

Function of Lymphocyte-activation gene 3 (LAG-3) In Immunity

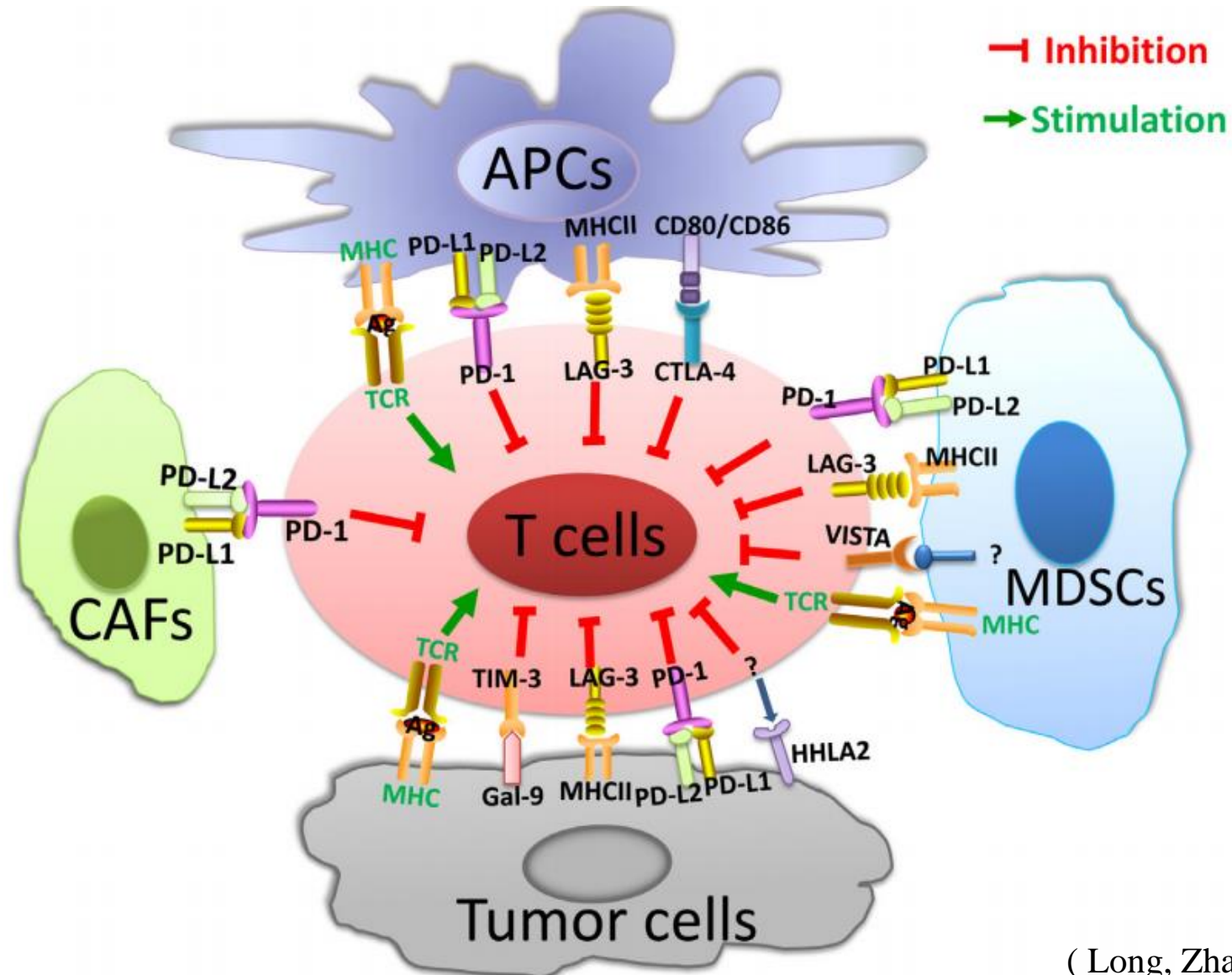
淋巴细胞激活基因-3在免疫中的作用

报告人：黄新平

组 员：谢思 李龙图 徐扬

2019.01.12

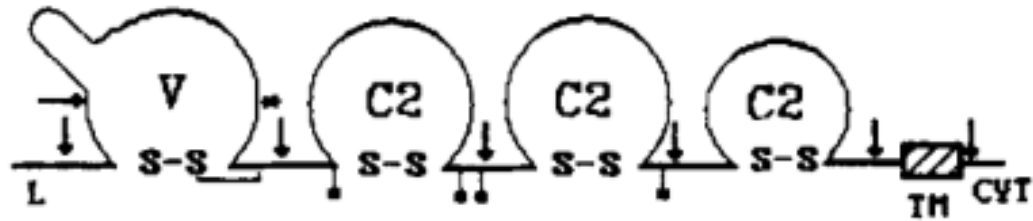
Tumor microenvironment and immune checkpoints : LAG-3



