



UNIVERSITY OF TURIN

*PhD in
EXPERIMENTAL MEDICINE AND THERAPY*

SEMINARIO

CANCER CACHEXIA: MOLECULAR MECHANISMS, DIAGNOSIS AND TREATMENT

Dr. SILVIA BUSQUETS

Departament de Bioquímica i Biomedicina Molecular
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Barcelona, Spain



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Campus

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de Barcelona
Campus



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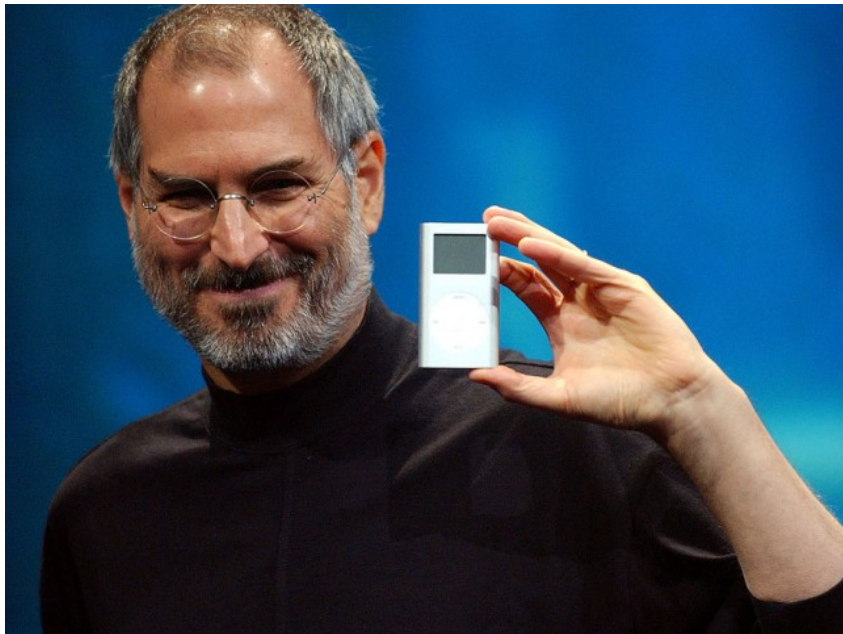
Departament de Bioquímica i Biomedicina Molecular

Universitat de Barcelona

Barcelona, Spain

MOLECULAR MECHANISMS OF CANCER CACHEXIA

Multiorgan syndrome systemic disorder



Steve Jobs
1955 - 2011



CACHEXIA



ΚΑΚΟΣ
kakos

ηΞΙΣ
hexis



bad condition

Cachexia, is a complex metabolic syndrome associated with underlying illness and characterized by **loss of muscle with or without loss of fat mass.**

CACHEXIA

DISEASES ASSOCIATED WITH THE CACHECTIC SYNDROME

- Acquired immune deficiency syndrome (AIDS)
- Sepsis
- Severe burn
- Chronic obstructive pulmonary disease (COPD)
- Cardiovascular pathology
- Neuromuscular disease hyperthyroidism
- Muscle atrophy and/or dystrophy
- **Cancer**
- ...

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

CACHEXIA

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

cachexia is directly responsible for the death of **at least 20%** of all cancer patients (cardiac/respiratory failure)

CME Palliative care

Cancer cachexia and fatigue

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

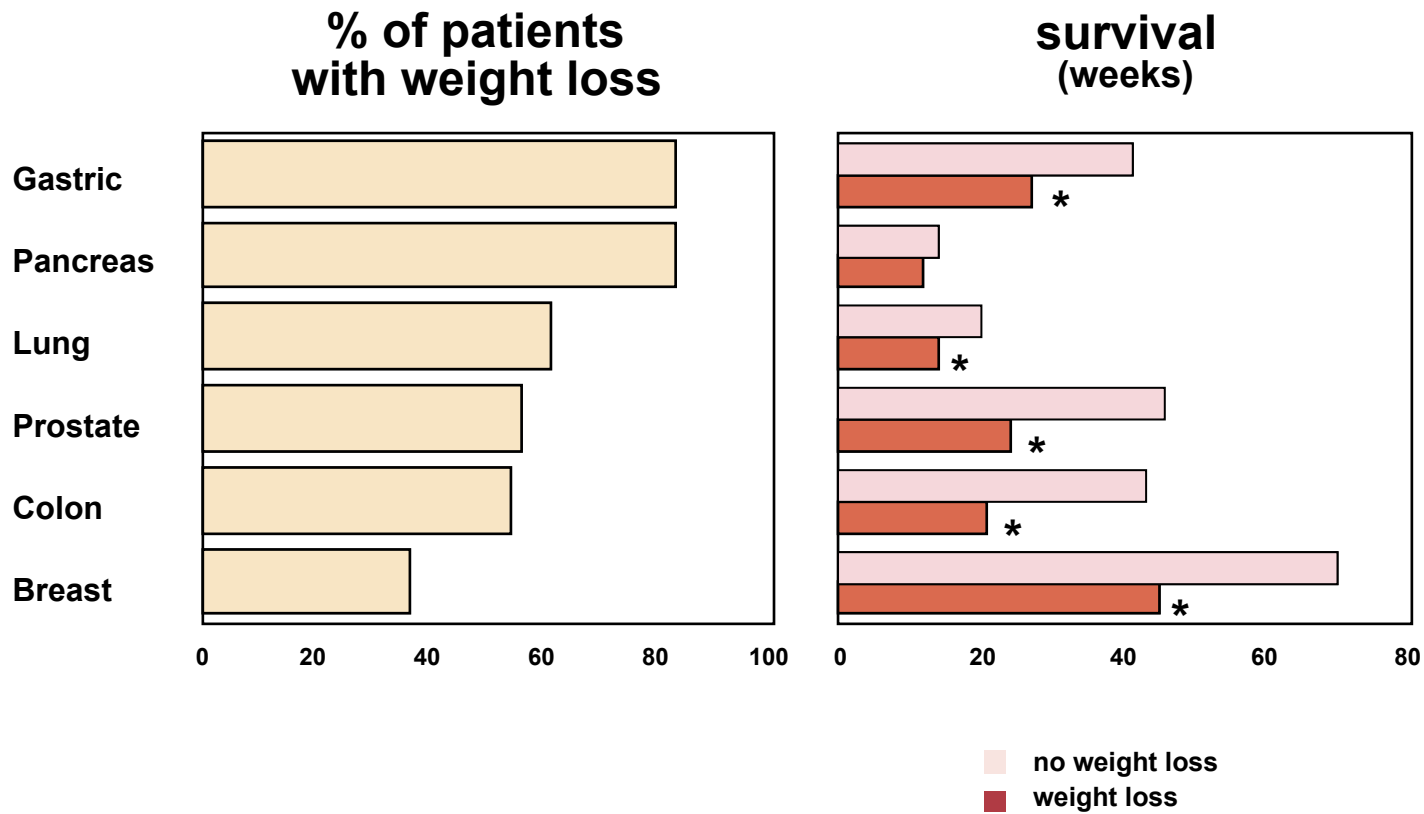
Richard JE Skipworth BSc(Hons) MBChB MRCS(Ed), Surgical Research Fellow

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

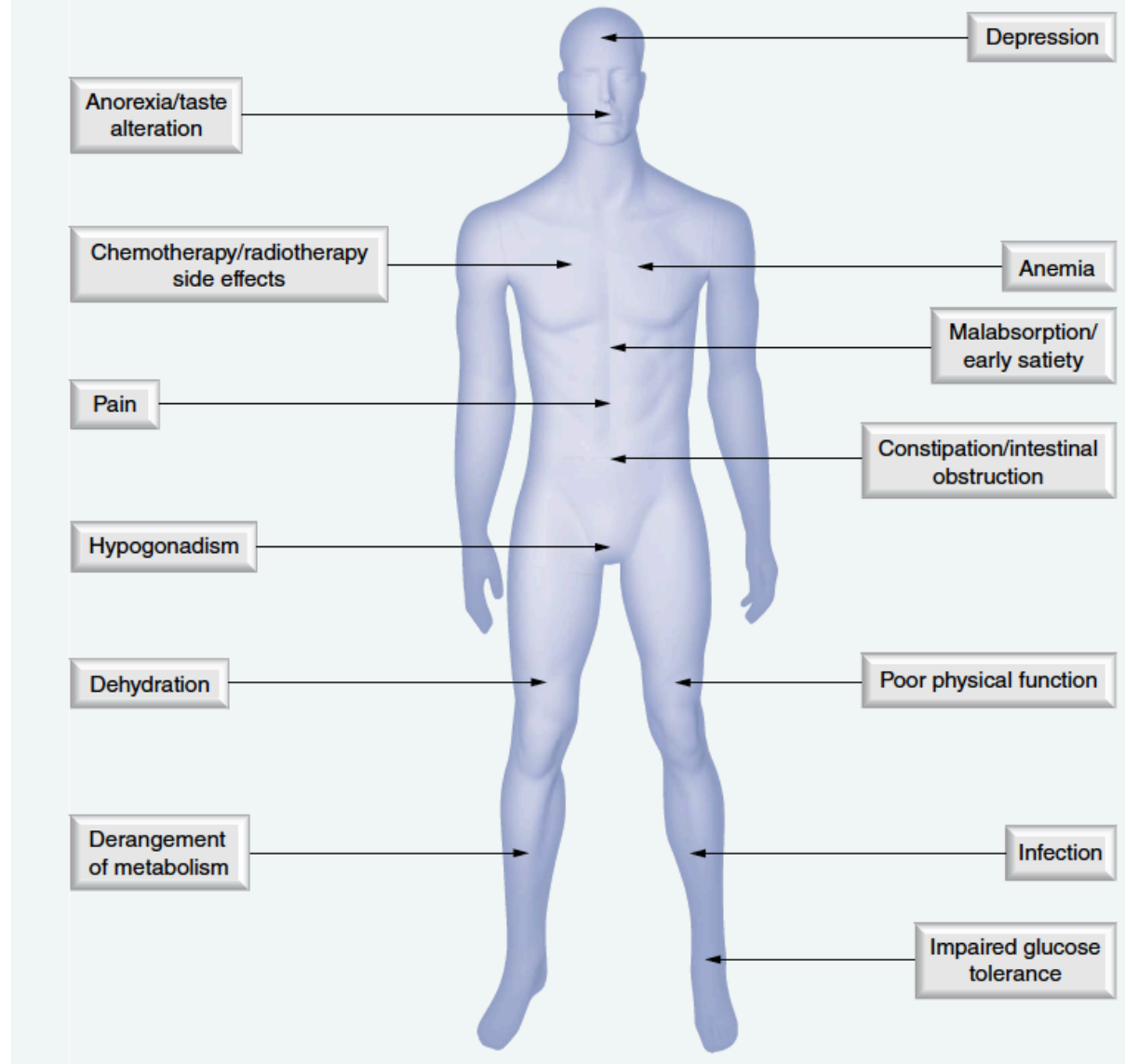
Clin Med 2006;6:140-3

CANCER CACHEXIA



DeWys et al; Am.J.Med. 69: 491 (1980)

Figure 1.2. Clinical features present in cancer cachexia.

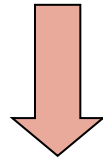


Neil Johns, Richard JE, Skipworth, Kenneth CH Fearon & James A Ross.

Prevalence and clinical features of cancer cachexia.

Cancer Cachexia. Future Medicine. 2012 doi:10.2217/EBO.12.147

CACHEXIA



Reduced survival time
Poor prognosis
Reduced reponse to therapy
Increased toxicity associated to treatment
Altered immune response
Reduced mobility
Increased risk of surgery complications
Reduced quality of life
Increased sanitary costs

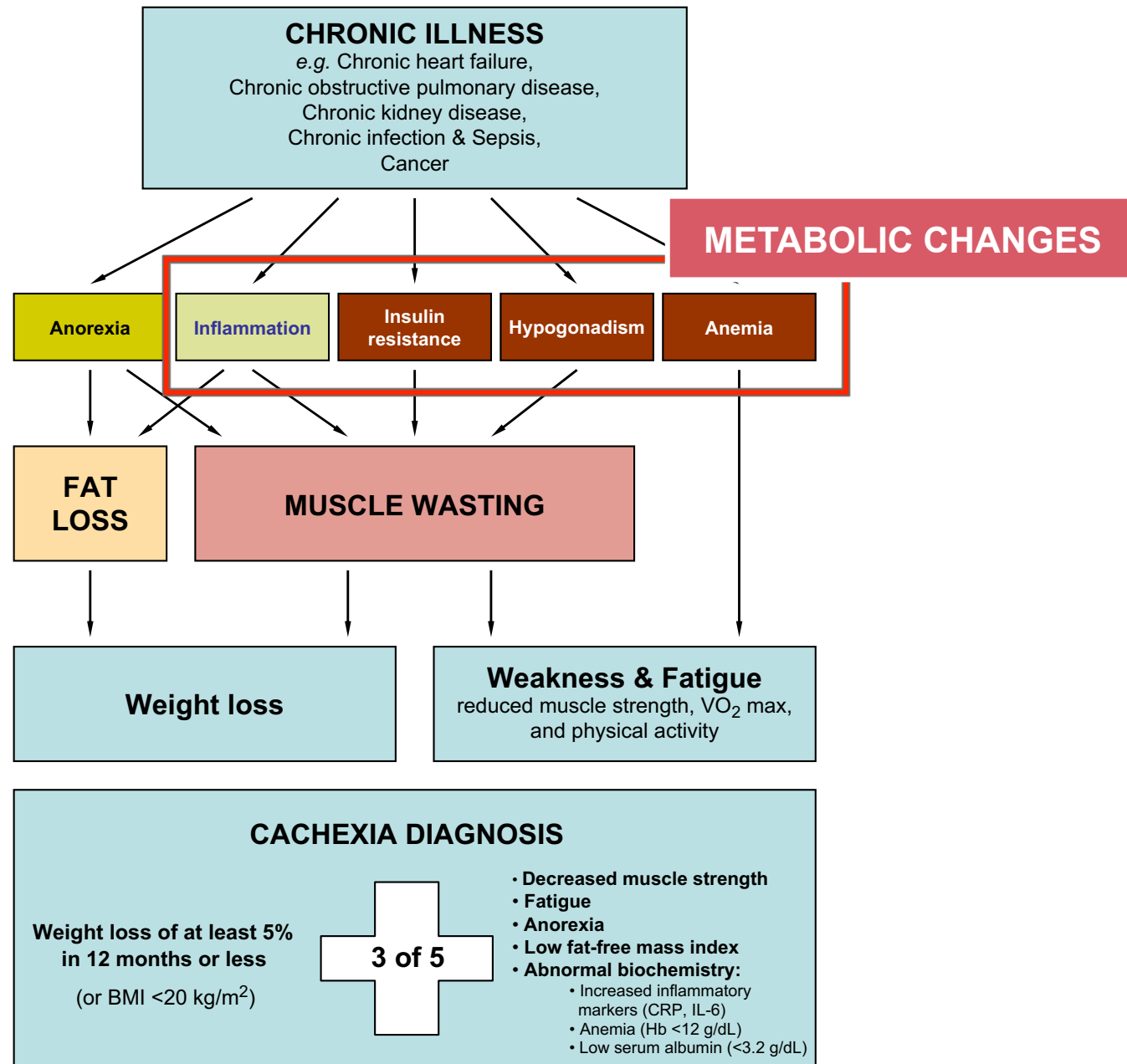
CONSENSUS DEFINITION OF CACHEXIA

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** or **growth failure in children**.

Anorexia, inflammation, insulin resistance and increased muscle protein breakdown are frequently associated with cachexia.

Evans et al. Cachexia a new definition. *Clinical Nutrition* 2008, 27:793



Molecular mechanisms

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 tissue wasting
- Multi-organ syndrome

Nature Reviews Cancer | AOP, published online 9 October 2014; doi:10.1038/nrc3829

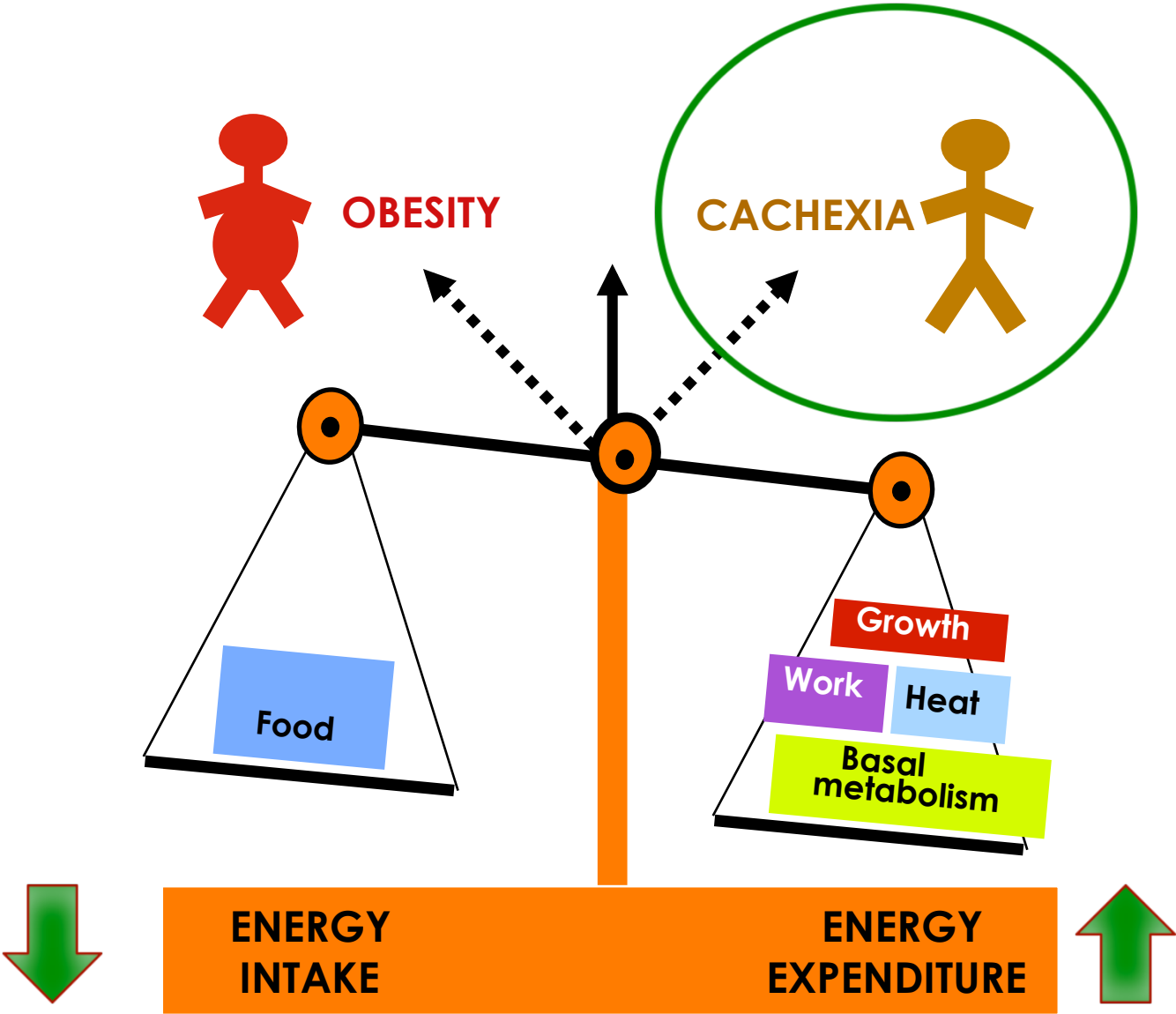
OPINION

Cancer cachexia: understanding the molecular basis

Josep M. Argilés, Silvia Busquets, Britta Stemmler and Francisco J. López-Soriano

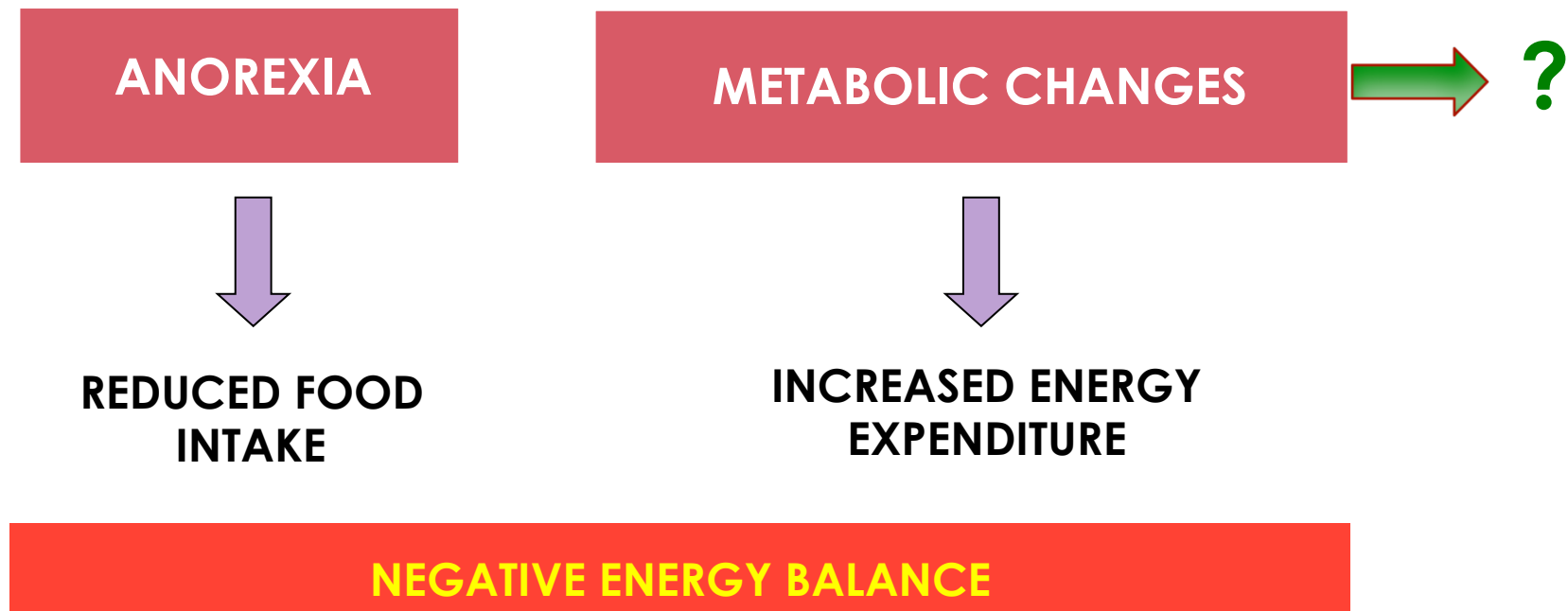
Abstract | Cancer cachexia is a devastating, multifactorial and often irreversible syndrome that affects around 50–80% of cancer patients, depending on the tumour type, and that leads to substantial weight loss, primarily from loss of skeletal muscle and body fat. Since cachexia may account for up to 20% of cancer deaths, understanding the underlying molecular mechanisms is essential. The occurrence of cachexia in cancer patients is dependent on the patient response to tumour progression, including the activation of the inflammatory response and energetic inefficiency involving the mitochondria. Interestingly, crosstalk between different cell types ultimately seems to result in muscle wasting. Some of the recent progress in understanding the molecular mechanisms of cachexia may lead to new therapeutic approaches.

