

## [Abstract 10]

### **SINGLE NUCLEOTIDE POLYMORPHISM OF THE HYALURONAN SYNTHASE 1 GENE-A POTENTIAL PREDISPOSING FACTOR FOR WALDENSTROM'S MACROGLOBULINEMIA.**

**Sophia Adamia, Tony Reiman, Steven P. Treon, Michael J. Mant, Andrew R. Belch and Linda M. Pilarski. Department of Oncology, University of Alberta and Cross Cancer Institute, Edmonton, AB, CANADA.**

Hyaluronan synthase 1, maps to chromosome location 19q13.4 synthesizes an extracellular matrix (ECM) molecule, hyaluronan (HA), and plays a significant role in malignancy. Recently, up-regulation of HAS1 transcription by oncogenic malignant transformation has been reported (Itano et al. 2004). Furthermore, in MM patients we have detected up-regulation of HAS1 transcripts and identified aberrant splice variants of this gene, HAS1Va, Vb, and Vc (Adamia et al). The statistical analysis of 58 MM showed that expression of HAS1Vb either alone or in combination with HAS1 and variants strongly correlate with poor survival (P=0.001). Despite recent progress in the study of WM, little is known about the biology underlying pathogenesis of this disease. Since WM shares clinical and pathological similarities with MM, we investigated the expression of HAS1 and HAS1 variants in WM patients. Our study demonstrated that 76-97% of CD20+ IgM+ cells obtained from the BM aspirates of patients with WM express aberrantly spliced variants of HAS1, HAS1Va and HAS1Vb, either alone or in concert with HAS1 and variants. To understand the mechanism underlying the aberrant splicing of HAS1 gene, which appears to be a characteristic of malignant clones of WM, as a first step we decided to identify the mutations promoting abnormal splicing of HAS1 potentially through the activation of cryptic, donor and acceptor, splice sites of the gene. Using an allelic discrimination genotyping assay we measured the frequency of polymorphism detected on HAS1 gene in 27 WM patients and 10 healthy donors. Our results suggest that in healthy individuals, the frequency of each of the two alleles was 50%, most likely as a result of stabilizing selection. Due to a probable heterozygote advantage, the majority of healthy donors are heterozygous. In contrast 89% of analyzed WM patients are homozygous. The expression analysis of HAS1 and variants in the same group of individuals demonstrated that patients who are heterozygous neither express aberrantly splice variants of HAS1 nor HAS1 full length. Similar results were obtained when healthy individuals were screened for the expression of HAS1 and its variants. However, WM patients expressing homozygosity expressed HAS1 and HAS1 variants in diverse combination. Thus, HAS1 homozygosity correlates with the expression of aberrant splice variants of HAS1 and may regulate aberrant splicing events, such as exon skipping and/or activation of new cryptic splice site, that give rise HAS1 splice variants since the polymorphism on HAS1 is located in the vicinity of splicing signals of the gene. Based on the results obtained thus far, we speculate that homozygosity for HAS1 allele predisposes individuals to WM. Studies of larger numbers of patients and healthy donors are ongoing to evaluate the prognostic significance of this finding.