Abstract # P311

Positive identification of neoepitope-specific T cell by tumor-normal DNA & RNA sequencing from breast cancer patient leading to yeast-based vaccine phase 1 trial delivering tumor-specific neoepitopes

CONTRIBUTING RESEARCHERS

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BACKGROUND

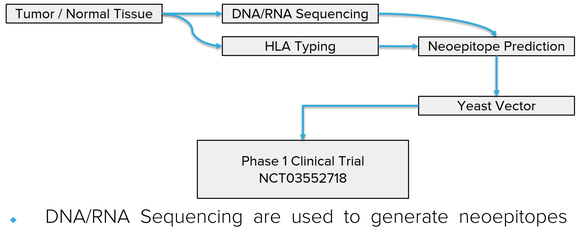
- Patient specific neoepitopes serve as ideal targets due to tumor specificity.
- Vaccines against personalized neoepitopes can generate immunological memory, tumor clearance, and durable remission by engendering T cell immunoreactivity.
- Delivering neoepitope vaccines via a proprietary yeast vehicle has the following advantages: (1) Distinct immunogenicity via TLR & Dectin-1 signaling, (2) Pre-made neoepitope peptides uptaken and presented by DCs, (3) Clinically-demonstrated, TAA-specific T cell responses, (4) Well-established safety in man (500+ patients dosed to date), (5) Exceptionally rapid production and manufacturing
- T cells isolated from tumor tissue specifically reactive to neoepitopes are indicative of potential neoepitope immunoreactivity
- Neoepitope-specific T cells represent a new path to patient-specific immunotherapy

METHODS

T Cell Isolation

- TILS were isolated from tumor tissue and expanded.
- Peptides, corresponding to neoepitopes, were pulsed with APCs and cocultured with isolated T-cells.
- Activated T-cells were assayed for functionality.

Clinical Trial

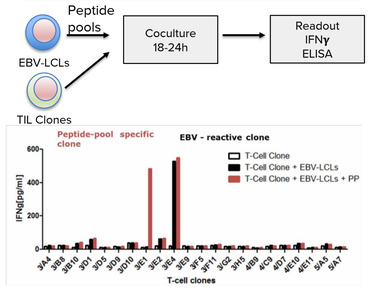


- DNA/RNA Sequencing are used to generate neoepitopes predicted to bind a patient's HLA alleles.
- A polytope of neoepitopes is expressed in *S. cerevisiae* and delivered subcutaneously.

RESULTS

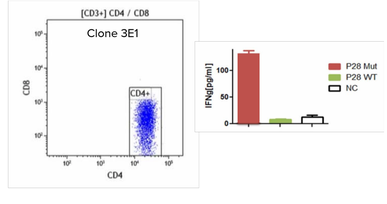
TIL Patient:

	Counts
Mutation Burden	46 Non-synonymous
Neoepitope Burden	158 Class 1, 265 Class 2

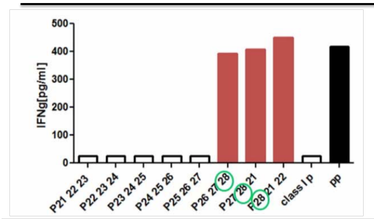


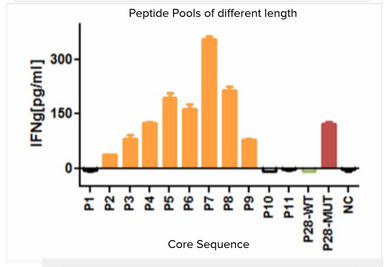
Clone 3E1 Recognizes T-> I mutation	
MUT	DRETNKSRGFAFVIFESPADAKDAA
WT	DRETNKSRGFAFVTFESPADAKDAA

ISOFORM	NM 001164803.1
HUGO	RBMX
PC	p.T55I (Missense)
BC	G -> A
POS	X:135961228-135961229



Seq-Derived, Bioinformatic Predicted Neoepitopes Engender Polyclonal, Highly-Specific T-Cell Response in a Breast Cancer Patient





P1	AFVIFESPADAKDAA
P2	FAFVIFESPADAKDA
P3	GFAFVIFESPADAKD
P4	RGFAFVIFESPADAK
P5	SRGFAFVIFESPADA
P6	KSRGFAFVIFESPAD
P7	NKSRGFAFVIFESPA
P8	TNKSRGFAFVIFESP
P9	ETNKSRGFAFVIFES
P10	RETNKSRGFAFVIFE
P11	DRETNKSRGFAFVIF
P28WT	DRETNKSRGFAFVTFESPADAKDAA
P28MUT	DRETNKSRGFAFVIFESPADAKDAA

HLA Typing	
HLA-A	A*01:01, A*24:02
HLA-B	B*07:02, B*27:05
HLA-C	C*02:02, C*07:02
HLA-DR	DRB1*14:01, DRB1*15:01
HLA-DP	DPA1*01:03 , DPA1*01:03, DPB1*02:01 DPB1*04:01

QUILT 2.025 CLINICAL TRIAL: First in Man Neoepitope Yeast Vaccine

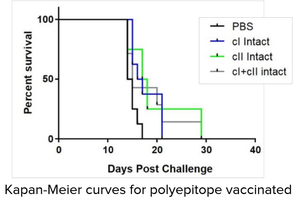
NCT03552718 Status

Consented Patients	12
Sequenced Patients	7
Avg Mutation Burden	98 Non-syn
Polytopes in Production	4

Yeast Polytope

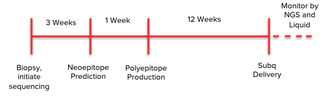
CUP1	Met	L	Neo1	L	NeoX

Proprietary Class I & II Targeting Motif is Necessary for Optimal Immunogenicity and Tumor Response



Kapan-Meier curves for polyepitope vaccinated B16-F10 tumor challenge mice

Timeline



CONCLUSIONS

- Using both Tumor / Normal sequencing of DNA and RNA from patient tumor samples allows identification of neoepitopes to serve as tumor specific antigens.
- In a breast cancer patient, we identified a TIL that recognizes a predicted neoepitope determined from sequencing data.
- Expansion, cloning and characterization of this TIL, reveals a CD4 T-Cell that is specific to a tumor mutation in the RBMX gene.
- NCT03552718 has accrued 12 patients and production of a yeast delivery system is ongoing.

ACKNOWLEDGMENTS

Hannah Kranich and Anita Kremer for their work in identifying t-cells, and Peter Fasching for patient samples.