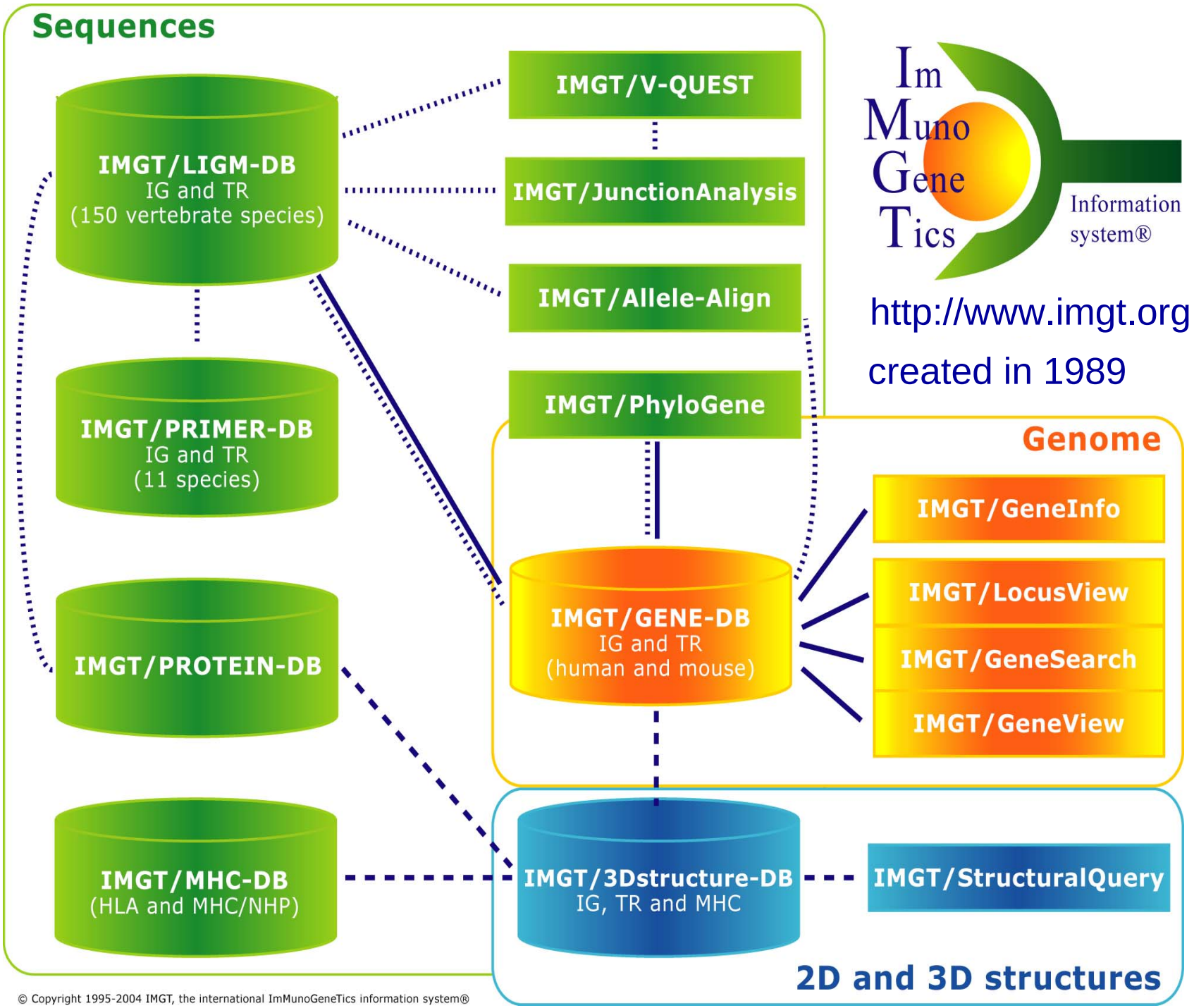
http://www.imgt.org

Standardized sequence and structure analysis of antibody using IMGT®

http://www.imgt.org

Marie-Paule Lefranc
Montpellier, France

Antibody Biology and Engineering
From Basic Mechanisms to Antibody-Based Therapeutics
March 7-12, 2010, Ventura, CA


Sequences
IMGT/LIGM-DB
IG and TR
(150 vertebrate species)
IMGT/V-QUEST
IMGT/JunctionAnalysis
IMGT/Allele-Align
IMGT/PRIMER-DB
IG and TR
(11 species)
IMGT/PhyloGene
IMGT/PROTEIN-DB
IMGT/MHC-DB
(HLA and MHC/NHP)
Genome
IMGT/GeneInfo
IMGT/GENE-DB
IG and TR
(human and mouse)
IMGT/LocusView
IMGT/GeneSearch
IMGT/GeneView
IMGT/3Dstructure-DB
IG, TR and MHC
IMGT/StructuralQuery
2D and 3D structures
Im
Muno
Gene
Tics
Information
system®
http://www.imgt.org
created in 1989
© Copyright 1995-2004 IMGT, the international ImMunoGeneTics information system®

http://www.imgt.org

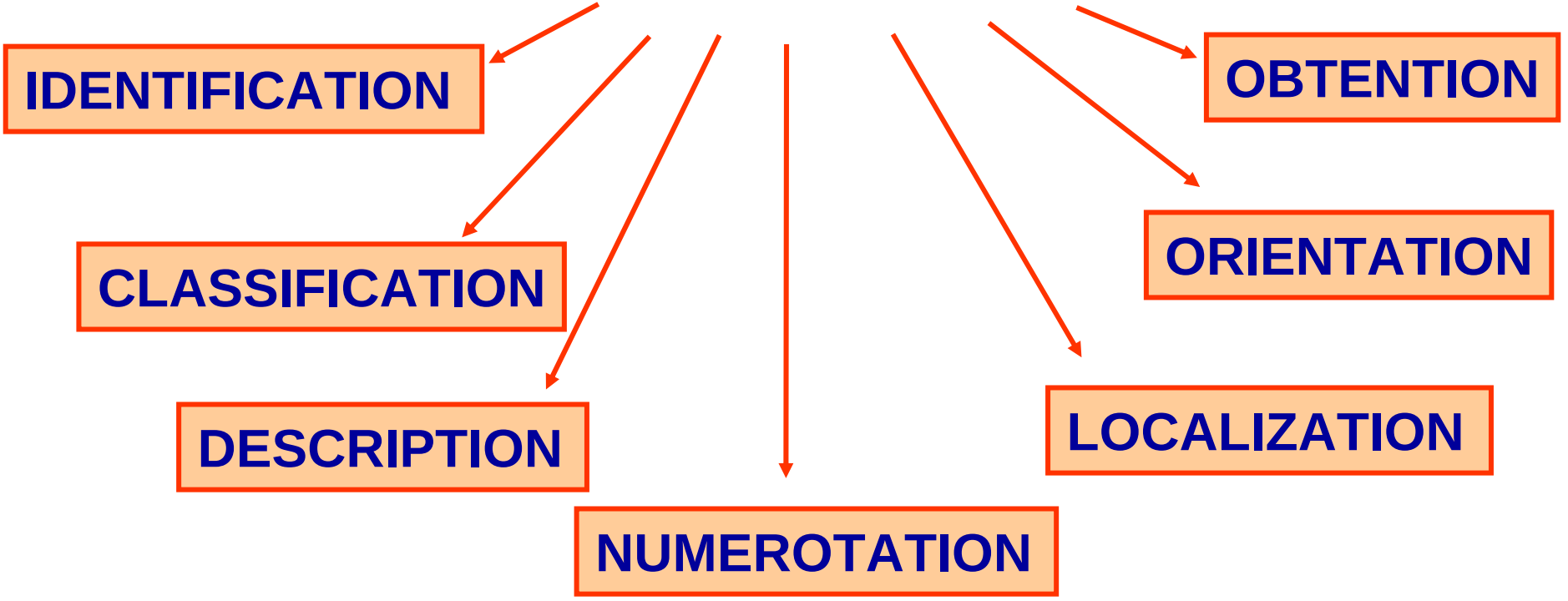
IMGT standards based on IMGT-ONTOLOGY

IMGT-ONTOLOGY

http://www.imgt.org

IMGT-ONTOLOGY seven axioms:

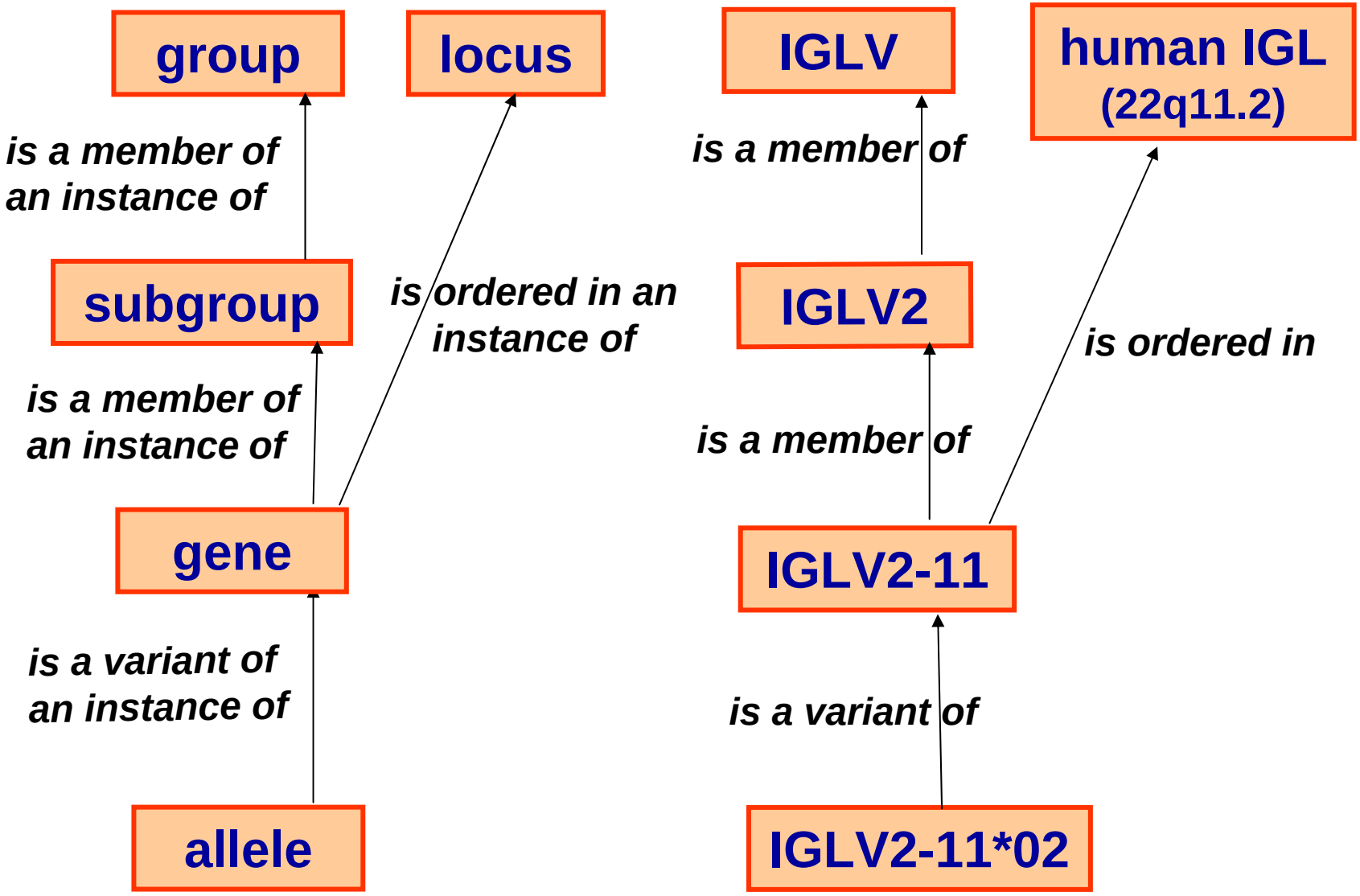
To share, reuse and represent knowledge in Immunogenetics and Life Sciences



Giudicelli and Lefranc, Bioinformatics (1999)

CLASSIFICATION axiom

http://www.imgt.org



Concepts of CLASSIFICATION

http://www.imgt.org

1. The IMGT-ONTOLOGY main concepts of classification
   - include ‘group’, ‘subgroup’, ‘gene’, ‘allele’.
   - have allowed to set up the nomenclature of the immunoglobulin (IG) and T cell receptor (TR) genes (V, D, J, C genes).

