



Immunohematology Case Studies 2016 - #7

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Clinical History



- 72 year old previously transfused Caucasian woman with gastro-intestinal bleeding
- Blood group O, R1R1 (D+C+c-E-e+), K negative
- Known anti-c
- 6 weeks after last transfusion additional antibody/antibodies reacting with ~ 6 of 10 R1R1 test cells.
- DAT positive with IgG (1+)
- Eluate (acid): negative

Panel 3



EXPIRES: 2017/01/20

CELL	Special Type	Donor	D	C	c	E	e	V	C*	K	k	Kp*	Kp*	Js*	Js*	Fy*	Fy*	Jk*	Jk*	Le*	Le*	P ₁	M	N	S	s	Lu*	Lu*	Xg*	U	TE
1		R1wR1 B1076	+	+	0	0	+	0	+	+	+	0	+	0	+	+	0	+	+	0	+	+	+	0	0	+	0	+	0	1	+
2		R1R1 B2534	+	+	0	0	+	0	0	0	+	0	+	0	+	+	+	+	0	0	0	+	+	0	0	0	+	+	0	2	+
3		R1R1 B8644	+	+	0	0	+	0	0	0	+	0	+	0	+	0	+	+	0	+	0	+	0	0	0	+	+	0	3	+	
4		R1R1 B8214	+	+	0	0	+	0	0	0	+	0	+	0	+	+	+	0	+	0	0	+	0	0	0	+	+	0	4	+	
5		R1R1 B7361	+	+	0	0	+	0	0	0	+	0	+	0	+	0	+	+	0	+	+	0	+	+	0	+	0	+	5	+	
6		R1R1 B7270	+	+	0	0	+	0	0	0	+	0	+	0	+	0	+	+	0	+	0	0	+	0	0	0	+	+	6	+	
7		RzR1 A4252	+	+	0	0	+	0	0	0	+	0	+	0	+	0	+	+	0	0	+	+	+	0	+	0	+	+	7	+	
8		R2R2 C2463	+	0	+	+	0	0	0	0	+	0	+	0	+	+	0	0	+	0	+	0	+	0	0	+	0	+	8	+	
9		R2R2 C5528	+	0	+	+	0	0	0	0	+	0	+	0	+	0	+	0	+	0	+	+	+	0	+	+	0	+	9	+	
10		R2R2 C3165	+	0	+	+	0	0	0	0	+	0	+	0	+	0	0	+	0	0	+	+	0	0	0	+	+	10	+		
11		R2R2 C4884	+	0	+	+	0	0	0	0	+	0	+	0	+	0	+	0	+	0	+	+	+	+	+	+	0	11	+		
12		R2R2 C5523	+	0	+	+	0	0	0	0	+	0	+	0	+	+	+	0	+	+	+	+	+	0	0	+	+	12	+		
13		R2R2 C5525	+	0	+	+	0	0	0	0	+	0	+	0	+	+	+	0	+	+	+	0	+	0	0	+	+	13	+		
14		RzR2 A3859	+	W	+	+	0	0	0	0	+	0	+	0	+	+	+	0	+	0	0	0	0	0	+	+	14	+			
15		POSITIVE CONTROL	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	PC	+	
16		NEGATIVE CONTROL	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	NC	0	

4 of 7 c-negative test cells positive (solid phase test)

