A photograph of a laboratory setting with a woman in a white lab coat working at a workstation. In the foreground, there are several bottles and a large glass flask. A blue circular overlay is positioned on the right side of the image, containing white text.

DELIVERING THE POWER  
OF **T CELLS** TO  
CANCER PATIENTS

## Targeting of Tumor-specific HLA Ligands with Bispecific T cell Engaging Receptor (TCER™) Molecules

European Antibody Congress, Nov 2<sup>nd</sup>, 2020

Sebastian Bunk, Senior Director Immatics



## Agenda

**TCER™ – Immatics' TCR Bispecifics**

**IMA401 TCER™ targeting MAGEA4/8**

**Summary**

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## Agenda

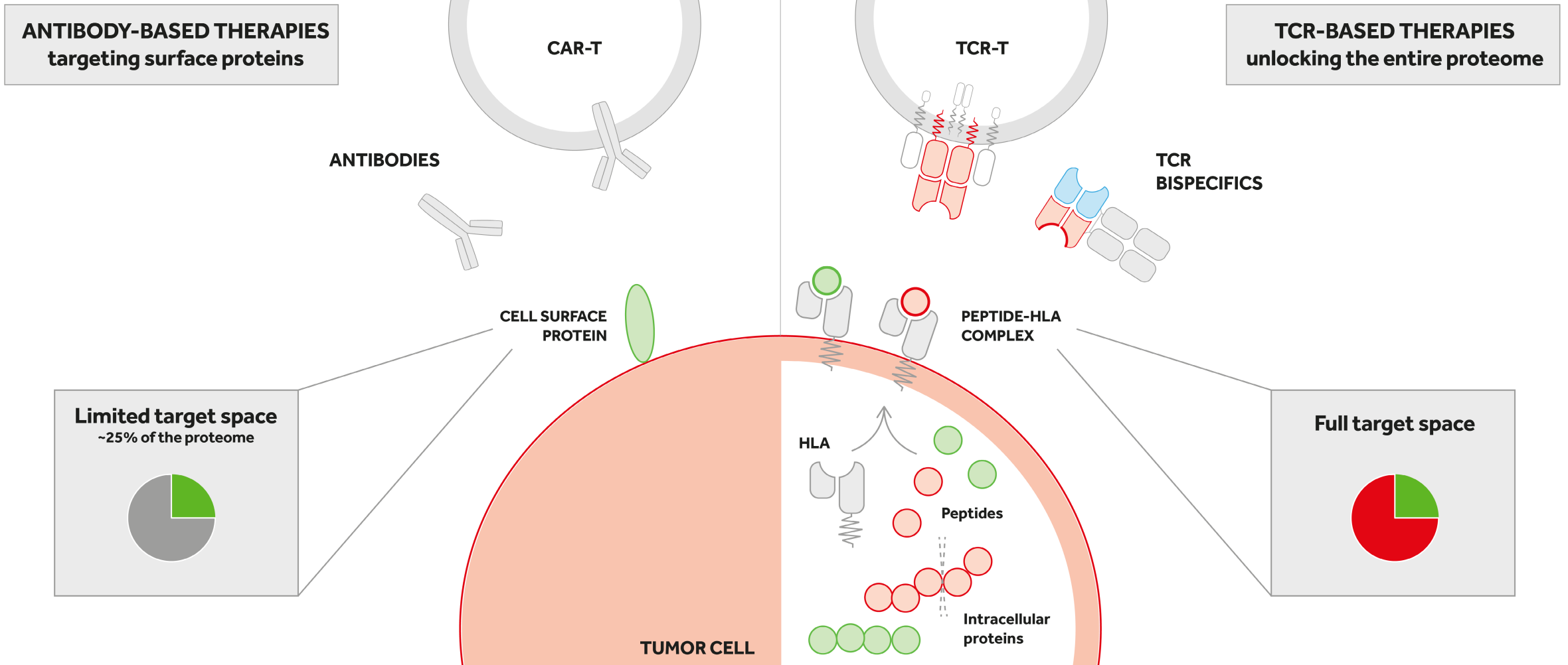
**TCER™ – Immatics' TCR Bispecifics**

IMA401 TCER™ targeting MAGEA4/8

Summary

# Making a Difference – Delivering the Power of T cells to Cancer Patients

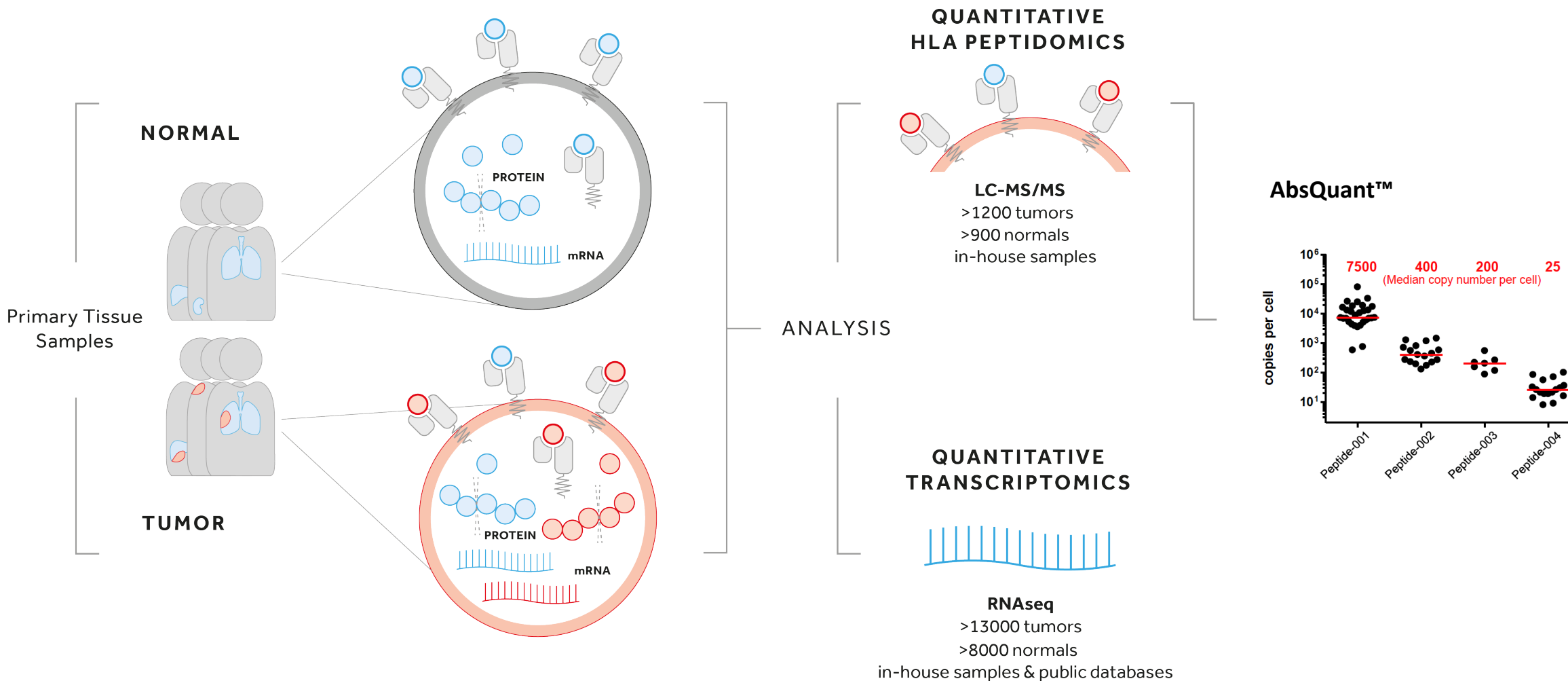
## Discovering Targets beyond the Cancer Cell Surface to Unlock Immunotherapies for Solid Cancers





