BIOGRAPHICAL SKETCH

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NAME: Michelle Monje MD PhD

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POSITION TITLE: Associate Professor of Neurology and Neurological Sciences

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
Vassar College, Poughkeepsie, NY	BA	05/1998	Biology
Stanford University, Stanford, CA	PhD	05/2004	Neuroscience
Stanford University, Stanford, CA	MD	05/2004	Medicine
Stanford University/Stanford Hospital, Stanford, CA		06/2005	Medicine Internship
Harvard Medical School/MGH/BWH, Boston, MA		06/2008	Neurology Residency
Stanford University/Lucile Packard Children's Hospital, Stanford, CA		06/2010	Neuro-Oncology Fellowship
Stanford University, Stanford California		10/2011	Postdoctoral Fellowship in Cancer Biology

A. Personal Statement

I am a neuroscientist and neuro-oncologist whose research program focuses at the intersection of neuroscience and brain cancer biology on neuron-glial interactions in health and oncological disease. The regulation of normal and malignant glial cells by neuronal activity is an area of particular emphasis. My lab demonstrated that neuronal activity regulates healthy glial precursor cell proliferation, new oligodendrocyte generation and adaptive myelination (Gibson et al., 2014 *Science*) and that this plasticity of myelin contributes to healthy cognitive function. We discovered that neuronal activity similarly promotes the proliferation of malignant glioma cells, driving glioma growth through both paracrine factors and through electrophysiologically functional neuron-to-glioma synapses (Venkatesh et al., 2015, *Cell*; Venkatesh et al., 2017 *Nature*; Venkatesh et al., 2019 *Nature*). Microglial interactions with neurons and neural precursor cells and microglial-mediated disruption of neuroplasticity mechanisms underlying cognitive function following cancer therapies is another area of deep focus. Together with these basic studies, my research program executes preclinical studies of novel therapeutics for high-grade gliomas and cancer therapy-related cognitive impairment in order to translate new therapies to the clinic.

B. Positions and Honors

2004 - 2005 Internal Medicine Internship, Stanford University Hospital
2005 - 2008 Neurology Residency, Partners Neurology Program, Massachusetts General Hospital/ Brigham and Women's Hospital/Harvard Medical School
2008 - 2010 Neuro-Oncology Fellowship, Stanford University and Packard Children's Hospitals
2010 - 2011 Instructor of Neurology and Neuro-Oncology, Stanford University
11/2011 –07/2018 Assistant Professor of Neurology, Stanford University
08/01/18 - Associate Professor of Neurology (with Tenure), Stanford University

Honors

1998 General and Departmental Honors upon college graduation
1998 Virginia Swinburne Brownell Prize for Excellence in Biology
1998 Phi Beta Kappa, Vassar College

2003 National Research Service Award (NRSA), MD, PhD pre-doctoral fellowship, NINDS
2006 Hagerty Foundation for Glioma Research Young Investigator Award
2010 K08 Mentored Clinical Scientist Career Development Award, NINDS
2011 2011 Peter A. Steck Memorial Award, PEDIATRIC BRAIN TUMOR FOUNDATION
2012 "A AWARD", ALEX'S LEMONADE STAND FOUNDATION
2013 New Faculty Physician Scientist Translational Research Award, CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE
2013 "Best Mentoring Award", STANFORD UNIVERSITY POSTDOCTORAL ASSOCIATION
2014 Anne T. and Robert M. Bass Endowed Faculty Scholar in Pediatric Cancer
2017 The Jerome Posner Neuro-Oncology Investigator Award, American Academy of Neurology
2017 The Innovative Researcher Award, DIPG Collaborative
2018 NIH Director's Pioneer Award
2019 Sidney Carter Award in Child Neurology, American Academy of Neurology
2019 Presidential Early Career Award in Science and Engineering (PECASE)
2020 Stanford Medicine Endowed Faculty Scholar
2020 F.E. Bennett Memorial Lectureship Award, American Neurological Association
2020 "Top 10 Breakthroughs in the Life Sciences" Award, Falling Walls Foundation
2021 The Neuro-Oncology Scientific Award, American Academy of Neurology
2021 American Association for Cancer Research (AACR) Team Science Award

BOARDING AND CERTIFICATION

2005 MEDICAL LICENSE, STATE OF CALIFORNIA, A93369
2008 NEUROLOGY, Certificate 55139
2013 Neuro-Oncology, UCNS subspecialty, certificate NO293-13

