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Title: *The Treatment of BRCA1/2 Hereditary Breast Cancer and Sporadic Breast Cancer with Poly(ADP-ribose) PARP-1 Inhibitors and Chemotherapy*

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Contracting Organization: Henry M. Jackson Foundation
Rockville, MD 20852

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14. ABSTRACT This year it is estimated that there will be over 250,000 new cases of breast carcinoma in situ and invasive breast cancer with an accompanying 40,000 deaths. Current therapies to treat breast cancer are relatively non-specific and highly toxic. There is an urgent need to develop safe and effective therapies for the therapeutic treatment of breast cancer. In this study, we looked at a new class of relatively non-toxic compounds called PARP-1 inhibitors and evaluated the use of these compounds in concert with standard chemotherapy and other therapeutic agents to treat both sporadic and hereditary breast cancer using a phased strategy from our statement of work: Task I: Dose response curves, Task II: In vivo mouse model allografts, Task III: In vivo mouse model xenografts, Task IV: Inhibition of Development of mammary tumor and Task V: Publication and presentation of results. We challenged standard concepts and use out of the box thinking to move forward the fight against breast cancer.					
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Introduction

This year it is estimated that there will be over 250,000 new cases of breast carcinoma in situ and invasive breast cancer with an accompanying 40,000 deaths. Current therapies to treat breast cancer are relatively non-specific and highly toxic. There is an urgent need to develop safe and effective therapies for the therapeutic treatment of breast cancer. In this study we look at a new class of relatively non-toxic compounds called PARP-1 inhibitors and evaluate the use of these compounds in concert with standard chemotherapy and other therapeutic agents to treat both sporadic and hereditary breast cancer using a phased strategy from our statement of work: Task I: Dose response curves. Task II In vivo mouse model allografts Task III: In vivo mouse model xenografts Task IV: Inhibition of Development of mammary tumor Task V: Publication and presentation of results. We challenge standard concepts and use out of the box thinking to move forward the fight against breast cancer. Here we report, the results gained after only one year of work under this grant.

Body

Here we report the results of this past years research in terms of the specific tasks out listed in the statement of work.

Task I: Dose response curves. This past year 320 dose response curves were produced with each curve representing data that has been replicated 6-10 times. An example of the dose response curve is shown in Figure I.

The highlights and results thereof include: 1) We report that BRCA1 hereditary breast cancer is not as specifically susceptible to PARP-1 inhibition alone. 2) BRCA2 breast cancer may be significantly resistant to taxanes. The observation that BRCA1 breast cancer may not be as resistant to taxanes as reported in the literature 3) Synergy between the PARP-1 inhibitor AG14361 and paclitaxel, docetaxel and 5-fluorouracil in inhibiting breast cancer. The enhancement of platinum agents and anthracyclines by PARP-1 inhibitors in the treatment of breast cancer cell lines 5) Knockdowns of specific genes may not necessarily represent naturally occurring breast cancer absent the gene(s) in question.

1) It has been reported that BRCA1 negative cells may be a thousand fold or more susceptible to PARP-1 inhibitors than BRCA1 positive cells in two papers published in nature (Bryant HE et al. and Farmer H et al.). These results have been reported at nearly every major conference since then including this years past ASCO in Chicago, AACR in San Diego and Breast Cancer symposium in Washington DC. However, these Nature papers utilized non-cancerous hamster epithelial cells with BRCA1 knocked down and

MCF-7 cells with BRCA1 knocked down. Our results using actual cancer cells comparing wild type, BRCA1 deficient cell lines gave IC₅₀ values of 60.5 µM, and 20.4 µM respectively. A difference of only 3 fold leading doubt of whether there is any clinically significant difference in the response of BRCA1 hereditary breast cancer to PARP-1 inhibition and leaving in doubt whether PARP-1 inhibitors can be used alone to treat breast cancer.(See figure 2). BRCA2 hereditary breast cancer is about 5 –fold more susceptible to PARP-1 inhibition than BRCA positive cells having an IC₅₀ of 12.3 µM on average. It is also very clear from the IC₅₀ values which are beyond any potential serum levels in humans that PARP-1 inhibition alone will not be useful clinically to treat Hereditary or Sporadic breast cancer.

2) Knock downs of BRCA1 in breast cancer cell lines suggest that BRCA1 hereditary breast cancer is resistant to treatment with taxanes (Chabalier et al.). Using actual tumors of both wild type and BRCA1 and BRCA2 negative cancer cell lines show an average IC₅₀ value when exposed to paclitaxel of the following: BRCA1/2 + 1.77 µM, BRCA1 – 5.08 µM and BRCA2 – of 17.7 µM. The p value comparing BRCA1 + with BRCA1 – is p=0.54 and between BRCA2+ and BRCA2- p= 0.04. Thus, there is no statistical difference between the sensitivity of BRCA wild type breast cancer cells and BRCA1 negative cells in their sensitivity to taxanes. There is a difference in the sensitivity between BRCA2 negative and BRCA2 positive cancer cells to taxanes however, .

3) The combination of paclitaxel and AG14361 together at their IC₅₀ values were decreased dramatically in BRCA+, BRCA1-, and BRCA2- cells lines with a median enhancement of 39.5x an average enhancement of 3,200x and a maximum enhancement

of 34,000x. (Fig 3). Similar results were found with docetaxel. The combination of 5-Fluorouracil and AG14361 together at their IC_{50} values showed a median enhancement of 3.0x, and average enhancement of 96x and maximum enhancement of 972x. (Fig 4). The anthracyclines also showed enhancement in the ability to inhibit breast cancer when combined with AG14361. The median IC_{50} value when combined with AG14361 has a median enhancement of 1.8 fold, an average enhancement of 5.4x and a maximum enhancement of 28.0x. (Fig 5). The platinum agents oxaliplatin, carboplatin and cisplatin had similar results to the anthracyclines when combined with AG14361. Other reports suggest potential synergy, with platinum agents this was not observed (Evers et al.)

- 4) The evidence provided in relation to using actual BRCA deficient tumor cell lines and comparing them to BRCA positive cell line to taxanes or PARP-1 inhibitors is different from results utilizing knockdowns of the BRCA gene from wild type cells. This suggests that knock down of specific genes may not always describe actual cancers in patients.

