

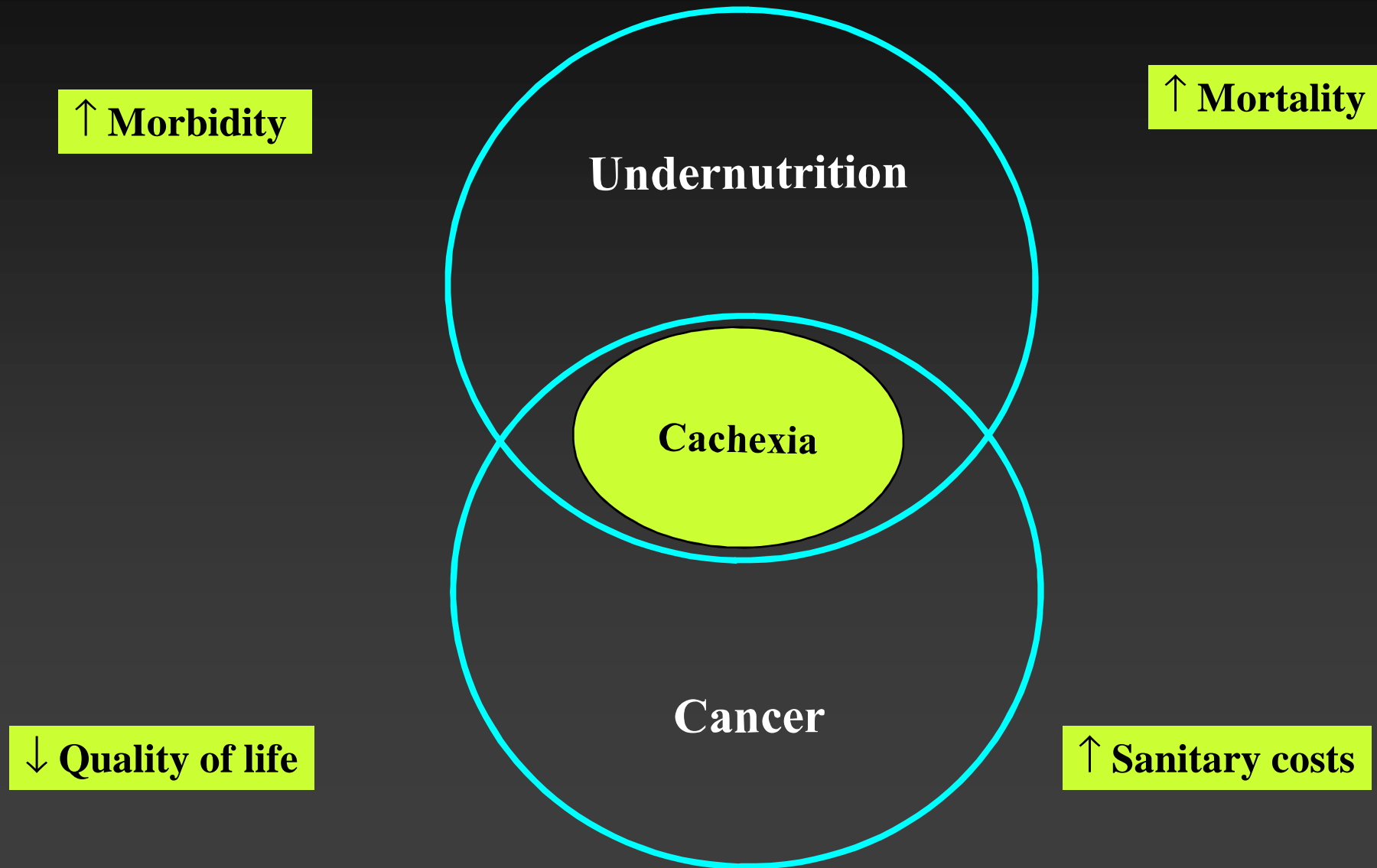
## **ESMO Symposium on Nutrition Zurich, March 2009**

