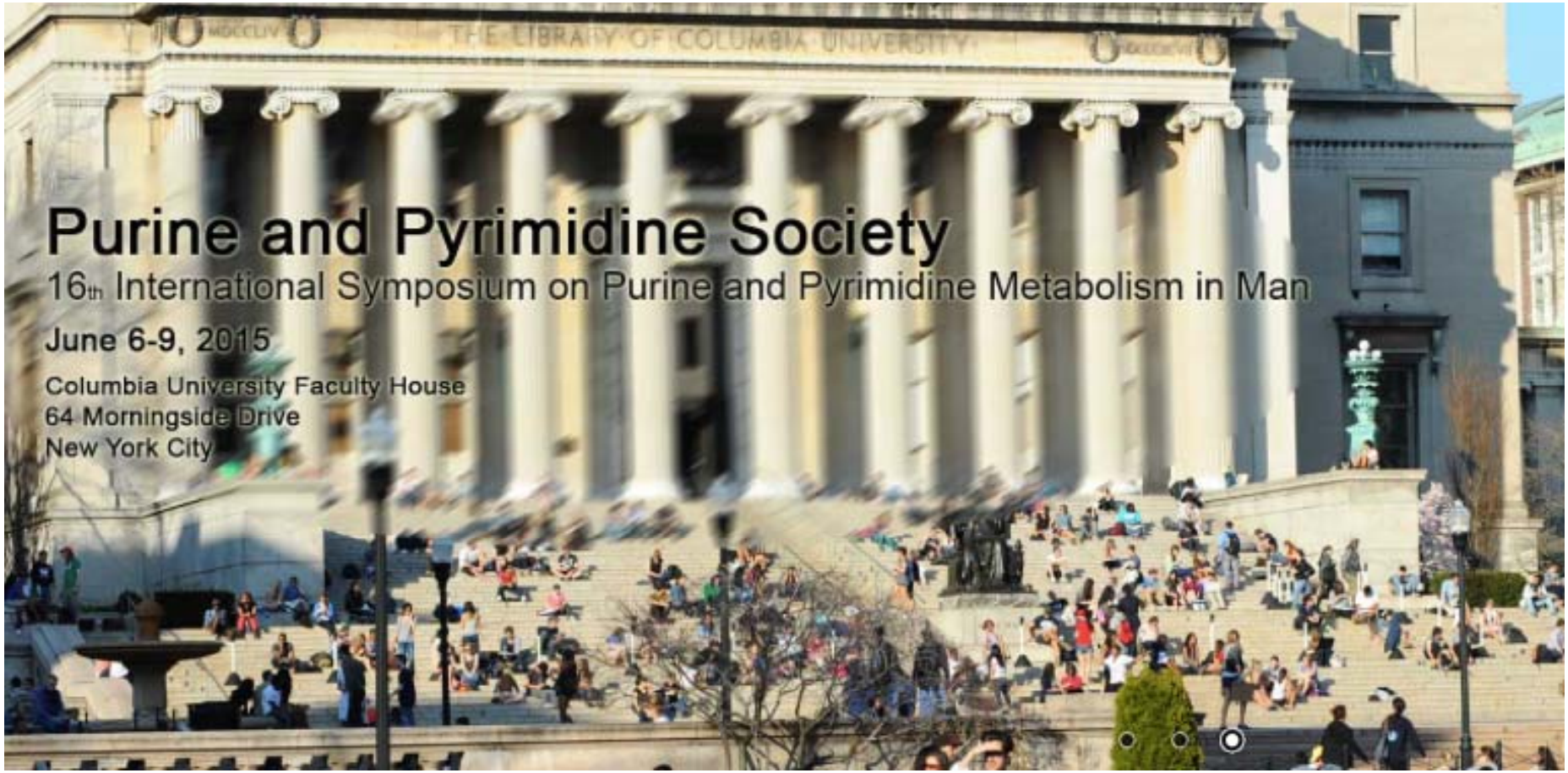
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Purine and Pyrimidine Society
16th International Symposium on Purine and Pyrimidine Metabolism in Man
June 6-9, 2015
Columbia University Faculty House
64 Morningside Drive
New York City

16th International Symposium on Purine and Pyrimidine Metabolism in Man

The Purine and Pyrimidine Society
Physicians and Scientists Investigating Purines and Pyrimidines in Man

Inhibitors of lactate dehydrogenase overcome the resistance towards gemcitabine in hypoxic mesothelioma cells, and modulate the expression of the human equilibrative transporter-1 (hENT1)

