

Award Number: W81XWH-10-1-0594

TITLE: Targeting Homology-Directed Recombinational Repair (HDR) of Chromosomal Breaks to Sensitize Prostate Cancer Cells to Poly (ADP-Ribose) Polymerase (PARP) Inhibition

PRINCIPAL INVESTIGATOR: Shih-Hsin Eddy Yang, M.D., Ph.D.

CONTRACTING ORGANIZATION: University of Alabama at Birmingham
Birmingham, AL 35294

REPORT DATE: August, 2012

TYPE OF REPORT: Annual Summary

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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				5e. TASK NUMBER	
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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) University of Alabama at Birmingham Birmingham, AL 35294-0111				8. PERFORMING ORGANIZATION REPORT NUMBER	
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14. ABSTRACT Our project aims to: 1. Determine whether IR-induced BRCA1 nuclear export will sensitize prostate cancer cells to PARP1 inhibition, and to determine whether these effects are dependent on CRM1 (Months 1-12). 2. To transiently reduce nuclear BRCA 1 using a tetracycline (tet)-re gulated expression of tr-BRCA1 a nd determine its effects on HDR and sensitivity to PARP1 inhibition in prostate cancer cells (Months 12-24). 3. To validate the role of induced DSB repair deficiency and sensitivity to PARP1 inhibition <i>in vivo</i> with prostate tumor xenograft models (Months 24-36). Our findings to date are: IR induces synthetic lethality with PARPI in LNCaP prostate cancer. The mechanism is due to IR-mediated BRCA1 nuclear export and subsequent generation of an HDR defect. These results are dependent on p53 and CRM1. For tumors without wildtype p53, we have found that expression of a truncated BRCA1 (tr-BRCA1) can achieve similar results as IR, including BRCA1 nuclear export, inhibition of HDR, and synthetic lethality with PARPi in both p53 wildtype and mutated prostate cancer cells. We are essentially on track with our proposed timeline. Lastly, we have obtained ACURO as well as IACUC approval to start validating our observations <i>in vivo</i>.					
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a. REPORT U	b. ABSTRACT U	c. THIS PAGE U			19b. TELEPHONE NUMBER (include area code)

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Progress Report July 31, 2012

Title: Targeting homology-directed recombinational repair of chromosomal breaks to sensitize prostate cancer cells to poly (ADP-ribose) polymerase (PARP) inhibition

Principal Investigator: Shih-Hsin Eddy Yang, M.D., Ph.D.

INTRODUCTION: Agents that target cancers which are deficient in double strand break (DSB) repair, such as poly (ADP-ribose) polymerase-1 (PARP1) inhibitors, have been demonstrated to have highly selective killing (57 fold) of BRCA1-mutated tumors while maintaining minimal toxicity in normal tissues⁽¹⁻⁵⁾. However, the majority of prostate cancers carry wild-type(WT) BRCA1^(6,7) and express elevated BRCA1 levels compared to normal prostate tissue⁽⁸⁾. Thus, to enhance the utility of PARP1 inhibitors in patients with prostate cancer, we proposed to sequester WT-BRCA1 from the nucleus where DSBs are repaired to the cytoplasm where apoptosis is activated to render a DSB repair defect and augment the cytotoxic response to PARP1 inhibition in prostate tumor cells. By inducing a DSB repair deficiency, sensitization of prostate cancers to PARP1 inhibitors can be an innovative therapeutic strategy and enhance therapeutic ratio for the majority of patients with prostate cancer.

BODY: We proposed the following tasks for the first 24 months of this grant as stated below and report the progress as follows:

Task 1. Determine whether IR-induced BRCA1 nuclear export will sensitize prostate cancer cells to PARP1 inhibition, and to determine whether these effects are dependent on CRM1 (Months 1-12):

- A) Assess the sensitivity of irradiated prostate cancer cells to PARP1 inhibition (Months 1-6)
 - a. Dose response to varying doses of IR (2 – 4Gy) and BRCA1 location by IHC
 - b. Time course of BRCA1 nuclear export following IR (4-48hrs following IR)
 - c. Sensitivity of irradiated prostate cancer cells to PARP1 inhibition (dose and time factors) via soft agar colony formation ability
- B) Determine whether sensitization of irradiated prostate cancer cells to PARP1 inhibition is dependent on CRM1 (Months 6-12)
 - a. Dose response of leptomycin B to inhibit IR-induced BRCA1 nuclear export
 - b. Sensitivity of irradiated prostate cancer cells to PARP1 inhibition following blockade of IR-induced, CRM1-mediated BRCA1 nuclear export

Progress on Task 1A: We have performed time course and dose response of LNCaP cells to 2-4 Gy IR and assessed BRCA1 location following such treatment. Interestingly, as shown in Fig.1, BRCA1 subcellular localization is altered (reduced nuclear with concomitant increased cytosolic) as early as 16 hrs following IR and persists up to 72hrs (data not shown). Doses of IR as low as 3Gy can achieve this shift of BRCA1 from the nucleus to the cytoplasm.

Given that IR can shift BRCA1 from the nucleus to the cytoplasm away from its repair substrates, we next hypothesized that prostate cancer cells exposed to IR will subsequently have a homology-directed recombination repair defect. To test this hypothesis, we utilized LNCaP cells stably expressing the DRGFP HDR repair substrate. In this assay, HDR activity correlates with GFP expression following the induction of a DSB generated by a restriction endonuclease. As shown in Fig. 2, IR indeed reduced % of GFP positive cells.

Lastly, given that IR reduces nuclear BRCA1 and subsequently generates a HDR repair defect, we next assessed tumor susceptibility to PARP inhibition following IR. Consistent with our hypothesis, sensitivity of irradiated prostate cancer cells to the PARP inhibitor ABT-888 as assessed by colony formation assays is augmented (Fig. 3).

These results suggest that IR generates a HDR repair defect by sequestering BRCA1 in the cytoplasm and subsequently, prostate tumor cells are rendered susceptible to PARP inhibition.

Additionally, it was previously reported that IR-induced BRCA1 nuclear export in breast cancer cells is dependent on p53. To assess whether BRCA1 nuclear export following IR in prostate cancer cells is also p53 dependent, we next performed the above experiments in PC-3 prostate cancer cells, which are deficient in p53. As shown in Fig. 4, IR does not result in BRCA1 nuclear export in PC-3 cells. Given this finding, we hypothesized that IR would not augment PC-3 cellular susceptibility to PARP inhibition. This is indeed what is observed (Fig. 5).

Progress on Task 1B: Previous reports suggest that IR-induced BRCA1 export is also dependent on CRM1. To test this hypothesis, we proposed that the CRM1 inhibitor leptomycin B would inhibit IR-induced BRCA1 export. As shown in Fig. 6, in the presence of leptomycin B, BRCA1 export is no longer apparent following IR. Additionally, leptomycin B prevented the IR-induced deficiency in HR (Figure 7), and subsequently prevent IR-induced synthetic lethality with PARP inhibition in LNCaP prostate cancer cells (Figure 8). Taken together, our data suggest that indeed IR induces BRCA1 nuclear export to generate a HR deficiency, which subsequently sensitizes prostate tumor cells to PARP inhibition. These effects are all dependent on CRM1, as leptomycin B, which inhibits CRM1, abrogates the observed effects.

KEY RESEARCH ACCOMPLISHMENTS FOR TASK 1:

- IR induces BRCA1 nuclear export in LNCaP but not the p53 deficient PC-3 cells
- IR generates a HDR repair defect in LNCaP cells
- IR induces synthetic lethality with PARP inhibition in LNCaP cells but not PC-3 cells
- Inhibition of CRM1 with leptomycin B abrogates IR-mediated BRCA1 export
- Inhibition of CRM1 with leptomycin B abrogates the IR-induced HR deficiency
- Inhibition of CRM1 with leptomycin B abrogates synthetic lethality of IR and PARP inhibition

FIGURES FOR TASK 1:

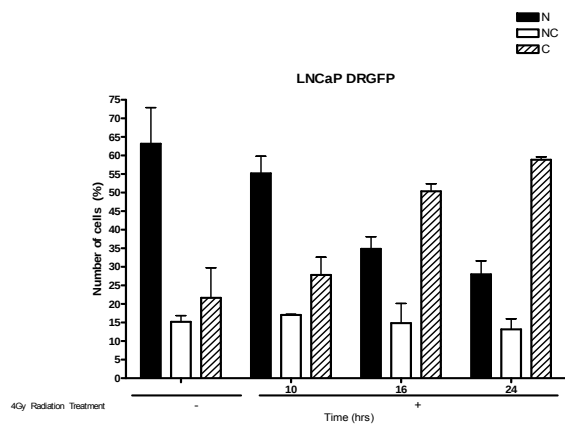


Figure1. IR increases cytosolic BRCA1 and reduces nuclear BRCA1 in LNCaP human prostate cancer cells.

