

Systems Pharmacology Model of the Co-stimulation Process of Immune Response in Systemic Lupus Erythematosus.

Leire Ruiz-Cerdá¹, Itziar Irurzun-Arana¹, Ignacio González-García^{1,2}, Chuanpu Hu³, Honghui Zhou³, An Vermeulen⁴, Iñaki F. Trocóniz¹, José David Gómez-Mantilla¹

(1) Pharmacometrics & Systems Pharmacology, Department of Pharmacy and Pharmaceutical Technology, University of Navarra, Pamplona, Spain. (2) Pharmacy and Pharmaceutical Technology Department. University of Valencia, Spain. (3) Model Based Drug Development, Janssen Research and Development, LLC, Spring House, USA (4) Janssen Research and Development, a division of Janssen Pharmaceutics NV, Beerse, Belgium



BACKGROUND AND OBJECTIVES

Systemic Lupus Erythematosus (SLE) is an autoimmune disease, which is characterized by the production of antibodies. There are 11 SLE diagnostic criteria, of which 4 are required for a formal diagnosis of lupus, also alterations in more than 40 genes have been associated with SLE, which illustrates how heterogeneous the SLE patients population can be. It is expected that SLE patients with different genetic patterns have different molecular alterations in their immune response; therefore, the same treatment in various patient subpopulations may not have the same therapeutic success. The aims of this project were: 1) identify plausible altered pathways of the immune response that may explain the heterogeneous alterations in SLE patients, 2) classify patients according to their alterations, and 3) identify an optimal therapy for each patient subpopulation.

