Unveiling Synergistic Drug Combinations for Immune-Mediated Inflammatory Diseases: Insights from the DoCTIS Consortium Using Systems Biology Approaches

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Introduction

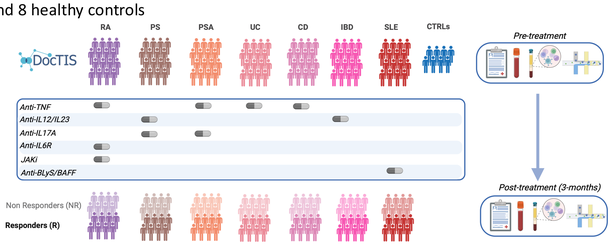
Targeted therapies have failed to provide sustained disease remission in most patients suffering from immune-mediated inflammatory diseases (IMIDs). Combining existing drugs could overcome this therapeutic ceiling. Deeply characterizing patients who show a very favorable initial response against those patients who do not show any sign of clinical improvement, could provide essential clues on the most potent drug combinations to be used in clinical practice.

Objective

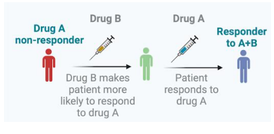
To identify clinically relevant effective drug combinations in immune-mediated inflammatory diseases through systems biology approaches in patient transcriptomic data

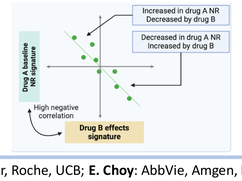
Methods

1. **Molecular characterization of 176 IMID patients that are responders or non-responders to currently approved biological monotherapies.** Generated genotyping, whole blood RNAseq and PBMCs single-cell RNAseq from each patient at two timepoints for 11 drug-IMID cohorts and 8 healthy controls



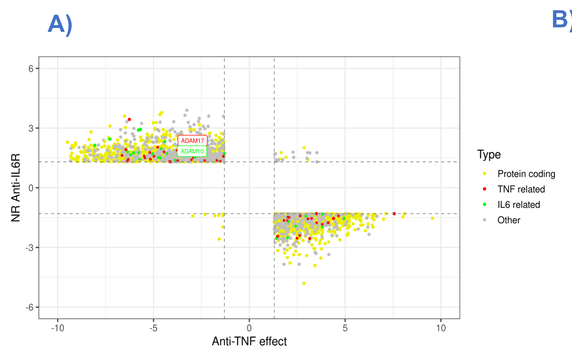
2. **Obtained treatment non-response and treatment effects signatures from each cohort.** Non-response signature: signed logP-value of the DGE analyses between responders and non-responders, sign positive if up-regulated in non-responders. Treatment effects signature: signed logP-value of the DGE analyses between post and pre-treatment, sign positive if up-regulated in post-treatment
3. **Drug combination prioritization based on anti-correlation between "omic" signatures.** Combinations evaluated based on several criteria such as the mitigation of non-response signature (MNRS)





Results

Anti-TNF reverses the non-response signature of Anti-IL6R in RA patients and Anti-IL6R reverses the non-response signature of Anti-TNF, as shown by the highly negative correlation between the non-response and longitudinal effects transcriptomic signatures



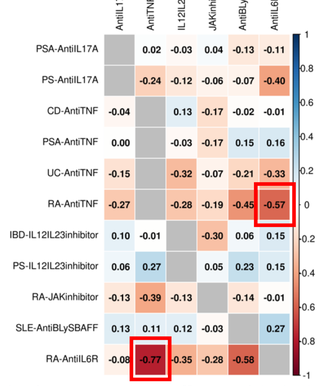


Figure 1: Gene-level drug complementarity evaluation. A) A highly negative correlation between Anti-TNF effects and Anti-IL6R non-response signatures (signed log-Pvalues) in RA patients indicate potential complementarity of the effects of these drugs. **B)** MNRS analysis summary. The numbers represent average coefficient across variations of the correlation analysis between non-response (rows) and drug effects (columns) signatures. Highly negative correlations represent robustness with respect to different assumptions.

Analysis of the differential expression at the pathway levels also show a highly negative correlation between the non-response and drug effects signatures.

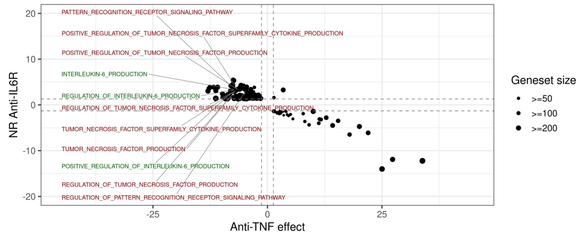


Figure 2. Drug complementarity at the pathway level of the AntiTNF-AntiIL6R combination in RA. Pathways related to TNF (red) and IL6 (green) are upregulated in Anti-IL6R non-responders and down-regulated by Anti-TNF. Gene sets: GO_BP. Enrichment method: fgsea

PBMCs from RA patients were profiled with scRNA-seq, and more than 35 different cell types were annotated by combining automated methods and manual curation of key markers

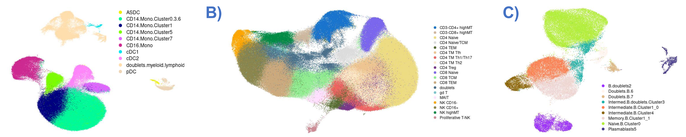


Figure 3. Single-cell RNAseq of RA patients analyzed by immune compartment. UMAP of A) Myeloid cells, B) T and NK cells, C) B cells.

A significant negative correlation between the transcriptional changes associated to antiIL6R NR signature and those associated to antiTNF longitudinal effect was observed in most cell types from the myeloid compartment.

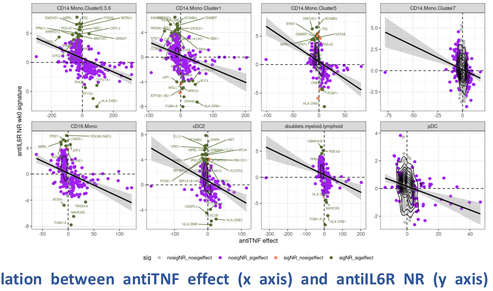


Figure 4. Correlation between antiTNF effect (x axis) and antiIL6R NR (y axis) signatures in myeloid cells. DEGs with pval adjusted < 0.05 in both signatures are in green.

Conclusions

- We have identified clinically relevant effective drug combinations in immune-mediated inflammatory diseases through a systematic computational approach in patient blood transcriptomic data
- This study provides support for the combination of Anti-TNF and Anti-IL6R therapies in RA patients as a means to significantly improve efficacy and achieve sustained disease remission
- ScRNA-Seq indicates that CD14+ monocytes are the main circulating cell type participating in the response to both drugs

Disclosures: S. Castañeda: Bristol-Myers Squibb(BMS), Eli Lilly, Merck/MSD, Pfizer, Roche, UCB; **E. Choy**: AbbVie, Amgen, Bio-Cancer, Biocon, Biogen, Bristol-Myers Squibb(BMS), Chugai, Eli Lilly, Fresenius Kabi, Galapagos, Gilead, Janssen, Novartis, Pfizer, Regeneron, Roche, RPharm, Sanofi, UCB Pharma; **H. Heyn**: Mirxes, Moderna, Nanostring, Omniscope, Singularity; **Sara Marsal** and **Toni Julià:** IMIDomics**;** The remaining authors declare no conflicts of interest

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