OMB No. 3145-0279 (Expiration Date 10/31/2026)

NIH BIOGRAPHICAL SKETCH COMMON FORM

Name: Stack, Mary Sharon

Persistent Identifier (PID) of the Senior/Key Person: https://orcid.org/0000-0003-4563-7390

Position Title: Professor of Chemistry & Biochemistry, Director Harper Cancer Research Institute

Organization and Location: University of Notre Dame, South Bend, Indiana, United States

PROFESSIONAL PREPARATION

INSTITUTION AND LOCATION	DEGREE	Start Date	Completion Date	FIELD OF STUDY
Duke University Medical School, Durham, North Carolina, United States	Not applicable (N/A) - Post-doctoral Fellowship	02/1989	06/1991	Biochemical Pathology
University of Louisville, Louisville, Kentucky, United States	Doctor of Philosophy (PHD)	09/1985	02/1989	Biochemistry
East Tennessee State University, Johnson City, Tennessee, United States	Master of Science (MS)	09/1983	06/1985	Biochemistry
Clemson University, Clemson, South Carolina, United States	Bachelor of Science (BS)	09/1977	12/1981	Biochemistry

Appointments and Positions

2011 - present	Professor of Chemistry & Biochemistry, Director Harper Cancer Research Institute, University of Notre Dame, South Bend, Indiana, United States
2007 - 2011	Professor, University of Missouri School of Medicine, Columbia, Missouri, United States
2006 - 2007	Professor, Northwestern University Feinberg Medical School, Chicago, Illinois, United States
2000 - 2005	Associate Professor, Northwestern University Feinberg Medical School, Chicago, Illinois, United States
1994 - 2000	Assistant Professor, Northwestern University Feinberg Medical School, Chicago, Illinois, United States
1991 - 1994	Research Assistant Professor, Duke University Medical School, Durham, NC, United States

Products

Products Closely Related to the Proposed Project

1. Harper EI, Hilliard TS, Sheedy EF, Carey P, Wilkinson P, Siroky MD, Yang J, Agadi E, Leonard AK, Low E, Liu Y, Biragyn A, Annunziata CM, Stack MS. Another Wrinkle with Age: Aged Collagen and Intra-peritoneal Metastasis of Ovarian Cancer. Aging Cancer. 2022 Jun;3(2):116-129. PubMed Central PMCID: PMC9518742.
2. Loughran EA, Leonard AK, Hilliard TS, Phan RC, Yemc MG, Harper E, Sheedy E, Klymenko Y, Asem M, Liu Y, Yang J, Johnson J, Tarwater L, Shi Z, Leevy M, Ravosa MJ, Stack MS. Aging Increases Susceptibility to Ovarian Cancer Metastasis in Murine Allograft Models and Alters Immune Composition of Peritoneal Adipose Tissue. Neoplasia. 2018 Jun;20(6):621-631. PubMed Central PMCID: PMC5994778.
3. Bodogai M, Park B, Braikia FZ, Naqing F, Kumaraswami K, Chen C, Ragonnaud E, Stack S, Ormanns S, Günther M, Ishikawa-Ankerhold H, De S, Ferrucci L, Sen R, Duren Z, Beerman I, Biragyn A. A distinct population of CD8(+) T cells expressing CD39 and CD73 accumulates with age and supports cancer progression. Nat Aging. 2025 Oct;5(10):2055-2069. PubMed PMID: 40999030.
4. Bahcecioglu G, Yue X, Howe E, Guldner I, Stack MS, Nakshatri H, Zhang S, Zorlutuna P. Aged Breast Extracellular Matrix Drives Mammary Epithelial Cells to an Invasive and Cancer-Like Phenotype. Adv Sci (Weinh). 2021 Nov;8(22):e2100128. PubMed Central PMCID: PMC8596116.
5. Safavi-Sohi R, Johnson J, Liu Y, Yang J, Hilliard TS, Wang Z, Barile C, Mijares J, Wang C, Chang HC, Whelan RJ, Stack MS. Peritoneal cavity-derived small extracellular vesicles from aged tumor-naïve hosts promote ovarian cancer adhesion and invasion. Cell Commun Signal. 2025 Jul 1;23(1):308. PubMed Central PMCID: PMC12211904.

