BIOGRAPHICAL SKETCH

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

NAME: Smart, Robert C.

eRA COMMONS USER NAME (credential, e.g., agency login): RCSMART

POSITION TITLE: Goodnight Distinguished Chair in Molecular Toxicology

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Massachusetts at Dartmouth, North Dartmouth, MA	BS	05/1978	Biology
University of Michigan, Ann Arbor, MI	PhD	06/1984	Toxicology
Roche Institute of Molecular Biology, Nutley, NJ	Post-doc	09/1986	Molecular Oncology

A. Personal Statement

My interests include keratinocyte, skin biology and skin cancer and focuses on the identification and characterization of genes/signaling pathways that are determinants of cancer, particularly as it relates to gene-environment interactions and apoptosis. We utilize genomic/genetic/molecular/cellular-based systems and powerful genetically engineered mouse models to define mechanisms through which environmental stressors induce skin cancer. We are especially interested in how cells respond to DNA damage and tumor stress to make decisions to live or die via regulated cell death. These decisions and the ability to influence these programmed cell death decisions have important implications for tumor development and tumor regression. We are currently studying the roles of the basic leucine zipper transcription factors, CCAAT/enhancer binding proteins (C/EBPs), Nrf2 and long noncoding RNAs in skin cancer and regulated cell death.

B. Positions, Scientific Appointments and Honors

Employment/Experience

2019-	Goodnight Distinguished Chair in Molecular Toxicology, College of Sciences, NCSU
2012-2019	WNR Distinguished Professor, Department of Biological Sciences, College of Sciences, NCSU
2010-2022	Director, Center for Human Health and the Environment, NCSU
2005-2013	Director of Graduate Program, Department of Environmental and Molecular Toxicology, NCSU
2001-2021	Director, NIEHS Training Program/Grant in Molecular Pathways to Pathogenesis, NCSU
2000-	Member of Genomic Sciences Graduate Program, NCSU
1997-2012	Professor, Department of Environmental and Molecular Toxicology, NCSU
1996-2012	Director of Molecular and Cellular Toxicology Graduate Study Option, NCSU
1996-	Associate Faculty Member, Comparative Biomedical Sciences, College of Veterinary Medicine, NCSU
1991-1997	Associate Professor, Department of Toxicology, NCSU
1989-1993	Director, NIEHS Training Program/Grant in Environmental and Biochemical Toxicology
1986-1991	Assistant Professor, Department of Toxicology, North Carolina State University, Raleigh, NC (NCSU)
1984-1986	Postdoctoral Fellow, Department of Molecular Oncology, Laboratory of Experimental Carcinogenesis and Metabolism, Roche Institute of Molecular Biology, Nutley, NJ

Honors

2019	Goodnight Distinguished Chair in Molecular Toxicology

2018 Elected Chair, NCSU Research Leadership Academy
2017 Alumni Association Outstanding Research Award
2017 Elected to NCSU Research Leadership Academy
2012 William Neal Reynolds Distinguished Professor

Scientific Service Appointment

2019 NCI, Onsite Review of NCI Laboratory of Cancer Biology and Genetics, Member of review team
2018 NIEHS, Environmental Health Science Review Committee, Ad Hoc Member
2016 NIEHS, Special Emphasis Panel for R25 applications, Chair
2016 NIEHS, Board of Scientific Councilors, Ad Hoc Member, Intramural Program Review
2015 NIH Systemic Injury by Environmental Exposure (SIEE) Special Emphasis Panel, Ad hoc Member
2012 NIEHS K awards Panel
2011 National Toxicology Program Technical Reports Review Panel
2010 NIH, Special Emphasis Panel
2009 NIEHS R13 Review Panel
2009 NIH, RC1 grant reviews
2009 NIEHS – Tenure and Promotion Committee, Ad Hoc Member
2003-2007 NIEHS, Environmental Health Science Review Committee, Member
2002 NIEHS, Tenure and Promotion Committee, Ad Hoc Member
2001 NIEHS Special Emphasis Panel, Review of Program Project Grant Application, *Ad hoc* member
2001 CIIT Centers for Health Research, Scientific Advisory Committee, *Ad hoc* member
2000 NCI, Laboratory of Cellular Carcinogenesis and Tumor Promotion, Reviewer of Intramural Program and Member of Site Visit Team
1999 NIAMS *Ad hoc* Reviewer
1997 NIEHS, Training Grant and Conference Grant Review
1997 NIEHS, SBIR-Phase 1
1997 NIEHS, RFP Review
1995 American Cancer Society, *Ad hoc* reviewer
1994 NIEHS, *Ad hoc* Reviewer
1992 NIEHS, SBIR-Phase 1 and 2
1992 NIEHS, RFP Review - Chairman
1991 NIEHS, Sixth Annual Report on Carcinogens
1991 NIEHS, SBIR-Phase 1
1990 NIEHS, Special Study Section, Training Grant Supplements
1990 NIEHS, RFP Review

