

## Toward Precision Therapy in ANCA-Associated Vasculitides: More Transcriptomic Data is Needed in the Quest for Reliable Biomarkers

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### Editorial

The diagnosis of anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) is often made in a context of emergency, and relies on clinical presentation, positivity of ANCA antibodies and/or histological documentation [1]. The severity of residual organ damage, in particular chronic kidney disease (CKD), depends on the precocity of diagnosis, the efficacy of induction treatment, and on the prevention of AAV relapses [2,3]. Recently, although targeted therapy with rituximab have shown efficacy for the induction [4,5] and maintenance [6] of remission in AAV, residual organ damage and infectious complications are still penalizing patients. The identification of reliable biomarkers could help personalize the level and/or duration of immunosuppression (i.e., precision medicine).

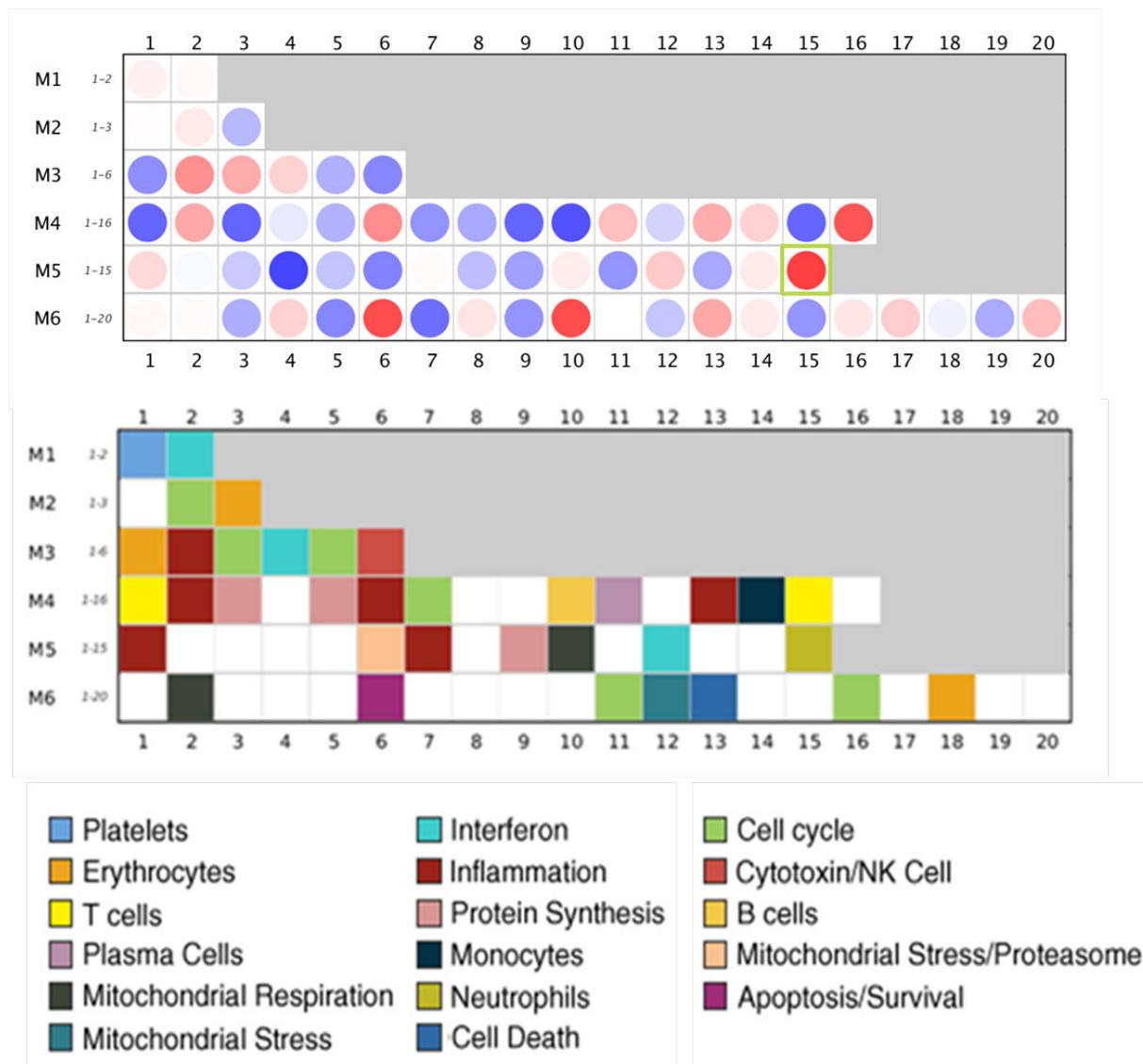
Indeed, type and severity of organ involvement are heterogeneous among patients, and ANCA positivity can be missing in patients with granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA) [7]. During follow-up, an increase in proteinuria or an impairment of renal function can result from chronic kidney disease progression, or from necrotizing pauci-immune crescentic glomerulonephritis, so that chronic renal lesions can be difficult to clinically discriminate from active vasculitis flare [8]. In such setting, renal biopsy is a valuable tool but remains an invasive procedure that cannot be repeated easily [9]. The follow-up of ANCA positivity and of anti-proteinase 3 (PR3) or anti-myeloperoxidase (MPO) antibodies titers is, to date, the most accurate biomarker available to evaluate disease activity and/or predict relapses [9]. Although several studies converge to show that severe flares were very unlikely in patients with negative ANCA [9-11], the clinical utility of ANCA follow-up to predict relapses is still debated [12], and no preemptive increase in immunosuppression is currently recommended in patients showing new ANCA positivity or a rise in anti-PR3/anti-MPO titer [13]. These markers could be more predictive of relapse in patients with renal involvement of AAV (versus non-renal patients) [14], but this needs to be confirmed in validation cohorts.