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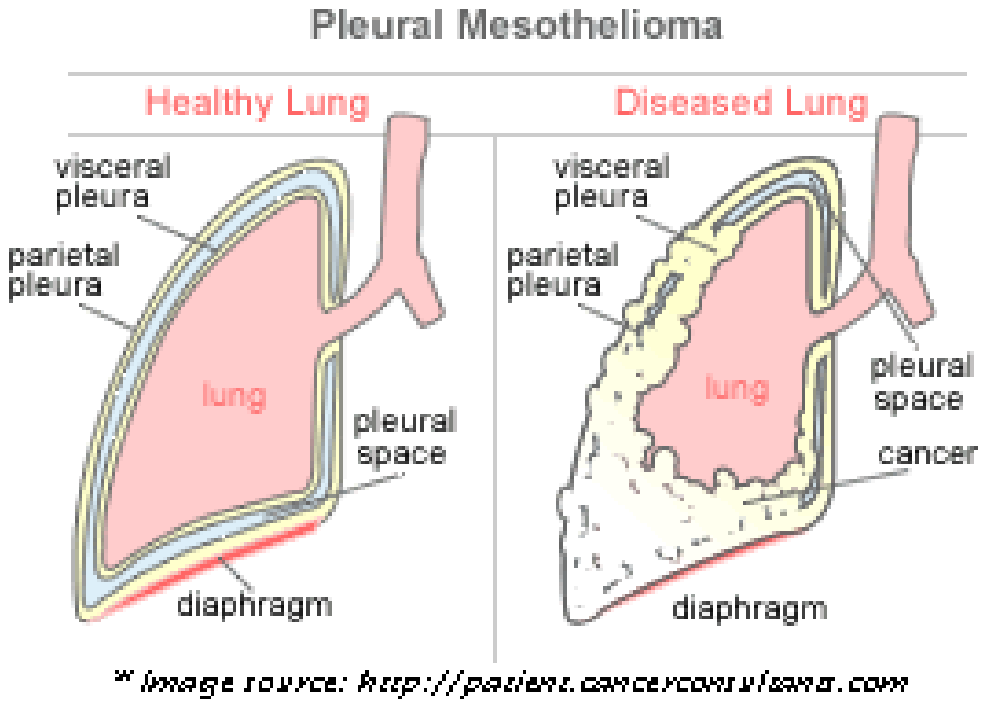
Outline

1. Introduction
    - Mesothelioma
    - LDH inhibitors
    - Gemcitabine
2. Effect of gemcitabine and LDH inhibitor NHI-1
3. Role of hypoxia
4. Effect of hypoxia on gemcitabine metabolizing enzymes
5. Effect of LDH inhibition

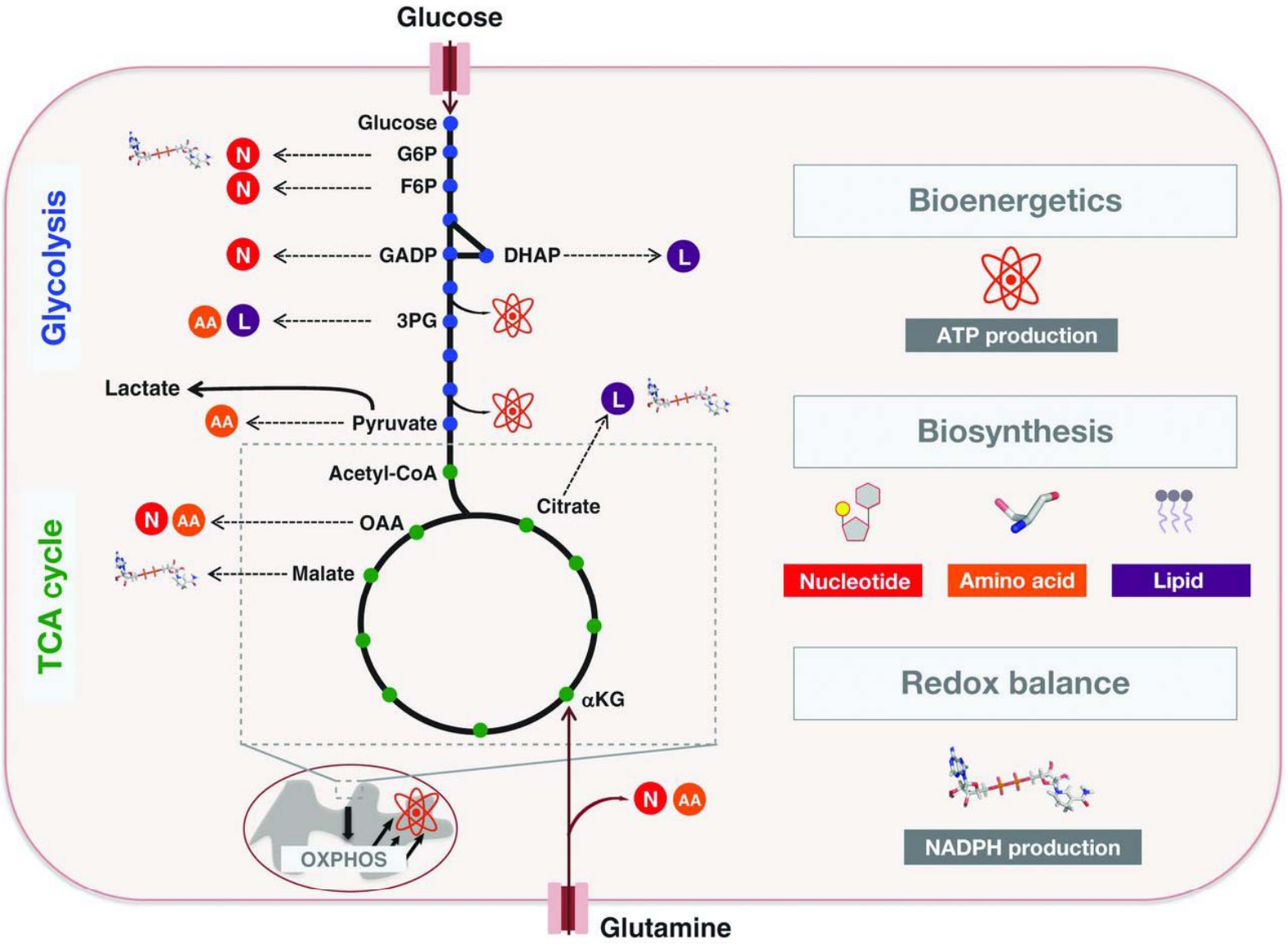
Pleural Mesothelioma; asbestos related



* Image source: http://patient.cancercons/sana.com

- 5 years survival of advanced stages between 5 and 15%
- Relatively insensitive to any therapy (usually platinum based with pemetrexed or 2nd line with gemcitabine)

