DCC-3116: A Selective ULK Kinase Inhibitor

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

June 18, 2019
such research has not been verified by any independent source.

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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

<table>
<thead>
<tr>
<th></th>
<th>Deliver on Ripretinib</th>
<th>Advance Clinical Programs</th>
<th>Invest in Next Research Wave</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Secure approval and launch in ≥4L GIST&lt;br&gt;Rapidly progress INTRIGUE in 2L GIST</td>
<td>Drive to initial clinical data for POC&lt;br&gt;Accelerate path to pivotal trials</td>
<td>Progress DCC-3116 to IND&lt;br&gt;Focus on next wave of targets</td>
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### Strong Clinical Stage Oncology Pipeline Of Novel Kinase Inhibitors

<table>
<thead>
<tr>
<th><strong>Ripretinib</strong>: Broad Spectrum Inhibitor of KIT &amp; PDGFRα</th>
<th>PRE CLINICAL</th>
<th>PHASE 1</th>
<th>PHASE 1B/2</th>
<th>PHASE 3</th>
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<tr>
<td>INVICTUS (≥4L GIST)</td>
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<td>deciphera</td>
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<td>INTRIGUE (2L GIST)</td>
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<td>GIST (2L, 3L, ≥4L)</td>
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<tr>
<td>Other Solid Tumors¹</td>
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<tr>
<th><strong>Rebastinib</strong>: Selective Inhibitor of TIE2</th>
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<tr>
<td>Solid Tumors in Combination with Paclitaxel (includes breast, ovarian &amp; endometrial cancers)</td>
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<td>Solid Tumors in Combination with Carboplatin (includes mesothelioma, ovarian &amp; breast cancers)</td>
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<tr>
<th><strong>DCC-3014</strong>: Selective Inhibitor of CSF1R</th>
<th>PRE CLINICAL</th>
<th>PHASE 1</th>
<th>PHASE 1B/2</th>
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<tr>
<td>Tenosynovial Giant Cell Tumors (TGCT)</td>
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<tr>
<td>Other Solid Tumors</td>
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<thead>
<tr>
<th><strong>DCC-3116</strong>: Selective Inhibitor of ULK</th>
<th>PRE CLINICAL</th>
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<th>PHASE 1B/2</th>
<th>PHASE 3</th>
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<tr>
<td>Autophagy Inhibitor for Targeting Mutant RAS Cancers</td>
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<th><strong>Additional Programs</strong></th>
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<th>PHASE 1B/2</th>
<th>PHASE 3</th>
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<tbody>
<tr>
<td>Immunokinase (undisclosed target)</td>
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<td>deciphera</td>
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</tbody>
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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

<table>
<thead>
<tr>
<th>Pipeline</th>
<th>Milestones</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ripretinib</strong></td>
<td>- INVICTUS (≥4ᵗʰ Line GIST: Pivotal Phase 3 Results (Expected Mid-2019))</td>
</tr>
<tr>
<td></td>
<td>- Phase 1 Expansion Data (2H 2019)</td>
</tr>
<tr>
<td><strong>Rebasitinib</strong></td>
<td>- Phase 1b/2 Carboplatin Combination Initiated (1H 2019)</td>
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<td>- Part 1 of the Phase 1b/2 Paclitaxel Combination Completed Enrollment (1H 2019)</td>
</tr>
<tr>
<td></td>
<td>- Part 1 of the Phase 1b/2 Paclitaxel Combination Data (2H 2019)</td>
</tr>
<tr>
<td><strong>DCC-3014</strong></td>
<td>- Phase 1 Dose Escalation Presentation (1H 2019)</td>
</tr>
<tr>
<td></td>
<td>- Phase 1 Escalation Data Update (2H 2019)</td>
</tr>
<tr>
<td><strong>Discovery Platform</strong></td>
<td>- Select Clinical Candidate Targeting ULK, Potential First-in-Class Autophagy Inhibitor to Treat mRAS Cancers (1H 2019)</td>
</tr>
<tr>
<td></td>
<td>- Initiate IND-enabling Studies (1H 2019)</td>
</tr>
</tbody>
</table>
Channing Der, Ph.D.

