Disclosure information

International Reviews of Cell and Molecular Biology
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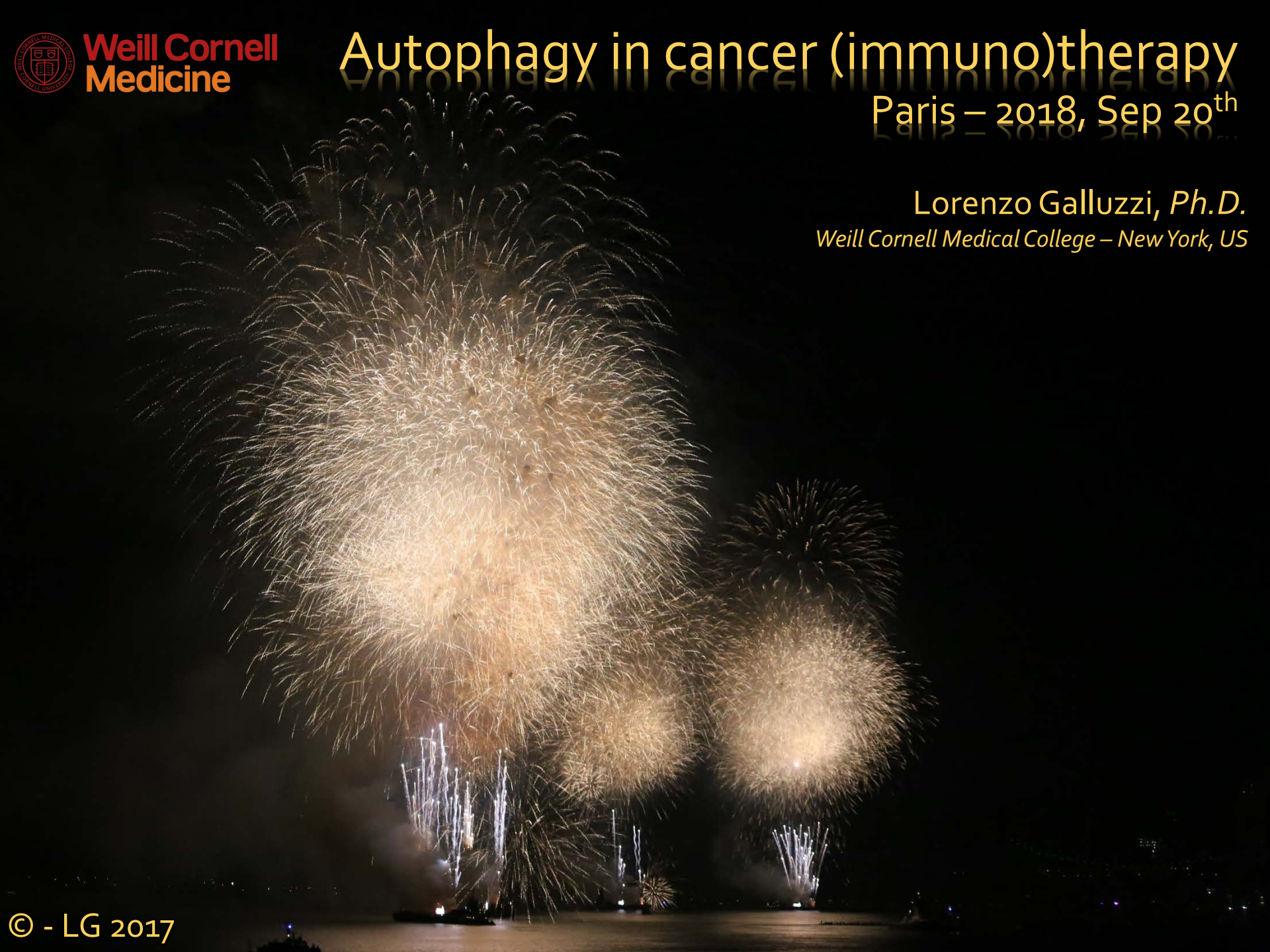
OncoImmunology
Founding Editor-in-Chief

OmniSEQ, VL47
AstraZeneca
Consultant



Autophagy in cancer (immuno)therapy

Paris – 2018, Sep 20th

Lorenzo Galluzzi, *Ph.D.*

Weill Cornell Medical College – New York, US

The Quantity-Quality dilemma

Paris – 2018, Sep 20th

Lorenzo Galluzzi, *Ph.D.*

Weill Cornell Medical College – New York, US

The Starbucks-Espresso dilemma

Paris – 2018, Sep 20th

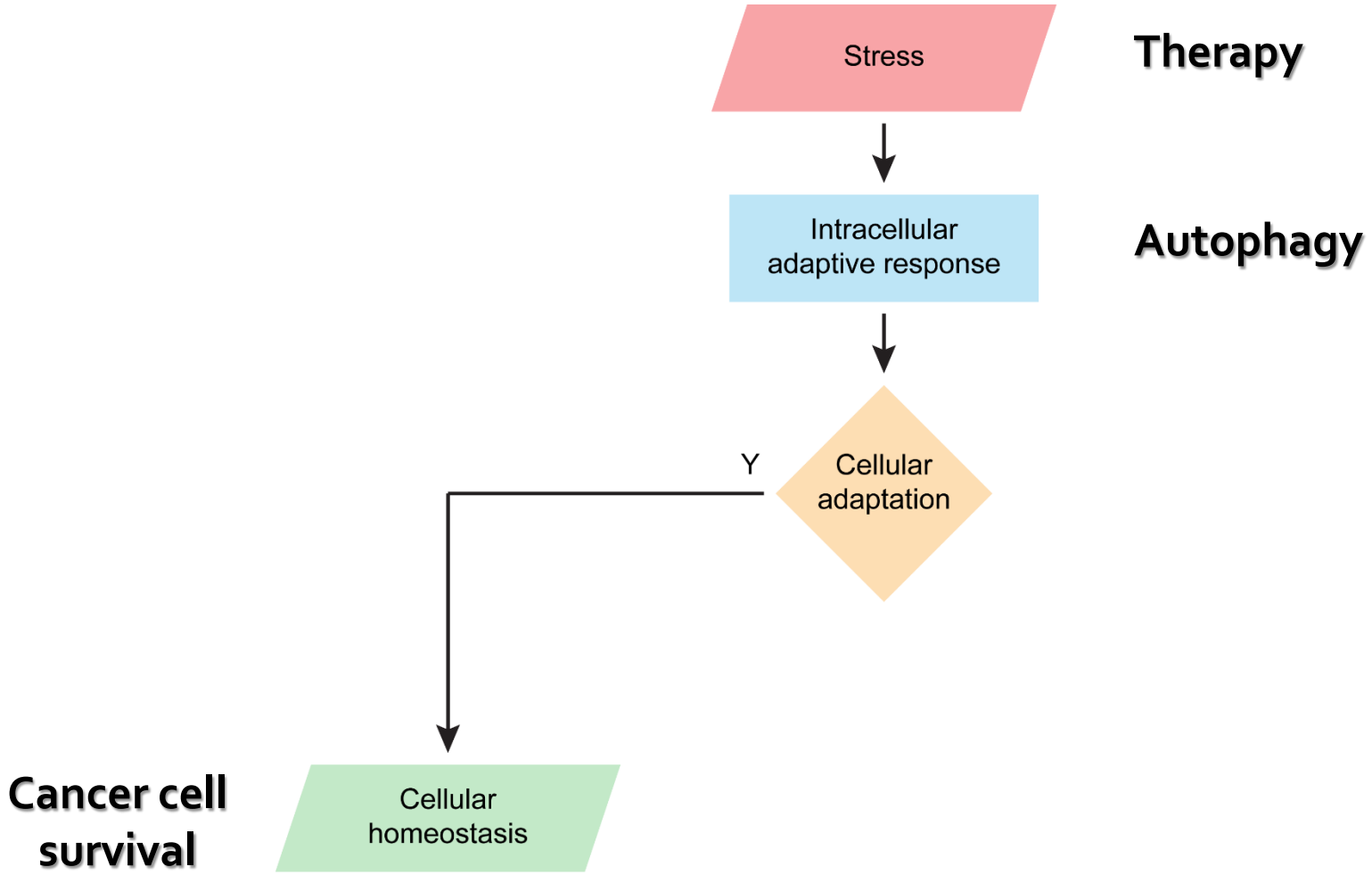
Lorenzo Galluzzi, *Ph.D.*

Weill Cornell Medical College – New York, US

General organization of stress responses

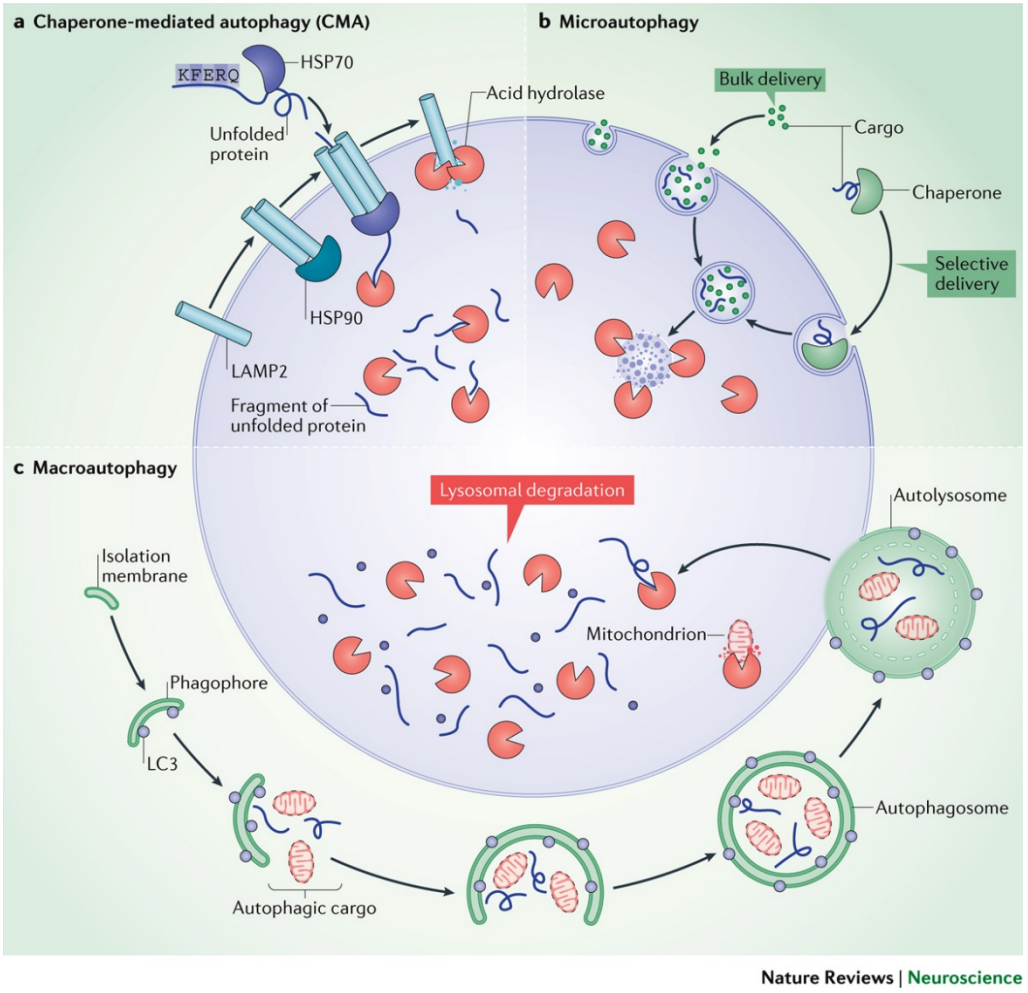
Stress

General organization of stress responses



Galluzzi et al. – NRCMB 2018

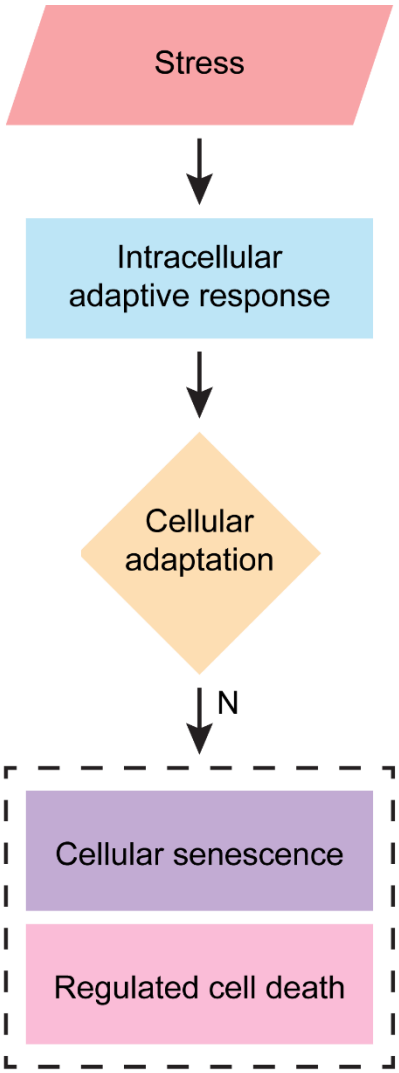
Autophagy



Evolutionary old mechanism that delivers cytosolic entities to lysosomal degradation, with prominent cytoprotective effects

