

DCC-3116: A Selective ULK Kinase Inhibitor

Potential First-in-Class
Autophagy Inhibitor to
Treat Mutant RAS Cancers

June 18, 2019

Disclaimer

Disclaimer

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Welcome

Key Opinion Leader

*Channing Der, Ph.D., Sarah Graham Kenan Distinguished Professor,
Department of Pharmacology, UNC School of Medicine*

Company Management

- *Steve Hoerter, President & Chief Executive Officer*
- *Daniel Flynn, Ph.D., EVP, Chief Scientific Officer & Founder*
- *Tucker Kelly, EVP & Chief Financial Officer*
- *Jen Robinson, Vice President, Investor Relations*

Agenda

- **Introduction**

Steve Hoerter, President & CEO

- **Autophagy & Mutant RAS Cancers**

*Channing Der, Ph.D., Sarah Graham Kenan Distinguished Professor,
Department of Pharmacology, UNC School of Medicine*

- **ULK Kinase Inhibitors & Autophagy**

Daniel Flynn, Ph.D., EVP, Chief Scientific Officer & Founder

- **Closing Remarks & Q & A**

Steve Hoerter, President & CEO

Setting the Stage for Building Long-Term Value

1

Deliver on Ripretinib

- Secure approval and launch in ≥ 4 L GIST
- Rapidly progress INTRIGUE in 2L GIST

2

Advance Clinical Programs

- Drive to initial clinical data for POC
- Accelerate path to pivotal trials

3

Invest in Next Research Wave

- Progress DCC-3116 to IND
- Focus on next wave of targets

Strong Clinical Stage Oncology Pipeline Of Novel Kinase Inhibitors

	PRE CLINICAL	PHASE 1	PHASE 1B/2	PHASE 3	COMMERCIAL RIGHTS
Ripretinib: Broad Spectrum Inhibitor of KIT & PDGFRα					
INVICTUS (≥4L GIST ¹)					decīphera*
INTRIGUE (2L GIST)					
GIST (2L, 3L, ≥4L)					
Other Solid Tumors ²					
Rebastinib: Selective Inhibitor of TIE2					
Solid Tumors in Combination with Paclitaxel (includes breast, ovarian & endometrial cancers)					decīphera
Solid Tumors in Combination with Carboplatin (includes mesothelioma, ovarian & breast cancers)					
DCC-3014: Selective Inhibitor of CSF1R					
Tenosynovial Giant Cell Tumors (TGCT)					decīphera
Other Solid Tumors					
DCC-3116: Selective Inhibitor of ULK					
Autophagy Inhibitor for Targeting Mutant RAS Cancers					decīphera
Additional Programs					
Immunokinase (undisclosed target)					decīphera

Significant 2019 Milestones Across the Pipeline

Ripretinib

- INVICTUS ($\geq 4^{\text{th}}$ Line GIST: Pivotal Phase 3 Results (Expected Mid-2019))
- Phase 1 Expansion Data (2H 2019)

Rebastinib

- ✓ Phase 1b/2 Carboplatin Combination Initiated (1H 2019)
- ✓ Part 1 of the Phase 1b/2 Paclitaxel Combination Completed Enrollment (1H 2019)
- Part 1 of the Phase 1b/2 Paclitaxel Combination Data (2H 2019)

DCC-3014

- ✓ Phase 1 Dose Escalation Presentation (1H 2019)
- Phase 1 Escalation Data Update (2H 2019)

Discovery Platform

- ✓ Select Clinical Candidate Targeting ULK, Potential First-in-Class Autophagy Inhibitor to Treat mRAS Cancers (1H 2019)
- ✓ Initiate IND-enabling Studies (1H 2019)

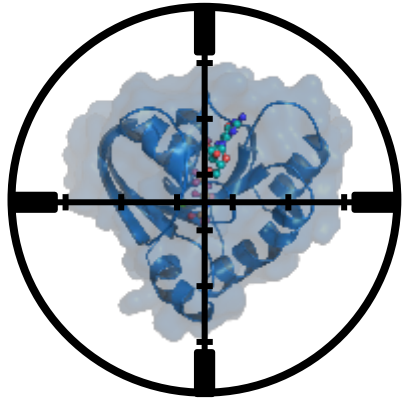


Channing Der, Ph.D.

*Sarah Graham Kenan Distinguished
Professor, Department of Pharmacology,
UNC School of Medicine*

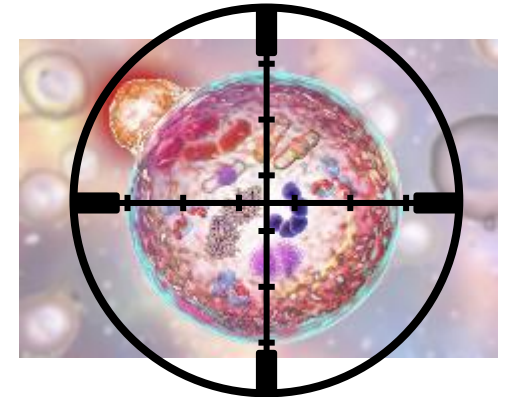
Autophagy & Mutant RAS Cancers

Deciphera Pharmaceuticals
June 18, 2019



KRAS
oncoprotein

Exploiting autophagy for the
treatment of RAS-mutant cancers



Autophagy

Key points

- ‘Undruggable’ RAS-mutant cancers: druggable after all?
- Autophagy: the Achilles’ heel of RAS-mutant cancers?
- Inhibitors of the ERK MAPK cascade – rendering KRAS-mutant cancers addicted to autophagy
- Combination ERK MAPK and autophagy inhibition: a pan-RAS therapy?
- Autophagy inhibition anti-tumor activity is due to targeting tumor cells and the tumor microenvironment
- ULK inhibitors: a more selective autophagy inhibitor?

RAS mutations are associated with the major causes of cancer deaths in the US

RAS mutation frequency

%	Cancer
97	Pancreatic ductal adenocarcinoma
52	Colorectal adenocarcinoma
43	Multiple myeloma
32	Lung adenocarcinoma
28	Skin cutaneous melanoma
25	Uterine corpus endometrioid carcinoma
13	Thyroid carcinoma
13	Uterine carcinosarcoma
12	Stomach adenocarcinoma
11	Acute myeloid leukaemia
11	Bladder urothelial carcinoma
8	Cervical adenocarcinoma
6	Head & neck squamous cell carcinoma

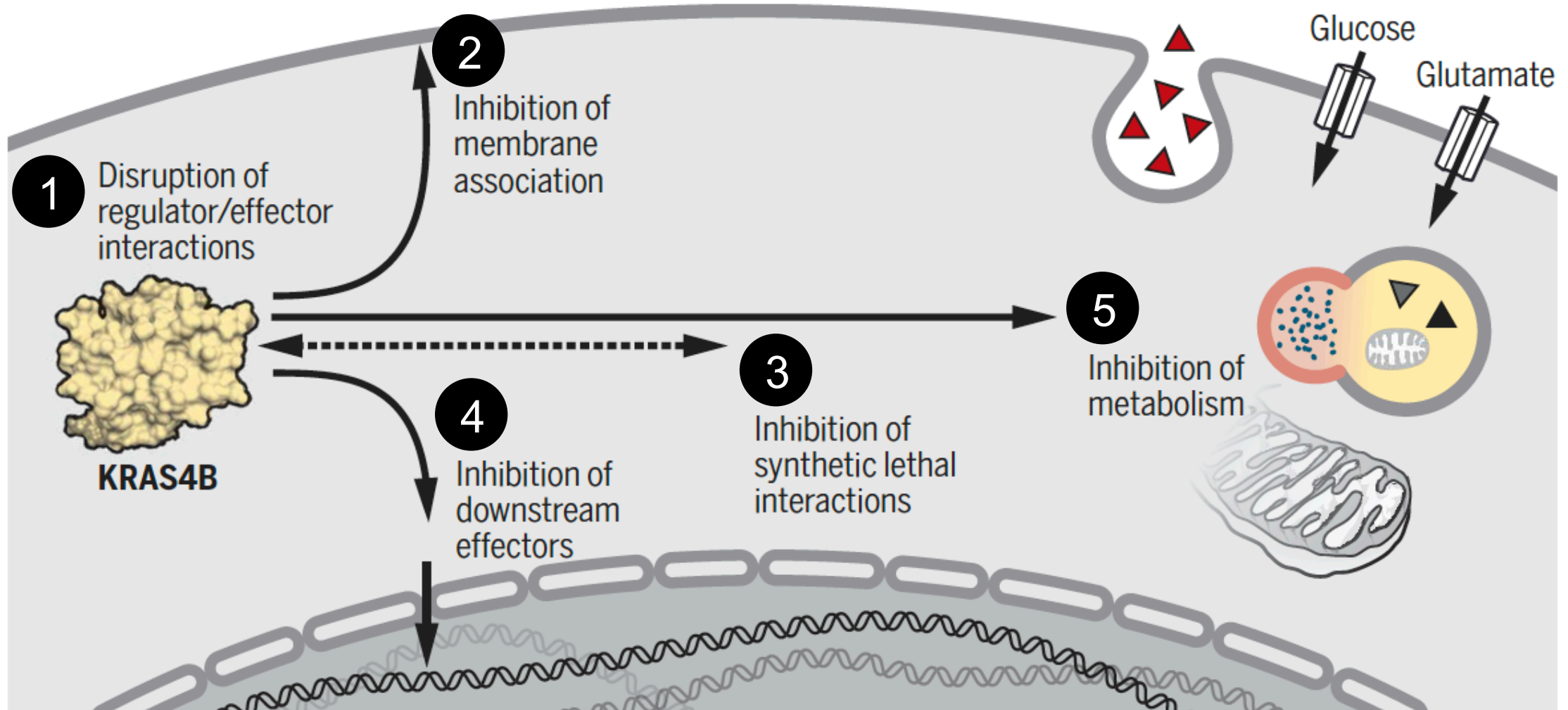
Cox et al (2014) Nat Rev Drug Discov 13:828

Estimated US cancer deaths

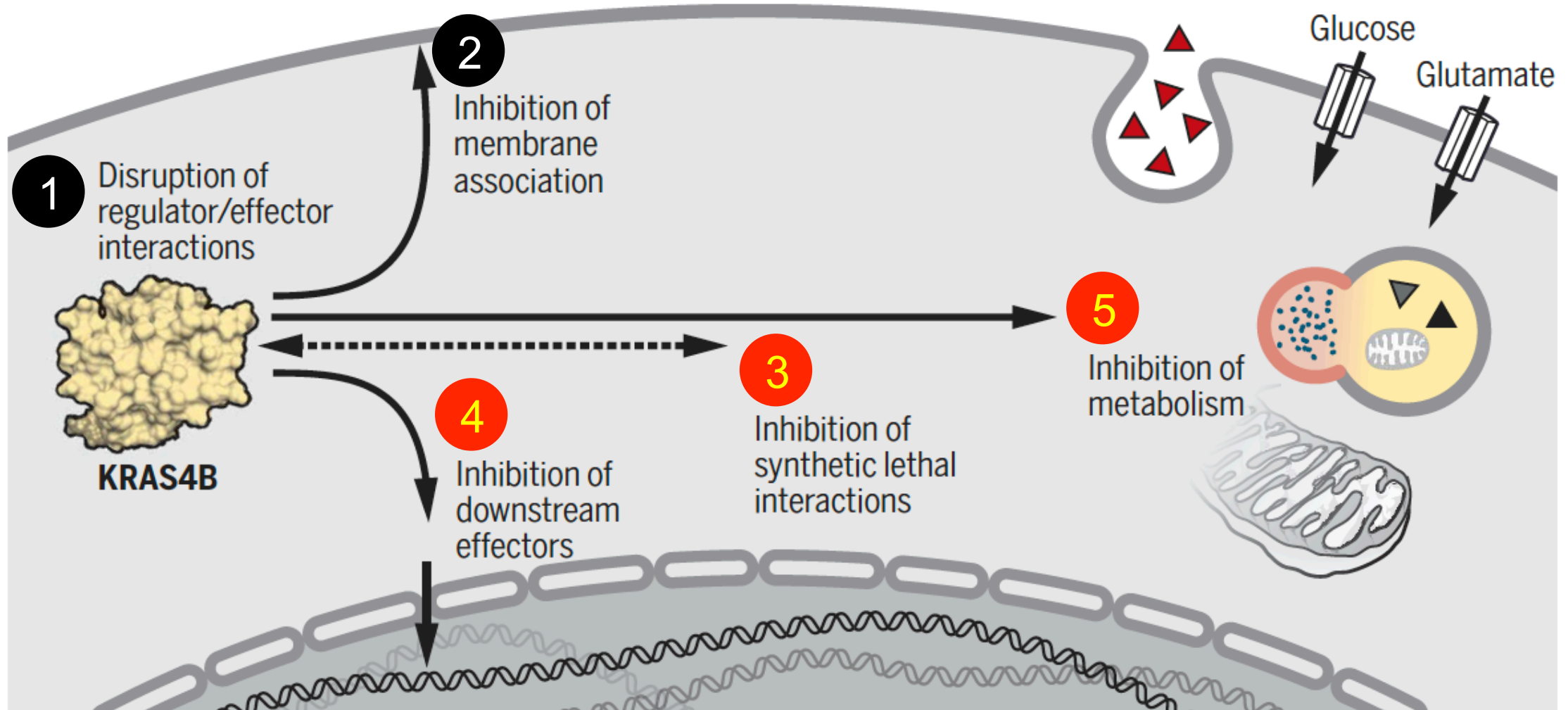
Site	Deaths	%
Lung & bronchus	142,670	23.5
Colon & rectum	51,020	8.4
Pancreas	45,750	7.5
Breast	42,260	6.9
Liver & intrahepatic bile duct	31,780	5.2
Prostate	31,620	5.2
Non-Hodgkin lymphoma	19,970	3.2
Brain & nervous system	17,760	2.9
Urinary bladder	17,670	2.9
Esophagus	16,080	2.6
Kidney & renal pelvis	14,770	2.4
Ovary	13,980	2.3
Myeloma	12,960	2.1

Siegel et al (2019) CA Cancer J Clin 69:10

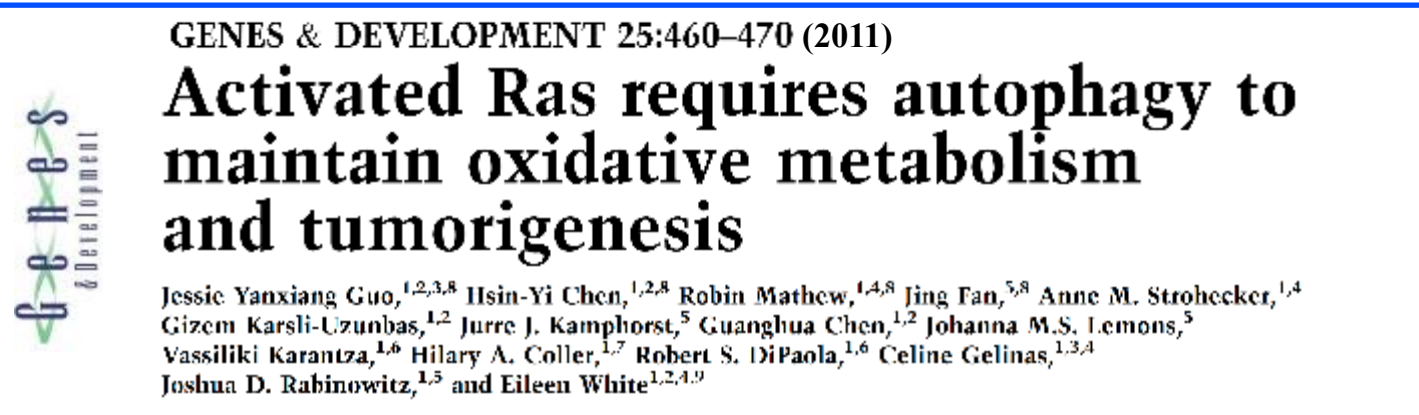
Current strategies for targeting RAS for cancer treatment



Pursuit of three strategies converge on autophagy



RAS mutant cancers are addicted to autophagy



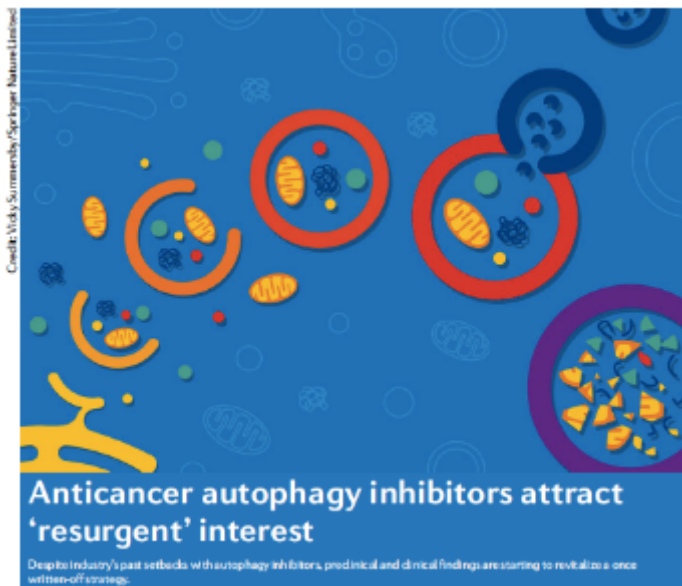
- Autophagy is elevated in RAS-mutant cancers
- Inhibition of autophagy impairs growth of RAS-mutant cancers
- ❖ Does mutant RAS cause increased autophagy? If yes, then how does RAS do this?

We were wrong – suppression of RAS
further elevated, rather than suppressed,
autophagy!

We begin a four year journey to figure out why
and what this means.

Three studies independently establish the therapeutic potential of concurrent ERK MAPK and autophagy inhibition in RAS-mutant cancer

NEWS & ANALYSIS 408 | JUNE 2019 | VOLUME 18



NATURE REVIEWS | DRUG DISCOVERY

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ARTICLES

Combination of ERK and autophagy inhibition as a treatment approach for pancreatic cancer

Kirsten L. Bryant¹, Clint A. Stalnecker¹, Daniel Zeitouni¹, Jennifer E. Klomp¹, Sen Peng², Andrey P. Tikunov³, Venugopal Gunda⁴, Mariaelena Pierobon⁵, Andrew M. Waters¹, Samuel D. George¹, Garima Tomar¹, Björn Papke¹, G. Aaron Hobbs¹, Liang Yan⁶, Tikvah K. Hayes⁷, J. Nathaniel Diehl⁷, Gennifer D. Goode⁴, Nina V. Chaika⁴, Yingxue Wang⁸, Guo-Fang Zhang⁸, Agnieszka K. Witkiewicz⁹, Erik S. Knudsen¹⁰, Emanuel F. Petricoin III⁵, Pankaj K. Singh⁴, Jeffrey M. Macdonald³, Nhan L. Tran¹¹, Costas A. Lyssiotis¹², Haoqiang Ying⁶, Alec C. Kimmelman¹³, Adrienne D. Cox^{1,14,15} and Channing J. Der^{1,7,15*}

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LETTERS

Protective autophagy elicited by RAF→MEK→ERK inhibition suggests a treatment strategy for RAS-driven cancers

Conan G. Kinsey^{1,2}, Soledad A. Camolotto¹, Amelie M. Boespflug^{1,3,4}, Katrin P. Guillen¹, Mona Foth¹, Amanda Truong¹, Sophia S. Schuman¹, Jill E. Shea⁵, Michael T. Seipp⁵, Jeffrey T. Yap^{1,6}, Lance D. Burrell¹, David H. Lum¹, Jonathan R. Whisenant^{1,2}, G. Weldon Gilcrease III^{1,2}, Courtney C. Cavalieri^{1,7}, Kaitrin M. Rehbein¹, Stephanie L. Cutler¹, Kajsa E. Affolter^{1,8}, Alana L. Welm^{1,9}, Bryan E. Welm^{1,5}, Courtney L. Scaife^{1,5}, Eric L. Snyder^{1,8} and Martin McMahon^{1,10*}

4508–4517 | PNAS | March 5, 2019 | vol. 116 | no. 10

MAP kinase and autophagy pathways cooperate to maintain RAS mutant cancer cell survival

Chih-Shia Lee^a, Liam C. Lee^{a,1}, Tina L. Yuan^{b,2}, Sirisha Chakka^{c,3}, Christof Fellmann^{d,4}, Scott W. Lowe^{d,e,f}, Natasha J. Caplen^c, Frank McCormick^{b,g,5}, and Ji Luo^{a,5}

Chasing after ERK leads us to autophagy

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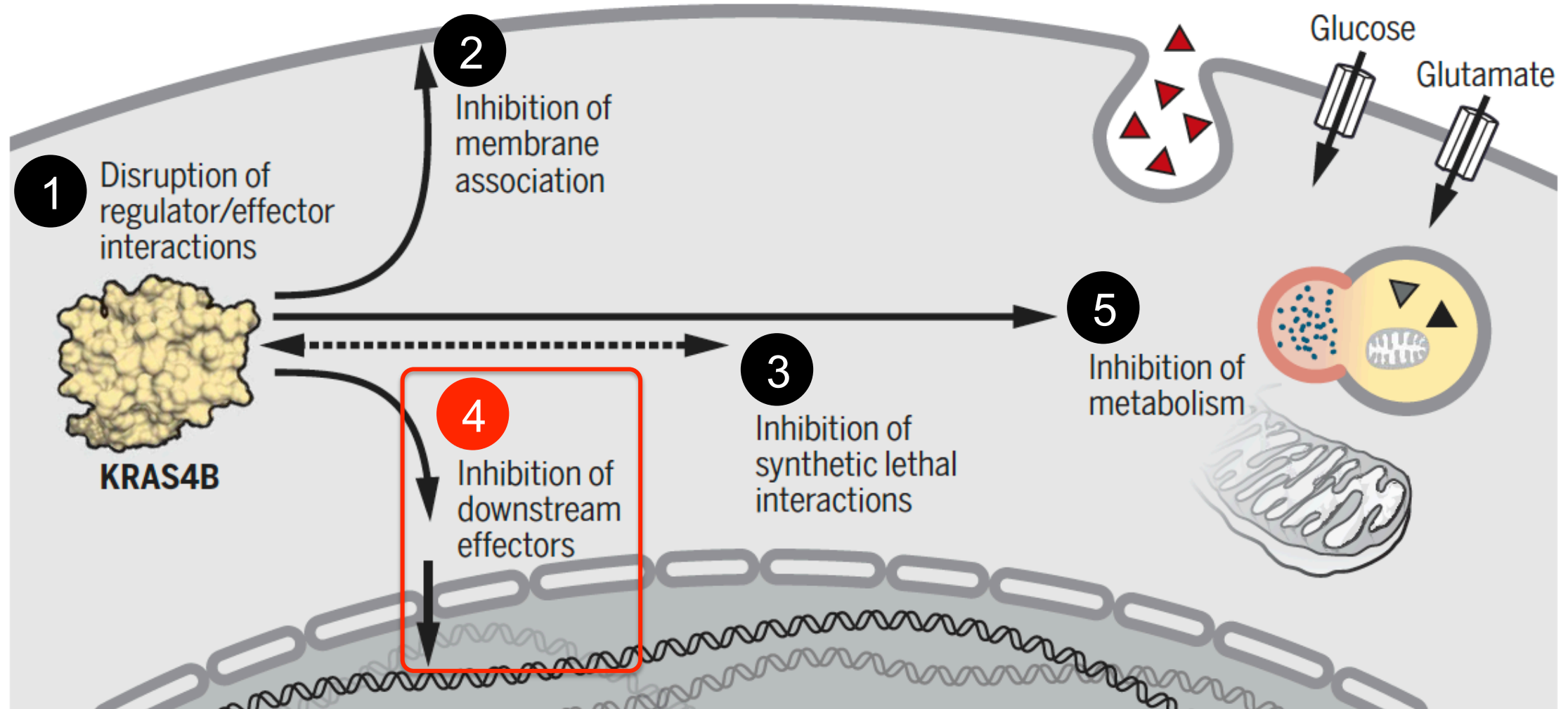
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ARTICLES

