OMB No. 0925-0001/0002 (Rev. 08/12 Approved Through 8/31/2015)

BIOGRAPHICAL SKETCH

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| --- |
| NAME: Ostrowski, Michael |
| eRA COMMONS USER NAME (agency login): MIKE\_OSTROWSKI |
| POSITION TITLE: Professor |

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

|  |  |  |  |
| --- | --- | --- | --- |
| INSTITUTION AND LOCATION | DEGREE (if applicable) | Completion Date  MM/YYYY | FIELD OF STUDY |
| Illinois Benedictine College, Lisle, IL | BS | 05/1975 | Chemistry |
| University of South Carolina, Columbia, SC | PHD | 01/1980 | Chemistry |
| National Cancer Institute, Lab of Tumor Virus Genetics, Bethesda, MD | Fellow | 05/1983 | Molecular Biology |

### A. PERSONAL STATEMENT

I currently serve as Professor and Vice-Chair in the Cancer Biology & Genetics Department in the College of Medicine and have served as co-director of the Ohio University Comprehensive Cancer Center Molecular Biology and Cancer Genetics Program since 1999. During the last two competitive renewals of our cancer center grant, this program has been rated as “Outstanding”, and was rated “Exceptional” during the most recent renewal review in 2015. I have served as member of study sections for both ACS and NIH, and currently frequently review NCI P01 proposals and special review panels. I serve on the external advisory boards for two NCI-designated cancer centers.

I am committed to team science and have established a number of successful collaborations over the past decade, including with my co-PIs on a NCI PO1 project, Gustavo Leone, Lisa Yee and Morag Park. These collaborations have helped me to increase my labs productivity as measured by both publications and grant support. I have over 130 peer reviewed publications. I have been continually funded by NIH since 1986 and am currently corresponding PI on an MPI R01 grant, renewed in 2015, that focuses on preventing the destruction of bone that occurs in tumor metastasis to that organ and the NCI P01 grant that was competitively renewed in 2012.

I am committed to education and training, and have trained 33 PhD students and currently have four PhD trainees in the lab. I have also trained 22 postdoctoral fellows, and currently work with two postdoctoral trainees. In my former role as department chair and CCC program leader I have helped organize a system for active career mentoring of junior faculty, and for grant reviews of all faculty.

**Publications Relevant to the Proposal**:

1. Trimboli AJ, Cantemir-Stone CZ, Li F, Wallace JA, Merchant A, Creasap N, Thompson JC, Caserta E, Wang H, Chong JL, Naidu S, Wei G, Sharma SM, Stephens JA, Fernandez SA, Gurcan MN, Weinstein MB, Barsky SH, Yee L, Rosol TJ, Stromberg PC, Robinson ML, Pepin F, Hallett M, Park M, **Ostrowski MC\***, Leone G\*. (\*co-corresponding authors) Pten in stromal fibroblasts suppresses mammary epithelial tumours. Nature. 2009 Oct 22;461(7267):1084-91 PubMed PMID: [19847259](http://www.ncbi.nlm.nih.gov/pubmed/19847259/); PubMed Central PMCID: [PMC2767301](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2767301/). \*co-corresponding authors
2. Bronisz A, Godlewski J, Wallace JA, Merchant AS, Nowicki MO, Mathsyaraja H, Srinivasan R, Trimboli AJ, Martin CK, Li F, Yu L, Fernandez SA, Pécot T, Rosol TJ, Cory S, Hallett M, Park M, Piper MG, Marsh CB, Yee LD, Jimenez RE, Nuovo G, Lawler SE, Chiocca EA, Leone G\*, **Ostrowski MC\*** Reprogramming of the tumour microenvironment by stromal PTEN-regulated miR-320. Nat Cell Biol. 2011 Dec 18;14(2):159-67. PubMed PMID: [22179046](http://www.ncbi.nlm.nih.gov/pubmed/22179046/); PubMed Central PMCID: [PMC3271169](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3271169/). \*co-corresponding authors
3. Liu X, Pitarresi JR, Cuitiño MC, Kladney RD, Woelke SA, Sizemore GM, Nayak SG, Egriboz O, Schweickert PG, Yu L, Trela S, Schilling DJ, Halloran SK, Li M, Dutta S, Fernandez SA, Rosol TJ, Lesinski GB, Shakya R, Ludwig T, Konieczny SF, Leone G, Wu J, Ostrowski MC. 2016. Genetic ablation of Smoothened in pancreatic fibroblasts increases acinar-ductal metaplasia. Genes Dev. Epublished Sept 15. PMID: [27633013](https://www.ncbi.nlm.nih.gov/pubmed/27633013). PubMed Central PMCID in Progress

