BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Stephen D. Hursting, PhD, MPH	Professor, Dept. of Nutrition, Nutrition Research Institute, and the Lineberger Cancer Center University of North Carolina at Chapel Hill
eRA COMMONS USER NAME (credential, e.g., agency login) SHURSTING	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Earlham College, Richmond, IN	BA	1980	Biology
University of North Carolina, Chapel Hill, NC	MPH	1984	Nutritional Epidemiology
University of North Carolina, Chapel Hill, NC	PhD	1992	Nutritional Biochemistry
National Cancer Institute, Bethesda, MD	Postdoctoral	1992-94	Molec. Carcinogenesis

A. Personal Statement

Dr. Hursting is Professor in the Department of Nutrition, the Nutrition Research Institute, and the Lineberger Comprehensive Cancer Center at the University of North Carolina at Chapel Hill. An international leader in the area of nutrition, metabolism and cancer, his lab is currently focused on the molecular and metabolic mechanisms underlying obesity-cancer associations, and the impact of obesity, energy balance modulation (eg, calorie restriction and exercise) or pharmacologic agents on cancer development, progression, and responses to chemotherapy. Primarily using genetically engineered mouse models of breast cancer (recently in parallel with several clinical trials), colon cancer and pancreatic cancer, Dr. Hursting has identified the IGF-1/Akt/mTOR and NF-kB signaling pathways as key targets for breaking the obesity-cancer link. His publications establishing causal links between obesity, cancer and several systemic factors (including IGF-1, insulin, leptin and IL-6) and components of their downstream signaling pathways (including mTOR and NF-κB), and his review articles updating and synthesizing the area of systemic factors (and their underlying metabolic and molecular mechanisms) linking obesity and several cancers, have reframed the discussion about ways to approach breaking the obesity-cancer link. Specifically, his publications and review articles shifted the focus in the field from adiposity *per se* to the metabolic perturbations typically accompanying obesity (starting with his 2003 *Annual Review of Medicine* article and extending to his *JCO* review in 2010, *Cancer Prevention Research* review in 2012, *J Mammary Gland Biology and Neoplasia* article in 2013, and *Clinical Pharmacology and Therapeutics* review in 2014). He has also established in several preclinical models of breast, pancreatic and colon cancer that obesity impacts the metastatic process and the response to various forms of chemotherapy. This proposal takes an integrated approach that leverages: a) strong preliminary data, research tools, and the unparalleled resources and infrastructure at the University of North Carolina; b) Dr. Hursting's >20 highly productive years of experience in the obesity, metabolism and breast cancer field; and c) Dr. Sergey Krupenko's outstanding research program focused on folate-related nutrient stress to efficiently identify and validate key molecular or metabolic targets that will lead to new, effective mechanism-based interventions to reduce the impact of obesity and/or excess folate intake on breast cancer burden.

Hursting SD, Lavigne JA, Berrigan DA, Perkins SN, Barrett JC. Calorie restriction, aging and cancer prevention: mechanisms of action and applicability to humans. *Annu Rev Med* 2003; 54:131-52.

Hursting SD, Berger N. Energy balance, host-related factors and cancer progression. *J Clin Oncol* 2010; 28:4058-65. PMC2982796.

Hursting SD, DiGiovanni J, Dannenberg AJ, Azrad M, LeRoith D, Demark-Wahnefried W, Kakarala M, Brodie A, Berger NA. Obesity, energy balance and cancer: new opportunities for prevention. *Cancer Prev Res* 2012; 5:1260-72. PMC3641761.

Ford NA, Devlin KA, Lashinger LM, Hursting SD. Deconvoluting the obesity and breast cancer link: secretome, soil and seed interactions. *J Mammary Gland Biol Neoplasia* 2013;18:267-75. PMC3874287.

Lashinger LM, Rossi EL, Hursting SD. Obesity and resistance to chemotherapy: interacting roles of inflammation and metabloi dysregulation. *Clin Pharmacol Ther* 2014; 96:458-63.

