Disclosure information

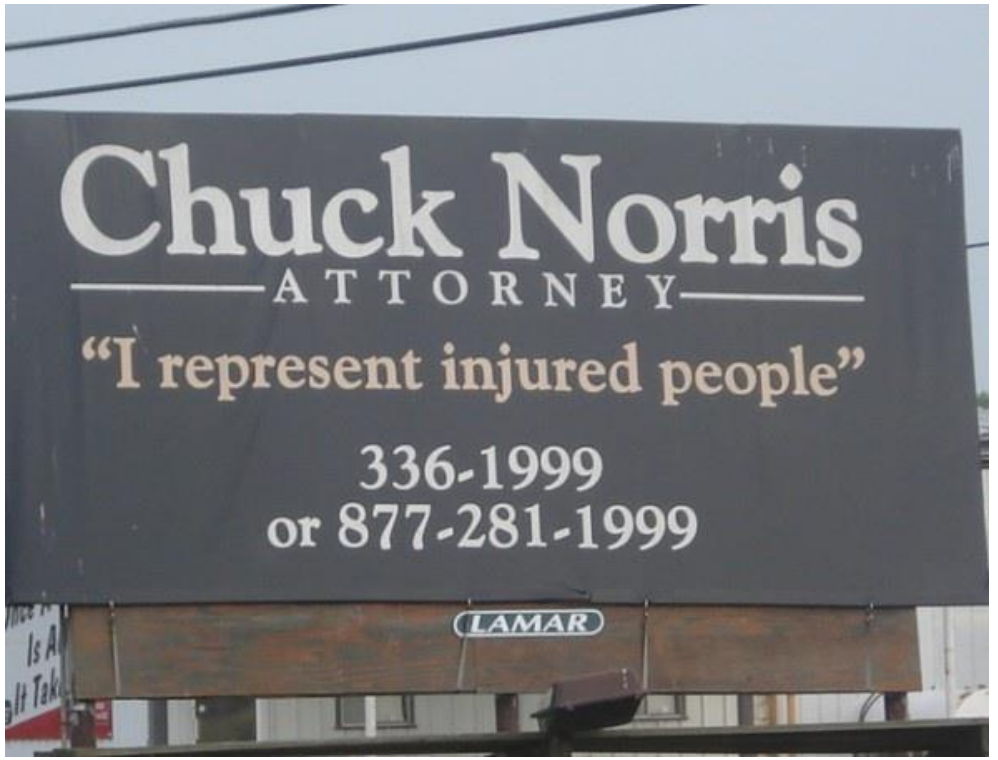
International Reviews of Cell and Molecular Biology
Editor-in-Chief

Molecular and Cellular Oncology
Founding Editor-in-Chief

OncoImmunology
Founding Editor-in-Chief

Oncotarget
Section Chief Editor

OmniSEQ
Consultant



Immunogenic cell death
Principles and misconceptions

San Francisco – May 14th 2018

Lorenzo Galluzzi, *Ph.D.*
Weill Cornell Medical College – New York, US

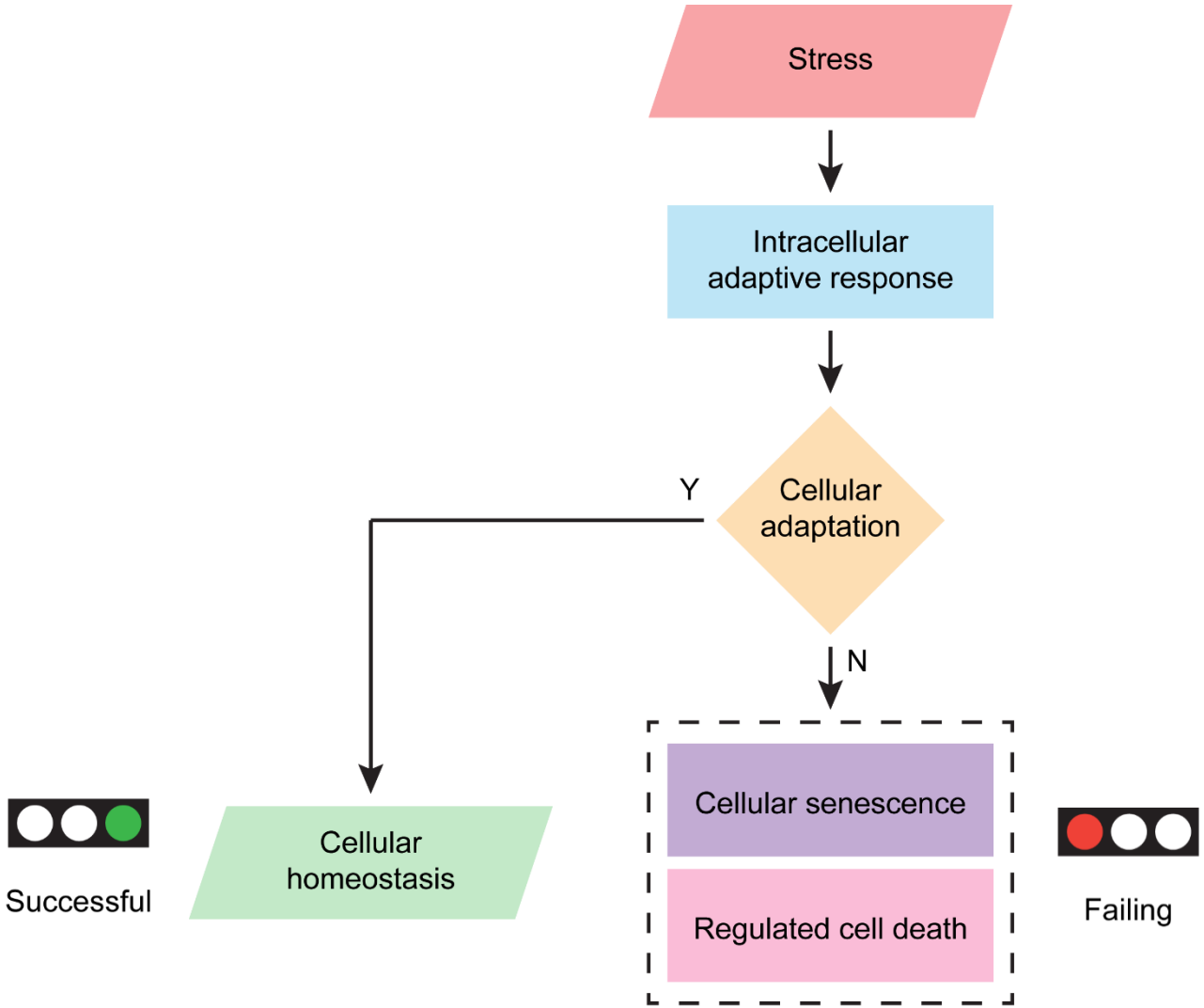
Behind the mask of cell death

San Francisco – May 14th 2018

Lorenzo Galluzzi, *Ph.D.*

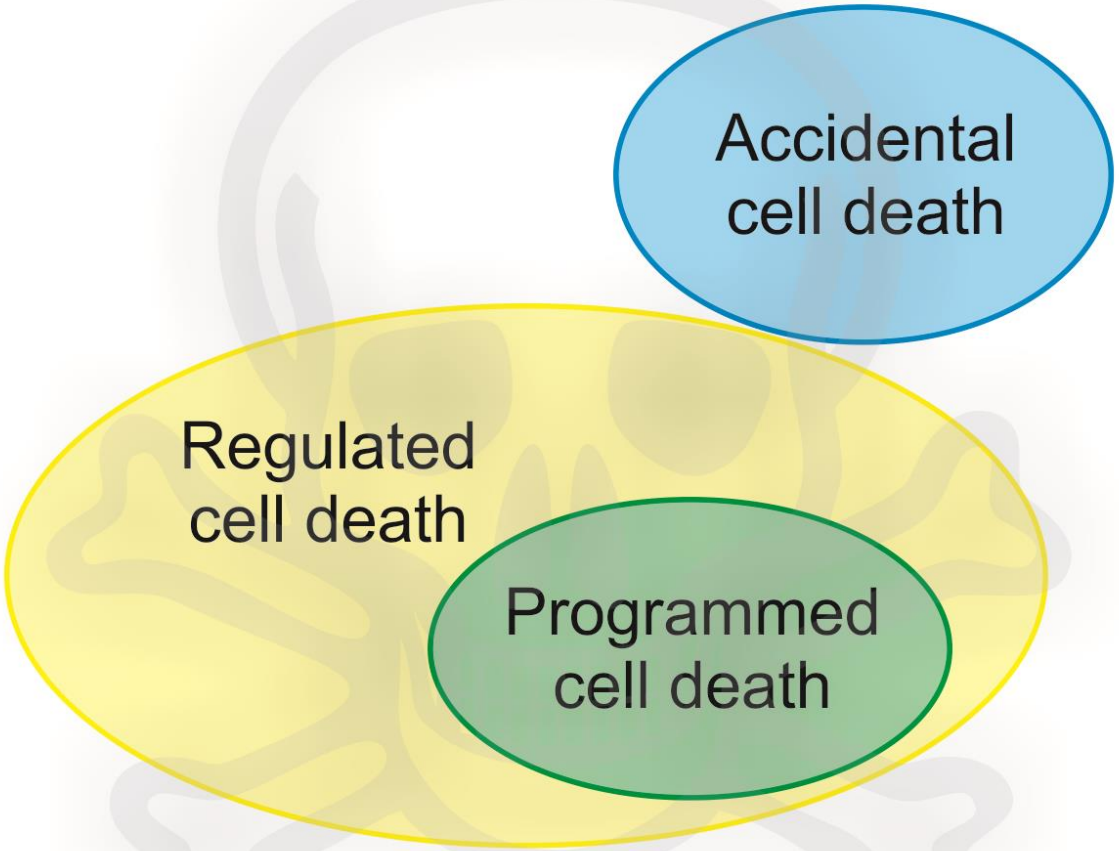
Weill Cornell Medical College – New York, US

