13° CONGRESO COLOMBIANO & 19° CONGRESO IBEROAMERICANO DE BANCOS DE SANGRE, MEDICINA TRANSFUSIONAL Y TERAPIA CELULAR

CONECTADOS CON EL PACIENTE

Octubre 31 a Noviembre 3 del 2024
Bogotá Colombia, Hotel Sheraton

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Asociación Colombiana de Bancos de Sangre y Medicina Transfusional

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Intereferencia de Tratamiento con Anticuerpos Monoclonales en Estudios Inmunohematologicos

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Conflicto de intereses

No hay conflicto de intereses que declarar

Objetivos

- Describir la terapia con anticuerpos monoclonales (MABs)
- Discutir la terapia con Daratumumab (anti-CD38)
- Discutir la terapia con Magrolimab (anti-CD47)
- Alternativas sugeridas para enfrentar la interferencia por terapia con anticuerpos monoclonales
- Ejemplos

Terapia con anticuerpos monoclonales

- **Características ideales del MAB**
  - **Abundante**
  - **Accesible**
  - **Consistente**
  - **Exclusivo de la superficie de células tumorales**

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3380347/

MABs; Tratamientos de Precision, Pero con Interferencia en Inmunohematologia

- El uso de anticuerpos monoclonales (MABs) es innovador en el tratamiento de enfermedades malignas
- Introducción de Rituximab en los 1990s
- La práctica de la inmunohematología se hizo más complicada y la interferencia en los tests de laboratorio producida por ciertas MABs terapias puede persistir por meses
- Otros MABs estan en desarrollo

Direct tumor cell killing

- cell surface receptor agonist activity (leading to apoptosis)
- cell surface receptor antagonist activity (inhibit signaling, reduce proliferation, induce apoptosis)
- cell surface enzyme neutralization (leading to signaling abrogation)
- conjugated antibody, delivery of payload (drug, toxin, radio-isotope, leading to cell death)

Immune-mediated tumor cell killing

- induction of phagocytosis
- complement activation
- antibody-dependent cell-mediated cytotoxicity (ADCC)
- target gene-modified T cells
- activate T cells (through inhibition of T cell inhibitory receptors, such as CTLA-4, or antibody-mediated cross presentation of antigen to dendritic cells)

Vascular and stromal ablation

- vessel receptor antagonism or ligand trap
- stromal cell inhibition
- conjugated antibody, delivery of payload

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3380347/

Antigen category	Examples of antigens	Tumor types expressing antigen
Cluster of differentiation (CD) antigens	CD20	non-Hodgkin lymphoma
	CD30	Hodgkin lymphoma
	CD33	Acute myelogenous leukemia
	CD52	Chronic lymphocytic leukemia
Glycoproteins	EpCAM	Epithelial tumors (breast, colon, lung)
	CEA	Epithelial tumors (breast, colon, lung)
	gpA33	Colorectal carcinoma
	Mucins	Epithelial tumors (breast, colon, lung, ovarian)
	TAG-72	Epithelial tumors (breast, colon, lung)
	Carbonic anhydrase IX	Renal cell carcinoma
	PSMA	Prostate carcinoma
	Folate binding protein	Ovarian tumors
Glycolipids	Gangliosides (e.g., GD2, GD3, GM2)	Neuroectodermal tumors, some epithelial tumors
Carbohydrates	Lewis-Y^2	Epithelial tumors (breast, colon, lung, prostate)
Vascular targets	VEGF	Tumor vasculature
	VEGFR	Epithelium-derived solid tumors
	$\alpha V\beta 3$	Tumor vasculature
	$\alpha 5\beta 1$	Tumor vasculature
Growth factors	ErbB1/EGFR	Glioma, lung, breast, colon, head and neck tumors
	ErbB2/HER2	Breast, colon, lung, ovarian, prostate tumors
	ErbB3	Breast, colon, lung, ovarian, prostate tumors
	c-MET	Epithelial tumors (breast, ovary, lung)
	IGF1R	Lung, breast, head and neck, prostate, thyroid, glioma
	EphA3	Lung, kidney, colon, melanoma, glioma, hematological malignancies
	TRAIL-R1, TRAIL-R2	Solid tumors (colon, lung, pancreas) and hematological malignancies
	RANKL	Prostate cancer and bone metastases
Stromal and extracellular matrix antigens	FAP	Epithelial tumors (colon, breast, lung, head and neck, pancreas)
	Tenascin	Glioma, epithelial tumors (breast, prostate)

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3380347/

•In 2012:
•25 mAbs, para enfermedades oncologicas, incluyendo siltuximab para enfermedad de Castleman, 12 para enfermedades inflamatorias y/o autoimmune, y 15 para otros entidades clinicas. Algunos mAbs han sido aprovadas para mas de una condicion clinica: alemtuzumab pra leucemia linfocitica (as Campath®) y multiple sclerosis (as Lemtrada®) and denosumab Perdida osea (as Prolia®) y metastasis oeas (as Xgeva®).

In 2022:
Antibody drug conjugates ADC; 10 para tratamiento de cancer, mas de 80 bajo investigacion.`

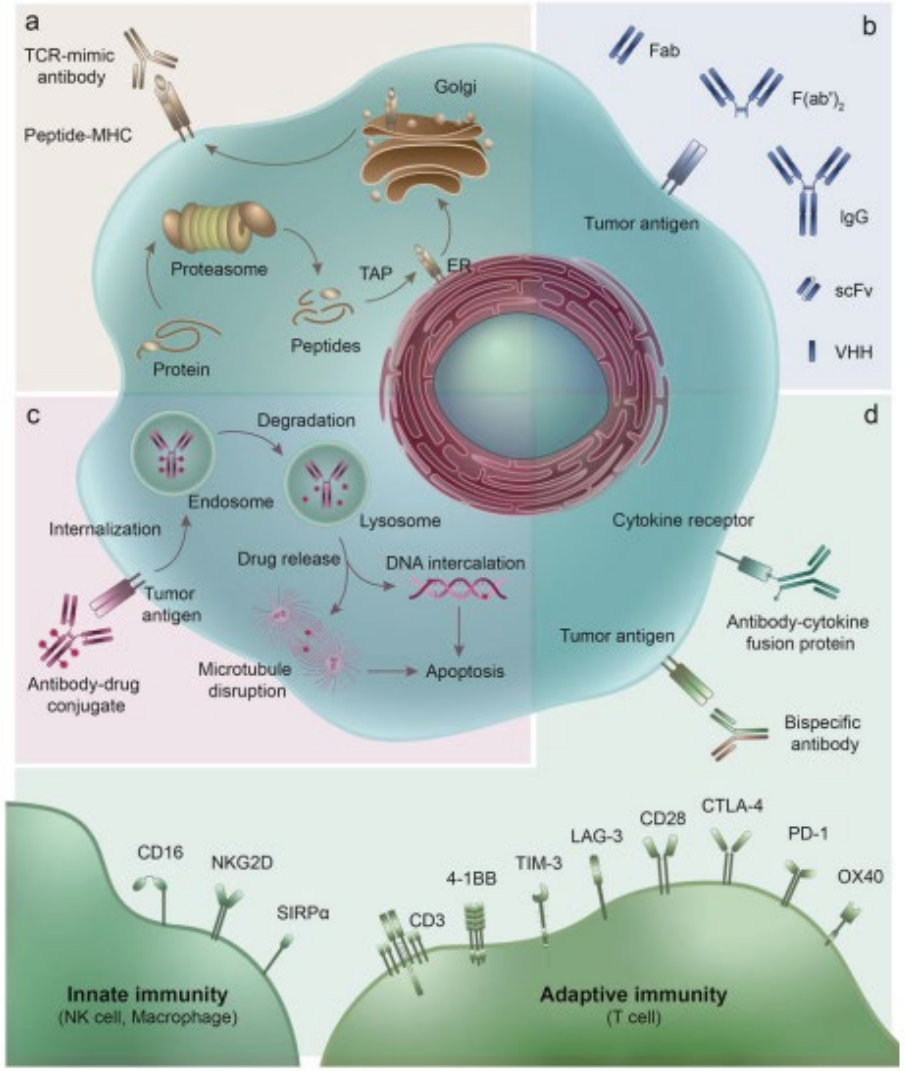

Fig. 1 Representative therapeutic antibodies and their derivatives. **a** TCR-mimic antibody; **b** IgG antibody and antibody fragments; **c** antibody-drug conjugate (ADC) and its mechanism of action; **d** multifunctional antibodies, such as bispecific antibodies, immunocytokine (antibody-cytokine fusion protein)

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Shijie Jin et al. Emerging new therapeutic antibody derivatives for cancer treatment. Signal Transduct Target Ther. 2022 Feb 7;7(1):39. doi: 10.1038/s41392-021-00868-x.