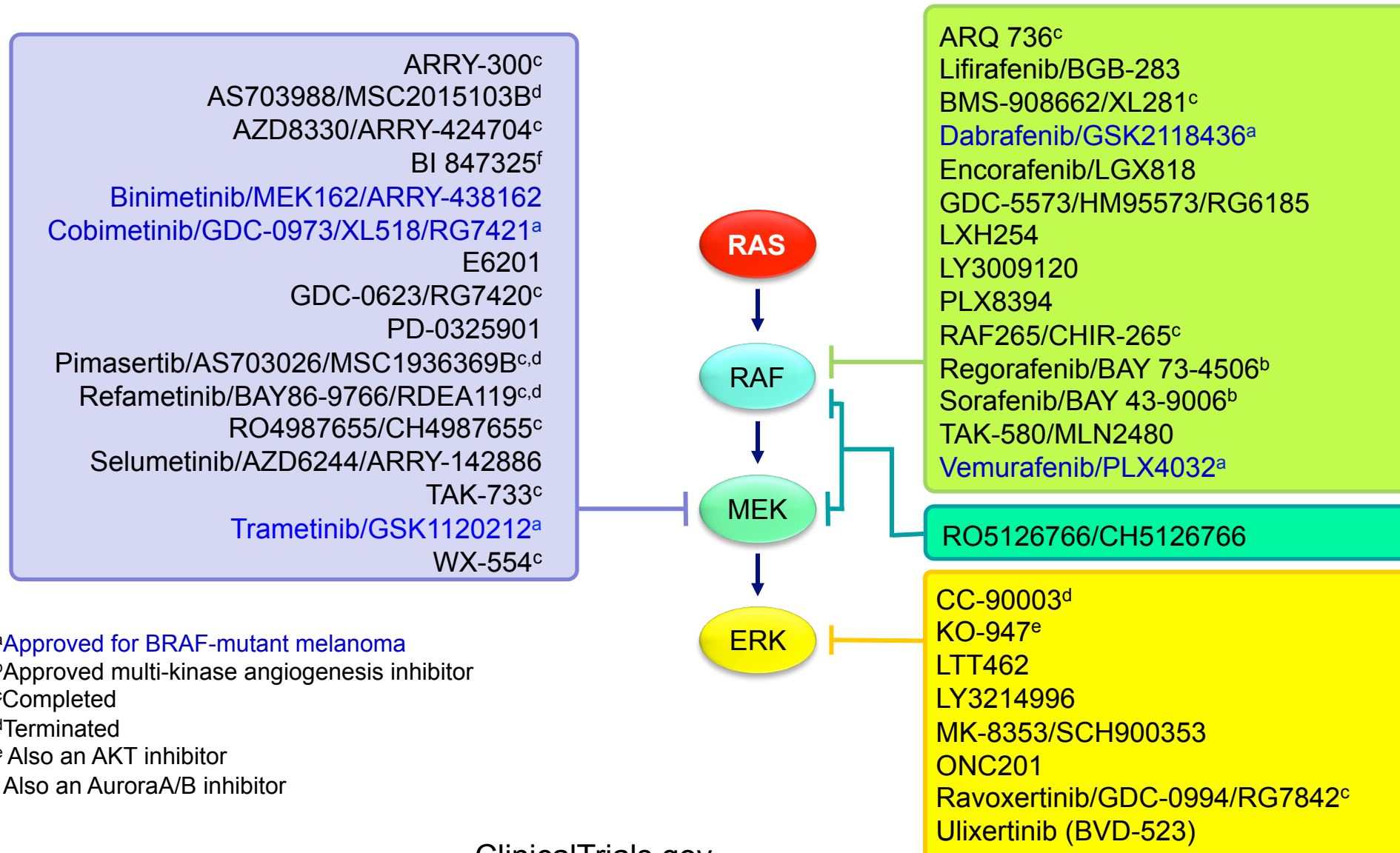
Combination of ERK and autophagy inhibition as a treatment approach for pancreatic cancer

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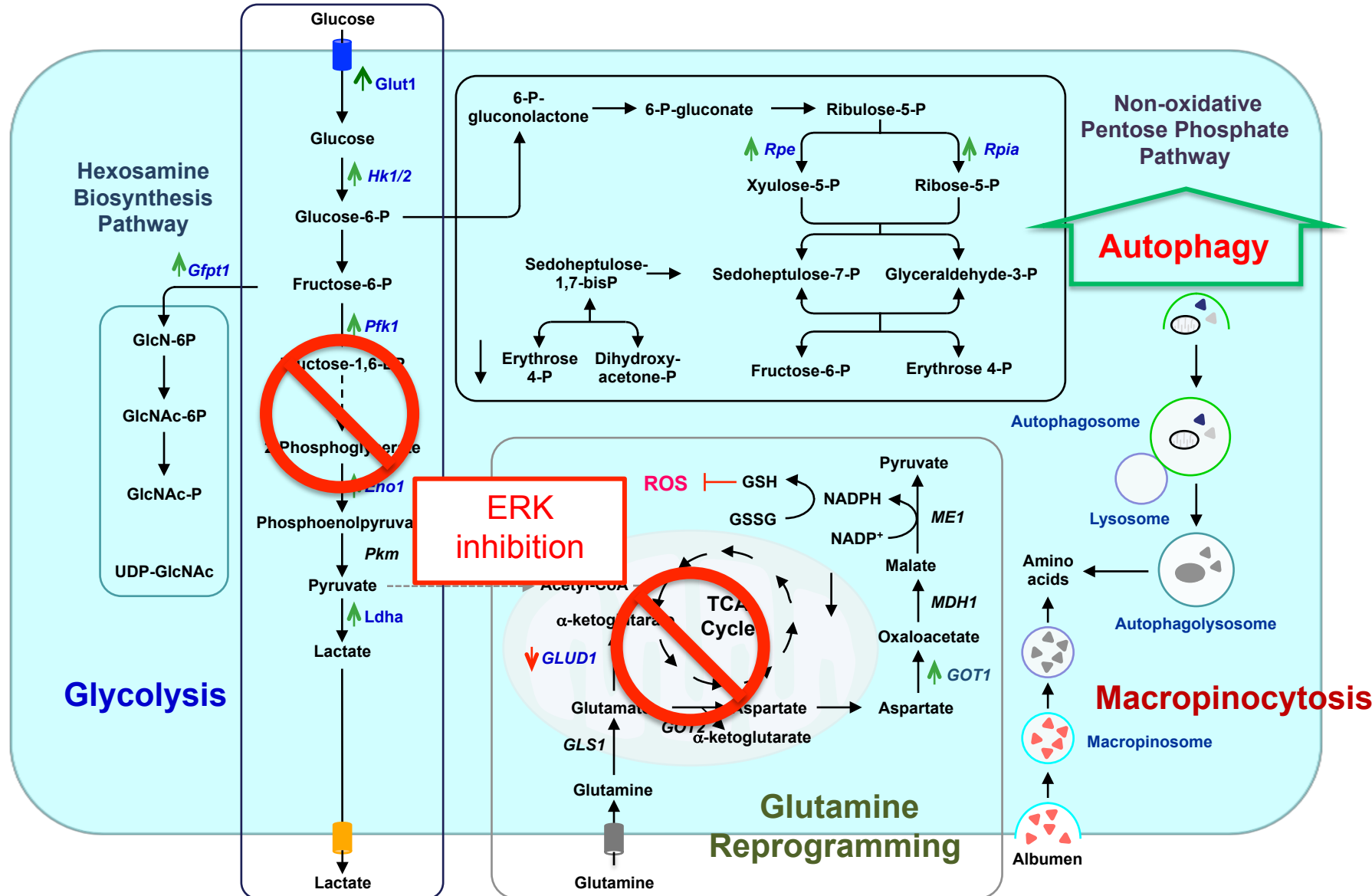
Targeting the RAF-MEK-ERK MAPK cascade



Clinical evaluation of RAF-MEK-ERK protein kinase inhibitors



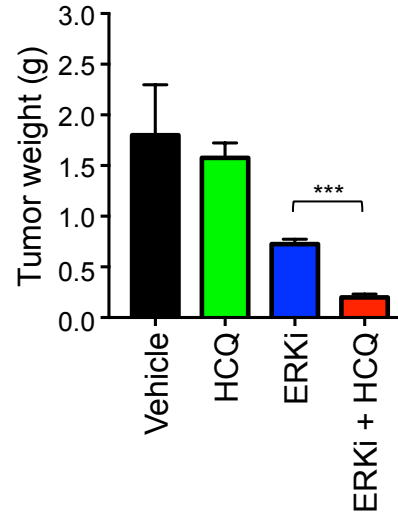
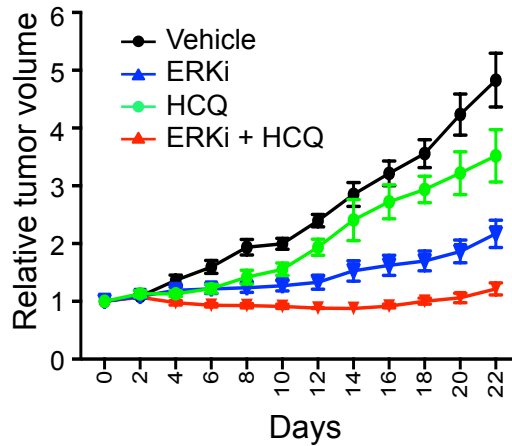
Suppression of ERK-dependent glycolysis and mitochondrial function causes increased autophagy



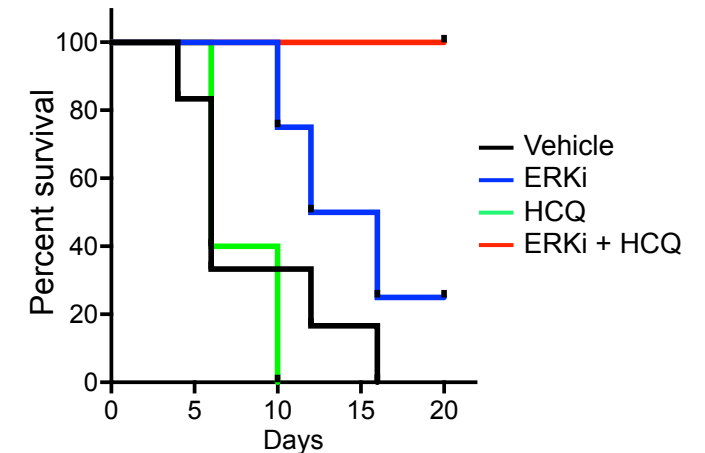
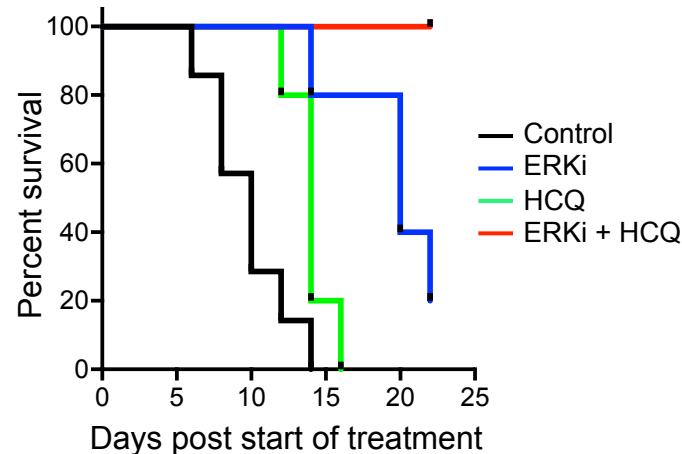
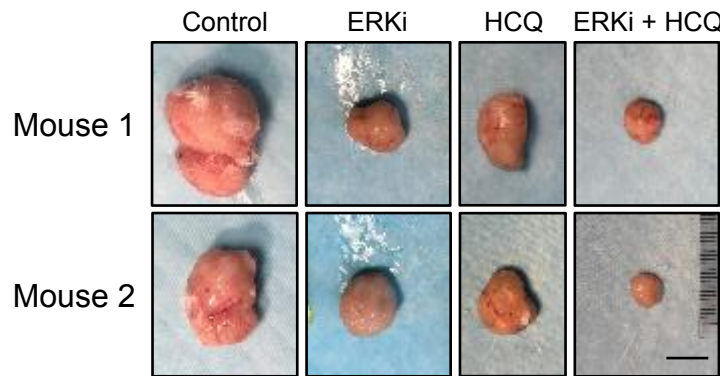
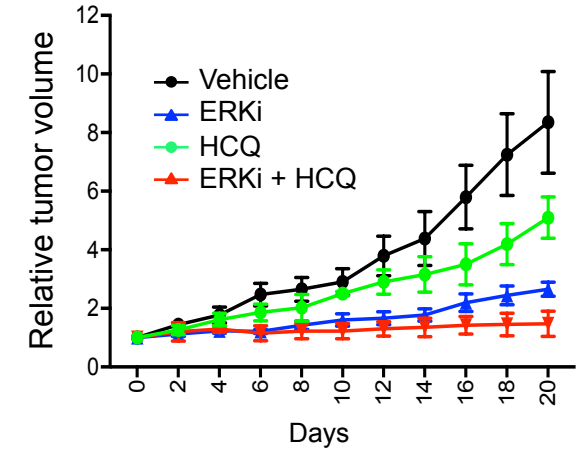
- Increased dependency on autophagy?
- Increased vulnerability to autophagy inhibition?

Concurrent ERK and autophagy inhibition suppresses pancreatic patient-derived xenograft tumor growth

AZ1013 PDX
KRAS G12D
TP53 R248W
NF1 I1186N
KMT2C R454I*
SMAD4 deletion
CDKN2A deletion



AZ97 PDX
KRASG12V
TP53 p.R248Q
SMAD4 p.Y131*
CDKN2A




Independently, another group reaches the same conclusion

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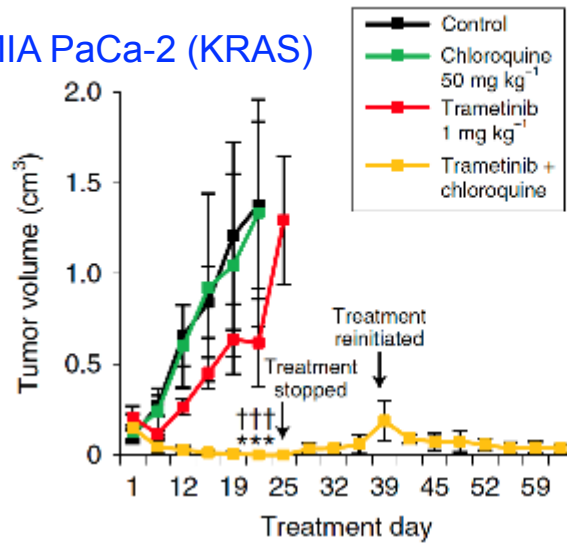
LETTERS

Protective autophagy elicited by RAF→MEK→ERK inhibition suggests a treatment strategy for RAS-driven cancers

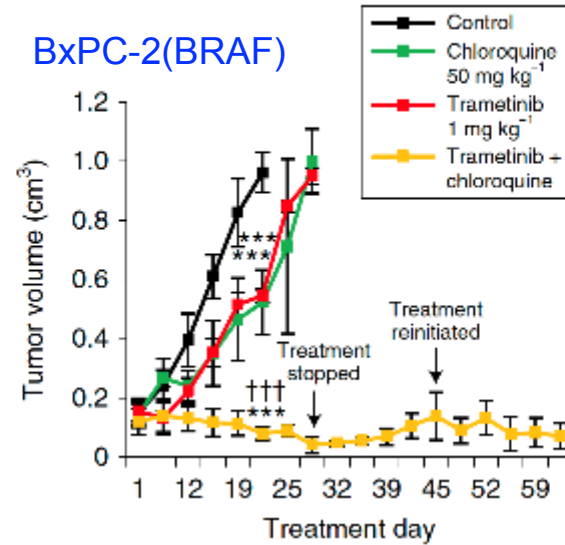
Conan G. Kinsey^{1,2}, Soledad A. Camolotto¹, Amelie M. Boespflug^{1,3,4}, Katrin P. Guillen¹, Mona Foth ¹, Amanda Truong¹, Sophia S. Schuman¹, Jill E. Shea⁵, Michael T. Seipp⁵, Jeffrey T. Yap^{1,6}, Lance D. Burrell¹, David H. Lum¹, Jonathan R. Whisenant^{1,2}, G. Weldon Gilcrease III^{1,2}, Courtney C. Cavalieri^{1,7}, Kaitrin M. Rehbein¹, Stephanie L. Cutler¹, Kajsa E. Affolter^{1,8}, Alana L. Welm^{1,9}, Bryan E. Welm^{1,5}, Courtney L. Scaife^{1,5}, Eric L. Snyder^{1,8} and Martin McMahon ^{1,10}★

Concurrent MEK and autophagy inhibition cooperates to cause tumor regression

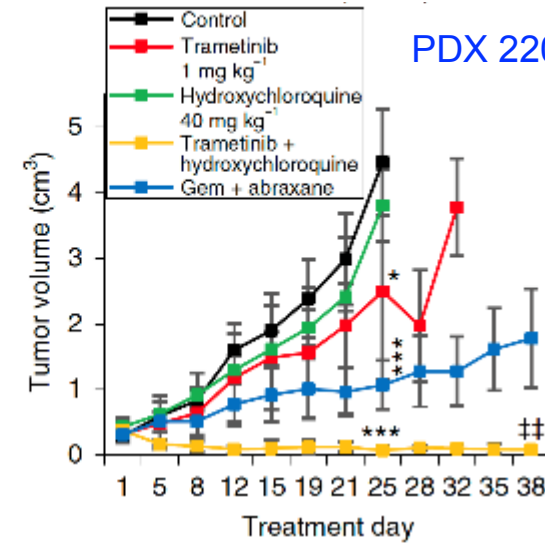
MIA PaCa-2 (KRAS)



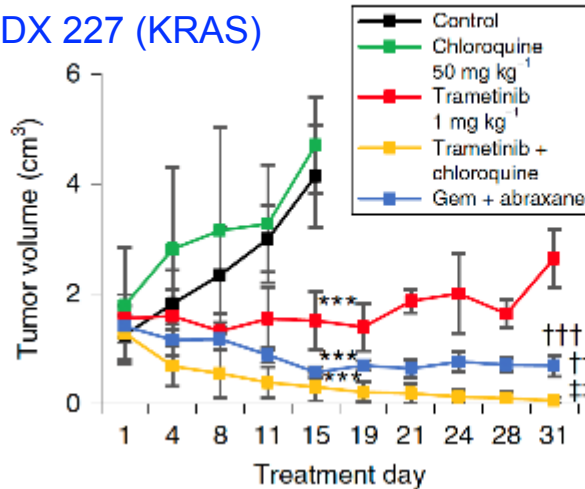
BxPC-2(BRAF)



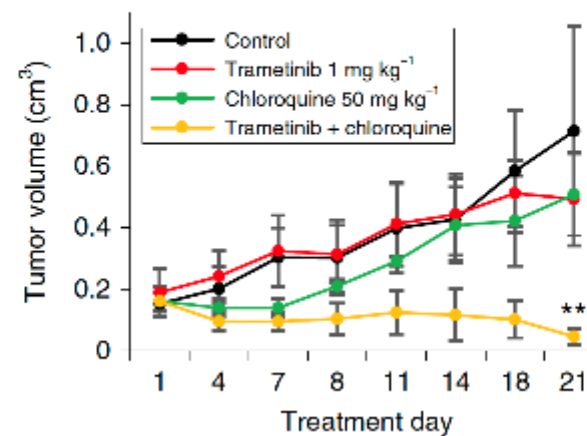
PDX 220 (KRAS)



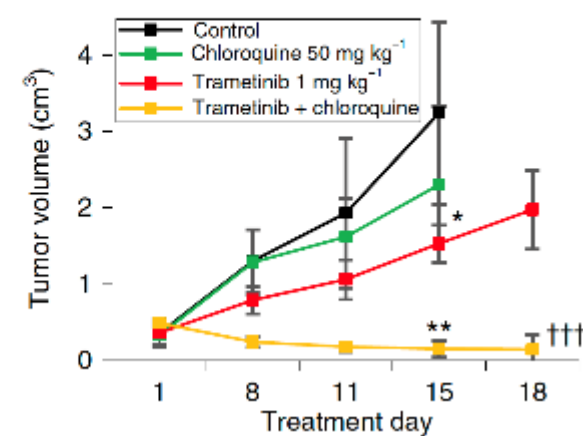
PDX 227 (KRAS)



HCLMeI002 (NRAS)



HCICRC004 CRC PDX (BRAF)

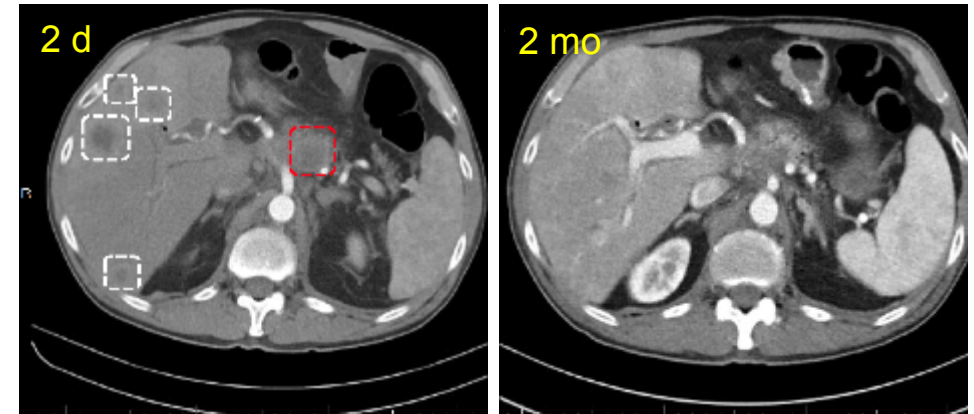


Proof-of-concept in a pancreatic cancer patient

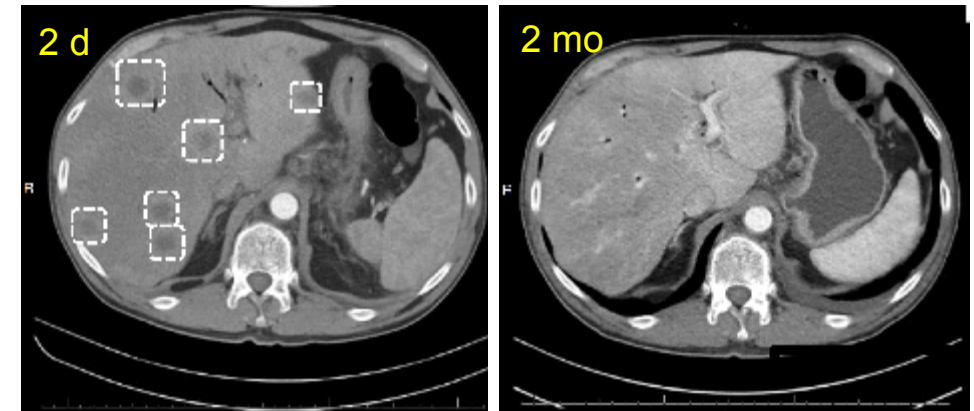
- 2 mg of trametinib plus 1200 mg HCQ daily over last two 2 months
- CA19-9 levels declined ~ 95%
- 50% reduction tumor mass
- Grade 1 rash and grade 1 fatigue
- No ocular and cardiac toxicities

CT Imaging

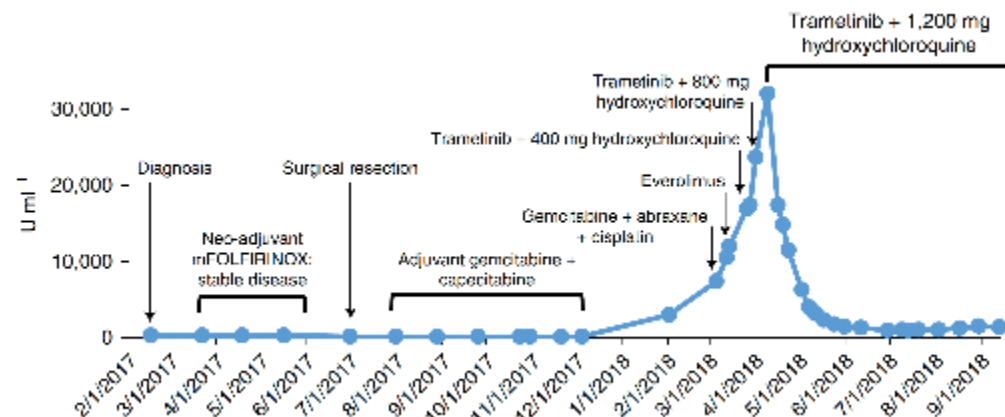
Pancreatic lesion



Liver metastasis lesion



CA19-9 tumor marker



And a third study, taking a different strategy, independently confirms our findings



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Natasha J. Caplen^c, Frank McCormick^{b,g,5}, and Ji Luo^{a,5}



RAS Synthetic Lethal Network (U01)

Peter Jackson/Stanford
Alejandro Sweet-Cordero/
Stanford
Michael Bassik/Stanford



Calvin Kuo/Stanford
Kevan Shokat (UCSF)

