BIOGRAPHICAL SKETCH

NAME **GEORGE, JOSEPH**	**POSITION TITLE** **Associate Professor,** Department of Hepatology, Kanazawa Medical University, Uchinada, Ishikawa 920-0293, Japan. **Email: georgej@kanazawa-med.ac.jp**
eRA COMMONS USER NAME **george1**	

EDUCATION / TRAINING

INSTITUTION AND LOCATION	DEGREE	MM/YY	FIELD OF STUDY
University of Kerala, INDIA	B.Sc.	06/1977 – 08/1980	Zoology/ Biochemistry
University of Calicut, INDIA	M.Sc.	10/1980 – 12/1982	Life Sciences/ Mol Biology
University of Madras, INDIA	Ph.D.	06/1989 – 02/1995	Biochemistry/Liver Fibrosis
Columbia University, NY, USA	Postdoctoral	09/2003 – 04/2005	Molecular Medicine
Medical University of SC, USA	Postdoctoral	08/2006 – 03/2008	Neurosciences
University of South Carolina, USA	Postdoctoral	04/2008 – 06/2009	Pathology/Immunology

A. Personal Statement

Dr. Joseph George is currently working as Associate Professor (tenured) in the Department of Hepatology, Kanazawa Medical University, Japan. Dr. George earned his doctorate (Ph.D.) in Biochemistry from the University of Madras, India. After his doctorate, he worked as a Senior Scientist in a biomedical company (Koken) in Tokyo. Dr. George did his postdoctoral research and training in the Department of Medicine, College of Physicians and Surgeons of Columbia University, New York and in the Department of Cancer Biology, University of Illinois at Chicago. Later he worked as Assistant Professor in the Division of Liver Diseases, Icahn School of Medicine at Mount Sinai, New York and as a Faculty Associate in the Department of Cancer Biology, Mayo Clinic, Jacksonville, Florida.

Dr. George's current research concentrates to elucidate the molecular mechanisms involved in the pathogenesis of hepatocellular carcinoma (HCC) and nanovesicles mediated targeted drug delivery. Different etiological factors such as ROS could induce oncogenes or produce mutations in tumor suppressor genes that trigger aberrant activation of various cellular and molecular pathways leading to carcinogenesis. Targeted drug delivery could be used for intracellular delivery of anticancer agents to tumor tissue or organ without affecting normal cells and may serve as an efficient modality for the successful treatment of malignant HCC.

Dr. George is a Fellow of the American Association for the Study of Liver Diseases (FAASLD), the highest honor among AASLD membership categories that recognizes superior professional achievement in clinical or academic practice and basic or clinical research. He serves as an Editorial Board member for several renowned journals and a peer reviewer (publons) for over 50 reputed scientific journals. Dr. George is a naturalized United States citizen through Green Card under the EB-1 category.

B. Positions and Honors

Positions and Employment

07/1983 – 03/1989 **Asst Research Officer**, Central Leprosy Teaching & Research Institute, Chengalpattu, India
03/1995 – 12/1998 **Research Associate**, Dept Biochemistry, Central Leather Research Institute, Madras, India
09/2000 – 08/2003 **Senior Scientist**, Tissue Engineering, Koken Bioscience Institute, Ukima, Tokyo, Japan
04/2005 – 09/2006 **Research Specialist**, Dept of Cancer Biology (Peoria), University of Illinois at Chicago, USA
07/2009 – 09/2010 **Assistant Professor**, Dept of Medicine, Mount Sinai School of Medicine, New York, USA
06/2014 – 03/2016 **Faculty Associate**, Dept of Cancer Biology, Mayo Clinic, Jacksonville, Florida, USA
10/2010 – Till date **Associate Professor**, Dept of Hepatology, Kanazawa Medical University, Uchinada, Japan

