Resume

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Senior Research Associate
Department of Internal Medicine, E. Doisy Research Center,
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Career Objectives

My research activities for more than 16 years have focused primarily on human health and pathogen. Excelling as a promising researcher as the opportunities unfold, I hope to establish as a successful researcher. I am looking for a suitable scientific position to establish my career to enlightening and enriching my scientific knowledge.

Contact Information

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Education

Ph.D.	Jadavpur University (Molecular Microbiology)	2012
M.Sc.	University of Kalyani (Microbiology)	2004
B.Sc.	University of Calcutta (Physiology)	2002

Title of the Ph.D thesis: Studies on pathogenic *Vibrio cholerae*: clonal segregation and regulation of virulence gene expression in relation to carbon utilization pathways.

Awards/Honors

SLU Young Investigator Award, 2020
American Society of Virology Travel Award, 2019
Post-doctoral Fellowship from Saint Louis University, 2018
ICMR Research Associateship, 2016
Post-doctoral Fellowship of IISER Mohali, 2014
ICMR Centenary Post-doctoral Fellowship, 2012

ICMR Senior Research Fellowship, 2010

Adhoc-Reviewer for Scientific Journals

Cellular & Molecular Life Sciences, Biochem J, Scientific Reports, Clinical Science, Cancer Management & Research, FEMS Microbiology Letters, Research in Microbiology, Cell Biology, The International Journal of Biochemistry & Cell Biology, Clinics and Research in Hepatology and Gastroenterology, Intervirology.

Contribution to Science

1. **SARS-CoV-2 associated pathogenic mechanism:** Pandemic situation with SARS-CoV-2 infection has led to nearly 3.5 million deaths. A clear mechanistic insight on SARS-CoV-2 associated pathogenesis is currently under rigorous investigation. We observed SARS-CoV-2 infection or viral spike protein expression in human epithelial cells inhibits ACE2 expression leading to the induction of AT1 signaling, and promotion of IL-6/soluble IL-6R release. This IL-6/soluble IL-6R promotes IL-6 trans-signaling in endothelial or immune cells to initiate coordination of a hyper-inflammatory response. We also identified that the exposure of human endothelial cells to the cell culture supernatant derived from SARS-CoV-2 spike protein expression display paracrine senescence in endothelial cells leading to enhanced leukocyte adhesion. Presently, I am aiming to elucidate detail mechanistic steps in SARS-CoV-2 associated immunothrombosis for novel therapeutic strategy.

2. **Chronic hepatitis C virus infection and hepatocellular carcinoma:** Hepatitis C virus (HCV) often causes persistent infection and is an increasingly important factor in the etiology of hepatocellular carcinoma (HCC). There is no preventive or therapeutic hepatitis C vaccine available. Direct antiviral agents have significantly improved outcome of HCV infection, although it does not prevent diseases progression and reinfection. The mechanisms by which HCV promotes HCC are poorly understood. From my work, we found a significant difference in TGF-β-induced activity for the HCV genotype 2a- or 3a-induced lipogenic pathway, exhibiting higher tri-glyceride synthesis and a decreased lipolytic mechanism. My results also suggested that HCV infection suppresses microRNA-181c in hepatocytes, resulting in ATM activation and apoptosis inhibition for promotion of hepatocyte growth. We established an HCV-associated HCC-PDX model as a powerful tool for evaluating anti-tumor candidate drugs. We observed combination treatment with selected signaling molecule-inhibitors exhibit efficient therapeutic potential for HCC. Further, we demonstrated an inhibition of Lin28 axis increases efficacy of Glycipan-3-CAR T cell therapy in hepatic tumor initiating stem cell population by reducing IDO1 expression. Currently, I am focusing to delineate the molecular mechanisms of HCV associated neoplastic transformation and cancer stem cell

generation to improve immune-therapeutic strategies. A different study on HCV vaccine development approach is also in progress.