B. POSITIONS AND HONORS

Positions and Employment

|  |  |
| --- | --- |
| 1983-1985 | Senior Staff Fellow, Lab of Tumor Virus Genetics, National Cancer Institute, Bethesda, MD |
| 1985-1995 | Assistant Professor, Department of Microbiology & Immunology, Duke University Medical Center, Durham, NC |
| 1995-1999  1999-2006  1999-Present | Associate Professor, Molecular Genetics Department, Ohio State University, Columbus, OH  Professor, Molecular Genetics Department, Ohio State University, Columbus, OH  Co-Director, Molecular Biology & Cancer Genetics Program, Ohio State University Comprehensive Cancer Center |
| 2006-2014  2008-2014 | Professor & Chair, Molecular & Cellular Biochemistry Department, Ohio State University Medical Center, Columbus, OH  Chair, Dean’s Basic Science Research Committee, College of Medicine, Ohio State University Medical Center |
| 2010-Present | Co-Director, Solid Tumor Biology Program, Ohio State University Comprehensive Cancer Center |
| 2014 - | Professor and Vice-Chair, Cancer Biology & Genetics Department , Ohio State University Medical Center, Columbus, OH |

Other Experience and Professional Memberships

|  |  |
| --- | --- |
| 1990 - 1994 | Member, Personnel Section C, American Cancer Society |
| 1999 - | Co-Director, Molecular Biology & Cancer Genetics Program, Ohio State University Comprehensive Cancer Center |
| 2000 - 2004 | Member, Cell Cycle and Growth Control Study Section, American Cancer Society |
| 2002 - 2007 | Member, Skeletal Biology, Development and Disease (SBDD) Study Section, NIAMSD, NIH |
| 2003 - 2003 | Review Panel Member, Biocenter Oulu, Finland |
| 2003 - 2008 | Editorial Board Member, Journal of Biological Chemistry |
| 2009 - 2009 | Program Committee & Chair for TME Mini-Symposium, AACR 100th Annual Meeting, Denver, CO |
| 2012 - 2012 | Review Panel Member, Helmholtz Research School in Cancer Biology, DKFZ, Heidelberg, Germany |
| 2013 - 2013 | Program Planning Committee, Chair for Tumor Microenvironment Heterogeneity Education Session, AACR 104th Annual Meeting, Washington, DC |
| 2013 - 2014  2015, 2016 | Co-Chair, Education Committee, Association of Medical and Graduate Departments of Biochemistry  Co-Organizer, 1st and 2nd Great Lakes Breast Cancer Symposium, Case Western Cancer Center |
| 2015, 2016 | Review Panel Member, NCI R35 Outstanding Investigator Awards |

Honors

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| --- | --- |
| 1986 | Scholar, Leukemia Society of America |
| 1994 | Visiting Scholar Award, University of Queensland, Australia |
| 2004 | Elected Fellow, American Association for the Advancement of Research |
| 2004 | Distinguished Professor, College of Biological Science, Ohio State University |

### C. Contribution to Science

**Complete List of Published Work:**

<http://www.ncbi.nlm.nih.gov/sites/myncbi/michael.ostrowski.2/bibliography/47919511/public/?sort=date&direction=descending>

