INSTITUT NATIONAL DE LA TRANSFUSION SANGUINE

Impact des nouvelles thérapeutiques par anticorps monoclonaux sur la prise en charge immuno-hématologique du patient

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LA RECHERCHE D'ANTICORPS ANTI-ÉRYTHROCYTAIRES

Exemple de panel de dépistage

	Rh-Hr						Kell						Duffy		Kidd		Lewis		P	MNS				Lutheran		Sex-linked
	D	C	E	c	e	C^w	K	k	Kp^a	Kp^b	Js^a	Js^b	Fy^a	Fy^b	Jk^a	Jk^b	Le^a	Le^b	P_1	M	N	S	s	Lu^a	Lu^b	Xg^a
I	+	0	0	0	+	0	+	+	0	+	0	+	0	0	0	+	0	0	0	+	+	0	+	0	+	0
II	+	+	+	+	0	0	0	+	0	+	0	+	+	+	+	0	+	+	+	+	0	+	+	0	+	+
III	0	0	0	+	+	0	0	+	0	+	0	+	+	0	0	+	0	+	0	+	+	0	+	0	+	+

LA RECHERCHE D'ANTICORPS ANTI-ÉRYTHROCYTAIRES

	RH						KEL				FY		JK		LE		MNS				P	LU			DO		YT		CO		XG	TIA IgG/C3	TIA IgG	TIA Papaïne IgG	TIA Trypsine IgG
	1	2	3	4	5	8	1	2	3	4	1	2	1	2	1	2	1	2	3	4	1	1	2	19	1	2	1	2	1	2	1				
1	0	+	0	0	+	0	0	+	0	+	+	+	+	+	0	0	+	0	+	0	+	0	+		+	+	+	0	+	0	+	++++	++++	++++	++++
2	0	0	+	+	+	0	0	+	0	+	+	+	+	0	0	+	0	+	0	+	+	0	+		+	+	+	0	+	0	+	++++	++++	++++	++++
3	0	0	0	+	+	0	+	+	0	+	+	0	0	+	0	+	+	0	+	+	+	+	+	0	+	+	+	+	+	0	+	++++	++++	++++	++++
4	0	0	0	+	+	0	0	+	0	+	0	+	+	+	+	0	+	+	+	+	+	+	+	+	+	0	+	0	+	0	+	++++	++++	++++	++++
5	0	0	0	+	+	0	0	+	0	+	0	+	+	+	0	0	+	0	+	0	+	0	+	+	0	+	+	0	+	0	+	++++	++++	++++	++++
6	0	0	0	+	+	0	0	+	0	+	0	+	+	0	0	+	+	+	0	+	0	+	+		+	+	+	0	+	0	+	++++	++++	++++	++++
7	+	0	+	+	0	0	+	0	0	+	0	+	0	+	0	+	0	+	0	+	+	0	+	+	+	0	+	0	+	0	+	++++	++++	++++	++++
8	+	+	0	0	+	+	0	+	0	+	+	0	0	+	0	+	+	+	+	0	+	+	+		0	+	+	0	+	0	+	++++	++++	++++	++++
9	+	+	0	0	+	0	+	+	0	+	+	+	+	0	0	+	0	+	+	+	0	0	+		0	+	+	0	+	0	0	++++	++++	++++	++++
10	+	+	0	+	0	0	+	0	+	+	+	0	+	+	0	+	0	+	0	+	+	0	+	+			+	0	+	0	+	++++	++++	++++	++++
11	+	0	0	+	+	0	0	+	0	+	+	+	+	0	+	0	+	0	+	0	0	0	+		0	+	+	0	+	0	+	++++	++++	++++	++++
12	+	+	+	0	+	0	0	+	0	+	+	+	+	0	0	+	+	+	0	+	+	0	+	+	+	0	+	0	+	0	+	++++	++++	++++	++++
13	+	+	0	0	+	0	0	+	+	+	+	+	+	0	0	+	+	+	0	+	0	0	+		0	+	+	0	+	0	0	++++	++++	++++	++++
14	+	+	0	0	+	0	+	+	0	+	+	+	+	+	0	+	+	0	+	0	+	0	+	0	0	+	+	0	+	0	0	++++	++++	++++	++++
15	0	0	0	+	+	0	0	+	0	+	+	0	+	0	0	+	0	+	0	+	+	0	+		+	+	+	0	+	0	0	++++	++++	++++	++++
Panel de référence lot 2007-45																									**Témoins autologues**						-	-	-	-

Mélange complexe d'anticorps ?

Anticorps "anti-public" ?

Combinaison des deux ?

LA RECHERCHE D'ANTICORPS ANTI-ÉRYTHROCYTAIRES

	RH						KEL				FY		JK		LE		MNS				P	LU			DO		YT		CO		XG	TIA IgG/C3	TIA IgG	TIA Papaïne IgG	TIA Trypsine IgG
	1	2	3	4	5	8	1	2	3	4	1	2	1	2	1	2	1	2	3	4	1	1	2	19	1	2	1	2	1	2	1				
1	0	+	0	0	+	0	0	+	0	+	+	+	+	+	0	0	+	0	+	0	+	0	+		+	+	+	0	+	0	+	++++	++++	++++	++++
2	0	0	+	+	+	0	0	+	0	+	+	+	+	0	0	+	0	+	0	+	+	0	+		+	+	+	0	+	0	+	++++	++++	++++	++++
3	0	0	0	+	+	0	+	+	0	+	+	0	0	+	0	+	+	0	+	+	+	+	+	0	+	+	+	+	+	0	+	++++	++++	++++	++++
4	0	0	0	+	+	0	0	+	0	+	0	+	+	+	+	0	+	+	+	+	+	+	+	+	+	0	+	0	+	0	+	++++	++++	++++	++++
5	0	0	0	+	+	0	0	+	0	+	0	+	+	+	0	0	+	0	+	0	+	0	+	+	0	+	+	0	+	0	+	++++	++++	++++	++++
6	0	0	0	+	+	0	0	+	0	+	0	+	+	0	0	+	+	+	0	+	0	+	+		+	+	+	0	+	0	+	++++	++++	++++	++++
7	+	0	+	+	0	0	0	+	0	+	0	+	0	+	0	+	0	+	0	+	+	0	+	+	+	0	+	0	+	0	+	++++	++++	++++	++++
8	+	+	0	0	+	+	0	+	0	+	+	0	0	+	0	+	+	+	+	0	+	+	+		0	+	+	0	+	0	+	++++	++++	++++	++++
9	+	+	0	0	+	0	+	+	0	+	+	+	+	0	0	+	0	+	+	+	0	0	+		0	+	+	0	+	0	0	++++	++++	++++	++++
10	+	+	0	+	+	0	0	+	0	+	+	0	+	+	0	+	0	+	0	+	+	0	+	+			+	0	+	0	+	++++	++++	++++	++++
11	+	0	0	+	+	0	0	+	0	+	+	+	+	0	+	0	+	0	+	0	0	0	+		0	+	+	0	+	0	+	++++	++++	++++	++++
12	+	+	+	0	+	0	0	+	0	+	+	+	+	0	0	+	+	+	0	+	+	0	+	+	+	0	+	0	+	0	+	++++	++++	++++	++++
13	+	+	0	0	+	0	0	+	+	+	+	+	+	0	0	+	+	+	0	+	0	0	+		0	+	+	0	0	0	0	++++	++++	++++	++++
14	+	+	0	0	+	0	+	+	0	+	+	+	+	+	0	+	+	0	+	0	+	0	+	0	0	+	+	0	+	0	0	++++	++++	++++	++++
15	0	0	0	+	+	0	0	+	0	+	+	0	+	0	0	+	0	+	0	+	+	0	+		+	+	+	0	+	0	0	++++	++++	++++	++++
Panel de référence lot 2007-45																									**Témoins autologues**						++++	++++	++++	++++

Autre configuration : témoins autologues positifs

Si transfusion récente, on ne peut pas interpréter les témoins autologues !