Other: Anti-metabolites such as gemcitabine and methotrexate showed antagonism when used with PARP-1 inhibitors in the ability to inhibit breast cancer growth.

Task I shall include this following year: Additional dose response curves evaluating the PARP-1 inhibitors ABT-888 and AZD-2281 and EGFR and mTOR inhibitors. The extension of the project to more human cell lines will take place this following year to improve the generalizability of the results.

Task II: In vivo mouse model allografts: 1) Mouse allografts representing murine mammary tumors with BRCA1 knocked out, or with BRCA wild type were implanted into nude mice and treated with the PARP-1 inhibitor AG14361. Results showed a mild specificity for BRCA1 tumors to AG14361 alone. There was a 35% inhibition of the tumor growth rate in BRCA1 negative tumors compared to a 25% reduction of growth rate in BRCA1 positive tumors. No remission of tumors was observed. Each arm consisted of 10 nude mice. 2) Synergy of AG14361 with Paclitaxel was shown against mouse allografts of BRCA1 – and + mammary tumors. 3) In vivo mouse allografts will not be carried out in much more detail do to results from experiments and feedback from national conferences. Initially, I was excited about the mouse allografts where I observed complete remission of 4 out 5 tumors when the PARP-1 inhibitor AG14361 15 mg/kg was combined with paclitaxel 5 mg/kg while no remissions were observed in the use of the PARP-1 inhibitor 15 mg/kg alone or with paclitaxel 5 mg/kg alone. However, after discussions with others in the areas at National Meetings there seemed to be push back on whether allografts of mouse/mouse would adequately serve as the best model for human breast cancers- at the least since human xenografts are possible those should be preferred. Hence, I intend to use the allograft model and look at 5-FU and AG14361 in combination but. We will now focus more on Task 4 the human/mouse xenograft.

Task III: In vivo mouse model xenografts:

1) The inoculation of human breast cancer cells into nude mice and the treatment of nude mice with PARP-1 inhibitors and other therapeutic agents: The inoculation and treatment of human breast cancer cells into nude mice turned out to be a bit tougher than expected. From 3 separate human cell lines, the tumors took on average 3-6 months to grow in the mouse 0.250 cm^2 being used as the point of tumor development - with not all mice obtaining tumors.

2) Establishment of efficient human/mouse tumors: Those tumors that developed were excised from euthanized mice and re-passed into nude mice again. All but one mouse developing tumors the second pass and a faster time to the development of a tumors 2 to 4 months this next time around. This upcoming year will focus on Task III. One preliminary study using MCF-7 BRCA + breast cancer tumor cells in 5 nude mice treated against the PARP-1 inhibitor versus HCC1937 BRCA1 – breast cancer tumor cells in 5 nude mice treated against the PARP-1 inhibitor showed no significant difference in response. Results were clouded however by 2 mice in the MCF-7 xenograft and 1 mouse in the HCC1937 not forming a tumor. The re-passing of tumors through the mice seems to have minimized the risk of non-tumor formation in human/mouse xenografts and thus has been successful. Xenograft studies are ongoing at this time.

Other: Taxane 1000 x fold and anthracycline 500 fold resistant human breast cancer cell lines have been developed to further promote this study.

Task IV: Inhibition of development of mammary tumor:

- 1) A preliminary study of 6 BRCA^{co/co}, MMTV-p53 mice with three being treated at 7 months daily until 13 months with AG14361 and three being treated with just saline. All three mice which were not treated developed tumors. None of the PARP-1 treated mice however develop tumors this is promising!!! Other research suggests that PARP-1 inhibitors may be useful in this regard. (Hay et al).
- 2) This year 20 mice will be treated with the PARP-1 inhibitor AG14361 beginning at age 7 months and treated until the age of 16 months. This will start in October/Nov. 2008. The potential mechanism of action has been alluded to by my collaborator (Wang et al.)

Task V: Publication and presentation of results:

Four manuscripts 2 indirectly and 2 directly will be submitted from this past years work and are near completion. Editing is being done at this time.

- a) The inhibition of breast cancer by Poly(ADP-ribose) polymerase inhibitors.

International Journal of Clinical Oncology. Submitting.

This paper will seek to show that PARP-1 inhibitors are not sufficient alone against hereditary breast cancer but in combination with other drugs may act synergistically in both sporadic and hereditary breast cancer. This paper challenges current thought in the field

- b) The resistance of BRCA2 hereditary breast cancer to Taxanes and the use of Poly(ADP) ribose polymerase inhibitors to reverse resistance. Clinical Cancer Research. Submitting.

This paper will describe the reversal of taxane resistance by PARP-1 inhibitors and describe the resistance of BRCA2 hereditary breast cancer to taxanes.

c) Re-evaluating the use of Anthracycline in the treatment of breast cancer in African American Women- Other options? J. National Med. Society. 2008 submitting.

It turns out that African American women though they are less likely to get breast Cancer, they are more likely to die from breast cancer. This seems to be due to less efficacy in the treatment of breast cancer with much higher toxicities in African American women as compared to Caucasians. This seems to be in part due to BRCA1 like triple negative breast cancer in the African American population 59% as compared to 10-15% in the Caucasian population. It is suggested that PARP-1 inhibitors in combination with taxanes may be useful in the African American population

d) D) Obesity, and breast cancer J. of Nursing and Bariatric Surgery. 2008 submitting.

This paper uses in part mechanisms worked out from this grant to explain the development of breast cancer in the obese and was requested after one of my National presentations.

2) Three presentations related indirectly or directly to this work and three abstracts. This work was presented at the Breast Cancer Symposium in Washington DC, the American Association of Cancer Research in San Diego, and at the National Medical Association in Atlanta this past year. All of which is being folded into the above manuscripts.