B. Positions and Honors

Positions Held

1985-1987	Research Assistant, Cancer Prevention Research Program, Fred Hutchinson Cancer Research Center, Seattle, WA
1989-1990	Graduate Teaching Assistant, Dept. of Nutrition, University of NC, Chapel Hill, NC
1990-1992	Biologist, National Institute of Environmental Health Sciences, Research Triangle Park, NC
1992-1994	Cancer Prevention Fellow, National Cancer Institute, NIH, Bethesda, MD
1994-1995	Senior Staff Fellow, National Cancer Institute, NIH, Bethesda, MD
1995-1999	Assistant Professor, Departments of Epidemiology and Carcinogenesis, UT MD Anderson Cancer Center, Houston, TX
1999-2005	Deputy Director, Office of Preventive Oncology, National Cancer Institute, Bethesda, MD
1999-2005	Chief, Nutrition and Molecular Carcinogenesis Section, NCI, Bethesda, MD
2005-2014	Professor, Department Chair, and McKean-Love Chair of Nutritional, Molecular and Cellular Sciences, Department of Nutritional Sciences, University of Texas, Austin, TX
2005-2014	Professor, Department of Molecular Carcinogenesis, University of Texas MD Anderson Cancer Center, Science Park-Research Division, Smithville, TX
2014-	Professor, Department of Nutrition, the Nutrition Research Institute, and the Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill

Awards and Honors

- University of Texas College of Natural Sciences Award for Outstanding Service (2014)
- NCI Cancer Prevention Fellowship Program Distinguished Alumni Award (2012)
- Russ Kline Memorial Lectureship, Ohio State Univ. (2011)
- Merit Award for Academic Excellence, Univ. of Texas-Austin (2010)
- NCI Group Merit Award for Excellence in Research on Serum Biomarkers (2009)
- Malcolm Trout Nutritional Science Award, Michigan State Univ. (2007)
- NCI Group Merit Award for Leadership/Excellence in Obesity & Cancer Research (2005)
- Jean Andrews Visiting Professorship Award, Univ. of Texas-Austin (2004)
- NCI Group Merit Award for Leadership/Excellence in Cancer Training & Research (2004)
- Ruth Pike Outstanding Contributions to Nutrition Research Award, Penn State Univ. (2003)
- NCI Mentor of Merit Award (2002)
- American Society of Nutritional Sciences/FASEB BioServ Research Award (2002)
- Outstanding Alumni Award, Department of Nutrition, Univ. of North Carolina (2001)
- Procter and Gamble Graduate Research Award, American Institute of Nutrition (1992)

Advisory Committee Membership

- National Cancer Institute Board of Scientific Counselors (2012-)
- American Cancer Society Council for Extramural Grants (2014-)
- American Institute for Cancer Research/World Cancer Res. Fund Expert Panel (2004-)
- NIH Chemo/Dietary Prevention Study Section (ad hoc, 2008-2014; member 2014-)

C. Contributions to Science

1. First to show that lifestyle factors impact genetically driven cancer using genetically engineered mouse models.. This work began when many new oncogenes or tumor suppressor genes were being discovered, and there was a sense in the cancer field that once mutations occurred in key genes such as p53, and cells accumulated enough of these genetic alterations, cancer was inevitable and lifestyle would have little impact. Our 1994 PNAS[a], 1995 and 1997 Cancer Res[b,c,] and 2002 Carcinogenesis[d] papers showed that maintaining a lean phenotype (by various interventions) in p53-null and p53-heterozygote mice (relative to an ad libitum-fed control diet, which resulted in overweight mice) delayed spontaneous tumor development, demonstrating that even though cancer is a genetic disease, lifestyle factors such as diet and exercise still could effect the outcome, and this stimulated further research on diet-gene interactions in cancer prevention.

