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-Shiong2,3 Steven C Benz1
1NantOmics LLC, Santa Cruz, CA; 2NantOmics LLC, Culver City, CA; 3CSS 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 derived from single nucleotide variants (SNVs) or insertions/ deletions (indels).
• 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.bcb.rpi.edu/services/NetMHC-3.4/) was used to predict MHC to neoepitope binding affinities.

Results
Cancer Neoepitope Loads Across TCGA Dataset

HLA Distribution Within the TCGA Dataset

Filling High Quality Neoepitopes in TNBC

Shared Neoepitopes Across Cancers

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

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

Contact
Corresponding Author: Steven C Benz
benzsc@nanthhealth.com

All neoepitopes were filtered against the HLA-A, HLA-B, HLA-C, and HLA-DPB1.

Neoepitope-MHC interactions restrict more commonly shared epitopes.

Development of personalized immunotherapies is dependent on accurate DNA and RNA sequencing.