Energy-wasting syndrome



Energy-wasting syndrome

Cancer cachexia is basically a **problem of energy balance**



Energy-wasting syndrome

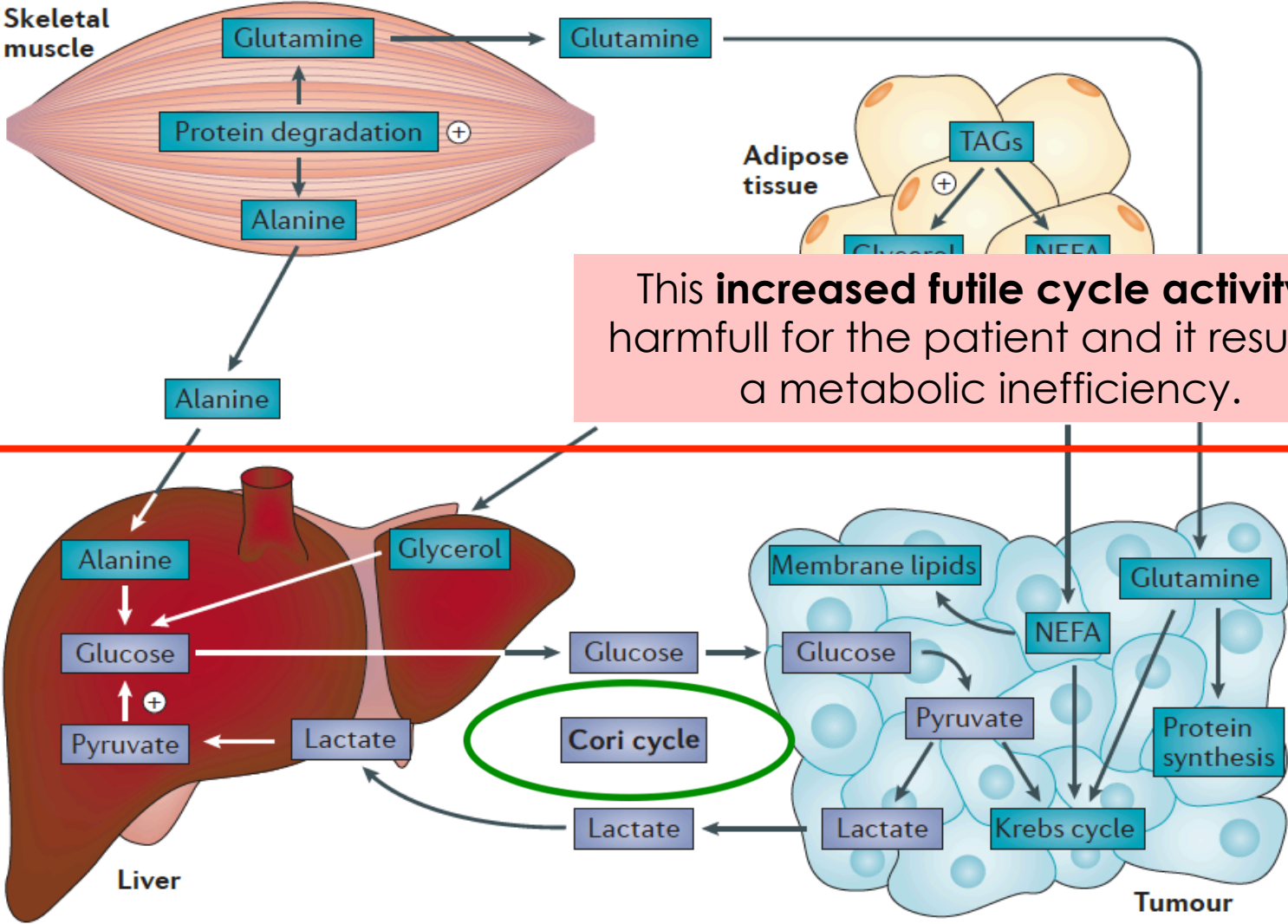


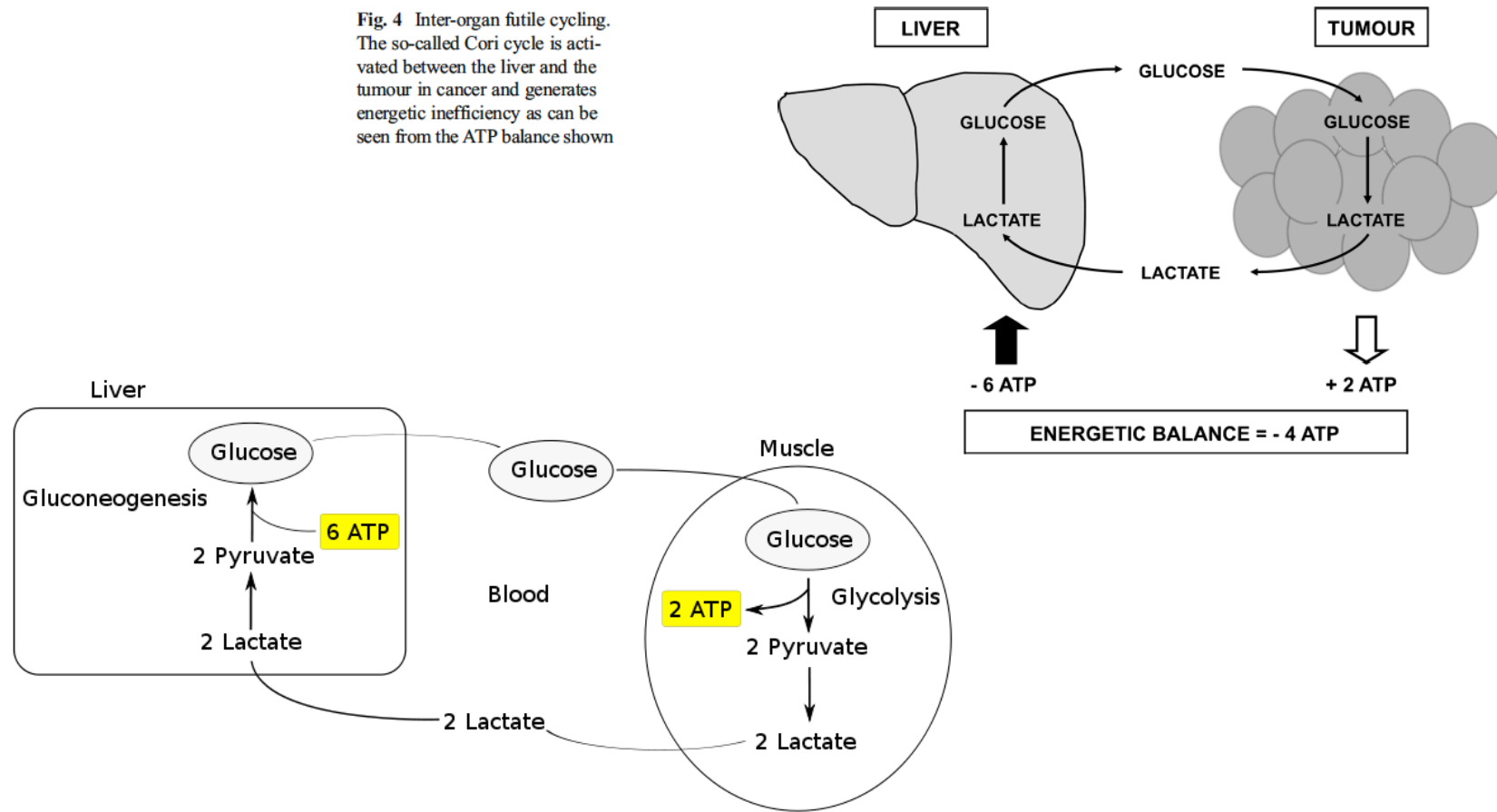
Figure 1 | Main metabolic adaptations associated with tumour burden.



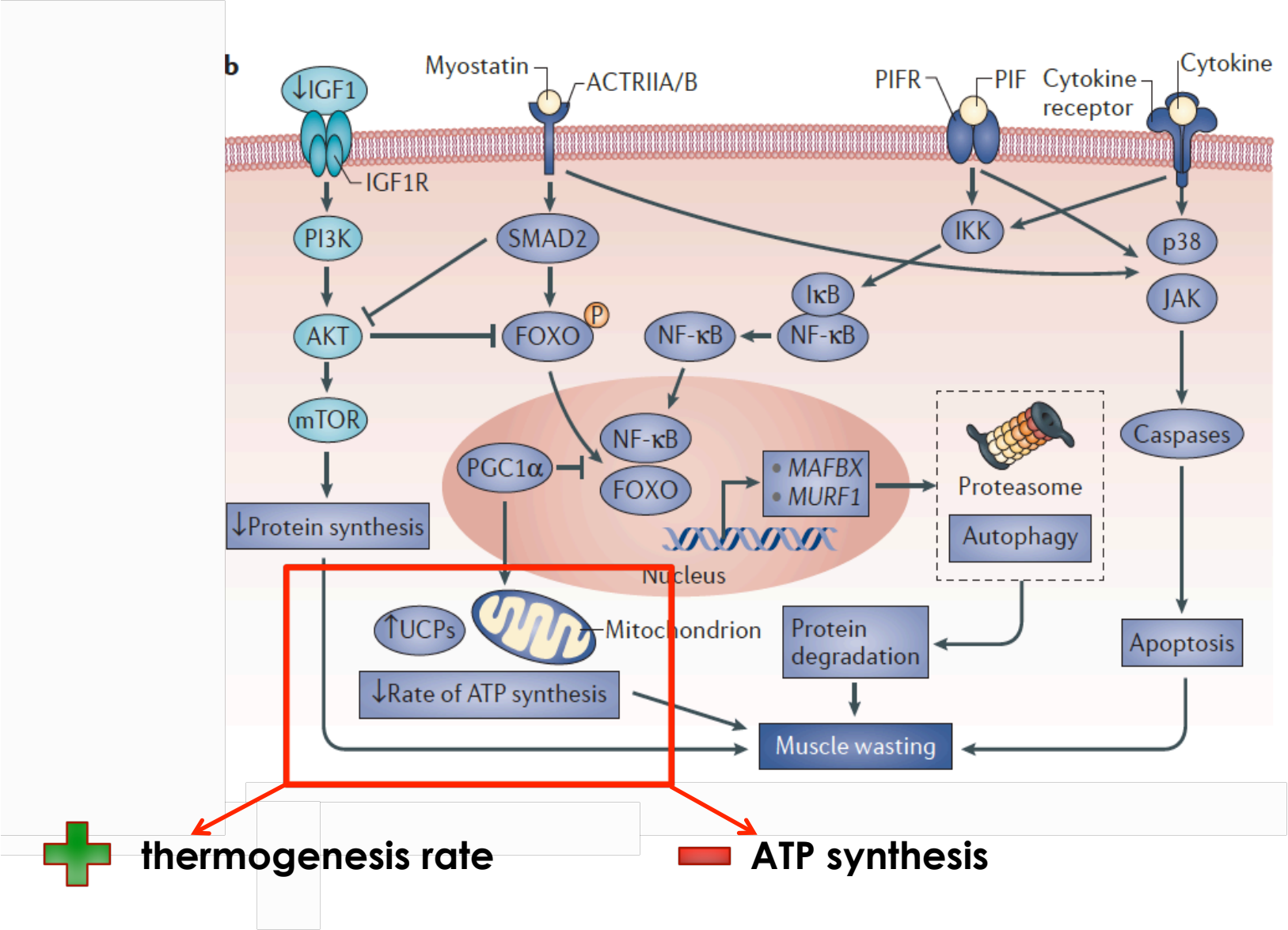
Cori cycle



Fig. 4 Inter-organ futile cycling. The so-called Cori cycle is activated between the liver and the tumour in cancer and generates energetic inefficiency as can be seen from the ATP balance shown



Energy-wasting syndrome



MITOCHONDRIA

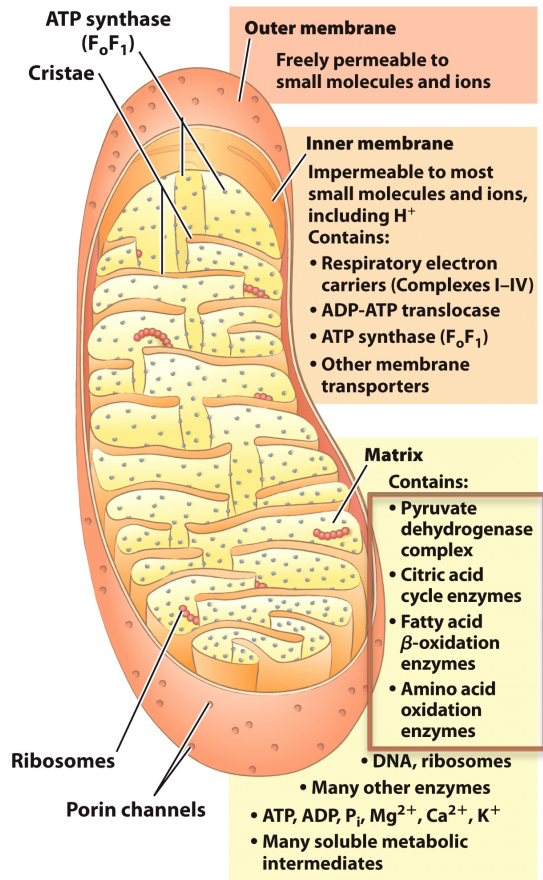


Figure 19-2a
Lehninger Principles of Biochemistry, Sixth Edition
© 2013 W. H. Freeman and Company

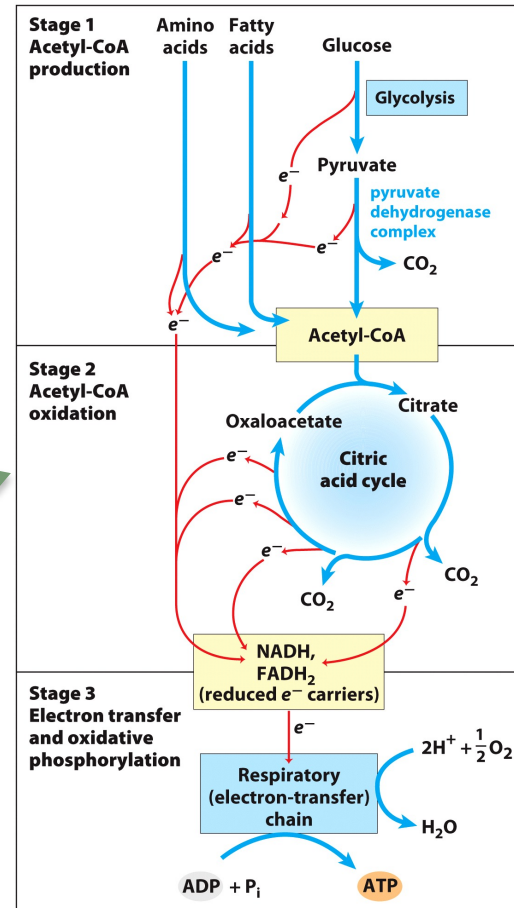


Figure 16-1
Lehninger Principles of Biochemistry, Sixth Edition
© 2013 W. H. Freeman and Company

MITOCHONDRIA: Oxidative phosphorylation

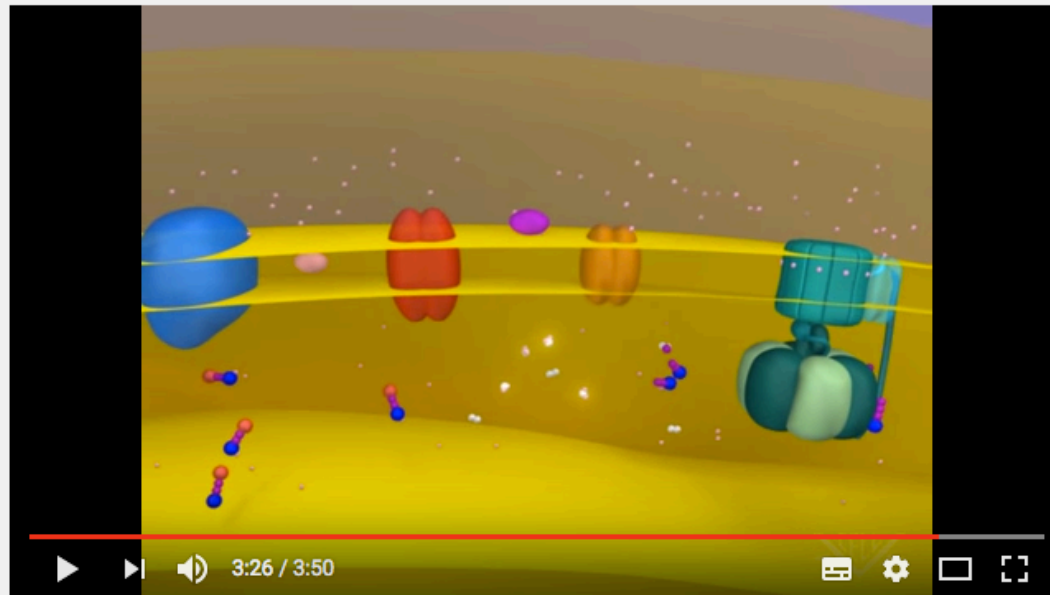


<https://www.youtube.com/watch?v=xbJonbzt5Kw>

T=0:41



Q Cerca



Cellular Respiration (Electron Transport Chain)



ndsuvirtualcell

Subscriu-m'hi 42.946

1.834.840 visualitzacions

Thermogenesis: mitochondrial Uncoupling

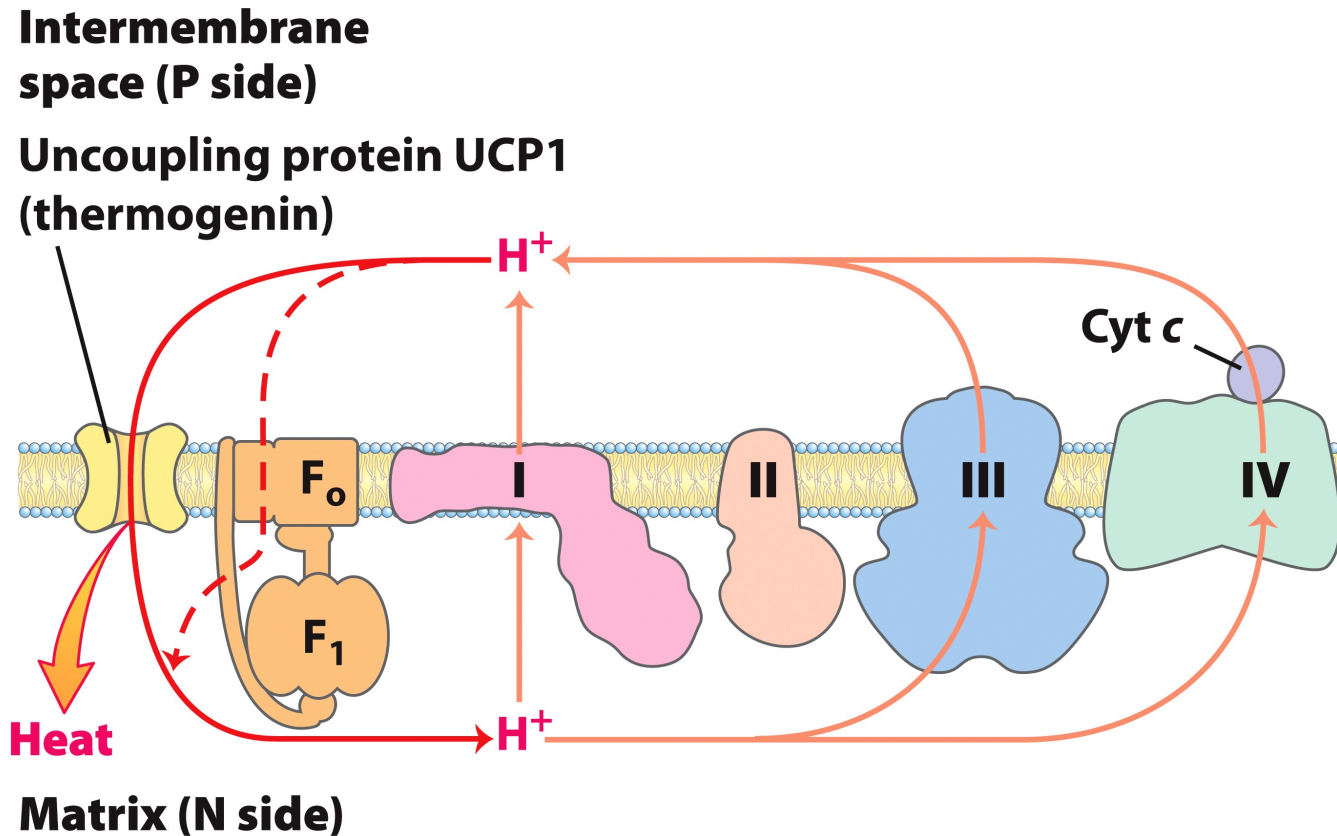
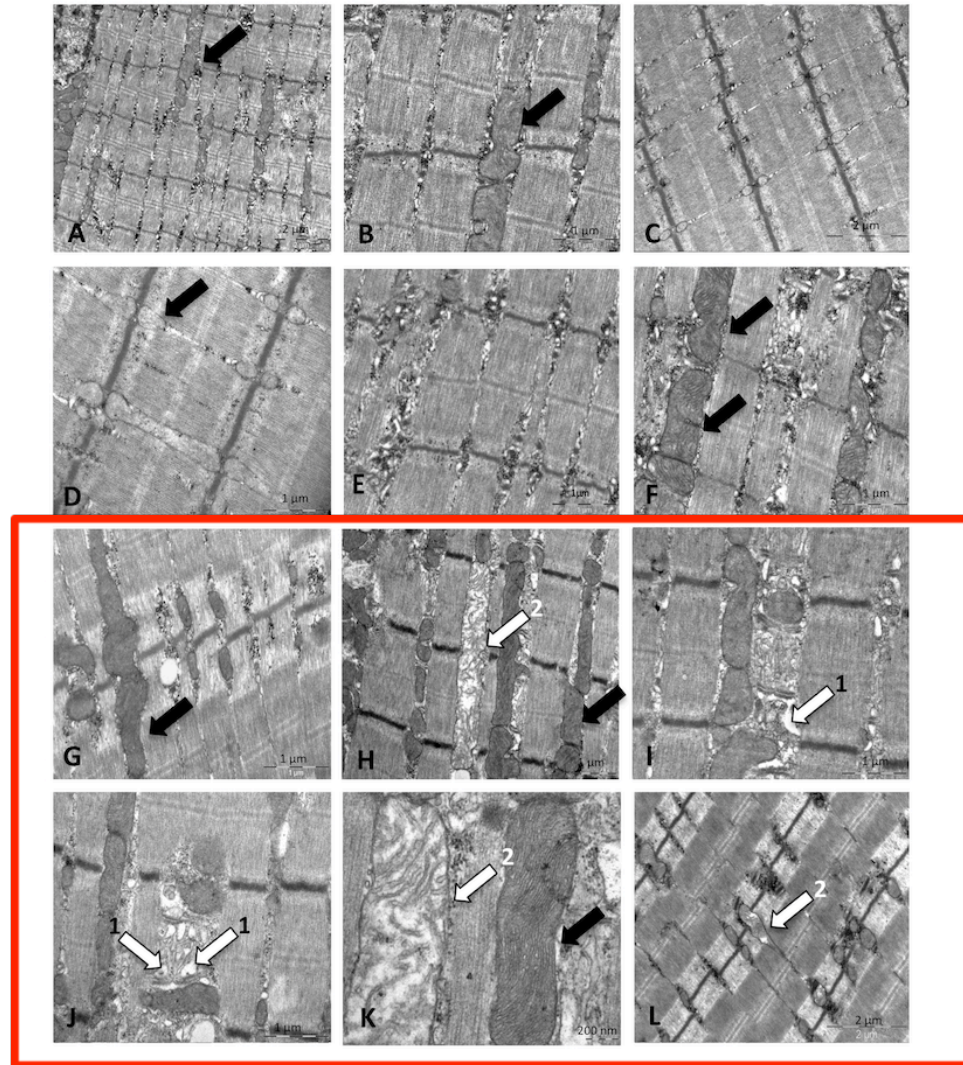


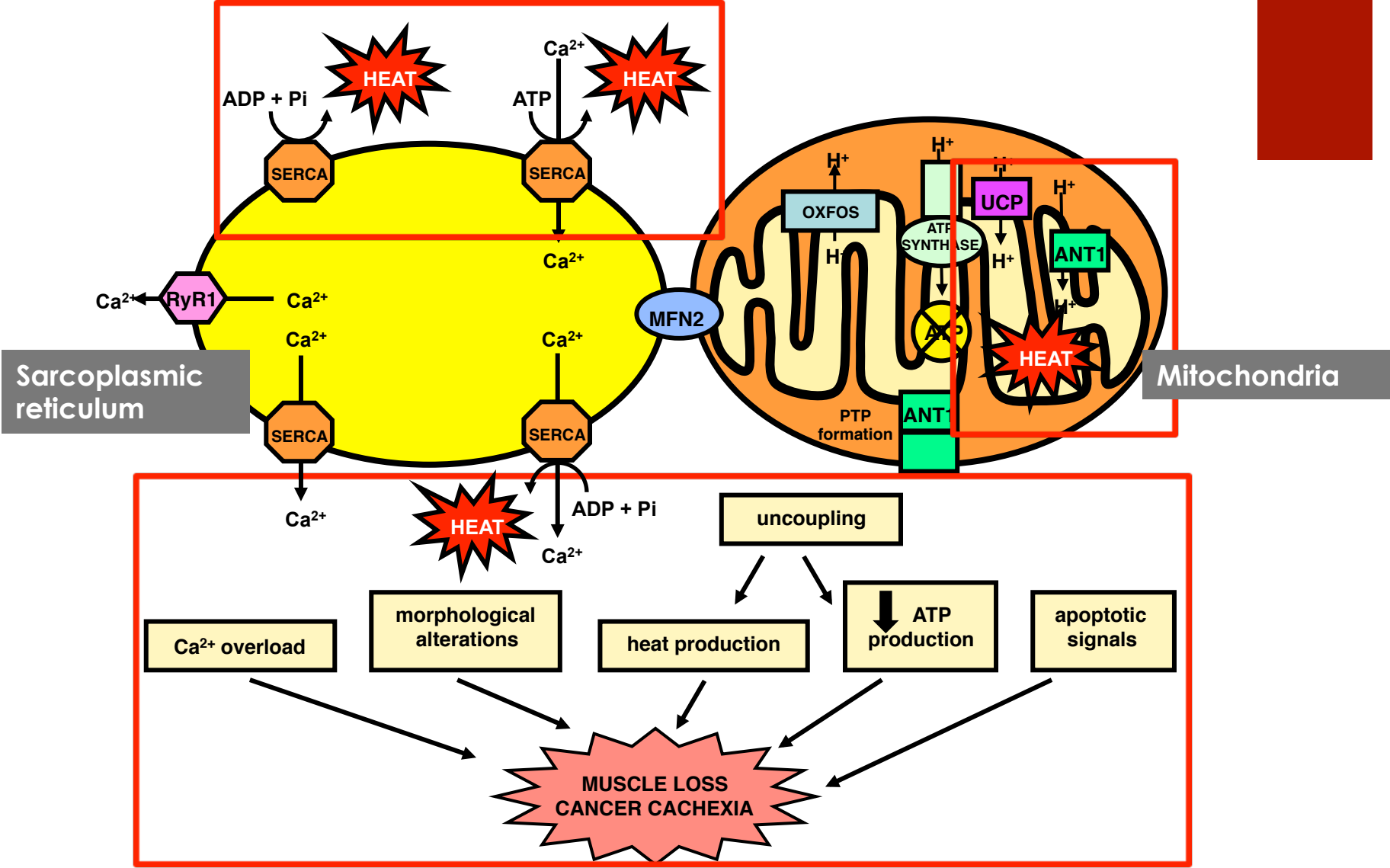
Figure 19-36
Lehninger Principles of Biochemistry, Sixth Edition
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Energy-wasting syndrome

