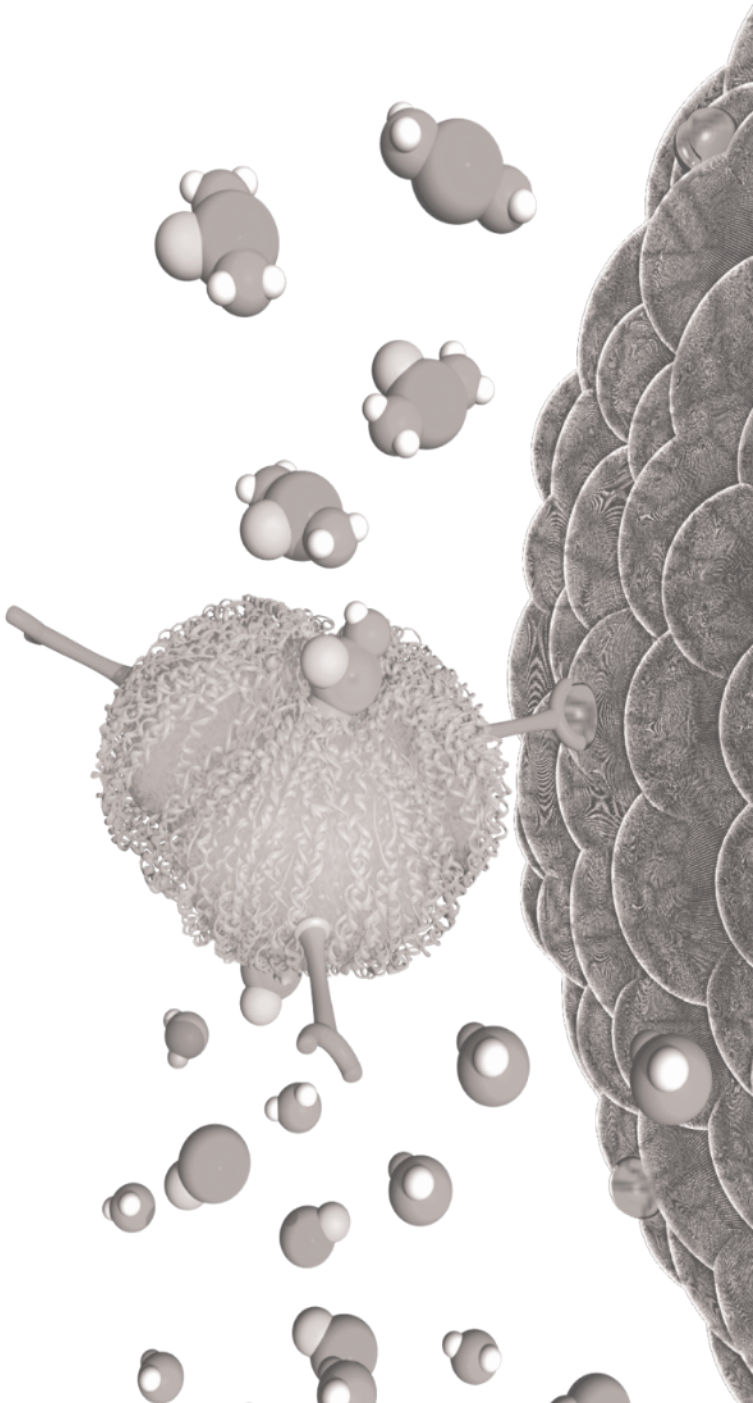
HelixBioPharmaCorp.

Therapeutic Strategy Against Tumor Acidity Induced Immune-Suppression: L-DOS47 a Clinical Candidate for Lung Cancer



Precision Lung Cancer Summit
Boston USA
Sept 2016

Forward-looking Statements

This presentation document contains certain forward-looking statements and information (collectively, "forward-looking statements") within the meaning of applicable securities laws. Forward-looking statements are statements and information that are not historical facts but instead include financial projections and estimates; statements regarding plans, goals, objectives, intentions and expectations with respect to Helix's future business, operations, research and development, including the focus of Helix on its DOS drug candidate generally and L-DOS47 in particular, the anticipated timelines for the commencement or completion of certain activities, including enrolment of patients in Helix's Phase I/II clinical trial for L-DOS47 in Poland, the expansion of the DOS47 platform into other compounds and indications and other information in future periods. Forward-looking statements, which may be identified by words including, without limitation, "expects", "plans", "will", "intends", "may", "pending", "objective", "exploring", "potential", "projected", "possible" and other similar expressions, are intended to provide information about management's current plans and expectations regarding future operations.

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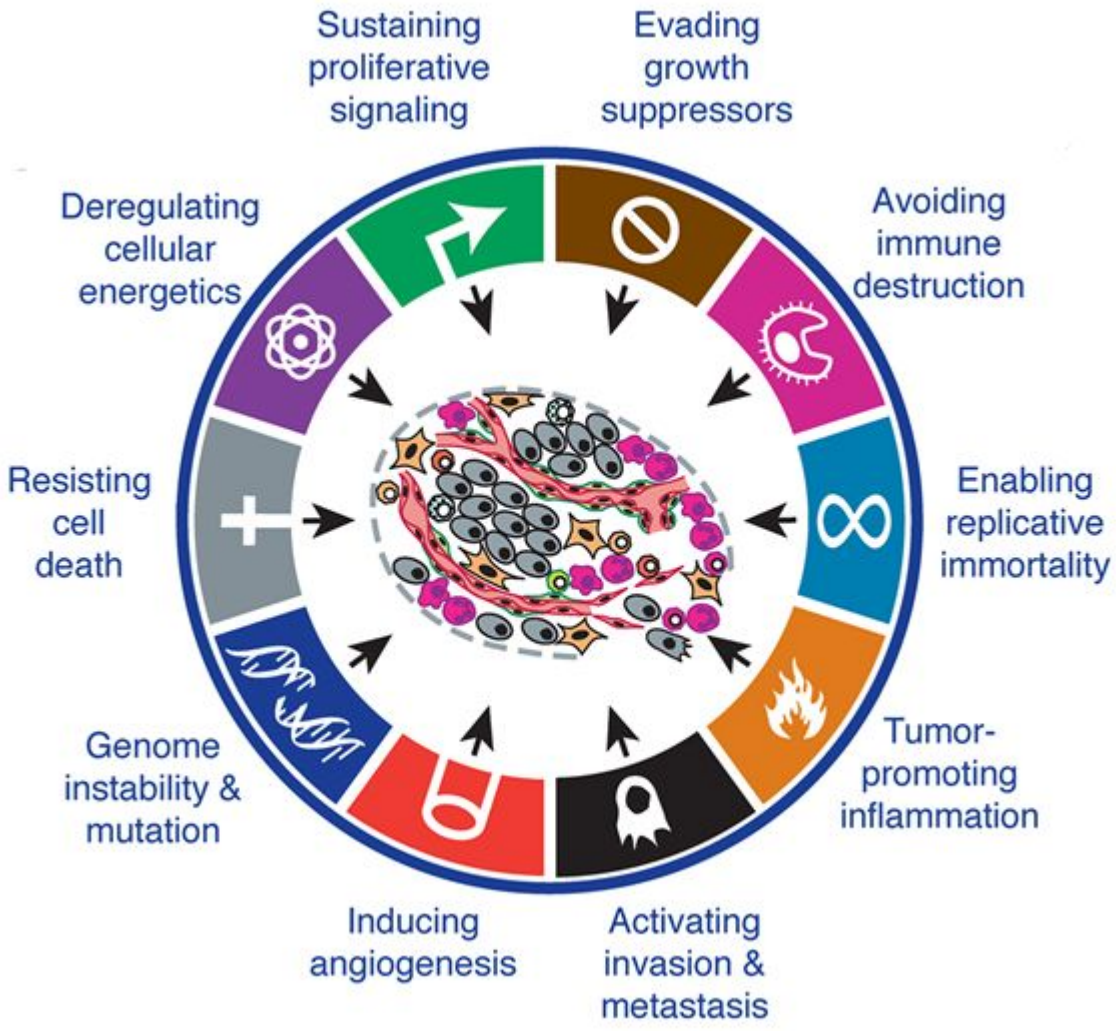
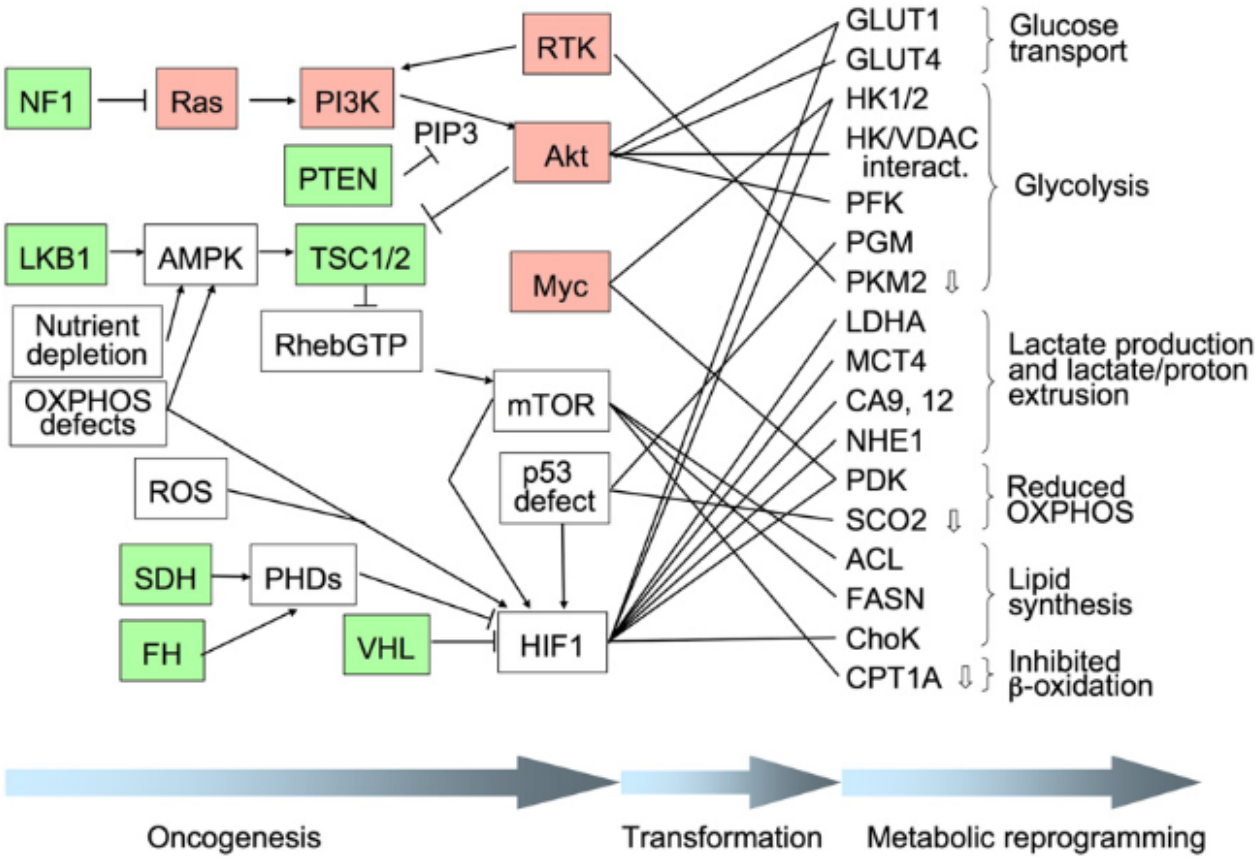
The Hallmarks of Cancer