Other Experience and Professional Memberships

Honors and Awards

1980–1982 Merit Scholarship for Master's in Life Sciences, University of Calicut, Kerala, INDIA
1982– Second Rank for Master's in Life Sciences, University of Calicut, Kerala, INDIA
1989–1992 Award of Senior Research Fellowship, Council of Scientific & Industrial Research, INDIA
1993–1995 Award of Senior Research Fellowship, Indian Council of Medical Research, New Delhi, INDIA
1995–1998 Award of Research Associate, Council of Scientific & Industrial Research, New Delhi, INDIA
1999–2000 Award of Postdoctoral Fellowship, Kanazawa Medical University, Uchinada, Ishikawa, JAPAN
2003–2005 Award of Postdoctoral Fellowship, Dept of Medicine, Columbia University, New York, USA

Professional Trainings

1987 – Radioimmunoassay, Radiopharmaceuticals Division, Bhabha Atomic Research Center, Bombay, INDIA
1987 – Radiolabelling and Radio-iodination Techniques, Bhabha Atomic Research Center, Bombay, INDIA
1988 – 1989 Diploma in Systems Analysis and Data Processing, Annamalai University, Tamil Nadu, INDIA
2001 – Advances in Tissue Engineering, Center for Excellence in Tissue Engineering, Rice University, Texas

Professional Membership

1990 – Life Member, Indian Association of Biomedical Scientists (IABMS), Chennai, INDIA
2005 – Active Member, American Association for Cancer Research (AACR), (Membership #125380)
2006 – Regular Member, American Association for the Study of Liver Diseases (AASLD), (#111392)
2019 – Regular Member, Asia-Pacific Association for the Study of Liver (APASL), (Member #MN-2082)
2020 – Fellow of the American Association for the Study of Liver Diseases (FAASLD), (Member #111392)

Professional Activities

2003 – Peer Reviewer, Over 50 world renowned International Scientific Journals with high Impact Factor.
2013 – Editorial Board Member, Medicine *(Wolters Kluwer/ LWW)* (*JCR Impact Factor 2013* → 4.867)
2013 – Academic Editor, PLOS ONE *(Public Library of Science)* (*JCR Impact Factor 2013* → 3.534)
2013 – Supervisor for Doctoral Program (Ph.D.), Dept of Hepatology, *Kanazawa Medical University*, Japan
2014 – External Examiner for adjudication of the Ph.D. Thesis, *University of Madras,* INDIA (No. Ph.D./Eval/487/2013/4045) and No. Ph.D.Eval./422/2016/286.
2018 – Editorial Board Member, Scientific Reports, *Nature Publishing Group (NPG)* (*IF 2018* → 4.011)
2018 – Committee Member, Academic Promotions, *King Abdulaziz University*, Jeddah, Saudi Arabia

C. Contributions to Science

A. ***Molecular mechanisms involved in the pathogenesis of hepatic fibrosis and liver cirrhosis***

Dr. George has made significant contributions to unravel the molecular mechanisms involved in the pathogenesis of hepatic fibrosis and liver cirrhosis with special emphasize on the role of oxidative stress. Hepatic fibrosis is the result of a perpetual wound healing response to a chronic stimuli (eg: ethanol) that leads to elevated levels of intracellular reactive oxygen species (ROS) and oxidative stress. These processes lead to cellular injury and trigger inflammatory responses releasing a variety of cytokines and growth factors. These events initiate activation and transformation of resting hepatic stellate cells into myfibroblast like cells and start excessive synthesis of connective tissue proteins, especially interstitial collagens. Regulation of the several steps involved in the activation and transformation of hepatic stellate cells offers a potential therapeutic target for the arrest of hepatic fibrosis and liver cirrhosis. *(Journal of Molecular Medicine 2020; 98: 1203-1213.* PDF*, Scientific Reports 2019; 9: 708* PDF*, Cell Death & Disease 2019; 10: 18* PDF*, Biological Chemistry 2018; 399: 499-509* PDF*, Journal of Cellular and Molecular Medicine 2017; 21: 3821-3835* PDF*, Gene Therapy 2007; 14: 790-803* PDF*).*