So, while preventing AAV relapses using the minimally toxic immunosuppressive regimen is the goal of every clinicians taking care of patients with AAV, reliable non-invasive biomarkers are still needed in the quest for precision medicine. Surprisingly, especially compared to other autoimmune systemic diseases, and apart from genome-wide association studies (GWAS) [15], few data on AAV have been published from OMICs approaches. In GEO (<http://www.ncbi.nlm.nih.gov/gds>) or ArrayExpress (<http://www.ebi.ac.uk/arrayexpress/>) repositories, for instance, only few datasets of gene expression profiling of peripheral blood mononuclear cells (PBMC)

[16], sorted lymphocytes [17], or microdissected glomeruli [18] are available in patients with AAV. To date, microarray data interpretation has been conducted with a knowledge-driven approach (Ingenuity Pathway Analysis or Gene Ontology) and has led to the identification of potential candidate biomarkers, namely ficolin-1 [16] and CC chemokine ligand [18]. The transcriptomic signature of purified CD8 T cells has been utilized to predict prognosis of patients with AAV or systemic lupus erythematosus (SLE) [17]. Although a 3 genes signature of CD8 T cells could accurately classify patients between those with good versus bad prognosis, pre-analytic constraint of cell sorting and purification prevented easy and reproducible use of those biomarkers in bedside clinical practice.

On the contrary, whole blood transcriptomic data, obtained from simple venipuncture, combined to data-driven analytic approaches could be of great interest in the identification of new biomarkers in AAV. A data-driven modular approach [19,20] has been used for the analysis of whole blood samples in the context of another systemic autoimmune disease, SLE, and has allowed to define more accurately the interferon signature in SLE [21], and to identify neutrophil signature as a biomarker of renal risk in SLE patients [22]. Such a strong neutrophil signature was also observed in AAV patients (Figure 1, unpublished data), which is not surprising given the central role of neutrophils in AAV pathogenesis [23]. The modular framework [19] has been constructed from a co-clustering algorithm on numerous samples. Modules are completely data-driven (as opposed to knowledge-driven constructed gene ensembles), and have been annotated a posteriori. Interestingly, the “neutrophil” module comprises the genes composing the “neutrophil” signature recently identified by the Immune Tolerance Network Research Group in whole blood of AAV patients as associated with disease activity and response to treatment [24]. The intensity of modular neutrophil signature is highly correlated to the upregulation of few representative genes, which can easily be measured by RT-PCR from whole blood samples as a “neutrophil score”, which makes this translatable to clinical practice (unpublished data).

Overall, we propose that more whole blood transcriptomic data should be generated, made publically available [19,25,26], and analyzed through non-biased data-driven approaches, in different cohorts of patients with AAV from different ethnicities. This could allow the design of new bedside biomarkers to evaluate AAV activity, monitor response to treatment and assess individual risk of relapse at a given time, to reduce both organ damage and immunosuppression toxicity, and finally allow providing precision medicine to patients with AAV.



**Figure 1:** Modular map of whole blood gene expression profile of 10 patients with severe active ANCA-associated vasculitis compared to match healthy controls. Modules up-regulated (in red) in AAV patients include M5.15, the module annotated “neutrophil” in the modular framework.

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