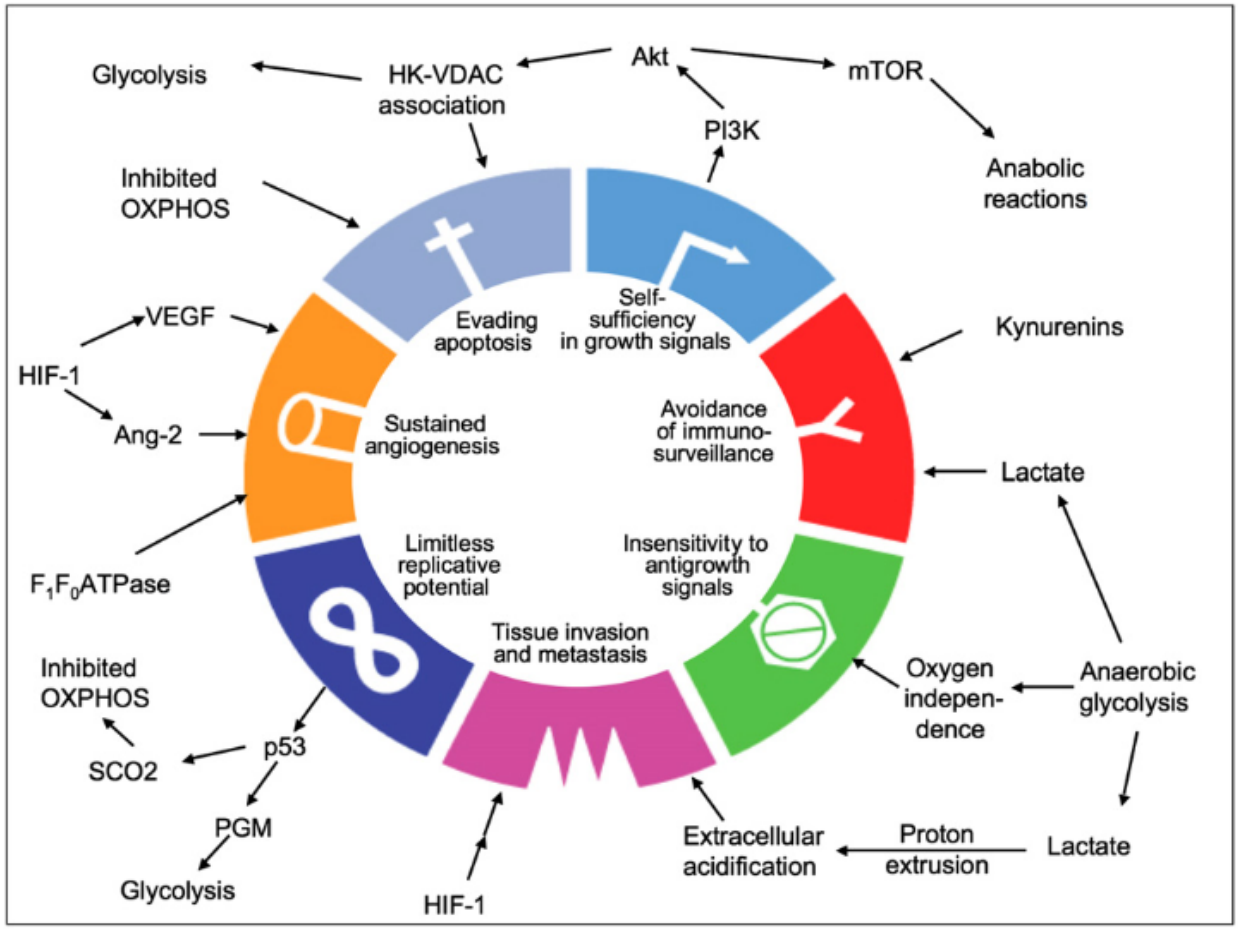
Cell 2011 144, 646-674

Metabolic Reprogramming



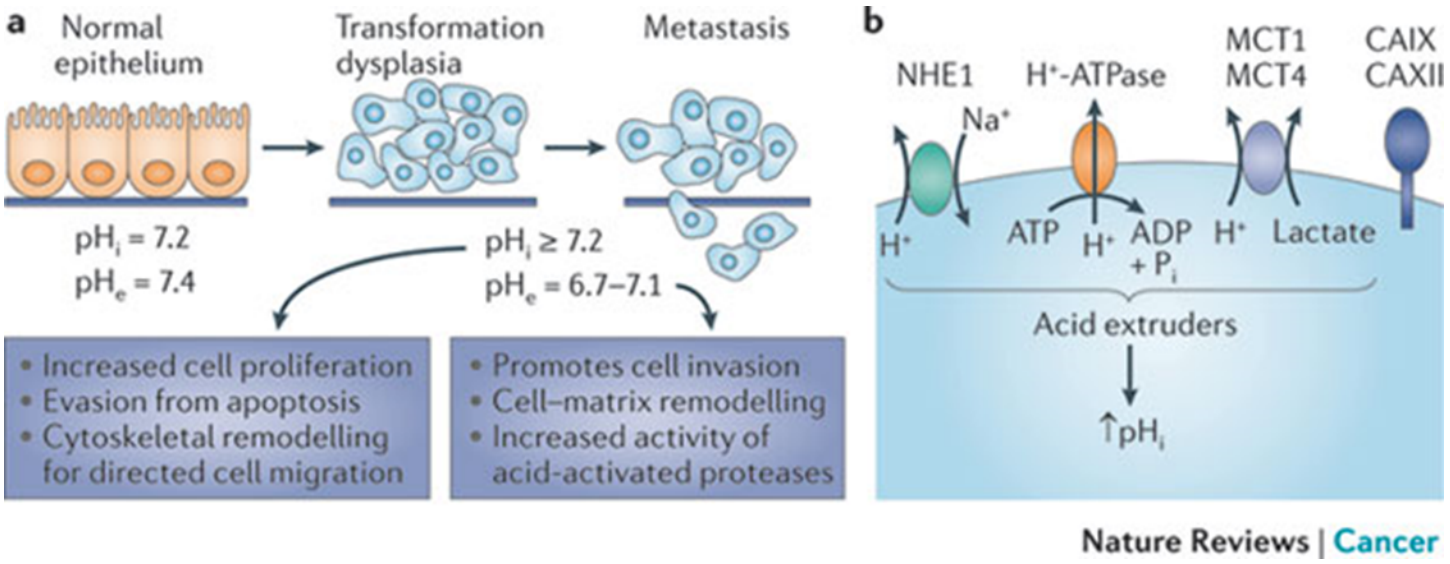
Cancer Cell 2008, 13 472-482

Cancer Hallmarks Link to Metabolism



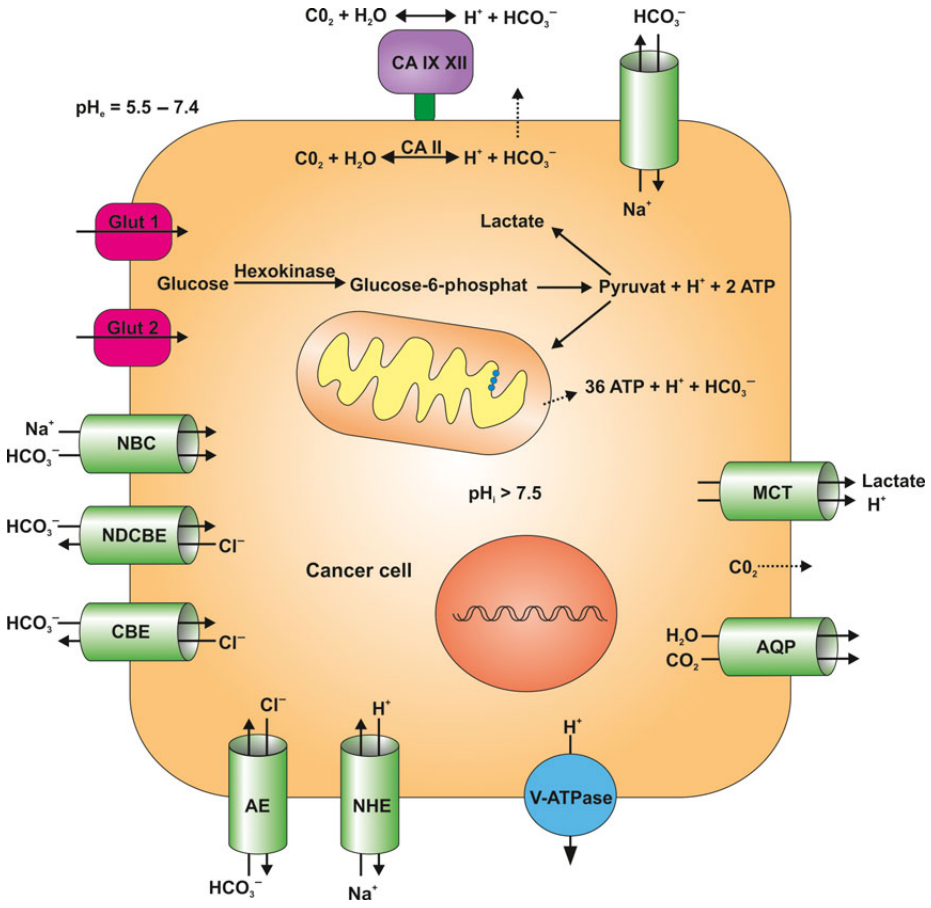
Cancer Cell 2008, 13 472-482

Dysregulated pH is Emerging as a Hallmark of Cancer



Nature Reviews Cancer 11, 671-677 (September 2011)