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

Autophagy & Mutant RAS Cancers
Exploiting autophagy for the treatment of RAS-mutant cancers

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

<table>
<thead>
<tr>
<th>%</th>
<th>Cancer</th>
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<tbody>
<tr>
<td>97</td>
<td>Pancreatic ductal adenocarcinoma</td>
</tr>
<tr>
<td>52</td>
<td>Colorectal adenocarcinoma</td>
</tr>
<tr>
<td>43</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>32</td>
<td>Lung adenocarcinoma</td>
</tr>
<tr>
<td>28</td>
<td>Skin cutaneous melanoma</td>
</tr>
<tr>
<td>25</td>
<td>Uterine corpus endometrioid carcinoma</td>
</tr>
<tr>
<td>13</td>
<td>Thyroid carcinoma</td>
</tr>
<tr>
<td>13</td>
<td>Uterine carcinosarcoma</td>
</tr>
<tr>
<td>12</td>
<td>Stomach adenocarcinoma</td>
</tr>
<tr>
<td>11</td>
<td>Acute myeloid leukaemia</td>
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<tr>
<td>11</td>
<td>Bladder urothelial carcinoma</td>
</tr>
<tr>
<td>8</td>
<td>Cervical adenocarcinoma</td>
</tr>
<tr>
<td>6</td>
<td>Head &amp; neck squamous cell carcinoma</td>
</tr>
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</table>

### Estimated US cancer deaths

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


Current strategies for targeting RAS for cancer treatment

1. Disruption of regulator/effecter interactions
2. Inhibition of membrane association
3. Inhibition of downstream effectors
4. Inhibition of synthetic lethal interactions
5. Inhibition of metabolism

Pursuit of three strategies converge on autophagy

1. Disruption of regulator/efferro interactions
   - KRAS4B

2. Inhibition of membrane association

3. Inhibition of synthetic lethal interactions

4. Inhibition of downstream effectors

5. Inhibition of metabolism

Glucose
Glutamate

RAS mutant cancers are addicted to autophagy

- Autophagy is elevated in RAS-mutant cancers
- Inhibition of autophagy impairs growth of RAS-mutant cancers
  - Does mutant RAS cause increased autophagy? If yes, then how does RAS do this?
We were wrong – suppression of RAS further elevated, rather than suppressed, autophagy!

We begin a four year journey to figure out why and what this means.
Three studies independently establish the therapeutic potential of concurrent ERK MAPK and autophagy inhibition in RAS-mutant cancer
Targeting the RAF-MEK-ERK MAPK cascade

1. Disruption of regulator/effecter interactions
2. Inhibition of membrane association
3. Inhibition of synthetic lethal interactions
4. Inhibition of downstream effectors
5. Inhibition of metabolism

Clinical evaluation of RAF-MEK-ERK protein kinase inhibitors

ARQ 736\(^c\)
Lifirafenib/BGB-283
BMS-908662/XL281\(^c\)
Dabrafenib/GSK2118436\(^a\)
Encorafenib/LGX818
GDC-5573/HHM5573/RG6185
LXH254
LY3009120
PLX8394
RAF265/CHIR-265\(^c\)
Regorafenib/BAY 73-4506\(^b\)
Sorafenib/BAY 43-9006\(^b\)
TAK-580/MLN2480
Vemurafenib/PLX4032\(^a\)

RO5126766/CH5126766

CC-90003\(^d\)
KO-947\(^e\)
LTT462
LY3214996
MK-8353/SCH900353
ONC201
Ravoxertinib/GDC-0994/RG7842\(^c\)
Ulixertinib (BVD-523)

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?

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

Independently, another group reaches the same conclusion.

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

Conan G. Kinsey¹,², Soledad A. Camolotto¹, Amelie M. Boespflug¹,³,⁴, Katrin P. Guillen¹, Mona Foth*¹, Amanda Truong¹, Sophia S. Schuman¹, Jill E. Shea⁵, Michael T. Seipp⁵, Jeffrey T. Yap¹,⁶, Lance D. Burrell¹, David H. Lum¹, Jonathan R. Whisenant¹,², G. Weldon Gilcrease III¹,², Courtney C. Cavalieri¹,⁷, Kaitrin M. Rehbein¹, Stephanie L. Cutler¹, Kajsa E. Affolter¹,⁸, Alana L. Welm¹,⁹, Bryan E. Welm¹,⁵, Courtney L. Scaife¹,⁵, Eric L. Snyder¹,⁸ and Martin McMahon*¹,¹⁰
Concurrent MEK and autophagy inhibition cooperates to cause tumor regression

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

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

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


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


**Keywords:** RAF, MEK, ERK, KRAS, Autophagy, Cancer, Treatment, Pancreatic cancer, Protective autophagy, RAS-driven cancers
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

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

- ‘Undruggable’ RAS-mutant cancers: druggable after all?
- Autophagy: the Achilles’ heel of RAS-mutant cancers?
- Inhibitors of the ERK MAPK cascade – rendering KRAS-mutant cancers addicted to autophagy
- Combination ERK MAPK and autophagy inhibition: a pan-RAS therapy?
- Autophagy inhibition anti-tumor activity is due to targeting tumor cells and the tumor microenvironment
- ULK inhibitors: a more selective autophagy inhibitor?
The first direct KRAS inhibitors enter clinical evaluation in 2018

Clinical evaluation of KRAS G12C-specific inhibitors

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

KRAS G12C inhibitors versus ERK MAPK + HCQ?

