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Streptococcus pyogenes candidate vaccine

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Group A *Streptococci* (GAS) diseases remain as a public health problem both in industrialized and development countries, leading to severe invasive infections, pharyngitis and pyoderma. These diseases can lead to autoimmune post-streptococcal sequelaein non-treated patients as Rheumatic Fever (RF) that affects children and young people and is caused by molecular mimicry with human proteins in which auto reactive B and T cells play an important role. Rheumatic Heart Disease (RHD) is the most severe sequel characterized by progressive and permanent valvular lesions. At least 517 000 people die per year due to severe GAS diseases. The prevalence of RHD is 15.6 million cases with 2, 82, 000 new cases 2, 33, 000 deaths each year. In Brazil, according to the WHO epidemiological model and data from IBGE (Brazilian Institute of Geography and Statistics), there are approximately 10 million cases of *Streptococcal pharyngitis* infections. These cases could lead to 30,000 new cases of RF, among which approximately 15,000 could become cardiac lesions. One important aspect of the recurrence of rheumatic fever episodes is the possibility of worsening valve damage. The vaccine we are developing against *S. pyogenesis* based on protective epitopes of C-terminal portion of the M protein. A peptide with 55 amino acids named StreptInCor (medical identity) was designed. The advantage of the StreptIncor vaccine model is the possibility of the vaccine epitope undergoing processing by antigen presenting cells (monocytes and/or macrophages) to generate several peptides that induce both B and T immune responses, resulting in a safe and robust immune response. Experimental assays have demonstrated that the StreptInCor peptide induces high titers of opsonic and neutralizing and protective antibodies in outbred immunized mice. Using HLA class II transgenic mice, it was possible to evaluate the immunogenicity and safety of the StreptInCor vaccine epitope for a period of one year. Specific and non-autoreactive antibodies were produced. No autoimmune or pathological reactions were observed in the heart or other organs. StreptInCor vaccine also induces regulatory T cells (Treg) that strongly indicate that the vaccine peptide may have therapeutic potential to control both inflammatory and autoimmune response in RF/RHD patients.

Biography

Luiza Guilherme was born in the South of Brazil, Irati, Paraná . She majored in Pharmacy and Biochemistry, in 1976. She spent three years in France, initially at the National Blood Transfusion Center (CNTS) with Dr Jean Yves Muller for 6 months followed by 2 years and 6 months at the Laboratory of Human Immunogenetics for Transplantation with Professor Jean Dausset and Professor Jacques Colombani. During this time she obtained my MSc degree on the HLA-D region, by describing a new antigen present in PHA stimulated T lymphocytes characterized as a new supertypic specificity that nowadays is defined as DQ molecule. In 1984 she also spent 6 months as a research fellow at the National Institute of Cancer Research, Lab of Clinical Pathology and Immunogenetics in Genoa, Italy supervised by Prof. Dr. Giovani Baptista Ferrara. In 1987 she spent 3 months at the Transplantation Department of Tokay University in Isehara, Japan under supervision of Prof. Kimiyoshi Tsuji. In these periods she specialized in the HLA system with a special focus on transplantation and disease associations. Upon her return to Brazil she had the opportunity to convey the knowledge acquired and she worked for several years in the histocompatibility for kidney, heart and bone marrow transplantation at the Lab of Immunology of Heart Institute, School of Medicine, University of São Paulo, headed by Prof. Jorge Kalil. In order to understand the mechanisms involved in the development of some autoimmune diseases, she started to study several autoimmune mediated diseases that could be associated with HLA class II molecules. In this field, she described the association of HLA-DR7 and DR53 with Rheumatic Fever (RF) in Brazilian patients. This work opened a new field of research for me and she obtained my PhD degree by showing that heart infiltrating T cells of rheumatic heart disease patients were able to recognize both streptococcal M protein peptides from N-terminal region and myocardium/valvular proteins. The results allowed us to show the occurance of CD4+ T cell molecular mimicry between beta hemolytic streptococci and heart tissue proteins in RHD. It was the first study demonstrating the presence of T cells cross reactive with bacterial products and human tissue proteins in an established post-infectious autoimmune disease. Once established some immunodominant crossreactive epitopes, she searched protective regions of the M protein and defined some C-terminal epitopes candidate to develop a safe and effective multivalent subunit vaccine against the group A streptococci, taking into account all the knowledge acquired on the autoimmunity mechanism involved in RF. She published 78 articles in journals such as Circulation, American J. Patahology, J. of Immunology, Internatinal Immunology, J. of Autoimmunity, J. of Biological Chemistry, Vaccine and 50 book chapters (30 international) and had 5 scientific works awarded. International Patents on vaccine anti-S. pyogenes.

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