DCC-3116: A Selective ULK Kinase Inhibitor

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

June 18, 2019

decīphera

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This presentation may contain forward-looking statements that are based on our current expectations, estimates and projections about our industry as well as management's beliefs and assumptions. Words such as "anticipates," "expects," "intends," "plans," "believes," "seeks," "estimates," "may," "will," and variations of these words or similar expressions are intended to identify forward-looking statements. These statements include statements regarding our DCC-3116 program, our expectations for and the possibility of our DCC-3116 candidate to inhibit ULK and autophagy and possibly treat or provide therapeutic benefit for a wide range of cancers, the timing of and our plans to conduct IND-enabling studies, file an IND and develop DCC-3116 for mutant RAS cancers, our expectations for and timing of data from our Phase 3 INVICTUS study, our business strategy, prospective products, clinical trial results, product approvals and regulatory pathways, timing and likelihood of success, plans and objectives of management for future operations, expectation of designating future clinical candidates, future results of anticipated products, commercial readiness planning, and the market opportunity for our drug candidates, and speak only at the time this presentation was prepared. Such statements are based upon the information available to us now and are subject to change. We will not necessarily inform you of such changes. These statements are not guarantees of future performance and are subject to certain risks, uncertainties and assumptions that are difficult to predict. Therefore actual results could differ materially and adversely from those expressed in any forward-looking statements as a result of various factors. Factors which could cause actual results to differ materially from those in the forward-looking statements include, among others, risks and uncertainties related to the designation of DCC-3116 as a new clinical candidate, the expected benefits and development of DCC-3116, delay of any current or planned pre-clinical, IND-enabling and/or clinical studies or the development of our drug candidates, including ripretinib, rebastinib, DCC-3014 and DCC-3116, our advancement of multiple early-stage and later-stage efforts, our history of significant losses since inception, our ability to obtain necessary capital when needed on acceptable terms, the timing and results from ongoing or future clinical and nonclinical trials, our ability to obtain regulatory approval or clearance of our drug candidates, our ability to plan for potential commercialization, competition from other products or procedures, our reliance on third-parties to conduct our clinical and non-clinical trials, our reliance on single-source third-party suppliers to manufacture clinical, non-clinical and any future commercial supplies of our drug candidates and our ability to obtain, maintain and enforce our intellectual property rights for our drug candidates. New risk factors and uncertainties may emerge from time to time, and it is not possible to predict all risk factors and uncertainties. There can be no assurance that the opportunity will meet your investment objectives, that you will receive a return of all or part of such investment. Investment results may vary significantly over any given time period. The appropriateness of a particular investment or strategy will depend on an investor's individual circumstances and objectives. Deciphera recommends that investors independently evaluate specific investments and strategies. For further information regarding these risks, uncertainties and other factors, you should read the “Risk Factors” section of Deciphera’s Quarterly Report on Form 10-Q for the fiscal quarter ended March 31, 2019 filed with the Securities and Exchange Commission (the "SEC"), and Deciphera’s other SEC filings.

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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

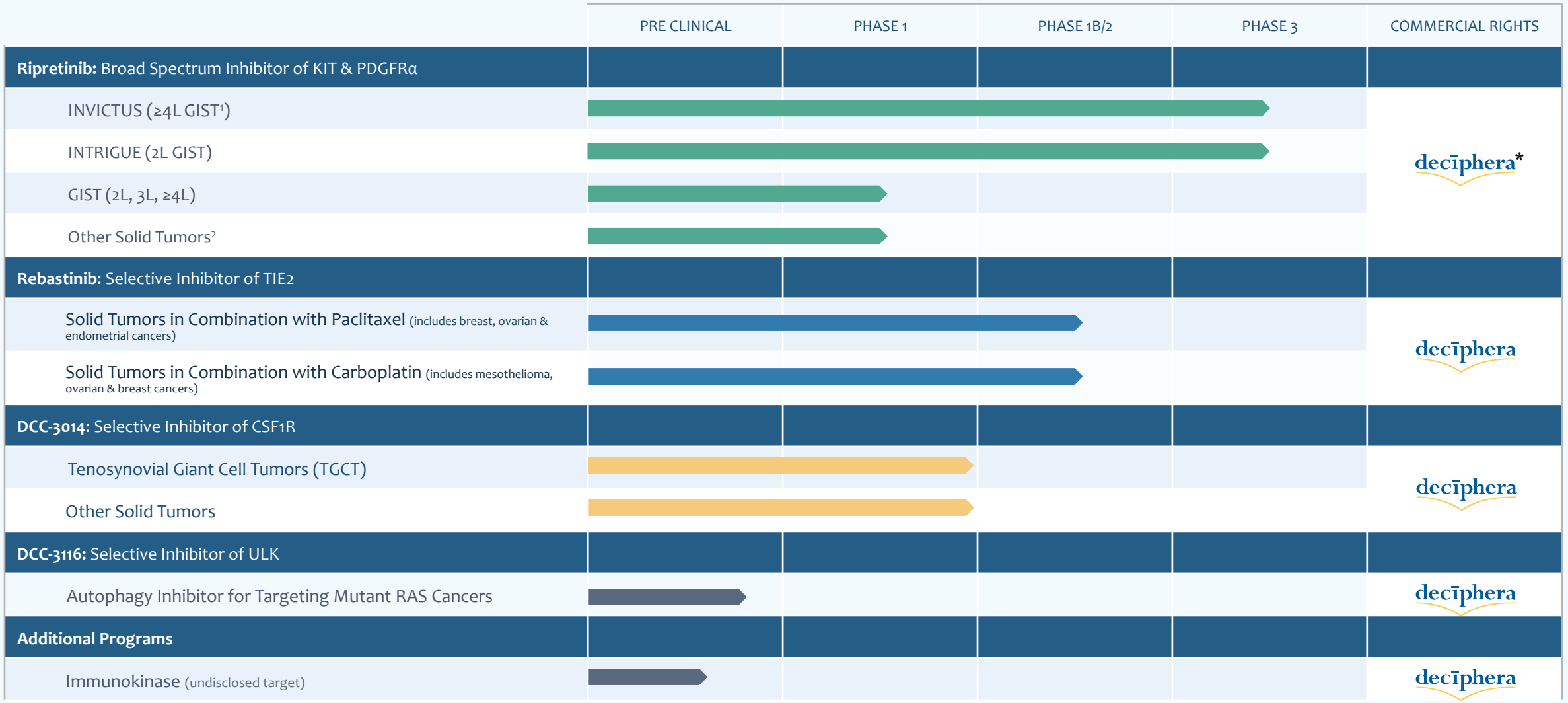
- **ULK Kinase Inhibitors & Autophagy**
  Daniel Flynn, Ph.D., EVP, Chief Scientific Officer & Founder

- **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 ≥4L 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



Notes: (1) GIST=gastrointestinal stromal tumors; (2) Includes systemic mastocytosis, malignant gliomas, non-small cell lung cancer, melanomas, soft tissue sarcoma & *patients with GIST and other solid tumors with renal impairment;*
**Development and commercialization partnership with Zai Labs in Greater China*

Significant 2019 Milestones Across the Pipeline

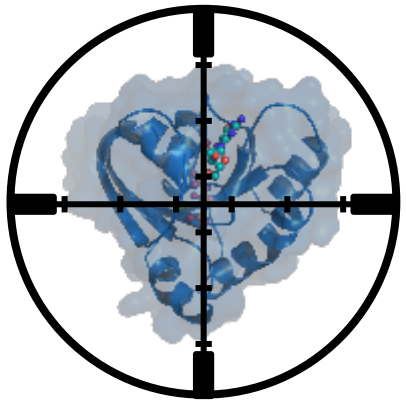
Ripretinib	☐ INVICTUS (≥4th Line GIST: Pivotal Phase 3 Results (Expected Mid-2019)) ☐ Phase 1 Expansion Data (2H 2019)
Rebastinib	☑ Phase 1b/2 Carboplatin Combination Initiated (1H 2019) ☑ Part 1 of the Phase 1b/2 Paclitaxel Combination Completed Enrollment (1H 2019) ☐ Part 1 of the Phase 1b/2 Paclitaxel 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

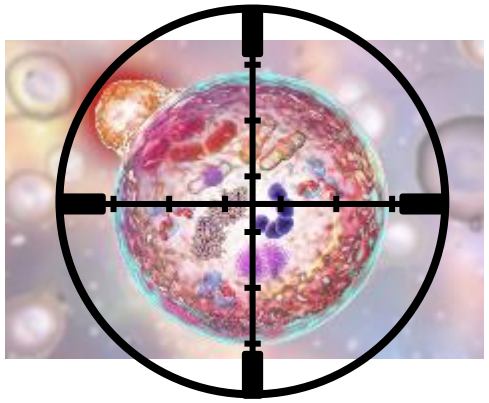
Autophagy & Mutant RAS Cancers

Deciphera Pharmaceuticals
June 18, 2019



KRAS oncoprotein

Exploiting autophagy for the treatment of RAS-mutant cancers



Autophagy

Channing J. Der, PhD
Sarah Graham Kenan Professor of Pharmacology
University of North Carolina at Chapel Hill
Lineberger Comprehensive Cancer Center

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

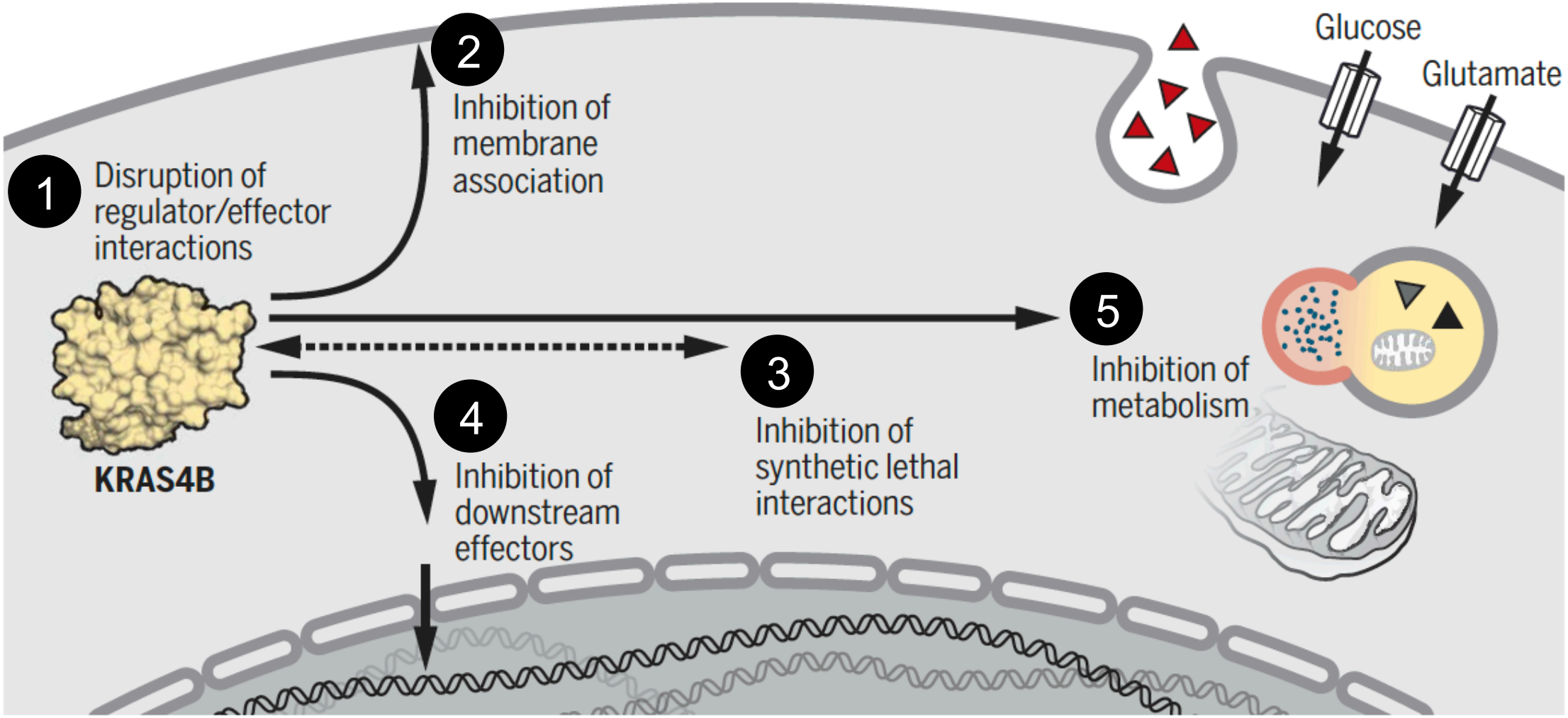
Cox et al (2014) Nat Rev Drug Discov 13:828

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

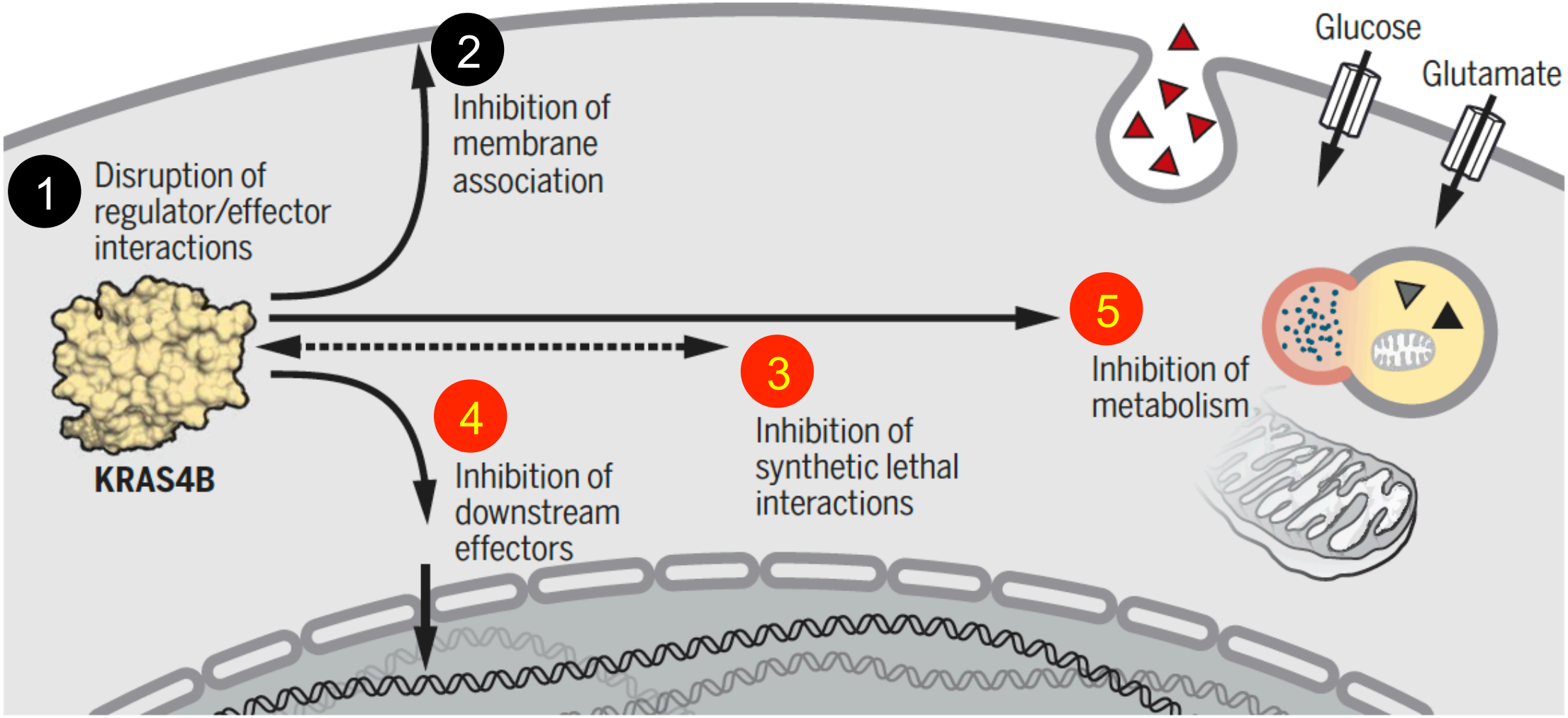
Siegel et al (2019) CA Cancer J Clin 69:10

Current strategies for targeting RAS for cancer treatment



Papke & Der (2017) Science 355:1158

Pursuit of three strategies converge on autophagy



Papke & Der (2017) Science 355:1158

RAS mutant cancers are addicted to autophagy

GENES & DEVELOPMENT 25:460–470 (2011)

Activated Ras requires autophagy to maintain oxidative metabolism and tumorigenesis

Jessie Yanxiang Guo,[1,2,3,8] Hsin-Yi Chen,[1,2,8] Robin Mathew,[1,4,8] Jing Fan,[5,8] Anne M. Strohecker,[1,4] Gizem Karsli-Uzunbas,[1,2] Jurre J. Kamphorst,[5] Guanghua Chen,[1,2] Johanna M.S. Lemons,[5] Vassiliki Karantza,[1,6] Hilary A. Coller,[1,7] Robert S. DiPaola,[1,6] Celine Gelinas,[1,3,4] Joshua D. Rabinowitz,[1,5] and Eileen White[1,2,4,9]

GENES & DEVELOPMENT 25:717–729 (2011)

Pancreatic cancers require autophagy for tumor growth

Shenghong Yang,[1] Xiaoxu Wang,[1,11] Gianmarco Contino,[2,3,11] Marc Liesa,[4] Ergun Sahin,[5] Haoqiang Ying,[5] Alexandra Bause,[6,7] Yinghua Li,[1] Jayne M. Stommel,[5] Giacomo Dell'Antonio,[8] Josef Mautner,[9] Giovanni Tonon,[10] Marcia Haigis,[6,7] Orian S. Shirihai,[4] Claudio Doglioni,[8] Nabeel Bardeesy,[2] and Alec C. Kimmelman[1,12]

- 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

NATURE MEDICINE VOL 25 | APRIL | 628-640 ARTICLES

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

Kirsten L. Bryant[1], Clint A. Stalnecker[1], Daniel Zeitouni[1], Jennifer E. Klomp[1], Sen Peng[2], Andrey P. Tikunov[3], Venugopal Gunda[4], Mariaelena Pierobon[5], Andrew M. Waters[1], Samuel D. George[1], Garima Tomar[1], Björn Papke[1], G. Aaron Hobbs[1], Liang Yan[6], Tikvah K. Hayes[7], J. Nathaniel Diehl[7], Gennifer D. Goode[4], Nina V. Chaika[4], Yingxue Wang[8], Guo-Fang Zhang[8], Agnieszka K. Witkiewicz[9], Erik S. Knudsen[10], Emanuel F. Petricoin III[5], Pankaj K. Singh[4], Jeffrey M. Macdonald[3], Nhan L. Tran[11], Costas A. Lyssiotis[12], Haoqiang Ying[6], Alec C. Kimmelman[13], Adrienne D. Cox[1,14,15] and Channing J. Der[1,7,15*]

NATURE MEDICINE VOL 25 | APRIL | 620-627 LETTERS

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

Conan G. Kinsey[1,2], Soledad A. Camolotto[1], Amelie M. Boespflug[1,3,4], Katrin P. Guillen[1], Mona Foth[1], Amanda Truong[1], Sophia S. Schuman[1], Jill E. Shea[5], Michael T. Seipp[5], Jeffrey T. Yap[1,6], Lance D. Burrell[1], David H. Lum[1], Jonathan R. Whisenant[1,2], G. Weldon Gilcrease III[1,2], Courtney C. Cavalieri[1,7], Kaitrin M. Rehbein[1], Stephanie L. Cutler[1], 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,1], 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

