

# 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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# 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*

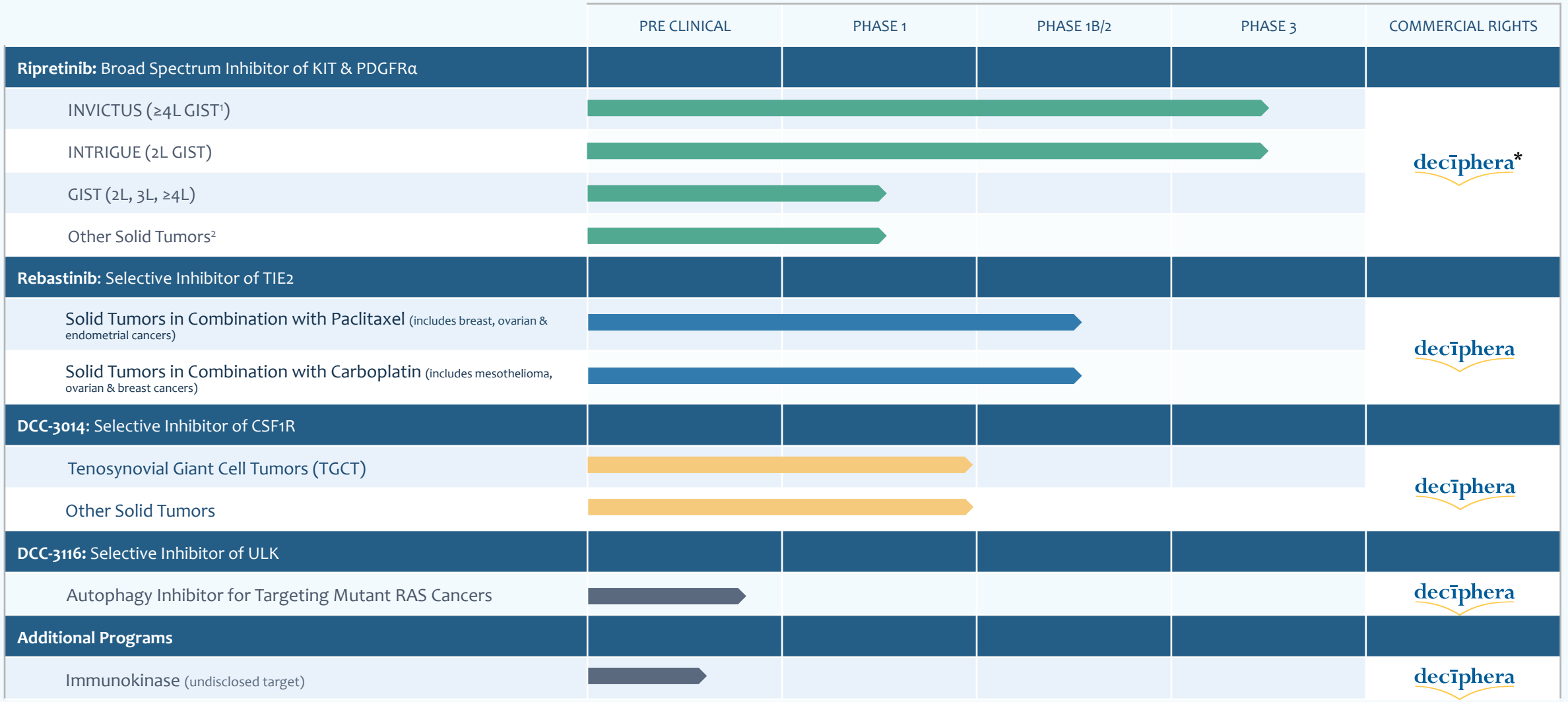
- **ULK Kinase Inhibitors & Autophagy**
  *Daniel Flynn, Ph.D., EVP, Chief Scientific Officer & Founder*

- **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<br>• Rapidly progress INTRIGUE in 2L GIST |
| 2 | Advance Clinical Programs | • Drive to initial clinical data for POC<br>• Accelerate path to pivotal trials |
| 3 | Invest in Next Research Wave | • Progress DCC-3116 to IND<br>• 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))<br>☐ Phase 1 Expansion Data (2H 2019) |
| **Rebastinib** | ☑ Phase 1b/2 Carboplatin Combination Initiated (1H 2019)<br>☑ Part 1 of the Phase 1b/2 Paclitaxel Combination Completed Enrollment (1H 2019)<br>☐ Part 1 of the Phase 1b/2 Paclitaxel Combination Data (2H 2019) |
| **DCC-3014** | ☑ Phase 1 Dose Escalation Presentation (1H 2019)<br>☐ 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)<br>☑ Initiate IND-enabling Studies (1H 2019) |

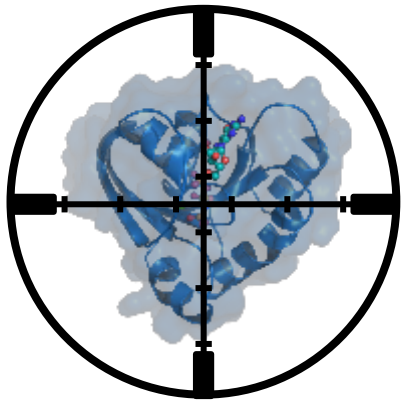


## Channing Der, Ph.D.

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

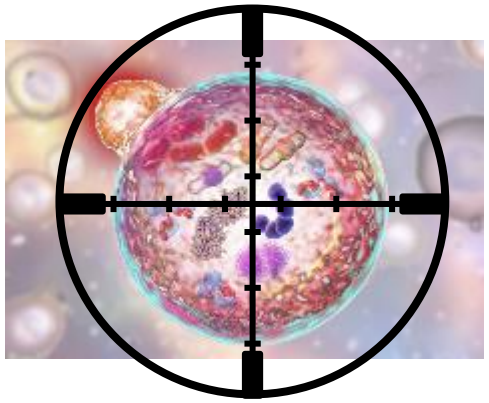
## Autophagy & Mutant RAS Cancers

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 |

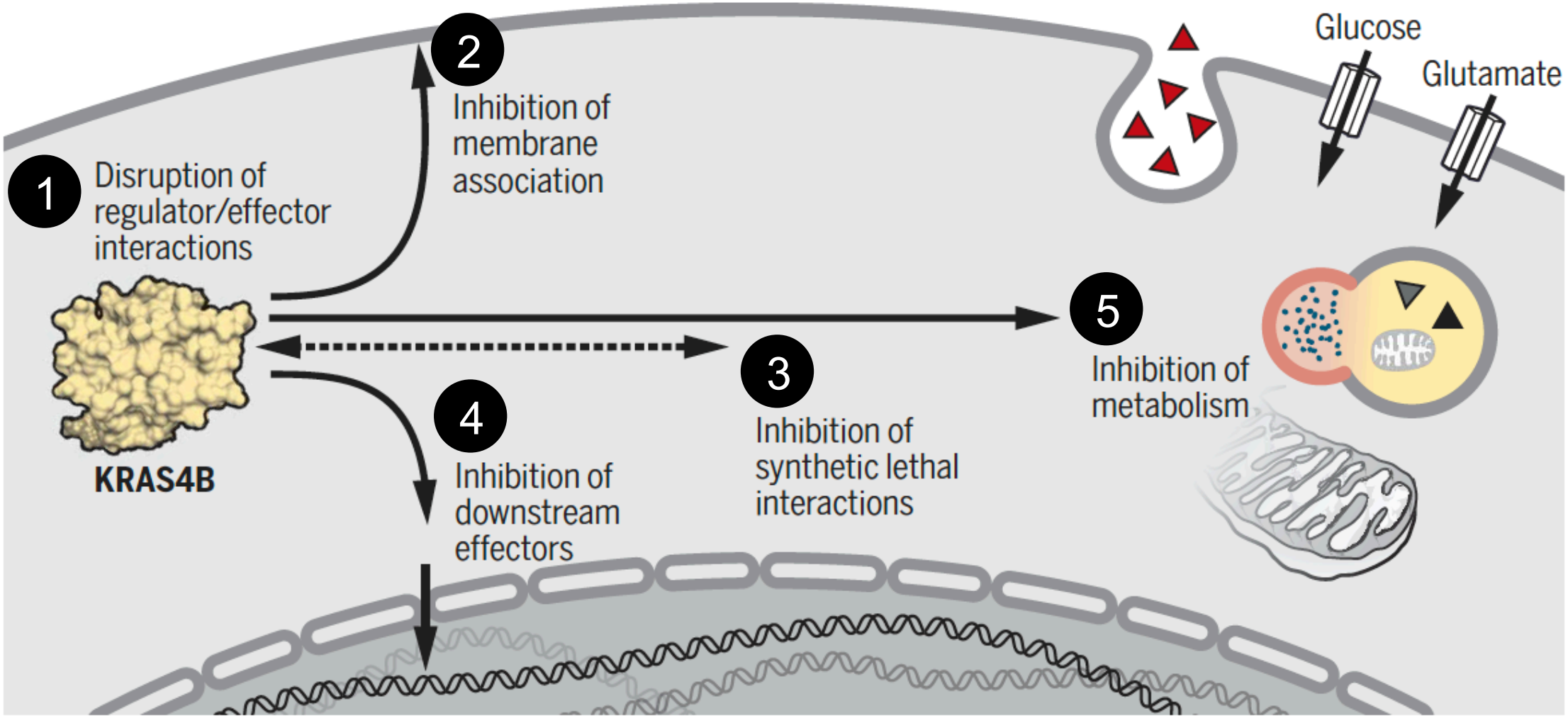
Cox et al (2014) Nat Rev Drug Discov 13:828

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 |

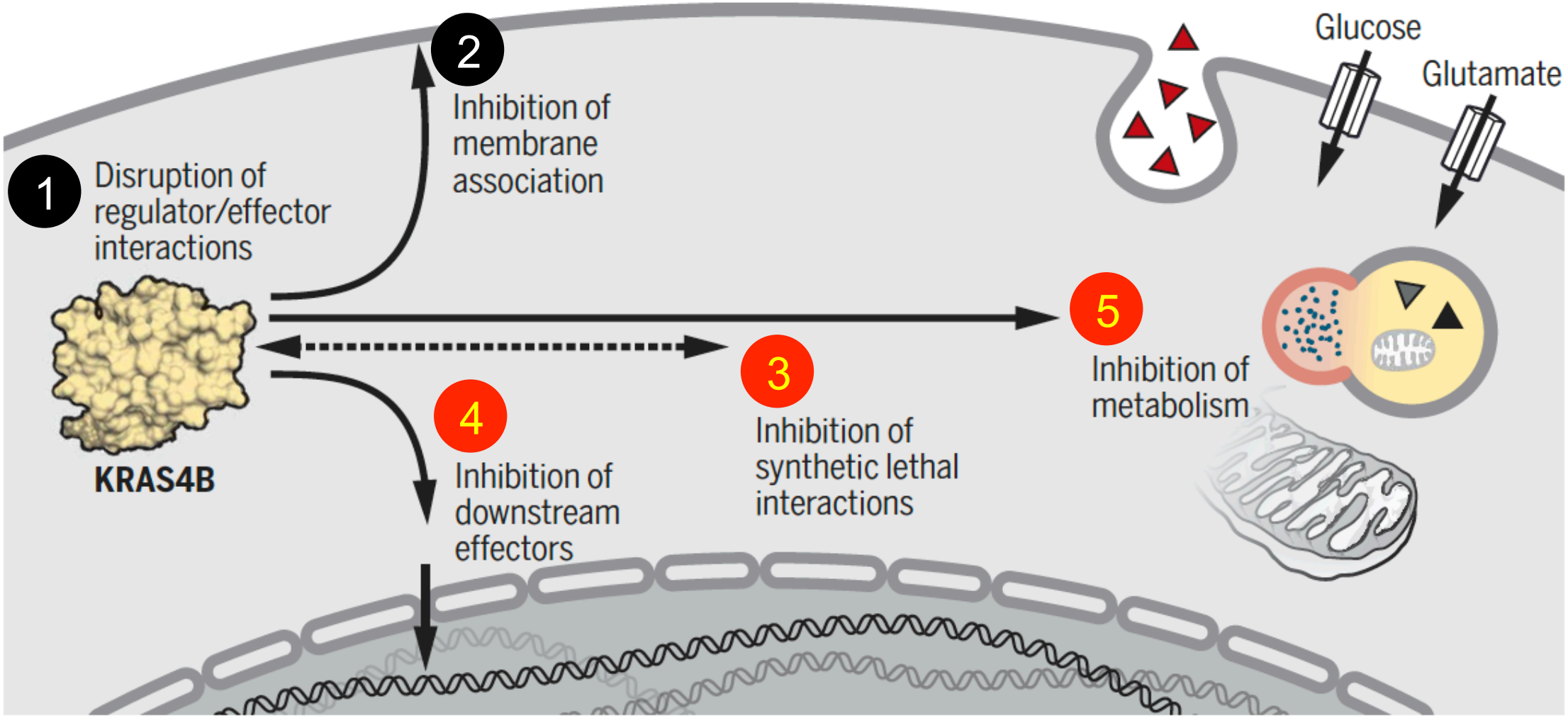
Siegel et al (2019) CA Cancer J Clin 69:10

# 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]

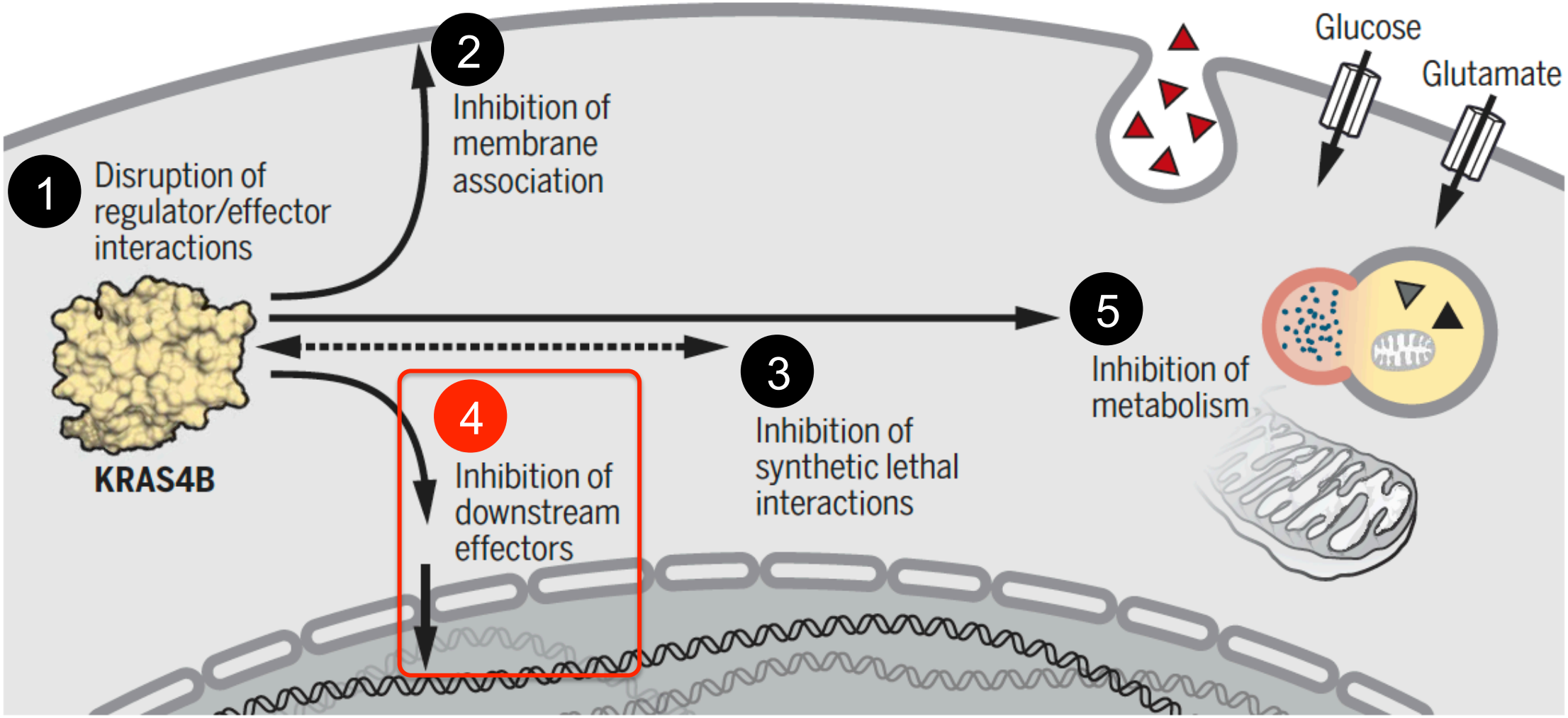
# Chasing after ERK leads us to autophagy

NATURE MEDICINE VOL 25 | APRIL | 628-640 ARTICLES

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

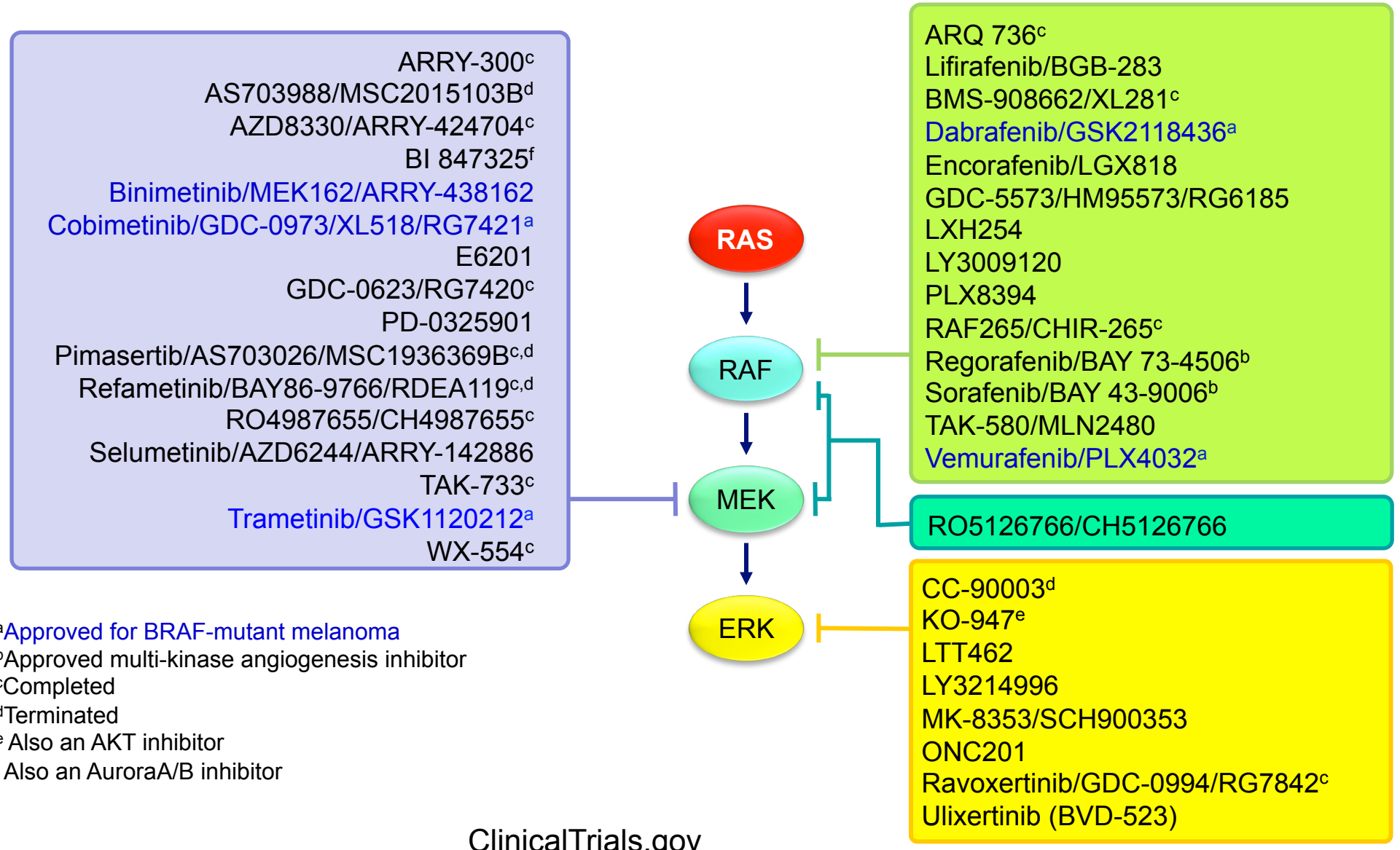
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# Targeting the RAF-MEK-ERK MAPK cascade