C. Contributions to Science

1. Elucidation of Novel Roles for C/EBPs in Epidermal Homeostasis

The basic leucine zipper transcription factors, CCAAT/enhancer binding proteins (C/EBPs) were discovered in the 1990s and several members of the family were shown to be important in regulating pre-adipocyte differentiation. Beginning in the 1990's we discovered that two members of the C/EBP family, C/EBPα and C/EBPβ were highly expressed in keratinocytes and we began studies to understand their function in the skin. Surprisingly, the deletion of either C/EBPα or C/EBPβ in skin specific knockout mice had little effect in the epidermis/skin. However, acute co-deletion of C/EBPα and C/EBPβ in adult mouse skin completely disrupted stratified squamous differentiation and blocked sebocyte differentiation in skin sebaceous glands and in specialized sebocytes of Meibomian glands of the eye. Our results indicated functional redundancies exist between C/EBPα and C/EBPβ and that they are critically involved in regulating sebocyte differentiation and epidermal homeostasis involving the basal to spinous keratinocyte transition and basal keratinocyte cell cycle withdrawal. We recently observed that the deletion of C/EBPβ in epidermis unleashes cooperative crosstalk involving p53 and Type 1 IFN response networks to activate extrinsic apoptosis and antiviral responses in keratinocytes in response DNA damage. Collectively the above findings have important implications for understanding epidermal homeostasis and cutaneous diseases. I served as the PI on all of these studies.

a. Oh H-S, **Smart RC**. Expression of CCAAT/enhancer binding proteins (C/EBP) is associated with squamous differentiation in epidermis and isolated primary keratinocytes and is altered in skin neoplasia. *J. Invest. Dermatol.* 110:101-107 (1998) PMID 9620302

b. Zhu S, Oh H-S, Shim M, Sterneck E, Johnson PF, **Smart RC**. C/EBPβ modulates the early events of keratinocyte differentiation involving growth arrest, keratin 1 and keratin 10 expression. *Mol. Cell. Biol.* 19:7181-7190 (1999) PMID 10490653
c. House JS, Zhu S, Ranjan R, Linder K, **Smart RC**. C/EBPα and C/EBPβ are required for sebocyte differentiation and stratified squamous differentiation in adult mouse skin. *PloS ONE* 5:9837 (2010) PMID 20352127
d. Tam HW, Hall JR, Messenger ZJ, Jima DD, House JS, Linder, Smart RC. C/EBPβ suppresses keratinocytes autonomous Type 1 IFN response and p53 to increase cell survival and susceptibility to UVB-induced skin cancer. *Carcinogenesis* 40:1099-1109 (2019) PMID 30698678

2. Discovery that C/EBPβ Functions in p53-mediated Apoptosis and Ras-Induced Tumorigenesis

While functional redundancies exist between C/EBPα and C/EBPβ, we identified novel critical functions that are specific to each family member. We discovered that C/EBPβ suppresses p53 function to inhibit apoptosis downstream of oncogenic Ras and DNA damage. Deletion of C/EBPβ in epidermal keratinocytes enhanced p53's pro-apoptotic function and prevented chemical carcinogen- and oncogenic Ras-induced skin tumorigenesis. Our current studies indicate C/EBPβ is required for Ras tumor survival and maintenance. Collectively, these studies suggest that targeting the deletion or inhibition of C/EBPβ could represent a potential future cancer therapy. I served as the PI on all of these studies.

a. Zhu S, Yoon K, Sterneck E, Johnson PF, **Smart RC**. CCAAT/enhancer binding protein-β (C/EBPβ) is a mediator of keratinocyte survival and skin tumorigenesis involving oncogenic Ras signaling. *Proc. Natl. Acad. Sci. USA* 99:207-212 (2002) PMID 11756662
b. Yoon KS, Zhu S, Ewing SJ, **Smart RC**. Decreased survival of C/EBPβ-deficient keratinocytes is due to aberrant regulation of p53 levels and function. *Oncogene* 26(3):360-367 (2007) PMID 16832342
c. Ewing SJ, Zhu S, Zhu F, House JS, **Smart RC**. C/EBPβ represses p53 to promote cell survival downstream of DNA damage independent of oncogenic Ras and p19Arf. *Cell Death and Diff* 15:1734-1744 (2008) PMID 1863607
d. Messenger ZJ, Hall JR, Jima D, House JS, Hann HW, Tokarz DA and **Smart RC**. C/EBPβ deletion in oncogenic Ras skin tumors is a synthetic lethal event. Cell Death and Dis 9:1054-1070 (2018) PMID 30323292

