北京大学
PEKING UNIVERSITY

The Bioinformatic Analysis of Programmed Cell Death Protein 1 (PD-1)

程序性死亡蛋白1的生物信息学分析

Rui Zhang

copyright 2007 peking university visual identity system

北京大学
PEKING UNIVERSITY

The Discovery of PD1

- Function: Inhibitory cell surface receptor involved in the regulation of T-cell function during immunity and tolerance. Upon ligand binding, inhibits T-cell effector functions in an antigen-specific manner. Possible cell death inducer, in association with other factors (from Uniprot).
- PD1 was first cloned from 2B4.11 (a murine T-cell hybridoma). (Ishida, Agata et al. 1992)
- The structure and chromosomal location of human PD1 gene was defined. (Shinohara, Taniwaki et al. 1994)

Stimulating 2B4. 11 with ionomycin and PMA, which can induce programmed cell death.

↓

Subtractive hybridization, and got the subtractive cDNA Library.

↓

After screening, 4 positive clones were got. And they are from one gene--PD1.

copyright 2007 peking university visual identity system

北京大学
PEKING UNIVERSITY

Sequence Analysis of PD1- ORF prediction

Yasumasa Ishida *et al* got PD1's cDNA sequence (X67914.1), and they predicted the amino acid sequence.

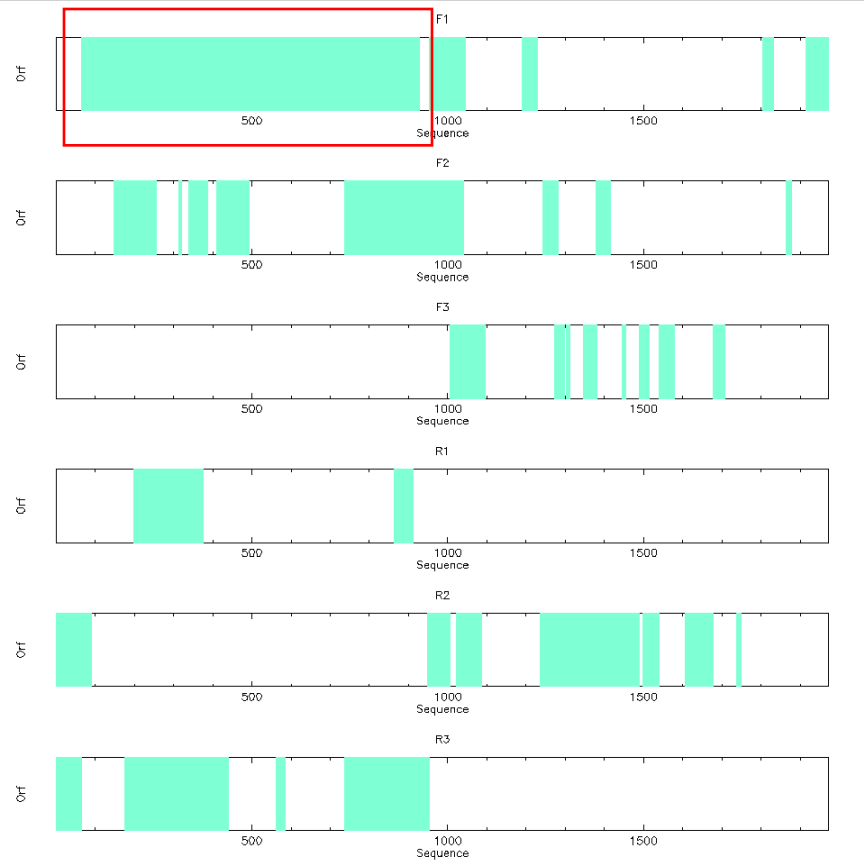


Figure 1 Result of PlotORF

copyright 2007 peking university visual identity system

北京大学
PEKING UNIVERSITY

Sequence Analysis of PD1- Topology prediction

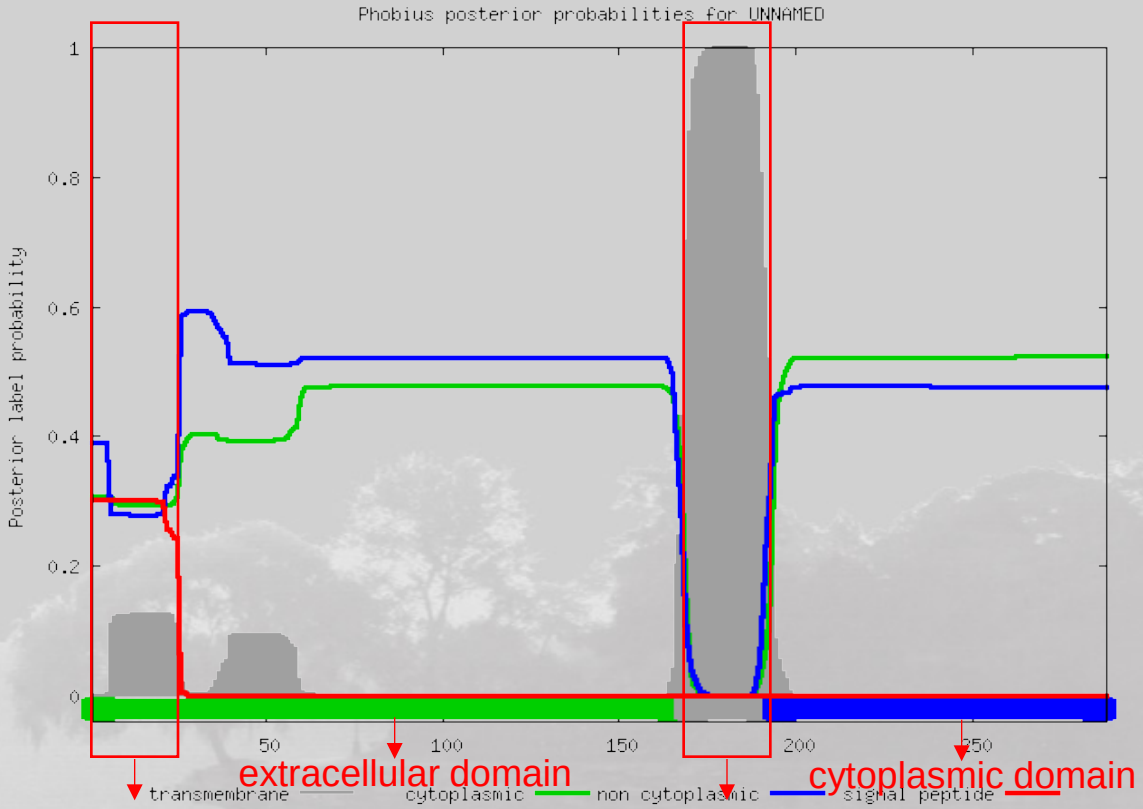


Figure 2 Result of Phobius. Phobius is a web server used to predicted the transmembrane topology and signal peptide**.**

