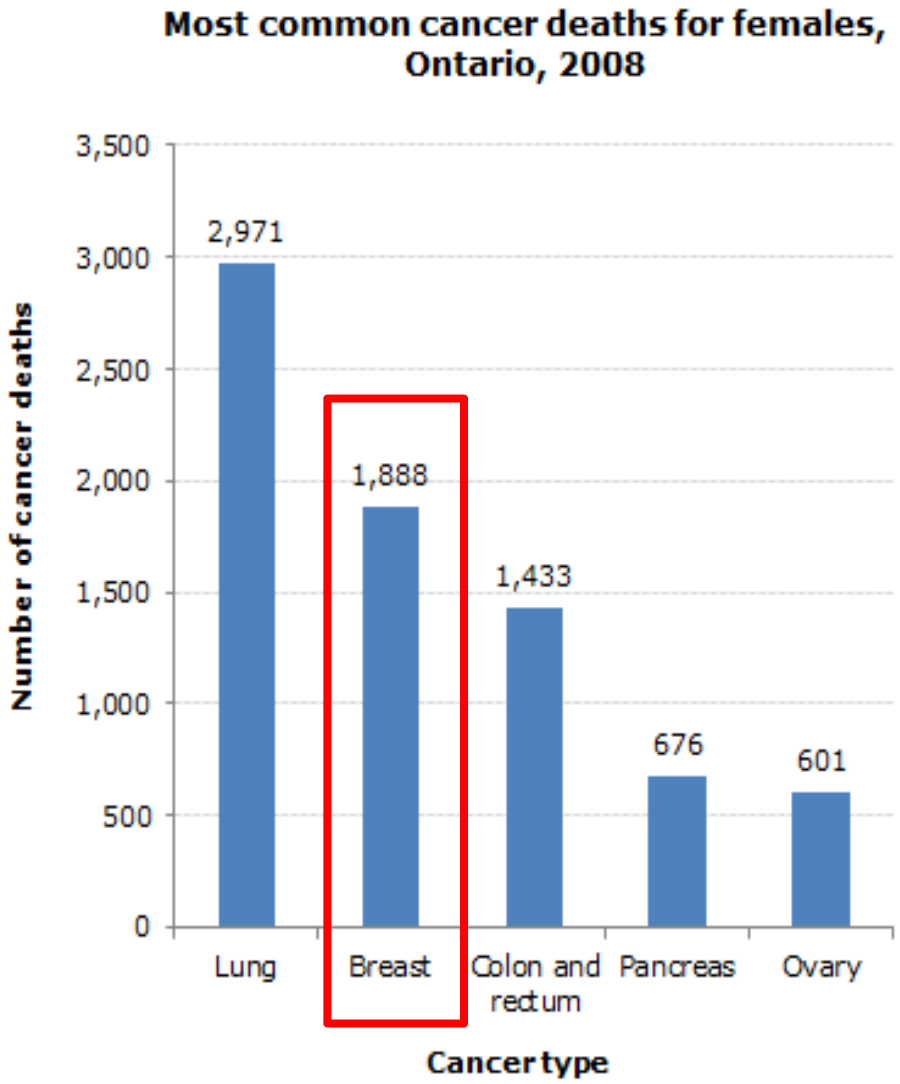
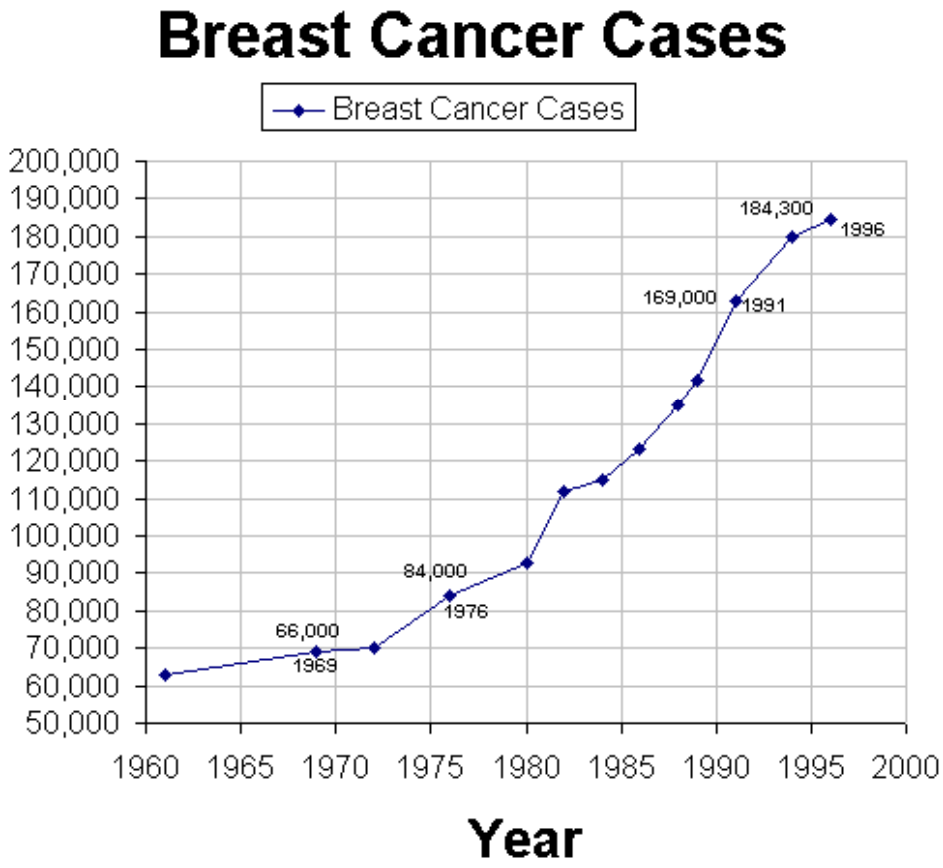
Use specific response toward environment as a selective marker for therapy in breast cancer cells.

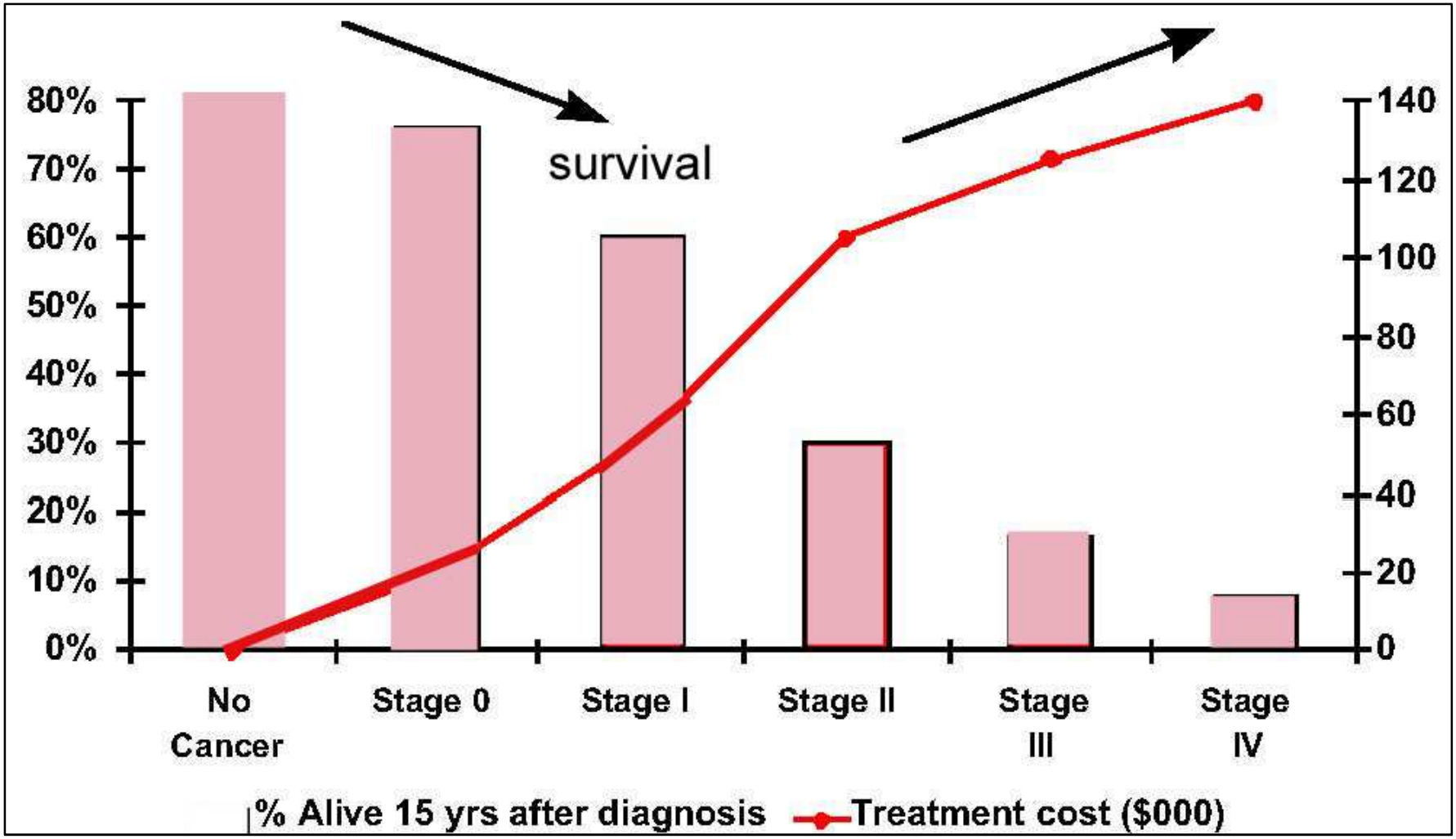
Hsiu-Ni Kung

Anatomy and Cell Biology, Medical school,
National Taiwan University





Source: Cancer Care Ontario (Ontario Cancer Registry, 2011)



Metastatic Breast Cancer Survival Rates

http://cancercarepliss.blogspot.tw/2011/07/metastatic-breast-cancer-survival-rates.html


440 mg
Trastuzumab


FLUOROURACIL
INJECTION, USP
5 g/100 mL
Rx Only


CYTOXAN
ADRIAMYCIN
DTIC-


Paraplatin
(CARBOPLATIN FOR INJECTION)
450 mg
Paraplatin
50 mg


Chemotherapy
Chemotherapy

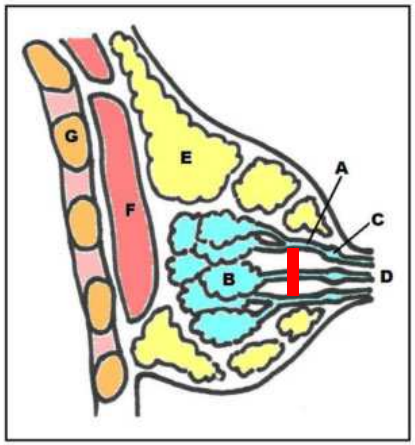

Epirubicin
Hydrochloride
Injection

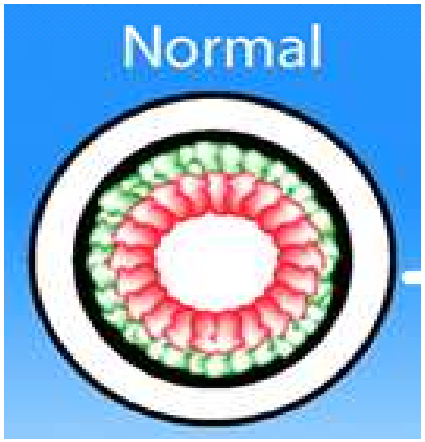

Herceptin®
Trastuzumab
440 mg
1 vial with 440 mg
active ingredient
+ 1 vial with 20 ml
solvent
Roche


NDC 50242-060-01
List No.:15734
100 mg
25 mg/mL
AVASTIN™
(bevacizumab)
For Intravenous Use
4 mL SINGLE-USE VIAL
NO PRESERVATIVES.
DISCARD UNUSED PORTION.
100 mg
25 mg/mL
Genentech