Table 1. The FDA-approved antibody–drug conjugates

Name	Target	Linker	Payload	Indication(s)	Year of FDA approval
Gemtuzumab ozogamicin (Mylotarg)	CD33	Acid-labile hydrazone-based linker	Calicheamicin derivative	AML	2000; withdrawn in 2010; reapproved in 2017
Brentuximab vedotin (Adcetris)	CD30	Cleavable valine-citrulline linker	MMAE	HL, sALCL	2011
Ado-Trastuzumab emtansine (Kadcyla)	HER2	Non-cleavable thioether linker	DM1	HER2-positive breast cancer	2013
Inotuzumab ozogamicin (Besponsa)	CD22	Acid-labile hydrazone-based linker	Calicheamicin derivative	R/R B-ALL	2017
Polatuzumab vedotin-piiq (Polivy)	CD79b	Cleavable valine- citrulline linker	MMAE	R/R DLBCL	2019
Enfortumab vedotin (Padcev)	Nectin-4	Cleavable valine-citrulline linker	MMAE	Advanced urothelial cancer	2019
Trastuzumab deruxtecan (Enhertu)	HER2	cleavable tetrapeptide-based linker	DXd (DX-8951 derivative)	HER2-positive breast cancer	2019
Sacituzumab govitecan (Trodelvy)	Trop-2	Cleavable CL2A linker	SN-38	TNBC	2020
Belantamab mafodotin (Blenrep)	BCMA	Non-cleavable maleimidocaproyl (mc) linker	MMAF	R/R multiple myeloma	2020
loncastuximab tesirine-lpyl (Zynlonta)	CD19	Cleavable valine-alanine linker	SG3199 (PBD dimer)	R/R DLBCL	2021

Shijie et al. Emerging new therapeutic antibody derivatives for cancer treatment. Signal Transduct Target Ther. 2022 Feb 7;7(1):39. doi: 10.1038/s41392-021-00868-x.

Anticuerpos Monoclonales (MABs); Los Desafíos en Inmunohematología

- **El uso de la terapia con MABs ha abierto una nueva era en el tratamiento del cáncer y de otras enfermedades**

Anti-CD38

Anti-CD38; Daratumumab (Dara), Isatuximab, MOR202 and TAK-079

- **CD38 fue descubierto en 1980 en timo**
- **Es una ADP ribose hydrolase ciclica**
- **Es una glicoproteína que se encuentra en la superficie de células inmunes incluyendo linfocitos CD4+, CD8+, Linfocitos B y natural killer cells**
- Niels W.C.J. van de Donk and Saad Z. Usmani. CD38 Antibodies in Multiple Myeloma: Mechanisms of Action and Modes of Resistance. Front Immunol. 2018; 9: 2134.

Anti-CD38; Daratumumab (Dara), Isatuximab, MOR202 and TAK-079

- **Abundante en células plasmáticas**
- **Activador de células B y T**
- **Perdida de CD38 está relacionado con deterioro inmunológico, cambios metabólicos y amnesia social (relacionado con autismo)**
- **Expresión aumentada de CD38 tiene un pronóstico desfavorable in CLL**

Niels W.C.J. van de Donk and Saad Z. Usmani. CD38 Antibodies in Multiple Myeloma: Mechanisms of Action and Modes of Resistance. Front Immunol. 2018; 9: 2134

Anti-CD38; Daratumumab (Dara), Isatuximab, MOR202 and TAK-079

- **Células de mieloma múltiple expresan CD38 en altos niveles**
- **Células normales de líneas mieloides y linfoide expresan CD38 en niveles bajos**
- **Anti-CD38 destruye células tumorales mediante mecanismos Fc-dependientes, como citotoxicidad dependiente de complemento (CDC), citotoxicidad celular dependiente de anticuerpos (ADCC) y fagocitosis dependiente de anticuerpos (ADCP)**

Niels W.C.J. van de Donk and Saad Z. Usmani. CD38 Antibodies in Multiple Myeloma: Mechanisms of Action and Modes of Resistance. Front Immunol. 2018; 9: 2134

Anti-CD38; Daratumumab (Dara), Isatuximab, MOR202 and TAK-079

- **CD38 juega un papel en adhesión y como ectoenzima**
- **Inhibición de función ectoenzimatica e inducción de apoptosis contribuyen a la destrucción de células de mieloma múltiple**
- **Anticuerpos anti-CD38 mejoran inmunidad antitumoral mediante reducción de células T y B reguladoras**

Niels W.C.J. van de Donk and Saad Z. Usmani. CD38 Antibodies in Multiple Myeloma: Mechanisms of Action and Modes of Resistance. Front Immunol. 2018; 9: 2134

Anti-CD38; Daratumumab (Dara), Isatuximab, MOR202 and TAK-079

- **Anti-CD38 tiene citotoxicidad dependiente de complemento (CDC), citotoxicidad celular dependiente de anticuerpos (ADCP), inhibición de función ectoenzimatica e inducción de apoptosis directa**

Niels W.C.J. van de Donk and Saad Z. Usmani. CD38 Antibodies in Multiple Myeloma: Mechanisms of Action and Modes of Resistance. Front Immunol. 2018; 9: 2134

Anti-CD38; Daratumumab (Dara), Isatuximab, MOR202 and TAK-079

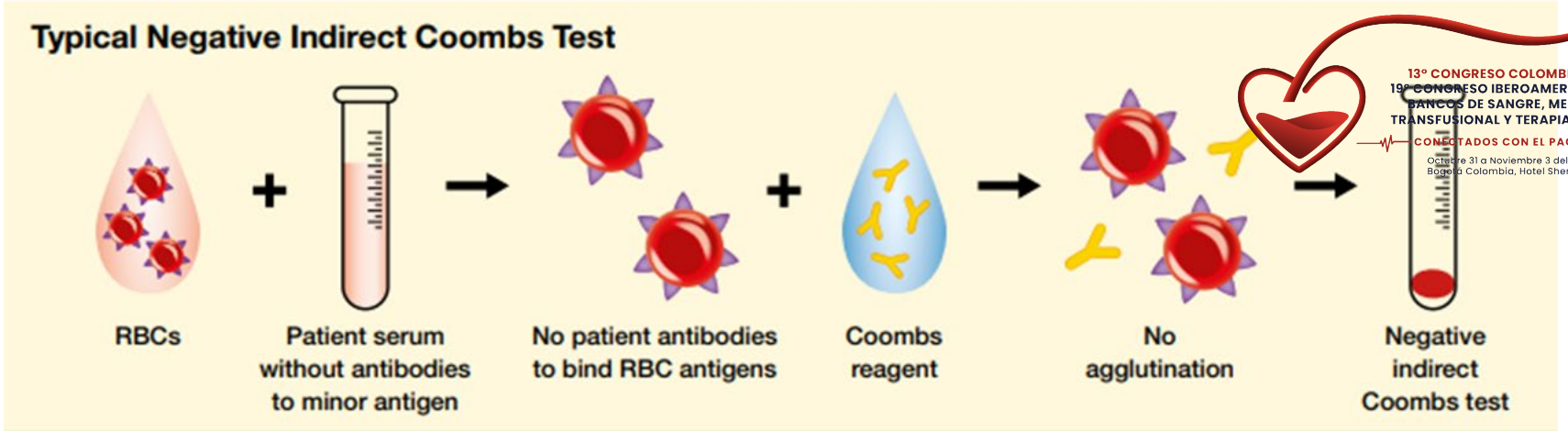
- **Citotoxicidad dependiente de complemento juega un papel en Daratumumab**
- **Inducción directa de apoptosis parece ser más significante en isatuximab**
- **Opción terapéutica para :Mieloma múltiple, linfoma difuso de células B grandes, linfoma folicular y linfoma de células del manto**

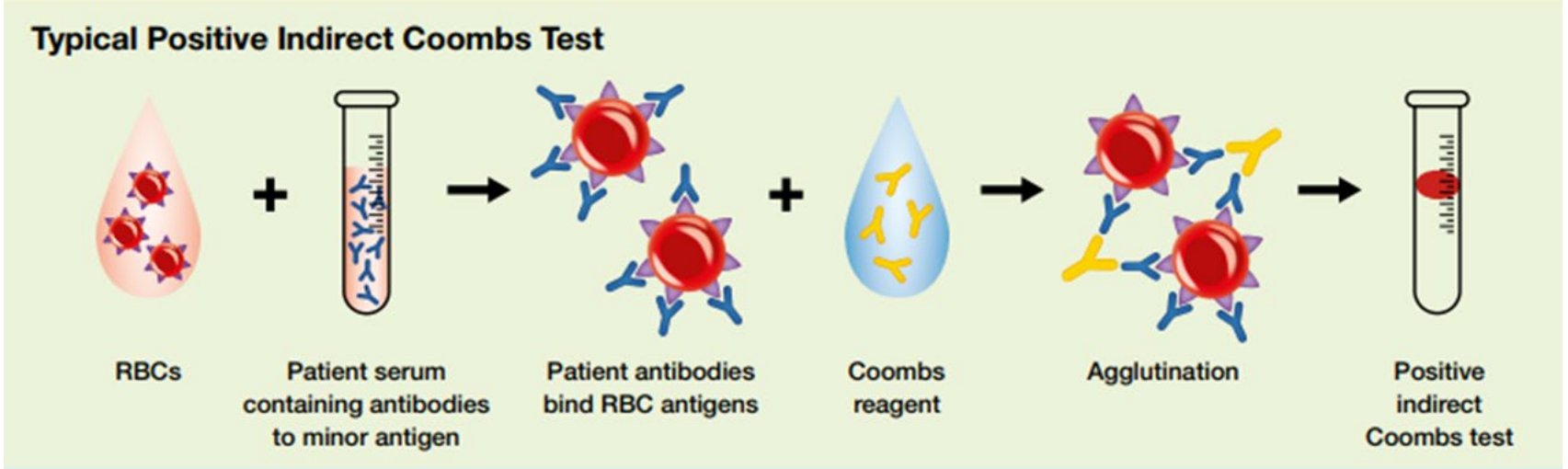
Niels W.C.J. van de Donk and Saad Z. Usmani. CD38 Antibodies in Multiple Myeloma: Mechanisms of Action and Modes of Resistance. Front Immunol. 2018; 9: 2134