2. IMGT gene names have been approved by the HUGO Nomenclature Committee (HGNC) in 1999.

3. New alleles are validated by the WHO-IUIS/IMGT nomenclature committee and entered in IMGT/GENE-DB.

4. IMGT/GENE-DB is the international reference database for IG and TR genes (direct links from NCBI Entrez Gene) and alleles.

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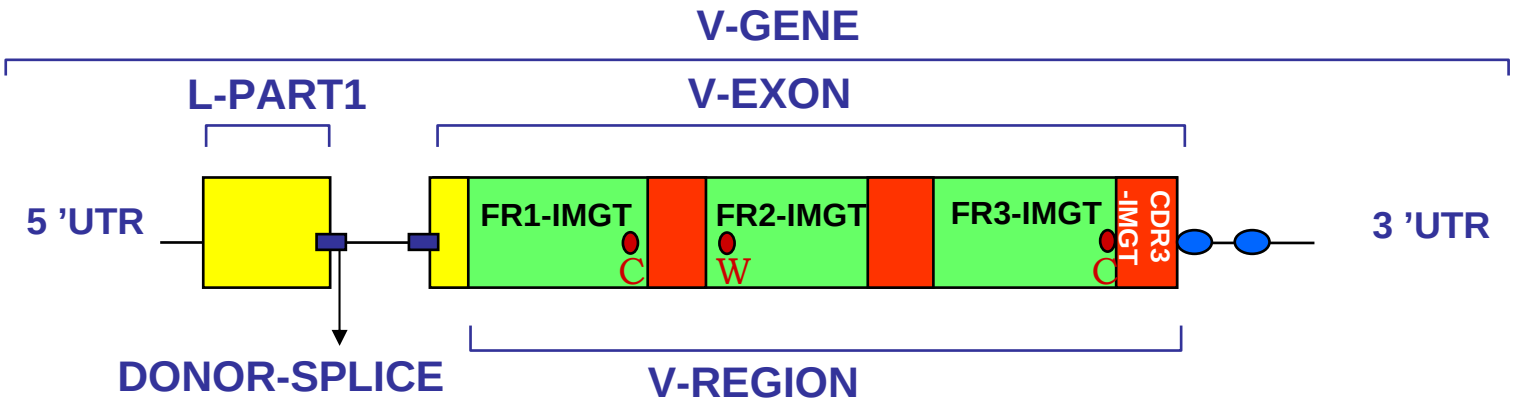
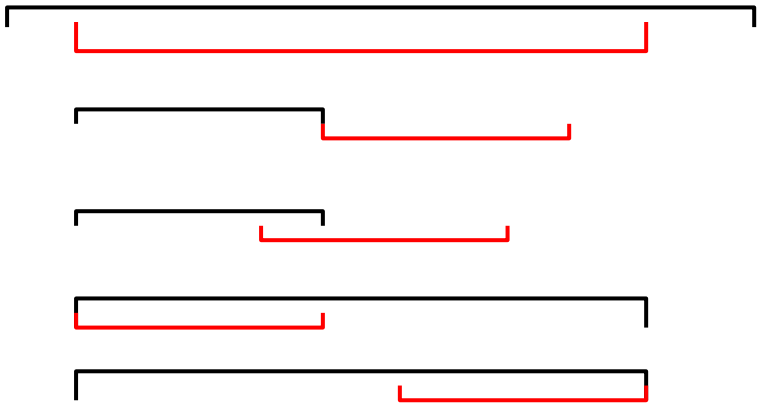
DESCRIPTION axiom

PROTOTYPE for a V-GENE



Label 1	Label 2
V-GENE	V-EXON
FR3-IMGT	CDR3-IMGT
L-PART1	DONOR-SPLICE
V-REGION	FR1-IMGT
V-REGION	CDR3-IMGT

Relations entre Labels



Concepts of DESCRIPTION

http://www.imgt.org

1. The IMGT-ONTOLOGY concepts of description:
   - comprise the standardized IMGT labels and their relations.
   - have allowed to describe the IG (or antibody) and TR sequences and structures, whatever the receptor type, the chain type or the species.

2. IMGT labels are used in all IMGT® databases and tools for the description of:
   - nucleotide and amino acid sequences (IMGT/LIGM-DB…)
   - 2D and 3D structures (IMGT/3Dstructure-DB…).

3. Sequence Ontology (SO) includes IMGT labels.

4. IMGT® databases can be queried using labels (a big 'plus' compared to generalist databases).

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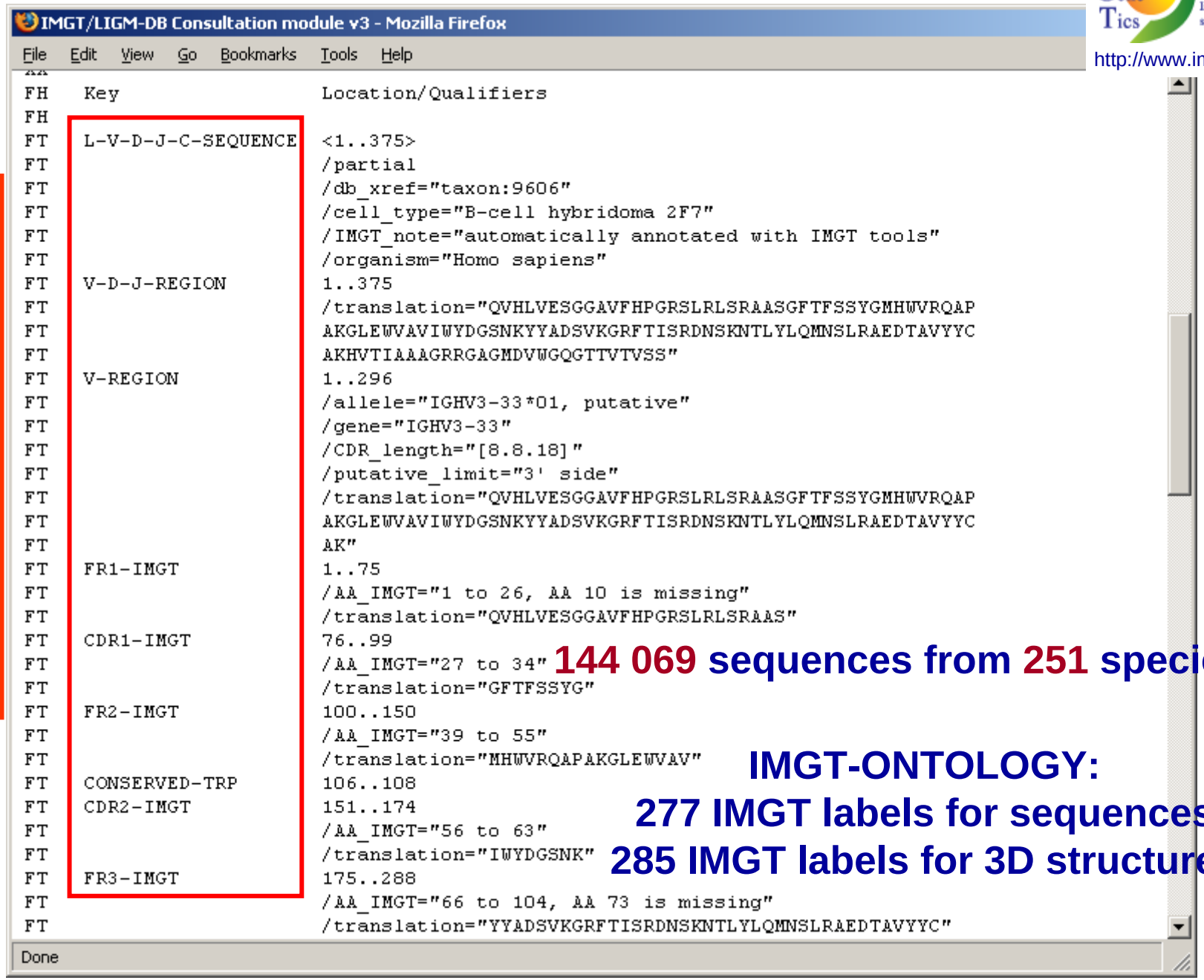
IMGT/LIGM-DB



DESCRIPTION

144 069 sequences from 251 species

IMGT-ONTOLOGY:
277 IMGT labels for sequences
285 IMGT labels for 3D structures

Im Muno Gene Tics Information system®
http://www.imgt.org

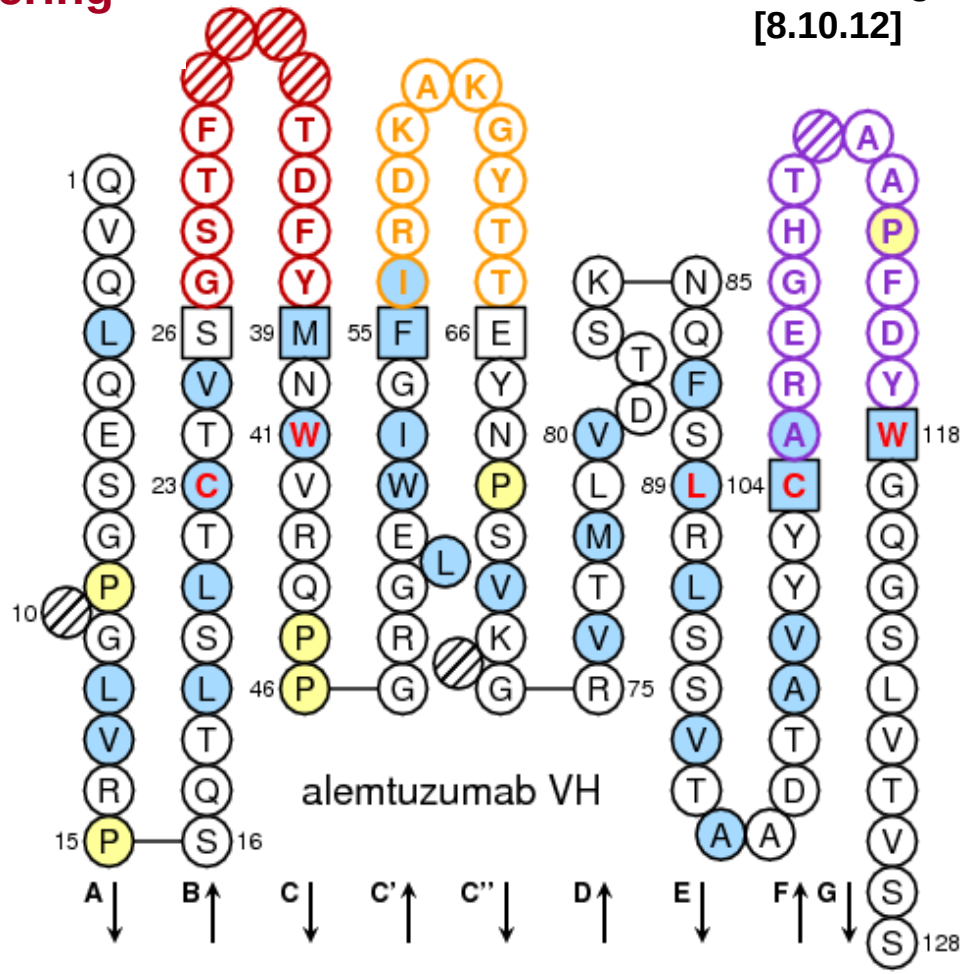
NUMEROTATION axiom

http://www.imgt.org

IMGT Collier de Perles

Based on the **IMGT unique numbering**
(first one in **1997**)