TAXOL

Breast tumor lineage

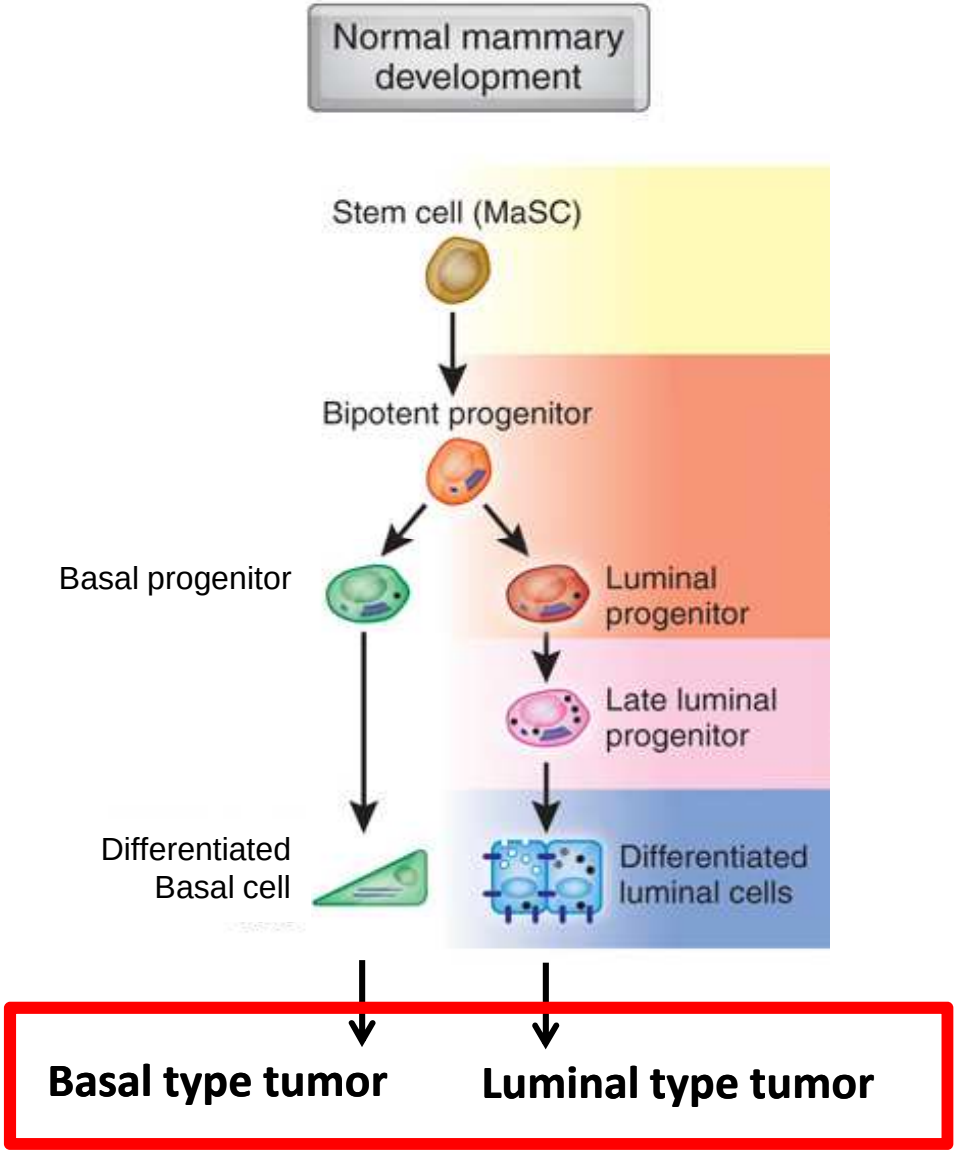




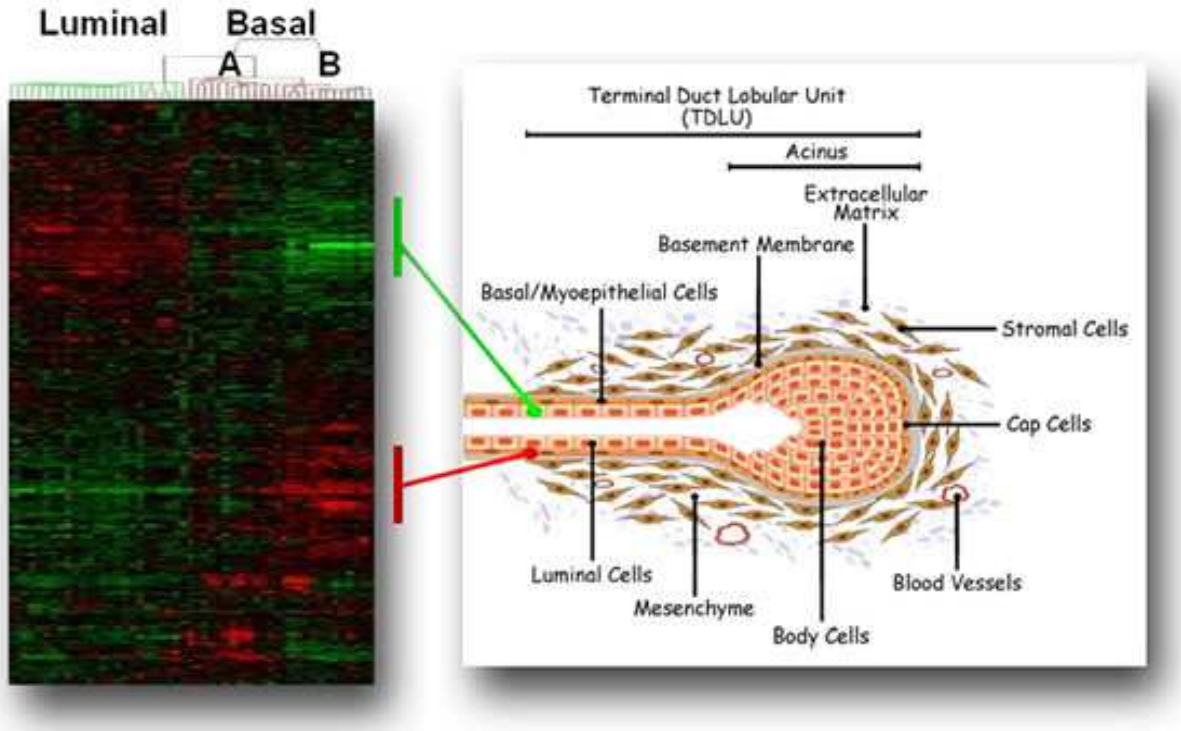
Basement membrane

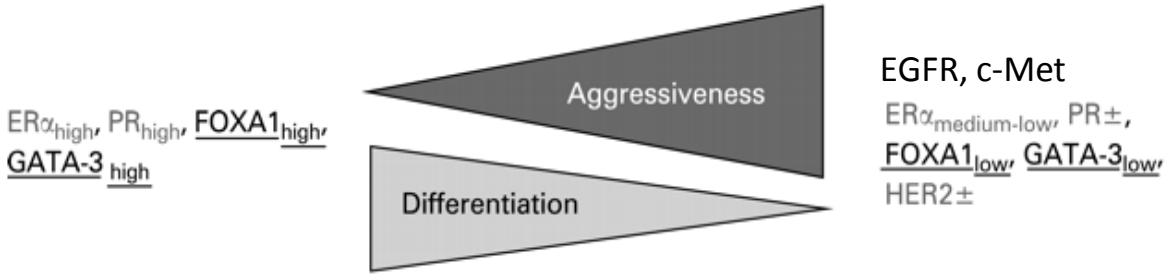
Basal cells

Luminal cells



(Aleix Prat and Charles M Perou, Nature review, 2009)

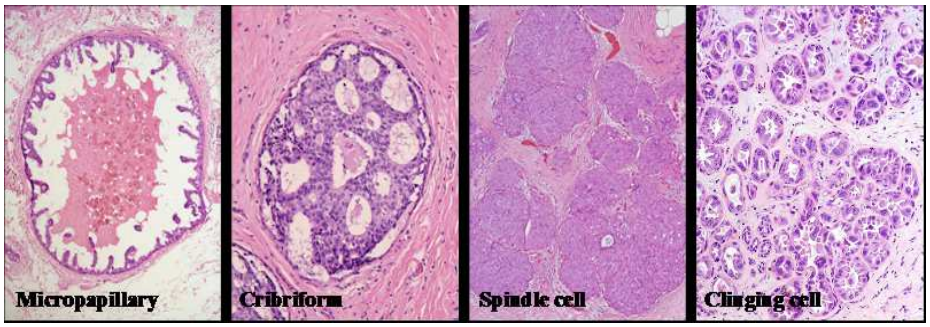




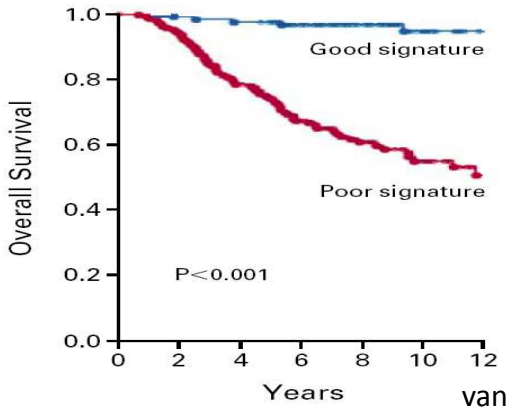
Luminal type tumor **Basal type tumor**

(Badve and Nakshatri, J Clin Pathol,2009)

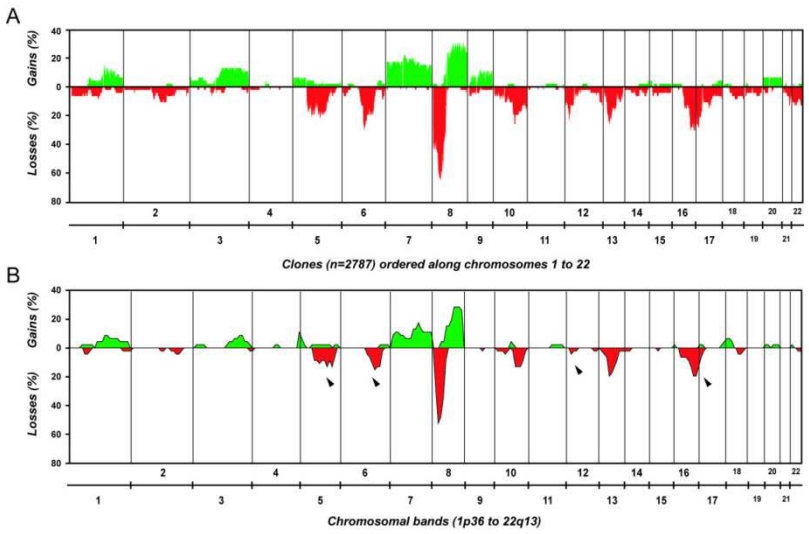
The Heterogeneity among Human Breast Cancers

