

BIOGRAPHICAL SKETCH

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NAME: Rankin, Gary O'Neal

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

POSITION TITLE: Professor and Chair of Pharmacology, Physiology and Toxicology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	Completion Date MM/YYYY	FIELD OF STUDY
University of Arkansas at Little Rock	B.S.	05/1972	Chemistry
University of Mississippi, Oxford, MS	Ph.D.	08/1976	Medicinal Chemistry
Medical College of Ohio, Toledo, OH	Postdoctoral	06/1978	Pharmacology

Please refer to the Biographical Sketch sample in order to complete sections A, B, C, and D of the Biographical Sketch.

A. Personal Statement

I am well qualified to serve as a mentor for junior scientists. I was Chair of the Department of Pharmacology from 1986-2005, and when my department was merged with the Department of Physiology, I was made Chair of the combined department, a position I still hold. Over the years, I have mentored numerous undergraduate (26), graduate (40) and medical students (18), postdoctoral fellows (7) and faculty members, both within and outside my department and institution. In addition, I am the principal investigator of the NIH-funded West Virginia IDeA Network of Biomedical Research Excellence (WV-INBRE). In this capacity, I oversee a state-wide network composed primarily of new investigators at primarily undergraduate institutions across West Virginia, and serve as mentor for several of them. I have also served as a mentor for COBRE investigators at Marshall University and reviewed COBRE and other IDeA applications for NIH. Thus, I have over 30 years of experience as a mentor in many different capacities. It is also worth noting that my laboratory has been involved in translational research. One of our recent projects involves examining the pharmacogenetics of humans who died from methadone overdose. Working with medical examiner's offices in West Virginia and Kentucky, we have obtained DNA from autopsy blood cards and are examining single nucleotide polymorphisms (SNPs) in cytochrome P450s (CYPs) related to methadone metabolism as a possible explanation for the overdose deaths and as a predictive tool for preventing methadone overdose in patients taking the drug for addiction treatment or cancer pain. We are also collaborating with Dr. Monica Valentovic, Marshall University, on a project to find adjunctive treatments to prevent cisplatin nephrotoxicity and with Dr. Yi Chen, Alderson Broaddus University, to find natural products that can be used in the treatment of ovarian cancer. Lastly, as part of our work in the field of nephrotoxicity, we have examined the role of renal transporters in the accumulation of the toxicants we are studying.

1. Richards-Waugh, L.L., Primerano, D.A., Dementieva, Y., Kraner, J.C., Rankin, G. O. (2014). Fatal methadone toxicity: Potential role of CYP3A4 genetic polymorphism. *J. Anal. Toxicol.* 38, 541-547.

- Huang, H., Chen, A.Y., Rojanasakul, Y., Ye, X., Rankin G.O., Chen, Y.C. (2015). Dietary compounds galangin and myricetin suppress ovarian cancer cell angiogenesis. *J. Functional Food*, 15, 464-475.
- Robertson, E.E., Rankin, G.O. (2006). Human renal organic anion transporters: Characteristics and contributions to drug and drug metabolite excretion. *Pharmacol. & Therapeut.* 109(3), 399-412.
- Rankin, G.O., Hong, S.K., Anestis, D.K., Ball J.G., Valentovic, M.A. (2008). Mechanistic aspects of 4-amino-2,6-dichlorophenol-induced in vitro nephrotoxicity. *Toxicology* 245, 123-129.

B. Positions and Honors

Positions and Employment

Assistant Professor, Dept. of Pharmacology, Marshall University School of Medicine, 1978-1982
 Associate Professor, Dept. of Pharmacology, Marshall University School of Medicine, 1982-1985
 Interim Chair, Dept. of Pharmacology, Marshall University School of Medicine, 1984-1985
 Professor and Chair, Dept. of Pharmacology, Marshall University School of Medicine, 1986-2005
 Associate Dean for Biomedical Graduate Education and Research Development, 1989-1992
 Professor and Chair, Dept. Pharmacology, Physiology & Toxicology, Joan C. Edwards School of Medicine, Marshall University, 2005- Present.

