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HUMAN ONCOLOGY & PATHOGENESIS PROGRAM

The James Fagin Lab

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[Research](#)

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James A. Fagin, MD

The focus of the Fagin lab is to understand the pathogenesis and the biology of thyroid cancers at single cell resolution with the goal of identifying new mechanism-based therapies. His group has been instrumental in characterizing somatic genetic changes associated with tumor initiation and progression in radiation-induced and sporadic thyroid cancer, and in defining their functional consequences. He showed that selective MEK and RAF kinase inhibitors restored thyroid differentiation and responsiveness to radioactive iodine in GEM models of the disease, which led to the development of innovative clinical trials showing significant promise of this therapeutic strategy. His group also defined novel mechanisms of adaptive resistance of BRAF-mutant thyroid cancers to MAPK pathway inhibitors. The improved efficacy of one of these approaches, the co-targeting of RAF and HER2/HER3 has recently been confirmed in phase II trials. In addition to these studies, the lab is currently working in the following areas:

1. Investigation of the role of the HIPPO pathway as a rheostat regulating adaptive resistance to small molecules targeting the MAPK pathway in thyroid cancer and other cell lineages.
2. Advanced thyroid cancers have increased frequency of mutations of genes encoding chromatin remodeling proteins, including several members of the SWI/SNF chromatin remodelling complex. His group is systematically exploring the impact of individual Swi/Snf and histone methyl transferase disruptions on the chromatin and transcriptional landscape of thyroid cancers in GEMM. Current evidence indicates that they lock thyroid tumor cells into an undifferentiated state that can no longer be reversed by MAPK pathway blockade, while creating new and unanticipated therapeutic vulnerabilities.
3. A hallmark of anaplastic thyroid cancers is their heavy infiltration with T cells and myeloid cells. He is investigating how profound MAPK pathway inhibition reprograms these tumors at single cell resolution. The lab is also investigating how cell autonomous antigen presentation and the tumor microenvironment contribute to promote T cell cytotoxicity. In a related project, his group is collaborating with the Levine lab to investigate whether tumor-infiltrating myeloid cells harboring mutations of *Tet2*, *Dnmt3a* or *Axsl1*, which are hallmarks of clonal hematopoiesis, confer refractoriness to therapy in GEMM with Braf-driven ATC.
4. The Fagin and Nai-Kong Cheung labs are collaborating to develop bispecific antibodies to target unique changes in the membrane proteome of thyroid cancers in response to MAPK pathway blockade.

[View Lab Overview \(https://www.sloankettering.edu/research-areas/labs/james-fagin/overview\)](https://www.sloankettering.edu/research-areas/labs/james-fagin/overview)



Featured News



[At Work: Endocrinology Service Chief James Fagin](#)

Endocrinologist James Fagin's thyroid cancer research involves understanding the disease's biology and genetics and identifying new therapy targets.



IN THE LAB

[Study Reveals Genetic Causes for Thyroid Cancer Increase after Chernobyl](#)

The study of some victims exposed to ionizing radiation from the 1986 Chernobyl nuclear power plant accident is yielding new information about how radiation-induced thyroid cancer develops.



IN THE LAB

[Investigators Sequence the Genome of a Rare Head and Neck Cancer](#)

Investigators have sequenced the genome of adenoid cystic carcinoma, a rare and deadly head and neck cancer. The work sets the stage for the sequencing of additional rare cancers at Memorial Sloan Kettering.

Publications Highlights

[Pathogenesis of cancers derived from thyroid follicular cells.](#) Fagin JA, Krishnamoorthy GP, Landa I. Nat Rev Cancer. 2023 Sep;23(9):631-650. doi: 10.1038/s41568-023-00598-y. Epub 2023 Jul 12. PMID: 37438605

[Genomic and Transcriptomic Characteristics of Metastatic Thyroid Cancers with Exceptional Responses to Radioactive Iodine Therapy.](#) Boucai L, Saqcena M, Kuo F, Grewal RK, Socci N, Knauf JA, Krishnamoorthy GP, Ryder M, Ho AL, Ghossein RA, Morris LGT, Seshan V, Fagin JA. Clin Cancer Res. 2023 Apr 14;29(8):1620-1630. doi: 10.1158/1078-0432.CCR-22-2882

