CURRICULUM VITAE

NAVEEN KAUSHAL
nuk12@psu.edu
Tel:814-441-7443

265, Blue Course Drive, Apt-1D
State College, PA 16803
USA

EDUCATION

Panjab University, Chandigarh, India

- **PhD Biophysics, Department of Biophysics**, (2004-2008)

  Thesis Title: "*Modulation of cell cycle regulators and Heat shock proteins by selenium induced oxidative stress during spermatogenesis in mice"*

  Advisor: Prof. M. P. Bansal

  Area of Study: Molecular Biology, Biophysics

- **M.Sc. (Hons. School) Biophysics**, **Department of Biophysics,** (2001-2004)

  Thesis Title: "*Effect of Cyclooxygenase inhibitors –Aspirin and Nimesulide on rat intestinal structure and functions*".

  Advisor: Prof. S. N. Sanyal

  Major subjects studied: Gene and Protein Engineering, Cancer Biology, Cell and membrane Biophysics, Molecular Biophysics, Medical Physics And Instrumentation, Radiation Biophysics

- **B.Sc. (Hons. School) Biophysics**, **Department of Biophysics,** (1998-2001)

– Major subjects studied: Mammalian Physiology, Anatomy, Cell Biology, Molecular Biology, Biophysical Chemistry, Physicochemical Techniques, Biochemistry and General Microbiology

RESEARCH EXPERIENCE

Department of Veterinary and Biomedical Sciences,
Pennsylvania State University, University Park PA16802, USA

- **Post-Doctoral Fellow:** (August 2008-till date)

  Advisor: Dr. Sandeep K. Prabhu

  Research Projects :

1. *Evaluation of the anti-inflammatory properties of selenium containing derivatives of Classical NSAID Celecoxib. [**Published] See Annexure I for details***
2. *The effect of selenium status on erythropoiesis in-vivo. [**Published] Annexure I***
3. *Regulation of cyclooxygenase-2 (COX-2) and prostaglandin pathway by Selenium derived selenoproteins in RAW 264.7 Macrophages. **[Published] Annexure I***
4. *Omega-3 fatty acid derived novel Cyclopentanone prostaglandin* Δ^{12}-prostaglandin J_3 *ablates leukemia by targeting Leukemic Stem cells (LSCs). **[Published] Annexure I***
5. *Potential role of Selenium dependent modulation of AA pathways in the ablation of*

leukemia by targeting Leukemic Stem cells (LSCs). ***[Ongoing]***

6. *Enhanced Metabolic Inactivation of PGE_2 by Selenium in Macrophages is Mediated by the Up regulation of 15-hydroxyprostaglandin dehydrogenase.* ***[Ongoing]***

- **Doctoral Research:** (2004-2008)
  Title: *Modulation of cell cycle regulators and Heat shock proteins by selenium induced oxidative stress during spermatogenesis in mice.* ***See Annexure I***
- **Research Assistant:** (05/2004-02/2007)
  Project funded by Indian Council of Medical Research (ICMR) Govt. of India, at Panjab University**,** Chandigarh, INDIA.

TEACHING EXPERIENCE

- **Assistant professor:** 02/2007-04/2008
  Department of Physiology, Gian Sagar Medical College and Hospital, Punjab, India.
- **Guest Faculty:** (2004-2007)
  Department of Biophysics, Panjab University, Chandigarh, India.

