Development of Highly Potent Bispecific T-Cell Engaging Receptors (TCER®) Targeting Tumor-Specific HLA Ligands

Sebastian Bunk, Martin Hofmann, Felix Unverdorben, Meike Hutt, Gabriele Pszolla, Katharina Kiesel, Sarah Missel, Sara Yousef, Leonie Alten, Claudia Wagner, Gisela Schimmack, Heiko Schuster, Oliver Schoor, Jens Fritsche, Norbert Hilf, Toni Weinschenk, Harpreet Singh-Jasuja, Dominik Maurer and Carsten Reinhardt

Immatics Biotechnologies GmbH, Tuebingen, Germany

Introduction

Bispecific T-cell receptor (TCR)-antibody fusion proteins against tumor-specific targets represent a promising class of cancer therapeutics. The molecules utilize a TCR moiety for targeting of human leucocyte antigen (HLA)-bound tumor-associated peptides derived from tumor cell antigens regardless of their extracellular or intracellular location. Immatics is developing TCR bispecifics against tumor-associated peptide-HLA targets, which have been identified and validated by its proprietary target discovery engine XPRESIDENT®. Immatics has further established a portfolio of technologies to discover and engineer TCRs originating from the natural repertoire of human donors. After affinity maturation of single chain TCRs (scTv), the mutant scTv candidates displaying enhanced stability and affinity serve as building blocks for the generation of soluble and highly potent bispecific TCR molecules. Here we present data supporting proof-of-concept for our novel class of bispecific T-Cell Engaging Receptors (TCER®).

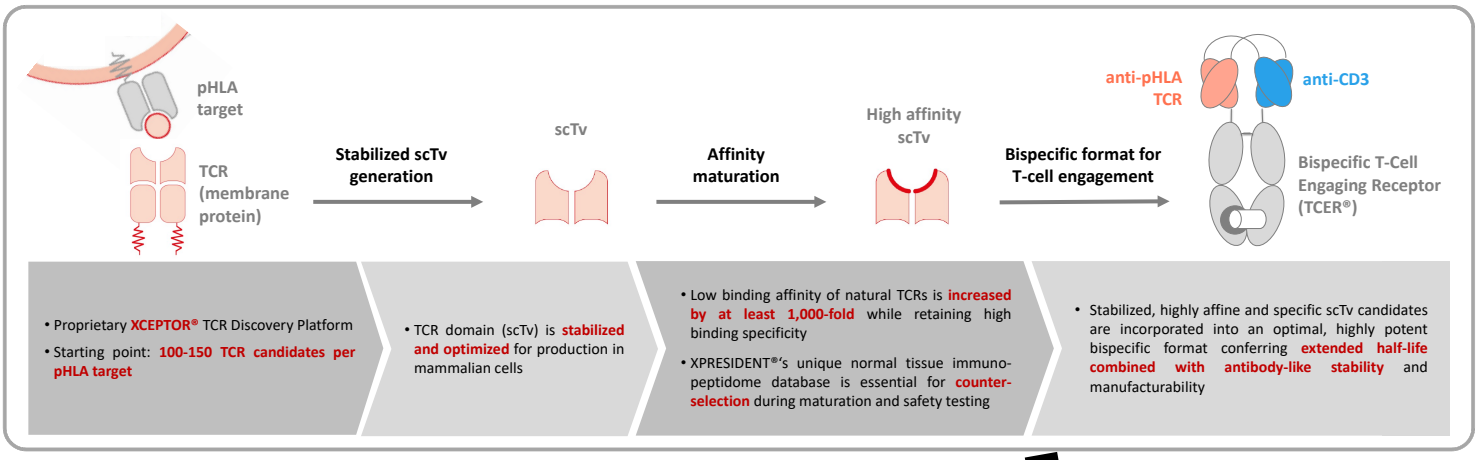

Figure 1: From parental TCR to soluble bispecific TCR. The workflow for the generation of soluble bispecific TCR molecules is schematically summarized. Parental TCRs with validated and specific r… of XPRESIDENT® peptide-HLA targets are conver… further stabilized by introducing framework mutations via yeast surface display. Stabilized scTvs with increased binding affinity are selected from scTv yeast display libraries with combinatorial …utations in CDR regions. To maintain bindin… affinity during the af… maturation the… are counter-selected against HLA complexes presenting peptides from normal tissues, which have high sequence similarity to the tumor target peptide. Finally, highly affine and specific sc… didates are incorporated into Imma… ific T-Ce… ging Receptor (TCER®).