LA RECHERCHE D'ANTICORPS ANTI-ÉRYTHROCYTAIRES

	RH						KEL				FY		JK		LE		MNS				P	LU			DO		YT		CO		XG	TIA IgG/C3	TIA IgG	TIA Papaïne IgG	TIA Trypsine IgG
	1	2	3	4	5	8	1	2	3	4	2		1	2	1	2	1	2	3	4	1	1	2	19	1	2	1	2	1	2	1				
1	0	+	0	0	+	0	0	+	0	+	+		+	+	0	0	+	0	+	0	+	0	+		+	+	+	0	+	0	+	++++	++++	++++	++++
2	0	0	+	+	+	0	0	+	0	+	+		+	0	0	+	0	+	0	+	+	0	+		+	+	+	0	+	0	+	++++	++++	++++	++++
3	0	0	0	+	+	0	+	+	+	+	+	0	0	+	0	+	+	0	+	+	+	+	+	0	+	+	+	+	+	0	+	++++	++++	++++	++++
4	0	0	0	+	+	0	0	+	0	+	0		+	+	+	0	+	+	+	+	+	+	+	+	+	0	+	0	+	0	+	++++	++++	++++	++++
5	0	0	0	+	+	0	0	+	0	+	0		+	+	0	0	+	0	+	0	+	0	+	+	0	+	+	0	+	0	+	++++	++++	++++	++++
6	0	0	0	+	+	0	0	+	0	+	0		+	0	0	+	+	+	0	+	0	+	+		+	+	+	0	+	0	+	++++	++++	++++	++++
7	+	0	+	+	0	0	0	+	0	+	0		+	0	0	+	0	+	0	+	+	0	+	+	+	0	+	0	+	0	+	++++	++++	++++	++++
8	+	+	0	0	+	+	0	+	0	+	+	0	0	+	0	+	+	+	+	0	+	+	+		0	+	+	0	+	0	+	++++	++++	++++	++++
9	+	+	0	0	+	0	+	+	0	+	+	+	+	0	0	+	0	+	+	+	0	0	+		0	+	+	0	+	0	0	++++	++++	++++	++++
10	+	+	0	0	+	0	0	+	0	+	+	0	+	+	0	+	0	+	0	+	+	0	+	+			+	0	+	0	+	++++	++++	++++	++++
11	+	0	0	+	+	0	0	+	0	+	+	+	+	0	+	0	+	0	+	0	0	0	+		0	+	+	0	+	0	+	++++	++++	++++	++++
12	+	+	+	0	+	0	0	+	0	+	+	+	+	0	0	+	+	+	0	+	+	0	+	+	+	0	+	0	+	0	+	++++	++++	++++	++++
13	+	+	0	0	+	0	0	+	+	+	+	+	+	0	0	+	+	+	0	+	0	0	+		0	+	+	0	+	0	0	++++	++++	++++	++++
14	+	+	0	0	+	0	+	+	0	+	+	+	+	+	0	+	+	0	+	0	+	0	+	0	0	+	+	0	+	0	0	++++	++++	++++	++++
15	0	0	0	+	+	0	0	+	0	+	+	0	+	0	0	+	0	+	0	+	+	0	+		+	+	+	0	+	0	0	++++	++++	++++	++++
Panel de référence lot 2007-45																									**Témoins autologues**						++++	++++	++++	++++

Autoanticorps ?

Autoanticorps masquant des alloanticorps ?

Anticorps anti-public ?

Combinaison de plusieurs des cas précédents ?

NOUVEAUX TRAITEMENTS PAR ANTICORPS MONOCLONAUX

CAS N°1

- Septembre 2012
- Patient âgé de 48 ans
- Greffé de moelle osseuse pour cause de Leucémie Aiguë Myéloïde (LAM)
- Rechute de la LAM
- Hb 70 g/l, mal tolérée
- Recherche d'anticorps : image d'anticorps anti-public dans le laboratoire => aucun CGR compatible
- Envoi d'échantillons sanguins au CNRGS

