The PRAME Opportunity – High Peptide Copy Numbers, Homogenous Expression and High Prevalence to Address a Broad Patient Population across Different Solid Cancers with TCR-based Therapeutics

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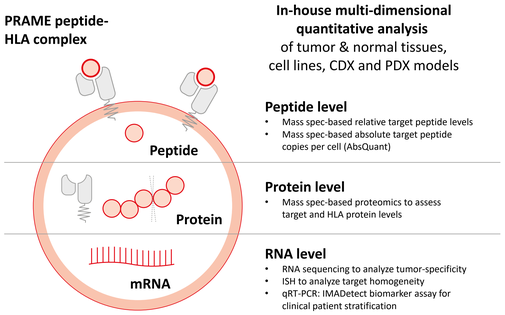
PRAME – Promising Opportunity for TCR-based Therapies

Several peptide-HLA targets for T cell receptor (TCR)-based immunotherapies are currently being evaluated in the field, however, many are limited by their overall low prevalence, low copy numbers or relevant expression in healthy tissues. A T cell target with nearly ideal properties has high, homogenous and prevalent expression across multiple cancers in the absence of significant safety/toxicity liabilities. Here, we describe the in-depth characterization of an HLA-A*02:01-presented peptide derived from the cancer germline antigen preferentially expressed antigen in melanoma (PRAME) that opens an avenue of new opportunities for patients with solid cancers which we aim to leverage by two distinct TCR-based therapeutic modalities, TCR-engineered T cells (ACTengine IMA203) and TCR Bispecifics (TCER IMA402).

Proprietary Technologies to Analyze PRAME on Every Cellular Level



In-house multi-dimensional quantitative analysis of tumor & normal tissues, cell lines, CDX and PDX models

Peptide level
- Mass spec-based relative target peptide levels
- Mass spec-based absolute target peptide copies per cell (AbsQuant)

Protein level
- Mass spec-based proteomics to assess target and HLA protein levels

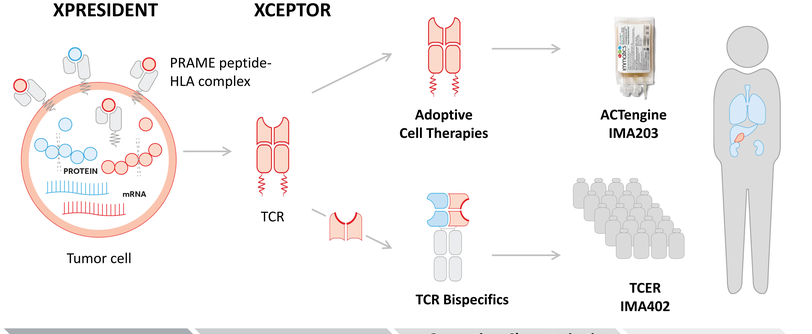
RNA level
- RNA sequencing to analyze tumor-specificity
- ISH to analyze target homogeneity
- qRT-PCR: IMADetect biomarker assay for clinical patient stratification

- HLA-A*02:01-presented PRAME peptide for development of TCR-based therapies selected among >30 possible PRAME-derived HLA-A*02:01 peptides
- Mass spectrometry (MS) and matched RNAseq data from healthy normal and tumor samples were processed and organized into a large quantitative immuno-peptidomics database using proprietary immunoinformatics platform XCUBE
- Based on matched RNAseq and MS data, we defined an RNA threshold which corresponds to actual peptide presentation (Fritsche *et al.*, 2018). This MS-guided RNA threshold is used for
  - clinical patient stratification
  - prevalence estimation

Figure 1. Immatics' XPRESIDENT-based multi-dimensional analysis of PRAME.

Bringing Two Distinct TCR-based Modalities to Cancer Patients by Targeting PRAME

Technology Platforms – Foundation of Deep Know-how | **Two Distinct Modalities** – Targeting PRAME | **Delivering the Power of T cells to Cancer Patients**



Discovery & Validation of Targets → **Identification & Engineering of TCRs** → **Generation, Characterization & Validation of Product Candidates** → **Clinical Trials**

Figure 2. Immatics' approach to develop TCR-based product candidates for cancer patients.

