46° Convegno Nazionale
di Studi di Medicina Trasfusionale
Rimini, 13-15 maggio 2026

What's new in Immunohematology

Jill Storry, Ph.D, FBBTS

Technical Director, Immunohematology, Labmedicine Skåne, Lund

Adj. Professor, Exp. Transfusion Medicine, Lund University

The undersigned Speaker, declares that:

in carrying out the function stated above at this event, I do not have any personal or third-party commercial interests, and that any relationships that I have had in the last two years with subjects with commercial interests are not such as to influence my function in order to draw any advantage.

Aims of this talk

- Historical look at blood group discovery
- From hemagglutination to genotyping
- New techniques and tools
- Interpretation barriers
- WP – Nomenclature and ISBT database
- What else can our blood group genes tell us?

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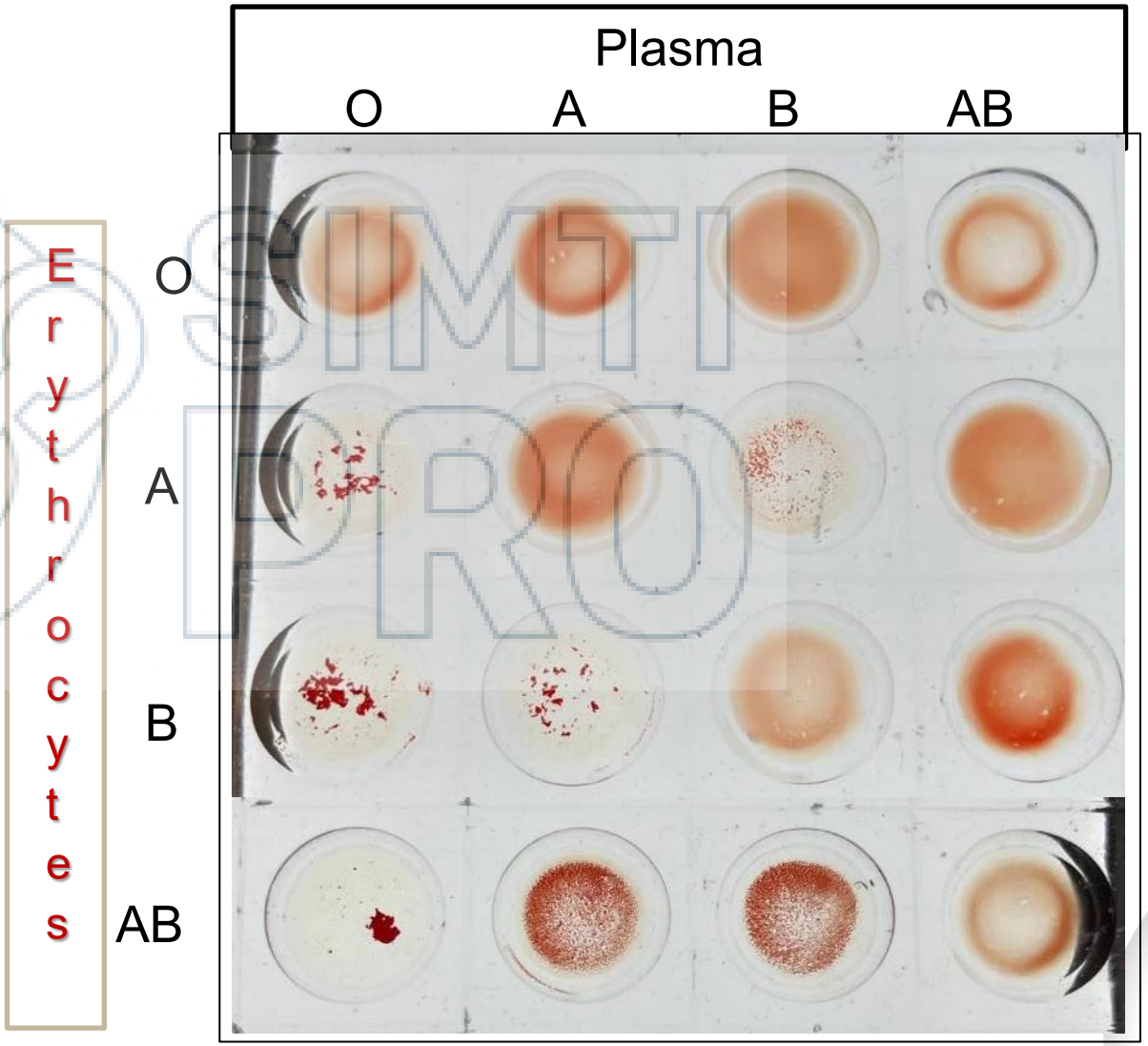
Looking back at hemagglutination

Landsteiner reported in 1900 that if he mixed the red blood cells and plasma from himself and his 5 colleagues:

- Some RBCs clumped, some did not
- Three patterns seen: A, B, C (now A, B, O)

Immunohematology was born!

- Same technique has been used for 125 years…



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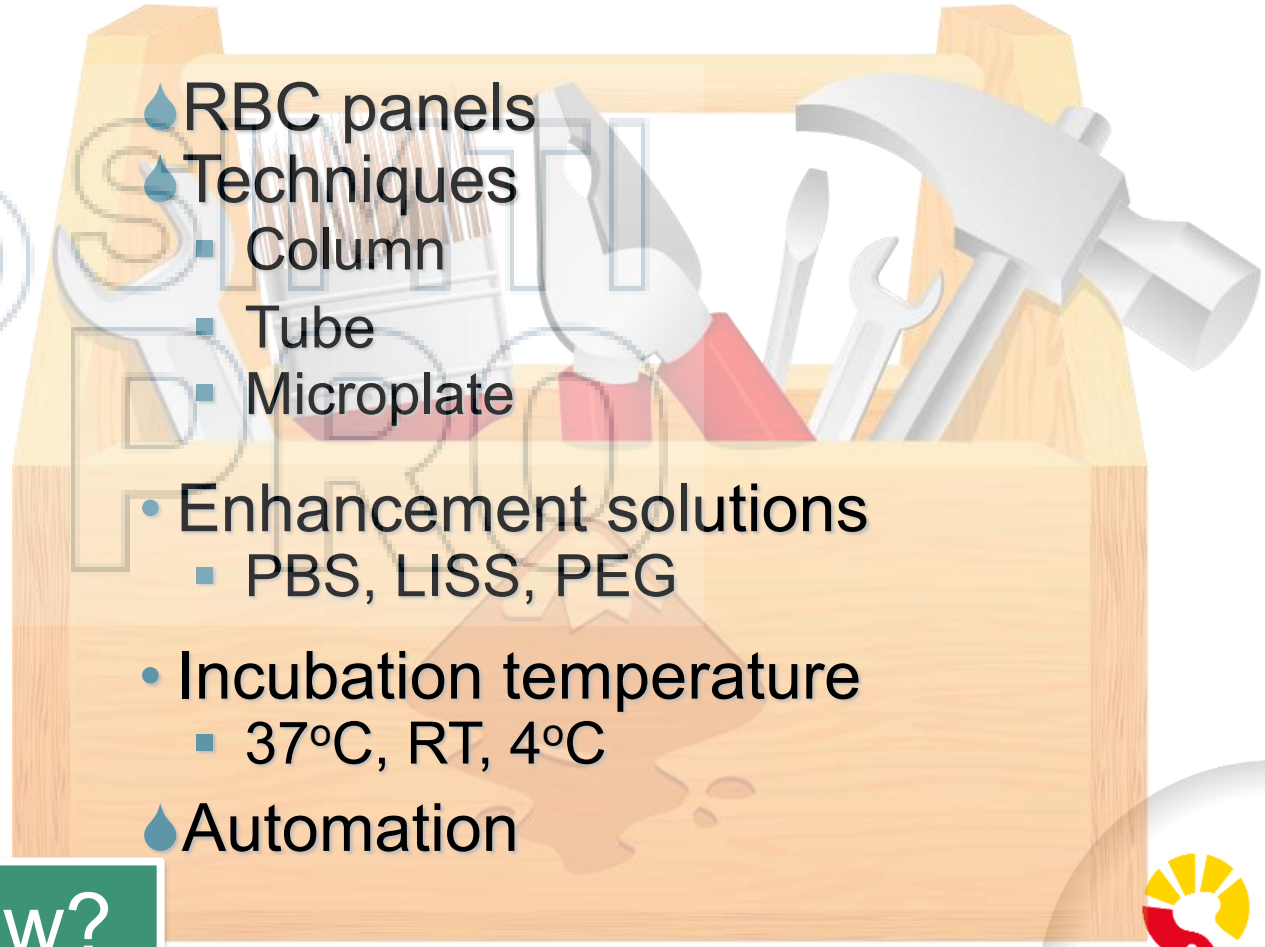
Hemagglutination remains the basis of blood group discovery

- ABO/D typing
- Antibody screen
- Antibody identification
- Crossmatching



- RBC panels
- Techniques
  - Column
  - Tube
  - Microplate
- Enhancement solutions
  - PBS, LISS, PEG
- Incubation temperature
  - 37°C, RT, 4°C
- Automation

So, what's new?

