Activation of Akt pathway and autophagy promotes resistance to FASN inhibition in colorectal cancer patient-derived xenograft models

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Background

Colorectal cancer (CRC) is the second leading cause of cancer-related death in the United States. Forty and six percent (FASN), a key enzyme of lipid biogenesis, is significantly up-regulated and activated in many cancers including CRC and is of interest as a potential biomarker for poor prognosis, higher risk of disease recurrence, and death. What we know about colorectal cancer and FASN inhibition are not fully understood.

• Increased expression and activity of FASN is associated with enhanced epithelial proliferation and metastasis in CRC.
• Oral FASN inhibitor (TVB-2440) entered a Phase I clinical trial (NCT02689432), and this study was used to select tumor patients demonstrating a favorable tolerability profile with no significant adverse events (3B-12 events).
• Tumor characteristics that would indicate responsiveness to FASN inhibition are not fully understood.

Purpose

(i) to determine the effect of FASN inhibition on tumor growth in CRC xenografts
(ii) to identify biomarkers associated with CRC responsiveness to FASN inhibition
(iii) to explore new combination strategies with FASN inhibitors.

Study Design

Stage IV colon cancer patients

Table 1. PDX models used for evaluation of FASN inhibition.

<table>
<thead>
<tr>
<th>PDX model</th>
<th>Stage</th>
<th>Gender</th>
<th>Pathology</th>
<th>PDX model</th>
<th>Stage</th>
<th>Gender</th>
<th>Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt 2377</td>
<td>T3N1bM1</td>
<td>69/F</td>
<td>Mucinous colonic adenocarcinoma</td>
<td>Pt 2402</td>
<td>T3N1M1</td>
<td>70/M</td>
<td>Metastatic medullary colonic carcinoma</td>
</tr>
<tr>
<td>Pt 2449</td>
<td>T3N1bM1</td>
<td>55/M</td>
<td>Metastatic adenocarcinoma (lung) consistent with metastasis from colon primary tumor</td>
<td>Pt 2459</td>
<td>T2N0M0</td>
<td>27/M</td>
<td>Mucinous colonic adenocarcinoma</td>
</tr>
<tr>
<td>Pt 2568</td>
<td>T3N1bM1</td>
<td>55/M</td>
<td>Metastatic medullary colonic carcinoma</td>
<td>Pt 2607</td>
<td>T3N1bM1</td>
<td>77/F</td>
<td>Metastatic adenocarcinoma (lung) consistent with metastasis from colon primary tumor</td>
</tr>
</tbody>
</table>

Materials & Methods

• Human tissue samples: Human CRC and matching normal colorectal tissues were obtained from surgical patients at UK Chandler department of surgery. The FASN inhibitors were used in NSG tissue (PDX model) and in combination with other agents.
• In vivo studies: The effect of TVB-3664 on tumor growth was assessed in PDX models. Tumor volume was expressed in mm³ (fold change).
• Western blot analysis of tissues from PDX models which were treated with TVB-3664 was conducted. Total Akt and APMPK were determined in tumors. The level of FASN expression and basal activation of Akt and AMPK may be associated with CRC responsiveness to FASN inhibition.
• The level of FASN expression may determine the sensitivity of tumors to FASN inhibition.
• Activation of Akt and autophagy pathways may be potential mechanisms of resistance to FASN inhibition.

Conclusions

• FASN is overexpressed in CRC. 79% of CRC patients who had surgery at the University of Kentucky have high expression of FASN (immunohistochemistry score ≥ 3+)
• PDX models exhibit a wide range of sensitivity to FASN inhibition by TVB-3664 (3B-12 biosciences).
• Inhibition of FASN by TVB-3664 in PDX models is associated with a significant decrease in abundance of FA, and PC in tumor tissues.
• A decreased pool of AMPK is a common change among TVB-3664 treated xenograft models.
• The level of FASN expression may determine the sensitivity of tumors to FASN inhibition.
• Activation of Akt and autophagy pathways may be potential mechanisms of resistance to FASN inhibition.

Acknowledgements

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Together, Our Workplace Can Help Reduce Lung Cancer in Casey County

Casey County Deaths
Women 2011-2015
- Lung and Bronchus: 33.3%
- Breast: 12.1%
- Colorectal: 11.1%
- Other: 40.4%

Casey County Deaths
Men 2011-2015
- Lung and Bronchus: 34.5%
- Breast: 7.0%
- Prostate: 10.6%
- Colorectal: 47.9%

Reduce Exposure to Secondhand Smoke

**Secondhand Smoke (SHS)**

**What is it?**
SHS is a mixture of smoke related to the smoker and smoke from the burning end of tobacco products.

**What can you do about it?**
- Make your car and home smoke-free.
- Outdoors, use the designated smoking area.
- Contact local policymakers to advocate for smoke-free areas.