3. **Microbial metabolites in colorectal cancer:** Colorectal cancer (CRC) is the second foremost cause of cancer mortality in the United States. In the Indian scenario, rapid surge of CRC incidences among the younger people were also reported by us. As the major exposure to microorganisms occurring in the gut particularly in large intestine, the involvement of the intestinal bacteria in CRC is a dynamic area for research. We have shown that bacterial metabolism can generate compounds such as glyoxylate or acyl-homoserine lactone (quorum sensing molecule) that inhibit the proliferation of human colon cancer cells. Our detailed analysis demonstrated that isolated and characterized nonpathogenic biofilm forming *Klebsiella pneumoniae* derived quorum sensing signal molecules AHLs trigger anti-inflammatory and inhibitory responses *in vitro* as well as *in vivo* on colon cancer growth by modulating the expression of NK-κβ molecule. Further, our study successfully depicted that supra-physiological concentration of glyoxylate reformed the intermediate metabolism to accumulate glycine concentration in colon cancer cells. This glycine accumulation modulates the molecular signaling mechanism and ultimately suppressed the viability of colon cancer cells accompanied with oxidative stress. Our observations should aid in developing strategies for effective therapies against CRC.

4. **Long chain fatty acid utilization of *Escherichia coli*:** As a predominant organism of human gut flora *E. coli* can utilize a wide variety of fermentable and non-fermentable carbon sources for heterotrophic growth. Long chain fatty acid (LCFA) is an important non-fermentable carbon source that serves as a rich energy resource for bacteria. However, the relevance of electron transport chain (ETC) in LCFA metabolism has not been examined. We performed a high-throughput genetic screen on oleate, a LCFA, using the Keio deletion library of *E. coli* and compared our results with published genome-wide screens of additional carbon sources. We found that the dependence of non-fermentable carbon sources on ETC components largely correlates with ATP yield. In particular, Nuo, which couples NADH oxidation to proton translocation, is the major NADH dehydrogenase for aerobic metabolism of non-fermentable carbon sources. Furthermore, our detailed analysis demonstrated that besides its electron carrier function in ETC, ubiquinone is required to mitigate elevated levels of reactive oxygen species generated by LCFA degradation. We found that ubiquinone is the key antioxidant in LCFA metabolism amongst known oxidative stress players in *E. coli*. Importantly, we showed that an uncharacterized gene, *yqiC*, which displayed growth defect only in LCFA, is also involved in ubiquinone biosynthesis. This study should help us to use LCFA with a new strategy for biofuel production.

5. **Carbohydrate metabolism of *Vibrio cholerae*:** The metabolic pathways play a critical role in pathogenesis of several micro-organisms. However, there

is lack of knowledge regarding the carbohydrate metabolism in *V. cholerae*. We were first to suggest that the Entner Doudoroff pathway is functional in *V. cholerae* and the utilization of gluconate, one of the important carbohydrate available in human intestine, is mediated only through this pathway. We have shown GntR protein acts as a negative regulator of this pathway and GntP is the only transporter present in gluconate utilization system of *V. cholerae*. Most importantly, we established that Entner Doudoroff pathway has relevance in *V. cholerae* pathogenesis. In addition, existence of Ashwell pathway is absent in *V. cholerae*. On the other hand, we were successful to reveal the functional existence of glyoxylate cycle in *V. cholerae* and show the metabolic pathway has a critical role in physiological transition state of the *V. cholerae* life cycle. Our study also showed that phosphoenol-pyruvate acts as a non-competitive inhibitor of isocitrate lyase, the most important enzyme of the glyoxylate cycle and the external addition of phosphoenol-pyruvate significantly decreases the level of *V. cholerae* pathogenesis. Finally, we were successful to use phosphoenol-pyruvate in oral rehydration solution to improve its remedy from cholera.

6. **Molecular epidemiology of *Vibrio cholerae*:** The etiological agent of the seventh cholera pandemic is *V. cholerae* O1 biotype El Tor, which has replaced classical biotype strains over a period. The strains with hybrid biotype traits have been currently circulated all over the world. We detected El Tor variant *V. cholerae* strains from India for first time and proposed a hypothetical model on the existence of multiple alleles of CTX phage and their eventual infections to the variety of *V. cholerae* strains. This ultimately led to the generation of circulating hybrid biotype traits or El Tor variants. My work established identification of different intermediate strains fitting to the proposed model of stepwise generation of El Tor variants as a molecular testimony of genetic rearrangements that occurred in a time frame when *V. cholerae* O139 evolved and such trail of events profoundly influenced overall cholera epidemiology.

