

PROMOTION RECOMMENDATION  
THE UNIVERSITY OF MICHIGAN  
MEDICAL SCHOOL  
DEPARTMENT OF MOLECULAR AND INTEGRATIVE PHYSIOLOGY  
DEPARTMENT OF INTERNAL MEDICINE

Costas A. Lyssiotis, Ph.D., assistant professor of molecular and integrative physiology, Department of Molecular and Integrative Physiology, and assistant professor of internal medicine, Department of Internal Medicine, Medical School, is recommended for promotion to associate professor of molecular and integrative physiology, with tenure, Department of Molecular and Integrative Physiology, and associate professor of internal medicine, without tenure, Department of Internal Medicine, Medical School.

Academic Degrees:

Ph.D.	2010	The Scripps Research Institute, La Jolla
B.S.	2004	University of Michigan

Professional Record:

2015-present      Assistant Professor of Molecular and Integrative Physiology,  
University of Michigan

2015-present      Assistant Professor of Internal Medicine,  
University of Michigan

Summary of Evaluation:

Teaching: Dr. Lyssiotis is an active instructor in the classroom, and lectures in Chemical Biology 502: Advanced Concepts in Chemical Biology, Cancer Biology 554: Science of Cancer, Pathology 581: Tissue, Cellular and Molecular Basis of Disease, PIBS 503: Course in Responsible Conduct in Research, and Physiology 514: Nutrient Metabolism and Gut Physiology. He has consistently received outstanding teaching evaluations for his knowledge, organized and engaging lectures. Dr. Lyssiotis is an outstanding mentor to trainees at all academic levels including clinical and post-doctoral fellows. Several of his trainees have received major national recognition, which illustrates his exceptional mentorship skills in training productive and successful junior scientists who are making ground breaking advances in pancreatic cancer research. Dr. Nneka Mbah, a post-doctoral fellow in his laboratory, was awarded a ChadTough Foundation Defeat DIPG Post-doctoral Fellowship in February 2020. In August 2020, Ayush Trivedi, a summer research fellow, received the 2020 Spring Blue Ribbon Winner from the Biomedical and Life Sciences Summer Fellowship Program for his work in the Lyssiotis lab.

Research: Dr. Lyssiotis' research focuses on the biochemical pathways and metabolic requirements that enable tumor growth and immune evasion. He uses mass spectrometry-based metabolomics technology to learn about metabolic processes in cancer. His research productivity is exceptional: he has published a total of 95 peer-reviewed articles in very prestigious journals. Dr. Lyssiotis is the principal investigator on six NIH R01 grants, one foundation grant and one industry grant and a co-principal investigator of one NIH P01 grant, and a foundation grant. Additionally, he is a co-investigator on eight additional grants. He is the holder of five patents.

Dr. Lyssiotis is a highly sought after speaker, with 50 extramural regional, national and international presentations to his credit. In 2017, he was invited by the National Cancer Research Institute Cancer Conference in Liverpool, United Kingdom. In 2018, he presented at grand rounds at the London Regional Cancer Program at the University of Western Ontario, Canada. In June 2020, he was invited to the American Association for Cancer Research, Annual Meeting Educational Session: Exploiting Metabolic Vulnerabilities in Cancer which was moved to a virtual seminar due to the COVID-19 pandemic. This past July, Dr. Lyssiotis was invited by the National Institutes of Health Consortium on Pancreatic Cancer Microenvironmental Networks which was also held virtually.

#### Recent and Significant Publications:

Little AC, Kovalenko I, Goo LE, Hong HS, Kerk S, Yates JA, Purohit V, Lombard D, Merajver S, Lyssiotis CA: Integration of high-content fluorescence imaging into the metabolic flux assay reveals insights into mitochondrial properties and functions. *Communications Biology*, 3:271, 2020. PMID: PMC7260371

Kremer DM, Nelson BS, Lin L, Sajjakulnukit P, Myers A, Thurston G, Halbrook CJ, Andren AC, Nwosu ZC, Cousmano N, Wisner S, Ramos J, Gao T, Yarosz, Badgley MA, Zhang L, Asara JM, Shah Y, Crawford HC, Olive KP, Lyssiotis CA: GOT1 Inhibition Primes Pancreatic Cancer for Ferroptosis through the Autophagic Release of Labile Iron. *Nature Chemical Biology*, in revision. Preprint available at [bioRxiv https://doi.org/10.1101/2020.02.28.970228](https://doi.org/10.1101/2020.02.28.970228)

Lee H-J, Kremer DM, Sajjakulnukit P, Zhang L, Lyssiotis CA: A large-scale analysis of targeted metabolomics data from heterogeneous biological samples provides insights into metabolite dynamics. *Metabolomics*, 15:103, 2019. PMID: PMC6616221

Halbrook CJ, Pontious C, Lee H-J, Kovalenko I, Zhang Y, Lapienyte L, Dreyer S, Kremer DL, Zhang L, Sajjakulnukit P, Zhang L, Nelson B, Hong H, Kemp S, Chang D, Biankin A, Crawford HC, Morton JP, Pasca di Magliano M, Lyssiotis CA. Macrophage Released Pyrimidines Inhibit Gemcitabine Therapy in Pancreatic Cancer. *Cell Metabolism*, 29:1390-1399, 2019. PMID: PMC6602533