Galluzzi et al. – Nat Rev Neurosci 2016

General organization of stress responses



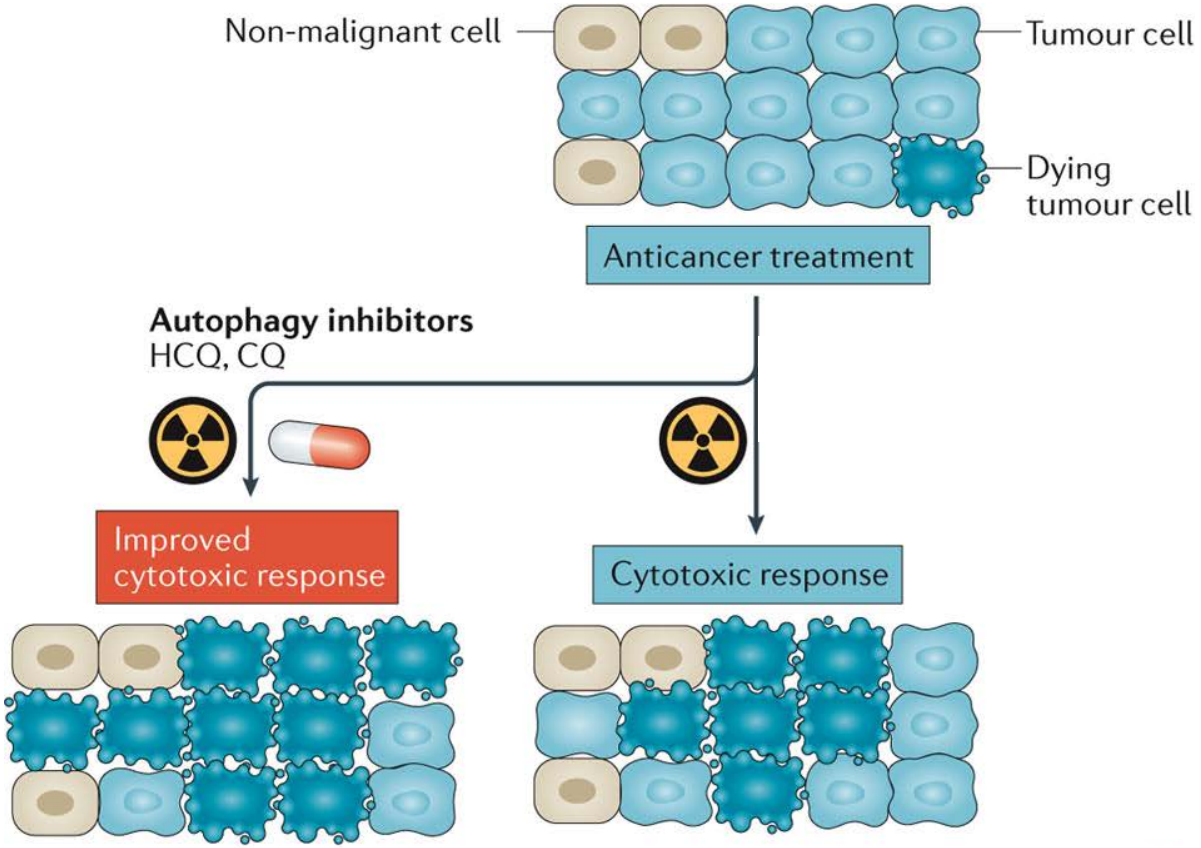
Chemotherapy

~~**Autophagy**~~

Cancer cell death

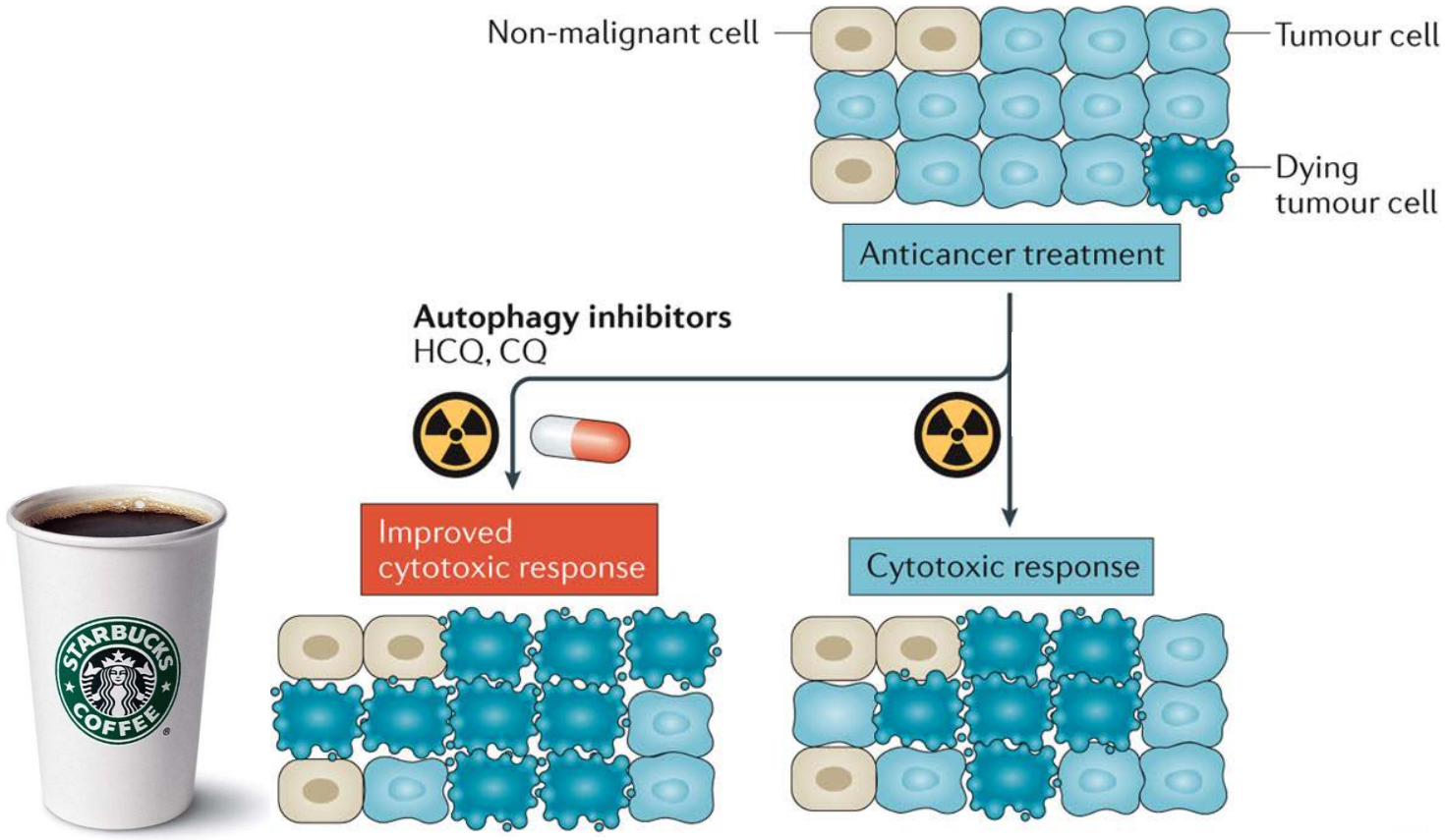
Galluzzi et al. – NRCMB 2018

Classical approach



Galluzzi et al. – Nat Rev Clin Oncol 2017

The "Starbucks" approach



Galluzzi et al. – Nat Rev Clin Oncol 2017

Inhibition of autophagy for cancer therapy

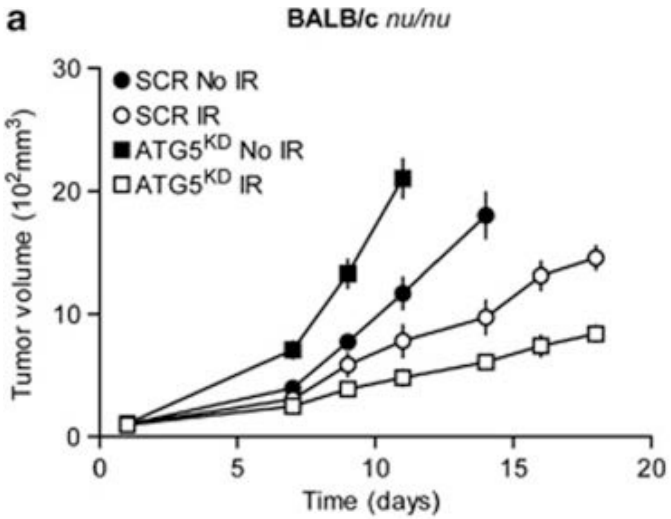


Table 1 | **Selected examples of the effects of autophagy modulation on the efficacy of anticancer therapy in mouse models**

Intervention	Host	Tumour type	Therapy	Notes	Refs
Therapeutic benefits from autophagy inhibition or detrimental effects from autophagy activation					
3-Methyladenine	*nu/nu* mice	HepG2 cells (H)	Radiation therapy	Hepatocellular carcinoma model; improved response to treatment in immunodeficient mice; pharmacological specificity issues	61
	nu/nu mice	EC9706 cells (H)	Radiation therapy	Oesophageal carcinoma model; improved response to treatment in immunodeficient mice; pharmacological specificity issues	62
Chloroquine, Lys05	*nu/nu* mice	1205Lu cells (H), C8161 cells (H), HT29 cells (H)	None	Melanoma and CRC models; standalone therapeutic effect in immunodeficient hosts; pharmacological specificity issues	48
Chloroquine	*nu/nu* mice	U87MG cells (H)	Temozolomide	Glioblastoma model; improved response to treatment in immunodeficient mice; pharmacological specificity issues	52
	SCID mice	HT29 cells (H)	Bevacizumab, oxaliplatin	CRC models; improved response to treatment in immunodeficient mice; pharmacological specificity issues	58
	C57BL/6 mice	B16-F10 cells (M)	Cisplatin, dacarbazine	Melanoma model; improved response mechanistically linked to vessel normalization, independent of autophagy inhibition	65
	C57BL/6×129 mice	MYC-driven lymphoma	Cyclophosphamide	Transgene-driven lymphoma model; pharmacological specificity issues	56
Hydroxychloroquine	*nu/nu* mice	Patient-derived pancreatic cancer (H)	None	Pancreatic cancer model; standalone therapeutic effect in immunodeficient hosts; pharmacological specificity issues	49
	SCID mice	H929 cells (H)	Doxorubicin, melphalan	Multiple myeloma model; improved response to treatment in immunodeficient mice; pharmacological specificity issues	53
	Rag2$^{-/-}$ mice	MDA-MB-231 cells (H)	Epirubicin	Breast cancer model; improved response to treatment in immunodeficient mice; pharmacological specificity issues	54
	Rag2$^{-/-}$ mice	JIMT-1 cells (H)	Gefitinib	Breast cancer model; improved response to treatment in immunodeficient mice; pharmacological specificity issues	57
Wortmannin	C57BL/6 mice	B16-F10 cells (M)	Silver nanoparticles	Melanoma model; pharmacological specificity issues	59
ATG4B-targeting shRNA, NSC185058	*nu/nu* mice	Saos-2 cells (H)	None	Osteosarcoma model; standalone therapeutic effect in immunodeficient hosts	71
ATG5-targeting shRNA, *ATG7*-targeting shRNA, chloroquine	*nu/nu* mice	MDA-MB-231 cells (H)	Cyclophosphamide and/or doxorubicin	Breast cancer model; improved therapeutic response in immunodeficient mice	55
ATG5-targeting shRNA, chloroquine	NOD/SCID mice	HT29 cells (H)	Photodynamic therapy	CRC model; improved therapeutic response in immunodeficient mice	60
Atg5-targeting shRNA, *ATG5*-targeting siRNA, *BECN1*-targeting siRNA	*nu/nu* mice	CT26 cells (M), A549 cells (H), H460 cells (H)	Radiation therapy	CRC and NSCLC models; improved therapeutic response in immunodeficient mice	74
ATG7-targeting siRNA, 3-Methyladenine	*nu/nu* mice	DLD-1 cells (H), HCT116 cells (H)	5-Fluorouracil	CRC models; improved therapeutic response in immunodeficient mice	50
ATG7-targeting shRNA, chloroquine	*nu/nu* mice	GBM39 cells (H)	Bevacizumab	Glioblastoma models; improved therapeutic response in immunodeficient mice	73
BECN1-targeting shRNA, chloroquine	*nu/nu* mice	FaDu cells (H)	Cisplatin	HNC model; improved therapeutic response in immunodeficient mice	51
MAP1LC3B-targeting shRNA, rapamycin	*nu/nu* mice	SK-N-BE2 cells (H), IMR-32 cells (H)	Genistein	Brain cancer models; improved therapeutic response in immunodeficient mice	72

Ko et al. – CDD 2014

Galluzzi et al. – Nat Rev Clin Oncol 2017

Clinical trials

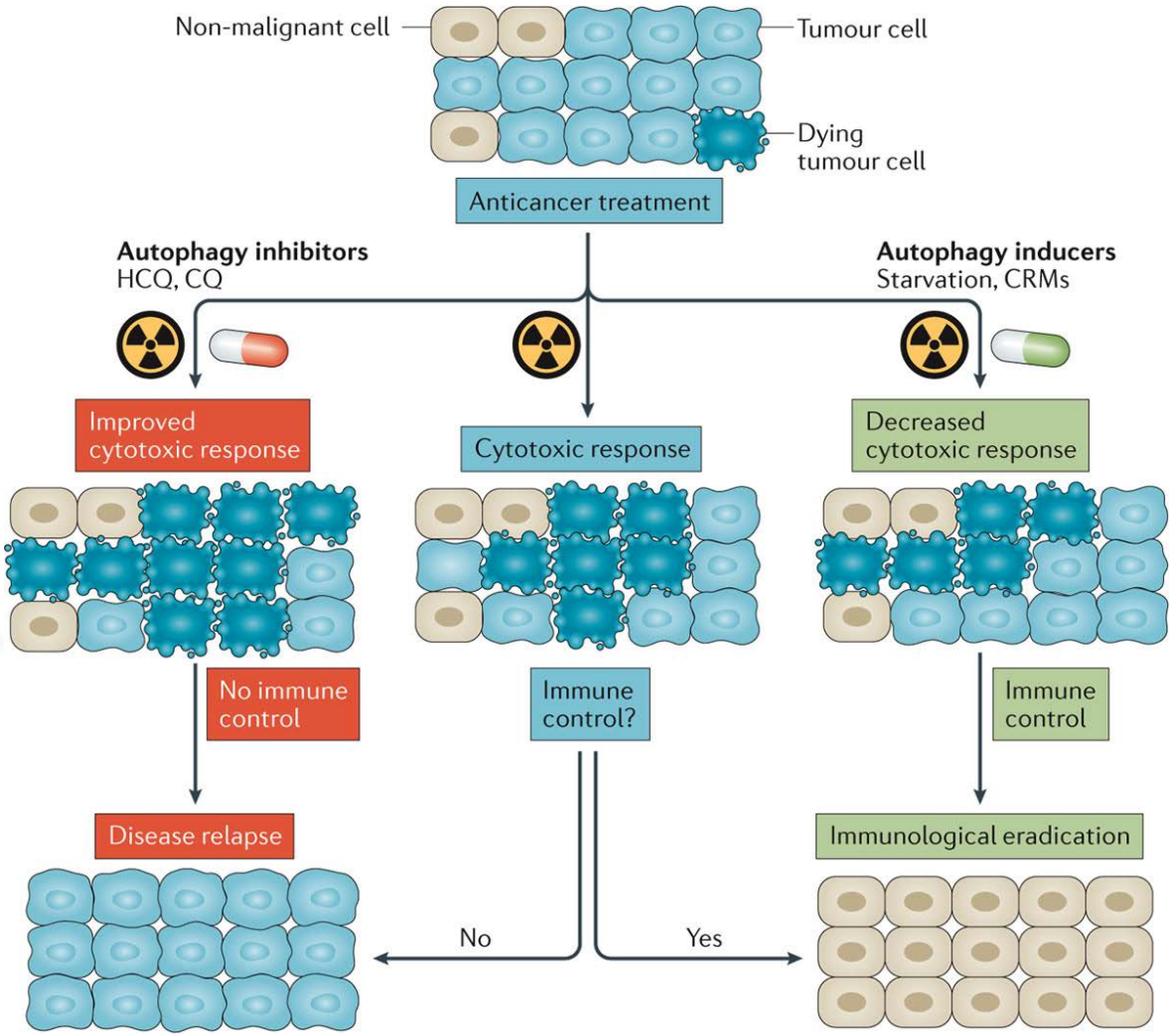
Table 2 | **Selected clinical trials evaluating inhibition of autophagy**

