FONDAZIONE
SIGMA-TAU

ITALIAN LECTURES 2013

DALLA PREVENZIONE ALLE TERAPIE AVANZATE:
NUOVE STRATEGIE PER AFFRONTARE LA PANDEMIA DIABETE

Camillo Ricordi, M.D.

Director, Diabetes Research Institute and Cell Transplant Center,
University of Miami
Chairman, Diabetes Research Institute Federation
President, The Cure Alliance

MILLER SCHOOL OF MEDICINE
UNIVERSITY OF MIAMI

DIABETES RESEARCH INSTITUTE
UNIVERSITY OF MIAMI

- Centro d'Eccellenza dell'Universita' di Miami
- **MISSIONE: Realizzare un Cura del diabete nalla maniera piu rapida, efficiente e sicura posibile**
- Sede del Centro Trapianti Cellulari dell' Universita' di Miami
- Prima cGMP Cell Factory per processazione di prodotti cellulari umani approvata da FDA per fornire prodotti per trials clinici sul territorio americano
- Centro di distribuzione di prodotti cellulari per ricerca finanziato dal NIH
- Certificata da FDA, FACT e AABB
- Over 140 Physicians, Scientists and Staff
- Centro della DRI Federation

L’Impatto Globale del Diabete

- **24 milioni di pazienti e $245 miliardi/anno in costi per l’assistenza sanitaria soltanto negli USA**
- **Aumento del 41% negli ultimi 5 anni**
- **350 milioni di pazienti nel mondo oggi proiettati a diventare oltre 500 milioni entro il 2020**

MINISTERO DELLA SALUTE

DIPARTIMENTO DELLA PROGRAMMAZIONE E

DELL'ORDINAMENTO DEL SISTEMA SANITARIO NAZIONALE

DIREZIONE GENERALE PER LA PROGRAMMAZIONE SANITARIA

Commissione Nazionale Diabete

Piano sulla Malattia Diabetica

2013

DIECI OBIETTIVI GENERALI

1. “Migliorare la capacità del SSN nell’erogare e monitorare i Servizi…”
2. “Prevenire o ritardare l’insorgenza della malattia attraverso l’adozione di idonei stili di vita…”
3. “Aumentare le conoscenze circa la prevenzione, la diagnosi il trattamento e l’assistenza…”
4. “Rendere omogenea l’assistenza…”
5. “Nelle donne diabetiche in gravidanza raggiungere outcome materni e del bambino equivalenti a quelli delle donne non diabetiche…”
6. “Migliorare la qualità di vita e della cura …”
7. “Organizzare e realizzare le attività di rilevazione…”
8. “Aumentare e diffondere le competenze tra gli operatori della rete assistenziale…”
9. “Promuovere l’appropriatezza nell’uso delle tecnologie”
10. “Favorire varie forme di partecipazione…”

Prevenzione, Dieta e il Ruolo dell'Infiammazione nelle Malattie Croniche Degenerative

OPEN ACCESS Freely available online PLoS MEDICINE

Combined Impact of Health Behaviours and Mortality in Men and Women: The EPIC-Norfolk Prospective Population Study

Kay-Tee Khaw[1*], Nicholas Wareham[2], Sheila Bingham[3], Ailsa Welch[1], Robert Luben[1], Nicholas Day[1]

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Accepted: October 26, 2007
Published: January 8, 2008

ABSTRACT

Background

There is overwhelming evidence that behavioural factors influence health, but their combined impact on the general population is less well documented. We aimed to quantify the potential combined impact of four health behaviours on mortality in men and women living in the general community.

Methods and Findings

We examined the prospective relationship between lifestyle and mortality in a prospective population study of 20,244 men and women aged 45–79 y with no known cardiovascular disease or cancer at baseline survey in 1993–1997, living in the general community in the United Kingdom, and followed up to 2006. Participants scored one point for each health behaviour: current non-smoking, not physically inactive, moderate alcohol intake (1–14 units a week) and plasma vitamin C >50 mmol/l indicating fruit and vegetable intake of at least five servings a day, for a total score ranging from zero to four. After an average 11 y follow-up, the age-, sex-, body mass–, and social class–adjusted relative risks (95% confidence intervals) for all-cause mortality(1,987 deaths) for men and women who had three, two, one, and zero compared to four health behaviours were respectively, 1.39 (1.21–1.60), 1.95 (1.70–-2.25), 2.52 (2.13–3.00), and 4.04 (2.95–5.54) $p < 0.001$ trend. The relationships were consistent in subgroups stratified by sex, age, body mass index, and social class, and after excluding deaths within 2 y. The trends were strongest for cardiovascular causes. The mortality risk for those with four compared to zero health behaviours was equivalent to being 14 y younger in chronological age.

Conclusions

Four health behaviours combined predict a 4-fold difference in total mortality in men and women, with an estimated impact equivalent to 14 y in chronological age.

Table 1. Health Behaviour Score: Score One Point for Each of the Health Behaviours Below for a Total Score of Zero to Four

Health Behaviour	How Scored
Smoking habit	Nonsmoker = 1
Fruit and vegetable intake	Five servings or more daily as indicated by blood vitamin C = ≥50 nmol/l = 1
Alcohol intake	One or more, but less than 14 units, a week = 1. One unit = approximately 8 g of alcohol; i.e., one glass of wine, one small glass of sherry, one single shot of spirits, or one half pint of beer
Physical activity	Not inactive = 1; i.e., if sedentary occupation, at least half an hour of leisure time activity a day; e.g., cycling, swimming; or else a nonsedentary occupation with or without leisure-time activity

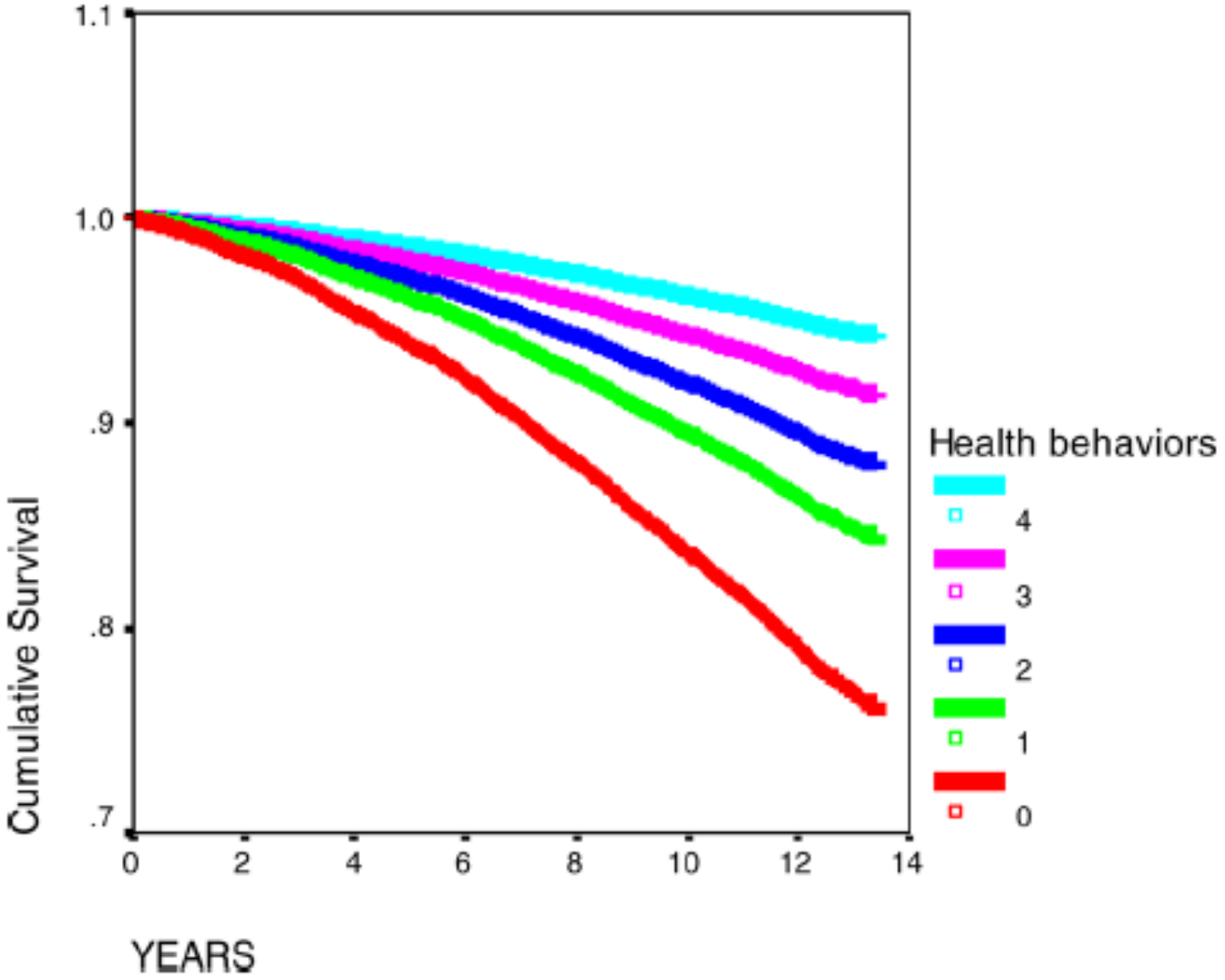

Figure 1. Survival Function According to Number of Health Behaviours in Men and Women Aged 45–79 Years without Known Cardiovascular Disease or Cancer, Adjusted for Age, Sex, Body Mass Index and Social Class, EPIC-Norfolk 1993–2006

JBC Papers in Press. Published on April 2, 2013 as Manuscript C113.464800
The latest version is at http://www.jbc.org/cgi/doi/10.1074/jbc.C113.464800

Ascorbate induces Ten-eleven translocation (Tet) methylcytosine dioxygenase-mediated generation of 5-hydroxymethylcytosine*

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From the John P. Hussman Institute for Human Genomics, Dr. John T. Macdonald Foundation Department of Human Genetics, University of Miami Miller School of Medicine, Miami, FL 33136.

Running title: *Ascorbate enhances the generation of 5-hmC*

[1]To whom correspondence should be addressed: Biomedical Research Building, Room 525 1501 NW 10th Avenue, University of Miami Miller School of Medicine, Miami, FL 33136, USA. Fax: (305) 243-2703. E-mail: gwang@med.miami.edu.

Keywords: Tet methylcytosine dioxygenase, ascorbate, 5-hydroxymethylcytosine

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Background: Tet methylcytosine dioxygenase converts 5-mC to 5-hmC in DNA.
Results: Ascorbate significantly and specifically enhances Tet-mediated generation of 5-hmC.
Conclusion: Our findings suggest that ascorbate enhances 5-hmC generation, most likely by acting as a cofactor for Tet methylcytosine dioxygenase to hydroxylate 5-mC. Thus, we have uncovered a novel role for ascorbate in modulating the epigenetic control of genome activity.

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STATE-OF-THE-ART PAPER

The Effects of Diet on Inflammation

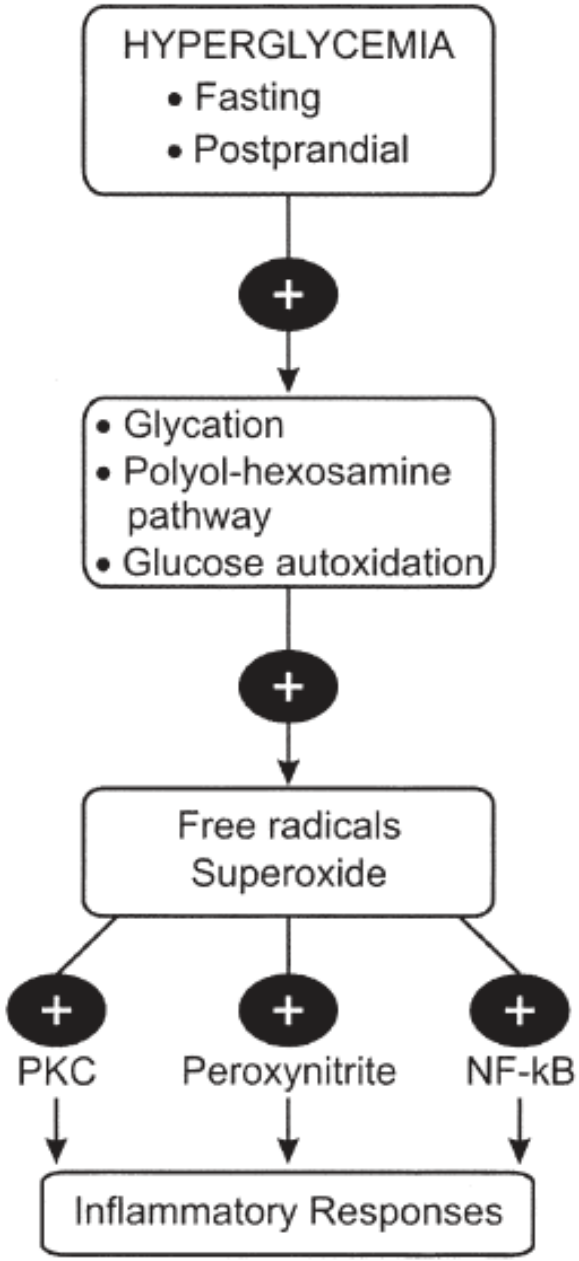
Emphasis on the Metabolic Syndrome

Dario Giugliano, MD, PhD,* Antonio Ceriello, MD,† Katherine Esposito, MD, PhD*
Naples, Italy; and Coventry, United Kingdom

Reducing the incidence of coronary heart disease with diet is possible. The main dietary strategies include adequate omega-3 fatty acids intake, reduction of saturated and trans-fats, and consumption of a diet high in fruits, vegetables, nuts, and whole grains and low in refined grains. Each of these strategies may be associated with lower generation of inflammation. This review examines the epidemiologic and clinical evidence concerning diet and inflammation. Dietary patterns high in refined starches, sugar, and saturated and trans-fatty acids, poor in natural antioxidants and fiber from fruits, vegetables, and whole grains, and poor in omega-3 fatty acids may cause an activation of the innate immune system, most likely by an excessive production of proinflammatory cytokines associated with a reduced production of anti-inflammatory cytokines. The whole diet approach seems particularly promising to reduce the inflammation associated with the metabolic syndrome. The choice of healthy sources of carbohydrate, fat, and protein, associated with regular physical activity and avoidance of smoking, is critical to fighting the war against chronic disease. Western dietary patterns warm up inflammation, while prudent dietary patterns cool it down. (J Am Coll Cardiol 2006;48: 677–85) © 2006 by the American College of Cardiology Foundation

CONCLUSIONS

Dietary patterns high in refined starches, sugar, and saturated and trans-fatty acids and poor in natural antioxidants and fiber from fruits, vegetables, and whole grains may cause an activation of the innate immune system, most likely by an excessive production of proinflammatory cytokines associated with a reduced production of anti-inflammatory cytokines. This imbalance may favor the generation of a proinflammatory milieu, which in turn produces endothelial dysfunction at the vascular level, and ultimately predisposes susceptible people to increased incidence of the metabolic syndrome and CHD. All the dietary strategies hitherto demonstrated to reduce CHD risk are associated with reduced inflammation, which may explain, at least in part, their benefit at the vascular level (Fig. 4). An inflammatory state may also prevent a favorable responsiveness of serum lipids to a reduced-fat low-cholesterol diet (104); if confirmed, these findings might generate the gloomy perspective in which the inflammatory state triggered by "Western" dietary patterns may in turn impair the lipid-lowering effect of low-fat diets.