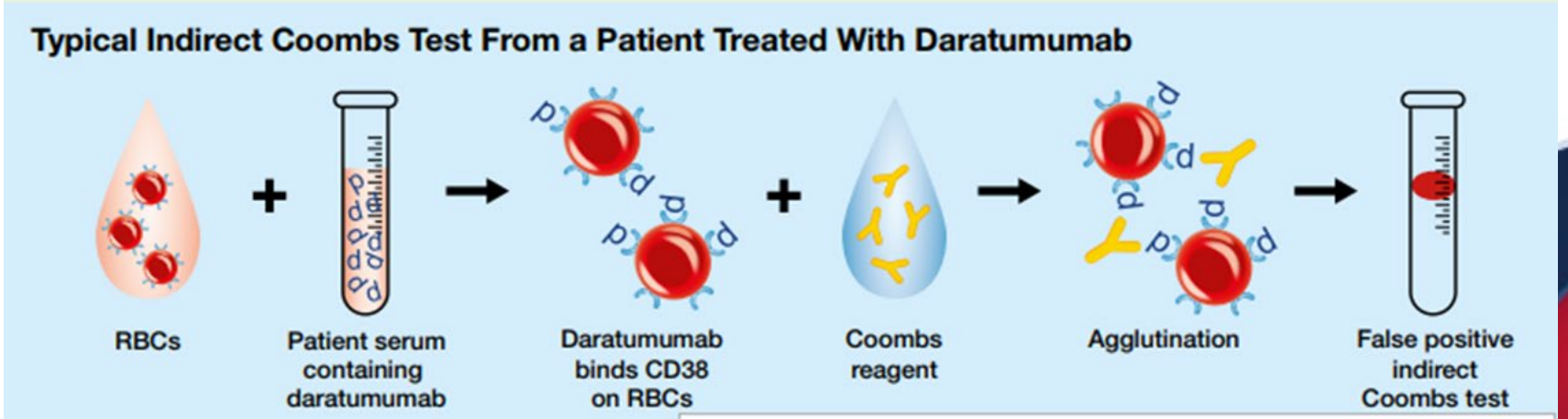
Anti-CD38; Daratumumab (Dara), Isatuximab, MOR202 and TAK-079

- **CD-38 está presente en poco número en la superficie de los eritrocitos**
- **Pan-reactividad en células de tamizaje**
- **Algunas veces el DAT es positivo**
- **Mayoría de casos DAT y autocontrol son negativos**
- **Eritrocitos de células de cordón expresan poco o ningún CD38, pudiéndose usar para detección de allo-anticuerpos**

Niels W.C.J. van de Donk and Saad Z. Usmani. CD38 Antibodies in Multiple Myeloma: Mechanisms of Action and Modes of Resistance. Front Immunol. 2018; 9: 2134







https://www.darzalex.com/faspro

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Donor	Ag = antigen Other	Rhesus								MNS				P	Lewis		Lutheran		Kell				Duffy		Kidd		Sex linked	No.
		D	C	E	c	e	f	C^w	V	M	N	S	s	P_1	Le^a	Le^b	Lu^a	Lu^b	K	k	Kp^a	Js^a	Fy^a	Fy^b	Jk^a	Jk^b	Xg^a	
																												SC I*
																												SC II*
																												SC III*
M7152AM		0	0	0	+	+	+	0	nt	+	+	0	+	+	0	+	0	+	0	+	0	nt	+	0	0	+	+	1
M7230CC		0	0	0	+	+	+	0	nt	0	+	+	+	+	0	+	+	+	+	+	0	nt	0	+	+	0	+	2
M5713HO		0	+	0	+	+	+	0	nt	+	0	+	0	+	+	0	0	+	0	+	0	0	+	+	+	0	+	3
M6491CC		0	0	+	+	+	+	0	nt	+	+	0	+	0	0	+	0	+	0	+	0	0	+	+	+	+	+	4
M6849CC	Kp(a+)	0	0	0	+	+	+	0	nt	+	0	+	+	+	0	+	0	+	0	+	+	0	+	+	+	0	+	5
M6780CC		+	0	0	+	+	+	0	nt	0	+	+	+	+	0	+	0	+	0	+	0	0	0	0	+	0	0	6
M7067AM		+	+	0	0	+	nt	+	nt	+	+	+	0	+	0	+	0	+	0	+	0	nt	0	+	+	+	+	7
M7387AM		+	+	0	0	+	nt	0	nt	0	+	0	+	+^w	0	0	0	+	+	+	0	nt	+	0	+	0	+	8
M5579AM		+	+^w	+	+	0	nt	0	nt	+	+	0	+	+	0	+	0	+	0	+	0	0	+	0	+	+	+	9
M6049HM	Di(a+)	+	0	+	+	0	nt	0	nt	+	+	0	+	+	0	+	0	+	0	+	0	0	+	+	+	+	+	10
M7050LS	Mi(a+)	+	+	0	0	+	nt	0	nt	+	+^w	0	+	0	+	+	0	+	0	+	0	nt	+	0	0	+	0	11
																												Auto
		D	C	E	c	e	f	C^w	V	M	N	S	s	P_1	Le^a	Le^b	Lu^a	Lu^b	K	k	Kp^a	Js^a	Fy^a	Fy^b	Jk^a	Jk^b	Xg^a	
																												12
																												13
																												14

vs = very strong
s = strong
vw = very weak
w = weak

Unless otherwise specified, Data-Cyte® Plus 2 cell donors have been phenotyped as follows:
Negative: M^s, Vw, Wr^a, Di^a
Positive: H, I, U, Kp^b, Js^b, Vel, Ge, Yt^a, Di^b

HX of DATA per Epic. Last Du
Current Tx Plan Carfilzomib

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No.	Rh	Donor	Ag = antigen Other	Rhesus								MNS				P	Lewis		Lutheran		Kell				Duffy		Kidd		Sex linked
				D	C	E	c	e	f	C^{w}	V	M	N	S	s	P_1	Le^a	Le^b	Lu^a	Lu^b	K	k	Kp^a	Js^a	Fy^a	Fy^b	Jk^a	Jk^b	Xg^a
SC I*																													
SC II*																													
SC III*																													
1	rr	M7152AM		0	0	0	+	+	+	0	nt	+	+	0	+	+	0	+	0	+	0	+	0	nt	+	0	0	+	+
2	rr	M7230CC		0	0	0	+	+	+	0	nt	0	+	+	+	+	0	+	+	+	+	+	0	nt	0	+	+	0	+
3	r'r	M5713HO		0	+	0	+	+	+	0	nt	+	0	+	0	+	+	0	0	+	0	+	0	0	+	+	+	0	+
4	r''r	M6491CC		0	0	+	+	+	+	0	nt	+	+	0	+	0	0	+	0	+	0	+	0	0	+	+	+	+	+
5	rr	M6849CC	Kp(a+)	0	0	0	+	+	+	0	nt	+	0	+	+	+	0	+	0	+	0	+	+	0	+	+	+	0	+
6	R$_0$r	M6780CC		+	0	0	+	+	+	0	nt	0	+	+	+	+	0	+	0	+	0	+	0	0	0	0	+	0	0
7	R$_1$R$_1^w$	M7067AM		+	+	0	0	+	nt	+	nt	+	+	+	0	+	0	+	0	+	0	+	0	nt	0	+	+	+	+
8	R$_1$R$_1$	M7387AM		+	+	0	0	+	nt	0	nt	0	+	0	+	+^{w}	0	0	0	+	+	+	0	nt	+	0	+	0	+
9	R$_2$R$_2$	M5579AM		+	+^{w}	+	+	0	nt	0	nt	+	+	0	+	+	0	+	0	+	0	+	0	0	+	0	+	+	+
10	R$_2$R$_2$	M6049HM	Di(a+)	+	0	+	+	0	nt	0	nt	+	+	0	+	+	0	+	0	+	0	+	0	0	+	+	+	+	+
11	R$_1$R$_2$	M7050LS	Mi(a+)	+	+	0	0	+	nt	0	nt	+	+^{w}	0	+	0	+	+	0	+	0	+	0	nt	+	0	0	+	0
Auto																													
Other cells				D	C	E	c	e	f	C^{w}	V	M	N	S	s	P_1	Le^a	Le^b	Lu^a	Lu^b	K	k	Kp^a	Js^a	Fy^a	Fy^b	Jk^a	Jk^b	Xg^a
12																													
13																													
14																													

No.			
SC I*	2		
SC II*	1		
SC III*	1		
1	1		
2	1		
3	1		
4	1		
5	1		
6	1		
7	1		
8	1		
9	1		
10	1		
11	1		
Auto	1		
12	=	TNP	2
13	=	=	1
14	=	=	TNP

DAT IgG
C3
saline ctrl

*Screening Cells
Usually cold reactive antibody
Usually warm or Coombs reactive Ab

vs = very strong
s = strong
vw = very weak
w = weak
NT = not typed

Unless otherwise specified, Data-Cyte® Plus 2 cell donors have been phenotyped as follows:
Negative: M^g, Vw, Wr^a, Di^a
Positive: H, I, U, Kp^b, Js^b, Vel, Ge, Yt^a, Di^b

pt on isatuximab - last dose: 8/21/23,
prev dose: 8/14/23

Name	Date	Drawn	Result	Date	Signature
ot					

Anti-CD38; Manejo

- **Equipo clínico notifica a el laboratorio que el paciente va a recibir anti-CD38**
- **Se ordena fenotipo o genotipo del paciente antes de recibir tratamiento**
- **Tratamiento de células de tamizaje con DTT**
- **Tratamiento de segmento de la unidad con DTT, se hace prueba cruzada usando este segmento**
- **Se libera una unidad de células rojas que es K negativa si el paciente es K negativo y antígeno negativo de acuerdo al genotipo**

Células tratadas con DTT: anti-CD38 no se une a células tratadas con DTT

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Células de tamizaje produciendo pan aglutinacion

Tamizaje positivo

Células tratadas con DTT

Tamizaje negativo

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(P-IG-3) "Where's DARA?" - A Medicinal Game of Anti-CD38 Hide And Seek

Chloe I. Homich, MLS(ASCP)SBB

- Anti-CD38 puede ser usado en combinación con otras drogas y el laboratorio puede no saber de ello
- Anti-CD38 se da inicialmente, pero persiste hasta 6 meses
- Dos regímenes que pueden incluir anti-CD38 combinado con otras drogas incluyen pomalidomide (Pomalyst) [POM] y bortezomib (Velcade) [VEL]; el anti-CD38 no esta incluido en el inserto de POM or VEL

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...mbre 3 del 2024
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Medicamento	Ensayo clinico con anti-CD-38
Azacitidine	Si
Bortezomib	Si
Doxorubicin	Si
Thalidomide	Si
Pomalidomida	Si
Teclistimab	Si
Elotuzumab	Si
Elranatamab	Si
Tacrolimus	Si
Sirolimus	Si
Melphalan	Si

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Tratamiento con DTT

- **Agente reductor**
- **Rompe los enlaces disulfuro entre aminoácidos, desnaturalizando o modificando ciertos antígenos del eritrocito**
- **Kell, Lutheran, YT, JMH LW, Cromer, Indian, Dombrock and Cartwright También son afectados**

TABLE 2 | Approaches for overcoming anti-CD38 monoclonal antibody interference with IAT.

