Khosrow Kashfi, PhD, FRSC, FRSB

Department of Molecular, Cellular & Biomedical Sciences
City University of New York School of Medicine
160 Convent Avenue, New York, NY 10031
Tel: (212) 650-6641
Fax: (212) 650-7692
Email: kashfi@med.cuny.edu
https://www.ccny.cuny.edu/profiles/khosrow-kashfi
www.avicennatherapeutics.com

Profile

Khosrow Kashfi is an Associate Medical Professor of Pharmacology at the City University of New York School of Medicine and is an elected Fellow of the Royal Society of Chemistry and an elected Fellow of the Royal Society of Biology. Dr. Kashfi is trained chemist, has a Master's degree in Polymer Physics and Engineering from Cranfield Institute Technology in England, and a PhD in Pharmacology from the University of Tennessee - The Health Science Center. He got interested in cancer prevention whilst working as a postdoctoral fellow at Cornell University Medical College. This interest was further developed at The Rockefeller University and since he became an independent investigator, he has been working on the molecular targets of nonsteroidal anti-inflammatory drugs (NSAIDs) and their various chimeras. His research is currently focused on the molecular targets of nitric oxide and hydrogen sulfide releasing NSAIDs (NOSH-NSAIDs) in cancer. He is the inventor of this class of pharmaceuticals and holds a number of worldwide patents in this general area.

Education

Ph.D., 1992, University of Tennessee
M.Sc., 1976, Cranfield Institute of Technology
B.S., 1974, Kingston Polytechnic

Research Interests

Biology of colon, breast, and pancreatic cancers and their chemo prevention
Regulation of lipid metabolism including eicosanoids.

Contributions to Science

Link to full publication list at NCBI
https://www.ncbi.nlm.nih.gov/sites/myncbi/khosrow.kashfi.1/bibliography/41456532/public/?sort=date&direction=ascending

1) Regulation of hepatic mitochondrial carnitine palmitoyltransferases. When I started my graduate studies focusing on intermediary metabolism, there were two overarching questions that were of immediate importance. (1) Which CPT was increased during diabetes and fasting? (2) Did malonyl-CoA and acyl-CoA bind to same site as it was assumed to be the case for many years? During my PhD work I demonstrated that the CPT, which was located on the mitochondrial outer membrane, was in fact the CPT whose activity was increased during diabetes and fasting. Further, I demonstrated that its Ki for inhibition by malonyl-CoA was increased by about 50-fold. I also showed that the malonyl-CoA binding site was distinct from the acyl-CoA binding site. When I submitted my PhD thesis, I had published 6 papers on this work with another 6 that were subsequently published directly from my thesis.

- **Kashfi K,** Weakley LJ, and Cook GA. (1988) The Effects of Diabetes on the Carnitine Palmitoyltransferase of Isolated Hepatic Mitochondrial Outer Membranes. *Biochem. Soc. Trans.* **16,** 1010-1011.
- **Kashfi K,** and Cook GA. (1991) Malonyl-CoA Inhibits Proteolysis of Carnitine Palmitoyltransferase. *Biochem. Biophys. Res. Comm.* **178,** 600-605.
- **Kashfi K,** and Cook GA. (1992) Proteinase Treatment of Intact Hepatic Mitochondria has Differential Effects on Inhibition of Carnitine Palmitoyltansferase by Different Inhibitors. *Biochem. J.* **282,** 909-914.
- **Kashfi K,** Mynatt RL, and Cook GA. (1994) Hepatic Carnitine Palmitoyltransferase-I Has Two Independent Inhibitory Binding Sites for Regulation of Fatty Acid Oxidation. *Biochim. Biophys. Acta.* **1212,** 245-252.
- Cook GA, Mynatt RL, and **Kashfi K.** (1994) Yonetani-Theorell Analysis of Hepatic Carnitine Palmitoyltransferase-I Inhibition Indicates Two Distinct Inhibitory Binding Sites. *J. Biol. Chem.* **269,** 8803-8807.
- **Kashfi K,** Cagen L, and Cook GA. (1995) Diabetes and Proteolysis: Effects on Carnitine Palmitoyltransferase-I and Malonyl-CoA Binding. *Lipids* **30,** 383-388.
- Park EA, Mynatt RL, Cook GA, and **Kashfi K.** (1995) Insulin Regulates Enzyme Activity, Malonyl-CoA Sensitivity and mRNA Abundance of Hepatic Carnitine Palmitoyltransferase-I. *Biochem. J.* **310,** 853-858