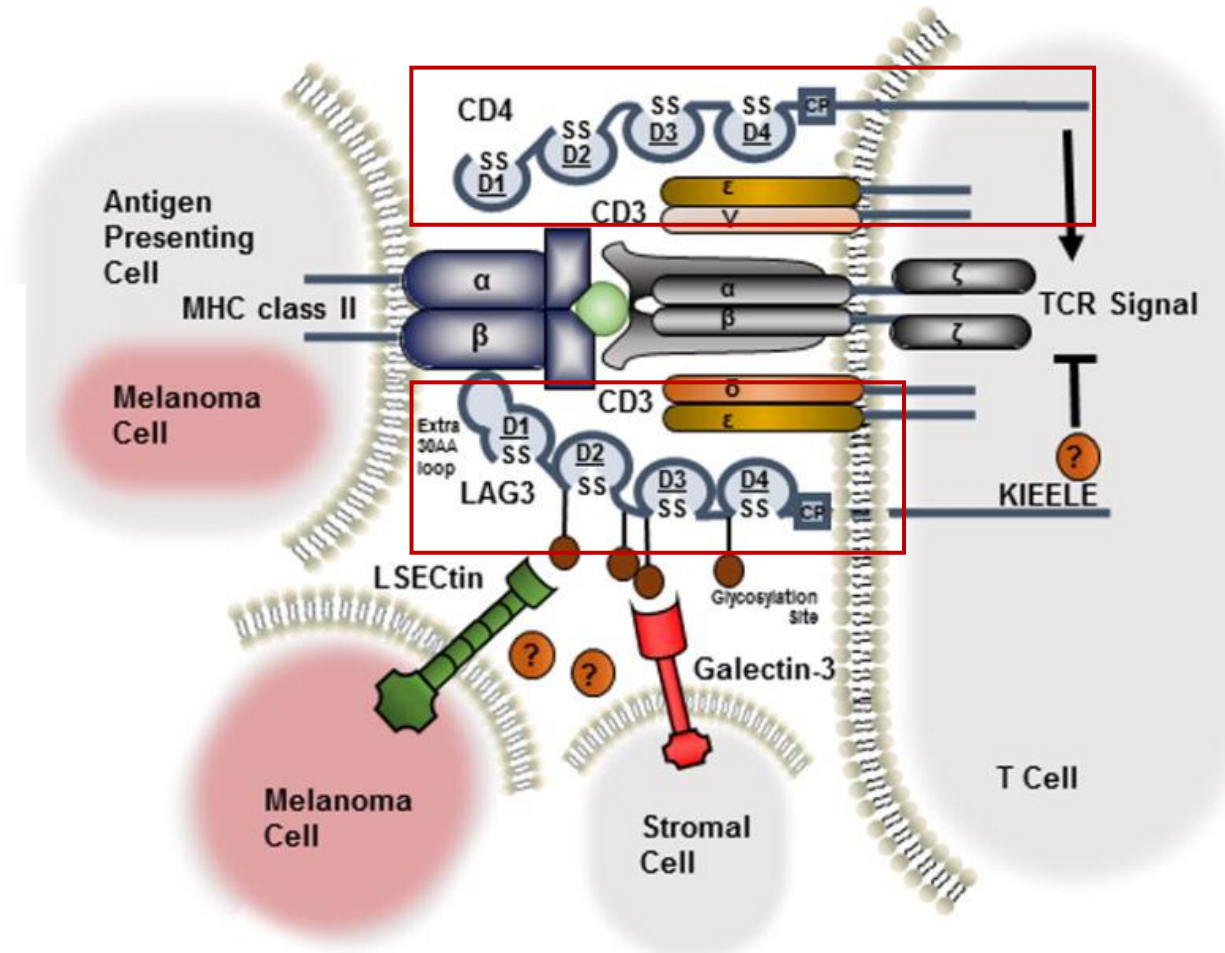
(Long, Zhang et al. 2018)

Ligand interaction and structural similarities between LAG3 and CD4

LAG-3



(Triebel et al.,1990)



(Andrews et al.,2017)

Understanding functions of LAG-3 by Uniprot

Protein | **Lymphocyte activation gene 3 protein**

Gene | **LAG3**






Organism | *Homo sapiens (Human)*

Status |  Reviewed - Annotation score:  - Experimental evidence at protein levelⁱ

Functionⁱ






Involved in lymphocyte activation. Binds to HLA class-II antigens.

GO - Molecular functionⁱ

- antigen binding  Source: ProtInc 
- MHC class II protein binding  Source: MGI 
- transmembrane signaling receptor activity  Source: Ensembl

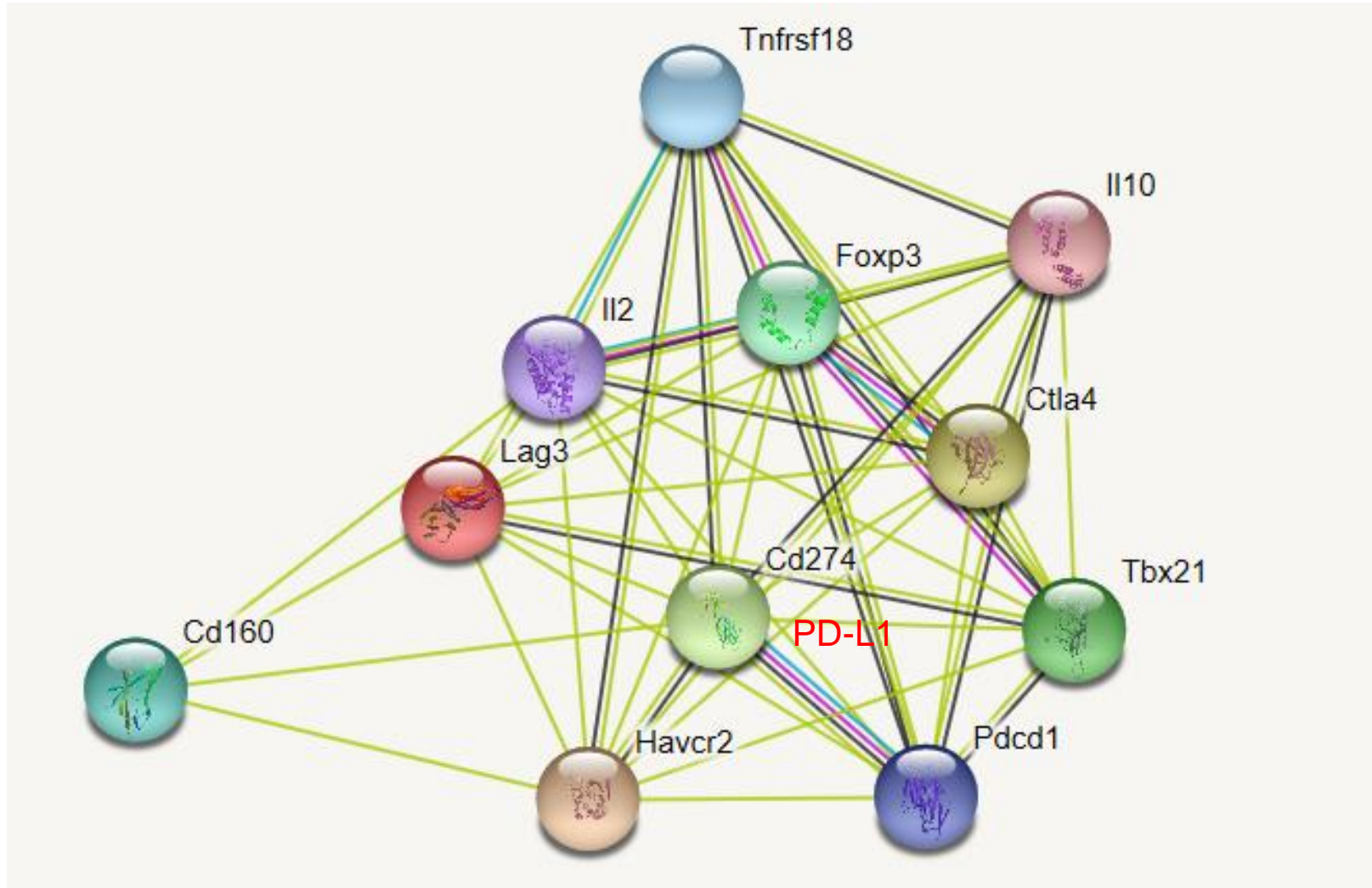
[View the complete GO annotation on QuickGO ...](#)

