PHAGE DISPLAY AND IMMUNE SYSTEM: IDENTIFICATION OF MOLECULAR TARGETS WITH DIAGNOSTIC AND THERAPEUTIC PROPERTIES IN IMMUNOLOGICAL DISORDERS

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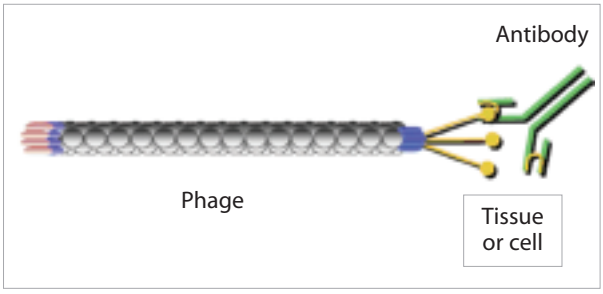
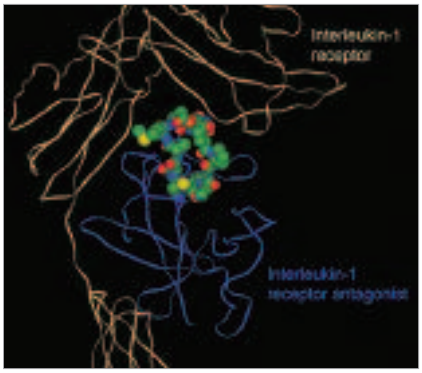


The different panning strategies used in the project: phage libraries used to select for antibodies or molecules on cell or tissue surface

Peptide phage display is a powerful tool that utilizes bacteriophages to screen cells, tissues or organs in search of receptor-pair ligands. Phage display particles are like biological nanoprobes, capable of interacting with the target though small peptides, genetically engineered to be expressed on the virus outer coat. Since the peptide sequence information is coded by bacteriophage genome, a single virus particle bound to a cell or tissue sample can be recovered by bacterial infection, amplified and the peptide identified. Few techniques allow studying molecular interactions of single molecules or cell without previous knowledge of the target. The aim of this project is to establish a web of knowledge and think tank in phage display technology in Brazil. The technique will be employed at full capacity, in different approaches but the main theme will be the immune system. Specifically: identification of epitopes in humoral response (IgG) to Papilomavirus and acute renal vascular rejection (Component A); identification of auto immune CD4+ T cell epitopes involved in the rheumatic fever disease (Component B); inflammation and endothelial cells in the atherosclerotic disease (Component C); B1 lymphocytes and tumor growth (Component O); thymus and regulatory cells development (Component E); study of the structural behavior of selected peptides and the dynamic of interaction with their respective receptors by nuclear magnetic ressonance. Below are the experimental details of each component of the project.

SUMMARY OF RESULTS TO DATE AND PERSPECTIVES

Immune recognition of self and non-self relies on the molecular biodiversity among other factors. Proteins and peptides are important components and orchestrators of this process, helping and guiding the cellular and humoral repertoire of our immunological system to distinguish between self and pathogenic. However, several diseases originate due to an imbalance in this intricate network of immune cells, antibodies and cytokines. Combinatorial technologies, such as phage display, are formidable tools to probe and investigate such disorders. Due to its high throughput and unbiased nature, peptide phage display libraries allow researchers to screen among millions of peptide permutations in order to identify antigens and epitopes involved in health and disease. These results can then be brought to the clinic in the form of new vaccines, antibody therapies or helping in the design of a new generation of safer and more efficient drugs. The aim of our project is to use phage display technology to study disorders of the immune system associated with specific pathogens (Papiloma virus and *S. pyogenes*), allograph rejection (kidney), and the endothelial dysfunction observed in atherosclerotic vessels. We also use phage display to study CD4CD25 regulatory T cells, important controllers of the immune system and whose function is affected in several diseases. Our goal is to understand the molecular mechanisms for the progression of these disorders, hoping that our results will, in time, translate into new and better therapeutic agents for the treatment of such disorders. In order to achieve our goal, the following studies are currently being conducted:



Peptides identified by phage display suggest a prominent role for interleukin-1 and family members in the pathogenesis of rheumatic fever

- Identification of antibody epitopes by phage display: Peptide sequences recognized by antibodies of the serum of HPV infected patients;
- Identification of antigens involved in acute vascular kidney rejection;
- Identification of T cell epitopes by phage display: Rheumatic fever as model;
- Identification of peptide ligands of activated endothelium: Atherosclerotic disease as a model;
- Identification of surface markers of B1 lymphocytes and melanoma cells: Immunomodulation of neoplasia by B1 lymphocytes, and
- Identification of markers of thymus and CD4+/CD25+regulatory cells in human thymus: Search for relevant molecules in maturation and activity of CD4+/CD25+regulatory cells.

MAIN PUBLICATIONS

All experiments have been concluded, with resulting manuscripts due for publication this year.

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