Other Experience

Stanford Graduate Admissions Committee, Cancer Biology PhD program (2016 – present)
Pediatric Brain Tumor Consortium (PBTC), Institutional PI/co-PI (2012-present)
AAN Neuro-Oncology Section Councilor (2014-2018)
Maternal and Child Health Research Institute at Stanford Executive Board (2017 –present)
Alex's Lemonade Stand Foundation Scientific Advisory Board (2018 – present)
Society for Neuro-Oncology Executive Board (2018 – present)
International Children's Brain Tumour Centre of Excellence Scientific Advisory Board (2019-present)
Editorial Board member, *Neuron, Cancer Cell*, *Cell Stem Cell*, *Cell Reports Medicine*, *Neuro-Oncology*

C. Contributions to Science

1. Neuron-glioma interactions drive malignant glioma growth

Hypothesizing that neuronal activity may influence glioma cells as it does normal glial precursor cells (see below), Dr. Monje's lab demonstrated that active neurons promote HGG proliferation *in vivo* using optogenetic control of cortical neuronal activity in a patient-derived pediatric glioblastoma orthotopic xenograft model. Neuronal activity-regulated secreted factors were found to promote the proliferation of a diverse group of gliomas, including DIPG, pediatric cortical glioblastoma, adult glioblastoma and adult anaplastic oligodendroglioma. The synaptic protein neuroligin-3 (NLGN3) was identified as a key mechanism; brain-derived neurotrophic factor (BDNF) also plays a role in activity-regulated glioma growth (Venkatesh et al., 2015 *Cell*). NLGN3 is secreted from both neurons and OPCs via activity-dependent activity of the ADAM10 sheddase, and ADAM10 inhibition robustly reduces HGG growth in vivo (Venkatesh et al., 2017 *Nature*). This work indicates the important role of active neurons in the brain tumor microenvironment, identifies secreted neuroligin-3 as an unexpected mechanism promoting neuronal activity-regulated cancer growth and outlines a promising novel treatment strategy for HGG.

Microenvironmental NLGN3 appears to be necessary for glioma growth, as HGG xenografts fail to grow in the *Nlgn3* KO mouse brain (Venkatesh et al., 2017 *Nature*). NLGN3 induces numerous oncogenic signaling mechanisms, including FAK signaling to the PI3K, Ras and Src pathways, although this alone is insufficient to explain this unexpected glioma. NLGN3 also induces expression of synapse-related genes in glioma cells, and Dr. Monje's group has now demonstrated that NLGN3 functions to promote electrophysiologically functional excitatory (AMAR-mediated) synapses between neurons and glioma cells. This synaptic and electrical integration into neural circuity drives glioma growth through voltage-dependent mechanisms (Venkatesh et al., 2019 *Nature*) and represents an important new avenue for glioma therapy.

a. Venkatesh HS, Johung T, Caretti V, Noll A, Tang Y, Nagaraja S, Gibson EM, Mount CW, Pollepalli J, Mitra SS, Woo PJ, Malenka RM, Vogel H, Bredel M, Mallick P, **Monje M** (2015) Neuronal activity promotes glioma growth through neuroligin-3 secretion, ***Cell***, 161(4):803-16. PMCID: PMC4447122

b. Venkatesh HS, Tam LT, Woo PJ, Nagaraja S, Gillespe SM, Lennon J, Ni J, Duveau DY, Morris PJ, Zhao JJ, Thomas CJ, **Monje M** (2017) Targeting neuronal activity-regulated neuroligin-3 dependency for high-grade glioma, ***Nature*** 549: 533-537. PMCID: PMC5891832

c. Venkatesh HS, Morishita W, Geraghty AC, Silverbush D, Gillespie SM, Arzt M, Tam LT, Espenel C, Ponnuswami A, Ni L, Woo PJ, Taylor KR, Agarwal A, Regev A, Brang D, Vogel H, Hervey-Jumper S, Bergles DE, Suvà ML, Malenka RC and **Monje M** (2019) Electrical and synaptic integration of glioma into neural circuits ***Nature*** 573:539-545 NIHMS 1537449