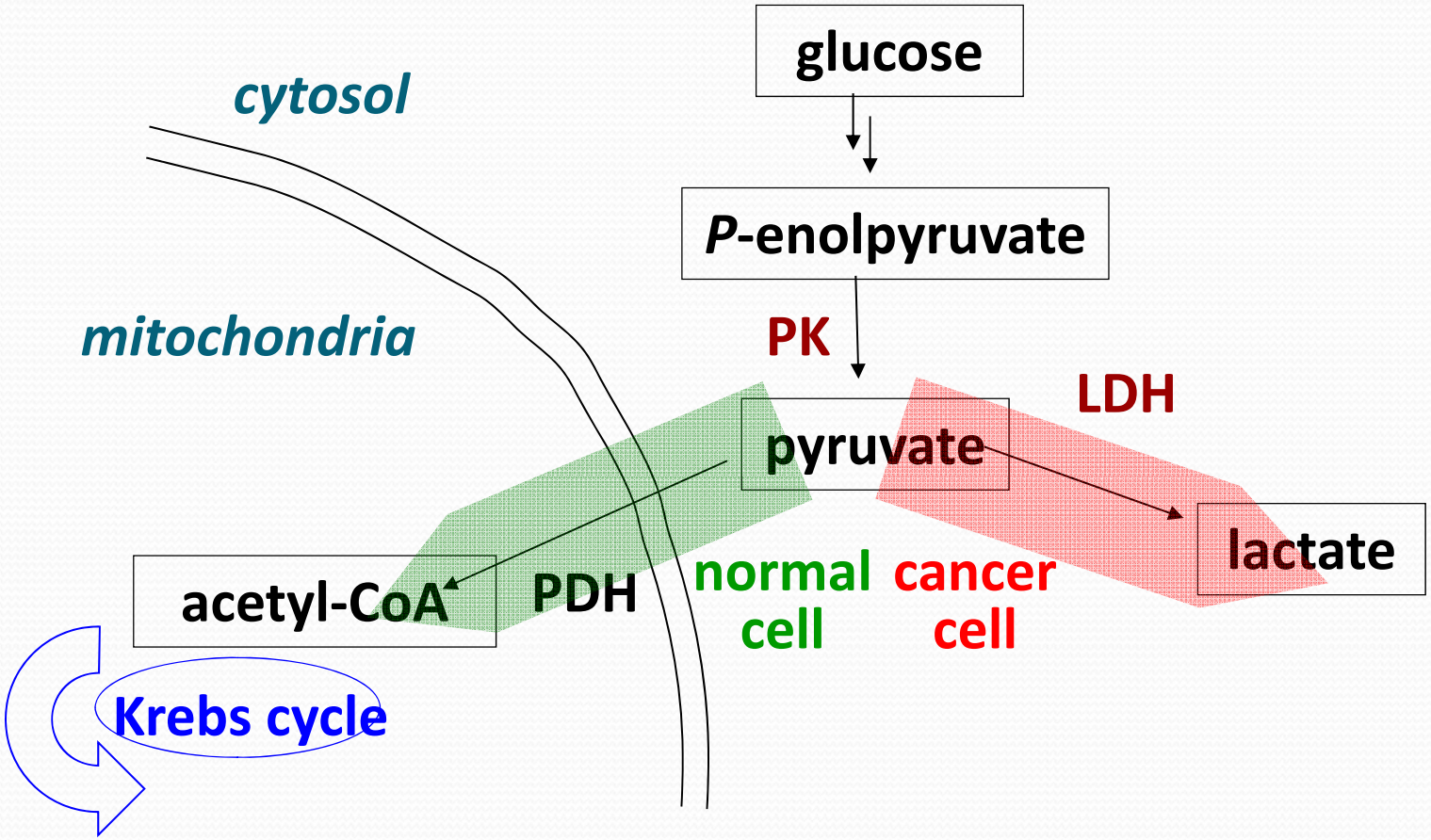
Role of glycolysis in nucleotide supply



Jason R. Cantor, and David M. Sabatini Cancer Discovery 2012;2:881-898

AACR American Association for Cancer Research CANCER DISCOVERY

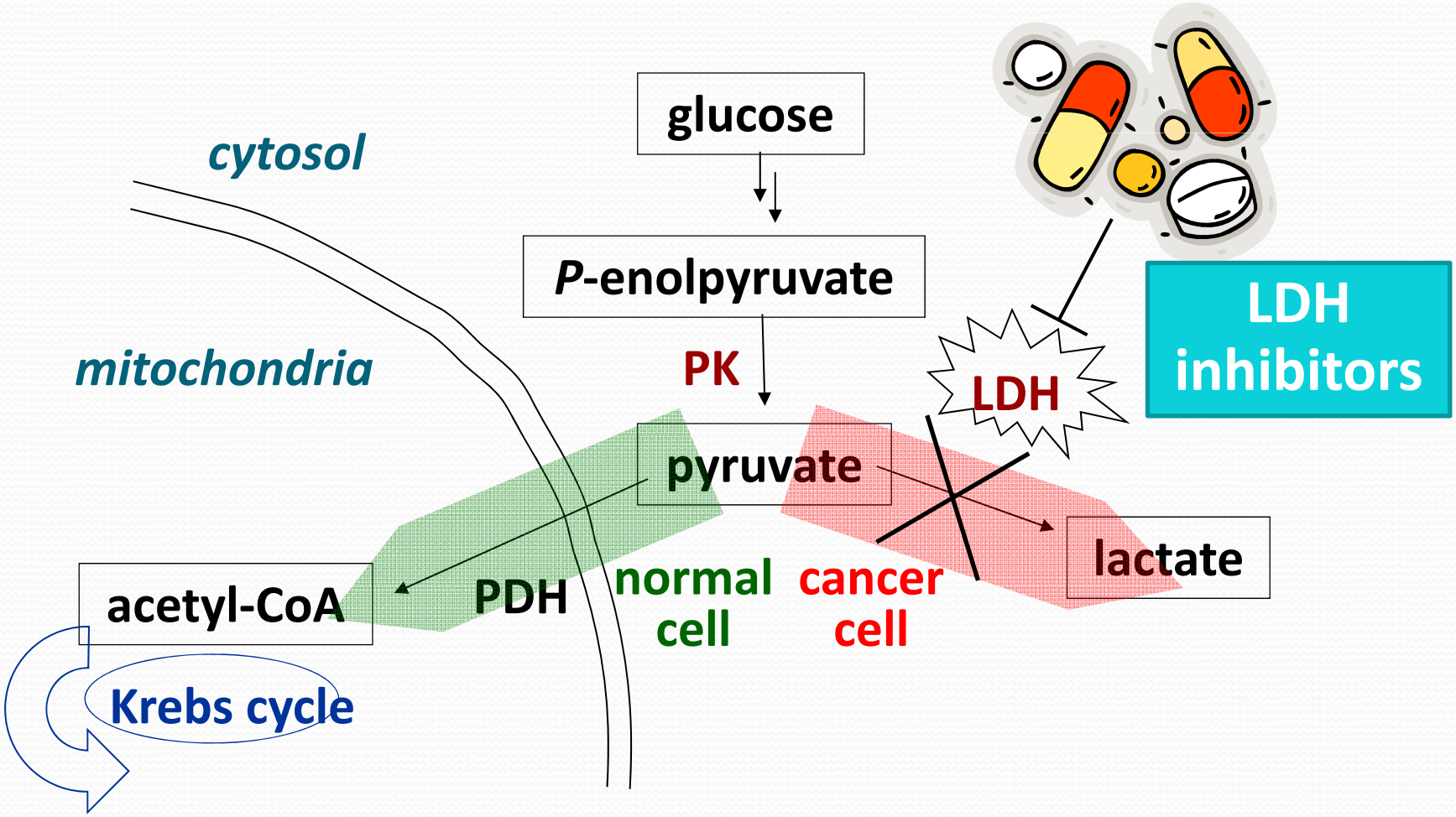
The glycolytic switch



In most cancer cells:

- Oxydation of NADH to NAD^+ for the production of ATP through glycolysis
- High consuption of glucose and production of lactate
- LDH plays a pivotal role for the energy supply

