

Nutrition in Cancer Therapy: Opportunities for Prevention & Treatment

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Presented on May 2, 2019

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Objectives

- **Identify evidence for and against nutrition supplementation in the patient with cancer**
- **Define current management for cancer cachexia**
- **Describe nutrition interventions that will improve outcomes**

Where does nutrition fit into cancer care ?

Depends on the Goals ?

Expected benefits of nutrition therapy in cancer treatment

improved tolerance

better therapeutic response

Improved QOL

Improved survival

Palliative

Goal of Nutrition:

Achievement best QoL

Symptom control

Patient tailored

Curative

Goal of nutrition:

Support patient through cancer therapy:

pre treatment

during therapy

post therapy

Promotes malnutrition

Key determinants of QoL after Cancer diagnosis

- Cancer location (30%)
- Weight loss (30%)
- Nutritional intake (20%)
- Chemotherapy (10%)
- Surgery (6%)
- Disease duration (3%)
- Stage of disease (1%)

Prevalence of Weight Loss in Cancer Patients

**Common
(>80%)**

**Intermediate
(54-65%)**

**Uncommon
(31-40%)**

**Head and Neck
Esophagus
Stomach
Pancreas
Lung**

**Colon
Ovarian
Lymphoma**

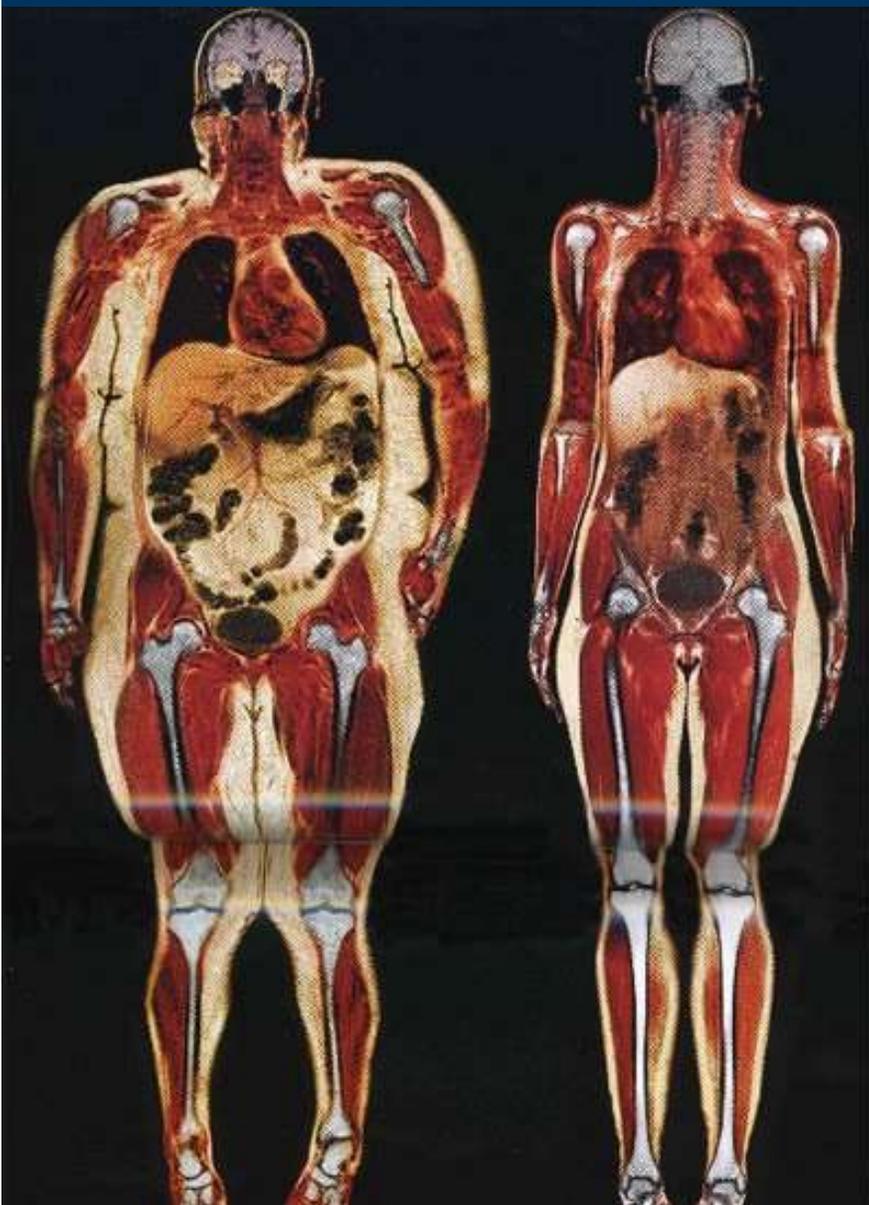
**Breast
Prostate
Leukemia
Sarcoma**

**Weight loss can be better outcome
predictor than TNM staging**

Fearon K NEJM 2011

Schattner, Shike: Modern Nutrition in Health and Disease, 10th Ed 2006

Nutritional and Metabolic Assessment of the Cancer Patient



Several screening tools are validated

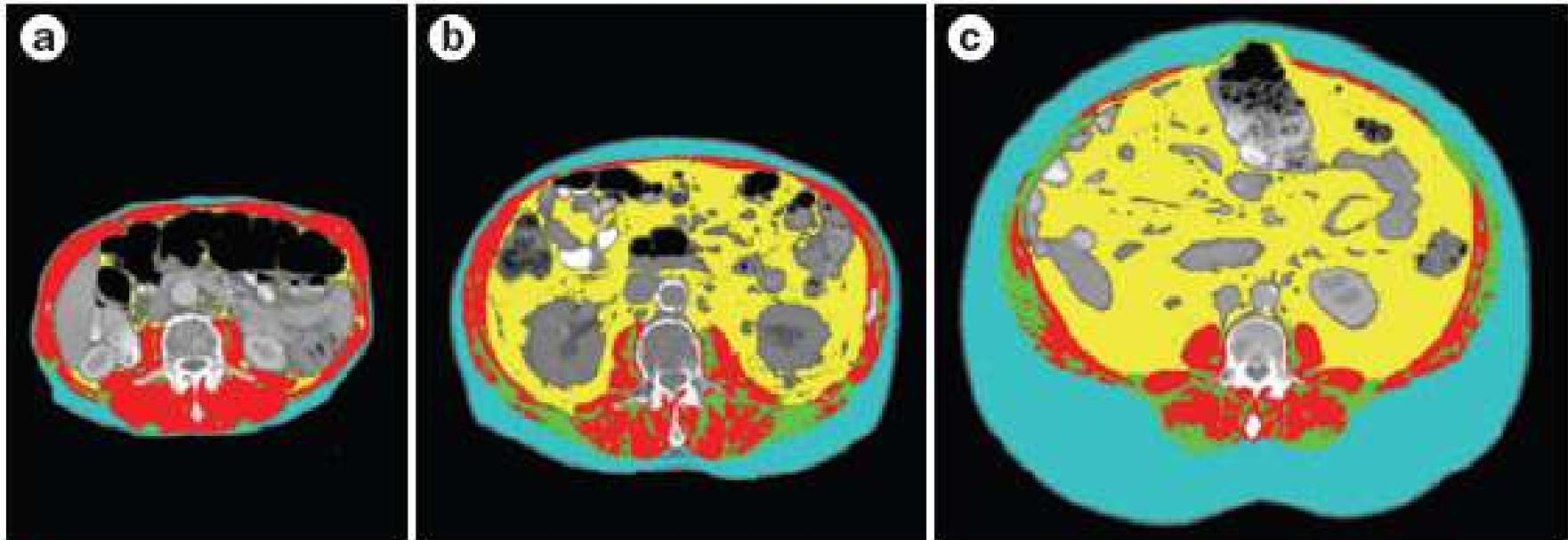
- MUST = Malnutrition Universal Screening Tool
- NRS 2002
- NUTRIC score (only validated in ICU pts)

Body composition

**Increasing importance
In cancer therapy:**

- 1) Tolerance to therapy
- 2) Calculating chemo doses
- 3) Predicting outcome in cancer therapy
medical
surgical

The Hidden Cachexia



- Total skeletal muscle (paraspinal, psoas, transverse/oblique abdominus, rectus abdominus)
- Visceral adipose tissue
- Subcutaneous adipose tissue
- Intermuscular adipose tissue

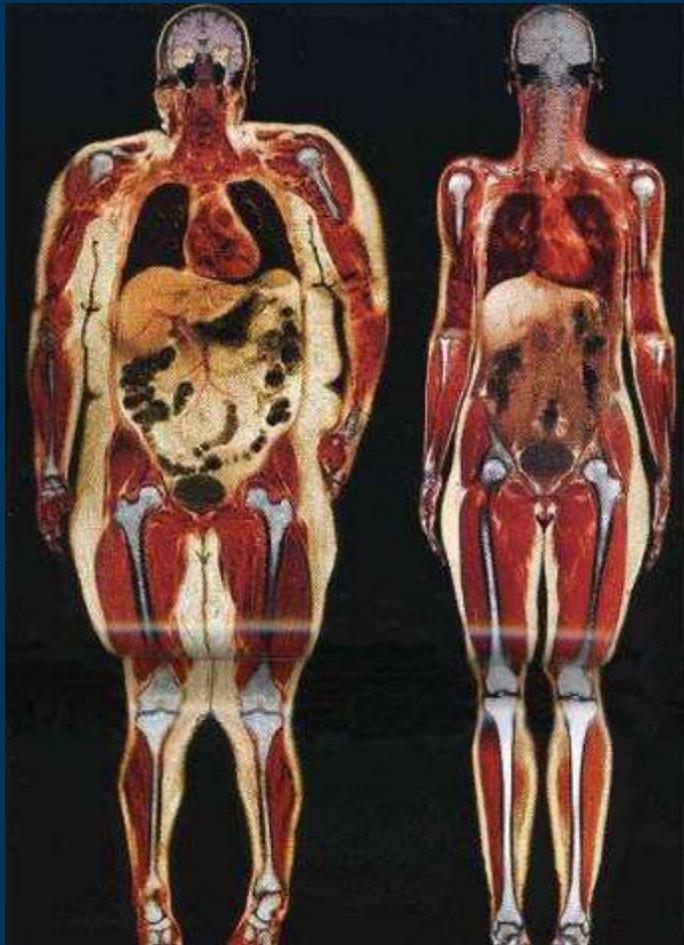
3 patients with esophageal cancer: all with similar amount of LBM

BMI 17

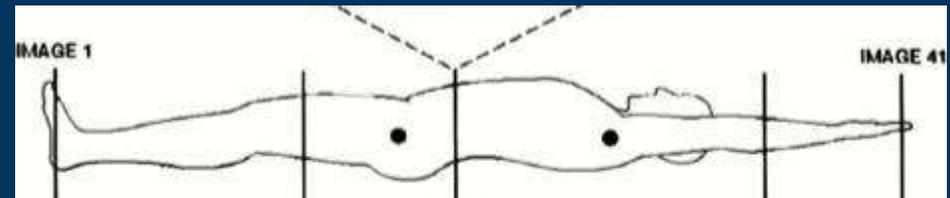
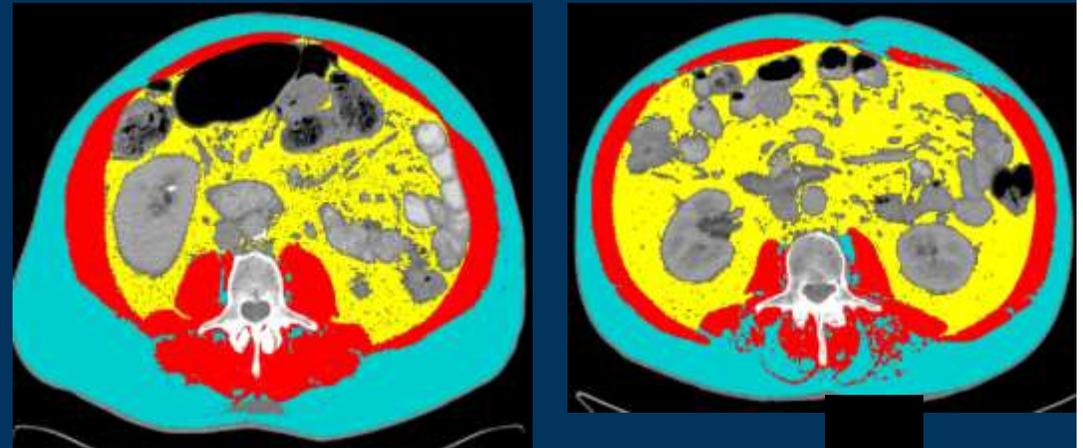
BMI 28

BMI 35

Body composition

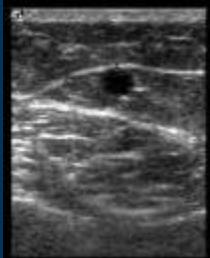
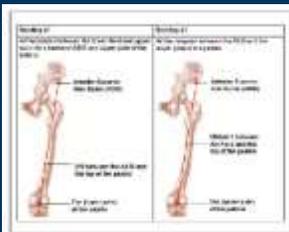


The coming assessment tool !



Diseases now proven to have correlated outcome and body composition.

Pancreatic Ca, Colorectal Ca, lymphoma, esophageal Ca, elderly trauma ICU, Hepatoma and AWR ?



Tillquist M JPEN 2013

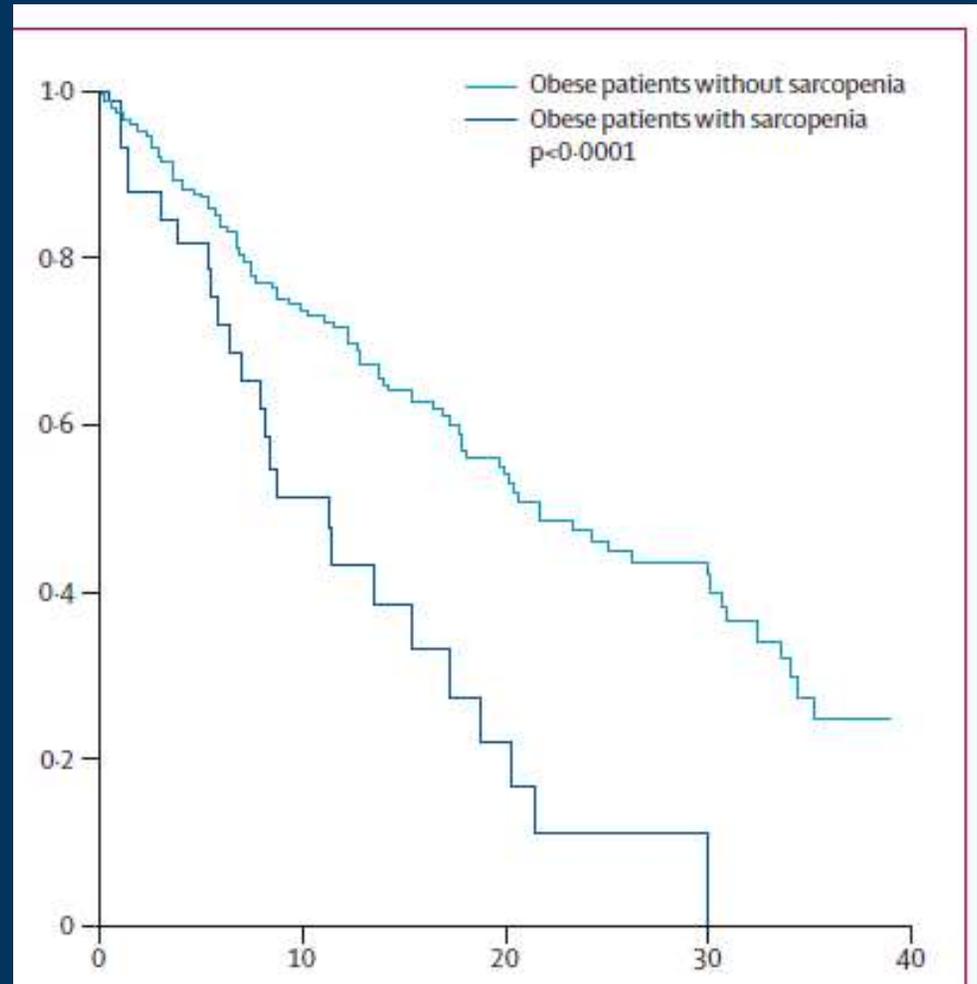
- 1) Peng P J GI Surgery 2012
- 2) Moisey LL CC 2013
- 3) Kirk PS et al J Surg Res 2015
- 4) Okumura S et al Surgery 2015
- 5) Prado CM Ann Med 2018

Sarcopenic obesity has a very poor prognosis

Sarcopenia is a predictor of survival independent of age, sex, functional status



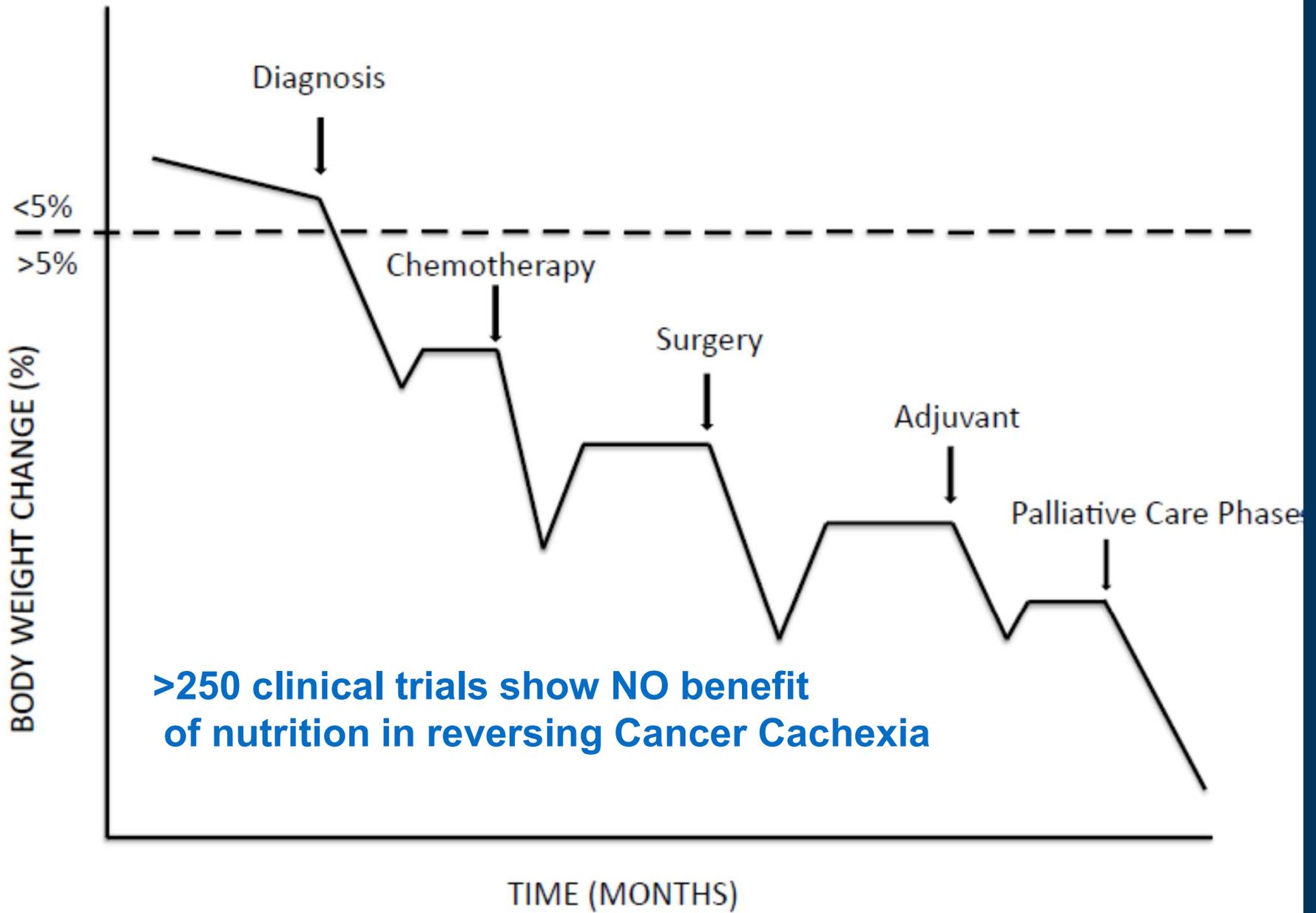
Cumulative survival



Survival (months)

Deutz NEP et al JAMDA 2019

Prado CMM, Baracos VE et al Lancet 2008



Samant SA et al Can J Physiol Pharm 2018
 Baracos V J Clinical Oncology 2013

Laviano A et al. Proc Nutrition Soc 2018

Metabolic Derangements Result in Cancer Cachexia

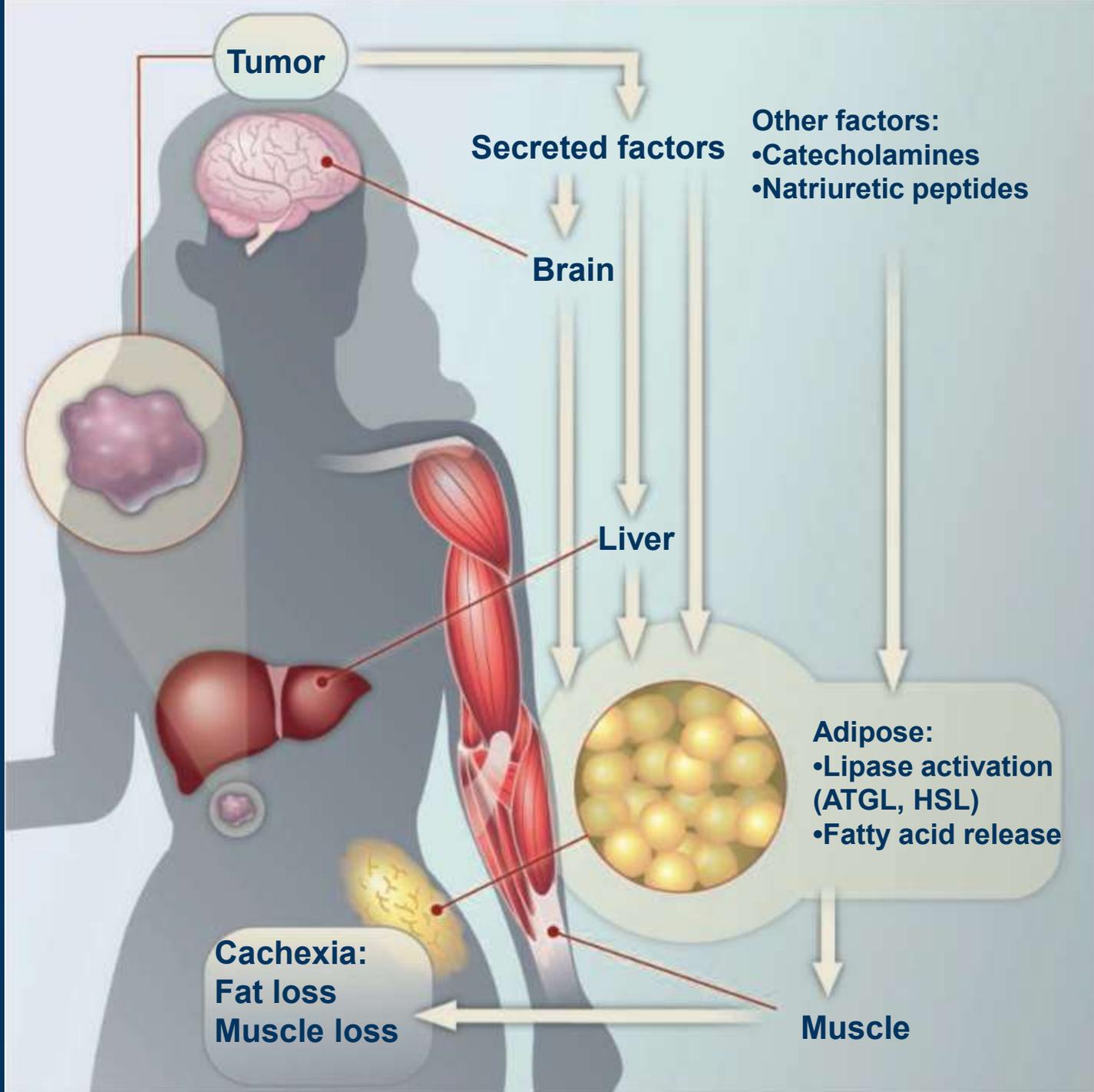
- Multi-factorial syndrome;
 - reduced food intake along with;
 - abnormal metabolism --
 - » muscle, adipose, CNS, immune tissue
 - systemic inflammation
- “Cachexia” results in reduction in:
 - Treatment tolerance
 - Response to therapy
 - Quality of life
 - Duration of survival



• Question:

Can appropriate and focused nutrition intervention alter this syndrome of progressive loss of skeletal muscle/adipose and functional impairment ?