copyright 2007 peking university visual identity system

北京大学
PEKING UNIVERSITY

Transmembrane Structure Analysis of PD1

170-190aa is the transmembrane segment.
>sp|Q02242|170-190
VIGIMSALVGIPVLLLLAWAL

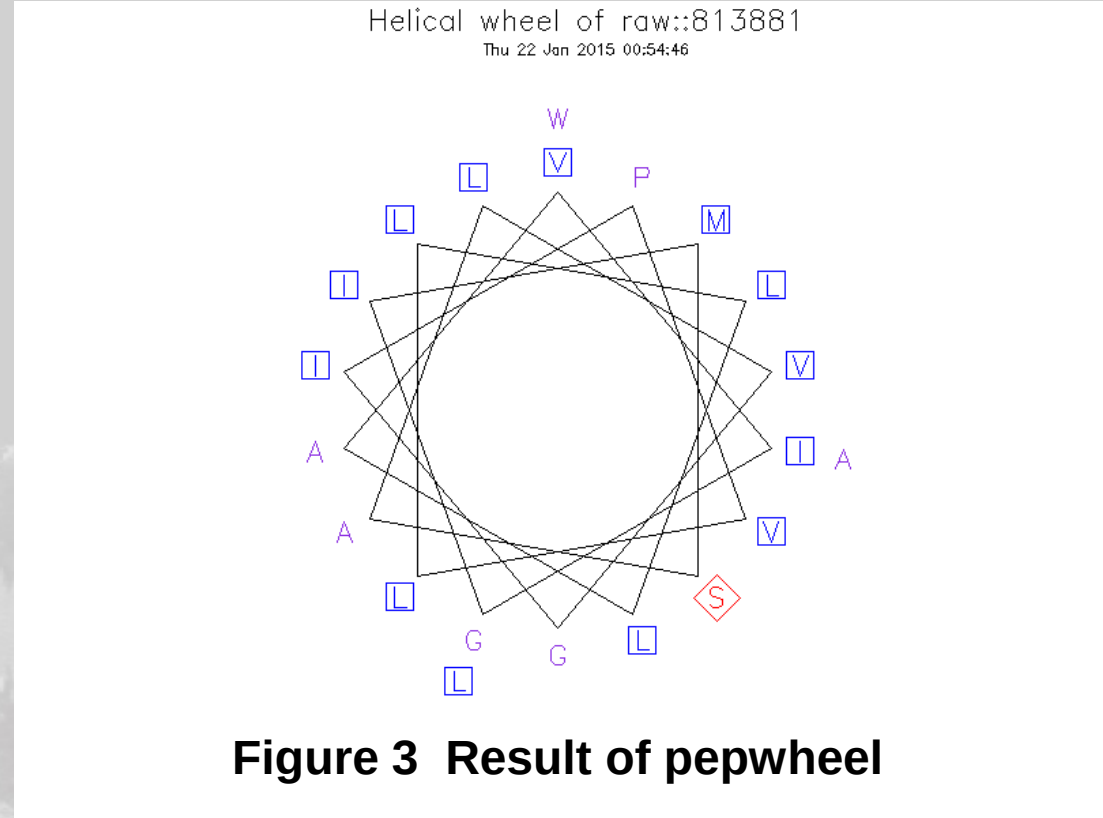
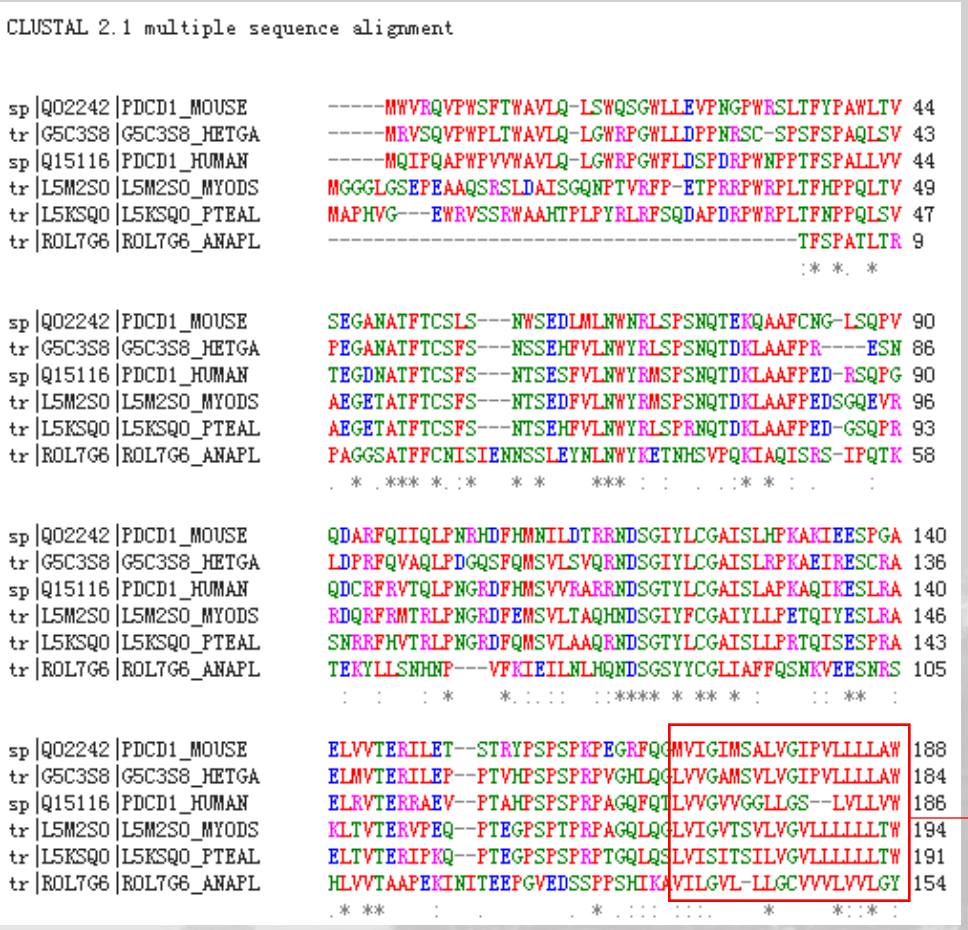


