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Immunity to α-Gal: Toward a Single-Antigen Pan-Vaccine To Control Major Infectious Diseases

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Recent developments point at the possibility of using the immunity to α-Gal to control infectious diseases.

Infectious diseases constitute a growing burden for human health worldwide. In particular, vector-borne diseases account for 17% of all infectious diseases and kill about 1 million people annually.[1] These diseases are caused by a diverse group of pathogens including viruses, bacteria, and protozoa that are transmitted by arthropod vectors such as ticks, mosquitoes, sandflies, kissing bugs, and tsetse flies.[1] Among the nonviral vector-borne diseases, malaria, leishmaniasis, Chagas disease, sleeping sickness, and Lyme disease represent the highest burden to human health. Further, vaccines are not available for the prevention and control of these diseases.[2] Among non-vector-borne diseases, tuberculosis caused by mycobacteria of the *Mycobacterium tuberculosis* complex is one of the world's most common causes of death from infectious diseases.[3]

All pathogens producing these deadly diseases have something in common: the galactose-alpha-1,3-galactose (α-Gal) epitope exposed on their surface (Table 1). During evolution, humans lost the ability to synthesize the carbohydrate α-Gal, which resulted in an almost unique capacity to produce high antibody titers against α-Gal.[4] The immunity to α-Gal may neutralize the pathogens with α-Gal on their surface, and therefore the induction of this protective immune response may constitute an effective intervention for the prevention and control of infectious diseases.[5] The study of the anti-α-Gal immunity will provide the basis to develop a single-antigen "pan-vaccine" to control major infectious diseases.

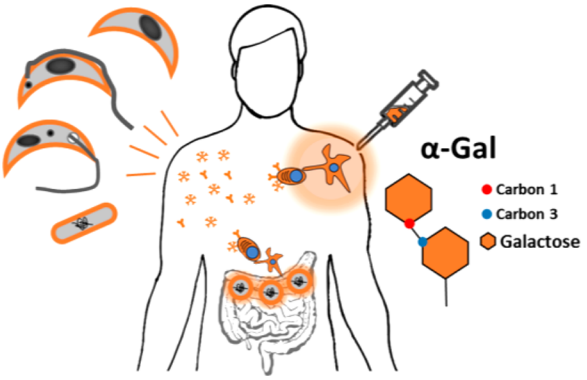

Figure 1. Immunization with the carbohydrate α-Gal could protect against *Trypanosoma*, *Leishmania*, *Plasmodium*, and *Mycobacterium* pathogens. Alternatively, probiotic bacteria producing α-Gal could be used to develop a probiotic-based vaccine.

During evolution, humans lost the ability to synthesize the carbohydrate α-Gal that resulted in an almost unique capacity to produce high antibody titers against α-Gal.

The paper recently published by Moura et al.[6] shows that vaccination with α-Gal protects against cutaneous and visceral leishmaniasis in the α-galactosyltransferase knockout mouse model designed to reproduce the anti-α-Gal response observed in humans. This work extends previous results showing that anti-α-Gal antibodies induced by α-Gal protect against *Trypanosoma cruzi* and *Plasmodium* spp.[4,7] In particular, Yilmaz et al.[4] showed that the anti-α-Gal immunity blocks the transmission of *Plasmodium* spp. by *Anopheles*

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Table 1. Presence of α-Gal in Vector-Borne Pathogens and Vaccine Availability

pathogens	vectors	diseases	vaccine[a]	presence of α-Gal	refs
Plasmodium falciparum	mosquitoes	malaria	no	yes	4
Leishmania infantum	sandflies	visceral leishmaniasis	no	yes	6
Leishmania amazonensis	sandflies	cutaneous leishmaniasis	no	yes	6
Trypanosoma brucei	tsetse flies	sleeping sickness	no	yes	11
Trypanosoma cruzi	kissing bugs	Chagas disease	no	yes	12
Borrelia burgdorferi	ticks	Lyme disease	no	yes	unpublished

[a]Based on WHO data.[2]

Collectively, these results suggest that the way forward to control major infectious diseases is the development and testing of probiotic-based vaccines containing bacteria with membrane-exposed α-Gal.

mosquitoes and targets *Plasmodium* sporozoites in the skin but not in the blood. Thus, the protective effect of anti-α-Gal antibodies was exerted in the dermis, via a complement-mediated mechanism that was no longer effective once sporozoites reach the blood.[4] Additionally, Moura et al.[6] showed that the anti-α-Gal immunity protects against *Leishmania* spp. challenge by decreasing parasite infection in the liver and spleen. These results support the efficacy of immunization with α-Gal against pathogens with α-Gal on their surface causing three of the most prevalent vector-borne diseases: malaria, leishmaniasis, and Chagas disease (Table 1). Interestingly, Yilmaz et al.[4] showed that not only immunization with α-Gal but also gut colonization by the human pathobiont *Escherichia coli* O86:B7, producing α-Gal on its surface, induces a protective anti-α-Gal immunity against *Plasmodium* transmission. These results confirmed that the production of natural anti-α-Gal antibodies is induced in response to gut microbiota bacteria and suggested that human microbiota composition may be associated with the incidence of malaria by an α-Gal-mediated mechanism.[8] Curiously, recent reports showed that the risk of *P. falciparum* infection is associated with gut microbiota composition in malaria-endemic regions.[9] Evidence of the role of the anti-α-Gal immunity can be noted in epidemiological studies. For instance, blood type B individuals produce less anti-α-Gal antibodies; in turn, the frequency of this blood type is positively associated with higher incidence rates of malaria and tuberculosis in endemic regions.[10] In addition to vector-borne pathogens (Table 1), *Mycobacterium* spp. were also found to produce α-Gal on their surface.[10]

Collectively, these results suggest that the way forward to control major infectious diseases is the development and testing of probiotic-based vaccines containing bacteria with membrane-exposed α-Gal.[5] The antibody response to α-Gal would be effective against various pathogens that contain α-Gal on their surface (Figure 1). Therefore, the use of probiotic-based vaccines exploiting this major evolutionary adaptation may constitute an effective strategy to reduce the impact of infectious diseases and improve human health worldwide. Furthermore, if effective, these vaccines constitute an affordable and orally administered intervention that could be easily used in the world's poorest countries.

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