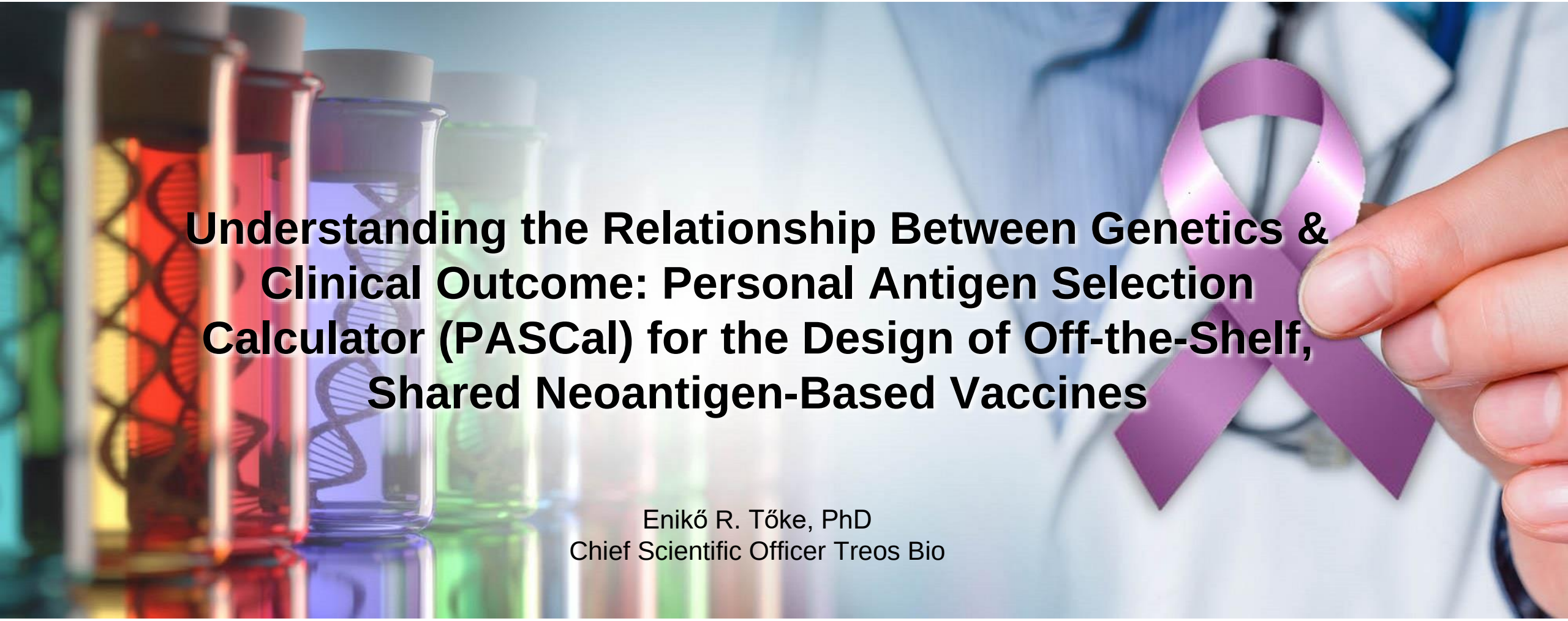
TREOS

Peptide Cancer Immunotherapy Digitally Matched To Patient Genetics

5th annual Neoantigen Based Therapies Summit

Weaponizing Vaccine and Cell Based Immunotherapies



Understanding the Relationship Between Genetics & Clinical Outcome: Personal Antigen Selection Calculator (PASCal) for the Design of Off-the-Shelf, Shared Neoantigen-Based Vaccines

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Presenter’s Disclosure

- Presenter holds shares at Treos Bio Ltd.

- No other financial disclosures to report

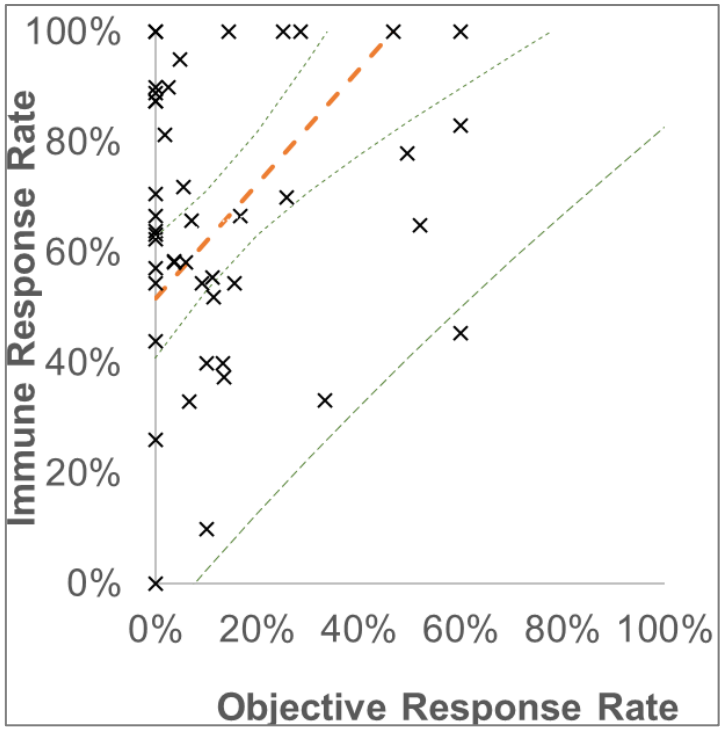
Background:
Cancer vaccines are still viewed as promising possibilities in modern cancer treatment despite lack of reliable efficacy to date

- Many oncology clinical trials have been conducted using vaccines which provoke an immune response, yet significant clinical benefit remains elusive.
- However, in some subgroups of patients, significant anti-tumor activity and meaningful clinical benefit has been achieved: Optimism still exists for these safe therapies…..many of us considering that immunotherapy (including vaccines) could be the only solution for a “cure” for cancer….
- It was observed that clinical responses to cancer vaccines are associated with T cell responses against multiple tumor antigens.
- Advances in molecular biology allowed development of neoantigen approaches using biopsies to find mutations unique to the patient. But just because the mutations were unique did not mean the human host would detect and react to each of the epitopes delivered in the individualised treatment.
- Consequently, inefficient epitope selection methods result in vaccines with limited clinical utility, highlighting the need for new, unconventional and more systematic approaches to realize the full potential of therapeutic vaccines.

Immune responses measured in clinical trials are not associated with tumor responses

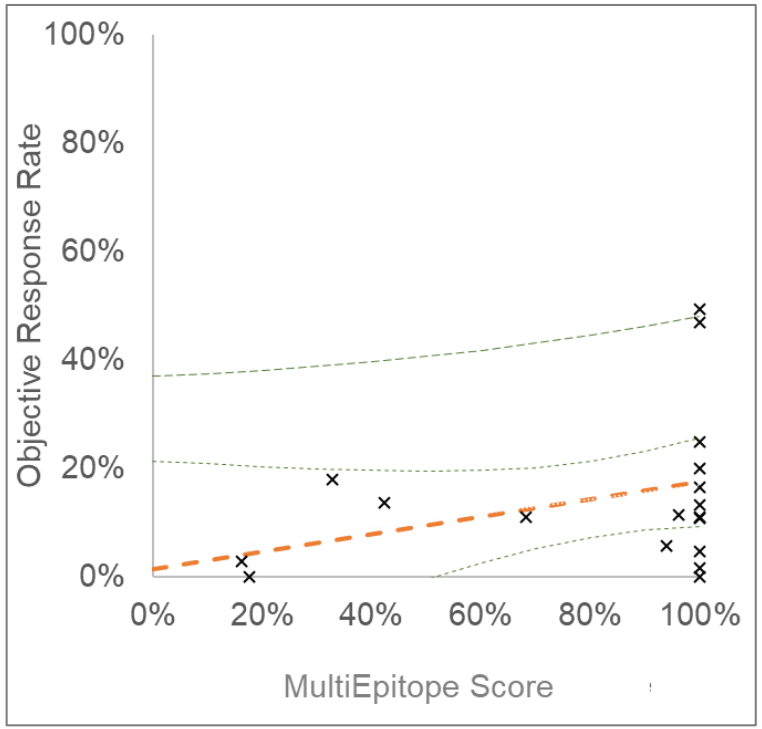
Meta-analysis conducted with published results of 49 clinical trial involving 32 cancer vaccines, 1,087 subjects*

Immune Response Rate (IRR) does not correlate with Objective Response Rate of vaccine clinical trials



(49 CTs; 1,087 subjects, 32 vaccines, p=0.294)

Having multiple HLA bindig epitopes against a vaccine does not predict clinical outcome



(20 CTs; 467 subjects; 19 vaccines, p=0.085)

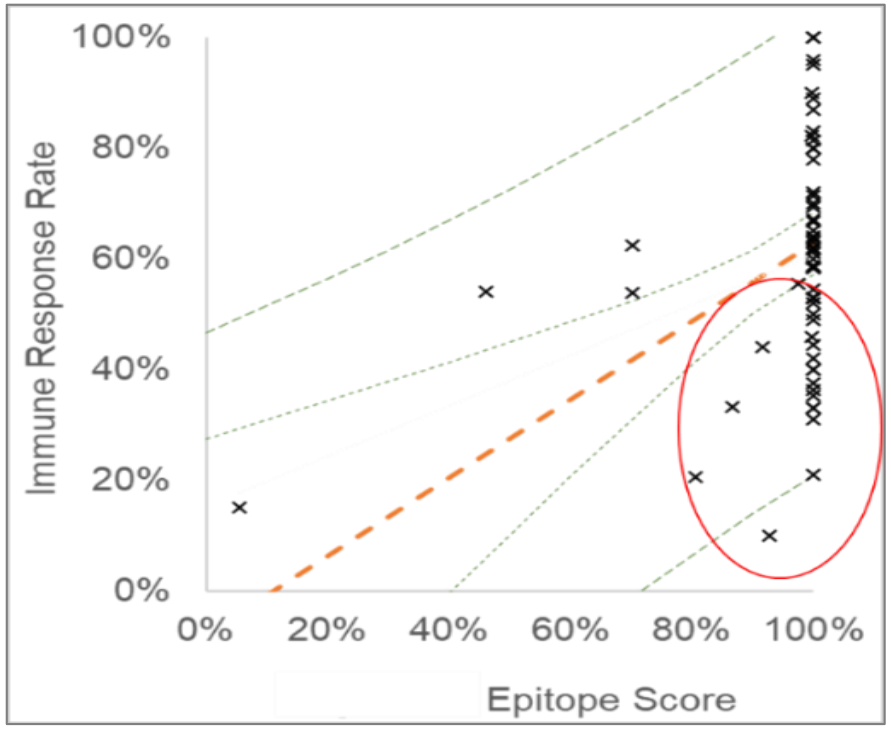
*Lorincz et al ESMO2019

HLA-restricted epitopes highly overestimate immune response rates of vaccine clinical trials*

Meta-analysis conducted with published results of 79 clinical trials involving 57 cancer vaccines with known sequences; 1,842 subjects*

→

Determine Epitope Score
frequency of HLA-restricted epitopes for an ethnically mixed, HLA-genotyped *in silico* cohort (n=433)

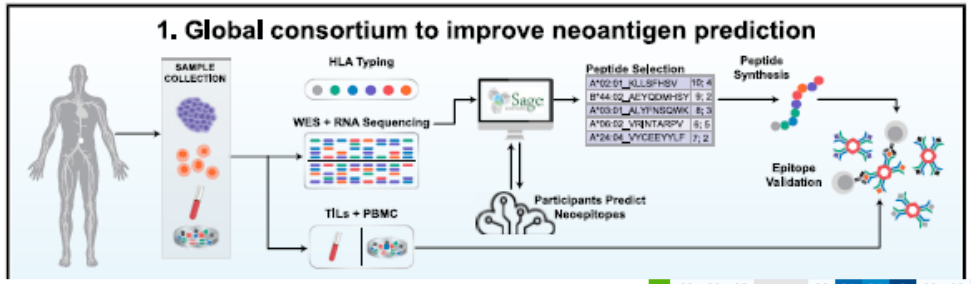


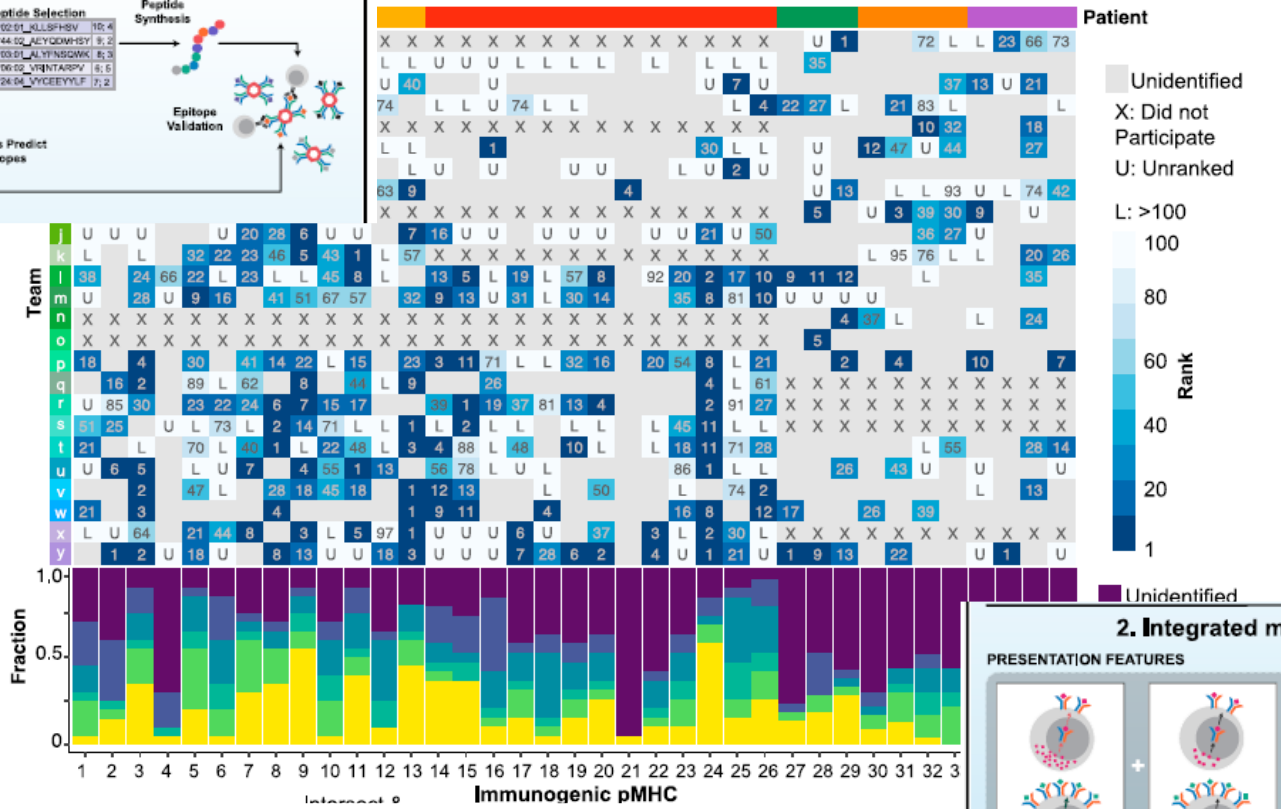
(n=79 CTs; 1,842 subjects; 57 vaccines; p=0.0127, R^2=0.0104)