*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

G12C inhibitors target only 2% of all cancers

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

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

Dr. Kirsten Bryant (University of North Carolina at Chapel Hill)
Aberrant RAF-MEK-ERK MAPK signaling in cancer

**CANCER GENES**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Mutations</th>
<th>Samples</th>
<th>%</th>
</tr>
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<tbody>
<tr>
<td>HRAS</td>
<td>2128</td>
<td>106386</td>
<td>2.0</td>
</tr>
<tr>
<td>KRAS</td>
<td>45050</td>
<td>262635</td>
<td>17.2</td>
</tr>
<tr>
<td>NRAS</td>
<td>7100</td>
<td>149804</td>
<td>4.7</td>
</tr>
<tr>
<td>BRAF</td>
<td>54084</td>
<td>302211</td>
<td>17.9</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>14875</td>
<td>135949</td>
<td>10.9</td>
</tr>
<tr>
<td>EGFR</td>
<td>28054</td>
<td>182304</td>
<td>15.3</td>
</tr>
<tr>
<td>NF1</td>
<td>2878</td>
<td>65211</td>
<td>4.4</td>
</tr>
<tr>
<td>TP53</td>
<td>41588</td>
<td>155424</td>
<td>26.8</td>
</tr>
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</table>

Total RAS: 23.9%

HRAS (2.0%), KRAS (17.2%), NRAS (4.7%)
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

**Ubc-cre^ERT2;Atg7^+/+**

- TAM
- **Autophagy-proficient (Atg7 wild-type)**
- 1 week
- Tumour cells

**Ubc-cre^ERT2;Atg7^floxflox**

- TAM
- **Autophagy-deficient (Atg7 wild-type)**
- 1 week
- Tumour cells

Autophagy-dependent activities of the microenvironment support tumor growth

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


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

Initiation → Nucleation → Maturation → Degradation

**Nutrient depletion, Stress**: AMPK

**mTORC1**: ULK1/2, ATG13, ATG101, FIP200

**VPS34**, Beclin-1, VPS15

**Hydrolases**

**Cargo**

**Nutrient abundance**

**Isolations membrane**: LC3-I, LC3-II

**Phagophore**: LC3-I, LC3-II

**Autophagosome**: LC3-II

**Lysosome**: Degradation & recycling

Yoshinori Ohsumi

2016 Nobel Prize in Physiology or Medicine

‘Self-eating’
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 Without 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**

### Initiation
- **Nucleation**
- **Maturation**
- **Degradation & recycling**

**Initiation**
- ULK1/2
- ATG13
- ATG101
- FIP200
- VPS15
- ATG14L
- Beclin-1
- VPS34
- mTORC1
- AMPK

**Nucleation**
- MRT67307
- MRT68921
- SBI-0206965

**Maturation**
- Spautin-1
- HCQ, CQ, Bafilomycin A1, Lys05, DQ661

**Degradation & recycling**
- Lysosome
- Rapalogs: MRT67307, MRT68921, SBI-0206965
- LY294002, VPS34-IN1, Wortmanin
- 3-MA
- Spautin-1

**Isolation membrane**
- LC3-I
- LC3-II

**Phagophore**
- LC3-II

**Autophagosome**
- LC3-II
- ATG4B
- NSC 185058

**Autolysosome**
- LC3-II

**Hydrolases**

**Cargo**

---

Klionsky et al (2016) Autophagy 12:1
Autophagy inhibitors: a focus on ULK inhibitors

Initiation → Nucleation → Maturation → Degradation & recycling

**Initiation**
- ULK1/2
- ATG13
- ATG101
- FIP200
- VPS15
- Beclin-1

**Nucleation**
- ATG14L
- VPS34

**Maturation**
- LC3
- LC3-I
- LC3-II

**Degradation & recycling**
- Lysosome
- Hydrolases
- Cargo

**Proteins**
- AMPK
- mTORC1
- DCC-3116

**Gene Expression**
Conclusions

- Inhibitors of the ERK MAPK cascade render KRAS-mutant cancers addicted to autophagy, enhancing their response to autophagy inhibitor treatment.