Drug	Tumour type	Number of patients	Therapy	Observations	Refs
Chloroquine	Brain metastases	73	Whole-brain irradiation	Improved control of metastases: RR 0.31, 95%, CI 0.1–0.9; $P = 0.046$; but no significant differences in response rate or overall survival	88
Hydroxychloroquine	Advanced-stage NSCLC	8	None	Mostly grade 1–2 adverse effects; no responses to hydroxychloroquine	86
		19	Erlotinib	Mostly grade 1–2 adverse effects; a single objective response to hydroxychloroquine plus erlotinib was observed	86
	Advanced-stage solid tumours	25	Rapamycin (sirolimus)	Overall response rate: 40%, disease control rate: 84%	90
		27	Vorinostat	Mostly grade 1–2 adverse effects; a single objective response and a further two patients had stable disease	84
		39	Temsirolimus	Mostly grade 1–2 adverse effects; no objective response, but the disease stabilization rate was >65%	89
		40	Temozolomide	Mostly grade 1–2 adverse effects; three partial responses and six incidences of disease stabilization (amongst patients with melanoma)	83
	Glioblastoma multiforme	76	Radiation therapy plus temozolomide	No significant improvement in overall survival	87
	Pancreatic carcinoma	20	None	Only 10% of patients had stable disease at 2 months	82
	Refractory myeloma	25	Bortezomib	Six patients had partial responses (of which three were minor) and 10 patients had stable disease	85

CI, confidence interval; NSCLC, non-small-cell lung cancer; RR, relative risk.

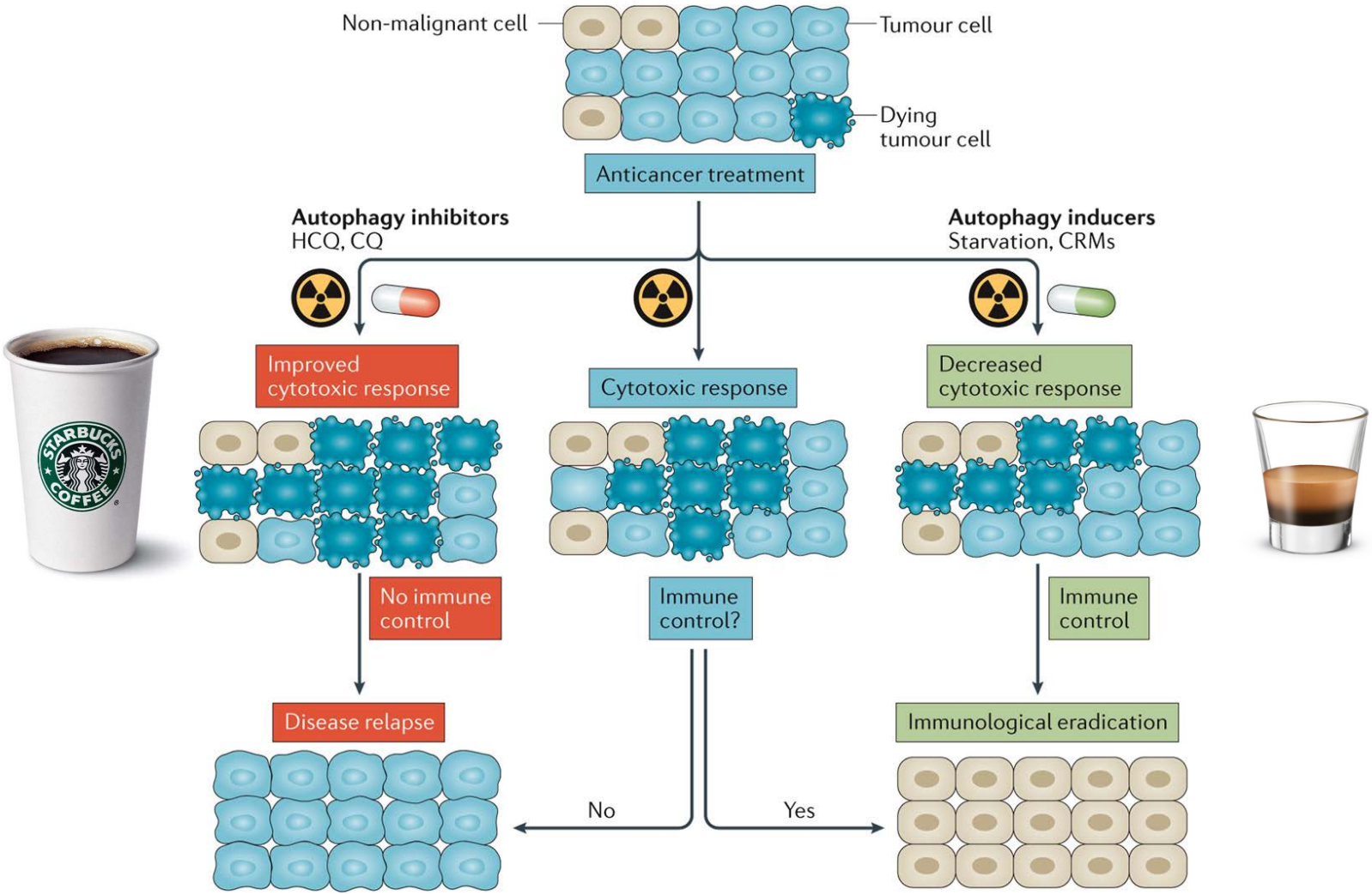
Galluzzi et al. – Nat Rev Clin Oncol 2017

Alternative approach



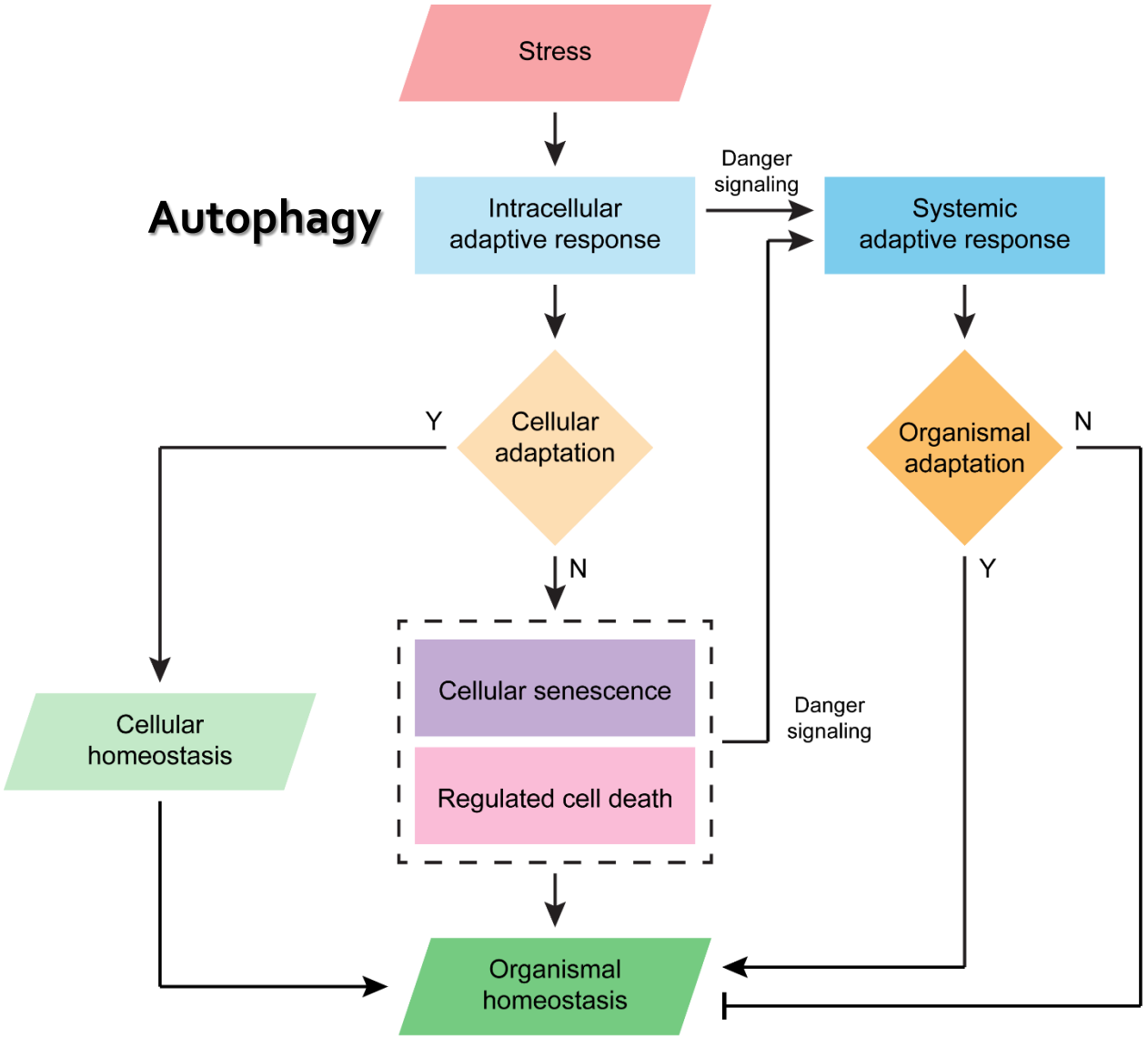
Galluzzi et al. – Nat Rev Clin Oncol 2017

The "Espresso" approach



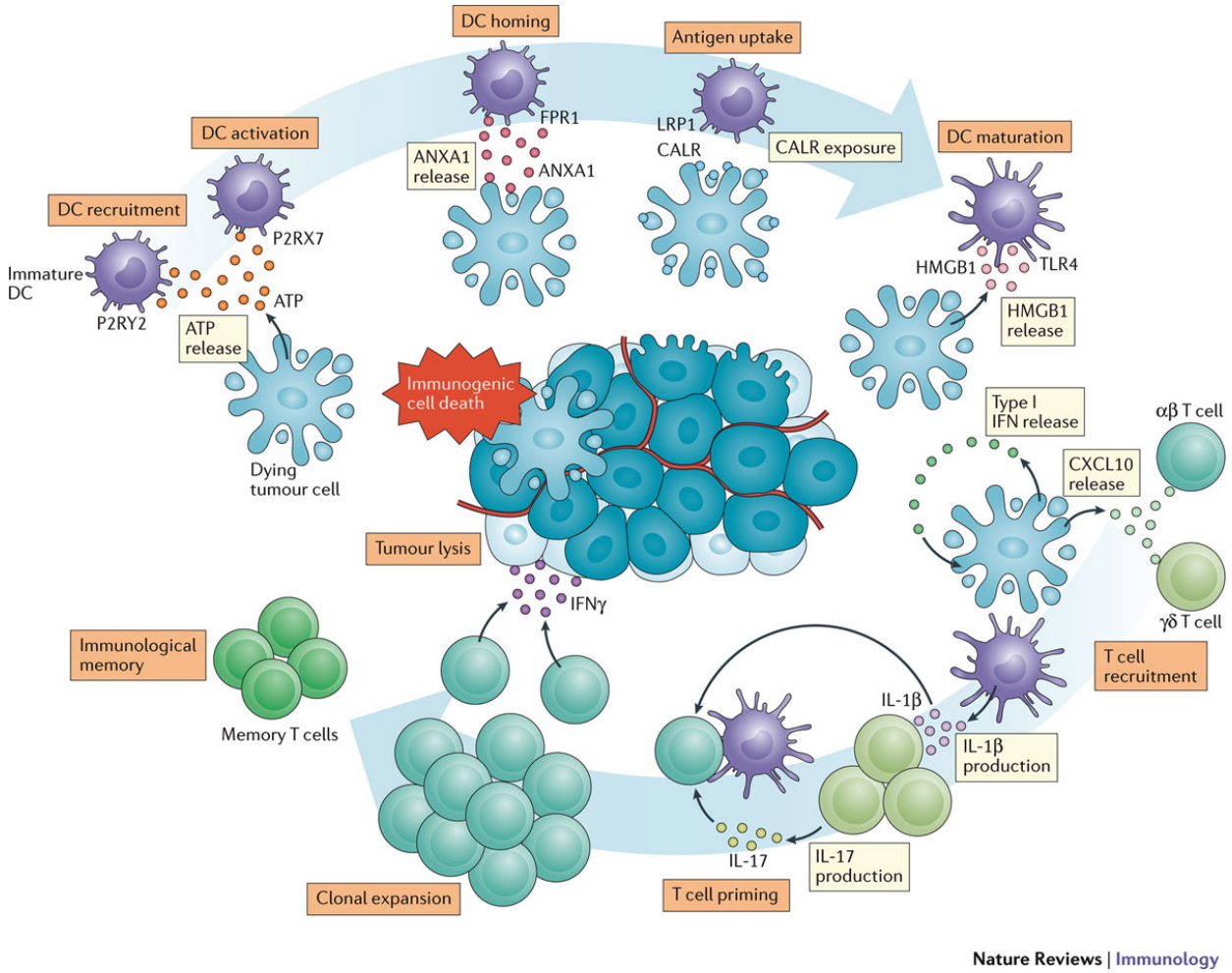
Galluzzi et al. – Nat Rev Clin Oncol 2017

