154. Adoptive T cell therapy for cancer
(University of Pennsylvania)

▶ Asset Overview

Product Type	Cell therapy
Disease Area	Oncology
Indication	Cancer
Current Stage	Lead Optimization
Target	Mutant KRAS epitopes
MoA	Adoptive transfer of mKRAS-TCR engineered CD8+ T cells leads to tumor eradication.
Brief Description	• Using blood samples form healthy donors and cancer patients, the team has devised a platform to identify and isolate TCR sequences that bind to peptide-HLA class I complexes with high specificity and potency for mKRAS. • Based on this knowledge, the team has developed a novel mKRAS cancer vaccine (currently being tested in an actively enrolling clinical trial) and has also advanced the data set needed to file an IND for mKRAS TCR-based adoptive T cell clinical trial. • In addition, knowledge of these immunogenic peptide-HLA complexes has driven the development of novel laboratory tools useful for discovery and patient assessment, such as reporter cell lines and dextramers. • The platform and approach is deployable for isolating TCRs specific for other mutated oncogenes, beyond KRAS
Intellectual Property	WO2020154617A1
Publication	Biochemical and functional characterization of mutant KRAS epitopes validates this oncoprotein for immunological targeting. Nat Commun, (2021)
Inventors	Adam BEAR, Robert Vonderheide, Gerald LINETTE, Beatriz Carreno

▶ Highlights

- Specific to tumor-associated KRAS mutants
- Does not affect healthy cells expressing wild-type KRAS
- Applicable for novel cancer vaccines
- Applicable for novel engineered adoptive T-cell therapy

▶ Key Data

Summary table of mKRAS-TCRs

ID	Epitope	Restriction	Vα	Vβ	CDR3α	CDR3β
TCRA3V	7-16V	A*03:01	TRAV19, TRAJ40	TRBV9, TRBD1, TRBJ2-5	CALSEAGTYKYIF	CASSVAGGGQETQY
TCRA11V	7-16V	A*11:01	TRAV12-1, TRAJ8	TRBV28, TRBD2, TRBJ2-7	CAVNPPDTGFQKLVF	CASSLSFRQGLREQYF
TCRB7R	10-19R	B*07:02	TRAV4, TRAJ41	TRBV7-2, TRBJ1-2	CLVGDFNSNSGYALNF	CASKVYGYTF

TCRs were identified following TCRVα and TCRVβ sequencing of flow cytometrically sorted p-HLA+/CD8+ T cells derived from cultures shown in Fig. 2b–d with CDR3 amino acid sequences specified.

