BIOGRAPHICAL SKETCH

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NAME: Ashley M. Laughney

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

POSITION TITLE: Assistant Professor, Weill Cornell Medicine (as of 7/1/2019)

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
University of Vermont, VT	B.S.	06/2007	Physics
Dartmouth College, NH	Ph.D.	06/2012	Engineering Sciences
Harvard Medical School/Massachusetts General Hospital, MA	Research Fellow	6/2014	Systems Biology
Memorial Sloan Kettering Cancer Center, NY	Research Associate	6/2019	Cancer Biology & Genetics

A. Personal Statement

I am a principal investigator in the Department of Physiology, Biophysics and Systems Biology (PBSB), the Institute for Computational Biomedicine (ICB), and the Sandra and Edward Meyer Cancer Center at Weill Cornell Medicine (WCM). Initially trained as an engineer and in systems biology, I developed functional spectroscopy (Dartmouth College) and single cell imaging and genomics methods in cancer biology (Harvard Medical School and Memorial Sloan Kettering). Combining high-throughput single cell transcriptional profiling with development of innovative computational tools and recruited expertise in synthetic biology, my research program tackles the genotype-to-phenotype problem in evolving, multi-cellular processes like cancer progression. Metastasis requires diverse functions including dissemination, adaptation to a less hospitable microenvironment, immune evasion and regeneration. Chromosomal instability (CIN) is a key driver of this transition through chronic sensing of genomic double-stranded DNA (dsDNA) in the cytosol (Bakhoum, Ngo, Laughney et al., *Nature* 2017). We have recently shown CIN-induced chronic STING signaling can be unleashed by loss of polycomb repressive complex 1 activity, enabling uveal melanoma metastasis (…Laughney, Nature Communications 2021). Systematically quantifying CIN-dependent ligand effects on the tumor ecosystem, we unexpectedly discovered chronic STING activation promotes interferon-selective tachyphylaxis and a switch to endoplasmic reticulum (ER) stress-dependent transcription for immune suppression (…Laughney, Bakhoum, Nature, *in press*). Chronicity of activation defines the functional output of STING signaling in cancer and explains lineage-specific immune susceptibilities we previously reported during the emergence of lung cancer metastasis (Laughney et al., *Nature Medicine* 2020). Altogether, our lab integrates systems biology methods with a hypothesis-driven framework to map genome-encoded components to complex cellular and *in vivo* functions. We apply these emerging techniques to understand how highly pleiotropic regulators such as STING switch from a tumor-suppressor to pro-tumoral function during the evolution of cancer metastasis.

Ongoing and recently completed projects that I would like to highlight include:

R01 CA280572
Laughney/Bakhoum, Role: Contact PI 06/08/23-05/30/28
Dissecting the impact of tumor-intrinsic chromosomal instability on the cancer ecosystem

R01 CA280414
Izar/Laughney, Role: MPI 05/01/23-04/30/28
Multi-cellular interactions defining the human brain metastatic niche

R01 CA256188-01
Laughney/Bakhoum, Role: Contact PI 08/01/21-12/31/25
Probing cytosolic nucleic acid sensing pathways in cancer

R21 CA266660-01A1
Laughney/Real, Role: Contact PI 09/12/22-08/31/24
Role of the smooth muscle layer in bladder cancer biology and progression

BWF Career Award at the Scientific Interface
Laughney (PI) 07/01/16-07/01/21
Uncovering Transcriptional Vulnerabilities in Latent Metastasis

B. Positions, Scientific Appointments, and Honors
Tenure-track Academic Positions

07/2019- Assistant Professor, Department of Physiology and Biophysics, WCM
07/2019- Assistant Professor, Institute for Computational Biomedicine, WCM

Other Academic Appointments and Positions

12/2019- Assistant Professor, Graduate School of Biomedical Sciences, Cornell University
12/2019- Assistant Member, Sandra and Edward Meyer Cancer Center, WCM

