BIOGRAPHICAL SKETCH

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NAME: Inna Smalley

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

POSITION TITLE: Assistant Professor

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 South Florida, Tampa FL USA	B.S.	12/2008	Biology
University of South Florida, Tampa FL USA	Ph.D.	07/2014	Cancer Biology
Moffitt Cancer Center, Tampa FL USA	Postdoctoral	07/25/2020	Tumor Biology

A. Personal Statement

I have more than 10 years of experience studying central nervous system (CNS) tumors. I have extensive expertise in studying the role of the tumor microenvironment in tumor growth and drug resistance. I have been exploring tumor microenvironments among different metastatic sites to elucidate what drives certain cells to certain metastatic sites. I am greatly interested in the mechanisms supporting tumor survival on therapy and immune evasion in different microenvironments, with a special focus on the CNS tumor site. As part of these efforts, I have established a rapid autopsy protocol for patients with CNS metastatic disease from lymphoma, melanoma, and breast cancer. This protocol allows us to bank various tissues and fluids (both tumor and "normal"), establish primary cultures, establish PDX models, and perform a wide array of genomic, transcriptomic, proteomic, and metabolomic assays to better understand various aspects of primary and metastatic disease. I co-lead our Leptomeningeal Disease Research Program and we have a strong history of translating basic science to investigator-initiated clinical trials in the CNS space. To help facilitate translational research, I have developed *in vitro* models of the CNS tumor environment and several murine models of CNS lymphoma, melanoma, and breast cancer. Furthermore, I have optimized the application of several spatial transcriptomics and single-cell analysis techniques for analyzing patient tumor specimens and cerebrospinal fluid-circulating tumor cells. I am a highly collaborative scientist and I am deeply committed to mentoring early career scientists. I have previously published under my maiden name: Inna V. Fedorenko.

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

NIH R01 (PI: Inna Smalley)
08/01/2026- 07/30/2031
"Targeting branched-chain keto acid accumulation in melanoma leptomeningeal disease."

NIH R21 (PI: Inna Smalley)
09/01/2022 - 08/31/2024
"Defining and targeting the immune-suppressive metabolic microenvironment of leptomeningeal melanoma metastases."

William G. "Bill" Bankhead, Jr., and David Coley Cancer Research Program Grant (PI: Inna Smalley)
01/01/2026 - 12/31/2028
"Understanding how tumor cells co-opt meningeal stroma in melanoma leptomeningeal disease."

Florida Breast Cancer Foundation Scientific Grant (PI: Inna Smalley)
07/01/2021 - 06/30/2022

"Defining and targeting the pro-tumorigenic metabolic microenvironment of leptomeningeal metastasis in triple-negative breast cancer."

Research Scholar Grant American Cancer Society (PI: Inna Smalley)
06/30/2023-06/30/2027
"Improving therapy for leptomeningeal Non-Hodgkin B cell lymphoma by targeting the metabolic tumor microenvironment"

NIH K99/R00 R00 CA226679-04 Pathway to Independence Award (PI: Inna Smalley)
04/01/2018-03/31/2023
"Defining the role of metabolic heterogeneity in melanoma dissemination and therapy escape."

Melanoma Research Alliance (MRA) Young Investigator Award (PI: Inna Smalley)
05/01/2022-04/30/2025
"Tumor-stroma metabolic crosstalk in melanoma brain metastases"

Moffitt Cancer Center Innovative Core Grant (PI: Inna Smalley)
01/17/2022-01/16/2023
"Developing spatial multi-omics approaches for the study of the tumor microenvironment."

Donald A. Adam Melanoma and Skin Cancer Center of Excellence (MSCCoE) and Cutaneous Oncology (PI: Inna Smalley)
10/01/2022-05/31/2023
"Sensitizing leptomeningeal melanoma to checkpoint inhibitor therapy."

