The Foundation for Collaborative Medicine & Research

Mitochondria Support

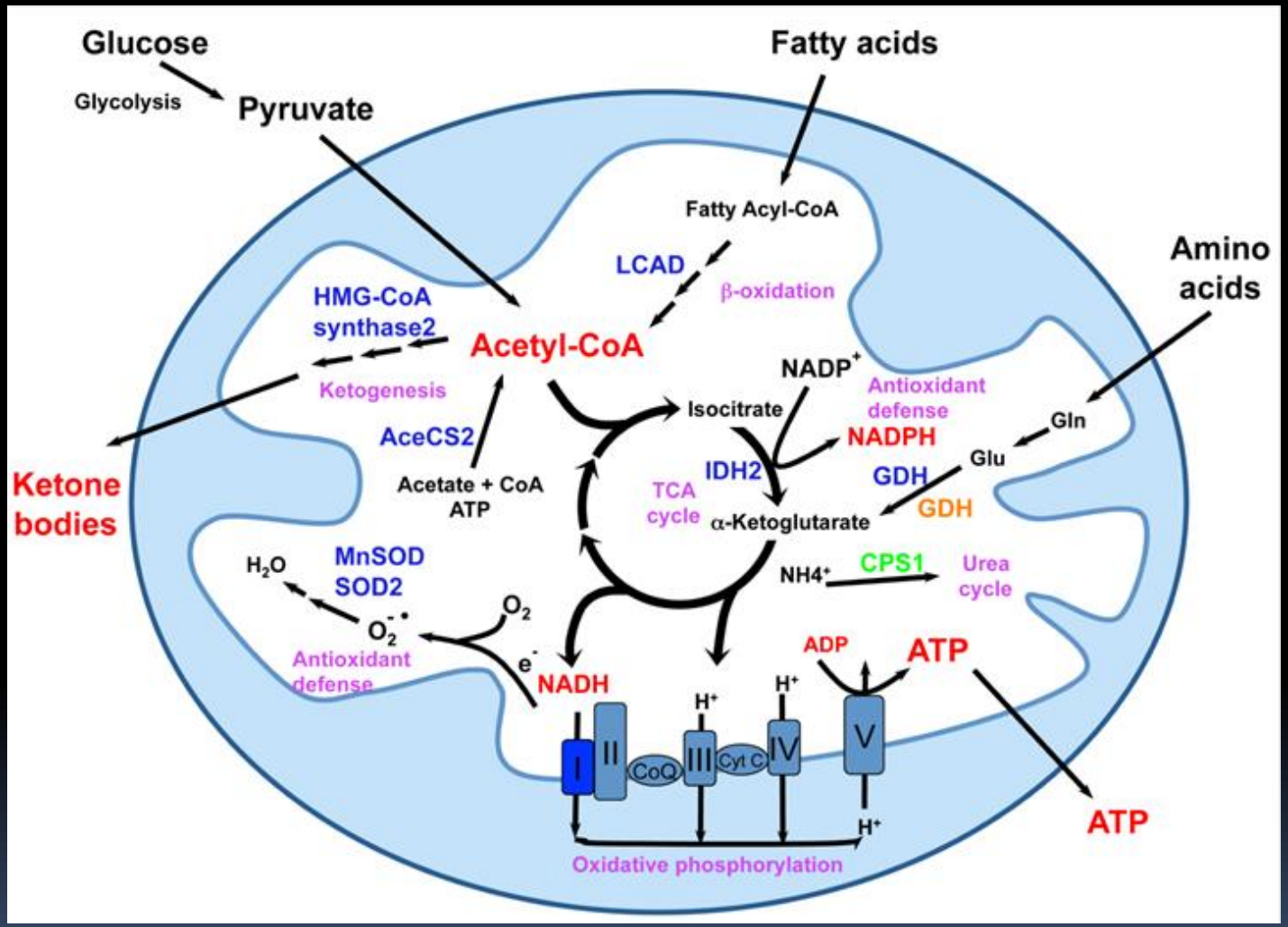
INTRODUCTION:

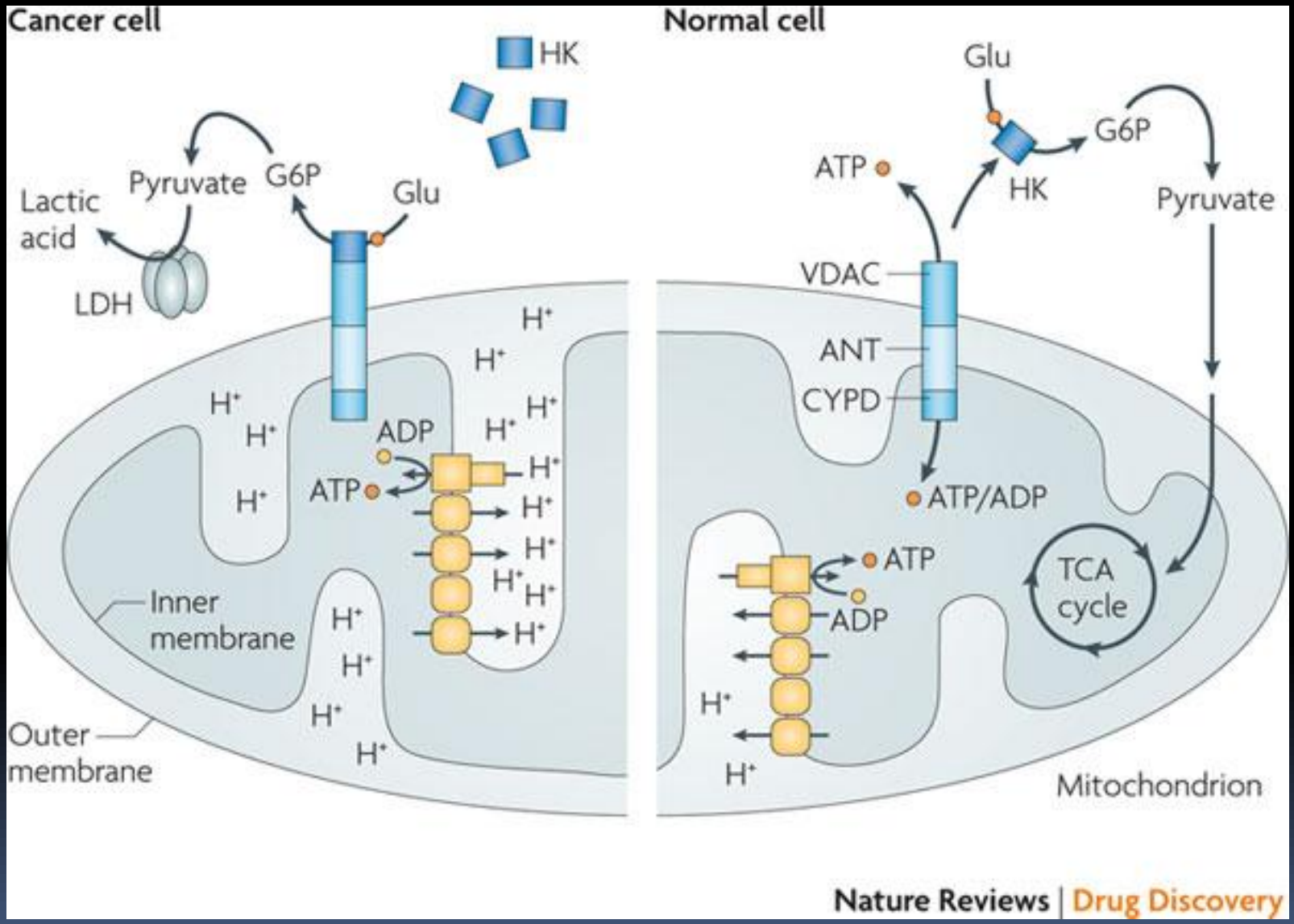
•1890 - Altman gave mitochondria the name "Bioblasts".