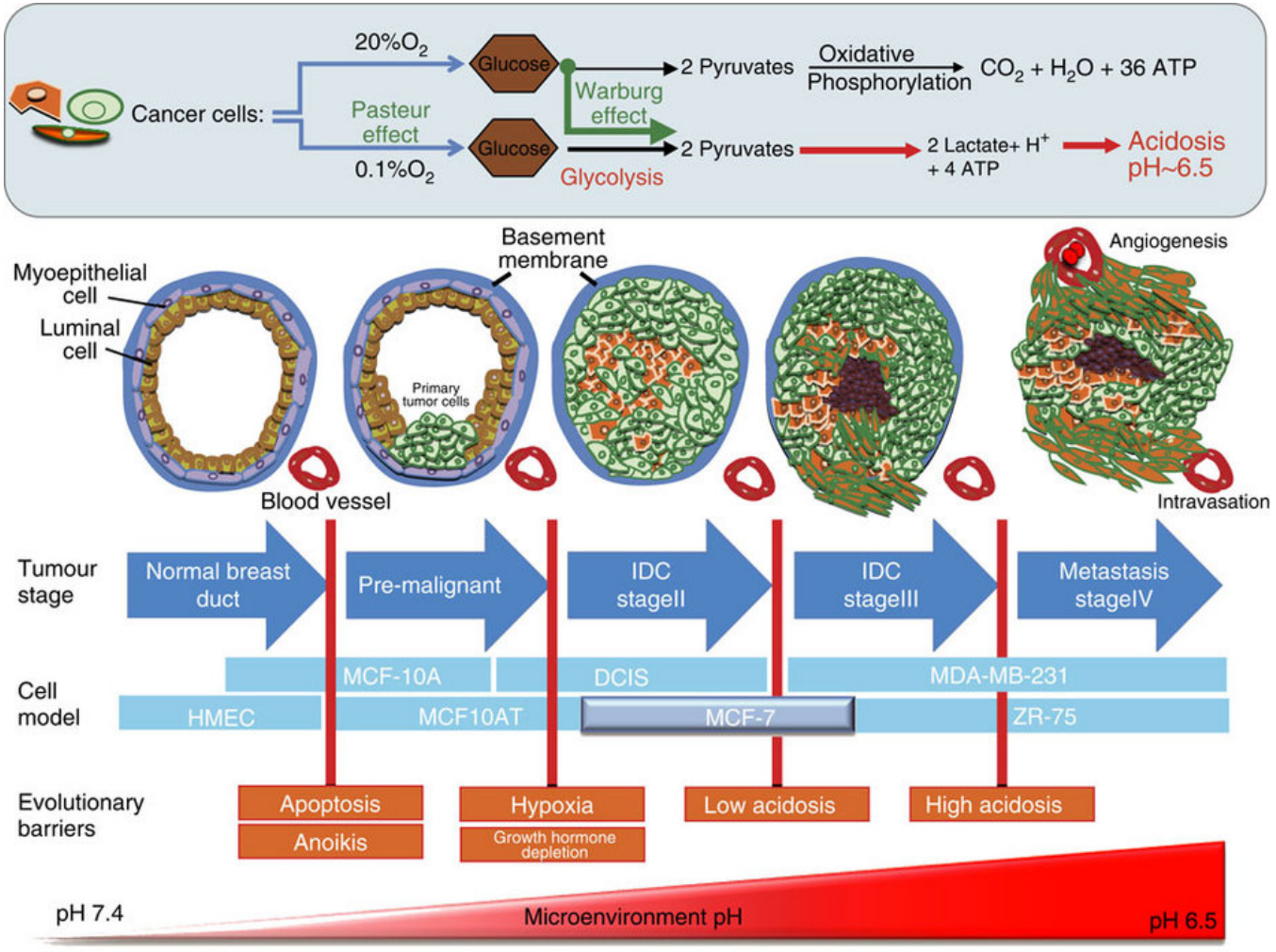
Cancer cell pH is regulated by a number of mechanisms



- Cancer cells upregulate Glut1 and Glut2 to import glucose for glycolysis
- Excess proton and lactate are excreted by monocarboxylate transpoters (MCTs); Na/Proton exchangers (NHEs); and proton pump vacuolar ATPase (V-ATPase)
- Other proteins that regulate pH include: anion exchangers (AEs); Bicarbonate transporters (BTs); Cl-/HCO3- exchangers (CBEs); Na+/HCO3- contransporter (NBC); NA+ dependent Cl-/HCO3- exchangers (NDCBE)
- CO2 regulation by carbonic anhydrases CAII, CAIX, CAXII also affect pH

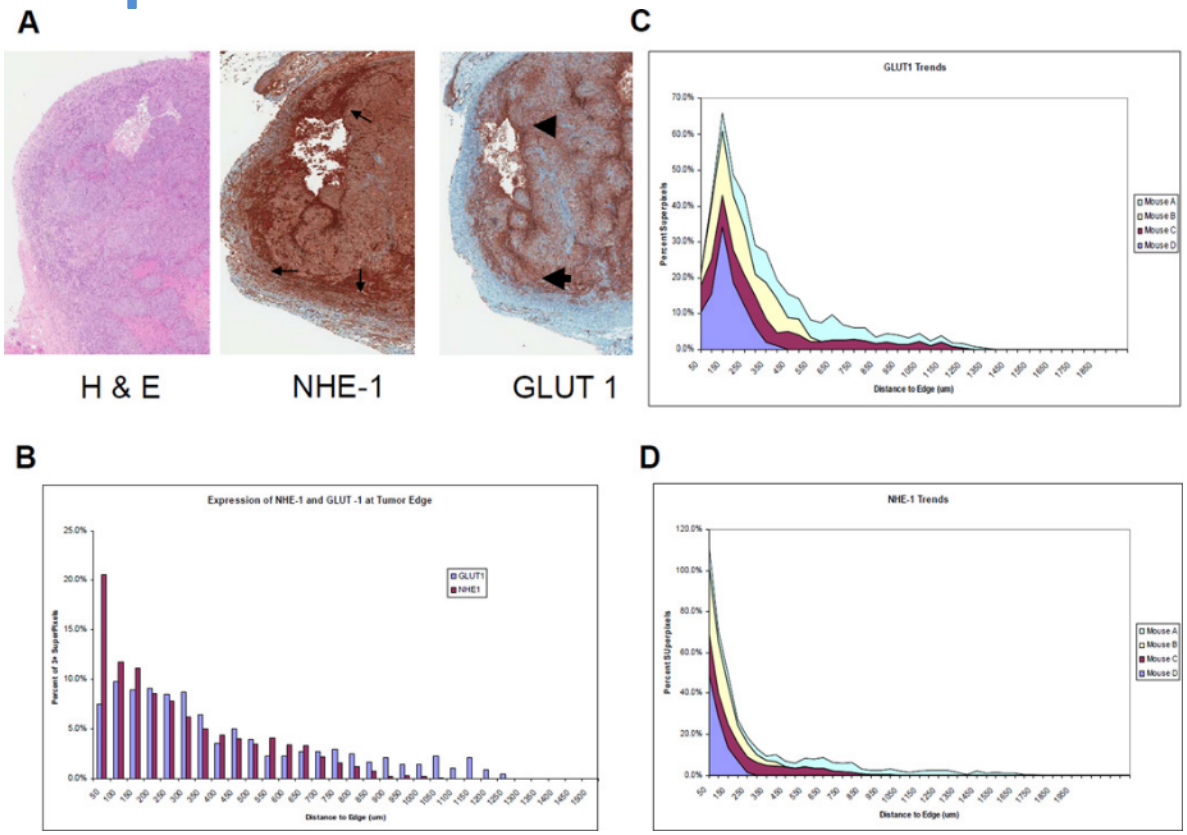
Pigment Cell Melanoma Res. 2016 May 27

Acidosis and Tumor Progression



Nature Communications 6:8752 2015

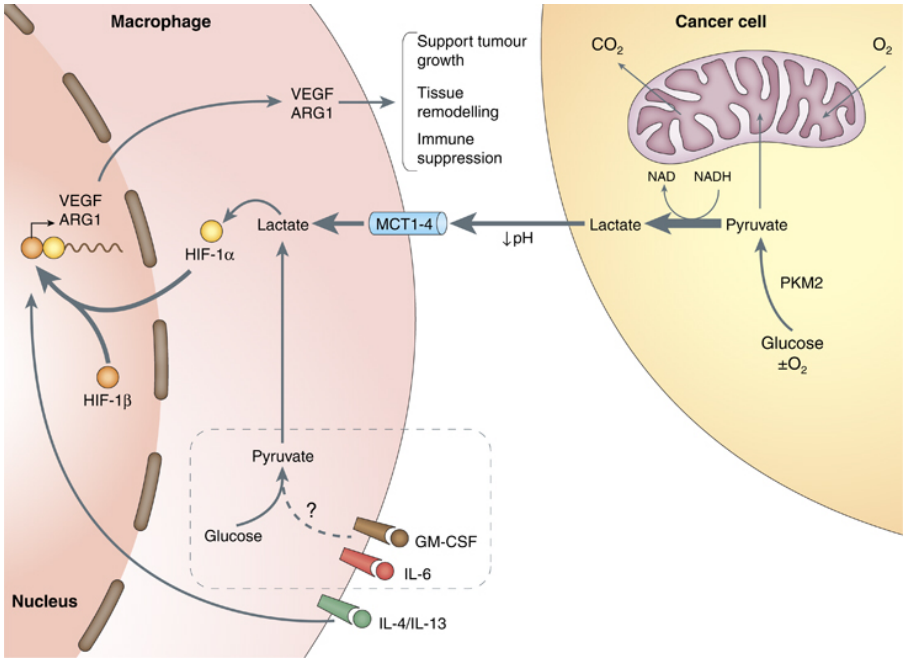
Low pH and Tumor Invasion



(A) The Tumor edge has an increased expression of NHE-1 (small thin arrows) and GLUT1 (large arrows), which is indicative of acidification caused by an increase in glycolysis. This is consistent with microenvironmental acidosis observed in vivo leading to subsequent invasion. (B) Expression of GLUT-1 and NHE-1 as a function of distance from the Tumor edge. (C) and (D) Expression trends of GLUT-1 and NHE-1 as a function of distance from Tumor edge in N=4 Tumors.

Cancer Res. 2013 Mar 1; 73(5): 1524–1535

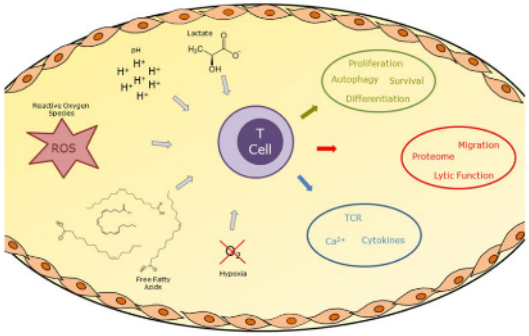
Lactate Lowers Tumor pH and Polarizes Macrophages



Macrophages integrate metabolic and environmental signals to promote Tumor growth. Tumor lactate which lower pH polarizes macrophage and up-regulate Arg1. Area within dotted rectangle indicates proposed mechanisms of action. ARG, arginase; HIF, hypoxia-inducible factor; MCT, monocarboxylate transporter; NADH, reduced nicotinamide adenine dinucleotide; PKM2, M2 isoform of pyruvate kinase; VEGF, vascular endothelial growth factor.