Honors

Professor of the Year, 1981-82; 1982-83; 1995-96; 2004; Marshall Univ. Meet the Scholar Award, 1985; Marshall Univ. Faculty Salute Award, 1986; Yeager Professor, 1987-91; WV Professor of the Year Semi-finalist, 1990; Research Award, Amer. Heart Assn., WV Affiliate, 1993-94; Alpha Omega Alpha, elected 1996; member, NIH Toxicology Study Sections (including ALTOX4), 1994-99; frequent member and/or Chair of NIH SBIR, Minority Pre-doctoral, or NRSA Study Sections, 1999-2003; Regular ad hoc PBKD Study Section, 2004 - 2006; ad hoc reviewer for four different NIH reviews (NIEHS, NIDDK, CMBK and RCMI-IDeA), 2007; Special Emphasis Panel Reviewer (NIDDK) and for RCMI-IDeA Study Section, 2008; ad hoc reviewer for nine different NIH reviews (Chair for three), 2009-2015; President, Association of Medical School Pharmacology Chairs, 2004-2007. President, Mechanisms Specialty Section (Society of Toxicology), 2008-2009. EPA Science Advisory Board member for IRIS document on Trichloroethylene, 2010; PhRMA Foundation Award of Excellence in Pharmacology/Toxicology – Finalist 2012 and 2013; 2013 Joseph Sam Distinguished Alumnus Award (Univ. Miss/Dept. Medicinal Chemistry); Institute of Medicine (IOM) Committee to Review Clinical Guidance for the Care of Health Conditions Identified by the Camp Lejeune Legislation, member, 2014. Chair, Division of Toxicology, American Society for Pharmacology and Experimental Therapeutics, 2000 and 2015.

C. Contribution to Science

- My early work focused on studying the nephrotoxicity induced by a succinimide-based agricultural fungicide, dimetachlone (N-(3,5-dichlorophenyl)succinimide; NDPS). It was known that NDPS was being developed in Japan for agricultural use but that it caused nephrotoxicity and promoted renal carcinogenesis of other chemicals with subacute exposure. My laboratory developed an acute model of NDPS nephrotoxicity, monitoring a large number of functional parameters, including the effect of NDPS treatment on renal transport of organic anions, organic cations, and amino acids. We conducted extensive structure-nephrotoxicity studies and determined how to modify the NDPS structure by adding methyl groups to the succinimide ring to maintain antifungal activity but eliminate nephrotoxicity. These findings led to the manufacture of newer agricultural fungicides that had a substituted succinimide ring and were not nephrotoxicants in mammals at reasonable exposure levels. We also determined that females were more sensitive than males to NDPS's nephrotoxic effects and discovered the mechanism of bioactivation of NDPS to nephrotoxic metabolites. Specifically, NDPS is oxidized on the succinimide ring in the liver and the –OH metabolite conjugated by sulfotransferase. The resulting sulfate conjugate (NSC) is carried via the blood to the kidney where it accumulates using probenecid-sensitive transporters to eventually release a maleimide (NDPM) which can alkylate nucleophiles on proteins and enzymes to cause cell death. We have also supplied NDPS to several investigators, including one at

NIH, to be used as a model compound for studying the development of chemical-induced interstitial nephritis.