Stratification based on matching HLA alleles was also not predictive: No significant difference in the IRR of trials with or without HLA pre-selection either (57% vs. 61%, p=0.711)

*Lorincz et al ESMO2019

TESLA*: Standardized evaluation of neo-epitope prediction pipelines used by 25 teams: Validation rate of immunogenic epitopes: 6%

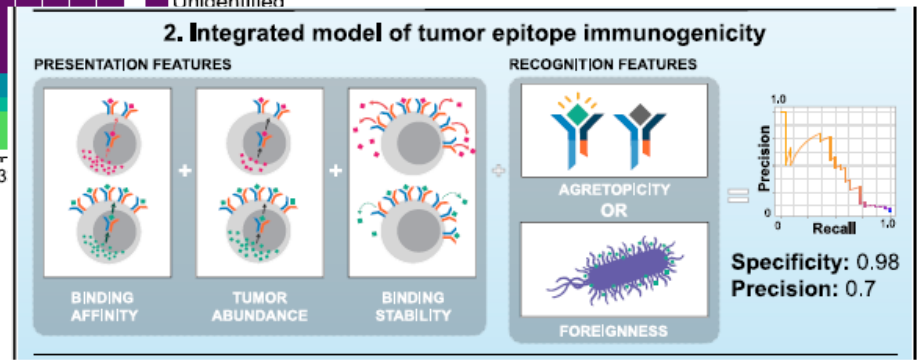




- **Diversity** of the predicted neo-epitopes was extremely high: range 7-81,904 peptides per tumor sample (median 204)
- **37 out of 608 peptides-MHC** were bound by patient-matched T cells (n=6 patient)
- For each TESLA team: **median 3 immunogenic peptide/ patient** out of 51 tested
- **No team included >20** out of 37 immunogenic peptides **in their top 100**

Key parameters revealed:

- **5 parameters govern** immunogenicity
- Applying these parameters **in a model, improved prediction**



*__Tumor Neoantigen Selection Alliance (TESLA)__, a global community-based initiative seeking to understand tumor epitope immunogenicity: 28 unique teams submitted ranked neoantigen predictions on these samples. In vitro immunogenicity analyses were performed on the predictions from 25 teams. *Wells et al. Cell 2020*

Individualized neo-epitope vaccination does not guarantee immune response

- *BioNTech*

CD8+ T cell responses were detected against 17% of all the predicted neo-epitopes by IFNγ ELISpot.

Median 1 immunogenic target / patient out of 10 *(Sahin et al. Nature 2017)*

- *Genocea Biosciences*

T cell responses were detected against 53% CD8+ and 88% CD4+ of all the selected neo-epitopes by IFNγ ELISpot. *(Cohen et al. J Clin Oncol. 2019)*

- *Neon*

CD8+ T cell response were detected against 28% of all neo-epitopes administered, CD4 T cell responses against 42% of all neo-epitopes administered.

Median 2 immunogenic targets / patient out of 13-20 *(Ott et al. Nature 2017)*

More precise epitope-prediction is required for personalised vaccine development.

Challenges and limitations of cancer immunotherapies revolve around heterogeneity of the disease and the patient

TUMOR HETEROGENEITY

- Variability of gene/antigen expression frequency by location and by time, within the same patient
- Low mutational burden in some tumors
- Not every tumor can be sampled for biopsy

ANTIGENICITY

PATIENT HETEROGENEITY

- Prevalent HLA alleles do not cover the heterogeneity of populations
- HLA-restricted epitopes do not elicit T cell response in HLA-matched patients
- HLA-downregulation in majority of tumors

IMMUNOGENICITY

Treos technology addresses the dual heterogeneities of cancer patient management

1. Addressing tumor heterogeneities: Private *vs* Shared Tumor Antigens

Cold Spring Harbor Perspectives in Biology

Is It Possible to Develop Cancer Vaccines to Neoantigens, What Are the Major Challenges, and How Can These Be Overcome?: Neoantigens: Nothing New in Spite of the Name

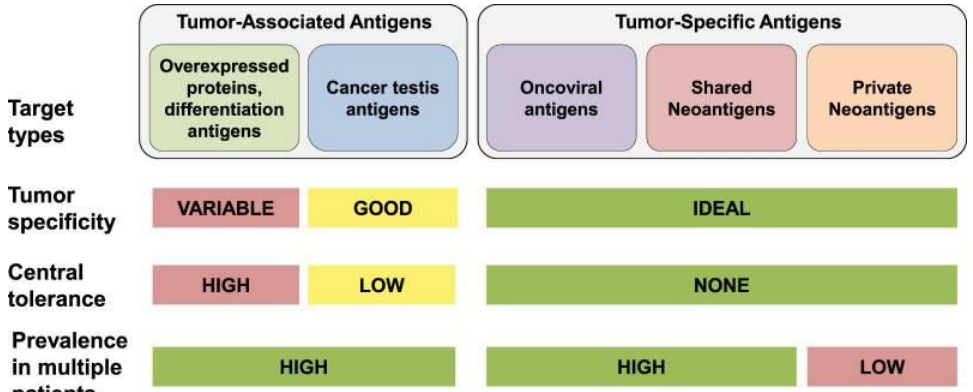
Olivera J. Finn and Hans-Georg Rammensee

Definition:

"The term neoantigen, applied to molecules newly expressed on tumor cells…."

- Oncoviral antigens
- Shared Tumor-specific antigens
- Private Tumor-specific antigens = **Mutated neoantigens**
- **Cancer Testis Antigens (CTAs)**

Tumor antigen features



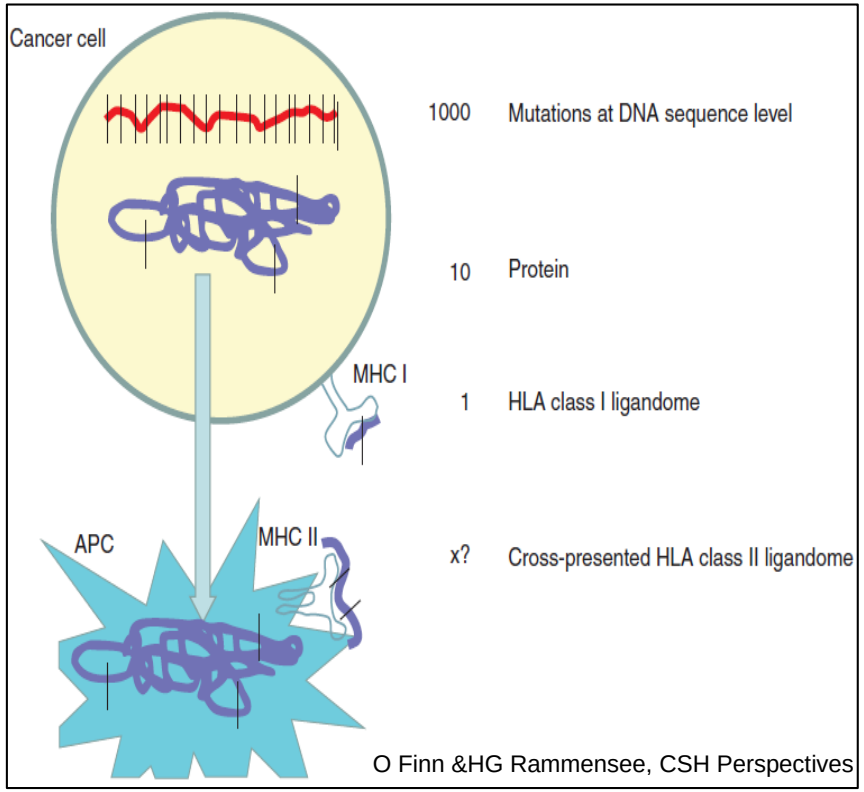
Hollingsworth & Jansen NPJ Vaccines 2019

Additional target antigen selection criteria addressing challenges

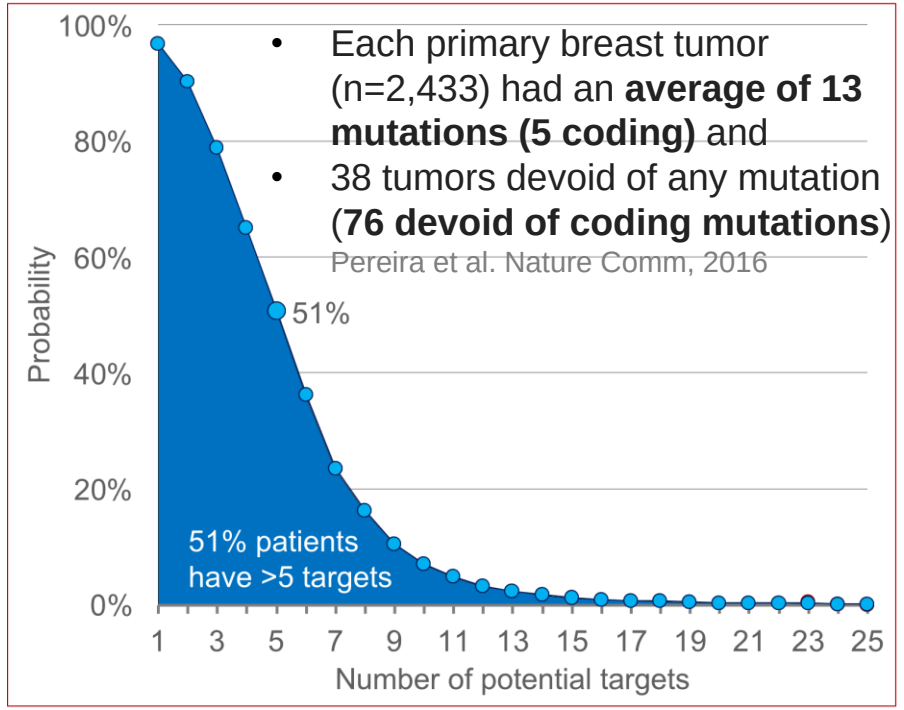
- Should be present on many cancer cells (*intra-/intertumoral heterogeneity*)
- Should be "constantly" present on cancer cells (*antigen-loss*)
- Should be abundantly expressed on cell surface (*mRNA/protein expression)*
- Should be abundantly presented by MHC molecules on cell surface (*HLA downregulation*)

Targeting multiple mutated neoantigens in each patient is challenging

Prevalence of neoepitopes is low especially in tumors with low mutational burden
~1% tumor mutations generate neoantigens in melanoma and <1% in other cancers



Mutation rate is low in many tumors – challenging to design personalized treatment for each patient



- Each primary breast tumor (n=2,433) had an **average of 13 mutations (5 coding)** and
- 38 tumors devoid of any mutation (**76 devoid of coding mutations**)

Pereira et al. Nature Comm, 2016

Company Indication*	Excluded patients from clinical trial due to low mutation rate
Neon (Melanoma)	2 / 10
BioNtech (Melanoma)	0 / 13
Dana-Farber/Harvard (Glioblastoma)	2 / 10
Immatics (Glioblastoma)	6 / 16

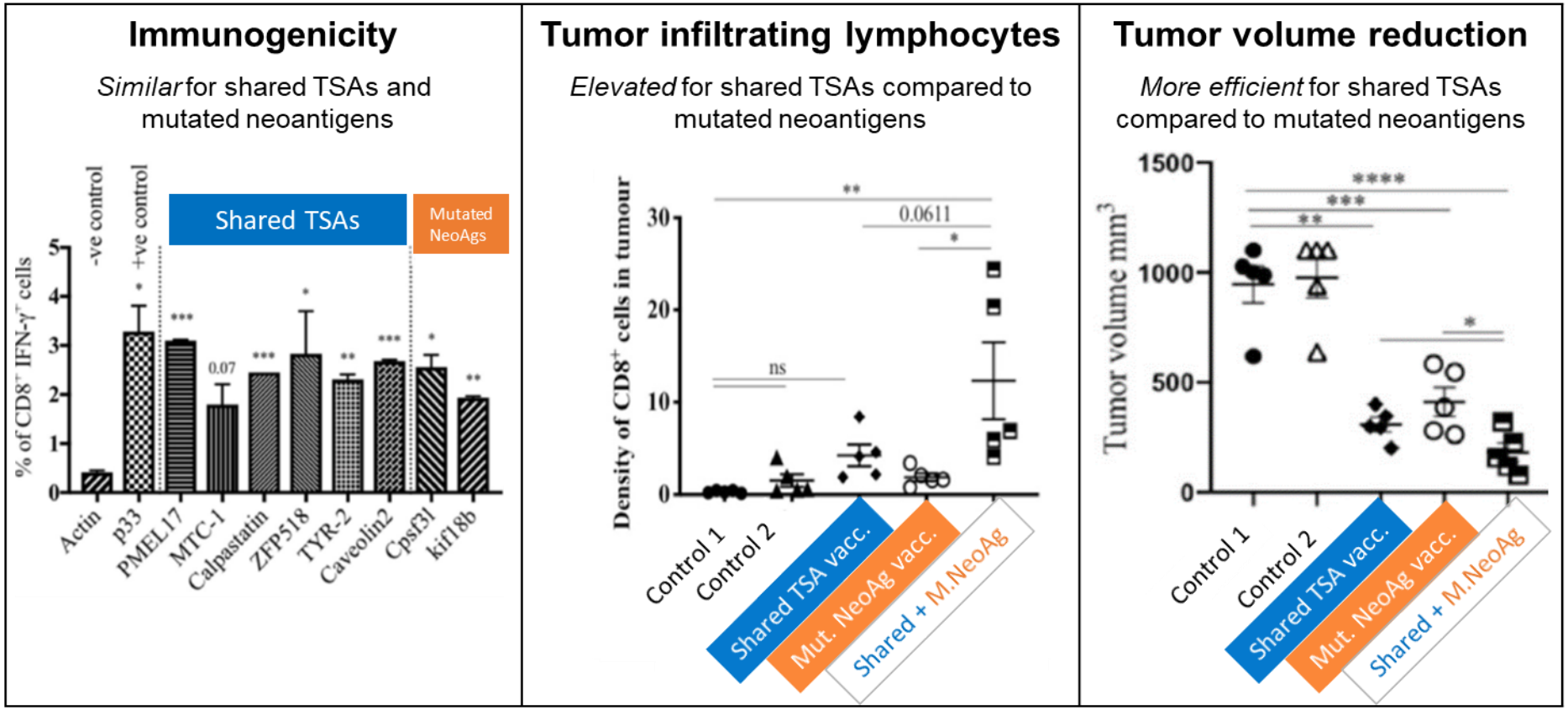
*Source: Ott et al. 2017; Keskin et al. 2018; Sahin et al. 2017; Hilf et al. 2018

