

盘点 大牛 生信课题组



From beginner to expert

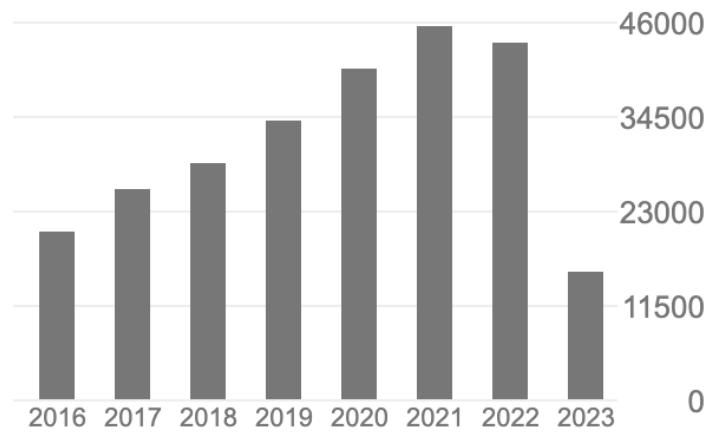
Gad Getz



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Disclosures

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Gad Getz directs the Cancer Genome Computational Analysis group at the Broad Institute of MIT and Harvard, where he is an institute member. Under Getz's leadership, the Cancer Genome Analysis group has established itself as a world leader in the development and application of genomic technologies and next-generation sequencing for analyzing cancer mutations.

In addition to his role at the Broad, Getz is a co-principal investigator in the Genome Data Analysis Center (GDAC) of the NCI/NHGRI TCGA (The Cancer Genome Atlas) project; a co-leader of the International Cancer Genome Consortium (ICGC) Pan-Cancer Analysis of Whole Genomes (PCAWG) project; a co-principal investigator of the Broad-led NCI Cloud Pilot; and a member of various NCI advisory committees. In addition, Getz directs the Bioinformatics Program at the Massachusetts General Hospital Cancer Center and Department of Pathology and serves as an associate professor of pathology at Harvard Medical School. Getz is also the inaugural incumbent of the Paul C. Zamecnik Chair in Oncology at the MGH Cancer Center. He has published numerous papers in recent years in prominent journals that describe new genes and pathways involved in different tumor types.

Getz received his B.S. degree in physics and mathematics from Hebrew University and an M.Sc. in physics from Tel-Aviv University. He later earned a Ph.D. in physics from the Weizmann Institute of Science in Israel. He completed his postdoctoral training at the Broad Institute of MIT and Harvard with Todd Golub, where he focused on developing computational tools and analyzing expression of miRNAs across cancer.

Lab Overview

The Getz lab is focused on cancer genome analysis, which includes (i) somatic events that cause cancer or lead to development of resistance, (ii) germline events that increase the risk for getting cancer, and (iii) using these events to identify subtypes of the disease and their relationship to clinical parameters and/or treatment outcomes. The team is building tools that are part of a robust analytical pipeline to analyze data coming from various national/international collaborative cancer genome projects, and these tools are revolutionizing how we analyze cancer genomes and use them in clinical settings.

Cancer genome analysis in the Getz lab includes two major steps: (i) Characterization – cataloging of all genomic events and the mechanisms that created them during the clonal evolution of the cancer, comparing events at the DNA, RNA and protein levels between tumor and normal samples from an individual patient; and (ii) Interpretation – analysis of the characterization data across a cohort of patients with the aim of identifying the alterations in genes and pathways that cause cancer or increase its risk as well as identifying molecular subtypes of the disease, their markers, and relationship to clinical variables.



