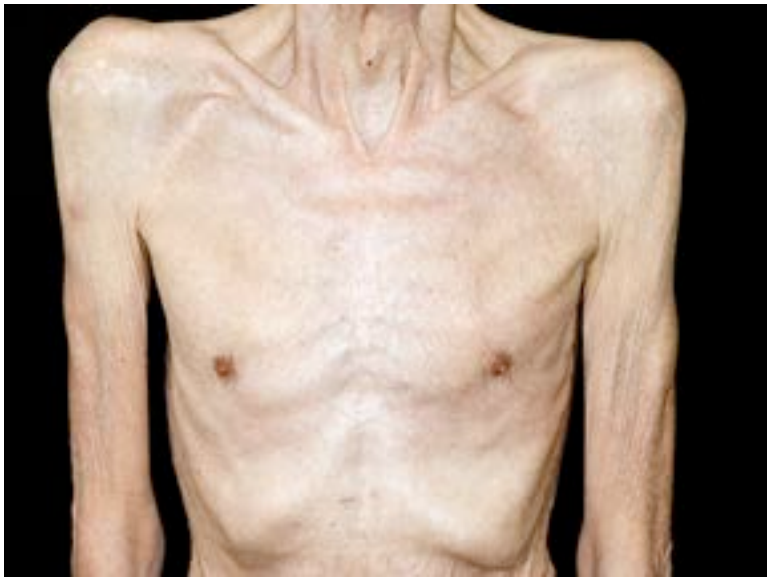
Molecular Mechanisms associated with the Cancer-Cachexia Syndrome

Prof. Dr. Josep M. Argilés
Department of Biochemistry & Molecular Biology
University of Barcelona, Spain

Disclosures: DANONE (Scientific Advisory Board), ABBOTT (Research Support) BAYER (Research Support), SMARTFISH (Research Support), ROTTAFARM/MADHAUS (Advisor)



Cancer cachexia is a devastating, multifactorial and often irreversible syndrome that affects around 50–80% of cancer patients, depending on the tumour type, and that leads to substantial weight loss, primarily from loss of skeletal muscle and body fat.

Table 2. The commonest malignancies in which cachexia develops as part of the clinical course.[6]

Malignancy	Patients with cachexia (%)
Gastric cancer	85
Pancreatic cancer	83
Non-small cell lung cancer	61
Small cell lung cancer	57
Prostate cancer	56
Colon cancer	54
Unfavourable non-Hodgkin's lymphoma	48
Sarcoma	40
Acute non-lymphocytic leukaemia	39
Breast cancer	36
Favourable non-Hodgkin's lymphoma	31

CME Palliative care

Cancer cachexia and fatigue

Grant D Stewart BSc(Hons) MBChB MRCS(Ed), Surgical Research Fellow

Richard JE Skipworth BSc(Hons) MBChB MRCS(Ed), Surgical Research Fellow

Kenneth CH Fearon MBChB(Hons) MD FRCS(Glas) FRCS(Ed) FRCS(Eng), Professor of Surgical Oncology

Department of Clinical and Surgical Sciences (Surgery), University of Edinburgh, Royal Infirmary, Edinburgh

Clin Med 2006;**6**:140–3

cachexia is indirectly responsible for the death of at least 20% of all cancer patients

Tumor-Related Weight Loss: Outcomes

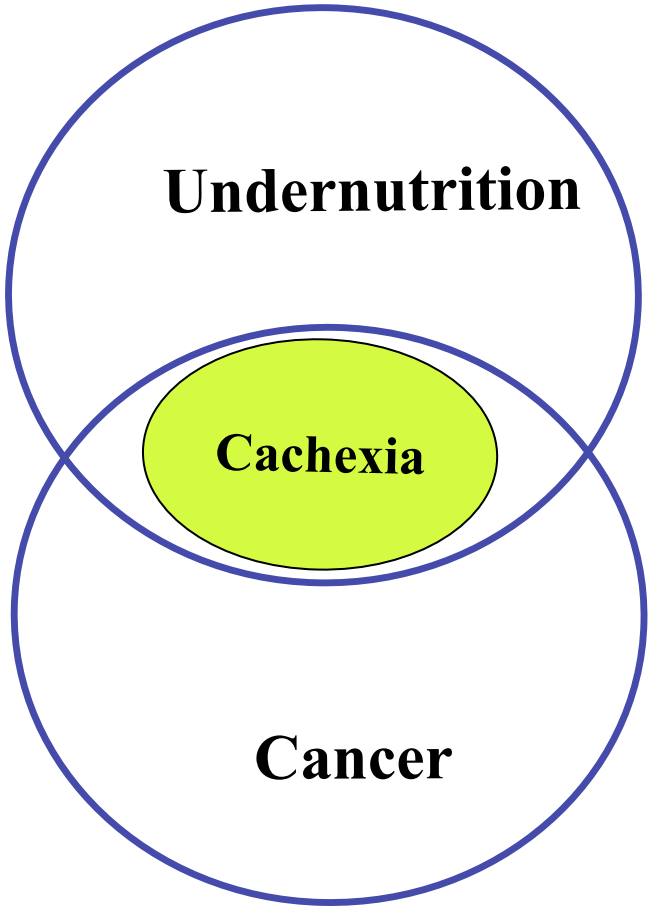
- ↓ Quality of Life
- ↓ Functional Status
- ↓ Response to Therapy
- ↓ Body Image

- ↑ Hospital Length of Stay
- ↑ Unscheduled Hospitalization
- ↑ Complications/Infections

Cancer and nutrition

↑ Morbidity

↑ Mortality



↓ Quality of life

↑ Sanitary costs

British Journal of Cancer (2006) 95, 431 – 434

www.bjcancer.com

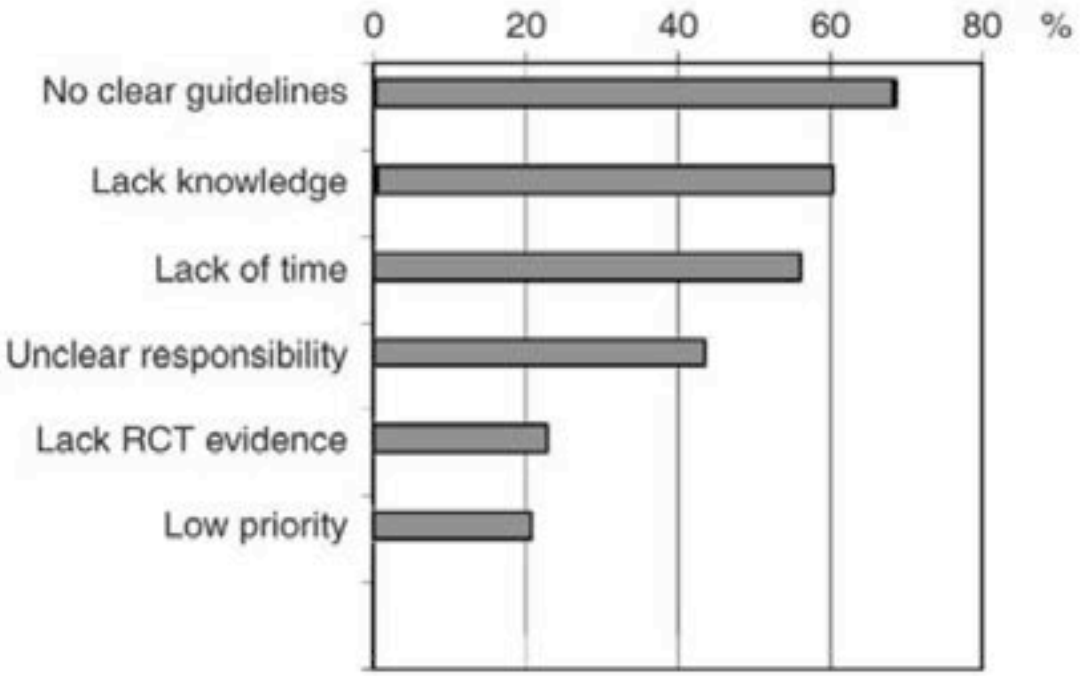
Short Communication

The views and practice of oncologists towards nutritional support in patients receiving chemotherapy

A Spiro[1,2,3], C Baldwin[1,2,3], A Patterson[4], J Thomas[4] and HJN Andreyev*[,2,3]

[1]Department of Medicine and Therapeutics, Imperial College Faculty of Medicine, Chelsea and Westminster Hospital, London, UK; [2]The Gastrointestinal Unit, Department of Medicine, Royal Marsden Hospital, Fulham Road, London SW3 6JJ, UK; [3]The Gastrointestinal Unit, Royal Marsden Hospital, Surrey, UK; [4]Department of Nutrition and Dietetics, King's College London, London, UK

Table 4 What barriers prevent inclusion of nutrition on oncologist patient care?



PubMed Analysis:
Cachexia [title] vs Obesity [title]

8743 *vs* 286327

=

1 : 33

5-year-mortality in Patients aged 50

cachexia (+ CHF/cancer) vs with obesity (no CHF/cancer)

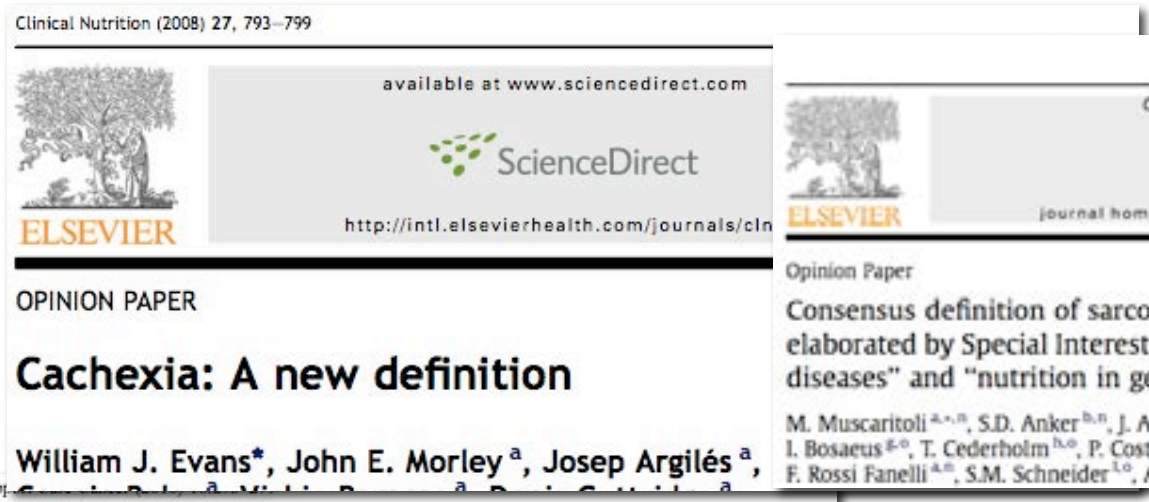
80% ***vs*** **4%**

BMI 18 ***BMI 30***

=

20 : 1

You cannot treat a disease that you cannot define



Clinical Nutrition (2008) 27, 793–799

available at www.sciencedirect.com

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ELSEVIER

OPINION PAPER

Cachexia: A new definition

William J. Evans*, John E. Morley [a], Josep Argilés [a], Connie Bales [a], Vickie Baracos [a], Denis Guttridge [a], Aminah Jatoi [a], Kamyar Kalantar-Zadeh [a], Herbert Lochs [a], Giovanni Mantovani [a], Daniel Marks [a], William E. Mitch [a], Maurizio Muscaritoli [a], Armine Najand [a], Piotr Ponikowski [a], Filippo Rossi Fanelli [a], Morrie Schambelan [a], Annemie Schols [a], Michael Schuster [a], David Thomas [a], Robert Wolfe [a], Stefan D. Anker [a]

Donald W. Reynolds Institute on Aging, University of Arkansas for Medical Sciences, 4301 W. Markham, Slot 806, Little Rock, AR 72205, USA