Citations:

1. Piña Y, Law V, Sahebjam S, Tran N, Siddarajappa N, Li J, Mo Q, Phadke MS, Arrington J, Macaulay R, Mokhtari S, Evernden B, Ahmed KA, Smalley I, Yu M, Smalley KSM, Forsyth PA. Phase IB Study of Avelumab and Whole Brain Radiotherapy (WBRT) in Patients with Leptomeningeal Disease (LMD) from Solid Tumors: Results and Molecular Analyses. Neuro Oncol. 2025 Aug 28 Epub ahead of print.
2. Khaled ML, Ren Y, Kundalia R, Alhaddad H, Chen Z, Wallace GC, Evernden B, Ospina OE, Hall M, Liu M, Darville LNF, Izumi V, Chen YA, Pilon-Thomas S, Stewart PA, Koomen JM, Corallo SA, Jain MD, Robinson TJ, Locke FL, Forsyth PA, **Smalley, I.** (2023). Branched-chain keto acids promote an immune-suppressive and neurodegenerative microenvironment in leptomeningeal disease. bioRxiv, 2023.2012.2018.572239. Preprint.
3. Alhaddad H, Ospina OE, Khaled ML, Ren Y, Vallebuona E, Boozo MB, Forsyth P, Pina Y, Macaulay R, Law V, Tsai KY, Cress WD, Fridley B, & **Smalley I.** (2023). Spatial transcriptomics analysis identifies a unique tumor-promoting function of the meningeal stroma in melanoma leptomeningeal disease. Cell Rep Med. 2024 Jun 18;5(6):101606.
4. **Smalley I**[#*], Chen Z[#], Phadke M, Wyatt C, Law W, Eroglu Z, Tran N, Forsyth P, Chen YA*, Smalley KSM*. Single-Cell Characterization of the Immune Microenvironment of Melanoma Brain and Leptomeningeal Metastases. Clinical Cancer Research. 25 May 2021, 27(14):4109-4125. # Contributed equally. ***Corresponding author.** PMCID: PMC8282775

B. Positions, Scientific Appointments, and Honors

Positions

2025-Present	Director of Recruitment, Cancer PhD Program at Moffitt Cancer Center
2020-Present	Assistant Member, Department of Metabolism and Physiology, Moffitt Cancer Center
2020-Present	Assistant Professor, Department of Oncologic Sciences, University of South Florida
0214-2020	Postdoctoral Fellow, Moffitt Cancer Center
2009-2014	Cancer Biology Ph.D. Program, University of South Florida
2008-2009	Research Assistant I, Research Assistant II, Moffitt Cancer Center
2007	SPARK Intern, Moffitt Cancer Center
2005-2008	Research Assistant (Volunteer), Moffitt Cancer Center

Service

Grant review: NCI Mechanisms of Cancer Therapeutics B (2023, 2025), American Cancer Society Postdoctoral Fellowship Cell Biology & Immunology (term member), Melanoma Research Foundation (since 2017)

Non-profit: Leptomeningeal Cancer Foundation Board of Directors

Review Editor: Frontiers in Oncology, Frontiers in Cell and Developmental Biology.
Peer review for journals: Nature Genetics, Nature Cancer, Science Advances, Science Translational Medicine, Science Signaling, Nature Communications, Cancer Research, npj Precision Oncology, Military Medical Research, Molecular Cancer Therapeutics, and Pigment Cell & Melanoma Research.

Honors

2025 Moffitt Cancer Center Junior Faculty Researcher of the Year
2018 AACR Scholar-In-Training Award for Special Conference on Immunobiology of Primary and Metastatic CNS Cancer
2015 Career Development Award from Melanoma Research Foundation
2014 Joanna M Nicolay Melanoma Foundation Research Scholar Award
2014 Keystone Symposia Future of Science Fund scholarship
2012 Scholarship from CSHL to attend Single Cell Analysis Course
2011 AACR Scholar-in-Training Award
2011 ARCS Scholar (three years of financial support)
2011 Outstanding Research Accomplishment Award, Cancer Biology Ph.D. Program

C. Contributions to Science

1. Cell-intrinsic and microenvironment-mediated drug resistance. Melanoma has become a poster-child for the development of oncogene-directed targeted therapies, exemplified by the development of small-molecule MAPK inhibitors for treatment of BRAF-mutant melanoma. Despite these successes, treatment failure seems near inevitable in the majority of cases. Our work was first to show that BRAF inhibitor resistance was mediated through recovery of ERK signaling, which still remains a main down-stream mechanism of a number of resistance strategies identified to date. We have also discovered a tumor-autonomous strategy of drug resistance through up-regulation of fibronectin and secretion of TGF-beta, which can also stimulate and co-operate with normal stromal fibroblasts to amplify drug resistance signaling through the PI3K/AKT axis. We have been first to show that BRAF inhibitor vemurafeib has direct effects on primary human-derived fibroblasts. Our findings on the use of HSP90 inhibitors to delay onset of drug resistance led to two recent clinical trials for dual BRAF+HSP90 inhibition as well as a triple BRAF+MEK+HSP90 combination. In the latest work, we provided the first evidence that transcriptional heterogeneity at the single cell level predicts for initial BRAF inhibitor sensitivity. We further demonstrate that manipulating transcriptional heterogeneity through personalized adaptive therapy schedules can delay the time to resistance.

