Collaborations Between UF and Moffitt (2015-16)

Role of LKB1-CRTC1 on glycosylated COX-2 and response to COX-2 inhibition in lung cancer

A sensitive NanoString-based assay to score STK11 (LKB1) pathway disruption in lung adenocarcinoma.

cAMP/CREB-regulated LINC00473: potential biomarker and therapeutic target for LKB1-inactivated cancer.
Z Chen, J Li, S Lin, C Cao, N Gimbrone, R Yang, A Fu, M Carper, E Haura, M Schabath, J Lu, A Amelio, D Cress, F Kaye, L Wu. Revised manuscript under peer review

Defining the FOXO/CRTC1 signaling pathway in anabolic metabolism, cancer, and aging

Frederic Kaye, MD
UF Division Hematology Oncology

Rui Xiao, PhD
UF Department of Aging and Geriatric Research
Lifespan is related to health span and this relationship has an important biological message

Several lines of data show that the genetic contribution to human lifespan is most noticeable at the highest median lifespan ages
Age related disability and morbidity occurs in the last 20% of the lives of control subjects, but is compressed to last 5% of supercentenarians. GWAS analysis suggests SNPs at APOE and FOXO1/3 genes.
Figure 1. The Hallmarks of Aging
The scheme enumerates the nine hallmarks described in this review: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication.
LETTERS TO NATURE

A C. elegans mutant that lives twice as long as wild type

Cynthia Kenyon, Jean Chang, Erlin Gensch, Adam Rudner & Ramon Tabtiang

Department of Biochemistry and Biophysics, University of California at San Francisco, San Francisco, California 94143–0554, USA

We have found that mutations in the gene daf-2 can cause fertile, active, adult Caenorhabditis elegans hermaphrodites to live more than twice as long as wild type. This lifespan extension, the largest yet reported in any organism\(^1\), requires the activity of a second gene, daf-16. Both genes also regulate formation of the dauer larva, a developmentally arrested larval form that is induced by crowding and starvation and is very long-lived\(^2-4\). Our findings raise the possibility that the longevity of the dauer is not simply a consequence of its arrested growth, but instead results from a regulated lifespan extension mechanism that can be uncoupled from other aspects of dauer formation. daf-2 and daf-16 provide entry points into understanding how lifespan can be extended.
Defining the FOXO/CRTC1 signaling pathway in anabolic metabolism, cancer, and aging

Frederic Kaye, MD
UF Division Hematology Oncology

Rui Xiao, PhD
UF Department of Aging and Geriatric Research
Study of young patients with lung cancer

mapping a t(11;19) breakpoint in a 35 yo pt with adeno-squamous lung cancer
Cloning the t(11;19) breakpoint

11q21 breakpoint

Maml2

1 2 3 4 5 6 7 8 9 10 11 12 13

Maml2: homolog for an essential NOTCH co-activator

19p13 breakpoint

Crtc1

1 2 3 4 5 6 7 8 9 10 11 12 13

Crtc1: aka Mect1/Torc1 unknown function

Crtc1-Maml2 detected
In primary tumors and cell lines

Maml2 intron1 276 kb exons 2-5

Crtc1 intron1 60 kb exons 2-18

Crtc1: exon 1 42 aa
Maml2: exons 2-5 981 aa

MEC

H292 H3118 MEC#A H727 H2009 M H292 MEC#B MEC#C

(-) (-)

600 bp- 194 bp-
CRTCs are essential CREB co-activator for gluconeogenesis program

CRTC phosphorylation regulated by calcium flux and signaling through AMPK/SIK kinases

The Kinase LKB1 Mediates Glucose Homeostasis in Liver and Therapeutic Effects of Metformin

Reuben J. Shaw,1,2* Katja A. Lamia,1,2 Debbie Vasquez,2 Seung-Hoi Koo,3,4 Nabeel Bardeesy,5 Ronald A. DePinho,6 Marc Montminy,3 Lewis C. Cantley1,2
• Crtc2 integrates signals to regulate anabolic metabolism

• Crtc1: bona fide cancer gene when activated by t(11;19)

• Crtc1 may participate in tumorigenesis when aberrantly activated by loss of LKB1

LKB1/AMPK signaling inhibit Crtc2 transcriptional activity
AMPK pathway senses ATP depletion

- Protein synthesis
- Glycogen synthesis
- Gluconeogenesis
- Fatty acid/cholesterol synthesis
- Glucose uptake
- Glycolysis
- Fatty acid oxidation
- Mitochondrial biogenesis
AMPK pathway senses ATP depletion
Lifespan extension induced by AMPK and calcineurin is mediated by CRTC-1 and CREB

William Mair\textsuperscript{1,2,3}, Janessa Morant\textsuperscript{e,2,3}, Ana P. C. Rodrigues\textsuperscript{1,4}, Gerard Manning\textsuperscript{1,4}, Marc Montminy\textsuperscript{1,3}, Reuben J. Shaw\textsuperscript{1,2,3} & Andrew Dillin\textsuperscript{1,2,3}
Gene targets for mutations in sporadic lung adenocarcinoma

Figure 1: Significantly mutated genes in lung adenocarcinomas. The height of the bars represents the number of somatic mutations in each indicated gene in 188 tumour and normal pairs. Standard, gene-specific and
STK11/LKB1 target for mutations in sporadic lung cancer

Figure 1 | Significantly mutated genes in lung adenocarcinomas. The height of the bars represents the number of somatic mutations in each indicated gene in 188 tumour and normal pairs. Standard, gene-specific and

Nature. 2008 Oct 23;455(7216):1069-75
<table>
<thead>
<tr>
<th>Organism</th>
<th>Hydra</th>
<th>C. elegans</th>
<th>Drosophila</th>
<th>Mammals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ligands</strong></td>
<td>HILPs</td>
<td>ILPs</td>
<td>DILPs</td>
<td>Insulin</td>
</tr>
<tr>
<td><strong>Receptors</strong></td>
<td>HTK7</td>
<td>DAF-2</td>
<td>dInR</td>
<td>InR</td>
</tr>
<tr>
<td><strong>Signal Transduction</strong></td>
<td>IRS</td>
<td>IST-1</td>
<td>chico</td>
<td>IRS</td>
</tr>
<tr>
<td></td>
<td>PI3K</td>
<td>AGE-1</td>
<td>dPI3K</td>
<td>PI3K</td>
</tr>
<tr>
<td></td>
<td>PTEN</td>
<td>DAF-18</td>
<td>dPTEN</td>
<td>PTEN</td>
</tr>
<tr>
<td></td>
<td>PDK</td>
<td>PDK-1</td>
<td>dPDK-1</td>
<td>PDK-1</td>
</tr>
<tr>
<td></td>
<td>AKT</td>
<td>AKT</td>
<td>AKT</td>
<td>AKT</td>
</tr>
<tr>
<td><strong>Transcription factors</strong></td>
<td>FOXO</td>
<td>DAF-16</td>
<td>dFoxO</td>
<td>Foxo</td>
</tr>
</tbody>
</table>
LKB1 links the AMPK pathway to cancer

LKB1

Metformin

AMPK/SIK

Crtc

• glucose/fatty acid metabolism
• aging
• cancer
Frederic Kaye, MD
Chunxia Cao, PhD
Min Zhang
UF Division Hematology Oncology

Rui Xiao, PhD
Lanlan Tang, PhD
UF Department of Aging and Geriatric Research

Lizi Wu, PhD
Zirong Chen
UF Department of Molecular Genetics and Microbiology

Supported by 2016
UF Health Cancer Center/UF Institute on Aging
Cancer-Aging Collaborative Team Grant application