Abstract: ENA-0510

Identifying Patient-specific Neoepitopes for Cell-based and Vaccine Immunotherapy within the Cancer Genome Atlas Reveals Rarely Shared Recurrent Neoepitopes

Andy Nguyen,[1] J Zachary Sanborn,[1] Charles J Vaske,[1] Shahrooz Rabizadeh,[2] Kayvan Niazi,[2] Patrick Soon-Shiong,[2,3] Steven C Benz[1]

[1]NantOmics LLC, Santa Cruz, CA; [2]NantOmics LLC, Culver City, CA; [3]CSS Institute of Molecular Medicine, Culver City, CA

Background

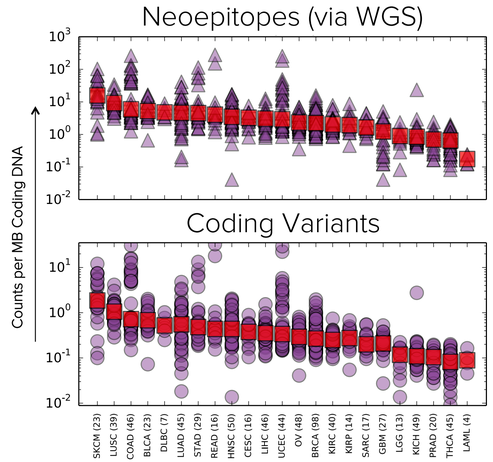
- Immunotherapies such as checkpoint inhibitors, CAR T cells, NK cells, and therapeutic vaccines are revolutionizing cancer medicine with remarkable responses in some patients.
- Immune cells attack both cancer related antigens such as HER2 and unique cancer neoantigens derived from private mutations.
- Checkpoint inhibitors allow immune cells to attack neoantigen presenting cancer cells that have otherwise evaded the immune system.
- We analyzed whole genome sequencing (WGS) and RNA sequencing (RNAseq) data from The Cancer Genome Atlas (TCGA) to identify neoepitopes (tumor-specific antigens derived from somatic tumor mutations) that could be exploited to develop next-generation, patient-specific cancer immunotherapies.

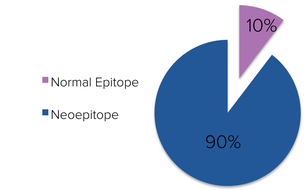
Methods

- TCGA WGS and RNASeq data were obtained from the University of California, Santa Cruz (UCSC) Cancer Genomics Hub (https://cghub.ucsc.edu/).
- Neoepitopes were identified by creating all possible permutations of either 9-mer or 15-mer amino acid strings derived from somatic single nucleotide variants (SNVs) or insertions/deletions (indels) in coding regions.
- Potential neoepitopes were filtered against all possible 9-mer and 15-mer sequences from reference human coding genes, in addition to all possible variation in dbSNP (http://www.ncbi.nlm.nih.gov/SNP) sites.
- In-silico HLA typing was performed using WGS and RNAseq data by alignment to the IMGT/HLA database. Typing results were obtained for HLA-A, HLA-B, HLA-C, and HLA-DRB1.
- NetMHC 3.4 (http://www.cbs.dtu.dk/services/NetMHC-3.4/) was used to predict MHC to neoepitope binding affinities.

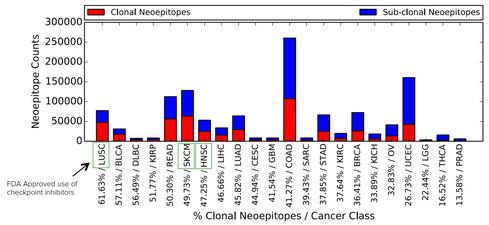
Results

Cancer Neoepitope Loads Across TCGA Dataset

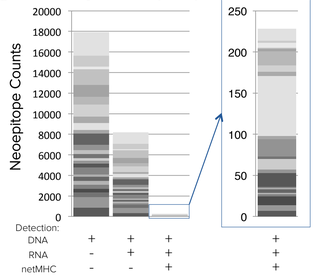




Clonality of Neoepitopes across cancer classifications

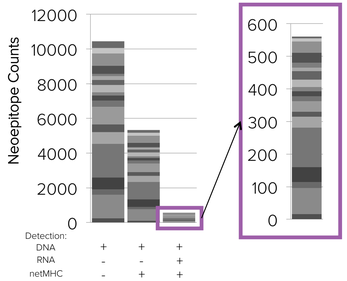


Filtering High Quality Neoepitopes in TNBC



TCGA Barcode	UCSC id	HUGO Gene	TPM	Neoepitope	Protein Change	Normal	Bound Allele	Bind Strength
TCGA-E2-A14X	uc003ean.2	NAA50	229.85	PTDAHVLQK	p.A145T	PADAHVLQK	A*11:01	146nM
TCGA-E2-A1LL	uc001asj.3	FBXO2	187.36	LLLHVLAAL	p.R57H	LLLRVLAAL	A*02:01	18nM

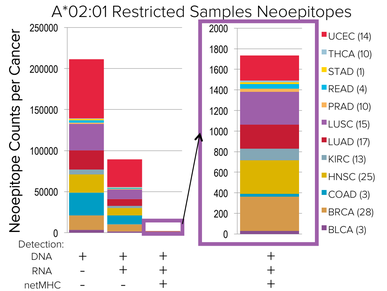
Filtering High-Quality Neoepitopes in HER2+ BRCA

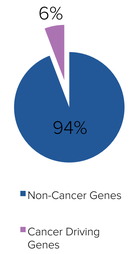


A Single Recurrent Neoepitope in TCGA HER2+ BRCA

TCGA Barcode	UCSC id	HUGO Gene	TPM	Neoepitope	Protein Change	Normal	Bound Allele	Bind Strength
TCGA-BH-A18R	uc003ean.2	FANCD2	21.39	FAKDGGLVT	P714L	FAKDGGPVT	C*03:03	131nM
TCGA-AO-A0JM			14.12				C*05:01	851nM

Filtering High-Quality Neoepitopes Across Cancers





Shared Neoepitopes Across Cancers

TCGA Barcode	UCSC id	HUGO Gene	Neoepitope	Protein Change	Normal	Cancers
TCGA-E2-A109, TCGA-CR-5249, TCGA-BA-6872, TCGA-CN-6989	uc001wxt.2	SOS2	YIHTHTFYV	p.T390I	YTHTHTFYV	(3) HNSC, BRCA
TCGA-EW-A1J5, TCGA-21-1082, TCGA-GD-A2C5, TCGA-75-5147	uc001zyl.4	USP8	SQIWNLNPV	p.R763W	SQIRNLNPV	LUAD, BLCA, LUSC, BRCA

Conclusions

- Nearly all identified neoepitopes are patient-specific. TNBC samples do not share any common neoepitopes.
- Neoepitope-MHC interactions restrict more commonly shared mutations.
- Development of personalized immunotherapies is dependent on accurate DNA and RNA sequencing.

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Contact

Corresponding Author:
Andy.Nguyen@nantomics.com

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