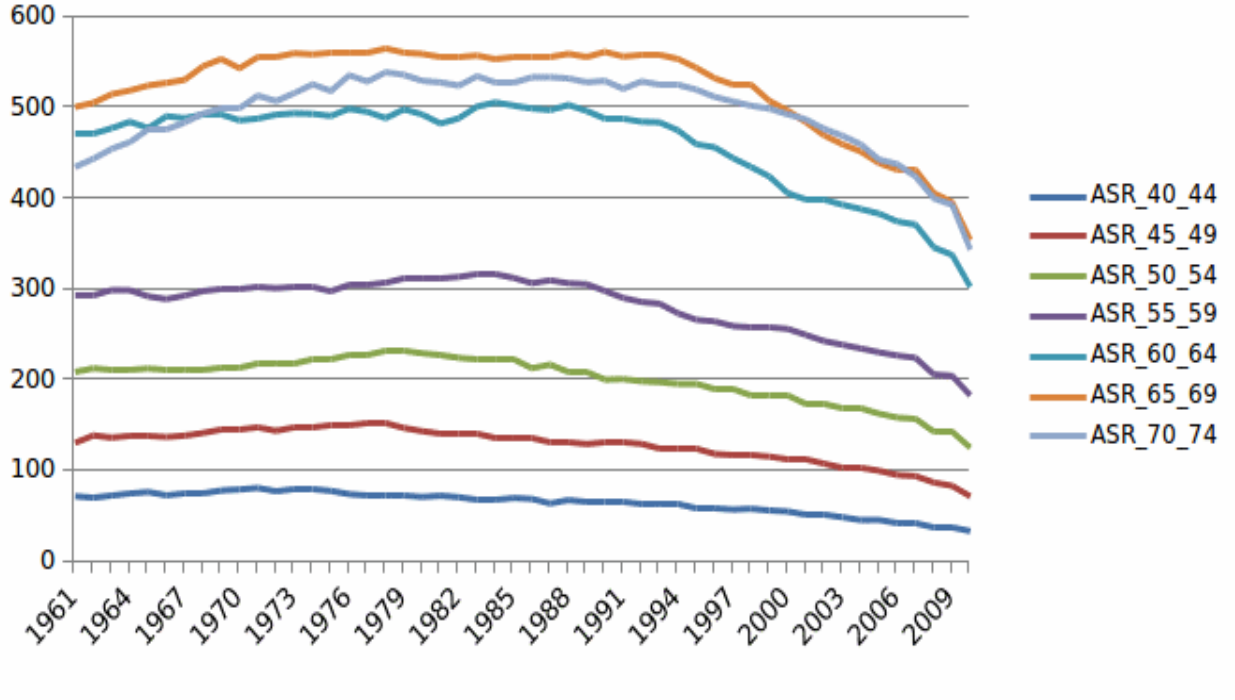
Will metastatic cancer be a curable disease ?

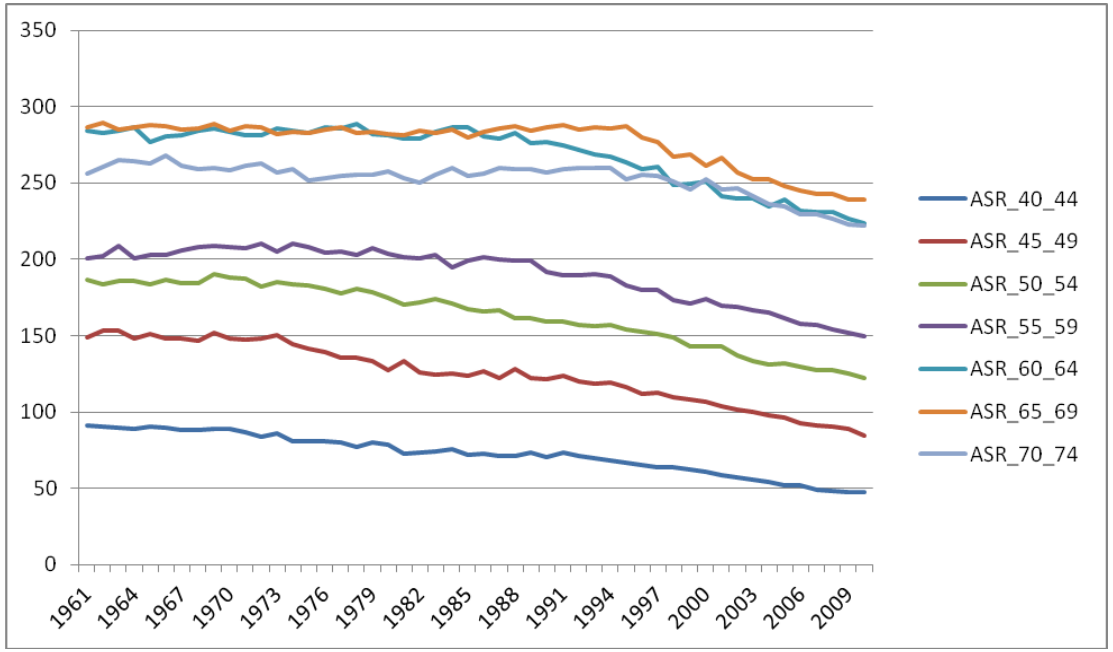
Cancer Treatment is not a success (so far..)

Overall cancer mortality, Age standardized ratio by age class in 19 western countries

MEN

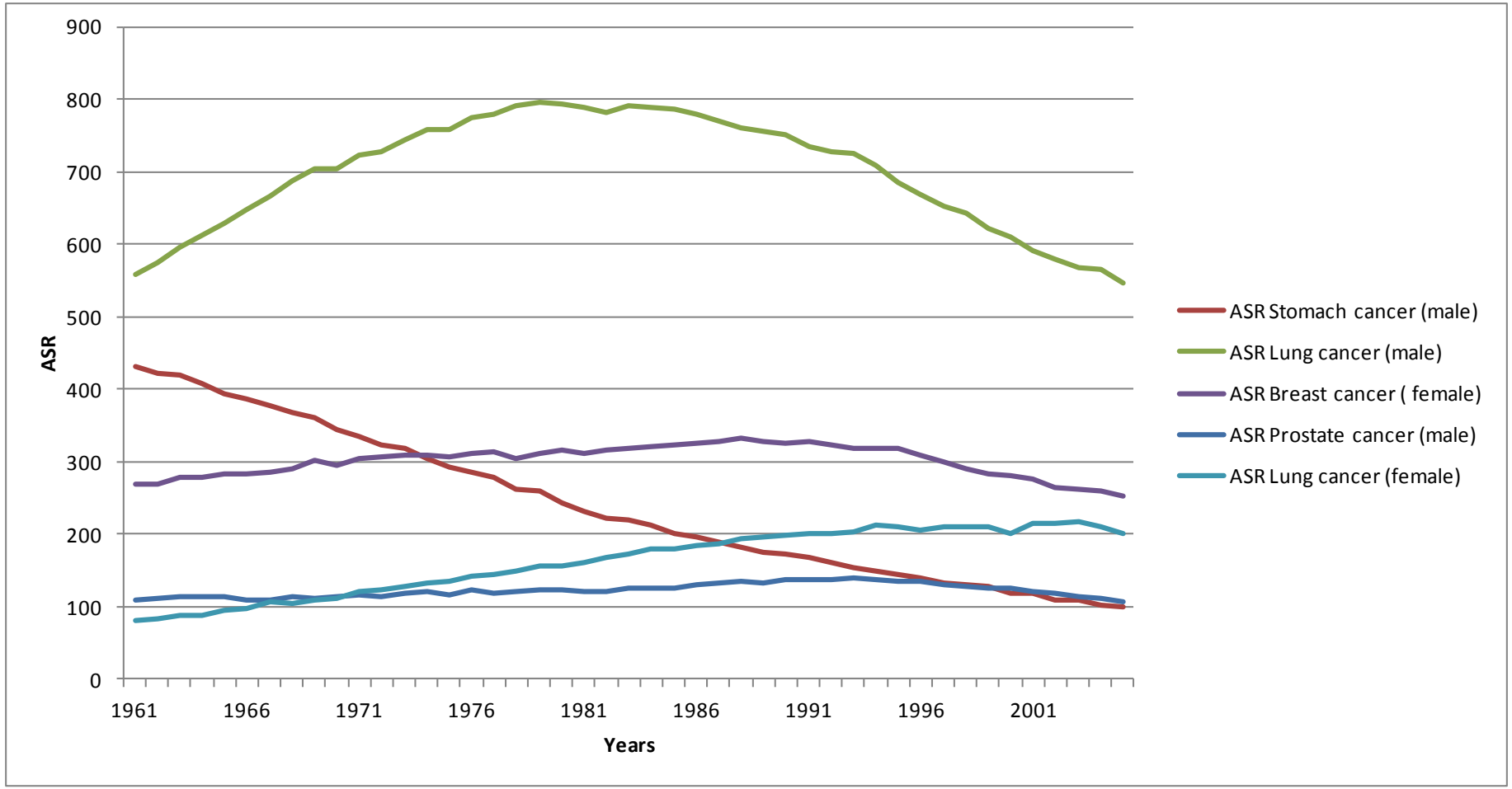


WOMEN



Summa et al. Submited

Age standardized ratio by cancer site in 19 countries



What is Cancer?

Cancer phenotype: Invariants

1- Increased pressure

2- Fractal shape

3- Increased glucose uptake

4- Intracellular alkalosis

What is Cancer?

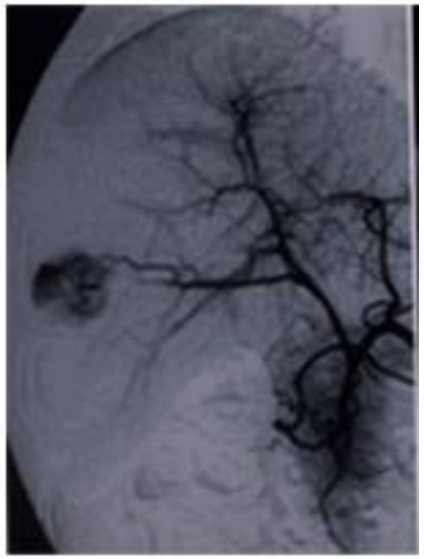
Cancer phenotype: 1 - Increased pressure

Measured Interstitial Pressures

Site Measured	Pressure (mmHg)
Normal Parenchyma	4
Cirrhosis	13
Primary Hepatic Tumor	25-26
Metastatic Hepatic Tumor	15-22

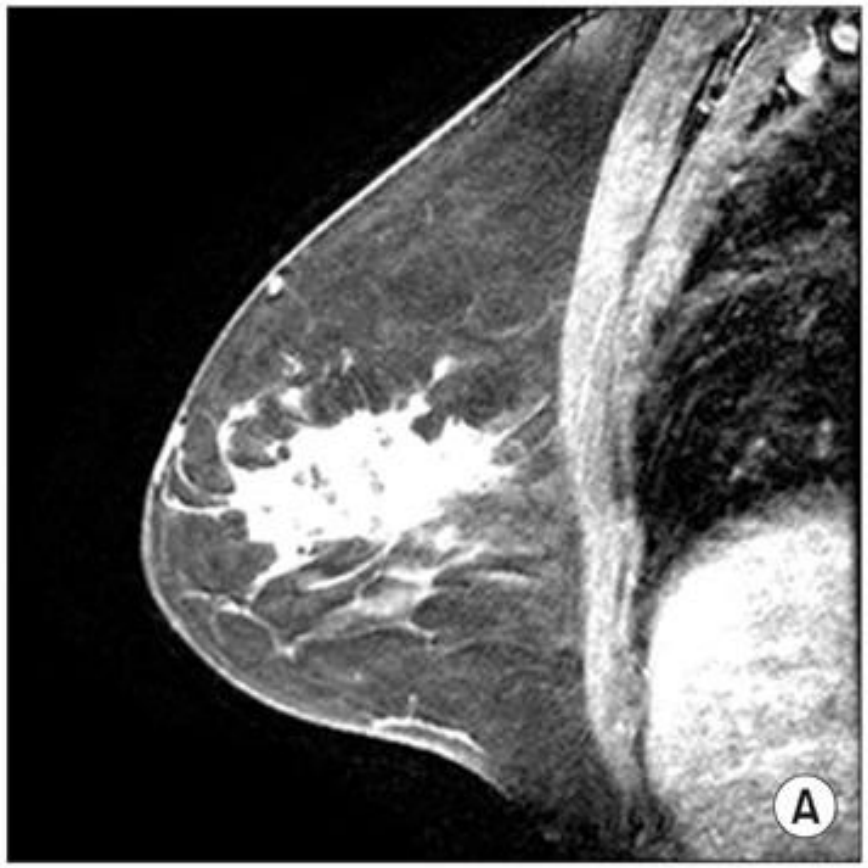
Interstitial Pressures compared to vascular pressures

Site	Pressure (mm Hg)
Tumor	15-26
Portal Vein	4
Mean Arterial	137



What is Cancer?

Cancer phenotype: 2 – Fractal shape

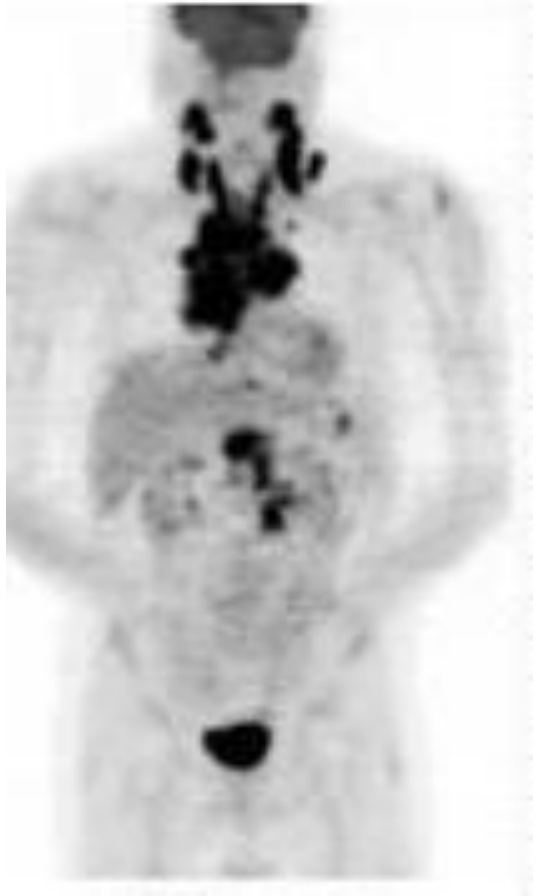


Fractal image of a breast carcinoma

Fleury et al., « Fractal » 2003

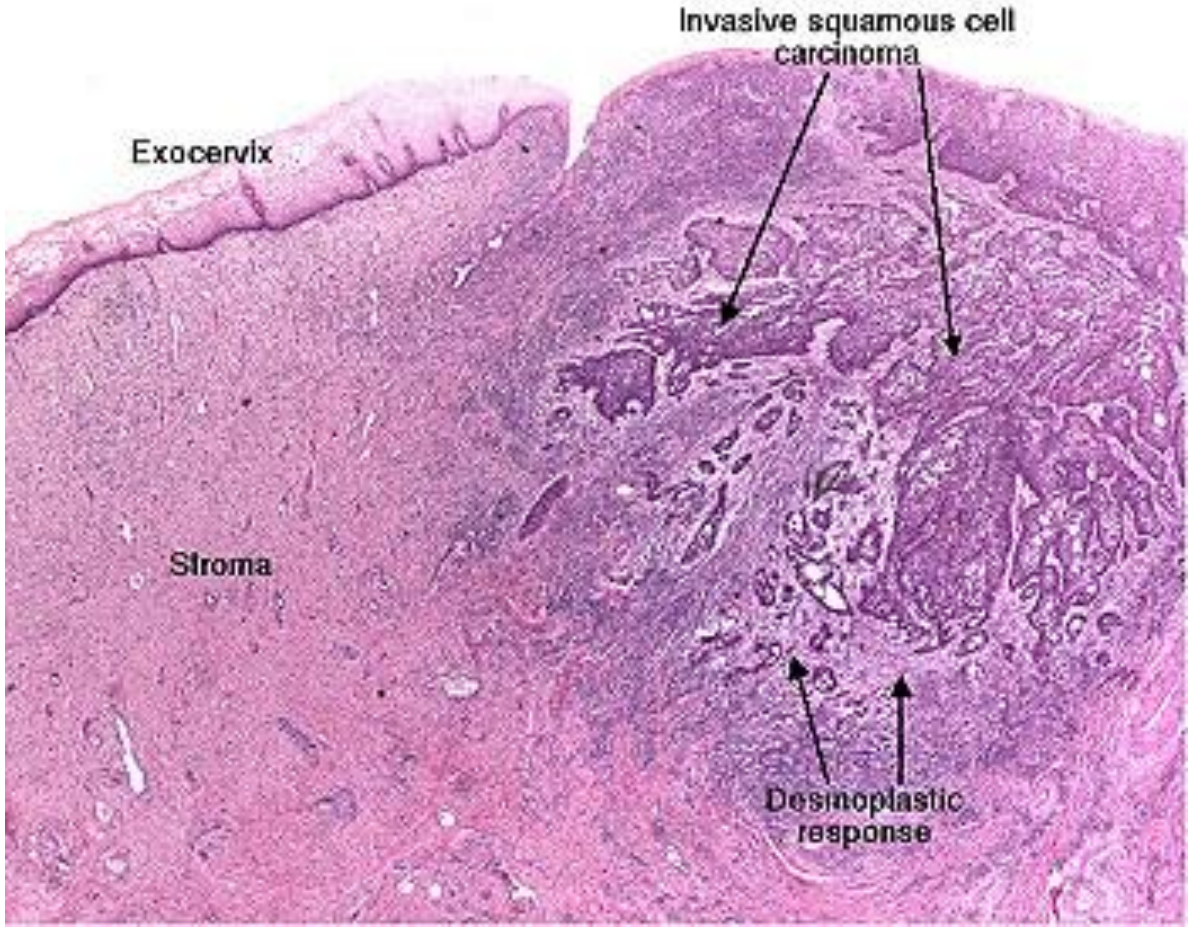
What is Cancer?