A high blood glucose level is harmful

High blood glucose →

Oxidative stress
Glycated proteins
High insulin levels

↓

☹ Blood lipids
☹ Blood clotting
☹ Blood pressure
☹ Insulin failure

←

Diabetes
Heart disease
Weight gain
Cancer

Jennie Brand-Miller
Professor of Human Nutrition
University of Sydney, Australia

Review Article

Anti-Inflammatory Nutrition as a Pharmacological Approach to Treat Obesity

Barry Sears[1] and Camillo Ricordi[2]

Hindawi Publishing Corporation
Journal of Obesity
Volume 2011, Article ID 431985, 14 pages
doi:10.1155/2011/431985

European Review for Medical and Pharmacological Sciences

Role of fatty acids and polyphenols in inflammatory gene transcription and their impact on obesity, metabolic syndrome and diabetes

B. SEARS, C. RICORDI*

Inflammation Research Foundation, Marblehead, MA (USA) and
*Diabetes Research Institute, University of Miami, Miami, FL (USA)

Cosa Attiva la Risposta Infiammatoria

- **Invasione Microbica**
- **Ferite / Traumi**
- **Dieta**

Cos'e' l'Infiammazione Silente?

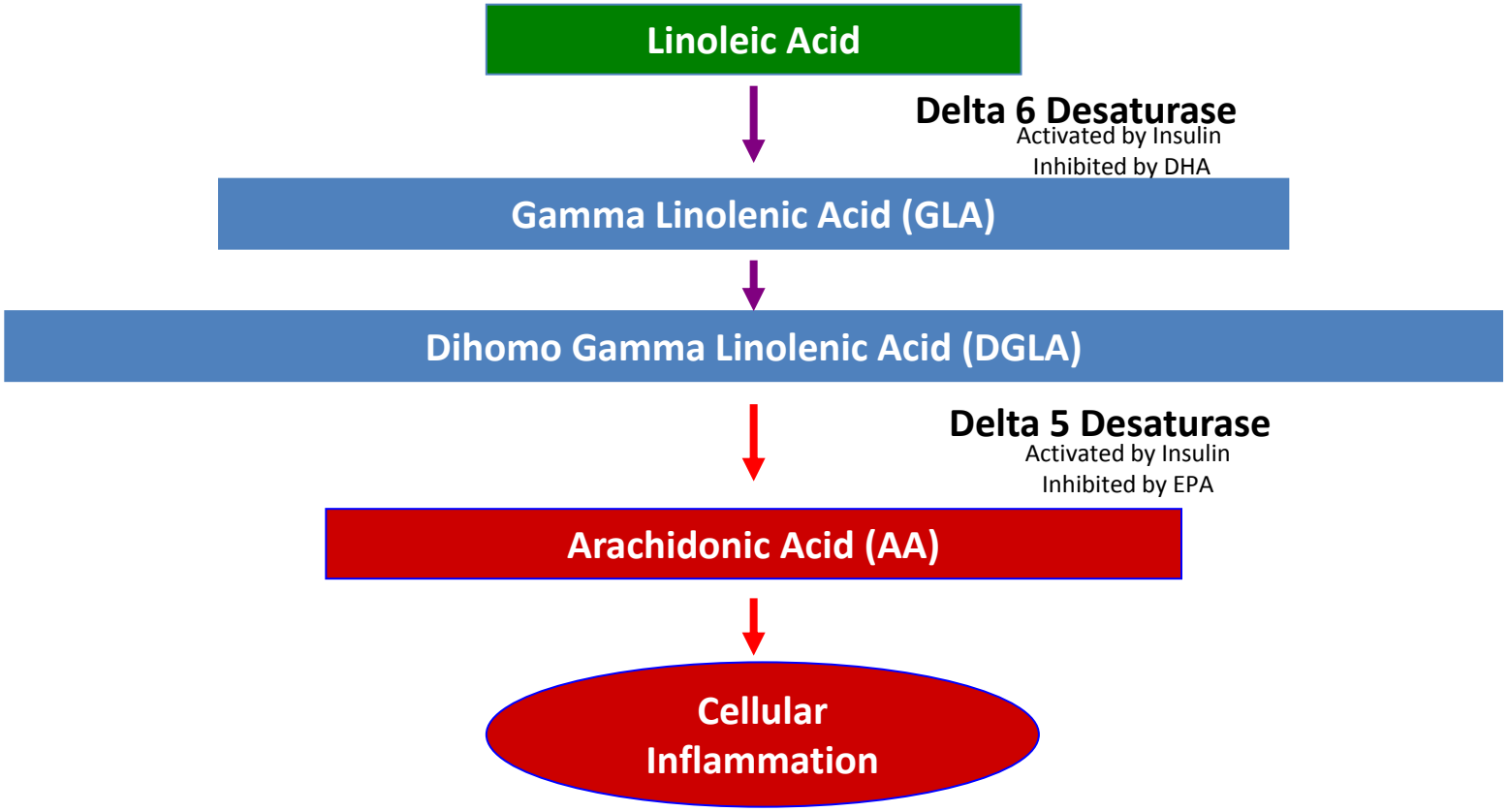
- **Infiammazione subliminale sotto il livello soglia del dolore**
- **Indotta dalla dieta**

Cosa Causa l’Infiammazione Silente?

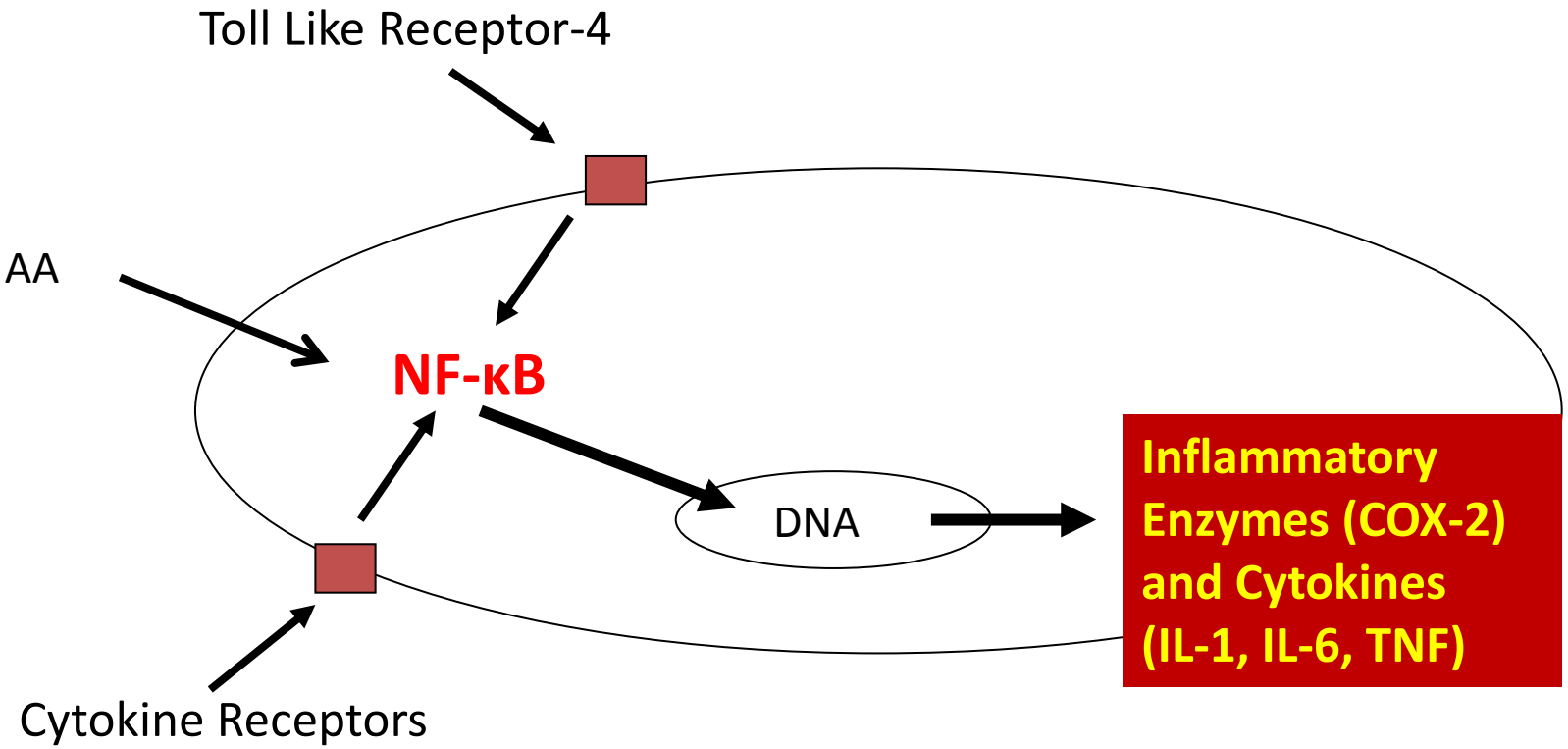
- Increased consumption of refined vegetable oils rich in omega-6 fatty acids
- Increased consumption of refined carbohydrates
- Decreased consumption of long-chain omega-3 fatty acids
- Decreased consumption of polyphenols

The first two factors increase the production of AA, thereby increasing pro-inflammatory responses, whereas the last two factors are important in generating anti-inflammatory responses by their interaction with specialized gene transcription factors.

Metabolismo degli Acidi Grassi Omega-6



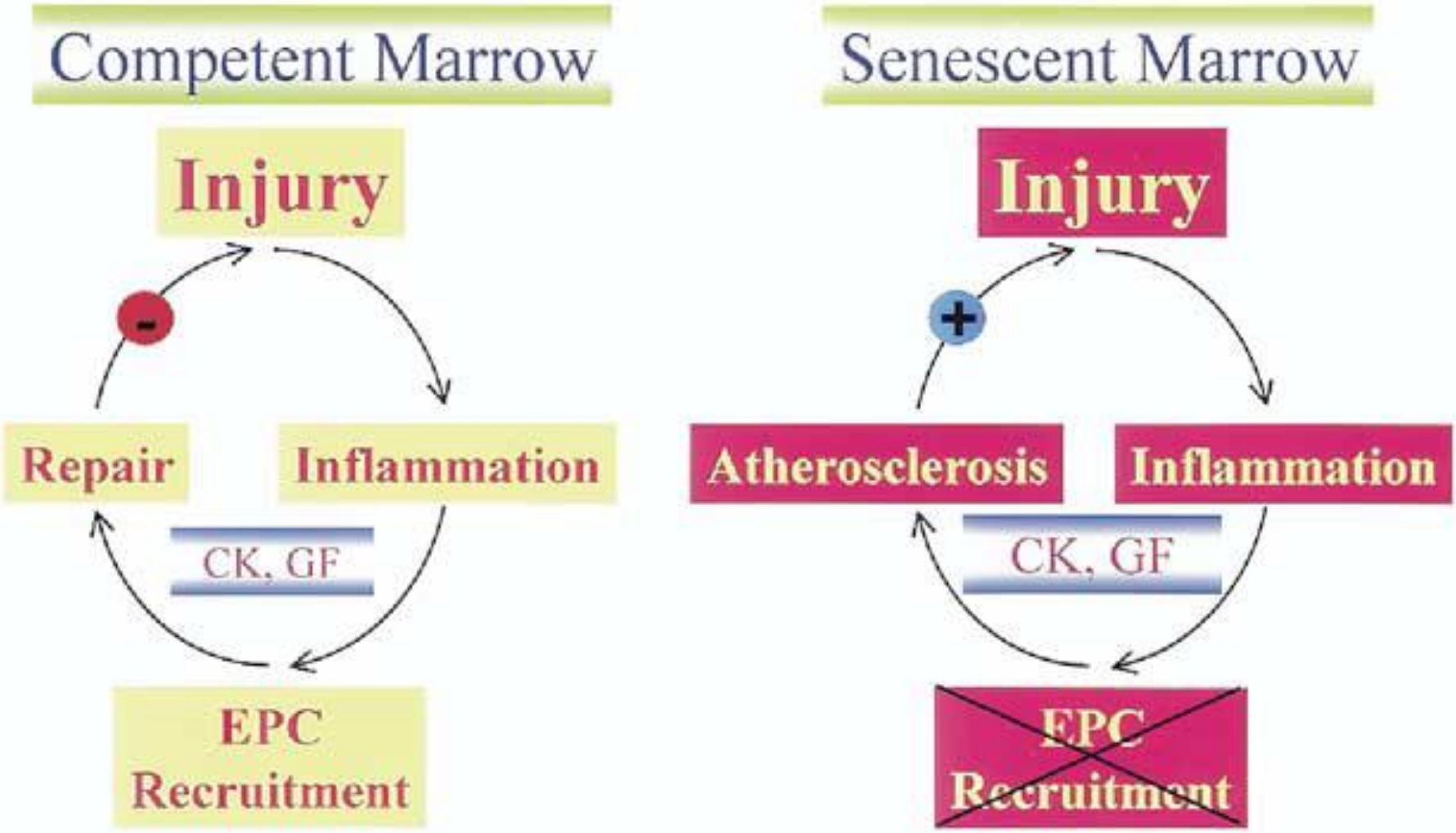
Infiammazione Cellulare Indotta dalla Dieta (Semplificata)



La Tempesta Perfetta (Nutrizionale) Sta Arrivando in Italia Attraverso i Suoi Bambini

Ages	<20	21-40	41-60	>60
AA/EPA Ratio	18.1	11.2	9.8	10.3

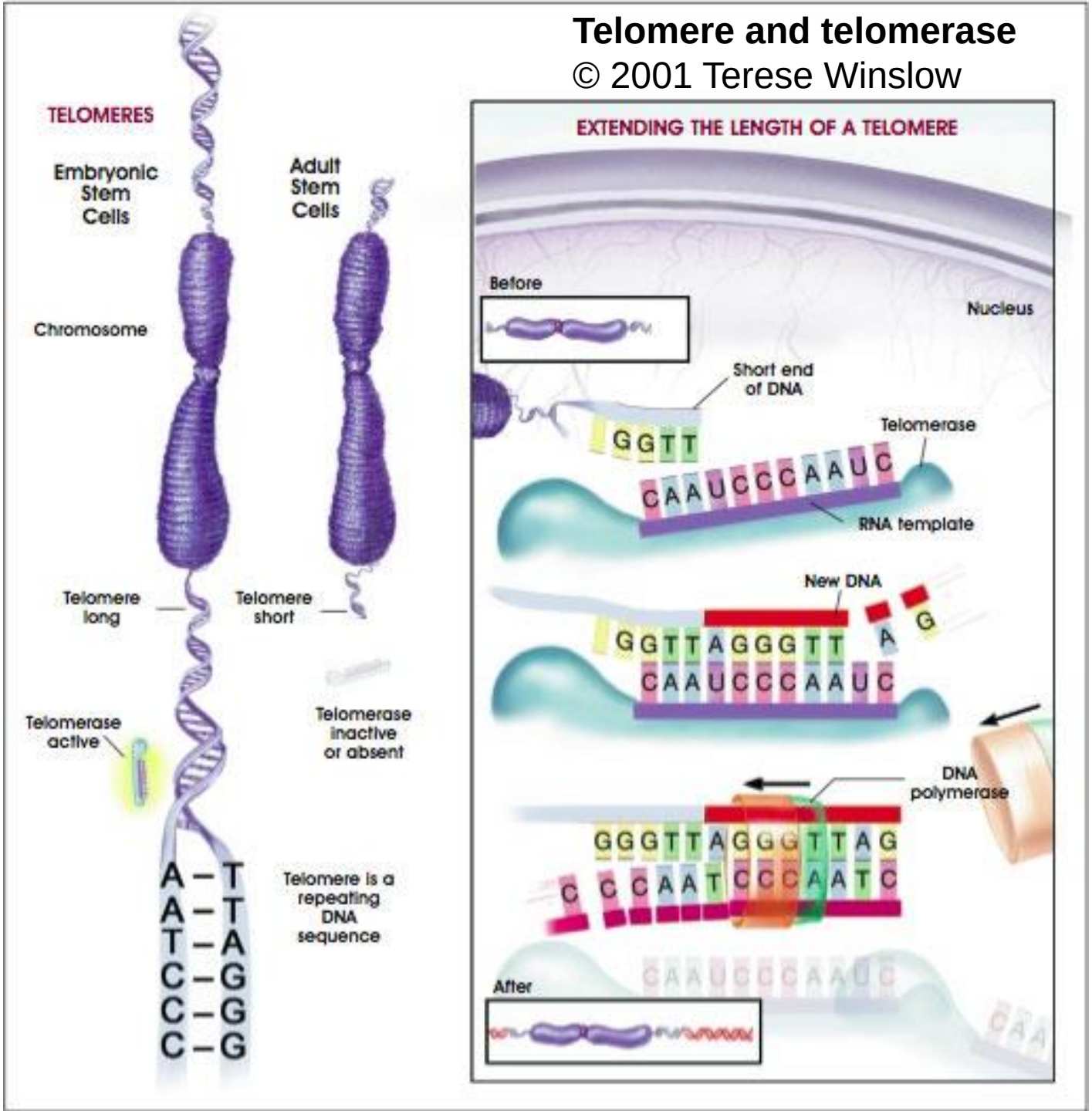
Rizzo et al. Lipids in Health and Disease 9:7 (2010)