B. ***Mechanisms of the pathogenesis of hepatocellular carcinoma and targeted drug delivery***

Among several etiological factors, ethanol play a significant role in the pathogenesis of gastrointestinal and liver cancer. The hepatic metabolism of ethanol upregulates cytochrome P4502E1 and produce ROS leading to oxidative stress. Free radicals could induce oncogenes or produce mutations in tumor suppressor genes that trigger aberrant activation of various cellular and molecular pathways leading to carcinogenesis. The perpetual and impaired wound healing response during chronic ethanol intake could lead to liver cirrhosis and hepatocellular carcinoma (HCC). Specific and effective treatment of HCC is very challenging due to genetic and phenotypic variants. We have successfully developed nanovesicles mediated targeted delivery of anticancer agents to HCC cells in culture and also to experimentally induced intrahepatic tumors in athymic nude mice. The technique of intracellular delivery of anticancer agents to tumor tissue could serve as an efficient modality for the successful treatment of malignant HCC. *(Digestive Diseases and Sciences 2013; 58: 1923-1933* PDF*, Journal of Cancer 2014; 5: 221-230* PDF*, Seminars in Liver Disease 2015; 35: 63-74* PDF, *Laboratory Investigation 2018; 98: 895-910* PDF*).*

C. *Reduction of hepatic ischemic and reperfusion injury during surgical procedures*

Cellular and tissue injury during ischemia and reperfusion is a major clinical problem during surgical procedures. Blood supply should be partially blocked during surgery which results in ischemia leading to cell and tissue injury. As an "insult to injury", the restoration of blood supply or reperfusion of ischemic tissue cause increased injury due to enhanced production of free radicals. Therefore, it is important to prevent generation of ROS and associated oxidative stress during reperfusion. We have demonstrated that treatment with GGsTop, a specific and potent inhibitor of γ-glutamyltransferase could reduce hepatic ischemia-reperfusion (IR) injury not only in healthy liver but also in livers with steatosis during obesity. Furthermore, it was shown that treatment with recombinant thrombomodulin, a novel anticoagulant and anti-inflammatory agent that inhibits secretion of high-mobility group box 1 (HMGB1), can prevent IR-induced hepatic injury and associated events by reduction of tumor necrosis factor-α and other inflammatory cytokines. *(Am J Physiol Gastrointest Liver Physiol 2016; 311: G305-G312* PDF; *British Journal of Pharmacology 2020; 177: 5195-5207* PDF*; European Journal of Pharmacology 2019; 863: 172681* PDF*)*

E. *Tissue engineering and regenerative medicine involving stem cells*

Tissue engineering and regenerative medicine is the method of replacing damaged or impaired cells or tissues with engineered or regenerated cells or organs to restore normal function. The engineered tissue or cells will be either functional at the time of implantation or has the potential to integrate and form the expected functional tissue or organ at a later stage. Three dimensional (3D) cell cultures on biodegradable scaffolds are widely employed for tissue engineering, where the specific cells can grow and multiply into a structure similar to tissues or organs in the living body. We have demonstrated that the honeycomb collagen sheet made from bovine atelocollagen is a biodegradable scaffold suitable for dermal tissue engineering. Furthermore, we have sown that the biodegradable honeycomb collagen sponge is an excellent scaffold for the differentiation and proliferation of bone marrow derived mesenchymal stem cells into osteoblasts. *(Journal of Biomedical Materials Research 2008; 87A: 1103-1111* PDF*, Biotechnology and Bioengineering 2006; 95: 404-411* PDF*, Cosmo Bio,* PDF*).*