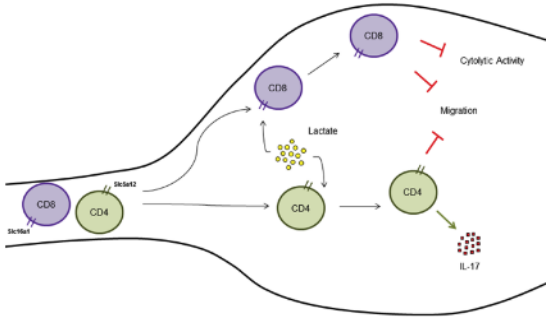
Nature 513:559-563 (2014)

T Cell Loss of Function from Low pH and Elevated Lactate Level



Am J. Clinic. Immunol. 2(2): 146-155 (2013

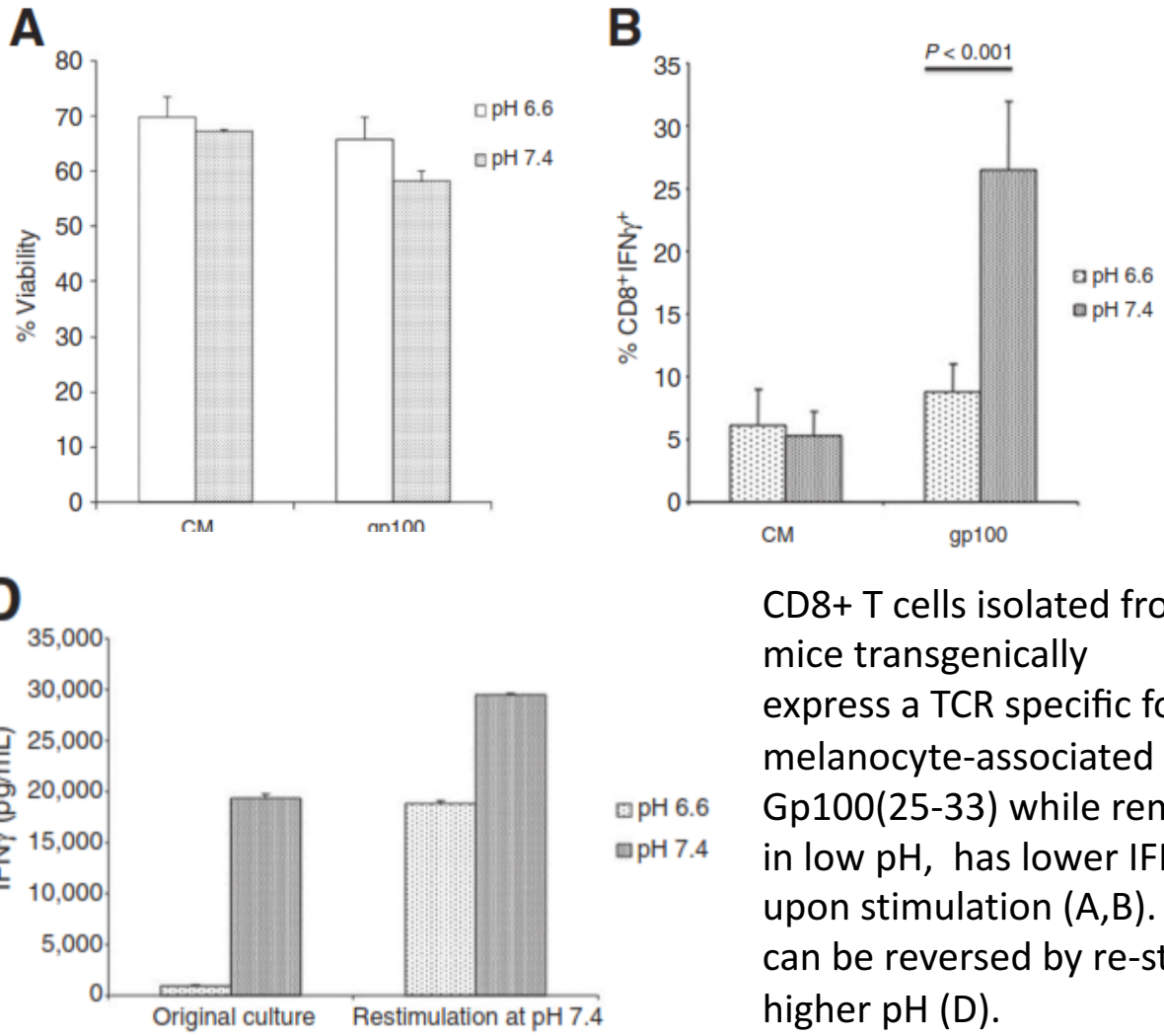
Several factors in the inflammatory microenvironment (e.g., oxygen concentration, pH, lactate, fatty acids and ROS) can influence the function of T cells and other immune cells on a number of levels and determine the outcomes of the inflammatory process.



PLoS Biol. 13(7) (2015)

The motility of CD4+ and CD8+ T cells is blocked once they get exposed to elevated levels of lactate in the inflammatory site. Lactic acid also causes loss of cytolytic activity by CD8+ T cells, and sodium lactate promotes the production of IL-17 by CD4+ T cells.

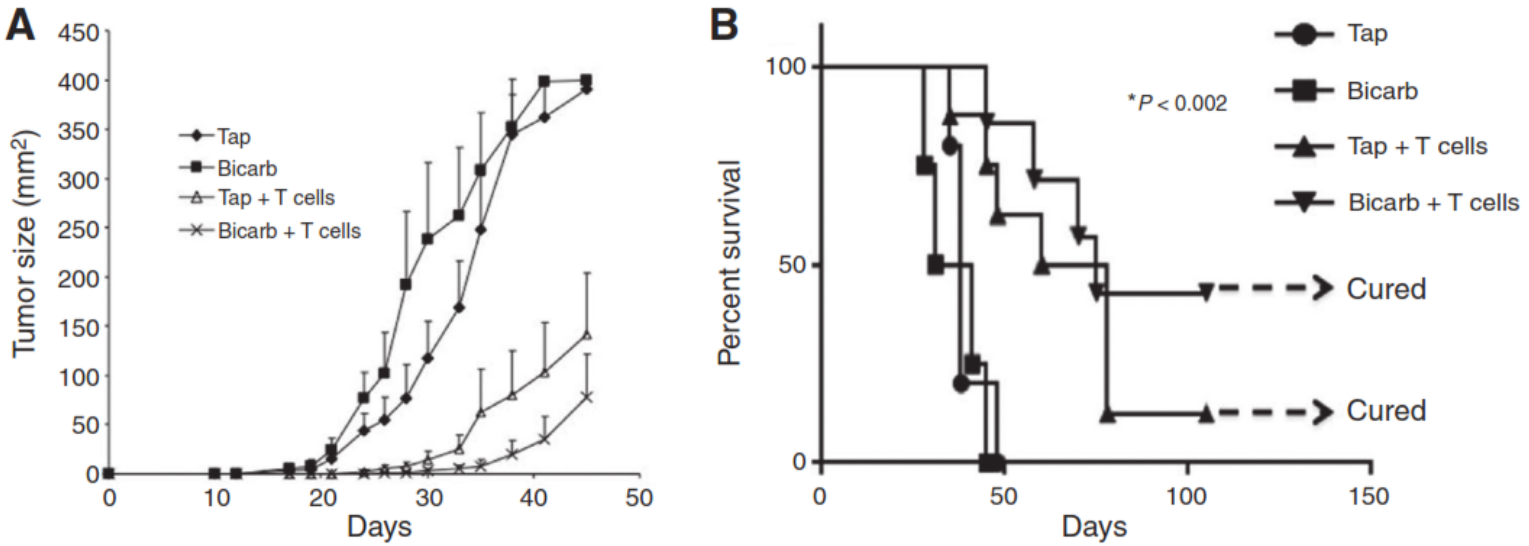
T Cell Loss of Function from Low pH



CD8+ T cells isolated from pmel mice transgenically express a TCR specific for the melanocyte-associated peptide, Gp100(25-33) while remain viable in low pH, has lower IFNg secretion upon stimulation (A,B). The effect can be reversed by re-stimulation in higher pH (D).

Cancer Res; 76(6) March 15, 2016

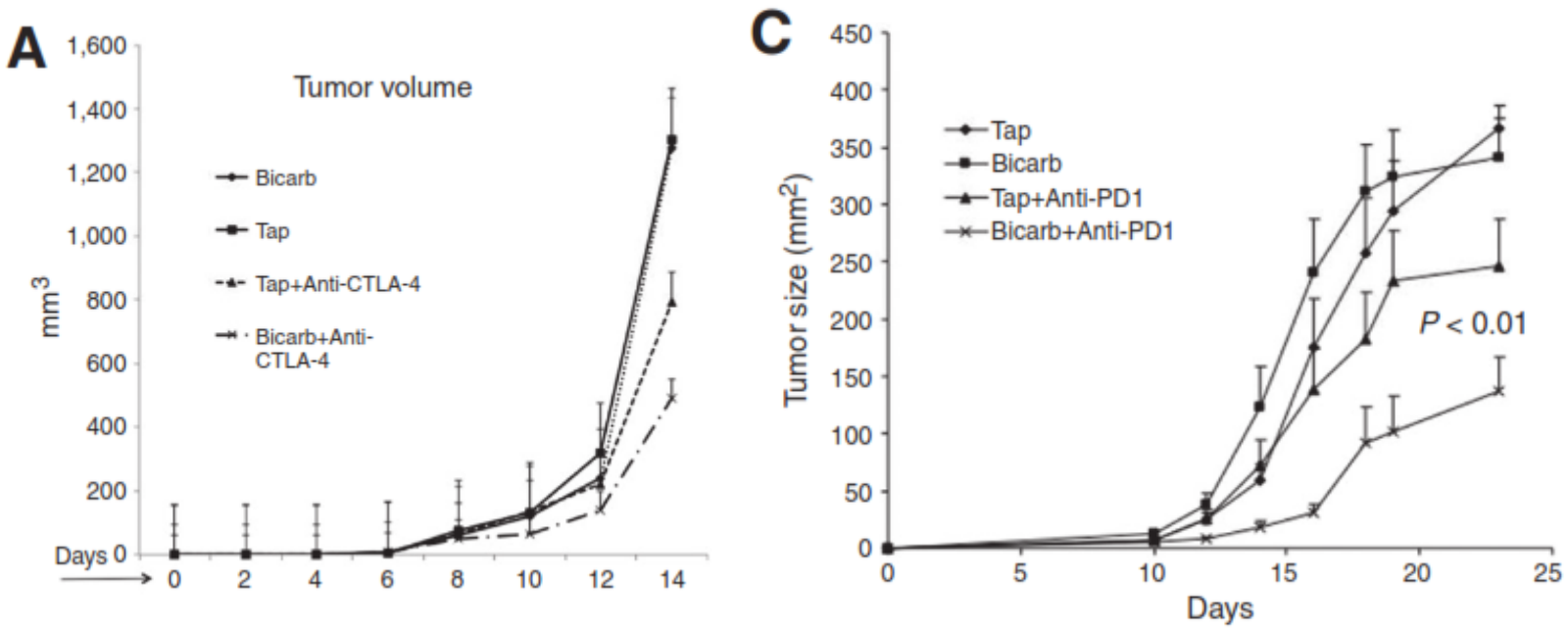
Acidity Affects Adoptive T cell Therapy



Effect of bicarbonate on adoptive T-cell transfer. A, Tumor growth after adoptive transfer of T cells or controls in combination with or without buffer therapy. Group mean differences between T cells vs. T cells vs bicarbonate were not significant. However, there was a survival advantage, as shown in the survival curve in B