Aim: evaluate drugs inhibiting LDH in pancreatic cancer cells



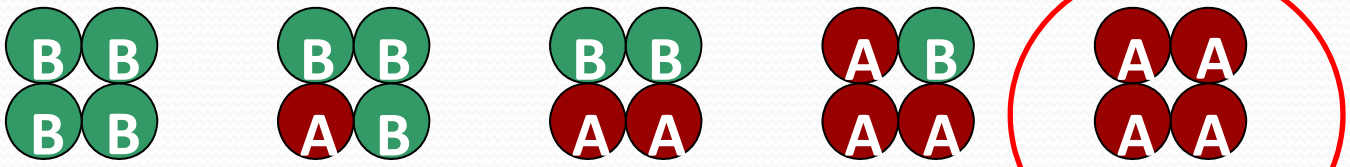
LDH features

LDH is a tetrameric enzyme with 5 isoforms, mostly located in the cytosol

Only two types of subunits

A or LDH-M, Muscle

B or LDH-H, Heart

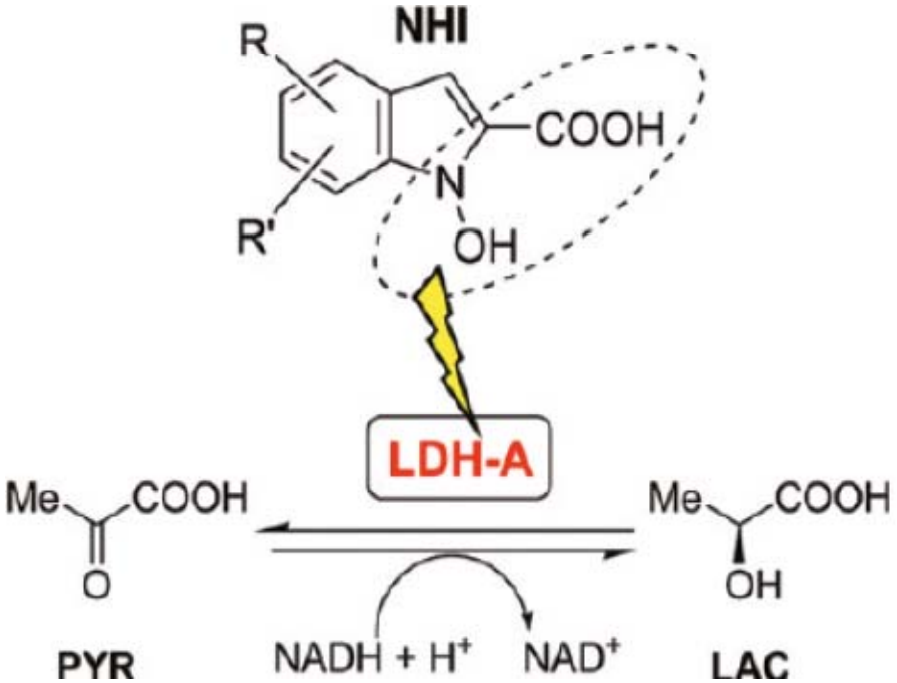


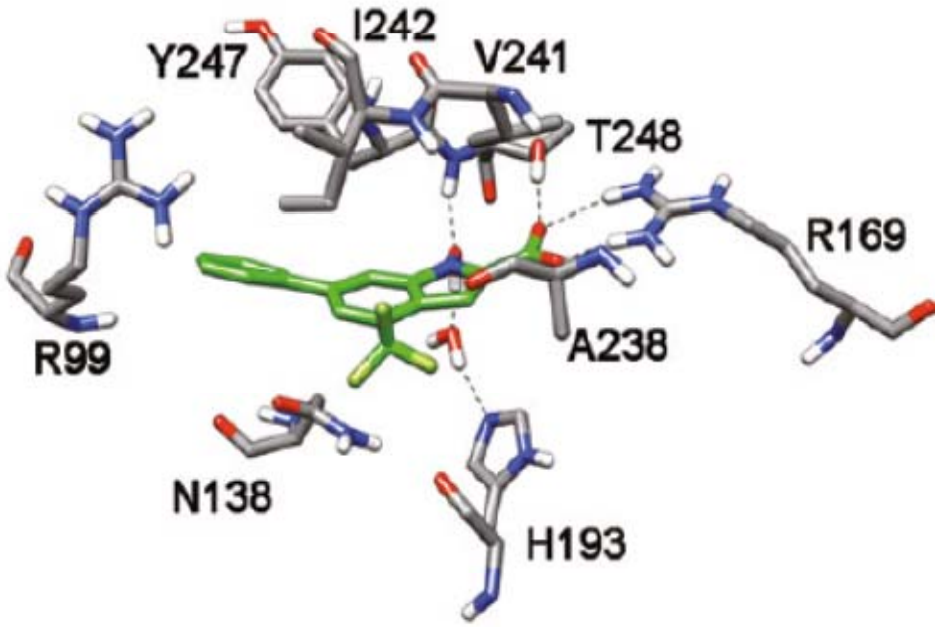
Prevalent in heart

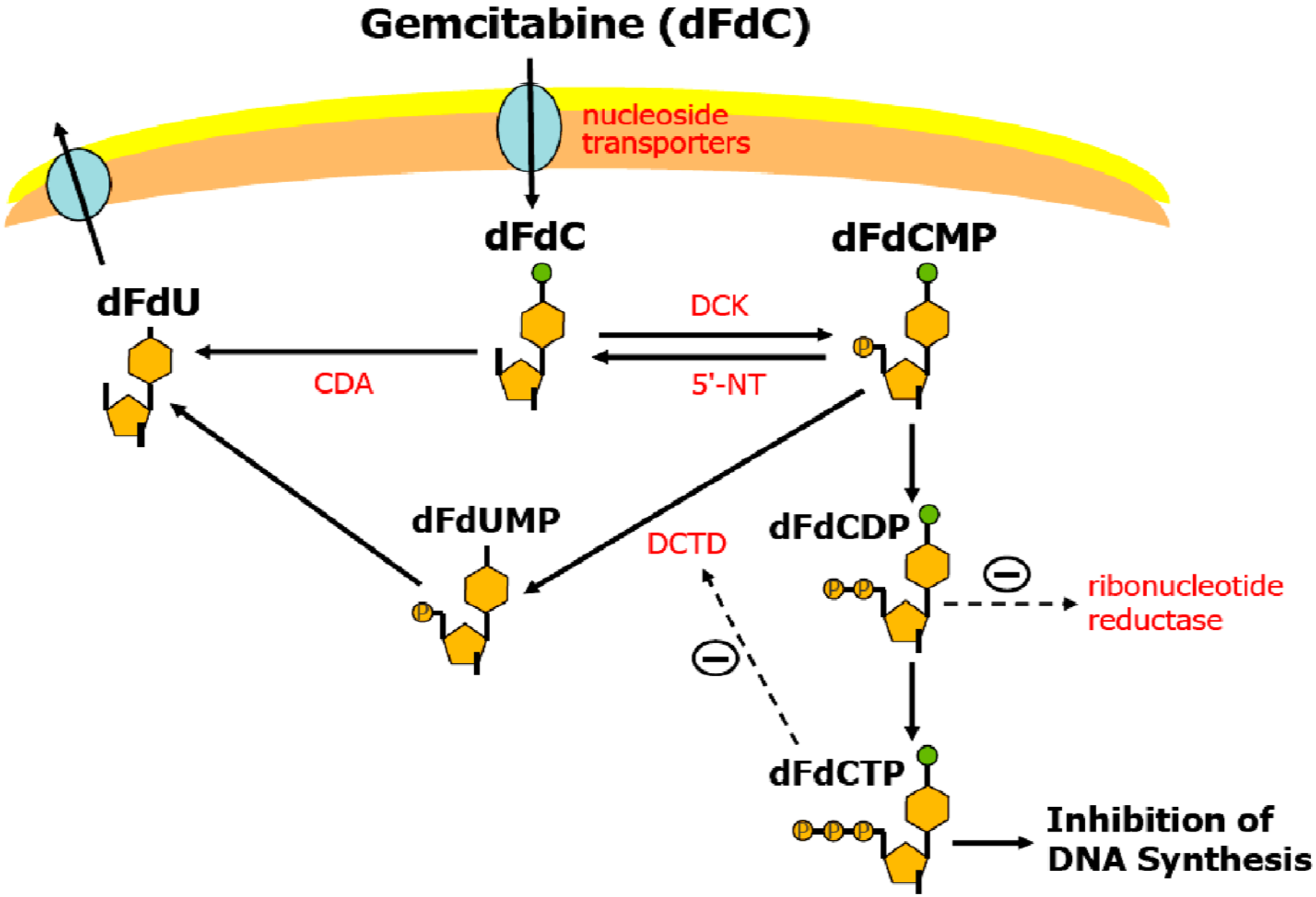
Prevalent in liver and skeletal muscle

- LDH5 overexpressed in highly invasive and hypoxic carcinomas
- LDH5 associated with Hypoxia Inducible Factor HIF-1α

