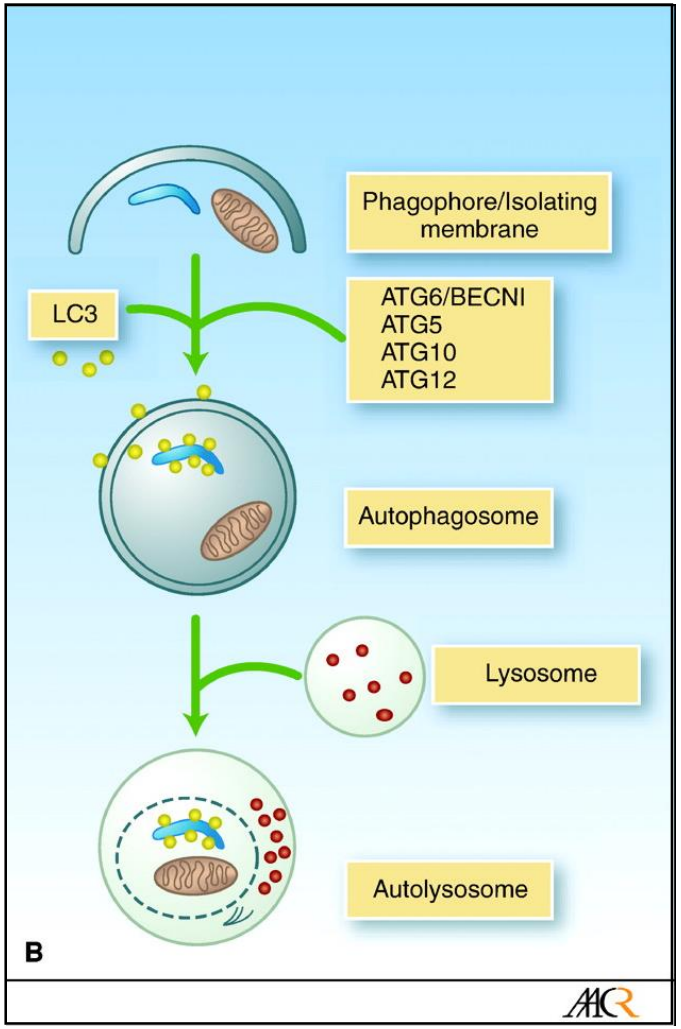
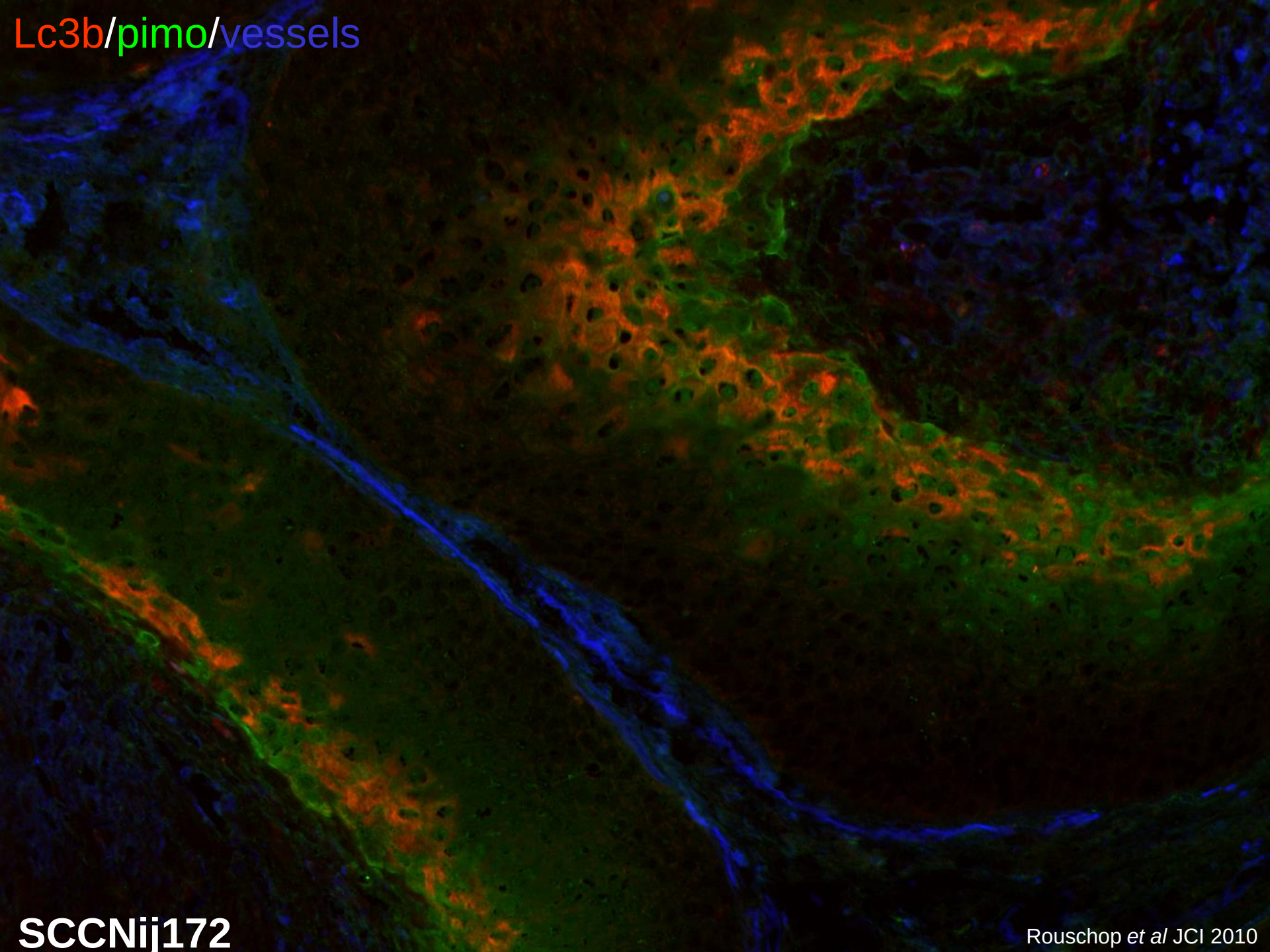
Targeting autophagy in relation to radiotherapy

Kasper Rouschop

Autophagy: “To eat oneself”