Cancer Res; 76(6) March 15, 2016

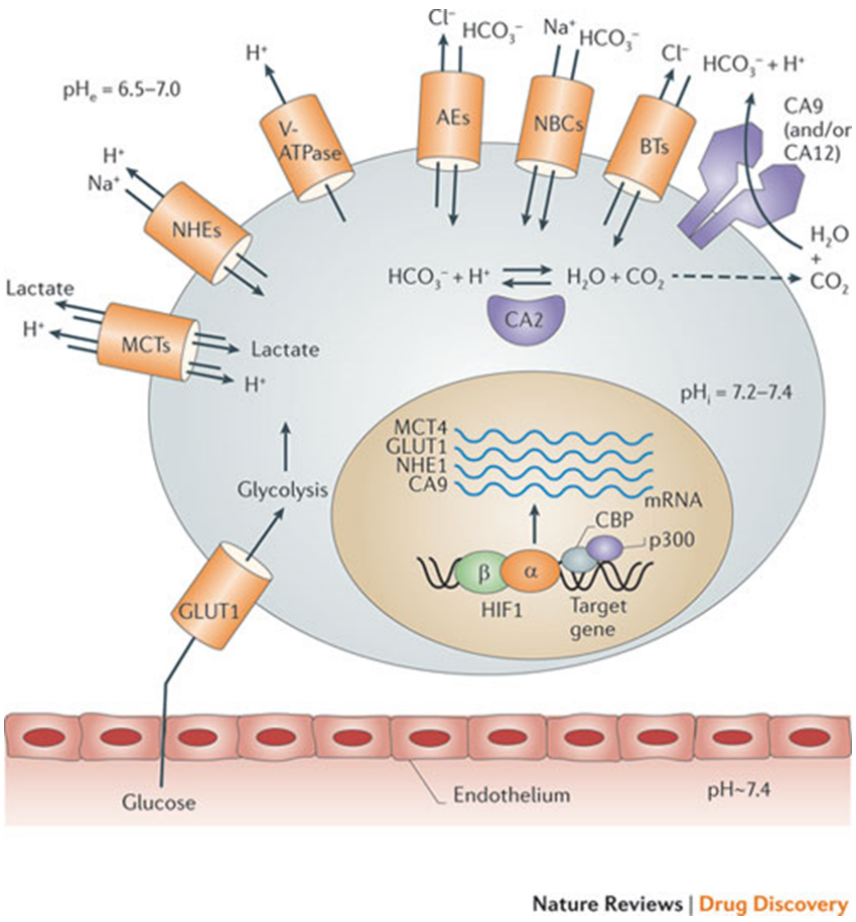
Tumor pH and Check-Point Inhibitors



Buffer therapy enhances efficacy of anti-immunotherapy in B16 melanoma. C57BL/6

Cancer Res; 76(6) March 15, 2016

Therapeutic Strategy Against Acidosis

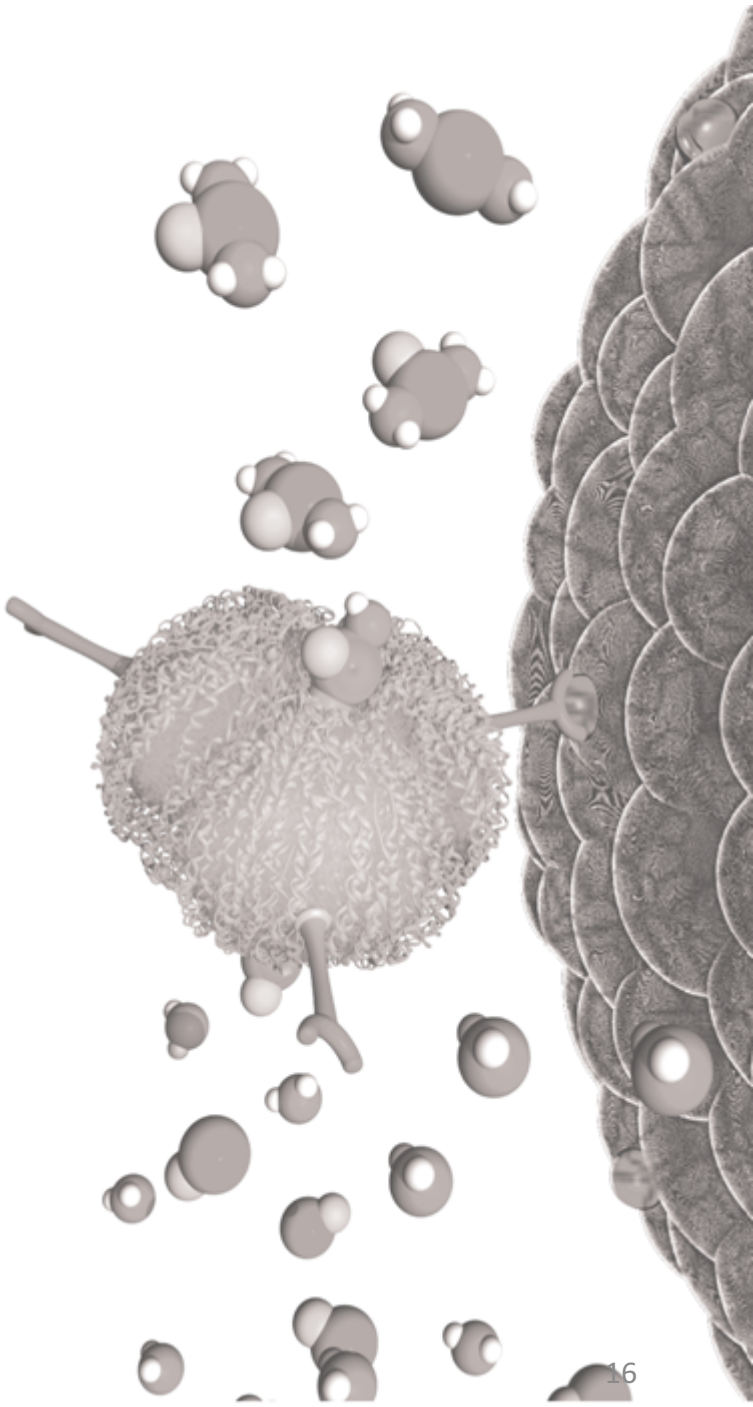


- Inhibitors (small molecules or antibodies) to target:
  - Carbonic anhydrase isoforms
  - V-ATPase inhibitors and proton pump inhibitors
  - Na+/HCO3− co-transporters, anion exchangers and Na+/H+ exchanger 1
  - Monocarboxylate transporter inhibitors
- Targeting a specific protein to combat Tumor acidity is not easily achieved; many of these regulators have multiple isoforms and some have critical function in cellular homeostasis
- Other strategy attempted includes systemic alkalization using sodium bicarbonate solution
- Helix's approach: targeted delivery of alkalizing enzyme