•1900 to 1930 - Scientists discovered the mitochondria produced 80% of the entire energy of the cell.

•1926 - Otto Warburg discovered that cancer cells produced their energy via glycolysis rather than glucose oxidation as in normal cells. He proposed that cancer mitochondria are the major target for developing cancer therapies.

•2011 - We are finally realizing how exceptional this research is in fighting cancer without damaging healthy cells.


Glucose
Glycolysis
Pyruvate
Fatty acids
Fatty Acyl-CoA
LCAD
β-oxidation
Amino acids
HMG-CoA synthase2
Acetyl-CoA
Ketogenesis
Ketone bodies
AceCS2
Acetate + CoA
ATP
NADP+
Antioxidant defense
Isocitrate
NADPH
IDH2
Gln
Glu
GDH
GDH
TCA cycle
α-Ketoglutarate
NH4+
CPS1
Urea cycle
H2O
MnSOD
SOD2
O2
O2-•
Antioxidant defense
e-
NADH
ADP
ATP
H+
H+
I
II
CoQ
III
Cyt C
IV
V
H+
ATP
Oxidative phosphorylation


Cancer cell
HK
Pyruvate
G6P
Glu
Lactic acid
LDH
H+
ADP
ATP
Inner membrane
Outer membrane
Normal cell
Glu
G6P
ATP
HK
Pyruvate
VDAC
ANT
CYPD
ATP/ADP
ATP
ADP
TCA cycle
Mitochondrion
Nature Reviews | Drug Discovery