*Evaluation of the nutritional status of a  
cancer patient*

### **The basic science of weight loss: What should oncologists know?**

**Prof. Dr. Josep M. Argilés  
Departamento de Bioquímica y Biología  
Molecular  
Universidad de Barcelona**

# *Cancer and nutrition*



**marked weight loss, anorexia,  
asthenia and anemia**

**Normal**

**Mild  
weight loss  
anorexia**

**Moderate  
weight loss  
anorexia**

**Severe  
weight loss  
anorexia**

**Death**

**Metabolic changes**

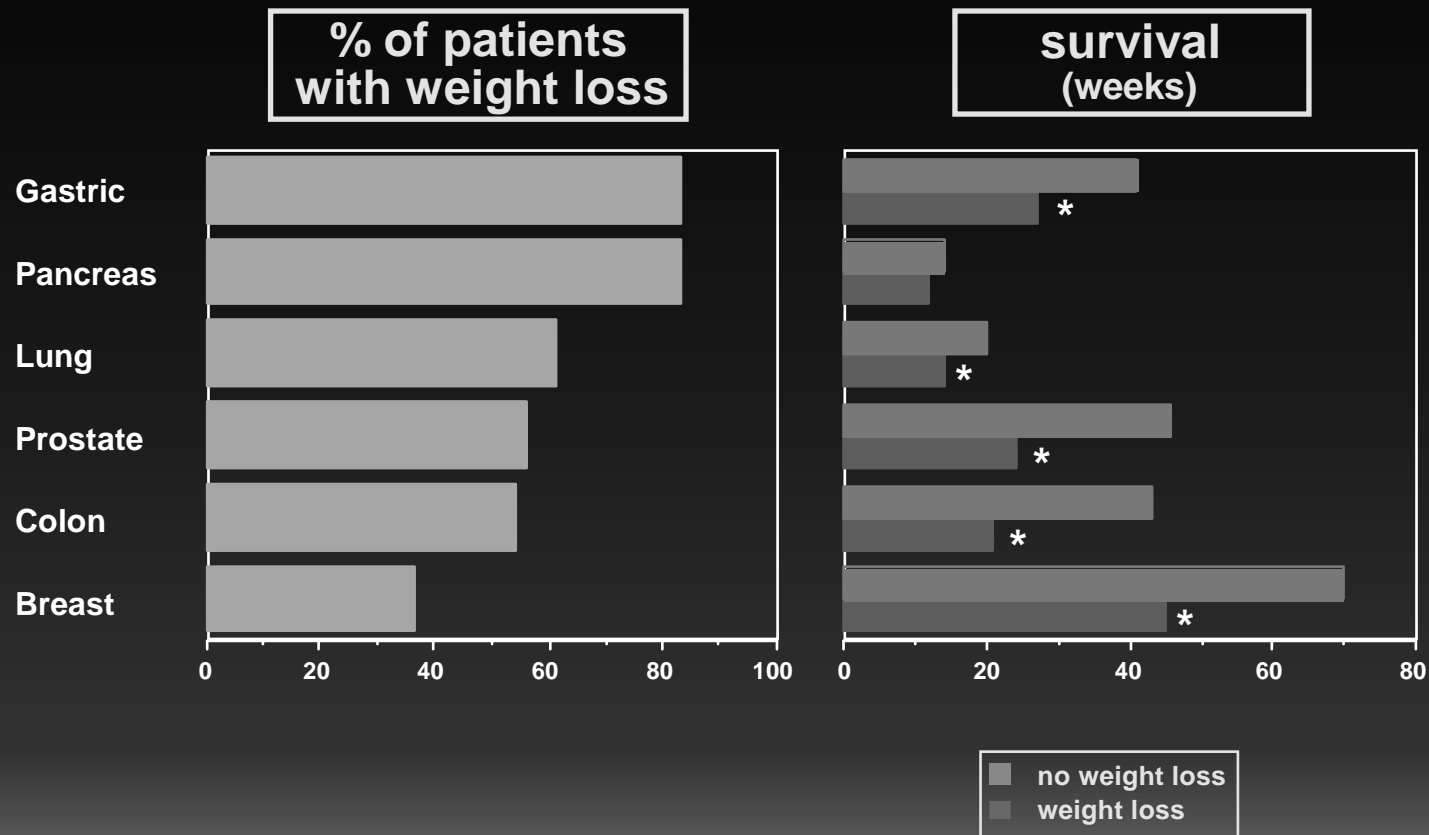
**Reduced activity**

**Muscle wasting obvious**

**Reduced survival**



# CACHEXIA



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

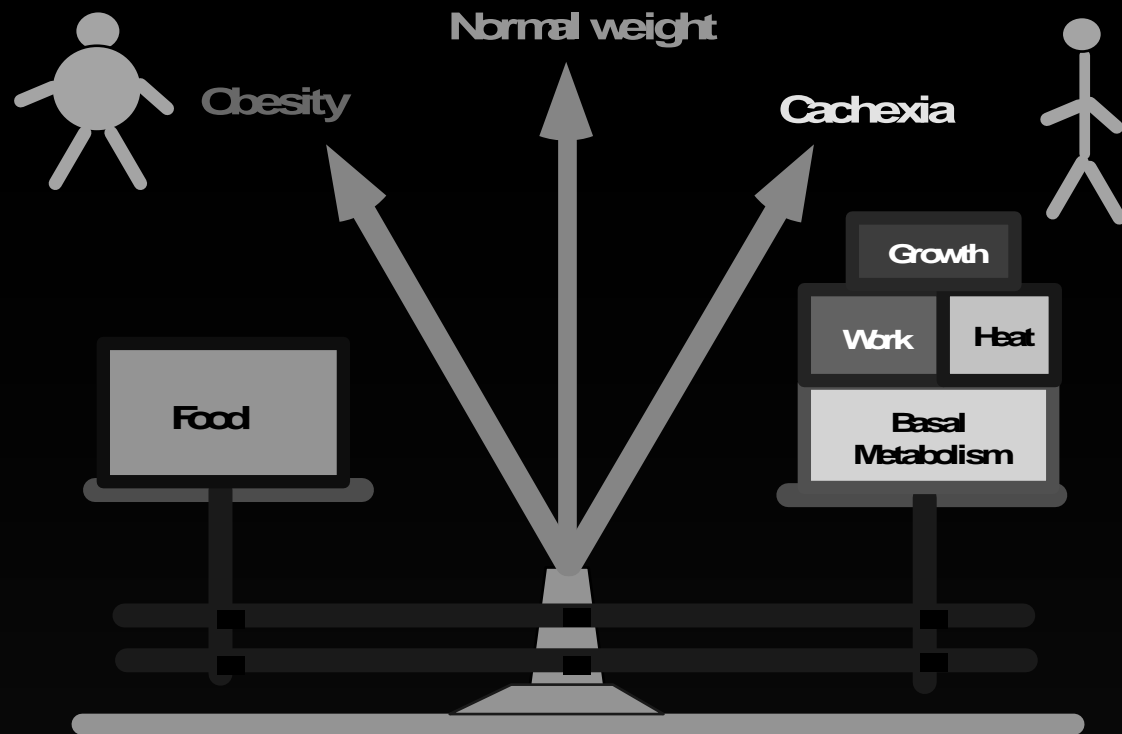
# A problem of energy balance

## Anorexia

*Reduced food intake*

**Metabolic alterations**

*Increased energy expenditure*



**TOTAL ENERGY EXPENDITURE  
(TEE)**

**BASAL METABOLIC RATE  
(REE)**