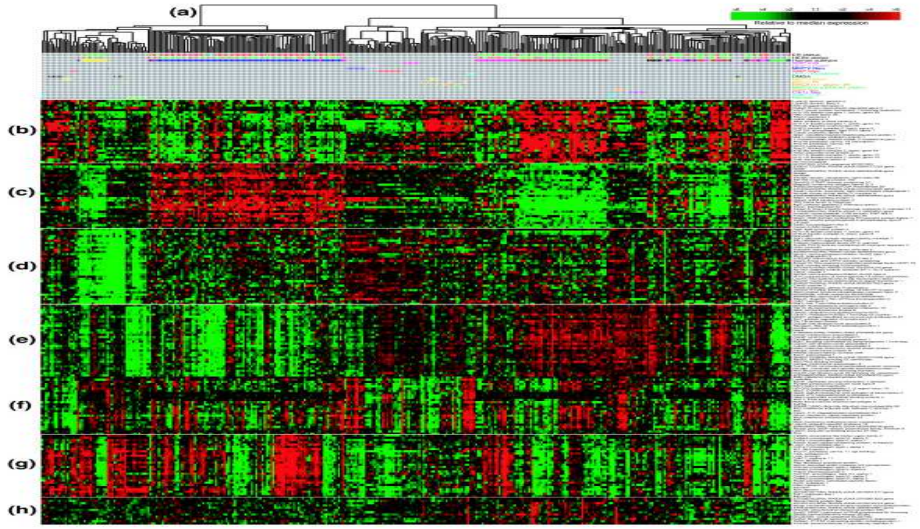


Yi-Hsuan Hsiao, et al., J. cancer, 2010



van de Vijver 2002



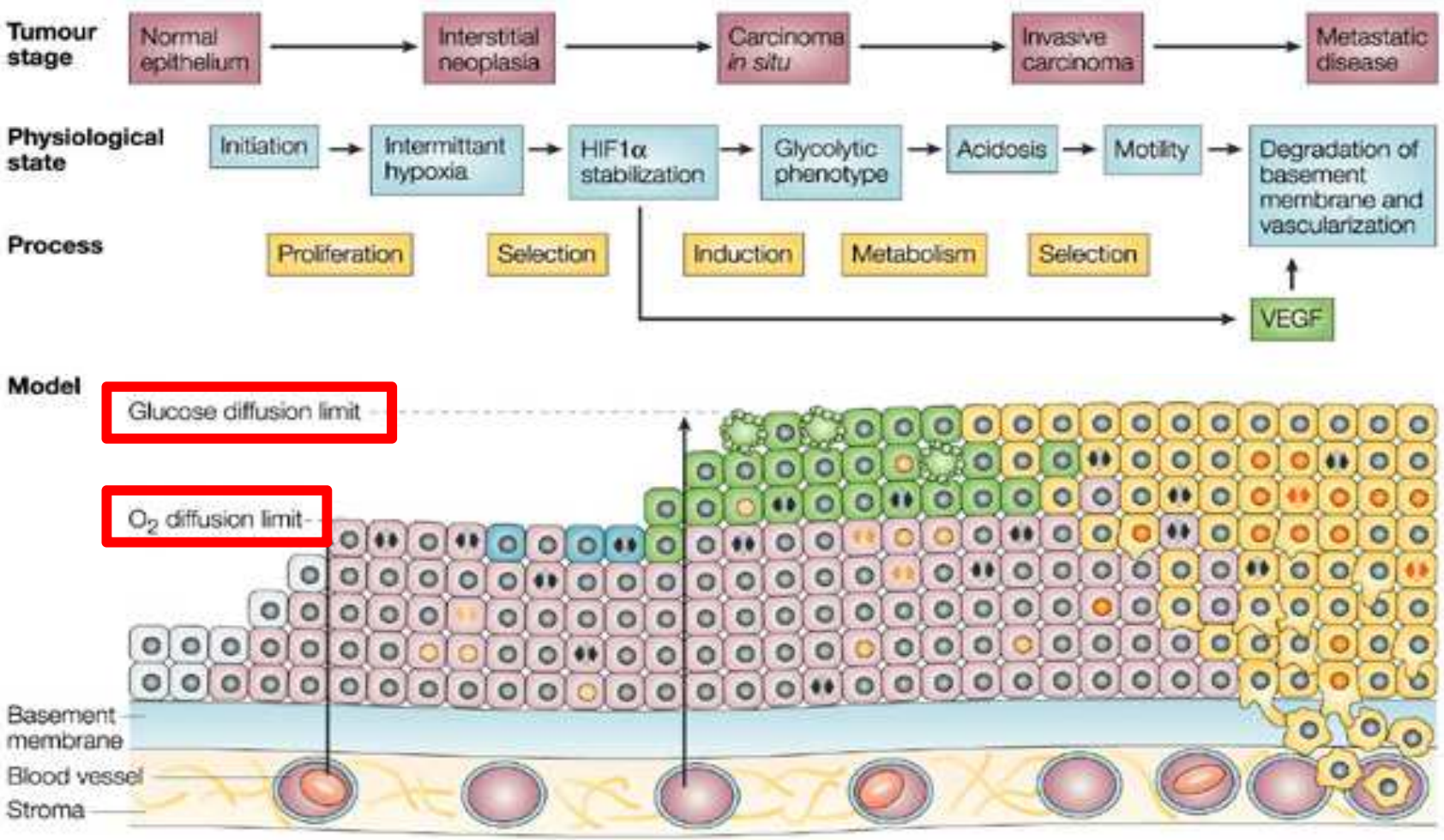


Jason I Herschkowitz, et al., Genomw biology. 2010

Genetic characteristics

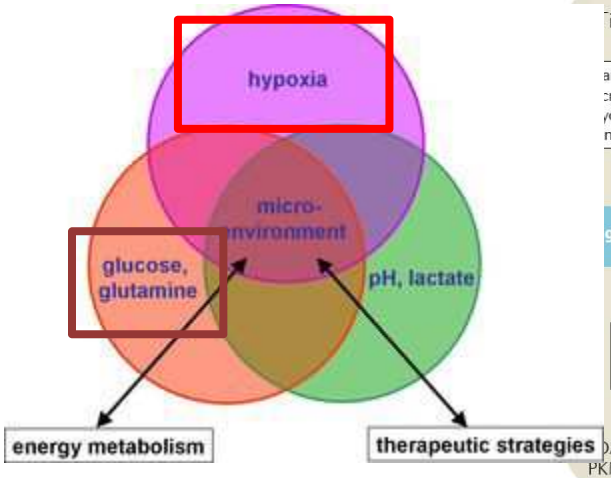
Non-genetic characteristics : environmental change (stress)

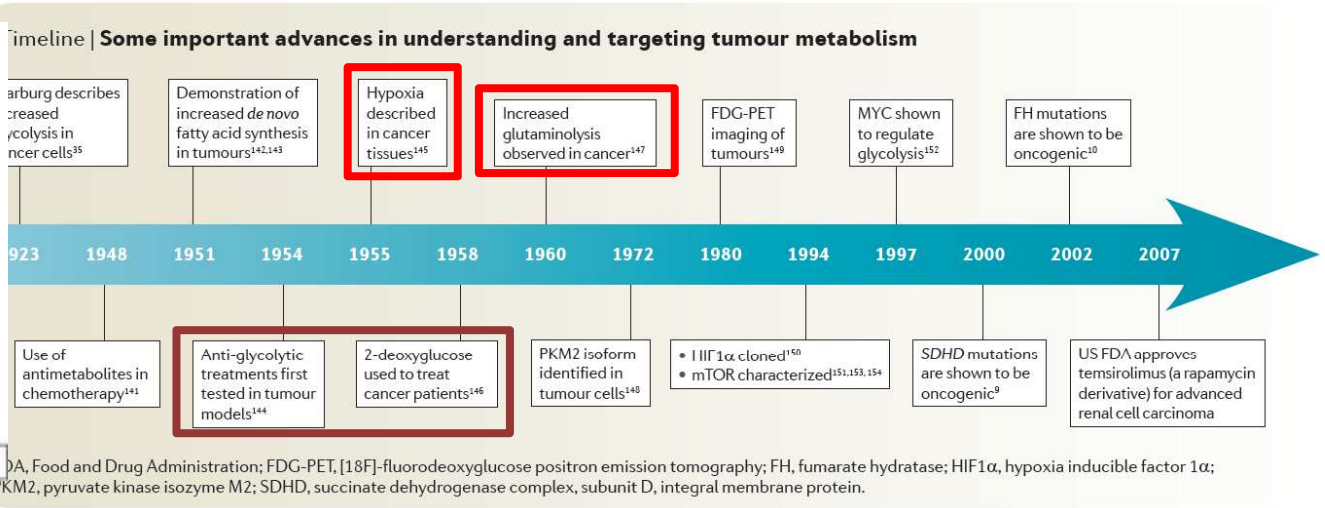
Microenvironmental stresses impact tumor phenotypes (short term) and exert selection pressure (long-term)



