Systems And Methods For Generating Class 1 Major Histocompatibility Complex Multimer Screening Reagents Using Chaperone Mediated Peptide Exchange

Tech ID: 32985 / UC Case 2018-408-0

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OTHER INFORMATION

KEYWORDS

MHC-I, Class I MHC, Antigenic peptide, Peptide receptive MHC, MHC multimers, MHC tetramers, MHC multimer reagents, MHC tetramer reagents, MHCI, Major Histocompatibility Complex, Class I, HLA-A*24, HLA-A*68, HLA-A*2, H-2D, H-2L, chaperone, TAPBPR

CATEGORIZED AS

- **Materials & Chemicals**
  - Biological
- **Research Tools**
  - Reagents

RELATED CASES

2018-408-0, 2020-251-0, 2020-284-0, 2020-297-0, 2019-975-0

BACKGROUND

MHC Class I multimers are key reagents that are used in the identification of antigen specific T cells + an antigenic peptide. The most useful form of such a reagent involves a Class I MHC molecule that is provided ready to be loaded with an antigenic peptide of interest. However, such molecules are inherently unstable.

Potential solutions to the instability have major drawbacks. Some MHC Class I molecules are provided with a conditional ligand that can be cleaved by exposure to UV light. These constructs are prone to aggregation and precipitation, must be stored and worked with in the dark, and they can have relatively poor peptide exchange efficiency. Other peptide receptive MHC class I molecules are engineered to have disulfide links holding the peptide to the MHC-I binding groove. In addition to altering natural peptide-MHC-I binding, such molecules are diffficult to express in bacterial vectors.

TECHNOLOGY DESCRIPTION

UC Santa Cruz researchers and the Office of Innovation Transfer have collaborated to produce a robust patent portfolio around a new method of producing peptide receptive class I MHC multimers that produce MHC-I molecules at a high yield with highly efficient peptide exchange.

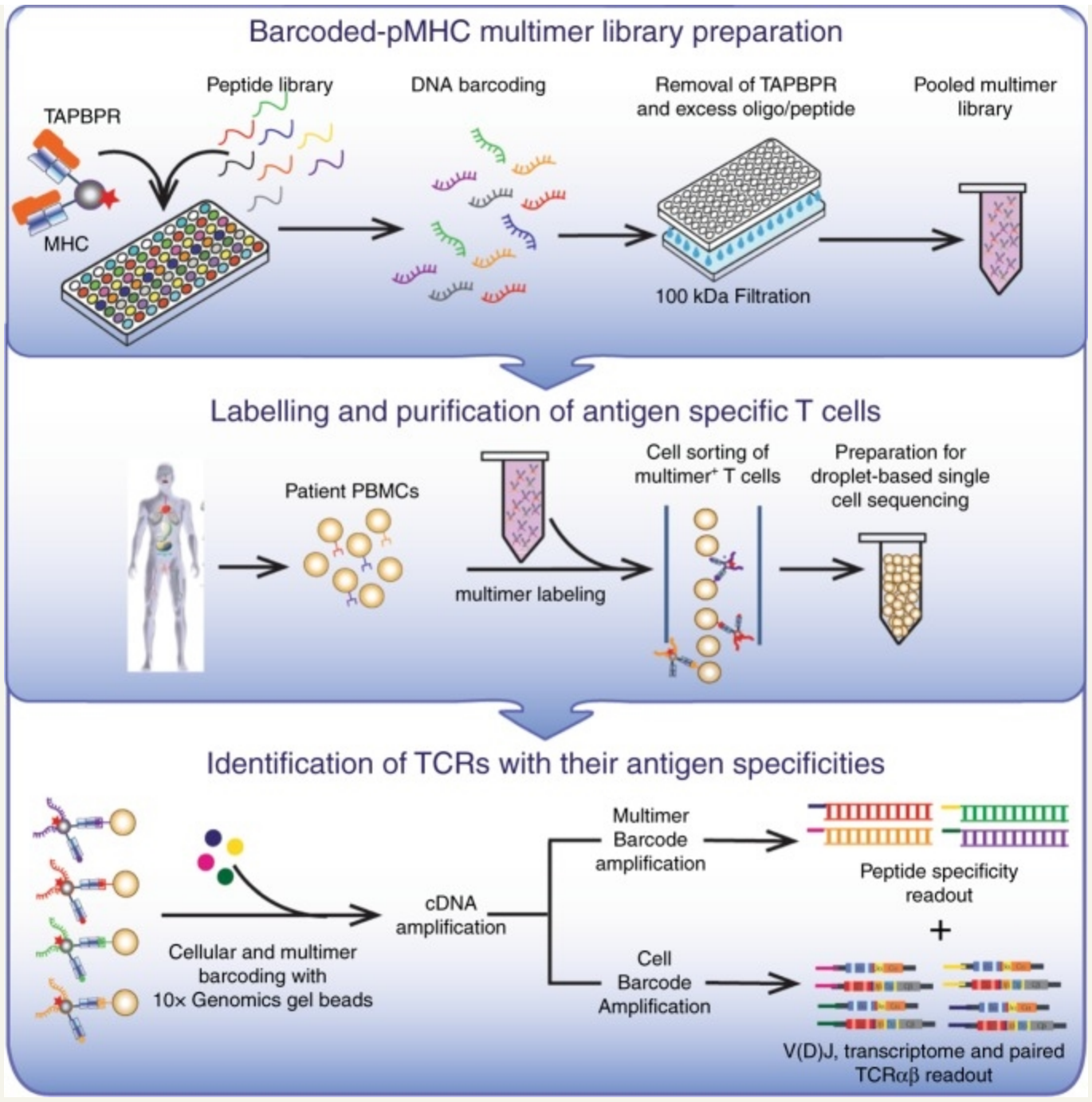
This system involves expression of MHC class I heavy chains and light chains in bacteria. The heavy chains and light chains are refolded in the presence of placeholder peptide and the chaperone TAPBPR. The placeholder peptide is a peptide with a Tm value of the particular MHC class I epitope that is below 50 degrees Celsius.