Key Accomplishments

- Development of **330** dose response curves of the response of breast cancer cell lines to multiple chemotherapeutic regimens alone and in combination with the PARP-1 inhibitor AG14361.
- Preliminary model preventing the development of hereditary mammary tumors in mice with PARP-1 inhibitors.
- Providing evidence that the resistance of BRCA1 breast cancer to taxanes may not be as clinically relevant as reported.
- BRCA2 breast cancer may be substantially resistant to taxanes and that this resistance can be overcome with PARP-1 inhibitors.
- Evidence suggesting that PARP-1 inhibitors may not be useful alone treating BRCA-1 hereditary breast cancer.
- Showing antagonism between PARP-1 inhibitors and most anti-metabolites *in vitro*.
- Showing enhancement of PARP-1 inhibitors and anthracyclines, platinum *In vivo*
- Showing synergy between PARP-1 inhibitors and paclitaxel in inhibiting breast cancer. *In vitro and in vivo*
- Showing enhancement/synergy between PARP-1 inhibitors and 5-Fluorouracil in inhibiting breast cancer. *In vitro*
- Showing the susceptibility of non-BRCA1 hereditary breast cancer to PARP-1 inhibitors in combination with chemotherapy
- The development of taxane and anthracycline resistant cell lines.

Reportable Outcomes

Manuscripts:

A) The inhibition of breast cancer by Poly(ADP-ribose) polymerase inhibitors.

International Journal of clinical oncology. Submitting.

B) The resistance of BRCA2 hereditary breast cancer to Taxanes and the use of

Poly(ADP) ribose polymerase inhibitors to reverse resistance. Clinical Cancer Research.

Submitting

C) Re-evaluating the use of Anthracycline in the treatment of breast cancer in African

American Women- Other options? J. National Med. Society. 2008 submitting

D) Obesity, and breast cancer J. of Nursing and Bariatric Surgery. 2008 submitting

Abstracts:

A) **De Soto JA**, Reconsidering Anthracycline Based Chemotherapy in the Treatment of Breast Cancer in African American Women. Journal of the National Medical Association 2008 (July 24, 2008).

B) **De Soto JA**, The Use of Poly(ADP-ribose) Polymerase Inhibitors in the Treatment of Breast Cancer, Dept. of Defense Breast Cancer Research Meeting –ERA of Hope.

Baltimore MD. June 25, 2008

C) **De Soto JA**, Deng CX. The resistance to Taxanes of BRCA2 associated breast cancer. American Association of Cancer Research, San Diego CA. April 2008.

Presentations:

De Soto JA, Re-evaluating Anthracycline Based Chemotherapy in the Treatment of Breast Cancer in African American Women. Journal of the National Medical Association 2008 (July 24, 2008).

Development of cell lines:

- A) This project has developed a new human cell line through the knockout of the BRCA2 gene. T-47D/BRCA2neg
- B) Development of Taxane and Anthracycline resistant cell lines.

Funding applied for based on work supported by this grant:

- A) Obtained a grant for \$300,000 from the Uniformed Services University to investigate the use of PARP-1 inhibitors to ovarian, pancreatic and colon cancer.
- B) Funding for a post-doc to work on the preceding grant was also obtained in the amount of \$180,000.
- C) In the process of applying for a 4 million dollar grant to apply the research obtained from this project to a clinical trial from the Susan G. Koman Foundation.

Employment or research opportunities applied for based on experience and supported by this grant:

A) Applied for an Asst. Professor position at the Uniformed Services University and was hired for this position in August of 2007.

B) In February of 2008, established and became the Principal investigator of the Laboratory of Experimental Therapeutics, Pharmacogenomics and Cancer Pharmacology.

C) In Sept of 2008 was named Chairman of the Faculty Senate Research Policy Committee.

Conclusions

Evidence suggests that PARP-1 inhibitors may be used to prevent the development of breast cancer. The use of PARP-1 inhibitors may be useful to overcome resistance to chemotherapeutic agents. In addition, further evidence suggests that the use of PARP-1 inhibitors may be useful against both sporadic and BRCA hereditary breast cancer in combination with standard chemotherapy and selected other agents. Specifically paclitaxel, 5-fluorouracil and genistein are synergist in their ability to develop kill breast cancer cells while, PARP-1 inhibitors enhance the ability of platinum agents and anthracyclines to kill breast cancer cells. Our evidence suggest that knockdowns of specific genes in a cancer cell line may be of limited value as the cell developed may not necessarily represent a cancer cell without the gene in question found naturally in humans. We also show that unlike previous reports PARP-1 inhibitors are unlikely to be useful when used alone against hereditary breast cancer.

Our results also suggest modest changes in this project: Evidence suggests that 90% BRCA1 breast cancers are triple negative (estrogen receptor negative, progesterone receptor negative and Her2/Neu receptor negative) and have up regulation of epidermal growth factor receptor (EGFR). Thus, we will now test PARP-1 inhibitors with EGFR inhibitors in combination and also look at mTOR inhibitors with PARP-1 inhibitors. The PARP-1 inhibitors AZD2281 and ABT-888 have advanced in clinical trials in addition to AG14361 thus comparison between the 3 PARP-inhibitors will be undertaken to seek out the most efficacious against breast cancer. The project is providing more results than expected and progressing faster than expected.

These results have lead to the translation into a proposed clinical trial using PARP-1 inhibitors to treat triple negative breast cancer in combination with standard chemotherapy in African American women.

References

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Hay T, Jenkins H, Samsom OJ, Martin NM, Smith GC, Clarke AR. Efficient deletion of normal BRCA2-deficient intestinal epithelium by poly(ADP-ribose) polymerase inhibition models potential prophylactic therapy. 2005 Cancer Res 15:10145-8.

Wang X, Liu L, Montagna C, Ried T, Deng CX. Haploinsufficiency of PARP1 accelerates BRCA-1 associated centrosome amplification, telomere shortening, genetic instability, apoptosis and embryonic lethality. 2007 Death Differ 14:924-31.

