348 INTERLEUKIN 2(IL-2) SYSTEMS IMMUNOLOGY MODELING: MACHINE LEARNING FOR CANCER IMMUNOTHERAPY

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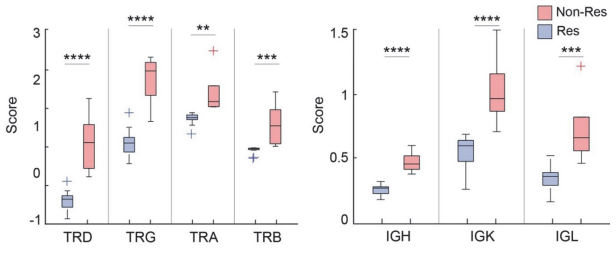
Background Clinical outcomes are correlated with aggregate B (BCR) and T cell receptor (TCR) diversity (the adaptome) in several infectious diseases and cancers. Advances in dimer avoidance multiplexed PCR (DAM-PCR) followed by next-generation sequencing (NGS) enable measurements of immune repertoire diversity and clonality, allowing prediction of cancer states and response to treatment. Clonotype-mediated predictions collapse a space of up to 1025 possible CDR3 variable region sequences into descriptors such as whole-sequence diversity. Broad descriptors, however, mask cancer-specific information embedded within clonotype sequences. Deep learning algorithms typically need large patient cohorts to make accurate predictions. We present a statistical model predicting response to IL-2 immunotherapy for small cohorts based on natural language processing (NLP) of CDR3 TCR and BCR clonotypes.

Methods In a completed Phase 2 trial (NCT01550367), the adaptome of 29 patients with metastatic clear cell renal carcinoma (RCC) treated with high dose (HD) IL-2 and the autophagy inhibitor, hydroxychloroquine (HCQ) were measured from peripheral blood samples by DAM-PCR. All seven TCR and BCR chains were measured at three treatment points (pre-treatment, 14D after HCQ initiation, and following recovery from the first cycle of IL-2 on D15). Outcomes were assessed by assigning two states (responder or non-responder) one year following treatment based on radiographic changes in tumor size. Cancer-specific amino acid motifs from TCR and BCR CDR3 sequences on D15 were mined by counting amino acid pairs and calculating a 400-feature transition probability matrix, scoring the likelihood of a motif belonging to the responder or non-responder cohort.

Results Seven-chain NLP analysis of CDR3 amino acid motifs at > 90% accuracy for each chain independently predicted patient response to IL-2 by D15 (figure 1). Furthermore, longitudinal monitoring of patient CDR3s across the three timepoints revealed a dichotomy in repertoire orchestration. Responding patients, convincingly, were more likely to demonstrate either a TCR-driven ($p<0.01$) or a BCR-driven ($p<0.001$) entropy bias while non-responding patients unanimously showed no significant bias.



Abstract 348 Figure 1 Classification of nonresponding (Non-Res) and responding (Res) patients based on scoring from Feature Selection Filter and Analysis. ****, $p<0.0001$; ***, $p<0.001$; **, $p<0.01$

Conclusions NLP of both TCR and BCR repertoires can provide early predictions of cancer response to treatment. Furthermore, seven-chain longitudinal monitoring across treatment revealed a surprisingly robust repertoire orchestration in responders that was not observed in non-responders, suggesting that the methodology proposed here can be used to gain new mechanistic insight into the role of repertoire evaluation in cancer immunotherapy.

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