GEL P	GEL G	PEG G	GEL PAPG	GEL TRYG				N° Gr	RH 1 2 3 4 5	KEL 1 2 3 4	FY 1 2	JK 1 2	LE 1 2	MNS 1 2 3 4	P 1	LU 1 2 19	DO 1 2	YT 1 2	CO 1 2	XG 1	Commentaire Antigène
##	##		—	—				1	0 + 0 + + 0	0 + 0 +	0 +	0 +	0 +	0 + 0 +	+	0 +	+ +	0 +	+ 0	0	
##	##		—	—				2	0 0 + + + 0	0 + 0 +	+ +	+ +	+ 0	+ + + +	+	0 + +	0 +	+ 0	+ 0	+	
##	##		—	—.	X2			3	0 0 0 + + 0	+ + 0 +	+ +	+ +	0 +	+ + + 0	0	0 + +	+ 0	+ 0	+ 0	+	CHRG:-1 ;COST:W1
##	##		—	(+)	X?			4	0 0 0 + + 0	0 + 0 +	+ 0	0 +	+ 0	0 + + +	+	0 + 0	+ +	+ 0	+ 0	+	
##	##		—	—				5	0 0 0 + + 0	0 + 0 +	0 +	+ 0	0 0	+ + + 0	+	0 +	+ +	+ 0	+ 0	0	
##	##		—	—				6	0 0 0 + + 0	0 + 0 +	0 +	+ +	0 +	+ 0 + 0	+	0 +	+ +	+ 0	+ 0	+	
##	##		—	—	X2			7	+ 0 + + 0 0	0 + 0 +	+ +	+ 0	0 +	+ 0 + 0	+	0 + 0	+	+ 0	+ 0	0	DO*1/DO*1
##	##		—	—				8	+ + 0 0 + +	0 + 0 +	+ +	+ 0	0 +	0 + 0 +	+	0 +	+ +	+ +	+ 0	+	
##	##		—	—				9	+ + 0 0 + 0	+ + 0 +	0 +	+ 0	0 +	0 + 0 +	+	+ +	+ +	+ 0	+ 0	0	
##	##		—	—				10	+ + 0 0 + 0	0 + 0 +	0 +	0 +	0 0	+ + 0 +	+	0 + 0	0 +	+ 0	+ 0	+	
##	##		—	—				11	+ 0 0 + + 0	0 + 0 +	0 +	0 +	0 +	+ + 0 +	+	0 + +	+ 0	+ +	+ 0	+	
##	##		—	—	X2			12	+ + + 0 + 0	0 + 0 +	+ 0	+ +	0 +	+ 0 + 0	+	0 + 0	+ +	+ 0	+ +	+	
##	##		—	—				13	+ + 0 0 + 0	0 + + +	+ +	+ 0	0 +	+ + 0 +	0	0 + 0	0 +	+ 0	+ 0	0	
##	##		—	—				14	+ + 0 0 + 0	0 + 0 +	0 +	+ 0	+ 0	+ 0 + +	+	0 + +	0 +	+ 0	+ 0	+	
##	##		—	+	X?			15	0 0 0 + + 0	0 + + +	+ 0	+ 0	+ 0	+ + 0 +	+	0 + +	+ +	+ 0	+ 0	+	CH/RG:W11
								21	0 + 0 + + 0	0 + 0 +	0 +	+ 0	0 +	0 + 0 +	+	0 +	+ +	+ 0	+ 0	+	
				+				22	0 0 + + + 0	0 + 0 +	0 +	W0	0 +	+ + 0 +	+	0 + 0	+ 0	+ 0	+ 0	+	
								23	0 + 0 + + 0	0 + 0 +	0 +	+ 0	0 0	+ 0 + 0	+	0 + 0	0 +	+ 0	+ 0	+	
				+				24	0 0 + + + 0	0 + 0 +	0 +	+ 0	0 0	+ 0 + 0	+	+ + 0	+ 0	+ 0	+ 0	+	
##	##		—	+	X2			25	0 0 + + + 0	0 + + +	0 +	+ 0	0 +	+ + + +	0	0 + +	+ +	+ +	+ 0	+	CH/RG:-11
				—.				26	+ + 0 0 + 0	0 + + +	+ +	+ +	0 +	0 + 0 +	+	0 + +	0 +	+ 0	+ +	+	
				—.				27	+ + + 0 + 0	0 + 0 +	+ +	+ 0	0 +	+ 0 0 +	+	0 +	+ +	+ +	+	+	
								28	+ + 0 0 + +	0 + 0 +	+ +	+ +	+ 0	0 + 0 +	0	0 +				+	
								29	+ + 0 0 + 0	+ + 0 +	+ +	+ 0	0 +	0 + + +	0	0 +	0 +	+	+ 0	0	
								30	+ + 0 0 + 0	0 + 0 +	0 +	0 +	0 0	+ 0 + +	+	0 + +	+	+ 0	+ 0	+	COST:W1
								31	+ 0 0 + + 0	0 + 0 +	+ +	+ +	+ 0	0 + 0 +	+	0 +	+ +	+ 0	+ 0	+	
				—.				32	+ + + 0 + 0	0 + 0 +	+ +	+ +	+ 0	0 + 0 +	+	0 + 0	0 +	+ 0	+ 0	+	
								33	+ + 0 0 + 0	0 + 0 +	+ +	+ 0	0 +	+ 0 0 +	+	+ +	+ 0	+ +	+ 0	+	
								34	+ + 0 0 + 0	+ + 0 +	0 +	+ +	+ 0	0 + 0 +	+	w + 0	+ +	+ 0	+ 0	0	
								35	+ + 0 0 + 0	0 + 0 +	0 +	0 +	0 +	+ + 0 +	+	0 + 0	0 +	+ 0	+ 0	0	
								36	+ + + 0 + 0	0 + 0 +	0 +	+ +	0 +	+ + 0 +	0	0 + +	+ 0	+ 0	+ 0	0	
				(+)				37	+ + + 0 + 0	0 + 0 +	0 +	+ +	0 +	+ + 0 +	+	0 + 0	+ +	+ 0	+ 0	0	COST:-1
								38	+ + 0 0 + +	0 + 0 +	+ +	+ +	0 +	+ + + +	+	0 + +	+ +	+ 0	+ 0	0	
+	+		—	—				39	+ + 0 0 + +	+ + 0 +	0 +	+ +	0 +	+ 0 + +	+	0 + 0	0 +	+ 0	+ 0	0	KN-
								40													
+	+		—	—																	

Test de Coombs direct négatif

Témoins « autologues » faiblement positifs

T auto

CAS N°1

- Toutes les hématies de phénotype rare testées sont positives
- **Hématies rares In(Lu) ou Lu(a-b+^{w}) sont de réactivité nettement plus faible** => anticorps du système Lutheran ? Non car hématies rares Lu(a-b-) ou Lu_{null} restent franchement positives

CAS N°1

RED CELLS

Mutations in *EKLF/KLF1* form the molecular basis of the rare blood group In(Lu) phenotype

Belinda K. Singleton,[1] Nicholas M. Burton,[2] Carole Green,[1] R. Leo Brady,[2] and David J. Anstee[1]

[1]Bristol Institute for Transfusion Sciences (BITS), National Blood Service, Bristol; and [2]Department of Biochemistry, University of Bristol, Bristol, United Kingdom

Comparison of normal erythroblasts and erythroblasts from persons with the rare In(Lu) type of Lu(a-b-) blood group phenotype showed increased transcription levels for 314 genes and reduced levels for 354 genes in In(Lu) cells. Many erythroid-specific genes (including *ALAS2*, *SLC4A1*) had reduced transcript levels, suggesting the phenotype resulted from a transcription factor abnormality. A search for mutations in erythroid transcription factors showed mutations in the promoter or coding sequence of *EKLF* in 21 of 24 persons with the In(Lu) phenotype. In all cases the mutant *EKLF* allele occurred in the presence of a normal *EKLF* allele. Nine different loss-of-function mutations were identified. One mutation abolished a GATA1 binding site in the *EKLF* promoter (−124T>C). Two mutations (Leu127X; Lys292X) resulted in premature termination codons, 2 (Pro190LeufsX47; Arg319GlufsX34) in frameshifts, and 4 in amino acid substitution of conserved residues in zinc finger domain 1 (His299Tyr) or domain 2 (Arg328Leu; Arg328His; Arg331Gly). Persons with the In(Lu) phenotype have no reported pathology, indicating that one functional *EKLF* allele is sufficient to sustain human erythropoiesis. These data provide the first description of inactivating mutations in human *EKLF* and the first demonstration of a blood group phenotype resulting from mutations in a transcription factor. (Blood. 2008;112: 2081-2088)

Mutation hétérozygote dans le gène codant pour le facteur de transcription érythroïde KLF1 (mécanisme dominant)

CAS N°1

REVIEW

Blood group phenotypes resulting from mutations in erythroid transcription factors

Belinda K. Singleton[a], *Jan Frayne*[b], *and David J. Anstee*[a]

Curr Opin Hematol 2012, 19:486–493

CAS N°1

RESEARCH ARTICLE

Human Mutation

OFFICIAL JOURNAL HGVS HUMAN GENOME VARIATION SOCIETY www.hgvs.org

Molecular Analysis of the Rare In(Lu) Blood Type: Toward Decoding the Phenotypic Outcome of Haploinsufficiency for the Transcription Factor KLF1

Virginie Helias,[1†] Carole Saison,[1†] Thierry Peyrard,[1,2] Eliane Vera,[1,2] Claude Prehu,[3] Jean-Pierre Cartron,[1] and Lionel Arnaud[1]*

[1] National Institute of Blood Transfusion (INTS), Paris, France; [2] National Reference Center for Blood Groups (CNRGS), Paris, France; [3] Laboratoire de Biochimie et Génétique, CHU Hôpital Henri Mondor, Créteil, France

Communicated by Sergio Ottolenghi

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Hématies rares In(Lu) : CD44 faible (Indian), AnWj-, CH/RG:-1, P1-,…

CAS N°1

Titrage en faveur d'un anticorps de type "HTLA" (*High Titer Low Affinity*)