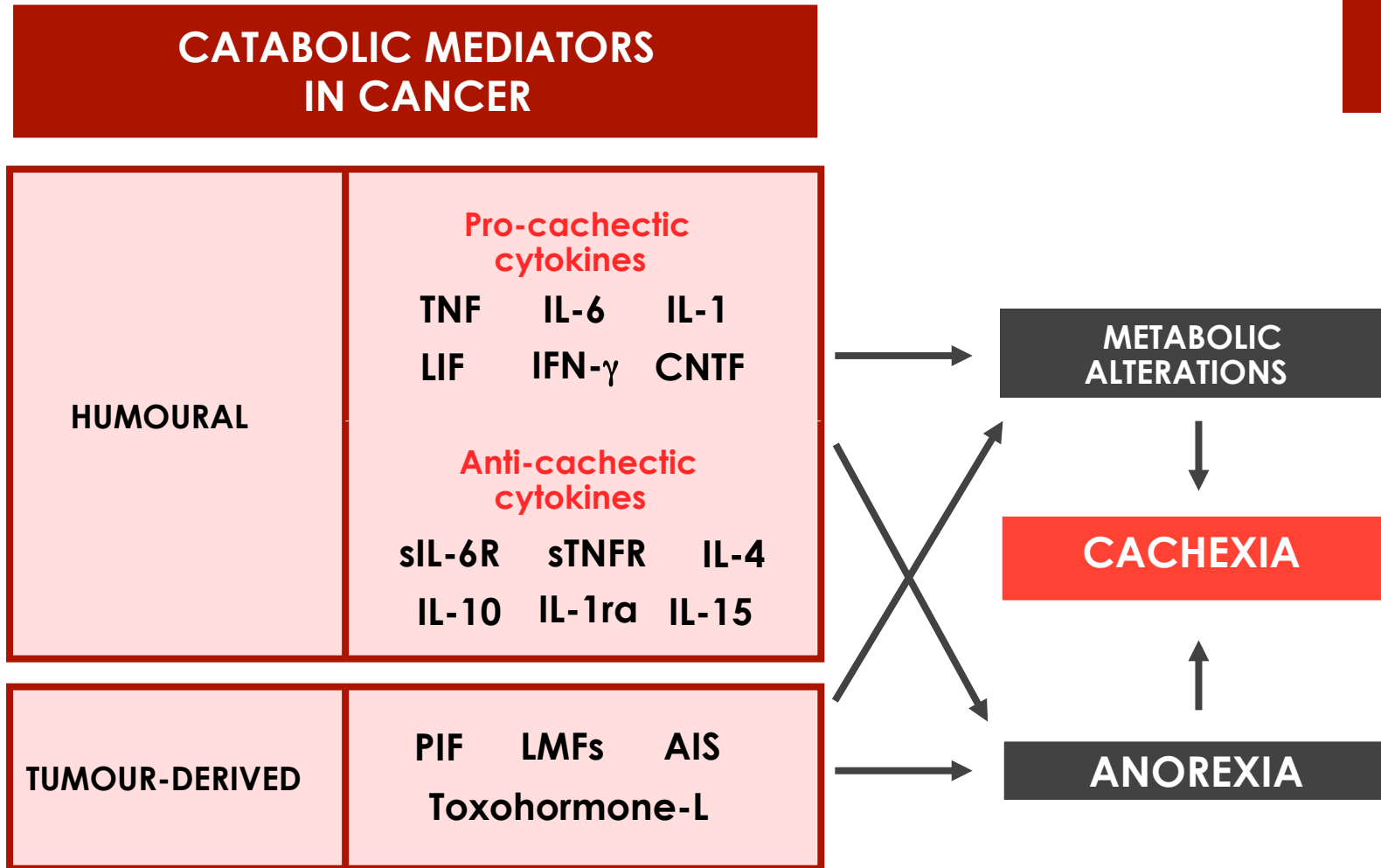
- Altered changes in mitochondrial morphology
- Decreased oxidative capacity
- Disrupted protein synthesis
- Changes in membrane fluidity
- Oxidatively modified mitochondrial proteins