CDR-IMGT lengths
[8.10.12]



Lefranc et al. Dev. Comp. Immunol. 27, 55-77 (2003)

NUMEROTATION axiom

http://www.imgt.org

IMGT Collier de Perles

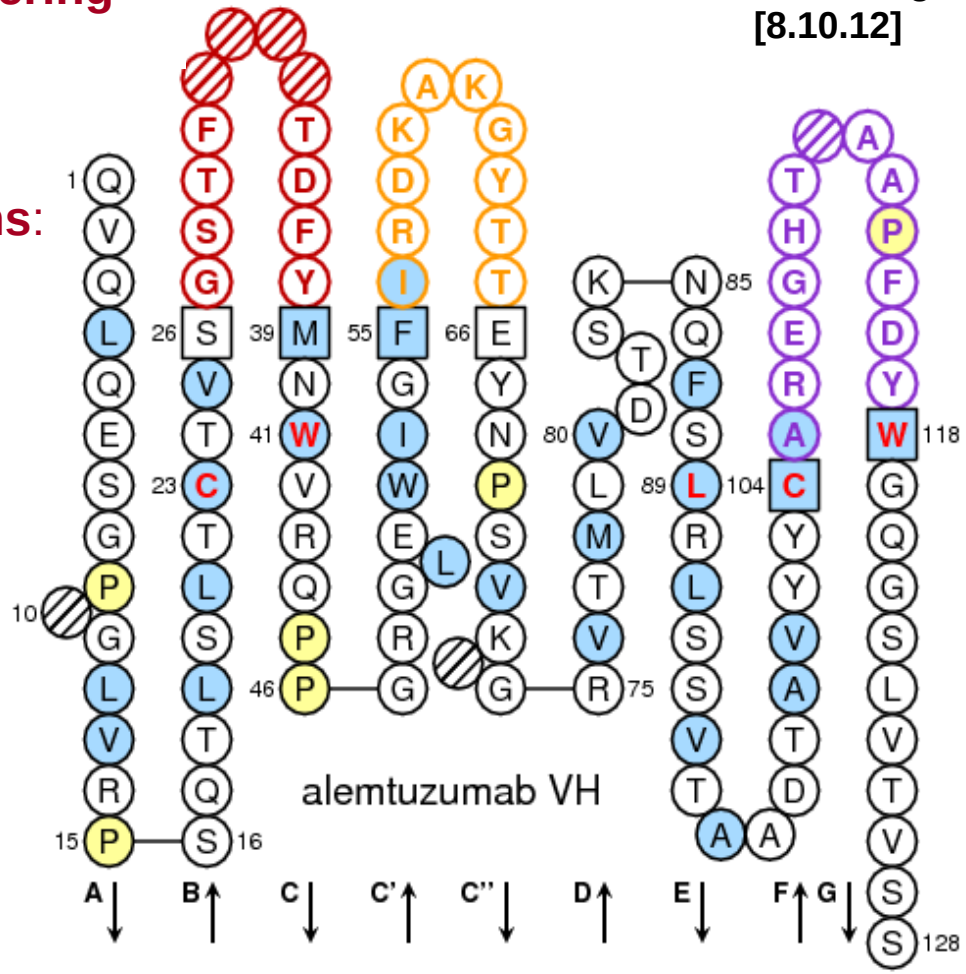
Based on the **IMGT unique numbering** (first one in **1997**)

- conserved AA (and codons) are always at the **same positions**:
  - **23** 1st-CYS
  - **41** CONSERVED-TRP
  - **89** hydrophobic
  - **104** 2nd-CYS
  - **118** J-PHE, J-TRP

- delimitation of the **FR-IMGT** and **CDR-IMGT** is standardized

- **CDR-IMGT lengths** are crucial information

CDR-IMGT lengths [8.10.12]



Lefranc et al. Dev. Comp. Immunol. 27, 55-77 (2003)

Concepts of NUMEROTATION

http://www.imgt.org

1. The IMGT-ONTOLOGY concepts of numerotation include:
- IMGT unique numbering
- IMGT Collier de Perles.

2. The concepts bridge the gap between sequences and 3D structures, at the amino acid (and codon) level, for:
- the variable domains (V-DOMAIN)
- the constant domains (C-DOMAIN).

4. The concepts are used for:
- mutations, polymorphisms
- CDR-IMGT lengths
- contact analysis, paratope definition.

5. WHO-INN programme requires the CDR-IMGT lengths for antibody.

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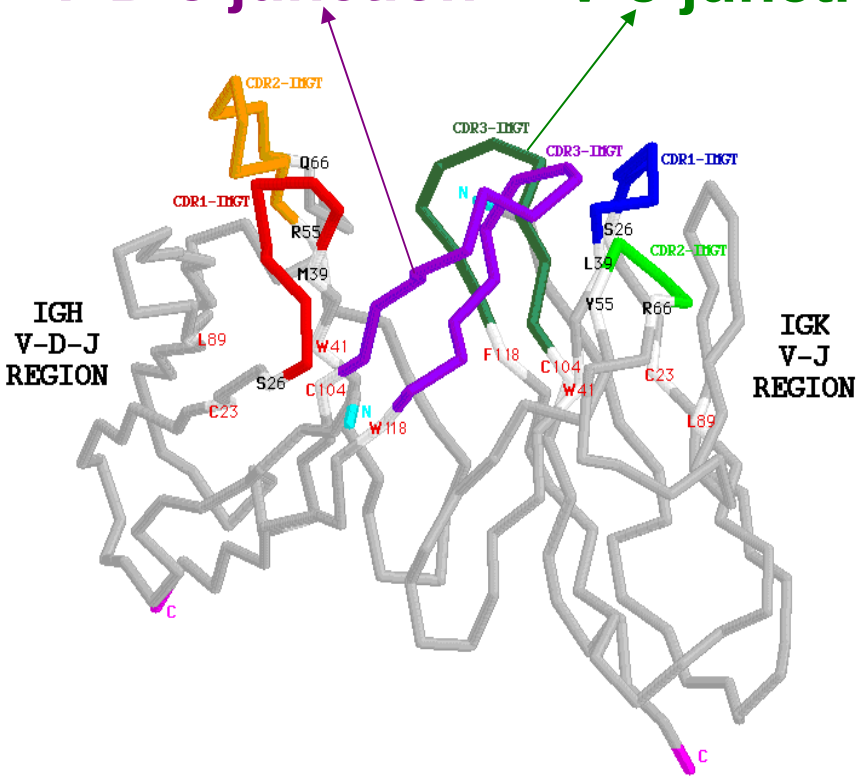
V-DOMAIN: VH and V-KAPPA

http://www.imgt.org

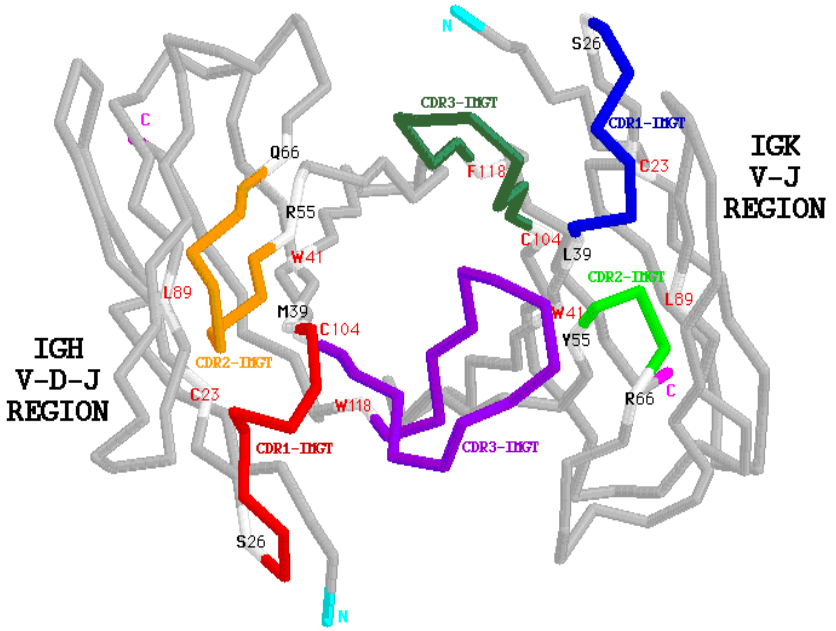
VH **V-KAPPA**

V-D-J junction **V-J junction**



Side view of the V-DOMAIN

VH **V-KAPPA**



View from above the CDR-IMGT

CDR: complementarity determining region
CDR3-IMGT (105-117)
V-D-J junction (104-118), V-J junction (104-118)

The 11 IMGT physicochemical AA classes

http://www.imgt.org

'Volume' classes		'Hydropathy' classes									
	in Å^3	Hydrophobic			Neutral			Hydrophilic			
Very large	189-228	F		W		Y					
Large	162-174	I	L	M					K	R	
Medium	138-154	V					H			E	Q
Small	108-117			C	P	T				D	N
Very small	60-90	A			G	S					
		Aliphatic		Sulfur		Hydroxyl	Basic			Acidic	Amide
						Uncharged	Charged				Uncharged
		Nonpolar				Polar					

Pommié et al. J. Mol Recognit. 17, 17-32 (2004)

IMGT/JunctionAnalysis

Analysis of the IG and TR junctions

http://www.imgt.org

JUNCTION alignments with translation and IMGT AA classes

Click on mutated (underlined) amino acid to see the original one:

		104	105	106	107	108	109	110	111	111.1	111.2	111.3	112.3	112.2	112.1	112	113	114	115	116	117	118
		C	S	P	G	G	S	A	Y						Y	H	E	H	F	Q	Q	W
#1	AY393054	tgt	agt	ccc	ggg	ggt	agt	gct	tat	...	...	...	...	...	tac	cac	gaa	cac	ttc	cag	cag	tgg
		C	V	K	P	T	D	D	D	G				H	R	A	E	Y	F	Q	Y	W
#2	AY393055	tgt	gtg	aaa	ccc	acg	gat	gat	gat	ggc	...	...	...	cac	cgg	gct	gaa	tac	ttc	cag	tac	tgg
		C	S	P	G	G	S	A	Y						Y	H	E	D	F	Q	Q	W
#3	AY393058	tgt	agt	ccc	ggg	ggt	agc	gct	tat	...	...	...	...	...	tac	cac	gaa	gac	ttc	cag	cag	tgg
		C	S	P	G	G	S	A	Y						Y	H	E	H	F	Q	Q	W
#4	AY393072	tgt	agt	ccc	ggg	ggt	agt	gct	tat	...	...	...	...	...	tac	cac	gaa	cac	ttc	cag	cag	tgg
		C	A	R	Q	N	P	P	E	Y	S	G	A	Y	H	D	G	W	F	D	P	W
#5	AY393088	tgt	gcg	aga	caa	aac	ccc	ccc	gag	tat	agt	ggc	gca	tat	cat	gat	ggg	tgg	ttc	gac	ccc	tgg
		C	A	R	E	M	L	Y	G	S	G	G	Y	Y	P	P	D	A	F	E	L	W
#6	AY393089	tgt	gcg	aga	gag	atg	ctc	tat	ggt	tcg	ggg	ggt	tat	tac	ccc	cct	gat	gca	ttt	gag	ctc	tgg
		C	A	R	Q	N	P	P	E	Y	S	G	A	Y	H	D	G	W	F	D	P	W
#7	AY393091	tgt	gcg	aga	cag	aat	ccc	ccc	gag	tat	agt	ggc	gca	tat	cat	gat	ggg	tgg	ttc	gac	ccc	tgg
		C	A	R	E	M	L	Y	G	S	G	G	Y	Y	P	P	D	A	F	E	V	W
#8	AY393092	tgt	gcg	aga	gag	atg	ctc	tat	ggt	tcg	ggg	ggt	tat	tac	ccc	cct	gat	gca	ttt	gag	gtc	tgg
		C	A	R	Q	N	P	P	E	Y	S	G	A	Y	H	D	G	W	F	D	P	W
#9	AY393094	tgt	gcg	aga	cag	aac	ccc	ccc	gag	tat	agt	ggc	gca	tat	cat	gat	ggg	tgg	ttc	gac	ccc	tgg