General organization of stress responses



Galluzzi et al. – NRCMB 2018

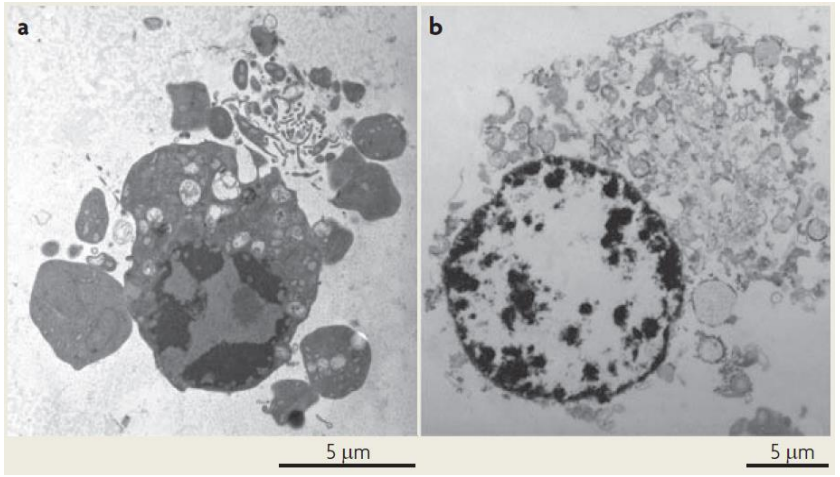
What is RCD?


Accidental
cell death
Regulated
cell death
Programmed
cell death

Main variants of RCD

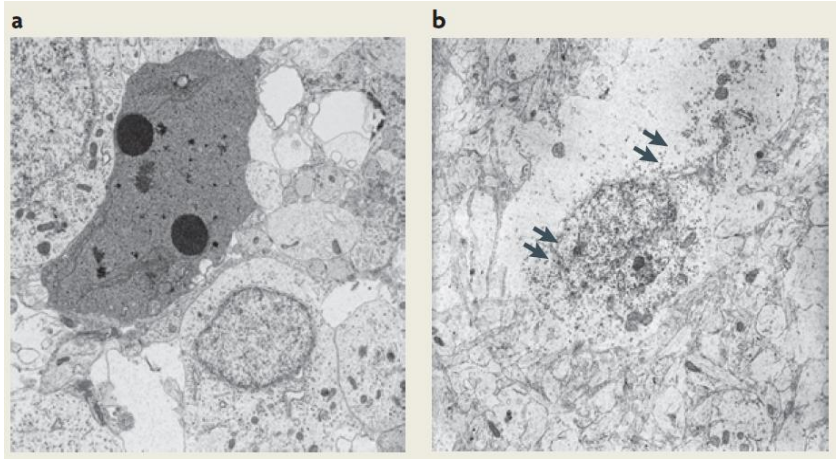
Morphological definition of cell death

Apoptosis



Necrosis

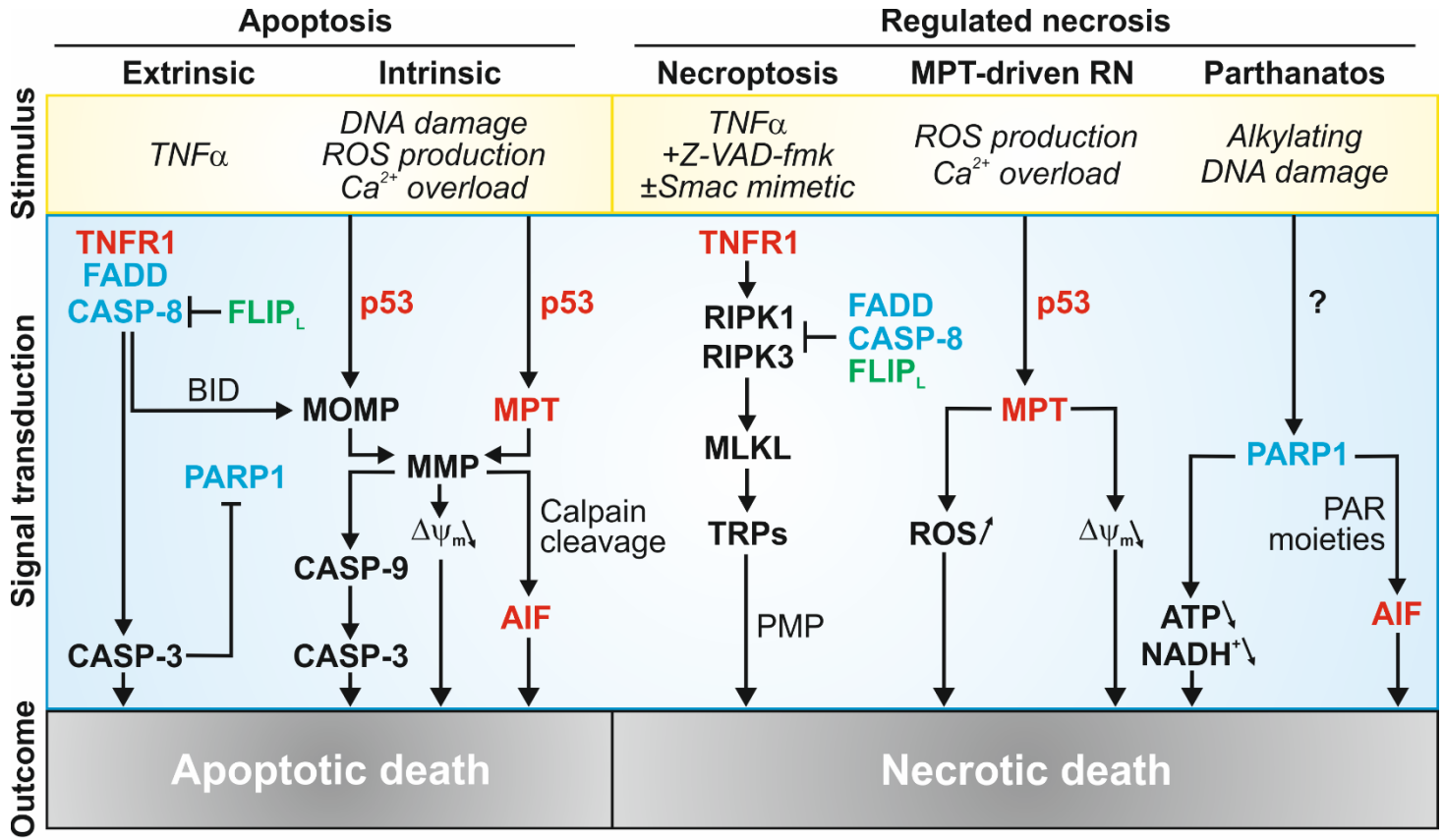
Apoptosis



Necrosis

Outdated and potentially misleading

Biochemical definition of cell death

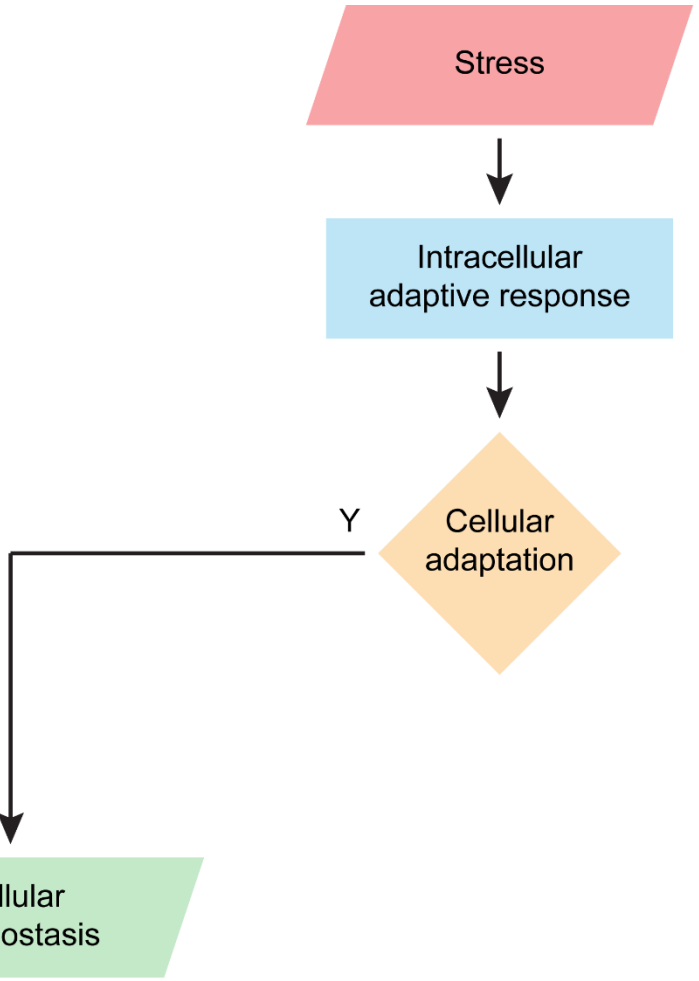


Based on measurable phenomena and pharmacological/genetic interventions

Molecular mechanisms of cell death: recommendations of the Nomenclature Committee on Cell Death 2018