a. Hursting SD, Perkins SN, Phang JM. Calorie restriction delays spontaneous tumorigenesis in p53-knockout mice. *Proc Natl Acad Sci USA* 1994; 91:7036-40. PMC44333.

b. Hursting SD, Perkins SN, Haines DC, Ward JM, Phang JM. Chemoprevention of spontaneous tumorigenesis in p53-knockout mice. *Cancer Res* 1995; 55:3949-53.

c. Hursting SD, Perkins SN, Brown C, Haines DN, Phang JM. Calorie restriction induces a p53-independent delay of spontaneous tumorigenesis in p53-deficient and wild-type mice. *Cancer Res* 1997; 57:2843-6.

d. Berrigan DA, Perkins SN, Haines DC, Hursting SD. Adult-onset calorie restriction and fasting delay spontaneous tumorigenesis in p53-deficient mice. *Carcinogenesis* 2002; 23:817-22.

2. Established that remaining lean, via calorie restriction and/or treadmill exercise, protected against cancer through distinct (but complementary) mechanisms. We showed that obesity prevention through low-calorie diets and/or exercise was protective against several cancers in genetically engineered mouse models (GEMMs), but through distinct mechanisms [e,f]; the calorie-restricted diet decreased circulating IGF-1 and cell proliferation, and also shifted the microbiome[g] (all in a p53-independent fashion), while exercise (treadmill or running wheel) impacted inflammation (but not IGF-1) and tumorigenesis in a p53-dependent manner[h].

e. Colbert LH, Mai V, Perkins SN, Berrigan D, Lavigne JA, Wimbrow HH, Alvord WG, Haines DC, Srinivas P, Hursting SD. Exercise and intestinal polyp development in APC^{Min} mice. *Med Sci Sports Exerc* 2003; 35:1662-9.

f. Mai V, Colbert LH, Berrigan D, Perkins SN, Pfeiffer R, Lavigne JA, Lanza E, Haines DC, Schatzkin A, Hursting SD. Calorie restriction and diet composition modulate spontaneous intestinal tumorigenesis in APC^{Min} mice through different mechanisms. *Cancer Res* 2003; 63:1752-55.

g. Mai V, Colbert LH, Perkins SN, Schatzkin A, Hursting SD. Intestinal microbiota: a potential diet-responsive prevention target in Apc(Min) mice. *Mol Carcinog* 2007; 46:42-8.

h. Colbert LH, Westerlind KC, Perkins SN, Haines DC, Berrigan D, Donehower LA, Fuchs-Young R, Hursting SD. Exercise effects on tumorigenesis in a p53-deficient mouse model of breast cancer. *Med Sci Sports Exerc* 2009; 41:1597-605. PMC3040490.

3. Established causal relationships between energy balance modulation, the IGF-1/Akt/mTOR pathway, and several cancers, and showed that inhibiting this pathway offsets the effects of obesity independent of weight or adiposity. We showed in multiple tumor models (and normal tissues) that obesity increased (and calorie restriction decreased) insulin and bioavailable IGF-1 levels and phosphorylation of every step along the Akt/mTOR pathway[i]. A-Zip/F1 fatless mice, which lack white adipose tissue but have elevated insulin, IGF-1 and tissue mTOR signaling, mimicked obese mice despite having no white adipose tissue[j]. Liver-specific IGF-deficient mice mimicked calorie restricted mice in terms of IGF-1, signaling through the Akt/mTOR pathway, and tumor development[k]. Rapamycin and metformin reverses mTOR pathway activation in obese mice and block the effects of obesity on tumor development. These findings helped to shift the focus in the field away from adiposity *per se* to a focus on obesity-associated metabolic perturbations (such as mTOR activation)[l].

i. Moore T, Beltran LD, Carbajal S, Hursting SD, DiGiovanni J. Energy balance modulates tumor promotion through altered IGF-1R and EGFR crosstalk. *Cancer Prev Res* 2012; 5:1236-46. PMC3482456.