F. *Mechanism of the drug interactions during multidrug regimens in Hansen's disease*

Drug-drug interaction is a serious and potent problem in clinical practice. Treatment for leprosy or Hansen's disease with multidrug regimens is very effective compared to monotherapy. The three major antileprosy drugs currently in use are dapsone, rifampicin, and clofazimine. We have noticed that during multidrug therapy, the potent antibiotic rifampicin induces the metabolism of dapsone, which results in decreased plasma half-life of dapsone and its metabolites. Furthermore, rifampicin induces its own metabolism and decreases its half-life during monotherapy. This happens because rifampicin markedly upregulates several cytochrome P450 (CYP) family of drug-metabolizing enzymes, especially CYP3A4. Even though dapsone does not induce any drug metabolizing enzyme, dapsone is metabolized in the liver mainly by CYP3A4 and the upregulated enzyme accelerates dapsone metabolism and reduces its plasma half-life during combination therapy. We have further observed that administration of dapsone in the acetylated form (acedapsone) could release the drug slowly into circulation up to 75 days and is more effective to use with rifampicin. *(Indian Journal of Medical Research 1988, 87:151–156* PDF*, Biochemical Pharmacology 2020; 177: 113993* PDF, *Indian Journal of Leprosy 1986, 58:401–406* PDF*).*

Selected Peer-reviewed Publications *(selected from more than 100 papers)*

1. Tsutsumi M*, **George J**, ... Takase S (2006) Effect of chronic dietary ethanol consumption on the promotion of chemically induced esophageal carcinogenesis in rats. ***Journal of Gastroenterology and Hepatology*** 21(5), 805–813. (PMID: 16704527) [PDF] DOI: 10.1111/j.1440-1746.2005.04040.x
2. **George J***, Kuboki Y, Miyata T (2006) Differentiation of mesenchymal stem cells into osteoblasts on honeycomb collagen scaffold. ***Biotechnology and Bioengineering*** 95(3), 404–411. (PMID: 16572435) [PDF] DOI: 10.1002/bit.20939
3. **George J*** (2006) Mineral metabolism in dimethylnitrosamine-induced hepatic fibrosis. ***Clinical Biochemistry*** 39(10), 984–991. (PMID: 16959231) [PDF] DOI: 10.1016/j.clinbiochem.2006.07.002
4. **George J**, Tsutsumi M* (2007) siRNA mediated downregulation of connective tissue growth factor prevents N-Nitrosodimethylamine induced hepatic fibrosis in rats. ***Gene Therapy*** 14(10), 790–803. (PMID: 17344905) [PDF] DOI: 10.1038/sj.gt.3302929
5. **George J**, Gondi CS, ... Rao JS* (2007) Restoration TFPI-2 in a human glioblastoma cell line triggers caspase mediated pathway and apoptosis. ***Clinical Cancer Research*** 13(12), 3507–3517. (PMID: 17575213) [PDF] DOI: 10.1158/1078-0432.CCR-06-3023
6. **George J*** (2008) Elevated serum beta-glucuronidase reflects hepatic lysosomal fragility following toxic liver injury in rats. ***Biochemistry Cell Biology*** 86(3), 235–243. (PMID: 18523484) [PDF] DOI: 10.1139/o08-038