- Unlike KRAS\textsuperscript{G12C} mutant-selective inhibitors, combination ERK MAPK and autophagy inhibitor treatment may be effective in a broader spectrum of EGFR/RAS/BRAF mutant human cancers.

- Moving forward, more potent and selective autophagy inhibitors will be needed to improve upon this combination.
ULK activity plays a metabolic role in RAS-mutant cancers

Molecular Cell
ULK1/2 Constitute a Bifurcate Node Controlling Glucose Metabolic Fluxes in Addition to Autophagy
Li et al., 2016, Molecular Cell 62, 359–370
May 5, 2016 ©2016 Elsevier Inc.
http://dx.doi.org/10.1016/j.molcel.2016.04.009
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

Direct inhibition of RAS: Quest for the Holy Grail?

Russell Spencer-Smith\textsuperscript{a,b,c}, John P. O’Bryan\textsuperscript{a,b,c,\textdagger}

\textsuperscript{a} Department of Pharmacology, University of Illinois at Chicago, Chicago, IL, USA
\textsuperscript{b} University of Illinois Cancer Center, University of Illinois at Chicago, Chicago, IL, USA
\textsuperscript{c} Jesse Brown VA Medical Center, Chicago, IL, USA

(85%)
(11%)
(4%)
Revitalized Interest in Autophagy

Autophagy is a signal transduction pathway with defined molecular components.

Yoshinori Ohsumi
Nobel Prize in Physiology & Medicine 2016
for the Study of Autophagy

Anticancer autophagy inhibitors attract ‘resurgent’ interest

Despite industry’s past setbacks with autophagy inhibitors, preclinical and clinical findings are starting to revitalize a once neglected area.
Overview of Autophagy and RAS Cancers
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

Strategies for Blocking Autophagy in Cancer

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

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

**Letters**

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

Conan G. Kinsey1, Soledad A. Camoletto1, Amelia M. Bossplug1,4, Katrin P. Guillien1, Mona Foth1,1, Amanda Truong1, Sophia S. Schuman1, Jill E. Shea1, Michael T. Seipp1, Jeffrey T. Yap1,1, Lance D. Burrell1, David H. Lym1, Jonathan R. Whisenant1,2, G. Weldon Gilcrease III1,2, Courtney C. Cavilleri1,2, Kaitrin M. Rebhun1, Stephanie L. Cutler1, Kajsa E. Affolter1, Alana L. Weim1,3, Bryan E. Weim1,5, Courtney L. Scaife1,3, Eric L. Snyder1,8 and Martin McMahon1,9

**Articles**

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

Kirsten L. Bryant1,2, Clint A. Stalnecker1,2, Daniel Zeitouni1, Jennifer E. Klop1,2, Sen Peng1,2, Andrey P. Tikunov1,2, Venugopal Gunda1,2, Mariaelena Pierobon1,2, Andrew M. Water1,2, Samuel D. George1,2, Garima Tomar1,2, Björn Papke1,2, G. Aaron Hobbs1,2, Liang Yan1,2, Tikvah K. Hayes1,2, J. Nathaniel Oleh1,2, Gennifer D. Goode1,2, Nina V. Chalka1,2, Yingxue Wang1,2, Guo-Fang Zhang1,2, Agnieszka K. Wilkiewicz1,2, Erik S. Knudsen1,2, Emanuela Metricein1,2, Pankaj K. Sing1,2, Jeffrey M. Macdonald1,2, Nhan L. Tran1,2, Costas A. Lyssiotis1,2, Haoqiang Ying1,2, Alec C. Kimmelman1,2, Adrienne D. Cox1,2,3 and Channing J. Dave1,2

**PNAS**

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

Chih-Shia Lee1,2, Lim C. Lee1,2, Tina L. Yuan1,2, Sirisha Chakka1,2, Christof Fellmann2,4, Scott W. Lowe1,2,3,4, Natasha J. Caplen1,2, Frank McCormick1,2,4,5, and Ji Luo1,2,4,5

1Laboratory of Cancer Biology and Genetics, Center for Cancer Research, National Cancer Institute, Bethesda, MD 20892; 2Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, CA 94158; 3Genetics Branch, Center for Cancer Research, National Cancer Institute, Bethesda, MD 20892; 4Cold Spring Harbor Laboratory, Cold Spring Harbor, NY 11724; 5Howard Hughes Medical Institute, Memorial Sloan Kettering Cancer Center, New York, NY 10065; 6Department 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)
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**

