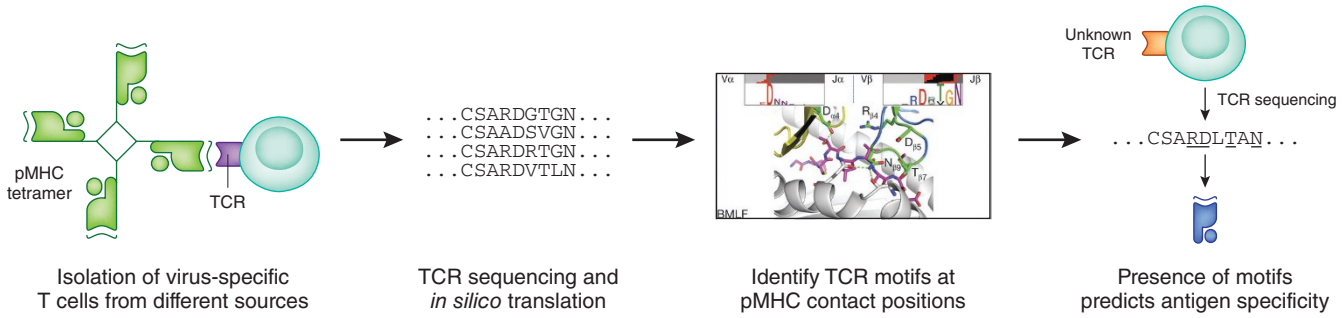

Figure 1 Predicting T cell antigen specificity from TCR sequence. T cells bearing TCRs that recognize a specified pMHC epitope are isolated by tetramer sorting or related methods. The TCRs are sequenced, translated *in silico*, and inspected for the presence of conserved motifs at pMHC contact positions inferred from structural data. Subsequently, any new T cell found to harbor these same motifs is predicted to recognize the same epitope as that seen by the original tetramer-sorted T cells. In future, building a comprehensive database of epitope-associated TCR motifs will greatly facilitate interpretation of the T cell repertoire.

peptide epitopes[5]. Here, Glanville *et al.*[2] define a new route to mimic TCRs, which, in a manner analogous to heteroclitic peptides, may yield more effective immunotherapies than natural TCRs.

Given these important advances, what's next? We now have version 1.0 of a pMHC–TCR map covering a few common epitopes from common viruses. Epitope and TCR landscapes remain vast, but it is not unreasonable to expect that methodical efforts to sort, sequence and cluster epitope-specific TCRs could lead to the establishment of a growing data resource. In principle, such a resource should reach a size sufficient for predicting the antigen specificity of any new TCR sequence obtained, and perhaps, as suggested by Dash *et al.*[1], support the development of a general model of TCR–pMHC recognition. It is important to bear in mind, however, that TCR–pMHC interactions are promiscuous. One pMHC can be recognized by many different TCRs, which is the basis of the present studies, but a single TCR can also recognize many different epitopes[6]. Promiscuity is essential because it allows finite numbers of T cells to confer broad immune protection, but it does complicate things. It is perhaps time to retire the notion of T-cell specificity in its conventional sense and to begin conceptualizing, defining, modeling and visualizing pMHC–TCR interactions as dynamic networks, with the goal of defining connectivity and context dependency at ever-higher resolution. With a data resource of that level of sophistication, we will be well-positioned to engineer T-cell immunity rationally and effectively.

COMPETING FINANCIAL INTERESTS
The author declares no competing financial interests.

1. Dash, P. *et al. Nature* **547**, 89–93 (2017).
2. Glanville, J. *et al. Nature* **547**, 94–98 (2017).
3. Woodsworth, D.J., Castellarin, M. & Holt, R.A. *Genome Med.* **5**, 98 (2013).
4. Altman, J.D. *et al. Science* **274**, 94–96 (1996).
5. Adegoke, A.O. & Grant, M.D. *Front. Immunol.* **6**, 377 (2015).
6. Wooldridge, L. *et al. J. Biol. Chem.* **287**, 1168–1177 (2012).

Research Highlights

Papers from the literature selected by the Nature Biotechnology editors. (Follow us on Twitter, @NatureBiotech #nbtHighlight)

Classification of common human diseases derived from shared genetic and environmental determinants
Wang, K., Gaitsch, H., Poon, H., Cox, N.J. & Rzhetsky, A. *Nat. Genet.* doi:10.1038/ng.3931 (2017)

Dual ifgMosaic: a versatile method for multispectral and combinatorial mosaic gene-function analysis
Pontes-Quero, S. *et al. Cell* **170**, 800–814.e18 (2017)

Identification of essential genes for cancer immunotherapy
Patel, S.J. *et al. Nature* doi:10.1038/nature23477 (2017)

***In vivo* CRISPR screening identifies *Ptpn2* as a cancer immunotherapy target**
Manguso, R.T. *et al. Nature* **547**, 413–418 (2017)

Simultaneous epitope and transcriptome measurement in single cells
Stoeckius, M. *et al. Nat. Methods* doi:10.1038/nmeth.4380 (2017)

Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade
Le, D.T. *et al. Science* **357**, 409–413 (2017)