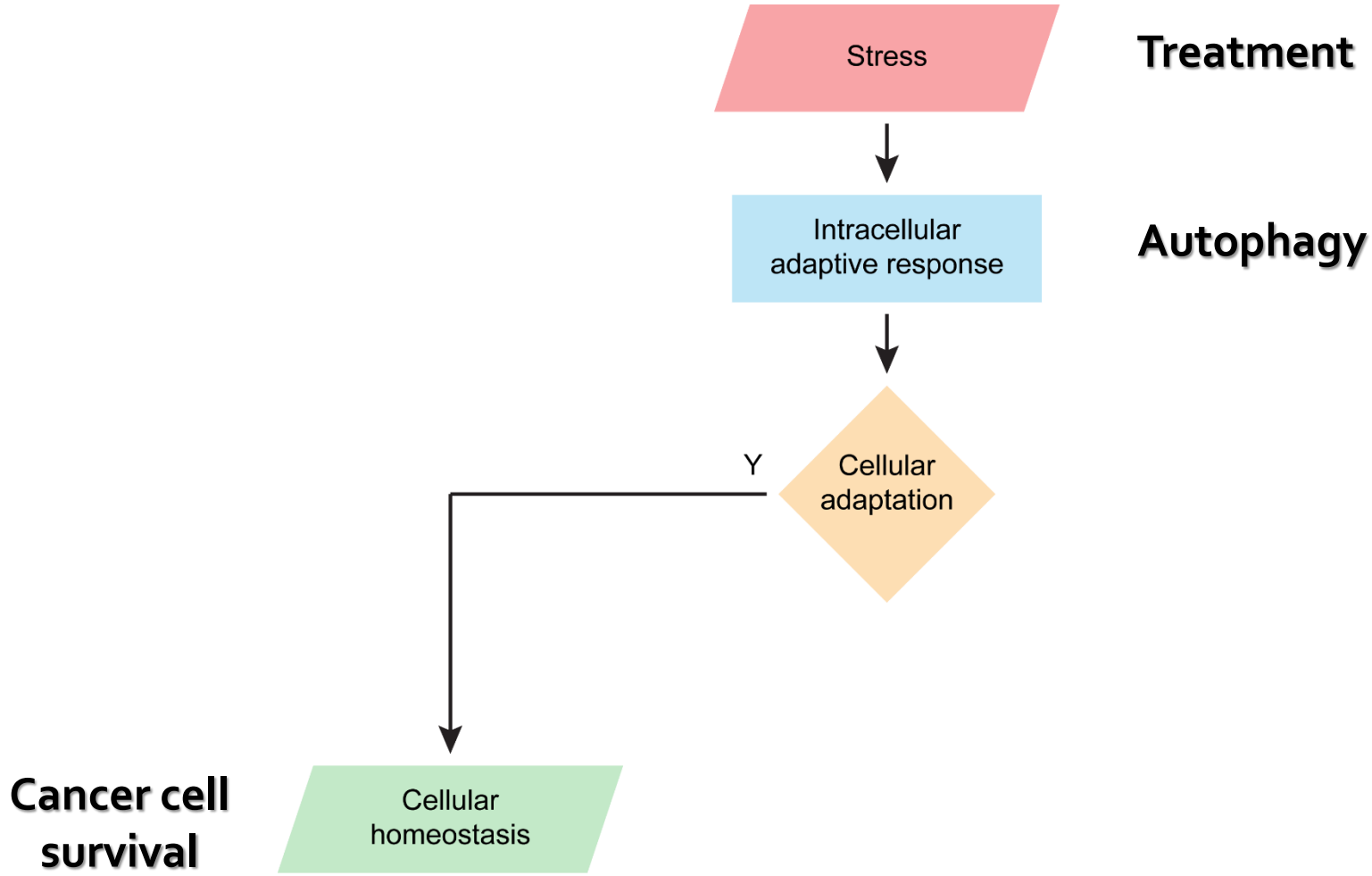
Lorenzo Galluzzi[1,2,3] · Ilio Vitale[4,5] · Stuart A. Aaronson[6] · John M. Abrams[7] · Dieter Adam[8] · Patrizia Agostinis[9] · Emad S. Alnemri[10] · Lucia Altucci[11] · Ivano Amelio[12] · David W. Andrews[13,14,15] · Margherita Annicchiarico-Petruzzelli[16] · Alexey V. Antonov[12] · Eli Arama[17] · Eric H. Baehrecke[18] · Nickolai A. Barlev[19] · Nicolas G. Bazan[20] · Francesca Bernassola[21] · Mathieu J. M. Bertrand[22,23] · Katiuscia Bianchi[24] · Mikhail V. Blagosklonny[25] · Klas Blomgren[26,27] · Christoph Borner[28,29] · Patricia Boya[30] · Catherine Brenner[31,32] · Michelangelo Campanella[4,5,33,34] · Eleonora Candi[16,21] · Didac Carmona-Gutierrez[35] · Francesco Cecconi[4,36,37] · Francis K.-M. Chan[38] · Navdeep S. Chandel[39] · Emily H. Cheng[40] · Jerry E. Chipuk[6] · John A. Cidlowski[41] · Aaron Ciechanover[42] · Gerald M. Cohen[43] · Marcus Conrad[44] · Juan R. Cubillos-Ruiz[2,45] · Peter E. Czabotar[46,47] · Vincenzo D'Angiolella[48] · Ted M. Dawson[49,50,51,52] · Valina L. Dawson[49,50,52,53] · Vincenzo De Laurenzi[54] · Ruggero De Maria[55] · Klaus-Michael Debatin[56] · Ralph J. DeBerardinis[57] · Mohanish Deshmukh[58] · Nicola Di Daniele[59] · Francesco Di Virgilio[60] · Vishva M. Dixit[61] · Scott J. Dixon[62] · Colin S. Duckett[63] · Brian D. Dynlacht[64,65] · Wafik S. El-Deiry[66,67] · John W. Elrod[68] · Gian Maria Fimia[69,70] · Simone Fulda[71,72,73] · Ana J. García-Sáez[74] · Abhishek D. Garg[9] · Carmen Garrido[75,76,77] · Evripidis Gavathiotis[78,79,80,81] · Pierre Golstein[82] · Eyal Gottlieb[42,83] · Douglas R. Green[84] · Lloyd A. Greene[85] · Hinrich Gronemeyer[86,87,88,89] · Atan Gross[90] · Gyorgy Hajnoczky[91] · J. Marie Hardwick[92] · Isaac S. Harris[93] · Michael O. Hengartner[94] · Claudio Hetz[95,96,97] · Hidenori Ichijo[98] · Marja Jäättelä[99] · Bertrand Joseph[100] · Philipp J. Jost[101] · Philippe P. Juin[102,103,104,105] · William J. Kaiser[106] · Michael Karin[107,108,109,110] · Thomas Kaufmann[111] · Oliver Kepp[3,112,113,114,115,116] · Adi Kimchi[117] · Richard N. Kitsis[79,80,81,118,119] · Daniel J. Klionsky[120,121] · Richard A. Knight[12] · Sharad Kumar[122] · Sam W. Lee[123] · John J. Lemasters[124,125] · Beth Levine[126,127,128] · Andreas Linkermann[129] · Stuart A. Lipton[130,131,132] · Richard A. Lockshin[133,134] · Carlos López-Otín[135] · Scott W. Lowe[136,137] · Tom Luedde[138] · Enrico Lugli[139,140] · Marion MacFarlane[12] · Frank Madeo[35,141] · Michal Malewicz[12] · Walter Malorni[142] · Gwenola Manic[4,5] · Jean-Christophe Marine[143,144] · Seamus J. Martin[145] · Jean-Claude Martinou[146] · Jan Paul Medema[147,148] · Patrick Mehlen[149,150,151,152,153,154] · Pascal Meier[155] · Sonia Melino[156] · Edward A. Miao[157,158,159] · Jeffery D. Molkentin[160] · Ute M. Moll[161] · Cristina Muñoz-Pinedo[162] · Shigekazu Nagata[163] · Gabriel Nuñez[164,165] · Andrew Oberst[166,167] · Moshe Oren[168] · Michael Overholtzer[169] · Michele Pagano[65,170,171] · Theocharis Panaretakis[172,173] · Manolis Pasparakis[174,175] · Josef M. Penninger[176] · David M. Pereira[177] · Shazib Pervaiz[178,179,180] · Marcus E. Peter[181,182] · Mauro Piacentini[4,69] · Paolo Pinton[60,183,184] · Jochen H.M. Prehn[185] · Hamsa Puthalakath[186] · Gabriel A. Rabinovich[187,188] · Markus Rehm[189,190] · Rosario Rizzuto[191] · Cecilia M.P. Rodrigues[192] · David C. Rubinsztein[193] · Thomas Rudel[194] · Kevin M. Ryan[83] · Emre Sayan[195] · Luca Scorrano[196,197] · Feng Shao[198] · Yufang Shi[199,200,201] · John Silke[47,202] · Hans-Uwe Simon[111] · Antonella Sistigu[55,203] · Brent R. Stockwell[204,205] · Andreas Strasser[46] · Gyorgy Szabadkai[191,206,207] · Stephen W.G. Tait[83] · Daolin Tang[208,209,210,211,212,213] · Nektarios Tavernarakis[214] · Andrew Thorburn[215] · Yoshihide Tsujimoto[216] · Boris Turk[217,218] · Tom Vanden Berghe[22,23] · Peter Vandenabeele[22,23] · Matthew G. Vander Heiden[219,220,221] · Andreas Villunger[222] · Herbert W. Virgin[223] · Karen H. Vousden[207] · Domagoj Vucic[224] · Erwin F. Wagner[225] · Henning Walczak[226] · David Wallach[227] · Ying Wang[228] · James A. Wells[229] · Will Wood[230] · Junying Yuan[93,231] · Zahra Zakeri[232] · Boris Zhivotovsky[100,233] · Laurence Zitvogel[112,234,235,236] · Gerry Melino[12,21] · Guido Kroemer[3,26,113,114,115,116,237]