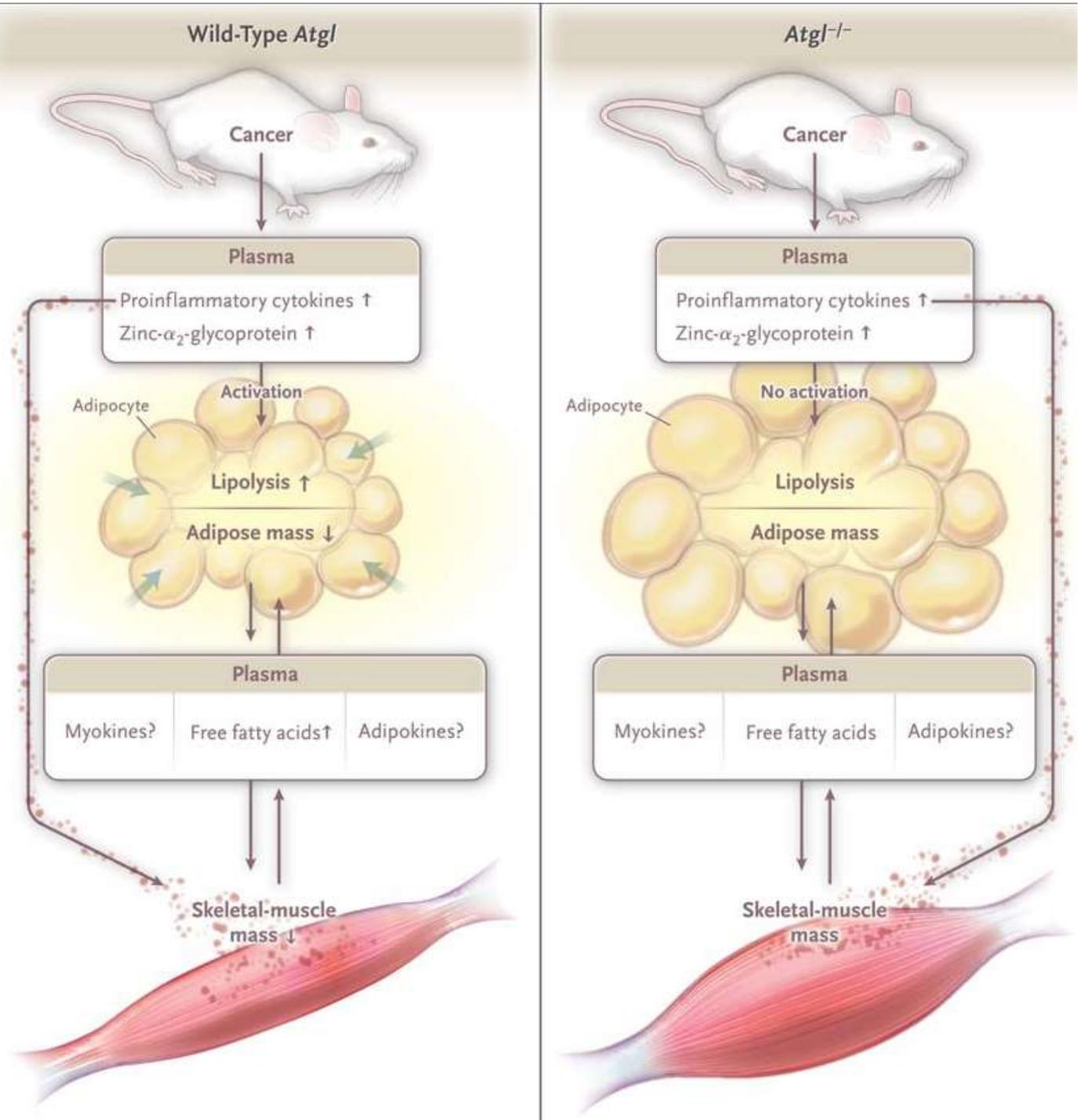
Drivers of Cachexia



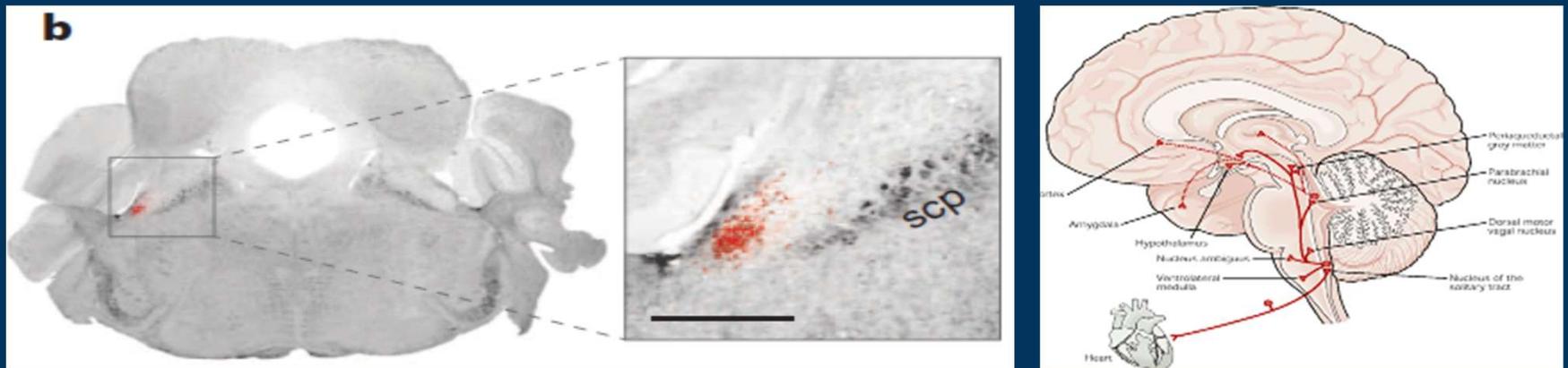
**Cross talk between
adipose and muscle.
KO mouse model**

**KO model adipose
triglyceride lipase:
(Atgl -/-)**

Fearon K NEJM 2011

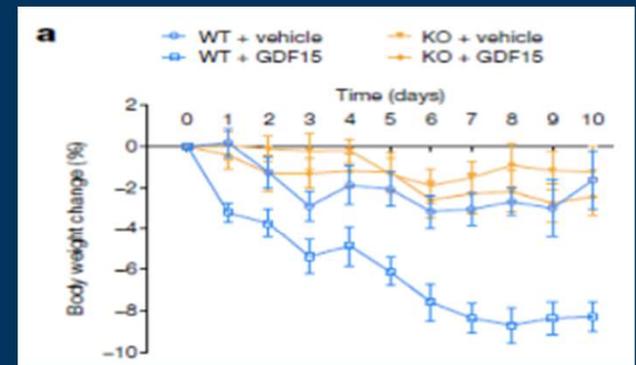
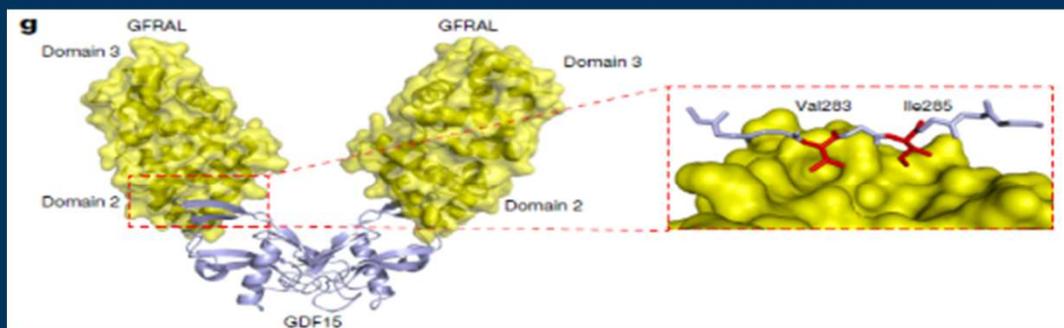


Genetic identification of a neural circuit that suppresses appetite

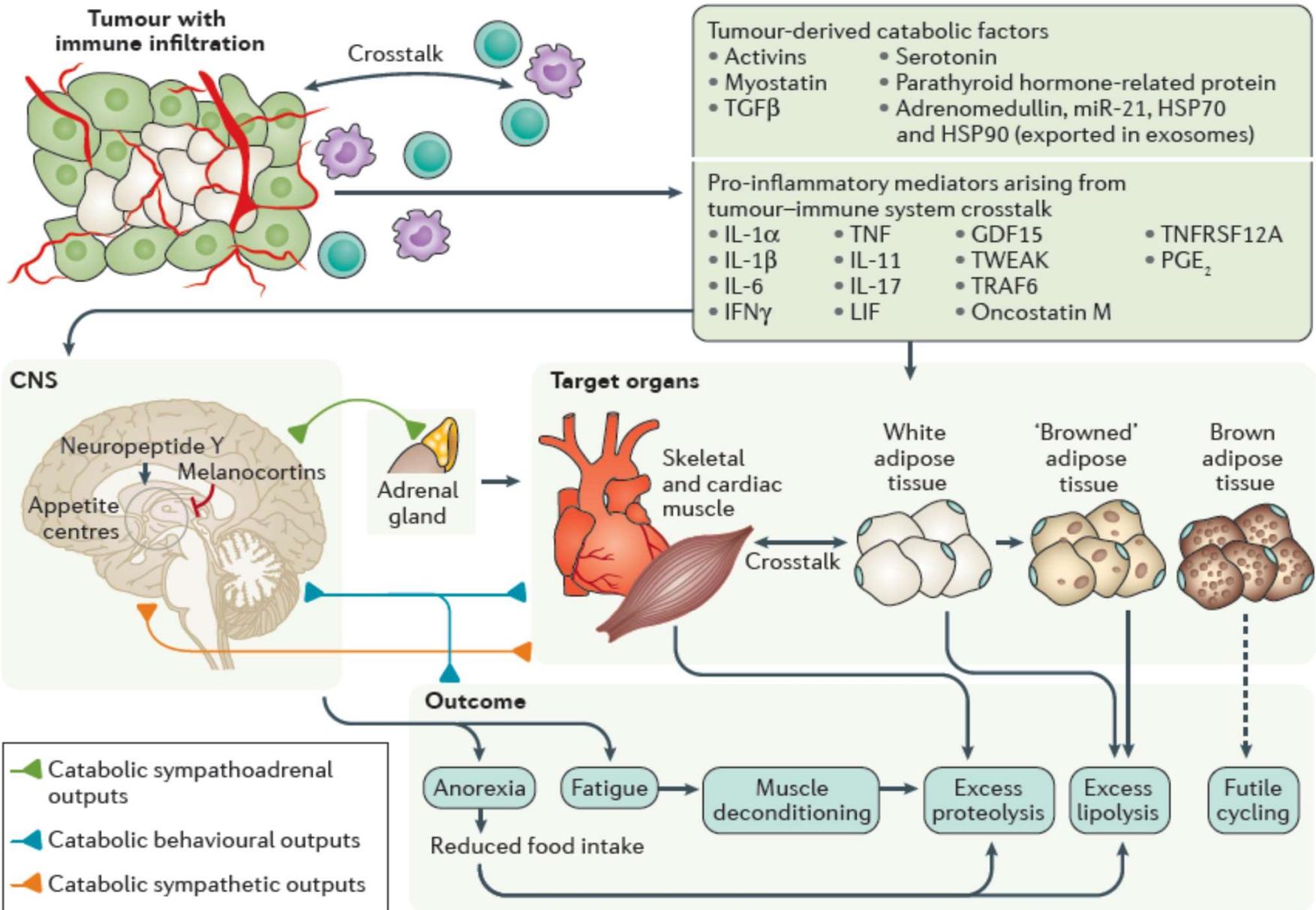


Carter ME et al. Nature 2013; 503:111-114

Non-homeostatic body weight regulation through a brainstem-restricted receptor for GDF15



Hsu J-Y et al. Nature 2017; 550:255-259





Appetite control in health



Homeostatic mechanism



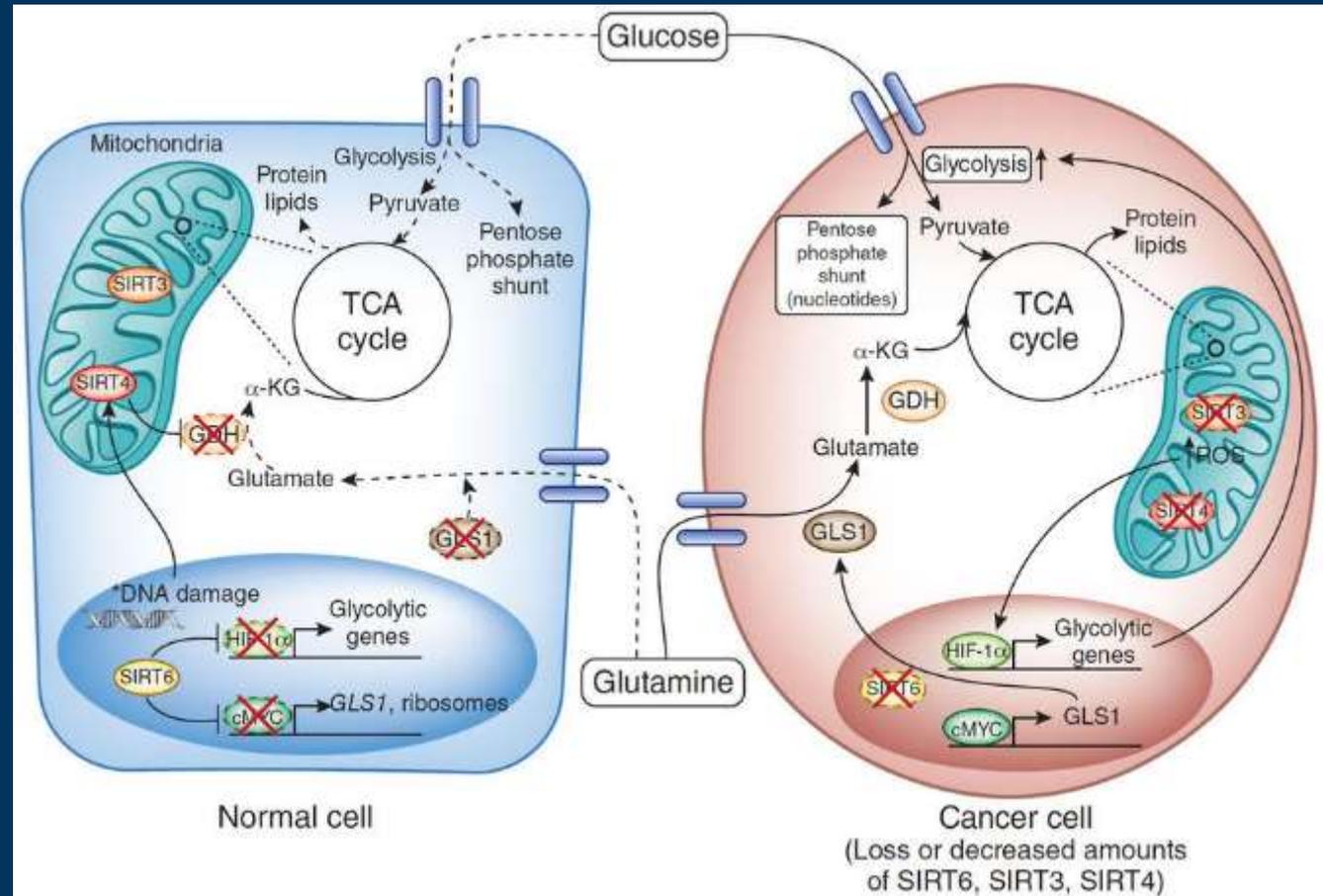
Appetite control in disease



Emergency pathway

The Warburg Effect

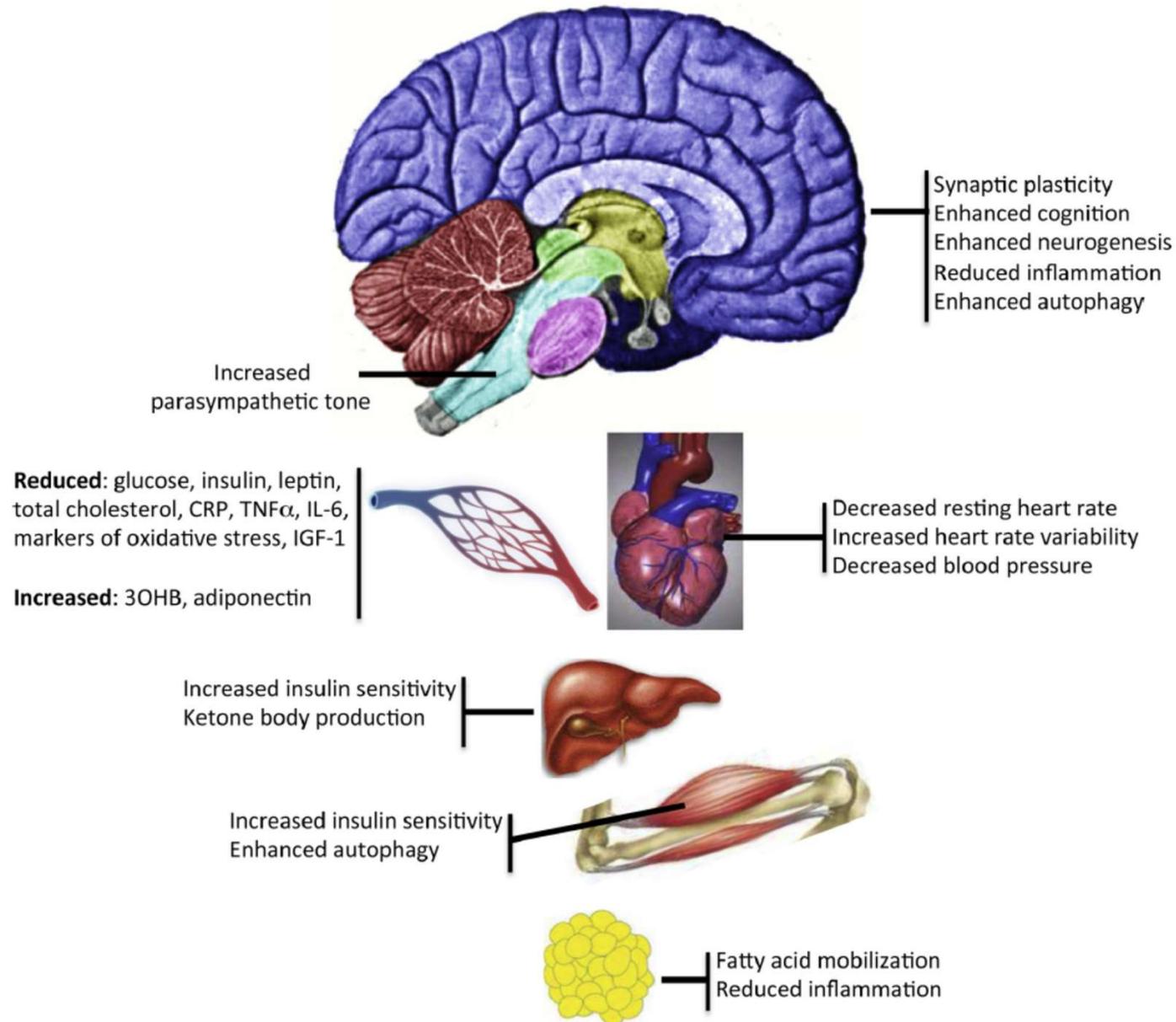
Otto H. Warburg
(1883 – 1970)



Cancer cells rewire their metabolism to promote growth, survival, proliferation, and long term maintenance. Increase uptake of glucose and conversion to lactate in the face of normal mitochondria ! The lactate alters Tumor Microenvironment !!

