

BIOGRAPHICAL SKETCH

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NAME: Steven M. Larson, MD, FACNM, FACR

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

POSITION TITLE: Donna and Benjamin M. Rosen Chair; Attending, Molecular Imaging and Therapy Service, Department of Radiology; Co-Leader, Imaging and Radiation Sciences, Memorial Sloan Kettering Cancer Center

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 <i>(if applicable)</i>	Completion Date	FIELD OF STUDY
University of Washington, Seattle, Washington	B.A.	06/1963	Zoology
University of Washington Medical School	M.D.	06/1968	Medicine
University of Washington, Seattle, Washington	Fellowship	06/1965	Nuclear Medicine
University of Washington, Seattle, Washington	Fellowship	06/1966	Nuclear Medicine
Virginia Mason Hospital, Seattle, Washington	Internship	07/1969	Medicine
Virginia Mason Hospital, Seattle, Washington	Resident	07/1970	Medicine
National Institutes of Health; and Surgeon, U.S. Public Health Service, Bethesda, Maryland	Clinical Associate	07/1972	Nuclear Medicine

A. Personal Statement

My primary expertise is in molecular imaging, targeted radio diagnosis, and therapy using small molecules and monoclonal antibodies. Dual-boarded in nuclear medicine and internal medicine, my clinical skills center on oncology, cancer immunology, and clinical thyroid cancer. I was responsible for directing and developing successful nuclear medicine and PET programs at several major institutions in the U.S., including the Veteran Administration Hospitals in Portland and Vancouver; University of Oregon, Portland; Seattle VA Hospital; Clinical Center, National Institutes of Health; and Memorial Sloan Kettering Cancer Center (MSK). I have extensive experience as an advisor to public and private institutions, having served, among other appointments, as a member of what is now the MED1 grant review committee of NIH, the DOE Office of Science Advisory Committee, and the American Board of Nuclear Medicine, and as Chair of the Radiopharmaceutical Advisory Committee of the USFDA, Co-Chair of the National Research Council of the NAS Committee on Molybdenum-99 production with non-enriched Uranium 235, Chair of the Molecular Imaging Committee of RSNA, and Co-Chair of the Clinical Imaging Steering Committee of the NCI, and Chair of the NIH Clinical "Impact" Study Section, as well as a member of the Academy of Medicine. I have received numerous awards for excellence in nuclear medicine, including the Hevesy Award, Cassen Prize, Wiley Prize (US FDA), and the Saul Hertz Award of the Society of Nuclear Medicine USA. I have published over 634 peer-reviewed publications in prestigious journals, and my current H-factor is approximately 111.

As an undergraduate student at the University of Washington in Seattle (UW), I worked as a radiochemistry technician in a radiobiology laboratory monitoring plants and animals for radioactive fallout from atmospheric atom bomb testing. This experience instilled in me a life-long interest in radiochemistry and radiation effects and honed my skills in inorganic and chelation chemistry. Once in medical school at UW, I worked in the laboratory of Wil B. Nelp, MD, nuclear medicine, and accepted an NIH-sponsored fellowship, which resulted in the invention of the first successful "kit" formulation, ^{99m}Tc-Sulder colloid, a widely used radiopharmaceutical. After training in internal medicine, I successfully competed for a USPHS fellowship in nuclear medicine and was appointed as second Lieutenant in the Public Health Service at the NIH in Bethesda, Maryland. I subsequently accepted my first faculty position as Assistant Professor at Johns Hopkins Medical Institutions, where I developed skills in written presentation of basic and clinical science and grantsmanship under the direct tutelage of Dr. Henry N. Wagner, a giant in nuclear medicine. I also helped develop a novel method still in use for detection and susceptibility testing for mycobacterium species, the most important of which is mycobacterium tuberculosis, a technique that is still in use today. As my career progressed, I developed an

interest in oncology and gained experience in managing large clinical and research groups. In the early 1980s, I accepted a post as Chief of Nuclear Medicine at the Clinical Center of NIH and was charged with the development of a PET program focused on brain research, including brain tumors and cancer molecular imaging. While at the NIH, I co-authored several highly cited papers on Alzheimer's disease and AIDS dementia that documented the long-term metabolic effects on glycolysis of brain regions. I also collaborated with Giovanni Di Chiro and Lou Sokoloff on the early studies of PET-FDG in brain tumor imaging, including treatment response. Subsequently, I was recruited by MSK to develop the program in oncologic imaging, using radio-antibodies and PET for both basic research and patient management applications.

