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The Hacohen laboratory consists of immunologists, geneticists, biochemists, technologists, physicians and computational biologists working together to develop new and unbiased strategies to understand basic immune processes and immune-mediated diseases, with an emphasis on the innate immune system and personalized medicine. We address three key questions in immunology (1) how are immune responses against cancer initiated, maintained and evaded? (2) what are the immune circuits that sense and control pathogens, such as viruses and bacteria? (3) how does immunity against the body develop, in particular, in patients with autoimmune lupus? In addition to discovering and studying specific molecular and cellular mechanisms, we also address how and why the immune response (to tumors, pathogens or self) varies so dramatically across individuals. Finally, we are adapting our unbiased analytical strategies into real-world therapeutics, having initiated clinical trials (with our collaborator Dr. Catherine Wu), in which patients are vaccinated against their own tumors with a fully personal vaccine that is designed based on a computational analysis of their personal tumor genome.

Initiators, resistors and targets of tumor immunity

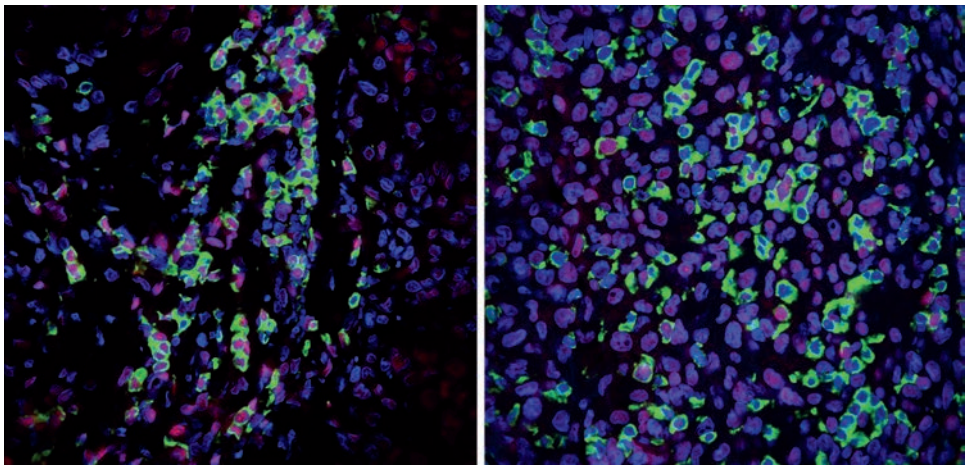
While cancer immunology has been deeply studied in animal models, there remain many open questions in human tumor immunology due to lack of tools to investigate human samples. We have developed genetic and genomics approaches to explain the large variance in anti-tumor immunity across people, and to discover how tumors evolve to resist productive immunity. We've identified somatic mutations in tumors that are associated with anti-tumor immunity in patients (Rooney et al., *Cell* 2015), discovered mutations in β2m in patients resistant to checkpoint therapy (Sade-Feldman et al., *Nat Comm* 2017) and found that TCF7+ T cells are associated with a response to anti-PD-1 immunotherapy in melanoma (Sade-Feldman et al., *Cell* 2019). We have also developed new methods to predict which tumor antigens are presented (Abelin et al., *Immunity* 2017, Sarkizova et al., submitted), which are now being used to develop novel therapeutic approaches and targets for immunotherapy, such as a personal tumor vaccine targeting multiple HLA-associated neoantigens in human tumors (together with Dr. Catherine Wu at DFCI, Ott et al., *Nature* 2017, Keskin *Nature* 2018).

Genes and networks underlying innate immunitys

We've used genome-wide CRISPR libraries to discover mammalian genes mediating the sensing of pathogens (Parnas et al., *Cell* 2015), impacting HIV infection (Park et al., *Nat Gen* 2017) and affecting influenza infection and dendritic cell biology (ongoing projects). We have also characterized innate myeloid cells (DCs and monocytes) in human blood as part of the human Immune Cell Atlas (Villani et al., *Science* 2017).

