Case Study Spotlight: Introducing Innovations at Each Step of TCR-T Therapy Development

TCR-Based Therapies for Solid Tumors Summit
April 4, 2023 Boston
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Medigene’s End-to-End Platform for TCR-T Therapy Development

Multiple, Combinable Technologies to Create Best-in-Class TCR-T Therapies for Cancer Patients

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

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

- TCR-T Therapy Optimization
  - SIN-γ- Retroviral Gene Transfer System
  - Cell Production Process & Quality Control
  - Drug Product Immune Assessment*

- Manufacturing Scale-up & Process Improvement

- Clinical Development
  - Patient Immune Monitoring*

Development Optimization, Efficacy Enhancements, Safety Enhancements

* Proprietary to MDG
# Exclusive to MDG
^ Proprietary to MDG / HMGU
Six Key Platform Technologies

- Allo-HLA TCR Priming
- JOVI Tag
- Precision Pairing
- iM-TCR
- EXPitope-M
- PD1-41BB Switch Receptor

* Proprietary to MDG
# Exclusive to MDG
^ Proprietary to MDG / HMGU
EXPItope-M*
Tool to Identify Immunogenic Epitopes as Potential TCR Target Specificities and Screen for Safety in silico
EXPltope-M - 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 cross-reactivity and binding affinities

- Prof. D. Frishman, Bioinformatics Faculty, Technical Uni. Munich
- Open access web tool for scientific community, hosted by TUM
  - Expitope
  - Expitope 3.0 coming soon!
    - 370,000+ annotated sequences, updated daily
    - 100+ HLA class I alleles, expanded by need
    - 20+ healthy tissues, growing continuously
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
Automated High-Throughput TCR Discovery Quickly Delivers Multiple TCR Candidates

Antigen selection

Healthy donor cells used for priming in DC-T cell co-cultures

Selection of antigen-specific T cell clones and their TCR sequences

Transgenic assessment of TCRs focusing on Sensitivity, Specificity, and Safety

TCR leads

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
Allo-HLA TCR Priming*
Bypass Central Tolerance to Isolate High-Affinity Natural TCRs for Improved Sensitivity and Safety
Allo-HLA TCR Priming Yields High-Affinity TCRs Without Need for Affinity Maturation

- **HLA-A2^{pos} donor**
  - Thymus:
    - HLA-A2-peptide complexes present
    - ✓ low affinity
  - Blood:
    - ❌ high affinity
    - TOLERANT peripheral T cell repertoire
    - Few higher-affinity TCRs are present for HLA-A2-self-peptide complexes

- **HLA-A2^{neg} donor**
  - Thymus:
    - low affinity to HLA-A2
    - HLA-A2-peptide complexes absent
    - ✓ high affinity to HLA-A2
  - Blood:
    - ✓ low affinity to HLA-A2
    - NON-TOLERANT peripheral T cell repertoire
    - Higher-affinity TCRs are present for HLA-A2-allo-peptide complexes
Allo-HLA-Primed TCR is Superior to Auto-HLA-Primed TCR Specific for MAGE-A4 CTA

Tumor Cell Panel Sensitivity *(in vitro)*

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

<table>
<thead>
<tr>
<th>Tumor Cell Line</th>
<th>IFNγ [pg/mL]</th>
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<tr>
<td>Mel A375</td>
<td>0 – 2000</td>
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<tr>
<td>NCI-H1755</td>
<td>2000 – 4000</td>
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<tr>
<td>UACC 62</td>
<td>4000 – 6000</td>
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<tr>
<td>NCI-H1703</td>
<td>6000 – 8000</td>
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<tr>
<td>U266</td>
<td>8000 – 10000</td>
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<tr>
<td>NCI-H2023</td>
<td>0 – 2000</td>
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<tr>
<td>SKOS2</td>
<td>2000 – 4000</td>
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<tr>
<td>MOF7</td>
<td>4000 – 6000</td>
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**MAGE-A4 mRNA levels**

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

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

Allo-HLA-Primed TCR and Affinity-Matured TCR Are Comparable

**Tumor Cell Panel Sensitivity**

- FM6
- U256
- Mel 024.39
- FM 5.29
- SAOS2
- MM 415
- SK-Mel 23

**TCR-T Cell Functional Avidity**

- Naked NY-ESO-1 TCR
- Benchmark TCR
- Untransduced

Untransduced: T cells lacking TCR-encoding viral vector
Allo-HLA TCR Priming Helps Find Optimal TCRs for Self-Antigens

Advantages of Allo-HLA-Primed to Discover TCRs

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

Generate allogeneic MHC-peptide ligands by expressing both antigen and HLA in DCs
JOVI-Tag*
Standardize Enrichment and Tracking of rTCR-Expressing T Cells to Select Safer TCRs

* Proprietary to MDG
JOVI-Tag Allows Easy Tracking and Enrichment of Cβ1+ rTCRs in Cβ1-Negative Recipient T Cells

rTCRs with Cβ1+ Constant Regions Specifically Bind Jovi-1 Antibody

CD8+ T cells with mixes of Cβ1 and Cβ2 endogenous TCRs

- Cβ1 TCR
- Cβ2 TCR
- JOVI.1(-biotin)
- anti-biotin microbeads
- retroviral particle encoding Cβ1 TCR

CD8+ T cells with Cβ1 endogenous TCRs bind Jovi-Aby

RV Transfer of Cβ1+ rTCRs

Specific depletion of Cβ1 T cells+

Antigen-specific expansion

Identify rTCR+ TCR-Ts by Jovi-1 Tag

Non-specific expansion

Enriched Cβ1+ T cells
JOVI-Tag - High Throughput Comparison of Multiple rTCRs Allows Selection of Safer and Best-in-Class TCRs