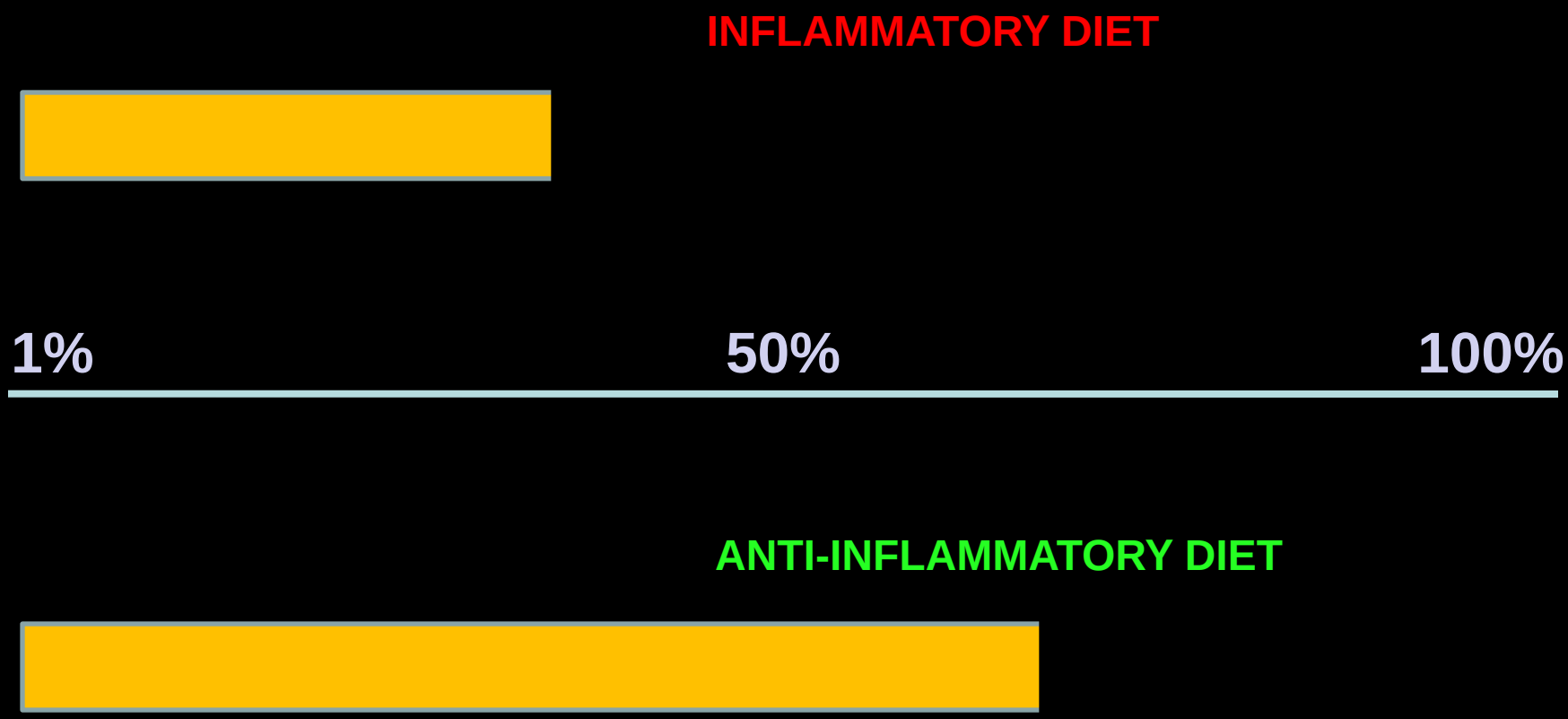
Senescence/reduction/absence of EPCs results in increase of inflammatory factors, with persistence of arterial lesions and promotion of arterial damage (worsening of atherosclerosis).

CK cytokines and other inflammation agonists; GF growth factors

Telomere and telomerase



Telomere Shortening:
Age 0 to 40



Telomere Shortening:
Age 40 - 70

INFLAMMATORY DIET

1% 50% 100%

ANTI-INFLAMMATORY DIET

MORIRE PER FAME O PER OBESITÀ?

OGGI NEL MONDO

UN TERZO
DELLA POPOLAZIONE
HA PROBLEMI DI NUTRIZIONE

PERSONE DENUTRITE
868 milioni

PERSONE OBESE O IN SOVRAPPESO
1,5 miliardi

PER OGNI PERSONA DENUTRITA CI SONO DUE PERSONE OBESE O IN SOVRAPPESO

OGGI DECESSI NEL MONDO OGNI ANNO PER

CARENZA DI CIBO
36 milioni

ECCESSO DI CIBO
29 milioni

I PRIMI 10 FATTORI DI RISCHIO MORTALITÀ

Il Global Burden of Disease elaborato per l'Organizzazione Mondiale della Sanità e diffuso nel 2012 ha l'obiettivo di capire come sono cambiate le malattie negli ultimi decenni.
Per la prima volta nella storia il rischio di mortalità per patologie legate alla cattiva alimentazione ha superato quello relativo a malattie determinate da insufficiente apporto calorico.

	2010	Var.% vs 1990
1	Ipertensione	+27%
2	Tabacco	+3%
3	Abuso di alcol	+28%
4	Inquinamento indoor da riscaldamento	-37%
5	Dieta povera di frutta	+29%
6	Elevato indice di massa corporea	+82%
7	Ipergliceмia	+58%
8	Sottonutrizione infantile	-61%
9	Inquinamento da polveri sottili	-7%
10	Inattività fisica	Assente nel 1990

FOOD FOR HEALTH

PARADOSSI ALIMENTARI E CORRETTI STILI DI VITA IN UNA SOCIETÀ CHE CAMBIA

L'ALIMENTAZIONE SANA UN IMPEGNO CORALE

«Difficilmente accettiamo che il nostro stile di vita abbia delle ricadute sulla nostra salute e l'obesità è considerata dalla società un problema estetico più che sanitario. Molti passi ancora devono essere fatti per migliorare la consapevolezza in campo nutrizionale e per innescare un riequilibrio nelle dinamiche cibo-salute».

DI CAMILLO RICORDI

GUIDO BARILLA
PAOLA TESTORI COGGI
GABRIELE RICCARDI
FRANCO SASSI
CAMILLO RICORDI
ELLEN GUSTAFSON
BCFN YES!
MICHELLE OBAMA
JEAN-MICHEL BORYS
ISTITUTO AUXOLOGICO ITALIANO
ALBERTO E GIOVANNI SANTINI
MASSIMO MONTANARI
DANIELLE NIERENBERG


Creare una rete nazionale di ricerca
Mobilitare l'opinione pubblica
Diffondere buone abitudini (in modo univoco)
Esplorare il legame tra cibo e salute

OBESITÀ: IMPATTI SULLA SALUTE PUBBLICA E SULLA SOCIETÀ

LE CAUSE

Ampia offerta di alimenti a prezzi contenuti che hanno un elevato apporto energetico e un basso livello nutrizionale

Progressivo calo dei prezzi del cibo e delle bevande a fronte di un aumento del reddito pro capite e di una più estesa capacità di acquisto a livello mondiale

Condizioni di lavoro: crescente terziarizzazione che causa lunghe giornate lavorative e alta sedentarietà

Alta urbanizzazione e lunghi e frequenti spostamenti in auto

Stili di vita: minore tempo dedicato alla preparazione e al consumo dei pasti, scarsa attività motoria, basso livello di educazione alimentare

LE DIMENSIONI DEL FENOMENO

OGGI

in sovrappeso **1 miliardo**

obesi **500 milioni**

2015

in sovrappeso **1,8 miliardi**

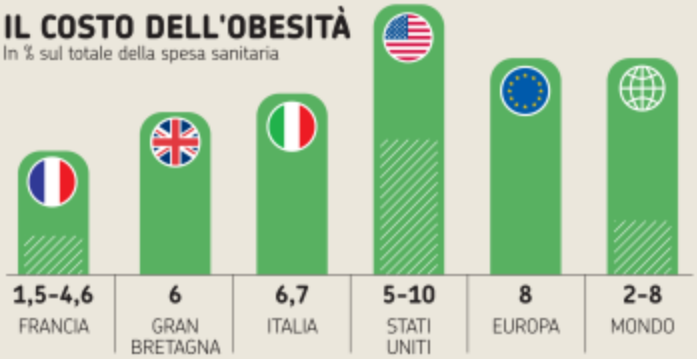
obesi **700 milioni**

All'obesità sono associati:

- Una più alta mortalità per l'insorgenza di patologie croniche
- Più alti impatti ambientali ed emissioni di gas serra
- Impatti negativi in termini di rendimenti scolastici e produttività lavorativa

IL COSTO DELL'OBESITÀ

In % sul totale della spesa sanitaria



Mediamente, la spesa sanitaria sostenuta da una persona obesa è **25%** **più alta** di quella di un soggetto normopeso

LE RACCOMANDAZIONI

4. Insegnare abitudini sane fin dall'infanzia facilitando l'accesso a strutture e spazi adeguati

1. Informare e mobilitare l'opinione pubblica affinché sia più consapevole e reattiva sulle conseguenze economiche, sociali e ambientali dell'obesità

5. Utilizzare in modo equilibrato la leva del prezzo, valutando con attenzione "pro" e "contro" dell'introduzione di disincentivi fiscali come le tasse sul "junk food"

2. Programmare un impegno congiunto di governi e settore privato, attivare piani integrati di medio-lungo periodo

6. Incoraggiare l'impegno dell'industria alimentare e della distribuzione in iniziative di salute pubblica promosse e guidate dai governi

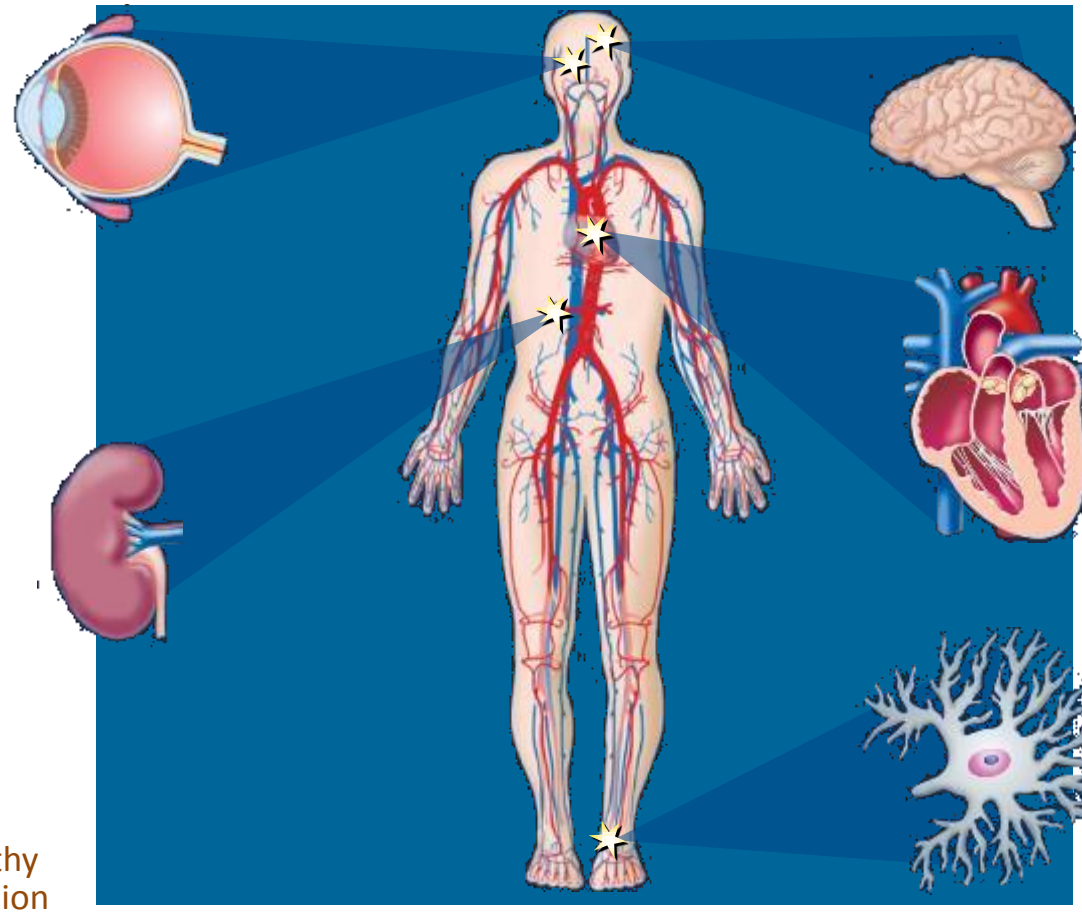
3. Diffondere la cultura della prevenzione affinché i comportamenti salutari diventino sempre più una scelta consapevole fin dalla gestazione

7. Dare battaglia all'ambiente obesogenico, combattere i fattori che inducono a stili di vita e scelte alimentari scorretti e rendono difficile compiere scelte salutari

Fonti: WHO, 2012; OCSE, *Health at a glance 2011*; *The economic burden of obesity worldwide: a systematic review of the direct costs of obesity*. Withrow D, Alter DA. 2011; Scuola Superiore Sant'Anna, 2009; *Cost obesity in France*. Emery, Dinet, Lafuma, Sermet, Khedmoud, Fagnoni. 2007; *Tackling obesities: future choices*, project report. Foresight, 2010; *Direct medical cost of overweight and obesity in the USA: a quantitative systemic review*. Tsai, Williamson, Glick. 2010

The Burden of Type 2 Diabetes: Micro- and Macrovascular Complications

NIDDK. Bethesda, MD: U.S. Department of Health and Human Services, National Institute of Health, 2005.
U.S. Renal Data System Annual Data Report 2009.