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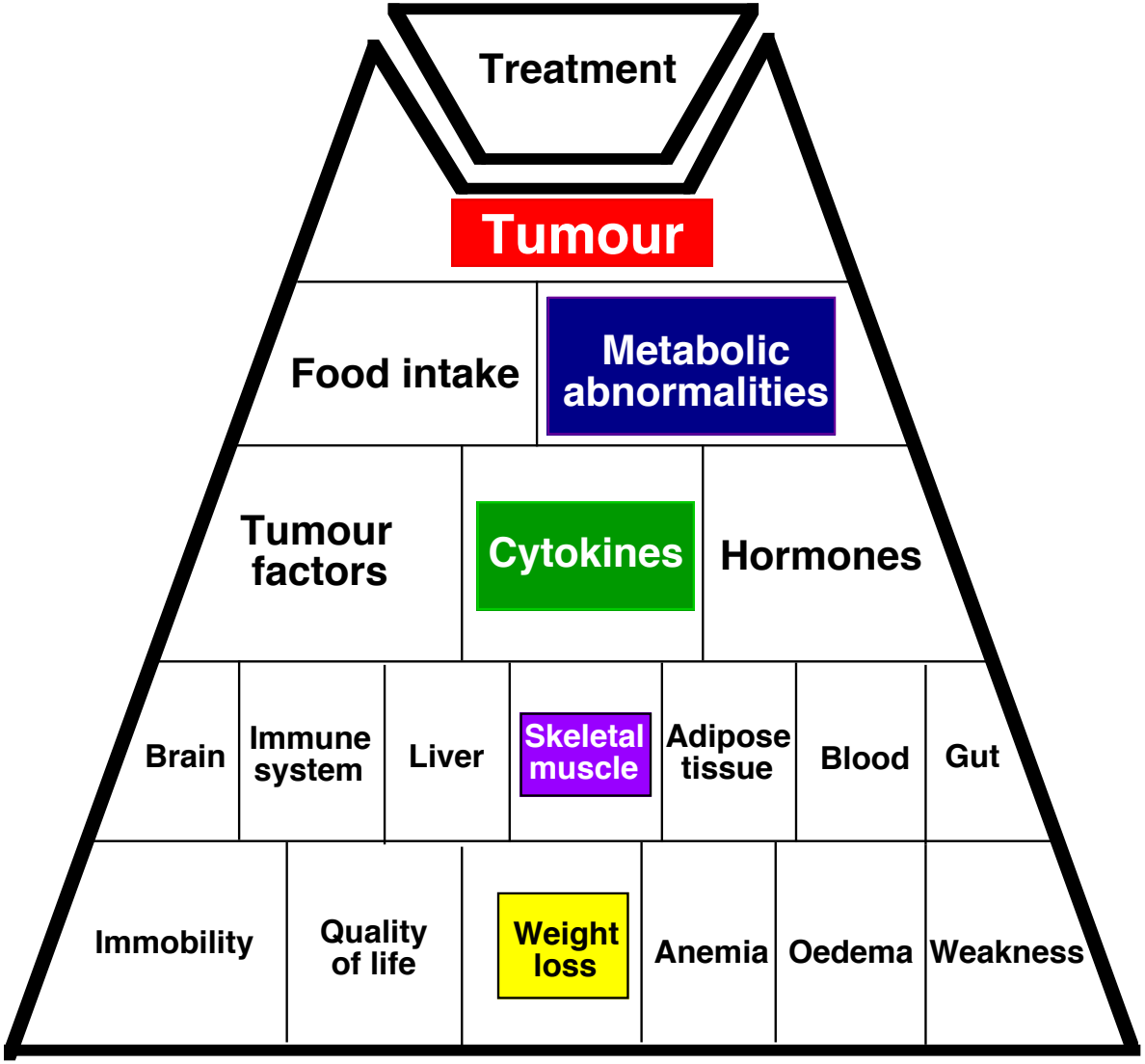
KEYWORDS
Anorexia;
Muscle wasting;
Inflammation;
Involuntary weight loss;
Wasting disease

Summary
On December 13th and 14th a group of scientists and clinicians met in Washington, DC, for the cachexia consensus conference. At the present time, there is no widely agreed upon operational definition of cachexia. The lack of a definition accepted by clinician and researchers has limited identification and treatment of cachectic patient as well as the development and approval of potential therapeutic agents. The definition that emerged is: "cachexia, is a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass. The prominent clinical feature of cachexia is weight loss in adults (*corrected for fluid retention*) or growth failure in children (*excluding endocrine disorders*). Anorexia, inflammation, insulin resistance and increased muscle protein breakdown are frequently associated with cachexia. Cachexia is distinct from starvation, age-related loss of muscle mass, primary depression, malabsorption and hyperthyroidism and is associated with increased morbidity. While this definition has not been tested in epidemiological or intervention studies, a consensus operational definition provides an opportunity for increased research.

Multiorgan syndrome systemic disorder

The Cachexia Pyramid

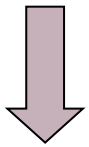


Cachexia is a multifactorial syndrome involving changes in several metabolic pathways, in many tissues and organs:

- **Energy balance disorder**
- **Tumour-driven inflammation**
- **Muscle wasting and atrophy**
- **Adipose tisue wasting**
- **Multi-organ syndrome**

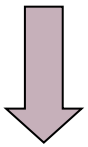
Cachexia: a problem of energy balance

ANOREXIA

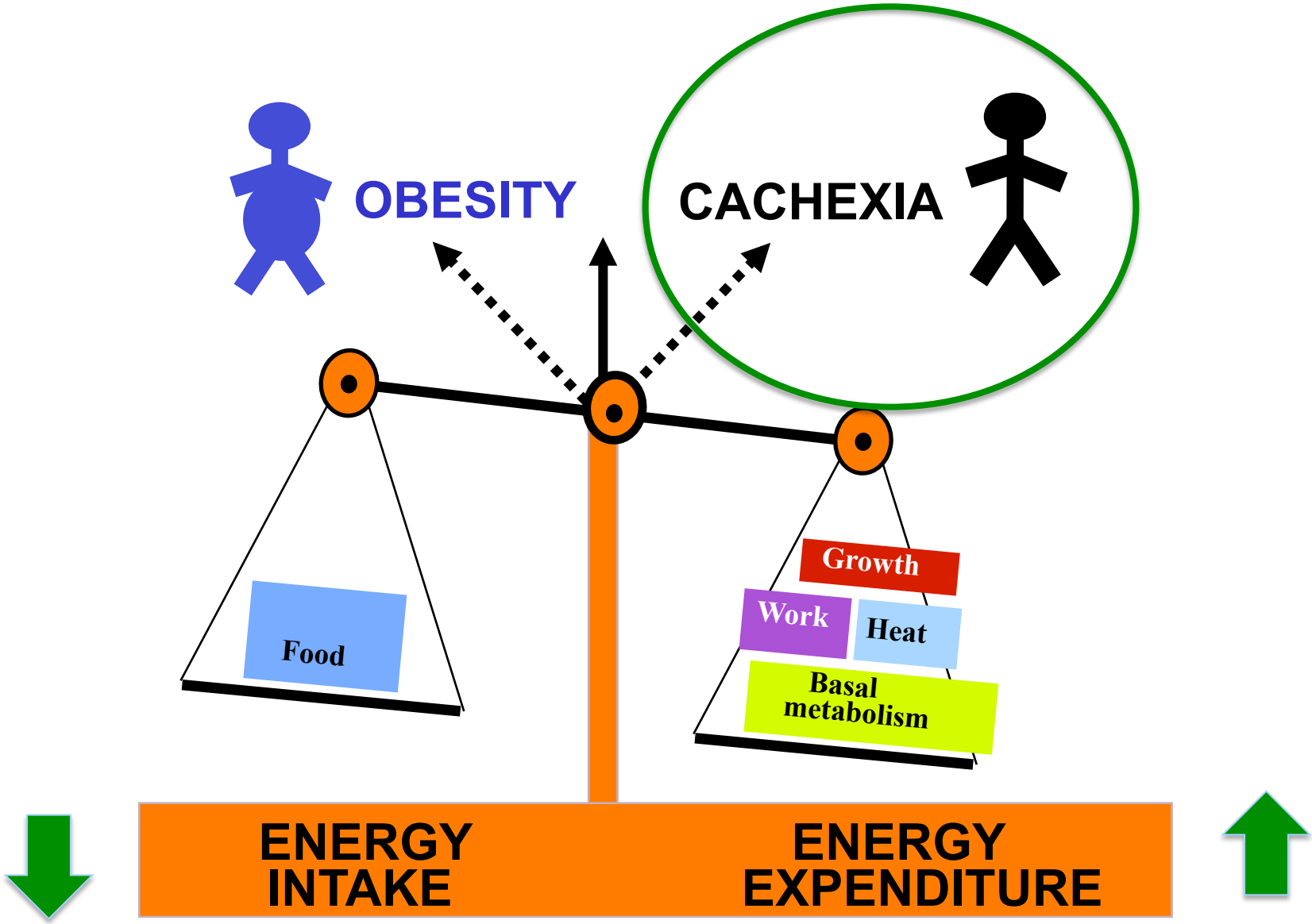


REDUCED FOOD INTAKE

METABOLIC CHANGES

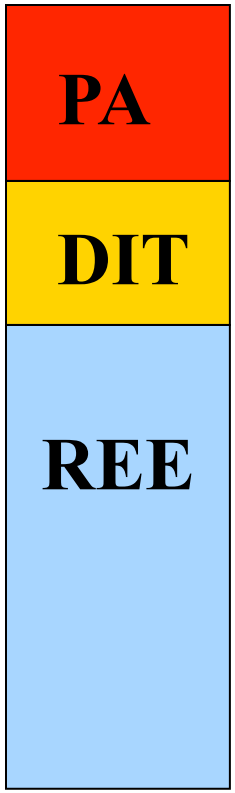


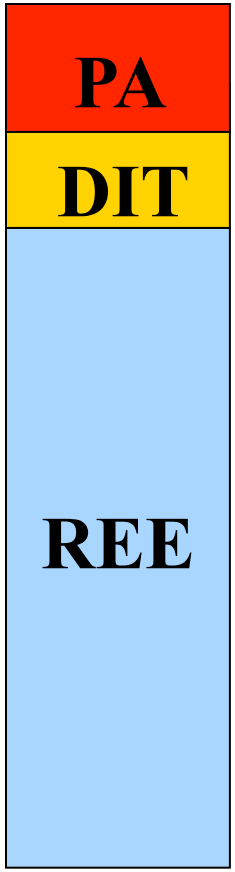
INCREASED ENERGY EXPENDITURE


OBESITY
CACHEXIA
Food
Growth
Work
Heat
Basal metabolism
ENERGY INTAKE
ENERGY EXPENDITURE