Currently, in collaboration with Simon Powell, I oversee, develop, and manage the scientific and operational structure for the Imaging and Radiation Sciences Program within the CCSG. We help to ensure that the highest-quality service is offered in support of the research of the Cancer Center's mission by maintaining state-of-the-art technologies that provide cost-effective services for researchers and their teams. I am the corresponding PI of an R01 (**CA201250-01A1**) entitled "¹²⁴I-Nal PET: Building block for precision medicine in metastatic thyroid cancer." This project builds on extensive prior imaging collaborations with Drs. James Fagin, Alan Ho, and Mike Tuttle (Thyroid Cancer Program). Additional key collaborators include Howard Scher, Mike Morris, and Peter Scardino of the prostate program, and joint work has led to the development of molecular imaging approaches to androgen receptor (AR) imaging as well as several novel radioantibodies that image downstream effectors of AR signaling. I also serve as the Director of the Ludwig Center for Radioimmunotherapy and Theranostics, working with Dr. Nai-Kong Cheung, Michel Sadelain, and Jedd Wolchok (Cancer Immunology); Jorge Carrasquillo, and Neeta Pandit-Taskar (Molecular Imaging and Therapy Service); Joe O'Donoghue, John Humm, and Pat Zanzonico (Medical Physics); and Sarah Cheal, David Ulmert, Darren Veach, Kishore Pillarsetty, and Simone Krebs (Larson Lab, Molecular Pharmacology Program, SKI).

- a. Scher HI, Beer TM, Higano CS, Anand A, Taplin ME, Efstathiou E, Rathkopf D, Shelkey J, Yu EY, Alumkal J, Hung D, Hirmand M, Seely L, Morris MJ, Danila DC, Humm J, **Larson S**, Fleisher M, Sawyers CL; Prostate Cancer Foundation/Department of Defense Prostate Cancer Clinical Trials Consortium. Antitumour activity of MDV3100 in castration-resistant prostate cancer: a phase 1-2 study. *Lancet*. 2010 Apr 24;375(9724):1437-46. Epub 2010 Apr 14. PMID: PMC2948179.
- b. Rathkopf DE, Morris MJ, Fox JJ, Danila DC, Slovin SF, Hager JH, Rix PJ, Chow Maneval E, Chen I, Gönen M, Fleisher M, **Larson SM**, Sawyers CL, Scher HI. Phase I study of ARN-509, a novel antiandrogen, in the treatment of castration-resistant prostate cancer. *J Clin Oncol*. 2013 Oct 1;31(28):3525-30. Epub 2013 Sep 3. PMID: PMC3782148.
- c. Palaskas N, **Larson SM**, Schultz N, Komisopoulou E, Wong J, Rohle D, Campos C, Yannuzzi N, Osborne JR, Linkov I, Kastenhuber ER, Taschereau R, Plaisier SB, Tran C, Heguy A, Wu H, Sander C, Phelps ME, Brennan C, Port E, Huse JT, Graeber TG, Mellinger IK. ¹⁸F-fluorodeoxy-glucose positron emission tomography marks MYC-overexpressing human basal-like breast cancers. *Cancer Res*. 2011 Aug 1;71(15):5164-74. Epub 2011 Jun 6. PMID: PMC3148325.
- d. Beattie BJ, Smith-Jones PM, Jhanwar YS, Schöder H, Schmidlein CR, Morris MJ, Zanzonico P, Squire O, Meirelles GS, Finn R, Namavari M, Cai S, Scher HI, **Larson SM**, Humm JL. Pharmacokinetic assessment of the uptake of 16beta-18F-fluoro-5alpha-dihydrotestosterone (FDHT) in prostate tumors as measured by PET. *J Nucl Med*. 2010 Feb;51(2):183-92. Epub 2010 Jan 15. PMID: PMC2866076.