Shared tumor antigen-based vaccines are proven to be at least as effective as mutated neoantigen vaccines

2 melanoma-specific vaccines derived from the same tumor:

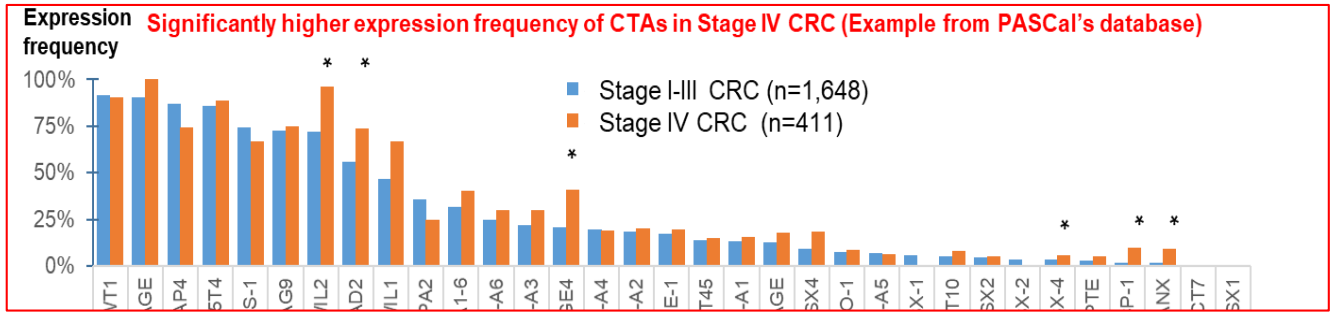
Shared TSA vaccine – containing shared germline Tumor Specific Antigens identified by Immunopeptidomics

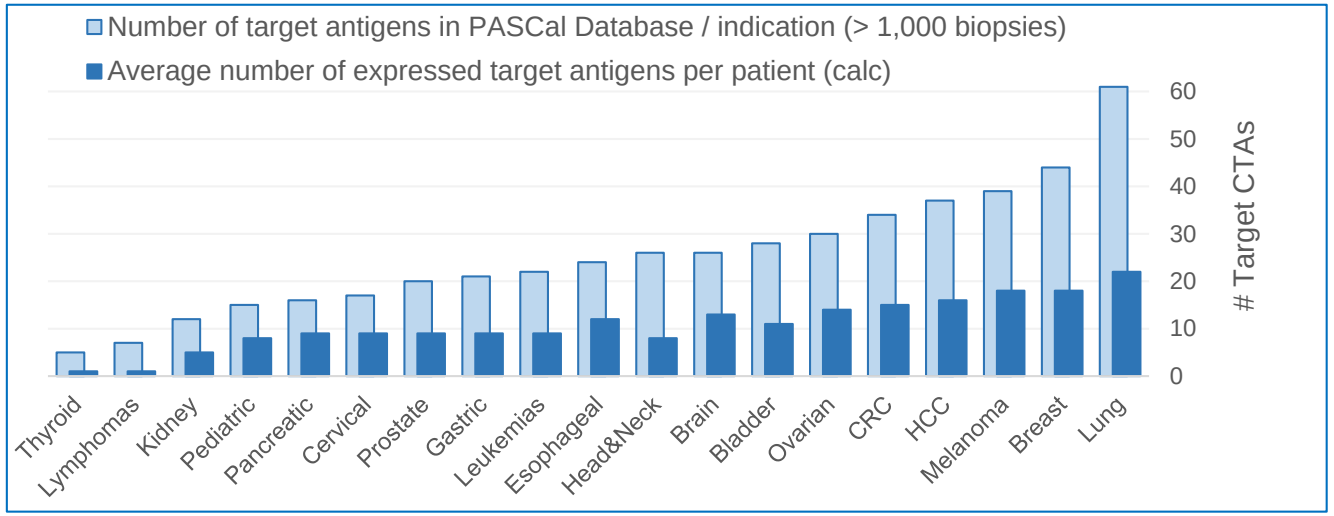
Mutated NeoAg vaccine – containing mutated neoantigens identified by Whole Exome Sequencing



Source: Mohsen et al. Frontiers Immunology 2019

Shared tumor antigens (CTAs) are prevalent in multiple tumors and patients





Cancer Testis Antigens (CTAs) have

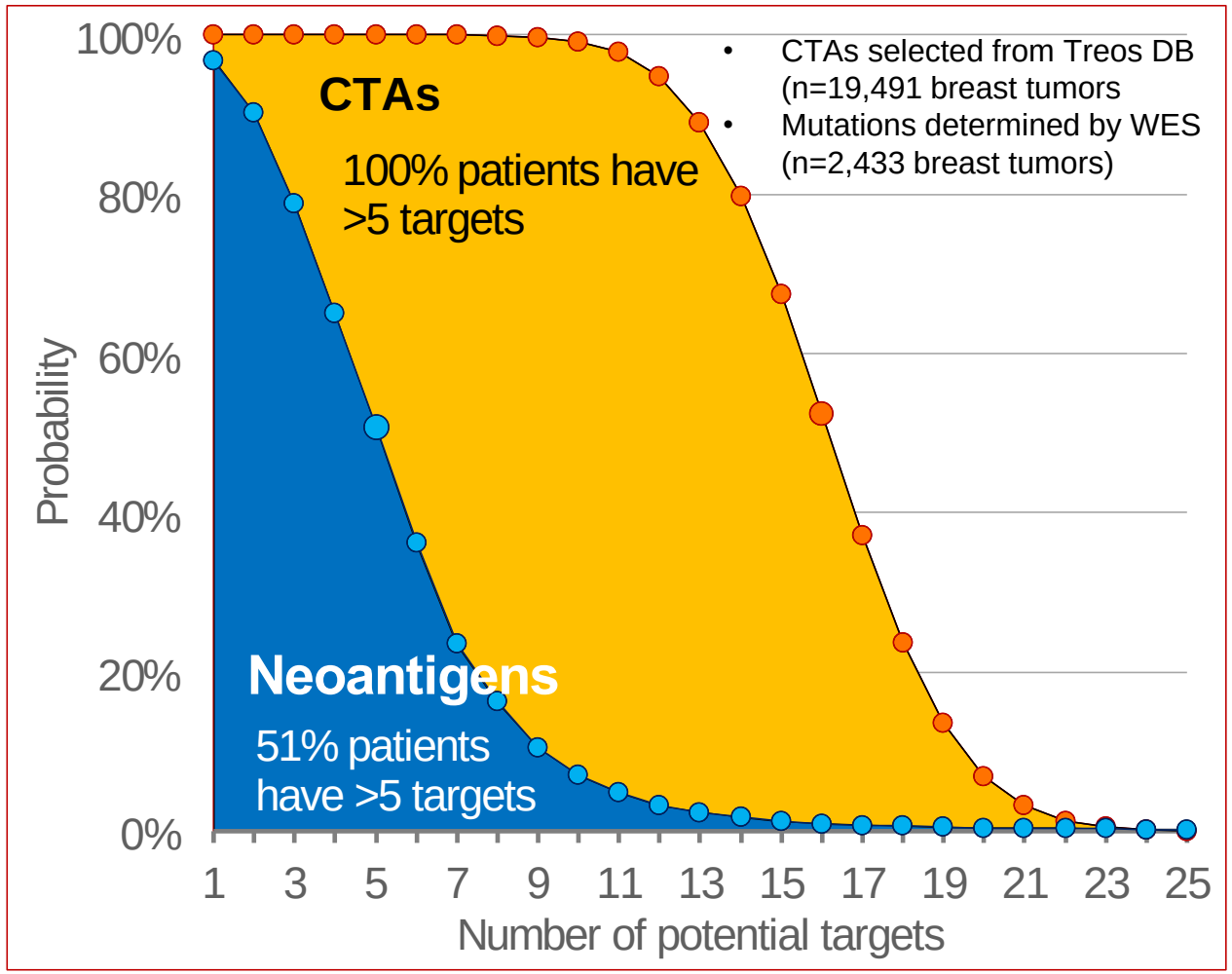
- spontaneous immunity in cancer patients
- oncogenic feature (sustained growth, angiogenesis, evading apoptosis)
- good tumor specificity (highly restricted expression patterns in normal tissues)
- high expression in cancer stem/initiating cells
- high expression in advanced stages of cancer
- higher expression in metastases

Antigen Expression Knowledgebase

Based on >96,000 tumor biopsies

- Collects CTA expression frequency data on mRNA/protein level (excludes gene expression data only)
- Only from samples of human origin (excluding cancer cell lines)
- Data covers various subtypes and stages of all the indications, *w/wo* prior treatments, etc
- >1,000 biopsies/disease captures the variability of antigen expression frequency by location and by time
- Average 30 CTAs / indication with average 10 expressed in each patient
- Established for 19 cancer indications / Continuous improvement

Frequently expressed CTAs enable precise targeting of multiple tumor antigens in a vaccine



Advantages:

- Selection from knowledgebase - no biopsy required
- High sample sizes and diversity across tumor tissues – address intra/intertumoral heterogeneities and potential antigen-loss (limitation of patient-specific sequencing)
- Inclusion of multiple (6-20) targets per vaccine could avoid tumor escape
- Applicable to virtually all patients

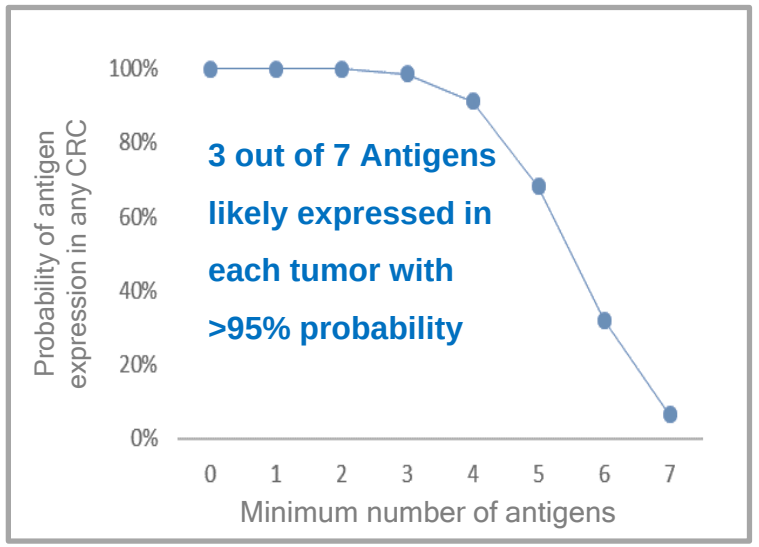
Limitation: few selected targets may not be expressed in the patient's tumor

Pereira et al. Nature Comm, 2016

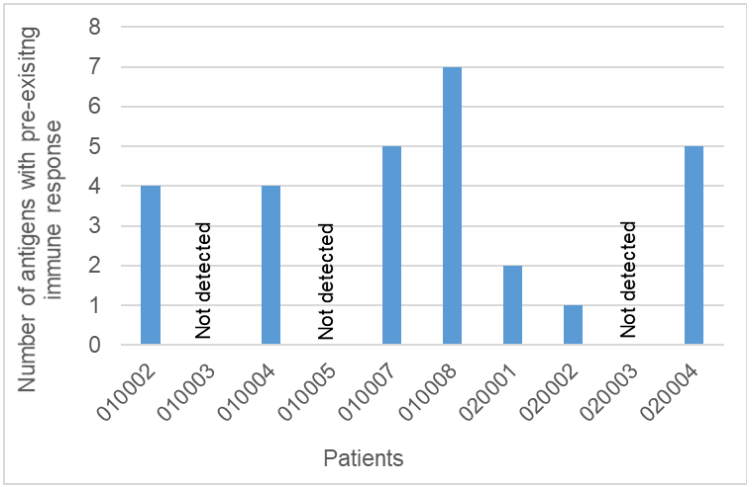
Shared tumor antigens targeted by PolyPEPI1018 vaccine are expressed on the tumors of mCRC patients

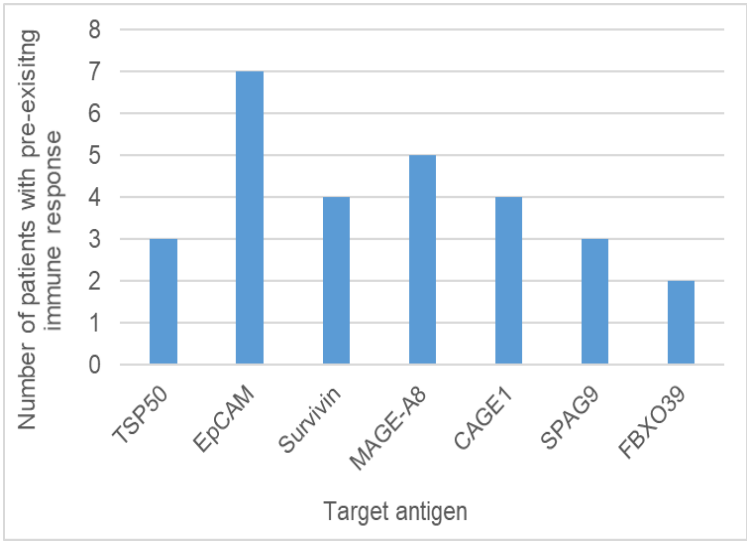
Pre-existing immune responses (ie before vaccination) indirectly confirm the expression of tumor antigens on the surface of the tumors

Tumor Antigens targeted by PolyPEPI1018	Expression Rate (2,391 CRC tissues)
TSP50	89%
EpCAM	88%
Survivin	87%
CAGE1	74%
SPAG9	74%
MAGE-A8	44%
FBXO39	39%



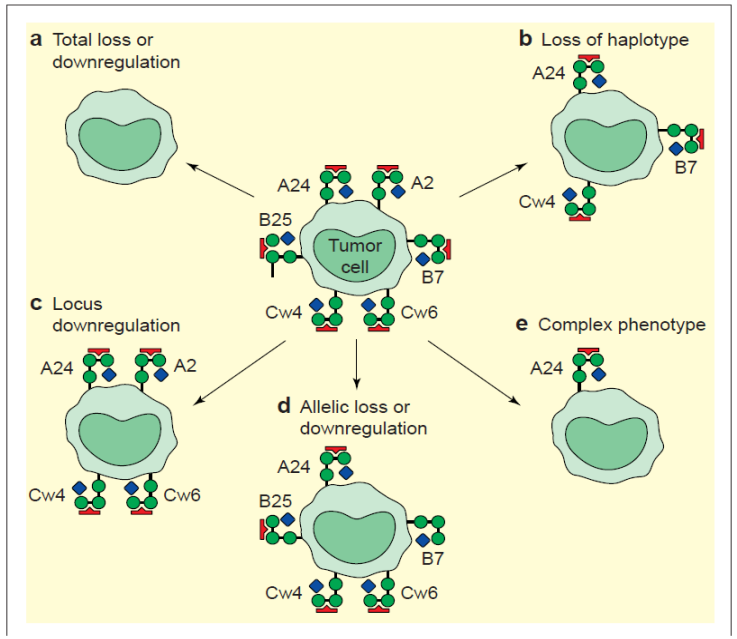
mCRC patients' PBMC tested using IFN-γ ELISpot for CD8+ T cells
(2 peptides / antigen used for stimulation)