Figure 3 Result of pepwheel

copyright 2007 peking university visual identity system

北京大学
PEKING UNIVERSITY

Sequence Analysis of PD1- Alignment



The identity between hPD1 and mPD1 is 59.31%.

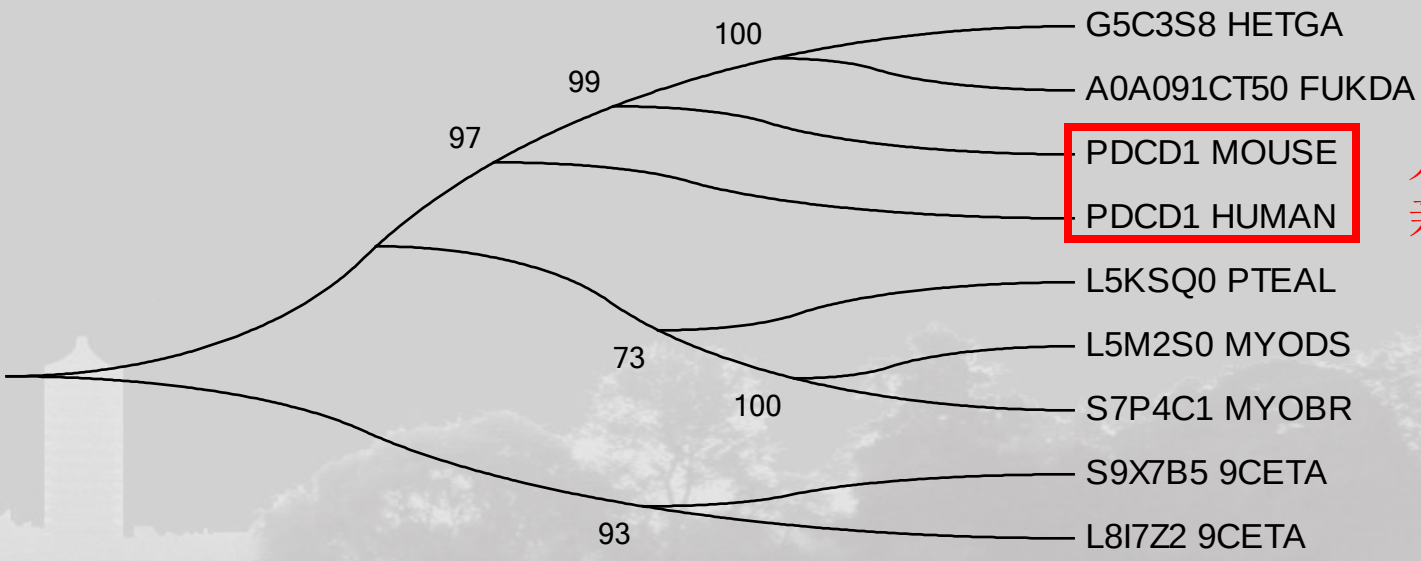
Transmembrane domain

Figure 4 Result of ClustalW2

copyright 2007 peking university visual identity system

北京大学
PEKING UNIVERSITY

Phylogenetic Tree



人与小鼠的PD1亲缘关系最近。

Figure 5 Phylogenetic tree of PD1 gene in different species.
The phylogenetic tree is constructed using Maximum Likelihood.