j. Nunez NP, Oh WJ, Rozenberg J, Perella C, Anver M, Barrett JC, Perkins SN, Berrigan D, Moitra J, Varticovski L, Hursting SD, Vinson C. Accelerated tumor formation in a fatless mouse with type 2 diabetes and inflammation. *Cancer Res* 2006; 66:5469-76

k. Lashinger LM, Malone LM, Brown GW, Daniels EA, Goldberg JA, Otto G, Fischer SM, Hursting SD. Rapamycin partially mimics the anticancer effects of calorie restriction in a murine model of pancreatic cancer. *Cancer Prev Res* 2011; 4:1041-51. PMC3131470.

l. Checkley LA, Rho O, Angel JM, Cho J, Blando J, Beltran L, Hursting SD, DiGiovanni J. Metformin inhibits skin tumor promotion in overweight and obese mice. *Cancer Prev Res* 2014; 7:54-64. PMC3918668.

4. Established that obesity promotes, and calorie restriction inhibits, epithelial-to-mesenchymal transition (EMT) and mammary tumor progression in models of basal-like and claudin-low breast cancer in association with alterations in circulating insulin, leptin and IGF-1, and downstream signals through the Akt and mTOR pathways[m,n]. In human-mouse co-trials, we observed concordant effects of calorie restriction on serum and tissue (fine needle aspirate samples) insulin, leptin and IGF-1 as well as signaling through the mTOR pathway[o], and are extending these translational studies to anti-inflammatory agents including NSAIDs and omega-3 fatty acids[p,q]. The energy balance effects on EMT and other metastases-related processes appear to involve epigenetic reprogramming of numerous genes, including histone modifications and gene body methylation changes in slug, snail, TGF-β and E-cadherin; altered gene body methylation of ER-α and ER-β, and changes in the levels of numerous oncogenic or metabolism-regulating microRNAs due to energy balance-

dependent effects on the microRNA processing enzyme dicer.

m. Dunlap SM, Chiao LJ, Nogueira L, Usary J, Perou CM, Varticovski L, Hursting SD. Dietary energy balance modulates epithelial-to-mesenchymal transition and tumor progression in murine claudin-low and basal-like mammary tumor models. *Cancer Prev Res* 2012; 5:930-42. PMC3822442.
n. Zhang Q, Hursting SD, Reizes O. Leptin regulates cyclin D1 in luminal epithelial cells of mouse Wnt-1 mammary tumors. *J Cancer Res Clin Oncol* 2012; 138:1607-12. PMC3520612.
o. Fabian CJ, Kimler BF, Phillips TA, Donnelly JE, Sullivan DK, Petroff BK, Zalles CM, Matheny T, Aversman S, Klemp JR, Mills GB, Yeh H, Hursting SD. Favorable modulation of benign breast tissue and serum risk biomarkers is associated with >10% weight loss in postmenopausal women. *Breast Cancer Res* 2013; 114:119-32. PMC3921968.
p. Bowers LW, Cavazos Maximo IX, Brenner AJ, Beeram M, Hursting SD, Price RS, Tekmal RR, Jolly CA, deGraffenried LA. NSAID use reduces breast cancer recurrence in overweight and obese women: role of prostaglandin-aromatase interactions. *Cancer Res* 2014; 74:4446-57. PMC Journal-in process
q. Fabian CJ, Kimler BF, Hursting SD. Omega-3 fatty acids for breast cancer prevention and survivorship. *Breast Cancer Res* 2015; epub ahead of print. PMC Journal-in process.