[Yap governs a lineage-specific neuregulin1 pathway-driven adaptive resistance to RAF kinase inhibitors.](#) Garcia-Rendueles MER, Krishnamoorthy G, Saqcena M, Acuña-Ruiz A, Revilla G, de Stanchina E, Knauf JA, Lester R, Xu B, Ghossein RA, Fagin JA. Mol Cancer. 2022 Dec 7;21(1):213. doi: 10.1186/s12943-022-01676-9. PMID: 36476495

[SWI/SNF Complex Mutations Promote Thyroid Tumor Progression and Insensitivity to Redifferentiation Therapies.](#) Saqcena M, Leandro-Garcia LJ, Maag JLV, Tchekmedyan V, Krishnamoorthy GP, Tamarapu PP, Tiedje V, Reuter V, Knauf JA, de Stanchina E, Xu B, Liao XH, Refetoff S, Ghossein R, Chi P, Ho AL, Koche RP, Fagin JA. Cancer Discov. 2021

May;11(5):1158-1175. doi: 10.1158/2159-8290.CD-20-0735. Epub 2020 Dec 14.
PMID: 33318036

[EIF1AX and RAS Mutations Cooperate to Drive Thyroid Tumorigenesis through ATF4 and c-MYC.](#) Krishnamoorthy GP, Davidson NR, Leach SD, Zhao Z, Lowe SW, Lee G, Landa I, Nagarajah J, Saqcena M, Singh K, Wendel HG, Dogan S, Tamarapu PP, Blenis J, Ghossein RA, Knauf JA, Rättsch G, Fagin JA. *Cancer Discov.* 2019 Feb;9(2):264-281. doi: 10.1158/2159-8290.CD-18-0606. Epub 2018 Oct 10. PMID: 30305285

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People

James A. Fagin, MD


Member, Human Oncology & Pathogenesis Program

Professor

- Physician-scientist James Fagin focuses on the pathogenesis of thyroid cancer and the role of oncogenic kinases.
- MD, University of Buenos Aires School of Medicine (Argentina)

 [646-888-2136](tel:646-888-2136)

Office Phone

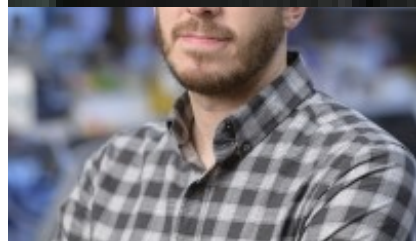
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Physician profile

Members

Lab

Alumni



Adrián Acuña Ruíz
Research Fellow



Laura Boucai
Associate Attending

Lab Affiliations

Achievements

- President, American Thyroid Association (2012)
- UK Clinical Endocrinology Trust

- Medal Lecture Award (2011)

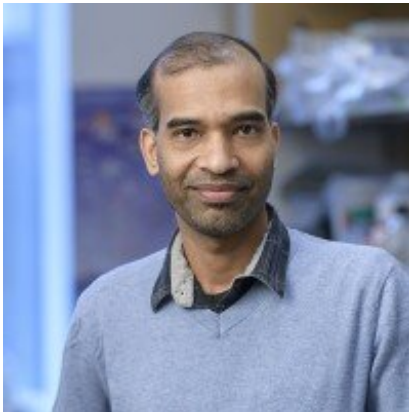


Emily Coty
Research Technician



Alan L. Ho
Associate Attending

- Sydney Ingbar Award, American Thyroid Association (2008)
- Merck Prize, European Thyroid Association Award (2007)
- Association of American Physicians Award (2001)



Gnana Prakasam
Krishnamoorthy
Senior Research Scientist



Rona Lester
Research Assistant
Eric Sherman
Attending

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Komal Solanki
Senior Research Technician



Vera Tiedje
Visiting Investigator

Get in Touch

 [646-888-2136](tel:646-888-2136)

Office Phone

Disclosures

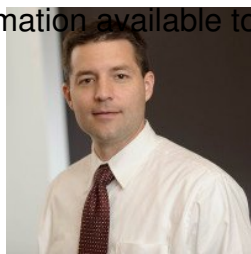
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These activities outside of MSK further our mission, provide productive collaborations, and promote the practical application of scientific discoveries.

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Chelsea Toussaint
Administrative Assistant



Brian Untch
Assistant Attending

community, we make that information available to the public. Not all disclosed interests and relationships present conflicts of interest. MSK reviews all disclosed interests and relationships to assess whether a conflict of interest exists and whether formal COI management is needed.

James A. Fagin discloses the following relationships and financial interests:

- Kura Oncology
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