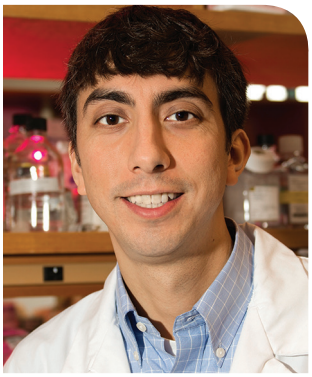
Aaron Hata, MD, PhD



Hata Laboratory

https://hatalab.mgh.harvard.edu

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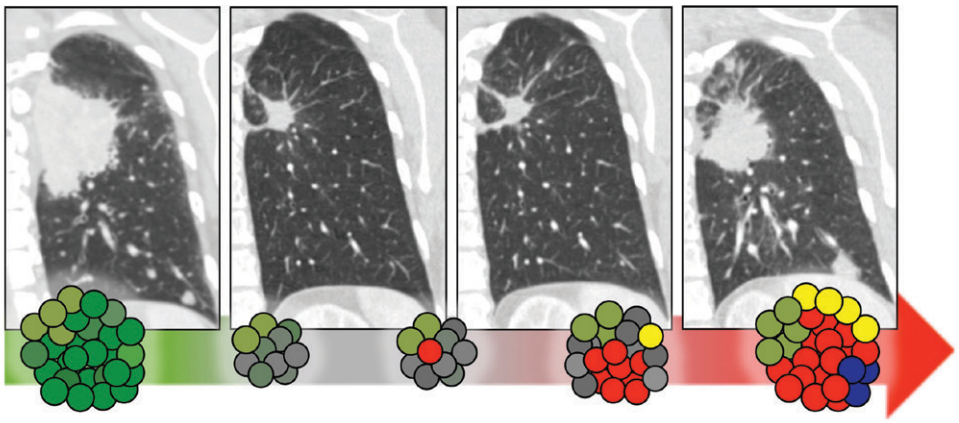
The research goal of **the Hata laboratory** is to advance the development of novel targeted and immunotherapy approaches to benefit patients with lung cancer. Our focus is on understanding biological mechanisms that dictate drug sensitivity and resistance in oncogene-addicted lung cancers (those with activating genetic alterations EGFR, ALK, KRAS, etc.). Our approach is highly translational, integrating assessment of clinical specimens with generation and analysis of patient-derived cell culture and mouse tumor xenograft (PDX) models, performed in close collaboration with clinicians in the MGH Thoracic Oncology group. We have discovered clinical mechanisms of acquired drug resistance and identified therapeutic strategies to overcome them. Our work has also shed light on how cancer cells adapt and evolve during the course of therapy and we are currently working to identify targetable vulnerabilities in cancer cells that can be exploited to prevent resistance from developing in the first place. Our ultimate goal is to translate our laboratory discoveries into clinical trials.

Mechanisms of acquired drug resistance to targeted therapies

Lung cancers that harbor activating EGFR mutations and ALK fusions are exquisitely sensitive to small molecule EGFR and ALK tyrosine kinase inhibitors, respectively. However, even though most patients experience dramatic responses, drug resistance invariably develops leading to disease relapse. Similar patterns of sensitivity and acquired resistance are also observed in other subsets of oncogene-addicted lung cancers treated with molecularly targeted therapies (e.g. ROS1 fusions, RET fusions, BRAF mutations, MET exon 14 skipping mutations). We work closely with oncologists in the MGH Center for Thoracic Cancers to identify and characterize mechanisms of acquired resistance in lung cancer patients treated with targeted therapies. By analyzing tumor biopsies or tumor DNA isolated from blood, we have identified acquired secondary mutations and other genomic alterations that cause drug resistance. To functionally interrogate mechanisms of drug resistance, we have developed a robust infrastructure for generating patient-derived cell lines and mouse patient-derived xenograft (PDX) models from lung cancer patients treated with targeted therapies at the MGH Cancer Center. These models have allowed us to identify novel mechanisms of acquired resistance and test potential new therapies to overcome them.