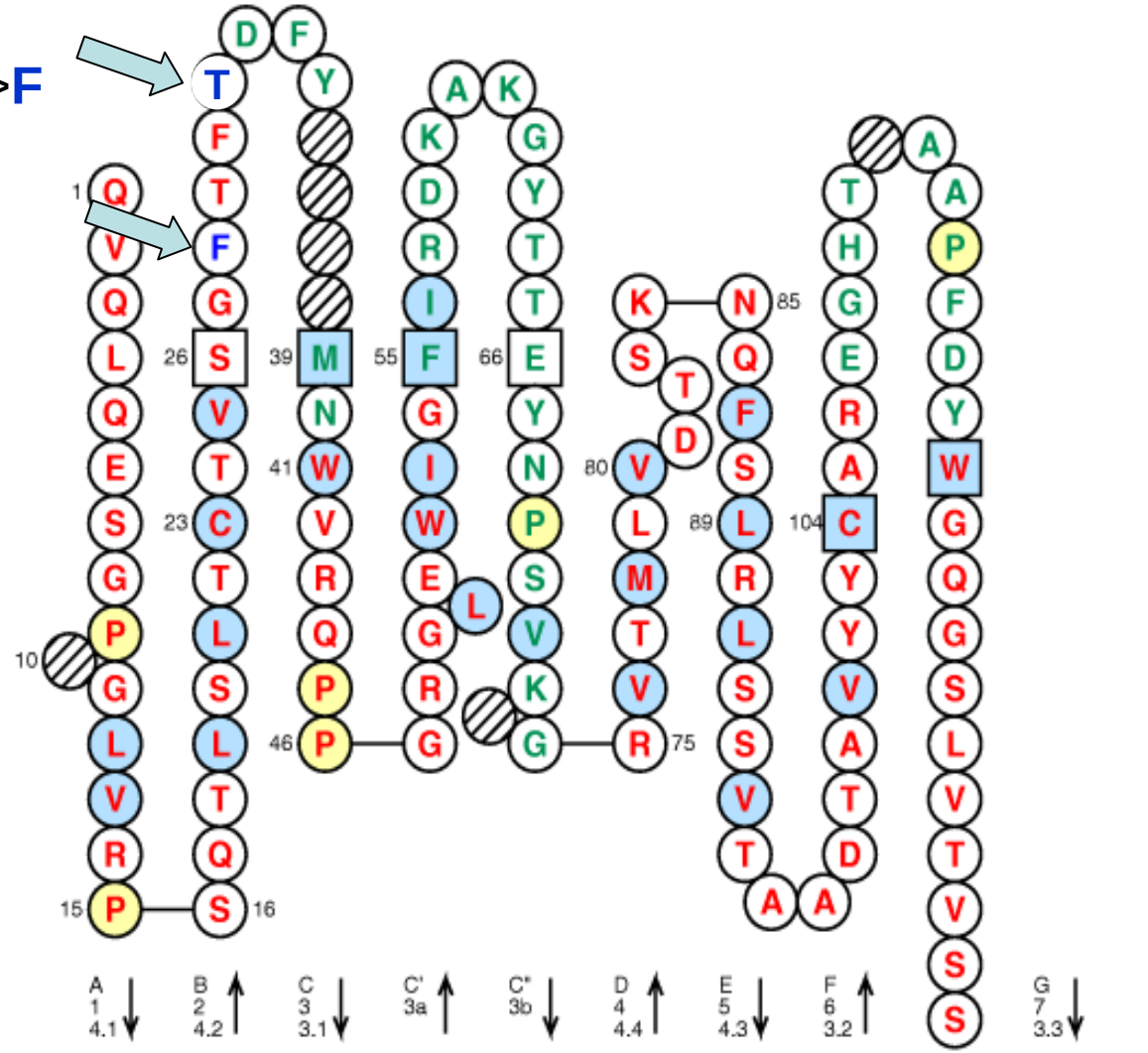
Yousfi Monod et al. Bioinformatics 20, i379-385 (2004)
Pommié et al. J. Mol Recognit. 17, 17-32 (2004)

Antibody humanization and engineering

http://www.imgt.org

Alemtuzumab (CAMPATH®)

2 mutations:
S31>**T**, S28>**F**



Towards «Potential immunogenicity evaluation»

http://www.imgt.org

- Comparison with the closest human germline genes and alleles
- Number of different AA in FR-IMGT

		V-REGION identity percent	FR-IMGT AA differences
VH	alemtuzumab	**73 %**	**14 /91**
	bevacizumab	**72.40 %**	**23**
	trastuzumab	**81.63 %**	**9**
V-KAPPA	alemtuzumab	**86.32 %**	**2 /89**
	bevacizumab	**87.40 %**	**7**
	trastuzumab	**86.32 %**	**6**

Magdelaine-Beuzelin C. et al. Crit. Rev. Oncol. Hemat. 64, 210-225 (2007)

IMGT/DomainGapAlign

Sequence name: alemtuzumab_H

http://www.imgt.org

Move your mouse over the amino acids in bold for the characterization of AA class changes

Closest reference gene and allele(s) from the IMGT domain directory

V gene and allele	Species	Domain	Smith-Waterman Score	Identity percentage	Overlap
IGHV4-59*01	Homo sapiens	1	494	73.0	100

J gene and allele	Species	Domain	Smith-Waterman Score	Identity percentage	Overlap
IGHJ4*01	Homo sapiens	1	94	92.9	14
IGHJ4*02	Homo sapiens	1	94	92.9	14
IGHJ4*03	Homo sapiens	1	94	92.9	14

Alignment with the closest genes and alleles from the IMGT domain directory

```
                       FR1-IMGT                CDR1-IMGT     FR2-IMGT              CDR2-IMGT               FR3-IMGT                             CDR3-IMGT       FR4-IMGT
                        (1-26)                  (27-38)       (39-55)               (56-65)                (66-104)                             (105-117)       (118-128)
                   A                 B             BC          C          C'          C'C"        C"          D            E            F            FG              G
                (1-15)            (16-26)       (27-38)     (39-46)    (47-55)      (56-65)     (66-74)     (75-84)      (85-96)     (97-104)     (105-117)       (118-128)
              ----------------> ------------>              ---------> --------->               ---------> ----------> -------------> --------->                  ------------>
              1         10   15 16     23 26 27          38 3941   46 47      55 56       65 66       74 75    80 84 85  89     96 97    104 105 11112 117 118        128
              |.........|....| |......|..| |...........| |.|....| |........| |.........| |........| |....|...| |...|.......| |.......| |.....||....| |..........|
alemtuzumab_H QVQLQESGP.GLVRP SQTLSLTCTVS GFTF....TDFY MNWVRQPP GRGLEWIGF IRDKAKGYTT EYNPSVK.G RVTMLVDTSK NQFSLRLSSVTA ADTAVYYC AREGHTAAPFDYW GQGSLVTVSS.
IGHV4-59*01   QVQLQESGP.GLVKP SETLSLTCTVS GGSI....SSYY WSWIRQPP GKGLEWIGY IYYS...GST NYNPSLK.S RVTISVDTSK NQFSLKLSSVTA ADTAVYYC AR          FDYW GQGTLVTVSS.
(Homo sapiens)              R    Q        FTF      TDF MN V          R     F  RDK    YT E     V  G     ML          R                                      S
              |-------------------------------------------V-REGION---------------------------------------------------------------------| |--N--| |---J-REGION---|
```

Region(s) and domain(s) identified in your sequence (corresponding to the closest genes and alleles)

Without gaps *Sequence in FASTA format* Download

With gaps *Sequence in FASTA format* Download

```
QVQLQESGPGLVRPSQTLSLTCTVSGFTFTDFYMNWVRQPPGRGLEWIGF
IRDKAKGYTTEYNPSVKGRVTMLVDTSKNQFSLRLSSVTAADTAVYYCAR
EGHTAAPFDYWGQGSLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV
KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ
TYICNVNHKPSNTKVDKKVEAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK
NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKL
TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
```

IMGT Collier de Perles

IMGT/DomainGapAlign

Towards «Potential immunogenicity evaluation»

http://www.imgt.org

V-REGION identity percent

CDR-IMGT lengths

FR-IMGT lengths

Closest human germline
IGHV4-59*01

Sequence name	V-REGION identity percentage	CDR-IMGT lengths	Number of different AA in CDR1- and CDR2-IMGT	FR-IMGT lengths	Number of different AA in FR-IMGT
alemtuzumab_H	73.0%	[8,10,12]	11	[25,17,38,11] = 91 AA	14

11 different AA in CDR1- and CDR2-IMGT

14 different AA in FR-IMGT 14/91

Ehrenmann et al. Nucl. Acids Res. 38, D301-307 (2010)

IMGT/DomainGapAlign

Towards «Potential immunogenicity evaluation»

http://www.imgt.org

Characteristics of the AA class changes:

CDR-IMGT	Number of different AA	Different AA with class changes
CDR1-IMGT (27-38)	6	G28>F (- - -) very dissimilar S29>T (+ - +) similar I30>F (+ - -) dissimilar S35>T (+ - +) similar S36>D (- - -) very dissimilar Y37>F (- + -) dissimilar
CDR2-IMGT (56-65)	5	Y57>R (- - -) very dissimilar Y58>D (- - -) very dissimilar S59>K (- - -) very dissimilar G63>Y (+ - -) dissimilar S64>T (+ - +) similar

FR-IMGT	Number of different AA	Different AA with class changes
FR1-IMGT (1-26)	2	K14>R (+ + +) very similar E17>Q (+ + -) similar
FR2-IMGT (39-55)	5	W39>M (+ - -) dissimilar S40>N (- - -) very dissimilar I42>V (+ - +) similar K48>R (+ + +) very similar Y55>F (- + -) dissimilar
FR3-IMGT (66-104)	6	N66>E (+ - -) dissimilar L71>V (+ - +) similar S74>G (+ + -) similar I78>M (+ + -) similar S79>L (- - -) very dissimilar K90>R (+ + +) very similar
FR4-IMGT (118-129)	1	T122>S (+ - +) similar

(Hydropathy Volume Physicochemical)
+ : conserved classes
- : different classes

- **very similar (+ + +)**
- **similar (+ - +), (+ + -)**
- **dissimilar (+ - -), (- + -), (- - +)**
- **very dissimilar (- - -)**

Ehrenmann et al. Nucl. Acids Res. 38, D301-307 (2010)

IMGT/DomainGapAlign:

Towards «Potential immunogenicity evaluation»

