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The Hacohen laboratory consists of immunologists, geneticists, biochemists, technologists, physicians and computational biologists working together to develop new and unbiased technologies and strategies to understand basic immune processes and immune-mediated diseases, with an emphasis on the innate immunity, tool development 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

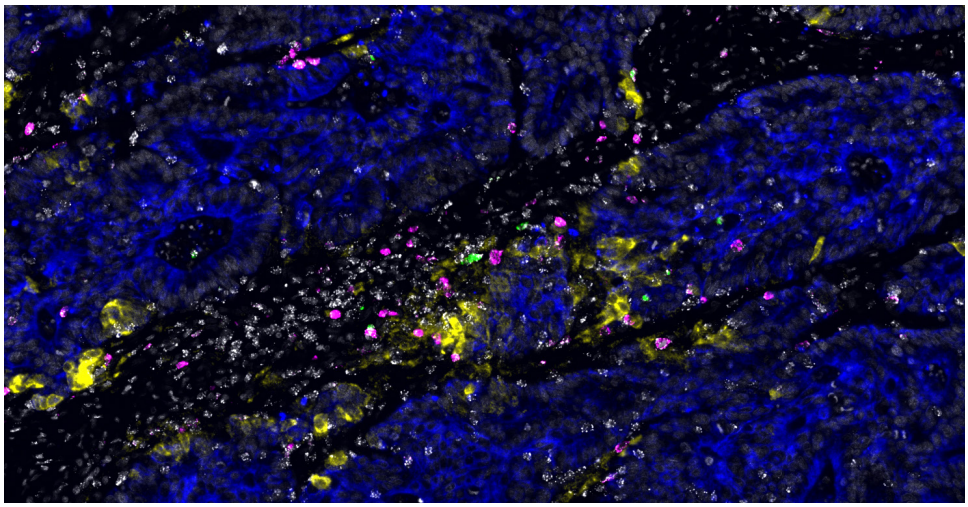
While cancer immunology has been deeply studied in animal models, there remain many open questions in human tumor immunology due to lack of tools to investigate human samples. We have developed genetic and genomics approaches to explain the large variance in anti-tumor immunity across people, and to discover how tumors evolve to resist productive immunity. We've identified somatic mutations in tumors that are associated with anti-tumor immunity in patients, and found T cell subtypes that are associated with a response to anti-PD-1 immunotherapy in melanoma and are studying their properties now (Sade-Feldman et al., *Cell* 2018). We have also developed new methods to predict which tumor antigens are presented (Abelin et al., *Immunity* 2017, Sarkizova et al., *Nat Biotech* 2020), which are now being used to develop novel therapeutic approaches and targets for immunotherapy, such as personal tumor vaccines 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 immunity

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 (Li et al., Nat Comm 2020) and other sensing pathways (ongoing). 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 to analyze human immune responses and



In the subset of mismatch repair-deficient human colorectal tumors, activated and likely tumor-reactive T cells (white, green, and magenta) are organized into "hubs" around malignant cells (blue) expressing chemokines (yellow) that attract T cells and other cells into spatially organized immune cell hubs. Credit : Joshua Pirl, Vjola Jorgji, Linda Nieman, Jonathan Chen.

Source: Pelka, Hofree, Chen et al. Cell. 2021

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 (Ray et al., *Nat Comm* 2021). We also study non-genetic variations in human immunity, and found a myeloid cell type and state ('MS1' that corresponds to MDSCs) strongly associated with severe infections (including COVID-19) and sepsis (Reyes et al, *Nat Med* 2020, *Science Tr Med* 2021), leading us to new hypotheses underlying these dangerous clinical trajectories.

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 in a small (Arazi et al., *Nat Imm* 2019) and large patient cohort (ongoing) and more recently in comparison to animal lupus models.

Selected Publications:

Pelka K, Hofree M, Chen JH, Sarkizova S, Pirl JD, Jorgji V... Ng K, Giannakis M, Nieman LT, Boland GM, Aguirre AJ, Anderson AC, Rozenblatt-Rosen O, Regev A, **Hacohen N**. Spatially organized multicellular immune hubs in human colorectal cancer. *Cell*. 2021 Aug 24:S0092-8674(21)00945-4.

Reyes M, Filbin MR, Bhattacharyya RP, Sonny A, Mehta A, Billman K... Baron RM, Goldberg MB, Blainey PC, **Hacohen N**. Plasma from patients with bacterial sepsis or severe COVID-19 induces suppressive myeloid cell production from hematopoietic progenitors in vitro. *Sci Transl Med*. 2021 Jun 16;13(598):eabe9599.

Sarkizova S, Klaeger S, Le PM, Li LW, Oliveira G, Keshishian H, Hartigan CR... Clauser KR, **Hacohen N**, Carr SA, Wu CJ, Keskin DB. A large peptidome dataset improves HLA class I epitope prediction across most of the human population. *Nat Biotechnol*. 2020 Feb;38(2):199-209. doi: 10.1038/s41587-019-0322-9.

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...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

Ott P, Hu X, Keskin DB, Shukla SA, Sun J, Bozbym DJ, Zhang W, Luoma A, Giobbie-Hurder A, Peter L, Chen C, Olive O, Carter TA, Li S, Lieb DJ, Eisenhaure T...Getz G, Wucherpfennig K, Neuberg D, Ritz J, Lander ES, Fritsch EF, **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, Shekhar 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).