Curatopes Melanoma – FAQ & Tutorial

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1. What is Curatopes?

Curatopes is a database of peptides which may be used for therapeutic vaccination against metastatic melanoma. It covers peptide candidates for 36 HLA class I alleles found commonly in the Caucasian population gene pool.

2. How is Curatopes different from existing databases on antigenic genes and peptides in tumors, e.g. CAPED[1] or CTDatabase[2]?

The existing databases on tumor antigens list genes that were identified experimentally as tumor markers, e.g. for melanoma. Curatopes takes a different, complementary approach and features peptides whose genes were selected through a prediction algorithm based on a combination of melanoma high-throughput expression data and large-scale expression databases for healthy tissues. Our analysis pipeline also scores the peptides to distinguish favorable and non-favorable candidates for therapeutic vaccination.

3. What is the point of incorporating each gene's expression in healthy tissue into the analysis?

In anticancer vaccination, the peptides that are supposed to fight the tumor cells might also be presented by healthy tissues. This can give rise to autoimmune side-effects and life-threatening tissue damage in patients. Hence, we tried to minimize the number of possible off-targets in our database by discarding genes expressed in healthy tissue and peptides whose sequence also appears in those genes. This way, we strive to make sure that the included peptides are as specific to melanoma as possible.

4. How do I know which peptides are good candidates?

The immunogenicity, i.e. the ability to trigger a significant immune response, of a given peptide is difficult to predict. In the first step, we use established tools to predict a peptide's HLA class I binding profile. In a second step, we derive a score from major immunoproperties of the epitopes and the peptide's expression in healthy tissues. The best peptides have a high score (the maximum is 100) because they combine sufficient expression in melanoma with low or absent expression in healthy tissue and favorable immunoproperties, which will allow them to effectively stimulate the anti-tumor response while being well-tolerated by the patient's body.

5. Have some of the epitopes in the database been validated?

We have not yet performed any experiments with the epitopes (please also see the Curatopes disclaimer online). By providing open access to the database, we hope to stimulate a discussion about guidelines for epitope selection.

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[1] https://caped.icp.ucl.ac.be/
[2] http://www.cta.lncc.br/

Figure 1. Overview screenshot of the Curatopes Melanoma web interface. The entry of "mage" into the upper left search box has highlighted tabs with matching genes in red color, in this case MAGE family member MAGE-A3 in the Superior tolerance (predicted) *and* All predicted epitopes *tabs.*

6. I have HLA profiles for my patients and would like to select some matching epitopes for them.

In the first step, you would decide how stringent you want to be in terms of peptide tolerability; this decision guides which of the four tables you are going to inspect (Figure 1). *Superior tolerance* epitopes are predicted to cause the least amount of dangerous autoimmune reactions, while those with *Enhanced tolerance* carry a higher risk. This is reflected in the number in the *Collateral Critical Tissue Targets* column – the higher it is, the more critical tissues surpass the expression threshold (see item 8 below for details) for the respective *Gene of Origin*.
Alternatively, you can browse or download the *All predicted epitopes* table to filter the whole set of Curatopes epitopes according to your own criteria.
The genes in the *Known melanoma epitopes* table did technically not pass the Curatopes filters, so we avoid making assumptions about them.

Once you have selected which table(s) to use, click on the corresponding tab to bring up the table. You can then filter the *HLA allele* column for the alleles in your profiles (Figure 2). This will reduce the visible records to the matching set of peptides.
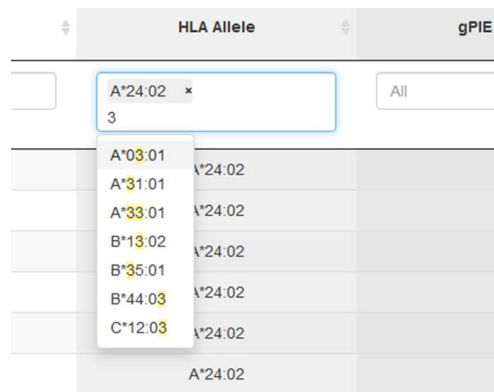
Figure 2. The HLA Allele *column filter. In the screenshot detail, allele A*24:02 is selected. Additional alleles can be selected from the dropdown list, which can be filtered by typing part of the allele identifier.*

7. Instead of an HLA profile, I have my gene(s) of interest and want to select some epitopes for them – how do I go about that?

If you have a clear idea of which genes interest you, use the search box in the left upper corner of the table area to highlight tables with genes matching your input. You can then click on any of the highlighted tabs and select the respective gene or genes by filtering the first column (*Gene of Origin*). If you target a specific HLA profile, you can also select the respective alleles in the *HLA allele* column filter and refine your selection as described in the answer to the previous question.

Note: Please keep in mind that the total number of genes in the database is 50 and thus rather small. The complete list of genes from which epitopes where predicted can be seen in the documentation.

8. Can you explain the four tables in more detail?

The database harbors three dedicated tables and one overview table:
- The *Superior tolerance* tab features 15 filtered genes which are expressed no higher than 10 TPM in all the tissues contained in the critical tissue list. From these genes, the top three peptides (by our scoring method) for each HLA allele are listed.
- The *Enhanced tolerance* tab contains the 20 filtered genes whose expression surpasses 10 TPM in at least one critical tissue. Accordingly, one would expect a higher likelihood of adverse immune reactions than for the epitopes in the superior-tolerance tab. Like in the superior-tolerance tab, the top three peptides (by our scoring method) for each combination of gene of origin and HLA allele are listed.
- The *Known melanoma epitopes* tab lists a collection of epitopes from the CAPED database. They are provided as a reference to previous efforts to identify good epitopes. Note that none of these epitopes met the Curatopes tolerability criteria.
- In addition, there is one tab that lists all epitopes we predicted and scored from the 35 genes that survived the Curatopes filters (*All predicted epitopes*).

The tables are sorted by decreasing gPIE score when you first load them and can be sorted by any other column. The *Make additional columns visible* button brings up columns with the numerical features that we used in the Curatopes filtering pipeline. A deeper inspection of the genes and transcripts of origin is available through links to GeneCards and Ensembl.

9. I have no specific target and simply want to browse the database.

In this case, you can take a look at the included genes and HLA alleles in the documentation and decide whether some of them tickle your fancy. You can also download complete tables by clicking the corresponding button at the bottom of the page.