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Currently recognized RBC blood group systems and antigens (WP meeting Milan 2025-05-31)

398 antigens

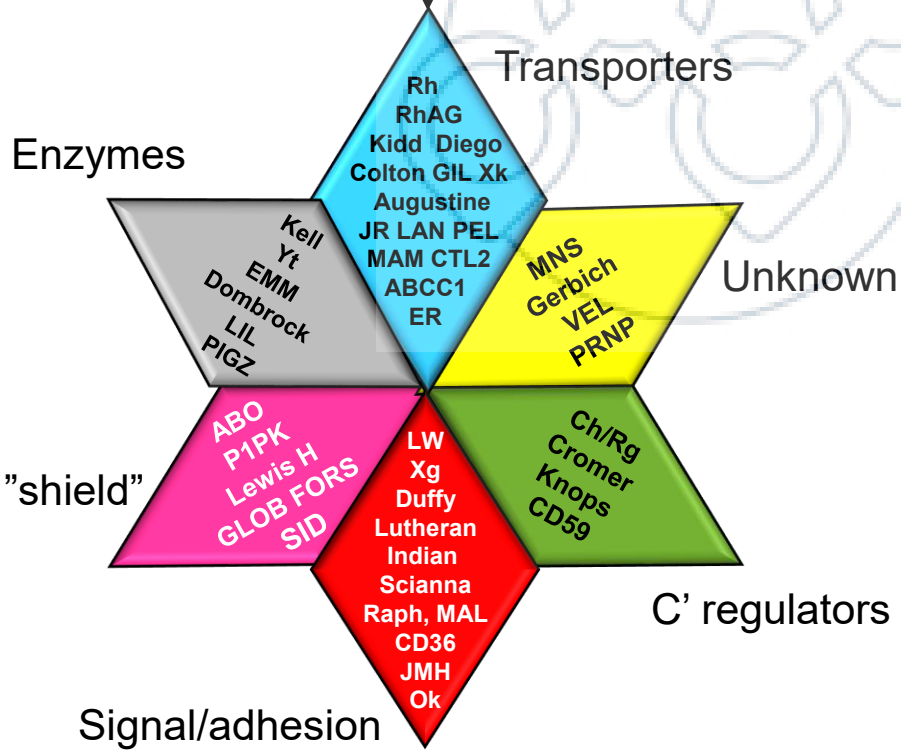
371 in **48** systems

27 ”orphans”

2 high prevalence

9 in collections

16 low prevalence



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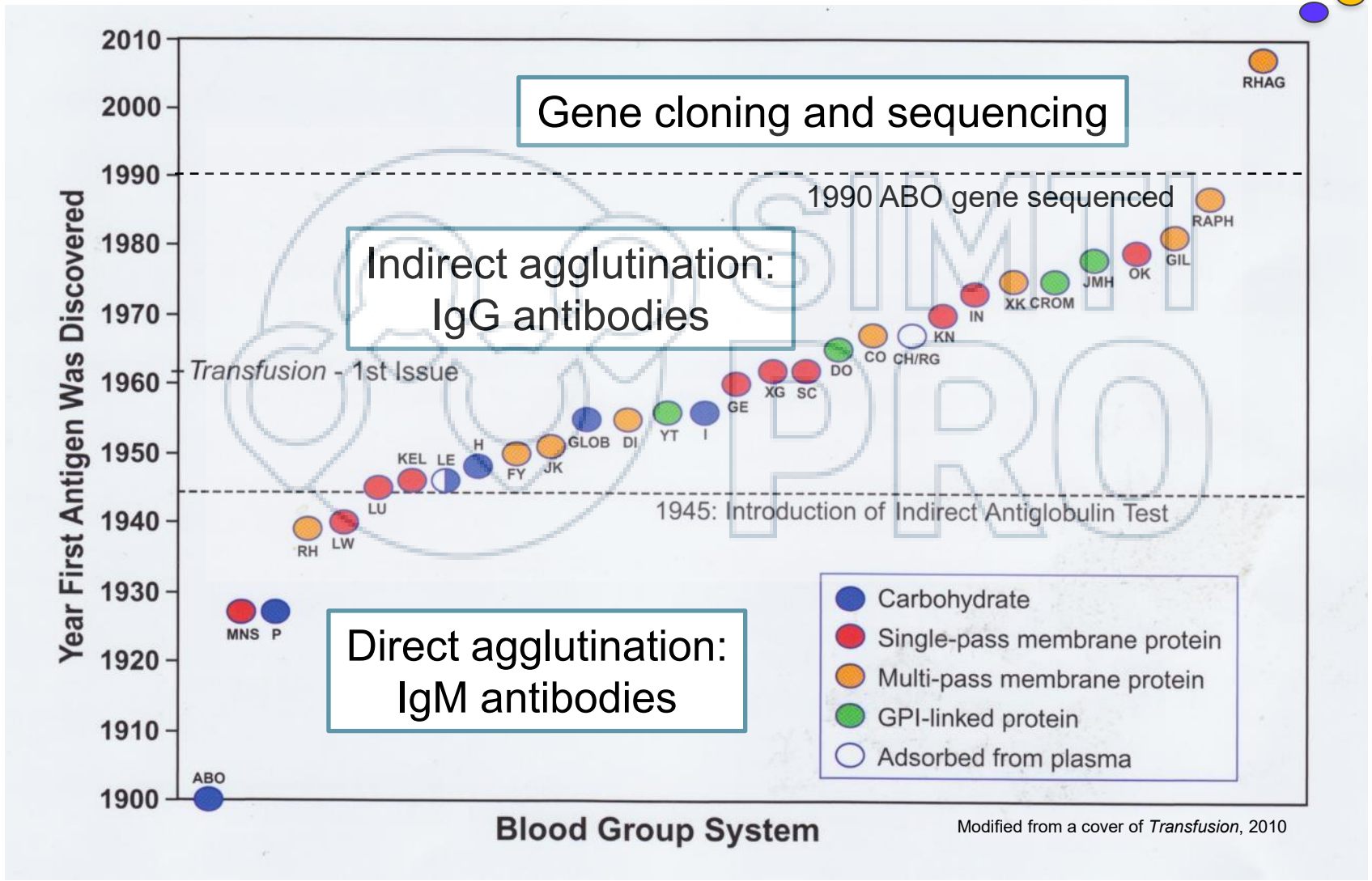
Blood group system discovery is technique-dependent: 1900-2014

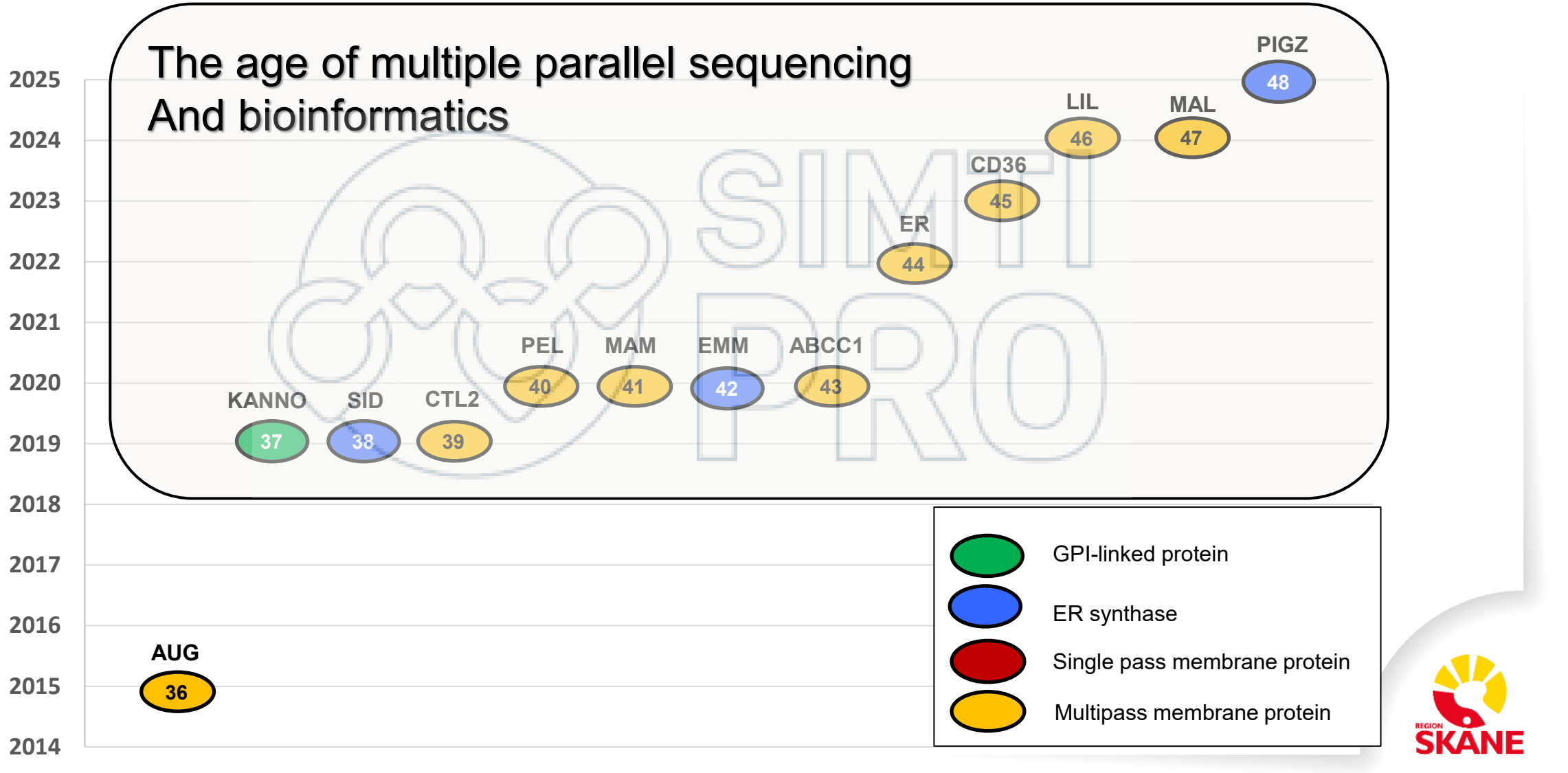
SNP arrays; WGS, WES



Modified from a cover of *Transfusion*, 2010

FORS JR LAN VEL CD59

Blood group system discovery 2015-2025



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Bioinfomatic blood group discovery as a tool in understanding cell biology

PA22-L04 | A null homozygous mutation in PIGZ leading to a free glycosylphophatidylinositol (GPI) deficiency causes a novel rare blood phenotype and mild intellectual disability

R Duval[1,2,3], Y Murakami[4], B Koehl[1,2,5], G Nicolas[1], D Vainqueur[1,2,6], JC Gelly[1], T Kinoshita[4], T Peyrard[1,2,3], S Azouzi[1,2,3]

[1]*BIGR, Université Paris Cité and Université des Antilles, INSERM,* [2]*Laboratory of Blood group antigens, Hematopoiesis and Sickle cell disease, UMR_S1134,* [3]*Centre National de Référence pour les Groupes Sanguins, Etablissement Français du Sang, Paris, France,* [4]*Center for Infectious Disease Education and Research, Osaka, Japan,* [5]*Hôpital Robert Debré, APHP, Paris,* [6]*Immunohematology Laboratory, Etablissement Français du Sang, Pointe-à-Pitre, France*