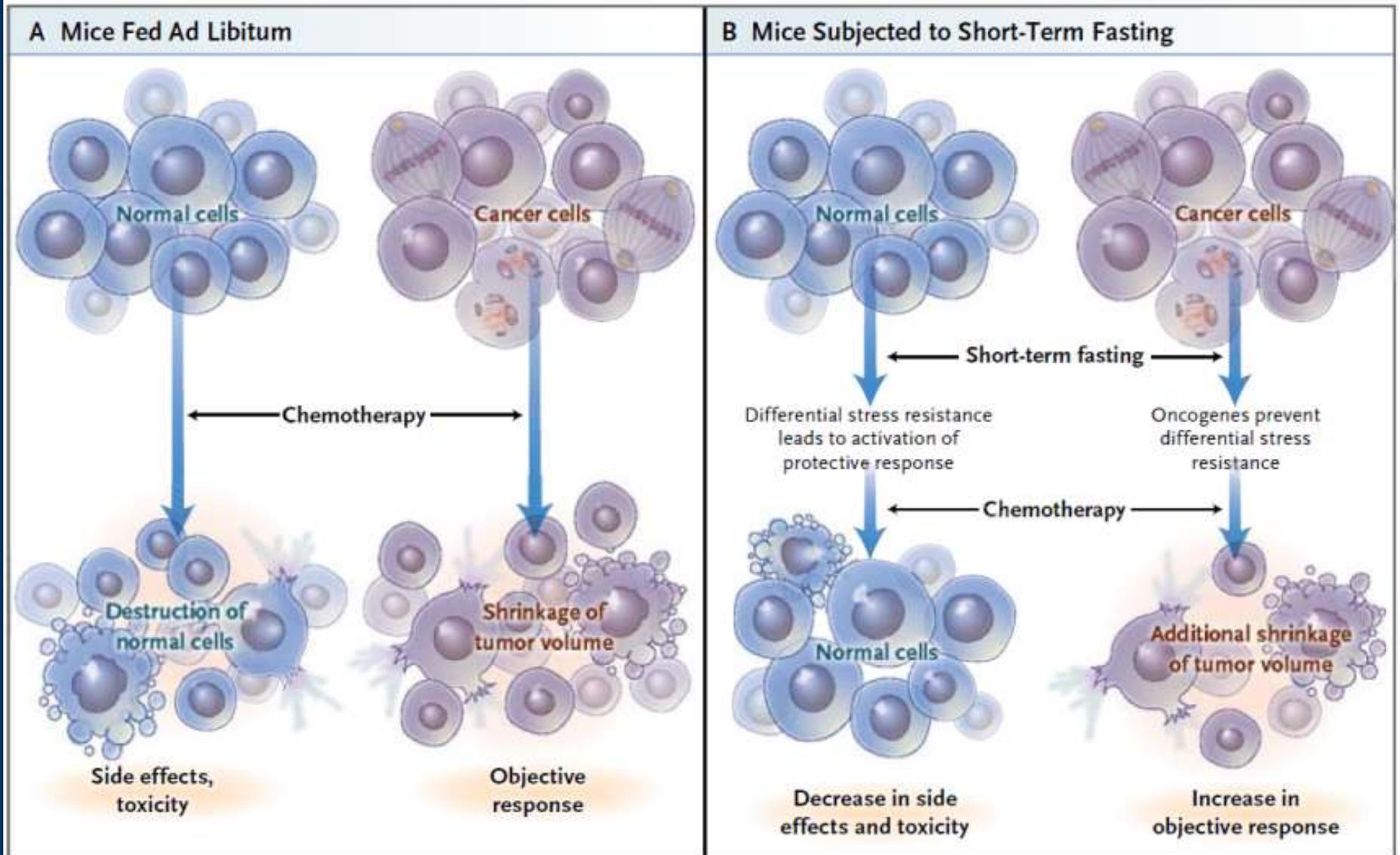
Liberti MV et al Trends Biochem Sci 2016 The Warburg Effect: How does it benefit cancer cells?
Potter M et al Biochem Soc Trans 2016 The Warburg Effect: 80 years on

Impact of intermittent fasting on health and disease processes



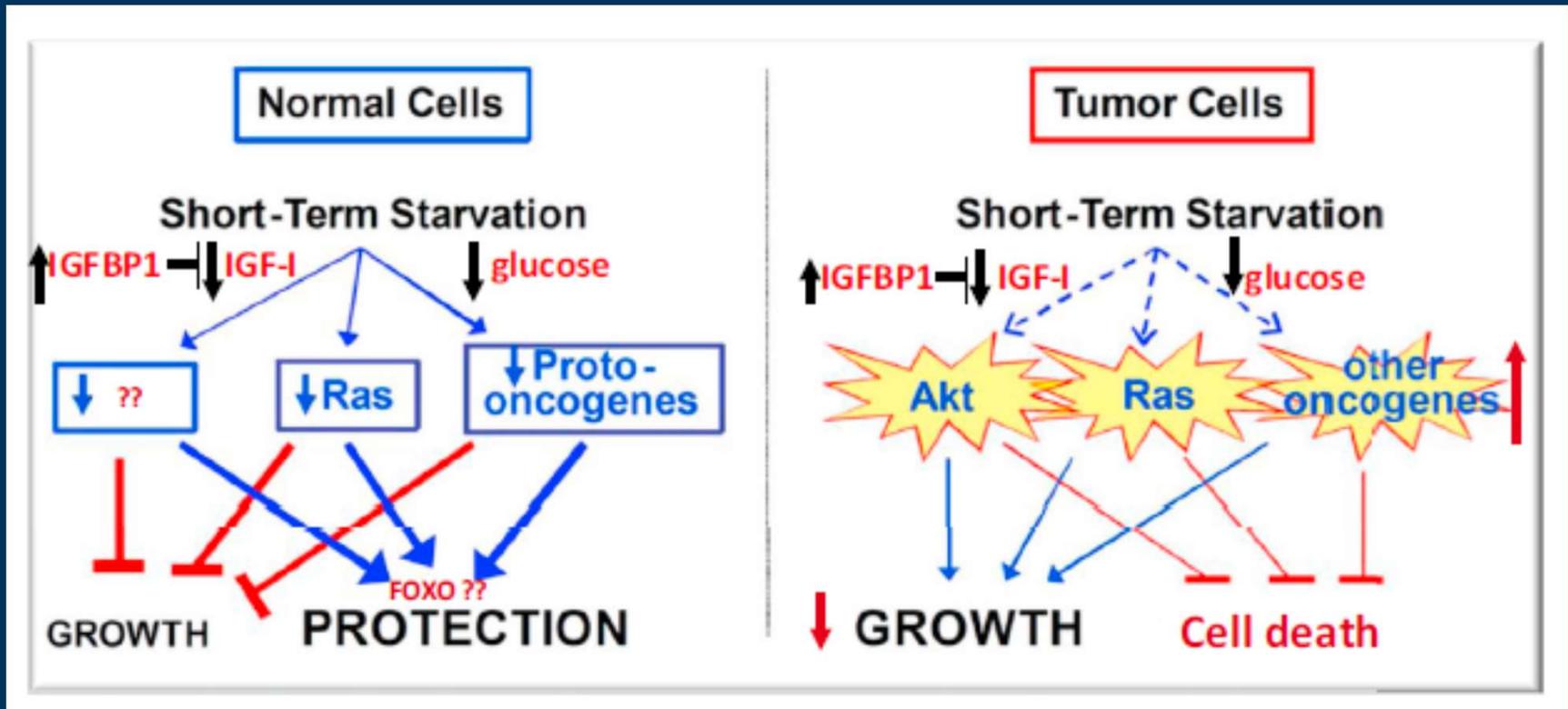
Toxicity in Chemotherapy — When Less Is More

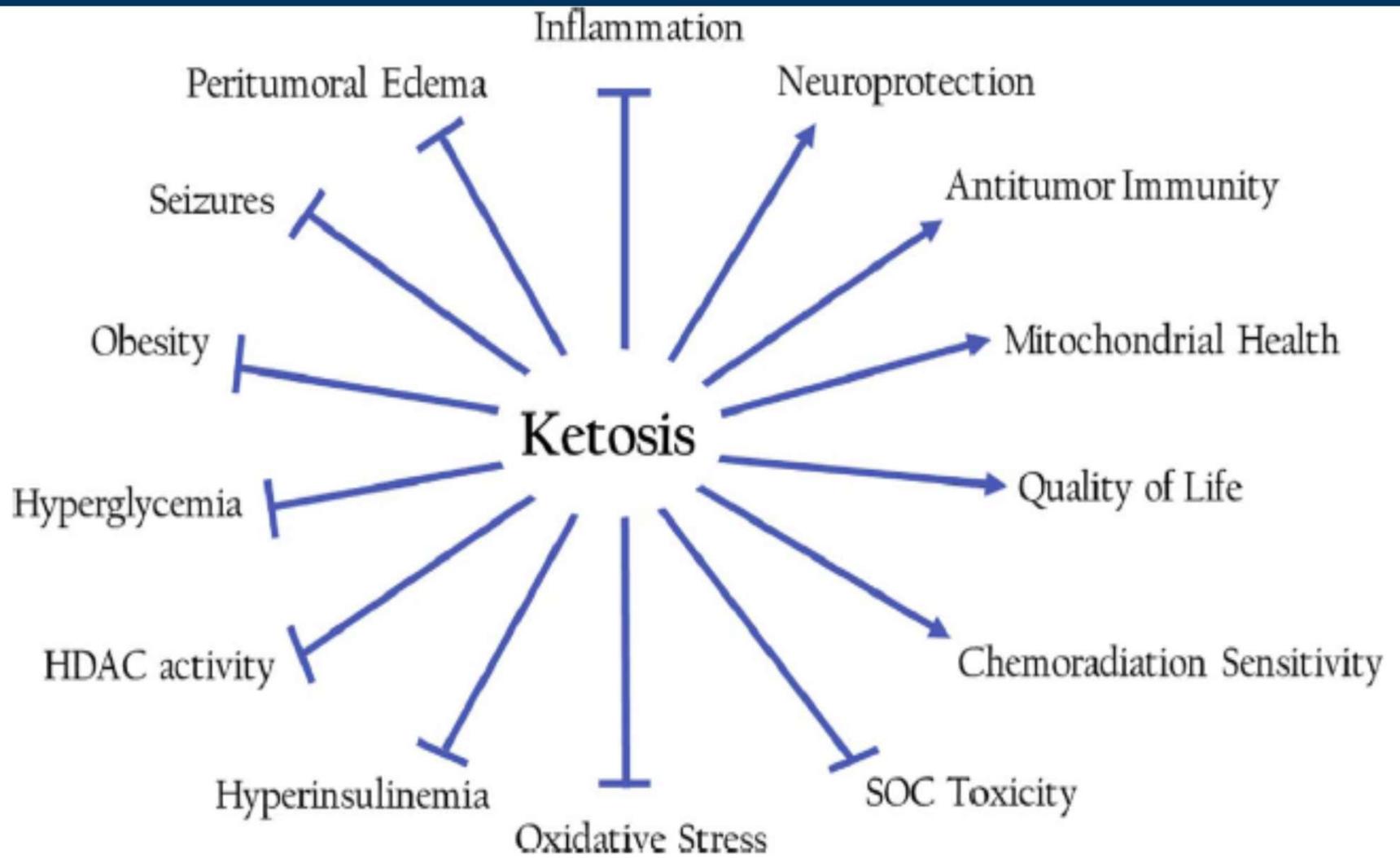
Alessandro Laviano, M.D., and Filippo Rossi Fanelli, M.D.

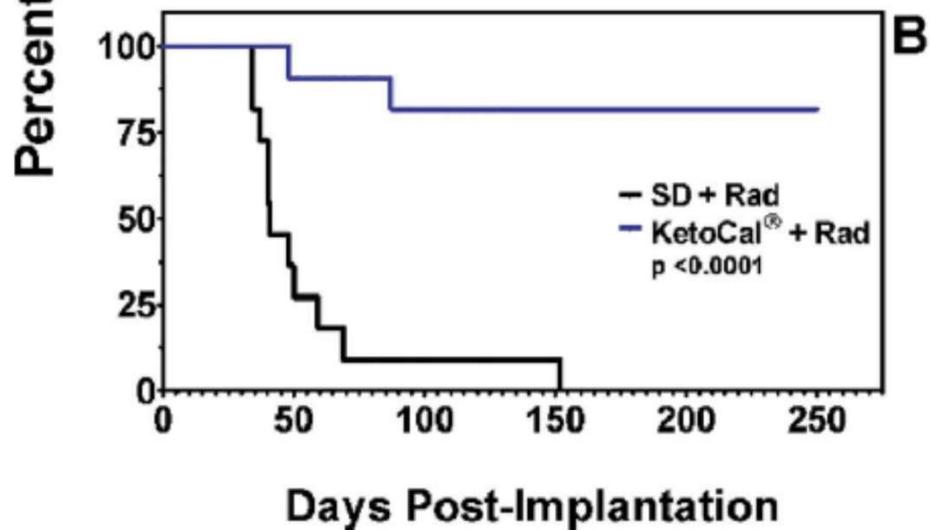
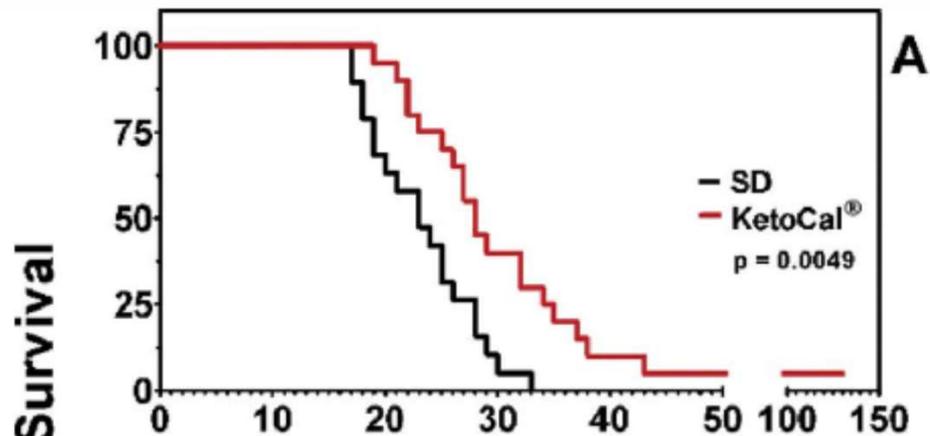


N Engl J Med 2012; 366:2319-2320

Fasting: Molecular Mechanisms and Clinical Applications





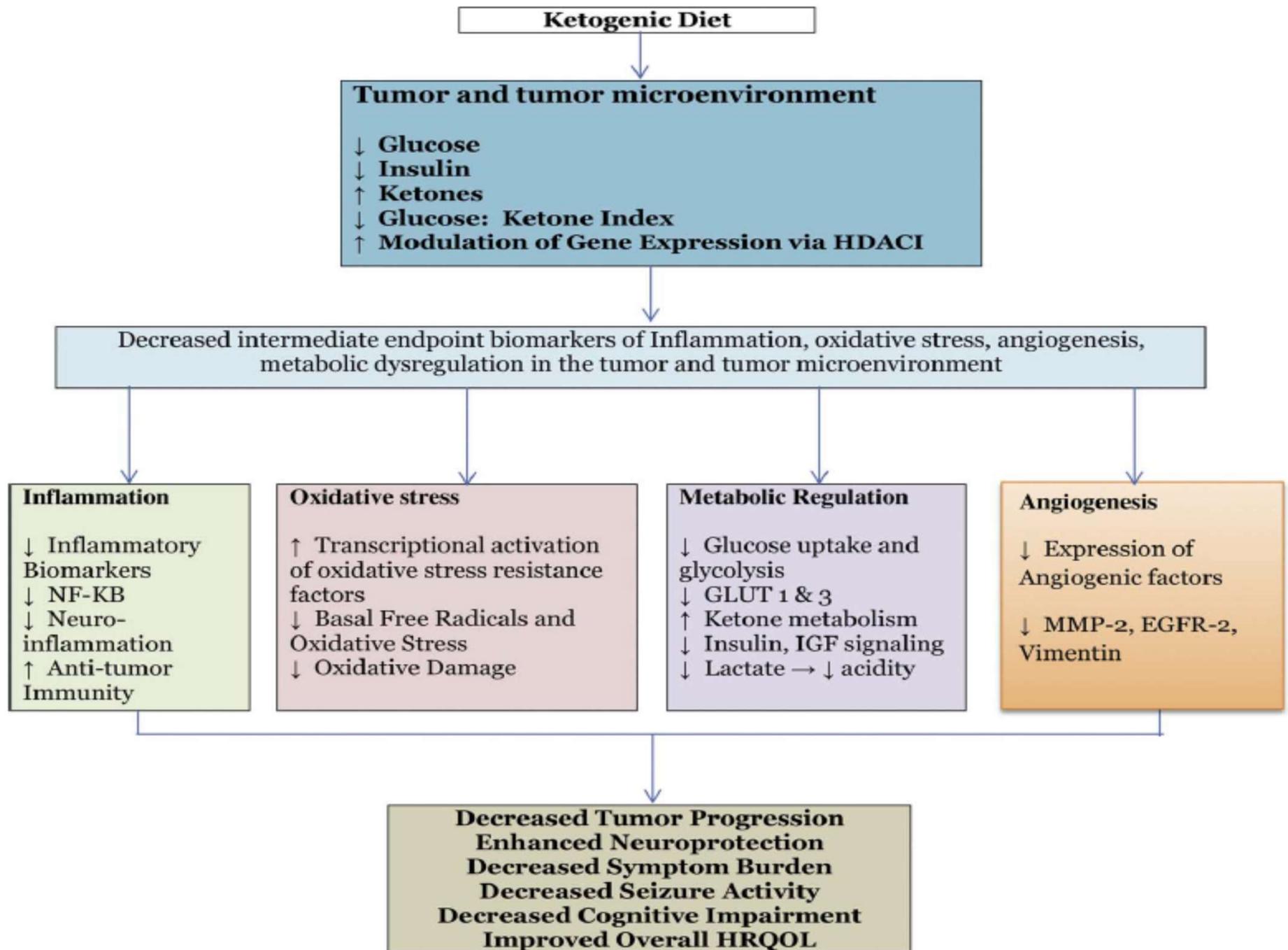


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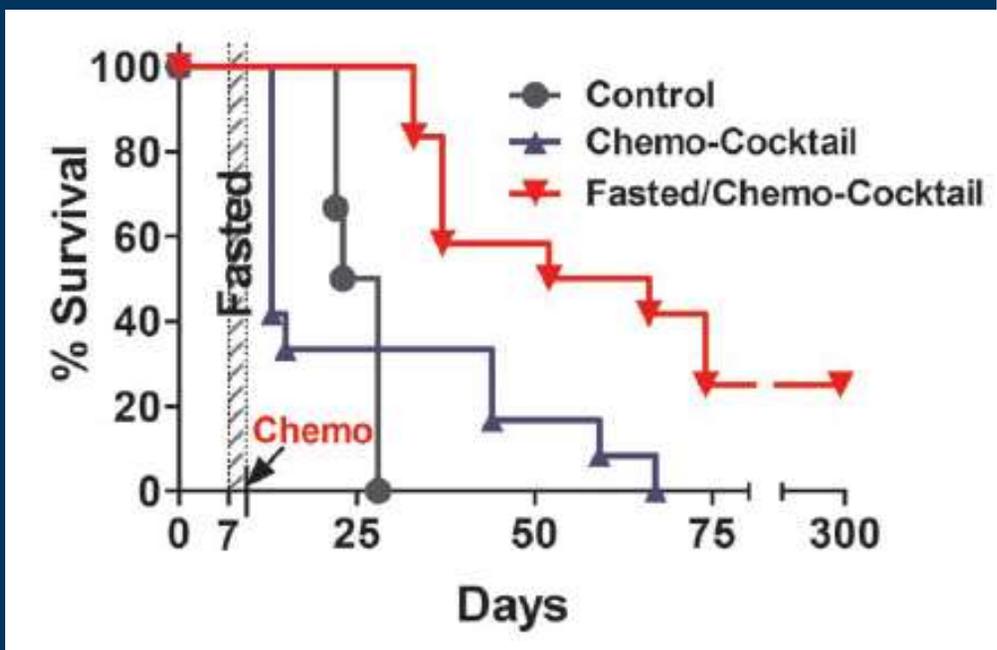
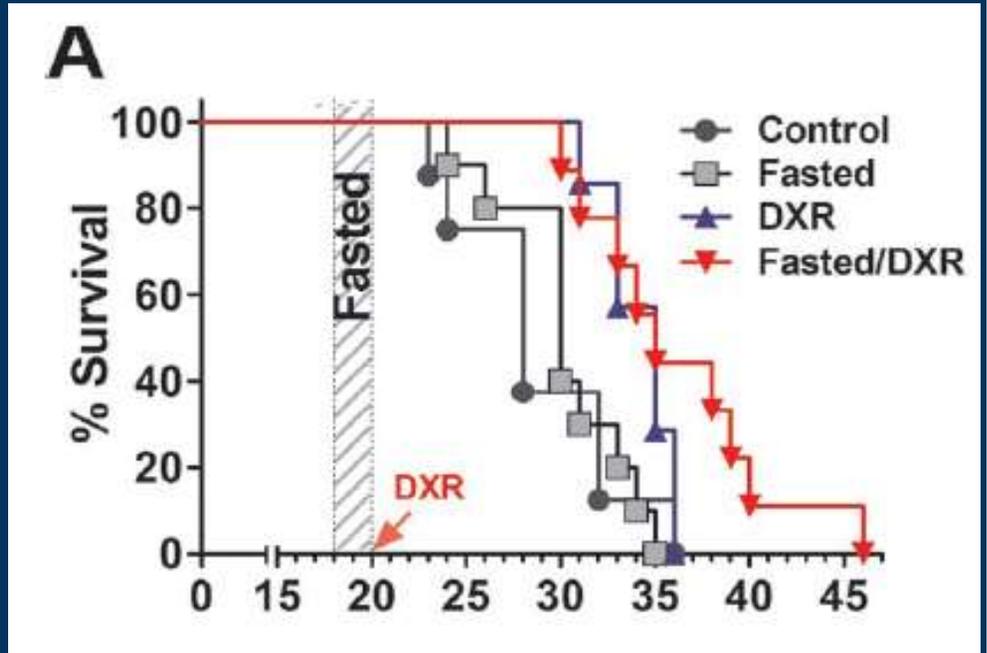
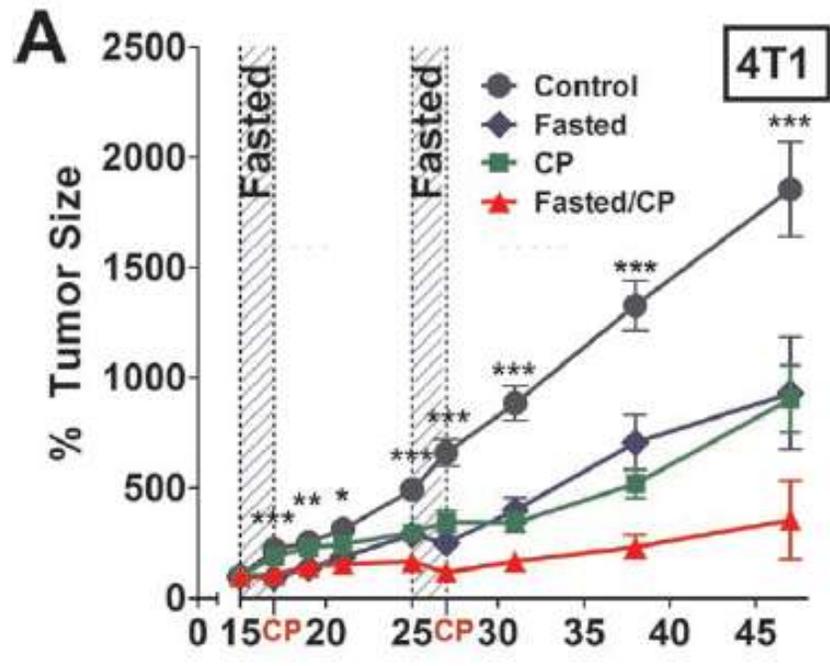
Treatment	Cohort Size	Median Survival (Days)
SD	19	23
KetoCal [®]	19	28
SD + Rad	11	41
KetoCal [®] + Rad	11	Undefined