<u>Cancer phenotype</u>: 3 – Increased glucose uptake



Pet Scan

Cancer phenotype: 4 – Intracellular alkalosis

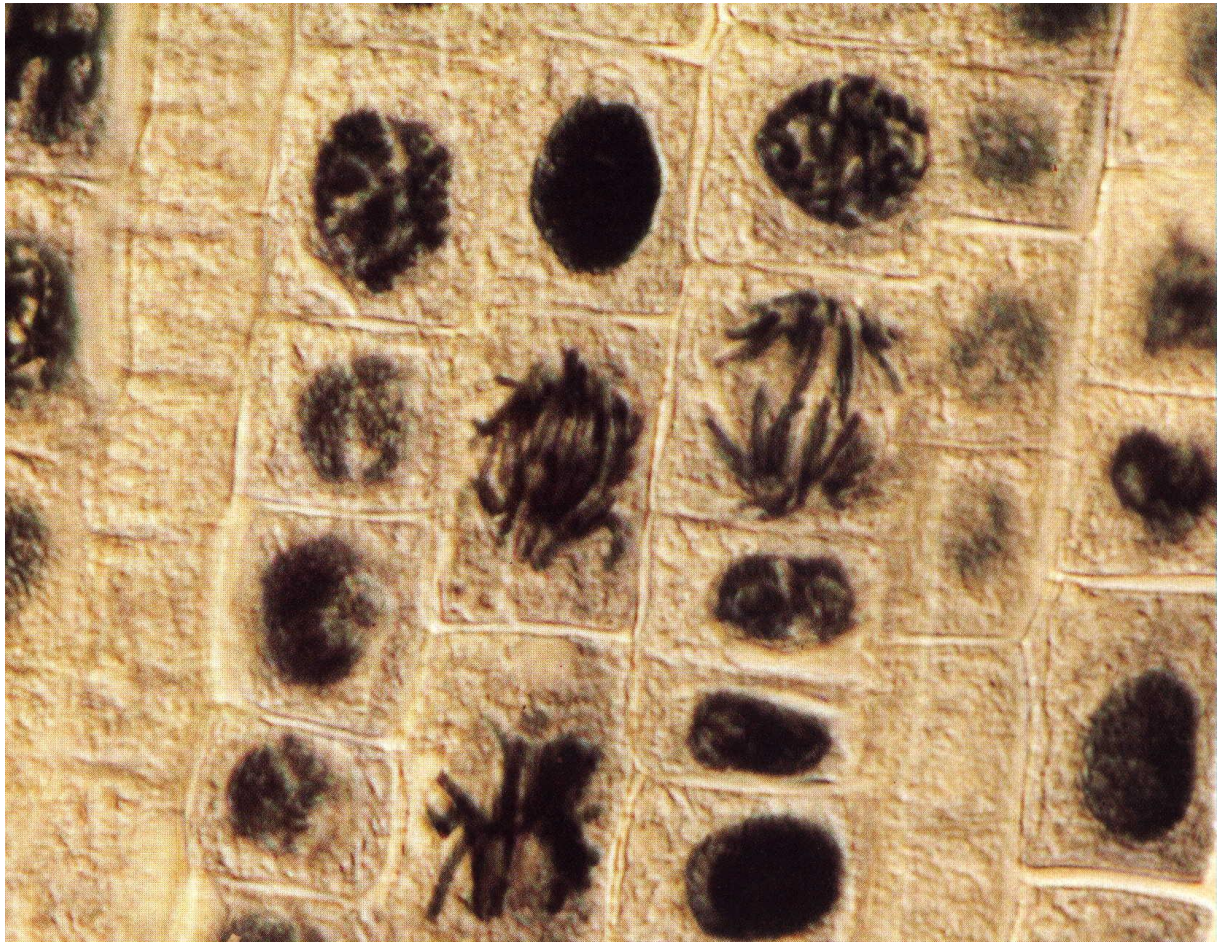


Hematoxylin and eosin stains are a pH based phenomenon

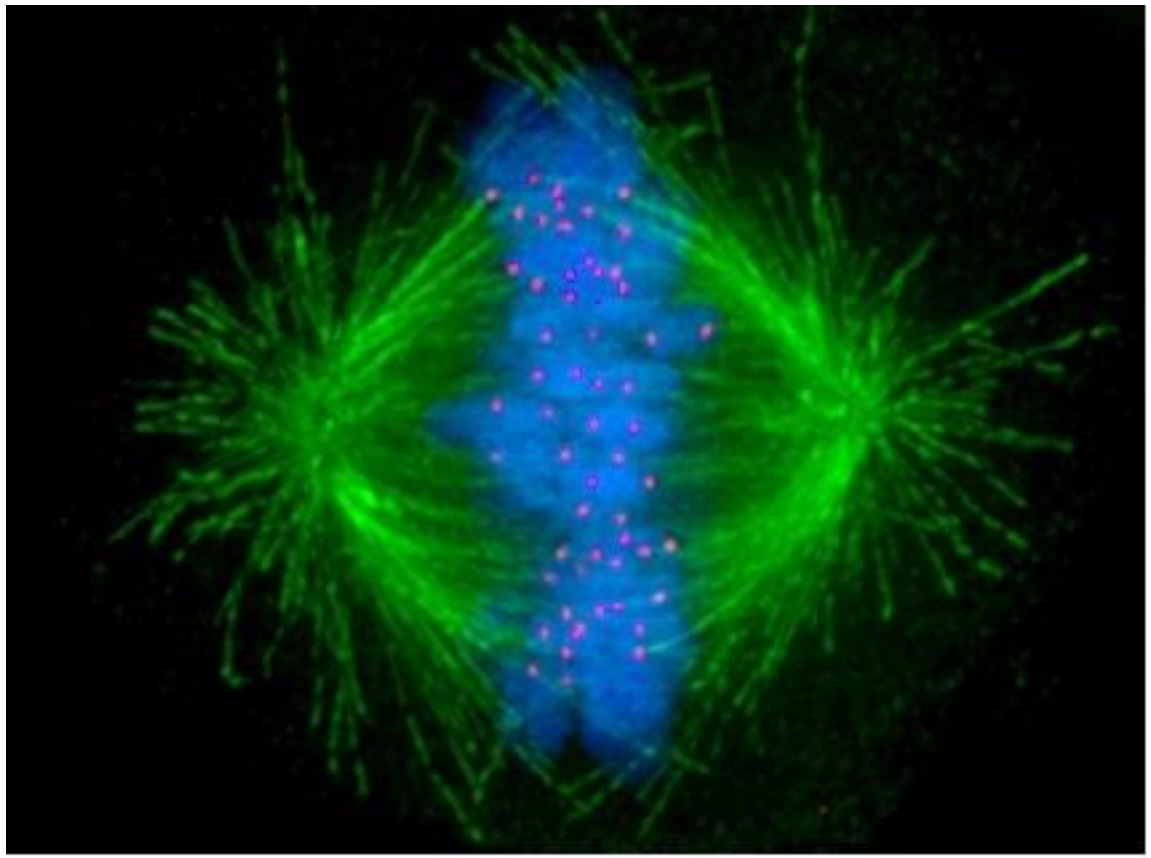
Cancer : between glycolysis and physical constraints.

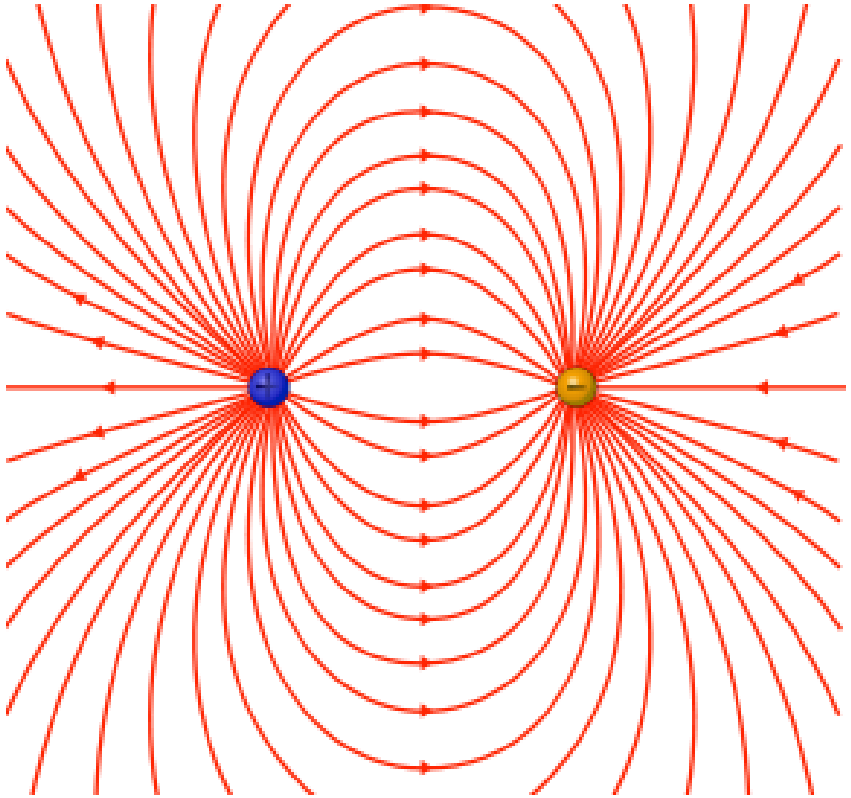
L. Schwartz Springer 2004

Cell Mitosis



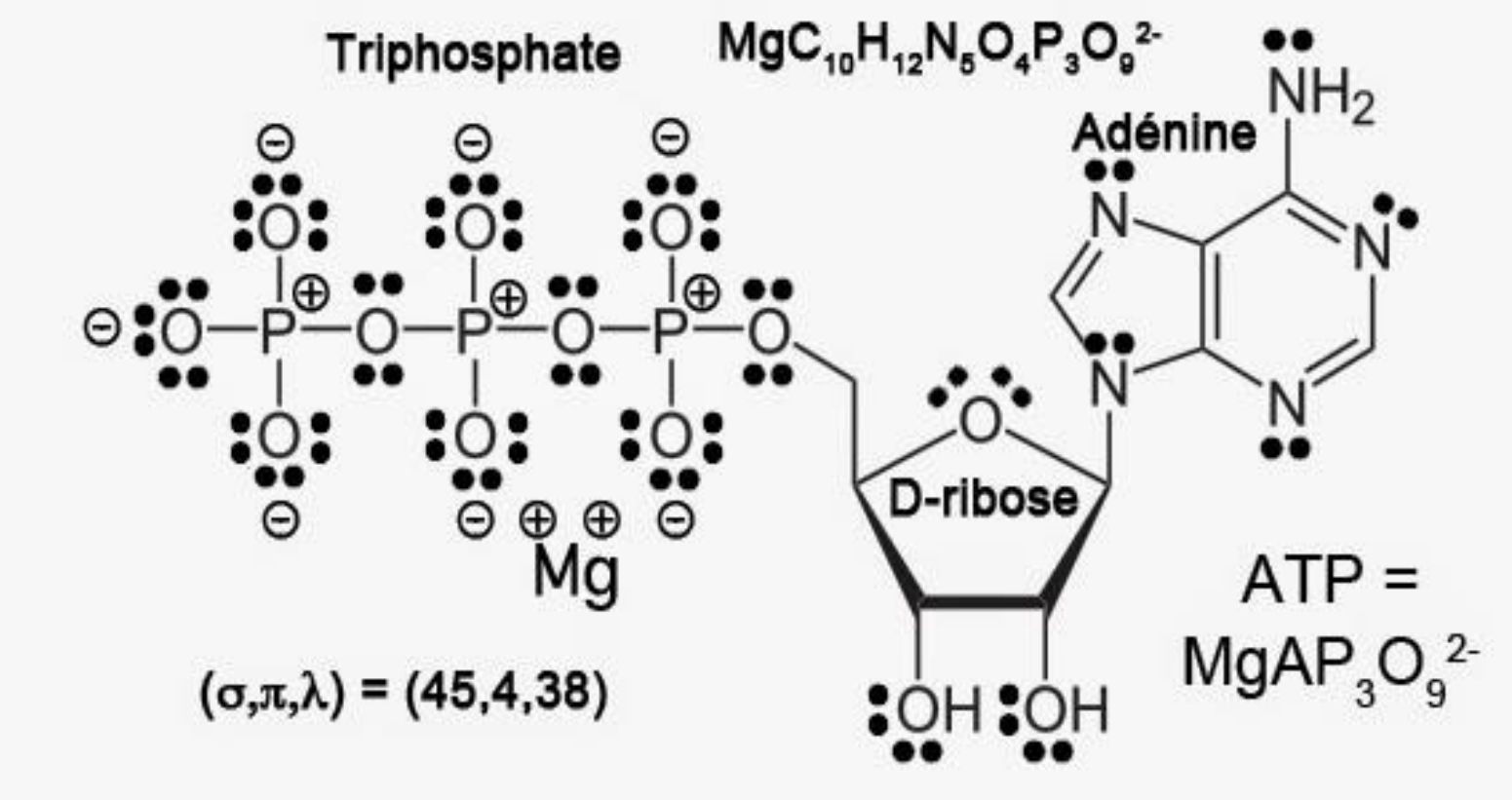
The cell is an electrical machine





Bioenergetics of Cell Metabolism

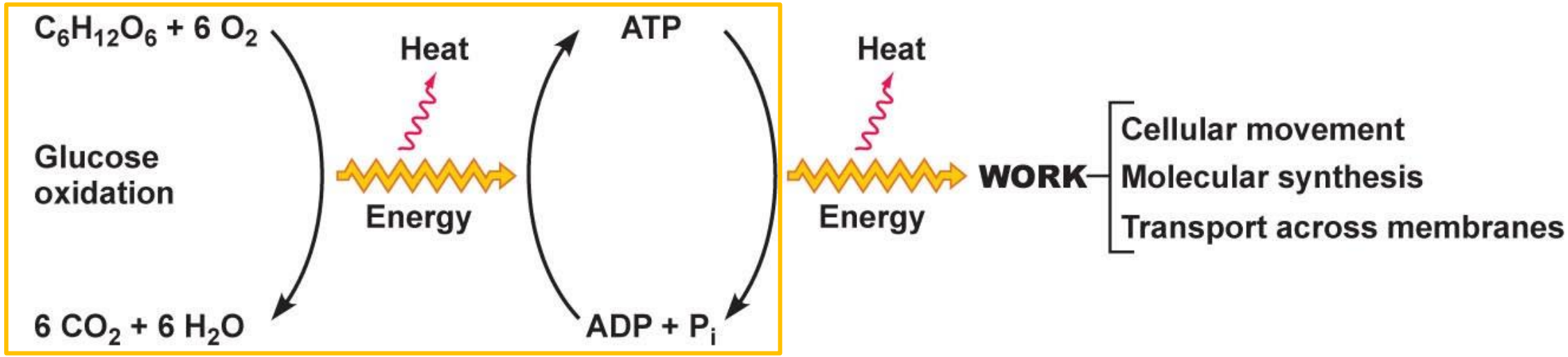
Adenosine triphosphate (ATP) : the energetic currency exchange



Wikipedia_image

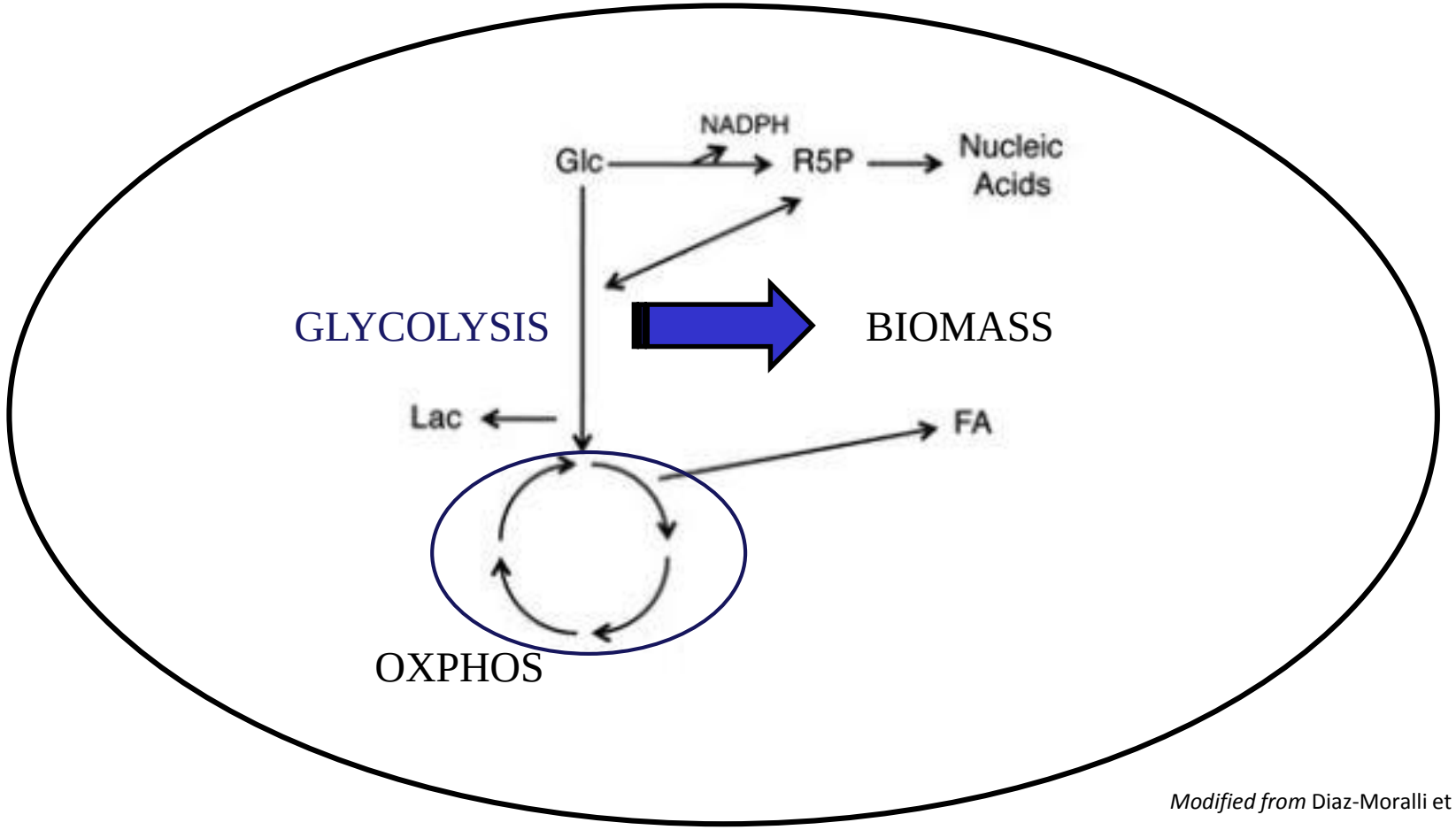
Bioenergetics of Cell Metabolism

ATP hydrolysis is the **molecular motor** of Life.



Glycolysis vs. Oxidative phosphorylation

The **central carbon metabolism** (CCM) oscillates between **biomass** and **energy** synthesis and times cell division.