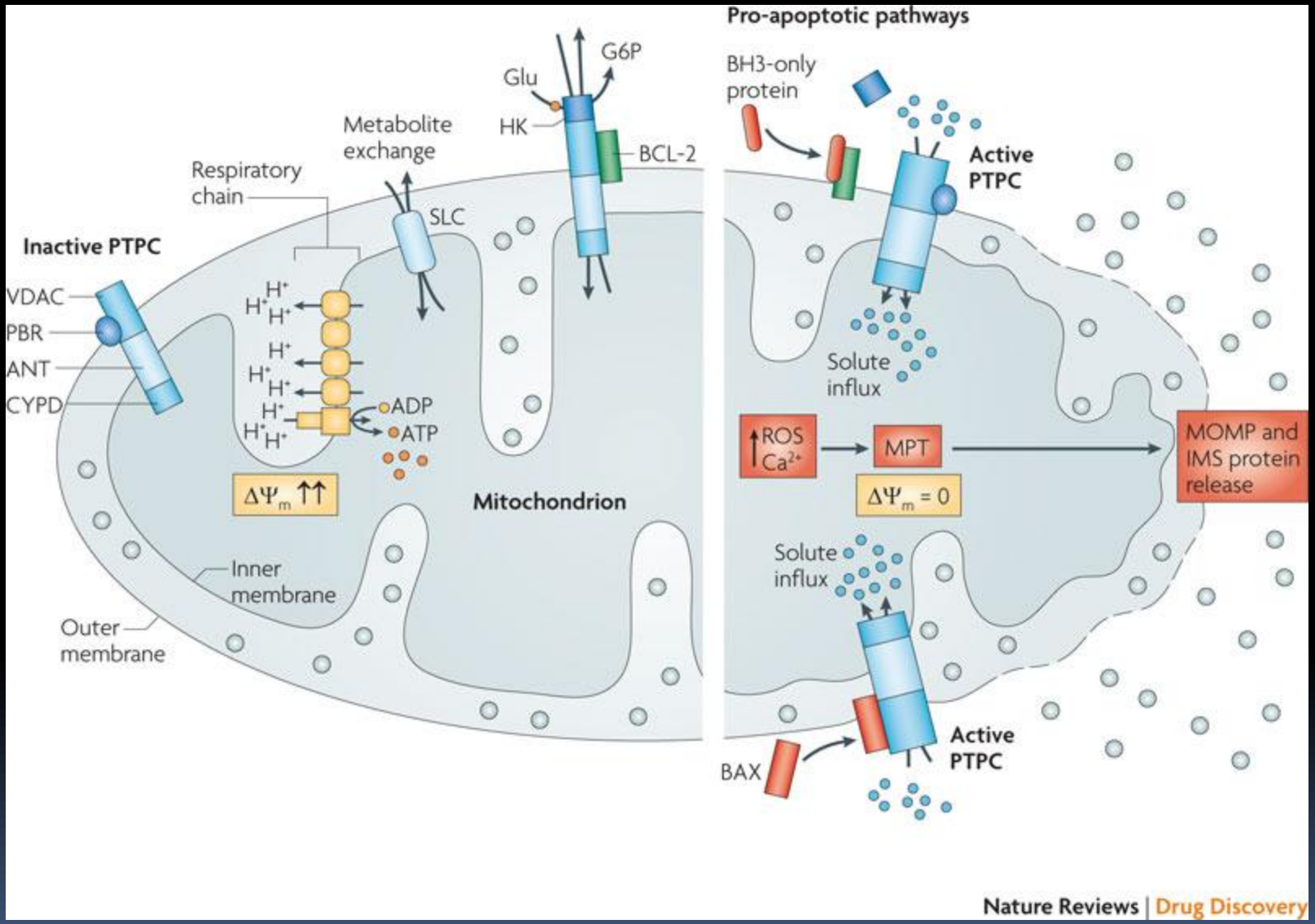
MITOCHONDRIAL CANCER TARGETS

A. Permeability transition pore complex (PTPC)

(1) Voltage dependent anion channel (VDAC) (outer membrane)

(2) Adenine nucleotide translocase (ANT) (inner membrane)

(3) Cyclophilin D (CYPD) (mitochondria matrix)


Pro-apoptotic pathways
BH3-only protein
Active PTPC
Solute influx
ROS
Ca2+
MPT
ΔΨm = 0
MOMP and IMS protein release
Solute influx
Active PTPC
BAX
Glu
G6P
HK
BCL-2
Metabolite exchange
SLC
Respiratory chain
Inactive PTPC
VDAC
PBR
ANT
CYPD
H+
ADP
ATP
ΔΨm ↑↑
Mitochondrion
Inner membrane
Outer membrane
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MITOCHONDRIAL CANCER TARGETS

B. Mitochondrial outer membrane permeabilization (MOMP)

(1) BCL-2
(2) HK2 (Hexokinase 2)
(3) PDK (Pyruvate dehydrogenase kinase)
(4) LDH (Lactate dehydrogenase)

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MITOCHONDRIAL CANCER TARGETS

C. ANT ligands for apoptosis

(1) Lonidamine

(2) Diazepam

increase efficacy of etoposides and ifosfamide

(combination 1 & 2 cytostatic in glioblastoma multiforme)