Diabetic Retinopathy

Leading cause of blindness in adults

Diabetic Nephropathy

Major cause of kidney failure

Estimated cost of diabetic nephropathy in the US is $13 billion

Stroke

CV Disease & Stroke account for ~65% of deaths in T2D patients

Cardiovascular Disease

Diabetic Neuropathy

Major cause of lower extremity amputations

Treatment Gaps in Type 2 Diabetes

- Despite the availability of 12 classes of anti-diabetic therapies, medical needs of people with T2D remain:
  - Progressive loss of beta cell function
  - Existing treatments do not sufficiently halt the progression of microvascular complications (blindness, amputations, end-stage renal disease)
  - To date, neither a specific therapy or glucose lowering per se has been shown definitively to confer cardiovascular benefit

Rationale for Adult Stem Cells in Type 2 Diabetes

- Emerging new components of diabetes pathophysiology
  - T2D as an inflammatory disease
- Concordance of MSC attributes with these emerging components of underlying pathophysiology
  - Anti-inflammatory effects
  - Immunomodulation

MSC = *Medicinal Signaling Cell*

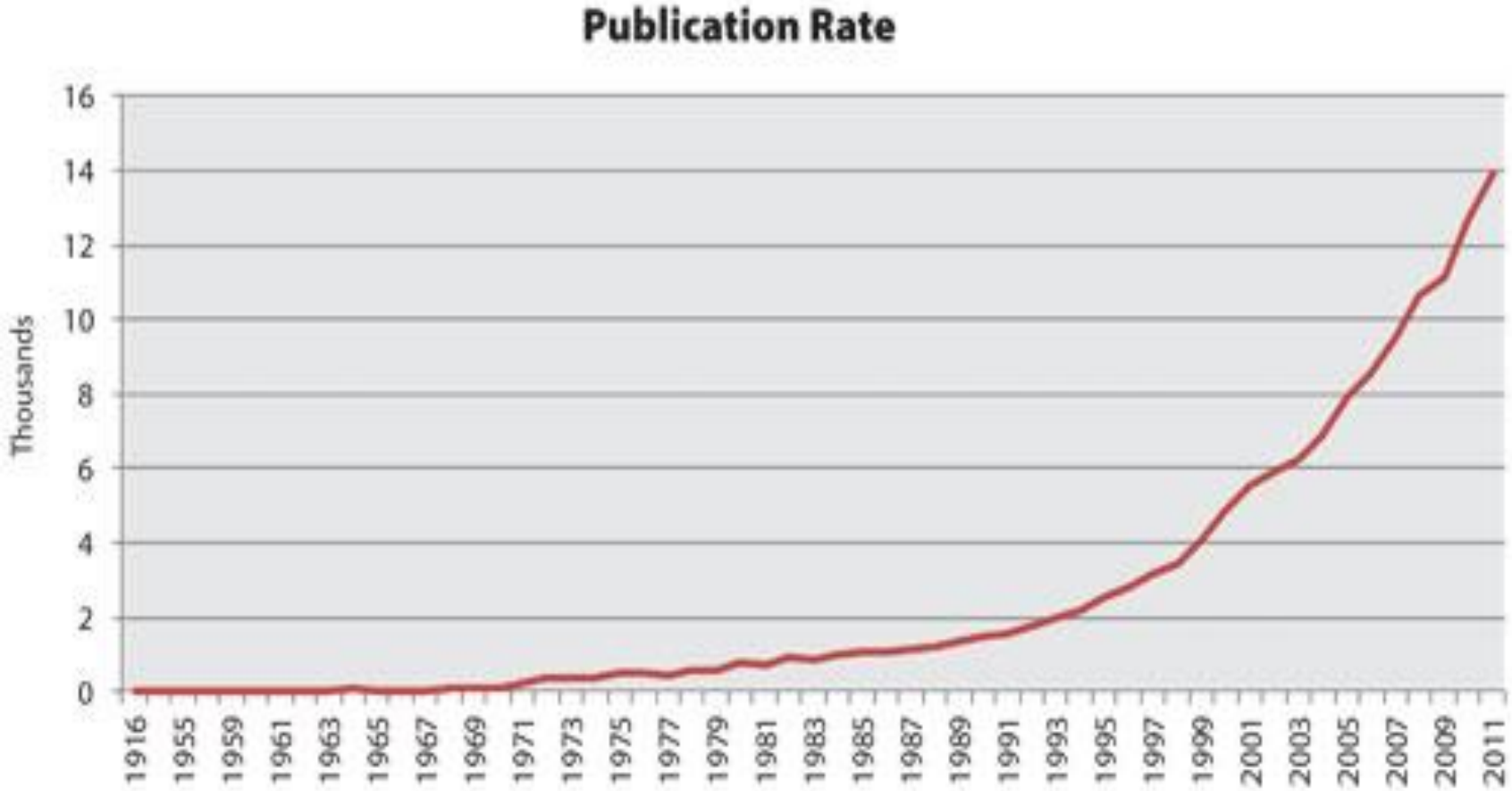
(the injury-specific DRUG STORE)

Arnold Caplan, Ph.D.

DRUGS ≠ REGENERATION:

- **Insulin** is used to treat diabetes but does not cure the disease. Need to regenerate islet cells or a pancreas.
- **Nitroglycerin** is used to treat cardiac angina (since 1879 for symptomatic relief) but does not cure the problem. Need to regenerate damaged or blocked cardiac tissue.
- No single drug causes regeneration of cardiac or other tissue, thus, use STEM CELLS.

PUBLICATIONS with *Stem Cells* in the Title or Abstract:



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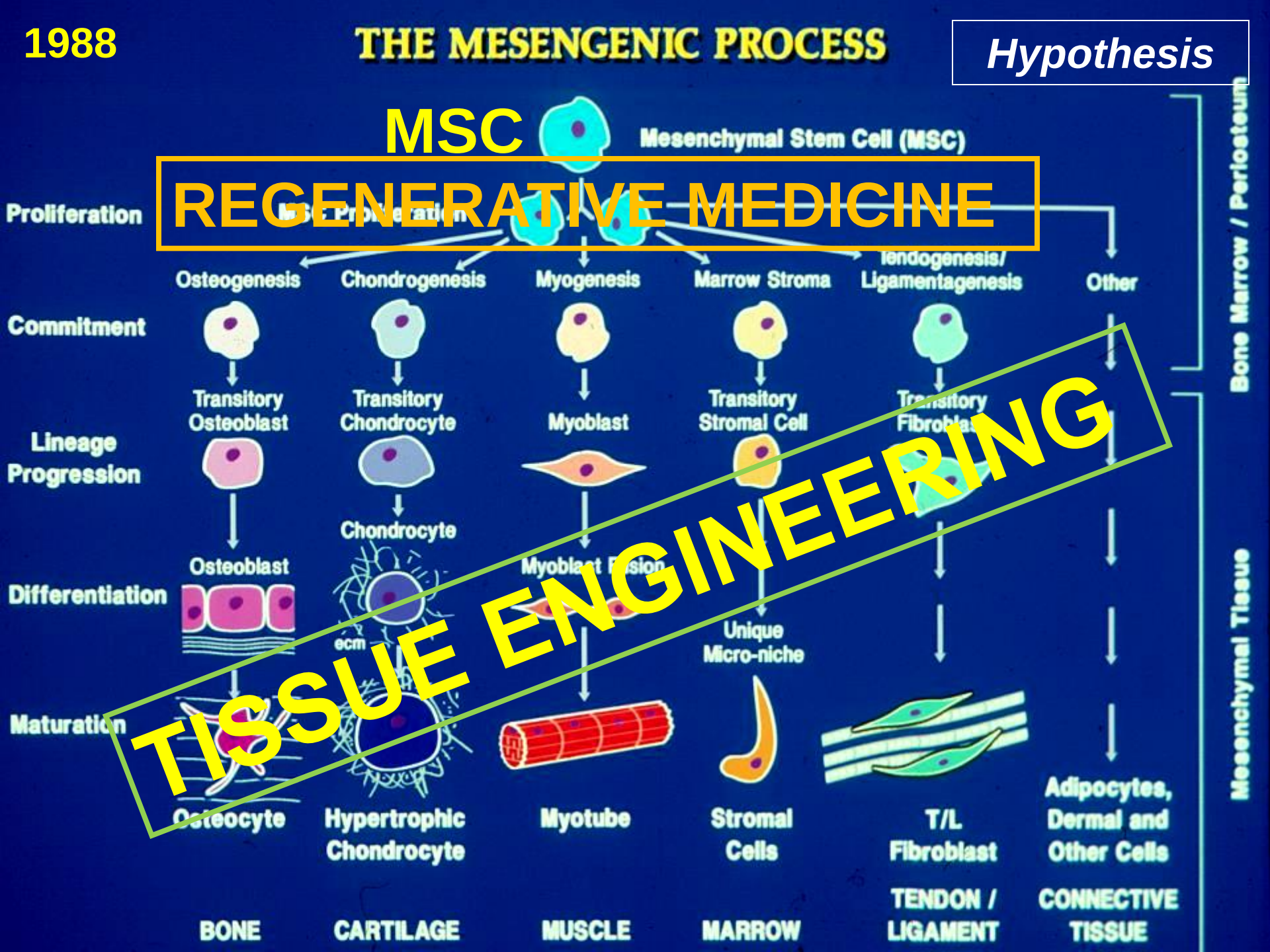
CLINICALTRIALS.GOV - February 2013

304 studies with search of: Mesenchymal Stem Cells

Clinical Conditions for MSC-therapy: ~25% autologous

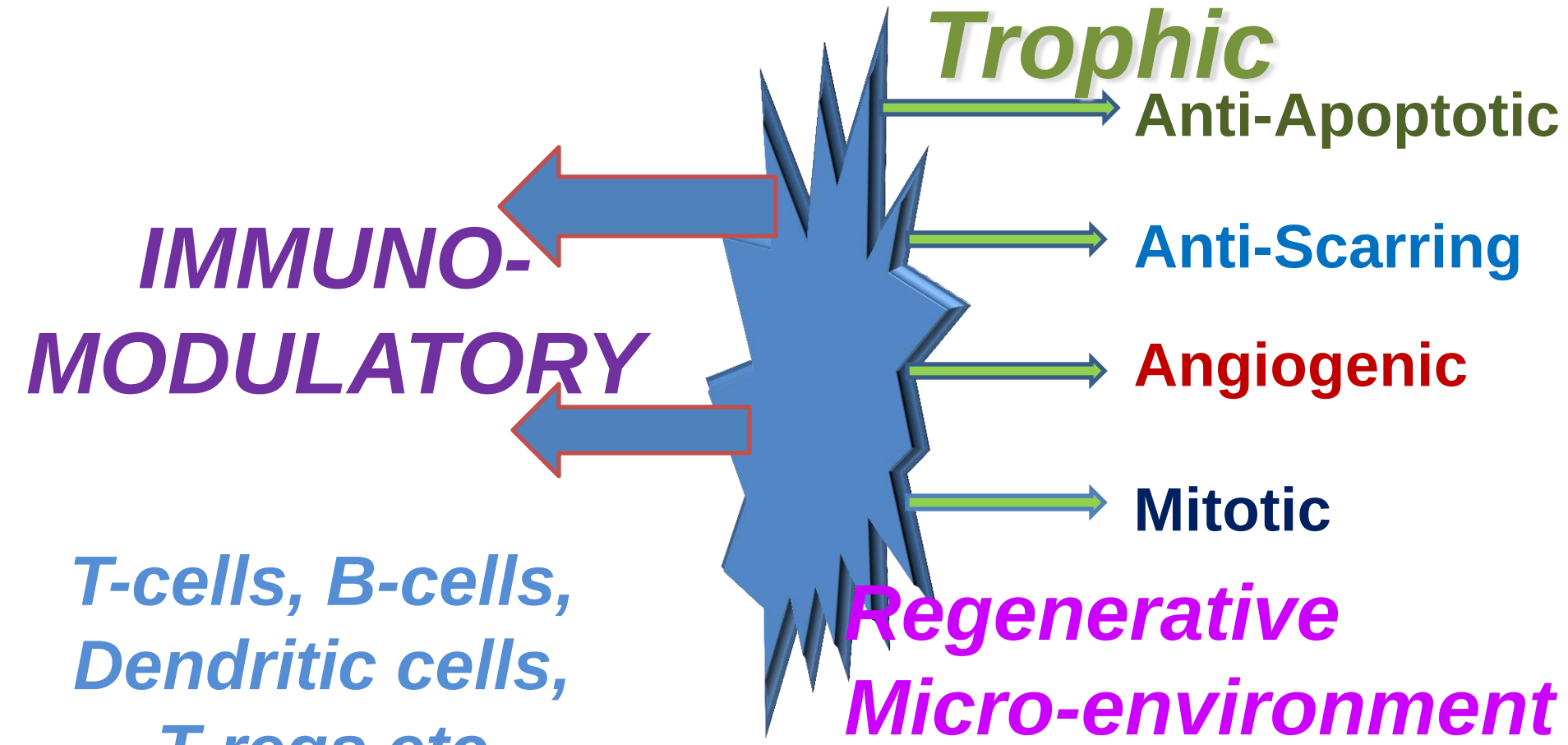
Ulcerative Colitis, Diabetes Mellitus, Type 1, Liver Cirrhosis,Nonunion Fractures, Diabetic Foot, Critical Limb Ischemia, Dilated Cardiomyopathy, Autoimmune Diseases; Immune System Diseases; Demyelinating Diseases; Nervous System Diseases; Demyelinating Autoimmune Diseases, CNS; Autoimmune Diseases of the Nervous System(MS), Sjogren's Syndrome, Graft Versus Host Disease; Chronic and Expanded Graft Versus Host Disease, Middle Cerebral Artery Infarction, Osteoarthritis, Aplastic Anemia, Maxillary Cyst; Bone Loss of Substance, Spinal Cord Injury, Parkinson's Disease, Crohn's Disease, Acute Myocardial Infarction, Multiple Sclerosis, Hematological Malignancies, Organ Transplantation, Ischemia; Stroke, Systemic Sclerosis, Hereditary Ataxia, Liver Failure, Retinitis Pigmentosa, Kidney Transplant; Rheumatoid Arthritis, Lumbar Spondylolisthesis Involving L4-L5, Chronic Allograft Nephropathy, Degenerative Arthritis; Chondral Defects; Osteochondral Defects, Progressive Multiple Sclerosis; Neuromyelitis Optica, Primary Biliary Cirrhosis, Osteonecrosis of the Femoral Head, Pened Chest Surgery for Programmes Coronary Bypass, Lupus Nephritis, Wilson's Disease, Multiple System Atrophy, Burns, Intervertebral Disc Disease, Chronic Myocardial Ischemia; Left Ventricular Dysfunction, Relapsing-Remitting Multiple Sclerosis; Secondary Progressive Multiple Sclerosis; Progressive Relapsing Multiple Sclerosis, Tibial Fracture, Bone Cyst,Buerger's Disease, Amyotrophic Lateral Sclerosis, Allogeneic Stem Cell Transplantation, Idiopathic Pulmonary Fibrosis, Type 2 Diabetes Mellitus, Refractory Systemic Lupus Erythematosus, Leukemia, Myeloid, Acute; Leukemia, Lymphoblastic, Acute; Leukemia, Myelocytic, Chronic; Myeloproliferative Disorders; Myelodysplastic Syndromes; Multiple Myeloma; Leukemia, Lymphocytic, Chronic; Hodgkin's Disease; Lymphoma, Non-Hodgkin, Degenerative Arthritis, Myelodysplastic Syndrome, ST-Elevation Myocardial Infarction, Pulmonary Disease, Chronic Obstructive; Pulmonary Emphysema; Chronic Bronchitis, Lower Back Pain; Disc Degeneration, Articular Cartilage Lesion of the Femoral Condyle, Osteoporotic Fractures, Bone Neoplasms, Solid Tumors; Acute Kidney Injury, Hereditary Cerebellar Ataxia, Primary Disease, Autism, Limbus Corneae Insufficiency Syndrome, Wound Healing, Dementia of the Alzheimer's Type, Non-ischemic Dilated Cardiomyopathy, Stroke, Epidermolysis Bullosa, Tibia or Femur Pseudo-arthrosis, Recovery Following Partial Medial Meniscectomy, Human Immunodeficiency Virus, Stable Angina; Heart Failure; Atherosclerosis; Multivessel Coronary Artery Disease, Osteogenesis Imperfecta, Emphysema, Progressive Hemifacial Atrophy; Romberg's Disease, Complex Perianal Fistula, Multiple Trauma, Osteodysplasia, Tibiotalar Arthrodesis; Subtalar Arthrodesis; Calcaneocuboid Arthrodesis; Talonavicular Arthrodesis; Double Arthrodesis (i.e. Calcaneocuboid and Talonavicular); Triple Arthrodesis (i.e. Subtalar, Calcaneocuboid, and Talonavicular), Recto-vaginal Fistula, Peripheral Vascular Diseases, Prostate Cancer; Erectile Dysfunction, Diabetic Wounds; Venous Stasis Wounds, Ovarian Cancer; Sarcoma; Small Intestine Cancer.