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Case history

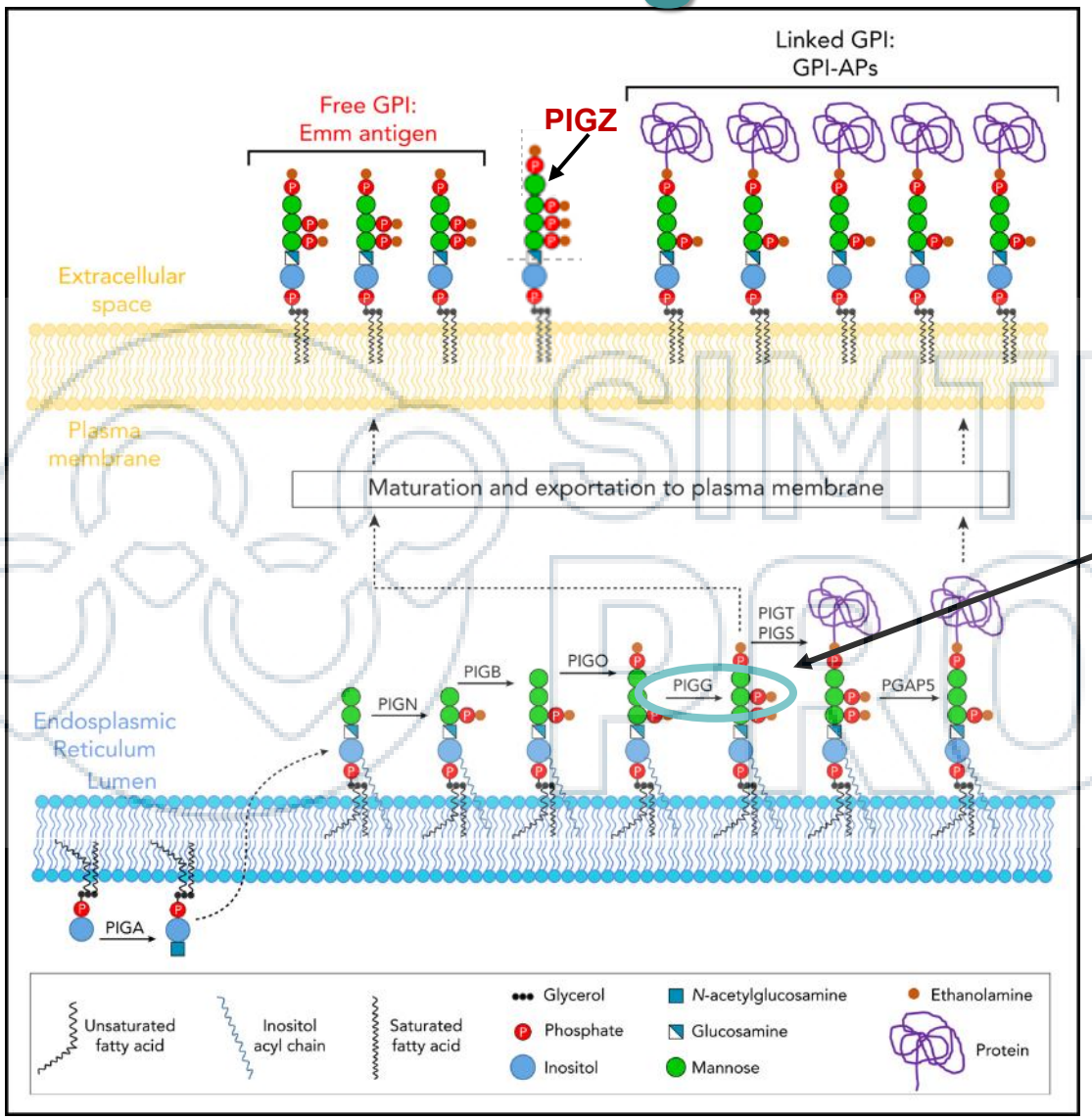
- 54 yo female patient of French Caribbean ancestry (Guadeloupe Island, French West Indies)
- 3 pregnancies:
  - 1st baby died aged 1, cause unknown
  - 2nd/3rd babies stillborn
- Plasma reacted with all RBCs excluding her own
- RBCs typed weakly Emm+

WES and Crispr-Cas9 approaches were used

- Homozygosity for rare variants found in 11 genes: *PIGZ* strongest candidate
- Confirmed by serial knockouts of all genes in the GPI synthesis pathway

Increased understanding of GPI synthesis

PIGZ enzyme builds another mannose and ethanolamine phosphate to free GPI ➡ GWADA antigen



Duval R, Nicolas G, Willemetz A, Murakami Y, Mikdar M, Vrignaud C, Megahed H, Cartron JP, Masson C, Wehbi S, Koehl B, Hully M, Siquier K, Chemlay N, Rotig A, Lyonnet S, Colin Y, Barcia G, Cantagrel V, Le Van Kim C, Hermine O, Kinoshita T, Peyrard T, Azouzi S. Inherited glycosylphosphatidylinositol defects cause the rare Emm-negative blood phenotype and developmental disorders. Blood. 2021;137(26):3660-3669.

Defects in the GPI pathway are associated with intellectual disabilities

- Pathological mutations described in 16 genes, including *PIGG*, and now *PIGZ*
- Also associated with phenotypic facial features and seizures
- $PIGZ_{null}$ patient did not require transfusion but reported as the rarest blood group in the world
- The antigen is called GWADA after the patient's origin.

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Gwada-negative: the rarest blood group on Earth

Published: July 9, 2025 5.33pm SAST

Peter Porrini/Shutterstock.com

In a routine blood test that turned extraordinary, French scientists have identified the world's newest and rarest blood group. The sole known carrier is a woman from Guadeloupe whose blood is so unique that doctors couldn't find a single compatible donor.

The discovery of the 48th recognised blood group, called "Gwada-negative", began when the woman's blood plasma reacted against every potential donor sample tested, including those from her own siblings. Consequently, it was impossible to find a suitable blood donor for her.

Authors

Martin L. Olsson
Medical Director of the Nordic Reference Laboratory for Blood Group Genomics, Region Skåne & Professor of Transfusion Medicine, Head of the Division, Lund University

Jill Storry
Adjunct Professor, Division of Transfusion Medicine, Lund University

Disclosure statement

Expanded use of genotyping tools – how can these techniques improve immunohematology?

Uses of genotyping

Patients (traditional)

- Positive DAT
- Transfusion <3 months
- Prophylactic matching for hematology patients, e.g. SCD, thalassemias, MDS, AIHA, Mab therapies
- *In utero* prediction of blood type, e.g. RhD from cffDNA

Donors (personalized)

- Broad blood group antigen profile
  - Reduced requirements for frozen blood banks
- Health markers
- Disease risk markers
- Blood storage markers
- Evaluation of transfusion outcome

Uses of genotyping

Patients (traditional)

- Positive DAT
- Transfusion <3 months
- Prophylactic matching for hematology patients, e.g. SC , thalassemias, MDS, b therapies
- *In utero* p e.g. RhD f

Donors (personalized)

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Relatively restricted (but important) applications

Uses of genotyping

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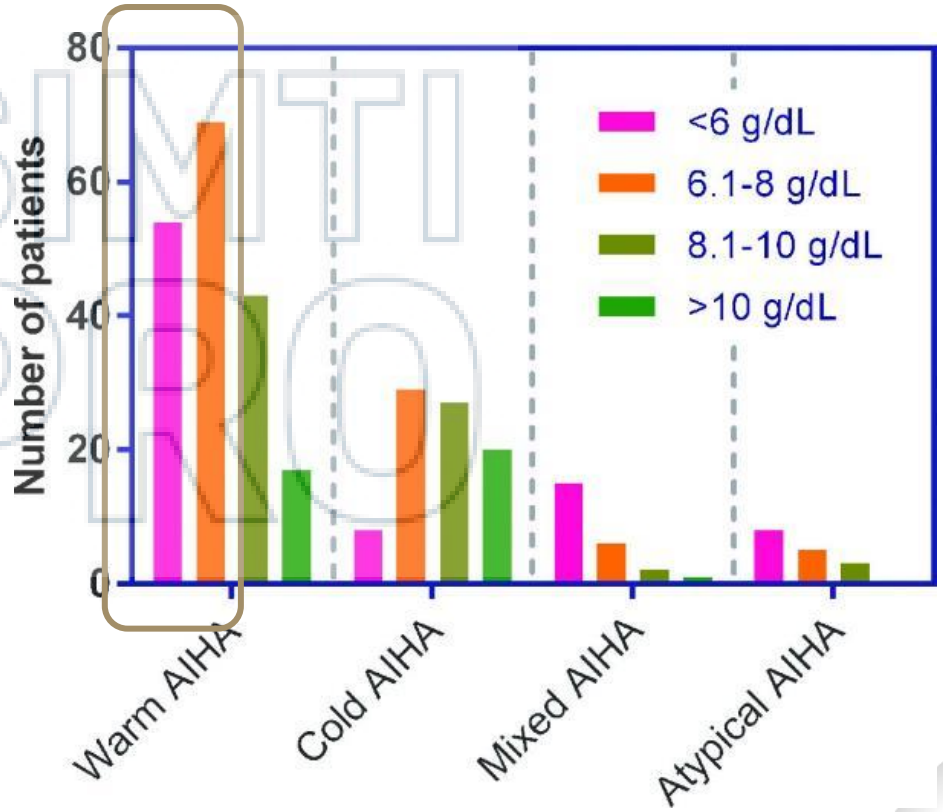
Red blood cell transfusion for hematologic disorders



Liu C, Grossman, BJ. Red blood cell transfusion for hematologic disorders. ASH 2015, Figure 2.