Genetic basis for inter-individual variations in immune responses

We have also developed genomic strategies



Immunofluorescence staining of T cells found in human melanoma biopsies from a patient who responded (left) and a patient who did not respond (right) to checkpoint anti-PD-1 therapy. Staining: nuclei (blue), CD8 (green) and TCF7 (red).

to analyze human immune responses and explain immune phenotypes with germline genotypes. We characterized the genetic basis for inter-individual variation in the innate immune response to viruses and bacteria (Lee et al., *Science* 2014; Raj et al., *Science* 2014; Ye et al., *Science* 2014). For example, we found that common alleles of IRF7 tune the strength of an individual's anti-viral response, and that genetic control of splicing is prevalent and important for the immune response (Ye et al., *Genome Res* 2018). Building on these studies, we have recently developed and are now using systematic methods to analyze the role of genetic and non-genetic variations in human immunity.

Drivers of autoimmunity

Deficiencies in nucleases that degrade DNA lead to accumulation of self DNA, activation of innate immune responses and development of autoimmune disorders, including systemic lupus erythematosus and Aicardi-Goutières syndrome in humans, and autoimmune arthritis, nephritis and myocarditis in mice. We have been interested in understanding how autoimmunity develops upon triggering of innate immunity by self DNA (rather than pathogen-derived DNA). In studying this question, we made the surprising observation that immunostimulatory DNA can arise from host damaged DNA that is exported from the nucleus to the lysosome (Lan et al., *Cell Rep* 2014). We hypothesize that this cellular process is a source of inflammation in autoimmunity, cancer, chemotherapy and aging (Lan et al., *Aging Cell* 2019). To deepen our understanding of pathways that drive autoimmunity, we have been analyzing immune responses in lupus nephritis patients, with an emphasis on cellular and molecular analysis of kidney biopsies and blood samples from lupus patients (Arazi et al., *Nat Imm* 2019).

Selected Publications:

Arazi A, Rao DA, Berthier CC, Davidson A, Liu Y, Hoover PJ, Chicoine A, Eisenhaure TM, Jonsson AH, Li S, Lieb DJ, Zhang F, Slowikowski K, Browne EP, Noma A, Sutherby D, Steelman S, Smilek DE, Tosta P, Apruzzese W, Massarotti E, Dall'Era M, Park M, Kamen DL, Furie RA, Payan-Schober F, Pendergraft WF 3rd, McInnis EA, Buyon JP, Petri MA, Putterman C, Kalunian KC, Woodle ES, Lederer JA, Hildeman DA, Nusbaum C, Raychaudhuri S, Kretzler M, Anolik JH, Brenner MB, Wofsy D, **Hacohen N**, Diamond B; Accelerating Medicines Partnership in SLE network. The immune cell landscape in kidneys of lupus nephritis patients. *Nature Immunology* 2019. Jul;20(7):902-914.

Ye CJ ... **Hacohen N**. Genetic analysis of isoform usage in the human anti-viral response reveals influenza-specific regulation of ERAP2 transcripts under balancing selection. *Genome Res*. 2018 Dec;28(12):1812-1825.

Sade-Feldman M, Yizhak K, Bjorgaard SL, Ray JP, de Boer CG, Jenkins RW, Lieb DJ, Chen JH, Frederick DT, Barzily-Rokni M, Freeman SS, Reuben A, Hoover PJ, Villani A-C, Ivanova E, Portell A, Lizotte PH, Aref AR, Eliane JP, Hammond MR, Vitzthum H, Blackmon SM, Li B, Gopalakrishnan V, Reddy SM, Cooper ZA, Paweletz CP, Barbie DA, Stemmer-Rachamimov S, Flaherty KT, Wargo JA, Boland GM, Sullivan RJ, Getz G and **Hacohen N**. Defining T cell states associated with response to checkpoint immunotherapy in melanoma. *Cell*. 2018 Nov 1;175(4):998-1013.e20.

Ott P ... **Hacohen N** & Wu CJ. An immunogenic personal neoantigen vaccine for patients with melanoma. *Nature*. 2017 Jul 13;547(7662):217-221.

Villani A-C, Satija R, Reynolds G, Sheknar K, Fletcher J, Sarkizova S, Griesbeck M, Butler A, Zheng S, Lazo S, Jardine L, Dixon D, Stephenson E, McDonald D, Filby A, Li W, De Jager PL, Rozenblatt-Rosen O, Lane AA, Haniffa M, Regev A, **Hacohen N**. Single-cell RNA-seq reveals new types of human blood dendritic cells, monocytes and progenitors. *Science*. 2017 Apr 21;356(6335).

Lee MN*, Ye C*... **Hacohen N**. Common genetic variants modulate pathogen-sensing responses in human dendritic cells. *Science*. 2014 Mar 7;343(6175):1246980.

*Equal contribution