B. Positions and Honors

Positions

1972-1975	Assistant Professor, Johns Hopkins Medical Institute, Baltimore, MD
1975-1976	Associate Professor, Oregon Health and Science University, Portland, OR
1976-1981	Associate Professor, University of Washington school of Medicine, Seattle, WA
1980-1988	Professor, University of Washington School of Medicine, Seattle, WA
1988-Present	Attending, Memorial Hospital, & Member, Sloan Kettering Institute (SKI), MSK, NY, NY
1988-Present	Professor of Radiology, Cornell University Medical College, NY, NY
1988-Present	Laboratory Head, Molecular Pharmacology and Chemistry Program, SKI, NY, NY
1995-2012	Director, Laurent and Alberta Gerschel PET Center, MSK, NY, NY
2001-2004	Director of Radiology Research, MSK, NY, NY
2004-2012	Vice Chairman for Radiology Research, MSK, NY, NY
2008-Present	Donna & Benjamin M. Rosen Chair in Radiology, MSK, NY, NY

Other Experience and Professional Memberships

1964-present Member, Society of Nuclear Medicine
1980-present Fellow, American College of Nuclear Physicians
1980-present Member, Radiological Society of North America
1988-present Member, American Society of Clinical Oncology
1990-present Member, American Society for Cancer Research
1991-present Fellow, American College of Radiology
1991-present Member, Institute for Clinical PET, Academy of Molecular Imaging
1995-present Fellow, New York Academy of Medicine
2000-present Member, Society of Nuclear Medicine Committee on Publications

Honors

2001 Wagner Lecture, Society of Nuclear Medicine, Toronto
2004 Radiological Society of North America Researcher of the Year
2005 Member, Institute of Medicine of the National Academy of Sciences
2005 Hevesy Nuclear Pioneer Award, Society of Nuclear Medicine
2005 Shining Spirit Award for Cancer Care, Paul Robert Carrey Foundation
2007 Peter Valk Award as the Distinguished Clinical Scientist of the Year
2008 Donna and Benjamin M. Rosen Chair in Radiology
2012 Benedict Cassen Prize for Research in Nuclear Medicine
2016 Saul Hertz Prize for Targeted Radiotherapy of the Society of Nuclear Medicine
2018 American College of Nuclear Medicine (ACNM) Gold Medal of Nuclear Medicine

C. Contributions to Science

1. **Radiopharmaceutical Development:** Since coming to MSK, I have led an effort to develop novel radiopharmaceuticals for implementation in research in both animals and humans. This effort has resulted in the introduction of over 40 new compounds, including radiolabeled antibodies, drugs, and nanoparticles, for application in oncology.
 - a. **Larson SM**, Nelp WB. Radiopharmacology of a simplified technetium-99m-colloid preparation for photoscanning. *J Nucl Med.* 1966;7(11):817-26.
 - b. Veach DR, Namavari M, Pillarsetty N, Santos EB, Beresten-Kochetkov T, Lambek C, Punzalan BJ, Antczak C, Smith-Jones PM, Djaballah H, Clarkson B, **Larson SM**. Synthesis and biological evaluation of a fluorine-18 derivative of dasatinib. *J Med Chem.* 2007;50(23):5853-7.
 - c. Benezra M, Hambarzumyan D, Penate-Medina O, Veach DR, Pillarsetty N, Smith-Jones P, Phillips E, Ozawa T, Zanzonico PB, Longo V, Holland EC, **Larson SM**, Bradbury MS. Fluorine-labeled dasatinib nanoformulations as targeted molecular imaging probes in a PDGFB-driven murine glioblastoma model. *Neoplasia.* 2012;14(12):1132-43. PMID: PMC3540940.
 - d. Phillips E, Penate-Medina O, Zanzonico PB, Carvajal RD, Mohan P, Ye Y, Humm J, Gönen M, Kalaigian H, Schöder H, Strauss HW, **Larson SM**, Wiesner U, Bradbury MS. Clinical translation of an ultrasmall inorganic optical-PET imaging nanoparticle probe. *Sci Transl Med.* 2014;6(260):260ra149. PMID: PMC4426391.
2. **Cancer Pharmacology Using Radiotracers:** Pharmacology studies provide insight into cancer biology.
 - a. Levchenko A, Mehta BM, Niu X, Kang G, Villafania L, Way D, Polycarpe D, Sadelain M, **Larson SM**. Intercellular transfer of P-glycoprotein mediates acquired multidrug resistance in tumor cells. *Proc Natl Acad Sci U S A.* 2005; 102(6):1933-8. Epub 2005 Jan 25. PMID: PMC545583.
 - b. Cheal SM, Xu H, Guo HF, Zanzonico PB, **Larson SM**, Cheung NK. Preclinical evaluation of multistep targeting of diasialoganglioside GD2 using an IgG-scFv bispecific antibody with high affinity for GD2 and DOTA metal complex. *Mol Cancer Ther.* 2014;13(7):1803-12. PMID: PMC4221074.
 - c. **Larson SM**, Pentlow KS, Volkow ND, Wolf AP, Finn RD, Lambrecht RM, Graham MC, Di Resta G, Bendriem B, Daghighian F, Yeh S, Wang G-J, Cheung NK. PET scanning of iodine-124-3F9 as an approach to tumor dosimetry during treatment planning for radioimmunotherapy in a child with neuroblastoma. *J Nucl Med.* 1992;33(11):2020-3.
 - d. Levchenko A, Mehta BM, Niu X, Kang G, Villafania L, Way D, Polycarpe D, Sadelain M, **Larson SM**. Intercellular transfer of P-glycoprotein mediates acquired multidrug resistance in tumor cells. *Proc Natl Acad Sci U S A.* 2005;102(6):1933-8. Epub 2005 Jan 25. PMID: PMC545583.