2. Neural precursor cell-glioma interactions in high-grade glioma invasion

The lateral ventricle subventricular zone (SVZ) stem cell niche is a frequent and consequential site of pediatric and adult glioma spread; in DIPG, we found that the tumor invades the lateral ventricle SVZ in ~65% of cases (Caretti et al, *Acta Neuropathologica* 2014). However, the cellular and molecular mechanisms mediating this are poorly understood. We demonstrated that neural precursor cell (NPC):glioma cell communication underpins this propensity of glioma to colonize the SVZ through secretion of chemoattractant signals toward which glioma cells home. Biochemical, proteomic, and functional analyses of SVZ NPC-secreted factors revealed the neurite outgrowth-promoting factor pleiotrophin, along with required binding partners SPARC/SPARCL1 and HSP90B, as key mediators of this chemoattractant effect. Pleiotrophin expression is strongly enriched in the SVZ, and pleiotrophin knockdown starkly reduced glioma invasion of the SVZ in the murine brain. Pleiotrophin, in complex with the binding partners, activated glioma Rho/ROCK signaling, and ROCK inhibition decreased invasion toward SVZ NPC-secreted factors. These findings demonstrate a pathogenic role for NPC:glioma interactions and potential therapeutic targets to limit glioma invasion.

a. Caretti V, Bugiani M, Freret M, Schellen P, Jansen M, van Vuurden D, Kaspers G, Fisher PG, Hulleman E, Wesseling P, Vogel H, **Monje M** (2014) Subventricular Spread of Diffuse Intrinsic Pontine Glioma**, *Acta Neuropathologica***, 128(4):605-7. PMCID: PMC4161623

b. Qin EY, Cooper DD, Abbott KL, Lennon J, Nagaraja S, Mackay A, Jone C, Vogel H, Jackson PK, **Monje M** (2017) Neural precursor-derived pleiotrophin mediates subventricular zone invasion by glioma, ***Cell*** 170 (5): 845-859. PMCID PMC5587159

3. Neuron-oligodendrocyte precursor cell interactions in adaptive myelination

Myelin is formed by mature oligodendrocytes in order to facilitate fast propagation of action potentials in axons. Small changes in myelin thickness can confer significant changes in conduction speed and may thus alter neural circuit function. The idea that active neurons may modulate myelination was supported by *in vitro* studies and by correlations between experience and myelin microstructure, but direct *in vivo* evidence demonstrating activity-regulated oligodendrocyte precursor cell (OPC) proliferation, generation of new oligodendrocytes or changes in myelin microstructure had been lacking. To address this gap in knowledge and provide *in vivo* evidence that activity-dependent changes in myelin represent an important form of neural plasticity, we used *in vivo* optogenetic techniques in awake, behaving mice to provide direct evidence of cortical projection neuronal activity-regulated changes in myelin-forming cells within the premotor circuit, with oligodendrogenesis-dependent influences on motor system function. This work demonstrated that neuronal activity regulates OPC proliferation, oligodendrogenesis and myelin structure in the murine brain with accompanying changes in neurological function (Gibson et al., 2014 ***Science***).

Our subsequent work demonstrated that adaptive myelination contributes to cognitive behavioral function, and that impairment of this plasticity in myelin contributes to cognitive impairment following methotrexate chemotherapy. We found that Bdnf-TrkB signaling is a required component of activity-dependent myelination in cortical projection neurons and that OPC-specific, inducible loss of TrkB expression results in cognitive behavioral impairment. Exposure to methotrexate chemotherapy results in a lasting reduction in neuronal Bdnf expression through microglial activation-dependent mechanisms, and TrkB agonism rescues cognition following remote chemotherapy exposure in a manner that depends upon OPC expression of TrkB. Taken together, these findings indicate that adaptive changes in myelin represent a type of behaviorally-relevant neural plasticity and that dysfunction of adaptive myelination can contribute to neurological disease (Geraghty et al., 2019 ***Neuron***).

a. Gibson EM, Purger D, Mount CW, Goldstein AK, Lin GL, Wood LS, Inema I, Miller SE, Bieri G, Zuchero JB, Barres BA, Woo PJ, Vogel H, **Monje M** (2014) Neuronal activity promotes oligodendrogliogenesis and adaptive myelination in the mammalian brain. ***Science,*** 344, 1252304. PMCID: PMC4096908

b. Geraghty A.C., Gibson E.M., Ghanem R., Greene J., Ocampo A., Goldstein A.K., Ni L., Yang T., Marton R.M., Pasca S.P., Greenberg M.E., Longo F.M., **Monje M**. (2019) Loss of adaptive myelination contributes to methotrexate chemotherapy-related cognitive impairment. ***Neuron,***103(2):250-265. PMCID PMC6697075
c. Steadman PE, Xia F, Ahmed M, Mocle AJ, Penning ARA, Geraghty AC, Steenland HW, **Monje M**, Josselyn SA, Frankland PW (2019) Disruption of Oligodendrogenesis Impairs Memory Consolidation in Adult Mice. ***Neuron*** 105(1):150-164.
d. Mount CW, Yaklcin B, Cunliffe-Koehler K, Sundaresh S, **Monje M** (2019) Monosynaptic tracing maps brain-wide afferent oligodendrocyte precursor cell connectivity. ***Elife***,8:e49291 DOI:10.7554/eLife.49291 PMCID PMC6800000