Bispecific TCR Leads Effectively Kill Tumor Cells

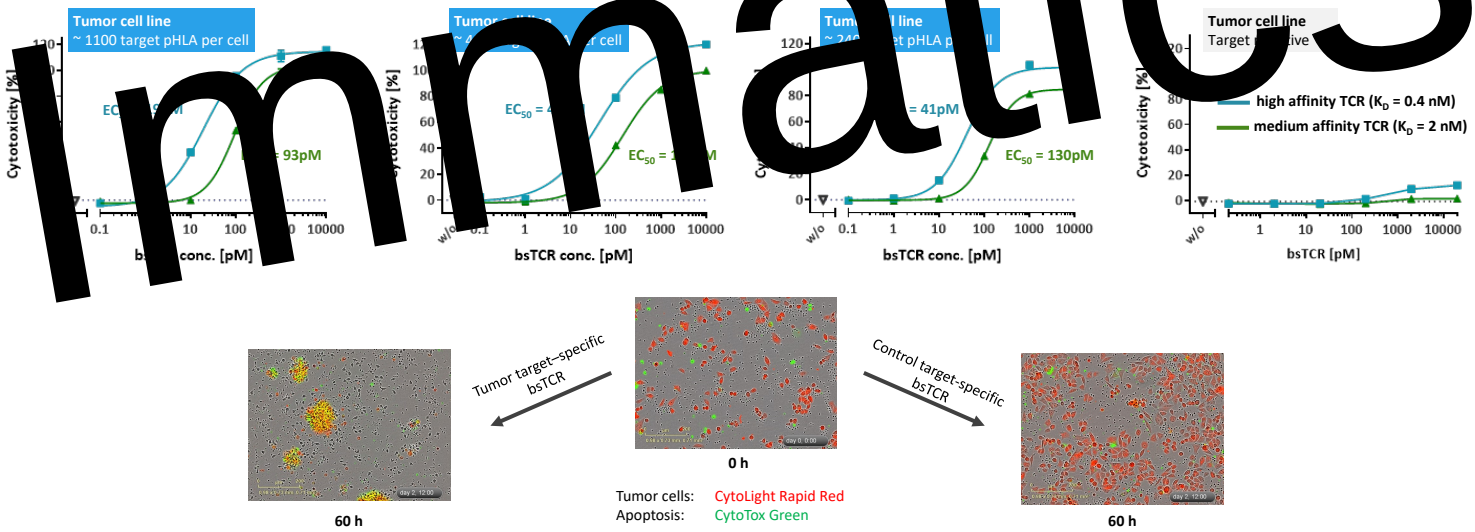

Figure 2: T cell-mediated cytotoxicity of TCER® lead candidates against tumor cells. Upper panel: CD8+ T cell-mediated cytotoxicity of two TCER® candidates carrying a medium (green curve) or high affinity (blue curve) TCR against tumor cells expressing different ranges of target pHLA copies per cell. Cytotoxicity was calculated according to LDH release (Promega) from tumor cells during coculture with CD8+ T cells for 48 hours at an effector to target ratio of 5. **Lower panel:** IncuCyte® live-cell analysis of target pHLA-expressing tumor cells (labeled with CytoLight Rapid Red) upon coculture with CD8+ T cells for 60 hours in the presence of a tumor target pHLA-specific TCER® and a control pHLA-specific TCER®, respectively.

Bispecific TCR Leads Are Highly Stable After scTv Optimization

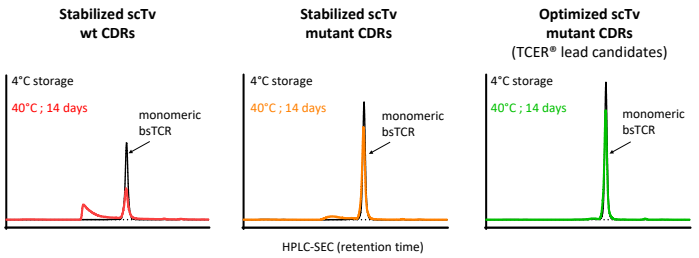

Figure 3: Stability of bispecific TCR leads. Bispecific TCR leads were formulated in PBS and subjected to heat stress at 40°C for 14 days. Non-stressed (black curve) and heat-stressed (colored curves) protein samples were analyzed by HPLC-SEC utilizing a TSKgel Bioassist G3SWXL column (Tosoh Bioscience).

Preclinical Data Package for Immatics' TCER® Programs

- 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
- Target-negative tumor cell lines
- Alloreactivity screening
- Cytokine release from whole blood
- XPRESIDENT®-guided off-target screening

- Yield and purity from CHO cells
- Melting temperature
- Freeze-thaw and storage stress stability
- Sequence liabilities
- N-glycan profiling of TCR domains

Immatics Biotechnologies GmbH
Immatics US, Inc.

www.immatics.com
info@immatics.com

Follow us on