Uses of genotyping

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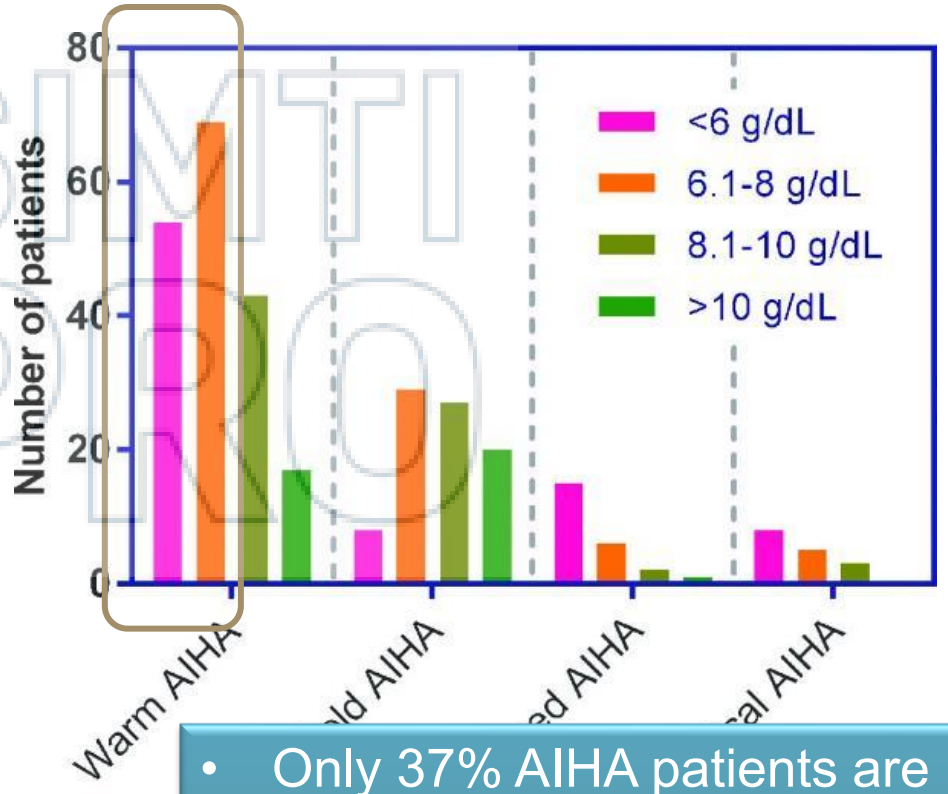

- Only 37% AIHA patients are transfused
- Poor overall response
- 15-40% produce alloantibodies

Liu C, Gross
hematologic

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blood donor and genotyping

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- Associated data

ARTICLE TYPE

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Development and validation of a universal **blood donor genotyping** platform: a multinational prospective study.

Gleadall NS, Veldhuisen B, Gollub J, Butterworth AS, Ord J, Penkett CJ, Timmer TC, Sauer CM, van der Bolt N, Brown C, Brugger K, Dilthey AT, Duarte D, Grimsley S, van den Hurk K, Jongerius JM, Luken J, Megy K, Miflin G, Nelson CS, Prinsze FJ, Sambrook J, Simeoni I, Sweeting M, Thornton N, Trompeter S, Tuna S, Varma R, Walker MR; NIHR BioResource; Danesh J, Roberts DJ, Ouwehand WH, Stirrups KE, Rendon A, Westhoff CM, Di Angelantonio E, van der Schoot CE, Astle WJ, Watkins NA, Lane WJ.

Blood Adv. 2020 Aug 11;4(15):3495-3506. doi: 10.1182/bloodadvances.2020001894.

PMID: 32750130 Free PMC article.

Dense **donor** typing allowed identification of 2 to 6 times more compatible **donors** to serve 3146 patients with multiple RBC alloantibodies, providing at least 1 match for 176 individuals for whom previously no **blood** could be found among the same **donors**. ...

2 Cite Share

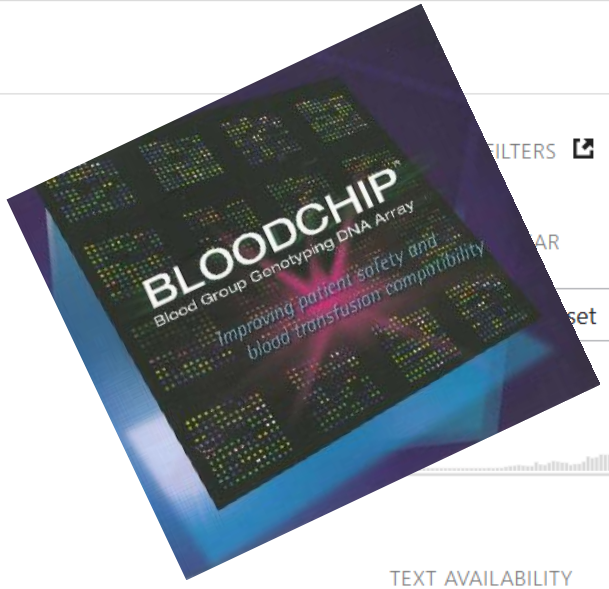
Mass-scale red cell **genotyping** of **blood donors**: from data visualization to historical antigen labeling and **donor** recruitment.

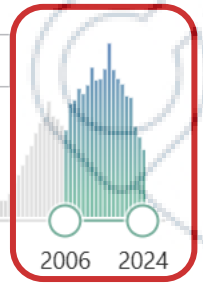
Denomme GA, Anani WQ.

Transfusion. 2019 Sep;59(9):2768-2770. doi: 10.1111/trf.15419. Epub 2019 Jun 27.

PMID: 31246285 Review.

The future lies with genetic blood typing for blood donors





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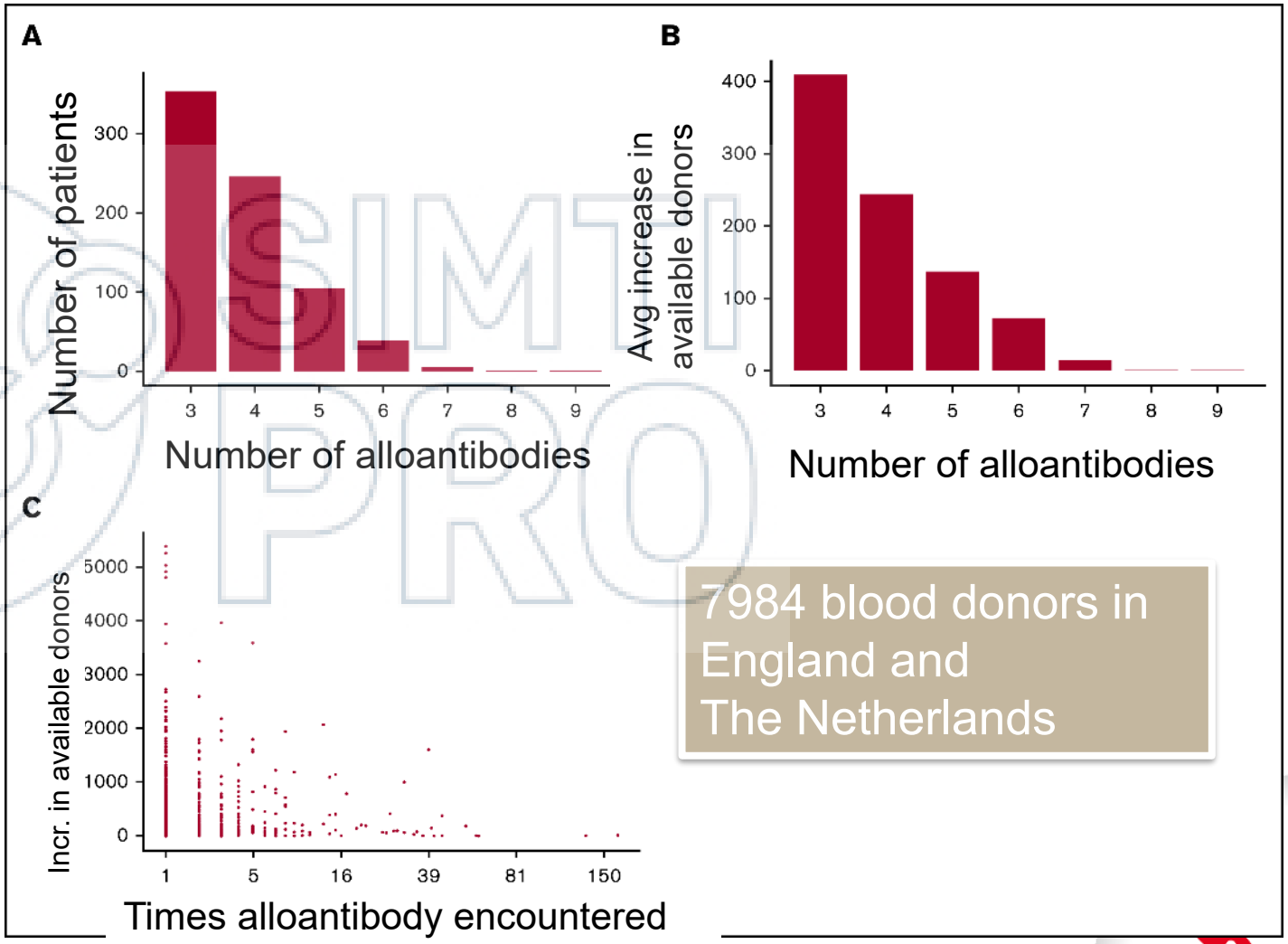
PMID: 31246285 Review.

https://pubmed.ncbi.nlm.nih.gov/32750130/

Development and validation of a universal blood donor genotyping platform: a multinational prospective study

Rapid identification of rare blood: MDS patient with anti-E, -Co^a and -Wr^a

➔ Identified 5 active donors among the 2692 Dutch donors



7984 blood donors in England and The Netherlands

Gleadall NS, Veldhuisen B, Gollub J, et al.Development and validation of a universal blood donor genotyping platform: a multinational prospective study, Blood Adv, 2020, Figure 7.