Awards and Honors

2022 Mastercard Research Assistance for Primary Parents (RAPP) Awardee
2019 MSK Scholars Society Prize
2019 SLAS Innovation Prize Finalist
2019 Kellen Junior Faculty Award
2017 Regeneron Prize for Creative Innovation Finalist
2016 Burroughs Wellcome Fund Career Award at the Scientific Interface (CASI)
2015 Center for Metastasis Research (CMR) Scholars Fellowship
2012 NIH T32 Postdoctoral Training Grant, Massachusetts General Hospital, Boston, MA
2007 David W. Juenker Physics Prize, University of Vermont
2007 Ron Chappelow Prize, University of Vermont
2005 Helix Research Grant, University of Vermont
2004 Green and Gold Scholarship (Full tuition, academic merit scholarship), University of Vermont

Committee Assignments

2023 Bioinformatics Curriculum Committee for the PBSB graduate program, WCM
2023 Faculty Advisor Board for the Epigenomics Core, WCM
2022 NCI Workshop on Future Fredrick National Laboratory for Cancer Research (FNLCR)
2021 Modeling Emergent Cellular Behaviors in Cancer, NCI Innovation Lab, Participant
2021- Metastasis Working Group, Weill Cornell Medicine
2018 Keystone Meeting: Lymphocytes and Their Role in Cancer, Session Chair
2016-2017 NIH/NCI CSBC/PSON Junior Investigator Meeting, Planning Committee Member

Professional Societies

2017 NIH/NCI CSBC/PS-ON Junior Investigator Meeting, Planning Committee Member
2014- New York Academy of Science, Member
2012- American Association for Cancer Research (AACR), Member
2007-2012 Society of Photonics in Engineering (SPIE), Member

Scientific Referee Activities

2020-present Grant Review Panel For: Chan Zuckerberg Initiative, Dutch Cancer Society (KWF Kankerbestrijding), British Lung Foundation

2009-present Medical Physics, Optics Letters, IEEE, Journal of Biomedical Optics, PLOS ONE, Breast Cancer Research, Nature Communications, Cell Systems, PNAS, eLife, Nature Medicine, Science Advances, Nature Biotechnology, Cancer Cell

Invited Talks (selected):

2024 Single-cell Cancer Biology Gordon Research Conference (GRC), New Hampshire, USA
2024 Tisch Cancer Institute at Icahn School of Medicine Seminar Series, New York, NY
2023 Foundation for Reproductive Medicine Conference, New York, NY
2023 2nd Probing Human Disease Using Single-Cell Technologies Conference, Cancun, Mexico
2023 Tumor-Immune Systems Biology Symposium, New York, NY
2023 Moffitt Cancer Center, Tampa, FL
2023 AACR Annual Meeting (Major Symposium), Orlando, FL
2023 Keystone Symposium on Single Cell Biology, Keystone, CO
2023 Special Section on Current Progress in Computational Biomedicine, JMM, Boston, MA
2022 MSKCC Computational Oncology Seminar Series
2022 BCB Cancer Heterogeneity and Immune Interactions Meeting, Bertinoro, Italy
2022 Cornell Intercampus Cancer Symposium, Ithaca, NY
2022 Centro Nacional de Investigaciones Oncológicas (CNIO), Madrid, Spain
2022 Probing Human Disease Using Single-Cell Technologies Conference, Cancun, Mexico
2021 Metastasis Working Group, Weill Cornell Medicine, New York, NY
2021 Lung Cancer Oncology Group, MSKCC, New York, NY
2021 Columbia University BME Seminar Series, New York, NY
2021 Tumor crosstalk with the microenvironment, MAP 2021 Virtual Congress (ESMO)
2021 Melanoma Research Retreat, MSKCC, New York, NY
2021 Thayer School of Engineering, Dartmouth College
2020 New York Cancer Genome Network Meeting
2020 NCI Cancer Systems Biology Annual Investigator Meeting
2019 NCI Division of Cancer Biology
2019 Cell Press Webinar on Cancer at Single Cell Resolution
2019 Next Generation Genomics, New York Genome Center
2018 Keystone Meeting, Lymphocytes and their Role in Cancer
2018 Cancer Genomics & Mathematical Data Analysis Symposium, Columbia University, NY
2017 NCI Systems Biology of Metastasis Meeting, MD Anderson Cancer Center
2016 Single Cell Genomics Workshop, New York Genome Center

