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# Defining the therapeutic window of NLRP6 modulation in graft-*versus*-host disease. Comment on: "NLRP6 regulates donor T cell activation and acute graft-*versus*-host disease *via* ZAP-70-Erk pathway"

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## Authors' contributions

All authors contributed equally to the conception and drafting of the manuscript and approved the submitted version.

## Disclosure

The authors declare no conflict of interest.

Matsuki E and colleagues address an important question in hematology: NLRP6 regulates donor T cell activation and acute graft-versus-host disease via ZAP-70-Erk pathway. [1] The article is valuable because it tackles a clinically recognizable problem and provides a useful basis for discussion. The key issue, however, is whether the NLRP6-ZAP-70-Erk pathway reflects a causal driver of donor T-cell activation or a marker of broader inflammatory activation after transplantation. This distinction matters because readers may otherwise move too quickly from an interesting observation to a clinical or methodological conclusion that the present evidence does not fully establish. We therefore believe the article should be read not only for its main result, but also for the assumptions that determine how far that result can travel.

The first issue is that the central mechanistic issue is directionality: NLRP6 may regulate signaling intensity, but acute graft-versus-host disease also creates cytokine and tissue-injury feedback loops that can secondarily alter donor T-cell signaling. The second is that A clinically useful interpretation requires knowing whether NLRP6 modulation preserves graft-versus-leukemia activity while reducing tissue damage. [2], [3] These concerns do not diminish the contribution of the study, but they define the conditions under which the findings can be applied. A strong letter should make this boundary visible, because the most important risk for readers is not that the result is uninteresting, but that its practical meaning is broader than the data can support. In this sense, the central question is not whether the work is useful; it is what exact decision, hypothesis, or future study the work can legitimately support.

This distinction has practical consequences for interpretation. If the study is read as definitive, readers may focus on the headline conclusion and overlook design features that shape the estimate, such as patient selection, timing of measurement, endpoint definition, missing data, operator behavior, or treatment pathway after enrollment. If it is read as a carefully bounded contribution, however, the same findings become more useful because they identify where the evidence is strong and where replication or refinement is still required. That framing is especially important for studies likely to influence clinical language before they change clinical practice.

A third issue is that the work would be more translational if pathway inhibition were benchmarked against T-cell expansion, exhaustion, tissue infiltration, and antitumor function in the same experimental framework. [4] The next study should therefore be designed around a small number of prespecified questions: which subgroup is most likely to benefit from the proposed interpretation, which outcome should be considered decisive, and what level of follow-up, technical quality, or data completeness would make the conclusion reproducible. Answering these questions would help move the field from an interesting report to a usable clinical or methodological standard. Such a design would also make negative or neutral findings more informative, because it would show whether the original signal fails generally or only under specific biological, technical, or operational conditions.

The findings should also be discussed with attention to negative and neutral results. A focused letter is most useful when it protects readers from a one-directional interpretation of promising data. If the reported strategy performs well only under selected conditions, that

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limitation should be visible early. If the observed effect is clinically attractive but operationally difficult, implementation barriers should be treated as part of the evidence rather than as a secondary concern. This is not a conservative posture for its own sake. It is a way to keep promising results actionable without turning them into recommendations before the necessary comparative or external evidence exists.

We would therefore encourage future work to report the elements that determine transportability. For clinical studies, these include baseline risk, co-interventions, follow-up intensity, competing events, safety, and patient-centered outcomes. For biomarker, registry, artificial-intelligence, or methodological studies, they include calibration, missingness, data provenance, annotation quality, temporal drift, and external validation. Making these elements explicit would allow readers to distinguish a robust finding from a finding that is promising but context-dependent.

In summary, NLRP6 regulates donor T cell activation and acute graft-versus-host disease via ZAP-70-Erk pathway is a meaningful contribution to the literature. [1] The pathway is promising, but the therapeutic window should be defined before NLRP6 is presented as a tractable target for acute graft-versus-host disease. Its greatest value lies in opening a practical discussion about how the reported evidence should be used, verified, and communicated. Clearer boundaries can strengthen, rather than weaken, the impact of a well-conducted study, because they show readers exactly what should change now and what still requires confirmation.

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