General organization of stress responses



Galluzzi et al. – NRCMB 2018

General organization of stress responses



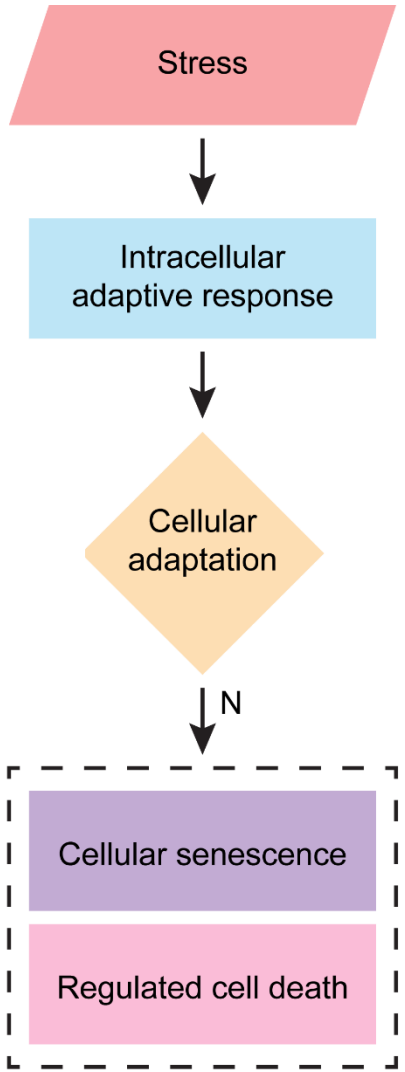
Galluzzi et al. – NRCMB 2018

Autophagy

An evolutionary old mechanism of adaptation that relies on

the lysosomal degradation of cytoplasmic entities

General organization of stress responses



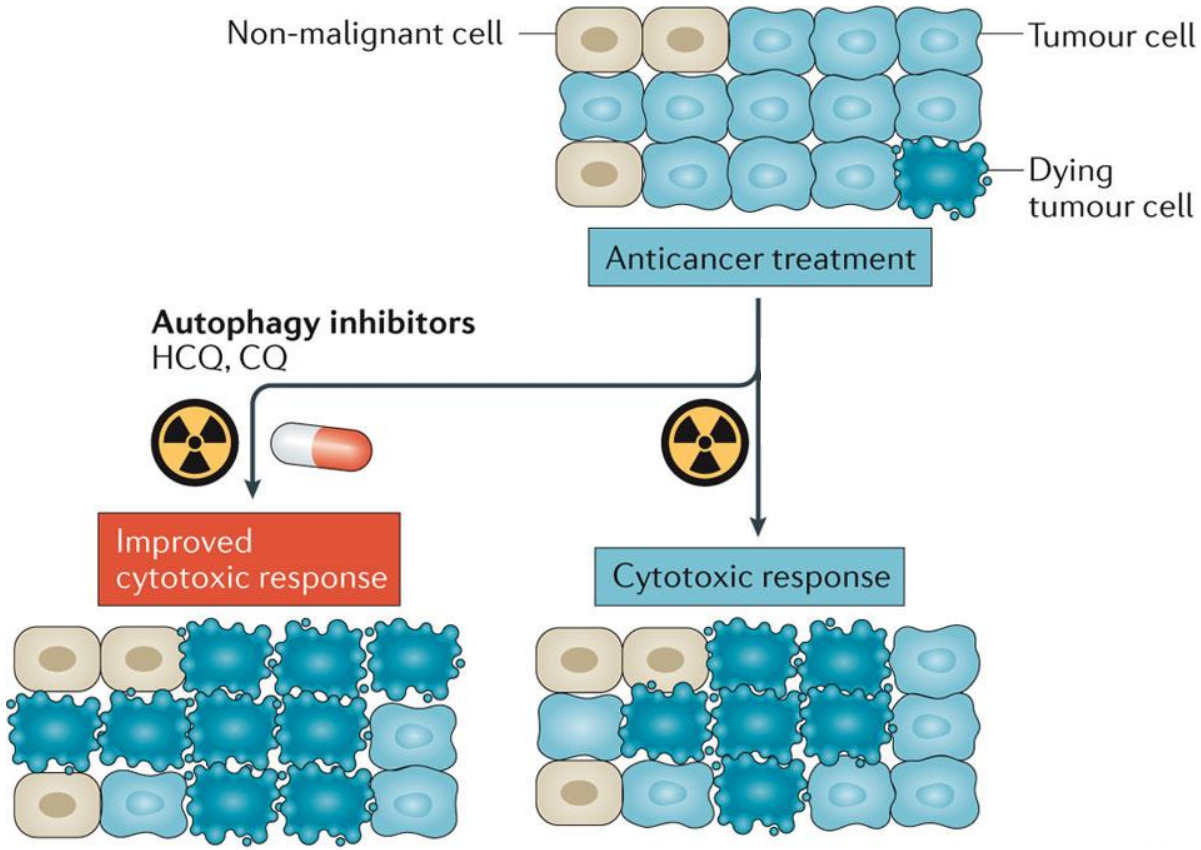
Treatment

~~**Autophagy**~~

Cancer cell death

Galluzzi et al. – NRCMB 2018

Classical approach



Galluzzi et al. – Nat Rev Clin Oncol 2017

Inhibition of autophagy for cancer therapy

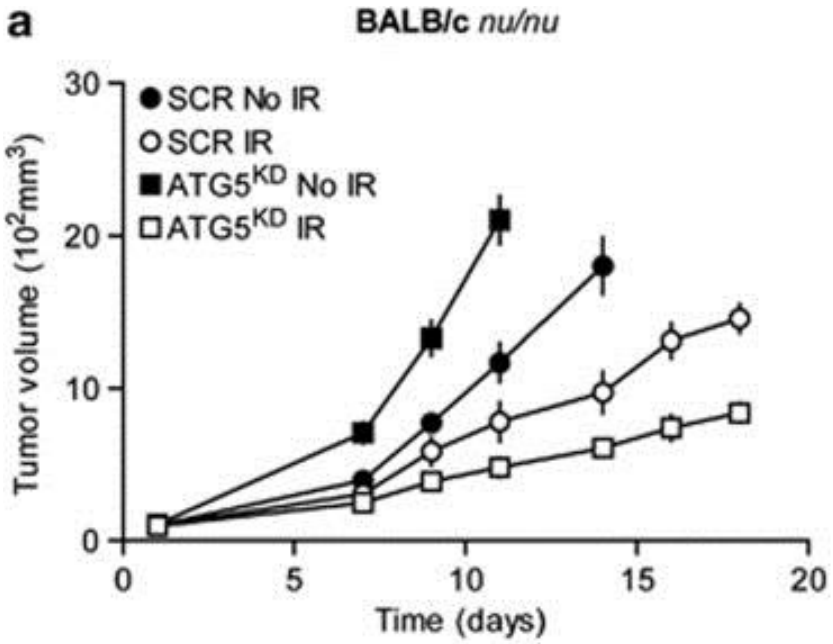


Table 1 | **Selected examples of the effects of autophagy modulation on the efficacy of anticancer therapy in mouse models**

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

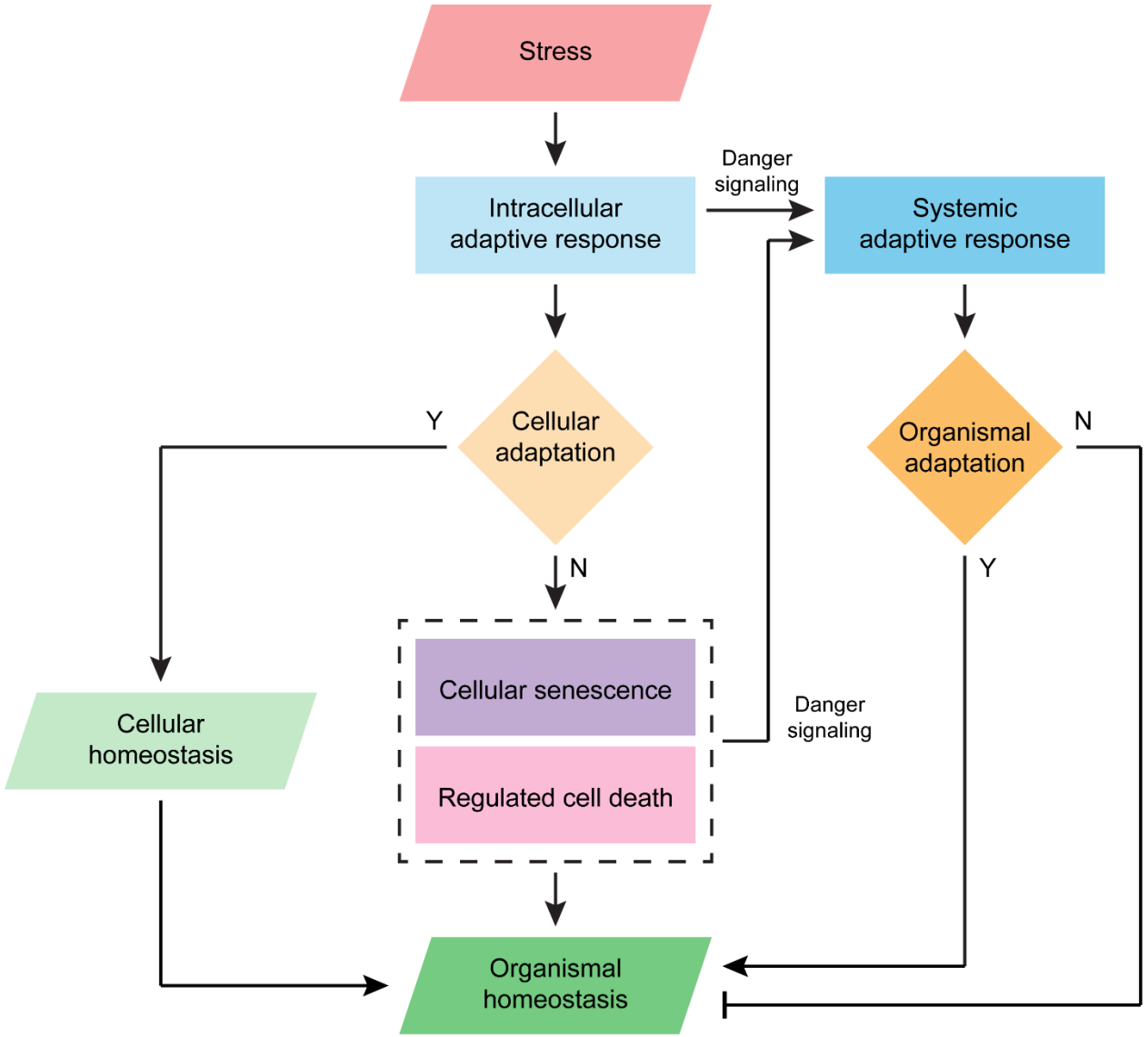
CI, confidence interval; NSCLC, non-small-cell lung cancer; RR, relative risk.