METHODS & RESULTS

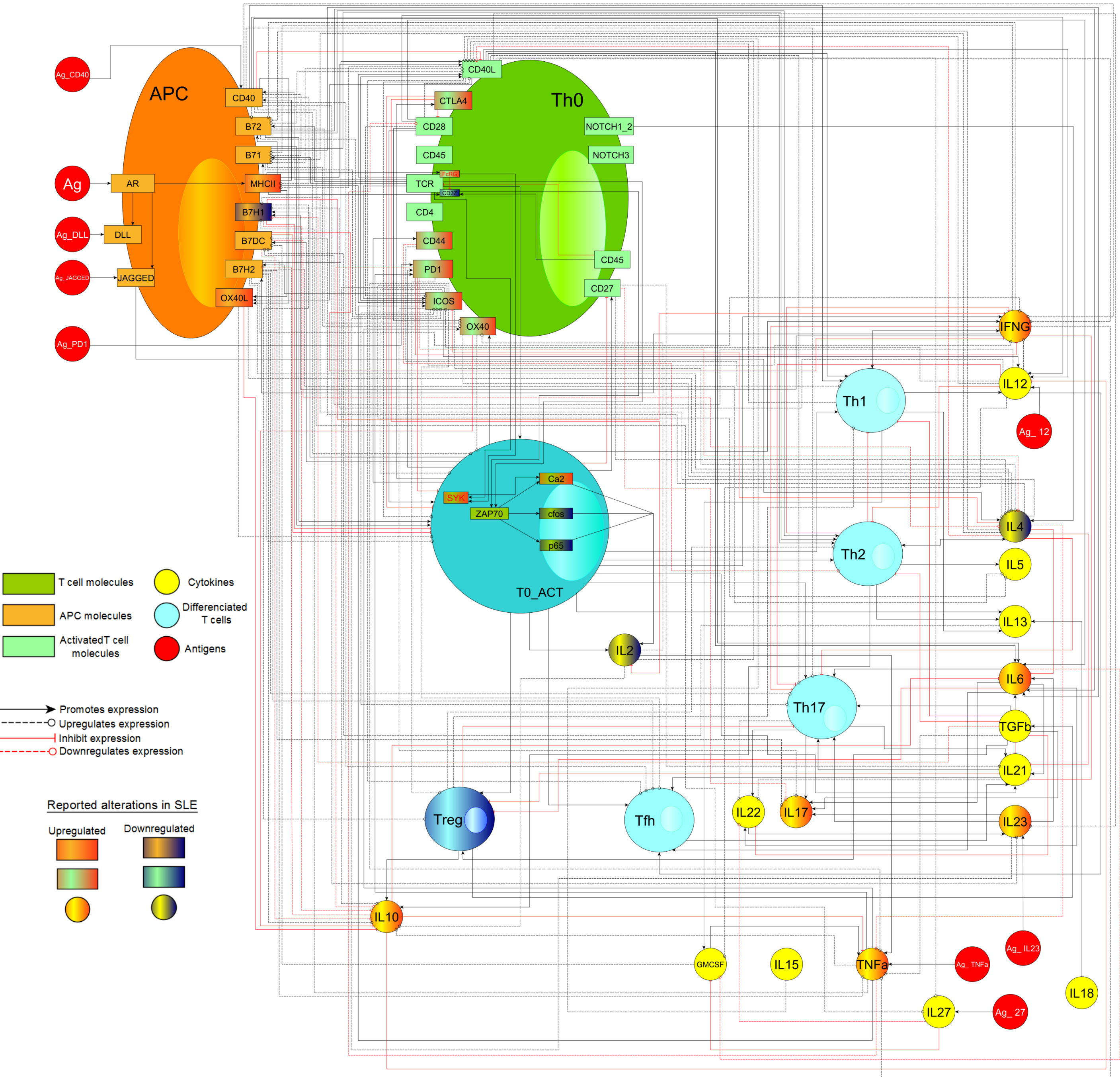


Figure 2. Boolean Network of the Antigen presentation focused on the alterations that has been reported for SLE patients. The network consisted of 56 nodes and 268 interactions. 23 of the 56 nodes have been reported to be altered in SLE patients. The network was built based on a bibliographic review of 234 publications.

Clustering analysis was performed to group the network nodes according to the alterations that those nodes may trigger after being up or down-regulated. Network implementation and all simulations and analyses were performed in R. Different Lupus manifestations were linked to different altered pathways of the immune response. Virtual lupus patients were classified into different categories, according to common manifestations reported in the literature and different specific therapies were identified. Manipulation of the ICOS-ICOSL, CD40-CD40L, IFNG and CD28-B71/B72 pathways were able to reduce the disease alterations in different patient subpopulations. No single treatment was able to reduce the manifestations in all patient subpopulations, advocating the need for personalized therapies.