PUBLICATIONS

Peer-reviewed Journals

1. **Kaushal N, Kudva AK**. Oxidative stress and inflammation: "The lesser of two evils" in carcinogenesis. *Journal of Postdoctoral Research.* 1 (2): February 2013
2. **Hegde S, Kaushal N,** , Chiaro C, Kodihalli RC, Hafer KT, Gandhi UH, Thompson JT, Vandel Heuvel JP, Kennett MJ, Hankey PA, Paulson RF and Prabhu KS (2011). Δ^{12}-prostaglandin J_3, an omega-3 fatty acid-derived metabolite, selectively ablates leukemia stem cells in mice. *Blood*. 118:6909-6919. (**Co-first Author**)
3. **Gandhi UH, Kaushal N**, Kodihalli CR, Hegde S, Nelson SM, Narayan V, Vunta H, Paulson RF and Prabhu KS (2011). Selenoprotein-dependent upregulation of hematopoietic prostaglandin D2 synthase in macrophages is mediated through the activation of peroxisome proliferator-activated receptor (PPAR)-γ. *J Biol Chem.* 286: 27471 – 27482. (**Co-first author**)
4. **Kaushal N**, Hegde S, Lumadue JA, Paulson RF and Prabhu KS (2011). The regulation of erythropoiesis by selenium in mice. *Antiox. Redox Signal.* 14 (8): 1403-12**.**
5. Ray M, Yu S, Sharda DR, Wilson CB, Liu Q, **Kaushal N**, Prabhu KS and Hankey PA (2010). Inhibition of TLR4-Induced I{kappa}B Kinase Activity by the RON Receptor Tyrosine inase and Its Ligand, Macrophage-Stimulating Protein. *J Immunol*. 185: 7309-16.
6. **Desai D, Kaushal N**, Gandhi UH, Arner RJ, D'Souza C, Chen G, Vunta H, El-Bayoumy K, Amin S and Prabhu KS (2010). Synthesis and evaluation of the anti-inflammatory properties of selenium-derivatives of celecoxib. *Chem Biol Interact*. 188: 446-56 (**Co- first author**).
7. **Kaushal N** and Bansal MP (2009). Selenium variation induced oxidative stress regulates p53 dependent germ cell apoptosis: plausible involvement of HSP70-2. *Eur J Nutr.* 48: 221-7.
8. **Kaushal N** and Bansal MP (2009). Diminished reproductive potential of male mice in response to selenium-induced oxidative stress: involvement of HSP70, HSP70-2, and MSJ-1. *J Biochem Mol Toxicol.* 23: 125-36.

9. Sood N, **Kaushal N**, Sanyal SN (2008). Effect of different non-steroidal anti-inflammatory drugs, aspirin, nimesulide and celecoxib on the disaccharide hydrolases and histo-architecture of the rat intestinal brush border membrane. *Nutri Hosp.* 23*:* 320-325.
10. **Kaushal N** and Bansal MP (2007). Dietary selenium variation-induced oxidative stress modulates CDC2/cyclin B1 expression and apoptosis of germ cells in mice testis. *J Nutr Biochem.* 18: 553-64.
11. **Kaushal N** and Bansal MP (2007). Inhibition of CDC2/Cyclin B1 in response to selenium-induced oxidative stress during spermatogenesis: potential role of Cdc25c and p21. *Mol Cell Biochem.* 298: 139-50.
12. Sanyal S N, Sood N and **Kaushal N** (2007). Alterations in the lipid profile and membrane dynamics of rat intestinal brush border membrane induced by different classes of nonsteroidal anti-inflammatory drugs. *Toxicol Mech Meth*. 17: 49-56.
13. **Kaushal N** and Sanyal SN (2006). Modulations in the intestinal disaccharide hydrolases and membrane dynamics: effect of non-steroidal anti-inflammatory drugs aspirin and nimesulide. *Mol Cell Biochem.* 294.107-15.
14. **Kaushal N** and Sanyal SN (2006). Alterations in L-Histidine transport in response to aspirin and nimesulide induced toxicity in rat intestine using everted intestinal sacs. *Toxicol Mech Meth.* 16: 379-84.
15. Sanyal S N and **Kaushal N** (2005). Effect of two non-steroidal anti-inflammatory drugs, aspirin and nimesulide on the D-glucose transport and disaccharide hydrolases in the intestinal brush border membrane**.** *Pharmacol Rep.* 57: 833-39.

