BIOGRAPHICAL SKETCH

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NAME: **William H. St. Clair, MD, PhD**

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

POSITION TITLE: Professor of Radiation Medicine

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
St. Ambrose College, Davenport, IA	B.S.	05/1978	Biology
University of Iowa, Iowa City, IA	M.S.	05/1982	Radiation Biology
University of Iowa, Iowa City, IA	Ph.D.	09/1985	Radiation Biology
Harvard School of Public Health, MA	Post Doc.	11/1987	Cancer Biology
University of Kentucky, Lexington, KY	M.D.	O5/1995	Medicine
The Christ Hospital, OH	Internship	O6/1996	Internal Medicine
Massachusetts General Hospital, MA	Residency	06/2000	Radiation Oncology

A. Personal Statement

The ultimate goal of my research program is to translate basic biological knowledge into a practical application for improving the control of cancer and the quality of life of cancer patients. My extensive background in science and medicine is directed toward understanding neoplasms and treatment of cancer. Early in my career I investigated the use of protease inhibitors as chemopreventive agents for the suppression of cancer, and I investigated the mechanisms through which the Bowman-Birk protease inhibitor protects against neoplastic transformation. As a Radiation Oncologist, one of my current major responsibilities is the care of prostate cancer patients, and I have been rated a Best Doctor in this area.

As a Physician Scientist, I am active in elucidating off-target side effects arising from radiation treatments and have performed preclinical and clinical studies to identify effective interventions. Generation of ROS is a major mechanism responsible for the therapeutic effect of ionizing radiation. Cancer cells are usually under higher oxidative stress than normal cells, suggesting that an additional increase in prooxidant level can trigger cell death. Thus, therapeutic approaches that use redox active antioxidants that push tumor cells into oxidative stress overload is consistent with my own research focus to selectively enhance the efficient killing of cancer cells by radiation therapy. I have performed several studies addressing the role and mechanism of a plant derived lactone, parthenolide (PN), in radiation therapy, which has inspired quite a few new and exciting research directions. Using the unique properties found from a study using PN, and in collaboration with Dr. Luksana Chaiswing, we have screened a library of 760 FDA-approved drugs that sensitize prostate cancer cells to radiation-induced cytotoxicity against radiation-induced injury and increase hydrogen peroxide level in cancer cells only. Azithromycin is one of the most potent drugs in enhancing radiation effect in cancer cells identified, and we are working on a preclinical study which should lead to opportunities to bring scientific discovery to the improvement of the treatment, quality of life and survival of cancer patients through innovative clinical trials that harness the power of scientific discoveries for positive change.

B. Positions and Honors

Positions and Employment

1988-1991 Assistant Professor, Department of Radiology, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, NC
2000-2006 Assistant Professor, Department of Radiation Medicine, University of Kentucky, Lexington, KY
2005-2006 Interim Chair, Department of Radiation Medicine, University of Kentucky, Lexington, KY

2006-2010 Associate Professor with tenure, Department Radiation Medicine, University of Kentucky, Lexington, KY
2010-present Professor, Department of Radiation Medicine, University of Kentucky, Lexington, KY
2010-present Co-Director, Gamma Knife Radiosurgery Program

Professional Memberships and Related Experience
American Association for the Advancement of Science, 1985-present
American Society for Therapeutic Radiology and Oncology, 1996-present
American College of Radiology, 2000-present
Radiation Research Society, 2003-present
American Association for Cancer Research, 2006-present

Awards and Honors
Bishops Scholarship for Undergraduate Students, 1974-1978
NIH Pre-doctoral Fellowship, University of Iowa, 1980-1985
NIH Post-doctoral Fellowship, Harvard University, 1985-1987
Castle Connolly America's Top Doctors, 2006-present