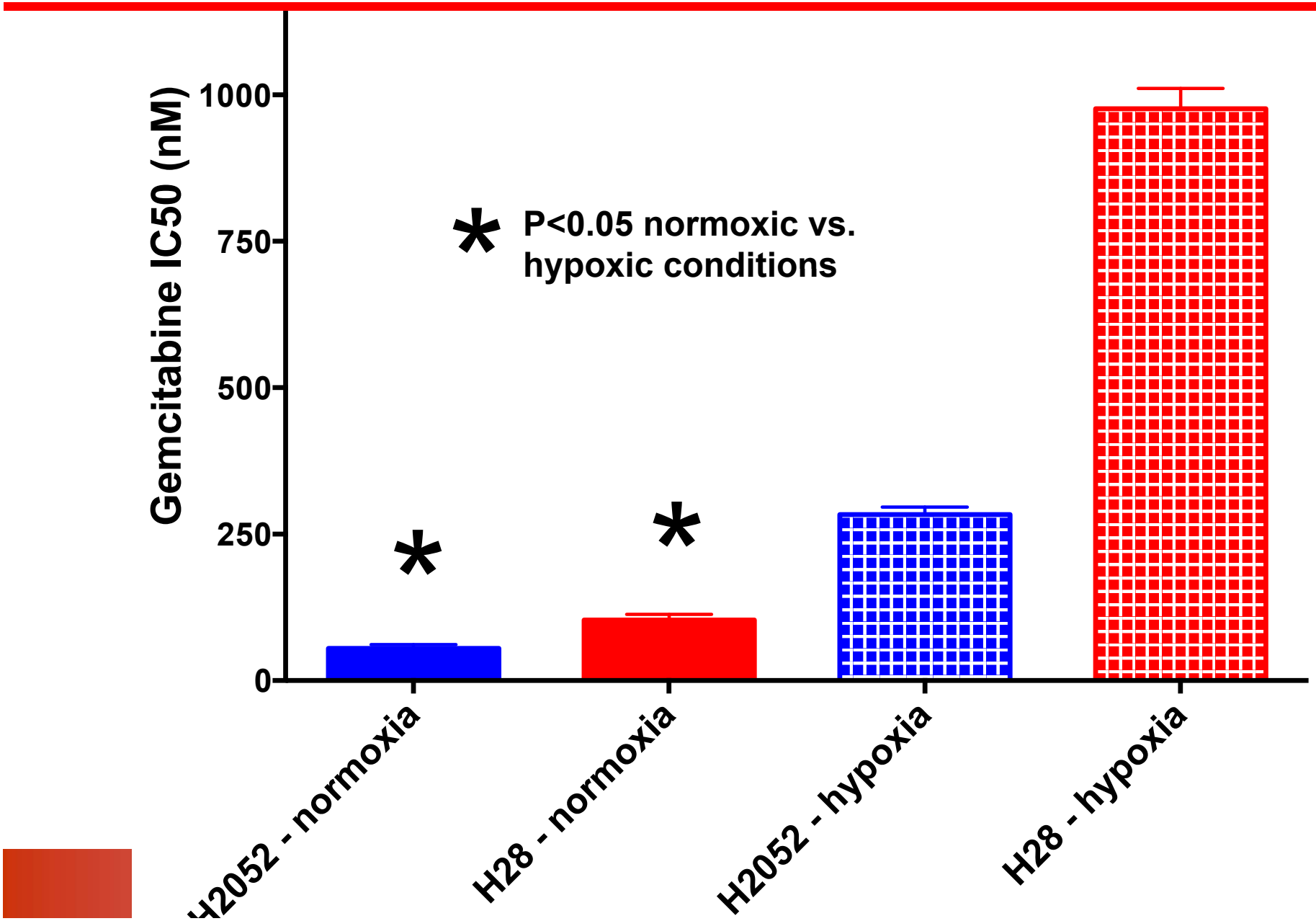
Optimization of LDH inhibitors



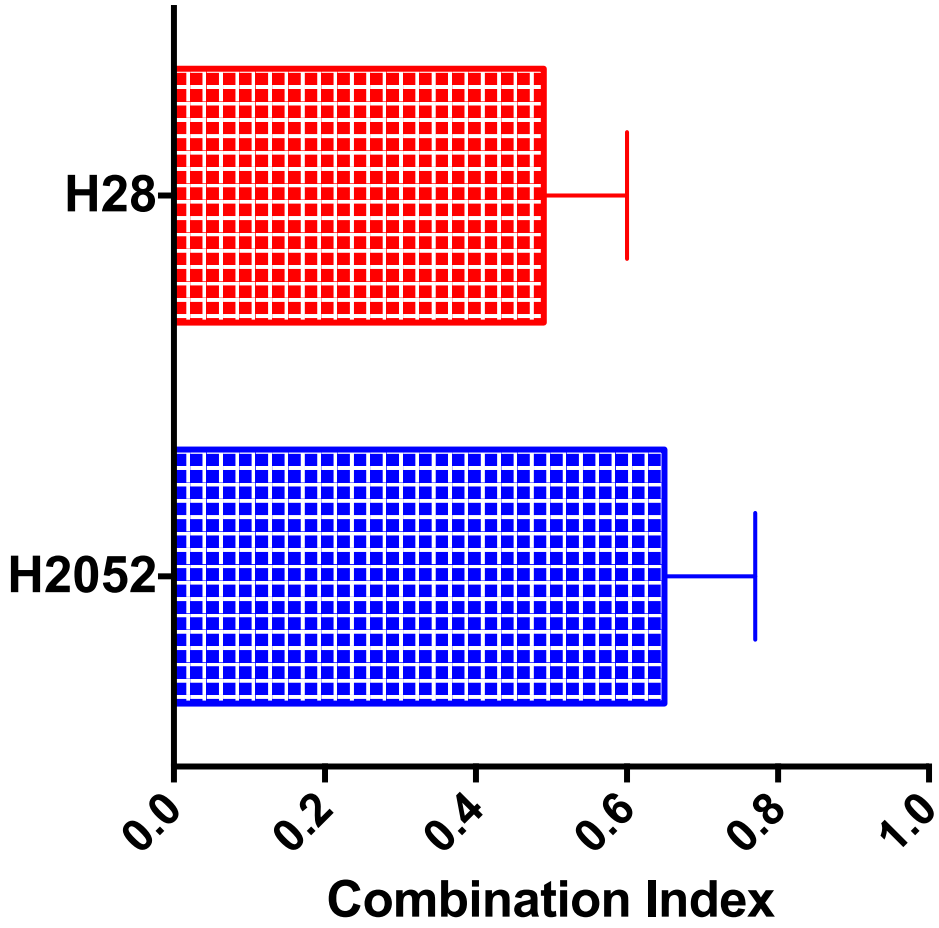



Gemcitabine (dFdC)
nucleoside transporters
dFdC
dFdCMP
dFdU
DCK
CDA
5'-NT
dFdUMP
DCTD
dFdCDP