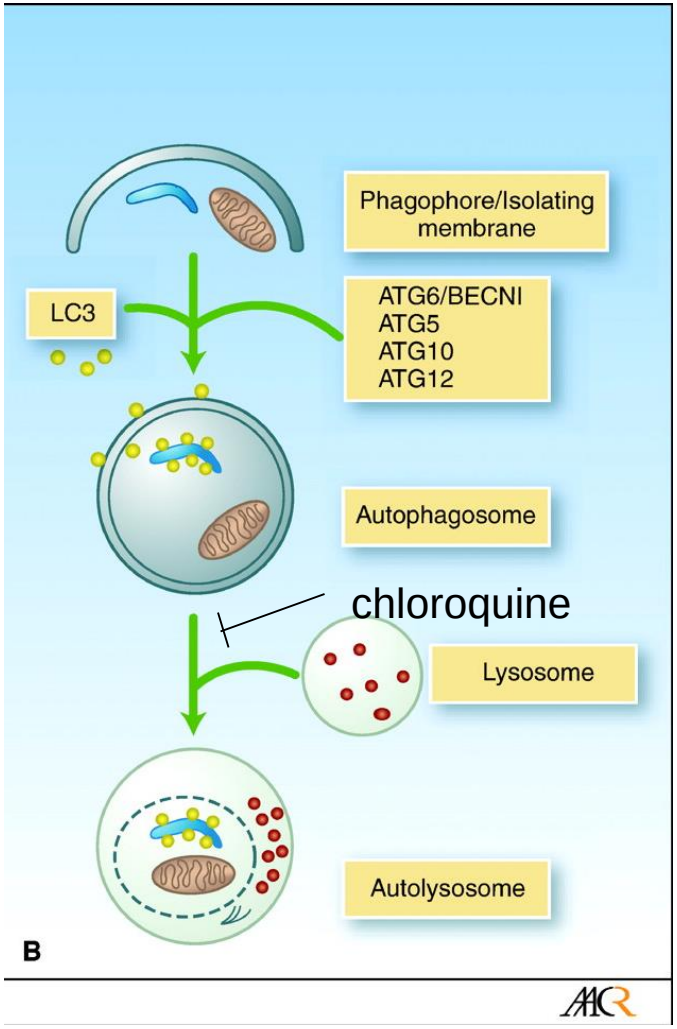


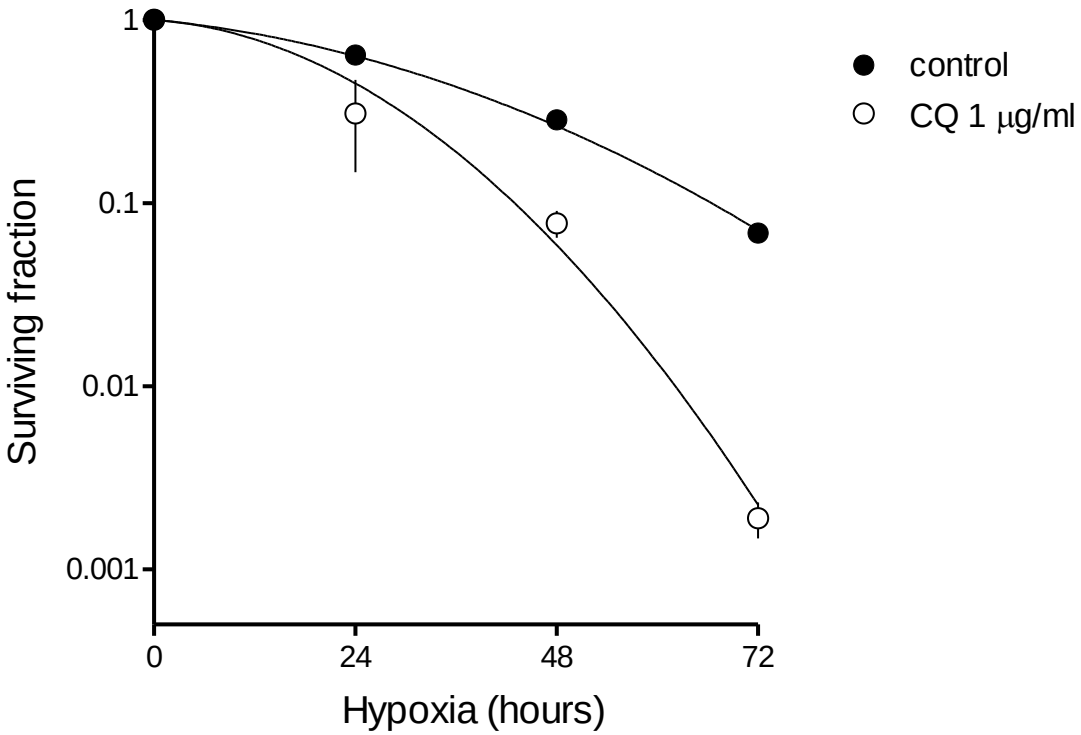
Hait, W. N. et al. Clin Cancer Res 2006;12:1961-1965



Rouschop *et al* JCI 2010

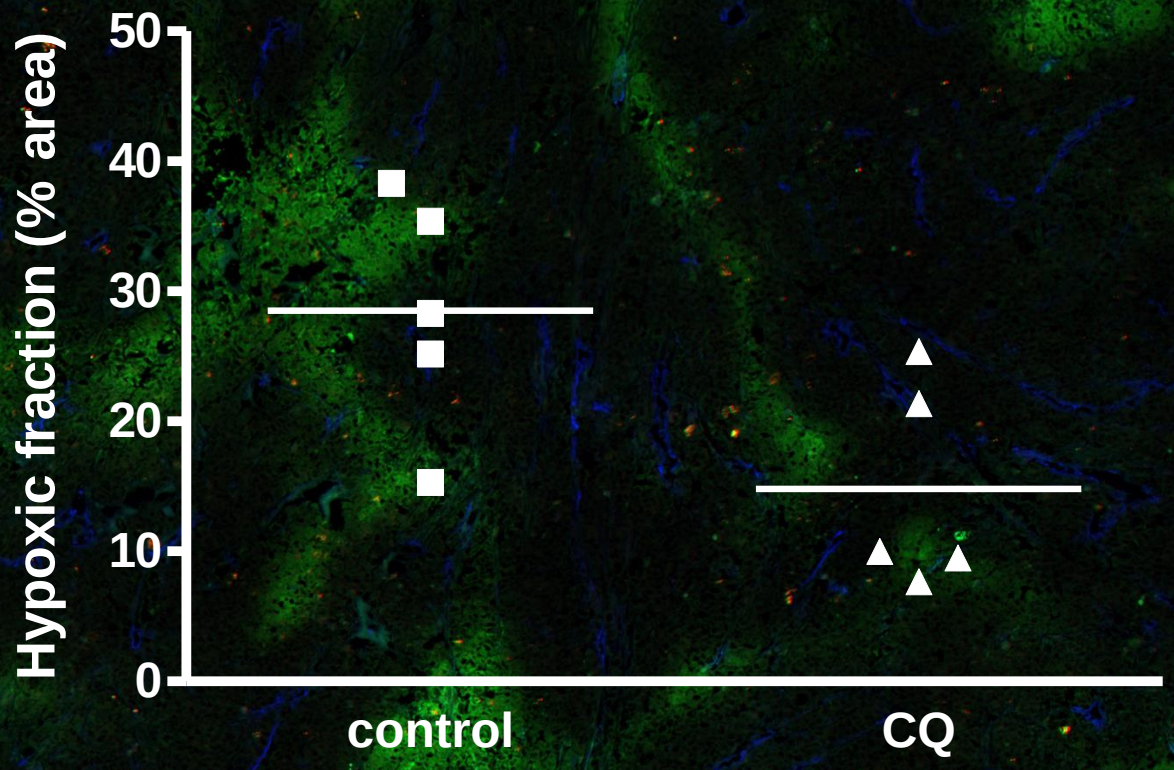
Inhibition of autophagy sensitizes cells to hypoxia