Energy-wasting syndrome



Tumour-driven inflammation



ANOREXIA

METABOLIC ALTERATIONS

CACHEXIA



WASTING

MUSCLE MASS LOSS

**INCREASED
PROTEOLYSIS**

**DECREASED PROTEIN
SYNTHESIS**

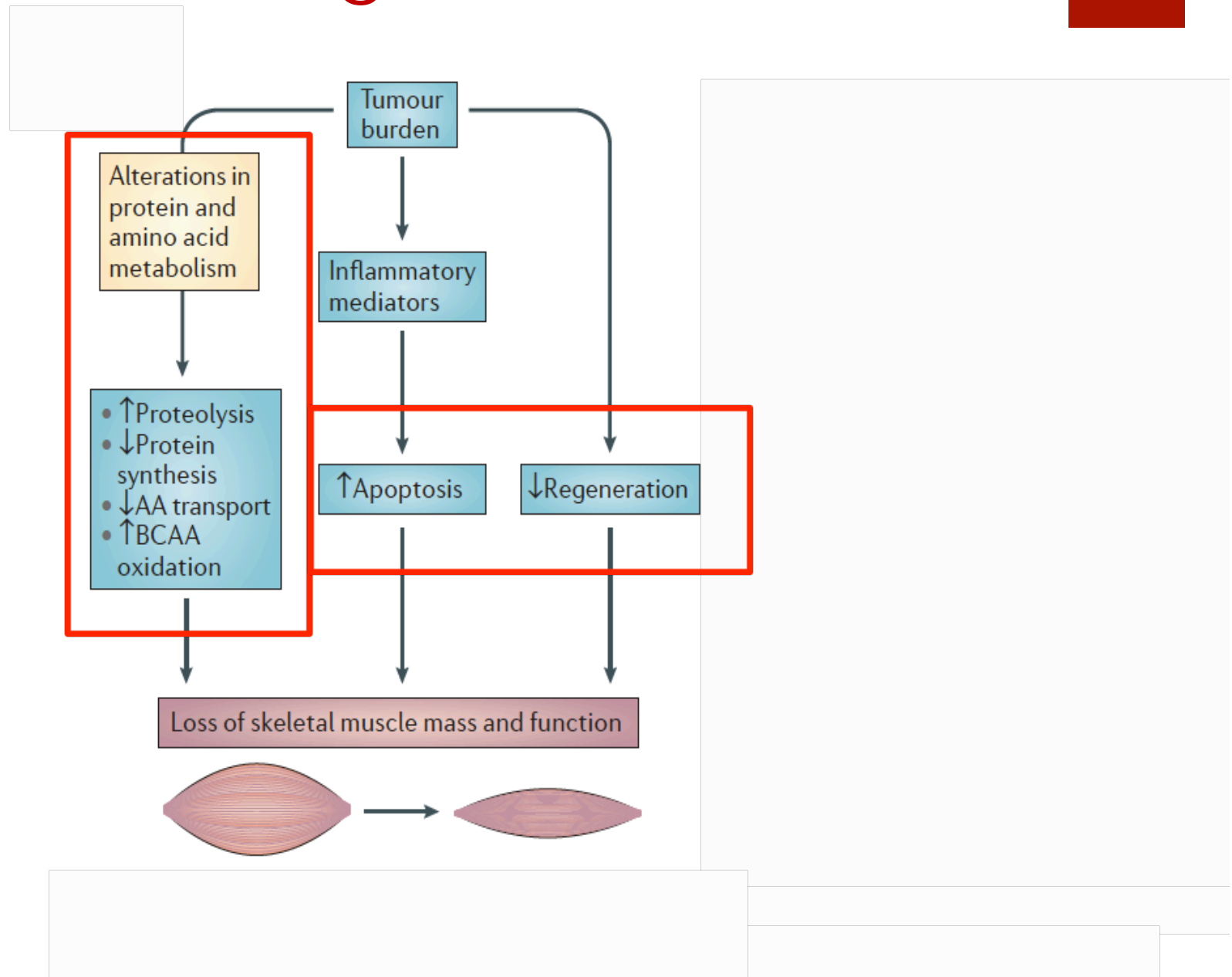
**INCREASED
APOPTOSIS**

**DECREASED
REGENERATION**

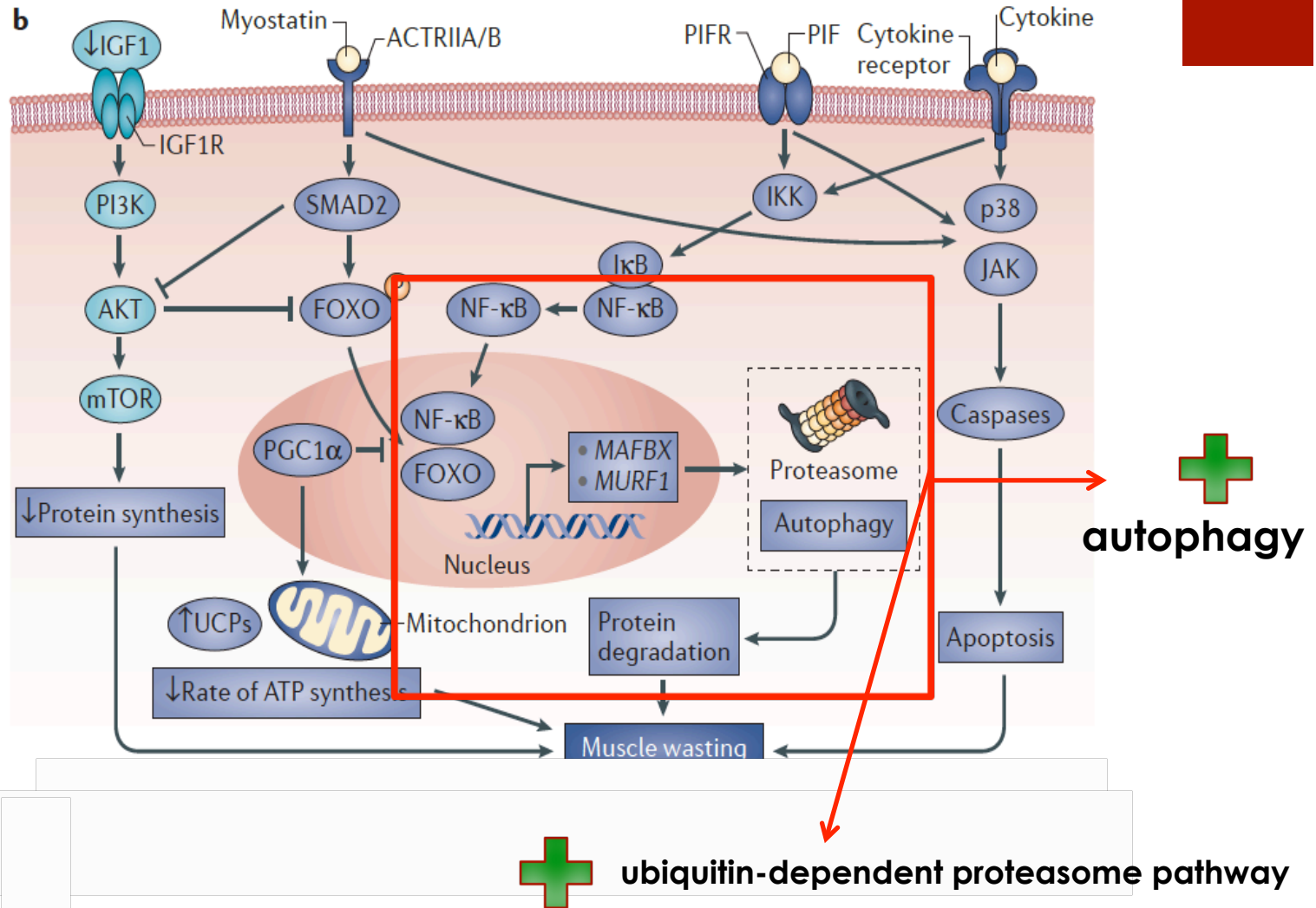
**DECREASED
PHYSICAL
PERFORMANCE**

**MORPHOLOGIC
CHANGES
(MITOCHONDRIA)**

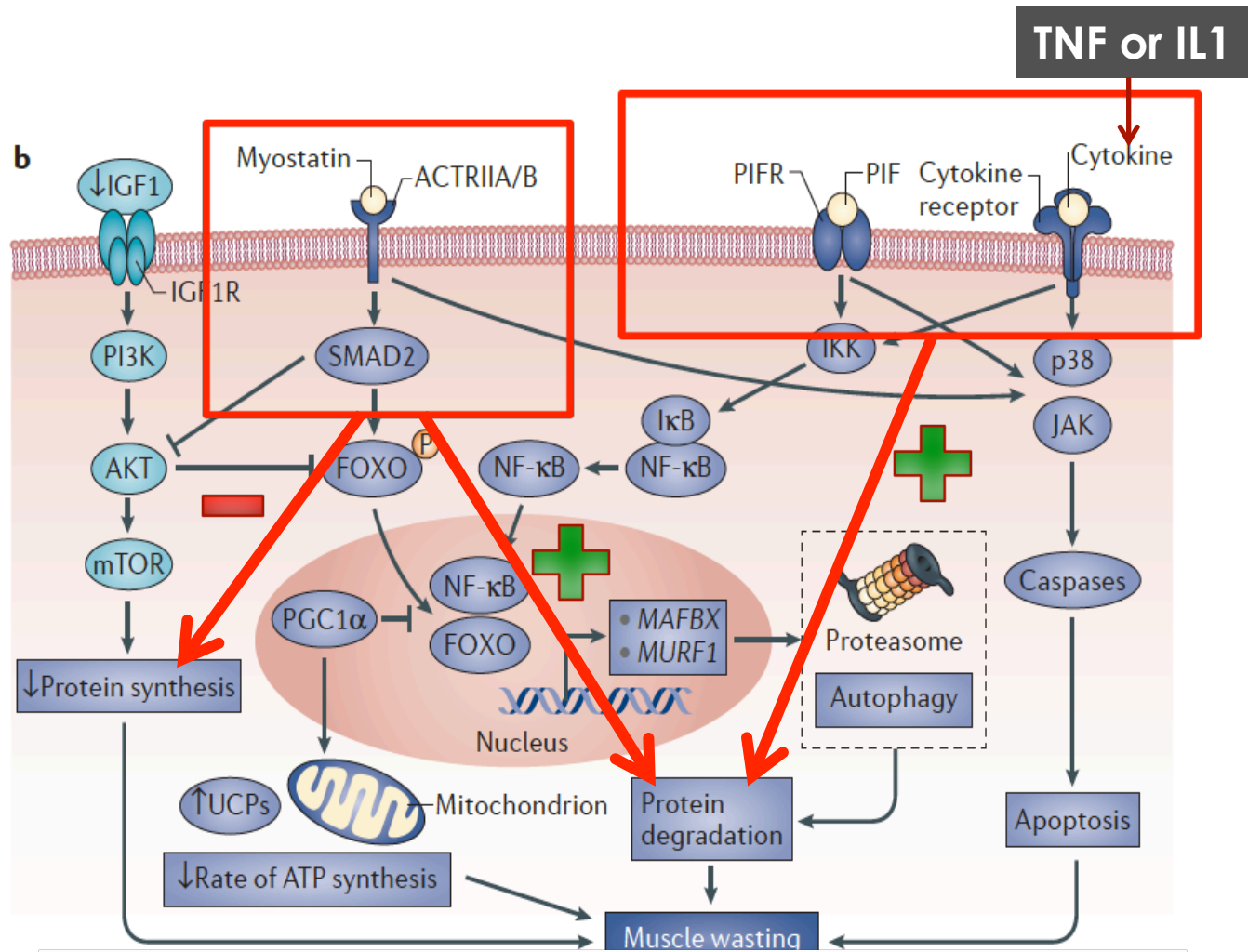
Muscle wasting



Muscle wasting

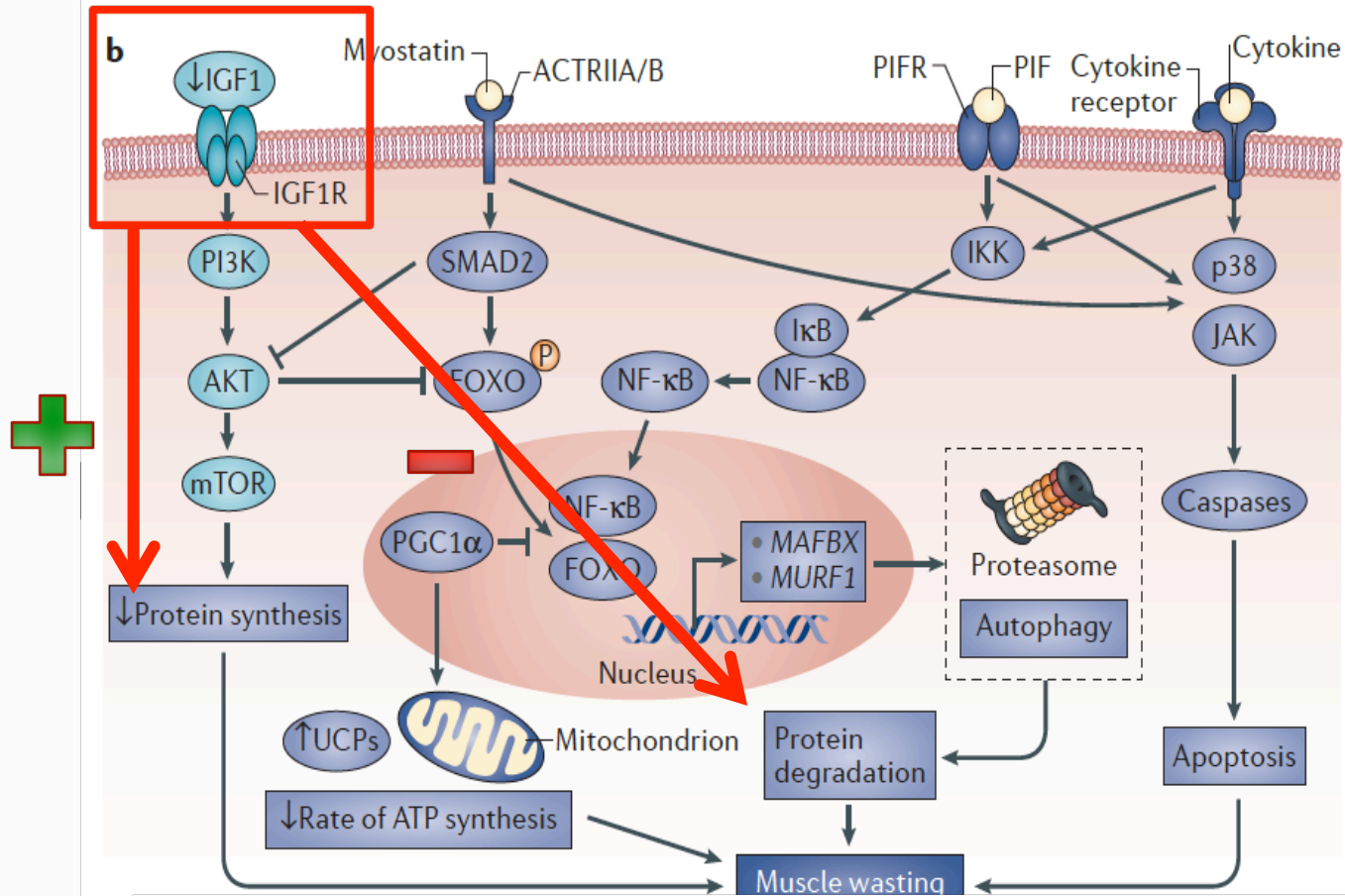


Muscle wasting

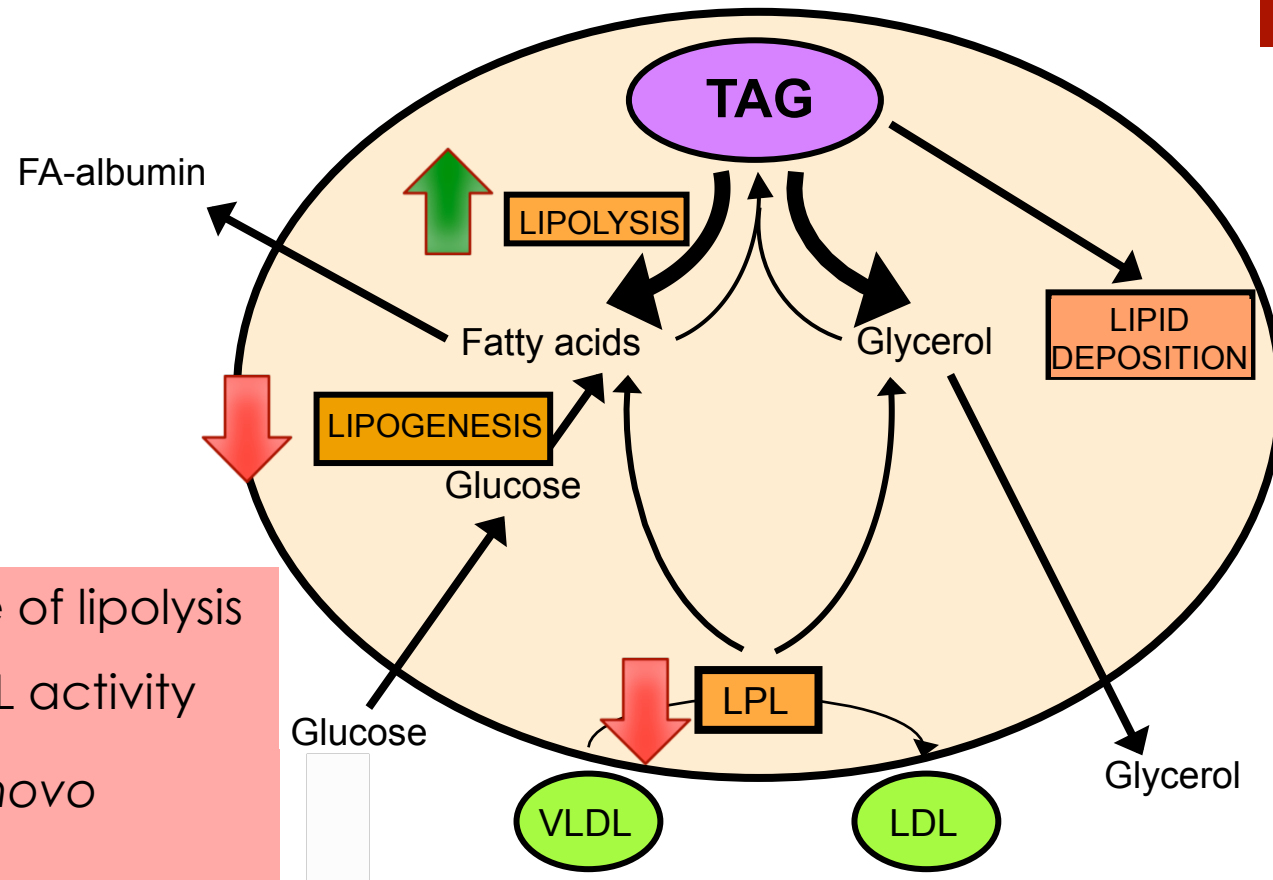


Muscle wasting

insulin-like growth factor 1



Adipose tissue wasting



1. Increased rate of lipolysis
2. Decreased LPL activity
3. Reduced *de novo* lipogenesis

Adipose tissue wasting

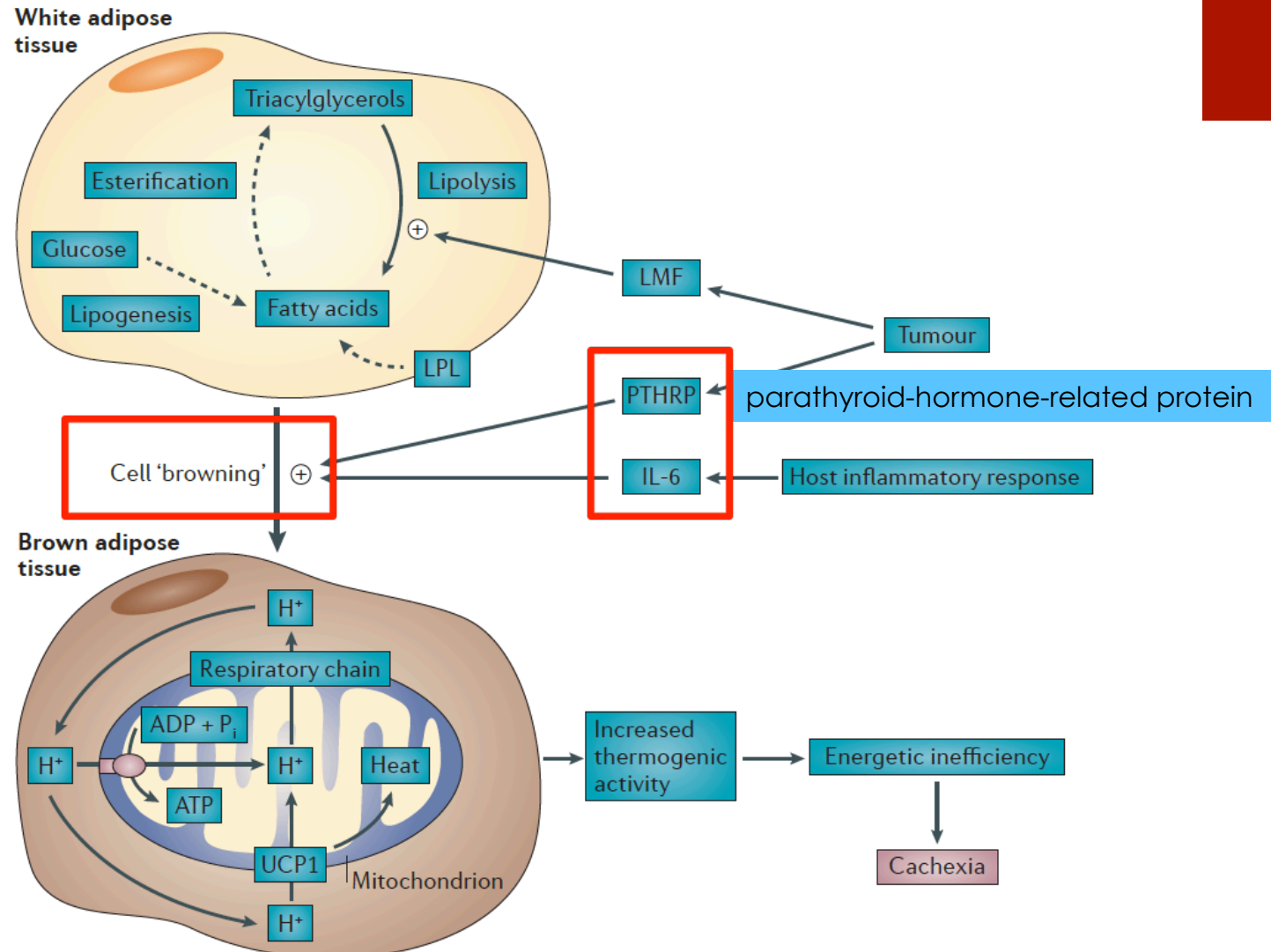
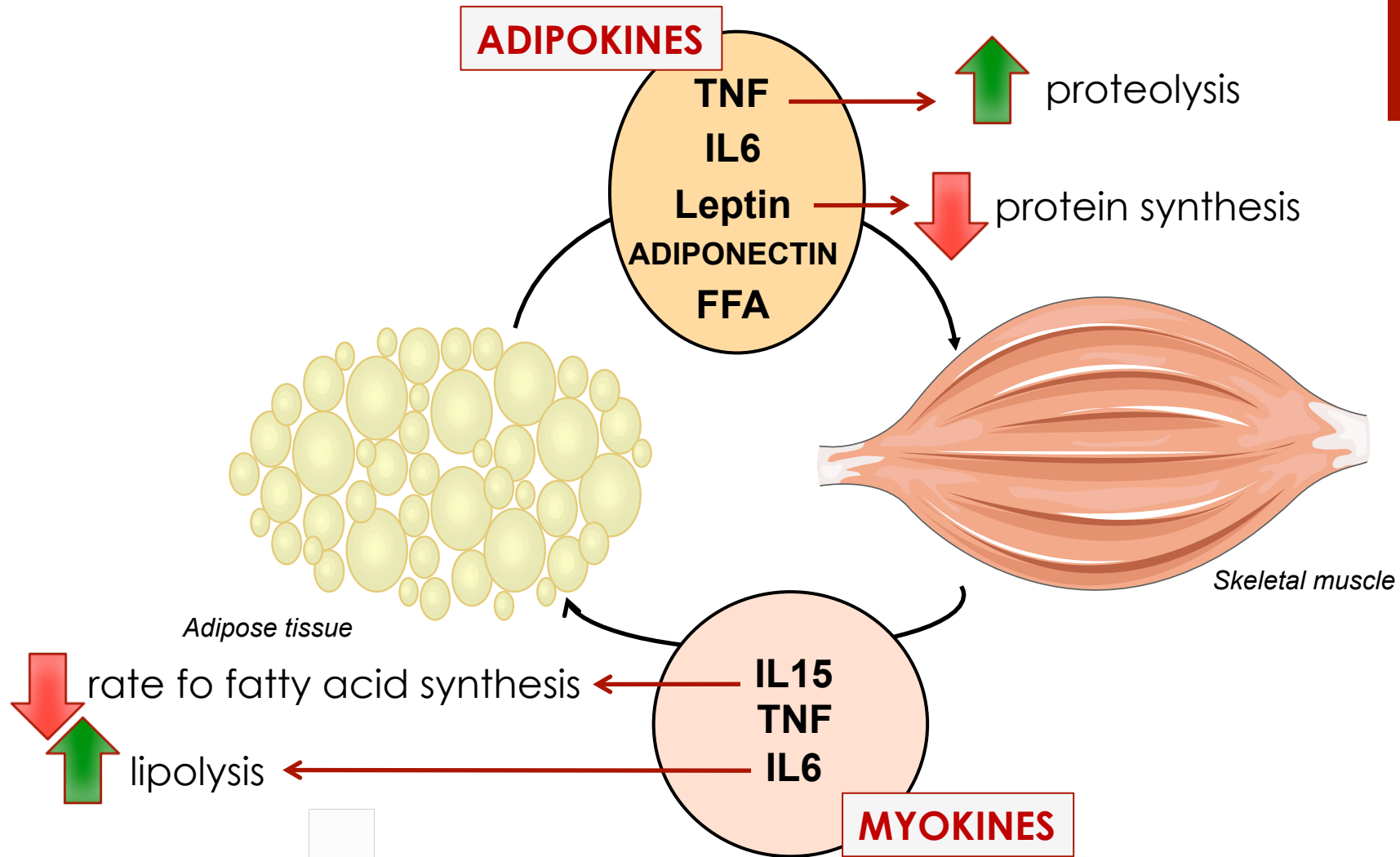
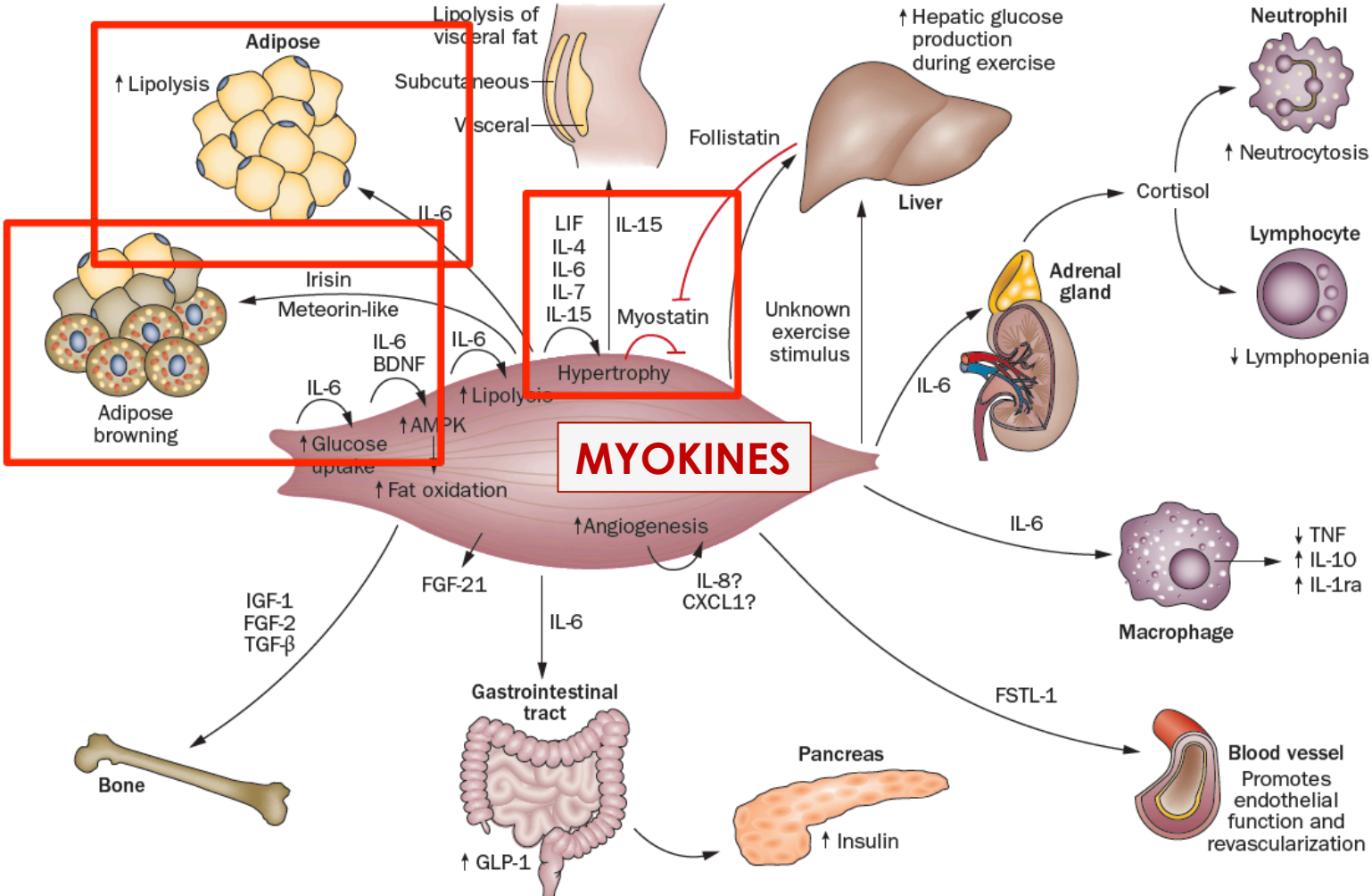


Figure 3 | Browning of white adipose tissue in cachexia.

Crosstalk between adipose tissue and muscle



Crosstalk between muscle and other tissues



Multi-organ syndrome

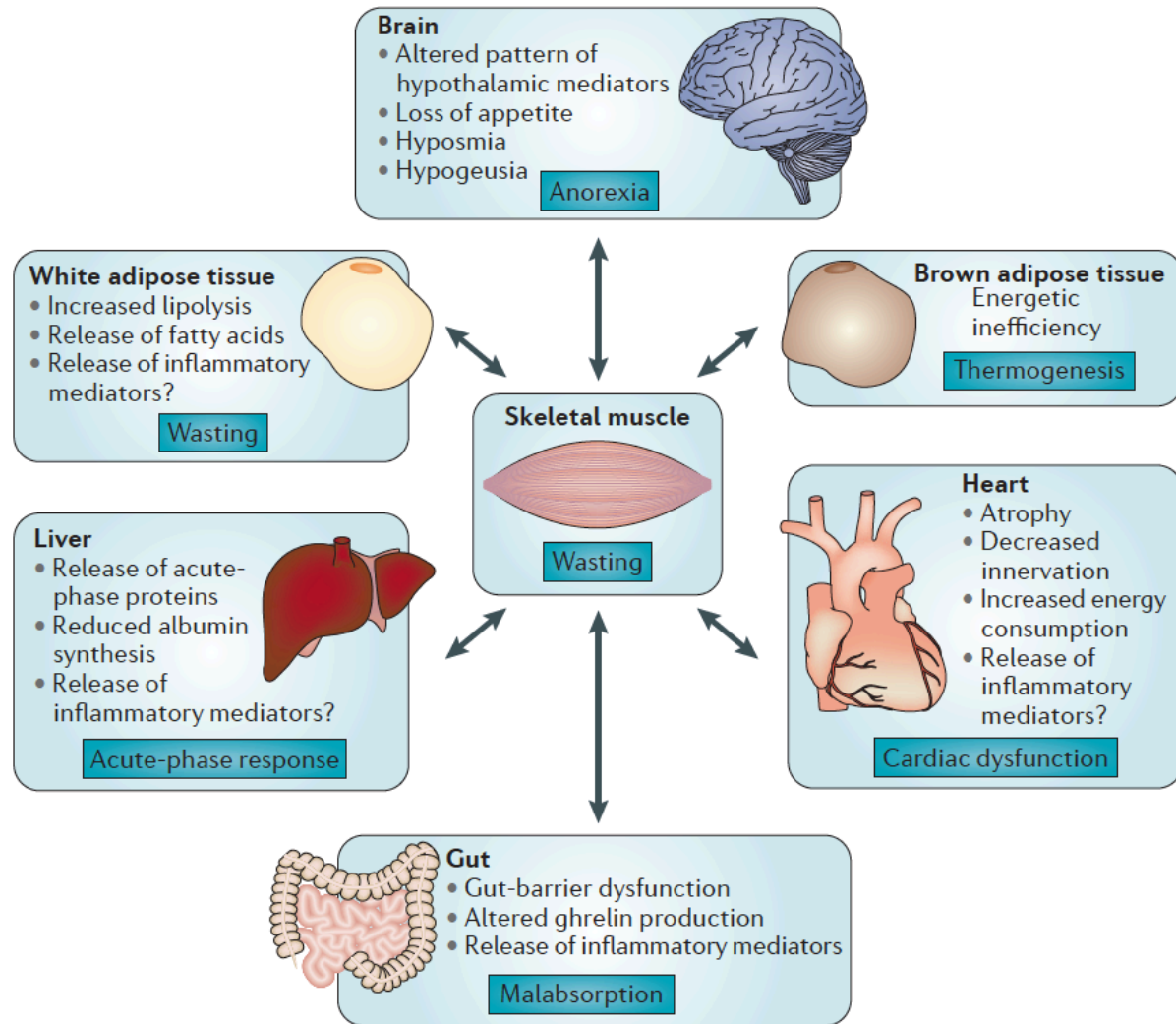


Figure 4 | Cachexia as a multi-organ syndrome.

Conclusions and perspectives

Knowledge of the molecular mechanisms

underlying cancer cachexia may allow

for the design of distinctive therapeutic approaches

that ameliorate or even successfully cure this syndrome.



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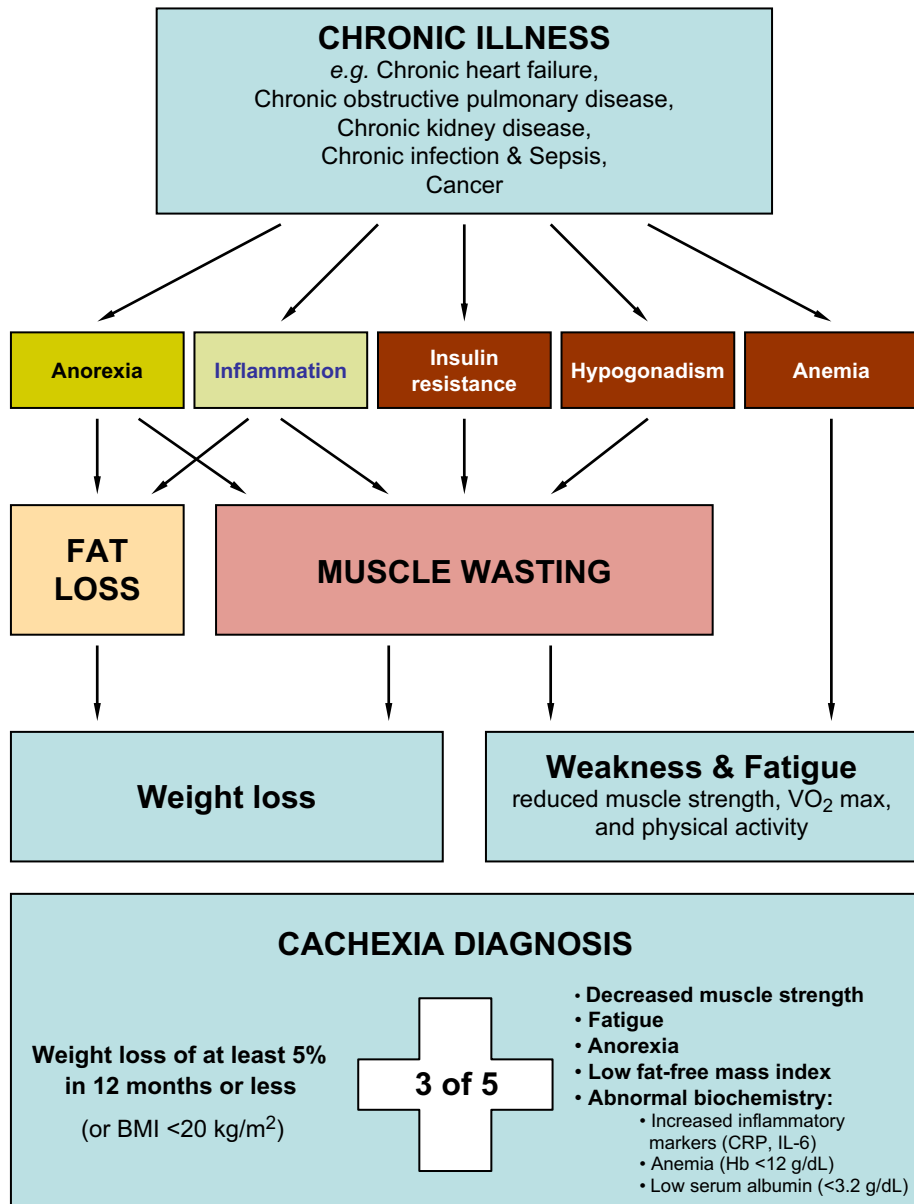
Departament de Bioquímica i Biomedicina Molecular

Universitat de Barcelona

Barcelona, Spain

DIAGNOSIS OF CANCER CACHEXIA

CASCO: A new tool for staging cachexia in cancer patients



Cachexia, is a complex metabolic syndrome associated with underlying illness and characterized by **loss of muscle with or without loss of fat mass.**

Definition and classification of cancer cachexia: an international consensus

Kenneth Fearon*, Florian Strasser*, Stefan D Anker, Ingvar Bosaeus, Eduardo Bruera, Robin L Fainsinger, Aminah Jatoi, Charles Loprinzi, Neil MacDonald, Giovanni Mantovani, Mellar Davis, Maurizio Muscaritoli, Faith Ottery, Lukas Radbruch, Paula Ravasco, Declan Walsh, Andrew Wilcock, Stein Kaasa, Vickie E Baracos

Lancet Oncol 2011; 12: 489-95

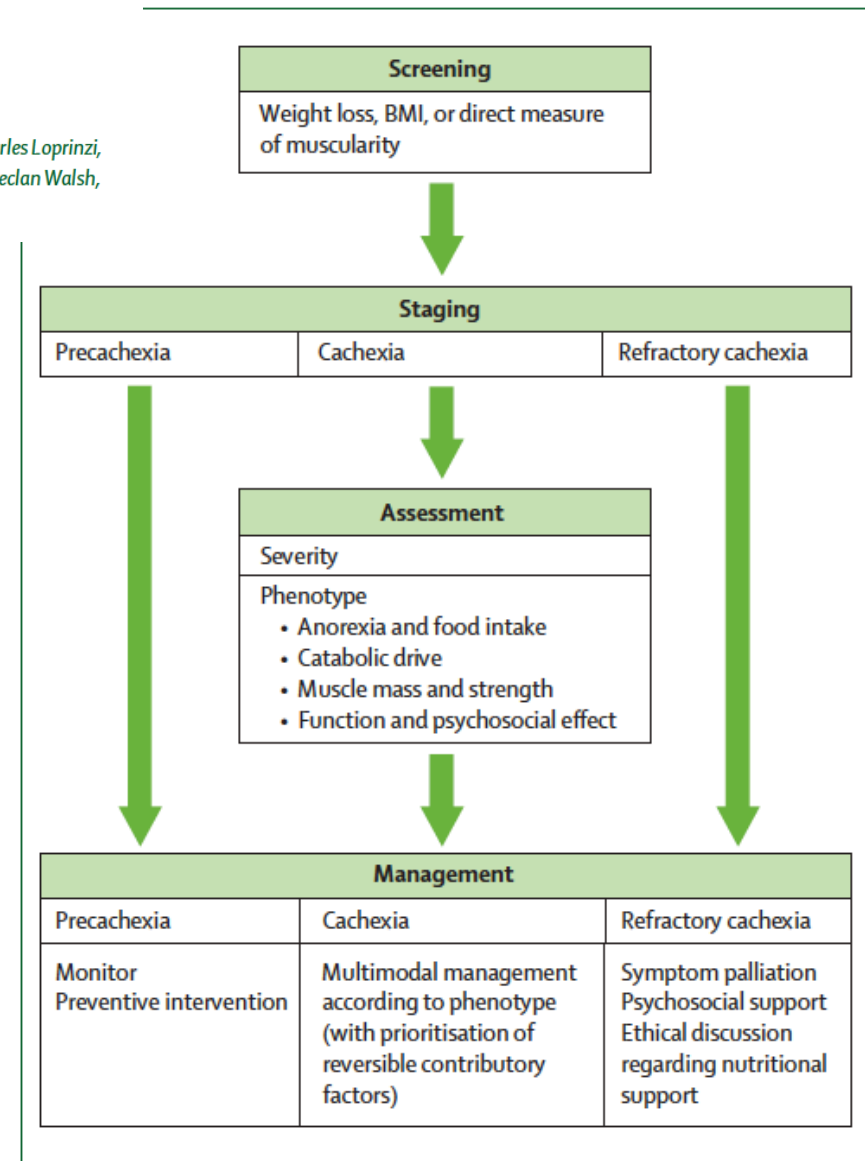


Figure 3: Management algorithm for cancer cachexia

Patients should be screened for cachexia, then undergo detailed assessment. All patients require optimum oncological and general medical management. Once patients with cachexia have been phenotyped, a detailed multimodal management plan (including nutrition, exercise, anti-inflammatory strategies, and other adjuncts) can be established. BMI=body-mass index.

Staging cachexia



- Cachexia has been defined but the definition does not consider the problem of staging it. **Classification of patients is important when considering therapy.**
- The objective of the **CAchexia SCORE (CASCO)** is to fulfill the existing gap in the classification of cachectic cancer patients.

CAchexia SCORe (CASCO)

J Cachexia Sarcopenia Muscle
DOI 10.1007/s13539-011-0027-5

ORIGINAL ARTICLE

The cachexia score (CASCO): a new tool for staging cachectic cancer patients

Josep M. Argilés · Francisco J. López-Soriano ·
Míriam Toledo · Angelica Betancourt · Roberto Serpe ·
Silvia Busquets

CASCO takes into consideration five components:

1. **Body weight and lean body mass loss (BWC)**
2. **Inflammatory, immunological, and metabolic disturbances (IMD)**
3. **Physical performance (PHP)**
4. **Anorexia (ANO)**
5. **Quality of life (QoL)**

Casco web page

<https://www.ub.edu/cancerresearchgroup/>

Biochemistry and Molecular Biology of Cancer Research Group

Cachexia is defined as a state of malnutrition and physical exhaustion and includes weight loss (up to 80% of lean and fat mass) due to a chronic disease. Cachexia occurs in many diseases such as cancer, acquired immunodeficiency syndrome, sepsis, diabetes, states immobilization, severe burns, chronic obstructive pulmonary disease, cardiovascular disease or old age, among others. Several studies associate the presence of wasting in patients with a decreased ability to survive. This means that there is a growing interest in developing drugs capable of dealing with this syndrome, drugs that would allow patients to cope with this disease and possess a higher quality of life in the meantime.

Nowadays there is no effective pharmaceutical treatment on the market that can resolve cachexia. Today, patients suffering with cachexia receive treatments (that is, if they are treated; it is not a common hospital practice) based on different types of drugs, which are mainly derived from progesterone (in particular, megestrol acetate) and steroids such as testosterone, nandrolone or ostarine.

Our research aims are the following:

- To develop a combined therapy to stop muscle wasting associated with cancer cachexia.
- To develop a score to be able to stage the cachectic syndrome taking into consideration both the metabolic and functional changes that take place during cancer cachexia.

Josep M^o Argilés (Catedràtic) jargiles@ub.edu
Francisco J. López-Soriano (Professor Titular) flopez@ub.edu
Silvia Busquets (Professora Agregada Interina) silviabusquets@ub.edu
Enrica Marmonti (Becària predoctoral)
<http://www.gruprecercabbmc.blogspot.com.es/>

[More Information here](#)

CASC-IN

CASC-IN

CASCO Identification


[Forgot password](#)



Facultat de Biologia
Diagonal, 645
08028 Barcelona
Tel. 934 034 609
Fax 934 021 559

PATIENT INFORMATION

CASCO

Welcome Casco 

Patient

BWC

IMD

PHP

ANO

QoL

Change to miniCASCO

New

Save

Export

View result

View patient history

View patient graphic

Exit



Patient information

Identification Number* ?

Date* ?