Galluzzi et al. – Nat Rev Clin Oncol 2017

Quantity

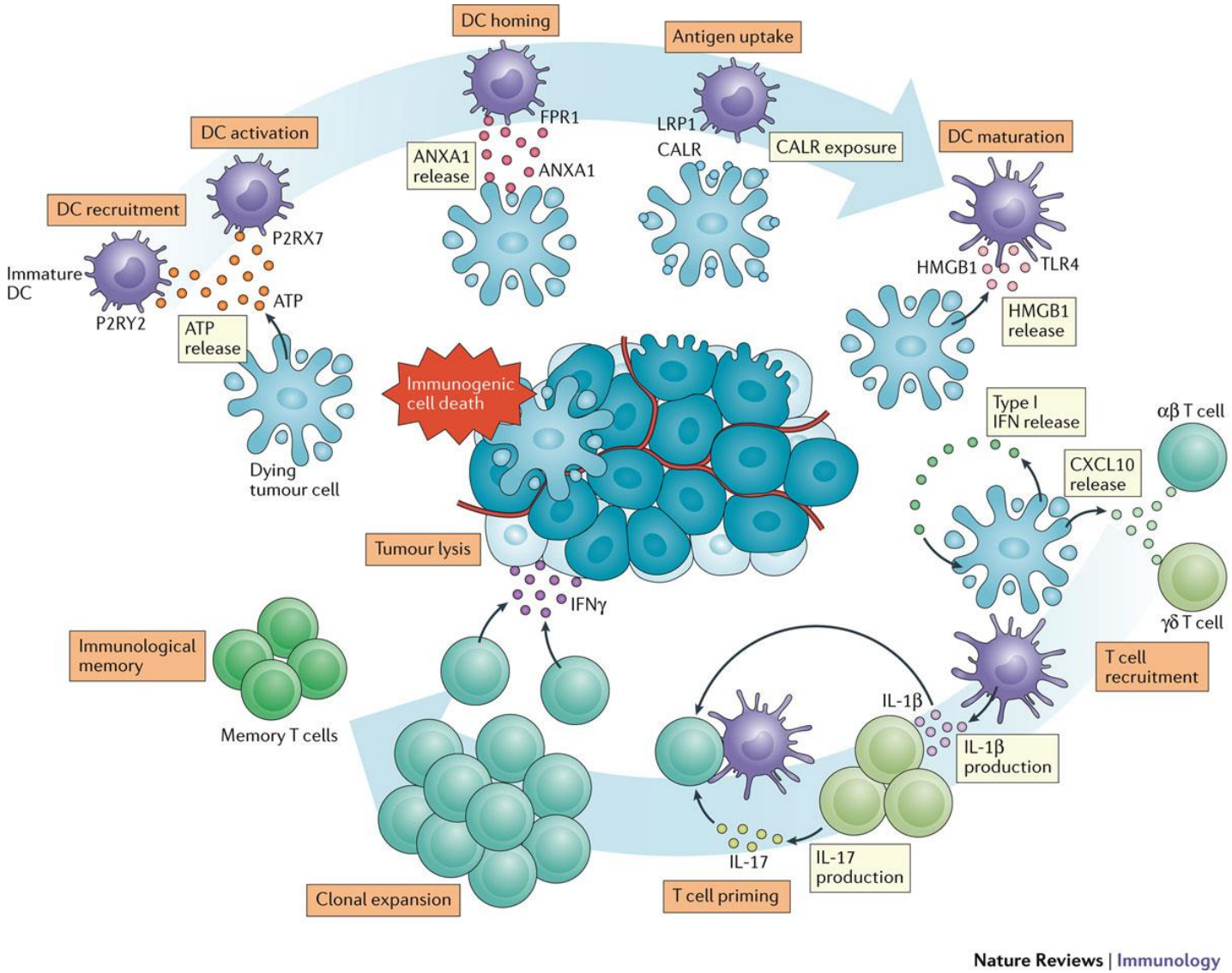
Quantity *versus* quality

Cellular adaptation and organismal homeostasis



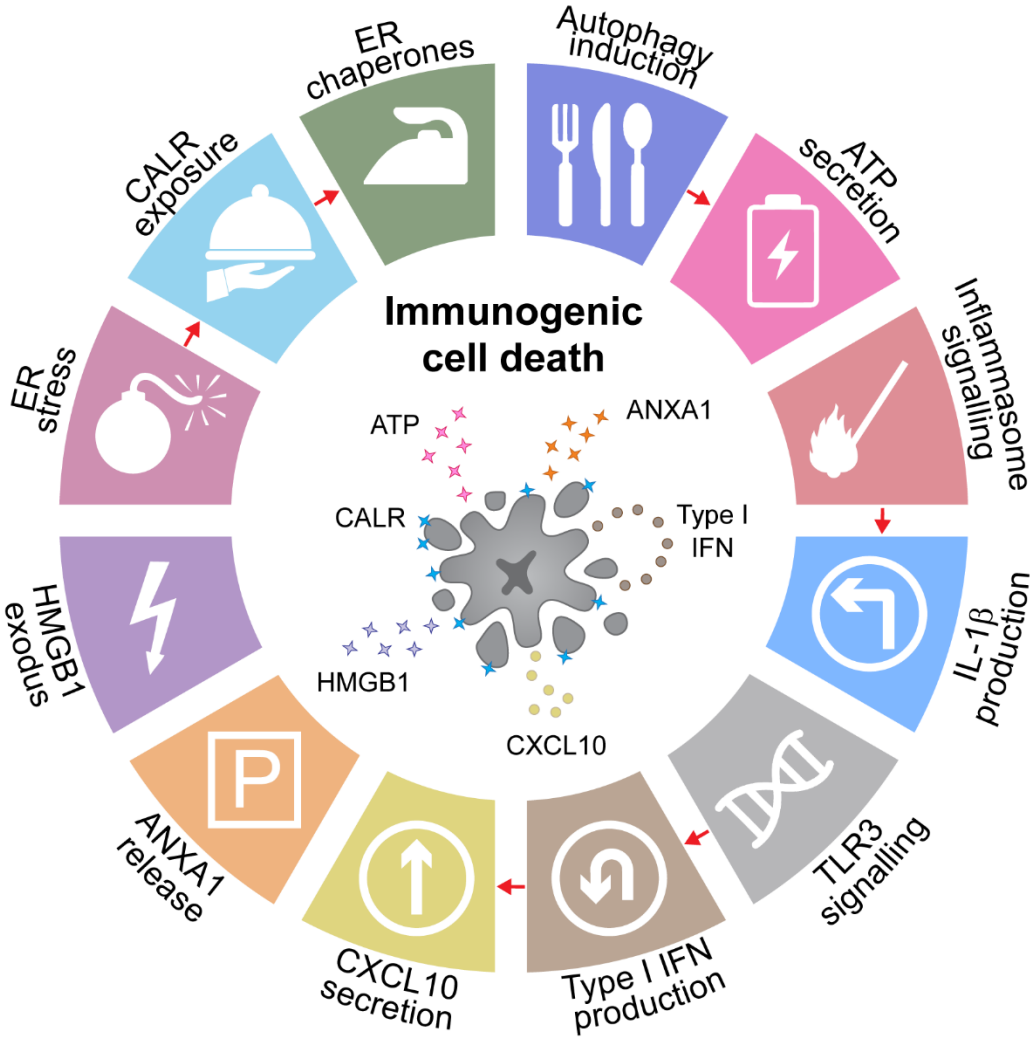
Galluzzi et al. – NRCMB 2018

Immunogenic cell death



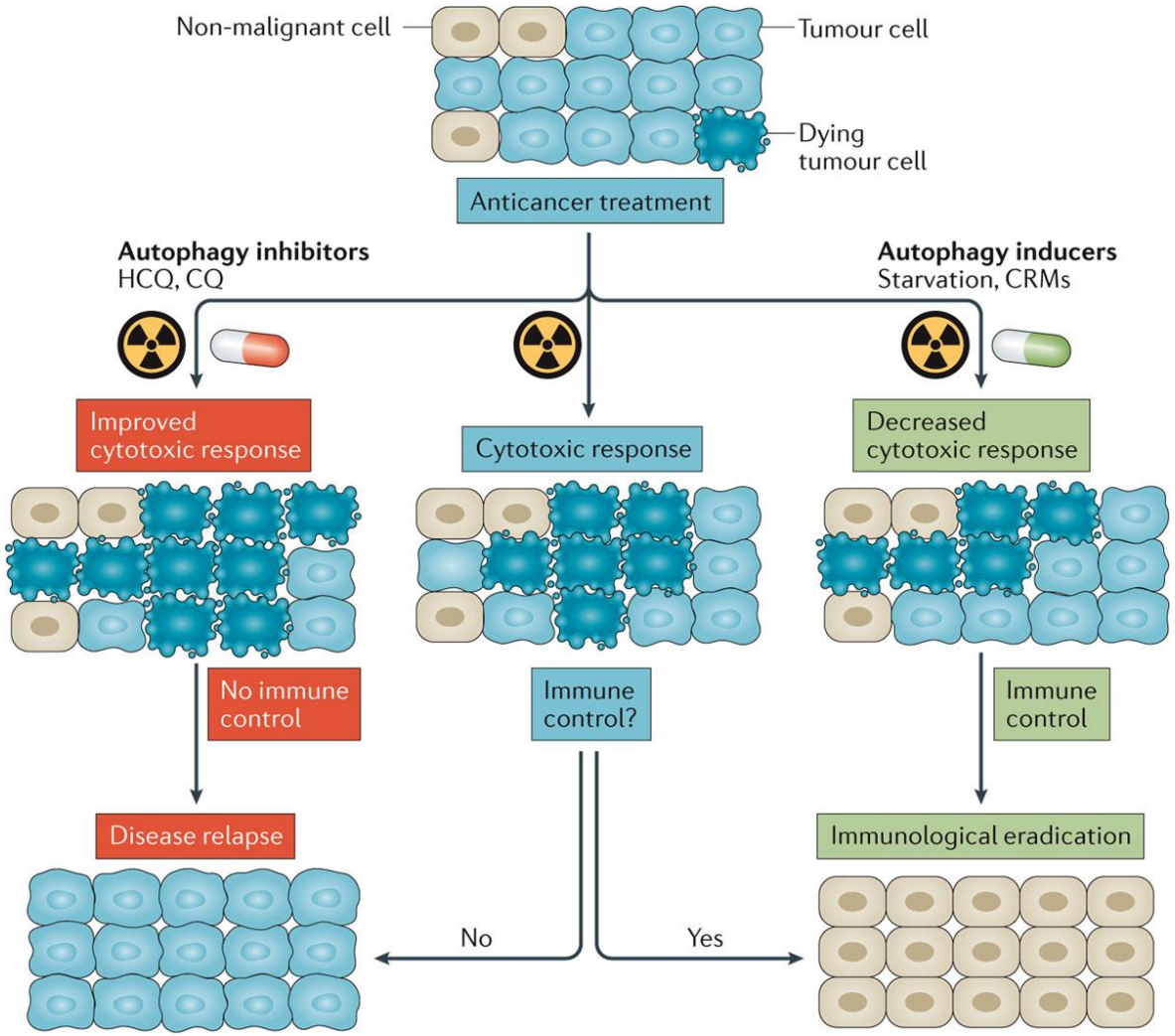