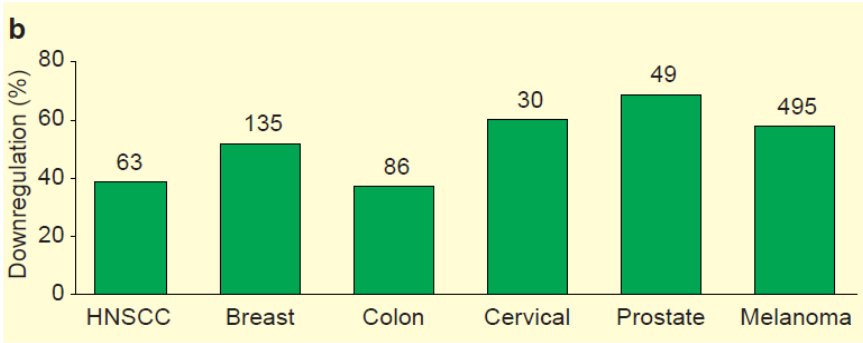




- **Average 3 antigens expressed in 7/10 subjects**
- **Each antigen expressed in average of 4 patients' tumor**

2. Addressing Patient heterogeneities: Epitopes selected for the complete HLA genotype of individuals (not only individual alleles) could mitigate the risk of tumor escape by HLA downregulation



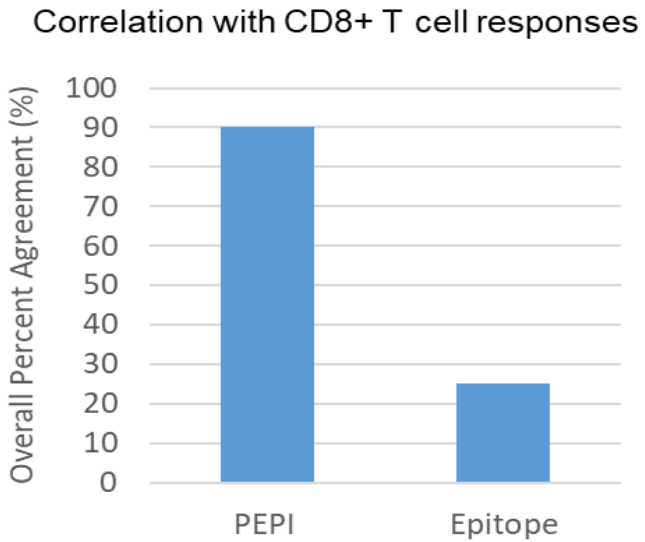


J. Hicklin et al, Molecular Medicine Today, 1999

- Each individual has 6 major HLA class I and 8 HLA class II alleles
- Tumors downregulate the expression of HLA alleles partially or totally

➔ There is a likelihood that single HLA allele-restricted epitopes do not present on the surface of the tumor cell resulting in no T cell recognition

➔ **P**ersonal **EPI**tope (**PEPI**) is an epitope restricted to multiple autologous HLA alleles of an individual and more likely to generate an immune response than single HLA allele-restricted epitopes*



PEPIs predict T cell responses upon peptide vaccination with Synthetic Long Peptide Vaccine encoding HPV16/18

Study performed in collaboration with Leiden University and LabCorp*
n=25 cervical cancer/VIN subjects

*Toke ER et al, JCO, 37, 2019 (suppl; abstr e14295)

HLA-genotypes – through PEPIs – determine cancer risk, too

HLA-genotypes supporting broader anti-tumor T cell responses indicate lower risk to cancer

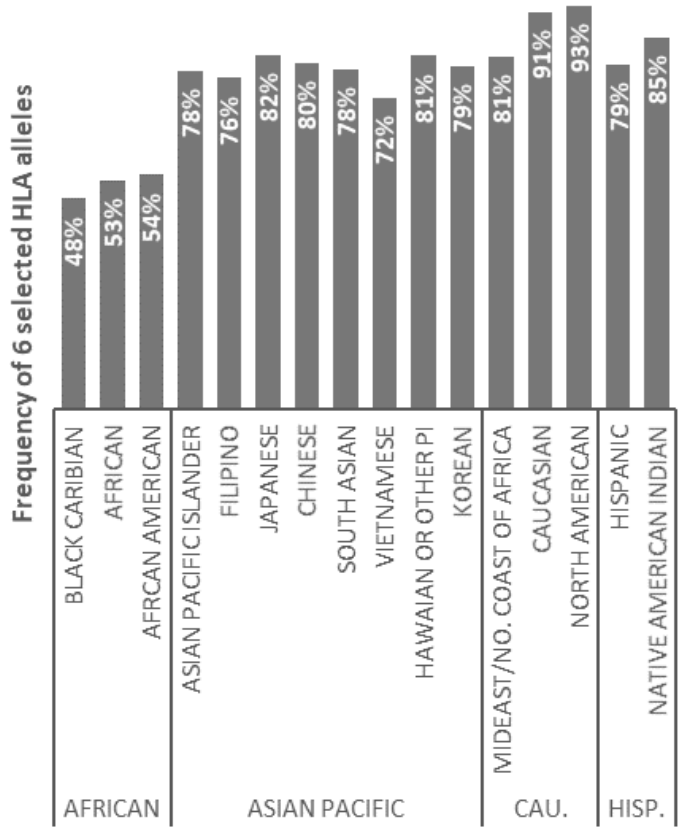
Cancer type	Cohort Size	Relative Risk (RR)		$RR_{extremities}$	AUC	p
		Risk Grp*	Protected Grp*			
Melanoma	513	2.34	0.41	5.69	0.69	<0.001
Lung (NSCLC)	370	1.84	0.41	4.49	0.66	<0.001
Renal cell	129	1.73	0.51	3.41	0.63	<0.001
Colorectal	121	1.28	0.55	2.35	0.55	0.008
Bladder	87	1.89	0.46	4.14	0.66	<0.001
Glioma	82	1.83	0.48	3.81	0.63	<0.001
Head and neck	58	1.21	0.51	2.38	0.62	0.001

Cancer risk predictor: ability of the HLA class I alleles of an individual to present PEPIs derived from 48 selected tumor antigens

I Miklos et al ESMO2019; I Miklos et al JCO, 37, 2019 (suppl; abstr e13132).

Prevalent HLA alleles do not represent heterogenous population

A combination of 6 prevalent HLA alleles frequently used for vaccine design does not equally represent ethnicities*



HLA-genotype data obtained from a US bone marrow database (n=16 x 1,000 each ethnicity)

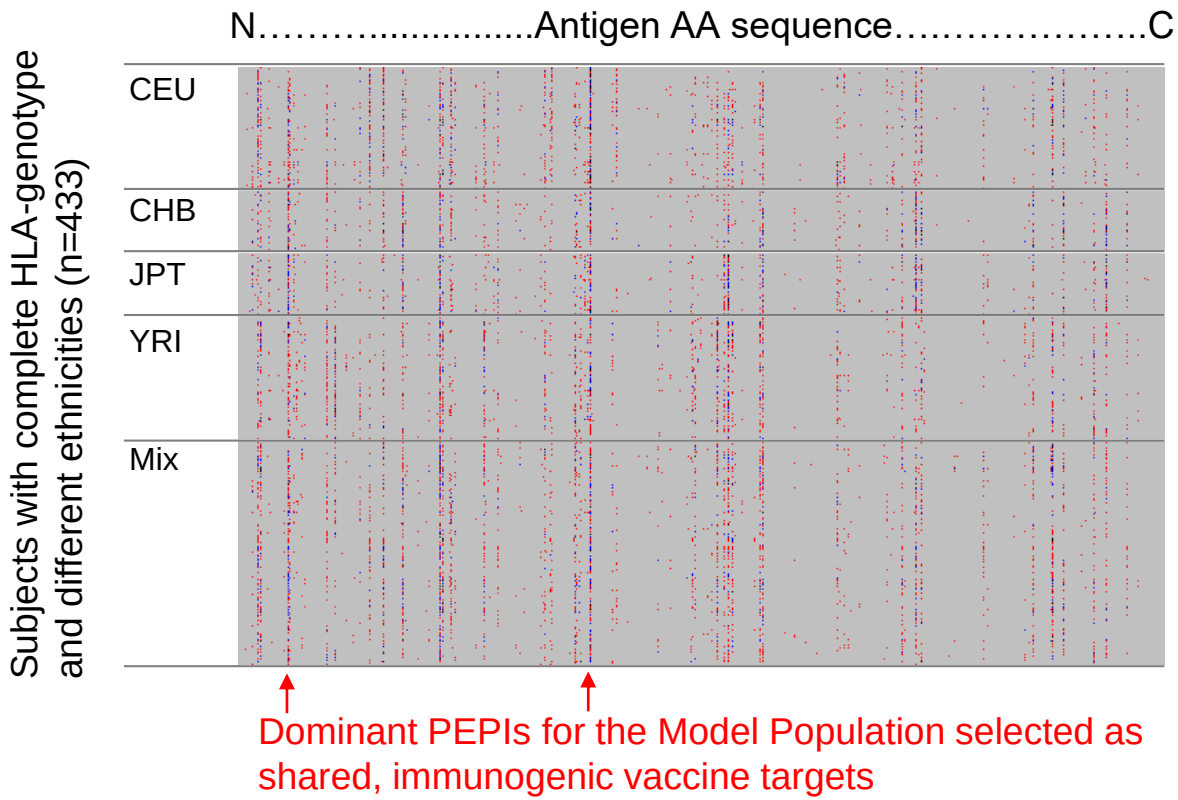
Use real subjects instead of HLAs

Model Population - *In silico* Human cohort of real subjects with complete HLA-genotype and different ethnicities to represent individuals as part of heterogeneous large population

Model Population represents 85% of humanity as determined by HLA diversity and HLA frequency**

*E Somogyi et al https://www.biorxiv.org/content/10.1101/2020.10.16.339937v1; ** Lorincz et al ESMO2019

In silico Human model correctly estimated immunogenicity of our PolyPEPI1018 vaccine in mCRC patients

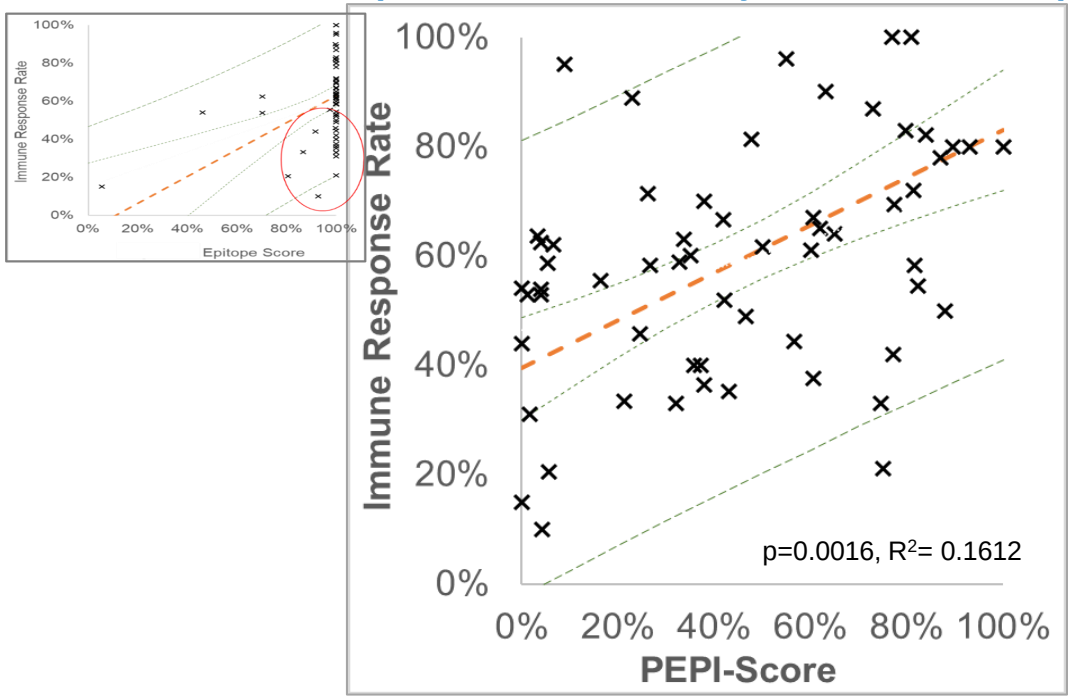


PolyPEPI1018 Peptides	Frequency of PEPIs in the Model Population (n=433)	Immune response rate in OBERTO-101 study* (n=10)
CRC_P1	53%	70%
CRC_P2	57%	70%
CRC_P3	43%	70%
CRC_P4	58%	70%
CRC_P6	57%	60%
CRC_P8	90%	70%
≥1 Peptide (PEPI Score)	98%	90%
≥2 Peptides	91%	90%
≥3 Peptides	73%	70%

*Hubbard et al ASCO 2020

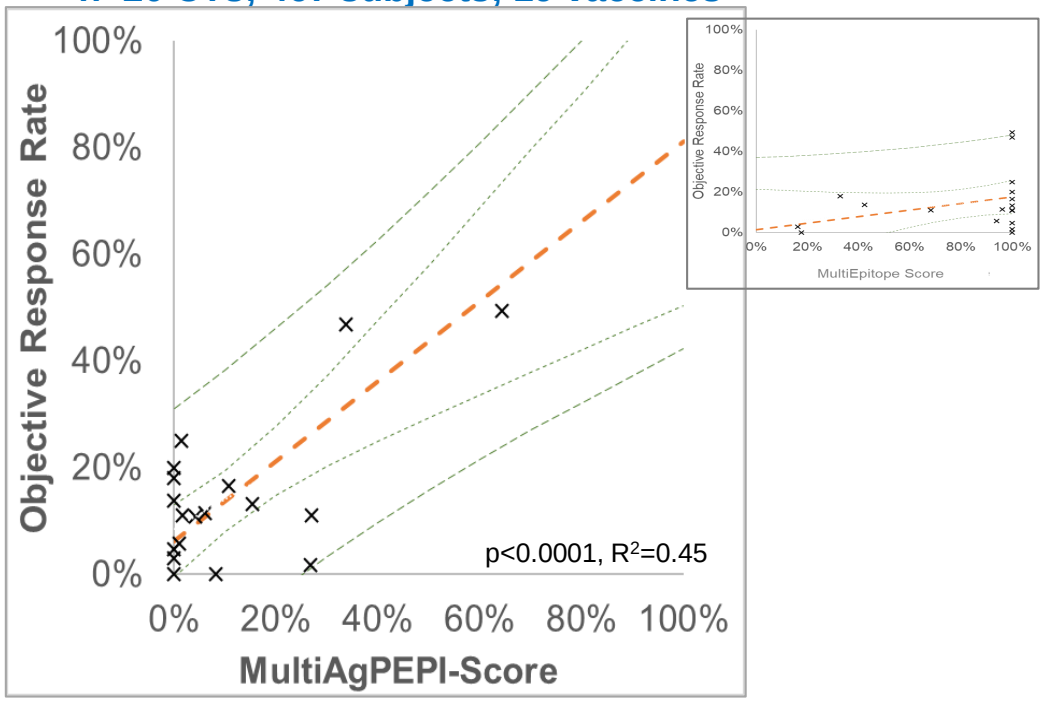
In silico Human model together with PEPI concept predict the response rates of vaccine clinical trials (not seen using epitopes)*

