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

NIH BIOGRAPHICAL SKETCH COMMON FORM

Name: Matherly, Larry

Persistent Identifier (PID) of the Senior/Key Person: https://orcid.org/0000-0001-6860-8133

Position Title: Professor

Organization and Location: Wayne State University, Detroit, Michigan, United States

PROFESSIONAL PREPARATION

INSTITUTION AND LOCATION	DEGREE	Start Date	Completion Date	FIELD OF STUDY
Pennsylvania State University, University Park, Pennsylvania , United States	DOCTOR OF PHILOSOPHY	09/1976	12/1981	Biochemistry
New Mexico State University, Las Cruces, New Mexico, United States	BACHELOR OF SCIENCE	09/1972	05/1976	Biology

Appointments and Positions

2000 - present	Professor, Wayne State University, Detroit, Michigan, United States
2016 - present	Associate Center Director for Basic Sciences, Karmanos Cancer Institute, Detroit, MI, United States
2016 - present	Division Chief for Basic Sciences, Department of Oncology , Wayne State University, Detroit, MI, United States
2010 - present	Professor, Department of Oncology , Wayne State University School of Medicine, Detroit , MI, United States
2010 - present	Director, Cancer Biology Graduate Program, Department of Oncology, Wayne State University School of Medicine, Detroit , MI, United States
2010 - 2021	Program Leader, Molecular Therapeutics Program, Karmanos Cancer Institute, Detroit, MI, United States
2006 - 2010	Associate Director, Cancer Biology Graduate Program, Wayne State University School of Medicine, Detroit, MI, United States
2000 - present	Professor, Department of Pharmacology, Wayne State University School of Medicine , Detroit, MI, United States
1994 - present	Scientific Member, Karmanos Cancer Institute, Detroit, MI, United States
1994 - 1999	Associate Member, Karmanos Cancer Institute/Wayne State University, Detroit, MI, United States
1994 - 1999	Associate Professor, Department of Pharmacology, Wayne State University School of Medicine, Detroit , MI, United States
1991 - 1994	Associate Member, Michigan Cancer Foundation, Detroit, MI, United States
1989 - 1994	Adjunct Faculty, Department of Pharmacology, Wayne State University School of Medicine, Detroit, MI, USA
1987 - 1991	Assistant Member, Michigan Cancer Foundation, Detroit, MI, United States
1984 - 1986	Instructor, Department of Pharmacology , Virginia Commonwealth University, Richmond, VA, United States
1981 - 1984	Postdoctoral Fellow, Department of Medicine , Virginia Commonwealth University , Richmond, VA, United States

Products

Products Closely Related to the Proposed Project

1. Matherly LH, Hou Z. Folate transporter offers clues for anticancer drugs. Nature. 2022 Dec;612(7938):39-41. PubMed Central PMCID: PMC9940820.
2. Matherly LH, Hou Z, Deng Y. Human reduced folate carrier: translation of basic biology to cancer etiology and therapy. Cancer Metastasis Rev. 2007 Mar;26(1):111-28. PubMed PMID: 17334909.
3. Desmoulin SK, Hou Z, Gangjee A, Matherly LH. The human proton-coupled folate transporter: Biology and therapeutic applications to cancer. Cancer Biol Ther. 2012 Dec;13(14):1355-73. PubMed Central PMCID: PMC3542225.
4. Dekhne AS, Hou Z, Gangjee A, Matherly LH. Therapeutic Targeting of Mitochondrial One-Carbon Metabolism in Cancer. Mol Cancer Ther. 2020 Nov;19(11):2245-2255. PubMed Central PMCID: PMC7921203.
5. Matherly LH, Barlowe CK, Phillips VM, Goldman ID. The effects on 4-aminoantifolates on 5-formyltetrahydrofolate

metabolism in L1210 cells. A biochemical basis of the selectivity of leucovorin rescue. J Biol Chem. 1987 Jan 15;262(2):710-7. PubMed PMID: 2948949.