Arnold Caplan, 2013


1988
THE MESENGENIC PROCESS
Hypothesis
MSC
REGENERATIVE MEDICINE
TISSUE ENGINEERING
Mesenchymal Stem Cell (MSC)
Proliferation
Commitment
Lineage Progression
Differentiation
Maturation
Osteogenesis
Chondrogenesis
Myogenesis
Marrow Stroma
Tendogenesis/ Ligamentagenesis
Other
Transitory Osteoblast
Transitory Chondrocyte
Myoblast
Transitory Stromal Cell
Transitory Fibroblast
Chondrocyte
Osteoblast
ecm
Unique Micro-niche
Osteocyte
Hypertrophic Chondrocyte
Myotube
Stromal Cells
T/L Fibroblast
Adipocytes, Dermal and Other Cells
BONE
CARTILAGE
MUSCLE
MARROW
TENDON / LIGAMENT
CONNECTIVE TISSUE
Bone Marrow / Periosteum
Mesenchymal Tissue

2013

natural INJURY RESPONSE



MSC=*pericyte*

FDA

- Cells and cell-based therapies are being managed by the FDA under the same logics as DRUGS are managed
- Cells are not single molecular agents but are, rather, site-regulated, adaptive agents capable of very complex functions involving a multitude of bioactive factors and reactivities
- These facts require new management logics and regulatory values

ADULT STEM CELLS STRATEGIES IN THE TREATMENT OF DIABETES

- Anti-inflammatory
- Immunomodulation
- Tolerance Induction

- Tissue remodeling and paracrine effects on native tissue precursor/stem cells

- Differentiation into insulin producing cells
- Tissue Reprogramming

Mesenchymal Stem Cells and T2DM (n=4)

ClinicalTrials.gov

NCT01413035. **Safety and Efficacy Study of Umbilical Cord/Placenta-Derived Mesenchymal Stem Cells to Treat Type 2 Diabetes**

Condition: T2DM. **Intervention:** MSC. **Study Type:** Interventional; **Phases:** 1/2. **Sponsor:** Shandong University. **Study Design:** Randomized; Safety/Efficacy Study; Parallel Assignment; Single Blind (Outcomes Assessor). **Primary Purpose:** Treatment. **Outcome Measures:** To assess efficacy and evaluate the incidence and severity of adverse events of transplantation treatment using UC/placenta-derived MSC in patients with T2DM. **# Enrolled:** 30. **Age Groups:** Adult / Senior

NCT01759823. **Cultured Mesenchymal Stem Cell Transplantation in T2DM**

Condition: T2DM. **Interventions:** Cultured Autologous BM-MSC transplantation; Other: control. **Study Type:** Interventional. **Phases:** 2/3. **Sponsor:** Postgraduate Institute of Medical Education and Research Chandigarh, India. **Study Design:** Randomized; Safety/Efficacy Study; Parallel Assignment; Single Blind (Subject). **Primary Purpose:** Treatment. **Outcome Measure:** Reduction of insulin requirement by ≥50% by the end of 6 months post transplant and Improvement in Glucagon stimulated C - peptide levels and insulin sensitivity by HYPERINSULINEMIC EUGLYCEMIC CLAMP. **# Enrolled:** 30. **Age Groups:** Adult / Senior

NCT01142050. **Stem Cell Therapy for Type 2 Diabetes Mellitus**

Condition: T2DM. **Intervention:** MSC. **Study Type:** Interventional; **Phase:** 1. **Sponsor:** Cellonis Biotechnology Co. Ltd. **Study Design:** Safety/Efficacy Study; Single Group Assignment; Open Label. **Primary Purpose:** Treatment. **Outcome Measures:** ITT; insulin dosage; HbA1c; Fast blood glucose (FBG) and Postmeal blood glucose (PBG); C-peptide levels; Serum Insulin levels; Serious adverse event frequency and severity. **# Enrolled:** 24. **Age Groups:** Adult / Senior

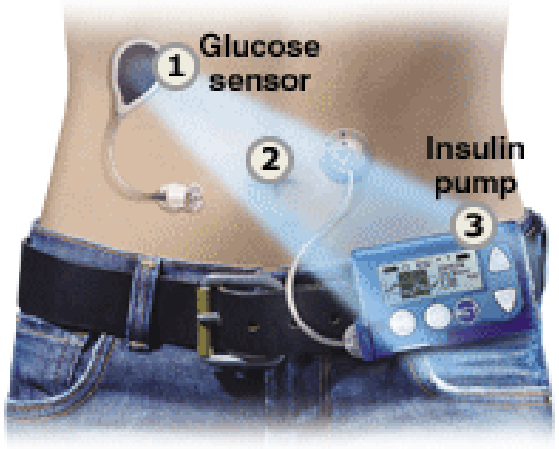
NCT01576328. **Safety Study of Mesenchymal Precursor Cells in Type 2 Diabetes**

Condition: T2DM. **Intervention:** Mesenchymal Precursor Cells (MPCs). **Study Type:** Interventional; **Phases:** 1/2. **Sponsor:** Mesoblast, Ltd. **Study Design:** Randomized; Safety Study; Parallel Assignment; Single Blind (Subject). **Primary Purpose:** Treatment. **Outcome Measure:** Primary objective of the study is to assess the safety and tolerability of MPC therapy. **# Enrolled:**60. **Age Groups:** Adult / Senior

Diabete di Tipo 1:

Quando il Tuo Sistema Immune Decide di Attaccarti

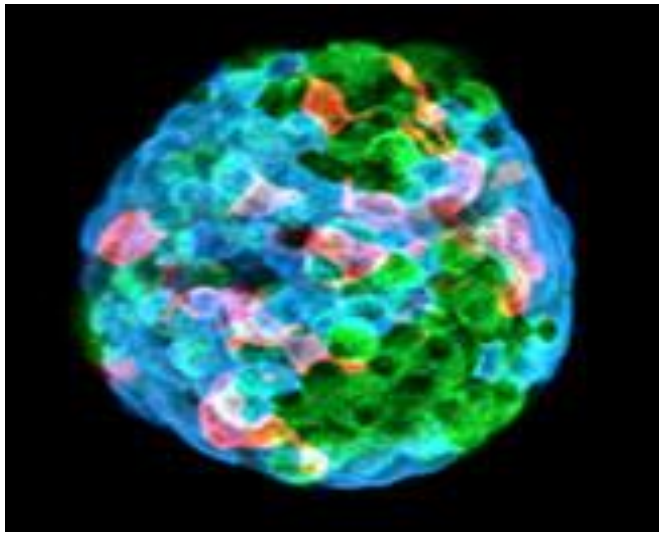
Trattamenti Convenzionali



Terapia Cellulare: Perche' le isole?

Hanno gia' un sensore per il glucosio a risposta immediata

Secrezione insulinica immediata e quando necessario



Mantengono livelli di glicemia normali senza il rischio di ipoglicemie

Fabbricano insulina e altri ormoni e non hanno bisogno di essere ricaricate

Possono funzionare per tutta la vita (in assenza di autoimmunita o rigetto)

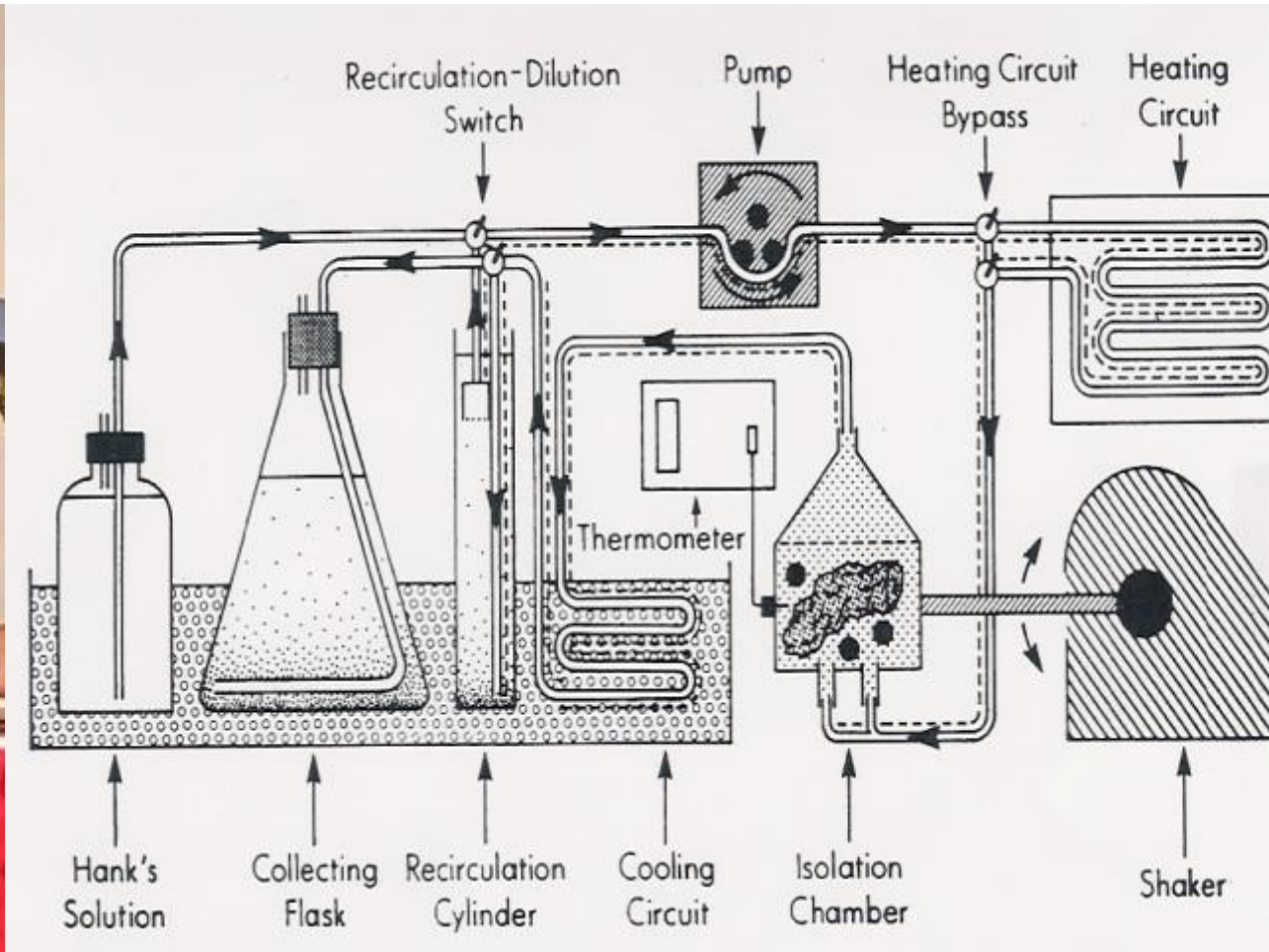
Quando si potra' parlare di una "CURA" ?

- Eliminazione dell'autoimmunita' o dei suoi effetti (e.g., induzione di tolleranza o barriere semipermeabili)
- Sostituzione, rigenerazione o riprogrammazione delle cellule produttrici di insulina senza introdurre altri problemi come quelli legati alla terapia anti-rigetto cronica

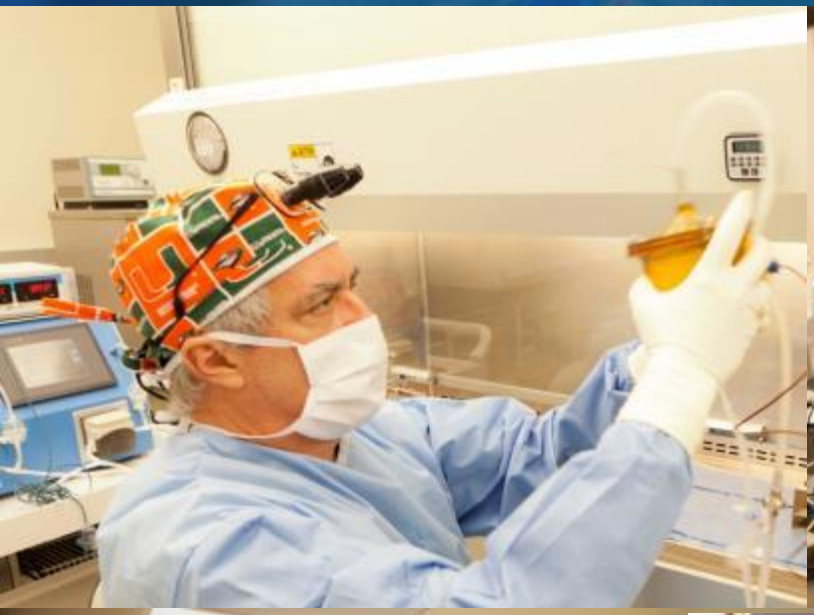
Reprinted from DIABETES, VOL. 37, NO. 4, APRIL 1988

Automated Method for Isolation of Human Pancreatic Islets

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



Collaborazione “Open Source”