3. Clinical PET Development for Brain and Cancer Imaging. I have helped develop positron emission tomography (PET) as a clinical tool for oncology. I was recruited to the NIH in 1983, in part to establish a state-of-the-art PET center for NIH researchers, and later PET clinical research in oncology at MSK.
 - a. Duara R, Grady C, Haxby J, Sundaram M, Cutler NR, Heston L, Moore A, Schlageter N, **Larson S**, Rapoport SI. Positron emission tomography in Alzheimer's disease. *Neurology*. 1986;36(7):879-87.
 - b. Yarchoan R, Berg G, Brouwers P, Fischl MA, Spitzer AR, Wichman A, Grafman J, Thomas RV, Safai B, Brunetti A, Perno, CF, **Larson, SM**. Response of human-immunodeficiency-virus-associated neurological disease to 3'-azido-3'-deoxythymidine. *Lancet*. 1987;1(8525):132-5.
 - c. Ho AL, Grewal RK, Leboeuf R, Sherman EJ, Pfister DG, Deandreis D, Pentlow KS, Zanzonico PB, Haque S, Gavane S, Ghossein RA, Ricarte-Filho JC, Domínguez JM, Shen R, Tuttle RM, **Larson SM**, Fagin JA. Selumetinib-enhanced radioiodine uptake in advanced thyroid cancer. *N Engl J Med*. 2013;368(7):623-32. PMID: PMC3615415.
 - d. Patronas NJ, Di Chiro G, Kufra C, Bairamian D, Kornblith PL, Simon R, **Larson SM**. Prediction of survival in glioma patients by means of positron emission tomography. *J Neurosurg*. 1985;62(6):816-22.
4. Quantitative Technologies to Enhance Response Assessment in Nuclear Medicine. I have developed methods for response assessment used widely in nuclear medicine, such as total lesion glycolysis (multiple PET manufacturers), PET VCAR (GE), bone scan index (Exini), and radiographic progression interpretation scheme (incorporated into large-scale trials for testing prostate cancer therapies; e.g., abiraterone, enzalutamide).
 - a. **Larson SM**, Erdi Y, Akhurst T, Mazumdar M, Macapinlac HA, Finn RD, Casilla C, Fazzari M, Srivastava N, Yeung HW, Humm JL, Guillem J, Downey R, Karpeh M, Cohen AE, Ginsberg R. Tumor treatment response based on visual and quantitative changes in global tumor glycolysis using PET-FDG imaging. The visual response score and the change in total lesion glycolysis. *Clin Positron Imaging*. 1999;2(3):159-171.
 - b. Morris MJ, Molina A, Small EJ, de Bono JS, Logothetis CJ, Fizazi K, de Souza P, Kantoff PW, Higano CS, Li J, Kheoh T, **Larson SM**, Matheny SL, Naini V, Burzykowski T, Griffin TW, Scher HI, Ryan CJ. Radiographic progression-free survival as a response biomarker in metastatic castration-resistant prostate cancer: COU-AA-302 results. *J Clin Oncol*. 2015;33(12):1356-63. PMID: PMC4881370.
