Dana-Farber Cancer Institute

SETHI LAB NEWSLETTER

JULY 1st, 2025

Our lab's mission is to transform clinical observations, patient data, and rigorous investigation into discoveries that create opportunities for meaningful advances in patient care. We are passionate about research because of its power to generate deeper insights into human disease and ultimately improve clinical practice. Our work focuses on unraveling the biology of how gastrointestinal cancers initiate, combining basic science with translational research. By bridging these worlds, we hope to develop new ways to prevent and treat these devastating diseases.

Facing an Uncertain Future for Science: As we share our lab's latest work, we must also acknowledge a harsh reality: the current funding climate for biomedical research in the U.S. has become dangerously unstable due to dramatic and shortsighted decisions by the current administration. The situation is made worse by parallel efforts to dismantle diversity, equity, and inclusion programs and weaken immigration pipelines that bring talented young scientists from every corner of the globe. Our own lab has lost the ability to include international collaborators on grants, and many promising proposals are going unfunded due to drastic budget reductions. More broadly, this climate sends the wrong message to the next generation. The pandemic already shifted many young people away from demanding but deeply meaningful careers in medicine and science. Now, massive funding cuts and anti-immigration policies only reinforce the perception that these lifelong callings are too uncertain to pursue - at a time when we need new minds and diverse perspectives more than ever. Please stand with us: write to your elected officials, support research groups, and help spread the word. Together, we can protect the engine of discovery that drives life-saving progress.

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RESEARCH UPDATES

- **July 2024 –** Initiated a project on KRAS therapeutics with support from Novartis (**Yingbo**). We contributed to a publication on diffuse subtype gastric cancer (**Daulet**, *Gut*)
- **Aug. 2024 –** Evidence that SOX9 directly binds BAF member SMARCB1 (**Raghawan**)
- **Sept. 2024** – Lab's first NIH R01 is funded by the NCI at NIH
- **Oct. 2024** – Major breakthrough: heme biosynthesis linked to stem cell biology (**Xiaolu**)
- **Nov. 2024 –** Mediator complex emerges as a gatekeeper of differentiation (**Yingbo**)
- **Dec. 2024** – Pearl and Xi join the lab!
- **Jan. 2025** – Invited to write broad review on gastric cancer (**Nilay**, *JAMA*)
- **Feb. 2025** – Major milestone in undefined polyposis organoid model development
- **March 2025 –** We contributed to a key publication in esophageal cancer, exposing malignant cell states at single cell resolution (**Siddhi, Raghawan,** *Cell Reports Medicine*)
- **June 2025** – Landmark publication showing that HDAC1/2 inhibitors can promote differentiation in colorectal cancer (**Zhixin, Pornlada, Paul,** *Gastroenterology*)

LAB MEMBERS AND MENTORSHIP

Updates and New Members:

Viviana Cortiana, BS: a visiting Italian medical student who was awarded a prestigious fellowship by the Armenise-Harvard Foundation to investigate KRAS inhibitors

Giovanna Panetta: a Harvard undergraduate who is studying immune surveillance in gastrointestinal precancer

Supakrit Kositbovornchai, MD: a medical school graduate from Siriraj Hospital (Thailand) who will lead drug discovery efforts in the lab (Harvard ICCB and Broad)

Jia Liu, PhD: a new postdoctoral fellow who is studying immunoediting in gastrointestinal precancer using in vivo immunodeficiency mouse models and single cell genomics

Pearl Lie, PhD: Scientist/lab manager who is leading the *in vivo* program, studying Sox9 in a novel mouse model, as well as immunoediting in gastrointestinal precancer

Xi Pu, BS: a visiting scholar and Clinical Medicine graduate from China who is studying gastric cancer and supporting the investigation of KRAS inhibitors

Anoushka Chinmayi: Master's student at Johns Hopkins studying SOX9 partners via *in silico* modeling

Zhixin Li, PhD: a computational biologist leading and supporting multiple studies related to single cell RNA and epigenetic programs in gastrointestinal cancers

David Chen: a University of Toronto medical student providing computational support for multiple projects

Raghawan Akhouri, PhD: a postdoctoral fellow who is leading biochemical and structural studies of SOX9 and BAF complex

