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## UNCOVERING THE HIDDEN STRUCTURE OF T CELL COMPOSITIONS IN PERIPHERAL BLOOD AFTER IMMUNE CHECKPOINT INHIBITOR

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**Background** Immune checkpoint inhibitors (ICIs) are a promising treatment option for many cancer patients, however heterogeneous outcomes within and across cancer types are a challenge in guiding treatment decisions. Additional biomarkers to guide the selective use of ICI would address an unmet clinical need. We have shown that pre-treatment peripheral blood immune characteristics detected by flow cytometry are related to clinical outcomes after ICI<sup>1</sup>. Our goal is to further mine high-parameter flow cytometry data from blood samples obtained longitudinally during ICI treatment to explore ICI's immunological mechanisms and pharmacodynamics in cancer patients. However, the current field lacks effective statistical and computational approaches to take full advantage of this complex dataset.

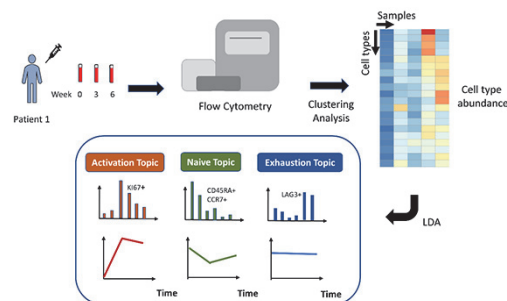
**Methods** We adapt a Latent Dirichlet Allocation (LDA) model, widely applied for topic discovery in text mining analysis, to explore the temporal evolution of T cell compositions from longitudinal single-cell flow cytometry data (figure 1). The LDA model considers cells as words, patient samples as documents, and biological processes as topics. With an analysis involving ~17 million T cells obtained from 138 pre- and on-treatment samples, we show the model's utility in delineating immune cell compositions and tracking dynamic changes over time in the peripheral blood from a cohort of 51 melanoma patients receiving combination CTLA-4 and PD-1 blockade. Without providing prior domain knowledge, LDA explores the hidden structure and identifies latent topics with great interpretability, allowing the discovery of possible clinical biomarkers.

**Results** We applied LDA and identified three latent topics in an unsupervised fashion; based on the topic contents, we labeled them the activation topic, naive topic, and exhaustion topic. The activation topic is mainly contributed by memory T cell clusters, which capture the major pattern of T cell expansion after ICI. The naive and exhaustion topics consist of naive T cell clusters and terminally differentiated T cell clusters, respectively. Patients with a large proportion of naive topics were shown to be more likely to experience severe ICI-related toxicity ( $P = 0.02$ ). Moreover, the exhaustion topic is strongly related to the LAG+ immunotype, which has been linked to poor clinical outcomes in the earlier study<sup>1</sup>.

**Conclusions** Here, we present a novel statistical and computational framework for investigating temporal dynamics of T cell compositions with the potential to characterize pharmacodynamics under ICI. We demonstrated LDA is effective in deconvoluting the high-parameter flow cytometry data and characterizes immunological topics that provide novel biological insights.

### REFERENCE

- Shen R, Postow MA, Adamow M, *et al*. LAG-3 expression on peripheral blood cells identifies patients with poorer outcomes after immune checkpoint blockade. *Sci Transl Med*. 2021;**13**:eabf5107.



**Abstract 1297 Figure 1** LDA reveals hidden structures in flow cytometry data

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