Nature Reviews Drug Discovery 10, 767-777

Targeting the Tumor Acidic Barrier

DOS47

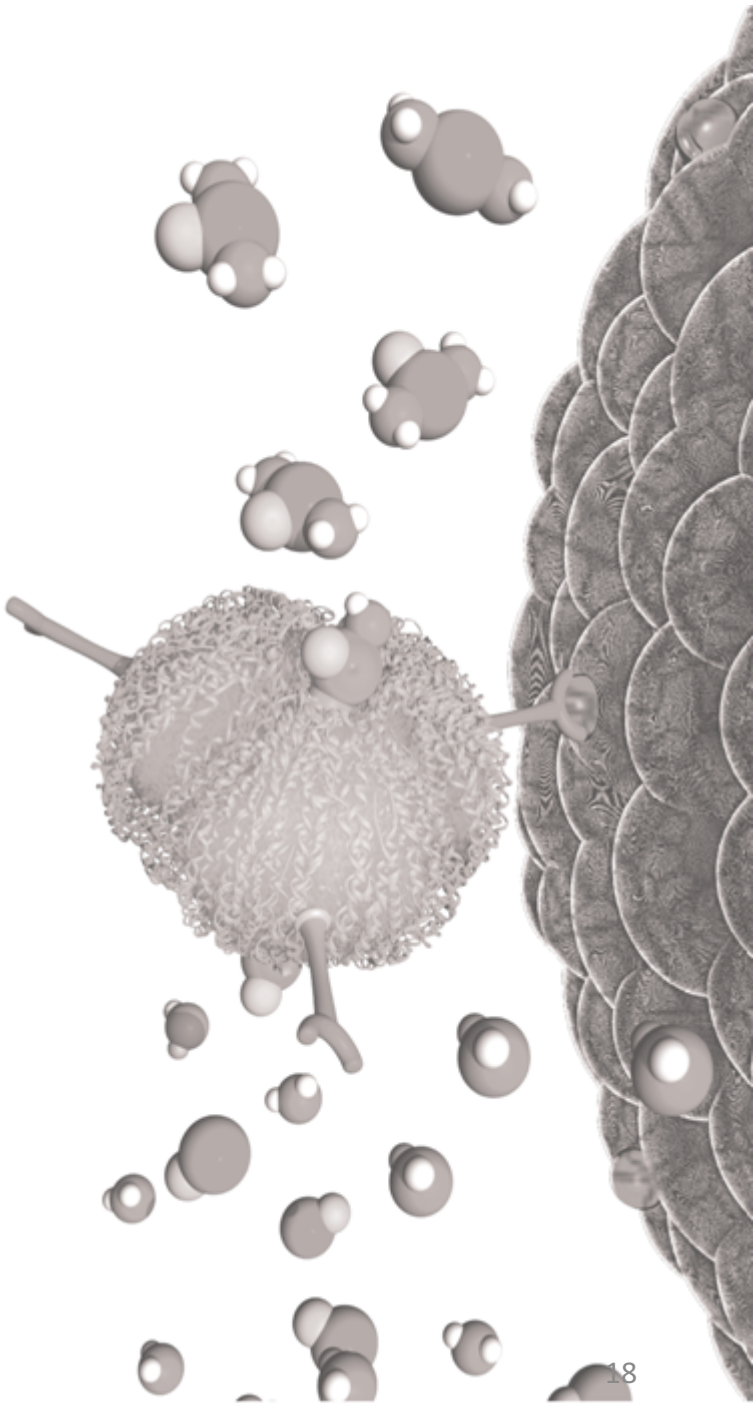


DOS47

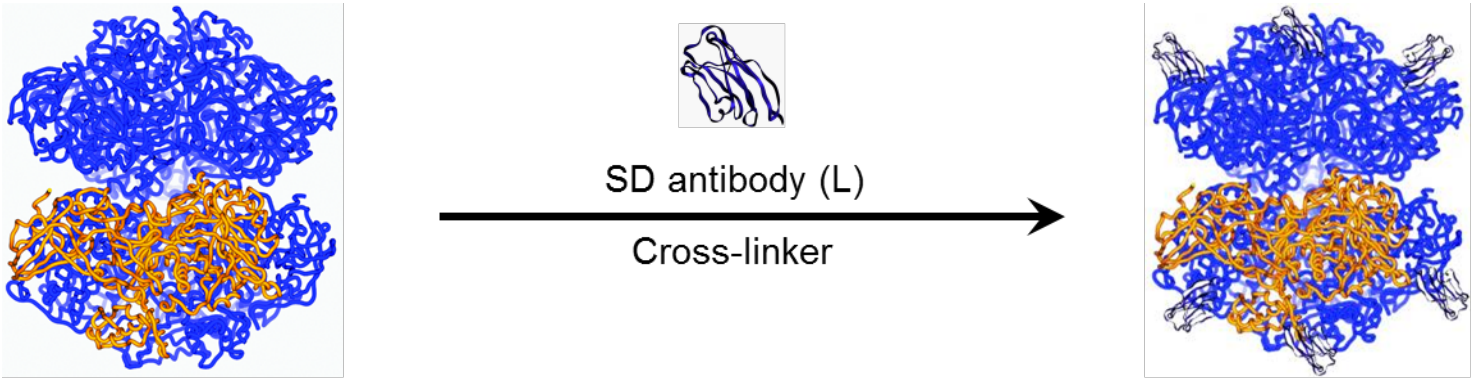
- DOS47 is a technology that changes the Tumor microenvironment from acidic to alkaline using the enzyme ‘urease’
- Alkalinizing the Tumor has the potential to
  - To exert direct cytotoxic effect on Tumors
  - to increase the action of certain chemo-therapies
  - to correct an impaired immune microenvironment

Helix First Clinical Drug Candidate

L-DOS47



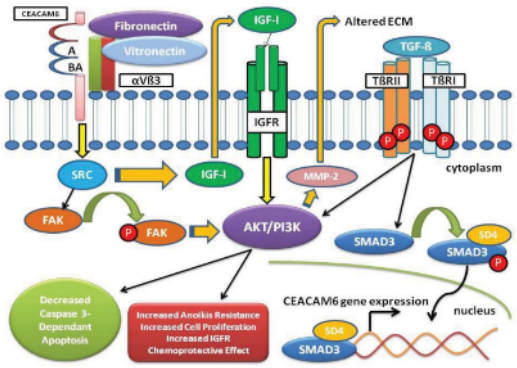
L-DOS47



- L-DOS47 is a conjugate of urease with a proprietary camelid single domain antibody specific for CEACAM6
- CEACAM6 is a cell surface Tumor antigen highly expressed on lung, colon, pancreatic and other cancer cells
- L-DOS47 is in clinical studies for the treatment of non-squamous, non-small cell lung cancer (NSCLC)

L-DOS47 – Dual Function

Antigen: CEACAM6

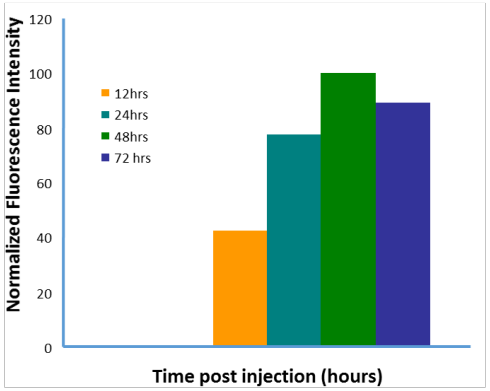


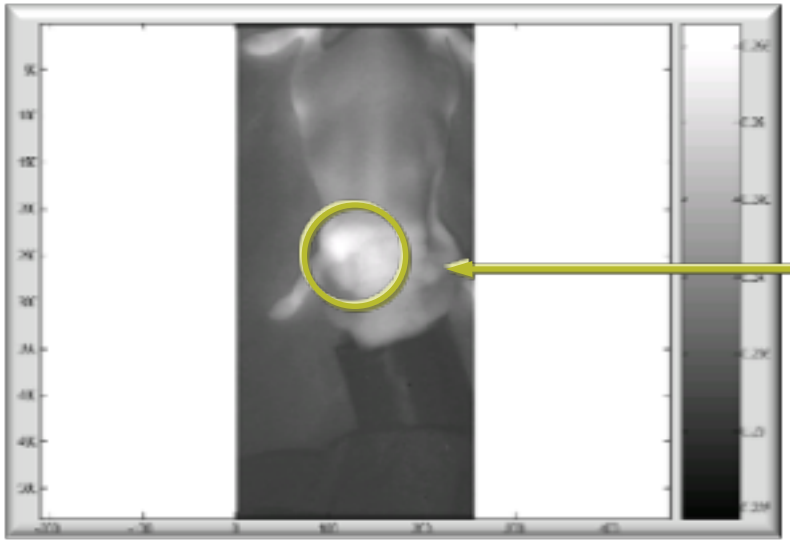
- Glycosylated 90 kDa (286aa) GPI-linked membrane protein
- Intercellular adhesion molecule forming homotypic and heterotypic bonds with CEACAM-1, 5 and -8
- Important for cell attachment and proliferation
- May act as a checkpoint inhibitor in Multiple Myeloma

Enzyme substrate: urea

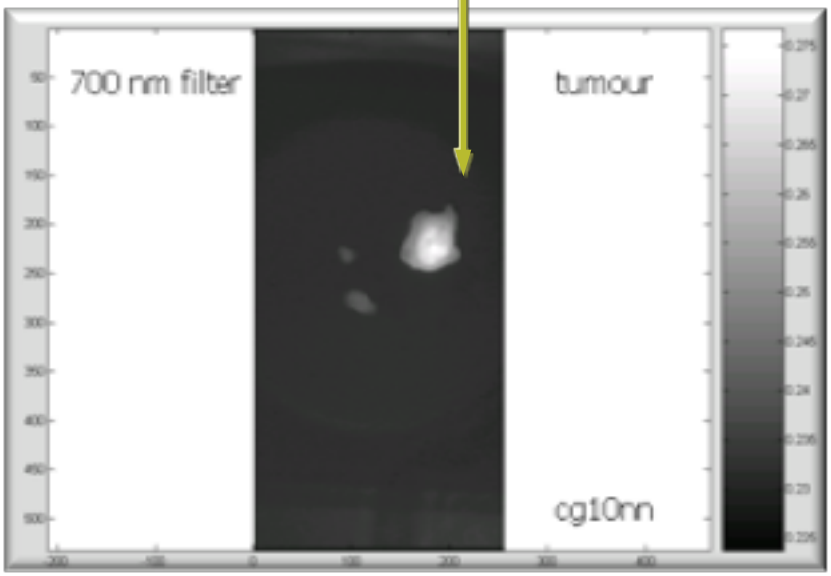
- Urea is a natural metabolite
- Ammonia/ Ammonium produced from urea hydrolysis is toxic to cells
- Apoptotic enzymes caspase 2 and 3 (A549 lung cell) and caspase 8 and 9 (BxPC3 pancreatic cells) are induced

