

# Central immunological position of the human blood group O(H).

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**Abstract:** Blood group A phenotype development is associated with impaired formation of adaptive and innate immunoglobulins due to clonal selection and phenotypic, glycosidic accommodation of plasma proteins. Moreover, it is significantly burdened with an increased risk of developing different types of cancer, while exerting strong susceptibility to severe malaria infection. Both the risk of developing cancer and susceptibility to malaria disease appear molecularly to be strongly related to phenotype formation, in which the blood group A-determining glycosyltransferases affect the levels of anti-A/Tn cross-reactive immunoglobulins on the one side, and on the other side, via the "serine repeat antigen", accomplish the contact and entry of the protozoan into the host. This contact, thus provided predominantly by blood group A cells, appears to be promoted also by cancer cells suggesting "A-like" Tn formation, which is inhibited by *Plasmodium* invasion, why blood group A is extremely rare in regions, in which malaria is endemic but malaria infection inversely associated with cancerous growth. Consequently, the blood group O phenotype, currently discussed to have a survival advantage of the overall risk of developing cancer when compared with non-O blood groups, rarely develops severe malaria, and despite susceptibility to severe cholera disease and extensive historical epidemics and pandemics occurring over the centuries, remains the worldwide most common blood type, due to a complex, superior immunity.

## **Introduction.**

The human gut microbiome has been a subject of comprehensive research for decades and the different aspects of interactions between host and microbes in health and disease are discussed in various intensive reviews, and natural immunoglobulins certainly arise from several sources and via different molecular processes. However, when adaptive production of anti-blood group B-reactive immunoglobulins, as occurring in White Leghorn chickens fed a diet containing *E.coli* O86:B7 lipopolysaccharide (1), was demonstrated for the first time to occur spontaneously in human (2), this way of isoagglutinin production could be documented exclusively for the histo (blood) group O(H). Bacterial endotoxins non-specifically stimulate the formation of all immunoglobulins, but prokaryotic "blood group A/B-like" antigenic structures apparently induce cross-reactive anti-A/B immunoglobulins (3; 4; 5), which due to clonal selection neither arise in blood group A nor in B individuals and occur predominantly or exclusively in blood group O. Consequently, in patients, suffering from ulcerative colitis causing increased enteral absorption, the minimally, likely non-specifically elevated anti-B-reactive 7S (IgG) and 19S (IgM) levels in blood group A plasma remained within normal range, whereas a statistically significant increase of anti-B-reactive IgG and IgM immunoglobulins involving less pronounced asymmetrically cross-reactive, anti-A-specific IgG, was measured exclusively in blood group O(H) plasma, and the IgG/IgM quotients showed a predominance of the IgG class (Fig.1). These early observations are in accordance with later investigations performed by current experimental tools; Stussi et al. detected anti-A/B cross-reactive IgG in 89% of blood group O and anti-B-reactive IgG in 4% of blood group A sera investigated (6), and vaccination by pneumococcal polysaccharides exclusively elicited anti-A/B cross-reactive IgG but did not affect the pre-existing anti-A/B-reactive IgM levels (7).

## **Different origins of adaptive and germline-encoded immunoglobulins in blood group O and non-O blood groups.**

While according to the danger theory (8) there is no adaptive immunity without innate immunity, the major part of human immunity is hardly acquired during a human's lifetime but considered to arise predominantly from the evolutionary memory and mechanisms of survival. Thus, an inborn origin has been postulated to explain isoagglutinin production in non-O blood groups (9; 10). Aside from adaptive, cross-reactive anti-AB production, mainly restricted to blood group O individuals, the majority of anti-A/B immunoglobulins, especially the classic comple-