Supporting Data

Figure I : *Example of Dose Response Curve (1 of 320+)*

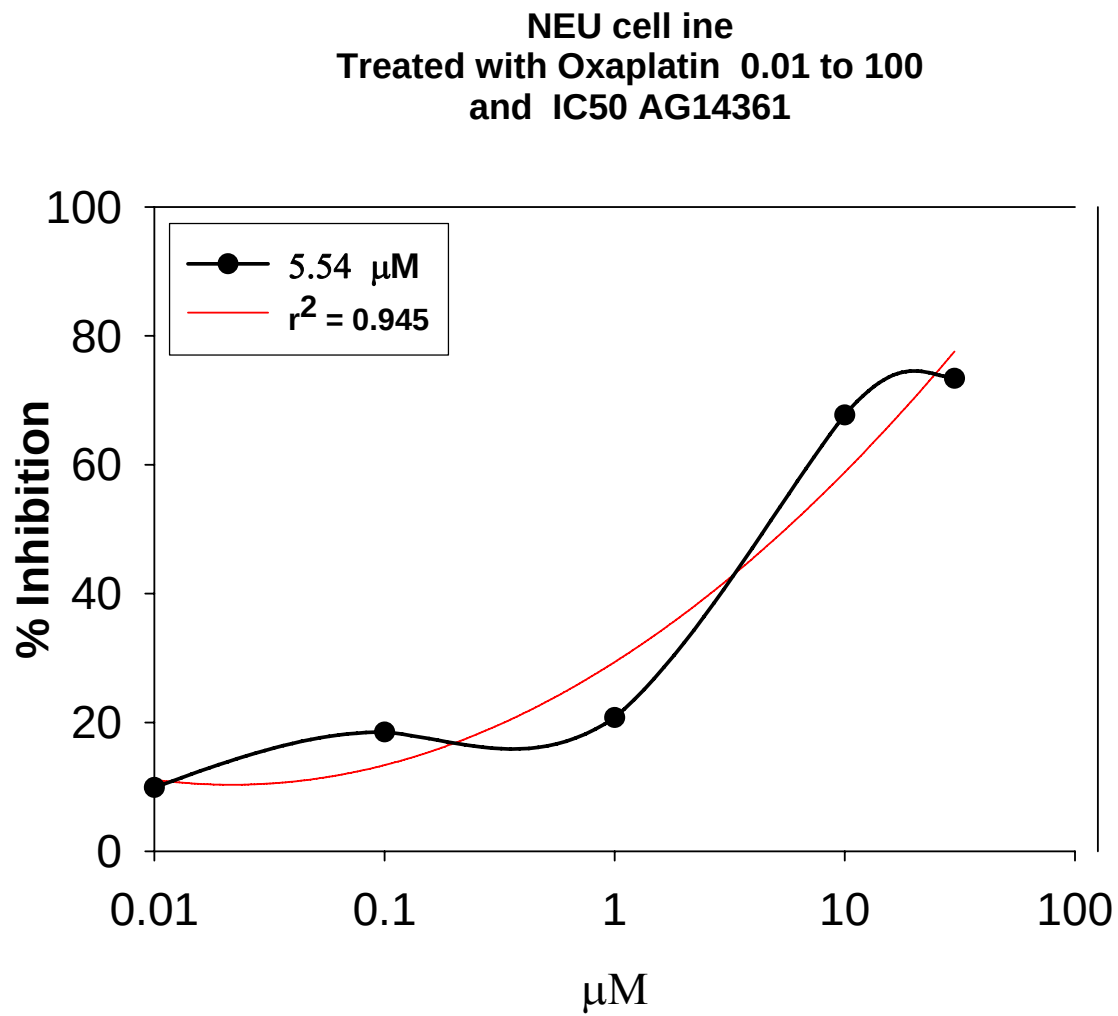


Figure 2: Comparison of Sporadic and Hereditary Breast Cancer to Inhibition with the PARP-1 inhibitor AG14361.

Cell Line	AG14361/ IC₅₀ (μM)
<i>BRCA-1 and BRCA-2 Positive Cells</i>	<i>Average IC₅₀ =60.5;StE= 19.3</i>
MCF-7	42
RAS	79
NEU	104
MDA-MB-231	17.0
<i>BRCA-1 Negative Cells</i>	<i>Average IC₅₀=20.4;StE= 2.2</i>
HCC1937	25.1
SUM149	22.0
780	20.1
69	14.5
<i>BRCA-1 Negative Cells</i>	<i>Average IC₅₀= 12.3StE= 4.3</i>
D632-1	4.9
D632-1	19.9
D631	12.2

Figure 2: Comparison of Breast Cancer Cell Lines to Inhibition by Paclitaxel

Cell Line	Paclitaxel IC₅₀ (μM)
<i>BRCA-1 and BRCA-2 Positive Cells</i>	<i>Average IC₅₀ =1.77; StE= 1.7</i>
MCF-7	0.132
RAS	6.87
NEU	0.0145
MDA-MB-231	0.077
<i>BRCA-1 Negative Cells</i>	<i>Average IC₅₀=5.08; StE= 3.8</i>
HCC1937	16.25
SUM149	0.077
780	0.0264
69	3.98
<i>BRCA-1 Negative Cells</i>	<i>Average IC₅₀= 17.7 StE= 2.7</i>
D632-1	12.7
D632-1	18.5
D631	22.0

Fig 3: IC₅₀ Paclitaxel and IC₅₀ AG14361 combined.

Cell Line	Pac/AG Change in IC ₅₀
<i>BRCA-1 and BRCA-2 Positive Cells</i>	<i>Median Change = 100.75x decrease</i>
MCF-7	39.5x decrease
RAS	1.85x decrease
NEU	34,000x decrease
MDA-MB-231	162x decrease
<i>BRCA-1 Negative Cells</i>	<i>Median Change = 9.0x decrease</i>
HCC1937	4.25x decrease
SUM149	27.5x decrease
780	No Change
69	13.7x decrease
<i>BRCA-1 Negative Cells</i>	<i>Median Change = 500x decrease</i>
D632-1	174x decrease
D632-1	638x decrease
D631	500x decrease

Fig4: IC50 5-FU and IC50 AG14361 combined

Cell Line	5-FU/AG Change in IC ₅₀
<i>BRCA-1 and BRCA-2 Positive Cells</i>	<i>Median Change = 2.6x decrease</i>
MCF-7	972x decrease
RAS	2.22x decrease
NEU	3.0x decrease
MDA-MB-231	1.78 x decrease
<i>BRCA-1 Negative Cells</i>	<i>Median Change = 0.8x decrease</i>
HCC1937	No change
SUM149	35.3x decrease
780	1.7x decrease
69	No change
<i>BRCA-1 Negative Cells</i>	<i>Median Change = 15x decrease</i>
D632-1	22x decrease
D632-1	8.1x decrease
D631	15x decrease

Fig5: IC50 Doxorubicin and IC50 AG14361 combined

Cell Line	Doxo/AG Change in IC ₅₀
<i>BRCA-1 and BRCA-2 Positive Cells</i>	<i>Median Change = 6.9x decrease</i>
MCF-7	28x decrease