GO - Biological processⁱ

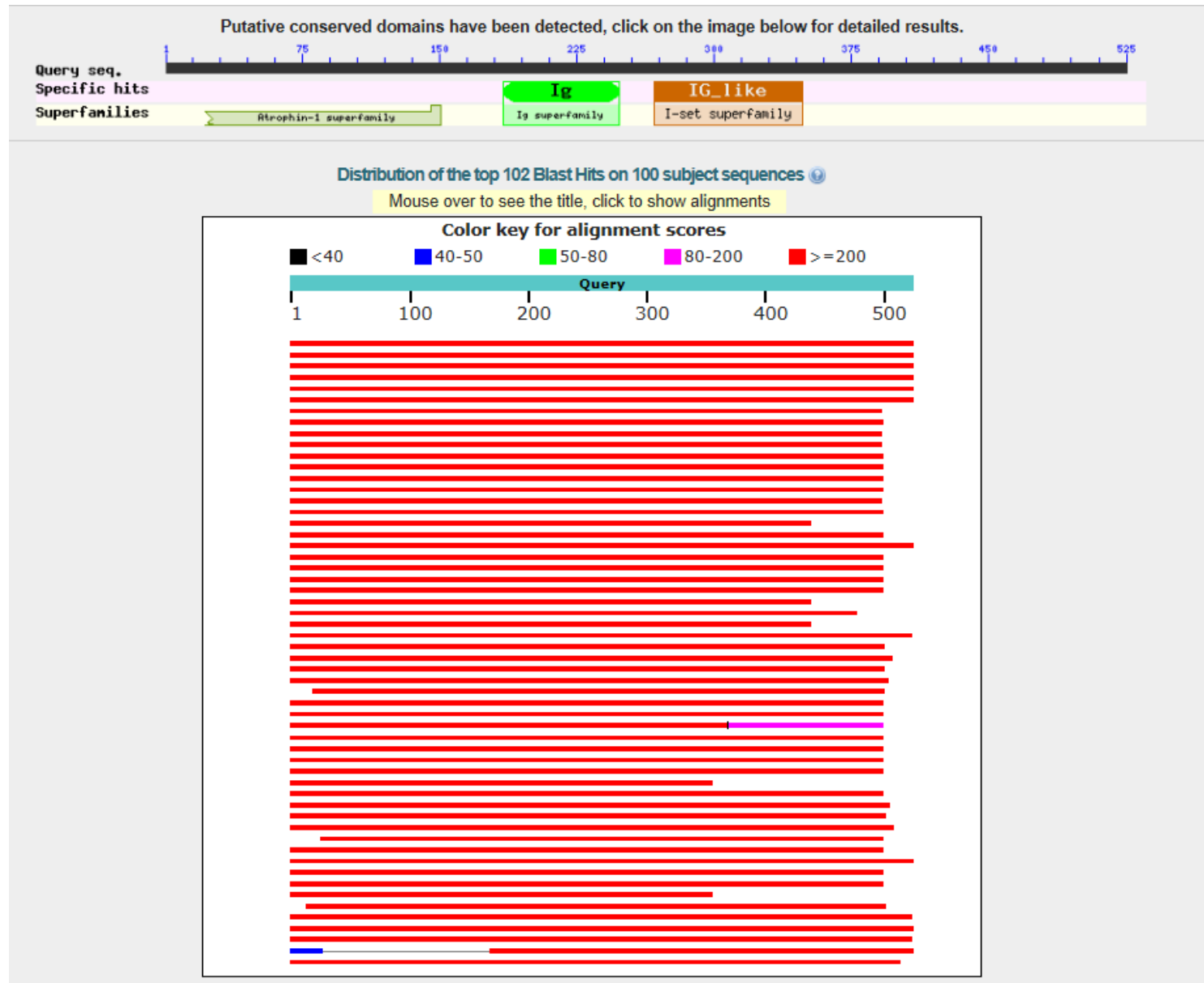
- antigen processing and presentation of exogenous peptide antigen via MHC class II  Source: Reactome
- cell surface receptor signaling pathway  Source: Ensembl
- negative regulation of interleukin-2 biosynthetic process  Source: Ensembl
- negative regulation of T cell activation  Source: Ensembl
- positive regulation of natural killer cell mediated cytotoxicity  Source: Ensembl

[View the complete GO annotation on QuickGO ...](#)

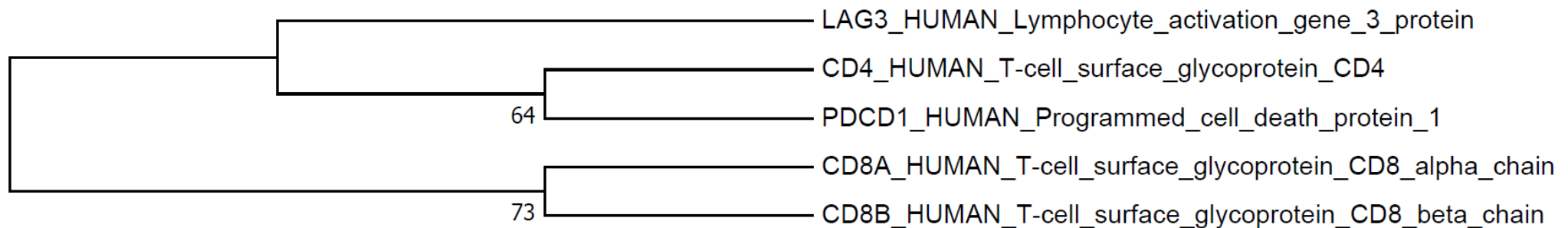
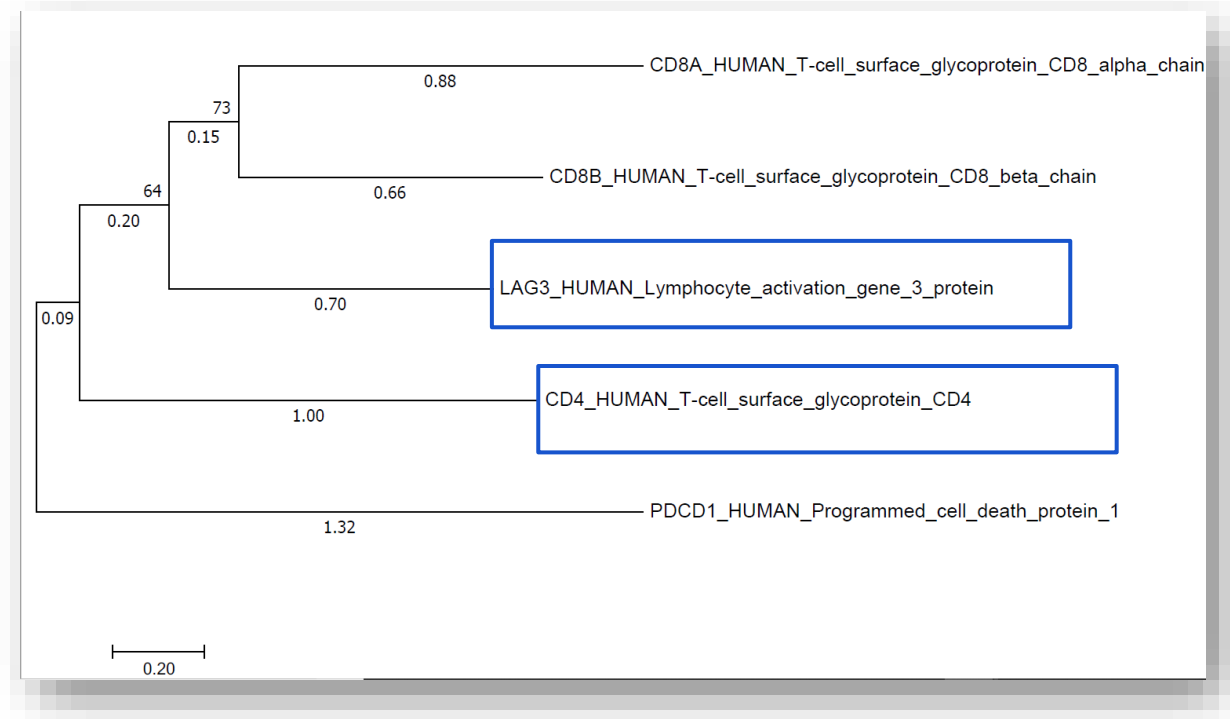
Interactions between lag-3 and other proteins in immunity