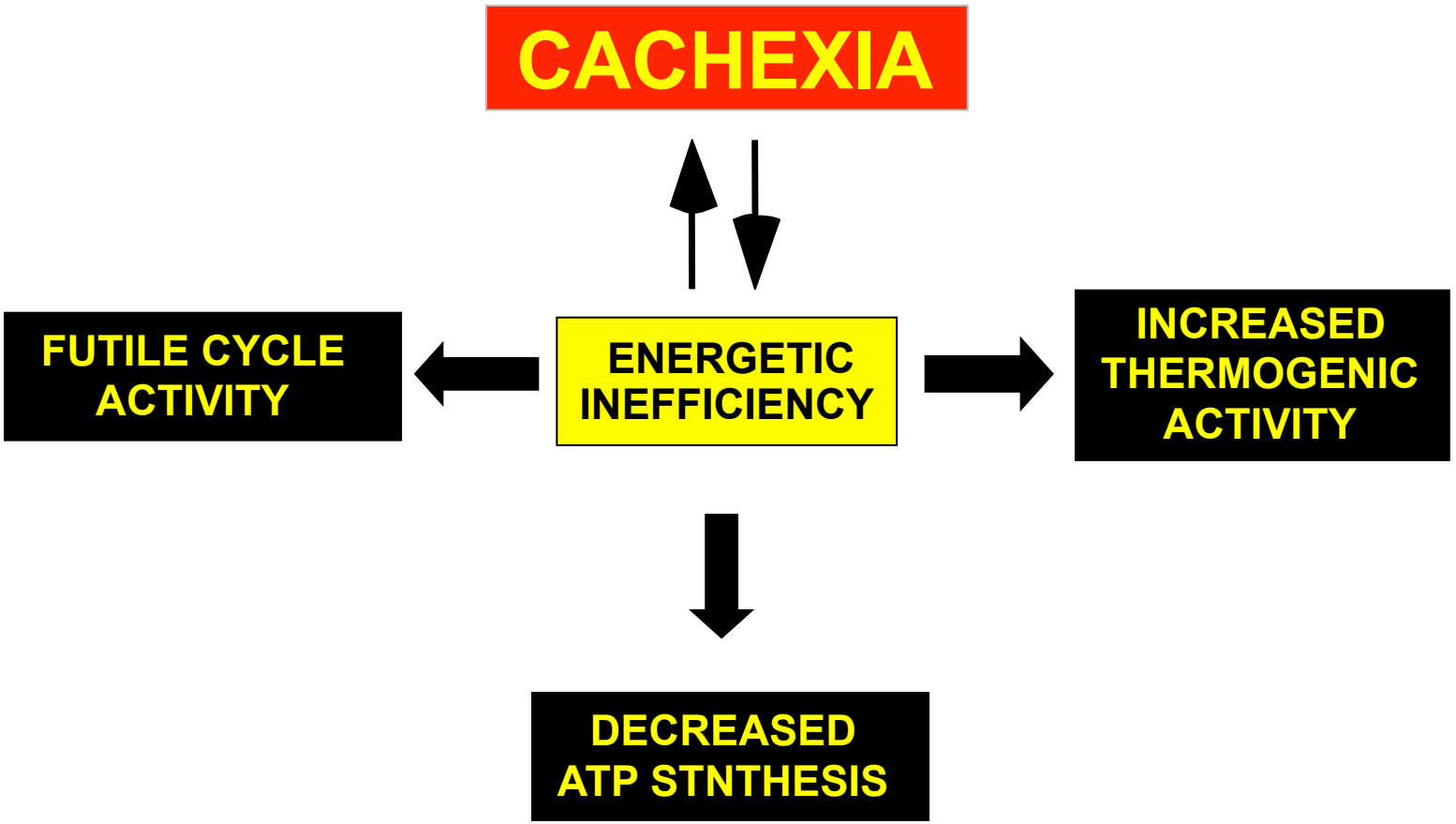
BASAL METABOLIC RATE (REE)
DIET-INDUCED THERMOGENESIS (DIT)
PHYSICAL ACTIVITY

Healthy

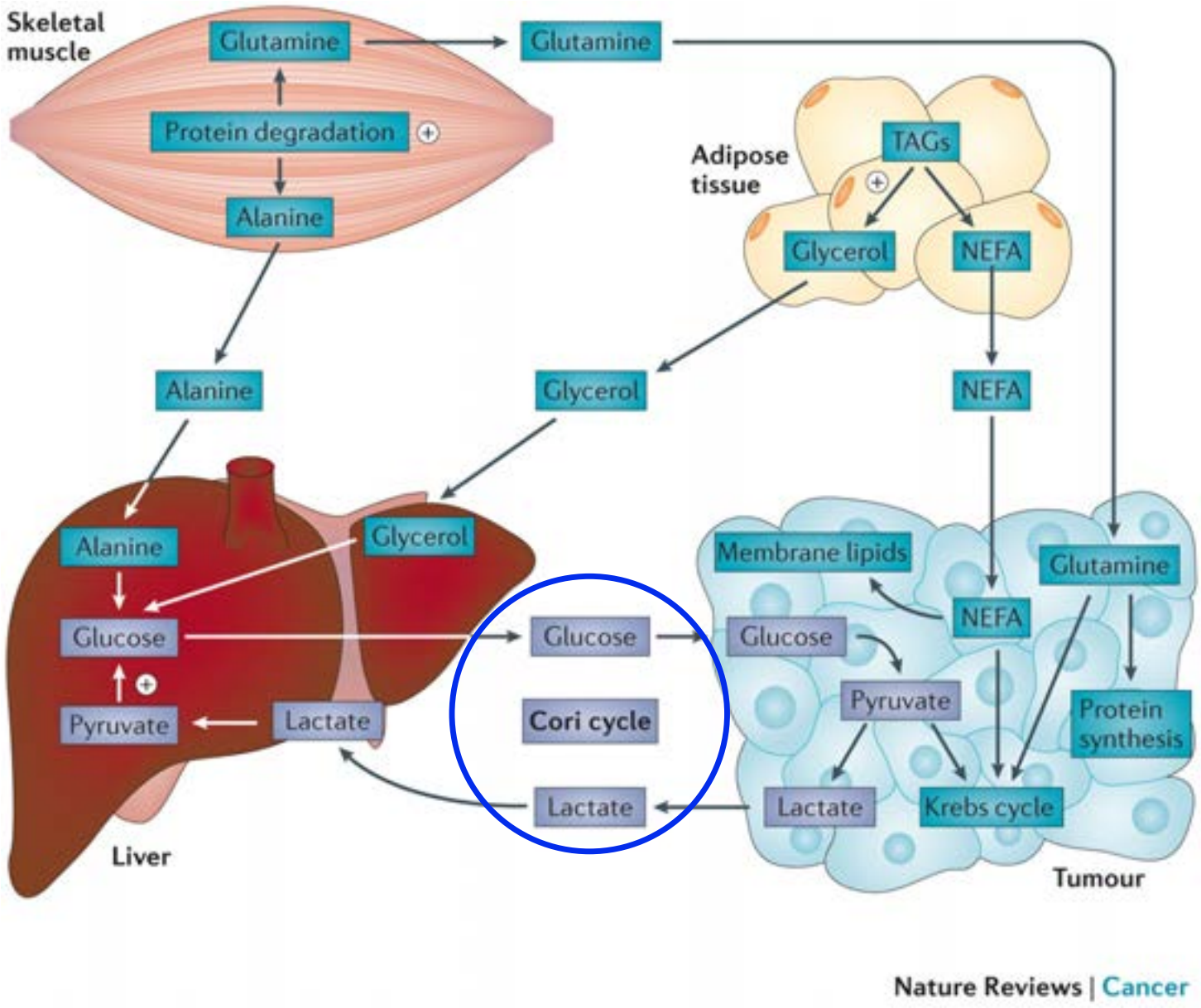




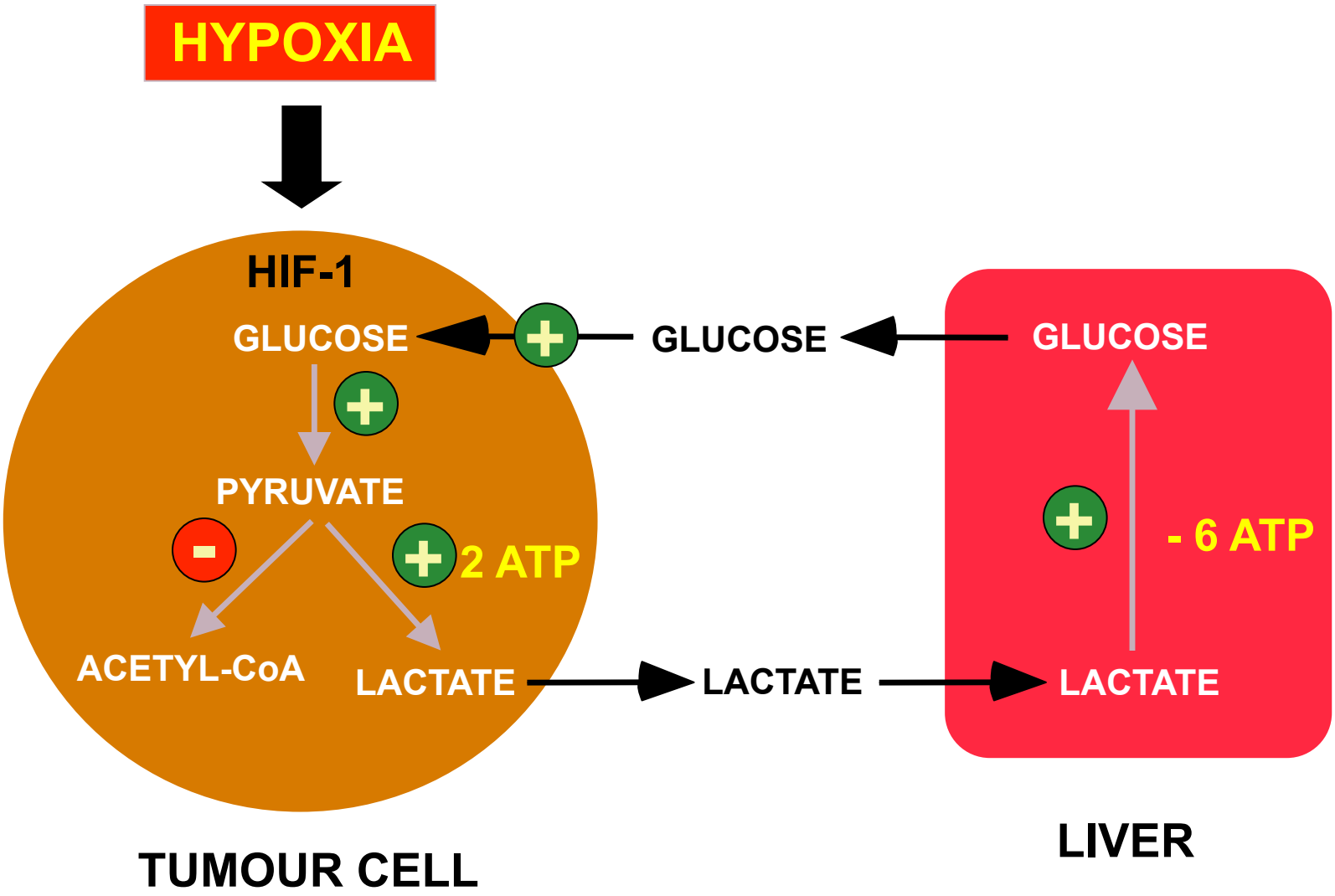
Cancer


CACHEXIA
FUTILE CYCLE ACTIVITY
ENERGETIC INEFFICIENCY
INCREASED THERMOGENIC ACTIVITY
DECREASED ATP STNTHESIS

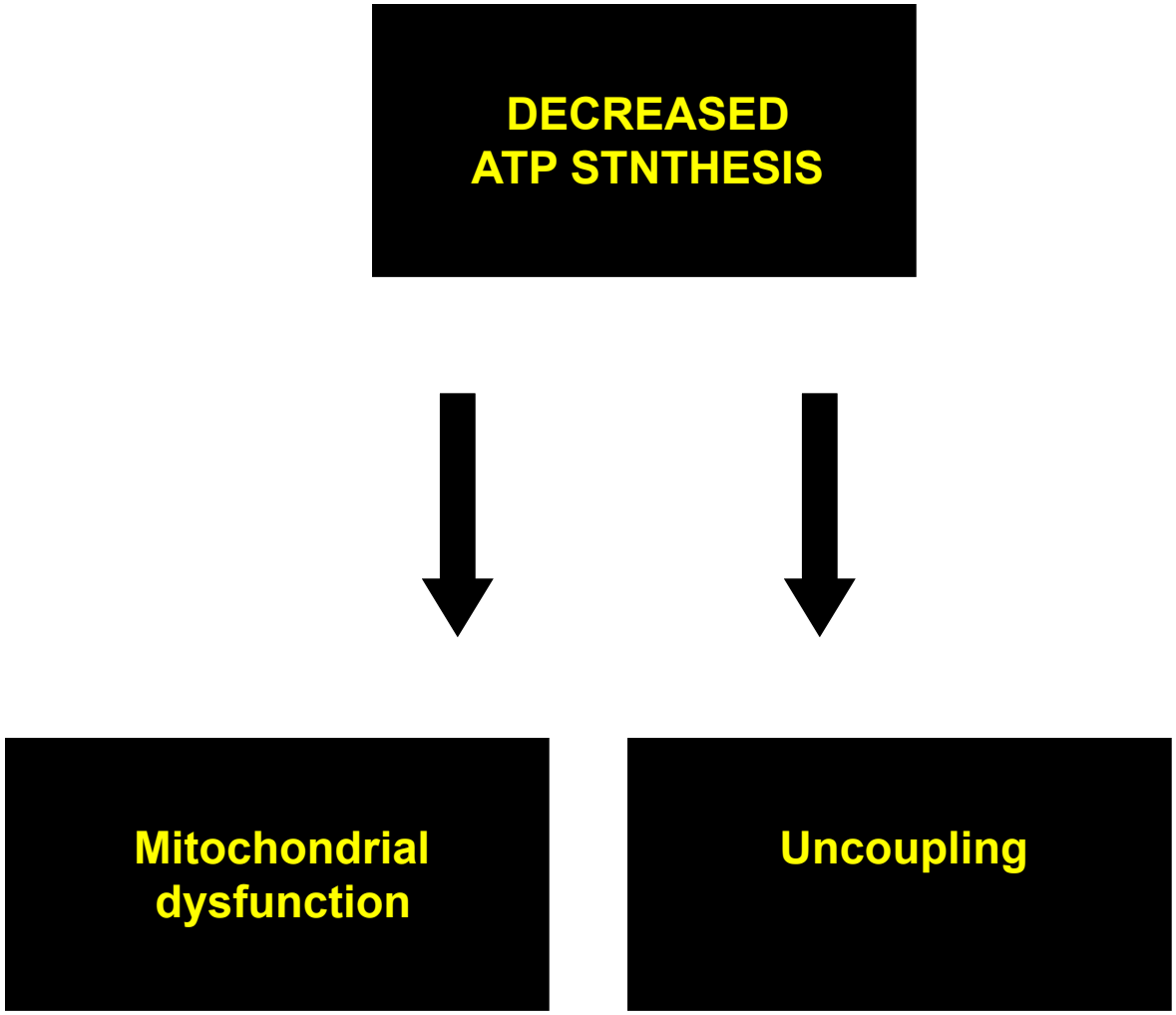
FUTILE CYCLE ACTIVITY



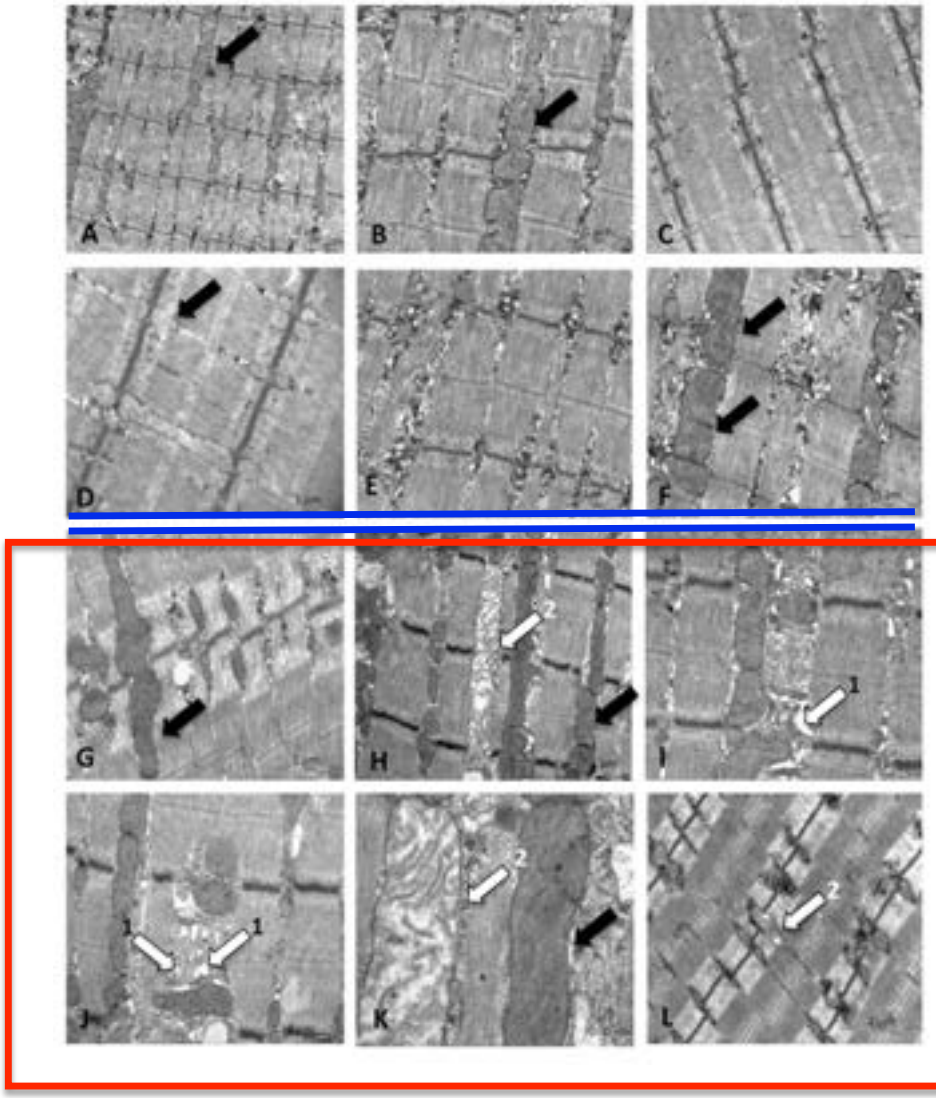
