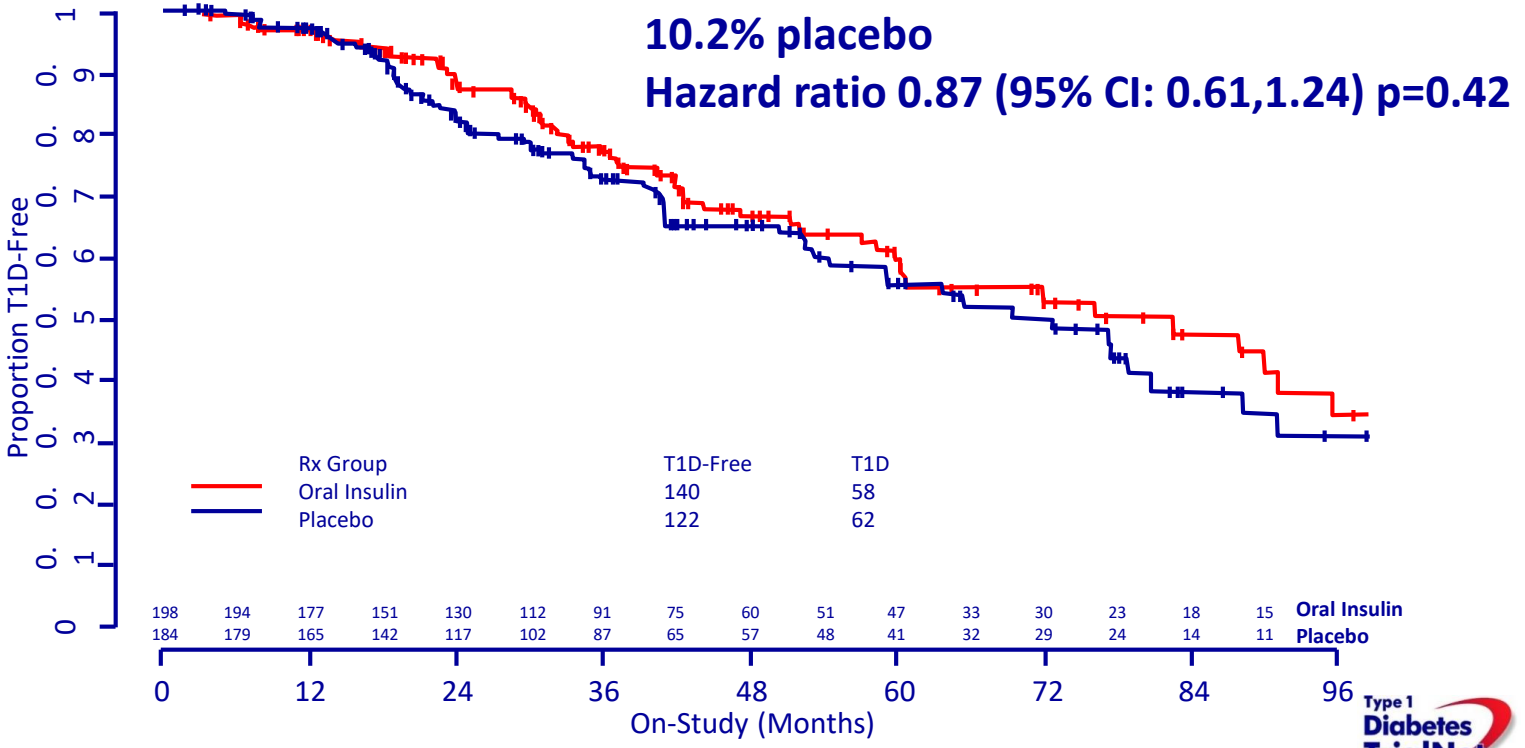
Effect of Oral Insulin on Prevention of Diabetes in Relatives of Patients With Type 1 Diabetes

A Randomized Clinical Trial

Writing Committee for the Type 1 Diabetes TrialNet Oral Insulin Study Group; Jeffrey P. Krischer, PhD; Desmond A. Schatz, MD; Brian Bundy, PhD; Jay S. Skyler, MD; Carla J. Greenbaum, MD

Annualized rate of diabetes 8.8% oral insulin; 10.2% placebo

Hazard ratio 0.87 (95% CI: 0.61,1.24) p=0.42



Presented at ADA San Diego June 12 2017

Type 1 Diabetes TrialNet

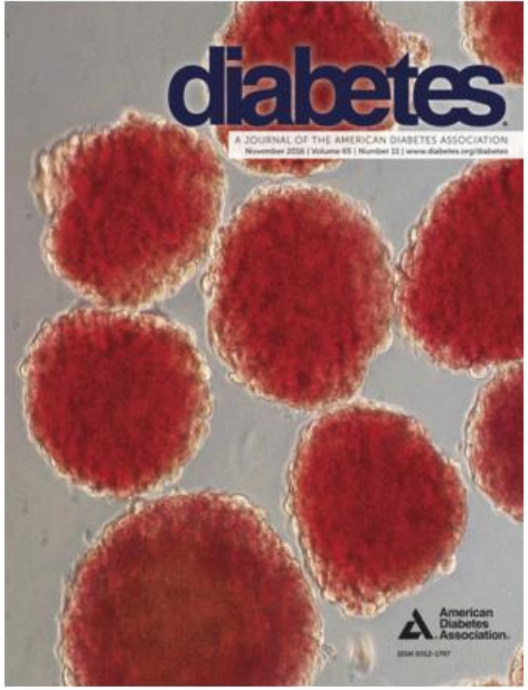
The Rationale for Combination Strategies: Lessons from Islet Transplantation

PERSPECTIVES IN DIABETES

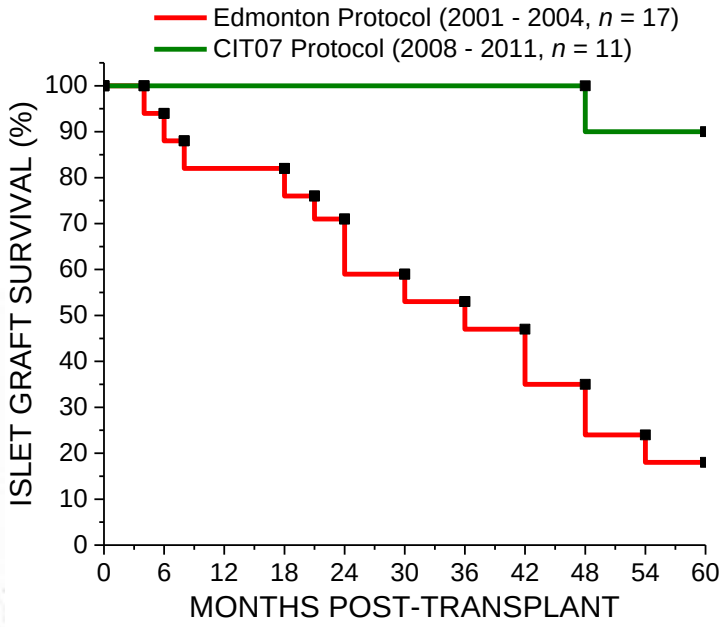
Stopping Type 1 Diabetes: Attempts to Prevent or Cure Type 1 Diabetes in Man

Jay S. Skyler and Camillo Ricordi

DIABETES, VOL. 60, JANUARY 2011 1



Islet Allograft Survival



Rickels … Naji. Unpublished data

NIH-sponsored Clinical Islet Transplantation Consortium Phase 3 Trial: Manufacture of a Complex Cellular Product at Eight Processing Facilities

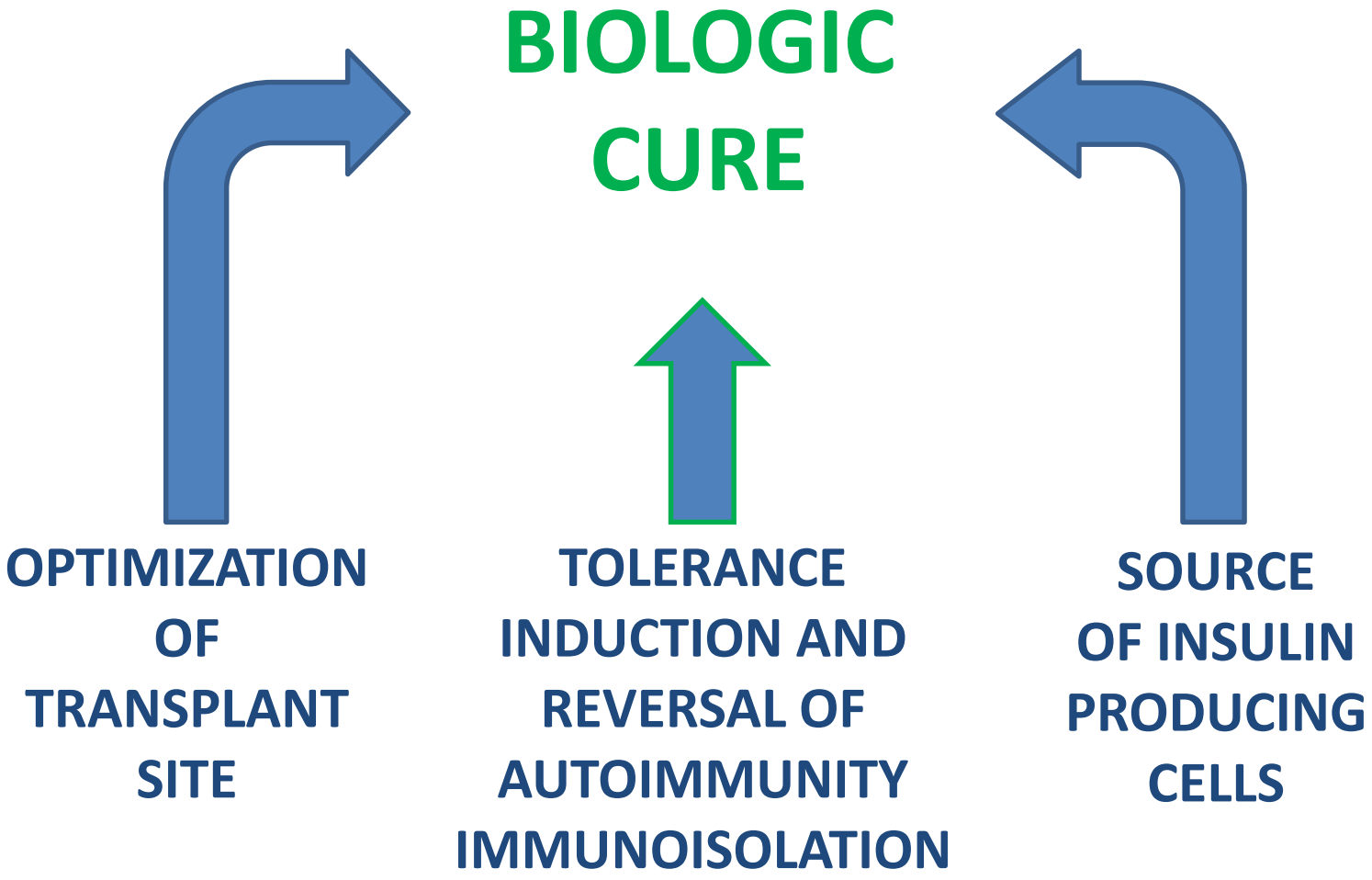
Camillo Ricordi, Julia S. Goldstein, A. N. Balamurugan, Gregory L. Szot, Tatsuya Kin, Chengyang Liu, Christine W. Czarniecki, Barbara Barbaro, Nancy D. Bridges, Jose Cano, William R. Clarke, Thomas L. Eggerman, Lawrence G. Hunsicker, Dixon B. Kaufman, Aisha Khan, David-Erick Lafontant, Elina Linetsky, Xunrong Luo, James F. Markmann, Ali Naji, Olle Korsgren, Jose Oberholzer, Nicole A. Turgeon, Daniel Brandhorst, Andrew S. Friberg, Ji Lei, Ling-jia Wang, Joshua J. Wilhelm, Jamie Willits, Xiaomin Zhang, Bernhard J. Hering, Andrew M. Posselt, A. M. James Shapiro

Diabetes 2016 Jul; db160234.
http://dx.doi.org.login.ezproxy.library.ualberta.ca/10.2337/db16-0234

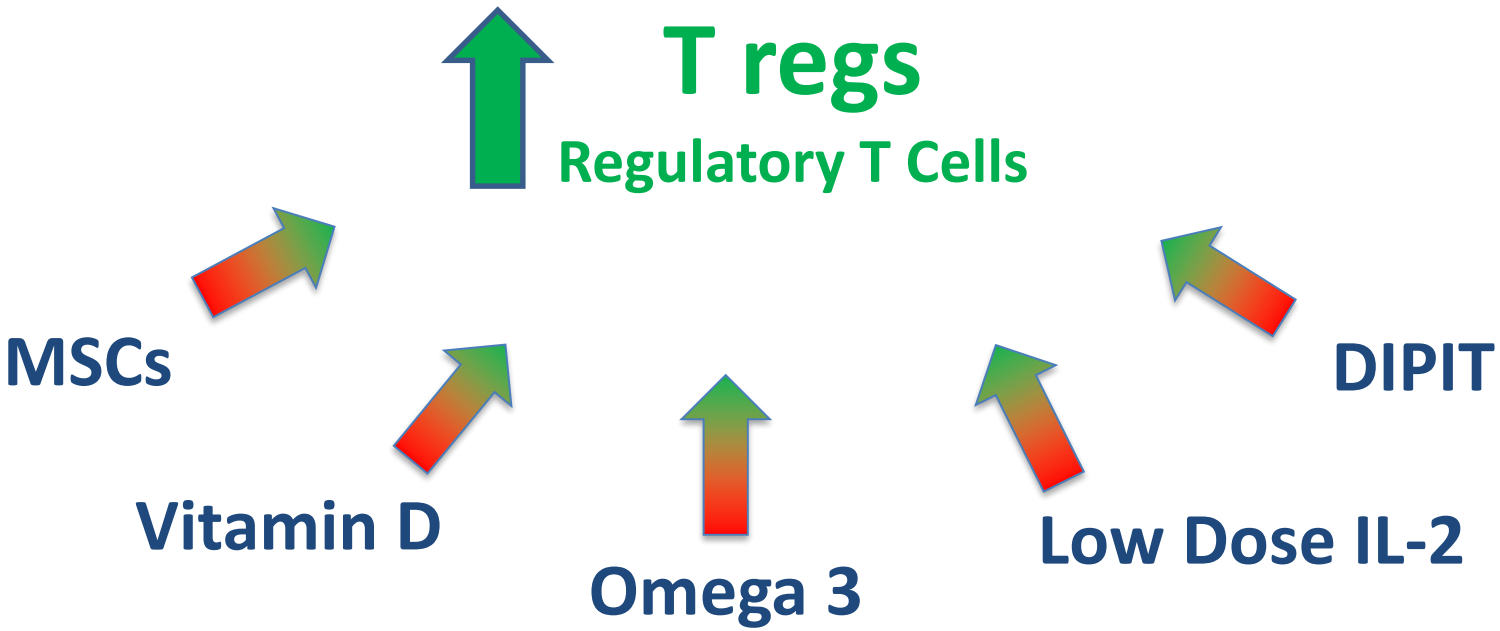
Remaining Challenges

- Delivery system/Transplant Site
- Immuno Protection
  - Immune Tolerance/Self Tolerance
  - Immunoisolation
- Adequate Supply to Transplant >100 Million Subjects
- Cost Efficiency