Cellular adaptation and organismal homeostasis



Galluzzi et al. – NRCMB 2018

Immunogenic cell death

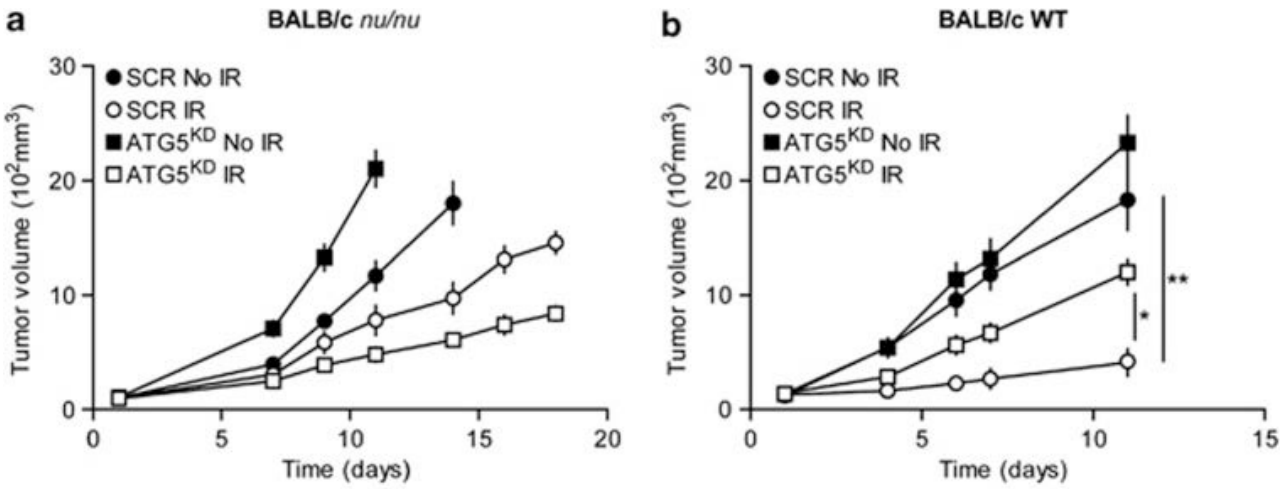


A peculiar variant of RCD that, in immunocompetent hosts, is sufficient to elicit an adaptive immune response against DCAAs

Galluzzi et al. - Nat Rev Immunol 2017

Autophagy activation for cancer therapy

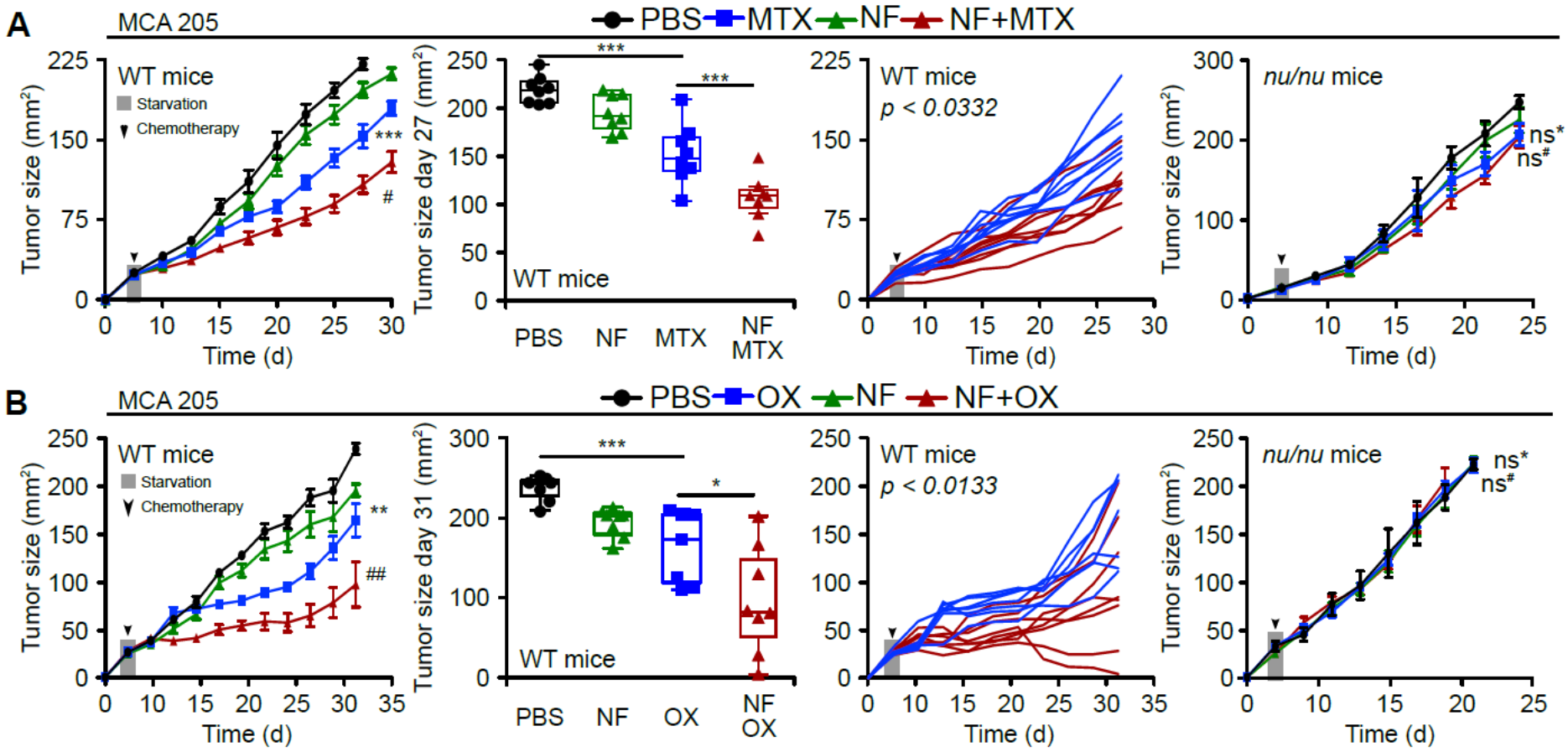
Detrimental effects of autophagy inhibition



Ko et al. – CDD 2014

Activation of autophagy for cancer therapy

Anticancer effects of caloric restriction

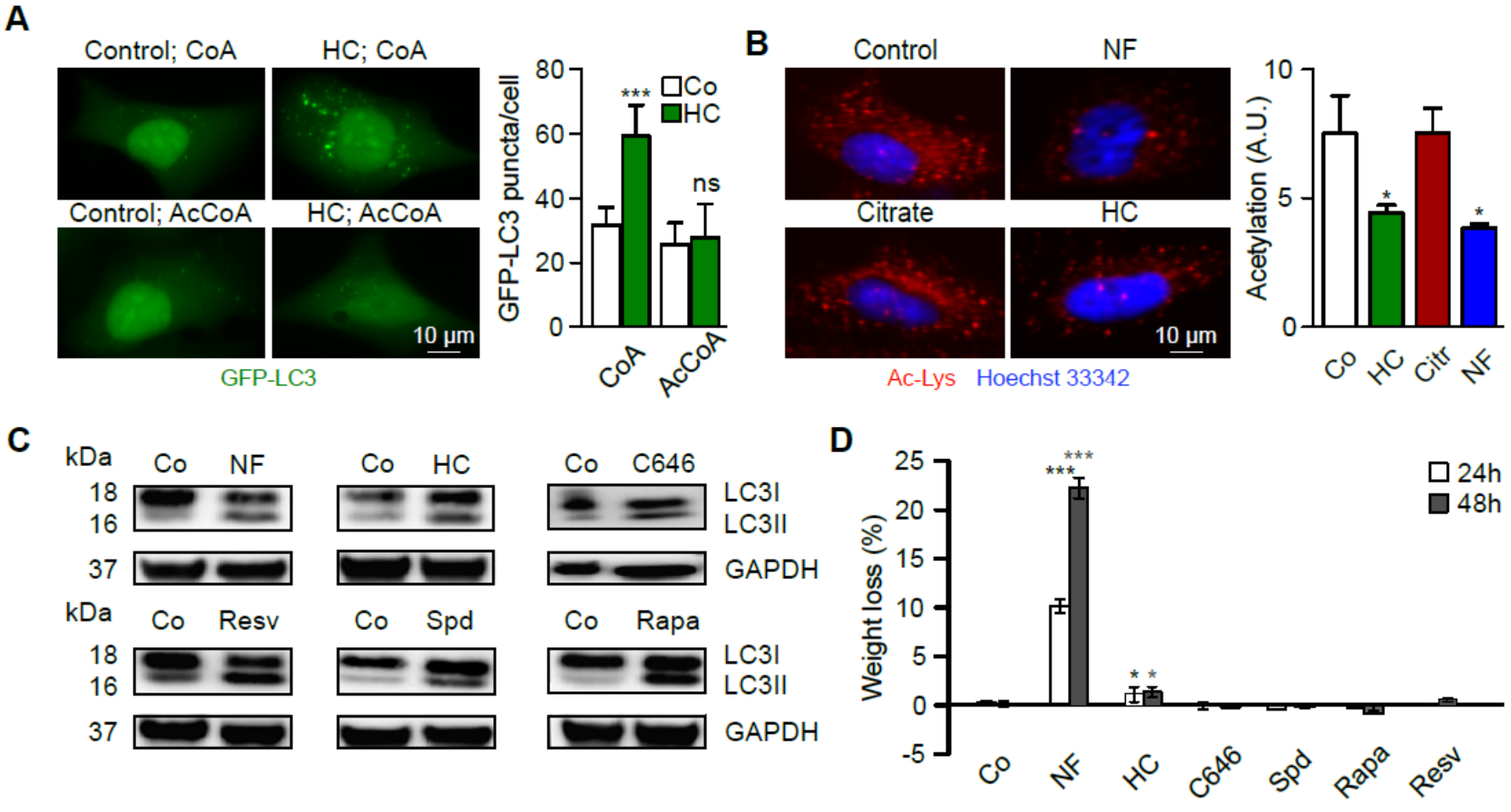


...depend on the immune system

Pietrocola et al. – Cancer Cell 2016

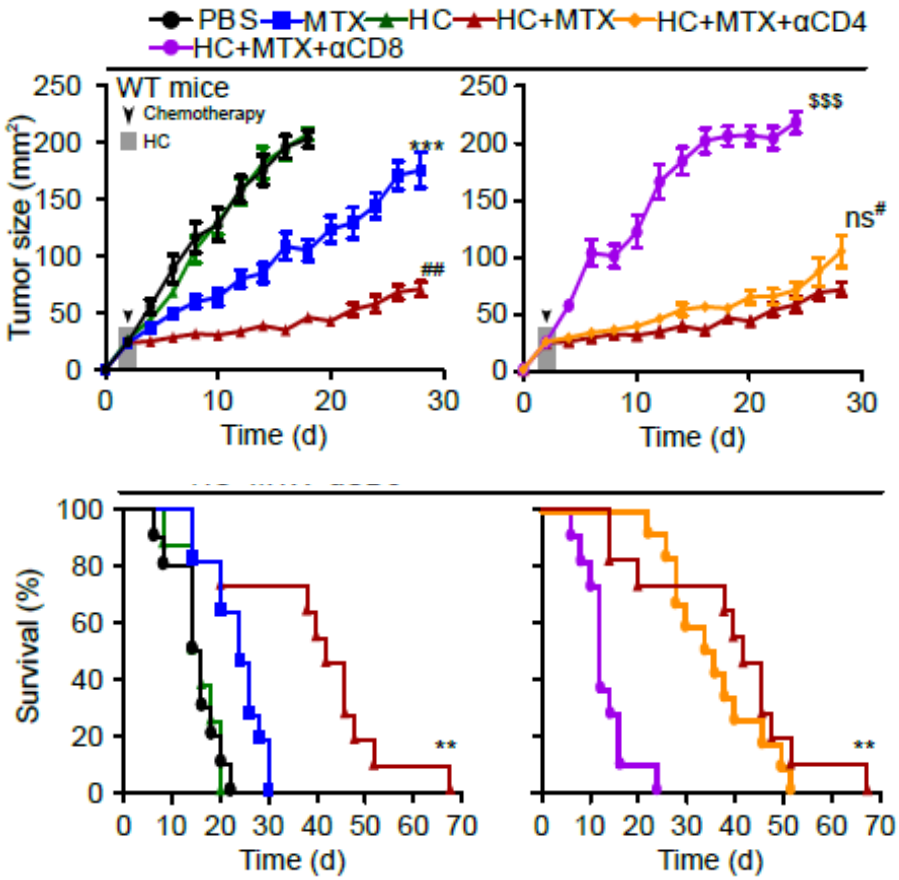
Activation of autophagy for cancer therapy

Molecules that mimic the cellular effects of fasting but do NOT induce a sizeable weight loss