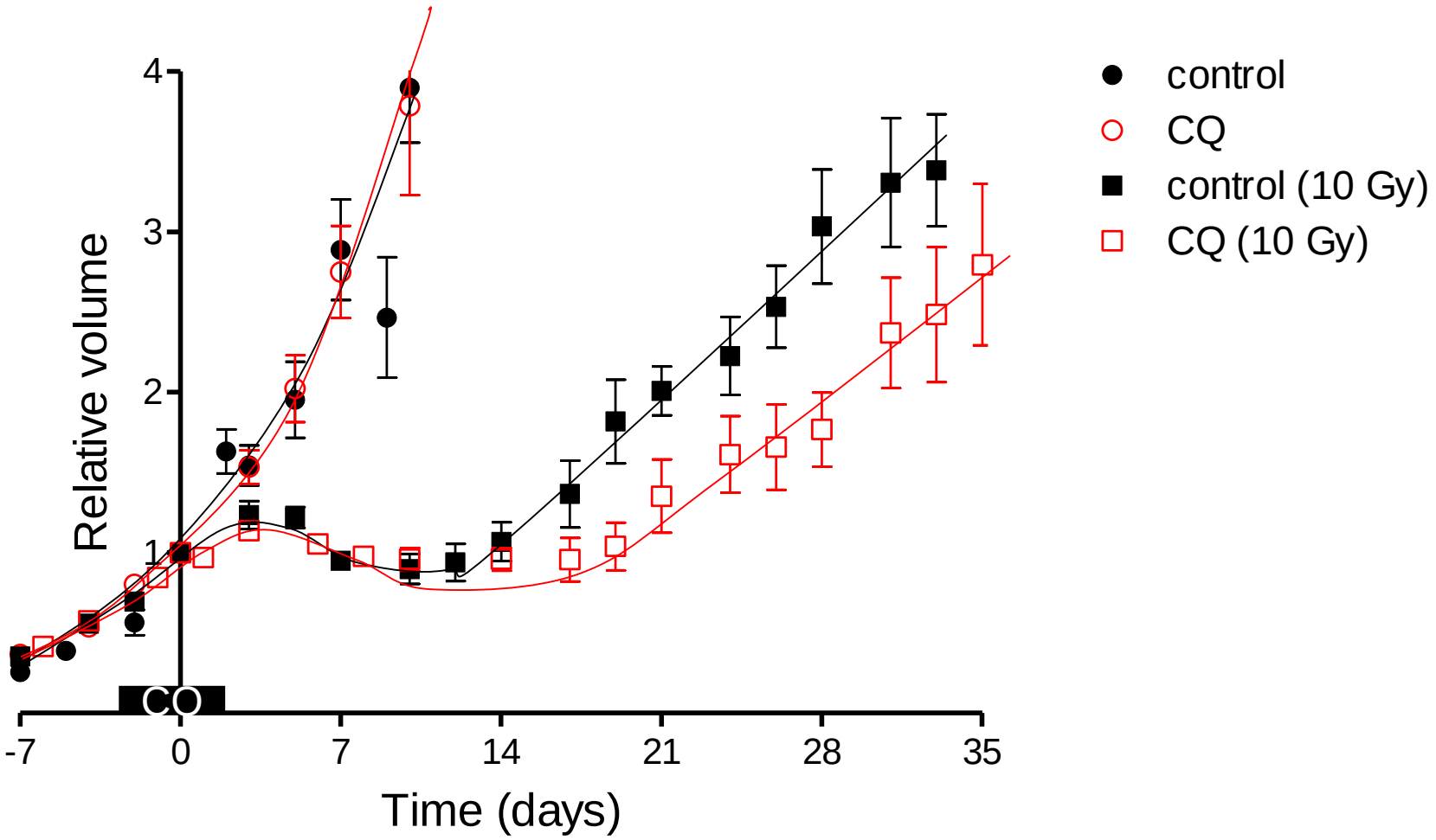


Rouschop *et al* JCI 2010

Autophagy-inhibition reduces tumor hypoxia



Autophagy inhibition sensitizes tumors to irradiation



Rouschop *et al* JCI 2010

Intrinsic radiosensitivity

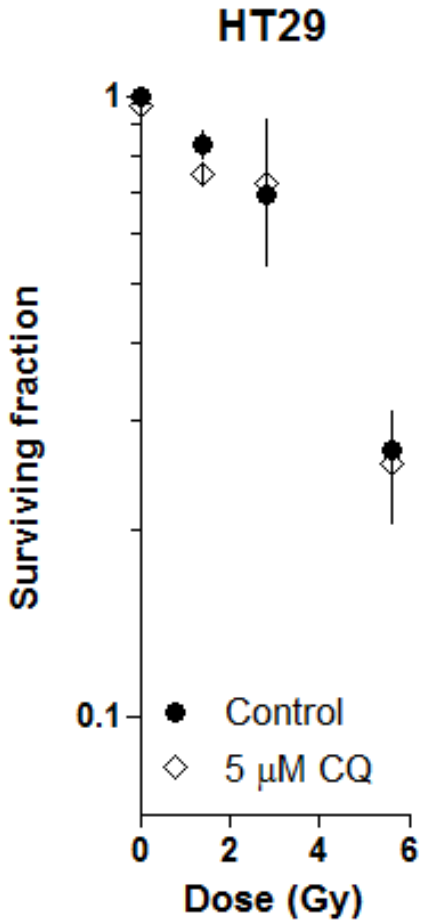
the role of autophagy after IR

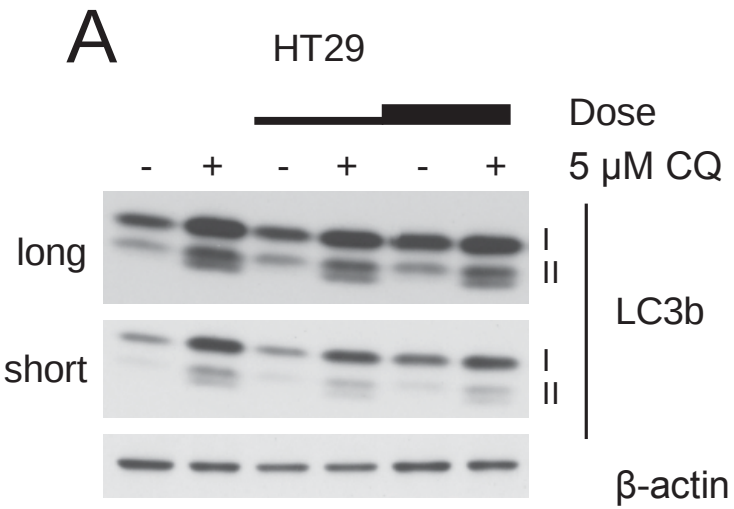
Autophagy

Radioprotective

Cytotoxic

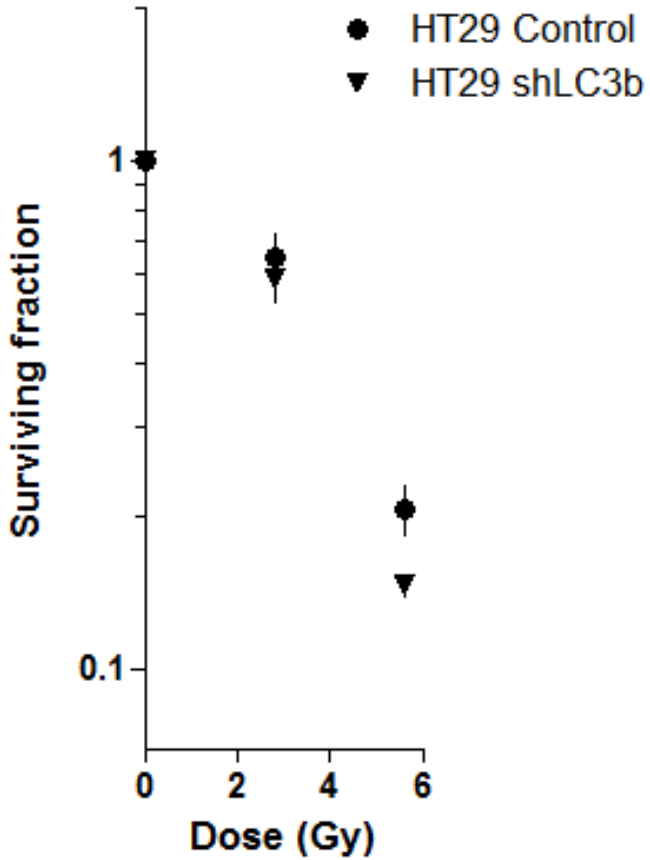
Chloroquine

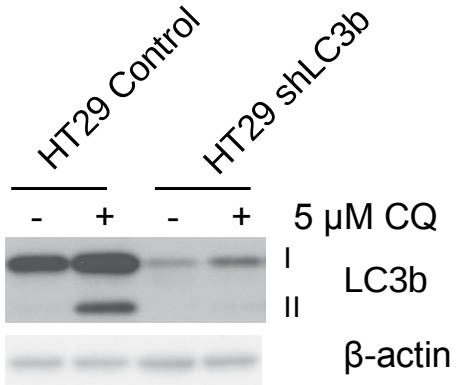




Schaaf *et al.* R&O 2015

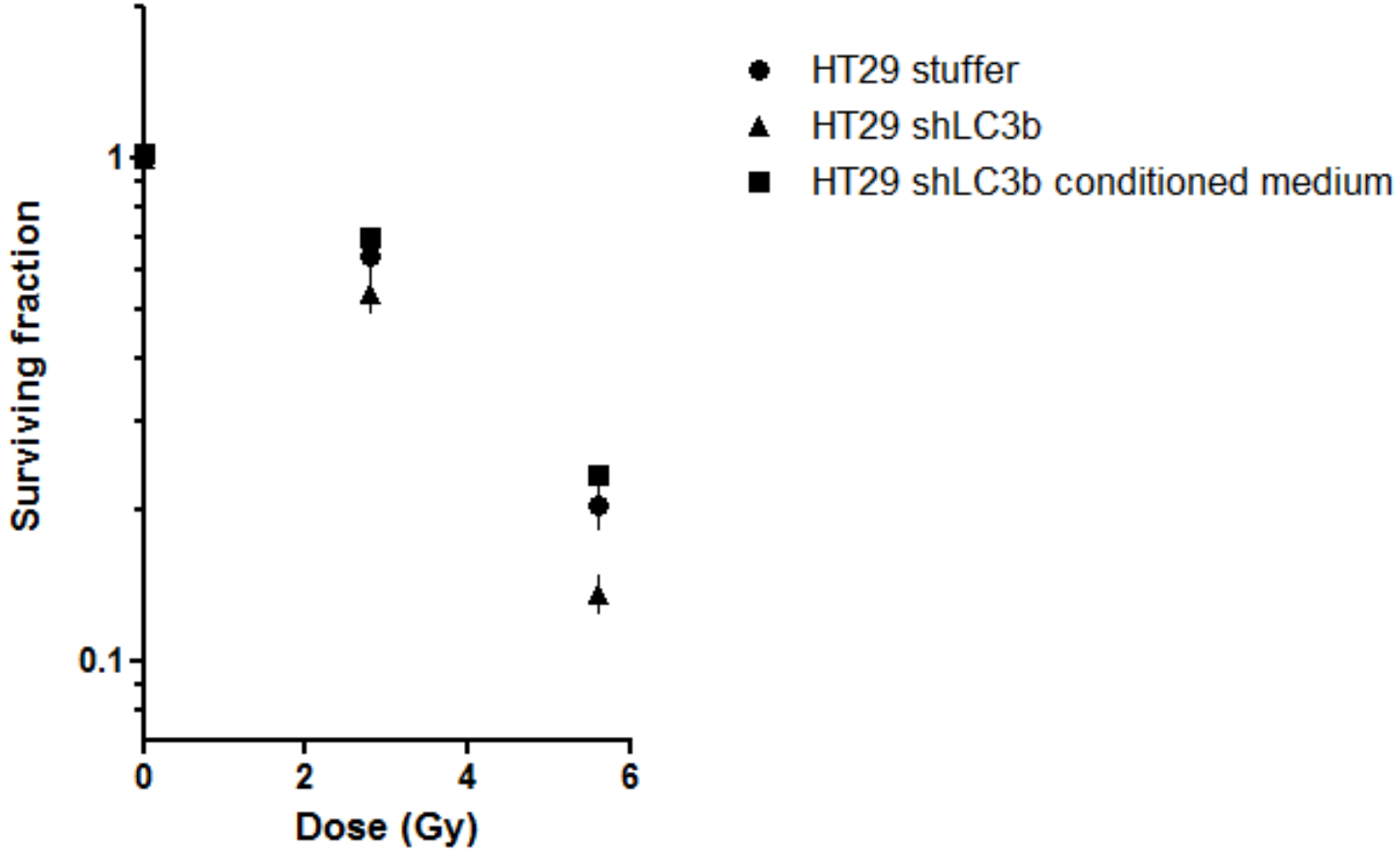
Genetic models





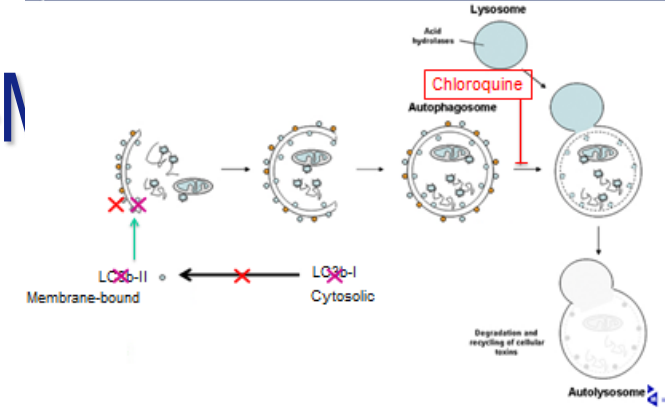
Schaaf *et al.* R&O 2015

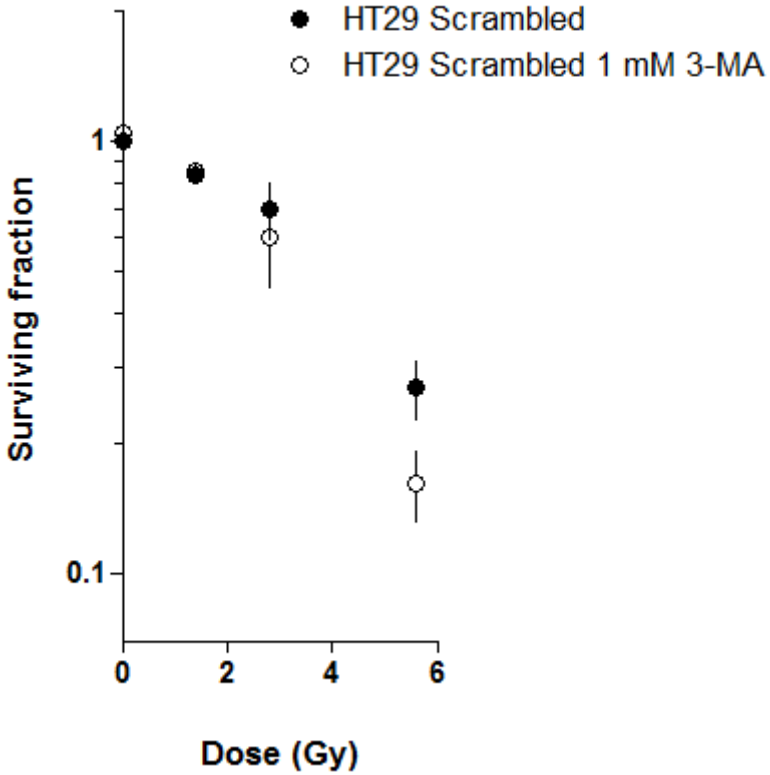
Autophagy (-machinery) involvement in unconventional secretion

