DISCUSSION matching aims

1. ATAC IN PSA SAMPLES AND LIMITATIONS

* 1 paragraph summarising the ATAC approach and looking at the site of inflammation
* 1 paragraph talking about the highlights of each cell type and some differences found across them
* 1 paragraph of limitations in terms of the technique, quality and also linking gene to region
* 1 paragraph concluding why monocytes looked particularly interesting due to proportion of DARs over total

-eRNA enrichment in NK for basophils may be due to more noisiness in the data, previously commented but it also showed specificity for the eRNA set in Nk cells

Finding for the IL7R, mention SNP from the paper (Ben eQTL SNP) and maybe the conditions for stimulation if not found changes in accessible chromatin

-mention some of the chemokines identified in the different cell types

-wnt signalling in CD8 interesting from the point of view of bone regeneration but in this case may be interesting because mCD8 are more proliferative than the ones found in the synovium http://www.jimmunol.org/content/193/6/2784.long

-nk cytotoxic in PB compared to tissue SF due to CD56 dim in SF: According to FACS analysis, the proportion of NK CD56$\textsuperscript{bright}$ was greater in PB compared to SF in this sample cohort (data not shown). This is consistent with the observed enrichment for NK cytotoxicity in PB open DARs and previous studies demonstrating that CD56$\textsuperscript{bright}$ NK cells are preferentially cytokine producers compared to the tissue resident ones.

1. BIOLOGICAL RELEVANCE OF THE MULTI-OMICS APPROACH
2. Not such as study appart from the one in Dolcino et al looking at specific cell populations at the different levels
   * Summary of the qPCR array observation and cd14 and cd8 seemed the ones with the greatest number of consistent changes in this study
   * Summary pathway enrichment for those genes and the link to network analysis:
     + Cross talk between pathways and relevance in disease of the three in CD14 monocytes and also Ca+linkto ATAc pathways and also NFkB nearby DAR
     + IL10 in mCD4: hypothesis about IL10 signalling and enhanced expansion of Tregs in SF. There is a DAR proximal to IL10
   * the ability to compare to healthy control and limitation of not having healthy synovial fluid (acellular) to fully understand which genes are tissue specific only
     + Mention commonalities with Dolcino analysis about top genes
     + hypoxia for GPR proteins observed in PB in CD8 in ATAC
     + also in qPCR vs PB and link to the GPR68 in CD4 which makes sense from the hypoxia point of view
   * 1 paragraph describing integration with limited success. Include the results from the overlap with bulk pathway analysis and context to ATAC:
   * \*some of them included eRNA transcribed regions in that cell type by CAGE
     + Only significant enrichment for CD14
     + IFN1 and IL7R example: link to Ben’s SNP and relevance of this receptor in monocytes
   * This links to the interest of further exploring monocytes at the scRNA seq level and try to find interesting subpopulations, as previously done by our paper in review
   * CCL2 example for one chemokine with consistent data at all the levels (synovial fluid measurements) not sure this is include in the cytof panel\*\*
   * 1 paragraph about the interest of further looking at integration with the sc results in monocytes
   * What proteomics says about those: number of clusters in cytof and cytokine expression in general
3. Limitations of the multi-omics approach

* Limitations of single cell in detection of low expressed genes compared to qpcr
* Aadvantages of identifying small populations with high expression of one gene and how they can contribute to the overall expression
* Difficulty to define cluster
* Limitations of integrating everything CCA
* Lacking controls
* Limited numbers

1. Integration of fine-mapping and patients derived epigenetic data
2. Future work
   * lncRNAs will be of interest at the cell type specific level-refer paper