BIOGRAPHICAL SKETCH

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NAME: **Satdarshan Pal Singh Monga, M.D.**

eRA COMMONS USER NAME (credential, e.g., agency login): **smonga7bareta**

POSITION TITLE: **Professor of Pathology and Medicine**

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 *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Dayanand Medical College & Hospital, Ludhiana and Punjab University, Chandigarh, India	M.D.	12/1993	Medicine and Surgery
Georgetown University & Department of Veterans Affairs Medical Center (DVAMC), Washington, D.C		06/1997	Postdoctoral Fellowship (Gastroenterology and Molecular Biology)
Temple University, Fels Cancer Institute, Philadelphia and DVAMC Washington, D.C		08/1999	Postdoctoral Fellowship (Gastroenterology and Molecular Biology)

A. Personal Statement.

For around 19 years, my research has focused on understanding the cellular and molecular basis of liver health and disease. Specifically, my lab is interested in understanding the role of signaling pathways such as Wnt/β-catenin in liver development, regeneration, inflammation, injury, fibrosis and tumorigenesis. The eventual goal of the lab is to gain better understanding of molecular aberrations for improved therapeutics for various hepatic diseases such as end stage liver disease (ESLD), liver failure, fibrosis and cancer. My lab has extensive experience in signaling mechanisms such as Wnt/β-catenin, HGF/Met, PDGF and Yap and we have generated many animal models and reagents to elucidate their role in various hepatic pathologies and in liver physiology. The eventual goal of the lab is to gain better understanding of molecular aberrations in various hepatic diseases for improved clinical outcomes.

For last 12 years, I have been involved with the Interdisciplinary Biomedical Graduate Program (IBGP) as part of the Cellular and Molecular Pathology and Molecular Pharmacology Graduate Programs. I am also the director and PI for the Cellular Approaches to Tissue Engineering & Regeneration program (T32) and training faculty on other grants such as Angiogenesis training program (T32) and on training grant for the Department of Medicine. I am deeply involved in MSTP training and am the course director for their longitudinal clinical clerkship. I have served as course director for various courses offered to the graduate students including “Stem Cells” and “Research Seminars in Regenerative Medicine”. I have trained several pre- and post-doctoral trainees. In addition, I have served as chair and member on thesis committees for various graduate students. I have also been involved with the admissions committee and recruitment committee for the IBGP program as well as for CATER program at the School of Medicine. *I consider the education and mentorship mission of our institute, division and training program, of pivotal importance in sustaining and further developing excellent and multidisciplinary research programs that will assure a successful impact on human disease in the long run.*

a. Thompson, M, **Monga SP**. Wnt/β-catenin signaling in Liver Health and Disease. Hepatology. 2007 May;45(5):1298-305.
b. Nejak-Bowen K, **Monga SP**. Beta-catenin signaling, liver regeneration and hepatocellular cancer: Sorting the good from the bad. Semin Cancer Biol. 2011 Feb;21(1):44-58. Epub 2010 Dec 21. PMCID: PMC3050081

c. Lade AG, **Monga SP**. Beta-catenin signaling in hepatic development and progenitors: Which way does the WNT blow? Dev Dyn. 2011 Mar;240(3):486-500. PMCID: PMC4444432
d. **Monga SP**. β-Catenin Signaling and Roles in Liver Homeostasis, Injury, and Tumorigenesis. Gastroenterology. 2015 Jun;148(7):1294-310. PMCID: PMC4494085

B. Positions and Honors

Positions and Employment

1999-2001: Research Associate, Department of Pathology, University of Pittsburgh, SOM, Pittsburgh, PA
2001-2003: Research Assistant Professor, Division of Cellular & Molecular Pathology, University of Pittsburgh
2004-2007: Assistant Professor of Pathology and Medicine, University of Pittsburgh, SOM, Pittsburgh, PA
2007-2012: Associate Professor of Pathology (Division of Experimental Pathology), University of Pittsburgh
2007-2012: Associate Professor of Medicine (Division of GI, Hepatology & Nutrition), University of Pittsburgh
2008-present: Director, Division of Experimental Pathology, University of Pittsburgh, SOM, Pittsburgh, PA
2012-present: Professor of Pathology (Division of Experimental Pathology), University of Pittsburgh, SOM
2007-present: Professor of Medicine (Division of GI, Hepatology & Nutrition), University of Pittsburgh, SOM
2013-present: Program Director, Cellular Approaches to Tissue Engineering and Regeneration (T32, NIBIB)
2013-present: Vice Chair of Experimental Pathology, University of Pittsburgh, SOM
2015-present: Assistant Dean, Medical Scientist Training program, University of Pittsburgh, SOM
2016-present: Director: Liver Research Center, UPMC and University of Pittsburgh, SOM

