pH live imaging: uno strumento utile per studiare e sviluppare nuove terapie per l'osteosarcoma

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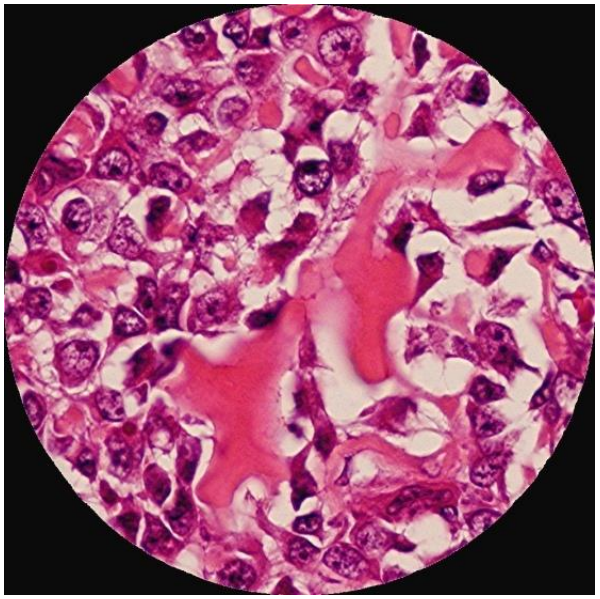
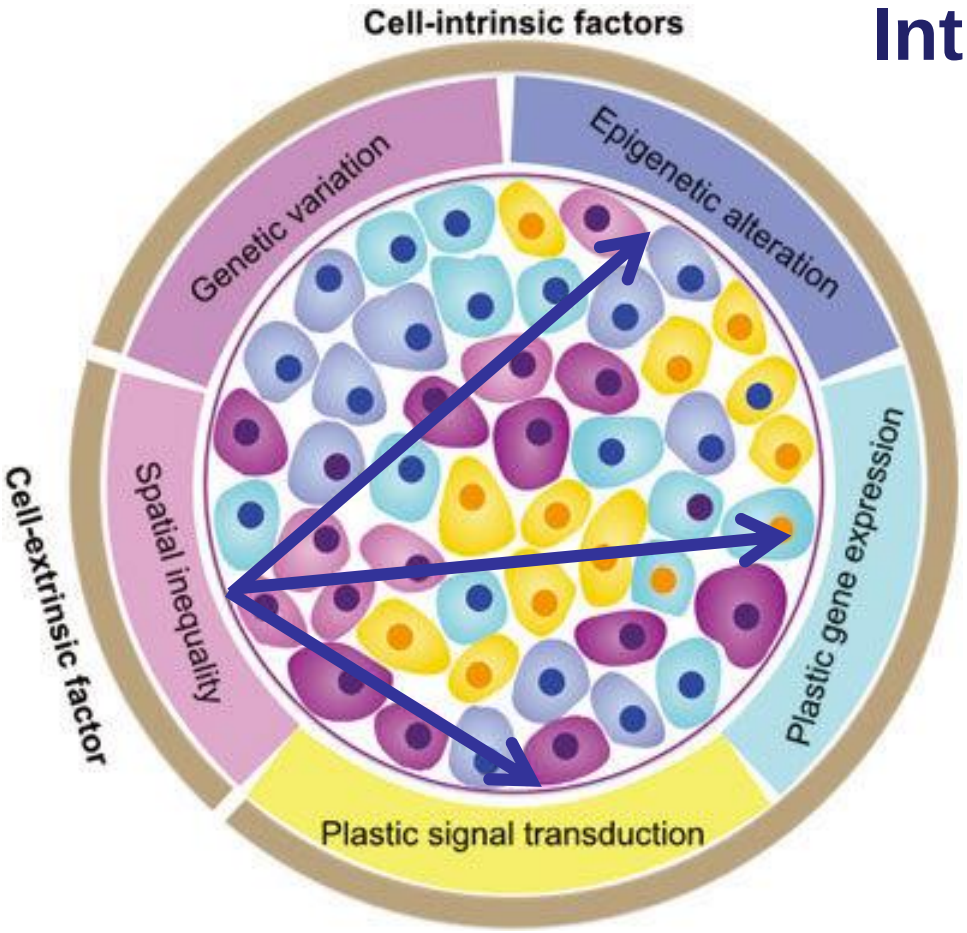
Osteosarcoma

- Rare
- Mesodermal origin (≠ carcinoma)
- Etiology largely unknown: no prevention
- Late diagnosis
- Metastases: very frequent (lung)
- Frequent in children and adolescents



Other then inter-tumor heterogeneity there is:

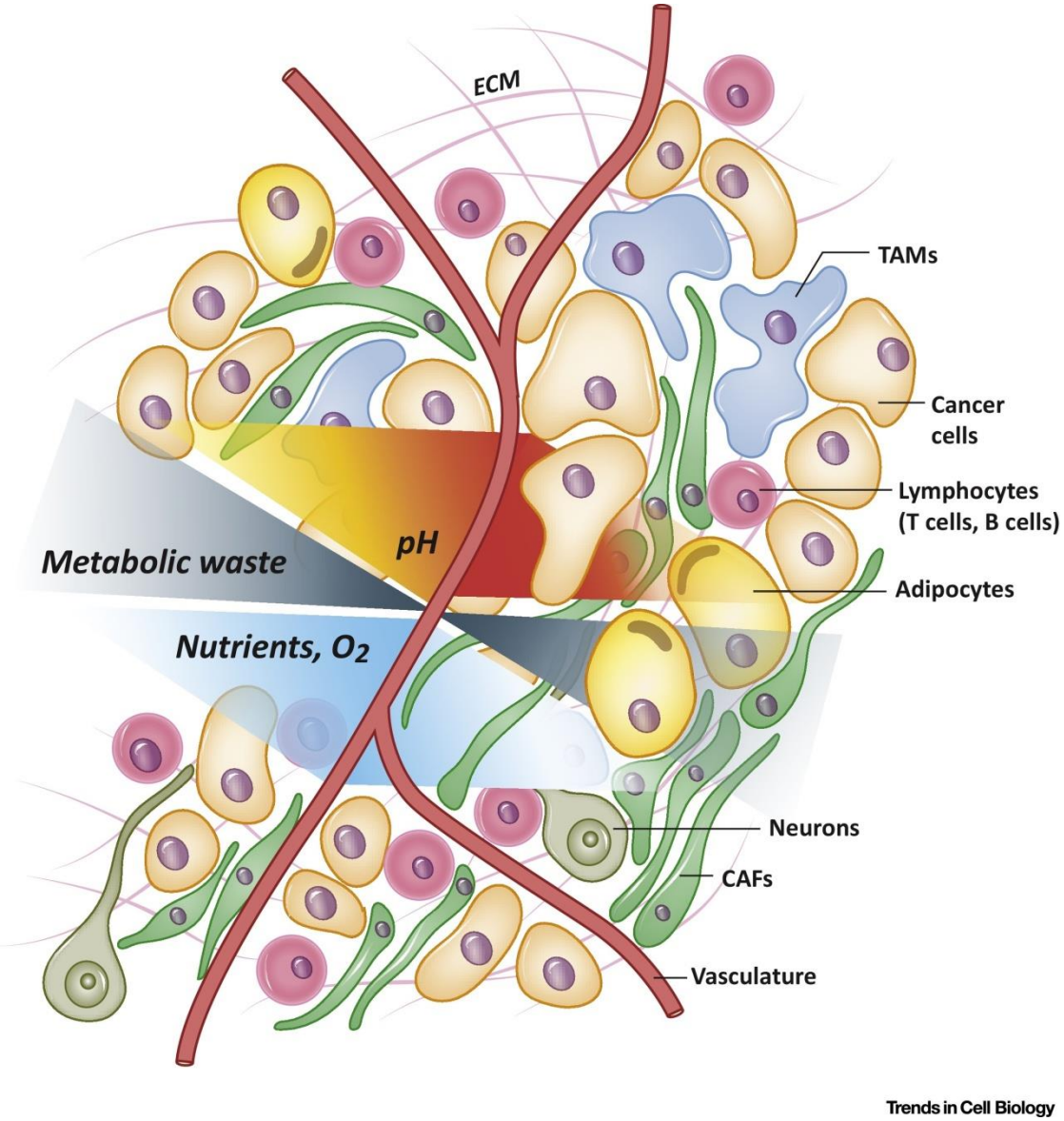


Intra-tumor heterogeneity

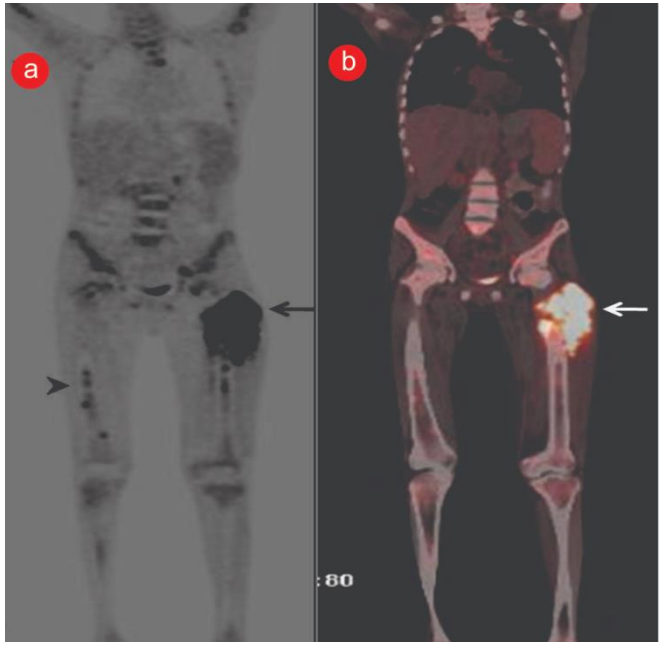
"*Understanding the specific driving forces behind different subtypes of intra-tumor heterogeneity will facilitate a better understanding of the nature of cancer, and will provide insight into the development of more effective cancer therapies*"

Spatial inequality

- ECM composition
- Metabolic waste
- O_2 tension
- **pH**
- Proximity with mesenchymal stromal cells (MSC, CAF), neurons, immune cells (lymphocytes, TAM M1/M2)



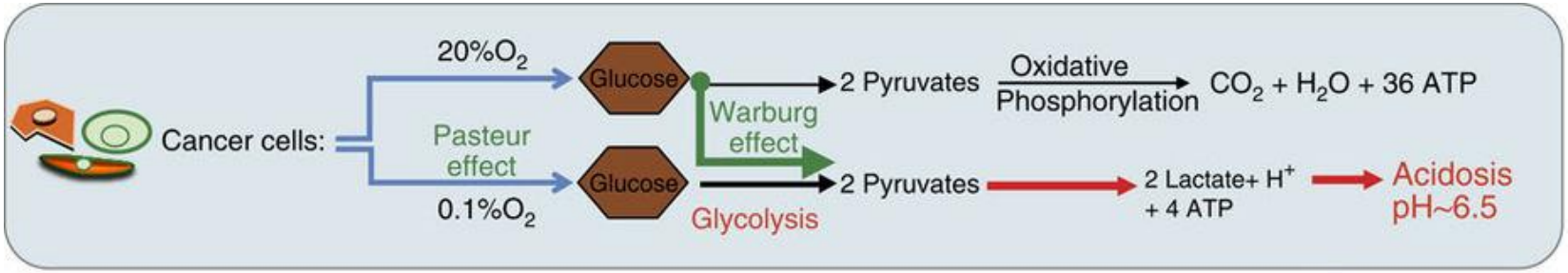
pH intra-tumor heterogeneity



FDG-PET: glucose uptake

Mouse fibrosarcoma = pH 6.71
J Magn Reson Imaging (2002) 16:430-50

Human sarcomas = pH 6.78
Sarcoma (2012)