ribonucleotide reductase
dFdCTP
Inhibition of DNA Synthesis

Hypoxia decreases gemcitabine sensitivity



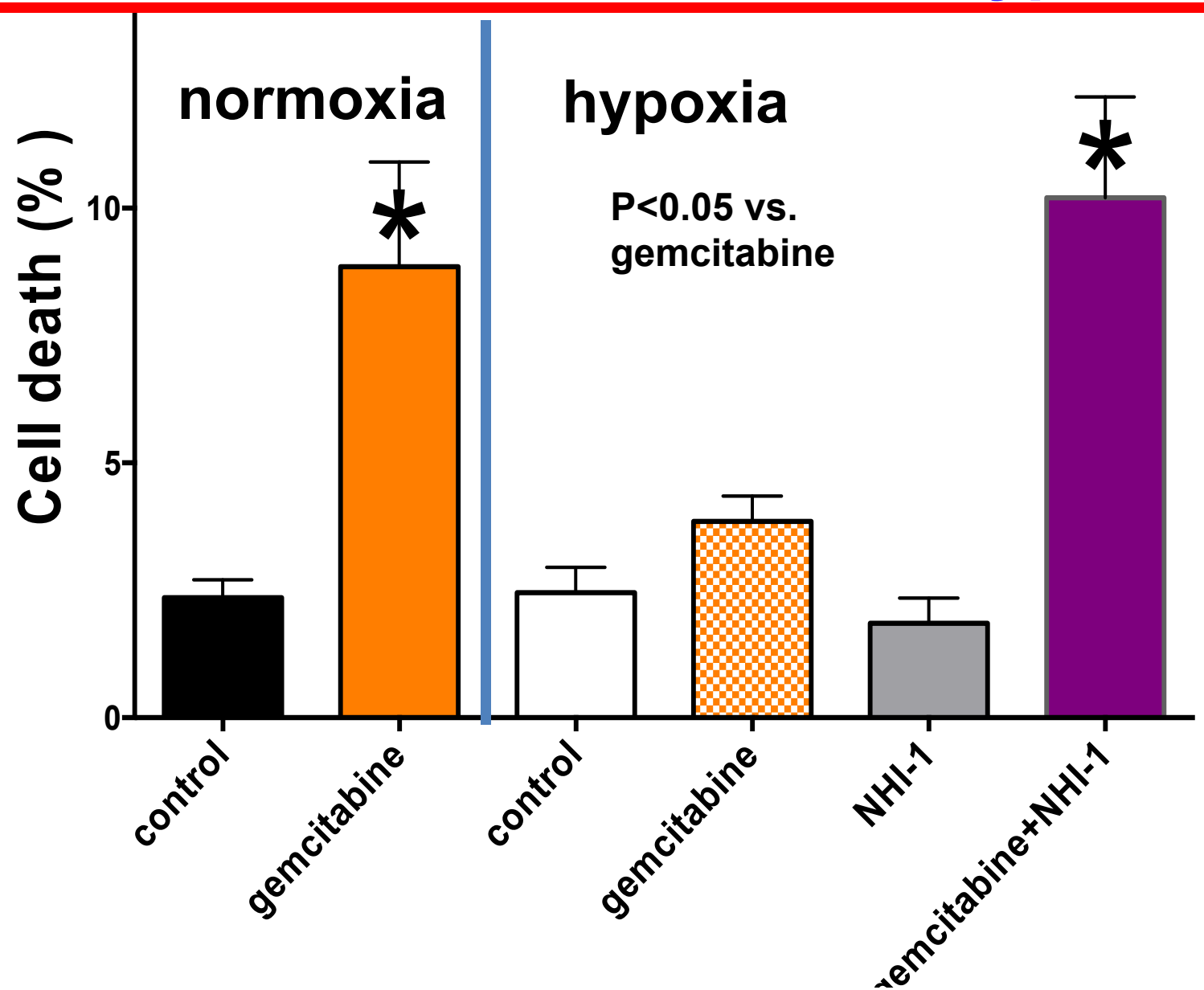
LDH inhibition synergizes with gemcitabine under hypoxia