**DIET-INDUCED THERMOGENESIS  
(DIT)**

**PHYSICAL ACTIVITY  
(PA)**

$$\text{TEE} = \text{REE} + \text{DIT} + \text{PA}$$



# TOTAL ENERGY EXPENDITURE (TEE)

Healthy

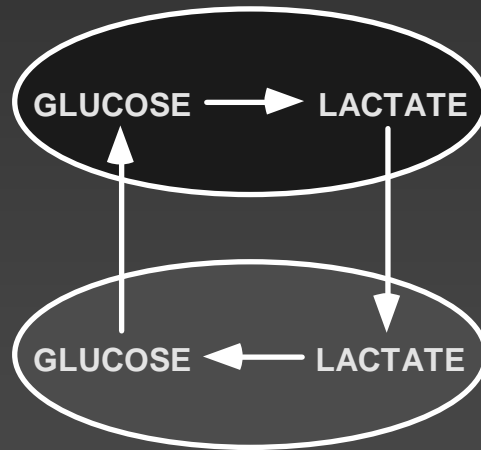


Cancer

**CACHEXIA**  $\rightleftharpoons$  **ENERGETIC INEFFICIENCY**

**FUTILE CYCLE  
ACTIVITY**

**TUMOUR**

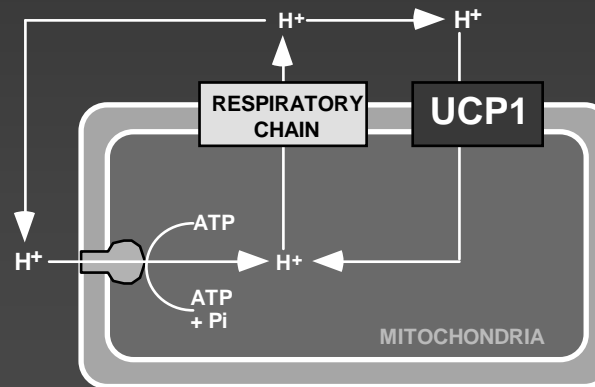


**LIVER**

**INCREASED  
THERMOGENIC ACTIVITY**

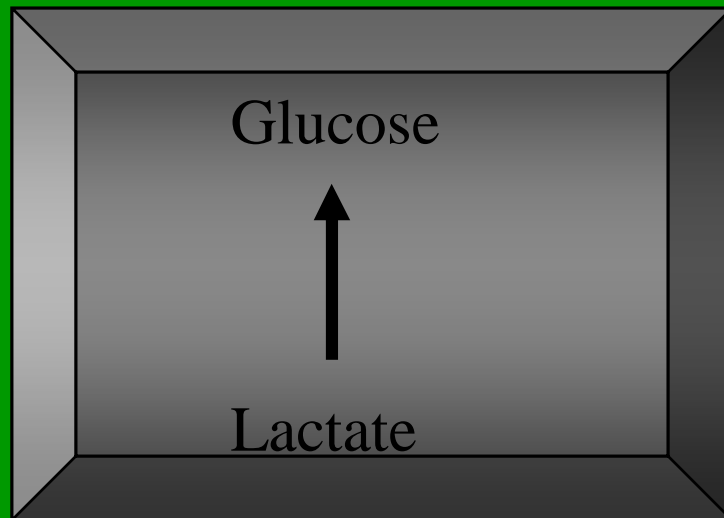
**UCP1 ACTIVITY IN BAT**

**OTHER UCPs (?)**



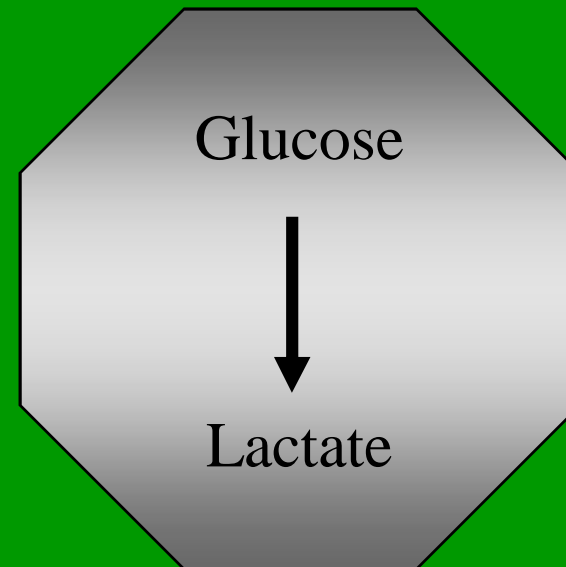
# Cori cycle (Tumour-Liver)

Liver



- 6 ATP

Tumour



+ 2ATP

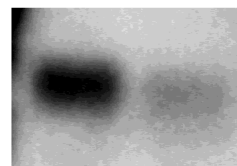
Energetic balance = - 2 ATP

# The UCP Family

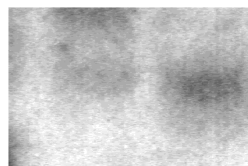
<b>UCP1</b>	<b>Brown adipose tissue (BAT)</b>
<b>UCP2</b>	<b>Ubiquitous</b>
<b>UCP3</b>	<b>Skeletal muscle and BAT</b>
<b>UCP4</b>	<b>Neural tissues</b>
<b>UCP5</b>	<b>Neural tissues (BMCP-1)</b>