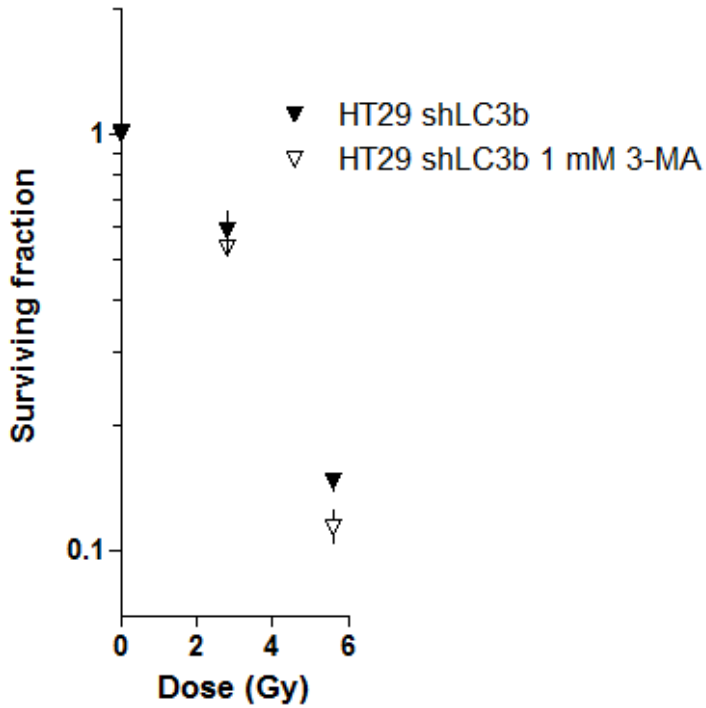


Ader I. *et al.* Oncogene 2002

3-methyladenine (3-M







Schaaf *et al.* R&O 2015

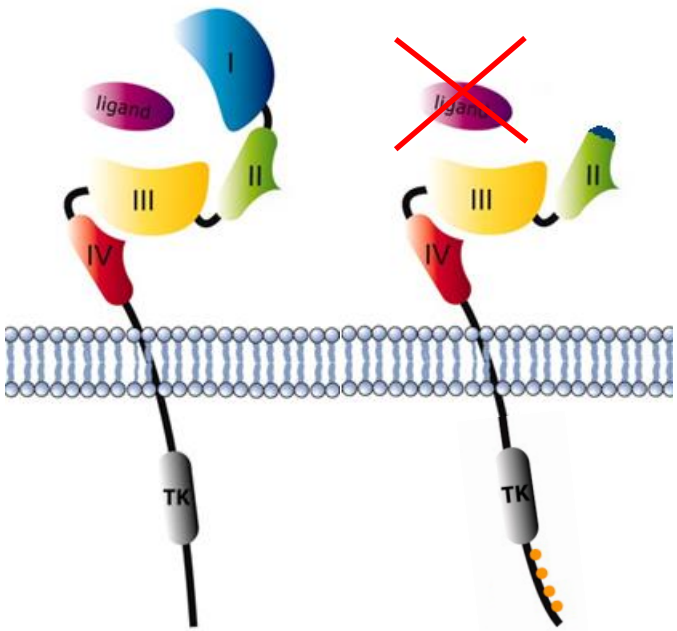
Intrinsic radiosensitivity

- Very litlle evidence for autophagy in regulation intrinsic radiosensitivity

- BUT….

- Targeting autophagy paralell to or prior to treatment may increase effect of therapy

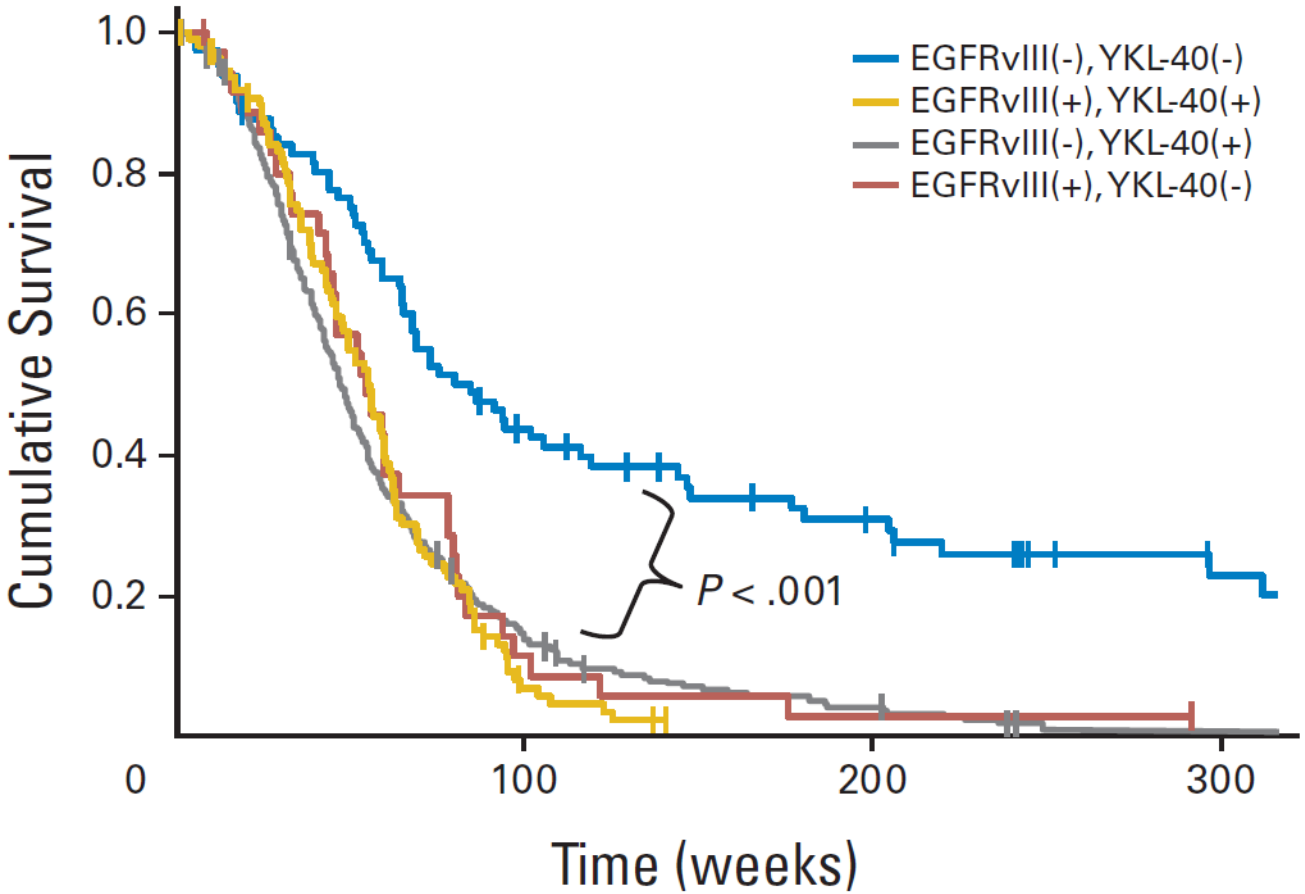
EGFRvIII



- Deletion of exon 2-7
- Present in 40% GBM
- No ligand required
- Constitutively active

- Important for cell proliferation, differentiation and survival
- Receptor or ligands overexpressed in many solid tumors
- High levels of EGFR are associated with poor survival

