OMB No. 0925-0001 and 0925-0002 (Rev. 10/2021 Approved Through 09/30/2024)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
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NAME: Hatice Ülkü Osmanbeyoğlu

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

POSITION TITLE: Assistant Professor, Biomedical Informatics, University of Pittsburgh

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 DateMM/YYYY | FIELD OF STUDY |
| --- | --- | --- | --- |
| Northeastern University | BS | 05/04 | Computer Engineering |
| Carnegie Mellon University | MS | 09/06 | Electrical and Computer Engineering |
| University of Pittsburgh | MS | 04/09 | Bioengineering |
| University of Pittsburgh | PhD | 12/12 | Biomedical Informatics |
| Memorial Sloan Kettering Cancer Center | Postdoctoral | 03/13-11/18 | Computational Biology |

**A. Personal Statement**My laboratory develops integrative computational approaches to leverage heterogeneous omics datasets. We have expertise in applying machine learning methods to analyze numerous omics data types (such as ATAC-seq, RNA-seq, scRNA-seq, scATAC-seq, CITE-seq, spatial transcriptomics) and multi-spectral imaging datasets. My multi-omics integration, machine learning and cancer systems biology background is ideally suited for the proposed research plan. For example, my group developed a partially interpretable neural network model with encoder-decoder architecture, called Chromatin-informed Inference of Transcriptional Regulators Using Self-attention mechanism (CITRUS), to model the impact of somatic alterations on cellular states and further onto downstream gene expression programs (1). With the availability of single cell multi-omics data, my laboratory developed a computational method called SPaRTAN (Single-cell Proteomic and RNA based Transcription factor Activity Network) by integrating parallel single-cell proteomic, and transcriptomic data (based on CITE-seq) with cis-regulatory information (e.g. transcription factor (TF) – target priors), to predict cell-specific TF and surface protein activities (2,3). We applied and experimentally test SPaRTAN using CITE-seq datasets from peripheral blood mononuclear cells (PBMCs) and then illustrate its broader utility by predicting signaling coupled TF activities in tumor infiltrating CD8+ T cells in the context of malignant peritoneal and pleural mesothelioma. Recently, we applied SPaRTAN to CITE-seq datasets for patients with varying severities of COVID-19 and healthy controls and developed a web resource linking surface proteins to TFs to identify cellular heterogeneity in host responses during SARS-CoV-2 infection (4). Recently, we also worked on several spatial data analysis projects and create web resources (e.g. 5). The proposed research builds organically on our prior work. To enhance accessibility, we plan to integrate these methods into user-friendly software packages and develop a web resource for the broader cancer research community.

**Publications/Preprints that highlight our experience and qualifications for this project**

1. Tao Y\*, Ma X\*, Palmer D, Schwartz R, Lu X, **Osmanbeyoglu HU**. Interpretable deep learning for chromatin-informed inference of transcriptional programs driven by somatic alterations across cancers. Nucleic Acids Res. 2022. Epub 2022/10/17. doi: 10.1093/nar/gkac881. PubMed PMID: 36243974. (\*equal contribution)
2. Ma X\*, Somasundaram A\*, Qi Z, Hartman D, Singh H, **Osmanbeyoglu HU** (2021) SPaRTAN, a computational framework for linking cell-surface receptors to transcriptional regulators. ***Nucleic acids research***, doi:10.1093/nar/gkab745 (\*equal contribution)
3. Sagan A, Ma X, Ramjattun K, **Osmanbeyoglu HU**. Linking Expression of Cell-Surface Receptors with Transcription Factors by Computational Analysis of Paired Single-Cell Proteomes and Transcriptomes. ***Methods Mol Biol*** 2023, 2660:149-169.
4. Ramjattun K\*, Ma X\*, Singh H, Gao SJ, **Osmanbeyoglu HU**. COVID-19db linkage maps of cell surface proteins and transcription factors in immune cells. ***J Med Virol***. 2023;95(6):e28887. Epub 2023/06/21. doi: 10.1002/jmv.28887. PubMed PMID: 37341527. (\*equal contribution)
5. Ma X, Lembersky D, Kim ES, Bruno TC, Testa JR, **Osmanbeyoglu HU**. Spatial landscape of malignant pleural and peritoneal mesothelioma tumor immune microenvironment. ***bioRxiv*** 2023.09.06.556559; doi: https://doi.org/10.1101/2023.09.06.556559

**Ongoing projects that I would like to highlight include:**

R35 GM146989 Osmanbeyoglu (PI) 09/15/22 - 08/31/2027

Computational methods for delineating cell context-specific regulatory programs

R01 CA276279 Casio (PI), Role: co-investigator 06/07/2023 - 05/31/2028

The Role of EGFL6 in Ovarian Tumor Immunity

R01 CA276279 Buckanovich (PI), Role: co-investigator 06/07/2023 - 05/31/2028

Evaluating unique aspects of quiescent ovarian cancer cell biology for therapeutic targets