Modified from Diaz-Moralli et al. (2013)

Glycolysis vs. Oxidative phosphorylation

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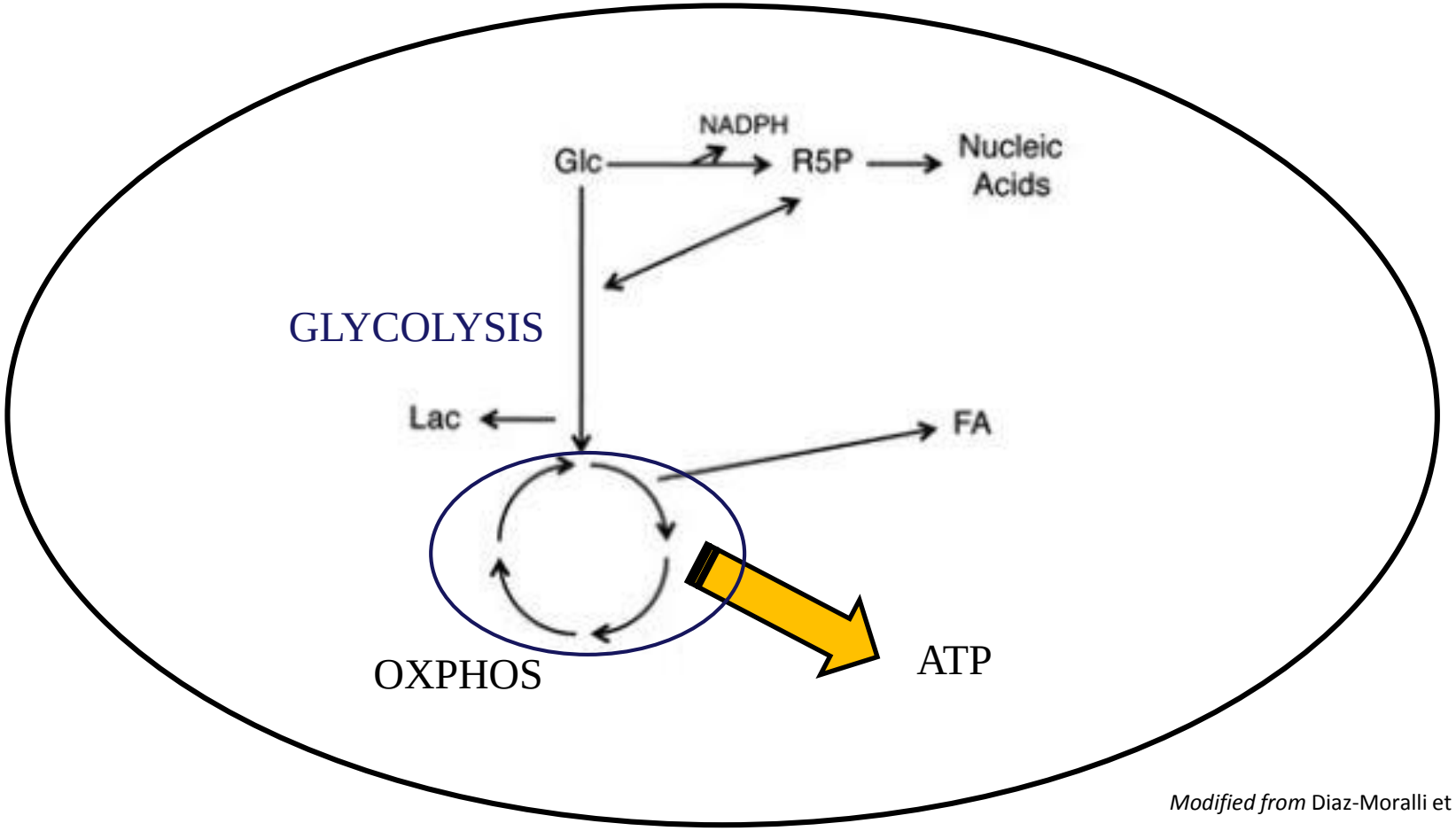
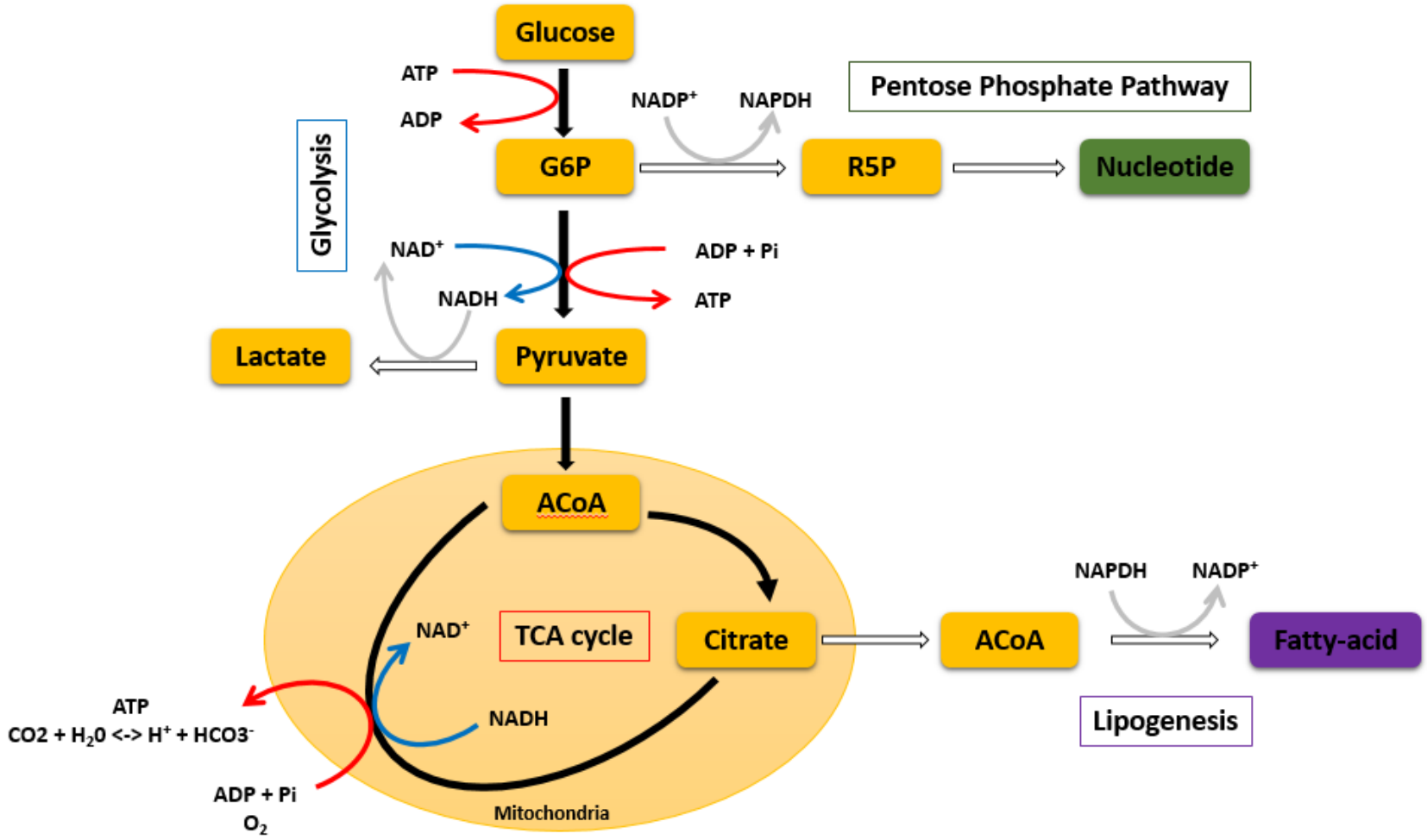


Modified from Diaz-Moralli et al. (2013)

Differentiated Cells

Differentiated cells have an **oxidative metabolism** based on **mitochondrial respiration** and **energy synthesis (ATP)**



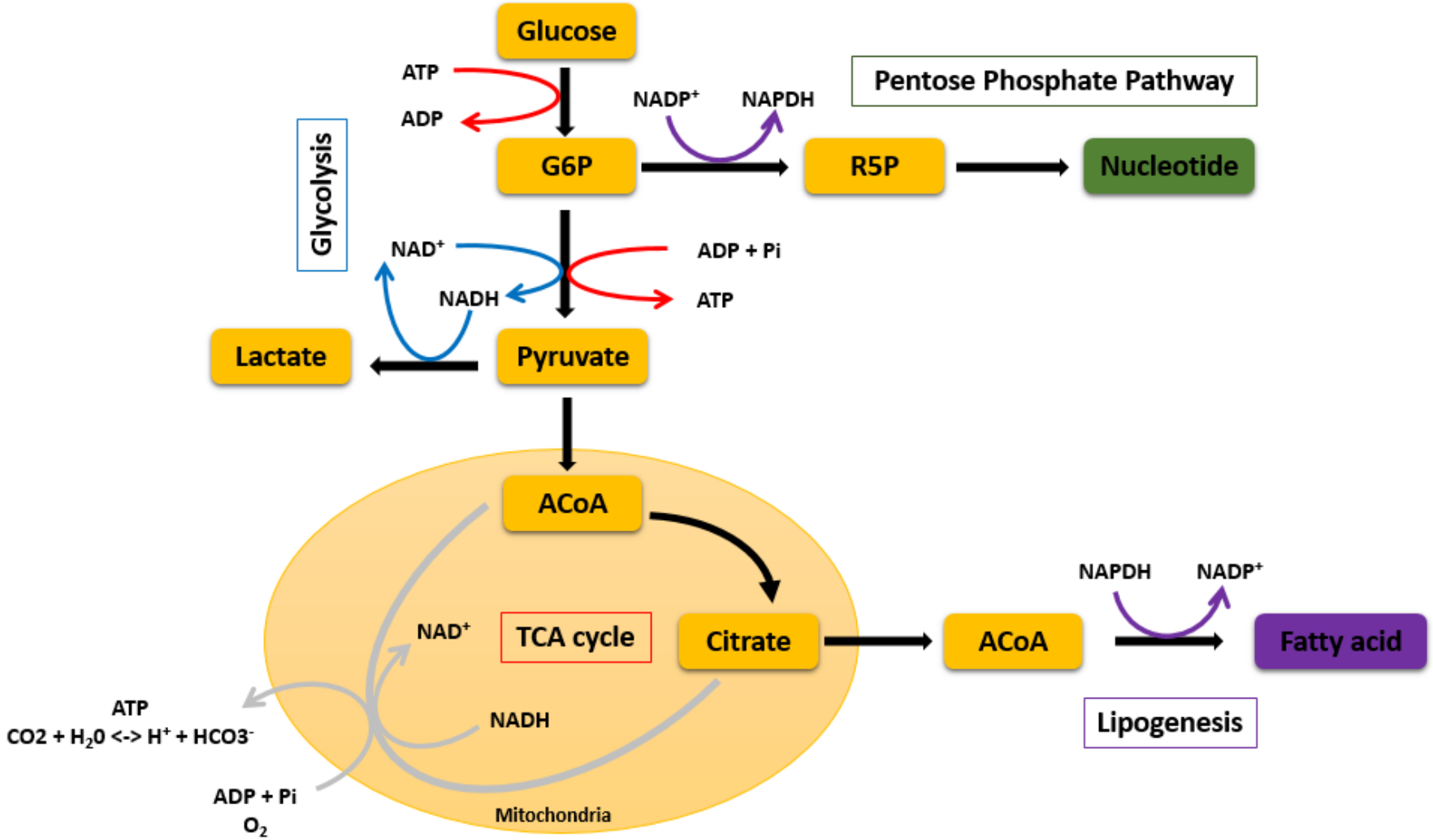
Differentiated Cells

- ATP = 9 pmol
- Acidic pH = 6.8
- NAD+/NADH ratio = 8-10

➢ **Differentiated cells** have an **oxidative metabolism** based on **mitochondrial respiration** and **energy synthesis (ATP)**

Proliferating Cells

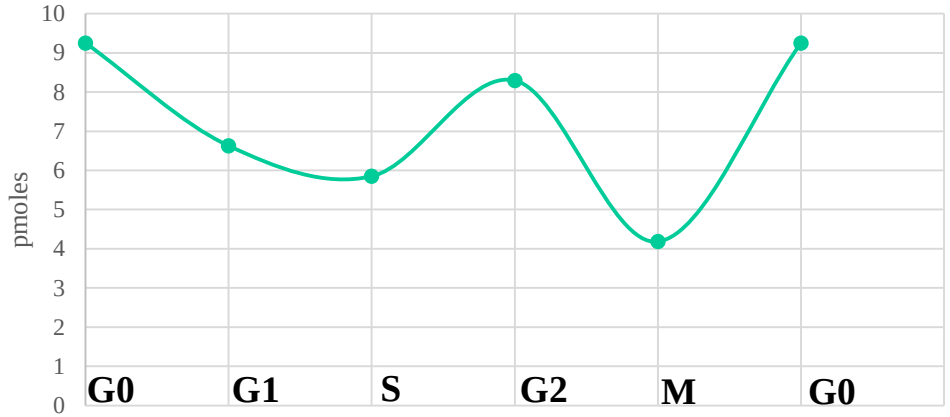
Rapidly **proliferating cells** have a **glycolytic metabolism** based on **glucose fermentation** and **biomass synthesis**



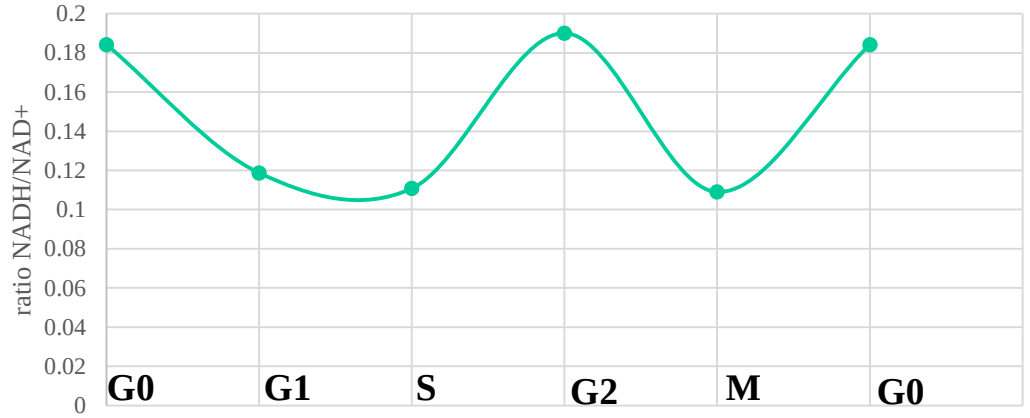
Intertwined redox oscillators

In the case of normal cells

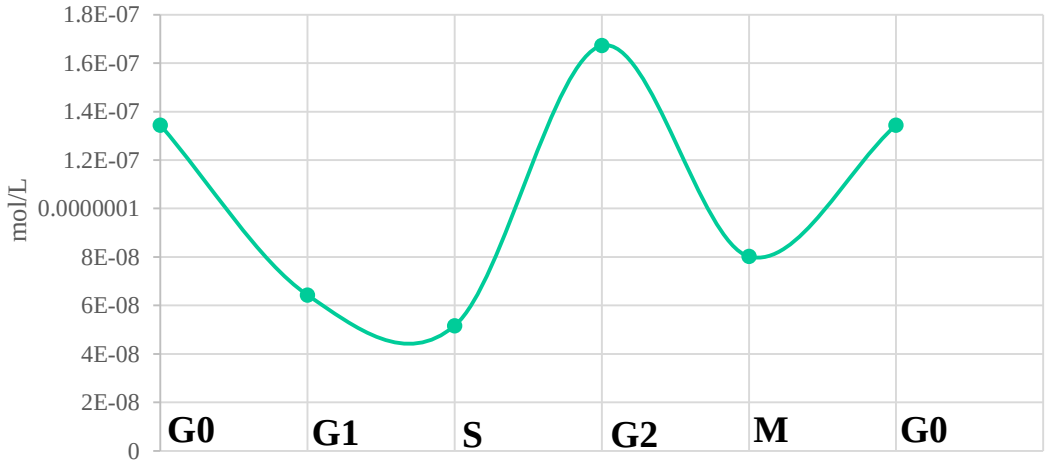
[ATP]



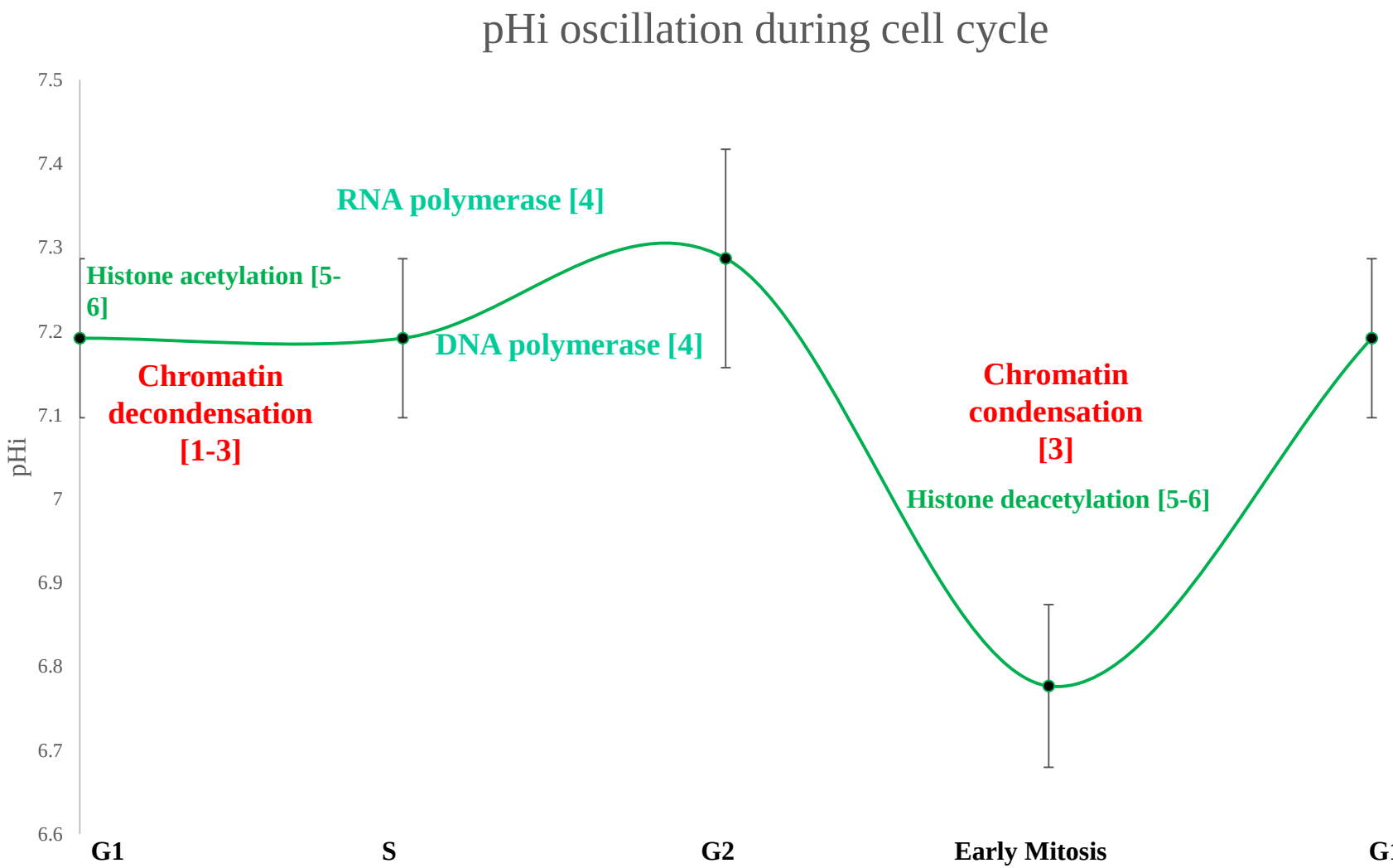
NADH/NAD+



[H+]



