

## [Abstract 08]

### **B-LYMPHOCYTE STIMULATOR PROTEIN (BLYS) IS EXPRESSED BY BONE MARROW MAST AND LYMPHOPLASMACYTIC CELLS IN WALDENSTROM'S MACROGLOBULINEMIA, AND PROVIDES SIGNALING FOR GROWTH, SURVIVAL AND IGM SECRETION.**

**Ditzel Santos D, Tournilhac O, Xu Lian, Hatjiharrisi E, Hunter Z, Branagan AR, Manning R, Anderson KC, Grewal I, Treon SP. Bing Program for Waldenstrom's Macroglobulinemia, Jerome Lipper Multiple Myeloma Center, Dana Farber Cancer Institute, and Harvard Medical School and Genentech, Inc., S. San Francisco CA, USA.**

B-lymphocyte stimulator protein (BLYS) is a member of the tumor necrosis family of ligands which is expressed by monocytes and neutrophils and regulates B-cell homeostasis and immunoglobulin production through its receptors BCMA, TACI and BAFF-R. In recent studies, we have shown that bone marrow (BM) mast cells (MC) are increased in WM patients and support tumor cell growth. We therefore evaluated sorted WM BM MC (CD117<sup>+</sup>FcεRI<sup>+</sup>) and lymphoplasmacytic cells (LPC) for BLYS, BCMA, TACI AND BAFF-R by multicolor flow cytometry and RT-PCR. Results were as follows:

|               | Flow Cytometry         |                       | RT-PCR                  |                         |
|---------------|------------------------|-----------------------|-------------------------|-------------------------|
|               | WM                     | MC                    | WM                      | MC                      |
| <b>BLYS</b>   | <b>5/7<br/>(71%)</b>   | <b>8/15<br/>(53%)</b> | <b>25/26<br/>(96%)</b>  | <b>20/23<br/>(86%)</b>  |
| <b>BCMA</b>   | <b>4/6<br/>(66%)</b>   | <b>7/8<br/>(87%)</b>  | <b>20/20<br/>(100%)</b> | <b>8/13<br/>(61%)</b>   |
| <b>TACI</b>   | <b>15/16<br/>(93%)</b> | <b>7/7<br/>(100%)</b> | <b>20/20<br/>(100%)</b> | <b>12/15<br/>(80%)</b>  |
| <b>BAFF-R</b> | <b>11/16<br/>(68%)</b> | <b>5/8<br/>(62%)</b>  | <b>20/20<br/>(100%)</b> | <b>11/11<br/>(100%)</b> |

By RT-PCR, BLYS was detected in MC from 5/7 normal donors. However, in contrast to MC from WM patients, BLYS was not expressed on the cell surface of MC from 7 normal donors using multicolor flow cytometry ( $p=0.02$ ). Importantly, recombinant human BLYS stimulated proliferation, enhanced survival and/or induced IgM secretion of WM LPC at concentrations of up to 1  $\mu\text{g/mL}$ . Paradoxically, at higher concentrations (5, 10  $\mu\text{g/mL}$ ) BLYS induced apoptosis of WM LPC. These studies therefore demonstrate that MC and LPC in WM patients express BLYS and BLYS receptors, and provide the framework for specific targeting of MC-LPC interactions in WM.