EGFRvIII expression on GBM is associated with worse prognosis



Pelloski et al, JCO 2007;25(16):2288-2294

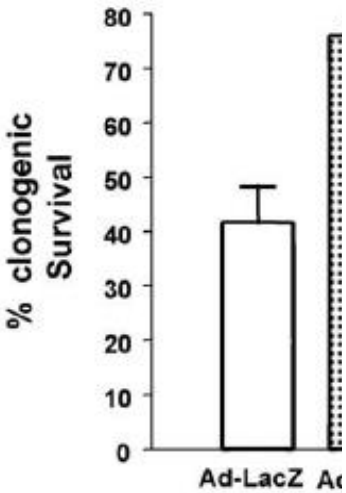
EGFRvIII

Increased resistance metabolic stressess

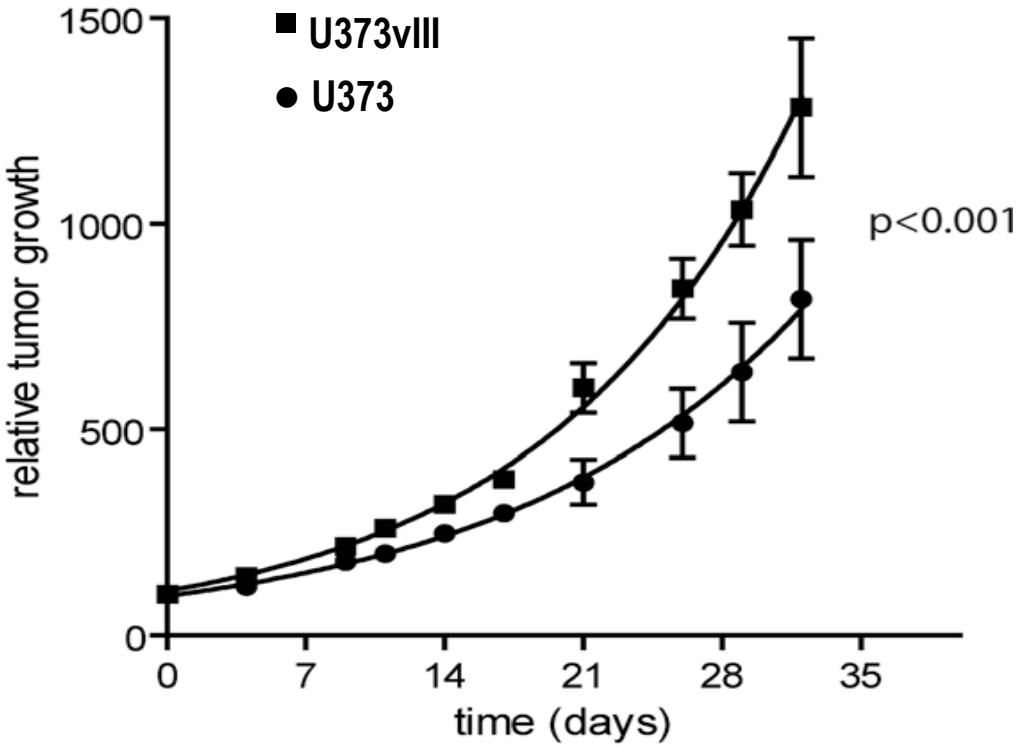
Accelerated tumor growth

Increased hypoxia

Increased

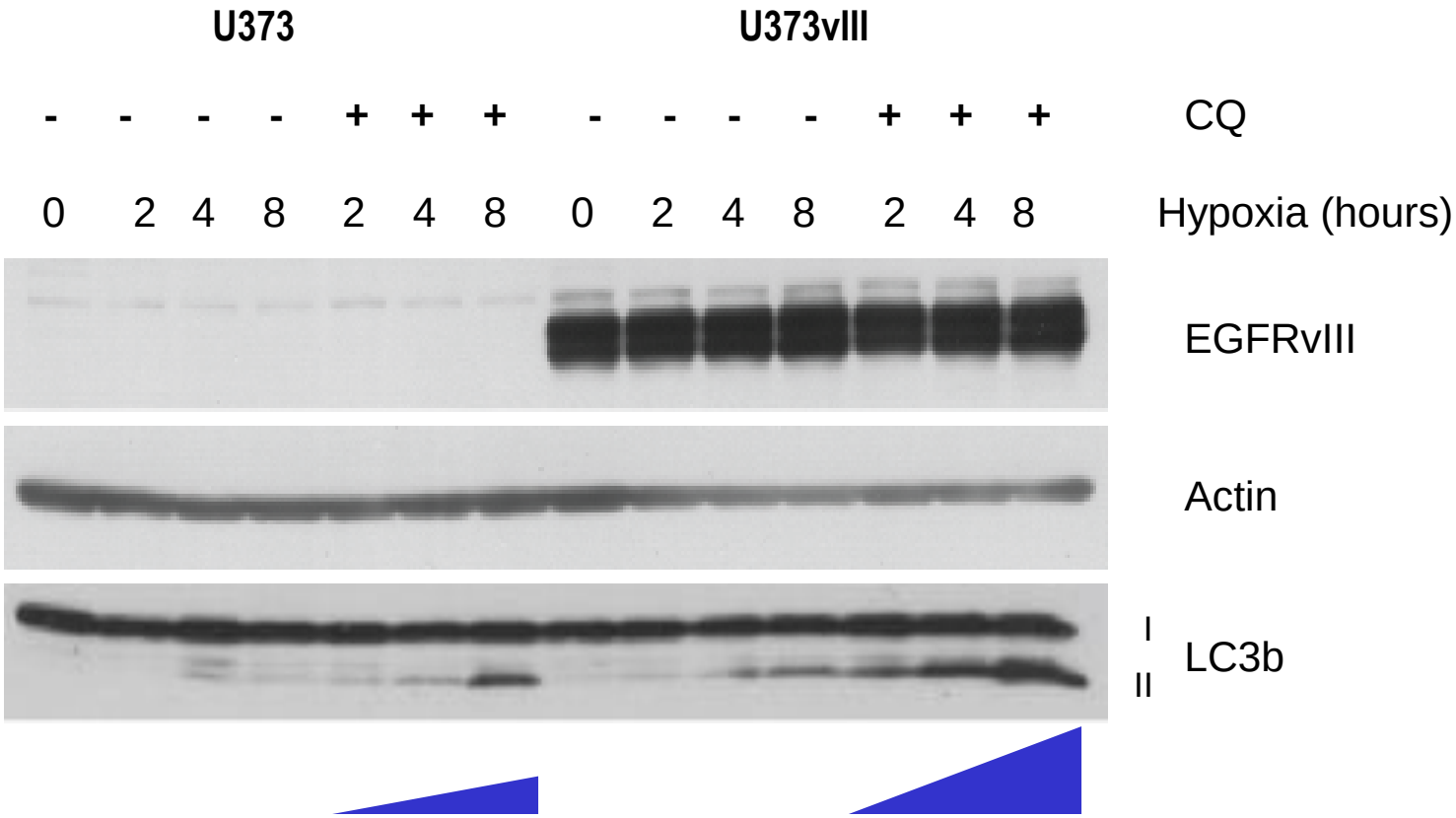


Lammering et a

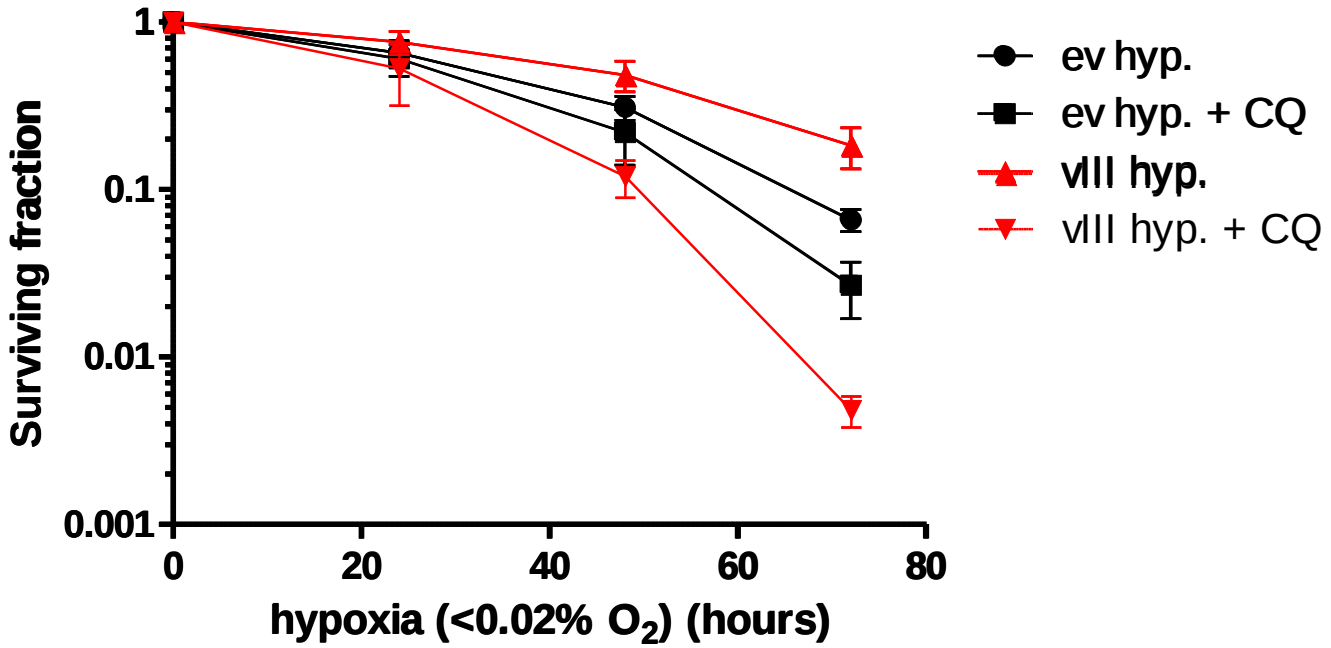


Theys et al, R&O 2009

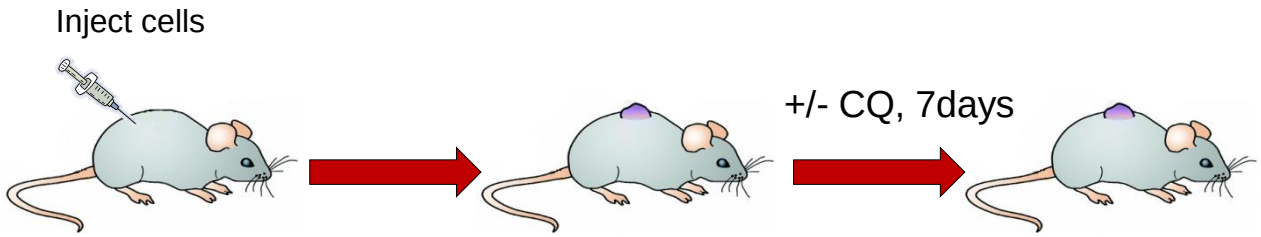
EGFRvIII expression is associated with increased autophagic flux