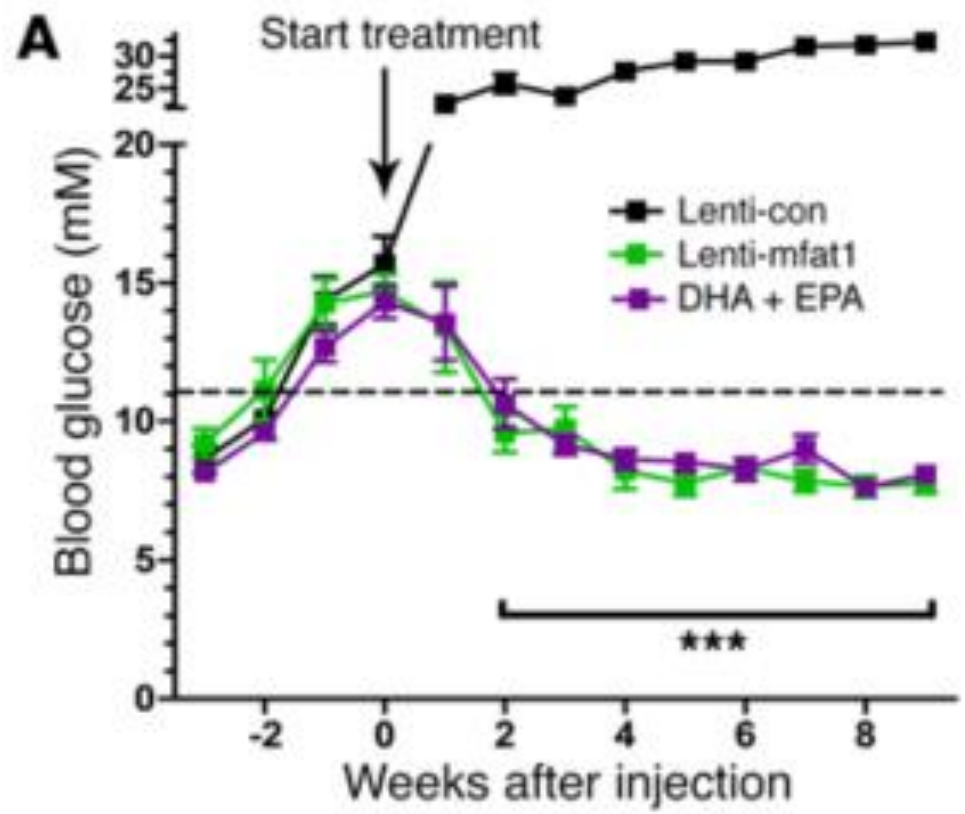
DRI BioHUB Strategy

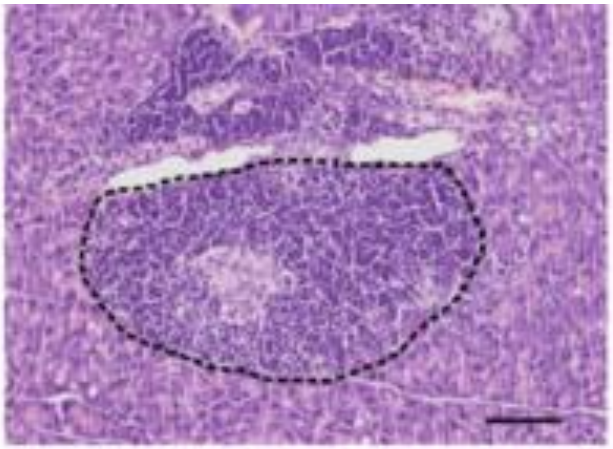


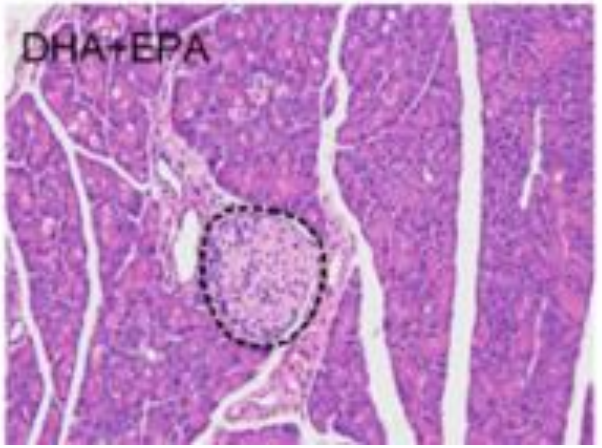
Moving from Immunosuppression to TOLEROGENIC IMMUNOMODULATION

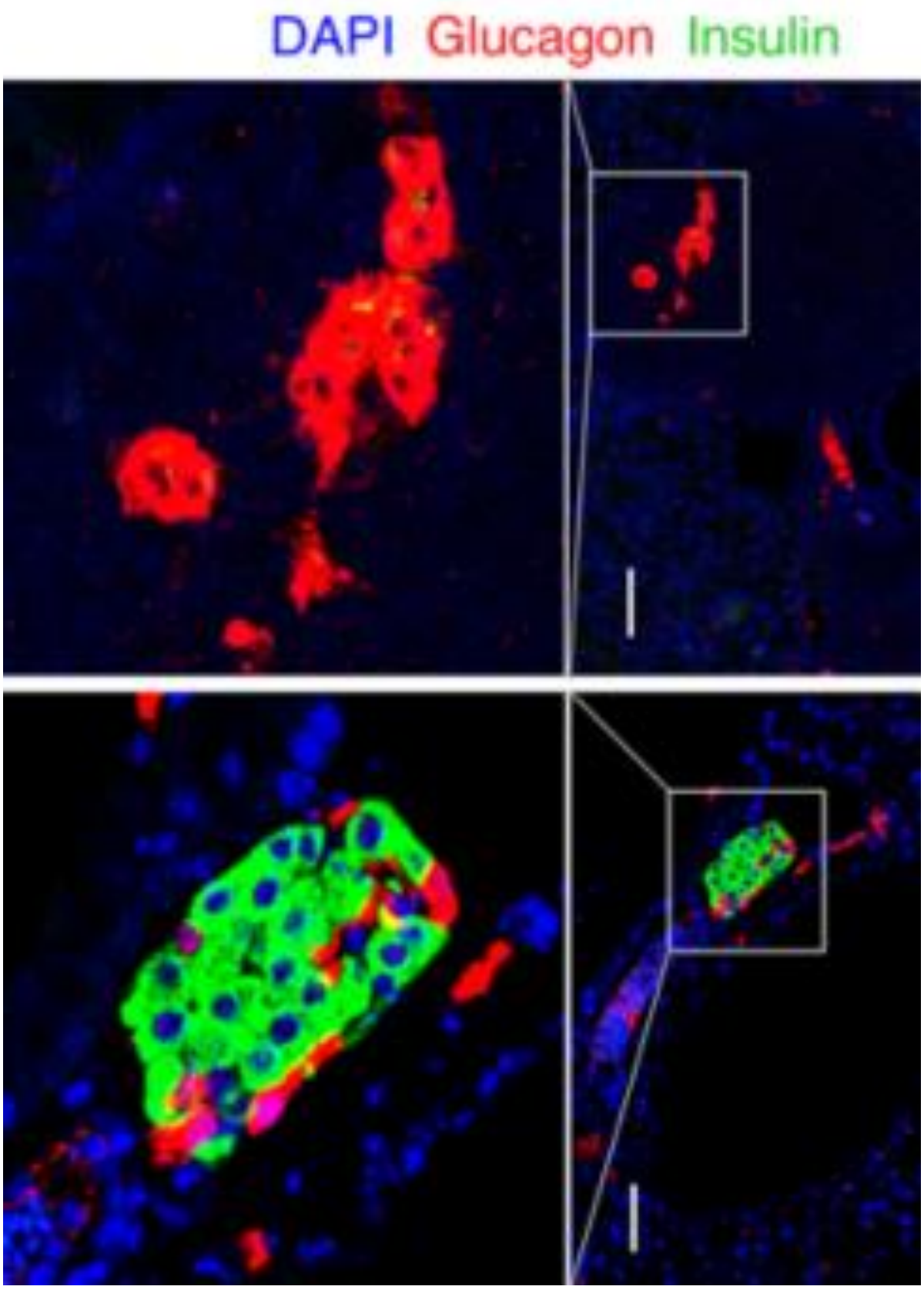


ω-3 polyunsaturated fatty acids ameliorate type 1 diabetes and autoimmunity








DAPI Glucagon Insulin

PBMC from Subjects with T1D

The Journal of Clinical Investigation RESEARCH ARTICLE

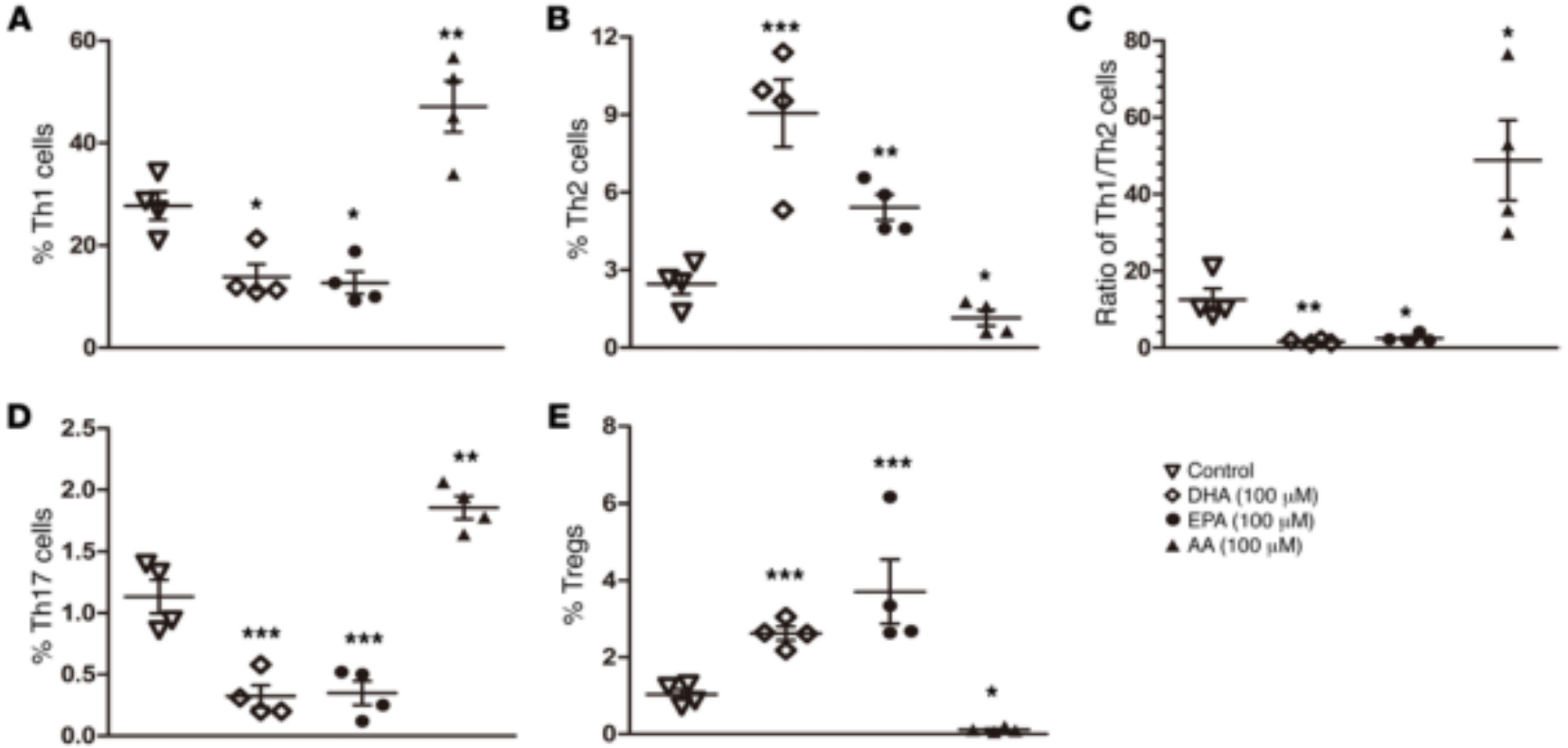
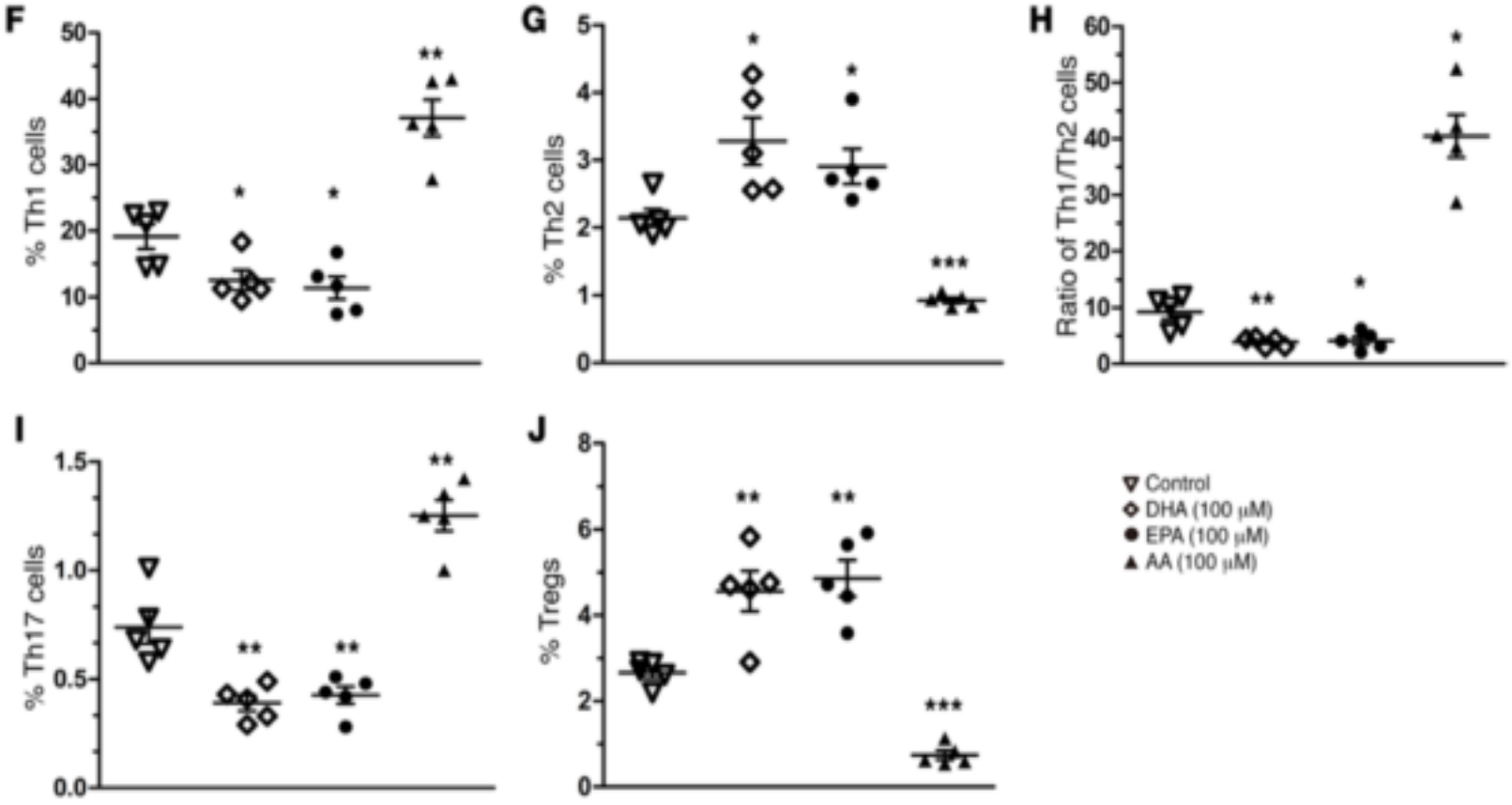


Figure 10. ω-3 and ω-6 PUFAs readjust CD4⁺ T cell differentiation in PBMCs from T1D patients and nondiabetic donors in vitro. Quantification of the percentage of intracellular staining of IFN-γ⁺, IL-4⁺, IL-7⁺, and CD25⁺FoxP3⁺ Th cells in PBMCs from 4 T1D patients (**A**–**E**) and 5 nondiabetic donors (**F**–**J**). Cells were cultured for 24 hours under PMA and ionomycin stimulation in the presence of DHA, EPA, and AA (100 μM) added at the time of activation. Representative flow cytometric images are shown in Supplemental Figures 9 and 10. *$P < 0.05$, **$P < 0.01$, and ***$P < 0.0001$ compared with the control group (Student's *t* test). Each point represents an individual patient or donor, and the data are representative of 3 independent experiments. All values represent the mean ± SEM.