Papke & Der (2017) Science 355:1158

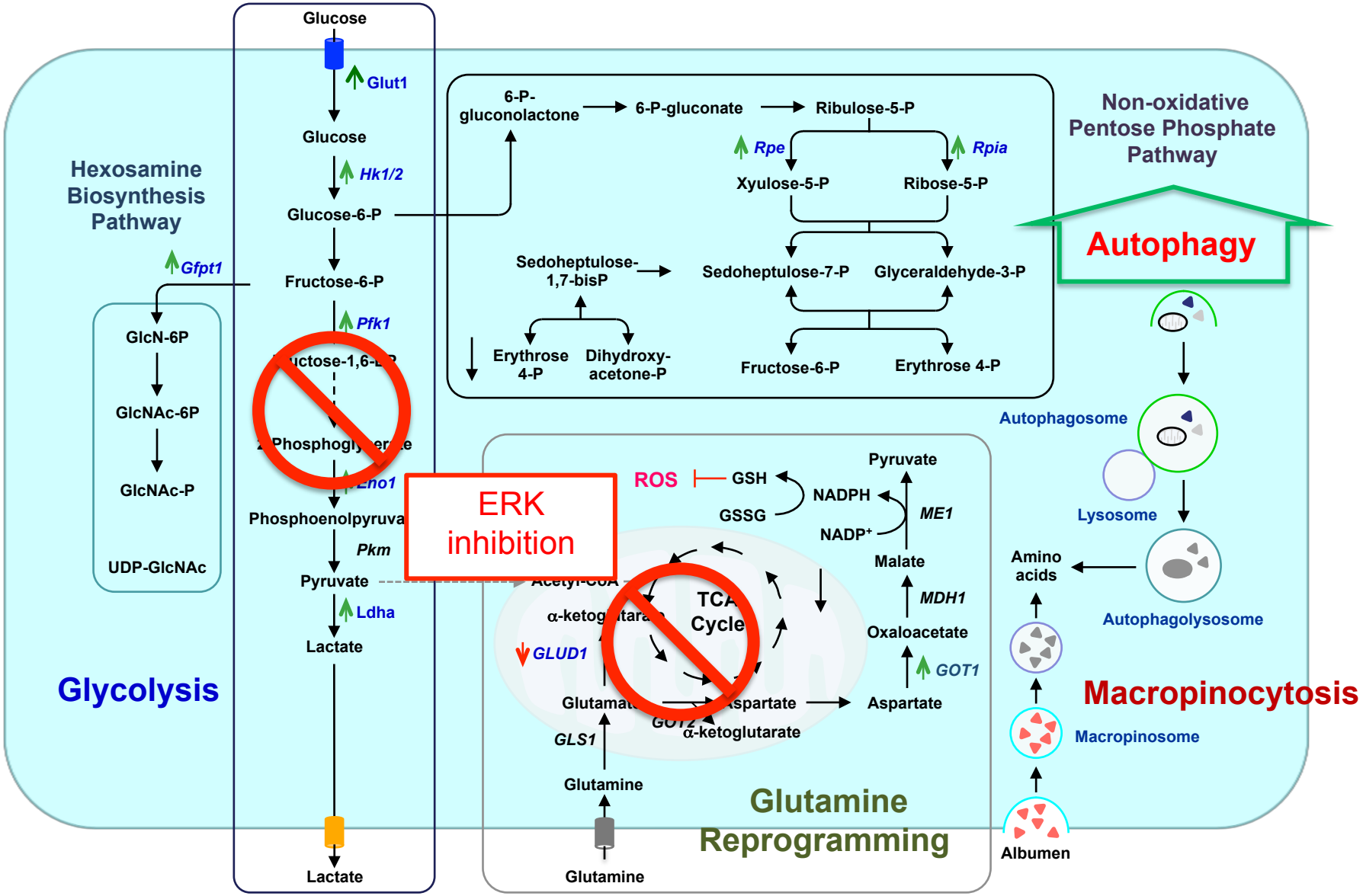
# Clinical evaluation of RAF-MEK-ERK protein kinase inhibitors




[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

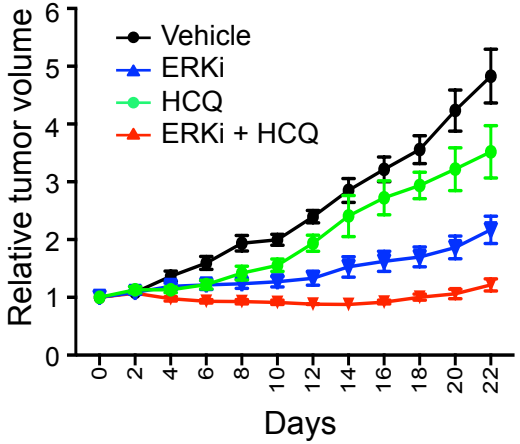


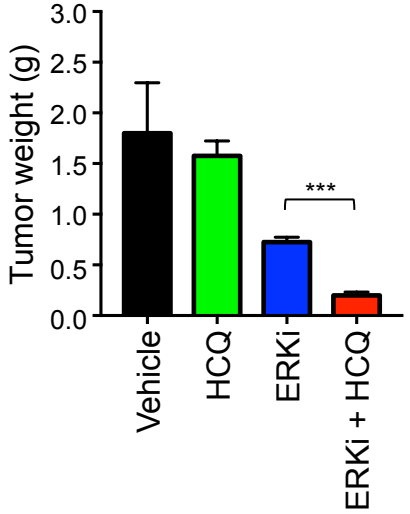

- Increased dependency on autophagy?
- Increased vulnerability to autophagy inhibition?

Bryant et al (2019) Nat Med 25:628

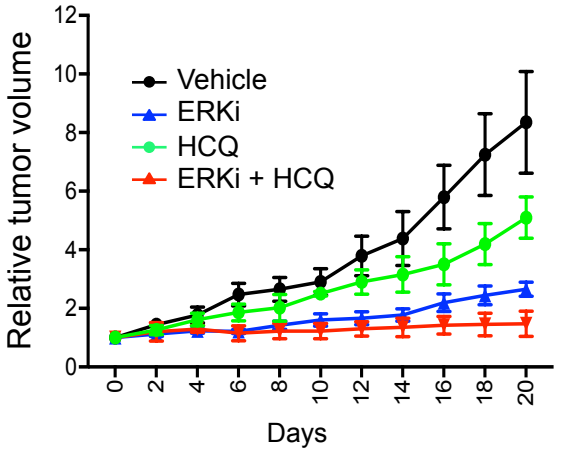
# Concurrent ERK and autophagy inhibition suppresses pancreatic patient-derived xenograft tumor growth

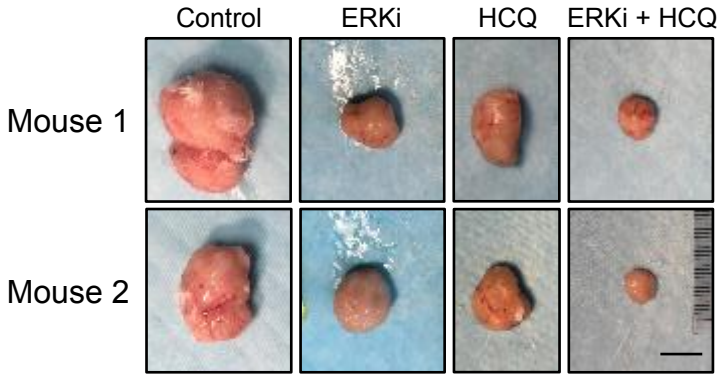
**AZ1013 PDX**
*KRAS* G12D
*TP53* R248W
*NF1* I1186N
*KMT2C* R4541*
*SMAD4* deletion
*CDKN2A* deletion

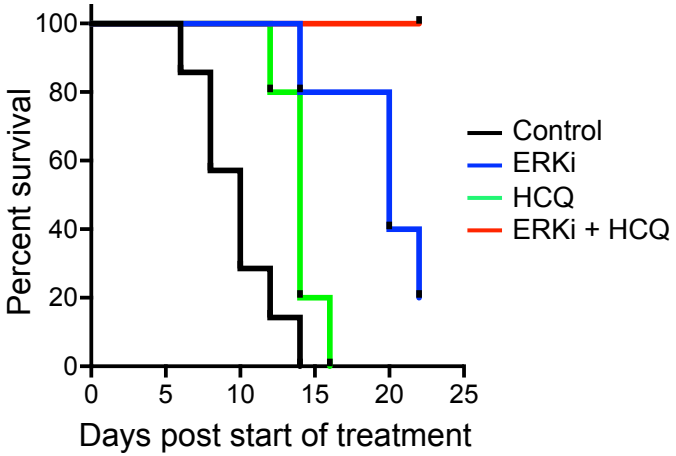


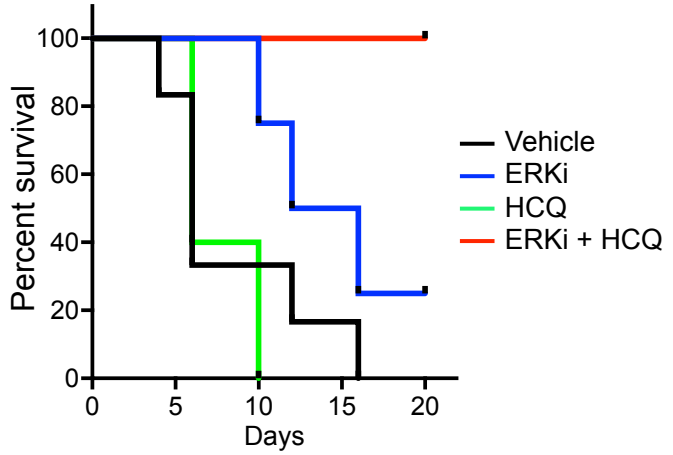




**AZ97 PDX**
*KRAS*G12V
*TP53* p.R248Q
*SMAD4* p.Y131*
*CDKN2A*




Bryant et al (2019) Nat Med 25:628

# Independently, another group reaches the same conclusion

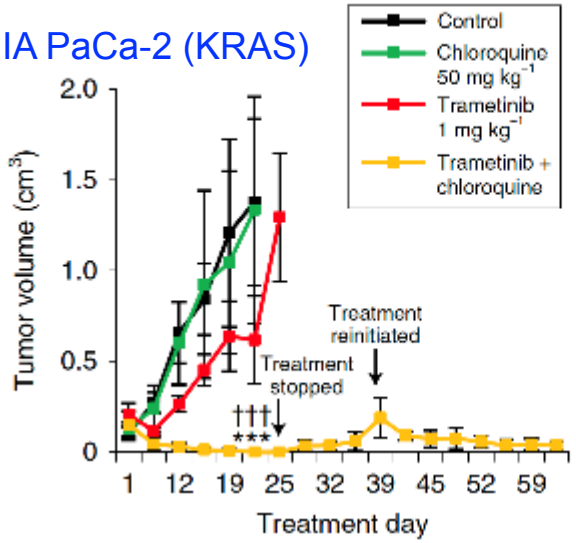
NATURE MEDICINE VOL 25 | APRIL | 620-627 LETTERS

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

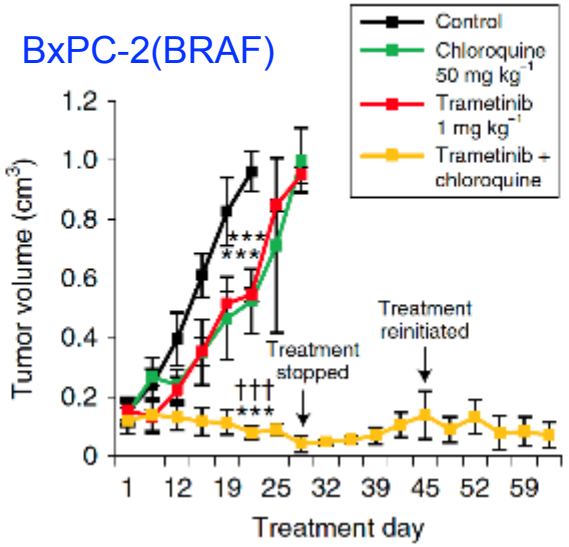
Conan G. Kinsey[1,2], Soledad A. Camolotto[1], Amelie M. Boespflug[1,3,4], Katrin P. Guillen[1], Mona Foth[1], Amanda Truong[1], Sophia S. Schuman[1], Jill E. Shea[5], Michael T. Seipp[5], Jeffrey T. Yap[1,6], Lance D. Burrell[1], David H. Lum[1], Jonathan R. Whisenant[1,2], G. Weldon Gilcrease III[1,2],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

# Concurrent MEK and autophagy inhibition cooperates to cause tumor regression

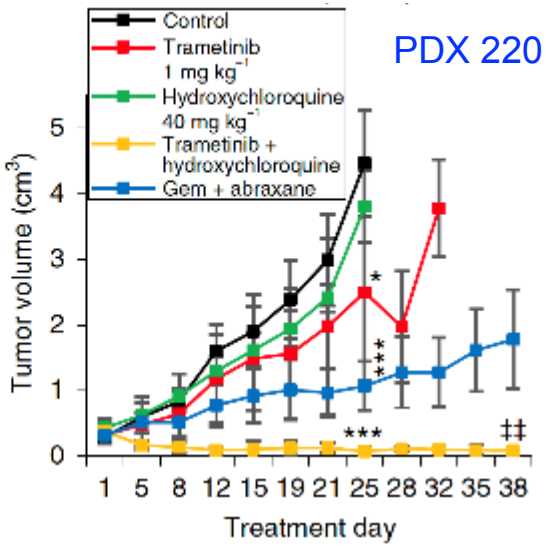
MIA PaCa-2 (KRAS)



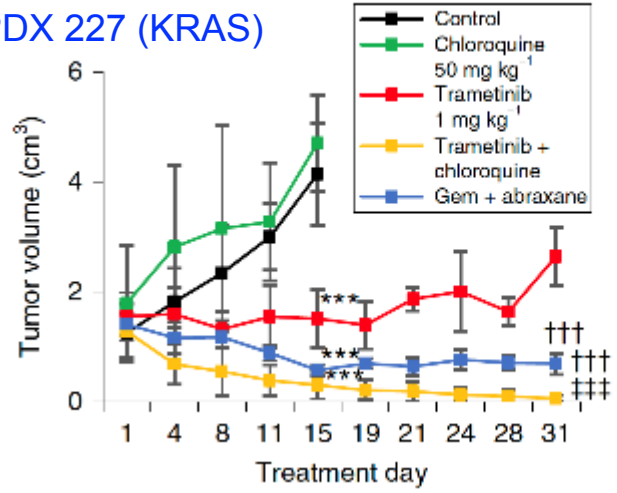

BxPC-2(BRAF)



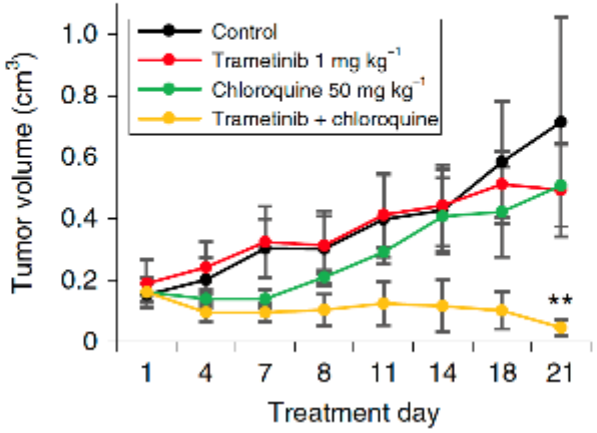

PDX 220 (KRAS)



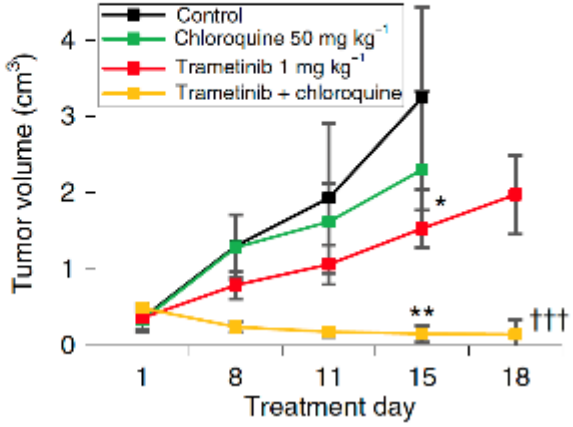

PDX 227 (KRAS)




HCLMel002 (NRAS)




HCICRC004 CRC PDX (BRAF)

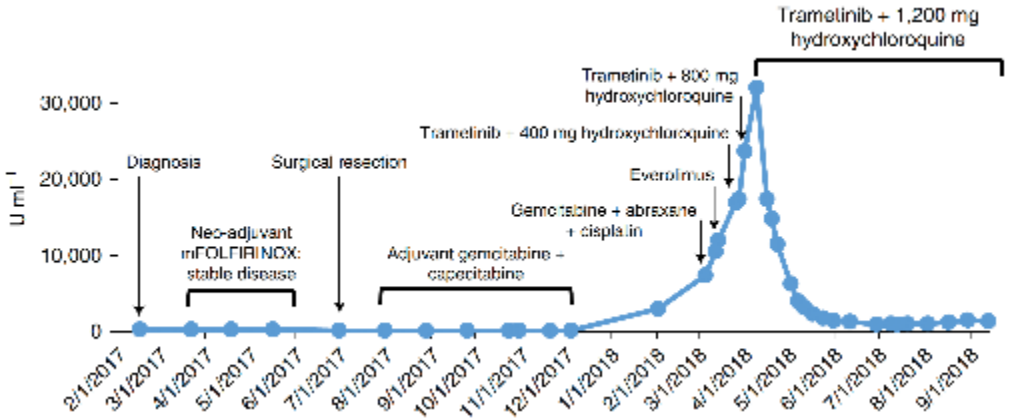



Kinsey et al (2019) Nat Med 25:620

# Proof-of-concept in a pancreatic cancer patient

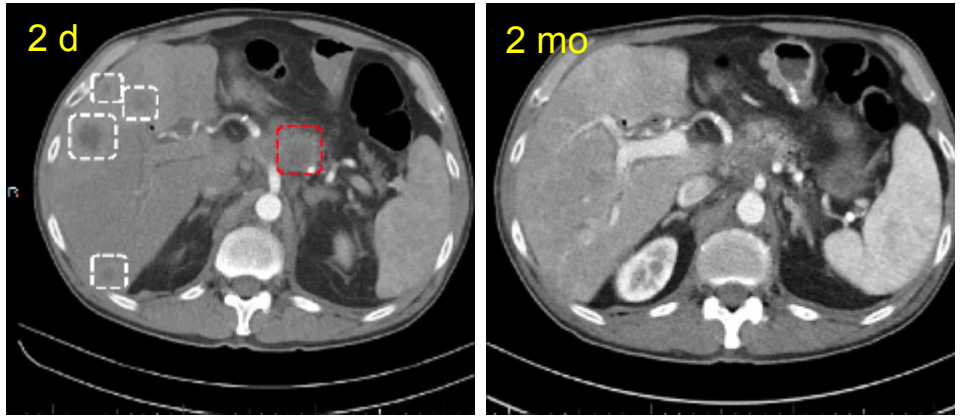
- 2 mg of trametinib plus 1200 mg HCQ daily over last two 2 months
- CA19-9 levels declined ~ 95%
- 50% reduction tumor mass
- Grade 1 rash and grade 1 fatigue
- No ocular and cardiac toxicities

## CA19-9 tumor marker

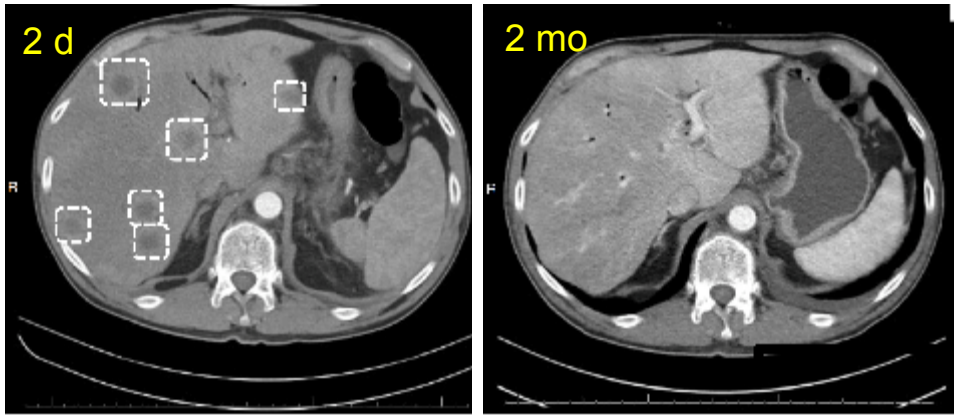



## CT Imaging

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

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

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

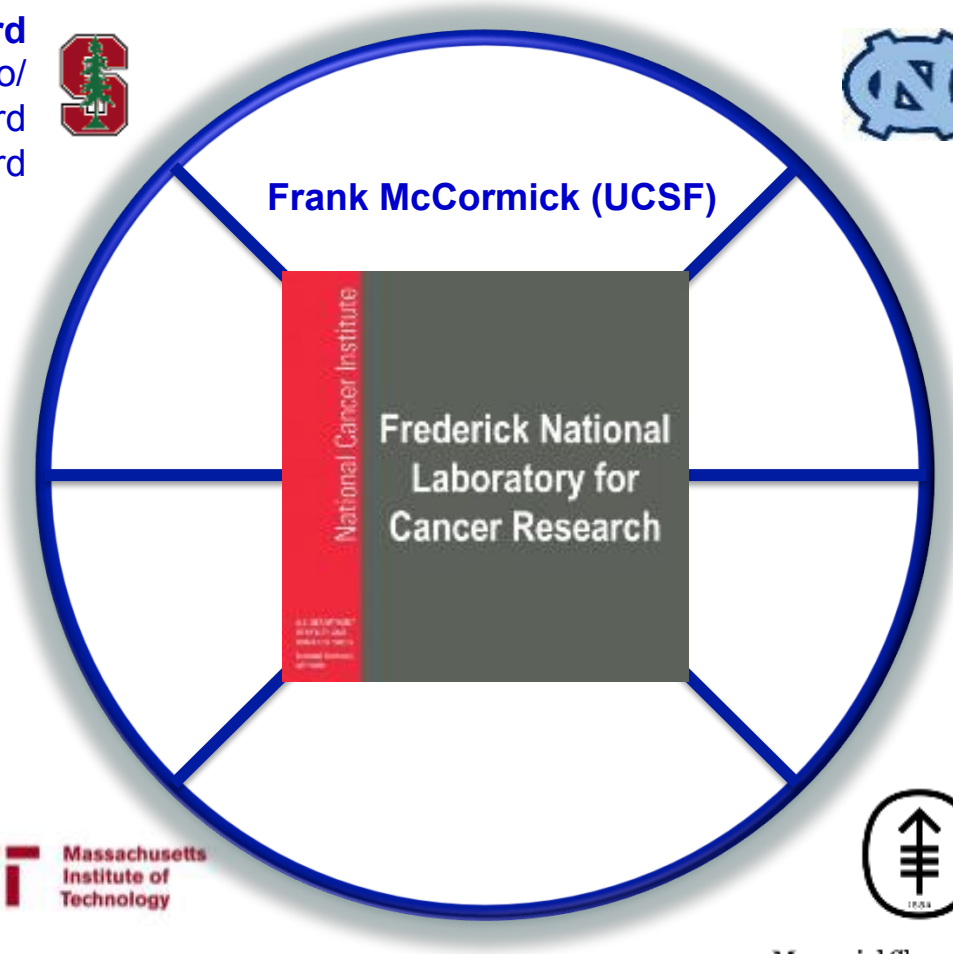
Chih-Shia Lee[a], Liam C. Lee[a,1], Tina L. Yuan[b,2], Sirisha Chakka[c,3], Christof Fellmann[d,4], Scott W. Lowe[d,e,f], Natasha J. Caplen[c], Frank McCormick[b,g,5], and Ji Luo[a,5]

