BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors. Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: MITRA, SIDDHARTHA S.

eRA COMMONS USER NAME (credential, e.g., agency login): MITRA.SIDDHARTHA

POSITION TITLE: Assistant Professor, Department of Pediatrics, University of Colorado School of 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
Panjab University, Chandigarh, India	B.Sc. (Hons)	06/1997	Biophysics
Panjab University, Chandigarh, India	M.Sc. (Hons)	07/1999	Biophysics
University at Buffalo, Buffalo, New York	M.S./Ph.D.	03/2005	Cell & Molecular Biology
Department of Physiology and Membrane Biology, University of California, Davis	Postdoctoral Scholar	12/2006	Cellular Neurobiology
Department of Neurosurgery, Stanford University	Postdoctoral Scholar	12/2010	Brain Tumor Stem Cells and Immunotherapy

A. Personal Statement

The over-arching goal of my research is to understand how a developing tumor interacts and modulates the immune microenvironment of the brain. Using this information my lab develops immune-modulating therapies against malignant brain tumors in adults and children. During my postdoctoral training, I gained extensive experience in developing patient-derived orthotopic xenograft models and antibody engineering. I developed the first cancer stem cell line for diffused intrinsic pontine glioma (DIPG), a fatal and devastating childhood brain cancer, which has greatly accelerated the search for anti-DIPG therapy. I have further developed xenograft models for multiple primary brain tumors including glioblastoma, oligo-astrocytoma, medulloblastoma, ATRT, and PNET and have created a library of cancer stem cell lines derived from adult and pediatric brain tumors, all of which are available for this project. In my role as Senior Scientist at Stanford University, I led the pre-clinical development of numerous immunotherapy candidates including anti-CD47 against adult and pediatric brain tumors at the Institute of Stem Cell Biology and Regenerative Medicine and the Stanford Ludwig Center for Cancer Stem Cell Research and Medicine. I most recently held the position of Director of the Translational Neuro-Oncology Center at Stanford University, which provided a standardized platform for academic and industry laboratories to test the efficacy of anti-tumor reagents against a range of adult and pediatric patient-derived orthotopic brain tumor xenografts and syngeneic mouse models, evaluate their immune modulating properties, and assess their efficacy or toxicity in combination with current standard of care involving radiation and chemotherapy. The center integrated the cross-disciplinary expertise available at Stanford University ranging from the development of novel immune therapies, small molecule inhibitors, blood brain barrier disrupting reagents, and next generation imaging techniques. Currently, as assistant professor of pediatrics at the University of Colorado School of medicine, the over-arching goal of the research in my laboratory, is to understand the dynamics of the immune microenvironment during neuro inflammation and tumor development and the targeting of immune evasion mechanisms in malignant brain tumors of adults and children.

B. Positions and Honors

Positions and Employment

Institution	Position	Dates	Field of Study
Ludwig Center for Cancer Stem Cell Research and Medicine, Institute of Stem Cell Biology and Regenerative Medicine, Stanford University Institutes of Medicine	Research Associate Senior Scientist and Seibel Investigator	01/2011 – 01/2013 01/2013 – 01/2018	Brain tumor immunotherapy Human Neural Stem Cells, Glioma Stem Cells and Antibody Therapies
Morgan Adams Foundation Pediatric Brain Tumor Research Program, University of Colorado School of Medicine	Assistant Professor	01/2018 – Present	Brain tumor immunotherapy Human Neural Stem Cells, Glioma Stem Cells and Antibody Therapies

Honors

2014 Seibel Scholar's Award from Seibel Stem Cell Institute
2010 Stanford University Children's Center for Brain Tumors Travel Award
2009 Stanford University Children's Center for Brain Tumors Travel Award
2002 Gap Junction Conference Young Investigators Award

