Doctoral Dissertation Defense Announcement

Wojciech K. Jankiewicz

“Developing Therapeutic Approaches to Chemotherapy-Induced Nephrotoxicity”

Candidate for Doctor of Philosophy in Pharmacology and Toxicology
Graduate School of Biomedical Sciences
Medical College of Wisconsin

Committee in Charge:
John D. Imig, Ph.D. (Advisor)
Dipak Panigrahy, M.D., Ph.D.
Sandra L. Pfister, Ph.D.
Alexander Starushchenko, Ph.D.
Carol L. Williams, Ph.D.

Friday, April 15th, 2022 at 9:00 AM (CST)

Live Public Viewing:
https://mcw-edu.zoom.us/j/97435508042?pwd=WlZaZnF6OWlwWkIzM1ZnTlIxE2pBUT09
Meeting ID: 974 3550 8042
Passcode: kH92jYQH
Graduate Studies

Molecular and Cellular Biology
Developmental & Stem Cell Biology
Mechanism of Cellular Signaling
Biochemistry of the Cell
Techniques in Molecular & Cell Biology
Classical and Molecular Genetics
Ethics & Integrity in Science
Research Ethics Discussion Series
Cellular Signal Transduction
Principles of Drug Action
Modern Drug Discovery & Development
Developing Therapeutic Approaches to Chemotherapy-Induced Nephrotoxicity

Nephrotoxicity a significant limitation of antiangiogenic chemotherapies. Antiangiogenic drugs are widely used in the treatment of solid tumors. They prevent tumor growth by blocking neovascularization. However, the resulting kidney damage is an important clinical challenge because we currently lack an ability to effectively treat it with pharmacological agents. We set out to investigate whether simultaneous soluble epoxide hydrolase (sEH) and cyclooxygenase-2 (COX-2) inhibition using a dual sEH/COX-2 inhibitor PTUPB could be an effective strategy for treating antiangiogenic therapy-induced kidney damage. We used a multikinase inhibitor, sorafenib, which is known to cause serious renal side effects. The drug was administered to male Sprague Dawley rats that were on a high-salt diet. Sorafenib was administered over the course of 56 days. The study included three experimental groups; (1) control group (naïve rats), (2) sorafenib group (rats treated with sorafenib only), and (3) sorafenib+PTUPB group (rats treated with sorafenib only for the initial 28 days and subsequently co-administered PTUPB from days 28 through 56). Blood pressure was measured every two weeks. After 28 days, sorafenib-treated rats developed hypertension and over the remainder of the study, sorafenib resulted in a further elevation in blood pressure. PTUPB treatment attenuated the sorafenib-induced blood pressure elevation. After 28 days, sorafenib rats developed pronounced proteinuria, which intensified significantly by the end of day 56. PTUPB mitigated sorafenib-induced proteinuria and, by day 56, it reduced proteinuria by 73%. Terminal kidney histopathology revealed intratubular cast formation, interstitial fibrosis, glomerular injury, and glomerular nephrin loss in sorafenib-treated rats. PTUPB treatment reduced histological features by 30 to 70% compared with the sorafenib-treated group and restored glomerular nephrin levels. Furthermore, PTUPB also acted on the glomerular permeability barrier by decreasing angiotensin-II-induced glomerular permeability to albumin. Finally, PTUPB improved the in vitro viability of human mesangial cells and did not interfere with sorafenib’s antitumor activity in prostate cancer cells. Collectively, our data demonstrated the potential of using PTUPB or dual sEH/COX-2 inhibition as a therapeutic strategy against sorafenib-induced glomerular nephrotoxicity. We next turned to investigate whether a chemotherapeutic with a high sEH inhibitory activity would be less cytotoxic to glomerular cells. We tested two sorafenib analogs that have a high potency as sEH inhibitors in cultured human podocytes and human renal mesangial cells. Sorafenib produced extensive loss in cell viability, activation of caspase 3/7 and apoptosis, and changes in mitochondrial activity. Specifically, sorafenib decreased oxidative respiration in mesangial cells while increasing glycolysis both in mesangial cells and podocytes. Interestingly, sorafenib also increased proton leak and decreased mitochondrial coupling in both cell types. We found that one of the analogs, t-CUPM, had a preferential cytotoxicity profile over sorafenib suggesting that the compound may be less nephrotoxic and may thus be an attractive compound for further investigation.
Curriculum Vitae

Education:

**PhD Candidate, Pharmacology and Toxicology**, expected 5/2022
Medical College of Wisconsin, Milwaukee, WI

**JD, Law**, 2017
Mitchell Hamline School of Law

**BA, Biochemistry**, 2012
Saint John’s University, Collegeville, MN

Honors:

**POLM Young Investigator Award**, Winter Eicosanoid Conference 2020
**Best Presentation Award in Drug Discovery**, Winter Eicosanoid Conference 2020
**First Place Poster Award**, Cardiovascular Center Retreat 2019
Cybaris IP Law Review, 2015
Dean’s List, Fall 2015, Mitchell Hamline School of Law

Science Experience:

**Research Assistant**, Medical College of Wisconsin, WI 08/2017 – Present
Designed studies and carried out experiments in a drug discovery lab devoted to the development of new kidney therapeutics. Focused on anti-VEGF-induced toxicity, multitarget small molecules, non-hydrolysable bioactive lipid analogs:

- participated in grant writing
- collaborated with medicinal chemists
- provided mentorship and training to junior trainees
- core skills – cell studies, animal studies, survival and non-survival surgeries, immunofluorescence, confocal microscopy, rtPCR, RNAscope, TUNEL.

Publications:

**First Author:**

**Co-Author:**