# 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]

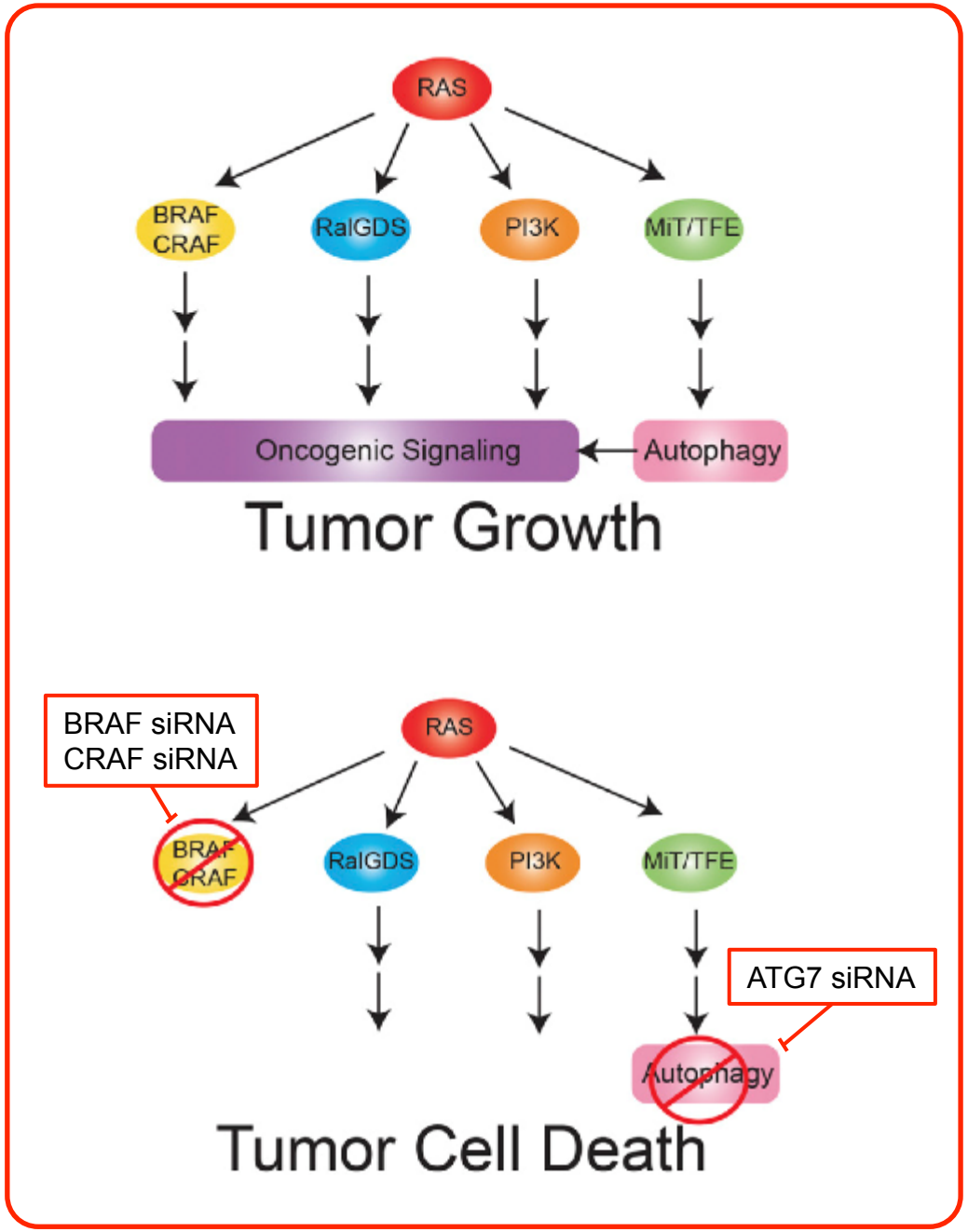
COMMENTARY

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

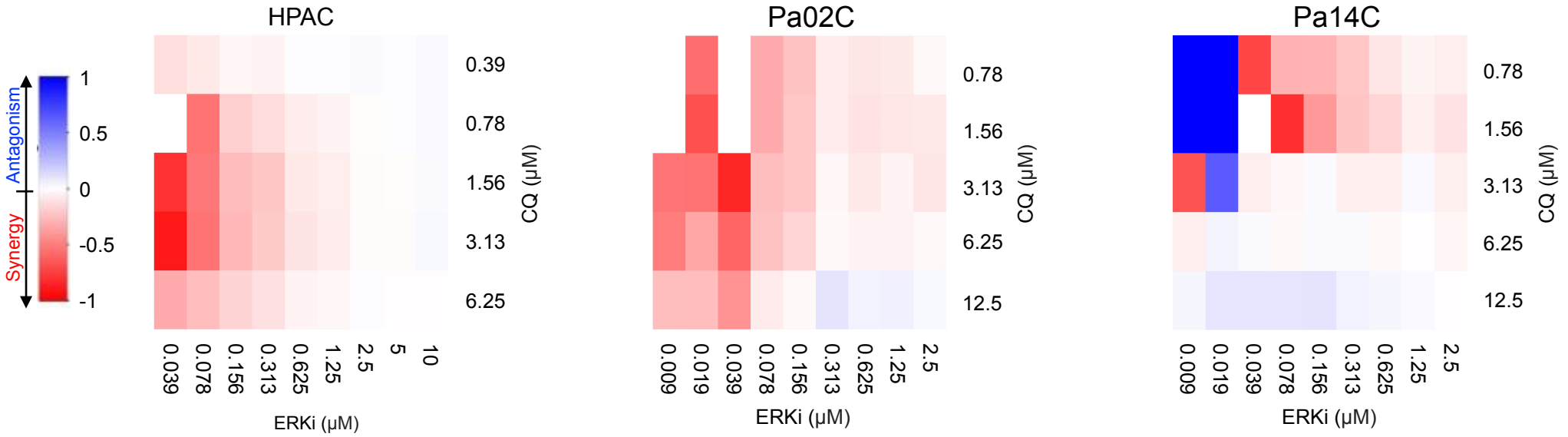
# Blockade of RAF and autophagy is the one-two punch to take out Ras

Eileen White[a,b,1]

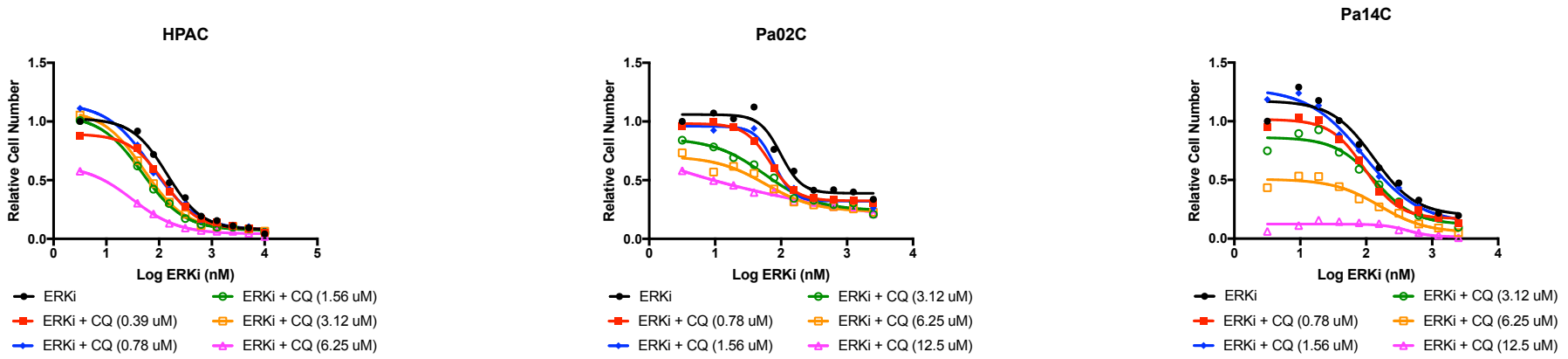
"Essential codependency of RAS-driven cancers on BRAF, CRAF, and autophagy. BRAF and CRAF provide key functional oncogenic signaling downstream of RAS that requires autophagy mediated by ATG7 to sustain survival. Coordinate blockade of BRAF, CRAF, and ATG7 provides the one-two punch and lethal blow to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



# RAFi* and chloroquine synergize in KRAS-mutant PDAC

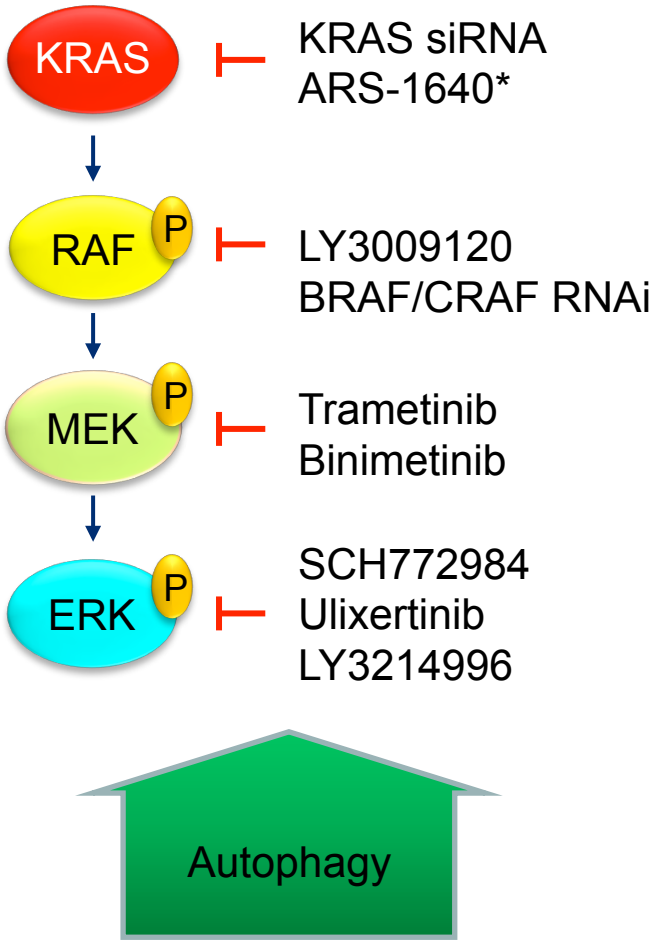



*LY3009120




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

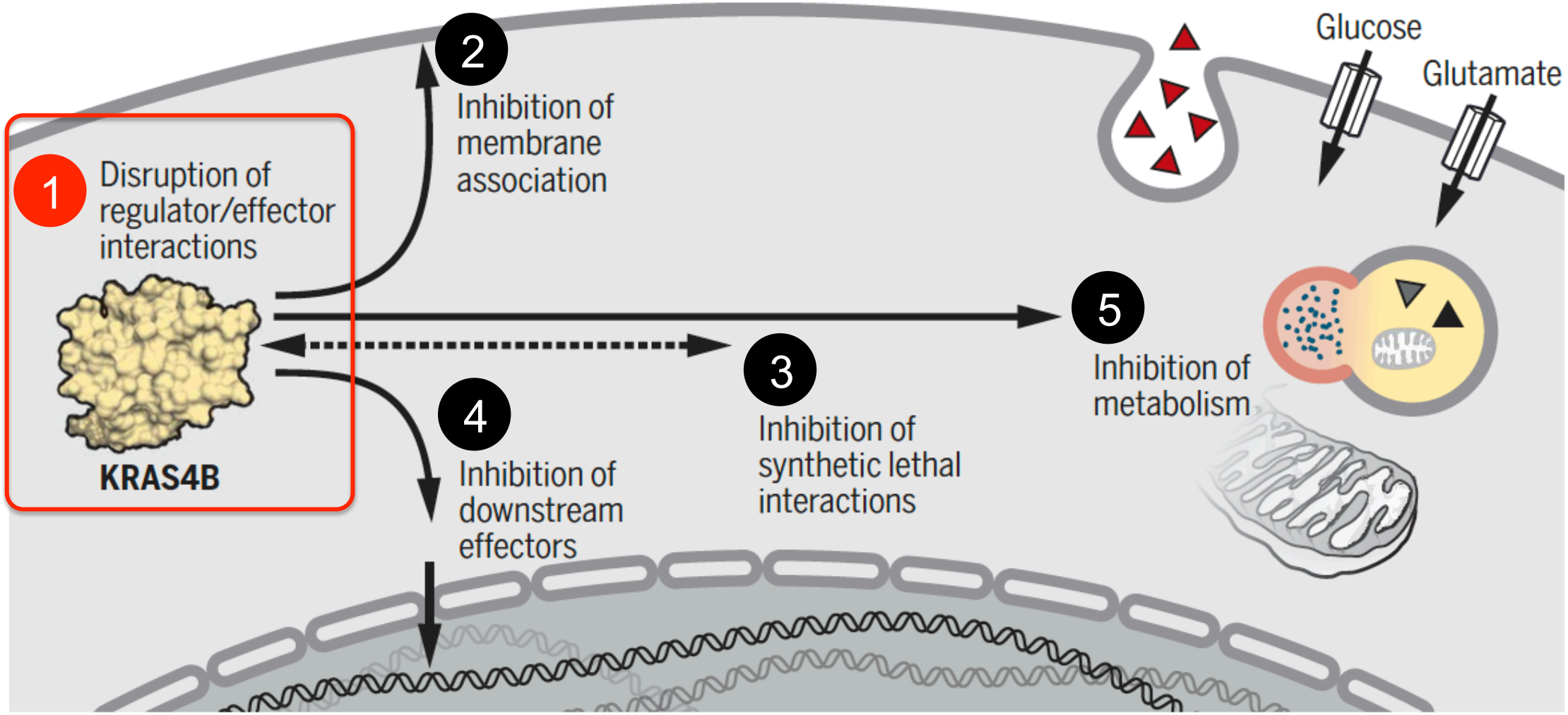
Undisclosed Pharma

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

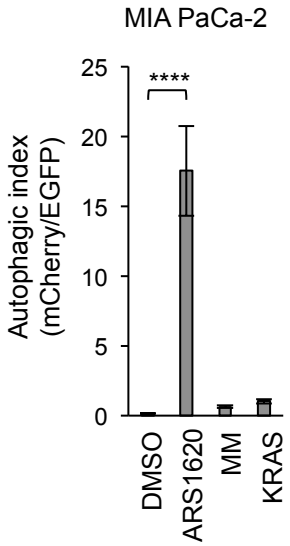
❖KRAS G12C inhibitors versus ERK MAPK + HCQ?

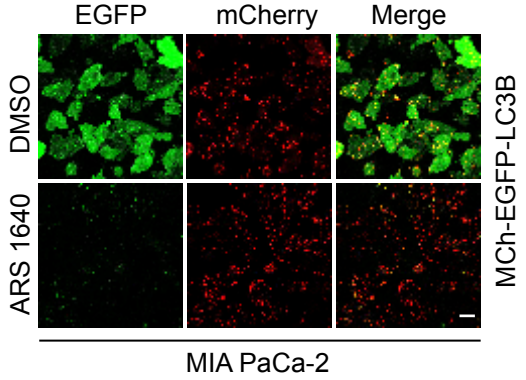
NIH U.S. National Library of Medicine
ClinicalTrials.gov

*Specific for one RAS mutation G12C

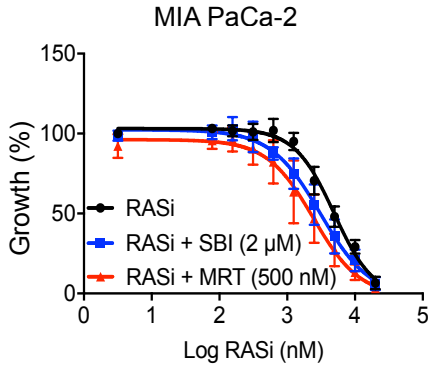
# Concurrent KRAS G12C and ULK inhibition causes pancreatic cancer cell death

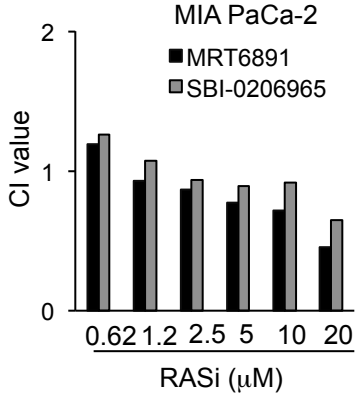
Treatment with the KRAS$^{G12C}$ inhibitor ARS-1620 increases autophagy

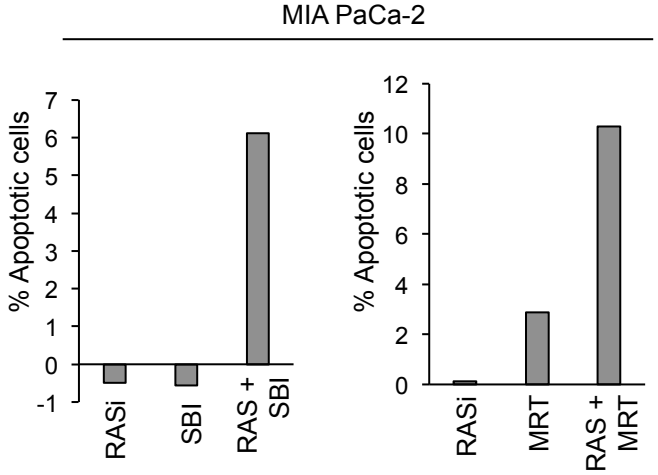



Cotreatment with ULK inhibitors enhance KRAS$^{G12C}$ inhibitor growth suppression

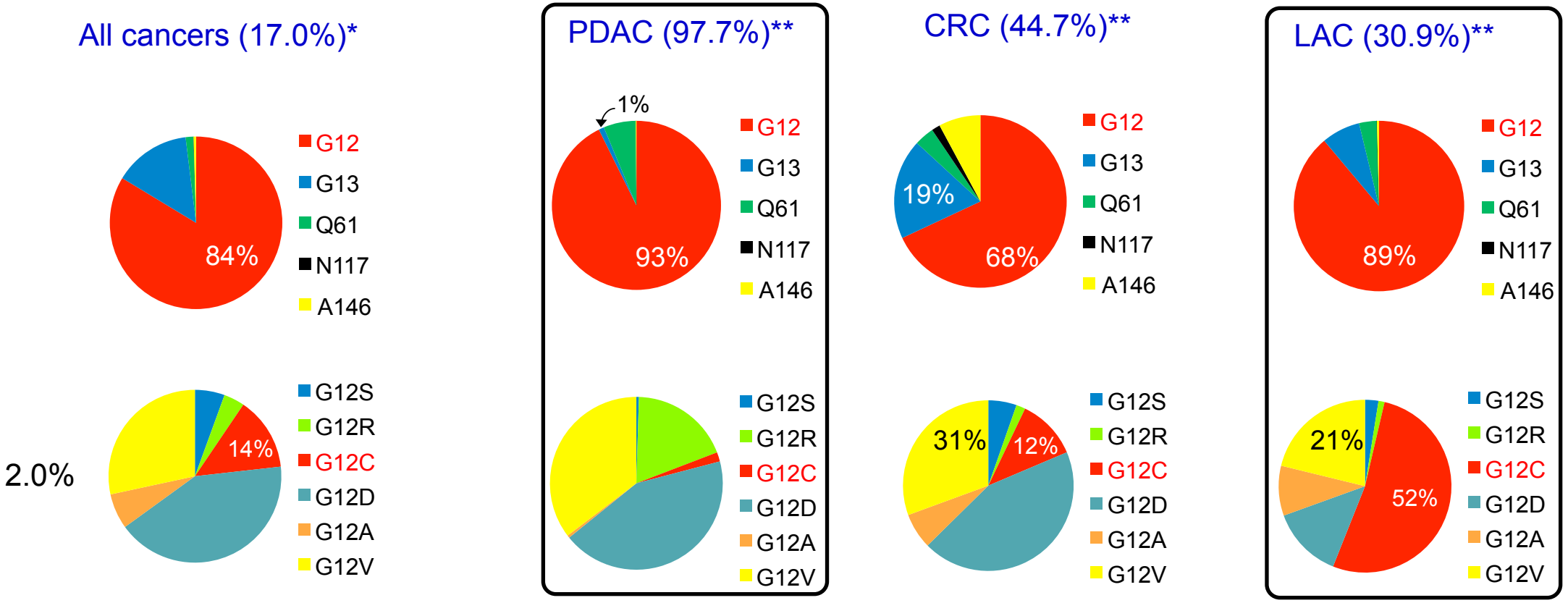



Bryant et al (2019) Nat Med 25:628

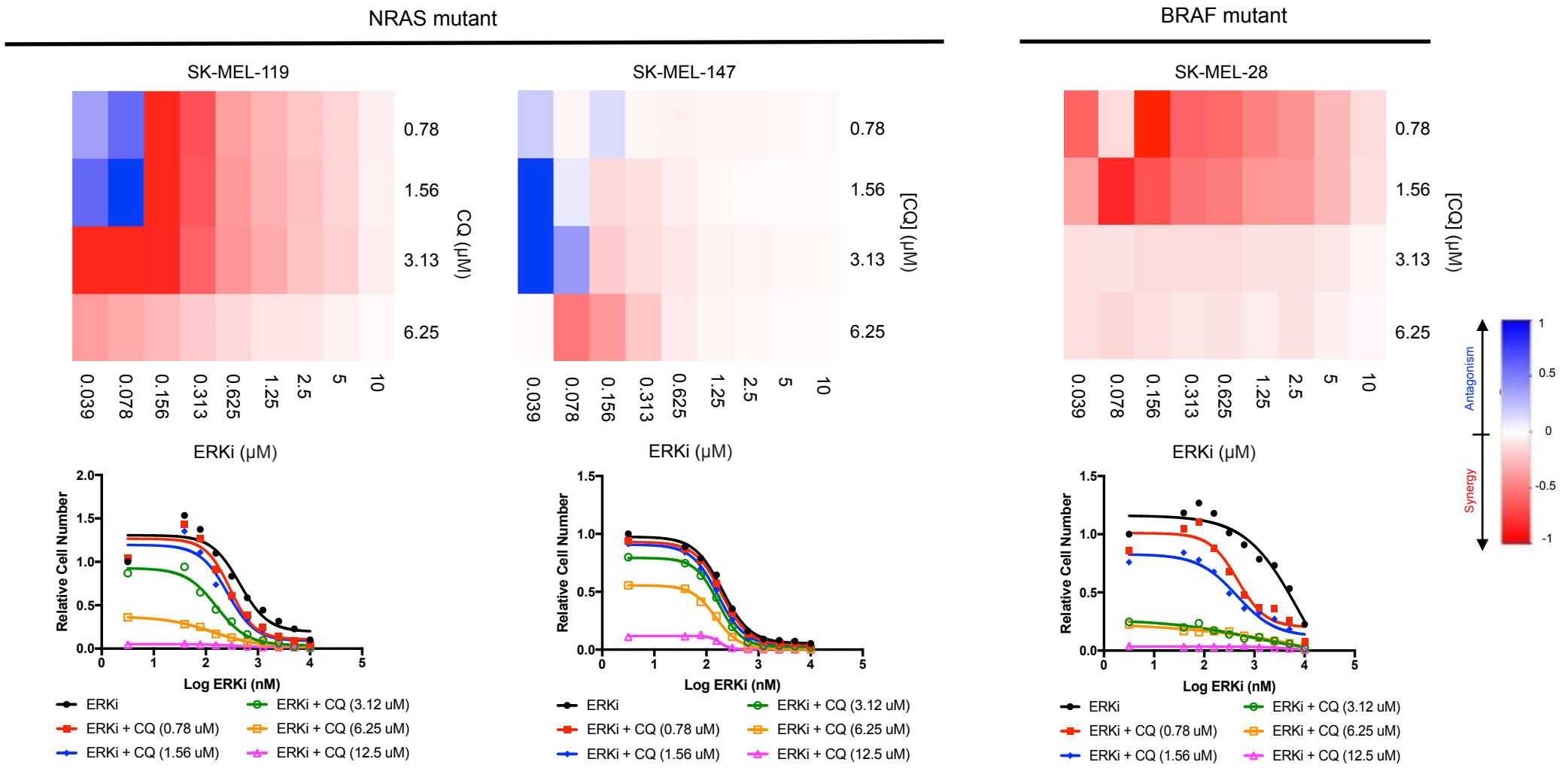
# G12C inhibitors target only 2% of all cancers