Galluzzi et al. - Nat Rev Immunol 2017

Mechanisms of ICD



Galluzzi et al. - Nat Rev Immunol 2017

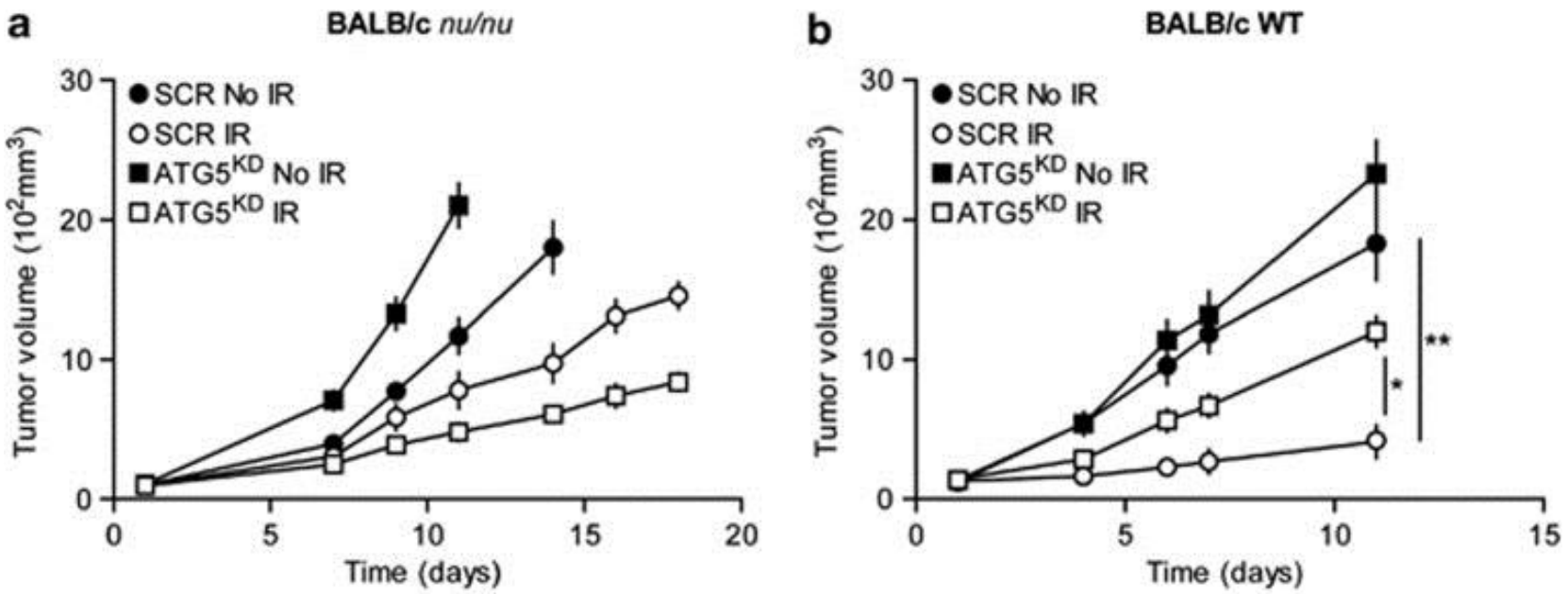
Alternative approach



Galluzzi et al. – Nat Rev Clin Oncol 2017

Autophagy activation for cancer therapy

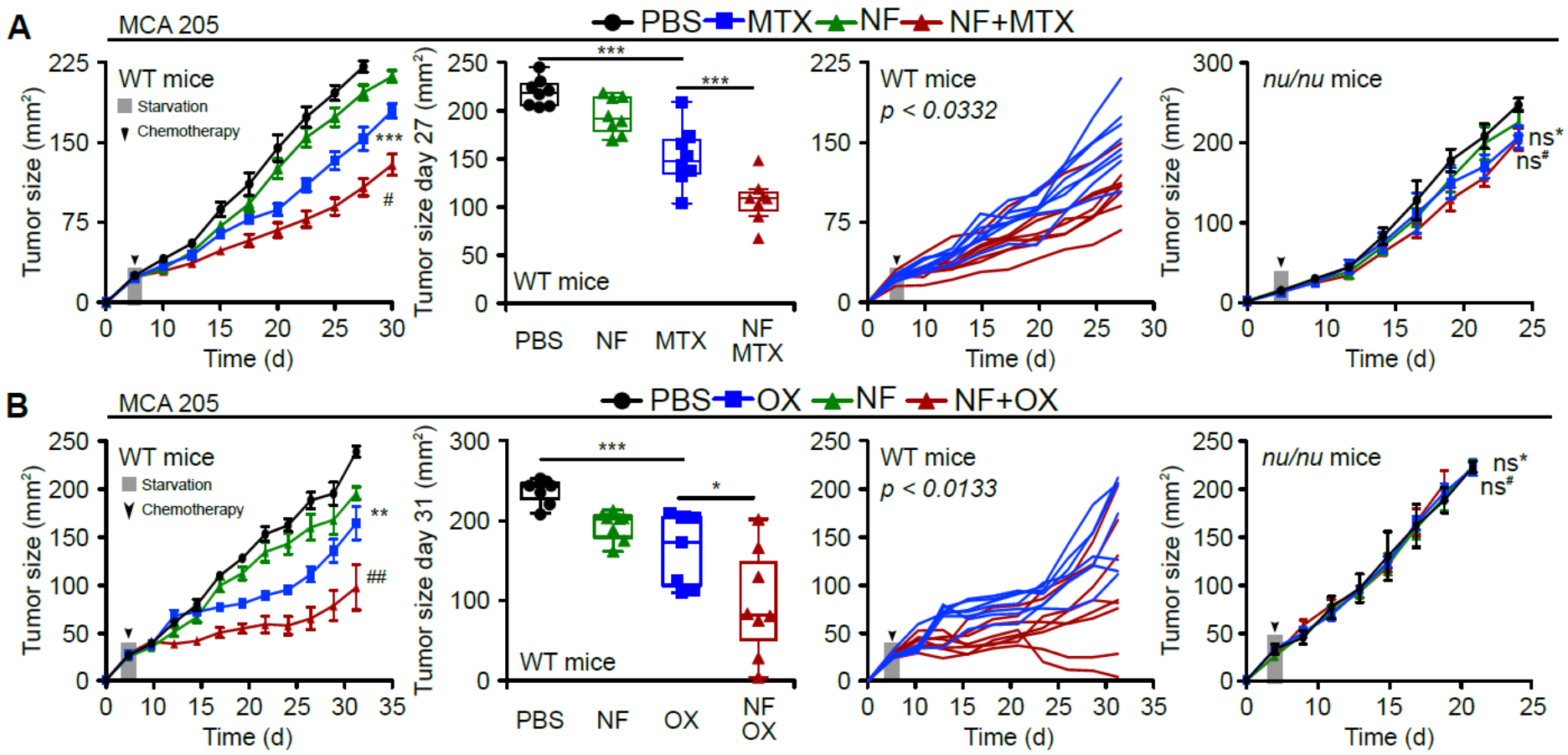
Detrimental effects of autophagy inhibition



