

In search of the CTD

If politics is the art of the possible, research is surely the art of the soluble. Both are immensely practical-minded affairs.

Peter B. Medawar,
first published in the *New Statesman*
(London, 19 June 1964).

A central theme of a recent Commentary in *Nature Immunology*¹, “T_H1-T_H2: a Procrustean paradigm,” was that better understanding of autoimmune inflammation would be achieved by evaluating the effects of individual cytokines outside the framework of the ‘classical T_H1-T_H2 dichotomy’ (CTD, for short). The ‘straw man’ of this Commentary is that somebody explicitly stated the CTD as follows: that because two things do exist, only these two things can exist.

Having studied signaling and transcription in T cells, I have often wondered where this CTD hypothesis was so clearly claimed and who is to blame for it. Given the abundance of commentaries critical of the CTD², one might assume that the literature contains a clear CTD claiming obligate twofold dichotomy that explains all immunity, end of story. Commentaries renouncing the CTD paint such a picture, but always lack this mysterious citation, relying instead on phrases like “many immunologists have assumed” or “these assumptions.”¹

But where did “these assumptions” arise and where were they published? The ‘straw man’ here is that many immunologists believe that T cells only show T_H1 or T_H2 cytokine profiles. Another implication of the

Commentary is that some people put credence in the claim that mixed phenotypes cannot exist and that such people do not appreciate the complexity of real responses other than the CTD. But again, I have never found the CTD published anywhere.

It is true that highly polarized responses can occur, and much productive work has arisen from the pursuit of the CTD in the last 15 years. The functions of STATs, NFAT, GATA factors and T-bet in cytokine signaling and transcriptional regulation are good examples. Molecular analysis has often shown great complexity and flexibility in the genetic unfolding of T cell responses, again prompted by a pursuit of the apparently unpublished CTD.

But who foisted the CTD onto unassuming immunologists? Could the original discoverers of distinct CD4 subsets, Tim Mossman and Robert Coffman³ or Charles Janeway and Kim Bottomly⁴, be to blame? I do not believe so, because they are perhaps the least dogmatic of all immunologists in adhering to the CTD. Indeed, Robert Coffman should be credited for first overturning the T_H1-T_H2 paradigm with work on regulatory T cells. Perhaps other contributors, such as Anne O’Garra and colleagues, are at fault? But then again, theirs was the first work to demonstrate the development of T regulatory cells *in vitro*, which clearly is a rejection of the CTD⁵. Other investigators have already evaluated *in vivo* responses to pathogens and concluded that although some show chronic infection and strong polarization,

others do not, again clearly rejecting the CTD. Many molecular biologists have used the CTD as a starting point to understand signaling, transcription and development of T cells, but few among this group whom I know adhere to a strict interpretation of the CTD.

Therefore, I am beginning to wonder if a CTD actually exists at all. If any readers of *Nature Immunology* believe in a CTD, please step forward and be counted. Perhaps the CTD was deliberate ‘disinformation’ to justify analysis of signaling and transcription in T cell development. However, it rather seems that the only clear statement of the CTD is in the very commentaries written to refute it—or could it be a deliberately oversimplified structure that is used as shorthand to describe and test hypotheses.

I do not believe the CTD was ever a theory that anyone actually stated as claimed, except to refute it. So if anyone can find the original CTD, lets once and for all bury this tired ‘straw man’ and let him rest in peace.

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1. Gor, D.O., Rose, N.R. & Greenspan, N.S. *Nat. Immunol.* **4**, 503–505 (2003).
2. Zhai, Y., Ghobrial, R.M., Busuttill, R.W. & Kupiec-Weglinski, J.W. *Crit. Rev. Immunol.* **19**, 155–172 (1999).
3. Mosmann, T.R., Cherwinski, H., Bond, M.W., Giedlin, M.A. & Coffman, R.L. *J. Immunol.* **136**, 2348–2357 (1986).
4. Bottomly, K. *Immunol. Today* **9**, 268–274 (1988).
5. Groux, H. *et al. Nature* **389**, 737–742 (1997).