BIOGRAPHICAL SKETCH

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NAME: Ashley M. Laughney

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

POSITION TITLE: Associate Professor, Weill Cornell Medicine (as of 2/10/2025)

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 expertise in synthetic biology, my research program tackles the genotype-to-phenotype problem in evolving, multi-cellular processes like cancer progression. Predicting protein function from sequence, also known as *genotype-to-phenotype* mapping, remains a central challenge in biology. This is because a significant fraction of proteins are highly pleiotropic; meaning they can perform more than one function and participate in a wide range of biological processes. As such, perturbations to a single gene can affect multiple, independent cellular responses – complicating our ability to infer protein function from sequence. Integrating innovative systems and synthetic biology approaches with a hypothesis-driven framework, my research program maps genome-encoded components to complex cellular and *in vivo* functions at scale. We focus on chromosomal instability (CIN) in cancer progression as our model of a multicellular, evolutionary process and develop approaches that ask how activation of the same protein or signaling pathway can lead to diverse functional outputs through *(i)* the evolution of distinct modular domains, (*ii*) *intra*-cellular genetic interactions and *(iii) inter*-cellular signaling networks (multicellular programs). We apply these emerging techniques to understand how highly pleiotropic regulators such as STING switch from a tumor-suppressor to pro-tumoral function during cancer evolution.

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

R01 CA282762
Laughney/Blenis, Role: Contact PI 03/01/25-02/30/30
A systems-level approach to therapeutically target STING in cancer

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, Role: 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

02/2025-	Associate Professor, Department of Physiology and Biophysics, WCM
02/2025-	Associate Professor, Institute for Computational Biomedicine, WCM
07/2019-2025	Assistant Professor, Department of Physiology and Biophysics, WCM
07/2019-2025	Assistant Professor, Institute for Computational Biomedicine, WCM

Other Academic Appointments and Positions

02/2025-	Associate Member, Englander Institute of Precision Medicine, WCM
02/2025-	Associate Professor, Graduate School of Biomedical Sciences, Cornell University
02/2025-	Associate Member, Sandra and Edward Meyer Cancer Center, WCM

Awards and Honors

2025	Irma T. Hirschl Career Scientist Award
2024	Pershing Square Sohn Prize for Young Investigators in Cancer Research
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

2024	NCI Exploratory Workshop on Math, Theory and Cancer Biology, Rockville, MD
2024	NCI Think Tank on Systemic Effects of Cancer, Rockville, MD
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	NCI Innovation Lab on Modeling Emergent Cellular Behaviors in Cancer
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

Scientific Referee Activities

2025	NCI Special Emphasis Panel/Scientific Review Group 2025/05 ZRG1 CTH-E (57) R
2025	NCI Metastasis Research Network (Metnet) Programatic Review Group
2020-present	Grant Reviewer: Chan Zuckerberg Initiative, Dutch Cancer Society, 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, Cancer Discovery, Science

Invited Talks (selected):

2025	Plenary Talk at Winter Q-Bio, Ko Olina, HI
2025	Cancer Metastasis: Non-Genetic Drivers, AACR Annual Meeting, Chicago, IL
2025	Prostate Cancer Academy Meeting, Los Angeles, CA, USA
2025	Keystone Symposia on Tumor Microenvironment: Metastasis and the Host, Banff, Canada
2024	MD Anderson Cancer Center GU Gallack Lab Meeting, Houston, TX
2024	BCB Cancer Heterogeneity and Immune Interactions Meeting, Bertinoro, Italy
2024	Prostate Cancer Academy Meeting, Los Angeles, CA, USA
2024	Spanish National Cancer Research Center-CNIO, Madrid, Spain
2024	Translational Approaches to Inflammatory Liver Injury and Repair, Banff, Canada
2024	New York Genome Center, New York, NY
2024	Plenary Speaker, NIH Junior Investigators Meeting, Bethesda, MD, USA
2024	Department of Genomic Sciences, University of Washington, Seattle, WA
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	San Antonio Breast Cancer Symposium, San Antonio, TX
2023	Foundation for Reproductive Medicine Conference, New York, NY
2023	Single Cell Mapping in Development and Cancer, NYU Grossman School of Medicine, NY
2023	Biomedical Engineering Program, UTSW Medical Center, Dallas, TX
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

C. Contributions to Science (selected from 33 peer-reviewed publications)

1. **Development & Cancer.** Using high-throughput single-cell sequencing, we identified regenerative cell types emerging during cancer progression and investigated histologic transformation—the process where cancer changes from one histologic type to another. 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," **Science.** 2024 Feb; 383(6683); (PMID: 38330136) **[#]Equal 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. Rogava M, Aprati TJ, Chi WY, Melms JC, Hug C, Davis SH, Earlie EM, Chung C, Deshmukh SK, Wu S, Sledge G, Tange S, Ho P, Amin AD, Caprio L, Gurjao C, Tagore S, Ngo B, Lee MJ, Zanetti G, Wanng Y, Chen S, Ge W, Melo LMN, Allies G, Rösler J, Gibney GT, Schmitz OJ, Sykes M, Creusot RJ, Tüting T, Schadendorf D, Röcken M, Eigentler TK, Molotkov A, Mintz A, Bakhoum SF, Beyaz S, Cantley LC, Sorger PK, Meckelmann SW, Tasdogan A, Liu D, **Laughney AM**, Izar B, "Loss of *Pip4kc* confers liver-metastatic tropism through insulin-dependent PI3K-AKT pathway activation," **Nature Cancer**. 2024 Mar; 5(3):433-447 (PMID:38286827)

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. 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.** 2023 Aug; (PMID: 27612508)
   [#]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. Di Bona M, Chen Y, Agustinus AS, Mazzagatti A, Duran MA, Deyell M, Bronder D, Hickling J, Hong C, Scipioni L, Tedeschi G, Martin S, Li J, Ruzgaitė A, Riaz N, Shah P, D'Souza EK, Brodtman DZ, Sidoli S, Diplas B, Jalan M, Lee NY, Ordureau A, Izar B, **Laughney AM**, Powell S, Gratton E, Santaguida S, Maciejowski J, Ly P, Jeitner TM, Bakhoum SF, "Micronuclear collapse from oxidative damage," **Science**. 2024 Aug; (PMID:39208110)
   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 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.

   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.** Real-time intraoperative tumor margin assessment that enables validation by pathology, the diagnostic gold standard, while overcoming the sampling limitations of microscopy and capturing intra-tumor heterogeneity. (PCT/US13/44803)
   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).

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https://www.ncbi.nlm.nih.gov/myncbi/1BK-6kMrCI45L/bibliography/public/