- **mKRAS**
  - AMG-510
  - LY3009120

- **MEK**
  - Trametinib

- **ERK**
  - Ulixertinib

- **LKB1**
  - AMPK
  - ULK
  - ATG13

- **Other Inputs Activate ULK**

Cancer Growth and Survival

**Activation by KRAS G12C Inhibition**

**Activation by MEK Inhibition**

**Activation by ERK Inhibition**
A New Potential Approach to Potentially Treat RAS Cancers

- 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

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

**KRAS LUNG CANCER**

- A549 – DCC-3116
  - IC\(_{50}\) 52 nM

**KRAS G12C PANCREATIC CANCER**

- Miapaca-2 – DCC-3116
  - IC\(_{50}\) 28 nM

**KRAS COLORECTAL CANCER**

- HCT116 – DCC-3116
  - IC\(_{50}\) 57 nM

**BRAF MELANOMA CANCER**

- A375 – DCC-3116
  - IC\(_{50}\) 40 nM

**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 IC50 of 32 nM for inhibition of autophagy induced by AMG-510
DCC-3116 Inhibits Autophagosome Formation and Lysosomal Degradation in KRAS Mutant Cancer Cells In Vitro

**AUTOPHAGOSOME FORMATION INHIBITION**

![Graphical representation of autophagosome puncta in A549 lung cancer cells](image)

**LC3 DEGRADATION INHIBITION**

![Graphical representation of LC3 levels in HCT-116 colorectal cancer cells](image)
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

**P-S318-ATG13 ELISA-A549 tumor samples**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Time 2 hr</th>
<th>Time 6 hr</th>
<th>Time 10 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veh</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DCC-3116 100 mg/kg</td>
<td>9,542</td>
<td>7,058</td>
<td>8,017</td>
</tr>
<tr>
<td>DCC-3116 50 mg/kg</td>
<td>7,643</td>
<td>5,140</td>
<td>1,715</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>% pATG13 inhibition</th>
<th>88</th>
<th>97</th>
<th>95</th>
</tr>
</thead>
<tbody>
<tr>
<td>% pATG13 inhibition</td>
<td>82</td>
<td>94</td>
<td>95</td>
</tr>
</tbody>
</table>

### MIAPACA-2 PANCREATIC CANCER

**P-S318-ATG13 ELISA-MiaPaca Tumor samples**

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<th>Time 10 hr</th>
</tr>
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<tbody>
<tr>
<td>Veh</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>trametinib 1 mg/kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DCC-3116 50 mg/kg + trametinib 1 mg/kg</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>DCC-3116 25 mg/kg + trametinib 1 mg/kg</td>
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<table>
<thead>
<tr>
<th>% pATG13 inhibition</th>
<th>86</th>
<th>71</th>
<th>49</th>
</tr>
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<tbody>
<tr>
<td>% pATG13 inhibition</td>
<td>80</td>
<td>63</td>
<td>24</td>
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### Free drug (nM)

<table>
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<tr>
<th>DCC-3116 50 mg/kg</th>
<th>DCC-3116 25 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>3,016</td>
<td>1,582</td>
</tr>
</tbody>
</table>

69
DCC-3116 + MEK Inhibitors Exhibited Reduced Tumor Growth in KRAS In Vivo Cancer Models

**KRAS MUTANT PANCREATIC**

**KRAS MUTANT LUNG**

**MiaPaca-2 Tumor Growth**

**A549 Tumor Growth**
DCC-3116 + MEK and ERK Inhibitors Exhibit Synergy in RAS Cancer Model

**MiaPaca-2 Tumor Growth**

- **Vehicle**
- **DCC-3116 25 mg/kg + trametinib**
- **DCC-3116 25 mg/kg + binimetinib**
- **DCC-3116 25 mg/kg + ulixertinib**

Marketed MEK Inhibitors
ERK Inhibitor
DCC-3116 + MAPK Inhibitors Exhibited Reduced Tumor Growth in BRAF in In Vivo Cancer Models
## 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
THANK YOU
[https://www.nature.com/articles/s41591-019-0368-8](https://www.nature.com/articles/s41591-019-0368-8)

[https://www.pnas.org/content/116/10/4508](https://www.pnas.org/content/116/10/4508)

[https://www.nature.com/articles/s41591-019-0367-9](https://www.nature.com/articles/s41591-019-0367-9)

[http://genesdev.cshlp.org/content/25/5/460.abstract](http://genesdev.cshlp.org/content/25/5/460.abstract)

[http://cancerdiscovery.aacrjournals.org/content/early/2018/01/09/2159-8290.CD-17-0952.full-text.pdf](http://cancerdiscovery.aacrjournals.org/content/early/2018/01/09/2159-8290.CD-17-0952.full-text.pdf)


[https://www.nature.com/articles/d41573-019-00072-1](https://www.nature.com/articles/d41573-019-00072-1)