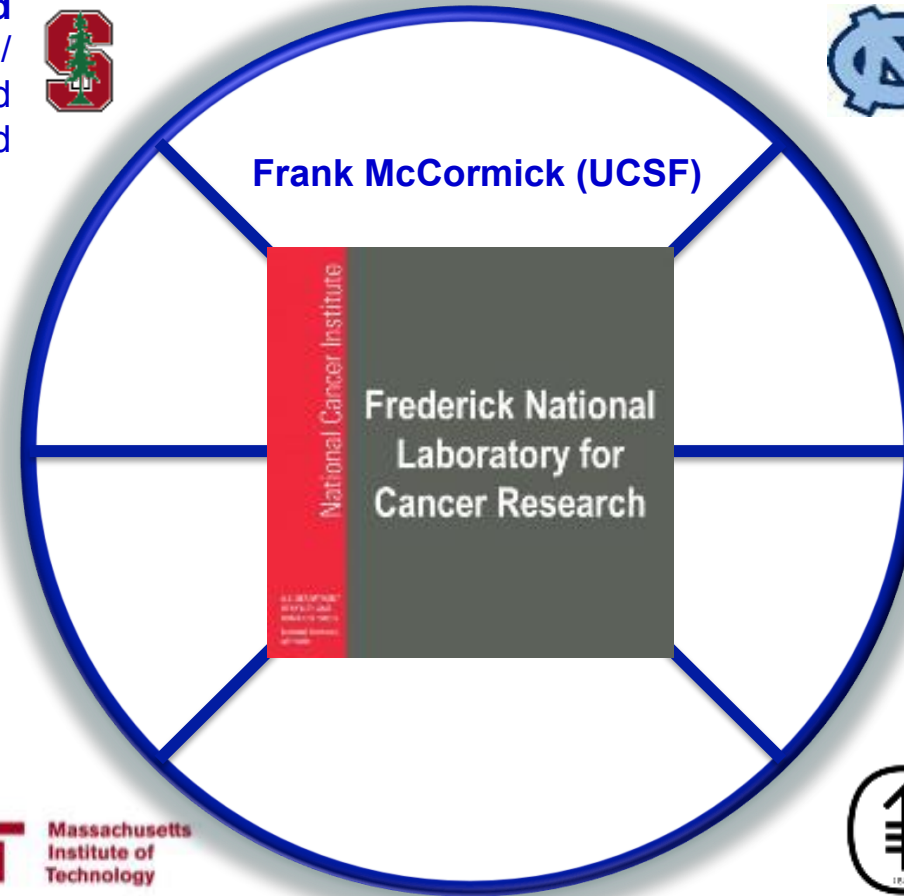


William Hahn/Broad

Tyler Jacks/MIT
David Root/Broad
Nabeel Bardeesy/MGH
Sangeeta Bhatia/MIT
Calvin Kuo/Stanford
Kasper Lage/Broad
Matthew Meyerson/Broad



Frank McCormick (UCSF)



Adrienne Cox/UNC
Channing Der/UNC
Ben Major/UNC
Kris Wood/Duke
Krister Wennerberg/FIMM



Kevin Haigis/BIDMC
Stephen Elledge/BWH
Frank Slack/BIDMC
Steven Gygi/HMS
Marcia Haigis/HMS
Doug Lauffenberger (MIT)



Memorial Sloan Kettering
Cancer Center

Charles Rudin/MSKCC
John Poirier/MSKCC

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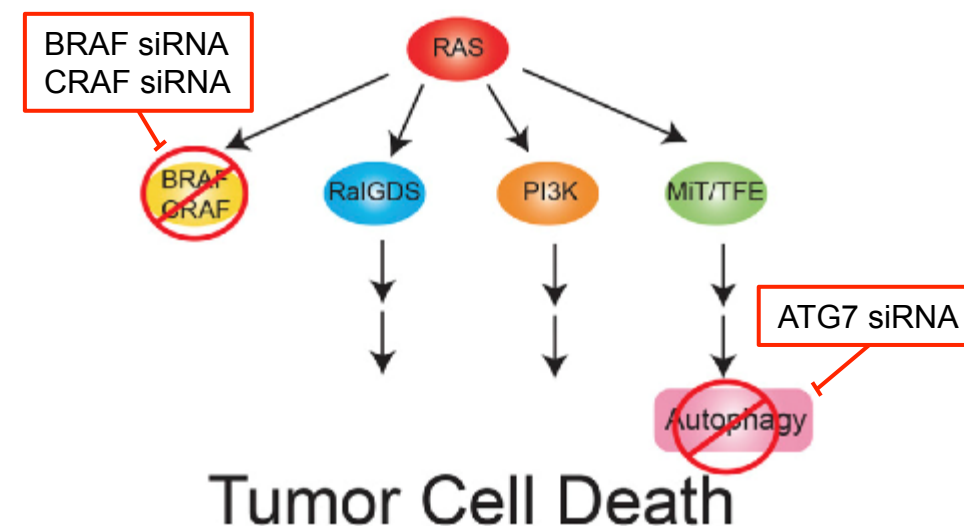
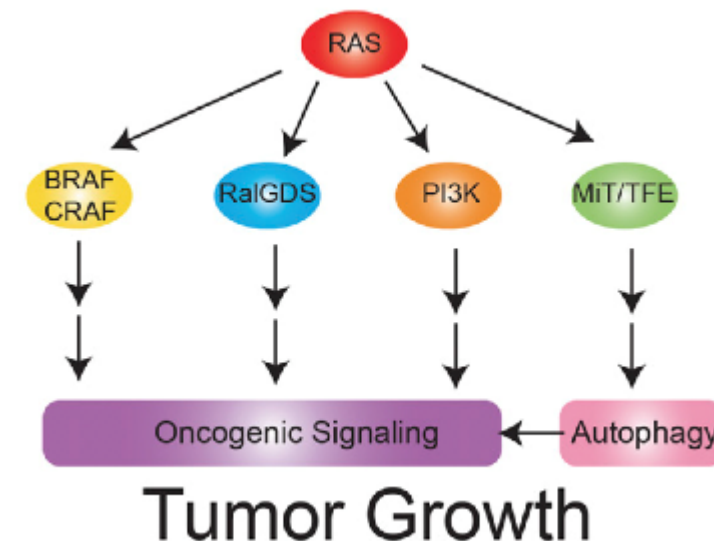
COMMENTARY

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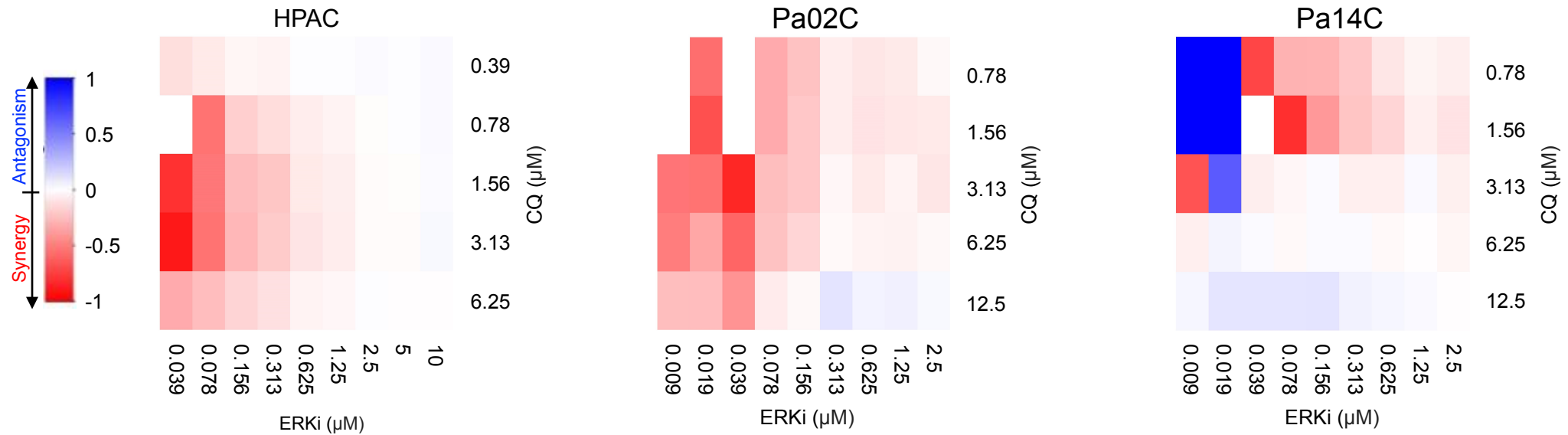
Blockade of RAF and autophagy is the one-two punch to take out Ras

Eileen White^{a,b,1}

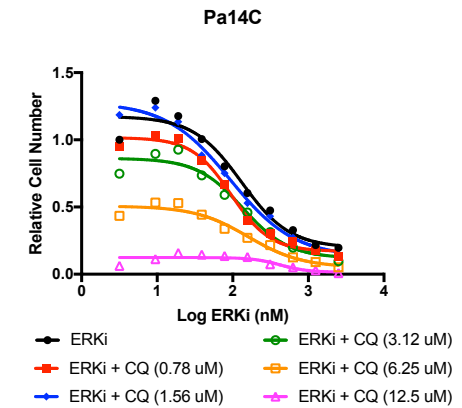
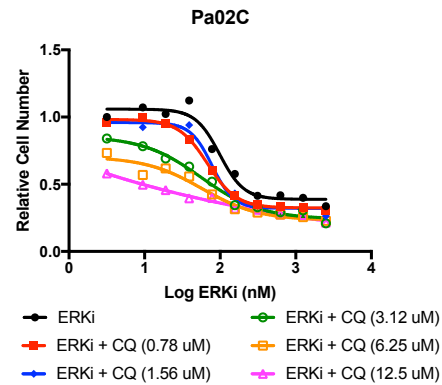
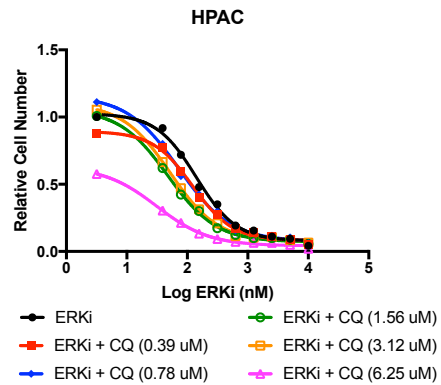
“Essential codependency of RAS-driven cancers on BRAF, CRAF, and autophagy. BRAF and CRAF provide key functional oncogenic signaling downstream of RAS that requires autophagy mediated by ATG7 to sustain survival. **Coordinate blockade of BRAF, CRAF, and ATG7 provides the one-two punch and lethal blow to Ras-driven cancer cells.**”



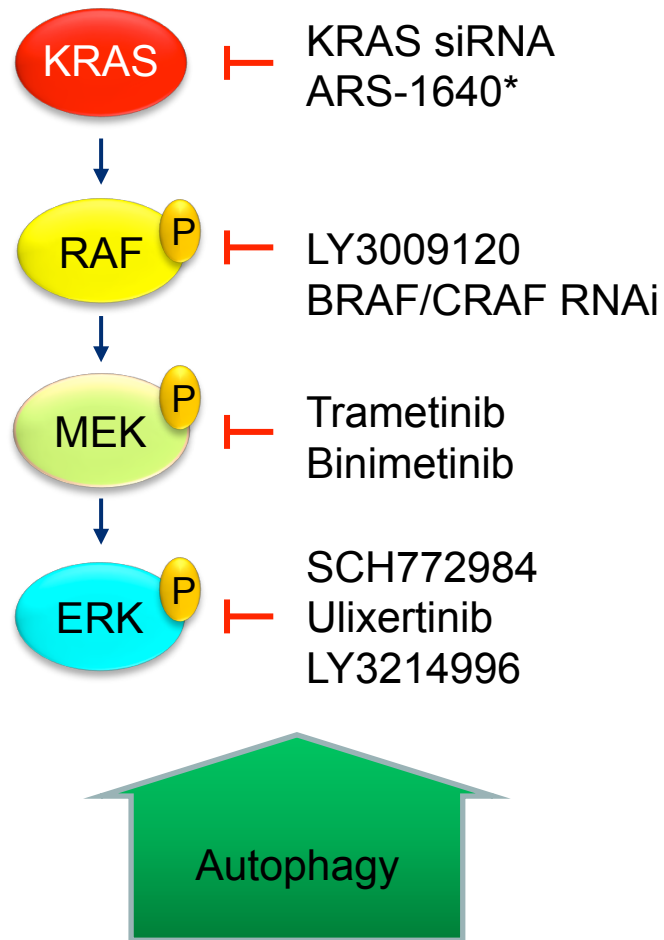
RAFi* and chloroquine synergize in KRAS-mutant PDAC



*LY3009120



Inhibition of RAF-MEK-ERK signaling causes compensatory increase in autophagy in KRAS-mutant cancer cells



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ARTICLES

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LETTERS

Protective autophagy elicited by RAF→MEK→ERK inhibition suggests a treatment strategy for RAS-driven cancers

Conan G. Kinsey^{1,2}, Soledad A. Camolotto¹, Amelie M. Boespflug^{1,3,4}, Katrin P. Guillen¹, Mona Foth¹, Amanda Truong¹, Sophia S. Schuman¹, Jill E. Shea⁵, Michael T. Seipp⁵, Jeffrey T. Yap^{1,6}, Lance D. Burrell¹, David H. Lum¹, Jonathan R. Whisenant^{1,2}, G. Weldon Gilcrease III^{1,2}, Courtney C. Cavalieri^{1,7}, Kaitrin M. Rehbein¹, Stephanie L. Cutler¹, Kajsa E. Affolter^{1,8}, Alana L. Welm^{1,9}, Bryan E. Welm^{1,5}, Courtney L. Scaife^{1,5}, Eric L. Snyder^{1,8} and Martin McMahon^{1,10*}

Initiation of pancreatic cancer clinical trials: combination MEK/ERK and autophagy inhibition



THREAD: A Phase I Trial of Trametinib and Hydroxychloroquine in Patients With Advanced Pancreatic Cancer (NCT03825289)



Phase I Trial of Binimetinib Plus Hydroxychloroquine in Metastatic Pancreatic and Colorectal Cancer

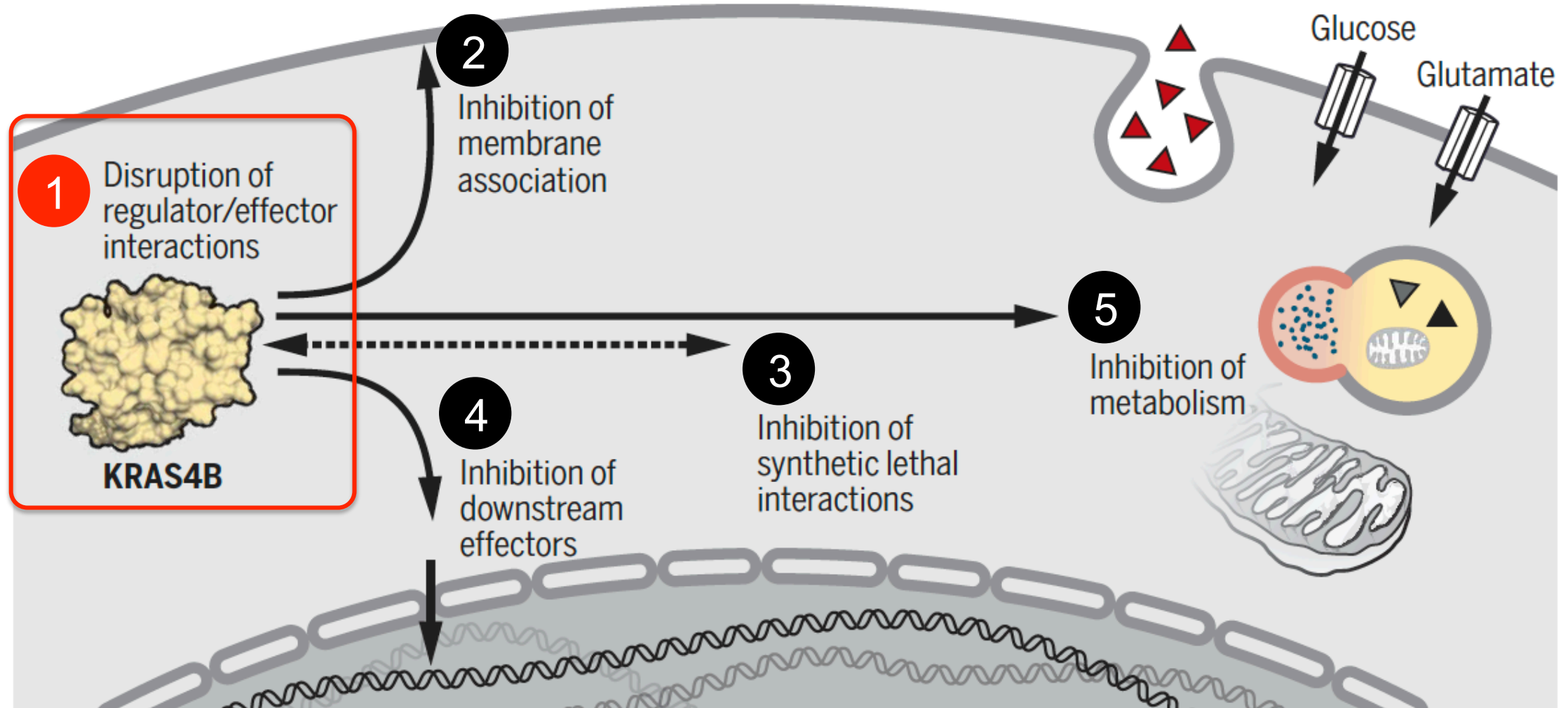
Undisclosed Pharma

Initiation of a Phase I Clinical Trial Evaluating Combination ERK and Autophagy (hydroxychloroquine) Inhibition in Pancreatic Cancer

Key points

- 'Undruggable' RAS-mutant cancers: druggable after all?
- Autophagy: the Achilles' heel of RAS-mutant cancers?
- Inhibitors of the ERK MAPK cascade – rendering KRAS-mutant cancers addicted to autophagy
- Combination ERK MAPK and autophagy inhibition: a pan-RAS therapy?
- Autophagy inhibition anti-tumor activity is due to targeting tumor cells and the tumor microenvironment
- ULK inhibitors: a more selective autophagy inhibitor?

The first direct KRAS inhibitors enter clinical evaluation in 2018



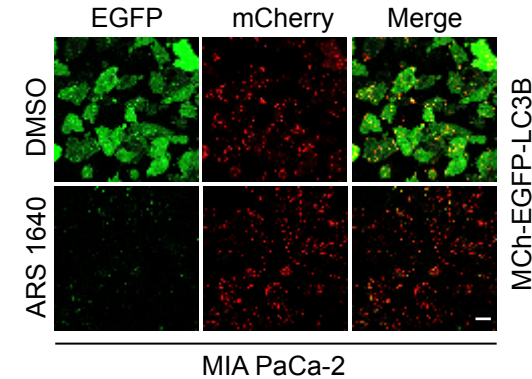
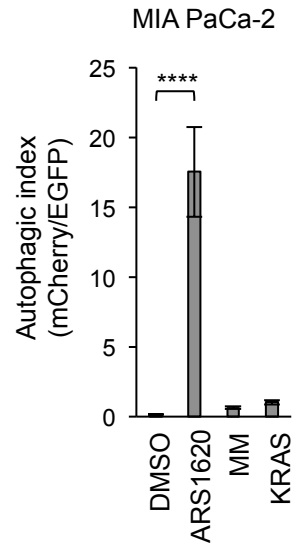
Clinical evaluation of KRAS G12C-specific inhibitors

- A Phase 1, Study Evaluating the Safety, Tolerability, PK, and Efficacy of AMG 510 in Subjects With Solid Tumors With a Specific KRAS Mutation (NCT03600883)
- MRTX849 in Patients With Cancer Having a KRAS G12C Mutation (NCT03785249)

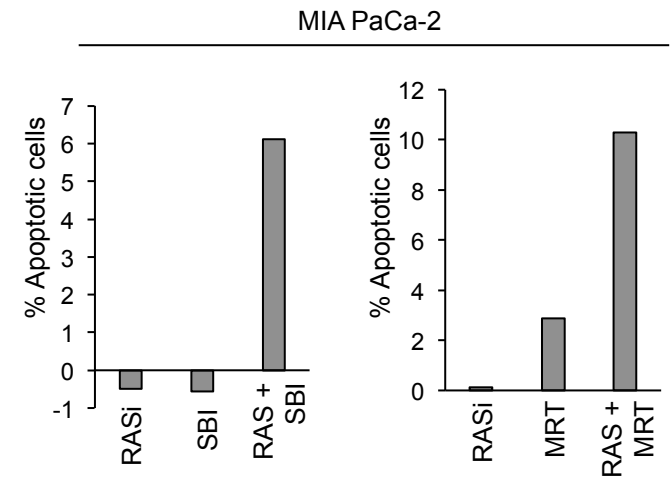
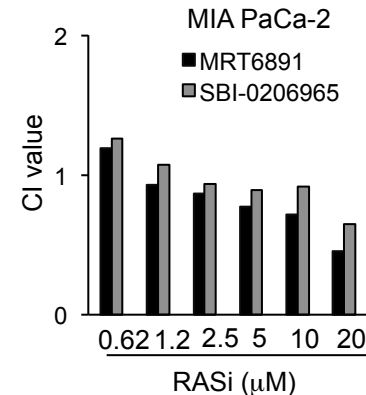
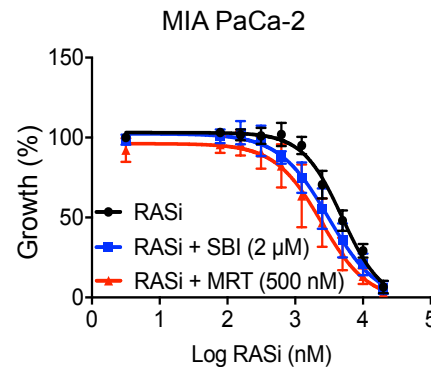
❖ KRAS G12C inhibitors versus ERK MAPK + HCQ?