Method	Mechanism	Advantages	Disadvantages
DTT	Denatures CD38 antigen on reagent RBCs	Cheap Easy to apply Well-validated and reliable	Denatures Kell antigen; must give K-negative RBCs (unless Kell status known) Destroys other clinically significant minor antigens (Lutheran, YT, JMH, LW, Cromer, Indian, Dombrock, and Knops systems)
Trypsin	Cleaves CD38 antigen on reagent RBCs	Cheap Easy to apply	Denatures several significant antigens (M, N, En^{a}TS, Ge2, Ge3, Ge4, Ch/Rg, and Lutheran) Not validated Less reliable than DTT at removing CD38 from reagent RBCs
Papain	Cleaves CD38 antigen on reagent RBCs	Cheap Easy to apply Reliable	Destroys many significant antigens, including MNS and Duffy systems as well as Ch/Rg, Ge2, and Ge4 Due to above, can only be used as a complementary method
RBC phenotype	Antigen profiling of patient RBCs	Only needs to be performed once Provides reliable information for future use Does not require future IAT testing if matched units available	Cannot be done if already started anti-CD38 therapy, or blood transfusion within 3 months Requires extended match to ensure no antibodies or future alloantibody formation Extended-match units may be scarce and better utilized for patients with known alloantibodies
RBC genotype	Antigen profiling of patient RBCs	Only needs to be performed once Provides reliable information for future use Does not require future IAT testing if matched units available Can be performed at any time	Expensive Requires extended match to ensure no antibodies or future alloantibody formation Extended-match units may be scarce and better utilized for patients with known alloantibodies
Anti-idiotype antibody	Neutralizes anti-CD38 antibody prior to IAT	Simple and would allow for normal blood bank testing once anti-CD38 antibody removed Commercially available (for daratumumab)	Expensive Not typically available in blood bank inventory Would require different reagent for each anti-CD38 monoclonal antibody
Soluble CD38 antigen	Neutralizes anti-CD38 antibody prior to IAT	Simple and would allow for normal blood bank testing once anti-CD38 antibody removed Applicable to any anti-CD38 monoclonal antibody Commercially available	Expensive Not typically available in blood bank inventory May be less efficacious than anti-idiotype antibody Would require large amount of soluble CD38 to neutralize therapeutic monoclonal antibodies
F(ab′)$_2$ fragments	Fragments preferentially bind CD38 and do not cause IAT positivity	Simple and would allow for routine blood bank testing after application	Not validated Not commercially available
Cord blood/In (Lu) RBCs	Reagent cells lack CD38 antigen	Easy to perform; no additional steps required	In (Lu) RBCs are rare Cord blood cell antigen expression differs from reagent RBCs; therefore, would need to be typed prior to use

https://www.frontiersin.org/files/Articles/414571/fimmu-09-02616-HTML/image_m/fimmu-09-02616-g002.jpg

Otras Alternativas

- **Uso de Tripsina, K es preservado, sin embargo, otros antigenos como M, N and Dombrock no se detectan despues del tratamiento. Tripsina no destruye totalmente CD38, por tanto, falla ante altas concentraciones de anti-CD38**
- **Células de cordón**
- **CD38 recombinante**
- **Prueba cruzada en seco**

Otras Alternativas

- **Células rojas tipo O serologicamente negativas para CD38**
  - **Son células rojas que no expresan el CD38 en su superficie**
- **Agentes neutralizadores, por el momento disponible solo para investigación**
- **Uso de eritrocitos In(Lu)**

Otras Alternativas

Solid phase antibody screening in the presence of anti-CD38 monoclonal antibodies: a potential alternative to avoid interference

Sir,

The IgG1 kappa anti-CD38 monoclonal antibody, daratumumab, has been registered in Australia for use in relapsed/refractory multiple myeloma since mid-2017.[1] In addition to being an antigen on the surface of plasma cells, CD38 is found on the surface of red blood cells and is important in regulation of intracellular calcium levels. A complicating issue for transfusion laboratories in the use of this effective new treatment, is that it interferes with pre-transfusion antibody screening tests, required for the safe delivery of compatible blood products. It is common for patients receiving treatment for multiple myeloma to require red cell transfusion, making screening for alloantibodies a challenge. The aim of this small pilot study is to examine an alternative method for the detection of red cell antibodies in the presence of daratumumab interference.

J. Perram et al. Solid phase antibody screening in the presence of anti-CD38 monoclonal antibodies: a potential alternative to avoid interference. Pathology. Volume 52, Issue 4p492-494June 2020.

Distinct effects of daratumumab on indirect and direct antiglobulin tests: a new method employing 0.01 mol/L dithiothreitol for negating the daratumumab interference with preserving K antigenicity (Osaka method)

Mika Hosokawa,[1] Hirokazu Kashiwagi,[2] Kotarosumitomo Nakayama,[1] Mikiko Sakuragi,[1] Mayumi Nakao,[1] Tamayo Morikawa,[1] Tomoko Kiyokawa,[1] Hiroshi Aochi,[1] Keisuke Nagamine,[1] Hirohiko Shibayama,[2] and Yoshiaki Tomiyama[1,2]

BACKGROUND: There is an increasing demand for daratumumab (DARA), an immunoglobulin (Ig)G1κ monoclonal antibody (MoAb) that recognizes CD38, to manage relapsed or refractory multiple myeloma (MM) patients. However, DARA leads to positive and panreactive agglutination reactions in indirect antiglobulin tests (IATs) in vitro (the DARA interference). In addition, effects of DARA on red blood cells (RBCs) in vivo remains elusive.
STUDY DESIGN AND METHODS: To develop a new method to negate the DARA interference, the effects of various concentrations of dithiothreitol (DTT) on RBC CD38 and Kell antigenicity in combination with an automatic blood cell washing centrifuge were compared with the AABB standard procedure in parallel. Moreover, direct antiglobulin tests (DATs) for RBCs in DARA-treated MM patients were examined.
RESULTS: A quantity of 0.01 mol/L DTT as well as the AABB procedure (equivalent to 0.15 mol/L DTT in our procedure) markedly reduced the reactivity of phycoerythrin-mouse anti-CD38 MoAb and DARA with RBCs. In sharp contrast to the AABB procedure, 0.01 mol/L DTT partially preserved K antigenicity and allowed the determination of phenotype of K antigen even in the presence of the DARA interference. In contrast, DAT for RBCs obtained from MM patients showed a weak positive or negative reaction. Immunoblotting further indicated that DARA induced loss of CD38 in vivo.
CONCLUSION: A simple and reliable method to negate the DARA interference with partially preserving Kell antigenicity is proposed (Osaka method). CD38 antigenicity is susceptible to 0.01 mol/L DTT treatment even in the presence of DARA. Our data also demonstrate distinct effects of DARA on IAT in vitro and DAT in vivo.

CD38 is a 46-kDa Type II transmembrane glycoprotein which consists of a short 20-amino-acid N-terminal cytoplasmic tail and a long 256-amino-acid extracellular domain.[1,2] CD38 is highly expressed on all malignant cells in multiple myeloma (MM), a malignant disorder characterized by neoplastic monoclonal expansion of plasma cells in the marrow. Of note, relatively low levels of CD38 expression on normal lymphoid and myeloid cells and in some tissues of nonhematopoietic origin enable this molecule to be an excellent target in the treatment of MM.[2,3] In fact, daratumumab (DARA; Genmab/Janssen), a humanized immunoglobulin (Ig)G_1κ monoclonal antibody (MoAb) to CD38, was approved for the treatment of relapsed and/or refractory MM patients in September 2017 in Japan as well as in November 2015 by the Food and Drug Administration in the United States based on

ABBREVIATIONS: DARA = daratumumab; MM = multiple myeloma.

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doi:10.1111/trf.14900

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CONECTADOS CON EL PACIENTE
Octubre 31 a Noviembre 3 del 2024
Bogotá Colombia, Hotel Sheraton

New method for overcoming the interference produced by anti-CD38 monoclonal antibodies in compatibility testing

Emma Castro Izaguirre[1], María del Mar Luis-Hidalgo[1], Luis Larrea González[1], Cristina Arbona Castaño[1]

Background - Plasma of patients taking anti-CD38 monoclonal antibodies (MoAbs) leads to panagglutination in the indirect antiglobulin test (IAT), that can mask clinically significant alloantibodies. Dithiothreitol (DTT) treatment of test RBCs is the more widespread method for avoiding this interference. Current DTT 0.2 mol/L method is time consuming and damages several red blood groups antigens. This study aims to evaluate low concentration DTT treatment of RBCs adapted for gel testing.