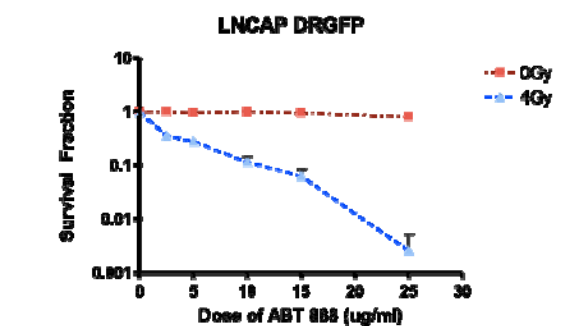


Figure 3. IR induces synthetic lethality with the PARP inhibitor ABT-888.

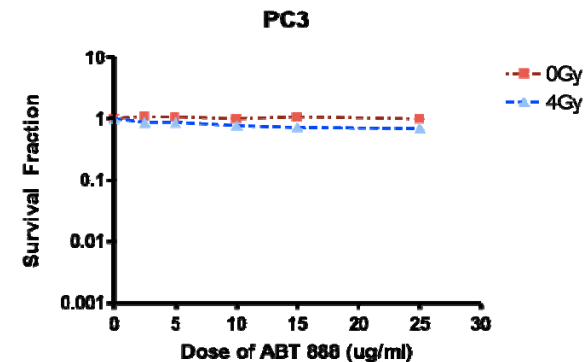


Figure 5. IR does not induce synthetic lethality with ABT-888 in PC-3 human prostate cancer cells.

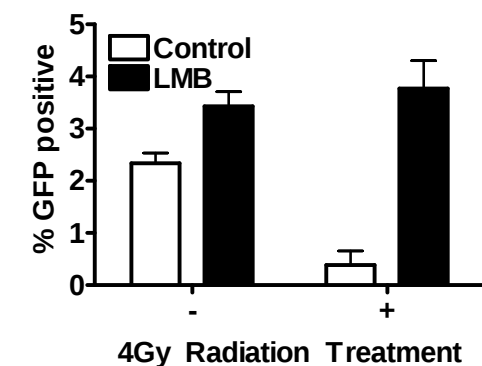


Figure 7. Leptomycin B abolishes the HR deficit induced by HR. additionally, it may enhance HR.

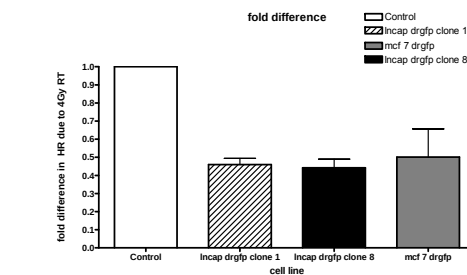


Figure 2. IR reduces HR repair in LNCaP human prostate cancer cells.

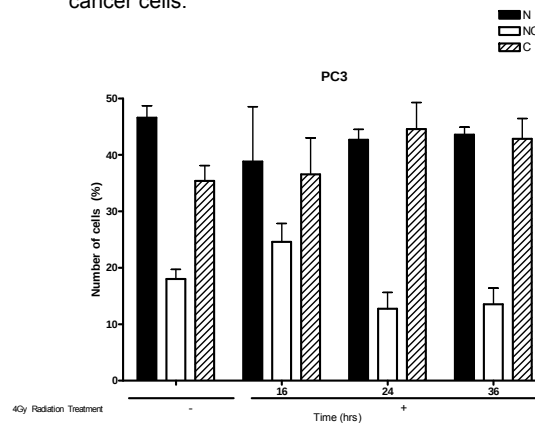


Figure 4. IR does not alter BRCA1 subcellular location in the p53 null PC-3 human prostate cancer cell line.

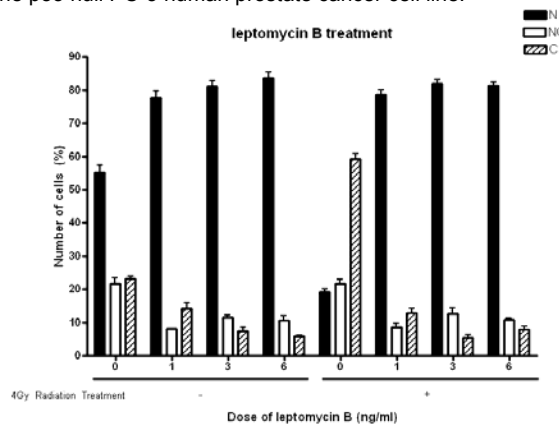
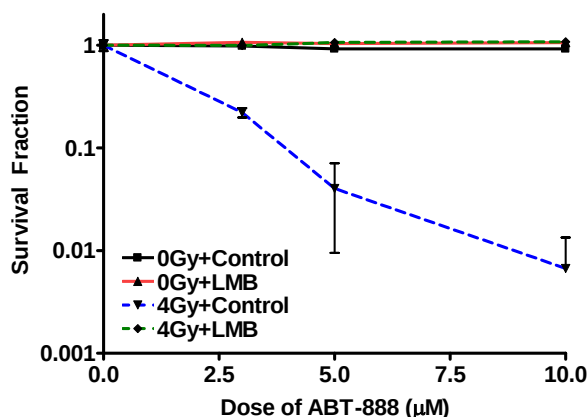


Figure 6. IR induced BRCA1 nuclear export is inhibited by leptomycin B, suggesting CRM1 dependence.



5 Figure 8. Leptomycin B abolishes synthetic lethality between IR and PARP inhibition.

Task 2. To transiently reduce nuclear BRCA1 using a tetracycline (tet)-regulated expression of tr-BRCA1 and determine its effects on HDR and sensitivity to PARP1 inhibition in prostate cancer cells (Months 12-24).

- A) Generate the LNCaP^{tr-BRCA1-TETOFF/DRGFP} stable cell line and validate tet-repressible expression of tr-BRCA1 via Western blot and integrated HDR reporter substrate by flow cytometry (Months 12-15)
- B) Validate tr-BRCA1-mediated BRCA1 nuclear export in clones via IHC (Months 16-18)
- C) Determine HDR capacity in LNCaP^{tr-BRCA1-TETOFF/DRGFP} cells with and without tr-BRCA1 using flow cytometric assessment of GFP expression (Months 18-21)
- D) Determine sensitivity of LNCaP^{tr-BRCA1-TETOFF/DRGFP} cells to PARP inhibition with and without tr-BRCA1 using soft agar colony formation ability (Months 21-24)

Progress on Task 2. We have had trouble generating stable cell lines expressing both the DRGFP repair substrate as well as the inducible tr-BRCA1. However, we were able to perform most of our proposed experiments using a transiently transfected inducible tr-BRCA1 when needed. As shown in figure 9, tr-BRCA1 indeed induces BRCA1 nuclear export in both LNCaP (p53 wt) and PC-3 (p53 null) cells. In LNCaP cells, tr-BRCA1 effects are compared with IR (left panel). For PC-3 cells, a time course was performed (right). Additionally, HR capacity was indeed reduced by tr-BRCA1 (Figure 10). Lastly, consistent with our hypothesis, tr-BRCA1 reduced colony forming ability of LNCaP and PC-3 cells when combined with the PARP inhibitor ABT-888 (Figure 11).

KEY RESEARCH ACCOMPLISHMENTS FOR TASK 2:

- Tr-BRCA1 induces BRCA1 nuclear export in LNCaP and PC-3 cells
- Tr-BRCA1 generates a HR repair defect in LNCaP cells
- Tr-BRCA1 induces synthetic lethality with PARP inhibition in LNCaP and PC-3 cells

FIGURES FOR TASK 2:

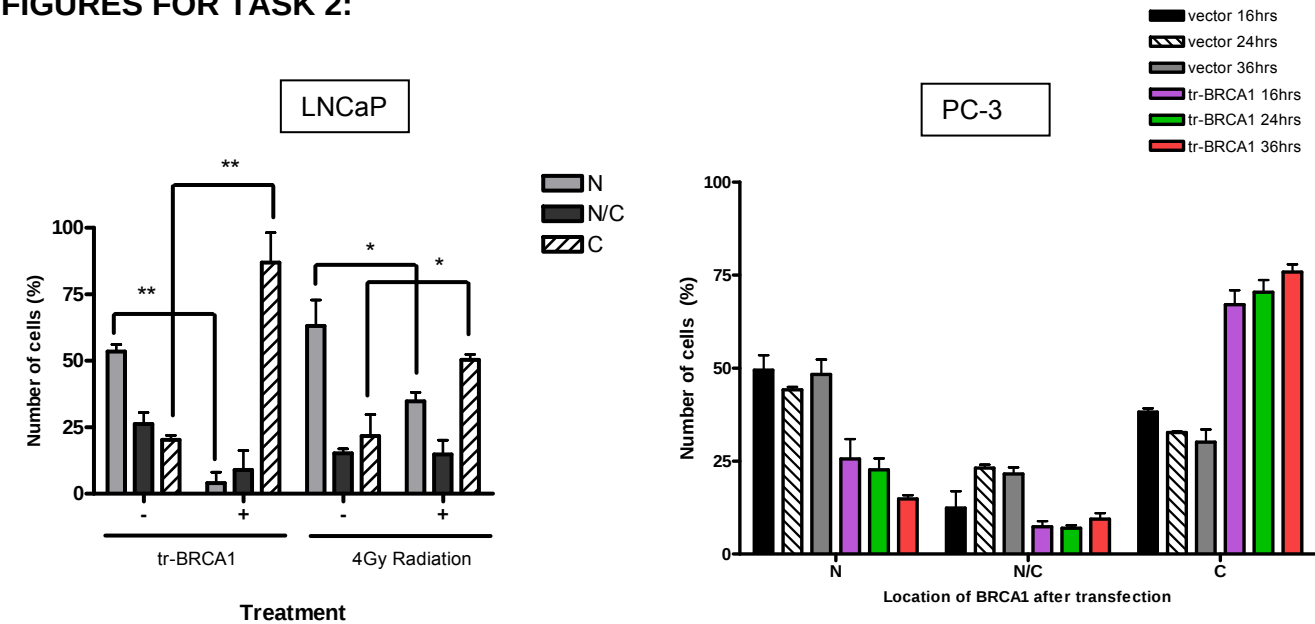


Figure 9. Tr-BRCA1 induces BRCA1 nuclear export independent of p53 status.

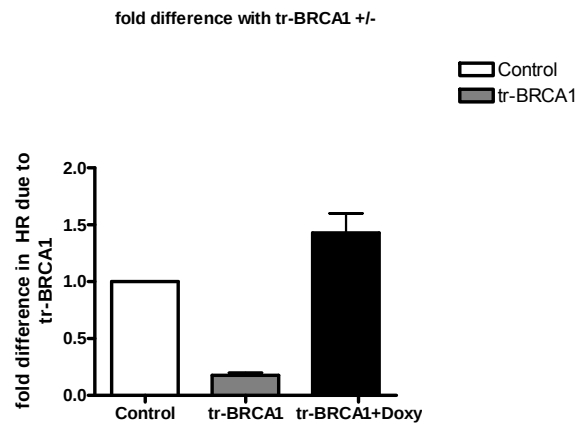


Figure 10. Tr-BRCA1 inhibits HR repair, while doxycycline, which turns off tr-BRCA1 expression, enhances repair.

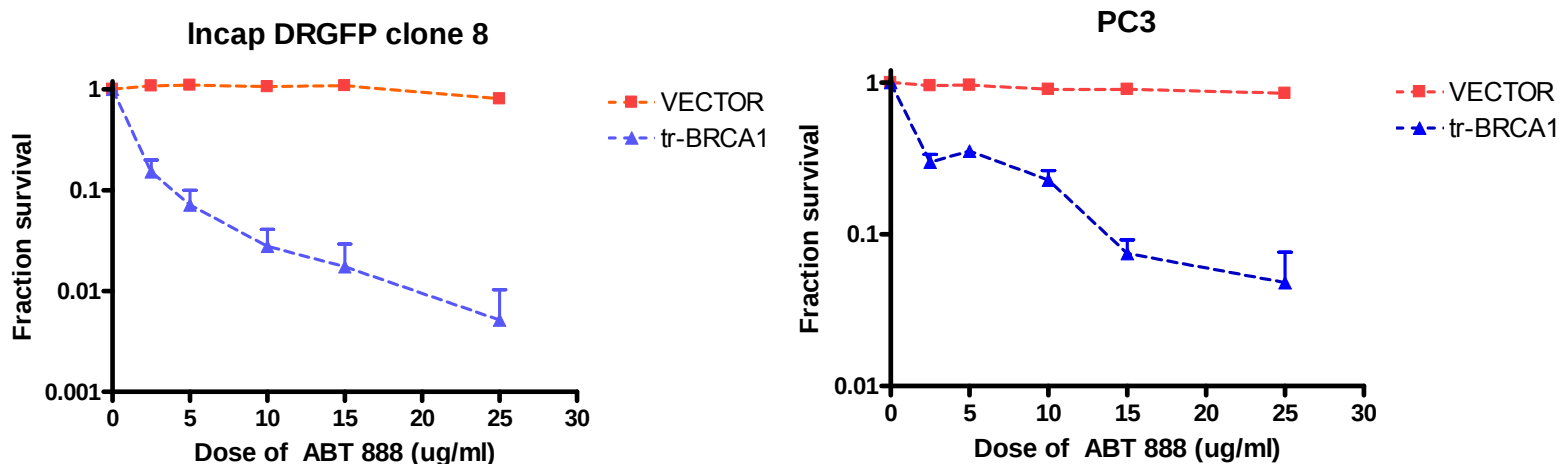


Figure 11. Tr-BRCA1 induces synthetic lethality with PARPi in LNCaP (left) and PC-3 (right).

Task 3. To validate the role of induced DSB repair deficiency and sensitivity to PARP1 inhibition *in vivo* with prostate tumor xenograft models (Months 24-36).

- A) Determine optimal cell number for grafting of LNCaP xenografts in mice (Months 24-36)
- B) To assess sensitivity of irradiated prostate tumor xenografts to PARP1 inhibition by tumor growth delay assays (Months 24-36)
- C) To assess resistance of prostate tumor xenografts to PARP1 inhibition following tet-repression of tr-BRCA1 expression by tumor growth delay assays (Months 24-36).

Progress on Task 3: We have begun LNCaP xenograft experiments to test *in vivo* effects of IR and PARPi. Currently, we are experiencing quite low tumor graft rates despite varying the tumor cell number. We may need to switch models which have better take rates. We are in the process of contacting Dr. Robert Matusik at Vanderbilt to obtain other models of AR+, p53 wild type prostate cancer models such as the CWR-22. We are also having problems establishing the stable expression of tr-BRCA1 in LNCaP cells, despite using a TETOFF system. It appears the tr-BRCA1 may be too toxic. A lentiviral approach will be tried, but given leakiness of TETOFF (and TETON), we are assessing other methods to induce stable expression.

REPORTABLE OUTCOMES: Provide a list of reportable outcomes that have resulted from this training grant to include:

We have presented data generated from this training grant at the ASTRO Annual Meeting 2010 and 2011. Both were invited oral presentations. Additionally, the 2010 presentation won the basic science award at ASTRO.

Importantly, training that occurred as a result of this grant has stimulated other research projects that investigate other methods of targeting DNA repair to render tumor cells susceptible to PARP inhibition. These projects have resulted in multiple grant awards, including a translational scholar award from the Sidney Kimmel Foundation for Cancer Research, and a career development award from the AACR/Genentech BioOncology. We have also submitted grant applications to the American Cancer Society as well as Department of Defense BCRP. Importantly, three clinical protocols have been initiated as a result of these studies.

Also, publications have resulted as a result of these “spin-off” projects. They are listed as follows:

1. Nowsheen, S, Bonner, JA, **Yang, ES***. The poly (ADP-Ribose) polymerase inhibitor ABT-888 reduces radiation-induced nuclear EGFR and augments head and neck tumor response to radiotherapy. *Radiother Oncol* 2011. 99: 331 – 338. ***Corresponding author**
2. Nowsheen, S, Trummell, H, Whitley, AC, Dobelbower, MC, LoBuglio, AF, Bonner, JA, **Yang, ES***. Cetuximab induces synthetic lethality with poly (ADP-Ribose) polymerase inhibition in head and neck cancer. *PLOS One* 2011. 6: e24148. ***Corresponding author.**
3. Nowsheen, S, Cooper, T, Bonner, JA, LoBuglio, AF, **Yang, ES***. Human HER2+ breast cancer susceptibility to poly (ADP-Ribose) polymerase inhibitors independent of a homologous recombination repair defect. *Cancer Research*, in press 2012. ***Corresponding author.**
4. **Yang, ES**, Nowsheen, S, Rahman, MA, Cook, R, Xia, F. Targeting BRCA1 localization to augment breast tumor susceptibility to poly(ADP-ribose) polymerase inhibition. *Cancer Research*, in revision 2012.
5. Nowsheen, S and **Yang, ES***. Targeting human epidermal growth factor receptor pathways to render triple negative breast cancer cells susceptible to PARP inhibition. *PLoS One*, in revision 2012. ***Corresponding author.**

CONCLUSION: In summary, IR induces synthetic lethality with PARP inhibition in LNCaP prostate cancer cells. The mechanism is due to IR-mediated BRCA1 nuclear export and subsequent generation of an HDR defect. These results are dependent on p53 and CRM1. For tumors without wildtype p53, we have found that expression of a truncated BRCA1 (tr-BRCA1) can achieve similar results as IR, including BRCA1 nuclear export, inhibition of HDR, and synthetic lethality with PARPi in both p53 wildtype and mutated prostate cancer cells. We are essentially on track with our proposed timeline. Lastly, we have obtained ACURO as well as IACUC approval to start validating our observations in vivo, although we are experiencing technical difficulties.