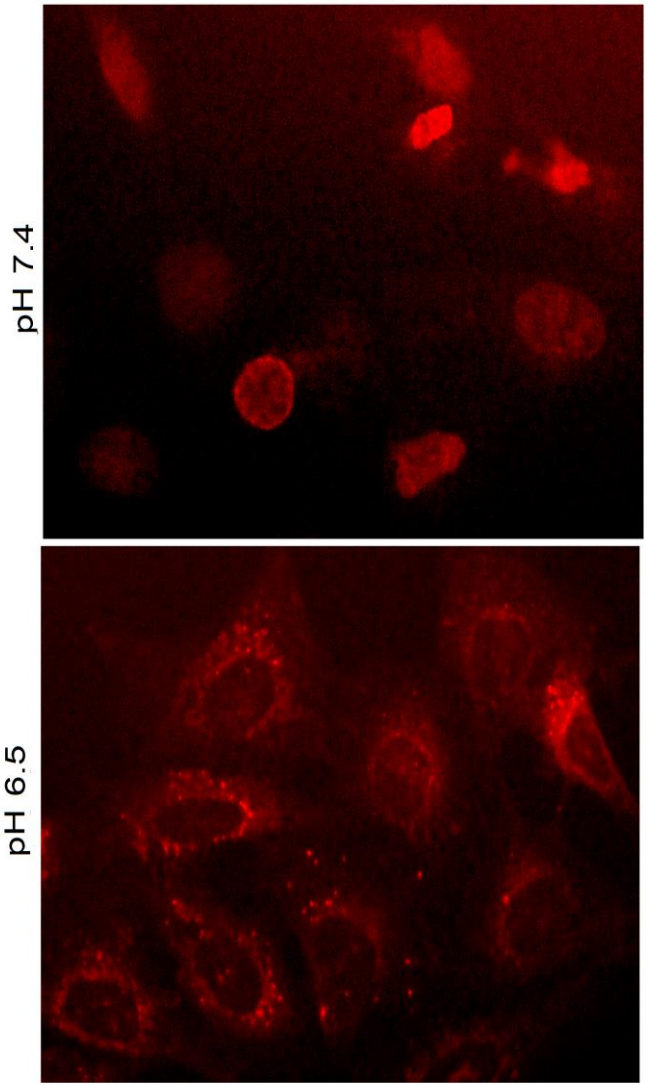


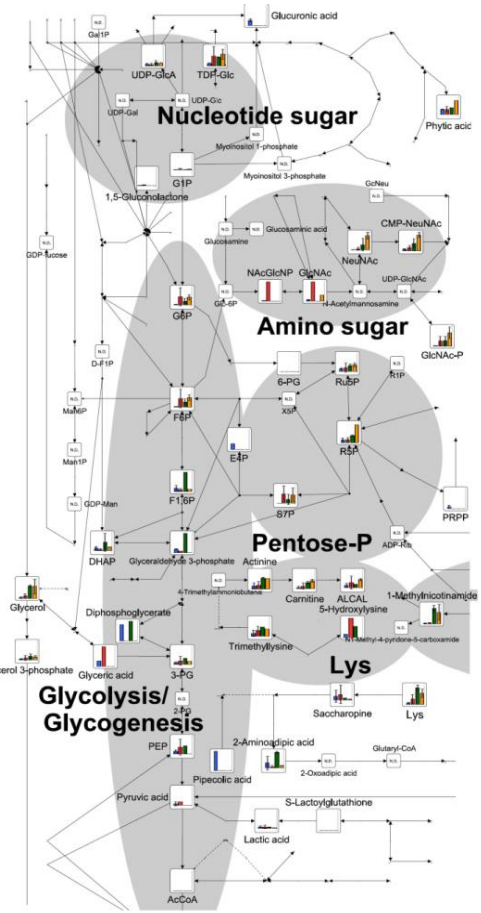
pH intra-tumor heterogeneity

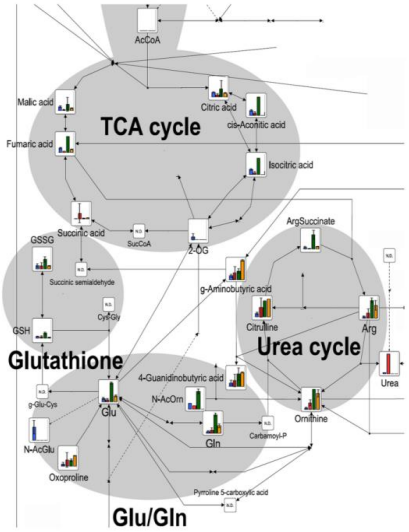
Altered pH gradient at the plasma membrane of osteosarcoma cells is a key mechanism of drug resistance.

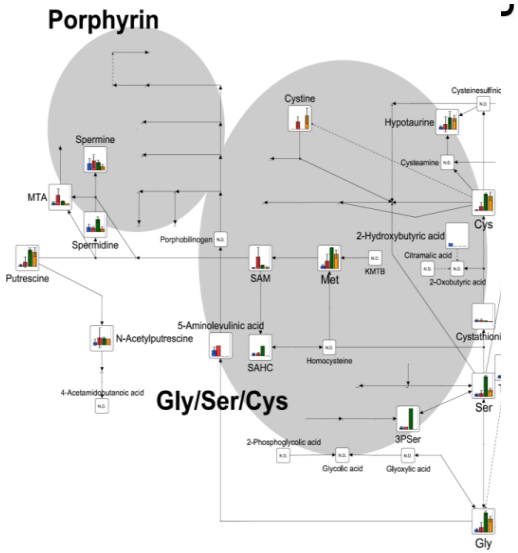
Avnet et al. Oncotarget. ***2016*** *Sep 27;7:63408-63423.*