Nature Reviews | Cancer

Microenvironments



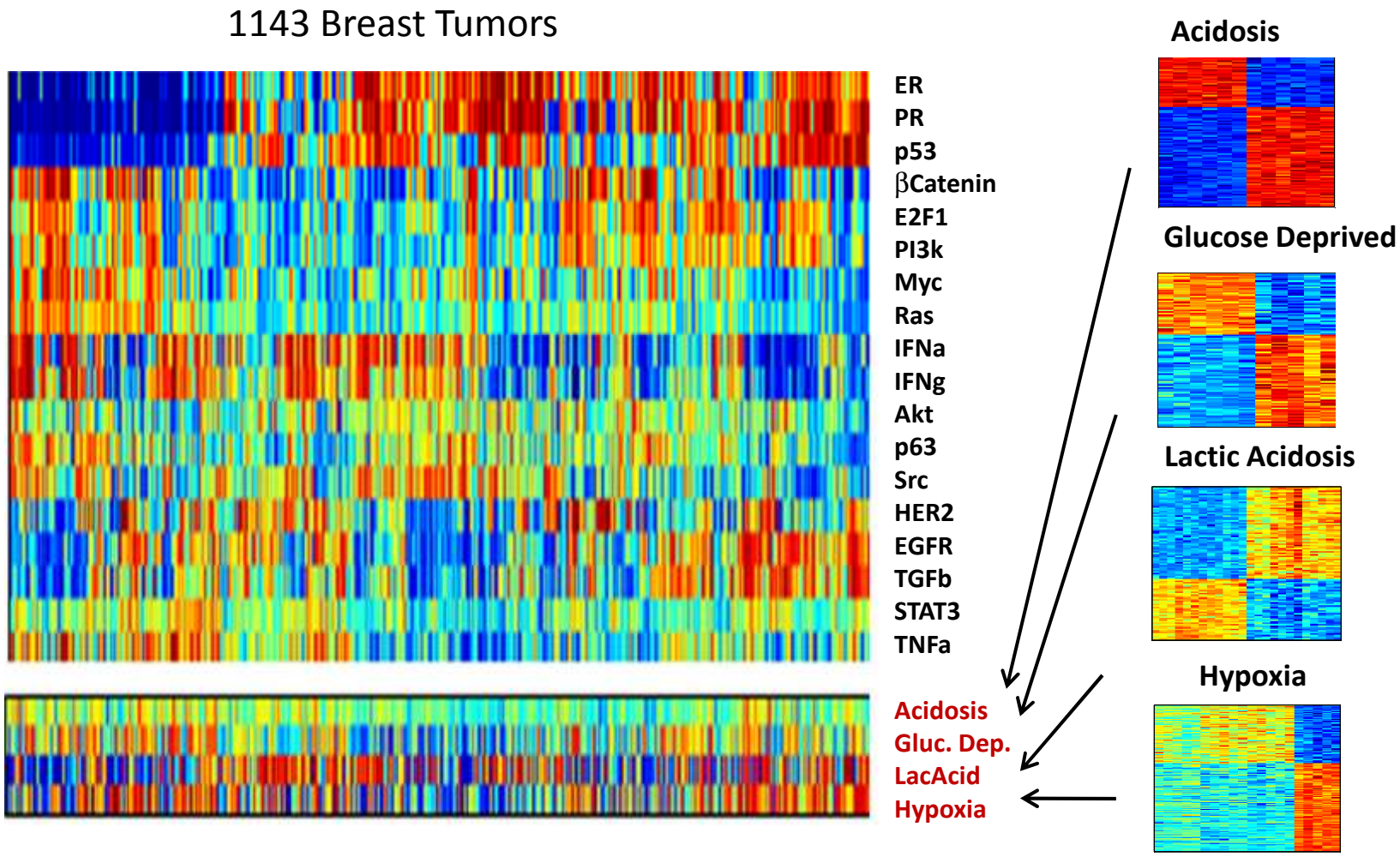


1. Hypoxia & heterogeneity

2. Glutamine requirement

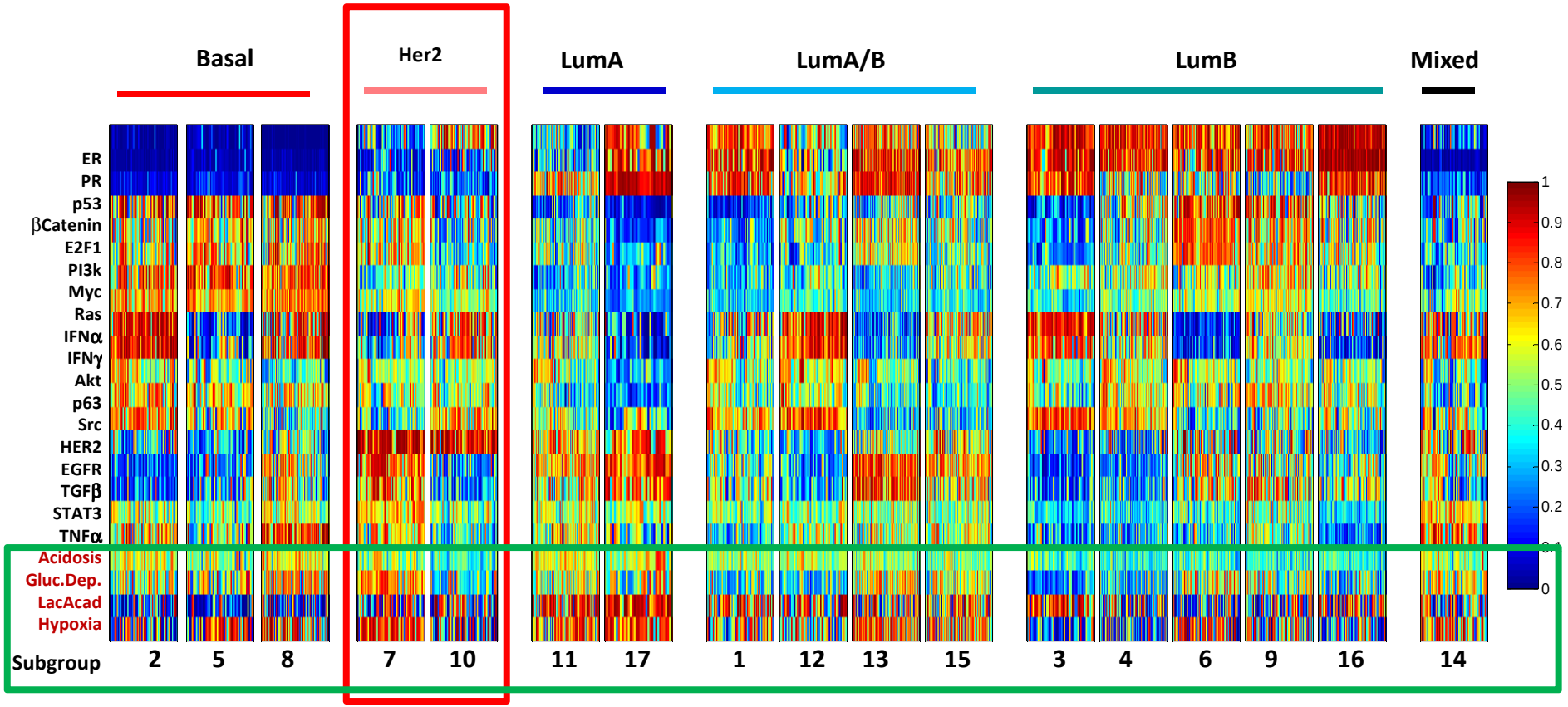
1. Hypoxia & heterogeneity

The integration of the non-genetic stress signatures with oncogenic signaling pathways



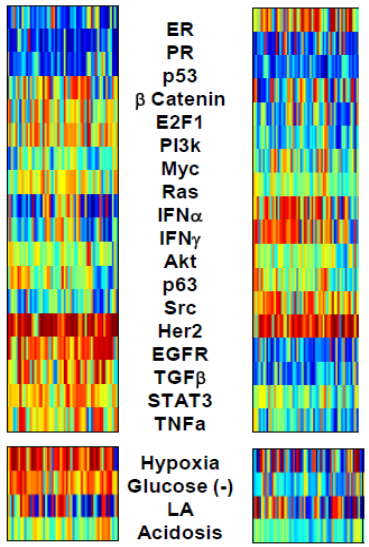
1. Hypoxia & heterogeneity

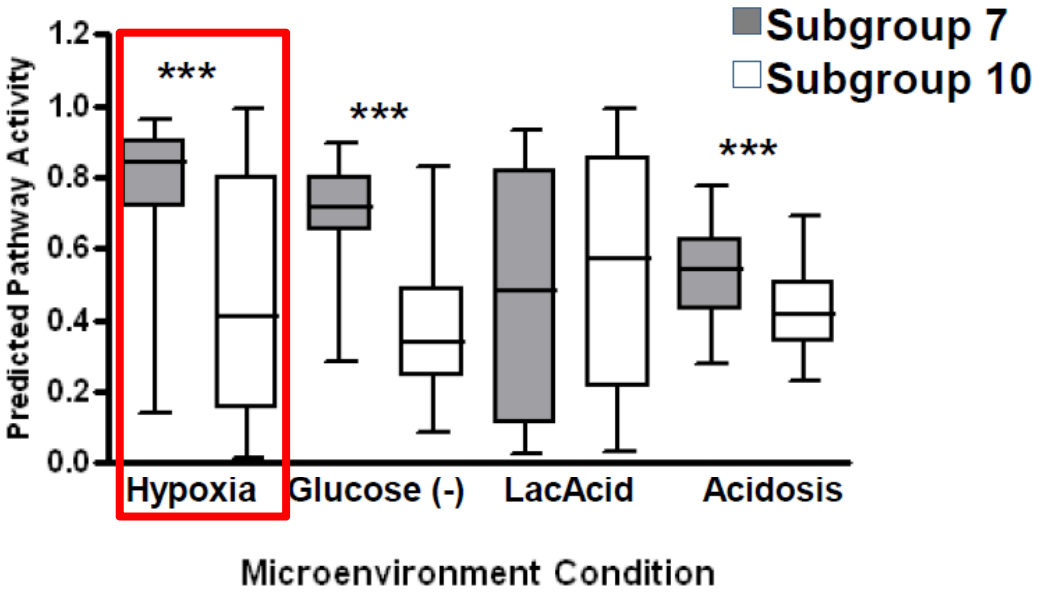
Microenvironment signaling identified subtypes among ERBB2+ Tumors.

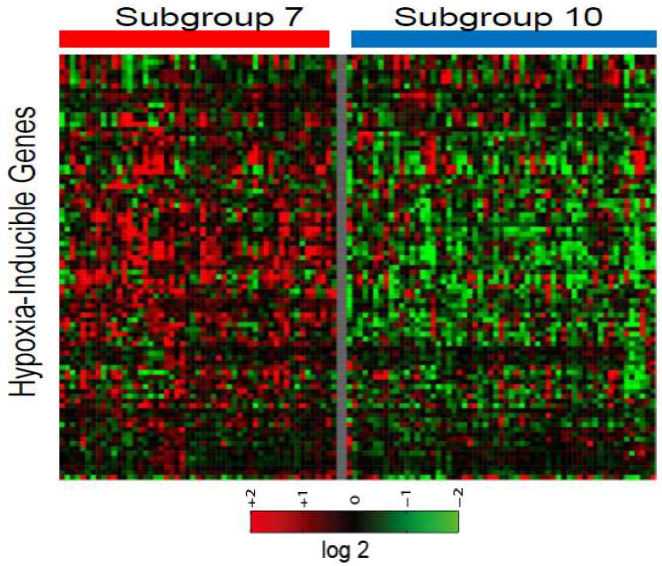


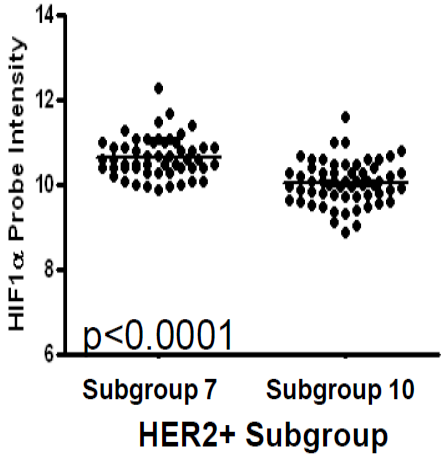
1. Hypoxia & heterogeneity

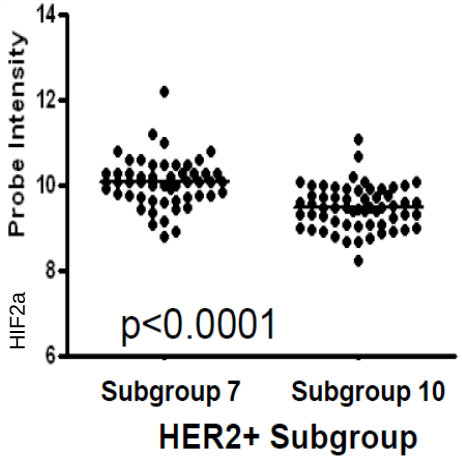
Hypoxia pathway is higher in subgroup 7.





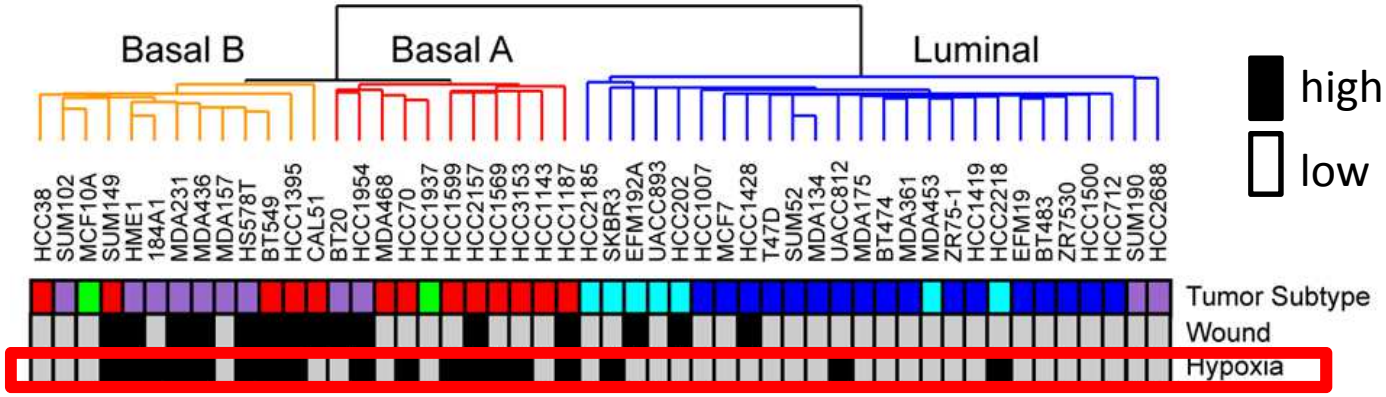






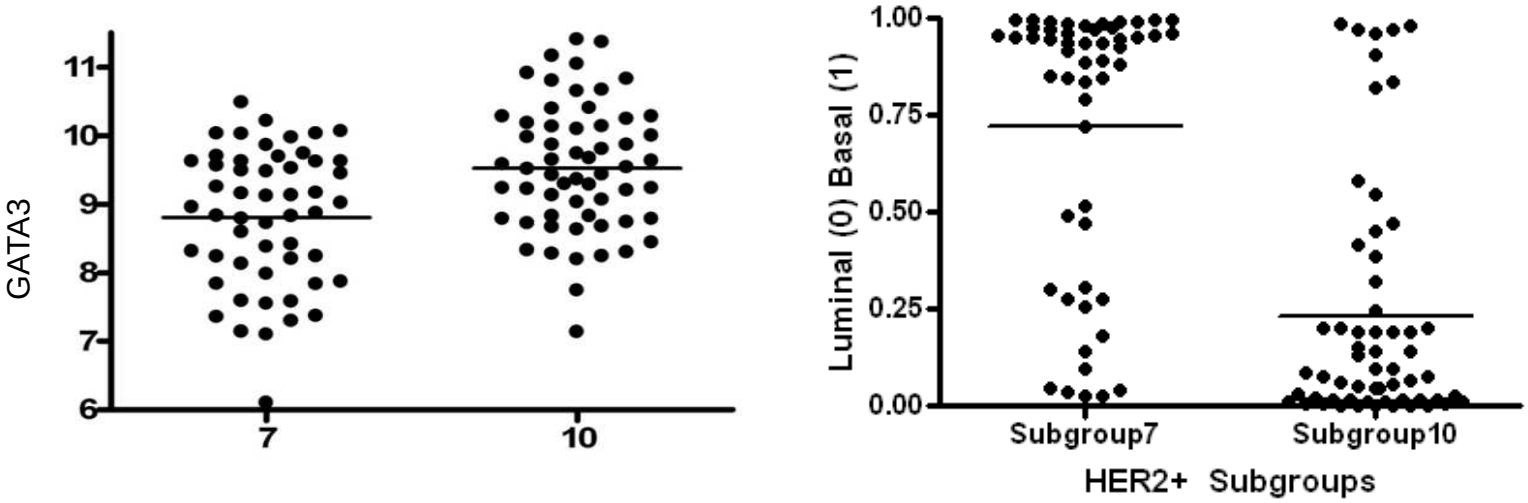
1. Hypoxia & heterogeneity

Subgroup 10 has higher expression of luminal regulator genes.