Other Significant Products Highlighting Contributions to Science

1. Hales EC, Orr SM, Larson Gedman A, Taub JW, Matherly LH. Notch1 receptor regulates AKT protein activation loop (Thr308) dephosphorylation through modulation of the PP2A phosphatase in phosphatase and tensin homolog (PTEN)-null T-cell acute lymphoblastic leukemia cells. J Biol Chem. 2013 Aug 2;288(31):22836-48. PubMed Central PMCID: PMC3829367.
2. O'Connor C, Schneider M, Katinas JM, Nayeen MJ, Shah K, Magdum T, Sharma A, Kim S, Bao X, Li J, Dann CE, Gangjee A, Matherly LH, Hou Z. Role of Mitochondrial and Cytosolic Folylpolyglutamate Synthetase in One-Carbon Metabolism and Antitumor Efficacy of Mitochondrial-Targeted Antifolates. Mol Pharmacol. 2024 Sep 17;106(4):173-187. PubMed Central PMCID: PMC11413923.
3. Nayeen MJ, Katinas JM, Magdum T, Shah K, Wong JE, O'Connor CE, Fifer AN, Wallace-Povirk A, Hou Z, Matherly LH, Dann CE 3rd, Gangjee A. Structure-Based Design of Transport-Specific Multitargeted One-Carbon Metabolism Inhibitors in Cytosol and Mitochondria. J Med Chem. 2023 Aug 24;66(16):11294-11323. PubMed Central PMCID: PMC10461232.
4. Dekhne AS, Shah K, Ducker GS, Katinas JM, Wong-Roushar J, Nayeen MJ, Doshi A, Ning C, Bao X, Frühauf J, Liu J, Wallace-Povirk A, O'Connor C, Dzinic SH, White K, Kushner J, Kim S, Hüttemann M, Polin L, Rabinowitz JD, Li J, Hou Z, Dann CE 3rd, Gangjee A, Matherly LH. Novel Pyrrolo[3,2-d]pyrimidine Compounds Target Mitochondrial and Cytosolic One-carbon Metabolism with Broad-spectrum Antitumor Efficacy. Mol Cancer Ther. 2019 Oct;18(10):1787-1799. PubMed Central PMCID: PMC6774887.
5. Ge Y, Haska CL, LaFiura K, Devidas M, Linda SB, Liu M, Thomas R, Taub JW, Matherly LH. Prognostic role of the reduced folate carrier, the major membrane transporter for methotrexate, in childhood acute lymphoblastic leukemia: a report from the Children's Oncology Group. Clin Cancer Res. 2007 Jan 15;13(2 Pt 1):451-7. PubMed PMID: 17255265.

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.

Certified by Matherly, Larry in SciENcv on 2026-08-10 22:36:47

NIH BIOGRAPHICAL SKETCH SUPPLEMENT

Name: Matherly, Larry

Persistent Identifier (PID) of the Senior/Key Person: https://orcid.org/0000-0001-6860-8133

Position Title: Professor

Organization and Location: Wayne State University, Detroit, Michigan, United States

Personal Statement

My principal research involves the membrane transport of folates, cancer drug development and discovery, basic preclinical studies of chemotherapy drug mechanisms and resistance, and translational studies of cancer with direct clinical application. I have been working in the area of folate and antifolate membrane transport and one-carbon metabolism for over 30 years and I have published extensively on these topics. Since we cloned the human reduced folate carrier (hRFC), the major tissue folate transporter, in the mid-1990s, my laboratory has been at the forefront of studies into the function, structure, mechanism and regulation of this physiologically and pharmacologically important system. In 2005, we directed a portion of our work toward the discovery and development of new folate-based therapeutics for ovarian cancer that selectively use folate receptor α without substrate activity for hRFC and that target critical one-carbon metabolic pathways. A recent aspect of this work involves targeting the folate receptor β-expressing tumor-associated macrophage population in high grade serous ovarian cancer. We extended our work to selectively targeting tumors via the human proton-coupled folate transporter (PCFT) for therapy which we found to be highly expressed in the majority of human solid tumors (including lung, pancreatic and ovarian cancers) and is active at the acidic pH of the tumor microenvironment. Other studies focused on the biology and regulation of PCFT such that this might lead to new therapeutic approaches for treating conditions associated with folate deficiency (e.g., hereditary folate malabsorption) and further development of novel PCFT-selective tumor-targeted small molecule therapeutics. In recent years, we have directed our studies toward a better understanding of one-carbon metabolism in the mitochondria and cytosol with the goal of identifying an entirely new generation of therapeutic agents that target both the tumor and the tumor microenvironment. Our translational studies include identifying molecularly-based prognostic biomarkers in malignant pleural mesothelioma, non-small cell lung cancer, epithelial ovarian cancer, and pediatric leukemias. Other studies have explored the relationships between glucocorticoids and pemetrexed therapeutic responses in lung cancer, and the complex interplay between Notch1 and AKT signaling in T-cell acute lymphoblastic leukemia.