Concurrent KRAS G12C and ULK inhibition causes pancreatic cancer cell death

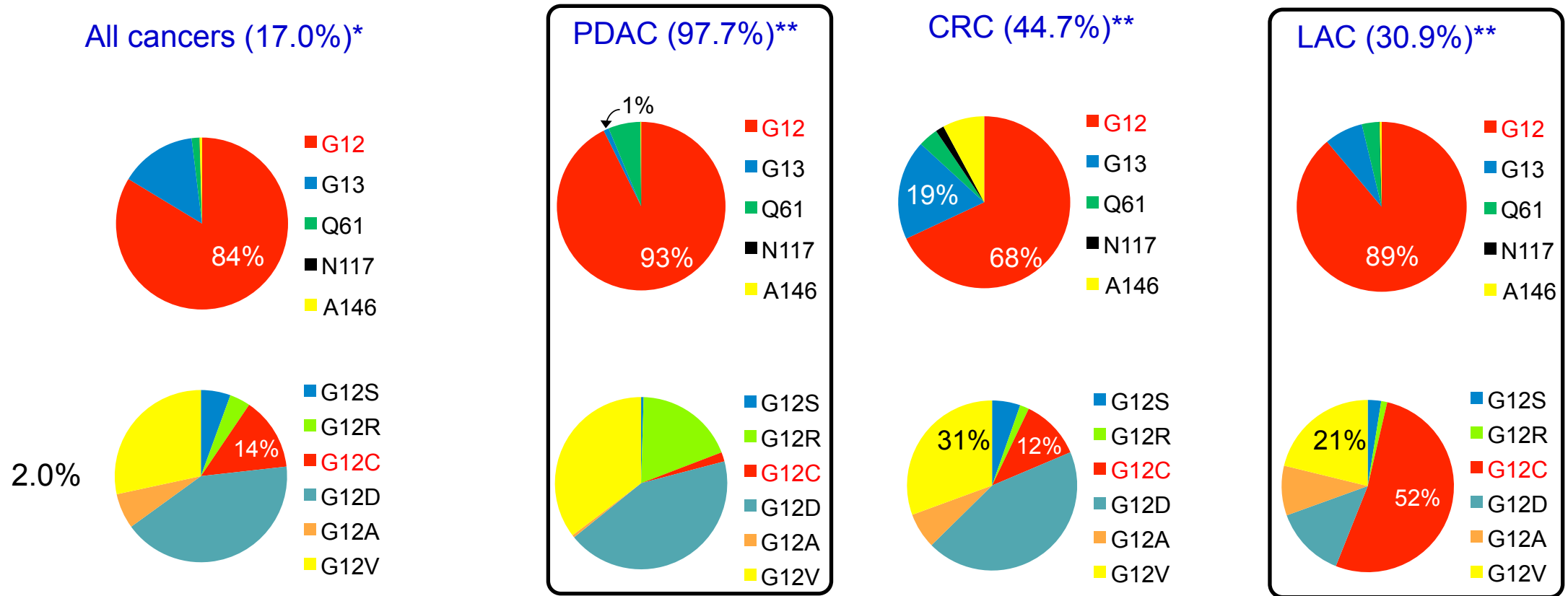
Treatment with the
KRAS^{G12C} inhibitor
ARS-1620
increases
autophagy



Cotreatment with
ULK inhibitors
enhance
KRAS^{G12C} inhibitor
growth
suppression

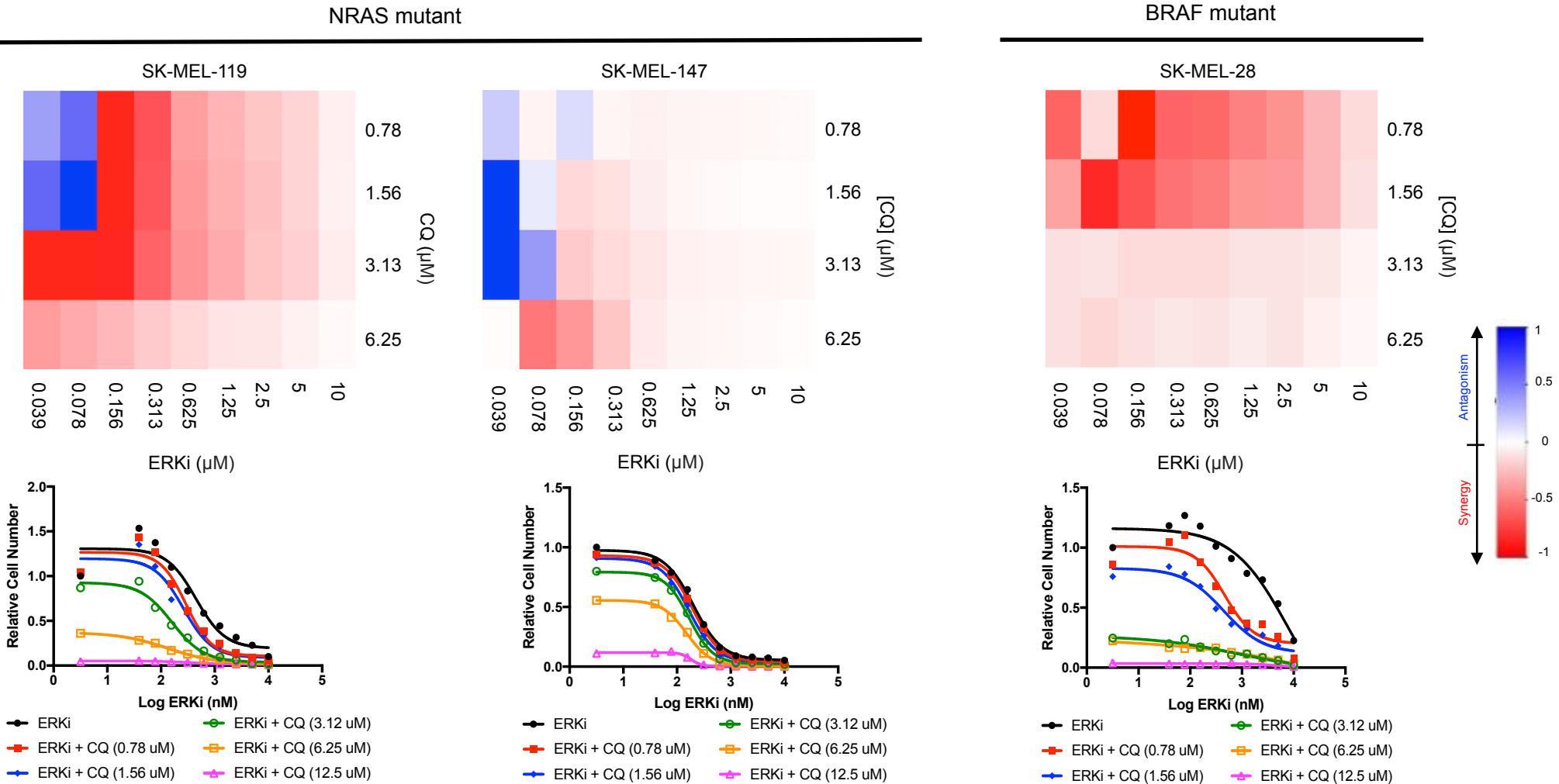


G12C inhibitors target only 2% of all cancers

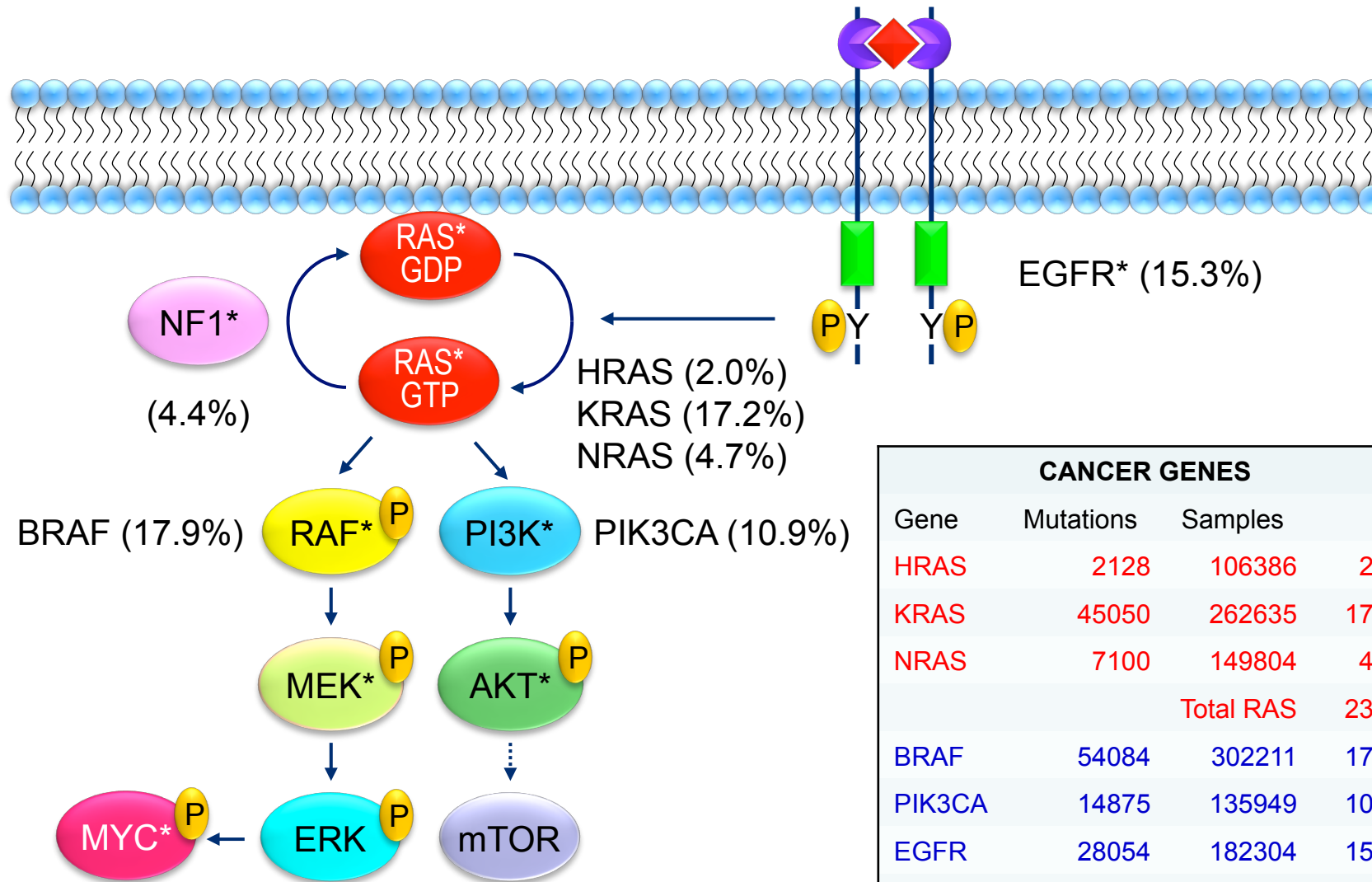


KRAS G12C mutations are common in lung (46% of KRAS mutations), infrequent in colorectal (8%), and rare in pancreatic (2%) cancer

ERKi and chloroquine cause synergistic growth suppression of NRAS- and BRAF-mutant melanoma



Aberrant RAF-MEK-ERK MAPK signaling in cancer

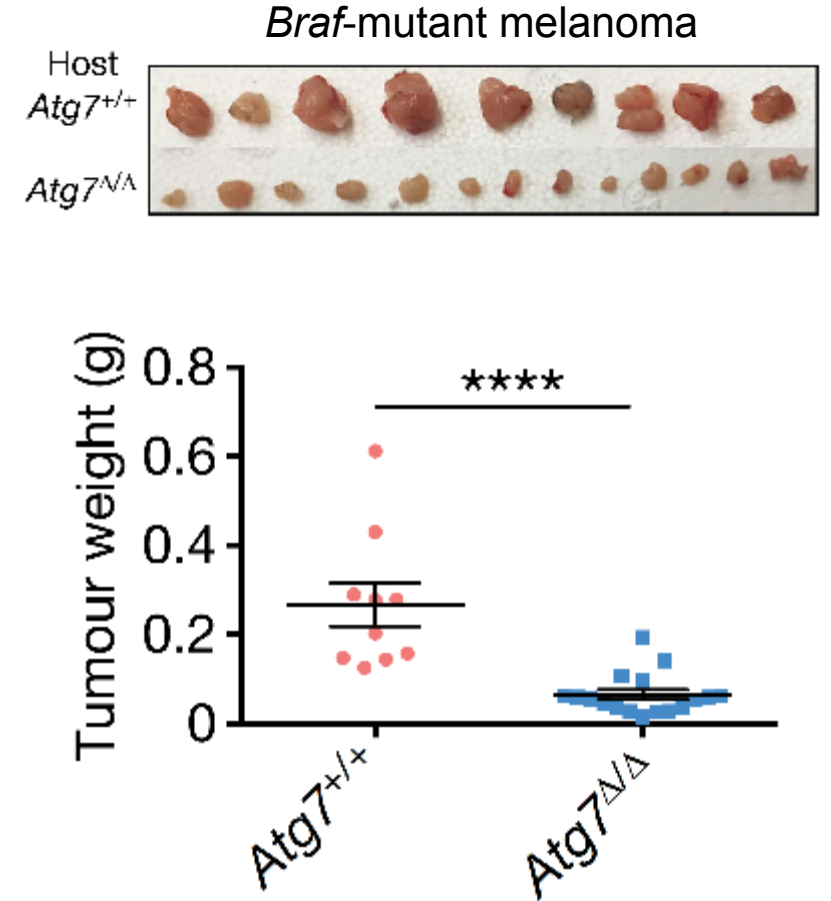
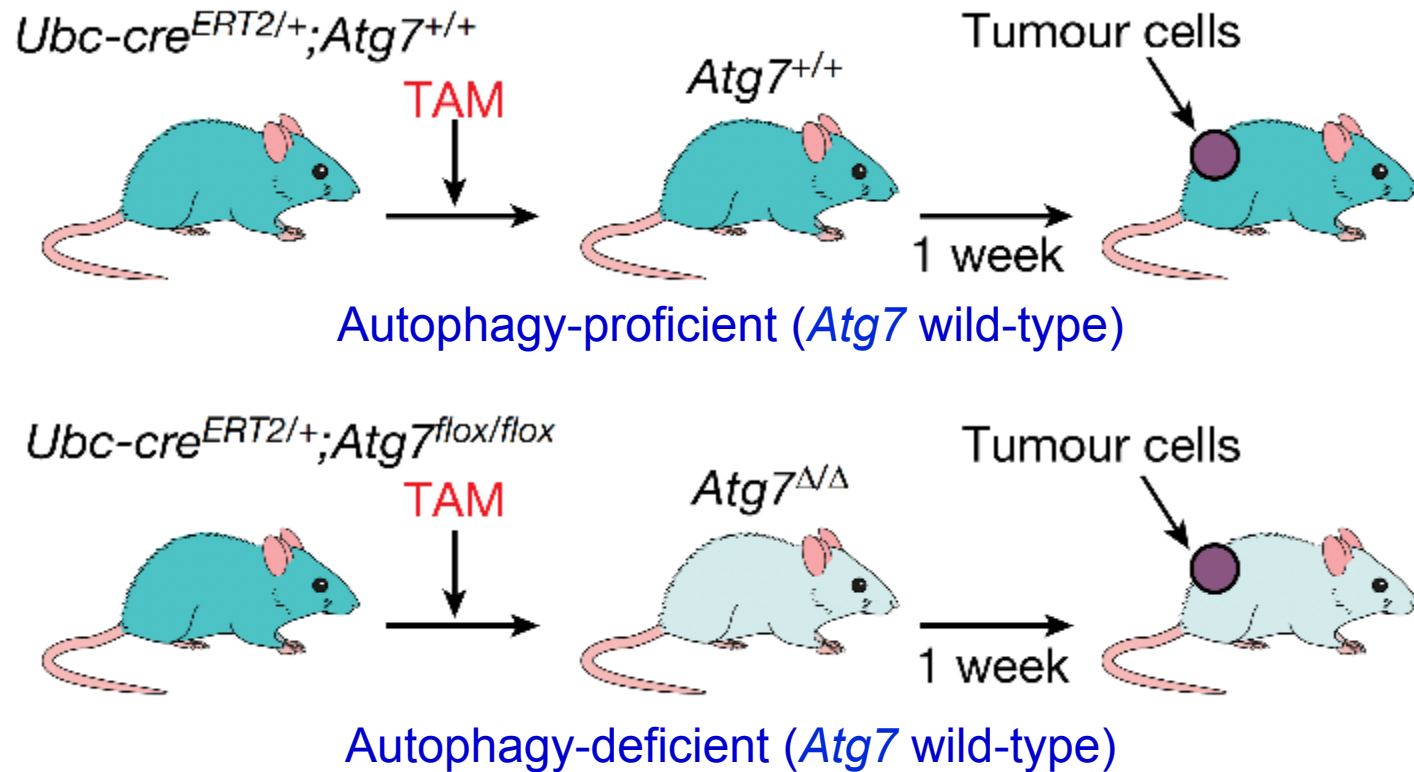


CANCER GENES			
Gene	Mutations	Samples	%
HRAS	2128	106386	2.0
KRAS	45050	262635	17.2
NRAS	7100	149804	4.7
Total RAS			23.9
BRAF	54084	302211	17.9
PIK3CA	14875	135949	10.9
EGFR	28054	182304	15.3
NF1	2878	65211	4.4
TP53	41588	155424	26.8

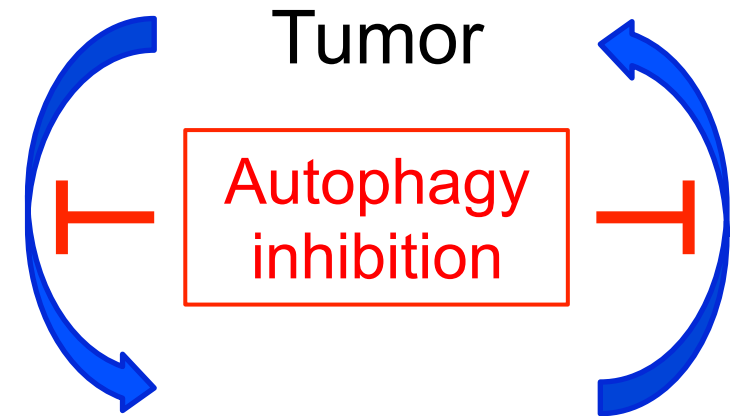
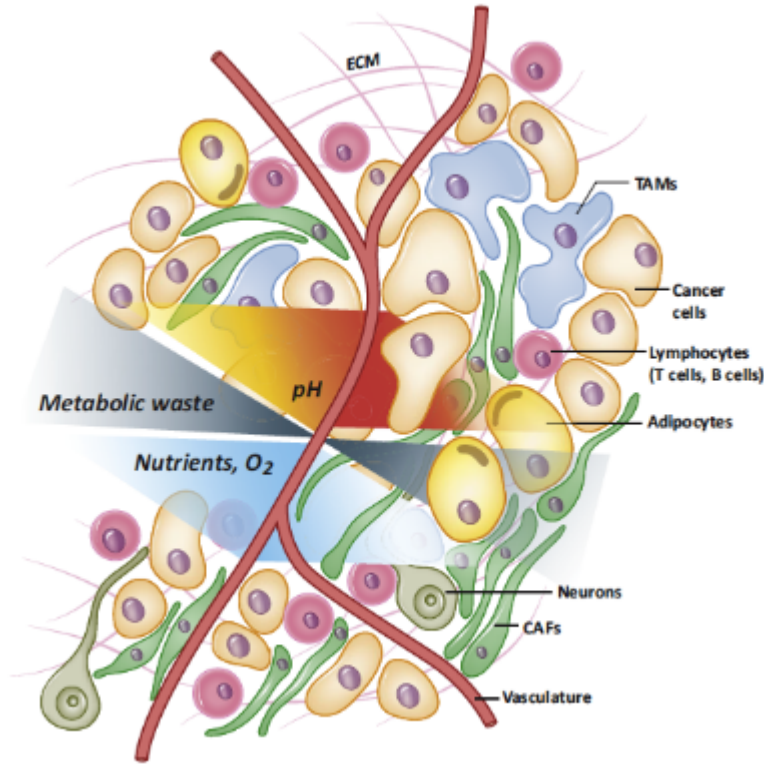
Key points

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- Autophagy: the Achilles' heel of RAS-mutant cancers?
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- Combination ERK MAPK and autophagy inhibition: a pan-RAS therapy?
- Autophagy inhibition anti-tumor activity is due to targeting tumor cells and the tumor microenvironment
- ULK inhibitors: a more selective autophagy inhibitor?

Host autophagy supports tumor growth



Autophagy-dependent activities of the microenvironment support tumor growth



Microenvironment

- Stroma (stellate cells)
- Immune cells (macrophages)

Sousa et al (2016) Nature 536:479

Cunha et al (2018) Cell 175:429

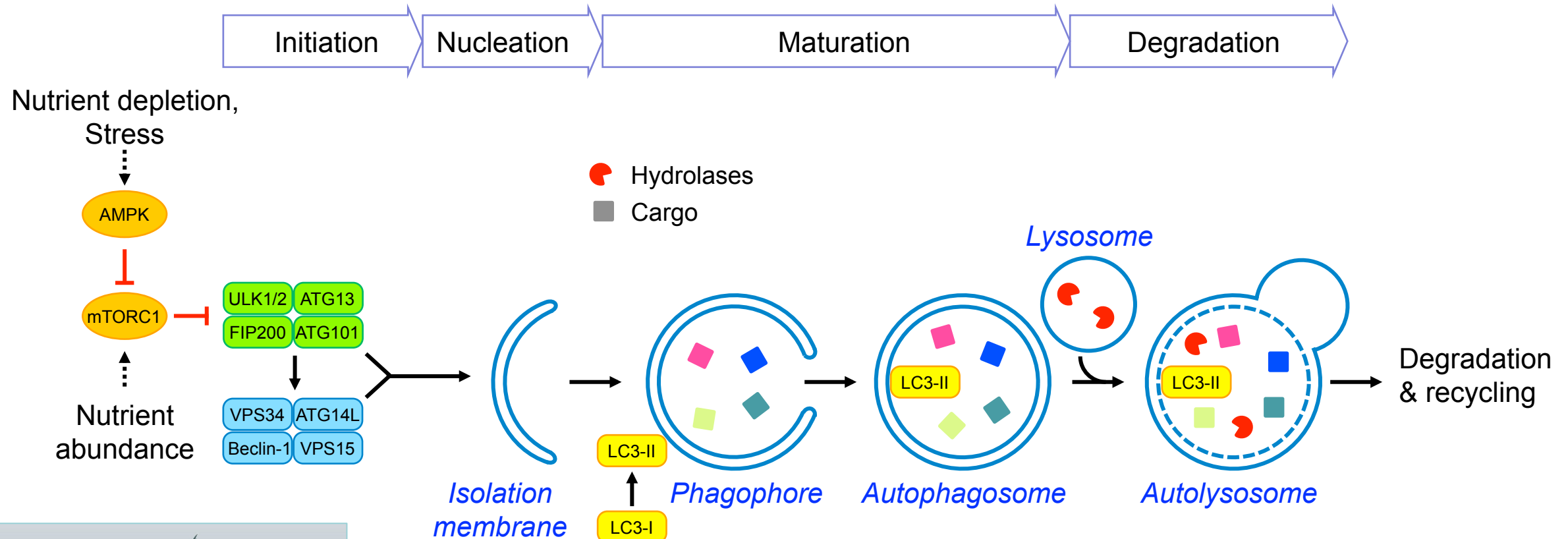
Lyssiotis & Kimmelman (2018) Trends Cell Biol 27:863

Autophagy inhibition impairs tumor growth by targeting both tumor cells and normal cells in the microenvironment

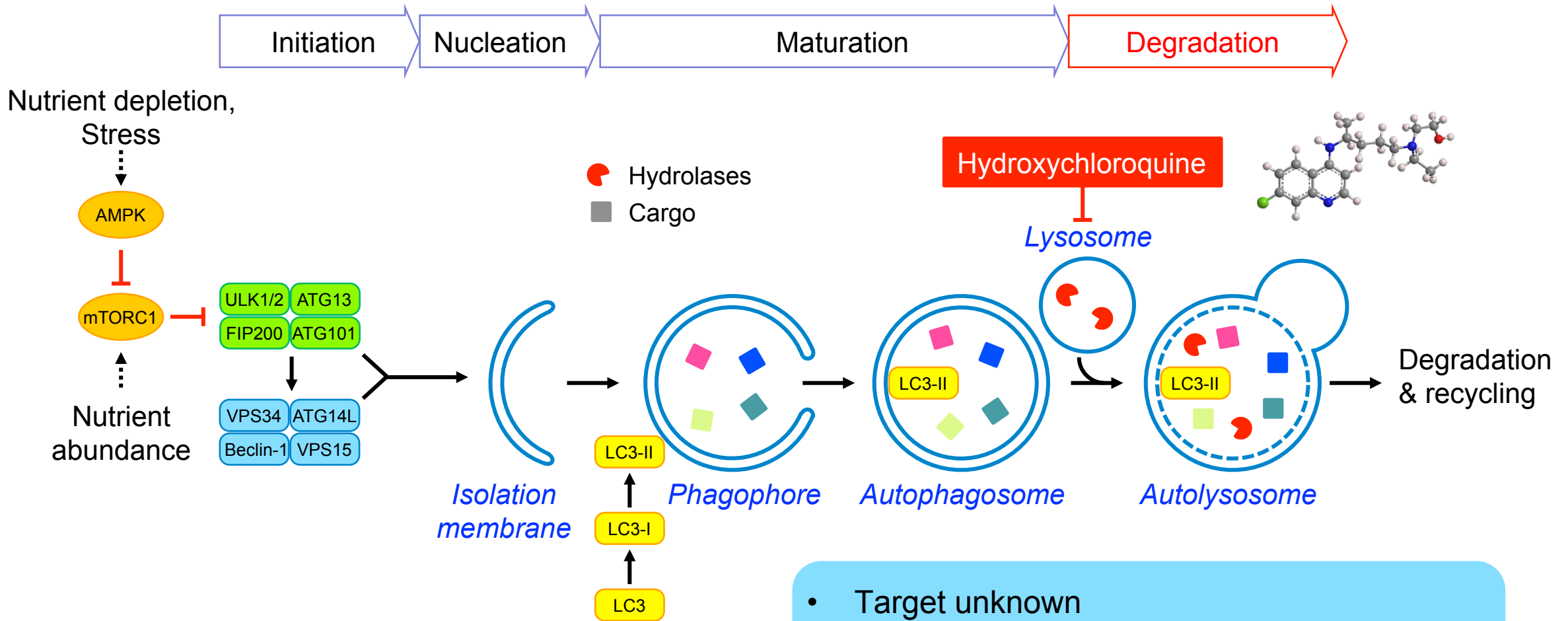
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Autophagy: “self-eating” and recycling cellular materials for nutrient and energy source