Invited Book Chapters

1. **Kaushal N**, Gandhi UH, Nelson SM, Narayan V and Prabhu KS. Selenium and Inflammation *In Selenium: Its Molecular Biology and Role in Human Health (2011);* 3rd Edition. Springer Publications
2. **Kaushal N**, Narayan V, Gandhi UH, Nelson SM, Kotha AK and Prabhu KS. *Chronic Inflammation: Molecular Pathophysiology, Nutritional & Therapeutic interventions (2012).* Chapter 19, 259-273, CRC Press, Taylor and Francis Publications.

ABSTRACTS PUBLISHED

Poster Presentations

1. Gandhi UH, **Kaushal N**, Hegde SN, Paulson RF and Prabhu KS*.* Cyclooxygenase pathway is indispensable for the Selenium-dependent targeting of Leukemic Stem Cells. (FASEB J) 25: 110.7 Experimental Biology 2011. Washington DC, USA
2. Nelson SM, Gandhi UH, **Kaushal N** and Prabhu KS (2010).Regulation of Arg-I expression in macrophages by selenium. Experimental Biol 2010,Anaheim, CA, USA
3. Gandhi UH, **Kaushal N** and Prabhu KS (2010). Selenium-dependent expression of hematopoietic prostaglandin D synthase in macrophages. Experimental Biology 2010, Anaheim, CA**,** USA.
4. **Kaushal N**, Desai D, Arner RJ, Gandhi UH, Amin SG and Prabhu KS (2009). Anti-inflammatory potential of Selecoxib. *FASEB J,* 23: 728.5. Experimental Biology, New Orleans, Louisiana, USA.
5. **Kaushal N**, Hegde SN, Gandhi UH, Paulson RF and Prabhu KS (2009). Selenium

status and erythropoiesis in mice. *FASEB J,* 23: 728.5. Experimental Biology, New Orleans, Louisiana, USA.

6. **Kaushal N** and Bansal MP (2006). CDC2 and Cyclin B1 Mediated Apoptosis In Mouse Testes By Selenium Induced Oxidative Stress. "8th International Symposium on Selenium in Biology and Medicine", University of Wisconsin, Madison, USA.
7. **Kaushal N** and Bansal MP (2005). Alteration in the mRNA expression of HSP70 by selenium induced oxidative stress. "DAE BRNS Life sciences symposium on Molecular Biology of stress Response and its applications", Bhabha atomic Research Centre, Mumbai, India).

INVITED TALKS

1. **Kaushal N**, Narayan V, Patterson AD and Prabhu KS (2012). 'Enhanced metabolic inactivation of PGE2 by Selenium in macrophages is mediated by the up regulation of 15-hydroxy-prostaglandin dehydrogenase'**.** Experimental Biology 2012, San Diego, CA, USA
2. **Kaushal N**, Hegde SN, Hankey PA, Paulson RF and Prabhu KS (2010). Selenium ablates Friend Virus induced Erythroleukemia in mice**.** Experimental Biology 2010, Anaheim, CA, USA.
3. **Kaushal N** and Bansal MP (2007). Significance of heat shock proteins and cell cycle regulators in the mechanism of male germ cell apoptosis in response to variations in dietary selenium: A new insight. National Conference organized by national society of Andrology, India
4. **Kaushal N** and Bansal MP (2007). Potential role of cell cycle regulators in the male germ cell apoptosis in response to dietary selenium variation induced oxidative stress. National symposium on Biophysics, India.

UPCOMING PUBLICATIONS

Manuscripts Under Preparation

1. Selenium supplementation of mice eradicates leukemia by targeting leukemia stem cells to apoptosis - the importance of the cyclooxygenase pathway.
2. Evaluation of stability and drug hypersensitivity of an omega-3 derived anti-leukemic prostaglandin: Δ^{12}-prostaglandin J_3.
3. Enhanced metabolic inactivation of PGE_2 by selenium in macrophages is mediated by the up regulation of 15-hydroxy-prostaglandin dehydrogenase (15PGDH).