RAS	13.6x decrease
NEU	No change
MDA-MB-231	1.2x decrease
<i>BRCA-1 Negative Cells</i>	<i>Median Change = 2.1x decrease</i>
HCC1937	1.6x increase
SUM149	6.0x decrease
780	No change
69	2.64x decrease
<i>BRCA-1 Negative Cells</i>	<i>Median Change = 1.8x decrease</i>
D632-1	3.47x decrease
D632-1	1.47x decrease
D631	1.8x decrease

CURRICULUM VITAE

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Education:

Year	Degree	Institution/Location/Area of Concentration
Dec 2005	Ph.D.	Pharmacology , Department of Pharmacology, Howard University Graduate School, Washington, DC
May 2005	M.D.	Medicine , Howard University College of Medicine, Washington, DC
June 2010	M.S.	National Security Studies , American Military University, Charlestown, WV
June 1995	B.S.	Biophysical Chemistry , Department of Chemistry, La Sierra University

Professional Experience: (Civilian and Military experience)

Year	Position title/Institution/Duty Station/Location	Scope of Role
2007-present	Assistant Professor & Principal Investigator, Director Laboratory of Experimental Therapeutics, Pharmacogenomics and Cancer Pharmacology, Department of Health, Injury, and Disease	Course coordinator for pathology and Pharmacology. Basic and PhD faculty member. P.I. for the Laboratory of Experimental Therapeutics, Pharmacogenomics and Cancer Pharmacology

Year	Position title/Institution/Duty Station/Location	Scope of Role
	Management, Graduate School of Nursing Uniformed Services University of the Health Sciences, Bethesda, MD	
2005-2007	IRTA Post-Doctoral Fellow – Translational Research in Clinical Oncology. National Institute of Diabetes, Digestive, and Kidney Diseases, National Institutes of Health, Bethesda, MD	Research at NIH was in the area of experimental therapeutics, cancer chemotherapy, diabetes, and translational research. Designed experiments utilizing chemistry, toxicology, pharmacology, and molecular biology. Carried out experiments, wrote papers, reviews, and grants. Presented papers orally at National meetings. Carried out statistical analysis. Evaluated basic research for use in the clinic. Carried out research with practical and relevant clinical applications.
2005-present	Adjunct Assistant Professor, Health, Pathopharmacology & Infectious Disease, Mountain State University, WV	Taught courses in microbiology/ infectious disease, anatomy, physiology, pathophysiology, and pathopharmacology. Determined materials to be covered, developed the syllabus, established criteria for grading, established tutorials, and counseled the students. Students included graduate, professional, pre-professional, and undergraduates. 20 courses taught.
2005-present	Medical Columnist, The Journal Newspaper, Martinsburg, WV	Write a monthly medical column on health issues of interest to the community. Topics covered include: infectious, genetic, developmental, and psychiatric disorders. Cancer, pathology,

Year	Position title/Institution/Duty Station/Location	Scope of Role
		social issues, and healthcare are also covered. Respond to questions from the community and guidance to solve individual health care concerns.
2002-2005	Pharmacology Instructor, Howard University College of Medicine, Washington, D.C.	Taught pharmacokinetics, pharmacodynamics, molecular biology, toxicology, chemotherapy, statistical applications, antimicrobials, and endocrinology to doctoral students and professional (P.A. and Medical) students.
1995-1997	Biochemistry Lab Instructor, La Sierra University, Riverside, CA	Instructed biochemical laboratory techniques to undergraduate students. Added in the development of laboratory curricula.
1992-1995	Research Assistant, La Sierra University, Riverside, CA	Molecular modeling, statistical analysis, computational chemistry, quantitative and qualitative analysis, and theoretical chemistry.
1990-1992	Nurse, Acute and Convalescent Nursing Care at Various Hospitals and Nursing Homes for an Agency	
1988-1989	Honorable Discharge Combat Medic, U.S. Army	Emergent healthcare of soldiers.

Honors and Awards: (Include Military, Educational, Professional)

2008	Named and Elected Member of ASCO	American Society of Clinical Oncology
2008	Signed U.S. Constitution	President Pro-Tempore of the United States Senate. Senator Robert C. Byrd
2007	Chief Judge	NIH FARE 2007, Oncology/ Hematology, Tumor Biology, and Chemotherapy, NIH, Bethesda, MD
2007	The Fellows Award for Research Excellence	The National Institutes of Health Bethesda, MD
2006	Certificate of Excellence for Pandemic Flu Preparation	Berkeley County Commission Berkeley, WV
2006	Named and Elected Fellow-F.A.I.C.	The American Institute of Chemists
2005	Outstanding Accomplishments in Research and Medicine Award	Howard University College of Medicine
2005	Grant	American Medical Association Foundation
2004	Grant	Marcus Family
2003	Travel Grant	The American Society for Pharmacology and Experimental Therapeutics
1998	Honorable Mention in Science	The National Science Foundation
1998	Ford Foundation Pre-Doctoral Fellow Award	The National Research Council
1989	The Combat Medic Achievement Award	Commandant of the U.S. Army Medical Corp.
1989	The Commanders' Award for Leadership	U.S. Army

Education – Non-Degree Granting:)

Year	Degree	Institution/Location/Area of Concentration
May 2006	Certificate	Clinical Research Curriculum The National Institutes of Health Bethesda, MD
Feb 2006	Certificate	Translational Research in Clinical Oncology, The National Cancer Institute, Bethesda, MD
1988	Certificate	Combat Medic Training, Academy of Health Sciences, U.S. Army, Ft. Sam Houston, TX (Valedictorian)

Publications Peer Reviewed:

De Soto JA, The inhibition of breast cancer by Poly(ADP-ribose) polymerase inhibitors. submitting: International Journal of clinical oncology

De Soto JA, The resistance of BRCA2 hereditary breast cancer to Taxanes and the use of Poly(ADP) ribose polymerase inhibitors to reverse resistance. Submitting to Clinical Cancer Research

De Soto JA. Re-evaluating the use of Anthracycline in the treatment of breast cancer in African American Women. J. National Med. Society. 2008 submitting

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Davis JH, **De Soto JA**, Fryar EB, Southerland WM, Bowen D. Sequential combination chemotherapy in human breast cancer: a basis for increased antineoplastic activity and bone marrow protection. Cell Mol Biol. 2007 May 15;53(3):18-26.

