CORRESPONDENCE

T-Cell Transfer Therapy Targeting Mutant KRAS

TO THE EDITOR: Tran et al. (Dec. 8 issue)[1] describe a remarkable case of a patient with metastatic colorectal cancer treated with autologous T cells specific for mutant KRAS G12D and restricted to the major histocompatibility complex class I allele HLA-C*08:02. The authors hypothesize that in the United States alone, thousands of patients per year may be eligible for T-cell–based immunotherapy targeting KRAS G12D. To estimate how common this opportunity may be, we identified 151 patients with *KRAS* G12D mutations out of 6125 patients in the Cancer Genome Atlas. Of these, only 4 had the HLA-C*08:02 allele as determined by a validated computational method.[2,3]

We then investigated immune activity in tumor samples using established gene signatures.[4,5] Comparing *KRAS* G12D–positive tumors with disease-matched *KRAS* wild-type tumors, we found no evidence of unique immune activity. Nor did we find evidence of unique immune activity in patients with the HLA-C*08:02 allele, regardless of *KRAS* mutation status.

Immunotherapy targeting KRAS G12D in patients with the HLA-C*08:02 allele appears to be an important but rare opportunity. Evaluation of other *KRAS* mutations and alleles is warranted.

Andrew J. Rech, Ph.D.
Robert H. Vonderheide, M.D., D.Phil.

University of Pennsylvania
Philadelphia, PA
rhv@upenn.edu

No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Tran and colleagues note that thousands of patients per year in the United States could be eligible for T-cell–based immunotherapy targeting KRAS G12D. We agree. In our National Institutes of Health–funded, population-based study, we have characterized 4346 colorectal adenocarcinomas since 1998.[1] To date, the prevalence of *KRAS* mutations is 1441 of 4346 (33.2%), with 37.9% of the *KRAS*-positive tumors harboring G12D mutations. HLA typing available for 3734 patients shows that 687 (18.4%) have at least one copy of HLA-C*08:02. We found that 85 of 3734 patients (2.3%) with colorectal cancer share the same HLA type and *KRAS* mutation as described by Tran et al. We have also sequenced the T-cell receptor (TCR) beta chain of tumor-infiltrating lymphocytes to characterize the adaptive immune response in 295 tumors so far, in addition to expert pathological assessment.[2] We detected 6338 shared TCR-β sequences among 2 or more patients, including 5 TCR-β sequences uniquely shared among patients with tumors positive for *KRAS* G12D and HLA-C*08:02 and 7 TCR-β sequences also shared by patients with *KRAS* G12D and HLA-C*08:02