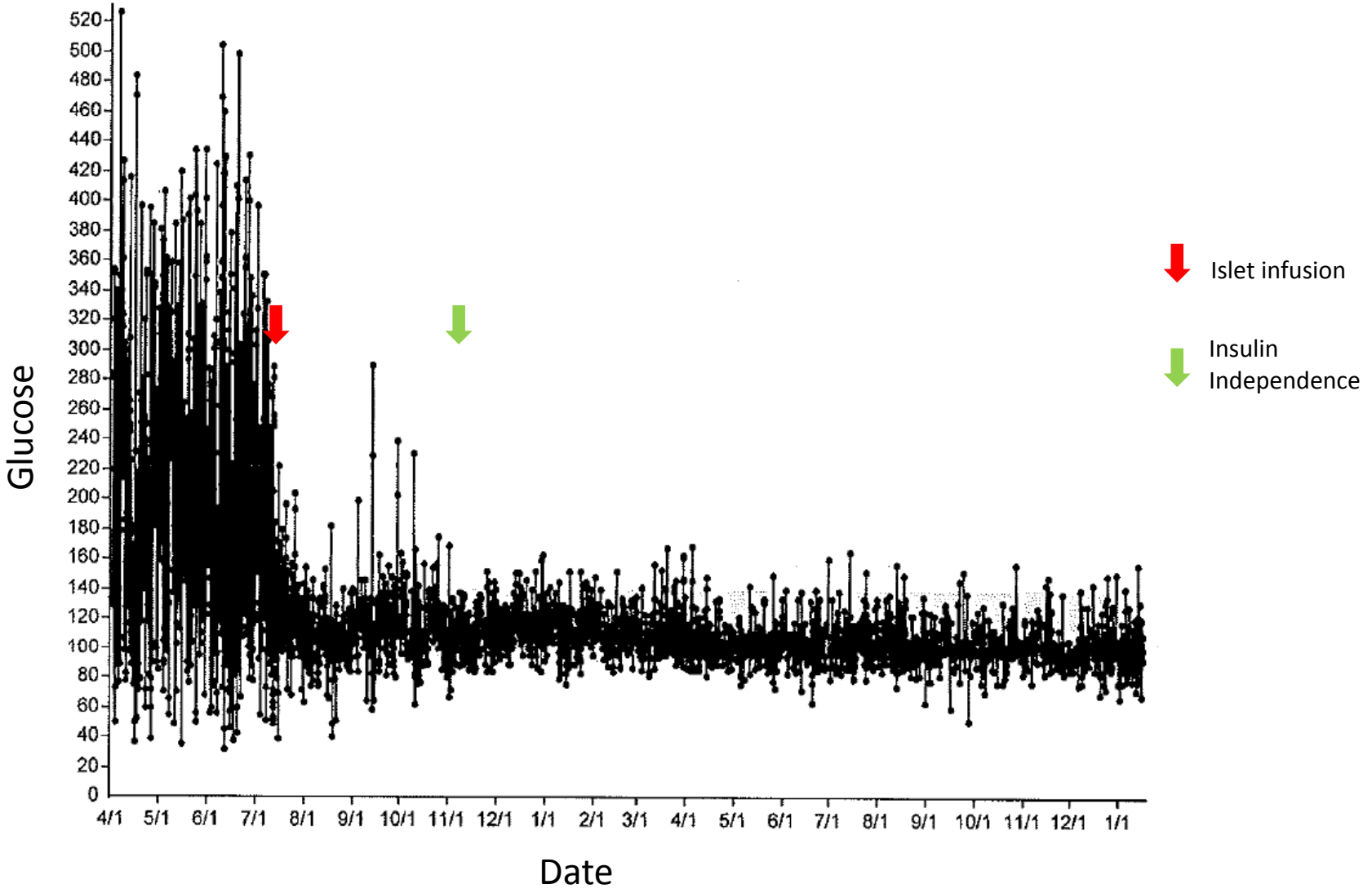




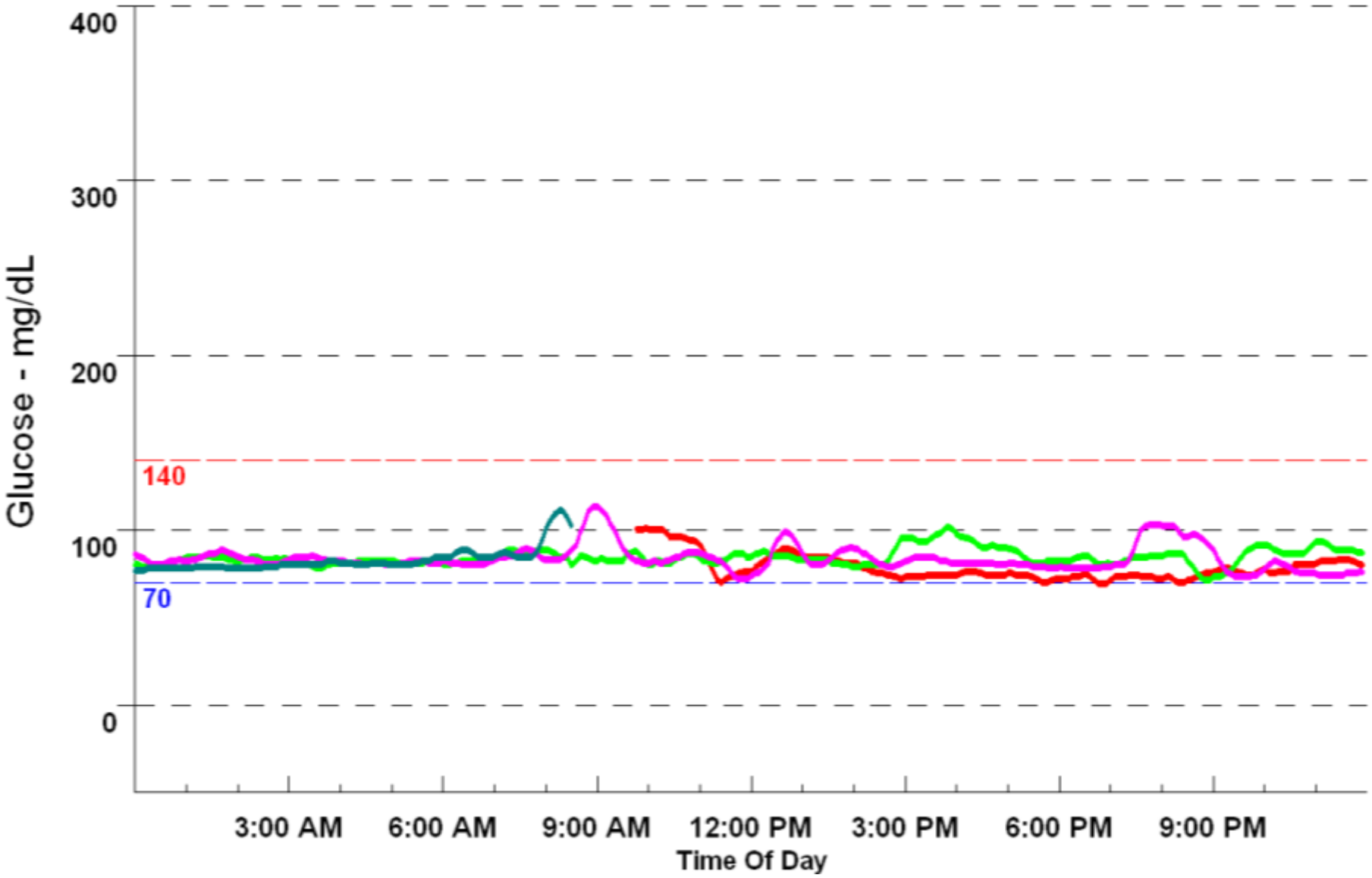
Clinical Islet Transplantation Consortium

Chairperson Steering Committee:
Dr. Camillo Ricordi
University of Miami

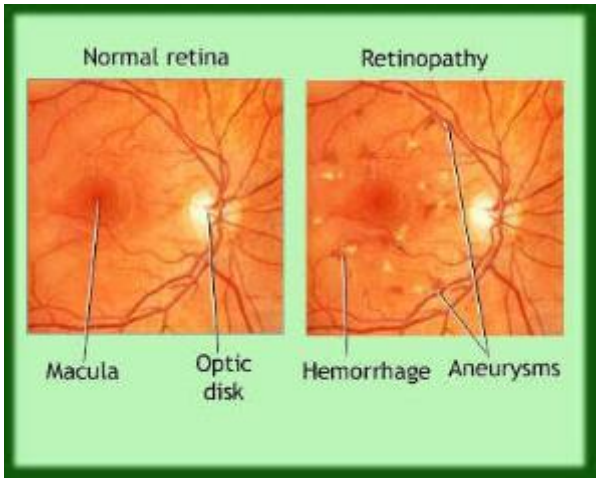
Stabilizzazione delle glicemie dopo singola infusione di isole (18 mesi post Tx)



Due anni dopo Tx



Retinopatia Diabetica: effetto della terapia intensiva insulinica vs. trapianto di isole



Number of Eyes

All subjects at study entry	Group A: medical therapy only		Group B: medical therapy until ICT		Group C: post ICT	
Retinopathy severity at entry	entry	progressed	entry	progressed	entry	progressed
Mild NPDR	8	0	8	0	8	0
Mod NPDR	7	1	12	0	12	0
Severe NPDR	3	1	3	1	2	0
PDR	13	2	28	5	29	0
Total	31	4	51	6	51	0

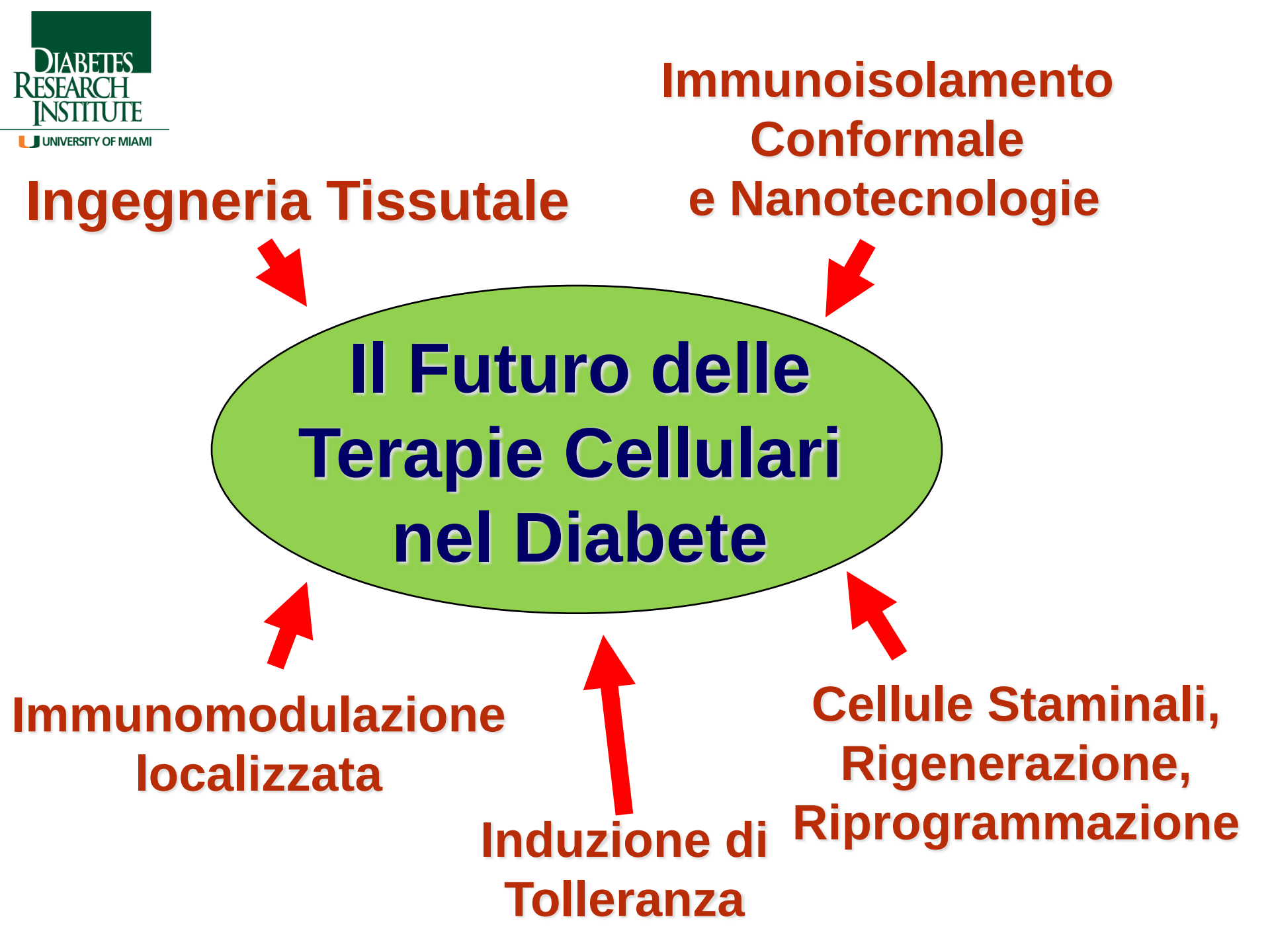
p < 0.01 for progression, groups A + B vs. group C
p < 0.02 for progression, group B vs group C

Transplantation 2008; 85(10):1400 and Transplantation 2011; 91(3): 373

Funzione Renale: effeto della terapia intensiva vs. trapianto di isole negli stessi 16 pazienti prima e dopo il trapianto

	Δ GFR (ml/min/1.73m^2/year)	
Groups	**Median**	**Interquartile range**
Medical	**-6.7**	**(-2.5 to -12.2)**
Post-ICT	**-1.3**	**(-4.1 to 0.1)**

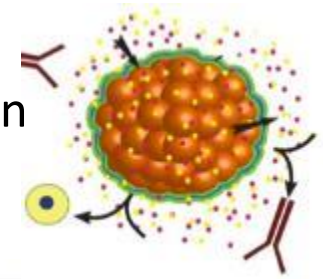
P med vs. ICT = 0.01, paired t test


Diabetes Research Institute
University of Miami
Ingegneria Tissutale
Immunoisolamento Conformale e Nanotecnologie
Il Futuro delle Terapie Cellulari nel Diabete
Immunomodulazione localizzata
Induzione di Tolleranza
Cellule Staminali, Rigenerazione, Riprogrammazione