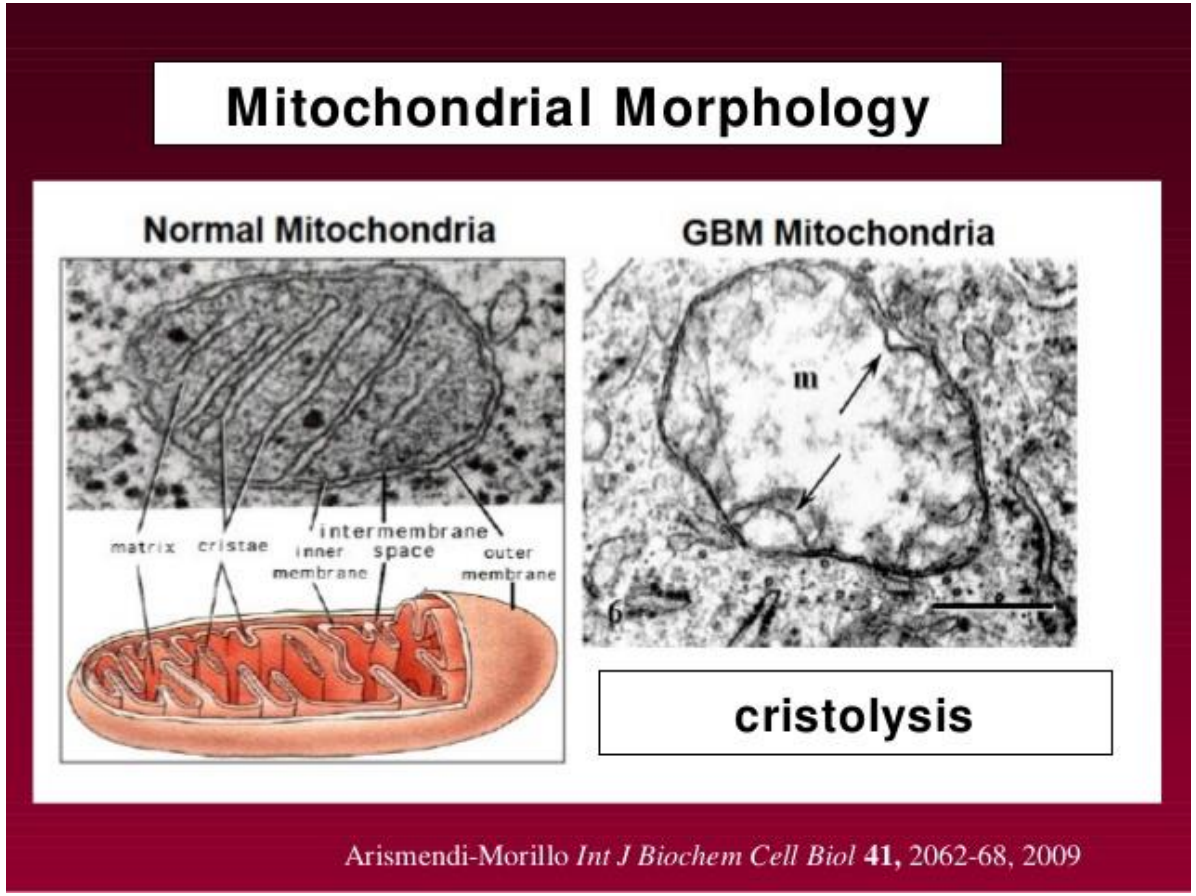
3. pHi Oscillation Regulates Cell Cycle



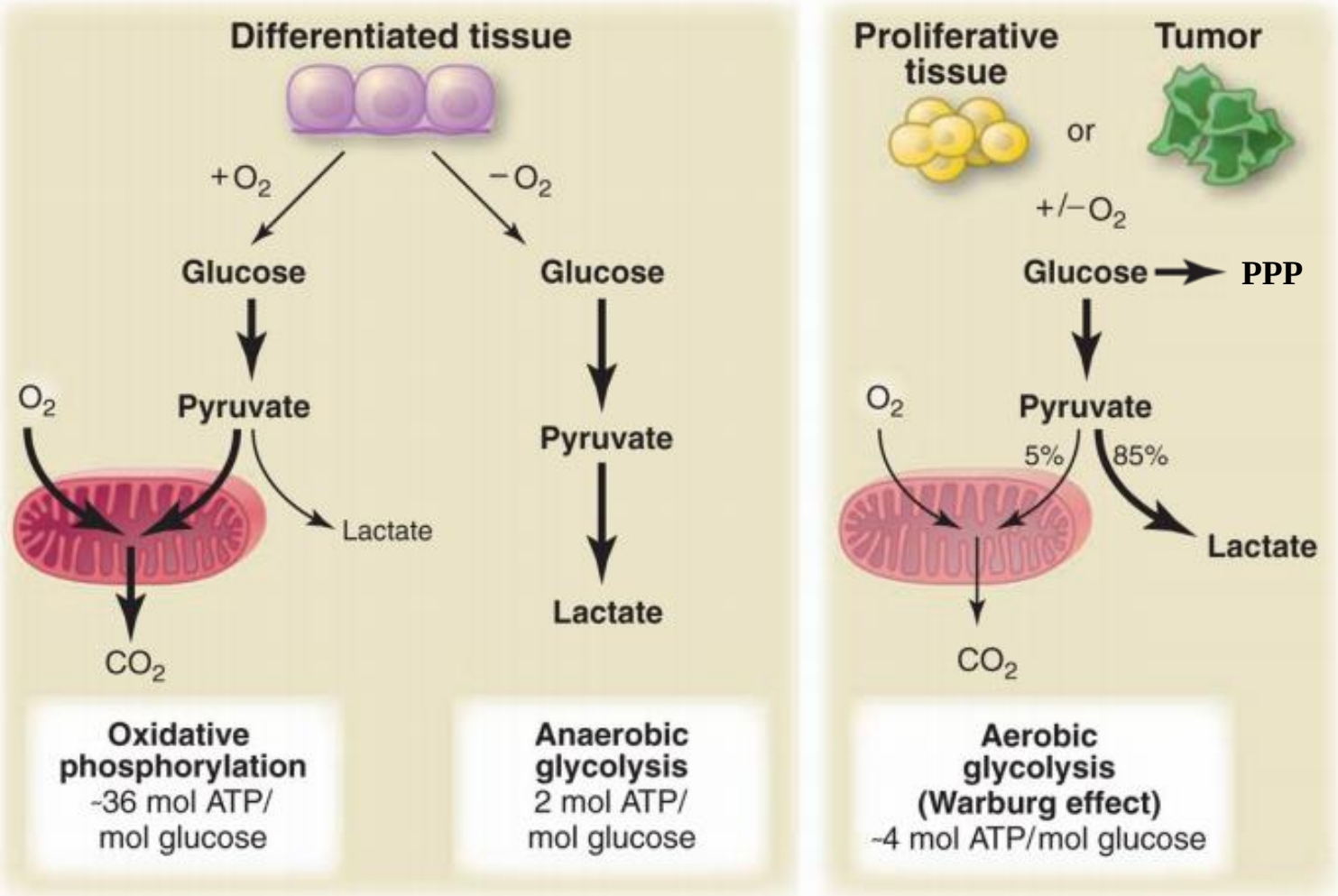
1. *Lois et al. (1983)*
2. *Allfrey et al. (1962)*
3. *Guo et al. (1989)*
4. *Grainger et al. (1979)*
5. *McBrian et al. (2013)*
6. *Kurdistani (2014)*

CANCER : A DECREASE IN ENERGY YELD

Mitochondria are not functional in cancer

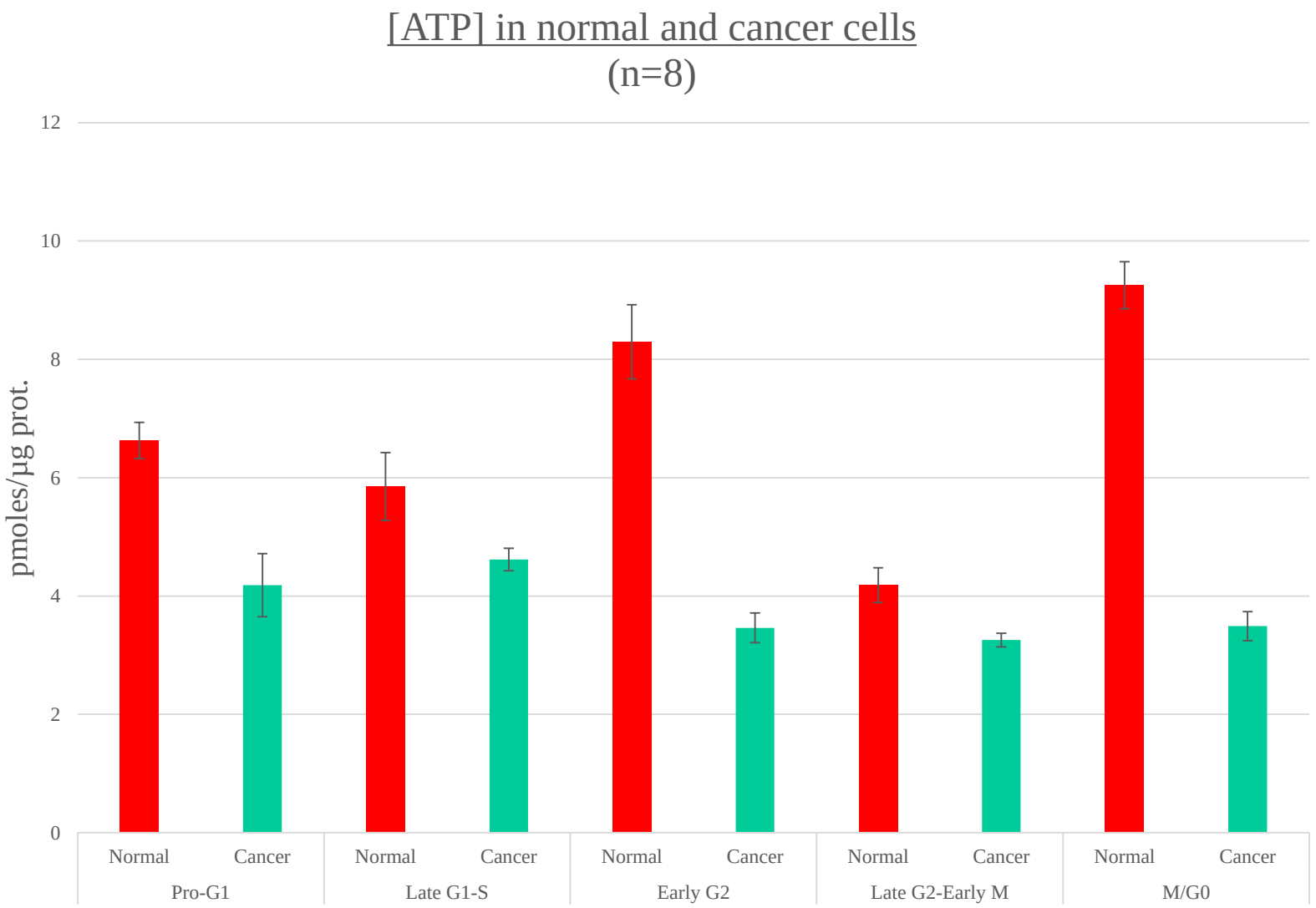


Warburg Effect : Reduced Energy Efficiency



Heiden et al. (2010)

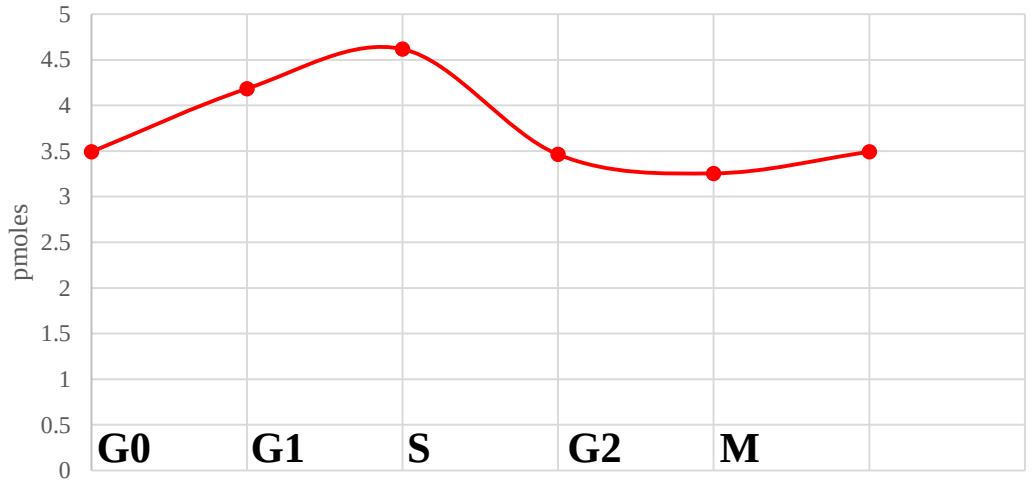
Cancer Cells are ATP-deprived



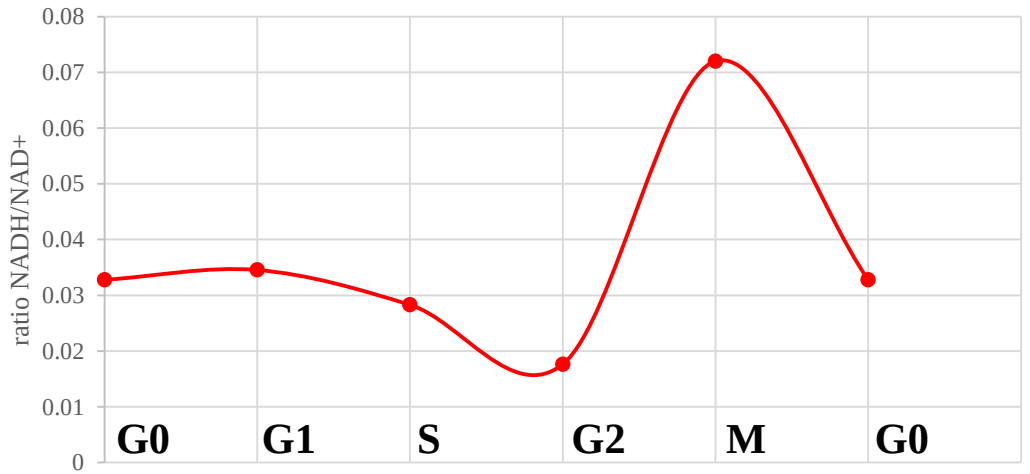
Intertwined redox oscillators

In the case of cancer cells

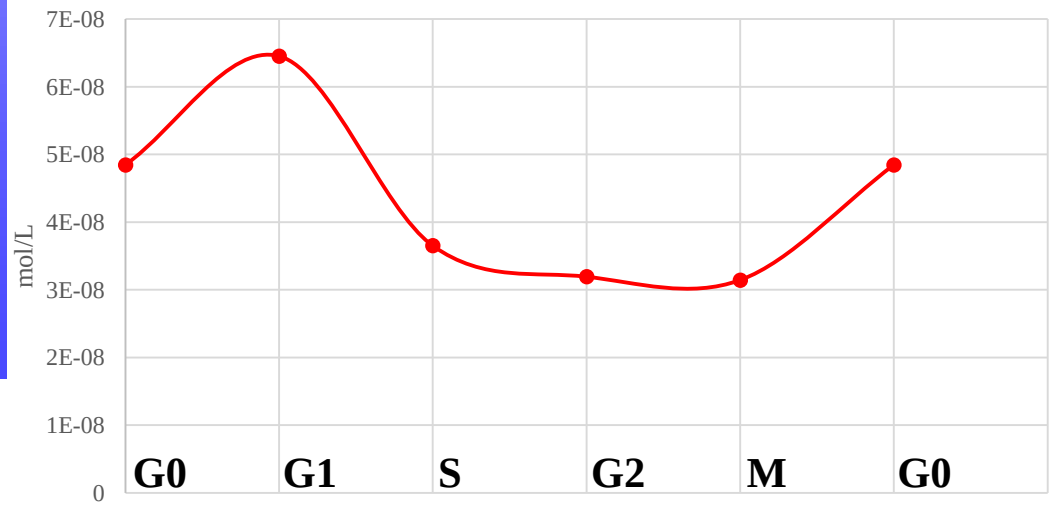
[ATP]



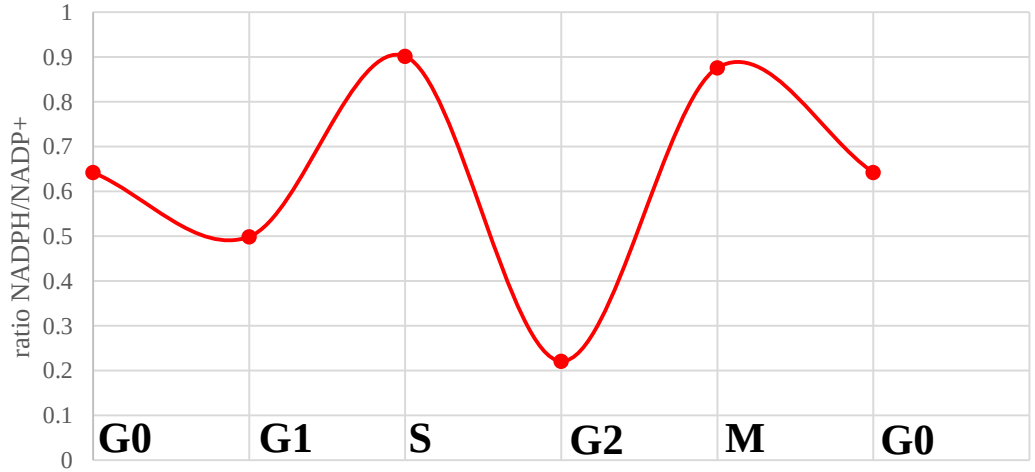
NADH/NAD+



[H+]

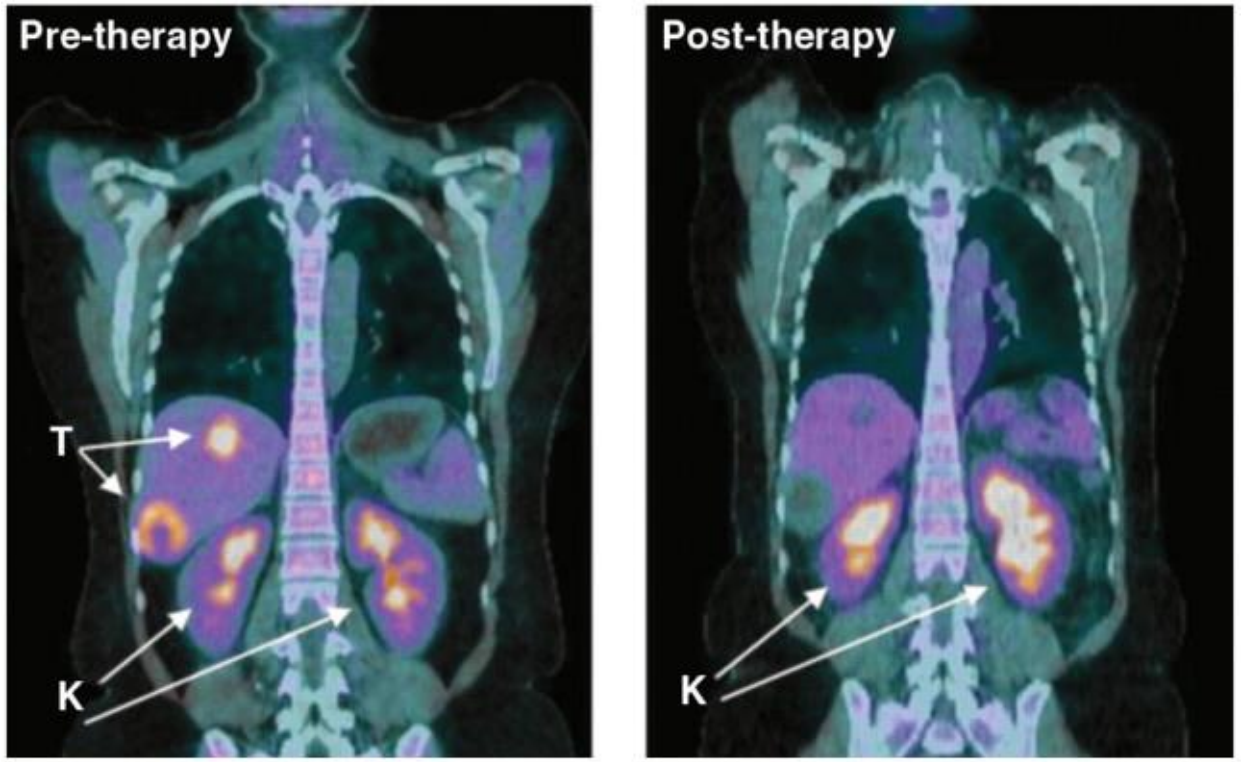


NADPH/NADP+



Cancer Drugs Change Cancer Metabolism

PET SCAN



T – tumor in liver (pre- and post-therapy)
K – kidney (does not contain tumor but concentrates FDG)

Source: *Science* 324, 1029 (2009).

