BIOGRAPHICAL SKETCH

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NAME: **H. Shelton Earp**

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

POSITION TITLE: **Director, UNC Cancer Care; Lineberger Professor of Cancer Research; Professor of Medicine & Pharmacology**

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
Johns Hopkins University, Baltimore, MD	A.B.	06/1966	Pre-med
University of North Carolina School of Medicine, Chapel Hill, NC	M.D.	06/1970	Medicine
Vanderbilt University Hospital, Nashville, TN	Internship	06/1971	Internal Medicine
North Carolina Memorial Hospital, Chapel Hill, NC	Residency	06/1975	Internal Medicine
University of North Carolina School of Medicine	Fellowship	06/1976	Endocrinology

A. Personal Statement

I began on the physician-scientist track during medical school, publishing both cell signaling and clinical translational research articles. After training in internal medicine and service in the Army, I returned to the UNC School of Medicine, resuming research as a fellow and a junior faculty member in cyclic nucleotide second messenger signaling. With the discovery of tyrosine kinases by Hunter and others, I turned my attention to the EGF receptor and liver regeneration and published what was probably the first in vivo study of EGF receptor kinase activity alteration (J Clin Invest. 1981 May;67(5):1580-3). In 1976, I received my first NIH grant and have been continuously funded by NIH since that time, the common thread being tyrosine kinase signaling in neoplastic disease including breast, prostate, liver and lung cancer, as well as pediatric leukemia and melanoma. Studies have revolved around the EGF receptor family, several intracellular tyrosine kinases (CADTK/Pyk2 (J Biol Chem. 1999 Mar 26;274(13):8917-24) and Ack (Canc Res. 2005 Nov 15;65(22):10514-23) and the TAM family of receptor tyrosine kinases, particularly MerTK. The Mer TK mechanistic project has developed into a drug discovery funded in the past by the NCI NeXT program and now a drug development effort.

My role as a physician scientist led me to cancer center administration, joining UNC Lineberger as faculty member and then as Associate, Deputy and Director. In those roles, I was involved in bringing all the components of UNC to inter- and trans-disciplinary cancer research. I recruited and helped mentor several hundred faculty across the basic, population, clinical, and translational sciences. I led, along with Edison Liu, our successful UNC Breast Cancer SPORE application in the programs first round (1992) and have been SPORE principle investigator for the past 17 years. I initiated an NCI funded partnership with our sister minority-serving institution, North Carolina Central University and have been PI on those grants for 13 years. In January 2014, I stepped down as UNC Lineberger Director, but retained my service as Director of UNC Cancer Care. I am pleased to serve as a senior advisor to Norman Sharpless, the Director of the UNC Lineberger Cancer Center.

B. Positions and Honors

Professional and Research Experience

1970-1971 Internship, Straight Medical Internship, Vanderbilt
1971-1974 Major - U.S. Army, Research Investigator

1974-1975 Junior Assistant Resident, Medicine, University of North Carolina
1975-1977 Fellowship, Endocrinology, University of North Carolina
1977-1982 Assistant Professor, Medicine; Assistant Director, UNC Lineberger Comp. Cancer Center
1982-1988 Associate Professor, Medicine, Associate Director, UNC Lineberger Comp. Cancer Center
1988-1997 Professor, Medicine, Pharmacology; Deputy Director, UNC Lineberger Comp. Cancer Center
1997-2014 Director, UNC Lineberger Comprehensive Cancer Center
1997-present Lineberger Professor of Cancer Research, Professor of Medicine and Pharmacology
2011-present Director, UNC Cancer Care

Honors and Awards

The University of North Carolina Distinguished Service Award (2015), Faculty Service Award UNC General Alumni Association (2009), UNC Faculty Thomas Jefferson Award (2008), Kaiser-Permanente Medical School Excellence in Teaching Award (1987), Medical School Basic Science Teacher Award (1985), Association of American Cancer Institutes: President (2005-2007), Board of Directors (2001-9); NCI Board of Scientific Advisors (2002-2007); IRG-A: NCI Cancer Centers Core Support Review Committee (1995-1999); American Cancer Society: Cell and Developmental Biology Study Section (1989-1993), Chair (1990-93).