APPENDICES: My CV is appended.

CURRICULUM VITAE

Date: June 26, 2012

PERSONAL INFORMATION

Name: Eddy Shih-Hsin Yang, MD, PhD
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RANK/TITLE

Assistant Professor
Department: Department of Radiation Oncology
Department of Pharmacology and Toxicology
Department of Cell, Developmental, and Integrative Biology

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Business Fax: (205) 975-0784
Email: eyang@uab.edu

HOSPITAL AND OTHER (NON ACADEMIC) APPOINTMENTS:

University of Alabama at Birmingham School of Medicine, Birmingham, AL
Cooper Green Hospital, Birmingham, AL
Childrens Health Systems of Alabama, Birmingham, AL
Veterans Administration Hospital, Birmingham, AL

PROFESSIONAL CONSULTANTSHIPS:

None

EDUCATION:

1997 – 1999 Doctorate of Medicine, Research Distinction
2003 – 2005 University of Miami School of Medicine, Miami, FL

1999 – 2003 Doctorate of Philosophy, Department of Molecular and Cellular Pharmacology
University of Miami School of Medicine, Miami, FL
NIH NRSA predoctoral fellow

1993 – 1996 Bachelor of Arts in Biology with honors, Russian Minor, Johns Hopkins
University, Baltimore, MD

MILITARY SERVICE: N/A**LICENSURE: AL Medical License**

BOARD CERTIFICATION:

USMLE Steps 1-3

Radiation Biology and Physics 2009

Clinical Radiation Oncology Written Boards 2010

Clinical Radiation Oncology Oral Boards 2011

POSTDOCTORAL TRAINING:

2010 LDR Brachytherapy Fellowship, Seattle Prostate Institute

2006 – 2010 Residency, Department of Radiation Oncology, Vanderbilt University School of Medicine, Nashville, TN

ABR Holman Research Scholar

Nucletron Prostate HDR Training Course 2009

Chief Resident 2009-2010

2005 – 2006 Internship, Department of Internal Medicine, Mount Sinai Medical Center, Miami Beach, FL

ACADEMIC APPOINTMENTS: (In reverse chronological order)

2012 – Present, Guest Professor, Guangdong Medical College, Zhanjiang, Guangdong Province, People's Republic of China

2010 – Present, Assistant Professor, Department of Radiation Oncology, University of Alabama at Birmingham

2010 – Present, Assistant Professor, Department of Cell, Developmental, and Integrative Biology, University of Alabama at Birmingham

2010 – Present, Assistant Professor, Department of Pharmacology/Toxicology, University of Alabama at Birmingham

2010 – Present, Associate Scientist, Comprehensive Cancer Center, University of Alabama at Birmingham

AWARDS/HONORS:

- | | |
|---|------|
| • American Society for Radiation Oncology (ASTRO) Annual Meeting Basic Science Abstract Award | 2012 |
| • American Association for Cancer Research (AACR) – Genentech Career Development Award | 2012 |
| • Breast Cancer Research Foundation of Alabama Research Award | 2012 |
| • Mini-symposium speaker, 14 th International Congress of Radiation Research, Warsaw, Poland | 2011 |
| • John R. Durant Award for Excellence in Cancer Research | 2011 |
| • Translational Scholar Award, Sidney Kimmel Foundation for Cancer Research | 2011 |
| • Medical Research Award, Gabrielle's Angel Foundation for Cancer Research | 2011 |
| • UAB CCTS/COCD Translational Science Pilot Award | 2011 |
| • Fighting Children's Cancer Foundation Award | 2011 |
| • Department of Defense (DOD) Physician Research Training Award | 2010 |

• UAB Breast SPORE Career Development Award	2010
• American Society for Radiation Oncology (ASTRO) Annual Meeting Basic Science Abstract Award	2010
• Best Poster Presentation Award, Vanderbilt University Research Forum 2010	2010
• American Brachytherapy Society Seattle Prostate Brachytherapy Fellowship Award	2010
• 3 rd place, Vanderbilt Ingram Cancer Center Research Retreat Poster Competition	2010
• Chief Resident, Dept of Rad Onc Vanderbilt University	2009
• Roentgen Resident Research Award	2009
• 3 rd place, Vanderbilt Ingram Cancer Center Research Retreat Poster Competition	2009
• Elliot V. Newman Best Oral Presentation Award, Vanderbilt University Research Forum 2009	2009
• NIH LRP Award Recipient	2008
• American Society for Radiation Oncology (ASTRO) Basic Science Travel Grant	2008
• American Society for Radiation Oncology (ASTRO) Research Resident Seed Grant	2008
• Radiological Society of North America (RSNA) Research & Education Foundation Grant	2008
• Elliot V. Newman Best Oral Presentation Award, Vanderbilt University Research Forum 2008	2008
• Three microgrants from the Vanderbilt Institute for Clinical and Translational Research	2008
• Chair Fund Recipient, Gordon Research Conference: Understanding the DNA Damage Response to Optimize Radiation Therapy	2007
• Radiological Society of North America (RSNA) Research & Education Foundation Grant	2007
• American Board of Radiology Holman Research Pathway	2006
• Alpha Omega Alpha Medical Fraternity	2005
• Award of Academic Merit, University of Miami School of Medicine	2003
• Second Place, Biomedical Sciences, University of Miami Graduate School Research and Creativity Forum	2003
• Travel Grant, University of Miami School of Medicine—The Medical Faculty Association Margaret Whelan Graduate Student Scholarship Fund	2002
• Second Place, Best Research Award, University of Miami School of Medicine Medical Faculty Association	2002
• First Place, Biomedical Sciences, University of Miami Graduate School Research and Creativity Forum	2002
• Travel Grant, Annual Meeting of the Society for Basic Urological Research (SBUR)	2000
• Travel Grant, NATO/FEBS Advanced Study Institute on Protein Modules in Cellular Signaling, National Science Foundation	2000
• Predoctoral Fellowship, NIH/NIEHS	2000
• Florida Medical Scholar	1999

- Predoctoral Fellowship, NIH/NCBI 1996
- Phi Beta Kappa 1996
- Deans' List every semester, Johns Hopkins University 1993–1996

PROFESSIONAL SOCIETIES/MEMBERSHIPS:

- American Society for Therapeutic Radiology and Oncology (ASTRO)
- American Society for Clinical Oncology (ASCO)
- American Association for Cancer Research (AACR)
- American Board of Radiology (ABR)
- Radiological Society of North America (RSNA)
- Radiation Research Society (RRS)
- American College of Radiation Oncology (ACRO)
- American Brachytherapy Society (ABS)
- Roentgen Society, Vanderbilt University
- Alpha Omega Alpha Medical Fraternity

COUNCILS AND COMMITTEES:

- Resident Curriculum Review, UAB Radiation Oncology 2012–Present
- Mock Board Examiner, Vanderbilt University Radiation Oncology 2012–Present
- Founder & Chair, Vanderbilt Roentgen Society 2009–Present
- Board Member, Vanderbilt Medical Alumni Association 2010–2014
- Chief Resident, Vanderbilt University Radiation Oncology 2009–2010
- Representative, House Staff Advisory Council 2009–2010
- Co-Director, Eastern Student Research Forum (ESRF) sponsored by the American Medical Association 1999–2000
- Registration Committee Chair for ESRF 1998–1999
- Class of 2001 Treasurer, University of Miami School of Medicine 1997–1998
- Board of Intramural Athletics, Johns Hopkins University 1994–1996

UNIVERSITY ACTIVITIES:

- Summer internship in biomedical science mentor 2012–
- GBS Winter Poster Session, Judge 2012–
- Clinical and translational science program mentor 2011–
- Medical Scientist Training Program (MSTP) Faculty Member 2011–
- Cancer Biology Member theme member within the Graduate Biomedical Sciences 2011–
- Cell, Molecular, and Developmental Biology theme member within the Graduate Biomedical Sciences 2011–
- Pathobiology and Molecular Medicine theme member within the Graduate Biomedical Sciences 2011–
- Neuroscience theme member within the Graduate Biomedical Sciences 2011–
- Post-doctoral research day, Judge, Cancer Biology 2011–
- ACS-U's Too Prostate Cancer Support Group 2011–
- Lung cancer working group, UAB-CCC 2011–
- Residency applicant interviewee 2010–
- Translational Breast Cancer Research Consortium 2010–
- Breast cancer working group, UAB-CCC 2010–
- Head & neck cancer working group, UAB-CCC 2010–

- Head and neck cancer “Think Tank” 2010-
- Genitourinary cancer working group, UAB-CCC 2010-
- Experimental Therapeutics, UAB-CCC 2010-

EDITORIAL BOARD MEMBERSHIPS:

PEER REVIEWER:

- *Cancer Research*
- *Molecular Cancer Therapeutics*
- *Frontiers in Radiation Oncology*
- *Cancer Biotherapy and Radiopharmaceuticals*
- *Current Molecular Medicine*
- *Cancer Letters*
- *Head and Neck*
- *Frontiers in Medicine*
- *J Cancer Science and Therapy*
- *Tumor Biology*

MAJOR RESEARCH INTERESTS: My laboratory interests focus on the targeting of DNA repair pathways to improve the therapeutic ratio. Specifically, we can enhance tumor susceptibility to DNA damage by novel combinations of targeted agents. Additionally, we aim to protect normal brain by augmenting DNA repair pathways.