C. Contributions to Science

1. Innate immune checkpoint immunotherapy against malignant adult and pediatric brain tumors.

Brain tumors are the most common malignant solid tumors in children and are responsible for the highest mortality among all pediatric cancers. Initiating macrophage-mediated tumor phagocytosis by blocking the anti-phagocytic CD47-SIRPα interaction has shown great promise for treatment of various malignancies. We demonstrated the effect of a humanized anti-CD47 antibody, Hu5F9-G4, on five etiologically distinct pediatric brain tumors *in vitro* and *in vivo*. Systemic Hu5F9-G4 treatment of patient-derived orthotopic xenografts models of pediatric glioblastoma, diffuse intrinsic pontine glioma (DIPG), atypical teratoid rhabdoid tumors (ATRT), primitive neuroectodermal tumors (PNET), and MYC-amplified medulloblastoma, including spinal and leptomeningeal metastasis (the primary cause of mortality in medulloblastoma patients), showed significant anti-tumor activity and survival benefit. I developed a novel co-transplant model of engrafted normal human CNS stem cells with medulloblastoma cells to further demonstrate the tumor-specific activity of Hu5F9-G4, suggesting the agent to be a potentially safe and effective therapeutic agent in the management of pediatric central nervous system malignancies that otherwise carry a grim prognosis. This approach is significantly different from the current generation of immunotherapy trials utilizing either adaptive check-point inhibitors or peptide vaccines. However, the activation of the innate immune system would be complimentary and developing combination immunotherapy regimens to achieve meaningful responses in malignant pediatric brain tumors is a major focus of my future research.

1. Gholamin S, Youssef OA, Rafat M, Esparza R, Kahn S, Shahin M, Giaccia AJ, Graves EE, Weissman I, **Mitra S**, Cheshier SH. Irradiation or temozolomide chemotherapy enhances anti-CD47 treatment of glioblastoma. *Innate Immunity. 2019 Sep 23* ***(co-senior author)***

2. Hutter GA , Theruvath JL , Graf CM , Zhang M, Schoen MK , Manz EM , Bennett ML , Olson A, Azad TD , Sinha R , Chan CT , Kahn SA , Gholamin S, Wilson C, Grant G, He J, Weissman IL, **Mitra SS**, Cheshier SH: Microglia are effector cells of CD47-SIRPα anti-phagocytic axis disruption against glioblastoma: *Proc Natl Acad Sci U S A 2019 Jan 2 (****corresponding author, and co-senior author)***

3. Gholamin S*, **Mitra SS***, , Feroze AH, Liu J, Zhang M, Kahn SA, Esparza R, Richard C, Ramaswamy V, Remke M, Volkmer AK, Willingham S, Ponnuswami A, McCarthy A, Lovelace P, Storm T, Schubert S, Narayanan C, Chu P, Raabe E, Harsh G, Taylor MD, Monje M, Cho YJ, Majeti R, Volkmer JP, Fisher PG,

Grant G, Steinberg GK, Vogel H, Edwards ME, Weissman IL & Cheshier SH: Disrupting the CD47-SIRPα anti-phagocytic axis by a humanized anti-CD47 antibody is an efficacious treatment modality for malignant pediatric brain tumors. *Science Translational Medicine: 2017 Mar 15;9(381).* ***(co-first author, corresponding author)***.

4. Zhang M, Hutter G, Kahn SA, Azad TD, Gholamin S, Xu CY, Liu J, Achrol AS, Richard C, Sommerkamp P, Schoen MK, McCracken MN, Majeti R, Weissman I, **Mitra SS**, Cheshier SH. Anti-CD47 Treatment Stimulates Phagocytosis of Glioblastoma by M1 and M2 Polarized Macrophages and Promotes M1 Polarized Macrophages In Vivo. PLoS One. 2016 Apr 19;11(4). ***(corresponding author and co-senior author)***

5. Willingham SB, Volkmer JP, Gentles AJ, Sahoo D, Dalerba P, **Mitra SS**, et.al.,The CD47-signal regulatory protein alpha (SIRPa) interaction is a therapeutic target for human solid tumors. *Proc Natl Acad Sci U S A*. 2012 Apr 24;109(17):6662-7. Epub 2012 Mar 26.

