

## 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

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#### 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.



## Sequence Analysis of PD1- ORF prediction

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





#### 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.



#### **Transmembrane Structure Analysis of PD1**

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



#### Figure 3 Result of pepwheel



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#### Sequence Analysis of PD1- Alignment

CLUSTAL 2.1 multiple sequence alignment		sp  Q02242  PDCD1_MOUSE tr  G5C3S8  G5C3S8_HETGA	ALAVFCSTSMSEARGAGSKDDTLKEE-PSAAPVPSVAYEELDF 230 VLAAVCSRAVFGKGRWPLLGLCTNNPPLSLKKEGPSAVPTVTMDYGVLDF 234
sp  Q02242  PDCD1_MOUSE tr  G5C3S8  G5C3S8_HETGA sp  Q15116  PDCD1_HUMAN tr  L5M2S0  L5M2S0_MYODS tr  L5KSQ0  L5KSQ0_PTEAL tr  R0L7G6  R0L7G6_ANAPL	MWVRQVPWSFTWAVLQ-LSWQSGWLLEVPNGPWRSLTFYPAWLTV 44 MRVSQVFWPLTWAVLQ-LGWRPGWLLDPPNRSC-SPSFSPAQLSV 43 MQIPQAPWPVVWAVLQ-LGWRPGWFLDSPDRPWNPPTFSPALLVV 44 MGGGLGSEPEAAQSRSLDAISGQNPTVRFP-ETPRRPWRPLTFHPPQLTV 49 MAPHVGEWRVSSRWAAHTPLPYRLRFSQDAPDRPWRPLTFNPPQLSV 47 TFSPATLTR 9 :* *. *	sp  Q15116  PUCD1_HUMAN tr  L5M2S0  L5M2S0_MYODS tr  L5KSQ0  L5KSQ0_PTEAL tr  ROLTG6  ROLTG6_ANAPL sp  Q02242  PDCD1_MOUSE tr  G5C3S8  G5C3S8_HETGA sp  Q15116  PDCD1_HUMAN	VLAVILSRAARGIIGARRIGUPLEUF-SAVPVFSVDYGELDF       228         VLATRGGCACRSEDQPFKEGPSVASVDYGELDF       227         VLAAFPRATRGVCACRSEDPPLKQGPSPGPVFSVVDYGELDF       233         CLVTYRRGDVQKPPSENTAEEEKPPVVSVSTVDYGVLEF       193         *.       ::::::::::::::::::::::::::::::::::::
sp  Q02242  PDCD1_MOUSE tr  G5C3S8  G5C3S8_HETGA sp  Q15116  PDCD1_HUMAN tr  L5M2S0  L5M2S0_MYODS	SEGANATFTCSLSNWSEDLMLNWNRLSPSNQTEKQAAFCNG-LSQPV 90 PEGANATFTCSFSNSSEHFVLNWYRLSPSNQTDKLAAFPRESN 86 TEGDNATFTCSFSNTSESFVLNWYRMSPSNQTDKLAAFPED-RSQPG 90 AEGETATFTCSFSNTSEDFVLNWYRMSPSNQTDKLAAFPEDSGQEVR 96	tr  L5M2SO  L5M2SO_MYODS tr  L5KSQO  L5KSQO_PTEAL tr  ROL7G6  ROL7G6_ANAPL	QRREKTPEPPAPCVPEQTEYATIVFPGRFGS-LRRASADSPQGP 270 QWREKTPEPSGFCVPELPPTTEYATIVFPSLPGSPSRRASADSPQGP 281 QWDPHTQLPPETCPDDQTEYATIIFPEEKPVTPERGKHLDERTWQ 239 * :: * * ******:*
tr  L5KSQ0  L5KSQ0_PTEAL tr  R0L7G6  R0L7G6_ANAPL	AEGETATFTCSFSNTSEHFVLNWYRLSPRNQTDKLAAFPED-GSQPR 93 PAGGSATFFCNISIENNSSLEYNLNWYKETNHSVPQKIAQISRS-IPQTK 58 . * .*** *.:* * * *** :::* * : :	sp  Q02242  PDCD1_MOUSE tr  G5C3S8  G5C3S8_HETGA sp  Q15116  PDCD1_HUMAN tr  L5M2S0  L5M2S0_MYODS	RPPRHEDGHCSWPL 288 RPPRQQDGHCSWPL 292 QPLRPEDGHCSWPL 288 QPLRLEDGHCSWPL 284
sp  Q02242  PDCD1_MOUSE tr  G5C3S8  G5C3S8_HETGA sp  Q15116  PDCD1_HUMAN	QDARFQIIQLPNRHDFHMNILDTRRNDSGIYLCGAISLHPKAKTEESPGA 140 LDPRFQVAQLPDGQSFQMSVLSVQRNDSGIYLCGAISLRPKAEIRESCRA 136 QDCRFRVTQLPNGRDFHMSVVRARRNDSGTYLCGAISLAPKAQIKESLRA 140 DDORFNTDLDWDDRFMCHTTAODDCCINCCAINLAPKAQIKESLRA 140	tr  L5KSQ0  L5KSQ0_PTEAL tr  R0L7G6  R0L7G6_ANAPL	RPLRPEDGHCSWPL 295 PPSQ 243 * :
tr [LSM2S0 [LSM2S0_MIODS tr [LSKSQ0 [LSKSQ0_PTEAL tr [R0L7G6 [R0L7G6_ANAPL	RDQRFRMIRLFNGRDFDMSVLIAARNDSGIFFCGAITLLFEIQITESLRA 146 SNRRFHVTRLPNGRDFQMSVLAAQRNDSGTYLCGAISLLPRTQISESPRA 143 TEKYLLSNHNPVFKIEILNLHQNDSGSYYCGLIAFFQSNKVEESNRS 105 	The identity	between hPD1 and mPD1 is
sp  Q02242  PDCD1_MOUSE tr  G5C3S8  G5C3S8_HETGA	ELVVTERILETSTRYPSPSPKPEGRFQGMVIGIMSALVGIPVLLLLAW 188 ELMVTERILEPPTVHPSPSPRPVGHLQGLVVGAMSVLVGIPVLLLLAW 184	59.31%.	
sp  Q15116  PDCD1_HUMAN tr  L5M2S0  L5M2S0_MYODS tr  L5KSQ0  L5KSQ0_PTEAL tr  R0L7G6  R0L7G6_ANAPL	ELRVTERRAEVPTAHPSPSPRPAGQFQTLVVGVVGGLLGSLVLLVW 186 KLTVTERVPEQPTEGPSPTPRPAGQLQGLVIGVTSVLVGVLLLLLLTW 194 ELTVTERIPKQPTEGPSPSPRPTGQLQSLVISITSILVGVLLLLLLTW 191 HLVVTAAPEKINITEEPGVEDSSPPSHIKAVILGVL-LLGCVVVLVVLGY 154	<ul> <li>Transmembrane</li> </ul>	e domain