Future of genotyping

- Multiple parallel sequencing technologies vs SNP arrays vs long read sequencing?
- MPS already introduced into routine HLA/transplantation laboratories
  - One highly complex locus
- Adapt the same technology for >50 blood group genes
- Both require:
  - Better bioinformatics
  - Greater data storage
  - Data protection

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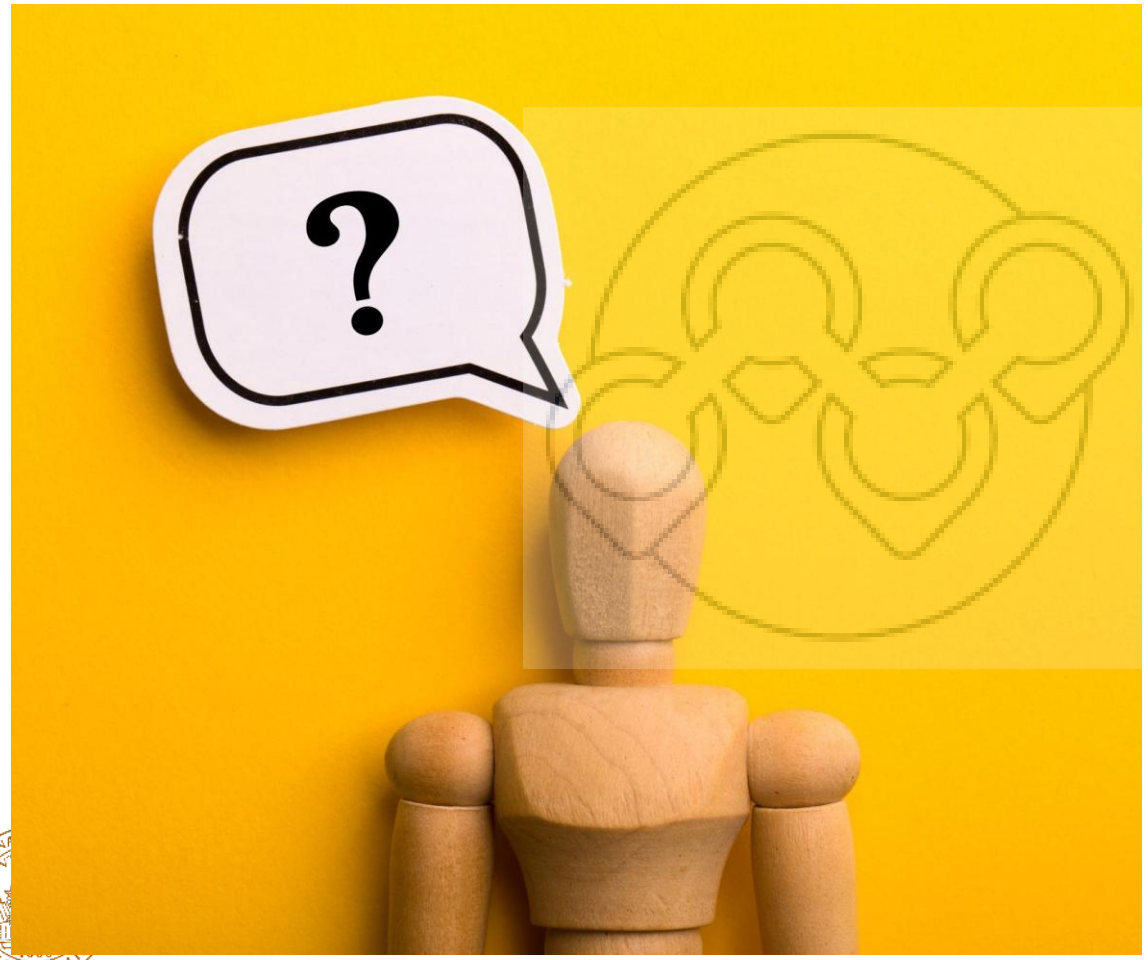
Blood transfusion Genomics Consortium (BGC)

- International partnership between blood services, research institutions and industry leaders
- Aim is to improve the safety and efficiency of blood and platelet transfusion by introducing cutting-edge genomics technology into routine clinical practice
- Developed a high-throughput microarray that can provide an inexpensive genotype
- Under validation in large blood centers world-wide

https://www.bgc.io

How (and to whom) do we relay the information?



- Genotyping on patients' samples
- Labelling of blood bags
- Donor/RBC "health" information

Biggest challenge to speeding up implementation

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Red Cell Immunogenetics and Blood Group Terminology

Welcome to the webpages of the ISBT Working Party for Red Cell Immunogenetics and Blood Group Terminology (RCI & BGT).

The ISBT Working Party (WP) Red Cell Immunogenetics and Blood Group Terminology maintains the official registry for all recognized blood group systems, and establishes standardized naming conventions for blood group systems, antigens and alleles used in transfusion medicine and related fields.

Since November 2025, all blood group allele data has been migrated to our new database system!

Our registry currently includes:

48 systems | 56 Genes | 398 Antigens | 2,001 Alleles

In this section

Red Cell Immunogenetics and Blood Group Terminology
Members, Assignments and Activities
Blood Group Terminology
Criteria for the establishment of new systems and antigens
Archive
RCI & BGT Resources

ISBT blood group allele nomenclature

- Provided an international uniform platform for reporting genotypes (to clinicians)
  - Primarily useful when applying genotyping platforms that focus on antigen-specific SNPs
- Provided a numerical system and framework to add newly described alleles
- Restricted to variants that affect blood group phenotype
  - Silent variants not captured

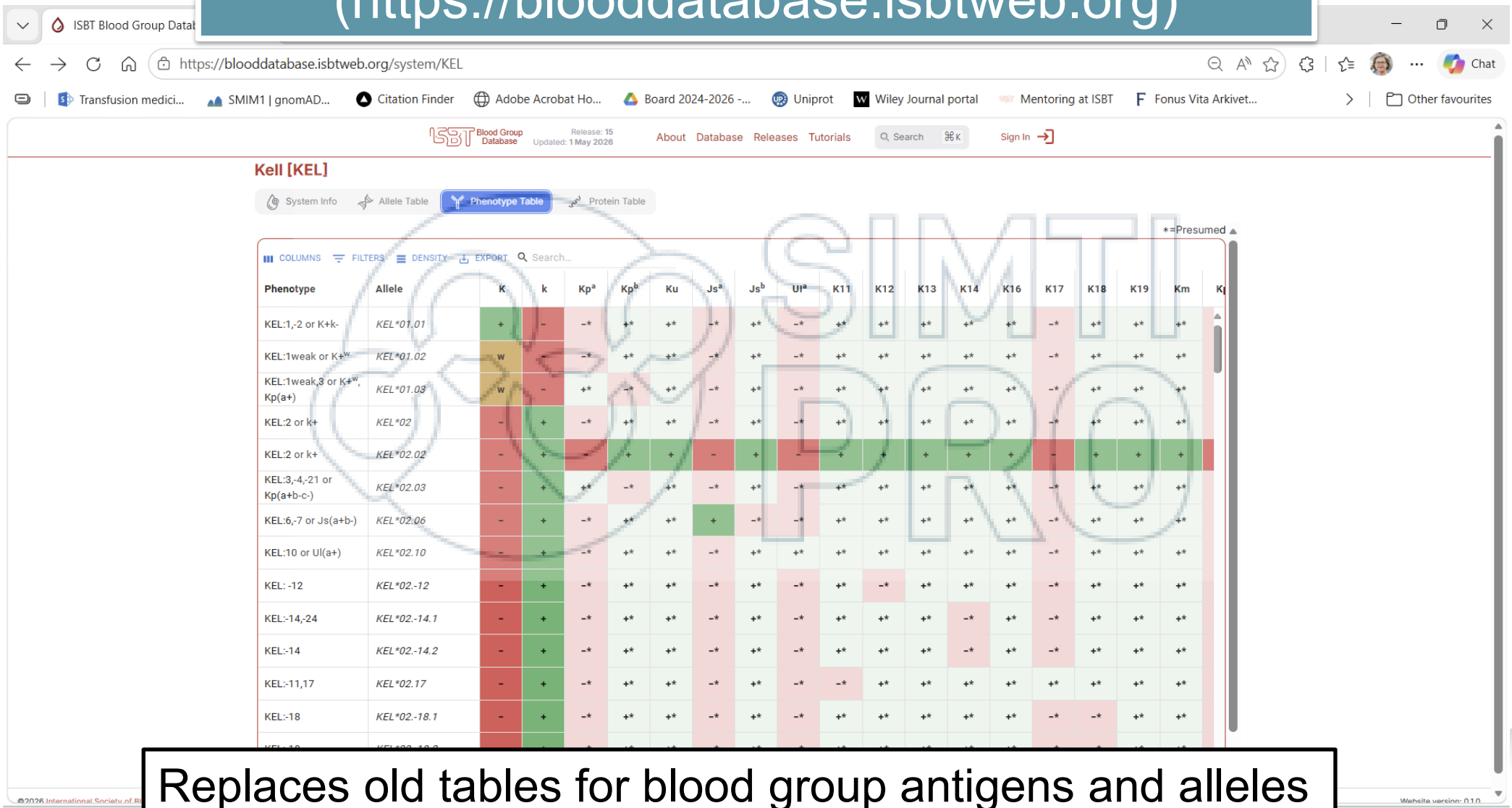
New ISBT Database launched November 2025

Overview | Systems (48) | Antigens (398) | Other (7)

Search for a system...

ABO ABO 001	MNS MNS 002	P1PK P1PK 003	RH Rh 004
LU Lutheran 005	KEL Kell 006	LE Lewis 007	FY Duffy 008
JK Kidd 009	DI Diego 010	YT Yt 011	XG Xg 012
SC Scianna 013	DO Dombrock 014	CO Colton 015	LW Landsteiner-Wiener 016
CH_RG Chido/Rodgers 017	H H 018	XK Kx 019	GE Gerbich 020
CROM Cromer 021	KN Knops 022	IN Indian 023	OK Ok 024

ISBT Blood Group Database (https://blooddatabase.isbtweb.org)



Replaces old tables for blood group antigens and alleles
New alleles will be uploaded in real time

Back to the future - revisiting ABO

nature microbiology

Article

https://doi.org/10.1038/s41564-024-01663-4

Akkermansia muciniphila exoglycosidases target extended blood group antigens to generate ABO-universal blood