(Jessica Kao, et al., 2009, Plos One)

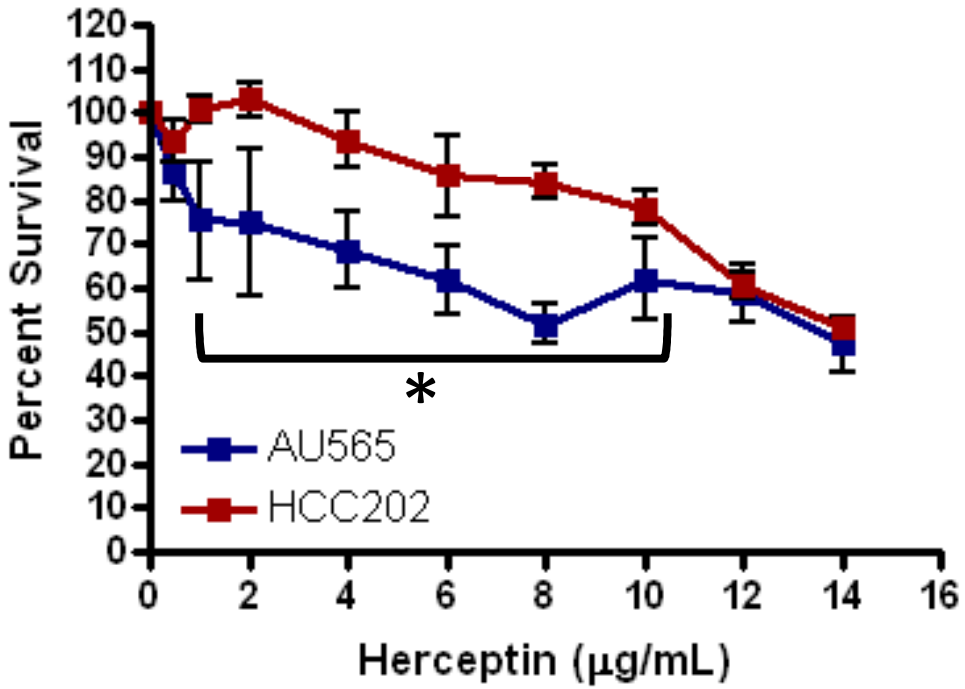
p<0.0001



1. Hypoxia & heterogeneity

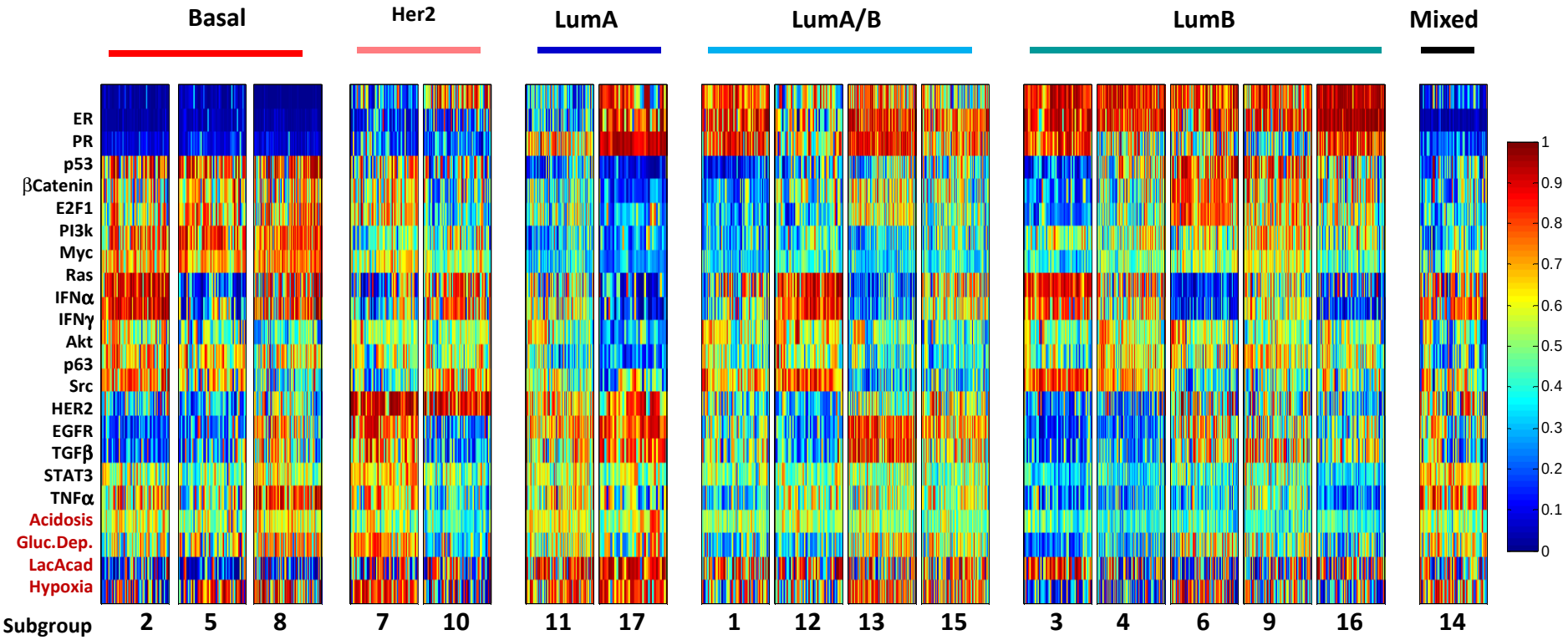
Different response to HER2 inhibitor treatment in AU565 (subgroup7) and HCC202 (subgroup10) .

Herceptin : HER2 inhibitor

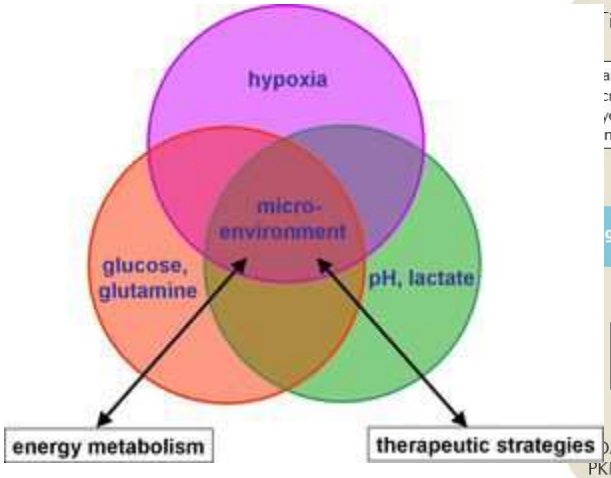


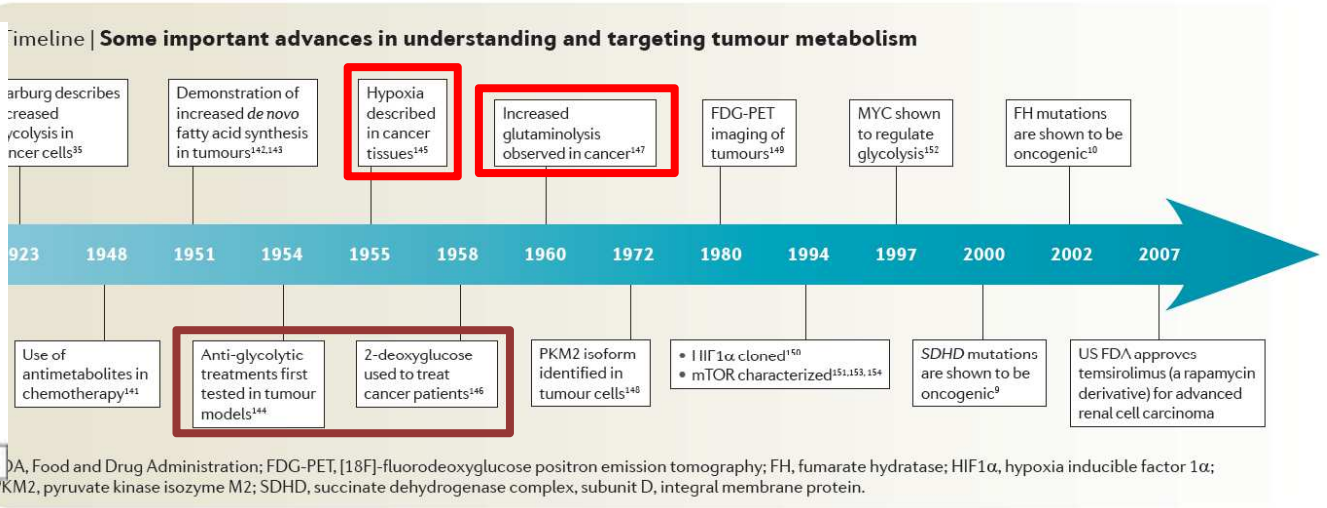
(Michael L Gatza et al., 2011, breast cancer research)