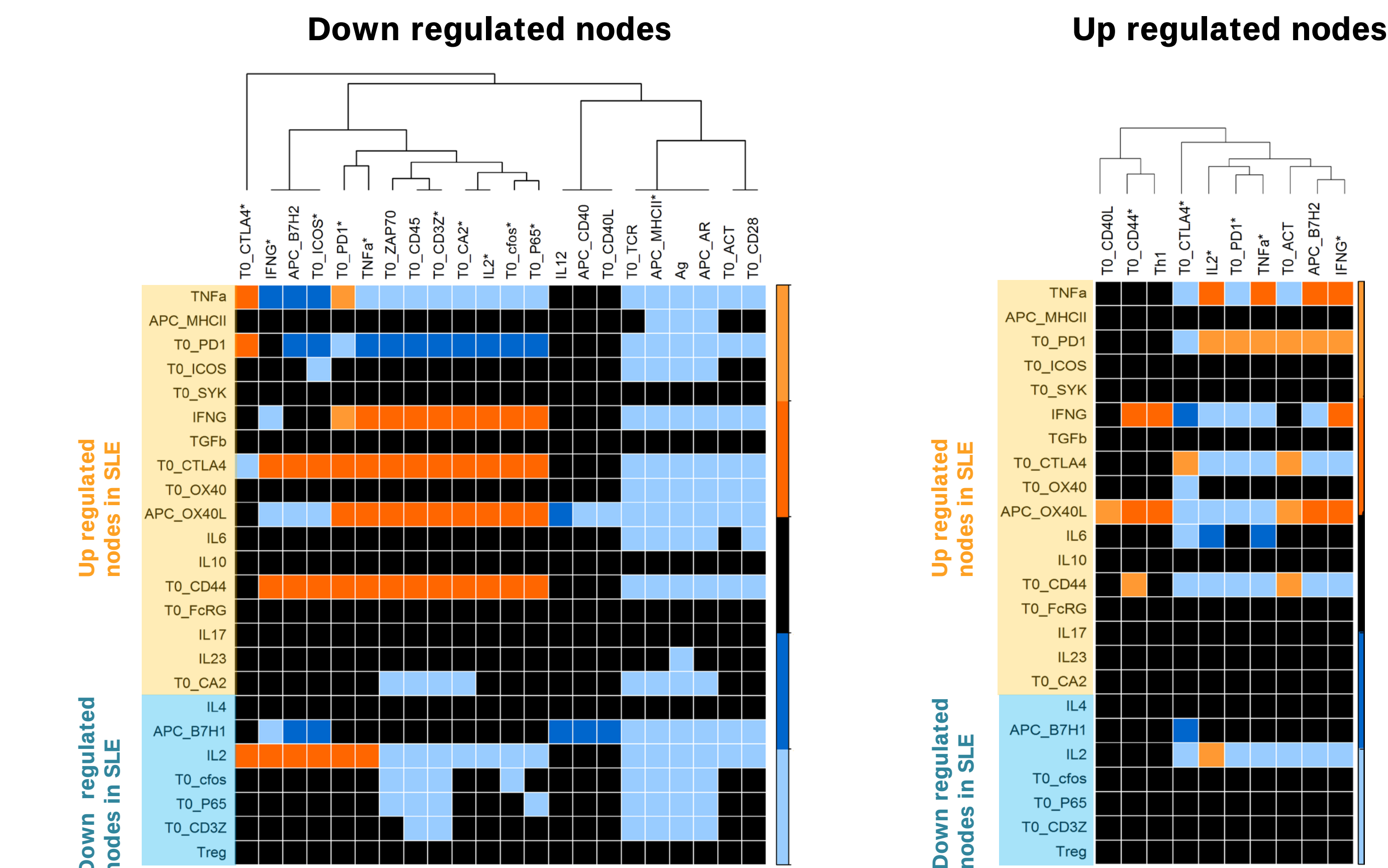


Figure 3. Identification of patient subpopulations. Reported alterations in SLE were grouped into different categories. Alterations in the PD1-PD1L and IL2 pathways, provoked the largest number of alterations similar to those reported for SLE patients.

CONCLUSIONS

Heterogeneity of SLE manifestations can be simulated by altering different pathways of the immune system. Patients can be classified into different categories according to their alterations and optimal treatments can be identified for each patient subpopulation.

NETWORK BUILDING AND VALIDATION

The immune response after exposure to autoantigens was modeled by a Boolean network [2, 3]. The Network was built based on a rigorous bibliographic review, focused on the components of the immune response that have been reported to be altered in SLE patients.