***H-index=56 (Google Scholar), 49 (Thomas Reuters Web of Science)***

1. With Gustavo Leone, we made the seminal observation that the loss of tumor suppressor PTEN in normal mammary fibroblasts causes a dramatic increase in the volume and bioactivity of the tumor microenvironment and that these changes dramatically accelerate mammary tumor progression. Our mouse model was the first to accurately reflect the human breast tumor microenvironment both at the cellular and molecular level, and allows mechanisms involved in communication between the different cell compartments to be studied. For example, loss of PTEN in the stroma leads to repression of microRNAs-320 and activation of Ets2, leading to production of a malignant secretome that promotes inflammation, angiogenesis and tumor progression. We have recently extended our studies of the tumor microenvirnment to pancreatic cancer and have recently demonstrated that ablation of the Hedgehog pathway in pancreatic stromal fibroblasts increases initiation and growth of pancreatic tumor cells through a non-canonical Akt-Gli2 pathway that leads to activation of EGFR signaling in epithelial cells,
   1. Trimboli AJ, Cantemir-Stone CZ, Li F, Wallace JA, Merchant A, Creasap N, Thompson JC, Caserta E, Wang H, Chong JL, Naidu S, Wei G, Sharma SM, Stephens JA, Fernandez SA, Gurcan MN, Weinstein MB, Barsky SH, Yee L, Rosol TJ, Stromberg PC, Robinson ML, Pepin F, Hallett M, Park M, **Ostrowski MC\***, Leone G\*. Pten in stromal fibroblasts suppresses mammary epithelial tumours. Nature. 2009 Oct 22;461(7267):1084-91. PubMed PMID: [19847259](http://www.ncbi.nlm.nih.gov/pubmed/19847259/); PubMed Central PMCID: [PMC2767301](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2767301/).

\*Co-corresponding authors

* 1. Bronisz A, Godlewski J, Wallace JA, Merchant AS, Nowicki MO, Mathsyaraja H, Srinivasan R, Trimboli AJ, Martin CK, Li F, Yu L, Fernandez SA, Pécot T, Rosol TJ, Cory S, Hallett M, Park M, Piper MG, Marsh CB, Yee LD, Jimenez RE, Nuovo G, Lawler SE, Chiocca EA, Leone G\*, **Ostrowski MC\***. Reprogramming of the tumour microenvironment by stromal PTEN-regulated miR-320. Nat Cell Biol. 2011 Dec 18;14(2):159-67. PubMed PMID: [22179046](http://www.ncbi.nlm.nih.gov/pubmed/22179046/); PubMed Central PMCID: [PMC3271169](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3271169/).

\*Co-corresponding authors

c. Liu X, Pitarresi JR, Cuitiño MC, Kladney RD, Woelke SA, Sizemore GM, Nayak SG, Egriboz O, Schweickert PG, Yu L, Trela S, Schilling DJ, Halloran SK, Li M, Dutta S, Fernandez SA, Rosol TJ, Lesinski GB, Shakya R, Ludwig T, Konieczny SF, Leone G, Wu J, **Ostrowski MC**. 2016. Genetic ablation of Smoothened in pancreatic fibroblasts increases acinar-ductal metaplasia. Genes Dev. Epublished Sept 15. PMID: [27633013](https://www.ncbi.nlm.nih.gov/pubmed/27633013). PubMed Central PMCID in Progress

2. With Gustavo Leone, we provided the first in vivo evidence for epithelial-mesenchymal transition in breast cancer models, demonstrating that EMT depended on the oncogene driving tumor progression. We were the first to develop and characterize knockin mice with Pten catalytic domain mutations modeled on mutations found in Cowden syndrome patients. This work demonstrated that different tumor spectrums were obtained with the different alleles. More recently we created and studied a model with a patient-derived mutation in the C2 domain of Pten, finding that this mutation predisposed to breast tumors, but not to thyroid, endometrial or prostate tumors, the other common tumors associated with germline mutation of Pten.