MASSACHUSETTS
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人员构成：

Admin: 4

Postdoc: 16

Scientist: 32

Graduate students: 7

Visiting scholar: 1

近五年文章：

CNS: 7

大子刊：19

小子刊：15

其他：3

研究方向一：癌症基因组特征分析

Characterizing the cancer genome

Cancer is a disease of the genome that is driven by a combination of possible germline risk-alleles together with a set of “driver” somatic mutations that are acquired during the expansion of increasingly fitter clones. In order to generate a comprehensive list of all inherited germline events as well as the somatic events that occurred during life, we are developing and applying highly sensitive and specific tools for detecting different types of mutations in massively-parallel sequencing data. The volume and complexity of these data require developing computational tools using state-of-the-art statistical and machine learning approaches to extract the signal from the noise. Among these tools are MuTect ([Cibulskis, et al., Nature Biotechnology 2013](#)), dRanger & BreakPointer ([Bass, Lawrence, et al., Nature Genetics 2011](#); [Chapman, et al., Nature 2011](#); [Drier, et al., Genome Research 2012](#)), SegSeq ([Chiang, Getz, et al., Nature Methods 2009](#)), CapSeg ([Landau, Carter, Stojanov, et al., Cell 2013](#)), HapSeg ([Carter, et al., Nature Precedings 2011](#)), MSMuTect ([Maruvka, et al., Nature Biotechnology 2017](#)), POLYSOLVER ([Shukla, et al., Nature Biotechnology 2015](#)), and RNA-MuTect ([Yizhak, et al., Science 2019](#)), as well as tools to detect various forms of contamination and artifacts, including ContEst ([Cibulskis, McKenna, et al., Bioinformatics 2011](#)), DeToxoG ([Costello, et al., Nucleic Acids Research 2013](#)), and deTiN ([Taylor-Weiner, Stewart, et al., Nature Methods 2018](#)).

Massive parallel sequencing, also known as next-generation sequencing (NGS), is a high-throughput DNA sequencing technology that allows for the simultaneous sequencing of millions of DNA fragments.

研究方向二：癌症相关基因检测

Detecting cancer-associated genes

We analyze the detected somatic events (see above) across a cohort of samples searching for genes and pathways, as well as non-coding genomic elements, that show significant signals of positive selection. To that end, we construct a statistical model of the background mutational processes and then detect genes that deviate from it. We have developed tools for detecting significantly gained or lost genes in cancer, including GISTIC ([Beroukhim, Getz, et al., PNAS 2007](#); [Mermel, et al., Genome Biology 2011](#)), and genes with increased density or irregular patterns of mutations, including the MutSig suite of tools ([Getz, Höfling H, et al. Science 2007](#); [Chapman, et al., Nature 2011](#); [Lawrence, Stojanov, Polak, et al., Nature 2013](#); [Lawrence, et al., Nature 2014](#); [Rheinbay, et al., Nature 2017](#)), CLUMPS/ EMPRINT ([Kamburov, et al., PNAS, 2015](#)), MSMutSig ([Maruvka, et al., Nature Biotechnology 2017](#)), NetSig ([Horn, Lawrence, et al., Nature Methods 2017](#)), and “driver”/“passenger” hotspots ([Hess, et al., Cancer Cell 2019](#)). Our work demonstrated the need to accurately model the heterogeneity of mutability across patients, sequence contexts, and the genome, when searching for cancer genes.

研究方向三：癌症突变特征识别

Advances in mutational signatures

We were the first to use a Bayesian version of non-negative matrix factorization (NMF) for mutational signature discovery, uncovering key mechanisms by which cancers accumulate mutations. We have now optimized the performance of our SignatureAnalyzer algorithm ([Kasar, Kim, et al., Nature Communications 2015](#); [Kim, Mouw, Polak, et al., Nature Genetics 2016](#)) by leveraging GPU computing to allow analysis of massive datasets ([Taylor-Weiner, Aguet, et al., Genome Biology 2019](#)), accelerating it to run ~200 times faster and enabling us to study larger datasets and obtain more accurate results. We demonstrated that asymmetries in mutational signatures can be used to study how and when they are generated, with signatures having transcriptional or replication asymmetries, describing a new mechanism of transcription-coupled damage and finding that APOBEC affects DNA during replication ([Haradhvala, Polak, et al., Cell 2016](#)). By studying a mutational signature that is most common in breast cancer and is associated with germline mutations in BRCA1/2 genes and loss of homologous recombination repair, we found that promoter methylation of RAD51C can also cause this signature ([Polak, Kim, Braunstein, et al., Nature Genetics 2017](#)). We also show that concurrent loss of mismatch repair and polymerase proofreading creates a unique signature, not represented by a linear combination of the two associated signatures ([Haradhvala, Kim, Maruvka, et al., Nature Communications 2018](#)).

Moreover, as part of the PCAWG efforts described above, we collaborated with other international leaders to describe the most comprehensive set of mutation signatures thus far by analyzing mutational signatures across a large number of whole genomes and whole exomes ([Alexandrov, Kim, et al., Nature 2020](#)). We also have applied our signature analysis tools to tumors with microsatellite instability (MSI): our MSI Detect analysis revealed that a unique cohort of constitutional MMRD syndrome cases have unique MS indel signatures that can be used to correctly classify them as MSI, even using normal cells from these patients ([Chung, Maruvka, et al., Cancer Discovery 2020](#)).