TEACHING EXPERIENCE:

TEACHING:

- Course co-director, Translational Medicine, University of Alabama-Birmingham 2012
- Lecturer, Carcinogenesis: DNA repair/Genome stability University of Alabama-Birmingham 2012
- Lecturer, GBS775: Cancer Treatment, University of Alabama-Birmingham 2011
- Radiobiology Review, DNA repair pathways, University of Alabama-Birmingham 2011
- Molecular Radiation Oncology Lecture Series, University of Alabama-Birmingham 2010
- Clinical Oncology Lecture Series for Vanderbilt University Medica Center Medical Physics Program 2006–2010

MENTORSHIP/TRAINING:

Research

- Tanu Patel, Summer Internship Biomedical Science Program
- Amber L. Guidry, PhD student, Dissertation committee member, Pathobiology and Molecular Medicine Program
- Monica Wieglos, PhD student, Dissertation mentor, Cancer Biology Program
- Jennifer Stanley, MD/PhD student, Dissertation mentor, Cancer Biology Program
- Monjri Shah, MD, Gyn-Onc Fellow
- Angela Ziebarth, MD, Gyn-Oncology Fellow
- Caroline Mills, PhD, Post-doctoral fellow
- Alex Whitley, MD, PhD, Radiation Oncology Resident, Research mentor,

- American Board of Radiology Holman Research Pathway
- Lisa Klepczyk, MD, Radiation Oncology Resident, Mentor, Clinical and Translational Science Training Program
- Aleksander Dragovic, MD, Radiation Oncology Resident
- Somaira Nowsheen, MS, MD/PhD Student Mayo
- Alice Weaver, rotation student, MD/PhD Program
- Joshua Jackson, rotation student, Cancer Biology Program
- Karla Mihalak, 2nd year graduate student, lab rotation, University of Miami School of Medicine.
- Drew Everhart, 2nd year graduate student, lab rotation, University of Miami School of Medicine.

Clinical Resident Rotations

- Jennifer Hung, MD
- John Stewart, MD
- Aleksander Dragovic, MD
- Marcus Wagner, MD
- Lisa Klepczyk, MD
- Grant Clark, MD
- Alexander Whitley, MD, PhD
- Markus Bredel, MD, PhD

MAJOR LECTURES AND VISITING PROFESSORSHIPS:

- | | |
|---|------|
| • Grand Rounds, Emory University, Atlanta, GA | 2012 |
| • Visiting Professor, Washington University, St Louis, MO | 2012 |
| • Invited speaker, Vanderbilt University Research Retreat | 2012 |
| • Guest Professor, Guangdong Medical College, People's Republic of China | 2012 |
| • Mini-symposium speaker, 14 th International Congress of Radiation Research, Warsaw, Poland | 2011 |
| • Invited speaker, UAB Comprehensive Cancer Center Research Retreat | 2011 |
| • Mini-symposium speaker, Annual Meeting of the Radiation Research Society, Maui, Hawaii | 2010 |
| • Invited lecturer, Mid-South Society of Radiation Therapists Spring Conference | 2006 |

CLINICAL PROTOCOLS:

ACTIVE:

UAB X101214005: A retrospective analysis of DNA repair and EGFR pathway molecular markers in HER2/Neu positive breast cancer patients in order to predict response to PARP inhibition

Role: Principal Investigator

UAB X110504004: Pilot study of the molecular determinants of cellular susceptibility to PARP inhibition in an ex-vivo model of human cervical cancer

Role: Principal Investigator

UAB X1219: Molecular determinants of cellular susceptibility to PARP inhibition in an ex-vivo model of human cholangiocarcinoma
Role: Principal Investigator

PENDING:

M10-897: A Randomized, Double-Blind, Phase 2, Dose-Ranging Study to Evaluate the Safety and Efficacy of Veliparib and Whole Brain Radiation Therapy Versus Placebo and Whole Brain Radiation Therapy in Subjects with Brain Metastases from Non-Small Cell Lung Cancer
Role: Institutional Principal Investigator

GRANT SUPPORT:

ACTIVE:

Physician Research Training Award (PI: YANG) 8/1/10 – 7/31/13 6.6 Cal Months
PC094457, Department of Defense \$413,949
Targeting homology-directed recombinational repair (HR) of chromosomal breaks to sensitize prostate cancer cells to poly (ADP-Ribose) polymerase (PARP) inhibition
The major goals of the project are to render prostate cancer cells with intact HR susceptible to PARP inhibition with radiation or dominant negative BRCA1 peptide.
Role: Principal Investigator

Career Development Award (PI: YANG) 7/1/12 – 6/30/14 0.36 Cal Months
American Association for Cancer Research \$100,000
Genentech BioOncology
HER2 overexpression confers susceptibility to PARP inhibition
The major goal of the project is to explore the mechanism by which HER2+ breast tumors are susceptible to PARP inhibition alone.
Role: Principal Investigator

Conventional Research Grant (PI: YANG) 2/1/11 – 1/31/14 0.6 Cal Months
Gabrielle's Angel Foundation for Cancer Research \$225,000
Mechanisms by which GSK3 β inhibition enhances nonhomologous end-joining repair of IR-induced double strand breaks
The major goals of the project are to investigate the mechanisms by which GSK3 β inhibition enhances nonhomologous end-joining repair in irradiated hippocampal neurons and to determine whether this is dependent on the tumor suppressor p53
Role: Principal Investigator

Translational Science Scholar Award (PI: YANG) 7/1/11 – 6/30/13 1.2 Cal Months
Sidney Kimmel Foundation for Cancer Research \$200,000
Can cetuximab induce synthetic lethality with PARP inhibition in head and neck cancer?
The major goal of the project is to determine the mechanisms by which cetuximab induces synthetic lethality with PARP inhibition.
Role: Principal Investigator

Bo Johnson Memorial Foundation (PI: YANG) 11/1/11 – 10/31/12
Pilot Project Grant for Esophageal Cancer \$50,000
Targeting EGFR Pathways to induce Synthetic Lethality of Esophageal Tumors to PARP Inhibition

The major goal of the project is to target EGFR to render esophageal tumors susceptible to PARP inhibition

Mentored grant for Alexander Whitley, MD, PhD

Role: Principal Investigator/Mentor

Pilot Grant Award (PI: YANG) 1/1/12 – 12/31/12

Breast Cancer Research Foundation of Alabama \$25,000

DNA repair independent mechanism of PARPi susceptibility

The major goal of the project is to determine the DNA repair independent mechanisms by which tumors are susceptible to PARP inhibition

Role: Principal Investigator

Career Development Award (PI: YANG) 9/1/10 – 8/31/12 0 Cal Months

UAB/NIH BREAST SPORE \$100,000

Targeting HER pathways to render triple negative breast cancer cells susceptible to PARP inhibition

The major goal of the project is to convert triple negative breast tumor susceptibility to PARP inhibition by targeting HER pathways with lapatinib.

Role: Principal Investigator

Translational Research Pilot Award (PI: YANG) 5/1/11 – 4/30/12 0 Cal Months

UAB Center for Clinical and Translational Science \$60,000

Targeting EGFR pathways to induce synthetic lethality of head and neck tumors to poly (ADP-Ribose) polymerase inhibitors (PARPi)

The major goal of the project is to induce synthetic lethality using EGFR and PARP inhibition *in vivo* in mice bearing orthotopically implanted head and neck tumor xenografts.

Role: Principal Investigator

UAB X101214005 (PI: YANG) 5/15/2012 – Present

UAB Radiation Oncology \$5,000

A retrospective analysis of DNA repair and EGFR pathway molecular markers in HER2/Neu positive breast cancer patients in order to predict response to PARP inhibition

Mentored intramural grant for Lisa Klepczyk, MD

Role: Principal Investigator/Mentor

UAB X110504004 (PI: YANG) 3/1/2012 – Present

UAB Radiation Oncology \$8,500

Pilot study of the molecular determinants of cellular susceptibility to PARP inhibition in an ex-vivo model of human cervical cancer

Mentored intramural grant for Aleksander Dragovic, MD

Role: Principal Investigator/Mentor

UAB X1219 (PI: JACOB) 5/1/2012 – Present

UAB Radiation Oncology \$3,500

Molecular determinants of cellular susceptibility to PARP inhibition in an ex-vivo model of human cholangiocarcinoma

Role: Co-Principal Investigator

Career Development Award (PI: JACOB) 1/1/11 – 12/31/12 0 Cal Months

UAB/NIH PANCREATIC SPORE \$50,000

Radiosensitization and SPARC interactions of ABI-007 in pancreatic cancer

The major goal of this project is to assess interactions and molecular determinants of the nano-albumin-bound paclitaxel (Abraxane, or ABI-007) with the SPARC protein that can determine response of tumors to Abraxane, radiation, or other chemotherapies.