- a. Rankin, G.O. (1997). Succinimides, in *Comprehensive Toxicology, Volume 7, Renal Toxicology*. R.S. Goldstein, ed., Pergamon, pp. 665-675.
 - b. Rankin, G.O., Hong, S.K., Anestis, D.K., Lash, L.H., Miles, S.L. (2001). In vitro nephrotoxicity induced by N-(3,5-dichlorophenyl)succinimide (NDPS) metabolites in isolated renal cortical cells from male and female Fischer 344 rats: evidence for a nephrotoxic sulfate conjugate metabolite. *Toxicology* 163, 73-82.
 - c. Rankin, G.O. (2004). Nephrotoxicity induced by C- and N-arylsuccinimides. *J. Toxicol. Environ. Health, Part B* 7, 399-416.
 - d. Rankin, G.O., Anestis, D.K., Valentovic, M.A., Sun, H., Triest, W.E. (2007). Nephrotoxicity induced by the R- and S- enantiomers of N-(3,5-dichlorophenyl)-2 hydroxysuccinimide (NDHS) and their sulfate conjugates in male Fisher 344 rats. *Toxicology*. 240, 38-47.
2. An outgrowth of our work examining the nephrotoxic potential of NDPS was an examination of the nephrotoxic potential of the halogenated anilines used to manufacture succinimide-based pesticides, dyes, pharmaceuticals and industrial intermediates. We have performed extensive structure-nephrotoxicity studies in vivo and in vitro, examined the nephrotoxic potential of aniline metabolites, explored renal enzyme systems that could contribute to the bioactivation of chloroanilines and their metabolites, and studied if antioxidants are important antidotes for exposure to these compounds. We have found that 3,5-dichloroaniline is the most potent nephrotoxicant among the mono- and dichloroanilines, chloroanilines have reactive intermediate metabolites capable of binding the cellular macromolecules, N-oxidation is the most likely biotransformation pathway leading to toxic aniline metabolites, that antioxidants are effective antidotes in vitro and in vivo, and that multiple renal enzyme systems, including CYPs and peroxidases, are capable of bioactivating anilines and their metabolites to toxic species. Our work is frequently cited as examples of the toxic nature of these compounds and their metabolites to the kidney.
- a. Dial, L.D., Anestis, D.K., Kennedy, S.R., Rankin, G.O. (1998). Tissue distribution, subcellular localization and covalent binding of 2-chloroaniline and 4-chloroaniline in Fischer 344 rats. *Toxicology* 131, 109-119.
 - b. Valentovic, M, Meadows, M.K., Harmon, R.C., Ball, J.G., Hong, S.K., Rankin, G.O. (1999). 2-Amino-5-chlorophenol toxicity in renal cortical slices from Fischer 344 rats: Effect of antioxidants and sulfhydryl agents. *Toxicol. Appl. Pharmacol.* 161, 1-9.
 - c. Racine, C., Ward, D., Anestis, D.K., Ferguson, T., Preston, D., Rankin G.O. (2014). 3,4,5-Trichloroaniline nephrotoxicity in vitro: Potential role of free radicals and renal biotransformation. *Int. J. Mol. Sci.* 15 (11): 20900-20912. Doi: 10.3390/ijms151120900.
 - d. Rankin, G.O., Sweeney, A., Racine, C., Ferguson, T., Preston D., Anestis, D.K. (2014). 4-Amino-2-chlorophenol: Comparative in vitro nephrotoxicity and mechanisms of bioactivation. *Chem.-Biol. Interact.* Oct 19; 222: 126-132.
3. A third area of work has been a study of the pharmacogenetics of CYPs related to methadone deaths. Our laboratory was asked to collaborate with the West Virginia Office of the Medical Examiner to investigate contributing factors related to the increased number of methadone deaths in the state. We have been examining single nucleotide polymorphisms (SNPs) in CYPs related to methadone metabolism as a possible explanation for the wide range of half-lives of methadone seen in patients and as a contributing factor in methadone overdose deaths. To date, we have identified SNPs in CYP3A4 and 2B6 that could be contributory to altered methadone metabolism. We are currently developing cell lines with these SNPs to determine functional effects. Ultimately, we hope to define key SNPs that can be predictive of longer methadone half-lives that could lead to overdose and the ability to predict at risk patients when given standard doses of methadone.
- a. Richards-Waugh, L.L., Primerano, D.A., Dementieva, Y., Kraner, J.C., Rankin, G. O. (2014). Fatal methadone toxicity: Potential role of CYP3A4 genetic polymorphism. *J. Anal. Toxicol.* 38, 541-547.