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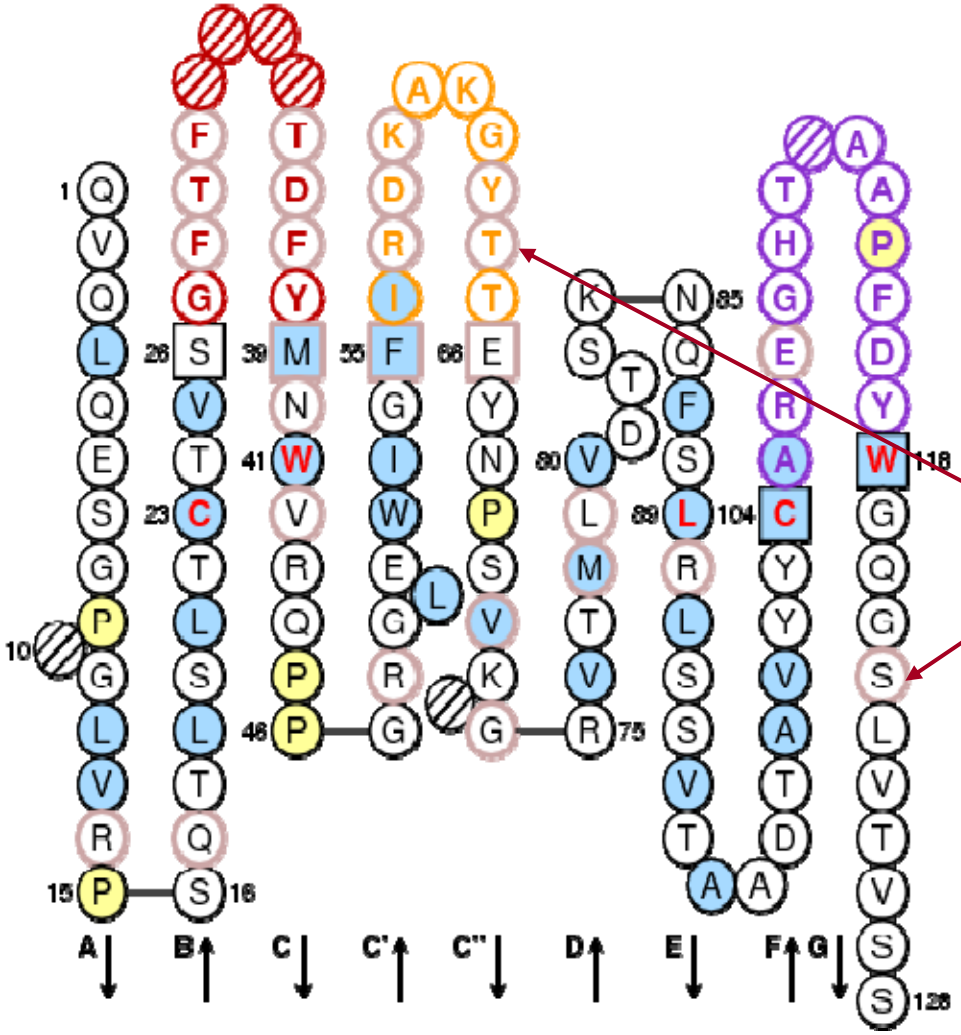
IMGT Collier de Perles



AA that are different compared to the closest germline V and J genes and alleles

(e.g. for alemtuzumab: 11 AA in CDR1- and CDR2-IMGT and 14 AA in the FR-IMGT, compared to *Homo sapiens* IGHV4-59*01)

Ehrenmann et al. Nucl. Acids Res. 38, D301-307 (2010)

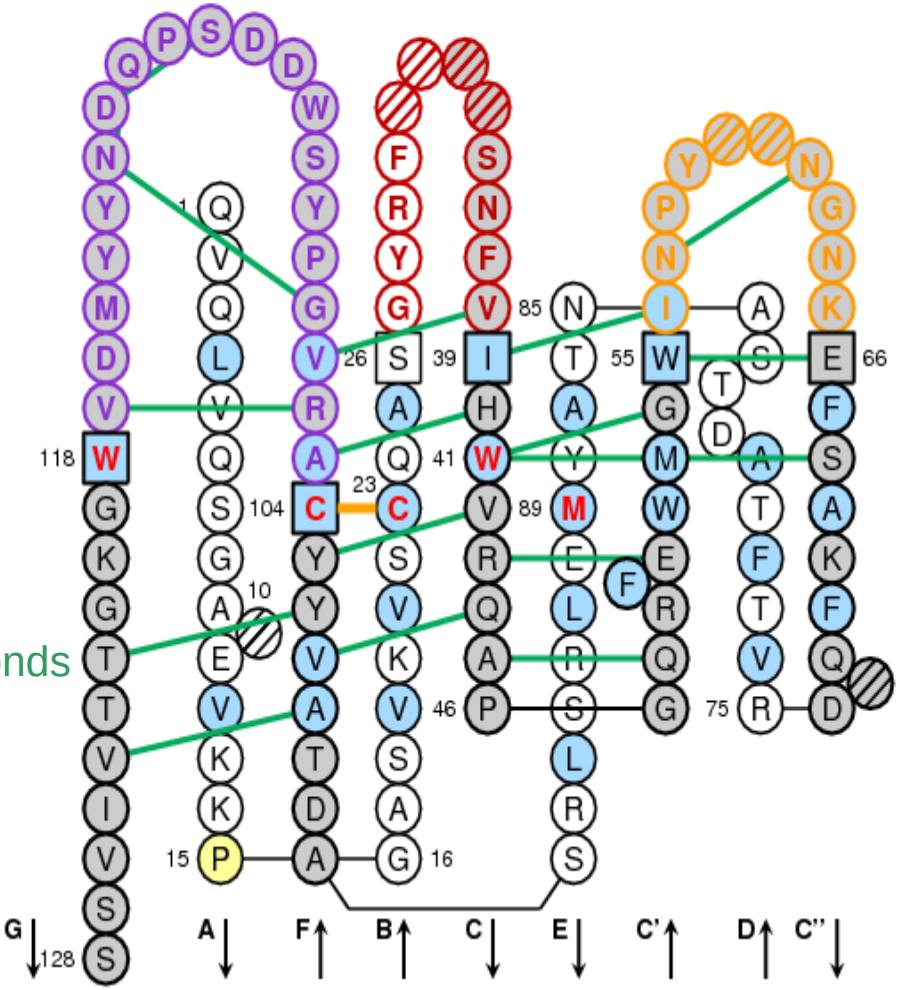
IMGT/3Dstructure-DB

http://www.imgt.org

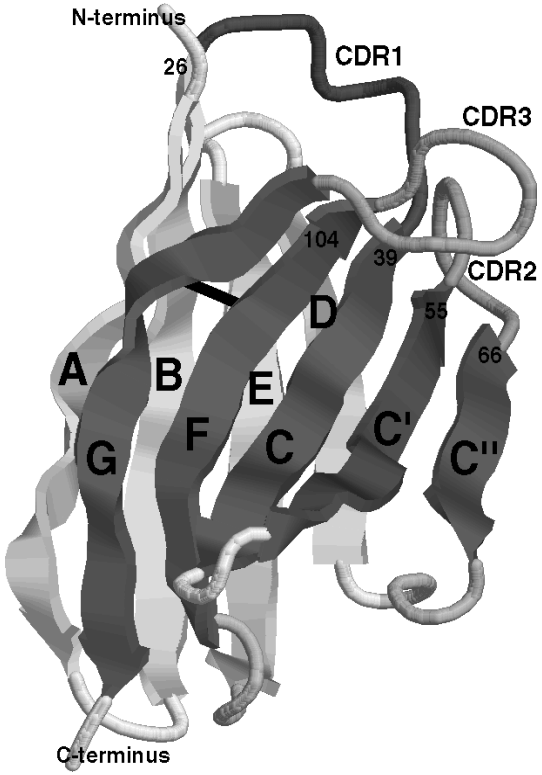
IMGT Collier de Perles : *Homo sapiens* (Human) IGHV V-DOMAIN from b12 (1hzh_H)

CDR-IMGT lengths [8.8.20]

Hydrogen bonds



V-DOMAIN



Lefranc et al. Nucl. Acids Res. 37, D1006-1012 (2009)

Contacts VH-(Ligand), V-KAPPA-(Ligand)

http://www.imgt.org

IMGT molecule name	IMGT description	Chain ID	IMGT chain description	Domain number	IMGT domain description
CAMPATH-1H, alemtuzumab, MABCAMPATH®	FAB-GAMMA-1_KAPPA	1ce1_H	VH-CH1	[D1]	VH
				[D2]	CH1
		1ce1_L	L-KAPPA	[D1]	V-KAPPA
				[D2]	C-KAPPA
CD52 (synthetic peptide)	Peptide	1ce1_P	Peptide		

	Unit 1		Unit 2		Residue contacts	Number of residues			Atom contact types		
	Domain	Chain	Domain	Chain		Total	From 1	From 2	Total	Polar	Hydrogen
DomPair	VH	1ce1_H	CH1	1ce1_H	19	17	8	9	125	9	1
DomPair			V-KAPPA	1ce1_L	63	45	24	21	532	61	6
DomPair			(Ligand)	1ce1_P	25	19	12	7	216	40	9
DomPair	CH1	1ce1_H	VH	1ce1_H	19	17	9	8	125	9	1
DomPair			C-KAPPA	1ce1_L	68	58	28	30	498	40	6
DomPair	V-KAPPA	1ce1_L	VH	1ce1_H	63	45	21	24	532	61	6
DomPair			C-KAPPA	1ce1_L	18	18	8	10	137	19	2
DomPair			(Ligand)	1ce1_P	16	14	7	7	171	37	5
DomPair	C-KAPPA	1ce1_L	CH1	1ce1_H	68	58	30	28	498	40	6
DomPair			V-KAPPA	1ce1_L	18	18	10	8	137	19	2

Contacts V-KAPPA-(Ligand)

http://www.imgt.org

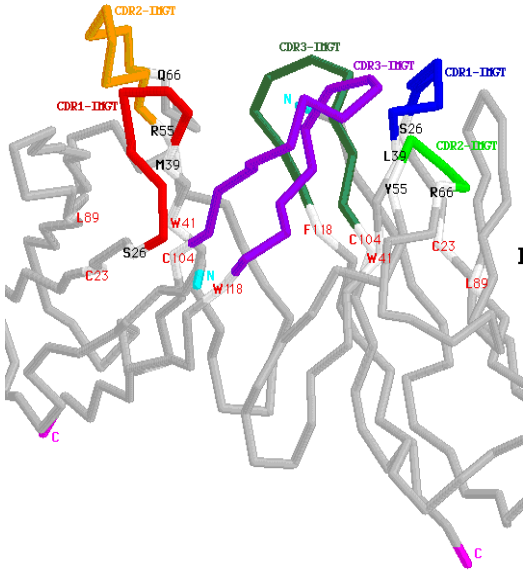
Summary:

Residue contacts	Number of residues			Atom contact types		
	Total	From 1	From 2	Total	Polar	Hydrogen
16	14	7	7	171	37	5

List of the Residue@Position pair contacts:

Click 'R@P' for IMGT Residue@Position cards

	Order						Order					Atom contacts		
	IMGT Num	Residue		Domain	Chain		IMGT Num	Residue		Domain	Chain	Total	Polar	Hydrogen
R@P	38	TYR	Y	V-KAPPA	1ce1_L	R@P	3	SER	S		1ce1_P	1	0	0
R@P	38	TYR	Y	V-KAPPA	1ce1_L	R@P	5	PRO	P		1ce1_P	21	0	0
R@P	56	ASN	N	V-KAPPA	1ce1_L	R@P	3	SER	S		1ce1_P	3	2	0
R@P	107	HIS	H	V-KAPPA	1ce1_L	R@P	4	SER	S		1ce1_P	20	4	1
R@P	107	HIS	H	V-KAPPA	1ce1_L	R@P	5	PRO	P		1ce1_P	12	2	0
R@P	107	HIS	H	V-KAPPA	1ce1_L	R@P	6	SER	S		1ce1_P	14	3	1
R@P	108	ILE	I	V-KAPPA	1ce1_L	R@P	5	PRO	P		1ce1_P	12	1	0
R@P	108	ILE	I	V-KAPPA	1ce1_L	R@P	6	SER	S		1ce1_P	12	3	0
R@P	109	SER	S	V-KAPPA	1ce1_L	R@P	6	SER	S		1ce1_P	11	2	0
R@P	114	ARG	R	V-KAPPA	1ce1_L	R@P	6	SER	S		1ce1_P	18	3	1
R@P	114	ARG	R	V-KAPPA	1ce1_L	R@P	7	ALA	A		1ce1_P	4	2	0
R@P	114	ARG	R	V-KAPPA	1ce1_L	R@P	8	ASP	D		1ce1_P	6	2	0
R@P	116	ARG	R	V-KAPPA	1ce1_L	R@P	2	THR	T		1ce1_P	1	1	0
R@P	116	ARG	R	V-KAPPA	1ce1_L	R@P	4	SER	S		1ce1_P	9	4	1
R@P	116	ARG	R	V-KAPPA	1ce1_L	R@P	6	SER	S		1ce1_P	20	6	1
R@P	116	ARG	R	V-KAPPA	1ce1_L	R@P	7	ALA	A		1ce1_P	7	2	0