9 9  
9 9  
0 0  
0 0  
1 2

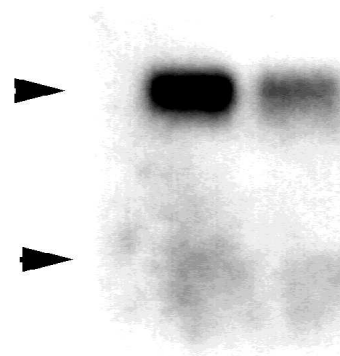
ucp3



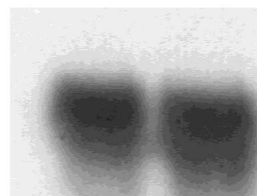
ucp2



ub



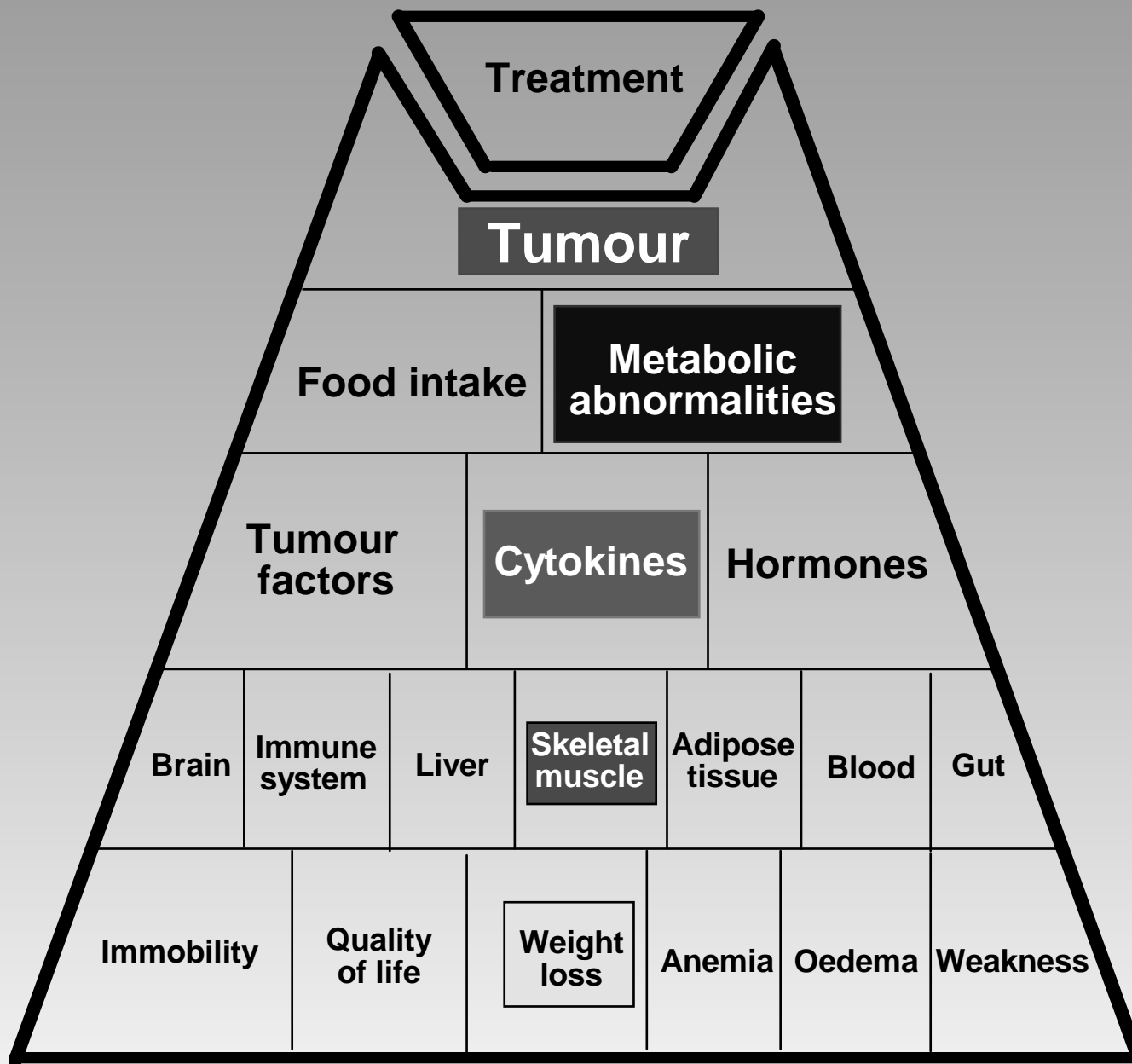
18s



# **Multiorgan syndrome**

## **Systemic disorder**

# The Cachexia Pyramid



# Mechanisms



# Anorexia

# **Molecules involved in cancer anorexia ??**

**Cytokines**

**Circulating hormones**

**Neuropeptides**

**Neurotransmitters**

**Amino acids**

**Tumour-derived factors**

**Anorexigenic  
Neuropeptide**

**Neurotensin**

**CART**

**GLP-1**

**Melanocortin**

**CRF**

**Orexigenic  
Neuropeptide**

**MCH**

**Orexin**

**Galanin**

**Opioid**

**NPY**

**Food intake ↑  
E expenditure ↓**

Blood

Vague  
nerve

Blood-brain barrier

**Glucagon**

**Leptin**

**CCK**

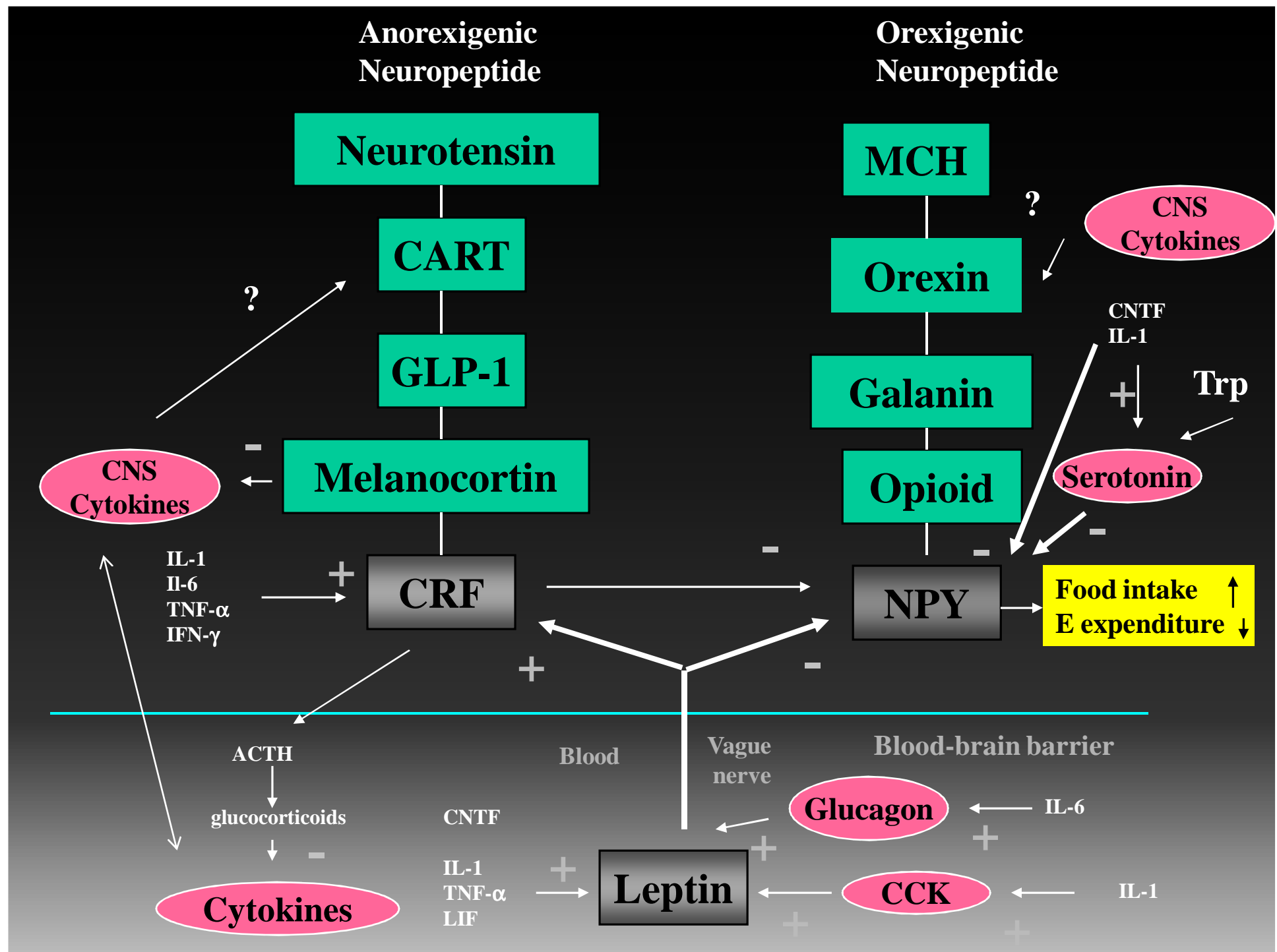
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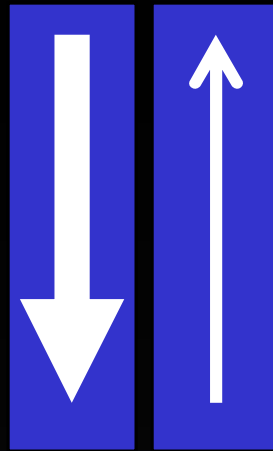
# Metabolic alterations