7. **George J***, Onodera J, Miyata M (2008) Biodegradable honeycomb collagen scaffold for dermal tissue engineering. ***Journal of Biomedical Materials Research Part A*** 87(4), 1103–1111. (PMID: 18792951) [PDF] DOI: 10.1002/jbm.a.32277
8. **George J**, Banik NL, Ray SK (2009) Combination of taxol and Bcl-2 siRNA induces apoptosis in human glioblastoma cells and inhibits invasion, angiogenesis, and tumor growth. ***Journal of Cellular and Molecular Medicine*** 13(10), 4205–4218. (PMID: 19473291) [PDF] DOI: 10.1111/j.1582-4934.2008.00539.x
9. **George J**, Banik NL, Ray SK* (2009) Combination of hTERT knockdown and IFN-gamma treatment inhibited angiogenesis and tumor progression in glioblastoma. ***Clinical Cancer Research*** 15(23), 7186–7195. (PMID: 19934306) [PDF] DOI: 10.1158/1078-0432.CCR-09-1425
10. **George J**, Banik NL, Ray SK* (2010) Survivin knockdown and concurrent 4-HPR treatment attenuated human glioblastoma in vitro and in vivo. ***Neuro-Oncology*** 12(11), 1088–1101. (PMID: 20679253) [PDF] DOI: 10.1093/neuonc/noq079
11. Mormone E, **George J**, Nieto N* (2011) Molecular pathogenesis of hepatic fibrosis and current therapeutic approaches. ***Chemico-Biological Interactions*** 193(3), 225–231. (PMID: 21803030) [PDF] DOI: 10.1016/j.cbi.2011.07.001
12. **George J*,** D'Armiento J (2011) Transgenic expression of human MMP-9 augments monocrotaline induced pulmonary arterial hypertension in mice**.** ***Journal of Hypertension*** 29(2), 299–308. (PMID: 21063214) [PDF] DOI: 10.1097/HJH.0b013e328340a0e4
13. Urtasun R, Lopategi A, **George** J, ... Nieto N* (2012) Osteopontin, an oxidant stress-sensitive cytokine,up-regulates collagen-I via integrin α(V) β(3) engagement and PI3K-pAkt-NFκB signaling. ***Hepatology*** 55(2), 594–608. (PMID: 21953216) [PDF] DOI: 10.1002/hep.24701
14. Hayashi N, **George J**,*... Tsutsumi M (2013) Irsogladine maleate for the Treatment of Recurrent Aphthous Stomatitis in HCV Patients on PEG-Interferon and Ribavirin: A Pilot Study. ***Journal of Gastroenterology and Hepatology*** 28(6), 1015–1018. (PMID: 23425065) [PDF] DOI: 10.1111/jgh.12137
15. Tsuchisima M, **George J***, ... Tsutsumi M (2013) Chronic ingestion of ethanol induces hepatocellular carcinoma in mice without additional hepatic insult. ***Digestive Diseases and Sciences*** 58(7), 1923–1933. (PMID: 23371017) [PDF] DOI: 10.1007/s10620-013-2574-4
16. Hayashi N, **George J***, Takeuchi M, ... Tsutsumi M (2013) Acetaldehyde-derived advanced glycation end-products promote alcoholic liver disease. ***PLoS ONE*** 8(7), e70034. (PMID: 23922897) [PDF] DOI: 10.1371/journal.pone.0070034
17. Minato T, Tsutsumi M, ... **George J*** (2014) Binge alcohol consumption aggravates oxidative stress and promotes pathogenesis of NASH from obesity induced simple steatosis. ***Molecular Medicine*** 20(2), 490**–**502. (PMID: 25180626) [PDF] DOI: 10.2119/molmed.2014.00048
18. George J**,** Patel T* (2015) Noncoding RNA as therapeutic targets for hepatocellular carcinoma. ***Seminars in Liver Disease*** 35(1), 62–73. (PMID**:** 25632936**)** [PDF] DOI: 10.1055/s-0034-1397350