PBMC from Non Diabetic Subjects



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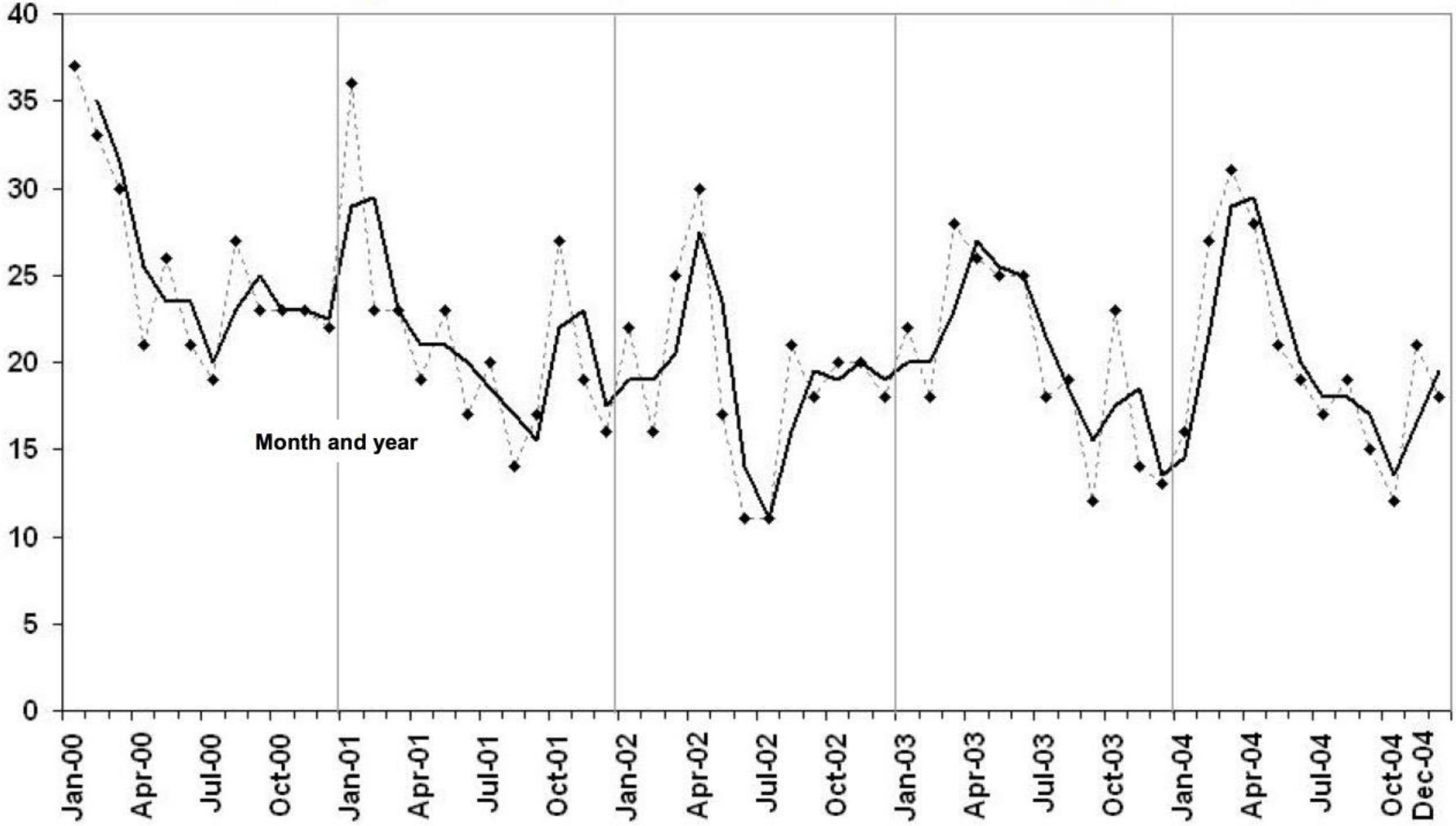
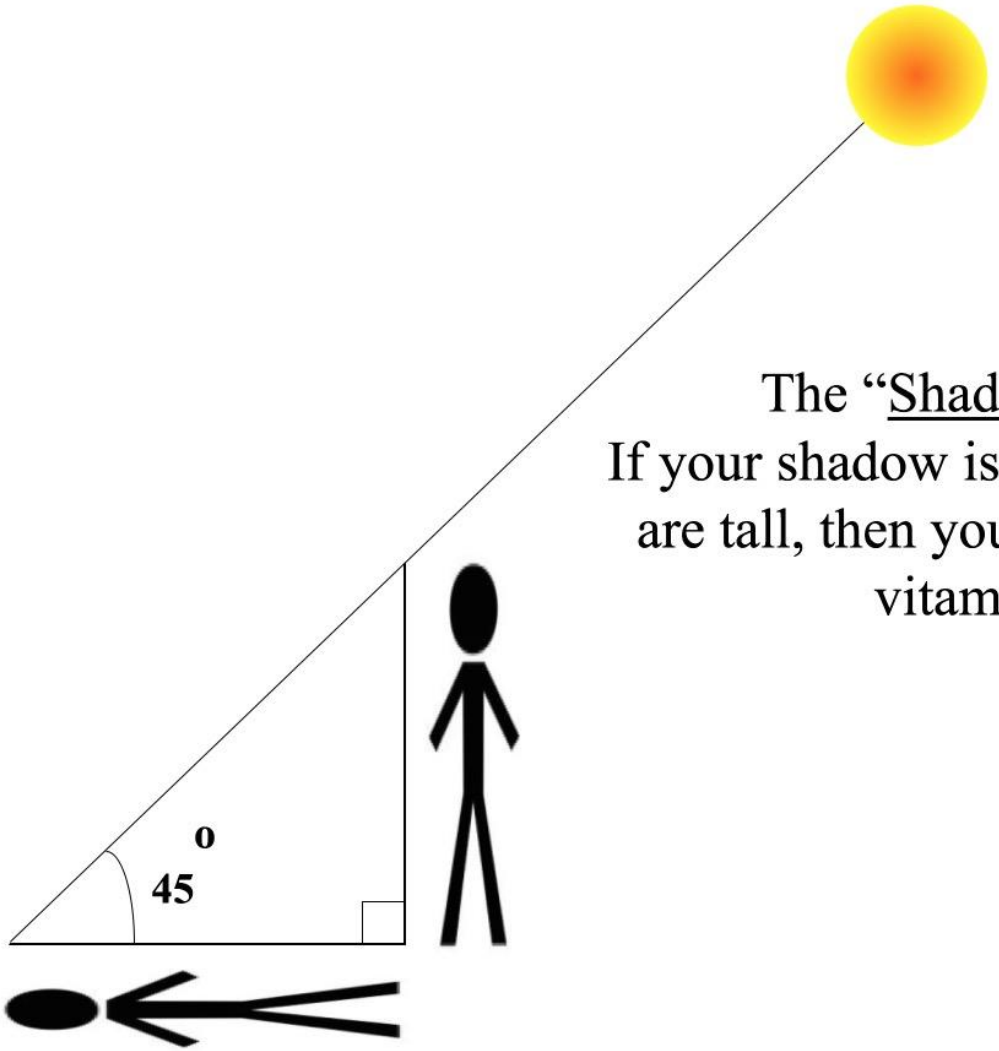
Type 1 Diabetes Incidence Peaks Annually in the Winter-Spring Season (Odds Ratio = 1.46, $p < 0.01$)



Incidence of Type 1 diabetes by month and year, active-duty DoD, 2000-2004, N = 2,918 new cases,18-44 years (median age 28 years)

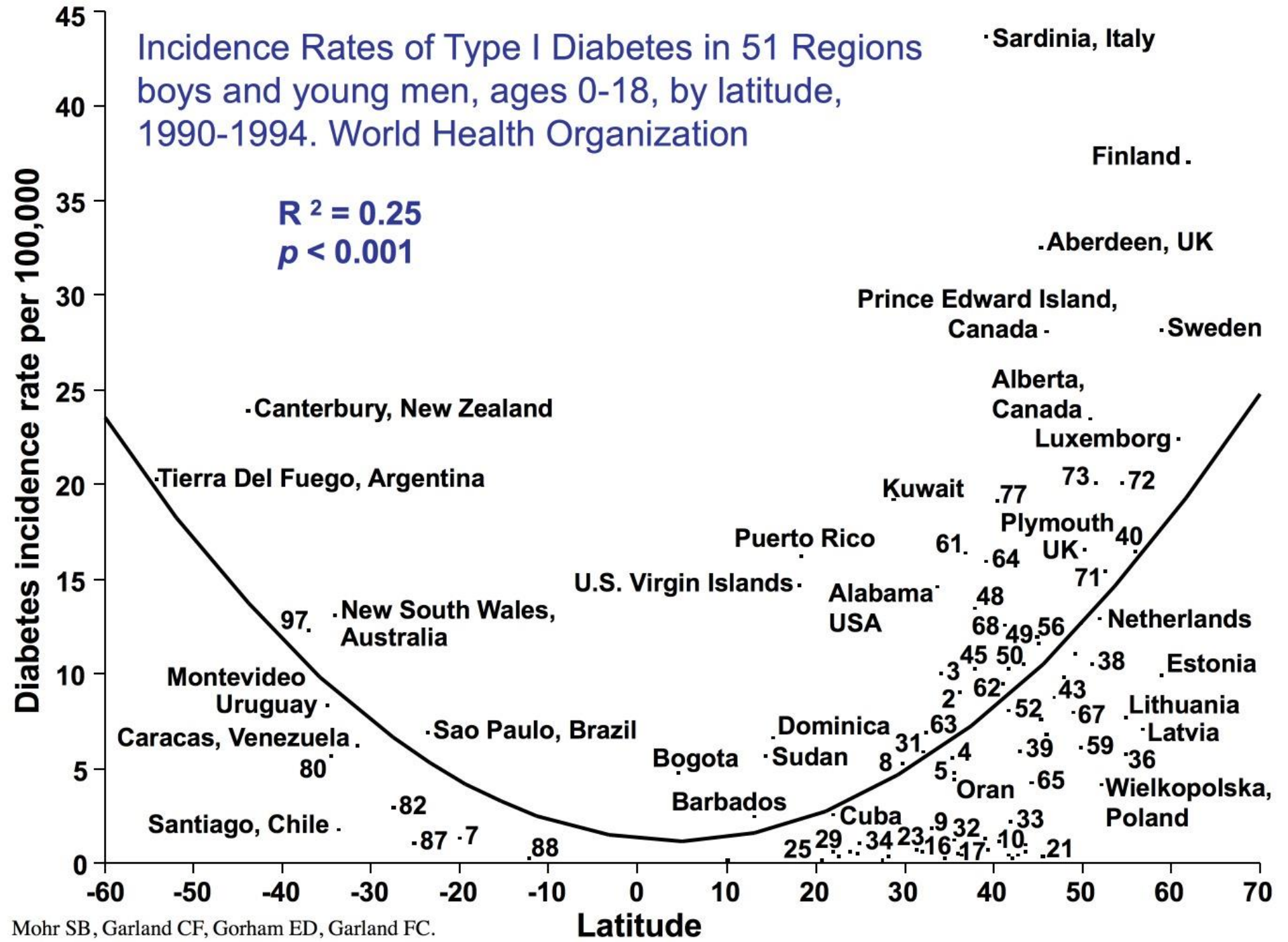
Gorham ED, Barrett-Connor E, Highfill-McRoy RM, Mohr SB, Garland CF, Garland FC, Ricordi C. Incidence of insulin-requiring diabetes in the US military. Diabetologia. 2009;52:2087-91

Solar Angle Limits UVB Photosynthesis



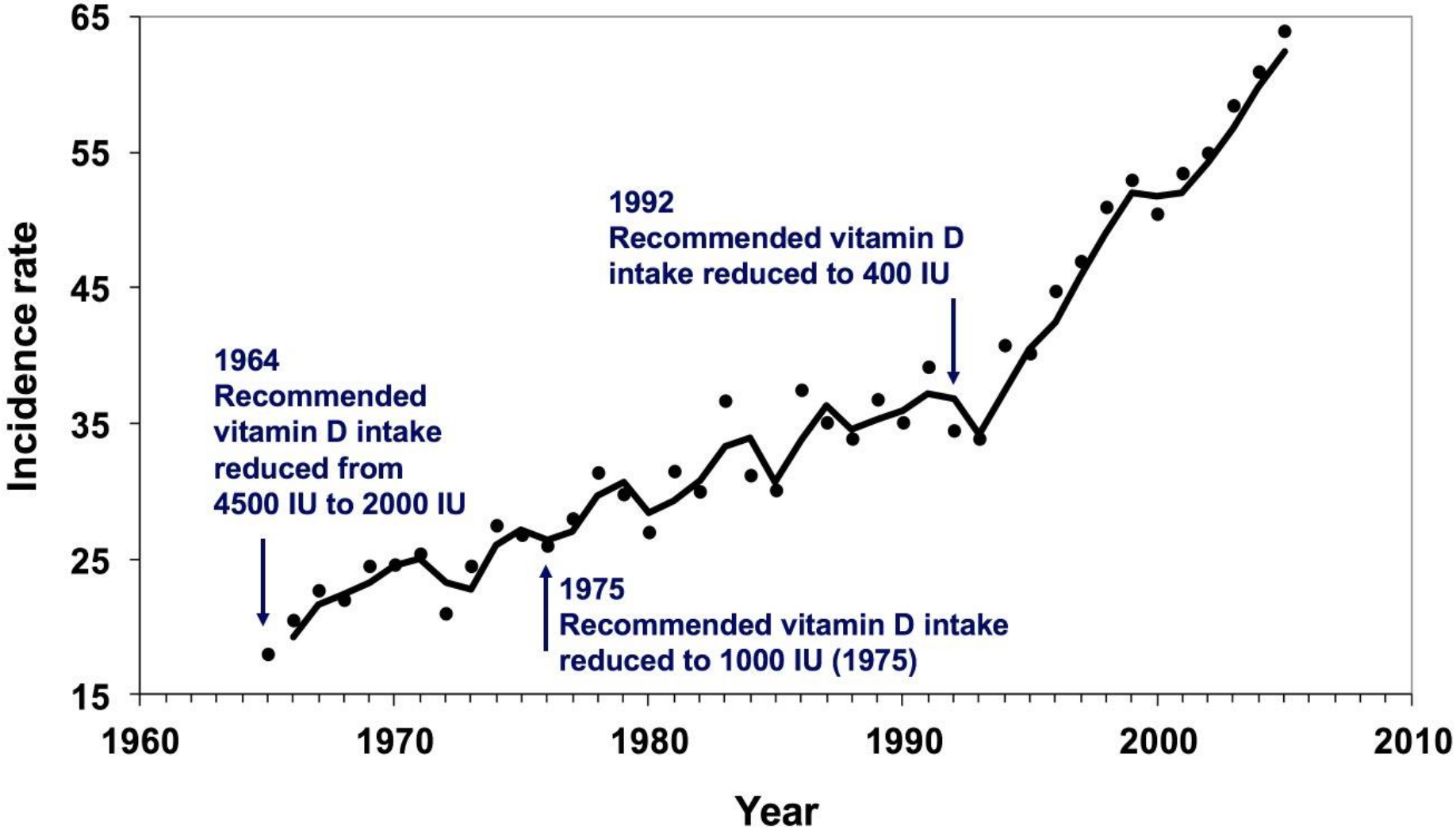
The "Shadow Rule"
If your shadow is longer than you are tall, then you will not make vitamin D

E. Gorham and C Garland, UCSD



Mohr SB, Garland CF, Gorham ED, Garland FC.
Incidence rates of type 1 diabetes in 51 regions worldwide. Diabetologia. 2008 Aug;51(8):1391-8.