*Skeletal muscle*

# CANCER CACHEXIA

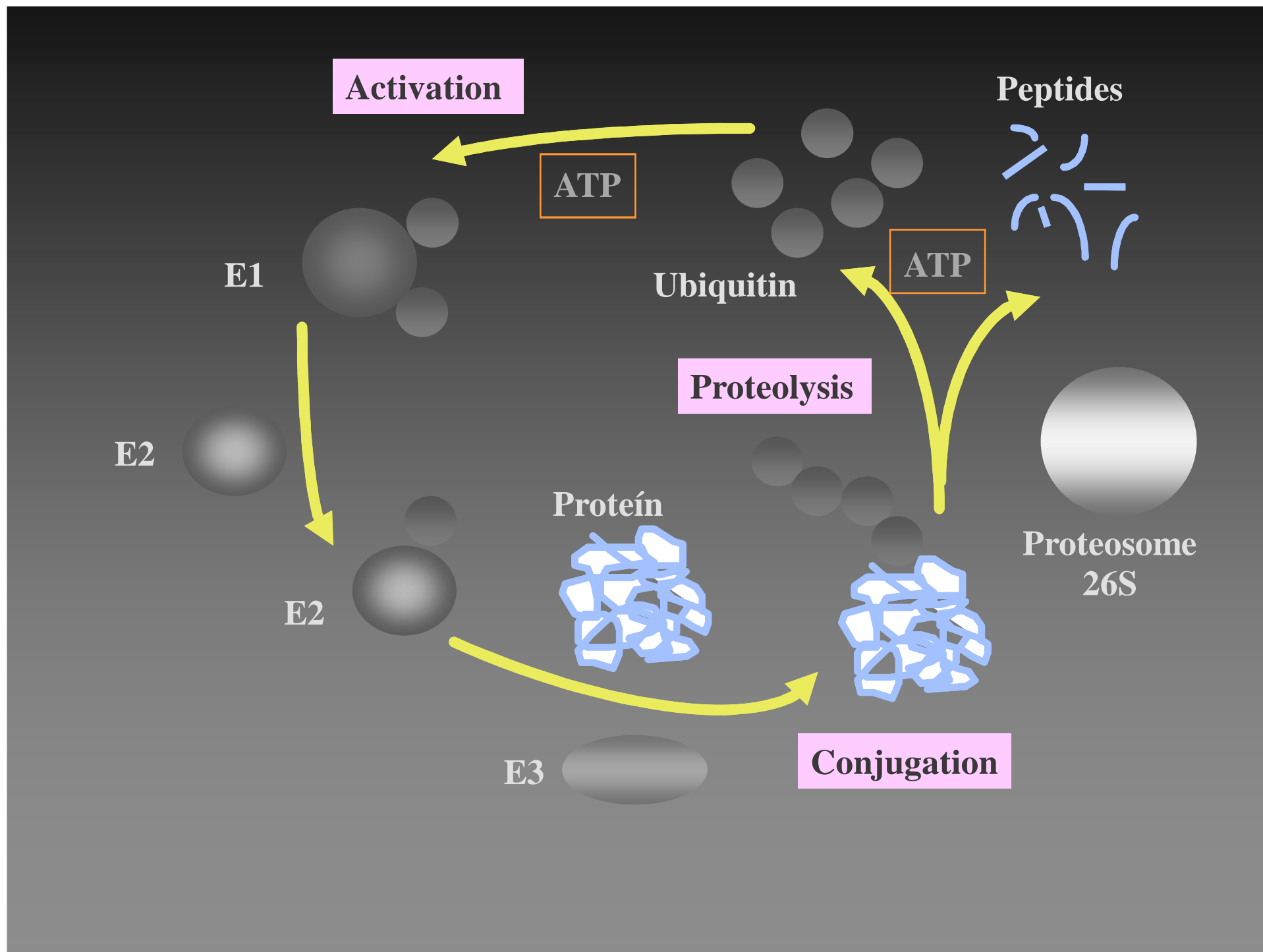
PROTEIN

$K_d$

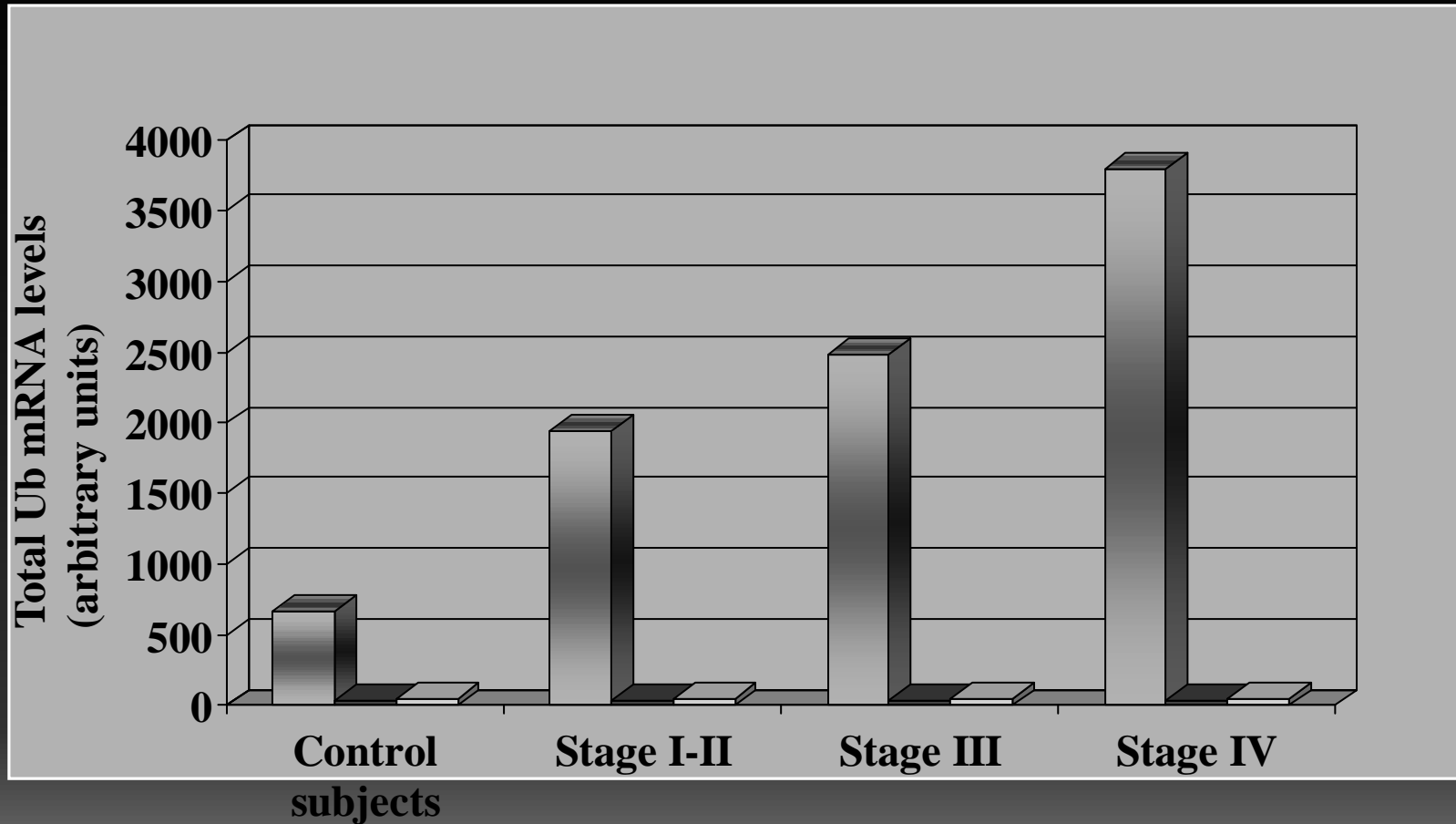


$K_s$

AMINO ACIDS



# Ubiquitin mRNA levels in skeletal muscle of gastric cancer patients



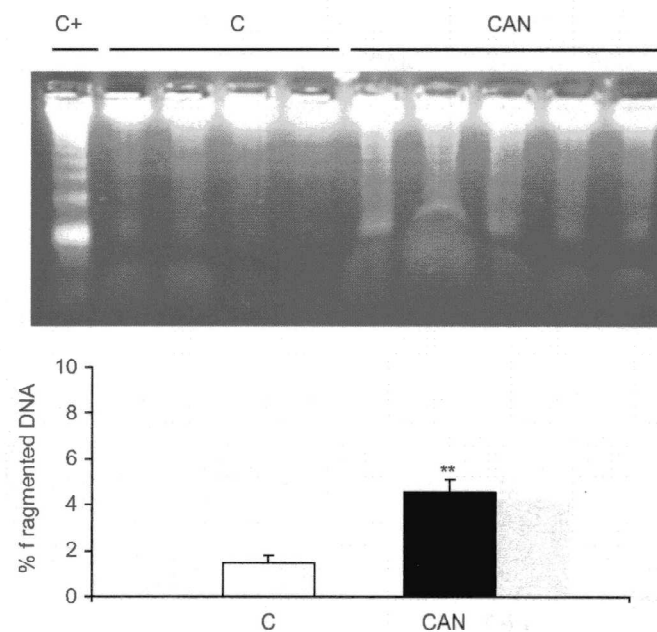
Patients lost 5.57% of body weight (n= 20)

Bossola et al. American Journal of Physiology 280: R1518-R1523 (2001)



# Apoptosis

# *Apoptosis in gastro-intestinal cancer patients*



**Figure 1** Skeletal muscle apoptosis in cancer patients. For further details, see the Materials