Xiaolu Wang, PhD: a postdoctoral fellow studying metabolic pathways and their dysregulation in GI cancers

Yingbo Huang, PhD: a postdoctoral fellow who is investigating resistance mechanisms to new KRAS inhibitors in CRC

Evan Hsiang: Harvard college undergrad, former Herchel Smith Fellow, and current AGA Young Gut Scholar studying SOX9 biochemical partners

Anopa Makovere: an undergraduate from Sattler College studying Sox9 and its biochemical partners

Departing Members:

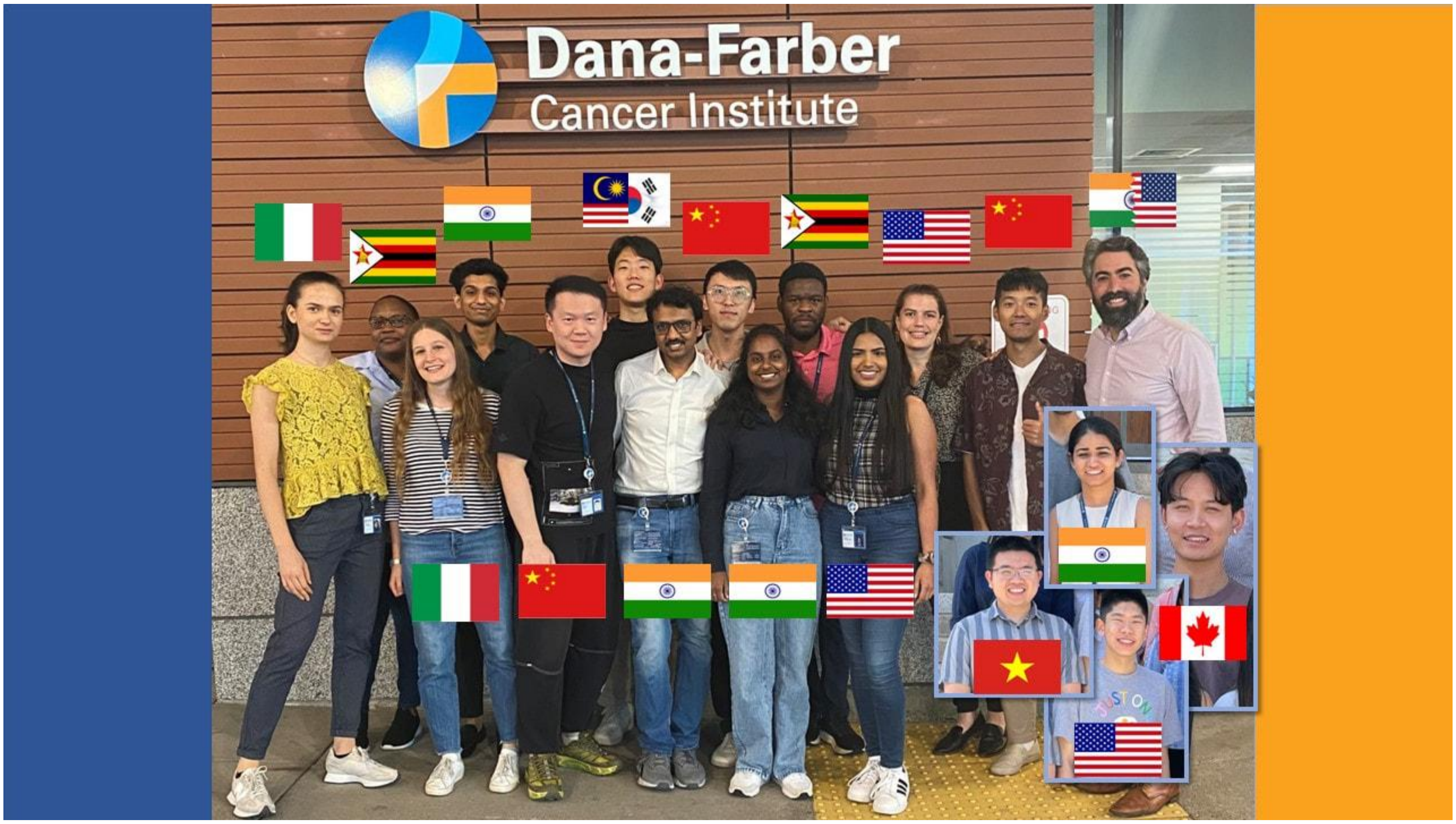
Paul Doan: a Harvard graduate turned technician who developed novel biotechnologies in the lab was accepted to UC Davis medical school. He published two co-first author papers while in the lab, which is simply remarkable!