# XPRESIDENT® – Discovery of True Cancer Targets

## Target Discovery and Validation Platform

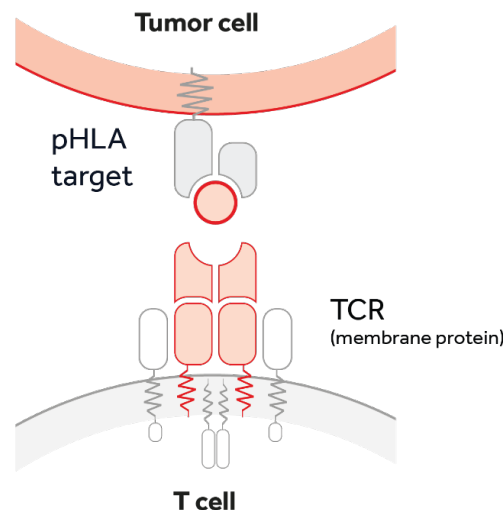


# XCEPTOR™ – Development of the Right TCR

## Pioneering Novel Therapeutic Modalities: T cell Receptors (TCRs) for ACT and Bispecifics

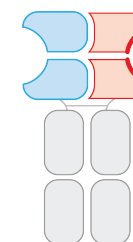
### Adoptive Cell Therapy

ACTengine®  
ACTallo®



### TCR Bispecifics

T cell engaging  
receptor (TCER™)



**Natural or optimized** natural TCR  
with **micromolar affinity** and  
favorable **specificity** profile

for genetic engineering of  
autologous and allogeneic T cells  
and direct clinical application

Proprietary **XCEPTOR™** Platform  
TCR Discovery,  
Engineering and Validation

Fast and efficient discovery of  
**multiple TCRs per target**

Unique XPRESIDENT®-guided **on-  
and off-target toxicity screening**  
to deselect cross-reactive TCRs

**Affinity-matured** natural  
TCR variable domains with **nanomolar  
affinity** and favorable **specificity** profile

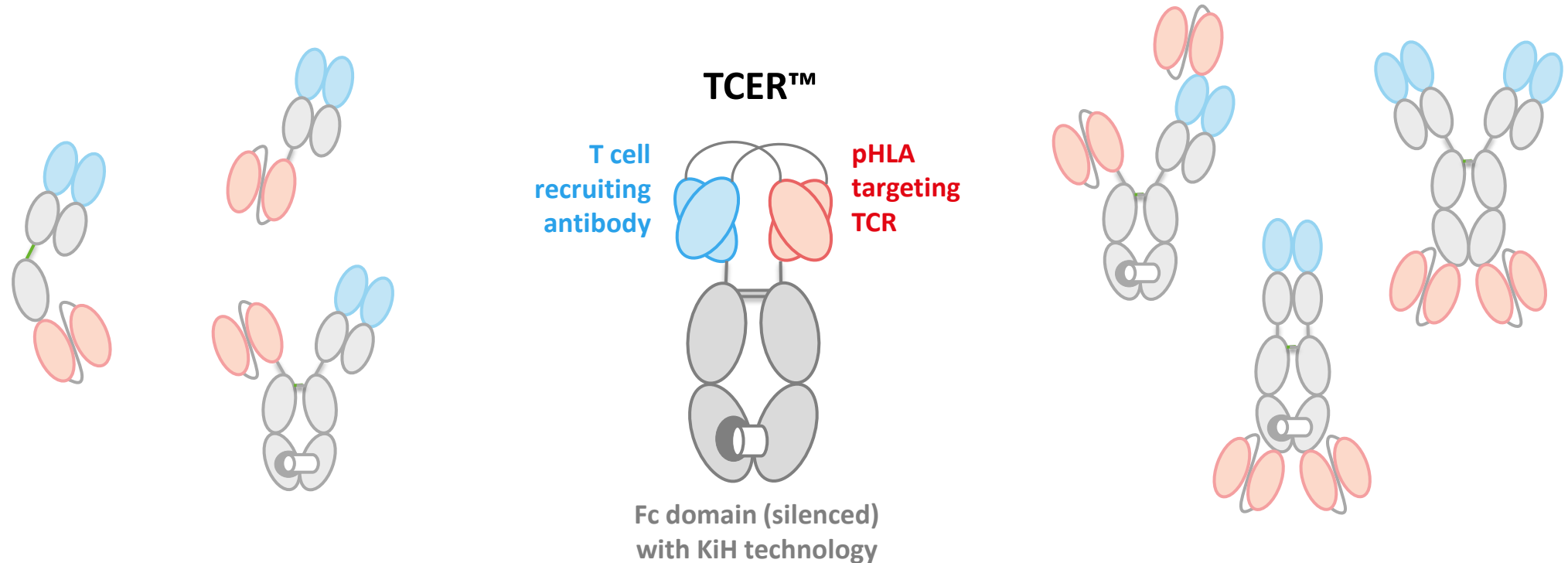
XPRESIDENT®-guided  
**similar peptide counterselection**  
during maturation

Highly potent TCR Bispecifics format with  
**extended half-life** and **antibody-like  
stability** and manufacturability



# Development of Immatics' T cell Engaging Receptor (TCER™) Molecules

## Superiority of TCER™ Format Over Six Alternative TCR Bispecific Formats



- Immatics developed the proprietary TCR Bispecific format **TCER™** for targeting of tumor-specific pHLA even at low copy numbers
  - Potency and stability of TCER™ format was superior over six alternative TCR Bispecific formats
  - TCER™ format successfully validated for different TCRs and different T cell recruiting antibodies