Country

Birthdate

Gender

Cancer type

Tumour stage

Date of cancer diagnosis

Comorbidities

Underlying Disease

Treatment (Drugs, nutrition, other)

Only for validation

Before applying CASCO, what is your perception of severity of patient's cachexia according to the following scale (normal, absence of cachexia) 0 1 2 3 4 5 6 7 8 9 10 (terminal, evident cachexia)

Index of cachexia

* required parameters

Body weight and lean body mass loss

CASCO Welcome Casco

Patient **BWC** IMD PHP ANO

Change to miniCASCO

New

Save

Export

View result

View patient history

View patient graphic

Exit

BODY WEIGHT LOSS AND COMPOSITION (BWC)

Body Weight Loss	Initial Weight	0
	Final Weight	0
	% Weight loss	

Weight loss < to 5%

Lean Body Mass	Lean Body Mass	<input checked="" type="radio"/> No change in LBM <input type="radio"/> Loss of LBM > 10%
	Methodology	<div style="border: 1px solid gray; padding: 2px;"><ul style="list-style-type: none">Bioelectrical impedance analysis (BIA)Dual-energy X-ray absorptiometry (DEXA)Regional computed tomography (CT)Magnetic resonance imaging (MRI)</div>

Values


<5%

≥5%, mild

≥10%, moderate

≥15%, severe

≥20%, terminal

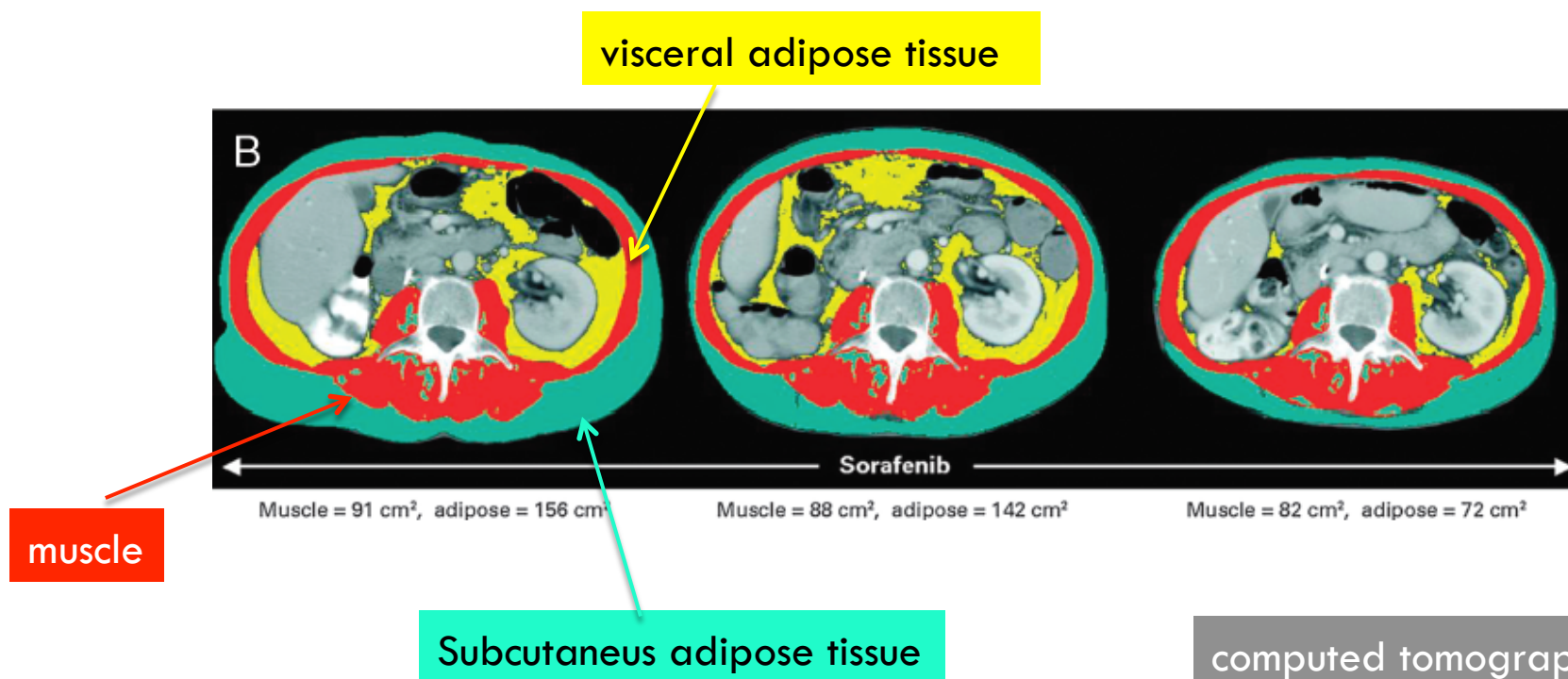


Body weight and lean body mass loss (BWC)


40%

Body weight and lean body mass loss

- Bioelectrical impedance analysis (BIA)
- Dual X-ray absorptiometry (DEXA)
- Cross-sectional imaging: **computed tomography (CT)** or magnetic resonance imaging (MRI).



Inflammatory, immunological and metabolic disturbances

CASCO Welcome Casco 

Patient BWC **IMD** PHP ANO QoI

Change to miniCASCO

New
Save
Export
View result


View patient history
View patient graphic

Exit

INFLAMMATION / METABOLIC DISTURBANCES / IMMUNOSUPPRESSION (IMD)

<p style="text-align: center;">Plasma CRP</p> <p>Inflammation</p> <ul style="list-style-type: none"> <input type="radio"/> 5 mg/l <= CRP <= 10 mg/l <input type="radio"/> 10 mg/l < CRP <=20 mg/l <input type="radio"/> CRP > 20 mg/l <input checked="" type="radio"/> Not Tested 	<p style="text-align: center;">Plasma IL6</p> <ul style="list-style-type: none"> <input type="radio"/> 4 pg/ml <= IL6 <=10 pg/ml <input type="radio"/> 10 pg/ml <= IL6 <=30 pg/ml <input type="radio"/> IL6 > 30 pg/ml <input checked="" type="radio"/> Not Tested
<p>Metabolic disturbances*</p> <ul style="list-style-type: none"> <input type="checkbox"/> Plasma Albumin < 3.2 g/dL <input type="checkbox"/> Plasma Pre-Albumin < 1.6 mg/dL <input type="checkbox"/> Plasma Lactate > 2.2 mM <input type="checkbox"/> Plasma Triglycerides > 200 mg/dL 	<ul style="list-style-type: none"> <input type="checkbox"/> Anemia: Hb < 12 g/dL <input type="checkbox"/> Plasma Urea > 50 mg/dL <input type="checkbox"/> ROS plasma levels > 300 FORT U <input type="checkbox"/> Glucose Tolerance test / HOMA index altered
<p>Immunosuppression* <input type="checkbox"/> Absolute lymphocyte number < 1200/uL</p>	


* not tested parameters should be left blank



Inflammatory, immunological, and metabolic disturbances (IMD)

20%

Physical performance

CASCO Welcome Casco 

Patient BWC IMD **PHP** ANO QoI

Change to miniCASCO

New
Save
Export
View result

View patient history
View patient graphic


Exit

PHYSICAL PERFORMANCE (PHP)

During the past week...

	Not at all	A little	Quite a bit	Very Much
1. Have you noticed any particular decrease in the physical activities (i.e. at work, at home, at leisure etc) that you normally carry out during the day?	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
2. Have you had any problem doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
3. Have you noticed any loss of handgrip force?	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
4. Did you have to put more effort on climbing stairs?	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
5. Have you felt tired after walking approximately half a kilometre?	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Question 2 copyright of 1995 EORTC Quality of Life Group. Extracted from QLQ-C30 and used with permission



LIBERTAS PERFUDET.
OMNIA LVCE

Physical performance (PHP)

15%

Anorexia

CASCO Welcome Casco

Patient BWC IMD PHP **ANO** QoI

Change to minicASCO

New

Save

Export

View result

View patient history

View patient graphic

Exit

ANOREXIA (ANO)

1. My appetite is:

- Very Poor
- Poor
- Average
- Good
- Very Good

2. When I eat:

- I feel full after eating only a few mouthfuls
- I feel full after eating about a third of a meal.
- I feel full after eating over half a meal.
- I feel full after eating most of the meal
- I hardly ever feel full

3. Food tastes:


- Very bad
- Bad
- Average
- Good
- Very good

4. Normally I eat:

- Less than one meal a day
- One meal a day
- Two meals a day
- Three meals a day
- More than three meals a day

Questions from 1-4 extracted from SNAQ of St. Louis GRECC Program of St. Louis VA Medical Center. Used with permission.

Simplified Nutrition Assessment Questionnaire (SNAQ)



Anorexia (ANO)

15%

Quality of life

The screenshot displays the CASCO web application interface. At the top, there are four overlapping blue navigation bars, each containing the text "CASCO" and "Welcome Casco" with a checkmark icon. Below these bars is a horizontal menu with tabs for "Patient", "BWC", "IMD", "PHP", "ANO", and "QoL". The "QoL" tab is selected and highlighted in grey.

On the left side, there is a vertical sidebar with several "View" buttons. A dropdown menu is open, listing the following options: "Change to minicASCO", "New", "Save", "Export", "View result", "View patient history", "View patient graphic", and "Exit".

The main content area is titled "QUALITY OF LIFE (QoL)". It features a table with two rows of questions and five columns of response options: "Excelent", "Fine", "Poor", and "Very Poor".

During the past week...	Excelent	Fine	Poor	Very Poor
24. How do you rate your overall health during the past week?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
25. How do you rate your overall quality of life during the past week?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Below the table, there is a "View previous" button and a status message: "Showing questions from 24 to 25". At the bottom of the main content area, there is a copyright notice: "Questions 1-25 copyright of 1995 EORTC Quality of Life Group. Extracted from QLQ-C30 and used with permission."

At the bottom left of the application, there is a logo for the University of Medicine and Health Sciences (UMHS) with the motto "LIBERTAS PERFVNDET" and "OMNIA LVCE".

At the bottom right of the application, there is a yellow box containing the text "Quality of Life Questionnaire [QLQ]-C30".

Quality of life (QoL)

10%

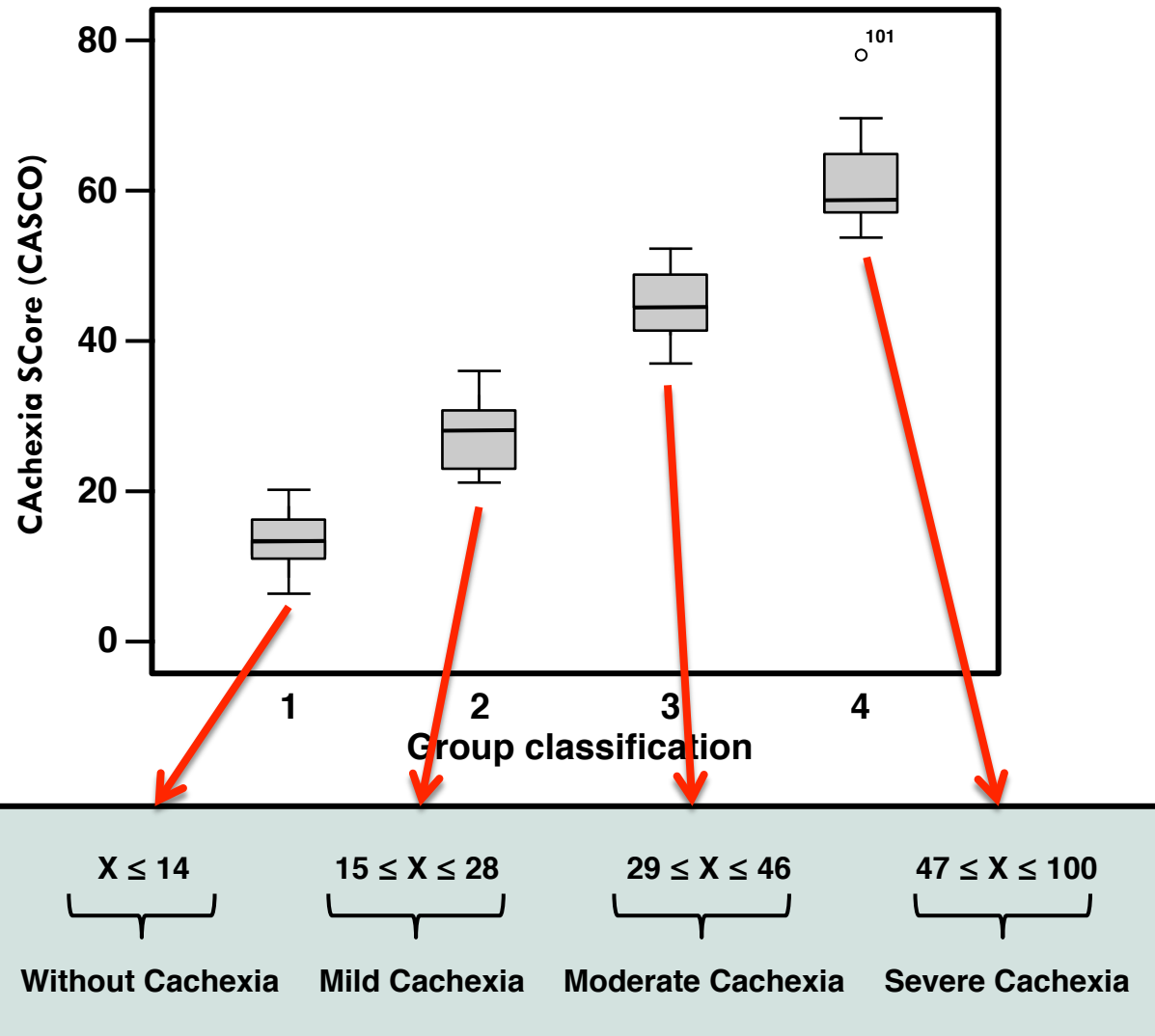
Validation of CASCO



Validation of the CAchexia SCORe (CASCO). Staging Cancer Patients: The Use of miniCASCO as a Simplified Tool

Josep M. Argilés^{1,2†}, Angelica Betancourt^{1†}, Joan Guàrdia-Olmos^{3,4}, Maribel Peró-Cebollero^{3,4}, Francisco J. López-Soriano^{1,2}, Clelia Madeddu⁵, Roberto Serpe⁵ and Silvia Busquets^{1,2}*

Degrees of cachexia



miniCASCO (CASCO's short form)

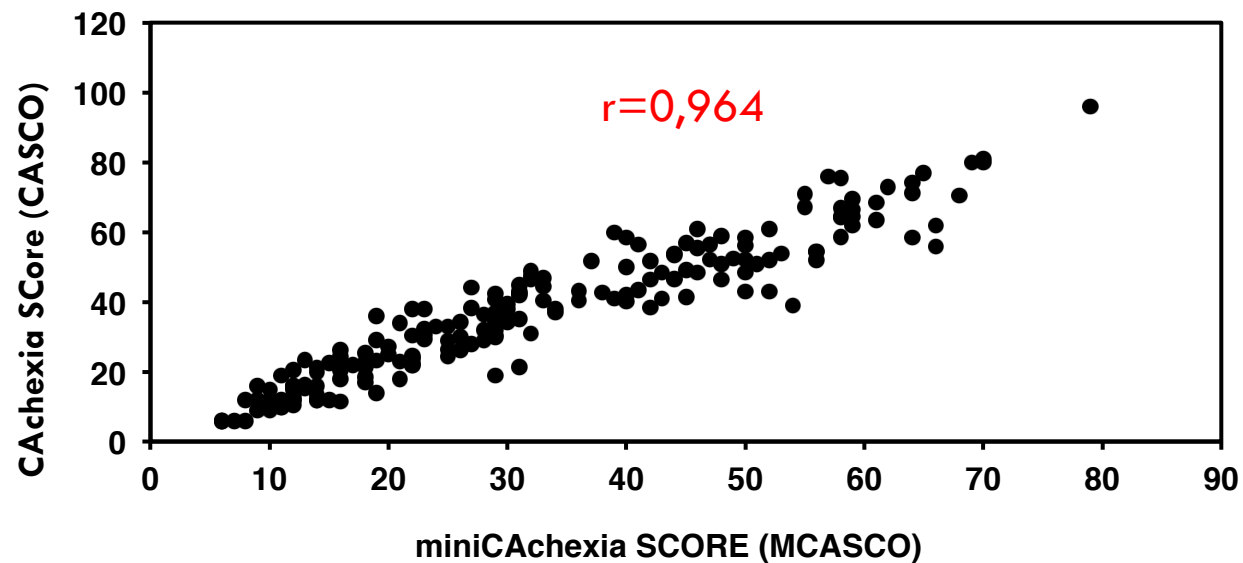
CASCO
(47 items)



miniCASCO
(21 items)

Reduction of the number of items

(component analysis: based on factorial loadings of the items in the component and the discrimination index)



miniCASCO (CASCO's short form)

The screenshot displays the miniCASCO web application interface. At the top, a dark red header contains the text "miniCASCO" on the left and "Welcome Casco" with a pencil icon on the right. Below the header is a navigation bar with tabs for "Patient", "BWC", "IMD", "PHP", "ANO", and "QoI". The "BWC" tab is selected. On the left side, there is a vertical menu with options: "Change to CASCO", "New", "Save", "Export", "View result", "View patient history", "View patient graphic", and "Exit". The main content area is titled "BODY WEIGHT LOSS AND COMPOSITION (BWC)" and contains two sections: "Body Weight Loss" and "Lean Body Mass". The "Body Weight Loss" section has input fields for "Initial Weight" (0), "Final Weight" (0), and "% Weight loss", with a note "Weight loss < to 5%". The "Lean Body Mass" section has a radio button for "No change in LBM" (selected) and a radio button for "Loss of LBM > 10%", and a "Methodology" dropdown menu. At the bottom left is the logo of the University of Medicine and Health Sciences (UMHS) with the motto "LIBERTAS PERFVNDET" and "OMNIA LVCE". At the bottom center, there is an equals sign between two blue rounded rectangles, each containing the text "CASCO (2 items)" and "miniCASCO (2 items)" respectively.

miniCASCO

Welcome Casco

Patient BWC IMD PHP ANO QoI

Change to CASCO

New

Save

Export

View result

View patient history

View patient graphic

Exit

BODY WEIGHT LOSS AND COMPOSITION (BWC)

Body Weight Loss

Initial Weight 0

Final Weight 0

% Weight loss

Weight loss < to 5%

Lean Body Mass

Lean Body Mass

No change in LBM

Loss of LBM > 10%


Methodology

LIBERTAS PERFVNDET

OMNIA LVCE

CASCO (2 items) = miniCASCO (2 items)

miniCASCO (CASCO's short form)

miniCASCO Welcome Casco 

Patient BWC **IMD** PHP ANO QoI

Change to CASCO

New
Save
Export
View result

View patient history
View patient graphic

Exit

INFLAMMATION / METABOLIC DISTURBANCES / IMMUNOSUPPRESSION (IMD)

Plasma CRP

Inflammation

- 5 mg/l <= CRP <= 10 mg/l
- 10 mg/l < CRP <= 20 mg/l
- CRP > 20 mg/l
- Not Tested

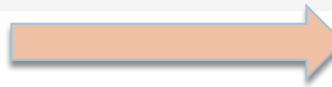
Metabolic disturbances* Plasma Albumin < 3.2 g/dL Anemia: Hb < 12 g/dL

Immunosuppression* Absolute lymphocyte number < 1200/uL

* not tested parameters should be left blank




CASCO
(11 items)



miniCASCO
(4 items)

miniCASCO (CASCO's short form)

miniCASCO Welcome Casco 

Patient	BWC	IMD	PHP	ANO	QoI
---------	-----	-----	-----	-----	-----

Change to CASCO

New
Save
Export
View result

View patient history
View patient graphic

Exit

PHYSICAL PERFORMANCE (PHP)

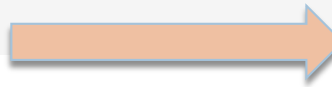
During the past week...

	Not at all	A little	Quite a bit	Very Much
1. Did you have to put more effort on climbing stairs?	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
2. Have you felt tired after walking approximately half a kilometre?	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Question 2 copyright of 1995 EORTC Quality of Life Group. Extracted from QLQ-C30 and used with permission



CASCO
(5 items)

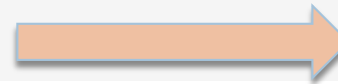


miniCASCO
(2 items)

miniCASCO (CASCO's short form)



CASCO
(4 items)



miniCASCO
(2 items)

miniCASCO (CASCO's short form)

The screenshot displays the miniCASCO web application interface. The main content area shows the 'QUALITY OF LIFE (QoL)' section with two questions:

During the past week...	Excelent	Fine	Poor	Very Poor
10. How do you rate your overall health during the past week?	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>
11. How do you rate your overall quality of life during the past week?	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>

Below the questions, there is a 'View previous' button and a status bar indicating 'Showing questions 10 and 11'. At the bottom, a 'RESULT' section shows a table with columns for 'BWC', 'IMD', and 'PHP', with values '0' and '3' respectively. A blue arrow points from the 'CASCO (25 items)' box to the 'miniCASCO (11 items)' box.

CASCO
(25 items)

miniCASCO
(11 items)

CONCLUSIONS

CASCO is a useful tool for the classification of cachexia according to 5 components:

- Body weight and lean body mass loss
- Inflammatory, immunological, and metabolic disturbances
- Physical performance
- Anorexia
- Quality of life

CASCO and miniCASCO could be also useful tools for the treatment and nutritional recommendations of cachectic cancer patients and will therefore allow for a more adequate therapy depending of the cachexia classification.



