**Background**

Aberrant regulation of biochemical networks governing the differentiation process of CD4+ T cells into one of their effector cells and their subsequent cytokine production leads to improper function of the immune system and many immune-related diseases. The seminal model to characterize the properties of CD4+ T cells suggests that these cells further develop into mutually exclusive, terminally differentiated Th1 or Th2 cell types [[1]](https://www.zotero.org/google-docs/?Tf2wAa)⁠. However, recent studies suggest that this model cannot sufficiently account for the full heterogeneity of immune responses and that: 1) additional effector T cells exist (e.g., Th17 [[2]](https://www.zotero.org/google-docs/?fM2XP2), Th9 [[3]](https://www.zotero.org/google-docs/?dPT89C), iTregs [[4]](https://www.zotero.org/google-docs/?T3uxmF)), 2) these cell type phenotypes exhibit a degree of plasticity (that is, under certain conditions, one cell subtype is able to switch and produce cytokine signatures specific to a different cell subtype; e.g., [[4]](https://www.zotero.org/google-docs/?vmdPl0)⁠), and 3) the differentiation process is governed by the regulation of a wide variety of types of receptors and pathways that are mutually cross-linked, forming highly interconnected signaling networks (rather than a single receptor pathway).

Modeling and simulations of a large-scale model of T cell signaling and gene regulation have the potential to improve our understanding of the richness of T cell differentiation and the regulatory process of cytokine production by helper T cells. In particular, simulations and analyses of a comprehensive model of signal transduction and gene regulation of CD4+ T cells can be used to test the hypothesis that additional cytokine profiles defining new CD4+ effector T cells exist and that the underlying phenotypes exhibit flexibility to provide more dynamics to immune response.

For example, to better understand how the extracellular cytokine milieu and signaling drive T cell differentiation, we constructed a signal transduction model and comprehensively interrogated its dynamics under 511 environmental conditions [[5]](https://www.zotero.org/google-docs/?cea9Y6). We found new evidence that T cell fates depend not only on specific combinations of stimulating cytokines but also quantitative (dosage) and temporal (timing) dynamics [[5,6]](https://www.zotero.org/google-docs/?6EqZqI). We also discovered and characterized novel complex (multi-fate) T cell phenotypes and their extracellular “recipes” that can potentially regulate the balance of each phenotype [[5]](https://www.zotero.org/google-docs/?fq3Avf). We are currently validating these multi-fate phenotypes experimentally. The ability to design T cell microenvironments that can elicit specific programming regimes has translational potential for many diseases, including cancer, autoimmune diseases, and transplantation.

**Project Objective**

* Using Cell Collective, construct a model of signal transduction pathways (networks) that govern the differentiation of naive T cells to **T helper 9** and **follicular T helper cells**.
  + To design the scope, build, and validate the model, use the modeling framework as described in [[7]](https://www.zotero.org/google-docs/?1nNyBG) in Figure 1.
  + As mentioned in [[7]](https://www.zotero.org/google-docs/?zDGkmd), pathway diagrams found in reviews and other articles provide a good starting point for the first model scope and draft. Given this project has a short timeline, we have identified the following papers that you can (but don’t have to if you find others) use to help you define the scope of your model:
    - Th9: <https://www.liebertpub.com/doi/10.1089/dna.2019.4729>
    - Tfh: <https://www.frontiersin.org/articles/10.3389/fimmu.2018.02412/full>
* Using Cell Collective, simulate the model to illustrate the stimulation of Th9 and Tfh cell differentiation. Share screenshots of your simulation results.

To be able to help you with your models, please share them with Dr. Helikar and Puniya. To share your model add their email addresses ([thelikar2@unl.edu](mailto:thelikar2@unl.edu) and [bpuniya2@unl.edu](mailto:bpuniya2@unl.edu)) under File->Share in Cell Collective, and save your model for the changes to take effect.

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