De Soto JA, Mandatory HPV vaccination? , *J. Fam. Pract.* 2007 April 56(4):267-268.

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Cao L, Kim S, Xiao C, Wang RH, Coumoul X, Wang X, Li WM, Xu XL, **De Soto JA**, Deng CX, ATM-Chk2-p53 activation prevents tumorigenesis at an expense of organ homeostasis upon Brca1 deficiency. *EMBO J.* 2006 17;25(10):2167-77. PMID 16675955

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De Soto JA, Bowen D, Southerland WM, Hawkins M, The Interaction of the Steroidal Antagonist Faslodex and Methotrexate, *Cell Mol Bio*, 2003 49(7): 1067-9. PMID 14682388

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Cronce DT, Famini GR, **De Soto JA**, Wilson LY, , Using Theoretical Descriptors in Quantitative Structure Property Relationships: Some Distribution Equilibria , *Journal of the Chemical Society, Perkins Transactions 2* 1998 44 :1230-7.

Peer Reviewed Proceedings

De Soto JA, Reconsidering Anthracycline Based Chemotherapy in the Treatment of Breast Cancer in African American Women. *Journal of the National Medical Association* 2008 (July 24, 2008).

De Soto JA, Deng CX. The resistance to Taxanes of BRCA2 associated breast cancer. *American Association of Cancer Research*, San Diego CA. April 2008.

De Soto JA, Deng CX, The Enhancement of Paclitaxel Cytotoxicity in Hereditary and Sporadic Breast Cancer by the Poly (ADP) Ribose Polymerase Inhibitor AG14361. Experimental Biology (FASEB), Washington, D.C. (April 28, 2007).

De Soto JA, The Inhibition of BRCA-2 Hereditary Breast Cancer with Poly(ADP-ribose) Polymerase (PARP-1) Inhibitors. National Institutes of Health Research Festival, Bethesda, MD, October 17, 2006.

Tominaga Y, **De Soto JA**, Wang RH, Deng CX, Chemoprevention and therapeutic treatment of BRCA1 associated breast cancer in conditional knockout mice. National AACR Meeting, Washington D.C. April 2, 2006.

De Soto JA, Davis JH, Fryer E, Southerland WM, Bowen D., Anti-Estrogen Cross Resistance in Human Breast Cancer, AACR National Meeting, Anaheim, CA, April 2005.

Davis JH, Fryer E, **De Soto JA**, Bowen D, Utilization of Tamoxifen, Methotrexate and 5-Fluorouracil: A basis for increased anti-Neoplastic activity and Protection of Bone Marrow. FASEB – Experimental Biology. National Meeting, April, San Diego CA. 2003.

De Soto JA, Davis JH, Bowen, Anti-Estrogens Antagonize the Anti-Proliferative Effects of Methotrexate in Human Breast Cancer, FASEB – Experimental Biology. National Meeting The FASEB Journal Abstracts, April, New Orleans LA. 2002 16(4):A176.

De Soto JA, Southerland WH, Hawkins M, Bowen D., Anti-Estrogen Modulation of High Dose Methotrexate Activity in Human Breast Cancer, National Meeting of the Association of Academic Minority Physicians, Journal of the Association of Academic Minority Physicians Proceedings, Washington D.C., Oct 2001 Volume:12(4):154.

De Soto JA, Cronce DT, Famini GR Wilson L. QSAR: The Use of Theoretical Descriptors in Molecular Modeling, American Chemical Society – National Meeting, Anaheim CA, Mar 1995

Invited articles

De Soto JA, Today's physician, 29 Sept 2008 C1-C2.

De Soto JA, Parkinson's disease, 25 Aug, 2008 C1.

De Soto JA, Breaking the myths of domestic violence, July 28, 2008 C1-C2.

De Soto JA, Underreported disease, the Journal, June 18, 2008 C-2.

De Soto JA, Ovarian cancer is on the rise in West Virginia, May 26, 2008 pgs. C1-2.

De Soto JA, Smoking still puts your health at risk, the Journal, April 28, 2008 C-2.

De Soto JA, The signs and symptoms of kidney stone disease, The Journal 1 April 2008.
pgs C1-C2

De Soto JA, Understanding inflammatory bowel disease, the Journal 25 Feb 2008. pgs
C1-2.

De Soto JA, The facts on Grinder's disease. The Journal 28 Jan 2008. pgs C1-2.

De Soto JA, What is the definition of life? The Journal 31 Dec 2007. pgs C1-2.

De Soto JA, Obesity, BMI and Political Correctness. The Journal 26 Nov 2007. pgs C1-
2.

De Soto JA, What you need to know about MRSA? The Journal 29 Oct, 2007. pgs C1-2.

De Soto JA, Should your daughter be vaccinated for HPV? The Journal Sept. 24, 2007.
pgs C1-2.

De Soto JA, Know the risks, signs, and symptoms of meningitis. The Journal August 27,
2007. pgs C1-2.

De Soto JA, Lyme disease, what it is and how to prevent it. The Journal, July 30, 2007
pgs C-1.

De Soto JA, Understanding Tuberculosis, The Journal, June 25, 2007, pgs C1-2.

De Soto JA, Malignant Melanoma, The Journal May 28, 2007 pgs C1-2.

De Soto JA, Hippocratic Oath and what it really means, The Journal Apr 23, 2007 pgs C1-2.

De Soto JA, Post-Traumatic Stress Disorder, The Journal, pgs C1-2, April 2, 2007 pgs C1-2

De Soto JA, There may be some good news for MS patients, The Journal, Mar pgs C1-2.

De Soto JA, Sickle cell anemia, The Journal, Feb pgs C-1-2.

De Soto JA, Get tested, colon cancer may be prevented, The Journal, Jan 1, 2007, pgs, C-1-2.

De Soto JA, Facts about HIV, The Journal, Nov 27, 2006, pgs C1-2.

De Soto JA, The future nursing shortage, The Journal Oct 2, 2006, pgs C1-2.

De Soto JA, Prostate hyperplasia, The Journal, Aug. 28, 2006, 2006, pgs C1-2.

De Soto JA, Stem cells can aid in the research of diseases. The Journal, July 31, 2006, pgs C-2-3.