Exemplary gating strategy

% Cβ1+ cells on CD8+ cells

% pentamer+ cells on Cβ1+ cells CD8+ cells

Donor A Donor B

Cb1+ on CD8+

multimer+ on Cb1+CD8+

Freq. of parental [%]
Precision Pairing*
Modify and Tailor TCR Constant Regions to Improve Functional Activity and Safety
Precision Pairing Improves TCR Alpha-Beta Chain Interactions

Suboptimal chain pairing allows more TCR mispairing and potential off-target reactivity

Improved rTCR pairing gives better surface expression and improves safety
Sensitivity & Functional Avidity is Improved in Precision Paired rTCRs

**Improved TCR Tumor Cell Sensitivity**

![Graph showing TCR activation](image)

**Improved TCR-T Cell Functional Avidity**

![Graph showing IFNγ production](image)

Specific peptide concentration [M] vs. IFNγ (pg/mL) for WT TCR, Precision-Paired TCR, and Untransduced TCR.
iM-TCR*
Novel Control Mechanism to Regulate TCR-T Therapy Efficacy & Safety
iM-TCR Strictly Controls rTCR Alpha-Beta Chain Pairing Through Ligand-Induced Dimerization for Better Efficacy and Safety

Advantages of iM-TCRs

- Strict control of TCR-T activity enhances safety
- Lack of TCR mispairing improves functional avidity
- TCR expression is time and ligand concentration dependent
- Transient tuning of TCR-T activity ex vivo for therapy of inflammation-sensitive indications like brain tumors
TCR Dimerization Strictly Controls Killing Capacity of iM-TCR-T Cells

Endpoint (40h) Start (0h)

wt-TCR Antigen-negative Antigen-positive

iM-TCR Antigen-negative Antigen-positive

Endoxifen

0µM 0µM 10µM 10µM
PD1-41BB Switch Receptor#
Next Generation Co-stimulatory Switch Receptor to Enhance TCR-T Cell Functions and Overcome an Immunosuppressive TME
PD1-41BB Switch Receptor Changes T Cell Inhibition into Activation

Tumor cell

PD-L1

HLA

PD-1

TCR

Apoptotic T cell

Exhausted T cell

41BB

Tumor cell

PD-L1

HLA

PD-1

TCR

Apoptotic tumor cell

Effector T cells
PD1-41BB Switch Receptor Improves Proliferation and Tumor Recognition

Enhanced TCR-T Cell Proliferation

Better T Cell Activation and Tumor Cell Line Recognition

Donor 1 Naked NY-ESO-1 TCR
Donor 1 MDG1015
Donor 2 Naked NY-ESO-1 TCR
Donor 2 MDG1015
Donor 3 Naked NY-ESO-1 TCR
Donor 3 MDG1015

IFNγ (pg/mL)

Enhanced TCR-T Cell Proliferation

"Naked" NY-ESO-1 TCR

CD8 & CD3

Cell count

CellTrace

NY-ESO-1 TCR with PD1-41BB

CD8 & CD3

Cell count

CellTrace

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

Improved Polyfunctionality (multi-cytokine production)

Greater Polyfunctional Strength Index

**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-1β; RANTES

**Regulatory**: IL-4; IL-10; IL-13; IL-22; TGF β 1; sCD137; sCD40L

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

*Superior Frequency of T Cells Producing Multiple Cytokines Compared to Naked TCR for Improved Anti-Tumor Activity*
PD1-41BB Switch Receptor Mitigates Tumor-Induced TCR-T Exhaustion

Superior Serial Killing Delivered by TCR-Ts with CTA-specific TCRs and PD1-41BB

**SKMel23_PD-L1**
- PRAME
  - Naked TCR
  - TCR_PD1-41BB
- Rechallenge with tumor
  - day 0
  - day 7
  - day 16

**Mel624.38_PD-L1**
- NY-ESO-1
  - Naked TCR
  - TCR_PD1-41BB
- Re-challenge with tumor
  - day 0
  - day 7
  - day 17

Orange = tumor spheroids
Grey = T cells
TCR-T Cells Retain Stemness by Maintenance of T Central Memory Cells After Four Rounds of Tumor Challenge

Day 0
Challenge 1
Challenge 2
Challenge 3
Challenge 4

T-mem subtypes of CD8+ TCRvβ1+

Tscm
Tcm
Tem
Temra
rest
PD1-41BB Switch Receptor Strongly Enhances TCR-T Cell Functions

- Overcome T cell exhaustion
- Mitigate inhibitory TME
- Sustained proliferation
- Enhanced functionality in vitro
- Maintenance of stemness
- In vivo efficacy

PD1-41BB
Validated Manufacturing Process with Successful Tech Transfer
92% Successful GMP Production of TCR-T Cells for MDG1011 Phase I Trial of Blood Cancers

1. Leukapheresis
2. Enrichment process
3. Activation of T cells

- CD8+ enrichment
- Intermediate product: cryopreserved CD8+ enriched cells
- CD8
- CD4
- T cell transduction using retromectin
- G-Rex device
- Cryo-bags
- anti-CD3 + anti-CD28
- Freezing
- Patient treatment
Evolution by Innovation: Connecting the Dots for TCR-T Therapies

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<th>Technologies</th>
<th>Suitable and Safe TCR Target</th>
<th>High-affinity 3S TCR</th>
<th>Higher-avidity TCR-T cells</th>
<th>Enhanced Activity in TME</th>
<th>Robust Manufacturing</th>
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- Best-in-Class TCR-T Therapy for Patients
Thank you for your attention