Targeting KRAS mutant lung cancers

Mutant-selective KRAS inhibitors have recently entered the clinic, however responses are seen in only a minority of patients. Work by our group revealed that many KRAS mutant lung cancers exhibit decreased oncogenic dependency and a dampened apoptotic response that contributes to intrinsic resistance to KRAS targeted therapy. To overcome this limitation, we are exploring novel therapeutic combinations that can overcome these



EGFR mutant lung cancers can develop acquired resistance to EGFR inhibitors (e.g. acquisition of the gatekeeper EGFR^{T790M} mutation) by selection of pre-existing EGFR^{T790M} cells, or via evolution of initially EGFR^{T790M}-negative drug tolerant cells that then develop the mutation during the course of treatment. EGFRi denotes EGFR inhibitor treatment, such as gefitinib or erlotinib. Reproduced from Hata and Niederst, et al. Nature Medicine 2016.

mechanisms and increase sensitivity to KRAS inhibitors. In addition, we are focused on understanding how both inter-patient and intratumoral heterogeneity may influence initial drug response and the development of acquired drug resistance.

Tumor adaptation and evolution during treatment

Despite the development of successive generations of targeted therapies with improved selectivity and potency, acquired resistance inevitably develops. To halt this perpetual cycle of drug resistance, we are investigating novel therapeutic strategies to alter the tumor evolution prior to the development of drug resistance. Our discovery that drug tolerant clones that survive initial therapy can acquire a "second genomic hit" enabling outgrowth of fully resistant clones suggests that these cells may comprise a cellular reservoir from which heterogeneous mechanisms of resistance may arise. Ongoing efforts are focused on characterizing persistent tumor cells that survive during drug treatment in both experimental models and patients and defining mechanisms that drive drug adaptation. By identifying targetable vulnerabilities of these cells, we hope to develop novel therapeutic strategies that will prevent acquired drug resistance.

Developing novel immunotherapy approaches for lung cancers with low mutation burden

EGFR mutant and ALK fusion lung cancers typically occur in never-smokers and consequently have low tumor mutation burden and poor response to currently approved immune checkpoint inhibitors. We are developing TCR cellular therapies and novel methods for reprograming tumor cell antigenicity to direct the immune system to recognize and fight EGFR and ALK lung cancers.

Selected Publications:

Noritaka T†, Lin JJ†, Li C†,... **Hata AN***, Heist RS*, Corcoran RB*. Clinical acquired resistance to KRASG12C inhibition through a novel KRAS switch-II pocket mutation and polyclonal alterations converging on RAS-MAPK reactivation. *Cancer Discov*. 2021 Aug;11(8):1913-1922.

Dagogo-Jack I†, Yoda S†,... Shaw AT*, **Hata AN***. MET Alterations Are a Recurring and Actionable Resistance Mechanism in ALK-Positive Lung Cancer. *Clin Cancer Res*. 2020 Jun 1;26(11):2535-2545.

Piotrowska Z†, Isozaki H†,... **Hata AN***, Sequist LV*. Landscape of acquired resistance to osimertinib in EGFR-mutant NSCLC and clinical validation of combined EGFR and RET inhibition with osimertinib and BLU-667 for acquired RET fusion. *Cancer Discovery*. 2018 Dec;8(12):1529.

Nangia V†, Siddiqui FM†,... Benes CH, Hughes PE, **Hata AN**. Exploiting MCL-1 dependency with combination MEK + MCL-1 inhibitors leads to induction of apoptosis and tumor regression in KRAS mutant non-small cell lung cancer. *Cancer Discovery*. 2018 Dec;8(12):1598-1613.

Yoda S, Lin JJ,... **Hata AN***, Shaw AT*. Sequential ALK Inhibitors Can Select for Lorlatinib-Resistant Compound ALK Mutations in ALK-Positive Lung Cancer. *Cancer Discovery*. 2018 Jun;8(6):714-729.

Hata AN†, Niederst MJ†,... Engelman, JA. Tumor cells can follow distinct evolutionary paths to become resistant to epidermal growth factor receptor inhibition. *Nature Medicine*. 2016; 22:262-9

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