2) Dietary regulation of xenobiotic metabolizing enzymes. For my postdoctoral work, I wanted to be in an area totally different from my graduate training. Hence, I joined Dr. Dannenberg's lab at Cornell University Medical College who at the time was looking at dietary regulation of xenobiotic metabolizing enzymes. I learned a lot in his lab and at Cornell I was fortunate enough to meet Dr. Basil Rigas who introduced me to Dr. Steven Shiff who at the time was at the Rockefeller University; both introduced me to NSAIDs and cancer.

- **Kashfi K,** Rimarachin JA, Weksler BB, and Dannenberg AJ. (1994) Differential Induction of Glutathione *S*-Transferases in the Rat Aorta Versus Liver. *Biochem. Pharma.* **47,** 1903-1907.
- **Kashfi K,** Yang EK, Roy Chowdhury J, Roy Chowdhury N, and Dannenberg AJ. (1994) Regulation of Uridine Diphosphate Glucuronosyltransferase Expression by Phenolic Antioxidants. *Cancer Res.* **54,** 5856-5859.
- **Kashfi K,** McDougall CJ, and Dannenberg AJ. (1995) Comparative Effects of Omeprazole on Xenobiotic Metabolizing Enzymes in the Rat and Human. *Clin. Pharma. Ther*. **58,** 625-630.

3) Nitric oxide-donating NSAIDs as agents for cancer prevention. NO-NSAIDs were developed as safer NSAIDs. The collaboration between my lab and the Rigas lab showed their utility as anti-cancer agents both in vitro and in vivo using various animal models of cancer. We were the first to show that these agents had a pleotropic mechanism of action, affecting multiple pathways important in cancer. We also showed that positional isomerism affected the potency of these agents. Whilst working with NO-aspirin, I recognized that if the linker/spacer between the aspirin backbone and the NO-donating moiety was aromatic, then most likely the effects that we were seeing with NO-aspirin was not due to the released NO but was due to formation of a quinone methide intermediate. This led to the synthesis of a variety of compounds confirming that the NO-releasing moiety was acting as leaving group; showing that the biological activity of some NO-aspirin analogs was essentially due to the spacer.

- **Kashfi K,** Ryann Y, Qiao LL, Williams JL, Chen J, Del Soldato P, Traganos F, and Rigas B. (2002) Nitric oxide-donating nonsteroidal anti-inflammatory drugs inhibit the growth of various cultured human cancer cells: evidence of a tissue type-independent effect. *J Pharmacol Exp Ther (Cover Issue)*. **303,** 1273-82.
- Williams J, Nath N, Chen J, Hundley T, Gao J, Kopelovich L, **Kashfi K**, and Rigas B. (2003) Growth Inhibition of Human Colon Cancer Cells by Nitric Oxide (NO)-Donating Aspirin is Associated with Cyclooxygenase-2 Induction and ß-Catenin/T-Cell Factor Signaling, Nuclear Factor-κB and NO Synthase 2 Inhibition: Implications for Chemoprevention. *Cancer Res*. **63,** 7613-7618.
- Nath N, **Kashfi K,** Chen J and Rigas B. (2003) NO-donating aspirin inhibits beta-catenin /TCF signaling in SW480 colon cancer cells more potently than aspirin by disrupting the nuclear beta-catenin–TCF association: Relevance to colon cancer chemoprevention. *Proc. Natl. Aca. Sci., USA* **100,** 12584-12589.
- Williams JL, **Kashfi K,** Ouyang N, del Soldato P, Kopelovich L, and Rigas B. (2004) NO-Donating Aspirin Inhibits Intestinal Carcinogenesis in MIN (*APC* $^{Min/+}$) Mice. *Biochem. Biophys. Res. Comm* **313,** 784-788.
- **Kashfi K,** Borgo S, Williams JL, Chen J, Glekas A, Traganos F, Benedini F, del Soldato P, Rigas B. (2005) Positional isomerism markedly affects the growth inhibition of colon cancer cells by NO-releasing aspirin: A structure-activity study *in vitro* and *in vivo*. *J Pharmacol Exp Ther* **312,** 978-988.
- Ouyang N, Williams JL, Tsioulias G, Gao J, Latropoulos M, Kopelovich L, **Kashfi K,** and Rigas B. (2006) NO-donating aspirin prevents pancreatic cancer in a hamster tumor model. *Cancer Res*. **66,** 4503-4511.
- **Kashfi K,** and Rigas B. (2007) The mechanism of action of nitric oxide-donating aspirin. *Biochem. Biophys. Res. Comm.* **358,** 1096-1101.