Annual age-adjusted incidence rates of type 1 diabetes, children ≤ 14 years old, per 100,000 population, Finland, 1965-2005



Mohr SB, et al. Am J Prev Med. 2010;39:189-90: Data from Harjutsalo V, et al. Time trends in the incidence of type 1 diabetes in Finnish children: a cohort study. Lancet 2008; 371:1777– 82, and Tuomilehto J, et al. Record-high incidence of type I (insulin-dependent) diabetes mellitus in Finnish children. Diabetologia 1999;42:655– 60.

Gauging Vitamin D Status

What is the best serum 25 (OH) Vitamin D concentration?

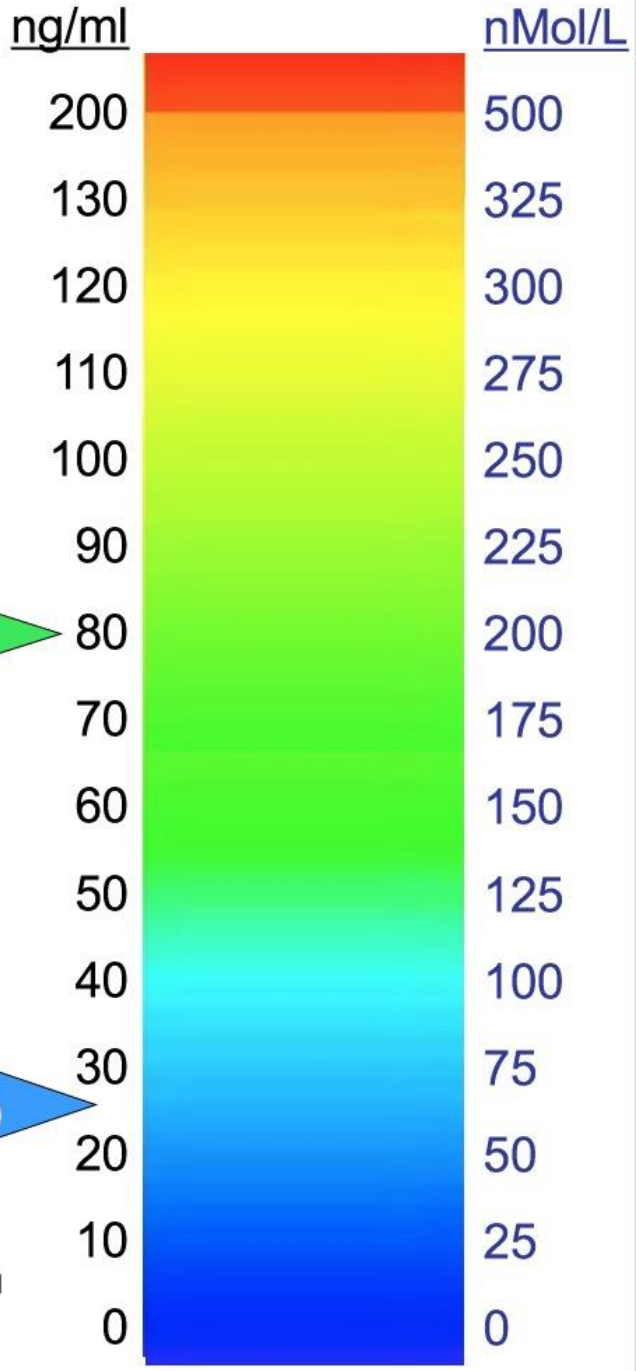
People living in sunny places with minimal clothing that doesn't limit vitamin D photosynthesis have serum 25(OH)D levels of 54 to 90 ng/ml (1).

A good target is:

80 ng/ml good target

A useful rule of thumb is that for every 100 IU of vitamin D_3 ingested, there is a gain of 1 ng/mL in serum 25 (OH)D (2).

25 ng/ml US median (NHANES 3)



1. Hollis BW. Circulating 25-hydroxyvitamin D levels indicative of vitamin D sufficiency: implications for establishing a new effective dietary intake recommendation for vitamin D. J Nutr. 2005;135:317-22

2. Heaney RP, Davies KM, Chen TC, Holick MF, Barger-Lux MJ. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. Am J Clin Nutr. 2003;77:204-10.

VITAL

THE VITAMIN D AND OMEGA-3 TRIAL *(VITAL)*

About the VITAL Study

Thank you video by Dr. JoAnn Manson

VITAL in the News

Ancillary Studies

Study Q&A

VITAL Signs
Download issues of our newsletter

Contact Us

Brigham and Women's Hospital

BWH Division of Preventive Medicine

For Healthcare Providers

For VITAL Investigators

Welcome to the VITAL Study

Welcome to the Web site of the *VIT*amin D and Omeg*A*-3 Tria*L* (VITAL) at Brigham and Women's Hospital, an affiliate of Harvard Medical School, in Boston, Massachusetts. VITAL is an ongoing research study in 25,874 men and women across the U.S. investigating whether taking daily dietary supplements of vitamin D3 (2000 IU) or omega-3 fatty acids (Omacor® fish oil, 1 gram) reduces the risk for developing cancer, heart disease, and stroke in people who do not have a prior history of these illnesses. Please click on Study Q&A to learn more about this important research endeavor.

JoAnn Manson, MD

The website is updated regularly to keep participants informed about the study's progress, as well as health topics that we hope are of interest. We also answer frequently asked questions from participants on this website.

Julie Buring, ScD

Thank you for your interest!

JoAnn Manson, MD
Julie Buring, ScD
VITAL Study Directors

Eat Weight Disord (2017) 22:27–41
DOI 10.1007/s40519-016-0312-6

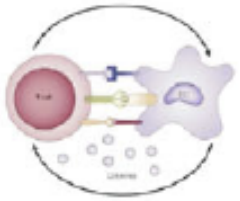
REVIEW

Vitamin D: not just the bone. Evidence for beneficial pleiotropic extraskeletal effects

Massimiliano Caprio[1,2] · Marco Infante[3] · Matilde Calanchini[3] · Caterina Mammi[1] · Andrea Fabbri[3]

Immune system

⩾ 40 ng/mL



↑ macrophage differentiation and activation

↑ cathelicidin, β2-defensin

↓ Th_1, Th_{17} cells ↑ Treg cells

ward off:
- type1 diabetes
- hashimoto's thyroiditis
- inflammatory bowel disease
- multiple sclerosis

CASE 1

European Review for Medical and Pharmacological Sciences 2016; 20: 3313-3318

Combination high-dose omega-3 fatty acids and high-dose cholecalciferol in new onset type 1 diabetes: a potential role in preservation of beta-cell mass

D.A. BAIDAL[1], C. RICORDI[1,3], M. GARCIA-CONTRERAS[1,2,3], A. SONNINO[4], A. FABBRI[5]

[1]Diabetes Research Institute, Clinical Cell Transplant Program, University of Miami, Miami, FL, USA
[2]School of Dentistry and Medicine, Catholic University of Valencia, Valencia, Spain
[3]Ri.MED Foundation, The Biomedical Research and Biotechnology Center, Palermo, Italy
[4]Massachusetts College of Pharmacy and Health Sciences, Boston, MA, USA
[5]Endocrine and Metabolic Diseases Unit, S. Eugenio & CTO A. Alesini Hospital, ASL Roma 2, Department of Systems Medicine, University Tor Vergata, Rome, Italy

CASE 1

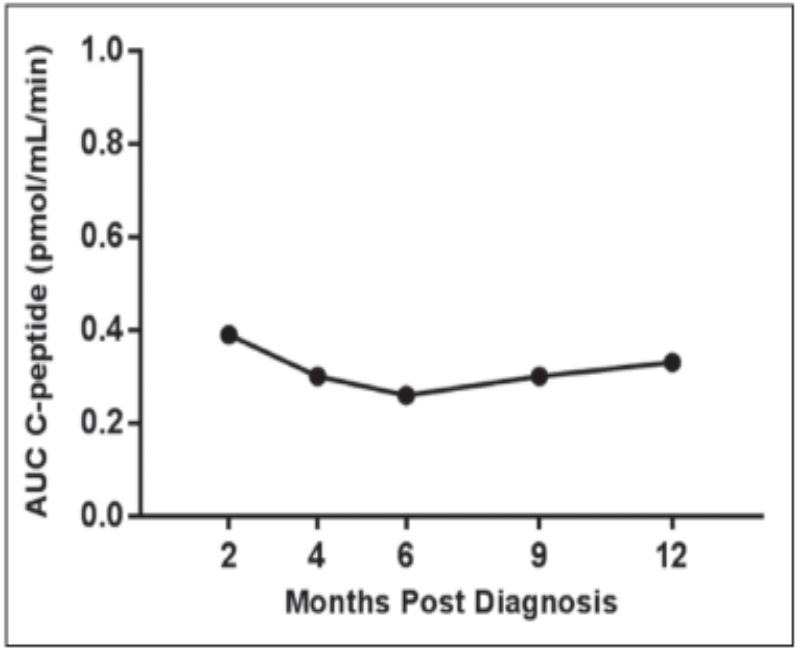


Figure 1. Decline in C-peptide area under the curve for the first 12 months following diagnosis of type 1 diabetes.

Table I. C-peptide variables derived from serial 2 hr MMTT.

Months post diagnosis	C-peptide variables from 2 hr MMTT		
	Fasting (nmol/L)*	90 min (nmol/L)*	AUC (nmol/L/min)*
2	0.20	0.43	0.39
4	0.14	0.34	0.30
6	0.11	0.30	0.26
9	0.18	0.31	0.30
12	0.05	0.55	0.33

*Divide units in nmol/L by 0.333 to convert to ng/mL.

CASE 2 and 3

Eur Rev Med Pharmacol Sci 2018; 22 (2): 512-515

DOI: 10.26355/eurrev_201801_14203

Administration of vitamin D and high dose of omega 3 to sustain remission of type 1 diabetes

F. Cadario, S. Savastio, R. Ricotti, A.M. Rizzo, D. Carrera, L. Maiuri, C. Ricordi

Department of Health Sciences, University of Eastern Piedmont, Novara, Italy.
CRicordi@med.miami.edu

CASE 2 and 3

Table I. Characteristics of patients at T1D onset.

	Case 1 (onset 11/21/2015)	Case 2 (onset 12/18/2016)
HbA1c % (mmol/mol)	9.6% (81)	11.1% (98)
25(OH)D_3 ng/ml	25.9	24.7
AA/EPA	33.67	20.45

Table II. First and last results after supplements.

	Case 1		Case 2	
	First result	Last result	First result	Last result
Vitamin D ng/ml	38.3	43.8	24.7	46
AA/EPA	1.76	2.97		2.5
Insulin IU/kg/d	0.07	0.09	0.1	0.11
C-peptide ng/ml	0.5	0.6	1.07	2.24
HbA1c % (mmol/mL)	5.8% (40)	5.9% (41)	6.8% (51)	5.7% (39)
Mean blood glucose	97 mg/dl	86 mg/dl	116 mg/dl	103 mg/dl
SD	20 mg/dl	21 mg/dl	48 mg/dl	32 mg/dl

		One year after	Two years after
Side effects	C1	None	None
	C2	None	
HbA1c % (mmol/mol)	C1	6.2 (44)	5.9 (41)
	C2	5.7 (39)	
IDAA1C*	C1	6.4	6.5
	C2	6.0	
MMTT (2h)	C1		
	C-peptide		0.71 ng/ml
	Blood glucose		143 mg/dl
	C2		
	C-peptide	0.8 ng/ml	
	Blood glucose	112 mg/dl	

CASE 4

- Subject: 30 year old male
- T1D diagnosis April 16 2017
- 1 week of insulin therapy while in the hospital
- 2 weeks after hospital discharge **complete suspension of exogenous insulin**
- In June 2017 starts Omega 3 and High-Dose Vit D + other vitamins (COIMBRA)

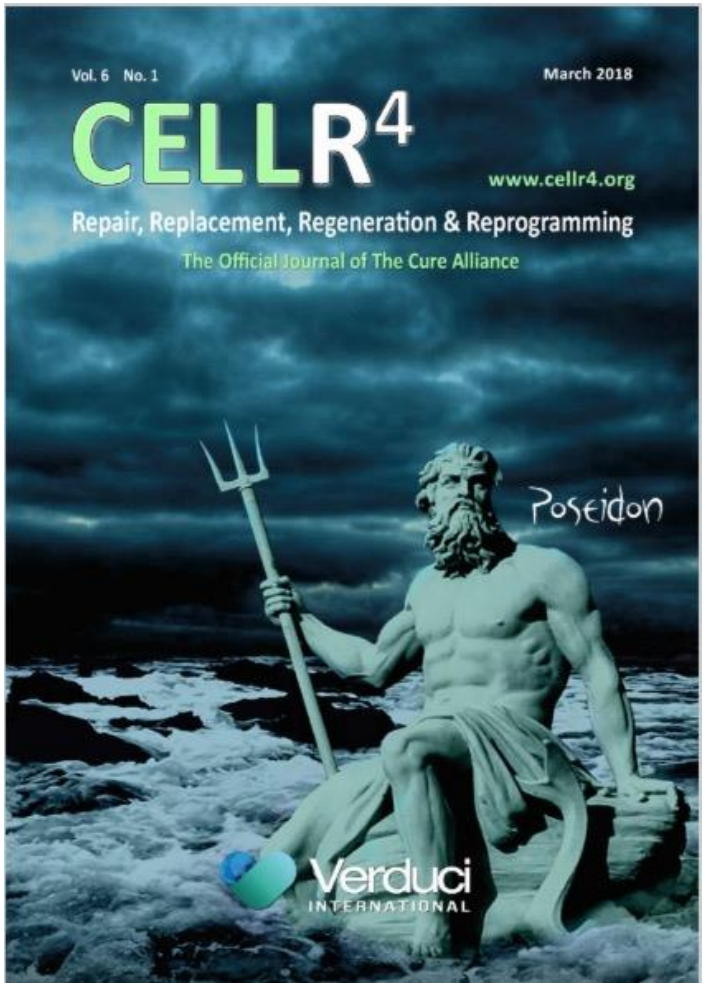
T1D Dx 04/2017	HbA1c (%)	Fasting C-Peptide (ng/ml)
05/2017	8.4	0.5
07/2017	5.6	0.6
10/2017	5.4	0.7
01/2018	5.4	0.8
04/2018	4.6	1.0

CellR4 2018; 6 (1): e2493

Editorial:

Can high-dose omega-3 fatty acids and high-dose vitamin D3 (cholecalciferol) prevent type 1 diabetes and sustain preservation of beta-cell function after disease onset?

