T Cell Receptors Targeting KRAS Mutants for Cancer Immunotherapy/Adoptive Cell Therapy

Summary (1024-character limit)
Researchers at the National Institutes of Health have identified a collection of TCRs that specifically target mutated KRAS antigen. These TCRs exclusively recognize the G12D or G12V variants of mutated KRAS, which are common hotspot driver mutations expressed by a variety of epithelial cancers, including pancreatic, colorectal and lung 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 can be used for a variety of experimental therapeutic, diagnostic and research applications.

NIH Reference Number
E-175-2016

Product Type
• Therapeutics

Keywords
• Mutated KRAS, T-cell receptors, immunotherapy, cancer, Rosenberg

Collaboration Opportunity
This invention is available for licensing and co-development.

Contact
• John D. Hewes
  NCI - National Cancer Institute

  240-276-5515

  John.Hewes@nih.gov

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 a 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 only tumor cells express driver mutations, making them an attractive cancer-specific therapeutic target. However, despite decades of research into the signaling of mutated KRAS and druggability 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 the 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 demonstrated to be 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.

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<th>Potential Commercial Applications</th>
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<td>• A component of a combination immunotherapy aimed at targeting mutated KRAS-driven cancers</td>
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<td>• An in vitro diagnostic tool to screen for cells expressing mutated KRAS in antigen detection assays</td>
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<td>• A research tool to investigate signaling in mutated KRAS antigen expressing cells</td>
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<td>• Use of portions of the TCRs in chimeric proteins for research and therapeutic purposes in mutated KRAS-driven cancers</td>
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<th>Competitive Advantages</th>
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<td>• 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.</td>
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<td>• Cancer-specific driver mutations: mutated KRAS variants are solely expressed by cancer cells, and not by healthy tissues.</td>
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<td>• Variety of HLA-restriction elements: extends the applicability of TCRs as they recognize mutated KRAS variants in the context of multiple HLA molecules.</td>
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Inventor(s)
Q. Wang, Z. Yu (NCI), K. Hanada (NCI), J. Yang (NCI), E. Tran (NCI), Y.-C. Lu (NCI), A. Pasetto (NCI), P.F. Robbins (NCI), Z. Zheng (NCI), S.A. Rosenberg

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
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• Foreign Filed: - Patent Application PCT/US2017/044615, Filed 31 Jul 2017
• Foreign Filed: - Patent Application PCT/US2018/051641, Filed 19 Sep 2018
• Foreign Filed: - Patent Application PCT/US2018/063581, Filed 03 Dec 2018
• U.S. Provisional: U.S. Provisional Patent Application Number 62/749,750, Filed 24 Oct 2018
• U.S. Provisional: U.S. Provisional Patent Application Number 62/795,203, Filed 22 Jan 2019

Related Technologies
• E-028-2015
• E-180-2015
• E-265-2015
• E-105-2012
• E-495-2013
• E-176-2014
• E-181-2016
• E-239-2017
• E-166-2018
• E-029-2019

Therapeutic Area
• Cancer/Neoplasm

NCI Technology Transfer Center https://techtransfer.cancer.gov/pdf/e-175-2016.pdf