Received: 26 July 2023

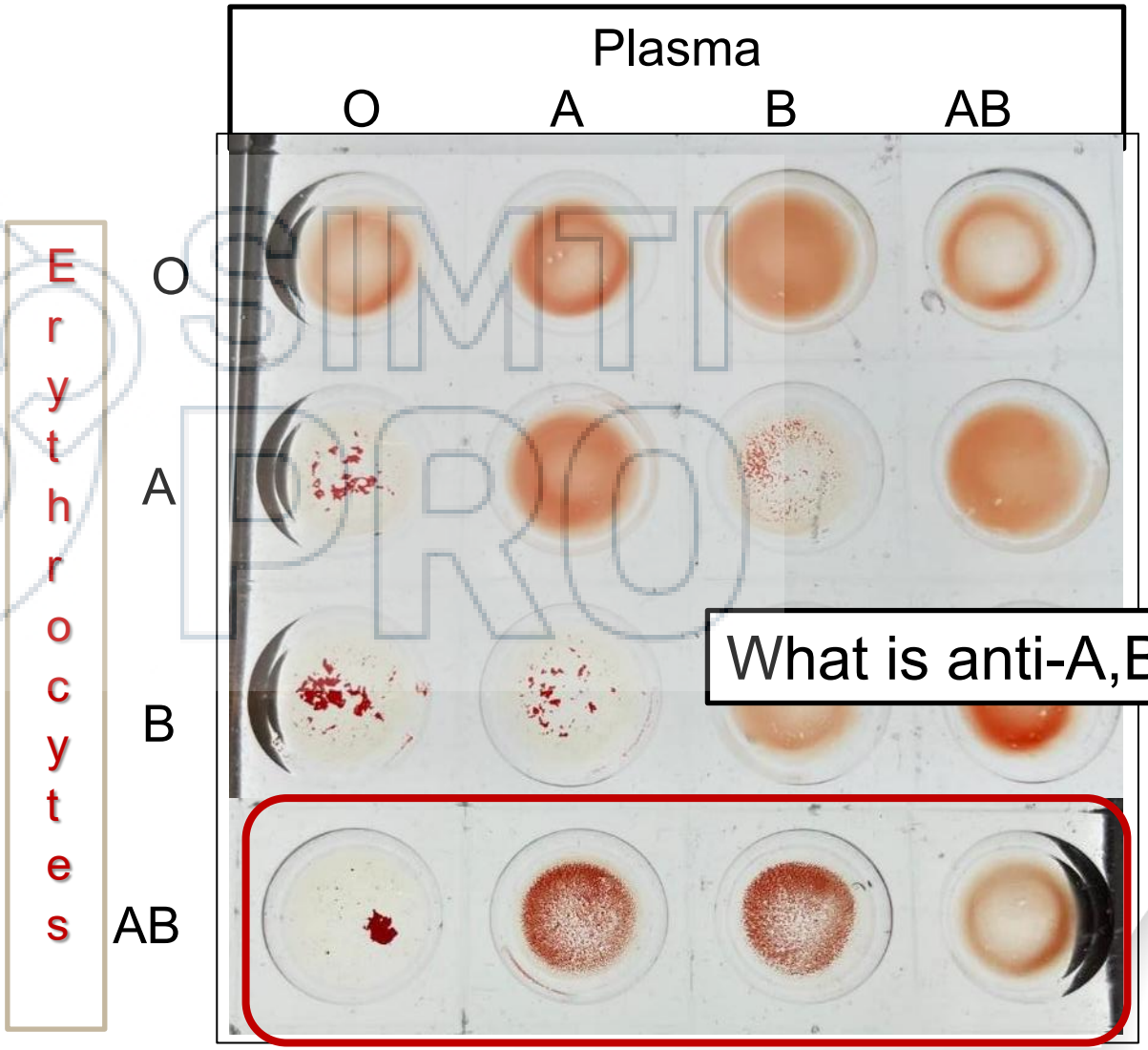
Accepted: 4 March 2024

Published online: 29 April 2024

Check for updates

Mathias Jensen[1,4], Linn Stenfelt[1,2,4], Jennifer Ricci Hagman[2,3], Michael Jakob Pichler[1], Julia Welkum[1], Tine Sofie Nielsen[1], Annika Hult[3], Jens Preben Morth[1], Martin L. Olsson[2,3,5] & Maher Abou Hachem[1,5]

Matching donor and recipient blood groups based on red blood cell (RBC) surface ABO glycans and antibodies in plasma is crucial to avoid potentially fatal reactions during transfusions. Enzymatic conversion of RBC glycans to the universal group O is an attractive solution to simplify blood logistics and prevent ABO-mismatched transfusions. The gut symbiont *Akkermansia muciniphila* can degrade mucin *O*-glycans including ABO epitopes. Here we biochemically evaluated 23 *Akkermansia* glycosyl hydrolases and identified exoglycosidase combinations which efficiently transformed both A and B antigens and four of their carbohydrate extensions. Enzymatic removal of canonical and extended ABO antigens on RBCs significantly improved compatibility with group O plasmas, compared to conversion of A or B antigens alone. Finally, structural analyses of two B-converting enzymes identified a previously unknown putative carbohydrate-binding module. This study demonstrates the potential utility of mucin-degrading gut bacteria as valuable sources of enzymes for production of universal blood for transfusions.



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Back to the future - revisiting ABO

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***Akkermansia muciniphila* exoglycosidases target**

genera

Received: 26 July 2

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Received: 8 October 2025 | Revised: 19 February 2026 | Accepted: 4 March 2026

DOI: 10.1111/trf.70175

ORIGINAL RESEARCH

TRANSFUSION

Revealing and quantifying polyclonal anti-A, B specificity in ABO histo-blood groups

Stephen Henry[1] | Holly Perry[2] | Polina Obukhova[3] | Tatiana Tyrtysh[3] | Ivan Ryzhov[3] | Nicolai Bovin[3] | Suvro Sankha Datta[4]

[1]School of Engineering, Computer and Mathematical Sciences, Faculty of Design and Creative Technologies, Auckland University of Technology, Auckland, New Zealand

[2]Department of Medical Laboratory Science, University of Otago, Dunedin, New Zealand

[3]Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry, Russian Academy of Sciences, Moscow, Russian Federation

[4]Department of Transfusion Medicine, Tata Medical Center, Kolkata, India

Correspondence
Stephen Henry, School of Engineering, Computer and Mathematical Sciences, Faculty of Design and Creative Technologies, Auckland University of Technology, Auckland, New Zealand.
Email: kiwi@aut.ac.nz
Suvro Sankha Datta, Department of Transfusion Medicine, Tata Medical Center, Newtown, Rajarhat, Kolkata 700160, India.
Email: suvro.datta@gmail.com

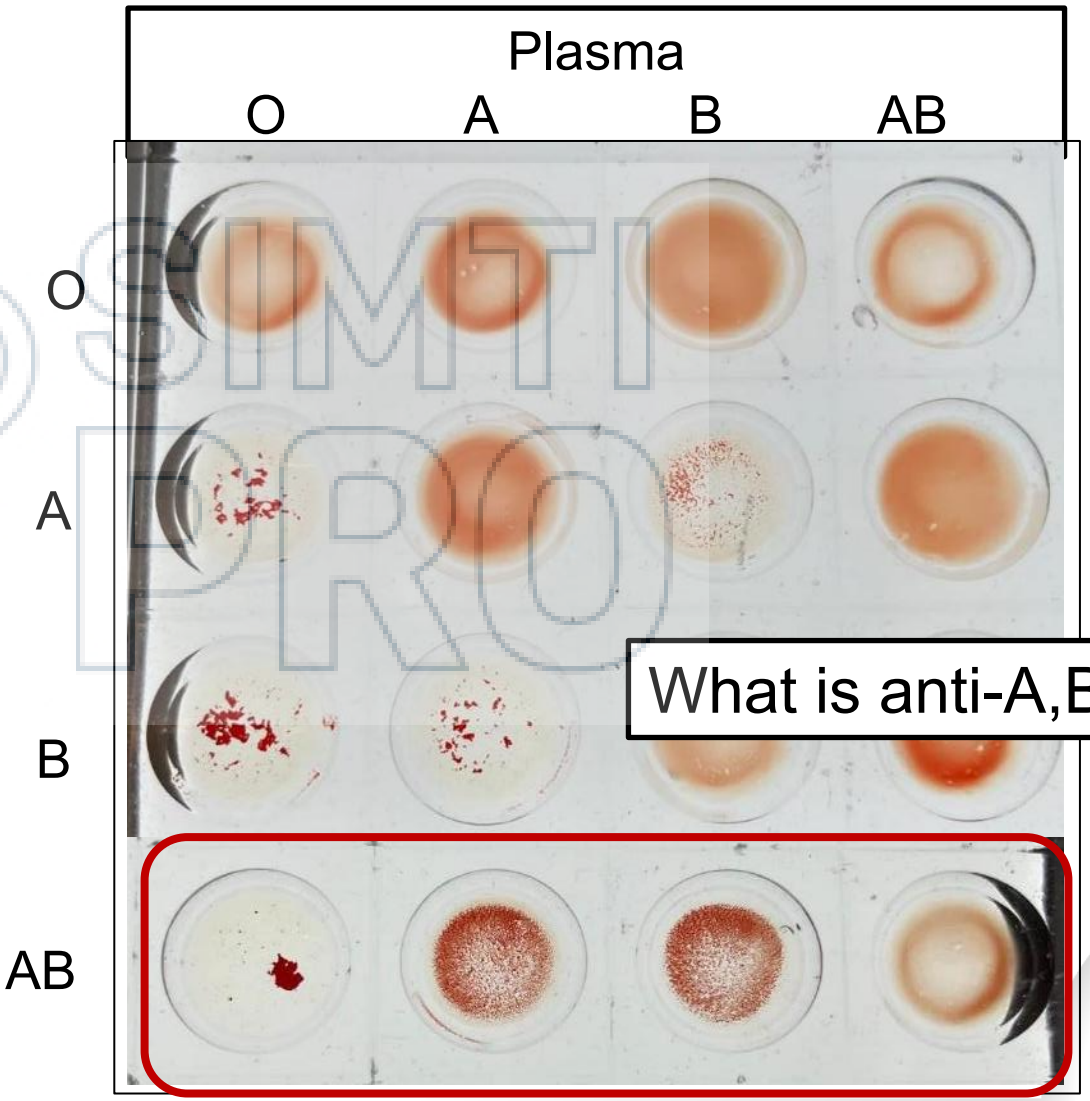
Abstract

Background: The clinically significant antibody anti-A,B together with anti-A and anti-B has been known for many decades to be present in blood group O plasma. As anti-A,B is only reactive when an A or B antigen is present, its contribution to titer cannot be easily distinguished from anti-A and/or anti-B.

Study Design and Methods: Chemically synthesized AB epitope (ABep) was attached onto red cells creating ABep-kodecytes; methodology was optimized and then used together with group A- and B-kodecytes to semi-quantitative undiluted plasma samples of all ABO blood groups for anti-A, anti-B, and anti-A,B. Standard titers with plasma dilutions against natural A_1 and B cells were performed in parallel.

Results: ABep20-kodecytes were able to semi-quantitate anti-A,B independently of anti-A and anti-B. Anti-A and anti-B levels were also able to be inferred by deduction of the anti-A,B contribution. There was a large range in the levels of anti-A,B in the group O samples, including in those determined to have high-titer ABO antibodies. Unexpectedly, some group A, B, and AB individuals were also found to have an anti-A,B-like antibody.

Discussion: Anti-A,B is a much more complex antibody than current understanding, and shows a range of activity over a large continuum, which includes in vitro detectable anti-A,B-like antibodies in non-group O samples. The ability to measure anti-A,B independently of anti-A and anti-B levels may be useful in evaluating clinical associations.