NATURE MEDICINE VOL 25 | APRIL | 628-640 ARTICLES

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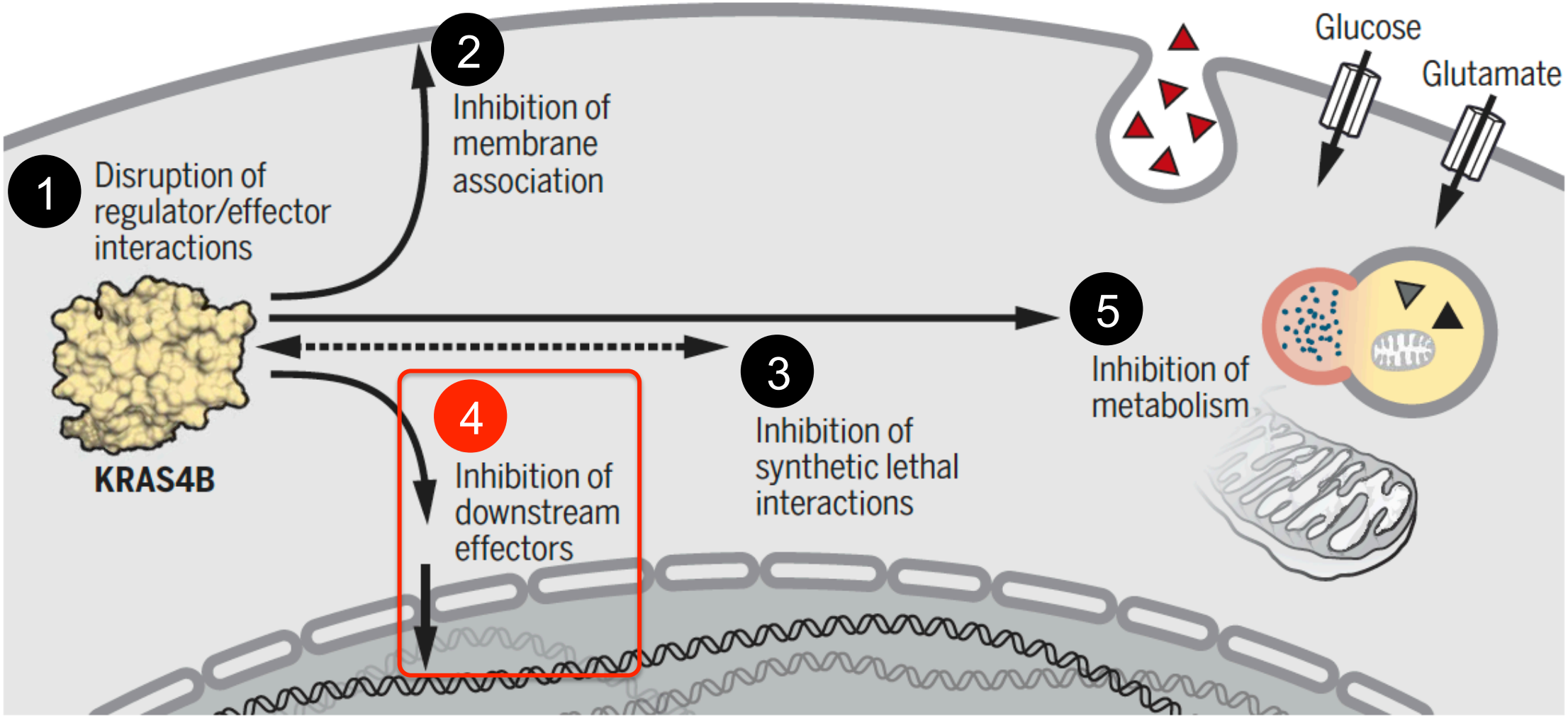
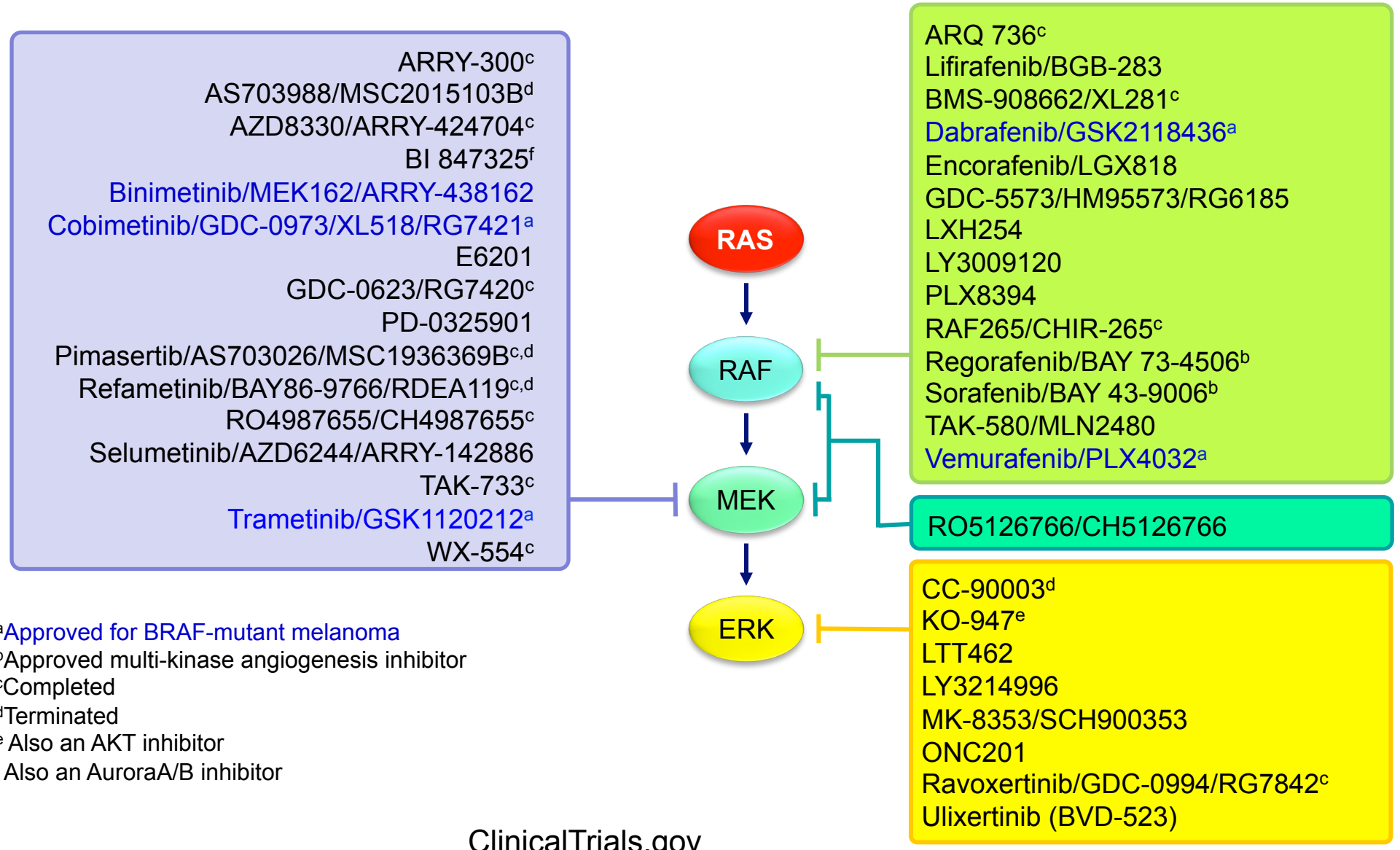
Targeting the RAF-MEK-ERK MAPK cascade



Papke & Der (2017) Science 355:1158

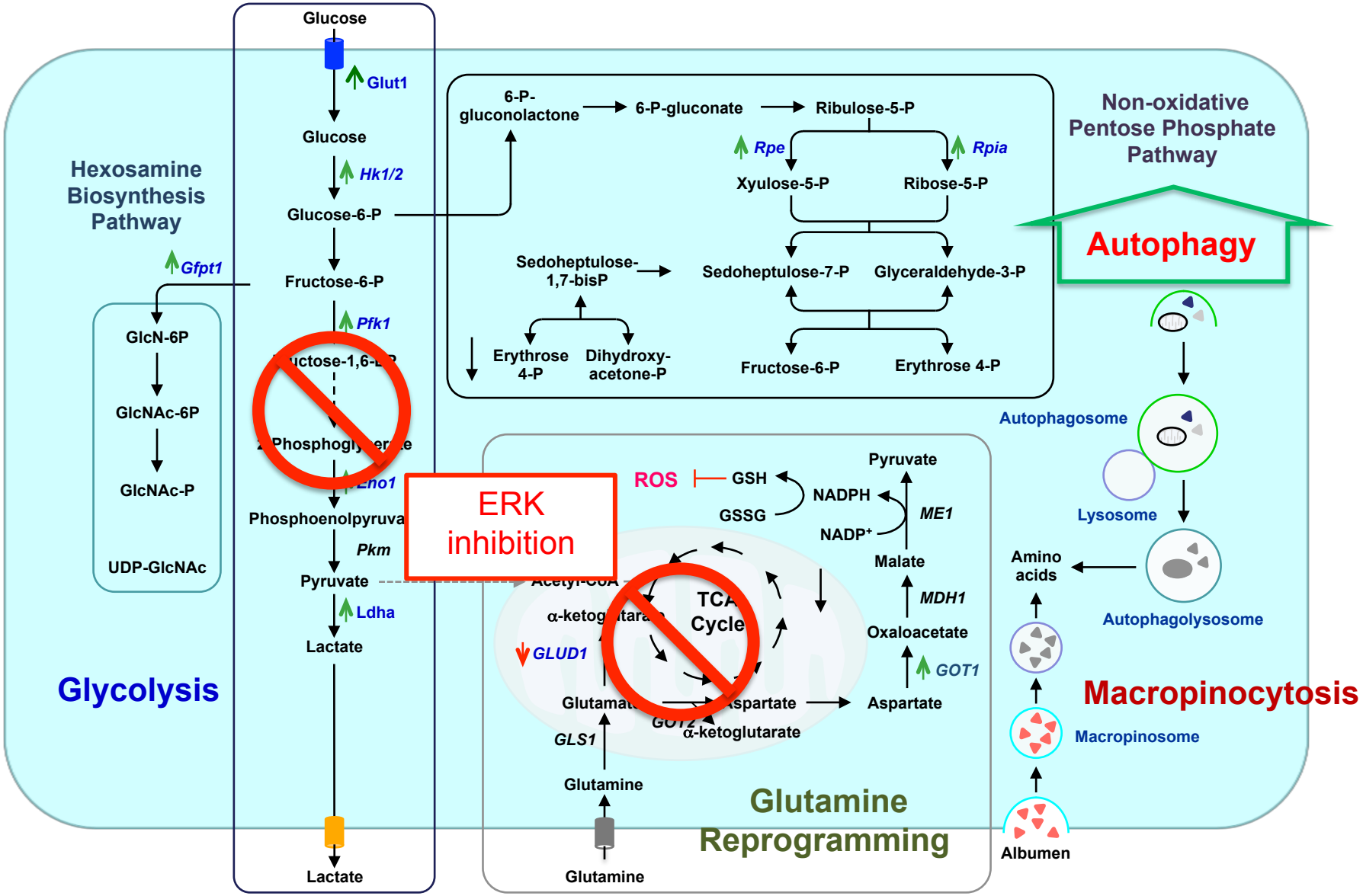
Clinical evaluation of RAF-MEK-ERK protein kinase inhibitors



[a]Approved for BRAF-mutant melanoma
[b]Approved multi-kinase angiogenesis inhibitor
[c]Completed
[d]Terminated
[e] Also an AKT inhibitor
[f] Also an AuroraA/B inhibitor

ClinicalTrials.gov

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

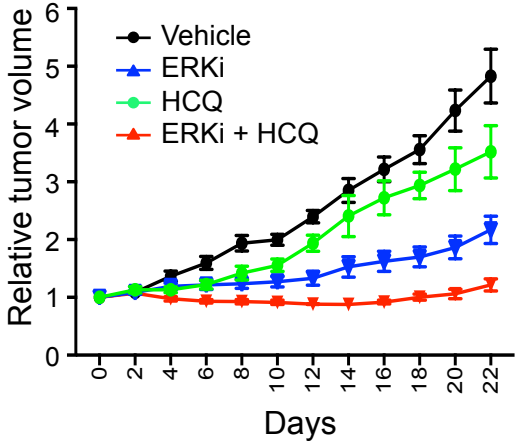


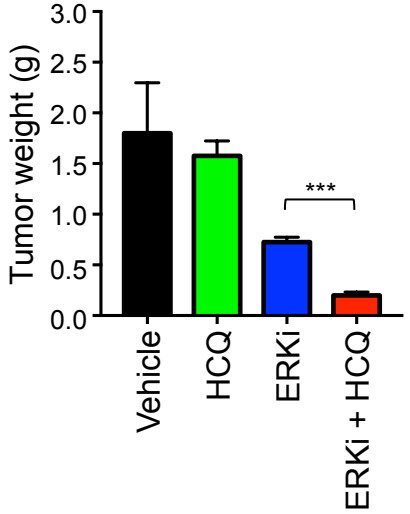
- Increased dependency on autophagy?
- Increased vulnerability to autophagy inhibition?

Bryant et al (2019) Nat Med 25:628

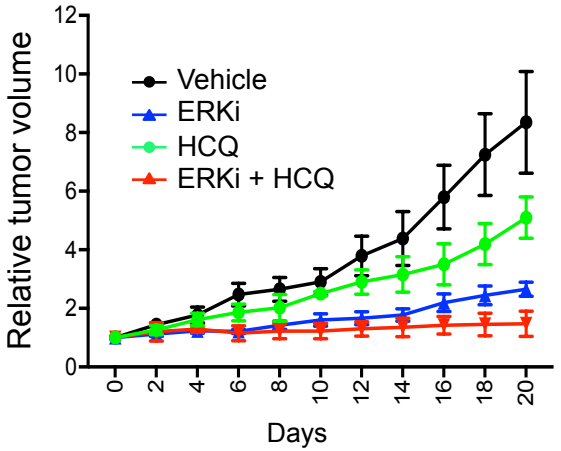
Concurrent ERK and autophagy inhibition suppresses pancreatic patient-derived xenograft tumor growth

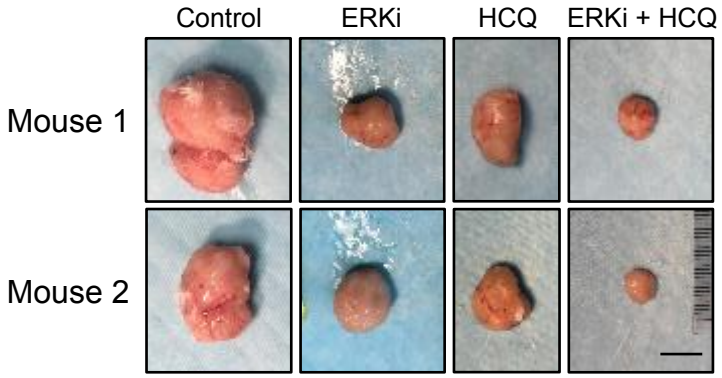
AZ1013 PDX
KRAS G12D
TP53 R248W
NF1 I1186N
KMT2C R4541*
SMAD4 deletion
CDKN2A deletion

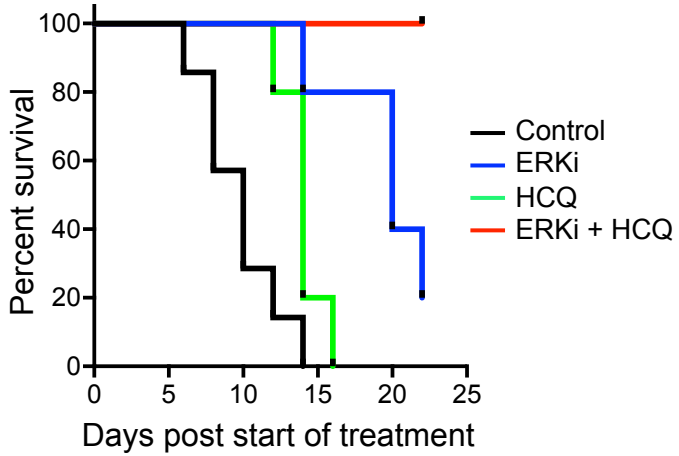


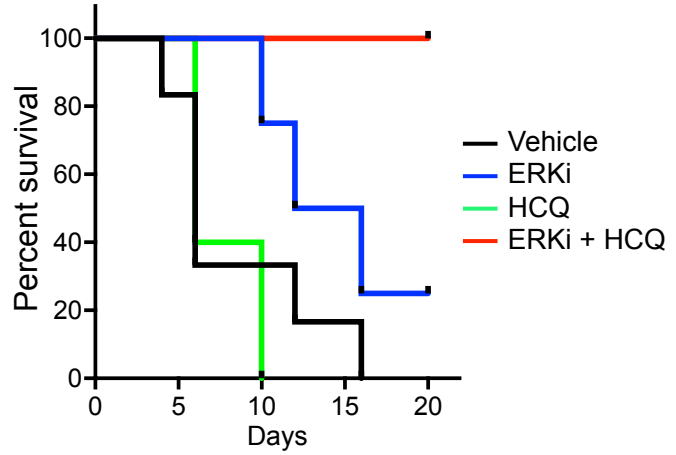


AZ97 PDX
*KRAS*G12V
TP53 p.R248Q
SMAD4 p.Y131*
CDKN2A









Bryant et al (2019) Nat Med 25:628

Independently, another group reaches the same conclusion

NATURE MEDICINE VOL 25 | APRIL | 620-627 LETTERS

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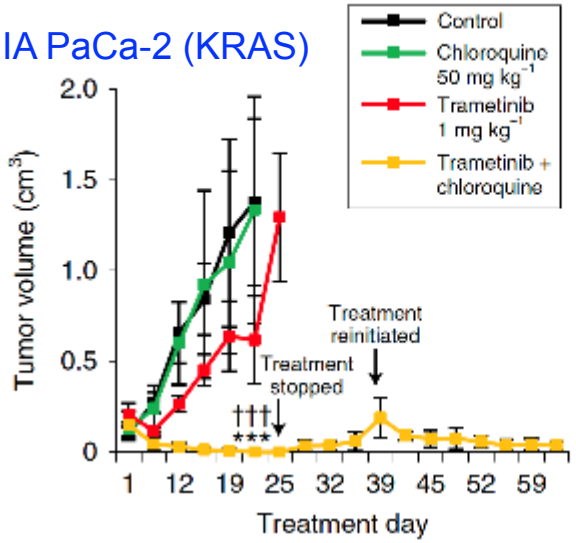
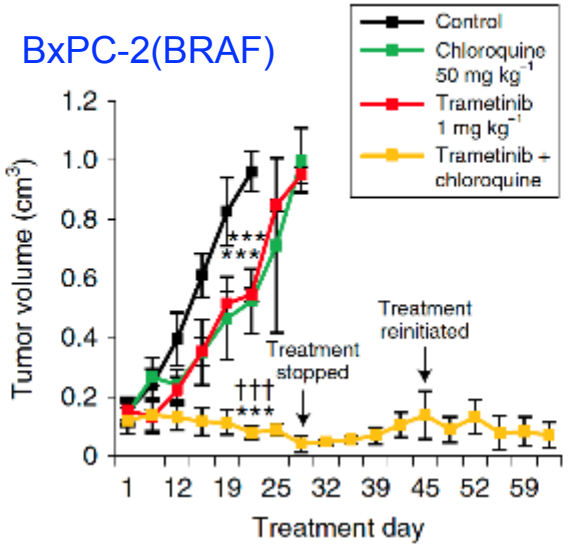
Concurrent MEK and autophagy inhibition cooperates to cause tumor regression

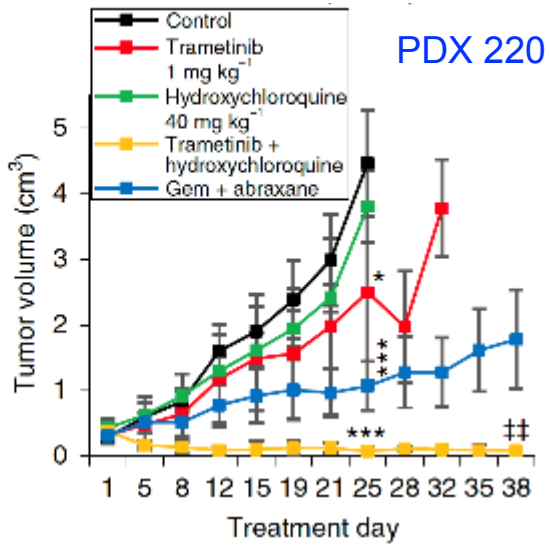
MIA PaCa-2 (KRAS)



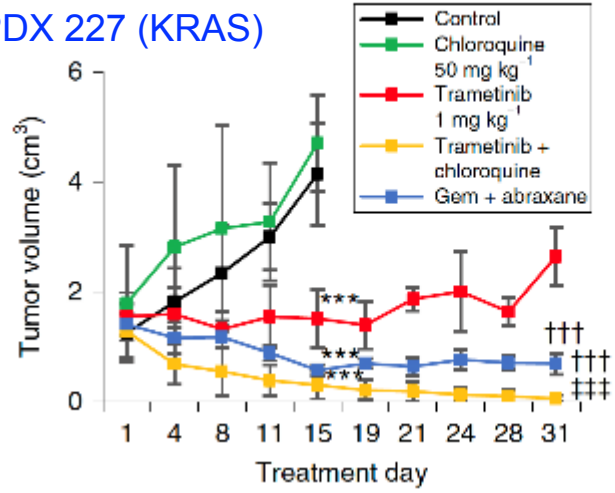
BxPC-2(BRAF)



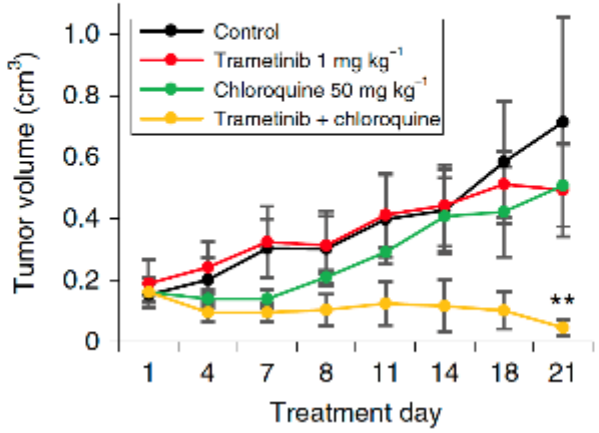
PDX 220 (KRAS)



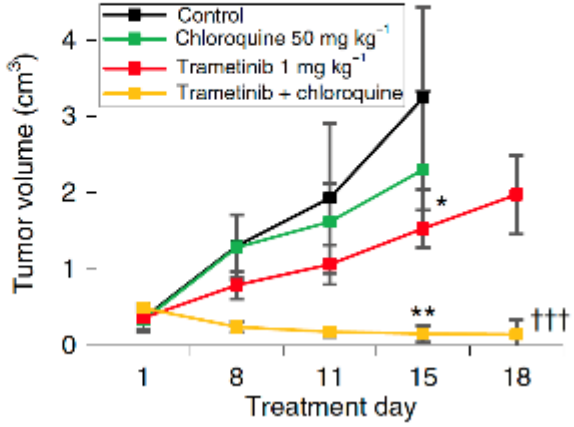
PDX 227 (KRAS)



HCLMel002 (NRAS)



HCICRC004 CRC PDX (BRAF)

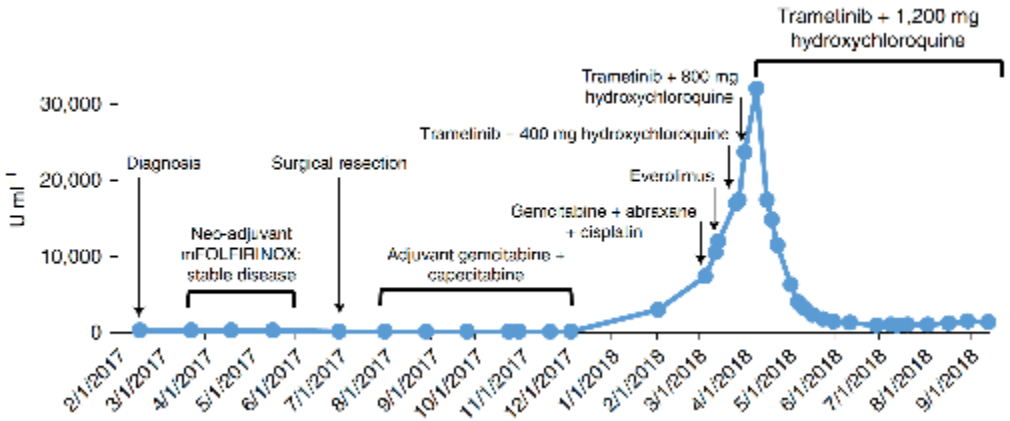


Kinsey et al (2019) Nat Med 25:620

Proof-of-concept in a pancreatic cancer patient

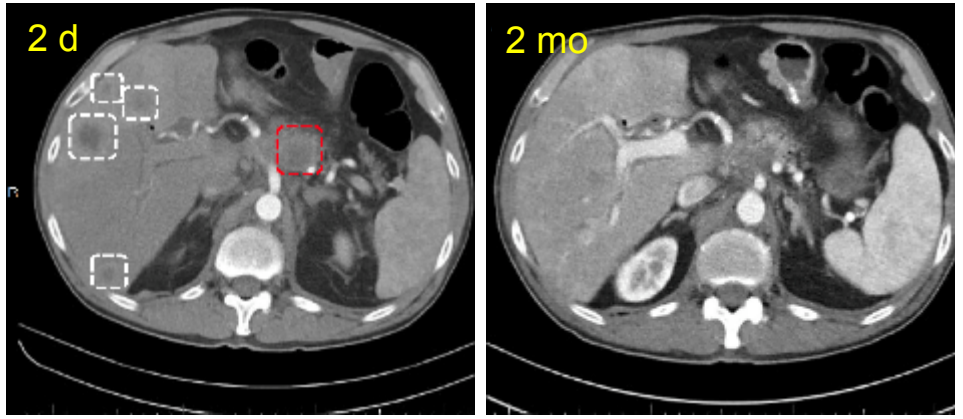
- 2 mg of trametinib plus 1200 mg HCQ daily over last two 2 months
- CA19-9 levels declined ~ 95%
- 50% reduction tumor mass
- Grade 1 rash and grade 1 fatigue
- No ocular and cardiac toxicities