Hydroxychloroquine inhibition of autophagy



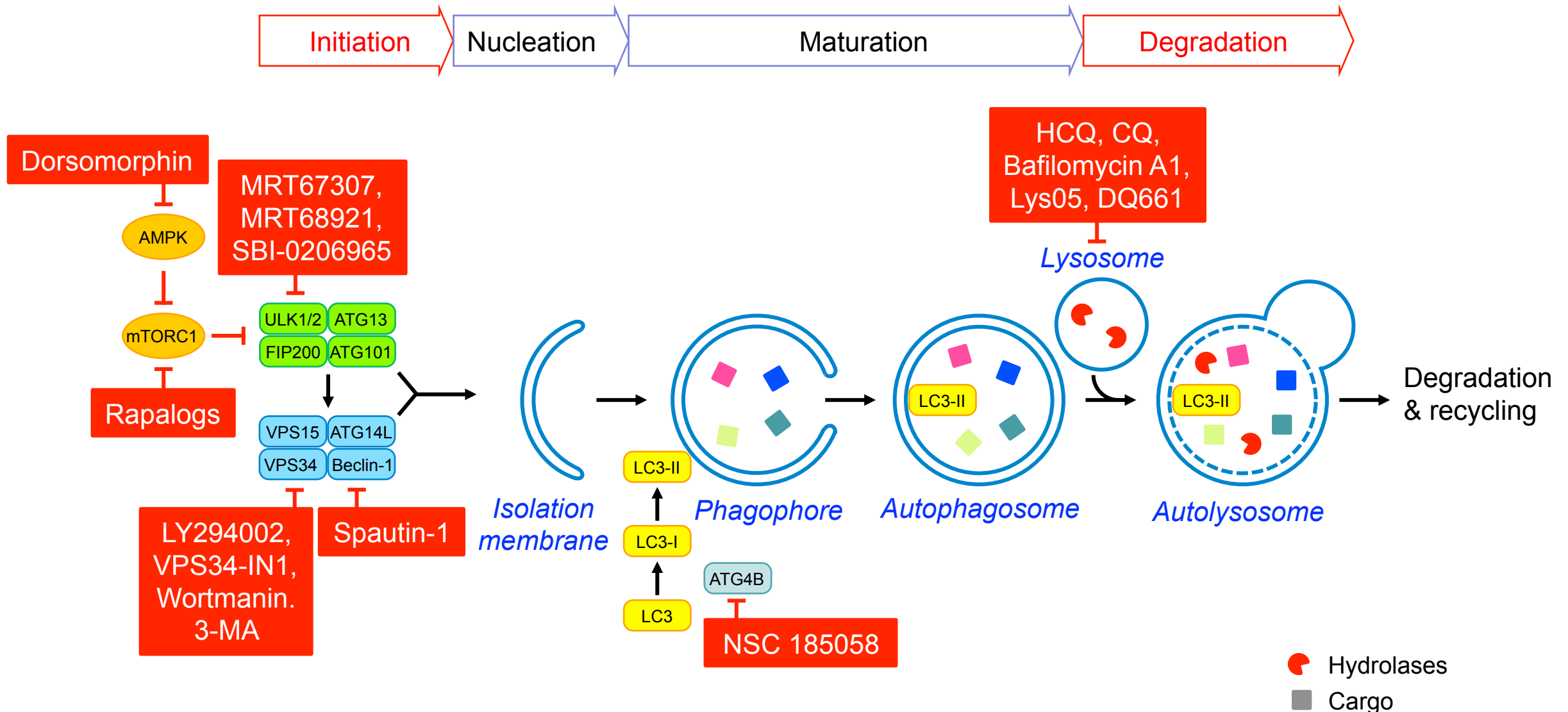
- Target unknown
- Elevate/neutralize the lysosomal/vacuolar pH
- Low potency and selectivity for autophagy

Hydroxychloroquine in pancreatic clinical trials

- Randomized Phase II Trial of Pre-Operative Gemcitabine and Nab Paclitacel With or With Out Hydroxychloroquine (NCT01978184)
- Phase II Study of Hydroxychloroquine in Previously Treated Patients With Metastatic Pancreatic Cancer (NCT01273805) - completed
- A Phase I/II/Pharmacodynamic Study of Hydroxychloroquine in Combination With Gemcitabine/Abraxane to Inhibit Autophagy in Pancreatic Cancer (NCT01506973) – active, not recruiting
- Randomized Phase II Trial of Pre-Operative Gemcitabine, Nab-Paclitaxel, and Hydroxychloroquine With or Without Avelumab (PGHA vs. PGH) (NCT03344172) - suspended

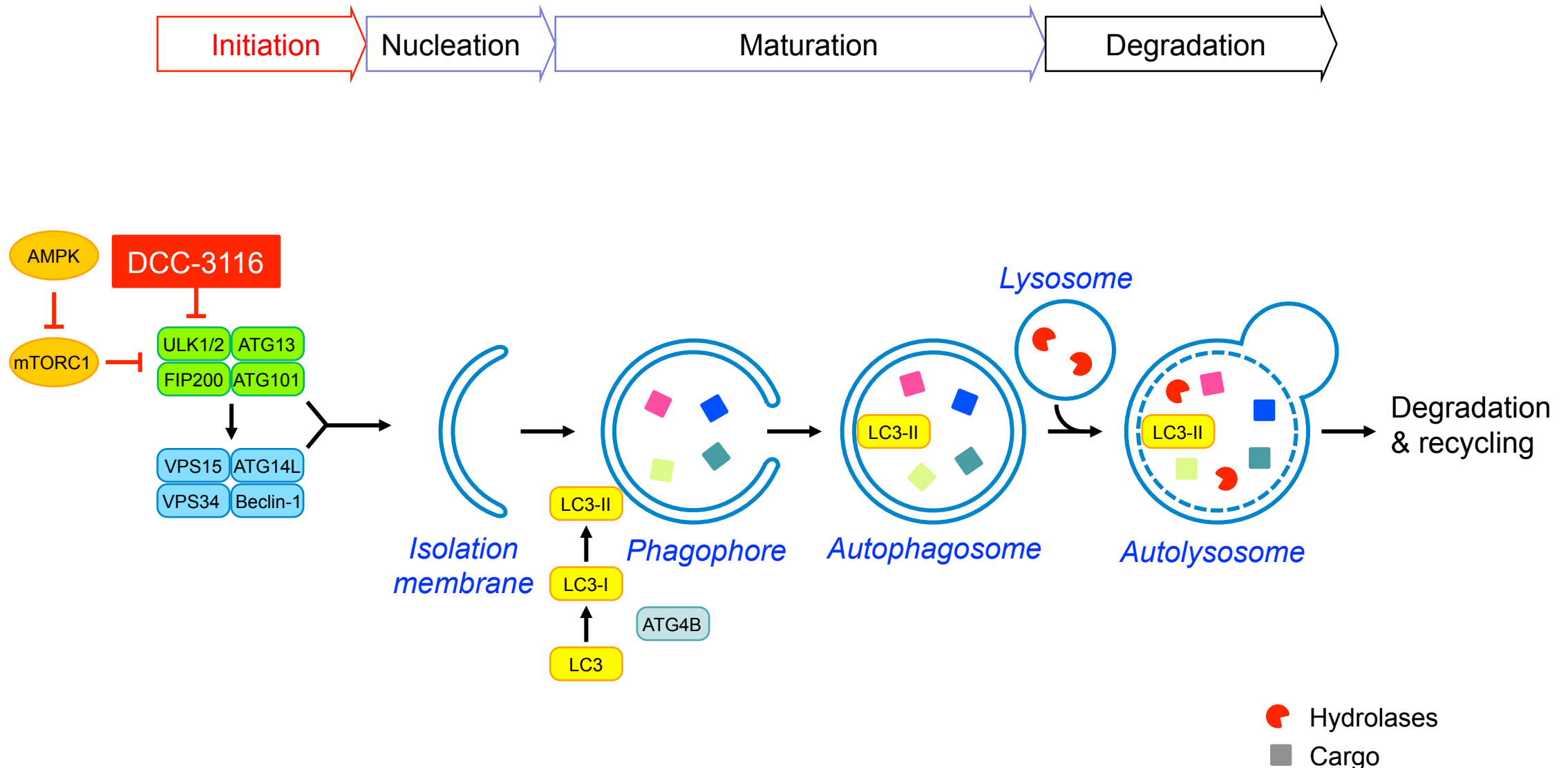
Hydroxychloroquine has shown limited activity as a monotherapy (NCT01273805, NCT01506973 and NCT03344172), but has shown promise in combination with preoperative gemcitabine plus nab-paclitaxel (NCT01978184)

Autophagy inhibitors



Galluzzi et al (2017) Nat Rev Drug Discov 16:487
 Klionsky et al (2016) Autophagy 12:1

Autophagy inhibitors: a focus on ULK inhibitors



Galluzzi et al (2017) Nat Rev Drug Discov 16:487
Klionsky et al (2016) Autophagy 12:1

Conclusions

- Inhibitors of the ERK MAPK cascade render KRAS-mutant cancers addicted to autophagy, enhancing their response to autophagy inhibitor treatment
- Unlike KRAS^{G12C} mutant-selective inhibitors, combination ERK MAPK and autophagy inhibitor treatment may be effective in a broader spectrum of EGFR/RAS/BRAF mutant human cancers.
- Moving forward, more potent and selective autophagy inhibitors will be needed to improve upon this combination

ULK activity plays a metabolic role in RAS-mutant cancers

Molecular Cell

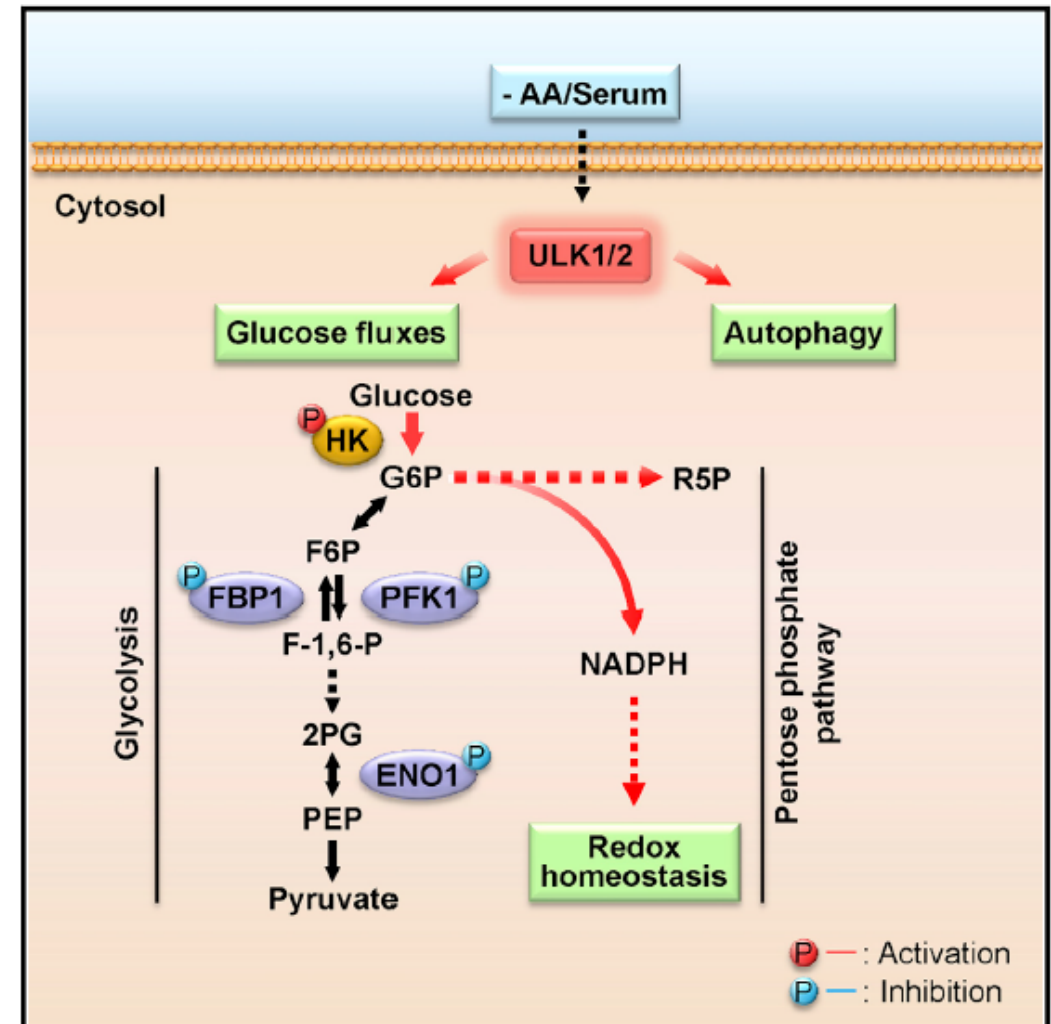
ULK1/2 Constitute a Bifurcate Node Controlling Glucose Metabolic Fluxes in Addition to Autophagy

Li et al., 2016, Molecular Cell 62, 359–370

May 5, 2016 ©2016 Elsevier Inc.

<http://dx.doi.org/10.1016/j.molcel.2016.04.009>

Article





Daniel Flynn, Ph.D.

EVP, Chief Scientific Officer & Founder

ULK Kinase Inhibitor & Autophagy

Rationale for DCC-3116 in RAS Cancers

RAS CANCERS DEPEND ON MEK/ERK SIGNALING & AUTOPHAGY FOR SURVIVAL

ULK KINASE IS AN INITIATING FACTOR FOR ACTIVATION OF AUTOPHAGY

DCC-3116 IS A POTENTIAL FIRST-IN-CLASS ULK KINASE INHIBITOR

STRONG PRELIMINARY PRECLINICAL VALIDATION

RAS Cancers Represent Significant Unmet Medical Need

RAS mutations are the most common activating mutations of all cancers

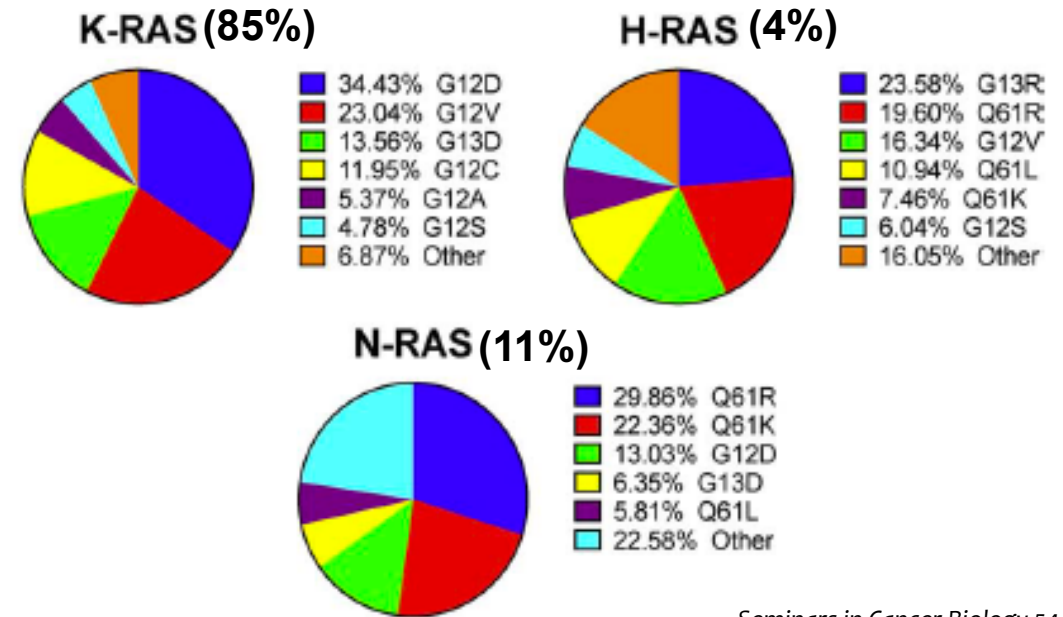
- Pancreatic: ~98%
- Colon: ~ 45%
- Lung: ~ 30%

RAS activates other pathways

- MAPK (RAF-MEK-ERK)
- PI₃K/AKT/mTOR

Mutant BRAF cancers are also addressable by DCC-3116

MAPK inhibitors have not been successful thus far as single agents



Seminars in Cancer Biology 54 (2019) 138–148



Direct inhibition of RAS: Quest for the Holy Grail?

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^a Department of Pharmacology, University of Illinois at Chicago, Chicago, IL, USA

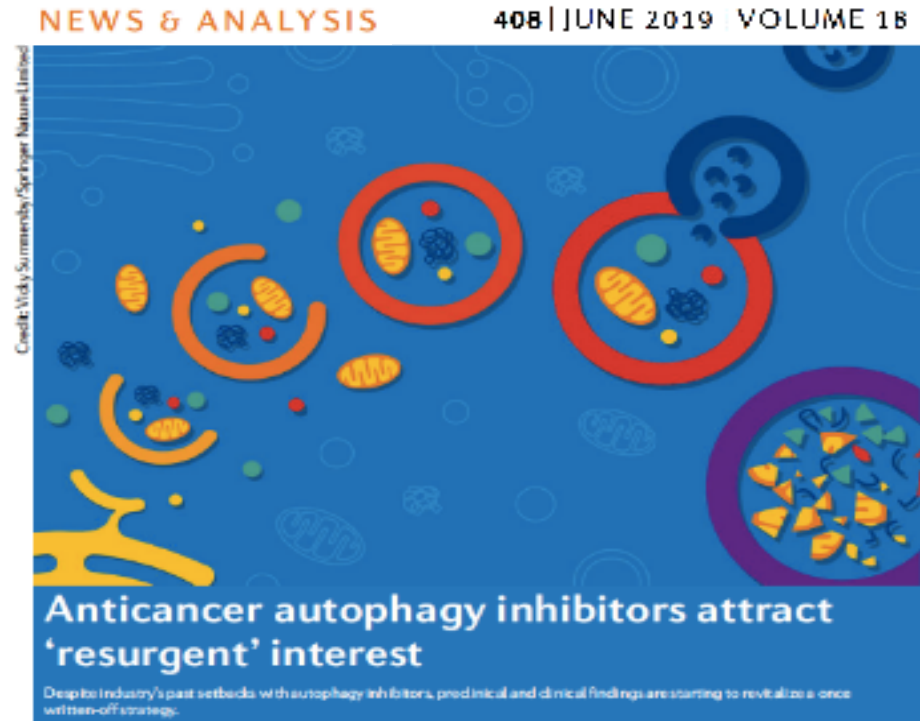
^b University of Illinois Cancer Center, University of Illinois at Chicago, Chicago, IL, USA

^c Jesse Brown VA Medical Center, Chicago, IL, USA

Revitalized Interest in Autophagy



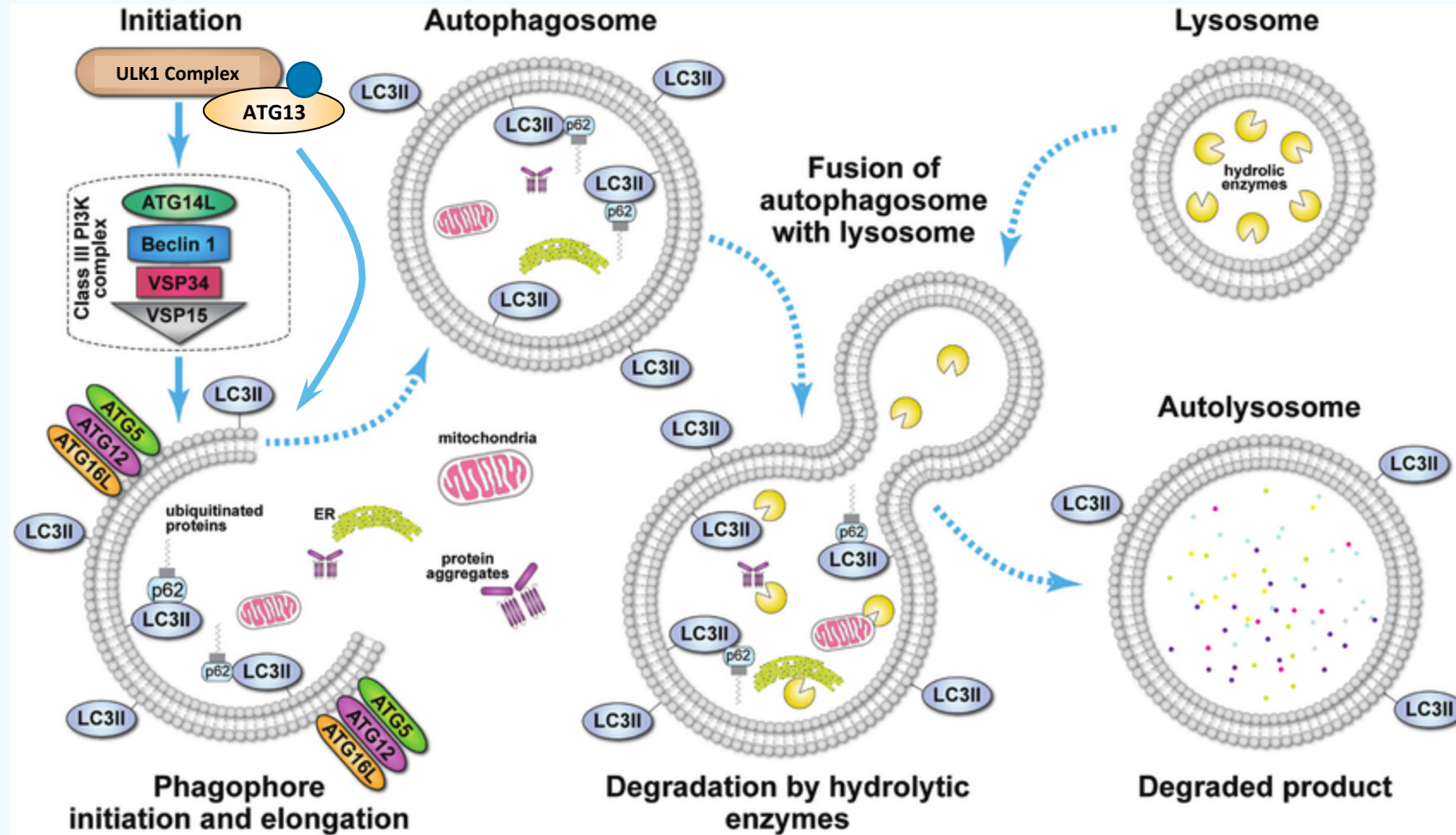
YOSHINORI OHSUMI
NOBEL PRIZE IN PHYSIOLOGY & MEDICINE 2016
FOR THE STUDY OF AUTOPHAGY



NATURE REVIEWS | DRUG DISCOVERY

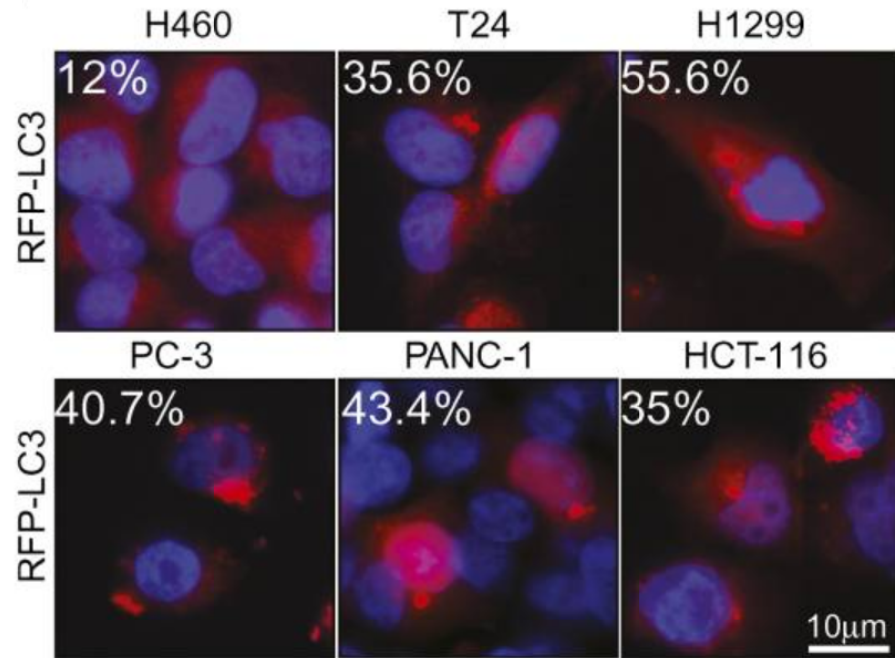
**AUTOPHAGY IS A SIGNAL TRANSDUCTION PATHWAY
WITH DEFINED MOLECULAR COMPONENTS**

Overview of Autophagy and RAS Cancers



Ndoye A and Weeraratna AT. Autophagy- An emerging target for melanoma therapy [version 1]. F1000Research 2016, 5:1888. (doi: 10.12688/f1000research.8347.1)

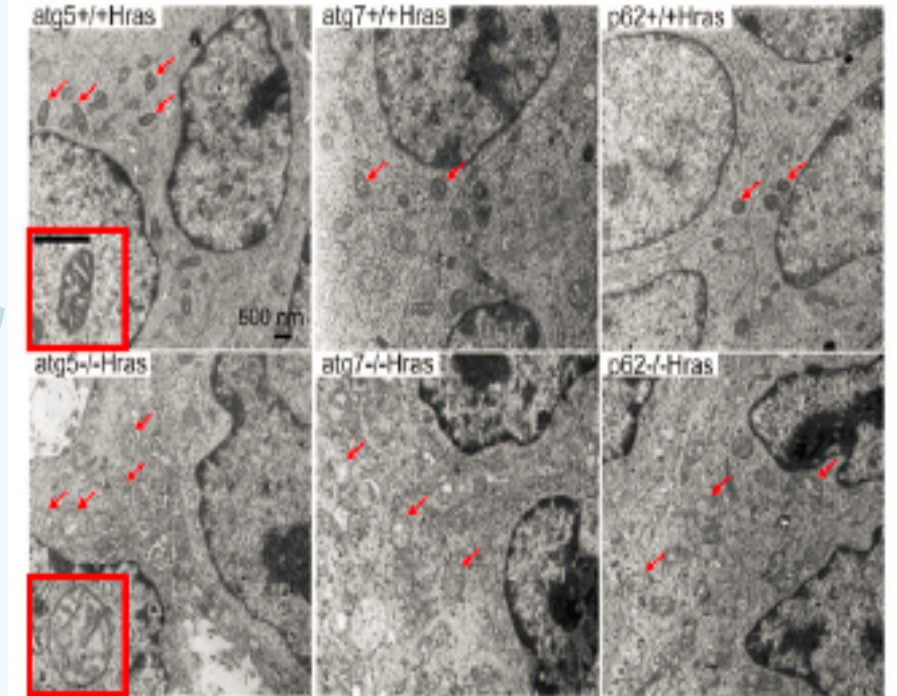
RAS Cancers Exhibit High Levels of Basal Autophagy



