Nature Reviews Immunology | AOP, published online 25 September 2015; doi:10.1038/nri3913

Journal club

A FIRST LOOK AT T_H CELL TRANSCRIPTOMES

For immunology trainees coming into the business, it might be hard to conceive of a time when the complete genomes of model organisms were not available as tools that can be readily accessed on mobile devices. Yes, there was science before the Immunological Genome Project (ImmGen) app, and the study published in 2000 by Rogge *et al.* provided a first glimpse of the transcriptomes of T helper (T_H) cells.

The explosive rate of discovery of cytokines in the late 1980s and 1990s raised obvious questions regarding the molecular basis of their actions. We and many others were interested in the effects of cytokines such as interleukin-4 (IL-4) and IL-12, which polarize T_H2 cell and T_H1 cell differentiation, respectively. Linking receptor activation by these cytokines to the phosphorylation and nuclear translocation of the transcription factors STAT6 and STAT4, respectively, was an exciting advance that helped to explain how genomic targets could be modulated by these cytokines (reviewed in Leonard and O'Shea, 1998). However, it was not obvious what it really meant to be a T_H1 cell or a T_H2 cell and how instructive cytokines drive the differentiation process.

> "there was science before the Immunological Genome Project (ImmGen) app"

The idea that gene induction could be measured quantitatively by expression profiling and the measurement of transcriptomes emerged in the mid-1990s (reviewed by Staudt and Brown, 2000). Using microarray technology, changes in the expression levels of genes in response to lymphocyte activation could now be determined. This seemed incredible on so many levels. Could we really reliably measure changes in the expression of thousands of genes? Genomic views of the immune system began to emerge. In this context, the paper by Rogge *et al.* was a real eye-opener. We believe that this was the first study to compare the transcriptomes of human T_H1 cells and T_H2 cells, using oligonucleotide arrays that covered 6,000 genes. In this study, the authors identified more than 200 differentially expressed genes, including those encoding cytokines, cytokine receptors, transcription factors, signalling molecules and metabolic factors: 'T_H-ness' was far more than just cytokines!

With the advent of next-generation sequencing in 2007 and attendant technologies such as ChIP–seq, RNA-seq and ATAC-seq, it now seems obvious that the actions of IL-12 and IL-4 can be deciphered by studying the transcriptomic and epigenomic effects of STAT4 and STAT6. Nonetheless, to this day, we enjoy revisiting this landmark paper by Rogge *et al*; the differentially expressed genes that they identified remain surprisingly provocative and worthy of consideration.

John O'Shea
National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, Maryland 20892, USA.
e-mail: John.Oshea@nih.gov

The author declares no competing interests.

ORIGINAL RESEARCH PAPER Rogge, L. *et al.* Transcript imaging of the development of human T helper cells using oligonucleotide arrays. *Nat. Genet.* **25**, 96–101 (2000)
FURTHER READING Leonard, W. J. & O'Shea, J. J. Jaks and STATs: biological implications. *Annu. Rev. Immunol.* **16**, 293–322 (1998) | Staudt, L. M. & Brown, P. O. Genomic views of the immune system. *Annu. Rev. Immunol.* **18**, 829–859 (2000)