 - c. Ulmert D, Kaboteh R, Fox JJ, Savage C, Evans MJ, Lilja H, Abrahamsson PA, Björk T, Gerdtsson A, Bjartell A, Gjerdtsson P, Höglund P, Lomsky M, Ohlsson M, Richter J, Sadik M, Morris MJ, Scher HI, Sjöstrand K, Yu A, Suurküla M, Edenbrandt L, **Larson SM**. A novel automated platform for quantifying the extent of skeletal tumour involvement in prostate cancer patients using the Bone Scan Index. *Eur Urol*. 2012;62(1):78-84. PMID: PMC3402084.
 - d. Fox JJ, Autran-Blanc E, Morris MJ, Gavane S, Nehmeh S, Van Nuffel A, Gönen M, Schöder H, Humm JL, Scher HI, **Larson SM**. Practical approach for comparative analysis of multilesion molecular imaging using a semiautomated program for PET/CT. *J Nucl Med*. 2011;52(11):1727-32. PMID: PMC3409842.
5. Antibodies and Biologicals. I am currently the Director of Radioimmunotherapy and Theranostics, Ludwig Cancer Immunotherapy Center, SKI. More than 30 radioantibody protocols for theranostic applications have been performed at MSK in the last 10 years, primarily based on quantitative PET.
 - a. Pandit-Taskar N, O'Donoghue JA, Beylertgil V, Lyashchenko S, Ruan S, Solomon SB, Durack JC, Carrasquillo JA, Lefkowitz RA, Gonen M, Lewis JS, Holland JP, Cheal SM, Reuter VE, Osborne JR, Loda MF, Smith-Jones PM, Weber WA, Bander NH, Scher HI, Morris MJ, **Larson SM**. ⁸⁹Zr-huJ591 immuno-PET imaging in patients with advanced metastatic prostate cancer. *Eur J Nucl Med Mol Imaging*. 2014;41(11):2093-105. PMID: PMC4404641.
 - b. Kramer K, Kushner BH, Modak S, Pandit-Taskar N, Smith-Jones P, Zanzonico P, Humm JL, Xu H, Wolden SL, Souweidane MM, **Larson SM**, Cheung NK. Compartmental intrathecal radioimmunotherapy: results for treatment for metastatic CNS neuroblastoma. *J Neurooncol*. 2010;97(3):409-18. PMID: PMC3533371.
 - c. O'Donoghue JA, Smith-Jones PM, Humm JL, Ruan S, Pryma DA, Jungbluth AA, Divgi CR, Carrasquillo JA, Pandit-Taskar N, Fong Y, Strong VE, Kemeny NE, Old LJ, **Larson SM**. ¹²⁴I-huA33 antibody uptake is driven by A33 antigen concentration in tissues from colorectal cancer patients imaged by immuno-PET. *J Nucl Med*. 2011;52(12):1878-85. PMID: PMC3394180.
 - d. Kramer K, Humm JL, Souweidane MM, Zanzonico PB, Dunkel IJ, Gerald WL, Khakoo Y, Yeh SD, Yeung HW, Finn RD, Wolden SL, **Larson SM**, Cheung NK. Phase I study of targeted radioimmunotherapy for leptomeningeal cancers using intra-Ommaya 131-I-3F8. *J Clin Oncol*. 2007;25(34):5465-70.