C. Contributions to Science

1. Identification of the Mer receptor tyrosine kinase and its role in the innate immune system.

Background: Prior to the genome sequencing, a number of laboratories were attempting to clone and sequence oncogenic tyrosine kinases. Our lab identified two, MerTK and CddTK/Pyk2. The latter was cloned when we purified the calcium-dependent tyrosine kinase activity from liver cells, and obtained protein sequence to design nucleic acid probes for cloning. We were "tied" with Dr. Schlesinger's group in identifying this TK. For Mer, we had defined T- and a B-cell tyrosine substrates using our own early p-tyr antibodies. We set out to clone the B-cell kinase using a B lymphoblastoid cDNA library.

Central Finding: By expression cloning in bacteria, we identified and constructed a full length clone for a then-orphan tyrosine kinase that we named Mer for its expression pattern in **M**acrophages, **E**pithelial tissues, and **R**eproductive tissue. Two other groups identified the second and third member of this new family, Axl and Tyro3. We spent the next decade identifying its role using our Mer knock-out mouse. Genetic deletion of Mer led to a hyperinflammatory state and autoimmunity. Next, we defined a mechanism; Mer was responsible for the clearance of apoptotic material through its recognition of phosphatidyl serene (PtdSer) through a bivalent ligand (Gas6 or Protein S) that recognized PtdSer with one face and bound to the receptor with the other. In fact, the whole TAM family evolved to recognize the complex lipid (phosphatidylserine) protein ligand (see our Nat Rev Cancer. 2014 Dec;14(12)769-85).

Our work showed that effercytosis (the ingestion of apoptotic material) resulted in polarizing the ingesting macrophage to a M2 alternatively activated macrophage that tolerized the innate immune system to the ingestion of self. This is an important homeostatic mechanism preventing autoimmunity. The Mer tyrosine kinase signal altered the cytokine transcriptional landscape from immunostimulatory (IL12) to immunosuppressive (IL10/TGFβ). My group led and funded Mer cloning identification, knockout mouse generation and its analysis.

Peer-Reviewed Publications:

1) Graham DK, Dawson TL, Mullaney DL, Snodgrass HR, **Earp HS**. Cloning and mRNA expression analysis of a novel human protooncogene, c-mer. **Cell Growth Differ**. 1994 Jun;5(6):647-57. Erratum in: Cell Growth Differ 1994 Sep;5(9):1022.
2) Camenisch TD, Koller BH, **Earp HS**, Matsushima GK. A novel receptor tyrosine kinase, Mer, inhibits TNF-alpha production and lipopolysaccharide-induced endotoxic shock. **J Immunol**. 1999 Mar 15;162(6):3498-503.
3) Scott RS, McMahon EJ, Pop SM, Reap EA, Caricchio R, Cohen PL, **Earp HS**, Matsushima GK. Phagocytosis and clearance of apoptotic cells is mediated by MER. **Nature**. 2001 May 10;411(6834):207-11.
4) Wallet MA, Sen P, Flores RR, Wang Y, Yi Z, Huang Y, Mathews CE, **Earp HS**, Matsushima G, Wang B, Tisch R. MerTK is required for apoptotic cell-induced T cell tolerance. **J Exp Med**. 2008 Jan 21;205(1):219-32. Epub 2008 Jan 14. PMCID: PMC2234377.

2. Studies of Mer and its role in neoplasia.

Background. Mer is almost never amplified or mutated in cancer cells, but is overexpressed in virtually every type of malignancy. Mer is expressed in tumor-associated macrophages.