Argilés et al. , Nature Rev. Cancer 14: 754-762 (2014)



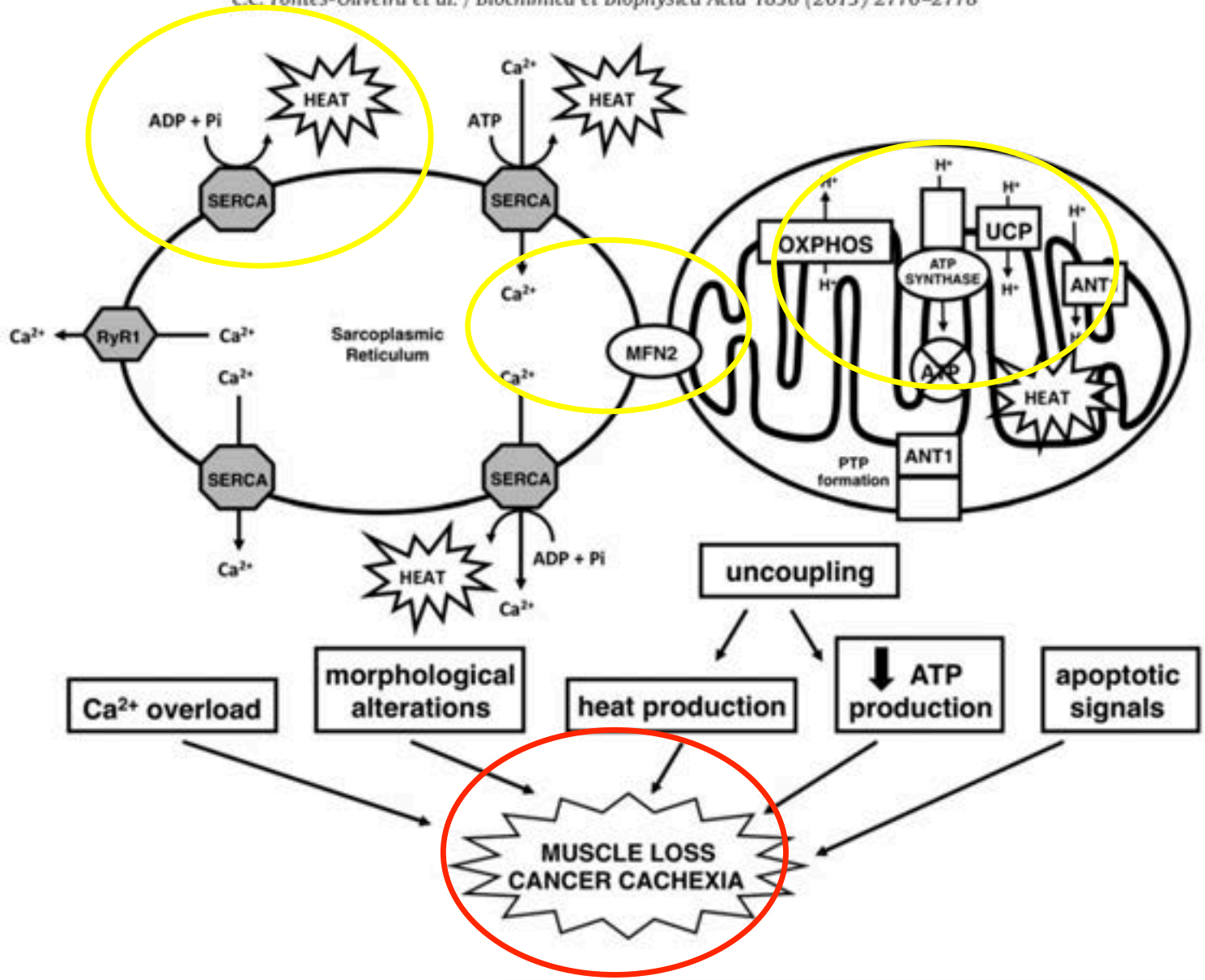
CORI CYCLE ⇨ aprox. 300 kcal/day


DECREASED
ATP STNTHESIS
Mitochondrial
dysfunction
Uncoupling

- Altered changes in mitochondrial morphology
- Decreased oxidative capacity
- Disrupted protein synthesis
- Changes in membrane fluidity
- Oxidatively modified mitochondrial proteins



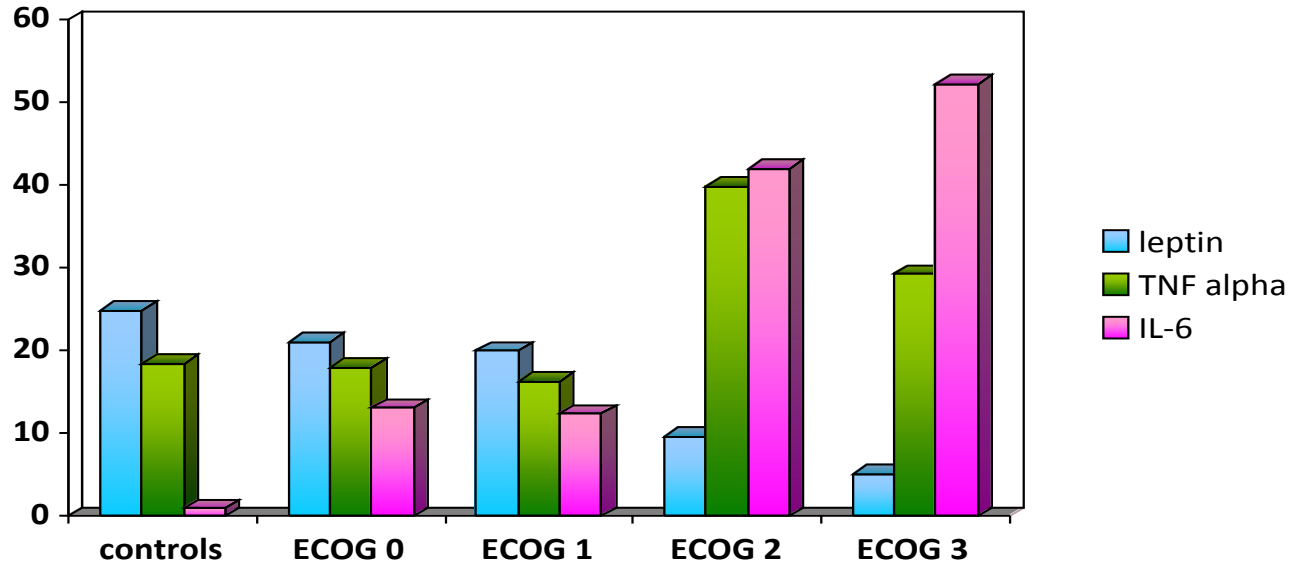
Fontes-Oliveira et al, BBA(2013) 1830, 2770-2778