**Completed Research Support (during the past three years)**

The ICI Fund (Innovation in Cancer Informatics) Osmanbeyoglu (PI) 06/01/19 - 05/30/22

Integrative computational framework for linking cell surface proteins to downstream transcriptional programs in cells

R01 CA218026 Buckanovich (PI), Role: co-investigator 12/01/21 - 11/30/23

The Function of EGFL6 in Ovarian Cancer Cell Biology, Tumor Initiation, and Therapy

R00 CA207871 Osmanbeyoglu (PI) 12/01/18 - 11/30/23 (NCE)

Algorithms to link signaling pathways with transcriptional programs for precision medicine

**B. Positions, Scientific Appointments, and Honors**

**Positions and Scientific Appointments**

2020 – Present Assistant Professor, Department of Biostatistics, University of Pittsburgh, Pittsburgh, PA

2019 – Present Assistant Professor, Department of Bioengineering, University of Pittsburgh, Pittsburgh, PA

2018 – Present Assistant Professor, Department of Biomedical Informatics, University of Pittsburgh, Pittsburgh, PA

2018 – Present Member, UPMC Hillman Cancer Center, Pittsburgh, PA

2016 – 2018 Postdoctoral Research Associate, Department of Computational and Systems Biology, Memorial Sloan Kettering Cancer Center, New York, NY

2013 – 2016 Postdoctoral Research Scholar, Department of Computational Biology, Memorial Sloan Kettering Cancer Center, New York, NY

2009 – 2012 Graduate Researcher, Department of Biomedical Informatics, University of Pittsburgh, Pittsburgh, PA

2006 – 2009 Graduate Researcher, Department of Bioengineering, University of Pittsburgh,

Pittsburgh, PA

2004 – 2005 Test Engineer, Ambient Corporation, Boston, MA

**Other Experience and Professional Memberships**

2021 – Present Guest editor, PLOS Computational Biology

2021 Co-chair for COVID-19 Challenge Program Ninth IEEE International Conference on Healthcare Informatics August 9-12, 2021. Victoria, British Columbia, Canada

2019 – 2021 Member, Women’s Task Force, Pittsburgh, PA, USA

2019 – 2023 Member, Program committee of ISMB/ECCB

2017 – Present Referee of the IEEE/ACM Transactions on Computational Biology and Bioinformatics, Clinical Colorectal Cancer, Bioinformatics, BMC Bioinformatics, PLOS Computational Biology, PLOS ONE, Nature Communications, Nature

2017 – 2019 Member, Program Committee, Workshop on Computation Biology, ICML

2017 – Present Member, American Association for Cancer Research

2017 Referee of the Women in Machine Learning Workshop

2013 – 2014 Representative, NCI’s Integrative Cancer Biology Program’s Early-Stage Investigators

Steering Committee Meeting

2012 Judge, Intel’s International Science & Engineering Fair, Pittsburgh, PA, USA

2012 Judge, Pittsburgh Regional Science Fair (PSEF), Pittsburgh, PA, USA

2006 – Present Member, International Society for Computational Biology

**Honors**

2022 Early Investigator Advancement Program (EIAP) Scholar

2019 Hillman Early-Career Fellow for Innovative Cancer Research

2017 EMBL Corporate Partnership Fellowship for Cancer Genomics conference at EMBL, Germany

2017 NCI Scholarship for Experimental Models of Human Cancer Course at The Jackson Laboratory

2017 Memorial Sloan Kettering Postdoctoral Research Award

2016 NIH/NCI K99/R00 Pathway to Independence Award

2014 Travel Award to the ISMB Conference

2012 Finalist, Best Performer in Phase 2 of DREAM7 Challenge, Breast Cancer Prognosis

2012 Travel Award to the Workshop for Women in Machine Learning

2012 NSF Travel Award to the Research in Computational Molecular Biology Conference

2012 Finalist, Best Trainee Paper Award, University of Pittsburgh, PA

2011 Doctoral Comprehensive Exam passed with High Honors, University of Pittsburgh, PA

2004 Winner, Computer Engineering Capstone Design Group Competition,

Northeastern University, Boston, MA

2004 Sears B. Condit Award, Northeastern University, Boston, MA

2003 Outstanding Junior Award, Northeastern University, Boston, MA

2002 – 2004 Dean’s List, Northeastern University, Boston, MA

**C. Contributions to Science**

**1. Cancer systems biology**. I have developed novel integrative algorithms for modeling gene regulatory programs using large-scale tumor data sets where multiple parallel sources of molecular profiling data are available. Distinguishing features of my methods are the use of regulatory sequence information together with modern supervised learning algorithms to train the models. For instance, I developed a novel statistical approach for exploiting parallel proteomics and mRNA expression data generated for large tumor sets through projects such as The Cancer Genome Atlas (TCGA) to link dysregulation of upstream signaling pathways with altered transcriptional response via the transcriptional circuitry. I used these models to mechanistically interpret the cancer-specific impact of somatic alterations in terms of dysregulated transcription factors (TFs) and signaling pathways. These studies demonstrate the power of integrative “big” data analysis for cancer research.