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

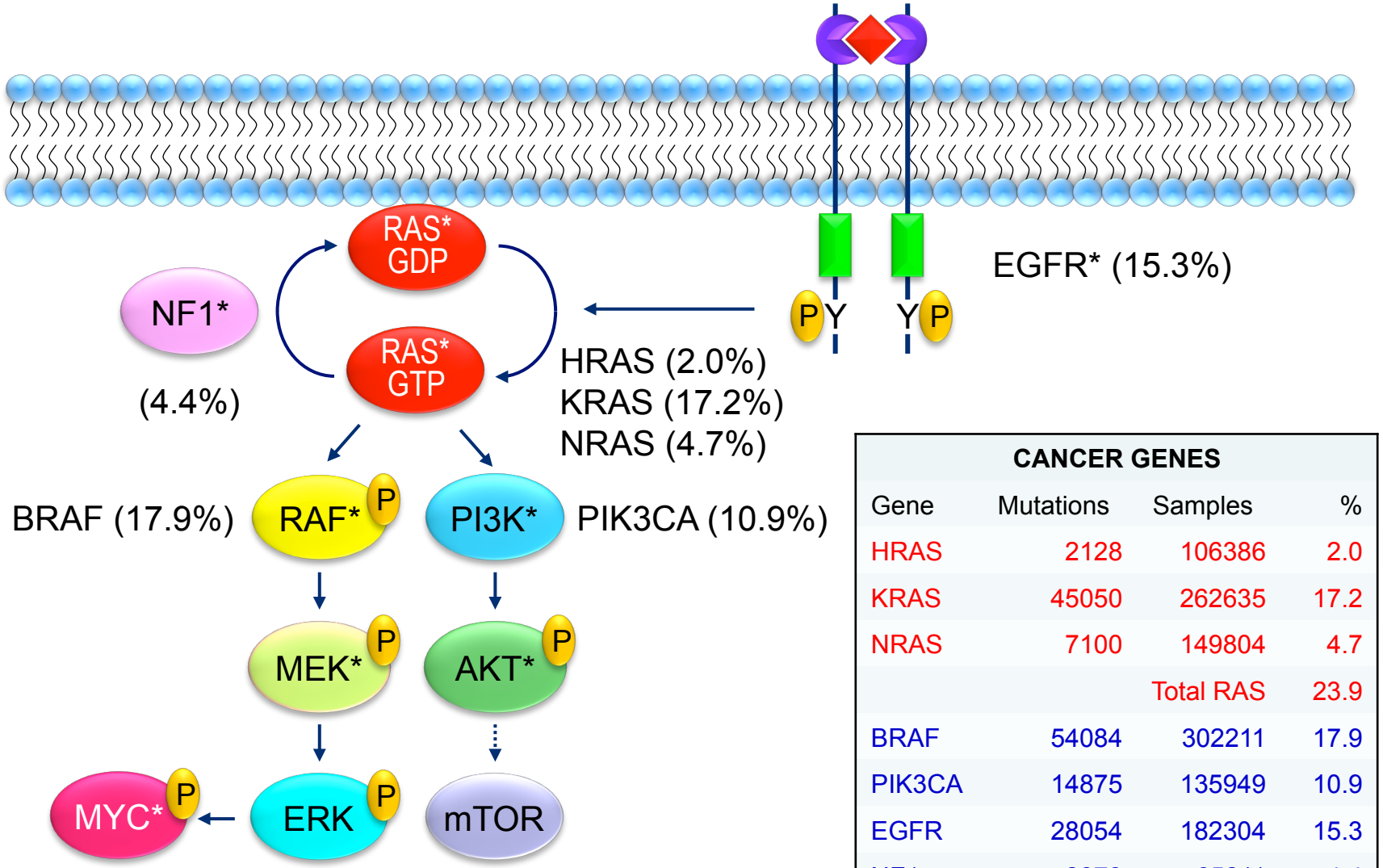
*COSMIC v88; **Cox et al (2014) *Nat Rev Drug Discov* 13:828

# 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



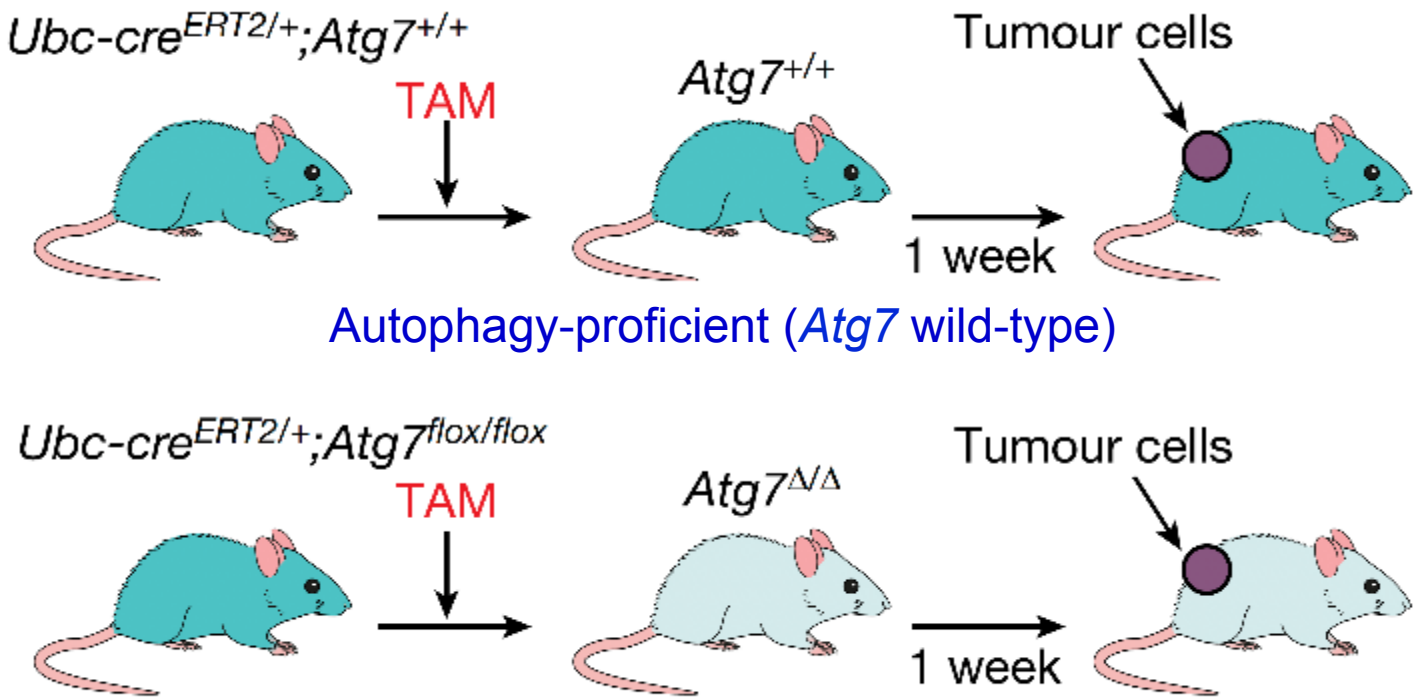

| CANCER GENES | | | |
|---|---|---|---|
| Gene | Mutations | Samples | % |
| HRAS | 2128 | 106386 | 2.0 |
| KRAS | 45050 | 262635 | 17.2 |
| NRAS | 7100 | 149804 | 4.7 |
| | | Total RAS | 23.9 |
| BRAF | 54084 | 302211 | 17.9 |
| PIK3CA | 14875 | 135949 | 10.9 |
| EGFR | 28054 | 182304 | 15.3 |
| NF1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

* COSMIC v89
Catalogue of somatic mutations in cancer

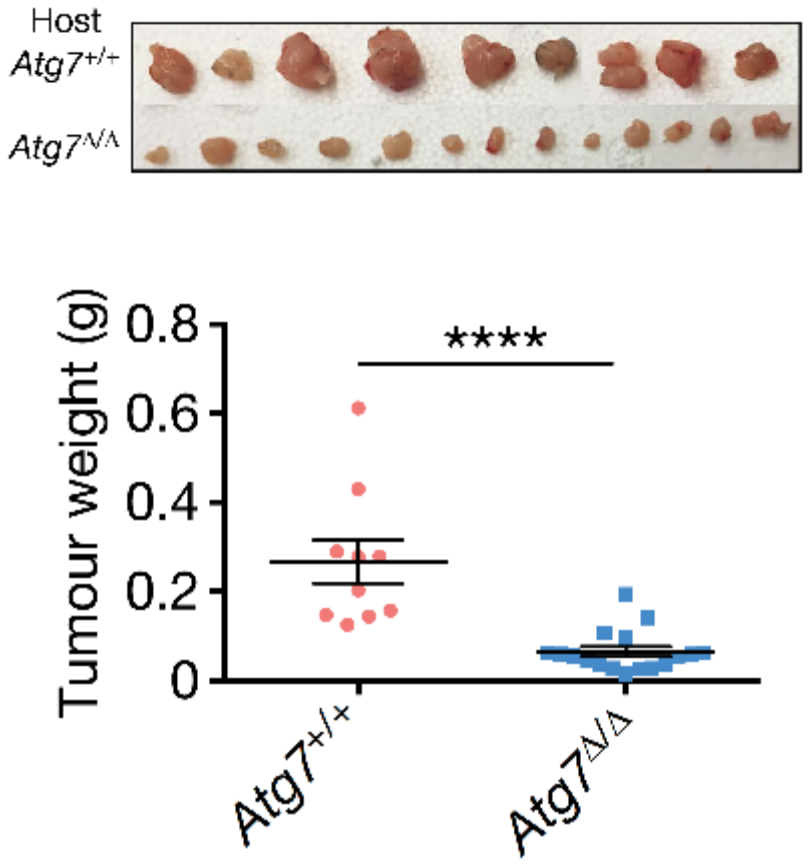
# Key points

- ‘Undruggable’ RAS-mutant cancers: druggable after all?
- Autophagy: the Achilles’ heel of RAS-mutant cancers?
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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

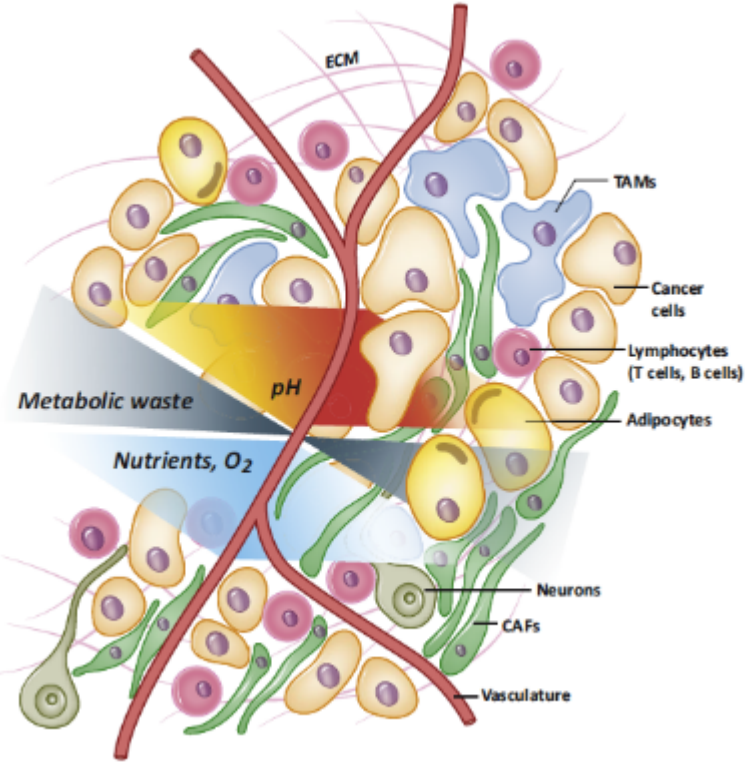



*Braf*-mutant melanoma

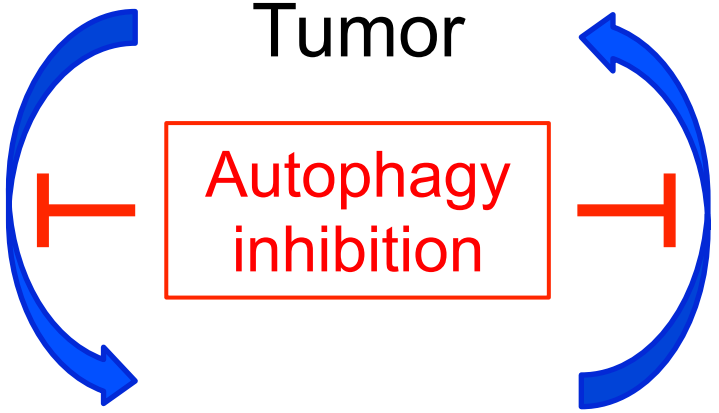



Poillet-Perez et al (2018) Nature 563:569

# Autophagy-dependent activities of the microenvironment support tumor growth




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




## Microenvironment

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

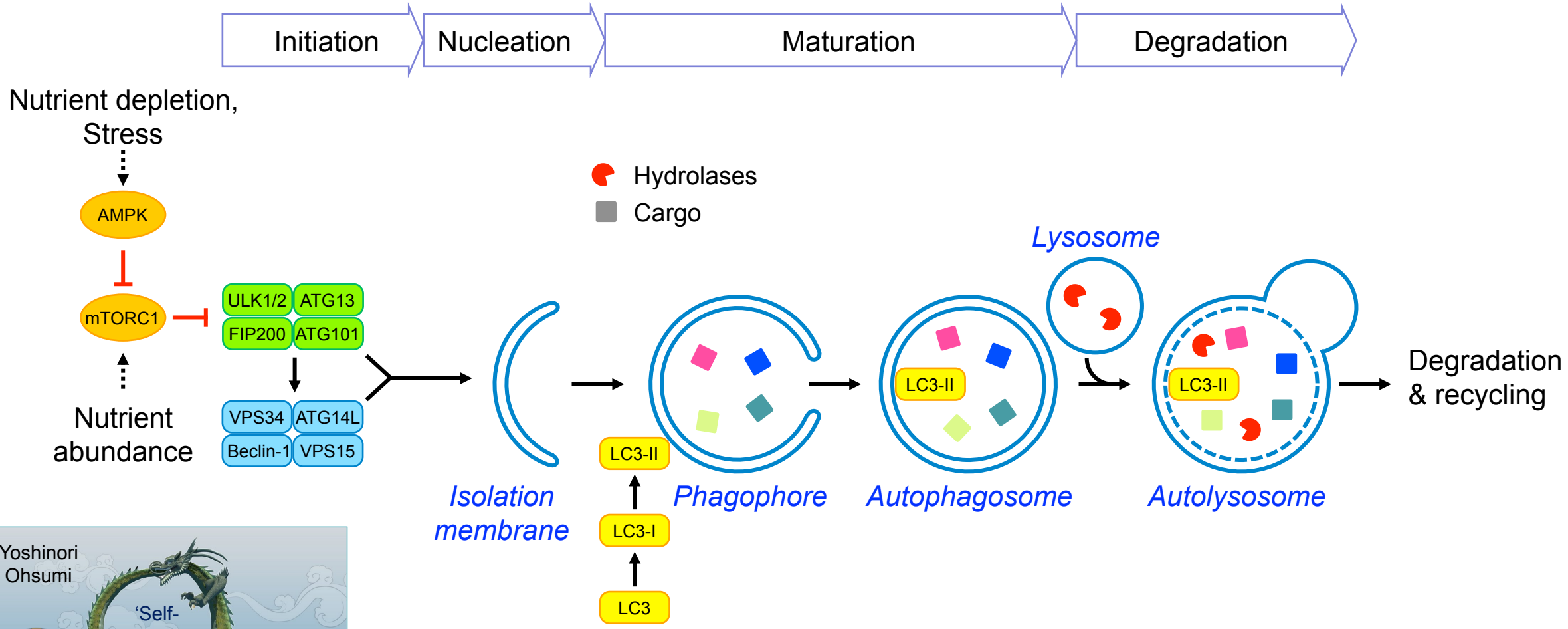
Sousa et al (2016) Nature 536:479
Cunha et al (2018) Cell 175:429

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

# Key points

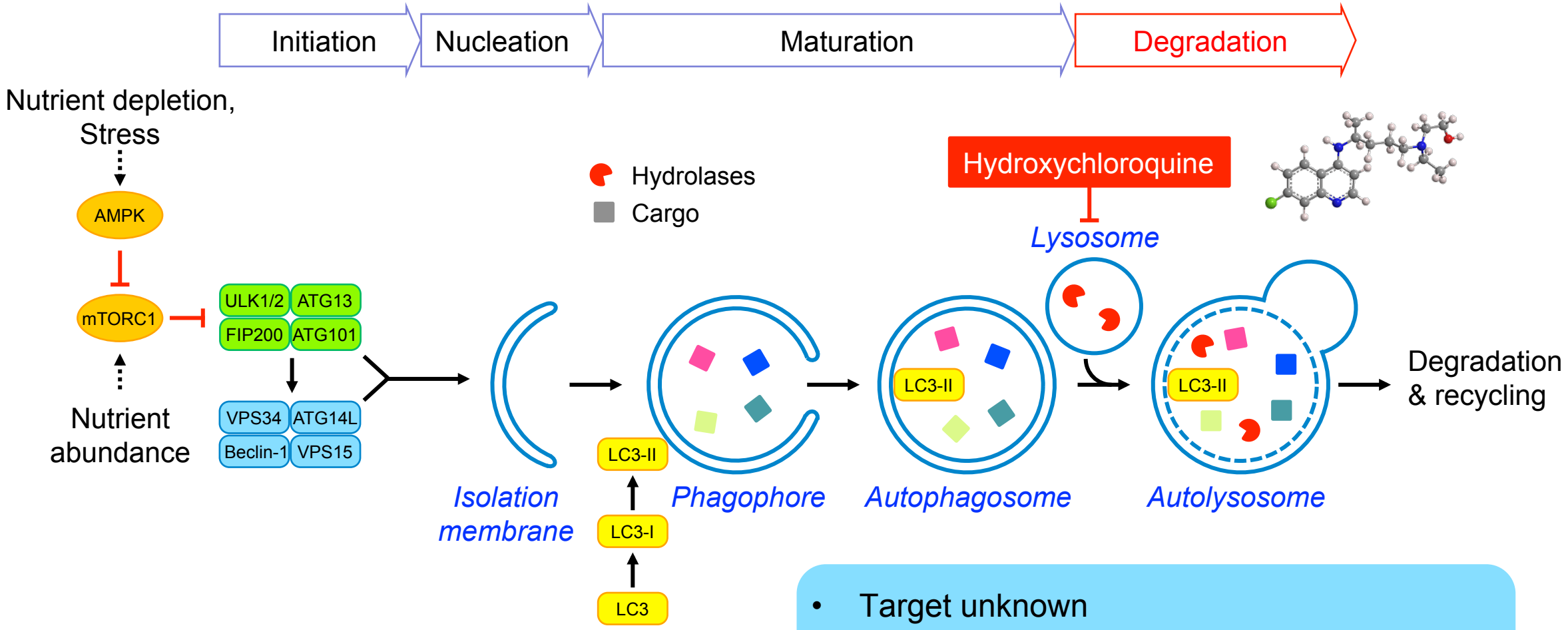
- ‘Undruggable’ RAS-mutant cancers: druggable after all?
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- ULK inhibitors: a more selective autophagy inhibitor?