copyright 2007 peking university visual identity system

北京大学
PEKING UNIVERSITY

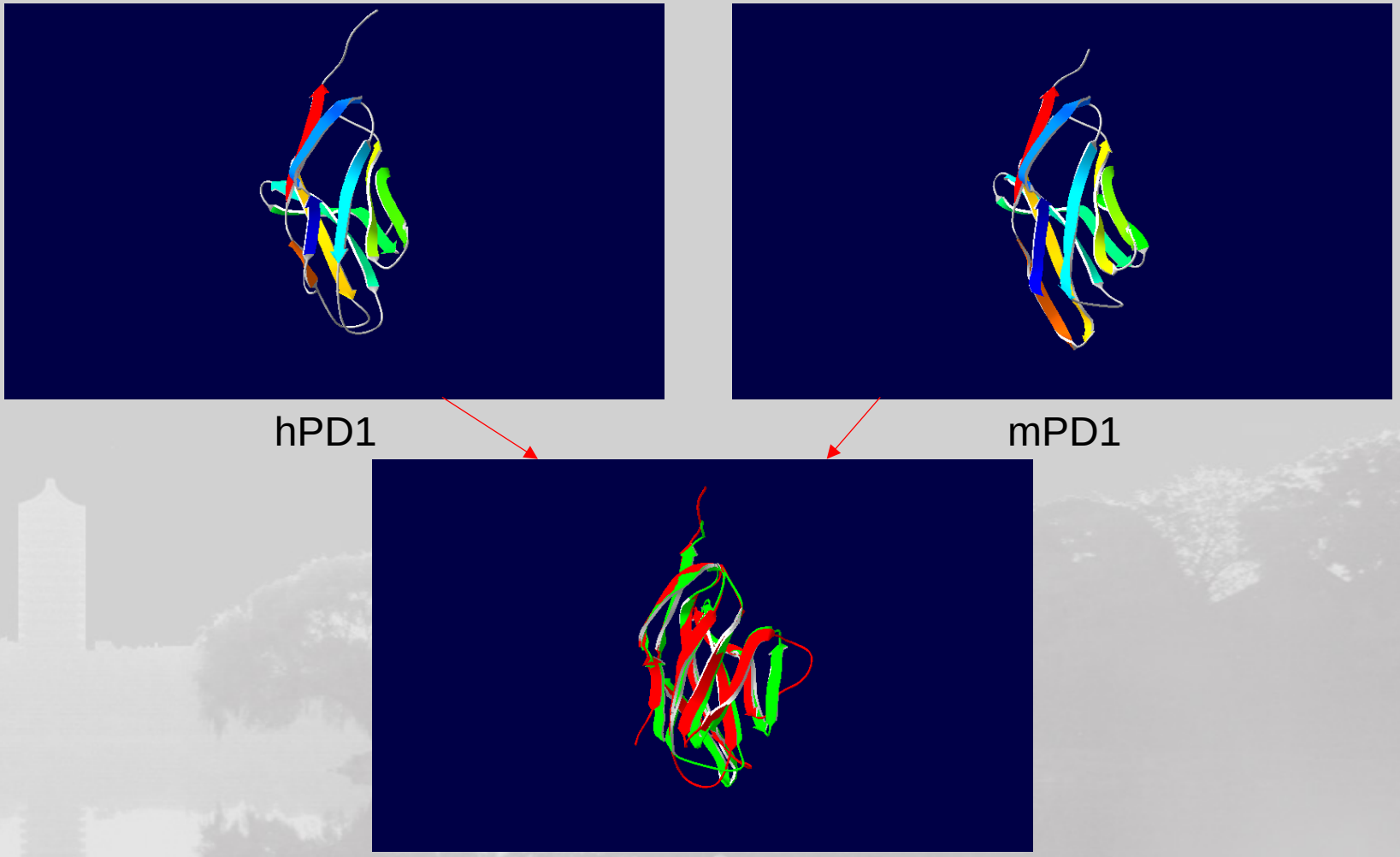
3D Structure of PD1 and PDL1

PDB ID	Title
3FN3	Dimeric Structure of PD-L1
3SBW	Crystal structure of the complex between the extracellular domains of mouse PD-1 mutant and human
3BOV	Crystal structure of the receptor binding domain of mouse PD-L2
3BIS	Crystal Structure of the PD-L1
3RNK	Crystal structure of the complex between mouse PD-1 mutant and PD-L2 IgV domain
3RNQ	Crystal structure of the complex between the extracellular domains of mouse PD-1 mutant and PD-L2
3BIK	Crystal Structure of the PD-1/PD-L1 Complex
3BP5	Crystal structure of the mouse PD-1 and PD-L2 complex
3BP6	Crystal structure of the mouse PD-1 Mutant and PD-L2 complex
2M2D	Human programmed cell death 1 receptor
1NPU	CRYSTAL STRUCTURE OF THE EXTRACELLULAR DOMAIN OF MURINE PD-1
3RRQ	Crystal structure of the extracellular domain of human PD-1