1. **Osmanbeyoglu HU**, Pelossof R, Bromberg JF, Leslie CS (2014) Linking signaling pathways to transcriptional response in breast cancer. ***Genome Res*** 24(11):1869-80. PMID: 25183703
2. **Osmanbeyoglu HU**, Toska E, Chan C, Baselga J, Leslie CS (2017) Pan-cancer modeling predicts the context-specific impact of somatic mutations on transcriptional programs. ***Nature Communications*** 8, 14249. PMID: 28139701
3. **Osmanbeyoglu HU#**, Shimizu F\*, Rynne-Vidal A\*, Alonso-Curbelo D\*, Chen HA, Wen HY, Yeung TL, Jelinic P, Ravazi P, Lowe SW, Mok SC, Chiosis G, Levine DA, Leslie CS#**,** Chromatin-informed inference of transcriptional programs in gynecologic and basal breast cancers (2019), ***Nature Communications***, **10**(1):4369. PMID: 31554806(**#=co-corresponding authors)**
4. Tao Y\*, Ma X\*, Palmer D, Schwartz R, Lu X, **Osmanbeyoglu HU**. Interpretable deep learning for chromatin-informed inference of transcriptional programs driven by somatic alterations across cancers. ***Nucleic Acids Res***. 2022. Epub 2022/10/17. doi: 10.1093/nar/gkac881. PubMed PMID: 36243974.

**2. Integrative methods for single cell and spatial biology: I have developed machine learning methods for single-cell/spatial multi-omics integration, integrating data from different omic layers (such as genomics, proteomics, transcriptomics, epigenomics) to gain a comprehensive understanding of cellular processes and disease mechanisms.**

1. Ma X\*, Somasundaram A\*, Qi Z, Hartman D, Singh H, **Osmanbeyoglu HU** (2021) SPaRTAN, a computational framework for linking cell-surface receptors to transcriptional regulators. ***Nucleic acids research***, doi:10.1093/nar/gkab745
2. Ramjattun K\*, Ma X\*, Singh H, Gao SJ, **Osmanbeyoglu HU**. (2023) COVID-19db linkage maps of cell surface proteins and transcription factors in immune cells. ***J Med Virol***. 2023;95(6):e28887. Epub 2023/06/21. doi: 10.1002/jmv.28887. PubMed PMID: 37341527.
3. Sagan A, Ma X, Ramjattun K, **Osmanbeyoglu HU**. Linking Expression of Cell-Surface Receptors with Transcription Factors by Computational Analysis of Paired Single-Cell Proteomes and Transcriptomes. ***Methods Mol Biol*** 2023, 2660:149-169.

4. **Omics approaches in immunology and immunotherapy.** I am also involved in many collaborative projects in immunology. For example, I developed an analysis pipeline for sequencing data sets that profile the T cellreceptor (TCR) repertoire in collaboration with the laboratory of Dr. Alexander Rudensky (HHMI and MSKCC). We investigated the genetic control of regulatory T cell development and, in particular, its selection of the TCR repertoire. Through our study of CNS3, a cis-regulatory element in the Foxp3 locus, we found a previously unrecognized mechanism that diversifies Treg cell TCR repertoire and its significance in achieving sufficient self-tolerance. I also worked with the laboratory of Dr. Ming Li (MSKCC) on elucidating the role of Ets family TFs in T cell homeostasis. Our work dissected novel transcriptional programs regulating immune responses in anticipation of future T-cell-based immunotherapies. In these projects, I led high throughput data analysis.