a) **Smalley I**, Kim E, Li J, Spence P, Wyatt CJ, Erolgu Z, Sondak VK, Messina JL, Babacan NA, Maria-Engler SS, De Armas L, Williams SL, Gatenby RA, Chen YA, Anderson ARA, Smalley KSM. Leveraging transcriptional dynamics to improve BRAF inhibitor responses in melanoma. eBioMedicine. 2019 Oct;48:178-190. PMCID: PMC6838387
b) **Fedorenko IV,** Wargo JA, Flaherty KT, Smalley KSM. BRAF inhibition generates a host/tumor niche that mediates therapeutic escape. J Invest Derm. 2015 Aug 24. 2015 Dec;135(12):3115-24. PMCID: PMC4648653
c) **Fedorenko IV**, Abel EV, Koomen JM, Fang B, Wood ER, Chen A, Fisher KJ, Iyengar S, Dahlman KB, Wargo JA, Flaherty KT, Sosman JA, Sondak VK, Messina JL, Gibney GT, Smalley KSM. Fibronectin induction abrogates the BRAF inhibitor response of BRAF V600E/PTEN-null melanoma cells. Oncogene. 2016 Mar 10;35(10):1225-35. PMCID: PMC4679729
d) Paraiso K.H.T., **Fedorenko, I.V.** , Cantini, L.P., Munko, A. C., Hall, M. S., Sondak, V. K., Messina, J. L., Flaherty, K.T., Smalley, K. S. Recovery of phospho-ERK activity allows melanoma cells to escape from BRAF inhibitor therapy. Br J Cancer 2010 Jun 8;102(12):1724-30. PMCID: PMC2883709

2. The biology of leptomeningeal metastasis. As new systemic therapies have improved the survival of late-stage melanoma patients, there is an emerging trend of increased incidence of leptomeningeal metastasis.

Leptomeningeal metastasis is a poorly understood and rapidly fatal complication of late stage cancer patients, most commonly occurring with melanoma, brest cancer, lung cancer and leukemia/lymphoma tumors. Patients with leptomeningeal metastasis have few effective therapeutic options, highlighting a critical need for better understanding of this devastating disease. To address this need, we have explored the proteomic and cellular composition of cerebrospinal fluid from leptomeningeal metastasis patients, examined how the cellular landscape compares to other metastatic sites and reveal a critical role of this microenvironment in resistance to targeted therapies. We have found that the meningeal stroma and factors secreted into the cerebrospinal fluid can protect melanoma cells from MAPK inhibitor therapy. We have found that the immune landscape at the leptomeninges is characterized by a repertoire of disfynctional T cells, alternatively activated pro-tumorigenic macrophages, and MDSC-like cells. We have also identified an accumulation of branched-chain keto acids in the CSF of LMD patients, and showed how it contributes to neurological degredation and immune suppression. This discovery has paved the way for adapting branched-chain keto acid lowering therapies to LMD. In this research space we have also made advancements in developing models, techniques and reagents for investigating leptomeningeal metastasis. We have developed patient-derived xenograft models, injectible models (allowing both immune compromised and immune-competent mouse models to be produced), *in vitro* primary circulating tumor cell models, and Ommaya-like reservoir devices for modeling intrathecal therapy administration in mice.

a) Khaled ML, Ren Y, Kundalia R, Alhaddad H, Chen Z, Wallace GC, Evernden B, Ospina OE, Hall M, Liu M, Darville LNF, Izumi V, Chen YA, Pilon-Thomas S, Stewart PA, Koomen JM, Corallo SA, Jain MD, Robinson TJ, Locke FL, Forsyth PA, **Smalley, I**. (2023). Branched-chain keto acids promote an immune-suppressive and neurodegenerative microenvironment in leptomeningeal disease. bioRxiv, 2023.2012.2018.572239. Preprint.
b) Alhaddad H, Ospina OE, Khaled ML, Ren Y, Vallebuona E, Boozo MB, Forsyth P, Pina Y, Macaulay R, Law V, Tsai KY, Cress WD, Fridley B, & **Smalley I.** (2023). Spatial transcriptomics analysis identifies a unique tumor-promoting function of the meningeal stroma in melanoma leptomeningeal disease. Cell Rep Med. 2024 Jun 18;5(6):101606.
c) **Smalley I**[#*], Chen Z[#], Phadke M, Wyatt C, Law W, Eroglu Z, Tran N, Forsyth P, Chen YA*, Smalley KSM*. Single-Cell Characterization of the Immune Microenvironment of Melanoma Brain and Leptomeningeal Metastases. Clinical Cancer Research. 25 May 2021, 27(14):4109-4125. # Contributed equally. ***Corresponding author**. PMCID: PMC8282775
d) **Smalley I,** Law V, Wyatt C, Fang B, Koomen, JM, Welsh E, Macaulay R, Forsyth PA, Smalley KSM. Serial proteomic analysis of CSF from patients with leptomeningeal melanoma metastases identifies signatures associated with disease progression and mediators of therapy resistance. Clin Cancer Res. 2020 May 1;26(9):2163-2175. PMCID: PMC7196498