INVITED BOOKS

Title: Molecular mechanism of oxidative stress
Publishers: Springer publications
Expected year of Publication: 2013

PATENTS FILED

Prabhu KS, **Kaushal N**, Paulson RF, Hegde S, Gandhi UH
Title: Anti-leukemic property of nutrient-derived metabolites
PSU Invention Disclosure Number: 2011-3813

AWARDS & HONORS

- "Future leader in Nutrigenomics" award by Nebraska Gateway to Nutrigenomics (NGN) Award Selection Committee, University of Nebraska – Lincoln: to be awarded May 2013.
- Awarded "Post Doctoral Travel Grant" by Penn State University to participate in "Experimental Biology 2012" held on April, 2012 in San Diego, CA, USA.

- Awarded “Partial Travel Grant” to participate in “Young Investigator Meeting (YIM) 2011” held in February, 2011 in Bhubaneswar, Orissa, India.
- Awarded “Full Travel Grant from Department of Biotechnology, Government Of India, for attending 8th International Symposium on Selenium in Biology and Medicine” held in university of Wisconsin, Madison, USA in July 2006.

TECHNICAL SKILLS

- Isolation of primary cells, Cell culture and Maintenance of cell lines: Primary and Secondary cells, Primary Leukemic Stem cells
- Excellent Animal Handling: Bone Marrow Transplantation, Phenotyping, Sub-Q, IP, IV Injections, Retro-orbital bleeding, tissue extraction.
- Gene and Protein expression analyses.
- Biochemical Analyses for enzyme kinetics and activities pertinent to redox regulations and inflammatory pathways.
- Microscopy and Histopathology: Staining Methods, Immunohistochemistry (IHC)
- Cloning and expression of target genes using detailed Molecular Biology techniques.
- Bio-analytical techniques: Flow Cytometry, and basic knowledge of HPLC., Mass Spectrometry (LC/MS; LC/MS/MS) of lipid metabolites

PROFESSIONAL CONTRIBUTIONS

Editorial Responsibilities

Editor "The Journal of Postdoctoral Research", USA.

Grants Reviewed

Reviewed grant for “Dutch Cancer Society”, Netherlands

Manuscripts Reviewed

Reviewed manuscripts for *“Nutrition and Metabolism”*, a Biomed Central Journal.

Reviewed manuscripts *“The Nutrition journal”,* a Biomed Central Journal

Books Reviewed

"The Elements of Immunology” published by Pearson Inc. (2009).

MEMBERSHIPS & AFFILIATIONS

1. Life time member of "Indian Biophysical Society", INDIA.
2. Affiliate member of "National Post-doctoral Society", USA.

PERSONAL INFORMATION

Date of Birth: Sept. 26, 1980 ***Citizenship***: Indian

Marital Status: Married

Research Summary

Post-doctoral Research

A. ***Evaluation of the anti-inflammatory properties of selenium containing derivatives of Classical NSAID Celecoxib*.** Celecoxib is a well known selective cyclooxygenase (COX)-2 inhibitor that belongs to class of NSAID's used to treat inflammation. However, at higher dose the use of celecoxib and other NSAIDs have critical side effects associated with them. The fact that Se down-regulates the transcription of COX-2 and other pro-inflammatory genes led to hypothesis of expanding the anti-inflammatory property of celecoxib at extremely low doses by incorporating selenium (Se) into celecoxib. We derived, two Se-derivatives of celecoxib namely; selenocoxib-2 and selenocoxib-3, in collaboration with Dr. Dhiman Desai, Hershey Medical Center, Pennsylvania. Of the two derivatives, selenocoxib-2 inhibited lipopolysaccharide (LPS)-induced activation of NF-κB leading to the down-regulation of expression of COX-2, iNOS, and TNFα more effectively than selenocoxib-3 and celecoxib in RAW264.7 and murine bone marrow-derived macrophages. The studies suggest that selenocoxib-2, but not celecoxib and selenocoxib-3, targets upstream events in the NF-κB signaling axis, the ability to effectively suppress NF-κB activation independent of cellular selenoprotein synthesis opens possibilities for a new generation of COX-2 inhibitors with significant and broader anti-inflammatory potential.