Panel 4



System			Rh - Hr						Kell				Duffy		Kidd		Lewis		P	MNS				Xg	Lutheran		Dombrock		Spezial-Antigene Special types	Results						
Rh - Hr	Component Lot		D	C	c	E	e	C ^w	K	k	Kp ^a	Kp ^b	Fy ^a	Fy ^b	Jk ^a	Jk ^b	Le ^a	Le ^b	P ₁	M	N	S	s	Xg ^a	Lu ^a	Lu ^b	Do ^a *	Do ^b *		IAT	Enzyme	4°C				
1 C ^w CD.ee R1 ^w R1	70214404393		+	+	0	0	+	+	0	+	0	+	0	+	+	+	+	0	+	0	+	0	+	+	0	+	0	+	0	+	+	+	1	0	0	0
2 CCD.ee R1R1	70214256026		+	+	0	0	+	0	+	+	0	+	+	0	0	+	0	+	+	+	0	+	0	+	0	+	+	+	+	+	+	+	2	2+	2+	0
3 ccD.EE R2R2	70114672898		+	0	+	+	0	0	0	+	+	+	+	0	0	+	0	+	0	+	+	+	0	0	+	0	+	+	+	+	+	+	3	4+	4+	2+
4 ccD.ee Ror	70314955181		+	0	+	0	+	0	0	+	0	+	0	0	+	0	0	+	+	+	+	+	+	+	0	+	0	+	+	+	+	4	2+	4+	0	
5 Ccddee r'r	70114135891		0	+	+	0	+	0	0	+	0	+	0	+	0	+	0	+	+	+	0	+	0	+	+	0	+	0	+	+	+	5	2+	4+	0	
6 ccddEe r'r	70114686941		0	0	+	+	+	0	0	+	0	+	+	+	0	+	0	0	0	+	+	+	+	+	0	+	0	+	+	+	+	6	2+	4+	0	
7 ccddee rr	70114254831		0	0	+	0	+	0	+	+	0	+	+	+	+	0	0	0	+	0	+	0	+	+	0	+	+	+	+	+	+	7	2+	4+	0	
8 ccddee rr	70314955178		0	0	+	0	+	0	0	+	0	+	+	0	+	0	0	0	+	0	+	0	+	+	0	+	+	+	+	+	+	8	2+	4+	0	
9 ccddee rr	70214525880		0	0	+	0	+	0	0	+	+	+	0	+	+	0	0	0	+	0	+	0	+	+	0	+	0	+	+	+	+	9	2+	4+	0	
10 ccddee rr	70214648907		0	0	+	0	+	0	0	+	0	+	+	0	0	+	0	0	+	0	+	0	+	+	+	0	+	+	+	+	+	10	4+	4+	1+	
11 CcD.ee R1r	70214133742		+	+	+	0	+	0	0	+	0	+	+	0	+	+	+	0	0	+	+	+	0	+	+	0	+	+	+	+	+	+	11	2+	4+	0
Patientenzellen Patient's cells																																				

Reaction pattern confirms anti-c; negative reactions with one of two R1R1 test cells.
 Anti-Do^a or anti-Yk^a ?
 Lu^a+ cells #3 and #10 strongly reactive in indirect antiglobulin test and positive at 4°C:
 anti-Lu^a identified

Panel 5: Dombrock genotyped test cells

R1R1, Do(a-b+) and Do(a+b-)



Indirect antiglobulin test/gel

28.08.2014 11:39

Dombrock

ISBT-Nummer Testzelle	Phänotyp	Cw	K	k	Kp(a)	Kp(b)	Fy(a)	Fy(b)	JK(a)	JK(b)	Le(a)	Le(b)	P1	M	N	S	s	Xg(a)	Lu(a)	Lu(b)	Wr(a)	Co(a)	Co(b)	Vw	ISBT
2370 8965	Do(a-b) cDee	0					0	+	0	+	+	0	+	0	+	+	+								#
2685 3257	- -	0					+	0	0	+		+	0	+	0	+	+		+						#
4515 8193	- -	0	+				0	+	0	+	0	+	0	+	0	+	+								+/#
1566 5602	- -	0					+	+	+	+		+	+	+	0	0	+		∅						∅
057 3209	- -	+					+	0	+	+	0	+	+	+	+	+	+		∅						∅
4515 2259	- -	0					+	+	+	+	0	+	0	+	0	+	+								#
1084 6862	Do(a+b) cDee	+					+	0	+	+	0	+	+	0	0	+									∅
2109 8949	- -	+					0	+	0	+	0	+	+	+	+	0	+								∅
2109 8703	- -	0					0	+	0	+	0	+	+	+	0	0									#
2811 9488	- -																								∅
4560 3192	- -	0					0	+	+	0	0	0	+	+	+	0	+								+
1508 8753	- -	0					+	+	+	+	0	+	+	+	+	0	+								#

p. AB (T) 1/2

No correlation with Dombrock phenotype: Anti-Do(a)
(and anti-Do(b)) ruled out

Interim results:

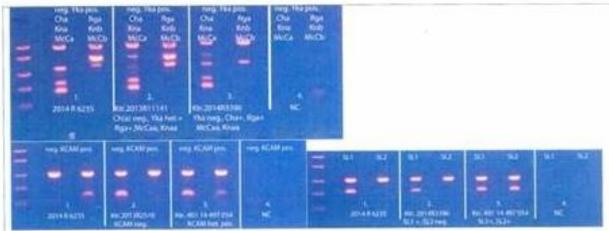


- Blood group O, R1R1 (D+C+c-E-e+), K negative
- Known anti-c
- New: anti-Lu^a
- New additional antibody with unclear specificity; not possible to identify with commercial panels
- Antibody reactive with ~ 60% of R1R1 test cells
- Common antibodies (including anti-Do^a and anti-Do^b) ruled out
- DTT treated red cells weak positive
- Plasma inhibition test with recombinant Knops blood group protein: no inhibition of the antibody

Genotyping



Patientendaten		LS	
Name, Vorname		1500	HGH 1509 HGH
Geb.-Dat.		850	Yka- 776 Yka+
Befund-Nr. oder Konserven-Nr.		400	Chido 498 Rodgers
Position auf Gel	1.	200	McCa 175 McCb
		80	Kna 145 Knb



Befund

Ch(a)	Rg(a)	KN1 Kn(a)	KN2 Kn(b)	KN3 McC(a)	KN6 McC(b)	KN5 Yka neg.	KN5 Yka pos.
Produkt Größe: 498 bp	Produkt Größe: 498 bp	Produkt Größe: 143 bp	Produkt Größe: 145 bp	Produkt Größe: 175bp	Produkt Größe: 175bp	Produkt Größe: 776bp	Produkt Größe: 776bp
+	+	+	-	+	-	-	+
KN9 KCAM pos.	KN9 KCAM neg.	KN4 SL1	KN7 SL2				
Produkt Größe: 94 bp	Produkt Größe: 94 bp	Produkt Größe: 212 bp	Produkt Größe: 212 bp				
+	-	+	-				

Yk(a) pos., Ch(a) pos.
Rg(a) pos., McC(aa),
Kn(aa), SL1 pos. SL2 neg. KCAM pos.

Primermix Nr.	1	2*	3	4	5	6	7*	8	9	10	11	12	13	14*	15	16
PCR-Produkt (Größe in bp)	166	165	184	184	207	207	193	195	218	216	197	197	213	214	181	179
Antigen	Kp		Lutheran		Diego		Wright		Cartwright		Colton		Knops		Dombrock	
Bezeichnung	Kpa	Kpb	Lua	Lub	Dia	Dib	Wra	Wrb	Yta	Ytb	Coa	Cob	Kna	Knb	Doa	Dob
Allel	KEL3	KEL4	LU1	LU2	DI1	DI2	DI3	DI4	Y1	Y2	CO1	CO2	KN1	KN2	DO1	DO2
Ergebnis-Bsp.	-	+	-	+	-	+	-	+	+	-	+	-	+	-	+	+
	Kp bb		Lu bb		Di bb		Wr bb		Yt aa		Co aa		Kn aa		Do ab	
Aktuelles Ergebnis	-	+	-	+	-	+	-	+	+	-	+	-	+	-	-	+

Patient's predicted phenotype:
Ch(a+), Rg(a+),
Kn(a+b-), McC(a+b-), Yk(a+),
KCAM+, SL:1,-2
Kp(a-b+), Lu(a-b+), Di(a-b+), Wr(a-b+),
Yt(a+b-), Do(a+b+)

Analysis of the results:



Based on reaction pattern (papain and DTT treated cells) and frequency of antigens in the Caucasian population:

- Which blood group system most probable?
Lutheran?
- Which antigen most probable?
 Au^b (Lu19)? / Au^a (Lu18)?
(refer to next slide)
- Plasma inhibition test with recombinant Lutheran blood group protein: no inhibition of the antibody