(3) Bisphosphonates: clodronate

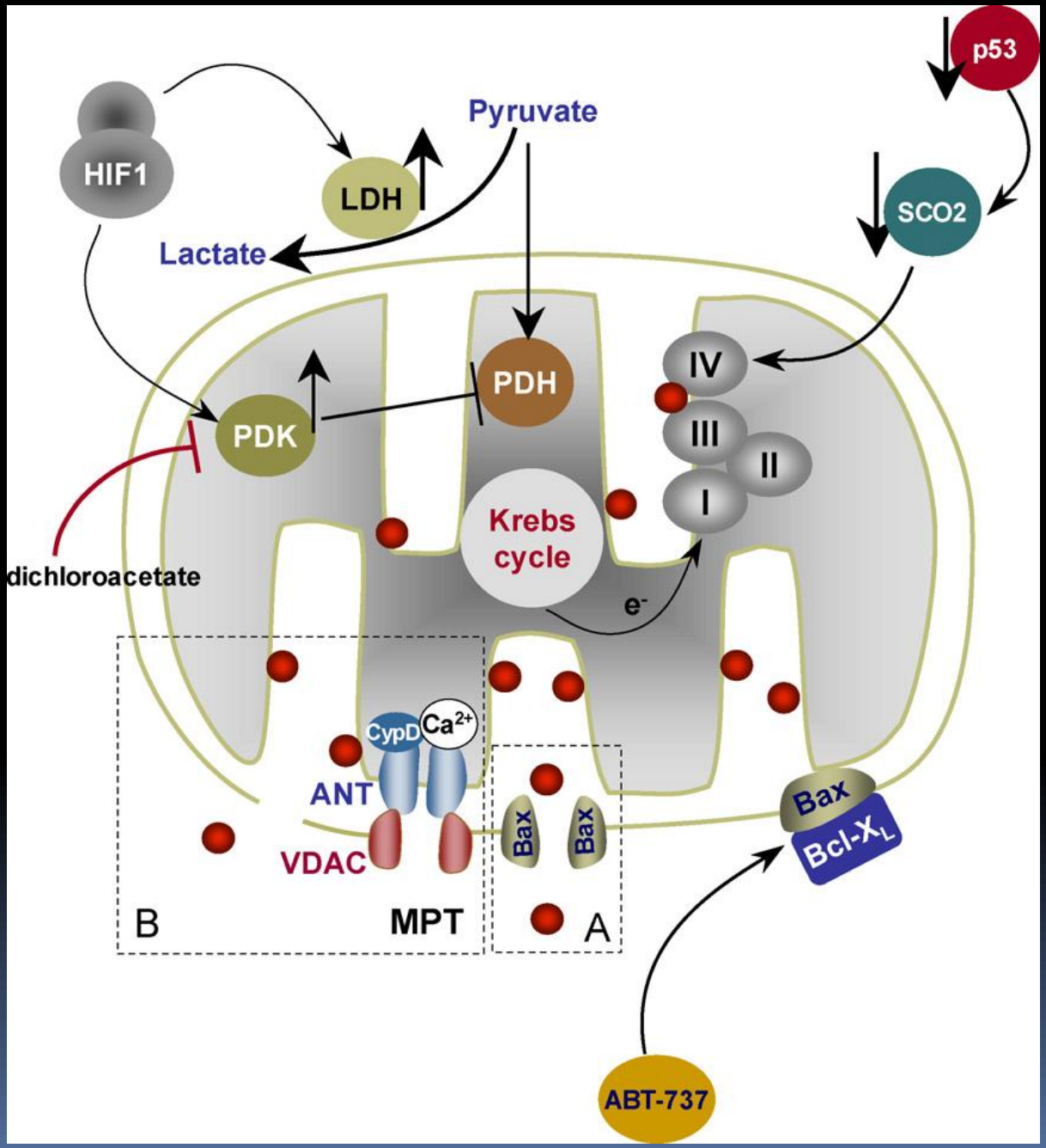
improves survival; decreases bone micrometastases post op breast cancer patients.