Correlation between
Predicted and Detected Immune Response Rate
(n=79 CTs; 1,842 subjects; 57 vaccines)



% subjects with at least one PEPI in the Model Population

Correlation between
Predicted and Detected Clinical Response Rate
n=20 CTs; 467 subjects; 19 vaccines



% subjects with multiple PEPIs on different antigens in the Model Population

*Lorincz et al ESMO2019

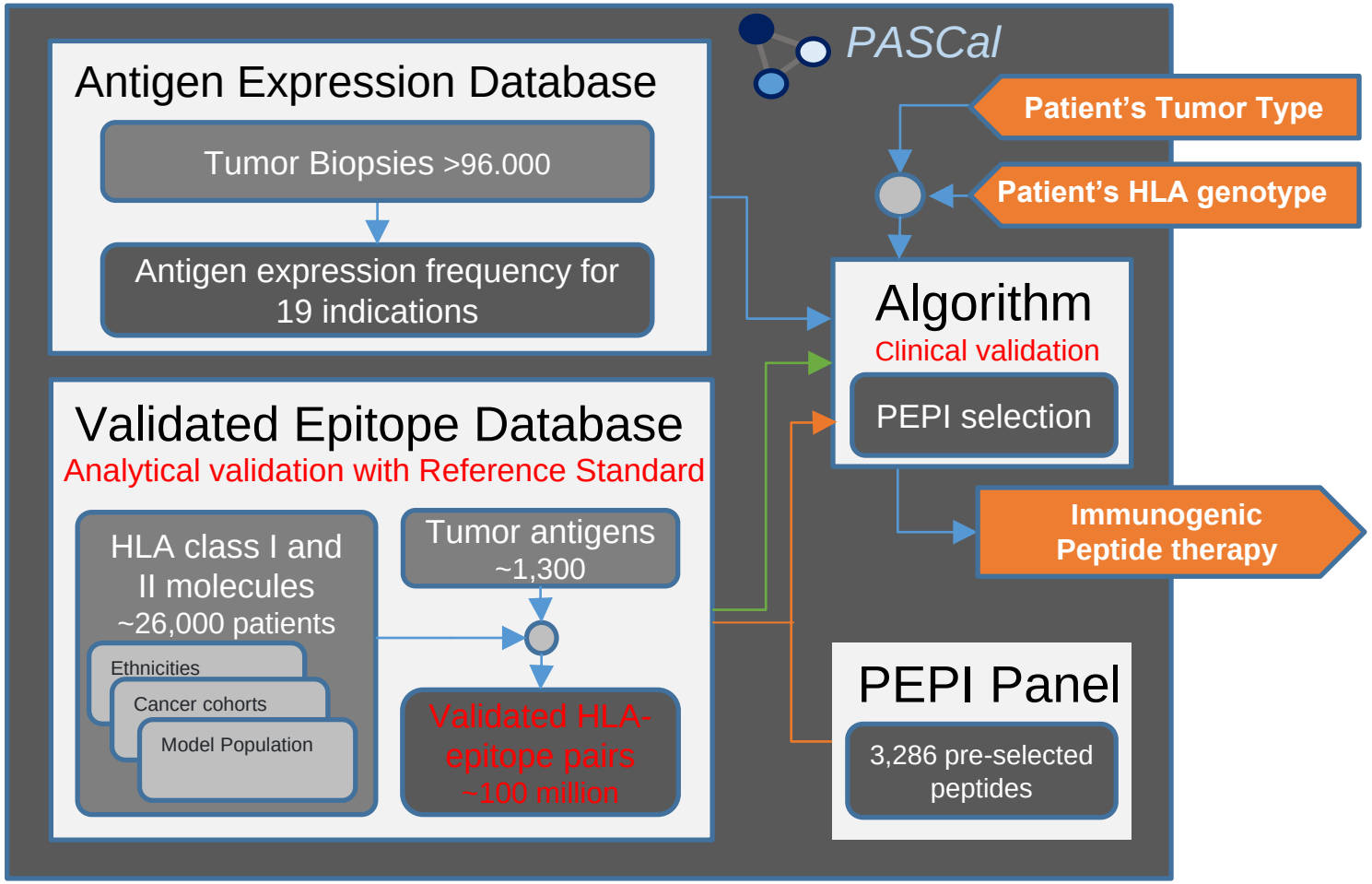
Understanding the Relationship between Genetics and Clinical Outcomes: *Personal Antigen Selection Calculator* (*PASCal)*

The Personal Antigen Selection Calculator (*PASCal*) is based on:

1. A knowledge base catalogues tumor-specific antigens: TREOS' proprietary antigen expression database is constructed from >96,000 biopsies from 19 different cancers
2. TREOS invention: ***PEPIs* = Personal EPItopes restricted to multiple HLA allele of a person** determine antigen-specific T cell responses*
3. A proprietary algorithm that determines a patient's immune response profile based on autologous HLA alleles with validated 84% accuracy
4. A peptide selection algorithm that identifies peptide sequences from the knowledge base built on HLA genetics of real individuals and tumor type.
   - Validated HLA-Epitope Pair Database – for the identification of PEPIs
   - No biopsy is required

*Toke ER et al, ASCO2019; ** Lorincz O et al, ASCO2019; ESMO2019

PASCal uses the analysis of Big Data to develop a genetic approach that selects most relevant peptides for vaccination



Analytical validation: reliability of epitope prediction

Reference standard: 427 experimentally proven binding and non binding HLA-peptide pairs

- Analytical Specificity: 93%
- Analytical Sensitivity: 93%
- Analytical Accuracy: 90%
- Analytical Precision: 100%

Clinical validation: prediction of subject's T cell responses

1. Retrospective analysis of 6 clinical trials involving 71 cancer patients and 9 HIV+ patients

- Positive Predictive Value: 84%
- Diagnostic efficiency: ROC AUC 0.73

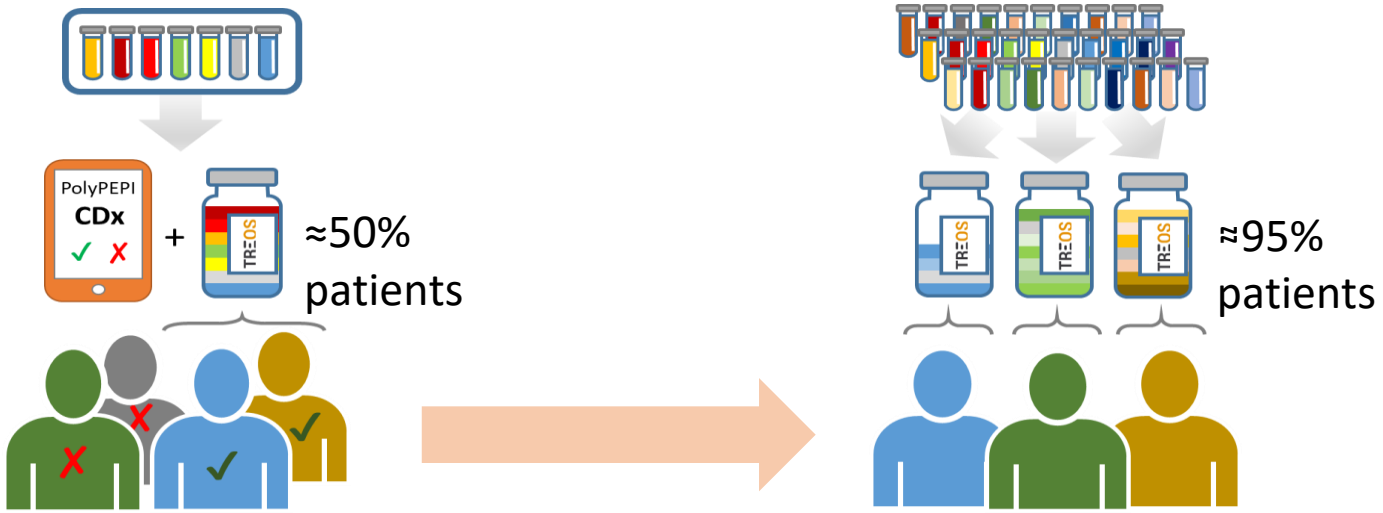
2. Prospective analysis of phase I/II clinical trial conducted with PolyPEPI1018 vaccine

- Positive Predictive Value: 79%

Developing two families of cancer vaccines <u>without</u> need for tumor biopsy

Diagnostics based on HLA sequencing (from cheek swab) enables selection of peptide cancer treatments

OFF-THE-SHELF (*PolyPEPI*)	Off-the-shelf Personalized (*PEPI Panel*)
PolyPEPI Vaccines Provides Broad Coverage of HLA Genotypes – treatment selected with CDx	Peptide mix selected from a pre-manufactured peptide "warehouse" based on patient's HLA-genotype and disease



Increasingly personalized treatment selection depends on the predicted responses

PolyPEPI-1018: Off-The-Shelf Immunotherapy for MSS Colorectal Cancer

PolyPEPI-1018 consists of **six synthetic peptides** derived from the **seven** immunogenic fragments of the most frequently expressed and conserved cancer testis antigens (**CTAs**) in CRC.

PolyPEPI-1018 is designed to induce polyvalent T cell responses in a large subpopulation of CRC patients using Treos proprietary *PASCal* computational tool, which identifies *Personal EPItopes* (*PEPIs*) that are likely to induce antigen-specific T cell responses in a subject.

- **Indication:** Add-on to standard of care treatment in patients with microsatellite stable metastatic colorectal cancer (MSS mCRC)
- **Type Of Therapy:** Add on peptide-based immunotherapy
- **Route of Administration:** Subcutaneous injection
- **Adjuvant:** Montanide ISA51 VG

Rationale:

- Checkpoint Inhibitors have shown success in many tumors, including MSI-H/dMMR CRC, but are ineffective in the >90% of mCRC patients who have MSS/pMMR disease (cold tumors)
- No vaccines have worked in “cold tumors” before
- We expect that our vaccine will be the first breakthrough in active immunotherapy for cold tumors (MSS mCRC and others)

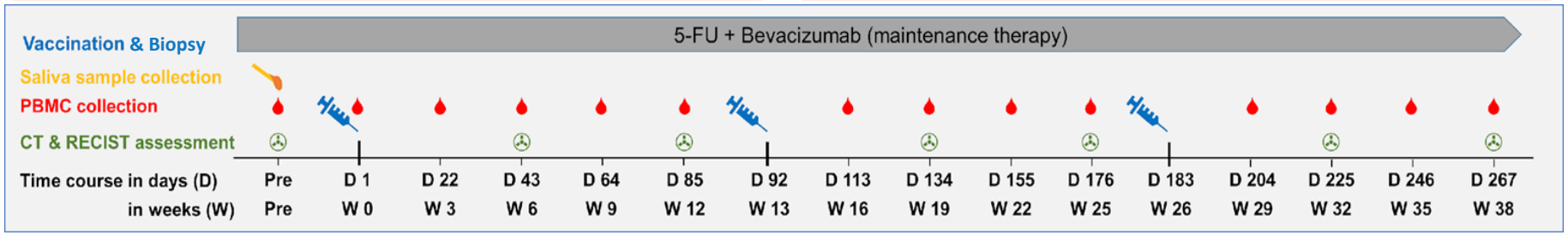
OBERTO-101: Phase I/II Clinical Trial of PolyPEPI-1018 for the Treatment of Metastatic Colorectal Cancer (MSS)

OBERTO-101 was a Phase I/II, open-label, single-arm, multi-center study to evaluate the safety, tolerability, immunogenicity and preliminary efficacy of single dose or multiple doses of PolyPEPI-1018 as an add-on to maintenance therapy in patients with mCRC after first-line induction chemotherapy

OBERTO-101 *(NCT 03391232)*
N=11

Part A
N=5
Single dose
12 weeks follow up
Safety, Tolerability, Immunogenicity

Part B
N=6
3 doses Q12W
38 weeks follow up
Safety, Tolerability, Immunogenicity, Preliminary Efficacy



MSS mCRC patients were treated with PolyPEPI-1018 just after their transition to maintenance therapy

OBERTO Key Results: PolyPEPI-1018 is very safe and well-tolerated

Adverse Events	Number of possibly or definitely related adverse events recorded		
	Grade 1	Grade 2	Grade 3
NON-INFECTIOUS ACUTE ENCEPHALITIS*	0	0	1
CONSTIPATION	0	1	0
ERYTHEMA MULTIFORME	0	1	0
ERYTHEMA-INJECTION SITES	0	1	0
FATIGUE	0	1	0
SUPERFICIAL THROMBOPHLEBITIS	0	1	0
ANEMIA	1	0	0
ARTHRALGIA	1	0	0
INJECTION SITE BURNING FEELING	1	0	0
INJECTION SITE REACTION-LEFT UPPER ARM	1	0	0
INJECTION SITE REACTION-SOME SUBCUTANEOUS NODULARITY	1	0	0
INJECTION SITE REACTION-SUBCUTANEOUS NODULES POSTERIOR ARMS AND UPPER LEGS	1	0	0
MYALGIA	1	0	0
SITE 1 BURNING FEELING	1	0	0
VOMITING	1	0	0
INJECTION SITE REACTION-RAISED ERYTHEMATOUS PATCHES UPPER ARM BILATERALLY AND LEFT THIGH	1**	0	0

* Adverse event was considered possibly related by the investigator, however, neither the safety review team nor the safety monitor of the CRO found relation to the vaccination. **Considered to be “mild adverse event” as non NCI CTCAE classification

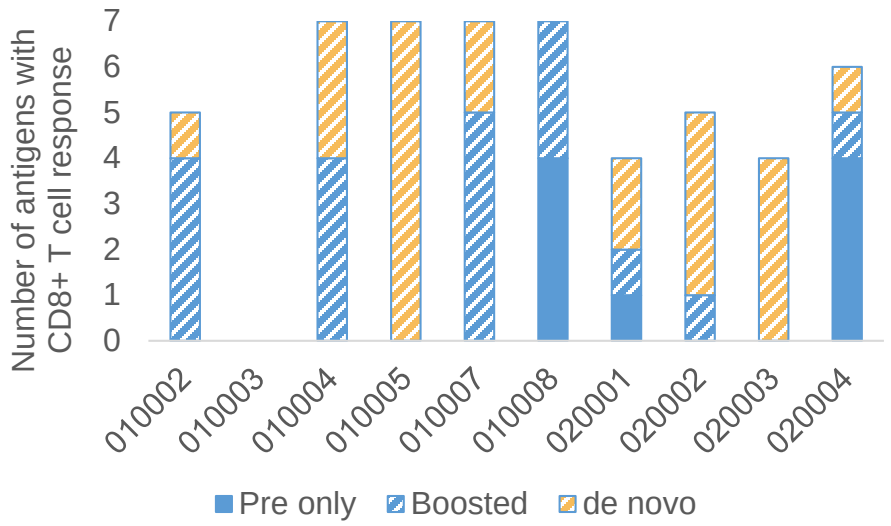
Serious adverse events	Relatedness
Disease progression	Unrelated
Embolism	Unlikely Related
Abdominal pain	Unrelated
Bowel Obstruction	Unrelated
Non-Infectious Acute Encephalitis	Possibly Related

Transient local erythema and edema at the site of injection were observed as expected, as well as a flu-like syndrome with minor fever and fatigue. One SAE “possibly related” to the therapy was recorded. No safety or tolerability issues recorded due to multiple vaccinations.