Kaas Q. et al.
Nucl. Acids Res. (2004)

Contacts VH-(Ligand)

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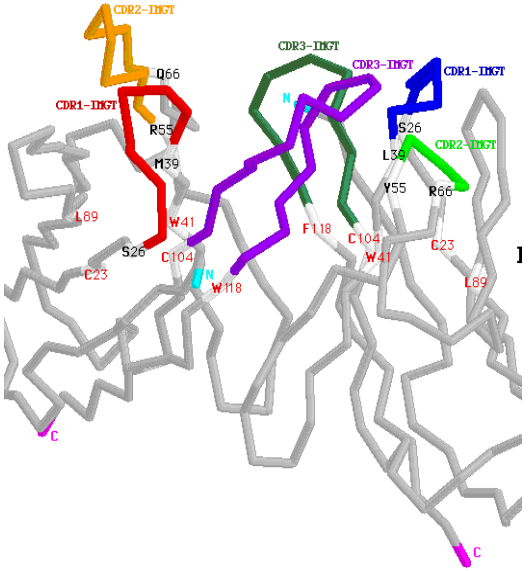
	IMGT Num	Residue		Domain	Chain		IMGT Num	Residue		Domain	Chain	Total	Polar	Hydrogen
R@P	38	TYR	Y	VH	1ce1_H	R@P	2	THR	T		1ce1_P	4	0	0
R@P	38	TYR	Y	VH	1ce1_H	R@P	7	ALA	A		1ce1_P	13	1	0
R@P	38	TYR	Y	VH	1ce1_H	R@P	8	ASP	D		1ce1_P	14	2	2
R@P	55	PHE	F	VH	1ce1_H	R@P	6	SER	S		1ce1_P	5	0	0
R@P	55	PHE	F	VH	1ce1_H	R@P	7	ALA	A		1ce1_P	16	0	0
R@P	55	PHE	F	VH	1ce1_H	R@P	8	ASP	D		1ce1_P	1	0	0
R@P	57	ARG	R	VH	1ce1_H	R@P	7	ALA	A		1ce1_P	9	3	2
R@P	57	ARG	R	VH	1ce1_H	R@P	8	ASP	D		1ce1_P	20	6	1
R@P	61	LYS	K	VH	1ce1_H	R@P	8	ASP	D		1ce1_P	11	2	1
R@P	66	GLU	E	VH	1ce1_H	R@P	7	ALA	A		1ce1_P	1	0	0
R@P	107	GLU	E	VH	1ce1_H	R@P	2	THR	T		1ce1_P	13	2	1
R@P	107	GLU	E	VH	1ce1_H	R@P	4	SER	S		1ce1_P	5	2	0
R@P	107	GLU	E	VH	1ce1_H	R@P	7	ALA	A		1ce1_P	5	0	0
R@P	108	GLY	G	VH	1ce1_H	R@P	1	GLY	G		1ce1_P	2	1	0
R@P	108	GLY	G	VH	1ce1_H	R@P	2	THR	T		1ce1_P	9	2	0
R@P	109	HIS	H	VH	1ce1_H	R@P	1	GLY	G		1ce1_P	24	4	0
R@P	109	HIS	H	VH	1ce1_H	R@P	2	THR	T		1ce1_P	21	5	0
R@P	109	HIS	H	VH	1ce1_H	R@P	3	SER	S		1ce1_P	9	2	1
R@P	110	THR	T	VH	1ce1_H	R@P	1	GLY	G		1ce1_P	1	1	0
R@P	110	THR	T	VH	1ce1_H	R@P	3	SER	S		1ce1_P	11	4	1
R@P	112	ALA	A	VH	1ce1_H	R@P	3	SER	S		1ce1_P	3	1	0
R@P	113	ALA	A	VH	1ce1_H	R@P	2	THR	T		1ce1_P	3	0	0
R@P	113	ALA	A	VH	1ce1_H	R@P	3	SER	S		1ce1_P	7	2	0
R@P	113	ALA	A	VH	1ce1_H	R@P	4	SER	S		1ce1_P	4	0	0
R@P	114	PRO	P	VH	1ce1_H	R@P	4	SER	S		1ce1_P	5	0	0



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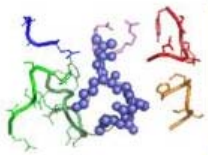
IMGT/2Dstructure-DB

Overview



Your query: INN entries. **International Nonproprietary Name (INN)**

Number of results: 53

Click on IMGT entry ID (2nd column) for entry card

	IMGT entry ID	IMGT molecule name	IMGT entry type	IMGT receptor description	Species	Proposed list	Recommended list	CAS number
1	7637	trastuzumab, 4D5V8, HERCEPTIN®	INN	IG-GAMMA-1_KAPPA	*Humanized*	L78 (1997)	R40 (1998)	180288-69-1
2	7906	cetuximab, Fab C225, IMC-225, ERBITUX™	INN	IG-GAMMA-1_KAPPA	*Chimeric*	L82 (1999)	R44 (2000)	205923-56-4
3	8005	alemtuzumab, Campath-1H, LDP-03, CAMPATH®/MABCAMPATH®	INN	IG-GAMMA-1_KAPPA	*Humanized*	L83 (2000)	R45 (2001)	216503-57-0
4	8017	bevacizumab, 12-IgG1, F(ab)-12 IgG1, Fab-12 IgG1, rhuMAb-VEGF, AVASTIN®	INN	FAB-GAMMA-1_KAPPA	*Humanized*	L83 (2000)	R45 (2001)	216974-75-3
5	8313	ranibizumab, Fab-12 variant Y0317, RhuFab, LUCENTIS®	INN	FAB-GAMMA-1_KAPPA	*Humanized*	L90 (2004)	R52 (2004)	347396-82-1
6	8380	pertuzumab, rhuMAB 2C4	INN	FAB-GAMMA-1_KAPPA	*Humanized*	L89 (2003)	R51 (2004)	380610-27-5
7	8598	naptumomab estafenatox	INN	FAB-GAMMA-1-SAG_KAPPA	*Mus musculus*	L96 (2006)	R58 (2007)	676258-98-3
8	8651	tadocizumab	INN	FAB-GAMMA-1_KAPPA	*Humanized*	L94 (2005)	R56 (2006)	339086-80-5
9	8658	efungumab	INN	SCFV-HEAVY-KAPPA	*Homo sapiens*	L95 (2006)	R57 (2007)	762260-74-2
10	8659	abagovomab	INN	IG-GAMMA-1_KAPPA	*Mus musculus*	L95 (2006)	R57 (2007)	792921-10-9
11	8669	atacicept	INN	FUSION-TNFRSF13B-FC-GAMMA-1	*Homo sapiens*	L95 (2006)	R57 (2007)	845264-92-8
12	8693	motavizumab	INN	IG-GAMMA-1_KAPPA	*Humanized*	L95 (2006)	R57 (2007)	677010-34-3
13	8734	bavituximab	INN	IG-GAMMA-1_KAPPA	*Chimeric*	L95 (2006)	R57 (2007)	648904-28-3
14	8739	aflibercept	INN	FUSION-FLT1-KDR-FC-GAMMA-1	*Homo sapiens*	L95 (2006)	R57 (2007)	862111-32-8
15	8750	rilonacept, ARCALYST™	INN	FUSION-IL1RAP-IL1R1-FC-GAMMA-1	*Homo sapiens*	L95 (2006)	R57 (2007)	501081-76-1
16	8753	lexatumumab	INN	IG-GAMMA-1_LAMBDA	*Homo sapiens*	L95 (2006)	R57 (2007)	845816-02-6
17	8818	ibalizumab	INN	IG-GAMMA-4_KAPPA	*Humanized*	L97 (2007)	R59 (2008)	680188-33-4
18	8832	tenatumomab, ST2146	INN	IG-GAMMA-2B_KAPPA	*Mus musculus*	L98 (2007)	R60 (2008)	592557-43-2 592557-41-0
19	8836	canakinumab	INN	IG-GAMMA-1_KAPPA	*Homo sapiens*	L97 (2007)	R59 (2008)	402710-27-4 402710-25-2
20	8862	etaracizumab, MEDI-522, hLM609	INN	IG-GAMMA-1_KAPPA	*Humanized*	L99 (2008)	R61 (2009)	892553-42-3
21	8864	otelixizumab	INN	IG-GAMMA-1_LAMBDA	*Humanized*	L98 (2007)	R60 (2008)	881191-44-2
22	8869	teplizumab	INN	IG-GAMMA-1_KAPPA	*Humanized*	L97 (2007)	R59 (2008)	876387-05-2
23	8887	lucatumumab	INN	IG-GAMMA-1_KAPPA	*Homo sapiens*	L98 (2007)	R60 (2008)	903512-50-5
24	8888	panobacumab, Aerumab 11	INN	IG-MU_KAPPA_J-CHAIN	*Homo sapiens* *Mus musculus*	L100 (2008)	Unpublished	885053-97-4
25	8894	gantenerumab	INN	IG-GAMMA-1_KAPPA	*Homo sapiens*	L97 (2007)	R59 (2008)	89957-37-9
26	8922	milatuzumab	INN	IG-GAMMA-1_KAPPA	*Humanized*	L98 (2007)	R60 (2008)	899796-83-9
27	8932	veltuzumab	INN	IG-GAMMA-1_KAPPA	*Humanized*	L98 (2007)	R60 (2008)	728917-18-8
28	8941	tanezumab, RN624	INN	IG-GAMMA-2_KAPPA	*Humanized*	L99 (2008)	R61 (2009)	880266-57-9
29	8942	anrukinzumab	INN	IG-GAMMA-1_KAPPA	*Humanized*	L98 (2007)	R60 (2008)	910649-32-0