C. Contributions to Science:

1. **Mechanistic based, bench to bedside approach to improve the detection and treatment planning of prostate cancer.** Prostate-specific antigen (PSA) is a serine protease produced by prostate epithelial cells. The serum concentration of PSA in men without prostate disease is usually less than 4 ng/ml. PSA serum levels exceeding 4 ng/ml are indicators of disease of the prostate, with 4-10 ng/ml being considered the gray zone between benign prostate hyperplasia and prostate cancer. Increased PSA levels, therefore, are used extensively as a marker of prostate cancer. Although the use of PSA to indicate prostate cancer has saved the lives of men with high levels of PSA, its impact on men with high-risk prostate cancer has been less predictable. Early PSA detection is more likely to reveal slow growing prostate cancer than the faster growing cancer that is associated with rapid progression. Importantly, a fraction of men with normal PSA are found to have prostate cancer. Thus, despite rapid advances in treatment techniques, the outcome of radiation therapy, especially for patients with tumors of unfavorable prognoses, remains to be improved. In a series of basic research studies based on the clinical practice of prostate cancer detection and using PSA as a predictor of prostate cancer development, we serendipitously discovered that aggressive prostate cancer had low levels of PSA and high levels of Interleukin 8 (IL8). We found that: 1) aggressive prostate cancers have high nuclear RelB, a member of the alternative pathway of NF-κB, and manganese superoxide dismutase (MnSOD), a critical antioxidant enzyme; 2) suppression of RelB in androgen independent-aggressive prostate cancer cells results in reduction of interleukin 8 (IL8) levels in tumor cells and reduced tumor growth in vivo; 3) overexpression of RelB in androgen responsive prostate cancer cells results in enhanced tumor growth and production of IL8 but reduced PSA production; and 4) suppression of RelB nuclear translocation enhances radiation sensitivity of prostate cancer. These findings reveal that a tumor supportive role of RelB may be mediated by increased expression of IL8 and suggest the use of IL8 as a marker for prostate cancer prognosis. To confirm that the relationship between IL8 levels and the aggressive nature of prostate cancer observed in cultured cells is a valid indicator of prostate cancer in moderately differentiated prostatic adenocarcinoma and patients with poorly differentiated prostatic adenocarcinoma. The result supports the hypothesis that aggressive prostate cancer cells produce the IL8 that may contribute to the high levels of IL8 observed in the serum of animals bearing aggressive prostate cancer cells and in prostate cancer patients. We envision that the constitutive expression of IL8 may have significant prognostic value for prostate cancer growth and response to therapy, especially response to aggressive types of cancer. Thus, we have initiated a clinical study to determine whether serum IL8 level is a predictive marker of prostate cancer response to radiation therapy using samples from cancer patients. These mechanistic based, bench to bedside approaches should provide novel insights into the mechanisms of prostate cancer resistant to radiation therapy and may provide practical, predictive measures for prostate cancer diagnosis, treatment planning and surveillance.

a. Josson S, Xu Y, Fang F, Dhar SK, St. Clair DK, **St. Clair WH.** Selective inhibition of RelB suppresses intrinsic radiation resistance in prostate cancer cells. Oncogene 25:1554-1559, 2006. PMCID: PMC2635023.
b. Xu Y, Josson S, Fang F, Oberley TD, St. Clair DK, Wan XS, Sun Y, Bakthavatchalu V, Muthusawamy A, **St. Clair WH.** RelB enhances prostate cancer growth: implications for the role of the nuclear factor-kappaB alternative pathway in tumorgenicity. Cancer Res 69:3267-3671, 2009. PMCID: PMC2756761.
c. Xu Y, Fang F, St. Clair DK, Sun Y, **St. Clair WH.** RelB-dependent differential radiosensitization effect of STI571 on prostate cancer cells. Mol Cancer Ther 9:803-812, 2010. PMCID: PMC2852498.
d. Xu Y, Fang F, St. Clair DK, **St. Clair WH.** Inverse Relationship between PSA and IL-8 in Prostate Cancer: An Insight into a NF-κB-mediated mechanism. PloS ONE 7:e32905, 2012. PMCID: PMC3293904.