ment-binding anti-A and anti-B-reactive isoagglutinins are, measured between 22 and 24<sup>0</sup>C, independent of any blood group, and exerted by a primarily polyreactive, non-immune, germline-encoded IgM molecule, which in the non-O blood groups undergoes the phenotype-specific, glycosidic accommodations of plasma proteins (10; 11). In proteomics analysis of *O*-GalNAc glycosylation in human serum, 407 intact *O*-GalNAc glycopeptides from 93 glycoproteins have been identified (12). In blood group A individuals, these *O*-glycosylations are, aside from *N*-glycosylations, most likely dominated by phenotype-specific GalNAc enzymatic transfer via *O*-linkages to functional serine/threonine or tyrosine residues, provided by the Fc region of the ancestral IgM molecule (13), on which the terminal serine appears to be the crucial structure (14), whereas a thus achieved reduction or exclusion of IgM anti-self reactivity necessarily impairs the adaptive and innate defense processes (11). This principle of phenotypic glycosidic accommodation might find its expression in  $\alpha$ 2-macroglobulin, which is considered an evolutionarily conserved arm of the innate immune system (15) and functionally connected to the structurally related IgM molecule (16), and exerts ABO(H) reactivity in strict correlation with the cell surfaces (17; 18).

### **How blood group O and A phenotype evolution and development are related to growth and infections by protozoan eukaryotes and prokaryotes.**

The principle of phenotypic accommodation (10; 11) has been postulated to contribute to the increased risk of human blood group A individuals of developing certain types of cancer, especially of the intestinal tract, only to name the adenocarcinomas of the pancreas (19), whereas blood O(H) group individuals are discussed to have a survival advantage in the overall risk of developing cancer when compared with non-O blood groups (20; 21). Moreover, this principle may, when the species barrier is overcome by interspecies glycosylations (22) and ABO glycosyltransferases accomplish the cross-species transmission of *O*-glycans in infectious diseases (23), provide an explanation of the pronounced susceptibility of blood group A individuals to malaria infection. Human blood group A-phenotype-specific GalNAc transferase activities, expressed by both cell surfaces and plasma proteins, and serine/threonine kinases from *Plasmodium falciparum* might provide the metabolic condition for the synthesis of adhesion and/or RIFIN proteins (24) involving RBC rosette formation. This is assumingly based on heterologous glycosylation that has long been discussed as the major carbohydrate modification in the intraerythrocytic stage of *Plasmodium falciparum* (25; 26), the role of ABO(H) phenotype primarily ignoring. The metazoan/eukaryotic, evolutionary first glycosylation of proteins, provided by GalNAc via

*O*-linkages on peptides displaying serine/threonine motifs, characterizes mammalian embryonic stem cell fidelity initiating germ cell maturation. When breaking the species barrier, this glycosylation may also promote the asexual reproduction of *Plasmodium merozoites*, involving immature gamete formation, and explain even the attachment of infected to uninfected RBCs. Indeed, when *Plasmodium falciparum* produces rosette formation predominantly from human blood group A RBCs (27) and does not complete such formation by blood group O(H) RBBs, this most likely occurs on the basis of heterologous "A-specific" GalNAc glycosylation, breaking a species barrier. Serine/threonine and tyrosine kinases (28; 29) are exported by *Plasmodium falciparum*, and during the asexual intraerythrocytic stage (23; 24), the red cell membrane exerts serine transferase activity, discussed as an anti-malaria drug target (30; 31). Thus, when the "serine repeat antigen", detected decades ago (32), is meanwhile accepted as a putative antigen precursor, heterologous *O*-GalNAc-glycosylation might explain the preferred binding of special *Plasmodium* strains (providing trans-species compatible serine positions) to blood group A red cells, whereas the pronounced susceptibility of blood group A individuals to malaria infection (33) might suggest the formation of anti-Tn-reactive structures (11) and a new molecular definition of the immunological (therapeutic) target.

From all this it follows, why blood group O(H) individuals, who cannot complete this self-destructive, likely transient hybrid connection, beyond that, maintain the natural (anti-A/Tn-cross-reactive?) antibody against it (11). Moreover, the suggested metabolic pathways may even provide an explanation for the growth inhibition, which is exerted by some *Plasmodium* strains on cancerous tissue; worldwide malaria incidence and cancer mortality are inversely associated (34), and should molecularly be explainable by enzyme-substrate competition in cancerous Tn formations, exposed to the serine (kinase) surplus of the "pathogen".