Research Experience

Postdoctoral Research Associate	:	Currently working as Senior Research Associate on hepatitis C virus infection and progression of liver diseases in Department of Internal Medicine, Saint Louis University, USA
Research Associate	:	Worked as Research Associate from Indian Council of Medical Research to study the role of microbial metabolites in the pathogenesis of colorectal cancer at Chittaranjan National Cancer Institute, Kolkata from April 2016 to March 2018.
Postdoctoral Research Fellow	:	Worked as Post-doctoral Research Associate to study different metabolic responses on bacterial physiology special reference to system biology at IISER, Mohali from April 2014 to April 2015.

Postdoctoral Research Fellow	:	Worked as ICMR post-doctoral research fellow on the project entitled "Studies on the physiological significance of glyoxylate cycle in pathogenic *Vibrio cholerae*" at NICED, Kolkata from May 2012 to April 2014.
Senior Research Fellow	:	Worked in ICMR senior research fellow on the project entitled "Carbohydrate utilization pathways of *Vibrio cholerae* and their relevance in regulation of expression of genes including virulence determinants" at NICED, Kolkata from February 2010 to January 2012.
Senior Research Fellow	:	Worked in DBT sponsored project entitled "Comparative Analysis of *luxO*, the Quorum sensing master regulator among O1, O139, NonO1, nonO139 *V. cholerae* strains" at NICED, Kolkata from July 2008 to January 2010.
Research Assistant	:	Worked in the Pulse net project entitled "Phenotypic and genotypic characterization of common enteric pathogens isolated from diarrheal patients" at NICED, Kolkata from May 2006 to May 2008.
Guest Researcher	:	Worked in a field of Bioinformatics based research on Gluconate metabolism of *V. cholerae* at Bose Institute, Kolkata; period of research April 2005 to June 2006.
Research Trainee	:	Industrial training on Research & Development and Quality control Dept. of East India Pharmaceutical Ltd., Kolkata. (As a part of M.Sc. curriculum). Worked on solid state fermentation on *Asperzillus*; period of training May 9th, 2004 to August 5th, 2004.
Research Trainee	:	Laboratory training on Medical Microbiology and Molecular biology in the Dept. of Microbiology at Bose Institute, Kolkata (As a part of M.Sc. curriculum). Work entitled "Study the *in vitro* and *in vivo* expression of an outer membrane protein of gram-negative bacteria with pathogenic potential." Period of training March 5th to July 31^{st,} 2003.

Teaching Experience

Worked for six months as guest lecturer in Microbiology for post-graduate student at West Bengal State University, Kolkata.

In IISER Mohali, conducted theoretical and practical classes on regular basis in Biological Sciences for BS and MS students for more than one year.

Frequently Used Methodology

Microbiological or cellular techniques: Isolation and identification of *V. cholerae, V. parahaemolyticus,* different types of *E. coli* from diarrhoeal specimen and strains preservation.; serological characterization of strains by slide agglutination; preparation of culture media and aseptic maintenance of bacterial cultures; to perform biochemical tests for species identification and antibiotic susceptibility assay by disc diffusion method, bacterial growth curve; minimum inhibitory concentration of different substances in bacterial growth; phage induction; dilution spotting; phage transduction; Viral culture (Hepatitis C Virus, SARS-CoV-2, Vaccinia Virus) and maintenance; Viral plaque assay; recombinant Vaccinia virus development; high throughput screening; different animal cell line culture and maintenance; human carcinoma cell line handling and maintenance; T lymphocyte and NK cell culture maintenance; CAR-T cell generation and expansion; tumor biopsy sample handling; cancer stem cell isolation and maintenance; PBMC isolation; Platelet isolation; Platelet activation assay; macrophage isolation and maintenance; dendritic cell and T cell interaction; colony forming assay; fluorescence microscopy; bright-field microscopy; phase contrast microscopy; etc.