I serve as Division Chief for Basic Sciences in the Department of Oncology at Wayne State University and as Associate Center Director for Basic Sciences at the Barbara Ann Karmanos Cancer Center. I have published more than 195 original research publications, am co-inventor on 10 US patents, and have been continuously supported by the NIH/NCI for my research for the past 33 years. I participate extensively in peer review for NIH, having served as an ad hoc and a regular member of NIH study sections back to 1995.

I am the Principal Investigator of a pre-doctoral T32 training grant (T32 CA009531) through the National Cancer Institute, currently in its 39th year of funding. I serve as an external advisor for T32CA251066 at the Van Andel Research Institute and CA009370 at the Salk Institute. I am also Principal Investigator on R25CA295446 for undergraduates.

Honors

2022	Outstanding Graduate Director Award, Wayne State University
2018	Dr. Michael J. Brennan Scientific Distinction Award , Karmanos Cancer Institute
2018 - 2022	Member, Molecular Therapeutic Study Section, NCI/NIH
2017	Ad hoc reviewer, ZCA1 GRB-S (A1), Cancer Drug Resistance Study Section, NCI/NIH
2016	Eunice and Milton Ring Endowed Chair in Cancer Research, Karmanos Cancer Institute
2015	Teaching Award, Wayne State University School of Medicine
2012	Teaching Award, Wayne State University School of Medicine
2012	Kale's Award in Oncology, Karmanos Cancer Institute
2009	Teaching Award, Wayne State University School of Medicine
2009	Center Director's Quarterly Research Award, Karmanos Cancer Institute
2008	Center Director's Quarterly Research Award, Karmanos Cancer Institute

2006	Teaching Award, Wayne State University School of Medicine
2005	Research Recognition Award, Wayne State University School of Medicine
2004	Member, Drug Development and Experimental Therapeutics Study Section, NCI/HIN
2004 - 2010	Ad hoc reviewer, ZRG1, Basic Mechanisms of Cancer Therapy Study Section, NCI/NIH
2000	President's Achievement Award, Karmanos Cancer Institute
2000 - 2003	Member, Experimental Therapeutics Study Section, NCI/NIH
1999	Research Recognition Award, Wayne State University School of Medicine
1998	Research Recognition Award, Karmanos Cancer Institute
1995	Ad hoc reviewer, Experimental Therapeutics 2 Study Section, NCI/NIH
1995 - 1999	Ad hoc reviewer, Experimental Therapeutics 1 Study Section, NCI/NIH
1992	Scholar Award, Leukemia Society of America
1985	Junior Faculty Award, American Cancer Society

Contributions to Science

1. Folate metabolism and the mechanistic basis for antifolate effect and leucovorin rescue. Early studies focused on basic mechanisms of classic antifolates such as methotrexate and the mechanism of "leucovorin rescue" from drug effects. We established that the dramatically increased antitumor efficacy of drugs such as aminopterin and the early Eli Lilly antipurine antifolate, lometrexol, was associated with substantially increased metabolism to polyglutamates over methotrexate. We showed that polyglutamylation of antifolate drugs was an important determinant of drug efficacy and of rescue of cells by leucovorin, reflecting increased intracellular pools of reduced folates that circumvented drug effects on target enzymes but more importantly competed for binding with drugs at the target enzymes. Finally, we demonstrated for the first time that folate cofactors within cells were "compartmentalized" via their binding to intracellular proteins and sequestration in cellular organelles and that treatment of tumor cells with antifolates such as methotrexate only partly "depleted" reduced folate forms with the formation of dihydrofolate due to the sequestration of reduced folates by these protein binding associations. Many of these studies were paradigm shifting for the field during this era (PMID 2948949).