Chemotherapy normalizes the radioactive glucose uptake

Can we do better than chemotherapy?

Our approach

Data-base

↓

28 molecules

↓

7 molecules

↓

7 combinations

Literature screening

- Metabolic activity
- Well-known molecules
- Data on human toxicity

Individual screening

- 5 cancer cell types
- proliferation and MTT test
- 1, 3, 5 days cultures

Combination screening

(same experimental conditions)

Results

- High clinical efficiency
- Universal and simple mechanisms
- Low regulatory risk and low cost

Literature screening

Drugs	Mechanism of action
Acetazolamide	Anhydrase carbonic inhibition
Albendazole	PEP carboxykinase inhibition
Amobarbital	NADH dehydrogenase
Amrinone	PDE-3 inhibition
Betaine	lipotropic factor
Capsaicin	NADH dehydrogenase
Dfructose 1,6 biphosphate	PKM2 activation
Dichloroacetate	PDHK1 inhibition
Dimercaprol	PDH activation
Farnesol	phospholipase D inhibition
Genistein	Phospholipase Cgamma inhibition
Gossypol	LDH inhibition
Hydrazine sulfate	PEP carboxykinase inhibition
Hydroxycitrate	ATP citrate lyase
Ketoconazole	Cyt. P450 demethylase inhibition
Lipoic acid	PDHK1 inhibition
Lithium chloride	PEPCK inhibition
Lonidamine	Hexokinase inhibition
Metformine	AMPK activation
Miltefosine	Choline kinase inhibition
Niacine	Lipolysis inhibition
Quinacrine	Phospholipase A2 inhibition
Quinine	Phospholipase A2 inhibition
Silibinine	IGFBP activation
Simvastatine	Lipolysis inhibition
Suramine	Citrate synthase inhibition
Tolbutamide	Potassium channel blocker
Xylitol	PP2A

METABLOC 1

Aim:

Identify a combination of two drugs active against altered cancer cell metabolism

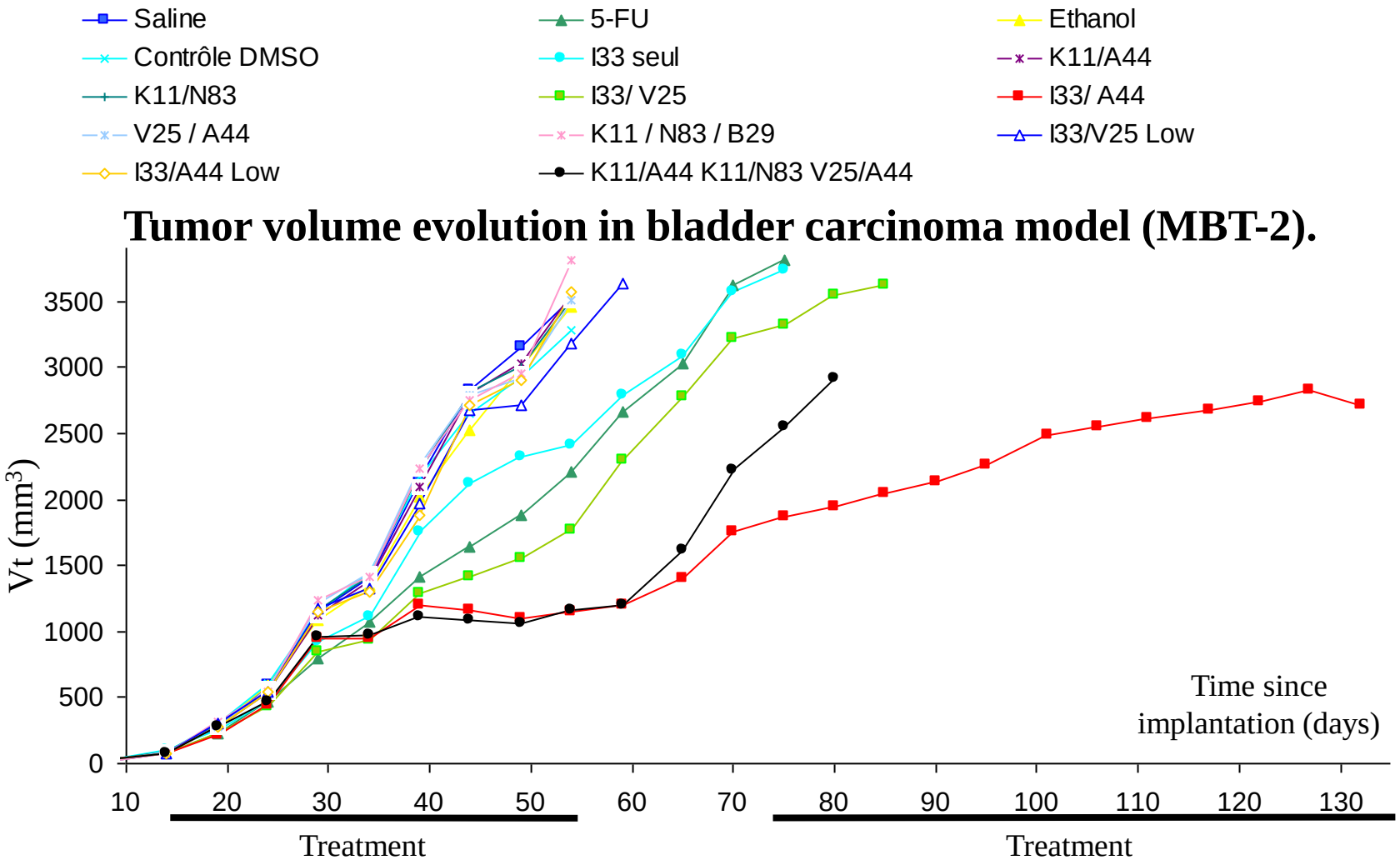
In vivo validation

Experiments

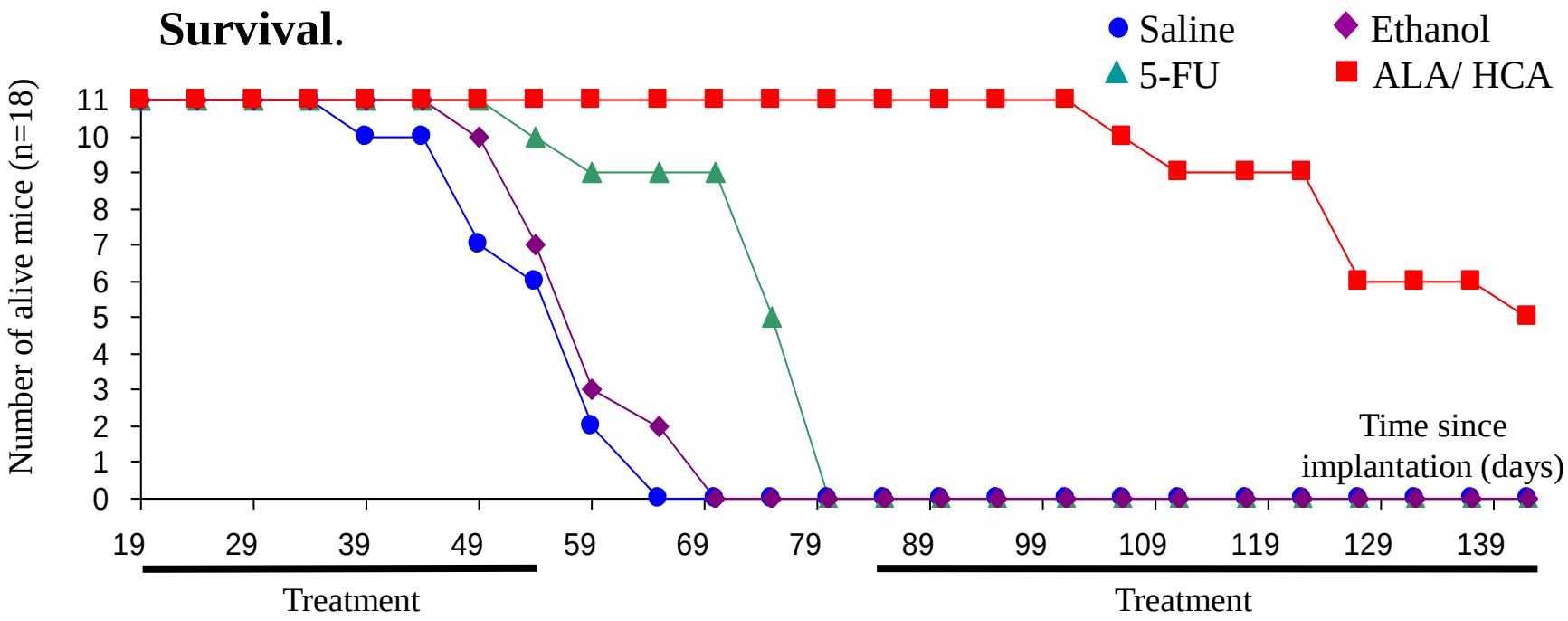
- Three syngeneic cancer models
  - MBT-2 bladder carcinoma
  - B16-F10 melanoma
  - LL/2 lung carcinoma

- Analysis of tumor volume and animal survival

Combination of molecules in bladder cancer

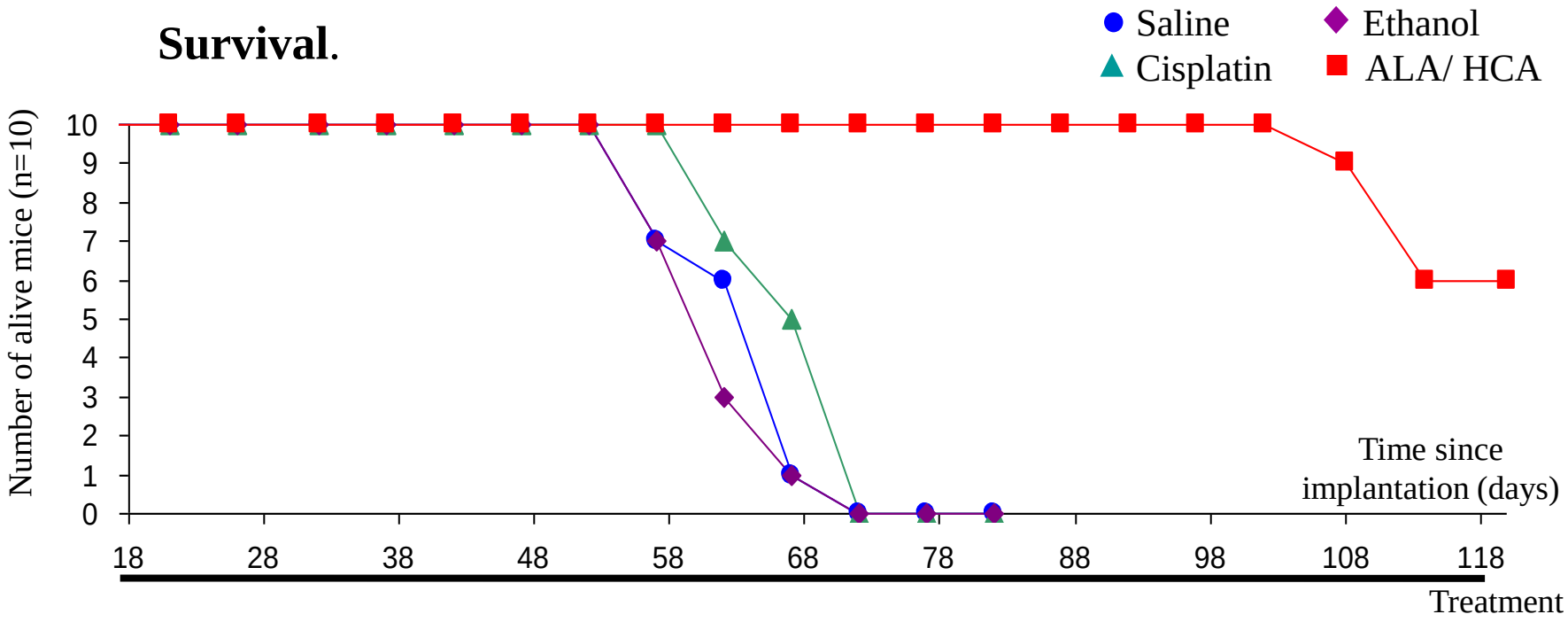


ALA/HCA in bladder carcinoma (MBT-2)



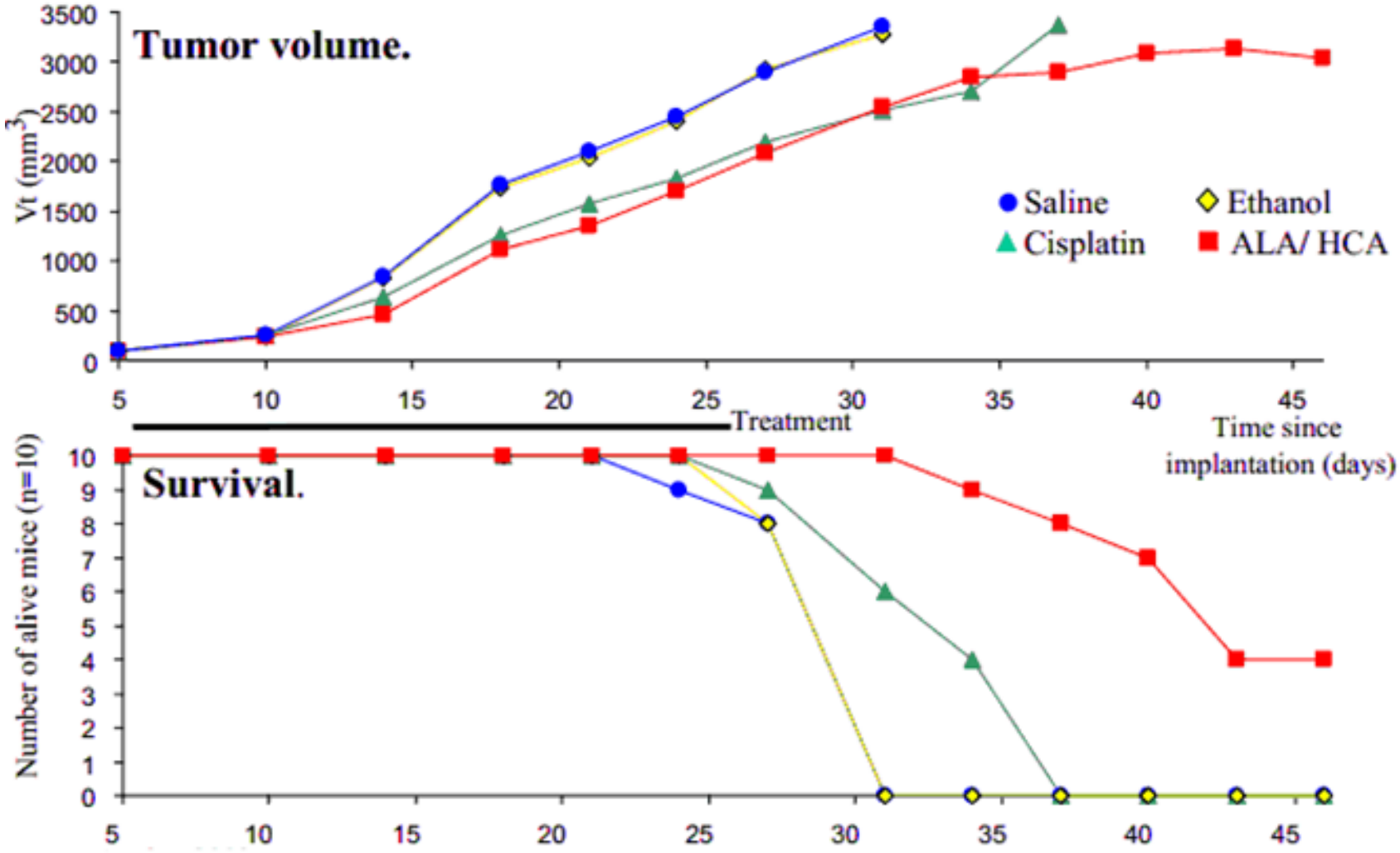
The ALA/HCA combination **reduces tumor development** rate and **doubles survival time** as compared to untreated mice.

ALA/HCA in melanoma (B16-F10)



The ALA/HCA combination **reduces tumor development rate** and **doubles survival time** as compared to untreated mice.