Pietrocola et al. – Cancer Cell 2016

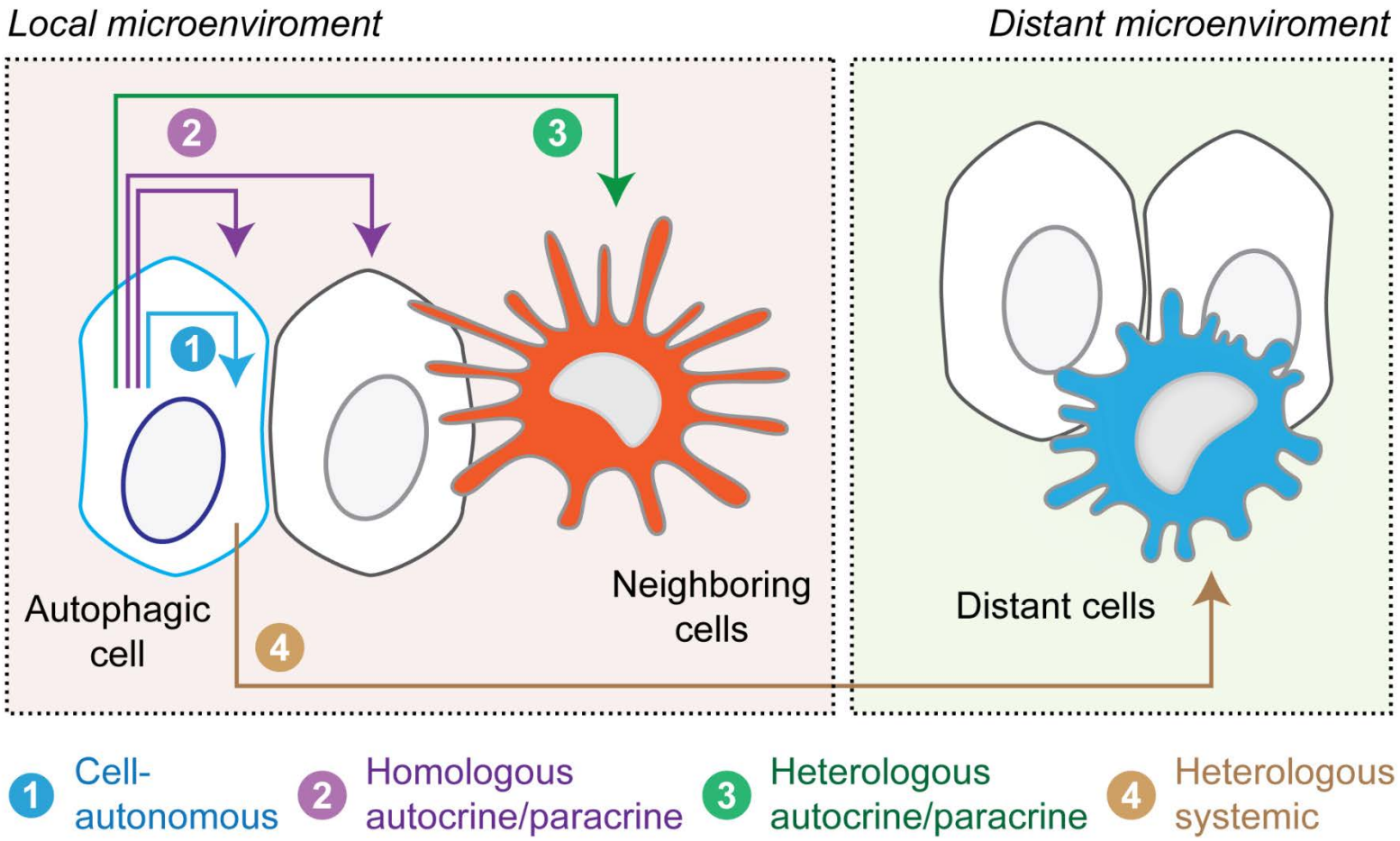
Activation of autophagy for cancer therapy



…also in models of carcinogen-driven breast cancer

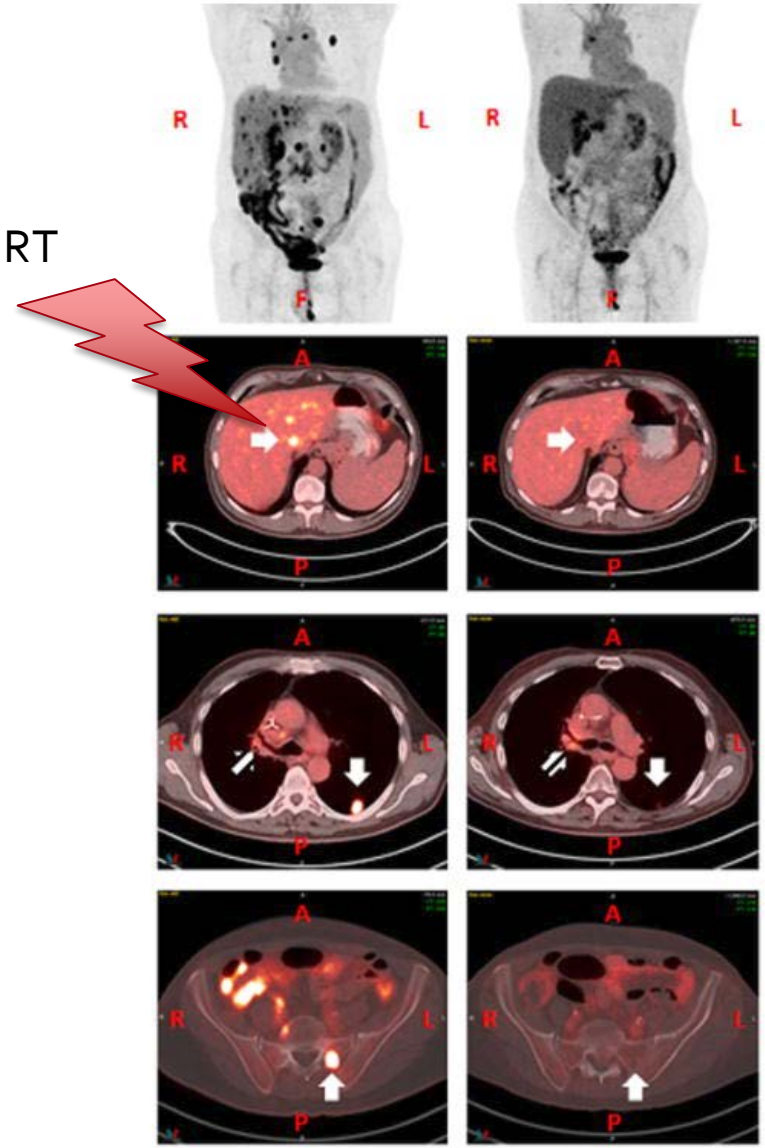
Pietrocola et al. – Cancer Cell 2016

Not as simple as it looks like



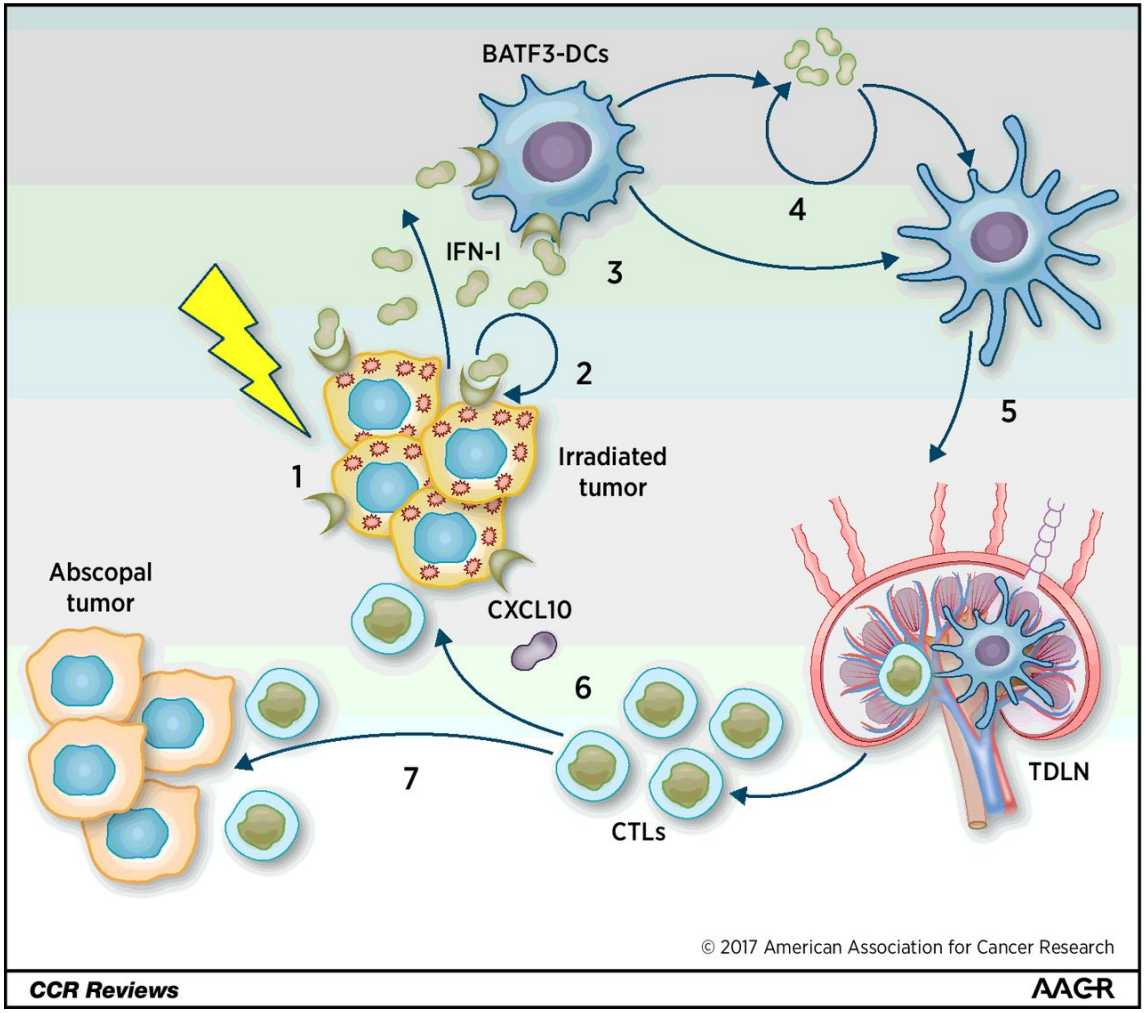
Rybstein et al. – Nat Cell Biol 2018

The abscopal response



Golden et al. – Cancer Immunol Res 2013

Abscopal responses in mice require type I IFN



Vanpouille-Box et al. – Clin Cancer Res 2018

Autophagy inhibits type I IFN secretion

Published online: March 1, 2018

Article

TRANSPARENT PROCESS

THE EMBO JOURNAL

Attenuation of cGAS-STING signaling is mediated by a p6 activate

Thaneas Praba
Maria H Christ
Morten K Skou
Ganes C Sen[7],
Martin R Jakob

LETTER

doi:10.1038/nature10992

Mitochondrial DNA that escapes from autophagy causes inflammation and heart failure

Takafumi
Tomokaz
& Kinya

Cell Death & Differentiation (2018) 25:782–794
https://doi.org/10.1038/s41418-017-0017-z

Cell Death & Differentiation

ARTICLE

Heart fail
industrial
is not inv
inflamma

Autophagy induced during apoptosis degrades mitochondria and inhibits type I interferon secretion