Figure 4 Result of ClustalW2

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#### **Phylogenetic Tree**



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



#### 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
<b>3RNQ</b>	Crystal structure of the complex between the extracellular domains of mouse PD-1 mutant and PD-L2
<b>3BIK</b>	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
<b>3RRQ</b>	Crystal structure of the extracellular domain of human PD-1

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



#### Structure of PD1







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



## 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。



## PD1 has attracted more and more attention

publication numbers by year



#### 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.



#### Applications of Monoclonal Antibody Drug of PD1

	预计上市	药物	方案	适应症
Î	2014年底	MK-3475	二线	Yervoy 治疗后复发黑色素瘤
3				
	2015年中	nivolumab	三线	鳞状 NSCLC
Ì	2015下半年	nivolumab	二线	鳞状 NSCLC
0	2015 下半年	nivolumab	二线	非鳞状 NSCLC
l	2016上半年	MK-3475	二线	转移性黑色素瘤
10 AN	2016年中	nivolumab	一线/二线	转移性黑色素瘤
3	2016年中	MK-3475		PD-L1 阳性 NSCLC
	2016下半年	nivolumab	二线	肾细胞癌
30.000	2016年底	MPDL3280A	二线/三线	NSCLC
3	2016年底	MEDI4736	三线	PD-L1 阳性 NSCLC
ĺ	2017年中	nivolumab+Yervoy		黑色素瘤
3	2017年底	MPDL3280A+ Avastin	一线	肾细胞癌
Ì	2018上半年	nivolumab+Yervoy		肾细胞癌
3	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.htmlusi identity system



# Thank you.