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**PERIPHERAL BLOOD CD4 T CELL GENE EXPRESSION
PROFILES AS PREDICTIVE BIOMARKERS IN EARLY
ARTHRITIS**

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Background/Aim CD4 T cells are thought to play a crucial role in the pathogenesis of rheumatoid arthritis (RA). Diagnosing the condition, particularly among patients who are seronegative for anticyclic citrullinated peptide (ACPA) antibodies, remains challenging in the clinic. The authors have explored the peripheral blood CD4 T cell transcriptome of early arthritis clinic attendees, looking for biomarkers of potential diagnostic utility.

Methods Total RNA from highly purified peripheral blood CD4 T cells of consenting patients with early arthritis naive to immunomodulatory therapies was expeditiously extracted and stored. Global transcription profiling of 168 samples, retrospectively selected based on definitive diagnosis at >1 year follow-up, was carried out using microarray technology. Data were normalised and corrected for batch effects. Transcripts differentially expressed at baseline between RA and 'non-RA' outcome groups were identified (t test) and confirmed using qRT-PCR (TaqMan low density arrays). From their pattern of expression among a 'training' subset of the data (representing 111 patients with clear diagnoses at inception), these putative biomarker transcripts were subjected to machine-learning approaches (receiver operator characteristic curves, support vector machines) to predict clinical outcome in a 'validation' subset representing 57 patients who presented with undifferentiated arthritis (UA). Their sensitivity and specificity as diagnostic tools could thereby be estimated.

Results A list of 25 transcripts identified from microarray analysis was confirmed on qRT-PCR to be differentially expressed (>1.2-fold change) between patients with early arthritis which evolves into RA and those who develop alternative arthritides (multiple test-corrected $p < 0.05$). The discriminatory utility of this early RA 'signature' was promising among the 'training' cohort (area under ROC curve=0.84), and a support vector machine derived from expression profiles in the same dataset was able to predict RA versus an alternative diagnosis in the UA 'validation' cohort with 75% accuracy. Since the ACPA-positive status of 11/12 patients with UA correctly predicted RA, the 'signature' was tested among ACPA-negative RA patients only ($n=5$) and its accuracy improved slightly (78%), with sensitivity, specificity and positive likelihood ratios of 83, 76 and 3.5, respectively. Functional analyses of these and additional differentially transcribed genes are underway in the hope of gaining new insight into the pathophysiology of early RA at the level of the CD4 T cell.

Conclusion High throughput expression profiling of peripheral blood in early arthritis cohorts may ultimately yield diagnostic and prognostic tools of clinical value and point to novel therapeutic targets for RA.