Lisa M. Lindqvist
Jonathan S. Oakh

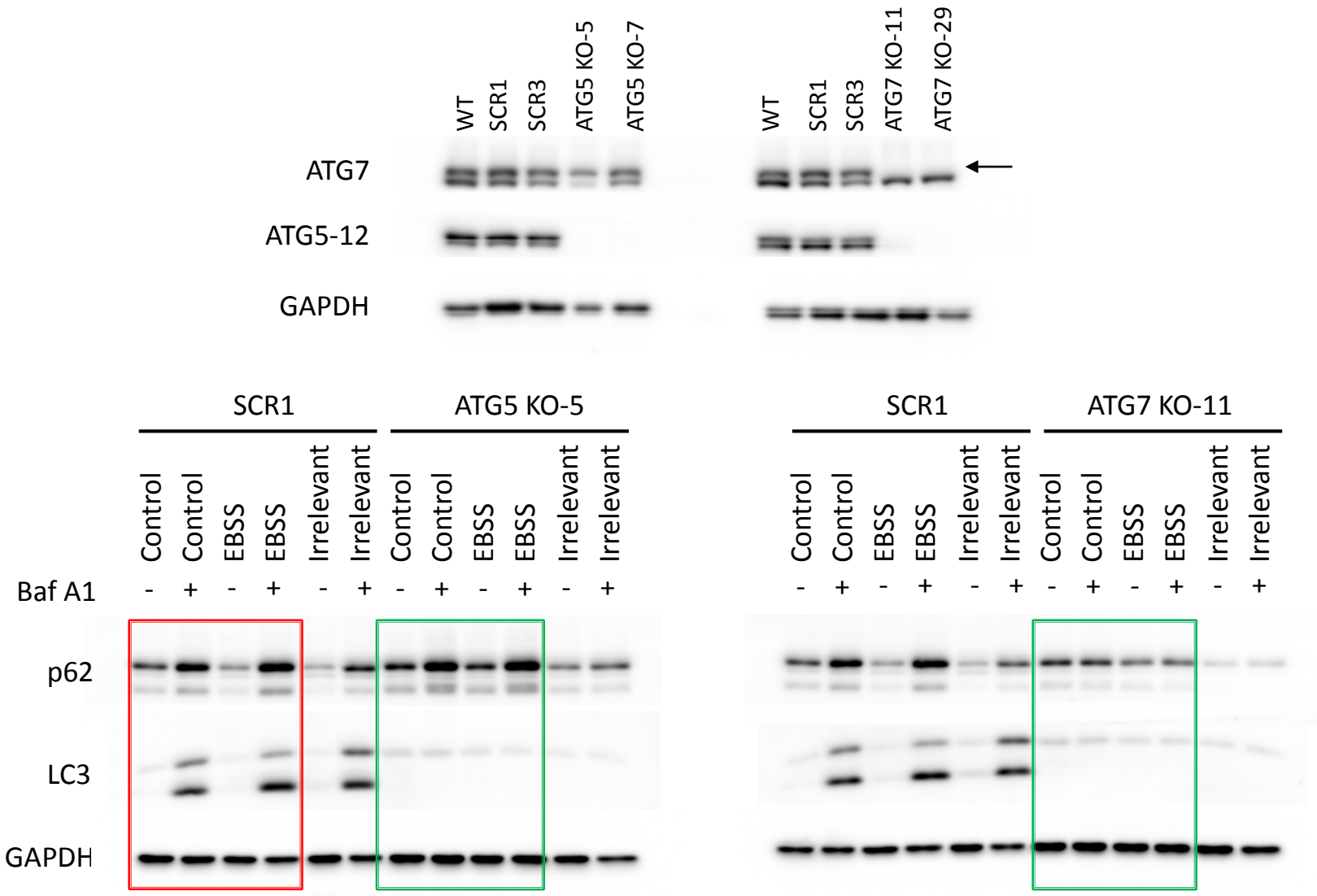
LETTER

https://doi.org/10.1038/s41586-018-0448-9

Parkin and PINK1 mitigate STING-induced inflammation

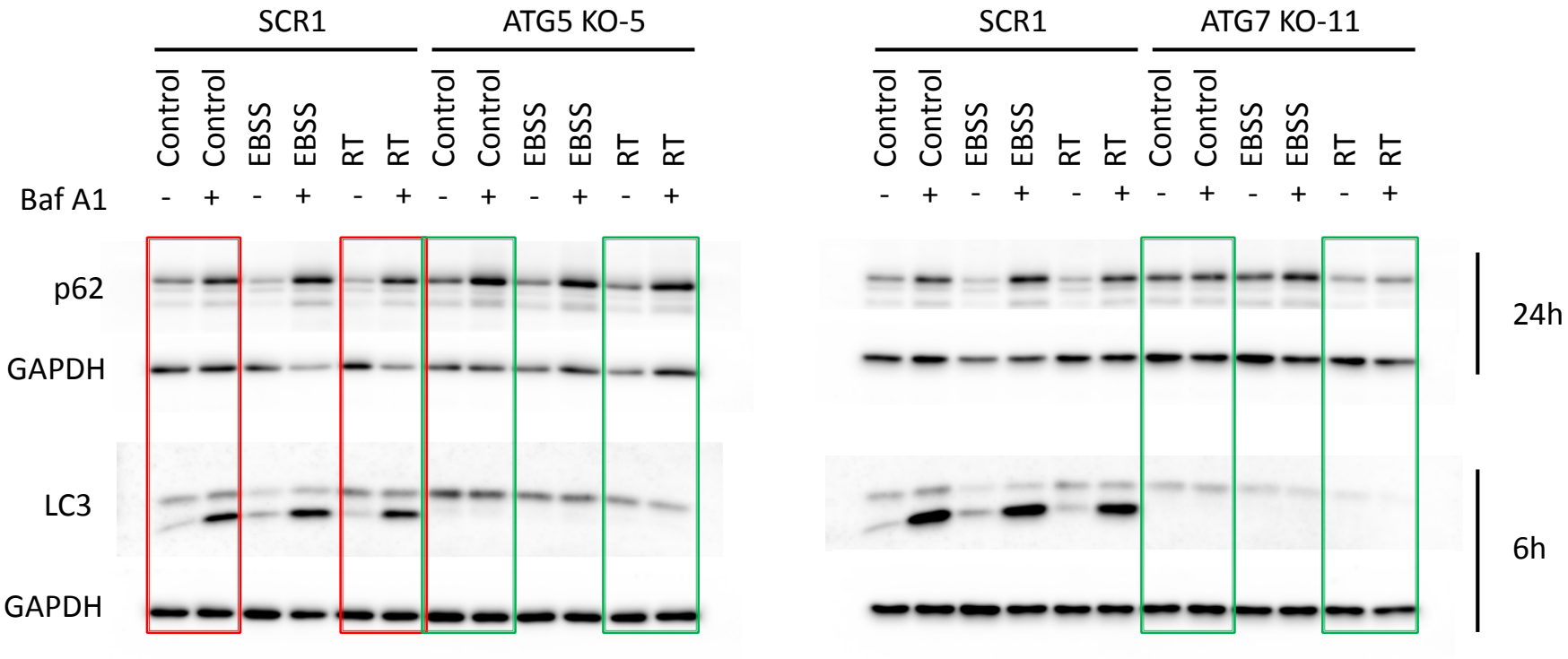
Danielle A. Sliter[1], Jennifer Martinez[2], Ling Hao[1], Xi Chen[3], Nuo Sun[4], Tara D. Fischer[1], Jonathon L. Burman[1], Yan Li[5], Zhe Zhang[1], Derek P. Narendra[6], Huaibin Cai[3], Max Borsche[7], Christine Klein[7] & Richard J. Youle[1]*

CRISPR model of autophagic deficiency



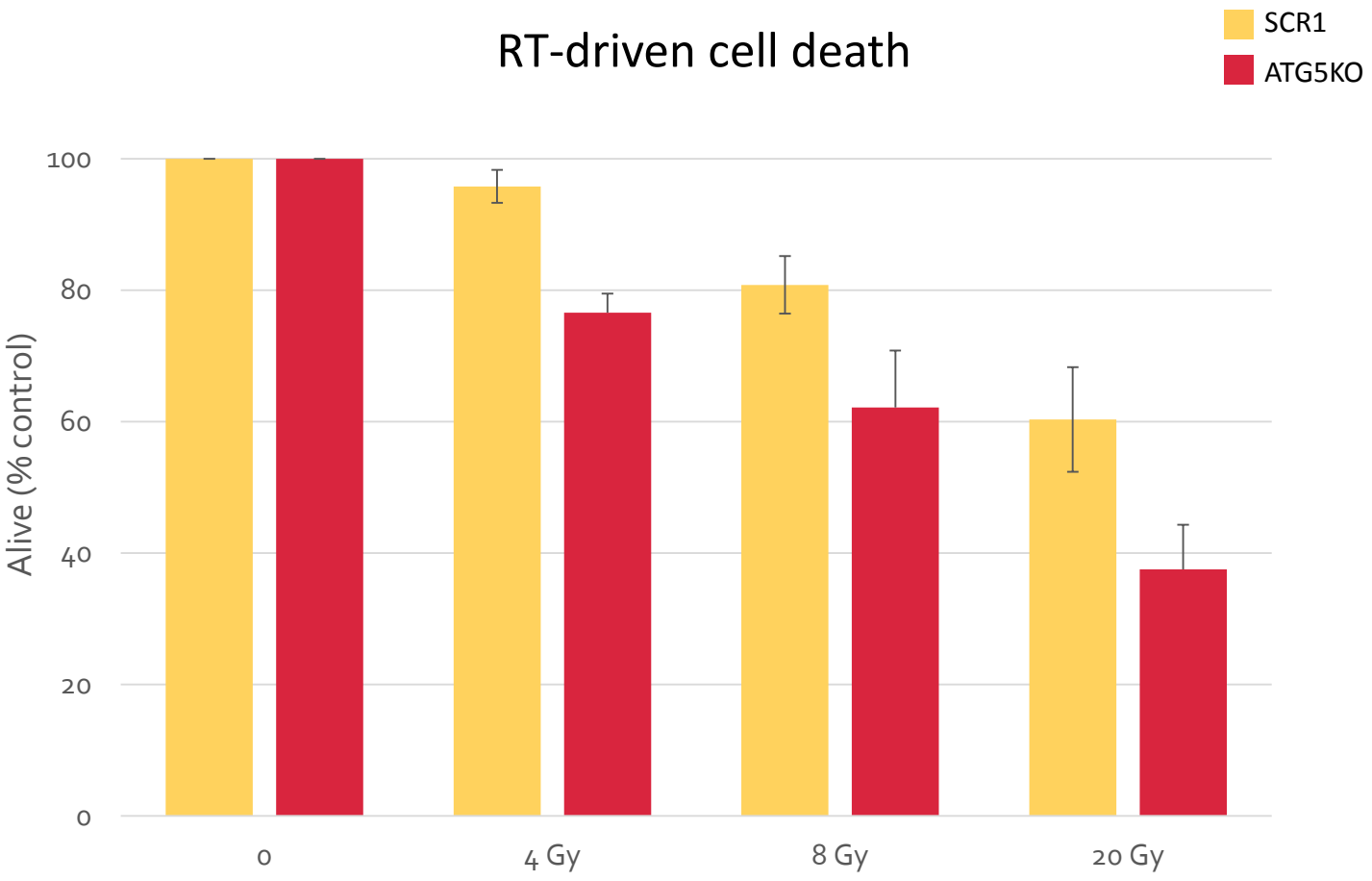
Rybstein, Yamazaki et al. – Unpublished data