Molecular biological techniques: Isolation of genomic DNA, plasmid DNA, total RNA; polymerase chain reaction (PCR); reverse transcriptase PCR (RT-PCR); real time PCR; nested PCR; RAPD, box PCR; Overlap extension PCR; restriction digestion; southern hybridization analysis; western blotting; ribotyping; nucleotide sequencing; plasmid modification; vector construction; differential cloning; insertion mutation; in frame deletion mutation; site directed mutagenesis; vector modification; bacterial gene silencing; protein over-expression & purification; immune-precipitation; micro-array; complementation of mutation; outer membrane vesicle isolation; transfection; siRNA transfection; miRNA array; etc.

Analytical methods: Agarose gel electrophoresis; SDS polyacrylamide gel electrophoresis; pulse field gel electrophoresis; density gradient gel electrophoresis; gel retardation assay; flow cytometric analysis; Ni-column based protein purification; estimation of protein, nucleic acid; hemolysin assay; different enzymatic assay; enzyme kinetics study; ELISA; biofilm assay; motility assay; cholera toxin assay; cAMP assay; $NAD/NADH_2$ assay; $NADP/NADPH_2$ assay; ATP/ADP assay; promoter fusion assay; fluorescence spectroscopy; lipid peroxidation measurement; quantification of ROS element; high performance liquid chromatography; affinity chromatography; hexosaminidase assay; MTT assay; Luciferase assay; T cell or NK cell mediated tumor killing assay; Immunofluorescence microscopy; Confocal microscopy; immunohistochemistry; complement activation assay, cytokine array; phagocytosis assay; etc.

Animal model: Suckling mice and adult mice colonization assay; RITARD model; rabbit ileal loop fluid accumulation assay; administration of oncogenic substances on mice; xenograft mouse model; PDX model; IVIS; AOM/DSS mouse model for colon cancer; polyp count and histological examination.

Bioinformatics: Alignment of different sequences; making phylogenetic tree; primer design; prediction of secondary structure of protein; detection of helix-turn-helix motif; prediction of protein localization site; analyzing data to demonstrate hydrophobicity graph, immunogenicity graph of a protein; prediction of binding site of regulator; system database analysis; different statistical analysis; etc.

Publications

1. Vijayamahantesh*****, **T. Patra*,** K. Meyer*****, M.A. Gabriel, D. Wissman, and R. Ray. Disruption of Hepatitis C Virus E2 glycoprotein and CD81 interaction elicits protective immune response. ***J. Virology.*** (2022) accepted. *****Co-first authors.

2. Mitra S., **T. Patra**, D. Saha, P. Ghosh, S.M. Mustafi, A.C. Varghese, and N. Murmu. Sub-chronic Cadmium and Lead compound exposure induces reproductive toxicity and development of testicular germ cell neoplasia *in situ* in murine model: Attenuative effects of Resveratrol. ***J. Biochemistry & Molecular Toxicology.*** (2022). p. e23058.

3. **Patra T#,** K. Meyer, R.B. Ray, T. Kanda, and R. Ray. Akt inhibitor augments anti-proliferative efficacy of a dual mTORC1/2 inhibitor by FOXO3a activation in p53 mutated hepatocarcinoma cells. ***Cell Death & Diseases.*** (2021). Vol.12, p. 1073. #Co-corresponding author.

4. Meyer K*****., **T. Patra*,** Vijayamahantesh and R. Ray. SARS-CoV-2 spike protein induces paracrine senescence and leukocyte adhesion in endothelial cells. ***J. Virology.*** (2021) Vol.95, no.17, p. e00794-21 *****Co-first authors.

5. **Patra T#.** and R. Ray. IL-6 Induction and Signaling: Horizons of COVID-19-related pathogenesis. ***DNA & Cell Biology.*** (2021) Vol.40, no.5, p. 639-642. #Coresponding author.