CA19-9 tumor marker

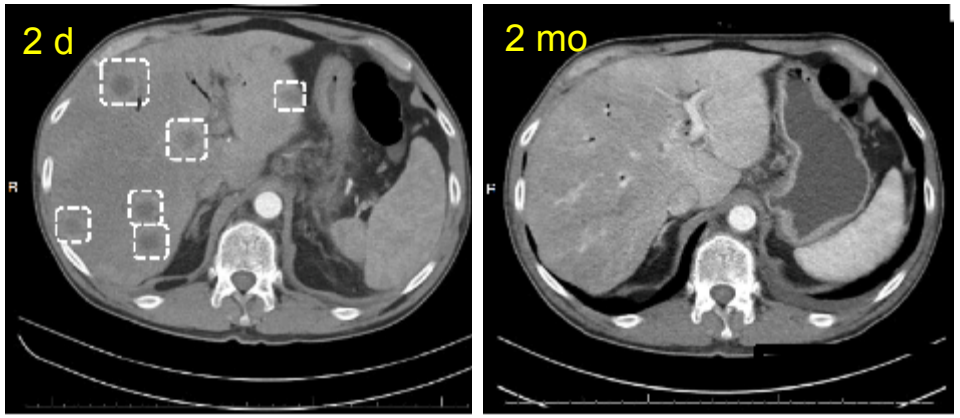


CT Imaging

Pancreatic lesion



Liver metastasis lesion



Kinsey et al (2019) Nat Med 25:620

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

PNAS

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

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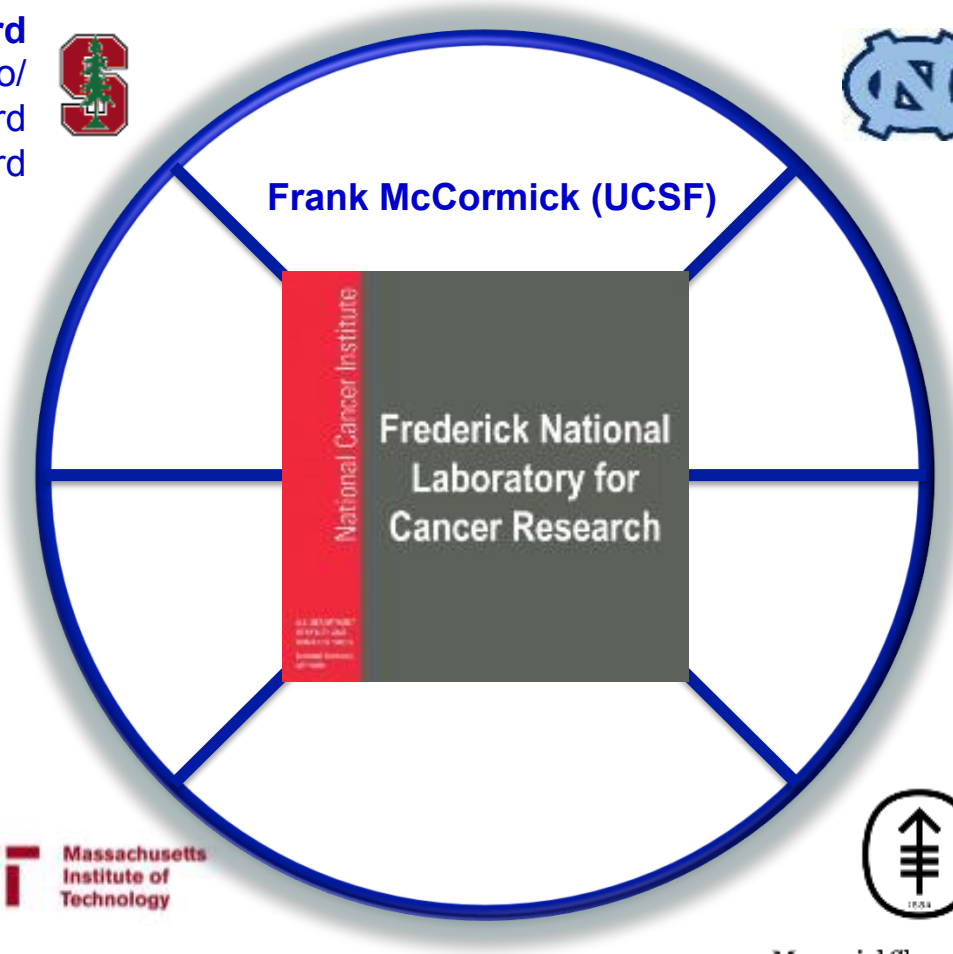
RAS Synthetic Lethal Network (U01)

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

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

Calvin Kuo/Stanford)
Kevan Shokat (UCSF)



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

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

Charles Rudin/MSKCC
John Poirier/MSKCC

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]

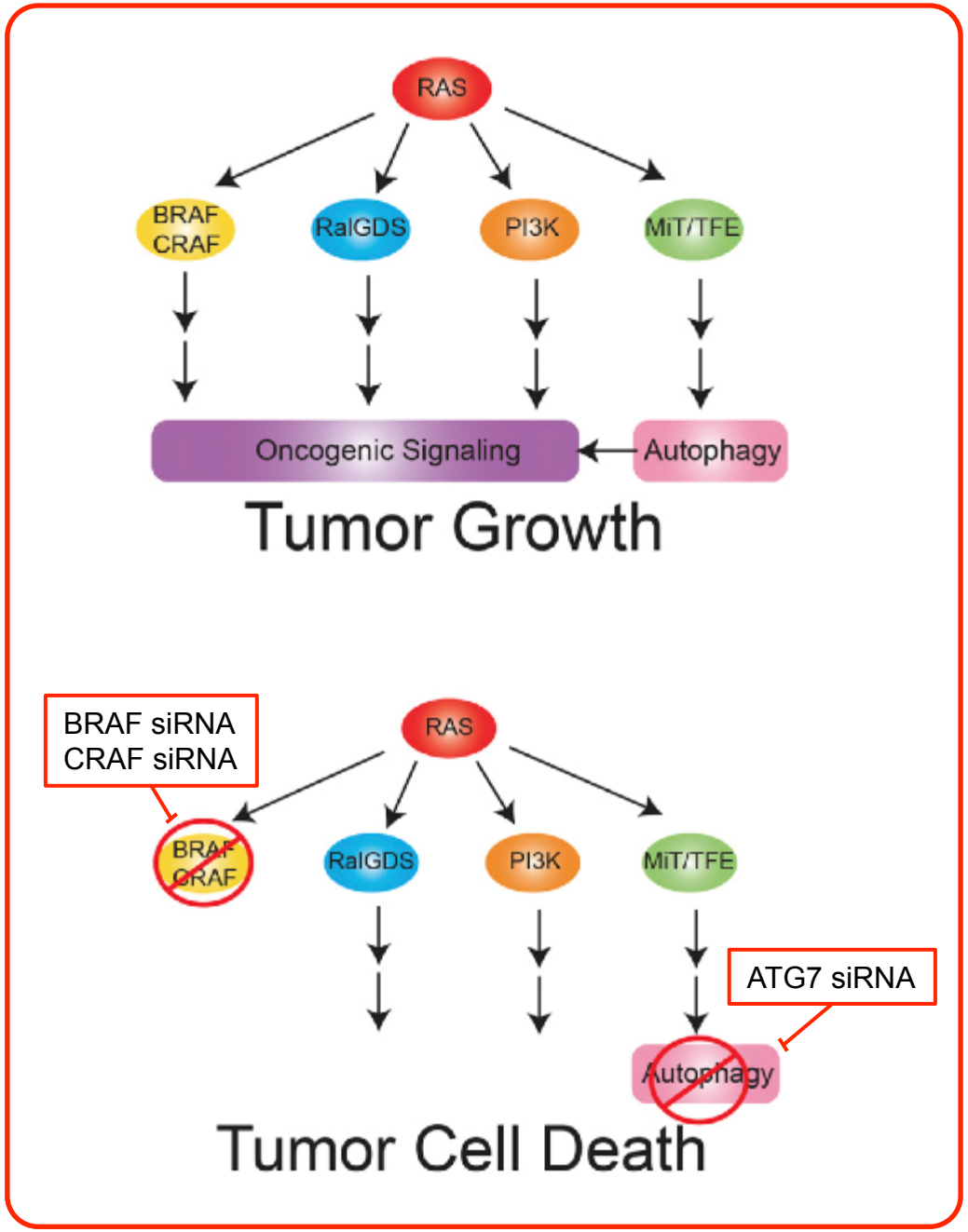
COMMENTARY

PNAS | March 5, 2019 vol. 116 | no. 10 | 3965–3967

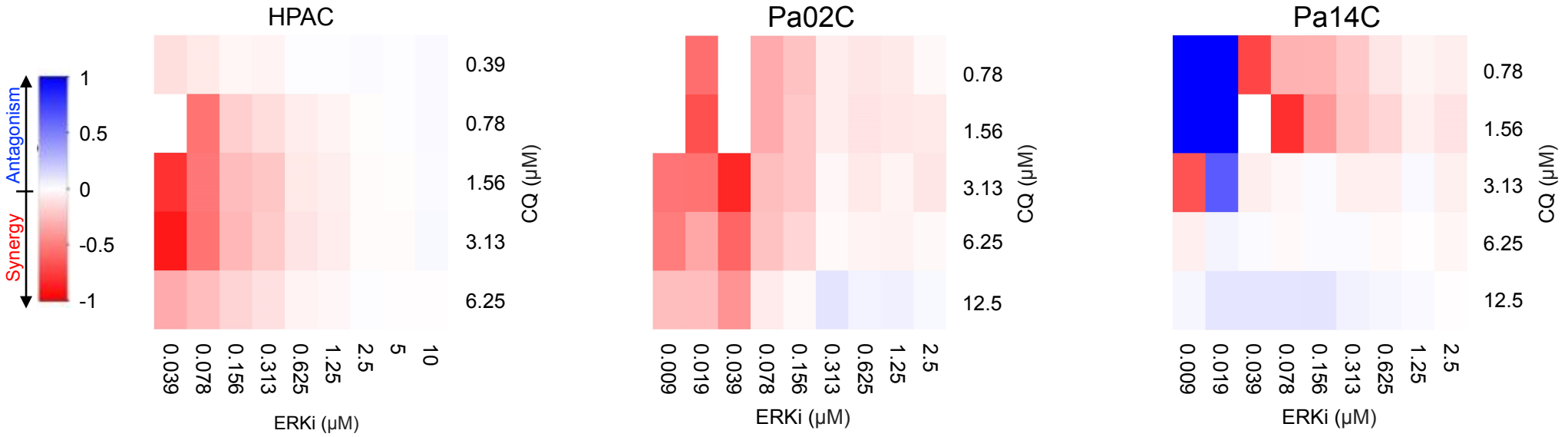
Blockade of RAF and autophagy is the one-two punch to take out Ras

Eileen White[a,b,1]

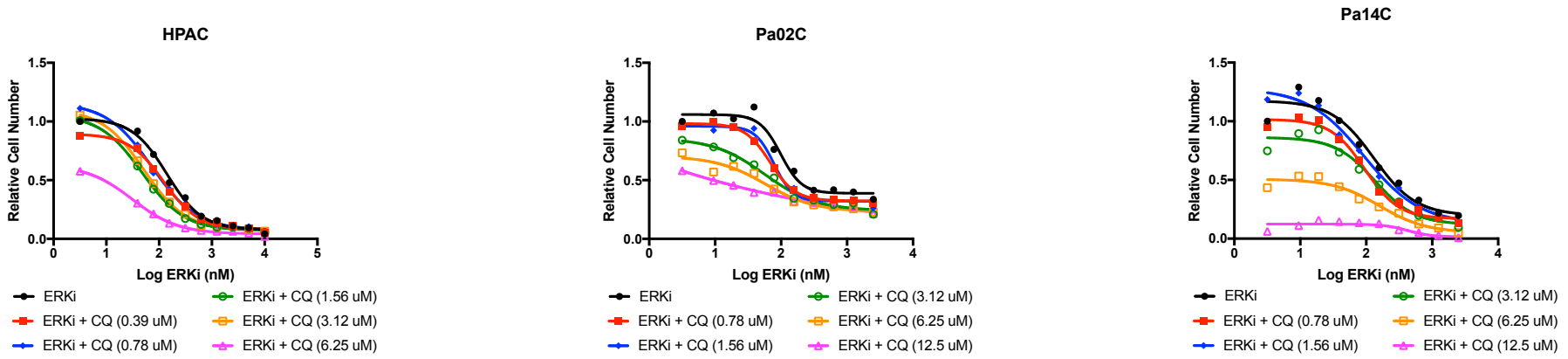
"Essential codependency of RAS-driven cancers on BRAF, CRAF, and autophagy. BRAF and CRAF provide key functional oncogenic signaling downstream of RAS that requires autophagy mediated by ATG7 to sustain survival. Coordinate blockade of BRAF, CRAF, and ATG7 provides the one-two punch and lethal blow to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



RAFi* and chloroquine synergize in KRAS-mutant PDAC

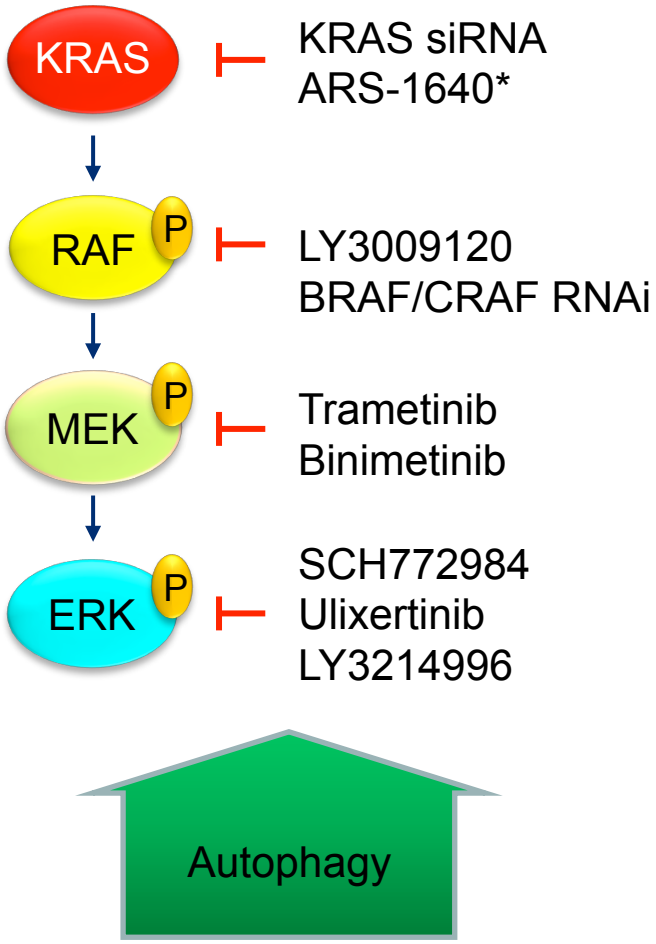


*LY3009120



Dr. Kirsten Bryant (University of North Carolina at Chapel Hill)

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



NATURE MEDICINE VOL 25 | APRIL | 628-640 ARTICLES

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

Kirsten L. Bryant[1], Clint A. Stalnecker[1], Daniel Zeitouni[1], Jennifer E. Klomp[1], Sen Peng[2], Andrey P. Tikunov[3], Venugopal Gunda[4], Mariaelena Pierobon[5], Andrew M. Waters[1], Samuel D. George[1], Garima Tomar[1], Björn Papke[1], G. Aaron Hobbs[1], Liang Yan[6], Tikvah K. Hayes[7], J. Nathaniel Diehl[7], Gennifer D. Goode[4], Nina V. Chaika[4], Yingxue Wang[8], Guo-Fang Zhang[8], Agnieszka K. Witkiewicz[9], Erik S. Knudsen[10], Emanuel F. Petricoin III[5], Pankaj K. Singh[4], Jeffrey M. Macdonald[3], Nhan L. Tran[11], Costas A. Lyssiotis[12], Haoqiang Ying[6], Alec C. Kimmelman[13], Adrienne D. Cox[1,14,15] and Channing J. Der[1,7,15*]

NATURE MEDICINE VOL 25 | APRIL | 620-627 LETTERS

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

Conan G. Kinsey[1,2], Soledad A. Camolotto[1], Amelie M. Boespflug[1,3,4], Katrin P. Guillen[1], Mona Foth[1], Amanda Truong[1], Sophia S. Schuman[1], Jill E. Shea[5], Michael T. Seipp[5], Jeffrey T. Yap[1,6], Lance D. Burrell[1], David H. Lum[1], Jonathan R. Whisenant[1,2], G. Weldon Gilcrease III[1,2], Courtney C. Cavalieri[1,7], Kaitrin M. Rehbein[1], Stephanie L. Cutler[1], 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

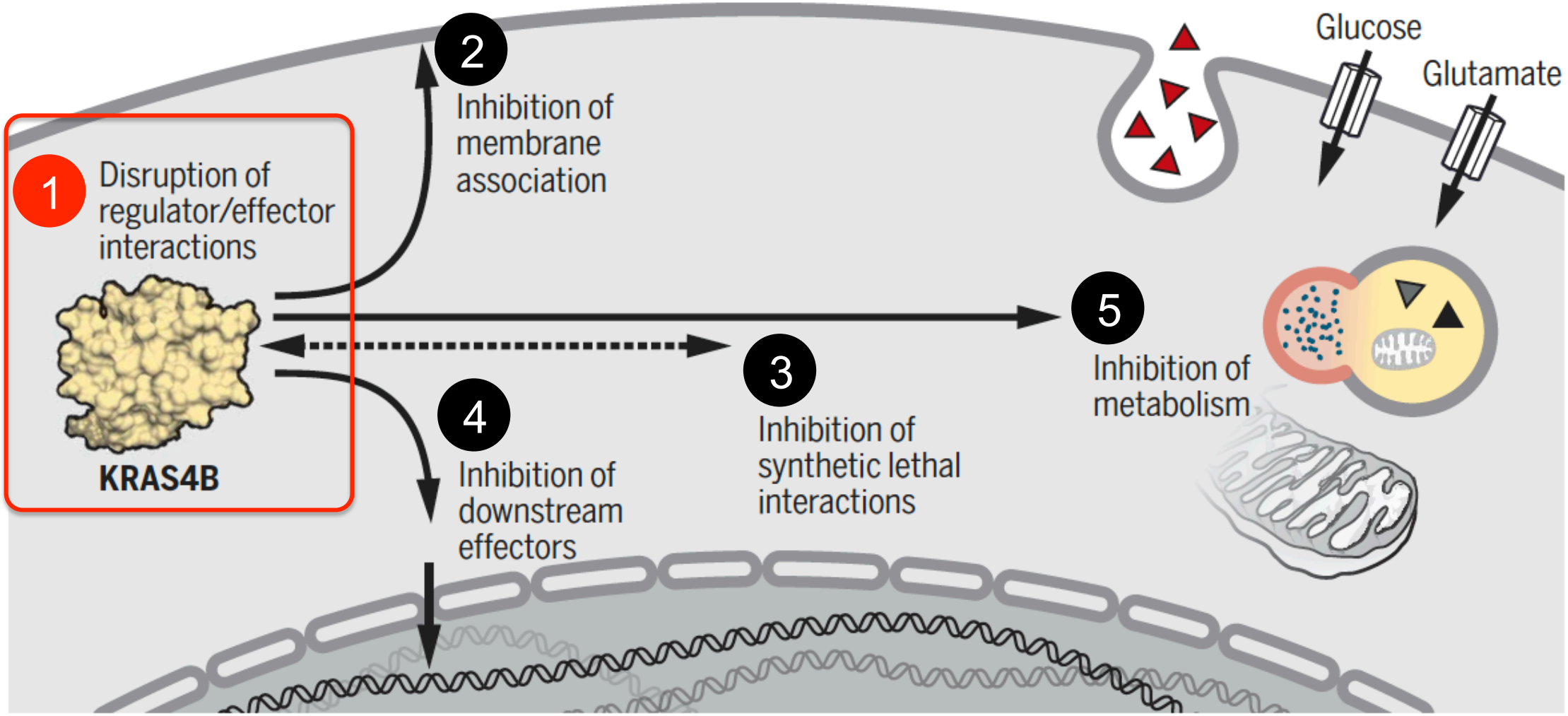
Undisclosed Pharma

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



Papke & Der (2017) Science 355:1158

Clinical evaluation of KRAS G12C-specific inhibitors

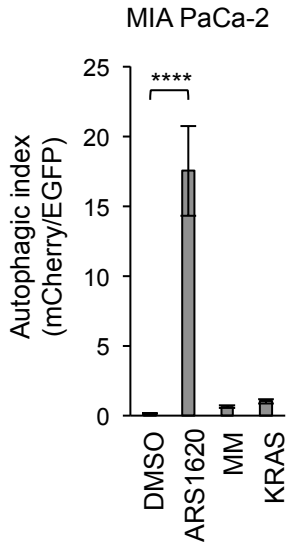
- A Phase 1, Study Evaluating the Safety, Tolerability, PK, and Efficacy of AMG 510 in Subjects With Solid Tumors With a Specific KRAS Mutation (NCT03600883)
- MRTX849 in Patients With Cancer Having a KRAS G12C Mutation (NCT03785249

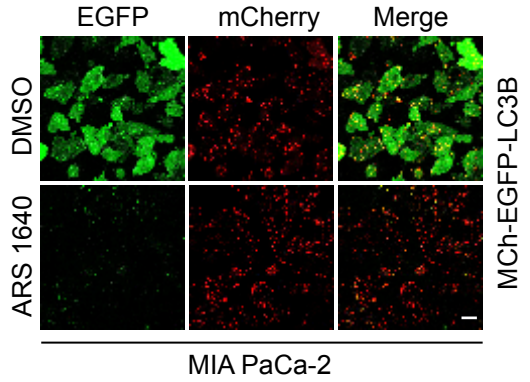
❖ KRAS G12C inhibitors versus ERK MAPK + HCQ?