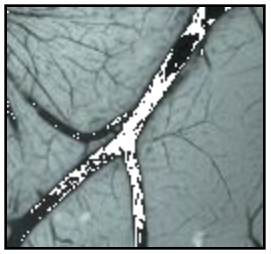
Ingegnerizzazione del Sito Ottimale

Modulating the Local Environment

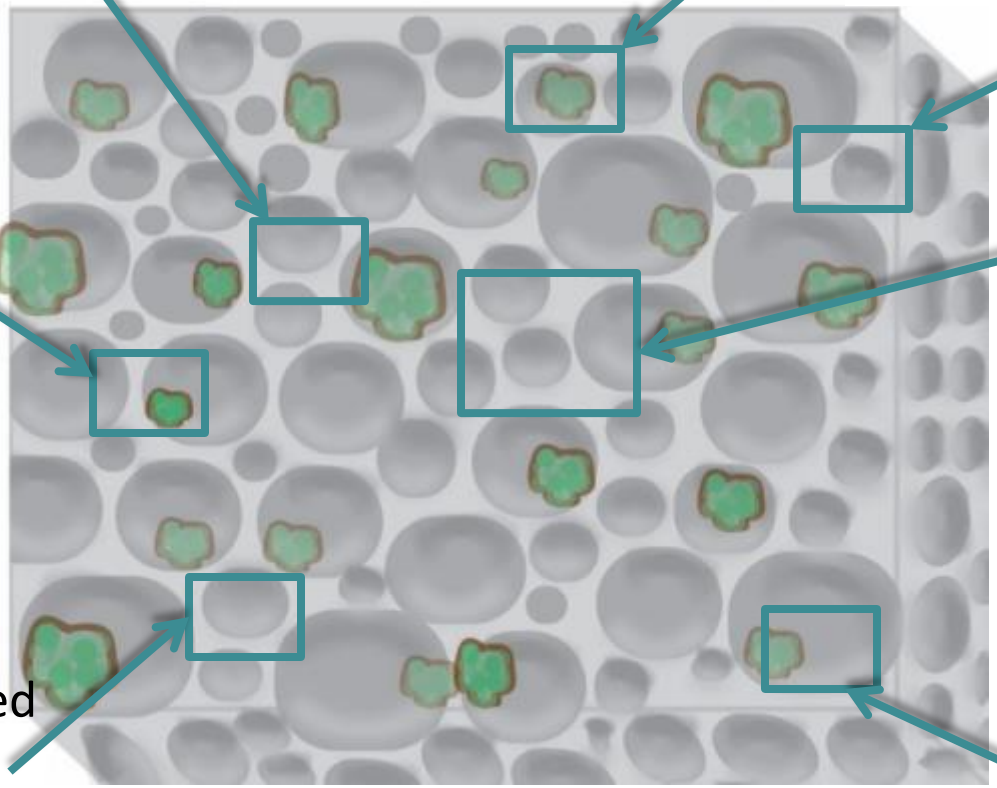
Encapsulation



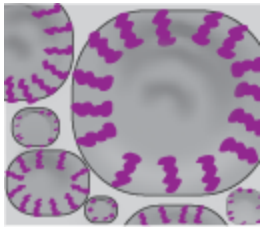
Vascular Infiltration



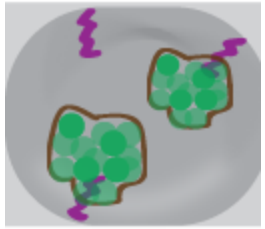
Co-delivery of "helper" cells

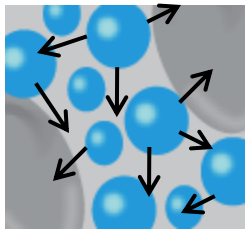


Bioactive Surfaces



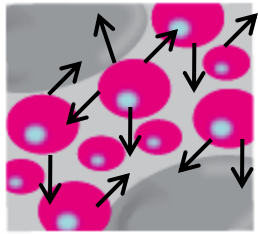
Mechanical Protection





Localized Drug Delivery

In situ oxygen generation



Multi-functional Platform

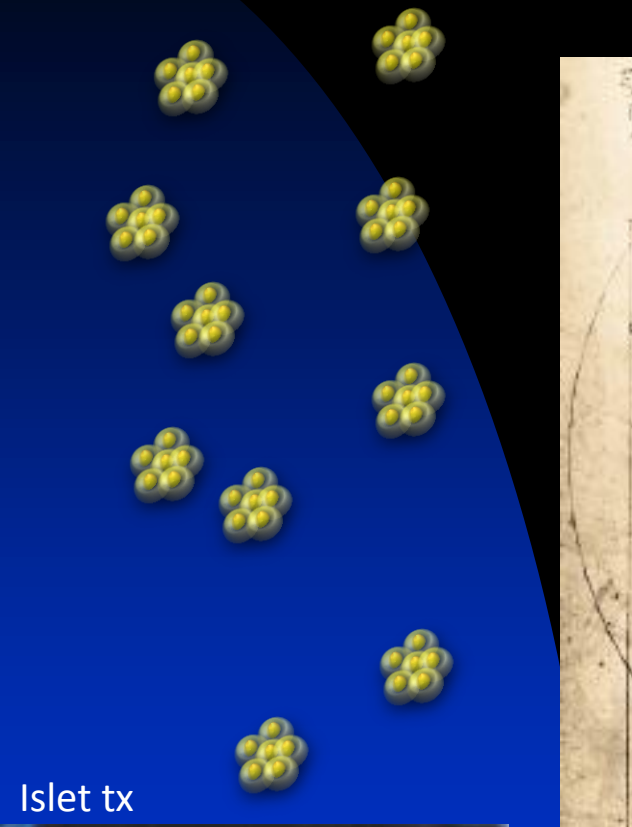
Tolerance Induction in HLA Disparate Living Donor Kidney Transplantation by Donor Stem Cell Infusion: durable chimerism predicts outcome

J Leventhal, M Abecassis, J Miller, L Gallon, D Tollerud, MJ Elliott, LD Bozulic, C Houston, N Sustento-Reodica and ST Ildstad

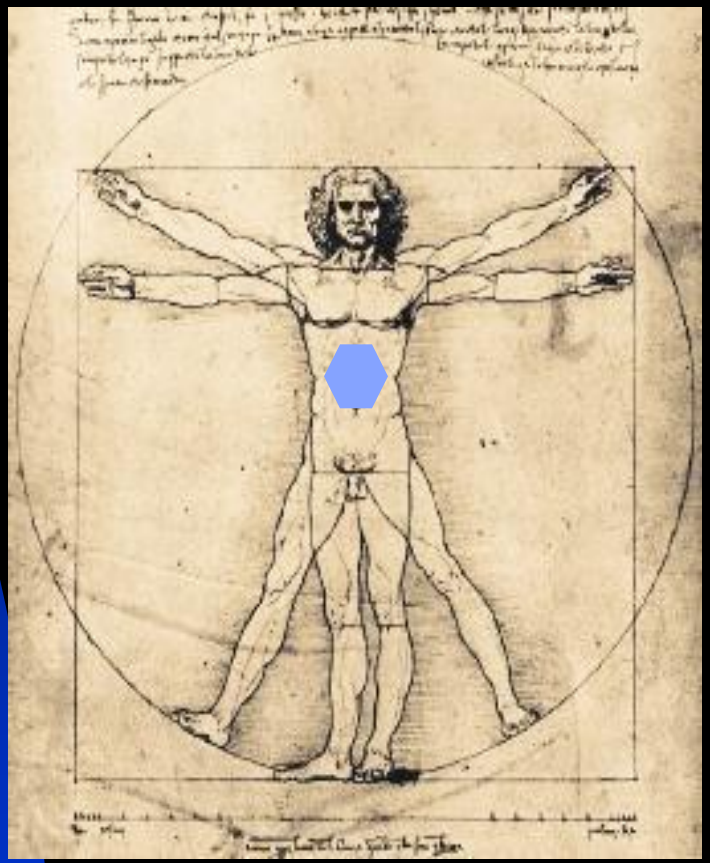
….. Complete immunosuppression withdrawal at one year post-transplant was successful in all patients with durable chimerism. There has been no GVHD or engraftment syndrome. Renal transplant loss occurred in 1 patient who developed sepsis following an atypical viral infection. Two subjects with only transient chimerism demonstrated subclinical rejection on protocol biopsy despite donor-specific hyporesponsiveness.

Conclusions. Low intensity conditioning plus FCRx safely achieved durable chimerism in mismatched allograft recipients. Sensitization represents an obstacle to successful induction of chimerism. Sustained T cell chimerism is a more robust biomarker of tolerance than donor-specific hyporeactivity.

Alternative nella Sostituzione di Cellule Insulino-Secernenti



Islet tx



Endogenous regeneration

DIABETES RESEARCH INSTITUTE
UNIVERSITY OF MIAMI

Sviluppo di fonti inesauribili di cellule che producono insulina:

- animali (xenotrapianti)

- cellule staminali dal cordone ombelicale
- cellule progenitrici amniotiche
- cellule staminali del tessuto adiposo
- cellule staminali embrionali
- cellule progenitrici nel pancreas adulto

- transdifferenziazione cellulare
- riprogrammazione cellulare

Cellule Staminali Derivate dal Tessuto Adiposo

- Adipose tissue is a potential source for stem cells (~400,000 cells/mL of tissue)
- 300-500-fold more cells in fat compared to the same volume of BM aspirate
- Marrow MSCs require exposure to TGF-β to be chondrocytes; ASCs require both TGF-β and BMP-6 to be chondrocytes. Therefore, marrow MSCS ≠ ADSCs.

Arnold Caplan, 2013

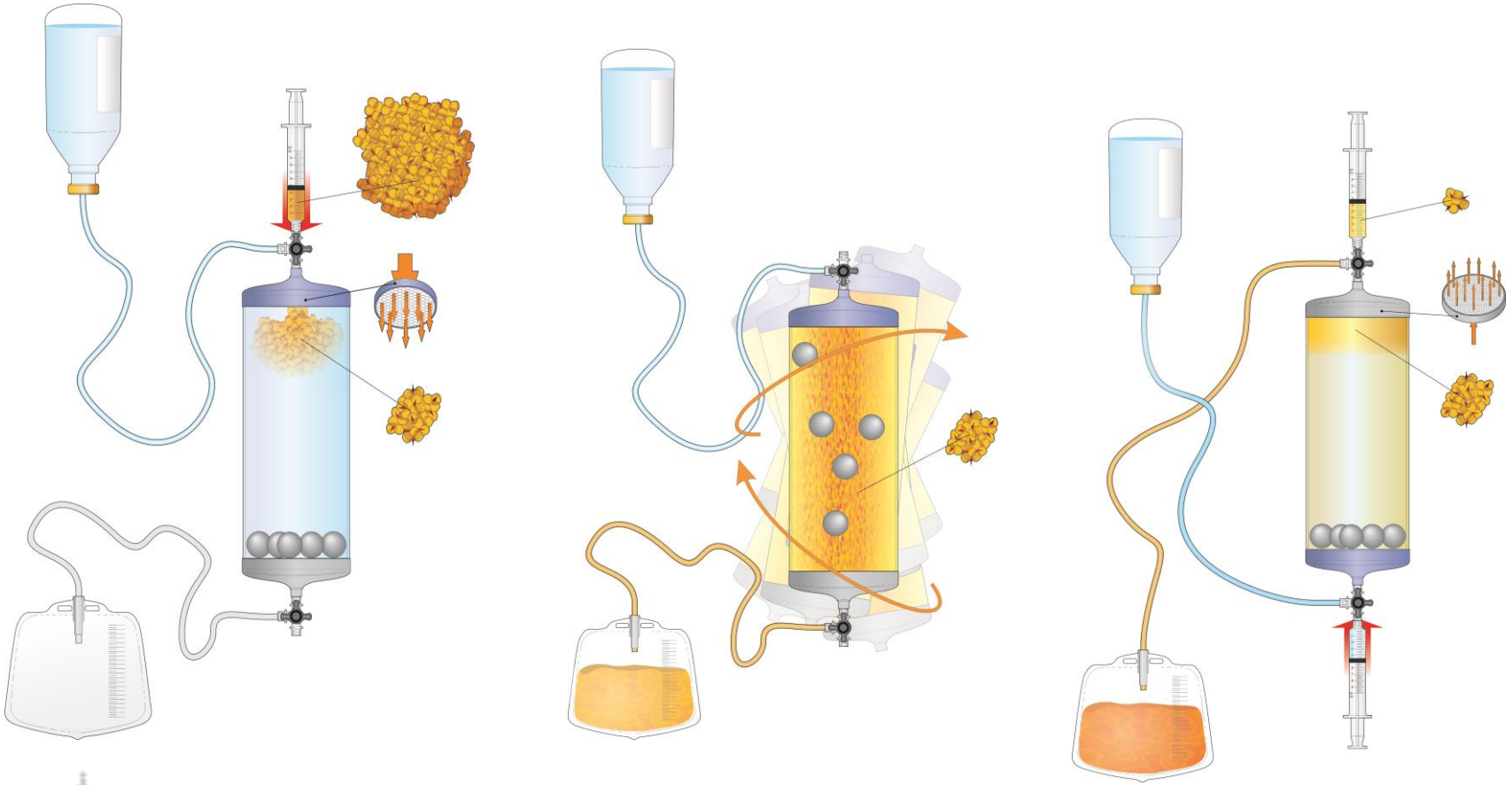
LIPOGEMS: Tecnologia Italiana in Medicina Rigenerativa

- Lipogems technology utilizes mild mechanical forces without the use of any enzyme blend
- Lipogems Cell Products show a PRESERVED STROMAL VASCULAR FRACTION highly enriched in PERYCYTES AND MSCs

Dr. Carlo Venura, 2013

LIPOGEMS

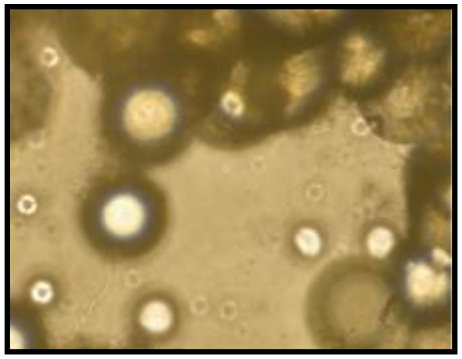
non-ezymatic cell processing

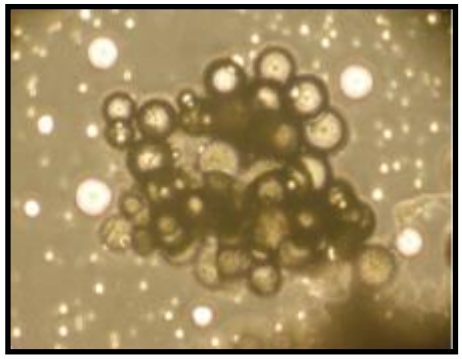


Comparative FACS Analysis

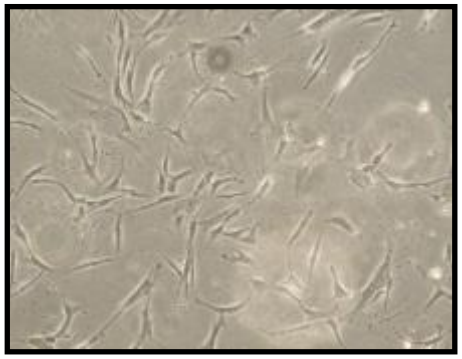
	Lipoaspirate	Lipogems
CD146	50.5 ± 4.6	54.5 ± 13.9
CD45	19.93 ± 6.0	9.7 ± 3.2
CD14	8.8 ± 1.8	3.1 ± 1.7
CD34	34.8 ± 9.6	18.1 ± 4.0
CD105	19.2 ± 8.0	20.5 ± 10.0
CD73	26.3 ± 10.6	7.1 ± 3.3
CD44	38.8 ± 15.6	19.3 ± 14.2
CD166	1.5 ± 1.4	2.1 ± 3.0
CD90	43.4 ± 8.7	45.2 ± 9.3
CD29	72.5 ± 7.9	73.0 ± 14.4
CD105+/73+/45-	4.8 ± 1.1	2.2 ± 1.6
CD146+/90+/34-	13.9 ± 2.0	23.2 ± 1.8
CD90+/29+/34-	11.6 ± 0.3	29.4 ± 12.7
CD146+/34+	8.3 ± 1.7	17.8 ± 0.5