Other Significant Products Highlighting Contributions to Science

1. Liu Y, Yang J, Hilliard TS, Wang Z, Johnson J, Wang W, Harper EI, Ott C, O'Brien C, Campbell L, Crowley B, Grisoli S, Stavrou NM, Juncker-Jensen A, Stack MS. Host obesity alters the ovarian tumor immune microenvironment and impacts response to standard of care chemotherapy. J Exp Clin Cancer Res. 2023 Jul 12;42(1):165. PubMed Central PMCID: PMC10337170.
2. Liu Y, Metzinger MN, Lewellen KA, Cripps SN, Carey KD, Harper EI, Shi Z, Tarwater L, Grisoli A, Lee E, Slusarz A, Yang J, Loughran EA, Conley K, Johnson JJ, Klymenko Y, Bruney L, Liang Z, Dovichi NJ, Cheatham B, Leevy WM, Stack MS. Obesity Contributes to Ovarian Cancer Metastatic Success through Increased Lipogenesis, Enhanced Vascularity, and Decreased Infiltration of M1 Macrophages. Cancer Res. 2015 Dec 1;75(23):5046-57. PubMed Central PMCID: PMC4668203.
3. Asem M, Young AM, Oyama C, Claure De La Zerda A, Liu Y, Yang J, Hilliard TS, Johnson J, Harper EI, Guldner I, Zhang S, Page-Mayberry T, Kaliney WJ, Stack MS. Host Wnt5a Potentiates Microenvironmental Regulation of Ovarian Cancer Metastasis. Cancer Res. 2020 Mar 1;80(5):1156-1170. PubMed Central PMCID: PMC8245162.
4. Amens JN, Bahçecioğlu G, Dwyer K, Yue XS, Stack MS, Hilliard TS, Zorlutuna P. Maternal obesity driven changes in collagen linearity of breast extracellular matrix induces invasive mammary epithelial cell phenotype. Biomaterials. 2023 Jun;297:122110. PubMed Central PMCID: PMC10192205.
5. Asem M, Young A, Oyama C, ClaureDeLaZerda A, Liu Y, Ravosa MJ, Gupta V, Jewell A, Khabele D, Stack MS. Ascites-induced compression alters the peritoneal microenvironment and promotes metastatic success in ovarian cancer. Sci Rep. 2020 Jul 17;10(1):11913. PubMed Central PMCID: PMC7367827.

Certification:

I certify that the information provided is current, accurate, and complete. This includes, but is not limited to, information related to current, pending, and other support (both foreign and domestic) as defined in 42 U.S.C. § 6605.

In accordance with Section 10632 of the CHIPS and Science Act of 2022 (42 U.S.C. § 19232), each individual identified as a senior/key person must certify that they are not a party to a malign foreign talent recruitment program.

Research Security Training Requirement for Federal Award Personnel: In accordance with Section 10634 of the CHIPS and Science Act of 2022 (42 U.S.C. § 19234), each individual identified as a senior/key person must certify that they have completed the requisite research security training that meets the requirements specified in Item 2 of Important Notice No. 149 within 12 months prior to proposal submission.

Misrepresentations and/or omissions may be subject to prosecution and liability pursuant to, but not limited to, 18 U.S.C. §§287, 1001, 1031 and 31 U.S.C. §§3729-3733 and 3802.

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NIH BIOGRAPHICAL SKETCH SUPPLEMENT

Name: Stack, Mary Sharon

Persistent Identifier (PID) of the Senior/Key Person: https://orcid.org/0000-0003-4563-7390

Position Title: Professor of Chemistry & Biochemistry, Director Harper Cancer Research Institute

Organization and Location: University of Notre Dame, South Bend, Indiana, United States

Personal Statement

My laboratory has focused for many years on regulation of metastasis, with specific emphasis on matrix remodeling and cell adhesion in epithelial ovarian cancer (OC). Metastatic OC cells colonize the peritoneal cavity following dissemination from the primary tumor, survive in suspension as multicellular aggregates (MCAs) in carcinomatous ascites fluid, attach to the peritoneal surface and locally invade into the collagen-rich sub-mesothelial matrix to anchor secondary lesions. We have developed a number of in vitro, 3-dimensional, and organotypic models of key events in OC metastatsis with which to evaluate the effect of various cellular and micro-environmental manipulations on metastatic success with an overarching focus on adhesion (cell-matrix and cell-cell) and proteolysis (pericellular and extracellular). We have used organotypic mesothelial-mimetic (meso-mimetic) cultures comprised of fibroblast-embedded 3D collagen gels overlaid with mesothelial cells as well as ex vivo tissue explant models of the peritoneum and omentum. More recently, we have focused extensively on xenograft and allograft studies of OC intra-peritoneal metastasis, with particular emphasis on methods to accurately quantify widely disseminated i.p. metastatic burden. Ongoing projects are aimed toward elucidating the contribution of host age and host obesity to OC metastatic success. Within this framework, understanding the multiple micro-environmental cues that contribute to metastatic success is a major focus of the laboratory. Throughout my career, I have been strongly committed to training of pre- and post-doctoral fellows and the mentoring of junior faculty. I am particularly committed to the development of a scientific workforce that more closely mirrors the population. Multiple previous trainees have received support from NIH (F31, F99, K01, K08) and NSF (DDRIG). Previous trainees are current faculty members (PhD and MD/PhD) at private and public universities, are involved in biotechnology research and scientific communications, and review biotechnology patents.