LAG3 is conserved in Mammalia (Blastp)



LAG3 and CD4 have some homology (MEGA)



(Bootstrap)

Article

Fibrinogen-like Protein 1 Is a Major Immune Inhibitory Ligand of LAG-3

Jun Wang,¹ Miguel F. Sanmamed,¹ Ila Datar,² Tina Tianjiao Su,¹ Lan Ji,¹ Jingwei Sun,¹ Ling Chen,³ Yusheng Chen,⁴ Gefeng Zhu,¹ Weiwei Yin,⁵ Linghua Zheng,¹ Ting Zhou,¹ Ti Badri,¹ Sheng Yao,¹ Shu Zhu,¹ Agedi Boto,^{1,2} Mario Sznol,⁶ Ignacio Melero,⁷ Dario A.A. Vignali,^{8,9} Kurt Schalper,² and Lieping Chen^{1,3,6,10,*}

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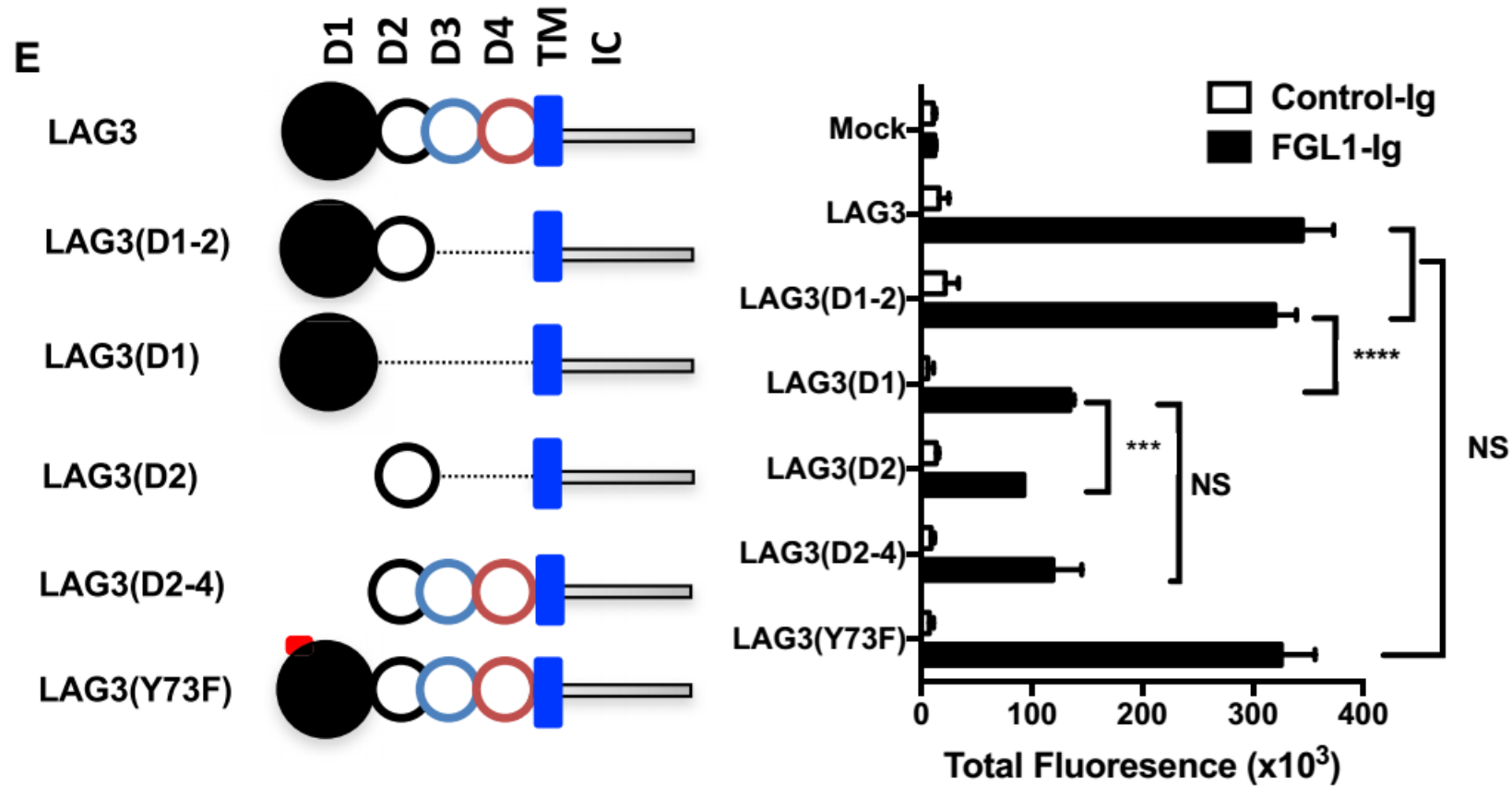
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<https://doi.org/10.1016/j.cell.2018.11.010>

LAG-3 interact with FGL-1 mainly by D1D2 domain



D1D2 domains are IG domain and Ig-like domain

NCBI

HOME SEARCH GUIDE NewSearch Structure Home 3D Macromolecular Structures Conserved Domains Pubchem BioSystems

Conserved domains on [gi|16761450|ref|NP_002277.4|] View Concise Results ?

lymphocyte activation gene 3 protein precursor [Homo sapiens]

Graphical summary Zoom to residue level hide extra options Show site features Horizontal zoom: x 1 Update graph ?