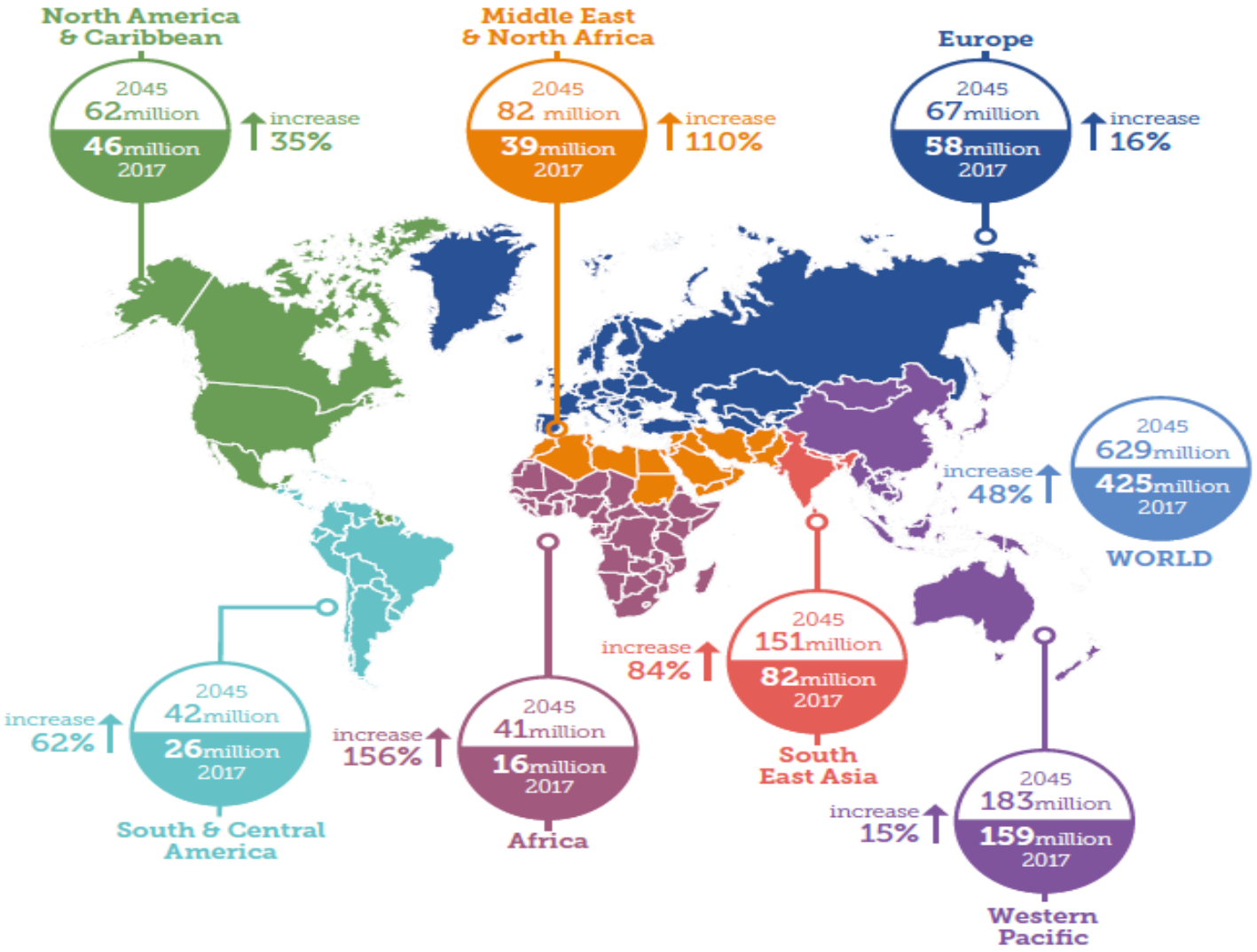
Ricordi C.[1-5], Lanzoni G.[1,3,4]



The rationale for this combination strategy is that Omega 3 LCPUFA (eicosapentaenoic acid, EPA, and docosahexaenoic acid, DHA) and Vitamin D can have beneficial effects not only on inflammatory markers, but also on immunomodulation-increasing regulatory T cells (Tregs), while decreasing Th17 cells and Th1/Th2 ratios[1,2]. In contrast, arachidonic acid (AA) showed an opposite effect on Tregs, Th17 cells and Th1/Th2 ratios. A very high AA/EPA ratio has been observed in subjects diagnosed with T1D and other autoimmune conditions (F.Cadario and C. Ricordi, personal communication and manuscript in preparation). This may reflect a diet-related pro-inflammatory baseline condition. This condition could predispose to or trigger the subsequent development of autoimmunity. In this direction, anti-inflammatory nutrition could have an important synergistic role, in addition to Vitamin D and Omega 3 LCPUFA supplementation, as already explored by Cadario and collaborators in pilot and ongoing clinical trials.

Diabetes: A global emergency

Number of people with diabetes worldwide and per region in 2017 and 2045 (20-79 years)



- **450 million people have DIABETES**
- **Diabetes caused 5 million deaths in 2017**
- **Every seven seconds a person dies from diabetes**
- **$260 Billion/Year in the US alone**

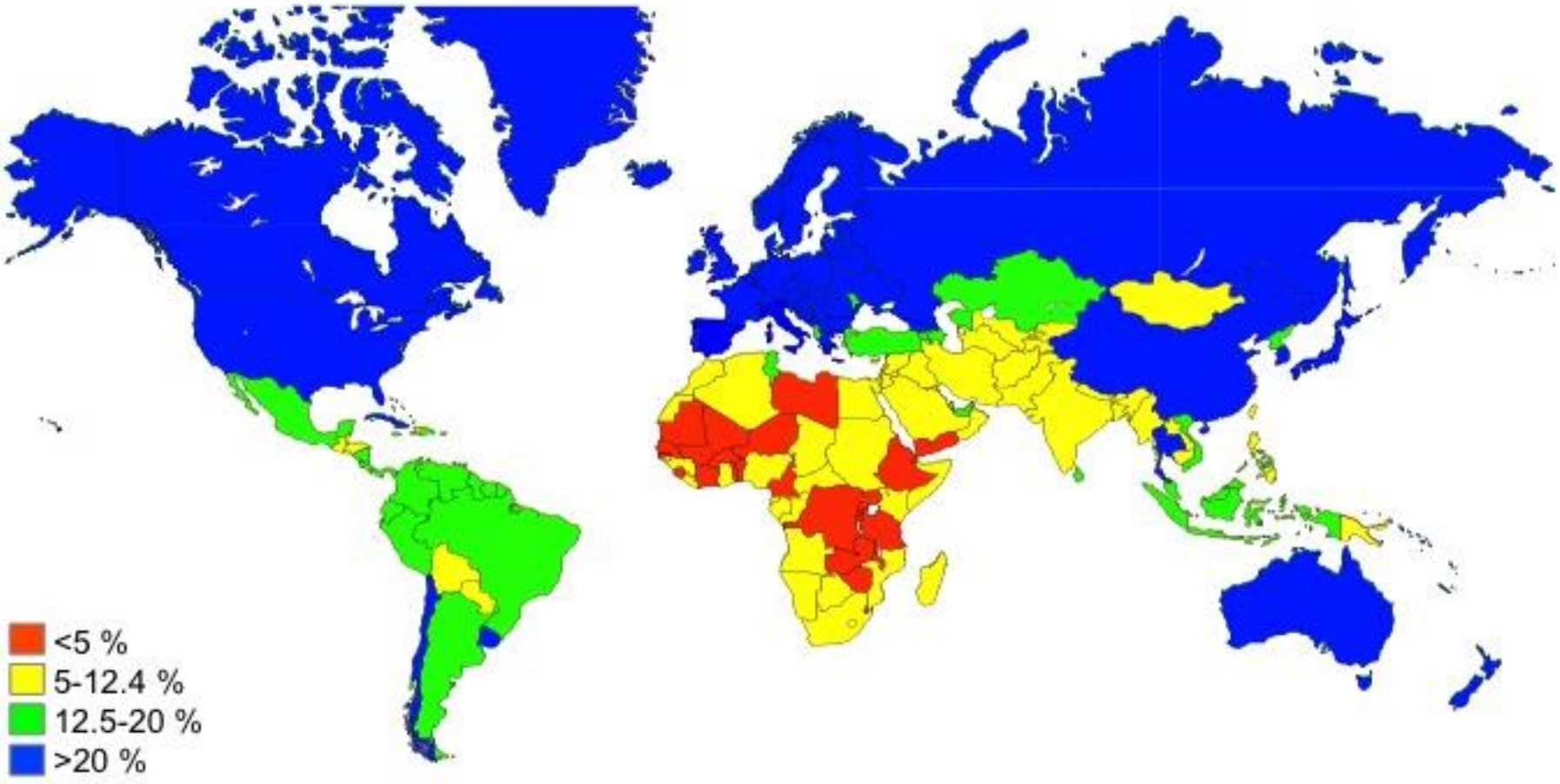
The challenge:

- Over 90% of individuals >65 years of age have at least one chronic disease, while >75% have at least two (co-morbidities).
- 30% of longevity is inherited.
- Today $150B is spent annually on Alzheimer's. The number of individuals with AD will triple by 2050 at which point the cost of care for AD patients alone will be as much as our current defense budget.
- By 2050 the number of individuals over 65 will more than double = the equivalent of adding 3 new states of FL inhabited only by seniors.
- Improving health span by 2.2 years via slowing aging will save $7.1T in disability and entitlement programs over the next 50 years.

Dr. Paul Robbins, Department of Metabolism and Aging , Scripps Florida

2025

% Aging World Population > 65 per Country



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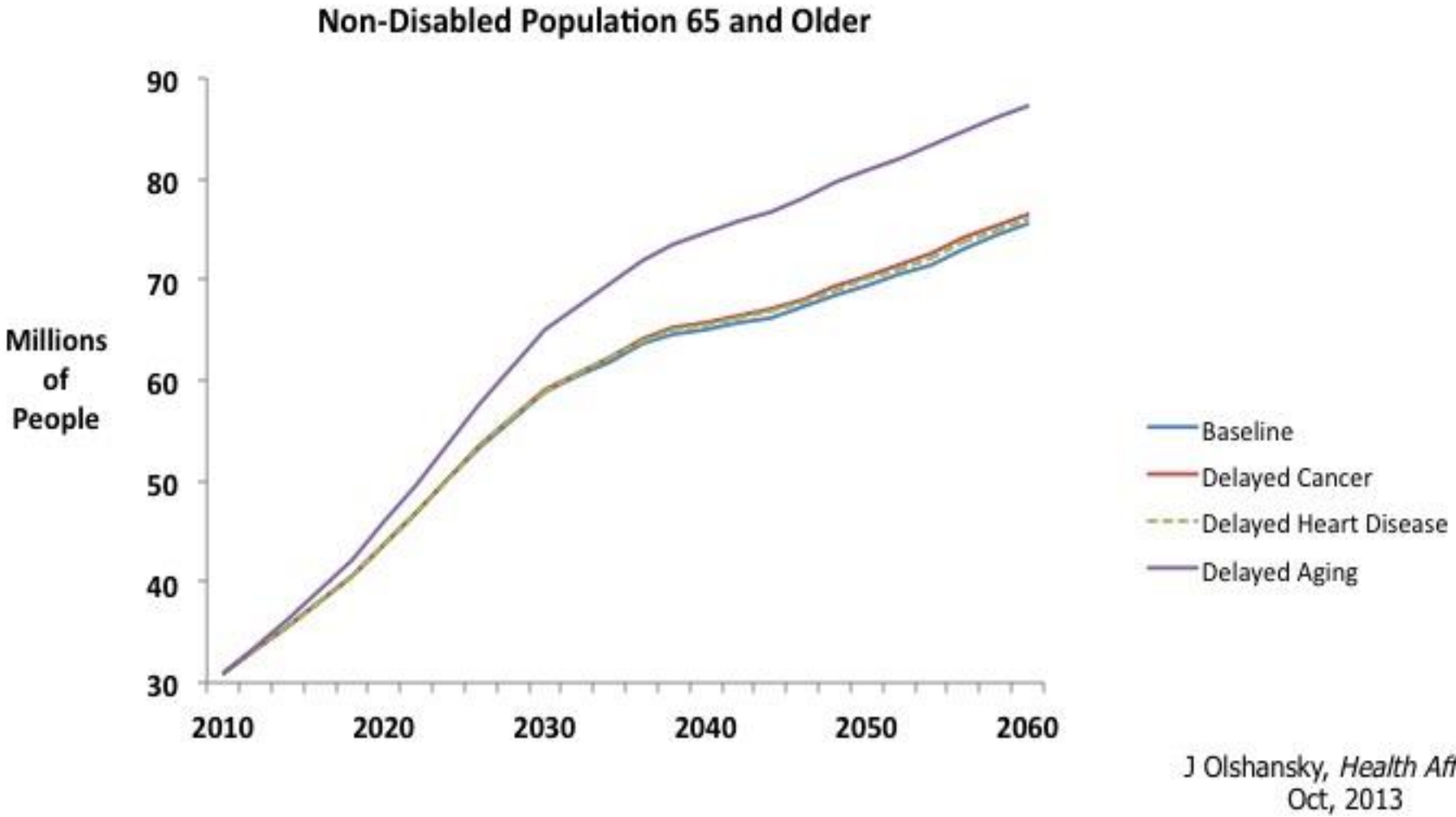
Delayed aging would have the largest impact on the number of healthy, older adults…