Ko et al. – CDD 2014

Activation of autophagy for cancer therapy

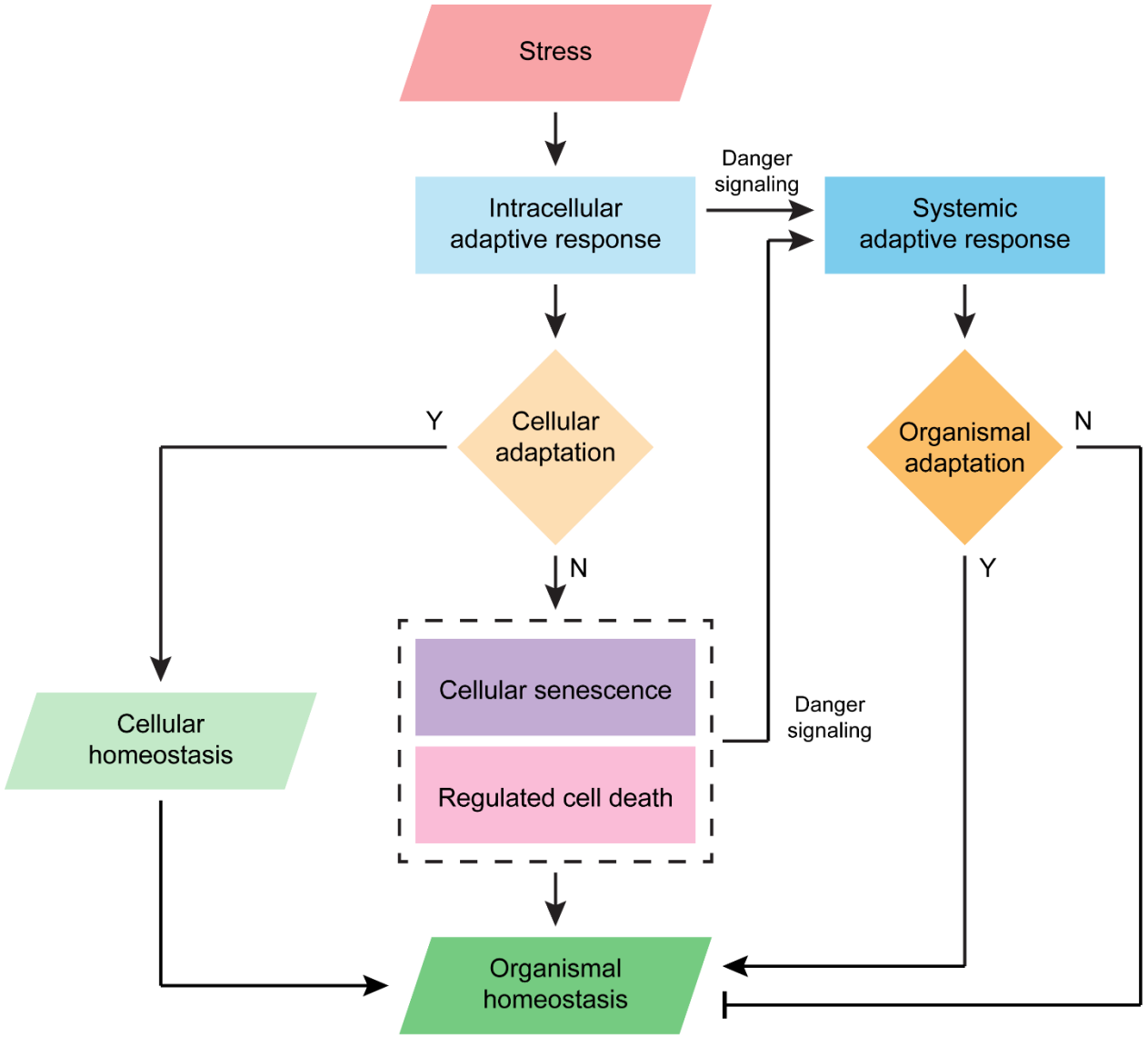
Anticancer effects of caloric restriction