Central Finding: We showed that Mer was overexpressed in lymphoblastoid cell lines and were the first to show Mer ectopic expression in pediatric acute lymphocytic leukemia as well as in pediatric and adult AML, and human metastatic melanoma. Along with my colleague, Doug Graham, who was the MD/PhD student in my lab who cloned Mer, we have a series of papers showing the overexpression of Mer in neoplastic cells provides a survival, chemoresistance signal that when inhibited results in chemosensitization and slower growth. In addition, Mer is expressed in the innate immune cells of the tumor microenvironment. We used our Mer knockout mouse to show that implantation of syngeneic tumor models in Mer-/- mice resulted in slower growth, fewer metastases, and a polarization of tumor-associated macrophages towards the M1 phenotype, away from the M2 tumor-associated macrophage. In collaboration with Stephen Frye and funded by NCI NExT, we have developed oral Mer TK inhibitors which we are advancing towards an IND in late 2015. We have data indicating that our Mer inhibitors will have a dual anti-tumor effort, decreasing a chemoresistance survival signal and enhancing anti-tumor innate immunity.

Peer-Reviewed Publications:

1) Graham D, DeRyckere D, Davies K, and **Earp HS**. The TAM Family: PhosphatidylSerine-Sensing Receptor Tyrosine Kinases Gone Awry in Cancer. **Nat Rev Cancer**. 2014 Dec;14(12)769-85. PMID: 25417589.
2) Schlegel J, Sambade MJ, Sather S, Moschos SJ, Tan AC, Winges A, Deryckere D, Carson CC, Trembath DG, Tentler JJ, Eckhardt SG, Kuan PF, Hamilton RL, Duncan LM, Miller CR, Nikolaishvili-Feinberg N, Midkiff BR, Liu J, Zhang W, Yang C, Wang X, Frye SV, **Earp HS**, Shields JM, Graham DK. MERTK receptor tyrosine kinase is a therapeutic target in melanoma. **J Clin Invest**. 2013 May 1;123(5):2257-67. Epub 2013 Apr 15. PMCID: PMC3639697.
3) Cook R, Jacobsen K, Wofford A, DeRyckere D, Stanford J, Prieto A, Redente E, Sandahl M, Hunter D, Strunk K, Graham D, **Earp HS**. MerTK inhibition in tumor leukocytes decreases tumor growth and metastasis. **J Clin Invest**. 2013 Aug 1;123(8):3231-42. Epub 2013 Jul 8. PMCID: PMC3726162.
4) Zhang W, DeRyckere D, Hunter D, Liu J, Stashko M, Minson KA, Cummings C, Lee M, Glaros TG, Newton DL, Sather S, Zhang D, Kireev DB, Janzen WP, **Earp HS**, Graham DK, Frye SV, and Wang X. UNC2025, a potent and orally bioavailable MER/FLT3 dual inhibitor. **J Med Chem**. 2014 Aug 28;57(16):7031-41. Epub 2014 Aug 6. PMCID: PMC4148167.

3. Conceptualization and long term support for the Carolina Breast Cancer Study (CBCS).

Background. African American women have a lower incidence of invasive breast cancer and yet suffer from higher mortality. The reasons are undoubtedly multifactorial. In my role as Cancer Center Deputy Director and co-PI of the initial UNC Breast Cancer SPORE in the early 1990s, we initiated a population based study that I have shepherded over three iterations for the past 20 years, assuring its continued funding and infrastructure.

Central Finding. The key element in CBCS is oversampling of African Americans (50%) and younger women (50%), home visits after rapid case ascertainment that allowed collection of questionnaire data, anthropomorphic measurements, blood for genomic DNA, and collecting blocks of surgical specimens. This has turned out to be prescient, as technology has allowed us to obtain not only immunohistochemical data but RNA expression data that have led to seminal findings. We are now in CBCS Phase 3 and have completed the ascertainment of the third cohort of 3,000 women and I remain Co-Principle Investigator. Key findings from my colleagues, each of whom I recruited to UNC Lineberger (Bob Millikan, Lisa Carey, and Chuck Perou), include the seminal observation that younger African American women have a significantly higher risk of the basal like triple negative breast cancer and epidemiologic data revealing that breast cancer risk is different for different subtypes. CBCS has produced over 100 papers. I am a co-author on several of the most important findings.

Peer-Reviewed Publications:

1. Carey LA, Perou CM, Livasy CA, Dressler LG, Cowan D, Conway K, Karaca G, Troester MA, Tse CK, Edmiston S, Deming SL, Geradts J, Cheang MC, Nielsen TO, Moorman PG, **Earp HS**, Millikan RC. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. **JAMA**. 2006 Jun 7;295(21):2492-502. PMID: 16757721.

