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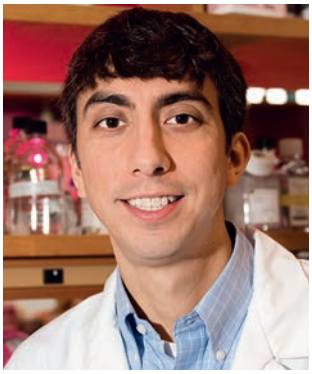

Hata Laboratory

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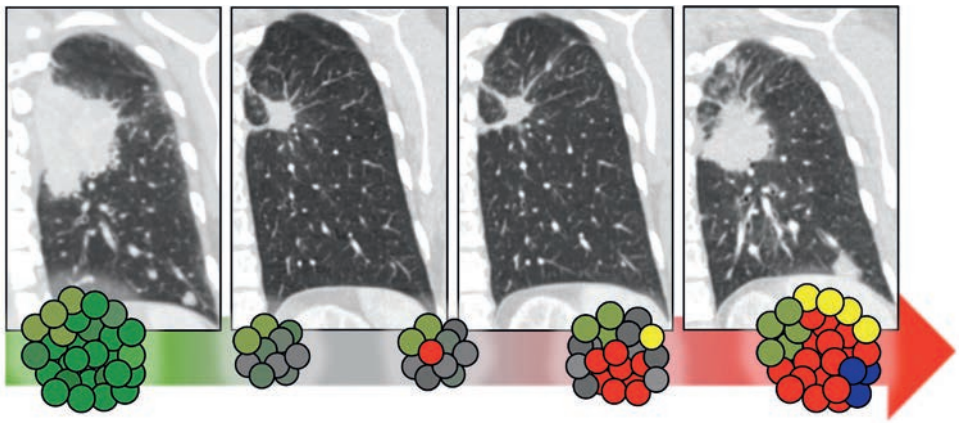
The research goal of **the Hata laboratory** is to advance targeted therapies to benefit patients with lung cancer. Our research focuses on understanding the biological underpinnings of sensitivity and resistance of oncogene-addicted lung cancers (those with activating genetic alterations EGFR, ALK, KRAS, etc.) to small molecule inhibitors of growth and survival signaling pathways. Our studies are highly translational, integrating assessment of clinical specimens with generation and analysis of patient-derived cell culture and mouse tumor xenograft (PDX) models, and are performed in close collaboration with clinicians in the MGH Thoracic Oncology group. This has enabled us to identify a number of promising therapeutic approaches for overcoming mechanisms of intrinsic and acquired drug resistance. More recently, we have begun to focus on understanding how cancer cells adapt and evolve during the course of therapy in order to identify vulnerabilities of persistent drug tolerant cancer cells that can be exploited to prevent resistance from developing. Our ultimate goal is to translate these findings into clinical trials.

Mechanisms of acquired drug resistance to targeted therapies

Lung cancers that harbor activating EGFR mutations and ALK-translocations 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 translocations, 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 are often able to detect mutations and other genomic alterations that cause drug resistance. We also culture tumor cells from biopsies as cell lines or PDX models in order to functionally interrogate pathways that contribute to drug resistance. These models also allow us to test novel therapies and select the most promising for clinical trials.

Targeting apoptotic regulators to overcome intrinsic resistance to targeted therapies

Despite the success in targeting oncogenic kinases such as EGFR and ALK, effective therapies for KRAS mutant lung cancers have remained elusive to date. The recent discovery of covalent inhibitors of the KRAS G12C oncoprotein have renewed hope that effective targeted therapies for this subset of lung cancer may be within reach. Work by our group and others has suggested that the many KRAS mutant lung cancers may exhibit decreased oncogenic dependency and a dampened apoptotic response that may lead to intrinsic resistance to KRAS targeted therapy. To overcome this limitation, we are exploring the use of BH3 mimetics that



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.

inhibit pro-survival BCL-2 family proteins such as MCL-1 and BCL-XL to increase sensitivity to inhibitors of KRAS-driven signaling pathways. In addition, we are focused on understanding how apoptotic dependencies may be shaped by the interplay between primary oncogenic driver and co-occurring genetic alterations in order to rationally deploy BH3 mimetic drug combination strategies in the clinic.

Tumor adaptation and evolution during treatment

The identification of secondary drug resistance mutations in EGFR and ALK patients progressing on first-generation TKIs has led to the development of next-generation TKIs to overcome them. However, acquired resistance develops to these new agents as well. To halt this perpetual cycle of drug resistance, novel strategies designed to alter the evolution of resistance mechanisms are needed. We recently demonstrated that genomic mechanisms of resistance can arise via evolution of drug tolerant clones that survive initial therapy and then acquire a secondary genomic alteration. This suggests that drug tolerant cells that survive initial treatment may comprise a cellular reservoir from which heterogeneous mechanisms of resistance may arise. We have ongoing efforts focused on characterizing persistent tumor cells that survive during drug treatment in both experimental models and patients. By identifying targetable vulnerabilities of these cells, we hope to develop novel therapeutic strategies that will disrupt this perpetual cycle of acquired resistance.

Patient-specific experimental modeling of oncogene addicted lung cancers

To facilitate our studies on drug sensitivity and 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 at the MGH Cancer Center. This effort is enabled by a close collaboration with clinicians in the MGH Center for Thoracic Cancers, Interventional Radiology, Interventional Radiology and Thoracic Surgery, and a team of dedicated research assistants and laboratory technicians. These models have allowed us to identify novel mechanisms of acquired resistance in EGFR and ALK lung cancers and test potential new therapies to overcome them.

Selected Publications:

Raoof S*, Mulford IJ*, Frisco-Cabanos H, Nangia V, Timonina D, Labrot E, Hafeez N, Bilton SJ, Drier Y, Ji F, Greenberg M, Williams A, Katterman K, Damon L, Sovath S, Rakiec DP, Korn JM, Ruddy DA, Benes CH, Hammerman PS, Piotrowska Z, Sequist LV, Niederst MJ, Barretina J, Engelman JA, **Hata AN**. Targeting FGFR overcomes EMT-mediated resistance in EGFR mutant non-small cell lung cancer. *Oncogene*. 2019 Jul 19.

Misale S, Fatherree JP, Cortez E, Li C, Bilton S, Timonina D, Myers DT, Lee D, Gomez-Caraballo M, Greenberg M, Nangia V, Greninger P, Egan RK, McClanaghan J, Stein GT, Murchie E, Zarrinkar PP, Janes MR, Li LS, Liu Y, **Hata AN***, Benes CH*. KRAS G12C NSCLC Models Are Sensitive to Direct Targeting of KRAS in Combination with PI3K Inhibition. *Clin Cancer Res*. 2019 Jan 15;25(2):796-807.

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

*denotes equal contribution