1. Hypoxia & heterogeneity



Microenvironments



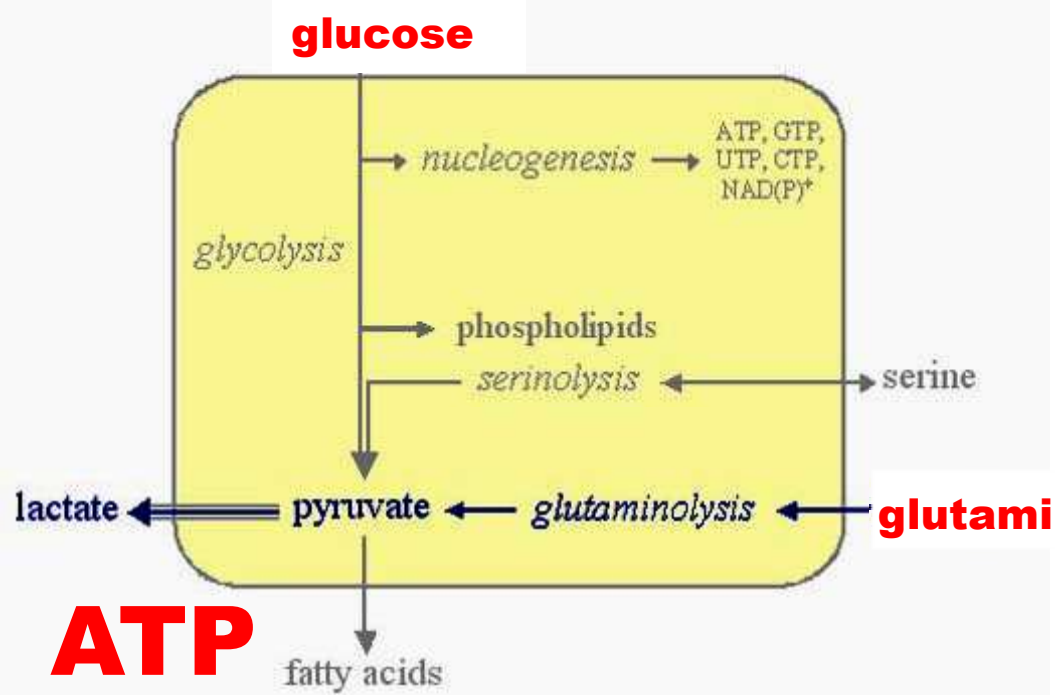


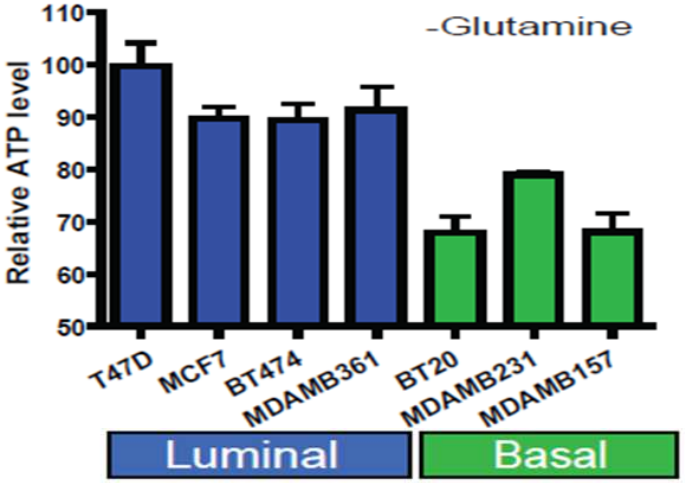
1. Hypoxia & heterogeneity

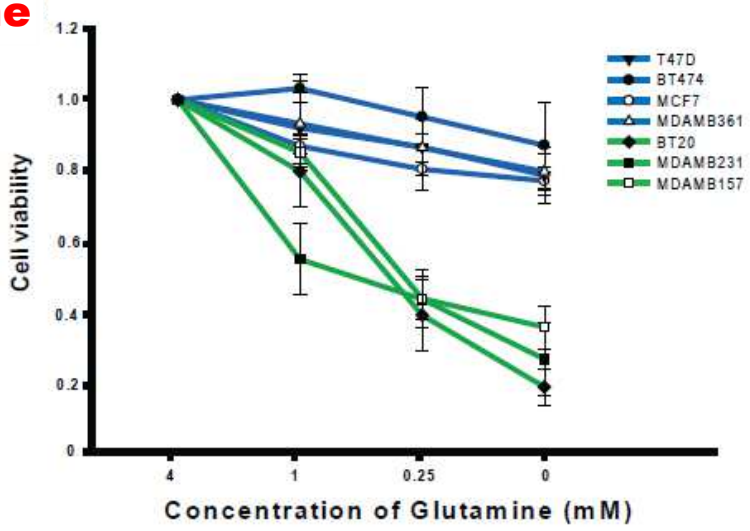
2. Glutamine requirement

2. Glutamine requirement

Basal cells use more glutamine as the energy source.

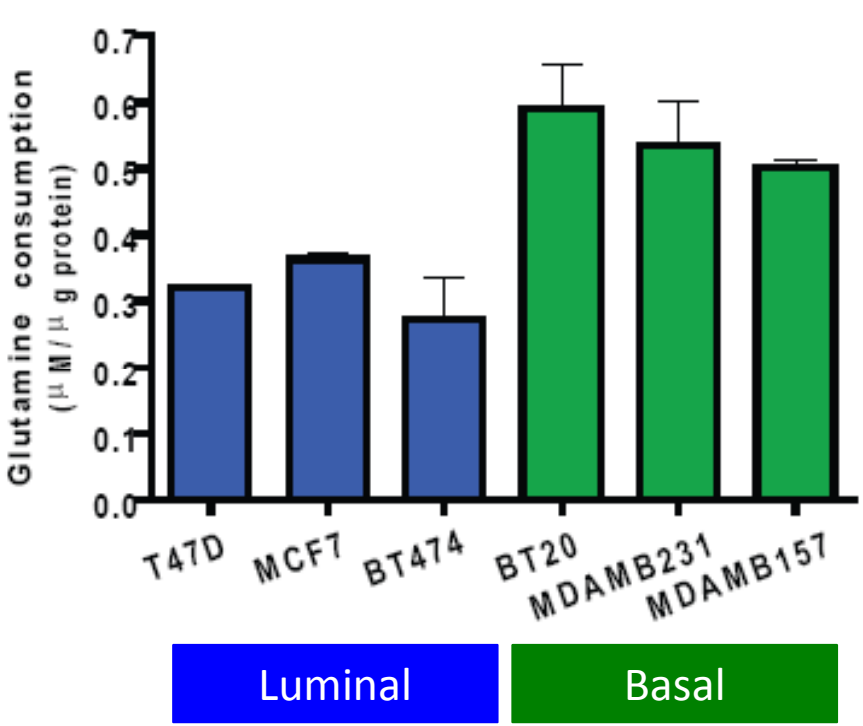


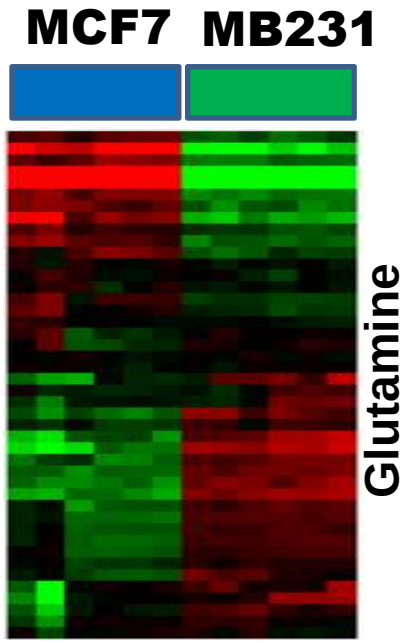


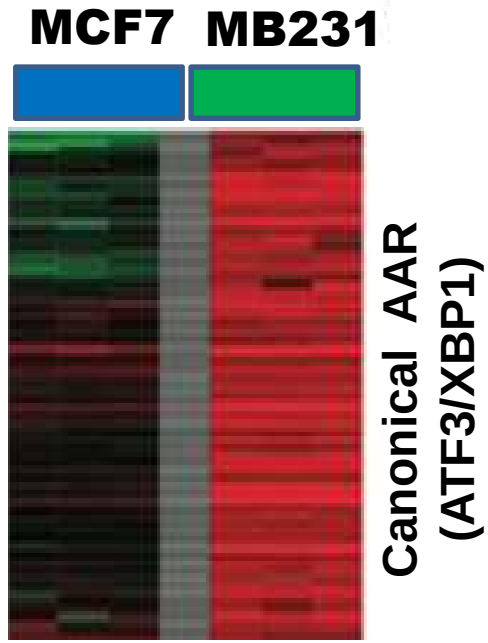


2. Glutamine requirement

Basal breast cells consume more glutamine, and exhibit canonical AAR response during glutamine deprivation



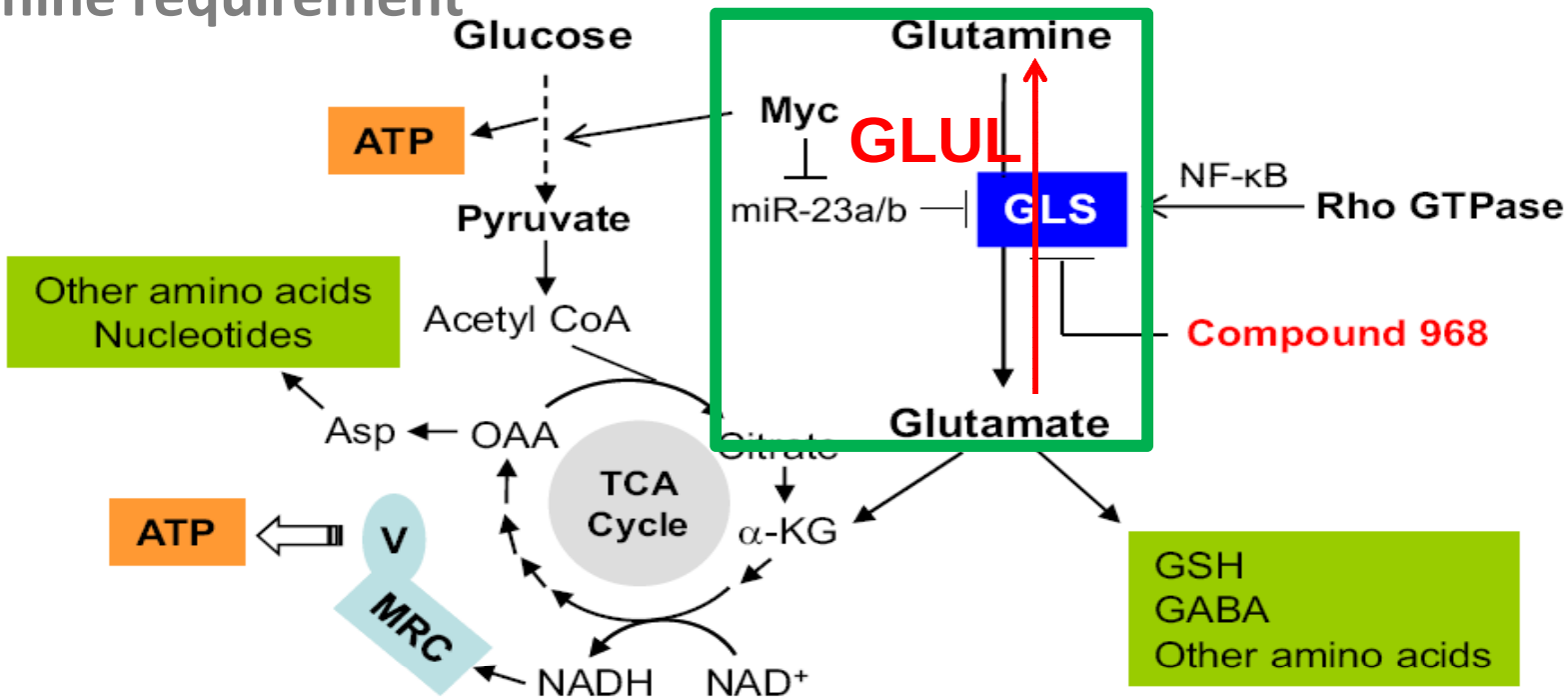




MCF7 / MDAMB231
without glutamine

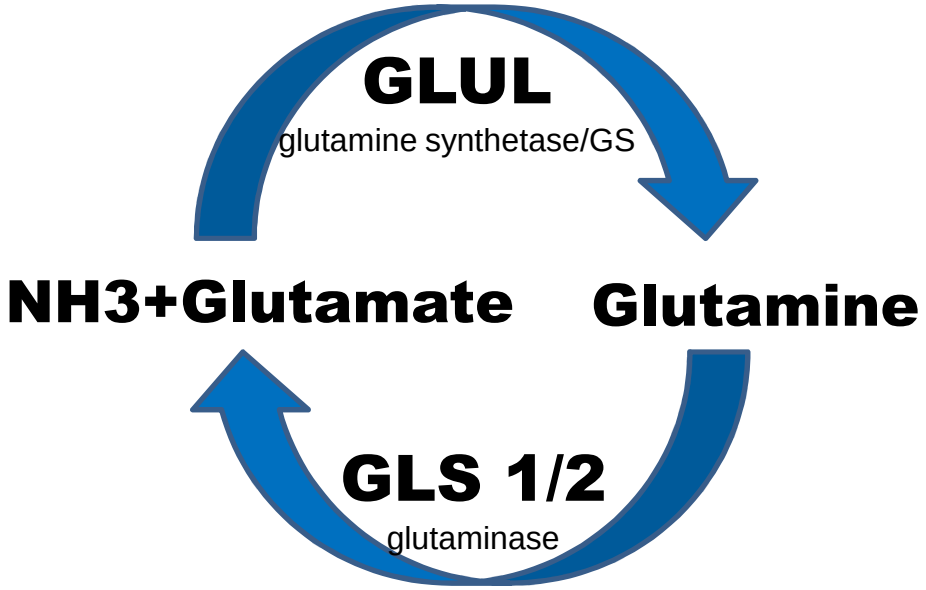
What are the genetic determinants of glutamine addiction vs. independence ?