Continuing with our interest in the Se biochemistry and its effect on Arachidonic acid metabolism, we began to delineate the role of prostaglandins (fatty acid metabolites of COX) in erythropoiesis and leukemogenesis. The proximity to experts like Drs. Robert F Paulson and Pamela Hankey (Correll)'s research groups provided me an opportunity to bring these ideas and hypothesis in the form of research projects. The first lead in this direction came with a simple observation of a drastic difference in the blood parameters like RBC count, platelet numbers etc in Se deficient and Se supplemented animals, forming the basis of my second project.

B. ***The effect of selenium status on erythropoiesis in-vivo*.** Se as an essential trace element is an important antioxidant to maintain redox tone in the body. The fact that erythropoiesis, as physiological process, is prone to oxidative stress and erythrocyte have high levels of GPx as antioxidants led to the hypothesis that antioxidants, such as selenium (Se) can regulate this process by redox modulation. We showed that Se deficiency caused anemia, increased denaturation of hemoglobin, methemoglobin, protein carbonyls, lipid peroxidation, Heinz bodies, and osmotic fragility of erythrocytes, when compared to the Se-supplemented and Se-adequate groups. Also Se deficiency increased oxidative stress upregulated forkhead transcription factor (FoxO3a) and hypoxia-inducible factor-(HIF)1α in the spleen and kidney of Se-deficient mice as well as in the proerythroblast G1E cells cultured in Se-deficient media. A significant increase in the expression of erythropoietin, a downstream target of HIF1α, and expansion of stress erythroid progenitors (burst forming units-erythroid) were seen in the Se-deficient mice. In summary, these results provide insight into the importance of adequate Se nutrition in regulating red cell homeostasis by mitigating oxidative stress-dependent modulation of FoxO3a and HIF1α to effect differentiation of erythroid progenitors.

The studies mentioned earlier and previous studies from the lab led us to further attempt to understand that modulation of PGs by Se and thereby the pathophysiological processes. Since

inflammation is mediated by these PGs and lies at helm of almost all disease states we decided to look for modulation of inflammatory process by selenium and its molecular mechanism/s in detail.

C. ***Regulation of cyclooxygenase-2 (COX-2) and prostaglandin pathway by Selenium derived selenoproteins in RAW 264.7 Macrophages.*** Macrophages have dual role in inflammation and its resolution. Previously, our lab has demonstrated that Se increases macrophage production of arachidonic acid (AA)-derived anti-inflammatory 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 (15d-PGJ_2) and decreases the proinflammatory PGE_2. We hypothesized that selenium reduces inflammation by modulating the AA metabolism by a differential regulation of various prostaglandin (PG) synthases favoring the production of PGD_2 metabolites, Δ^{12}-PGJ_2 and 15d-PGJ_2. Se supplementation in RAW264.7 macrophages and primary bone marrow-derived macrophages led to a dose-dependent increase in the expression of hematopoietic-PGD_2 synthase (H-PGDS) and a corresponding increase in Δ^{12}-PGJ_2 and 15d-PGJ_2. Alternatively, the expression of nuclear factor-κB-dependent thromboxane synthase and microsomal PGE_2 synthase was down-regulated by selenium. Studies with organic non-bioavailable forms of Se and the genetic manipulation of cellular Se incorporation machinery indicated that selenoproteins were necessary for H-PGDS expression and 15d-PGJ_2 production. Treatment of selenium-deficient macrophages with rosiglitazone, a peroxisome proliferator-activated receptor (PPAR) γ ligand, up-regulated H-PGDS. We showed the presence of an active peroxisome proliferator-activated receptor-response element in murine *Hpgds* promoter suggesting a positive feedback mechanism of H-PGDS expression. Using a Friend virus infection model of murine leukemia (in collaboration with Dr. Paulson), the onset of leukemia was observed only in selenium-deficient and indomethacin-treated selenium-supplemented mice but not in the selenium-supplemented group or those treated with 15d-PGJ_2. These results suggest the importance of selenium in the shunting of AA metabolism toward the production of PGD_2 metabolites and resolution of inflammation, which may have clinical implications.