Fontes-Oliveira et al. (2013) BBA: 1830: 2770-2778

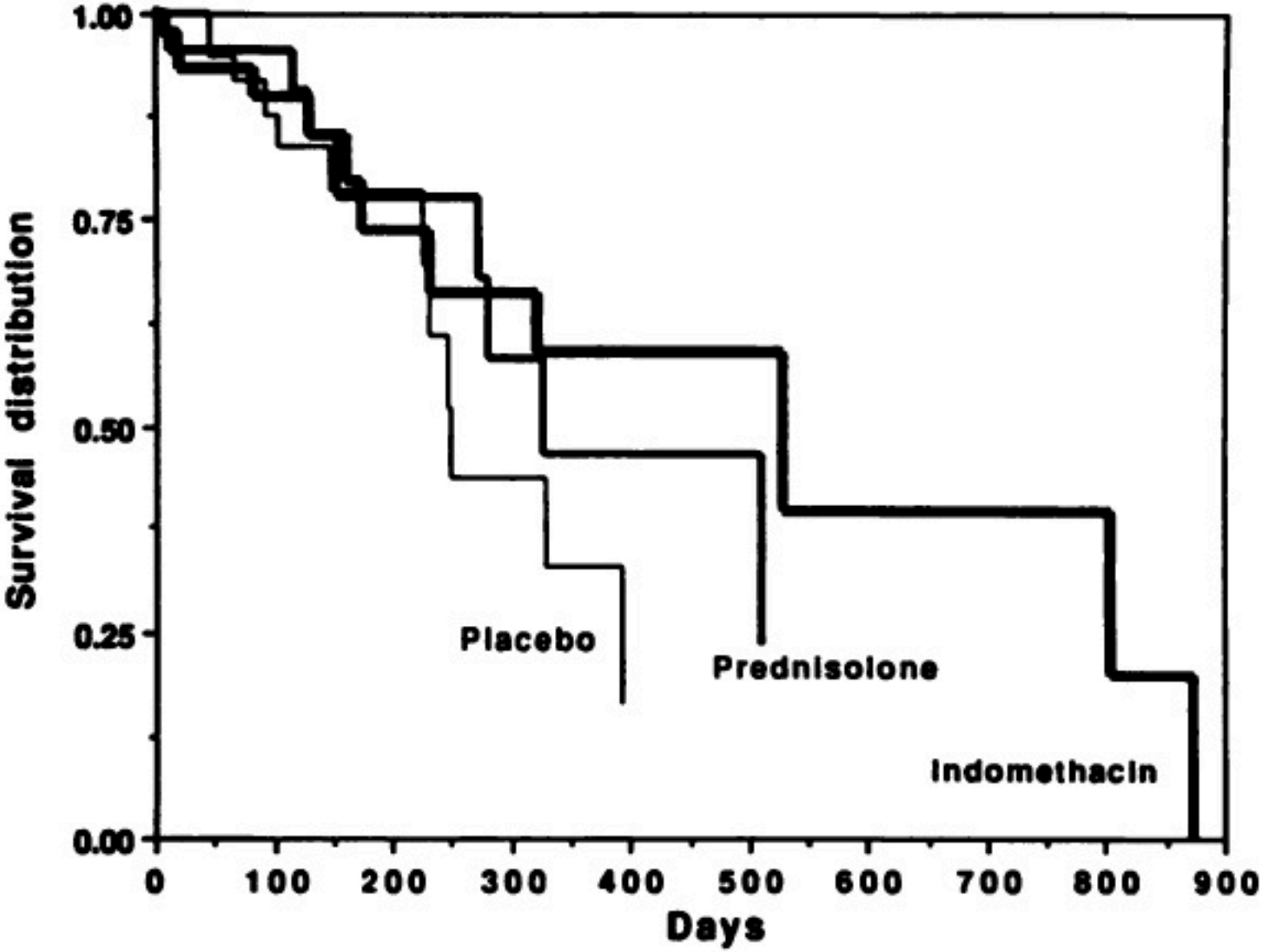
Tumour-driven inflammation

Serum levels of leptin and proinflammatory cytokines in a population of cancer patients according to performance status



Lowest ECOG PS (2 and 3) are associated with highest levels of proinflammatory cytokines (especially IL-6)

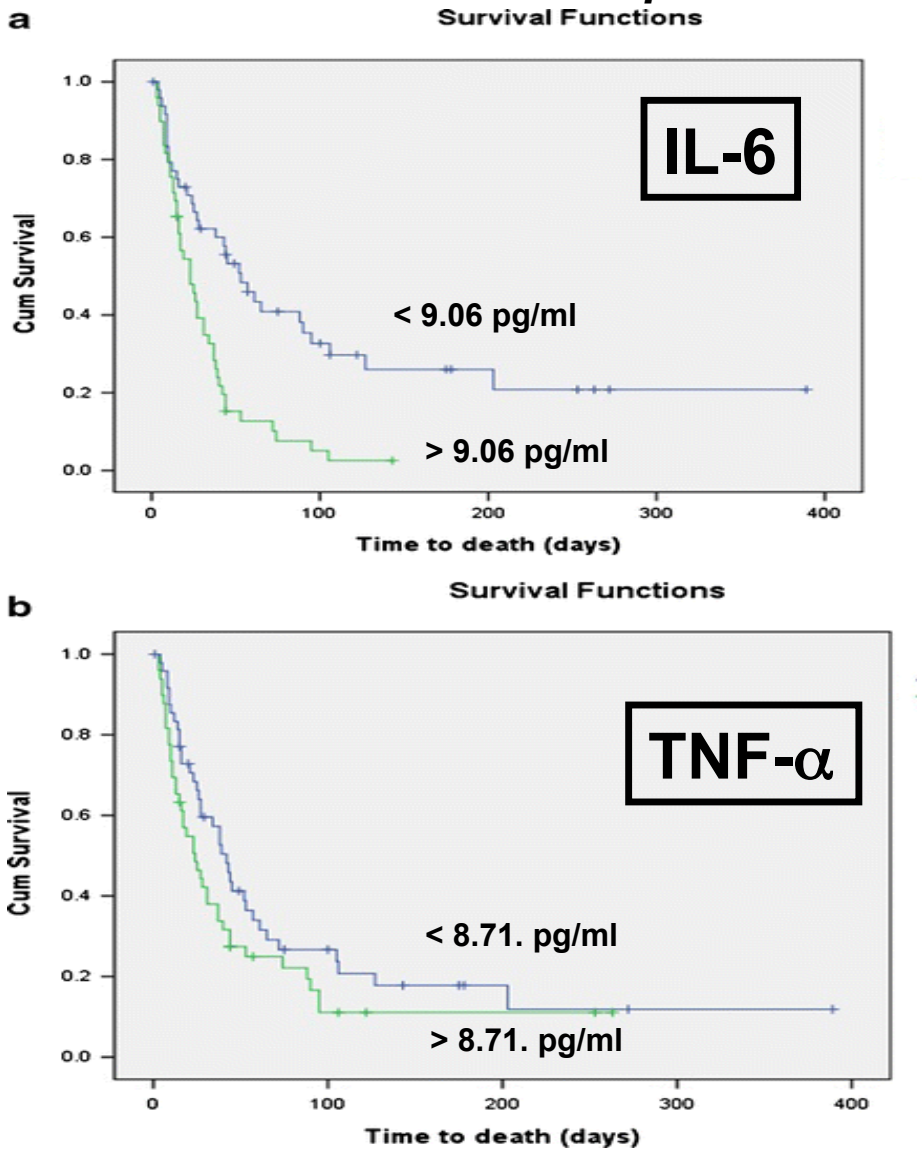
Mantovani G. et al. (2000) J Mol Med 78: 554-561



Lundholm et al., (1994) Cancer Res. 54:5602-6

IL-6 and Survival

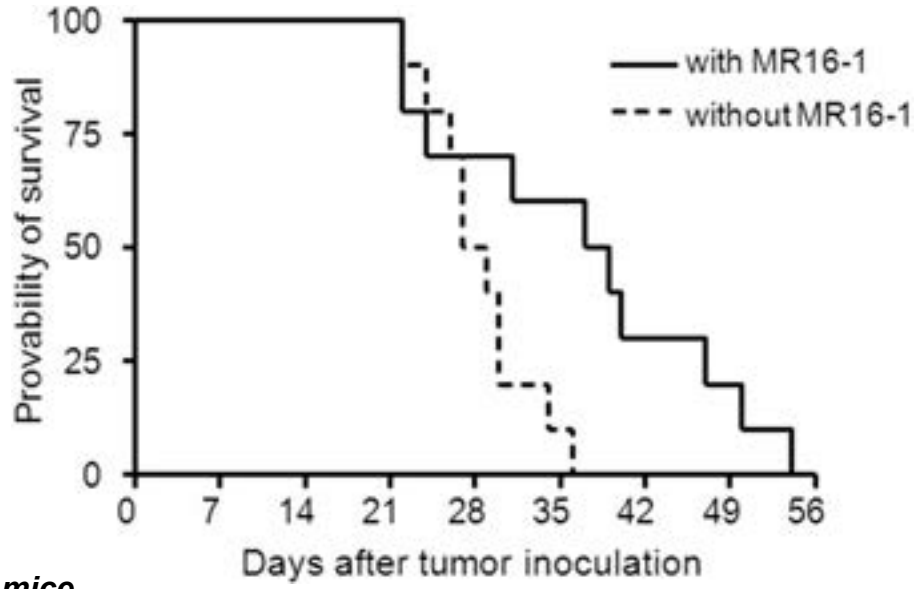
Advanced cancer patients



Suh et al., Support Care Cancer (2013) 21:3071–3077

Tocilizumab, a proposed therapy for the cachexia of IL6-expressing lung cancer

Parameters	Healthy control groups		Cancer cachexia group	
	Group 1 (n = 10) without MR16-1	Group 2 (n = 10) with MR16-1	Group 3 (n = 8) without MR16-1	Group 4 (n = 8) with MR16-1
Carcass weight (g)	25.9 ± 1.3	26.0 ± 1.5	22.1 ± 0.9*	24.1 ± 2.3****
Gastrocnemius muscle (mg)	128.1 ± 49.2	115.4 ± 32.2	60.4 ± 29.3*	106.6 ± 22.8***
Quadriceps muscle (mg)	102.7 ± 46.5	114.2 ± 33.6	14.7 ± 8.6*	48.5 ± 21.2***
Biceps femoris muscle (mg)	145.4 ± 27.9	174.6 ± 85.3	27.1 ± 12.3*	59.4 ± 28.9***
Fat tissue around testis (mg)	490.5 ± 80.8	468.4 ± 70.7	169.4 ± 48.1*	312.4 ± 90.3****
White blood cell (/μL)	4,667 ± 2,317	3,867 ± 1,892	48,350 ± 18,288*	4,100 ± 880***
Hematocrit (%)	32.8 ± 2.5	35.4 ± 1.2**	9.4 ± 4.4*	21.8 ± 2.1***
Platelet ($\times 10^4$/μL)	54.8 ± 25.7	69.3 ± 20.9	102.2 ± 28.1**	68.5 ± 28.5
Triglyceride (mg/dL)	87.0 ± 18.2	81.2 ± 28.1	23.0 ± 9.1*	48.0 ± 14.4***
Glucose (mg/dL)	311.6 ± 174.9	260.0 ± 40.6	29.6 ± 9.5*	101.0 ± 36.0***