*Specific for one RAS mutation G12C

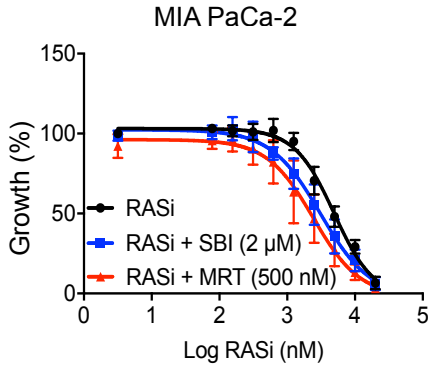
Concurrent KRAS G12C and ULK inhibition causes pancreatic cancer cell death

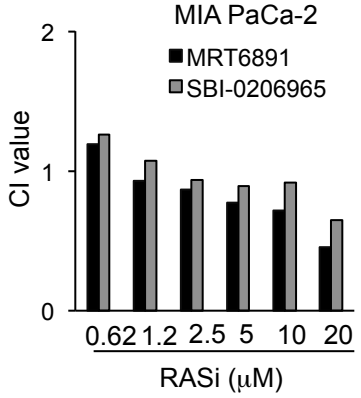
Treatment with the KRAS^{G12C} inhibitor ARS-1620 increases autophagy

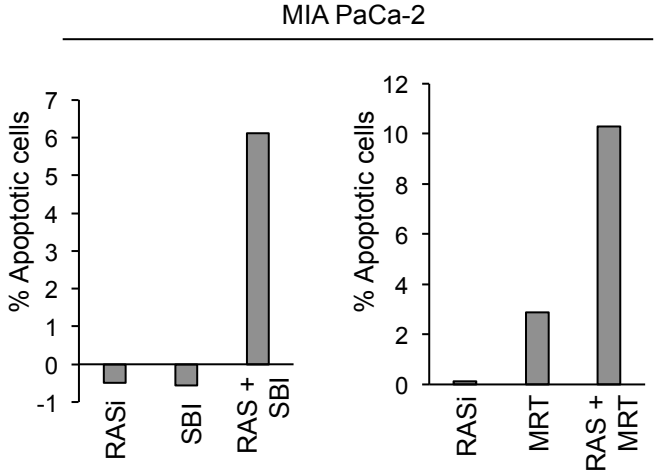




Cotreatment with ULK inhibitors enhance KRAS^{G12C} inhibitor growth suppression

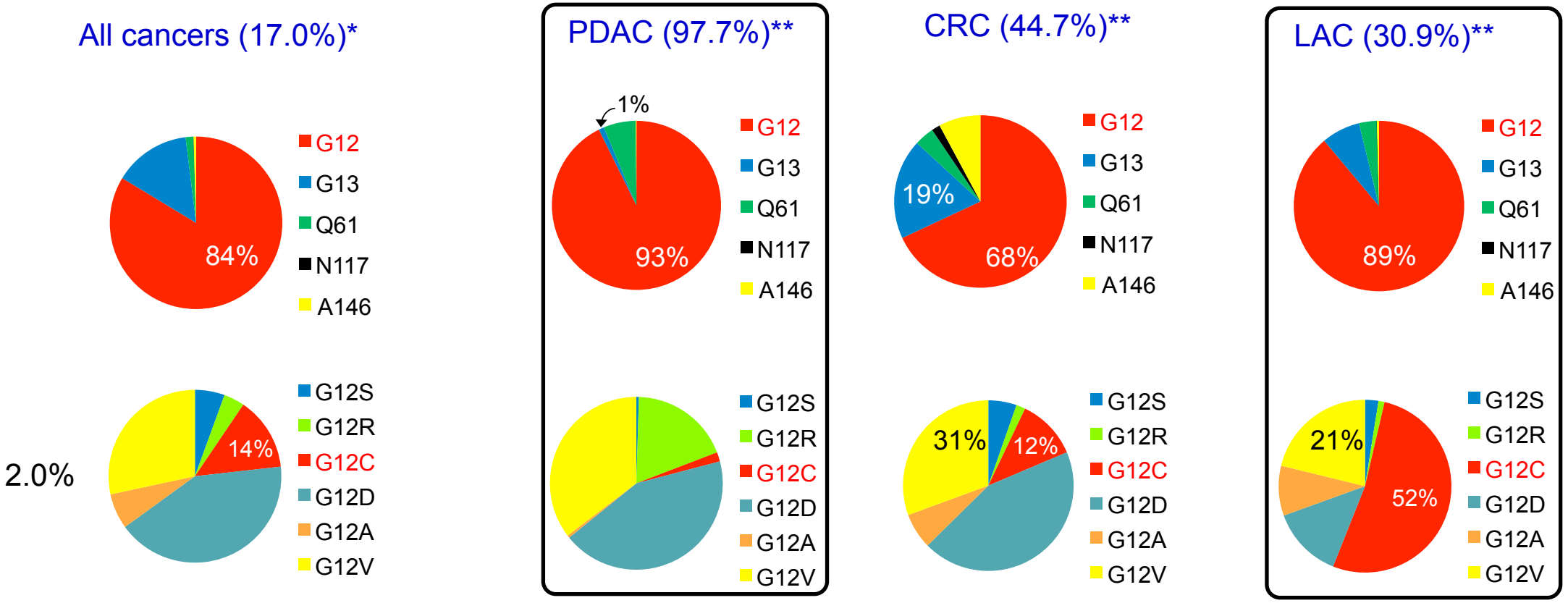






Bryant et al (2019) Nat Med 25:628

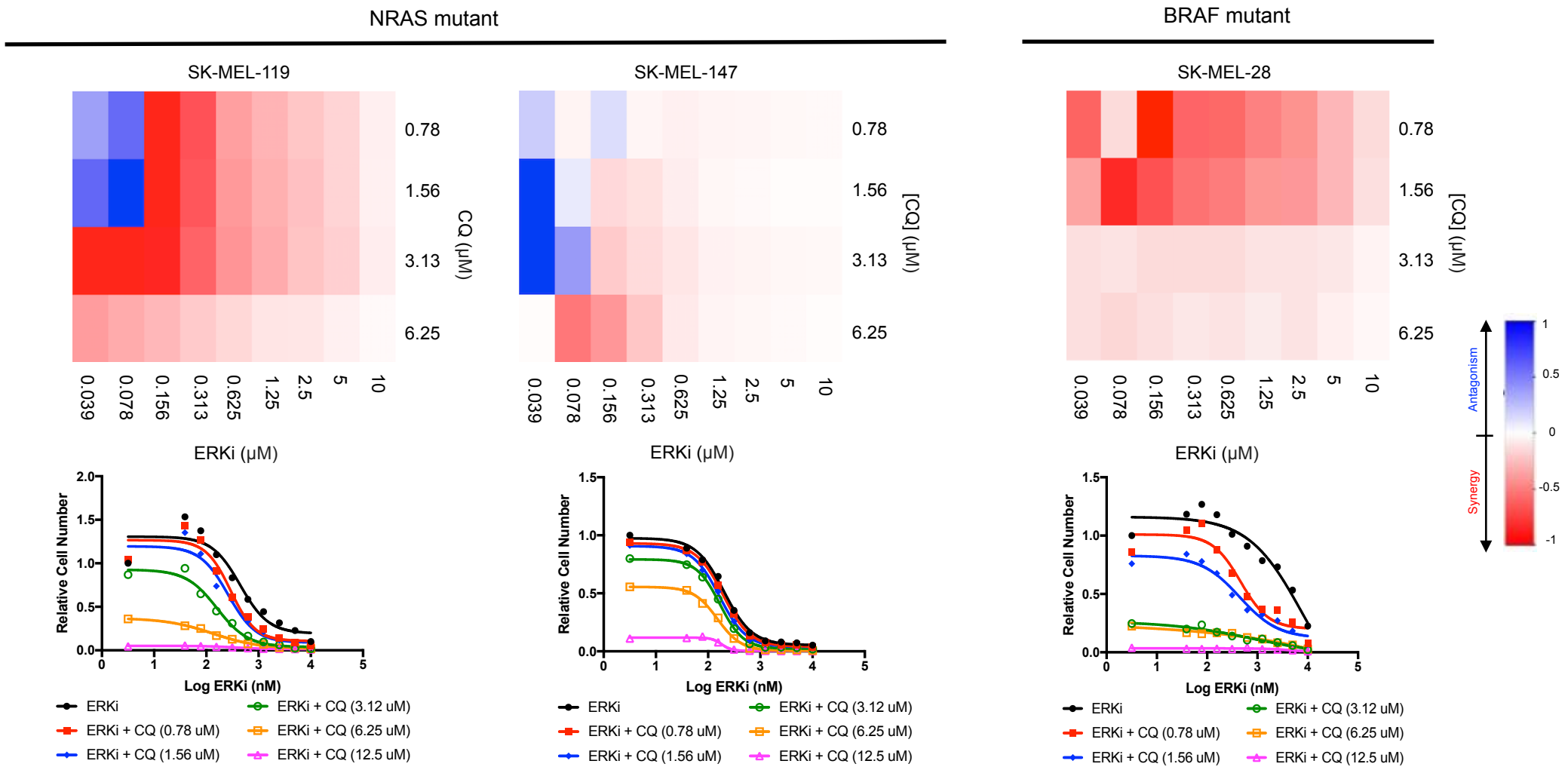
G12C inhibitors target only 2% of all cancers



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

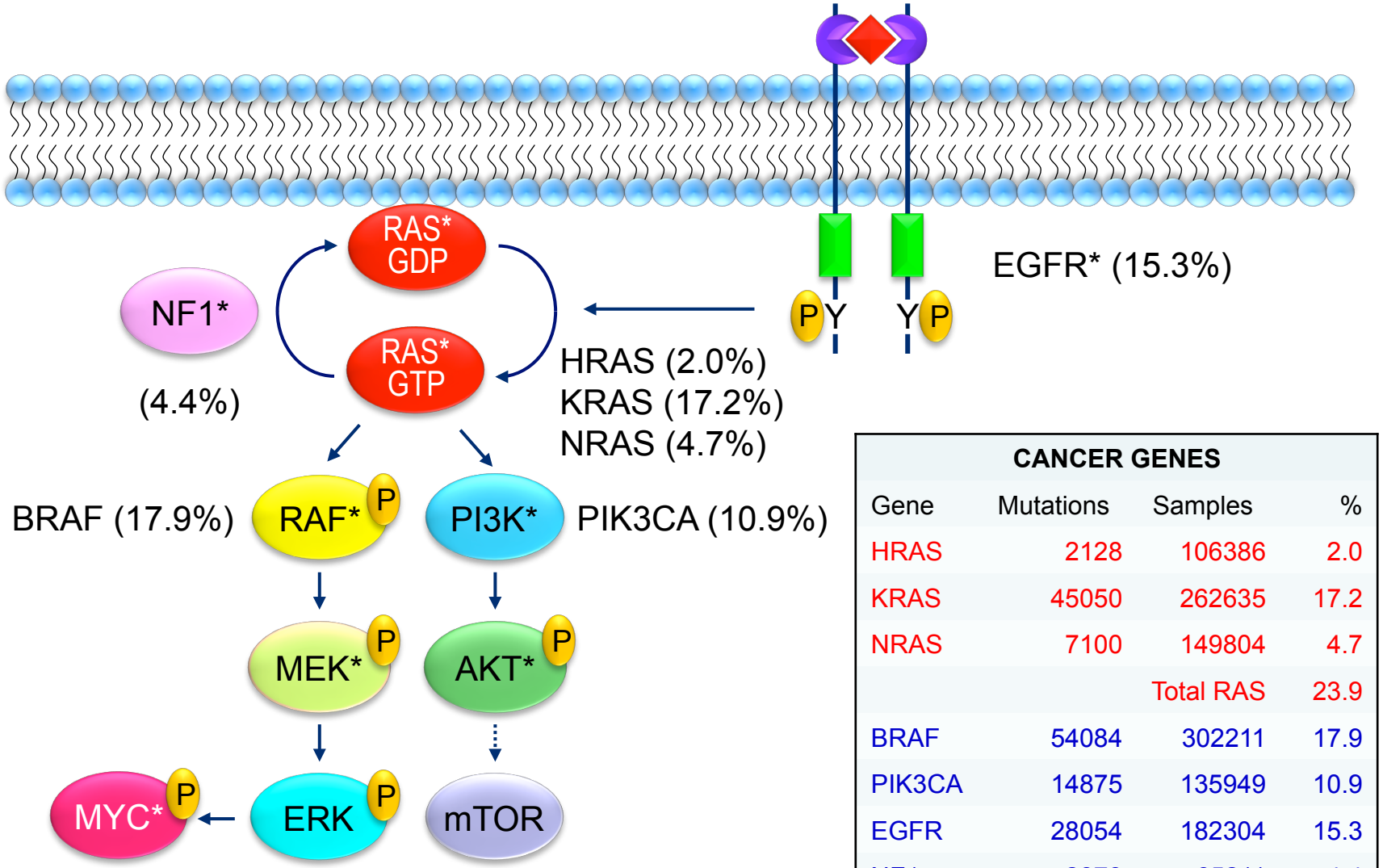
*COSMIC v88; **Cox et al (2014) *Nat Rev Drug Discov* 13:828

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



Dr. Kirsten Bryant (University of North Carolina at Chapel Hill)

Aberrant RAF-MEK-ERK MAPK signaling in cancer



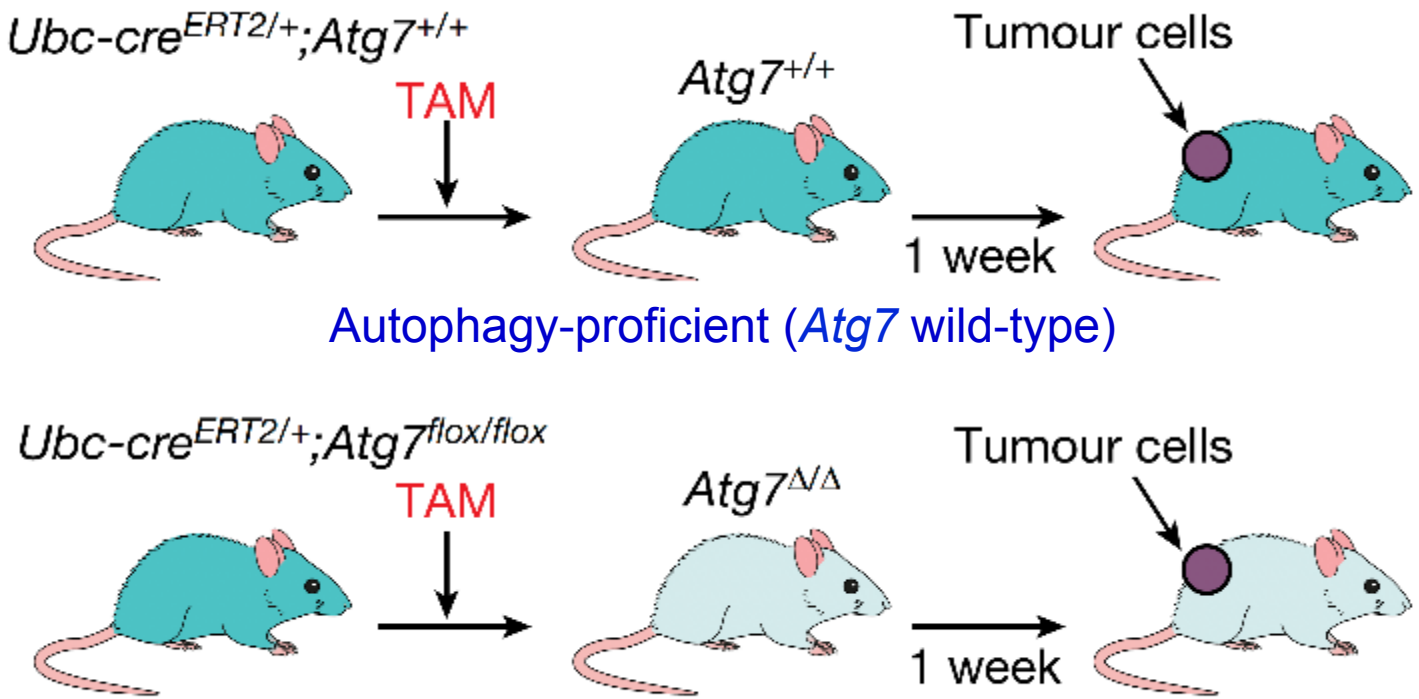
CANCER GENES			
Gene	Mutations	Samples	%
HRAS	2128	106386	2.0
KRAS	45050	262635	17.2
NRAS	7100	149804	4.7
		Total RAS	23.9
BRAF	54084	302211	17.9
PIK3CA	14875	135949	10.9
EGFR	28054	182304	15.3
NF1	2878	65211	4.4
TP53	41588	155424	26.8

* COSMIC v89
Catalogue of somatic mutations in cancer

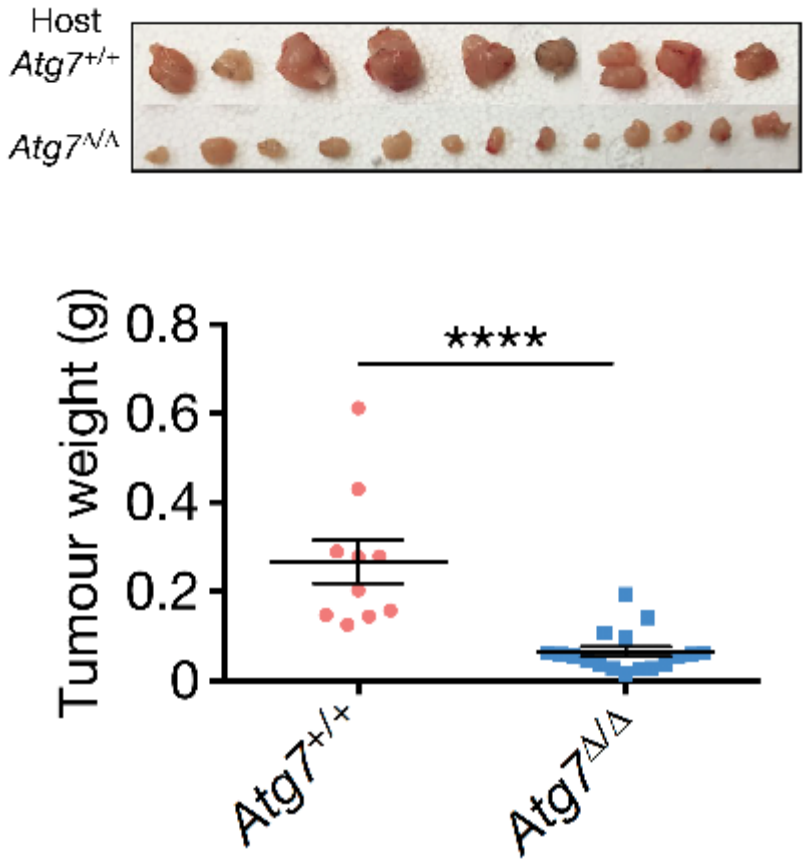
Key points

- ‘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?

Host autophagy supports tumor growth

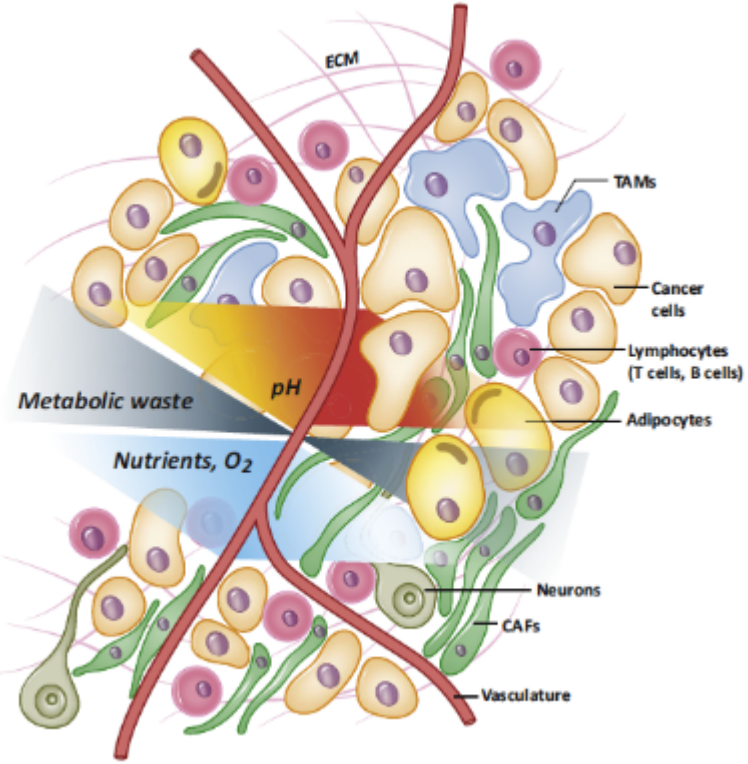


Braf-mutant melanoma

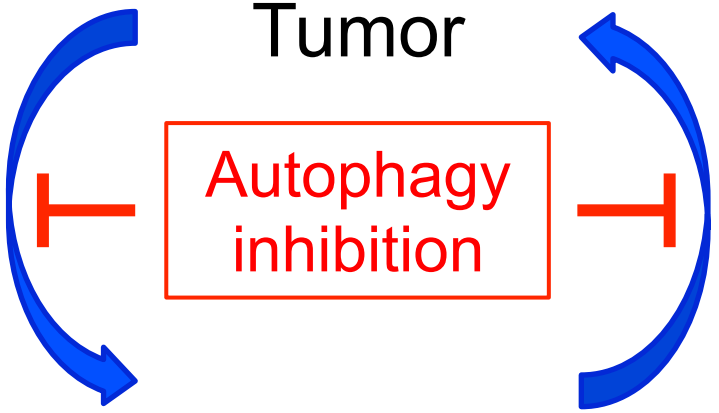


Poillet-Perez et al (2018) Nature 563:569

Autophagy-dependent activities of the microenvironment support tumor growth



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



Microenvironment

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

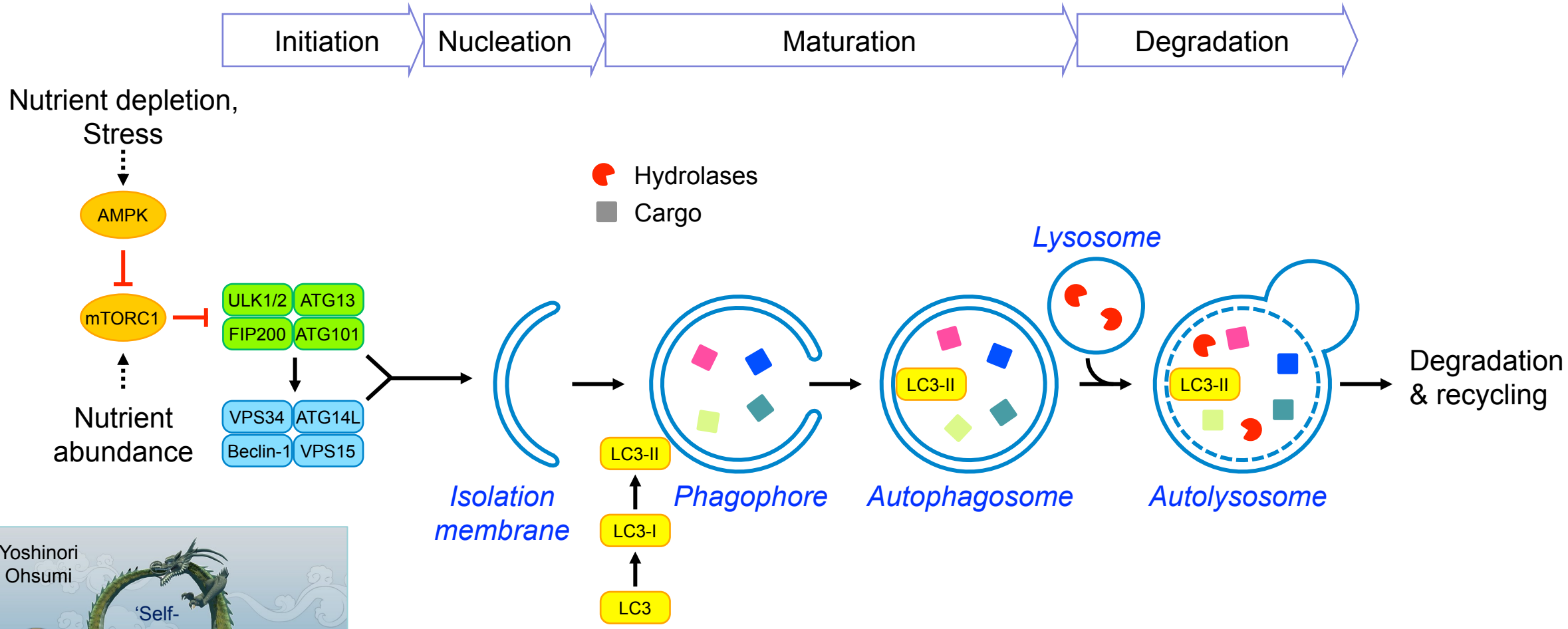
Sousa et al (2016) Nature 536:479
Cunha et al (2018) Cell 175:429

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

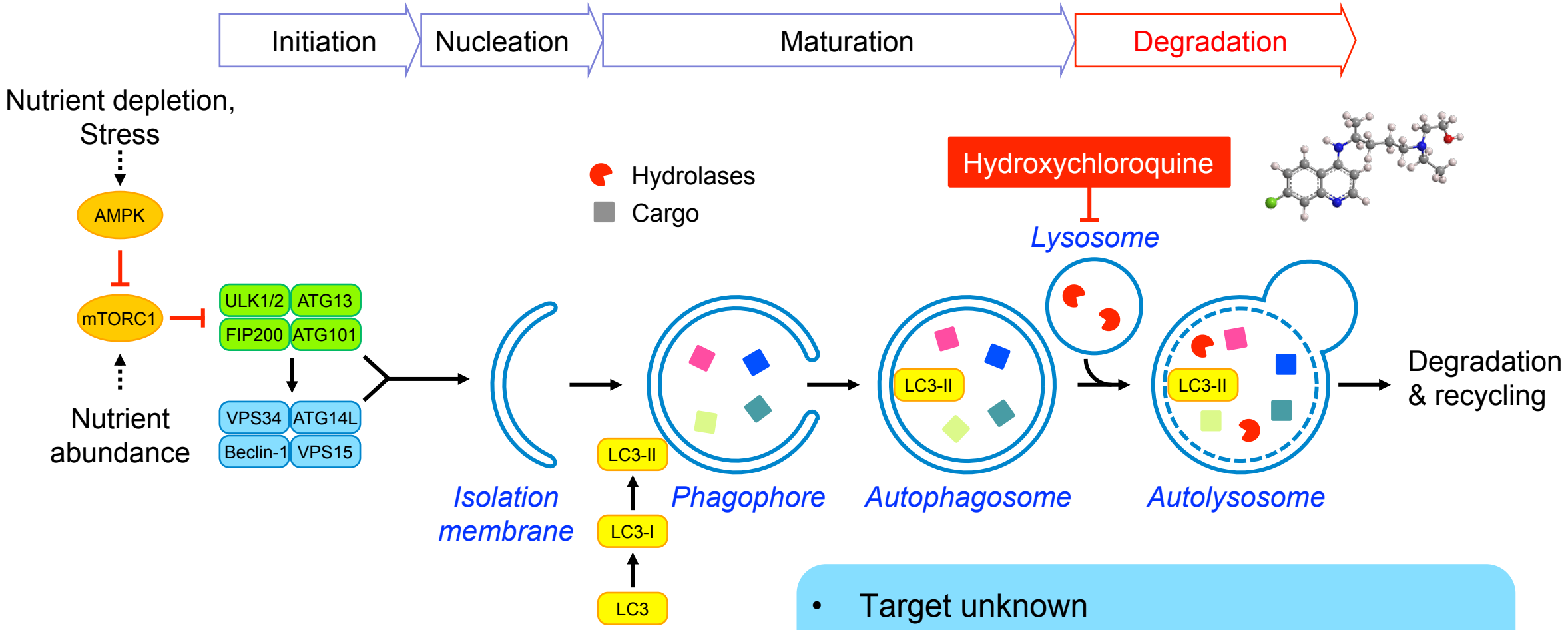
Key points

- ‘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?