6. **Patra T#.,** S.K. Bose, Y.C. Kwon, K. Meyer, and R. Ray. Inhibition of p70 isoforms of S6K1 induces anoikis to prevent transformed human hepatocyte growth. ***Life Sciences.*** (2021) Vol.265, p.118764. #Co-corresponding author.

7. **Patra T#.,** K. Meyer, L. Geerling, T.S. Isabell, D.F. Hoft, J. Brien, A.K. Pinto,

R.B. Ray, and R. Ray. SARS-CoV-2 spike protein promotes IL-6 trans-signaling by activation of angiotensin II receptor signaling in epithelial cells. ***PLOS Pathogen.*** (2020) Vol.16, no.12, p. e1009128. #Co-corresponding author.

8. **Patra T#.**, K. Meyer, R.B. Ray, and R. Ray. A combination of AZD5363 and FH535 induces lethal autophagy in transformed hepatocytes. ***Cell Death & Diseases.*** (2020) Vol.11, p.540. #Co-corresponding author.
9. Nazzal M., S. Sur, R. Steele, M. Khatun, **T. Patra,** N. Phillips, J. Long, R. Ray and R.B. Ray. Establishment of a PDX tumor from hepatitis C associated liver cancer and evaluation of Imatinib treatment efficacy. ***Hepatology.*** (2020) Vol.72, no. 2, p. 379-388.
10. **Patra T.**, K. Meyer, R.B. Ray, and R. Ray. Hepatitis C virus mediated inhibition of miR-181c activates ATM signaling and promotes hepatocyte growth. ***Hepatology.*** (2019) Vol.71, no. 3, p. 780-793.
11. **Patra T.,** Sasaki R., K. Meyer, R.B. Ray, and R. Ray. TGF-β acts as a regulatory molecule for lipogenic pathway among hepatitis C virus genotype specific infection. ***J. Virology.*** (2019) Vol. 93, no. 18, p. e00811-19.
12. **Patra T.,** R.B. Ray, and R. Ray. Strategies to circumvent host innate immune response by hepatitis C virus. ***Cells.*** (2019), Vol. 8, no. 274, P. 1-14.
13. **Patra T.,** P. Ghosh, N. Alam and N. Murmu. Supra-physiological concentration of glyoxylate inhibits the proliferation of human colon cancer cells through oxidative stress. ***Life Sciences.*** (2018) Vol. 207, p. 80-89.
14. **Patra T.**, S. Mandal, N. Alam and N. Murmu. Clinicopathological trends of colorectal carcinoma patients in a tertiary cancer centre in Eastern India. ***Clinical Epidemiology Global Health.*** (2018), Vol. 6, no.1, p. 39-43.
15. Agarwal S., K. Jaswal, A. Shiver, H. Balecha, **T. Patra** and R. Chaba. Ubiquinone is a Key Antioxidant during Long Chain Fatty Acid Metabolism in *Escherichia coli*. ***FASEB J***. (2018), Vol. 32, p. e538.3.
16. Agarwal S., K. Jaswal, A. Shiver, H. Balecha, **T. Patra** and R. Chaba. A genome-wide screen in *Escherichia coli* reveals that ubiquinone is a key antioxidant for metabolism of long chain fatty acids. ***J. Biological Chemistry.*** (2017), Vol. 292, no.49, p. 20086-20099.
17. Roy S., **T**. **Patra**, T. Golder, S. Chatterjee, H. Koley and R. K. Nandy. Characterization of gluconate (Gnt) utilization system of *Vibrio cholerae* with

special reference to virulence modulation. ***FEMS Pathogen Diseases.*** (2016), Vol. 74, no. 8, p. 1-10.

18. **Patra T.,** H. Koley, T. Ramamurthy, A.C. Ghose and R.K. Nandy. Entner-Doudoroff pathway is obligatory for gluconate utilization and contributes towards the pathogenicity of *Vibrio cholerae*. ***J. Bacteriology.*** (2012), Vol. 194, no.13, p. 3377-3385.