4. Microglial-neural precursor cell interactions in cancer therapy-associated cognitive impairment

Cranial radiation therapy frequently causes a debilitating cognitive syndrome in both children and adults. Hippocampal dysfunction, manifest as deficits in new memory encoding, is a prominent feature of the long-term cognitive sequelae of radiation therapy. As a graduate student in the laboratory of Dr. Theo Palmer, Dr. Monje demonstrated that radiation therapy induces a specific blockade in neuronal differentiation of hippocampal neural stem cells, with relative preservation of gliogenesis, due to radiation-induced dysfunction of the neurogenic microenvironment rather than a cell-intrinsic mechanism preventing neuronal differentiation (Monje et al, *Nature Med*. 2002). Dr. Monje went on to show that radiation-induced activation of hippocampal microglia mediates this perturbation of the neurogenic microenvironment, and showed for the first time that microglial inflammation can inhibit neurogenesis. The mechanism of microglial inhibition of neurogenesis was found to be interleukin-6 (IL-6)-mediated induction of non-canonical Notch signaling and nonsteroidal anti-inflammatory therapy during cranial radiation partially preserved hippocampal neurogenesis in a rodent model (Monje et al, *Science* 2003). Dr. Monje then demonstrated that radiation similarly inhibits human neurogenesis (Monje et al, *Annals of Neurology* 2007) and this correlates with long-term structural and functional deficits in the hippocampi of adult survivors of childhood cranial radiation exposure (Monje et al, *Pediatric Blood and Cancer* 2011). Dr. Monje's work subsequently demonstrated that a similar principle underlies chemotherapy-related cognitive impairment, with chemotherapy-induced microglial inflammation resulting in neuroinflammatory astrocyte activation and dysregulation of oligodendroglial lineage dynamics, ultimately disrupting myelination. In a murine model, microglial depletion normalizes glial dynamics and cognitive function after chemotherapy (Gibson et al, *Cell* 2019).

a. Monje ML, Mizumatsu S, Fike J, Palmer TD, (2002) Irradiation induces neural precursor cell dysfunction**.** ***Nature Medicine*** 8**,** 955 – 962.
b. Monje ML, Toda H and Palmer TD (2003) Inflammatory blockade restores neurogenesis, ***Science*** 302 (5651), 1760- 5.
c. Monje ML, Vogel H, Masek M, Ligon KL, Fisher PF, Palmer TD (2007) Impaired human hippocampal neurogenesis after treatment for CNS malignancies. ***Annals of Neurology***, 62 (5), 515 – 520.
d. Gibson E.M., Nagaraja S., Ocampo A, Tam L.T., Wood L.S., Pallegar P.N., Greene J.J., Geraghty A.C., Goldstein A.K., Ni. L., Woo P.J., Barres B.A., Liddelow S., Vogel H., **Monje M**. (2019) Methotrexate chemotherapy induces persistent tri-glial dysregulation that underlies chemotherapy-related cognitive impairment, ***Cell,*** 176 (1), 43-55. PMCID PMC6329664

5. Developmental origins, new model systems and epigenentic dysfunction in diffuse intrinsic pontine glioma

High-grade gliomas (HGG) of childhood occur with remarkable spatio-temporal specificity and this age and region-specific incidence suggests dysregulation of postnatal neurodevelopment. In 2008, when Dr. Monje began studying HGG of the pons (DIPG), the second most common malignant pediatric brain tumor and the leading cause of brain cancer death in children, little was known about pediatric HGG due to a dearth of tumor tissue available for research. As a postdoctoral fellow, she identified a novel population of neural precursor cells restricted to the ventral brainstem that expresses an imunophenotype most consistent with early oligodendroglial lineage precursor cells and found that this cell type increases in density at a time in mid-childhood that closely corresponds with the incidence of DIPG, suggesting a candidate cell of origin for DIPG (Monje et al, *PNAS* 2011). Chromatin analyses of DIPG together with iPSC modeling strongly support an oligodendroglial lineage precursor as the cell of transformation for DIPG (Nagaraja et al., *Cancer Cell* 2017; Nagaraja et al., *Molecular Cell* 2019).