While malaria infection is discussed to contribute to the variable global distribution of ABO blood groups in the human population, the geographical distribution of gene frequencies highly depends on racial and ethnic diversity, and no statistics between ABO(H) blood groups gives true pictures. Although the species-independent ABO gene polymorphism has been intensively analyzed in primates (35; 36), an understanding of the ramifications of this polymorphism has been elusive (discussed by Arend 37). In particular, analyses of the AO exon and intron in individuals with an "A- weak B" phenotype have revealed a novel O1v-A2 hybrid allele that results in missense mutations in the A-transferases and/or transferees, whereas unusual O alleles, including O2 at the ABO locus might be implicated in unexpected blood group phenotypes (38). Thus, specifically the blood group O(H), the worldwide most common blood type, is no longer

considered a genetic entity (38; 39; 40); it is contaminated with weak A alleles, which may exert weak A-determining enzyme activities that promote severe malaria infections but let the patient's blood group serologically look like O(H), making true statistics impossible. Consequently, the reports on the susceptibility of blood group O(H) individuals to most viral and bacterial infections are controversial, whereas there is a strong and established link between special types of cholera infections and the human blood group O(H) phenotype (41; 42). Similar to malaria, the contact between host and the pathogen may again be accomplished by phenotypic glycosylation. However, the more complex pathogenesis is initiated by the "receptor destroying enzyme", a mixture of hydrolases discovered by Burnet and Stone (43) as early as 1947 and dominated by a neuraminidase associated with secretion of adhesion proteins (44), causing RBC pan-agglutination and rosette formation (45), known as Hübener-Thomsen Friedenreich phenomenon (46). These adhesion proteins highly suggest fucosyltransferase activity (47), accomplishing the contact of the pathogen to an increased H-receptor expression on the blood group O cell surfaces, a suggestion that is substantiated by inhibition of the pan-agglutination by L-fucose (48). At present, the lowest prevalence of the O blood group in the world is in the Ganges delta, where cholera has likely been endemic for centuries (49). However, despite extensive cholera epidemics and pandemics occurring all over the planet in the past, and like malaria, certainly also contribute to the global distribution of ABO(H) blood groups in the human population, blood group O(H) has, according to the published figures (50), survived as the most common blood type worldwide.

### **Conclusions.**

The central immunological position of the human histo (blood) group O(H), remains evident in its comprehensive presentation of both non-immune IgM and adaptive IgM/IgG antibodies against all non-O(H) blood groups, involving their cross-specific developmental and/or "aberrant" structures (19) (Fig. 2), as there are the early metazoan eukaryotic *O*-glycans, T (Thomsen-Friedenreich) (51) and Tn, "T nouvelle" antigen (52). These ancestral glycans arise from *O*-glycosylations, which are with similar peptide backbones already used by lower metazoans, such as mollusks and the fruit fly *Drosophila melanogaster* (53; 54) moreover, in the snail *Helix pomatia* are associated with the release of a hexamerically (55) structured Tn-complementary, hemagglutinating defense protein. In 1973, Hammarström demonstrated that the binding patterns and capacity of this molluscan defense protein to human blood group A RBC are strikingly similar to the corresponding values for the mammalian IgM molecule (56). It is this hexamer-

ic structure and its binding patterns and capacity, which give rise to speculation regarding an evolutionary relationship to the mammalian non-immune anti-A-reactive IgM molecule, while its germline appears, like that of the polyreactive ancestral IgM of the human blood group O, not to be burdened with A/B phenotypic accommodations; *Helix pomatia* and other snails never develop cancer. Although the distributions of ABO blood groups are varying strongly between countries and geographical areas due to uncountable reasons, the human histo (blood) group O clearly represents the worldwide most common blood type (50), which may alone signify a survival advantage in general due to a superior complex immunity, in which the human-specific nonimmune anti-A-reactive IgM or isoagglutinin might be identified as the authentic complementary protein to the trans-specific, developmental Tn epitope (11). This complement-binding protein may exert its immunological power in major ABO-incompatible transplantations, mirroring its actual role in the internal defense processes, which in the non-O blood groups are affected through phenotypic, identical glycosylation of cell surfaces and plasma proteins.