PRAME Expression is Highly Cancer-Associated

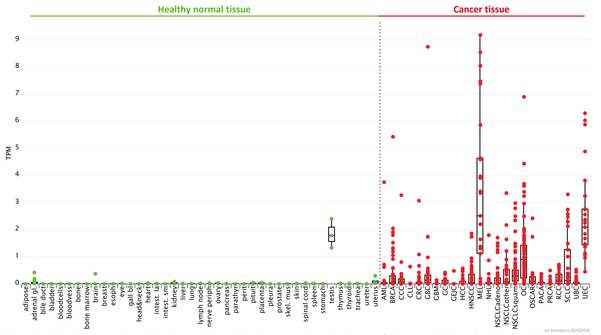


Figure 3. PRAME exon expression based on in-house RNA sequencing data. Expression of all exons encoding the PRAME target peptide in normal tissues from various organs and in different hematologic and solid cancer types. Each dot represents the maximum TPM value across all peptide-encoding exons in one sample. Box-and-whisker plots represent TPM values of multiple samples per organ or tumor entity. TPM: transcripts per million.

- PRAME RNA expression is elevated across multiple different solid tumor types
- Stable PRAME RNA expression across early and late tumor stages and tumor subtypes
- Minimal expression in some normal tissues except testis, not translating into relevant peptide presentation (see Figure 4)

PRAME Peptide Is Presented across Multiple Tumors

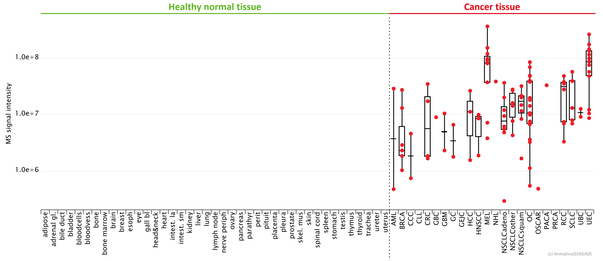


Figure 4. HLA*02:01-presented PRAME relative presentation levels on HLA-A*02 positive normal and tumor tissues quantified via MS. Each dot represents the median PRAME pHLA-derived MS intensity as an indicator for target abundance in one sample. Box-and-whisker plots represent signal intensities of multiple samples per organ or tumor entity.

- HLA-A*02:01-presented PRAME peptide can be measured directly via mass spectrometry in over 20 solid and liquid tumor entities
- PRAME RNA expression does not translate into relevant presentation on healthy normal tissues
- Quantification using Immatics' highly sensitive AbsQuant technology reveals PRAME target density of 100-1,000 copies per cell in tumor tissues

PRAME Is Homogenously Expressed across Different Solid Tumors

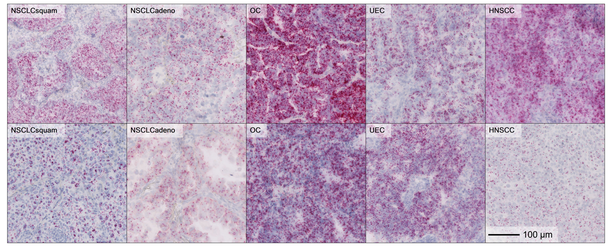
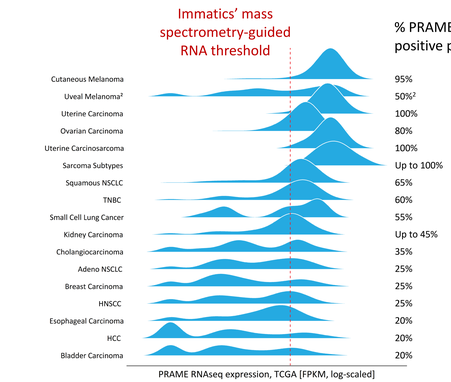


Figure 5. Spatial expression of PRAME analyzed by in situ hybridization (ISH) in various tumor types (NSCLCsquam, NSCLCadeno, OC, UEC, HNSCC). Representative images from two patients per tumor type. Positive signal intensity is visualized as red dots or clusters of red dots using Fast Red. Nuclei are stained with haematoxylin. Scale bar 100 µm.

- *In situ* hybridization was used to analyze PRAME expression homogeneity in several solid tumor samples
- Histologic analysis of PRAME RNA in different solid tumors demonstrates homogenous expression of PRAME with a high frequency of positive tumor cells

Clinical Validation of PRAME as Multi-Tumor Target for TCR-based Therapies



Cutaneous Melanoma 95%
Uveal Melanoma[2] 90%
Uterine Carcinoma 90%
Ovarian Carcinoma 70%

Patient screening data obtained via IMADetect biomarker assay in Immatics' clinical trials support high prevalence of PRAME

Clinical validation of Immatics' mass spectrometry-guided RNA threshold for PRAME: Confirmed responses were observed at high and low PRAME-expression levels above the threshold