Table 1 List of the structure of PD1 or PDL1 from The RCSB PDB.

copyright 2007 peking university visual identity system

Structure of PD1



hPD1 and mPD1 Fit

Figure 6 The structure of hPD1 and mPD1. The Figure is produced with Swiss-PDB Viewer.

copyright 2007 peking university visual identity system

北京大学
PEKING UNIVERSITY

Structure of PD1/PDL1 complex

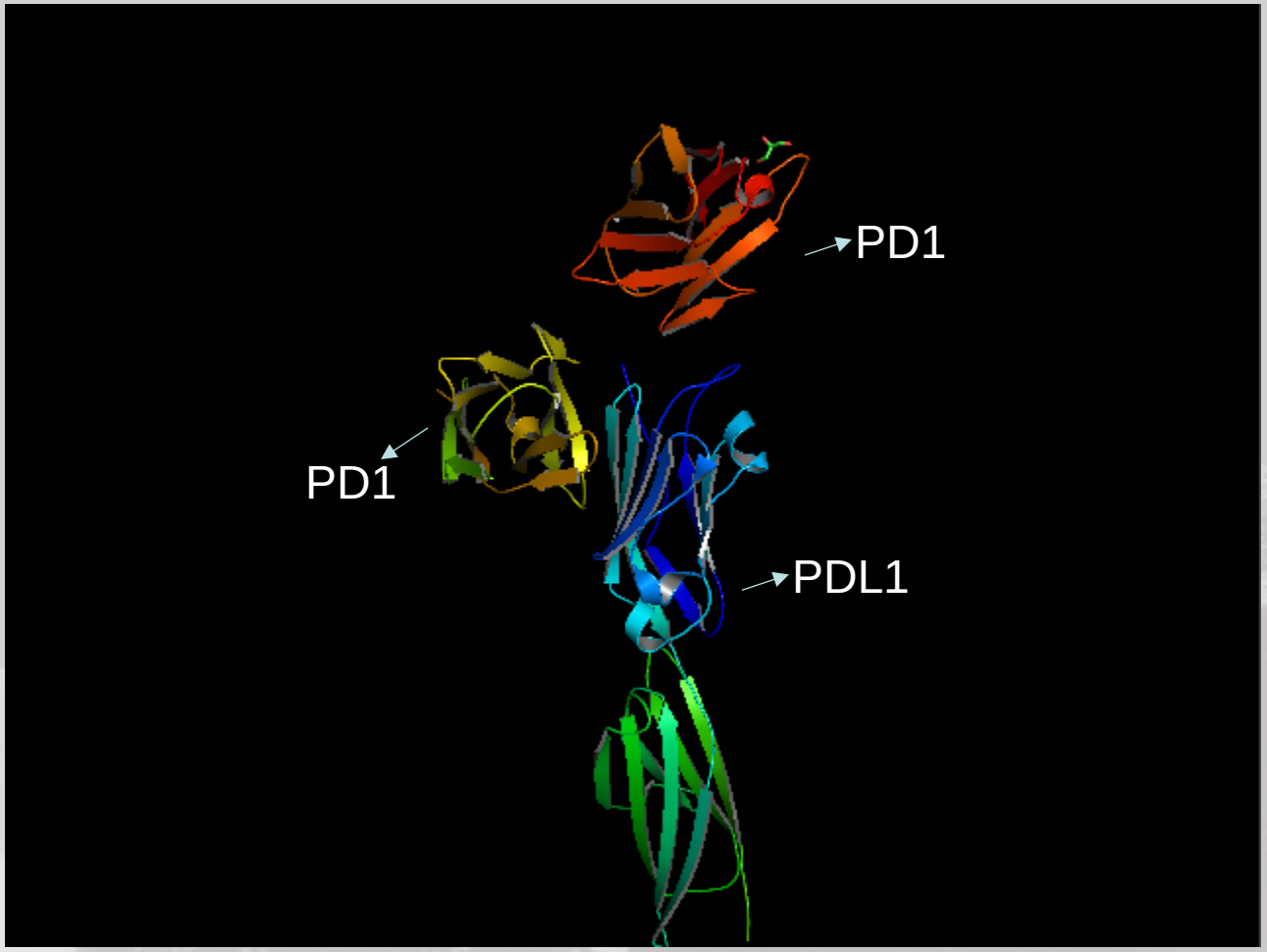


Figure 7 The structure of PD1/PDL1 complex. The Figure is produced with PyMOL software.

copyright 2007 peking university visual identity system

北京大学
PEKING UNIVERSITY

Binding Surface of PD1/PDL1 complex

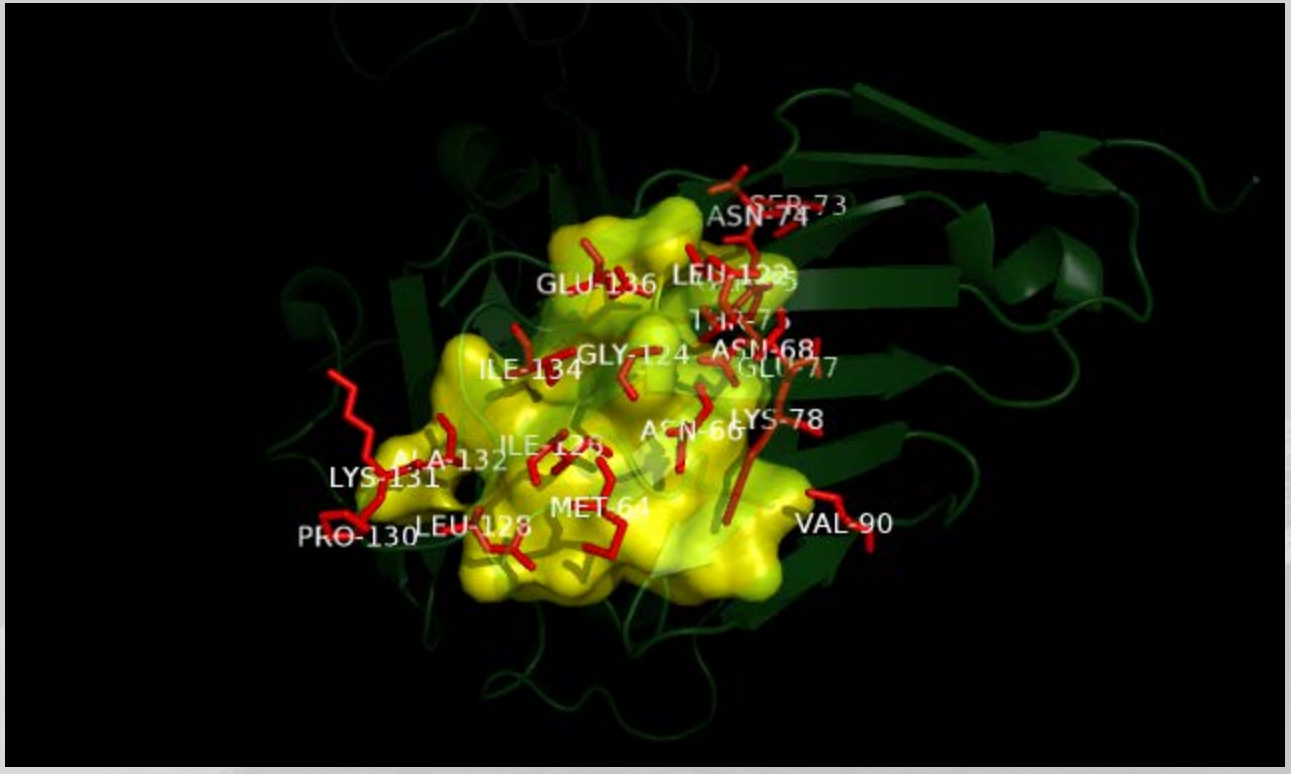


Figure 8 The structure of PD1/PDL1 binding site. The Figure is produced with PyMOL software.

