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1 **Diversification of IgA Antibody Specificities by Mild**
2 **Chemical Modification?**

3

4 Title:

5 **Diversification of IgA antibody specificities by mild chemical modification?**

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25 Intravenous immunoglobulin (IVIG) or subcutaneous immunoglobulin (SCIG)
26 consisting mainly of IgG antibodies are used for substitution therapy in humoral
27 immunodeficiency or as a high-dose treatment for inflammatory and autoimmune
28 conditions. The antibodies in these preparations are derived from thousands of blood
29 donors and collectively represent the donors' IgG repertoires, which in humans is
30 both public and private [1,2]. Mild chemical modification of antibodies has been
31 proposed as one of several strategies to improve the efficacy of polyclonal
32 immunoglobulin preparations [3], as this approach can lead to further diversification
33 of antibody specificities beyond somatic recombination, junctional diversity and
34 somatic hypermutation [4]. Indeed, mild chemical modification of IVIG has shown to
35 improve survival in experimental models of sepsis and aseptic systemic inflammatory
36 response syndromes [5], and to enhance pro-apoptotic effects on leukocytes under
37 inflammatory conditions [6].

38 While IVIG and SCIG preparations mainly consist of IgG antibodies, evidence
39 suggests that IgA formulations might also be beneficial for clinical applications and
40 exhibit idiosyncratic advantages [3,7]. The heavily N-glycosylated secretory
41 component (SC) that stabilizes IgA also prevents rapid proteolysis of IgA dimers and
42 multimers in the hostile environment of the digestive tract. Therefore, the oral route
43 might one day be used for passive digestive transfer of specific or polyclonal IgA that
44 could be very beneficial to IgA-deficient patients that presently do not benefit from
45 any specific treatment [8]. Any technical clue, as the one tested by Gorshkova et al.
46 in this issue of *Pharmacology* [9], to further diversify anti-microbiota reactivity of
47 future therapeutic IgA preparations, would therefore be more than welcome. Indeed,
48 IgA polyreactivity appears to represent a key biological feature of this antibody,

49 eventually accounting for its ability to regulate immune/microbiota homeostasis
50 [8,10].

51 Gorshkova et al. report that protein-modifying agents can alter the repertoire
52 of secretory IgA and that exposure to acidic pH broadens the range of reactivities to
53 common and distinct pathogens [9]. Specifically, low pH treatment of colostrum and
54 breast milk IgA broadened the recognition of bacterial antigens from *E. coli* and *S.*
55 *aureus*, but also Colo205 cell antigens, and increased IgA binding to viral antigens
56 from hepatitis C or D virus, human immunodeficiency virus type 2 and norovirus.
57 However, the recognition of select bacterial antigens was also lost by low pH
58 treatment. It remains unclear whether low pH treatment might partially denature
59 some IgA, potentially leading to non-specific interactions. Conversely, it is also
60 possible that bound materials that might co-purify with antibodies are removed by
61 acid treatment, thereby offering more options for specific interactions. As opposed to
62 low pH, treatment with ferrous ions had little or no effect on IgA binding to these
63 antigens, while heme exposure increased reactivities of colostrum, but not breast
64 milk, secretory IgA. Components of milk might affect the integrity of antibodies or
65 block antibody reactivities, eventually requiring material processing prior to analysis
66 [11], such as casein depletion by sodium phosphates employed in the study by
67 Gorshkova. However, the divergent effect of modifying treatment on colostrum and
68 milk IgA by heme, highlights the potential importance of co-factors that might directly
69 influence IgA reactivities or effects of mild protein-modifying agents on antibodies in
70 a biological context.

71 Microarray technology allows for the high-throughput analysis of antibody
72 immunosignatures [1,2,12], and has been used to analyse reactivity profiles of IgA
73 [13,14]. Gorshkova et al. tested native or modified secretory IgA against an array of

74 4'345 linear B cell epitopes, and while decreased or increased binding patterns were
75 observed upon modification by different agents, treatment with acidic pH enhanced
76 the polyspecificity of IgA in particular for common pathogens [9]. It is therefore
77 tempting to speculate from the results of Gorshkova al. that mere gastric exposure of
78 IgA preparations might improve their efficacy. Further in vivo studies will now be
79 needed to document how such modified IgA preparations might impact functional
80 microbial fitness and host-microbial mutualism [14], in any sort of way. However, it is
81 clear that that the report of Gorshkova and colleagues in this issue of *Pharmacology*
82 is an important first step.

83

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87 **DISCLOSURES**

88 The authors have no conflicts of interest to declare.

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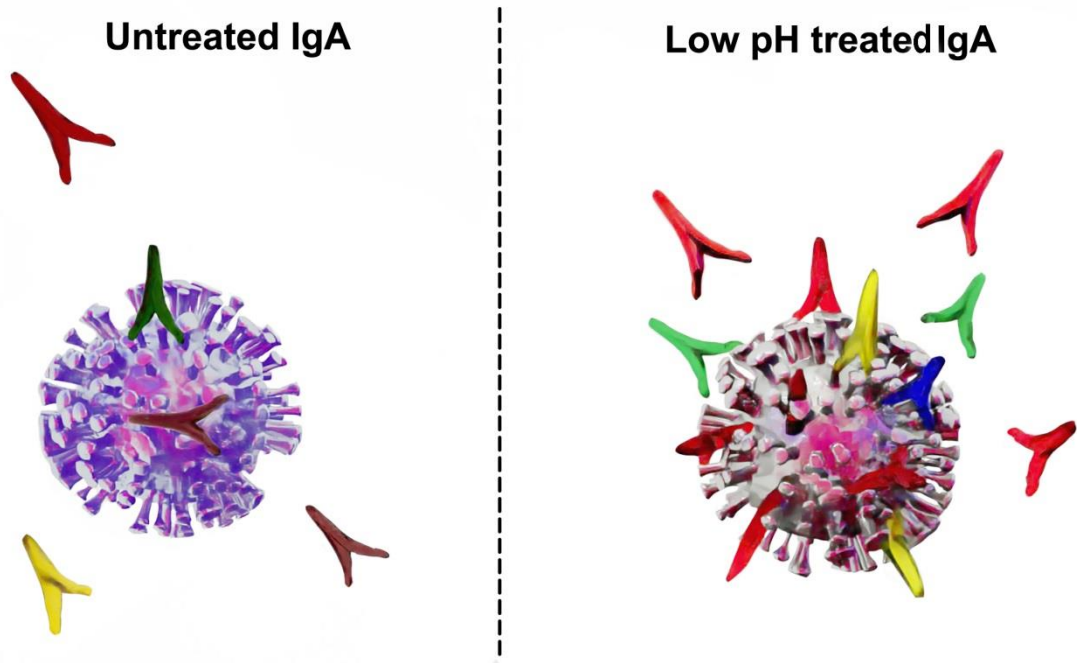
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134 **FIGURE LEGEND**

135 **Fig. 1.** Proposed concept of enhanced reactivities of IgA under mild protein-
136 modifying conditions. Exposure to low pH enhances the range of viral epitopes
137 recognized by secretory IgA.



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