## Agenda

TCER™ – Immatics' TCR Bispecifics

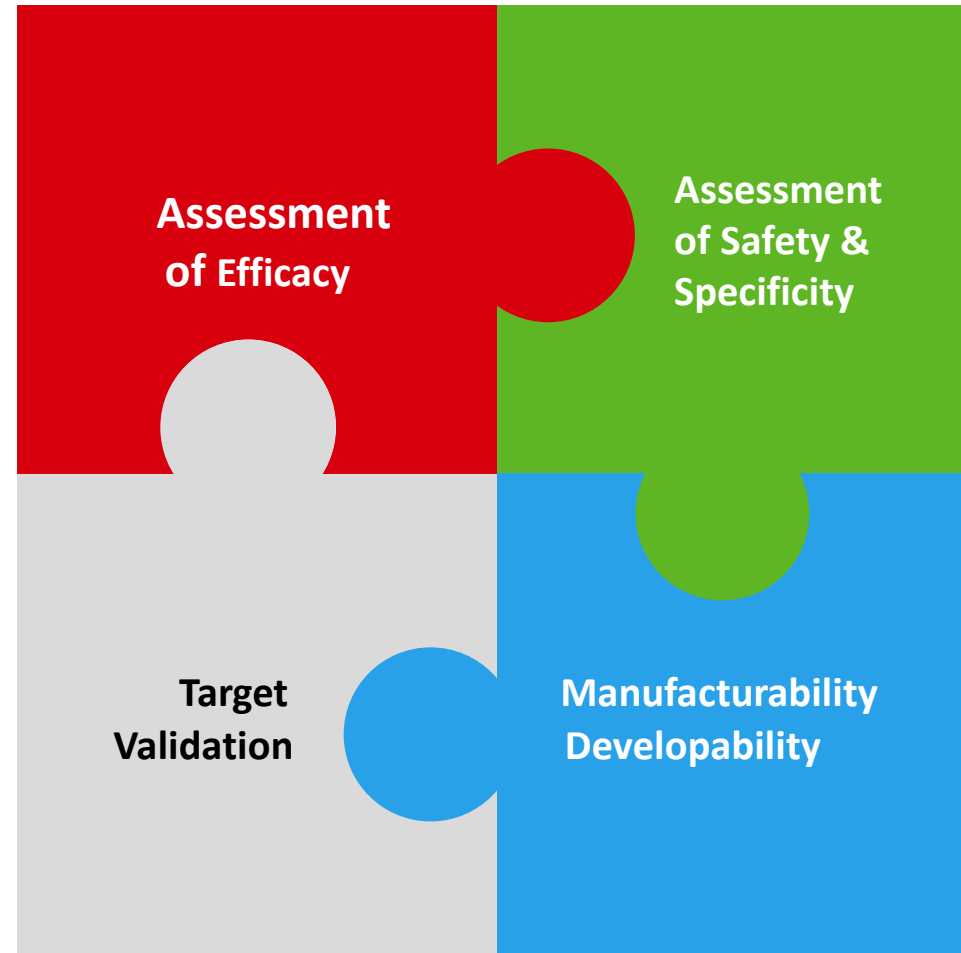
**IMA401 TCER™ targeting MAGEA4/8**

Summary

# IMA401 TCER™ Program

## Summary of Preclinical Data Package for TCER™ Characterization

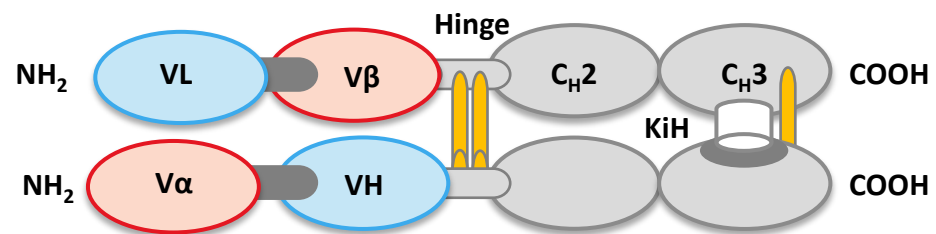
- Tumor cell lines presenting target pHLA at endogenous levels
  - Tumor cell-mediated cytokine release and proliferation of T cells
  - Tumor xenografts in mice
  - Pharmacokinetic and -dynamic
- 
- XPRESIDENT® data package
  - Absolute quantification of target pHLA copies (AbsQuant™)
  - Homogeneity of target pHLA presentation within tumors



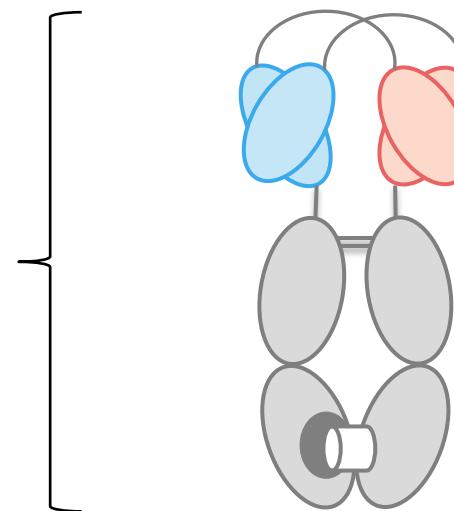
- Normal tissue cell types and iPSC-derived normal cells (n≥25)
  - Target-negative tumor cell lines
  - Alloreactivity screening
  - Cytokine release from whole blood
  - XPRESIDENT®-guided off-target screening based on similarity to target peptide sequence and TCR binding motif
- 
- Yield and purity from CHO cells
  - Melting temperature
  - Freeze-thaw and storage stress stability
  - Sequence liabilities
  - N-glycan profiling of TCR domains

# IMA401 TCER™ Targeting MAGEA4/8

## Design and Characteristics



T cell-recruiting Ab      anti-MAGEA4/8 TCR  
 low affinity              high affinity:  $K_D \sim 2$  nM



# IMA401 TCER™ – MAGEA4/8 Target Peptide on HLA-A\*02

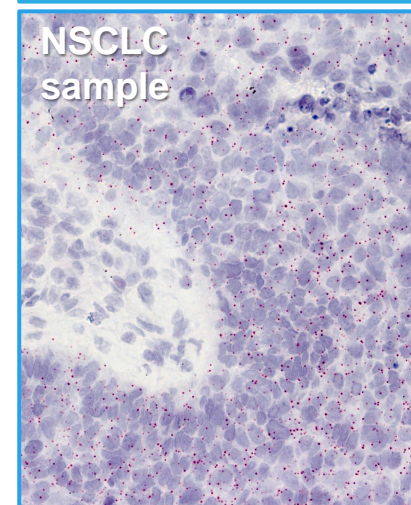
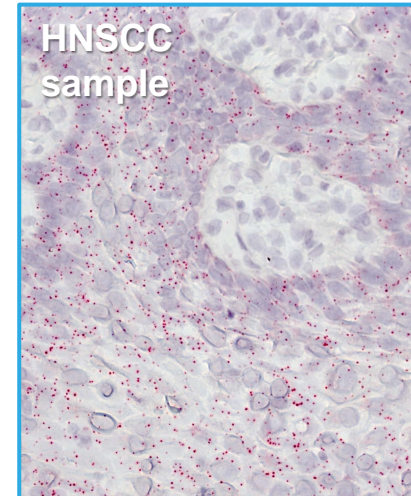
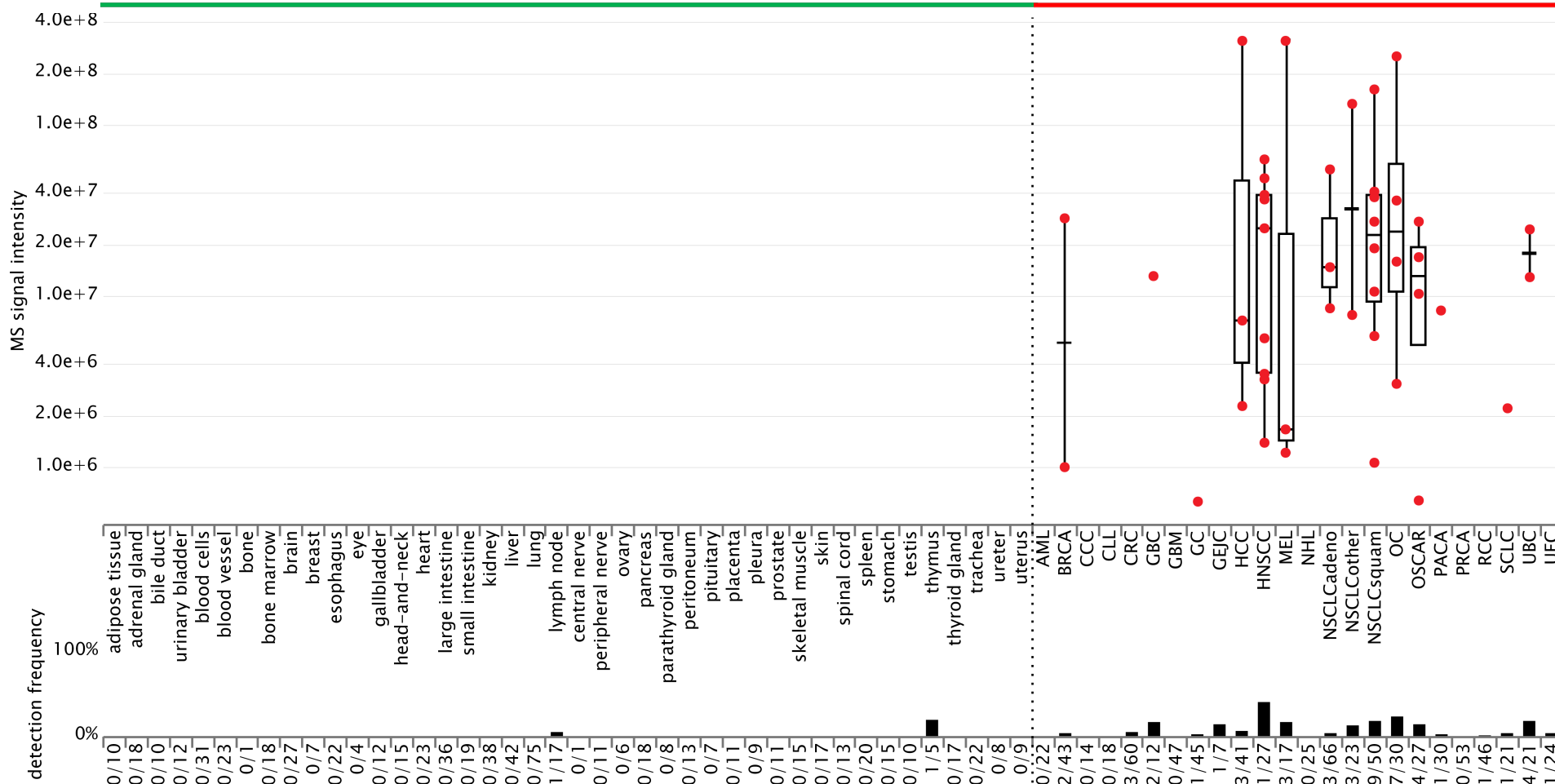
## Mass Spectrometry and ISH Analysis