Materials and methods - Four DTT concentrations (0.01, 0.02, 0.03, and 0.04 mol/L), and three gel test brands were evaluated on six DARA patient's samples. Briefly, the method consists of pipetting 50 µL of 0.8% RBCs on AHG micro columns, followed by 25 µL of DTT, thoroughly mixing and 15 min incubation at 37 °C. Then, 25 µL of serum/plasma is added to proceed to IAT. In order to asses the effect of DTT 0.04 mol/L on different blood group antigens, serial dilutions of sera containing anti-K, -k, -Kp^b, -Lu^b, -Yt^a and anti-JMH antibodies were tested against DTT-RBCs. One sample of a DARA patient with known alloantibodies as well as samples of two patients inoculated with anti-K and anti-Fy^a were evaluated.

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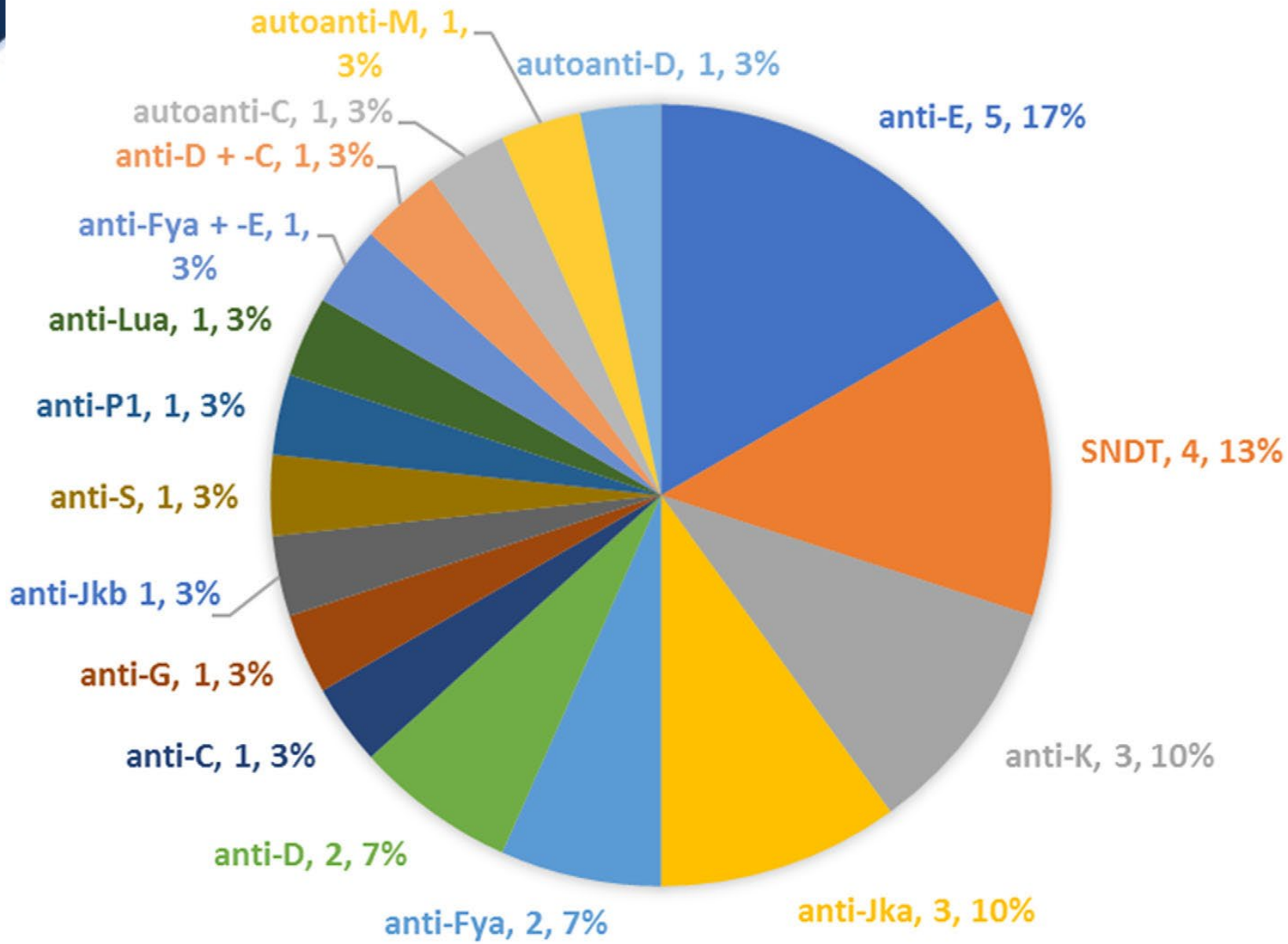
UNDERLYING RED CELL ANTIBODIES DETECTED IN 734 PATIENTS ON ANTI-CD38 THERAPY



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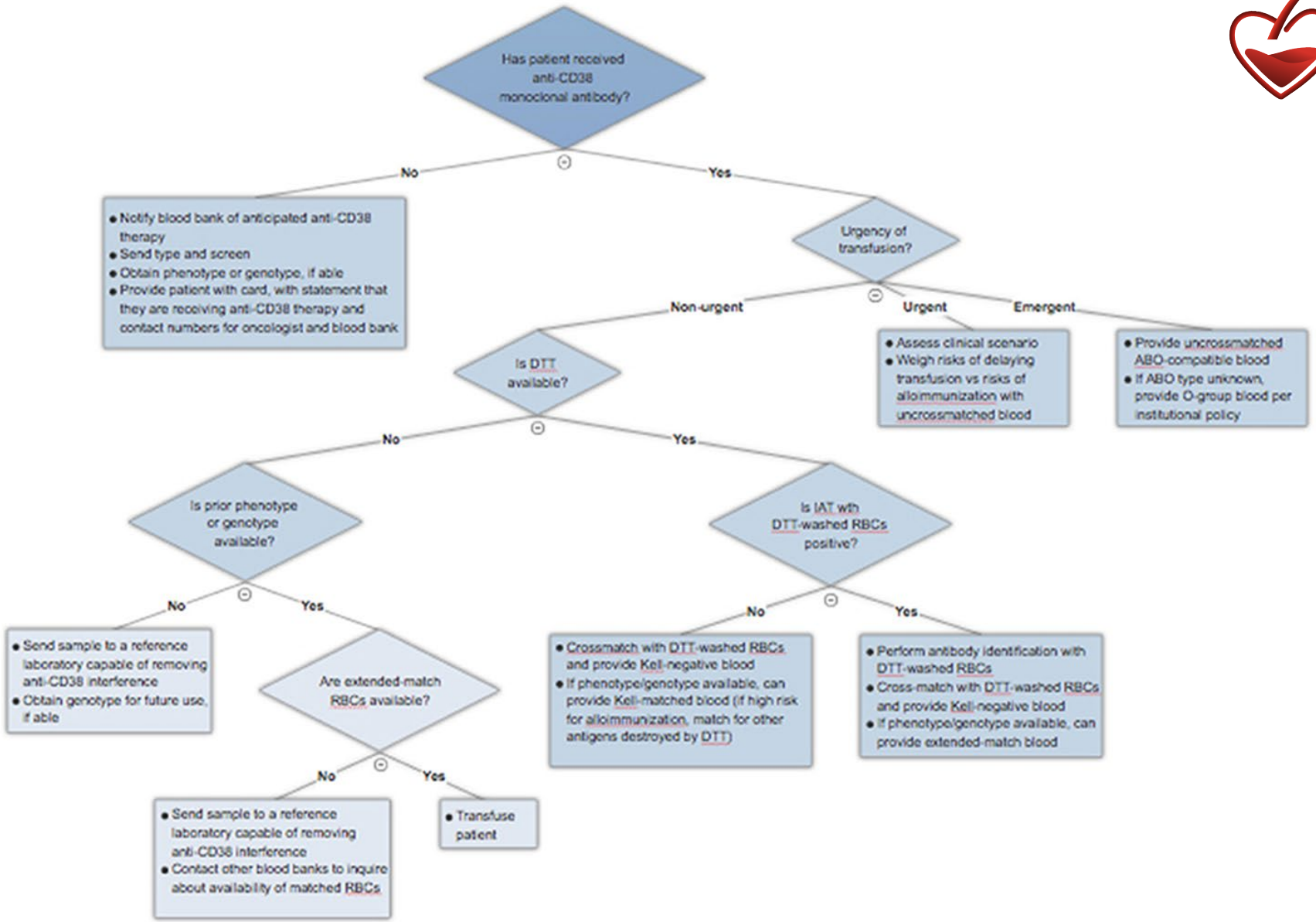
Bullock et al. Alloimmunization rate of patients on Daratumumab: A retrospective cohort study of patients in England. Transfusion Medicine . 17 August 2021 https://doi.org/10.1111/tme.12808

Transfusion management for patients on anti-CD38 monoclonal antibodies



https://www.frontiersin.org/files/Articles/414571/fimmu-09-02616-HTML/image_m/fimmu-09-02616-g002.jpg