Mouse Glioma model

Poff A et al Sem Cancer Biol 2018



Fasting Cycles Retard Growth of Tumors and Sensitize a Range Of Cancer Types to Chemotherapy



Lee C, et al Sci Trans Med 2012

Metabolic Derangements: Tumor cells invent new pathways to overcome the normal regulatory pathways

- **Carbohydrate**

 - Insulin resistance

 - Dramatic increased glucose turnover to lactate –in face of normal mitochondria

 - Glucose infusion fails to shut off carbohydrate turnover

 - Increased “wasteful” metabolic (Cori) cycle from lactate

- **Protein metabolism**

 - Loss of adaptive response to starvation (increased catabolism, anabolic resistance)

 - Increased protein turnover (impaired synthesis, increase degradation)

 - Proteolysis due to increased ubiquitin proteasome pathway

- **Fat metabolism**

 - Depletion of adipose tissue, lipid stores (anorexia, decrease intake)

 - Imbalance of lipogenesis and lipolysis

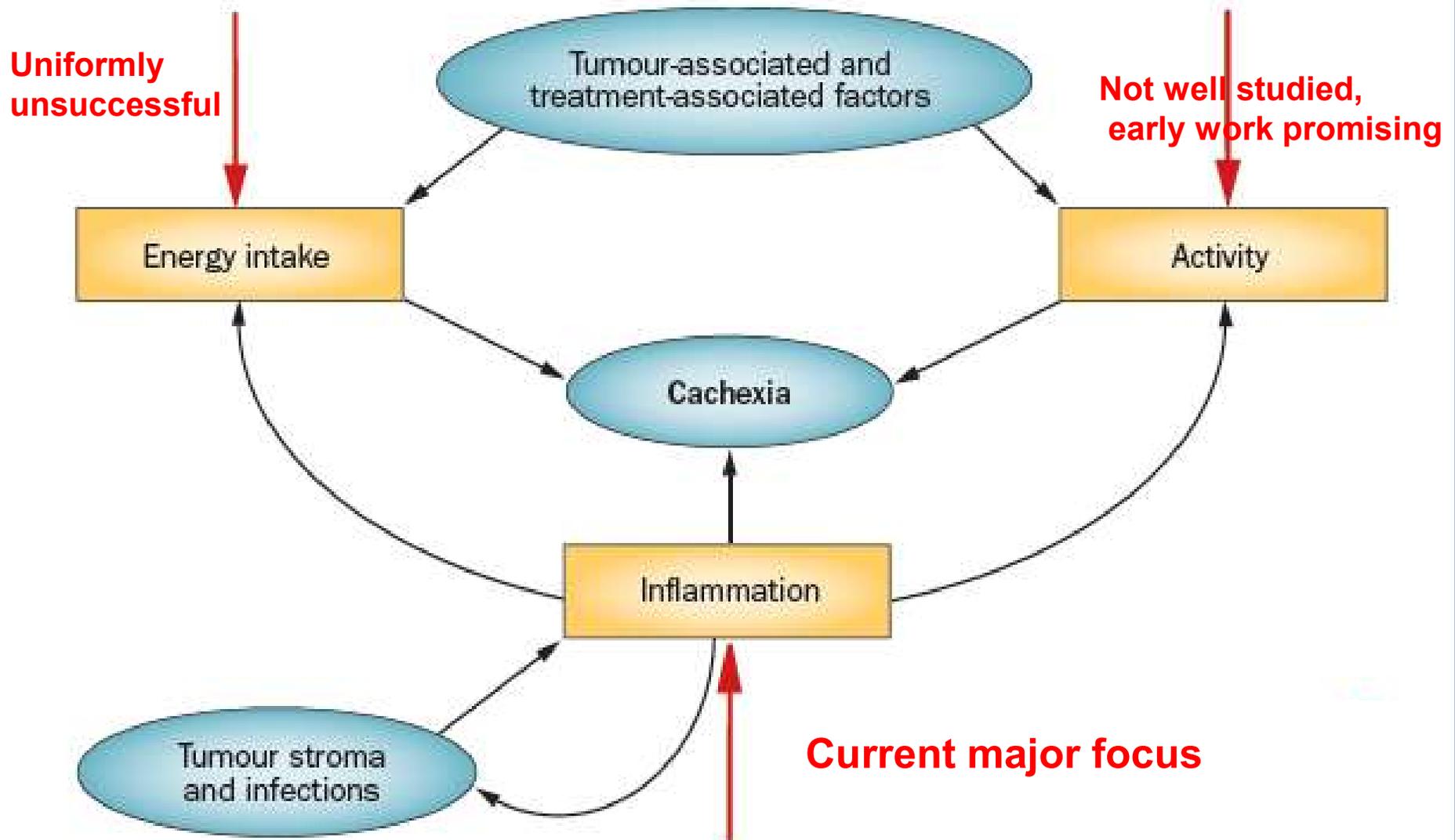
 - Tumors produce Lipid Mobilizing Factor

Suzuki H et al Cancer Cachexia—Pathophysiology and management. J Gastroenterology 2013

Israel M et al The Metabolic Advantage of Tumor Cells. Molecular Cancer 2011

Liberti MV et al Biochem 2019

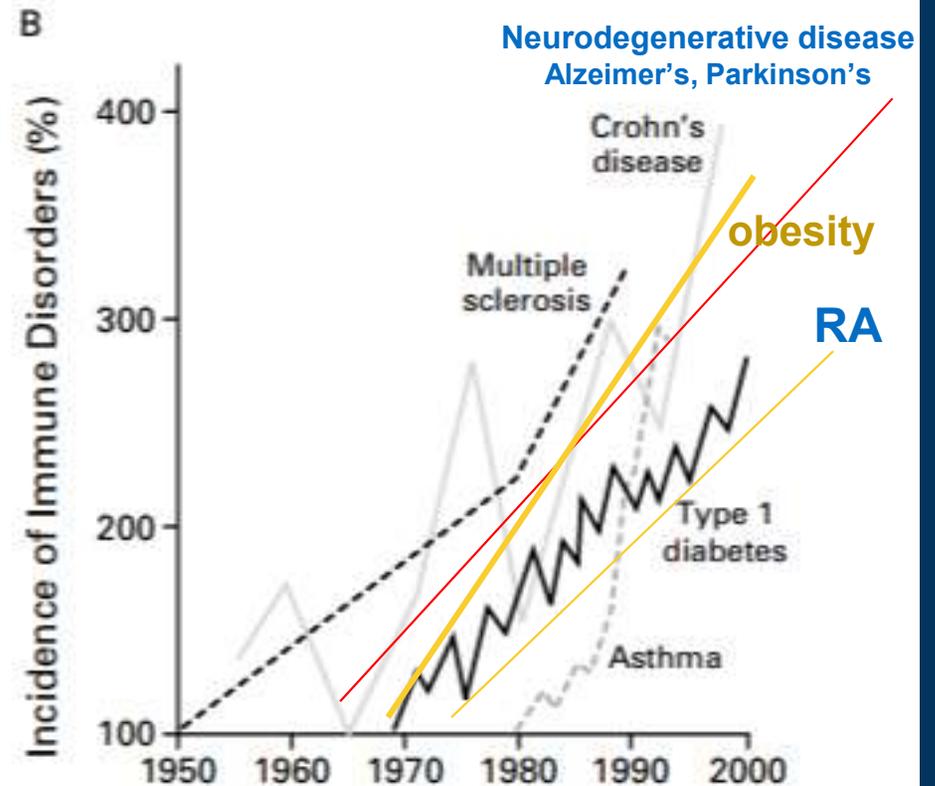
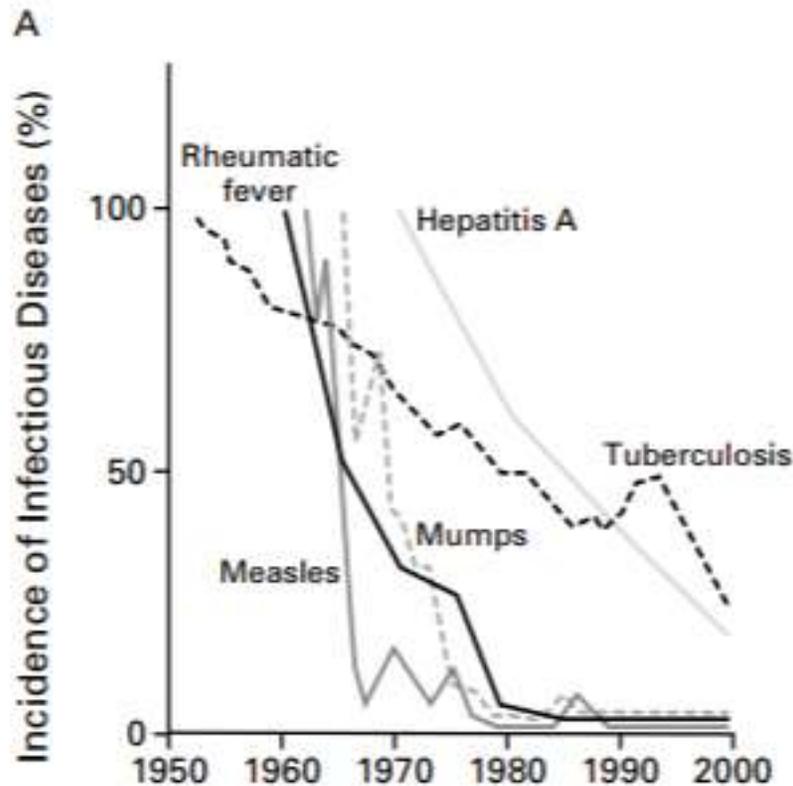
Success will require a multifaceted approach



Diseases where Inflammation is thought to be part or all of the etiology of the disease!

- **Diabetes**
- **Obesity**
- **Metabolic syndrome**
- **Heart disease**
 - atherosclerosis
- **Neuropsychiatric**
 - Depression
 - Anorexia nervosa
 - Alzheimer's
 - Parkinsons
- **Hepatic diseases**
 - NASH
 - cirrhosis
- **Infectious disease**
 - General, TB, Malaria
- **Asthma**
- **Allergy**
- **Inflammatory Bowel Disease**
- **Autoimmune diseases**
- **Peptic ulcer disease**
- **HIV / AIDS**
- **Cancer**
 - **Metabolic effects (cachexia)**
 - **metastasis**
- **Critical Care / Surgery**
 - Trauma
 - Pancreatitis
 - Transplantation
 - Sepsis
 - ARDS / ALI
- **Hypoxia**
- **Aging**
- **etc. etc etc**

Inflammatory Diseases are Overwhelming Infectious Diseases



Bach JF et al NEJM 2002

Bach JF et al Nature Rev Immunology 2017

Serhan CN et al JCI 2018

***H. pylori* infection**

H. pylori infects at least half of the world's population. The prevalence among middle-aged adults is over 80% in many developing countries, as compared with 20% to 50% in industrialized countries.

WHO classifies *H. pylori* as class one carcinogen

Suerbaum & Michetti NEJM 2002; 347:1175

Morowitz MJ Ann Surg 2011; 253:1094-1101

Associations: **Chronic Inflammation and Cancer**

- **Helicobacter pylori and gastric Ca**
- **Hepatitis C and liver Ca**
- **Human papilloma virus and cervical Ca**
- **Chronic cystitis and bladder Ca**
- **Chronic pancreatitis and pancreatic Ca**
- **Chronic reflux (Barrett's esophagus) and esophageal Ca**
- **IBD and colorectal Ca**
- **Asbestosis and mesothelioma**

Cancer association with inflammation

- **Estimated that 20% - 40% of cancer death worldwide are related to chronic infection and/or inflammation**
 - **gastrointestinal and lung cancers accounting for the substantial portion of the total burden**

Human neutrophils can induce malignant transformation which suggests that phagocytic cells are carcinogenic

**Morowitz MJ Ann Surg 2011
Kamp D Oncology 2011
Zitvogel L et al Nature Immunology 2017**

Inflammation is an indispensable participant in neoplastic process and promotes all stages of tumorigenesis

DNA damage

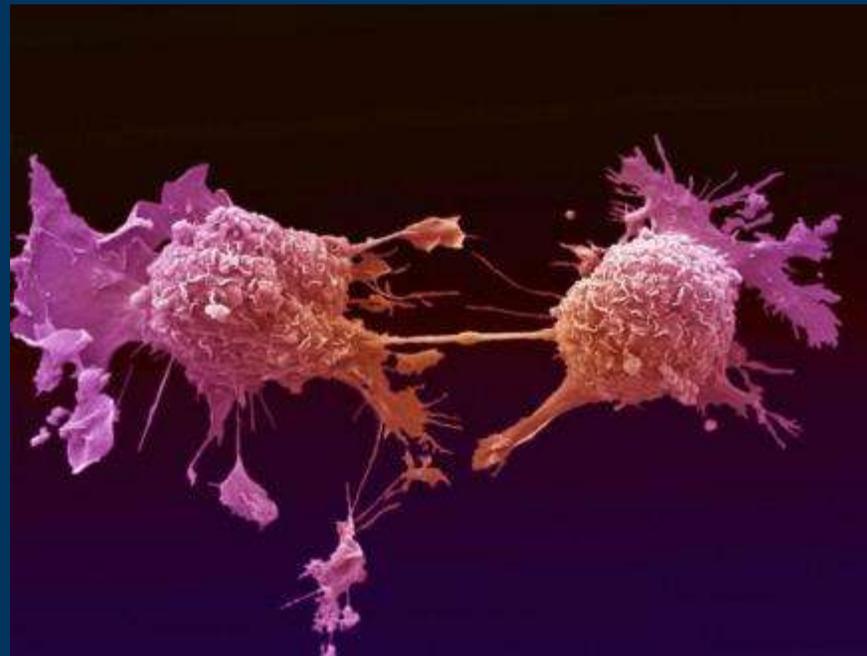
Insensitivity to growth inhibitors

Evasion of apoptosis

Tissue invasion and metastasis

Limitless replicative potential

Sustained angiogenesis



Self-sufficiency in growth signals

Inflammatory microenvironment

Nutrients / compounds with anti-inflammatory activity

- Vitamin C
- Vitamin E
- Zinc
- Selenium
- Probiotics
- Omega-3 FA (EPA/DHA)
- Carnitine
- Curry paste
- Resveratrol
- Glutamine
- Arginine
- Taurine
- Cysteine
- Willow Bark
- Leucine
- Threonine
- Glutathione
- Creatine
- Caffeine
- Glucosamine
- Echinacea
- Garlic
- Boswellia
- Turmeric
- Saffron
- Shark cartilage
- Ginger
- Licorice
- Chamomile
- Capsaicin

Omega 3 Fatty Acids: Acute Care Setting

◆ Clinical Data

- ◆ ↓ inflammatory response
- ◆ ↓ cardiac arrhythmias
- ◆ ↑ tissue microperfusion
- ◆ ↑ graft function
- ◆ ↓ cancer in cell lines
- ◆ Limits omega-6 immune suppression
- ◆ Maturation of CNS
- ◆ ↑ clearance

◆ Biochemical Data

- ◆ Biological regulators
- ◆ Cell membrane structure and function
- ◆ Influences membrane fluidity
- ◆ Alters receptors activity
- ◆ Eicosanoid metabolism
- ◆ Cytokine production
- ◆ Gene expression

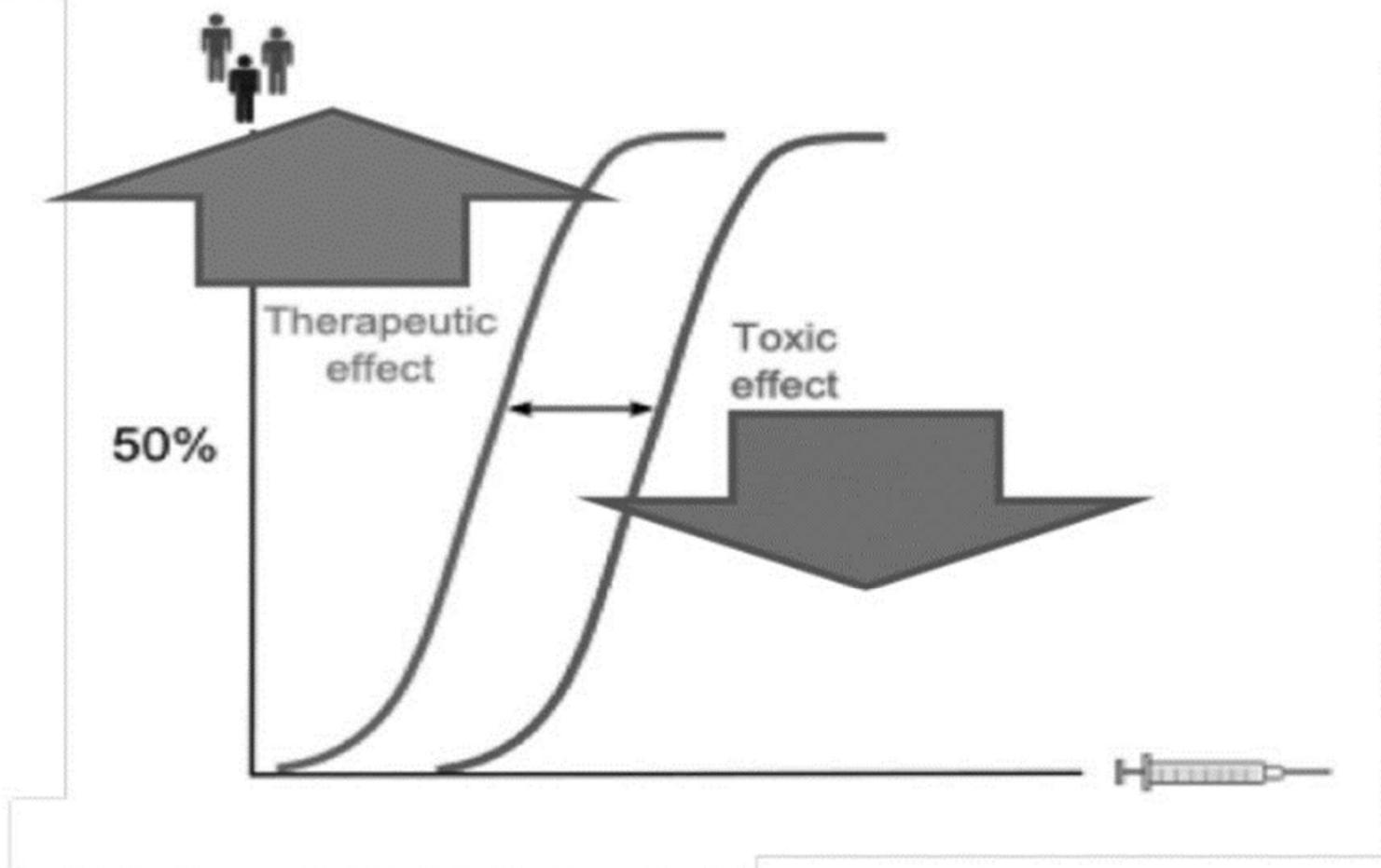
*Effects noted within 1 to 3 hours via
parenteral route 1-3 days via enteral*

Fish consumption and CRC

- Literature confusing with many small studies
- Meta-analysis
 - 22 studies prospective cohort
 - 19 case controlled trials
- Conclusion:
 - High fish consumption decrease CRC 12%