1. Trimboli AJ, Fukino K, de Bruin A, Wei G, Shen L, Tanner SM, Creasap N, Rosol TJ, Robinson ML, Eng C, **Ostrowski MC**\*, Leone G\*. Direct evidence for epithelial-mesenchymal transitions in breast cancer. Cancer Res. 2008 Feb 1;68(3):937-45. PubMed PMID: 18245497.

\*Co-corresponding authors

1. Wang H, Karikomi M, Naidu S, Rajmohan R, Caserta E, Chen H-Z, Rawahneh M, Moffitt J, Stephens J, Fernandez SA, Weinstein M, Wang X, Sadee W, La Perle K, Stromberg P, Rosol TJ, Eng C, **Ostrowski MC**\* and Gustavo Leone\*. (\*co-corresponding authors).Allele-specific Tumor Spectrum in Pten Knockin Mice PNAS USA 2010 107:5142-5147.  [PubMed PMID: 20194734](http://www.ncbi.nlm.nih.gov/pubmed/?term=PMID%3A+20194734) PubMed Central PMCID: [PMC2841921](http://www.ncbi.nlm.nih.gov/pubmed/?term=PMID%3A+20194734)
2. Caserta E, Egriboz O, Wang H, Martin C, Koivisto C, Pecot T, Kladney R, Shen C, Shim K-S, Pham T, Karikomi MK, Mauntel MJ, Majumder S, Cuitino MC, Tang X, Srivastava A, Yu L, Wallace J, Mo X, Park M, Fernandez SA, Pilarski R, La Perle KM, Rosol TJ, Coppola V, Castrillon DH, Timmers C, Cohn DE, O'Malley DM, Backes F, Suarez A, Goodfellow P, Chamberlin HM, Macrae ER, Shapiro CL, **Ostrowski, MC**\*and Leone G\*. (\*co-corresponding authors). Non-catalytic PTEN missense mutation predisposes to organ-selective cancer development in vivo. Genes & Development 2015. 29(16):1707-20. PubMed PMID: [26](http://www.ncbi.nlm.nih.gov/pubmed/22179046/)302789; PubMed Central PMCID: 1489PMC4569.

3. Our group identified Ets1 and Ets2 as direct targets of ras/MAPK signaling, and demonstrated that Ets factors are required for ras-medicated cellular transformation. In more recent work, using a conditional Ets2 allele generated in our group, we demonstrated these factors are required for angiogenesis during development. Further Ets2, located on human chromosome 21, contributes to tumor-suppression mediated by trisomy in mouse models of Down's syndrome, providing the first direct experimental evidence that trisomy of the minimal Down's 21 region suppresses cancer.

* 1. Langer, S.J., Bortner, D.M., Roussel, M.R., Sherr, C.J., and **Ostrowski, M.C**. 1992. Mitogenic signaling by the CSF-1 receptor and ras is suppressed by the ets-2 DNA binding domain and restored by myc overexpression. Mol. Cell. Biol. 12: 5355-5362. PubMed PMID: [1448070](http://www.ncbi.nlm.nih.gov/pubmed/2851730/); PubMed Central PMCID: [PMC360473](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC365446/).
  2. Yang BS, Hauser CA, Henkel G, Colman MS, Van Beveren C, Stacey KJ, Hume DA, Maki RA, **Ostrowski MC**. Ras-mediated phosphorylation of a conserved threonine residue enhances the transactivation activities of c-Ets1 and c-Ets2. Mol Cell Biol. 1996 Feb;16(2):538-47. PubMed PMID: [8552081](http://www.ncbi.nlm.nih.gov/pubmed/8552081/); PubMed Central PMCID: [PMC231032](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC231032/).
  3. Sussan TE, Yang A, Li F, Ostrowski MC, Reeves RH. Trisomy represses Apc(Min)-mediated tumours in mouse models of Down's syndrome. Nature. 2008 Jan 3;451(7174):73-5. PubMed PMID: [18172498](http://www.ncbi.nlm.nih.gov/pubmed/18172498/).
  4. Wei G, Srinivasan R, Cantemir-Stone CZ, Sharma SM, Santhanam R, Weinstein M, Muthusamy N, Man AK, Oshima RG, Leone G, **Ostrowski MC**. Ets1 and Ets2 are required for endothelial cell survival during embryonic angiogenesis. Blood. 2009 Jul 30;114(5):1123-30. PubMed PMID: [19411629](http://www.ncbi.nlm.nih.gov/pubmed/19411629/); PubMed Central PMCID: [PMC2721789](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2721789/).