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



Hydroxychloroquine inhibition of autophagy



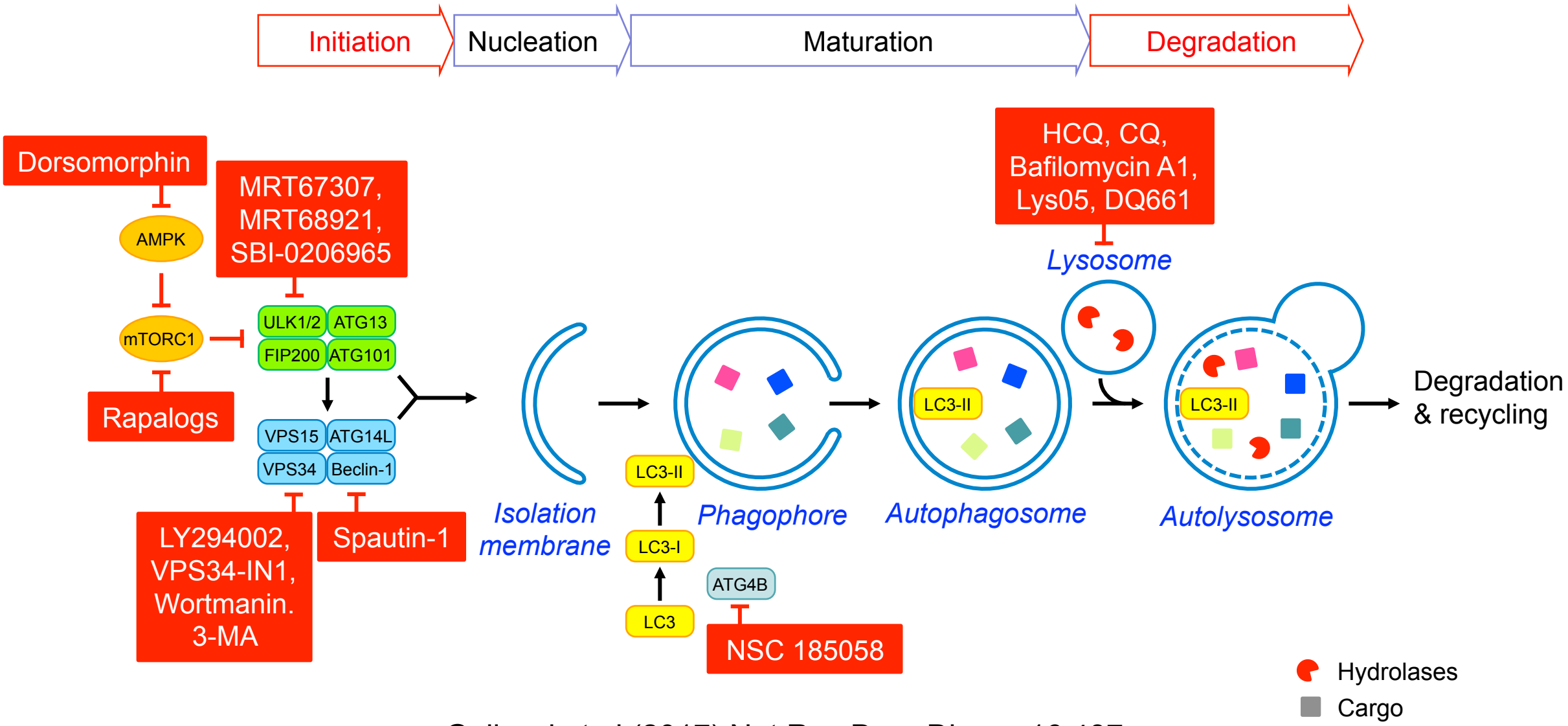
- Target unknown
- Elevate/neutralize the lysosomal/vacuolar pH
- Low potency and selectivity for autophagy

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

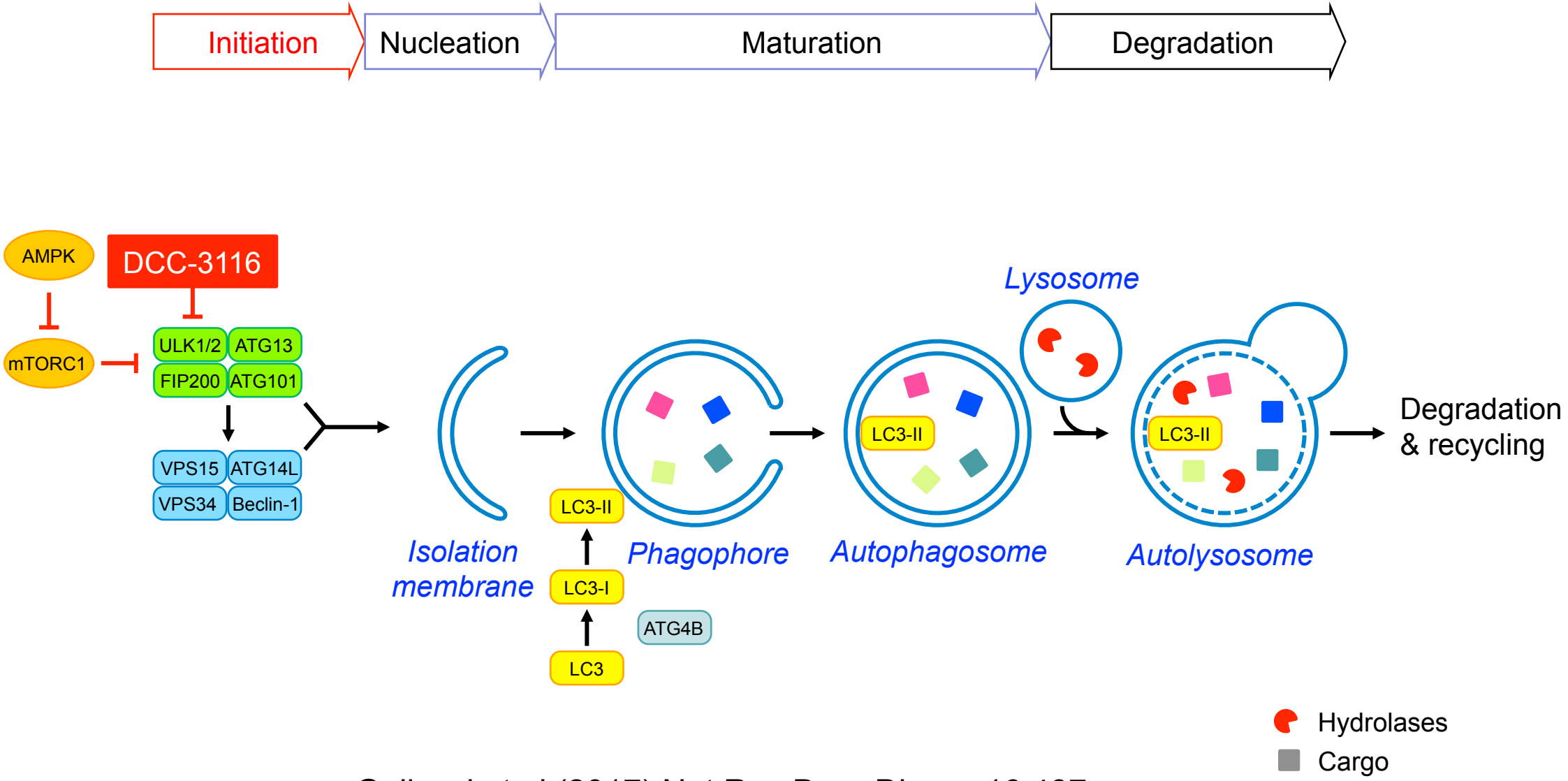
Hydroxychloroquine has shown limited activity as a monotherapy (NCT01273805, NCT01506973 and NCT03344172), but has shown promise in combination with preoperative gemcitabine plus nab-paclitaxel (NCT01978184)

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

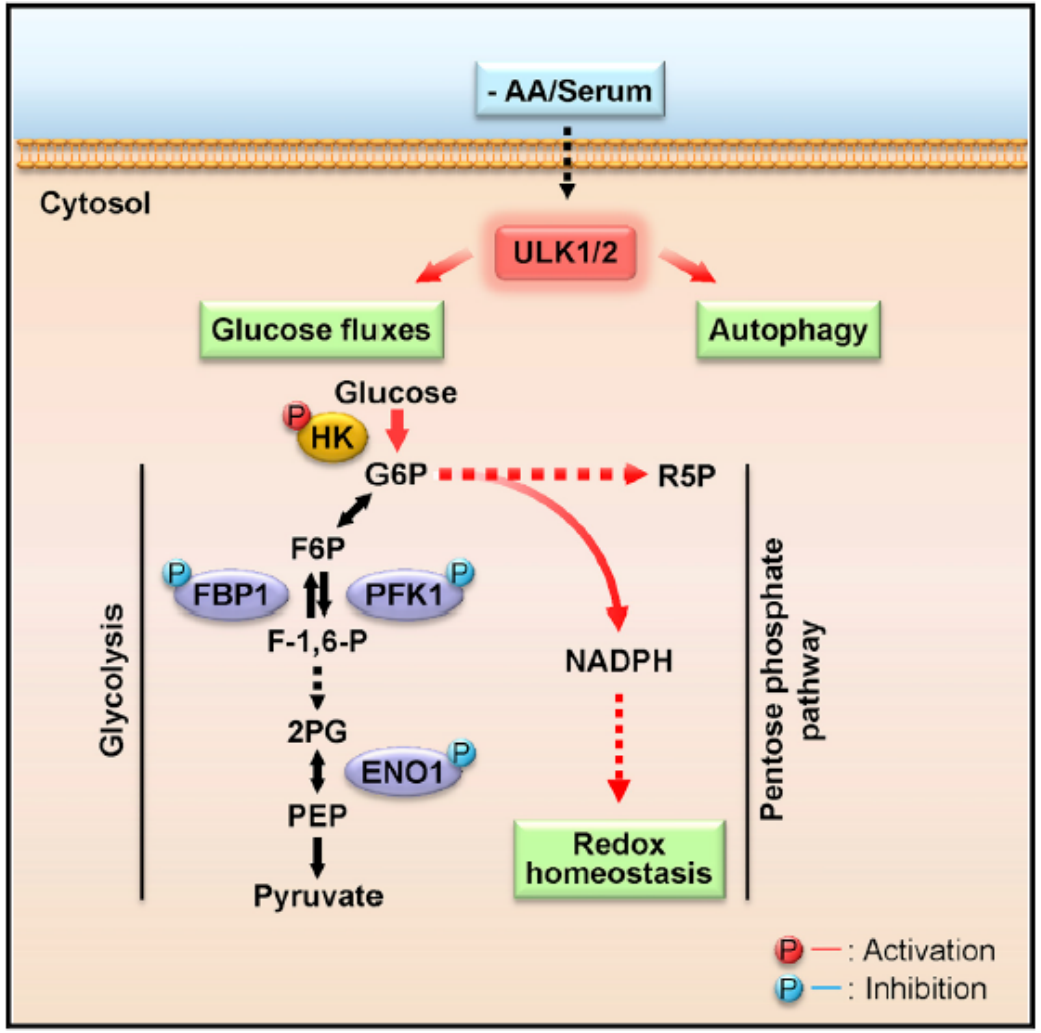
ULK activity plays a metabolic role in RAS-mutant cancers

Article

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



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

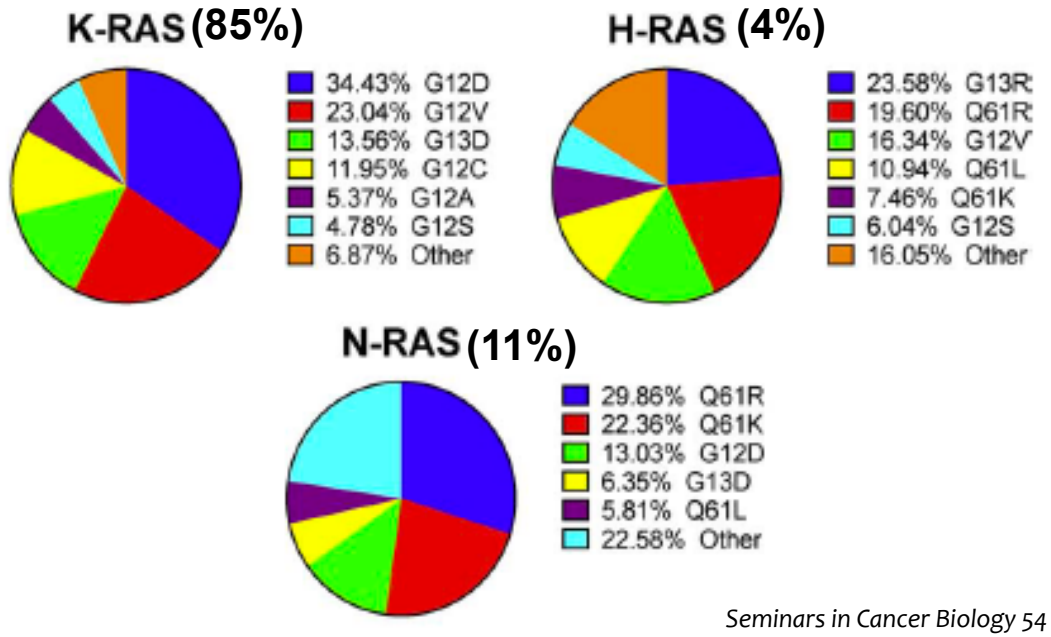
- Pancreatic: ~98%
- Colon: ~ 45%
- Lung: ~ 30%

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

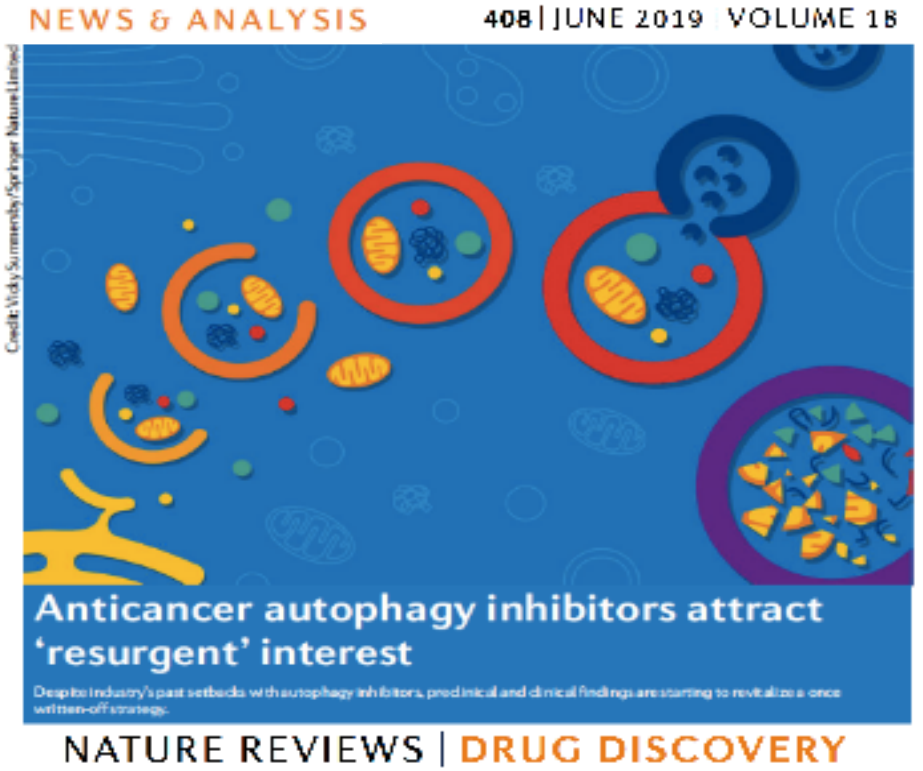
Direct inhibition of RAS: Quest for the Holy Grail?

Russell Spencer-Smith[a,b,c], John P. O'Bryan[a,b,c,*]

[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*

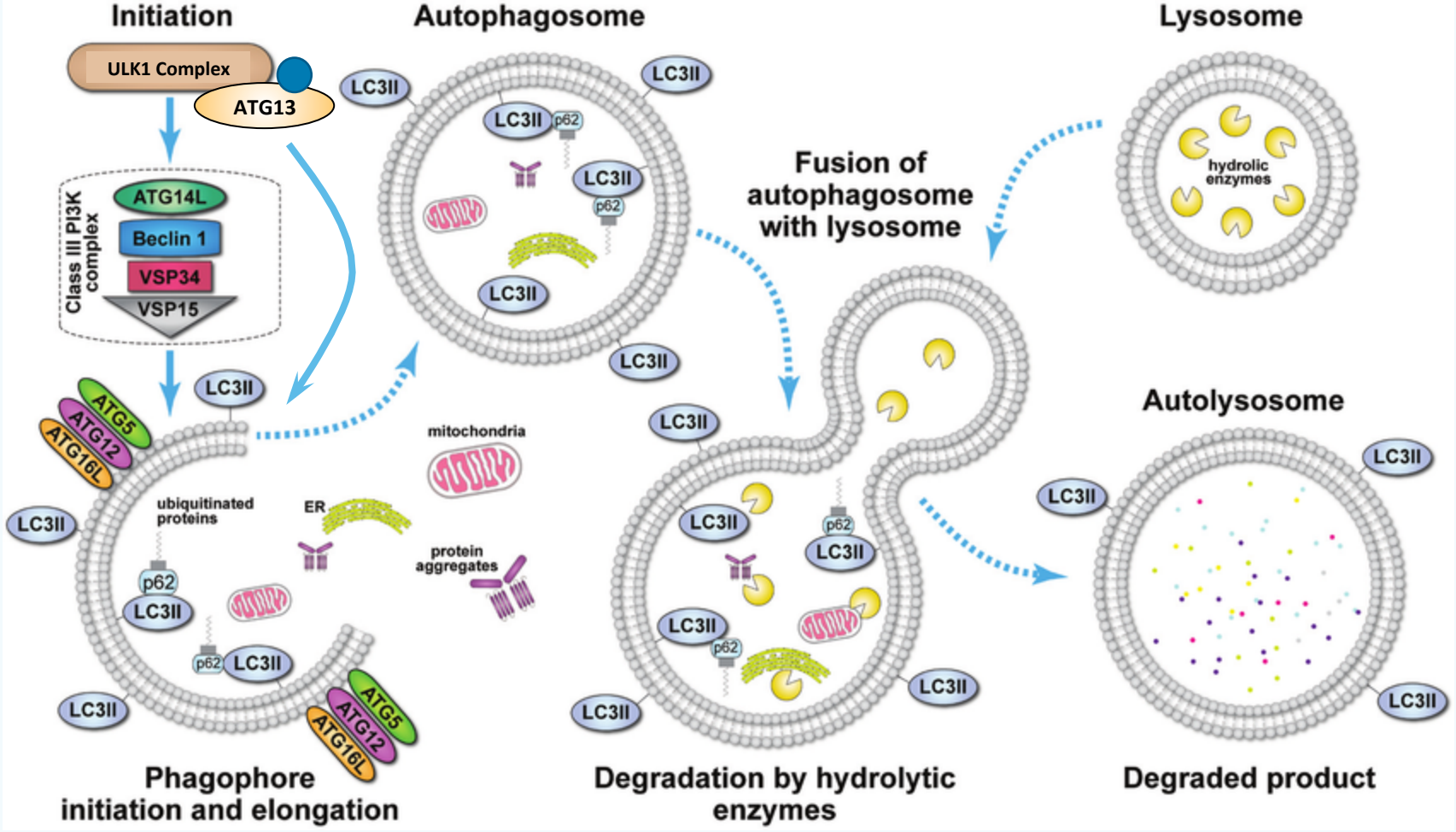
Revitalized Interest in Autophagy

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



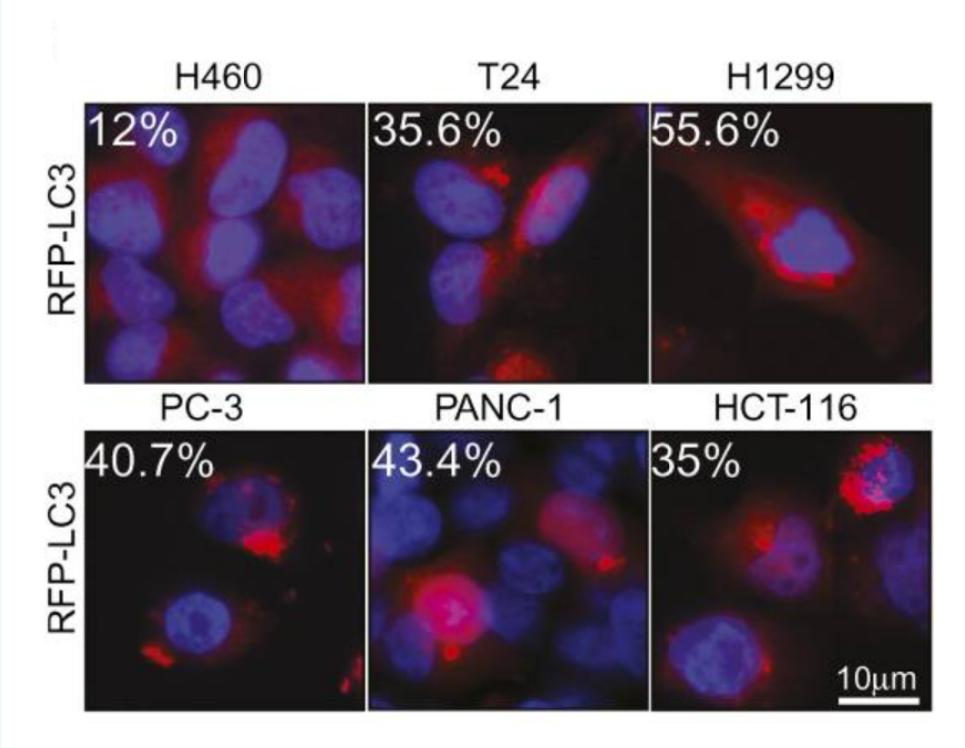
AUTOPHAGY IS A SIGNAL TRANSDUCTION PATHWAY
WITH DEFINED MOLECULAR COMPONENTS

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)