Normal tissue

MAGEA4/8 Peptide  
(MS Detection)

Cancer tissue

MAGEA4 RNA  
(ISH)



Status as of Oct 2020

(c) Immatics(00DD24)

# IMA401 TCER™ – MAGEA4/8 RNAseq Profile and Prevalence

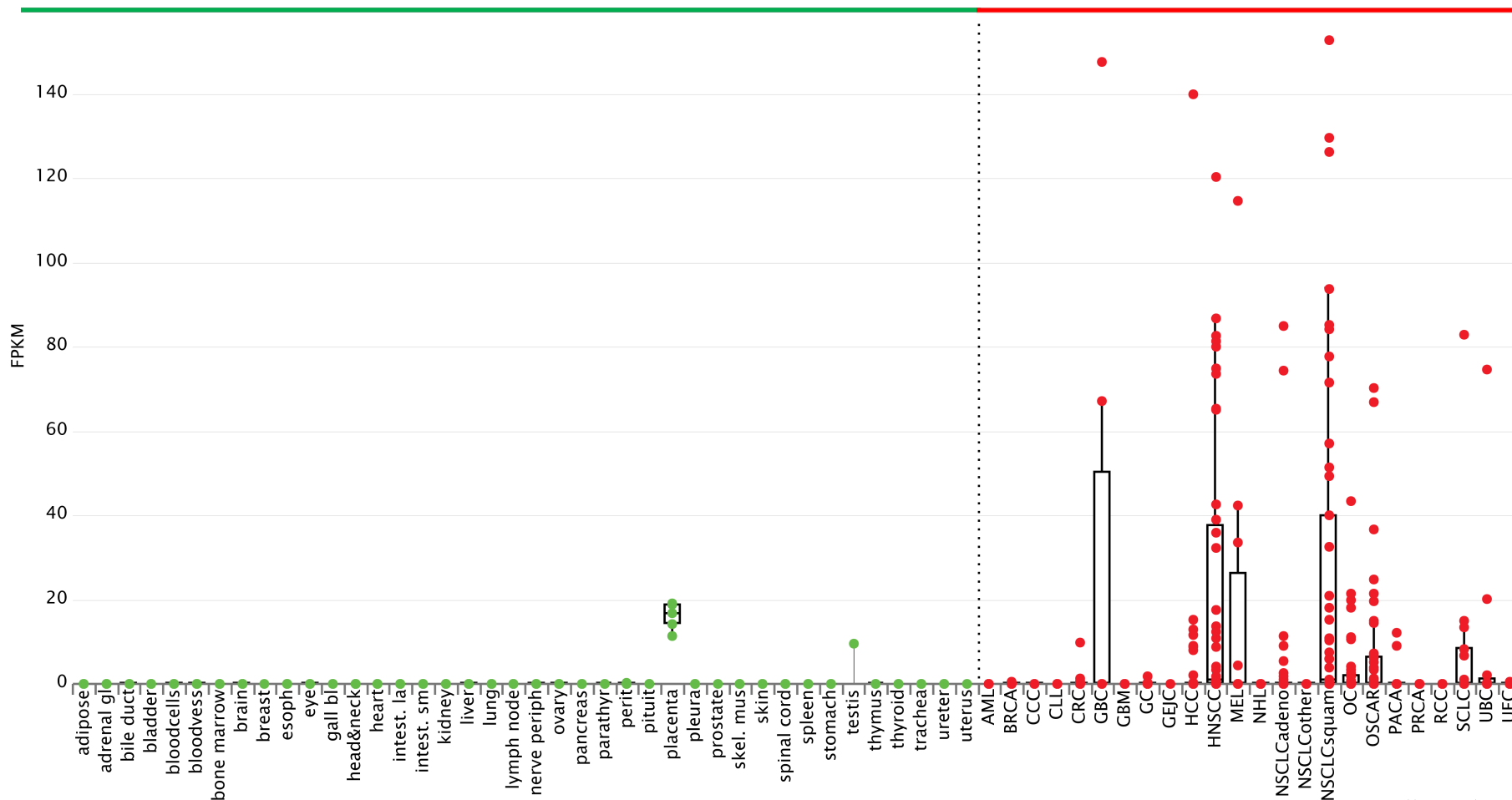
## Relative mRNA Levels in Tumors and Normal Tissues

Normal tissue

MAGEA4/8 exon expression (RNAseq)

Cancer tissue

Target prevalence in selected cancer indications



(c) Immatics (00D558)