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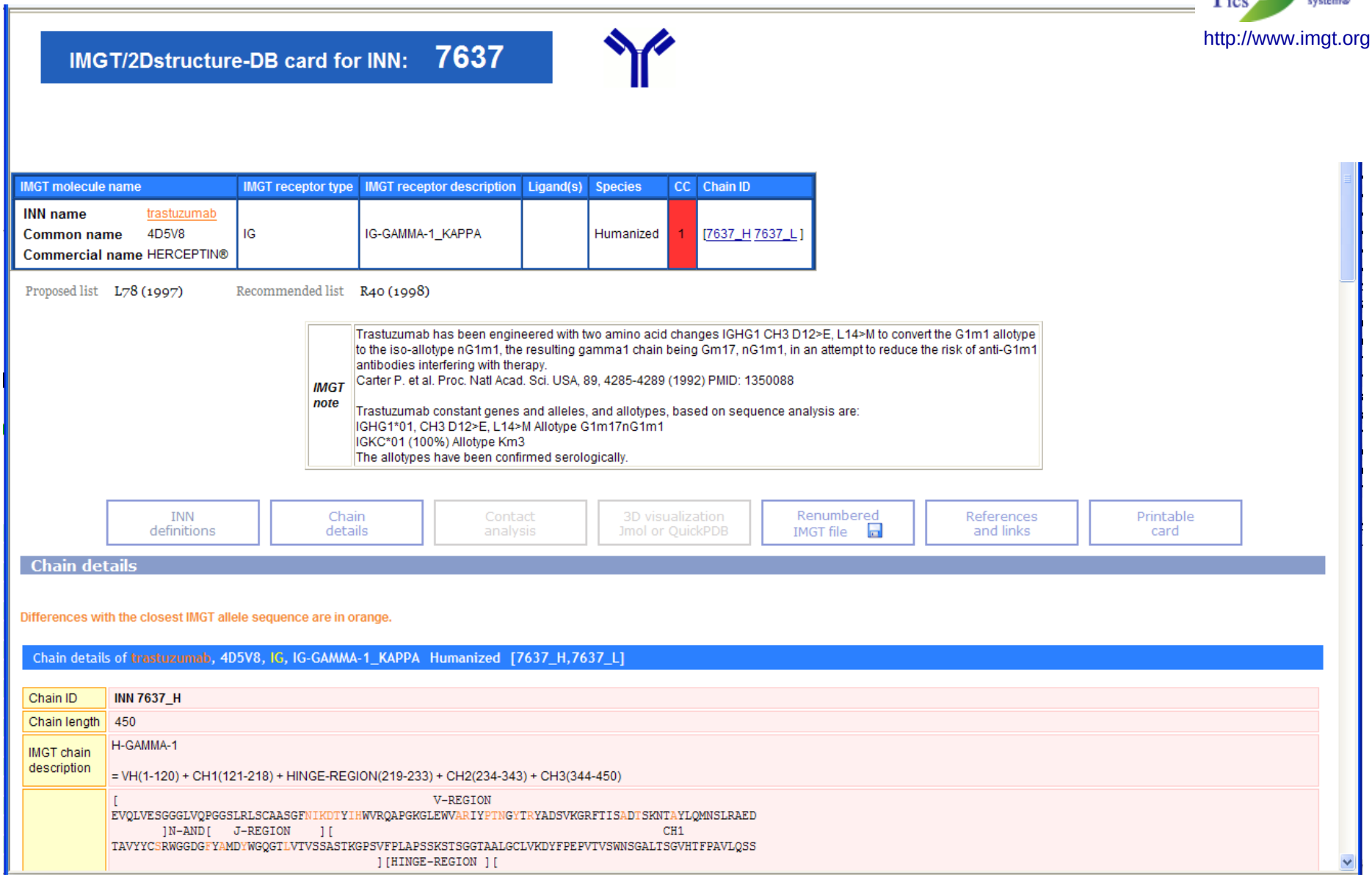
IMGT/2Dstructure-DB

http://www.imgt.org



IMGT/2Dstructure-DB card for INN: 7637

IMGT molecule name		IMGT receptor type	IMGT receptor description	Ligand(s)	Species	CC	Chain ID
INN name	trastuzumab	IG	IG-GAMMA-1_KAPPA		Humanized	1	[7637_H 7637_L]
Common name	4D5V8						
Commercial name	HERCEPTIN®						

Proposed list L78 (1997) Recommended list R40 (1998)

IMGT note

Trastuzumab has been engineered with two amino acid changes IGHG1 CH3 D12>E, L14>M to convert the G1m1 allotype to the iso-allotype nG1m1, the resulting gamma1 chain being Gm17, nG1m1, in an attempt to reduce the risk of anti-G1m1 antibodies interfering with therapy.
Carter P. et al. Proc. Natl Acad. Sci. USA, 89, 4285-4289 (1992) PMID: 1350088

Trastuzumab constant genes and alleles, and allotypes, based on sequence analysis are:
IGHG1*01, CH3 D12>E, L14>M Allotype G1m17nG1m1
IGKC*01 (100%) Allotype Km3
The allotypes have been confirmed serologically.

INN definitions | Chain details | Contact analysis | 3D visualization Jmol or QuickPDB | Renumbered IMGT file | References and links | Printable card

Chain details

Differences with the closest IMGT allele sequence are in orange.

Chain details of trastuzumab, 4D5V8, IG, IG-GAMMA-1_KAPPA Humanized [7637_H,7637_L]

Chain ID	**INN 7637_H**
Chain length	450
IMGT chain description	H-GAMMA-1 = VH(1-120) + CH1(121-218) + HINGE-REGION(219-233) + CH2(234-343) + CH3(344-450)
	[V-REGION EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAED]N-AND[J-REGION][CH1 TAVYYCSRWGGDGFYAMDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS][HINGE-REGION][

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IMGT/2Dstructure-DB

Chain details of trastuzumab, 4D5V8, IG, IG-GAMMA-1_KAPPA Humanized [7637_H,7637_L]

DESCRIPTION

Chain ID	INN 7637_H
Chain length	450
IMGT chain description	H-GAMMA-1 = VH(1-120) + CH1(121-218) + HINGE-REGION(219-233) + CH2(234-343) + CH3(344-450)

Chain sequence

```
[                                          V-REGION
EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAED
      ]N-AND[    J-REGION    ][                                                    CH1
TAVYYCSRWGGDGFYAMDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
                                    ][HINGE-REGION ][
GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDTPPPCPRCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS
                 CH2                                                              ][
HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE
                                       CH3                                                 ]
LTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
```

Sequence in FASTA format *Sequence in IMGT format*

CLASSIFICATION

V-DOMAIN

IMGT domain description	VH
IMGT gene and allele name	IGHV3-66*01 (81.60%)(Human) , IGHV3-66*02 (81.60%)(Human) , IGHV3-66*04 (81.60%)(Human) *Alignment details*
IMGT gene and allele name	IGHJ6*01 (76.50%)(Human) , IGHJ6*02 (76.50%)(Human) *Alignment details*
2D representation	IMGT Collier de Perles or IMGT Collier de Perles on 2 layers
Contact analysis	*Not available*
CDR-IMGT lengths	[8.8.13]
Sheet composition	*Not available*

NUMEROTATION

```
                          [   CDR1   ]                 [  CDR2  ]
EVQLVESGG.GLVQPGGSLRLSCAASGFNI....KDTYIHWVRQAPGKGLEWVARIYPT..NGYTRYADSVK.GRFTISADTSKNTAYLQ
               [   CDR3    ]
MNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSS
```

IMGT/DomainGapAlign results

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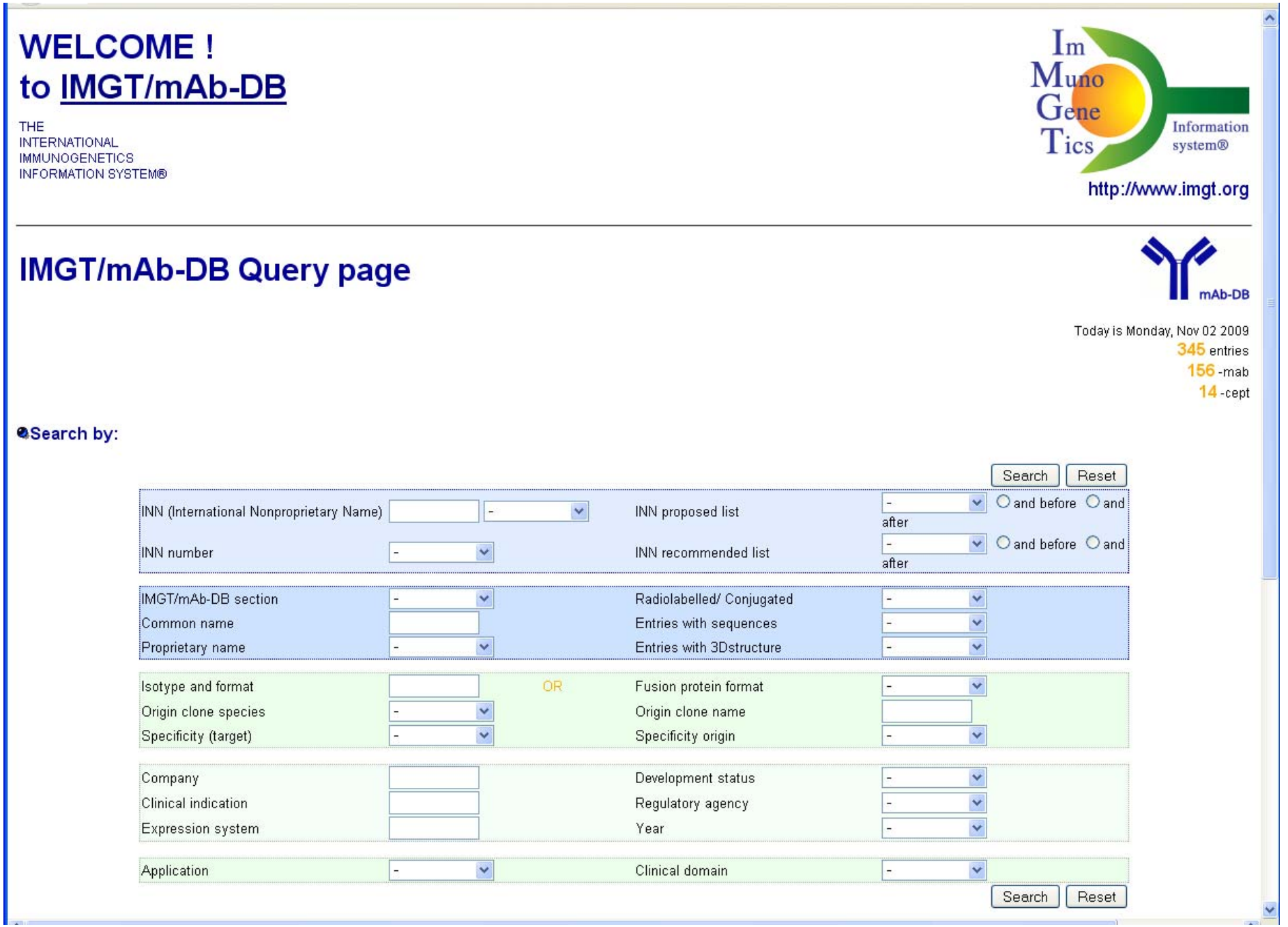

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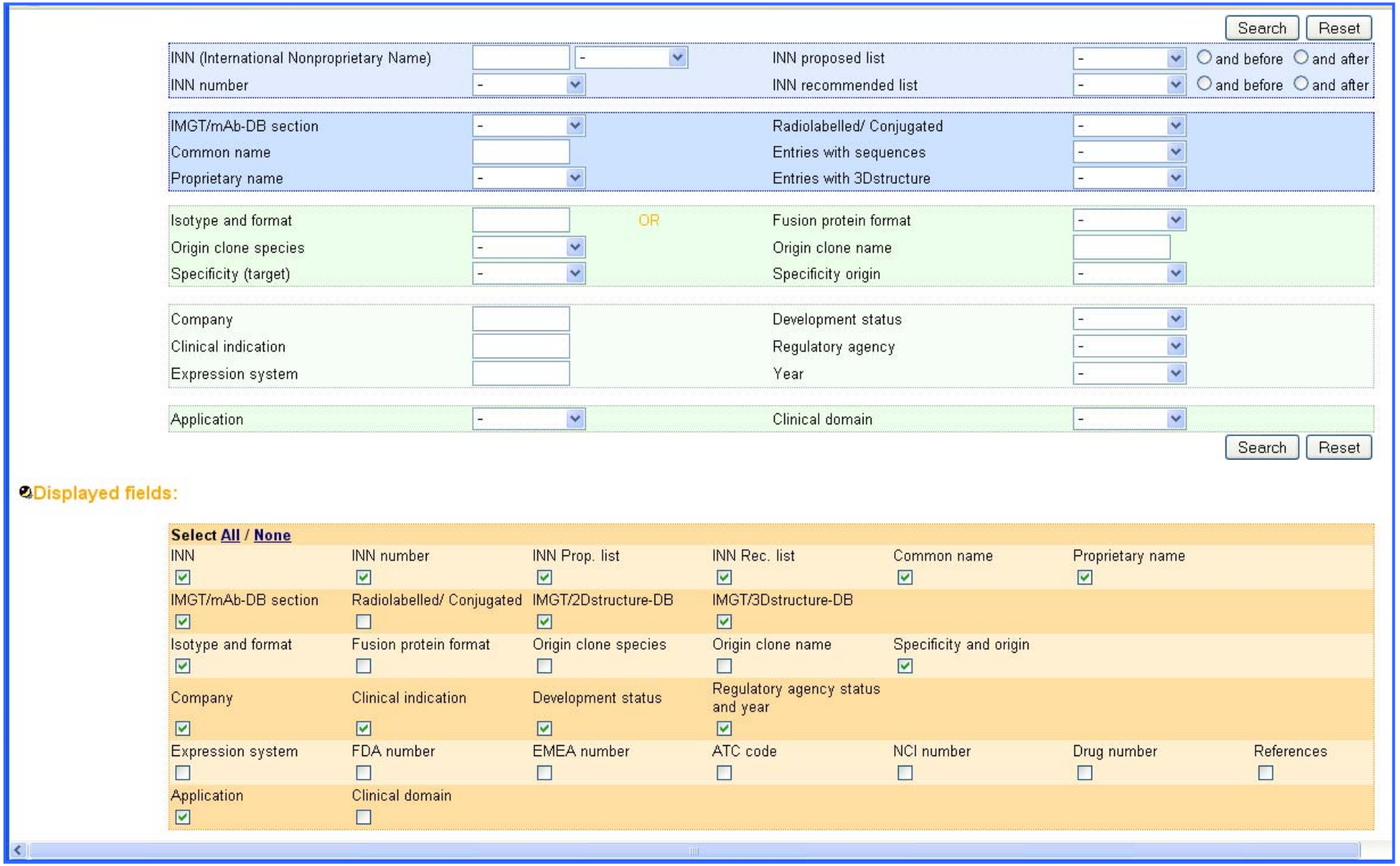
IMGT/mAb-DB