Specific Delivery to Tumors





Tumor specific localization



Full Body Scan

A549 Tumor (8 x 7 mm)
L-DOS47-Cy5.5

Filtered Scan

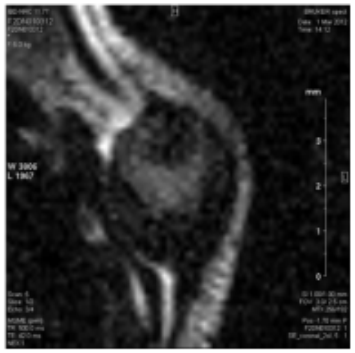
L-DOS47-Cy5.5
Cy5.5 emission max
@710nm

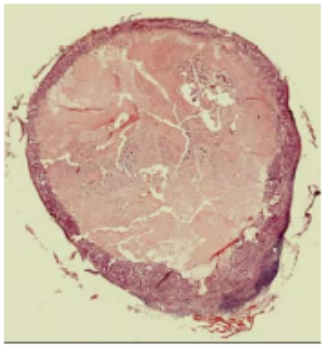
L-DOS47 Affects Metabolism

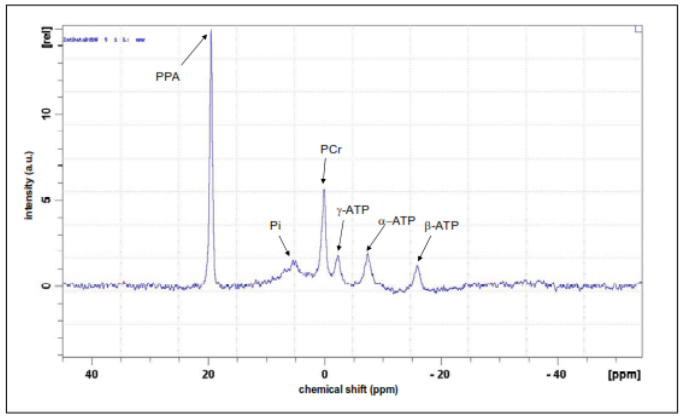
1H-NMR anatomical imaging

32P-NMR microenvironment

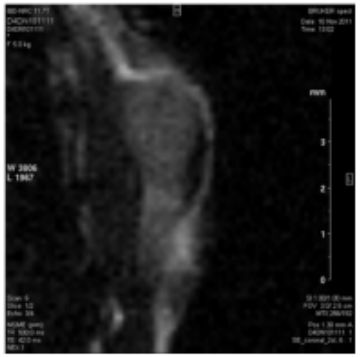
A control

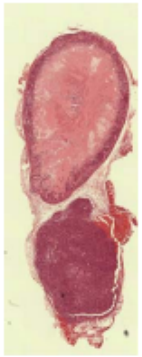


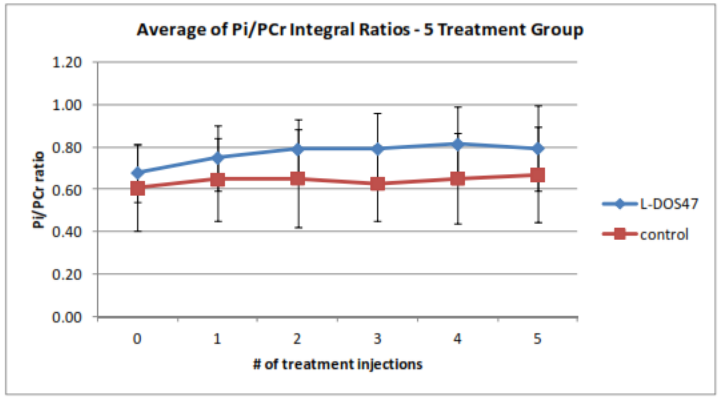




B Treatment







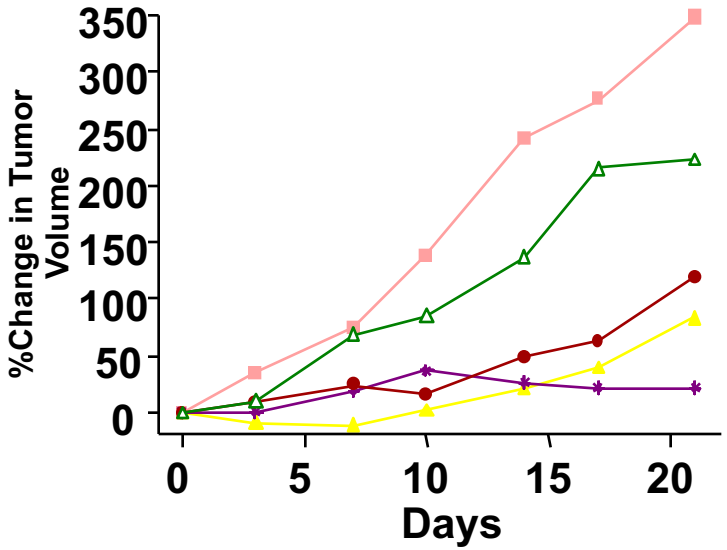
NMR imaging on A549 xenograft mice showing a change in energy metabolism (Pi/Pcr) as a result of L-DOS47 treatment

L-DOS47 Cytotoxic to CEACAM6-Positive Tumor Cells

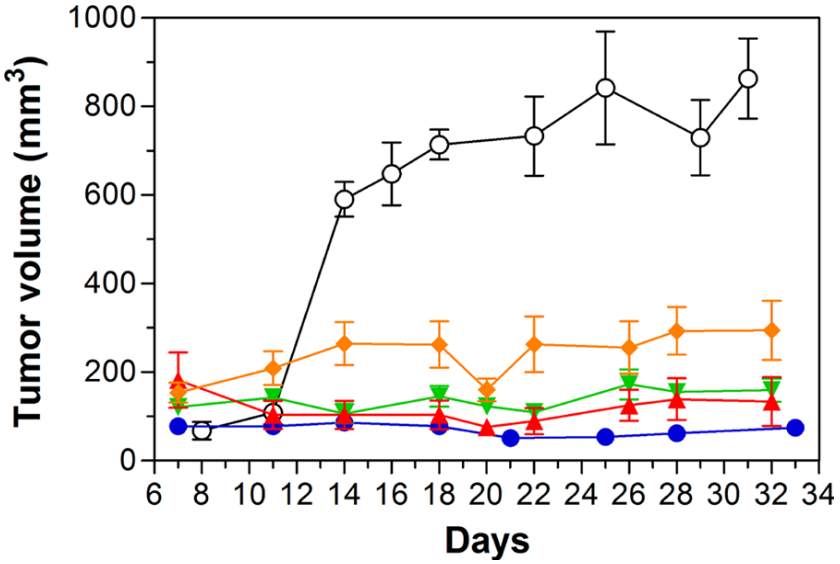
Cell lines		Binding assay	Cytotoxicity assay
A549	Lung carcinoma	++	+
H460	Lung carcinoma	-	ND
H647	Lung carcinoma	+	ND
H23	Lung adenocarcinoma	-	+
BxPC-3	Pancreatic adenocarcinoma	+++	+++
Capan-1	Pancreatic adenocarcinoma	+++	++
MIA PaCa-2	Pancreatic carcinoma	+	+
MDA-MB231	Breast adenocarcinoma	-	-
JIMT-1	Breast carcinoma	-	ND
MCF-7	Breast carcinoma	-	-
BT-474	Breast ductal carcinoma	+	-
HCC-1954	Breast ductal carcinoma	+++	+++
ZR-75-30	Breast ductal carcinoma	+++	+++
HCC-1806	Breast squamous cell carcinoma	-	ND
LS174T	Colon adenocarcinoma	++	++
SW620	Colorectal adenocarcinoma	-	ND
HL-60	Promyelocytic leukemia	-	ND

Certain Lung, pancreas, breast and colon cell lines are good models

L-DOS47 Inhibits Tumor Growth in Lung and Pancreatic Models



A549 (lung)
L-DOS47 (10,20,35U/kg)
Cisplatin control



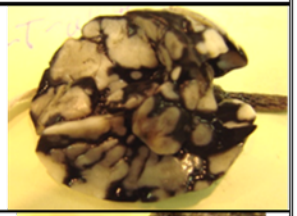
BxPC3 (Pancreatic)
L-DOS47 (7,35,175ug/kg)
Paclitaxel control

Tian et. al. Bioconjug Chem. 2015 Jun 17;26(6):1144-55

L-DOS47 Binds to CEACAM6 Positive Cancer Patient Tissues

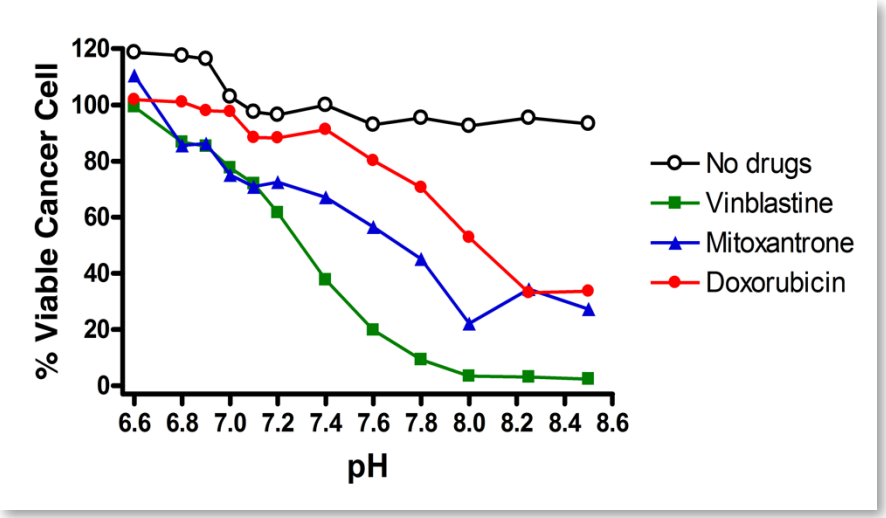
Samples	Tumor Tissue		Age-matched Normal Tissue
	Positive	Negative	Negative
Kidney carcinoma		12/12	12/12
Parathyroid adenoma		1/1	n/a
Plaenta, umbilical cord, allantois	n/a		1/1
Myofibroblastic Tumor		1/1	n/a
Prostate carcinoma		4/4	4/4
Thyroid carcinoma		2/2	2/2
Pancreas adenocarcinoma	7/57 weak 8/57 v. weak	42/57	25/25
Neuroendocrine Tumors		9/9	n/a
Brain, heart muscle, testis, spleen	n/a		30/30
Testis - teratoma and seminoma		3/3	3/3
Parotis Tumor		1/1	1/1
Cervix squamous carcinoma		2/2	n/a
Thymoma		2/2	n/a
Colon adenocarcinoma	14/24 weak	10/24	24/24
- lymph node metastasis		3/3	
Breast adenocarcinoma		13/13	13/13
- lymph node metastasis		2/2	
Leiomoma - lung metastasis		1/1	n/a
Ovary carcinoma		4/4	n/a
Bladder carcinoma		42/42	36/36
- lymph node metastasis	1/1 strong		
- squamous carcinoma metastasis		2/2	
Lung - small cell carcinoma		1/1	5/5
- adenocarcinoma	5/5 strong		
Stomach adenocarcinoma		3/3	3/3
Liver carcinoma		4/4	4/4
Soft tissue Tumors		3/3	n/a
Melanoma		48/48	18/18
- metastasis		18/18	

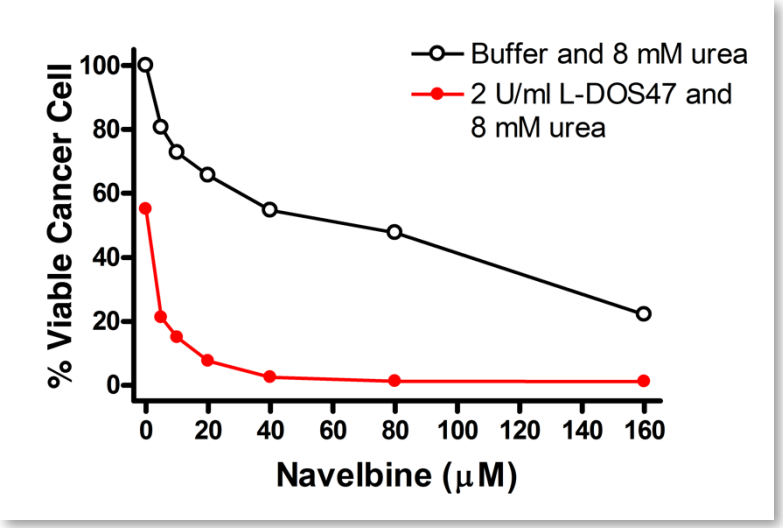
Tumor Formation Inhibition

Group	Cell Treatment	Final Concentration (µg/mL)	Mean number of lung tumors[#] 3 weeks	Mean number of lung tumors[#] 10 weeks	Representative lung images
1	Untreated	-	103.8 ± 30.0	110.6 ± 50.0	
2	Isotype	10	44.6 ± 5.1	60.4 ± 14.3	
3	L-DOS47	10	28.0* ± 7.2	50.0 ± 17.7	
4	L-DOS47	15	18.2* ± 7.8	112.2 ± 52.5	