UNIVERSITY OF TURIN

PhD in
EXPERIMENTAL MEDICINE AND THERAPY

SEMINARIO

CANCER CACHEXIA: MOLECULAR MECHANISMS, DIAGNOSIS AND TREATMENT

Dr. SILVIA BUSQUETS

Departament de Bioquímica i Biomedicina Molecular

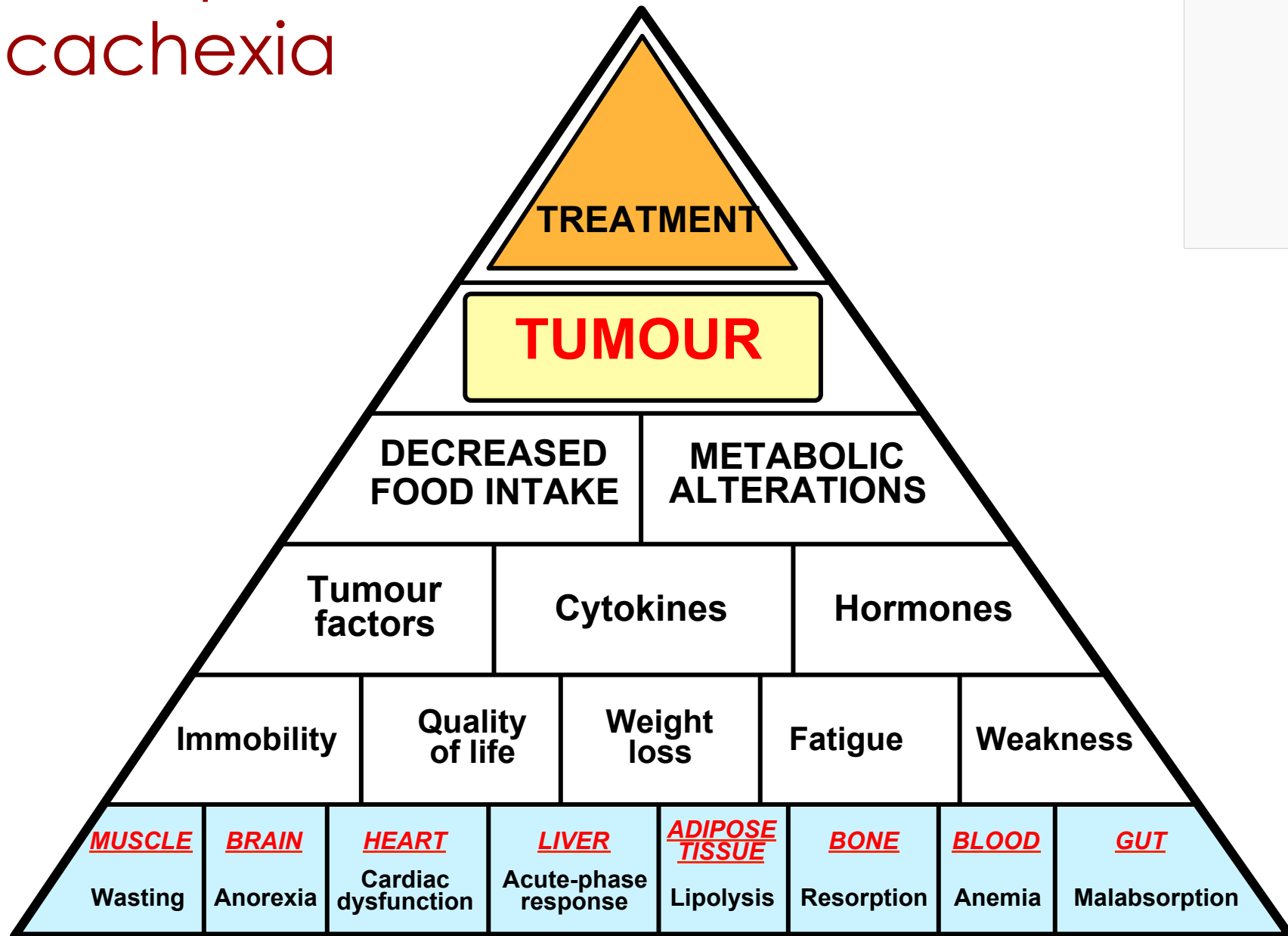
Universitat de Barcelona

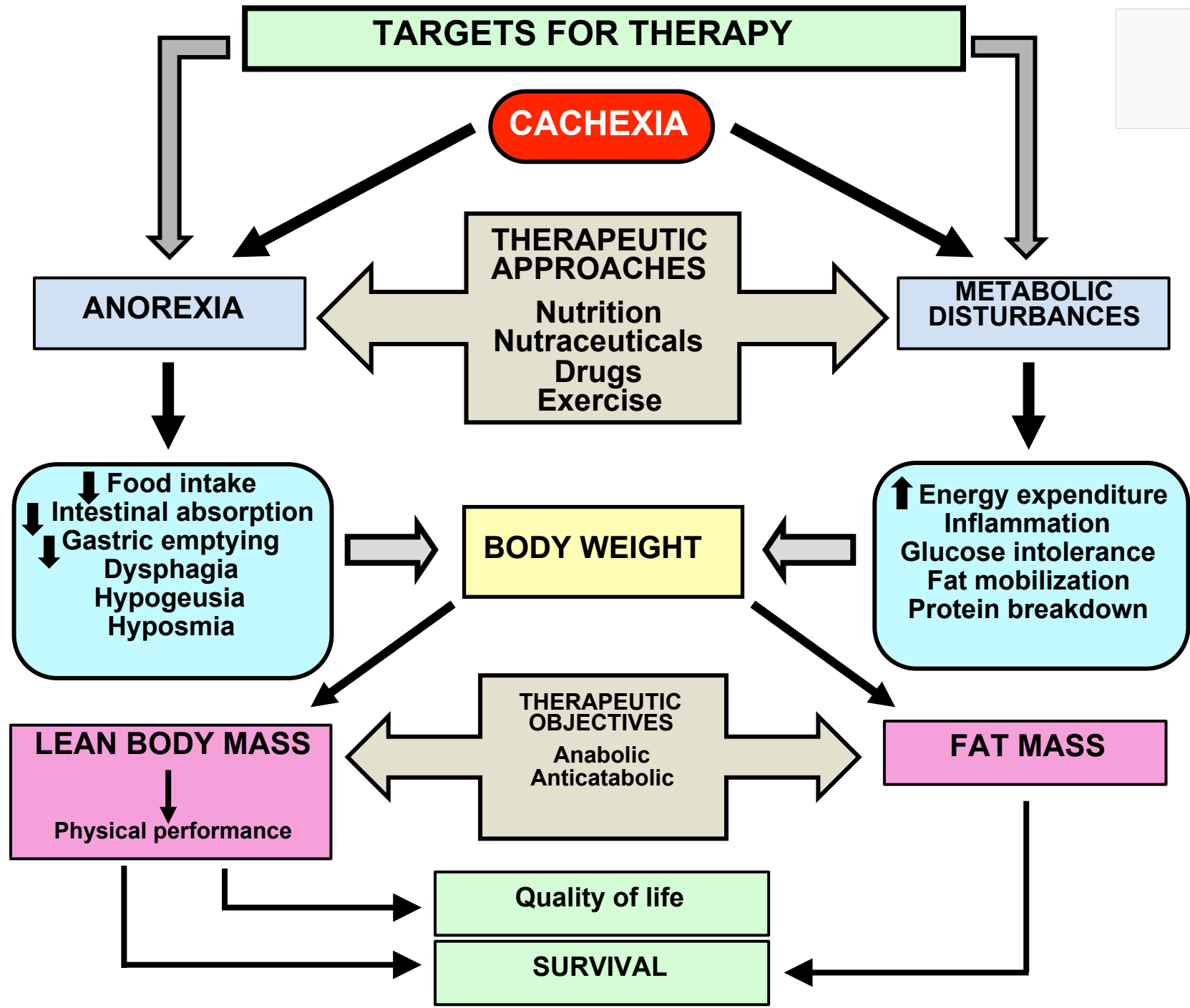
Barcelona, Spain

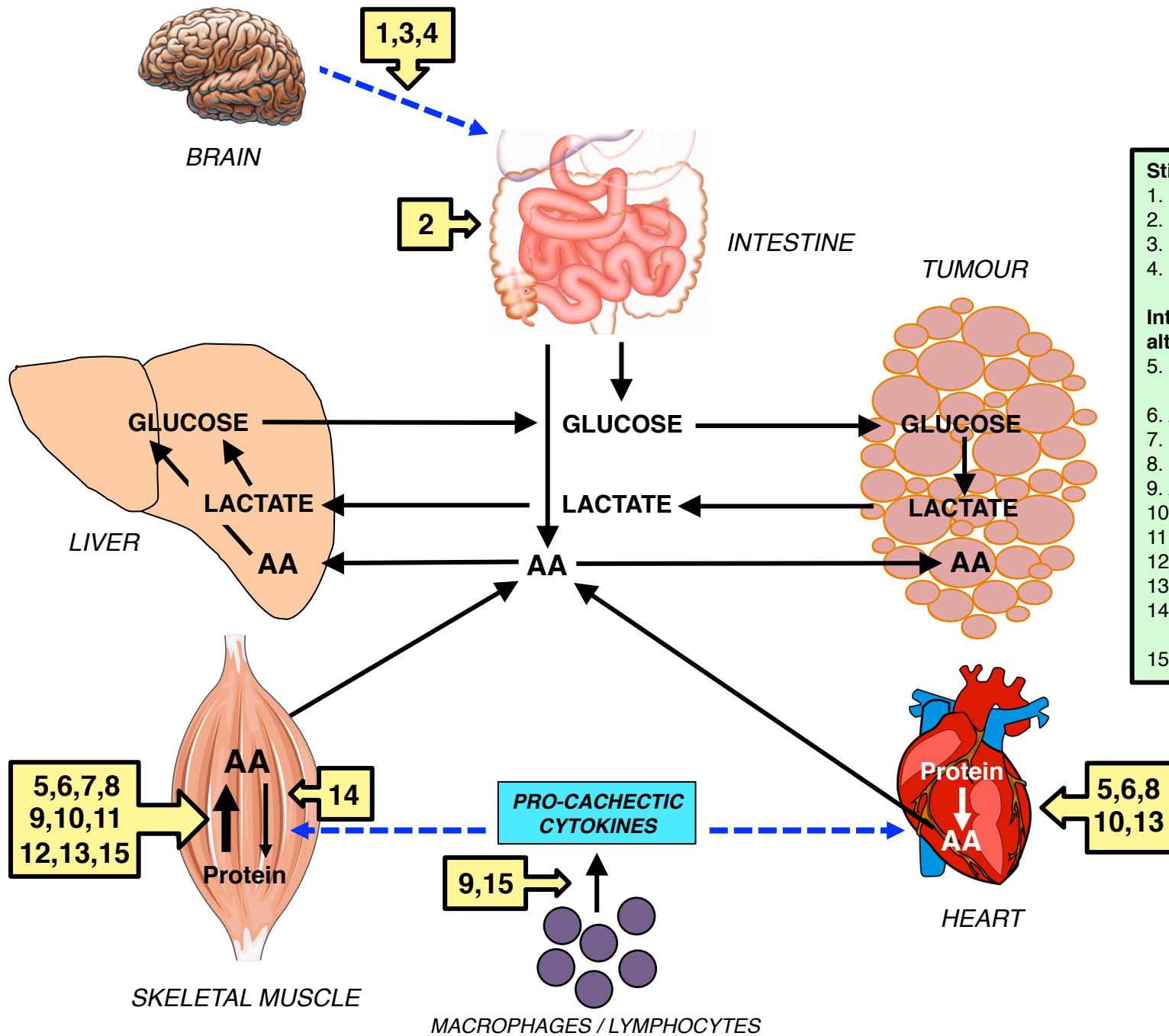
TREATMENT OF CANCER CACHEXIA

Complete reversal on muscle wasting in an animal model of cancer cachexia: additive effects of myostatin inhibition and beta-2 agonist treatment

Therapies to counteract cachexia







- Stimulating appetite:**
1. Megestrol acetate
 2. Ghrelin agonists
 3. MC4 receptor antagonists
 4. Serotonin antagonists
- Interfering with metabolic alterations:**
5. Pro-cachectic cytokine antagonists
 6. Anti-cachectic cytokines
 7. COX-2 inhibitors
 8. Beta-2 agonists
 9. ACE inhibitors
 10. Beta blockers
 11. SARMs
 12. Myostatin antagonists
 13. Proteasome inhibitors
 14. Phosphodiesterase inhibitors
 15. ω 3-fatty acids

ANOREXIA

METABOLIC ALTERATIONS

CACHEXIA



MUSCLE MASS LOSS

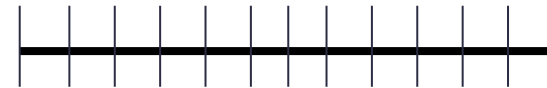
- INCREASED PROTEOLYSIS**
- DECREASED PROTEIN SYNTHESIS**
- INCREASED APOPTOSIS**
- DECREASED REGENERATION**
- MORPHOLOGICAL CHANGES**
- DECREASED PHYSICAL PERFORMANCE**

Experimental Cachexia model



Tumor inoculation

Lewis lung carcinoma



Day 1

15



Sacrifice and sample collection

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14



Lewis lung carcinoma



Experimental Cachexia model



Lewis lung carcinoma

	Control	Tumor	P -value
Initial Body Weight (g)	17 ± 0.2	17 ± 0.5	NS
Final Body Weight (g)	22 ± 1	14 ± 1	<0.001
Weight Increase (%)	29%	-17%	
Muscles (mg/100g Initial Body Weight)			
GASTROCNEMIUS	764 ± 16	381 ± 6	<0.001
TIBIALIS	241 ± 8	123 ± 7	<0.001
SOLEUS	42 ± 1	37 ± 3	NS
EDL	58 ± 4	39 ± 3	<0.01
HEART	656 ± 10	530 ± 6	<0.001

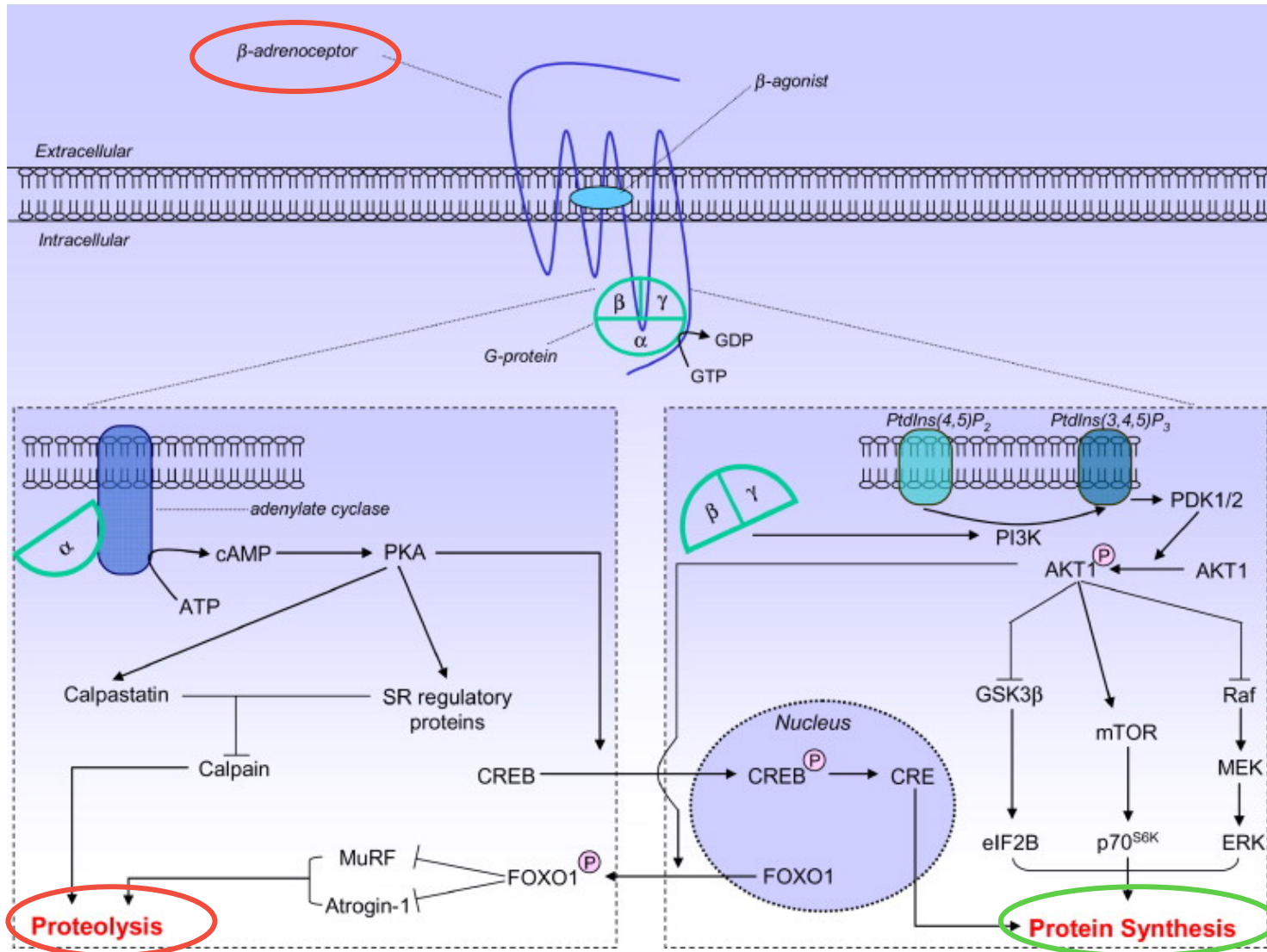
P-value: Student *t*-test

Lewis lung carcinoma (LLC)
vehicle (saline)-treated animals
(placebo control)



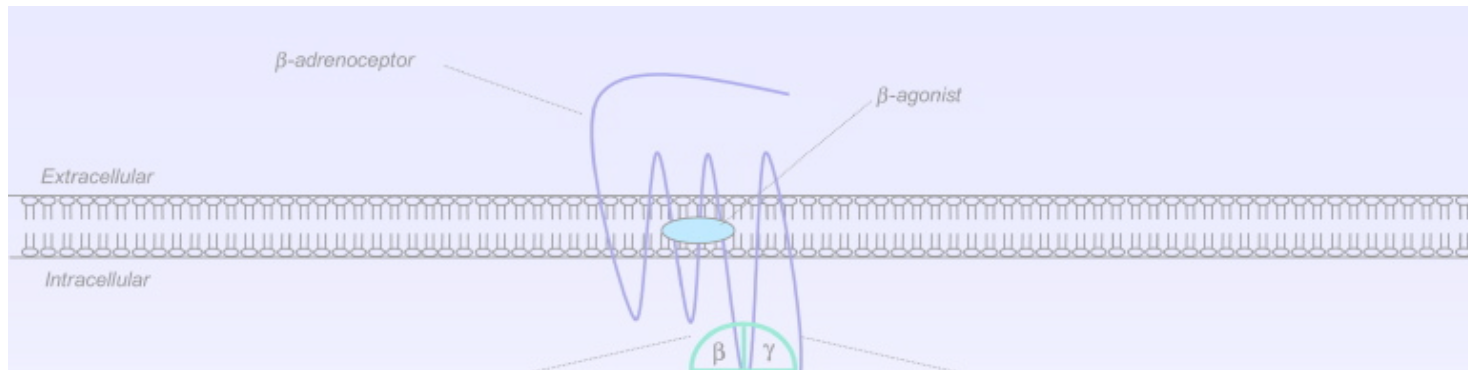
LLC-treated animals with:
soluble receptor antagonist of myostatin
(10 mg/kg BW s.c. twice a week)
+
Formoterol
(1 mg/kg BW s.c. once a day)





Possible β 2-adrenergic signaling pathways involved in skeletal muscle hypertrophy following administration of a β 2-agonist.

Figure obtained from: Lynch GS, Schertzer JD, Ryall JG. Therapeutic approaches for muscle wasting disorders. Pharmacol Ther. 2007 Mar;113(3):461-87.

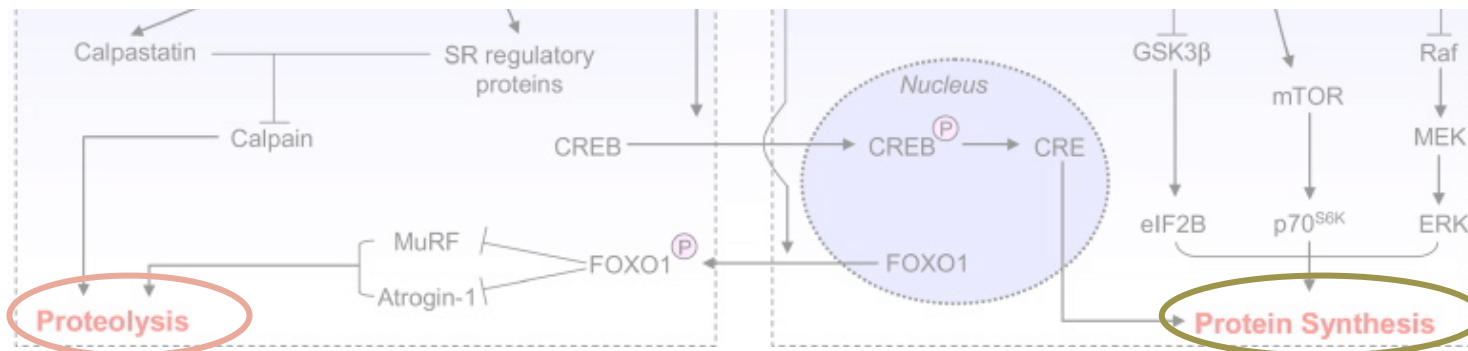


[CANCER RESEARCH 64, 6725–6731, September 15, 2004]

Anticachectic Effects of Formoterol: A Drug for Potential Treatment of Muscle Wasting

Sílvia Busquets, Maria T. Figueras, Gemma Fuster, Vanessa Almendro, Rodrigo Moore-Carrasco, Elisabet Ametller, Josep M. Argilés, and Francisco J. López-Soriano

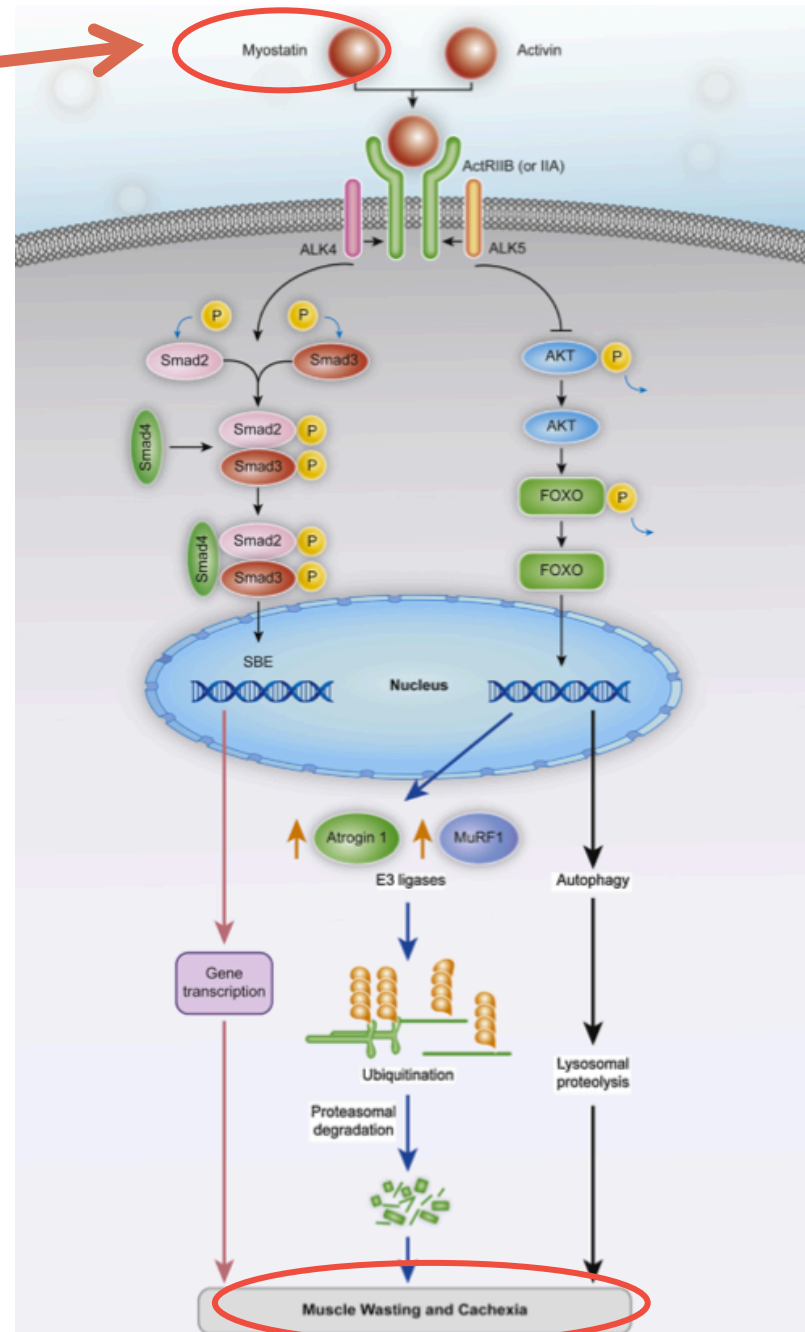
Cancer Research Group, Departament de Bioquímica i Biologia Molecular, Facultat de Biologia, Universitat de Barcelona, Barcelona, Spain



Possible β_2 -adrenergic signaling pathways involved in skeletal muscle hypertrophy following administration of a β_2 -agonist.

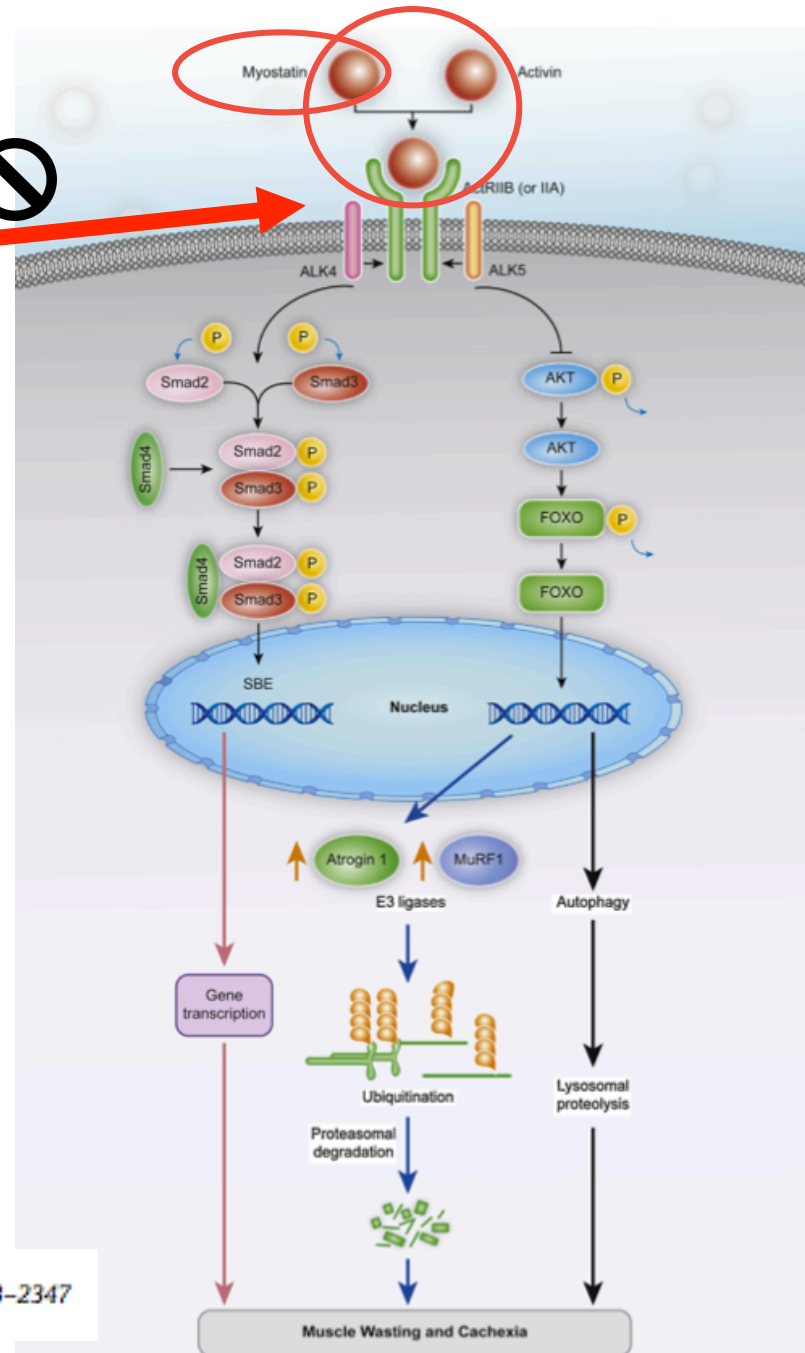
Figure obtained from: Lynch GS, Schertzer JD, Ryall JG. Therapeutic approaches for muscle wasting disorders. *Pharmacol Ther.* 2007 Mar;113(3):461-87.