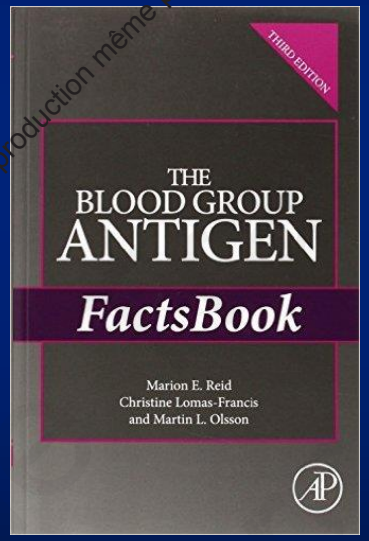
Gel G, 15 min à 37°C

SERUM	Pur	1/2	1/4	1/8	1/16	1/32	1/64	1/128	1/256	1/512	1/1024	1/2048
Pool GR n° 3, 7, 10 panel 2012-15	++++	++++	++++	+++	+++	+	(+)	—	—	—	—	—
T auto	++	+	+	+	+	+	(+)	(+)	—	—	—	—

Traitement des hématies du panel d'identification par le DTT 200mM => plus de réactivité du sérum

Ficin/ Papain	Trypsin	α-Chymo-trypsin	200 mM DTT/AET	Possible specificity
Negative	Negative	Negative	Positive	Bp[a]; Ch/Rg; XG
Negative	Negative	Negative	Negative	IN; JMH
Negative	Negative	Positive	Positive	M, N, En[a]TS; Ge2, Ge4
Negative	Positive	Negative	Positive	'N'; Fy[a], Fy[b]
Variable	Positive	Negative	Positive	S, s
Variable	Positive	Negative	Weak or negative	YT
Negative	Positive	Positive	Positive	En[a]FS
Positive	Negative	Negative	Weak or negative	LU, MER2
Positive – Papain Weak or negative – Ficin	Negative	Negative	Negative	KN
Positive	Negative	Weak	Negative	DO
Positive	Positive	Negative	Weak	CROM
Positive	Positive	Negative	Positive	Some DI (3rd loop)
Positive	Positive	Positive/weak	Negative	LW
Positive	Positive/weak	Positive/weak	Positive	SC
Positive	Positive^	Positive^	Negative	KEL^ (except KALT, which is trypsin-sensitive)
Positive	Positive	Positive	Positive	AnWJ; En[a]FR, U; P1PK; RH; LE; Fy3; JK; most DI; CO; H; Ge3; OK; I/i; P, FORS; JR; LAN, Cs[a]; ER; LKE, PX2; Vel,‡ ABTI; At[a]; Emm; AnWj; Sd[a]; PEL; MAM
Positive	Positive	Positive	Enhanced	Kx

^Kell blood group system antigens are sensitive to treatment with a mixture of trypsin and α-chymotrypsin.
‡DTT may be variable.



CAS N°1

CAS N°1

- Le CNRGS contacte le prescripteur pour connaître plus de détails sur le contexte clinique et les éventuels traitements en cours
- Patient sous traitement expérimental par anticorps monoclonal anti-CD44
- CD44 porte le système de groupe sanguin Indian (IN) !

CAS N°1

Indian Blood Group System

Number of antigens	**4**
Low prevalence	In^{a}
High prevalence	In^{b}, INFI, INJA

Terminology

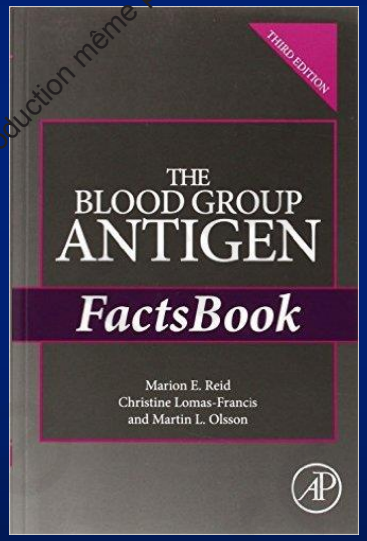
ISBT symbol (number)	IN (023)
CD number	CD44
Obsolete name	ISBT Collection 203
History	Named because the first In(a+) people were from India.

Expression

Other blood cells	Neutrophils, lymphocytes, monocytes
Tissues	Brain, breast, colon epithelium, gastric, heart, kidney, liver, lung, placenta, skin, spleen, thymus, fibroblasts

Gene

Chromosome	11p13
Name	*IN* (*CD44*)
Organization	At least 19 exons distributed over 50 kbp of gDNA (10 exons are variable). The hemopoietic isoform uses exons 1 to 5, 15 to 17, and 19
Product	CD44, Indian glycoprotein, Hermes antigen



CONCLUSION CAS N°1

- Anti-CD44 se fixe sur les hématies du panel, car porteuses du système de groupe Indian
- Anti-CD44 assimilé à un anticorps anti-public « passif » => peut masquer la présence d'alloanticorps courants
- Témoins autologues très faiblement positifs voire négatifs => **Mime un alloanticorps anti-public !** Explication inconnue : fort affaiblissement de CD44 sur les hématies autologues (internalisation ?), phénomène de blocage antigénique ?

CONCLUSION CAS N°1

- Premier cas rapporté en France, de nombreux autres cas ont suivi
- Transfusion avec du sang standard sans problème apparent
- Contrairement à ce qui est décrit dans la littérature, les antigènes Indian ne sont pas totalement détruits par la trypsine

CAS N°1

Test de Coombs direct négatif

GEL P	GEL G	PEG G	GEL PAPG	GEL TRYG				N° Gr	RH 1 2 3 4 5 8	KEL 1 2 3 4	FY 1 2	JK 1 2	LE 1 2	MNS 1 2 3 4	P 1	LU 1 2 10	DO 1 2	YT 1 2	CO 1 2	XG 1
								1	0 + 0 + + 0	0 + 0 +	0 +	+ 0	0 0	+ + 0 +	+	0 + 0	+ +	+ 0	+ 0	+
								2	0 0 + + + 0	0 + 0 +	+ +	+ 0	0 +	0 + 0 +	+	+ + 0	+ +	+ +	+ 0	+
								3	0 0 0 + + 0	+ + 0 +	0 +	0 +	0 +	+ + 0 +	+	+ + 0	0 +	+ 0	+ 0	0
								4	0 0 0 + + 0	0 + 0 +	0 +	+ +	+ 0	+ 0 0 +	+	+ + +	+ +	+ +	+ 0	+
								5	0 0 0 + + 0	0 + 0 +	+ +	0 +	0 0	+ 0 0 +	0	0 + +	0 +	+ 0	+ 0	+
								6	0 0 0 + + 0	0 + 0 +	0 +	+ 0	0 +	+ 0 + 0	+	0 + +	+ 0	+ 0	+ 0	+
								7	+ 0 + + 0 0	0 + 0 +	+ 0	+ 0	0 +	0 + 0 +	0	0 + +	+ +	+ +	+ 0	+
								8	+ + 0 0 + +	+ 0 0 +	+ +	+ +	+ 0	+ + + +	+	0 + +	0 +	+ 0	+ 0	+
								9	+ + 0 0 + 0	+ + 0 +	0 +	+ 0	0 0	0 + + +	+	0 + +	+ +	+ +	+ 0	+
								10	+ + 0 0 + 0	0 + 0 +	0 +	+ 0	0 +	+ + 0 +		0 +	+ 0	+ +	+ 0	+
								11	+ 0 0 + + 0	0 + 0 +	0 +	+ 0	0 +	+ + 0 +	+	0 + 0	0 +	+ 0	+ 0	+
								12	+ + + 0 + 0	0 + 0 +	0 +	0 +	0 +	+ + + 0	0	0 + +	0 +	+ 0	+ 0	+
								13	+ + 0 0 + 0	0 + 0 +	+ 0	+ 0	0 +	+ + +	+	0 + 0	+ +	+ +	+ 0	0
								14	+ + 0 + + 0	0 + + +	0 +	0 +	0 +	+ + + +	+	0 + 0	0 +	+ 0	+ 0	+
								15	0 0 0 + + 0	0 + 0 +	0 +	0 +	+ 0	+ 0 + +	+	0 + +	+ 0	+ 0	+ +	+
T auto																				

Autre cas avec anti-CD44 de forte concentration

=> Témoins autologues négatifs

=> hématies trypsinées fortement positives !