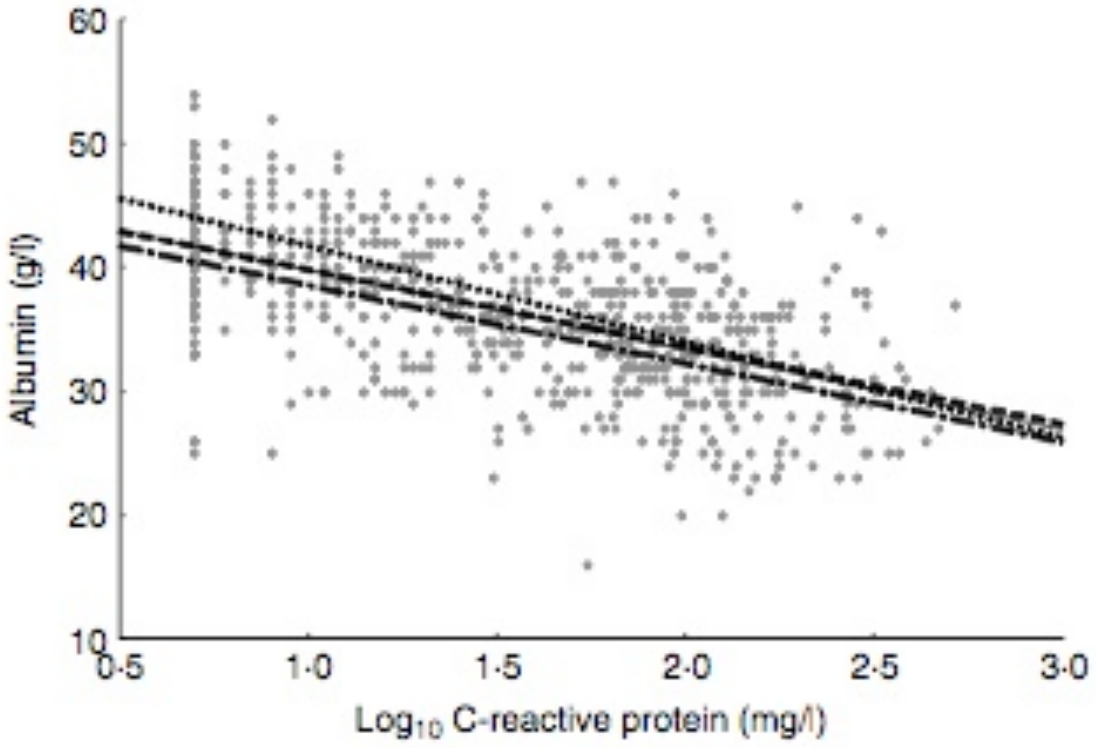


Lewis lung carcinoma-bearing mice

Ando et al. (2014) PLOS One 9(7):e102436

Inflammation and survival in cancer

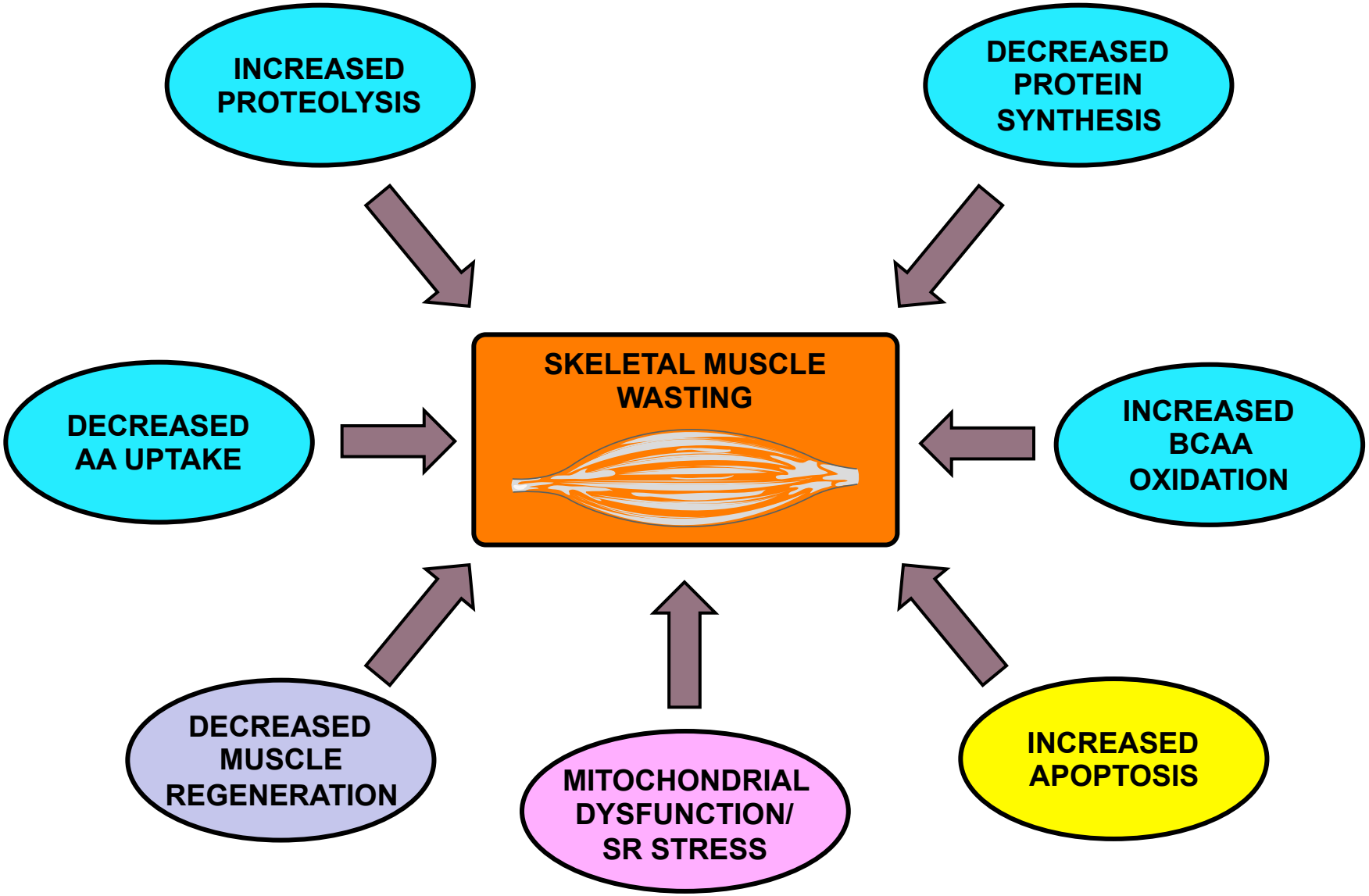
*Glasgow Pronostic Score: a **predictor of survival** independent of tumour stage, performance status or treatment*



Score 2 : patients with elevated C-reactive protein serum levels (>10 mg/L) and hypoalbuminemia (<35 g/L)
Score 1: patients with either elevated C-reactive protein serum levels (>10 mg/L) or hypoalbuminemia (<35 g/L))
Score 0: patients with normal C-reactive protein serum levels and normal albuminemia

McMillan D.C. (2008) Proc. Nutr. Soc. 67:257-262

Muscle wasting and atrophy


INCREASED PROTEOLYSIS
DECREASED PROTEIN SYNTHESIS
DECREASED AA UPTAKE
SKELETAL MUSCLE WASTING
INCREASED BCAA OXIDATION
DECREASED MUSCLE REGENERATION
MITOCHONDRIAL DYSFUNCTION/ SR STRESS
INCREASED APOPTOSIS