4) Hydrogen sulfide-donating NSAIDs as agents for cancer prevention. After H2S was shown to be a physiologically relevant gasotransmitter, H2S-NSAIDs were developed as alternatives to NO-NSAIDs. They exhibited safer gastrointestinal profiles compared to their native counterparts and had strong anti-inflammatory properties.

Based on this, my lab synthesized four H2S-donating NSAIDs and evaluated their anti-cancer properties and mechanism of action in various in vitro and in vivo models including estrogen negative breast cancer. Three of our papers were published back-to-back in Biochemical Pharmacology in 2012.

- Chattopadhyay M, Kodela R, Nath N, Dastagirzada YM, Velázquez-Martínez CA, Boring D, and **Kashfi K.** (2012) Hydrogen sulfide-releasing NSAIDs inhibit the growth of cultured human cancer cells: A general property and evidence of a tissue type-independent effect. *Biochem Pharmacol.* **83,** 715-722.
- Chattopadhyay M, Kodela R, Nath N, Barsegian A, Boring D, and **Kashfi K.** (2012) Hydrogen sulfide-releasing aspirin suppresses NF-κB signaling in estrogen receptor negative breast cancer cells *in vitro* and *in vivo*. *Biochem Pharmacol.* **83,** 723-732.
- Chattopadhyay M, Kodela R, Nath N, Street CA, Velázquez-Martínez CA, Boring D, and **Kashfi K**. (2012) Hydrogen sulfide-releasing aspirin modulates xenobiotic metabolizing enzymes *in vitro* and *in vivo*. *Biochem Pharmacol.* **83,** 733-740.
- Chattopadhyay M, Nath N, Kodela R, Gan ZY, and **Kashfi K**. (2013) Hydrogen sulfide-releasing aspirin inhibits the growth of leukemic Jurkat cells and modulates β-catenin expression. *Leukemia Res.* **37** (10), 1302-8.
- Kodela R, Nath N, Chattopadhyay M, Nesbitt DE, Velázquez-Martínez CA, and **Kashfi K.** (2015) Hydrogen sulfide-releasing naproxen suppresses colon cancer cell growth and inhibits NF-κB signaling. *Drug Des Devel Ther.* **9,** 4873–4882.

5) NOSH-NSAIDs a new class of anti-inflammatory pharmaceuticals. From the literature we knew that NO and H2S enhance the local mucosal defense mechanisms and based on their chemistry and the structural components of NO-NSAIDs and H2S-NSAIDs, I postulated that an NSAID possessing moieties that could donate both of these gasotransmeters might be more potent and effective than either one alone. This led to the synthesis and characterization of a new class of anti-inflammatory and anti-cancer compounds, that I have coined NOSH-NSAIDs, of which six have been reported thus far. All compounds reported retain the pharmacological properties to their respective parent compound but unlike their native counterparts are GI safe and should also have enhanced cardiovascular and renal safety profiles because both NO and H2S have been shown to have safety profiles in these organs. NOSH-NSAIDs have potent anti-inflammatory properties and in vitro are active against a variety of human cancer cell lines with nano-molar IC50s. In vivo animal models of cancer, NOSH-NSAIDs are very effective and potent and my lab is actively studying their mechanisms of action. Word-wide patents on this class of compounds were recently issued.