Evaluation of Cellular LC-3 Puncta

Competent Autophagy

Incompetent Autophagy



Swollen Mitochondria Accumulate in Cells where Autophagy is Blocked

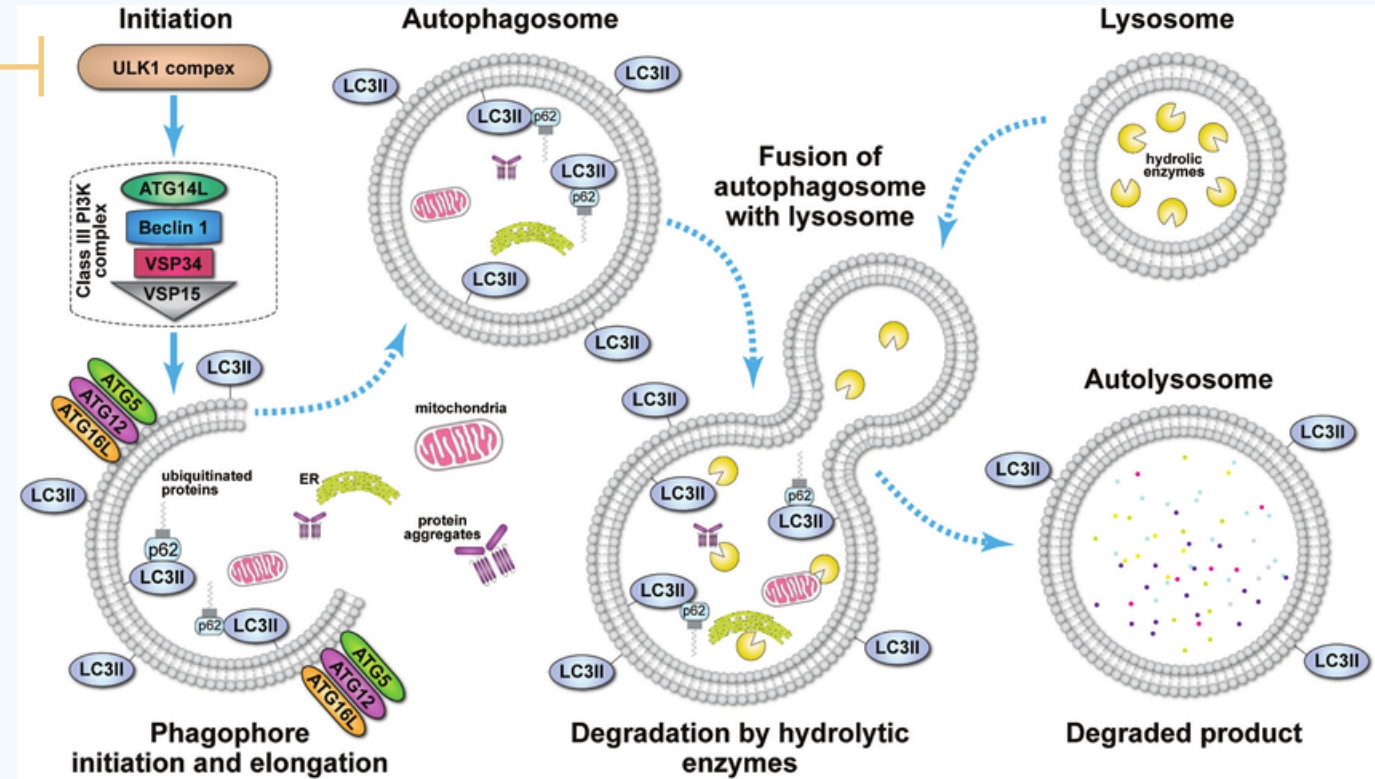
Genes and Development 2011;25:460-70

Strategies for Blocking Autophagy in Cancer

ULK Inhibition

- ULK is initiating factor of autophagy
- Druggable serine/threonine kinase
- Receives and processes key input from nutrient and stress sensors

DCC-3116



Adapted from: Ndoye A and Weeraratna AT. Autophagy- An emerging target for melanoma therapy [version 1]. F1000Research 2016, 5:1888. (doi: 10.12688/f1000research.8347.1)

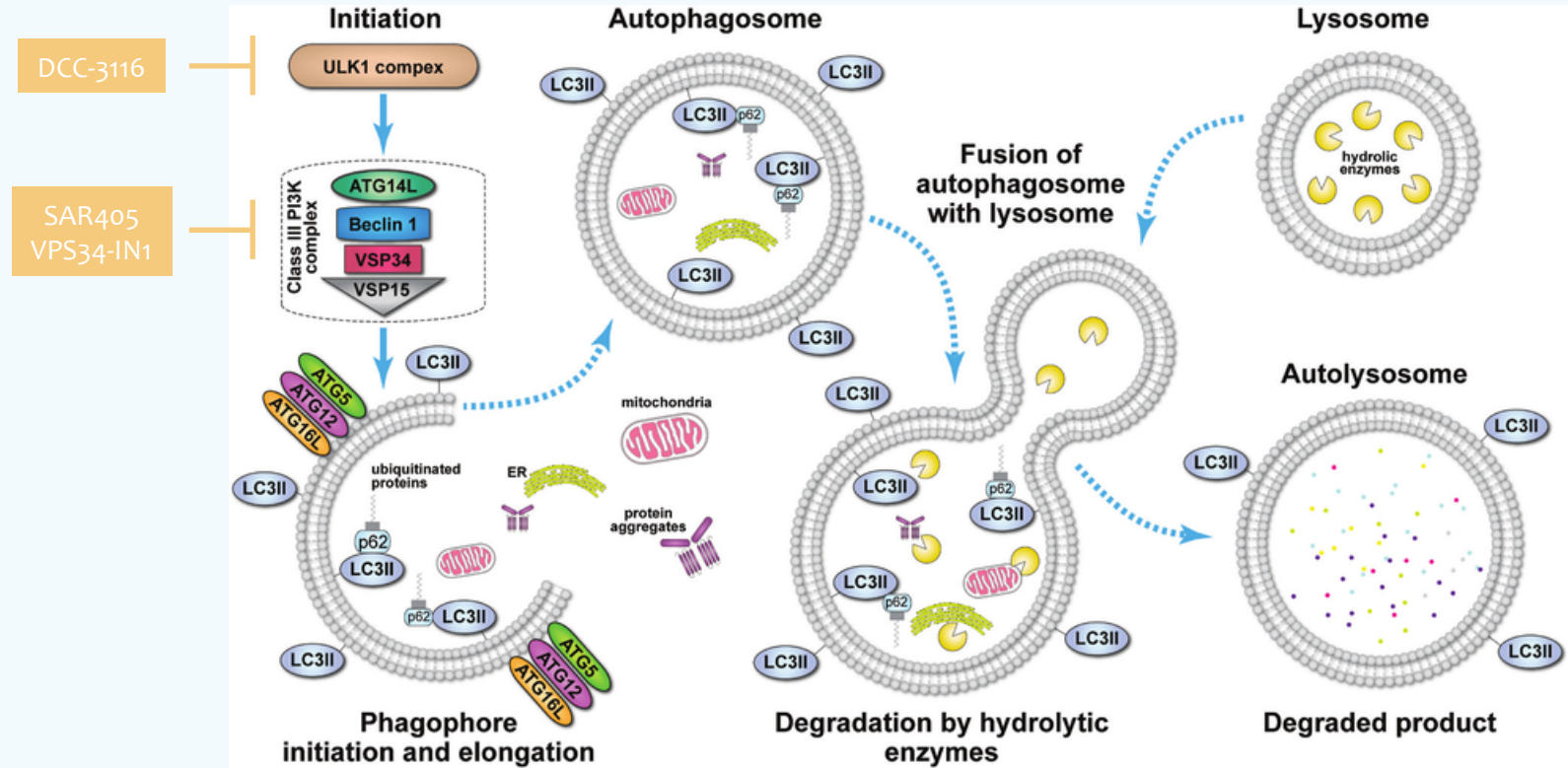
Strategies for Blocking Autophagy in Cancer

ULK Inhibition

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VPS34 Complex Inhibition

- Druggable lipid kinase target
- ULK can bypass VPS34
- Interference with normal lysosomal house-keeping functions



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Strategies for Blocking Autophagy in Cancer

ULK Inhibition

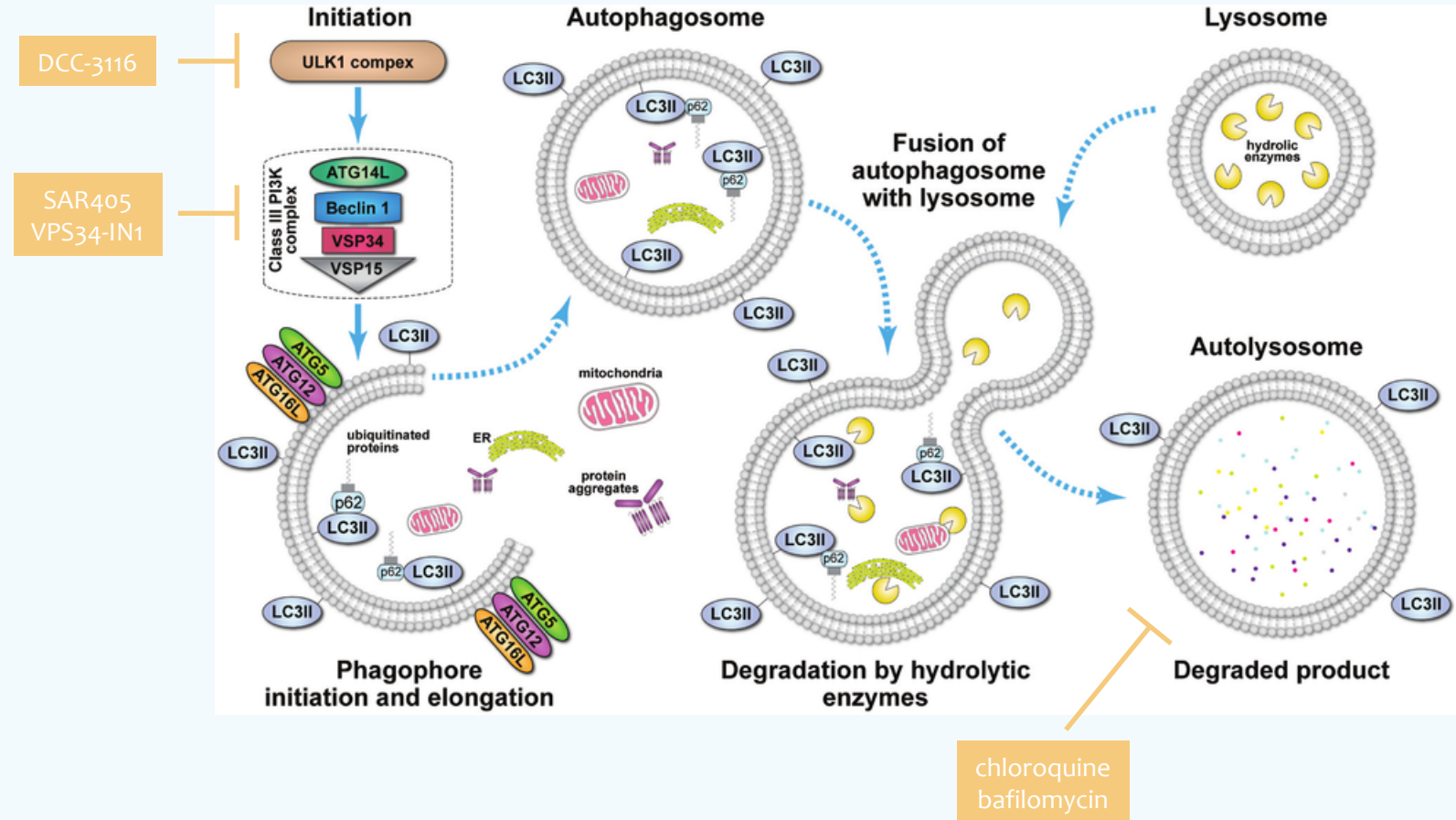
- ULK is initiating factor of autophagy
- Druggable serine/threonine kinase
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VPS34 Complex Inhibition

- Druggable lipid kinase target
- ULK can bypass VPS34
- Interference with normal lysosomal house-keeping functions

Lysosomal Inhibition

- Indirect and non-selective inhibition by preventing degradation of the contents
- Elevated pH inactivates hydrolases
- Interference with normal lysosomal house-keeping functions



Adapted from: Ndoye A and Weeraratna AT. Autophagy- An emerging target for melanoma therapy [version 1]. F1000Research 2016, 5:1888. (doi: 10.12688/f1000research.8347.1)

RAS Cancers Exhibit Addiction to Autophagy

THREE 2019 PUBLICATIONS INDEPENDENTLY VALIDATE COMBINED INHIBITION OF MAPK & AUTOPHAGY PATHWAYS AS NEW TARGETED APPROACH FOR POTENTIAL IN RAS CANCERS

nature
medicine

Letters

<https://doi.org/10.1038/s41591-019-0367-9>

Protective autophagy elicited by RAF→MEK→ERK inhibition suggests a treatment strategy for RAS-driven cancers

Conan G. Kinsey^{1,2}, Soledad A. Camolotto¹, Amelie M. Boespflug^{1,3,4}, Katrin P. Gullien¹, Mona Foth¹, Amanda Truong¹, Sophia S. Schuman¹, Jill E. Shea⁵, Michael T. Seipp⁵, Jeffrey T. Yap^{1,6}, Lance D. Burrell¹, David H. Lum¹, Jonathan R. Whisenant^{1,2}, G. Weldon Gilcrease III^{1,2}, Courtney C. Cavalieri^{1,7}, Kaitrin M. Rehbein¹, Stephanie L. Cutler¹, Kajsia E. Affolter^{1,8}, Alana L. Welm^{1,9}, Bryan E. Welm^{1,5}, Courtney L. Scaife^{1,5}, Eric L. Snyder^{1,8} and Martin McMahon^{1,10*}

Articles

<https://doi.org/10.1038/s41591-019-0368-8>

Combination of ERK and autophagy inhibition as a treatment approach for pancreatic cancer

Kirsten L. Bryant¹, Clint A. Stalneck¹, Daniel Zeitouni¹, Jennifer E. Klomp¹, Sen Peng², Andrey P. Tikunov³, Venugopal Gunda⁴, Mariaelena Pierobon⁵, Andrew M. Waters¹, Samuel D. George¹, Garima Tomar¹, Björn Papke¹, G. Aaron Hobbs¹, Liang Yan⁶, Tikvah K. Hayes⁷, J. Nathaniel Diehl⁷, Gennifer D. Goode⁴, Nina V. Chaika⁴, Yingxue Wang⁸, Guo-Fang Zhang⁸, Agnieszka K. Witkiewicz⁹, Erik S. Knudsen¹⁰, Emanuel F. Petricoin III⁵, Pankaj K. Singh⁴, Jeffrey M. Macdonald³, Nhan L. Tran¹¹, Costas A. Lyssiotis¹², Haoqiang Ying⁶, Alec C. Kimmelman¹³, Adrienne D. Cox^{1,14,15} and Channing J. Der^{1,7,15*}

PNAS

MAP kinase and autophagy pathways cooperate to maintain RAS mutant cancer cell survival

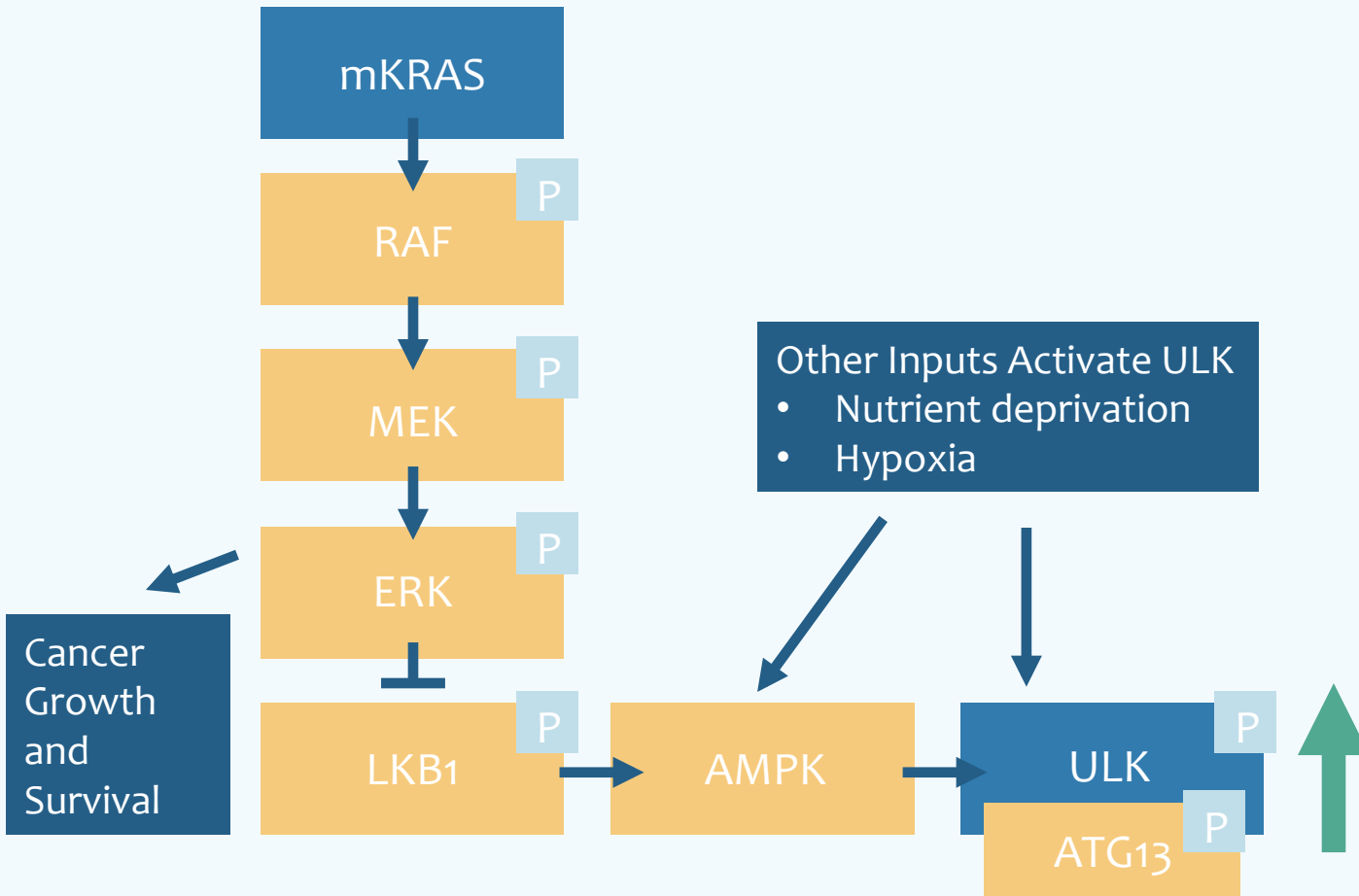
Chih-Shia Lee^a, Liam C. Lee^{a,1}, Tina L. Yuan^{b,2}, Sirisha Chakka^{c,3}, Christof Fellmann^{d,4}, Scott W. Lowe^{d,e,f}, Natasha J. Caplen^c, Frank McCormick^{b,g,5}, and Ji Luo^{a,5}

^a Laboratory of Cancer Biology and Genetics, Center for Cancer Research, National Cancer Institute, Bethesda, MD 20892; ^b Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, CA 94158; ^c Genetics Branch, Center for Cancer Research, National Cancer Institute, Bethesda, MD 20892; ^d Cold Spring Harbor Laboratory, Cold Spring Harbor, NY 11724; ^e Howard Hughes Medical Institute, Memorial Sloan Kettering Cancer Center, New York, NY 10065; ^f Department of Cancer Biology & Genetics, Memorial Sloan Kettering Cancer Center, New York, NY 10065; and Cancer Research Technology Program, Frederick National Laboratory for Cancer Research, Leidos Biomedical Research, Frederick, MD 21702

Edited by Ronald A. DePinho, University of Texas MD Anderson Cancer Center, Houston, TX, and approved December 17, 2018 (received October 18, 2018)

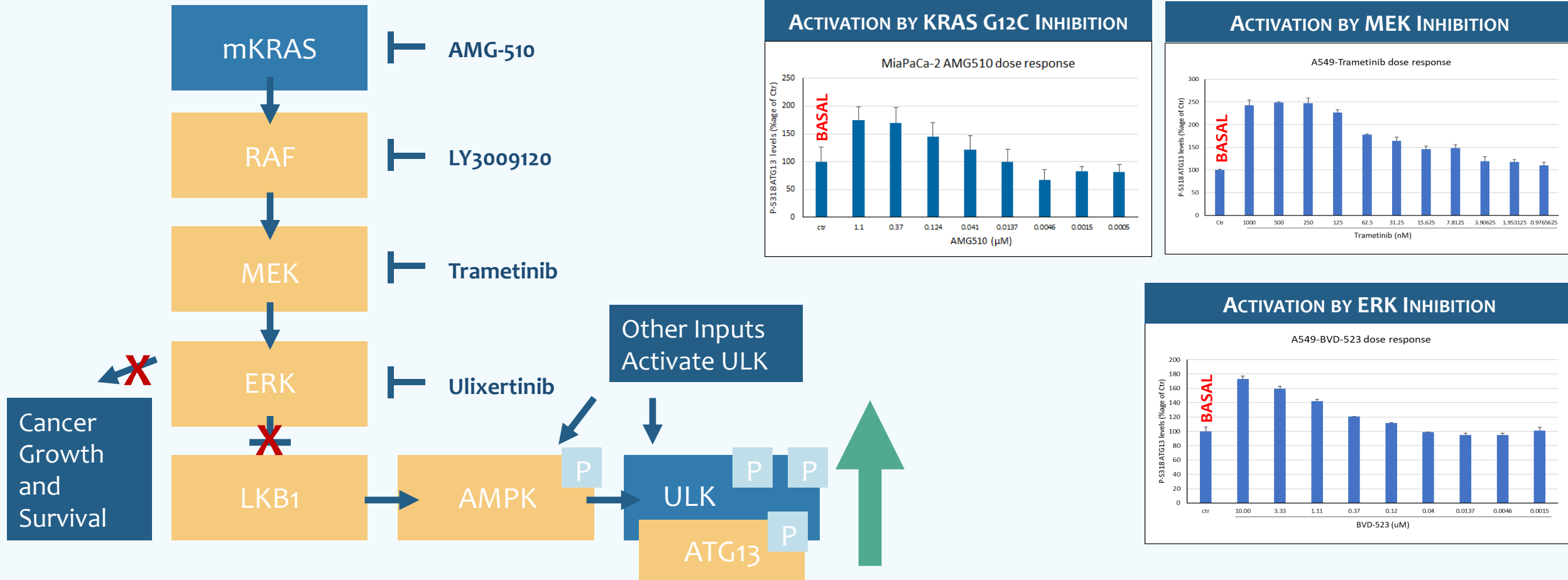
KRAS Activation Drives Tumor Growth and Tonic Regulation of ULK