Enhances Other Chemotherapeutics

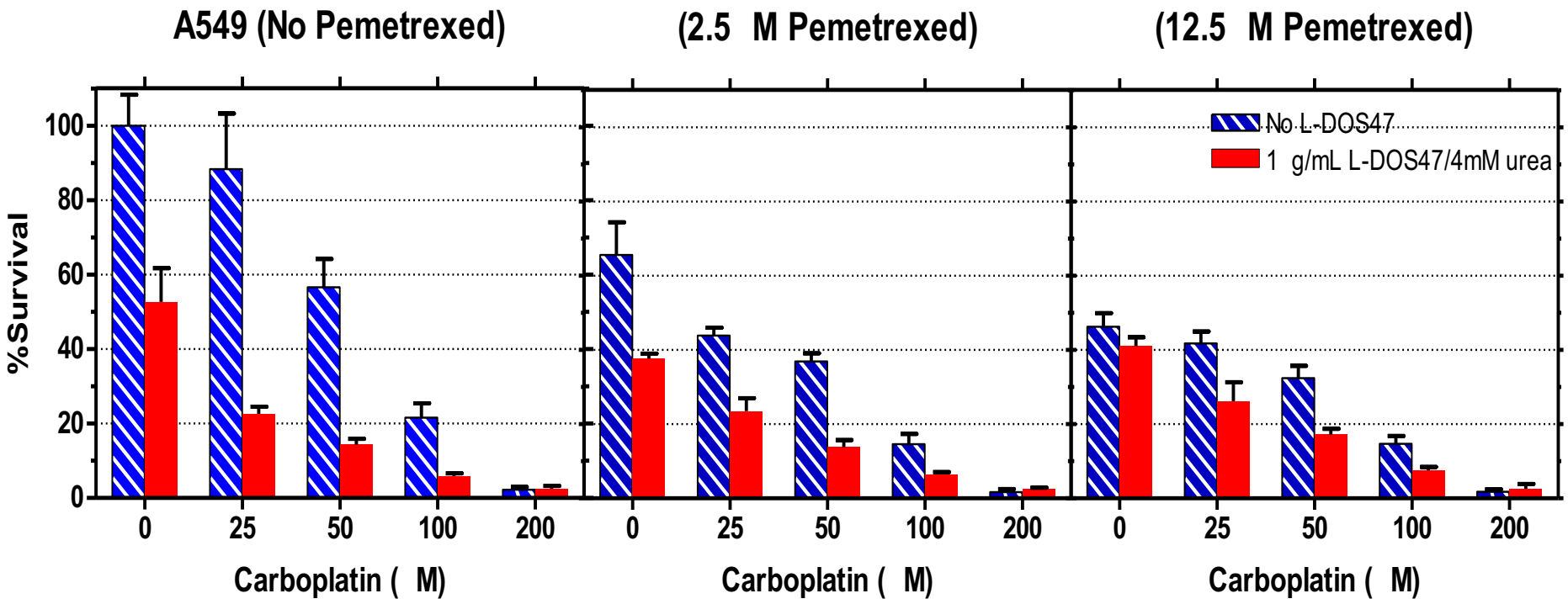
- L-DOS47 enhances chemo drugs





The cytotoxic effect of weakly basic drugs is directly related to the solution pH (left panel). At an acidic Tumor pH (<6.8), the effectiveness of these drugs is significantly reduced. L-DOS47 can dramatically raise the effectiveness of these drugs (e.g. navelbine, right panel). This synergistic effect is directly related to its enzymatic properties of generating ammonia from urea and raising solution pH. Depending on the dosages and available urea, a 2–10 fold drug effect enhancement can be observed.

L-DOS47 Enhances Pemetrexed and Carboplatin



A549 cells were treated with various concentrations of pemetrexed and/or carboplatin with or without 1 μg/mL L-DOS47 and 4mM urea. The results showed that L-DOS47/ urea treatment significantly enhanced the cytotoxicity of carboplatin alone (25-100μM), pemetrexed alone (2.5μM), or in combination. Further increase the concentration of pemetrexed to 12.5μM did not increase the cytotoxic effects.

L-DOS47 Clinical Update

- L-DOS47 Phase I / II Trial (LDOS002)
  - Monotherapy in advanced NSCLC patients
  - Currently enrolling Phase II patients
- L-DOS47 Phase I with Expansion Trial (LDOS001)
  - Combination with pemetrexed and carboplatin
  - Currently enrolling in cohort 2
- L-DOS47 Phase II (LDOS003)
  - Combination with vinorelbine and cisplatin
  - In the planning phase

L-DOS47 Phase I / II Trial (LDOS002)

- Monotherapy treatment protocol in NSCLC patients that have not responded to other treatments;
- Stage IIIb / IV, metastatic, and progression after several lines of chemo, rad, surgery or chemo-naïve patients that have refused other lines of therapy;
- Dosed once a week for 2 weeks, 1 week rest (3-week cycle);
- Conducted in 5 Centers in Poland to assess safety (phase I) and then preliminary efficacy (phase II);
- Centers include The Maria Sklodowska-Curie Institute of Oncology, Military Institute of Health Institute, Mazovian Centre of Pulmonary Diseases and Tuberculosis in Otwock, Department of Oncology, Poznan University of Medical Sciences, National Tuberculosis and Lung Diseases Research Institute
- Phase II dosing regimen changed to twice a week dosing for 2 weeks, 1 week rest (3-week cycle);

Demography and NSCLC Baseline Characteristics (up to 12 Cohorts)

Demography	Total (N=40)	NSCLC History	Total (N=40)
Age	*Mean = 61.2* *Min, Max (34, 83)*	**Tumor Histology**	*Adeno = 38 (95%)* *Large Cell = 1 (2.5%)* *Unknown = 1 (2.5%)*
Weight (kg)	*Mean = 69.1* *Min, Max (48, 95)*	**Tumor Staging**	*Stage IIIB = 7 (17.5%)* *Stage IV = 33 (82.5%)*
Gender **Male** **Female**	*21 (52.5%)* *19 (47.5%)*	**Prior Therapy**	*None = 8 (20%)* *Chemo/Target = 32 (80%)* *Radiation = 21 (52.5%)* *Surgery = 11 (27.5%)*
Race **Caucasian**	*40 (100%)*	**Prior Chemo/Target Therapy**	*Adjuvant = 2 (5%)* *Locally Advanced = 3 (7.5%)* *Metastatic Disease = 31 (77.5%)* *None = 9 (22.5%)*
ECOG **0** **1** **2**	*11 (27.5%)* *27 (67.5%)* *2 (5%)*	**Best Response**	*Unknown = 5 (16.1%)* *CR = 1 (3.2%)* *PR = 9 (29%)* *Stable = 9 (29%)* *PD = 7 (22.6%)*

Clinical Observations Up to Cohort 12

- 21/40 patients had an overall response of SD at cycle 2
- 10/40 patients had an overall response of SD at cycle 4
- Patient 01-047 enrolled in cohort 9 (1.84µg/kg) was progression free for 10 cycles (approx. 7 months)
- None of the patients treated to-date have had a partial or complete response as defined by RECIST v1.1 definition
- One DLT reported in cohort 13 (Grade 4 Back Pain)

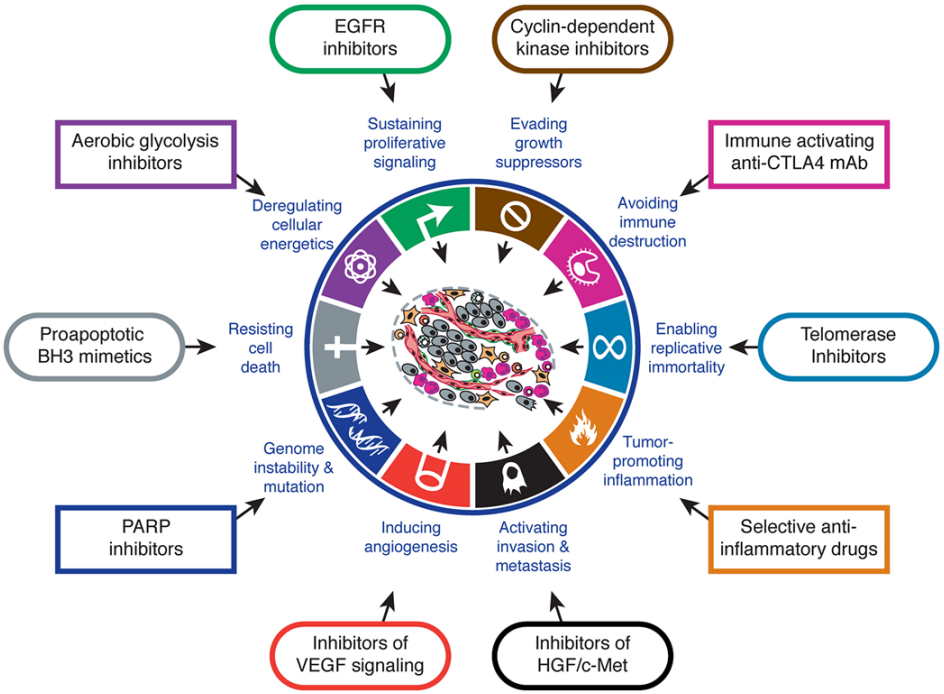
L-DOS002 Phase I

- Currently has completed 16 cohorts (13.55 ug/kg)
- One Dose Limiting Toxicity (DLT);
- No safety issues beyond those observed in pre-clinical toxicology studies or expected in the population of patients being studied;
- Immunogenicity consistent with what was observed pre-clinically;
- Phase II currently enrolling.

L-DOS47 Phase I with Expansion Trial (LDOS001)

- Combination therapy in first-line treatment of NSCLC:
  - Stage IIIb / IV, metastatic, and chemo-naïve;
  - Given in combination with standard pemetrexed/carboplatin treatment;
  - Dosed continuously each week;
  - Monitor radiologically every 6 weeks;
- Conducted in 3 Centers in US to assess safety (phase I) and then preliminary efficacy (expansion);
- Clinical sites include MD Anderson, Hershey Penn State, and Case Western;
- second cohort of patients enrolling
- One partial response observed previously reported

DOS47: Breaking Down Tumor Acidic Barrier



- L-DOS47 is the only targeted enzymatic approach to combat Tumor acidosis
- L-DOS47 is being studied as monotherapy and chemo combo in the clinic
- A second DOS47 candidate that targets VEGFR2 is in preclinical development
- Active R&D work are exploring DOS47 action with check-point inhibitors, cell based therapies and chemotherapeutics

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