Lipogems Product Ex-Vivo Expansion

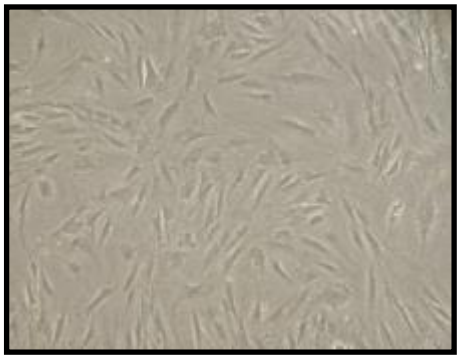




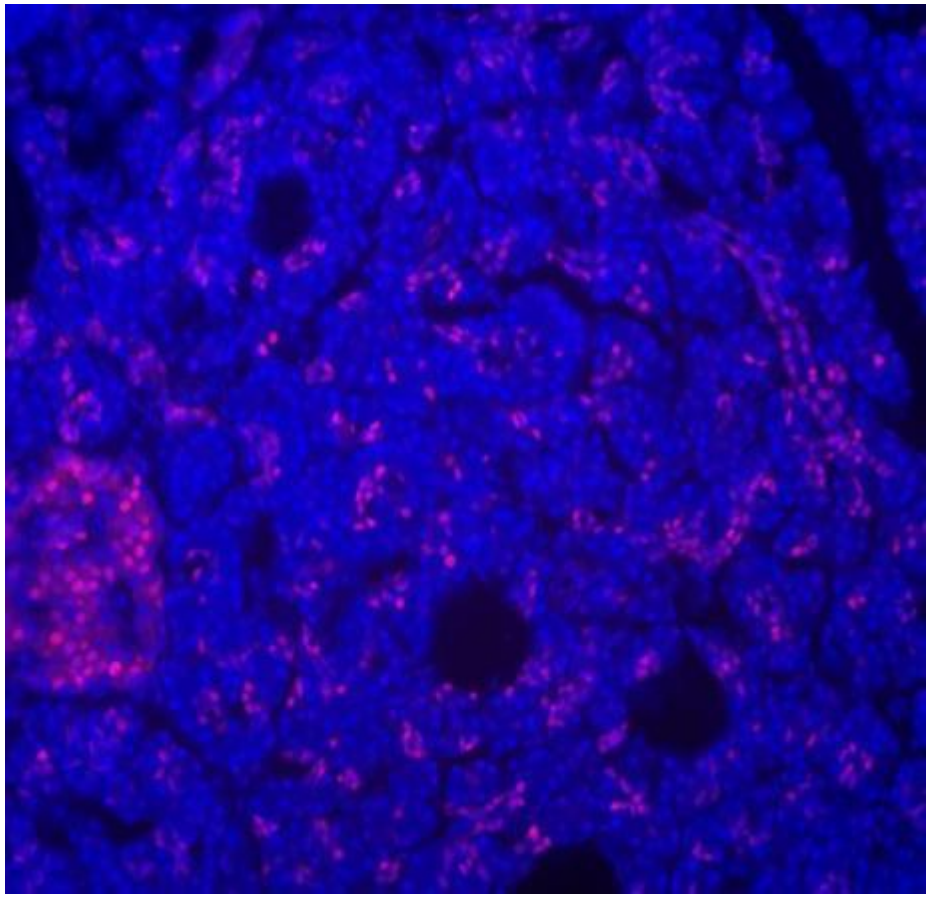
Day 3

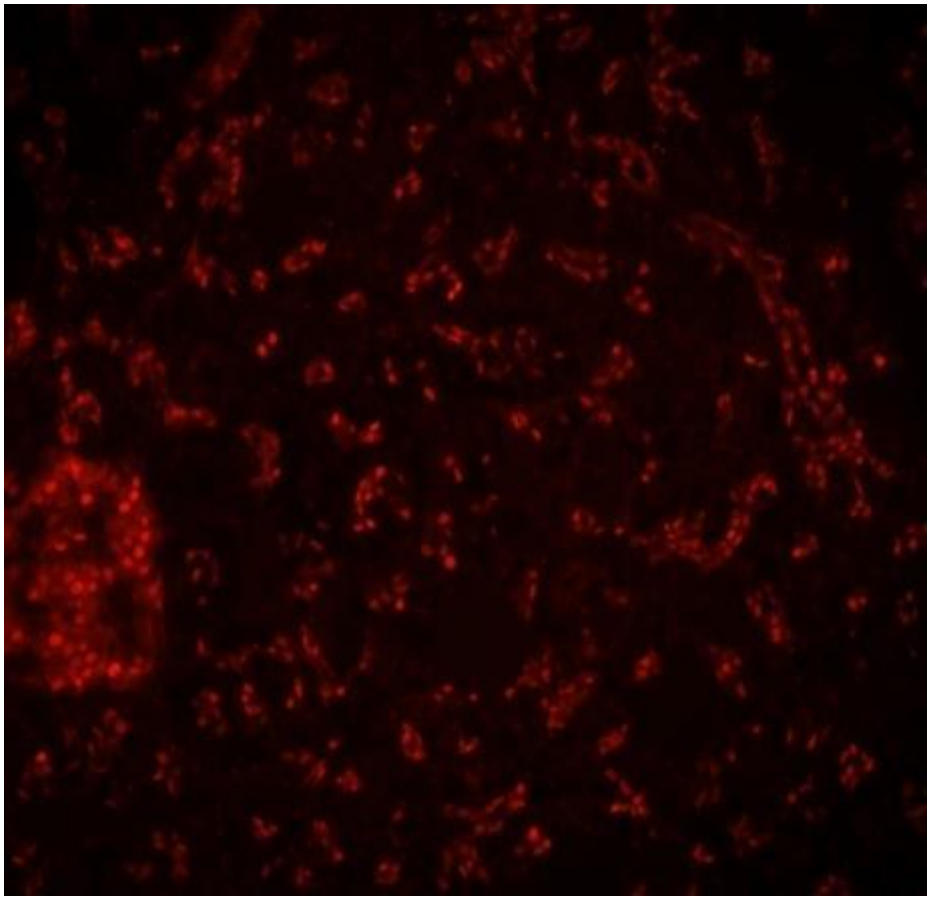


Day 4



Cellule Progenitrici nel Pancreas Umano





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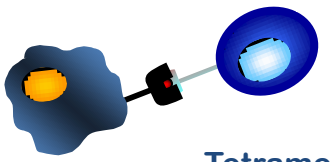
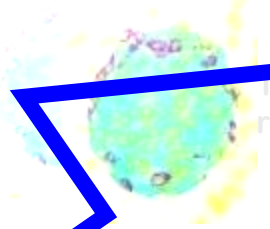
Telescience DRI Federation

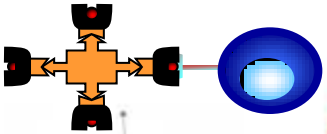


Tetramers

Protein Technolog

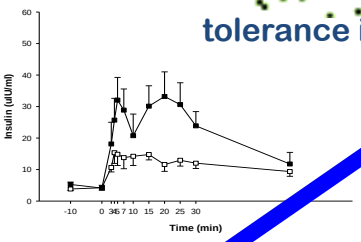


Improved Preservation and New Implantation Sites



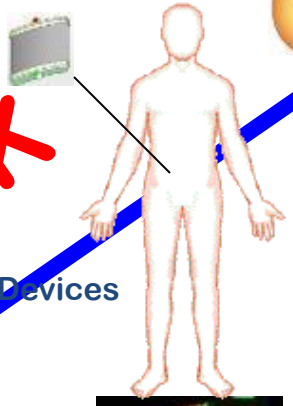
Gene therapy

tolerance induction

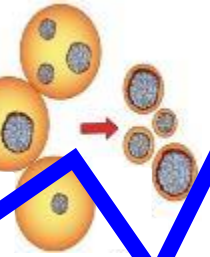


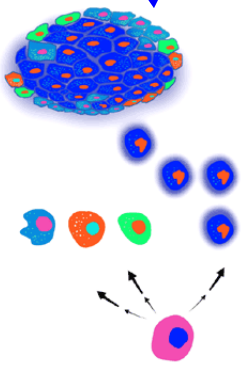
FAST-TRACK

Xenotransplantation

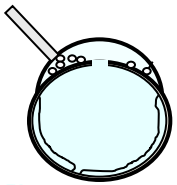


Hybrid Devices

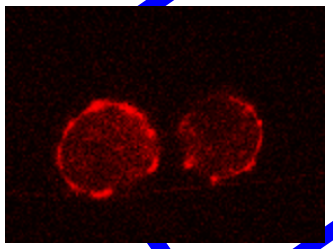




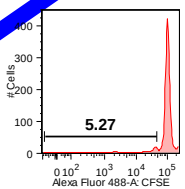
Stem Cells

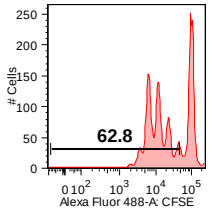


Multi-Photon In-Vivo Imaging

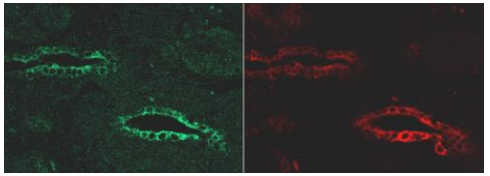


Tolerogenic DCs



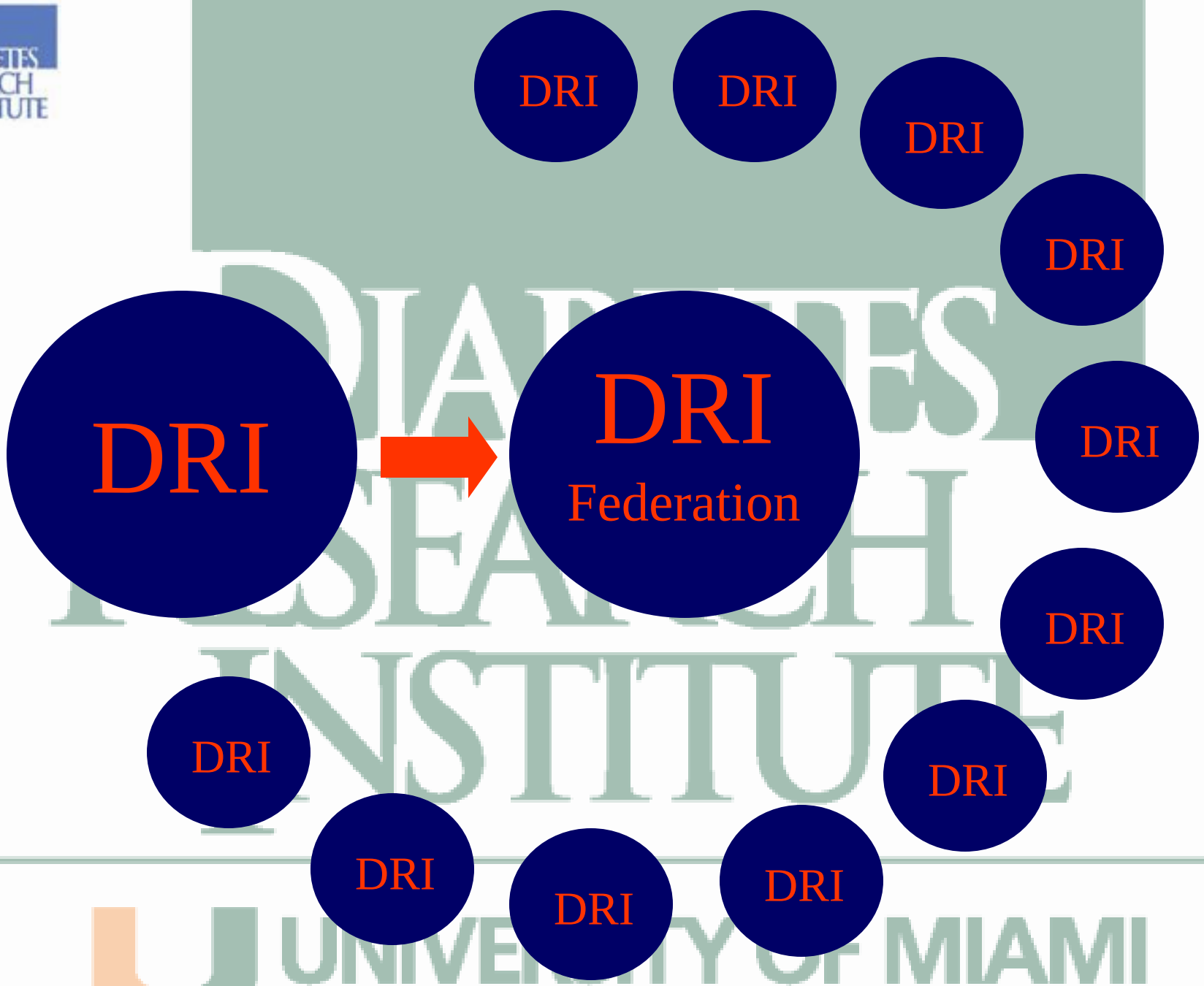


liver transdifferentiation



Regeneration

stem cells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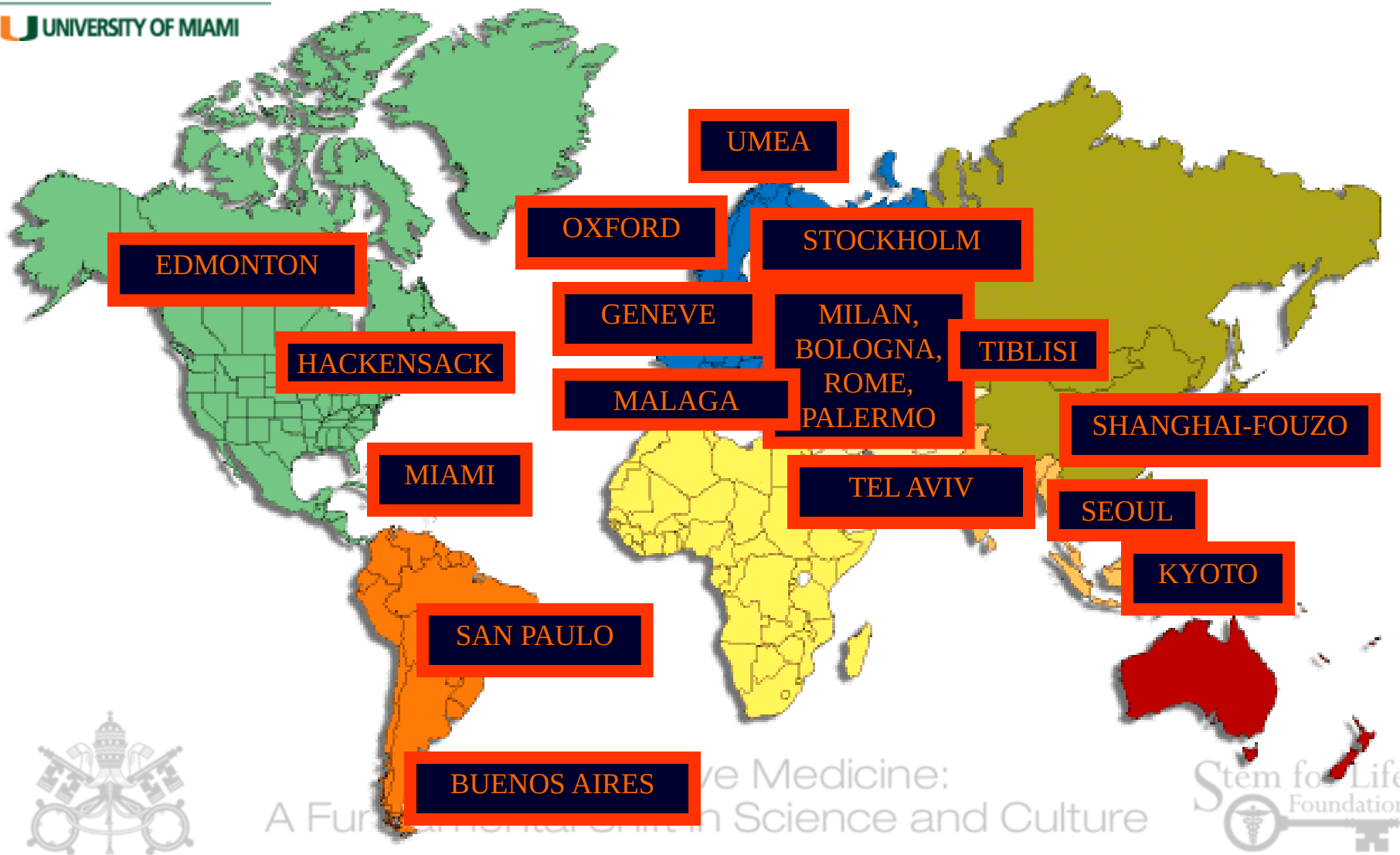
DRI FEDERATION



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THE CURE ALLIANCE

The Cure Alliance (CA) is an **international not-for-profit**, collegial association of scientists, physicians, surgeons, other professionals and committed individuals who share the **vision to promote international collaborations while overcoming the impediments and barriers to the development of cures for disease conditions now afflicting humankind**

Multi-Disciplinary Challenge


Alice Tomei


Jeffrey Hubbell


Rodolfo Alejandro

Clinicians


Jay Skyler


Luca Inverardi


Cherie Stabler

Biomedical Engineers

Immunologists


Norma Kenyon


Chris Fraker


Peter Buchwald

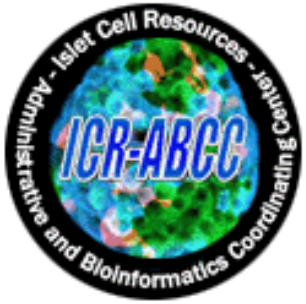
Pharmacologists

Animal Model Experts


Antonello Pileggi

DIABETES RESEARCH INSTITUTE FOUNDATION

THE LEONA M. AND HARRY B. HELMSLEY CHARITABLE TRUST



JDRF Juvenile Diabetes Research Foundation International

dedicated to finding a cure

FONDAZIONE SIGMA-TAU