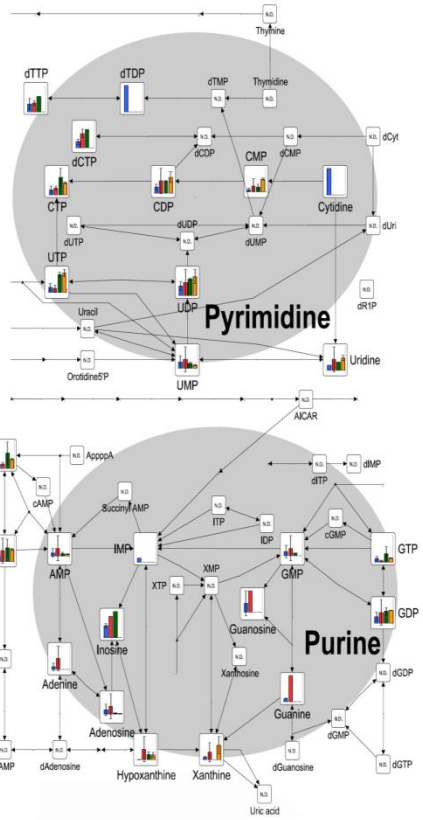
DXR uptake at different pH







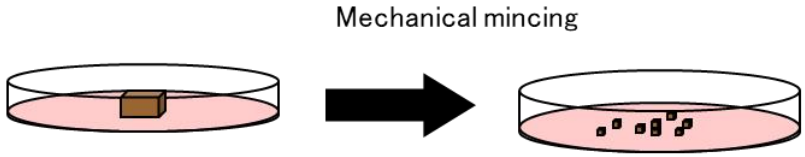


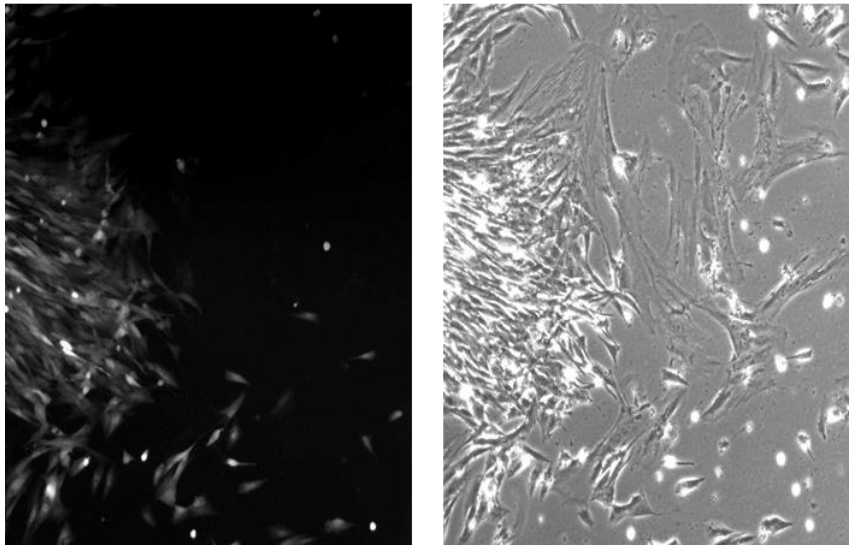


Metabolic adaptation to acidosis is coupled to epigenetic stability in osteosarcoma cells.

Chano et al. Am J Cancer Res. ***2016*** *Mar 15;6:859-75*

intra-tumor heterogeneity: acidosis-inflammation-MSC





Mesenchymal stroma

Role of mesenchymal stem cells in osteosarcoma and **metabolic reprogramming** of tumor cells.
Bonuccelli G, et al. Oncotarget. 2014;5:7575-88.

Blocking Tumor-Educated MSC **Paracrine Activity** Halts Osteosarcoma Progression.
Baglio SR, et al. Clin Cancer Res. 2017;23:3721-3733.

Tumor-Activated Mesenchymal Stromal Cells Promote Osteosarcoma Stemness and Migratory Potential **via IL-6 Secretion**.
Cortini M, et PLoS One. 2016;11:e0166500.

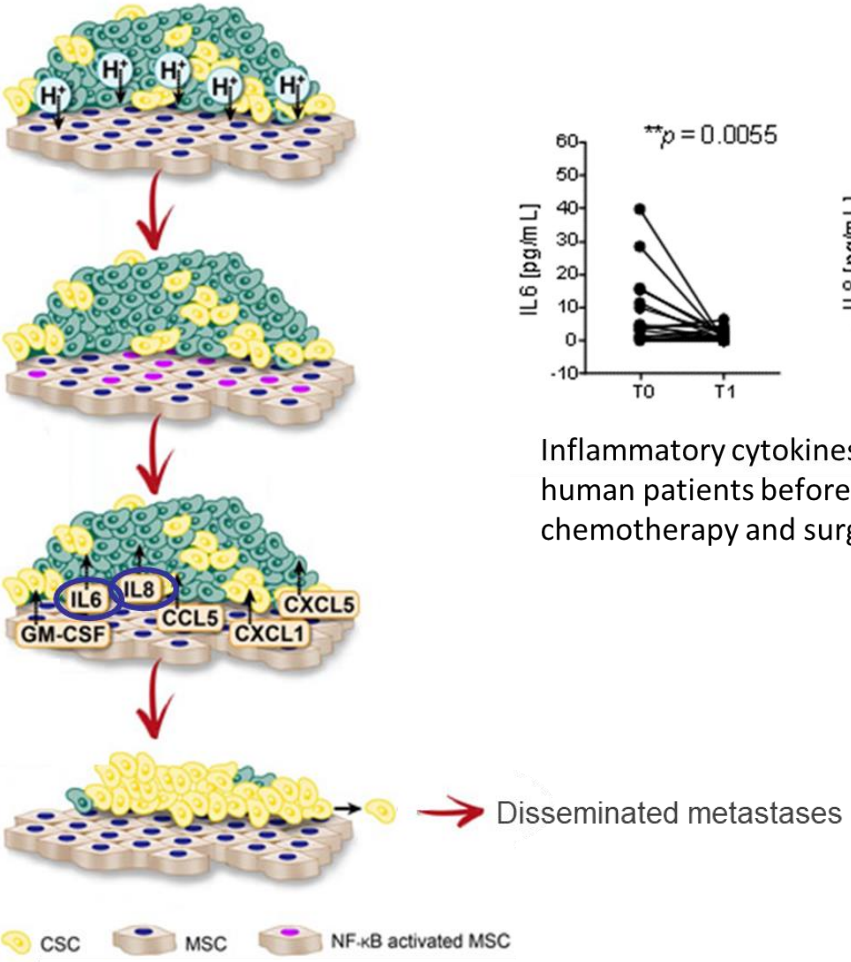
Acidosis as a proinflammatory stimulus via MSC