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# Selective immune response of blood group O individuals to increased enteral absorption.

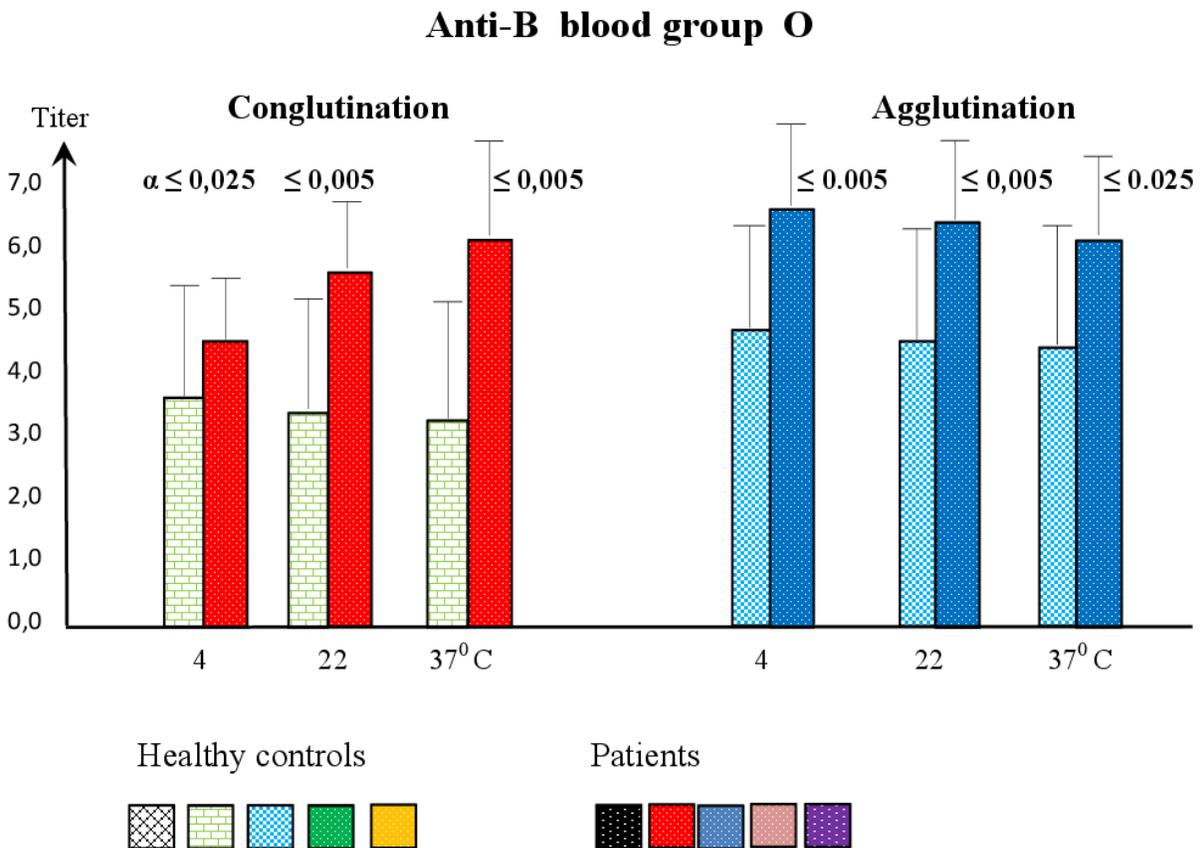
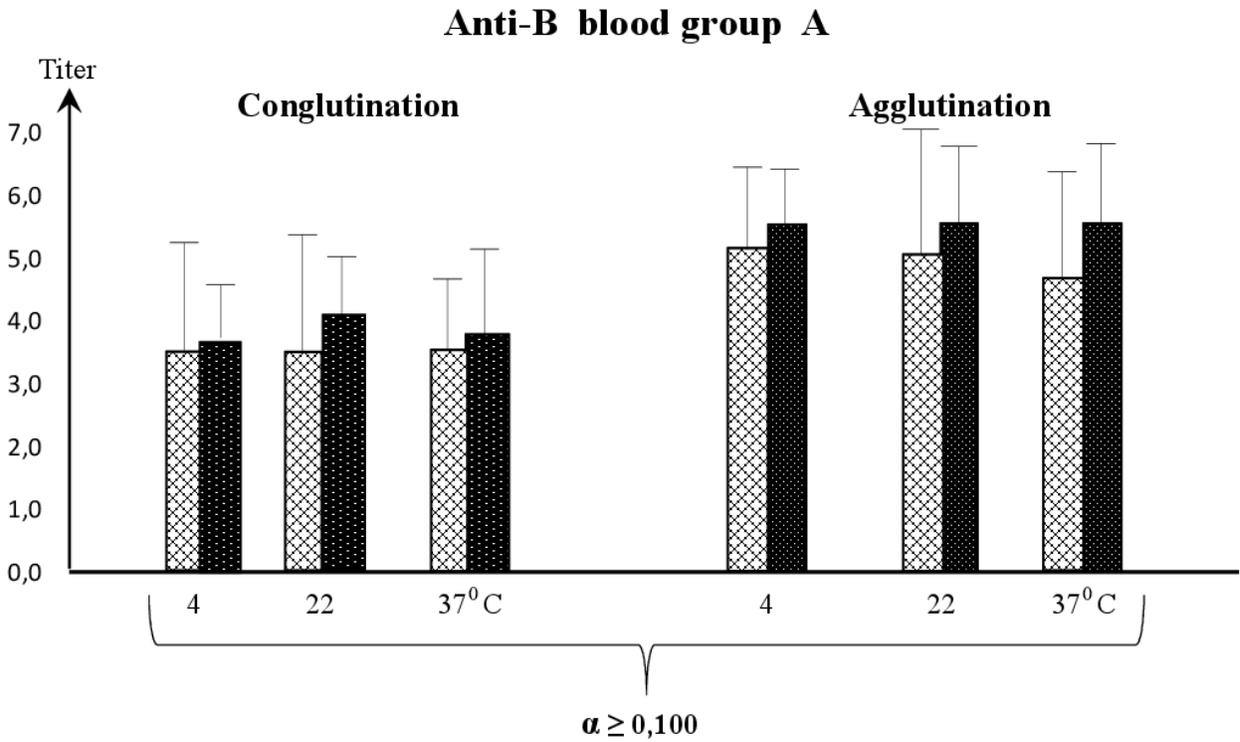
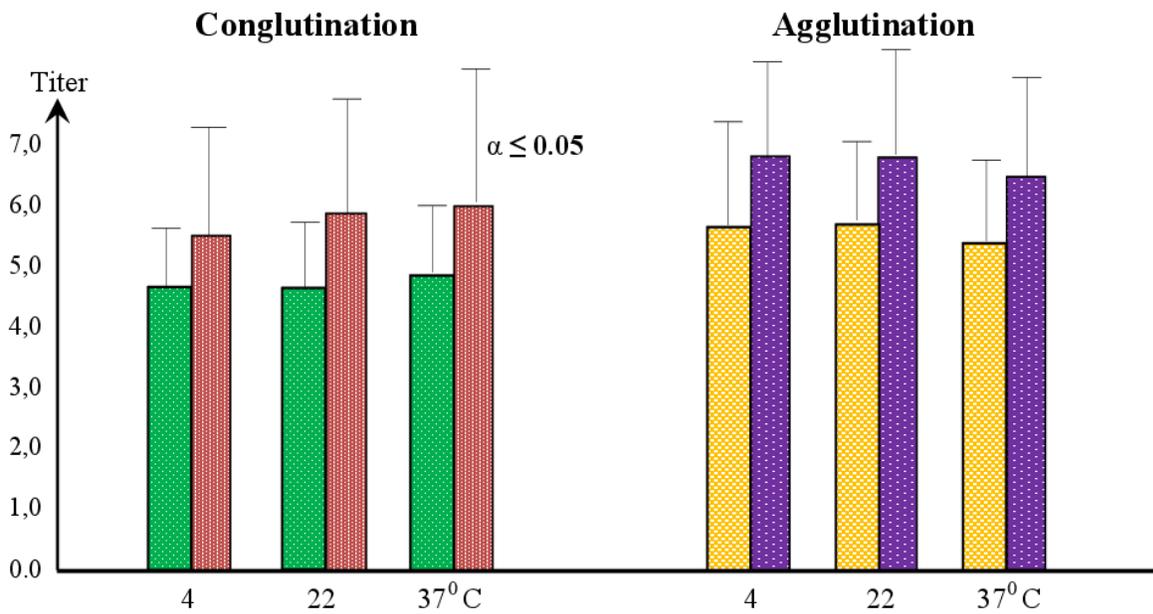