4. We have a long-standing interest in CSF1R signaling in myeloid cells/macrophages and demonstrated that Ets2 is a nuclear target of CSF1R signaling, activated by Erk and Jnk kinases. We have studied this pathway in breast cancer models and demonstrated that the CSF1R/Ets2 pathway in tumor macrophages promotes tumor metastasis. Targets of the pathway include a set of microRNAs that promote M2-like macrophage phenotypes, including angiogenesis and tumor growth. These miRs are expressed in myeloid cells at the sites of tumor metastasis in human patient samples and in non-canonical blood monocytes in stage IV breast cancer patients.

* 1. Fowles, L.F., Martin, M.L., Nelsen, L.L., Stacey, K.J., Redd, D. Clark, Y.M., Nagamine, Y. McMahon, M., Hume, D.A., and **Ostrowski M.C**. 1998. Persistent Activation of MAP kinases p42/p44 and ets-2 phosphorylation in response to CSF-1/c-fms signaling. Mol. Cell. Biol. 18, 5148-5156. PubMed PMID: [9710599](http://www.ncbi.nlm.nih.gov/pubmed/11027273/); PubMed Central PMCID: [PMC109100](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC86413/).
  2. Smith JL, Schaffner AE, Hofmeister JK, Hartman M, Wei G, Forsthoefel D, Hume DA, **Ostrowski MC**. ets-2 is a target for an akt (Protein kinase B)/jun N-terminal kinase signaling pathway in macrophages of motheaten-viable mutant mice. Mol Cell Biol. 2000 Nov;20(21):8026-34. PubMed PMID: [11027273](http://www.ncbi.nlm.nih.gov/pubmed/11027273/); PubMed Central PMCID: [PMC86413](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC86413/).
  3. Zabuawala T, Taffany DA, Sharma SM, Merchant A, Adair B, Srinivasan R, Rosol TJ, Fernandez S, Huang K, Leone G, **Ostrowski MC**. An ets2-driven transcriptional program in tumor-associated macrophages promotes tumor metastasis. Cancer Res. 2010 Feb 15;70(4):1323-33. PubMed PMID: [20145133](http://www.ncbi.nlm.nih.gov/pubmed/20145133/); PubMed Central PMCID: [PMC2822898](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2822898/).
  4. Mathsyaraja H, Thies K, Taffany DA, Deighan C, Liu T, Yu L, Fernandez SA, Shapiro C, Otero J, Timmers C, Lustberg MB, Chalmers J, Leone G, **Ostrowski MC**. CSF1-ETS2-induced microRNA in myeloid cells promote metastatic tumor growth. Oncogene. 2014 Sep 22;34(28)3651-61 PubMed PMID: [25241894](http://www.ncbi.nlm.nih.gov/pubmed/25241894/); PubMed Central PMCID: [PMC4369473](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4369473/).

5. We have studied how myeloid precursors differentiate into bone resorbing osteoclasts. These studies combine genetic models, molecular biology and functional genomics to address the fundamental problem of how myeloid precursors are committed to this specific cell lineage. Our work has revealed that the microphthalmia transcription factor (MITF) partners with the myeloid master regulator Ets-factor PU.1 to regulate genes required for osteoclast differentiation and function. MITF is a direct target of a RANKL/p38 MAPK pathway required for osteoclast differentiation. This work contributes to a general understanding of how committed precursors are directed by local signals to differentiate into one cell type but not related cells types, that is, to an osteoclast and not a macrophage or dendritic cell.