ULK IS ACTIVE IN RAS CELLS, YET SIGNALING THROUGH KRAS MEDIATES A GOVERNOR ON ULK



MAPK Pathway Inhibition Leads to Release of Tonic Inhibition of ULK

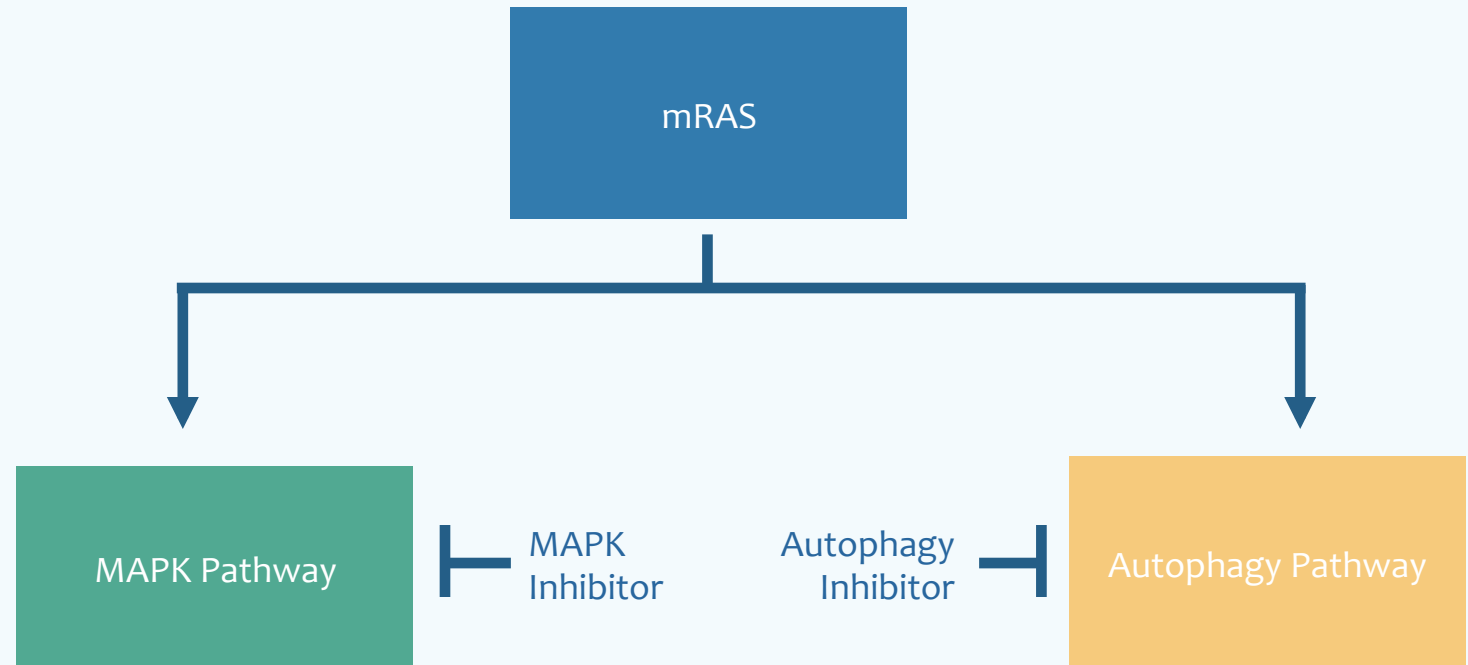
AUTOPHAGY IS A COMPENSATORY SURVIVAL MECHANISM IN MAPK PATHWAY INHIBITOR-TREATED RAS CANCERS



A New Potential Approach to Potentially Treat RAS Cancers

INHIBITORS TARGETING BOTH EFFECTOR PATHWAYS DOWNSTREAM OF RAS SIGNALING

- mRAS cancers signal through the MAPK signaling pathway
- mRAS cancers are addicted to autophagy for survival
- A drug combination of a MAPK pathway inhibitor and an autophagy pathway inhibitor potentially targets all mRAS cancers (KRAS, NRAS, HRAS)



DCC-3116 in Combination with a MAPK Pathway Inhibitors and Other Anti-Tumor Agents in RAS Cancers

POTENTIAL COMBINATION THERAPIES WITH ULK INHIBITORS

MEK Inhibitors

- Trametinib, binimetinib

ERK Inhibitors

- Ulixertinib, LY3214996

RAF Inhibitors

- LY3009120 (pan-RAF inhibitor)

KRAS G12C Small Molecule Covalent Inhibitors

- AMG-510, MRTX 849

Other

- Targeted therapies
- Chemotherapies

DCC-3116 is a Potent & Selective ULK Inhibitor Designed to Inhibit Autophagy

Summary

Highly Potent (IC_{50} at 1 mM ATP)

- ULK1 4.7 nM
- ULK2 35 nM

Highly Selective

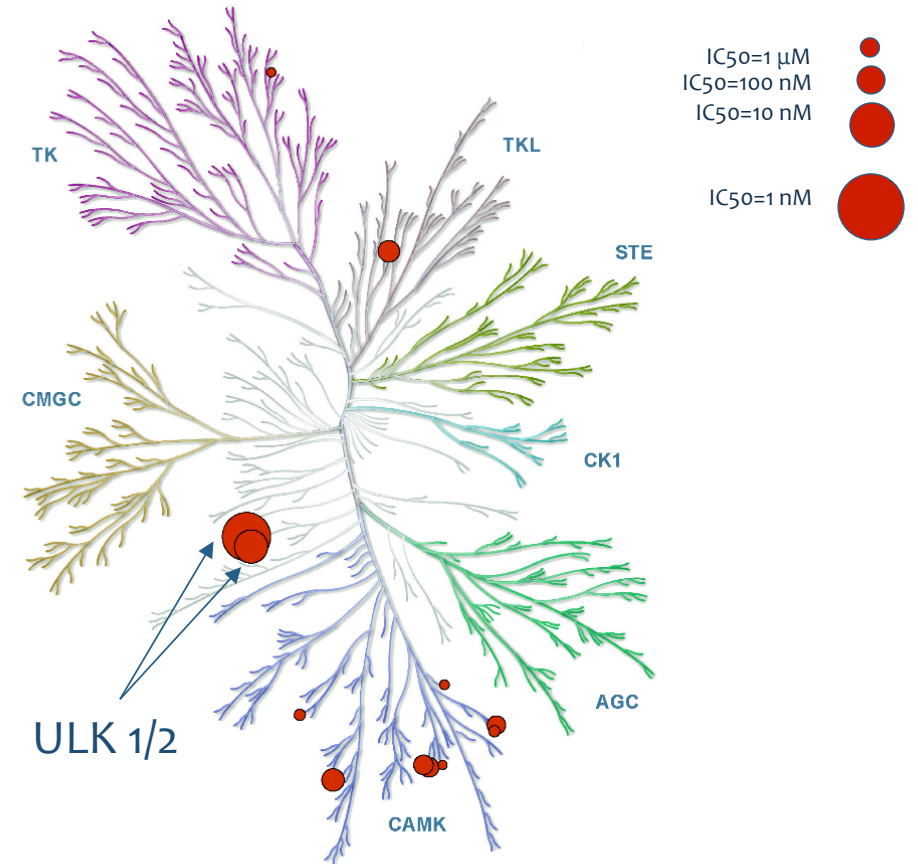
- No off-target kinases within 30-fold of ULK1
- Only 5 kinases within 100-fold of ULK1

Designed to avoid CNS exposure

- Low Ratio Brain_{ff}/Plasma_{ff} (4.3%) to avoid CNS autophagy

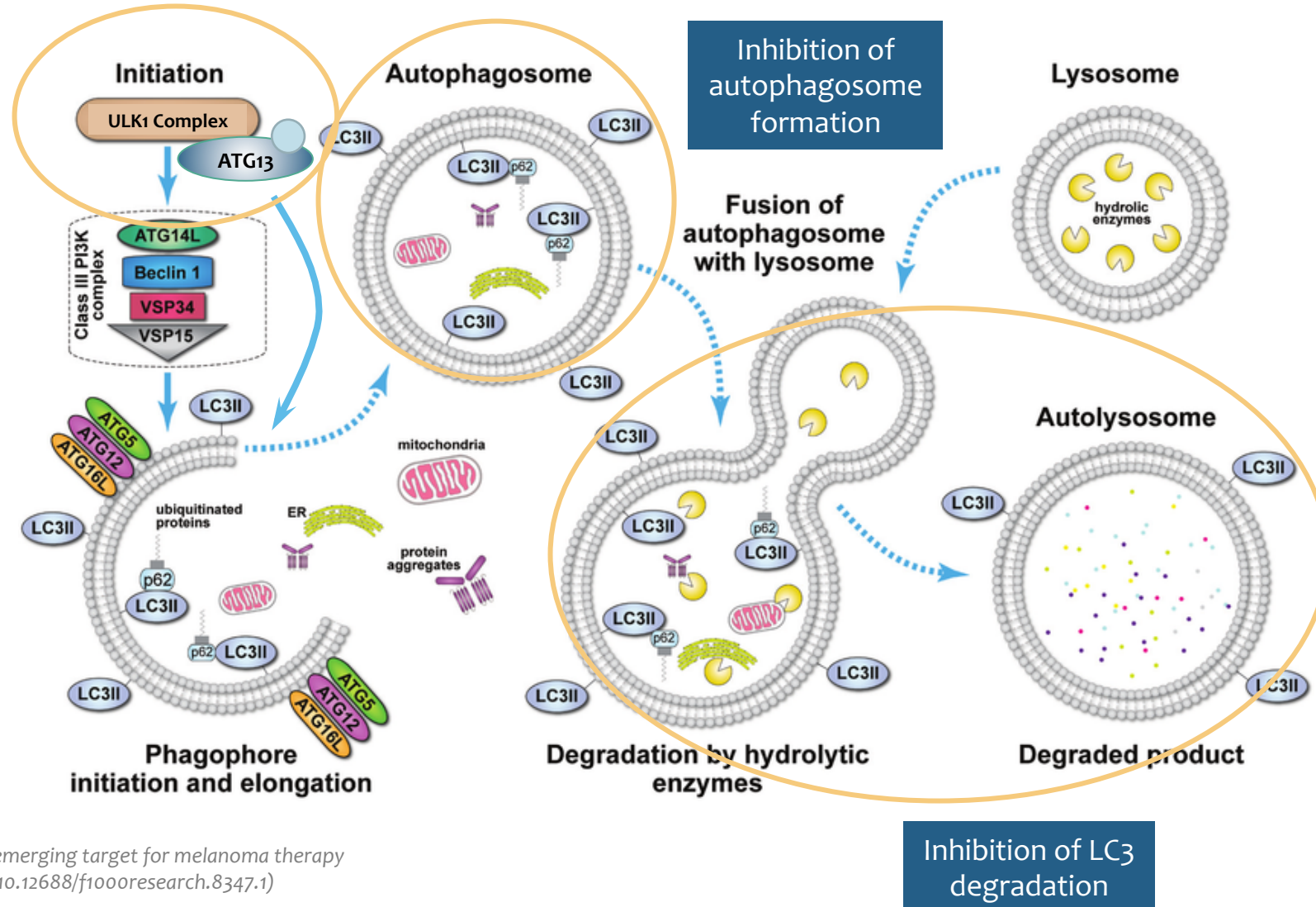
IND Filing Expected in Mid-2020

DCC-3116: A SELECTIVE ULK1/2 INHIBITOR



DCC-3116 Inhibits Autophagy in Cellular Assays

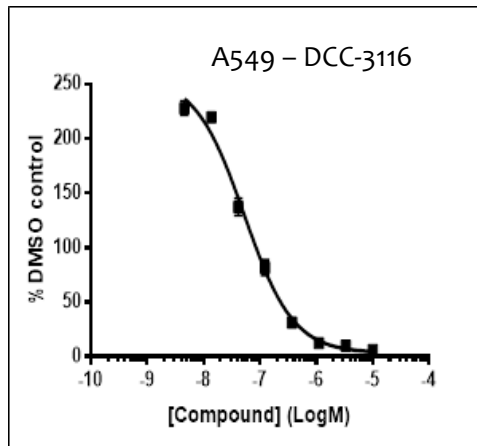
Inhibition of ULK phosphorylation of substrate ATG13 in the presence of MAPKi



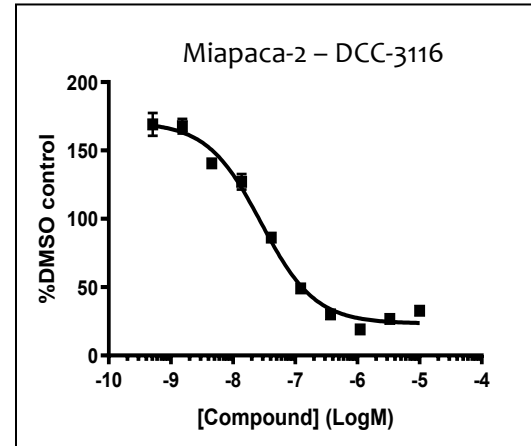
Ndoye A and Weeraratna AT. Autophagy- An emerging target for melanoma therapy [version 1]. F1000Research 2016, 5:1888. (doi: 10.12688/f1000research.8347.1)

DCC-3116 Potently Inhibits ULK in Multiple RAS Cancer Cell Lines

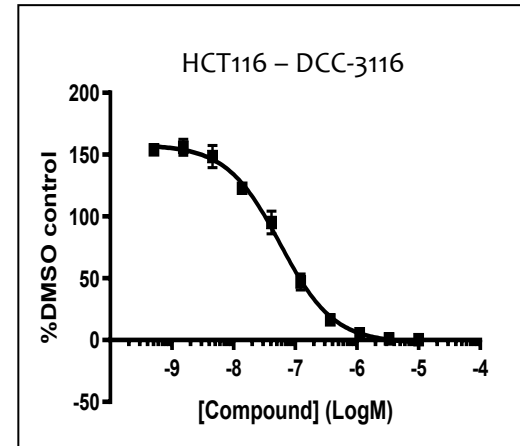
KRAS LUNG CANCER



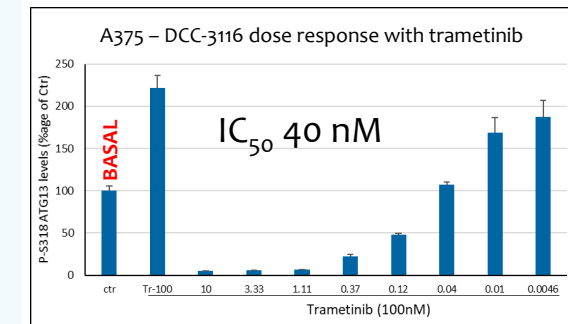
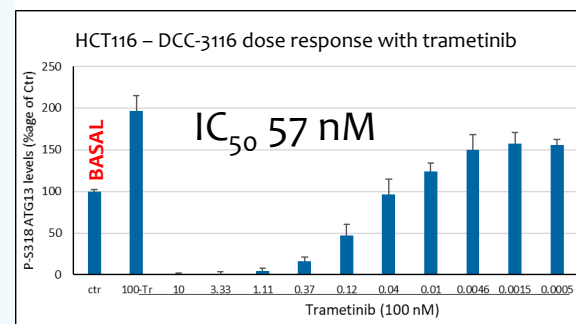
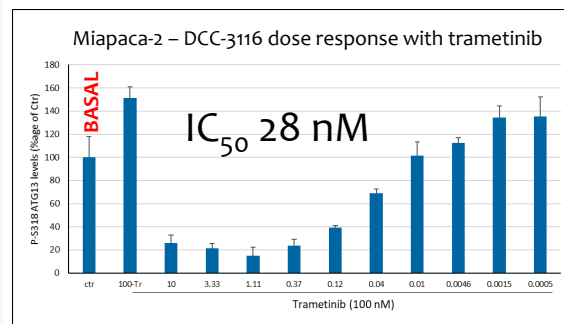
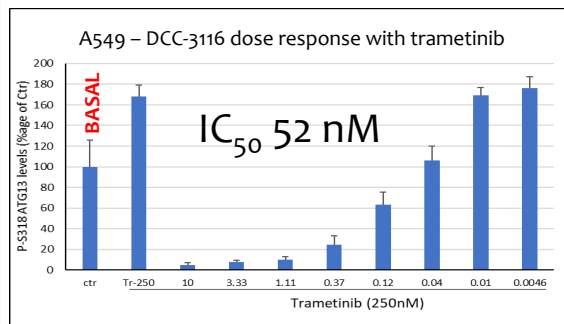
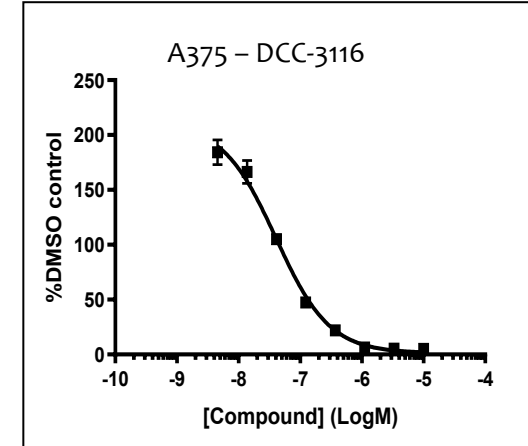
KRAS G12C PANCREATIC CANCER



KRAS COLORECTAL CANCER



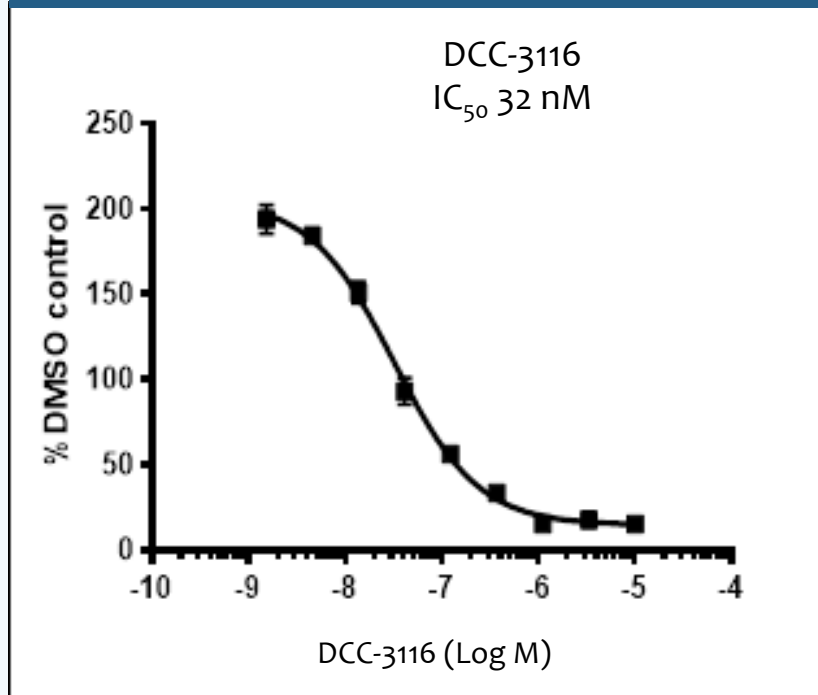
BRAF MELANOMA CANCER



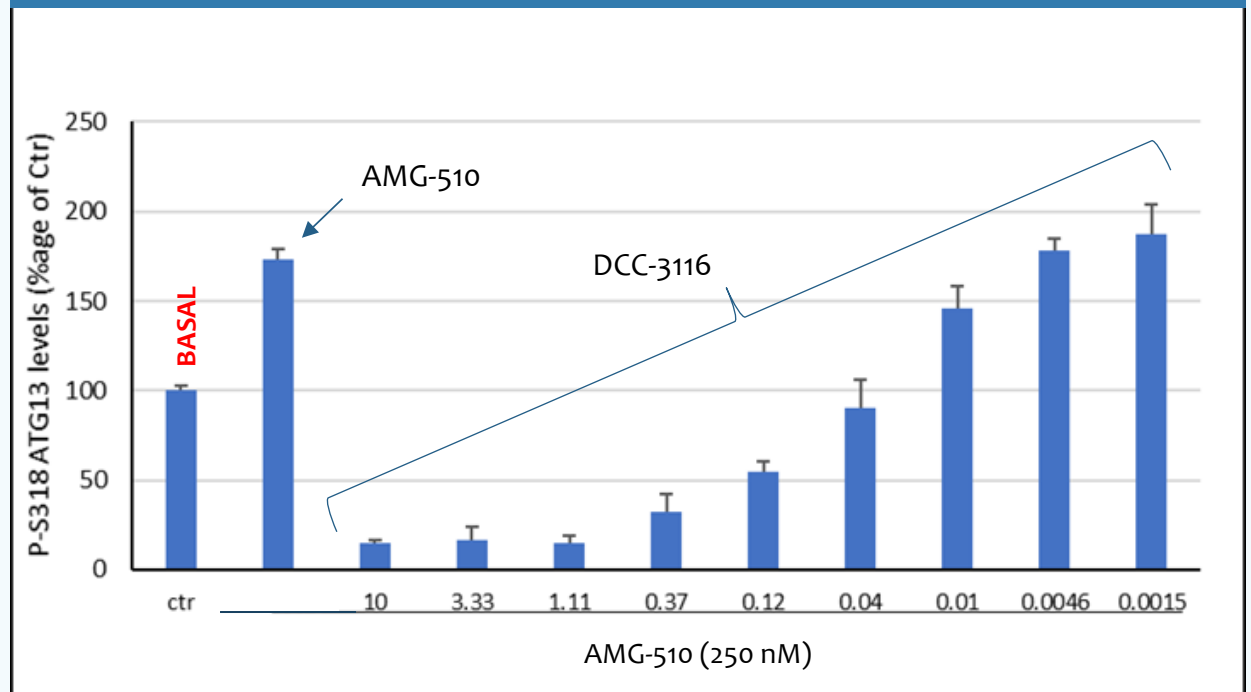
BASAL AND MAPK INHIBITOR-MEDIATED COMPENSATORY INCREASED AUTOPHAGY ARE INHIBITED

DCC-3116 Inhibits Compensatory Autophagy *In Vitro* from KRAS G12C Inhibitors

DCC-3116 IC₅₀ OF 32 nM FOR INHIBITION OF AUTOPHAGY INDUCED BY AMG-510

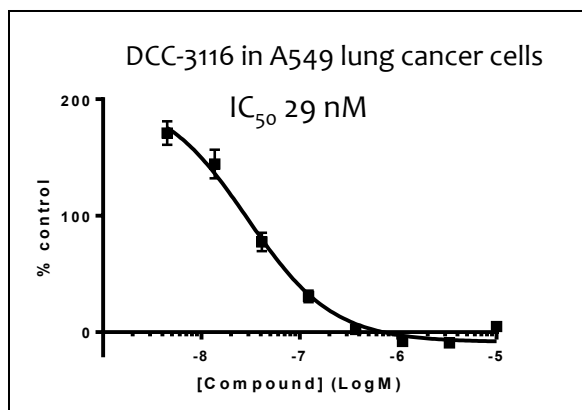


MIAPACA-2 PANCREATIC CANCER STUDY WITH AMG-510

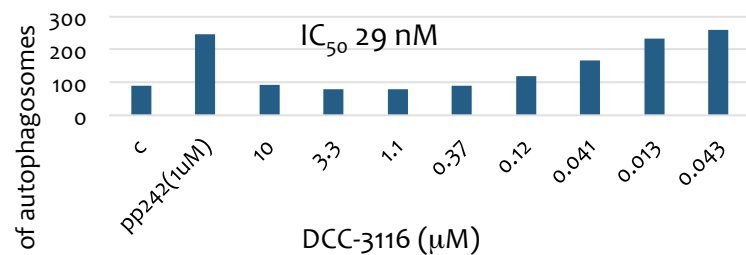


DCC-3116 Inhibits Autophagosome Formation and Lysosomal Degradation in KRAS Mutant Cancer Cells *In Vitro*

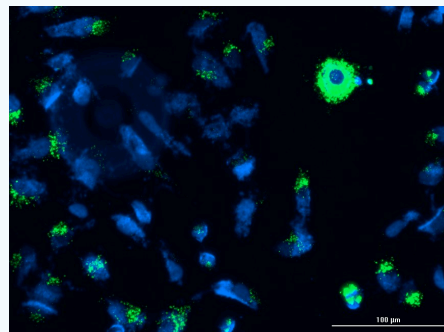
AUTOPHAGOSOME FORMATION INHIBITION



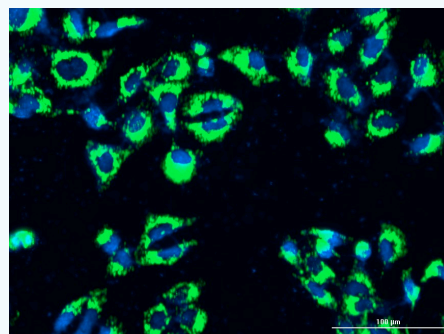
Graphical representation of autophagosome puncta in A549 lung cancer cells