PolyPEPI-1018 induced significant immune responses against multiple antigens

Peptide treatment elicited CD8⁺ T cell responses against at least 3 CRC-specific antigens in majority of patients

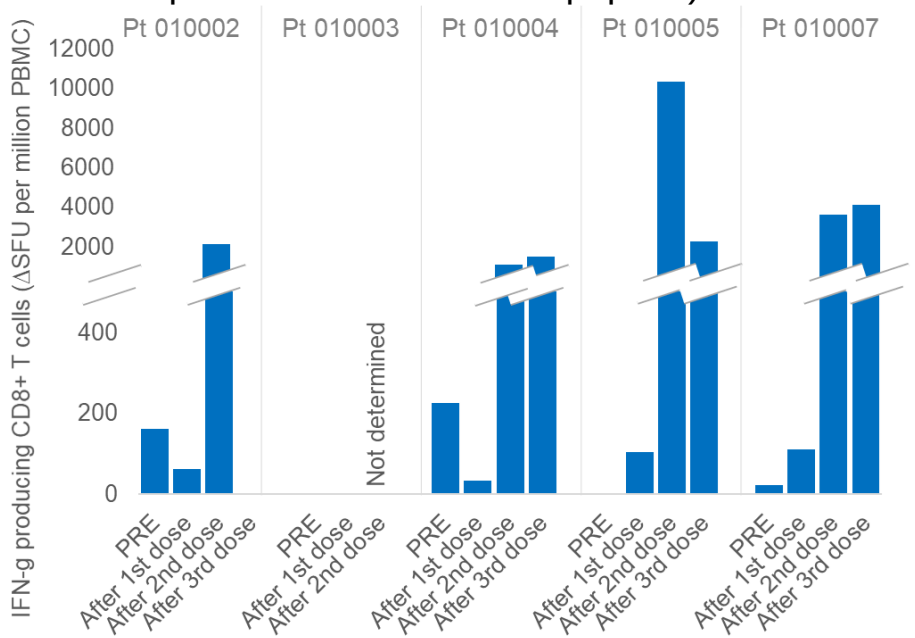
Patients with immunological responses	Percentage (n)
CD4⁺ T cell responses	100% (10/10)
CD8⁺ T cell responses	90% (9/10)
CD8⁺ T cell responses against **≥3 antigens**	80% (8/10)
Both CD8⁺ and CD4⁺ T cell responses	90% (9/10)
Ex vivo detected CD8⁺ T cell responses	66% (6/9)
Ex vivo detected CD4⁺ T cell responses	89% (8/9)



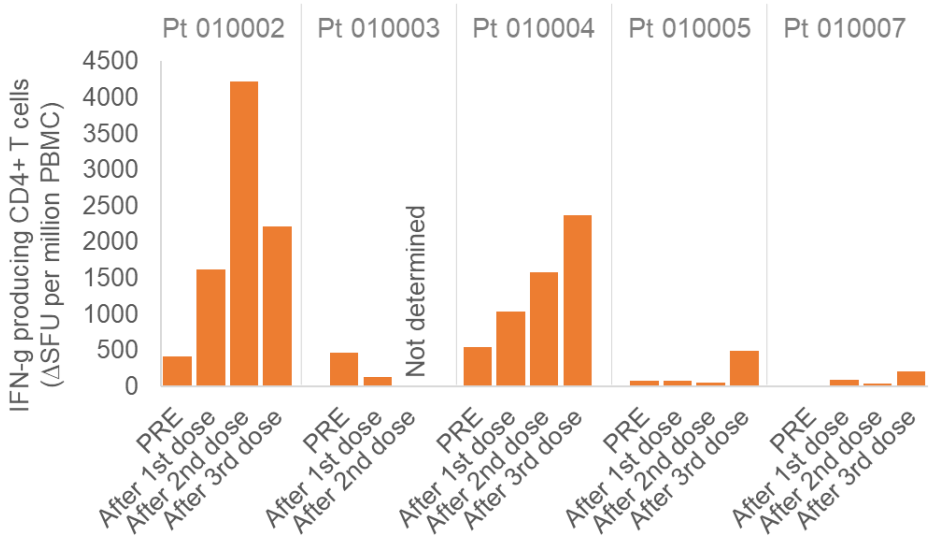
PolyPEPI-1018 treatment restored (boosted) pre-existing immunity as well as induced *de novo* antigen-specific T cell responses against multiple antigens

Multiple doses of PolyPEPI-1018 increased the level of immune responses

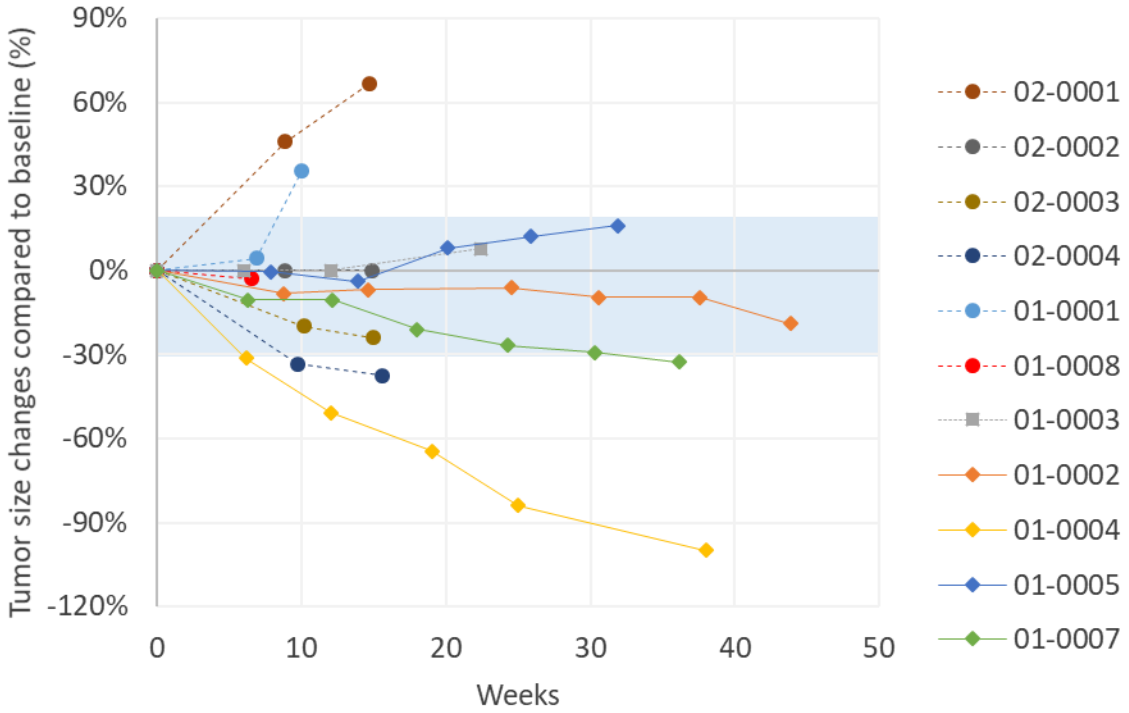
CD8+ T cell responses
(detected with 9mer peptides specific for each vaccine peptide)



CD4+ T cell responses
(detected with the 30mer vaccine peptides)



Maintenance therapy combined with PolyPEPI1018 vaccine led to continuous tumor reduction in mCRC (MSS) patients



Patients with single dose ● 2 doses■ 3 doses◆ .

Both patients with objective response in the multiple dose group qualified for **curative surgery** (Pt 01-0004 and 01-0007)

Tumor responses were assessed every 6 weeks by CT according RECIST 1.1 compared to study baseline: W0

Study	Dose(s)	ORR	DCR
Part A+B (n=11)	≥ 1	27%	72%
Part B (n=6)	≥ 2*	33%	67%

ORR: Objective response rate (RECIST 1.1); DCR: Disease control rate; *except one pt.

Improved PFS in MSS-mCRC with PolyPEPI1018 vaccine as maintenance combination therapy

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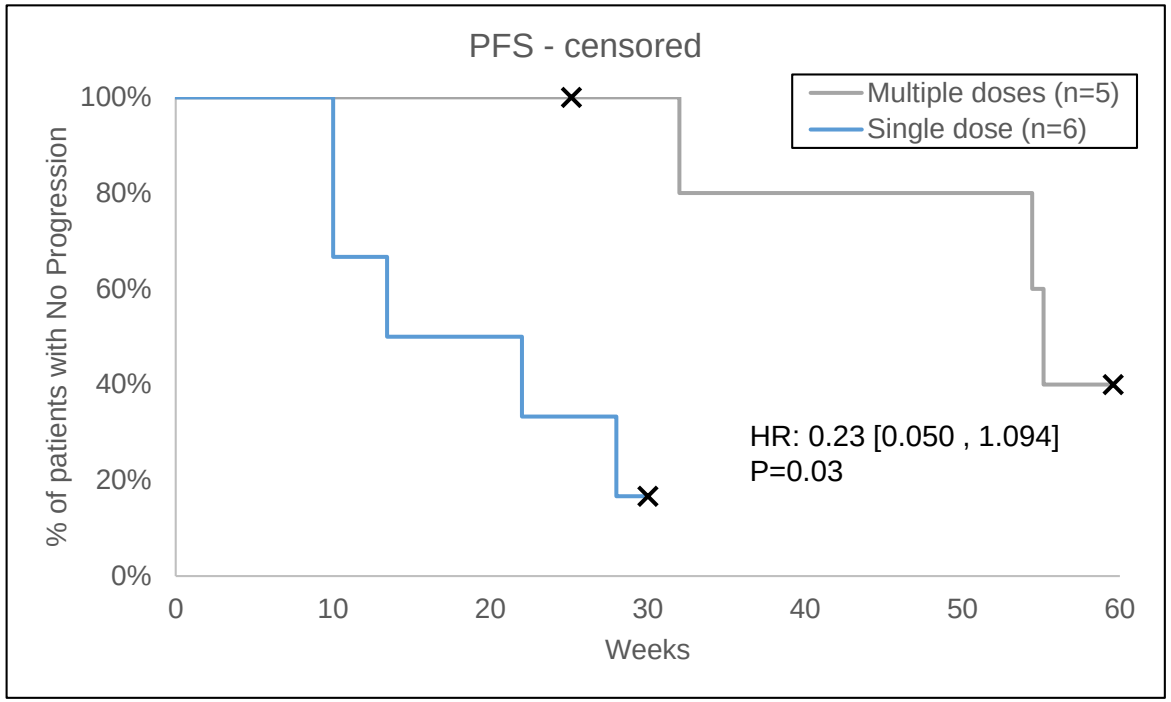
OBERTO-101

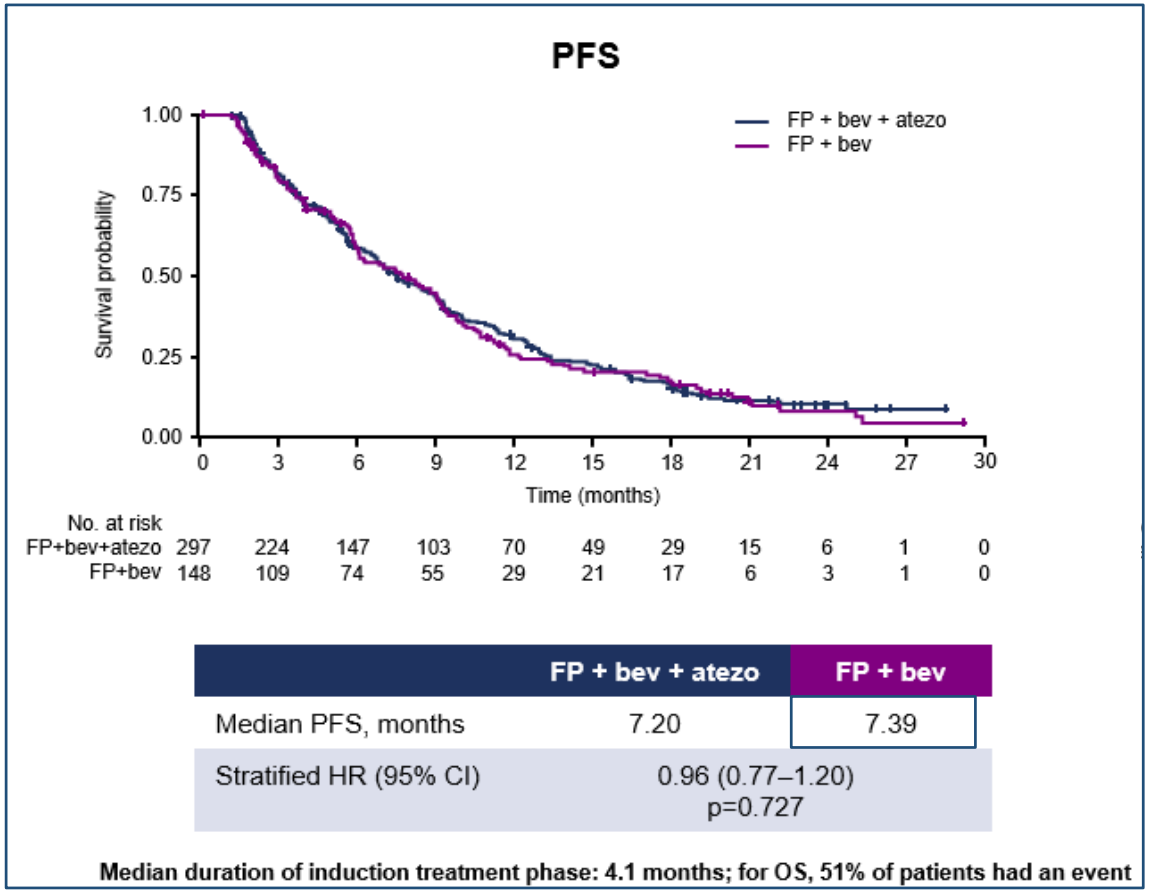


PFS (Progression-free survival) = the time from the date of initiating maintenance therapy to the date of first progression of disease (including post trial data) (RECIST 1.1)

