Improving TCR-T Therapeutic Persistence and Efficacy with Switch Receptors

8th Annual CAR-TCR Engineering a Disease-Free World
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Medigene’s Ethos - Optimal TCRs for Potential Best-in-Class TCR-T Therapies

End-to End (E2E) Platform - Designed to generate highest levels of safety, efficacy & durability

Develop Best-in-Class, Optimal TCRs

Optimize TCR-T Therapies

1. Suitable and Safe TCR Target
2. High Specificity, High Sensitivity, Safe, “3S” TCR, Optimal Affinity
3. Higher Avidity TCR-T Cells
4. Enhanced Activity in TME
5. Robust GLP Manufacturing

Target Screening → TCR Generation → TCR-T Therapy Optimization → Manufacturing Scale-up & Process Improvement → Best-in-Class TCR-T Therapy for Patients

Expitope → Allo-HLA TCR Priming → Precision Pairing → Costimulatory Switch Proteins → GMP Drug Products

End-To-End (E2E) Technology Platform
Multiple combinable, exclusive and proprietary technologies, combined with proprietary work processes and selection algorithms
Medigene’s End-to-End Platform for TCR-T Therapy

Multiple combinable, exclusive and proprietary technologies to create best-in-class TCR-T therapies for cancer patients

Target Screening
- Expitope
- Allo-HLA TCR Priming*
- CrossTag* Vector System
- JOVI Tag* Enrichment Technology
- Robotic Functional HTS

TCR Generation
- Precision Pairing*
- PD1-41BB Switch#

TCR-T Therapy Optimization
- CD40L-CD28 Switch*
- Inducible iM-TCR*

Manufacturing Scale-up & Process Improvement
- SIN-γ- Retroviral Gene Transfer System
- Cell Production Process & Quality Control
- Drug Product Immune Assessment*

Clinical Development
- Patient Immune Monitoring*

Development Optimization

Efficacy Enhancements

Safety Enhancements

* Proprietary to MDG
# Exclusive to MDG
^ Proprietary to MDG / HU
Expitope
Webtool to Identify Immunogenic Epitopes as Potential TCR Targets
Enhanced Screen for Cross-Reactive Epitopes in silico
Expitope - Qualitative and Quantitative Target Safety Assessments at RNA and Proteome Levels

Unmet need

• Cross-reactivation of unwanted T cell response may result in significant, often lethal toxicity

Medigene’ solution: Expitope

• In silico epitope expression assessment in various tissues and cell lines allows for screening of potential cross-reactivity and off-target toxicity
• Identifying target epitopes for TCR isolation; predicting binding affinities and cross-reactivities

- Prof. D. Frishman, Bioinformatics Faculty, Technical Uni. Munich
- Open access web tool for scientific community, hosted by TUM
  - [http://webclu.bio.wzw.tum.de] expitope
  - 370,000+ annotated sequences, updated regularly
  - 100+ HLA class I alleles, expanding by need
  - 20+ healthy tissues, growing continuously
  - Easy access Website
medigene

TCR Generation
Medigene TCR Generation – Selecting Optimal Affinity 3S TCRs

Refined and robust workflows established

High Specificity
pHLA recognition reaches pre-defined thresholds

High Sensitivity
Optimal affinity to recognize and kill tumor cells with low levels of antigen / epitope

Safety
Clear differentiation between tumor and healthy cells
No recognition of allogeneic HLAs

Additional Attributes
Natural high heterodimer pairing ➔ High avidity through high surface expression on recipient T cells
CD8 co-receptor independency ➔ Strong TCR-mediated functions in both CD4 and CD8 T cells
TCR Generation – DC-T Cell Priming Using Healthy Donors

Healthy donors provide high TCR sequence diversity for better choice of lead TCRs

Advantages of priming approach

✓ Ready access to healthy donors
  ✓ autologous DCs
  ✓ autologous T cells

✓ ivtRNA is versatile source of antigen

✓ HTS yields thousands of specific T cell clones for lead TCR selection

✓ RV TCR transfer vector is efficient and fast
Allo-HLA TCR Priming Helps Find Optimal TCRs for Self-Antigens

Bypasses *Central Tolerance* that limits TCR affinities to self-antigens like CGAs

Advantages of Allo-HLA-Priming to Discover TCRs

- Higher-affinity TCRs
- Any HLA allotype
- Any target antigen
- No patient samples
- No need for affinity maturation

DCs and T cells come from HLA-A2-negative donors so T cells not subjected to deletional tolerance.
Transgenic assessment of dozens of independent TCR sequences

10-30 healthy donors of T cells used for priming in DC-T cell co-cultures

Assessment of thousands of single cell clones (e.g. 60K) to select hundreds of specific T cell clones to perform individual NGS TCR sequencing