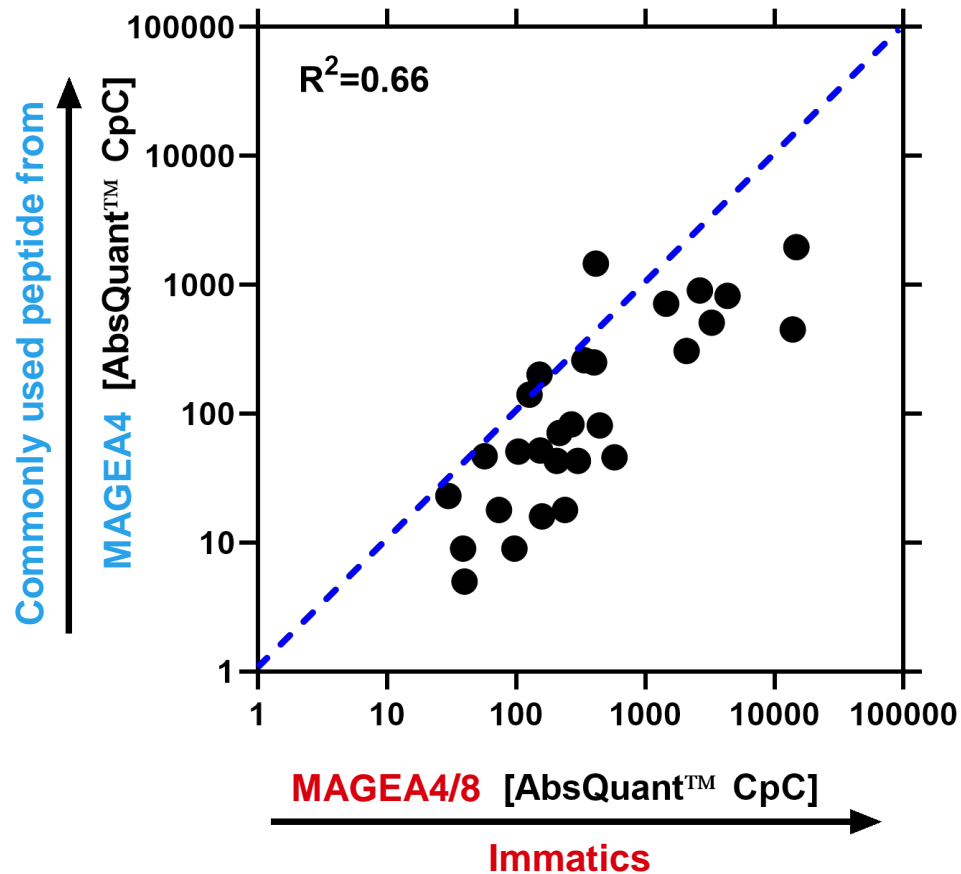
Indications	Target prevalence
Squamous non-small cell lung carcinoma	50%
Head and neck squamous cell carcinoma	35%
Bladder carcinoma	30%
Uterine carcinosarcoma	25%
Esophageal carcinoma	25%
Ovarian carcinoma	20%
Melanoma	20%
<i>plus several further indications</i>	

Target prevalences are based on TCGA data combined with a XPRESIDENT®-determined target individual MS-based mRNA expression threshold

Status as of Sep 2020

# IMA401 TCER™ – MAGEA4/8 Target Peptide on HLA-A\*02

Targeting the Most Relevant Peptide from MAGEA4 with up to 10,000 Copy Numbers per Tumor Cell



## Objective

- Comparison of copy numbers of Immatics MAGEA4/8 target (IMA401 TCER™ & IMA201 ACTengine®) and a commonly used MAGEA4 target on the very same tumor tissues by using AbsQuant™

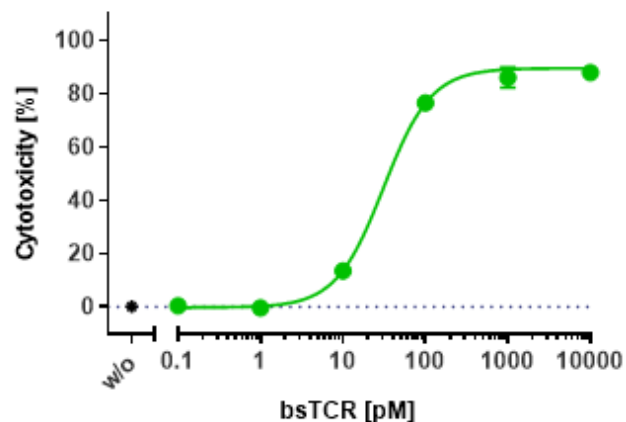
## Conclusions

- **Up to 10,000 MAGEA4/8 target copies** per tumor cell detected in tumor samples
- Immatics' MAGEA4/8 target is presented with **>5-fold higher copy numbers** per tumor cell compared to a commonly used MAGEA4 target peptide in other ongoing clinical trials

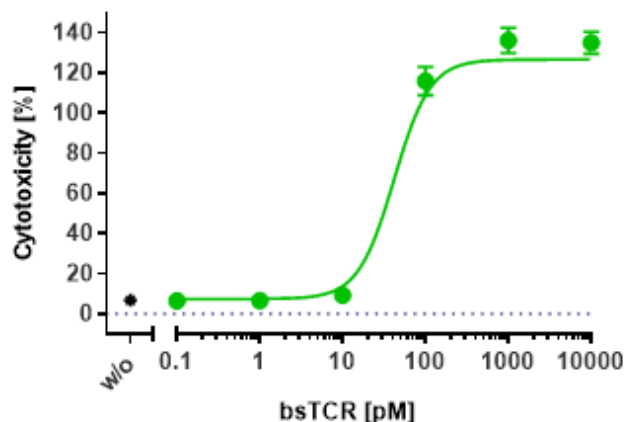
# IMA401 TCER™ – *In Vitro* Efficacy Assessment

## PBMC-mediated Cytotoxicity of TCER™ Against Tumor Cells

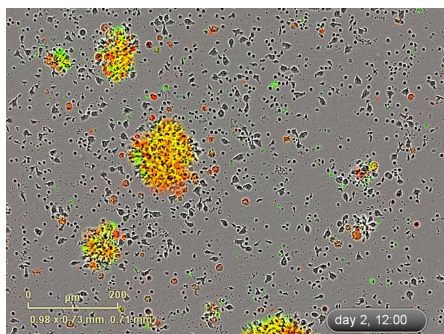
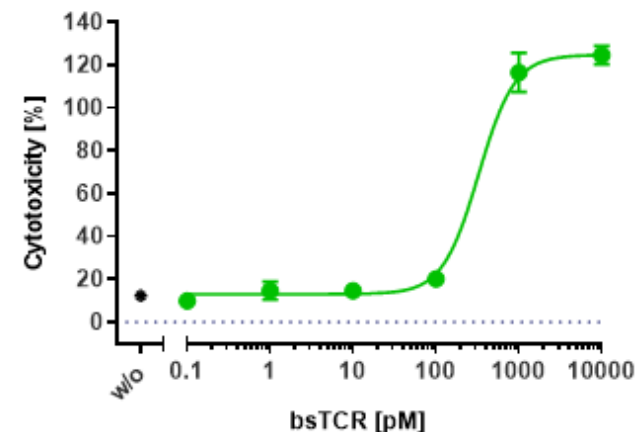
Tumor cell line  
~1000 target pHLA per cell  
EC50 = 31 pM