Professional Memberships

1999-present: PLUTO (American Association of University Pathologists)
2009-present: American Society for Clinical Investigations (ASCI)
2006-present: American Association for The Study of Liver Diseases (AASLD)
2002-present: American Society of Investigative Pathology (ASIP)
2001-present: American Association of Cancer Research (AACR)
1999-present: American Gastroenterology Association (AGA)

Other Experience (Selected)

2008-2010: Program Chair, ASIP
2008-2013: Standing member, Hepatobiliary pathophysiology study section
2008-present: Associate Editor, American Journal of Pathology
2009-2013: Associate Editor, BMC-Cancer
2009-present: Liver Center External Advisory Committee, Albert Einstein, College of Medicine, Yeshiva University
2010: Chair, Meeting and Courses Task Committee for ASIP
2012-present: Editor-in-Chief: Current Pathobiology Reports, Springer Journals
2014-2016: Associate Editor, Journal of Hepatology
2008: Organizer of 2010 FASEB Summer Research Conference in 2010 on Liver Pathobiology
2011-present: Scientific Advisory Board, Virtual Liver Network, Germany
2012: Merck Pharmaceuticals, HCC Advisory committee
2012-2013: Phase-Rx Inc., Consultant, Liver Cancer Treatment
2012-2013: Bristol Myers Squibb, Liver Fibrosis Scientific Advisory Board
2013-2015: Program Chair, ASIP (responsible for annual meetings in 2015 and 2016)
2014-present: Abbvie Hepatic Disease Steering committee
2014-present: Editorial Committee: Annual Reviews of Pathology
2015-present: Editor-in-Chief, Gene Expression: The Journal of Basic Liver Research
2016-present: Associate Editor: Seminars in Liver Disease
2016-present: Secretary Treasurer: ASIP
2016-present: Dicerna Pharmaceuticals Liver Fibrosis Scientific Advisory Board

Honors (Selected)

2003: American Cancer Society, Research Scholar Award
2006: Recipient of Senior Vice Chancellor Award, University of Pittsburgh, SOM
2009: Elected to American Society for Clinical Investigations (ASCI)
2010: William E. Brown Outstanding MSTP mentor award, University of Pittsburgh
2011: Distinguished Mentor Merit Award, Biomedical Graduate Student Association, University of Pittsburgh
2012: Endowed Chair for Experimental Pathology, University of Pittsburgh
2013: Winner of the Outstanding Investigator Award, ASIP (2014)
2015: Medical Student Research Mentoring Merit Award, University of Pittsburgh, School of Medicine

C. Contribution to Science

1. Work from my lab has characterized the role of **Wnt/β-catenin signaling in liver regeneration**. Earlier studies as a postdoctoral fellow, formed the basis of my first R01 that have been funded since 2003. Using rat partial hepatectomy model and eventually genetic mouse models lacking β-catenin in hepatocytes, we showed its role in regulating cyclin-D1 expression after hepatectomy. Further, we determined that β-catenin activation during murine liver regeneration was under the control of Wnt signaling as mice lacking Wnt co-receptors LRP5/6, also showed a defect in liver regeneration similar to β-catenin KO. We have now identified an important role of macrophages as being sources of specific Wnt proteins that regulate β-catenin activity in hepatocytes in a paracrine fashion. Ongoing studies are also determining role of sinusoidal endothelial cells in this process. We also showed that β-catenin activation is critical for regeneration after toxicant induced liver injury in mice and patients. We have also demonstrated an important role of Wnt5a in terminating β-catenin signaling during regeneration when its signaling is no longer required after hepatocyte proliferation has concluded. β-Catenin activity was immediate after acetaminophen injury and essential for liver regeneration. Eventually, we have demonstrated that activation of β-catenin provides regenerative advantage to the liver in transgenic mice & after transient Wnt-1 overexpression. More recently, we have identified tri-iodothyronine to be a notable stimulant of β-catenin activation to induce cyclin-D1 expression and eventually liver regeneration. The role of β-catenin signaling in liver regeneration is now well appreciated and many labs have now reproduced the work and also added to the mechanisms of β-catenin activation during the process.