The system has advantages over other systems in that it provides greater MHC-I protein expression in E. coli cells but also provides more efficient peptide exchange. Existing systems can only do one. Result is 5-10x yield in total peptide-MHC compared to other systems

	Photosensitive Peptide	Disulfide Mutant	TAPBPR
Yield/Liter of refolding	4.0 +/- 0.5 mg	0.5 +/- 0.2 mg	5.0 +/- 1.5 mg
Peptide exchange efficiency	30-40%	80-90%	80-90%
Total pMHC yield	1.6 mg	0.4 mg	4 mg

Any MHC can be adapted to this technique. Specific placeholder peptides are provided for HLA-A*02, H-2D, and H-2L.

DNA barcoded MHC-I molecules can readily be prepared to better pair TCR sequence with antigen specificity:



Related inventions:

2019-975 - a system that uses peptide receptive MHC-I made using TAPBPR to purify a antigenic peptides from a peptide library. The peptides bind to immobilized peptide receptive MHC-I conjugated to a column, then are later eluted.

2020-284 - specific placeholder peptides and methods for creating peptide receptive HLA-A*68:02 and HLA*A24:02

2020-297 - an invention resulting from the surprising result that TAPBPR acts catalytically on MHC-I/placeholder peptide complexes to form peptide receptive MHC-I. A 1:10,000 ration of TAPBPR:MHC-I placeholder peptide produces peptide receptive MHC-I as efficiently as a 1:1 ratio.

2020-251 - co-expression of TAPBPR with MHC-I in mammalian cells. This has the following advantages: (a) placeholder peptides are not needed, (b) peptide receptive MHC-I can be purified directly from the culture, (c) the MHC-I molecules are glycosylated as they would be in a mammalian immune system.

APPLICATIONS

Peptide-receptive MHC-I multimer reagents

MHC-I reagents

Identifying antigenic peptides

Identifying and purifying T cell populations

ADVANTAGES

Peptide receptive MHC-I is provided - user can select the peptide

More efficient MHC-I expression than other methods

More efficient peptide exchange than other methods

More biologically accurate (no engineered disulfide bonds)

Easier to make (no need to work in the dark)

INTELLECTUAL PROPERTY INFORMATION

Country	Type	Number	Dated	Case
United States Of America	Published Application	20230059548	02/23/2023	2019-975
European Patent Office	Published Application	EP 4 136 098	02/22/2023	2020-284
European Patent Office	Published Application	4085069	11/09/2022	2019-975
European Patent Office	Published Application	4085068	11/09/2022	2020-297
European Patent Office	Published Application	402841.2	07/20/2022	2020-251
United States Of America	Published Application	20210371499	12/20/2021	2020-284
United States Of America	Published Application	20210155670	05/27/2021	2020-251
United States Of America	Published Application	20210079461	03/18/2021	2018-408

Additional Patent Pending

RELATED MATERIALS

- High throughput pMHC-I tetramer library production using chaperone-mediated peptide exchange - 04/20/2020
- Molecular determinants of chaperone interactions on MHC-I for folding and antigen repertoire selection - 12/03/2019

RELATED TECHNOLOGIES

- Systems And Methods For The Preparation Of Peptide Receptive Mhc-I/Chaperone Complexes With Native Glycan Modifications

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