3. Understanding melanoma brain metastasis. Melanoma brain metastasis is a challenging complication to treat as tumors at this site tend to be less sensitive to systemic therapy than extra-cranial disease. The mechanisms governing metastatic spread to the brain can provide insights on which tumors are likely to spread to the brain and possible prevention strategies. Understanding the cellular environment of melanoma brain metastasis and how it changes on therapy is also key to improving therapeutic outcomes for late-stage melanoma patients. My contribution to the field in the following work summarizes the current state of brain metastasis in melanoma patients, including treatments, challenges and the urgent need to better understand this unique metastatic site in order to improve therapies. We have uncovered EphA2 as a critical mediator of melanoma brain metastasis. Using single-cell analysis techniques, we have discovered therapy-specific changes in the immune landscape of brain metastases and identified a novel population of dendritic cells (DC3) which are strongly correlated with improved overall survival in patients.

a) **Smalley I**[#*], Chen Z[#], Phadke M, Wyatt C, Law W, Eroglu Z, Tran N, Forsyth P, Chen YA[*], Smalley KSM[*]. Single-Cell Characterization of the Immune Microenvironment of Melanoma Brain and Leptomeningeal Metastases. Clinical Cancer Research. 25 May 2021, 27(14):4109-4125. # Contributed equally. ***Corresponding author**. PMCID: PMC8282775
b) Zhang C, **Smalley I***, Emmons MF, Sharma R, Izumi V, Messina J, Koomen JM, Pasquale EB, Forsyth PA, Smalley KSM* Non-canonical EphA2 signaling is a driver of tumor-endothelial cell interactions and metastatic dissemination in BRAF inhibitor resistant melanoma. Journal for Investigative Dermatology. 2020 Sep 2;S0022-202X(20)32047-9 ***Corresponding author**. PMCID: PMC7921215
c) Eroglu Z, Holmen SL, Chen Q, Khushalani NI, Amaravadi R, Thomas R, Ahmed KA, Tawbi H, Chandra S, Markowitz J, **Smalley I**, Liu JKC, Chen YA, Najjar YG, Karreth FA, Abate-Daga D, Glitza IC, Sosman

JA, Sondak VK, Bosenberg M, Herlyn M, Atkins MB, Kluger H, Margolin K, Forsyth PA, Davies MA, Smalley KSM. Melanoma central nervous system metastases: An update to approaches, challenges, and opportunities. Pigment Cell Melanoma Res. 2019 May;32(3):458-469. PMCID: PMC7771318

d) Abate-Daga D, Ramello MC, **Smalley I**, Forsyth PA, Smalley KSM. The biology and therapeutic management of melanoma brain metastases. Biochem Pharmacol. 2018 Jul;153:35-45. PMCID: PMC5959746

4. Understanding and treating non-BRAF mutant melanoma. Although MAPK-targeted therapies have been greatly improving outcomes for *BRAF*-mutant melanoma patients, the field has seen little progress in the treatment of patients who do not have an activating mutation in BRAF. To address this issue, we investigated various strategies for successfully targeting these tumors. Using high-throughput proteomic analysis, we delineated the differences in basal signaling between *BRAF*-mutant and *BRAF*-WT melanomas, as well as their respective patters of signaling adaptations in response to MAPK-targeting therapies. Our analysis identified enriched signaling in a number of receptor tyrosine kinases as well as other targets of amuvatinib. We found amuvatinib to selectively inhibit growth, induce apoptosis and inhibit long-term colony formation growth of *BRAF*-WT melanomas. We demonstrated for the first time that AKT inhibition in combination with chemotherapy may have clinical activity in *BRAF*-WT melanoma and show that an autophagy inhibitor may prevent resistance to these drugs. This body of work provides evidence for single-agent and combination treatments worth investigating clinically to improve outcomes for *BRAF*-WT melanoma patients. I served as the primary or co-investigator on all these studies.