a. Tan X, Behari J, Cieply B, Michalopoulos GK, **Monga SP.** Beta-catenin knockout reveals its role in liver growth and regeneration. Gastroenterology. 131: 1561-1572, 2006. PMID: 17101329
b. Apte UA, Singh S, Zeng G, Cieply B, Virji M, Wu T and **Monga SP.** β-Catenin activation promotes liver regeneration after acetaminophen-induced liver injury. Am J Pathol. 2009 Sep;175(3):1056-65. PMCID: PMC2731124
c. Fanti M, Singh S, Ledda-Columbano GM, Columbano M, **Monga SP.** Triiodothyronine induces hepatocyte proliferation by protein kinase A-dependent β-catenin activation in rodents. Hepatology. 2014 Jun;59(6):2309-20. PMCID: PMC3979513
d. Jing Yang, Laura E. Mowry, Kari Nichole Nejak-Bowen, Hirohisa Okabe, Cassandra R. Diegel, Richard A. Lang, Bart O. Williams, **Monga SP.** Beta-catenin signaling in murine liver zonation and regeneration: A Wnt-Wnt situation. Hepatology 2014 Feb 20. PMCID: PMC4139486

2. Work from my lab has also defined an important role of **β-catenin signaling during hepatic development**. Using embryonic livers from various stages of hepatic development, we were the first to demonstrate active β-catenin signaling in developing livers at the time of hepatoblast expansion. Using embryonic liver cultures, we showed its important role in hepatoblast proliferation, hepatocyte maturation and bile duct differentiation. Eventually we conditionally knocked out β-catenin in developing hepatoblasts using cre-lox, which led to embryonic lethality. This validated the role of β-catenin in liver development since lethality was associated failure of hepatoblast proliferation, bile duct differentiation and lack of hepatocyte maturation. Many other labs have now shown the role of β-catenin in hepatic development and have tried to identify the ligands necessary for β-catenin activation during hepato-biliary development including Wnt2b, Wnt9, Wnt5a, FGF and others. We have continued to work on hepatic development and have recently shown a calpain-mediated cleavage of β-catenin which may be switching its proliferative function to maturation function in hepatocytes.

a. Monga SP, Monga HK, Tan X, Mule K, Pediaditakis P, Michalopoulos GK. Beta-catenin antisense studies in embryonic liver cultures: role in proliferation, apoptosis, & lineage specification. Gastroenterology. 2003 Jan;124(1):202-16. PMID: 12512043.
b. Micsenyi A, Tan X, Sneddon T, Michalopoulos GK, Monga SP. β-Catenin is Temporally Regulated During Normal Liver Development. Gastroenterology 2004 Apr;126(4):1134-46. PMID: 15057752
c. Tan X, Yuan, Y, Zeng G, Apte U, Thompson M, Cieply B, Stolz D, Michalopoulos GK, Kaestner KH, Monga SP. β-Catenin deletion in hepatoblasts disrupts hepatic morphogenesis and survival during mouse development. Hepatology. 2008 May;47(5):1667-79. PMID: 18393386
d. Lade A, Ranganathan S, Luo J, Monga SP. Calpain Induces N-terminal Truncation of β-Catenin in Normal Murine Liver Development: Diagnostic implications in hepatoblastomas. J Biol Chem. 2012 Jun 29;287(27):22789-98. PMCID: PMC3391133

3. While β-catenin is a known major downstream effector of Wnt signaling pathway, it can interact with various

other proteins independent of Wnt signaling. One of the major contribution of my laboratory to the general Wnt field have been **identification of novel interactions of β-catenin and its roles especially their relevance in hepatic pathobiology**. One such interaction we have identified is with the HGF receptor Met. HGF leads to tyrosine phosphorylation of β-catenin at specific residues (Y654 & Y670). We also showed that part of HGF's mitogenic activity is β-catenin dependent both *in vitro* and *in* vivo. Many others have now identified key role of Y654-β-catenin in various pathologies including tumor biology. We also identified a novel complex of β-catenin with p65 subunit of NF-κB in hepatocytes. This complex suppressed p65 activity by restraining it in the cytoplasm. Inhibiting β-catenin to activate NF-κB may have implications in inflammation and injury. We have also demonstrated an important role of β-catenin in cholesterol and bile acid metabolism in hepatocytes.