Tumor cell line  
~230 target pHLA per cell  
EC50 = 42 pM

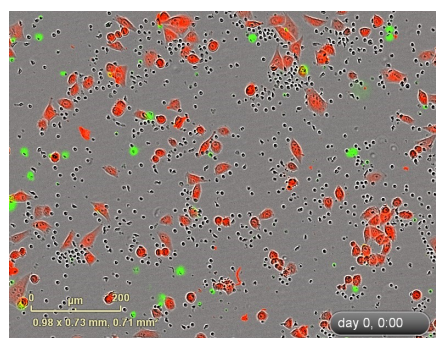


Tumor cell line  
~120 target pHLA per cell  
EC50 = 330 pM



60h

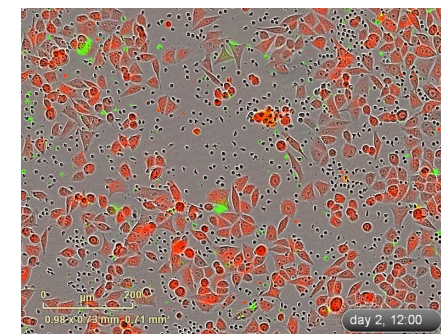
Tumor target-specific  
TCER™



0h

Tumor cells: CytoLight Rapid Red  
Apoptosis: CytoTox Green

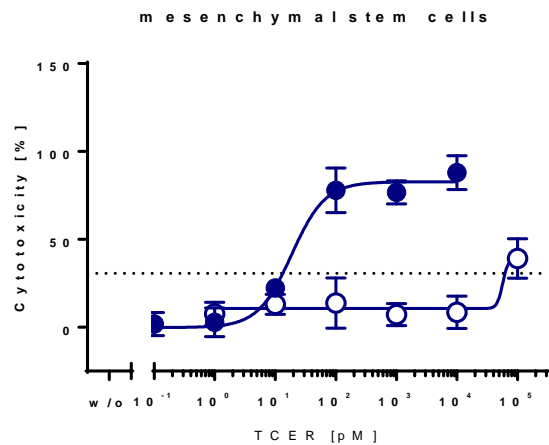
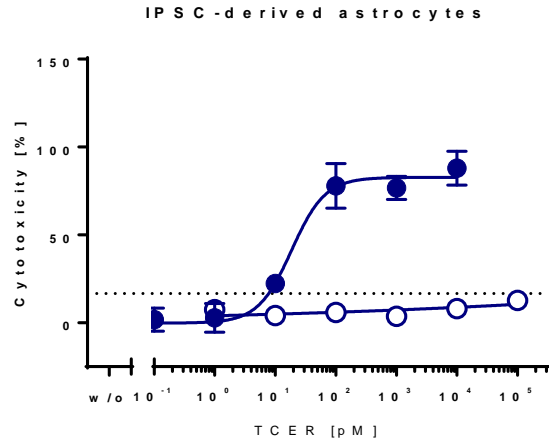
Control TCER™



60h



# IMA401 TCER™ – *In Vitro* Safety Assessment with Normal Tissue Cells



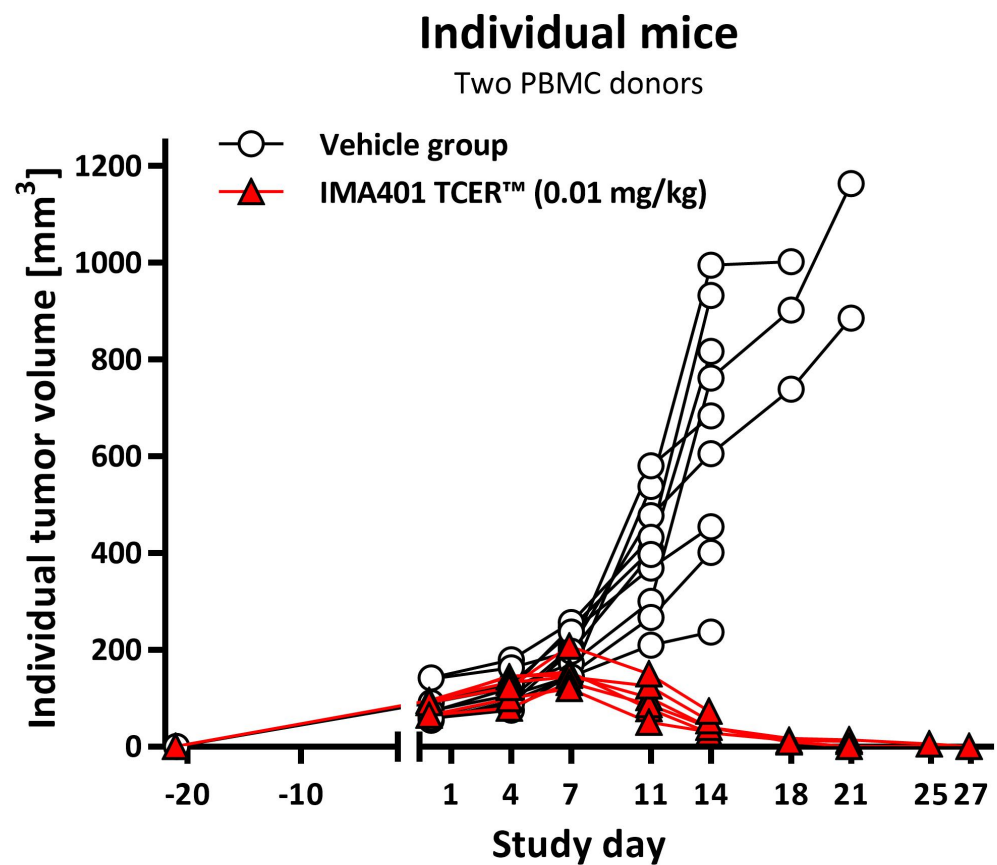
- target-positive tumor cell line (Hs695T)
- primary cell type

Normal Tissue Type	Therapeutic Window (x-fold)
iPSC-derived Astrocytes	>10,000
iPSC-derived GABA neurons	>10,000
iPSC-derived Cardiomyocytes	>10,000
Osteoblasts	10,000
Pulmonary Fibroblasts	>10,000
Dermal Microvascular Endothelial Cells	1,000
Mesenchymal Stem Cells from Bone Marrow	1,000
Tracheal Smooth Muscle Cells	>10,000
Epidermal Keratinocytes	>10,000
Renal Cortical Epithelial Cells	>10,000
Adrenal Cortical Cells	1,000
Cardiac Microvascular Endothelial Cells	>10,000
Chondrocytes	>10,000
Coronary Artery Endothelial Cells	>10,000
Nasal Epithelial Cells	>10,000
Pulmonary Artery Smooth Muscle Cells	>10,000

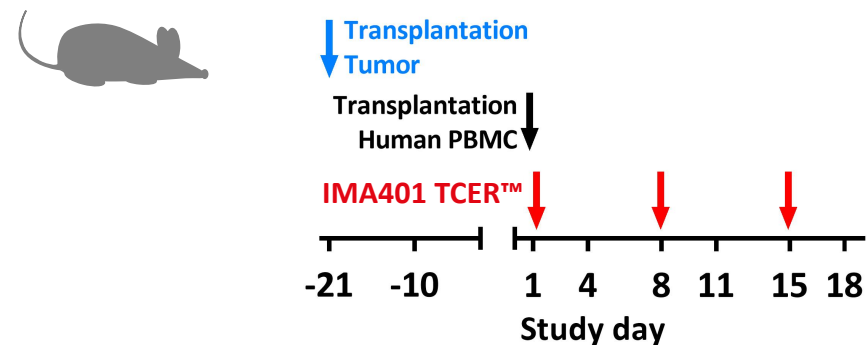
- Cytotoxicity against N≥15 different human normal tissue cell types
- IMA401 TCER™ shows a **minimum of 1,000-fold therapeutic window** between normal tissue cell reactivity and tumor cell reactivity