PD1与PDL1的结合位点可能会成为小分子药物的设计靶点。

copyright 2007 peking university visual identity system

北京大学
PEKING UNIVERSITY

PD1 has attracted more and more attention

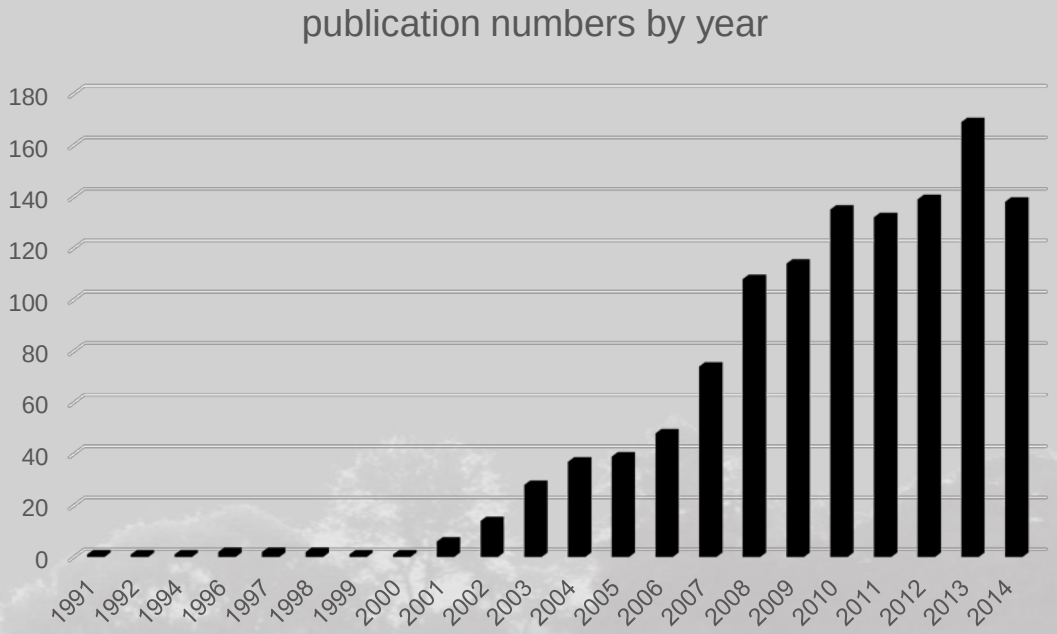


Figure 9 Publication numbers of PD1 in PubMed.

In 2013, cancer immunotherapy was awarded by ‘Science’ as the most important scientific breakthrough.
And in 2014, Suzanne Topalian, researcher on nivolumab-PD1 antibody drug, was awarded as one of the *Nature*'s 10.

copyright 2007 peking university visual identity system

北京大学
PEKING UNIVERSITY

Applications of Monoclonal Antibody Drug of PD1

预计上市	药物	方案	适应症
2014 年底	MK-3475	二线	Yervoy 治疗后复发黑色素瘤
2015 年中	nivolumab	三线	鳞状 NSCLC
2015 下半年	nivolumab	二线	鳞状 NSCLC
2015 下半年	nivolumab	二线	非鳞状 NSCLC
2016 上半年	MK-3475	二线	转移性黑色素瘤
2016 年中	nivolumab	一线/二线	转移性黑色素瘤
2016 年中	MK-3475		PD-L1 阳性 NSCLC
2016 下半年	nivolumab	二线	肾细胞癌
2016 年底	MPDL3280A	二线/三线	NSCLC
2016 年底	MEDI4736	三线	PD-L1 阳性 NSCLC
2017 年中	nivolumab+Yervoy		黑色素瘤
2017 年底	MPDL3280A+ Avastin	一线	肾细胞癌
2018 上半年	nivolumab+Yervoy		肾细胞癌
2018 上半年	nivolumab+Yervoy		NSCLC
2018 上半年	MEDI4736	二线	III 期 NSCLC

Table 2 未来几年癌症免疫治疗药物的审批进度

来自http://blog.sciencenet.cn/blog-799746-859794.html

copyright 2007 peking university visual identity system

北京大学
PEKING UNIVERSITY

Thank you.

copyright 2007 peking university visual identity system