2. Glutamine requirement



GLUL
(Glutamine synthetase, GS)

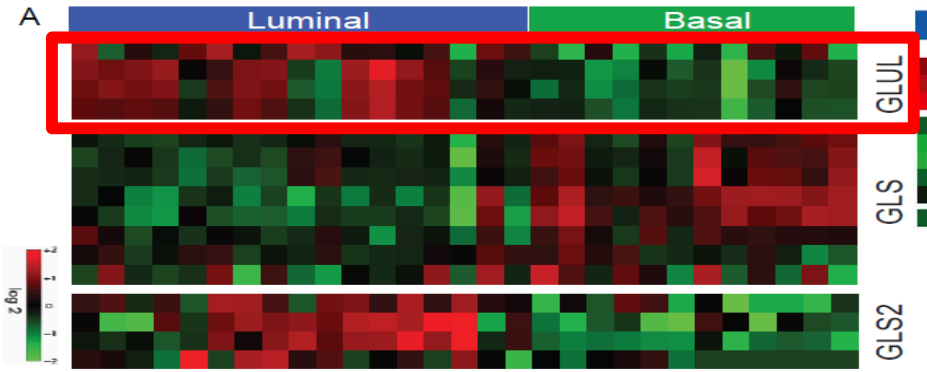
GLS1- Liver
GLS2- Kidney
(Glutaminase)



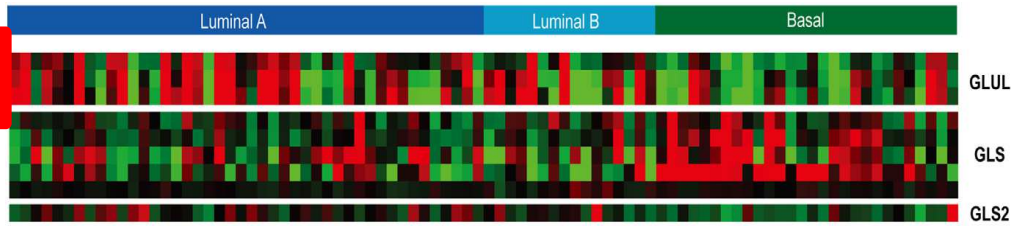
2. Glutamine requirement

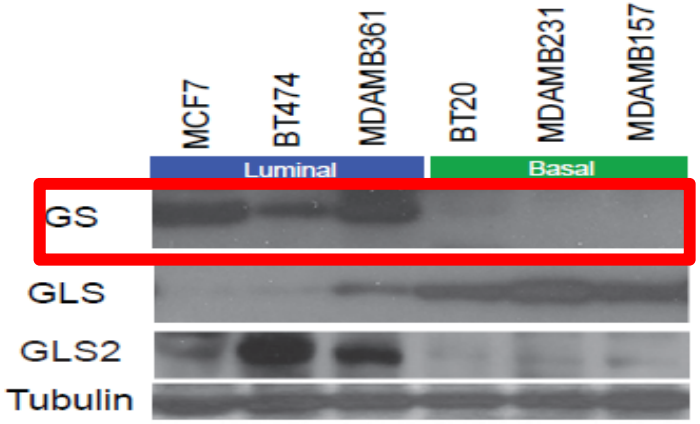
Luminal-specific expression of GLUL and higher intracellular glutamine synthetase level

Breast cancer cells

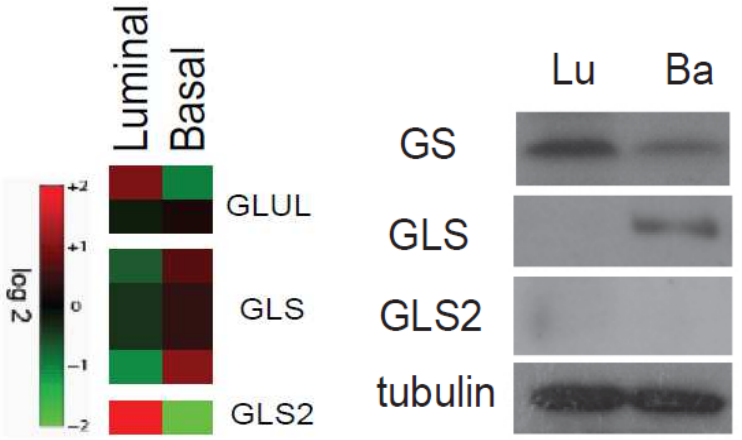


Breast tumors





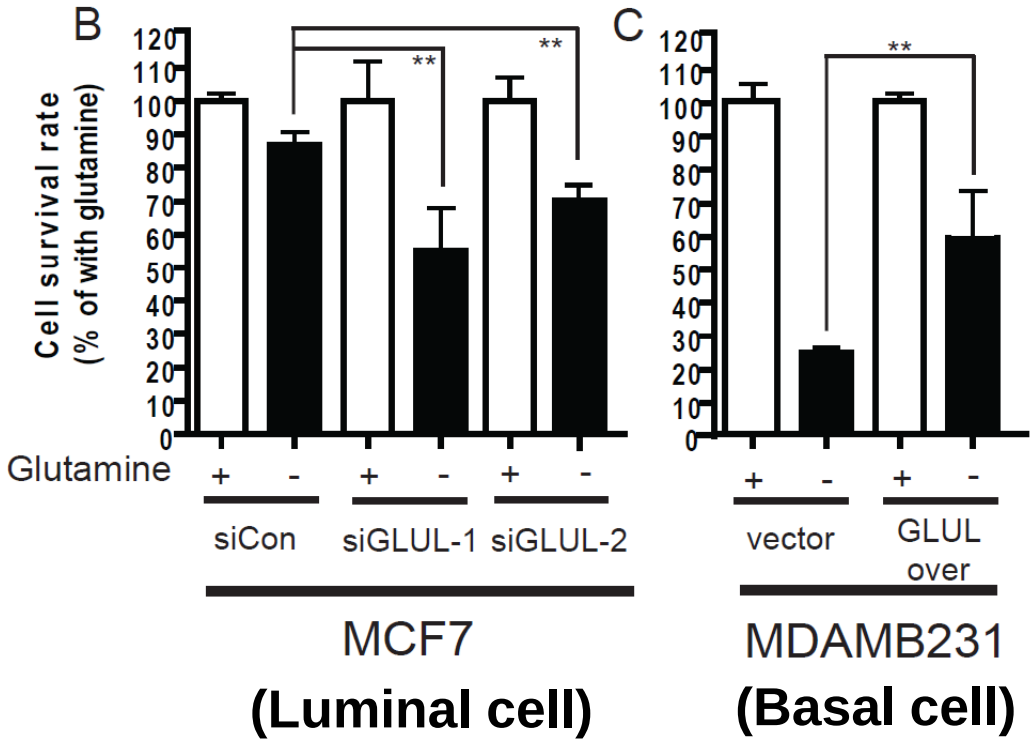
Primary breast cells



2. Glutamine requirement

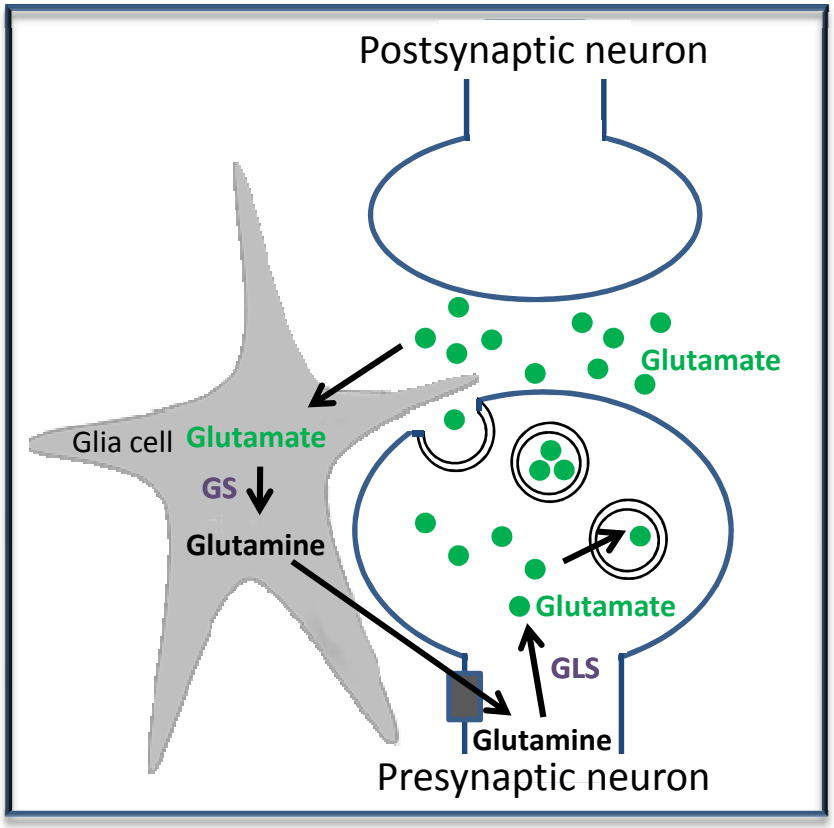
High level of GLUL confer resistance of glutamine deprivation.