- Kodela R, Chattopadhyay M, and **Kashfi K.** (2012) NOSH-aspirin: A novel nitric oxide- hydrogen sulfide-releasing hybrid: A new class of anti-inflammatory pharmaceuticals. *ACS Med. Chem. Lett*. **3,** 257–262.
- Chattopadhyay M, Kodela R, Olson KR, and **Kashfi K.** (2012) NOSH-aspirin (NBS 1120), a novel nitric oxide- and hydrogen sulfide-releasing hybrid is a potent inhibitor of colon cancer cell growth *in vitro* and in a xenograft mouse model. *Biochem. Biophys. Res. Comm.* **419,** 523-528.
- Kodela R, Chattopadhyay M, and **Kashfi K.** (2013) Synthesis and biological activity of NOSH-naproxen (AVT-219) and NOSH-sulindac (AVT-18A) as potent anti-inflammatory agents with chemotherapeutic potential. *Med Chem Commm* **4** (11), 1472–1481.
- Lee M, McGeer E, Kodela R, **Kashfi K,** and McGeer PL. (2013) NOSH-aspirin (NBS-1120) a novel nitric oxide and hydrogen sulfide releasing hybrid attenuates

neuroinflammation induced by microglial and astrocytic activation: A new candidate for treatment of neurodegenerative disorders. *GLIA* **61** (10), 1724-34.

- Fonseca MD, Cunha FQ, **Kashfi K**, Cunha TM. (2015) NOSH-Aspirin (NBS-1120), a dual nitric oxide and hydrogen sulfide-releasing hybrid, reduces inflammatory pain. *Pharmacol Res Perspect.* Jun;3(3):e00133, 1-8
  - **Kashfi K,** Chattopadhyay M, Kodela R. (2015) NOSH-sulindac (AVT-18A) is a novel nitric oxide- and hydrogen sulfide-releasing hybrid that is gastrointestinal safe and has potent anti-inflammatory, analgesic, antipyretic, anti-platelet, and anti-cancer properties. Redox Biol. 6, 287-296.
- Kodela R, Chattopadhyay M, Velázquez-Martínez CA, and **Kashfi K.** (2015) NOSH-aspirin (NBS-1120), a novel nitric oxide- and hydrogen sulfide-releasing hybrid has enhanced chemo-preventive properties compared to aspirin, is gastrointestinal safe with all the classic therapeutic indications. *Biochem Pharmacol.* **98**(4):564-72.
- Chattopadhyay M, Kodela R, Duvalsaint PL, and **Kashfi K.** (2016) Gastrointestinal safety, chemotherapeutic potential, and classic pharmacological profile of NOSH-naproxen (AVT-219) a dual NO and H_2S-releasing hybrid**.** *Pharmacol Res Perspect.* Mar 4;4(2):e00224, 1-15, doi: 10.1002/prp2.224

Publications

Sodium hydrosulfide has no additive effects on nitrite-inhibited renal gluconeogenesis in type 2 diabetic rats.
Jeddi S, Gheibi S, **Kashfi K**, Ghasemi A.Life Sci. 2021 Oct 15;283:119870.

Lipoproteins and cancer: The role of HDL-C, LDL-C, and cholesterol-lowering drugs.
Patel KK, **Kashfi K.** Biochem Pharmacol. 2021 Jun 12:114654.

Diabetoporosis: Role of nitric oxide.
Yousefzadeh N, Jeddi S, **Kashfi K**, Ghasemi A. EXCLI J. 2021 Apr 16;20:764-780.

Amino acid-based H_2S donors: *N*-thiocarboxyanhydrides that release H_2S with innocuous byproducts.
Kaur K, Enders P, Zhu Y, Bratton AF, Powell CR, **Kashfi K**, Matson JB.Chem Commun (Camb). 2021 Jun 3;57(45):5522-5525.

Lost-in-Translation of Metabolic Effects of Inorganic Nitrate in Type 2 Diabetes: Is Ascorbic Acid the Answer?
Bahadoran Z, Mirmiran P, **Kashfi K**, Ghasemi A. Int J Mol Sci. 2021 Apr 29;22(9):4735.

Resolution of inflammation: An organizing principle in biology and medicine.
Panigrahy D, Gilligan MM, Serhan CN, **Kashfi K.** Pharmacol Ther. 2021 Apr 27;227:107879.

Acidified Nitrite Accelerates Wound Healing in Type 2 Diabetic Male Rats: A Histological and Stereological Evaluation.
Afzali H, Khaksari M, Jeddi S, **Kashfi K**, Abdollahifar MA, Ghasemi A. Molecules. 2021 Mar 26;26(7):1872. doi: 10.3390/molecules26071872.

Long-term co-administration of sodium nitrite and sodium hydrosulfide inhibits hepatic gluconeogenesis in male type 2 diabetic rats: Role of PI3K-Akt-eNOS pathway.