a. Zeng G, Apte U, Micsenyi A, Bell A, Monga SP. Tyrosine residues 654 & 670 in β-catenin are crucial in regulation of Met-β-catenin interactions. Exp Cell Res. 2006 Aug 10. PMCID: PMC1820835
b. Apte U, Micsenyi A, Muller P, Zeng G, Kaestner K, Monga SP. Role of β-catenin in HGF-induced hepatomegaly in mice. Hepatology. 2006 Oct;44(4):992-1002. PMID: 17006939
c. Nejak-Bowen KN, Kikuchi A, Monga SP. β-Catenin-NF-κB interactions in murine hepatocytes: A complex to die for. Hepatology 2013 Feb;57(2):763-74. PMCID: PMC3566301
d. Behari J, Yeh TH, Krauland L, Otruba W, Cieply B, Hauth B, Apte U, Wu T, Evans R, Monga SP. Liver specific β-catenin knockout mice exhibit defective bile acid and cholesterol homeostasis and increased susceptibility to diet-induced steatohepatitis. Am J Pathol. 2010 Feb;176(2):744-53. PMCID: PMC2808081

4. Activation of β-catenin signaling due to mutations or other mechanisms, in various tumors such as hepatoblastomas (HB) and a subset of HCCs, is known for more than 15 years now. However, what has been unclear is the functional and phenotypic characterization of these tumors that harbor β-catenin gene mutations. We have **contributed to the field of HB and HCC biology** through detailed characterization of patient samples to investigate genotype-phenotype relationship from a β-catenin perspective. We have identified an inverse correlation of β-catenin mutations and cirrhosis such that HCCs with CTNNB1 mutations have lesser fibrosis as compared to non-mutated counterparts. In fact we used transgenic mice expressing ser45-mutated β-catenin in hepatocytes and showed no change in incidence of HCC in these mice after exposure to fibrosis-inducing agents such as thioactemide. We also have identified biomarkers that could identify CTNNB1 mutations, as β-catenin immunohistochemistry is not always reliable. To that end we have identified EGFR, glutamine synthetase, regucalcin and lect2. In fact, we identified serum lect2 to reproducibly diagnose β-catenin gene mutations in murine models of HCC, however this was not specific for HCC patients. We have also identified cooperation of β-catenin with other pathways to lead to tumorigenesis. In fact its association and synergism with Yes Associated protein (Yap) was shown to lead to development of HB.

a. Cieply B, Zeng G, Singh T-P, Geller DA, Monga SP. Unique phenotype of hepatocellular cancers with exon-3 mutations in beta-catenin gene. Hepatology 2009 Mar;49(3):821-31
b. Lee JM, Yang J, Newell PN, Singh S, Parwani A, Friedman SL, Nejak-Bowen KN, Monga SP. Beta-catenin signaling in hepatocellular cancer. Implications in inflammation, fibrosis and proliferation. Cancer Letters, 2014, Feb 1;343(1):90-7. PMCID: PMC3874258
c. Okabe H, Delgado E, Lee JM, Yang J, Kinoshita H, Hayashi H, Tsung A, Behari J, Beppu T, Baba H, Monga SP. Monga· Role of leukocyte cell-derived chemotaxin 2 as a biomarker in hepatocellular carcinoma. PLOS ONE 2014 Jun 3;9(6):e98817. PMCID: PMC4043833
d. Tao J, Calvisi DF, Ranganathan S, Cigliano A, Zhou L, Singh S, Jiang L, Fan B, Terracciano L, Armeanu-Ebinger S, Ribback, Dombrowski F, Evert M, Chen X, **Monga SP**. Wnt/β-catenin and Yap pathways synergize to promote hepatoblastoma development in mice and men. Gastroenterology, 2014 May 14. pii: S0016-5085(14)00610-6. PMCID: PMC4143445