1. Feng Y, Veeken J, Shugay M, Putintseva EV, **Osmanbeyoglu HU**, Dikiy S, Hoyos BE, Moltedo B,Hemmers S, Treuting P, Leslie CS, Chudakov M, Rudensky AY (2015) A mechanism for expansion of regulatory T-cell repertoire and its role in self-tolerance. ***Nature***, 528(7580):132-136. PMID:26605529
2. Luo C, **Osmanbeyoglu HU**, Do MH, Bivona MR, Toure A, Kang D, Xie Y, Leslie CS, Li M (2017) Ets transcription factor GABP controls T cell homeostasis and immunity. ***Nature Communications*** 8,1062. PMID: 29051483
3. Cascio S, Chandler C, Zhang L, Sinno S, Gao B, Onkar S, Bruno T, Vignali D, Mahdi H, **Osmanbeyoglu HU**, Vlad A, Coffman L, Buckanovich RJ (2021) Blocking of CA-MSC-induced desmoplasia reprograms the tumor immune microenvironment and enhances the efficacy of PD-L1 therapy. ***Sci Adv***. 2021 Nov 12;7(46):eabi5790.
4. Onkar S, Cui J, Zou J, Cardello C, Cillo AR, Uddin MR, Sagan A, Joy M, **Osmanbeyoglu HU**, Pogue-Geile KL, McAuliffe PF, Lucas PC, Tseng GC, Lee AV, Bruno TC, Oesterreich S, Vignali DAA. Immune landscape in invasive ductal and lobular breast cancer reveals a divergent macrophage-driven microenvironment. **Nature Cancer**. 2023. doi: 10.1038/s43018-023-00527-w.

**4. Cancer Epigenetics and drug response.** I have expertise in the analysis of many next generation sequencing data types (DNase-seq, ATAC-seq, transcription factor and histone modification ChIP-seq, RNA-seq, GRO-seq, Repli-seq) as well as high throughput chromatin conformation capture technologies (especially ChIA-PET). During my graduate studies, I integrated diverse high throughput data to understand estrogen receptor (ER)-mediated transcription in breast cancer. This work provides insights into dysregulation of expression programs in ER-positive breast cancer. Later, I applied my expertise, in collaboration with Dr. José Baselga’s laboratory, to investigate the epigenetic mechanisms leading to the activation of ER-dependent transcription upon PI3Kα inhibition in breast cancer models. Our study also revealed that understanding then interaction between cell signaling and epigenetic regulation at a systems levelis critical for design of therapeutics.

1. **Osmanbeyoglu HU**, Lu KN, Oesterreich S, Day RS, Benos PV, Coronnello C, Lu X (2013) Estrogen represses gene expression through reconfiguring chromatin structures. ***Nucleic acids research*** 41(17):8061-71. PMID: 23821662
2. Toska E, **Osmanbeyoglu HU\***, Castel P\*, Chan C, Dickler M, Hendrickson RC, Scaltriti M, Leslie CS, Armstrong SA, Baselga J (2017) PI3K pathway regulates ER-dependent transcription in breast cancer through the epigenetic regulator KMT2D, ***Science***, 355 (6331), 1324-1330. PMID: 28336670
3. Watters RJ, Hartmaier RJ, **Osmanbeyoglu HU**, Gillihan RM, Rae J, Liao L, Chen K, Li W, Lu X, Oesterreich S (2017) Steroid receptor coactivator-1 can regulate osteoblastogenesis independently of estrogen, ***Molecular and Cellular Endocrinology***, 448:21-27. PMID:31554806
4. Lee S, **Osmanbeyoglu HU** (2022) Chromatin accessibility landscape and active transcription factors in primary human invasive lobular and ductal breast carcinomas, ***Breast Cancer Research*** **24,** 54.

5. **Developing machine-learning algorithms for biomedical applications.** I designed machine-learning algorithms that can be used when labeled data is scarce and difficult to obtain experimentally in the case of transmembrane helix prediction and host-viral protein-protein interaction prediction. I also utilized natural language processing methods to compare the pattern landscape of microbial proteomes.

1. **Osmanbeyoglu HU**, Wehner JA, Carbonell JG, Ganapathiraju MK (2010) Active machine learning for transmembrane helix prediction. ***BMC Bioinformatics*** 11 Suppl 1: S58. PMCID: PMC3009531
2. **Osmanbeyoglu HU**, Ganapathiraju MK (2011)Rapid deployment of viral-human interactome prediction for new viruses. Proc of the American Medical Informatics Association Summit onTranslational Bioinformatics*.*
3. **Osmanbeyoglu HU**, Ganapathiraju MK (2011) N-gram analysis of 970 microbial organisms reveals presence of biological language models. ***BMC Bioinformatics*** 12: 12. PMID: 21219653
4. **Osmanbeyoglu HU**, Hartmaier RJ, Oesterreich S, Lu X (2012) Improving ChIP-seq peak-calling for functional co-regulator binding by integrating multiple sources of biological information. ***BMC Genomics*** 13 Suppl 1: S1. PMCID: PMC3439677

Complete List of Published Work in MyBibliography & Google Scholar:

<https://www.ncbi.nlm.nih.gov/myncbi/1VSu0TlSb8ikW/bibliography/public/>

<https://scholar.google.com/citations?user=YzCsmdgAAAAJ&hl=en>