(4) Retinoids – all trans retinoic acid

MITOCHONDRIAL CANCER TARGETS

D. MOMP Targets

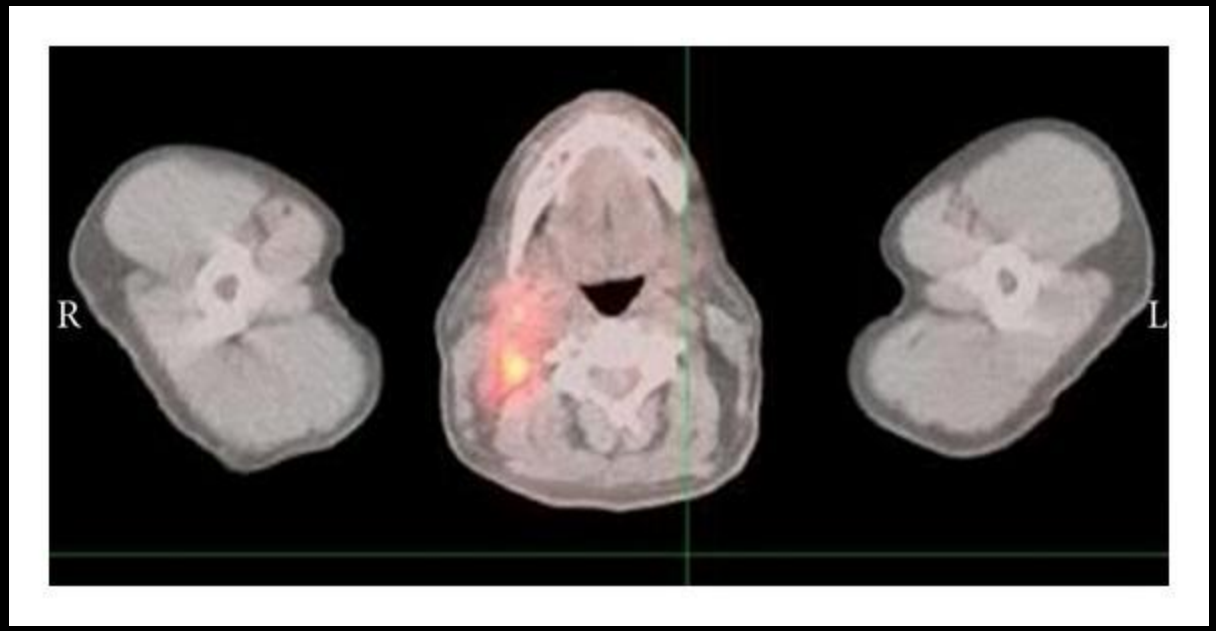
(1) Betacarotene – anti BCL-2
(2) 2-Bromopyruvate (3BP) anti HK2
(3) Dichloroacetate (DCA) anti PDK1
(4) Betulinicacid (depolarizes)
(5) Resveratrol
(6) Alpha tocopherol succinate


p53
Pyruvate
HIF1
LDH
Lactate
SCO2
PDH
PDK
IV
III
II
I
Krebs cycle
dichloroacetate
e-
CypD
Ca2+
ANT
VDAC
Bax
Bax
Bax
Bcl-XL
B
MPT
A
ABT-737