# IMA401 TCER™ – Efficacy Assessment in Cell Line-Derived Tumor Model

## Hs695T Tumor Xenograft Model in NOG Mice



### Treatment schedule



- IMA401 TCER™ shows high anti-tumor activity in HS695T xenograft models
- Remission observed in all mice at very low dose of IMA401 (0.01 mg/kg)

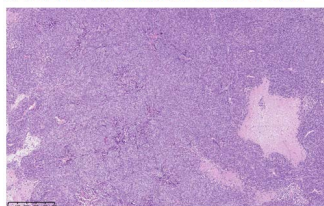
# IMA401 TCER™ – Efficacy Assessment in Patient-Derived Tumor Model

## LXFA 1012 Tumor Xenograft Model in NOG Mice

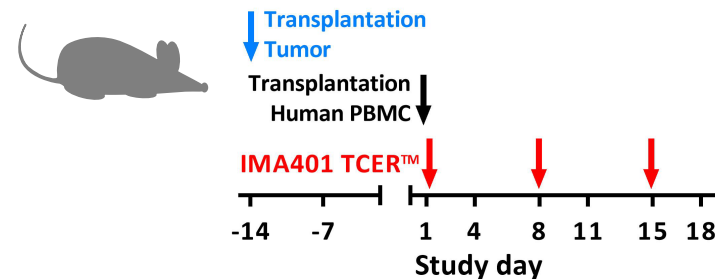
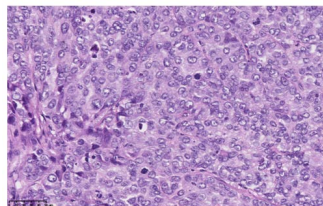
### LXFA 1012 (NSCLC, adenocarcinoma, passage 9):

- Male, Caucasian, age 58, no therapy prior to surgery
- Site of origin: lung, differentiation poor
- Date of surgery: 1987, Freiburg Medical Center
- Volume doubling time: 7.3 day
- Histology:
  - Stroma content, 4%
  - Vascularization, high
  - Grading, undifferentiated

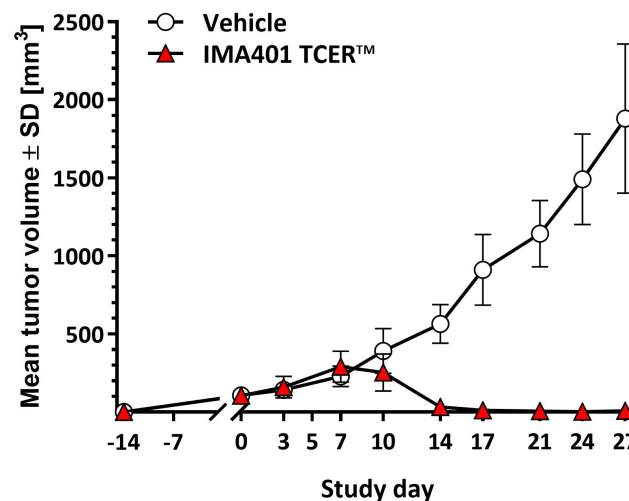
PASSAGE: 12N2, MAGNIFICATION: 5.0X



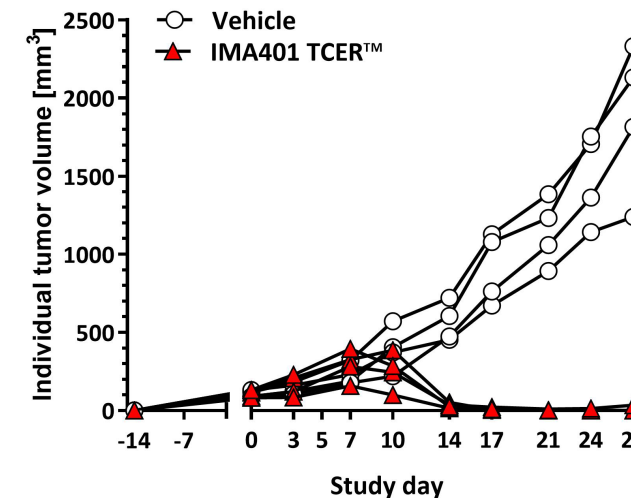
PASSAGE: 12N2, MAGNIFICATION: 40.0X



Group averages



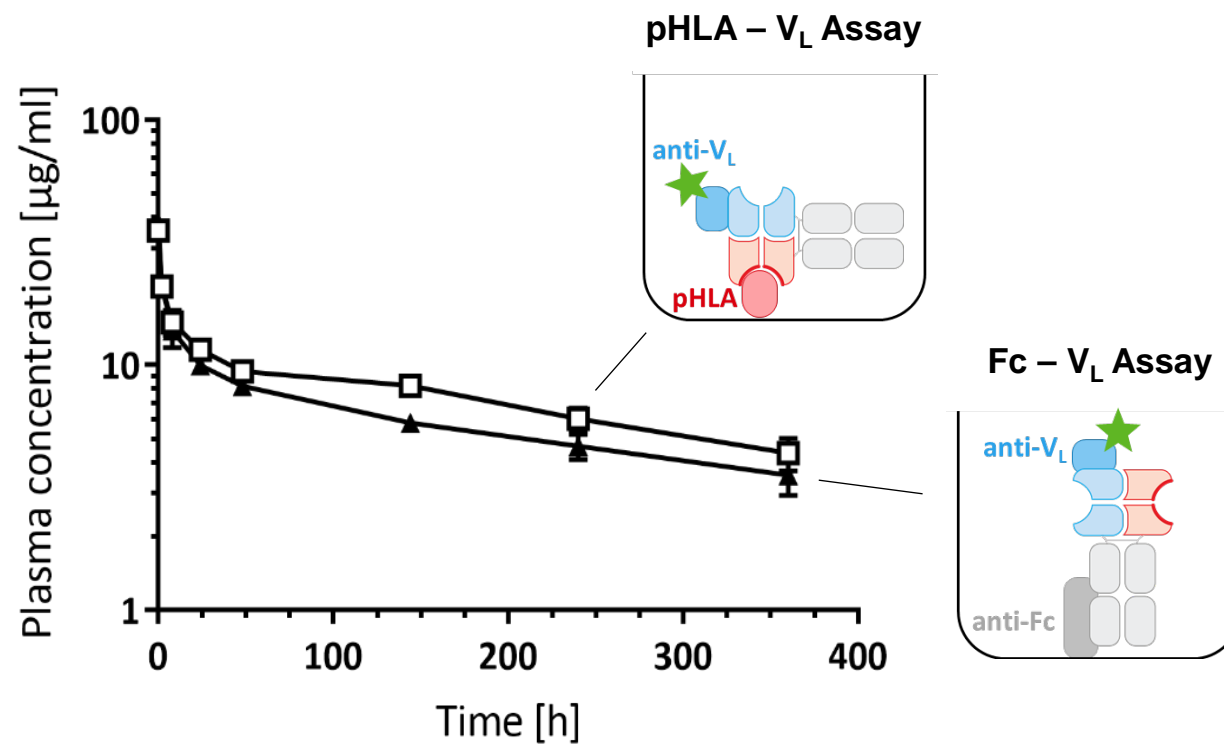
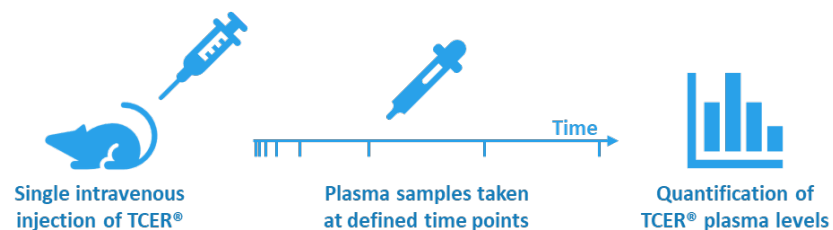
Individual mice  
Two PBMC donors