2. Development of primary adult and pediatric brain tumor stem cell lines.

The relative lack of good primary human cell-based animal models remains a significant limitation in the discovery and application of new advances from bench side to bedside in the care of patients, both adult and pediatric, afflicted with neoplasms of the central nervous system. With a background in mammalian developmental biology and my desire to further the availability and practicality of such models, along with the strong support of clinical faculty, residents, and colleagues at Stanford, I was able to develop a rigorous experimental program to develop novel dissociation and culture protocols with the aim of generating primary human cell lines from surgically-resected or postmortem brain tumor samples. These lines have now led to major findings such as the identification of EGFRvIII in tumor stem cells (Cancer Research, 2014), the development of the first *in vitro* culture model and xenograft model for DIPG (PNAS 2010), and a comprehensive library of cell lines for cMyc-amplified sub group (Group3) of medulloblastoma, which have now been used in three major publications (PNAS 2015, Clin Cancer Res 2014, Nature Medicine 2014). These cell lines have been distributed around the world to multiple groups for high throughput screening to identify novel drugs to bring to the clinic. By setting up a team comprised of pediatric neurosurgeons, neuropathologists, and clinical and surgical support staff, I have established a highly successful tissue acquisition network where we are now are able to acquire for research a vast array of pediatric brain tumors from surgical resections and diagnostic biopsies. These have been funneled into development of live primary cell banks and are being used by multiple groups such as The German Cancer Center in Heidelberg, Sick Kids Hospital in Toronto, and Imperial College in London for functional studies to identify novel therapeutics against pediatric brain tumors.

1. Theruvath JT, Sotillo E, Mount C, Graef CM, Delaidelli A, Heitzeneder S, Labanieh, Dhingra S, Leruste A, Majzner RG, Xu P, Mueller S, Yecies DW, Finetti MA, Williamson D, Johann PD, Kool M, Pfister S, Hasselblatt M, Frühwald MC, Delattre O, Surdez D, Bourdeaut F, Puget S, Zaidi S, **Mitra SS**, Cheshier SH, Sorensen PH, Monje M, Mackall CL: Locoregionally Administered B7-H3-targeted CAR T Cells for Treatment of Atypical Teratoid/Rhabdoid Tumors: *Nature Medicine* 2020 Apr 27 (***Cover Article)***

2. Kahn SA, Wang X, Nitta R, Gholamin S, Theruvath JL, Hutter GA, Azad TA, Wadi L, Bolin S, Ramaswamy V, Esparza R, Liu KW, Edwards M, Swartling F, Li G, Wechsler-Reya R, Reimand J, Cho YJ, Taylor MD, Weissman IL, **Mitra SS**, Cheshier SH: Notch1 regulates the initiation of metastasis and self-renewal of Group 3 medulloblastoma: *Nature Communications 2018 Oct 8;9(1):412* ***(co-Senior author)***

3. Garzia L, Kijima N, Morrissy AS, De Antonellis P, Guerreiro-Stucklin A, Holgado BL, Wu X, Wang X, Parsons M, Zayne K, Manno A, Kuzan-Fischer C, Nor C, Donovan LK, Liu J, Qin L, Garancher A, Liu KW, Mansouri S, Luu B, Thompson YY, Ramaswamy V, Peacock J, Farooq H, Skowron P, Shih DJH, Li A, Ensan S, Robbins CS, Cybulsky M, **Mitra S**, Ma Y, Moore R, Mungall A, Cho YJ, Weiss WA, Chan JA, Hawkins CE, Massimino M, Jabado N, Zapotocky M, Sumerauer D, Bouffet E, Dirks P, Tabori U, Sorensen PHB, Brastianos PK, Aldape K, Jones SJM, Marra MA, Woodgett JR, Wechsler-Reya RJ, Fults DW, Taylor MD: A Hematogenous Route for Medulloblastoma Leptomeningeal Metastases. *Cell*. 2018 Feb 22;172(5):1050-1062

4. Tang Y, Gholamin S, Schubert S, Nguyen B, Masoud S, Vue N, Balansay B, Bandopadhayay P, Bergthold B, Yu F, Oh S, Chen S, Ponnuswami A, Monje M, Lee A, Atwood S, Whitson R, Woo P, **Mitra SS**, Cheshier S, Qi J, Beroukhim R, Tang J, Wechsler-Reya R, Oro AE, Bradner J, Cho Y-J. Epigenetic regulation of Hedgehog transcriptional output by BET bromodomain proteins reveals a therapeutic strategy that overcomes acquired and a priori resistance to Smoothened antagonists. *Nature Medicine.* 2014 Jul;20(7):732-40.