19. **Patra T.,** S. Chatterjee, A. Roychowdhuri, A.K. Mukhopadhyay, T. Ramamurthy and R.K. Nandy. Emergence and progression of *Vibrio cholerae* O1 El Tor variants and progenitor strains of Mozambique variants in Kolkata, India. ***International J. Medical Microbiology.*** (2011), Vol. 301, no.4, p. 310-317.

20. Raychoudhuri, A., **T. Patra**, K. Ghosh, R. K. Nandy, Y. Takeda, T. Rammamurthy, G. B. Nair, A. K. Mukhopadhyay. Classical ctxB in *Vibrio cholerae* O1, Kolkata, India. ***Emerging Infectious Diseases.*** (2009), Vol. 15, no.1, P. 131-132.

21. Chatterjee, S*., **T. Patra***, K. Ghosh, A. Raychoudhuri, G. P. Pahzani, M. Das, B. L. Sarkar, R. K. Bhadra, A. K. Mukhopadhyay, Y. Takeda, G. B. Nair, T. Ramamurthy, and R. K. Nandy. *Vibrio cholerae* O1 clinical strains of 1992 at Kolkata with progenitor traits of 2004 Mozambique variant. ***J. Medical Microbiology.*** (2009), Vol. 58, P. 239-247. *****Co-first authors.

22. **Patra T.**, S. Roy, H. Koley, and R. K. Nandy. Defective glyoxylate cycle attenuates *Vibrio cholerae* virulence through an extra cytoplasmic stress response. ***Molecular Microbiology.*** (In revision).

23. **Patra T*.** and R. Ray. SARS-CoV-2 spike expressing cells modulates monocyte hyper-inflammatory response for prothrombotic stimulus. (Submitted in Inflammation). *****Co-corresponding author.

24. **Patra T*.,** D.M. Cunningham, K. Meyer, K. Toth, R.B. Ray, A. Heczey and R. Ray. Targeting Lin28 axis enhances glypican-3-CAR T cell efficacy against tumor initiating hepatic stem cell population. (Submitted in Molecular Therapy). *****Co-corresponding author.

Oral/Poster Presentation

38th ASV Annual Meeting: held in University of Minnesota, Minneapolis USA, July 20-24, 2019. “Hepatitis C virus mediated activation of ribosomal protein S6 kinase1 promotes hepatocyte growth by regulating anoikis”.

8th Zonal Oncology Symposium: held in Saroj Gupta Cancer Centre & Research Institute, Kolkata, January 31, 2017. "*Klebsiella pneumoniae* quorum sensing signal molecules facilitating immunomodulatory activity on colon cancer cells."

Bacterial Expression II: held in National Center for Biological Sciences India, December 1-5, 2015. "Understanding the connection between Long Chain Fatty Acid (LCFA) utilization and oxidative stress response in *Escherichia coli*."

Molecular Genetics of Bacteria and Phages Meeting: held in University of Wisconsin Madison USA, August 4-8, 2015. "Ubiquinone combats oxidative stress generated by Long Chain Fatty Acid utilization in *Escherichia coli*."

Proceedings of the Centenary Session of the Indian Science Congress: section of medical sciences held in Kolkata, January 3-7, 2013. "Organization and function of gluconate utilization system in *Vibrio cholerae*: relevance to pathogenesis."

US-Japan Cooperative Medical Science Program: Cholera & Other bacterial enteric infections held in Chiba Japan, December 12-14, 2012. "Gluconate utilization system of *Vibrio cholerae* and its role in pathogenesis."

International Symposium on Fifty Years of Discovery of Cholera Toxin held in Kolkata, October 25-27, 2009. "An *in silico* approach to understand the role of gluconate utilization system of *Vibrio cholerae* in association to its pathogenesis."

US-Japan Cooperative Medical Science Program: Cholera & Other bacterial enteric infections held in University of Texas, USA, December 5-7, 2007. "Mozambique variant of *Vibrio cholerae* O1: Emergence or resurgence?"

National Symposium on 21st Century Research in Biochemistry and Biophysics held in University of Kalyani, February 1-5, 2007. "Molecular tracking of reemerged *Vibrio cholerae* O1 biotype El Tor, serotype Inaba".

Signature