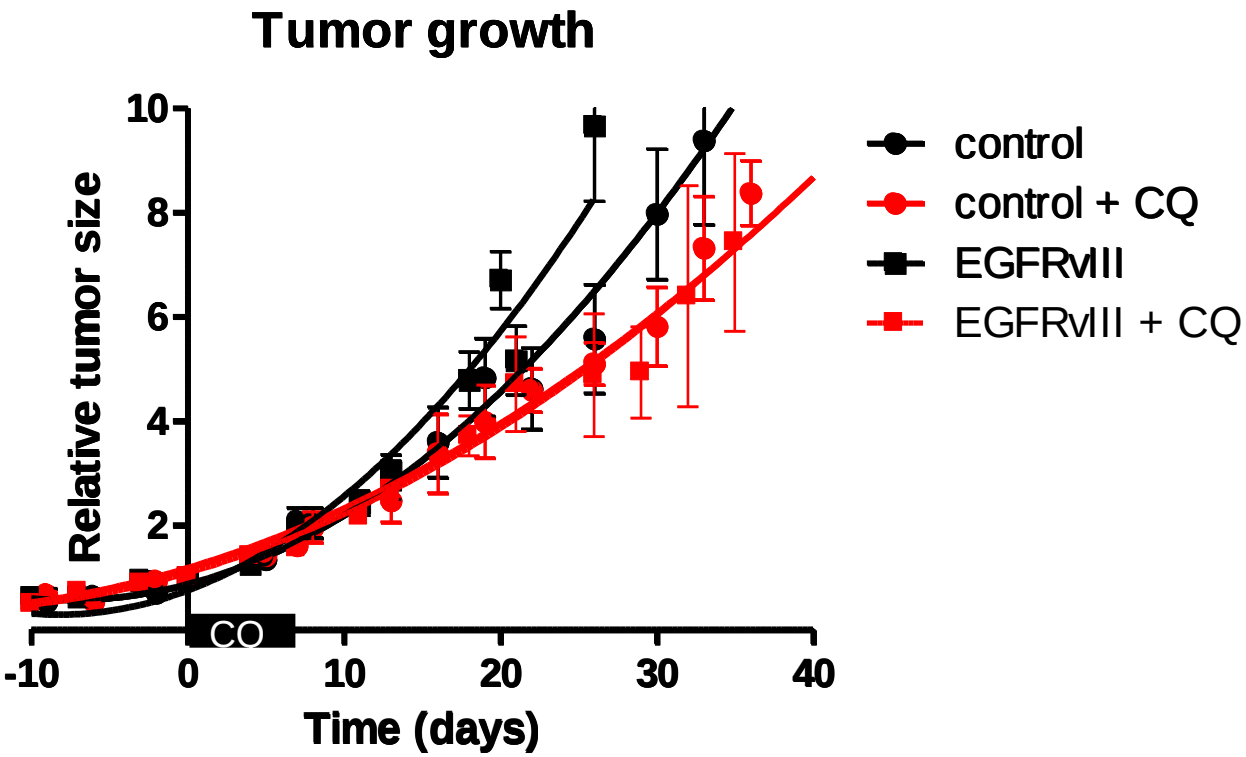


Survival advantage of vIII+ cells is abolished by inhibition of autophagy

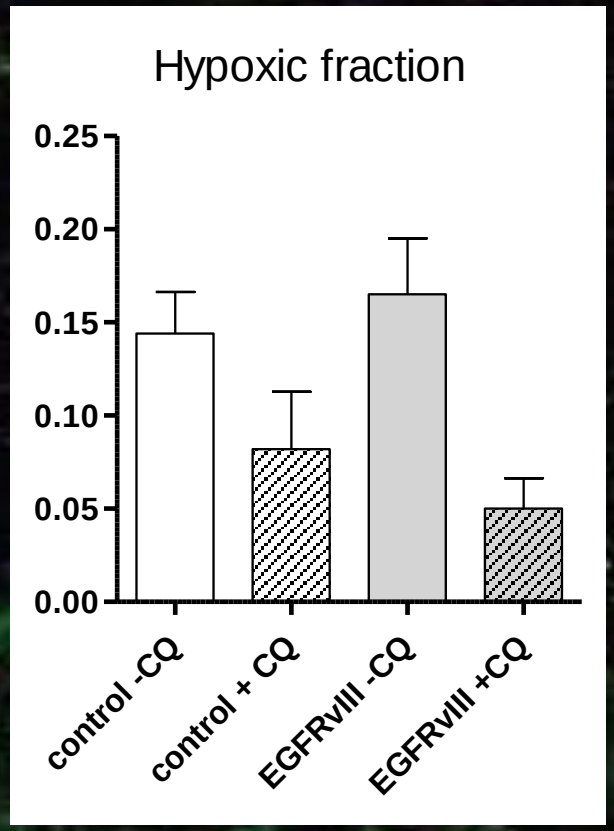


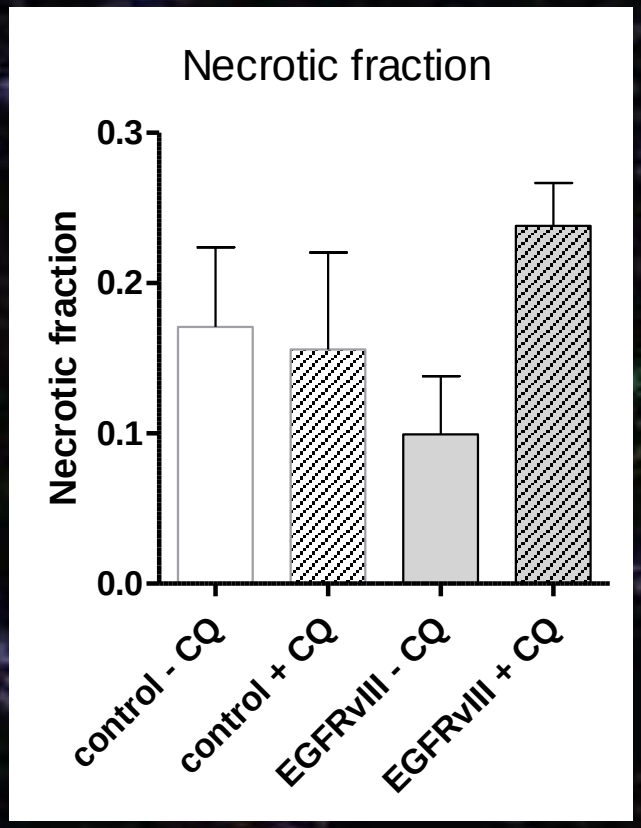
Chloroquine reduces tumor growth of GBM xenografts