Extracellular acidification by tumor cells

NF-kB activation by short-term acidosis in the reactive mesenchymal stroma

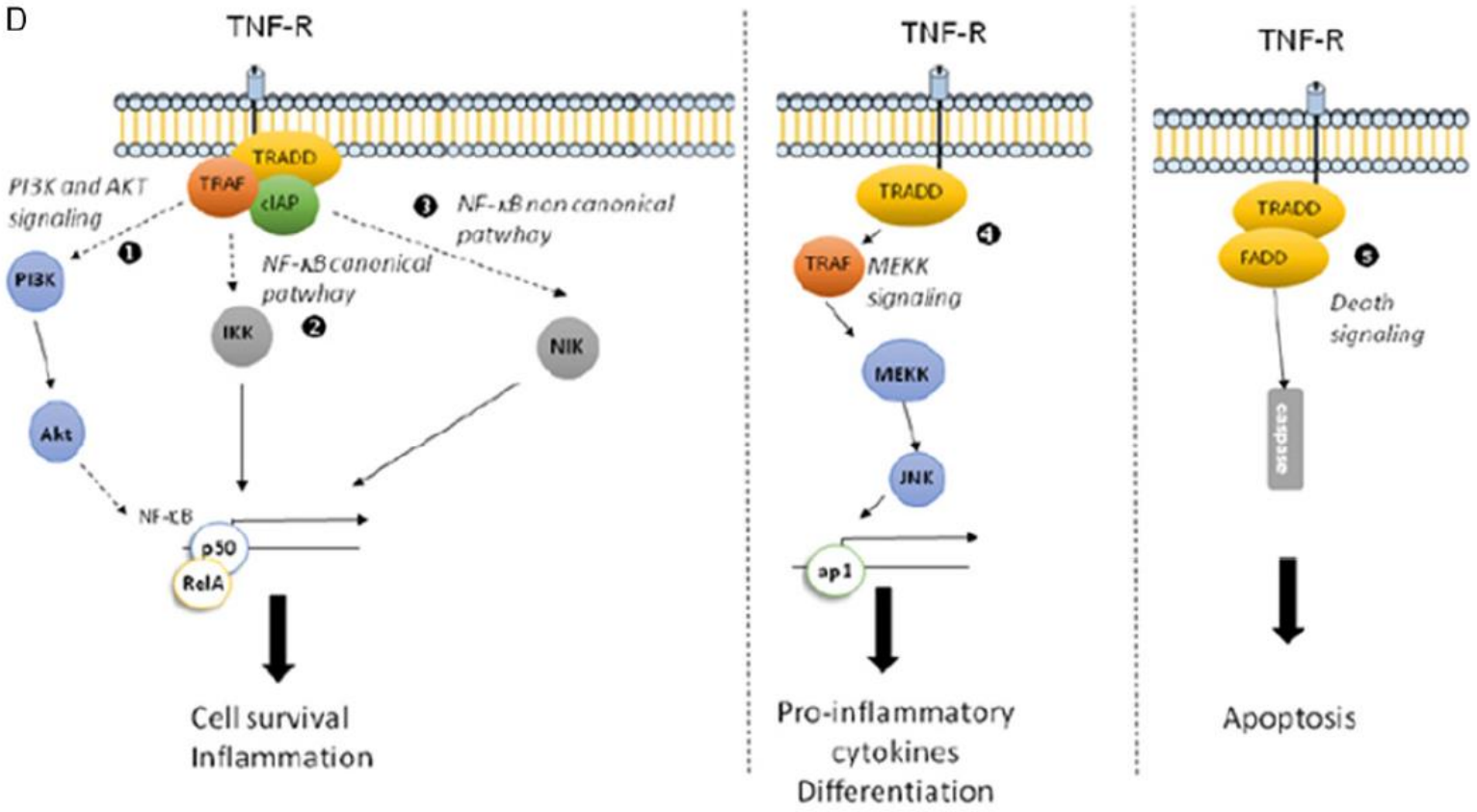
Secretion of paracrine factors from the reactive mesenchymal stroma

Tumor stemness, migration, and invasion induced by reactive mesenchymal stroma



Inflammatory cytokines in the serum of human patients before and after the chemotherapy and surgery

Cancer-associated mesenchymal stroma fosters the stemness of osteosarcoma cells in response to intratumoral acidosis **via NF-κB activation**.
Avnet S, et al. Int J Cancer. 2017;140:1331-1345.