5. Monje M*, **Mitra SS***, Edwards M, Fisher P, Weissman IL, Wong AJ, Beachy P. A Hedgehog-Responsive Precursor of the Childhood Hindbrain as a Candidate Cell of Origin for Diffuse Intrinsic Pontine Glioma. *Proc Natl Acad Sci U S A*. 2011 Mar 15;108(11):4453-8. Epub 2011 Mar 1.*)* ***(*co-first author)***

3. Identification of the "pre-malignant" neural stem cell in glioblastoma multiforme.

Normal human brain development requires exquisite timing of differentiation programs. Most of the cellular milieu found in the brain comes from "neural stem cells" (NSCs), a term used loosely to describe cells that demonstrate the capacity to (i) self-renew, (ii) generate neurons and glia, and (iii) give rise to daughter cells through asymmetric cell division. NSCs are derived from more primitive cells that have the capacity to generate NSCs as well as stem cells of other tissues. The classic pathway of lineage development is where NSCs give rise to neural progenitor cells (NPCs), and, subsequently, to terminally-differentiated cells. Fetal telencephalic neuroepithelial cell populations in mammalian embryonic brains contain multipotent NSCs that can self-renew and give rise to the three major central nervous system (CNS) cell types—neurons, astrocytes, and oligodendrocytes. Using an unbiased high throughput flow cytometry approach followed by functional stem cell assays, I was able to identify cell surface markers that purify mixed populations of multipotent neural stem/progenitor cells. Using a combinatorial approach of multiple (up to 8) cell surface expressed proteins, including Notch1, SSEA-1, and EGFR, I was able to prospectively separate out long-term self-renewing multi-potent neural stem cells from their short-term self-renewing multi-potent neural progenitor cells in the human fetal brain subventricular zone. I subsequently isolated similar populations in pediatric and adult human subventricular zones isolated from patients undergoing surgical procedures **not** related to brain tumors. Having identified the cell surface markers that can prospectively segregate neural stem and progenitor cells, I expanded the study to understand the genesis of glioblastoma multiforme (GBM), where I have identified similar subpopulations of cells in GBM. *In vivo* limiting dilution tumorigenic experiments show that the tumor-initiating population arises from the neural progenitor cell (NPC) population, whereas targeted qPCR analysis for known GBM mutations in sorted populations and flow cytometric re-analysis of xenografts show that the cell of origin is still the neural stem cell. Furthermore, RNAseq analysis of sorted populations now suggests that the gene signature of the molecular subtype classification in GBM is not evident in the glioma stem cell but rather the epigenetic signature is, giving us novel insights into the genesis of tumor development.

1. Kahn SA, Wang X, Nitta R, Gholamin S, Theruvath JL, Hutter GA, Azad TA, Wadi L, Bolin S, Ramaswamy V, Esparza R, Liu KW, Edwards M, Swartling F, Li G, Wechsler-Reya R, Reimand J, Cho YJ, Taylor MD, Weissman IL, **Mitra SS**, Cheshier SH: Notch1 regulates the initiation of metastasis and self-renewal of Group 3 medulloblastoma: *Nature Communications 2018 Oct 8;9(1):412* ***(co-Senior author)***

2. Bakhshinyan D, Venugopal C, Adile A, Garg N, Manoranjan B, Hallett R, Wang X, Mahendram S, Vora P, Vijayakumar T, Subapanditha M, Singh M, Kameda-Smith MM, Qazi M, McFarlane N, Mann A, Ajani O, Yarascavitch B, Ramaswamy V, Farooq H, Morrissy S, Cao L, Sydorenko N, Baiazitov R, Du W, Sheedy J, Weetall M, Moon YC, Lee CS, Doble B, Kwiecien J, Delaney K, Cho YJ, **Mitra SS**, Kaplan D, Taylor MD, Davis T, Singh S: BMI1 is a therapeutic target in recurrent medulloblastoma: *Oncogene* 2019 Mar;38(10):1702-1716.