Sousa CM, Biancur DE, Wang X, Halbrook CJ, Sherman MH, Zhang L, Kremer D, Hwang RF, Witkiewicz AK, Ying H, Asara JM, Evans RM, Cantley LC, Lyssiotis CA, Kimmelman AC: Pancreatic Stellate Cells Support Tumor Metabolism Through Autophagic Alanine Secretion. *Nature* 536:479–483, 2016. PMID: PMC6602533

Service: Since arriving at the University of Michigan, Dr. Lyssiotis has provided exceptional service to our institution and his academic community. Institutionally, he has been the conference organizer for Cayman Chemical symposiums. He serves in the executive committee of two T32 training grants: Cancer Biology, Immunology and Integrative Biology. Dr. Lyssiotis is also involved in several interest groups holding seminars, journals clubs and combined research meetings. In the Department of Molecular and Integrative Physiology, Dr. Lyssiotis serves as a member of the seminar series, graduate program committee, department remodeling committee and the annual Physiology Forum committee. At the national level, Dr. Lyssiotis organized a virtual symposium on Cancer Metabolism and Signaling for the New York Academy of Sciences

and educational session chair for the Annual American Association for Cancer Research Meeting on COVID19 pandemic research. Dr. Lyssiotis serves as a journal reviewer for over 20 journals including the prestigious, *Cell*, *JCI Insight* and *Nature*.

External Reviewers:

Reviewer A: “His work has been consistently of the highest quality, and his efforts to define mechanisms that underlie the complex interplay between metabolism and tumor cell fitness have yielded important insights into the biological drivers and therapeutic barriers of pancreatic cancer.”

Reviewer B: “Costas has continued to help pioneer the study of altered metabolism in pancreas cancer, most recently extending beyond purely cell intrinsic adaptations to identifying multiple aspects of a critical and previously unappreciated, metabolic dialog between the evolving tumor cell and surrounding stromal cells...The prominent journals in which these studies appeared, together with the several editorial commentaries accompanying their publication speak to the impact of the work on the field. At the same time, Costas has developed novel methodologies to enable both new types of inquiries in cancer metabolism and also expand the accessibility of such undertakings to a wider community”

Reviewer C: “His CV speaks for itself. The only additional comment I would make is that he clearly is a great colleague, based on the number of collaborative papers he has, and based on my interactions with him. He gives back to both U Michigan and to the field with key service as a reviewer and a scholar if you just have questions about metabolomics.”

Reviewer D: “He spoke on his work about the release of pyrimidines from tumor-associated macrophages. These pyrimidines seem to form the basis of intercellular communication, and also appear to confer chemoresistance to Gemcitabine, a frequently prescribed anti-pyrimidine nucleoside. Costas’s chemical biology roots were evident in this work, and it’s clear that he has the broad skill set necessary to make fundamental discoveries about biology that may translate into real therapeutic opportunities, which is rare.”

Reviewer E: “It is clear that Costas is a rising star in the area of cancer metabolomics, particularly in pancreatic cancer where he is already among the most well-known investigators in the field. He is truly the total package. His work exemplifies a deep understanding of biology/physiology, he is using the most cutting-edge technical approaches to tackle his questions, he has expertise in chemical biology, and he is extremely well connected.”

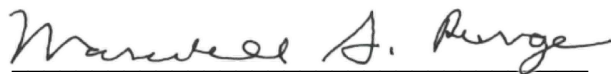
Reviewer F: “Dr. Lyssiotis also has a very impressive record of service. He has served as an ad hoc member of many grant review panels and was recently named a permanent member of CAMP NIH study section. Beyond this, Dr. Lyssiotis has a strong record of service to the university and the international research community through paper review, conference organization and many other activities. Given all of these impressive features of his resume, Dr. Lyssiotis has a very good reputation and standing in the field as evidenced by invited seminars and being invited as a speaker at international conferences.”

Reviewer G: “In subsequent work, Dr. Lyssiotis found that stromal macrophages release pyrimidines which the cancer cells use for nucleotide synthesis (Halbrook et al., *Cell Metabolism*,

2019). Both of these papers represent milestones as they forced the metabolism field away from solely a cancer cell focus to also consider the dynamics between cancer and stromal cells as well as the vasculature...Most interestingly to me, he has been greatly pushing the number of metabolites that can be reliably analyzed using a targeted approach and so far measured over 600, a remarkable achievement (Lee et al., *Metabolomics*, 2019)...A very noteworthy aspect of Dr. Lyssiotis is his collegiality and highly collaborative nature. I have never seen anyone, even if I consider very senior investigators, with as many collaborative grants, projects, and papers as Dr. Lyssiotis. I think this is wonderful and speaks to his very interactive and curious character, which shines forth when you interact with him in person.”

Summary of Recommendations:

Dr. Lyssiotis is an outstanding scientist and leader in the field of pancreatic cancer research. His research is well funded and he has an impressive record of publications in top-tier journals. His research is collaborative and he is undoubtedly a rising star in his field. I am pleased to recommend Costas A. Lyssiotis, Ph.D. for promotion to associate professor of molecular and integrative physiology, with tenure, Department of Molecular and Integrative Physiology, and associate professor of internal medicine, without tenure, Department of Internal Medicine, Medical School.



Marschall S. Runge, MD, PhD  
Executive Vice President of Medical Affairs  
Dean, Medical School

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