Longitudinal Monitoring of NeoEpitope-Specific T Cell Repertoires in Patient Blood Following Cancer Immunotherapy

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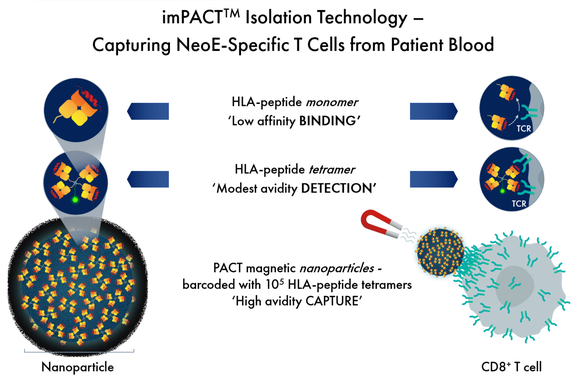
Abstract

T cells targeting neoepitopes derived from mutations exclusive to the tumor are one of the main drivers of cancer immunotherapy efficacy. Tracking these neoepitope (neoE)-specific T cells during cancer immunotherapy has been hampered by the impracticality of repeated sampling from the tumor, and by the low frequency of neoE-specific T cells in peripheral blood. An ultra-sensitive and high-throughput technology (imPACT™) has been developed for the identification and isolation of neoE-specific T cells from peripheral blood. Subjects with pMMR colorectal cancer (which are not generally responsive to anti-PD1), endometrial adenocarcinoma and other solid tumors were treated with AB122 (anti-PD-1 antibody) as part of an ongoing dose-escalation clinical trial to evaluate the safety of the drug. Pre-treatment blood samples were analyzed to identify the baseline repertoire of neoE-specific T cells. Evolution of this repertoire during AB122 treatment was monitored to enable correlation of immune phenotyping with clinical outcomes. These data enable us to analyze T cells targeting neoEs and identify driver mutations that correlate with, and may be responsible for therapeutic benefit. In addition, monitoring changes of the neoE-specific T cell repertoire in response to immunotherapy can inform next steps of treatment. More broadly, this platform technology promises to significantly advance our understanding of T cell-mediated mechanisms of cancer immunotherapy.

Methods



Conclusions

- **imPACT technology is ultra-sensitive (i.e. capture neoE-specific T cells at frequencies as low as 1 target CD8 T cell per 5M PBMC) and capable of monitoring the dynamics of neoE-specific T cell profiles in peripheral blood for patients undergoing immunotherapy.**
- **imPACT technology also assesses the phenotype of neoE-specific T cells - informing that those T cells in blood are antigen-experienced & have trafficked to the tumor before.**
- **Longitudinal immune monitoring holds potential to establish when and how patients benefit from treatment.**
- **The robust drug-induced neoE-specific T cell expansion in patients (such as that seen with PACT131) could be used to identify pseudo-progressors, which might otherwise be deemed to be non-responders.**