...depend on the immune system

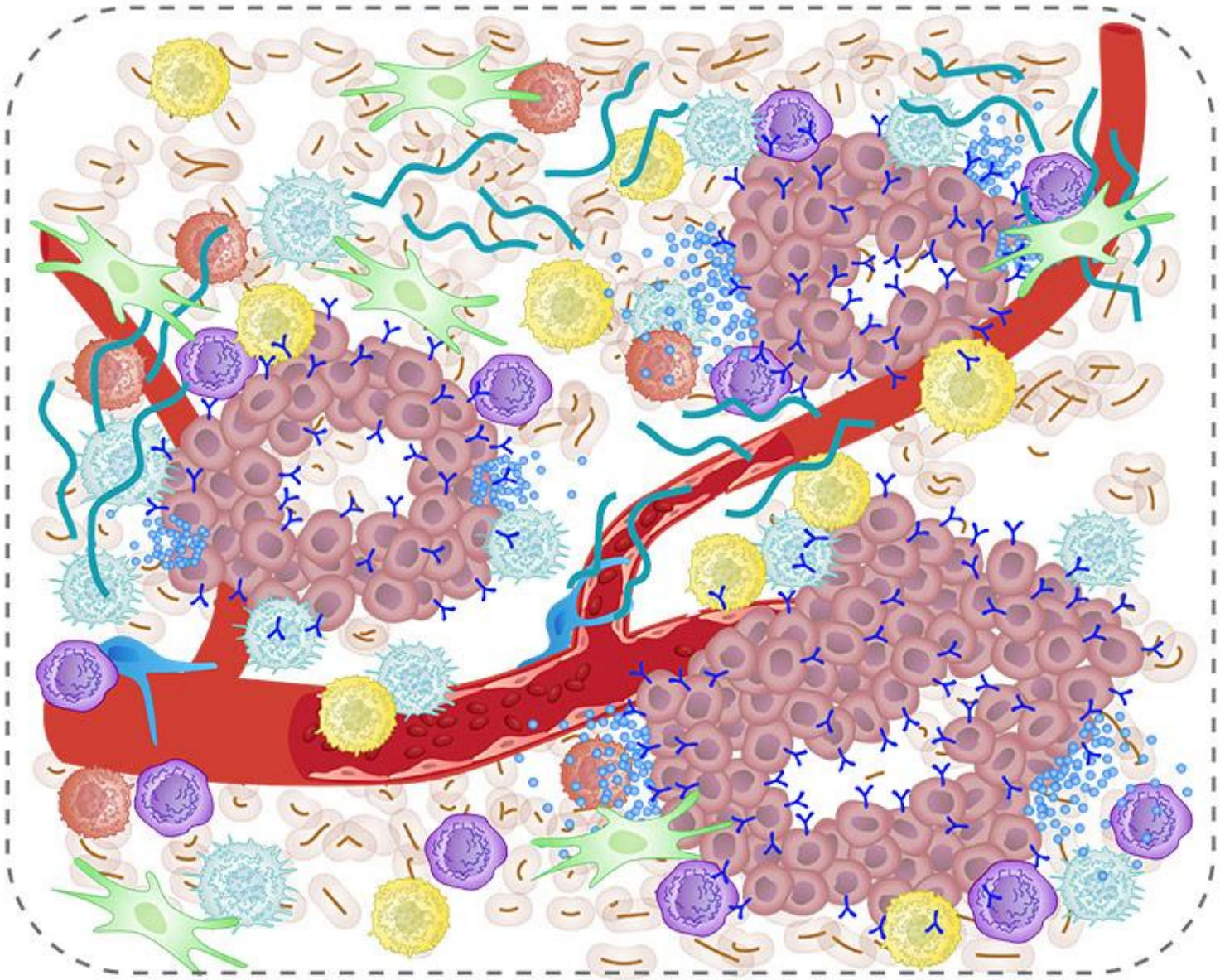
Pietrocola et al. – Cancer Cell 2016

(Immunogenic) cell death in context



Galluzzi et al. – NRCMB 2018

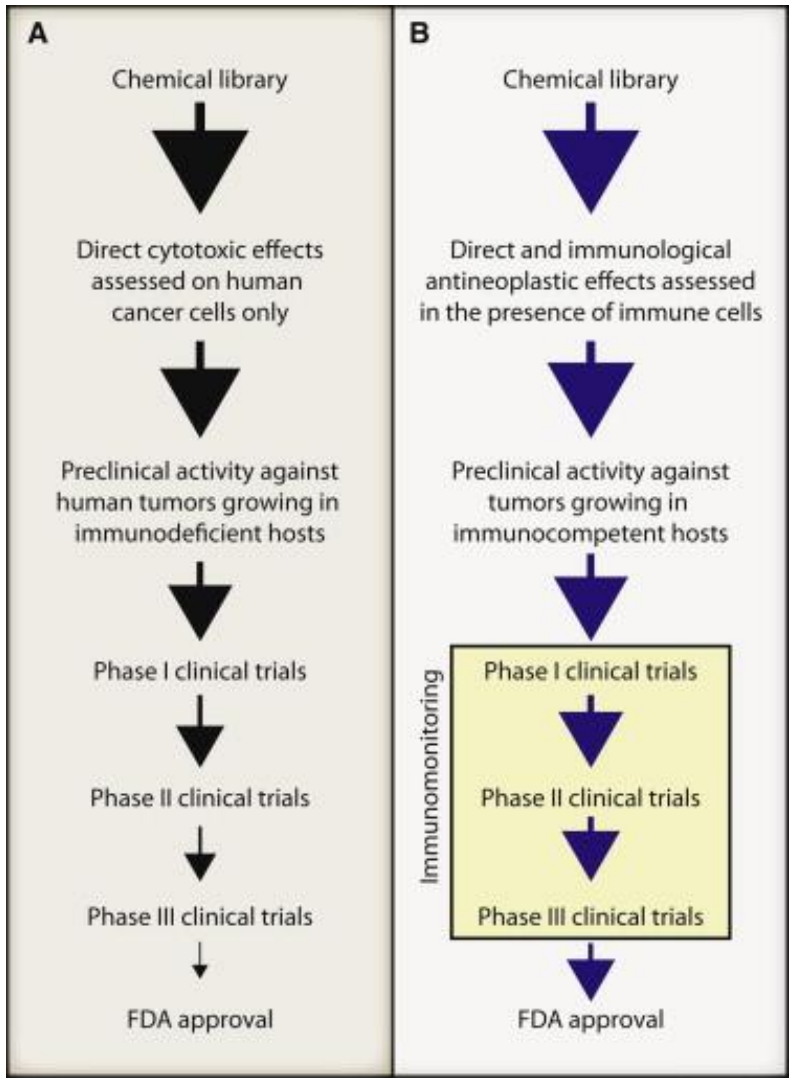
Not as simple as it looks like



Implications for drug development

Self/Non-self theory

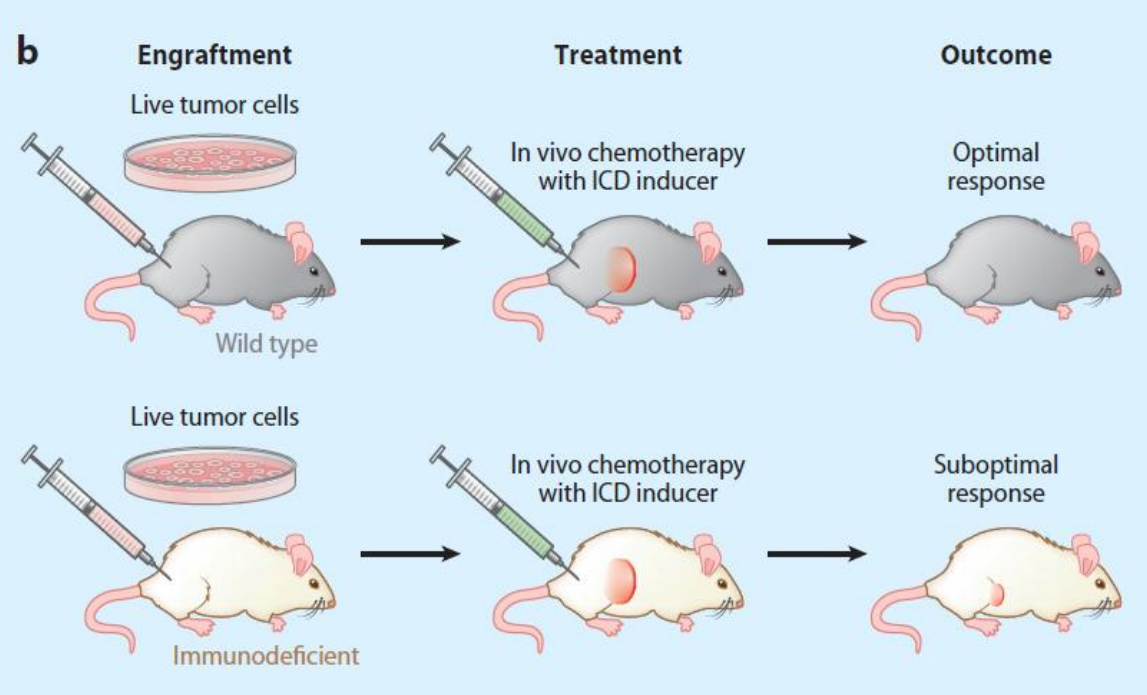
Cancer-centric view



Galluzzi et al. – Immunity 2013

Models for ICD studies

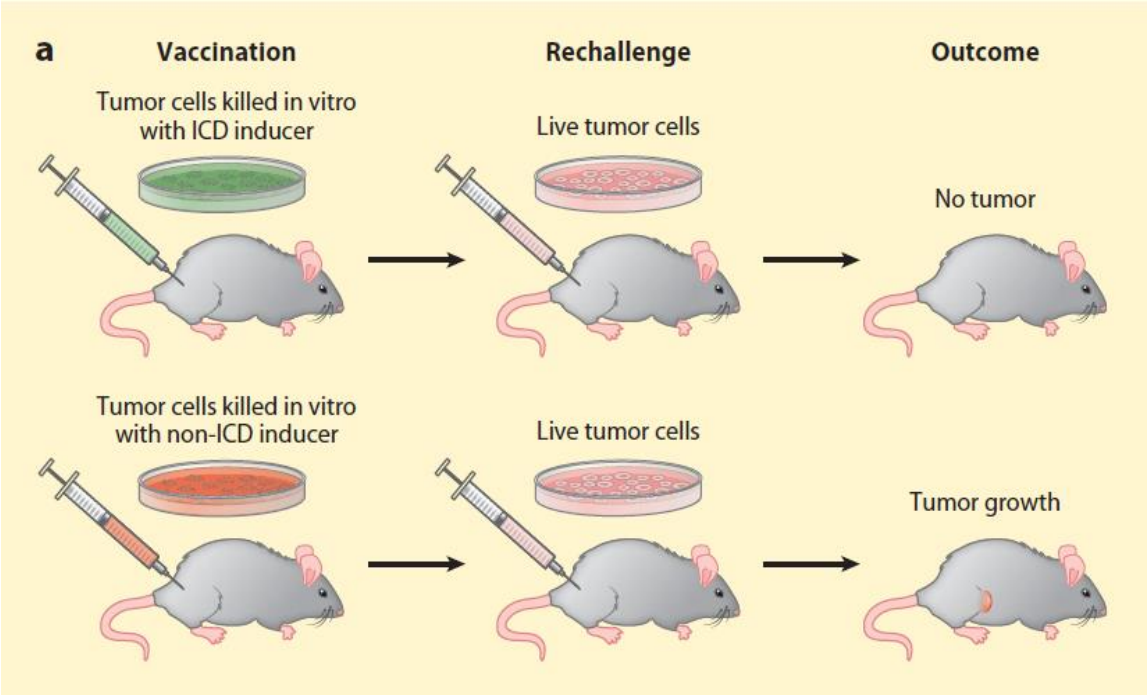
Tumor growth experiments



Kroemer, Galluzzi et al. – Annu Rev Immunol 2013

Models for ICD studies

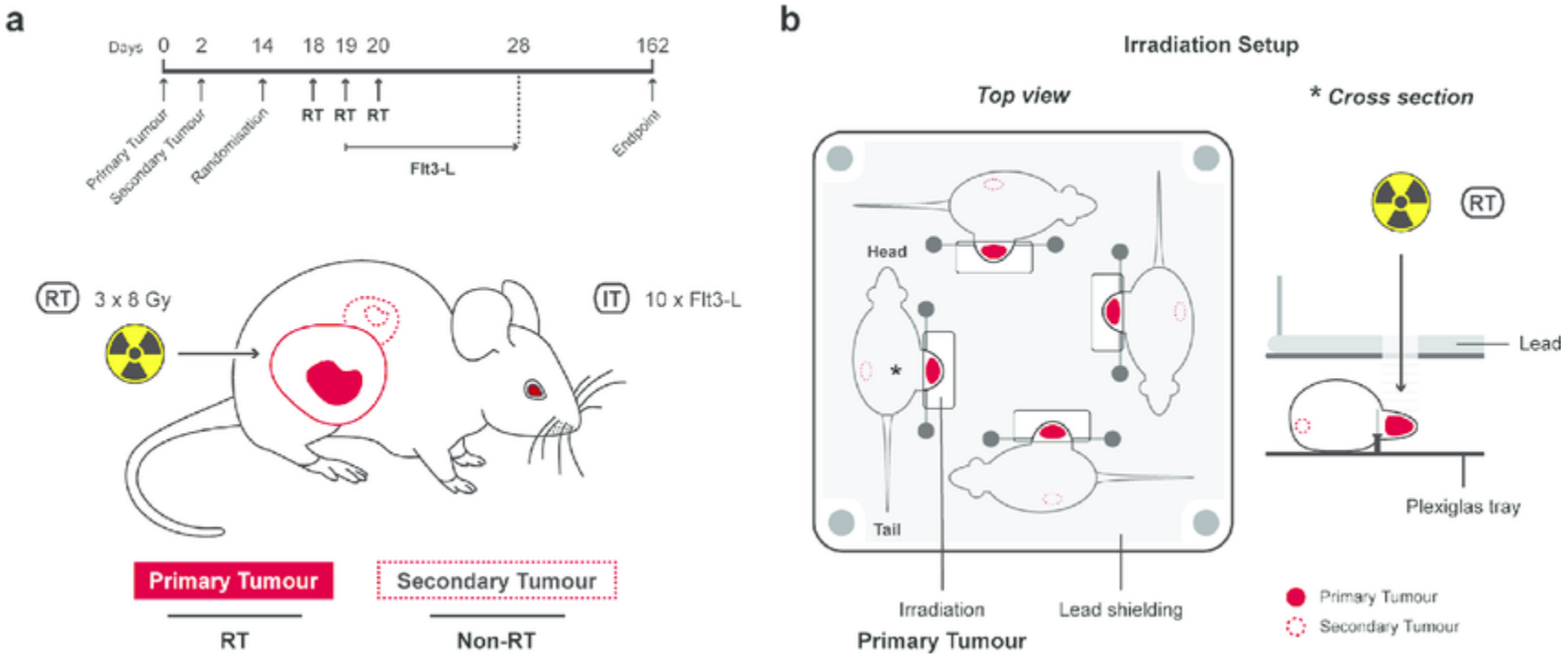
Vaccination experiments



Kroemer, Galluzzi et al. – Annu Rev Immunol 2013

Models for ICD studies

The abscopal effect



Habets et al. – PLoS One 2016

The quantity-quality conundrum

A lot of cell death

Immunogenic cell death

"Size matters not. Look at me. Judge me by my size do you?" - Yoda

Acknowledgements

The Galluzzi Lab

Taka Yamazaki

Aitziber Buqué

Marissa Friedman

Jonathan Chen

The Demaria Lab

Sandra Demaria

Claire Vanpouille-Box

Karsten Pilones

Nils Rudqvist

Erik Wennerberg

Claire Lhuillier

Selina Chen-Kiang

John Ng

Olivier Elemento

Silvia C. Formenti

Paolo Pinton

Frank Madeo

Laurence Zitvogel

Guido Kroemer

Ilio Vitale

Chema Bravo-San Pedro