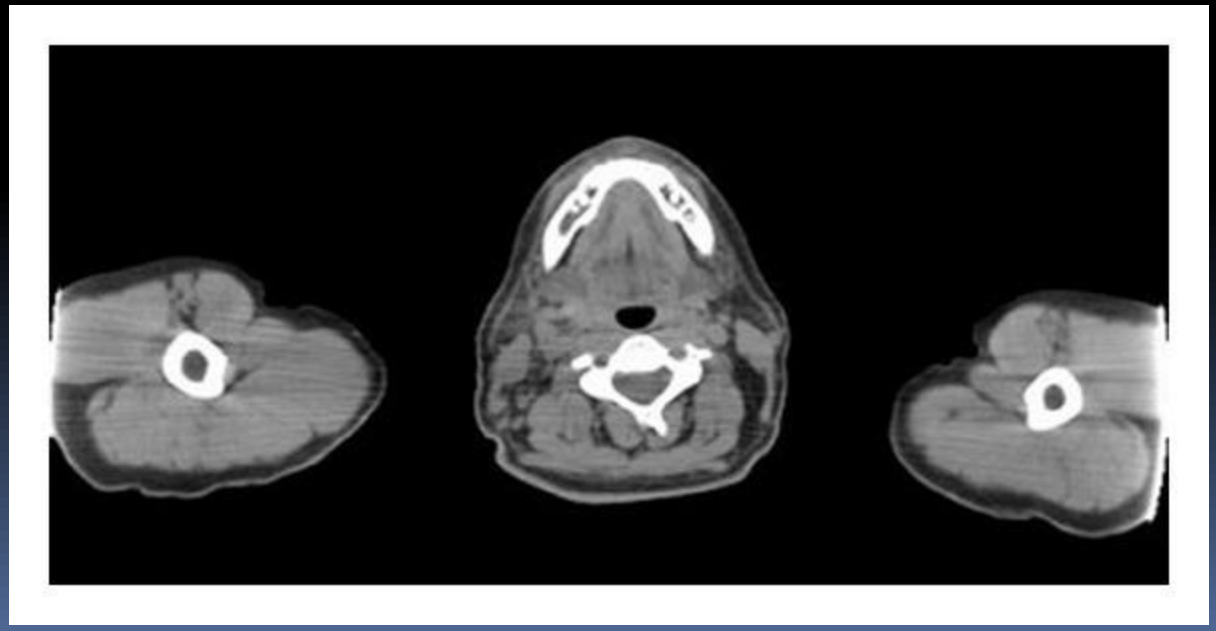
DCA

The PDK inhibitor induces apoptosis by shifting metabolism from glycolysis to glucose oxidation (resulting in mitochondrial depolarization), and upregulating the K^+ channel Kv1.5.

