P1.129
The 37th EPS and 14th IPS Symposia

Epitope-directed peptide screening and machine learning for HER2-targeted antibody-mimetic peptides

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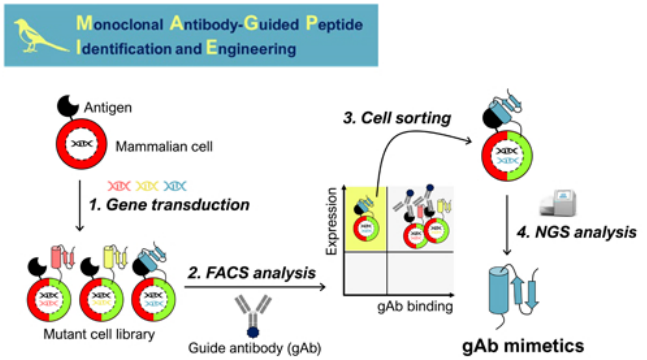
https://doi.org/10.17952/37EPS.2024.P1129

INTRODUCTION

Small antibody mimetics can serve as lower cost alternatives to current monoclonal antibody drugs. Recently, we developed an epitope-directed peptide screening system called Monoclonal Antibody-Guided Peptide Identification and Engineering (MAGPIE) screen [1]. In this system, candidate peptides are bound to antigens on the mammalian cell surface by displaying peptide library on antigen-expressing cells, followed by evaluation of their epitope by a fluorescently labelled guide antibody (gAb) that bind to the desired epitope.

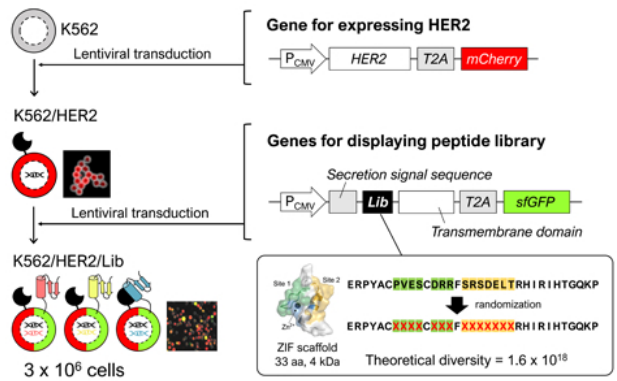
The current study described the development of human epidermal growth factor receptor 2 (HER2)-targeted antibody-mimetic peptides using a combination of MAGPIE screen and machine learning.



RESULT

1. Construction of mutant cell library

Cells coexpressing HER2 and peptide library were constructed by lentiviral gene transduction.

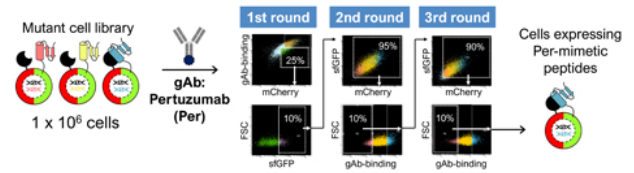


Mutant cell library was constructed.

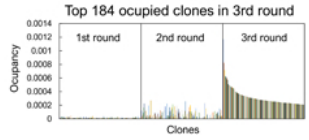
2. MAGPIE screen of Pertuzumab-mimetic peptides

Cells expressing Pertuzumab-mimetic peptides were sorted with gAb and their sequences and affinity were analyzed.

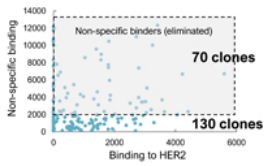
1. Cell sorting with gAb



2. NGS analysis



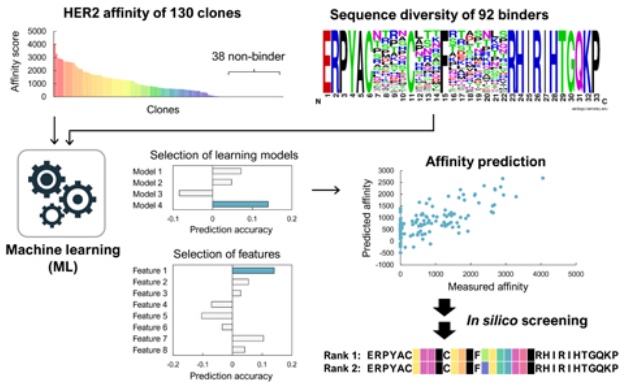
3. Binding to HER2 (ELISA)



130 clones were identified.

3. Prediction of high-affinity peptides

Prediction model for Per-mimetic peptides was constructed by machine learning using HER2 affinity and sequences of 130 clones as training data.

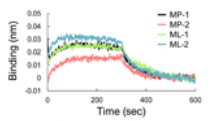


Two candidate peptides were predicted.

4. Characterization of predicted peptides

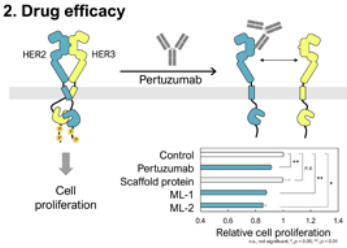
Affinity and drug efficacy of predicted peptides were evaluated by biolayer interferometry and cell proliferation assay, respectively.

1. Affinity



	K_D (nM)	k_{on} (10^4 $M^{-1}s^{-1}$)	k_{off} (10^{-2} s^{-1})
MP-1	35.9	53.0	1.90
MP-2	252	9.14	2.30
ML-1	**5.88**	125	0.735
ML-2	**7.39**	177	1.31

2. Drug efficacy



Predicted peptides had high binding affinity and good drug efficacy.

CONCLUSION and PROSPECTS

1. MAGPIE screen could identify many antigen-binding peptides with various affinities and sequences.
2. Predicted peptides had high binding affinity and good drug efficacy like Pertuzumab.
3. Smart design can be used with any available mAbs.

[Ethics] All recombinant DNA experiments were performed with approval of the recombinant DNA advisory committees of Tokyo Institute of Technology (No. I2016020, I2021017).
[COI] We have no financial relationship to disclose.

PUBLICATION

1. "Antibody-guided design and identification of CD25-binding small antibody mimetics using mammalian cell surface display", *Sci Rep*, **11 (1)**, 22098 (2021)
2. PCT/JP2022/39963

[Acknowledgement]
We thank the FACS Core Laboratory at the Institute of Medical Science, University of Tokyo for providing us with technical assistance in operating flow cytometer. This study was supported by AMED under Grant Numbers JP19am0401023h0001, JP20am0401023h0002, JP21am0401023h0003, and JP22am0401023h0004.