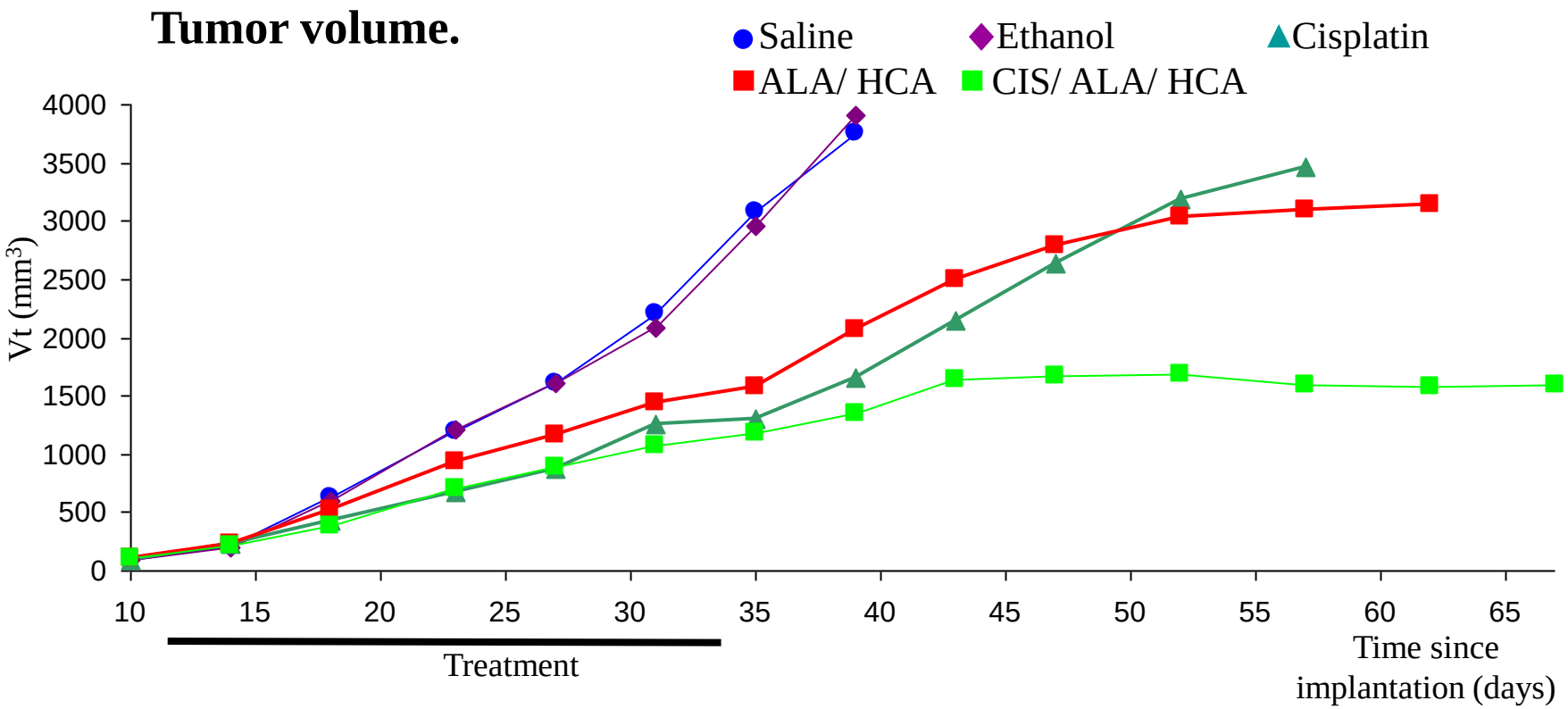
LLC tumor model



Well-known molecules

	ALA	HCA
Name	Lipoic acid	Calcium hydroxycitrate
Indications	• Anti-oxidant • Dietary supplement • Diabetic neuropathy	Weight loss agent
Toxicity	• No toxicity at 1200mg/day during 2 years • No mutagenic or genotoxic activity	• No toxicity at 5g/day during 8 weeks • No mutagenic or genotoxic activity

Enhanced efficacy of chemotherapy

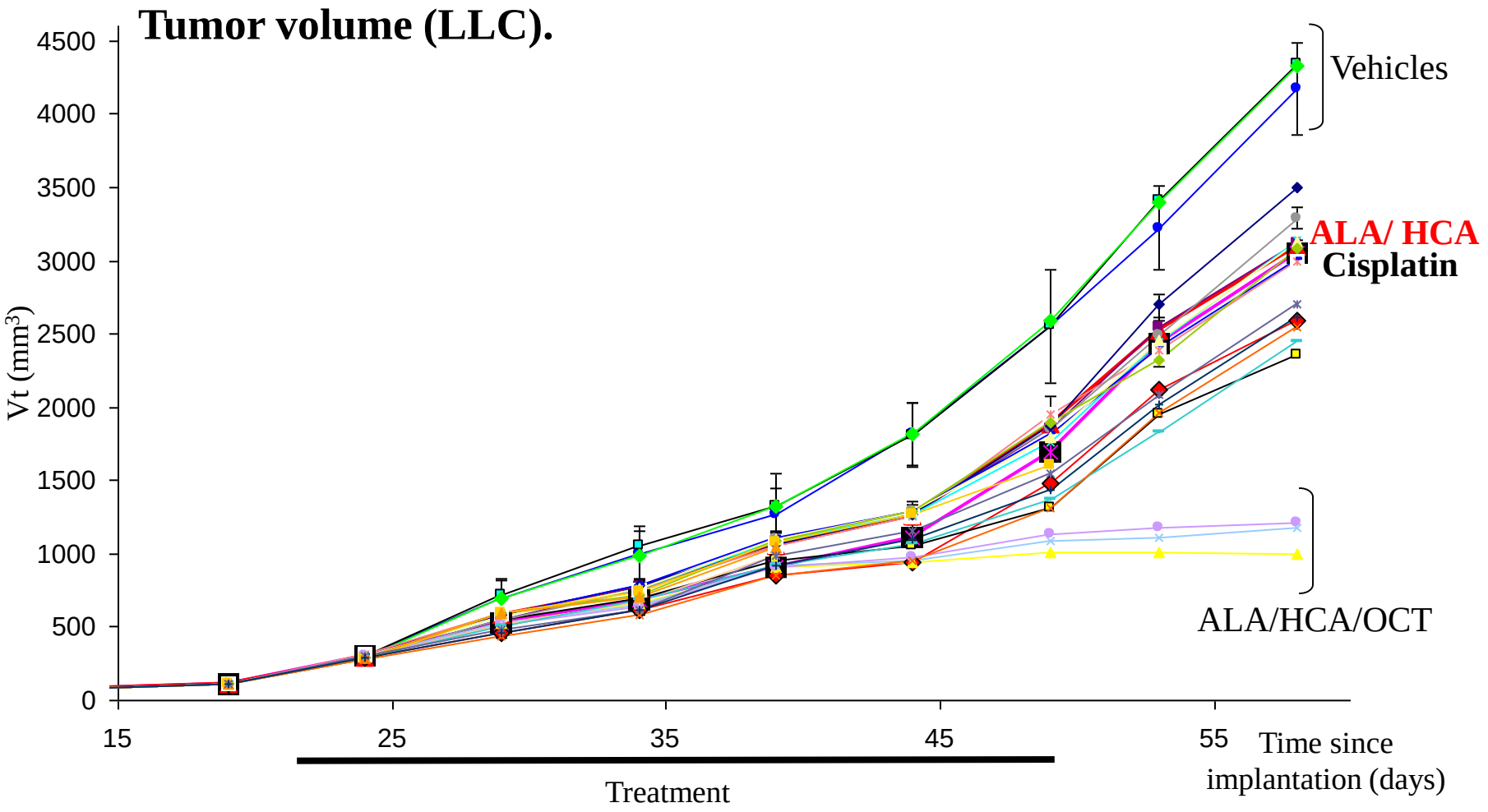


Addition of ALA/HCA enhanced the efficiency of cisplatin treatment (LLC model).

In vivo screenings

Drugs	Mechanism of action
6-diazo-5-oxo-L-norleucine	Glutaminase inhibition
Agmatine	Polyamine synthesis inhibition
Alpha cetoglutarate	Citrate synthase inhibition
Amiloride	Na+/H+ antiport inhibition
Apigenine	IGFBP activation
Bicalutamide	IGFBP activation
Bromocriptine	Hypothalamic D2 receptor agonist
Butyrate sodium	HDAC inhibition
Chitosan	PK-M2 inhibition
Choline Chloride	lipotropic factor
Citrate	Citrate synthase inhibition
Cryogenine	PEP carboxykinase inhibition
Curcumin	AID inhibition
D-alanine	Alanine transaminase inhibition
Epigallocatechin gallate	PK-M1/M2 splicing regulation
Fluoxetine	Serotonine reabsorption inhibition
Ibuprofen	NSAIDS
Indole 3 carbinol	Triglycerides reduction
Ketoconazole	Cyt. P450 demethylase inhibition
Lactoferine	Oxydative stress reduction
Letrozole	Aromatase inhibition
L-norvaline	Arginase inhibition
Melatonine	anti-oxydant, anti-proliferative
Menadione	Tyr kinase receptor inhibition
Oméprazole	IGFBP activation
Oxythiamine	Transketolase inhibition
PEG8000	PK activation
Pegvisomant	GH receptor inhibition
Pralidoxime	Alanine transaminase inhibition
Retinoic acid	Cellular differentiation activation
Sulpiride	GH secretion inhibition
Suramine	Citrate synthase inhibition
Valproate sodium	HDAC inhibition
Vitamine B12	lipotropic factor

Screening of 19 combinations



Combination of ALA/ HCA/ OCT/ CAP

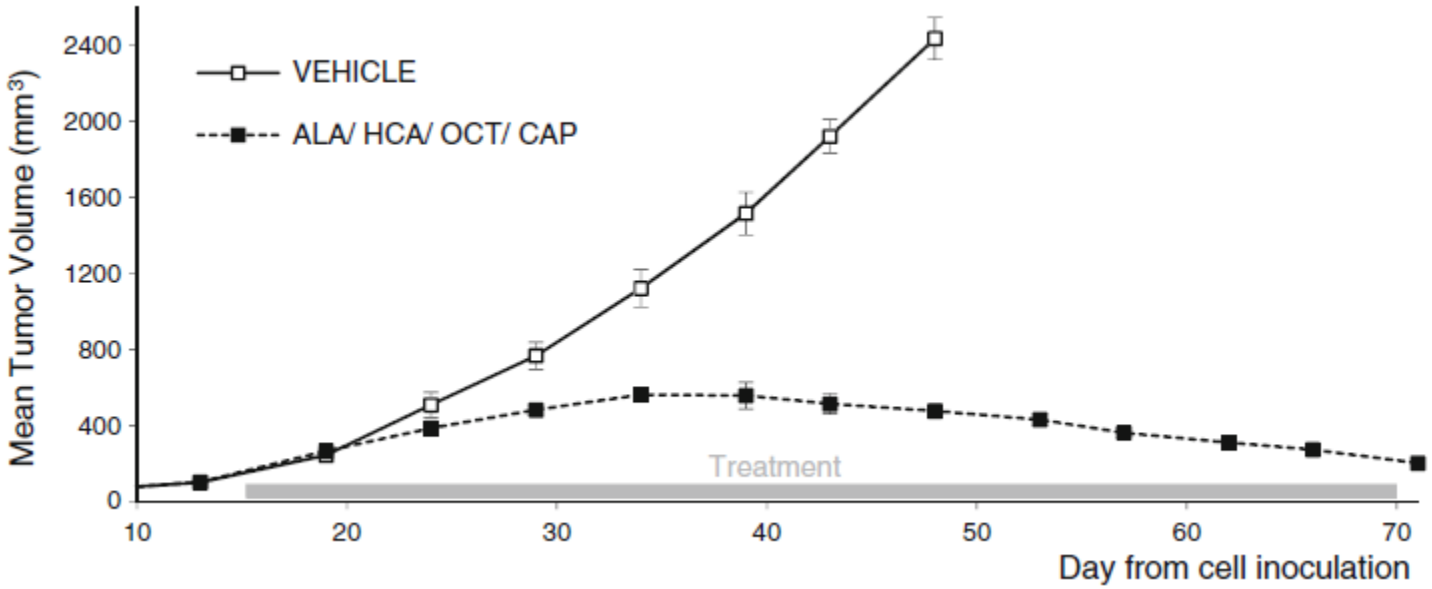


Fig. 5 Anti-tumor activity of the α-lipoic acid, hydroxycitrate, capsaicin and octreotide combination in the melanoma model. Mean tumor volume curves for each condition of treatment are compared to the references, vehicle and cisplatin. Legends: *OCT* octreotide; *grey bar* treatment administration (days 17–71).

First report of tumor regression with a metabolic treatment

Schwartz L. Invest New Drugs. 2013 Apr;31(2):256-64.

First patient

7/2001: Adenocarcinoma of the colon pT4 N0

10/ 2009 : Peritoneal metastasis

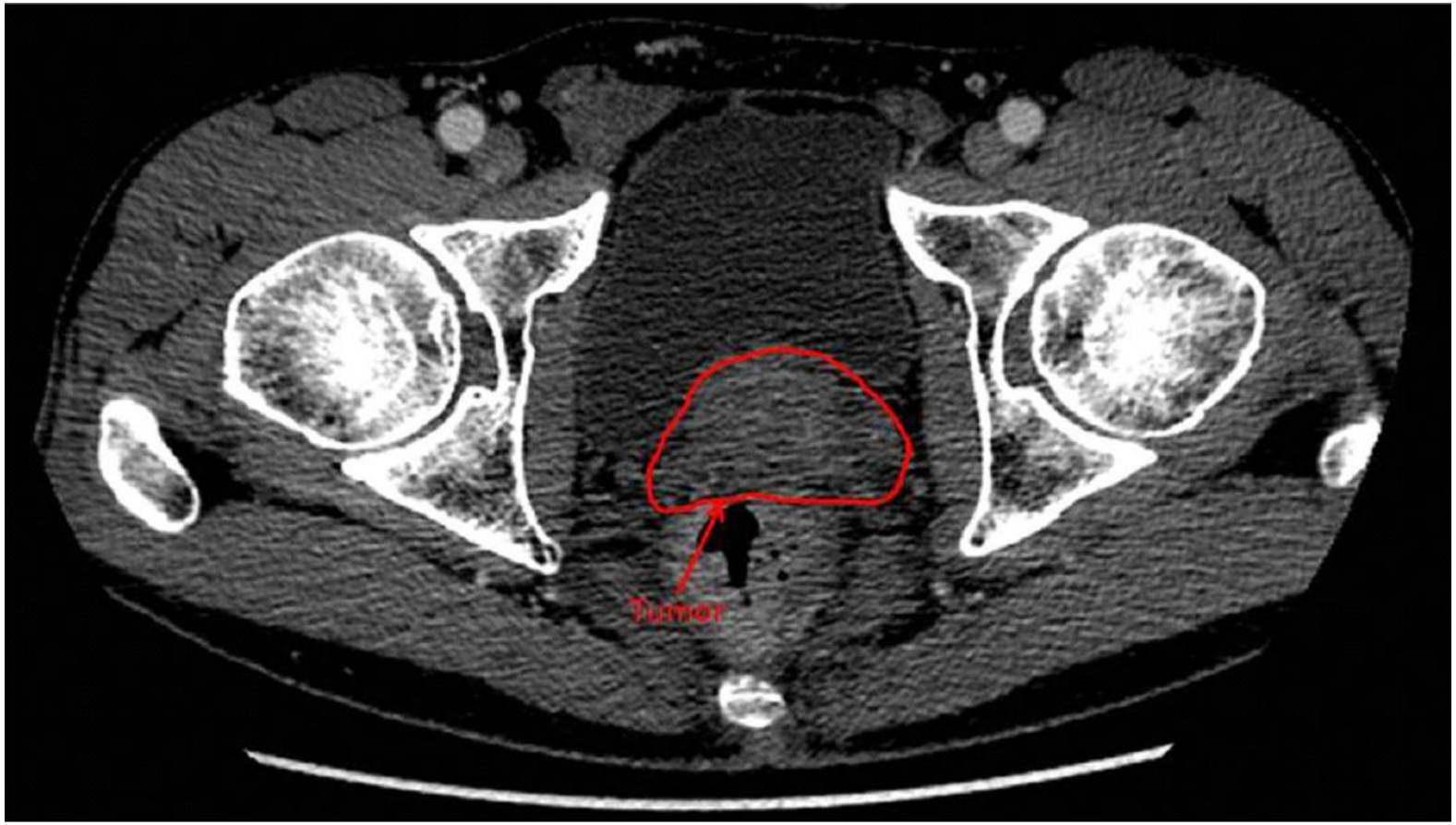
12/2009 : Chemotherapy at Institut Gustave Roussy (Villejuif)
5-FU, Cisplat, Avastin

12/2009 oral ALA and HCA

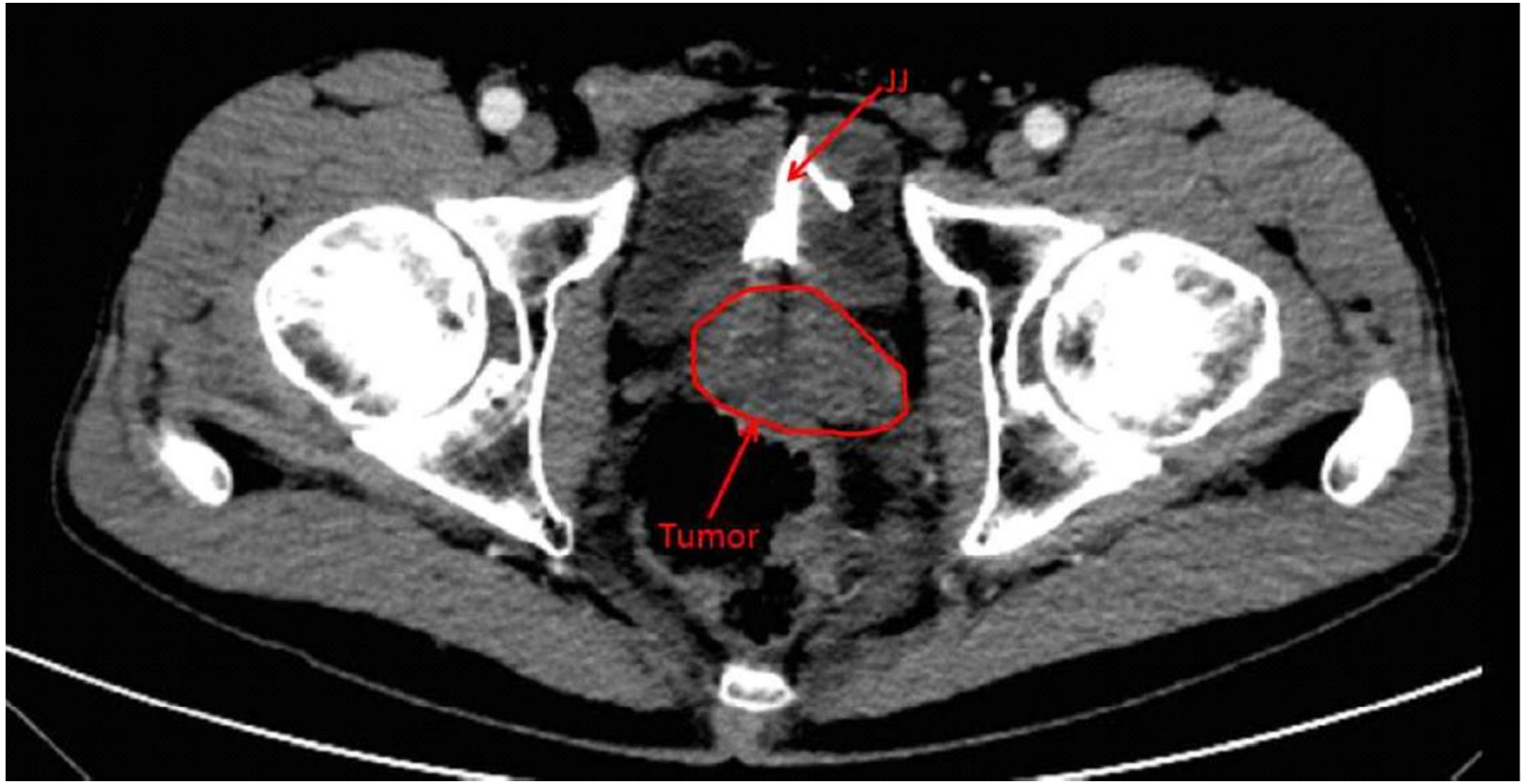
3/ 2010 : Avastin discontinued because of poor tolerance
7/ 2010 : abdominal radiotherapy followed by Gemcitabine