Results

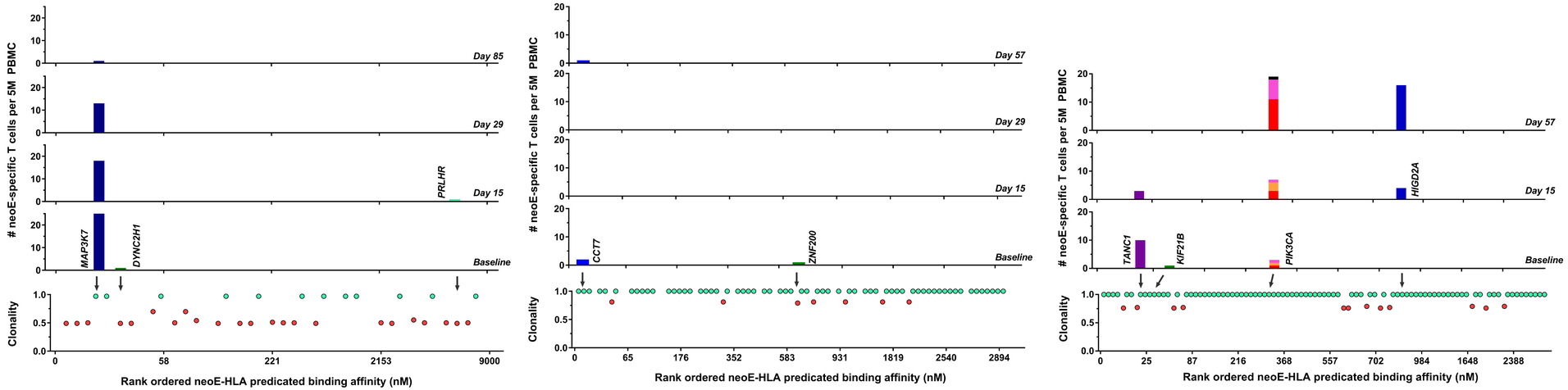


Figure 1. Landscape of neoE-specific T cells captured from blood of trial subjects using imPACT™. *Patients with colorectal cancer (PACT157, long stable disease, left; PACT132, progressive disease, middle) and endometrial adenocarcinoma (PACT131, right) were treated with AB122 (anti-PD1 antibody) as part of an ongoing dose-escalation clinical trial to evaluate the safety of the drug. PBMC were collected at different time points and analyzed by imPACT technology to monitor the on-treatment evolution of mutation-targeted T cell repertoires.*

(Top) Longitudinal evolution of neoE-specific T cells in peripheral blood during treatment. (Bottom) neoE clonality and predicted neoE-HLA binding affinity. *Green dot indicates a clonal mutation, while red dot indicates a sub-clonal mutation. Please refer to abstract #1979 for additional data of receptor occupancy for these patients.*

Gene	MAP3K7	DYNC2H1	PRLHR
HLA	A02:01	A02:01	C06:02
neoE	TLY(D)HQLQPL	LLFGDLLS(R)VA	SVKLH(R)NRVV

Gene	CCT7	ZNF200
HLA	A68:02	C12:03
neoE	ETIKNPRL(S)TV	KQSFILRVL(P)

Gene	TANC1	KIF21B	PIK3CA	HIGD2A
HLA	C05:01	A11:01	A11:01	B35:01
neoE	STDSPS(C)STL	ARSVSSIM(V)R	RA(D)IDKIYVR	LATAAAI(L)TYG

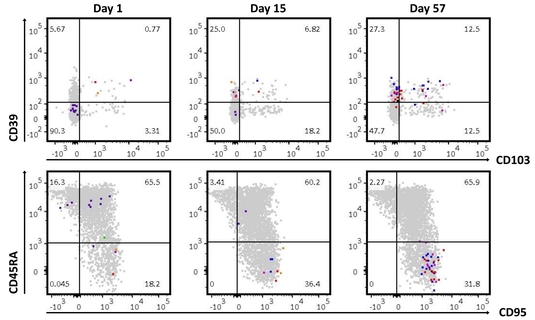


Figure 2: Phenotype characterization of neoE-specific T cells from PACT131. *CD95+ T cells are antigen-experienced. CD39+CD103+ positivity suggests that T cells have trafficked through the tumor compartment.*

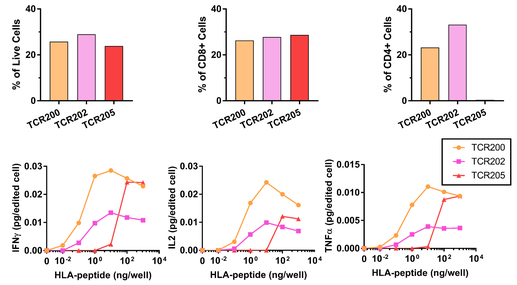


Figure 3. Functional T cell characterization & affinity of 3 TCR clones against the same PIK3CA neoE target captured from PACT131 blood. *No cytokine release was detectable against non-cognate neoEs.*