3. Identification that C/EBPα Functions in DDR, G_1/S Checkpoint and Skin Cancer

With respect to unique functions of C/EBPα, we discovered a new role of C/EBPα in the DNA damage-induced G_1/S checkpoint and we were the first to show C/EBPα functions as a tumor suppressor of epithelial cancer in a genetically engineered mouse model. We have gone on to demonstrate that C/EBPα's expression is silenced human skin cancer and the inactivation of C/EBPα in mouse skin confers susceptibility to UVB-induced skin cancer. Recently, we have discovered C/EBPα regulates the G_1/S checkpoint through a mechanism involving the degradation of p21 via the E3 ubiquitin ligase $CRL4^{Cdt2}$. I served as PI on these studies.

a. Yoon K, **Smart RC**. CCAAT/enhancer binding protein-α (C/EBPα) is a DNA-damage inducible p53-regulated mediator of the G1 checkpoint. *Mol. Cell. Bio.* 24:10650-10660 (2004) PMID 15572670
b. Loomis KD, Zhu S, Yoon K, Johnson PF, **Smart RC**. Genetic ablation of C/EBPα in epidermis reveals its role in suppression of epithelial tumorigenesis. *Cancer Res.* 67:6768-6776 2007 PMID 17638888
c. Thompson EA, Zhu S, Hall JR, House JS, Ranjan R, Burr JA, He YY, Owens DM, Smart RC. C/EBPα expression is downregulated in human nonmelanoma skin cancers and inactivation of C/EBPα confers susceptibility to UVB-induced skin squamous cell carcinomas. *J Invest Dermatol*. 31:1339-1346 (2011) PMID 21346772
d. Hall JR, Bereman MS, Nepomuceno AI, Thompson EA, Muddiman DC, **Smart RC**. C/EBPα regulates $CRL4^{Cdt2}$-mediated degradation of p21 in response to UVB-induced DNA damage to control the G1/S checkpoint. *Cell Cycle* 22:1-9 (2014) PMID 25483090

4. Demonstration that Lipid Second Messengers, Diacylglycerols, Have Tumor Promoting Activity

In the 1980s, protein kinase C was identified as the phorbol ester receptor and it was implicated in skin tumor promotion. We postulated that diacylglycerols which are lipid second messengers and the endogenous ligand for PKC could function as endogenous tumor promoters. We went on to demonstrate that diacylglycerols have tumor promoting activity and can clonally expand cells containing oncogenic Ras in vivo. We documented a role for the down-regulation on certain PKC isoforms in tumor promotion and developed a PKCα transgenic mouse

that was critical in revealing its role in cutaneous inflammation and the regulation of expression of pro-inflammatory mediators. I served as PI in all of these studies.

a. **Smart RC**, Huang M-T, Conney AH. sn-1,2-Diacylglycerols mimic the effects of 12-0-tetradecanoylphorbol-13-acetate in vivo by inducing biochemical changes associated with tumor promotion in mouse epidermis. *Carcinogenesis* 7:1865-1870 (1986) PMID 3769135
b. **Smart RC**, Mills KJ, Hansen LA, Conney AH. Synthetic lipid second messenger, sn-1,2-didecanoylglycerol: A complete tumor promoter in mouse skin. *Cancer Res*. 49:4455-4458 (1989) PMID 2743335
c. Hansen LA, Monteiro-Riviere NA, **Smart RC**. Differential down regulation of protein kinase C by TPA and diacylglycerol: Association with epidermal hyperplasia and tumor promotion. *Cancer Res*. 50:5740-5745 (1990) PMID 2393848
d. Wang HQ, **Smart RC**. Overexpression of protein kinase C-α in the epidermis of transgenic mice results in striking alterations in phorbol ester-induced inflammation and COX-2, MIP-2, and TNF-α but not tumor promotion. *J. Cell Sci*. 112:3497-3506 (1999) PMID 10504298

5. Discovery of the Estrogen Receptor in Skin and Hair Follicles

We studied sexual dimorphic responses to tumor promoters in skin, we discovered the expression of ERα and ERβ in skin and the role of estrogen in the regulation of tumor promotion, hair follicle stem cells and the hair follicle cycle. I was the PI on all of these studies.

a. Moser GJ, **Smart RC***.* Characterization of mirex-induced tumor promotion; structure activity relationships, sexual dimorphism and presence of Ha-ras mutation. *Carcinogenesis* 14:1155-1160 (1993) PMID 8508502
b. Oh H-S, **Smart RC**. An estrogen receptor pathway regulates the telogen-anagen hair follicle transition and influences interfollicular epidermal cell proliferation. *Proc. Natl. Acad. Sci. USA* 93:12525-12530 1996 PMID 8901615
c. Chanda S, Robinette CL, **Smart RC**. 17β-Estradiol and ICI 182,780 regulate the hair follicle cycle in mice through an estrogen receptor-β pathway. *Amer. J. Physiol*. 278: 202-210 (2000) PMID 10662703
d. Porter KL, Chanda S, Wang H-Q, Gaido KW, **Smart RC**, Robinette CL. 17β-Estradiol is a primary hormonal regulator of mirex tumor promotion. *Tox Sci* 69:42-48 2002 PMID 12215659