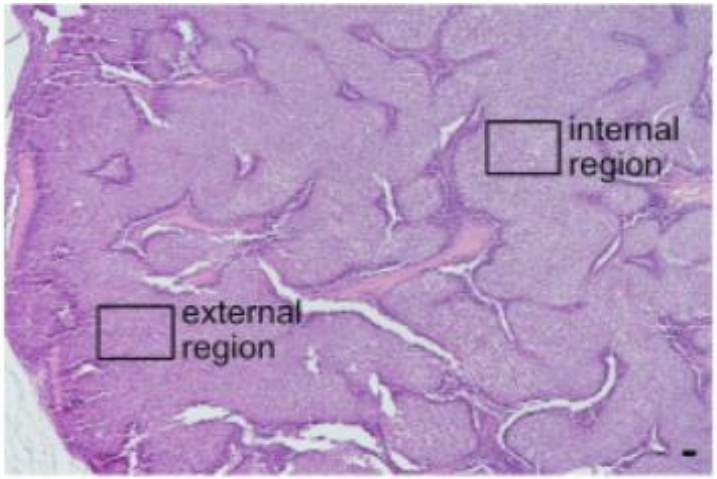


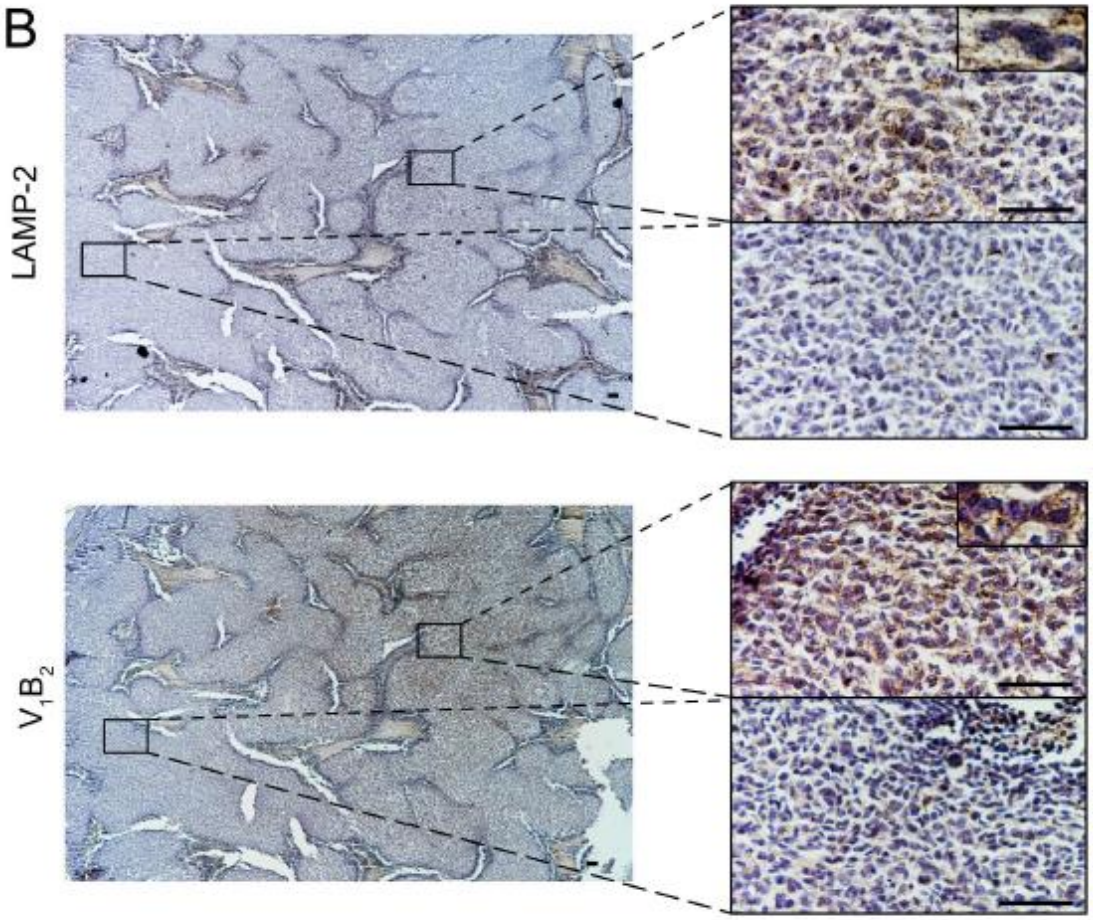
Am J Cancer Res 2019;9(2):XXX-XXX
www.ajcr.us /ISSN:2156-6976/ajcr0083000

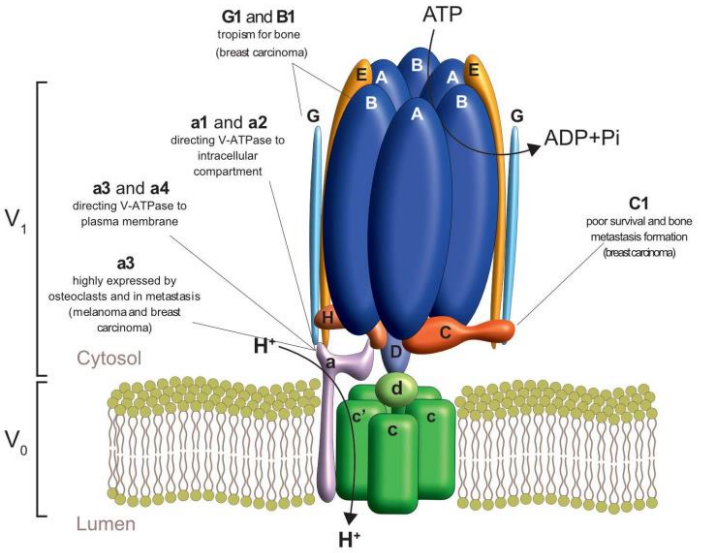
Original Article

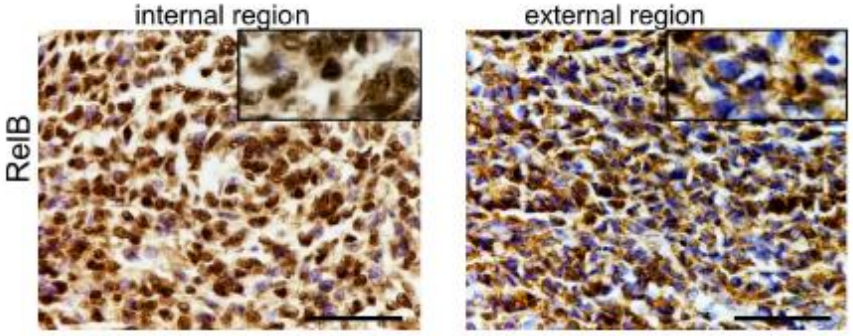
Acid microenvironment promotes cell survival of human bone sarcoma through the activation of cIAP proteins and NF-κB pathway