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






# Hydroxychloroquine inhibition of autophagy



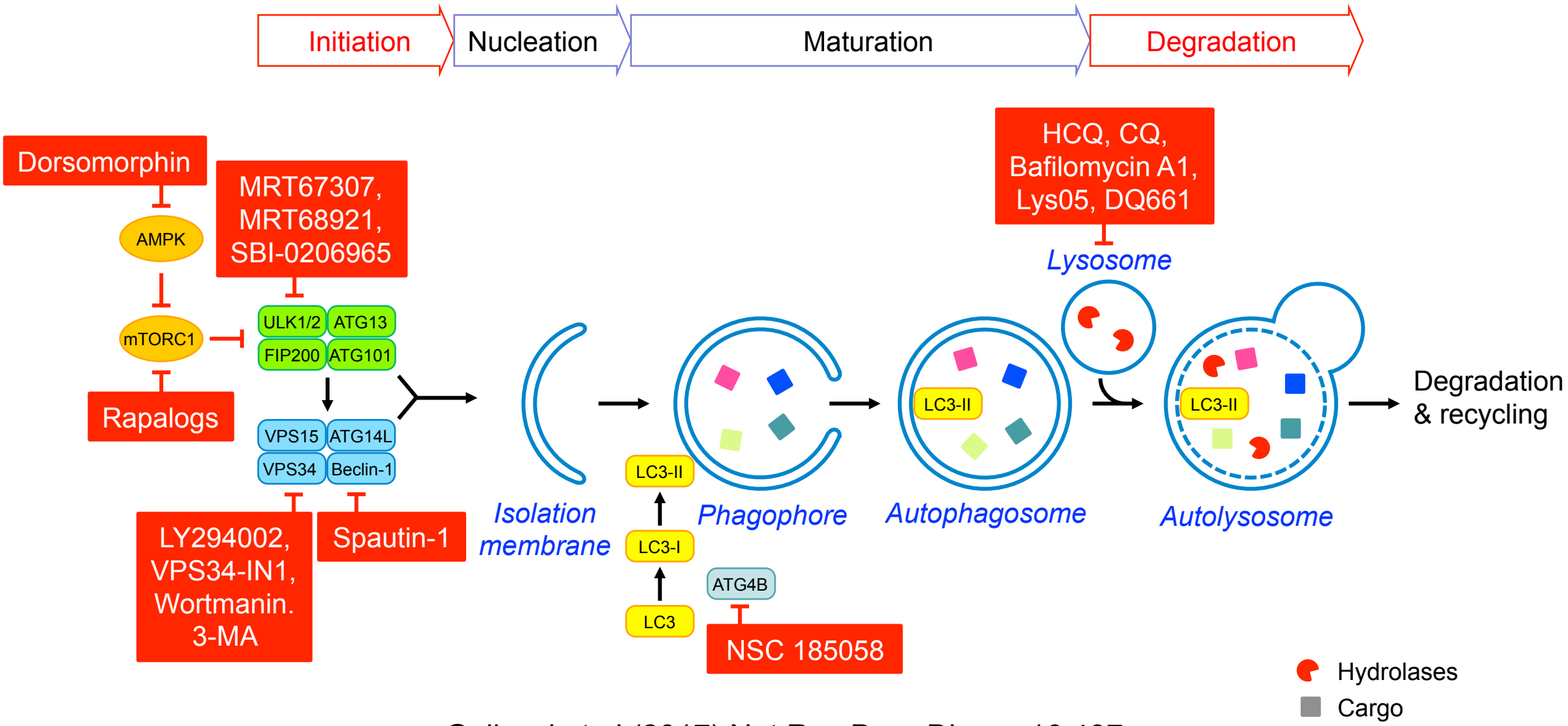

- Target unknown
- Elevate/neutralize the lysosomal/vacuolar pH
- Low potency and selectivity for autophagy

# 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

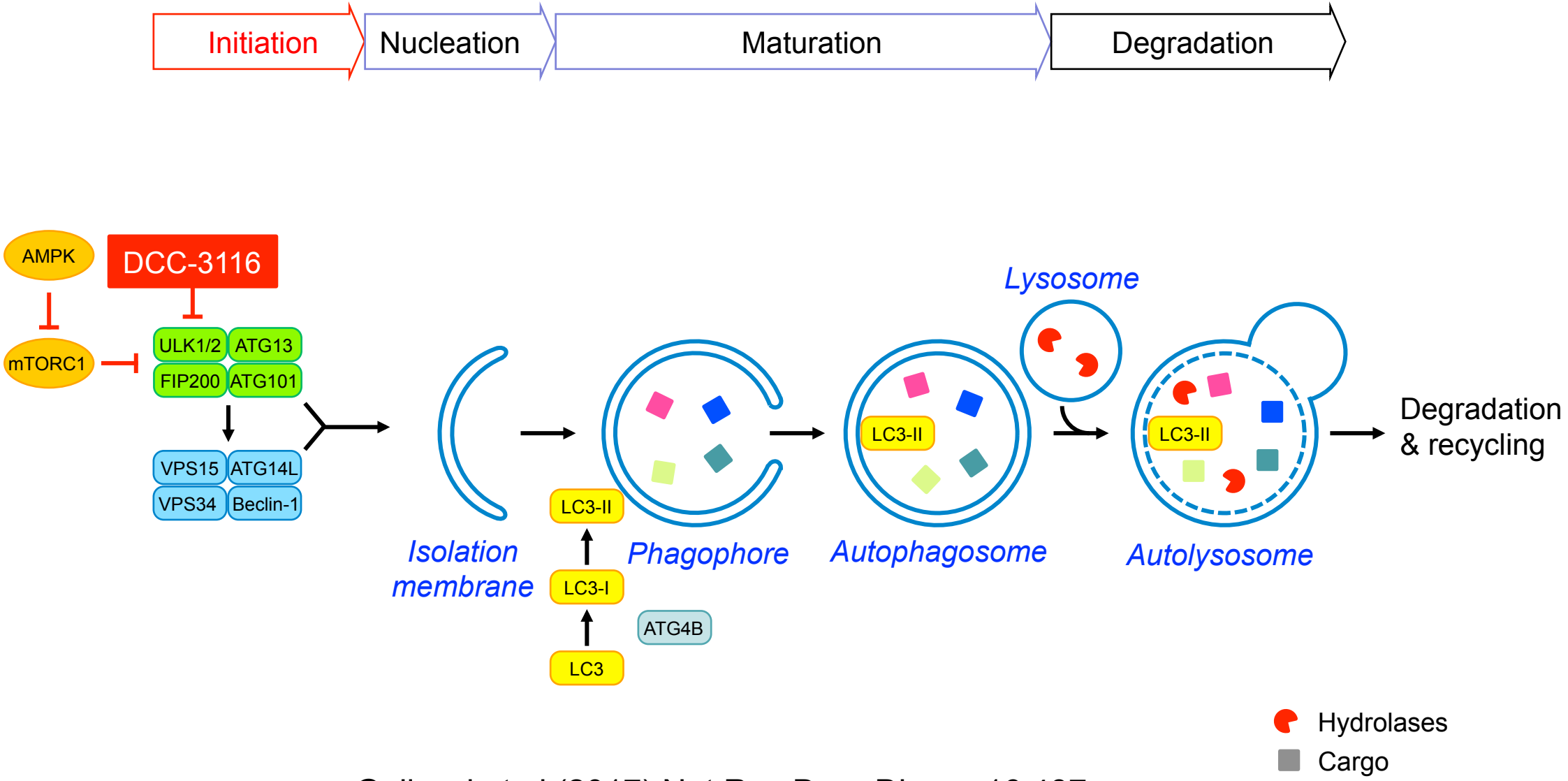
Hydroxychloroquine has shown limited activity as a monotherapy (NCT01273805, NCT01506973 and NCT03344172), but has shown promise in combination with preoperative gemcitabine plus nab-paclitaxel (NCT01978184)

# 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

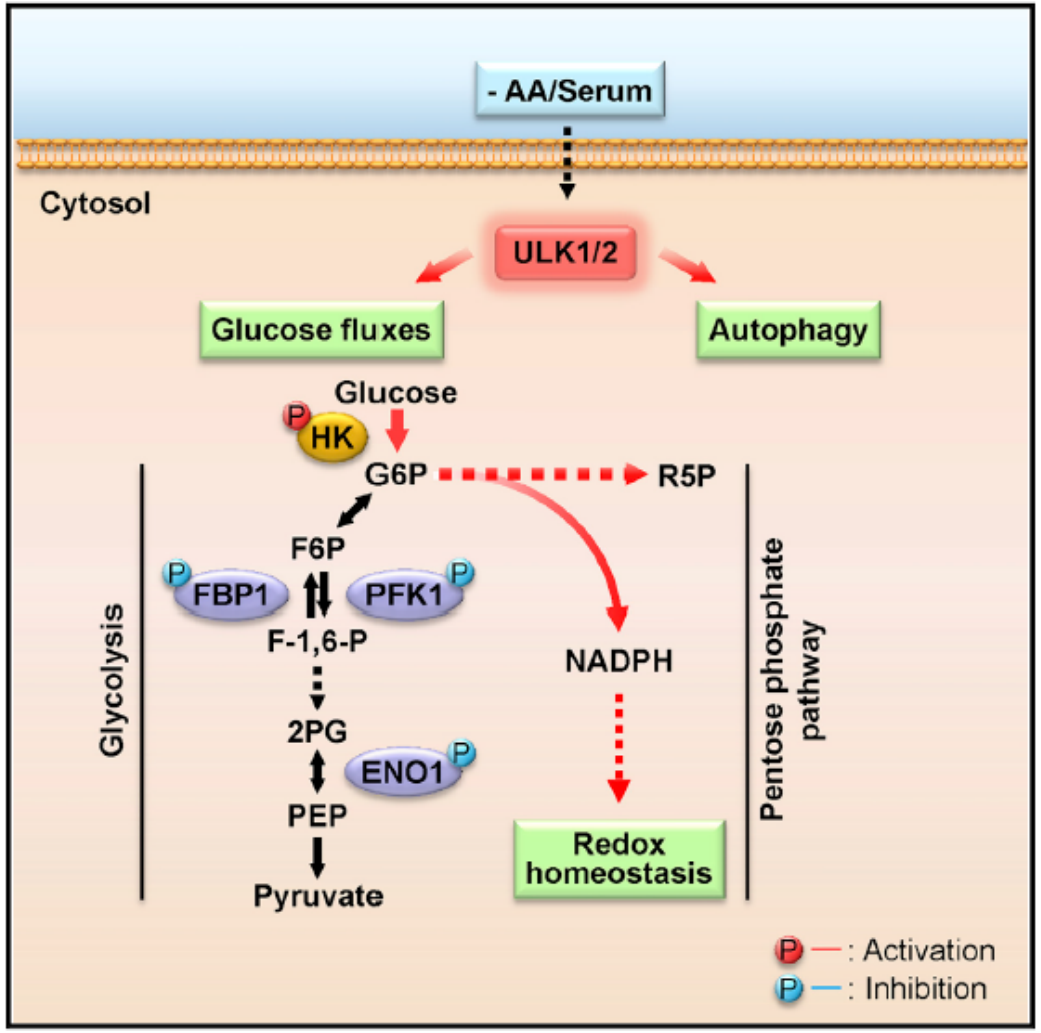
# ULK activity plays a metabolic role in RAS-mutant cancers

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

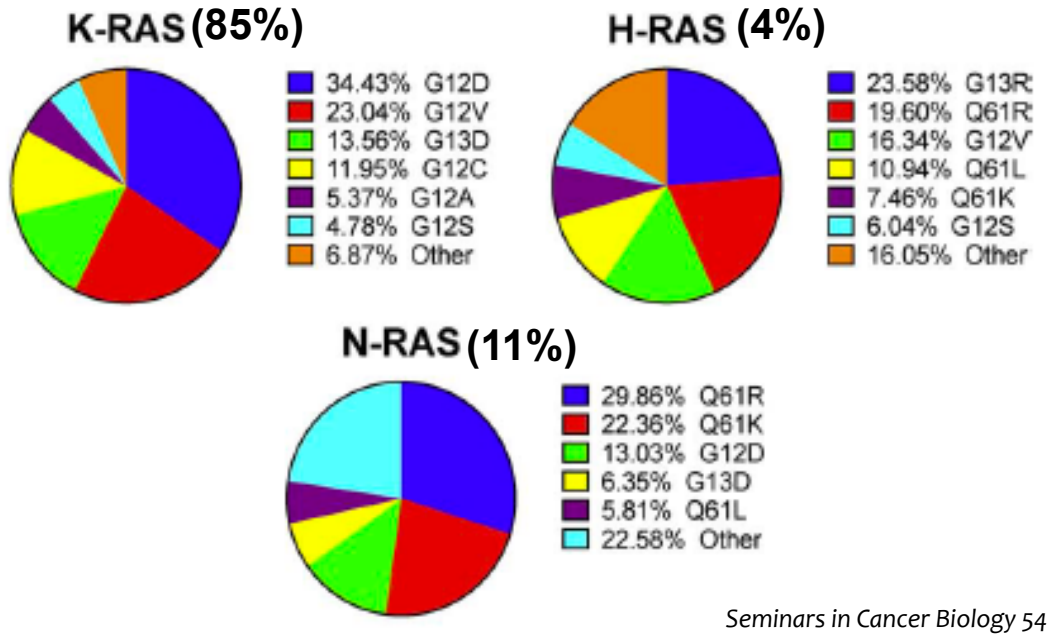
- Pancreatic: ~98%
- Colon: ~ 45%
- Lung: ~ 30%

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?**

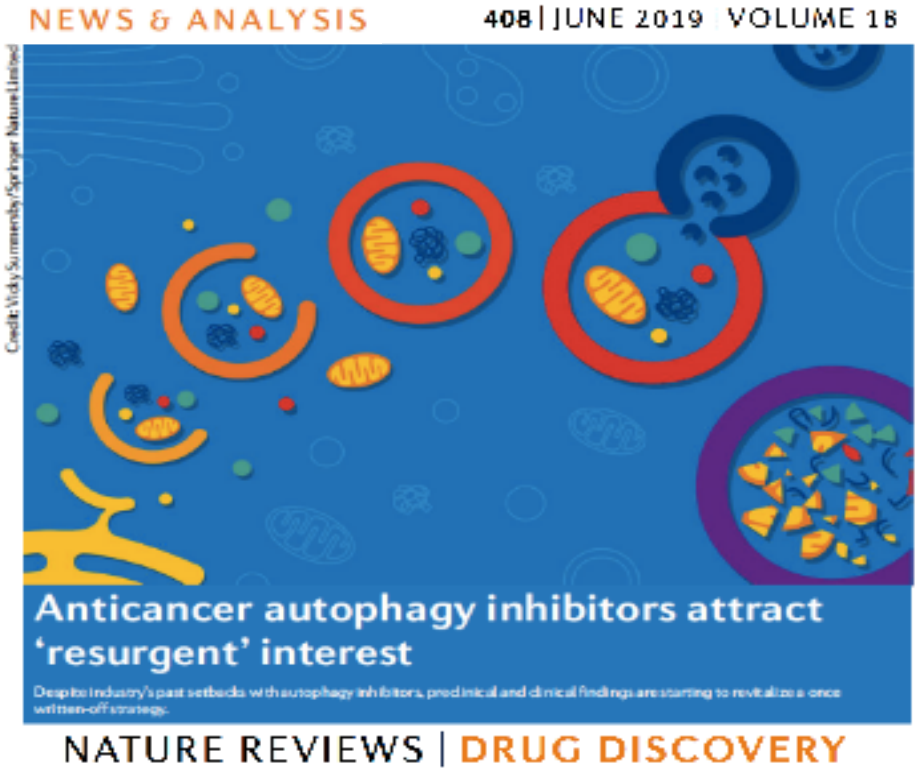
Russell Spencer-Smith[a,b,c], John P. O'Bryan[a,b,c,*]

[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

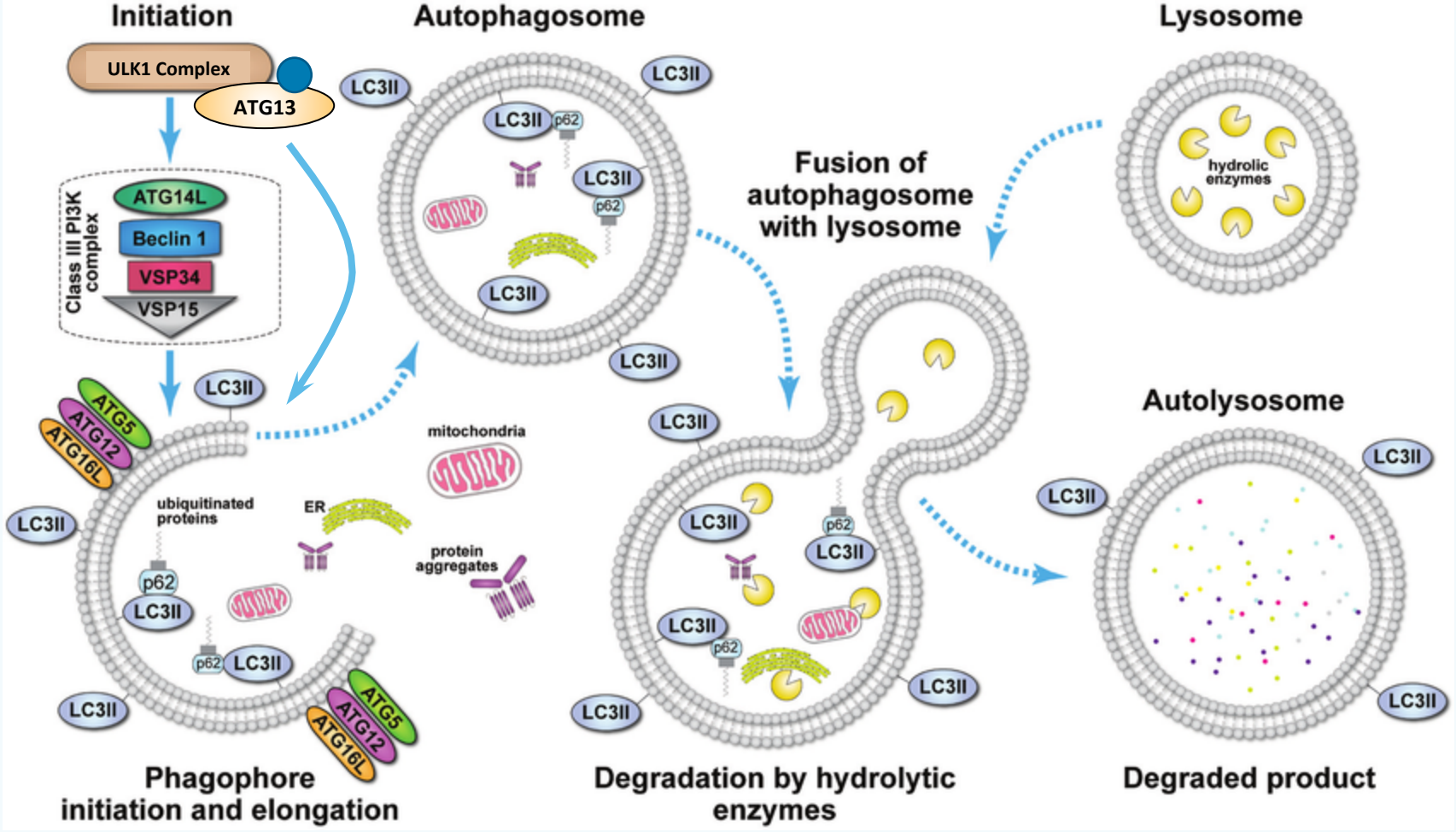



YOSHINORI OHSUMI
NOBEL PRIZE IN PHYSIOLOGY & MEDICINE 2016
FOR THE STUDY OF AUTOPHAGY



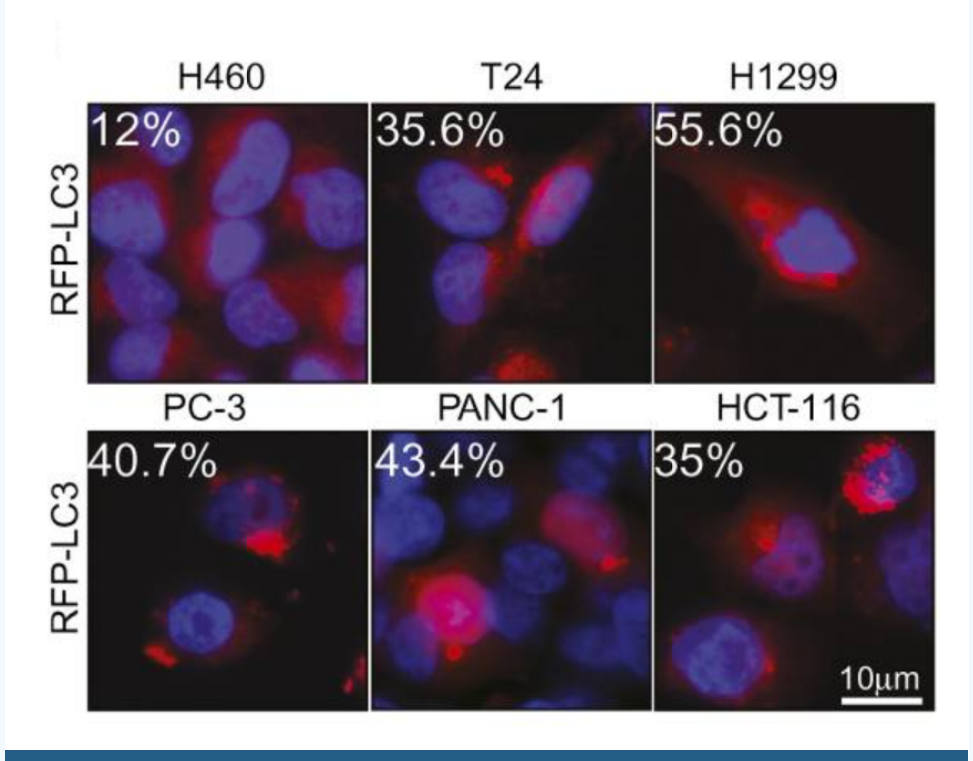

AUTOPHAGY IS A SIGNAL TRANSDUCTION PATHWAY
WITH DEFINED MOLECULAR COMPONENTS

# 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)*

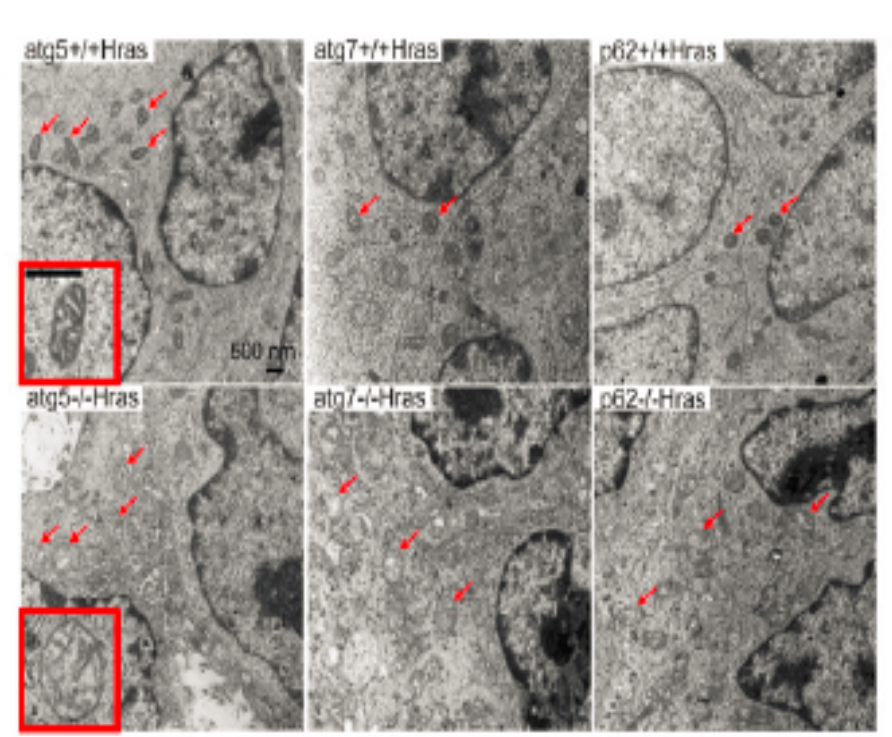
# RAS Cancers Exhibit High Levels of Basal Autophagy