Figure 6. PRAME target expression and prevalences in selected solid cancer types based on in-house and TCGA data (https://www.cancer.gov/tcga). [1] PRAME target expression and prevalence based on TCGA (for SCLC: in-house) RNAseq data combined with a proprietary MS-guided RNA expression threshold; [2] TCGA: early & late-stage primary tumor samples, Immatics clinical trials: late-stage/metastatic tumor samples; Role of PRAME in metastasis of uveal melanoma: Field *et al.* 2016 Clinical Cancer Research

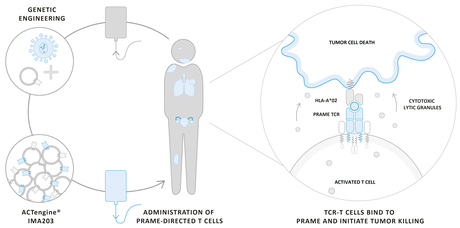


Figure 7. ACTengine IMA203 TCR-T targeting PRAME. For application as TCR-engineered T cell therapy (TCR-T) approach, the IMA203 PRAME TCR is engineered via lentiviral transduction into a patient´s own T cells whose tumor has been tested positive for PRAME. The TCR-T cells are designed to bind to the PRAME pHLA target to induce a robust and specific anti-tumor response to fight the cancer.

- High clinical activity of IMA203 TCR-T: 50% (6/12) confirmed objective response rate (cORR) in patients with at least 1 billion infused TCR-T cells across Phase 1a and 1b; thereof 80% cORR (4/5) in Phase 1b patients alone with all responses ongoing at data cut-off*
- Most frequent treatment-emergent adverse events (TEAEs) were cytopenia, cytokine release syndrome, and grade 1 and 2 immune effector cell associated neurotoxicity syndrome. The TEAE profile is acceptable and adverse events were manageable
- Confirmed responses across different solid tumor types: cutaneous melanoma, ovarian cancer, head and neck cancer, uveal melanoma, and synovial sarcoma

* Immatics ACTengine® IMA203 TCR-T Targeting PRAME Monotherapy Interim clinical Data Update on Oct 10, 2022 (data cut-off Sep 6th, 2022)

Conclusions

Here, we demonstrate comprehensive target characterization and validation data supporting the favorable target properties of PRAME that can be exploited for the benefit of patients. Preclinical data of PRAME show that the target is
- highly cancer-associated,
- presented at high target density,
- homogenously expressed and
- highly prevalent across many solid cancers

underlining its potential to reach a large cancer patient population.

The data obtained during the ongoing Phase 1 trial provide clinical validation of PRAME as a highly promising T cell target for solid cancers. Confirmed clinical responses were observed at all PRAME-expression levels above threshold, indicating IMA203's potential to provide clinical benefit for all PRAME biomarker-positive cancer patients with tolerable adverse events. The predicted high PRAME prevalence across key indications has so far been supported by prevalence rates obtained during the clinical screening of patients.

Acknowledgements: We are immensely grateful to the patients and their families.

Abbreviations: adipose: adipose tissue; adrenal gl: adrenal gland; bloodvess: bloodvessel; esoph: esophagus; gall bl: gallbladder; intest. la: large intestine; intest. sm: small intestine; nerve periph: peripheral nerve; parathyr: parathyroid gland; perit: peritoneum; pituit: pituitary; skel. mus: skeletal muscle; thyroid: thyroid gland; AML: acute myeloid leukemia; BRCA: breast cancer; CCC: cholangiocellular carcinoma; CLL: chronic lymphocytic leukemia; CRC: colorectal cancer; GBC: gallbladder cancer; GBM: glioblastoma; GC: gastric cancer; GEJC: Gastro-esophageal junction cancer; HCC: hepatocellular carcinoma; HNSCC: head and neck squamous cell carcinoma; MEL: melanoma; MPNST: malignant peripheral neve sheath tumor; NHL: Non-Hodgkin lymphoma; NSCLCadeno: non-small cell lung cancer adenocarcinoma; NSCLCother: NSCLC samples that could not unambiguously be assigned to NSCLCadeno or NSCLCsquam; NSCLCsquam: squamous cell non-small cell lung cancer; ORR: objective response rate; OC: ovarian cancer; OSCAR: esophageal cancer; PACA: pancreatic cancer; PRCA: prostate cancer; RCC: renal cell carcinoma; TNBC: triple-negative breast cancer; SCLC: small cell lung cancer; UBC: urinary bladder carcinoma; UEC: uterine and endometrial cancer.

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