Figure 1

### Anti-A blood group O



### Conglutination ÷ Agglutination

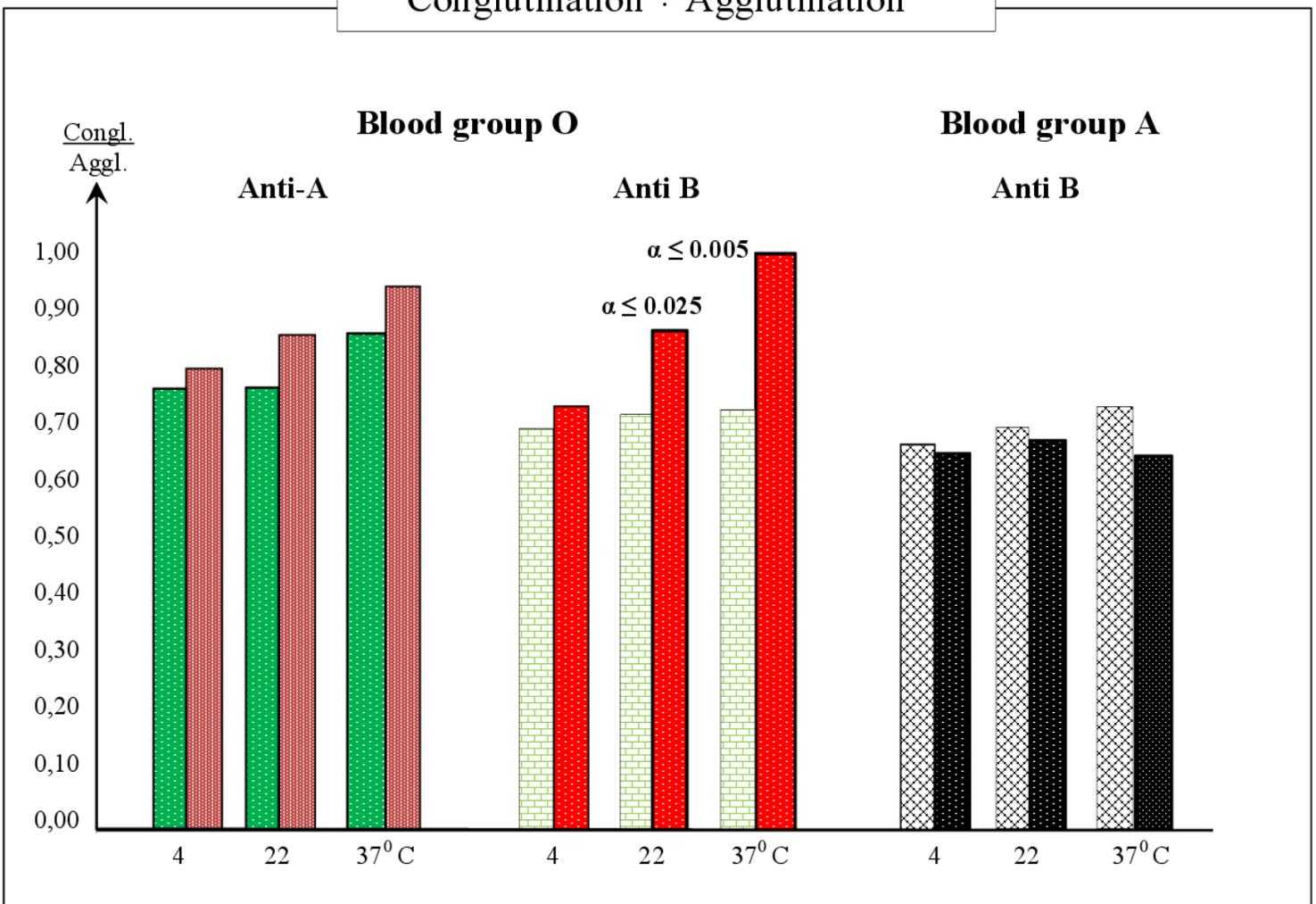


Figure 1 continued

Fig. 1. Spontaneous variations in the production of anti-A/B isoagglutinins in 21 individuals suffering from ulcerative colitis (blood group A = 11, blood group O = 10), and in 42 normal persons (blood group A = 22, blood group O = 20), are investigated under double-blind conditions. The grade of immunization and dominance of the 7S (IgG) conglomerating and 19S (IgM) agglutinating immunoglobulins are determined through conglutinin and agglutinin titers and their quotients at three different temperatures. Using the non-parametric *Wilcoxon* procedure, the minimally elevated anti-B-reactive IgG and IgM levels in blood group A plasma remain within normal range, whereas the blood group O patients show a statistically significant stimulation of an IgG conglomerating and IgM agglutinating anti-B, involving asymmetrically cross-reactive, less pronounced anti-A specific IgG, and the IgG/IgM quotients indicate a predominance of the IgG class. The figure is reconstructed from the data published in: Arend, P. & Fehlhaber, G. Varying influence of increased enteral antigen absorption on the behavior of "natural" antibodies in O and A blood group subjects. Comparative blood group serological studies on patients with ulcerative colitis and healthy persons [Article in German]. *J Mol Med (Klinische Wochenschrift)*. 1969; 47 535-541, (2), doi:10.1007/BF01715818