**Evaluation of Cellular LC-3 Puncta**

Competent Autophagy

Incompetent Autophagy




**Swollen Mitochondria Accumulate in Cells where Autophagy is Blocked**

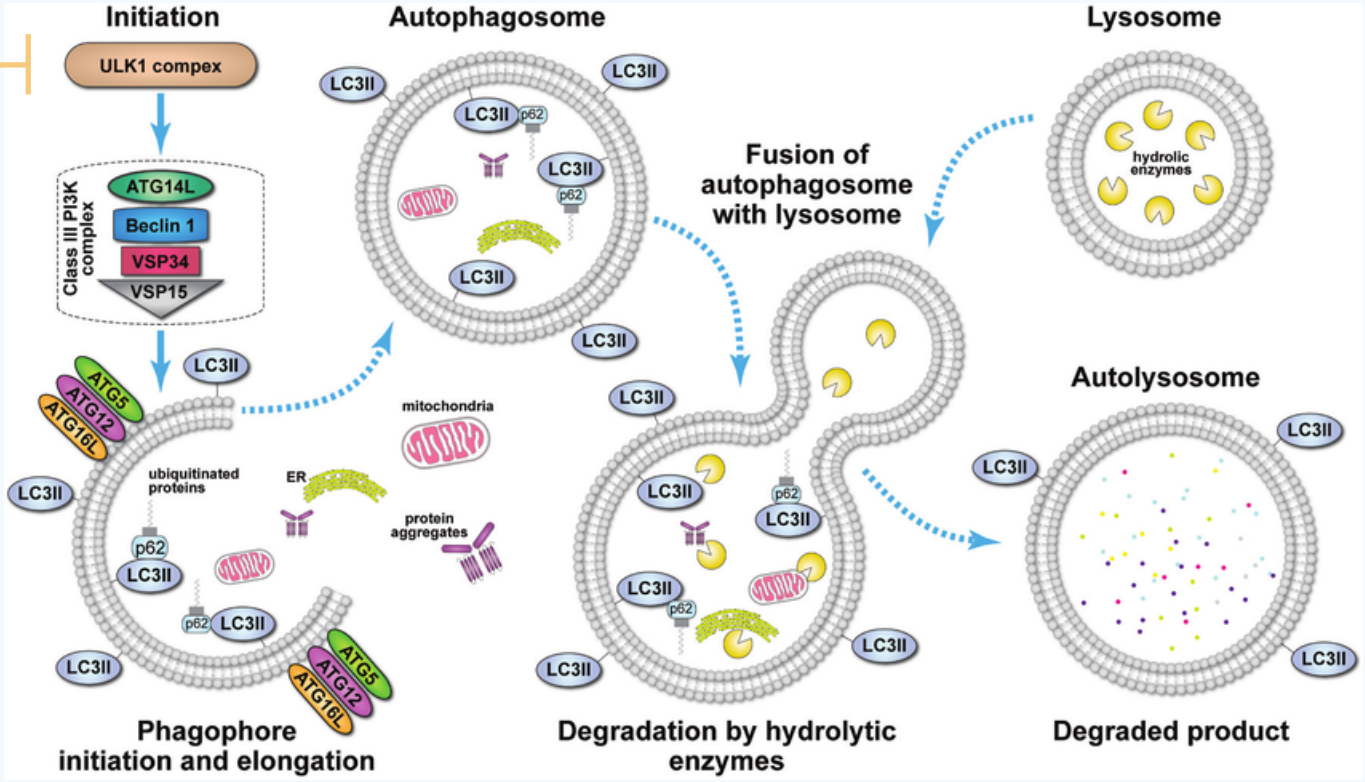
*Genes and Development* 2011;25:460-70

# 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)*

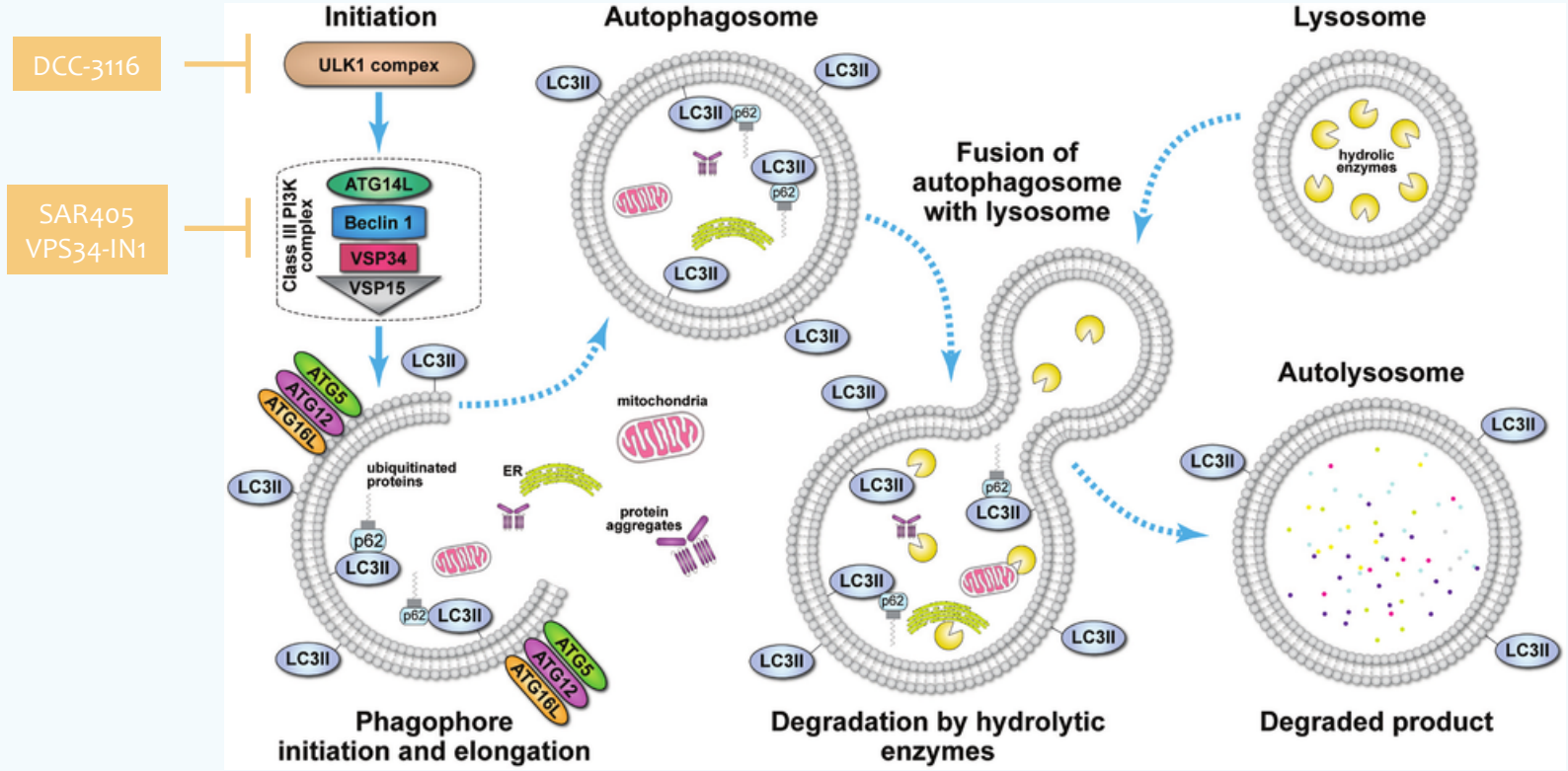
# Strategies for Blocking Autophagy in Cancer

## ULK Inhibition

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

## VPS34 Complex Inhibition

- Druggable lipid kinase target
- ULK can bypass VPS34
- 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)*

# Strategies for Blocking Autophagy in Cancer

## ULK Inhibition

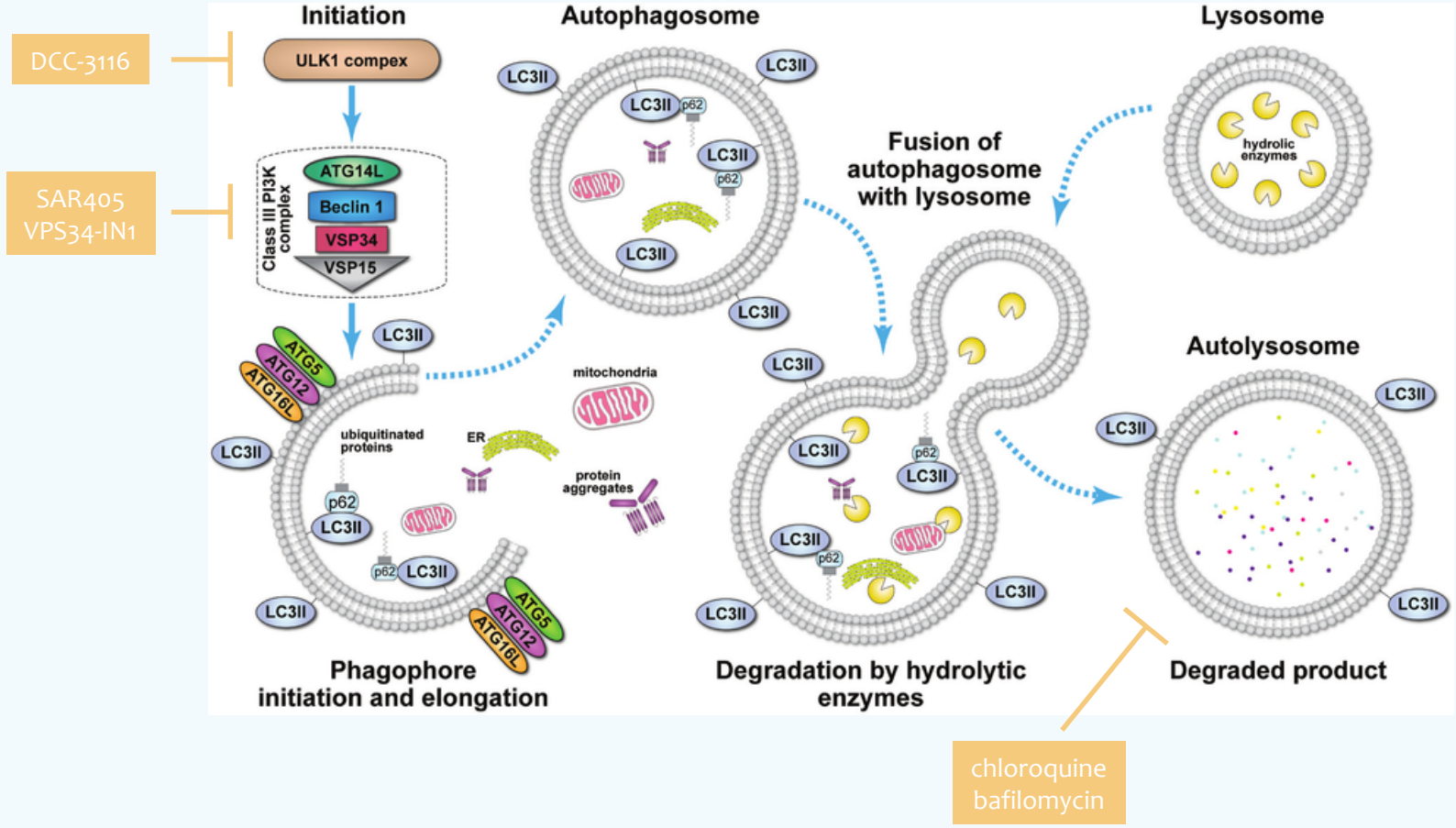
- ULK is initiating factor of autophagy
- Druggable serine/threonine kinase
- Receives and processes key input from nutrient and stress sensors

## 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

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]*

PNAS

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

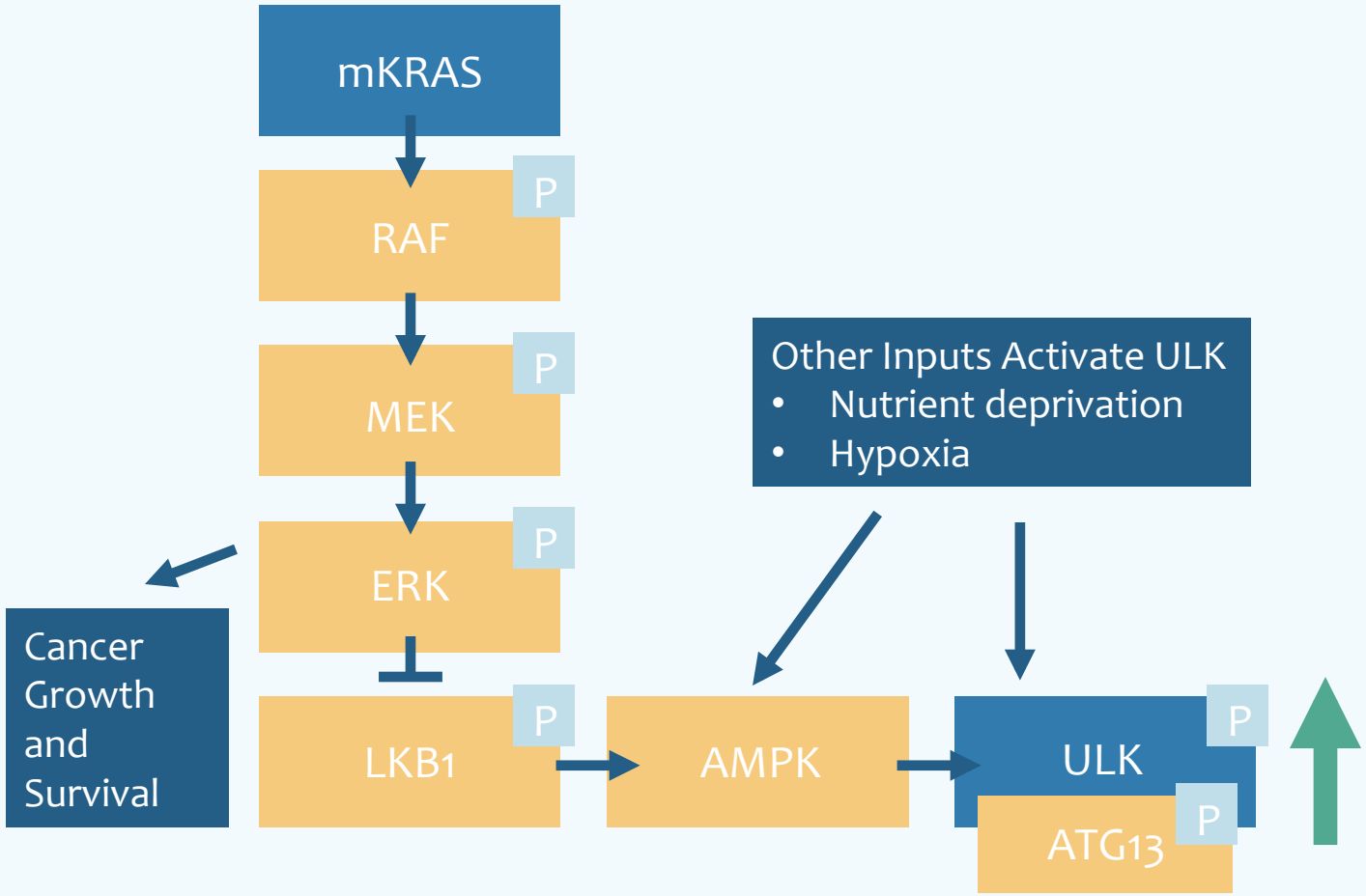
Chih-Shia Lee[a], Liam C. Lee[a,1], Tina L. Yuan[b,2], Sirisha Chakka[c,3], Christof Fellmann[d,4], Scott W. Lowe[d,e,f], Natasha J. Caplen[c], Frank McCormick[b,g,5], and Ji Luo[a,5]

[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)

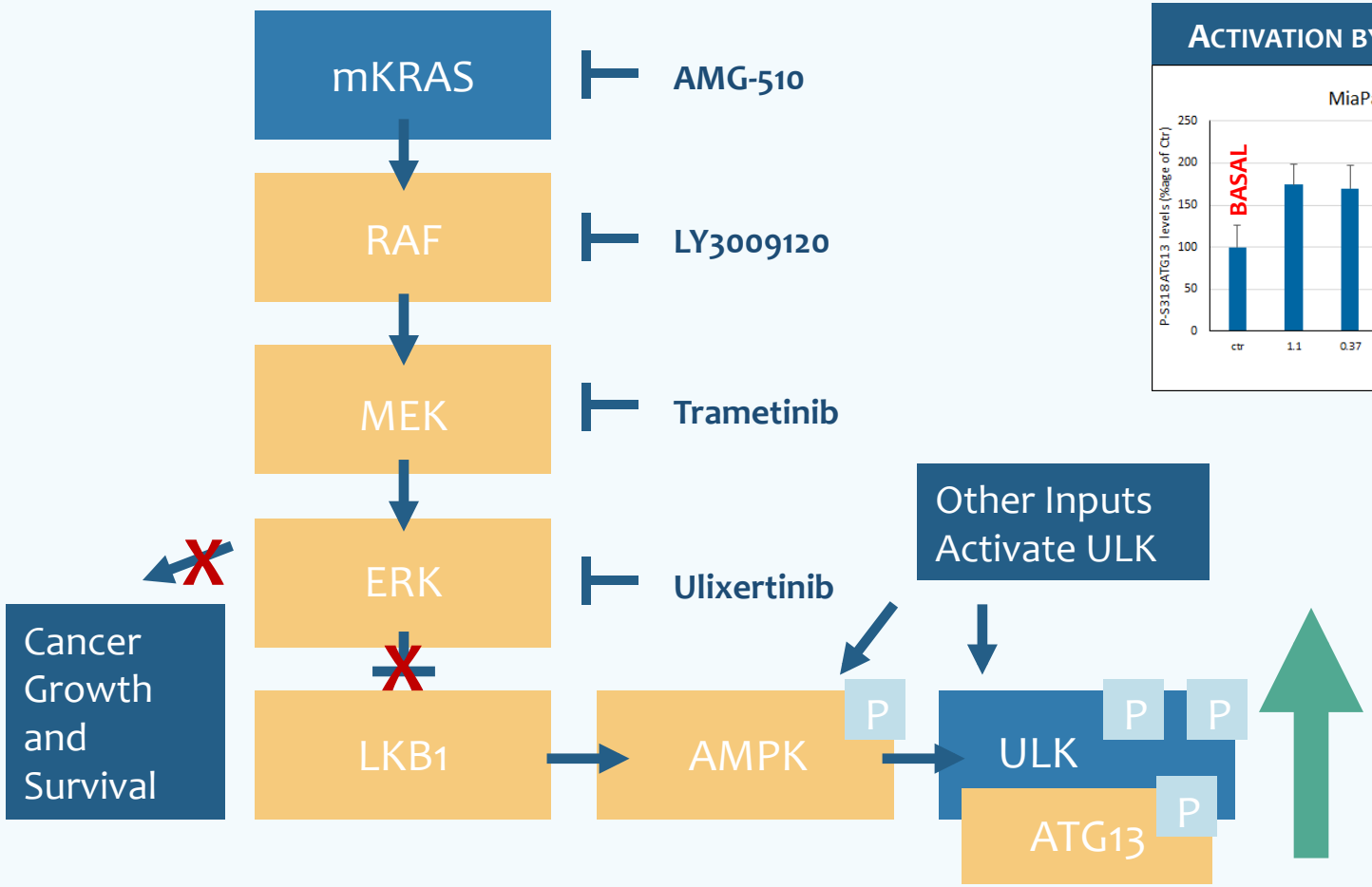
# KRAS Activation Drives Tumor Growth and Tonic Regulation of ULK