Honors

2023	Editorial Board, Aging and Cancer, Aging and Cancer (journal)
2023	Scientific Advisory Board Member, Saolta-University of Galway Cancer Network, Organization of European Cancer Institutes, Galway, Ireland
2021	External Advisory Board Member, Sanford Burnham Prebys Cancer Center, La Jolla, CA
2019 - 2025	Member, NIH Study Section, Tumor Progression & Metastasis; Tumor Evolution, Heterogeneity & Metastasis
2019 - 2022	Executive Committee, Cancer Biology Training Consortium (CABTRAC)
2015	Lifetime Achievement Award, American Cancer Society Lakeshore Division
2012	Fellow of AAAS, American Association for the Advancement of Science
2012 - 2017	Ovarian Cancer Reserach Program Integration Panel, Department of Defense Ovarian Cancer Research Program
2011	Ann F. Dunne & Elizabeth Riley Endowed Professor, University of Notre Dame
2011 - 2015	Gordon Research Conference Chair, Matrix Metalloproteinases Gordon Research Conference
2008 - 2011	Mulligan Endowed Professor of Cancer Research, University of Missouri
2003	External Advisory Board Member, Karmanos Cancer Institute Comprehensive Cancer Center, Wayne State University, Detroit MI
2001 - 2025	Associate Editor, Cancer Research, Cancer Research (journal)
2000 - 2006	Member, NIH Study Section, Pathology B; Tumor Progression & Metastasis
1982 - 1983	Fulbright Scholarship for Graduate Study Abroad, Universitat Bonn, Bonn, Germany

Contributions to Science

1. Host Aging and Ovarian Cancer. Despite age being a significant risk factor for OvCa, few studies address the impact of aging on metastasis. We demonstrated that the aged host is more susceptible to metastatic success using two murine syngeneic allograft models and cells derived from both the fallopian tube and ovarian surface epithelium (Loughran et al., 2018,

Neoplasia). Follow-up mechanistic studies evaluating age-related changes in the peritoneal ultrastructure found altered omental fenestration and collagen fiber structure and organization and demonstrated that the aged peritoneal cavity is a permissive metastatic niche for OvCa metastasis (Harper et al., 2022, Aging Cancer). Moreover, small extracellular vesicles isolate from the peritoneal cavity of tumor-naive aged mice enhance aggressive behavior in ovarian cancer cells and promote adhesion to the omentum in vivo (Safavi-Sohi, 2025, Cell Comm. Signl.) Studies in colorectal cancer and aging showed enhanced i.p. metastases in aged male mice and identified a potential target for anti-metastatic treatment (Wang et al., 2025, Aging Cancer). In collaborations, we have also examined the aged ECM in mammary glands, showing that the aged ECM harbors biochemical, physical and mechanical cues contributing to pre-malignant phenotypes in healthy mammary cells (Bahcecioglu et al., 2021, Advanced Sci.). Collaborative work with the Biragyn lab at National Institute on Aging identified a unique population of T cells in aged mice, termed DP8 cells, with tumor-promoting activity (Bodogai et al., 2025, Nature Aging) . Targeting this population can reduce tumor growth in aged mice, suggesting a novel therapeutic approach to block tumor growth in aged hosts.

2. Additional Host Contributions to Ovarian Cancer Metastasis. We have demonstrated that obesity is a significant regulator of ovarian cancer metastatic success and is associated with upregulation and nuclear localization of sterol regulatory element binding protein 1 (SREBP1) using three distinct in vivo model systems together with in vitro organotypic and ex vivo culture systems, (Liu et al., 2015, Cancer Research). Obesity is also associated with altered peritoneal macrophage polarization, adipocyte hypertrophy and tumor fibrosis (Liu et al., 2015, 2023, J. Exp. Clin. Can. Res.). Moreover, host obesity alters lipogenic programming in tumors and impacts response to standard of care (SoC) chemotherapy, such that mice on high fat diet (HFD) have significant residual tumor burden following treatment (Liu et al., 2023). In HFD mice, targeting SREBP1 processing using Nelfinavir (an inhibitor of site-1 protease) delays tumor recurrence (Yang et al., 2026, in review). Ongoing studies are also evaluating the impact of co-housing aged with young mice. These studies demonstrate that aged co-housed mice have a more “young-like” peritoneal tumor burden (unpublished). This is likely due to changes in the gut microbiome that affect regions beyond the gut, including the OvCa tumor microenvironment (reviewed in Dominique et al., 2024, Aging and Cancer). In additional models, we have also demonstrated that host peritoneal mesothelial cells contribute Wnt5a to the tumor microenvironment, leading to activation of Fgr kinase and enhanced metastatic seeding (Asem et al., 2020, Cancer Research). Together these studies support a mechanistic consideration of host factors in evaluation of ovarian cancer progression and metastasis and identify targets for therapeutic intervention.