Increasing the therapeutic index



EPA/DHA in Cancer: Animal Models

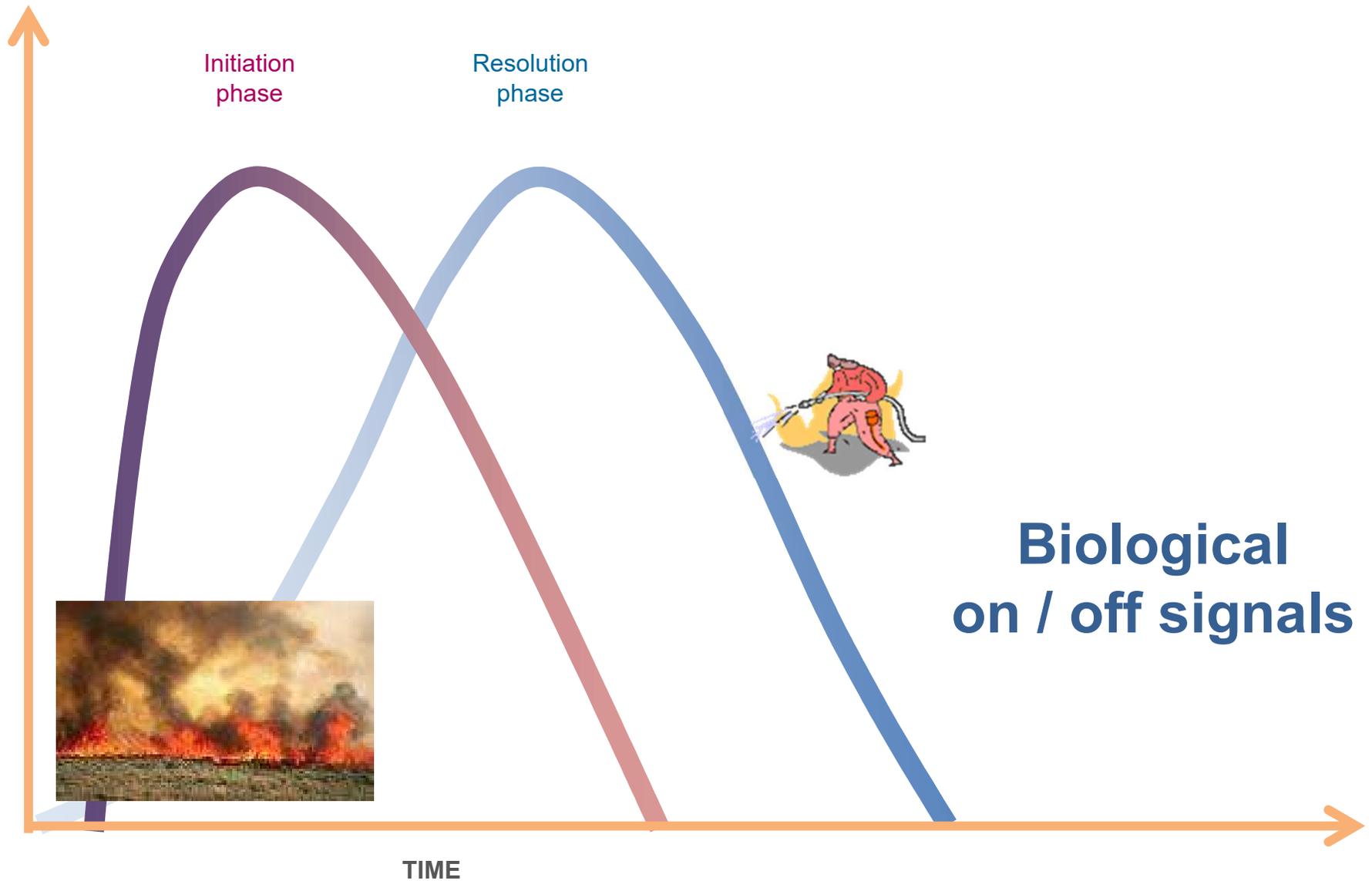
- **Tumor effects:**
 - Decrease tumor cell proliferation
 - Enhance tumor cell apoptosis
 - Promote cell differentiation
 - Limit tumor angiogenesis
 - Modulate tumor-extracellular matrix interaction
- **Therapeutic effects:**
 - Enhances tumor toxicity to antineoplastic drugs
 - Antracyclines, cisplatin, alkylating agents, vincristine, 5-FU
 - Offers protection to non-tumor tissues
 - Cyclophosphamide, arabinosylcytosine, doxorubicin, CPT-11
 - Multiple mechanisms and tissues showing benefit
 - Gut weight, histopathology, epithelial apoptosis, inflammatory mediators

Acute and Chronic Inflammation

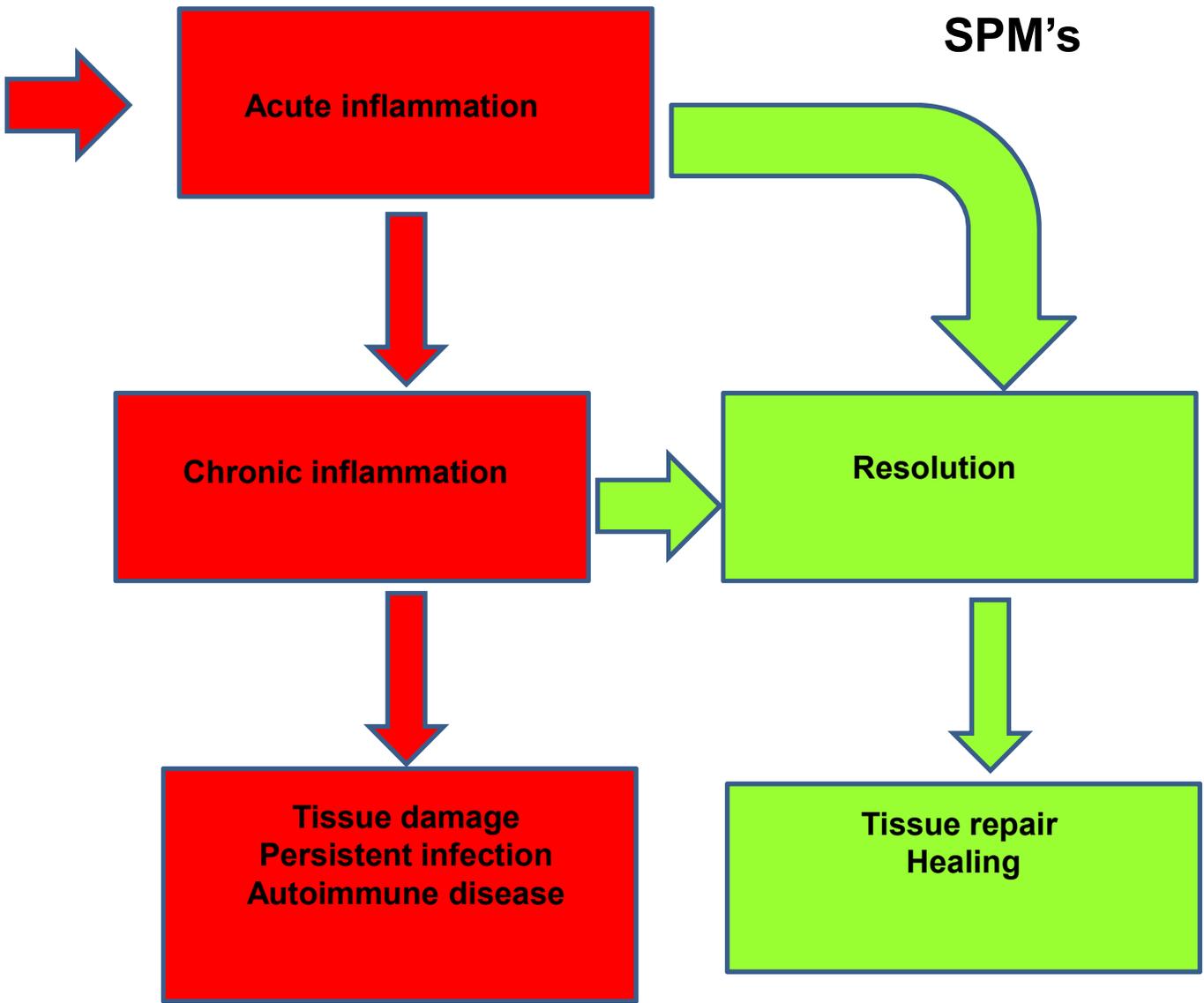
**We have been lost in
trying to prevent
inflammation**

**we forgot resolution of
inflammation**

Inflammation has two phases: initiation and resolution



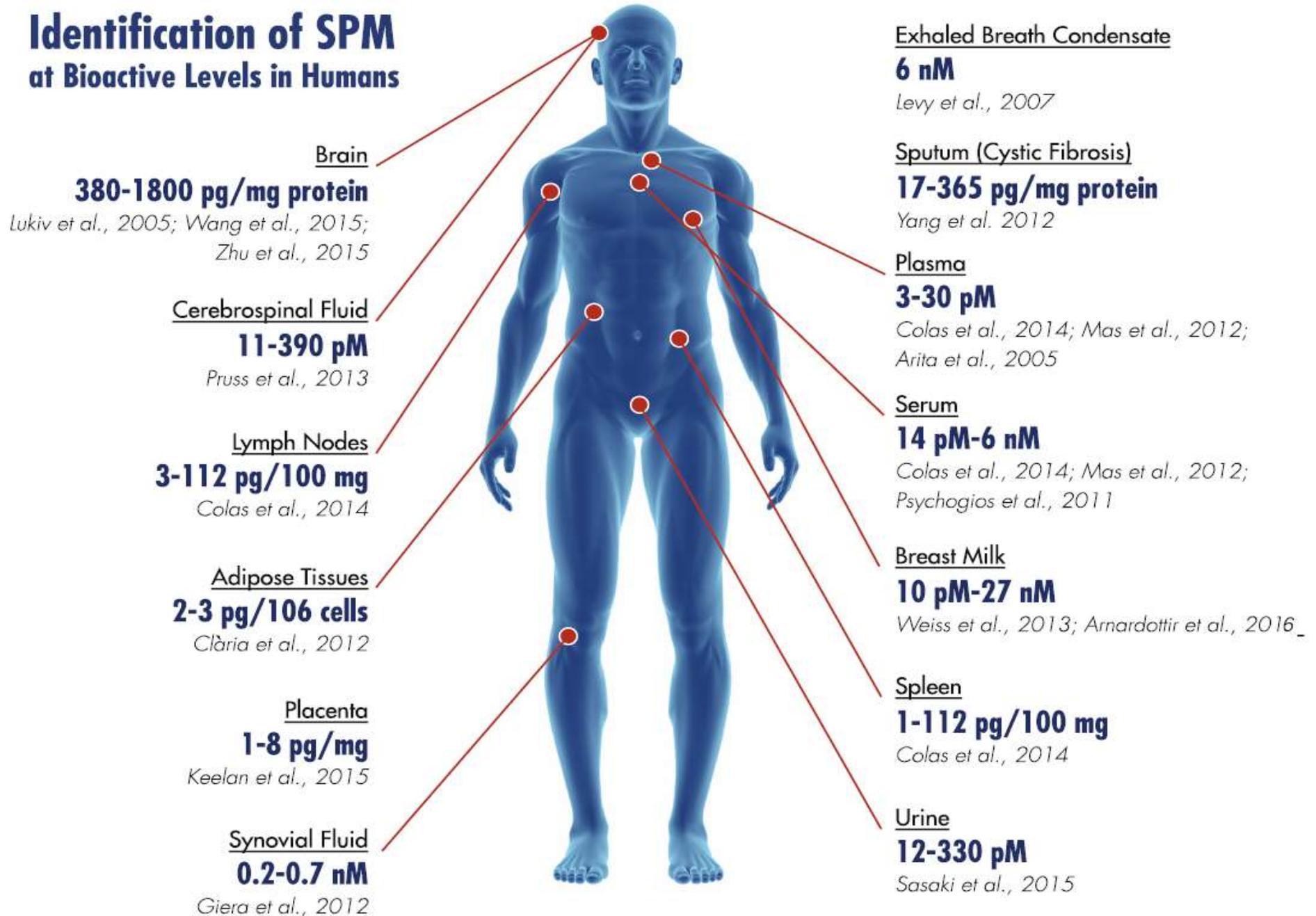
Tissue injury
Microbes



Resolvins,
Protectins
Maresins



Identification of SPM at Bioactive Levels in Humans



Does supplemental PO fish oil increase SPM products ?

- N=8 healthy subjects po intake 4.4gm/d x 1 month
- Omega 3 index after one month:
 - 5% +/-1 increased to 9% +/-2
- SPM “downstream” mediators
 - Increase;
 - 2.3 x 18-OH-HEPE
 - 1.7 x 15-OH-HEPE
 - 1.9 x 5-HEPE
 - 3.6 x 4-OH-DHA

SPMs in Cancer: protective role in Cancer development, progression and treatment

- **Bioactive lipid mediators**
 - **Cancer allows or stimulates persistent inflammation**
 - **Cancer shows defective inflammation resolution signals**
- **SPMs have both direct and indirect actions in cancer**
 - **Direct on epithelial cells**
 - **Indirectly on cancer associated stroma**
 - **Clearing Ca debris following therapy**
- **SPM's implicated in steps of neoplastic progression**
 - **Cell proliferation/survival**
 - **Inflammation**
 - » **Key target for bioactive lipids i.e. SPM's**
 - **Angiogenesis**
 - » **Key target for SPM — decreasing VEGF, HIF-1,**
 - **Metastasis**

Eltweri AM et al Clin Nutr 2017
Prevete N et al Pharm Res 2017
Sulciner ML et al J Exp Med 2018

Resolvins suppress tumor growth and enhance cancer therapy

Megan L. Sulciner,^{1,2,3*} Charles N. Serhan,^{4*} Molly M. Gilligan,^{1,2,3*} Dayna K. Mudge,^{1,2,3*} Jaimie Chang,^{1,2,3} Allison Gartung,^{1,2,3} Kristen A. Lehner,^{1,2,3} Diane R. Bielenberg,⁵ Birgitta Schmidt,⁶ Jesmond Dalli,⁴ Emily R. Greene,^{1,2,3} Yael Gus-Brautbar,^{1,2,3} Julia Piwowarski,^{1,2,3} Tadanori Mammoto,⁵ David Zurakowski,^{7,8} Mauro Perretti,¹² Vikas P. Sukhatme,^{3,9} Arja Kaipainen,¹³ Mark W. Kieran,^{10,11*} Sui Huang,^{14*} and Dipak Panigrahy^{1,2,3*}

Journal of Experimental Medicine 2018

- **Cancer treatment a double edge sword:**
 - Cancer therapy reduces tumor burden by killing tumor cells
 - Creates tumor cell debris that stimulates inflammation and tumor
- **Debris-stimulated tumors were inhibited by anti-inflammatory and pro-resolving lipid mediators**
 - Resolvin D1 (RvD1), RvD2, or RvE1
- **Enhancing endogenous clearance of tumor cell debris is a new therapeutic target in cancer therapy**

Where are we in regards to SPM in cancer management ?

- **SPM can play crucial role in controlling inflammatory process and inhibiting angiogenesis**
 - **Altering neoplastic progression via cell proliferation**
 - **Inflammatory control**
 - **Altering angiogenesis**
 - **Changing metastatic potential**
- **Significant potential for SPMs in cancer prevention and therapy**
 - **Prevention via modulating “tumor environment”**
 - **Macrophage phenotype M1, decrease VEGF etc**
 - **Chemo, radiation, surgery**
 - **Clearing tumor debris**

Prevete N et al Pharm Res 2017

Greene ER, Serhan CN et al Prostaglandins Lipid Mediators 2011

Sulciner ML et al J Experimental Medicine 2018

What is the evidence that SPM's are relevant to human disease?

- **Evolutionarily conserved** (function at nanogram to picogram levels)

- Flatworms
- Frogs
- Mice
- Humans



- **SPM serum profiles correlated with outcome**

- Sepsis: Increased levels – associated with 28 day decreased mortality
- Surgical infections- less antibiotics required
- CF – improved *P. aeruginosa* clearance
- TB – disease activity associated with SPM serum level
- **Ca therapy- alters angiogenesis, tumor microenvironment**
- Herpes eye infection: increased vision , viral clearance
- In-vitro healthy vol: WBC improved bacterial clearance
- Post-op Hepatobiliary surgery decrease inflammation, infections

» Resolvin E1 correlates with inflammation

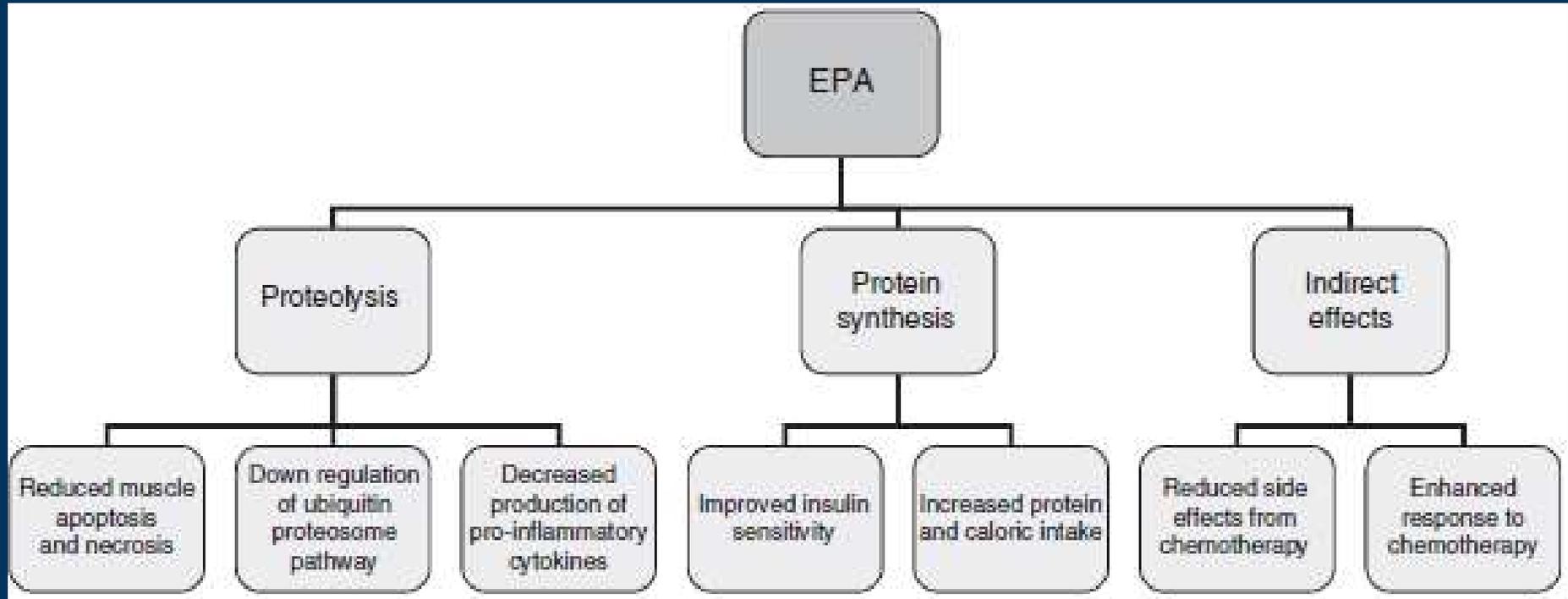
Dalli J Molecular Biol 2017

Dalli J et al Crit Care Med 2017

Serhan CN FEBS 2017

Uno H et al Surgery 2016

Summary: Proposed influence of EPA in Cancer



Loss of Lean Body Mass and Outcome ?

“Sequential Metabolic Changes Following Induction of SIRS in Patients with Severe Sepsis or Major Blunt Trauma” ¹

- ↑ over REE peaks 4-5 days
- Continues 9-12 days, still ↑ 21 days
- 16% TBP lost first 21 days (67% from muscle)
- ? Mechanism, not just pro-inflammatory cytokines

Loss of lean body mass clinical consequences ²

10% impaired Immune function

20% impaired wound and rehabilitation

30% pneumonia and pressure ulcers

40% Death (pneumonia)

1) Plank. WJS 24:630-638, 2000

2) Martindale R Physiologic Basis of Surgery 2008

3) Martindale R et al JPEN 06

Protein in the Critical Care Setting: Basic Principles

- Essentially all protein is functional with no storage form of protein
 - Small amount in gut protein available between meals
 - Autophagy may utilize “non-functional” intracellular proteins
- Skeletal muscle largest available pool nitrogen
 - Skeletal muscle largest glucose disposal site
 - Muscle loss starts early after ICU admission
- In the ICU setting
 - Protein synthesis rate relatively unchanged (some decrease)
 - Protein degradation dramatically increased
 - degradation is uniformly distributed among cellular proteins – contractile, mitochondrial etc
 - Most critically ill receive 0.6 to 0.8 g/kg/d (reported in observational studies)
- Associations:
 - Poor outcomes noted in ICU patients with sarcopenia on admission

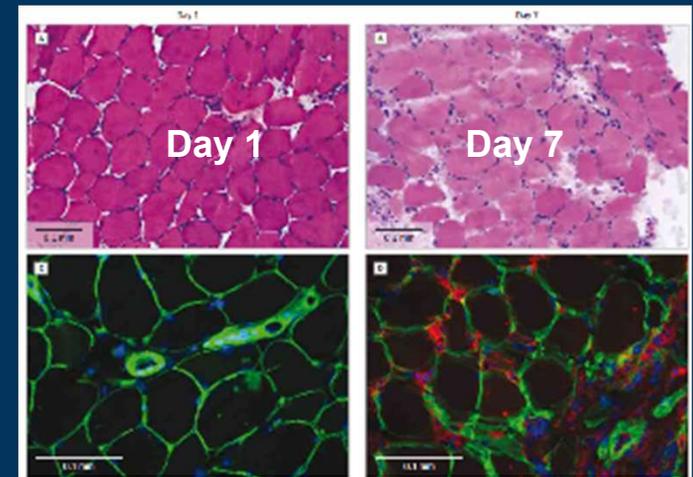
Acute Skeletal Muscle Wasting in Critical Illness

Prospective study of 63 critically ill patients

- Expected stay > 7 days, Vent > 48 hours
- 3 methods to determine muscle loss
 - Serial US
 - Histology
 - Biochemistry – DNA/Protein ration and fractional synthesis breakdown rates. (Leucine uptake etc)