Dr. Monje developed the first available patient-derived cell culture and orthotopic xenograft models of diffuse intrinsic pontine glioma (DIPG; Monje et al, *PNAS*, 2011) as a postdoctoral fellow and her lab has continued to

develop many additional patient-derived cell cultures and correlate xenograft models of DIPG and other types of pediatric and adult high-grade gliomas. Dr. Monje has distributed these unique patient-derived HGG cell cultures to several dozens of laboratories worldwide. An effort led by Dr. Monje coalesced all available DIPG cell culture models in an international collaborative effort to identify an effective therapeutic strategy. Chemical screening efforts in patient-derived DIPG cultures identified the multi-histone deacetylase (HDAC) inhibitor panobinostat as a promising therapeutic (Grasso et al, *Nature Med*. 2015). Dr. Monje is leading a phase I clinical trial of panobinostat for DIPG presently ongoing at Pediatric Brain Tumor Consortium (PBTC) institutions (NCT02717455). In follow-on studies, high-throughput single and combination agent screening identified a synergistic combination strategy of panobinostat together with the proteasome inhibitor marizomib (Lin et al., 2019 *Science Translational Medicine*). Similarly, disrupting transcription, either by Brd4 or CDK7 blockade, synergizes with HDAC inhibition (Nagaraja et al., *Cancer Cell* 2017).

Utilizing the patient-derived cell culture and xenograft models developed by her lab, Dr. Monje defined the cell surfaceosome of DIPG and demonstrated high cell surface expression of an antigen called GD2. In collaboration with Crystal Mackall's lab, Dr. Monje's group subsequently found that an immunotherapeutic strategy employing chimeric antigen receptor (CAR) T cells targeting GD2 are strikingly effective in preclinical models of DIPG and related childhood gliomas that share the H3K27M mutation (Mount et al, *Nature Medicine* 2018); Dr. Monje is leading a GD2 CAR T cell clinical trial at Stanford (NCT04196413).

a. Grasso CS, Y. Tang, N. Truffaux…E. H. Raabe, E. Hulleman, P. T. Spellman, X. N. Li, C. Keller, R. Pal, J. Grill, **Monje M** (2015) Functionally defined therapeutic targets in diffuse intrinsic pontine glioma. ***Nature Med***, 21(6): 555- 559. PMCID: PMC4862411

b. Nagaraja S, Vitanza N, Woo PJ, Taylor KR, Liu F, Zhang L, Li M, Meng W, Ponnuswami A, Sun W, Ma J, Hulleman E, Swigut T, Wysocka J, Tang Y, **Monje M** (2017) Transcriptional dependencies in diffuse intrinsic pontine glioma, ***Cancer Cell***, 31(5):635-652. PMCID: PMC5462626

c. Mount CW, Majzner RG…Vogel H, **Monje M*** and Mackall CL* (2018) Potent antitumor efficacy of anti-GD2 CAR T cells in H3-K27M(+) diffuse midline gliomas. ***Nature Medicine*** 24(5):572-579. PMCID PMC6214371

d. Lin G.L., Wilson K.M…Warren K.E.*, Thomas C.J.*, **Monje M*** (2019) Therapeutic opportunities for diffuse midline glioma identified from high-throughput combination drug screening. ***Science Translational Medicine***, 11(519):eaaw0064.

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/pubmed/?term=monje-m+stanford

D. Additional Information: Research Support and/or Scholastic Performance

NIH Director's Pioneer Award DP1NS111132 9/30/2018 - 6/30/2023

Glioma Circuitry: Bridging Systems Neuroscience and Cancer

The goal of this project is to applying systems neurobiology techniques to understand the synaptic circuit map and dynamic electrical properties of high-grade gliomas.

Role: Principal Investigator

NINDS R01NS092597 04/01/16 -3/31/22

Neuronal-activity regulated mechanisms of glioma growth

The goals of this proposal are to determine the relative contribution of neuroligin-3 (NLGN3) secretion on glioma growth using patient-derived pediatric high-grade glioma xenograft models such as DIPG, to define the enzymatic mechanism of NLGN3 activity-regulated cleavage and secretion, and to identify the glioma cell binding partner(s)/receptors of NLGN3 in pediatric high-grade glioma/DIPG.

Role: Principal Investigator

NCI P50CA165962 9/17/2019 – 8/312024

SPORE (MGH): Targeted therapies for glioma

I am co-leading one of the projects in the Massachusetts General Hospital/Harvard Cancer Center SPORE grant, entitled Targeting the Neuronal Microenvironment in Glioma which aims to translate a therapeutic strategy to block neuroligin-3 in the adult glioblastoma microenvironment and to discern the mechanisms mediating evolved adult glioblastoma resistance to neuroligin-3 blockade.

Role: Co-Principal Investigator