Adoptive transfer of mKRAS-TCR T cells leads to in vivo eradication of KRAS G12V+ tumor cells
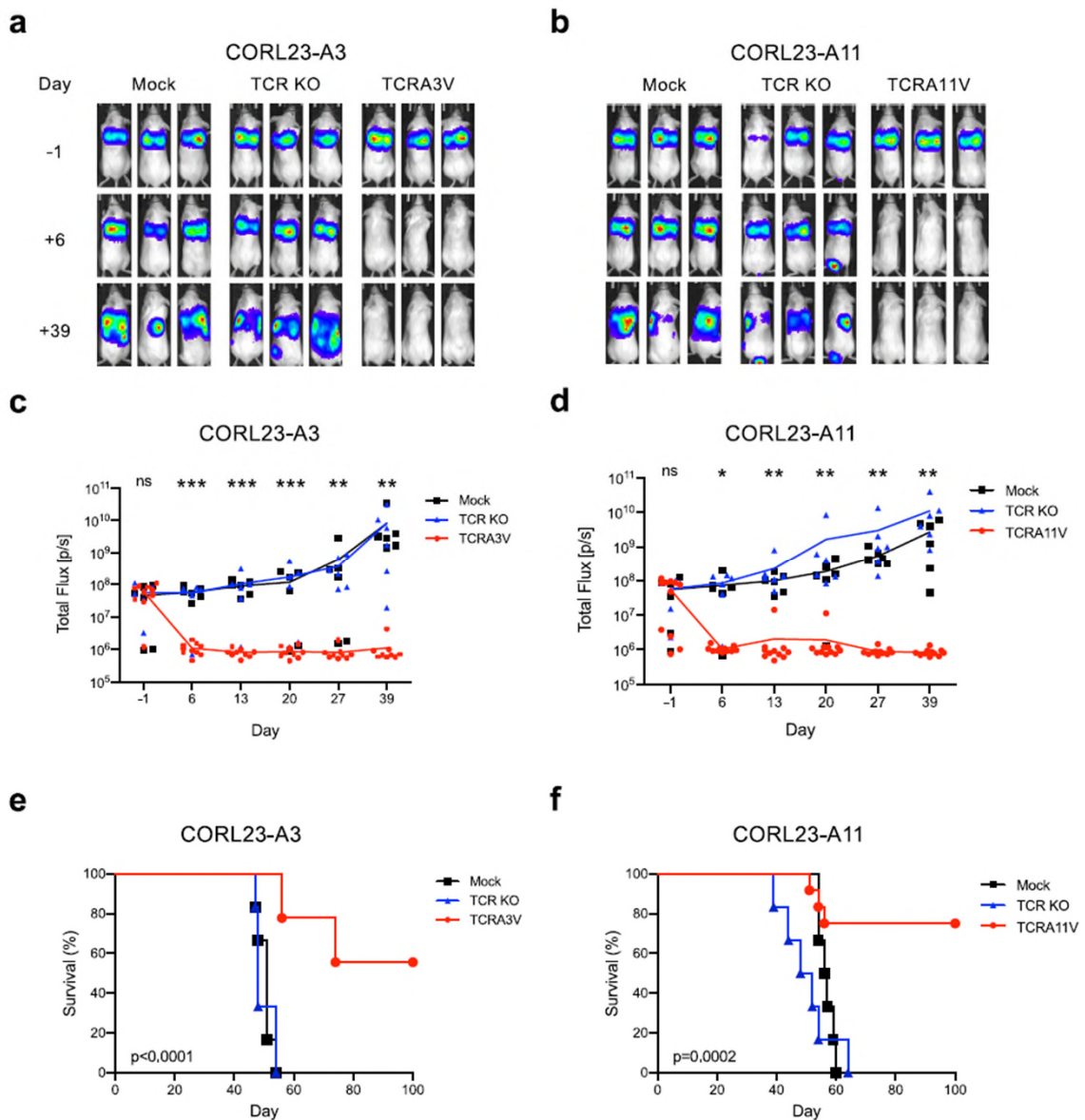
To be continued

▶ Key Data

Adoptive transfer of mKRAS-TCR T cells leads to in vivo eradication of KRAS G12V+ tumor cells

Adoptive transfer of mKRAS-TCR T cells leads to in vivo eradication of KRAS G12V+ tumor cells in a xenograft model of metastatic lung cancer.

CORL23-A3 or CORL23-A11 tumors expressing CBR luciferase were engrafted into NSG mice via intravenous tail vein injection. Mice were left untreated (Mock) or treated with TCR $\alpha\beta$ null (TCR KO) or mKRAS-TCR engineered CD8+ T cells 4 days after tumor engraftment. Tumor burden was assessed by bioluminescence imaging before and after treatment, and overall survival was monitored over time. Representative bioluminescence imaging prior to and following treatment of NSG mice bearing a CORL23-A3 pulmonary tumors treated with TCRA3V T cells and b CORL23-A11 pulmonary tumors treated with TCRA11V cells compared to control groups. Total Flux quantification over time of c CORL23-A3 and d CORL23-A11 tumor-bearing mice as shown in (a) and (b). Colored lines represent mean Total Flux values over time with individual data points corresponding to treatment groups presented as indicated in the figure legend. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$; one-way ANOVA followed by Tukey's HSD post-test comparing Mock and TCRA3V or TCRA11V treated mice. No statistical difference was observed between Mock and TCR KO treated mice. Kaplan–Meier analysis of overall survival of e CORL23-A3 and f CORL23-A11 tumor-bearing mice. Colored lines correspond to treatment groups as indicated in the figure legend. p values as indicated; log-rank testing comparing Mock and TCRA3V or TCRA11V treated mice. No statistical difference was observed between Mock and TCR KO treated mice. Number of mice in representative experiment is as follows: CORL23-A3 Cohort—Mock (n = 6), TCR KO (n = 6), TCRA3V (n =10). CORL23-A11 Cohort—Mock (n = 6), TCR KO (n = 6), TCRA11V (n = 12). Source data are provided as a Source Data file.