System	Number of Antigens	Antigens
001 ABO	4	A, B, AB, A1
002 MNS	46	M, N, S, s, U, He, Mi ^a , M ^c , Vw, Mur, M ^g , Vr, M ^e , Mt ^a , St ^a , Ri ^a , Cla, Ny ^a , Hil, M ^y , Far, S ^D , Mit, Dantu, Hop, Nob, En ^a , En ^a KT, 'N', Or, DANE, TSEN, MINY, MUT, SAT, ERIK, Os ^a , ENEP, ENEH, HAG, ENAV, MARS, ENDA, ENEV, MNTD, SARA, Kipp
003 P1Pk	3	P1, P ^k , NOR
004 RH	54	D, C, E, c, e, f, Ce, C ^w , C ^x , V, E ^w , G, Hr ₀ , Hr, hr ^s , VS, C ^G , CE, D ^w , c-like, cE, hr ^H , Rh29, Go ^a , hr ^B , Rh32, Rh33, Hr ^B , Rh35, Be ^a , Evans, Rh39, Tar, Rh41, Rh42, Crawford, Nou, Riv, Sec, Dav, JAL, STEM, FPTT, MAR, BARC, JAHK, DAK, LORC, CENR, CEST, CELO, CEAG, PARG, CEVF
005 LU	20	Lu ^a , Lu ^b , Lu3, Lu4, Lu5, Lu6, Lu7, Lu8, Lu9, Lu11, Lu12, Lu13, Lu14, Lu16, Lu17, Au^a, Au^b , Lu20, Lu21, LURC, LUIT
006 KEL	35	K, k, Kp ^a , Kp ^b , Ku, Js ^a , Js ^b , Ul ^a , K11, K12, K13, K14, K16, K17, K18, K19, Km, Kp ^c , K22, K23, K24, VLAN, TOU, RAZ, VONG, KALT, KTIM, KYO, KUCI, KASH, KELP, KETI, KHUL, KYOR
007 LE	6	Le ^a , Le ^b , Le ^{ab} , Le ^{bH} , ALe ^b , BLe ^b
008 FY	5	Fy ^a , Fy ^b , Fy3, Fy5, Fy6
009 JK	3	Jk ^a , Jk ^b , Jk3
010 DI	22	Di ^a , Di ^b , Wr ^a , Wr ^b , Wd ^a , Rb ^a , WARR, ELO, Wu, Bp ^a , Mo ^a , Hg ^a , Vg ^a , Sw ^a , BOW, NFLD, Jn ^a , KREP, Tr ^a , Fr ^a , SW1, DISK
011 YT	2	Yt ^a , Yt ^b
012 XG	2	Xg ^a , CD99
013 SC	7	Sc1, Sc2, Sc3, Rd, STAR, SCER, SCAN
014 DO	8	Do ^a , Do ^b , Gy ^a , Hy, Jo ^a , DOYA, DOMR, DOLG
015 CO	4	Co ^a , Co ^b , Co3, Co4
016 LW	3	LW ^a , LW ^b , LW ^{ab}
017 CH/RG	9	Ch1, Ch2, Ch3, Ch4, Ch5, Ch6, WH, Rg1, Rg2
018 H	1	H
019 XK	1	Kx
020 GE	11	Ge2, Ge3, Ge4, Wb, Ls ^a , An ^a , Dh ^a , GEIS, GELP, GEAT, GETI
021 CROM	18	Cr ^a , Tc ^a , Tc ^b , Tc ^c , Dr ^a , Es ^a , IFC, WES ^a , WES ^b , UMC, GUTI, SERF, ZENA, CROV, CRAM, CROZ, CRUE, CRAG
022 KN	9	Kn ^a , Kn ^b , McC ^a , SI1, Yk ^a , McC ^b , SI2, SI3, KCAM
023 IN	4	In ^a , In ^b , INFI, INJA
024 OK	3	Ok ^a , OKGV, OKVM
025 RAPH	1	MER2
026 JMH	6	JMH, JMhk, JMHL, JMhG, JMhM, JMhQ
027 I	1	I
028 GLOB	1	P
029 GIL	1	GIL
030 RHAG	4	Duclos, OI ^a , DSLK, RHAG4
031 FORS	1	FORS1
032 JR	1	Jr ^a
033 LAN	1	Lan
034 VEL	1	Vel
035 CD59	1	CD59-1

Further serological tests (1)