C. Contributions to Science (selected from 30 peer-reviewed publications)

1. **Development & Cancer.** Using high-throughput single cell sequencing, we have revealed emergence of regenerative cell types in cancer progression and demonstrated that evolution of metastasis is in fact a dynamic state of equipoise between tumor cell lineage plasticity and innate immune surveillance. An archetypal model of lineage plasticity in cancer is histologic transformation – a process whereby a cancer's initial histology is altered and presents as a new histologic type. Through chronological single cell sequencing and lineage tracing of the first GEMM recapitulating histologic transformation of lung adenocarcinoma to a bona fide neuroendocrine cancer, we converge on lineage-dependent adaptation to driver oncogenes, specifically a unique cellular tolerance for Myc - as the oncogenic driver of the pulmonary neuroendocrine lineage - as the major barrier to histologic transformation in the lung.
   a. Gardner EE[#], Earlie EM, Li K, Thomas J, Hubisz MJ, Stein BJ, Zhang C, Cantley LC, **Laughney AM[#]**, **Varmus H[#]**, "Lineage-specific intolerance to oncogenic drivers restricts histologic transformation," https://www.biorxiv.org/content/10.1101/2023.06.21.545980v1 (*in review*). **[#]Co-corresponding authors**
   b. Deyell M, Garris CS, **Laughney AM**, "Cancer metastasis as a non-healing wound," **British Journal of Cancer**. 2021 March; 124: 1491-1502 (PMID: 33731858)

c. **Laughney AM**, Hu J, Campbell NR, Bakhoum SF, Setty M, Lavallee V, Xie Y, Masilonis I, Carr AJ, Allaj V, Mattar M, Rekhtman N, Xavier J, Mazutis L, Poirier JT, Rudin CM, Pe'er D*, Massagué J*, "Regenerative lineages and immune-mediated pruning in lung cancer metastasis," **Nature Medicine**. 2020 Feb; 26(2):259-269 (PMID:32042191)

d. Ganesh K, Basnet H*, Kaygusuz Y*, **Laughney AM*,** He L, O'Rourke KP, Reuter V, Huang YH, Er EE, Masilionis I, Weiser MR, Saltz LB, Garcia-Aguiar J, Koche R, Lowe SW, Pe'er D, Shia J, Massagué J*, "Regenerative origin of L1CAM+ metastasis initiating cells," **Nature Cancer 1**, 28-45 (2020) *these authors contributed equally to this work (PMID: 32656539)

2. **Modeling Inter-Cellular Network Dynamics.** One way in which cells adapt emergent functions is through context-dependent interactions with their environment. Exploiting intrinsic biological variability in single cell data, we have developed a fundamentally new, systems level approach called *ContactTracing* that predicts *the effect* of ligand-receptor-mediated interactions on the tumor microenvironment. Foundational work towards benchmarking and validation of this method was performed in isogenic breast cancer models distinguished by tumor cell-intrinsic rates of chromosomal instability (CIN). Through this, we identified tumor ligands emanating from an ER-stress response as potential mediators of immune suppression in chromosomally unstable tumors. Indeed, CIN-induced chronic STING activation led to rapid interferon-selective desensitization and a switch to ER-stress-dependent transcription; validating this innovative methodology and identifying a targetable mediator of cancer metastasis.

   a. Li J*, Hubsiz MJ*, Earlie EM*, Duran MA*, Hong C, Varela AA, Lettera A, Deyell M, Tavora B, Havel J, Phyu SM, Amin AD, Budre K, Kamiya E, Cavallo J-A, Garris CS, Powell S, Reis-Filho J, Wen H, Bettigole S, Khan A, Izar B, Parkes EE, **Laughney AM**[#], Bakhoum SF[#], "Non-cell-autonomous cancer progression from chromosomal instability," **Nature.** (*in press*)
   [#]Equal contributions: co-senior and co-corresponding authors