Query seq. 1 75 150 225 300 375 450 525

Specific hits

Superfamilies

Atrophin-1 superfamily Ig superfamily I-set superfamily

[Search for similar domain architectures](#) ? [Refine search](#) ?

List of domain hits ?

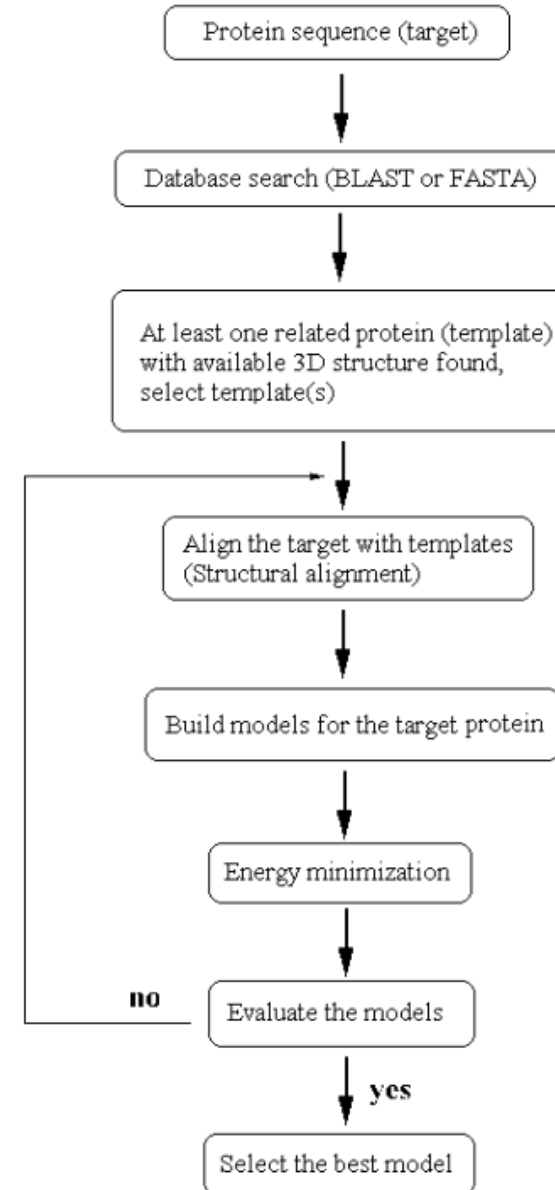
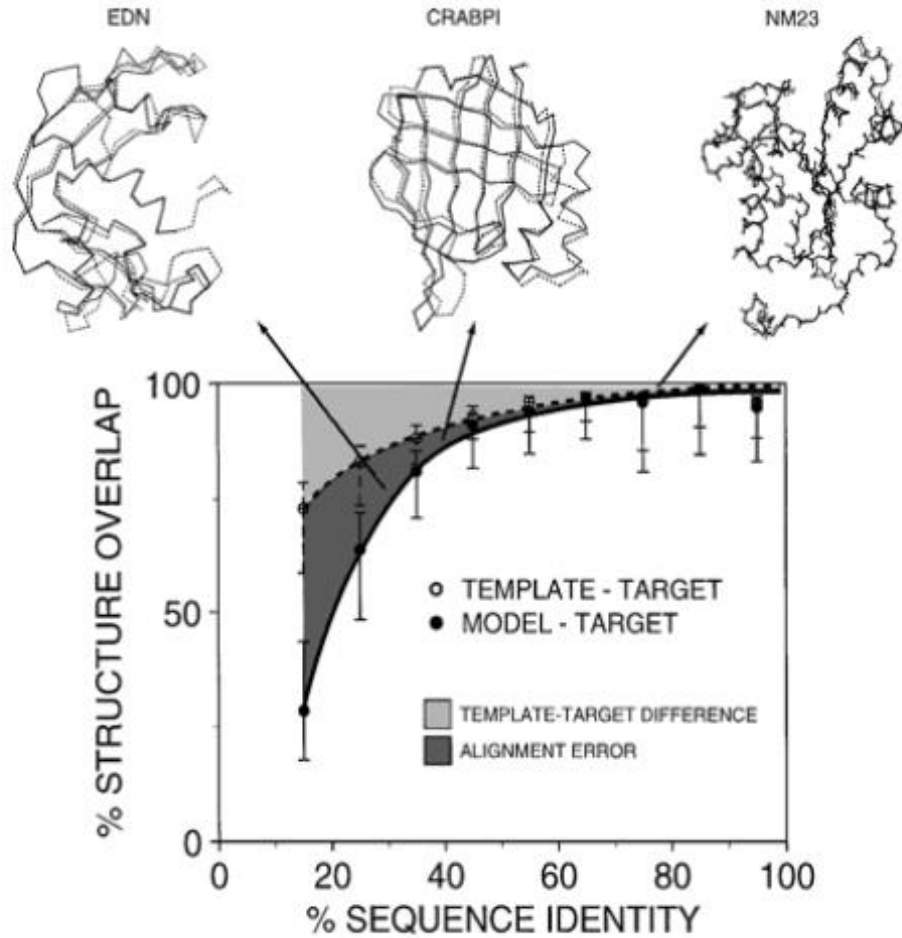
Name	Accession	Description	Interval	E-value
[+] IG_like	smart00410	Immunoglobulin like; IG domains that cannot be classified into one of IGv1, IGc1, IGc2, IG.	267-348	2.12e-06
[+] Ig	cd00096	Immunoglobulin domain; Immunoglobulin (Ig) domain found in the Ig superfamily. The Ig ...	185-248	6.77e-05
[+] Atrophin-1 super family	cl26464	Atrophin-1 family; Atrophin-1 is the protein product of the dentatorubral-pallidolusian ...	22-151	6.45e-04

References:

- Marchler-Bauer A et al. (2017), "CDD/SPARCLE: functional classification of proteins via subfamily domain architectures.", *Nucleic Acids Res.*45(D)200-3.
- Marchler-Bauer A et al. (2015), "CDD: NCBI's conserved domain database.", *Nucleic Acids Res.*43(D)222-6.
- Marchler-Bauer A et al. (2011), "CDD: a Conserved Domain Database for the functional annotation of proteins.", *Nucleic Acids Res.*39(D)225-9.
- Marchler-Bauer A, Bryant SH (2004), "CD-Search: protein domain annotations on the fly.", *Nucleic Acids Res.*32(W)327-331.