2. Cloning of the human reduced folate carrier and characterization of transcriptional and post-transcriptional regulation. In the mid-to-late1990s, we made a number of seminal contributions to the field. In 1995, we were one of 3 groups who almost simultaneously reported the cloning and molecular characterization of the human reduced folate carrier (hRFC), the major tissue folate transporter (PMID 17334909). This was soon followed by characterization of hRFC gene structure including identification up to 5 promoters and a remarkable heterogeneity in transcript structure resulting from use of alternative promoters and upstream non-coding exons, and alternate splicing. We established the biological impact of transcript heterogeneity including its effects on hRFC levels due to differences in transcript stabilities and we identified novel hRFC protein isoforms resulting from use of an alternative translational start sites. We were the first to characterize the complex transcriptional and post-transcriptional regulation of hRFC in order to understand the molecular basis for our finding that hRFC is ubiquitously expressed in human tissues and tumors.

3. Structural and mechanistic studies of major folate transporters. The cloning of the human reduced folate carrier (hRFC) and proton-coupled folate transporter (PCFT) provided impetus to biochemically characterize protein structure as a means to explore the mechanism of membrane transport and the role of these transporters in drug delivery, efficacy and resistance. We made a number of seminal findings ranging from characterizing key functional/structural features and secondary and tertiary structures of both hRFC and PCFT by site-directed and insertion/deletion mutagenesis, epitope tagging, and cysteine-scanning accessibility methods. We also demonstrated that both RFC and PCFT exist primarily as homo-oliogomeric proteins (PMID 17334909; PMC3542225; PMC9940820).

4. Translational studies of pediatric acute lymphoblastic leukemias. In the mid-1990s we turned our attention to translational studies of antifolate pharmacology and molecular biology in pediatric patients with acute lymphoblastic leukemia (ALL). Our studies included (i) characterization of an important role of elevated dihydrofolate reductase and impaired membrane transport of methotrexate by the human reduced folate carrier (hRFC) in pediatric ALL patients, (ii) demonstration of an increased frequency of elevated dihydrofolate reductase in T-cell ALL specimens over B-precursor ALLs, as an explanation for differences in methotrexate efficacy seen clinically, and (iii) establishing the prognostic importance of hRFC levels to pediatric ALL patients treated with methotrexate-based chemotherapy and strikingly elevated hRFC levels in hyperdiploid B-precursor ALLs. (iv) We identified high frequency polymorphisms and alternate spice forms for hRFC in pediatric B-precursor ALL specimens and provided the first functional characterization of the high frequency G/A polymorphism at position 80 in hRFC that has been studied throughout the world. (v) We also characterized the transcriptional regulation and the role of hRFC promoter methylation in pediatric ALL specimens. Most recently, (vi) we turned our attention to the potential prognostic and

therapeutic role of NOTCH1 mutations in pediatric T-cell ALLs and (vii) identified a novel regulation by NOTCH1 of PP2A and AMPK in T-ALLs (PMC3829367; PMID 17255265).

5. Development of a new generation of tumor-targeted therapeutics: In the mid-2000s, we evolved our folate transport and metabolism studies to include a substantial commitment to drug discovery. We began fruitful collaborations with Aleem Gangjee (Duquesne University), an accomplished medicinal chemist with interests ranging from antifolates to tubulin-targeted agents, and Charles Dann, a structural biologist. Lisa Polin, an expert in mouse xenograft models and the director of the AMTEC core at the Karmanos Cancer Institute, was also an important collaborator. We made a number of unique observations with potential clinical impact. Using medicinal chemistry and molecular modeling based on crystal structures for glycinamide ribonucleotide formyl transferase (GARFTase) and folate receptors with bound ligands, and a unique pharmacophore model for the proton-coupled folate transporter (PCFT), we developed several novel series of 6-substituted pyrrolo[2,3-d]pyrimidine and thieno[2,3-d]pyrimidine analogs with substantial selectivity for the human folate receptors and the human PCFT over the human reduced folate carrier (hRFC) (PMC3542225). Most recently, we identified novel 5-substitutedpyrrolo[3,2-d]pyrimidine compounds as multi-targeted inhibitors for serine hydoxymethyltransferase 2 (SHMT2) in mitochondria and de novo purine nucleotide biosynthesis in the cytosol (PMC7921203; PMC6774887; PMC10461232; PMC11413923). These analogs show potent in vitro and in vivo efficacies toward human tumor models and xenografts (including patient-derived xenograft and syngeneic mouse models). Based on our promising studies with the most active agents, we are collaborating with Flag Therapeutics to advance our most promising compounds for further preclinical testing with plans for IND submission. One of our lead molecules (AGF94)received “Orphan Drug Designation” from the US FDA.

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.

Certified by Matherly, Larry in SciENcv on 2026-08-1022:36:47