3. Leiss L, Mutlu E, Øyan A, Yan T, Tsinkalovsky O, Sleire L, Petersen K, Rahman MA, Johannessen M, **Mitra SS**, Jacobsen HK, Talasila KM, Miletic H, Jonassen I, Li X, Brons NH, Kalland KH, Wang J, Enger PØ. Tumor-associated glial host cells display a stem-like phenotype with a distict gene expression profile and promote growth of GBM xenografts. BMC Cancer. 2017 Feb 7;17(1):108.

4. Nitta R, Gholamin S, Feroze A, Agarwal M, Cheshier S, **Mitra SS**, Li G. CK2 Alpha regulates Glioblastoma cancer stem cell growth through the beta-catenin pathway. *Oncogene* 2014 Sep 22.

5. Emlet DR*, Gupta P*, Holgado-Madruga M*, Del Vecchio CA*, **Mitra SS*,** Han SY, Li G, Jensen KC, Vogel H, Xu LW, Skirboll SS, Wong AJ. Targeting a glioblastoma cancer stem-cell population defined by EGF receptor variant III. *Cancer Research*. 2014 Feb 15;74(4):1238-49. ***(*co-first author)***

Complete List of Published Works in My Bibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/siddhartha.mitra.1/bibliography/47451746/public/?sort=date&direction=ascending.

D. Additional Information: Peer-Reviewed Research Support

Current

American Cancer Society 01/01/2020 – 12/31/2020
ACS-IRG 16-184-56
Project Title: Targeting the Adenosinergic Immunosuppressive pathway in Pediatric Diffused Midline Glioma
Role: Principal Investigator

Childhood Cancer Research Grant 01/01/2019 – 12/31/2020
The Andrew McDonough B+ Foundation
Project Title: Overcoming innate immune evasion in pediatric high-grade glioma
Role: Principal Investigator

Alex's Lemonade Stand 03/01/2019-08/31/2020
Crazy 8 Pilot Funding
Characterizing the surface-some of Atypical Teratoid Rhabdoid Tumors
Role: Principal Investigator

Brain Tumor Research Grant 01/01/2020-12/31/2020
Plachy-Rubin Foundation
Project Title: Targeting Macrophages For Immunotherapy in Glioblastoma Multiforme
Role: Principal Investigator

Brain Tumor Research Grant 03/01/2020-02/28/2021
Morgan Adams Pediatric Brain Tumor Foundation
Project 1: Development of Human Immune System Mouse Models of ATRTs
Project 2: Combinatorial Immunotherapy against High Risk Medulloblastoma
Role: Principal Investigator

New Faculty Recruitment Funds 02/01/2018 – 02/01/2022
Goal: Brain tumor immunotherapy research

Recently Completed

American Cancer Society 01/01/2019 – 12/31/2019
ACS-IRG
Project Title: Enhancing Myeloid Checkpoint Immunotherapy Using Radiation Induced Immunogenic Cell Death
Role: Principal Investigator
Emerson Collective Cancer Research Fund (Mitra) 04/01/2017 – 03/31/2019
Potentiating Immunotherapy against Malignant Brain Tumors through Targeted Suppression of Claudin-5 to Modulate the Blood-Brain Barrier'
Role: Co-Principal Investigator
OligoNation and National Brain Tumor Society 05/01/2016 – 09/01/2018
Anti-CD47 Based Multimodality Immunotherapy against Malignant Oligodendroglioma'
Role: Co-Investigator
Seibel Foundation and Seibel Stem Cell Institute (Mitra) 01/01/2014 – 12/31/2015
Delineating Lineage Hierarchy in Human Adult and Pediatric Glioblastoma'
Role: Principal Investigator