4. Lastly, we have been collaborating with other investigators looking at the effects of natural products on reducing the toxicity of anticancer drugs and/or serving as anticancer drugs. We have assisted in examining the effects of resveratrol on reducing the nephrotoxicity of cisplatin and as a cancer chemotherapeutic agent against melanoma. We have found that resveratrol does reduce cisplatin nephrotoxicity (Valentovic, et al. - manuscript submitted), but that it is ineffective in treating human melanoma xenograft tumors in nude mice. We have also been collaborating/facilitating an examination of additional natural products as anticancer agents against ovarian cancer. To date, our interactions have demonstrated that kaempferol and several other polyphenolic agents are effective as anticancer agents, but that the natural products identified so far might be better as adjunctive therapy.
 - a. Niles, R.M., Cook, C.P., Meadows, G.G., Fu, Y.-M., McLaughlin, J.L., Rankin, G.O. (2006). Resveratrol is rapidly metabolized in a thymic (Nu/Nu) mice and does not inhibit human melanoma xenograft tumor growth. *J.Nutrition*. 136, 2542-2546.
 - b. Luo, H., Rankin, G.O., Juliano, N., Jiang B.H., Chen, Y.C. (2012). Kaempferol inhibits VEGF expression and in vitro angiogenesis through a novel ERK – NFκB-cMyc-21 pathway. *Food Chemistry* 130,321-328.
 - c. Huang, H. , Chen, A.Y., Rojanasakul, Y. , Ye, X. , Rankin G.O. , Chen, Y.C. (2015). Dietary compounds galangin and myricetin suppress ovarian cancer cell angiogenesis. *J. Functional Food*, 15, 464-475.
 - d. Li, B. , Rankin, G.O. , Rojanasakul,Y. , Cutler, S.J. , Tu Y. , Chen, Y.C. (2014). Chaetoglobosin K induces apoptosis and G2 cell cycle arrest through p53-dependent pathway in cisplatin-resistant ovarian cancer cells. *Cancer Lett.* 356(2 Pt B):418-33.

Complete List of Published Work in My Bibliography

<http://www.ncbi.nlm.nih.gov/myncbi/collections/bibliography/47563629/>

D. Research Support

On-going

1. 2 P20GM103434 Rankin (PI) 09/19/14 – 07/31/19
NIH/NIGMS
WV-INBRE

The goals of this project are to create a biomedical research network among West Virginia undergraduate institutions with a central theme of cellular and molecular biology and an emphasis on cardiovascular disease and cancer research. The project will also enhance undergraduate student training in and awareness of biomedical research to enhance the likelihood that they will pursue health related careers.

Recently Completed

1. 2 P20-RR016477/8 P20GM103434 Rankin (PI) 05/01/09 – 09/18/14
NIH/NCRR/NIGMS
WV-INBRE

The goals of this project are to create a biomedical research network among West Virginia undergraduate institutions with a central theme of cellular and molecular biology and an emphasis on cardiovascular disease and cancer research. The project will also enhance undergraduate student training in and awareness of biomedical research to enhance the likelihood that they will pursue health related careers. With the dissolution of NCRR, this grant was transferred to NIGMS in 2012.

2. 3P20-RR016477-09S1 Rankin (PI) 07/13/09 – 09/30/10
NIH/NCRR

WV-INBRE

The project will enhance the summer research experience for undergraduate faculty and student and high school science teacher training in biomedical research. For students, a goal is to enhance the likelihood that they will pursue health related careers. It is a supplement to the WV-INBRE primary award.

3. 3P20RR016477-09S2 Rankin (PI) 09/17/09-09/16/12
NIH/NCRR
WV-INBRE

This T1 & T2 Translational ARRA Supplement to the WV-INBRE award was designed to explore the development of biomarkers from cardiac adipocytes that might be useful in predicting myocardial infarction. Dr. Nalini Santanam was the research project director.

4. 3 P20-RR016477-09S3 Rankin (PI) 07/13/09 – 09/30/10
NIH/NCRR
WV-INBRE

The project will enhance the summer research experience for HSTA high school science educators and provide HSTA graduates in undergraduate programs the opportunity to work on WV-INBRE funded projects during the academic year. For students, a goal is to enhance the likelihood that they will pursue health related careers. It is a supplement to the WV-INBRE primary award.

5. 3P20RR016477-09S4 Rankin (PI) 09/25/09-09/24/12
NIH/NCRR
WV-INBRE

This T1 and T2 Translational ARRA Supplement to the WV-INBRE was designed to explore the ability of resveratrol to attenuate the nephrotoxicity induced by the cancer chemotherapeutic agent cisplatin using HK-2 cells as the model/ Dr. Monica Valentovic was the research project director.