# BIOGRAPHICAL SKETCH

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NAME: Smart, Robert C.

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

POSITION TITLE: William Neal Reynolds Distinguished Professor

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 research 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. 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 role of the basic leucine zipper transcription factors, CCAAT/enhancer binding proteins (C/EBPs) and long noncoding RNAs in this process. Below are two key springboard publications that represent areas we are actively researching; one is on lincRNA-21 aka tumor protein p53 corepressor 1 (Trp53cor1) and its role in apoptosis and skin cancer and another is on the regulatory role of C/EBPβ in the Type IFN response and cooperation with p53.

Hall JR, Messenger ZM, Tam HW, Phillips SW, Recio L, and **Smart RC**. Long noncoding RNA lincRNA-p21 is the major mediator of UVB-induced and p53-dependent apoptosis in keratinocytes. *Cell Death and Disease* Mar 19;6:e1700 2015 PMID 25789975

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* Jan 29 (2019) PMID 30698678

My group was first to report roles for C/EBP transcription factors in chemical carcinogen-, UVB-induced and oncogenic Ras-induced skin cancer, the DNA damage response (DDR), apoptosis and squamous and sebocyte differentiation. My laboratory has made significant contributions through the characterization of genes/pathways involved in critical processes such as cell proliferation, differentiation, apoptosis, inflammation and carcinogen-induced cancer. My research program has been continuously funded by NIH R01s/P01s from NCI and/or NIEHS since 1988-2021. I have published over 90 peer-reviewed publications and book chapters. In recognition of my expertise, I have been invited to participate on numerous NIH panels (>25) and as a speaker at national/international conferences/seminars (>65).

I am the Director of the NIEHS Training Grant (22 years) *Molecular Pathways to Pathogenesis in Toxicology,* a University-wide interdisciplinary training program that involves twenty-three preceptors from 3 colleges and 5

departments. I am the current and founding Director of Center Director of *Center for Human Health and the Environment* (CHHE). CHHE is an NIEHS funded Environment Health Science Core Center (P30) that brings together ~65 investigators from across NC State's campus to form interdisciplinary teams to conduct research aimed at the understanding and prevention of the adverse impacts of environmental factors on human health.

I participate as an associate faculty member in following graduate programs; Genomic Sciences, Comparative Biomedical Sciences, Cell Biology, and Pharmacology. I have served as the major advisor for 18 predoctoral and 11 postdoctoral students and 6 junior faculty members, including one that received the prestigious NIEHS ONES award. All of these junior faculty mentored by me have secured NIH R01 funding. Several of my former students/postdocs, have received NIEHS-funded R01, R00/K99 and F32 awards. I currently serve as Co-Mentor for three NC State faculty with K01 or K22 awards.

I am very committed to continue to use my experience and knowledge to provide effective administrative and scientific leadership to the CHHE.

## B. Positions and Honors

**Employment/Experience**

| | |
|---|---|
| 1984-1986 | Postdoctoral Fellow, Department of Molecular Oncology, Laboratory of Experimental Carcinogenesis and Metabolism, Roche Institute of Molecular Biology, Nutley, NJ |
| 1986-1991 | Assistant Professor, Department of Toxicology, North Carolina State University, Raleigh, NC (NCSU) |
| 1989-1993 | Director, NIEHS Training Program/Grant in Environmental and Biochemical Toxicology |
| 1991-1997 | Associate Professor, Department of Toxicology, NCSU |
| 1996 | Associate Faculty Member, Comparative Biomedical Sciences, College of Veterinary Medicine, NCSU |
| 1996-2012 | Director of Molecular and Cellular Toxicology Graduate Study Option, NCSU |
| 1997-2012 | Professor, Department of Environmental and Molecular Toxicology, NCSU |
| 2000 | Member of Genomic Sciences Graduate Program, NCSU |
| 2001 | Director, NIEHS Training Program/Grant in Molecular Pathways to Pathogenesis, NCSU |
| 2005-2013 | Director of Graduate Programs, Department of Environmental and Molecular Toxicology, NCSU |
| 2011 | Director, Center for Human Health and the Environment, NCSU |
| 2012 | WNR Distinguished Professor, Department of Biological Sciences, College of Sciences, NCSU |