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We try to predict the structure of LAG3 by homology modeling



We get the structure of LAG-3 via SWISS-MODEL

Start a New Modelling Project

Target Sequence:

(Format must be FASTA, Clustal, plain string, or a valid UniProtKB AC)

Target `MWEAQFLGLLFLQPLWVAPVKPLQPGAEVAVVWAQEGAPALPCSPITPLQDLSLLRRAGVTWQHQPDSGPPAAAPGHPLAPGPHPAAPSSWGPRPRRYTVLSVGGGLRSGRLE`

Target `LQPRVQLDERGRQRGDFSLWLRPARRADAGEYRAAVHLRDRALSCRLRLRLGQASMTASPPGSLRASDWVILNCSFSRPDRPASVHWFRNRGQGRVFPVRESPHHHLAESFLFLPQ`

Target `VSPMDSGPGWCILTYRDGFNVSIMYNLTVLGLPEPTPLTVYAGAGSRVGLPCRLPAGVGTRSFLTAKWTPPGGGPDLVTGDNGDFTLRLEDVSAQAQAGTYTCHIHLQEQLNAT`

Target `VTLAIITVTPKSFSGSPGSLGKLLCEVTPVSGQERFVWSSLDTPSQRSFSGPWLEAQEAQLLSQFPWQCQLYQGERLLGAAVYFTELSSPGAQRSGRAPGALPAGHLLLFLILGVLS`

Add Hetero Target

Reset

Project Title:

Untitled Project

Search For Templates

Build Model

By using the SWISS-MODEL server, you agree to comply with the following [terms of use](#) and to cite the corresponding [articles](#).

Supported Inputs

Sequence(s)