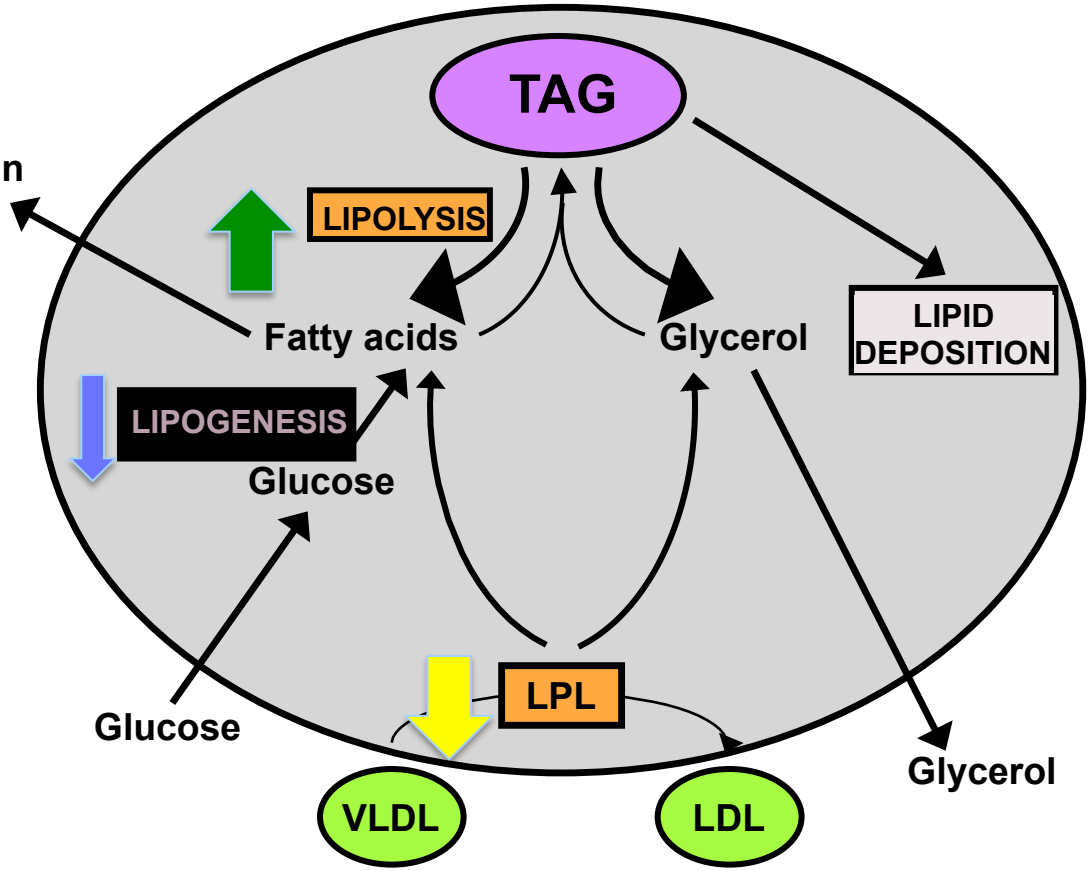
Adipose tissue wasting

Adipose tissue wasting

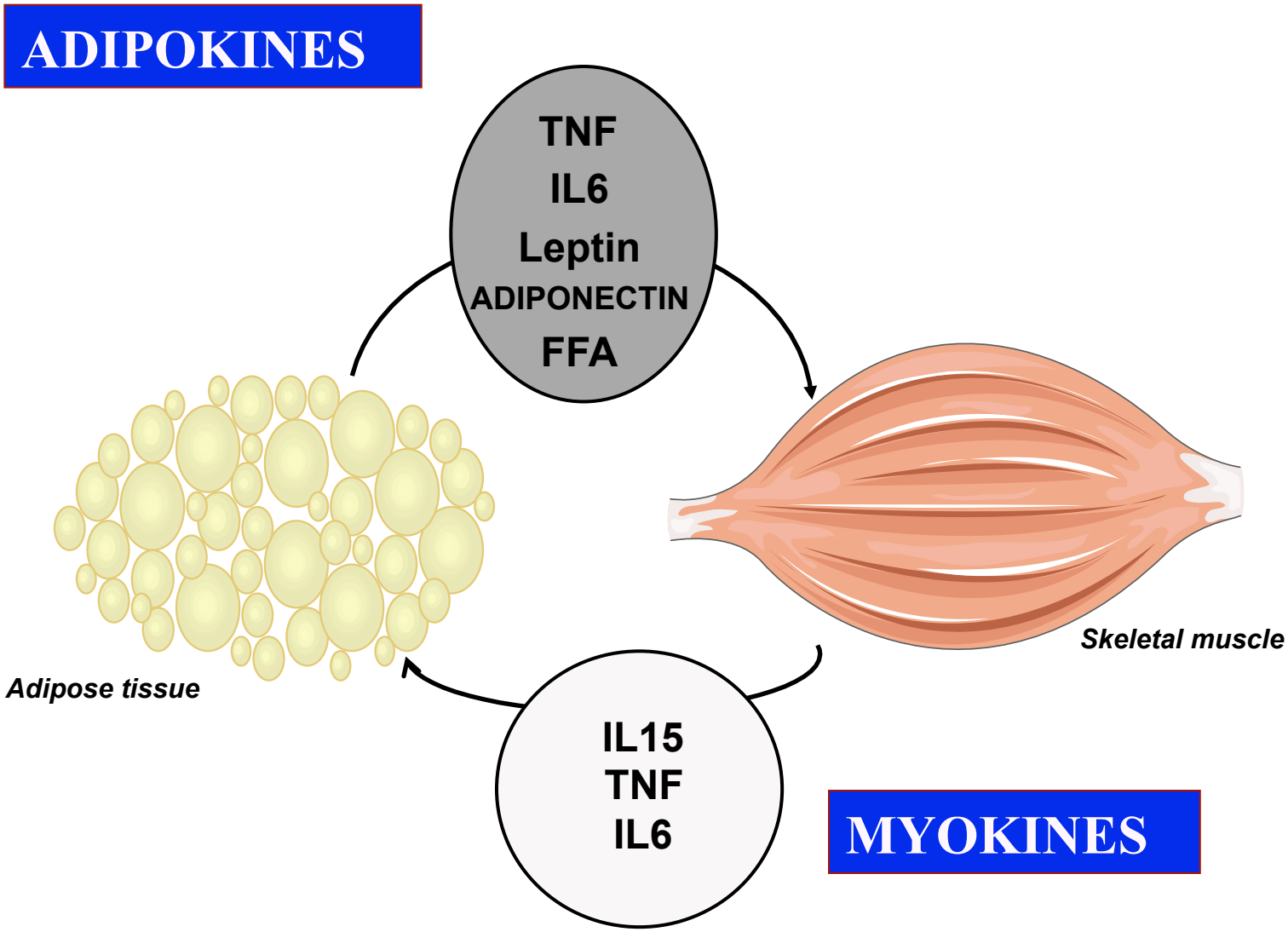
1. Increased rate of lipolysis

2. Decreased LPL activity

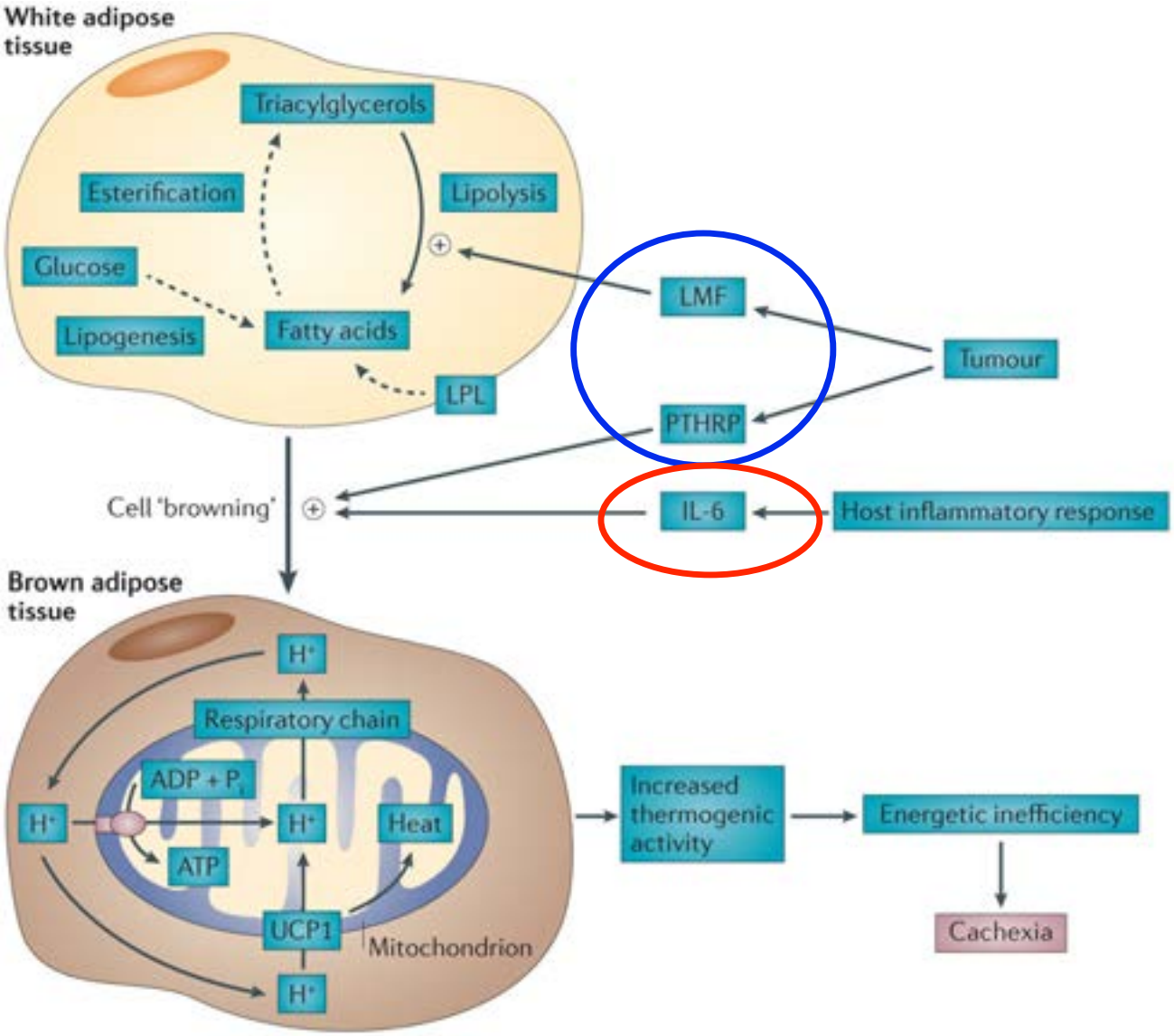
3. Reduced *de novo* lipogenesis



Cross-talk between adipose tissue and muscle

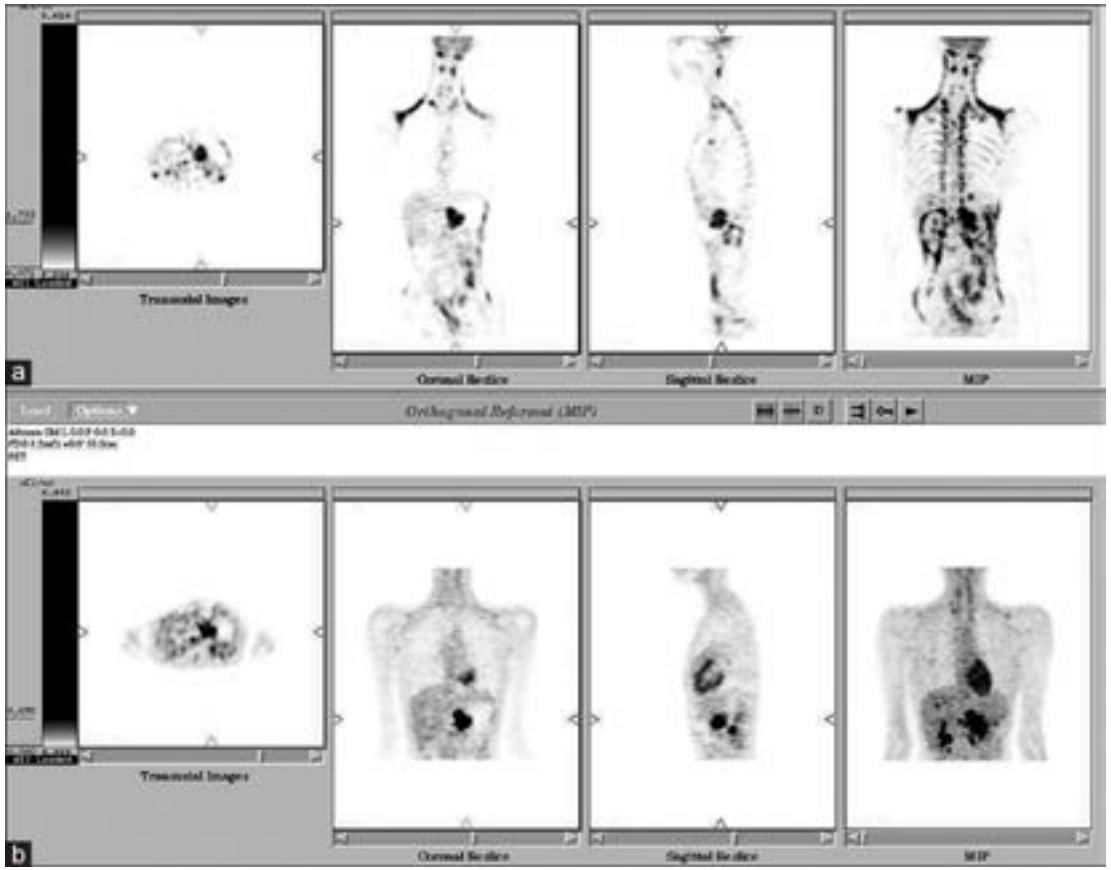


Argilés et al. Med Res Rev, 25, No. 1, 49–65, 2005



Argilés et al. (2014) Nature Rev. Cancer 14: 754-762

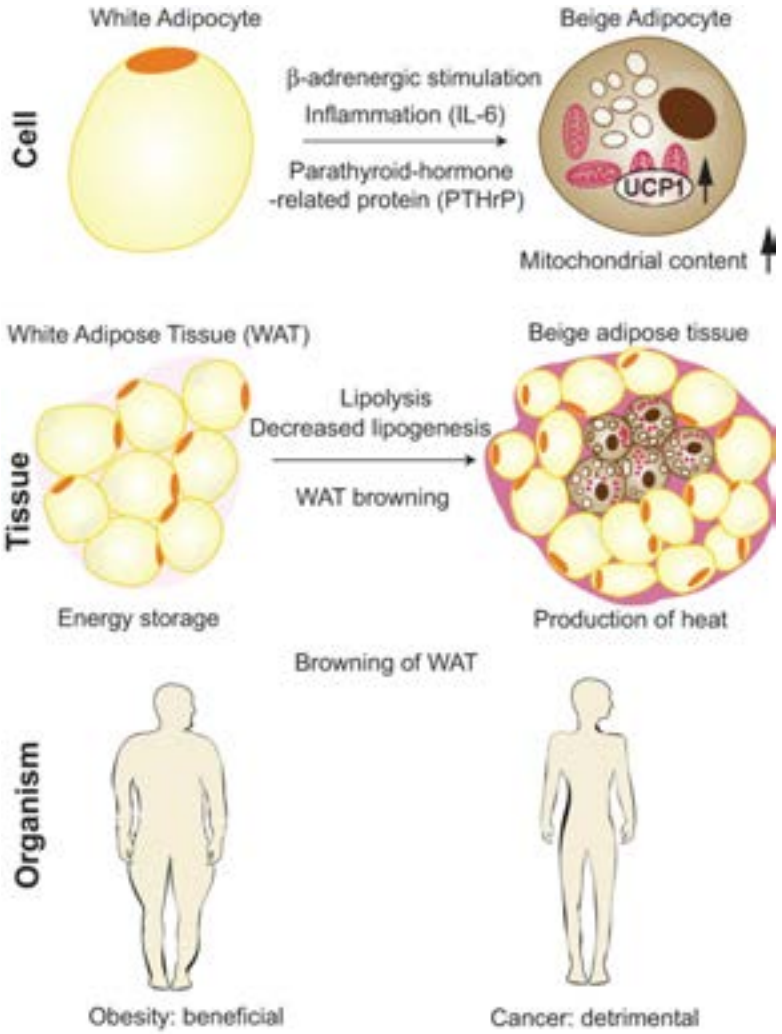
PET Imaging



(a) Upper row: Whole body FDG-.PET acquired 60 min after intravenous injection of FDG demonstrating intense and extensive FDG uptake in the brown adipose tissue in the supraclavicular and paravertebral regions bilaterally in addition to uptake in the neoplasm. (b) Lower row: Repeat FDG-PET following propranolol intervention on a different day demonstrates there was no FDG uptake in the BAT, though the uptake in the neoplasm persists

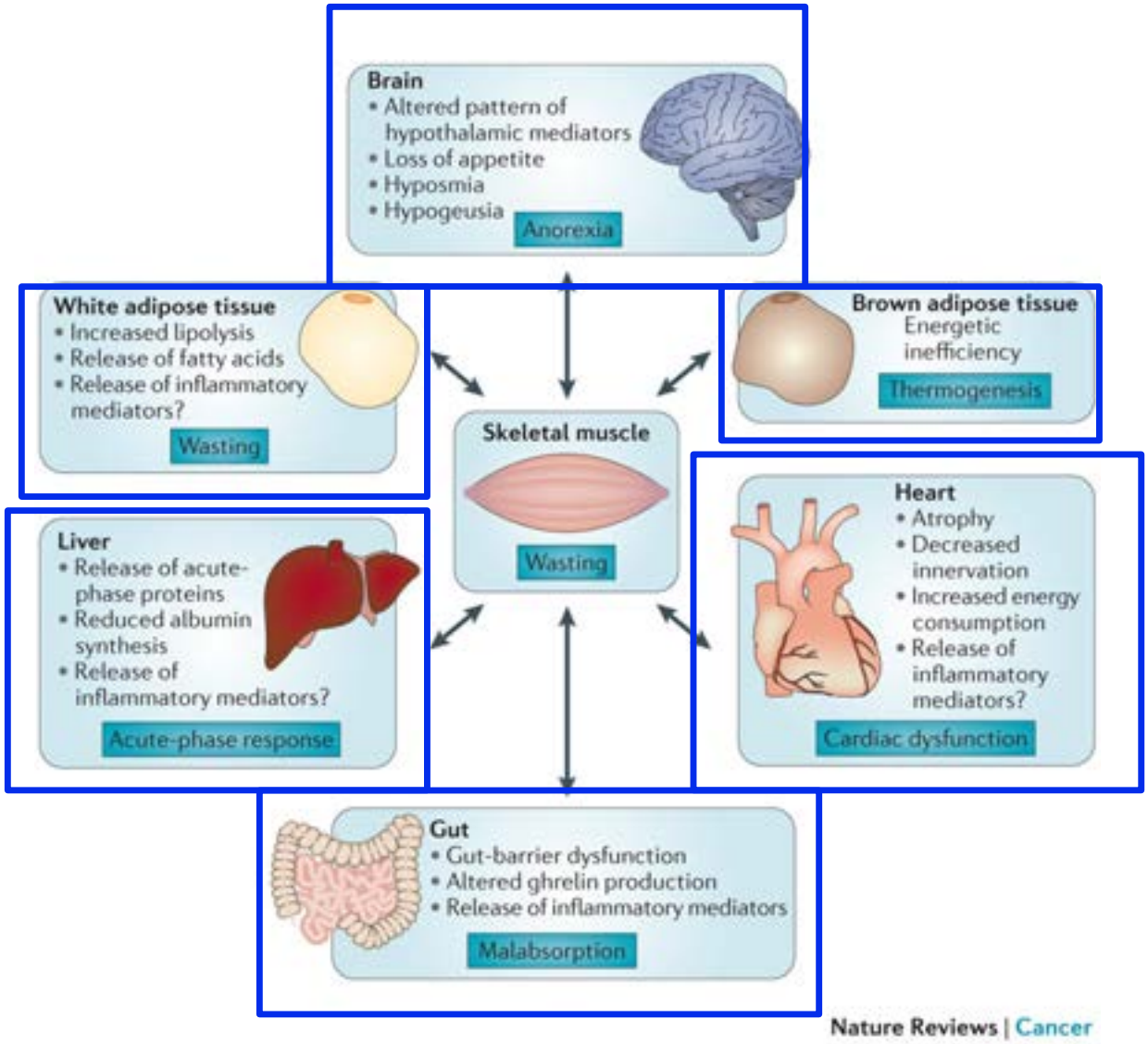
Basu (2015) Indian J.Cancer 52: 223-224

Mechanisms and consequences of WAT browning in cancer cachexia



Petruzzelli & Erwin F. Wagner (2016) Genes Dev. 30:489-501

Multiorgan syndrome



Argilés et al. (2014) Nature Rev. Cancer 14: 754-762

Treating cachexia: elements to be taken into consideration

Drugs in cachexia clinical trials:endpoints

Stimulate food intake
Enhance absorption/Gastric emptying
Preserve LBM
Enhance QoL
Control cancer
Promote health

