Abstract #4512

High-throughput Identification of Neoepitopes for Development of Patient-specific Cancer Immunotherapies

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

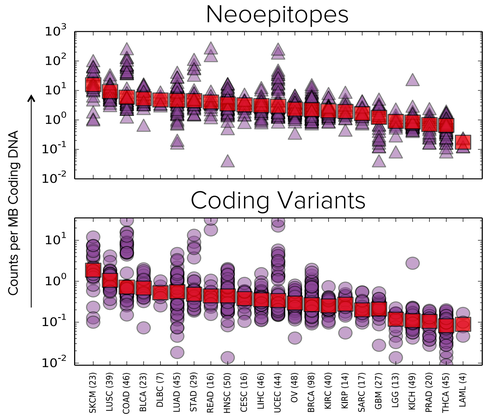
- Immunotherapies such as checkpoint inhibitors, CAR T cells, NK cells, and therapeutic vaccines are revolutionizing cancer medicine with remarkable responses in some patients.
- Current clinical immunotherapy strategies include targeting tumor associated antigens (TAAs) such as HER2 (trastuzumab) or targeting immune cell checkpoints (ipilimumab, nivolumab).
- Many patients fail to have responses with these drugs suggesting a lack of specific immune cells or insufficient amounts of the TAAs.
- 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 mutations from cancer) that could be exploited to develop next-generation, patient-specific cancer immunotherapies.

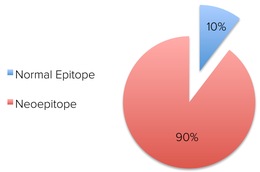
Methods

- 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 single nucleotide variants (SNVs) or insertions/deletions (indels).
- All neoepitopes were filtered against all possible 9-mer and 15-mer sequences from every known human gene along with dbSNP (http://www.ncbi.nlm.nih.gov/SNP) sites to include all possible variations.
- In-silico HLA typing was performed using WGS and RNAseq data along with alignments 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.

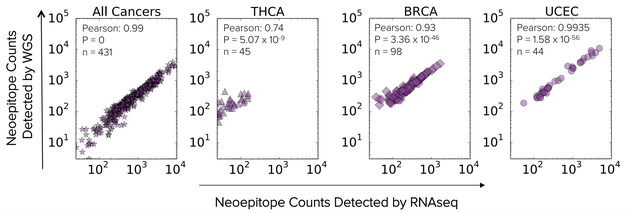
Results

Cancer Neoepitope Loads Across TCGA Dataset

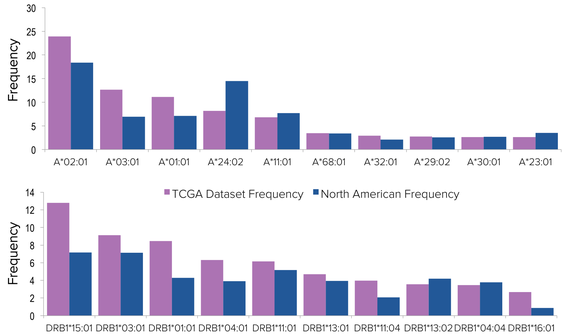




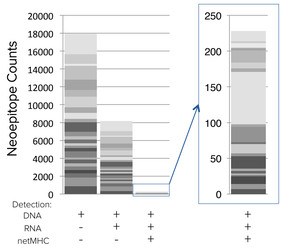
High Neoepitope Burden Gives Rise to More Expressed Neoepitopes



HLA Distribution Within the TCGA Dataset



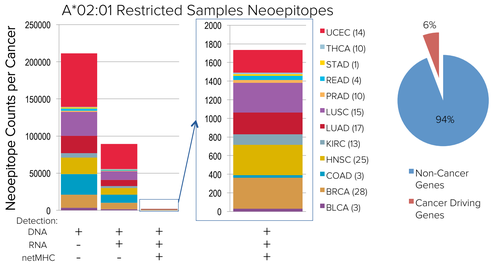
Filtering High Quality Neoepitopes in TNBC



Sampling of TNBC Neoepitopes

TCGA Barcode	HLA-A Typing	UCSC id	HUGO Gene Name	TPM	Neoepitope	Protein Change	Normal	Bound Allele	Bind Strength
TCGA-E2-A14X	A*23:01, A*11:01	uc003ean.2	NAA50	229.85	PTDAHVLQK	p.A145T	PADAHVLQK	A*11:01	146nM
TCGA-E2-A1LL	A*02:01, A*02:01	uc001asj.3	FBXO2	187.36	LLLHVLAAL	p.R57H	LLLRVLAAL	A*02:01	18nM

Filtering High Quality Neoepitopes Across Cancers



Shared Neoepitopes Across Cancers

TCGA Barcode	UCSC id	HUGO Gene Name	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

- Most identified neoepitopes are patient-specific.
- Neoepitope-MHC interactions restrict more commonly shared mutations.
- Development of personalized immunotherapies is dependent on accurate DNA and RNA sequencing.

Acknowledgement

We would like to thank Kathryn Boorer, PhD, of NantHealth, LLC for writing assistance.

Contact

Corresponding Author:
Andy.Nguyen@nantomics.com

Use a QR Scanner to Download this Poster