RT drives bona fide autophagic flux



Rybstein, Yamazaki et al. – Unpublished data

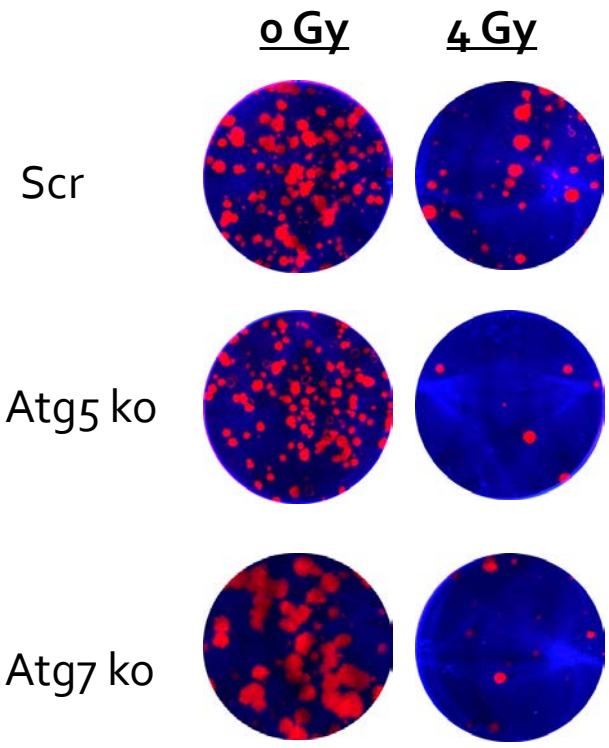
Autophagy supports cancer cell survival

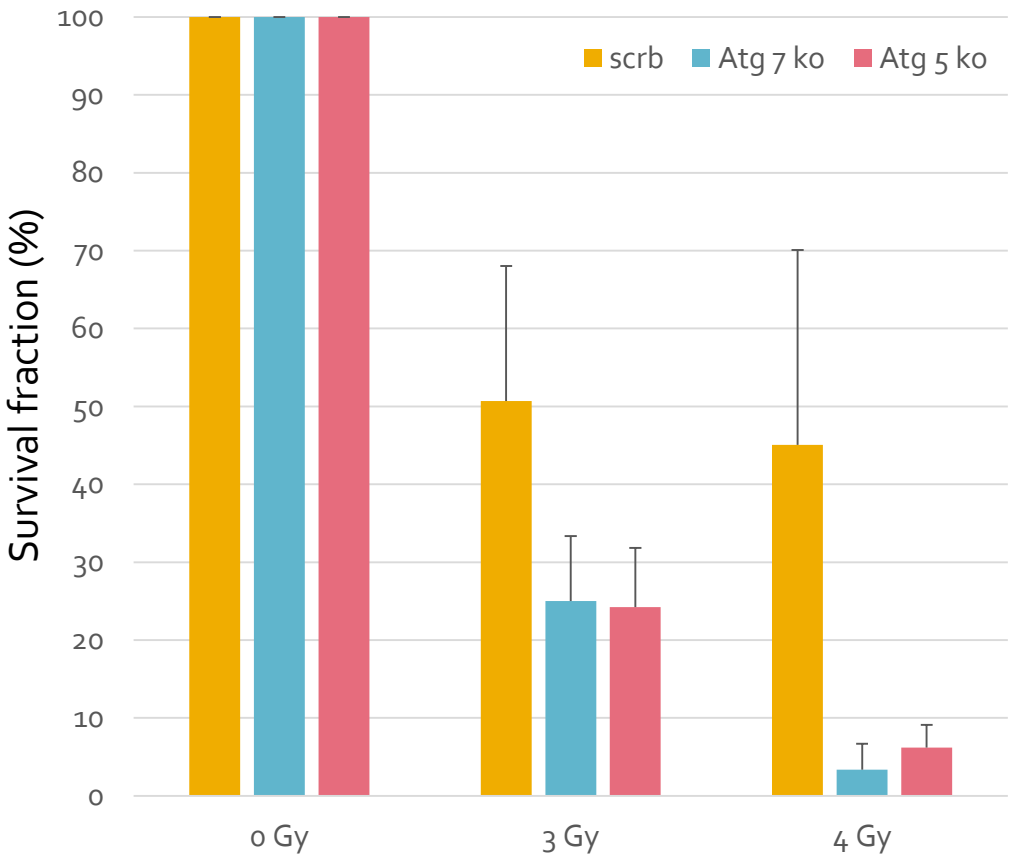


Rybstein, Yamazaki et al. – Unpublished data

Autophagy supports cancer cell survival

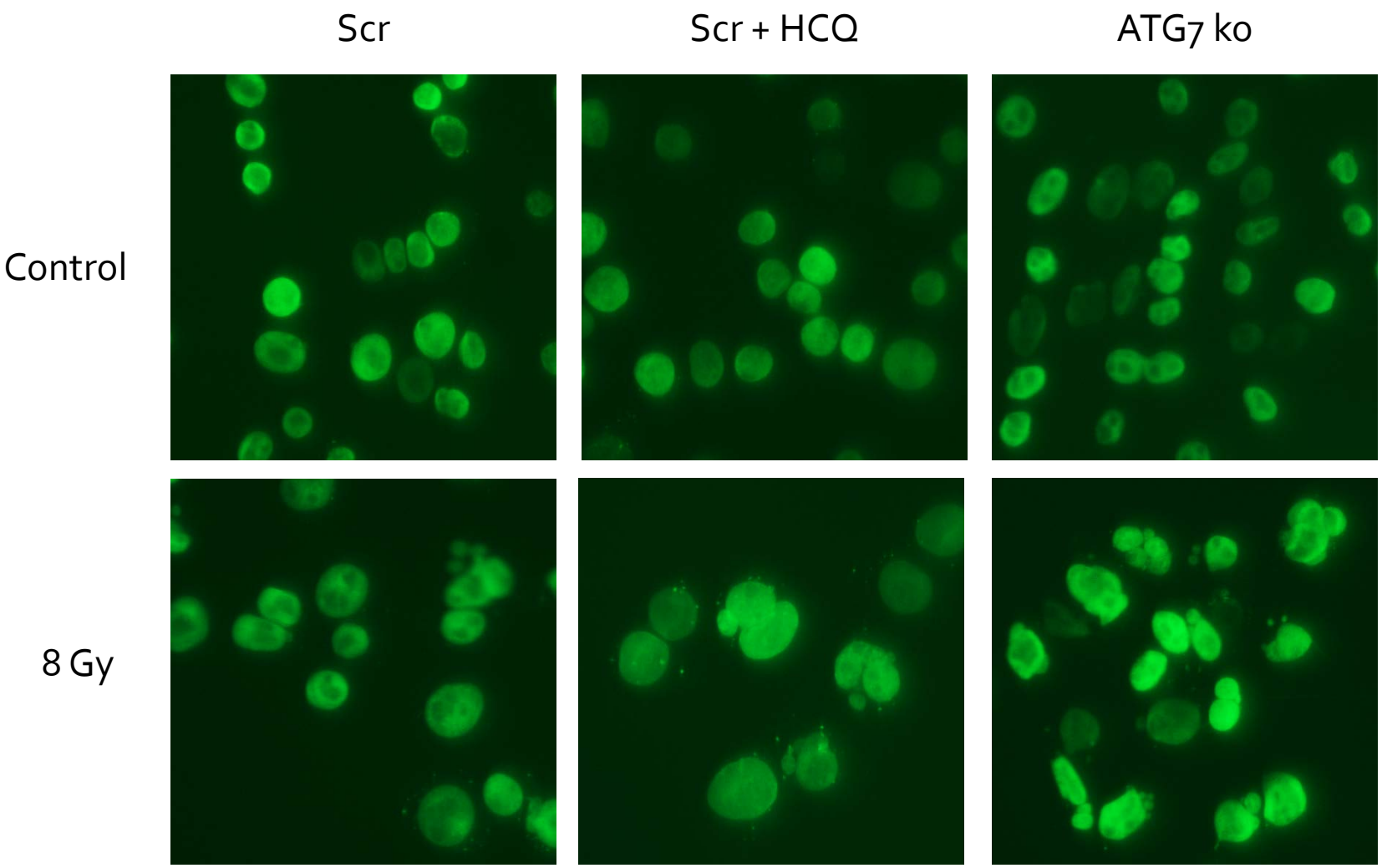
Clonogenic response to RT





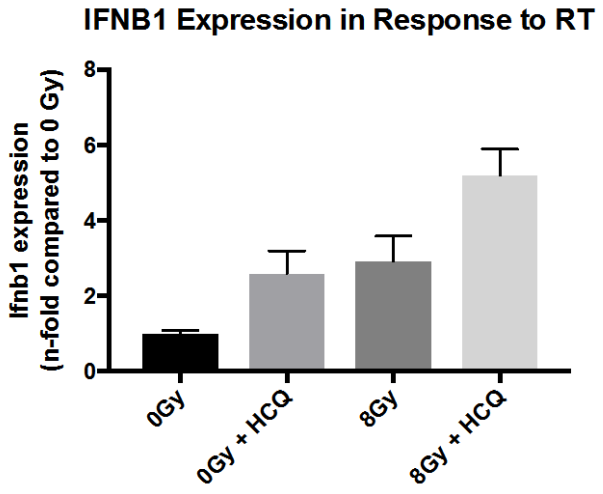
Rybstein, Yamazaki et al. – Unpublished data

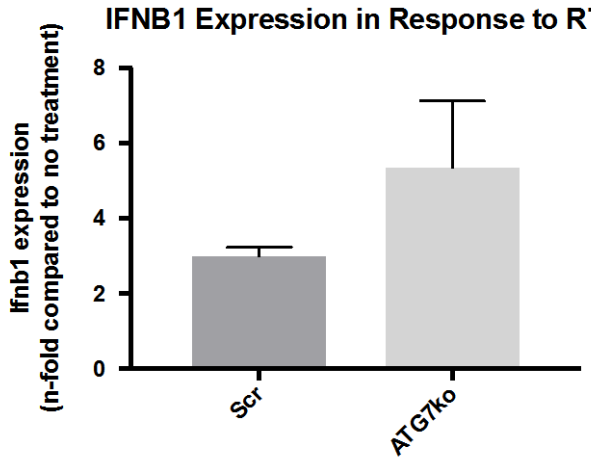
Autophagy limits cytosolic DNA accumulation

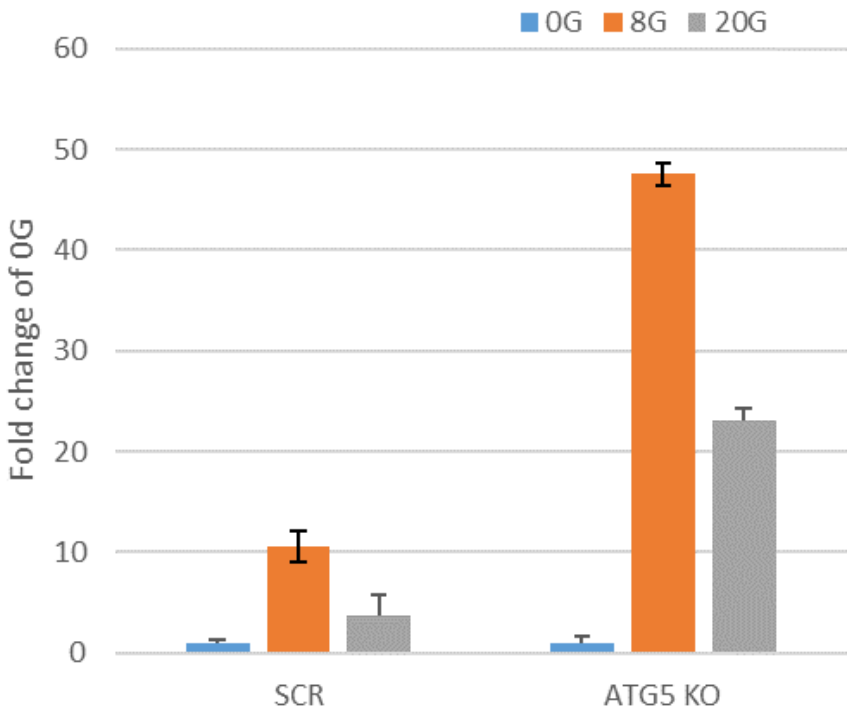


Rybstein, Yamazaki et al. – Unpublished data

Autophagy inhibits RT-driven type I IFN

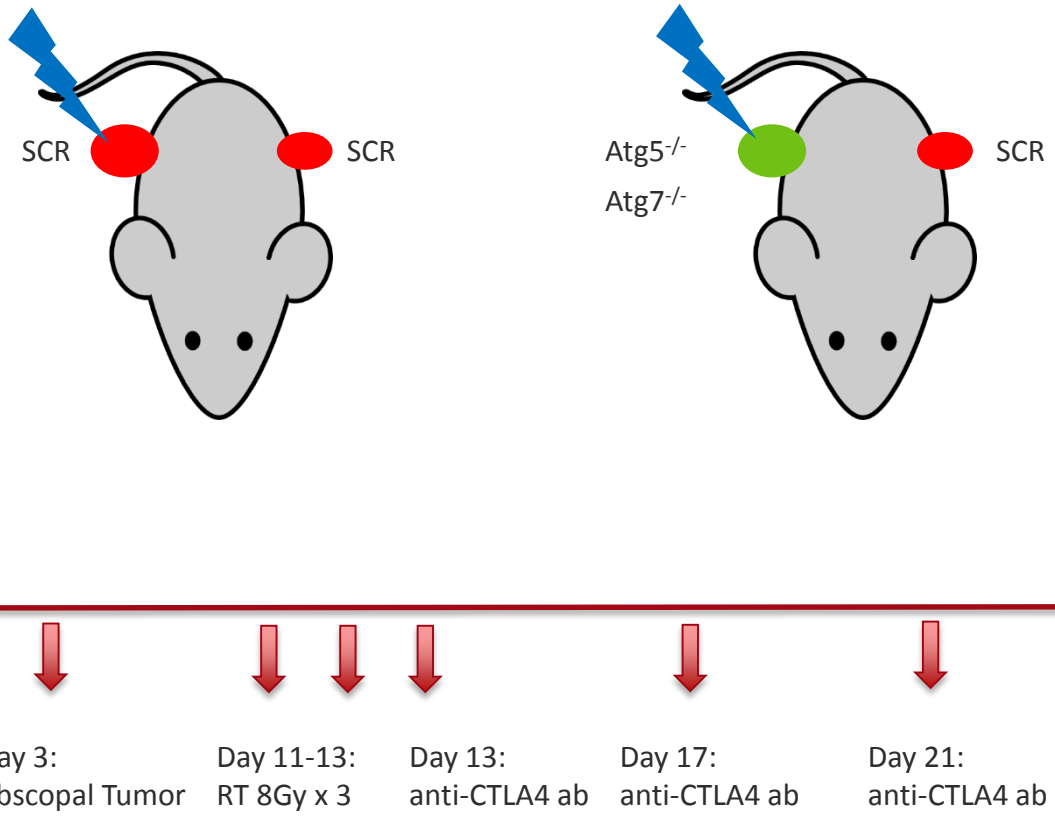






Rybstein, Yamazaki et al. – Unpublished data

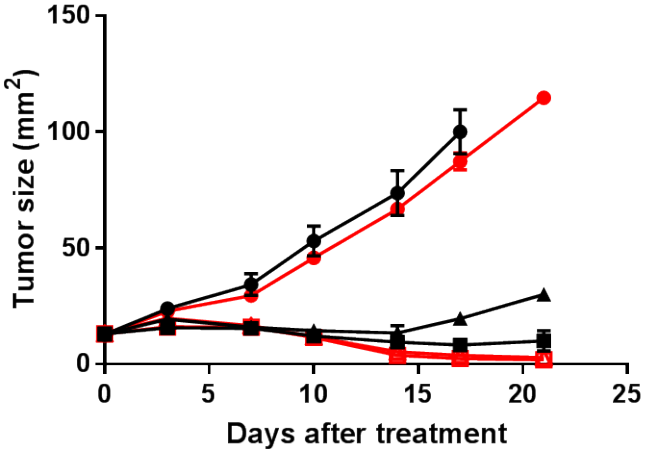
Autophagy inhibits abscopal responses



Autophagy inhibits abscopal responses

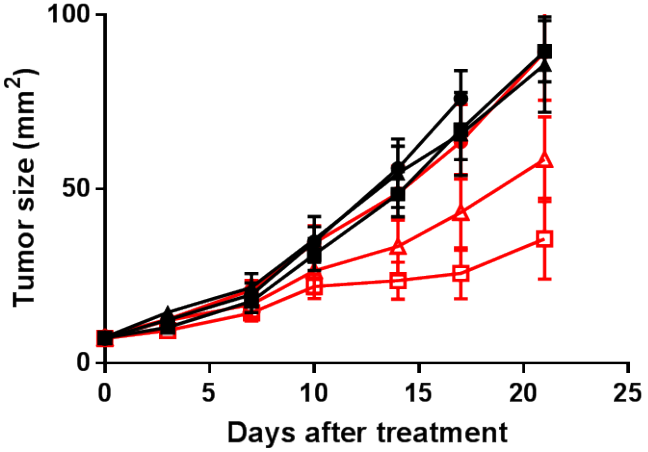
1st tumor (SCR)

ctr	0/5
RT 8x3Gy	0/5
RT 20Gy	1/5
9H10	0/5
RT 8x3Gy + 9H10	3/5
RT 20Gy + 9H10	4/5



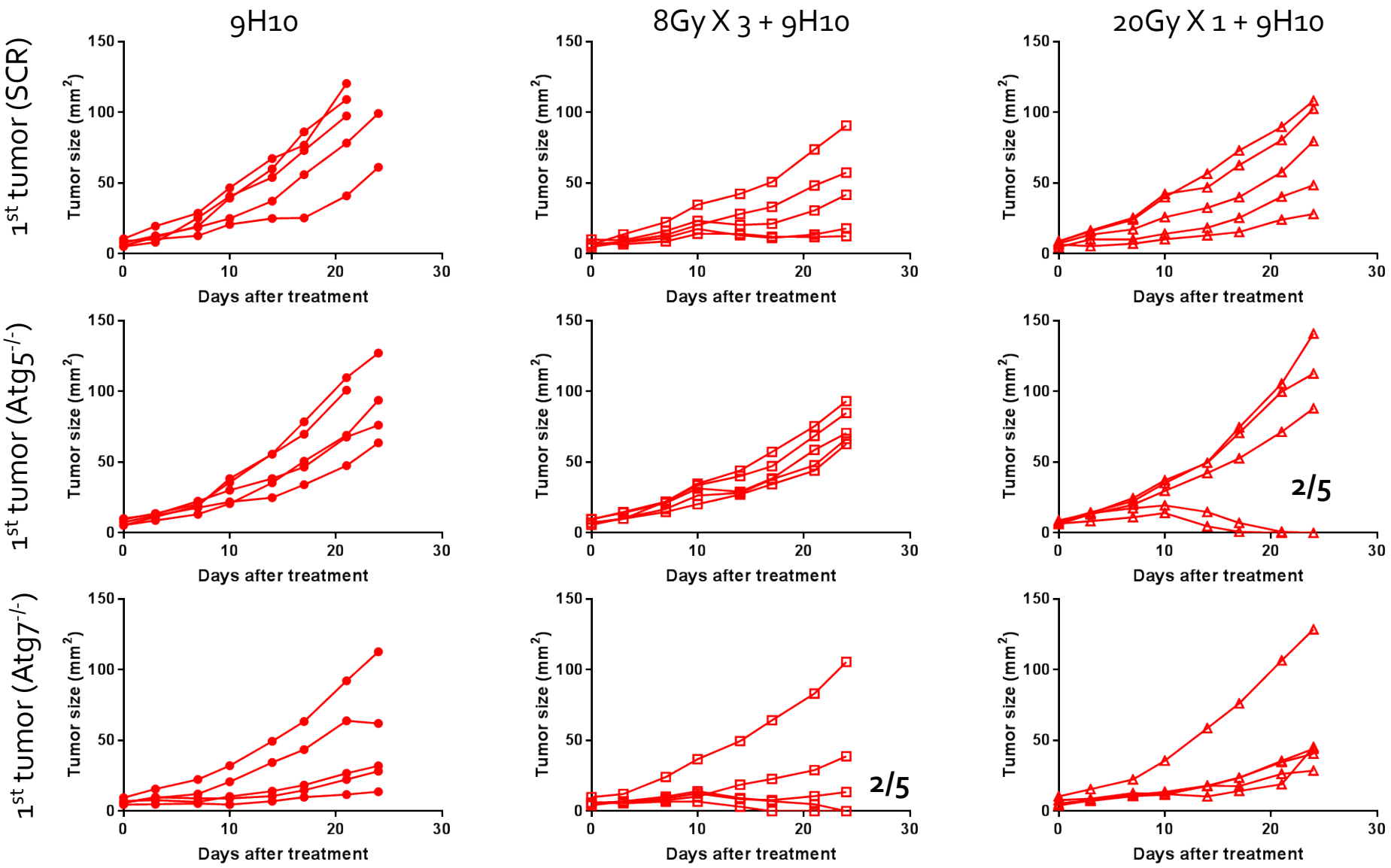
2nd tumor (SCR)