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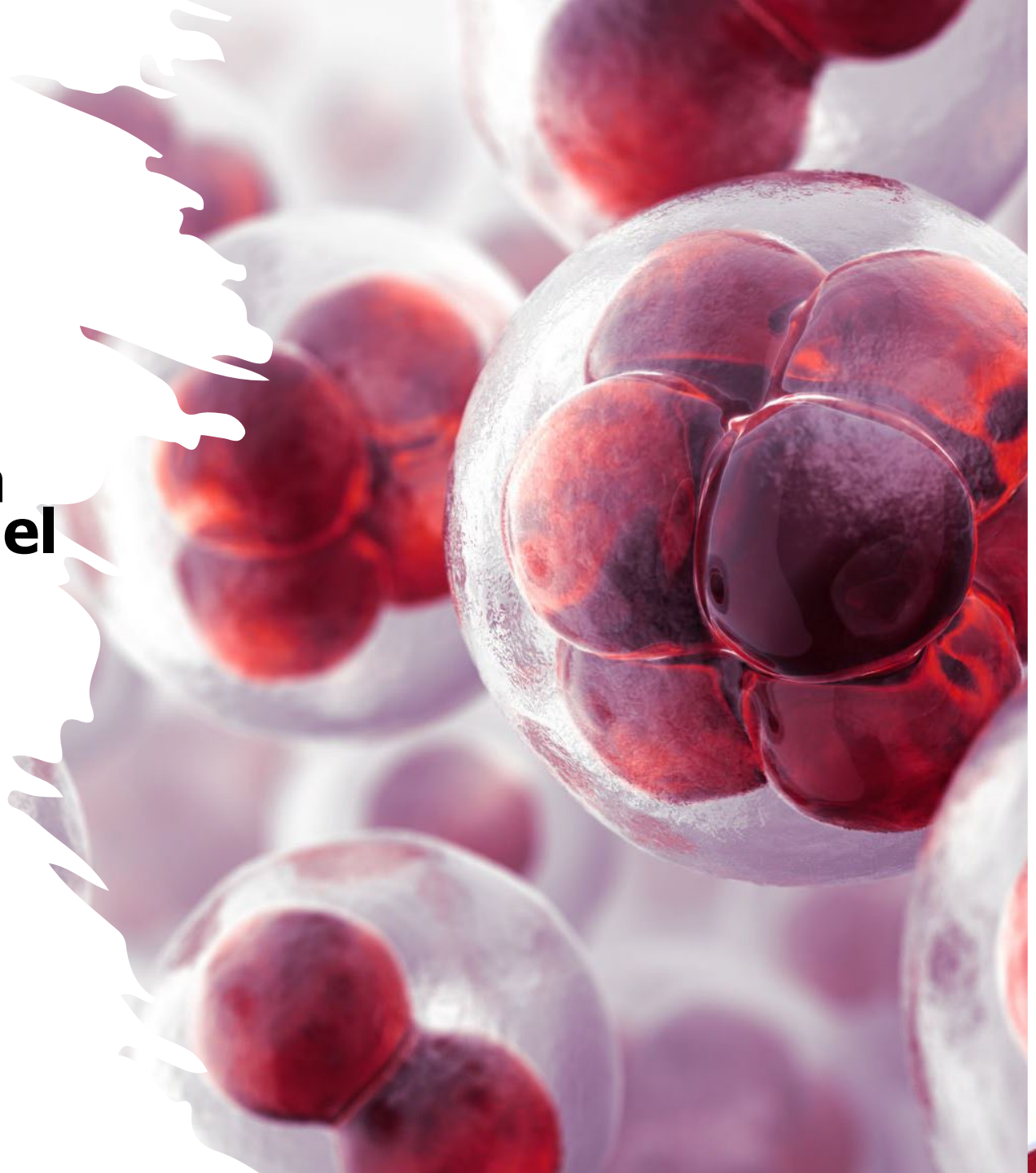
El uso de MABs ha Abierto una nueva era en la terapia del cancer y de otras enfermedades

Anti-CD47



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Hu5F9-G4 (Anti-CD47): Interferencia en Inmunohematología

- **Terapia con anti-CD47 está asociado con pan-reactividad del plasma en todas las fases del tamizaje de anticuerpos**
- **Terapia con anti-CD47 interfiere con el tipaje ABO directo y reverso.**
- **Anti-CD47 actúa como IgM, aunque es IgG**
- **Se puede ver aglutinación espontanea de eritrocitos en algunas muestras**

Hu5F9-G4 (Anti-CD47): Interferencia en inmunohematología

- CD47 es una glicoproteína expresada en todas las células, que se une a una proteína reguladora (SIRPα) presente en macrófagos, regulando fagocitosis
- Expresión de CD47 disminuye con la edad de la celula, cambiando la conformación y permitiendo fagocitosis
- en células malignas, CD47 esta incrementado, escapando así la fagocitosis
- Expresión elevada de CD47 en malignidades está asociado con mortalidad
- El bloqueo de CD47 facilita la fagocitosis, promoviendo actividad antitumoral

Hu5F9-G4 (Anti-CD47)

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- **Posibles objetivos en malignidades hematológicas**
  - **Leucemia mielógena aguda**
  - **Linfoma no Hodgkin**
  - **Linfoma cutáneo de celulas T**
  - **ALL**
  - **Mieloma múltiple**
- **Posibles objetivos en tumores solidos**
  - **Mama**
  - **Ovario**
  - **Colon**
  - **Hígado**
  - **Cerebro**

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Anti-CD47

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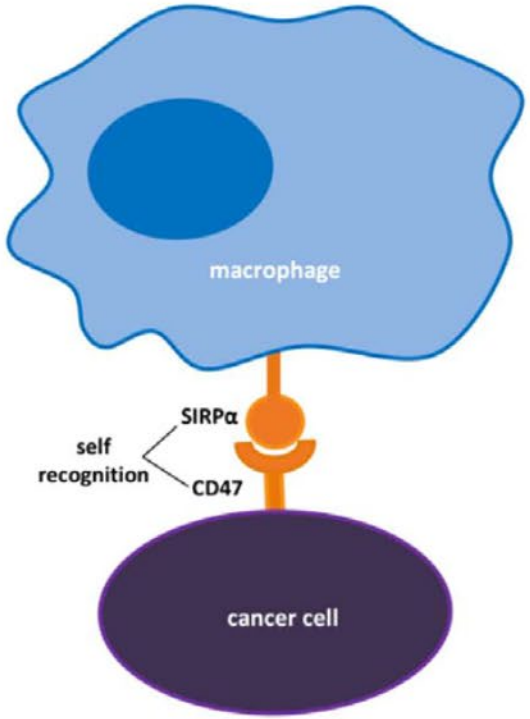
- **Humanized IgG4**
  - **Hu5F9-G4 (Magrolimab)**
  - **SRF231**
  - **Lemzoparlimab**
- **CD47 agonista con proteínas de fusión**
  - **TT1-62 (Trillium) anti SIRPα proteína de fusión (de acuerdo al laboratorio productor, se une mínimamente a los eritrocitos)**
  - **ALX148 anti-CD47 proteína de fusión (cáncer gástrico, tumor de cuello y cabeza)**
- **En investigación**
  - **TG-1804, IBI322, HX009, N1801**

Hu5F9-G4 (Anti-CD47): Interferencia en Inmunohematología

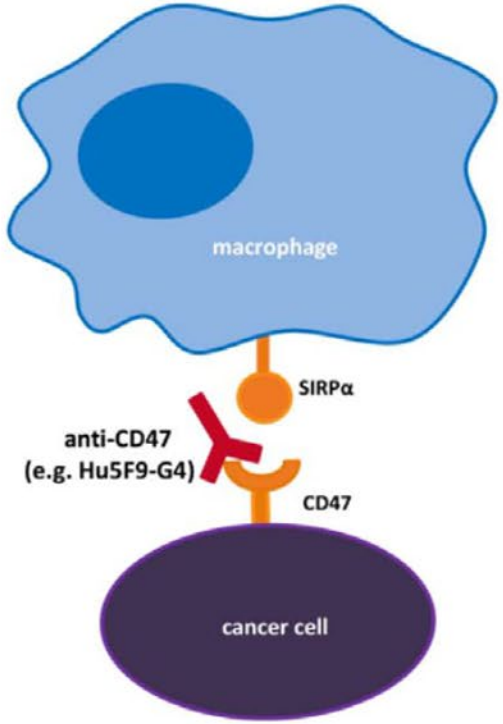
- **Anti-CD47 se une a células tumorales interfiriendo con el mensaje de "no fagocitosis" y permitiendo la acción del macrófago**
- **CD47 tiene una expresión alta en eritrocitos**
- **CD47 es parte del complejo Rh en los eritrocitos**
- **Células D – (ce/ce) tienen la mayor expresión de CD47**
- **Células (D--) tienen expresión reducida de CD47**
- **Células Rh null no tienen expresión detectable de CD47**

Inhibitory Signal
"Don't eat"

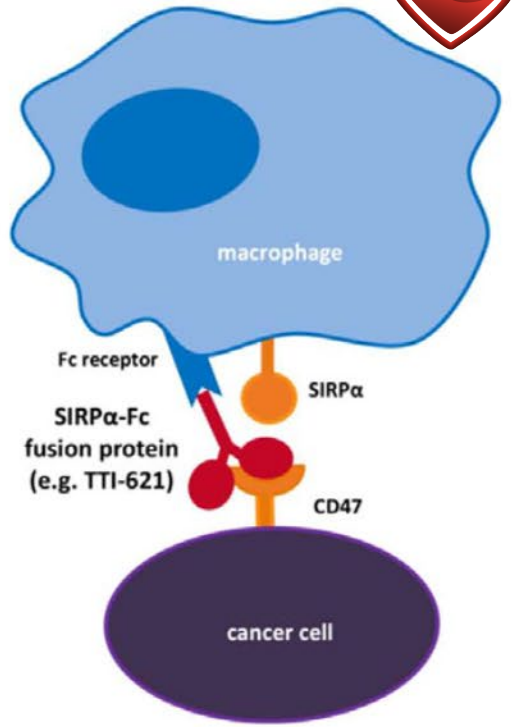


The self recognition signal of the CD47/ SIRPα interaction
= escape phagocytosis

Blocking of Inhibitory Signal
"Eat" = Phagocytosis



anti-CD47
Disruption of the anti-phagocytic signal by blocking CD47/ SIRPα interaction with a antibody directed against CD47