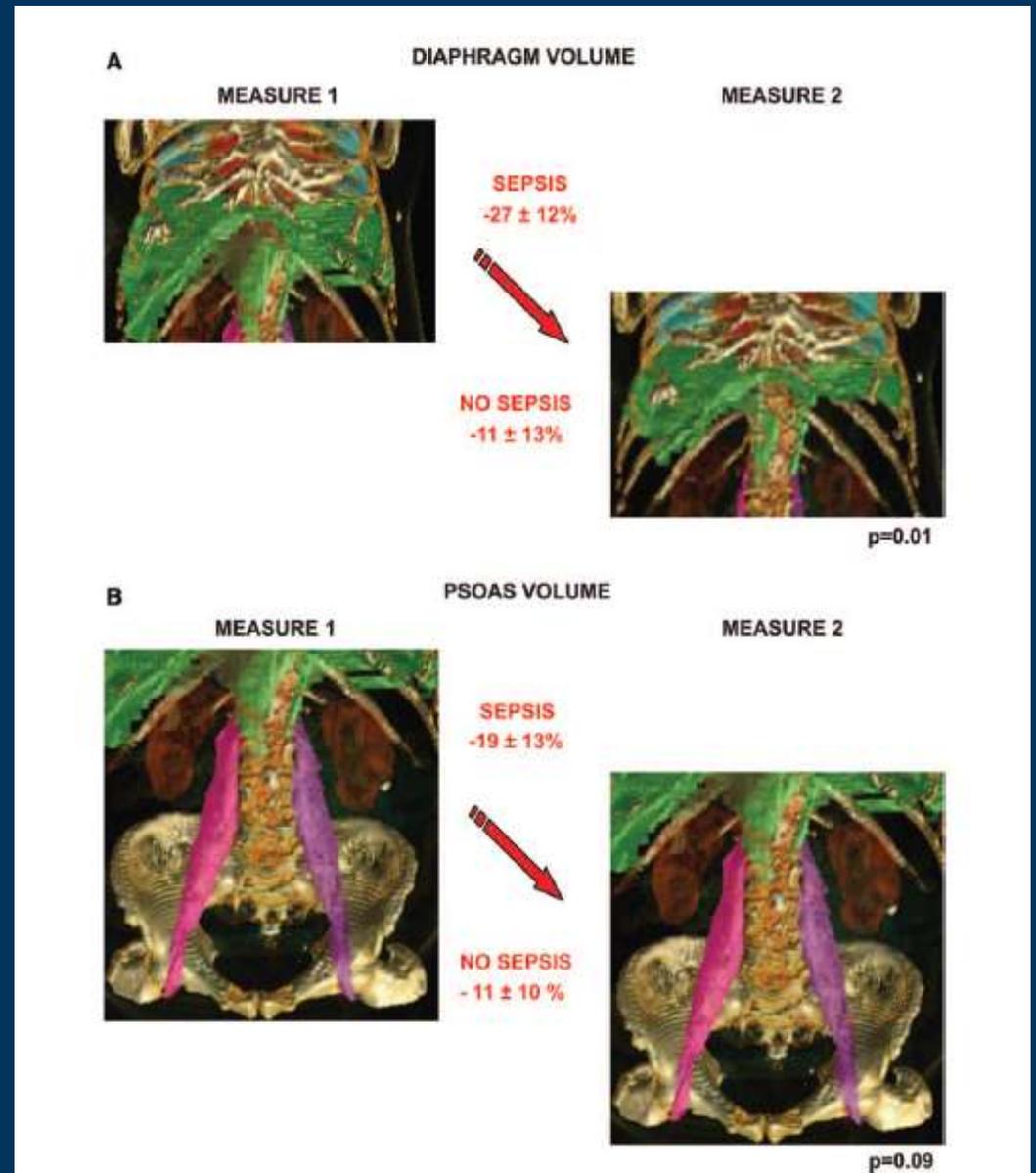
– Conclusions

- CSA of rectus femoris decrease 10% US
- CSA of muscle fibers decrease 17.5%
- Ratio protein to DNA decrease 29%
- >40% of patients showed myofibril necrosis
 - » Significant inflammatory changes in muscle noted
- Muscle wasting occurred despite delivery of 0.7gm/kg protein



Short Term Outcomes

- All skeletal muscle undergoes atrophy when patient is admitted to the ICU !
- Volumetric CT measurements allow core and diaphragm measurements
- Diaphragm loss is greater than psoas



Jung B, et al. Sepsis is associated with a preferential diaphragmatic atrophy. *Anesthesiology*. 2014. 120(5):1182-1191

Mechanistic data support increased infusion of AA's or protein increases net protein uptake in muscle

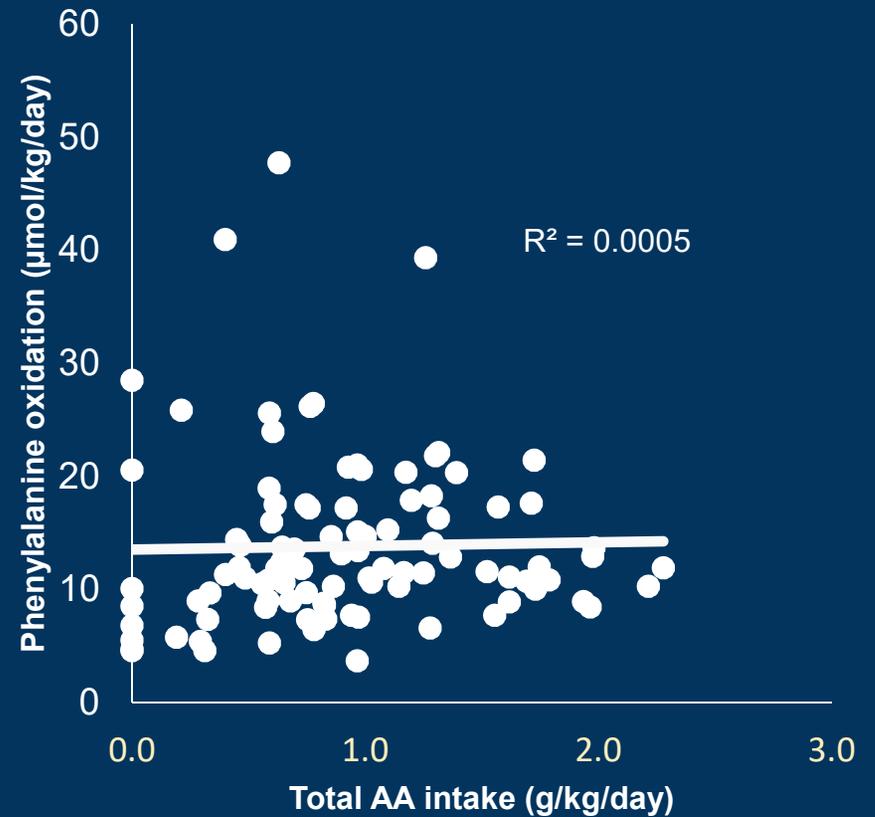
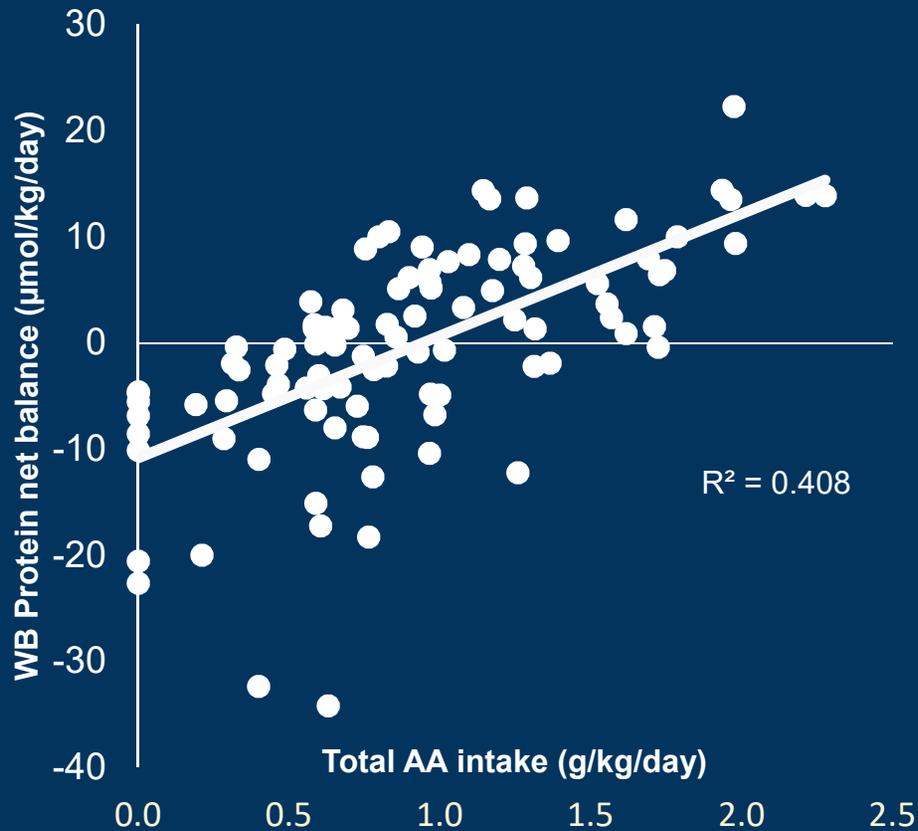
“Older” studies

Cuthbertson - Shils M-- Cahill G--Cerra F--Vars S--Plank L--Cynober L -- Wolfe R

More recent studies

- **Weijs P et al 2014**
 - Protein goal beneficial, energy goal not an issue
- **Rooyackers O et al Clin Nutr 2015**
 - WB protein synthesis – MOF
 - Critically ill able to utilize additional AA loads
- **Berg A et al Crit Care 2013**
 - Protein kinetics hypocaloric vs normocaloric feeding
 - increased protein improved outcome
- **Liebau F et al Am J Clin Nutr 2015**
 - Enteral protein WB protein turnover
 - Additional protein beneficial
- **Zusman O et al Crit Care 2016**
 - Higher protein associated with improved mortality
- **Rehal MS et al Critical Care 2017**
 - Increase protein increase synthesis

What happens to exogenously administered amino acid?



Rooyackers O et al Clin Nutr 2015, Berg A Crit Care 2013
Liebau F et al 2015 Am J Clin Nutr 2015
Liebau F et al 2016 Curr Opin Clin Nutr Met Care 2016

Is *anabolic resistance* observed in critical illness real ?

- **Anabolic resistance driven by insensitivity to anabolic effect of AA's, primarily leucine**
 - **In ICU (stressed) patients muscle free Leu is higher than the non-stressed**
- **6 factors partially explain anabolic resistance**
 - **Splanchnic sequestration following normal feeding**
 - **Decreased AA availability and uptake in muscle**
 - **Blunted response to anabolic AA stimulus**
 - **Immobilization increases resistance to anabolism**
 - **Route of nutrient delivery**
 - **Loss or changes in satellite cells**

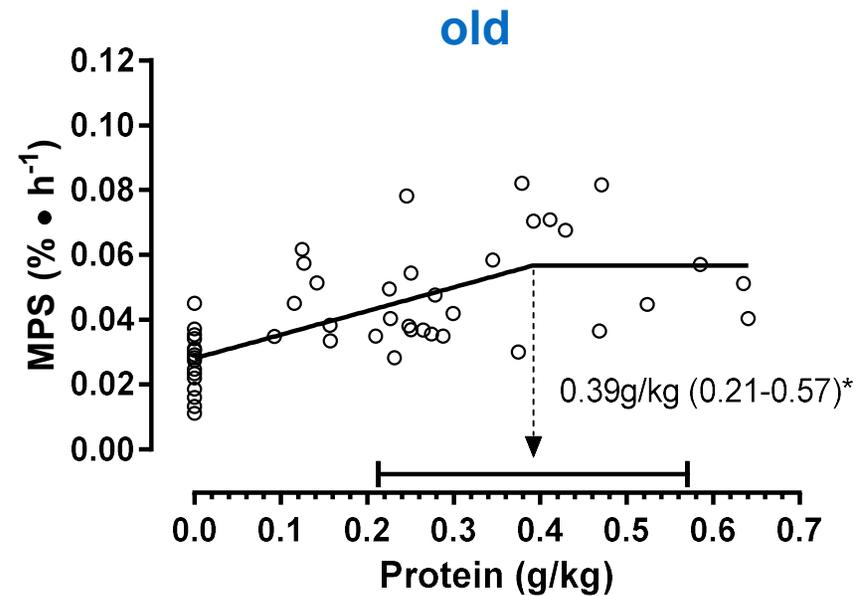
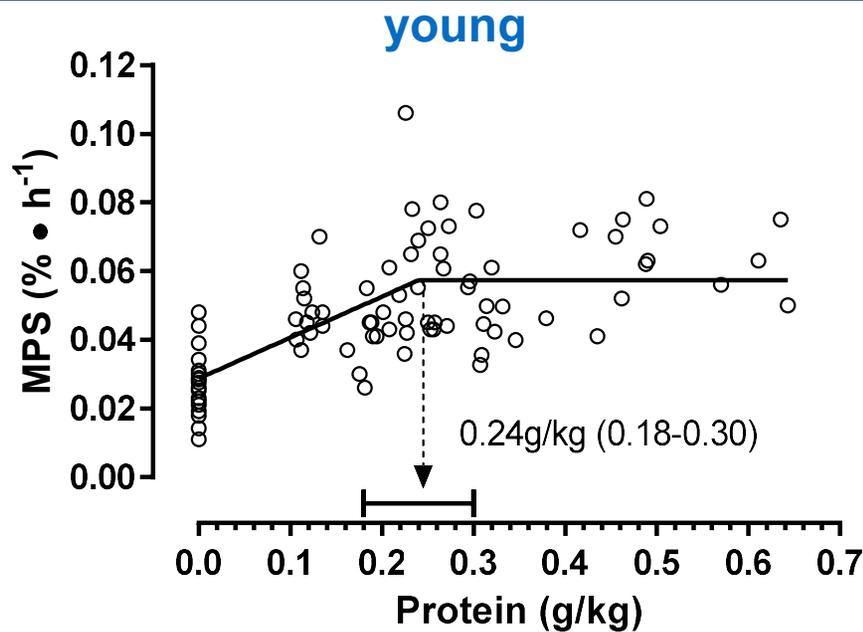
Rooyackers O et al Curr Opin Nutr Met Care 2019

Magne H et al Nutrition Res Rev 2013

Parent BA et al J Trauma Acute Care Surg 2017

Ham DJ et al Curr Opin Met Care Nutr 2016

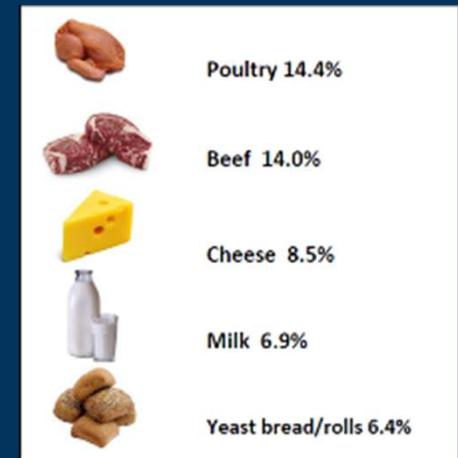
Anabolic Resistance: Older men require more protein to optimally stimulate muscle protein synthesis



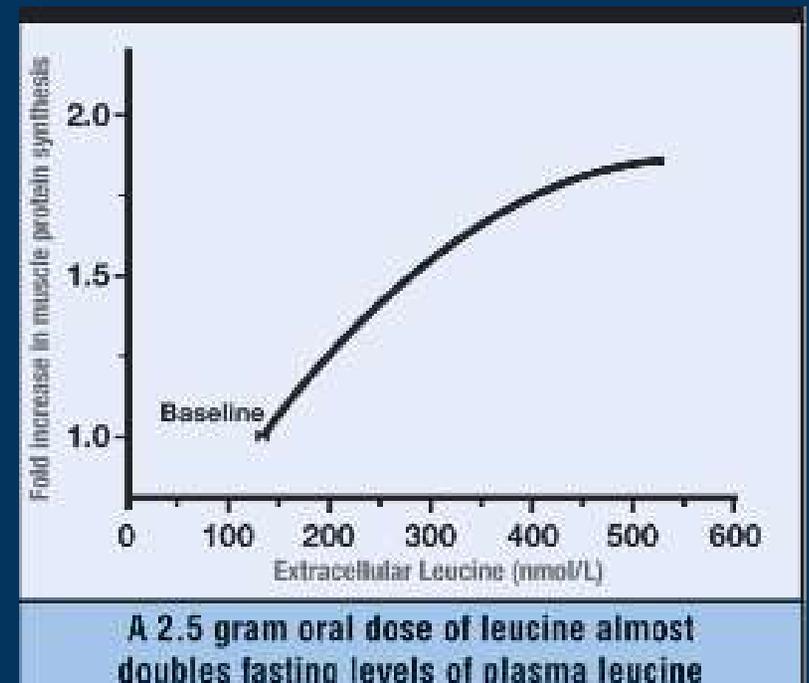
MPS = Muscle Protein Synthesis

What has been suggested to protect from sarcopenia

- Increasing the amount of protein to overcome anabolic resistance
- Supplemental leucine or leucine metabolites (HMB)
- Whey protein
- Additional Gln, Arg, BCAA
 - Fish oils
- Resistance exercise



Sources of protein in "western diet"



Does the source of protein alter kinetics ? animal vs. plant protein

- Total energy intake is important to factor in
- Plants with fewer EAA
 - EAA threshold up to 10 gm but 20-40 gm no increase in myofibrillar protein
- Plants with lower digestibility
 - Greater splanchnic extraction of plant protein
 - Fewer anabolic specific AA, i.e. leucine

TABLE 2 PDCAAS of common protein foods¹

Source	PDCAAS
Milk	1.00
Whey	1.00
Egg	1.00
Soy protein isolate	1.00
Casein	1.00
Beef	0.92
Soy	0.91
Pea	0.67
Oat	0.57
Whole wheat	0.45



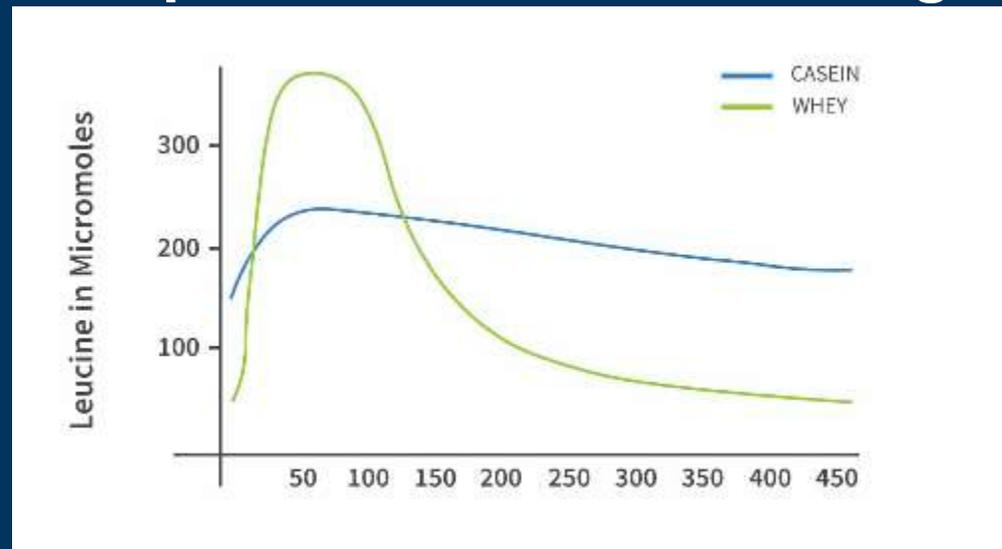
**No data in hospital
patient setting**

van Vliet S et al J Nutrition 2015
Baum JI et al Nutrients 2016

PDCAAS = protein digestibility corrected AA score

What about specific types of protein ?

- **Whey protein**
 - Rapidly empties from stomach
 - Essential to non-essential ratio better (26% BCAA)
 - **Increase in insulin secretion noted when compared to other protein sources (insulinotropic)**
 - Indirectly increase AA increase insulin leads to increase muscle uptake
 - Increase in plasma AA noted after ingestion



Effects of Whey Protein Supplementation Pre- or Post-Resistance Training on Muscle Mass, Muscular Strength, and Functional Capacity in Pre-Conditioned Older Women: A Randomized Clinical Trial

[Nutrients May 2018](#)

Hellen C. G. Nabuco ^{1,2,*} , Crisieli M. Tomeleri ^{2,3} , Paulo Sugihara Junior ², Rodrigo R. Fernandes ² , Edilaine F. Cavalcante ² , Melissa Antunes ², Alex S. Ribeiro ⁴, Denilson C. Teixeira ^{2,5} , Analiza M. Silva ⁶, Luís B. Sardinha ⁶ and Edilson S. Cyrino ^{2,5} 

Review

The Effect of Whey Protein Supplementation on the Temporal Recovery of Muscle Function Following Resistance Training: A Systematic Review and Meta-Analysis

[Nutrients Feb 2018](#)

Robert W. Davies ^{1,2,*} , Brian P. Carson ^{1,2}  and Philip M. Jakeman ^{1,2} 

Insulinotropic Effects of Whey: Mechanisms of Action, Recent Clinical Trials, and Clinical Applications

[Ann Nutr Metab 2016](#)

Rachel L. Adams Kenneth Shane Broughton

Is there an upper limit of protein or AA delivery ?

The answer to this question will vary depending on methodology and research group

- Higher upper limit advocates !
 - Deutz NEP, Wolfe R et al 2013
 - Maximal FSR occurs with 20 to 30 gm protein bolus
 - net protein synthesis must be measured
 - higher protein level suppresses protein breakdown
 - “anabolic response” is the sum of FSR + the decrease in catabolism noted with high level of protein
- As high as 3 gm/kg/d via PN in adolescent patients safe
 - Verbruggen SC et al
- 2016 Protein summit rec’s >1.2gm/kg/d (up to 2.5)
 - Guidelines from ESPEN, SCCM, ASPEN, Canada, Asia-Pacific are consistent

Deutz NEP, Wolfe RR Clinical Nutrition 2013

Verbruggen SC et al Crit Care Med 2011

Hurt RT et al Nutr Clin Practice 2017

Are probiotics a potential tool to control cellular injury during adjuvant chemoradiation ?