**Honors**

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

**Service**

| | |
|---|---|
| 1990 | NIEHS, RFP Review |
| 1990 | NIEHS, Special Study Section, Training Grant Supplements |
| 1991 | NIEHS, SBIR-Phase 1 |
| 1991 | NIEHS, Sixth Annual Report on Carcinogens |
| 1992 | NIEHS, RFP Review - Chairman |
| 1992 | NIEHS, SBIR-Phase 1 and 2 |
| 1994 | NIEHS, *Ad hoc* Reviewer |
| 1995 | American Cancer Society, *Ad hoc* reviewer |
| 1997 | NIEHS, RFP Review |
| 1997 | NIEHS, SBIR-Phase 1 |
| 1997 | NIEHS, Training Grant and Conference Grant Review |
| 1999 | NIAMS *Ad hoc* Reviewer |
| 2000 | NCI, Laboratory of Cellular Carcinogenesis and Tumor Promotion, Reviewer of Intramural Program and Member of Site Visit Team |
| 2001 | CIIT Centers for Health Research, Scientific Advisory Committee, *Ad hoc* member |
| 2001 | NIEHS Special Emphasis Panel, Review of Program Project Grant Application, *Ad hoc* member |
| 2002 | NIEHS, Tenure and Promotion Committee, Ad Hoc Member |
| 2003-2007 | NIEHS, Environmental Health Science Review Committee, Member |

2009 NIEHS – Tenure and Promotion Committee, Ad Hoc Member
2009 NIH, RC1 grant reviews
2009 NIEHS R13 Review Panel
2010 NIH, Special Emphasis Panel
2011 National Toxicology Program Technical Reports Review Panel
2012 NIEHS K awards Panel
2015 NIH Systemic Injury by Environmental Exposure (SIEE) Special Emphasis Panel, Ad hoc Member
2016 NIEHS, Board of Scientific Councilors, Ad Hoc Member, Intramural Program Review
2016 NIEHS, Special Emphasis Panel for R25 applications, Chair
2018 NIEHS, Environmental Health Science Review Committee, Ad Hoc Member

**C. Contributions to Science**

**1. Elucidation of 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. Finally, we recently observed that the deletion of C/EBPb 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. Collectivelly 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* Jan 29 (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

**D. Additional Information: Research Support and/or Scholastic Performance**

**Ongoing Research Support**

P30 ES025128 Smart (PI) 4/1/15-3/31/20 NIH/NIEHS
*Center for Human Health and the Environment*
The aim of the Center for Human Health and Environment is to understand how human health, at both the individual and population level, is impacted by environmental factors and to implement this knowledge to prevent and/or reduce the adverse impacts of environment factors on human health.
Role PI

T32 ES07046 Smart (PI) 7/1/15-6/30/20 NIH/NIEHS
*Molecular Pathways to Pathogenesis in Toxicology*
The goal is to provide trainees with the skill and knowledge necessary to investigate and elucidate how environmental toxicants/cellular stressors contribute to toxicity and influence disease outcomes.
Role PI

R01 ES024471 Smart (PI) 6/01/16-5/31/21 NIH/NIEHS
*Role of Long Intergenic Noncoding RNA in UVB-induced Apoptosis and Skin Cancer*
The goals of this project are to define the regulation and function of lincRNA-p21 in keratinocytes and to develop mouse genetic models to define the molecular function of lincRNA-p21 in controlling keratinocyte gene expression, apoptosis and skin cancer in response to UVB radiation.
Role PI

R21 ES029353 Hoppin (PI) 11/1/17-10/31/19 NIH/NIEHS
*Assessing impact of drinking water exposure to GenX (hexafluoropropylene oxide dimer acid) in the Cape Fear River Basin, North Carolina*
The goal of this project is to conduct a community-based study to assess human exposure by measuring GenX in biological samples of community residents.
Role Co-I

**Completed Research Support last 3 years**

R01 CA46637 Smart (PI) 6/1/07-5/31/15 NIH/NCI
*Role of C/EBPs in Cell Survival and Neoplasia*
The goal of this grant is to understand the molecular mechanisms through which C/EBPβ influences the neoplastic process in skin epithelia and regulates tumor cell survival.
Role PI

R01 GM068812 Ninomiya-Tsuji (PI) 4/01/04-2/28/15 NIH/NIGMS
*TAK1 signaling network in tissue homeostasis*
Type NIH R01 GM068812-07 04/01/2004-02/28/2015
The objective of this project is to delineate the pathway and functional role of TAK1 in epithelial and endothelial tissue homeostasis.
Role Co-I