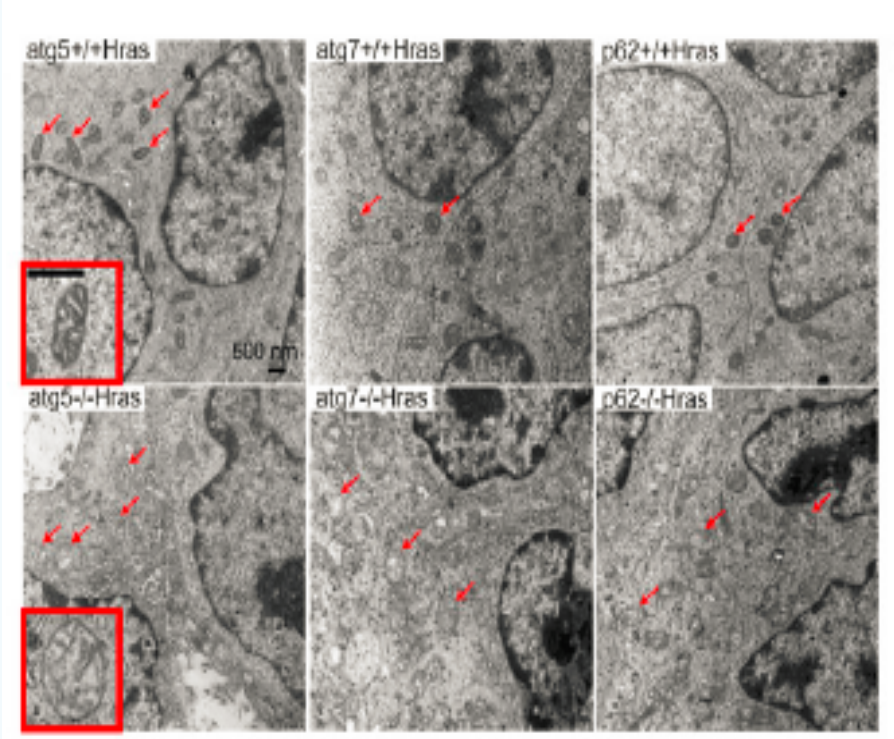
RAS Cancers Exhibit High Levels of Basal Autophagy



Evaluation of Cellular LC-3 Puncta

Competent Autophagy

Incompetent Autophagy



Swollen Mitochondria Accumulate in Cells where Autophagy is Blocked

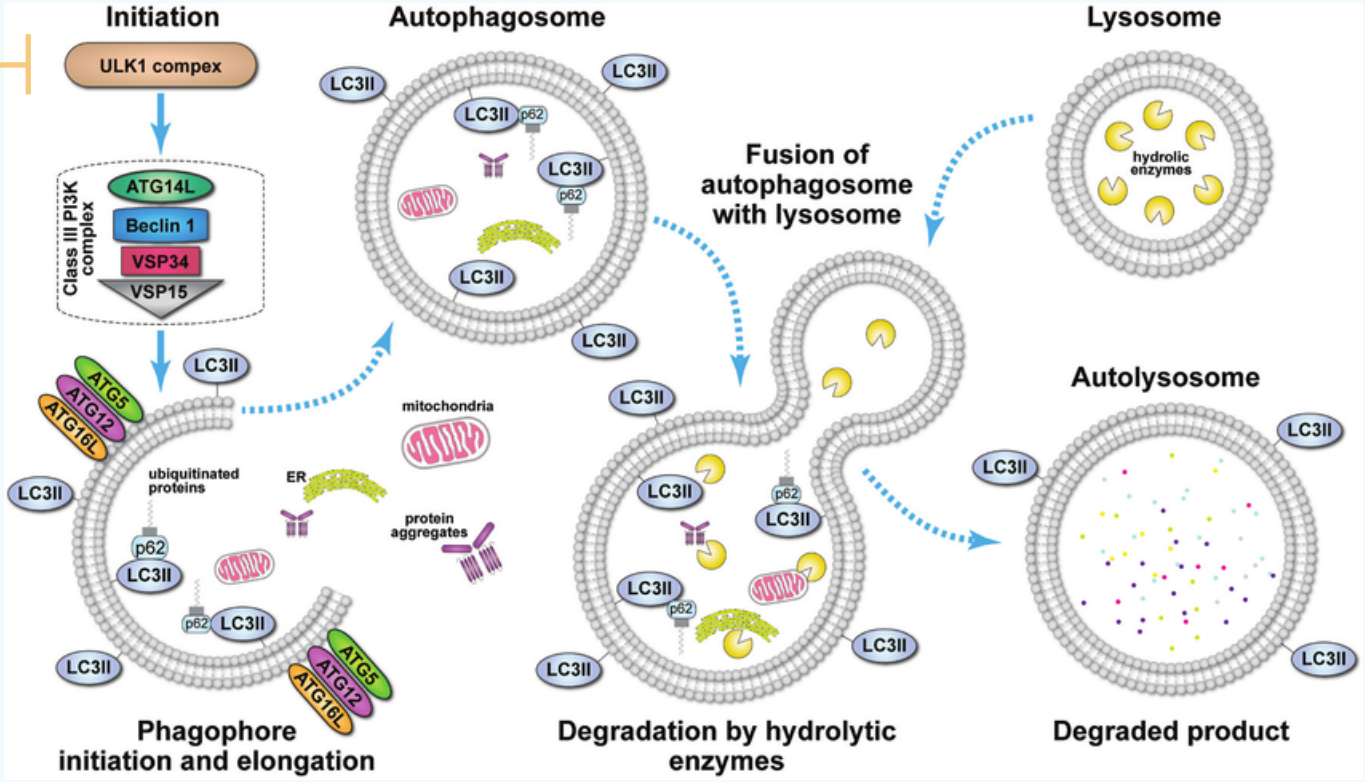
Genes and Development 2011;25:460-70

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)

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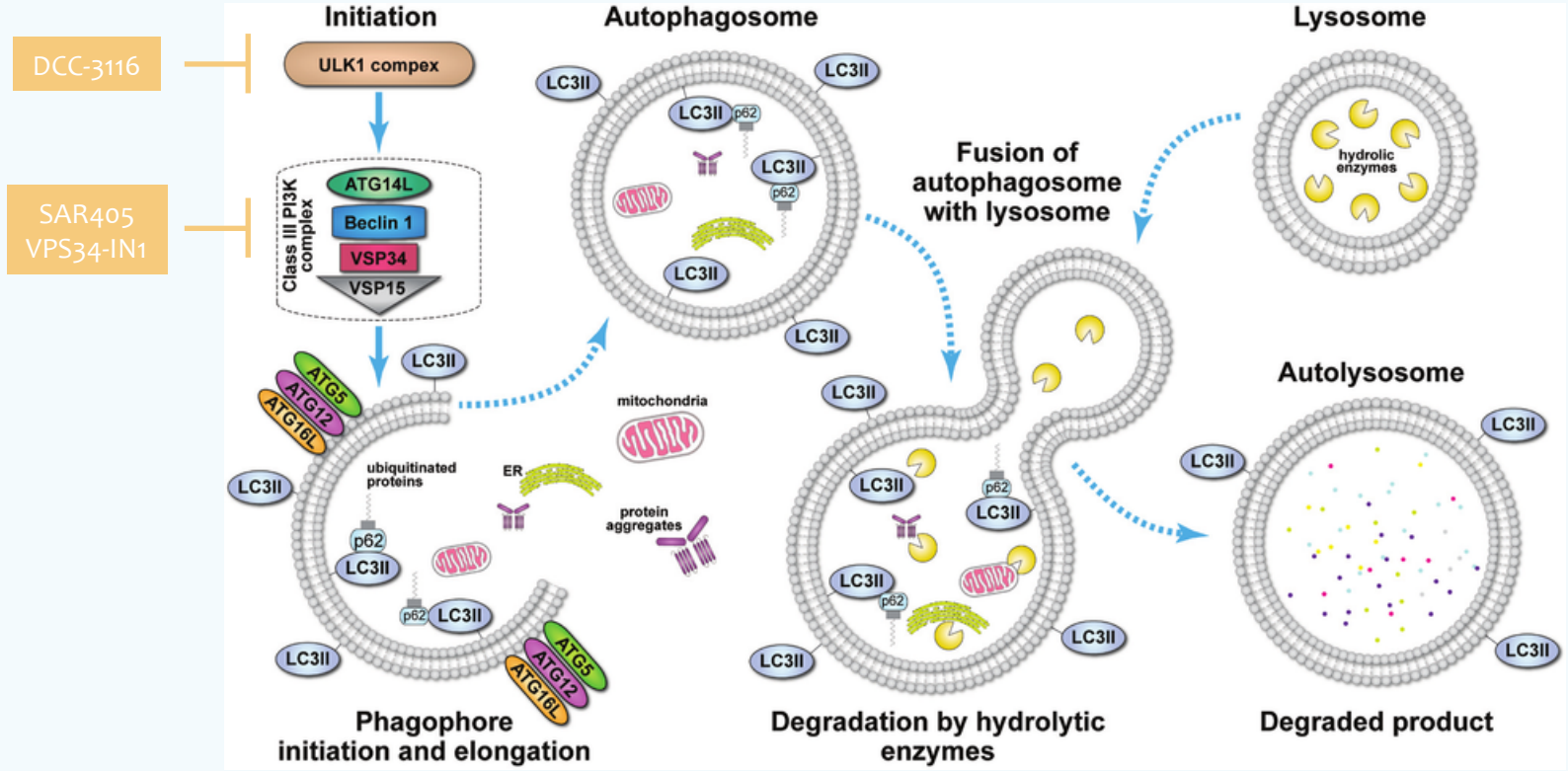
VPS34 Complex Inhibition

- 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

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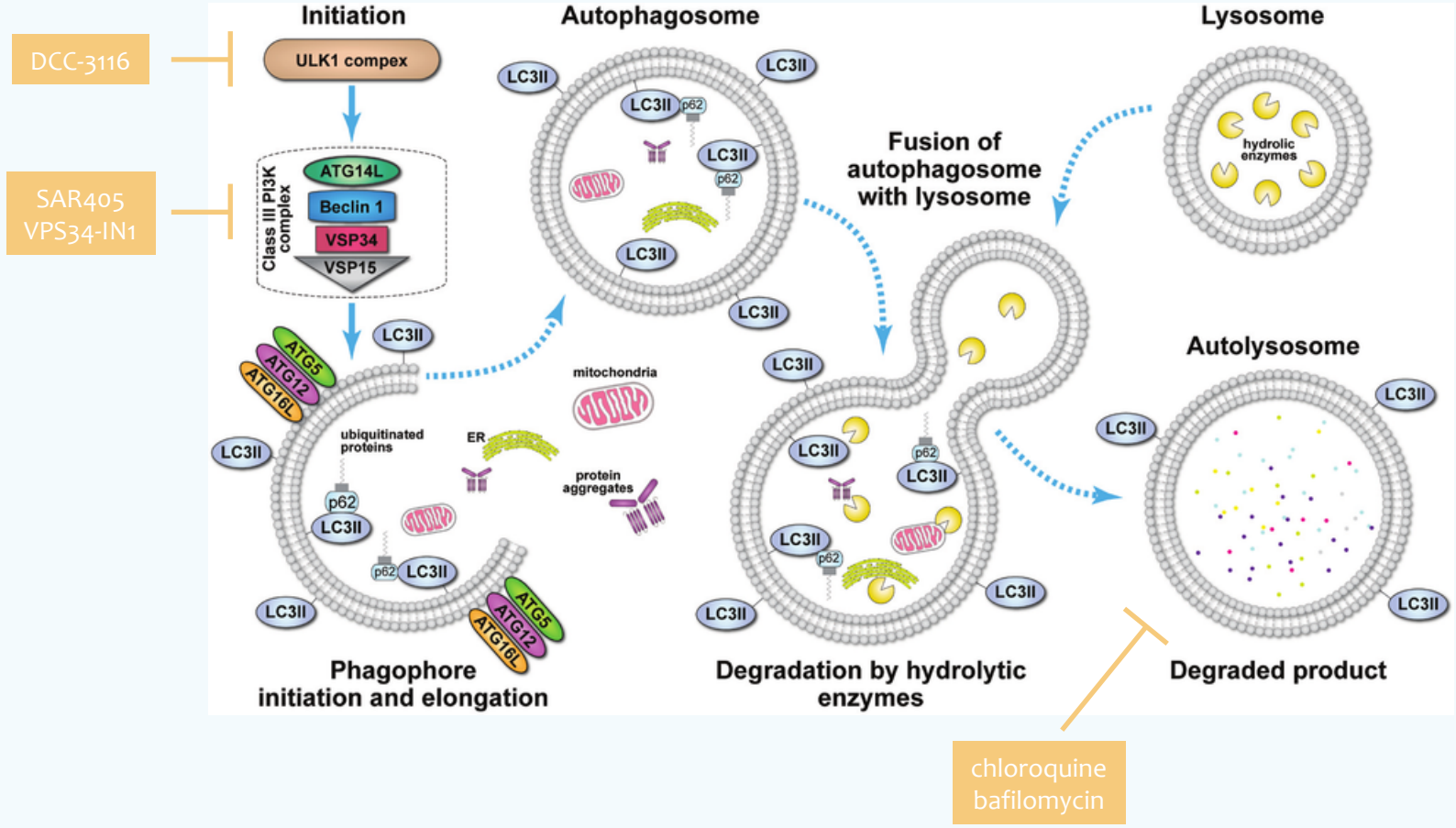
VPS34 Complex Inhibition

- 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. Camolotto[1], Amelie M. Boespflug[1,3,4], Katrin P. Gullien[1], Mona Foth[1], Amanda Truong[1], Sophia S. Schuman[1], Jill E. Shea[5], Michael T. Seipp[5], Jeffrey T. Yap[1,6], Lance D. Burrell[1], David H. Lum[1], Jonathan R. Whisenant[1,2], G. Weldon Gilcrease III[1,2], Courtney C. Cavalieri[1,7], Kaitrin M. Rehbein[1], Stephanie L. Cutler[1], 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]*

Articles

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

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

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PNAS

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

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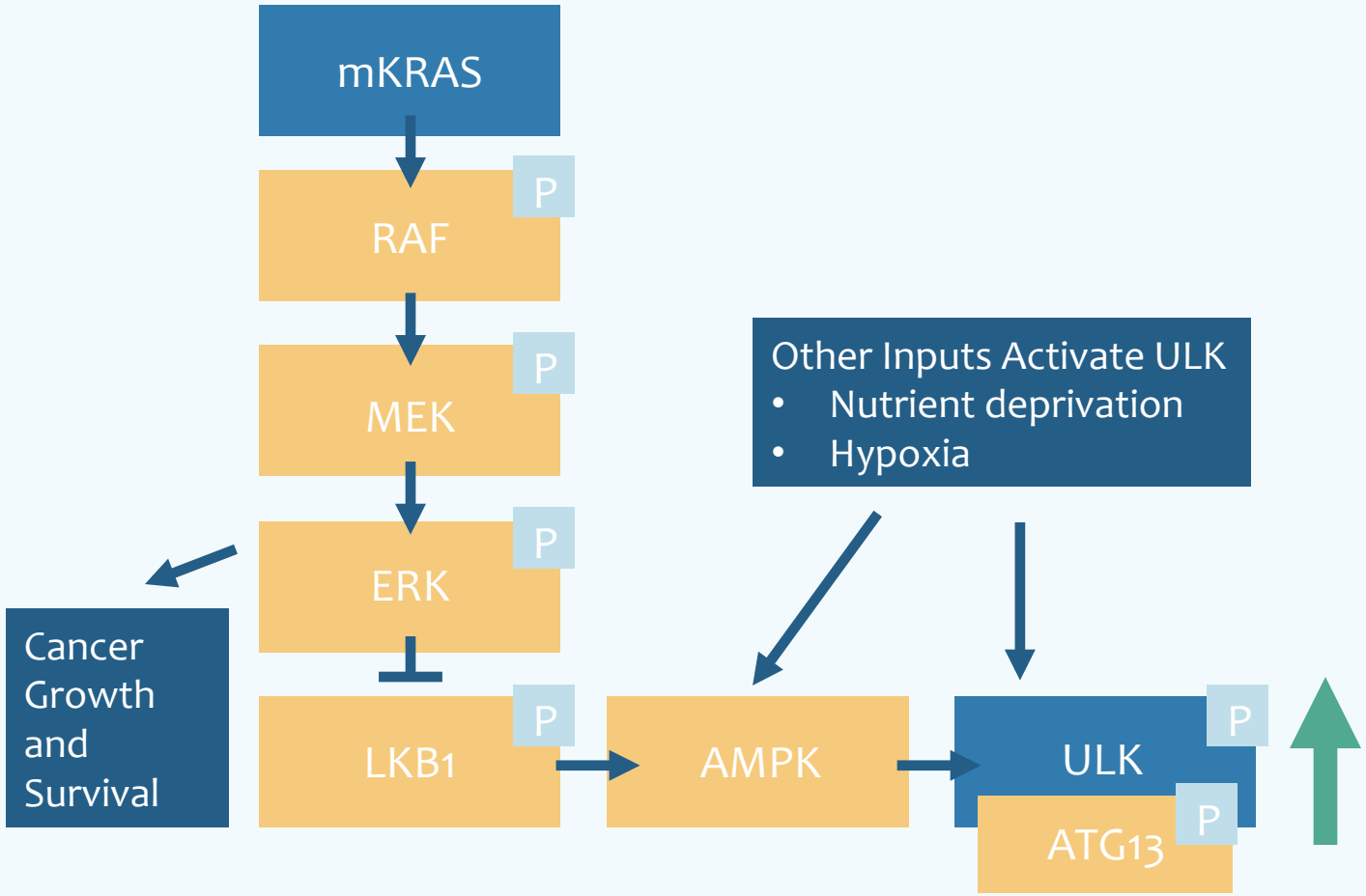
Edited by Ronald A. DePinho, University of Texas MD Anderson Cancer Center, Houston, TX, and approved December 17, 2018 (received October 18, 2018)

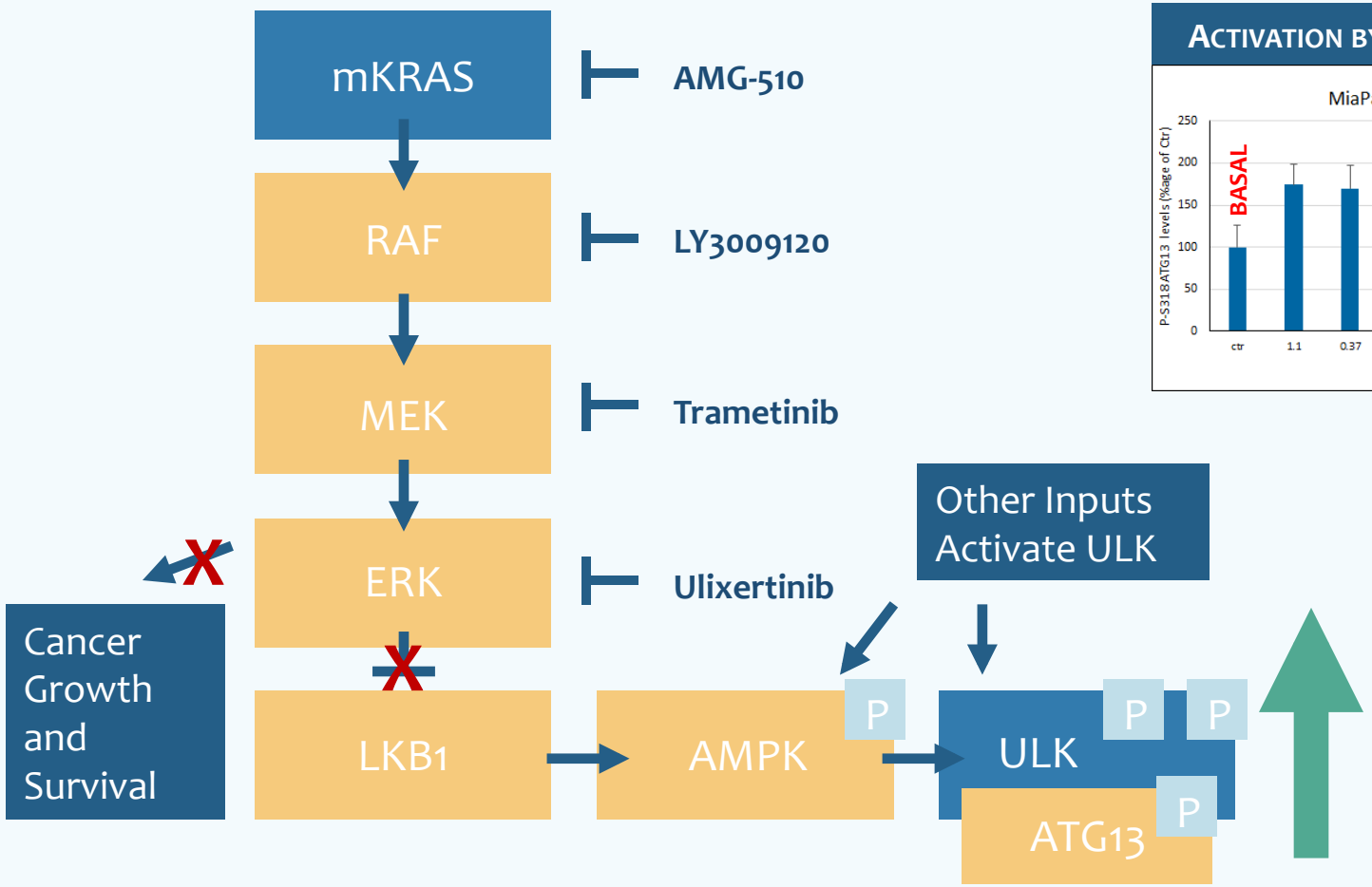
KRAS Activation Drives Tumor Growth and Tonic Regulation of ULK