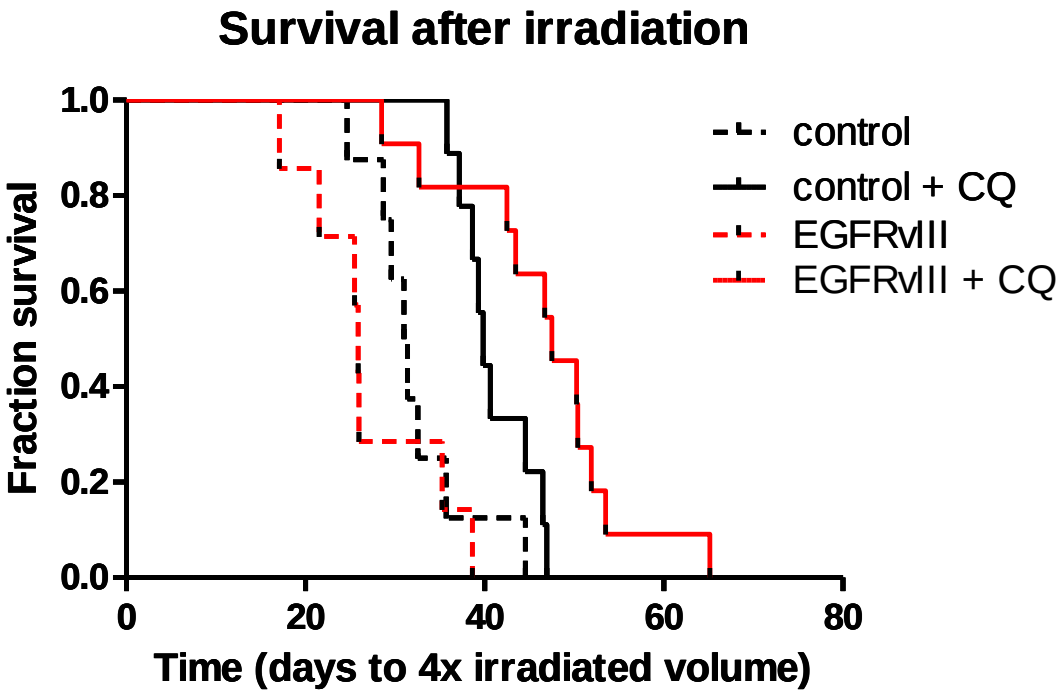


Chloroquine reduces hypoxia and increases necrosis in EGFRvIII GBM xenografts

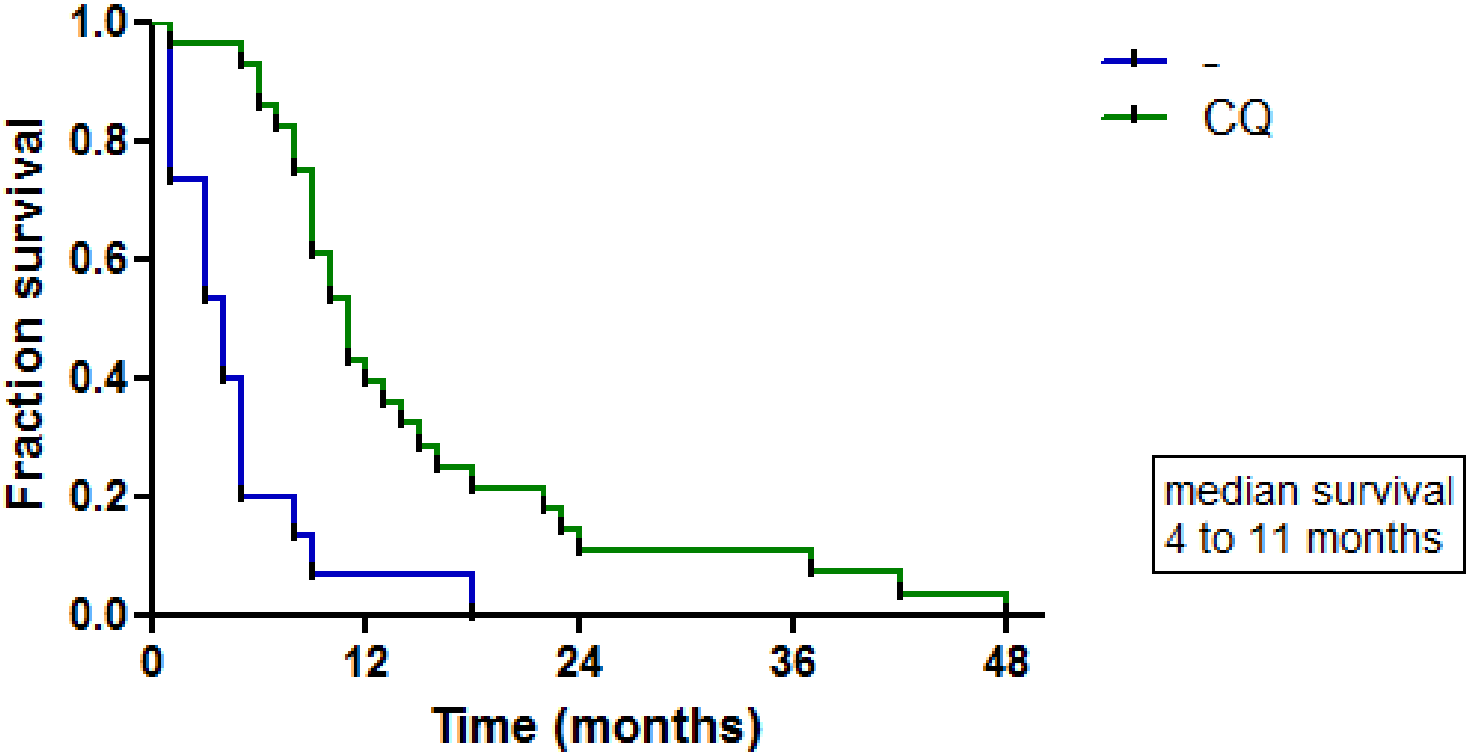




Chloroquine improves radioresponsiveness of GBM xenografts

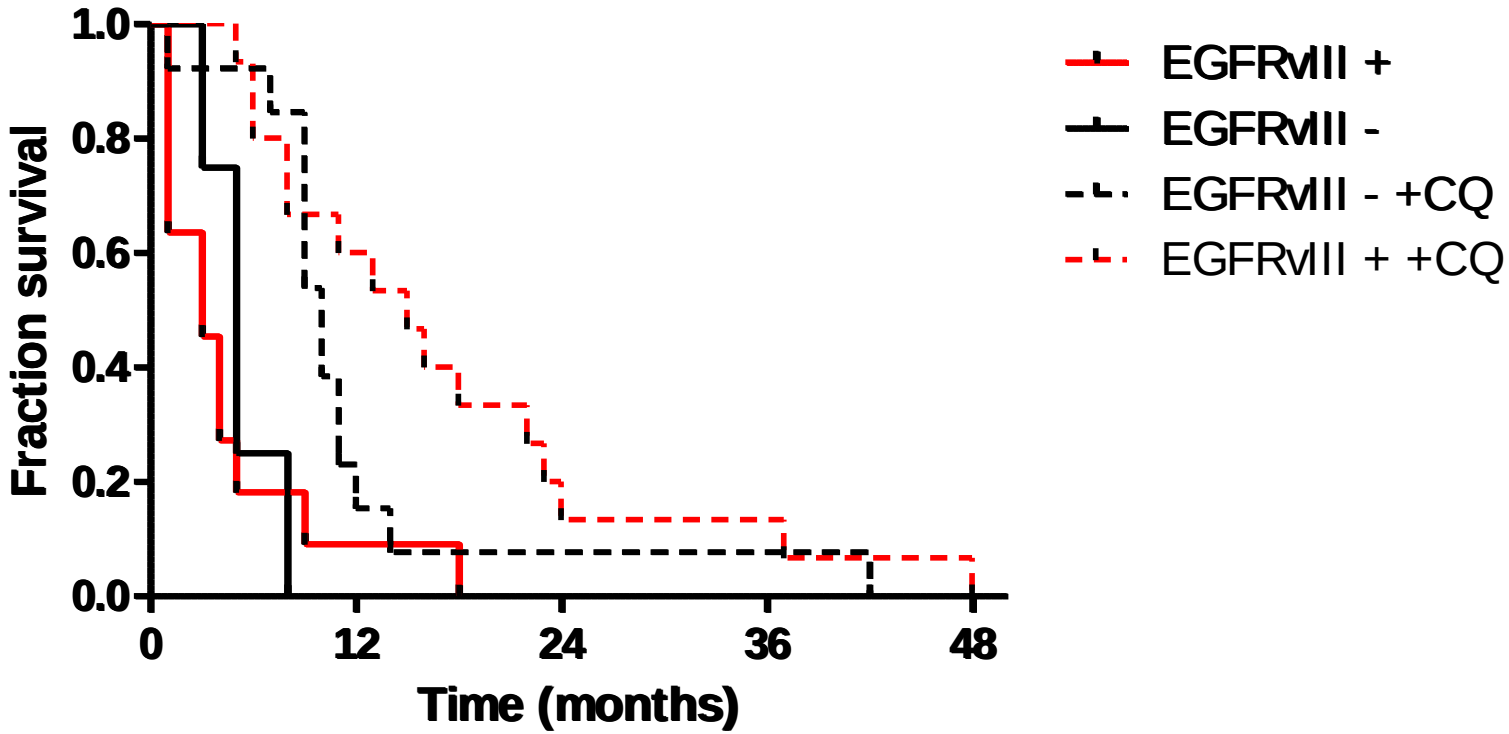


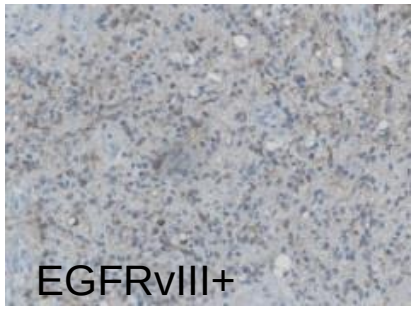
CQ treatment increases survival of GBM patients

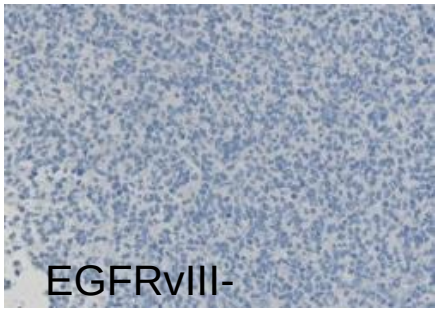


Sotelo et al, Ann Intern Med. 2006;144:337-343

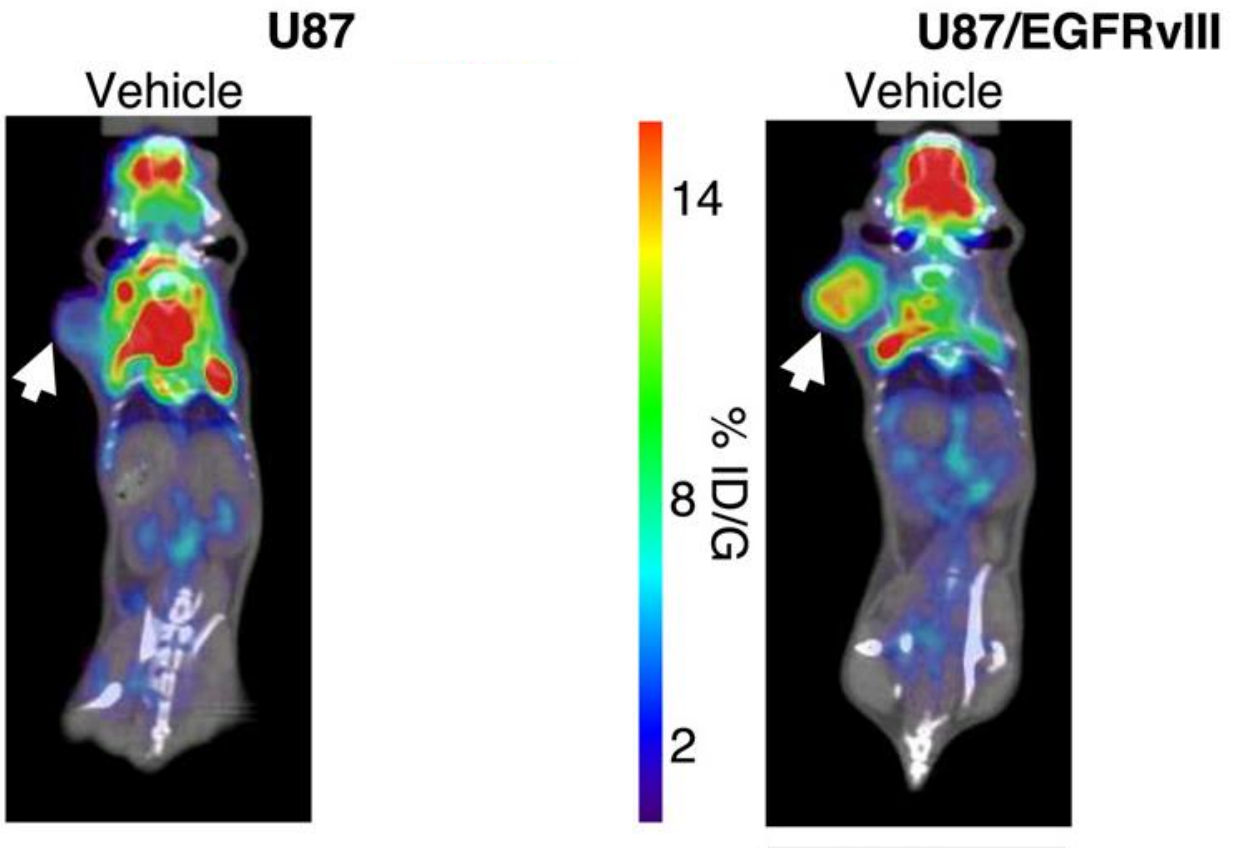
CQ treatment increases survival of GBM patients