Transgenic assessment of dozens of independent TCR sequences

Antigen selection

High-throughput automation
- Standardization and reproducibility
- Functional screen of thousands of T cell clones
- Fast isolation of high-affinity TCRs

3S TCR selection for Specificity, Sensitivity & Safety
- TCRs developed from healthy donor T cells
- Assay algorithm to select optimal target-specific TCRs
  - Potency / efficacy — high-affinity TCRs with optimal tumor cell cytotoxicity and highest peptide sensitivity
  - Safety / specificity — exhaustive assessment to minimize potential cross-reactivity

3S TCR leads
Allo-HLA-Primed TCR is Superior to Auto-HLA-Primed TCR Specific for MAGE-A4 CGA/CTA

**Tumor Cell Panel Sensitivity (in vitro)**

- **Auto TCR**
- **Allo TCR**

<table>
<thead>
<tr>
<th>Tumor Cell</th>
<th>MAGE-A4 mRNA levels</th>
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<tbody>
<tr>
<td>Mel A375</td>
<td>NC1-H1755</td>
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<tr>
<td>UACC-62</td>
<td>NCI-H1703</td>
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<tr>
<td>U266</td>
<td>NCI-H2023</td>
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<tr>
<td>SAOS2</td>
<td>MOF7</td>
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**Effect on Tumor Volume (in vivo)**

- **Vehicle**
- **Untransduced**
- **Auto TCR**
- **Allo TCR**

*"Murine Xenograft model" used for TCR-T treatment of subcutaneous MelA375 solid tumors

Greater Sensitivity for Tumor Cells with Rapid & Complete Effect on Tumor Volume vs. Auto-TCR

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Validated Approach to Acquire Optimal Affinity 3S TCRs

Decades of TCR development in cancer-germline antigens & more recently neoantigens

- **MAGE-A4 A*02** (2Seventy Bio)
- **NY-ESO-1 / LAGE-1a A*02** (MDG1015)
- **PRAME A*02 (VLD)** (MDG1011)
- **KRAS G12V A*11** (MDG2011)
- **PRAME A*02 (SLL)** (BIONTECH)
- **KRAS G12V A*03** (MDG2012)
- **KRAS G12D A*11** (MDG2021)
PD1-41BB Costimulatory Switch Protein Armors and Enhances TCR-T Cells by Changing Inhibition into Activation

- Inhibits T Cell Activity
- Induces T Cell Exhaustion
- Drives T Cell Apoptosis

- Blocks PD-L1-Mediated Inhibition
- Provides T Cell Costimulation
- Enhances TCR-T Activity and Survival
PD1-41BB CSP Positively Impacts Multiple TCR-T Cell Functions

- Sustained proliferation
- Maintenance of stemness
- In vivo efficacy
- Mitigate inhibitory TME
- Overcome T cell exhaustion
- Enhanced functionality \textit{in vitro}
CD40L-CD28 Costimulatory Switch Protein Provides Dual Enhancement of TCR-T Cells

- Reduces TME Penetration
- Limits Tumor Cell Killing
- Allows T Cell Exhaustion & Apoptosis

- Activates Local Endothelium for T Cell Entry
- Allows TCR-T Cells to Shape Negative TME
- Mitigates T Cell Exhaustion & Apoptosis
CD40L-CD28 Switch Protein – Mechanisms of Enhancement

CD40L-CD28 alters TME via external interactions with CD40 and provides T cell costimulation

**CD40L**

1. Activates endothelium for T cell transmigration
2. Licenses DCs to prime new T cells and recruit NK cells
3. Enables T cells to kill tumor cells via CD40 (HLA dependent & independent mechanisms)

**CD28**

4. Activates costimulatory pathway in TCR-T cells
   - improves T cell proliferation
   - enhances T cell functions
   - limits T cell exhaustion & apoptosis

Adapted from https://www.frontiersin.org/articles/10.3389/fimmu.2021.750478/full
TCR-T Therapy Optimization Using Costimulatory Switch Proteins

Two unique CSPs provide complementary mitigation of the immunosuppressive TME

PD1-41BB

- Blocks PD1-PDL1 inhibitory axis
- Improves T cell persistence in TME
- Increases cytokine secretion & tumor cell killing
- Increases T cell proliferation

CD40L-CD28

- Enhances tumor penetration
- Broadens TME immune responses
MDG1015
3rd Generation NY-ESO-1 / LAGE-1a Targeted TCR-T Therapy – Optimal Affinity
3S TCR Combined with PD1-41BB CSP
Optimal Affinity 3S TCR Generated for CGA – NY-ESO-1/LAGE-1a