Phase I clinical study of RG7356, an anti-CD44 humanized antibody, in patients with acute myeloid leukemia

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Keywords: *RG7356, relapsed/refractory acute myeloid leukemia, anti-CD44 humanized antibody, phase I trial, cell adhesion*

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ABSTRACT

RG7356, a recombinant anti-CD44 immunoglobulin G1 humanized monoclonal antibody, inhibits cell adhesion and has been associated with macrophage activation in preclinical models. We report results of a phase I dose-escalation study of RG7356 in relapsed/refractory acute myeloid leukemia (AML).

Eligible patients with refractory AML, relapsed AML after induction chemotherapy, or previously untreated AML not eligible for intensive chemotherapy were enrolled and received intravenous RG7356 at dosages ≤ 2400 mg every other week or ≤ 1200 mg weekly or twice weekly; dose escalation started at 300 mg.

Forty-four patients (median age, 69 years) were enrolled. One dose-limiting toxicity occurred (grade 3 hemolysis exacerbation) after one 1200 mg dose (twice-weekly cohort). The majority of adverse events were mild/moderate. Infusion-related reactions occurred in 64% of patients mainly during cycle 1. Two patients experienced grade 3 drug-induced aseptic meningitis. Pharmacokinetics increased supraproportionally, suggesting a target-mediated drug disposition (TMDD) at ≥ 1200 mg. Two patients achieved complete response with incomplete platelet recovery or partial response, respectively. One patient had stable disease with hematologic improvement.

RG7356 was generally safe and well tolerated. Maximum tolerated dose was not reached, but saturation of TMDD was achieved. The recommended dose for future AML evaluations is 2400 mg every other week.

Coombs tests' positivity was observed in 83% of the tested patients following RG7356 administration; however, this was not associated with hemolysis, except in 1 patient who presented with hemolysis exacerbation after the first infusion. In toxicology studies (*in vitro* blood compatibility studies), RG7356 did not show any hemolytic potential (F. Hoffmann-La Roche Ltd, unpublished data). Based on these data, the risk of hemolysis following RG7356 administration seems minimal, but the occurrence of false-positive immunohematologic tests has to be anticipated for patients who may require RBC transfusions. This is explained by the high expression of CD44 on erythrocytes [25], which carries the Indian blood group system [26].

CAS N°2

- Décembre 2013
- Patiente traitée pour un myélome
- Demande de transfusion en urgence relative
- Recherche d'anticorps ininterprétable par le laboratoire

CAS N°2

TDA négatif

GEL P	GEL G	PEG G	GEL PAPG	GEL TRYG				N° Gr	RH 1 2 3 4 5 8	KEL 1 2 3 4 6 7	FY 1 2	JK 1 2	LE 1 2 3	MNS 1 2 3 4	P 1	LU 1 2 19	DO 1 2	YT 1 2	CO 1 2	XG 1
+	(+)		+	−				1	0 + 0 + + 0	0 + 0 +	0 +	+ +	0 +	+ 0 + +	+	0 + +	+ 0	+ 0	+ 0	+
+	−		+	−				2	0 0 + + + 0	+ + 0 +	+ +	+ +	0 +	0 + 0 +	0	0 + 0	+ 0	+ 0	+ 0	0
(+)	−		+	−				3	0 0 0 + + 0	+ + 0 +	+ +	+ 0	0 0	+ 0 + +	W	0 + +	0 +	+ 0	/ 0	+
+	(+)		+	−				4	0 0 0 + + 0	0 + 0 +	0 +	0 +	+ 0	+ 0 + +	+	0 + +	+ 0	+ 0	/ +	
(+)	−		+	−				5	0 0 0 + + 0	0 + 0 +	+ 0	0 +	0 0	/ 0 0 +	+	0 +	0 +	+ 0	+ 0	+
+	(+)		+	−				6	0 0 0 + + 0	0 + 0 +	0 +	+ +	0 +	+ + + 0	0	+ 0 0	+ +	+ 0	+ 0	0
+	(+)		+	−				7	+ 0 + + 0 0	0 + 0 +	+ +	+ 0	0 +	+ 0 + 0	0	0 +	0 +	+ 0	+ 0	+
+	+		+	−				8	+ + 0 0 + +	0 + 0 +	+ +	+ +	+ 0	0 + 0 +	0	0 +	0	+ 0	+ 0	+
+	+		+	−				9	+ + 0 0 + 0	+ + 0 +	+ +	0 +	0 +	0 + 0 +	+	0 + 0	+ +	+ +	+ 0	0
+	(+)		+	−				10	+ + 0 0 + 0	0 + + +	0 +	0 +	0 +	+ + + +	0	0 + 0	+ +	+ +	+ 0	+
−	−		−	−				11	+ 0 0 + + 0	0 + 0 +	+ 0	+ +	0 /	+ + 0 /	0	+ + 0	0 +	+ +	+ 0	0
+	+		+	(+)				12	+ + + 0 + 0	0 + 0 +	+ +	+ 0	0 +	+ + + 0	+	0 + +	0 +	+ +	+ 0	+
(+)	−		(+)	−				13	+ + 0 0 + 0	0 + 0 +	+ +	+ +	0 +	0 + 0 +	+	+ 0	0 +	+ +	+ /	+
+	(+)		+	−				14	0 0 0 + + 0	0 + + +	+ 0	+ 0	0 +	+ + +	+	0 +	0 +	+ 0	+ 0	+
+	+		+	−				15	0 + 0 0 + 0	0 + 0 +	+ +	+ +	0	+ + + +	+	0 + +	0 +	+ +	+ 0	+

Témoins autologues négatifs

Impossible d'adsorber cet anticorps malgré de nombreux cycles d'alloadsorption ! => alloanticorps courants masqués ?

CAS N°2

ABO	RH 1 2 3 4 5 8	KEL 1 2 3 4	FY 1 2	JK 1 2	LE 1 2	MNS 1 2 3 4 5	P 1	LU 1 2 19	DO 1 2	YT 1 2	CO 1 2	XG 1		GEL P	GEL G	GEL PAPG	GEL TRYG
-1,-2,-3 (O)	+ + + - + -	- + - +	- +	+ -	- +	+ + + +	-	- + -	- +	+ -	+ -	+		-	-	+	-
-1,-2,-3 (O)	+ - + + - -	- + - +	+ +	+ -	+ -	+ + - +	+	- + +	+ -	+ -	+ -	+		(+)	(+)	+	-
-1,-2,-3 (O)	- - - + + -	+ - +	- +	- +	- +	+ - + +	+	- +	+ +	+ +	+ -	+		(+)	+	+	-
-1,-2,-3 (O)	- - - + +	+ + - +	+ -	- +	- -	+ + + +	+	- + +	+ +	+ +	+ -	-		-	-	+	-
-1,-2,-3 (O)	- - - + + -	- + - +	+ +	- +	- -	+ + - +	-	- W						-	-	-	-
-1,-2,-3 (O)	- - + + + -	+ + - +	+ +	+ +	- +	+ + + -	-	- + +	+ -	+ -	+ -	+		+	(+)	+	-
-1,-2,-3 (O)	- - + + -	- + - +	- +	+ +	+ -	+ + + +	+	+ + +	+ -	+ -	+ -	+		+	+	+	-
-1,-2,-3 (O)	+ - + + - -	- + - +	+ +	+ -	- +	- + - +	+	- + +	- +	+ -	+ -	-		+	+	+	-
-1,-2,-3 (O)	- - - + + -	- + - +	+ +	+ -	- +	+ - - +	+	- + -	- +	+ -	+ -			+	(+)	+	-
-1,-2,-3 (O)	+ - - + + -	- + - +	- +	- +	- +	+ + - +	+	- + -	- +	+ +	+ -	+		+	(+)	+	-