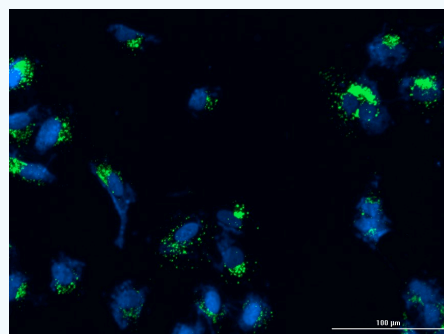
Control



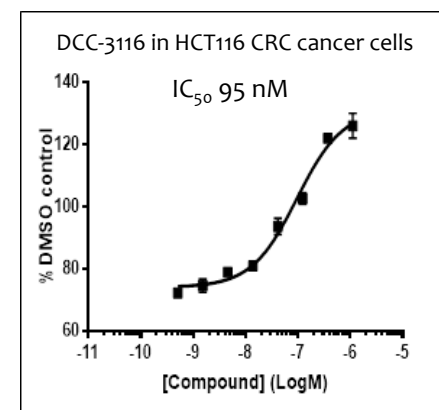
mTOR inhibitor



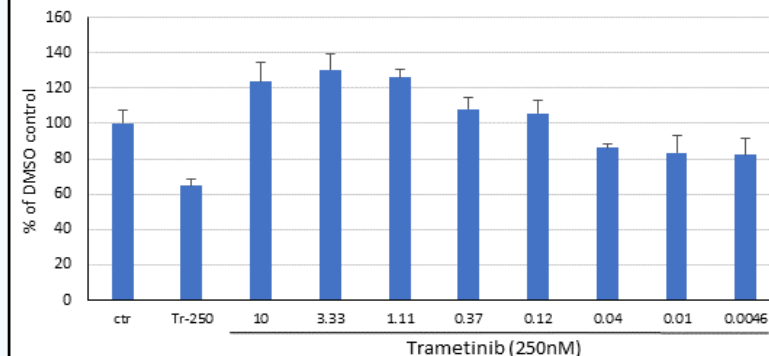
DCC-3116 + mTORi



LC3 DEGRADATION INHIBITION

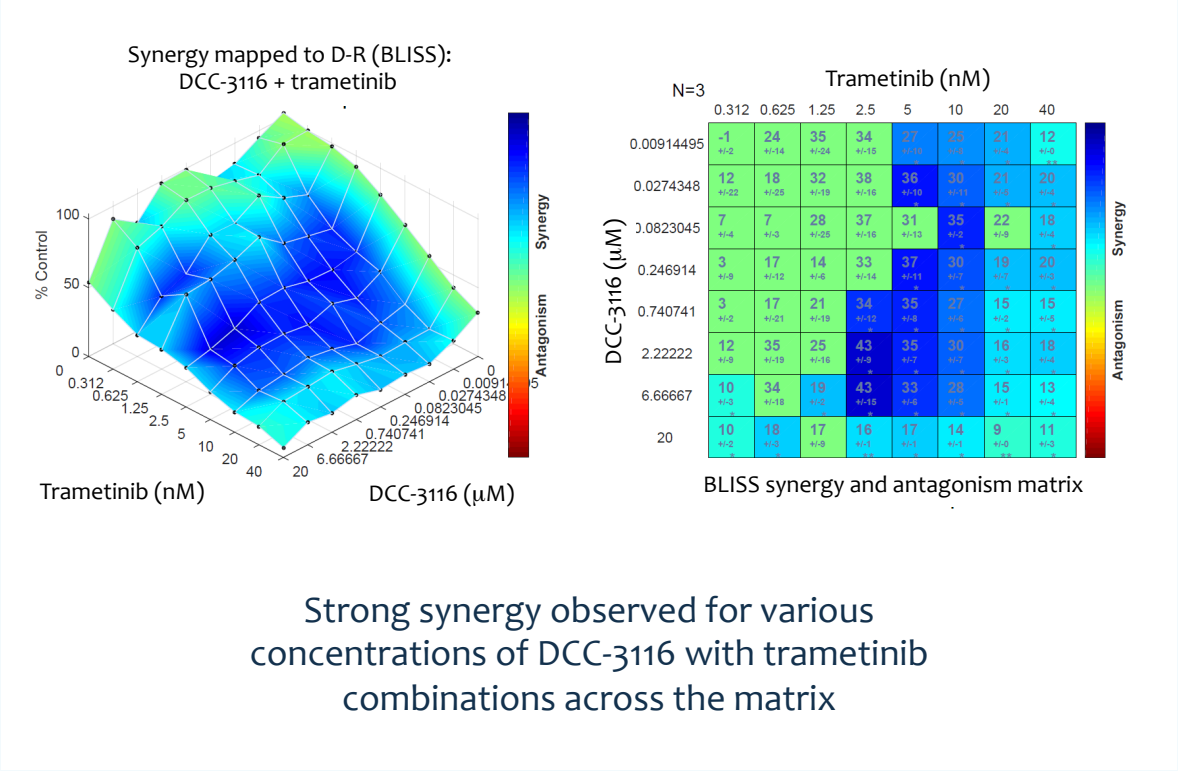


Graphical representation of LC3 levels in HCT-116 colorectal cancer cells

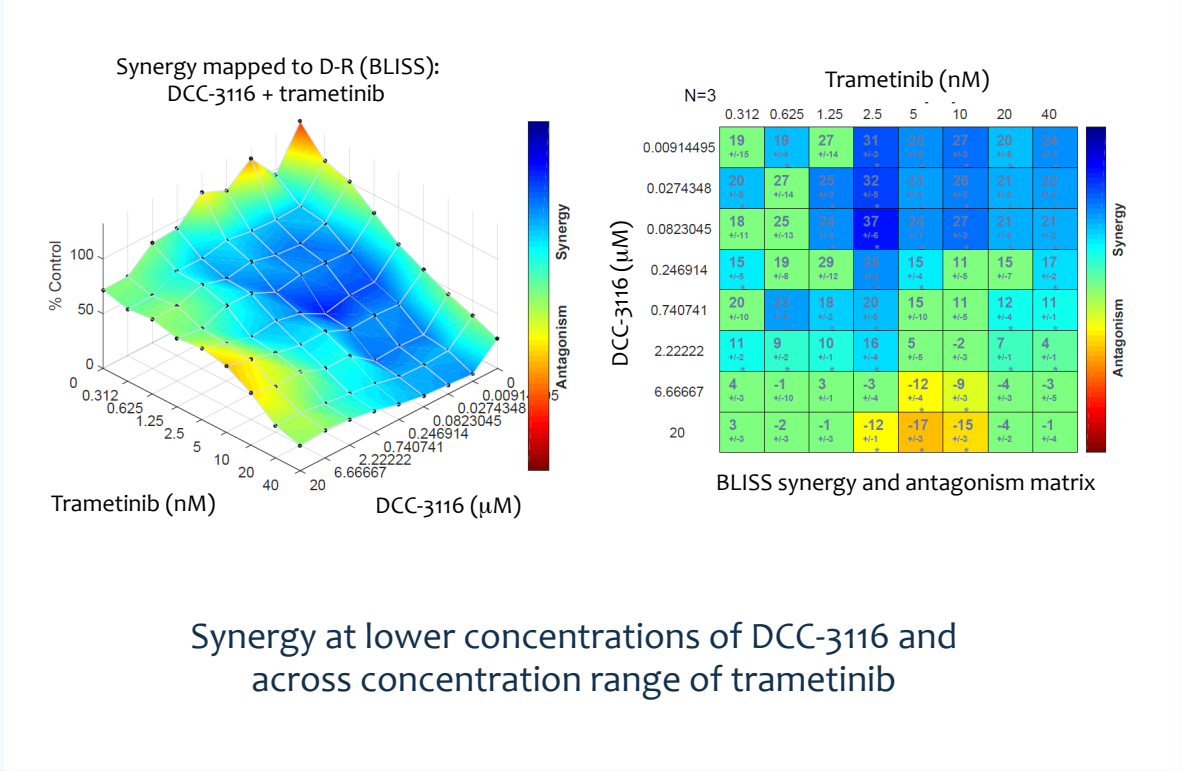


DCC-3116 + Trametinib Synergize to Inhibit Pancreatic Cancer Cell Proliferation *In Vitro*

INHIBITION OF CELL PROLIFERATION IN KRAS MUTANT MIAPACA-2 PANCREATIC CANCER CELLS

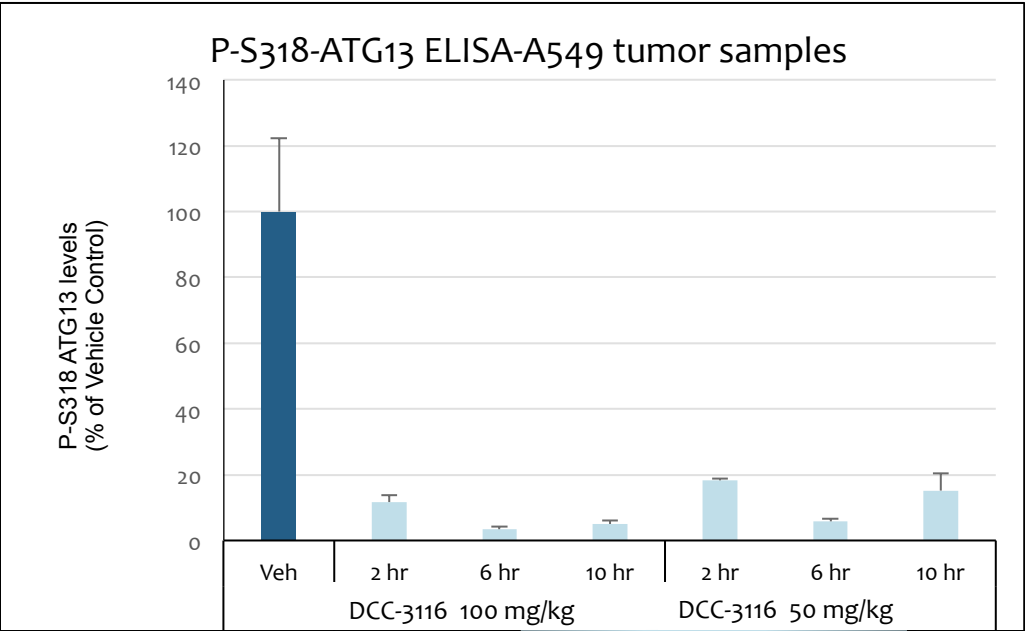


INHIBITION OF CELL PROLIFERATION IN BRAF MUTANT BxPC3 PANCREATIC CANCER CELLS



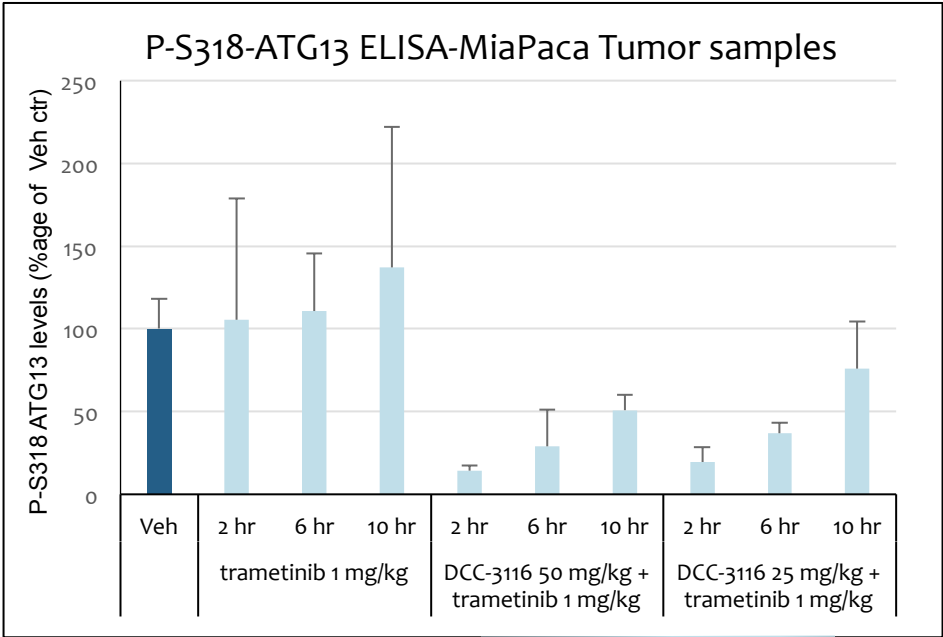
DCC-3116 Durably Inhibits ULK *In Vivo* in KRAS Cancer PK/PD Models

A549 LUNG CANCER



	DCC-3116 100 mg/kg			DCC-3116 50 mg/kg		
	2 hr	6 hr	10 hr	2 hr	6 hr	10 hr
Free drug (nM)	9,542	7,058	8,017	7,643	5,140	1,715
% pATG13 inhibition	88	97	95	82	94	95

MIAPACA-2 PANCREATIC CANCER

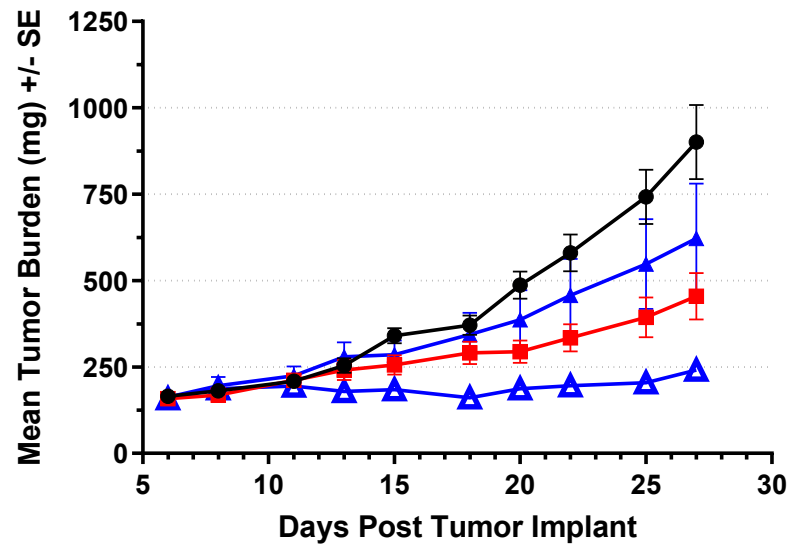


	DCC-3116 50 mg/kg			DCC-3116 25 mg/kg		
	2 hr	6 hr	10 hr	2 hr	6 hr	10 hr
Free drug (nM)	3,016	1,079	243	1,582	581	254
% pATG13 inhibition	86	71	49	80	63	24

DCC-3116 + MEK Inhibitors Exhibited Reduced Tumor Growth in KRAS *In Vivo* Cancer Models

KRAS MUTANT PANCREATIC

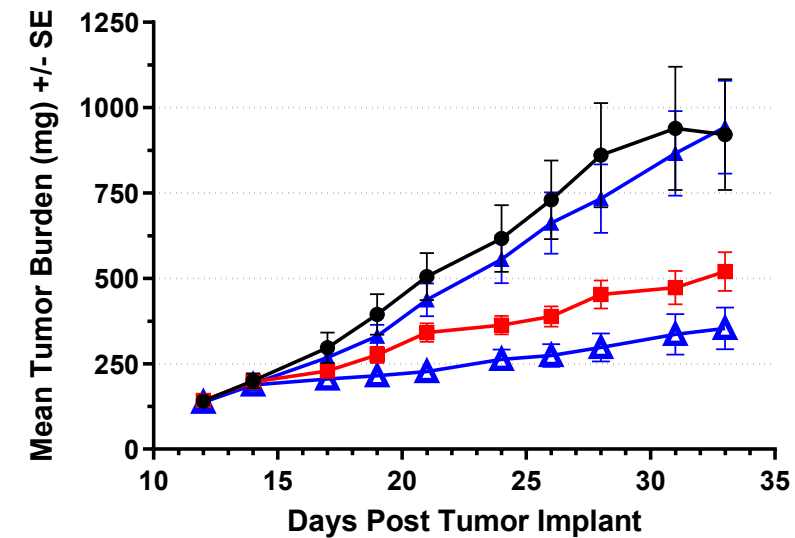
MiaPaca-2 Tumor Growth



- Vehicle
- trametinib 0.5 mg/kg PO QD
- ▲ DCC-3116 100 mg/kg PO BID
- ▲ DCC-3116 100 mg/kg + trametinib

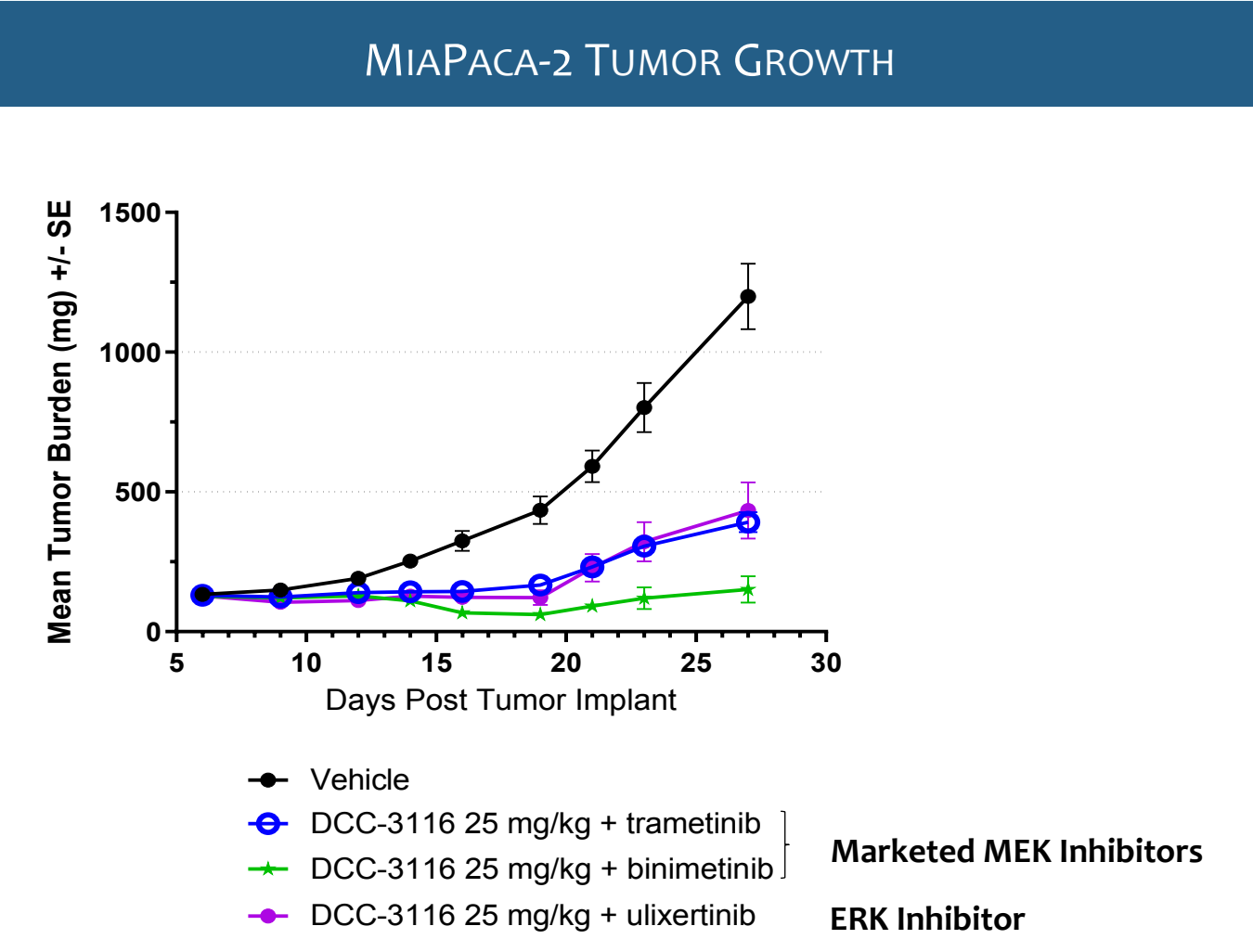
KRAS MUTANT LUNG

A549 Tumor Growth



- Vehicle
- trametinib 1 mg/kg PO QD
- ▲ DCC-3116 100 mg/kg PO BID
- ▲ DCC-3116 100 mg/kg + trametinib

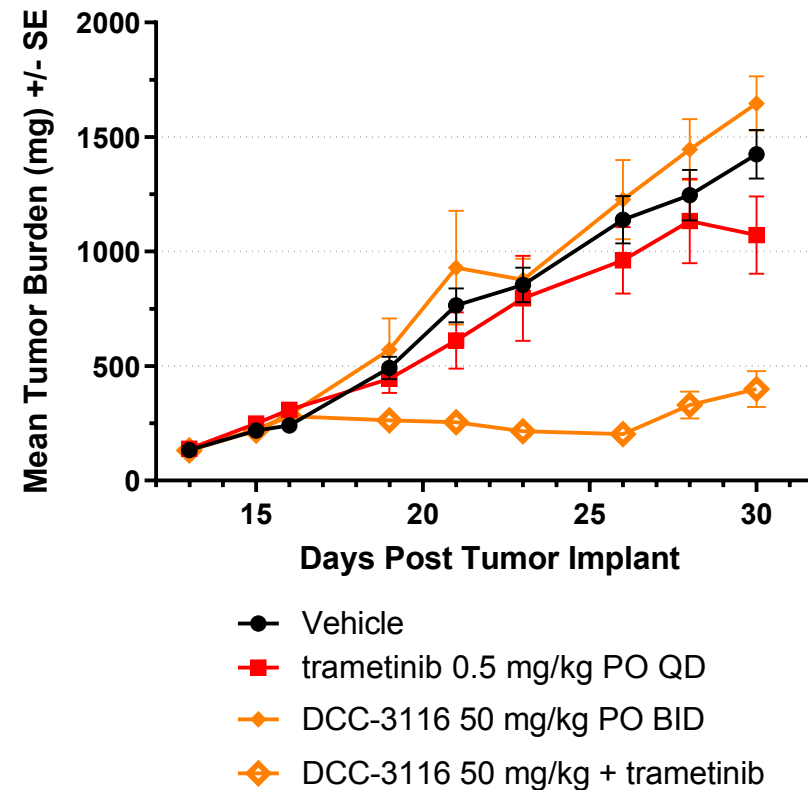
DCC-3116 + MEK and ERK Inhibitors Exhibit Synergy in RAS Cancer Model



DCC-3116 + MAPK Inhibitors Exhibited Reduced Tumor Growth in BRAF in *In Vivo* Cancer Models

BRAF MUTANT MELANOMA

A375 Tumor Growth



Rationale for DCC-3116 in RAS Cancers

RAS CANCERS DEPEND ON MEK/ERK SIGNALING & AUTOPHAGY FOR SURVIVAL	<ul style="list-style-type: none">• RAS cancers have high basal levels of autophagy• RAS cancers increase autophagy for survival as resistance mechanism to drug treatments
ULK KINASE IS AN INITIATING FACTOR FOR ACTIVATION OF AUTOPHAGY	<ul style="list-style-type: none">• First-in-class target opportunity for new therapeutic in RAS cancer• Differentiated approach to autophagy inhibition
DCC-3116 IS A POTENTIAL FIRST-IN-CLASS ULK KINASE INHIBITOR	<ul style="list-style-type: none">• Highly selective and potent inhibitor of ULK kinase• Designed for combination approach
STRONG PRELIMINARY PRECLINICAL VALIDATION	<ul style="list-style-type: none">• DCC-3116 inhibits autophagy in RAS cancer cell lines• DCC-3116 potently and durably inhibits autophagy <i>in vivo</i>• Combination of DCC-3116 plus MAPK pathway inhibitors synergize to block RAS cancers <i>in vivo</i>



Steve Hoerter

President & CEO

Closing Remarks & Q & A

Q & A





THANK YOU

Relevant Publications for DCC-3116

1. Bryant, Kirsten L. et al. “Combination of ERK and autophagy inhibition as treatment approach for pancreatic cancer.” *Nature Medicine* 2019; 25: 628-640.

<https://www.nature.com/articles/s41591-019-0368-8>

2. Lee, Chih-Shia et al. “MAP kinase and autophagy pathways cooperate to maintain RAS cancer cell survival.” *PNAS* 2019; 16(10): 4508-4517.

<https://www.pnas.org/content/116/10/4508>

3. Kinsey, Conan G. et al. “Protective autophagy elicited by RAF → MEK → ERK inhibition suggests a treatment strategy for RAS-driven cancers.” *Nature Medicine* 2019; 25: 620-627.

<https://www.nature.com/articles/s41591-019-0367-9>

4. Guo, Jessie Yanxiang et al. “Activated Ras requires autophagy to maintain oxidative metabolism and tumorigenesis.” *Genes & Development* 2011; 25: 460-470.

<http://genesdev.cshlp.org/content/25/5/460.abstract>

5. Yang, A. et al. “Autophagy sustains pancreatic cancer growth through both cell-autonomous and nonautonomous mechanisms.” *Cancer Discovery* 2018; 8: 276-287.

<http://cancerdiscovery.aacrjournals.org/content/early/2018/01/09/2159-8290.CD-17-0952.full-text.pdf>

6. Papke, B et al. “Drugging RAS: Know the enemy.” *Science* 17 March 2017; 1158-1163.

<https://www.ncbi.nlm.nih.gov/pubmed/28302824>

7. Cox, AD et al. “Drugging the undruggable RAS: Mission possible?” *Nat Rev Drug Discov* 2014; 13(11):828-51.

<https://www.ncbi.nlm.nih.gov/pubmed/25323927>

8. Dolgin, Elie. “Anticancer autophagy inhibitors attract ‘resurgent’ interest.” *Nature Reviews Drug Discovery* 2019; 18: 408-410.

<https://www.nature.com/articles/d41573-019-00072-1>