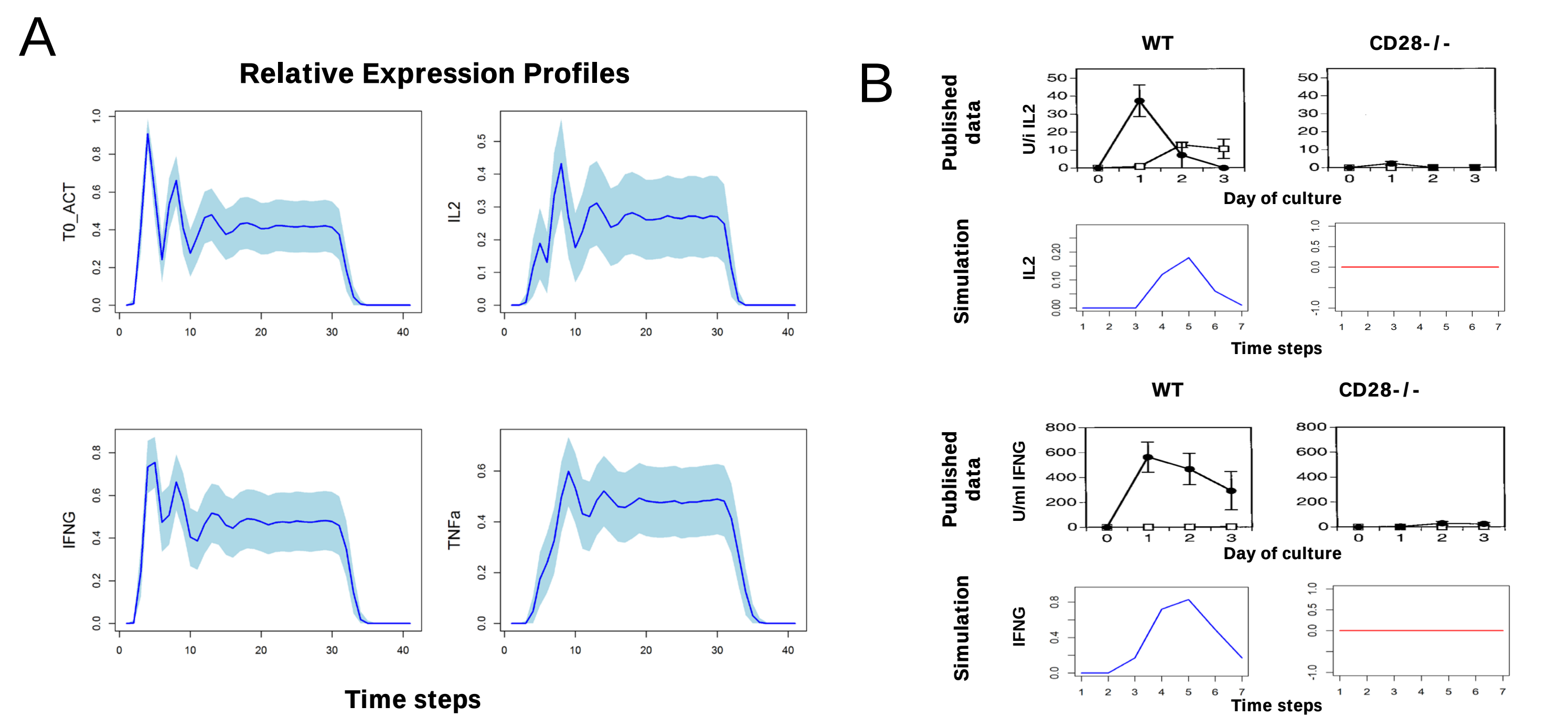


Figure 4. A) Relative expression profiles were obtained by averaging 10,000 evolutions of the network after simulating exposure to autoantigens. When possible, components of the network were validated by comparison of simulated nodes to published data (B).

We simulated a continuous autoantigen exposure perturbing the network by simulated up-regulation or down-regulation of different nodes in the network in order to identify which ones could trigger alterations similar to those observed in SLE patients.

Clustering analysis was performed to group the network nodes according to the alterations that those nodes may trigger after being up or down-regulated. Network implementation and all simulations and analyses were performed in R. Different Lupus manifestations were linked to different altered pathways of the immune response. Virtual lupus patients were classified into different categories, according to common manifestations reported in the literature and different specific therapies were identified. Manipulation of the ICOS-ICOSL, CD40-CD40L, IFNG and CD28-B71/B72 pathways were able to reduce the disease alterations in different patient subpopulations. No single treatment was able to reduce the manifestations in all patient subpopulations, advocating the need for personalized therapies.