Hématies de groupe rare In(Lu) négatives (mutation du gène *KLF1* à l'état hétérozygote)

Hématies de sang de cordon négatives

CAS N°2

ABO	RH	KEL	FY	JK	LE	MNS	P	LU	DO	YT	CO	XG		GEL P	GEL G	GEL PAPG	GEL TRYG
	~~1~~ 2 3 ~~4~~ ~~5~~ ~~8~~	1 ~~2~~ 3 ~~4~~	~~1~~ 2	~~1~~ 2	1 ~~2~~	1 2 3 4 5	~~1~~	1 ~~2~~ ~~19~~	1 2	1 2	1 2	1					
-1,-2,-3 (O)	+ + - + + -	- + - +	- +	- +	+ -	- + - +	+	- +	- +	+ -	+ -	+					
-1,-2,-3 (O)	- - - + + -	- + - +	+ +	+ +	- +	+ - + +	+	- +		- +							
-1,-2,-3 (O)	- - + + + -	+ - +	+ +	+ +	- +	+ + - +	+	+ - +	+ -	+ +	+ -	+					
-1,-2,-3 (O)	- - - + + -	- + + -	+ +	+ +	- +	+ + - +	+	- +			-						
-1,-2,-3 (O)	+ + - + + -	+ - - +	+ +	- +	- +	+ + - +	+	- +									
-1,-2,-3 (O)	+ - - + + -	- + - +	- +	+ -	- +	+ - - -	+	- +									

Hématie de groupe rare S-s- négative => ???

Noter les réactions de - à 4+ selon le schéma ci-dessous.

Grossesse : oui ☐ non ☐

Rhophylac (date et dose) :

Nouveau Malade
Ac i CD38

CONCLUSION ASP

Sérothèque
Boite :
Position :

Visa biologiste

Daratumumab

Nombreux autres cas adressés au CNRGS

Un nouvel anticorps monoclonal le daratumumab en monothérapie dans le traitement du myélome multiple réfractaire ou en rechute

Valentine Richez
Laurence Legros
Xavier Leleu

Les patients atteints de myélome multiple (MM) rechutent habituellement après avoir reçu des traitements comprenant des inhibiteurs du protéasome et des immunomodulateurs, bien que ces deux classes thérapeutiques soient les plus actives dans le MM. Il a été montré dans une étude rétrospective de l'International Myeloma Foundation que les patients, réfractaires ou intolérants au bortézomib et au lénalidomide (thalidomide dans les pays où le lénalidomide n'est pas disponible), avaient une survie médiane sans rechute (RFS) de cinq mois et une médiane de survie globale (OS, pour *overall survival*) estimée à neuf mois [1]. Ces patients ont donc un pronostic sombre et ne peuvent survivre qu'avec le développement de nouveaux agents et classes thérapeutiques.

Le daratumumab est un anticorps monoclonal humanisé de type IgG1κ dirigé contre le CD38, glycoprotéine transmembranaire de type II surexprimée à la surface des plasmocytes tumoraux. Des études précliniques ont démontré l'effet cytotoxique en monothérapie du daratumumab sur les cellules cibles exprimant le CD38 par plusieurs mécanismes : cytotoxicité directe, lyse complément-dépendante, recrutement de cellules effectrices (mécanisme ADCC pour *antibody dependant cell mediated cytotoxicity*) [2].

Une équipe européenne vient de publier une étude de phase I/II, s'intéressant à l'utilisation du daratumumab en monothérapie dans le traitement des patients atteints de MM en rechute et/ou réfractaires (R/R) [3]. Une première partie de l'étude est consacrée à un test en prédose puis à une escalade de doses par paliers, permettant l'administration du daratumumab à des posologies comprises entre 0,005 et 24 mg/kg. Dans une seconde partie, deux posologies différentes (8 mg/kg et 16 mg/kg) administrées avec une prémédication et selon plusieurs schémas ont été testées sur une cohorte de soixante-douze patients, avec pour objectifs d'étudier la tolérance et l'efficacité de ce nouveau traitement.

Comme attendu avec un anticorps monoclonal, la dose maximale tolérée n'a pas été identifiée au sein de la

DARZALEX® : protocole débuté aux USA en mai 2013, approuvé par la FDA en novembre 2015. AMM en France le 20.05.2016

Il existe des cas de traitements hors myélome ! (LAM)

DARZALEX® (daratumumab) Important Safety Information – Professional

WARNINGS AND PRECAUTIONS

Interference with Serological Testing - Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab infusion. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum. The determination of a patient's ABO and Rh blood type are not impacted. Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX. Type and screen patients prior to starting DARZALEX.

Traitement des hématies au DTT 200mM, 37°C, 30 minutes

Attention, détruit les systèmes KEL, YT, JMH, DO, IN, KN, LW

SP254

Development of a Robust Method to Negate the Daratumumab Interference with Routine Blood Bank Testing

C I Chapuy[1], R T Nicholson[1], M D Aguad[1], J P Laubach[2], B Chapuy[4], P Doshi[3], R M Kaufman[1]. *[1]Pathology, Brigham and Women's Hospital, Boston, MA, United States; [2]Hematologic Oncology, Dana-Farber Cancer Institute, Boston, MA, United States; [3]Janssen, Inc., Spring House, PA, United States; [4]Medicine, Dana-Farber Cancer Institute, Boston, MA, United States*

Background/Case Studies: Daratumumab (DARA), a promising novel therapy for multiple myeloma, is an IgG_1 human monoclonal antibody (Ab) that recognizes CD38 on myeloma cells. On routine screening, we observed that five of five DARA-treated patients had a positive Ab screen and a plasma panagglutinin in solid-phase and tube testing. Because CD38 is expressed on red blood cells (RBCs), we hypothesized that the observed panreactivity was caused by binding of DARA to endogenous CD38 on reagent RBCs. We explored methods to negate the DARA interference by removing RBC surface CD38. **Study Design/Methods:** HL60 cells were stably transfected with a plasmid encoding human CD38. CD38-negative HL60 cells were used as controls. Binding of DARA to HL60 cells or RBCs was assessed by flow cytometry using PE-labeled anti-human globulin. To remove cell surface CD38, HL60 cells or RBCs were preincubated with dithiothreitol (DTT) or trypsin. Routine blood bank serological (tube) methods were used to test samples from DARA-treated patients, as well as normal plasma samples spiked with DARA and/or alloAb (e.g., anti-E). For serological studies of DTT, reagent RBCs (3-5% cell suspension in PBS) were incubated with 0.2M DTT at 37°C for 30 min. **Results/Findings:** Normal plasma samples spiked with DARA (0.1-10 µg/mL) and incubated with reagent RBCs recapitulated the interference observed with samples from DARA-treated patients. Flow cytometry confirmed DARA binding to RBCs and CD38+ HL60 transfectants, but not to CD38– controls. Eluates prepared from DARA-treated RBCs bound to CD38+ HL60 cells but not to CD38– controls. Preincubating CD38+ HL60 cells with DTT reduced DARA binding by 92%, while preincubating these cells with trypsin reduced DARA binding by 40%. Using DTT-treated RBCs allowed clinically significant Abs to be identified serologically in the presence of DARA (Table). The panreactivity of all DARA-treated patient samples was eliminated by using DTT-treated RBCs. **Conclusion:** DARA potently interferes with routine blood bank serological tests by directly binding to RBC CD38. DTT pretreatment of reagent RBCs is a robust method to negate the DARA interference, allowing the safe provision of RBC units to DARA-treated patients. Because DTT denatures Kell antigens, K- RBC units are provided to these patients.