Target-Template Alignment

User Template

DeepView Project

CD4 serve as a template of structure prediction



All Projects

LAG3 Created: today at 19:58

Summary

Templates 50

Models



Template Results

Templates

Quaternary Structure

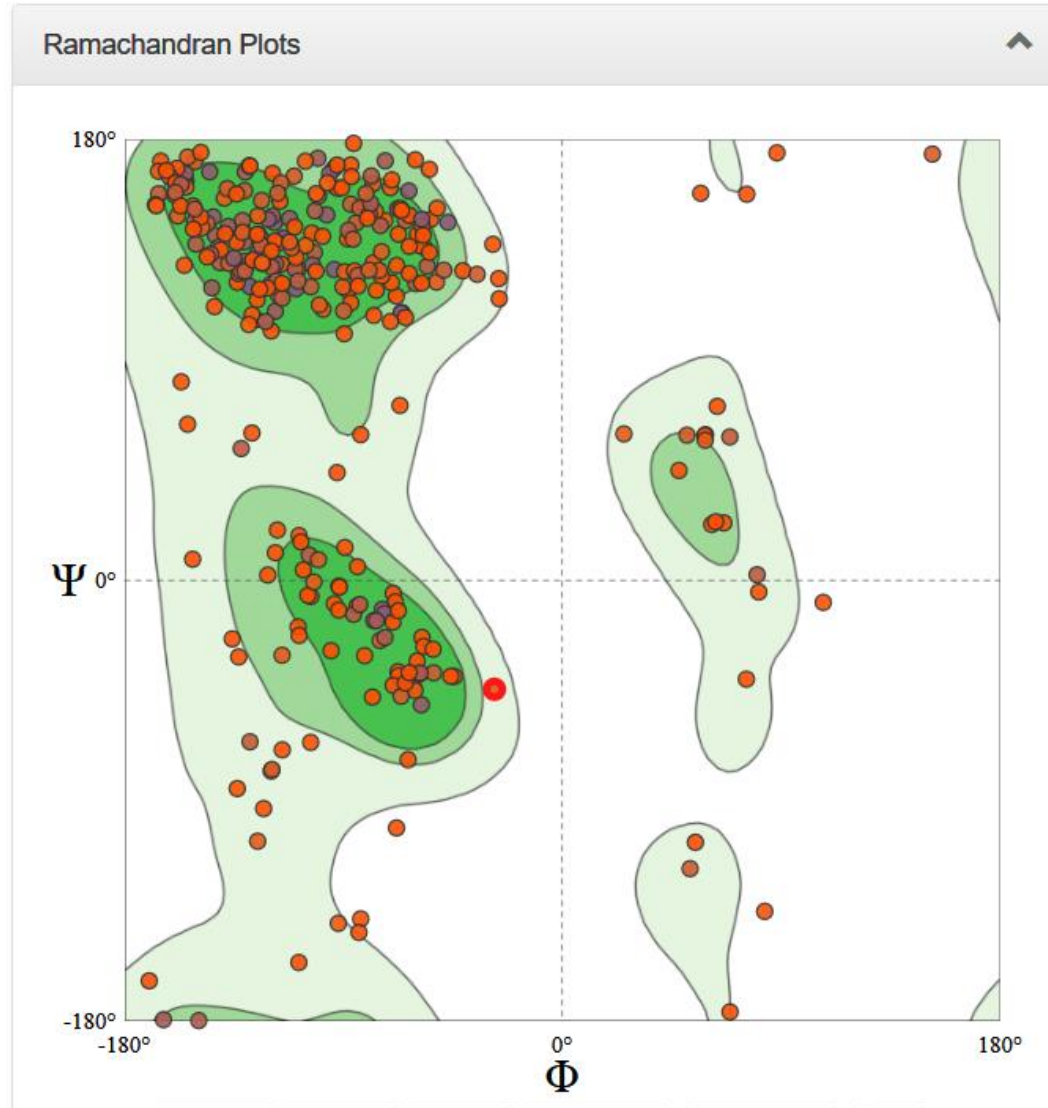
Sequence Similarity

Alignment of Selected Templates

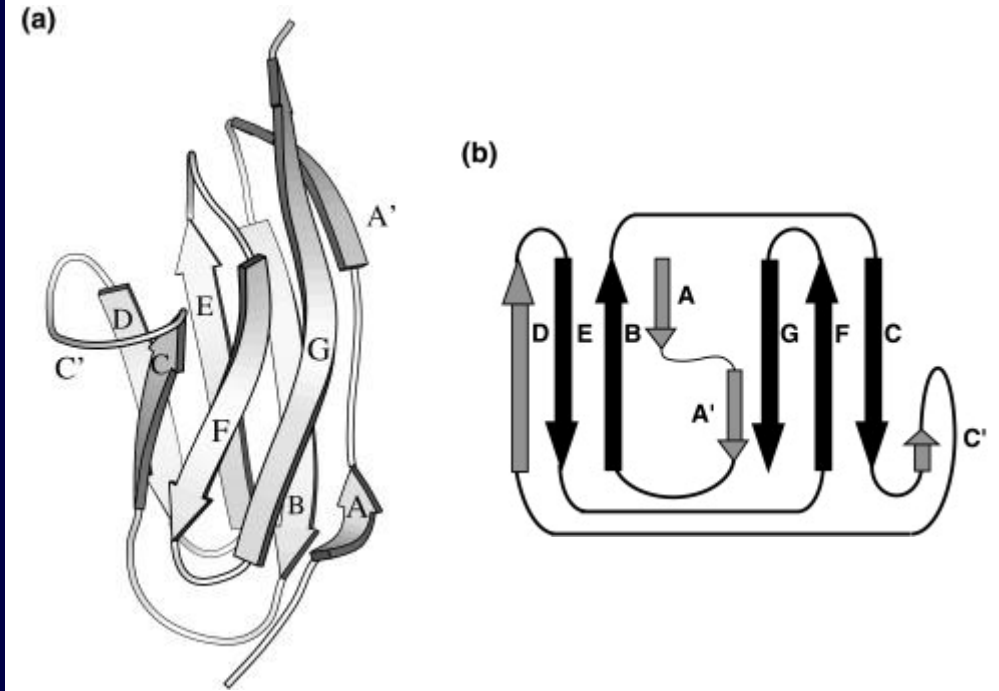
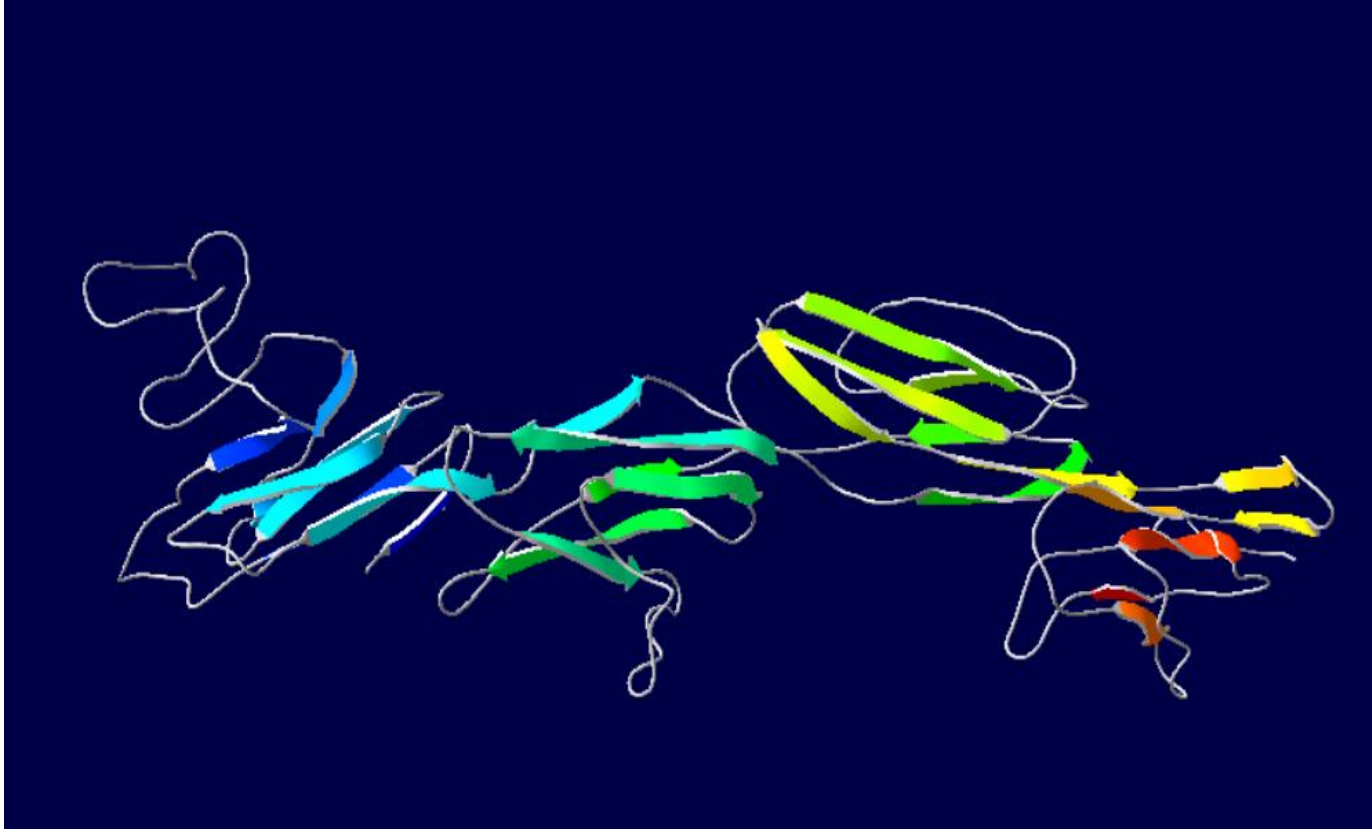
More

Sort	Name	Title	Coverage	GMQE	QSQE	Identity	Method	Oligo State	Ligands
<input type="checkbox"/>	3t0e.1.E	T-cell surface glycoprotein CD4		0.37	-	19.76	X-ray, 4.0Å	hetero-pentamer Δ	None
<input checked="" type="checkbox"/>	5f5.1.A	Myelin-associated glycoprotein		0.37	-	17.50	X-ray, 3.8Å	homo-dimer Δ	2 x FUC ☞ , 2 x SIA ☞ , 2 x GAL ☞ , 10 x NAG ☞ , 2 x MAN ☞
<input type="checkbox"/>	5ifu.1.A	Myelin-associated glycoprotein		0.37	-	17.50	X-ray, 4.3Å	homo-dimer Δ	2 x BMA ☞ , 12 x NAG ☞ , 4 x MAN ☞
<input type="checkbox"/>	6met.1.B	T-cell surface glycoprotein CD4		0.37	-	19.52	EM	hetero-trimer Δ	1 x A2G ☞ , 17 x NAG ☞ , 2 x MAN ☞
<input type="checkbox"/>	5u1f.1.I	T-cell surface glycoprotein CD4		0.37	-	19.52	EM, 6.8Å	hetero-9-mer Δ	None
<input type="checkbox"/>	1win.1.A	TCELL SURFACE GLYCOPROTEIN CD4		0.37	-	19.52	X-ray, 4.0Å	monomer Δ	None