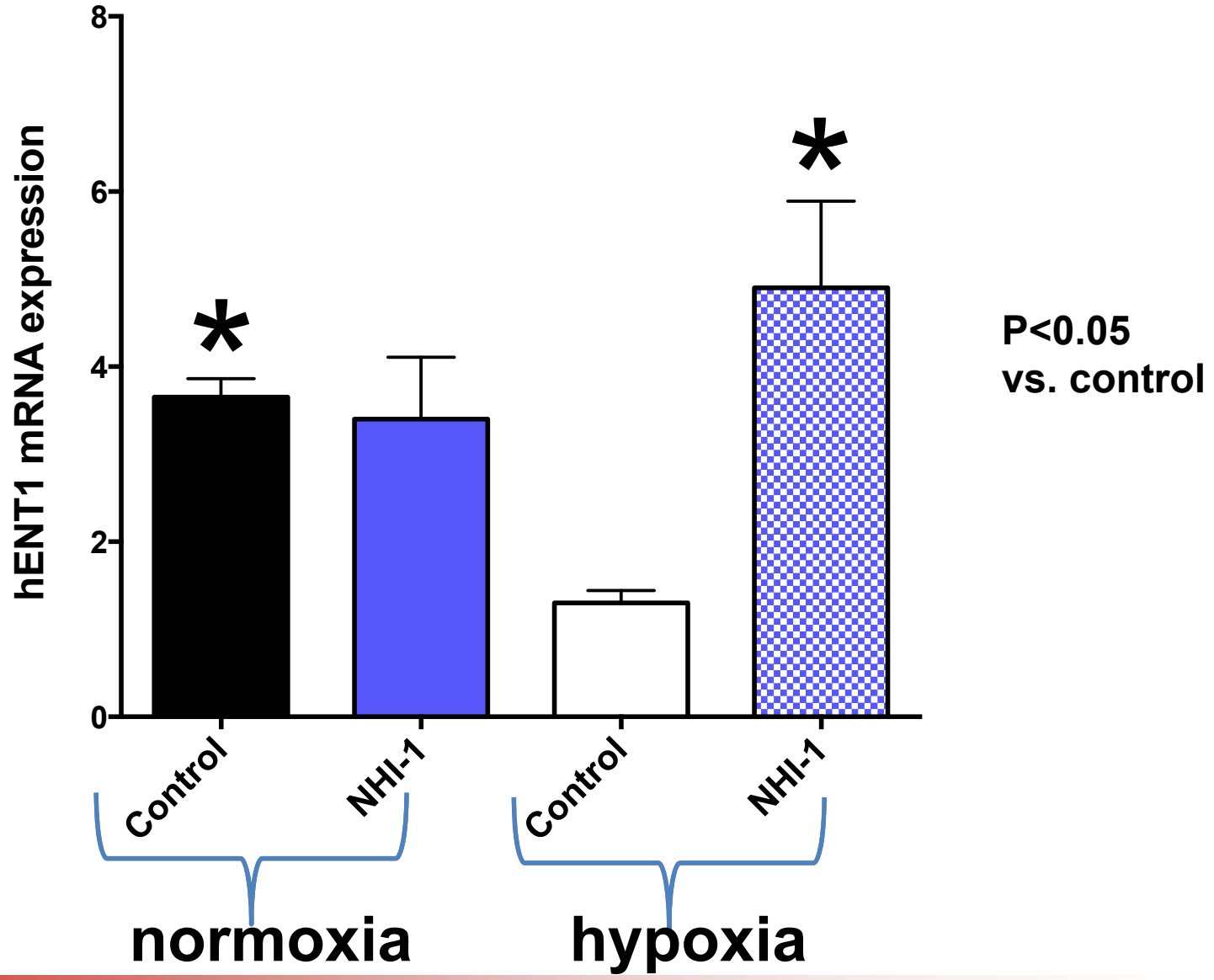
Combination index:

CI >1.2: antagonism
0.8 < CI < 1.2: additive
CI < 0.8: synergism

NHI-1 enhances gemcitabine induced cell death in H28 cells under hypoxia



LDH inhibition restores hENT1 expression



Conclusions

✓**The new LDH inhibitor NHI-1**

1) **Blocked cell proliferation under hypoxic conditions**
2) **Interacted synergistically with gemcitabine**
3) **Induced apoptosis**
4) **Rescued hENT1 mRNA expression in hypoxic conditions**

➢**LDH-A inhibition synergism with gemcitabine forms a novel strategy targeting hypoxic alterations of glucose metabolism for mesothelioma**

Acknowledgements

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