3. Organotypic, Ex Vivo and In Vivo Models of Ovarian Cancer. Understanding the dynamics of tumor progression and metastasis requires the development of model systems that better mimic in vivo biology. In recent years, we have devoted considerable effort to model system development. In two large multi-laboratory collaborative efforts, we have shared these results with the scientific community. A detailed and comprehensive review summarized current model systems for the study of ovarian cancer (Lengyel et al., 2013, Oncogene), including hanging-drop multi-cellular aggregate (MCA) cultures, complex meso-mimetic models involving collagen-embedded fibroblasts overlaid with mesothelial cells, 3D collagen gels (Lengyel et al., 2013), ex vivo tissue explant studies and in vivo intraperitoneal xenografts (Lengyel et al. 2013; Mitra et al., 2015, Gyn. Oncology). We have evaluated the in vivo growth parameters of a variety of ovarian cancer cell lines that recapitulate the mutational profile found in human ovarian tumors (Mitra et al., 2015). In more recent studies, we have also used serial in vivo passaging to identify and characterize a novel adhesion mechanism, mediated via the adhesion molecule AMIGO2, in ovarian cancer metastatic seeding (Liu et al., 2021, Cancer Letters). Using mice genetically deficient in mesothelin expression, we reported a significant decrease in metastatic burden in MSLN-KO mice, accompanied by abnormal mesothelial cell surface architecture and altered omental collagen fibril organization (Hilliard et al., 2021, Int J Mol Sci).

4. Molecular and Tissue Biophysics. A Physical Biochemistry course as a graduate student instilled a long-standing interest in molecular biophysics and led to a publication using tools such as analytical ultracentrifugation to probe proteinase:inhibitor interactions (Stack et al., 1987, Arch Biochem Biophys). More recently, we have begun to address changes in tissue biomechanical properties and how this contributes to regulation of biological processes. We have found that Wnt/beta-catenin signaling can be regulated in by integrin-mediated matrix adhesion and is susceptible to alterations in matrix stiffness (for example, by changing collagen concentration or cross-linking collagen), leading to loss of Dkk1, a Wnt inhibitor, and upregulation of MT1-MMP (Barbolina et al., 2013, J Biol Chem). Current work is focused on evaluating the unique force environment of the peritoneal cavity and how ascites-induced changes in intra-peritoneal pressure may regulate metastatic success via multiple mechanisms including elaboration of tunneling nanotubes (Klymenko et al., 2018, Disease Models Mechanisms; Asem et al. 2020, Scientific Reports). Additional studies are exploring therapeutic strategies to normalize the ultrastructure of aged omental collagen in vivo (Harper et al., 2023, Int J Mol Sci). Collaborative studies with the Zorlutuna laboratory have examined maternal obesity impacts collagen curvature and biomechanical properties leading to enhanced breast cancer invasion (Amens et al., 2023, Biomaterials).

5. Cross-Talk Among Cellular Adhesion Receptors, ECM, and Proteinases. Matrix metalloproteinase (MMP) substrates are primarily extracellular matrix (ECM) components. We have devoted considerable effort to understanding how interaction of

metastasizing ovarian tumor cells with ECM proteins regulates the expression and activity of matrix-degrading proteinases. In early studies, we demonstrated that adhesion to collagen mediated by beta1 integrin induced expression of MMP-14 (Ellerbroek et al., 1999, Cancer Research). We further demonstrated that simple bivalent integrin ligation (for example, by a polypeptide fragment of collagen) was not sufficient to induce MMP-14. Rather ligation and lateral clustering of integrins, such as are induced by interaction with a 3D matrix, were required and integrin-induced Src signaling to the Egr1 transcription factor regulated this process (Barbolina et al, 2013, J Biol Chem). Examining integrin-cadherin crosstalk, we demonstrated that multivalent integrin engagement disrupted cadherin-based cell-cell adhesion via a MMP-dependent mechanism, freeing junctional beta-catenin to translocate to the nucleus and participate in transcriptional control of Wnt/beta-catenin target genes (including MMPs) (Burkhalter et al., 2011, J Biol Chem). Alteration in matrix stiffness was also sufficient to regulate gene expression, with stiffer gels upregulating MT1-MMP via downregulation of the Wnt inhibitor DKK1 (Barbolina et al., 2013). More recent studies show cadherin-dependent changes in multicellular aggregate ultrastructure that translate into differential adhesion to and penetration of ex vivo peritoneal explants and 3D collagen gels and support a combined role for MT1-MMP and N-cadherin in ovarian cancer intraperitoneal invasion (Klymenko et al., 2017, Oncogene; Klymento et al., 2017, Neoplasia).

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