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What can ECO-RBCs tell us?

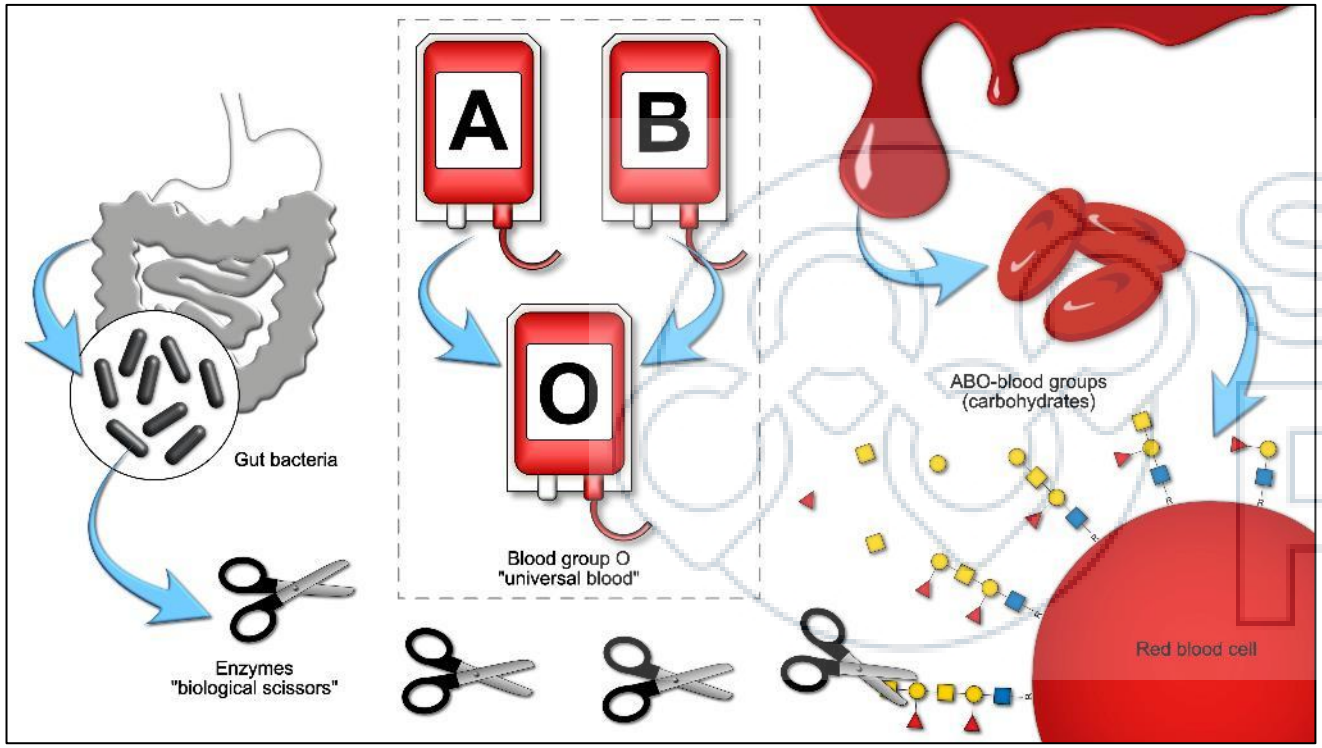
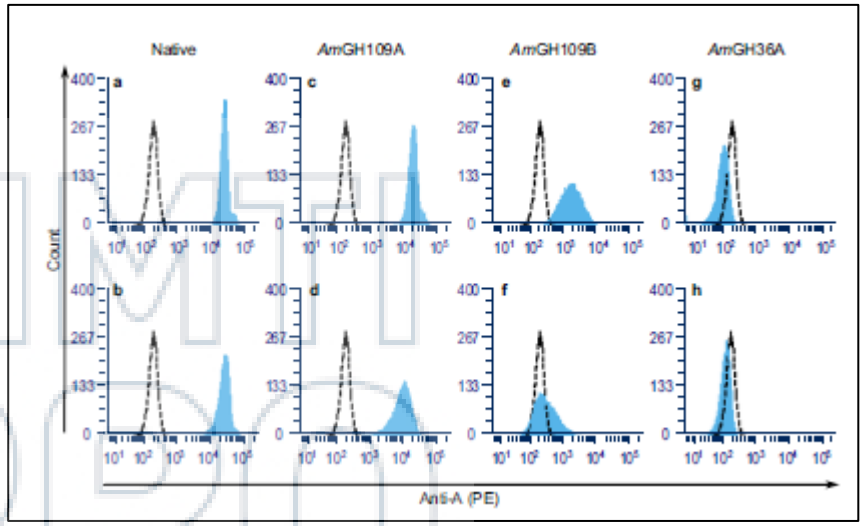
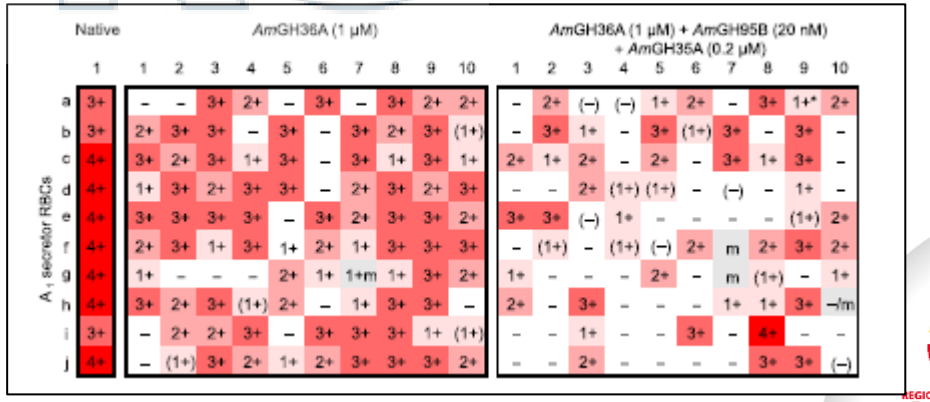


Illustration courtesy of Dr. Jennifer Ricci Hagman



ECO-treated group A RBCs are phenotypically group O…



…yet are crossmatch-positive with >50 % group O plasma!

Jensen M, Stenfelt L, Ricci Hagman J, Pichler MJ, Weikum J, Nielsen TS, Hult A, Morth JP, Olsson ML, Abou Hachem M. Akkermansia muciniphila exoglycosidases target extended blood group antigens to generate ABO-universal blood. Nat Microbiol. 2024 May;9(5):1176-1188. doi: 10.1038/s41564-024-01663-4.

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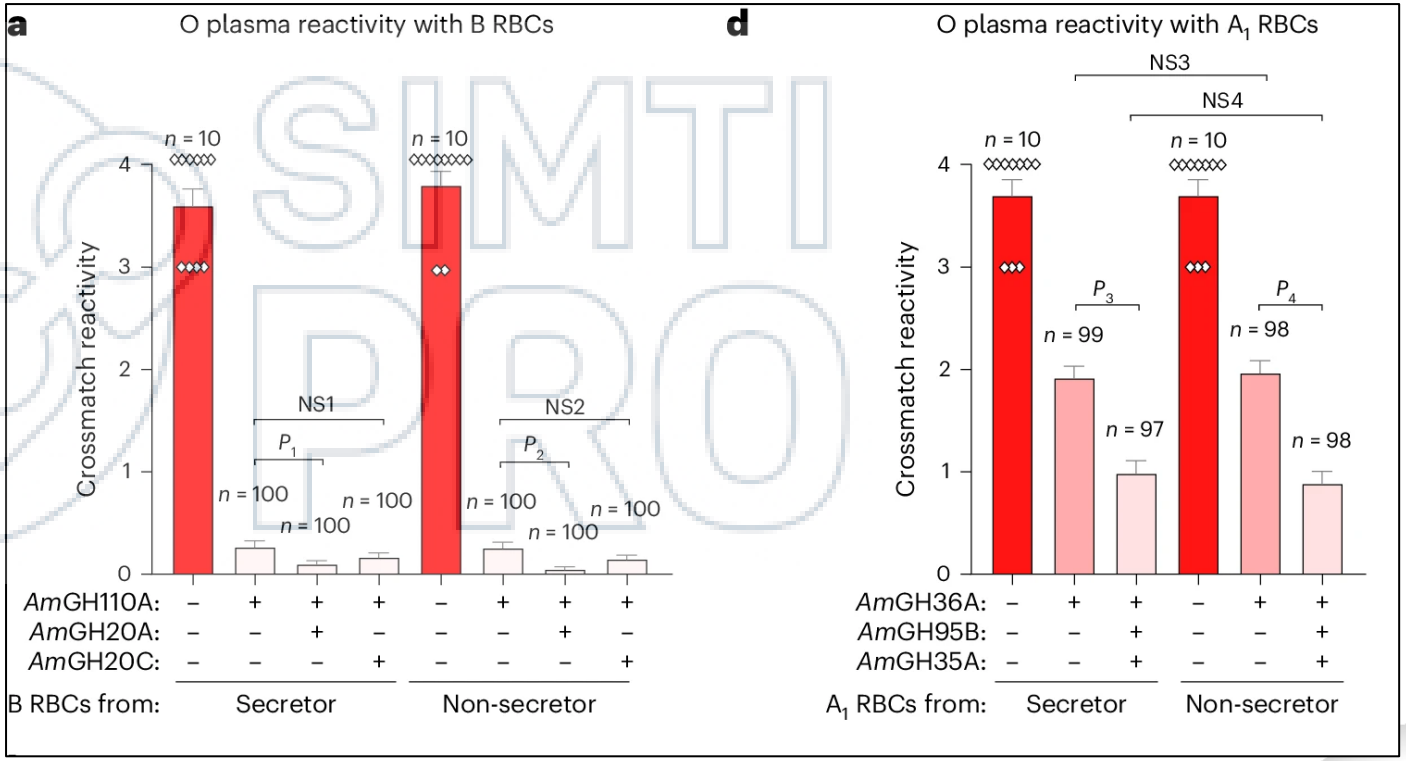
What can ECO-RBCs tell us?