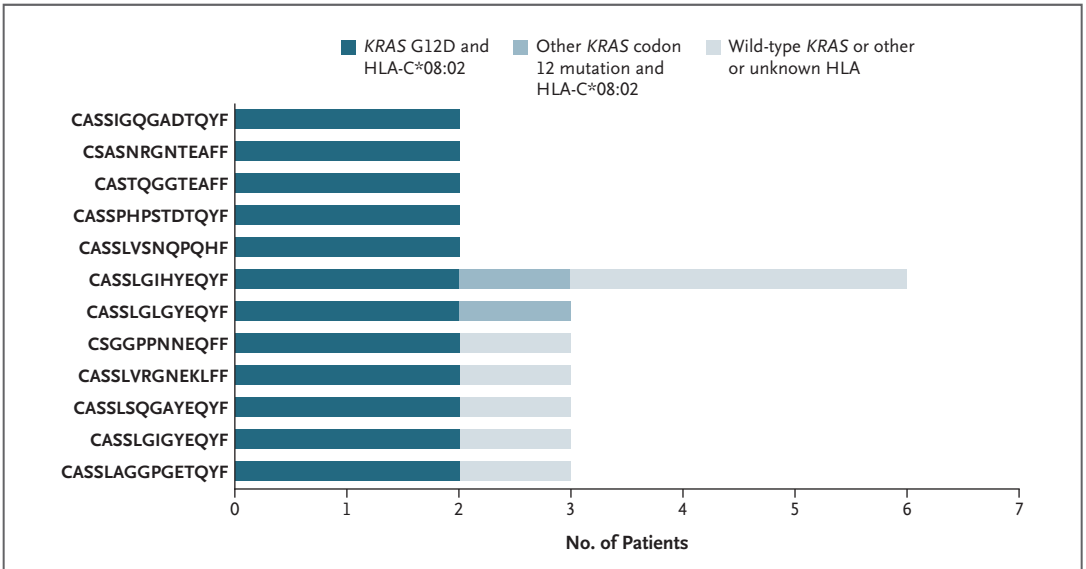

Figure 1. Patients with Shared T-Cell Receptor β Sequences Whose Tumors Harbor *KRAS* Mutations Presented by HLA-C*08:02.

and other combinations of *KRAS* mutations and HLA (Fig. 1).

Asaf Maoz, M.D.

USC Norris Comprehensive Cancer Center
Los Angeles, CA

Gad Rennert, M.D., Ph.D.

Technion Carmel Medical Center
Haifa, Israel

Stephen B. Gruber, M.D., Ph.D.

USC Norris Comprehensive Cancer Center
Los Angeles, CA
sgruber@usc.edu

No potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: The data cited by Rech and Vonderheide in their letter are not consistent with the frequency of HLA-C*08:02 and of the *KRAS* G12D mutation in the U.S. population. The frequencies of the *KRAS* G12D mutation are highest in pancreatic, colorectal, and lung adenocarcinomas, being present in approximately 40%, 12%, and 4% of each of these tumor types, respectively.[1] There were approximately 373,000 estimated new cases and 249,000 deaths in the United States in 2016 due to these cancers,[2] and the frequency of HLA-C*08:02 is approximately 8% in U.S. whites and blacks.[3] Therefore, the number of cases and deaths in the United States in 2016 in patients bearing these tumor types expressing the *KRAS* G12D mutation and HLA-C*08:02 are estimated to be approximately 3300 and 2300, respectively. Our colleagues in the Surgery Branch of the National Cancer Institute (NCI) have also identified T-cell receptors that target *KRAS* G12D–mutated and *KRAS* G12V–mutated epitopes in the context of HLA-A*11:01,[4] an HLA class I allele expressed in approximately 14% of whites, which may enable KRAS to be targeted in a larger number of patients.

Furthermore, of the 61 gastrointestinal tract tumors analyzed by whole-exome sequencing in the NCI Surgery Branch, 15 expressed the *KRAS* G12D mutation, 6 expressed HLA-C*08:02, and 2 expressed the *KRAS* G12D mutation plus HLA-C*08:02 (Table 1). These results are similar to those observed in the population studies described above.

The article by Rooney et al. that is cited by Rech and Vonderheide provided evidence for an association between "established" gene signatures that relied on measurement of "local immune infiltrates," as determined by evaluation of granzyme A and perforin expression, and the num-

Table 1. Prevalence of *KRAS* G12D Mutation and HLA-C*08:02 among Patients Evaluated in the Surgery Branch of the National Cancer Institute.

Type of Cancer	Positive for *KRAS* G12D	Positive for HLA-C*08:02	Positive for *KRAS* G12D and HLA-C*08:02
	number of patients/total number (percent)		
Pancreatic	2/5 (40)	0/5	0/5
Colon	8/28 (29)	4/28 (14)	2/28 (7)
Rectal	3/7 (43)	1/7 (14)	0/7
Biliary tract	2/17 (12)	1/17 (6)	0/17
Gastric	0/4	0/4	0/4
Non–small-cell lung	0/9	1/9 (11)	0/9

ber of predicted HLA-binding mutant peptides, but it did not provide any information on bona fide T-cell responses to those candidate antigens. Although tumors in that study that possessed fewer than 200 nonsynonymous somatic mutations generally appeared to have relatively low cytolytic activity, we have consistently identified neoepitope-reactive T cells in patients with gastrointestinal cancer, all of whose tumors possessed fewer than 200 nonsynonymous somatic mutations.[5]

Steven A. Rosenberg, M.D., Ph.D.
Eric Tran, Ph.D.
Paul F. Robbins, Ph.D.
National Cancer Institute
Bethesda, MD
sar@nih.gov

Since publication of their article, the authors report no further potential conflict of interest.

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