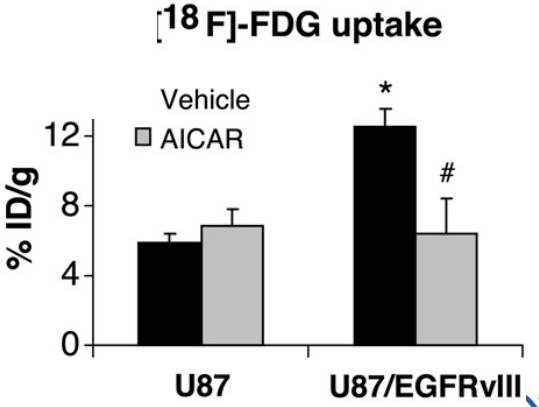






EGFRvIII have higher energy demand

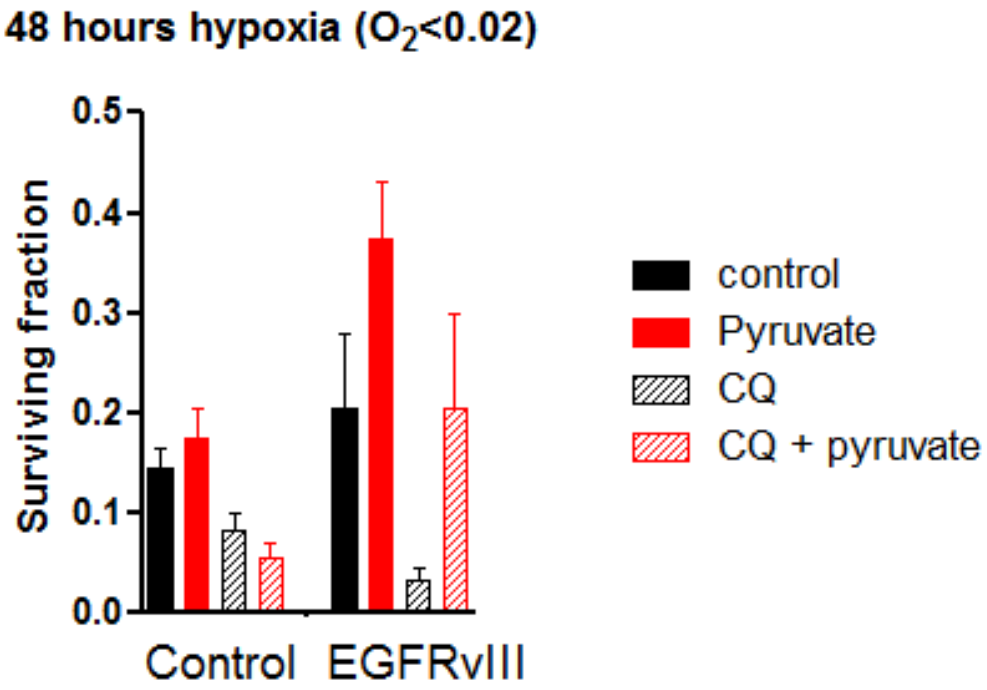




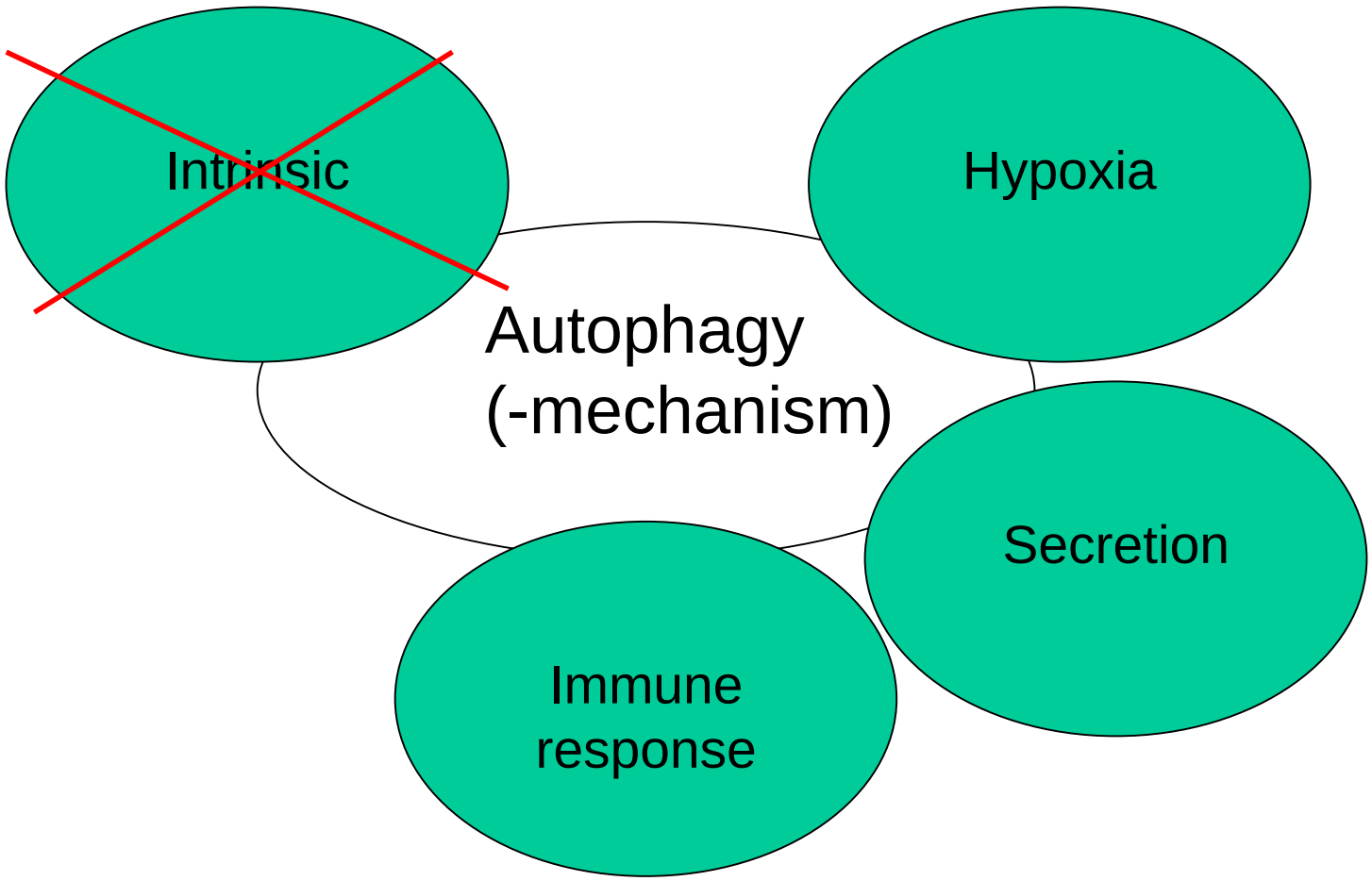
Deliang Guoa, Isabel J. Hildebrandtb, Robert M. Prinsc, Horacio Sotoc, Mary M. Mazzottad, Julie Danga, Johannes Czerninb,g, John Y.-J. Shyyh, Andrew D. Watsond, Michael Phelpsb,g,1, Caius G. Radub,g, Timothy F. Cloughesye,f, and Paul S. Mischel **PNAS, 2009**

EGFRvIII have higher energy demand

EGFRvIII have higher energy demand



Summary


Intrinsic
Hypoxia
Autophagy
(-mechanism)
Secretion
Immune
response

Conclusions

- Autophagy inhibition results in sensitization of tumors to irradiation.
- This is independent of changes in intrinsic radiosensitivity
- Selection of tumors with high autophagy-dependency is important may lead to increased therapy response of tumors

Acknowlegdements

- MaastRO
- Inge Compter
- Ludwig Dubois
- Laura van Dam
- Danielle Eekers
- **Barry Jutten**
- Tom Keulers
- Philippe Lambin
- Guido Lammering
- **Marco Schaaf**
- **Hanneke Peeters**
- Kim Savelkouls
- Jan Theys
- Marc Vooijs

- Radiation Oncology, Nijmegen
- Jan Bussink
- Hans Peters

- Instituto Nacional de Neurología y Neurocirugía , Mexico
- Julio Sotelo

www.STOPHersentumoren.nl Stichting

DUTCH CANCER SOCIETY

GROW

MAASTRO