7/ 2011: discontinuation of chemotherapy
10/2014: death

CT of the perirectal mass at the date of discovery (Nov. 2009)



CT of the same region, on June 2012



First italian patient

Glioblastoma multiforme started Metabloc in early 2008

Multiple relapses but alive and reasonably well in 5/2015

In the mean time

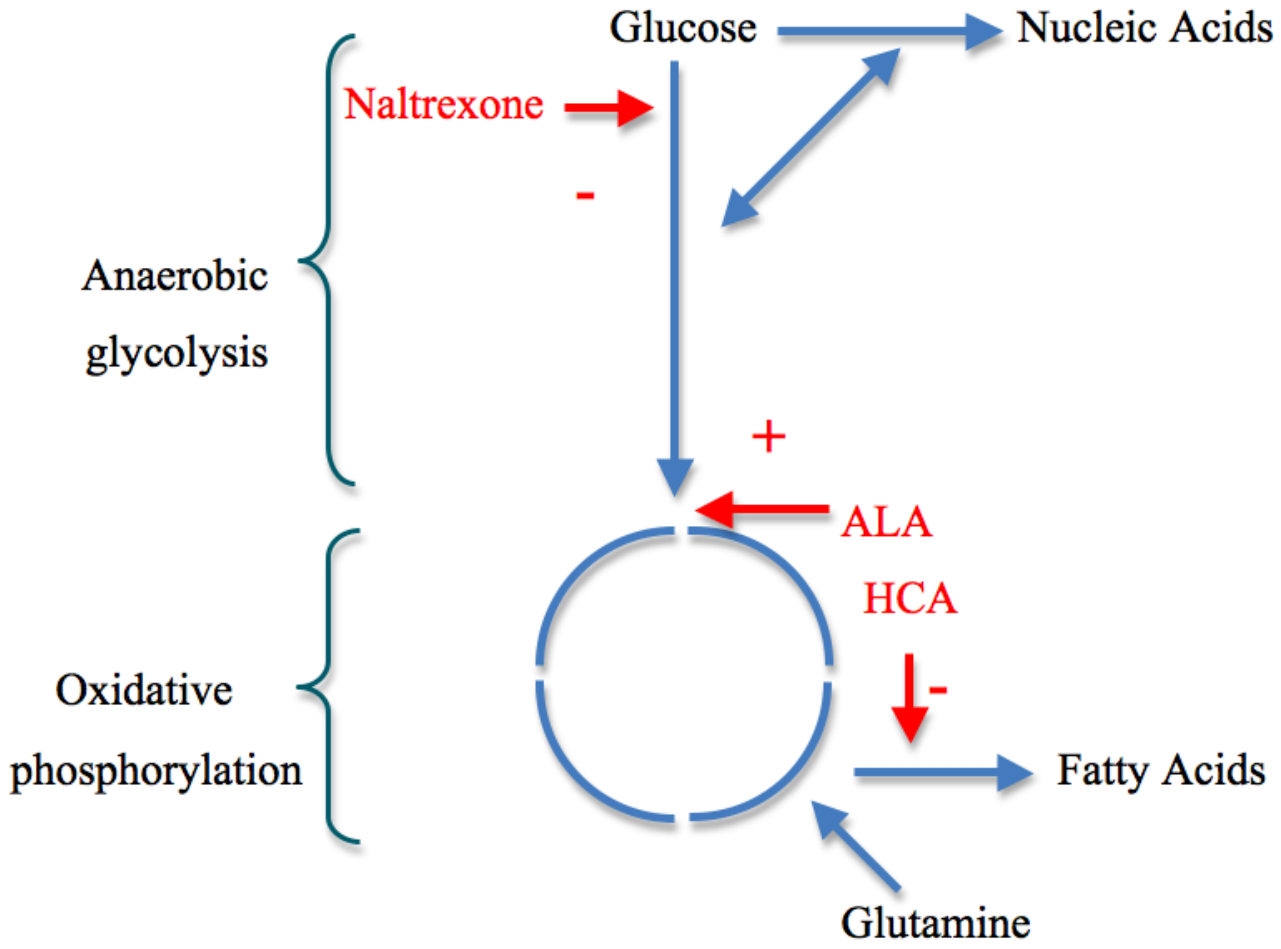
- Dr Burt Berkson (New Mexico)

- 10 cases of uncurable advanced cancer :
- Long term stabilization with IV Lipoic acid and low dose naltrexone
- Number of patients treated not stated

Integrative Cancer Therapies 2009 (4) 416–422

Compassionate use in desperate patients

Targeting the Central Carbon Metabolism



Inclusion criteria

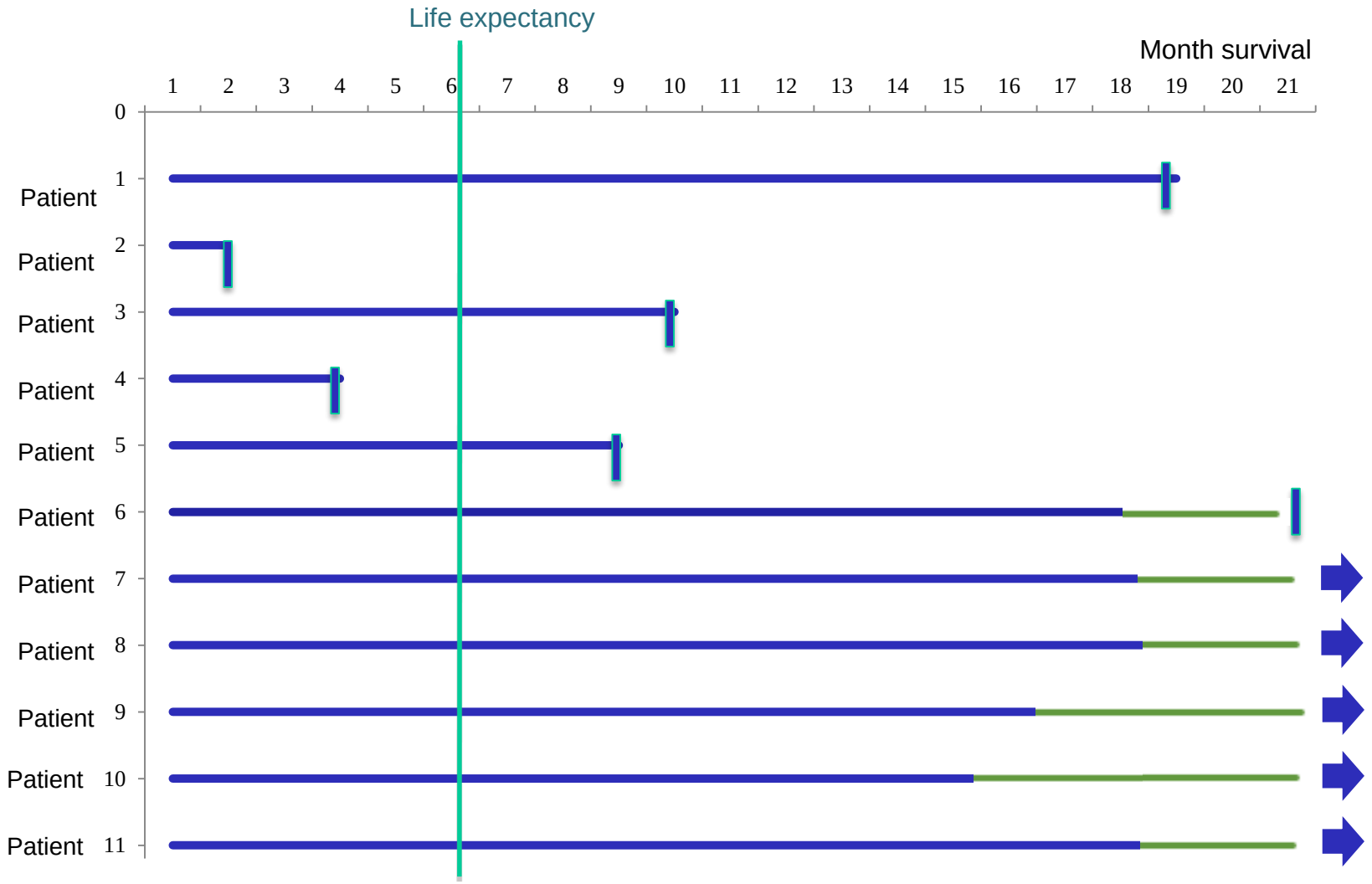
- Metastatic carcinoma
- Standard chemotherapy failed
- Offered only palliative care
- Karnofsky status between fifty and eighty
- Life expectancy estimated to be between 2 and 6 months

Treatment Protocol: chemoresistant tumors

<u>Chemoresistant advanced metastatic cancer</u> :

- lipoic acid 600 mg IV (Thioctacid® (Meda Pharma)
- hydroxycitrate 500 mg t.i.d (Solgar)
- low-dose naltrexone 5 mg (Revia) at bed time

Clinic results for the first 11 patients



Treatment Protocol: chemosensitive tumors

<u>Advanced metastatic cancer</u> :

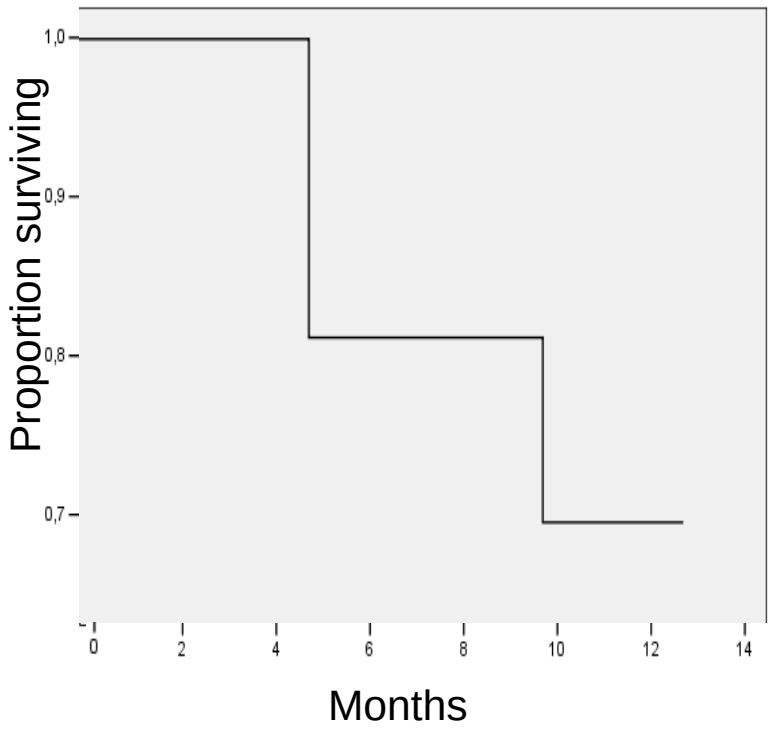
- lipoic acid 1, 8gr (Tiobec®)
- hydroxycitrate 500 mg t.i.d (Solgar)
- low-dose naltrexone 5 mg (Revia) at bed time

- In combination with standard chemotherapy

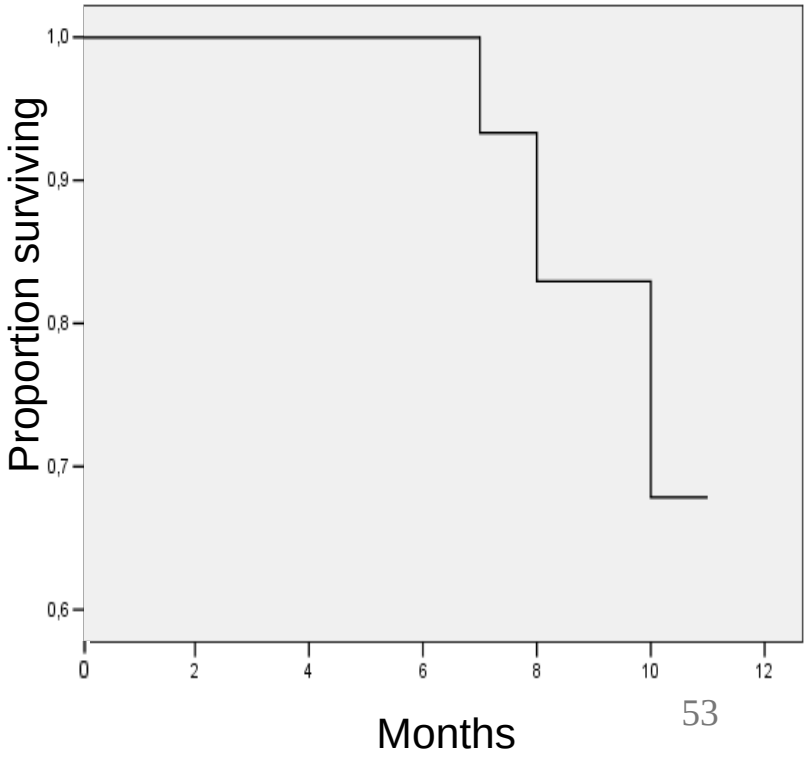
Second Series of Clinical treatment

- Group I: Metabolic treatment only (n=17)
- Group II: Metabolic treatment and chemotherapy (n=27)
- 12 months treatment

Group I



Group II



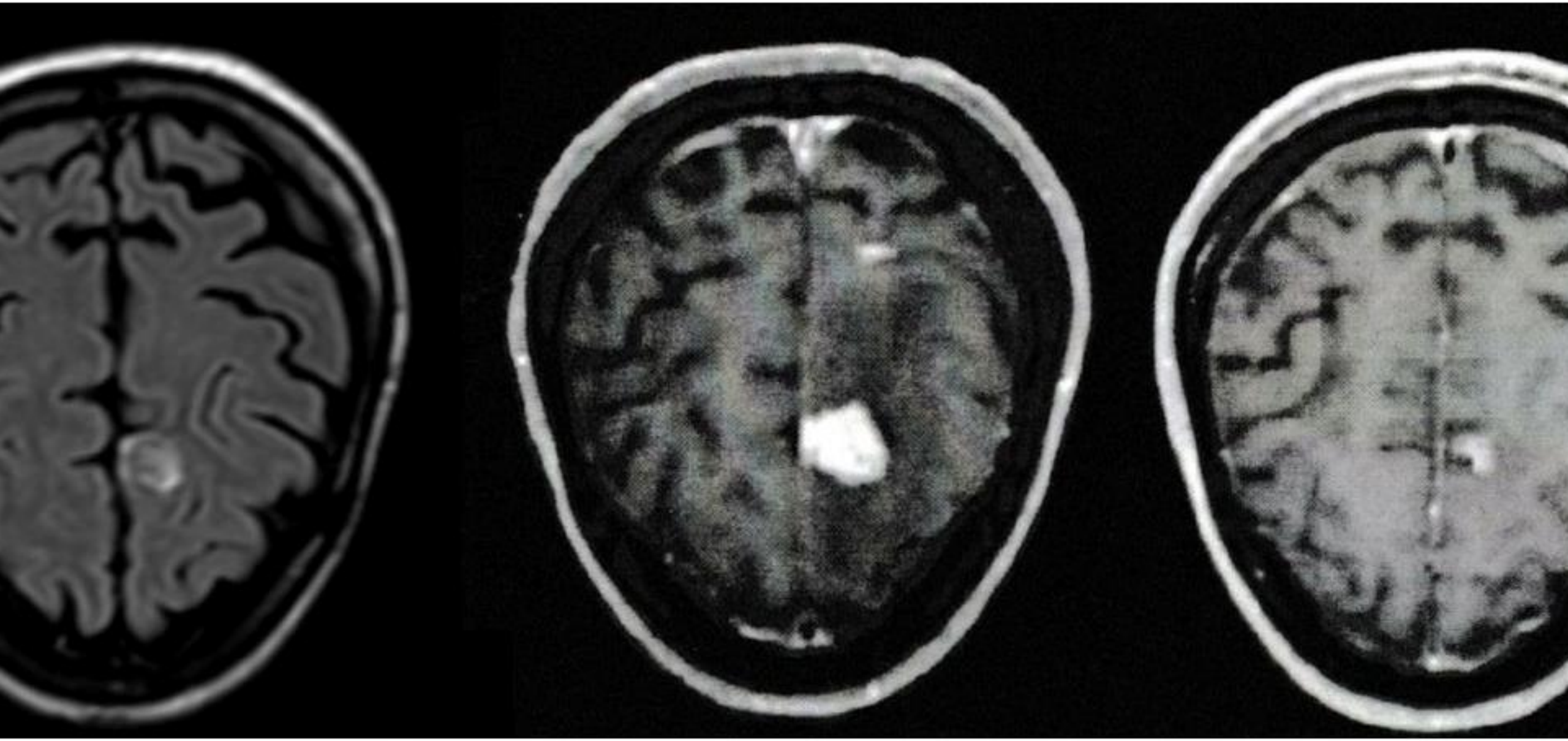
Florentine

- 3/2006 Sarcoma of the uterus : surgery + RT + chemotherapy (TEC)
- 2008 Radiation induced enteritis
- 1/2013 multiple brain metastasis (N sup 15)
  - Palliative radiatiotherapy (30gy in 10 fractions)
  - Sent home to die
- 3/ 2013 start metabloc
- 5/ 2015 NED

Yun

56 year old lady

- 3/13 Squamous cell carcinoma of the lung with bone and brain metastasis (N sup 20)
- Treatment gifetinib, partial response
- 2/14 because of tumor progression , continue gifetinib and start metabolic treatment partial response
- 6/14 brain irradiation 30Gy/10 fractions. During radiation acute psychosis, weight loss.
- 8/14 The husband is told that she is going to die
- 9/14 starts Alimta for palliative care and metabolic treatment
- 5/ 15 She lives an almost normal life