Siddhi Balamurali, BS: a Cornell graduate turned technician who is departing for a data analyst position

Jinxian He, MD: a visiting scholar from China who returned to his position as a physician

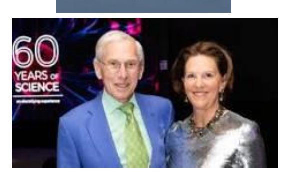
Yashika Parashar, MD, MMSc: a physician from India & Harvard MMSc graduate studying polyposis and HER2+ gastric cancer

Haram Kim: a Princeton graduate turned technician who is pursuing a career in music



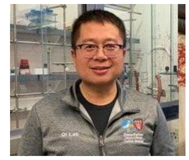
FUNDING & PHILANTHROPY

- We were awarded a **four-year grant** from the **American Cancer Society** (2025-2029) to study how SOX9 imparts epigenetic regulation in CRC
- We are supported by a **five-year R01 grant** from the **National Cancer Institute** (2024-2029) to study the function of SOX9 and developmental reprogramming.
- We benefit from a **three-year grant** from the **DFCI Innovation Research Fund** (2024-2027) to study how SOX9 interacts with the BAF complex in CRC.
- We have made progress on **three-year grant** from **Novartis's Drug Discovery & Translational Research Program** (2024-2027) to study KRAS therapeutics.
- We are completing a **four-year grant** from the **Department of Defense** (2021-2025) to study hyperactive stem cell programs (CSVCC; 8 scholars).
- We greatly depend on **Howard and Wendy Cox** who funded a **five-year drug discovery effort (2022-2027)** to identify next-generation therapeutics for GI cancers using a novel platform. This project involves close collaborations with James Cleary, Jun Qi, & Harvard ICCB.



- We finished a two-year grant from **Colorectal Cancer Alliance** to understand the mechanism of action of a pro-differentiation therapeutic.

- Thank you to those who generously contributed to the lab to support esophageal, gastric, colorectal, and small intestinal cancer research:
    - Dave's Fund for Esophageal Cancer Research
    - David Fischer and Carol O'Connor-Fischer
    - Duncan Richardson
    - Howard & Wendy Cox Colorectal Cancer Therapeutics Discovery Fund
    - Paul Derocher Fund for Small Intestine Cancer Research
    - Nick Tierney Gastric Cancer Fund
    - Pan-Mass Challenge (PMC) Team Detect Me If You Can
    - American Cancer Society, Inc.
    - Colorectal Cancer Alliance
    - Gastric Cancer Foundation
    - The DeGregorio Family Foundation
    - Karin Grunebaum Cancer Research Foundation
    - American Gastroenterological Association Research Foundation


Jun Qi, PhD


James Cleary, MD, PhD

Please consider joining our Jimmy Fund Team and walking with me on **Oct 5th, 2025** in Boston, MA. We have raised almost $100,000 for young-onset colorectal cancer research since 2021. We value this critical partnership between research and community.

DEDICATION

We dedicate our efforts in memory of **Adam Opiela** a 30-year-old young man whose life was cut short by metastatic colorectal cancer on **July 25, 2021**. Adam was more than a patient; he was a kind, thoughtful, and compassionate soul whose presence left an indelible mark on everyone who knew him. His strength, generosity, and quiet resilience in the face of an unforgiving disease continue to inspire our work each day. Adam's story is a powerful reminder of why we must do better. He faced cancer with courage and grace, but his passing underscores the urgent need for earlier detection, more effective treatments, and a deeper understanding of the biology driving colorectal cancer, especially in young adults, where cases are rising at an alarming rate. His memory fuels our commitment to discovery, compassion, and progress. Our goal is to ensure that future patients benefit from the advances in science that Adam's family has so generously supported, even in the midst of hardship. He will always remain at the heart of our mission.

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