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

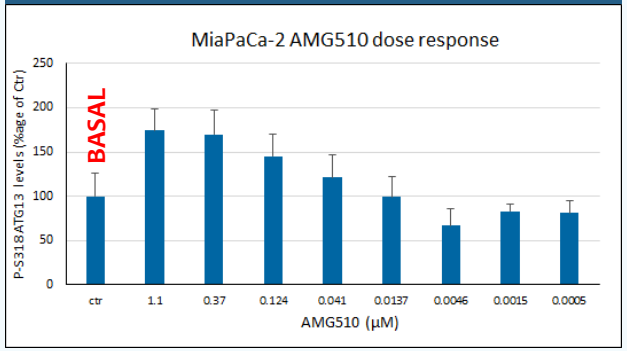


# MAPK Pathway Inhibition Leads to Release of Tonic Inhibition of ULK

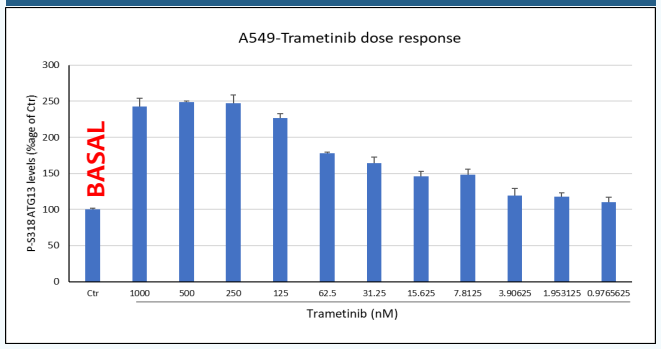
## Autophagy is a compensatory survival mechanism in MAPK pathway inhibitor-treated RAS cancers



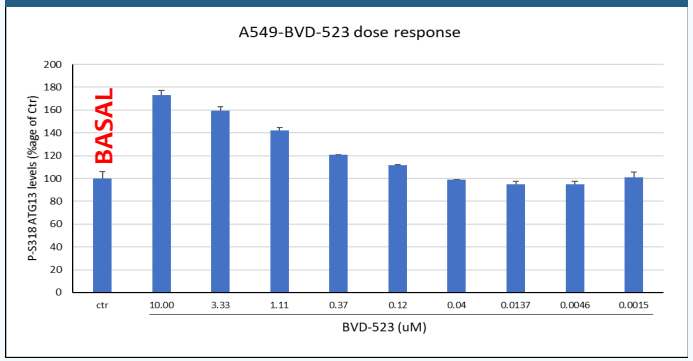

### Activation by KRAS G12C Inhibition




### Activation by MEK Inhibition



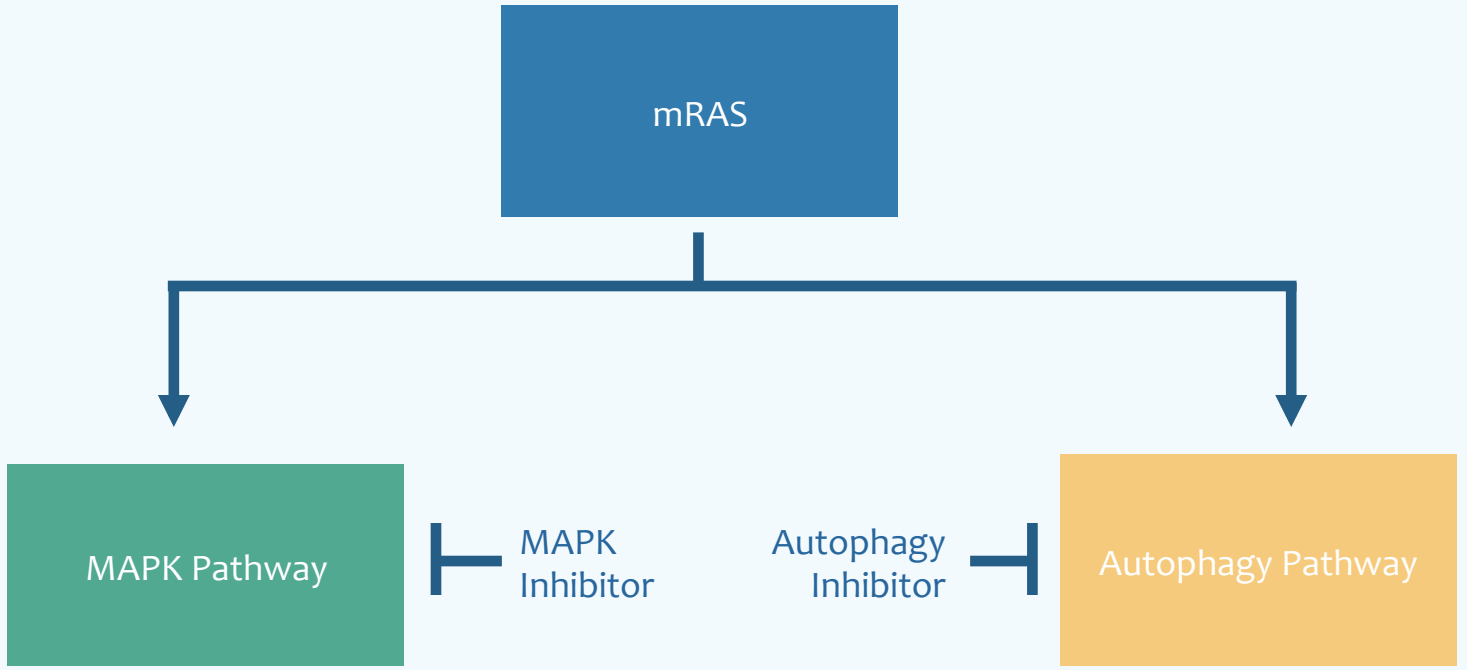

### Activation by ERK Inhibition



# 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

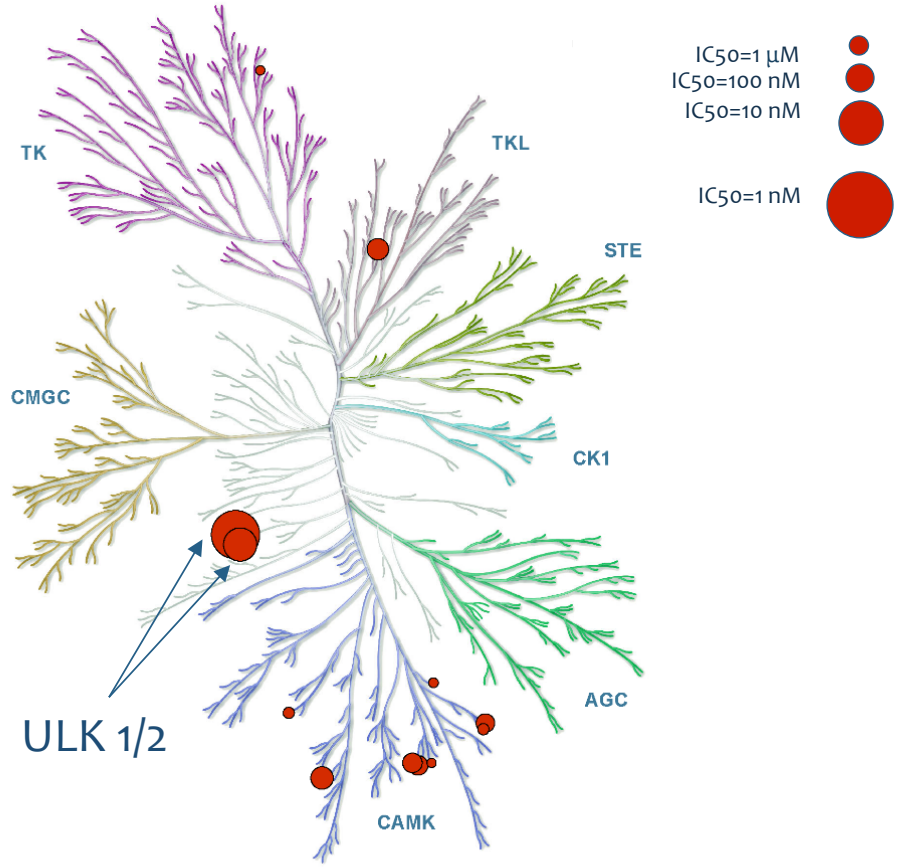
- No off-target kinases within 30-fold of ULK1
- Only 5 kinases within 100-fold of ULK1

### Designed to avoid CNS exposure

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

### IND Filing Expected in Mid-2020

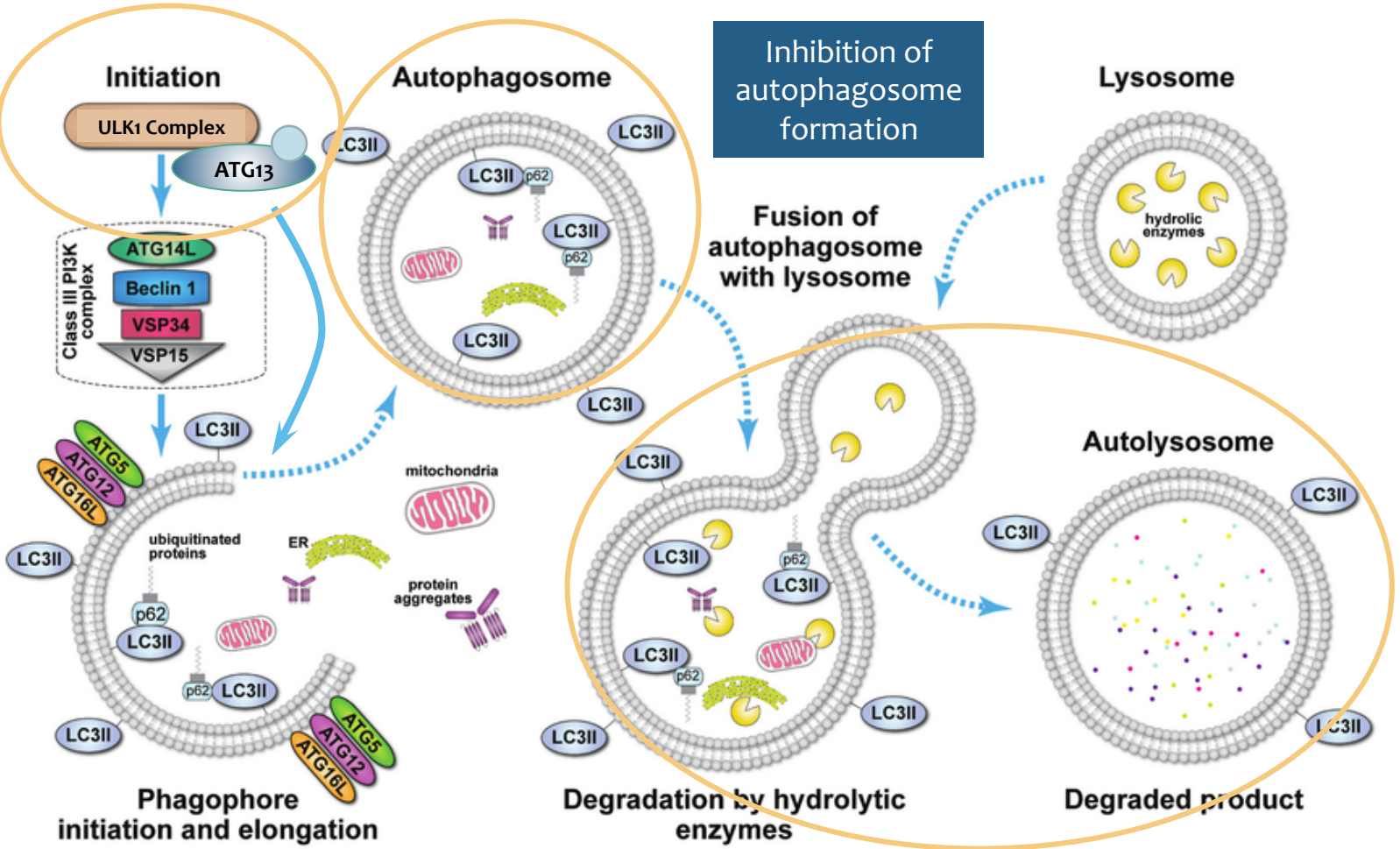
## DCC-3116: A Selective ULK1/2 Inhibitor




*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

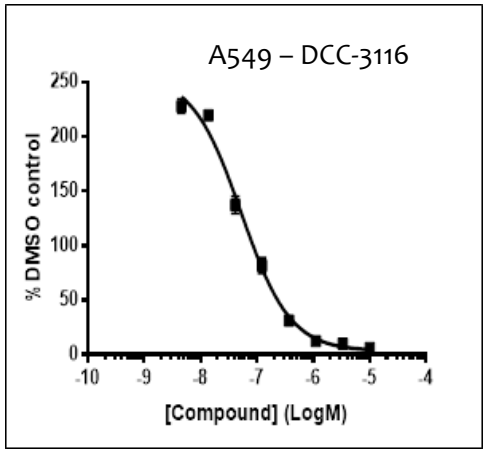


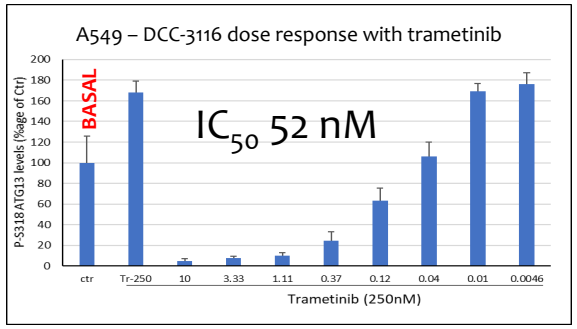

Inhibition of LC3 degradation

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

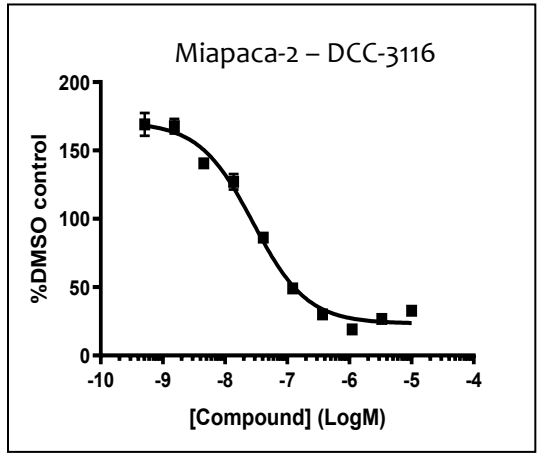
# DCC-3116 Potently Inhibits ULK in Multiple RAS Cancer Cell Lines

