HUMAN ONCOLOGY & PATHOGENESIS PROGRAM

The James Fagin Lab

Research

James A. Fagin, MD
Head, Division of Subspecialty Medicine; Member, Human Oncology & Pathogenesis Program

Professor

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 →

Featured News

[At Work: Endocrinology Service Chief James Fagin]

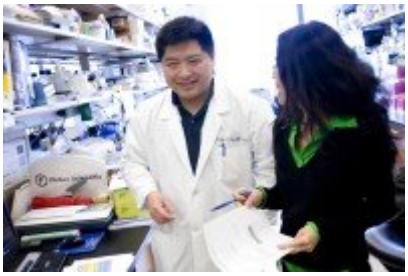
Endocrinologist James Fagin’s thyroid cancer research involves understanding the disease’s biology and genetics and identifying new therapy targets.

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

Montero-Conde C, Ruiz-Llorente S, Dominguez JM, Knauf JA, Viale AJ, Sherman EJ, Ryder M, Ghossein RA, Rosen N, Fagin JA. Relief of feedback inhibition of HER3 transcription by RAF and MEK inhibitors attenuates their antitumor effects in BRAF mutant thyroid carcinomas. Cancer Discovery 2013, May;3(5):520-33.

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, Dominguez JM, Shen R, Tuttle RM, Larson SM, Fagin JA. Selumetinib-enhanced radioiodine uptake in advanced thyroid cancer. Engl J Med 2013; Feb 14;368(7):623-32.

Chakravarty D, Santos E, Ryder M, Knauf J, Liao XH, West B, Bollag G, Kolesnick R, Thin T,

Rosen N, Zanzonico P, Larson S, Refetoff S, Ghossein R, Fagin JA. Small-molecule MAPK inhibitors restore RAI incorporation in murine thyroid cancers with conditional BRAF activation. J Clin Invest. 2011 121(12):4700-11.

Franco AT, Malaguarnera R, Refetoff S, Liao XH, Lundsmith E, Kimura S, Pritchard C, Marais R, Davies TF, Weinstein LS, Chen M, Rosen N, Ghossein R, Knauf JA, Fagin JA. Thyrotrophin receptor signaling dependence of Braf-induced thyroid tumor initiation in mice. Proc Natl Acad Sci U S A. 2011 Jan 10 108(4):1615-20.

Chen X, Mitsutake N, LaPerle K, Akeno N, Zanzonico P, Longo V, Mitsutake S, Kimura E, Geiger H, Santos E, Wendel HG, Franco A, Knauf JA, Fagin JA. Endogenous Expression Of HrasG12V Induces Developmental Defects and Neoplasms with Copy Number Imbalances Of The Oncogene. Proc. Natl Acad Sci USA, 2009 12;106(19):7979-84.

View All Publications

People

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Professor

Physician-scientist James Fagin focuses on the pathogenesis of thyroid cancer and the role of oncogenic kinases.

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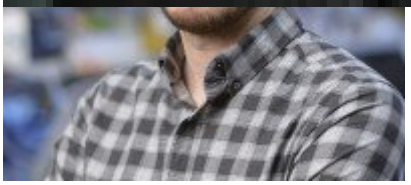

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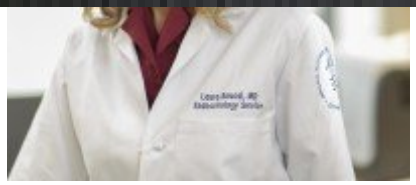

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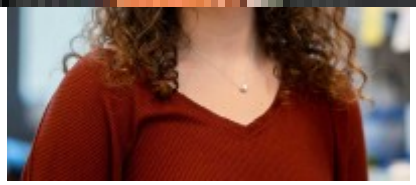

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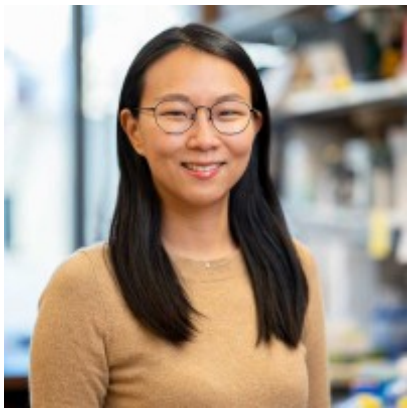

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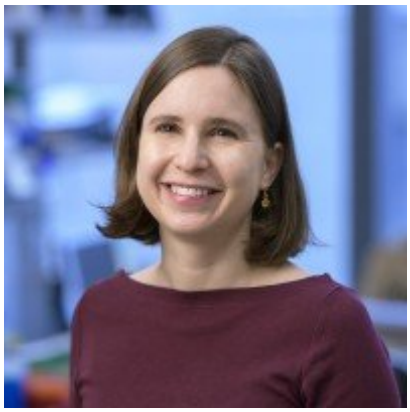

Vera Tiedje

Senior Research Scientist

Brian Untch

Assistant Attending

Mandakini Venkatramani

Research Scholar

Lab Alumni
+

Lab Affiliations
+

Achievements

President, American Thyroid Association (2012)

UK Clinical Endocrinology Trust Medal Lecture Award (2011)

Sydney Ingbar Award, American Thyroid Association (2008)

Merck Prize, European Thyroid Association Award (2007)

Association of American Physicians Award (2001)

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

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