Reduce Tobacco Use

**Cancers**
- Head or Neck
- Lung
- Larynx
- Stomach
- Pancreas
- Liver
- Colon
- Bladder

**Chronic Diseases**
- Heart Disease
- Hardening of the Arteries
- Chronic Lung Disease & Asthma
- Reduced Fertility
- Aortic Rupture
- Pneumonia
- Blindness
- Hip Fracture
- Gum Infection

Reduce Exposure to Radon

**Radon**

**What is it?**
Radon is a naturally occurring radioactive gas that cannot be seen or smelled.

**Why is it dangerous?**
Radon attaches to dust or tobacco smoke and gets into the lungs.

**What can you do about it?**
- Test your home.
- Know your radon level.
- Ask a certified radon professional to fix high radon levels.

**Radon & Secondhand Smoke**

Breathing radon is dangerous, but it is much less harmful than secondhand smoke.

Talk to Your Doctor About Cancer Screening

Get Screened for Lung Cancer!

**You are at high risk IF:**
- You are between 55 and 80 years old AND
- You are currently smoking or quit in the last 15 years AND
- You fit all the smoking history of at least 30 pack-years*

*Based on the recommendation of the United States Preventive Services Task Force and the Centers for Disease Control and Prevention.

This poster was supported by Grant or Cooperative Agreement Number, NUSDOP006313 (Kentucky Cancer Consortium) and DP13-1314 National Networks to Reduce Cancer and Tobacco Related Disparities (SelfMade Health Network) funded by the Centers for Disease Control and Prevention. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the Centers for Disease Control and Prevention or the Department of Health and Human Services.

Cancer Data from the Kentucky Cancer Registry: www.kcr.uky.edu
Markey Cancer Center Research Communications Office:
A Centralized Research Administration Infrastructure Enhancing Faculty Productivity
Heather N. Russell-Simmons, Cathy Anthony, Marcia Ballard, Jonathan Coffman, Donna Gilbreath, Terry L. Keys, Danielle Story, Jennifer F. Rogers, Jennifer Bybee, David M. Gosky, Nathan L. Vanderford
Markey Cancer Center, University of Kentucky, Lexington, Kentucky

BACKGROUND
The University of Kentucky's (UK) Markey Cancer Center (MCC) is a premier cancer research center and patient care facility. Markey's basic, translational, and clinical research supports its mission to reduce cancer incidence and mortality in Kentucky, where cancer rates are extraordinarily high. Cancer center programs include research, treatment, education, and community engagement, focused on the underserved population of Appalachian Kentucky.

In support of this wide-ranging mission, the Research Communications Office (RCO) was created in 2009 to help cancer researchers obtain grant funding and publish material in support of their research. Since its creation, RCO's scope has grown to encompass pre-award and budgetary planning, event planning, and coordination with Markey's public relations and marketing personnel.

The framework and philosophy of this centralized research administration infrastructure serves as a case study on efforts to enhance faculty productivity.

RCO STAFF AND RESPONSIBILITIES
MCC RCO Staff and Responsibilities.

- Daily management of personnel and budget
- Serve as the key point of contact for the office, often helping initiate new projects and communicate RCO skills and expertise
- Lead project coordinator and manager for proposal development, especially for multi-college and/or multi-department interactions
- Manage the solicitation and peer-review process for all MCC developmental research projects/pilot funds
- Lead tracking and routine reporting efforts for the cancer center (for example, membership and publication output)
- Liaison between MCC and UK College of Medicine Sponsored Research Administrative Services and UK Office of Sponsored Projects Administration
- Assist researchers in identifying funding opportunities
- Ensure compliance with funding opportunity guidelines
- Disseminate information about guideline changes for major grant sponsors
- Budget development for large multi-component projects
- Coordinate completion of data tables and institutional information components for training grant and career development applications
- Editing grants and manuscripts for grammar, content and compliance
- Creation and editing of images and figures
- Project management for small grants
- Maintain and coordinate creation for MCC website and social media
- Web project liaison to UK HealthCare Marketing and Public Relations
- Weekly Markey Research Seminars
- Patient Advisory Group
- Cancer conferences
- Markey Cancer Center Research Day
- Coordination of developmental funds program
- Track, evaluate, and report on pilot awards and funded projects.

RCO PROCESS
Researcher contacts RCO for assistance
RCO Whiteboard meetings assign tasks for individuals and group
RCO works through drafts with researcher
Project completed: Final drafts submitted to funding agency, journal, etc.
Researcher receives Survey to measure RCO service

PROJECTS
4% Abstracts, Books, Dissertations
6% Website, Newsletters
19% Manuscripts
22% Other

2010
2017

26%
Grants & Grant Support
23% Presentations


2018 Trending up

CAMPUS DIVERSITY OF RCO USE

39 UK Departments used RCO services between 2010 – 2017.

RCO RECOGNITION
Markey Difference Maker of the Year 2012 and 2013, Firefiled 2016

Markey Difference Maker of the Year 2012 and 2013, Firefiled 2016

RCO SERVICES
MCC RCO Project Types and Services Offered.