Donor	Phenotype	Extended Typings
A3224	RzR1	f: I+; Ge+; Tj(a+); Vel+; Yt(a+); Di(b+); U+; Co(a+); Sc:1; Sc:2; Wr(a-); Mg-; Vw-; Di(a-); Co(b-); Bg(a-); Yt(b-); Mi(a-); Dantu-; Do(a-); Do(b+); Lu-14; Hy+; M(a-); Jo(a+); LW(a+); LW(b-) *DNA typed
B5269	R1wR1	I+; Ge+; Tj(a+); Vel+; Yt(a+); Di(b+); U+; Co(a+); Wr(a-); Mg-; Vw-; Di(a-); Co(b-); Bg(a-); Mi(a-); Dantu-
C4687	R2R2	f: I+; Ge+; Tj(a+); Vel+; Yt(a+); Di(b+); U+; Co(a+); Wr(a-); Mg-; Vw-; Di(a-); Co(b-); Bg(a-); Mi(a-); Dantu-; Lu-14
D1058	Ror	f+; I+; Ge+; Tj(a+); Vel+; Yt(a+); Di(b+); U+; Co(a+); Sc:1; Sc:2; Wr(a-); Mg-; Vw-; Di(a-); Co(b-); Bg(a-); Yt(b-); He-; Go(a-); Mi(a-); Dantu-; Do(a-); Do(b+); Lu-14; Hy+; Jo(a+); LW(a+); LW(b-) *DNA Typed, U variant
E847	r'r	I+; Ge+; Tj(a+); Vel+; Yt(a+); Di(b+); U+; Co(a+); Wr(a-); Mg-; Vw-; Di(a-); Co(b-); Bg(a-); Mi(a-); Dantu-; Lu-14
F730	r'r	f+; I+; Ge+; Tj(a+); Vel+; Yt(a+); Di(b+); U+; Co(a+); Wr(a-); Mg-; Vw-; Di(a-); Co(b-); Bg(a-); Mi(a-); Dantu-; Do(a+); Lu-14
G1093	rr	f+; I+; Ge+; Tj(a+); Vel+; Yt(a+); Di(b+); U+; Co(a+); Sc:1; Sc:2; Wr(a-); Mg-; Vw-; Di(a-); Co(b-); Bg(a-); Yt(b-); Mi(a-); Dantu-; Do(a-); Do(b+); Lu-14; Hy+; Jo(a+); LW(a+); LW(b-) *DNA Typed
H177	rr	f+; I+; Ge+; Tj(a+); Vel+; Yt(a+); Di(b+); U+; Co(a+); Jr(a+); Sc:1; Wr(a-); Mg-; Vw-; Di(a-); Co(b-); Bg(a+); Yt(b-); Mi(a-); Dantu-; Do(a+); Lu-14; Yk(a+); McCd+; Sl(a+); M(a-)
H924	rr	f+; I+; Ge+; Tj(a+); Vel+; Yt(a+); Di(b+); U+; Co(a+); Sc:1; Sc:2; Wr(a-); Mg-; Vw-; Di(a-); Co(b-); Bg(a-); Yt(b-); Mi(a-); Dantu-; Do(a+); Do(b+); Lu-14; Hy+; M(a-); Jo(a+); LW(a+); LW(b-) *DNA typed
B5219	R1R1	f: I+; Ge+; Tj(a+); Vel+; Yt(a+); Di(b+); U+; Co(a+); Sc:1; Sc:2; Wr(a-); Mg-; Vw-; Di(a-); Co(b-); Bg(a-); Yt(b-); Dantu-; Do(a+); Do(b+); Lu-14; Ch+; Rg-; Yk(a+); McC(a+); Hy+; M(a-); JMH+; Cs(a-); Au(a+); Au(b-); Sd(a+); Cx-; Jo(a+); LW(a+); LW(b-) *DNA typed
R408	R1r	f+; I+; Ge+; Tj(a+); Vel+; Yt(a+); Di(b+); U+; Co(a-); Jr(a+); Wr(a-); Mg-; Vw-; Di(a-); Co(b+); Bg(a-); Yt(b-); Mi(a-); Dantu-; Do(a+); Lu-14; M(a-)