Fusion protein / dual decoy receptor
Disruption of the anti-phagocytic signal by blocking CD47/ SIRPα interaction and simultaneously activating the immune system by interaction with Fc receptors

Cancer progression

Phagocytosis of cancerous cell

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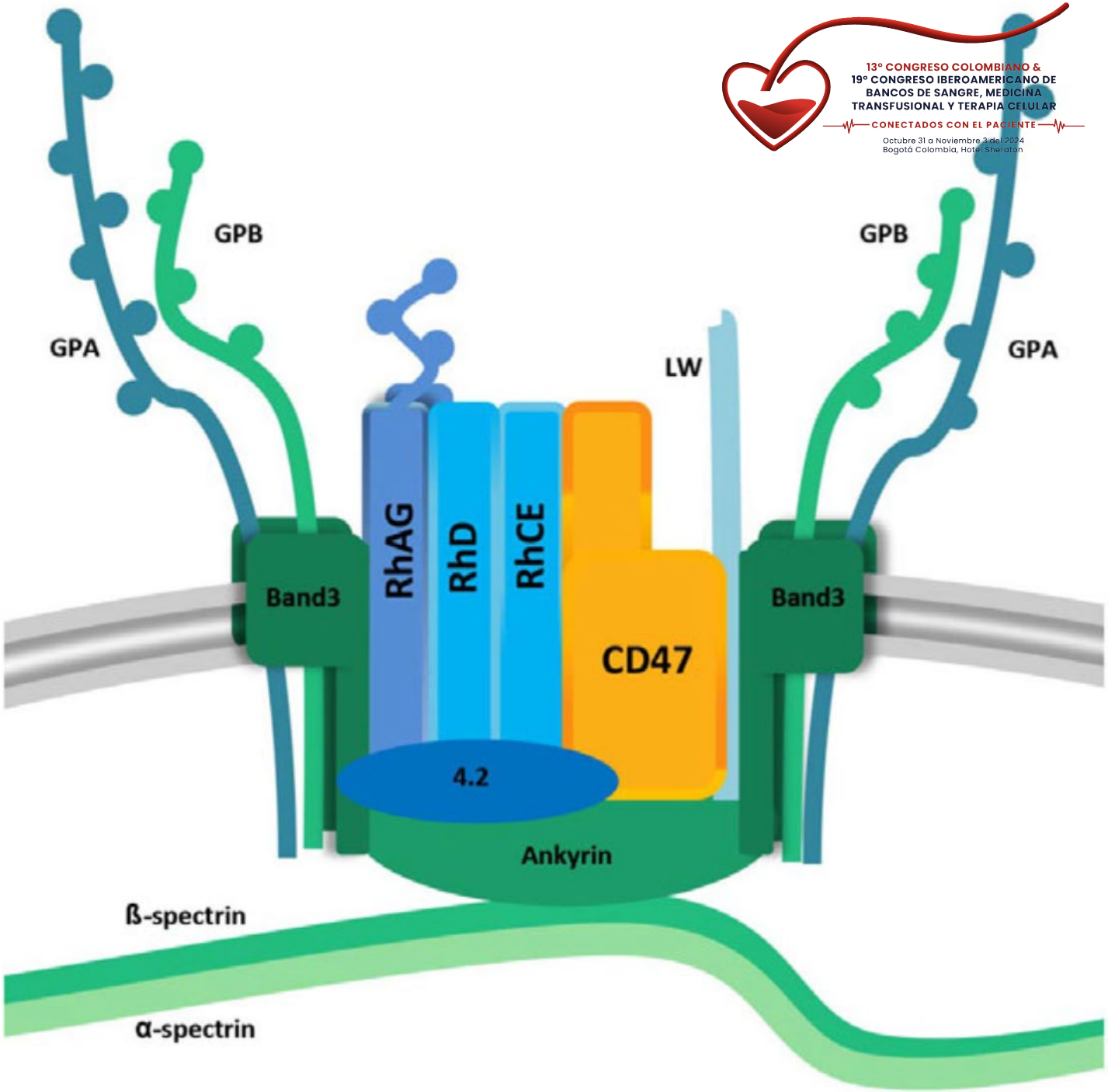
Fig. 2. CD47 is a member of the Rh complex in the RBC membrane. The diagram shows CD47 associates with RhCE/D and Rh-associated glycoprotein (RhAG), which associates with the Band 3 complex. Known points of interaction are between protein 4.2 and CD47 and between RhAG and band 3 with attachment to the spectrin skeleton via ankyrin. Other members of the complex include glycophorin A (GPA), glycophorin B (GPB), and LW.

https://onlinelibrary.wiley.com/doi/full/10.1111/trf.15033



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Hu5F9-G4 (Anti-CD47): Interferencia en Inmunohematología

- **Terapia con anti-CD47 está asociado con pan-reactividad del plasma en todas las fases del tamizaje de anticuerpos**
- **Terapia con anti-CD47 interfiere con el tipaje ABO directo y reverse.**
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- **Se puede ver aglutinación espontanea de eritrocitos en algunas muestras**

Reagent Red Blood Cells 0.8%±0.1%

Hx: RACT, UNA

No.	Rh	Donor	Ag = antigen Other	Rhesus								MNS				P	Lewis		Lutheran		Kell				Duffy		Kidd		Sex Inf.		
				D	C	E	c	e	f	C^{w}	V	M	N	S	s	P$_1$	Le^a	Le^b	Lu^a	Lu^b	K	k	Kp^a	Js^a	Fy^a	Fy^b	Jk^a	Jk^b	Xg^a		
SC I*																													SC I*	4	Lot#015
SC II*																													SC II*	4	
SC III*																													SC III*	3	
1	rr	M7152AM		0	0	0	+	+	+	0	nt	+	+	0	+	+	0	+	0	+	0	+	0	nt	+	0	0	+	+	1	3	
2	rr	M7230CC		0	0	0	+	+	+	0	nt	0	+	+	+	+	0	+	+	+	+	+	0	nt	0	+	+	0	+	2	3	
3	r'r	M5713HO		0	+	0	+	+	+	0	nt	+	0	+	0	+	+	0	0	+	0	+	0	0	+	+	+	0	+	3	4	
4	r''r	M6491CC		0	0	+	+	+	+	0	nt	+	+	0	+	0	0	+	0	+	0	+	0	0	+	+	+	+	+	4	3	
5	rr	M6849CC	Kp(a+)	0	0	0	+	+	+	0	nt	+	0	+	+	+	0	+	0	+	0	+	+	0	+	+	+	0	+	5	4	
6	R$_o$r	M6780CC		+	0	0	+	+	+	0	nt	0	+	+	+	+	0	+	0	+	0	+	0	0	0	0	+	0	0	6	3	
7	R$_1$R$_1^w$	M7067AM		+	+	0	0	+	nt	+	nt	+	+	+	0	+	0	+	0	+	0	+	0	nt	0	+	+	+	+	7	3	
8	R$_1$R$_1$	M7387AM		+	+	0	0	+	nt	0	nt	0	+	0	+	+^{w}	0	0	0	+	+	+	0	nt	+	0	+	0	+	8	3	
9	R$_2$R$_2$	M5579AM		+	+^{w}	+	+	0	nt	0	nt	+	+	0	+	+	0	+	0	+	0	+	0	0	+	0	+	+	+	9	3	
10	R$_2$R$_2$	M6049HM	Di(a+)	+	0	+	+	0	nt	0	nt	+	+	0	+	+	0	+	0	+	0	+	0	0	+	+	+	+	+	10	4	
11	R$_1$R$_1$	M7050LS	Mi(a+)	+	+	0	0	+	nt	0	nt	+	+^{w}	0	+	0	+	+	0	+	0	+	0	nt	+	0	0	+	0	11	3	
Auto																													Auto	=	
Other cells				D	C	E	c	e	f	C^{w}	V	M	N	S	s	P$_1$	Le^a	Le^b	Lu^a	Lu^b	K	k	Kp^a	Js^a	Fy^a	Fy^b	Jk^a	Jk^b	Xg^a		
12				* Patient on Mrgo lunch Started 5/29/23, last dose 8/14/23 *																										12		
13																													13		
14																													14		

*Screening Cells
Usually cold reactive antibody
Usually warm reactive Ab

vs = very strong
s = strong
vw = very weak
w = weak
NT = not typed

Unless otherwise specified, Data-Cyte® Plus 2 cell donors have been phenotyped as follows:
Negative: M^g, Vw, Wr^a, Di^a
Positive: H, I, U, Kp^b, Js^b, Vel, Ge, Yt^a, Di^b

* Pheno Complete *
* Give C=, K=, Fyb=, S= *

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Reagent Red Blood Cells 0.8%±0.1%