- IMA401 TCER™ shows **high anti-tumor activity in Patient-derived xenograft model** of non-small cell lung adenocarcinoma
- **Remission observed in all mice (3 out of 4 mice with complete remission)**

# IMA401 TCER™ – Pharmacokinetics

## PK Analysis in NOG Mice

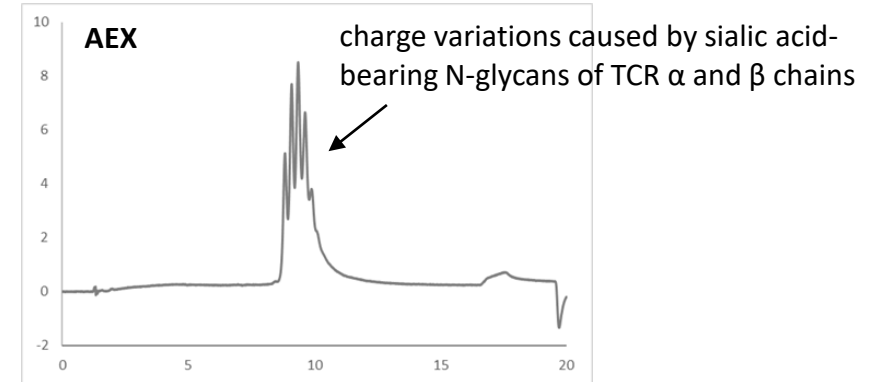
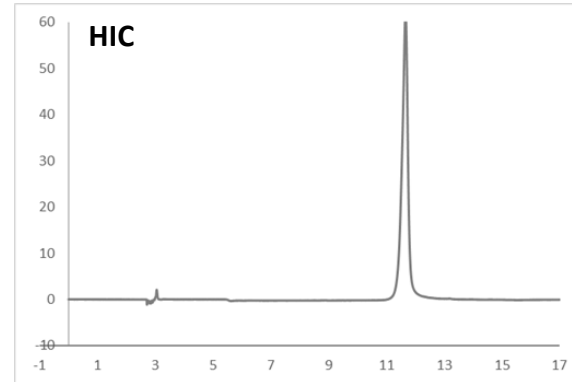
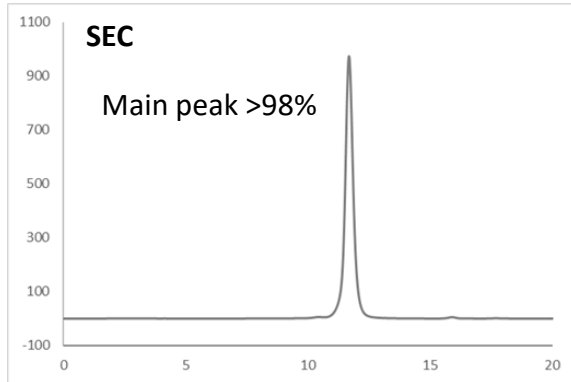


- Two different PK assays established to ensure functional integrity of protein domains
- **Terminal half-life: 10-11 days**

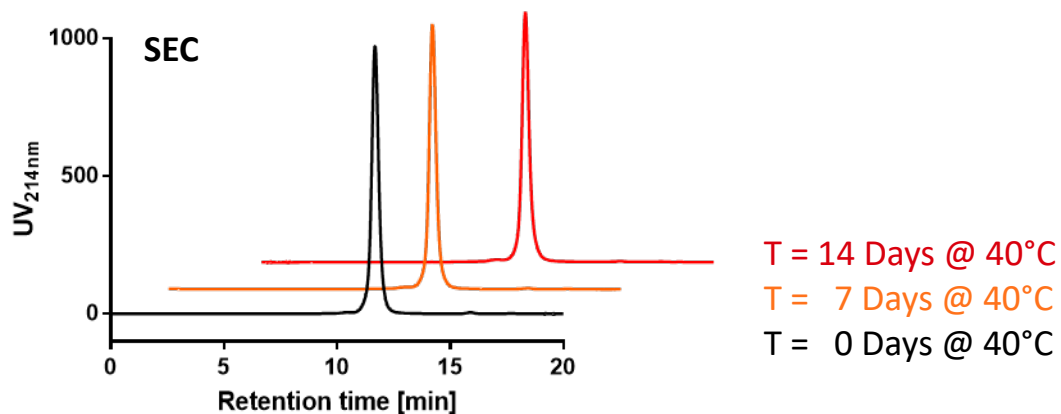
# IMA401 TCER™ – CMC Data

## Developability Assessment – Analytical Data

High quality IMA401 preparations obtained with standard 2-column purification process



IMA401 in PBS show excellent stabilities even prior to formulation development



- IMA401 TCER™ demonstrate high purity following an established 2-column purification process
- IMA401 TCER™ shows very low HMW formation/fragmentation even prior to development of optimal formulation



## Agenda

TCER™ – Immatics' TCR Bispecifics

IMA401 TCER™ targeting MAGEA4/8

**Summary**

# Excellent Profile of First TCER™ Program IMA401 Targeting MAGEA4/8

## Summary

### MAGEA4/8 Target Peptide

- **HLA-A\*02-restricted MAGEA4/8 peptide** targeted by TCER™ IMA401 and by ACTengine® IMA201 program is presented at 5-fold higher copy numbers per cell (up to 10,000) compared to a commonly used MAGEA4 target peptide in other ongoing clinical trials

### Compelling Preclinical Data

- **High *in vitro* potency** ( $EC_{50} < 100$  pM) in killing of tumor cells with physiological MAGEA4/8 peptide levels
- Favorable safety profile with **minimum of 1,000-fold therapeutic window** for normal cell reactivity
- **Complete remission of established tumors** in xenograft mouse models treated once weekly at low doses
- Favorable pharmacokinetics **with 10-11 days terminal half-life** in mice

### Favorable CMC Characteristics

- **High production yields of 2-4 g/liter** for selected CHO clone
- Well-progressing CMC development confirms **excellent purity and stability of the molecule**

### IND/IMPD Expected for YE 2021



Tübingen



Houston

### IMA401 Team, Tübingen, Germany

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Leonie Alten	Meike Hutt	Heiko Schuster
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Daniela Dichtler	Silke Koch	Stefanie Spalt
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Sebastian Bunk, Sr. Dir. Immunology
Claudia Wagner, Dir. Immunology
Regina Mendrzyk, Dir. Immunology
Sarah Missel, Sr. Dir. Translational Development
Oliver Schoor, VP Target Research
Carsten Reinhardt, CDO
Toni Weinschenk, CIO
Harpreet Singh, CEO


### Collaborations



Immunology





A close-up photograph of a woman in a laboratory setting. She is wearing safety glasses and a lab coat, looking intently at a computer monitor. The background is slightly blurred, showing laboratory equipment.

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