Sofia Avnet[1], Tokuhiro Chano[2], Annamaria Massa[1], Gloria Bonuccelli[1,5], Silvia Lemma[1], Luigi Falzetti[1], Giulia Grisendi[3], Massimo Dominici[3], Nicola Baldini[1,4]


internal region
external region


B
LAMP-2
V1B2

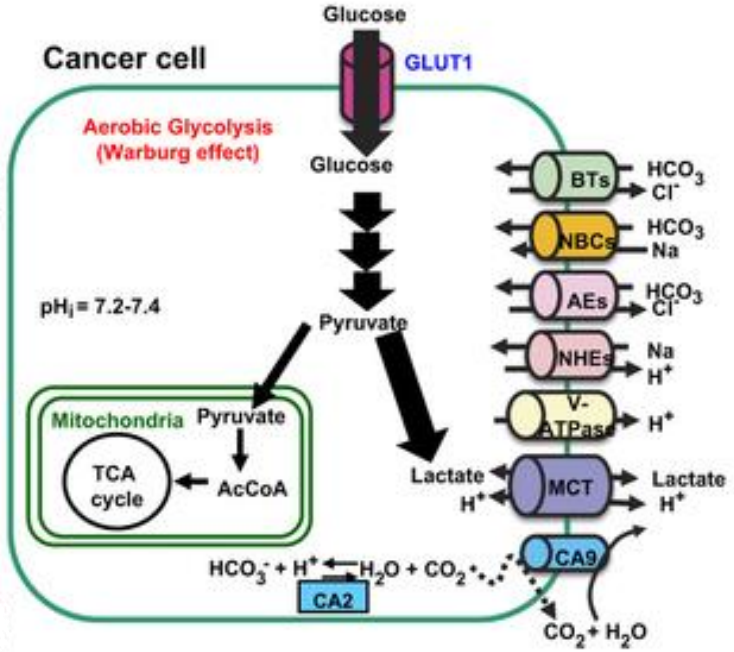

G1 and B1
tropism for bone
(breast carcinoma)
ATP
a1 and a2
directing V-ATPase to
intracellular
compartment
ADP+Pi
a3 and a4
directing V-ATPase to
plasma membrane
C1
poor survival and bone
metastasis formation
(breast carcinoma)
a3
highly expressed by
osteoclasts and in metastasis
(melanoma and breast
carcinoma)
V1
V0
Cytosol
Lumen
H+
H+


internal region
external region
RelB

Proton pumps/ion transporters or high proton concentrations: therapeutic targets

V-ATPase as an effective therapeutic target for sarcomas
(Perut et al. Exp Cell Res. 2014 Jan 1;320(1):21-32.)

Carbonic anhydrase IX inhibition is an effective strategy for osteosarcoma treatment.
(Perut F. Expert Opin Ther Targets. 2015;19(12):1593-605)



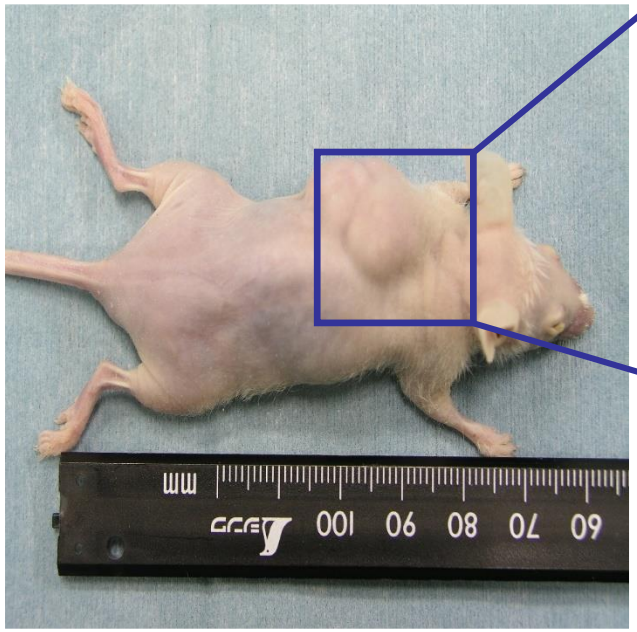
ACRIDINE ORANGE COMBINED PHOTODYNAMIC THERAPY AND SURGERY AS A NOVEL APPROACH TO TREAT FELINE INJECTION-SITE SARCOMA.

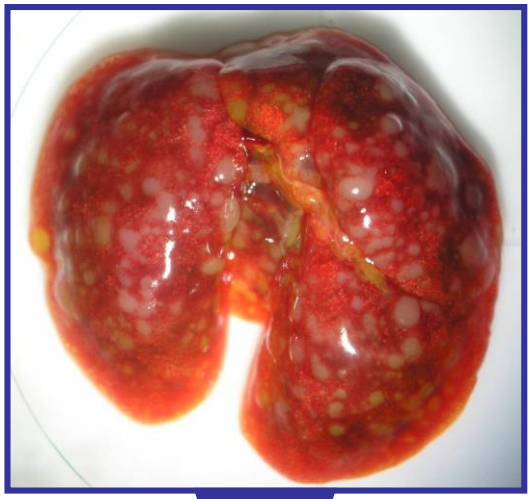
Costa F, Avnet S, Martano M, Morello E, Paolo Buracco, Katsuyuki Kusuzaki, Nicola Baldini