研究方向四：癌症异质性和克隆进化

Heterogeneity and clonal evolution of cancer

Cancer samples are heterogeneous, containing a mixture of normal cells and cancer cells that often represents multiple subclones. We developed, and continue to develop, tools for characterizing the heterogeneity of cancer samples using copy-number and mutation data measured on bulk samples, including ABSOLUTE ([Carter, et al., Nature Biotech 2012](#)) and Phylogic ([Landau, Carter, Stojanov, et al., Cell 2013](#)), and now also using single cells. We recently used this concept as the foundation for our extended PhylogicNDT suite of tools for analyzing tumor heterogeneity from which we can infer the clonality of mutations, estimate the number of subclones and infer their phylogenetic relationships, as well as their distribution over space and time ([Leshchiner, Livitz, Gainor, Rosebrock, et al., bioRxiv 2019](#)). These tools have the ability to analyze tumor evolution, heterogeneity, and dynamics based on multiple samples from the same patient that have been harvested longitudinally (e.g., pre- and post-treatment) or spatially (e.g., across multiple organs, or within the same tumor), enabling us to study resistance to therapy and introduce these concepts into clinical trial strategies. PhylogicNDT has been used to address high-priority questions in cancer biology, including: (i) detecting cancer clones; (ii) inferring phylogenetic trees; (iii) inferring order and timing of events in individual patients and across subsets of patients; (iv) associating mutational signatures to each branch in the phylogenetic tree; and (v) estimating the clonal composition of each tumor sample ([Parikh, Leshchiner, Elagina, et al., Nature Medicine 2019](#); [Gruber, Bozic, Leshchiner, Livitz, et al. Nature 2019](#); [Gerstung, Jolly, Leshchiner, Dentro, Gonzalez, et al., Nature 2020](#) (PCAWG efforts in whole genomes); [Dentro, Leshchiner, Haase, et al., Cell 2021](#)).

Cancer heterogeneity refers to the presence of genetic, phenotypic, and functional differences within a tumor or among different tumors.

研究方向五：癌症免疫应答检测和特征分析工具开发

Development of tools for the detection and characterization of immune responses in cancer

We have developed a tool, POLYSOLVER ([Shukla, et al., Nature Biotechnology 2015](#)), for genotyping HLA alleles and identifying somatic mutations in these genes in tumors. We used mutation data and HLA haplotypes to infer neoantigens across cancer, and predicted neoantigens were used as part of a vaccination trial in melanoma and GBM.

Together with Dr. Nir Hacohen, we recently reported clustering-based analysis of single cells in melanoma patients receiving immune checkpoint blockade that showed two distinct states of CD8+ T cells associated with patient tumor regression or progression ([Sade-Feldman, Yizhak, et al., Cell 2018](#)). In addition to delineating the epigenetic landscape and clonality of these T cell states, this study further identified a transcription factor in CD8+ T cells, TCF7, that predicted positive clinical outcome in checkpoint-treated patients. Overall, this study presented a more generalized strategy for identifying predictors, mechanisms, and targets for enhancing checkpoint immunotherapy. Analysis of a much larger cohort with bulk DNA and RNA sequencing showed that expression signatures that combines genes reflecting the differentiation state of the melanoma cells and genes reflecting the immune infiltrating cells can improve the prediction of who will respond to immune checkpoint blockade therapy ([Freeman, Sade-Feldman, et al., Cell Reports Medicine 2022](#))

Together with Drs. Steve Lipkin, Nir Hacohen, Zsophia Stadler, and Catherine Wu, we are using our understanding of MSI cancers to explore the use of vaccines to prevent or delay the development of tumors in patients that have a predisposition for tumors with MSI due to inherited defects in the mismatch repair pathway (Lynch syndrome).

研究方向六：单细胞肿瘤微环境分析

Single-cell analysis of the tumor microenvironment

Our efforts to understand cancer biology at the single-cell level have made major advances in the last few years. For example, in close collaboration with Dr. Irene Ghobrial's lab, we performed single-cell RNA sequencing of tumor cells in bone marrow biopsies from Multiple Myeloma patients to map out how the composition and expression of each immune population change during disease progression, from the earliest asymptomatic stages to overt MM. Specifically, our analysis revealed loss of memory cytotoxic T cells and major histocompatibility complex class II dysregulation in CD14+ monocytes ([Zavidij, Haradhvala, Mouhieddine, et al., Nature Cancer 2020](#)). Additional studies in the lab are using single-cell data to focus on studying MM tumor cells and their relationship to the microenvironment ([Boiarsky, et al., medRxiv preprint 2022](#)), as well as understanding the response and resistance to CAR-T therapy in diffuse large B-cell lymphoma (DLBCL) ([Haradhvala, Leick, Maurer, Gohil, et al., medRxiv preprint 2022](#)).