Jeddi S, Gheibi S, Carlström M, **Kashfi K**, Ghasemi A. Life Sci. 2021 Jan 15;265:118770. doi: 10.1016/j.lfs.2020.118770.

Effects of hydrogen sulfide on mitochondrial function and cellular bioenergetics.
Paul BD, Snyder SH, **Kashfi K.** Redox Biol. 2021 Jan;38:101772.

Endogenous flux of nitric oxide: Citrulline is preferred to Arginine.
Bahadoran Z, Mirmiran P, **Kashfi K**, Ghasemi A. Acta Physiol (Oxf). 2021 Mar;231(3):e13572.

SP1-independent inhibition of FOXM1 by modified thiazolidinediones.
Tabatabaei Dakhili SA, Pérez DJ, Gopal K, Haque M, Ussher JR, **Kashfi K**, Velázquez-Martínez CA. Eur J Med Chem. 2021 Jan 1;209:112902.

Inorganic nitrate, a natural anti-obesity agent: A systematic review and meta-analysis of animal studies.
Bahadoran Z, Jeddi S, Gheibi S, Mirmiran P, **Kashfi K**, Ghasemi A. EXCLI J. 2020 Jul 6;19:972-983.

Importance of Systematic Reviews and Meta-analyses of Animal Studies: Challenges for Animal-to-Human Translation.
Bahadoran Z, Mirmiran P, **Kashfi K**, Ghasemi A. J Am Assoc Lab Anim Sci. 2020 Sep 1;59(5):469-477.

Acidified nitrite improves wound healing in type 2 diabetic rats: Role of oxidative stress and inflammation.
Afzali H, Khaksari M, Norouzirad R, Jeddi S, **Kashfi K**, Ghasemi A.Nitric Oxide. 2020 Oct 1;103:20-28.
The Principles of Biomedical Scientific Writing: Citation.
Bahadoran Z, Mirmiran P, **Kashfi K**, Ghasemi A. Int J Endocrinol Metab. 2020 Apr 27;18(2):e102622.

Roles and Interaction of the MAPK Signaling Cascade in Aβ25-35-Induced Neurotoxicity Using an Isolated Primary Hippocampal Cell Culture System.
Iloun P, Hooshmandi E, Gheibi S, **Kashfi K**, Ghasemi R, Ahmadiani A. Cell Mol Neurobiol. 2021 Oct;41(7):1497-1507.

Protective effect of intermediate doses of hydrogen sulfide against myocardial ischemia-reperfusion injury in obese type 2 diabetic rats.
Jeddi S, Gheibi S, **Kashfi K**, Carlström M, Ghasemi A. Life Sci. 2020 Sep 1;256:117855.

Nitric oxide in cancer and beyond.
Kashfi K. Biochem Pharmacol. 2020 Jun;176:114006.

The Principles of Biomedical Scientific Writing: Abstract and Keywords.
Bahadoran Z, Mirmiran P, **Kashfi K**, Ghasemi A. Int J Endocrinol Metab. 2020 Jan 28;18(1):e100159.

The evolving landscape for cellular nitric oxide and hydrogen sulfide delivery systems: A new era of customized medications.
Dillon KM, Carrazzone RJ, Matson JB, **Kashfi K.** Biochem Pharmacol. 2020 Jun;176:113931.

Tumor associated macrophages and 'NO'.
Nath N, **Kashfi K.**Biochem Pharmacol. 2020 Jun;176:113899.

Dose-Dependent Effects of Long-Term Administration of Hydrogen Sulfide on Myocardial Ischemia-Reperfusion Injury in Male Wistar Rats: Modulation of RKIP, NF-κB, and Oxidative Stress.
Jeddi S, Gheibi S, **Kashfi K**, Carlström M, Ghasemi A. Int J Mol Sci. 2020 Feb 19;21(4):1415.

NOSH-aspirin (NBS-1120) inhibits pancreatic cancer cell growth in a xenograft mouse model: Modulation of FoxM1, p53, NF-κB, iNOS, caspase-3 and ROS.
Chattopadhyay M, Kodela R, Santiago G, Le TTC, Nath N, **Kashfi K.** Biochem Pharmacol. 2020 Jun;176:113857.