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

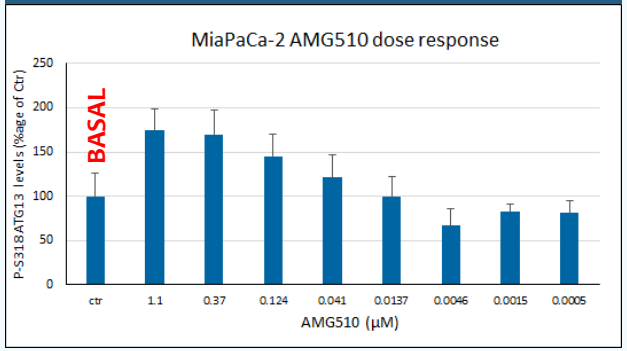


MAPK Pathway Inhibition Leads to Release of Tonic Inhibition of ULK

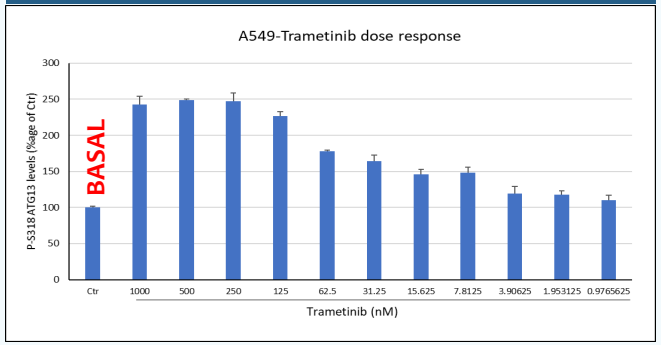
Autophagy is a compensatory survival mechanism in MAPK pathway inhibitor-treated RAS cancers



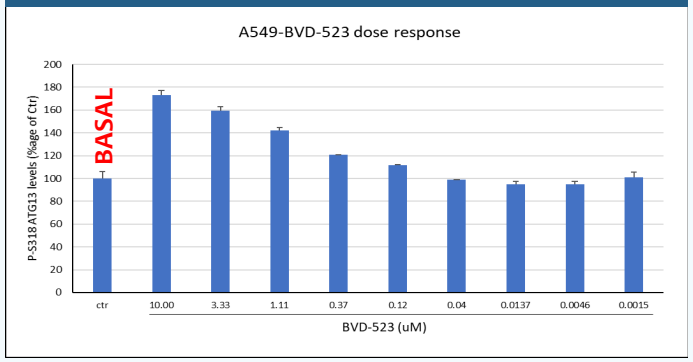
Activation by KRAS G12C Inhibition



Activation by MEK Inhibition



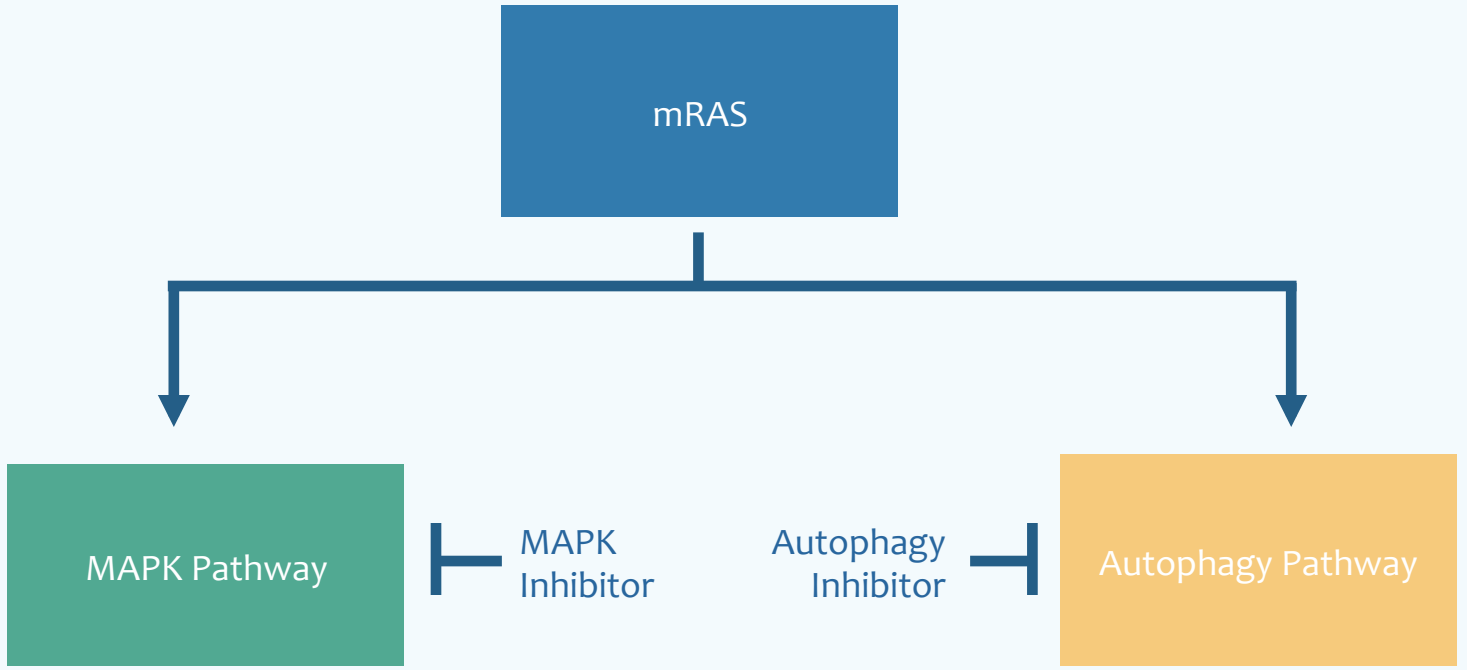
Activation by ERK Inhibition



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

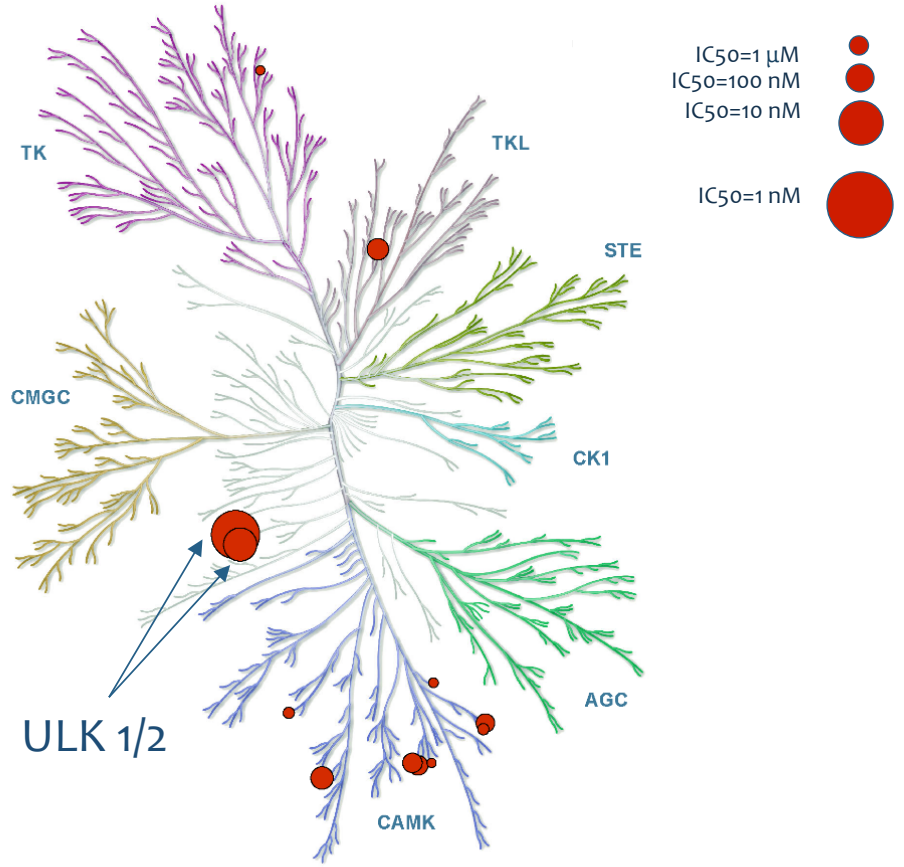
- No off-target kinases within 30-fold of ULK1
- Only 5 kinases within 100-fold of ULK1

Designed to avoid CNS exposure

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

IND Filing Expected in Mid-2020

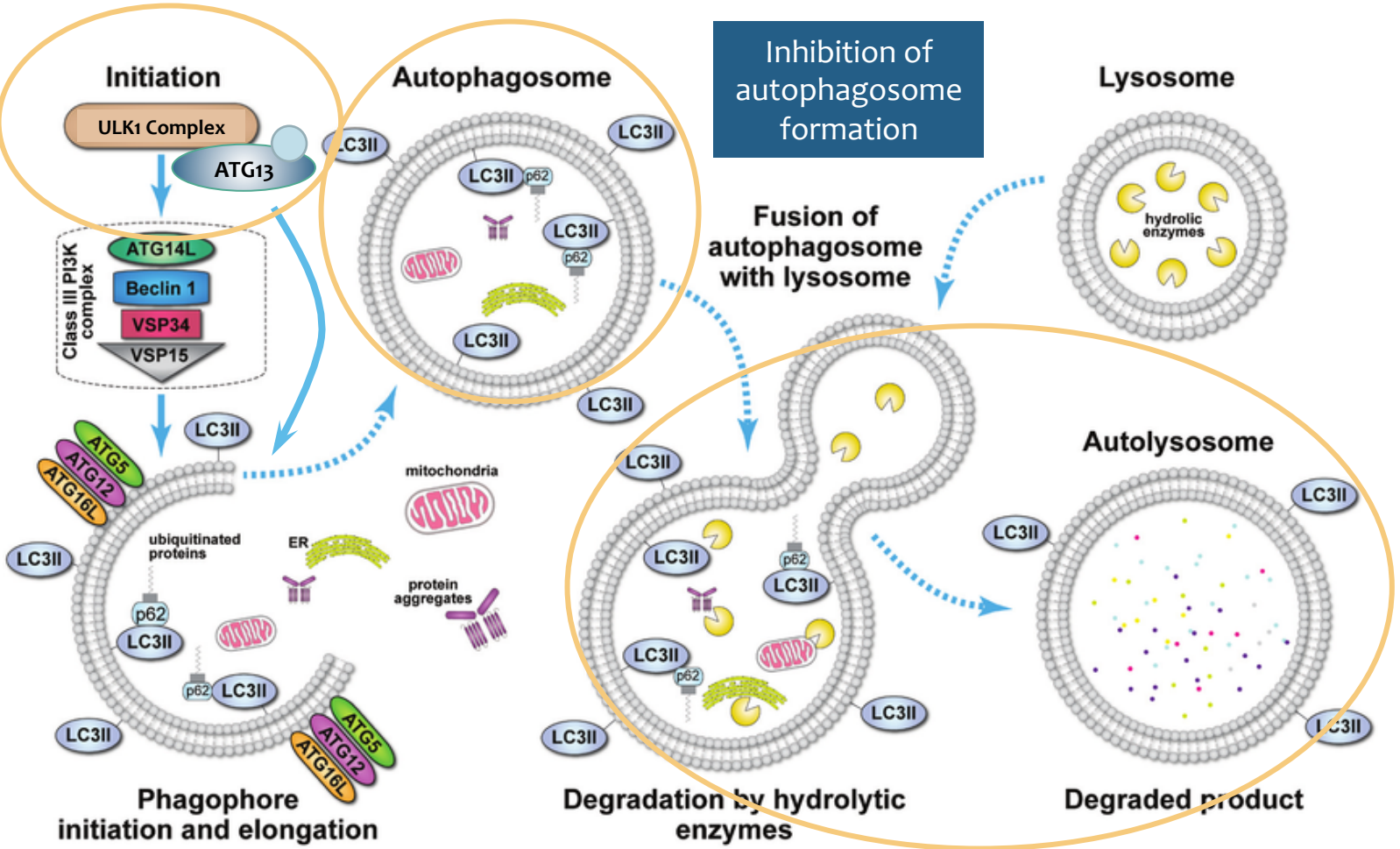
DCC-3116: A Selective ULK1/2 Inhibitor



Source and Notes: Composite of enzyme and cellular kinase phosphorylation data was used. The size of the red circle corresponds to the IC_{50} value obtained. No circles are plotted for kinases with IC_{50} > 1 µM; Illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com).

DCC-3116 Inhibits Autophagy in Cellular Assays

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

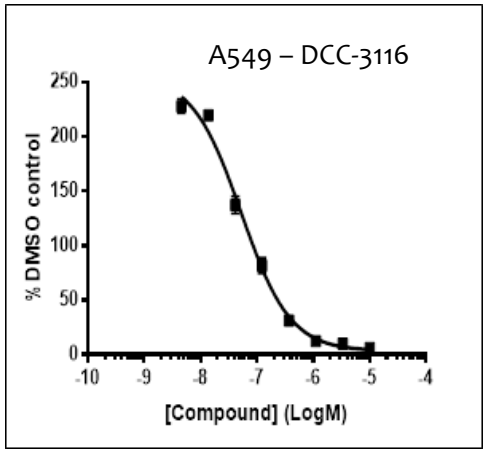


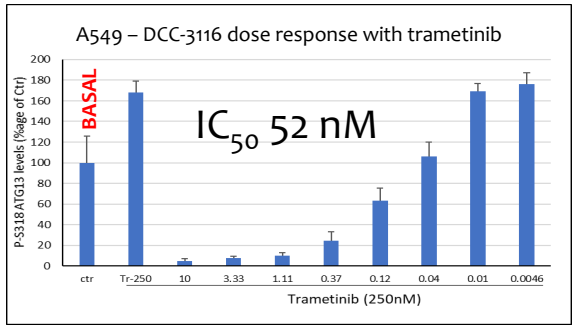
Inhibition of LC3 degradation

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

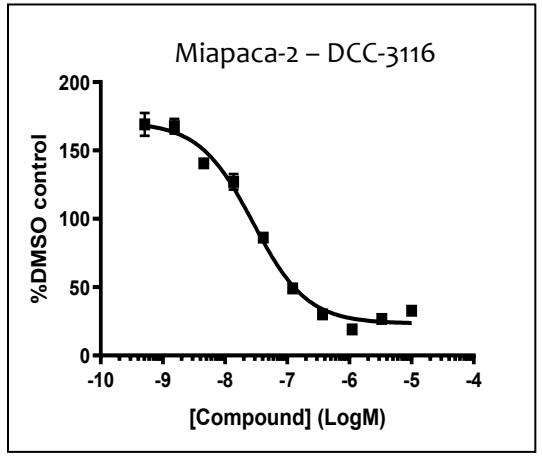
DCC-3116 Potently Inhibits ULK in Multiple RAS Cancer Cell Lines

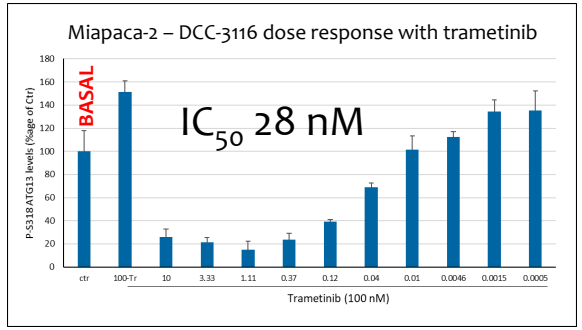
KRAS Lung Cancer



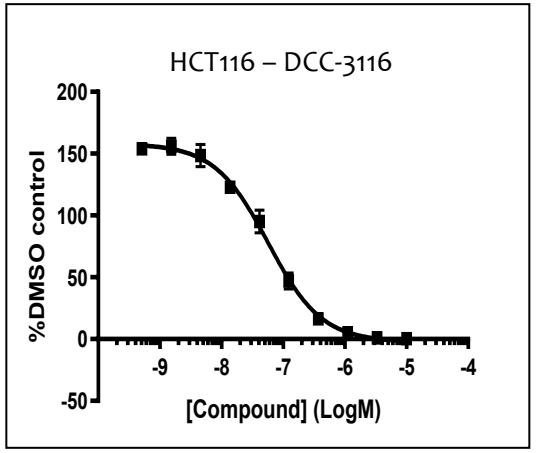


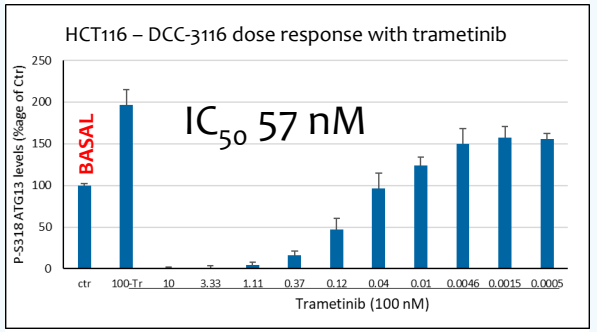
KRAS G12C Pancreatic Cancer



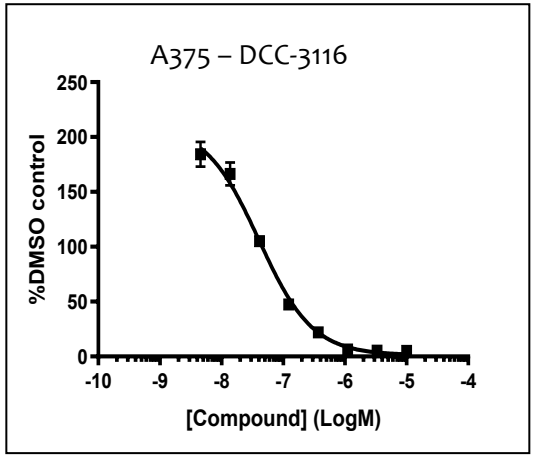


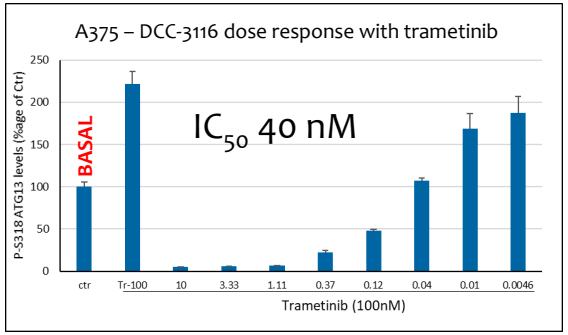
KRAS Colorectal Cancer





BRAF Melanoma Cancer

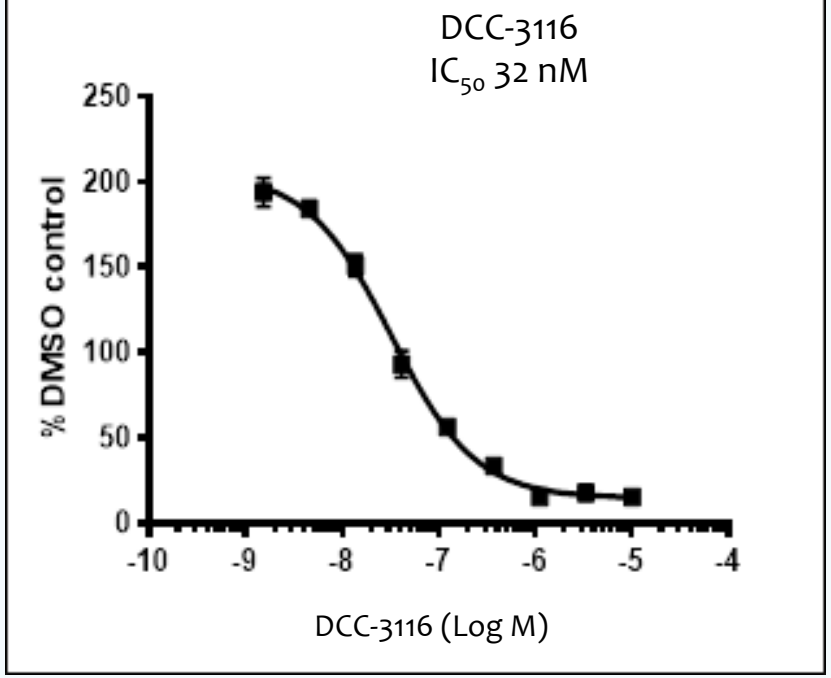




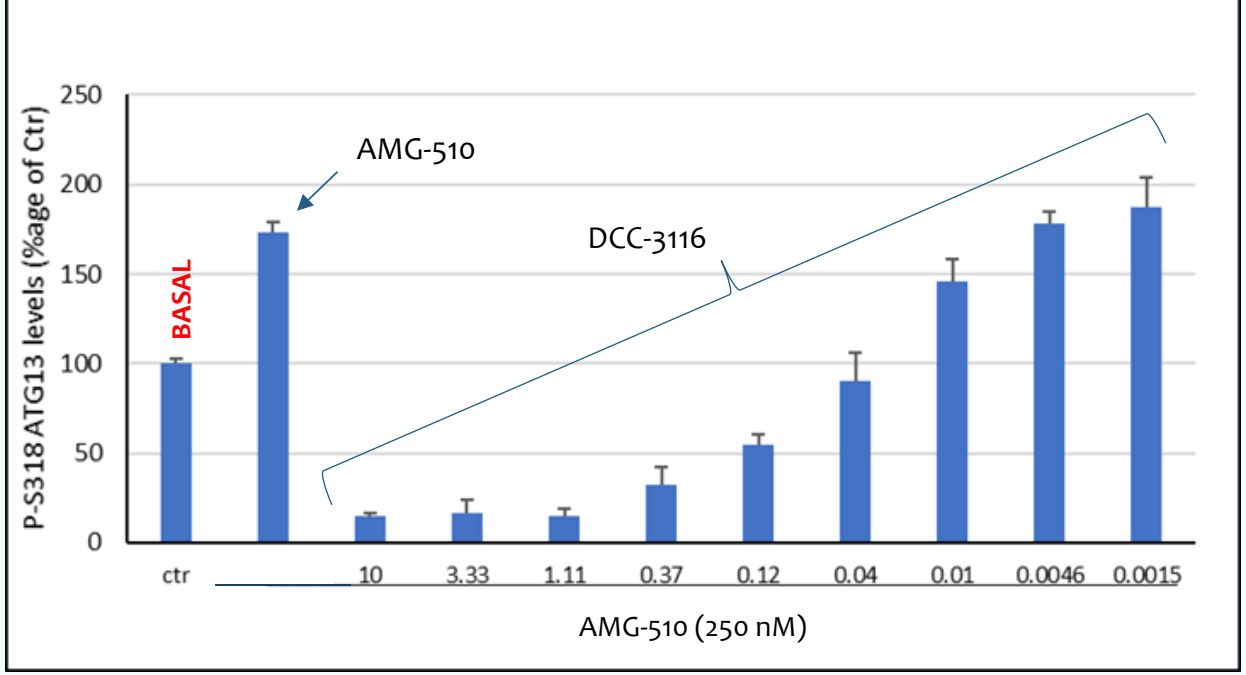
Basal and MAPK inhibitor-mediated compensatory increased autophagy are inhibited