Cachexia diagnosis & staging

Multidisciplinary team

Multimodal treatment (anabolic + anticatabolic)

Nutritional counseling
Nutritional supplements
Drugs
Exercise program

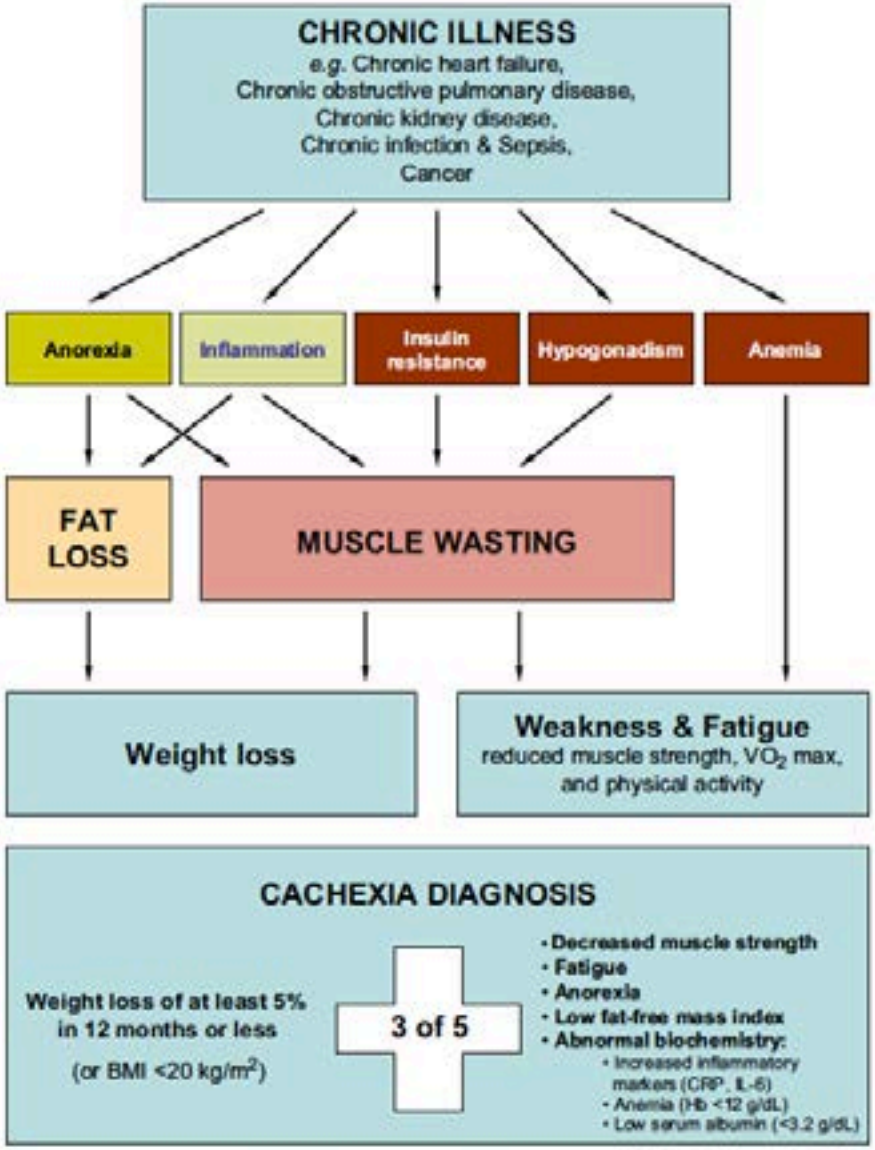
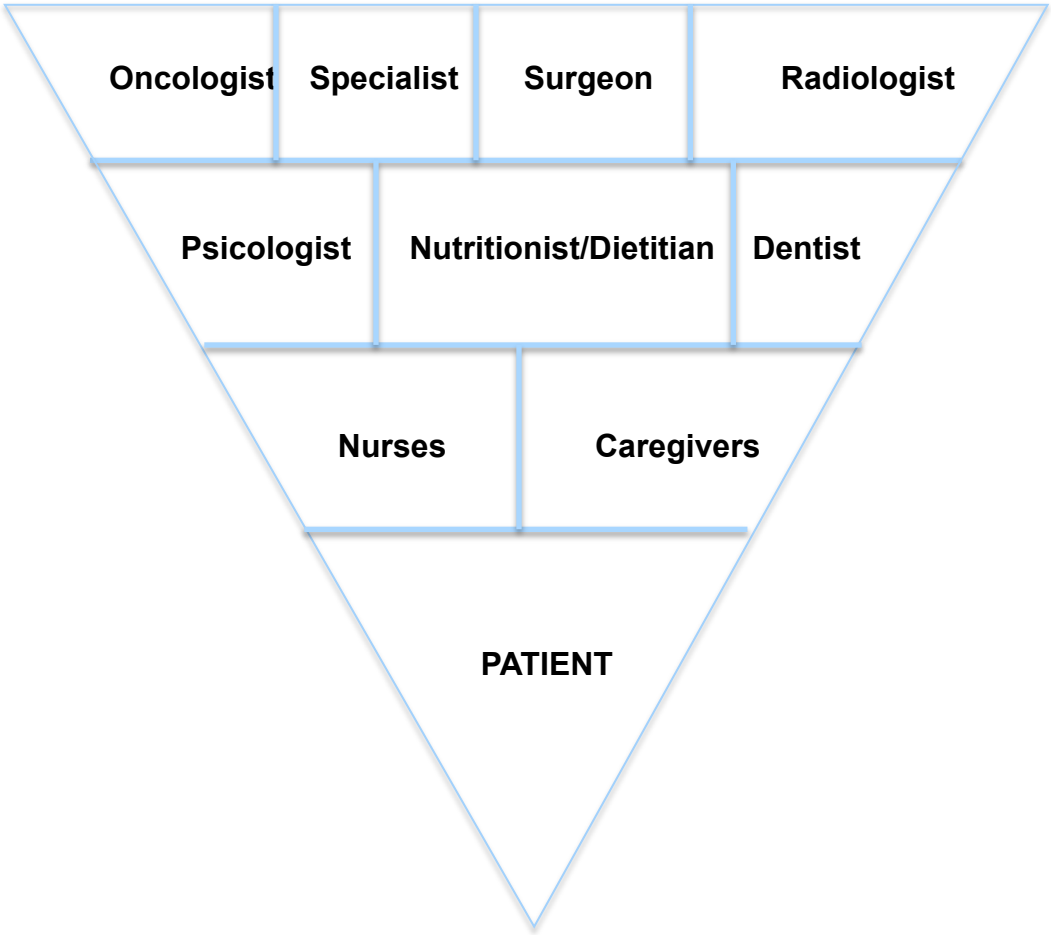
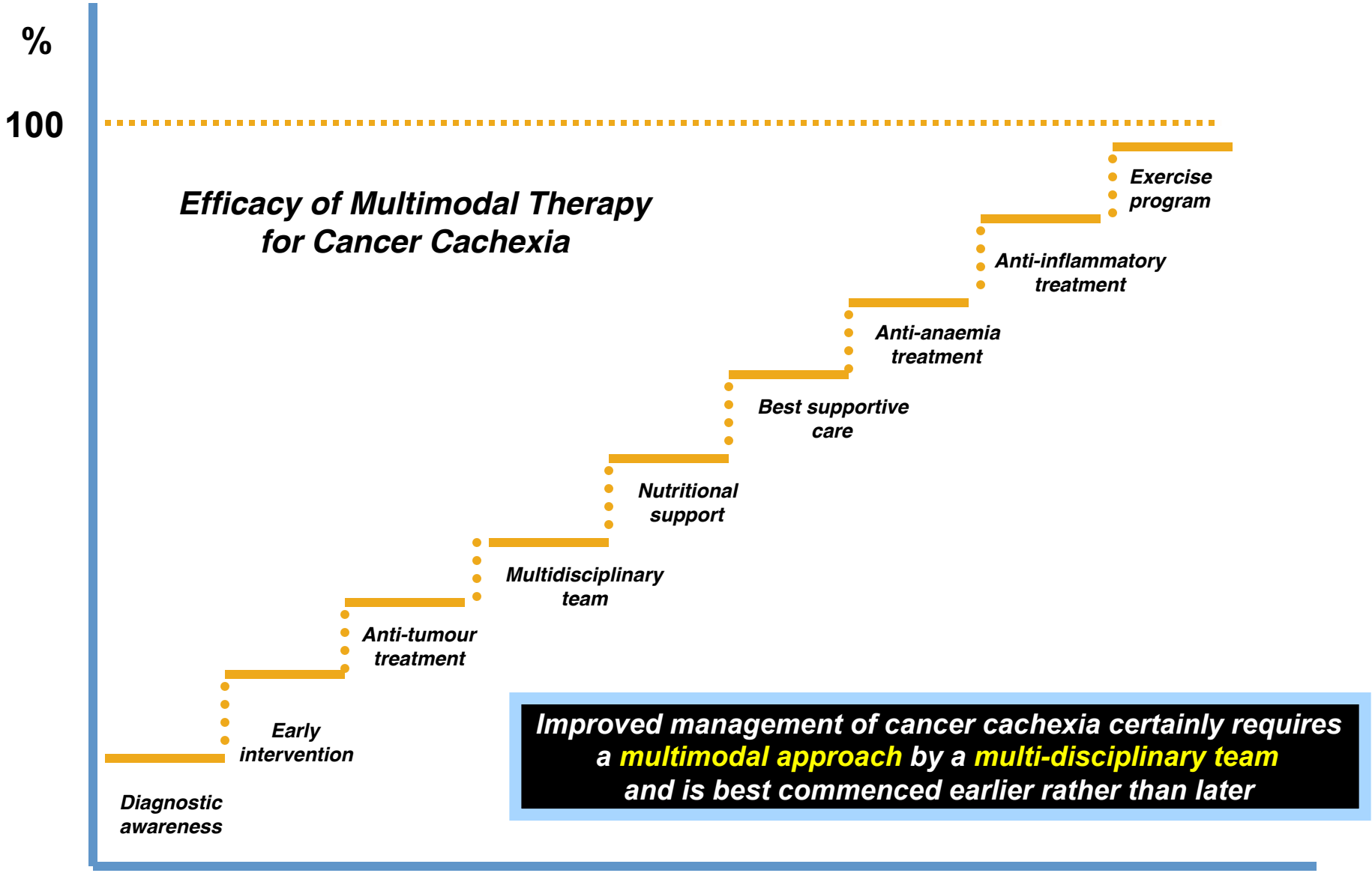


Figure 1 Conceptual representation of the definition: cachexia results from adaptation to an underlying illness such as cancer. The illness creates an environment that may be characterized by inflammation, loss of appetite (anorexia), low levels of testosterone and other anabolic hormones, and anemia. Decreased food intake and anorexia result in loss of body and muscle mass. In addition, inflammation, insulin resistance, and low levels of anabolic hormones result in muscle wasting.

Evans et al. Clin. Nutr. 27, 793-799, 2008

The Inverted Pyramid of Cancer Management

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100
Efficacy of Multimodal Therapy for Cancer Cachexia
Diagnostic awareness
Early intervention
Anti-tumour treatment
Multidisciplinary team
Nutritional support
Best supportive care
Anti-anaemia treatment
Anti-inflammatory treatment
Exercise program
Improved management of cancer cachexia certainly requires a multimodal approach by a multi-disciplinary team and is best commenced earlier rather than later

To take home:

Cancer cachexia is an energy balance and multi-organ syndrome

Systemic inflammation, particularly cytokines, drives many of the metabolic changes associated with muscle wasting. Special attention should be given to both muscle and adipose-released cytokines and the intercommunication between the two tissues

The role of adipose tissues –both white and brown– deserves further research and may lead to new therapeutic strategies