The successful completion of this project and interesting findings in the Leukemia model shifted my attention towards the implications of PGs in modulating the mechanisms underlying the leukemia. Also, the fact that fish oil which is rich in ω -3 PUFA has been found to show beneficial effects in various cancers. Therefore, we decided to connect the dots to observe the metabolism of ω-3 fatty acids such as EPA its pathophysiological benefits.

D. ***Omega-3 fatty acid derived novel Cyclopentanone prostaglandin Δ^{12}-prostaglandin J_3 ablates leukemia by targeting Leukemic Stem cells (LSCs)***. EPA can be metabolized by COX enzymes giving to rise to 3-series PGs like 2 series PGs given by AA. However, to our surprise no detailed studies were available which indicate the complete metabolism of 3 series metabolites particularly PGD3. Therefore, we decided to take a metabolic approach to explain the anti-cancer properties of EPA. The studies were based on hypothesis that EPA-derived cyclopentenone PGJ_3 metabolites affect the development of leukemia by targeting the leukemia stem cells (LSC) for apoptosis. Targeting these LSCs is of paramount importance to successfully combat the relapse of leukemia. We have found that a series of novel and naturally produced CyPG can be formed from the metabolism of dietary fish-oil omega-3 polyunsaturated fatty acid (n-3 PUFA), eicosapentaenoic acid (EPA). These metabolites such as PGJ_3, Δ^{12}-PGJ_3, and 15-deoxy-$\Delta^{12\text{-}14}$-PGJ_3 (15d-PGJ_3) have never been reported. We found that Δ^{12}-PGJ_3 a major metabolite completely alleviate the development of leukemia by targeting LSCs. Two well-studied murine models of leukemia were used

where Δ^{12}-PGJ_3 was administered in mice infected with Friend erythroleukemia virus (FV) or those transplanted with hematopoietic stem cell (HSC) expressing chronic myelogenous leukemia (CML) oncoprotein BCR-ABL. Interestingly, Δ^{12}-PGJ_3 was found to specifically target the Leukemic Stem Cells (LSCs) to treat leukemia and there was no relapse of the disease was observed. We have also proposed a molecular mechanism of Δ^{12}-PGJ_3 to induce apoptosis in LSCs. These studies are aimed at targeting the LSC, which are well-known for their refractoriness to commonly used clinical agents, using endogenous metabolites.

Doctoral Research

Title: *Modulation of cell cycle regulators and Heat shock proteins by selenium induced oxidative stress during spermatogenesis in mice* -----

Year: 2004-2008

Summary: During my PhD I have studied the selenium mediated modulation of various cell cycle regulators, heat shock proteins and apoptotic pathways in male germ cells in a redox sensitive manner. Selenium as described earlier is an essential nutrient and work in a very narrow physiological range. Under the deficient and supra-nutritional concentrations it induces oxidative stress in the body and may pose deleterious effects. My research work demonstrated that dietary selenium induced oxidative stress differentially modulates the expression of inducible and constitutive HSP70s during spermatogenesis in mice testis. Also, the cell cycle regulators such as CDC2, cyclin B1, p21 beside others which are the key regulators for normal completion of spermatogensis were modulated by Se induced oxidative stress. The attenuation of testes specific HSP70-2 by nutritional selenium various induced oxidative stress causes male germ cell apoptosis by p53 dependent apoptotic pathway. This is a potential cause of infertility in men.

Overall, my research in the field of Selenium biochemistry and its redox regulation can open new vistas to development of treatment protocols for various pathological states including infertility, cancers and inflammatory conditions.