No significant difference in baseline characteristics between single and multiple dose groups

MUNICH 2018 ESMO congress

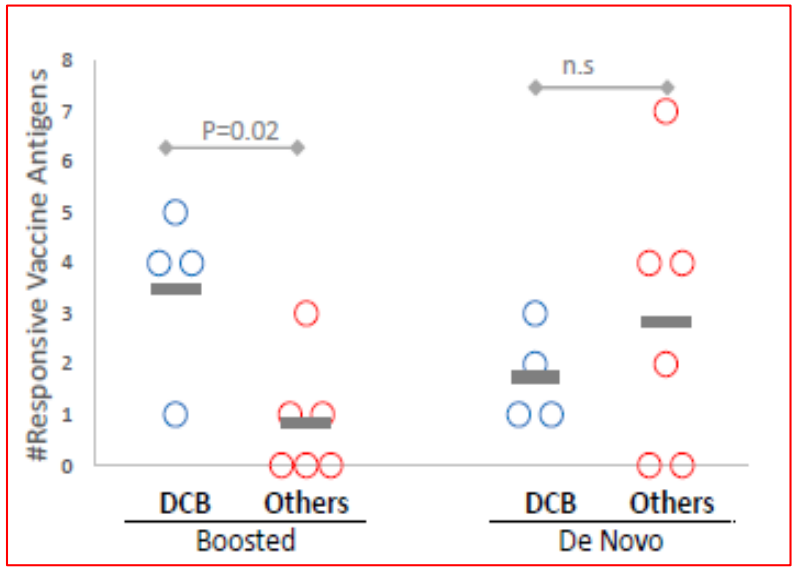
MODUL Cohort 2



	FP + bev + atezo	FP + bev
Median PFS, months	7.20	7.39
Stratified HR (95% CI)	0.96 (0.77–1.20) p=0.727	

Median duration of induction treatment phase: 4.1 months; for OS, 51% of patients had an event

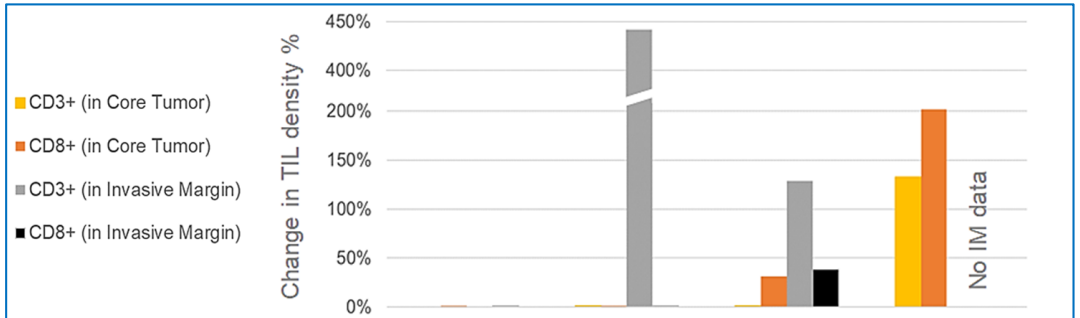
Immune responses induced by PolyPEPI1018 at both peripheral and tumor level indicate clinical benefit*



At peripheral level:

Patients with durable clinical benefit (DCB) had T cell responses boosted against higher number of tumor antigens

Boosted: mean number of spots (ELISpot) after vaccination is at least 2 times higher compared to pre-vaccination, De novo: response is detected only after vaccination



Patient	020002	020004	010002	010007
Number of doses received	1 dose	1 dose	3 doses	3 doses
Best Objective Response	SD	PR	SD	PR
Tumor volume change	+ 3 %	- 38%	-20 %	-33%
Progression (from Week 0)	28 weeks	22 weeks	54 weeks	> 54 weeks

At tumor level:

3/3 Patients with durable clinical benefit (DCB) had increased T cell infiltration (TIL) post treatment

(assessed by HalioDx's proprietary Immunoscore CR TL assay)

Patients with durable clinical benefit (DCB): Patients achieving objective tumor response and/or long-term (>50 weeks) Stable disease

*Hubbard et al ASCO2020

Antigen-specific immune responses are determined by autologous HLA alleles

CD8+ T cell responses are accurately predicted by Personal epitopes (PEPIs) of a subject

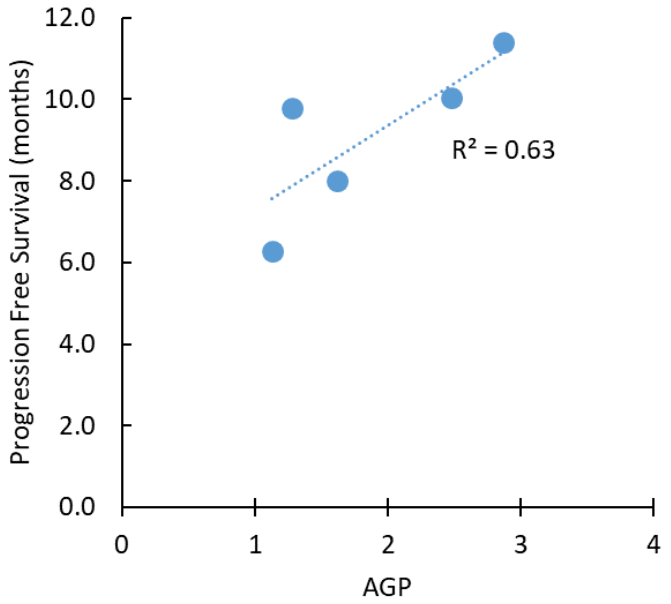
Patient/AG	010002		010003		010004		010005		010007		010008		020001		020002		020003		020004	
	Mea.	Pred	Mea.	Pred	Mea.	Pred	Mea.	Pred	Mea.	Pred	Mea.	Pred	Mea.	Pred	Mea.	Pred	Mea.	Pred	Mea.	Pred
TSP50	-	-	-	-	+	-	-	-	+	+	+	+	+	+	+	-	+	+	+	+
EpCAM	+	+	-	-	+	+	+	+	+	-	+	+	+	+	+	-	+	-	+	+
Survivin	+	+	-	-	+	+	-	-	+	-	+	-	-	-	+	-	+	-	+	-
MAGE-A8	+	-	-	-	-	-	-	-	+	-	+	+	+	-	+	-	-	-	+	+
CAGE1	+	+	-	-	+	+	-	+	+	-	+	+	+	+	-	+	-	-	-	+
SPAG9	-	-	-	+	-	-	-	-	+	-	+	+	-	-	-	+	+	-	+	+
FBXO39	-	+	-	+	-	-	+	-	+	+	+	+	-	-	+	+	+	+	+	+
PPV	**79%**																			
NPV	**51%**																			
OPA	**64% (p=0.01)**																			

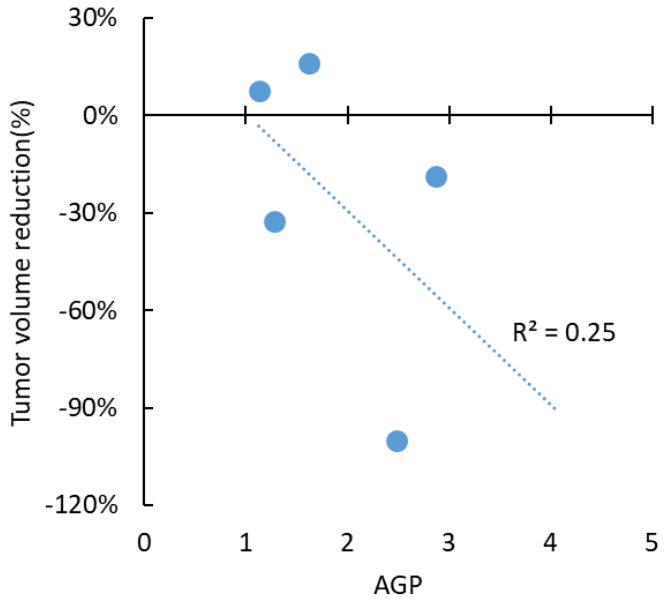
Mea: Measured by ELISpot using 9mer test peptides of the Personal Epitopes (PEPIs);
Pred: PEPIs predicted for the specific vaccine antigen

Predicted tumor-directed immune responses indicate treatment benefit

Both PFS and Tumor Volume Reduction tend to correlate with AGP*

AGP = Predicted multiantigenic immune responses against likely expressed antigens





*AGP: expressed Antigens with PEPIs - number of PEPIs corrected with the probability of expression of the antigens having the PEPIs

AGP may be developed as a biomarker for selection of likely responders
based only on individual HLA obtained from cheek swab

PFS (Progression-free survival)=time from the date of initiating maintenance therapy to the date of first progression of disease (RECIST 1.1)
*for patients receiving multiple doses, n=5

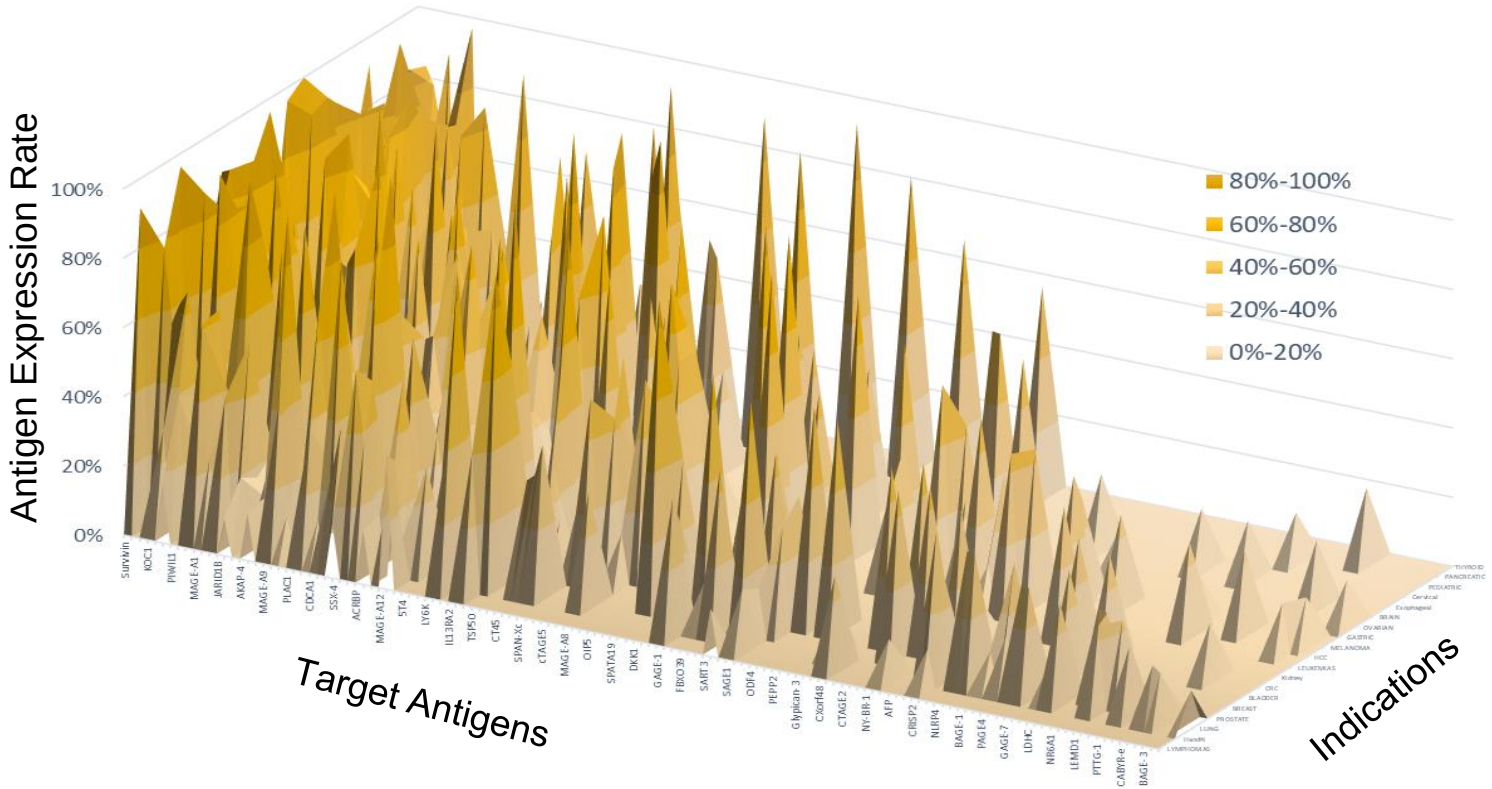
OBERTO Phase I/II Trial Data Validates Treos' Approach for the Prediction of Immune Responses

- Analysis of the complete HLA-set for OBERTO patients demonstrated that the antigen specific immune responses were correctly predicted (PPV = 79%). The first time direct relationship between autologous HLAs and CD8+ T cell responses is demonstrated.
- Multiantigenic CD8+ T cell responses against at least 3 antigens detected for 80% of patients without pre-selection of subjects. Vaccine design using *in silico* Human cohort accurately modelled vaccine clinical immunogenicity (this model is potentially more accurate than preclinical animal models).
- mCRC patients had spontaneous immunity against CTAs targeted by the vaccine – validating our approach of selecting frequently expressed CTAs in a given cancer. In addition, pre-existing immunity is considered a pre-requisite for the efficacy of immunotherapies (including checkpoint inhibitors).
- HalioDx proprietary assay Immunoscore CR TL (CD3/CD8) was performed on the metastatic liver biopsies of four patients and showed that treatment turned Immunologically "cold" tumors into "hot" tumors – demonstrating vaccine induced immune responses at tumor level (efficient targeting by PEPIs)
- Three OBERTO patients controlled their disease for at least 12 months, thereby delaying second-line treatment; mPFS =12.5 months compares favorably to the MODUL2 trial (N=148) with its relevant cohort (mPFS = 7.39 months). Interestingly, in the MODUL population, checkpoint inhibitor plus maintenance therapy did not improve mPFS (N=297). No objective responses (PR or CR) were recorded in that trial.
- Three patients had objective responses (PR) by RECIST v1.1 – unexpected during maintenance treatment
- Two OBERTO patients improved to the point where curative surgery was attempted.
- Patients experiencing tumor shrinkage had both predicted (by the TREOS candidate CDx) and measured responses against higher number of therapeutic antigens and increased densities of TILs.

[1] *Hubbard et al ASCO2020*
[2] *Grothey et al ESMO2018*

PEPI Panel – A Unique Approach For Personalized Cancer Vaccination

3,286 immunogenic 20mer peptides derived from 184 antigens associated with 19 cancer indications - **based on 16,000 subjects' HLA genotype** (both class I&II alleles) were pre-selected into "PEPI Panel" library and are available for personalized treatment from a warehouse.