a) **Fedorenko IV**, Fang B, Munko AC, Paraiso KHT, Gibney GT, Koomen JM, Smalley KS. Phosphoproteomic analysis of basal and therapy-induced adaptive signaling networks in BRAF and NRAS mutant melanoma. Proteomics. 2015 Jan;15(2-3):327-39. PMCID: PMC4389901

b) **Fedorenko IV**, Fang, B, Koomen, JM, Gibney, GT, Smalley, KS. Amuvatinib has cytotoxic effects against NRAS but not BRAF mutant melanoma. Melanoma Research. 2014 Oct;24(5):448-53. PMCID: PMC4384823

c) Rebecca VW, Massaro R, **Fedorenko IV**, Gibney GT, Sondak VK, Amavaradi RK, Jin S, Maria-Engler SS, Kudchadkar RR, Smalley KSM: Inhibition of autophagy enhances the effects of the AKT inhibitor MK-2206 when combined with paclitaxel and carboplatin in BRAF wild-type melanoma. Pigment Cell and Melanoma Research 2014 May;27(3):465-78. PMCID: PMC3988257

d) **Fedorenko IV**, Gibney GT, Smalley KSM. NRAS mutant melanoma: biological behavior and future strategies for therapeutic management. Oncogene. 2013 Jun 20;32(25):3009-18. PMCID: PMC3978385

5. Novel analytic approaches for single-cell and spatial transcriptomics data. Some of the most important but challenging questions in understanding tumor biology and the tumor microenvironment require the use of cutting edge technologies with no established analytical methods. In order to be able to analyze the rare cells that are found in patient cerebrospinal fluid and characterize the tumor microenvironment as a whole, we have optimized single-cell RNAseq analysis pipelines and developed the interactive ISCVA analytics platform. Using this platform, we have been able to identify novel targets for immunotherapy in acral melanoma and compare the tumor microenvironment across leptomeningeal, brain and skin metastases in melanoma. We found the brain and the skin tumor microenvironment to be more closely related in the composition of the immune compartment, while leptomeningeal metastases (despite the anatomical proximity to the brain) were very unqiue in the severity of the immune-cold and dysfunctional immune landscape. We have also developed a MetLab tool for analyzing tumor heterogeneity, which has allowed us to better understand how melanoma tumor heterogeneity and diversity changes on BRAF inhibitor therapy. Finally, to better understand the tumor microenvironment within the spatial context of the tissue, we have developed novel analytical tools for use with spatial RNAseq data such as that originating from the 10x Visium or Nanostring GeoMx platforms.

a) Li J[#], **Smalley I[#],** Chen Z, Wu J, Phadke M, Teer J, Nguyen T, Karreth F, Koomen J, Sarnaik A, Zager J, Khushalani N, Tarhini A, Sondak V, Rodriguez P, Messina J, Chen YA, and Smalley KSM. Single cell characterization of the cellular landscape of acral melanoma identifies novel targets for immunotherapy. Clinical Cancer Research. March 04, 2022. # Contributed equally. PMCID: PMC9106889

b) Ospina OE, Wilson CM, Soupir AC, Berglund A, **Smalley I,** Tsai K, and Fridley BL. Quantification and visualization of the tumor microenvironment heterogeneity using spatial transcriptomics. Bioinformatics. February 2022. PMID: 35258565

c) Ospina OE, Manjarres-Betancur R, Gonzalez-Calderon G, Soupir AC, **Smalley I**, Tsai KY, Markowitz J, Khaled ML, Vallebuona E, Berglund AE, Eschrich SA, Yu X, Fridley BL. spatialGE Is a User-Friendly

Web Application That Facilitates Spatial Transcriptomics Data Analysis. Cancer Res. 2025 Mar 3;85(5):848-858.

d) Li J, **Smalley I**, Schell MJ, Smalley KSM, Chen YA. SinCHet: a MATLAB toolbox for single cell heterogeneity analysis in cancer. Bioinformatics. 017 Sep 15;33(18):2951-2953. PMCID: PMC5870537

Complete List of Published Work: 56 publications
https://www.ncbi.nlm.nih.gov/myncbi/inna.smalley.1/bibliography/public/