Role: Co-Investigator

IMPACT Award (PI: YANG)

7/1/10 – 6/30/12

0 Cal Months

UAB School of Medicine

\$150,000

This award supports biomedical research aligned with the research priorities of UAB, including the UAB School of Medicine's research strategic plan, and is used for recruiting and setup of Dr. Yang's laboratory.

Role: Principal Investigator

COMPLETED:

5F30ES005910-04 (PI: YANG)

4/1/02 – 6/30/05

National Institute of Environmental Health Sciences, National Institute of Health

NRSA F30 Fellowship Grant

Vitamin D mediated growth inhibition of prostate cancer cells

Role: Principal Investigator

RR0725 (PI: YANG)

7/1/07 – 12/31/08

Radiological Society of North America Research and Education Foundation

Role of lithium and specific GSK-3 inhibitors in neural protection during cranial irradiation

Role: Principal Investigator

Microgrant, CTSA UL1RR024975 (PI: YANG)

3/1/08 – 11/30/08

Vanderbilt Institute for Clinical and Translational Research

Targeting BRCA1 location to enhance prostate cancer sensitivity to PARP inhibitors

Role: Principal Investigator

Microgrant, CTSA UL1RR024975 (PI: YANG)

3/1/08 – 11/30/08

Vanderbilt Institute for Clinical and Translational Research

BRCA1 subcellular localization and lung cancer response to Tarceva

Role: Principal Investigator

RR0813 (PI: YANG)

7/1/08 – 12/31/09

Radiological Society of North America Research and Education Foundation

Neuroprotection via enhanced repair of radiation-induced DNA damage by GSK3 inhibitors

Role: Principal Investigator

Resident Research Grant (PI: YANG)

7/1/08 – 12/31/09

American Society for Therapeutic Radiology and Oncology

Targeting homologous recombination repair to sensitize cancer cells to PARP inhibitors

Role: Principal Investigator

Microgrant, CTSA UL1RR024975 (PI: YANG)

9/1/08 – 3/31/09

Vanderbilt Institute for Clinical and Translational Research

GSK3 inhibition and DNA repair

Role: Principal Investigator

Pilot Grant Award (PI: YANG)

2/1/2011

Fighting Children's Cancer Foundation

Funds were used to generate preliminary data investigating mechanisms of neuroprotection by GSK3 inhibition
Role: Principal Investigator

OTHER:

BIBLIOGRAPHY:

MANUSCRIPTS:

Already Published:

1. De Marzo, AM, Marchi, VL, Yang, ES, Veeraswamy, R, Lin, X, and Nelson, WG. Abnormal regulation of DNA methyltransferase expression during colorectal carcinogenesis. *Cancer Research* 1999. 59: 3855 - 3860.
2. Yang, ES, Maiorino, CA, Roos, BA, Knight, SR, and Burnstein, KL. 1,25-(OH)₂ vitamin D₃-mediated growth inhibition of an androgen ablated prostate cancer cell model involves the cyclin-dependent kinase inhibitor p27. *Molecular & Cellular Endocrinology* 2002. 186(1): 69 – 79.
3. Yang, ES and Burnstein, KL. Vitamin D inhibits G1 to S progression in LNCaP prostate cancer cells through p27^{Kip1} stabilization and Cdk2 mislocalization to the cytoplasm. *Journal of Biological Chemistry* 2003. 278: 46847 – 46868.
4. Knight-Krajewski, S, Welsh, CF, Liu, YQ, Lyons, L, Faysal, J, Yang, ES, and Burnstein, KL. Deregulation of the Rho GTPase, Rac1, suppresses cyclin-dependent kinase inhibitor p21^{CIP1} in androgen-independent human prostate cancer cells. *Oncogene* 2004. 23: 5513 - 5522.
5. Yang, ES*, Moretti, L*, Kim, KW, Lu, B. Autophagy signaling in cancer and its role as a novel target to enhance cancer therapy. *Drug Resistance Updates* 2007. 10: 135 – 143. *co-first authors.
6. Jaboin, JJ, Shinohara, ET, Moretti, L, Yang, ES, Kaminski, JM, Lu, B. The role of mTOR inhibition in augmenting radiation induced autophagy. *Tech Cancer Research & Treatment* 2007. 6(5): 433 – 448.
7. Li, L, Wang, H*, Yang, ES*, Arteaga, CL, Xia, F. Erlotinib attenuates homologous recombinational repair of chromosomal breaks in human breast cancer cells. *Cancer Research* 2008. 68(22): 9141 – 9146. *co-authors.
8. Yang, ES*, Wang, H*, Jiang, G, Newshean, S, Fu, A, Hallahan, DE, Xia, F. Lithium-mediated protection of hippocampal cells involves enhancement of DNA-PK dependent repair in mice. *J Clinical Investigation* 2009. 119(5): 1124 – 1135. *co-first authors.
9. Yang, ES, Murphy, BM, Chung, CH, Netterville, JL, Burkey, BB, Gilbert, J, Yarbrough, WG, Sinard, R, Cmelak, AJ. Evolution of clinical trials in head and neck cancer. *Critical Reviews in Oncology/Hematology* 2009. 71: 29 – 42.
10. Yang, ES*, Wu, FY*, Willey, CD, Atkinson, JB, Ely, K, Garrett, G, Cmelak, AJ. Refractory lympho-epithelial carcinoma of the nasopharynx: A case report illustrating a protracted clinical course. *Head and Neck Oncology* 2009. 1:18. *co-first authors
11. Pawlowski, JM, Yang, ES, Malcolm, AW, Coffey, CW, Ding, GX. Reduction of dose delivered to organs-at-risk in prostate cancer patients via image-guided radiation therapy (IGRT). *IJROBP* 2010. 76: 924 – 934.

12. **Yang, ES** and Xia, F. DNA damage-induced BRCA1 shuttling. *FEBS Journal* 2010. 277: 3079 – 3085.
13. **Yang, ES***, Wang, H*, Jiang, J, Nowsheen, S, Feng, Z, Xia, F. DNA damage-induced cytotoxicity is dissociated from BRCA1's function in DNA repair but is dependent on its cytosolic accumulation. *Cancer Research* 2010. 70: 6258 – 6267. *co-first authors.
14. **Yang, ES**, Nowsheen, S, Thotala, D, Hallahan, DE, Xia, F. GSK3 α inhibition enhances repair of double strand breaks in irradiated hippocampal neurons. *Neuro-Oncology* 2011. 13: 459 – 470.
15. Bonner, JA, Willey, CD, **Yang, ES**, Dobelbower, MC, Sanford, LL, Bright, SJ, Buchsbaum, DJ, Raisch, KP. Treatment of Small Cell Lung Cancer with TRA-8 in Combination with Cisplatin and Radiation. *Radiother Oncol* 2011. doi:10.1016/j.radonc.2011.05.083.
16. Deeley, MA, Chen, A, Datteri, R, Noble, J, Cmelak, A, Donnelly, E, Malcolm, A, Moretti, L, Jaboin, J, Niermann, K, **Yang, ES**, Yu, DS, Yei, F, Koyama, T, Ding, GX, Dawant, BM. Comparison of manual and automatic segmentation methods for brain structures in the presence of space-occupying lesions: a multi-expert study. *Phys Med Biol* 2011. 56:4557-77.
17. Nowsheen, S, Bonner, JA, **Yang, ES**. The poly (ADP-Ribose) polymerase inhibitor ABT-888 reduces radiation-induced nuclear EGFR and augments head and neck tumor response to radiotherapy. *Radiother Oncol* 2011. 99: 331 – 338.
18. Nowsheen, S, Trummell, H, Whitley, AC, Dobelbower, MC, LoBuglio, AF, Bonner, JA, **Yang, ES**. Cetuximab induces synthetic lethality with poly (ADP-Ribose) polymerase inhibition in head and neck cancer. *PLOS One*, 2011. 6: e24148.
19. Bonner, JA, **Yang, ES**, Trummell, HQ, Nowsheen, S, Willey, CD, Raisch, KP. Inhibition of STAT-3 results in greater cetuximab sensitivity in head and neck squamous cell carcinoma. *Radiother Oncol* 2011. 99: 339 – 343.
20. **Yang, ES***, Jiang, J*, Nowsheen, S, Wang, H, Wang, T, Wang, Y, Billheimer, D, Chakravarthy, AB, Brown, M, Haffty, B, Xia, F. p53-dependent BRCA1 nuclear export controls cellular susceptibility to DNA damage. *Cancer Research* 2011. 71: 5546 – 5557. *co-first authors.
21. Mills, CN, Nowsheen, S, Bonner, JA, **Yang, ES**. Emerging roles of glycogen synthase kinase 3 in the treatment of brain tumors. *Front Mol Neurosci* 2011. 4: 47.
22. Nowsheen, S, Whitley, AC, **Yang, ES**. Biomarkers to assess the targeting of DNA repair pathways to augment tumor response to therapy. *Current Molecular Medicine*, 2012. PMID 22292444.
23. Jarboe, JS, Anderson, JC, Duarte, CW, Mehta, T, Nowsheen, S, Hicks, PH, Whitley, AC, Rohrbach, TD, McCubrey, RO, Chiu, S, Burleson, TR, Bonner, JA, Gillespie, GY, **Yang, ES**, Willey, CD. MARCKS Regulates Growth, Radiation Sensitivity and is