Differential digestion with a cocktail of enzymes reveals extended structures such as A type 3 and ExtB, and there are others:
…under extensive investigation with different cocktails of gut enzymes



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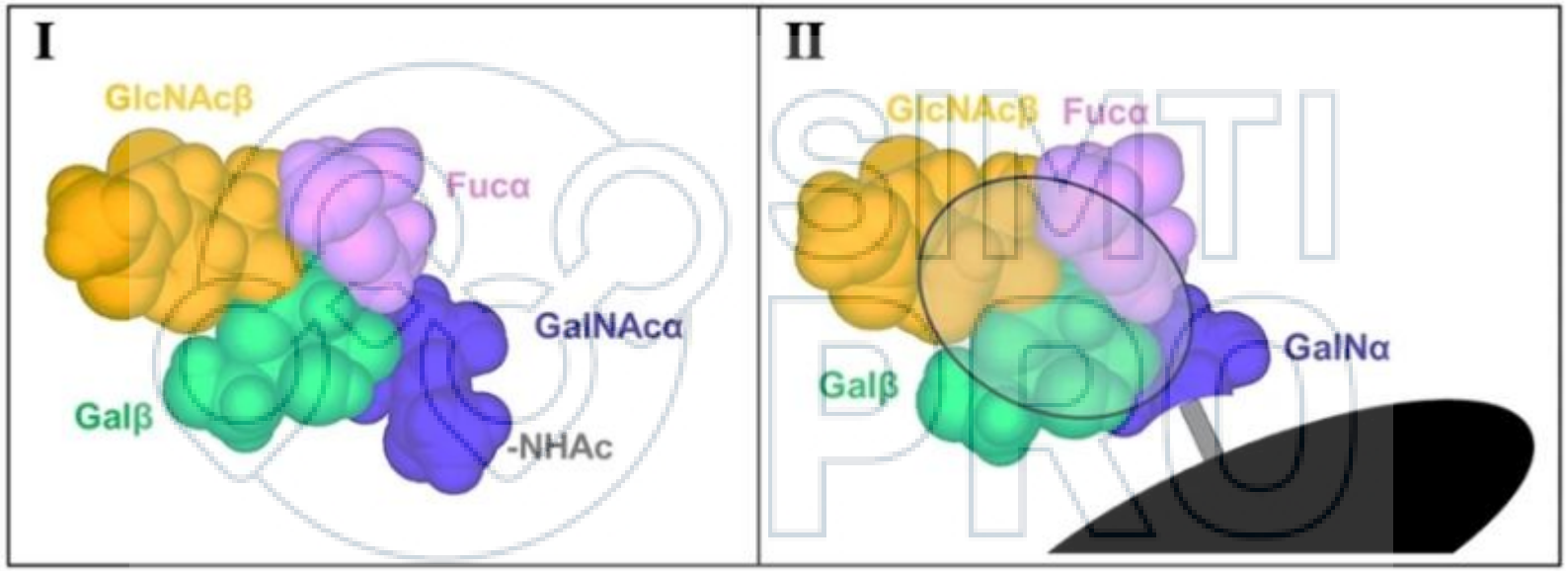
Anti-A,B is an epitope shared by the A and B antigen stuctures



Henry S, Perry H, Obukhova P, Tyrtysh T, Ryzhov I, Bovin N, Datta SS. Revealing and quantifying polyclonal anti-A, B specificity in ABO histo-blood groups. Transfusion. 2026 May;66(5):965-975.

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Mapping specificity with synthetic A/B antigens inserted into group O RBCs

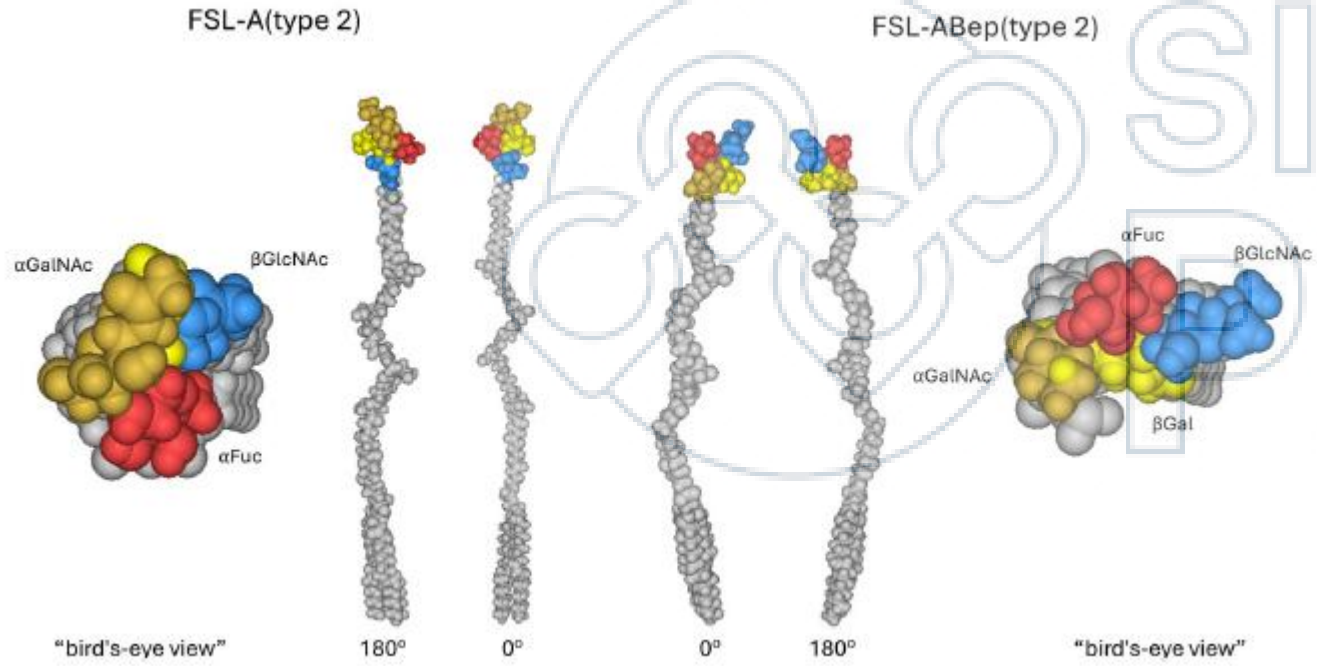

TABLE 2 Frequency of ABep20-kodecyte reactivity within different ABO blood groups.

Blood group	*n*	ABep20 reactivity[a]	*n*	%
O	82	0	8	9.8
		w	5	6.1
		+	6	7.3
		++	40	48.8
		+++	18	22.0
		++++	5	6.1
A	132	0	127	96.2
		Pos	5	3.8
B	182	0	173	95.1
		Pos	9	4.9
AB	50	0	45	90.0
		Pos	5	10.0

[a]ABep20-kodecyte reactivity grades for blood group O are recorded as w to +++ grades as in Table 1. Positive reaction grades are simply reported as Pos (positive) for all other blood types and are typically 2+.

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What's new in Immunohematology

- Serological incompatibility still drives discovery but "-omics" techniques solve the problem
- Technological advances help us to improve patient safety by Identifying better matched blood
  - Reduce the need for rare blood banks
  - Identifying storage markers in blood donors
- Gut feelings – teaching us more about ABO

The Blood Group @ LU

Our research aims to uncover new roles of the ***red blood cell*** surface in health and disease, with a special focus on the polymorphic molecules known as ***blood groups***.

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Division of Transfusion Medicine
Department of Laboratory Medicine

REGION SKÅNE

Clinical Immunology & Transfusion Medicine
LabMedicine, Skåne University Hospital

Annika Hult
Ph.D., staff scientist

Nysa McGowan
Ph.D.,Post- doc

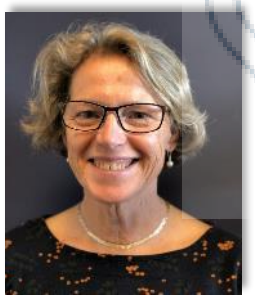
Stephan Hasse
Ph.D., Post-doc

Martin L. Olsson
Professor, MD, Ph.D.

Linn Stenfelt
Ph.D., Post- doc.

Anja. Nylander
M.D., Ph.D student

Abdul Ghani Alattar
M.D., Ph.D.



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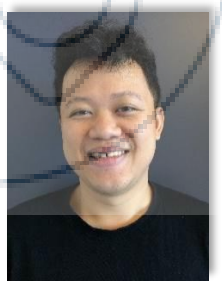
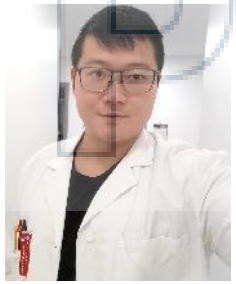
Adj. Prof, Ph.D.,
Deputy group leader

Åsa Hellberg
Ph.D., Reference laboratory coordinator

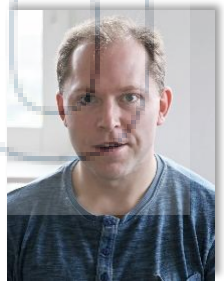


Yan Quan Lee
Ph.D,
Laboratory Manager



William Shen
M.D., Ph.D. student

Jennifer Ricci Hagman
Ph.D. , post-doc



Mattias Möller
M.D., Ph.D. student
Bioinformatician

Namrata Singh
PhD., post-doc

Our work is funded by:

ALF

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Knut och Alice Wallenbergs Stiftelse

OLLE ENGKVISTS STIFTELSE

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Vetenskapsrådet

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Grazie!

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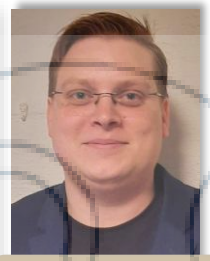

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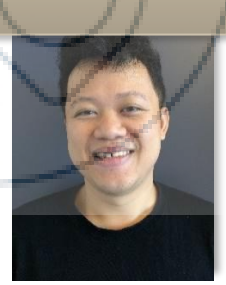

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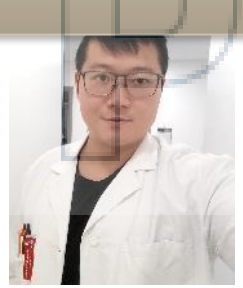

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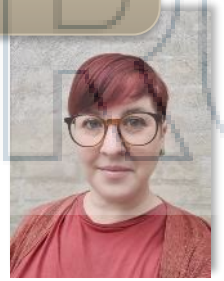

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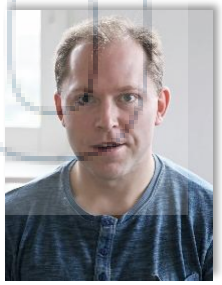

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