Juin 2014

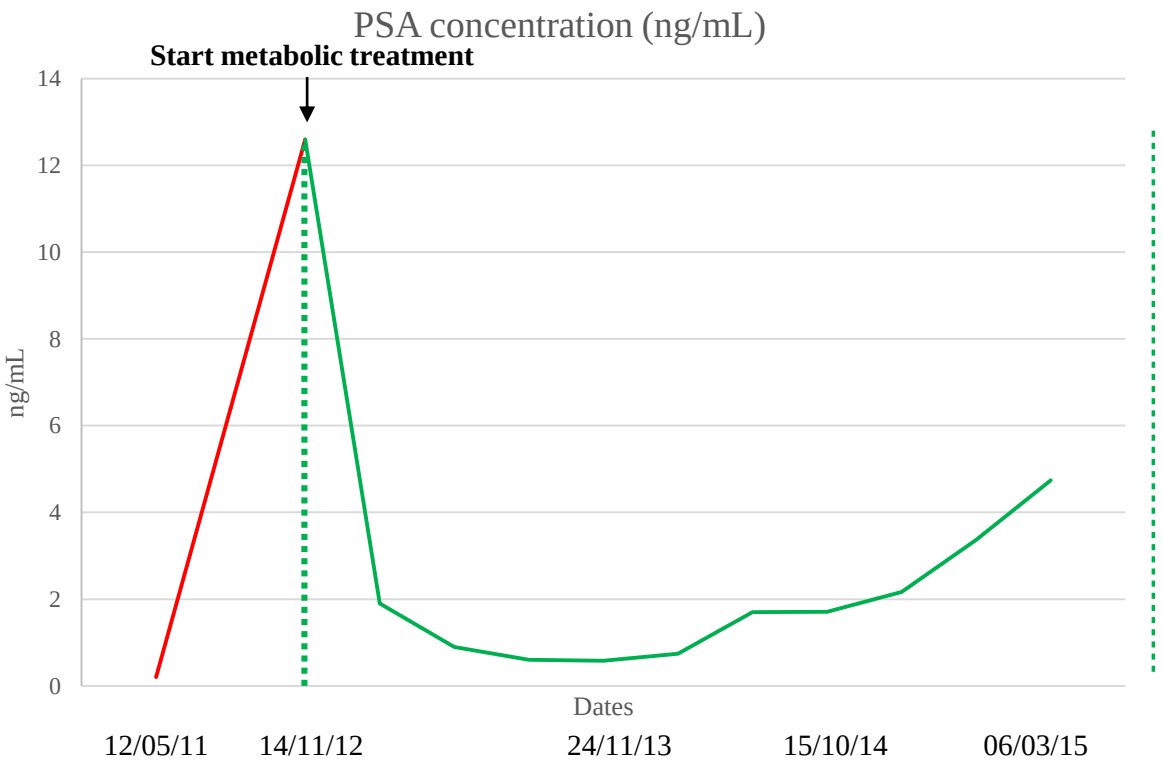
Septembre 2014

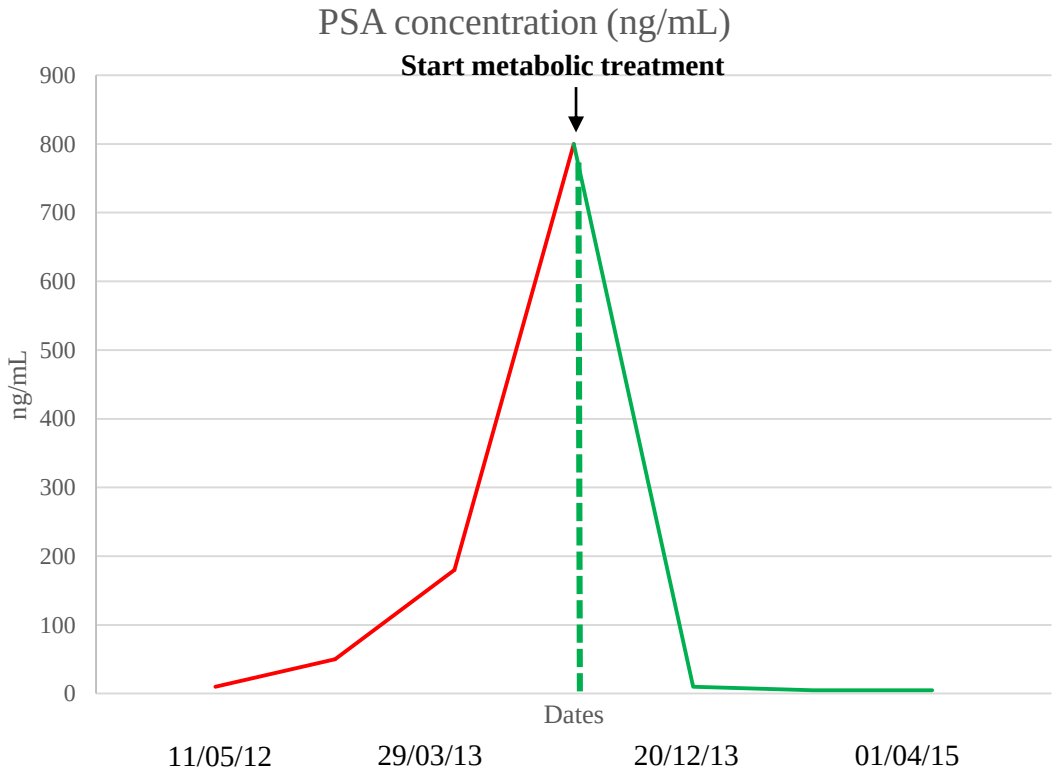
Juin 2015

Marina

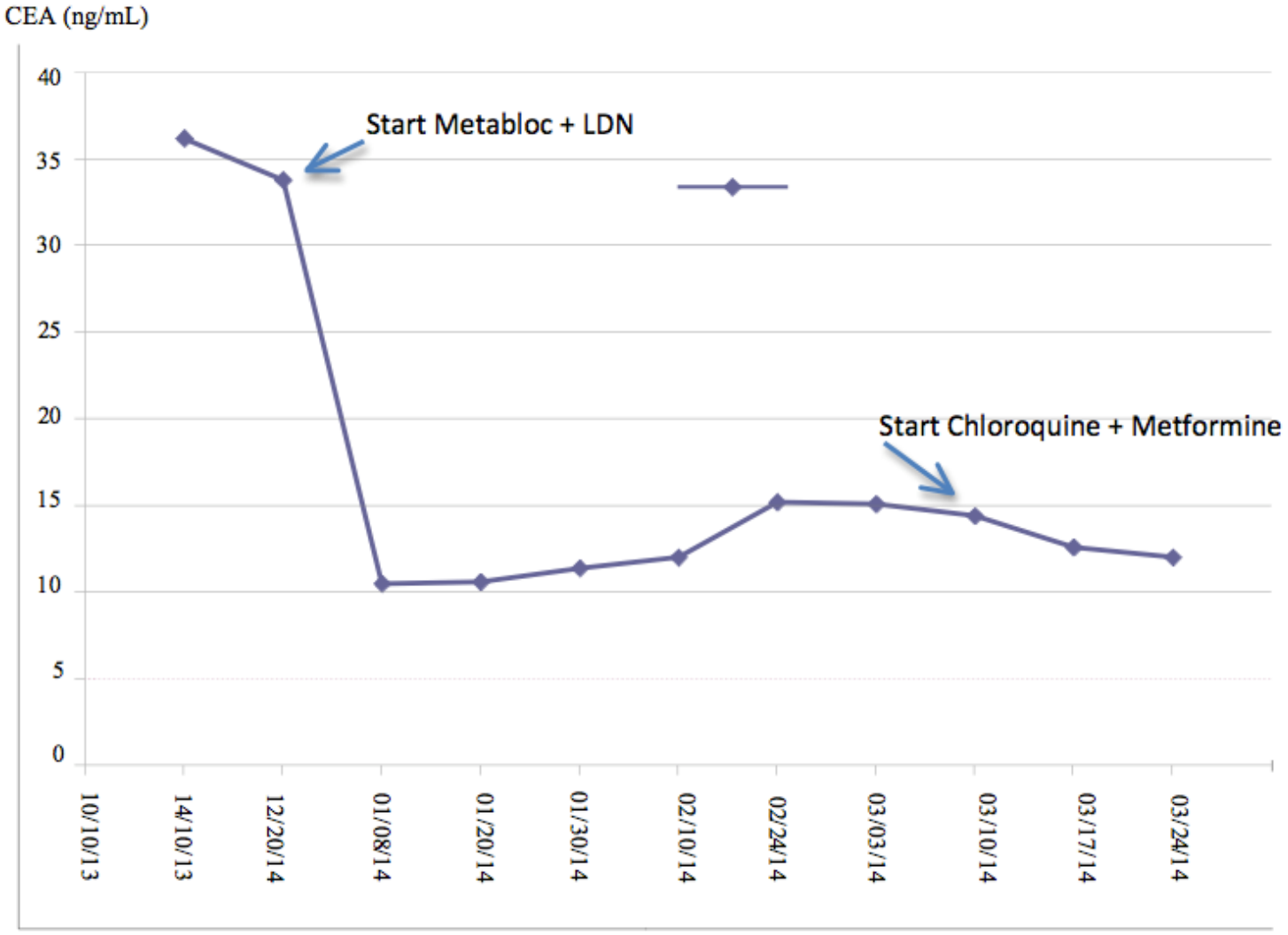
- 2/12 Cholangiocarcinoma partial hepatectomy
- 5/12 Lung metastasis
- 5 FU and cisplatin ineffective
  - Stutent ineffective
  - Other treatment option sent home to die
- 2/13 start LDN, LA, HCA
  - Tumor stabilisation for 16 months
- 2/15 Death

PSA in hormone resistant prostate cancer

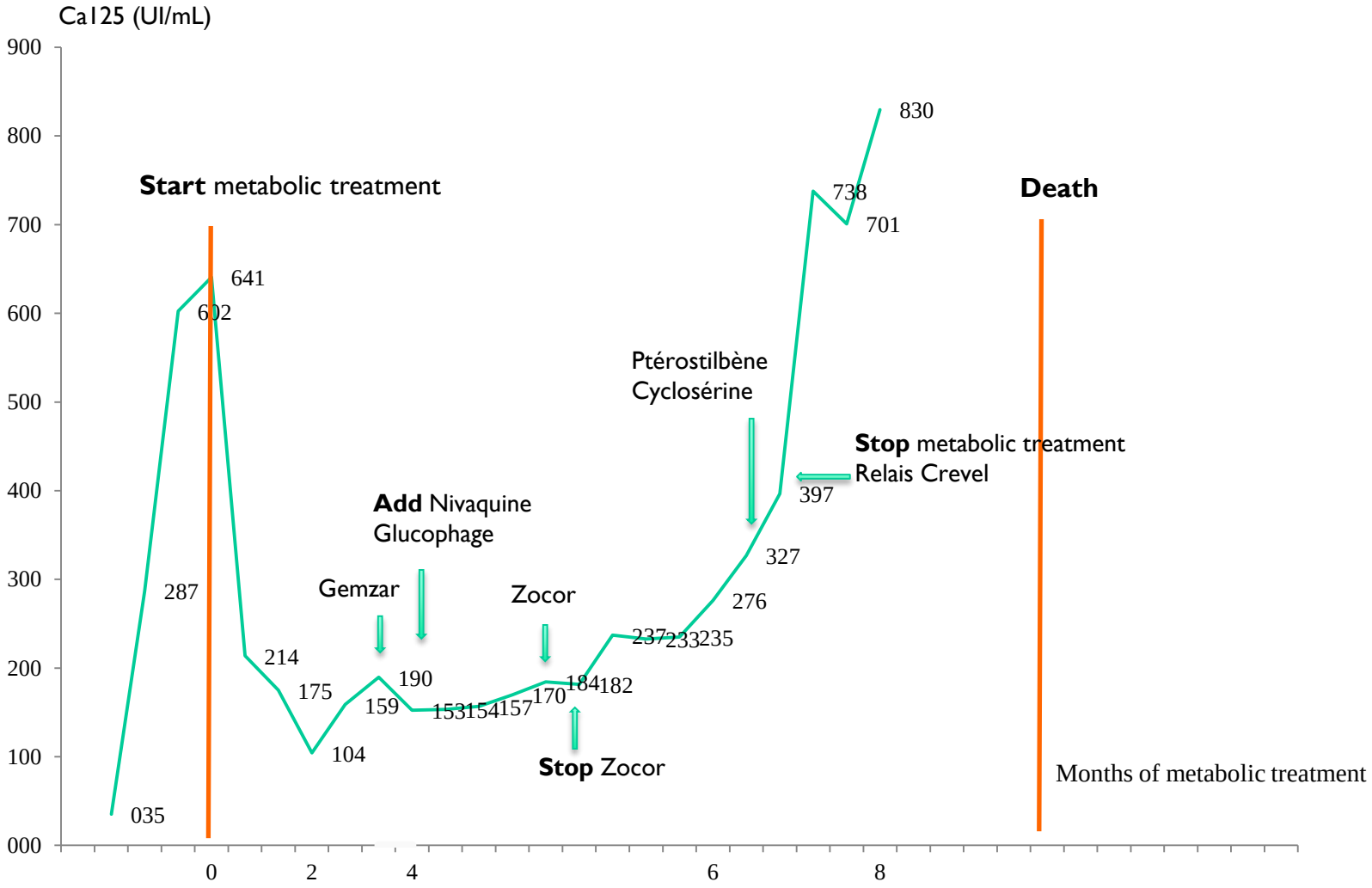




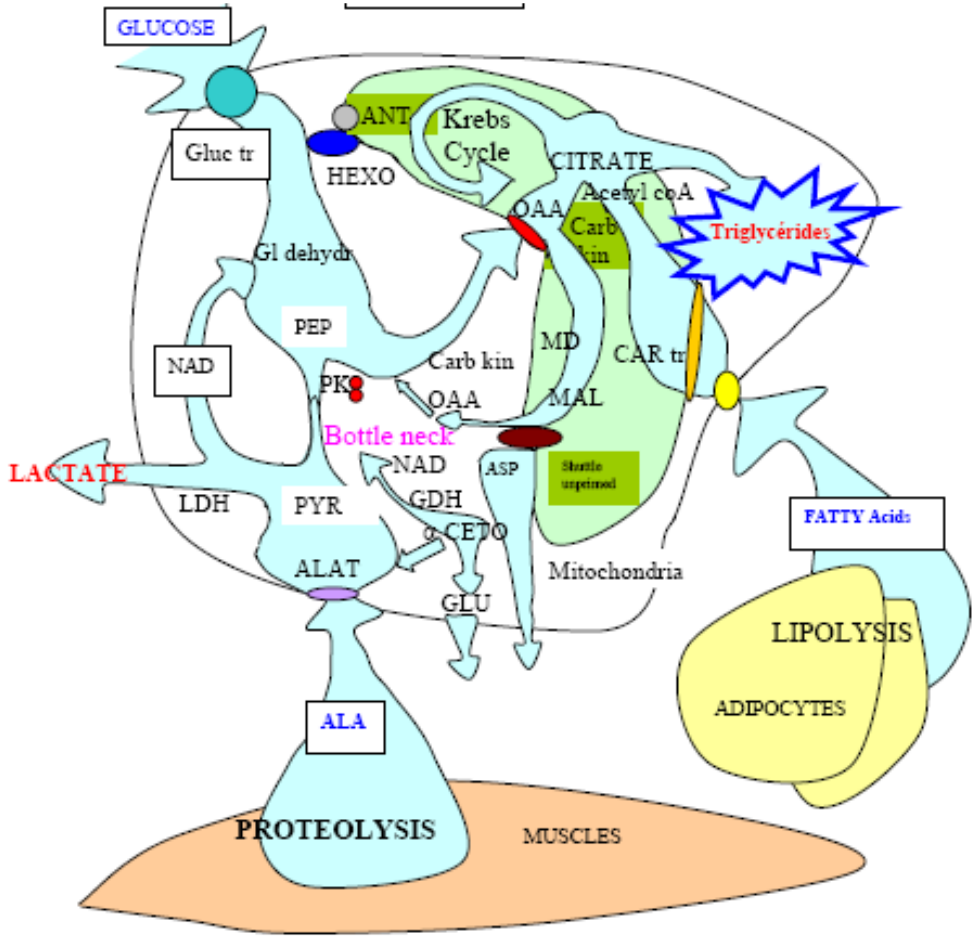
Metastatic colon cancer (3 different lines of chemotherapy)



Decrease level of tumor markers followed by regrowth



Targets for a combined anti-tumoral therapy



Schwartz and Israel 2005

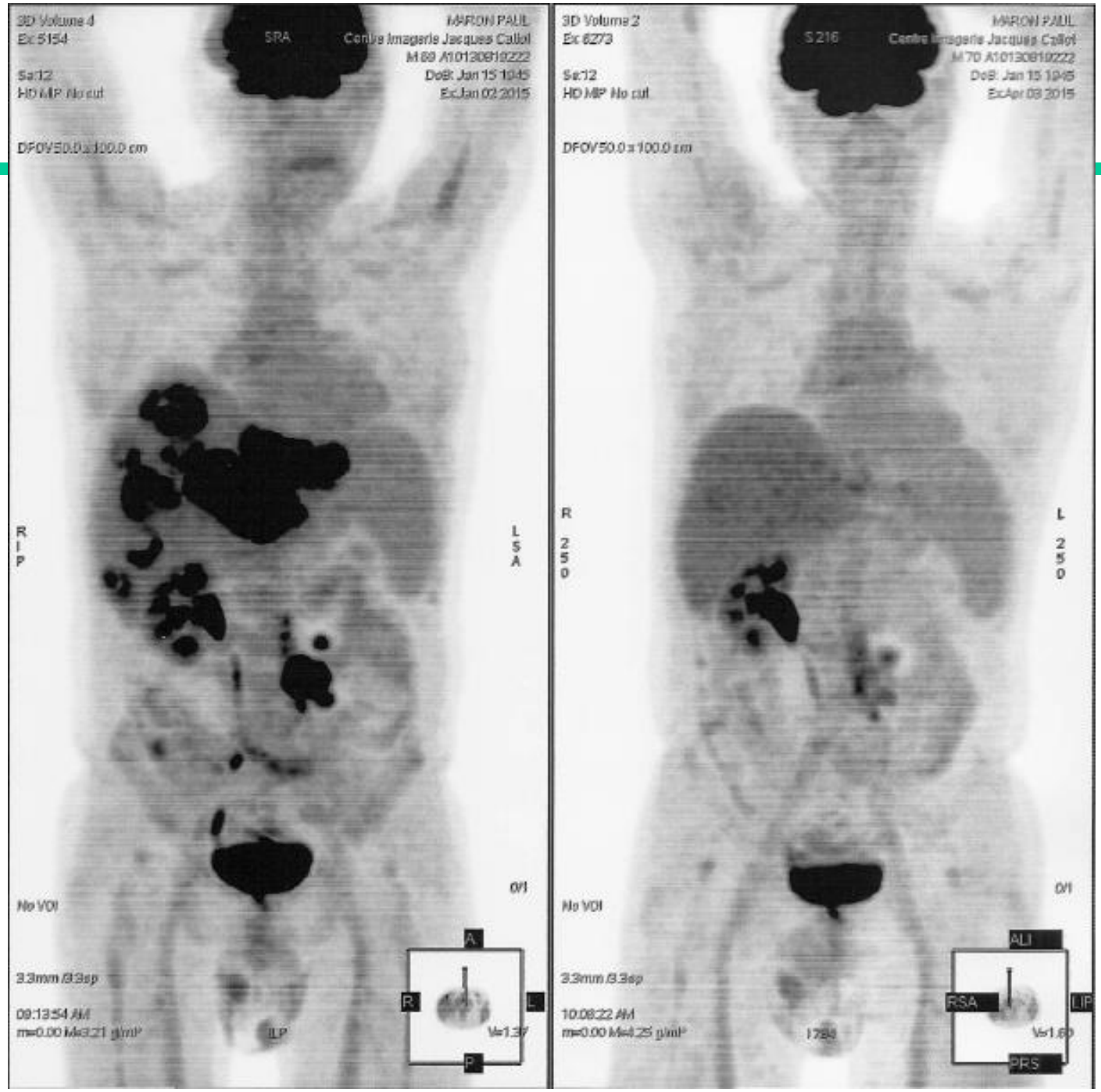
How to improve METABLOC?

A)Decrease glucose uptake

B)Decrease intracellular pH

PET scan

Colon carcinoma with liver metastasis



PET scan

Regular administration of Metabloc Digoxin and 5 FU
(2 months later)

As of september 2015, it is probable that:

1) Cancer is the simple consequence of mitochondrial inactivation.
2) Alzheimer's disease has a lot of common features with cancer
3) It is a matter of time before effective treatment will reach the market
4) There will be economical/political changes