Central immunological position of the  
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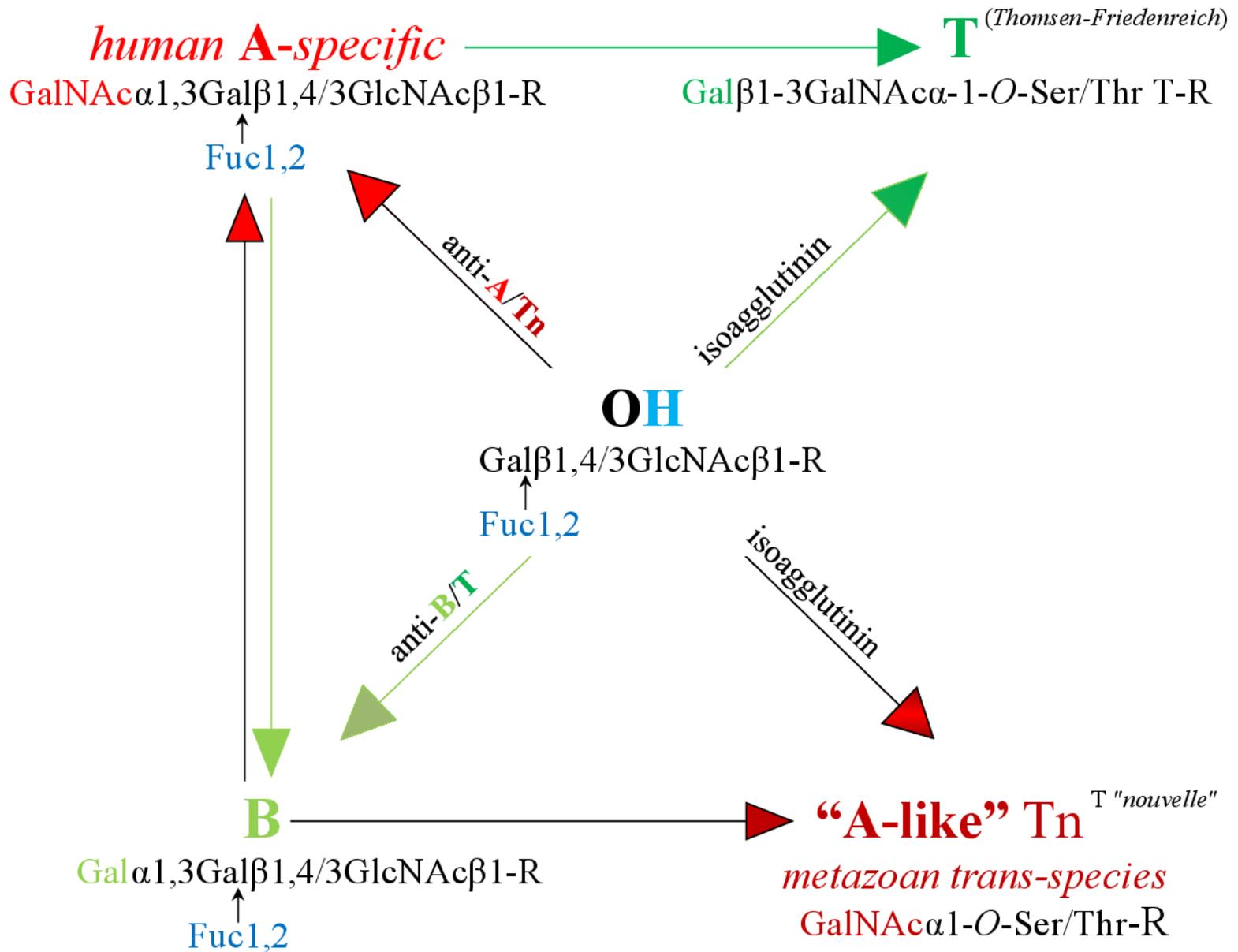


Fig. 2

Fig. 2. The central immunological position of blood group O(H) is evident in its comprehensive presentation of both adaptive and germline-encoded “natural” antibodies against all mature A and B glycans and their cross-reactive developmental structures Tn and T. The human A-specific (A-allelic) glycosylation and trans-species “A-like” Tn formation are developmentally connected via the formation of cross-reactive anti-A/Tn isoagglutinin. According to Hofmann et al. (19), blood O(H) sera bind to both Tn and T antigens, and the anti-A isoagglutinin levels in blood group O(H) and blood group B sera are associated with anti-Tn antibody, which does not react with blood group B red cells or T glycoconjugates. By contrast, the anti-B antibodies of blood group A sera and blood group O(H) sera bind to B and T glycoconjugates but not to A or Tn glycoconjugates. The authors explain this selective cross-reactivity of isoagglutinins with Tn and T antigens via phenotype-specific terminal moieties; the terminal *N*-acetylgalactosamine is shared by A and Tn antigens, and the terminal galactose is, although with different configuration, shared by B and T antigens. This fig. is part of (11): Arend P. Early ovariectomy reveals the germline encoding of natural anti-A- and Tn-cross-reactive immunoglobulin M (IgM) arising from developmental O -GalNAc glycosylations. (Germline-encoded natural anti-A/Tn cross-reactive IgM). *Cancer Med* [Internet]. 2017 Jun 5 [cited 2017 Jun 15];6 (7):1601–13. Available from: <http://doi.wiley.com/10.1002/cam4.1079>