TRANSFUSION
2014-Vol. 54 Supplement

Si patient KEL:1, faire le phénotype KEL2

When blood transfusion medicine becomes complicated due to interference by monoclonal antibody therapy

Marlies Oostendorp,[1] Jeroen J. Lammerts van Bueren,[2] Parul Doshi,[3] Imran Khan,[3] Tahamtan Ahmadi,[3] Paul W.H.I. Parren,[2,4] Wouter W. van Solinge,[1] and Karen M.K. De Vooght[1]

TRANSFUSION 2015;55;1555–1562

Resolving the daratumumab interference with blood compatibility testing

Claudia I. Chapuy,[1] Rachel T. Nicholson,[1] Maria D. Aguad,[1] Bjoern Chapuy,[2] Jacob P. Laubach,[2] Paul G. Richardson,[2] Parul Doshi,[3] and Richard M. Kaufman[1]

TRANSFUSION 2015;55;1545–1554

CURRENT OPINION

New mAb therapies in multiple myeloma: interference with blood transfusion compatibility testing

Curr Opin Hematol 2016

Karen W.K. De Vooght, Marlies Oostendorp, and Wouter W. van Solinge

KEY POINTS

- Because CD38 is weakly expressed on human erythrocytes, therapeutic CD38-targeting antibodies interfere with routine pretransfusion laboratory tests.
- In trials with anti-CD38 mAb, the plasma of all treated patients demonstrated panreactivity on RBC panel testing, complicating the selection of compatible RBC units for transfusion.
- Possible strategies to deal with anti-CD38 interference are the neutralization of anti-CD38 mAbs in plasma by sCD38 or antiidiotype antibodies, CD38 denaturation on test RBCs using DTT, use of CD38-deficient cord blood test cells, and the selection of extensively blood group typed RBCs for transfusion.
- All reported mitigation strategies have advantages and disadvantages, and it depends on the resources and expertise of the laboratory what strategy to choose.
- As the selection of suitable RBC units can be seriously delayed, hospitals should have protocols in place that allow one to communicate this interference with patients, laboratories, and physicians in a timely manner.

CONCLUSION CAS N°2

- Anti-CD38 (daratumumab) de plus en plus utilisé
  Problème majeur : cet anticorps ne s'adsorbe pas
  => techniques alternatives pour rechercher des alloanticorps courants masqués
  - Trypsine (pas toujours disponible, ne marche pas toujours)
  - Traitement du panel DTT 200mM (pas possible avec les panels commerciaux classiques car hématies très diluées, détruit les antigènes Kell)
  - Hématies de sang de cordon (panel peu accessible)
  - Hématies rares In(Lu) (laboratoires de référence)
  - Panel informatif développé en interne : sujets trouvés au CNRGS naturellement déficitaires en CD38 sur leurs hématies
  - Génotypage de groupes sanguins (ne résout pas tout !)
  - CD38 soluble : récemment commercialisé, mais très cher et quantité importante à utiliser pour inhibition efficace

CONCLUSION

Interference of New Drugs with Compatibility Testing for Blood Transfusion

TO THE EDITOR: New drugs may have important yet underappreciated clinical consequences in patients requiring blood transfusion. Interference with routine methods for compatibility testing for blood transfusion puts patients at risk for delays in receiving compatible blood. Even if laboratory methods are developed to circumvent the drug-related artifacts, it takes time to establish them in general laboratories.

Daratumumab (a monoclonal antibody that binds with high affinity to the CD38 molecule; manufactured by Janssen), which was recently approved by the Food and Drug Administration as a therapy for multiple myeloma, provides an illustrative case. Once enrollment in the phase 1–2 trial began, staff at the trial site quickly observed that daratumumab consistently interfered with routine blood-compatibility testing. Standard serologic methods to eliminate panreactive antibodies failed to resolve the interference, at times delaying needed blood transfusions for patients treated with daratumumab.

It was eventually shown that daratumumab in patients' plasma directly binds to CD38 on reagent red cells used in the blood bank, causing the false positive antibody screens. A dithiothreitol-based method to eliminate the interference was discovered in an investigator-initiated study[1] and was later shown to be both effective and widely generalizable in a multicenter international study performed by the Biomedical Excellence for Safer Transfusion (BEST) Collaborative (data not shown); both studies were sponsored by Janssen. A neutralization method with the use of an anti-daratumumab idiotype has shown promise[2]; however, the antiidiotype method is

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N ENGL J MED 375;3 NEJM.ORG JULY 21, 2016

not readily available. A third approach is to issue phenotypically or genotypically matched red-cell units.[3,4]

In the specific case of the interference of daratumumab, a practical solution for blood banks has been developed. However, establishing this solution as a routine method in hospital blood banks will be a major challenge.

High-dose intravenous immune globulin is another example of antibodies that interfere with routine immunohematologic assays. We are concerned that other drugs, particularly monoclonal antibodies, that are under development may similarly interfere with compatibility testing at blood banks, putting patients who require transfusion at risk for delays in receiving compatible blood. Blood products are essential and sometimes lifesaving treatments, and interference by a new drug can result in unanticipated delays in the delivery of care to patients.

We believe that there is a pressing need for active investigation of whether a new drug may interfere with routine testing at blood banks. We recommend that investigations be performed early during drug development, certainly during phase 1 studies involving healthy volunteers. If interference with compatibility tests is found, we recommend that it be clearly drawn to the attention of clinicians and blood banks with advice about how to overcome the interference.

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

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- **Anti-CD38 : déclencheur d'une réelle prise de conscience d'un nouveau problème dans la prise en charge immuno-hématologique des patients**
- **Entraîne de nombreuses investigations au laboratoire d'immuno-hématologie pouvant entraîner un retard important de l'acte transfusionnel**
- **Pas ou peu d'information avant l'instauration des essais cliniques sur les possibles interférences avec les tests pré-transfusionnels (RAI) => les firmes doivent désormais être sensibilisées vis-à-vis de ce problème (tests adéquats, information des acteurs concernés)**

- **Question récurrente : quel est le risque hémolytique en cas de transfusion de globules rouges chez un patient traité ?**
- **Certains problèmes pouvaient être prévisibles (anti-CD44 et groupe sanguin Indian), d'autres moins (CD38 n'est pas un groupe sanguin)**
- **Nouvelles molécules probablement à risque dans le futur !**

PLOS | ONE

RESEARCH ARTICLE

Pre-Clinical Development of a Humanized Anti-CD47 Antibody with Anti-Cancer Therapeutic Potential

Jie Liu[1], Lijuan Wang[1], Feifei Zhao[1], Serena Tseng[1], Cyndhavi Narayanan[1], Lei Shura[1], Stephen Willingham[1], Maureen Howard[1], Susan Prohaska[1], Jens Volkmer[1], Mark Chao[1], Irving L. Weissman[1]*, Ravindra Majeti[1,2]*

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Avis et recommandations du Comité des médicaments orphelins (COMP) de l'Agence européenne des médicaments (EMA) d'octobre 2015 - Point d'information

20/11/2015

Med

DM DIV Cos PT Aut

Agence nationale de sécurité du médicament et des produits de santé

Le Comité des médicaments orphelins (COMP) de l'Agence européenne des médicaments s'est réuni du 6 au 8 octobre 2015 à Londres. Ce Comité est chargé d'examiner les demandes de désignations[1] déposées par des personnes physiques ou morales souhaitant développer des médicaments destinés au traitement de maladies rares, appelés médicaments « orphelins ». Le COMP a rendu au cours de cette session 16 avis favorables pour la désignation de médicaments orphelins ainsi que 0 avis favorables pour le maintien du statut orphelin de 4 médicaments.