5. Developed pancreatic cancer models and showed energy balance modulation impacts pancreatic cancer in an IGF-1-dependent manner. We started an initiative on obesity, pancreatitis, and pancreatic ductal adenocarcinoma (PDAC) in response to emerging epidemiologic data showing the importance of obesity as one of the few modulatable risk factors for PDAC. Pancreatic tumor development in most existing animal models occurs too early in life to adequately test the effects of energy balance modulation on tumorigenesis, so we developed, characterized and used new GEMMs and orthotopic transplant models of pancreatitis and PDAC. Most notably we generated and characterized a murine Kras Ink4A$^{+/-}$ model of spontaneous PDAC that closely reflects human PDAC (Kras mutations occur in over 90% of human PDAC, often in association with loss of Ink4A). These mice develop pancreatic intraepithelial neoplasia lesions that progress (~100%) to PDAC by 25 weeks of age, making the mice amenable to energy balance interventions prior to PDAC development. Using our PDAC models, we found that obesity enhances (and calorie restriction decreases) the development, progression, and response to chemotherapy (specifically gemcitabine) of PDAC in association with alterations in circulating insulin and IGF-1, and their downstream signals through the Akt and mTOR pathways[r]. Insulin and IGF-1 are also involved in regulating the NF-kB pathway, and hence inflammatory cytokine levels, in PDAC[s]. Moreover, we showed that rapamycin and metformin suppress PDAC development through both shared (mTOR inhibition) and distinct mechanisms[t]. Given the role of mTOR activation in the obesity-PDAC link, we became concerned with reports of PDAC patients increasingly using branched chain amino supplementation (particularly leucine) to prevent muscle wasting during the early stages of cancer cachexia. Leucine promotes skeletal muscle regeneration through activation of mTOR signaling, and we hypothesized that leucine supplementation could also activate mTOR signaling in the pancreatic cancer cells and accelerate tumor growth. We reported that leucine supplementation, while effective at protecting against cachexia-induced loss of muscle mass, accelerates pancreatic tumor growth in vitro and in vivo in association with increased mTOR and NF-kB signaling[u]. This important cautionary tale has stimulated additional research in this area, and there is growing support that higher levels of branched chain amino acids, like leucine, increase PDAC risk.

r. Lashinger LM, Harrison LM, Rasmussen AJ, Logsdon CD, Fischer SM, McArthur MJ, Hursting SD. Dietary energy balance modulation of Kras- and Ink4A/Arf$^{+/-}$-driven pancreatic cancer: the role of insulin-like growth factor-1. *Cancer Prev Res* 2013; 6:1046-55. PMC3874288.
s. Lashinger L, Harvey A, Hays D, Harrison LM, Lewis K, Otto G, Fischer SM, Hursting SD. Calorie restriction decreases murine and human pancreatic tumor growth, nuclear factor-κB and inflammatory gene expression in an insulin-like growth factor-1–dependent manner. *Plos One* 2014; 9(5):e94151. doi: 10.1371/journal.pone.0094151. PMC4013119.
t. Ciffarrelli V, Lashinger LM, Devlin K, Dunlap SM, Huang J, Kaaks R, Pollak M, Hursting SD. Metformin and rapamycin inhibit pancreatic tumor growth and progression in obese diabetic mice by distinct microRNA-regulated mechanisms. *Diabetes* 2015; epub ahead of print. PMC Journal-in process.
u. Liu K, Lashinger LM, McArthur MJ, Fischer SM, Hursting SD. Leucine supplementation differentially enhances pancreatic cancer growth in lean and overweight mice. *Cancer Metab* 2014, 2(1):6. doi: 10.1186/2049-3002-2-6. PMC Journal-in process.