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

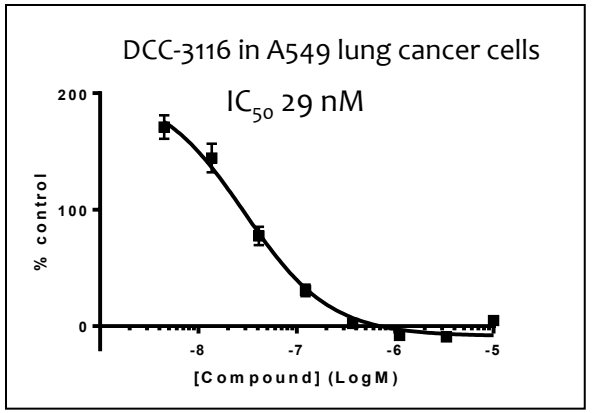


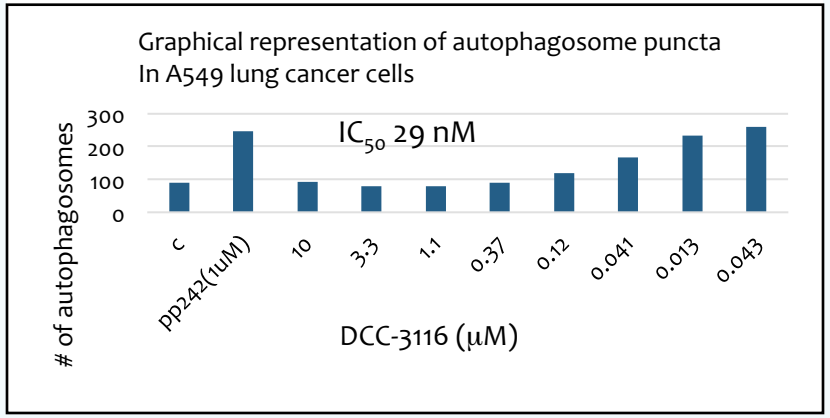
Miapaca-2 pancreatic cancer study with AMG-510

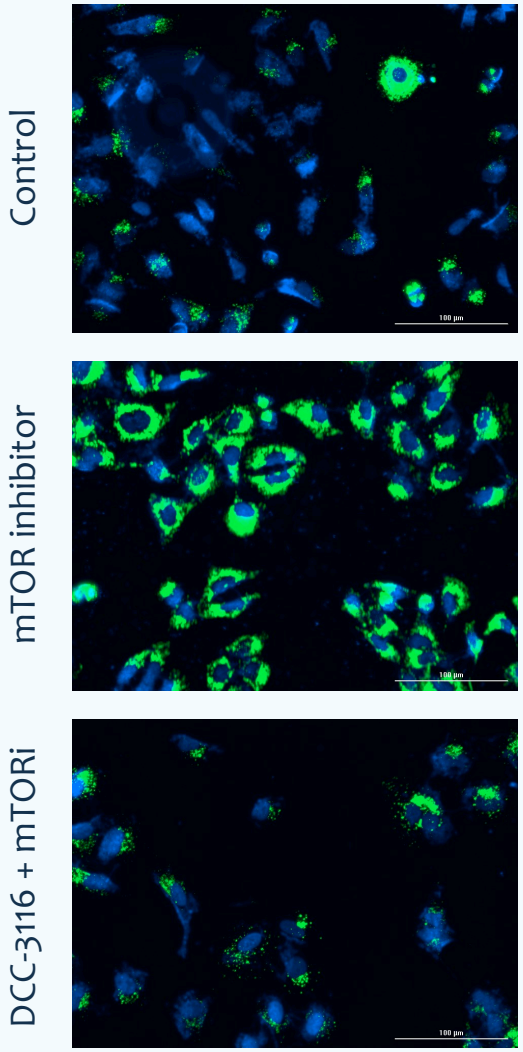


DCC-3116 Inhibits Autophagosome Formation and Lysosomal Degradation in KRAS Mutant Cancer Cells *In Vitro*

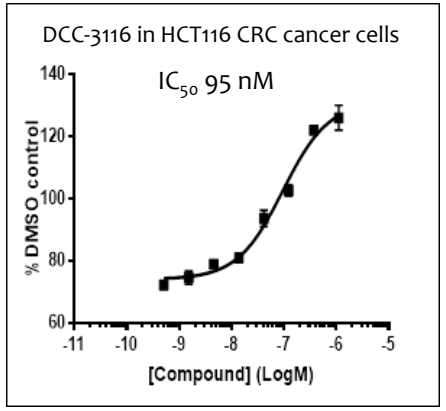
AUTOPHAGOSOME FORMATION INHIBITION

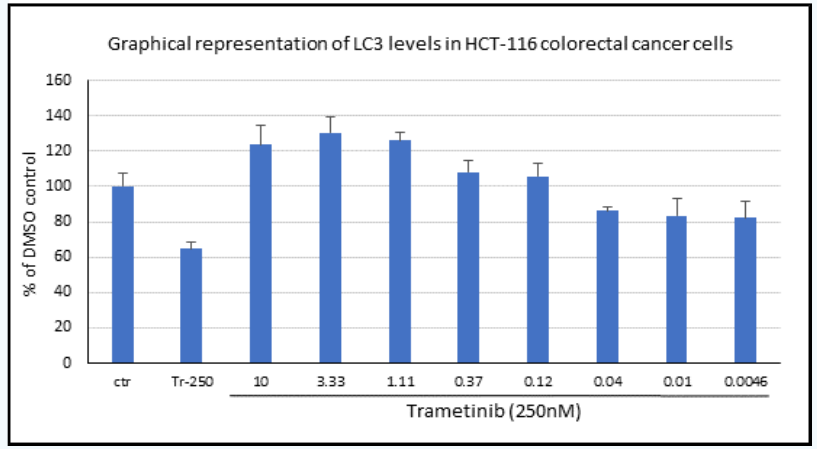






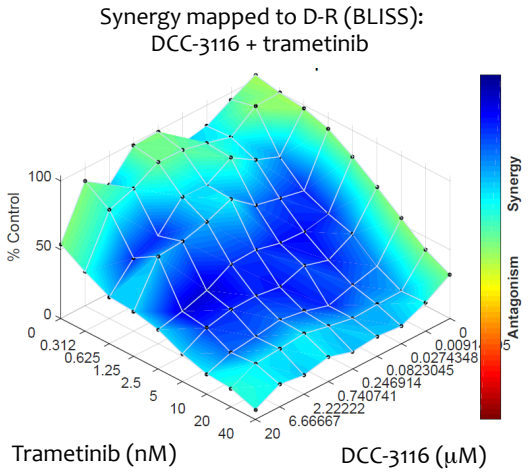
LC3 DEGRADATION INHIBITION

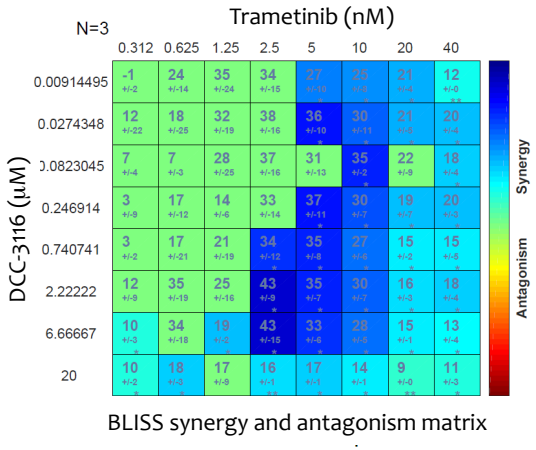




DCC-3116 + Trametinib Synergize to Inhibit Pancreatic Cancer Cell Proliferation *In Vitro*

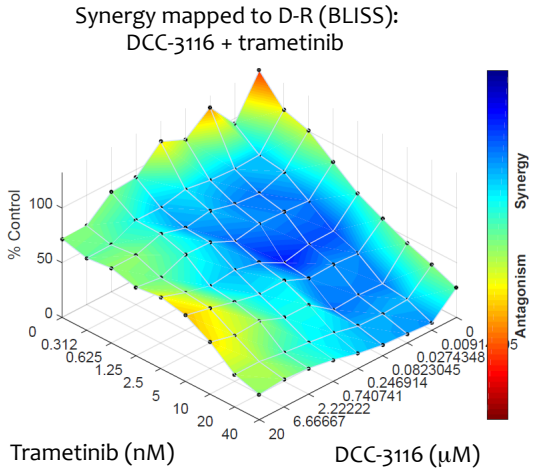
Inhibition of cell proliferation in KRAS mutant MiaPaCa-2 pancreatic cancer cells

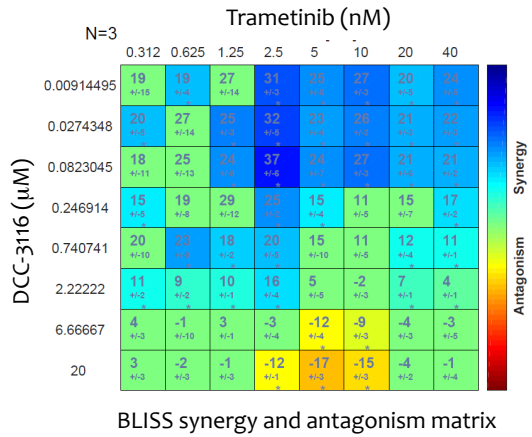




Strong synergy observed for various concentrations of DCC-3116 with trametinib combinations across the matrix

Inhibition of cell proliferation in BRAF mutant BxPC3 pancreatic cancer cells

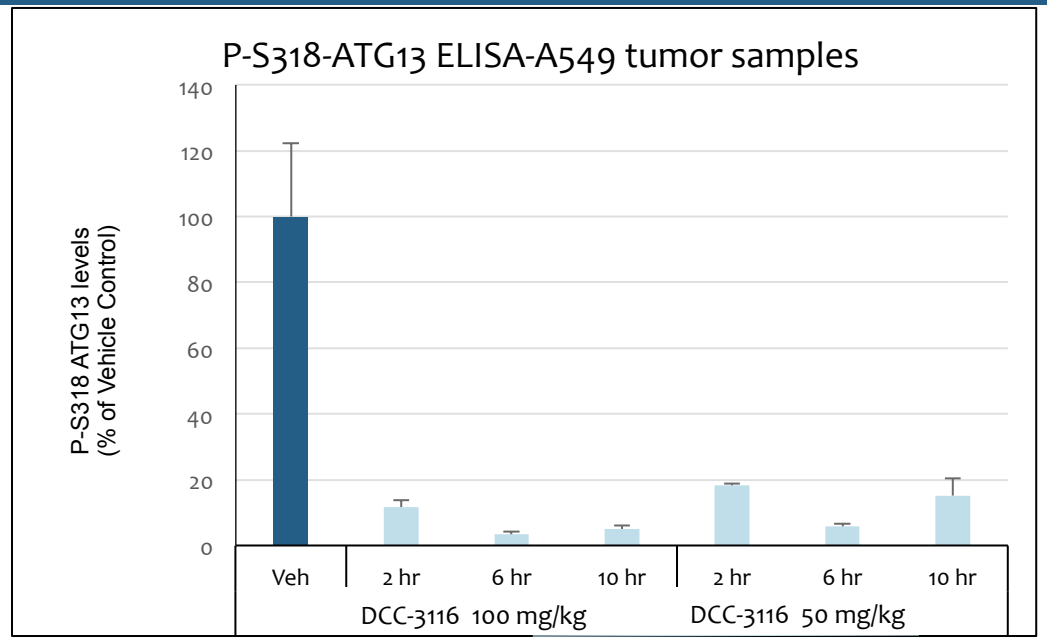




Synergy at lower concentrations of DCC-3116 and across concentration range of trametinib

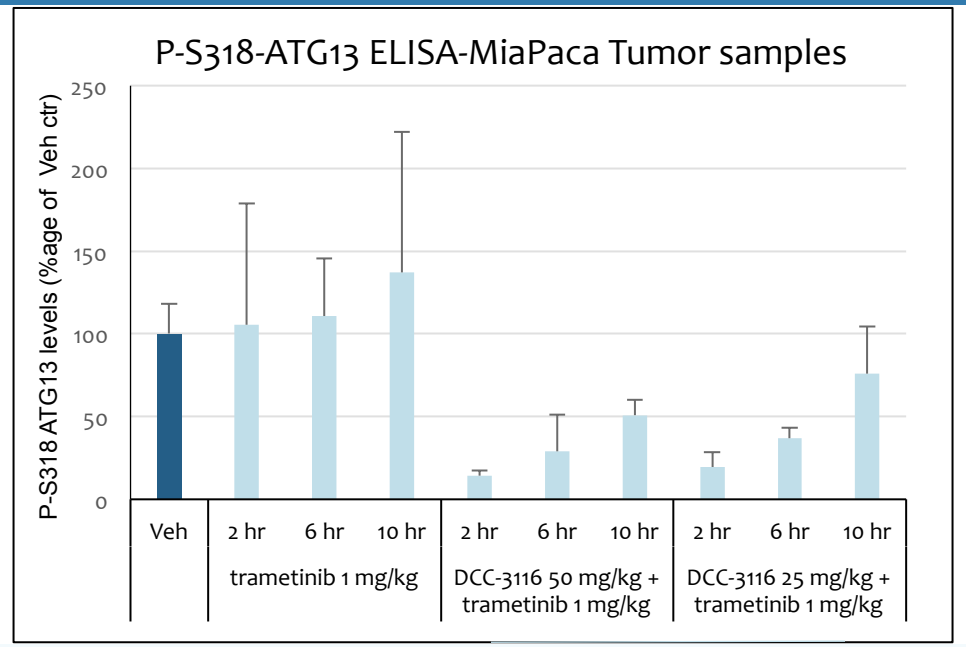
DCC-3116 Durably Inhibits ULK *In Vivo* in KRAS Cancer PK/PD Models

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

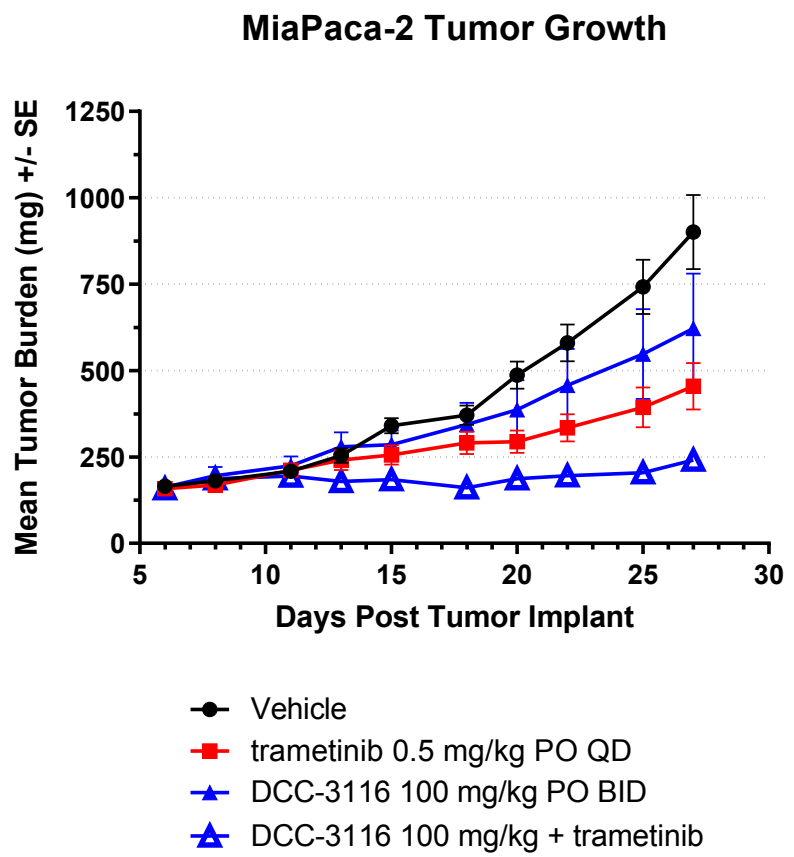
MiaPaCa-2 Pancreatic Cancer



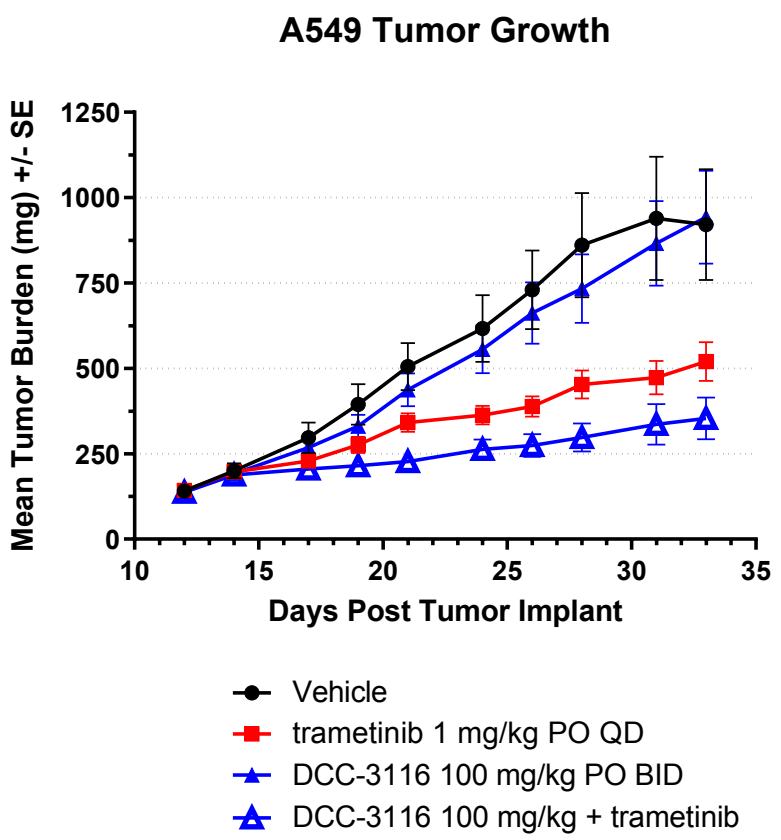
	DCC-3116 50 mg/kg			DCC-3116 25 mg/kg		
	2 hr	6 hr	10 hr	2 hr	6 hr	10 hr
Free drug (nM)	3,016	1,079	243	1,582	581	254
% pATG13 inhibition	86	71	49	80	63	24

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

KRAS MUTANT PANCREATIC

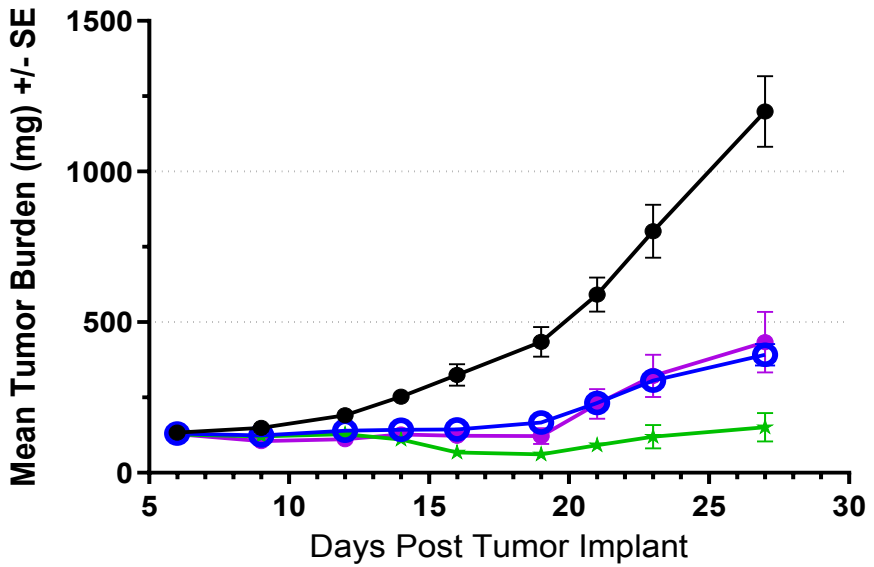


KRAS MUTANT LUNG



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

MiaPaCa-2 Tumor Growth

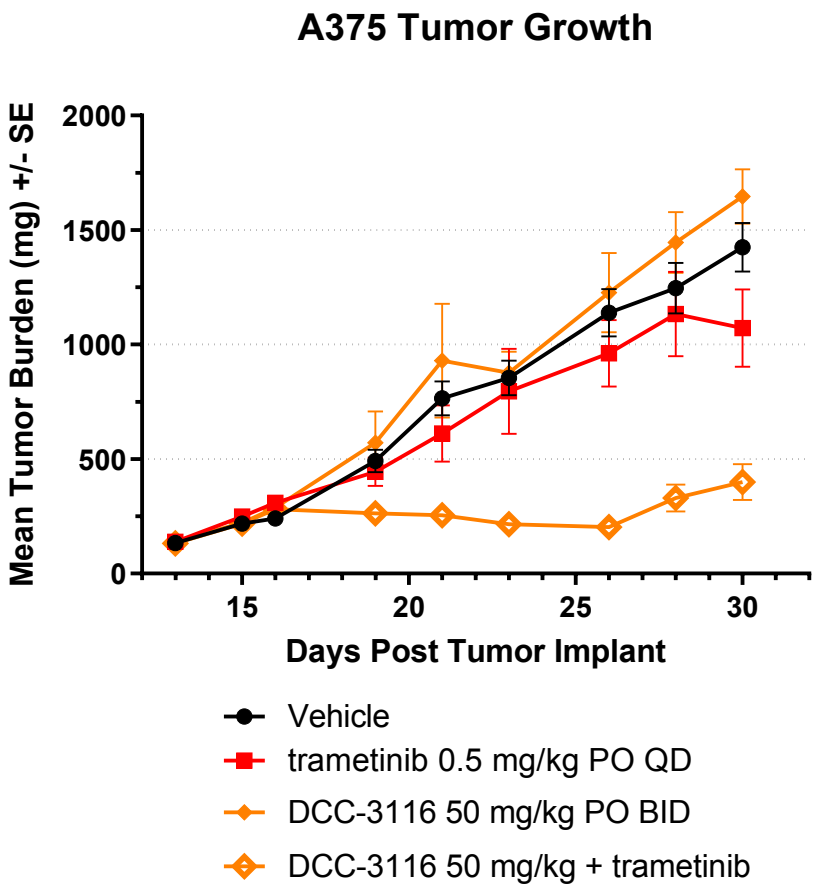


Marketed MEK Inhibitors

ERK Inhibitor

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

BRAF MUTANT MELANOMA



Rationale for DCC-3116 in RAS Cancers

RAS CANCERS DEPEND ON MEK/ERK SIGNALING & AUTOPHAGY FOR SURVIVAL	• 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	• 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	• Highly selective and potent inhibitor of ULK kinase • Designed for combination approach
STRONG PRELIMINARY PRECLINICAL VALIDATION	• DCC-3116 inhibits autophagy in RAS cancer cell lines • DCC-3116 potently and durably inhibits autophagy *in vivo* • Combination of DCC-3116 plus MAPK pathway inhibitors synergize to block RAS cancers *in vivo*

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 elicted 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