Non-mutated Allo-HLA-primed TCR and affinity-matured (mutated) TCR are comparable

Tumor Cell Panel Sensitivity

TCR-T Cell Functional Avidity

Advantages of Allo-HLA-Priming to Discover TCRs

✓ Higher-affinity TCRs
✓ Any HLA allotype
✓ Any target antigen
✓ No patient samples
✓ No need for affinity maturation
CD8⁺ Transduced TCR-T Cells Co-Express TCR +/- PD1-41BB

Donor A

Donor B
PD1-41BB Switch Receptor Enhances and Sustains TCR-T Cell Proliferation

Enhanced TCR-T proliferation with TCR+PD1-41BB vs. Naked TCR

<table>
<thead>
<tr>
<th>Count</th>
<th>Percent Divided</th>
<th>Proliferation Index</th>
<th>Expansion Index</th>
<th>Division Index</th>
<th>Replication Index</th>
<th>Std. Deviation</th>
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<tbody>
<tr>
<td>Naked TCR</td>
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<td>1.98</td>
<td>2.09</td>
<td>0.48</td>
<td>5.49</td>
<td>1.36</td>
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<tr>
<td>TCR+PD1-41BB</td>
<td>42.7</td>
<td>2.91</td>
<td>5.05</td>
<td>1.24</td>
<td>10.5</td>
<td>0.98</td>
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</tbody>
</table>

Analyzed by FlowJo
Superior Frequency of T Cells Producing Multiple Cytokines Compared to Naked TCR for Improved Anti-Tumor Activity

**Improved Polyfunctionality (multi-cytokine production)**

- **UT**
- **TCR**
- **MDG1015**

**Mel624.38_PD-L1**
- 2 analytes
- 3 analytes
- 4 analytes
- 5+ analytes

**MelA375_PD-L1**

**Greater Polyfunctional Strength Index**

- **UT**
- **TCR**
- **MDG1015**

**Mel624.38_PD-L1**

**MelA375_PD-L1**

**Effector**: Granzyme B; IFN-γ; MIP-1α; Perforin; TNF-α; TNF-β

**Stimulatory**: GM-CSF; IL-2; IL-5; IL-7; IL-8; IL-9; IL-12; IL-15; IL-21

**Chemoattractive**: CCL-11; IP-10; MIP-1α; RANTES

**Regulatory**: IL-4; IL-10; IL-13; IL-22; TGF-β1; sCD137; sCD40L

**Inflammatory**: IL-1β; IL-6; IL-17α; IL-17F; MCP-1; MCP-4

*Superior Frequency of T Cells Producing Multiple Cytokines Compared to Naked TCR for Improved Anti-Tumor Activity*
TCR-T Cells Display Rapid Killing Capacity for Both Target Antigens

Strong pre-clinical data supports addition of PD1-41BB to a TCR targeting NY-ESO-1 / LAGE-1a

Rapid Killing Assay: 0 – 96 hours

MelA375 (NY-ESO-1+)

Mel624.38 (LAGE-1+)
TCR-T Cells Display Sustained Killing Upon Tumor Rechallenge

Sustained TCR-T Cell Killing Requires pHLA and PD1-L1 Signals from Tumor Cells

- TCR
- TCR+ PD1-41BB
- TCR
- TCR+ PD1-41BB
- TCR
- TCR+ PD1-41BB
- TCR
- TCR+ PD1-41BB

Day 0 | Day 3 | Day 7 | Day 14/17

Mel624.38_PD-L1_NLR
LAGE-1a +++
PD-L1 +++

NCI-H1755_NLR
NY-ESO-1 +++
PD-L1 -

647V_NLR
NY-ESO-1 -
PD-L1 ++
Medigene’s Ethos - Optimal TCRs for Potential Best-in-Class TCR-T Therapies

End-to End (E2E) Platform - Designed to generate highest levels of safety, efficacy & durability

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End-To-End (E2E) Technology Platform
Multiple combinable, exclusive and proprietary technologies, combined with proprietary work processes and selection algorithms
MDG1015: First-in-Human Clinical Study with PD1-41BB Switch Receptor
CTA / IND approval expected 2H 2024

**Ph1**
- Multi-center, first in human, open label, dose-escalation and cohort expansion phase 1 study
- Aim: To assess the safety, feasibility and preliminary efficacy of MDG1015

- Adult patients
- HLA-A*02:01-positive and NY-ESO-1 and/or LAGE-1a-positive patients eligible

- Multiple indications selected based predominantly on target expression, PD-L1 expression and patient availability
  - Synovial Sarcoma will be one of the indications

- IND/CTA approval expected in the second half of 2024
- First patient enrolled planned for second half of 2024, subject to financing
Thank you for your attention