De Soto JA, Breast feed your baby, The Journal, June 22, 2006, pgs C2-3.

De Soto JA, The state of our health care, The Journal, May 30, pgs C2, 2006

De Soto JA, Recognizing and understanding hypothyroidism, The Journal, May 1, 2006, pgs C2.

De Soto JA, Why you should be concerned about the Avian flu, The Journal, Mar 27, 2006, pgs C2-C3.

De Soto JA, Facts, causes, concerns of diabetes, The Journal, Feb 27, 2006, pgs C2-C3

De Soto JA, Breast Cancer: The who's and why's, The Journal, Dec 26, 2005, pgs C2-C3.

De Soto JA, ADHD: Do we really have all the facts? The Journal, Dec 5, 2005, pgs C2-C3.

De Soto JA, Sex and Infertility, The Journal, Oct 31, 2005, pgs C1-2.

Other publications (including web pages)

De Soto JA, HPV Vaccine, http://en.wikipedia.org/wiki/Hpv_vaccine.

De Soto JA, Approaches in Chemo-Hormonal Therapy in the Treatment of Human Breast Cancer: The Modulation of High Dose MTX Cytotoxicity by Anti-Estrogens. Doctoral Dissertation, Advisor: Donnell Bowen Ph.D., Professor of Pharmacology & Oncology. Dec 2005

Media Appearances

The Herald Daily, Speaking out against the strip mining of our mountains, May, 14 2008.

Family Wellness First, Cervical cancer vaccine, Newsletter 030 Jan 11, 2007.

Radio Appearance, WVTS Talk Radio, Will the HPV Vaccine Actually Work?, Jan 12, 2007.

The American Policy Round Table, WV Shouldn't force HPV vaccinations. Jan 23, 2007.

Radio Appearance, WVTS Talk Radio, Is mandating the HPV Vaccine Ethical? Feb 5, 2007.

Television Documentary: The HPV Debate; Cranberry Lodge Productions, Feb 17, 2007.

The Rural Democrat, Bill Watch, Feb 26, 2007.

Honest Human, Standing with those who are standing up, Feb 27, 2007.
Washington Times, CDC opposes law for vaccine, Feb 27, 2007.

Vaccine Autoimmune Project, What is wrong with the vaccine mandate in Illinois?, Mar 5, 2007.

Eagle Forum, HPV mandate stirs protest, Mar 2007.

Planet Chiropractic.com, Risk, informed consent, chiropractic practice, Mar 22, 2007.

International Health News, Vaccinate all 11-12 year old girls against HPV?, Sept, 2007.

Research Activities/Projects/Funding:

Date	Title of Activity/Project/Position (ex. PI, Co PI/Funding Source (If applicable)/Amount (if applicable)
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2008-2013	PI, Uniformed Services University of the Health Sciences, The
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2007-2010	Treatment of Ovarian, Colon, Pancreatic and Prostate Cancer with Poly-ADP Ribose Polymerase (PARP-1) Inhibitors. \$300,000. PI, Department of Defense Breast Cancer Research Program, Era of Hope Grant, The Treatment of BRCA1/2 Hereditary Breast Cancer and Sporadic Breast Cancer with Poly(ADP-ribose) PARP-1 Inhibitors and Chemotherapy. \$300,000.
2007-2009	PI, Start Up Grant , USUHS 150,000

Consultation Services

Date	Institution/Purpose/Location
2007-current	Reviewer, International Journal of the Medical Sciences
2007-current	NNMC, Bethesda, MD
2007-current	NIDDK, National Institutes of Health, Bethesda MD
2006-2007	Reviewer, Journal of the National Medical Association
2005-2007	Berkeley County Dept. of Health, Martinsburg WV

Presentations:

National/International

Date	Presentation Title/Sponsor/Location(optional)
July 24,2008	De Soto JA, Reconsidering Anthracycline Based Chemotherapy in the Treatment of Breast Cancer in African American Women. National Conference of the National Medical Association, Atlanta Georgia
June 25, 2008	De Soto JA, The Use of Poly(ADP-ribose) Polymerase Inhibitors in the Treatment of Breast Cancer, Dept. of Defense Breast Cancer Research Meeting –ERA of Hope. Baltimore MD.
Nov. 25, 2006	De Soto JA, The Diagnosis, Treatment and Prognosis of Hereditary and Sporadic Colon Cancer in African Americans. FBCG National Convention, Outstanding Clinician/Researcher, Riverdale, MD
Oct 3, 2005	De Soto JA, Deng C-X, Introducing the use of Poly(ADP-ribose) inhibitors PARP1 in the treatment of human breast cancer. La Sierra University, Combined Chairman's Biological and Chemical Guest Lecturer Series, Riverside, Ca.
July 25, 2005	De Soto JA, The Treatment of Refractory Schizoaffective Disorder with a Novel Dopamine & Serotonin Partial Agonist Aripiprazole. National Conference of the National Medical Association, Philadelphia PA

Local/Regional)

Date	Presentation Title/Sponsor/Location(optional)
May 14, 2008	De Soto JA, Protecting the Aquifer from Environmental Pollution, Dept. of Environmental Protection WV, Hedgesville.
April 12, 2007	De Soto JA, The Use of Standard Chemotherapy with PARP1 inhibitors in the Treatment of Hereditary Breast Cancer, University of Charleston.
Oct. 03, 2005	De Soto, JA, Deng C-X, Introducing the Use of Poly (ADP-ribose) inhibitors PARP1 in the treatment of human breast cancer. La Sierra University, Combined Chairman's Biological and Chemical Guest Lecturer Series, Riverside, CA

Teaching Experience:

UNIFORM SERVICES UNIVERSITY OF THE HEALTH SCIENCES

Graduate Courses

Date	Course No.	Topic/Course Level
Fall 2008	GSN	Pathophysiology for Advanced Nursing Practice
Spring 2007	GSN 51052	Pathology for Advanced Nursing Practice
Fall 2007	GSN 51044	Pharmacology for Advanced Nursing Practice

Guest Lectures

Date	Course No.	Topic/Course Level (ex. PhD)
Fall 2007	GSN 53061	Therapeutic Intervention in Chemical Warfare/Military Readiness Course