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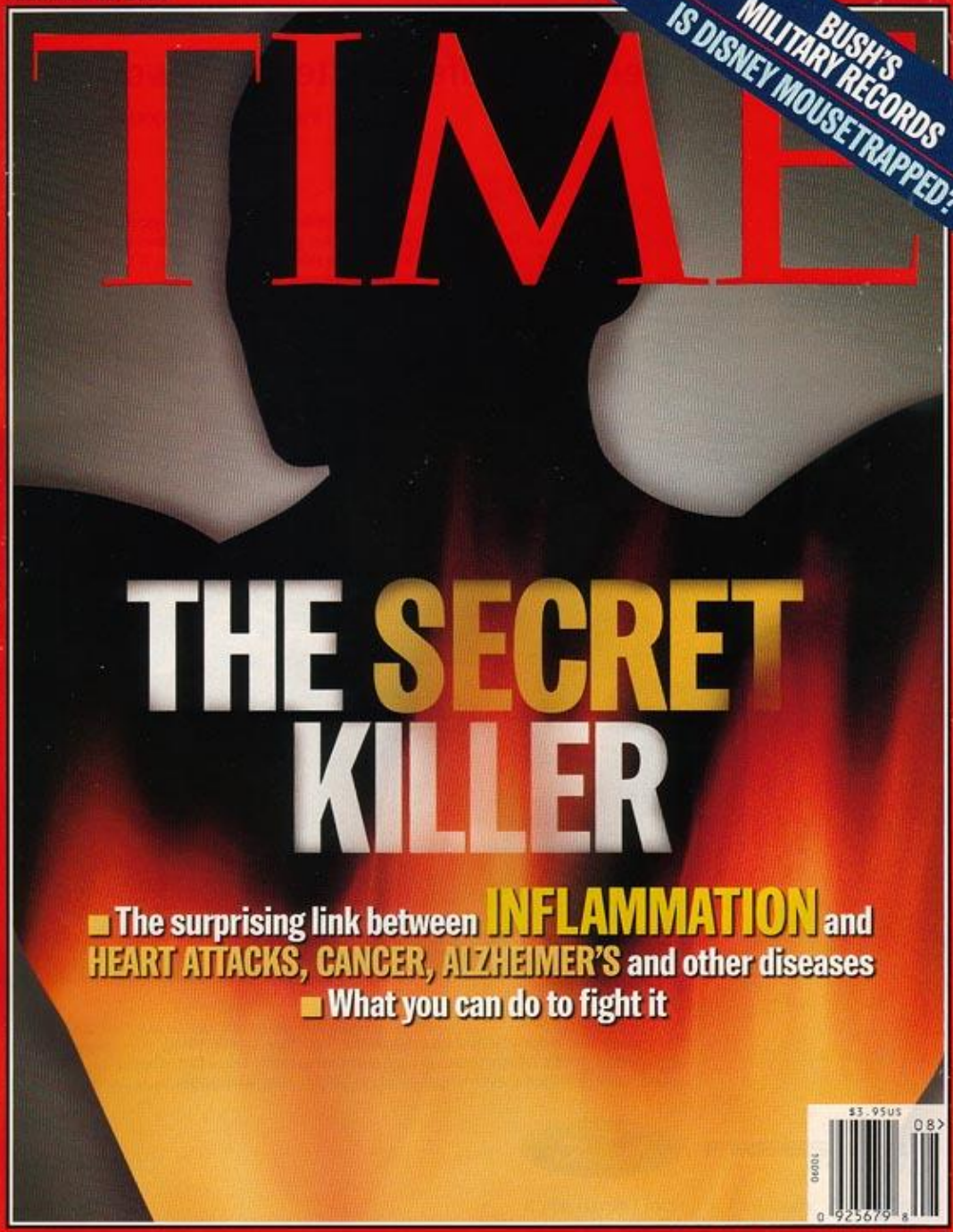
Prevention, Diet, Lifestyle and Role of Inflammation in Diabetes and Chronic Degenerative Disease Conditions

FEBRUARY 23, 2004

TIME

BUSH'S MILITARY RECORDS
IS DISNEY MOUSETRAPPED?



THE SECRET KILLER

- The surprising link between **INFLAMMATION** and **HEART ATTACKS, CANCER, ALZHEIMER'S** and other diseases
- What you can do to fight it

$3.95US
08
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www.time.com AOL Keyword: TIME

Events That Turn On Inflammatory Responses

- Microbial invasion
- Injuries
- Diet

Phases of Inflammation

Initiating Event

Pro-inflammatory Initiation Response

Cellular Destruction

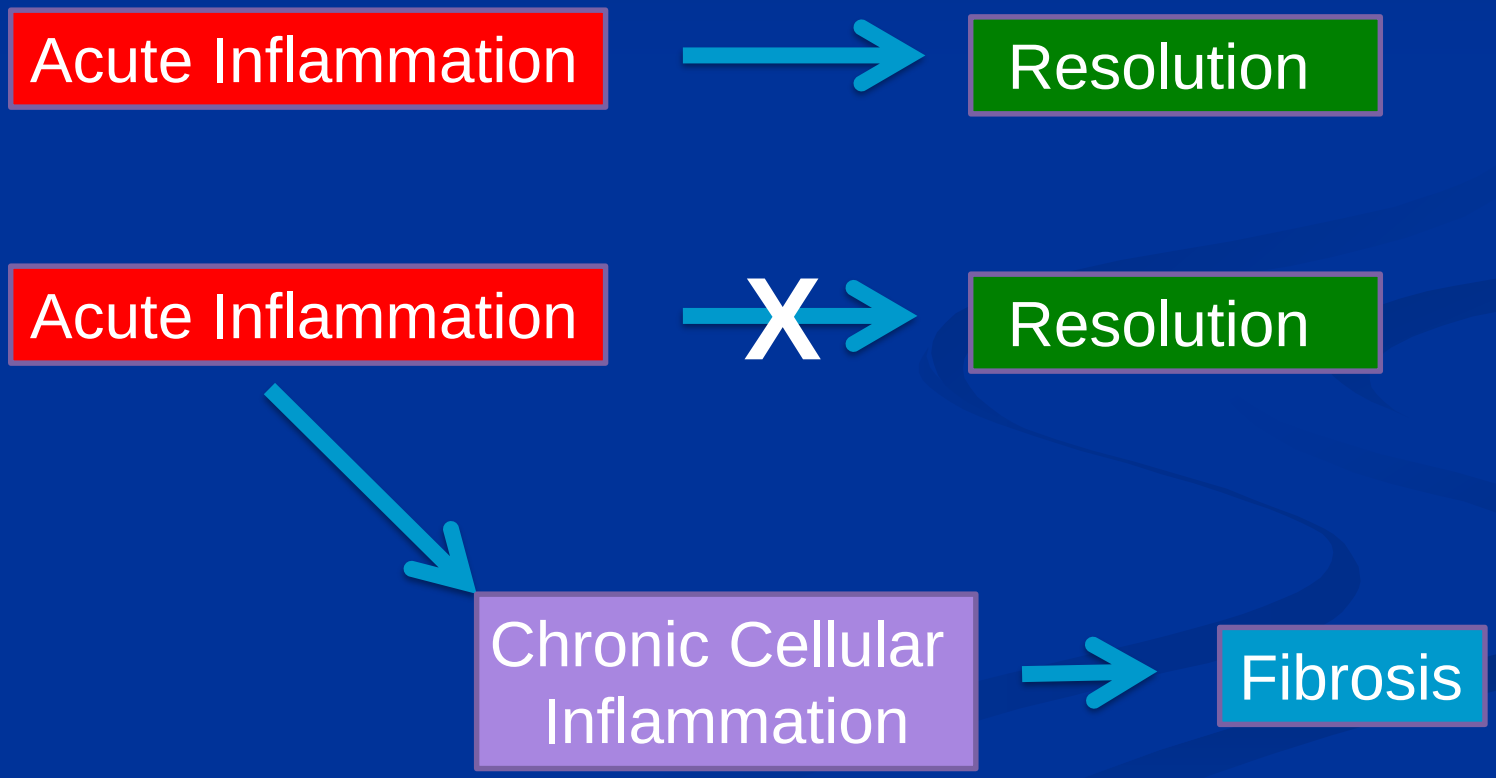
Anti-Inflammatory Resolution Response

Cellular Rejuvenation

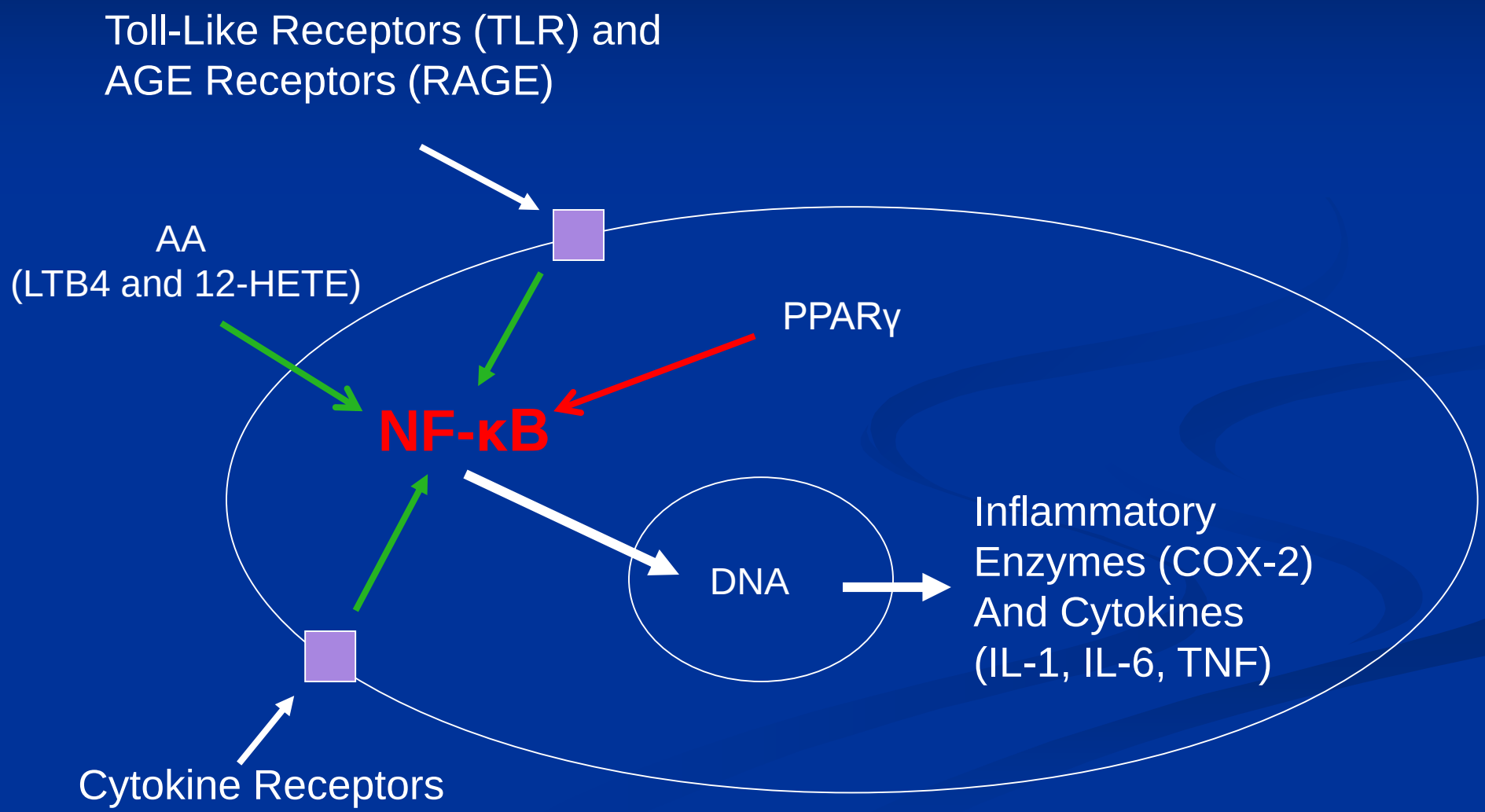
Useful Definitions

- Pro-inflammatory
  - Promotes initiation of inflammation
- Anti-inflammatory
  - Inhibits initiation of inflammation
- Pro-resolution / pro-resoleomic
  - Promotes resolution of inflammation

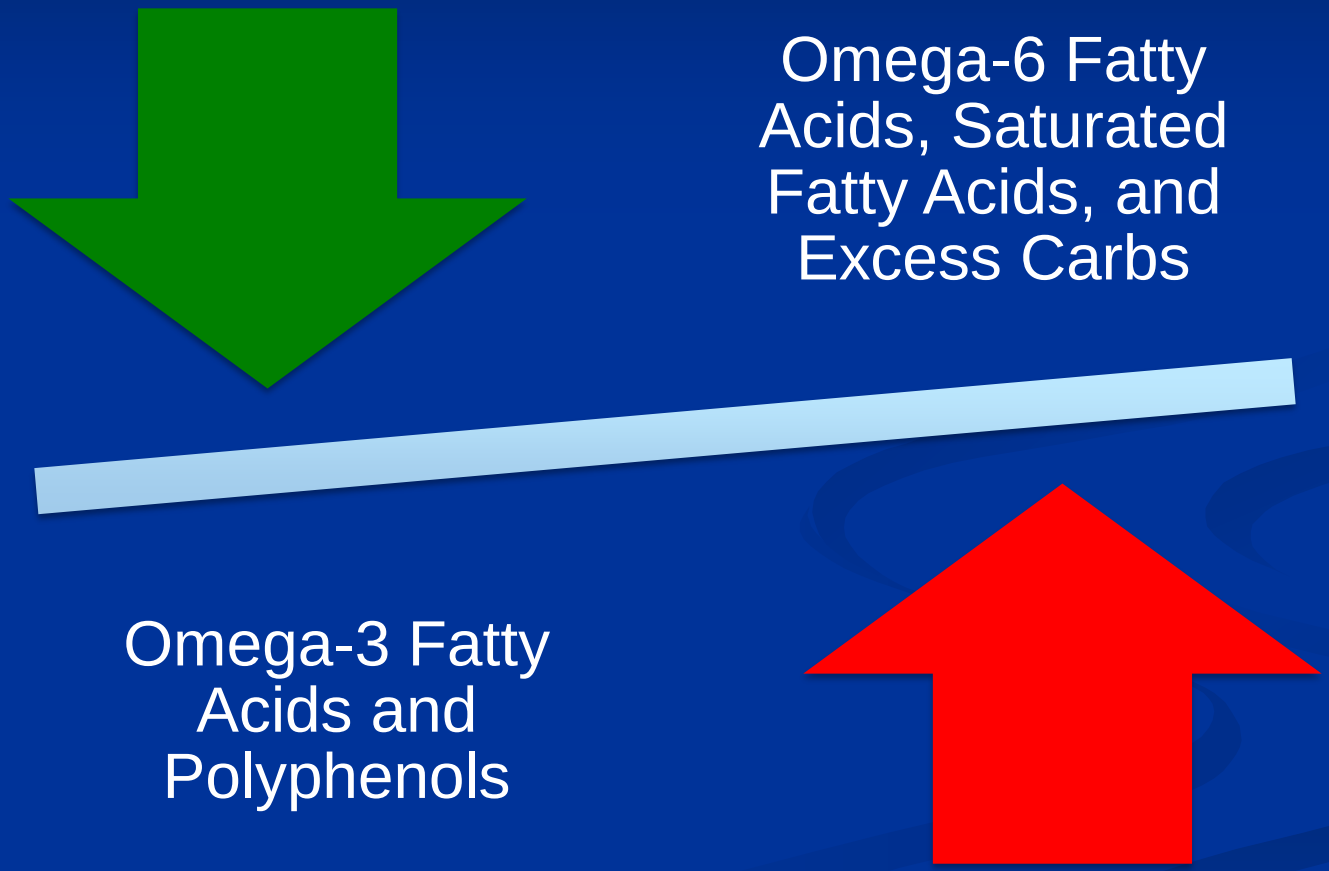
What Happens When Inflammation Is Not Resolved?