Myostatin acts as a negatively muscle growth regulator



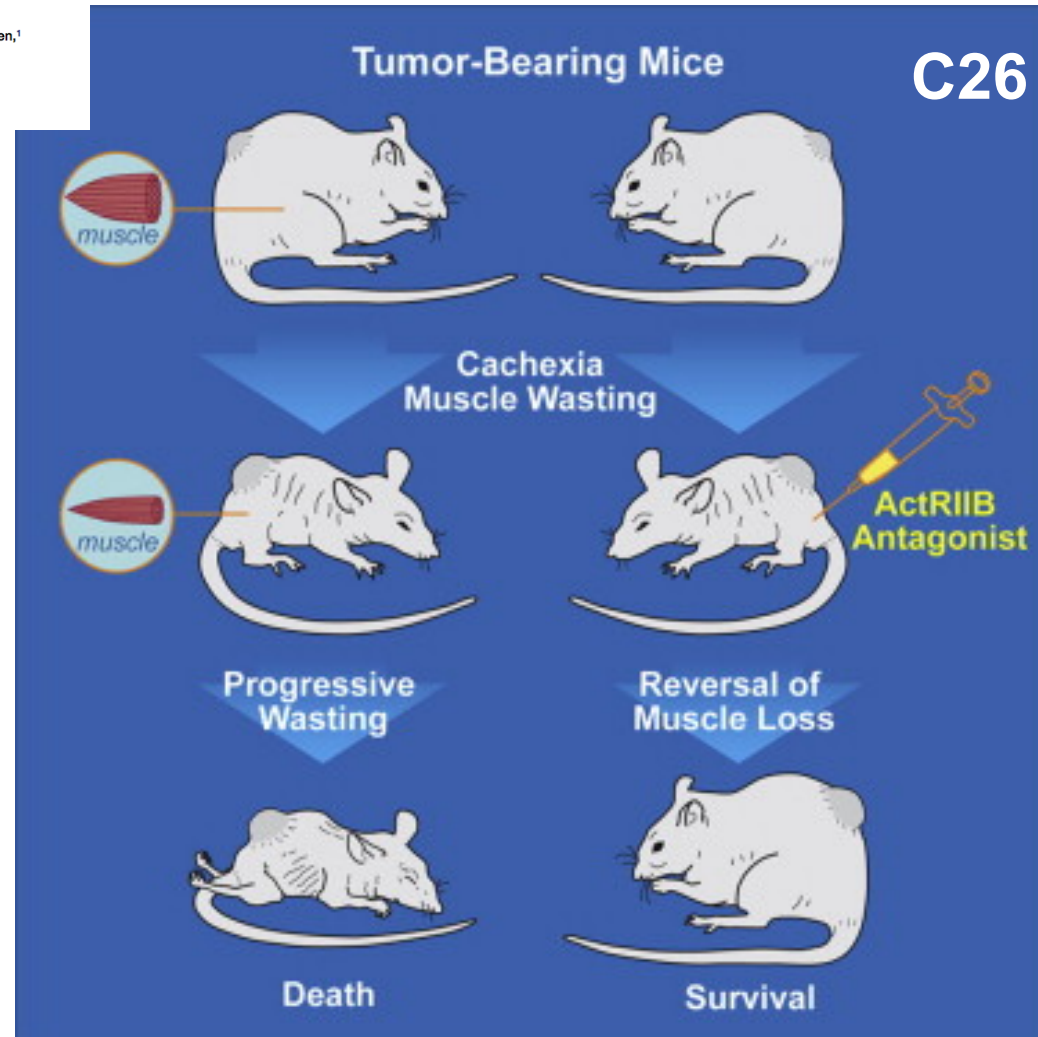
sActRIIB

soluble receptor antagonist of myostatin



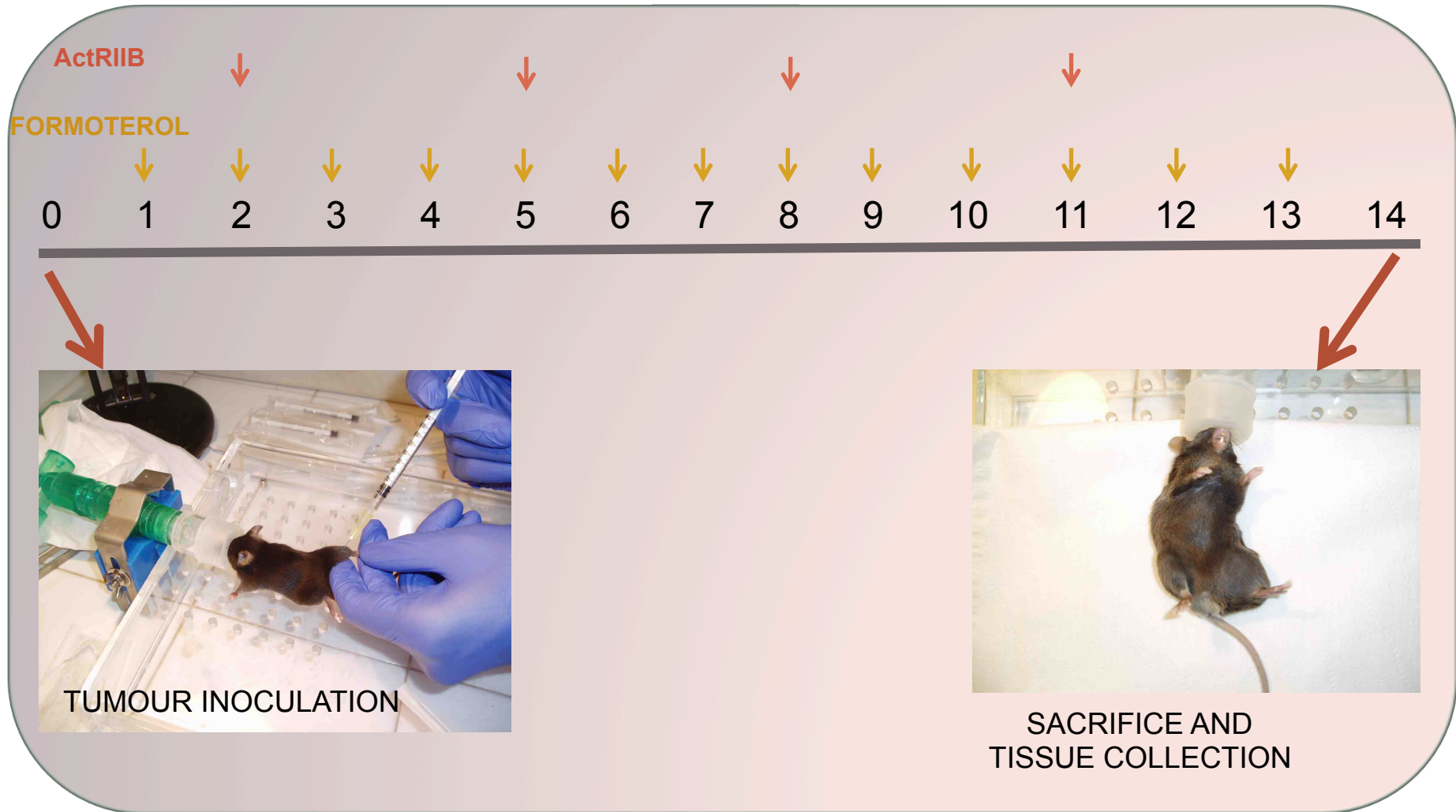
Reversal of Cancer Cachexia and Muscle Wasting by ActRIIB Antagonism Leads to Prolonged Survival

Xiaolan Zhou,¹ Jin Lin Wang,¹ John Lu,¹ Yanping Song,¹ Keith S. Kwak,¹ Qingsheng Jiao,¹ Robert Rosenfeld,¹ Qing Chen,¹ Thomas Boone,¹ W. Scott Simonet,¹ David L. Lacey,¹ Alfred L. Goldberg,² and H.Q. Han^{1*}
¹Departments of Metabolic Disorders and Protein Science, Amgen Research, Thousand Oaks, CA 91320, USA
²Department of Cell Biology, Harvard Medical School, Boston, MA 02115, USA
 *Correspondence: hqhan@amgen.com
 DOI 10.1016/j.cell.2010.07.011

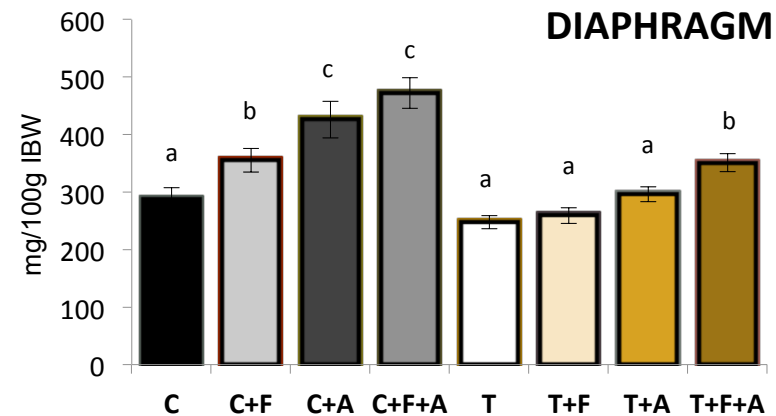
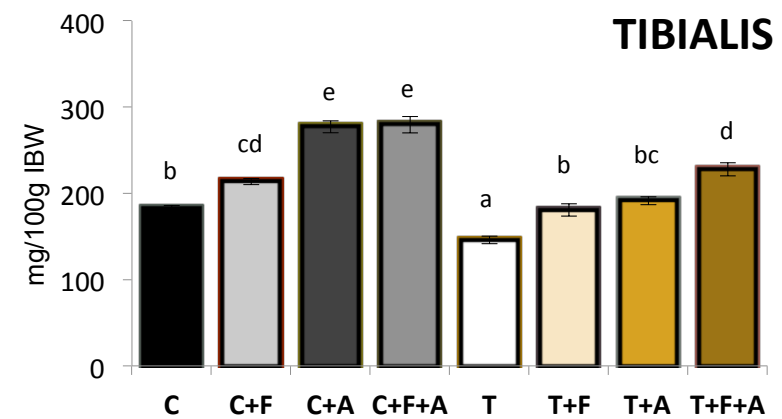
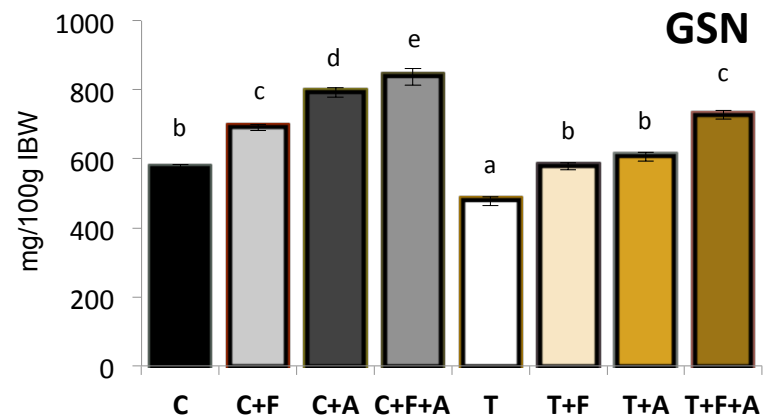


Control
Control + ActRIIB
Control + Formoterol
Control + ActRIIB + Formoterol

LLC
LLC + ActRIIB
LLC + Formoterol
LLC + ActRIIB + Formoterol



MUSCLE WEIGHTS

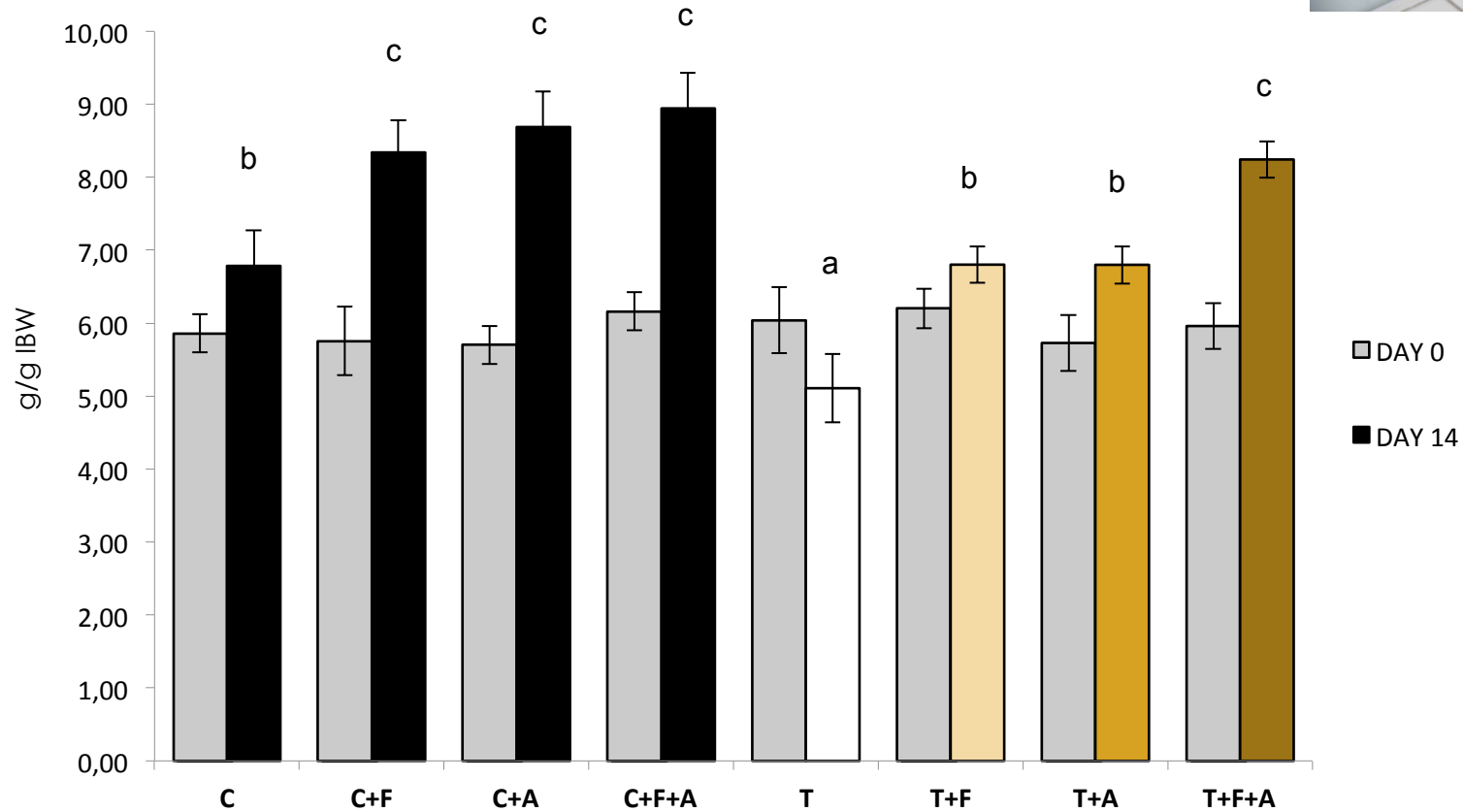


Results are mean \pm S.E.M. for the number of animals indicated in parentheses. Muscle weights are expressed as mg/100 g of initial body weight. GSN: gastrocnemius muscle. Statistical significance of the results by **full factorial three-way ANOVA** (fixed factors: tumour, formoterol treatment, and soluble receptor antagonist of myostatin treatment). Statistically significant difference by *post hoc* Duncan test. Different superscripts indicate significant differences between groups.

SKELETAL MUSCLE STRENGTH



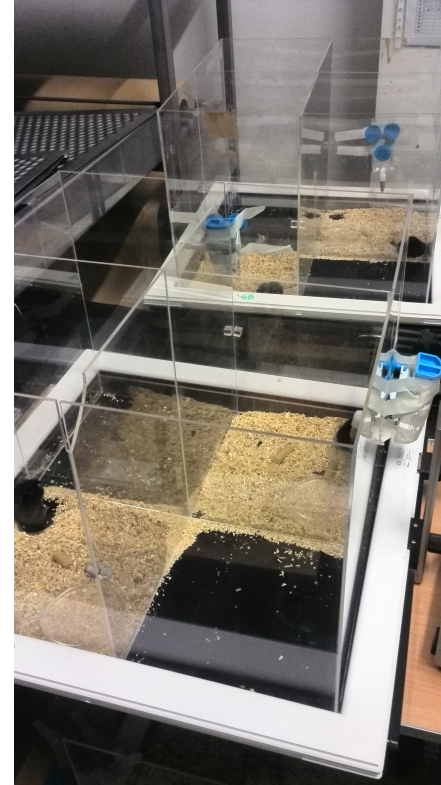
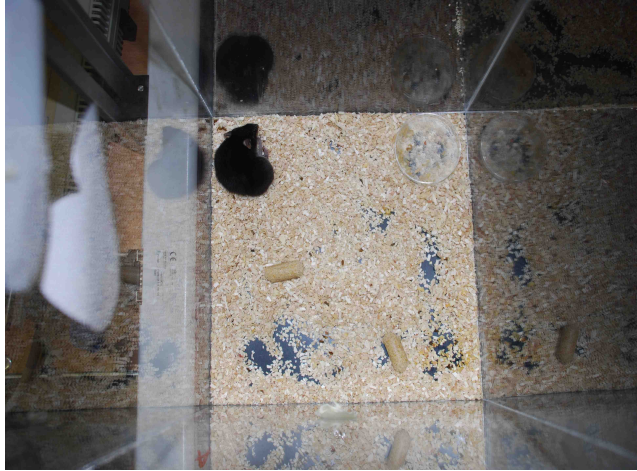
SKELETAL MUSCLE STRENGTH



Grip force is expressed as g/g initial body weight. Statistical significance of the results by full factorial three-way ANOVA (fixed factors: tumour, formoterol treatment, and soluble receptor antagonist of myostatin treatment).

Statistically significant difference by *post hoc* Duncan test. Different superscripts indicate significant differences between groups.

PHYSICAL ACTIVITY

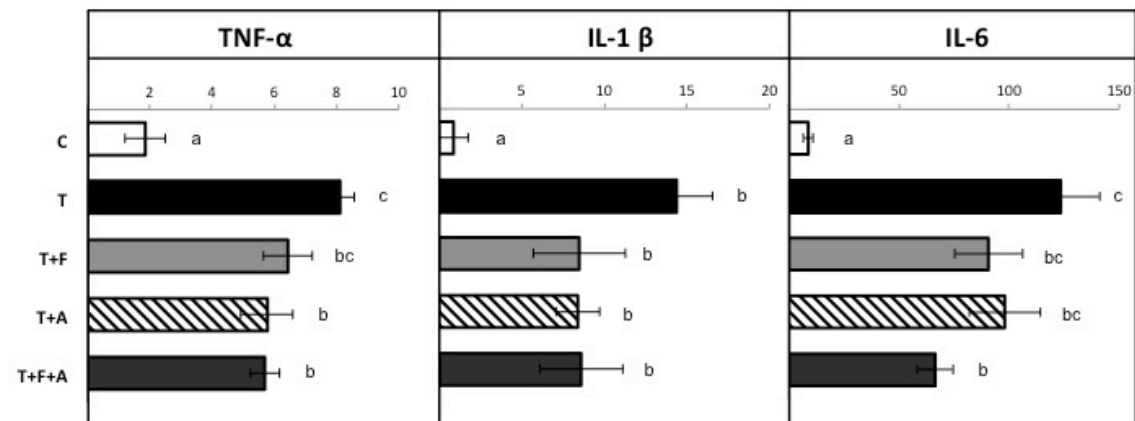


IR ACTIMETER System and ACTITRAK software from PANLAB

PHYSICAL ACTIVITY

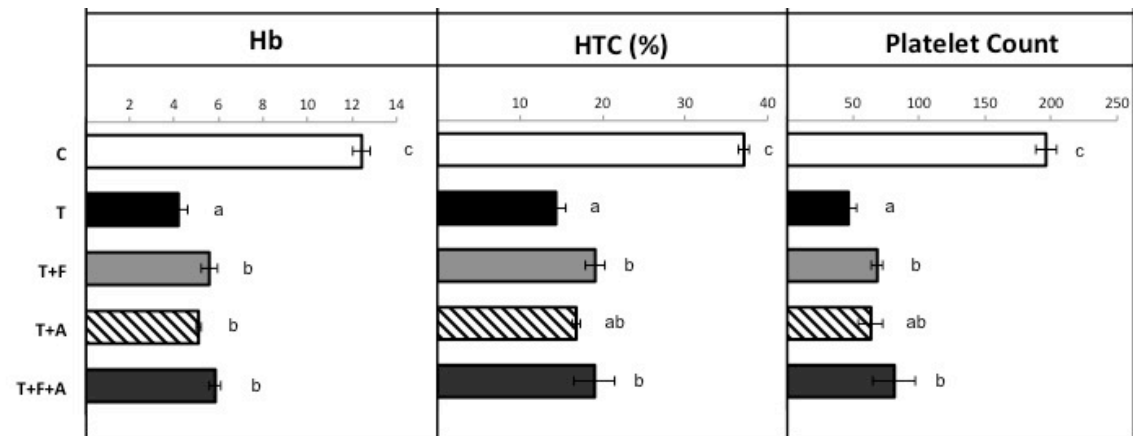
	C (10)	T (10)	T + F (10)	T + A (10)	T + A + F (7)	ANOVA
Physical activity						p-value
Total activity	65321 ± 2643 ^b	15451 ± 1152 ^a	19627 ± 1085 ^a	17041 ± 1383 ^a	19900 ± 631 ^a	0,000
Stereotyped movement	5312 ± 300 ^b	1893 ± 327 ^a	1545 ± 118 ^a	1769 ± 157 ^a	1888 ± 154 ^a	0,000
Locomotor movements	60010 ± 2636 ^b	13558 ± 1060 ^a	18082 ± 1019 ^a	15272 ± 1326 ^a	18012 ± 689 ^a	0,000
Velocity and distance						
Mean Velocity (cm/s)	0,64 ± 0,03 ^c	0,10 ± 0,03 ^a	0,14 ± 0,01 ^{ab}	0,13 ± 0,01 ^{ab}	0,17 ± 0,01 ^b	0,000
Travelled distance (cm)	46443 ± 990 ^c	7190 ± 737 ^a	10623 ± 1062 ^{ab}	9324 ± 784 ^{ab}	12172 ± 768 ^b	0,000
Time (%)						
Resting	73,3 ± 1,4 ^a	93,4 ± 0,6 ^c	89,7 ± 1,5 ^{bc}	90,3 ± 1,1 ^{bc}	87,3 ± 1,9 ^b	0,000
Slow movements	17,9 ± 1,2 ^c	6,2 ± 0,5 ^a	9,4 ± 1,3 ^{ab}	9,0 ± 1,0 ^{ab}	11,7 ± 1,7 ^b	0,000
Fast movements	8,8 ± 0,03 ^b	0,4 ± 0,08 ^a	0,9 ± 0,20 ^a	0,6 ± 0,11 ^a	1,0 ± 0,16 ^a	0,000

PLASMA CYTOKINE LEVELS



Results are mean \pm S.E.M. for the number of animals indicated in parentheses. Cytokines are expressed as pg/ml plasma. Statistical significance of the results by one-way ANOVA. Statistically significant difference by *post hoc* Duncan test. Different superscripts indicate significant differences between groups.

BLOOD MARKERS



Results are mean \pm S.E.M. for the number of animals indicated in parentheses. Cytokines are expressed as pg/ml plasma. Statistical significance of the results by one-way ANOVA. Statistically significant difference by *post hoc* Duncan test. Different superscripts indicate significant differences between groups.

FOOD INTAKE

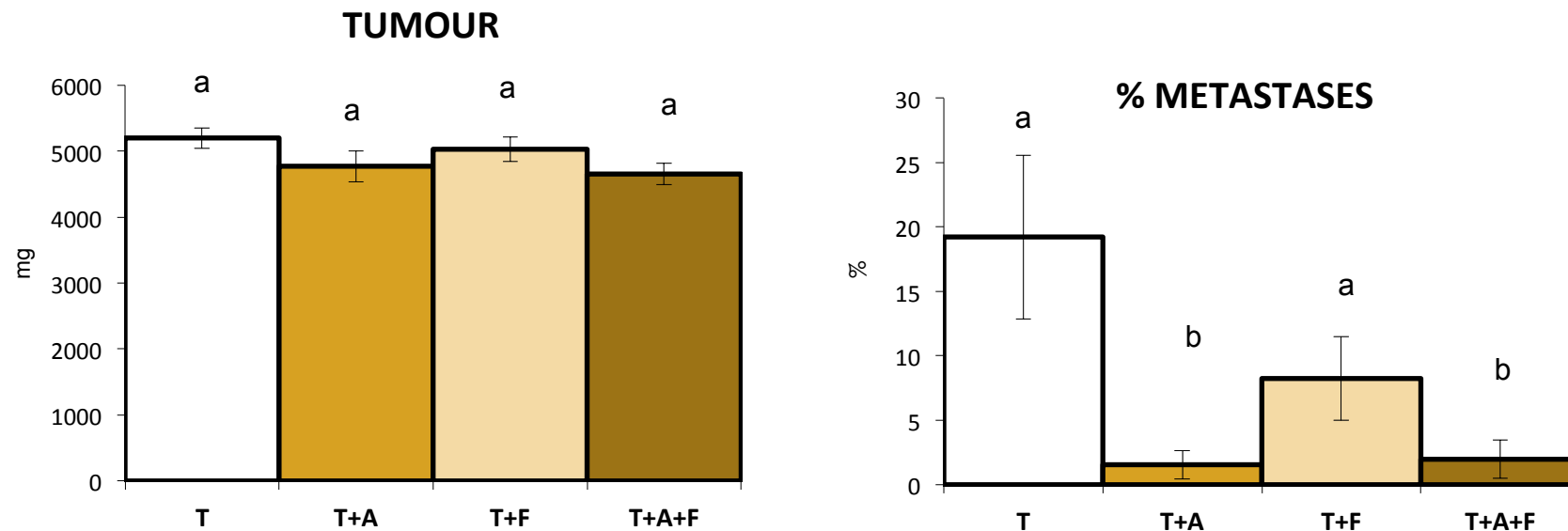
Food Intake	C (7)	C + F (7)	C + A (7)	C + A + F (7)
g/100 g IBW	226 ± 7 ^{ab}	258 ± 4^c	260 ± 8^c	256 ± 13^c
	T (8)	T + F (8)	T + A (8)	T + A + F (8)
g/100 g IBW	216 ± 7 ^a	221 ± 3 ^a	215 ± 3 ^a	240 ± 4^b

Statistical significance of the results by full factorial three-way ANOVA (fixed factors: tumour (T), formoterol treatment (F), and soluble receptor antagonist of myostatin treatment (A)).