5. One of the major contributions of our lab has been to demonstrate the **impact of therapeutic β-catenin inhibition for the treatment of HCC**. We have first demonstrated not all HCC cases will benefit from β-catenin suppression and in fact its inhibition may do more harm than good if β-catenin is suppressed in non-active tumors. However, a subset of HCC patients with β-catenin activation signature will be outstanding candidates for precision therapy. For this we have identified several novel inhibitors or repurposed drugs that could have potential clinical implications. More recently, we demonstrated in vivo that suppression of β-catenin in β-catenin-mutated HCCs results in complete response and hence patients in this group would greatly benefit. Lastly, we showed redundancy of β-catenin and γ-catenin only at hepatocyte membrane such that β-catenin

suppression is well tolerated at adherens junctions due to upregulation of γ-catenin.

a. Zhang X, Tan X, Zeng G, Misse A, Singh S, Kim Y, Klaunig J, Monga SP. Conditional β-catenin loss in mice promotes chemical hepatocarcinogenesis: role of oxidative stress and PDGFRα/PIK3CA signaling. Hepatology, 2010 Sep;52(3):954-65. PMCID: PMC3100799
b. Wickline E, Du Y, Stolz DB, Kahn M, Monga SP. γ-Catenin at adherens junctions: Mechanism and biological implications in hepatocellular cancer after β-catenin knockdown. Neoplasia. 2013 Apr;15(4):421-34. PMCID: PMC3612914
c. Delgado E, Yang J, So J, Leimgruber S, Kahn M, Ishitani T, Shin S, Mustata G, Monga SP. Identification and characterization of a novel small molecule inhibitor of beta-catenin signaling. Am J Pathol. 2014 Jul;184(7):2111-22. PMCID: PMC4076560
d. Delgado A, Okabe H, Preziosi M, Russell JO, Alvarado TF, Oertel M, Nejak-Bowen KN, Zhang Y, **Monga SP**. Complete response of Ctnnb1-mutated tumors to β-catenin suppression by locked nucleic antisense in mouse hepatocarcinogenesis model. J Hepatol. 2015 Feb;62(2):380-7. PMCID: PMC4300253

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40483915/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

R01CA204586 **Monga (MPI)** **04/01/2016-03/31/2021**
Grant Title: Role of Wnt/β-catenin In Liver Development/Regeneration
The main goal of this proposal is to examine the role of β-catenin and Yap interactions and biological implications in Hepatoblastoma

R01DK100287 **Monga (PI)** **07/01/13-06/30/17**
Targeting β-catenin in hepatic pathology: Novel interactions, novel paradigms.
The main goal of this proposal is to examine the role of β-catenin in liver cancer as a therapeutic target, utilizing novel in vivo and ex vivo studies and models

R01DK095498 **Monga (PI)** **01/04/13-03/31/18**
Role of Platelet derived growth factor receptor-α in Liver Pathobiology
The main goal of this proposal is to examine the role of PDGFRα in liver development, regeneration and hepatic fibrosis using in vivo and ex vivo models

R01DK62277 **Monga (PI)** **01/01/04-12/31/18**
Role of Wnt/β-catenin In Liver Development/Regeneration
The main goal of this proposal is to examine the role of β-catenin during liver development, liver regeneration using various transgenic and knockout models.

T32EB001026 **Monga (PI)** **07/01/03-08/31/19**
Cellular Approaches to Tissue Engineering and Regeneration (CATER)
The main purpose of this predoctoral training grant is to provide a solid foundation to Bioengineering and Interdisciplinary biomedical graduate students in the discipline of Regenerative Medicine through research, courses, professional development programs and networking.

Grant No. I# 0048249 **Monga (PI)** **03/6/15 – 03/6/17**
Therapeutic targeting of β-catenin for treatment of hepatic pathologies
The goal of this corporate research agreement with Dicerna Pharmaceuticals, Cambridge, MA, is to test the uptake and efficacy of lipid nanoparticle based β-catenin siRNA to suppress β-catenin expression in animal models of hepatic pathologies.

Grant No. I# 0050815 **Monga (PI)** **11/11/15-11/11/17**
Molecular Aberrations in Liver Fibrosis
The goal of this corporate research agreement with Abbvie Pharmaceuticals is to examine the role of Wnt signaling in hepatic fibrosis, using genetic knockout mice subjected to various protocols of liver injury and fibrosis. Specifically tested will be the animals that have restricted Wnt secretion from macrophages and stellate cells.

Grant No. St. Baldrick's Foundation **Monga (Co-PI)** **07/01/15-06/30/16**
Regulation of Hepatoblastoma Metabolism by Mitochondrial Sirtuins
This work could potentially identify novel targets for cancer therapies in hepatoblastoma and other human cancers.