Cellular Inflammation Made Simple



Dietary Controls on NF-κB Activity



What Causes Cellular Inflammation?

The Perfect Nutritional Storm

- Increased Omega-6
- Increased Refined Carbohydrates
- Decreased Omega-3
- Decreased Polyphenols

Resolvins: Agents of Resolution

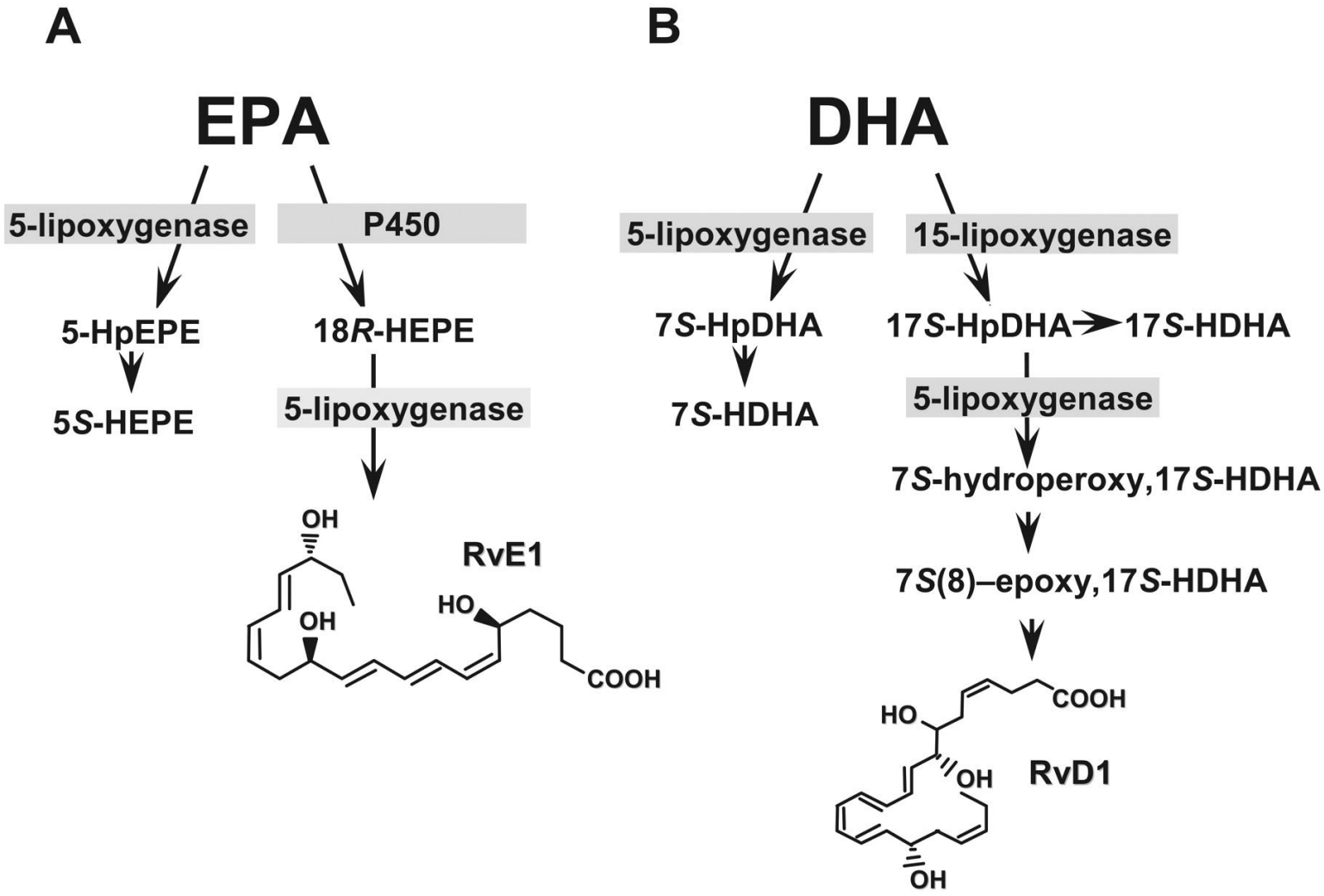


Table 1. Comparison of CHD parameters in Japanese and Americans relative to national cardiovascular mortality rates.

CHD Parameter	Japanese	Americans
Total Cholesterol (mg/dl)	218	213
LDL Cholesterol (mg/dl)	132	135
Smokers	49%	8%
AA/EPA ratio	2.6	11
CHD Mortality (per 100,000)	46.2	160

Measuring Cellular Inflammation

- AA/EPA ratio in the blood
  - Upstream marker
  - Tipping point for NF-κB activation
  - Indication of resolution potential
- C-reactive protein
  - Downstream marker
  - No indication of resolution potential
  - Less reliable

AA/EPA Ratio
Indicates Extent of Cellular Inflammation

AA/EPA	Comments
< 1	Potential increase in bleeding
1-3	Ideal for resolution of inflammation
3-6	Good
6-10	Beginning to move out of range
10-15	Cellular inflammation beginning to rise
> 15	Cellular inflammation is systemic

How Much Omega-3 Fatty Acids Do You Need?

Maintain Wellness	2.5 g/day
Treat Obesity, Diabetes, and CHD	5 g/day
Treat Chronic Pain	7.5 g/day
Treat Neurological Disease	>10 g/day

Other Auto-Immune Conditions Improved by Omega-3 Fatty Acids

Rheumatoid Arthritis

- *Royal Transactions of the Philosophical Society* (1786)
  - About 15 grams EPA and DHA per day
- Kremer. *Del Med J* 60:679 (1988)
- Kremer et al. *Arthritis and Rheum* 33:810 (1990)
  - 3.15 to 6.3 grams EPA and DHA per day
- Lee et al. *Arch Med Res* 43:356 (2012)
  - > 2.7 grams of EPA and DHA is effective

Lupus

- Westberg and Tarkowski. *Scan J Rheum* 19:137 (1990)
  - Short-term benefit
- Wright et al. *Ann Rheum Dis* 67:841 (2008)
  - 3 g EPA and DHA per day
- Halade et al. *Exp Bio Med* 238:610 (2013)
  - Strong dose-response (1 vs. 4%) in NZBxNZF mice

openheart

The importance of a balanced ω-6 to ω-3 ratio in the prevention and management of obesity

Artemis P Simopoulos,[1] James J DiNicolantonio[2]

To cite: Simopoulos AP, DiNicolantonio JJ. The importance of a balanced ω-6 to ω-3 ratio in the prevention and management of obesity. *Open Heart* 2016;**3**:e000385. doi:10.1136/openhrt-2015-000385

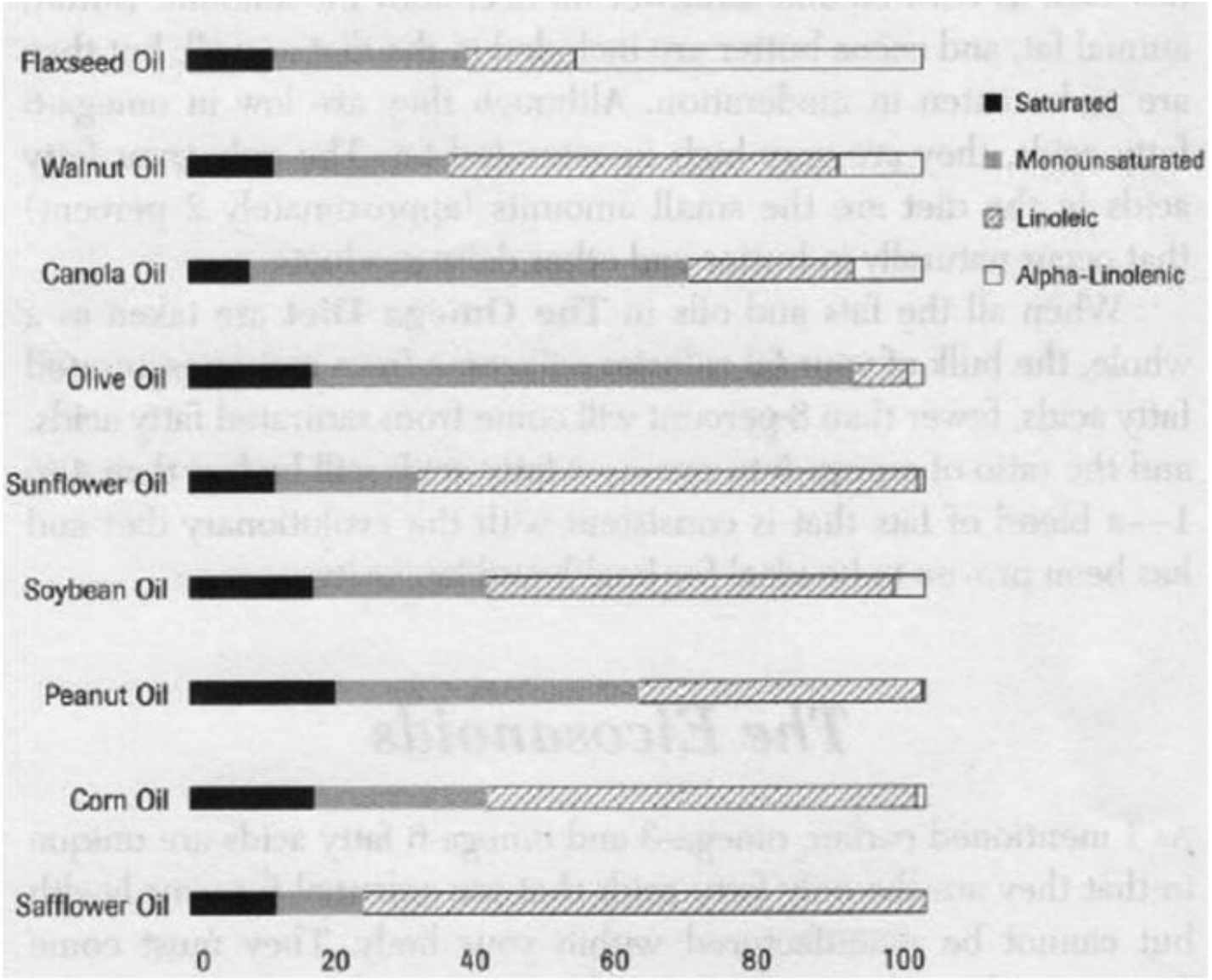
In 1980, a significant segment of the US population was already overweight or obese, but obesity standards did not exist. Therefore, the National Institutes of Health (NIH) held the Workshop on Body Weight, Health and Longevity to correct the deficiency so that data could be improved. The workshop concluded:

continues to increase its weight and similar situations exist in other countries, both developed and developing. In developing countries, obesity coexists with undernourished and malnourished individuals. So far, no country has been able to either prevent overweight and obesity or maintain weight loss of its population.

Table 2 ω6 to ω3 ratios in various populations

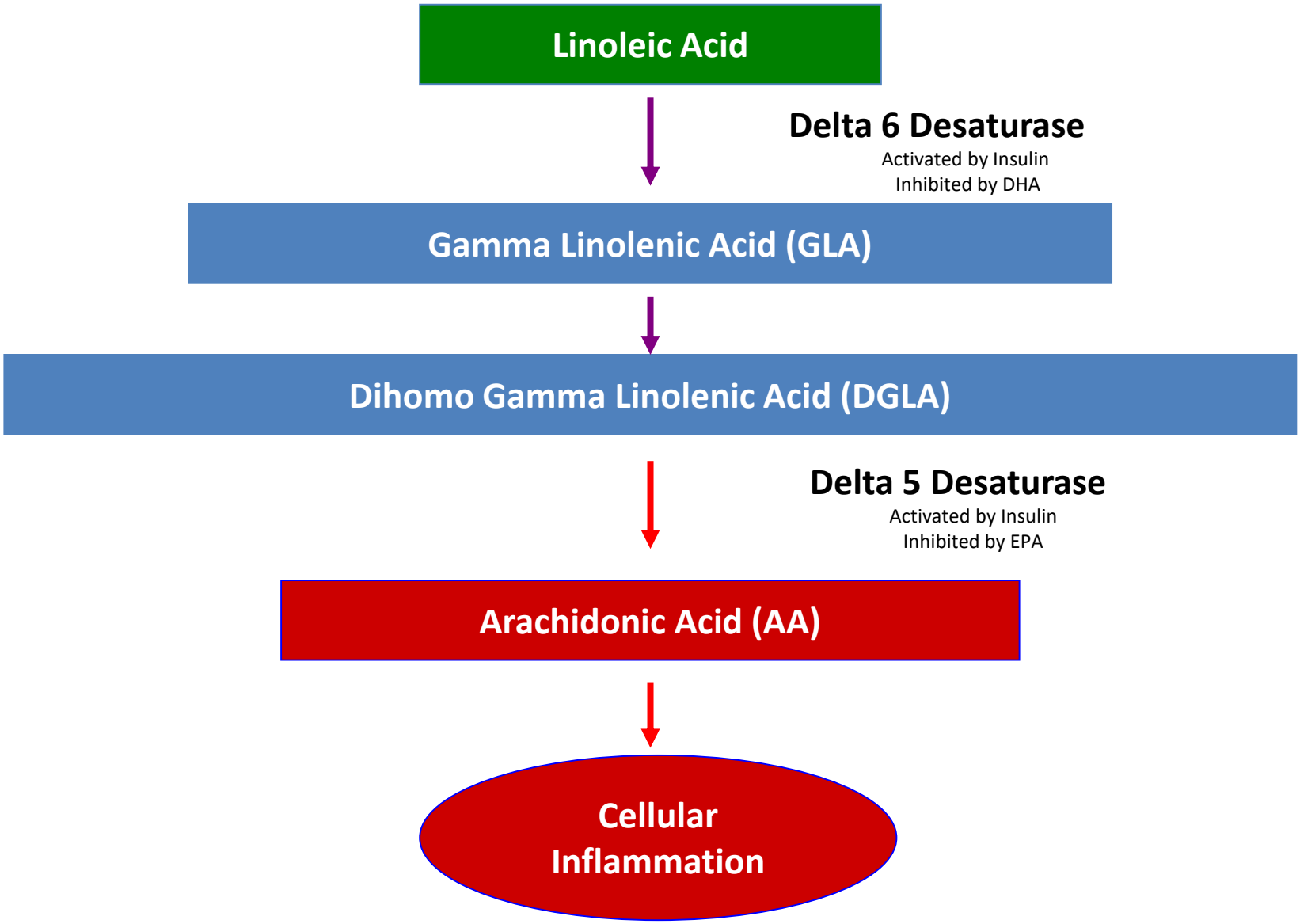
Population	ω6:ω3	Reference
Palaeolithic	0.97*,†	Eaton *et al*[37]
Greece prior to 1960	1.00–2.00	Simopoulos[14]
Current USA	16.74	Eaton *et al*[37]
UK and Northern Europe	15.00	Sanders (2000)[39]
Japan	4.00	Sugano and Hirahana (2000)[40]
India rural	5–6.1	Pella *et al* (2003)[41]
India urban	38–50	Pella *et al* (2003)[41]

*Data from Eaton *et al*.[37]
†Assuming an energy intake of 35:35 of animal:plant sources.