   b. Adler FR, Anderson ARA, Bhushan A, Bogdan P, Bravo-Cordero JJ, Brock A, Chen Y, Cukierman E, DelGiorno KE, Denis GV, Ferrall-Fairbanks MC, Gartner ZJ, Germain RN, Gordon DM, Hunter G, Jolly MK, Karacosta LG, Mythreye K, Katira P, Kulkarnii RP, Kutys ML, Lander AD, **Laughney AM**, Levine H, Lou E, Lowenstein PR, Masters KS, Pe'er D, Peyton SR, Platt MO, Purvis JE, Quon G, Richer JK, Riddle NC, Rodriguez A, Snyder JC, Szeto GL, Tomlin CJ, Yanai I, Zervantonakis IK, Dueck H, "Modeling collective cell behavior in cancer: Perspectives from an interdisciplinary conversation," **Cell Systems**. 2023 Apr; (PMID: 37080161)

   c. Li Z, Low V, Luga V, Sun J, Earlie E, Parang B, Ganesh KS, Cho S, Endress J, Schild T, Hu M, Lyden D, Jin W, Guo C, Dophoure N, Cantley L, **Laughney AM**, John Blenis, "Tumor-produced and aging-associated oncometabolite methylmalonic acid promotes cancer-associated fibroblast activation to drive metastatic progression," **Nature Communications**. 2022 Oct; (PMID:36266345)

   d. Rozenblatt-Rosen, O, Regev, A, Oberdoerffer, P, Nawy, T, Hupalowska, A, Rood, JE et al. "The Human Tumor Atlas Network: Charting Tumor Transitions across Space and Time at Single-Cell Resolution". **Cell**. 2020;181 (2):236-249. doi: 10.1016/j.cell.2020.03.053. (PMID:32302568).

3. **Quantifying Chromosomal Instability in Tumor Evolution & Metastasis.** Copy number alterations have long been associated aggressive, metastatic tumors. However, it was unknown whether these alterations were associated with - or were drivers - of metastasis. Using tools to dial up or dial down tumor cell-intrinsic rates of chromosome missegregation (a cellular process called chromosomal instability, or CIN) in otherwise aneuploid cancer models, we demonstrated that the dynamic process of CIN is indeed a potent driver of cancer metastasis. Unexpectedly, we discovered CIN drives metastasis by inducing tumor-promoting inflammation through its chronic activation of the cGAS-STING cytosolic DNA-sensing pathway. In uveal melanoma, we additionally discovered loss of a crucial epigenetic regulator, PRC1, leads to chromosome segregation errors that promote CIN-induced STING signaling. We have modeled the impact of CIN on tumor evolution from a Darwinian perspective using both stochastic and Markov Chain models.

   a. Bakhoum MF, Francis JH, Agustinus A, Earlie EM, Abramson DH, Duran M, Masilionis I, Dibona M, Shoushtari AN, Goldbaum MH, Mischel PS*, Bakhoum SF*, **Laughney AM***, "Loss of Polycomb Repressive Complex 1 activity and chromosomal instability drive uveal melanoma progression" **Nature Communications.** 2021 Sep 13; 12(1), 5402 (PMID: 34518527)

b. Elizalde S, **Laughney AM**, Bakhoum SF, "A Markov chain for numerical chromosomal instability in clonally expanding populations," **PLOS Computational Biology.** 11 Sep 2018;14(9):e1006447. (PMID: 30204765)

c. Bakhoum SF, Ngo B, **Laughney AM**, Cavallo JA, Murphy CJ, Ly P, Sha P, Sriram RK, Watkins TBK, Taunk NK, Duran M, Pauli C, Shaw C, Chadalavada K, Rajasekhar VK, Genovese G, Venkatesan S, Birkbak NJ, McGranahan N, Lundquist M, LaPlant Q, Healey JH, Element O, Chung CH, Lee NY, Imielenski M, Nanjangud G, Pe'er D, Cleveland DW, Powell SN, Lammerding J, Swanton C, Cantley LC, "Chromosomal instability drives metastasis through a cytosolic DNA response," **Nature**. 25 Jan 2018; 553: 467-472. (PMID: 29342134) *cover article*

d. **Laughney AM**, Elizalde S, Genovese G, Bakhoum SF, "Dynamics of tumor heterogeneity derived from clonal karyotypic evolution," **Cell Reports.** 2015 Aug 4; 12(5):809-20. (PMID: 26212324) *cover article*