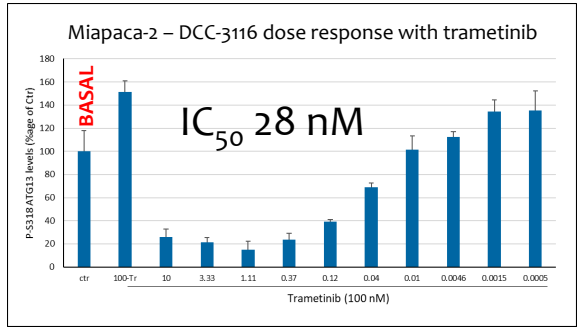
## KRAS Lung Cancer



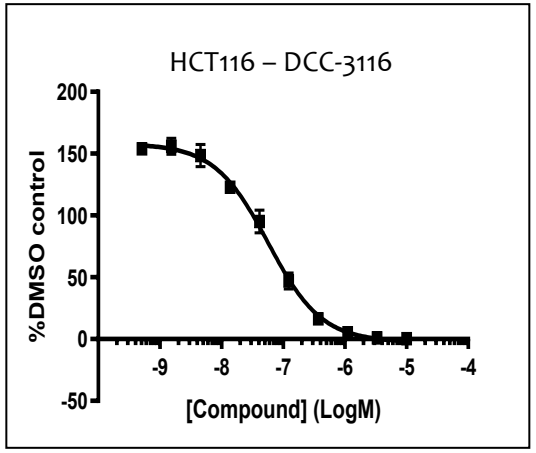



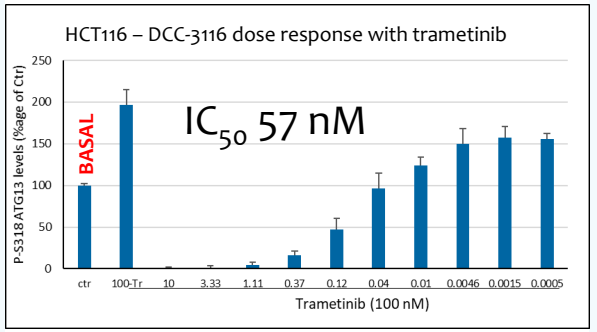

## KRAS G12C Pancreatic Cancer



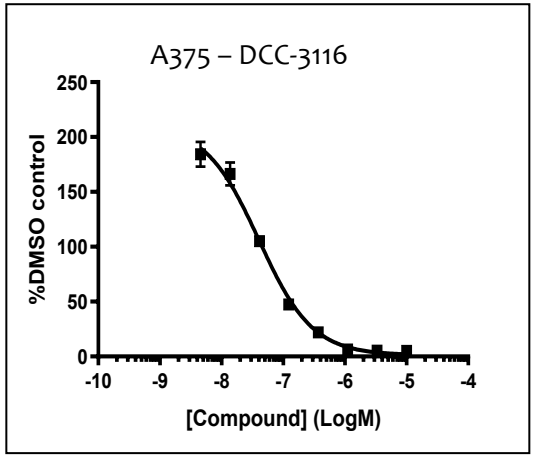



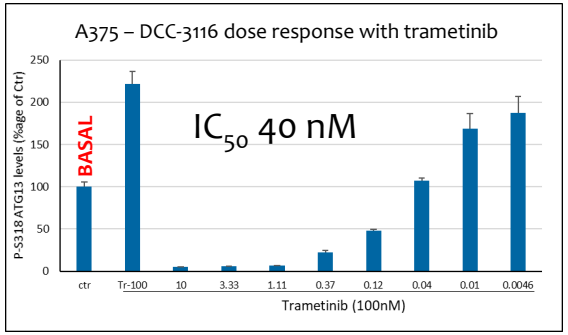

## KRAS Colorectal Cancer




## BRAF Melanoma Cancer

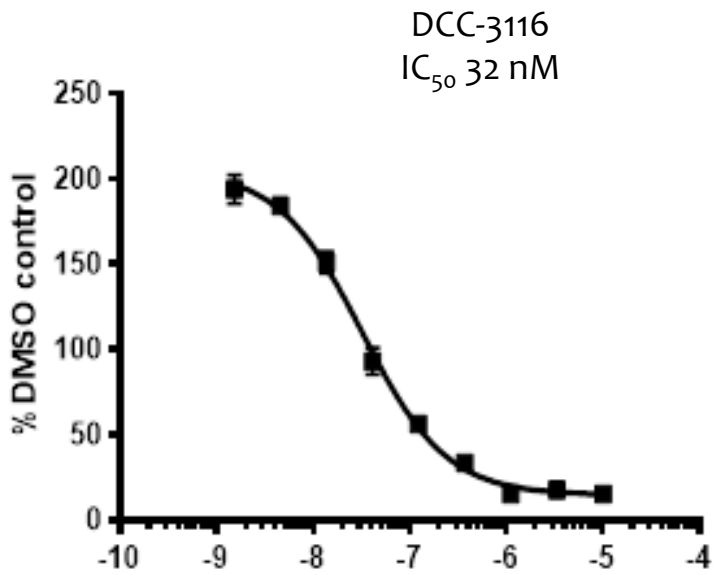


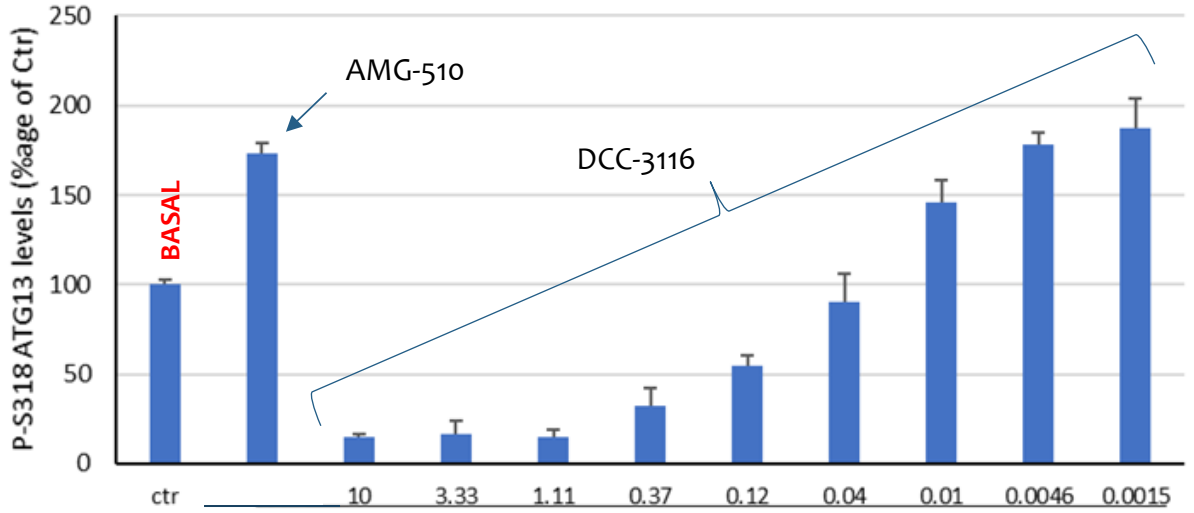

**Basal and MAPK inhibitor-mediated compensatory increased autophagy are inhibited**

# 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

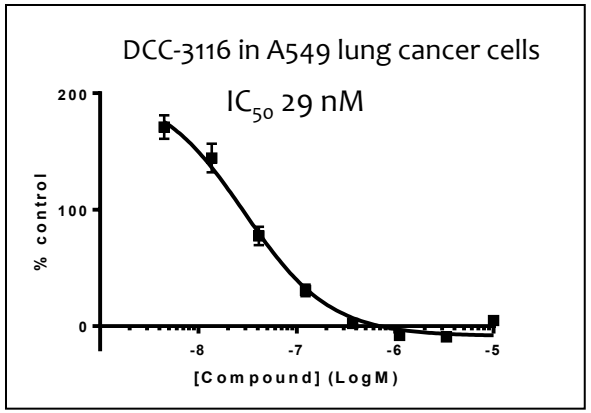


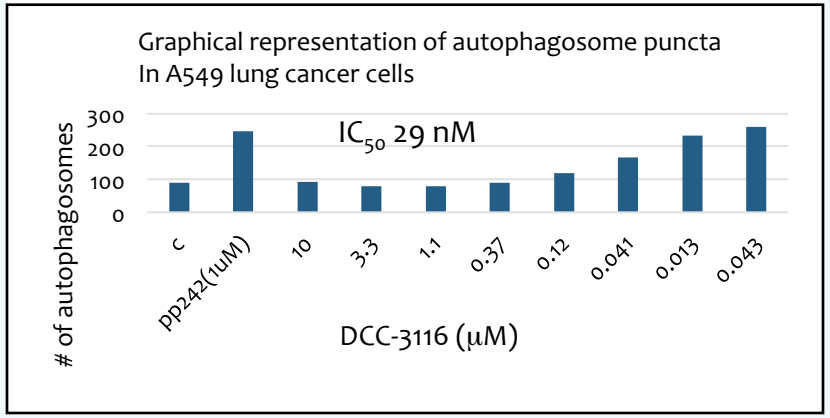

## Miapaca-2 pancreatic cancer study with AMG-510

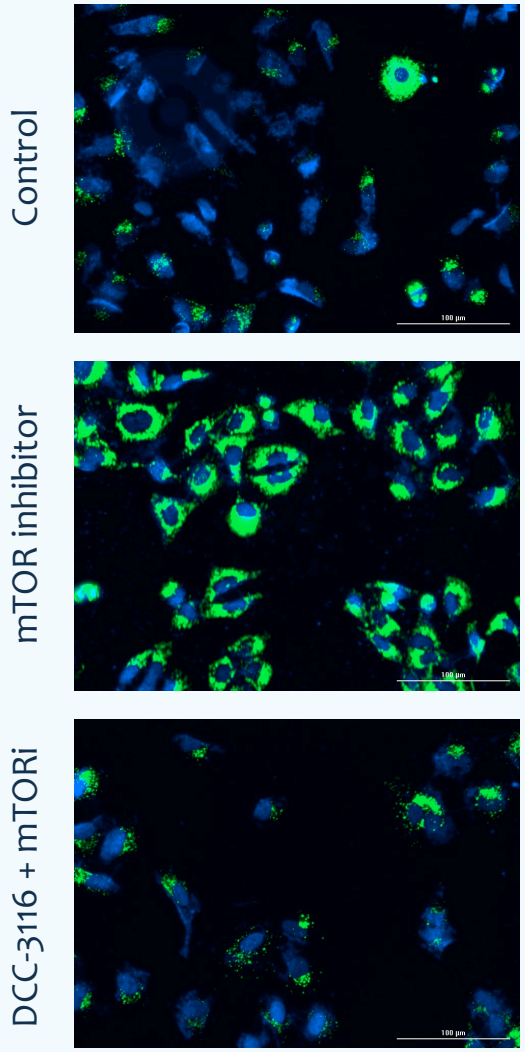


# DCC-3116 Inhibits Autophagosome Formation and Lysosomal Degradation in KRAS Mutant Cancer Cells *In Vitro*

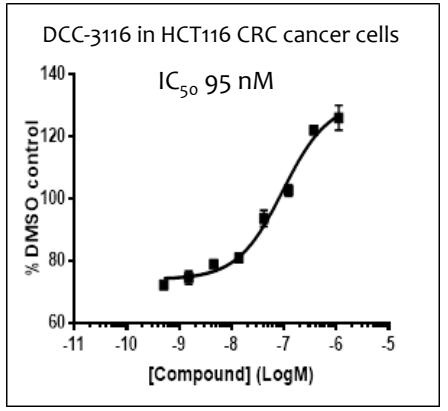
## AUTOPHAGOSOME FORMATION INHIBITION

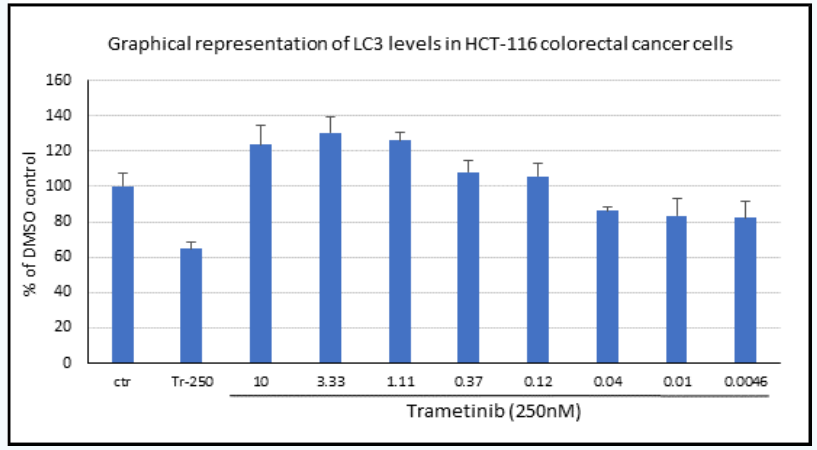


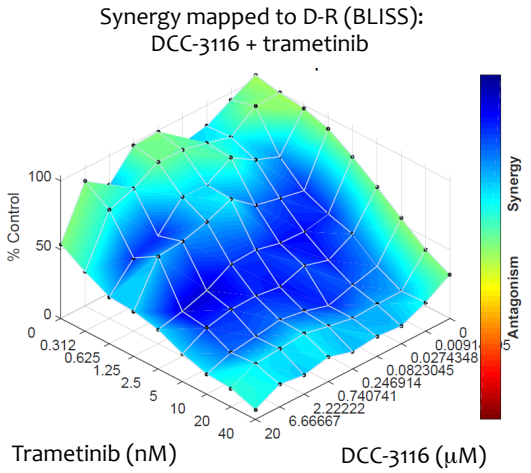

## LC3 DEGRADATION INHIBITION

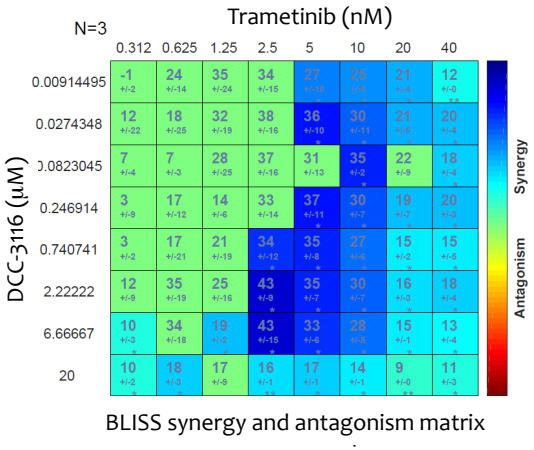


# DCC-3116 + Trametinib Synergize to Inhibit Pancreatic Cancer Cell Proliferation *In Vitro*

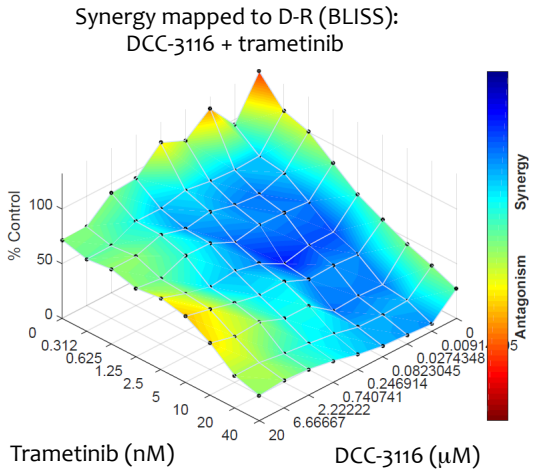
## Inhibition of cell proliferation in KRAS mutant MiaPaCa-2 pancreatic cancer cells

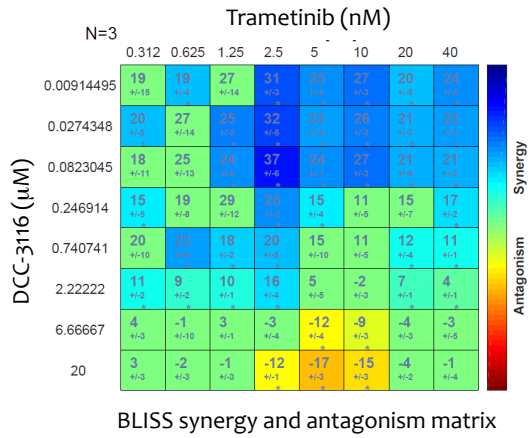



Strong synergy observed for various concentrations of DCC-3116 with trametinib combinations across the matrix

## Inhibition of cell proliferation in BRAF mutant BxPC3 pancreatic cancer cells

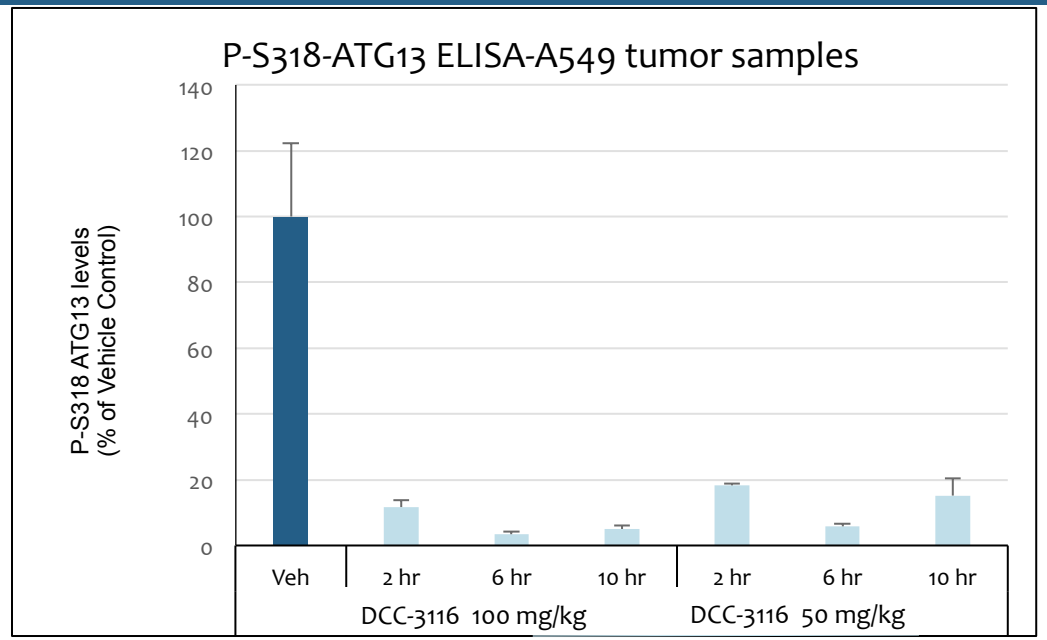



Synergy at lower concentrations of DCC-3116 and across concentration range of trametinib

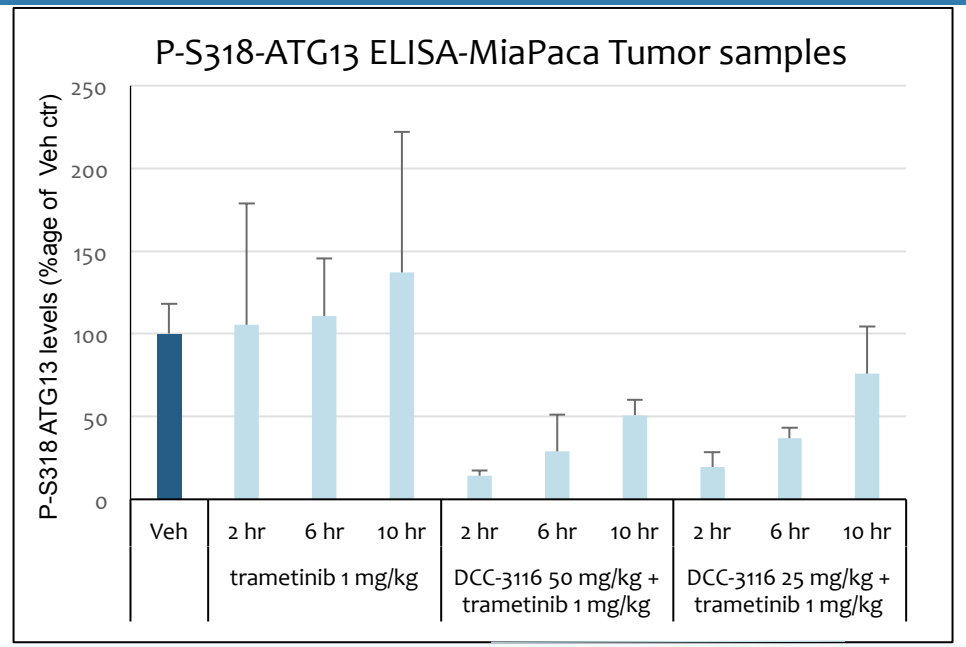
# DCC-3116 Durably Inhibits ULK *In Vivo* in KRAS Cancer PK/PD Models

## 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 |

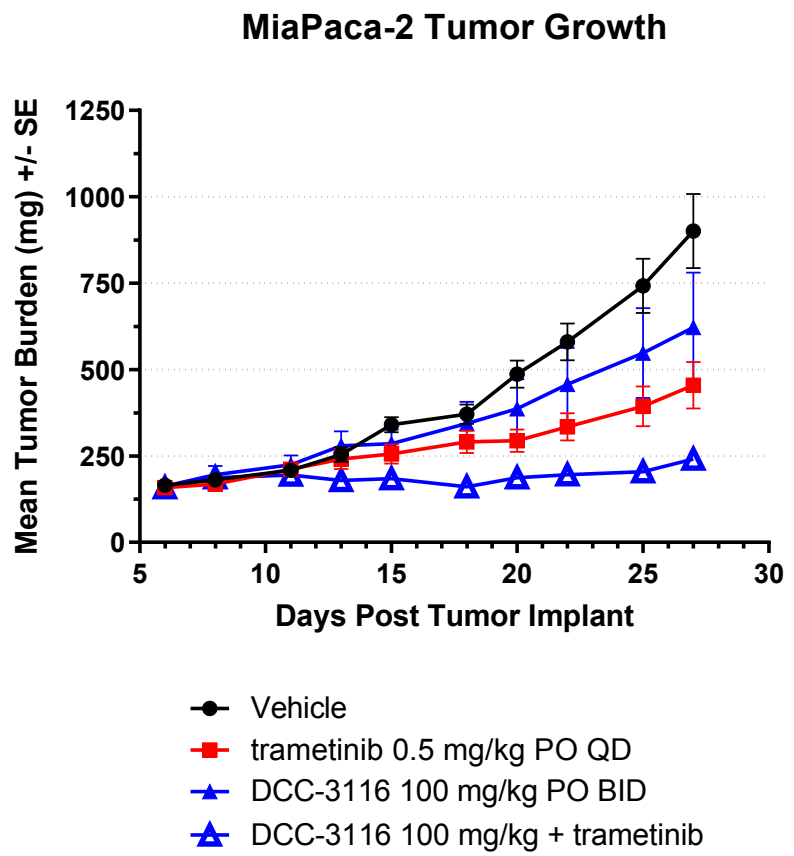
## MiaPaCa-2 Pancreatic Cancer



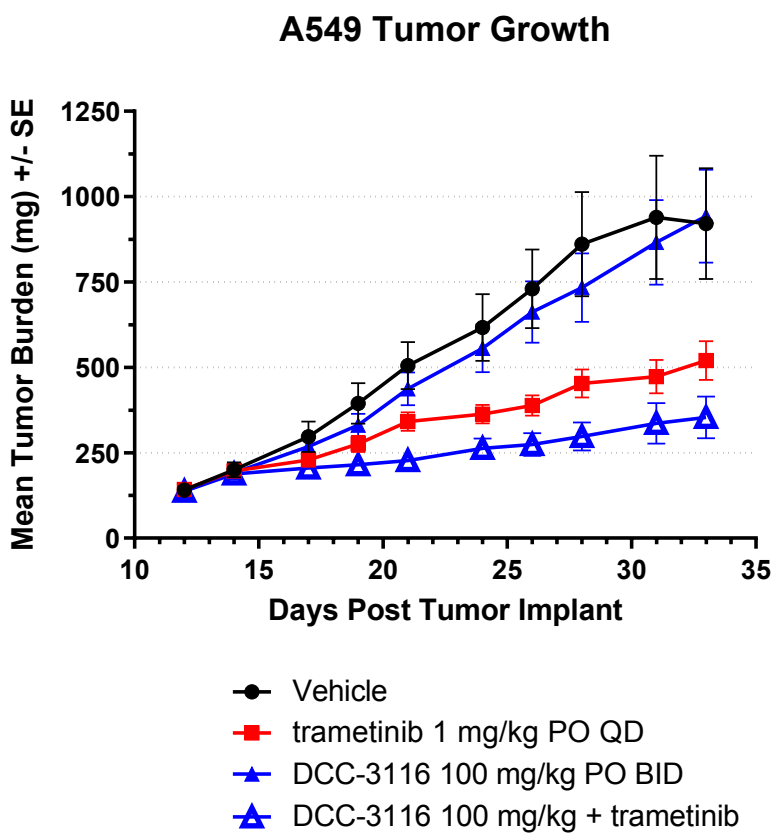

| | DCC-3116 50 mg/kg | | | DCC-3116 25 mg/kg | | |
|---|---|---|---|---|---|---|
| | 2 hr | 6 hr | 10 hr | 2 hr | 6 hr | 10 hr |
| Free drug (nM) | 3,016 | 1,079 | 243 | 1,582 | 581 | 254 |
| % pATG13 inhibition | 86 | 71 | 49 | 80 | 63 | 24 |

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

## KRAS MUTANT PANCREATIC

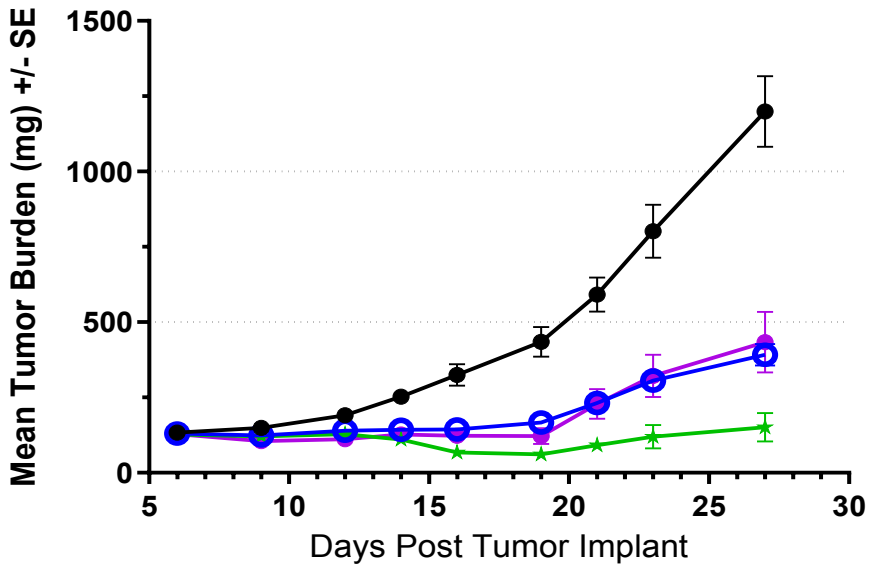



## KRAS MUTANT LUNG



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

## MiaPaCa-2 Tumor Growth

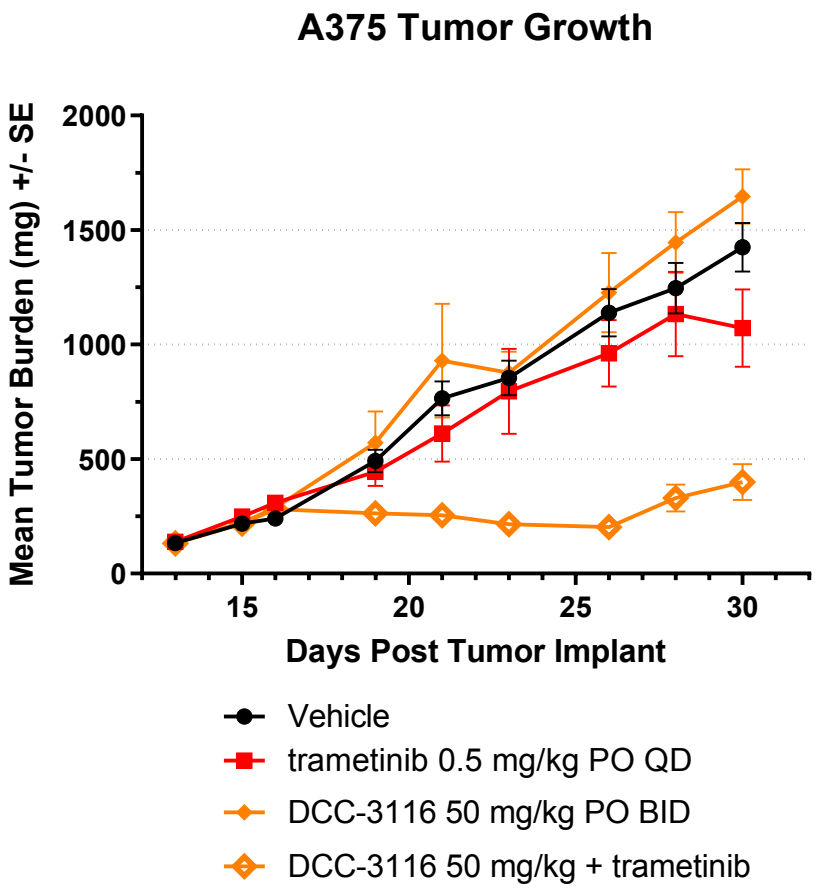



**Marketed MEK Inhibitors**

**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<br>• 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<br>• Differentiated approach to autophagy inhibition |
| **DCC-3116 IS A POTENTIAL FIRST-IN-CLASS ULK KINASE INHIBITOR** | • Highly selective and potent inhibitor of ULK kinase<br>• Designed for combination approach |
| **STRONG PRELIMINARY PRECLINICAL VALIDATION** | • DCC-3116 inhibits autophagy in RAS cancer cell lines<br>• DCC-3116 potently and durably inhibits autophagy *in vivo*<br>• 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