Single commercial R1R1, Au(b-) test cell available

VIAL	Special Type	Donor	D	C	c	E	e	V	C ^v	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					
1		RzR1 A3224	+	+	0	+	+	0	0	0	+	0	+	0	+	0	+	0	+	0	+	+	+	+	0	+	0	+	+	+	1			
2	Wr(a+)	R1wR1 B5269	+	+	0	0	+	0	+	0	+	0	+	0	+	+	0	0	+	+	0	+	+	+	+	+	0	+	0	2				
3		R2R2 C4687	+	0	+	+	0	0	0	0	+	0	+	0	+	+	+	0	+	0	0	+	0	+	0	+	0	+	+	3				
4		Ror D1058	+	0	+	0	+	0	0	0	+	0	+	0	+	0	0	+	+	0	+	+	+	+	0	0	+	+	+	4				
5		r'r E847	0	+	+	0	+	0	0	0	+	0	+	0	+	0	+	0	+	+	0	+	+	0	+	+	0	+	0	5				
6		r'r F730	0	0	+	+	+	0	0	0	+	0	+	0	+	+	+	+	0	+	0	+	+	+	+	+	0	+	+	6				
7		rr G1093	0	0	+	0	+	0	0	+	+	0	+	0	+	0	+	0	+	0	+	+	0	+	0	+	0	+	0	7				
8	Bg(a+)	rr H177	0	0	+	0	+	0	0	0	+	0	+	0	+	+	0	+	+	+	0	0	+	0	0	+	+	+	0	8				
9		rr H924	0	0	+	0	+	0	0	0	+	0	+	0	+	+	0	+	0	0	0	+	0	+	+	+	0	+	+	9				
10	Au(a+); Au(b-)	R1R1 B5219	+	+	0	0	+	0	0	+	0	+	0	+	0	+	+	0	0	+	+	+	+	+	+	0	0	+	0	10				
TC	Co(a-b+)	R1r R408	+	+	+	0	+	+	0	0	+	0	+	0	+	+	+	+	+	0	+	+	0	+	+	+	0	+	0	TC				

Negative with patient's plasma

Further serological tests (2)



- Patient's plasma with two R1R1 test cells of InLu type (serologically negative for AnWj and all Lutheran antigens):
negative
- Cross-matching patient's plasma with 10 random R1R1, Lu(a-) donors (next slide)

Further serological tests (3)



# Red cell concentrates	Donor #	Cross-match
70114614162	10080703	positive +
70114106163	20821027	positive +/++
70114436640	45158816	positive +/++
70114614240	10587786	positive +/++
70114106095	48357127	negative
70114106189	26531373	negative
70114315315	20929871	positive +/++
70114315326	21975346	positive +/++
70114106187	25000617	negative
70214558239	15080957	negative

Cross-matching patient's plasma with 10 Random R1R1, Lu(a-) donors
6 of 10 donors positive

Further genotyping



- A PCR-SSP method was established for the Au(a/b) mutation
- The patient and the 10 blood donors were genotyped by using this method

Further serological and molecular tests (4)



Patient's genotype: **Au(a+b-)**

# Red cell concentrate	Donor #	Cross-match	AU Genotype
70114614162	10080703	positive +	a+b+
70114106163	20821027	positive +/++	a-b+
70114436640	45158816	positive +/++	a+b+
70114614240	10587786	positive +/++	a-b+
70114106095	48357127	negative	a+b-
70114106189	26531373	negative	a+b-
70114315315	20929871	positive +/++	a+b+
70114315326	21975346	positive +/++	a+b+
70114106187	25000617	negative	a+b-
70214558239	15080957	negative	a+b-

Cross-matching patient's plasma with 10 random R1R1, Lu(a-) donors and genotyping of the donors for Au(a/b) showed complete concordance between the Au^b genotype and cross-match result

Conclusions



- Previously transfused patient with known anti-c developed anti-Lu^a and anti-Au^b (Lu19)
- The antibody specificity of anti-Au^b could not be determined when using commercial panels because of lack of Au(a/b) typed test cells
- Plasma inhibition test with recombinant Lutheran blood group protein: **no inhibition of the antibody** (obviously the protein did not contain the Au^b antigen)
- The antibody was identified after genotyping of the patient and the test donors was performed

Lessons Learned by the Case



- Genotyping can provide crucial information to identify uncommon red cell antibodies
- Extended serological pre-testing using untreated and enzyme treated test cells is necessary for a rational application of molecular methods
- Recombinant blood group antigen proteins can be helpful for solving complex serological cases
- The donors of red cells for antibody identification panels should be genotyped for as many alleles as possible to improve the serological diagnostics