and methods section. DNA fragmentation was assessed by monitoring the laddering in an agarose gel. The results are expressed as % of DNA fragmentation. The results are mean values  $\pm$  S.E.M. of a minimum of five samples. C+: 40  $\mu$ g of liver DNA from anti-Fas-treated mice (positive control). C: control group, CAN: cancer patients. Values that are significantly different by the Student's *t*-test from the non tumour-bearing patients are indicated by \*\**p*<0.01.

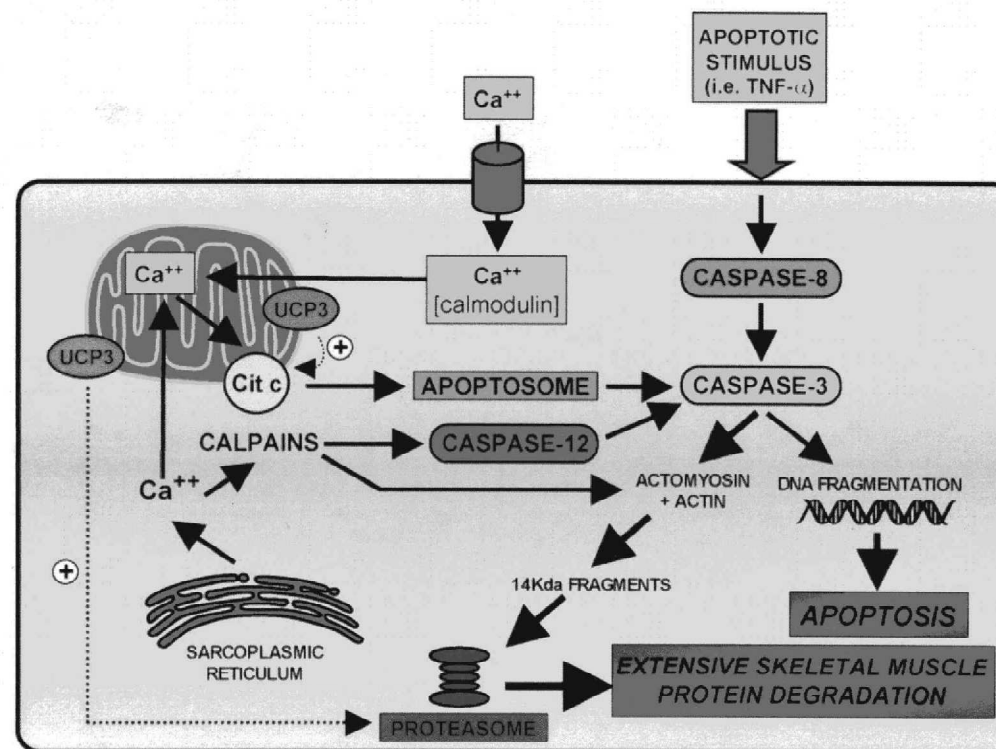
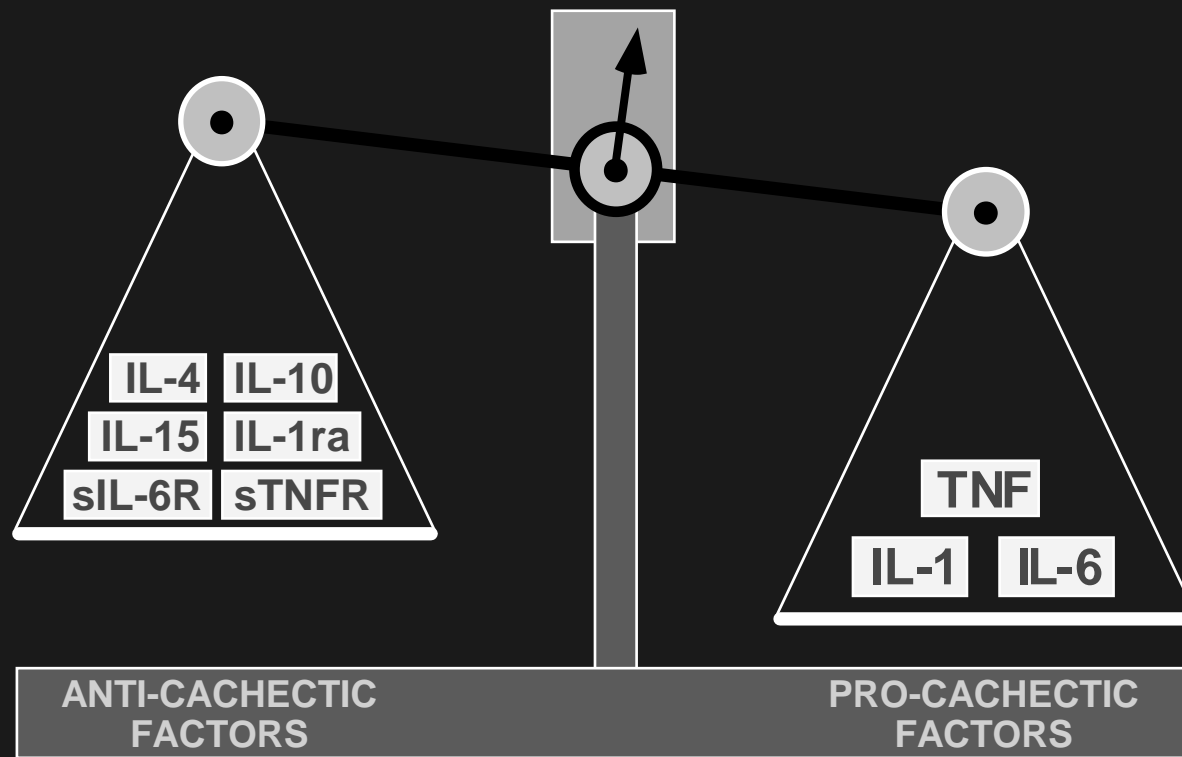