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WELCOME !
to IMGT/mAb-DB

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http://www.imgt.org

Your query: IMGT/mAb-DB INN = trastuzumab

Number of results: 1

IMGT/ mAb-DB id	INN (International Nonproprietary Name)	INN Num.	INN Prop. list	INN Rec. list	Common name	Proprietary name	IMGT/mAb-DB section	IMGT/ 2D	IMGT/ 3D	Isotype and format	Specificity (target) [origin]	Company	Clinical indication	Development status	Regulatory agency status and year	Application
97	trastuzumab	7637	78 (1997)	40 (1998)	4D5V8, Herceptin	HERCEPTIN®	Humanized	7637	1n8z	IgG1κ	ERBB2 (Epidermal Growth Factor Receptor 2; HER-2; p185c-erbB2; NEU; EGFR2) [*Homo sapiens*]	F. Hoffmann-La Roche Ltd. (Basel Switzerland) (EU) / Genentech Inc. (S. San Francisco CA USA) (US)	Breast cancers (as adjuvant)	Phase III		
													Metastatic breast cancers overexpressing ERBB2	Phase M	AMM Market authorization (Roche) August 2000, FDA approval October 1998	Therapeutic
													Non-small-cell lung cancers	Phase II		

Created: 03/04/2009
Last updated:

IMGT/mAb-DB has been developed by Yan Wu and Patrice Duroux (LIGM, Montpellier, France)
IMGT/mAb-DB scientific officer: Marie-Paule Lefranc (Marie-Paule.Lefranc@igh.cnrs.fr)

IMGT/mAb-DB Documentation
Monoclonal antibodies with clinical indications

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Conclusions

http://www.imgt.org

Towards «Potential immunogenicity evaluation» using IMGT-ONTOLOGY:

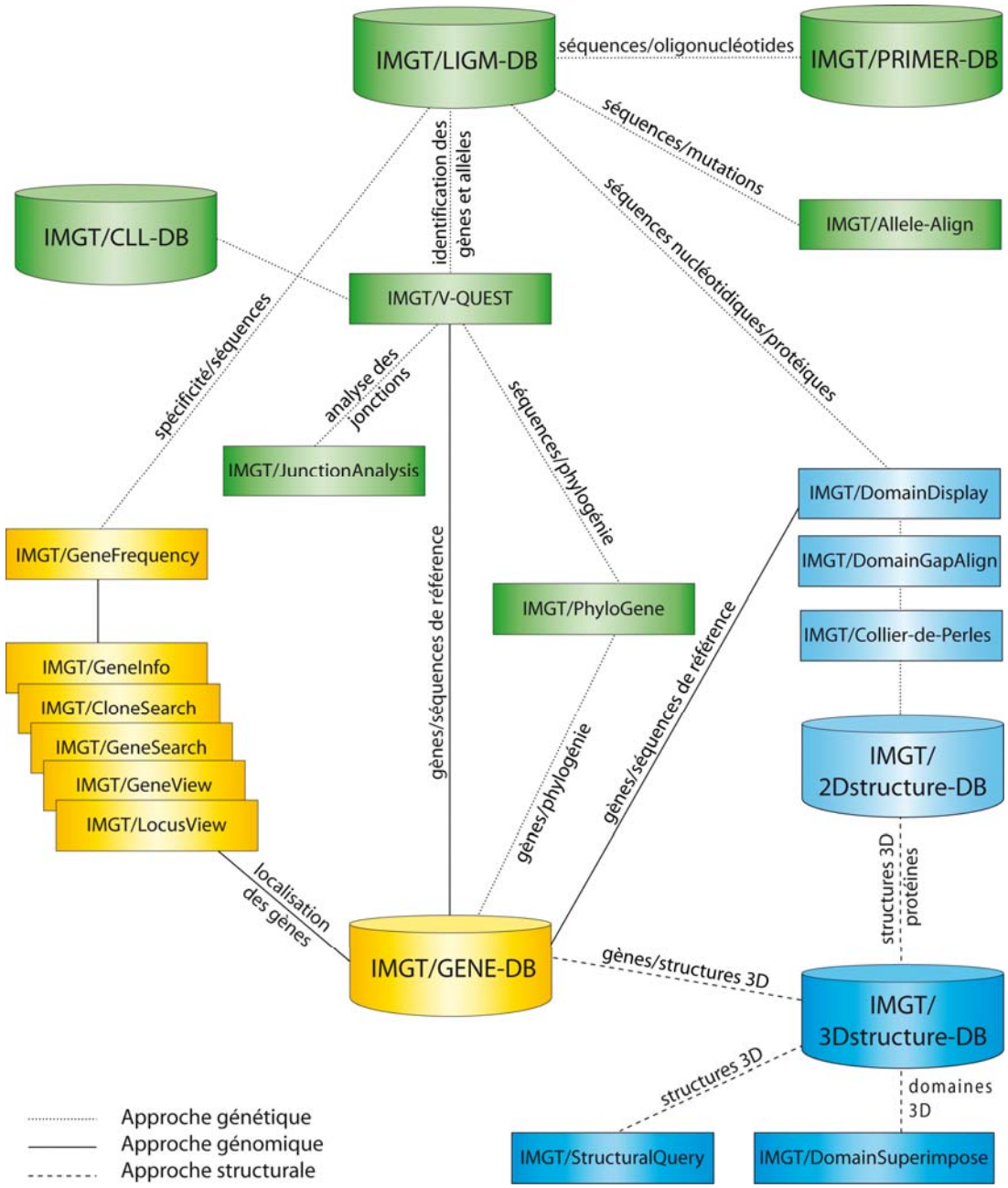
- Standardized analysis of V-DOMAIN
  - IMGT Collier de Perles
  - IMGT/DomainGapAlign
    - CDR-IMGT and FR-IMGT delimitations
    - CDR3-IMGT (V-J and V-D-J junctions)
    - description of AA differences

- Standardized analysis of antibody/antigen contacts
  - IMGT/3Dstructure-DB

- Bridging the gap between sequences and 3D structures and vice versa
  - IMGT/2Dstructure-DB cards (INN)

IMGT®

http://www.imgt.org



- 6 databases
- 15 online tools

- Sequences
- Genes
- Structures

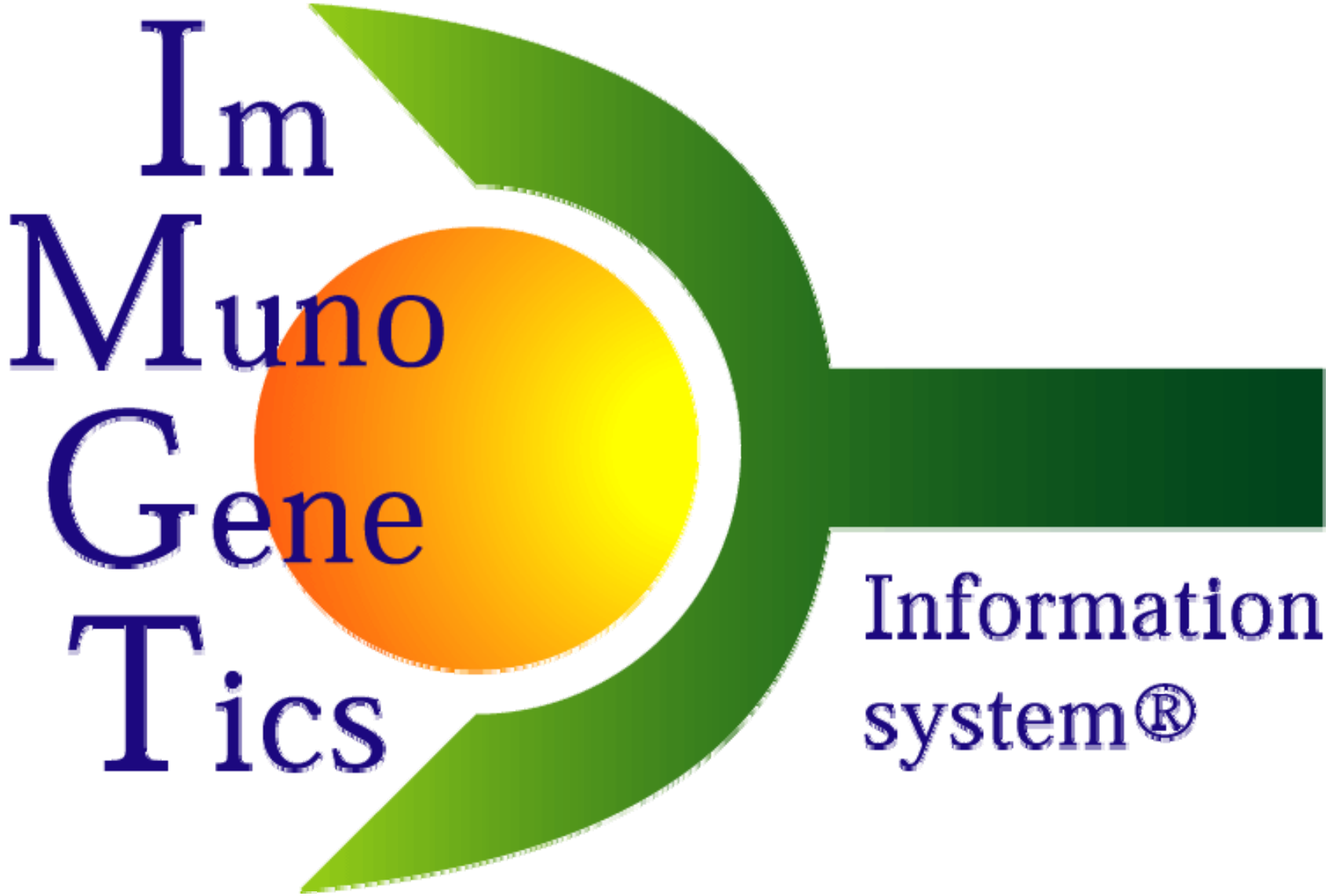
- Immunoglobulins (IG) (or antibodies)
- T cell receptors (TR)
- MHC
- IgSF and MhcSF

Acknowledgements

BioSTIC-LR
ACI IMPbio
GIS AGENAE
Plan Pluri-Formation Université Montpellier 2
ANR FLAVORES
ANR BIOSYS
GIS IBiSA
Grand Plateau Technique Régional Languedoc-Roussillon GPTR
«ImmunoGrid», 6th PCRDT, STREPS IST

and the companies that support the IMGT efforts of standardization.

Many thanks to the IMGT® team at Montpellier, France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