- Grants
  - Ensure all funding organization guidelines are met, review for correct grammar and spelling, check organization, confirm formatting consistency among the various components, including the budget, text and graphics. Complex grants require coordination among several entities with the RCO as a planning hub, providing timelines, organization, centralized communication, and acting as a clearhouse for communication.
- Manuscripts and Book Chapters
  - Review formatting for adherence to publisher guidelines, check for grammar, spelling and consistency, ensure that writing is clear and concise, verify reference style, review graphics for quality, improve or rewrite figures as needed, provide figures in appropriate resolution and file format, submit text and graphics files to the selected journal or publisher, reviews proofs, and collect copyright forms as needed.
- Presentations
  - Assistance with an oral presentation or poster by editing and submitting reference abstract, reviewing preliminary slides or posters, improving figures, condensing text, adding animation where appropriate and ensuring consistent style throughout a slide presentation.
- Internal Communications
  - Writing and distributing the Markey Minute, a weekly newsletter that provides a single, encompassing news source covering a weekly calendar of tumor boards, seminars, symposia, events and news. Writing and distributing the Markey Quarterly, a newsletter that provides a more in-depth exploration of the people and accomplishments at MCC. PDFs copies of the quarterly newsletter archived online.
- Website
  - Maintain and create content for the MCC website and social media. Serve as web project liaison for UK HealthCare Marketing and Public Relations.
- Pre-Award
  - Coordinate submission of information requested by sponsors prior to award, work with researchers to ensure that IRB, IACUC, and biosafety approvals are obtained prior to award, provide revised budget or other information to the UK Office of Sponsored Projects Administration for account establishment.
- Event Planning
  - Coordinate research-related events such as Markey Cancer Research Day, weekly seminars, Grand Rounds and patient-centered education.

LESSONS LEARNED
- Secure critical buy-in from leadership.
- Long-term success of institutional research communication services is dependent on the support of leaders at the highest levels of the organization.
- Use metrics and quality measures to reveal areas of unmet need.
- Emphasize a team-oriented culture.
- Metrics and quality measures provide important insight about services offered, as well as gaps in those offerings.
- Hire staff who excel with individual challenges but also fully embrace highly collaborative environments.

CONCLUSIONS
We have presented an infrastructure that successfully enhances research productivity at our institution. Based on our experiences, we believe the ability to provide research communication services, and to grow and meet identified needs among researchers, is a unique opportunity for other institutions.
Appalachian Kentucky communities experience increased socioeconomic disparities and an undue burden of cancer, particularly malignancies that are preventable and screenable such as lung, colorectal, breast, and cervical cancer. Understanding Appalachian residents' perceptions of cancer is important for designing health communication messaging and educational programming to improve cancer health literacy and decrease related disparities.

Based on these initial results, Appalachian residents commonly reported unfavorable perceptions of and beliefs about cancer that may influence their self-efficacy and locus of control related to behaviors that may help prevent or screen for cancer. Tailored, culturally-appropriate health communication messaging that (1) promotes the power of preventive behaviors (e.g., physical activity, healthy diet, tobacco cessation) and screening exams (e.g., mammography, colonoscopy, low-dose CT scans, Pap testing) to improve cancer outcomes and (2) provides factual information about increasing survival rates for all cancer sites may help to address Appalachian's negative beliefs about cancer.

As part of an administrative supplement from the National Cancer Institute, the University of Kentucky Markey Cancer Center developed and administered a health-related survey – ASK: Assessing the Health Status of Kentucky – during summer 2017 in the 54 counties of eastern Kentucky designated as Appalachian. Survey items assessed a range of topics including: cancer information-seeking, cancer fatalism, cancer knowledge and beliefs, cancer screening and other health behaviors (e.g., tobacco use), and socio-demographics. Data collection methods included a probabilistic address mailing (N=3200) and community-based, in-person administration (N=200). Herein, we report on preliminary findings from the (unweighted) mailed sample (n=786, 25% response rate) as compared to national (unweighted) data from NCI's Health Information National Trends Survey (HINTS) 3 and 4 related to perceptions of and beliefs about cancer.

Compared to national HINTS respondents, Appalachian Kentuckians were more likely to strongly or somewhat agree that:
- “Everything causes cancer” (59% vs. 67%, respectively)
- There’s not much one can do to lower their chances of developing cancer (27% vs. 32%)
- Perceive that there are too many different recommendations about preventing cancer (74% vs. 80%)
- Automatically equate cancer to death (53% vs 71%)
- Would rather not know their chances of developing cancer (31% vs. 38%)

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