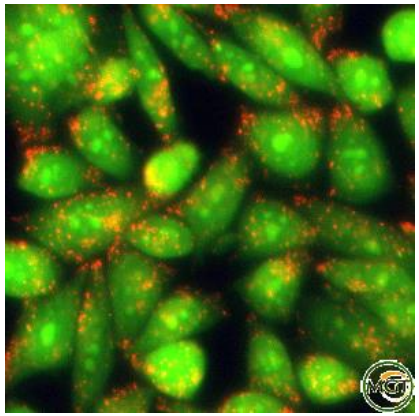
Poster 6

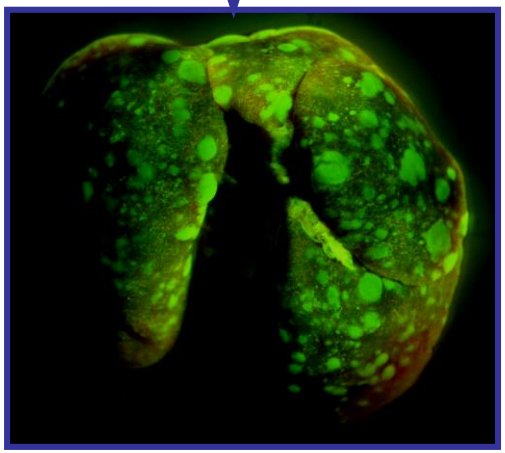
pH imaging

Kusuzaki K, Anticancer Res (2000) 20:3019-24





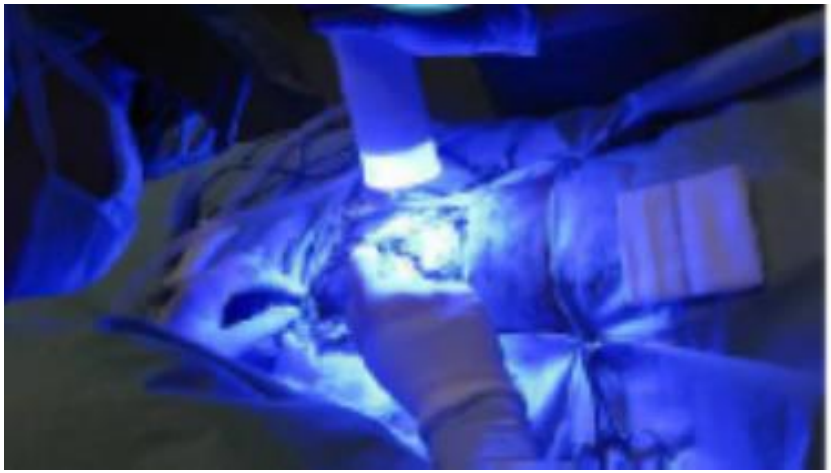




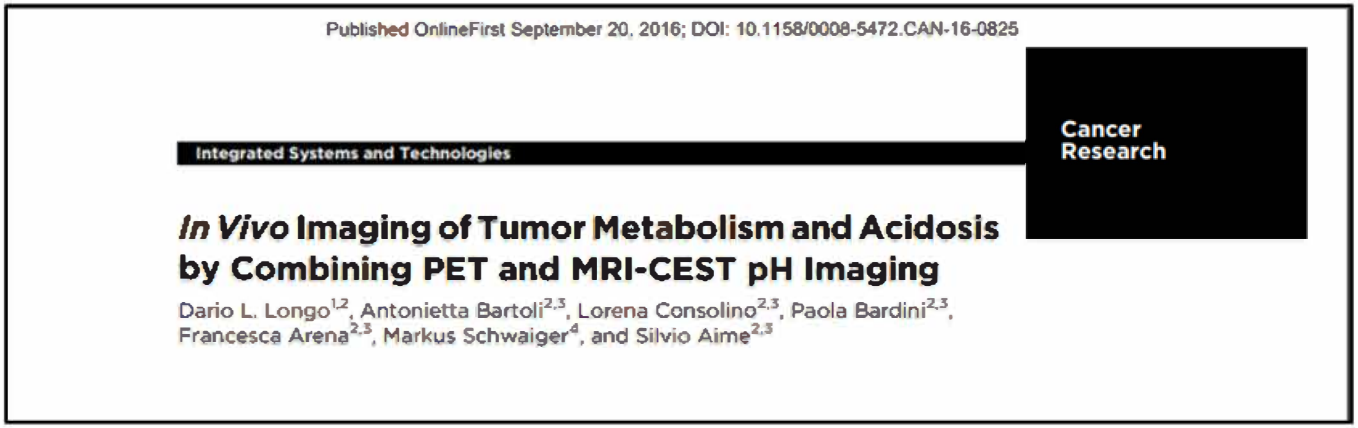
Clin Orthop Relat Res. 2013 Mar;471(3):792-802. doi: 10.1007/s11999-012-2616-9.

Can a less radical surgery using photodynamic therapy with acridine orange be equal to a wide-margin resection?

Matsubara T[1], Kusuzaki K, Matsumine A, Nakamura T, Sudo A.



pH imaging



Published OnlineFirst September 20, 2016; DOI: 10.1158/0008-5472.CAN-16-0825

Integrated Systems and Technologies

Cancer Research

In Vivo Imaging of Tumor Metabolism and Acidosis by Combining PET and MRI-CEST pH Imaging

Dario L. Longo[1,2], Antonietta Bartoli[2,3], Lorena Consolino[2,3], Paola Bardini[2,3], Francesca Arena[2,3], Markus Schwaiger[4], and Silvio Aime[2,3]

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Cancer Metastasis Rev. 2019 Feb 14. doi: 10.1007/s10555-019-09782-9. [Epub ahead of print]

Imaging tumor acidosis: a survey of the available techniques for mapping in vivo tumor pH.

Anemone A[1], Consolino L[1], Arena F[2,3], Capozza M[3], Longo DL[4,5].

CONCLUSION

Intratumor acidosis foster tumor evolution and is a key challenge in osteosarcoma treatment and imaging