This prediction is reliable via procheck

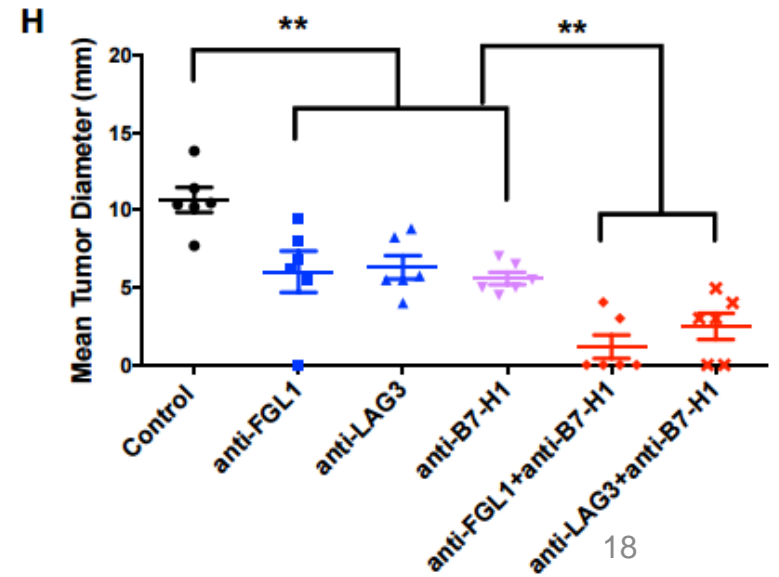
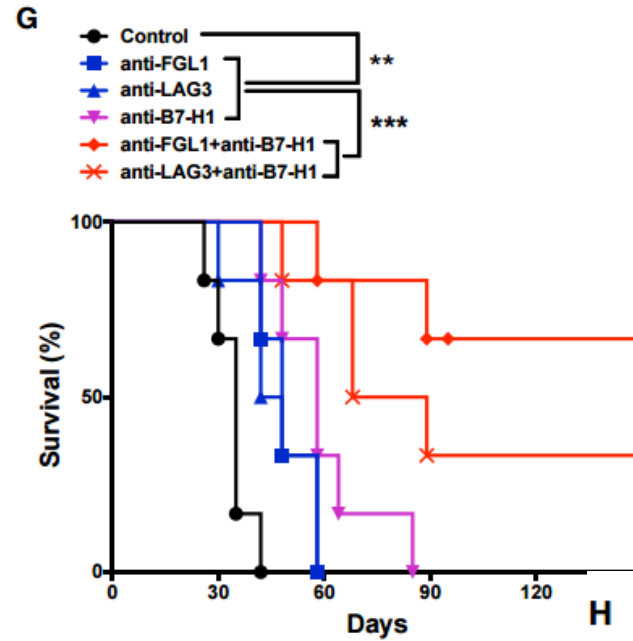
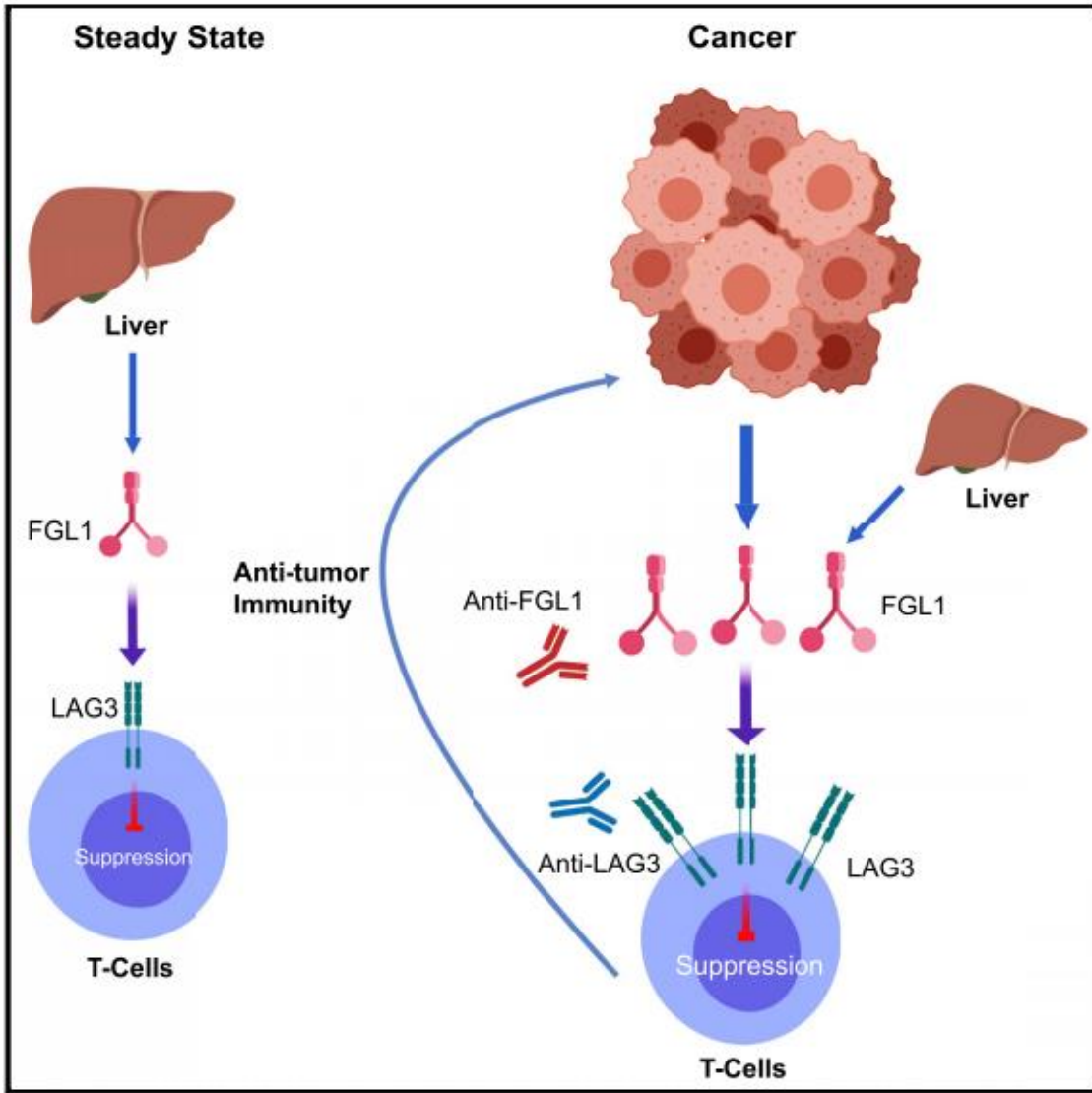


The LAG-3 contains parallel β -sheet



Susan B.FowlerJaneClarke structure (2001)

FGL1-LAG-3 is an important immune evasion mechanism and have implications for the design of cancer immunotherapy



Thank You