- a Novel Prognostic Factor for Glioma. *Clinical Cancer Research*, in press 2012.
24. Jarboe, JS, Jaboin, JJ, Anderson, JC, Newsheer, S, Stanley, JA, Ruijtenbeek, R, Tu, T, Hallahan, DE, **Yang, ES**, Bonner, JA, Willey, CD. Kinomic profiling approach identifies Trk as a novel radiation modulator. *Radiother Oncol*, in press 2012.
 25. Newsheer, S, Aziz, K, Tran, PT, Gorgoulis, VG, **Yang, ES**, Georgakilas, AG. Epigenetic inactivation of DNA repair in breast cancer. *Cancer Letters*, in press 2012.
 26. Newsheer, S, Xia, F, and **Yang, ES**. Assaying DNA damage in hippocampal neurons using the comet assay. *Journal of Visualized Experiments*, in press 2012.
 27. McDonald, A, Bishop, JM, Dobelbower, MC, Kim, RY, **Yang, ES**, Smith, H, Wu, X, Fiveash, JB. Hypofractionated prostate radiotherapy with or without conventionally fractionated nodal irradiation: clinical toxicity observations and retrospective daily dosimetry. *Prostate Cancer*, in press 2012.
 28. Newsheer, S, Cooper, T, Bonner, JA, LoBuglio, AF, **Yang, ES**. Human HER2+ breast cancer susceptibility to poly (ADP-Ribose) polymerase inhibitors independent of a homologous recombination repair defect. *Cancer Research*, in press 2012.
 29. Newsheer, S and Yang, ES. The intersection between DNA damage response and the apoptotic pathways. *Experimental Oncology*, in press 2012.

In revision:

30. **Yang, ES**, Newsheer, S, Rahman, MA, Cook, R, Xia, F. Targeting BRCA1 localization to augment breast tumor susceptibility to poly(ADP-ribose) polymerase inhibition. *Cancer Research*, in revision 2012.
31. Ziebarth, A, Newsheer, S, Steg, AD, Shah, MM, Dobin, ZC, Han, H-D, Lopez-Berestein, G, Sood, AK, Conner, MB, **Yang, ES**, Landen, CN. Endoglin (CD105) contributes to platinum resistance and is a target for tumor-specific therapy in epithelial ovarian cancer. *Clinical Cancer Research*, in revision 2012.
32. Newsheer, S and **Yang, ES**. Targeting human epidermal growth factor receptor pathways to render triple negative breast cancer cells susceptible to PARP inhibition. *PLoS One*, in revision 2012.

BOOK CHAPTERS:

1. Moretti, L, **Yang, ES**, Hallahan, DE, Lu, B. Lithium as a differential radioprotector following cranial irradiation. In *CURED II: Late Effects of Cancer Treatment on Normal Tissues (LENT)*. Edited by R. Rubin, L.S. Constone, L.B. Marks, and P. Okunieff. Springer: New York, 2008.
2. Ding, G., **Yang, E.S.**, Niermann, K., Xia, F. & Cmelak, A.J. MRI in Radiation Therapy Planning. In *Quantitative MRI in Cancer* (eds. Yankeelov, T.E., Pickens, D.R. & Price, R.R.) 265-276 (CRC Press, Taylor & Francis Group, New York, 2012).
3. Newsheer, S and **Yang, ES**. Staying a step ahead of cancer. In *Cancer Prevention – From Mechanisms to Translational Benefit*. Edited by A. Georgakilas. InTech,

2012.

COMMENTARIES:

1. **Yang, ES** and Chakravarthy, AB. Commentary on “Comprehensive locoregional treatment and systemic therapy for postmastectomy isolated locoregional recurrence,” *IJROBP* (2008) 72: 1456 – 1464. In *Breast Diseases: A Year Book Quarterly*, volume 20. E Singletary and TA Buchholz, Eds. Mosby, Inc.
2. **Yang, ES** and Chakravarthy, AB. Commentary on “Regional nodal recurrence after breast conservation treatment with radiotherapy for women with early-stage breast carcinoma,” *IJROBP* (2009) 73: 1475 – 1481. In *Breast Diseases: A Year Book Quarterly*, volume 20n2. E Singletary and TA Buchholz, Eds. Mosby, Inc

SELECTED PUBLISHED ABSTRACTS/POSTER EXHIBITS (from over 40):

1. **Yang, ES**, David-Beabes, G, Veeraswamy, R, Brooks, JD, and Nelson, WG. Expression of Human 5-methylcytosine DNA Methyltransferase in Human Prostate, Prostate Cancer, and the Prostate Cancer Cell Lines. Johns Hopkins University School of Medicine, Baltimore, MD. *Proceedings of the American Association for Cancer Research*, 1997.
2. **Yang, ES**, Iida, N, and Bourguignon, L. Novel CD44 Splice Variants in Human Ovarian Cancer. Department of Anatomy and Cell Biology, University of Miami School of Medicine, Miami, FL. *American Medical Association's Eastern Student Research Forum*, 1998.
3. **Yang, ES**, Maiorino, CA, and Burnstein, KL. Antiproliferative Effects of 1,25-(OH)₂ Vitamin D₃ in an Androgen Ablated Prostate Cancer Cell Model. Department of Molecular and Cellular Pharmacology, University of Miami School of Medicine, Miami, FL. *Endocrine Society*, March 2000; *NATO/FEBS Advanced Study Institute on Protein Modules in Cellular Signalling*, August 2000; *Society of Basic Urological Research*, November 2000.
4. **Yang, ES** and Burnstein, KL. 1,25-(OH)₂ Vitamin D₃-Mediated Upregulation of the Cyclin Dependent Kinase Inhibitor p27^{Kip1} May Involve Decreased Nuclear Import. Department of Molecular and Cellular Pharmacology, University of Miami School of Medicine, Miami, FL. *University of Miami Graduate School Research and Creativity Forum*, March 2002; *Annual Zubrod Memorial Lectureship and Poster Session*, June 2002.
5. **Yang, ES** and Burnstein, KL. 1,25-(OH)₂ vitamin D₃-mediated upregulation of p27^{Kip1} in LNCaP cells involves decreased p27^{Kip1} degradation and correlates with decreased nuclear localization of cyclin-dependent kinase 2. Department of Molecular and Cellular Pharmacology, University of Miami School of Medicine. *University of Miami Graduate School Research and Creativity Forum*, March 2003; *Proceedings of the American Association for Cancer Research*, July 2003.
6. **Yang, ES**, Lu, B, and Hallahan, DE. Lithium-mediated neuroprotection during cranial irradiation: A phase I trial. Department of Radiation Oncology, Vanderbilt University Medical Center. *Proceedings of the American Society of Radiation Oncology*, October 2007.