Complete List of Published Work in MyBibliography:

<http://www.ncbi.nlm.nih.gov/sites/myncbi/steven.larson.1/bibliography/47640692/public/?sort=date&direction=ascending>

D. Research Support

1 R01 CA173592-01 (PI: Fagin) 09/19/2014 - 08/31/2019
NIH/NCI - Maximizing effectiveness of radioiodine therapy by inhibition of MAPK signaling

We will build on recent experimental and clinical breakthroughs by our research group that show that in a large fraction of patients, RAI refractoriness can be reversed by blocking ERK pathway activity (Role: Co-Investigator)

1 P50 CA172012-01 (PI: Fagin) 09/19/2014 - 08/31/2019
NIH/NCI (Core C) - SPORE in Thyroid Cancer (RP2: Maximizing Effectiveness of Radioiodine Therapy by Inhibiting MAPK Signaling; Core C: Administrative Core)

The goals of this SPORE in Thyroid Cancer are to leverage new insights on disease pathogenesis to improve the outcome of patients with thyroid cancer at all stages of presentation (Role: Co-Investigator)

1 R01 CA201250-01A1 (PI: Larson/Humm/Tuttle) 08/05/2016 - 07/31/2021
NIH/NCI (NIH) - ¹²⁴I-Nal PET: Building block for precision medicine in metastatic thyroid cancer

1 R01 CA233896-01 (PI: Cheal) 12/10/2018 - 11/30/2023
NIH/NCI (NIH) - DOTA-based pre-targeting of alpha emitters

We have developed a targeted theranostic molecular radiotherapy method known as the DOTA-PRIT platform based on antibodies suitable for use in treating common human tumors. Our studies in animal models have shown superior therapeutic index (TI). We propose using animal models of human colorectal cancer and human breast cancer to adapt the DOTA- PRIT platform for safe and effective tumor-targeting of actinium-225. Role: Co-investigator

GC230630 (PI: Morris) 12/31/2017 - 12/30/2019
Prostate Cancer Foundation

Characterizing mechanisms of sensitivity and resistance to anti-androgen therapy with whole-body
Role: Co-Investigator

5 P30 CA008748-53 (PI: Thompson/Larson) 01/20/2017 - 12/31/2023
NIH/NCI - Cancer Center Support Grant (Imaging and Radiation Sciences)

The CCSG funds support MSK's research infrastructure. These shared resources facilitate the research activities of the clinical, translational and laboratory programs at the Cancer Center (Role: MPI)

Completed Support

1 R01 CA207645-01 (PI: Osborne) 07/22/2016 - 06/30/2019
NIH/NCI (NIH) - A new technique to make ⁶⁸Ga-labeled pharmaceuticals widely available for clinical use

W81XWH-14-1-0444 (PI: Ulaner) 09/30/2014 - 09/29/2018
Congressionally Directed Medical Research Programs - Could HER2 heterogeneity open new therapeutic options in patients with HER2- primary breast cancer?

Our central hypothesis is that imaging with a targeted HER2 radiotracer will allow us to identify patients with HER2- primary breast cancers who develop HER2+ metastases, and who may benefit from the addition of HER2 therapy (Role: Consultant)

5 R01 CA161280-05 (PI: Bradbury) 03/12/2012 - 06/30/2018
NIH/NCI (NIH) - Renally Excreted Multimodal Core-Shell Silica Nanoparticles as Tumor-Selective Radiotherapeutic Platforms for Nanomedicine

1R21CA162602-01A1 (PI: Larson) 09/26/2011 - 08/31/2017
NIH/NCI (NIH) - ¹²⁴I-cG250 ImmunoPET Imaging of Sunitinib Treatment Response in Renal Cell Cancer

5 P50 CA086438-14 (PI: Larson/Blasberg) 06/01/2000 - 06/30/2016
NIH/NCI (NIH) - MSKCC Center for Molecular Imaging in Cancer (Research Project 4 - Refining Antiandrogen Therapy for Prostate Cancer through Positron Emission Tomography)

GC224325 (PI: Scheinberg/Larson) 01/01/2015 - 03/31/2016
Experimental Therapeutics Center - Pre-targeted Radioimmunotherapy (PRIT) in Breast Cancer and Other HER2-Expressing Human Tumors (Role: Co-PI)