Pre-manufactured, most prevalent immunogenic peptides

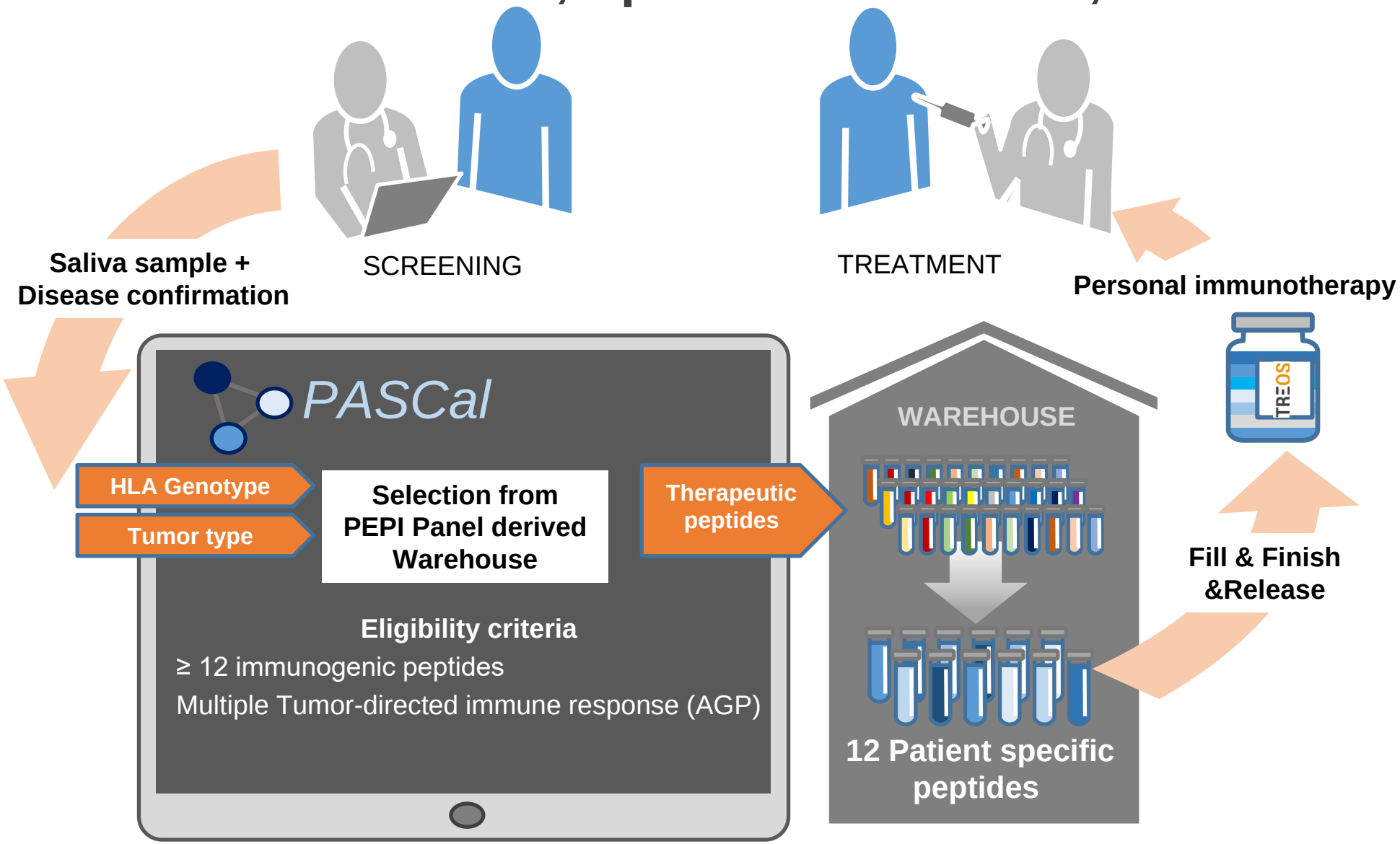
Antigen Expression Knowledgebase and PEPI concept enabled us to select the most important immunogenic peptides associated with and shared between 19 cancer indications and 16,000 subjects.

Available and affordable to virtually all subjects

In silico trial simulations show that we could select 12 peptides for 90-100% of HLA-genotyped subjects depending on indication (100-300 peptide library per indication).

More cost-effective to establish a warehouse than manufacture "on-demand".

TREOS Process for Creating Personalized Peptide Treatments Allows Industrialization, Speed to Treatment, Lower Cost



Personalized vaccines produce promising responses in proof-of-concept studies as an add-on to standard-of-care

Therapy: 12-13 peptides in sterile solutions with *Montanide*
Administration: subcutaneous injection into 2 arms and 2 thighs
Doses received: multiple doses (≥3 doses/patient)
Patients were clinically monitored conform their standard-of-care

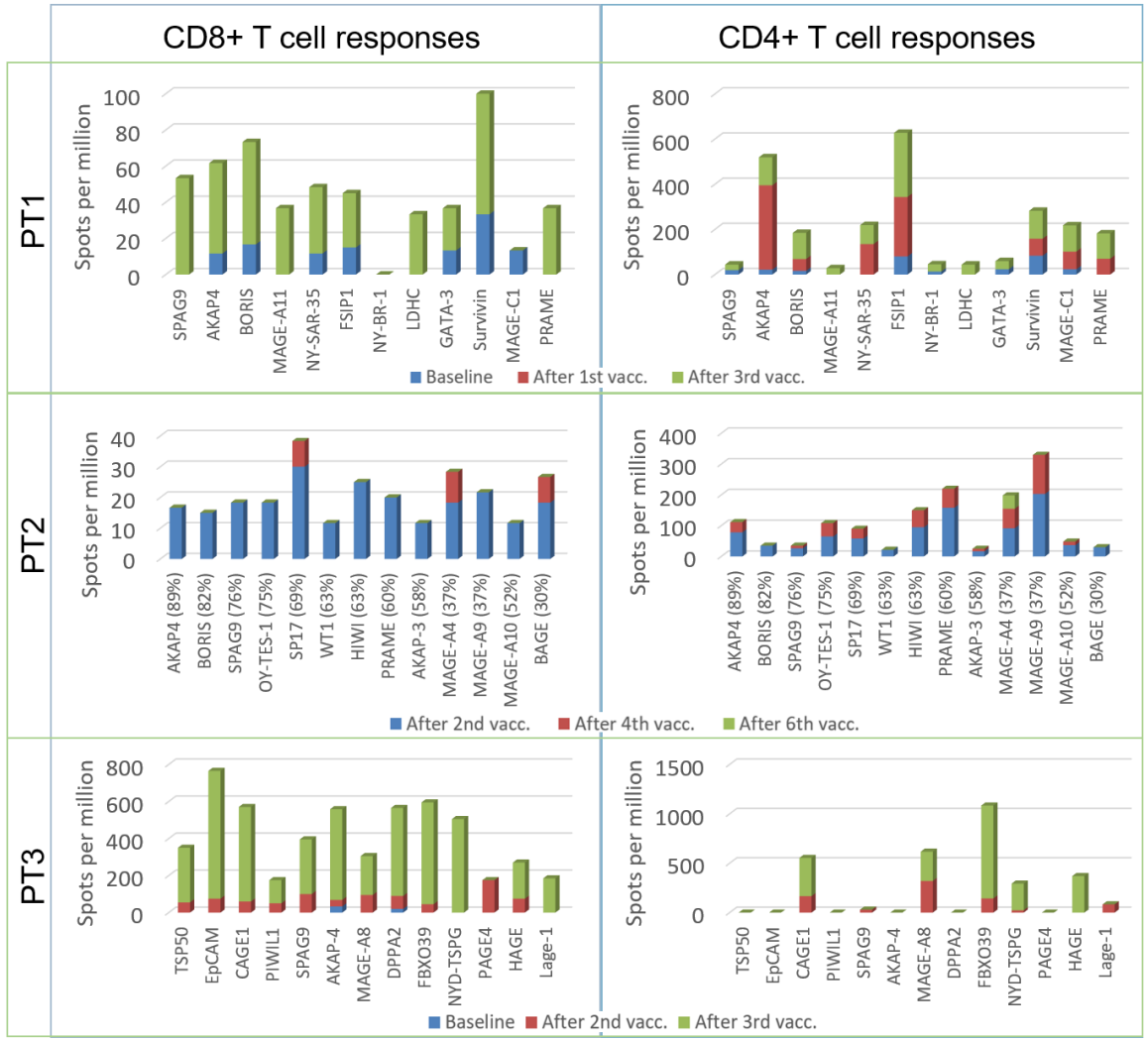
Patient	Pathology	Safety	Tumor specific T cell responses		
			Patient-specific peptides included in the therapeutic (#PEPIs)	BioAssay-Detected $CD8^+$ responses	BioAssay-Detected $CD4^+$ responses
PT1	Metastatic Breast Cancer	Safe and well tolerated*	12	11	12
PT2	Metastatic Ovarian Cancer	Safe and well tolerated*	13	13	13
PT3	Metastatic Colorectal Cancer	Safe and well tolerated*	13	13	7
Average number of peptides creating immunogenic response per patient				12	

*Flu like syndrome, fatigue, palpitations and low fever, redness, itchiness at the site of the injections.

***PASCal*-selected epitopes (PEPIs) produced CD8+ responses with 97% of peptides, compared to reported results from Neon (28%), BioNTech (17%) and Genocea (53%).**

Source: Neon: Ott et al, Nature 2017; BioNTech: Sahin et al, Nature 2017; Genocea: ASCO 2019; Treos: Somogyi et al ESMO 2019; Csiszovszki et al SITC 2019

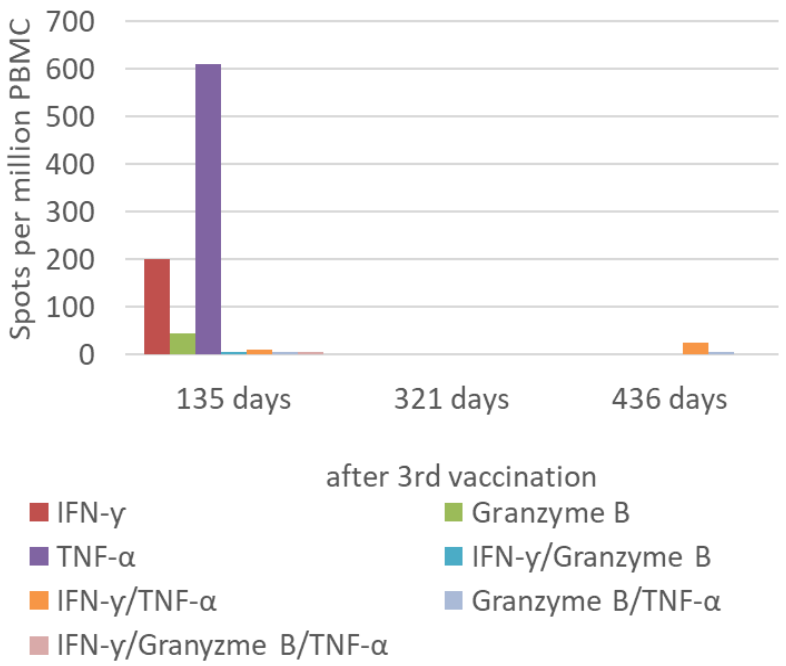
Pre-existing and *de novo* induced immune responses after personalized vaccination against multiple antigens



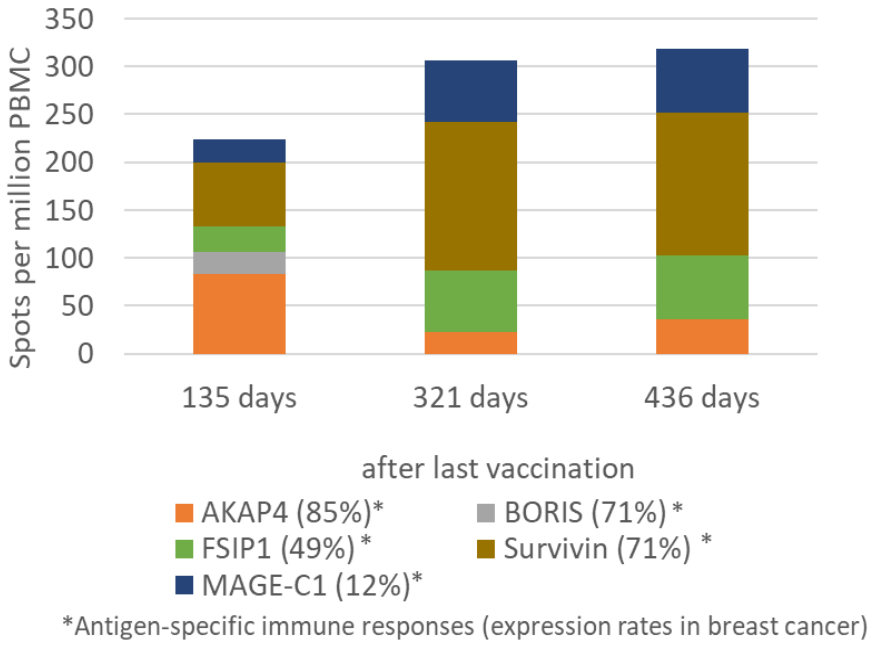
Somogyi et al ESMO 2019; Csiszovszki et al SITC 2019

Personalized vaccination induced long lasting and polyfunctional immune responses

Effector (*Ex vivo*) CD8+ T cell responses were detected 135 days (**4.5 months**) after last vaccination.



Memory CD8+ T cell responses were detected **14 months** (436 days) after last vaccination against 4 tumor antigens.



*Antigen-specific immune responses (expression rates in breast cancer)

Somogyi et al ESMO 2019; Csiszovszki et al SITC 2019

Key takeaways:

Personal Epitope selection strategy provides for safe and effective therapeutic peptides when both tumor and patient heterogeneities are taken into consideration

- Most tumors, especially at the metastatic stage represent a fast evolving group of heterogeneous tumor cells
- Tumors differ in antigen expression profile (eg increased CTA expression frequency) but many antigens are also shared among and between tumors
- Antigen expression knowledgebase based on large number of tumor specimens could efficiently address tumor heterogeneity by location and by time
- Each tumor requires a combination of personal epitopes to activate the immune system to increase the probability of tumor cell recognition and tumor killing
- PASCal identifies not only the most optimal antigens, but also the epitopes to which a patient's immune system will respond
- Vaccine design based on frequent personal epitopes for a heterogeneous model population provides broad HLA genotype coverage ensuring large proportion of patients potentially eligible for vaccine treatment – when selected with CDx based on patients' HLA genotype (both off-the-shelf and personalized vaccines)
- Personal epitopes for shared tumor antigens significantly outperform all reported immunogenicity results of mutated neoantigens in terms of the number of peptides that activate the immune system*
- Efficacy data demonstrates ability to turn 'cold tumors' into 'hot tumors' for the first time for peptide immunotherapies** potentially opening the door to making currently ineffective treatments into effective treatments

*Somogyi et al. ESMO 2019 & Csiszovszki et al. SITC 2019 ** Hubbard et al. ASCO 2020

Thank you for your attention!

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