

## **Identification of antigenic determinants in WM**

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**INTRODUCTION:** There is a growing body of data supporting the role of antigenic stimulation and inflammation in the development of B lymphoproliferative disorders. According to this hypothesis, chronic antigenic stimulation contributes to but is not sufficient for malignant transformation. This hypothesis suggests that the inciting inflammatory agent might be the paraprotein target.

**BACKGROUND:** There is scant information on paraprotein targets. The literature includes case reports of paraproteins immunoreactive with HIV, cytomegalovirus, or streptolysin-O. Paraproteins have also been associated with immunoreactivity to bacterial carbohydrates and autoimmunity associated antigens. Many of these studies are complicated by the fact that whole sera were tested, without separating the paraproteins from other (polyclonal) immunoglobulins. It is not clear if the described pattern of immunoreactivity is actually due to the paraprotein.

**RESULTS:** We developed a method to identify the cognate antigens to which paraproteins bind. Using random combinatorial peptide libraries, we first reconstruct the epitope to which the paraprotein binds. Specific experimental methods (to be described) are required for identifying accurate peptide epitopes. We then search the protein database for close matches. We empirically identified the bioinformatic requirements for an informative database search. Analysis of myeloma paraproteins identified the target from the first group of patients as human cytomegalovirus (HCMV). Immunoreactivity to HCMV co-migrated with the paraprotein in antigen affinity blots, linking the binding activity to the paraprotein. In several instances, more than one paraprotein in the same patient was immunoreactive with the same virus, albeit to different viral proteins. Preliminary data indicate that the *Herpesviridae*, including HCMV, are common targets of myeloma paraproteins. In collaboration with Dr. S. Treon, we have recently applied these methods to the analysis of paraproteins in Waldenstrom's macroglobulinemia. Our preliminary findings reveal a different pattern of immunoreactivity.

**CONCLUSION:** Our findings are in agreement with published experimental data, suggesting that gammopathies may be associated with chronic exposure to an inflammatory stimulus. The *Herpesviridae* fit this profile, as they are latent viruses, capable of life-long reactivation and shedding. Our preliminary data with Waldenstrom's macroglobulinemia paraproteins will be described.