2. Millikan RC, Newman B, Tse CK, Moorman PG, Conway K, Dressler LG, Smith LV, Labbok MH, Geradts J, Bensen JT, Jackson S, Nyante S, Livasy C, Carey L, **Earp HS**, Perou CM. Epidemiology of basal-like breast cancer. **Breast Cancer Res Treat**. 2008 May;109(1):123-39. Epub 2007 Jun 20. Erratum in: Breast Cancer Res Treat. 2008 May;109(1):141. Dressler, Lynn G [added]. PMCID: PMC2443103.

4. Studies of the EGF Receptor Family and RTK signaling.

Background. This family has been implicated in neoplastic growth of virtually all tumor types.

Central Finding. My lab has made important observations regarding family members over the years including one of the earliest proofs of homodimerization (Ref 1), the first identification of an RTK spliced isoform that encodes a secreted RTK (EGFR rat gene) extracellular domain (Ref 2), the signaling of EGFR from endosomal vesicles (Ref 3), differential signaling from EGFR and HER2 in prostate cancer (Ref 4), recent work on the diametrically opposed actions (differentiation vs proliferation) of HER4 spliced isoforms (Ref 5 & 6), and recently studies of RTK roles in drug resistance (Ref 7).

Peer-Reviewed Publications:

1. Fanger BO, Austin KS, **Earp HS**, Cidlowski JA. Cross-linking of epidermal growth factor receptors in intact cells: detection of initial stages of receptor clustering and determination of molecular weight of high-affinity receptors. **Biochemistry**. 1986 Oct 21;25(21):6414-20.
2. Petch LA, Harris J, Raymond VW, Blasband A, Lee DC, **Earp HS**. A truncated, secreted form of the epidermal growth factor receptor is encoded by an alternatively spliced transcript in normal rat tissue. **Mol Cell Biol**. 1990 Jun;10(6):2973-82. PMCID: PMC360661.
3. McCune BK, **Earp HS**. The epidermal growth factor receptor tyrosine kinase in liver epithelial cells. The effect of ligand-dependent changes in cellular location. **J Biol Chem**. 1989 Sep 15;264(26):15501-7.
4. Gregory CW, Whang YE, McCall W, Fei X, Liu Y, Ponguta LA, French FS, Wilson EM, **Earp HS 3rd**. Heregulin-induced activation of HER2 and HER3 increases androgen receptor transactivation and CWR-R1 human recurrent prostate cancer cell growth. **Clin Canc Res**. 2005 Mar 1;11(5):1704-12.
5. Strunk KE, Husted C, Miraglia LC, Sandahl M, Rearick WA, Hunter DM, **Earp HS 3rd**, Muraoka-Cook RS. HER4 D-box sequences regulate mitotic progression and degradation of the nuclear HER4 cleavage product s80HER4. **Canc Res**. 2007 Jul 15;67(14):6582-90. PMCID: PMC2917069.
6. Muraoka-Cook RS, Sandahl MA, Strunk KE, Miraglia LC, Husted C, Hunter DM, Elenius K, Chodosh LA, **Earp HS 3rd**. ErbB4 splice variants Cyt1 and Cyt2 differ by 16 amino acids and exert opposing effects on the mammary epithelium in vivo. **Mol Cell Biol**. 2009 Sep;29(18):4935-48. Epub 2009 Jul 13. PMCID: PMC2738276.
7. Duncan J, Whittle M, Nakamura K, Abell A, Midland A, Zawistowski J, Johnson N, Granger D, Jordan N, Darr D, Usary J, Kuan PF, Smalley D, Major B, He X, Hoadley K, Zhou B, Sharpless N, Perou C, Kim W, Gomez S, Chen X, Jin J, Frye S, **Earp HS**, Graves L, Johnson G. Dynamic Reprogramming of the Kinome in Response to Targeted MEK Inhibition in Triple Negative Breast Cancer. **Cell.** 2012 Apr 13;149(2):307-21. PMCID:PMC3328787.

Complete List of Published Work in MyBibliography:
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