2. **Preclinical studies to develop an anticancer regimen that improves the efficacy of radiation therapy by sensitizing tumor tissue to radiation while simultaneously protecting normal tissue against the side effects of radiation therapy.** A growing body of data indicates that prostate cancer has an elevated oxidative stress level compared to normal tissue. We have recently identified the antioxidant Parthenolide (PN), a sesquiterpene lactone derived from the leaves of the traditional herbal medicine feverfew (Tanacetum parthenium), as having a differential effect on the sensitivity of prostate cancer cells and normal prostate epithelial cells to ionizing radiation. However, due to its poor water solubility, PN is not biologically available *in vivo* in a sufficient amount to be therapeutically effective. In collaboration with Dr. Peter Crooks, a renowned medicinal chemist who has synthesized the water soluble prodrug aminoparthenolide, DMAPT, that is currently in Phase I clinical trial in Europe, we have conducted a series of experiments that demonstrate that DMAPT fumerate salt from PN is a promising compound that warrants further investigation. In a series of experiments using cultured human cells and in an experimental therapeutic setting, we have demonstrated that: 1) PN inhibits the NF-kappaB pathway and activates the phosphatidylinositol-3-kinase/Akt pathway in prostate cancer cells, and the radiosensitization effect of parthenolide is due, in part, to the inhibition of the NF-kappaB pathway; 2) PN selectively activates NADPH oxidase and mediates intense oxidative stress in prostate cancer cells by both increasing ROS generation and decreasing antioxidant defense capacity; 3) KEAP1 is the downstream redox target that contributes to parthenolide's radiosensitization effect in prostate cancer cells. *In vivo*, DMAPT increases radiosensitivity of mouse xenograft tumors but protects normal prostate and bladder tissues against radiation-induced injury. Mechanistically, DMAPT increases the level of cellular ROS and causes oxidation of thioredoxin (TrX) in prostate cancer cells, leading to a TrX-dependent increase in a reduced state of KEAP1, which in turn leads to KEAP1-mediated PGAM5 and Bcl-xL (BCL2L1) degradation. In contrast, DMAPT increases oxidation of KEAP1 in normal prostate epithelial cells, leading to increased Nrf2 (NFE2L2) levels and subsequent Nrf2-dependent expression of antioxidant enzymes. These results reveal a novel redox-mediated modification of KEAP1 in controlling the differential effect of DMAPT on tumor and normal cell radiosensitivity.
Currently, in the United States alone, more than 2 million men are prostate cancer survivors, and the number of prostate cancer survivors worldwide is constantly increasing, which has created a pressing need for healthcare protocols that support a high quality of life for survivors. One area that presents a significant challenge in improving quality of life for survivors is injury to normal tissues caused by radiation therapy. The long-term goal of my research program is to translate basic biological knowledge into a practical application for improving the control of cancer and quality of life for cancer patients. Thus, I will continue to participate in the development of novel therapeutic approaches aimed at increasing radiation therapy efficacy while protecting normal tissue from the toxicity that is a side effect of radiation theapy.

a. Xu Y, Fang F, St. Clair DK, Sompol P, Josson S, **St. Clair WH.** SN52, a novel NF-κB inhibitor, sensitizes prostate cancer cells to ionizing radiation by specifically blocking nuclear translocation of RelB:p52 dimer. Mol Cancer Ther 7: 2367-2376, 2008. PMCID: PMC2692185.
b. Sun Y, St. Clair DK, Xu Y, Crooks PA, **St. Clair WH.** A NADPH oxidase dependent redox signaling pathway mediates the selective radiosensitization effect of parthenolide in prostate cancer cells. Cancer Res 70:2880-2890, 2010. PMCID: PMC2848907.
c. Xu Y, Fang F, Miriyala S, Crooks PA, Oberley TD, Chaiswing L, Noel T, Holley AK, Zhao Y, Kiningham KK, St Clair DK, **St Clair WH.** KEAP1 Is a Redox sensitive target that arbitrates the opposing

radiosensitive effects of Parthenolide in normal and cancer cells. Cancer Res 73:4406-4417, 2013. PMCID: PMC3715565.

d. Wei X, Xu Y, Xu F, Chaiswing L, Schnell D, Noel T, Wang C, Chen J, St. Clair DK, **St. Clair WH**. RelB is a central regulator that adjudicates the differential effects of ascorbic acid in normal and cancer cells. Cancer Res 77:1345-1356, 2017. PMCID: PMC5354963.