Le COMP a rendu un avis favorable pour la désignation médicaments orphelins de médicaments développés dans les maladies rares suivantes :

- Glomérulosclérose segmentaire focale (médicament chimique)
- Leucémie lymphoblastique aiguë (thérapie cellulaire)
- Leucémie lymphoïde chronique/ lymphome lymphocytaire à petites cellules (thérapie cellulaire)
- Carcinome nasopharyngé (azacitidine)
- Maladie du greffon contre l'hôte (protéine de fusion)
- Syndrome respiratoire du Moyen-Orient (interferon alfa-n3)
- Hypersomnie idiopathique (pentetrazol)
- Tumeur à cellules plasmacytoïdes dendritiques blastiques (protéine de fusion)
- Cancer de l'ovaire (médicament chimique)
- Maladie de Wilson (thérapie génique)
- Amaurose congénitale de Leber (thérapie génique)
- Achromatopsie due à une mutation du gène CNGB3 (thérapie génique)
- Lymphome folliculaire (thérapie cellulaire)
- Leucémie aiguë myéloïde (anticorps monoclonal anti CD47)

ClinicalTrials.gov

A service of the U.S. National Institutes of Health

CAMELLIA: Anti-CD47 Antibody Therapy in Haematological Malignancies

This study is currently recruiting participants.

See Contacts and Locations

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Anti-CD47 Antibody As a Targeted Therapeutic Agent for Human Lung Cancer and Cancer Stem Cells

*Liang Liu[1,2,3,4†], Lin Zhang[1,3,4†], Lin Yang[5], Hui Li[1,3,4], Runmei Li[2,3,4], Jinpu Yu[1,3,4], Lili Yang[1,3,4], Feng Wei[1,3,4], Cihui Yan[1,3,4], Qian Sun[1,3,4], Hua Zhao[1,3,4], Fan Yang[2,3,4], Hao Jin[1,3,4], Jian Wang[1,3,4], Shizhen Emily Wang[1,3,4,6] and Xiubao Ren[1,2,3,4]**

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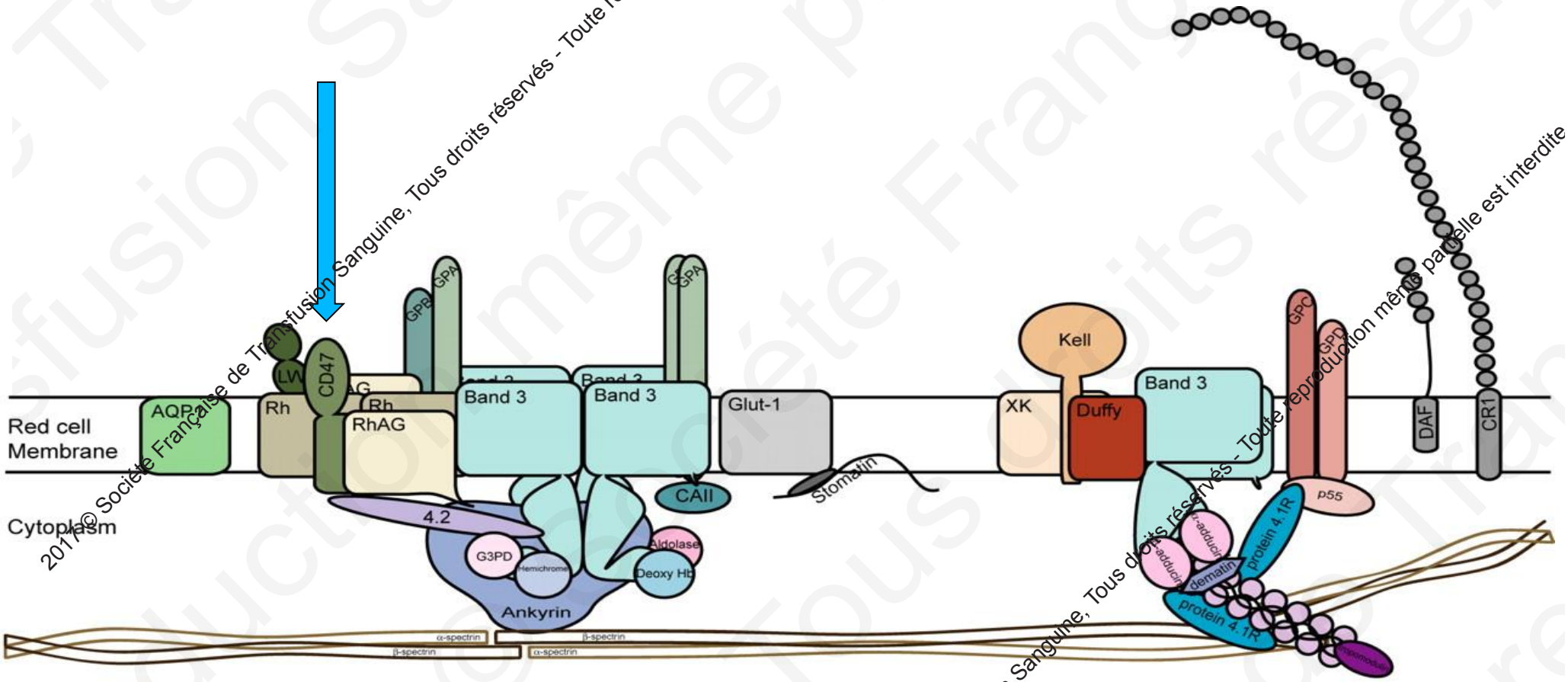
Structure of the human red cell membrane showing the major surface proteins and minor proteins Fy and CR1.



David. J. Anstee Blood 2010;115:4635-4643

- **CD47 : « Integrin Associated Protein ». Superfamille des Ig**
- **Rôle dans l'adhésion, migration cellulaire et apoptose**
- **Signal « ne me mangez pas » (*don't eat me*). L'anti-CD47 abolit ce signal.**
- **Ubiquitaire sur les cellules humaines**
- **Fortement exprimé sur les cellules tumorales**
- **Se fixe sur les hématies et a été rapporté comme causant des AHAI**
- **Essais cliniques principalement sur LAM**

- Plusieurs CHU en France concernés
- Semble causer des problèmes d'interprétation de l'épreuve sérique ABO avec des faibles faux positifs (cause inconnue)
- Possibles problèmes de typage ABO/D (puit contrôle faiblement positif, cause ?)
- Epreuves d'adsorptions pas toujours efficaces

MERCI POUR VOTRE ATTENTION