4. **Imaging Single Cell Pharmacokinetics *In Vivo*.** Using intravital microscopy and fluorescent imaging drugs, we investigated pharmacokinetic mechanisms of drug resistance in taxane-refractory breast tumors.

a. Miller A, Gadde S, Pfirschke C, Engblom C, Sprachman M, Kohler RH, Yang KS, **Laughney AM**, Wojtkiewicz G, Kamaly N, Bhonagiri S, Pittet M, Farokhzad OC, Weissleder R, "Predicting therapeutic nanoparticle efficacy using a companion MR imaging nanoparticle," **Science Translational Medicine** 2015 Nov. 18; 7(314):314ra183 (PMID: 26582898)

b. **Laughney AM**, Kim E, Sprachman MA, Miller MA, Kohler RH, Yang KS, Orth JD, Mitchison TJ, Weissleder R, "Single-cell pharmacokinetic imaging reveals a therapeutic strategy to overcome drug resistance to the microtubule inhibitor eribulin," **Science Translational Medicine.** 2014 Nov. 5; 6(261):261ra152. (PMID: 25378644)

c. Sprachman MM†, **Laughney AM†**, Weissleder R, "In vivo imaging of multidrug resistance using a third generation MDR1 inhibitor," **Bioconjugate Chem.** 2014. (PMID: 24806886). **†These authors contributed equally to this work.**

d. Sarit SA**†**, **Laughney AM†,** Kohler RH, Weissleder R, "Photoactivatable Drug-Caged Fluorophore Conjugate Allows Direct Quantification of Intracellular Drug Transport," **Chemical Commun**. 2013 Oct 18; 49:11050-11052 (PMID: 24135896) **†These authors contributed equally to this work**

5. **Quantitative Imaging for Real-Time Tumor Margin Assessment.** We developed new quantitative imaging technologies for real-time intraoperative tumor margin assessment to improve the completeness of local tumor excision during breast conserving therapy, the standard of care for patients with early invasive breast cancers. This patented design (PCT/US13/44803) is of great clinical utility because it enables validation by pathology, the diagnostic gold standard, while overcoming the sampling limitations of microscopy and capturing intra-tumor heterogeneity.

a. **Laughney AM**, Krishnaswamy V, Rizzo EJ, Schwab MC, Barth RJ, Cuccia DJ, Tromberg BJ, Paulsen KD, Pogue BW, Wells WA, "Spectral discrimination of breast pathologies in situ using spatial frequency domain imaging," **Breast Cancer Research** 2013, 15(4): R61 (PMID: 23915805).

b. **Laughney AM**, Krishnaswamy V, Rice T, Cuccia D, Barth RJ, Tromberg BJ, Paulsen KD, Pogue BW, Wells WA, "System analysis of spatial frequency domain imaging for quantitative mapping of surgically resected breast tissues," **Journal of Biomedical Optics** 2013 Mar. 18(3):036012 (PMID: 23525360).

c. **Laughney AM**, Krishnaswamy V, Rizzo E, Schwab M, Barth R, Pogue BW, Paulsen KD, Wells WA, "Scatter spectroscopic imaging distinguishes breast pathologies in tissues relevant to surgical margin assessment," **Clinical Cancer Research** 2012,18(22): 6315-25 (PMID: 22908098). * *Highlighted in: Bigio, IJ, "Real-time pathology to guide breast surgery: seeing alone is not believing." Clinical Cancer Research. 18(22): 6083-85 (2012).*

d. **Laughney AM**, Krishnaswamy V, Garcia-Allende PB, Conde OM, Wells WA, Paulsen KD, Pogue BW, "Automated classification of breast pathology using local measures of broadband reflectance," **Journal of Biomedical Optics** 2010, 15(6):066019 (PMID: 21198193).

Complete List of Published Works:
https://www.ncbi.nlm.nih.gov/myncbi/1BK-6kMrCI45L/bibliography/public/