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## The World of Th1/Th2 Subsets: First Proof

Jerry R. McGhee<sup>1</sup>



This paper (1), and those that followed by this group over the next several years, has had a significant impact on the field of immunology. This first paper in the series is remarkable in its own right, and you will no doubt enjoy reading it. My goal in this brief introduction is to set the stage for this reading and point out special features that placed this work well above what had come before. Of course, this was the initial proof at a clonal level that CD4<sup>+</sup> Th cells could be divided into two broad classes (or types) based strictly upon the produced pattern of cytokines (which were called lymphokines in 1986). This paper was cited a total of 3862 times when I last checked and it is truly a “citation classic.” It should also be pointed out that this work appeared before immunologists had cloned and characterized the TCRs, both  $\alpha\beta$  and  $\gamma\delta$ , or had described the TCR-associated proteins of the CD3 complex. Cellular immunologists (as those in this area were called in 1986) did have the surface markers Ly-1 and Ly-2, and the mAb GK1.5, which recognizes L3T4 or CD4. All Th cell clones in this study were CD4<sup>+</sup> (and we now know they were  $\alpha\beta$  TCR<sup>+</sup>) and Ly-2<sup>-</sup> (which essentially means they were CD8<sup>-</sup> (i.e., not CTLs)).

Several groups had investigated Th cells, which could be divided into two (or more) subgroups (see Refs. 1–6 in the Mosmann et al. classic paper). These studies had used expression of MHC class II, binding to nylon wool, or limiting dilution analysis to reach the conclusion of two or more subsets. However, all of these studies used Ag-specific but “polyclonal” Th cell populations, and thus could not prove the existence of Th1 and Th2 subsets. Of course, we now know that effector CD4<sup>+</sup> Th cells come in two broad classes—Th1- and Th2-type, as they were first named in this classic paper. The CD4<sup>+</sup> Th1-type cells produce IFN- $\gamma$ , IL-2, and other cytokines for control of cell-mediated immunity (CMI). The Th2 cell subset produces IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13 for mediation of Ab responses.

To fully appreciate this Mosmann et al. classic, we should step back in time to recognize the unique methods and labor-intensive work required for the conclusions drawn from this paper. The conclusion that separate CD4<sup>+</sup> Th1 and Th2 cells exist is now obvious to all who work in either experimental or human T cell systems. Today, we have the full benefit of multiple mAbs to each cytokine as well as cDNAs for analysis at both mRNA and protein levels. However, it should be appreciated that the authors of this paper only had available mAbs to

IL-2, which they had made themselves! Both Th1-type cytokines IL-2 and IFN- $\gamma$  and the cytokines produced by both Th1 and Th2 cells, i.e., IL-3 and GM-CSF, were assayed by use of cell lines. Furthermore, no Th2-type cytokines had yet been cloned including the key cytokine IL-4 (which now defines the Th2 cell subset), and all of the cytokine activity was assessed through use of cell lines. In 1986, it was just becoming clear that B cell-stimulating factor-1 (BSF-1) was the same as mast cell growth factor 2 (MCGF2; note MCGF1 is IL-3) and T cell growth factor 2 (TCGF2). As it would later be shown, the cytokines IL-4, IL-5, IL-6, and IL-10 all affect B cell growth and its differentiation into plasma cells. Remarkably, these investigators sorted this out without a single separated or well-characterized Th2-type cytokine. One should ask, “How did they do this?” First, most of us who visited the DNAX Research Institute of Molecular and Cellular Biology in Palo Alto, CA, at the time heard firsthand from Tim Mosmann and Bob Coffman these exciting results. Dr. Mosmann had earlier published the MTT colorimetric dye assay, which allowed these immunologists to quickly assess T cell proliferation (see their Ref. 15). They benefited from cDNA for IL-2, IL-3, and GM-CSF, which allowed transfection of COS cells for production of these cytokines in purified form for their biologic assays. Despite this help, it was necessary for the authors to establish over 50 different Ag-specific CD4<sup>+</sup> T cell clones. They subdivided these established clones into Th1 or Th2 through assessment of seven different cytokine activities!

I will not provide details of their work but will point out key features for you to discover. A major benefit was the finding that certain cell lines responded “predominantly” to a single cytokine, which they termed “dominant assays.” For example, the HT2 mouse T cell line responds well to IL-2; however, as they showed in this paper, it also responds to BSF-1 (or IL-4). We now know this was due to the expression of both IL-2 and IL-4 receptors. Please note that these two cytokines share the  $\gamma$ -chain receptor. Please also appreciate that it was necessary for the authors to produce the anti-IL-2 mAbs to show that the Th2 cells producing BSF-1 (or IL-4) could be assayed in the HT2 system in the presence of excess mAbs to IL-2. Through these experiments (see Figs. 1 and 2 and Table I in their paper), they noted that Th1 cells produced IL-2 (but not BSF-1), while Th2 cells produced BSF-1 (IL-4), but not IL-2.

Another important observation was that Th1 or Th2 clones, which were Ag specific, gave the same Th1 or Th2 profile after activation with the polyclonal T cell activator Con A. This proved that the individual T cell clones were indeed clonal in nature. This had hampered previous work suggesting two (or even more) T cell subsets. None of these earlier studies had used

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clonal T cell populations and thus did not definitively prove the existence of two separate T cell subsets.

I really like the *Discussion*, which slowly builds upon the data presented. In this, the authors point out that two Th cell subsets exist based upon: 1) lymphokine (cytokine) bioactivities, 2) Th cell function, and 3) biosynthetic labeling. We still perform 1) and 2) in our studies today. However the availability of multiple mAbs to individual cytokines (many of which were produced by these authors themselves) allow the use of sensitive ELISAs for individual cytokine analysis, and it is no longer necessary to perform biosynthetic labeling to differentiate cytokines. As you will no doubt see from reading this paper, the authors' conclusions that Th1 cells produce IL-2, IL-3, and IFN- $\gamma$  were based upon excellent bioassays coupled with copious growth by robust CD4<sup>+</sup> Th1 cells producing relatively large quantities of these three cytokines. What is remarkable is that the conclusions were reached that Th2 cells produce BSF-1 (IL-4) and

other unique cytokines. These Th2 cells is notoriously more difficult to grow clonally. They overcame this difficulty by meticulous work and clever use of "dominant" cell lines for bioassays. In a series of later papers, these authors went on to show that Th2 cells produce IL-4, IL-5, and IL-10. They also were able to later conclude that CD4<sup>+</sup> Th1-type cells were the major players for host CMI or delayed-type hypersensitivity responses, while CD4<sup>+</sup> Th2-type cells producing cytokines like IL-4, IL-5, and others were the major helpers for B cell and Ab responses.

I hope you enjoy reading this classic paper as much as I always do.

## References

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