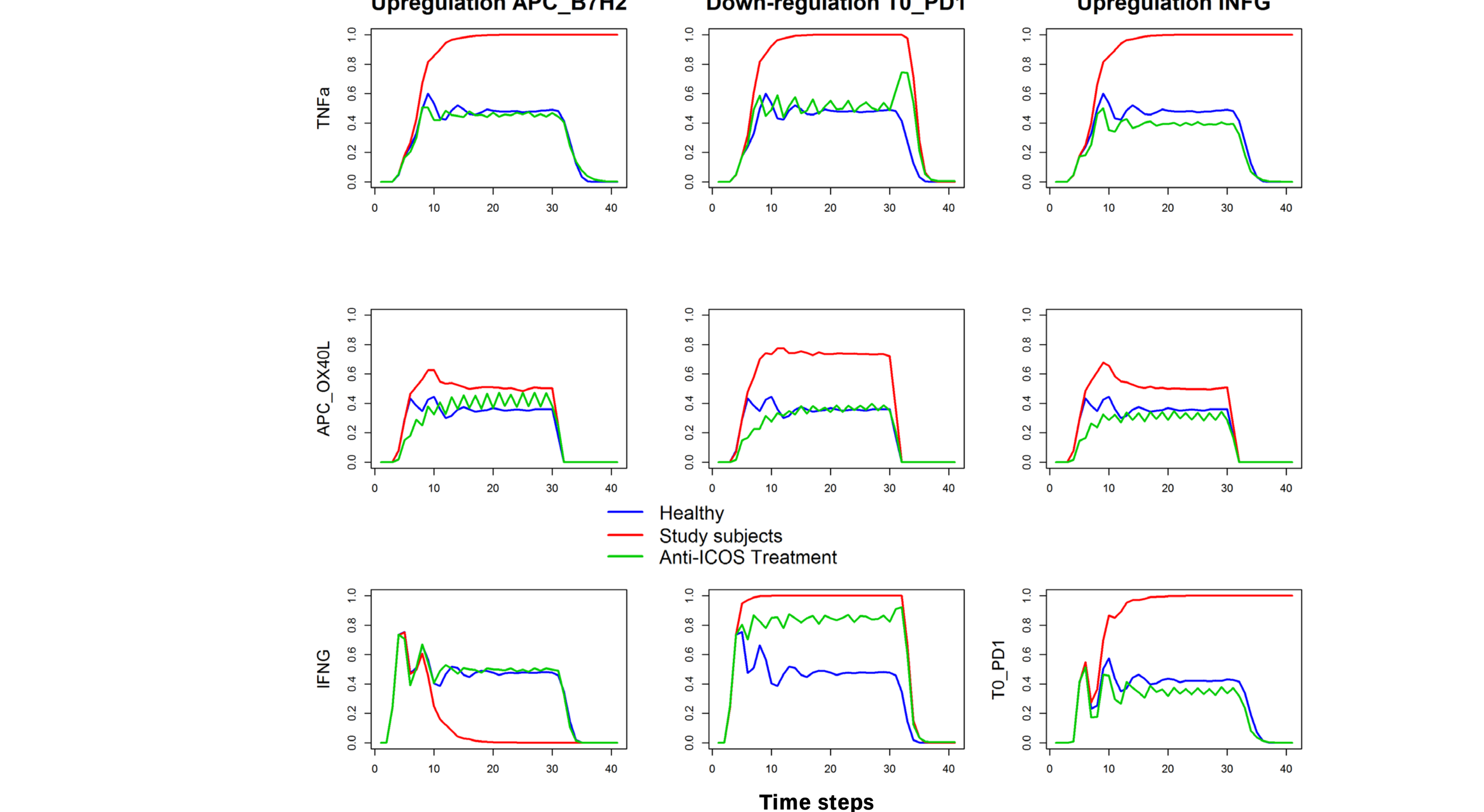


Figure 4. Simulation of drug/treatment in simulated SLE patients with alterations in TNFa, OX40L, IFNG and PD1 expressions due to three different underlying alterations, ICOSL up-regulation, PD1 down-regulation and IFNG up-regulation. Anti-ICOS treatment was effective in managing alterations of TNFa, OX40 and in IFNG but not controlled in patients with down-regulation of PD1.

References

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