Masters Scholarly Project Guidance

Date	Student	Title/Position
Spring 2008	Watson/Sanchez	Committee Member

Dissertation Guidance

Date	Student	Title/Position
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Post-Doctoral Guidance

Date	Post-Doctoral Fellow	Title/Position
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2008	Dr. Hyun-Seok Kim	Post-doctoral fellow
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Other University Teaching Experience

Date	Course	Role/Institution
Spring 2007	Microbiology for Nursing Professionals 4 credits	Coordinator Mountain State University
Spring 2007	Microbiology Lab for Nursing Professionals 1 credit	Coordinator Mountain State University
Spring 2007	Anatomy & Physiology for Nursing Professionals 4 credits	Coordinator Mountain State University
Spring 2007	Anatomy & Physiology Lab for Nursing Professionals 1 credit	Coordinator Mountain State University
Fall 2006	Microbiology for Nursing Professionals 4 credits	Coordinator Mountain State University
Fall 2006	Microbiology lab for Nursing Professionals 1 credit	Coordinator Mountain State University
Fall 2006	Anatomy & Physiology for Nursing Professionals 4 credit	Coordinator Mountain State University
Fall 2006	Anatomy & Physiology lab for Nursing Professionals 1 credit	Coordinator Mountain State University
Summer 2006	Anatomy & Physiology for Nursing Professionals 4 credits	Coordinator Mountain State University
Summer 2006	Anatomy & Physiology lab for Nursing Professionals 1 credit	Coordinator Mountain State University
Summer 2006	Microbiology for Nursing Professionals 4 credits 4 credits	Coordinator Mountain State University

Summer 2006	Microbiology lab for Nursing Professionals 1 credit	Coordinator Mountain State University
Spring 2006	Microbiology for Nursing Professionals 4 credits	Coordinator Mountain State University
Spring 2006	Microbiology lab for Nursing Professionals 1 credit	Coordinator Mountain State University
Spring 2006	Anatomy & Physiology for Nursing Professionals 4 credits	Coordinator Mountain State University
Spring 2006	Anatomy & Physiology lab for Nursing Professionals	Coordinator Mountain State University
Fall 2005	Microbiology for Nursing Professionals 4 credits	Coordinator Mountain State University
Fall 2005	Microbiology Lab for Nursing Professionals 1 credit	Coordinator Mountain State University
Fall 2005	Anatomy & Physiology for Nursing Professionals 4 credits	Coordinator Mountain State University
Fall 2005	Anatomy & Physiology Lab for Nursing Professionals 1 credit	Coordinator Mountain State University
Summer 2005	Microbiology for Nursing Professionals 4 credits	Coordinator Mountain State University
Summer 2005	Microbiology Lab for Nursing Professionals 1 credit	Coordinator Mountain State University
Summer 2005	Anatomy & Physiology for Nursing Professionals 4 credits	Coordinator Mountain State University
Summer 2005	Anatomy & Physiology Lab for Nursing Professionals 1 credit	Coordinator Mountain State University
Spring 2005	Basic and Clinical Pharmacology 5 units	Instructor Howard University College of Medicine
Spring 2004	Basic and Clinical Pharmacology 5 units	Instructor Howard University College of Medicine

Continuing Ed/Workshops/Seminars:

Date	Title/Organization/Location (City/State)	
2009 Sept	Breast Cancer Symposium, Washington DC	2.5 CME
2008 Aug	Breast Cancer Clinical Case Discussion	2.5 CME
2008 July	Prostate Cancer Update, Research to Practice V1/1	4.5 CME
2008 June	American Society of Clinical Oncology National Meeting, Breast Cancer Curricula, Chicago.	10.0 CME
2008 June	Breast Cancer Update Research to Practice V7III	4.5 CME
2008 May	Lung Cancer Update Research to Practice V5I1	4.5 CME
2008 April	Ovarian Cancer Update Research to Practice V1I1	4.5 CME
2008 Mar	Colorectal Cancer Update Research to Practice V7I1	4.5 CME
2008 Feb	Breast Cancer Update Research to Practice V7I1	4.5 CME

Academic/Service Activities:

Date	Title (Chair/Member)	Service/Committee
2008-2009	Chair	Research Policy Committee – Faculty Senate
2008-2009	Member	USUHS Merit Review Committee
2008-2009	Member	USUHS Board of Academic Counselors
2008-2009	Member	CAPT committee working group – Faculty Senate
2008-2009	Member	USUHS Joint Patent, Technology and Research Group
2008-2009	Member	Education committee – Faculty Senate
2008-current	Member	USUHS Faculty Senate
2008-current	Member	Walter Reed Army Institute of Research, Institutional Review Board (HURC).
2007-2008	Member	USUHS renovations committee
2007-2008	Member	Faculty Senate- Comparability and faculty welfare committee
2007-2008	Member	Research policy committee – Faculty Senate
2007-current	Member	Ph.D. promotions committee
2007-current	Member	Ph.D. graduate committee

Membership in Professional Organization:

Date	Organization
2008-current	Active Associate Member, American Society for Clinical Oncology
2007-current	Active Member, American Medical Association
2007-current	Active Member, American Association for Cancer Research
2006-current	Member, National Hispanic Medical Association
2005-current	Associate Member, National Medical Association
2005-current	Active Member, American Society for Pharmacology& Exper, Ther.
1996-current	Active Fellow Member, American Institute of Chemist
1995-current	Active Member, American Chemical Society

Other Leadership Activities:

Date	Title/Organization
2008-2009	Chair – Republican Party Eastern Panhandle WV
2008- current	Vice-Chair National Ethics Committee AIC
2007 - current	Minority Affairs Consortium, American Medical Association
2006-2009	Chairman, Emergency Services Advisory Council Berkeley County
June 9, 2006-current.	Chief Medical Evaluator - Medical Response and Treatment, Eastern Panhandle Pandemic and Emergency Response Table Top Exercise, Martinsburg WV

Community Activities:

Date	Position/Organization/Location
2008 June 21	Delegate, WV State GOP Convention
2008 Feb 5	Delegate, WV United States Presidential Convention - GOP
2006-current	Humane Society of the United States
2006-2007	Physicians for Peace
2006-2009	Local Emergency Planning Committee
2006-current	The Innocence Project
2005-2006	National Institute of Diabetes, Digestive and Kidney Diseases Institutional Review Board. Ad hoc Member.