Fig. 1. Caspase-3: apoptosis and protein degradation signalling.

# Mediators



# Signaling

**SIGNALS**



**TRANSDUCTION PATHWAYS**  
**???**



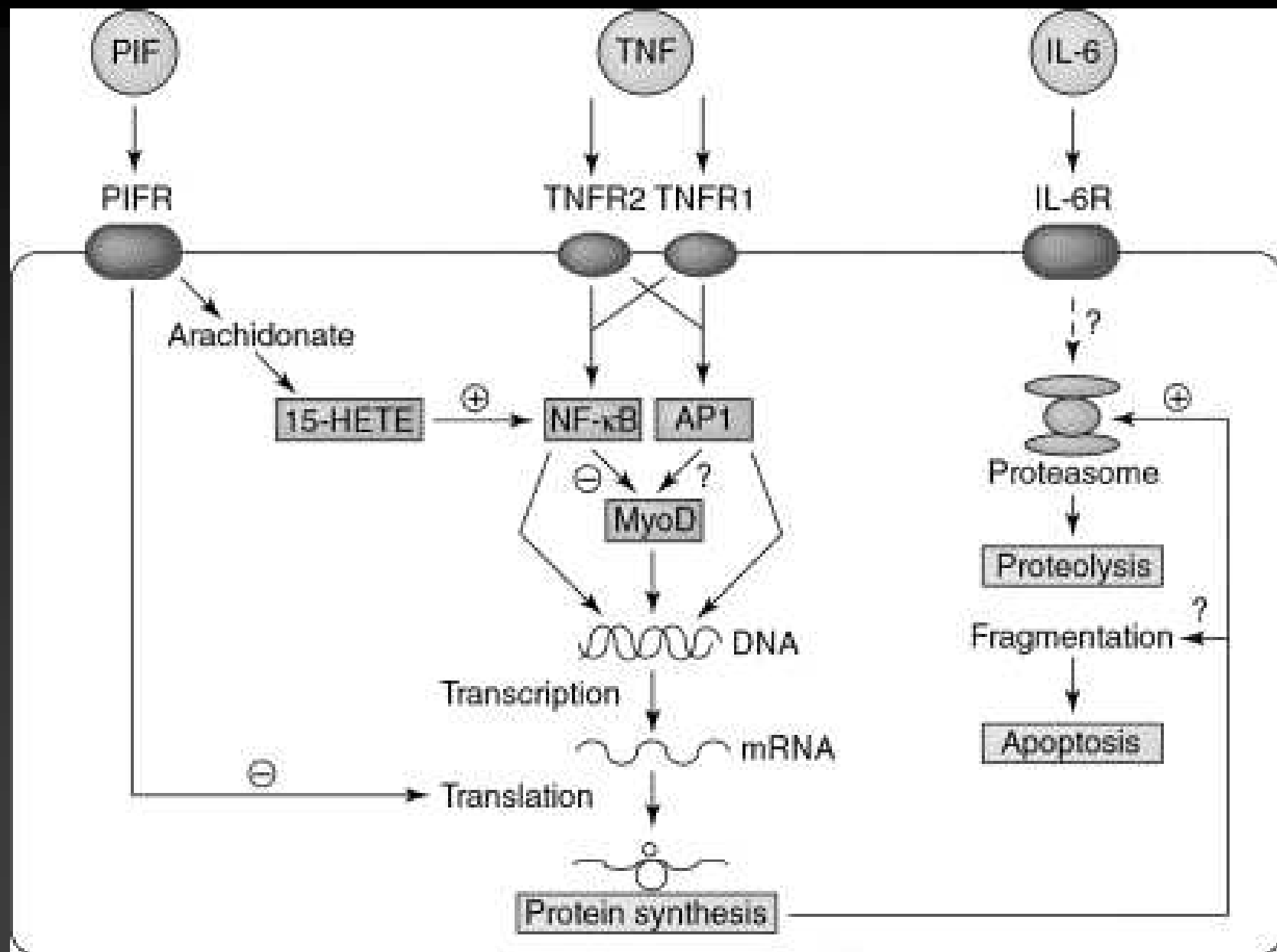
**EFFECTS**



**MUSCLES**



**LIVER**





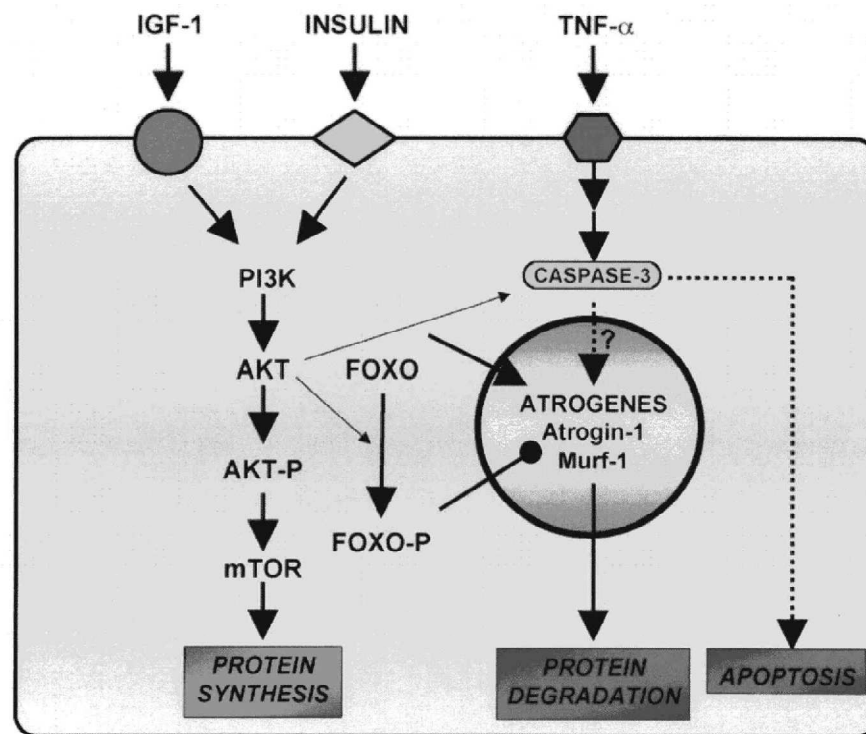


Fig. 2. The role of PI3K in signalling protein turnover in skeletal muscle.

# CACHEXIA

TNF & other cytokines

UCP 3



NF-KB, AP-1

ROS

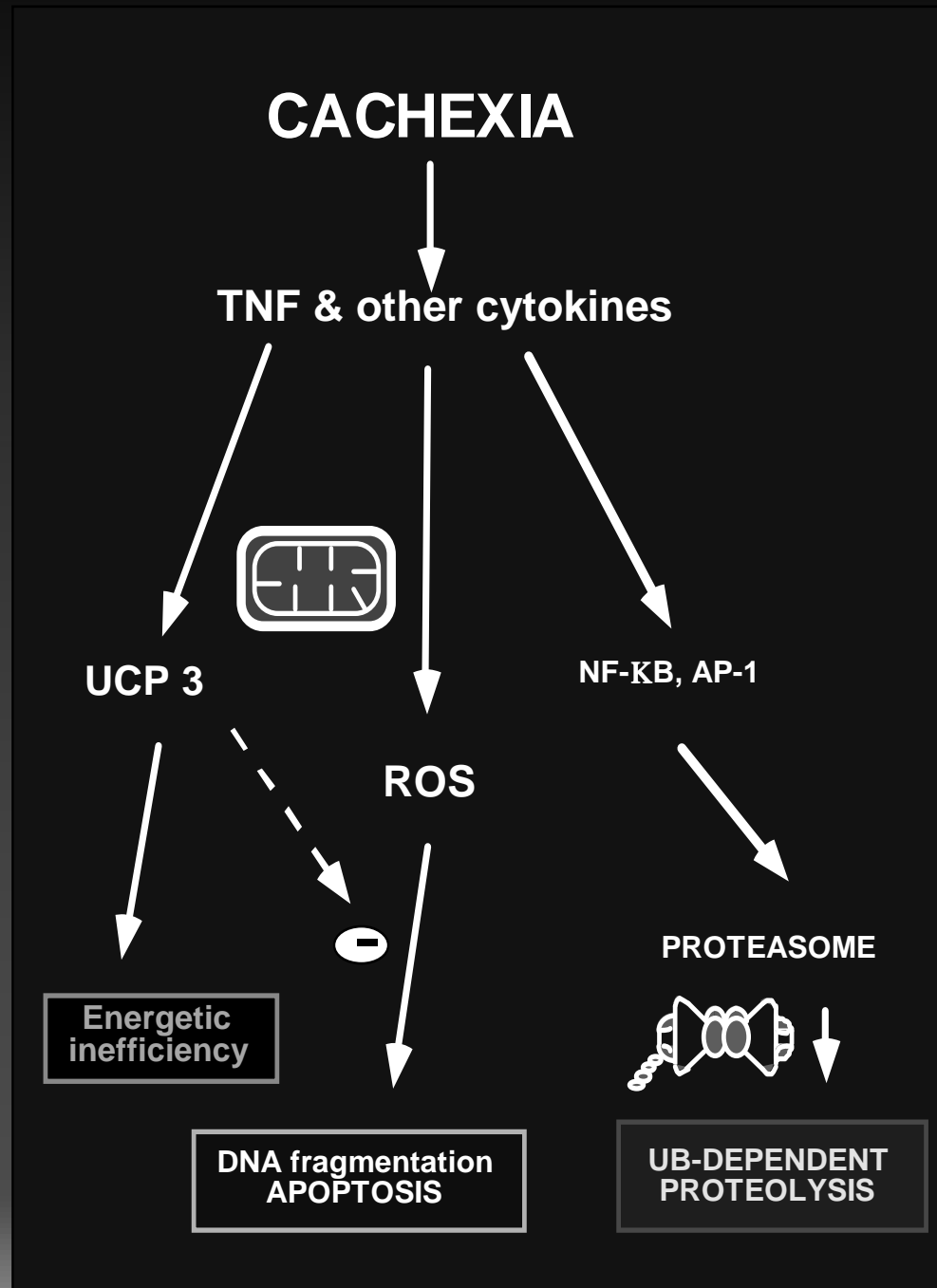
Energetic  
inefficiency

PROTEASOME



DNA fragmentation  
APOPTOSIS

UB-DEPENDENT  
PROTEOLYSIS



***Intervention?***

# ***Developing cancer-specific nutritional approaches***

## ***Objectives***

**Increase body weight**

**Stimulate food intake**

**Decrease inflammation**

**Decrease energy expenditure**

**Enhance absorption/Gastric emptying**

**Preserve LBM (anabolic + anticatabolic)**

**Enhance QoL**

**Control cancer**

**Promote health**



 **5<sup>th</sup> CACHEXIA  
CONFERENCE**  
*Barcelona 5-8 December 2009*

**1<sup>st</sup> ANNOUNCEMENT**

TOPICS:

- Cachexia in many illnesses
- Cachexia versus sarcopenia
- Physiology and biochemistry of cachexia
- Therapy

**Abstract submissions are welcome**

- Online submission open from May 1, 2009
- Deadline September 15, 2009
- Poster presentation
- Poster awards

*The conference is CME-certified*

For further information visit [www.cachexia.org](http://www.cachexia.org)

**Thank you!**