NHL

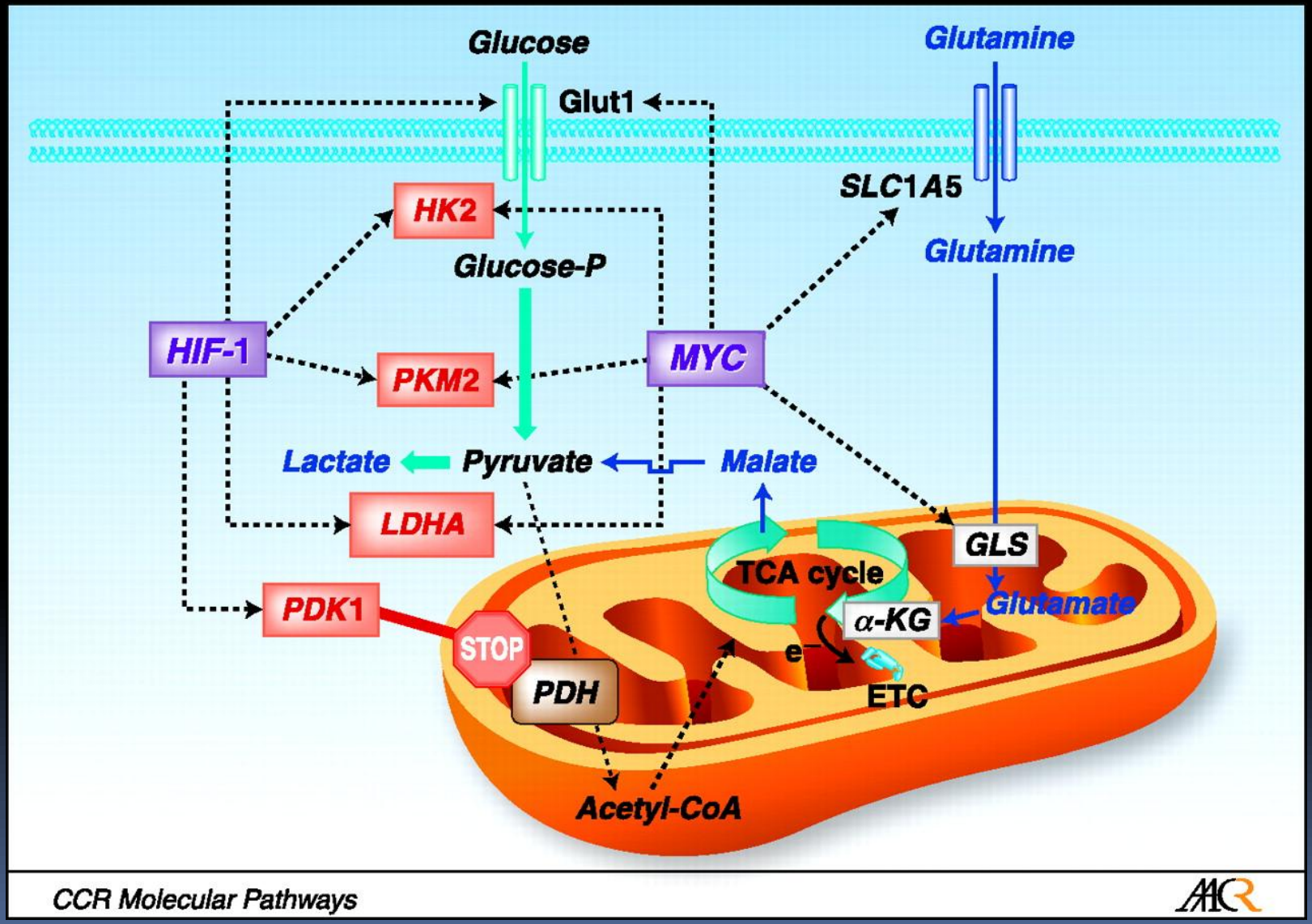


NHL
+
DCA



7 weeks

Myc and HIF-1 regulate glucose metabolism and stimulate the Warburg effect.



MTC
Tumor marker
39,000

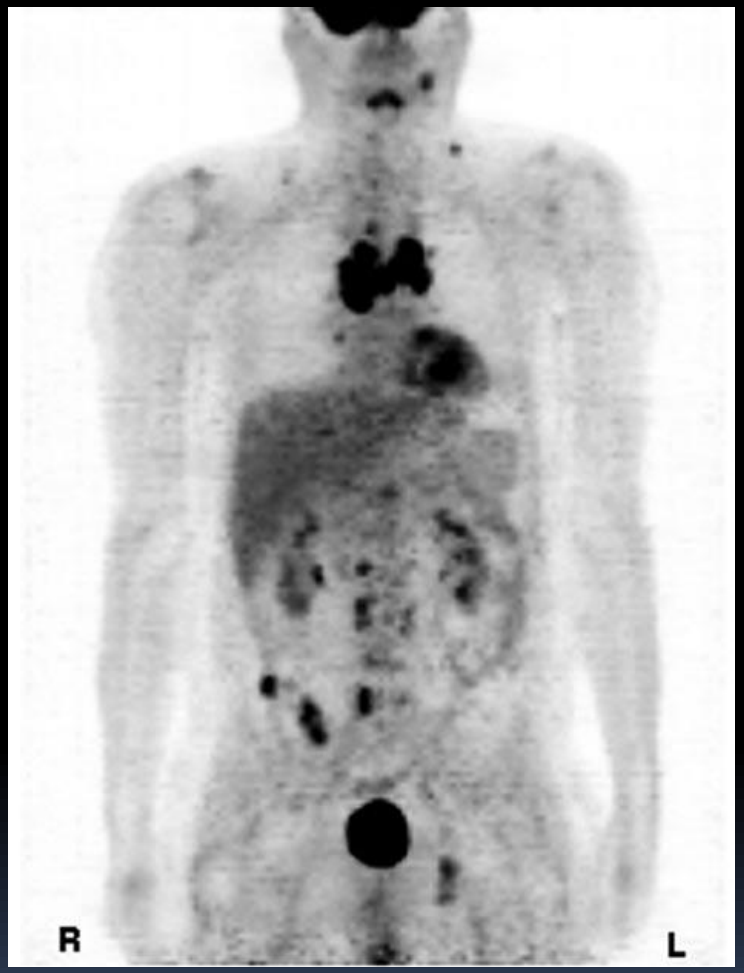
MTC

+

DCA

Tumor Marker

2,000


R
L


R
L

CONCLUSION:

Mitochondria in cancer cells exhibit abnormal changes that can be targeted to destroy only cancer cells and not normal cells. Activation or inhibition of these targets are showing tremendous success in cancer therapies, reversing tumors and dramatically prolonging survival. Our patients will benefit from this new mitochondrial research that is changing the direction of cancer therapy. Instead of temporary remission, we are now finding cures.

The future of medicine is in our hands

TODAY!

SAVING LIVES, ONE AT A TIME