Results are mean ± S.E.M. for the number of animals indicated in parentheses.

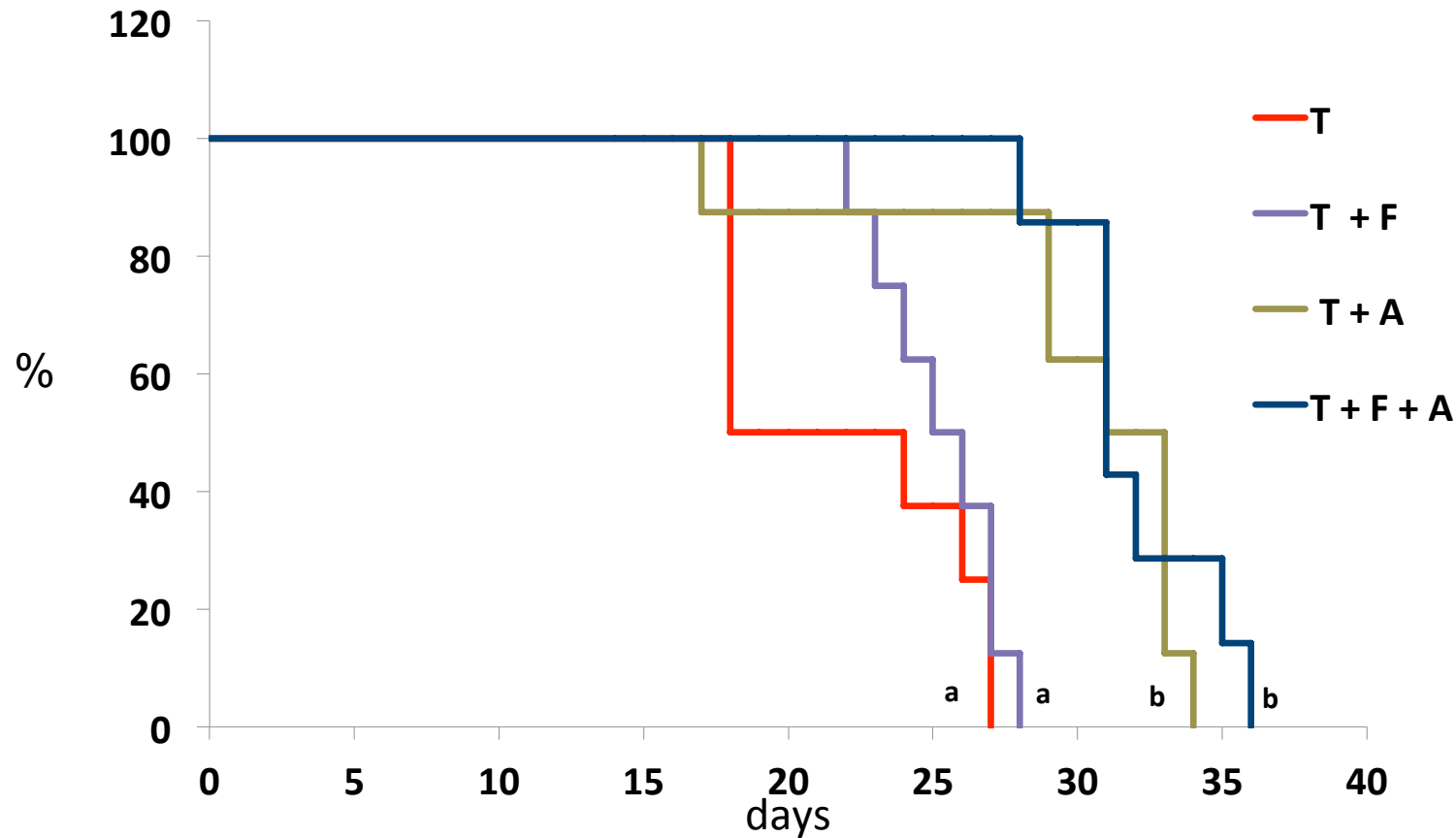
Food intake is expressed in g/100g of initial body weight and refers to the ingestion during the period of the experiment prior to sacrifice that took place 14 days after tumour inoculation.

TUMOUR MASS AND METASTASES



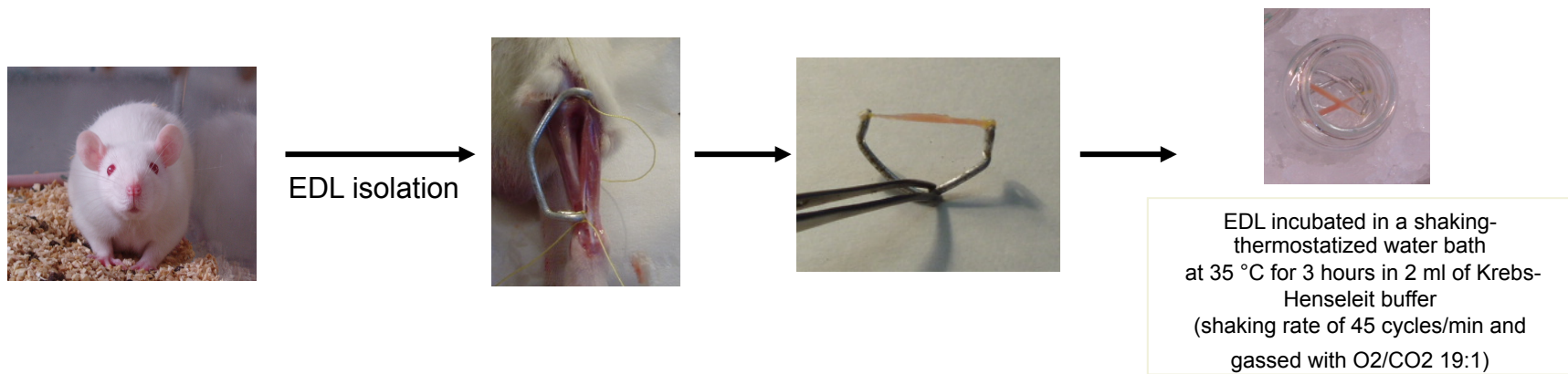
Tumor mass is expressed in g and metastases are expressed as percentage of the lung volume. Statistical significance of the results by full factorial **two-way ANOVA** (fixed factors: formoterol treatment (F), and soluble receptor antagonist of myostatin treatment (A)). Statistically significant difference by *post hoc* Duncan test. Different superscripts indicate significant differences between groups.

SURVIVAL

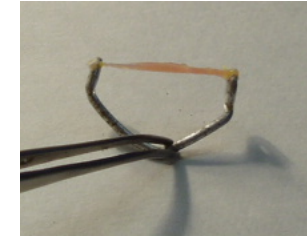
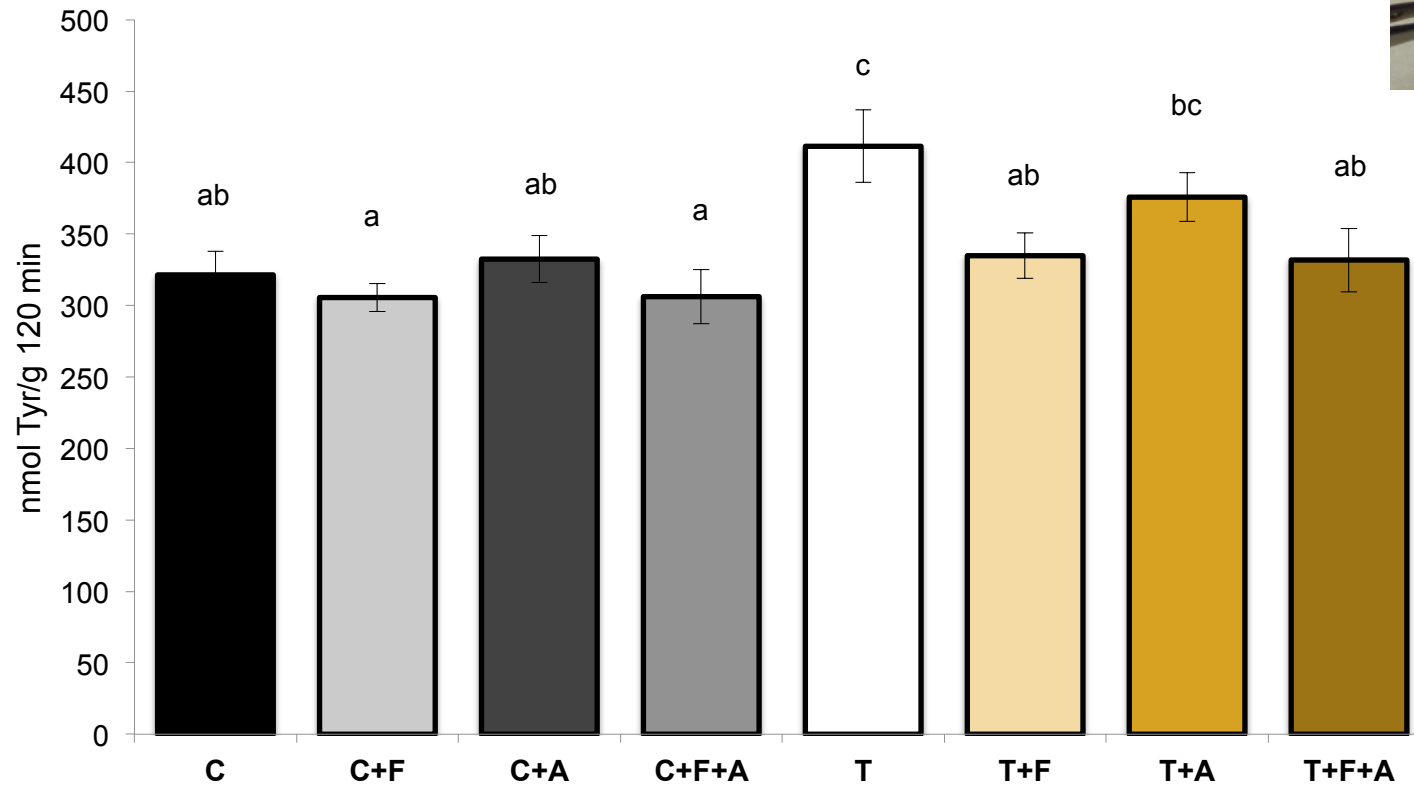


Kaplan-Meier survival analysis. Comparison of Survival curves were analyzed by Log-rank test (Mantel-Cox).
The global comparison for the treatments has a P value=0.000.
Different subscripts means significant differences detected by pairwise comparisons (Bonferroni correction).
P values < 0.05 were considered significant.

PROTEIN DEGRADATION: MEASURED *EX VIVO* AS TYROSINE RELEASE, USING INCUBATED ISOLATED EDL MUSCLES



PROTEIN DEGRADATION: MEASURED *EX VIVO* AS TYROSINE RELEASE, USING INCUBATED ISOLATED EDL MUSCLES



Proteolytic rates were measured in the presence of cycloheximide (0.5 mmol/L) and are expressed as nanomoles tyrosine per gram and 2 hours of incubation. Statistical significance of the results by full factorial three-way ANOVA (fixed factors: tumour (T), formoterol treatment (F), and soluble receptor antagonist of myostatin treatment (A)). Statistically significant difference by *post hoc* Duncan test. Different superscripts indicate significant differences between groups.

PROTEIN DEGRADATION: PROTEOLYTIC SYSTEMS

PROTEOLYTIC SYSTEMS IN MUSCLE

Lysosomal

Cathepsins

Non-Lysosomal

Ca²⁺-dependent system (calpains)

ATP-ubiquitin-dependent system

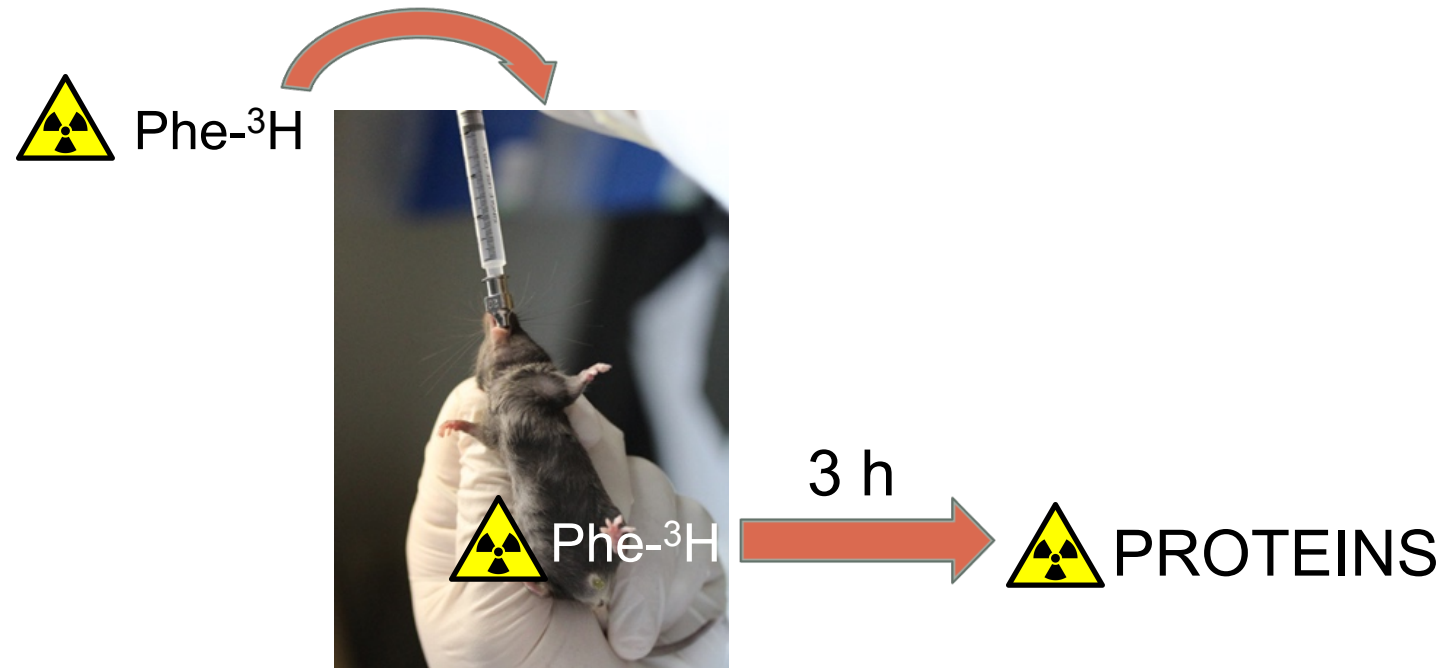
PROTEIN DEGRADATION: GENE EXPRESSION OF PROTEOLYTIC SYSTEMS IN TIBIALIS MUSCLE

Table 3. Effects of the combination of formoterol and sActRIIB treatment on tibialis muscle gene expression in mice bearing the Lewis lung carcinoma

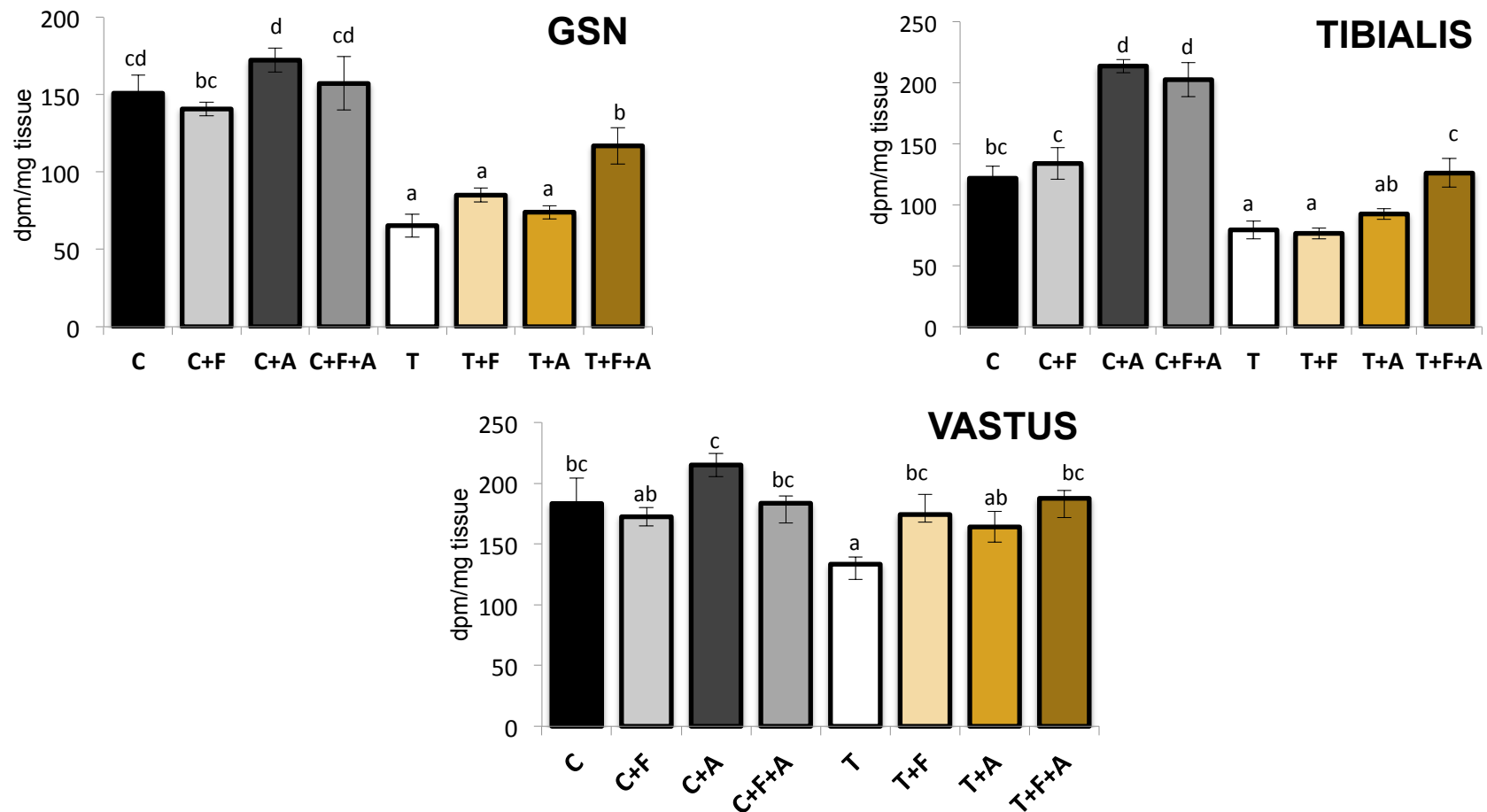
Proteolytic system	C (6)	T (7)	T + F (7)	T + A (6)	T + A + F (7)	ANOVA
						<i>p</i> values
Ubiquitin-dependent						
Atrogin-1	100 ± 23 ^a	264 ± 20 ^c	196 ± 21 ^{bc}	250 ± 34 ^{bc}	173 ± 33 ^{ab}	0.000
MuRF-1	100 ± 22 ^a	206 ± 14 ^b	167 ± 29 ^{ab}	206 ± 45 ^b	178 ± 34 ^{ab}	0.000
Ubiquitin	100 ± 6 ^a	158 ± 8 ^b	118 ± 10 ^a	153 ± 9 ^b	109 ± 15 ^a	0.000
E2	100 ± 5 ^{ab}	118 ± 6 ^c	103 ± 6 ^{ab}	108 ± 7 ^{bc}	89 ± 4 ^a	0.000
C8 proteasome subunit	100 ± 6 ^a	160 ± 8 ^c	135 ± 7 ^b	145 ± 8 ^{bc}	120 ± 10 ^{ab}	0.000
Calcium-dependent						
m-Calpain	100 ± 8 ^{ab}	147 ± 7 ^c	116 ± 6 ^b	107 ± 6 ^b	86 ± 8 ^a	0.000
Lysosomal						
Cathepsin B	100 ± 6 ^b	126 ± 8 ^b	35 ± 20 ^a	92 ± 8 ^b	7 ± 2 ^a	0.000

Results are mean ± SEM for the number of animals indicated in parentheses. C: mice without tumor; T: tumor-bearing mice; T + F: treated with formoterol; T + A: treated with sActRIIB; T + A + F: treated with both sActRIIB and formoterol. Statistical significance of the results by one-way ANOVA following a *post hoc* Duncan test. Different superscripts indicate significant differences between groups.

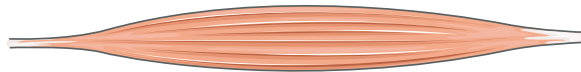
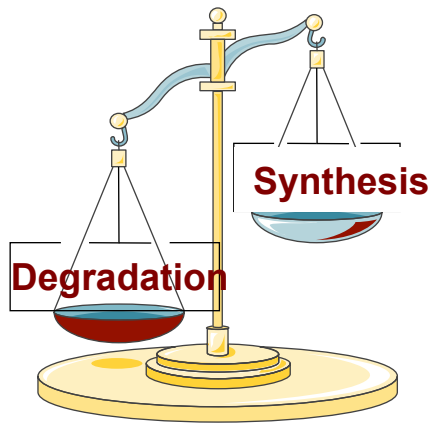
PROTEIN SYNTHESIS: MEASURED *IN VIVO* USING TRITIATED PHENYLALANINE



PROTEIN SYNTHESIS: MEASURED *IN VIVO* USING TRITIATED PHENYLALANINE



Statistical significance of the results by full factorial three-way ANOVA (fixed factors: tumour (T), formoterol treatment (F), and soluble receptor antagonist of myostatin treatment (A)).
Statistically significant difference by *post hoc* Duncan test. Different superscripts indicate significant differences between groups.

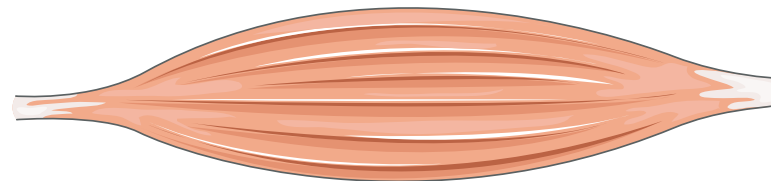
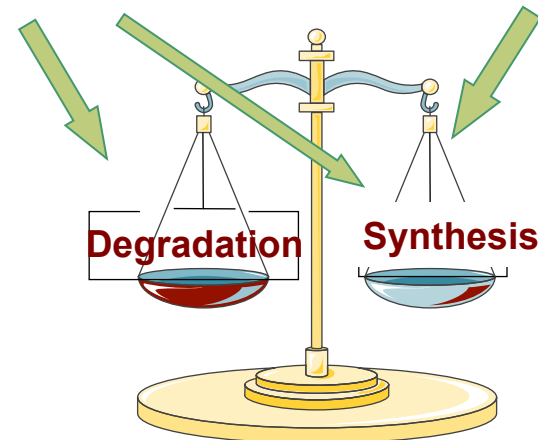


Muscle wasting



FORMOTEROL

sActRIIB



Combining formoterol and the soluble ActRIIB seems to be a very promising treatment for experimental cancer cachexia.

Lewis lung carcinoma (LLC)



LLC-treated animals with:
**soluble receptor
antagonist of myostatin
+
Formoterol**





IJC

International Journal of Cancer

Complete reversal of muscle wasting in experimental cancer cachexia: Additive effects of activin type II receptor inhibition and β -2 agonist

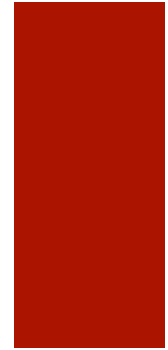
Miriam Toledo¹, Sílvia Busquets^{1,2}, Fabio Penna¹, Xiaolan Zhou³, Enrica Mamonti¹, Angelica Betancourt¹, David Massa¹, Francisco J. López-Soriano^{1,2}, H.Q. Han³ and Josep M. Argilés^{1,2}

¹ Cancer Research Group, Departament de Bioquímica i Biologia Molecular, Facultat de Biologia, Universitat de Barcelona, Barcelona, Spain

² Institut de Biomedicina de la Universitat de Barcelona (IBUB), Barcelona, Spain

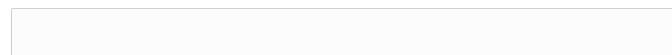
³ Departments of Metabolic Disorders and Protein Science, Amgen Research, Thousand Oaks, CA

Conclusions and perspectives



- **Treatment of cancer cachexia:**

- because cachexia is a multifactorial syndrome, a **multimodal approach** is needed.
- Multimodal therapy should incorporate at least a double strategy, both **anticatabolic and anabolic**.
- Treatment should be started right from the moment of cachexia diagnosis (need of a diagnosis tool).



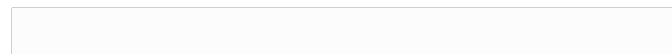
Conclusions and perspectives

CANCER CACHEXIA TREATMENT

anabolic/anticatabolic drugs
+
adequate nutritional support



moderate-to-high
endurance exercise





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B:KC Barcelona Cancer Hub HUB High International Research Campus

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