19. Matsue Y, Tsutsumi M, Hayashi N, ... **George J*** (2015) Serum osteopontin predicts degree of hepatic fibrosis and serves as a biomarker in patients with hepatitis C virus infection. ***PLoS ONE*** 10(3), e0118744. (PMID: 25760884) [PDF] DOI: 10.1371/journal.pone.0118744
20. Toshikuni N*, Ozaki K, **George J**, Tsutsumi M (2015) Serum endocan as a survival predictor for patients with liver cirrhosis. ***Canadian Journal of Gastroenterology and Hepatology*** 29(8), 427–430. (PMID: 26669300) [PDF] DOI: 10.1155/2015/153805
21. Tamura K, Hayashi N, **George J,** ... Tsutsumi M* (2016) GGsTop, a novel and specific γ-glutamyl transpeptidase inhibitor, protects hepatic ischemia-reperfusion injury in rats. ***American Journal of Physiology - Gastrointestinal and Liver Physiology*** 311(2), G305–G312. (PMID: 27365338) [PDF] DOI: 10.1152/ajpgi.00439.2015
22. **George J,** Tsutsumi M, Tsuchishima M* (2017) MMP-13 deletion decreases profibrogenic molecules and attenuates *N*-Nitrosodimethylamine induced liver injury and fibrosis in mice. ***Journal of Cellular and Molecular Medicine*** 21(12), 3821–3835. (PMID: 28782260) [PDF] DOI: 10.1111/jcmm.13304
23. **George J**, Yan IK, Patel T* (2018) Nanovesicle-mediated delivery of anticancer agents effectively induced cell death and regressed intrahepatic tumors in athymic mice. ***Laboratory Investigation*** 98(7), 895–910. (PMID: 29748614) [PDF] DOI: 10.1038/s41374-018-0053-4
24. **George J*** (2018) Determination of selenium during pathogenesis of hepatic fibrosis employing hydride generation and inductively coupled plasma mass spectrometry. ***Biological Chemistry*** 399(5): 499–509. (PMID: 29408794) [PDF] DOI: 10.1515/hsz-2017-0260
25. **George J***, Tsuchishima M, Tsutsumi M (2019) Molecular mechanisms in the pathogenesis of N-nitrosodimethylamine induced hepatic fibrosis. ***Cell Death and Disease*** 10(1), 18 (PMID: 30622238 [PDF] DOI: 10.1038/s41419-018-1272-8
26. **George J***, Tsutsumi M, Tsuchishima M (2019) Alteration of trace elements during pathogenesis of N-nitrosodimethylamine induced hepatic fibrosis. ***Scientific Reports*** 9(1), 708 (PMID: 30679730 [PDF] DOI: 10.1038/s41598-018-37516-4
27. Hirakawa Y, ... **George J***, Ueda Y, Tsutsumi M (2019) Recombinant thrombomodulin prevented hepatic ischemia-reperfusion injury by inhibiting high-mobility group box 1. ***European Journal of Pharmacology*** 863, 172681 (PMID: 31542482) [PDF] DOI: 10.1016/j.ejphar.2019.172681
28. **George J*** (2020) Metabolism and interactions of antileprosy drugs. ***Biochemical Pharmacology*** 177, 113993 (PMID: 32339493) [PDF] DOI: 10.1016/j.bcp.2020.113993
29. **George J***, Tsuchishima M, Tsutsumi, M (2020) Metabolism of *N*-Nitrosodimethylamine, methylation of macromolecules, and development of hepatic fibrosis. ***Journal of Molecular Medicine*** 177(22), 5195–5207 (PMID: 32666246) [PDF] DOI: 10.1007/s00109-020-01950-7.
30. Kubota R, Hayashi, N, ... **George J*** (2020) Inhibition of γ-GGsTop ameliorates ischemia–reoxygenation tissue damage in rats with hepatic steatosis. ***British Journal of Pharmacology*** 177(22), 5195–5207 (PMID: 32910829) [PDF] DOI: 10.1111/bph.15258

D. Research Support

Ongoing Research Support

1. **Joseph George** (Role: PI) Title: *Investigation on differential expression, diagnostic implication, and therapeutic application of microRNAs in hepatocellular carcinoma* Period: Mar 2020 – Mar 2022 (*Funding agent:* Japan Society for the Promotion of Science, Tokyo, JAPAN) (Funder ID: 10.13039/501100001691)

Completed Research Support

1. **Joseph George** (Role: PI) Title: *Structural and functional alterations of liver during fibrosis.* Grant No. 3/1/2/3/92-NCD-III (9201540) Period: Apr 1993 – Mar 1996 (*Funding agent:* Indian Council of Medical Research, New Delhi, INDIA) (Funder ID: 10.13039/501100001411)
2. **Joseph George** (Role: PI) Title: *Effect of rifampicin and 4, 4'-diaminodiphenyl sulfone (DDS) on mammalian liver microsomal enzymes.* Grant No. 5/3-5(1)/85-BMS-II (8500050) Period: Jan 1986 – Mar 1989 (Indian Council of Medical Research, New Delhi) (Funder ID: 10.13039/501100001411)