# Genomic and bioinformatic profiling of mutational neoepitopes reveals new rules to predict anticancer immunogenicity

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The mutational repertoire of cancers creates the neoepitopes that make cancers immunogenic. Here, we introduce two novel tools that identify, with relatively high accuracy, the small proportion of neoepitopes (among the hundreds of potential neoepitopes) that protect the host through an antitumor T cell response. The two tools consist of (a) the numerical difference in NetMHC scores between the mutated sequences and their unmutated counterparts, termed the differential agretopic index (DAI), and (b) the conformational stability of the MHC I–peptide interaction. Mechanistically, these tools identify neoepitopes that are mutated to create new anchor residues for MHC binding, and render the overall peptide more rigid. Surprisingly, the protective neoepitopes identified here elicit CD8-dependent immunity, even though their affinity for Kd is orders of magnitude lower than the 500-nM threshold considered reasonable for such interactions. These results greatly expand the universe of target cancer antigens and identify new tools for human cancer immunotherapy.

We applied our method to mutliple independent tumors. In actuality, the pipeline, including the DAI algorithm, was first derived empirically on the data from Meth A tumor cell line, and was then tested on CMS5 cell line. The antitumor activity predicted from the DAI algorithm was significantly stronger in CMS5 than in Meth A. This variation is most likely a reflection of the immuno-suppressive mechanisms unique to the Meth A tumor and thus unrelated to the merits of the DAI algorithm per se. The DAI algorithm has since been tested in yet another mouse tumor, the B16 melanoma, and data on T cell responses in this line as well, are consistent with significant superiority of DAI over NetMHC alone. Although the present study is focused on identification of MHC I–restricted epitopes of CD8 T cells, the analysis can also be extended to MHC II-restricted epitopes of CD4 T cells.