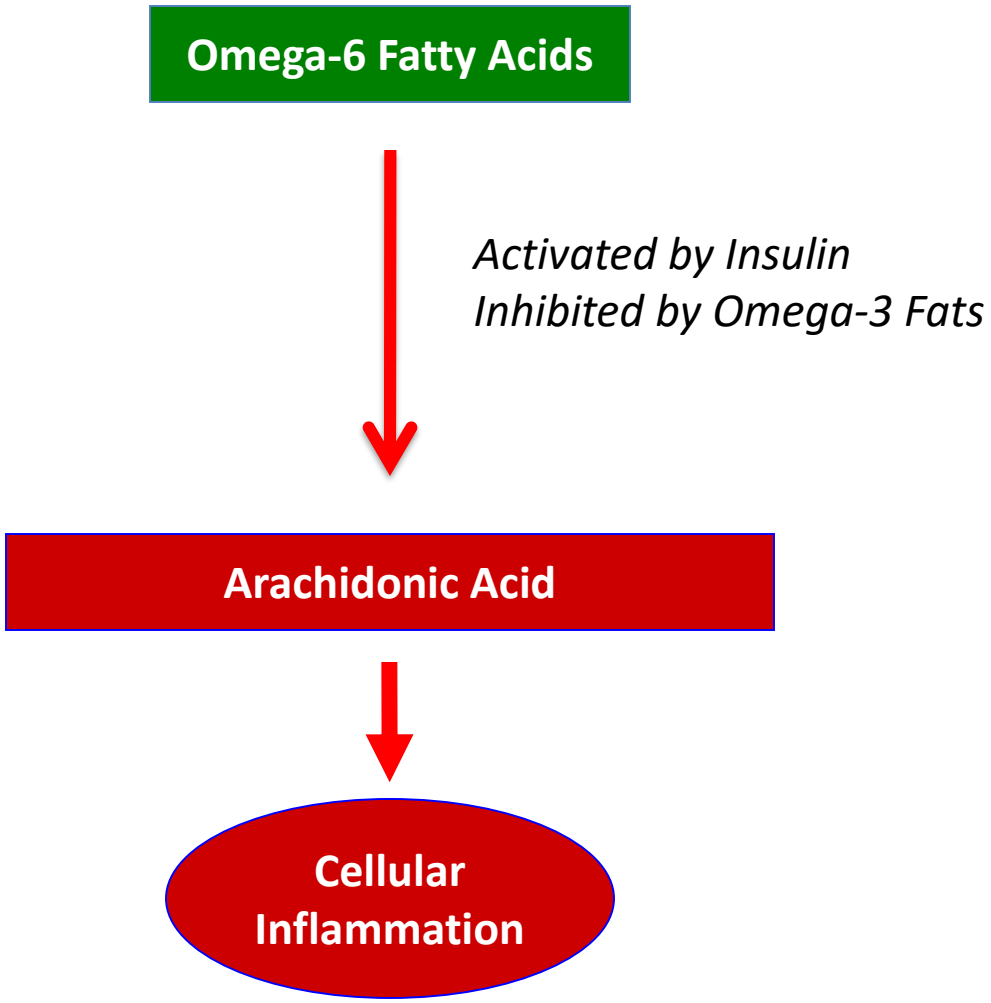


Simopoulos AP, DiNicolantonio JJ. *Open Heart* 2016;**3**:e000385. doi:10.1136/openhrt-2015-000385

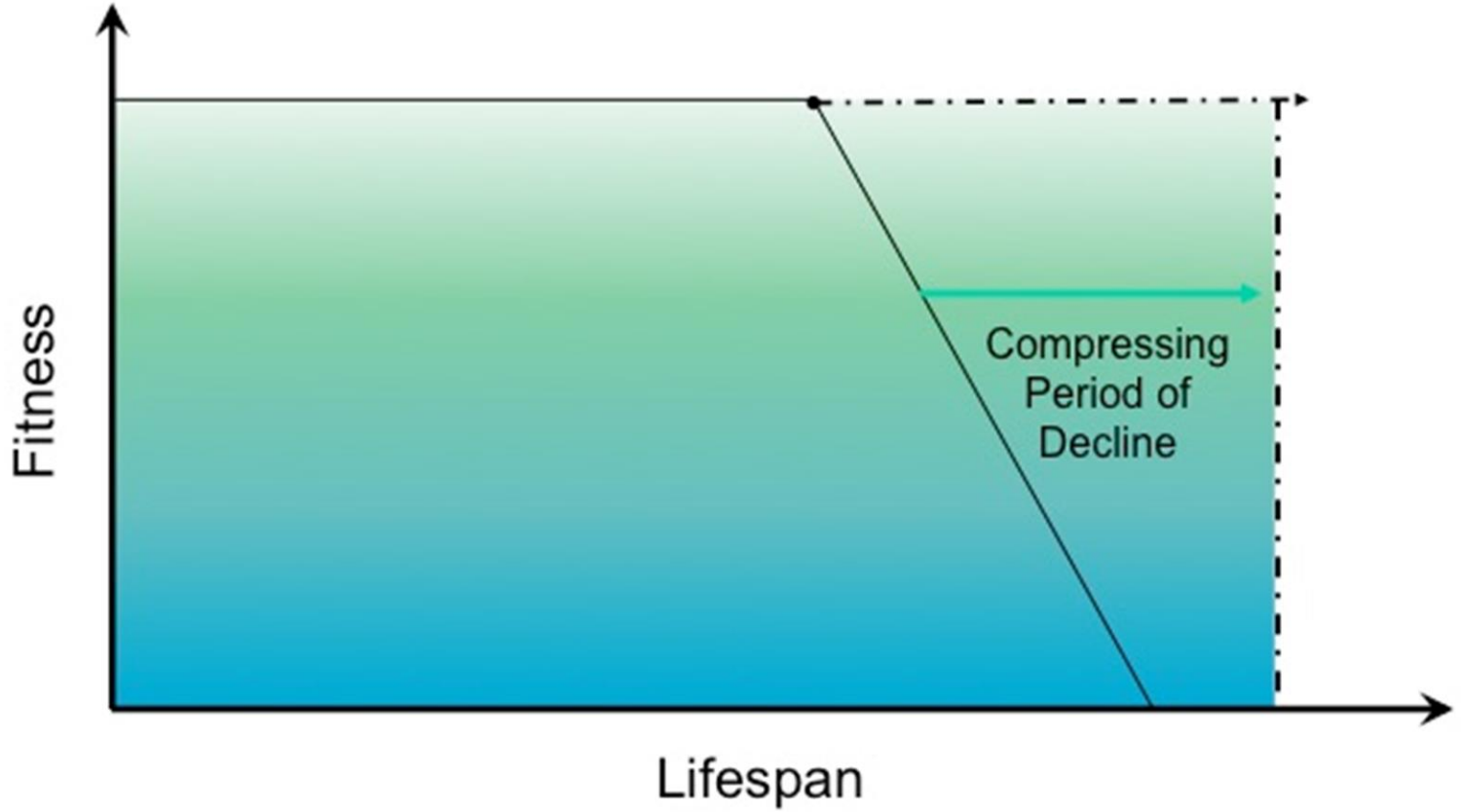
Omega-6 Fatty Acid Metabolism



Let's Make It Simple



The goal is to extend health span, compressing the period of decline, not necessarily lifespan



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Telomere Shortening:
Age 0 - 40

INFLAMMATORY DIET

1% 50% 100%

Healthy Lifespan Potential

ANTI-INFLAMMATORY DIET

Telomere Shortening:
Age 40 - 70

INFLAMMATORY DIET

1% 50% 100%

Healthy Lifespan Potential

ANTI-INFLAMMATORY DIET

Mediterranean Diet and Telomere Length: Population Based Cohort Study

BMJ 2014; 349 doi: http://dx.doi.org/10.1136/bmj.g6674

M Crous-Bou, TT Fung, J Prescott et al.

- In this large study (121,700 subjects followed since 1976), greater adherence to the Mediterranean diet was associated with longer telomeres

- The results further support the benefits of adherence to the Mediterranean diet for promoting health and longevity

PROLONGING HEALTHY LIFESPAN IS JUST ONE OF THE THE BURNING ISSUES FOR OUR PLANET

- **CLIMATE CHANGE**
  - *8-20% reduction in **cultivated surface area** by 2050*
  - *5-25% reduction in **production level** by 2050*

- **WATER MANAGEMENT**
  - ***less** water/**more needs***
  - ***70% of the world water consumption** linked with agriculture*

- **AGRICULTURAL PRODUCTIVITY**
  - *Productivity growth slowed*

- **POPULATION GROWTH**
  - *7 billion in 2011*
  - *9 billion in 2050*

- **GLOBAL FOOD PARADOXES**
  - *Malnutrition - hunger*
  - *Obesity and Diabetes epidemic*
  - *Food Waste*
  - *increase in meat consumption*

    ⇨ *pressure on grains production*

- **URBANIZATION**

  Total population in urban areas (%) in **2030**:
  - ***Africa: 55%***
  - ***Asia: 66%***
  - ***South America: 74 %***
  - ***Food deserts***

- **NEW SCIENCE AND FOOD TRENDS**
  - *Better food products formulation*
  - *More stringent legislations*
  - *Food fears*

THE GLOBAL PARADOXES ON FOOD AND NUTRITION

DIE OF HUNGER OR OBESITY?

805
MILLION

VS

1,5
BILLION

FEED PEOPLE, ANIMALS OR CARS?

WORLD GRAIN PRODUCTION AND ITS USE

47%
Human food

33%
Animal fodder

7%
Biofuels

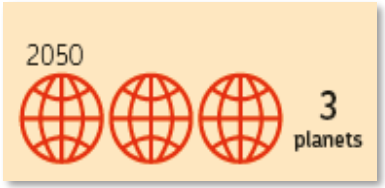
FEED WASTE OR FEED THE HUNGRY?

1,3
BILLION TONS ARE WASTED EACH YEAR:

=

4 TIMES WHAT IT WOULD TAKE TO FEED THE 868 MILLION PEOPLE WHO ARE HUNGRY

THE PLANET'S BALANCE IS NEGATIVE!



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Peter Buchwald
Christopher Fraker
Dora M.Berman
Armando J. Medez
Diego Correa
Elina Linetsky
Raj Hirani
CITP Team
cGMP Team
Regulatory / QA Team

Andrea Fabbri
Francesco Cadario
Silvia Savastio

The following individuals provided substantial input during protocol development:

- Rodolfo Alejandro, M.D. $^{\Psi}$
- David Alejandro Baidal, M.D.*
- Carlos Eduardo Blaschke, F.M.G.
- Khemraj Hirani, Ph.D., RPh, RAC, CHRC
- Della Lorraine Matheson, R.N., CDE
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- Camillo Ricordi, M.D.$^{\Psi}$
- Luis A. Roque, Quality Assurance Auditor
- Janine Sanchez, M.D. *
- Juliana Maria Vera Ortiz, M.D.

* *Principal/Co- Investigator(s)*
$^{\Psi}$ *Sponsor*

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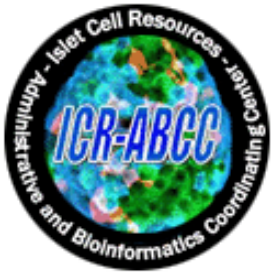

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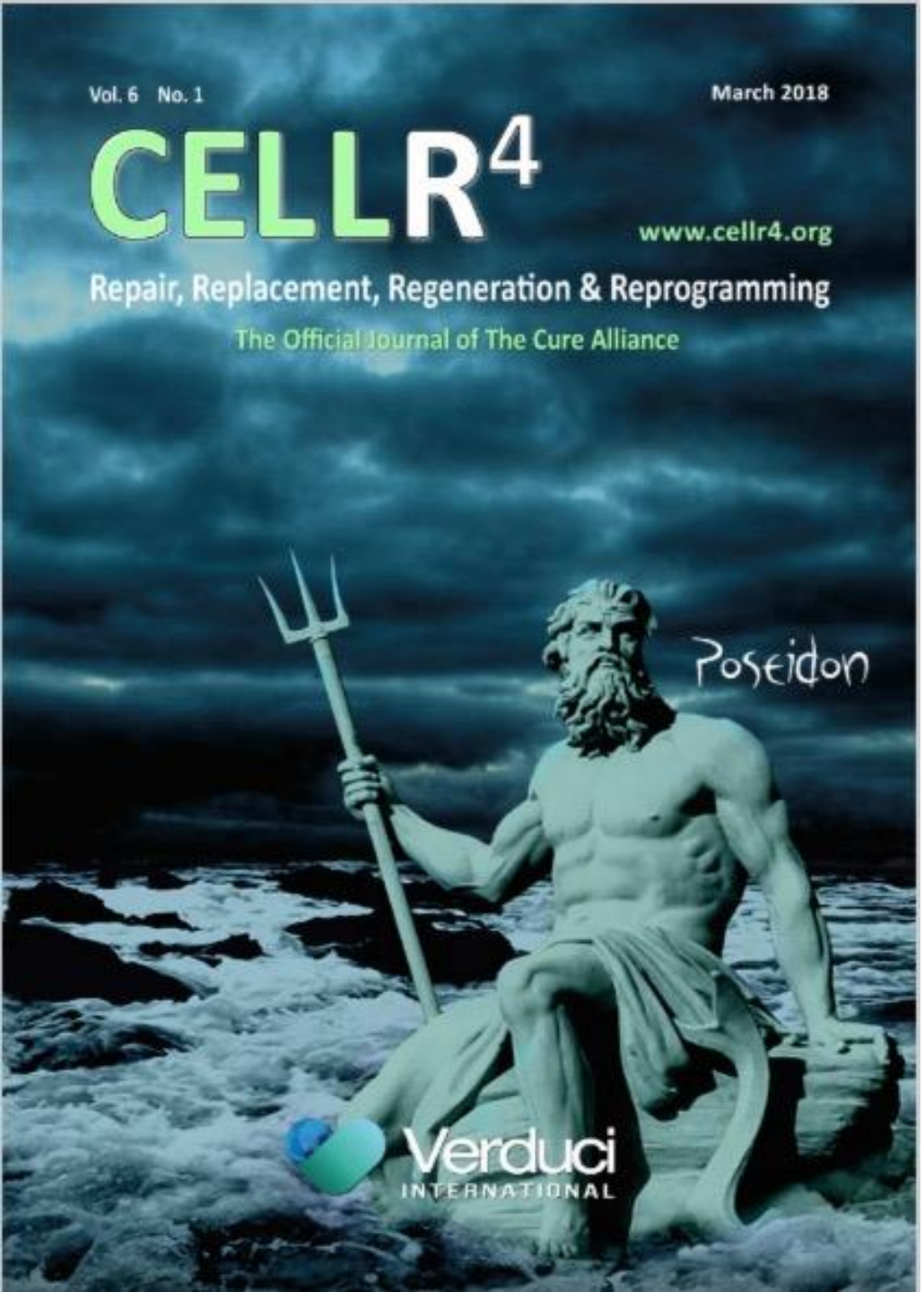

The Cure Alliance

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www.CellR4.org

An **international not-for-profit** association of scientists, physicians and committed individuals who share the **vision to promote international collaborations** while **overcoming the impediments and barriers to** the development of **cures**

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