T CELL RECEPTORS TARGETING KRAS MUTANTS FOR CANCER IMMUNOTHERAPY/ADOPTIVE CELL THERAPY

SUMMARY
The National Institutes of Health (NIH) seeks research co-development or licensees for a collection of T-cell receptors (TCRs) that specifically target the mutated KRAS antigen.

REFERENCE NUMBER
E-175-2016

PRODUCT TYPE
• Therapeutics

KEYWORDS
• Kirsten Rat Sarcoma, Viral Oncogene Homolog Gene, Mutated KRAS, T-cell Receptors, TCR, Immunotherapy, Adoptive Cell Therapy, Rosenberg

COLLABORATION OPPORTUNITY
This invention is available for licensing and co-development.

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DESCRIPTION OF TECHNOLOGY
Mutations in the Kirsten rat sarcoma viral oncogene homolog (KRAS) gene are among the most common oncogenic drivers in human cancers, affecting nearly one third of all solid tumors. Point mutations in the KRAS gene most frequently affect amino acid position 12, resulting in the substitution of the native glycine (G) residue for aspartic acid (D), valine (V), cysteine (C) or arginine (R). The mutations in KRAS occur early in the process of carcinogenesis, and since only tumor cells express driver mutations, they are an attractive cancer-specific therapeutic target. However, despite decades of research into the signaling of mutated KRAS and drug-ability of these mutations with selective inhibitors, no effective therapy has been developed for these common mutated KRAS-driven cancers.

T cell receptors (TCRs) are proteins expressed on the cell surface of T lymphocytes that can recognize peptide antigens from infected and malignant cells in the context of human leukocytes antigen (HLA) molecules with exquisite specificity. Subsequent T cell activation leads to an immune response which
aims to eliminate abnormal cells. T lymphocytes that naturally lack specificity for a tumor antigen can be equipped to express a tumor antigen-specific TCR using genetic engineering. Adoptive transfer of these tumor antigen-specific TCR-engineered T cells into patients with cancer has been demonstrated as a promising cancer treatment strategy.

Scientists at the NIH have identified a collection of TCRs that specifically recognize mutated KRAS variants G12D and G12V (Table 1). These two variants are the most common KRAS driver mutations expressed by a variety of epithelial cancers, including pancreatic (70%), colorectal (36%), and lung (20%) cancer. The mutated KRAS variants are recognized by the TCRs in the context of HLA-A*11:01 or HLA-C*08:02. These TCRs are expected to eliminate human cancer cells that express both the appropriate mutated KRAS variant and HLA molecule upon adoptive transfer into patients with cancer. Furthermore, these TCRs can be used for a variety of other experimental therapeutic, diagnostic, and research applications.

**Table 1: Collection of mutated KRAS TCRs**

<table>
<thead>
<tr>
<th>No.</th>
<th>TCR (ID in Reference)</th>
<th>KRAS Variant</th>
<th>HLA Restriction</th>
<th>Epitope (variant underlined)</th>
<th>TCR Origin</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TCR (TRAV12N-3<em>01/TRBV4</em>01)</td>
<td>G12D</td>
<td>A*11:01</td>
<td>VVGAQ6VGK, 10-mer</td>
<td>Murine</td>
<td>E-028-2015</td>
</tr>
<tr>
<td>2</td>
<td>TCR (TRAV19<em>01/TRBV13-1</em>02)</td>
<td>G12V</td>
<td>A*11:01</td>
<td>VVGAQ6VGK, 10-mer</td>
<td>Murine</td>
<td>E-180-2015</td>
</tr>
<tr>
<td>3</td>
<td>TCR (TRAV3-3<em>01/TRBV4</em>01)</td>
<td>G12V</td>
<td>A*11:01</td>
<td>VVGAQ6VGK, 9-mer</td>
<td>Murine</td>
<td>E-180-2015</td>
</tr>
<tr>
<td>4</td>
<td>TCR (TRAV4<em>01/TRBV5-6</em>01)</td>
<td>G12D</td>
<td>C*08:02</td>
<td>GADGVGKSA, 10-mer</td>
<td>Human</td>
<td>E-265-2015</td>
</tr>
<tr>
<td>5</td>
<td>TCR-1 (TRAV4<em>01/TRBV5-6</em>01)</td>
<td>G12D</td>
<td>C*08:02</td>
<td>GADGVGKSA, 9-mer</td>
<td>Human</td>
<td>E-175-2016</td>
</tr>
<tr>
<td>6</td>
<td>TCR-2 (TRAV4<em>01/TRBV5-6</em>01)</td>
<td>G12D</td>
<td>C*08:02</td>
<td>GADGVGKSA, 9-mer</td>
<td>Human</td>
<td>E-175-2016</td>
</tr>
<tr>
<td>7</td>
<td>TCR-3 (TRAV4<em>01/TRBV5-6</em>01)</td>
<td>G12D</td>
<td>C*08:02</td>
<td>GADGVGKSA, 9-mer</td>
<td>Human</td>
<td>E-175-2016</td>
</tr>
<tr>
<td>8</td>
<td>TCR-4 (TRAV12-2<em>01/TRBV10-2</em>01)</td>
<td>G12D</td>
<td>C*08:02</td>
<td>GADGVGKSA, 10-mer</td>
<td>Human</td>
<td>E-175-2016</td>
</tr>
</tbody>
</table>

**POTENTIAL COMMERCIAL APPLICATIONS**
- A component of a combination immunotherapy aimed at targeting mutated KRAS-driven cancers
- An in vitro diagnostic tool to screen for cells expressing mutated KRAS in antigen detection assays
- A research tool to investigate signaling in mutated KRAS antigen expressing cells
- Use of portions of the TCRs in chimeric proteins for research and therapeutic purposes in mutated KRAS-driven cancers

**COMPETITIVE ADVANTAGES**
Highly expressed target antigens: mutated KRAS variants, particularly G12D and G12V, are frequently expressed by the most common epithelial cancers, including pancreatic (70%), colorectal (36%), and lung (20%) cancer.

Cancer-specific driver mutations: mutated KRAS variants are solely expressed by cancer cells and not by healthy tissues.

The variety of HLA-restriction elements: extends the applicability of TCRs as they recognize mutated KRAS variants in the context of multiple HLA molecules.

INVENTOR(S)
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DEVELOPMENT STAGE
Clinical

PUBLICATIONS
QJ Wang et al. "Identification of T-cell Receptors Targeting KRAS-mutated Human Tumors" [PMID:26701267]
Tran et al. "T-Cell Transfer Therapy Targeting Mutant KRAS in Cancer" [PMID:27959684]
E. Tran et al. "Immunogenicity of somatic mutations in human gastrointestinal cancers" [PMID:26516200]

PATENT STATUS
• Foreign Filed: Provisional Application No. PCT/US2015/062269 filed 24 Nov 2015
• Foreign Filed: Provisional Application No. PCT/US2016/050875 filed 9 Sep 2016
• Foreign Filed: Provisional Application No. PCT/US2017/044615 filed 31 Jul 2017

RELATED TECHNOLOGIES
• E-028-2015
• E-180-2015
• E-265-2015
• E-105-2012
• E-495-2013
• E-176-2014

THERAPEUTIC AREA
• Cancer/Neoplasm

NCI Technology Transfer Center