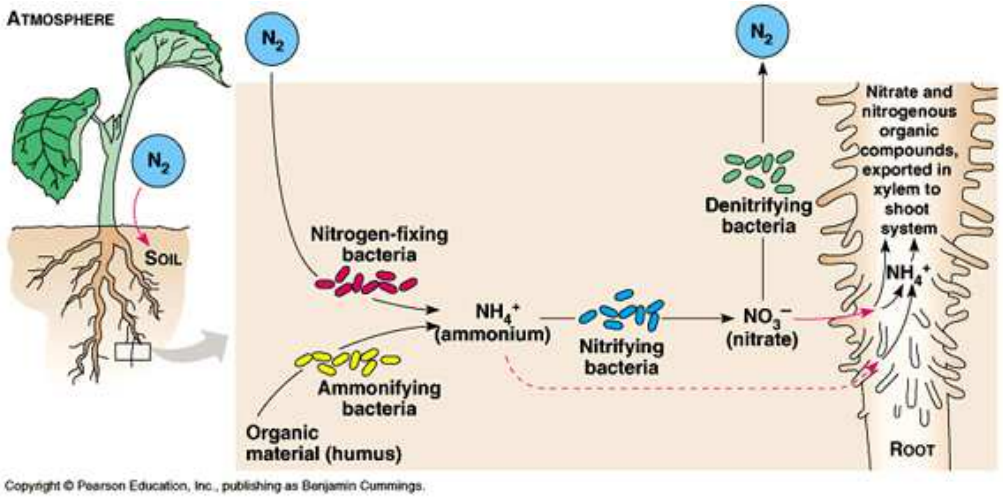
MCF7: higher GLUL
MDAMB231: lower GLUL

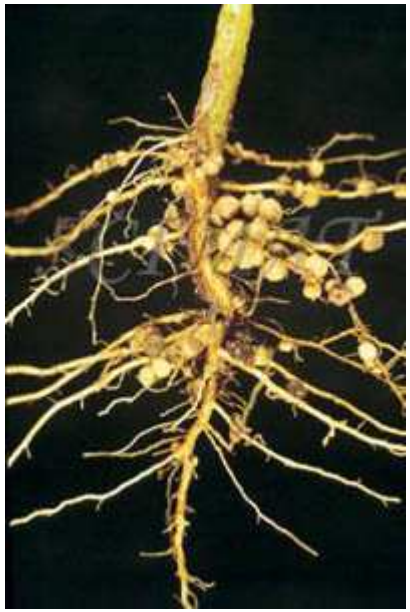


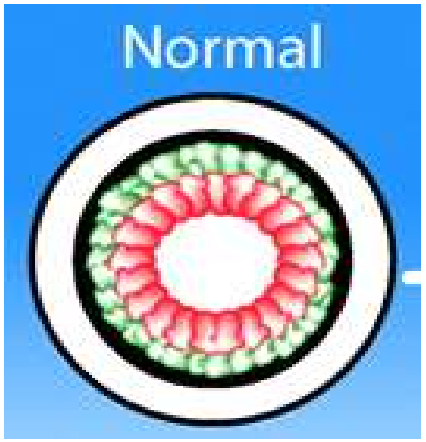
2. Glutamine requirement

Glutamine symbiosis





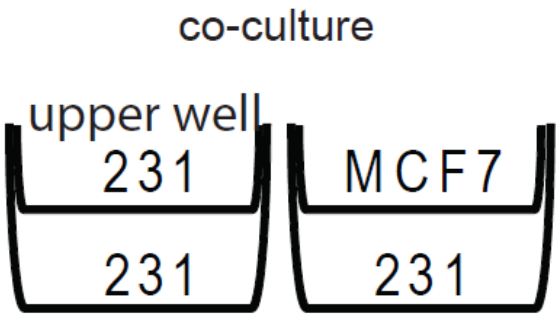


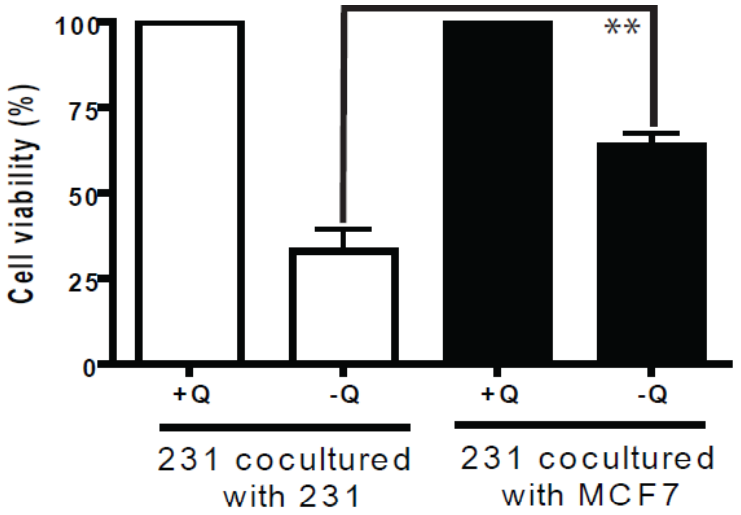


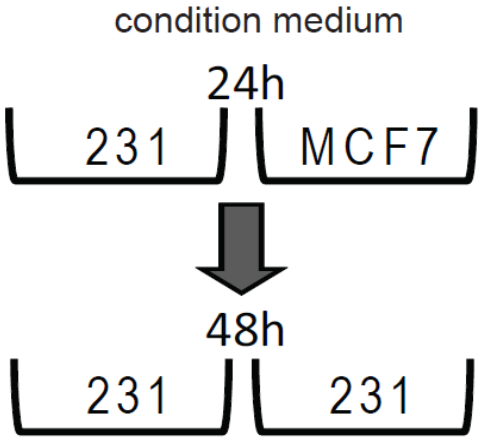
Glutamine symbiosis

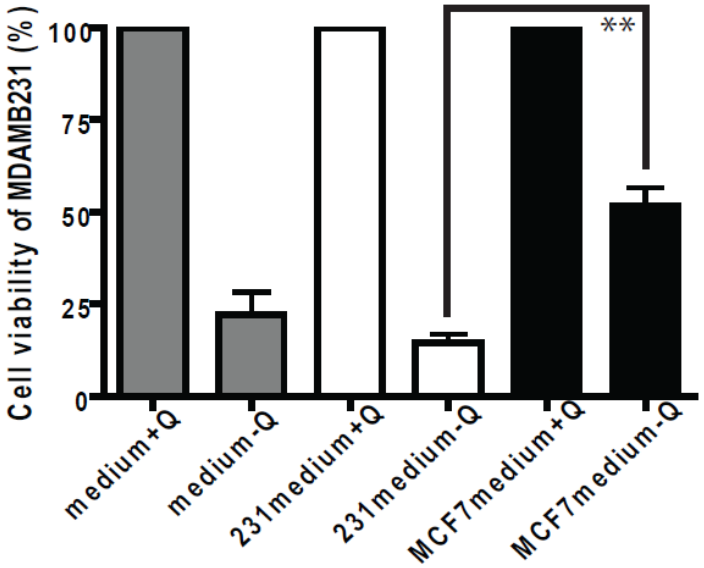
2. Glutamine requirement

Luminal and basal cells have Glutamine symbiosis

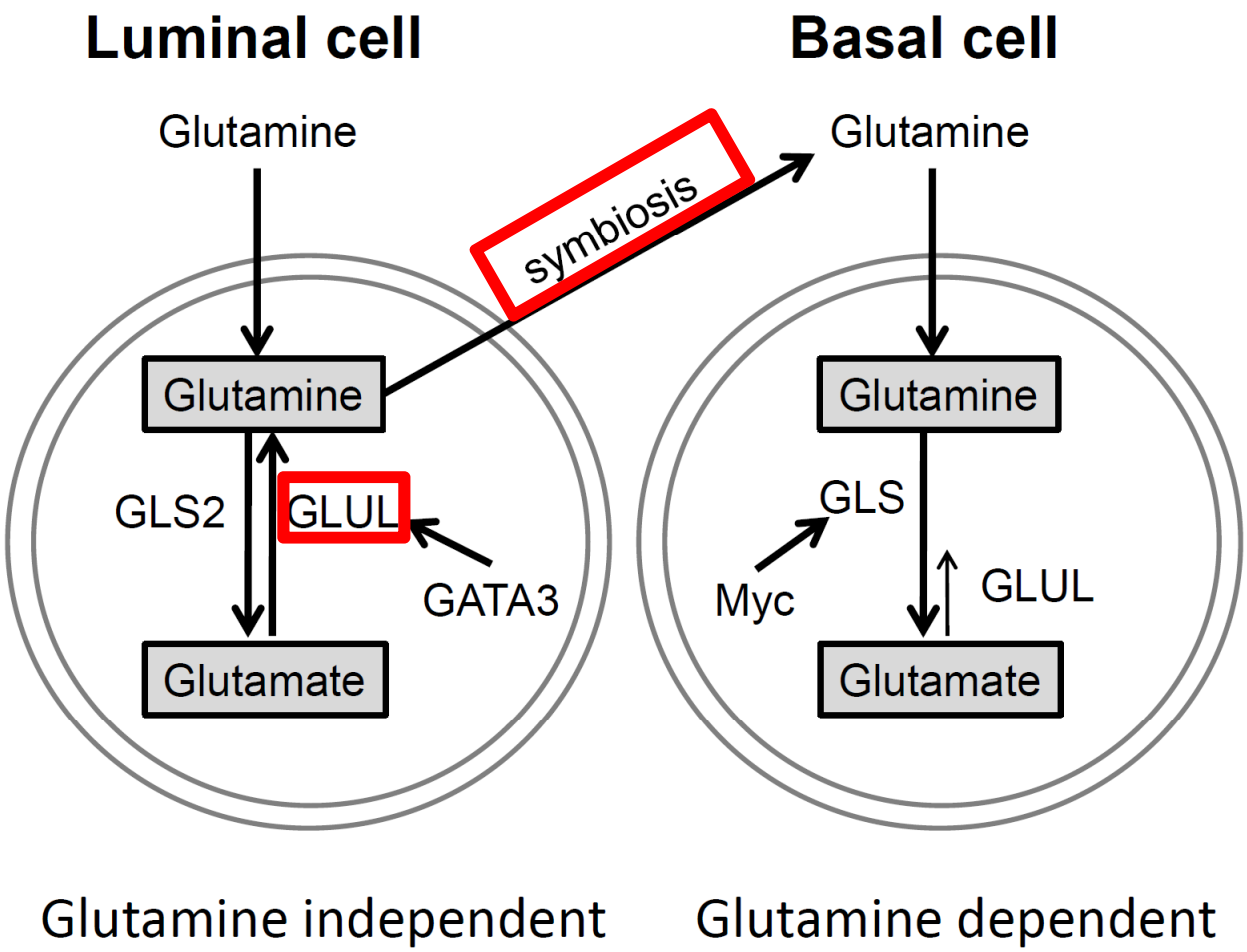


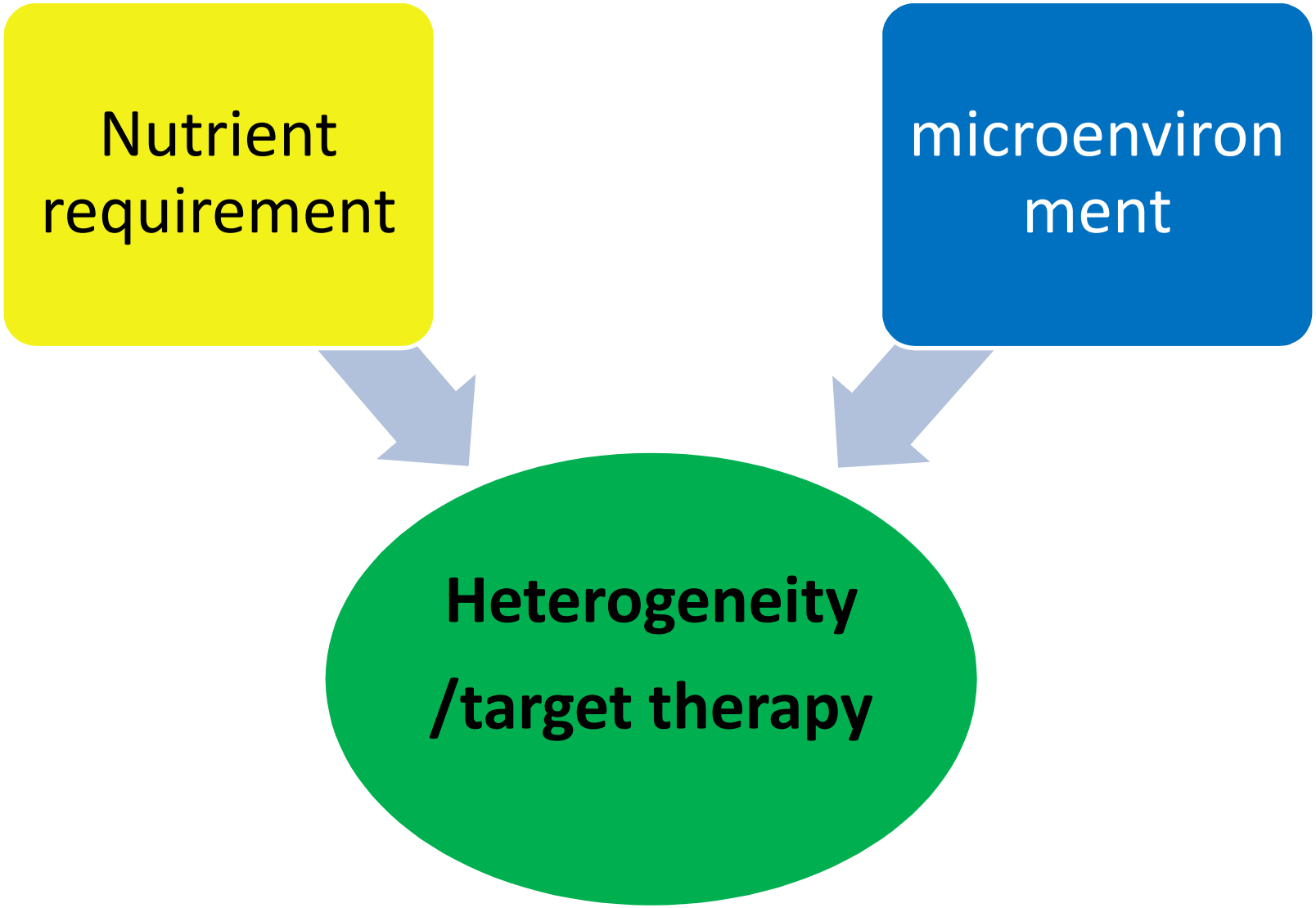






2. Glutamine requirement




Nutrient requirement
microenvironment
Heterogeneity /target therapy

Jhih-Pu Syu Hsiang-Yun Huang

Jen-Tsan Ashley Chi

Michael L. Gatza

Jeffrey R. Marks