7. **Yang, ES**, Wang, H, Hallahan, DE, Xia, F. Lithium-mediated protection of hippocampal cells involves enhancement of DNA-PK dependent nonhomologous end joining of chromosomal breaks. Department of Radiation Oncology, Vanderbilt University Medical Center. *Chair Fund Award, Gordon Research Conference: Understanding the DNA damage response to optimize radiation therapy, January 2008.*
8. **Yang, ES**, Wang, H, Li, L, Xia, F. Dissociation of BRCA1's DNA repair function from DNA damage-induced cytotoxicity: A dependence on BRCA1 localization. Department of Radiation Oncology, Vanderbilt University Medical Center. *Proceedings of the American Society of Radiation Oncology, September 2008.*
9. **Yang, ES**, Wang, H, Nam, EA, Wang, Y, Billheimer, D, Chakravarthy, AB, Brown, M, Haffty, B, Xia, F. Can sporadic breast cancers with genetically wild-type BRCA1 behave phenotypically like BRCA1-associated breast tumors? Department of Radiation Oncology, Vanderbilt University Medical Center. *Proceedings of the American Society of Radiation Oncology, November 2009.*
10. **Yang, ES**, Newsheer, S, Xia, F. Targeting BRCA1 localization to convert tumor cell susceptibility to PARP inhibition. Department of Radiation Oncology, University of Alabama-Birmingham. *Proceedings of the American Society of Therapeutic Radiation Oncology, November 2010.*
11. Klepczyk, L, Newsheer, S, Xia, F, **Yang, ES**. BRCA1 Nuclear Export Sensitizes Prostate Cancer Cells to Poly (ADP-ribose) Polymerase-1 (PARP1) Inhibition via the CRM1/exportin Pathway. Department of Radiation Oncology, University of Alabama-Birmingham. *Proceedings of the American Society of Radiation Oncology, October 2011.*
12. Fiveash J, Bishop JM, Jacob R, Kim RY, Dobelbower MC, **Yang ES**, McDonald A, Smith H, Wu X: Daily Rectal Dosimetry in Patients with Late Grade 2 or Greater Rectal Toxicity after Hypofractionated Image Guided Radiation Therapy for Prostate Cancer. *Proceedings of the American Society of Radiation Oncology, October 2011.*
13. Whitley AC, **Yang ES**, Shen S, Spencer S, Minnich DJ, Dobelbower MC. Comparison of respiratory gate triggered kilovoltage (kV) portal images (GTPI) versus kV cone-beam computed tomography images (CBCT) for patient alignment and verification thoracic stereotactic body radiotherapy (SBRT) patients with implanted fiducial markers. *Proceedings of the American Society of Radiation Oncology, October 2011.*
14. Whitley, AC, Newsheer, S, Cooper, T, Trummel, H, LoBuglio, AF, Bonner, JA, **Yang, ES**. Cetuximab induces synthetic lethality with the poly(ADP-Ribose) polymerase inhibitor ABT-888 in head and neck cancer. *Gordon Research Conference, March 2012.*
15. Whitley, AC, Newsheer, S, Cooper, T, LoBuglio, AF, Bonner, JA, **Yang, ES**. Synthetic lethal interactions between EGFR and PARP inhibition in multiple tumor types. *Proceedings of the American Association for Cancer Research, April 2012.*

16. **Yang, ES**, Newsheer, S, Cooper, T, Bonner, JA, LoBuglio, AF. Human HER2+ breast tumor susceptibility to PARP inhibitors independent of a homologous recombination repair defect. *Proceedings of the American Society of Clinical Oncology, June 2012.*
17. Newsheer, S, Cooper, T, LoBuglio, AF, Bonner, JA, **Yang, ES**. Synthetic lethal interactions between EGFR and PARP inhibition in triple negative breast cancer. ***Poster discussion.** *Proceedings of the American Society of Radiation Oncology, October 2012.*

ORAL PRESENTATIONS/INVITED TALKS:

1. Wang, Z, **Yang, ES**, and Burnstein, KL. Vitamin D3 Inhibits Cancer Cell Proliferation through Nuclear Exclusion and Decreased Activity of Cyclin-Dependent Kinase 2. *Podium presentation at Keystone Symposia: Hormonal regulation of tumorigenesis, February 2005.*
2. **Yang, ES**. Early Stage Breast Cancer. *Mid-South Society of Radiation Therapists Spring Conference, May 2006.*
3. **Yang, ES**, Wang, H, Jiang, G, Hallahan, DE, Xia, F. Lithium-mediated protection of hippocampal cells involves enhancement of DNA-PK dependent nonhomologous end joining of chromosomal breaks. *Vanderbilt University Research Forum, April 2008.* Elliot V. Newman Best Oral Presentation Award.
4. **Yang, ES**, Wang, H, Li, L, Xia, F. Dissociation of BRCA1's DNA repair function from DNA damage-induced cytotoxicity: A dependence on BRCA1 localization. *ASTRO Annual Meeting, September 2008.* ASTRO Basic Science Travel Grant.
5. **Yang, ES**, Newsheer, S, Thotala, D, Hallahan, DE, Xia, F. Inhibition of GSK3 β enhances repair of double strand breaks in hippocampal neurons. *Vanderbilt Research Forum, April 2009.* Elliot V. Newman Best Oral Presentation Award.
6. **Yang, ES**, Wang, H, Nam, EA, Wang, Y, Billheimer, D, Chakravarthy, AB, Brown, M, Haffty, B, Xia, F. Can sporadic breast cancers with genetically wild-type BRCA1 behave phenotypically like BRCA1-associated breast tumors? *ASTRO Annual Meeting, November 2009.*
7. **Yang, ES**, Newsheer, S, Xia, F. Targeting BRCA1 localization to convert tumor cell susceptibility to PARP inhibition. *Mini Symposium, Radiation Research Society Annual Meeting, September 2010.*
8. **Yang, ES** and Willey, CD. Combined EGFR/PI3K/mTOR inhibition with radiation for locally advanced head and neck cancer. *Center for Clinical and Translational Science (CCTS) Concepts Meeting, October 2010.*
9. **Yang, ES**. Induced synthetic lethality with cetuximab and the PARP inhibitor ABT-888 in head and neck cancer. *UAB Head and Neck Cancer Research "Think Tank," October 2010.*
10. **Yang, ES**, Newsheer, S, Xia, F. Targeting BRCA1 localization to convert tumor cell susceptibility to PARP inhibition. *ASTRO Annual Meeting, November 2010.*

11. **Yang, ES.** PARP inhibition in HER2+ breast cancer. *UAB Breast Cancer Working Group, December 2010.*
12. **Yang, ES.** Cetuximab induces synthetic lethality with PARP inhibition in head and neck cancer cells. *UAB Comprehensive Cancer Center Seminar Series, December 2010.*
13. **Yang, ES.** Advances in prostate cancer. *American Cancer Society Us Too Prostate Cancer Support Group, February 2011.*
14. **Yang, ES.** **Synthetic lethality with PARP inhibition in sporadic cancer.** *Clinical and Translational Research Concepts, UAB Comprehensive Cancer Center, March 2011.*
15. **Yang, ES.** Synthetic lethality with PARP inhibition in sporadic head and neck cancer. *UAB Head and Neck Working Group, March 2011.*
16. **Yang, ES.** Potential determinants of sporadic tumor susceptibility to PARP inhibition. *Molecular Pharmacology Seminar Series, April 2011.*
17. **Yang, ES.** Advances in breast cancer therapies. *Top Oncology Treatment Advances, Russell Medical Center, May 2011.*
18. **Yang, ES.** Personalized medicine for head and neck cancer. *Southeast Cancer Foundation, September 2011.*
19. **Yang, ES.** Targeting the epidermal growth factor receptor (EGFR) family to render tumor cells susceptible to poly (ADP-ribose) polymerase (PARP) inhibition. *Invited mini-symposium speaker, 14th International Congress of Radiation Research, Warsaw, Poland, September 2011.*
20. **Yang, ES.** Synthetic lethal interactions between EGFR and PARP inhibition in head and neck cancer. *Invited speaker, UAB Comprehensive Cancer Center Research Retreat, October 2011.*
21. Klepczyk, L, Nowsheen, S, Xia, F, **Yang, ES.** BRCA1 Nuclear Export Sensitizes Prostate Cancer Cells to Poly (ADP-ribose) Polymerase-1 (PARP1) Inhibition via the CRM1/exportin Pathway. *ASTRO Annual Meeting, October 2011.*
22. **Yang, ES.** C.A.M.S. Seminar. *Invited speaker, UAB MSTP Program Lecture Series, January 2012.*
23. **Yang, ES.** Advances in cancer research. *Invited speaker, Southeast Cancer Foundation Regional Oncology Active Research (R.O.A.R.) Gala, January 2012.*
24. **Yang, ES.** "PARP-erasing" DNA damage in tumors. *Science Hour, Department of Radiation Oncology, UAB, February 2012.*

25. **Yang, ES**. Cancer susceptibility to PARP inhibition: It's not all about DNA repair. *Invited speaker, UAB Comprehensive Cancer Center Experimental Therapeutics Seminar Series, February 2012.*
26. **Yang, ES**. Susceptibility of HER2+ breast cancer to PARP inhibition. *Invited speaker, Vanderbilt University Research Retreat, June 2012.*
27. **Yang, ES**, Nowsheen, S, Cooper, T, Bonner, JA, LoBuglio, AF. Human HER2+ breast tumor susceptibility to PARP inhibitors independent of a homologous recombination repair defect. *ASTRO Annual Meeting, October 2012.*
28. Bonner, JA, Trummell, H, Nowsheen, S, **Yang, ES**. The role of STAT-3 in cetuximab-induced radiosensitization in head and neck cancer cells. *ASTRO Annual Meeting, October 2012.*
29. Whitley, AC, Jackson, J, Trummel, H, Bonner, JA, **Yang, ES**. Erlotinib induces synthetic lethality with the poly (ADP-Ribose) polymerase (PARP) inhibitor ABT-888 in esophageal cancer. *ASTRO Annual Meeting, October 2012.*