Full list of publications available at http://www.ncbi.nlm.nih.gov/pubmed/?term=hursting+S

D. Research Support

Ongoing Research Support

5R01CA135274 Cui (PI) 04/01/13-03/30/18
Overcoming gemcitabine resistance in pancreatic cancer.
Aims are to test nanoparticle-based approaches to overcome resistance mechanisms in normoweight and obese Kras/Ink4a mice, a model of pancreatic ductal adenocarcinoma. Role: Co-I

BCRF-2014-15 Hursting (PI) 10/01/2014-09/30/2015
Breast Cancer Research Foundation Grant: Obesity and Breast Cancer: Epigenetic Targets
Aims are to determine the effects of obesity (with and without omega-3 fatty acid supplementation) on mammary tumor development, DNA methylation and histone modifications in mouse models of basal-like, luminal-type and claudin-low breast cancer. Role: PI

SGK-10-001037 Fabian/Hursting (Dual PIs) 05/01/10-04/30/15
Susan Komen for the Cure Prevention Promise Grant: Flaxseed Lignan as a Preventive Strategy for Premenopausal Women at High Risk for Development of Breast Cancer
Primary aim is to conduct a multi-institutional placebo controlled trial of secoisolariciresinol diglycoside (SDG) commercially available as (Brevail®) in premenopausal women at increased risk of breast cancer, with mechanistically focused co-trials in multiple mouse models of mammary cancer. Role: Co-PI

KUMC Program Project Pilot Award Fabian and Hursting (Dual-PI's) 01/01/14-12/31/15
Combined Weight Loss and Omega-3 Fatty Acids for Breast Cancer Prevention
Primary aim is to generate preliminary preclinical data on the effects of weight loss combined with n-3 fatty acid supplementation in mouse models of obesity and basal-like breast cancer. This work provides the foundation for a P01 submission in 2015 linking preclinical and clinical studies of combination weight loss and n-3 fatty acid interventions in obese women and mice. Role: Dual PI (with Dr. Carol Fabian, Kansas Univ. Cancer Ctr)

UNC Nutrition Research Institute Collaborative Grant. Hursting and Krupenko (Dual-PI's) 01/01/15-6/1/15
Dietary Regulation of EMT and mTOR in Breast Cancer
The aim is to test if obesity and high dietary folate cooperate to reprogram metabolism and promote several hallmarks of mammary cancer. Role: Dual-PI (with Dr. Sergey Krupenko, UNC Nutrition Research Institute)

UNC President's Faculty Recruitment and Retention Fund Hursting, PI 06/01/14-
Salary support (33%) to develop a nutrition and cancer prevention research program linking the UNC Department of Nutrition, the UNC Lineberger Comprehensive Cancer Center, and the UNC Nutrition Research Institute.

Completed Research Support (past 3 years)

National Institutes of Health, National Cancer Institute. R01: Akt/mTOR Signaling in Energy Balance Modulation of Epithelial Carcinogenesis. Aims were to determine the impact of energy balance manipulation on skin tumor promotion and cell signaling pathways in wild-type and liver IGF-1 deficient mice and to determine the role of the Akt/mTOR pathway. Role: PI. 4/1/09-8/30/14.

National Institutes of Health, National Cancer Institute. R01: Obesity and Pancreatic Cancer: The Role of IGF-1. Aims were to determine the impact of energy balance manipulation on pancreatic cancer development in a K5.COX-2 transgenic mouse model of pancreatitis-driven pancreatic cancer (with and without IGF-1 deficiency) and to determine the role of the IGF-1/Akt/mTOR pathway in proliferation and inflammation. Role: Dual-PI (with Dr. Susan Fischer, UT-MD Anderson Cancer Center). 4/1/09-8/30/14.

Breast Cancer Research Foundation Grant: Obesity Effects on Mammary Cancer Risk and Therapeutic Response. Aims were to determine the effect of obesity on cell signaling and the response to anticancer agents in mouse models of basal-like, luminal-type and claudin-low breast cancer. Role: PI. 10/1/11-9/30/14.

National Institutes of Health, National Institute of Environmental Health Sciences, R21 grant: Environmental Estrogens and Uterine Leiomyoma. Aims were to test the ability of calorie restriction and/or exercise to offset the effects of bisphenol A and other environmental estrogens on uterine leiomyoma development in the Eker rat. Role: Dual PI (with Dr. Cheryl Walker, Texas A and M University). 7/01/11-6/30/13.