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~~

~~-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 insighths in the integration of chromatin accessibility, gene expression and proteomics data in PsA (allows subsections)
   * ~~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~~
   * ~~Dolcino commonalities~~
   * ~~1 paragraph describing integration with limited success. Include the results from the overlap with bulk pathway analysis and context to ATAC for particular set of immune relevant genes(not mention enrichment yet)~~
   * ~~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~~
     + ~~Monocytes TLR is upregulated in SF not in CD4 and cD8 and try to find evidence in literature to link to TNF upregulation in CD8 through other means~~
     + ~~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~~ 
     + ~~Footprint systemic genes examples maybe~~
     + ~~also in qPCR vs PB and link to the GPR68 in CD4 which makes sense from the hypoxia point of view(%\textit{GPR68} is a G protein-coupled receptor, expressed in T cells, amongst other cells, that undergoes activation through pH acidification, characteristic of synovial tissues under inflammation \parencite{Biniecka2016}. \textit{GPR68} activation leads to an increase of Ca$^2$$^+$ levels and subsequent activation of immune-related pathways \parencite{Saxena2011}.)~~
     + ~~AREG biology: %\textit{AREG} deficiency in mouse models have shown an impaired immunosupressive response by Treg cells \parencite{Zaiss2013}, which could be contributing to the exacerbated immune response in the synovium.~~

~~•Come back to integration significant enrichment and specific examples to lead to single cell~~

* + - ~~FN1 (only synovium) and IL7R (down in PB vs controls) example: link to Ben’s SNP and relevance of this receptor in monocytes.~~
      * ~~Link to network analysis This network analysis also highlighted relationship between \textit{IL7R} and \textit{IL2RG} coding for the two chains of the IL-7R. %Interestingly, these two nodes were only significantly up-regulated in SF CD14$^+$ monocytes when compared to PB, supporting the novel cell and context specific role of IL-7R and IL-7R polymorphism under inflammatory conditions in CD14$^+$ monocytes\parencite{Al-Mossawi2018}. 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~~
  + ~~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~~
  + Just a note of ATAC integration again but more general, rather than specific together with qpcr expression
    - %Regarding the low number of qPCR DEGs between SF and PB in total CD14$^+$ monocytes reproduced by the scRNA-seq in any of the two main clusters identified could be explained by the differences in the cell sorting (FACS versus \textit{in silico} expression markers), the low number of replicates for each assay as well as different sensitivity of the two technologies.
    - The limited overlap between qPCR and scRNA-seq DEGs could also partly explain the absence of overlap between enriched pathways across the two gene expression analysis.
  + ~~Clusters of monocytes by cytof and general cytokine expression in general(maybe move after CCL2 example)~~
  + CCL2 example for one chemokine with consistent data at all the levels (synovial fluid measurements) not sure this is include in the cytof panel\*\*
  + Mention this is only the beginning of the integration

1. Challenges and limitations of the multi-omics approach
   * Not all the data is paired
   * and limitation of not having healthy synovial fluid (acellular) to fully understand which genes are tissue specific only

* 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
   * Increased sample size
   * Paired data from all the patients
   * RNAseq bulk
   * lncRNAs will be of interest at the cell type specific level-refer paper
   * scATAC
   * development of methods for integration