- **Studied well in animals, clinical studies very mixed in results.**
 - **Over 200+ articles in 2010 alone reporting GI protection mechanisms**
- **5-FU – decreased diarrhea general response 7/11 human studies positive**
- **MTX- mostly animal models. Protects prevents loss of mucosal integrity and body weight**
- **CPT-11 – used as prophylaxis with success human studies**
- **Multiple cellular mechanisms:**

Inhibition of cachexia

Mouse model

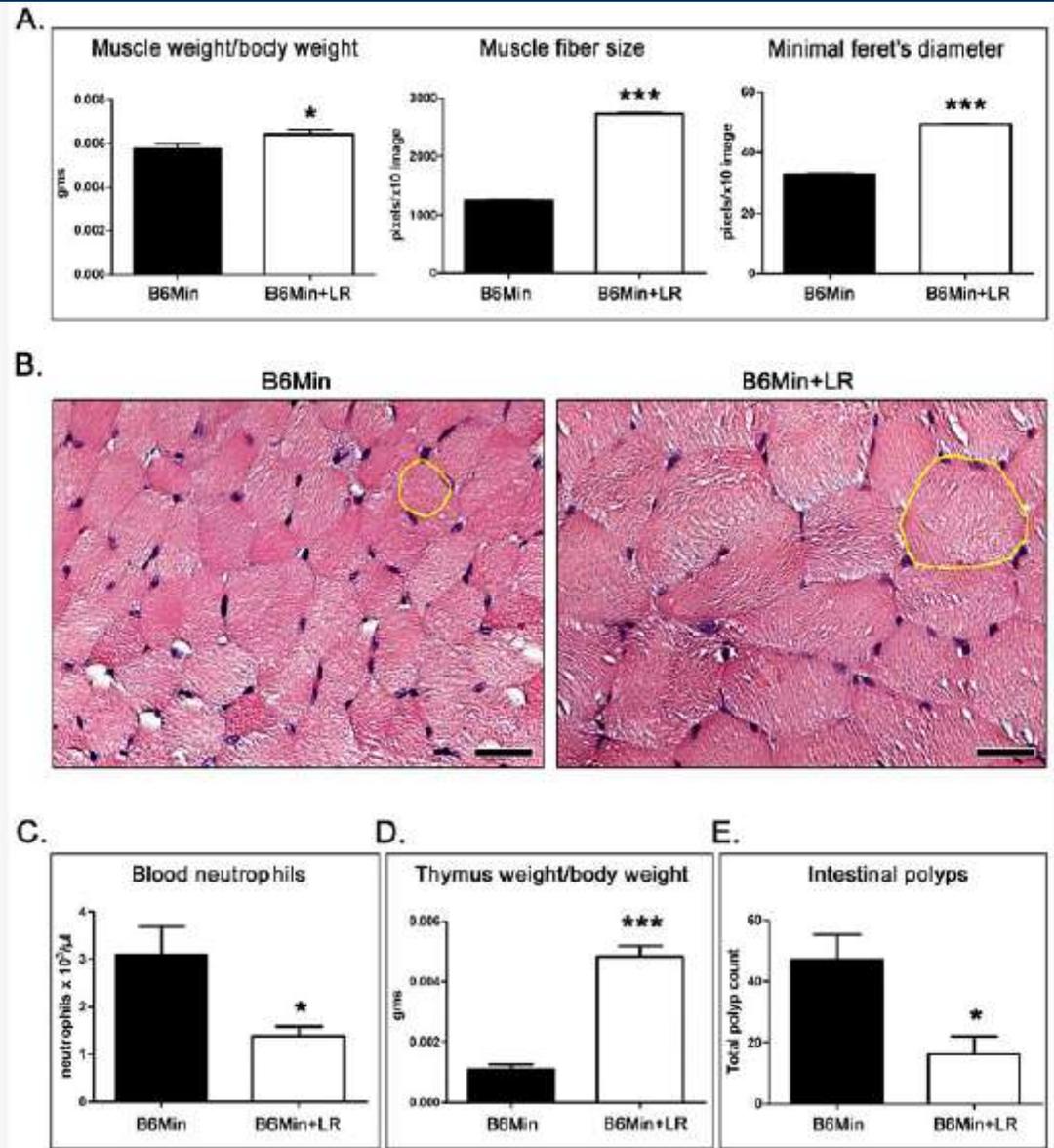
ApcMin predisposes to Ca
+/- L.Reuteri

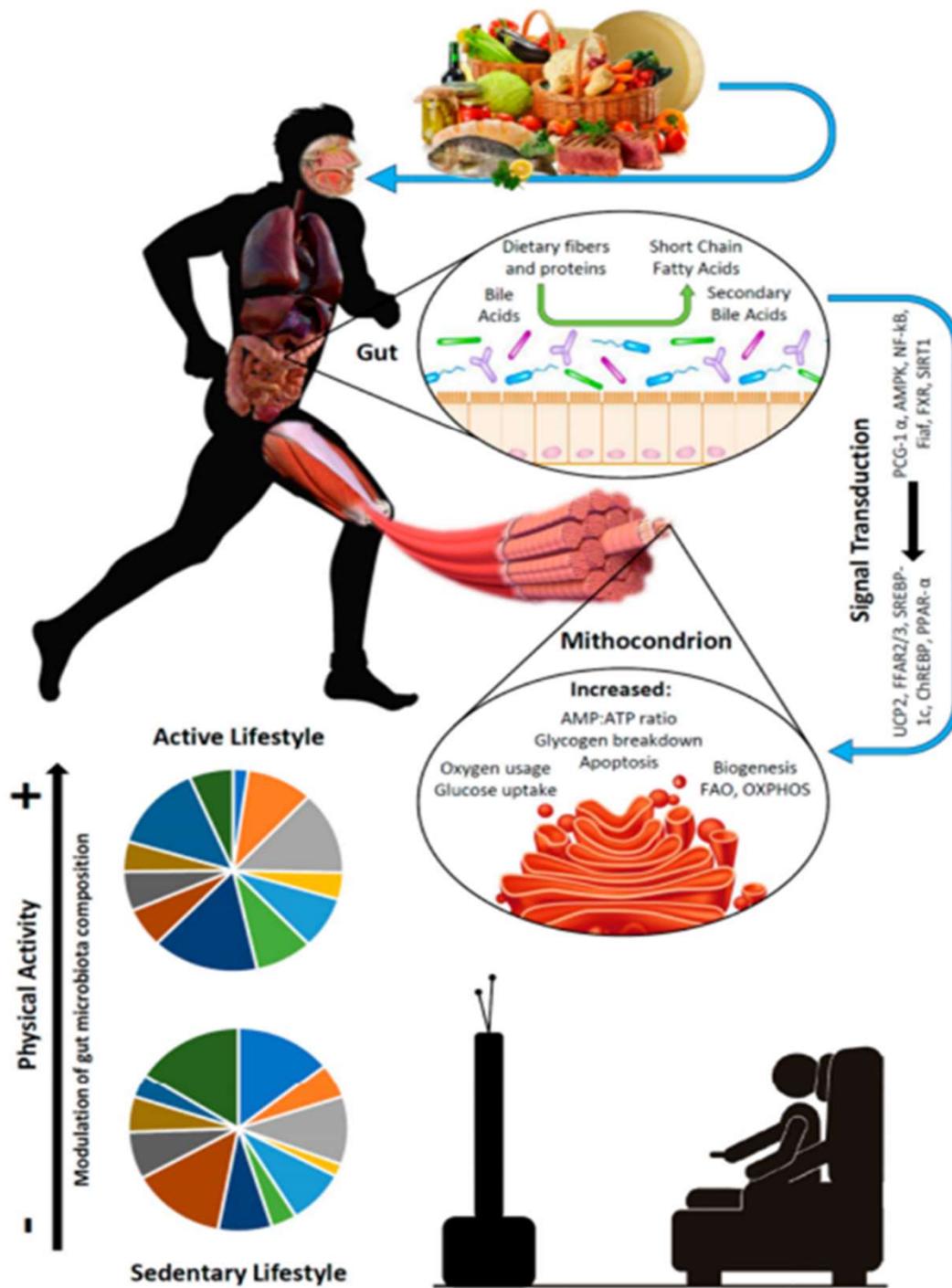
Decrease inflammation

Decrease cachexia

Upregulation of transcription
factor FoxN1

Significantly decrease muscle
loss





Evidence supports SCFA enhancing muscle function and mitochondrial biogenesis in the myocyte.

Essentially potentiating the benefit of exercise in muscle maintenance

Nutrition and Cancer Prevention: Why is the Evidence Lost in Translation?

Katie M Di Sebastiano,¹ Gayathri Murthy,¹ Kristin L Campbell,² Sophie Desroches,³ and Rachel A Murphy¹

Advances Nutrition 2019

What nutritional data is being lost ?

How about cancer prevention: Whole Grains

- **Aune D et al BMJ 2016**
 - 45 studies
 - Decrease in all cause mortality
 - Modest amounts
 - 3 serving per day
- **Zong G et al Circulation 2016**
 - Prospective cohort studies 786,076 participants
 - Whole grains
 - Decrease all cause mortality
 - CVD, Cancer, etc
- **Reynolds A et al Lancet 2019**
 - Series of systematic reviews and meta-analyses
 - 185 prospective trials, 58 clinical trials
 - 15 to 30% in cardiac disease, stroke, DM2, **GI cancer**----
 - appears to be a dose response
 - Decrease all cause mortality

Complications of Obesity

Metabolic

- Diabetes, NAFL, gallstones

Structural

- GERD, pseudotumor Cerebri

Inflammatory

- Arthritis, autoimmune

Degenerative

- Degenerative joint disease

Neoplastic

- Prostate, breast, ovarian, endometrial,
 - cervical, lymphoma, renal cell

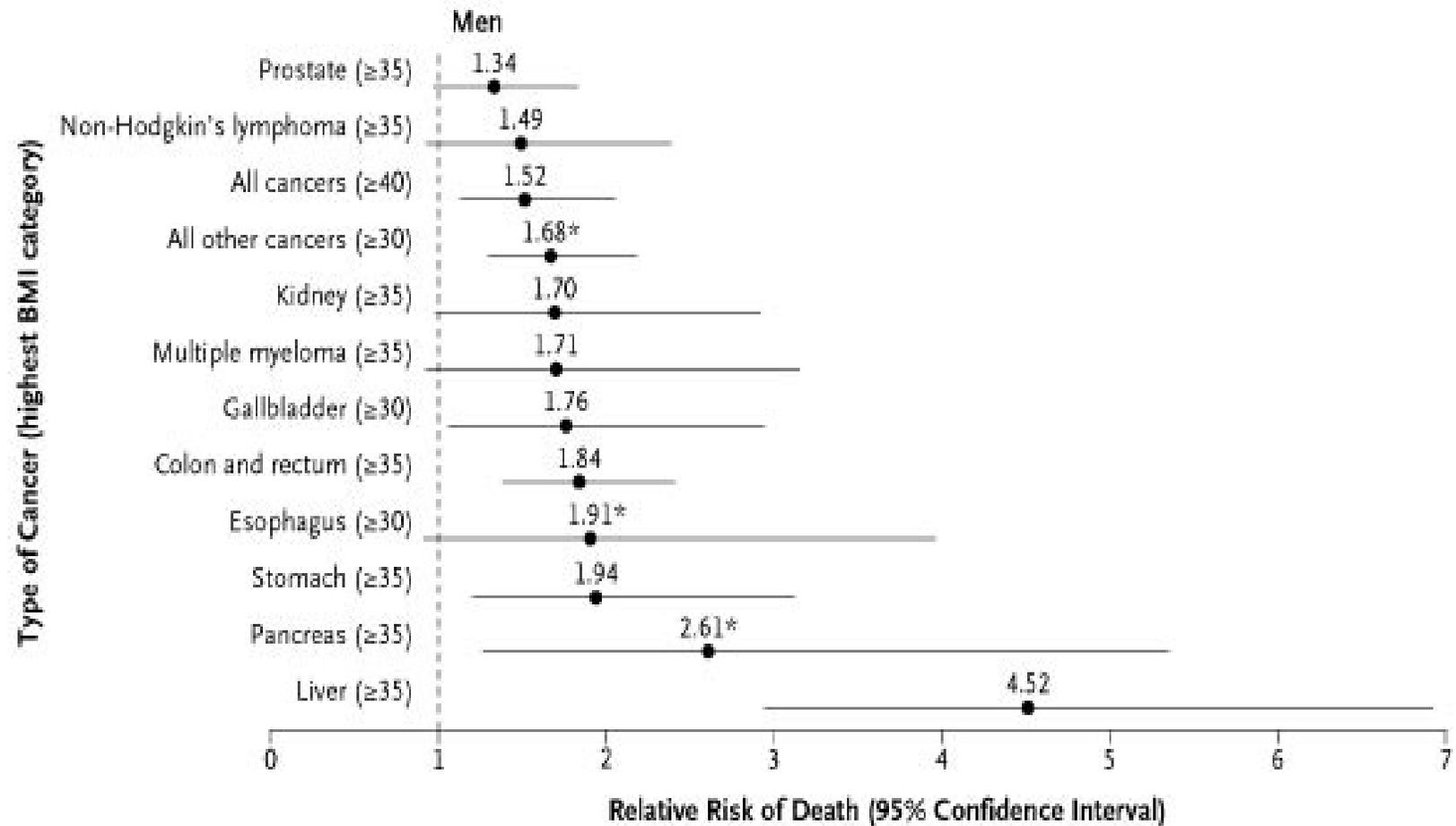
Psychological

- Depression, anxiety panic attacks,
 - eating disorders

60

Obesity: Cancer

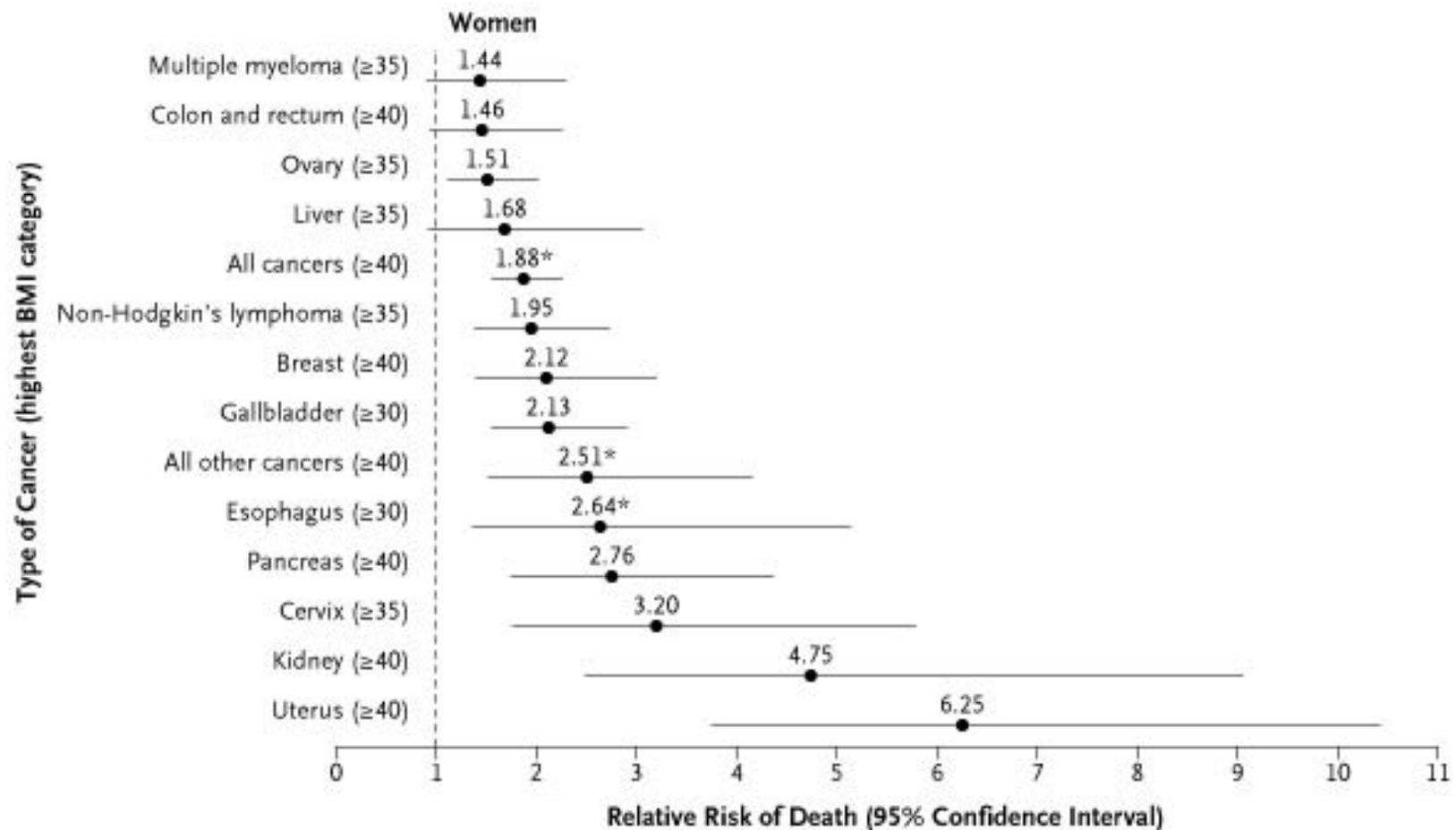
Men



Calle: NEJM (2003);348:17

Obesity: Cancer

Women



Calle: NEJM (2003);348:17

Does Sugar “feed” the Cancer ?

- In general consuming sugar does not stimulate growth of cancer cells
- Obesity: end result of too much sugar is highly associated with cancer
 - Prostate, breast, ovarian, endometrial, cervix, lymphoma and renal cell

Importance of Vitamin D in Cancer

Every Cell in Body
has Vit D Receptors

- Gut – ↑ Ca^{++} absorption
Bone - Ca^{++} mobilization
- Reduces mortality
- Immune modulator
 - Affects T and B cells,
immunoglobulin, and cytokines
 - ↓ Risk of asthma, colds, URIs
 - Affects TLR-4 to bind Tuberculosis
- Pancreas receptors, deficiency ↑ risk diabetes
- **Inhibits cancer growth**
 - Sun exposure delays onset colon, prostate, breast cancer**
- Reduces skin proliferation - Used to treat psoriasis
- Muscle function – Deficiency causes aches, pain, ↓ strength, falls
- Pregnancy - Defic ↑ risk pre-eclampsia, need for C-Section
- Deficiency ↑ risk of MS, RA, Osteoarthritis, HTN ?
 - In aging $25\text{OH} < 25\text{nmol/L}$ is deficient
 - Deficiency reported in > 70 % of elderly living in the community

Diagnosing and Treating Vit D Deficiency

- **Diagnosis (based on 25-OH Vit D levels)**
 - Deficient < 10 ng/ml, insufficient 11-20 ng/ml
 - Optimal 30-60 ng/ml (>30 ng/ml to ↓ PTH)
- **Dosing Vit D**
 - Rx of major deficiency 50,000 IU/week x 8 wks
 - Supplementation 0-50 yrs (200 IU/d), 50-70 yrs (400 IU/d),
>70 yrs (600 IU/d), but 800-1000 IU/d may be better ?
- **Criticism**
 - Effect size greater in observational studies vs PRCTs
 - Confounding factors (obesity, exercise, milk intake, chronic dz)
 - measurement of DBP in various states
- **Institute of Medicine statement**
 - Benefits beyond bone health may not be reliable**
 - Healthy adults should take 600 IU/d to optimize bone health

Antioxidant Supplements in Cancer ?

- **Observations ?**
 - **Antioxidant levels lower in patients w/cancer**
 - **45-80% of patients reportedly use antioxidant supplements during anti-neoplastic treatments**

Antioxidants in Cancer Treatment and Prevention

- **Antioxidants in prevention: strongly supported by animal data and human data**
 - **Some of larger trials without any benefit**
- **Antioxidants during therapy not recommended as they may alter effective of chemotherapy**
 - **Most chemo agents act via oxidant**

Antioxidants and Prostate Cancer Prevention (SELECT Trial)

- **Deficiency felt to increase risk**
 - Heredity, ethnic origin, age
- **Nutritional issues suggested to alter incidence**
 - Dietary fat, cooked meat, micronutrients, vitamins, fruit and vegetable intake, phytoestrogens (isoflavonoids, flavonoids, lignans)
- **SELECT trial**
 - PRCT with Se, Vit E or combination
 - Stopped for futility Oct 2011

Can nutrition therapy be harmful in cancer ?

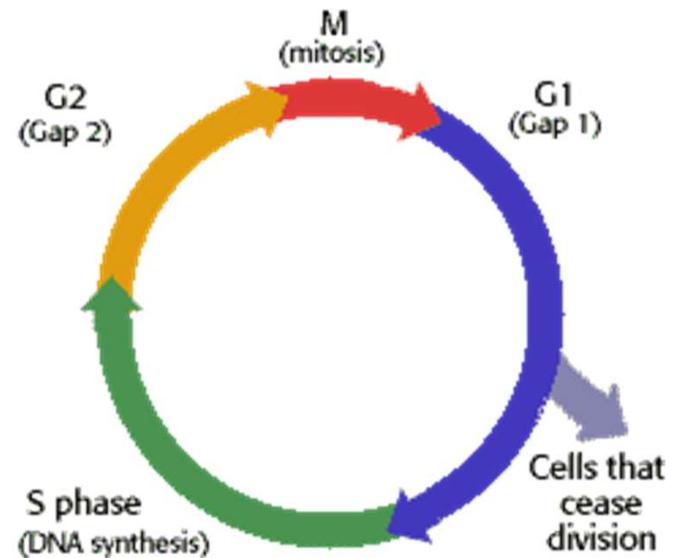
- **Excess calories**
 - Hyperglycemia
 - Fatty liver
- **Refeeding syndrome**
- **“Excessively” aggressive enteral feeding**
 - Feeding in hemodynamic instability
 - Aspiration
 - Feeding the compromised gut --- bacterial or toxin translocation
- **Access complications**
 - PEG, J tube, Nasojejunal feeding
 - PN line infections, pneumothorax
- **Giving nutrition during chemotherapy will nullify effects of chemo**
 - Most chemo agents are potent oxidizing agents
- **Nutrition stimulating cancer growth ?**
- **Nutrition support at end of life cost effectiveness ?**

Does Nutrition Stimulate Cancer Growth ?

- **Difficult to get definitive answer !**
 - Ethical issues in study design
 - Complexity of tumor growth characteristics in-vivo
 - Heterogeneity of tumors between cell type and even tumors of same class

- **Methods used in attempt to answer question:**

- **Tumor size**
 - Result from increased growth
 - Results from apoptosis
- **Relative number of tumor cells**
- **# cells in the S phase**
 - DNA synthesis or replication
- **Ploidy**
 - DNA content
- **Thymidine uptake**
- **Tumor protein synthesis**
- **Measure cell cycle kinetics**
 - Followed by label with bromodeoxyuridine



ESPEN guidelines on nutrition in cancer patients[☆]

Jann Arends^a, Patrick Bachmann^b, Vickie Baracos^c, Nicole Barthelemy^d, Hartmut Bertz^a, Federico Bozzetti^e, Ken Fearon^{f,†}, Elisabeth Hütterer^g, Elizabeth Isenring^h, Stein Kaasaⁱ, Zeljko Krznaric^j, Barry Laird^k, Maria Larsson^l, Alessandro Laviano^m, Stefan Mühlebachⁿ, Maurizio Muscaritoli^m, Line Oldervoll^{i,o}, Paula Ravasco^p, Tora Solheim^{q,r}, Florian Strasser^s, Marian de van der Schueren^{t,u}, Jean-Charles Preiser^{v,*}

C1 – 4	Immunonutrition (arginine, N-3 fatty acids, nucleotides) in perioperative care
Strength of recommendation STRONG	<i>In upper GI cancer patients undergoing surgical resection in the context of traditional perioperative care we recommend oral/enteral immunonutrition.</i>
Level of evidence	High
Questions for research	Specifying the role of the individual constituents of immunonutrition regimens

Peri-operative metabolic manipulation with fish oil and arginine to improve outcome: fact or fantasy ?

