



# Technical Advances in Transcriptional Profiling are Accelerating the Classification of Rheumatoid Arthritis



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**Abbreviations:** RA: Rheumatoid Arthritis; IHC: Immunohistochemistry; SLE: Systemic Lupus Erythematosus; RNA-Seq: RNA Sequencing; NGS: Next-Generation Sequencing

## Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that may affect many, if not all, synovial joints all over the body. RA is extremely prevalent, affecting about 0.7% of adults and over 21 million people worldwide. The mean age of onset of RA is typically between 50 and 60 years. Despite the fact that antibody-based biologic therapeutics, such as anti-TNF, anti-IL6, anti-B-cell and anti-T-cell, have revolutionized the management of RA only about 65-70% of patients respond to any of the currently available biologic treatments [1]. Furthermore, a so-called successful response may equate to only 50% reduction in symptoms and many patients eventually stop responding over time. Consequently, the disease may result in chronic painful deformities with a decrease in life expectancy of approximately 5-10 years. Thus, there is an urgency to find more effective therapies for over 50% of patients with RA [2].

The recognition of immunologically defined disease subsets of RA, using both immunohistochemistry (IHC) and gene expression data from synovial tissues [3,4] and blood [5] has produced an integrative understanding of the pathobiology of RA. Synovial phenotypes in RA have been correlated with response to biologics, with the myeloid (innate immune-mediated) and lymphoid phenotypes (predominantly adaptive immune-mediated) being associated with differential clinical responses; the myeloid subtype responds to anti-TNF and the adaptive subtype responding to anti-IL6R therapy in established RA. The other two less common pathotypes include the stromal and fibroid (pauci-immune), both of which are more resistant to therapy. Our current understanding of how these different synovial RA pathotypes develop remains incomplete [4]. The

development of different RA pathotypes may be linked to an impaired ability of synovial stromal cells to correctly modulate the complex immune cell interactions in the RA synovium.

One major approach that is currently being used to address the unmet need for more effective therapies for RA involves the search for novel biomarkers to accurately predict therapeutic responses and simultaneously define, at a detailed level, the nature of the molecular networks associated with different subtypes of RA. It is anticipated that this information will clarify the variability in clinical responses to different therapies, thereby enabling the most effective use of existing drugs and speeding the development of novel targeted therapies.

Until relatively recently all attempts to find such transcriptomic predictors of response to biologics have been limited by small sample-size and disease heterogeneity, which has likewise hampered data interpretation. These inherent drawbacks have been addressed by longitudinal studies of bigger patient cohorts, using unbiased analytical approaches that take into account all aspects of the gene expression signature, including disease heterogeneity and clinical covariates, such as smoking and the patient's age (RA is a disease of ageing).

The field of transcriptomic analysis in complex inflammatory and autoimmune disease has recently been given a considerable boost by the publication of a study that reported seven major subtypes of systemic lupus erythematosus (SLE) in a large cohort of paediatric patients [6]. These developments highlight the importance of systematic, unbiased and genome-wide studies capable of delivering personalized immune-monitoring, with associated patient stratification in a range of conditions,

essentially achieved by revealing the broad range of molecular networks that underlie disease pathogenesis and progression.

### Choice of Transcriptomics Methodologies

The two most useful methods for whole transcriptome gene expression profiling are microarray analysis and RNA sequencing (RNA-Seq). Microarray analysis uses microchips containing arrays of probes (short DNA oligonucleotides) that are used to detect and interrogate the expression of thousands of genes at the same time. RNA-Seq technology employs next-generation sequencing (NGS) to quantify the amount of RNA in a biological sample and thereby, analyse dynamic changes of gene expression in the cellular transcriptome. Microarray analysis is a reliable method for gene expression profiling, and is currently more cost effective than RNA-Seq for the interrogation of gene expression in large numbers of samples. However, with further technical advances it is most likely RNA-Seq will eventually displace microarrays for routine analyses, but for the moment these techniques can be complementary to each other [7].

### Bioinformatics And Complex Data Analytics Methods

Bioinformatics research is characterized by complex data analytics methods for large and gradually expanding datasets. A detailed description of the analytics methods currently in use for transcriptomics analyses are outside the scope of this work; suffice to report that the modular analysis approach, pioneered by Chaussabel et al. in 2008 [8], is widely used for the study of immune dysregulation in a number of conditions, as shown by the aforementioned study of paediatric patients with SLE [6].

In summary, carefully designed and sufficiently powered transcriptomics studies have the potential to identify biomarkers and key molecular networks that may lead to novel molecular

targets for clinical trials, thus enabling the most effective use of existing therapies and development of novel drugs to treat these debilitating conditions. Any research that may lead to reduced suffering for patients and less money spent by the health services is a worthwhile exercise indeed.

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### References

1. Smolen JS, Aletaha D, McInnes IB (2016) Rheumatoid arthritis. *Lancet* 388(10055): 2023-2038.
2. Gul HL, Ferreira JF, Emery P (2015) Remission in rheumatoid arthritis: is it all the same? *Expert Rev Clin Pharmacol* 8(5): 575-586.
3. Dennis G, Holweg CT, Kummerfeld SK, Choy DF, Setiadi AF, et al. (2014) Synovial phenotypes in rheumatoid arthritis correlate with response to biologic therapeutics. *Arthritis Res Ther* 16(2): R90.
4. Pitzalis C, Kelly S, Humby F (2013) New learnings on the pathophysiology of RA from synovial biopsies. *Curr Opin Rheum* 25(3): 334-344.
5. Oswald M, Curran ME, Lamberth SL, Townsend RM, Hamilton JD, et al. (2015) Modular analysis of peripheral blood gene expression in rheumatoid arthritis captures reproducible gene expression changes in tumor necrosis factor responders. *Arthritis Rheumatol* 67(2): 344-351.
6. Banchereau R, Hong S, Cantarel B, Baldwin N, Baisch J (2016) Personalized immunomonitoring uncovers molecular networks that stratify lupus patients. *Cell* 165(3): 551-565.
7. Mantione KJ, Kream RM, Kuzelova H, Ptacek R, Raboch J, et al. (2014) Comparing Bioinformatic Gene Expression Profiling Methods: Microarray and RNA-Seq. *Med Sci Monit Basic Res* 20: 138-142.
8. Chaussabel D, Quinn C, Shen J, Patel P, Glaser C, et al. (2008) A modular analysis framework for blood genomics studies: application to systemic lupus erythematosus. *Immunity* 29(1): 150-164.



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