Hx: RACT

No.	Rh	Donor	Ag = antigen Other	Rhesus								MNS				P	Lewis		Lutheran		Kell				Duffy		Kidd			No.	Gel
				D	C	E	c	e	f	C^w	V	M	N	S	s	P_1	Le^a	Le^b	Lu^a	Lu^b	K	k	Kp^a	Js^a	Fy^a	Fy^b	Jk^a	Jk^b	Xg^a		
SC I*																													SC I*	2
SC II*																													SC II*	2
SC III*																													SC III*	2
1	rr	M6471CC		0	0	0	+	+	+	0	nt	+	+	+	+	+	+	0	+	+	0	+	0	0	0	+	0	+	+	1	3
2	rr	M0377CC		0	0	0	+	+	+	0	nt	+	0	+	+	+vw	0	0	0	+	+	+	0	0	+	0	0	+	+	2	2
3	r'r	M5713HO		0	+	0	+	+	+	0	nt	+	0	+	0	+	+	0	0	+	0	+	0	0	+	+	+	0	+	3	2
4	r''r	M4268CC		0	0	+	+	+	+	0	nt	+	+	+	+	+vw	0	+	0	+	0	+	0	0	0	+	+	+	+	4	2
5	rr	M3776HM	Kp(a+)	0	0	0	+	+	+	0	nt	0	+	0	+	0	0	+	0	+	0	+	+	0	0	+	+	+	+	5	2
6	Rzr	M7202AM		+	0	0	+	+	+	0	nt	0	+	+	0	+	0	+	0	+	0	+	0	nt	0	0	+	0	+	6	2
7	$R_1R_1^w$	M6992AM		+	+	0	0	+	nt	+	nt	+	+	0	+	+w	0	+	0	+	0	+	0	nt	0	+	+	0	+	7	2
8	R_1R_1	M5901AM		+	+	0	0	+	nt	0	nt	+	+	0	+	0	0	+	0	+	+	+	0	0	+	0	0	+	0	8	2
9	R_2R_2	M6872LS		+	+w	+	+	0	nt	0	nt	+	+	0	+	+	0	+	0	+	0	+	0	0	+	0	+	0	0	9	2
10	R_2R_2	M6487TR		+	0	+	+	0	nt	0	nt	+	+	+	+	+w	+	0	0	+	0	+	0	0	+	+	+	0	+	10	2
11	R_1r	M6505LS	Di(a+)	+	+	0	+	+	+	0	nt	+	0	+	+	+w	0	+	0	+	0	+	0	0	0	+	0	+	+	11	2
Auto																													Auto	2
Other cells				D	C	E	c	e	f	C^w	V	M	N	S	s	P_1	Le^a	Le^b	Lu^a	Lu^b	K	k	Kp^a	Js^a	Fy^a	Fy^b	Jk^a	Jk^b	Xg^a	DAT	IS	Sm	cc
12				* Patient on TTI-622 since 1/10/23, last dose 8/15/23 *																								AH6	12	=	=	2
13																												C3	13	=	=	1
14																												SC	14	=	=	0

*Screening Cells
Usually cold reactive antibody
Usually warm or Coombs reactive Ab

vs = very strong
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Give O = E = K = Jk6 = Fy6 = S

Hu5F9-G4 (Anti-CD47): Interferencia en Inmunohematología

- **CD47 no es removido por papaína, tripsina, α-quimotripsina o 0.2 DTT**
- **Se puede observar el efecto "carryover"**
- **El anti-IgG monoclonal gama clone de immucor no detecta anticuerpos IgG4, y puede evitar la interferencia en la fase IAT**
- **Aloadsorciones múltiples de plasma con eritrocitos tratados con papaina pueden remover suficientes anticuerpos para permitir un tamizaje, un tipaje reverso y prueba cruzada valida**

Velliquette RW, Aeschlimann J, Kirkegaard J, Shakarian G, Lomas-Francis C, Westhoff CM. Monoclonal anti-CD47 interference in red cell and platelet testing. Transfusion. 2019 Feb;59(2):730-737. doi: 10.1111/trf.15033. Epub 2018 Dec 5. PMID: 30516833.

Hu5F9-G4 (Anti-CD47): Interferencia en Inmunohematología

- **Las plaquetas expresan CD47**
- **Adsorción con plaquetas es menos eficiente**
- **La cantidad de ciclos de adsorción dependerá de la cantidad de anti-CD47 circulando en el plasma del paciente**
- **Adsorcion con PEG precipita el plasma, produciendo resultados falso negativos**
- **Anti-CD47 interfiere con la detección de anticuerpos específicos anti-HLA clase I y con prueba cruzada de plaquetas**

Velliquette RW, Aeschlimann J, Kirkegaard J, Shakarian G, Lomas-Francis C, Westhoff CM. Monoclonal anti-CD47 interference in red cell and platelet testing. Transfusion. 2019 Feb;59(2):730-737. doi: 10.1111/trf.15033. Epub 2018 Dec 5. PMID: 30516833.

TABLE 3. Comparison between the RBC expression and the characteristics of pretransfusion interference observed with anti-CD38 (Daratumumab/DARA or Isatuximab) and anti-CD47 (Hu5F9-G4) therapy

Differences in	CD38	CD47
RBC expression	Low	High
Epitope/antigen shedding	Yes	No
Testing	***Anti-CD38**	**†Anti-CD47**
Subclass	IgG1	IgG4
ABO interference	No	Yes
D and extended antigen typing problems	No	Possible
Antibody screen and crossmatch interference	IAT only (1+)	All phases (3+ to 4+)
Mitigation	Treat test RBCs with 0.2 M DTT or Trypsin	Use Immucor/Gamma monoclonal anti-IgG for IAT
Alloadsorption onto RBCs or platelets	No	Yes – multiple 3× to 4×
DAT/auto control (cause)	Negative or w+ (antigen loss)	Negative or w+ (blocking)
Eluate	Negative or w+	Strongly positive (3+ to 4+)
Platelet Capture-P antibody screen interference	Variable	Yes
Platelet PakPlus antibody detection interference	No	No

* Anti-CD38 (daratumumab, DARA, and isatuximab).
† Anti-CD47 (Hu5F9-G4).
DTT = dithiothreitol; IAT = indirect antiglobulin testing.

Estrategias de Manejo

- Genotipo o fenotipo antes de empezar tratamiento
- Proveer unidades antígeno negativo
- Adsorción con eritrocitos
- Adsorción con plaquetas

Estrategias de Manejo

- Uso de anti-IgG monoclonal que no detecte IgG4
- Útil con Hu5f9-G4
- Útil con TTI-622
- ALX148 produce interferencia

IMMUNOHEMATOLOGY

Original article

Pretreatment with Daudi cells eliminates anti-CD47 monoclonal antibody interference in immunohematology testing

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Background - Anti-CD47 monoclonal antibodies have increasing clinical applications in the treatment of cancer. However, anti-CD47 monoclonal antibodies interfere with immunohematology testing in patients who require blood transfusion. As the current approaches to removing any interferences have technical problems, new methods need to be developed to resolve anti-CD47 interference in immunohematology testing.

Materials and methods - We evaluated the Daudi cell line for the adsorption of free anti-CD47 monoclonal antibodies from patients' plasma to facilitate immunohematology testing in patients treated with anti-CD47 monoclonal antibody. CD47 expression was identified on the Daudi cells using flow cytometry and confocal microscopy. Next, we tested the ability of intact Daudi cells mixed with simulating plasma and clinical samples to achieve efficient removal of interfering anti-CD47 monoclonal antibodies. The indirect antiglobulin test was used to verify whether interference from anti-CD47 monoclonal antibodies in plasma was eliminated and whether the detection of other irregular antibodies was affected. The effect of eliminating interference was also investigated in relation to the time that the Daudi cells were stored after having been fixed with paraformaldehyde.

Results - CD47 expression was higher on Daudi cells than on red blood cells. Analysis of the indirect antiglobulin test results revealed that anti-CD47 monoclonal antibody-treated patients' plasma absorbed by Daudi cells for 15 min at 37°C could completely prevent the interference of anti-CD47 monoclonal antibodies in immunohematology testing while the detection of the tested antibodies, including anti-D and anti-K, was unaffected.

Discussion - By decreasing the incubation time, we discovered that interferences in samples with agglutination strengths below 2+ could be eliminated after incubation for 5 min. Of importance, Daudi cells can be preserved with 4% paraformaldehyde for 14 days as short-term storage reagents. This is the first study in which Daudi cells were used to effectively resolve the interference of anti-CD47 monoclonal antibodies in pretransfusion tests.

Keywords: *blood transfusion, anti-CD47 monoclonal antibodies, blood group serology, immunohematology.*

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TABLE 2 Red cell antigen expression in transfused patients, rate of antigenically mismatched transfusions, and expected alloimmunization rates

Antigen	Number of antigen-negative or unknown patients (n)	Average number of mismatched units per patient	Closest alloimmunization rate (E)[5]	Expected number of alloantibodies ($n \times E$)
C	19	12.1	0.67%	0.127
c	16	10.3	1.60%	0.256
E	32	4.2	2.77%	0.914
e	14	15.0	0.51%	0.094
K	38	1.2	0.94%	0.357
Fy(a)	24	9.8	0.64%	0.068
Fy(b)	23	12.5	0.49%	0.070
Jk(a)	22	10.6	2.11%	0.245
Jk(b)	17	10.3	0.30%	0.035
S	26	7.6	0.24%	0.020
s	17	13.8	0.00%	0.000
Total				2.186

Note: No new alloantibodies were observed in these patients.

Carll, T. et al. Alloimmunization rates in transfused patients receiving anti-CD47 antibody therapy. Transfusion. 2022 Apr;62(4):916-918. doi: 10.1111/trf.16825.

Otros MABs

- **LW (Landsteiner-Wiener)es una molécula de adhesión (ICAM-4) y un ligando para algunas integrinas (α4β1, αvβ5, αvβ1)**
- **Natalizumab: Anticuerpo monoclonal para sclerosis múltiple y enfermedad de Chron**
- **Se liga a integrina α4 reaccionando con LW**

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Thank you!