3. **Clinical Radiation Medicine.** Ionizing radiation represents a powerful tool for treating malignant and benign diseases. During my career as a Radiation Oncologist, I have endeavored to define safe and effective ways to use this tool for the maximum benefit of both cancer bearing patients and patients with benign conditions. The goal is not only to successfully treat cancer but also to minimize the side effects of radiation therapy to normal tissues. I have also made novel contributions by using highly conformal treatments such as Gamma Knife Radiosurgery for trigeminal neuralgia to using en-face electron therapy for the treatment of benign conditions such as bulbar sialorrhea in ALS patients.

a. **St. Clair WH**, Adams JA, Bues M, Fullerton BC, La Shell S, Kooy HM, Loeffler JS, and Tarbell NJ. Advantage of protons compared to conventional x-ray or IMRT in the treatment of pediatric medulloblastoma. Int J Radiat Oncol Biol Phys 58:727-734, 2004.

b. Jahraus CD, Bettenhausen D, Malik U, Sellitti M, **St. Clair WH**. Prevention of acute radiation-induced proctosigmoiditis by balsalazide: a randomized, double-blind, placebo controlled trial in prostate cancer patients. Int J Radiat Oncol Biol Phys 63:1483-1487, 2005.

c. Kasarskis EJ, Hodskins J, **St. Clair WH**. Unilateral parotid electron beam radiotherapy as palliative treatment for sialorrhea in amyotophic lateral sclerosis. J Neurol Sci 301:155-157, 2011.

d. Young B, Shivazad A, Kryscio RJ, **St. Clair WH**, Bush HM. Long-term outcome of high-dose gamma knife surgery in treatment of trigeminal neuralgia. J Neurosurg 119:1166-1175, 2013.

Full List of Publications:
http://www.ncbi.nlm.nih.gov/pubmed/?term=St.Clair+WH

D. Research Support.

Ongoing

R01 CA205400 (MPI: St Clair, D [contact]; St Clair W) 04/01/16-03/31/21
NIH
"Distinct redox mechanism in normal and cancer cells as a novel therapeutic target"
Goals: To facilitate the translation of novel radiation sensitizers for clinical use and fill critical gaps in scientific knowledge of how differences in redox conditions of normal and tumor cells trigger differential responses to pro-oxidants.
Role: MPI

GT-201 (PI: Kudrimoti, M) 02/24/16-02/23/18
Galera Therapeutics, Inc.
"15-28-HN-28-GT (GT-201): A Phase 2 Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial of the Effects of Intravenous GC4419 on the Incidence and Duration of Severe Oral Mucositis (OM) in Patients Receiving Post-Operative or Definitive Therapy"
Goal: Clinical Trial
Role: Co-I

NLG-2102 (PI: Villano, J) 03/04/16-03/31/18
NewLink Genetics
"15-NEURO-06-NLG (NLG-2102) A Phase 1/2 Study of the Combination of Indoximod + Temozolomide for Adult Patients with Temozolomide-Refractory Primary Malignant Brain Tumors"
Goal: Clinical Trial
Role: Co-I

ICT-107-301 (PI: Villano, J) 12/03/15-05/02/18
ImmunoCellular Therapeutics Limited

“15-GBM-10-IT (ICT-107-301) A Phase III study of ICT-107 plus maintenance temozolomide (TMZ) in newly diagnosed GBM”
Goal: Clinical Trial
Role: Co-I

Recently Completed

R01 CA143428 (MPI: St. Clair, D; St. Clair, W) 01/01/11-11/30/15
NCI
“RelB Mediated-redox Regulation of Radiation Therapy”
The goal of this project is to test the hypothesis that MnSOD is an important link between RelB and the expression of IL8 and PSA in prostate cancer cells. The study includes in-depth mechanistic studies in cultured cells and proof-of-concept studies in animal models that are translated to clinical settings.