ENGINEERED CAR-T THERAPIES

Workshop on Scientific and Regulatory Challenges of Genetically Modified Cell-based Cancer Immunotherapy Products

November 15-16, 2016
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Combining Technology Platforms

To enhance the power of the immune system against cancer

Chimeric Antigen Receptor
Tumors recognition

TALEN® Nuclease
T-Cell properties
TALEN® - Gene Editing Tool

TALEN® gene editing tool with best-in-class characteristics:

- **Precision**: 99.8% of chromosome sequences can be targeted using more selective TALEN® scaffolds
- **Efficacy**: Routinely 97% efficiency in single gene knock-out at R+D level
- **Safety**: Industry-leading off-target safety profile with very low toxicity (undetectable off target cleavage)
TALEN® - Gene TALEN® Gene Editing Process

A custom TALEN® is created to target the precise gene sequence

TALEN® binds to its target sequence as a heterodimer, separated by a spacer region

Following binding, FokI nuclease heads clip the DNA at the target sequence

Cleavage generates DNA double-strand breaks that can be repaired by NHEJ

The DNA is degraded at the cleavage site and nucleotides are lost

DNA ends are rejoined, resulting in a mutation that inactivates the target gene

Gene Inactivation or Knockout (KO)
Efficient Gene inactivation using TALEN® mRNA

Pulse Agile Electroporation System
Cuvette or Large volume chamber (12 ml)
2x10⁶ -10⁹ cells

- TALEN® TCRα: 1 allele KO: 83%
- TALEN® CD38: 2 alleles KO: 60%
- TALEN® CD52+TCRα: 3 alleles KO: 51%
- TALEN® CD52+TCRα+geneX: 5 alleles KO: 30%

Mutation frequency (%)

Bar chart showing mutation frequency for different genes

Graphs showing flow cytometry analysis for TCRα, CD38, CD52, and CD52+TCRα+geneX
TALEN® Technology permits highly specific cleavage

HBB

ON-Site

OFF-Site

ON-site/OFF-site > 94 % identity

HBD

Detection level

Juillerat et al (scientific report 2015)
Combining Technology Platforms

To enhance the power of the immune system against cancer

Chimeric Antigen Receptor

Enhancing Tumor Recognition

Tumor Surface

Tumor antigen

scFV

Hinge

T-Cell Surface

41BB

CD3ζ

Activation and Co-stimulatory Domains

TALEN® Gene Editing

Enhancing T-Cell Properties

TALEN

F00i (nuclease)

16 RVDs

Gene Inactivation or Knockout (KO)

‘Off-The-Shelf’ CAR T-Cells

Expanding Patient Access

Healthy donor

MNC isolation

Activation

CAR Addition / Gene Editing

Amplification

Allogeneic cell transfer

Patients

Expanding Patient Access
Towards “off-the-shelf” adoptive T-cell immunotherapy

- CAR expression to redirect T-cells to tumor antigens
- Suicide gene for safety
- TRAC disruption using TALEN® to eliminate TCR from the cell surface and avoid GvHD
- Lymphodepletion (alemtuzumab or Cy/ Flu)
- Additional gene editing
Enhancing the power of T-cells by Gene Editing

T-cell Characteristics

- Allogeneic, non alloreactive CAR T-Cells
- Resistance to chemotherapy
- Resistance to lymphodepleting agents
- Resistance to tumor inhibition
- Suppressed cross T-Cell reaction

Targeted Patient Benefits

- Off-the-shelf product (KO TCR)
- Compatible with SoC, use in combination therapies
- Enhanced engraftment (KO CD52, KO DCK)
- Enhanced efficacy (KO PD1, KO CTLA4,...)
- Better suited for specific tumors (i.e. CS1/SLAMF7, CD38)
“Off the shelf” CAR T-cell GMP Manufacturing Process

Cellectis’ Proprietary, GMP, Off-The-Shelf, Allogeneic CAR T-Cell Manufacturing Process

- On-purpose lymphocytes apheresis
- Frozen quality controlled starting material (MNCs)

Healthy Donor Leukopacks → From One Leukopack → Lentiviral Vector → Gene Editing TALEN® + Pulse Agile → Amplification X 100 → Filtration → Fill, Finish and Freeze → Stored/ Shipped to Hospitals

- Day 0 - Day 3 - Day 5 - Day 6-17 - Day 18

- CAR addition using a viral vector
- TALEN® transfer using proprietary Pulse Agile electroporation technology
- Critical step for:
  - Efficient and safe gene knock-out
  - Cell survival and expansion
  - High efficiency
  - High Yield
- Expansion of engineered cell in controlled culture systems
- Purification of TCR-negative cells
- Fill & finish and controlled rate freezing on the last day
- Full Quality Control after freezing
Efficient anti-tumor activity of “off the shelf” CAR T-cells

NSG mice treated with CAR+ T-cells, 1 or 7 days post tumor cell injection (Daudi-luc cells)
Genomic integrity of TALEN® modified T-cells

Potential offsite targets*: at close match sequences at hybrid sequences from mispairing of half nucleases

*Juillerat et al. (2014) Nucleic Acids Res. 42:5390
Genomic integrity of TALEN® modified T-cells

Detection of translocations by qPCR:

Translocations detectable at $10^{-2}$-$10^{-4}$ but no proliferative advantage
TCR\(\alpha\)-deficient T-cells do not induce GvHD

NOG mice irradiated (2.5 Gy) 1 day before T-cell injection (i.v., 30x10^6 cells)

- GvHD development occurs in all mice injected with non modified T-cells
- No clinical symptoms of GvHD were observed in mice injected with TCR\(\alpha\)-deficient T-cells.
# Pipeline

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* or European equivalent
Off the shelf/Gene edited CAR T-Cell therapy

**Genomic stability**

**Off-target cleavage**
Best method? Sensitivity?
in-silico prediction, genome wide sequencing, « DSB capture » methods

**Translocations**
qPCR assays, karyotype/FISH

**Other genomic stability assays**
IL2 independent proliferation assay

**Graft versus host disease (GvHD)**

**Lymphodepletion strategy**

**Manufacturing**
Choice of starting materials, batch to batch consistency, final product testing, product stability
THANK YOU

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