- **35 articles met inclusion**
- **Results: Arginine – Fish oil containing solutions**
 - **Significant reduction in overall infections**
 - **Significant reduction in hospital stay**
 - **Subgroup analysis shows consistent treatment effect regardless of type of surgery**
 - **Infection rates varied between formula types**
 - **No decrease in mortality**
 - **Greatest effect when given pre and post operatively**

Drover J. Heyland D et al JACS 2011

- **Analysis of 26 RCT (2496 patients) open GI surgery**
 - **Isonitrogenous / isocaloric formulations**
 - **Open GI surgery**
 - **GRADE system used to stratify quality of studies**
- **Results:**
 - **5-7 days required to show benefit**
 - **26/26 reported infectious complications decreased 36%**
 - **20/26 reported non-infectious complications decreased 18%**
 - **20/26 reported length of stay decrease LOS**
 - **26/26 reported no benefit in mortality**

Marimuthu K et al Ann Surg 2012

Effect of Timing of Pharmaconutrition (Immunonutrition) Administration on Outcomes of Elective Surgery for Gastrointestinal Malignancies: A Systematic Review and Meta-Analysis

- **21 studies, 2005 patients**
- **GI malignancies**
- **Outcome:**
 - **No difference in mortality**
 - **Significantly decrease:**
 - **Infections**
 - **Inflammatory markers**
 - **Anastomotic dehiscence**

Osland E et al JPEN 2014

Immunoenhancing Enteral and Parenteral Nutrition for Gastrointestinal Surgery

A Multiple-Treatments Meta-Analysis

Takero Mazaki,† Yukimoto Ishii,*† and Ichiro Murai**

- **74 studies, 7574 patients**
- **Meta-analysis using multi-treatment analysis**
 - **Use of immune enhancing nutrition outperformed other nutrition regimens in reducing:**
 - **Overall complications**
 - **Infections**
 - **IAA**
 - **Anastomotic leak**
 - **Sepsis**
 - **Mortality**

Mazaki T et al Ann Surg 2014

The impact of preoperative Immune Modulating Nutrition on outcomes in patients undergoing surgery for gastrointestinal cancer. A systematic review and meta-analysis

- **16 studies with strict criteria and study quality**
- **Decrease in:**
 - **Infections**
 - **Length of hospital stay**
 - **Non-significant change in mortality**
 - » (signal but not quiet positive)

What is the optimal nutrient makeup for the surgical oncology patient ?

- **Pre-operative (weeks prior)**
 - High protein, with exercise program if possible
- **Immediate Preoperative (5 to 7 days prior)**
 - Metabolic modulating formulation
 - Arginine, Fish oils, glutamine
 - Carbo-loading
- **Early post op (start within 24 h if possible)**
 - Nutrient balance
 - High protein
 - Whey vs casein: Specific amino acids; Leu, Gln, Arg
 - Fat content
 - MCT
 - Fish Oil
 - Vitamins
 - Antioxidants, Vit D

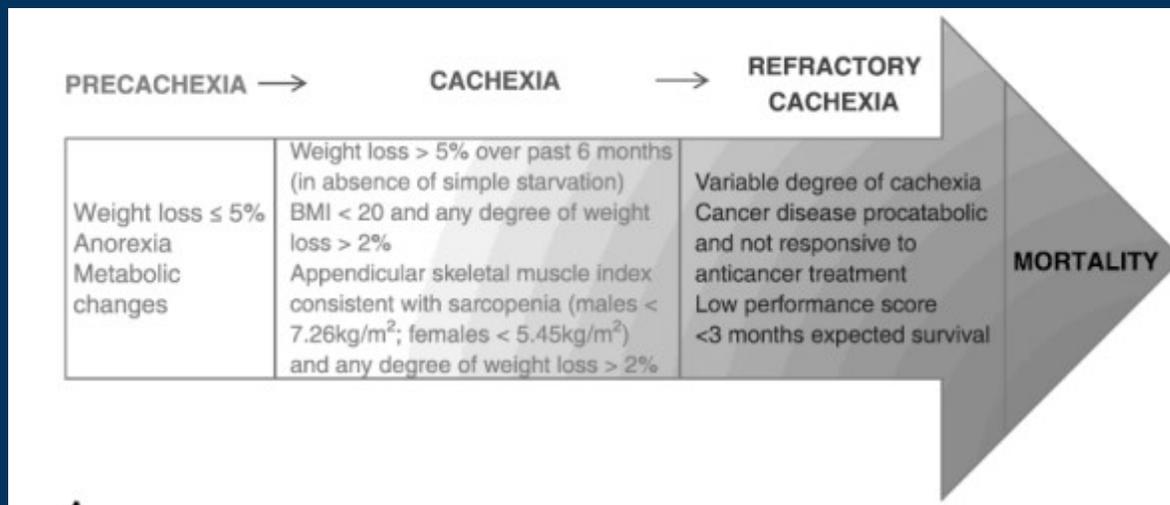
What is NOT ready for prime time !

- **Appetite stimulants – majority of data report not helpful**
 - Megestrol acetate, cannabanooids
 - Ghrelin analogs stimulating appetite or melanocortin blocking agents --- partially reversing Ca associated anorexia
 - Ghrelin given daily increase appetite, energy balance, decrease fat loss, trend toward increase fat free mass
- **Anabolic steroids**
 - SARM's (selective androgen receptor modulators)
- **Nutritional supplements**
 - Carnitine – significant improvements in hepatic lipid metabolism
 - Melatonin
- **Anti-inflammatory agents**
 - Thalidomide, pentoxifylline, various mono-clonal Ab

Penet MF et al The Ca Journal 2015
von Haehling S et al Int J Card 2015

Adequate EARLY intervention can alter course prognosis and mortality

- In the optimal setting:
 - Improves QoL
 - Improves functional capacity and physical activity
 - Modulates immune function
 - Reduces treatment related morbidity
 - Improves tolerance to therapy
 - May improve treatment response
 - May improve survival



Ravasco P et al Am J Clin Nutr 2012
Laviano A et al Proc Nutr Soc 2015
Penet MF et al The Ca Journal 2015

Systematic review and meta-analysis of the evidence for oral nutritional intervention on nutritional and clinical outcomes during chemo(radio)therapy: current evidence and guidance for design of future trials

M. A. E. de van der Schueren^{1,2*}, A. Laviano³, H. Blanchard⁴, M. Jourdan⁴, J. Arends⁵ & V. E. Baracos⁶

- **11 Studies included**
 - **Limited focused studies**
 - **Very heterogeneous populations**
 - **Inadequately powered to show individual effects on toxicity and survival**
- **Conclusion**
 - **Signal towards overall positive effect**
 - **Subgroup analysis: beneficial effects driven by high protein, FO**

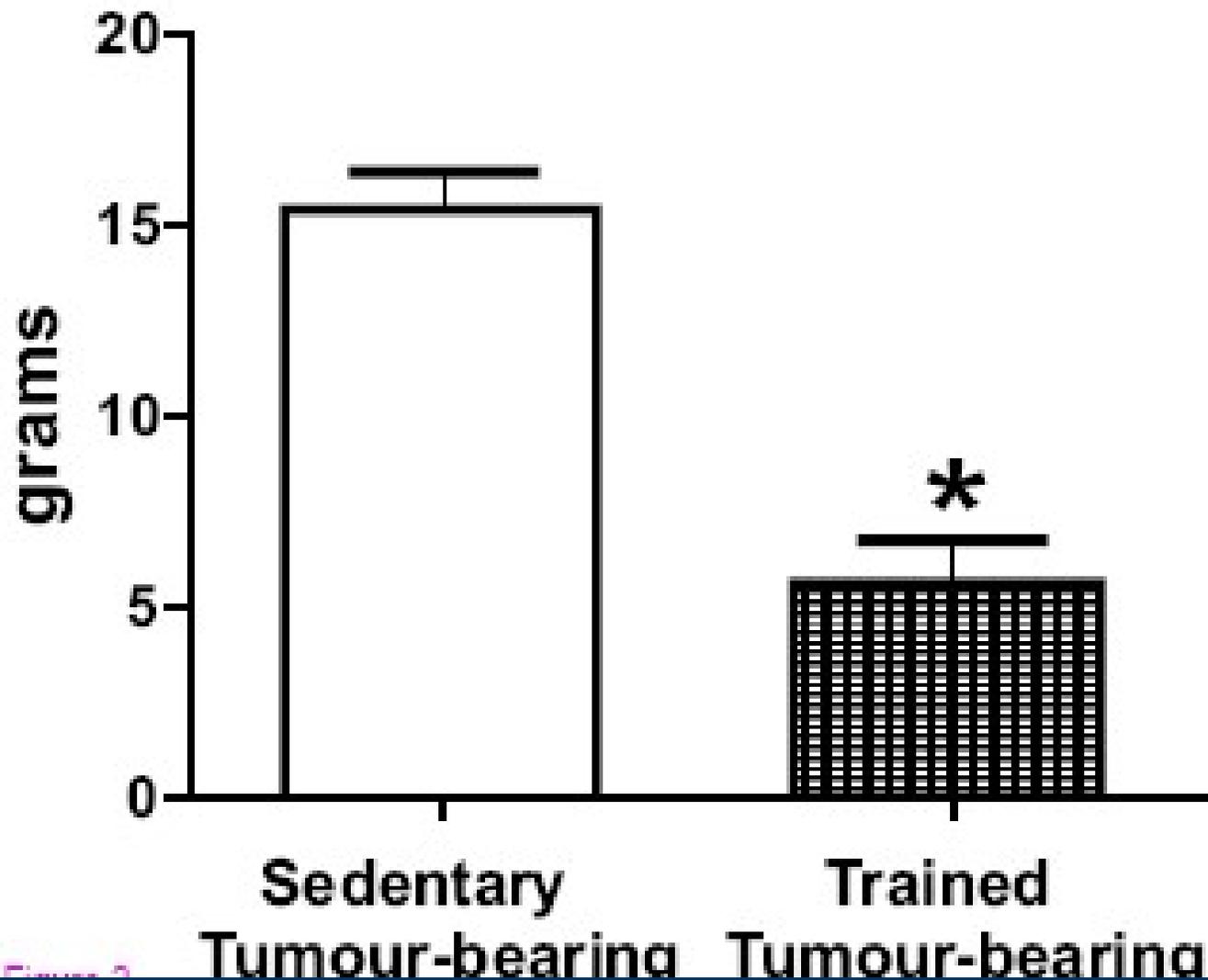
Conclusions: Nutrition issues in cancer care Take Home Messages !

- **Set goals early: Palliative vs Curative**
- **Cachexia is insidious and develops much earlier in cancer patients than previously recognized**
- **Early identification and early treatment of nutritional deficits are mandatory to show any clinically relevant benefits**
 - **Surgical oncology – preop prehabilitation**
- **Nutrition in Cancer therapy should be individualized for optimal outcome**
 - **Nutrition --- targeted multimodal therapy --- exercise**
 - **Counseling by MD makes a difference**
 - **Telling pt eat better alone does not work !**

Conclusions

- **Starving a cancer cell is clinically difficult**
- **Cancer cells have highly efficient metabolic plasticity**
 - **Metabolic plasticity is driven by environmental factors including inflammation, chemicals and nutrients.**
 - **Pre-clinical studies suggest that the management of cancer cells can be obtained by a press-pulse approach (i.e., chronic metabolic pressure and cyclical acute interventions)**
- **Cancer nutritional management should include;**
 - **Looking for secondary cause for anorexia – pain, nausea**
 - **Target reduced food intake**
 - **Address inflammation – anti-inflammatory drugs or nutrients**
 - **Whole grains should be part of prevention strategy**
 - **Enhance resistance exercise**

Tumor weight

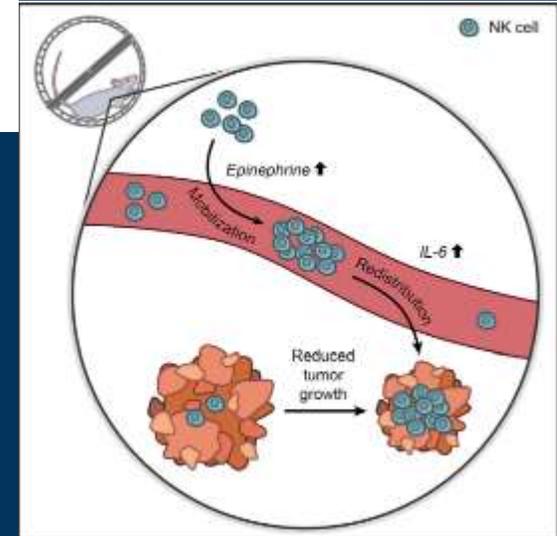


Voluntary Running Suppresses Tumor Growth through Epinephrine- and IL-6-Dependent NK Cell Mobilization and Redistribution

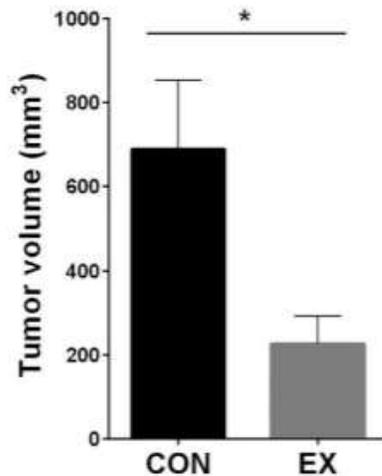
Pedersen L et al Cell Metabolism 2016

Exercise inhibits tumor growth across several over a range of tumor models and anatomic locations

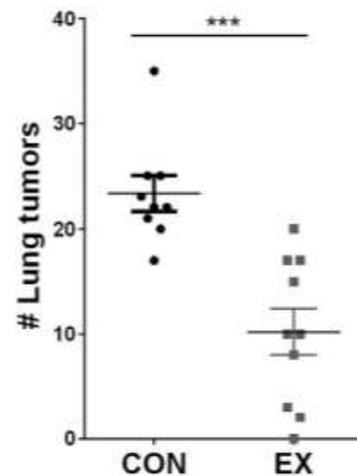
Proposed mechanisms:(1) vascularization and blood perfusion, (2) immune function, (3) tumor metabolism, and (4) muscle-to-cancer cross-talk,



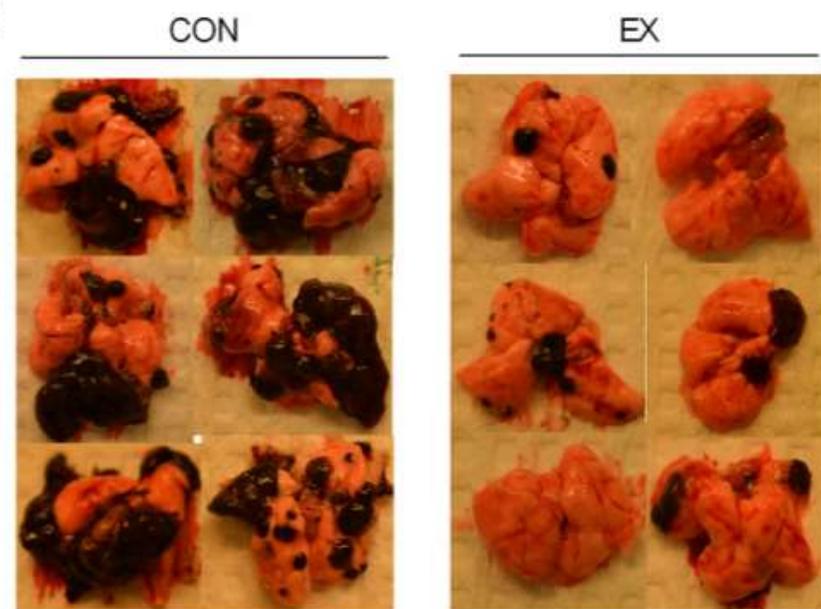
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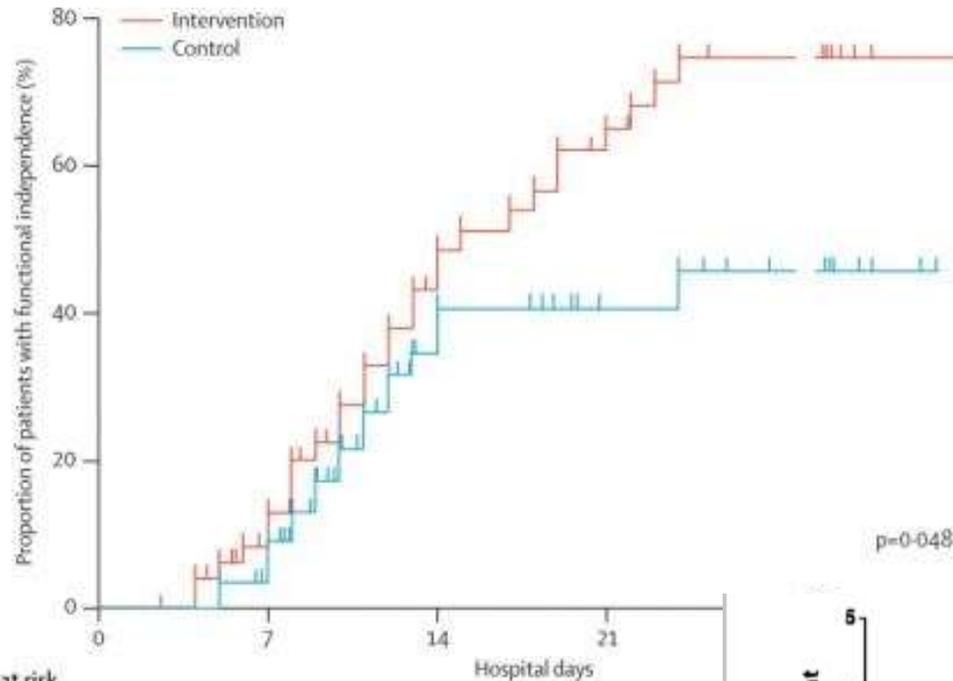
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Exercise in pre and post-op cancer surgical management

- **Exercise with appropriate AA and nutrition shown to be anabolic in multiple models**
 - **Burn (Wolfe 1990's)**
 - **Cancer (Biolo 2010)**
 - **Post-op (Baracos 2013)**
- **Exercise: multiple mechanisms of benefit**
 - **Increases nutritive blood flow to muscle (decreases precapillary shunting)**
 - **Anti-inflammatory – via gene expression**
 - **Lowers insulin resistance**
 - **Increase nutrient uptake in multiple tissue beds**
 - **Animal models- reduced inflammation, decreased wasting, longer survival**

Early mobilization



Number at risk		Hospital days			
		0	7	14	21
Control	55	51	21	13	
Intervention	49	40	21	13	

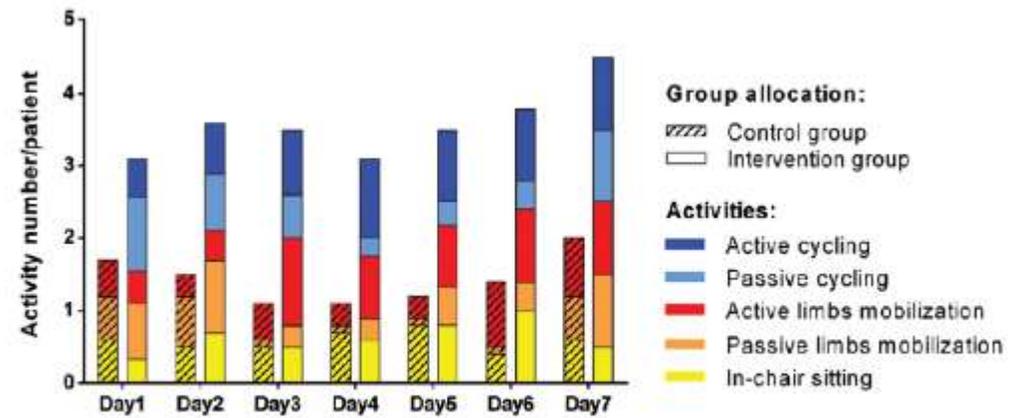
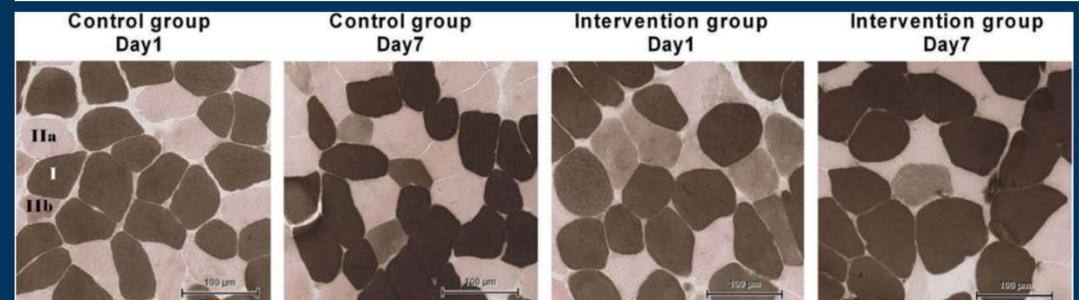


Figure 1. Amount of mobility activities performed per patient during the first week.

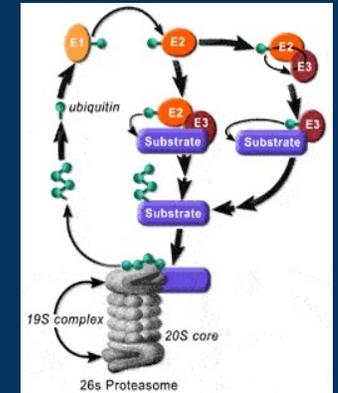


Patel BK, Pohlman AS, Chest 2014.
 Hickman CE et al Critical Care Medicine 2018

“Thy Food Shall Be Thy Remedy”

“Hippocrates”

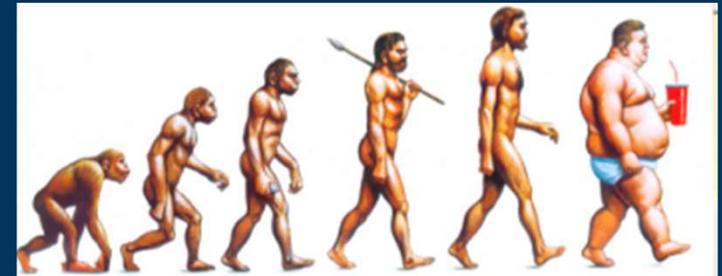
- Some of the effects of aging can be:
Prevented
Mitigated



Appropriate choice of:

Nutrient source
Quantity and Quality
Route of delivery

- Continued rigorous evaluation of assumptions, hypothesis



“The good physician treats the disease; the great physician treats the patient who has the disease.”

William Osler (1849-1919)

Questions

Nutrition-related resources and tools are available
from the Nestlé Nutrition Institute at
[nestlenutrition-institute.org](https://www.nestlenutrition-institute.org)

Visit MyCE at
[MyCEeducation.com](https://www.MyCEeducation.com)
Offering CE to dietitians and nurses