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Sade-Feldman Laboratory

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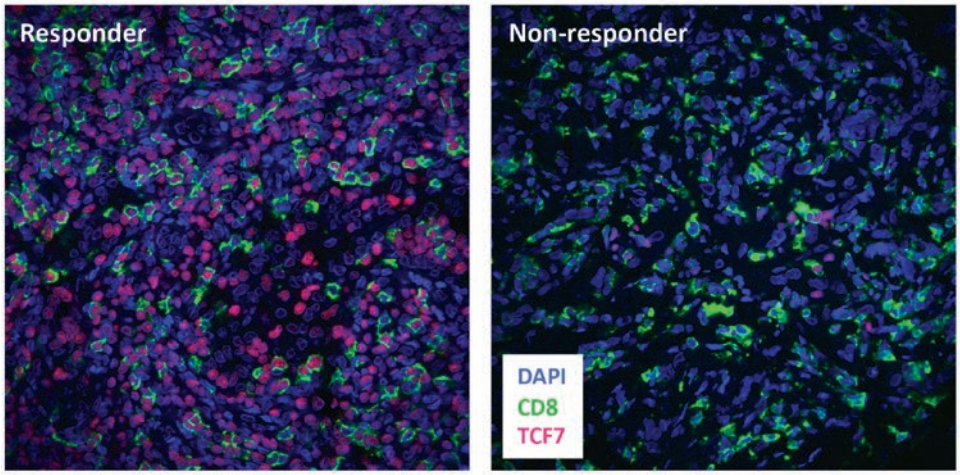
The Sade-Feldman laboratory focuses on identifying response and resistance mechanisms in cancer patients treated with immunotherapies. In the last decade, the treatment of solid tumors has been revolutionized by the development and FDA approval of checkpoint blockade (CPB) immunotherapies. While long-lasting responses are induced, only a small subset of patients benefits from these treatments. Thus, identifying the key components that drive or prevent effective immunity against tumors remains an unmet clinical need. Treatment response to immunotherapy and other therapies (e.g., targeted and chemotherapies) is influenced by complex interactions between multiple cell types in the tumor microenvironment (TME) and the heterogeneous population of tumor cells. The Sade-Feldman laboratory integrates single-cell multi-omics methods, computational biology, patient data-driven functional genomic screens, and detailed mechanistic studies to delve deeper into this intricate ecosystem and the mechanisms behind therapy response and resistance. Combining these approaches enables us to understand resistance mechanisms to immunotherapy, predict patient response, prioritize targets for validation, and identify new drug targets and combinations for cancer treatment.

While there have been numerous successful trials and FDA approvals of antibodies that block the immune regulatory checkpoints, CTLA4, PD-1, PD-L1, and LAG3, for the treatment of multiple cancer types, most patients will not respond and will succumb to the disease. The success of these immune-based therapies mainly relies on identifying tumor antigens presented on MHC-I molecules by cytotoxic immune cells. Working together with scientists, computational biologists, oncologists, surgeons, and pathologists at Mass General, our lab has discovered several mechanisms underlying the control of tumors by the immune system: I. Point mutations, deletions, or loss of heterozygosity (LOH) in beta-2-microglobulin (B2M) as a resistance mechanism to immunotherapy (Sade-Feldman et al. *Nature Comm* 2017); II. High expression of the transcription factor TBX3 in de-differentiated malignant cells as a resistance mechanism (Freeman et al. *Cell Reports Med* 2022); III. T cell states associated with clinical outcomes in melanoma patients treated with CPB inhibitors (Sade-Feldman et al. *Cell* 2018); IV. Inflammatory factors that control the differentiation and function of suppressive myeloid cells (MDSCs) (Sade-Feldman et al. *Immunity* 2014) and their clinical significance in melanoma patients treated with CPB inhibitors (Sade-Feldman et al. *Clinical Cancer Research* 2015); and V. Interferon-induced APOBEC3 as an acquired resistance mechanism to CPB in HNSCC (Lin et al. *NPJ Precis Oncol* 2022) and the prognostic impact of CXCL9/SPP1 polarity of tumor-associated macrophages in HNSCC patients with recurrent advanced disease (Bill R et al. *Science* 2023).

While these studies enabled us to understand some mechanisms of resistance to checkpoint blockade immunotherapy, still many questions remain open:

1. Despite the FDA approval of standard chemotherapy with immune checkpoint blockade (in NSCLC, SCLC, and HNSCC),



Ref: Sade-Feldman et al. *Cell* 2018

Representative overlaid images of melanoma tumors from responder and non-responder patients stained with DAPI (blue), CD8 (green), and TCF7 (red). A higher proportion of CD8+TCF7+ at baseline is observed in patients who responded to anti-PD1 immunotherapy.

we still don't fully understand how drug A affects the activity of drug B and the contribution of each drug to therapy resistance when combined.

2. Are there any shared primary or acquired resistance mechanisms between different diseases (e.g., melanoma, NSCLC, and HNSCC)?
3. While our translational efforts generate many hypotheses and predictors of outcomes, we still don't know the function of those genes/pathways and their impact on treatment response.
4. Can we identify ways to overcome resistance mediated by the loss of antigen presentation by perturbing tumor intrinsic pathways?
5. To date, most of our efforts have been focused on patients with metastatic disease receiving immunotherapy. However, there is an unmet clinical need to identify targets that can synergize with traditional therapies for local and recurrent advanced disease, particularly in cancers with a poor response to such treatments.

To address the above questions, we use a systems biology approach that involves three main steps: I. discover cellular and molecular factors associated with effective/failed therapy using integrative analysis of single-cell multi-omics datasets from human tumors; II. Perform systematic functional genetic screens to determine the role of human genes associated with outcomes; III. Characterize the key sensitivity/resistance mechanisms to understand the intra- and inter-cellular circuits underlying their action.

Main current projects in the lab:

1. Identify and validate factors conferring sensitivity and resistance to patients treated with mono or combinatorial (e.g., targeted and chemotherapy) immunotherapy by bridging together analyses of human tumors with systemic perturbations and mechanistic studies in animal and human models.
2. Identify tumor intrinsic pathways that can sensitize cells to immunotherapy in the absence of the MHC-I antigen-presentation machinery.
3. Discover targets to overcome radiation and chemotherapy resistance in local and recurrent advanced cancers.

By combining detailed human observations and rigorous functional tests, these studies are expected to reveal the basis for therapeutic resistance and response, creating a roadmap for identifying targets for therapeutic development.

Selected Publications:

Bill R, Wirapati P, Messemaker M, Roh W, ..., Lin D, Pai SI, **Sade-Feldman M**, Pittet MJ. CXCL9:SPP1 macrophage polarity identifies a network of cellular programs that control human cancers. *Science*. 2023 Aug 4;381(6657):515-524.

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Sade-Feldman M*, Kanterman J*, Klieger Y, Ish-Shalom E, Olga M, Saragovi A, Shtainberg H, Lotem M, Baniyash M. Clinical Significance of Circulating CD33+CD11b+HLA-DR- Myeloid Cells in Patients with Stage IV Melanoma Treated with Ipilimumab. *Clin Cancer Res*. 2016 Dec 1;22(23):5661-5672.

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