ctr	0/5
RT 8x3Gy	0/5
RT 20Gy	0/5
9H10	0/5
RT 8x3Gy + 9H10	0/5
RT 20Gy + 9H10	0/5



Rybstein, Yamazaki et al. – Unpublished data

Autophagy inhibits abscopal responses



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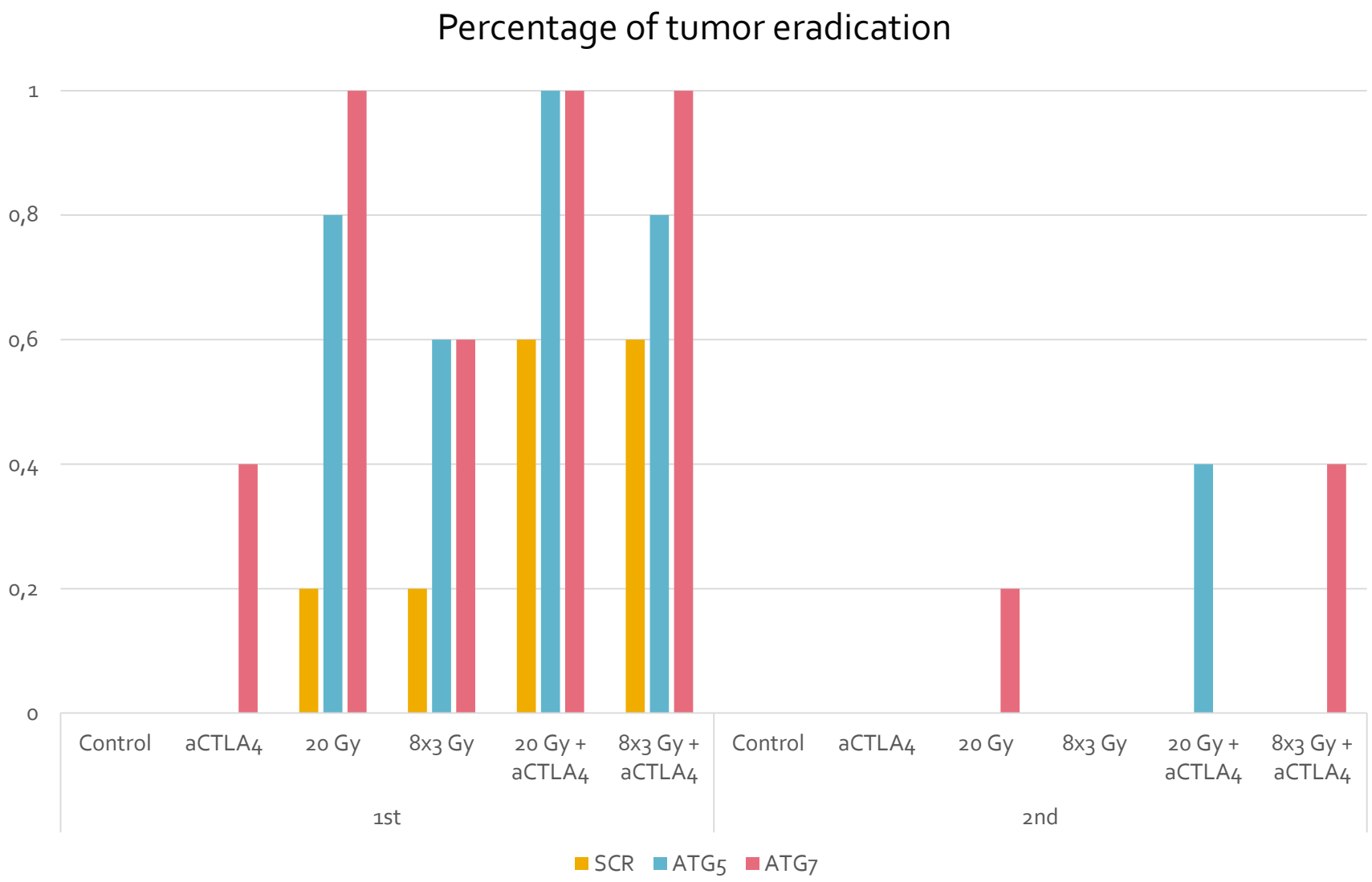
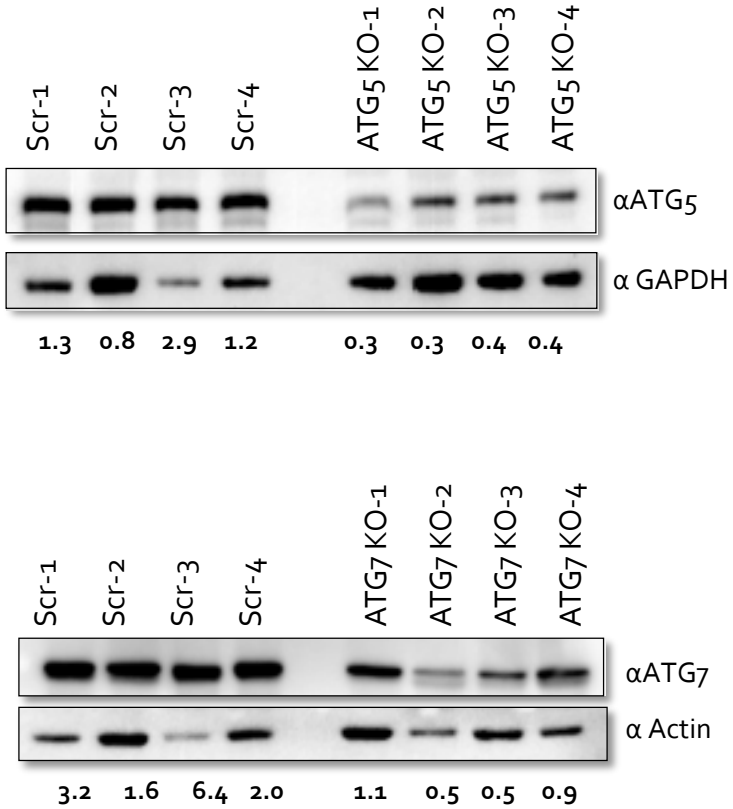
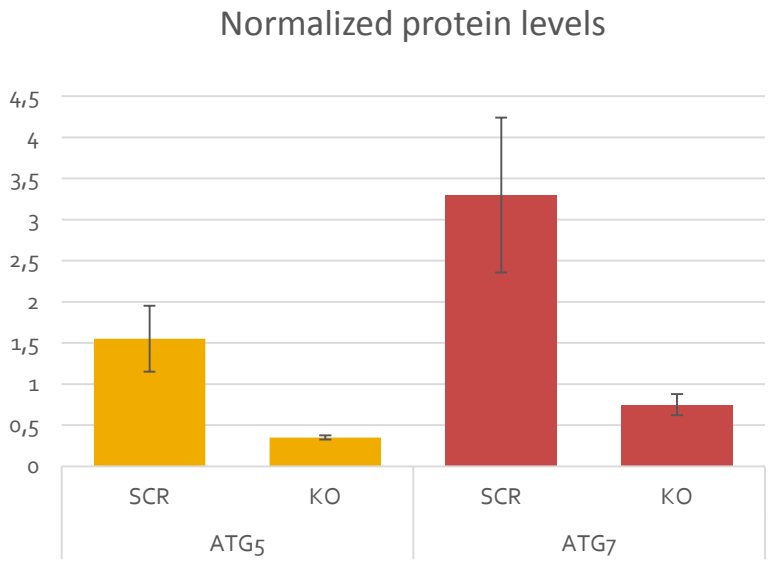
Autophagy inhibits abscopal responses



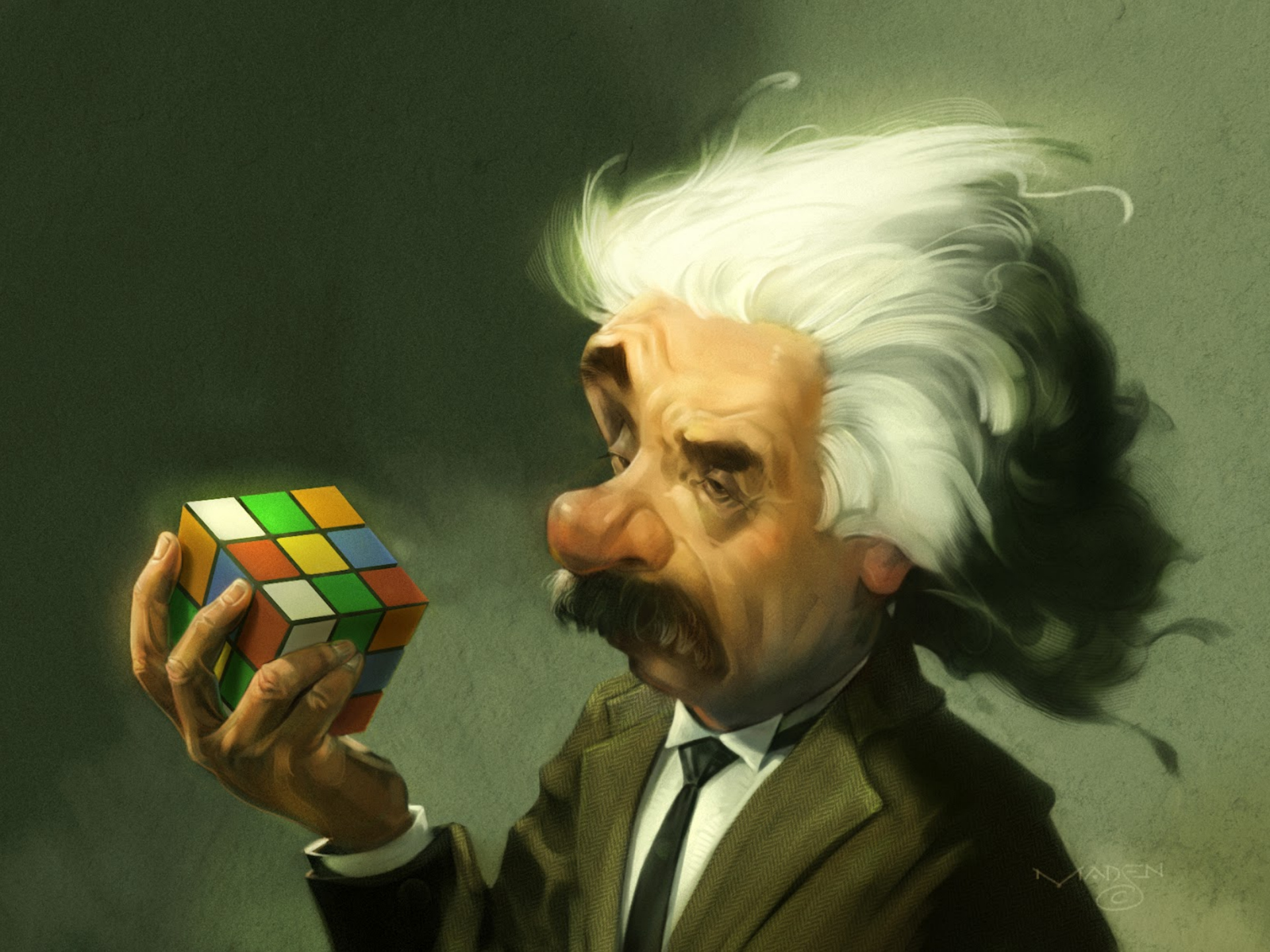
Autophagy inhibits abscopal responses





Rybstein, Yamazaki et al. – Unpublished data

Autophagy inhibition or activation?


MADEN

The Starbucks-Espresso dilemma

A lot of cell death

Immunogenic cell death

The Starbucks-Espresso conundrum

A lot of immunogenic cell death (?)

The quantity-quality dilemma

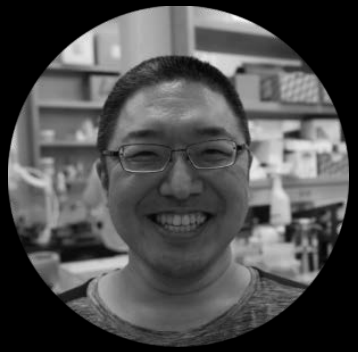
Read the room!

Rule for New Yorkers #1

lab galluzzi

Weill Cornell Medicine
Sandra and Edward Meyer Cancer Center

Weill Cornell Medicine



Takahiro Yamazaki

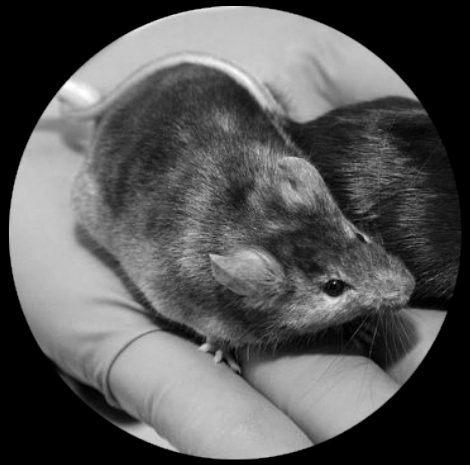
Aitziber Buqué

Ai Sato

Jonathan Chen

Marissa Rybstein

Mr. Mouse and family



Spritz (#lazygolden)

Acknowledgements

The Kroemer Lab

Guido Kroemer

Federico Pietrocola

Erika Vacchelli

Isabelle Martins

Mickael Michaud

Valentina Sica

The Demaria Lab

Sandra Demaria

Claire Vanpouille-Box

Karsten Pilones

Nils Rudqvist

Erik Wennerberg

Claire Lhuillier

Sheila Spada

Selina Chen-Kiang

Andy Dannenberg

Paolo Pinton

Frank Madeo

Laurence Zitvogel

Silvia Formenti

Ilio Vitale

Chema Bravo-San Pedro