1. Luchin A, Suchting S, Merson T, Rosol TJ, Hume DA, Cassady AI, **Ostrowski MC**. Genetic and physical interactions between Microphthalmia transcription factor and PU.1 are necessary for osteoclast gene expression and differentiation. J Biol Chem. 2001 Sep 28;276(39):36703-10. PubMed PMID: [11481336](http://www.ncbi.nlm.nih.gov/pubmed/11481336/).
2. Mansky KC, Sankar U, Han J, **Ostrowski MC**. Microphthalmia transcription factor is a target of the p38 MAPK pathway in response to receptor activator of NF-kappa B ligand signaling. J Biol Chem. 2002 Mar 29;277(13):11077-83. PubMed PMID: [11792706](http://www.ncbi.nlm.nih.gov/pubmed/11792706/).
3. Sharma SM, Bronisz A, Hu R, Patel K, Mansky KC, Sif S, **Ostrowski MC**. MITF and PU.1 recruit p38 MAPK and NFATc1 to target genes during osteoclast differentiation. J Biol Chem. 2007 May 25;282(21):15921-9. PubMed PMID: [17403683](http://www.ncbi.nlm.nih.gov/pubmed/17403683/).
4. Hu R, Sharma SM, Bronisz A, Srinivasan R, Sankar U, Ostrowski MC. Eos, MITF, and PU.1 recruit corepressors to osteoclast-specific genes in committed myeloid progenitors. Mol Cell Biol. 2007 Jun;27(11):4018-27. PubMed PMID: [17403896](http://www.ncbi.nlm.nih.gov/pubmed/17403896/); PubMed Central PMCID: [PMC1900027](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1900027/).

### D. RESEARCH SUPPORT

**Ongoing Research Support** 2015/02/01-2020/01/31

R01AR0447-16, NIAMS/NIH (MPI, Ostrowski, Sharma)

MITF: Regulating Osteoclast Gene Expression and Function

Our overriding hypothesis is that PU.1 and MITF are at the apex of an osteoclast transcription factor network in osteoclasts and their myeloid precursors that initiates and maintains the differentiated state in response to signals received from the local microenvironment.

2/01/2015-1/31/2020

5 P01 CA097189-10, National Cancer Institute/NIH

Ostrowski, Michael (PI)

Genetic Analysis of the Breast Tumor Microenvironment

This Program Project focuses on how the stroma of breast tumors promotes growth and spread of breast cancer, using human samples and mouse models.

Role: PI, Project Leader (Project 1), and Core Director (Core D).

6/1/2012-5/31/2017

R21 AI124687-01 (MPI: Ostrowski; Lesinski) 03/01/2016 – 02/28/2017

NIH

Stromal IL-6/JAK-STAT signaling and pancreatitis

In Aim 1 we will determine the role of stromal IL-6-mediated signaling in pancreatitis using novel knockout mouse models. In Aim 2 we will evaluate the impact of targeting IL-6/Jak-STAT signaling in murine models of CP.

R01 CA20825301 (MPI: Lesinski, Ostrowski) 09/01/2016 – 08/31/2021

NIH/NCI

Enhancing immune therapy in pancreatic cancer by targeting IL-6

This proposal will enhance our understanding of how the stroma influences carcinogenesis and immune suppression in PDAC.

5 P30 CA016058-37, NCI/NIH (Michael Caligiuri (PI), Ostrowski, Program Leader)

OSU Comprehensive Cancer Center Support Grant

The overall goal of the OSUCCC is to reduce cancer morbidity and mortality through continued basic, translational and clinical research. Dr. Ostrowski is co-leader of the Program in Molecular Biology & Cancer Genetics Role: CPI