

could allow for greater cross-trial comparisons and eventually improved precision in treatment selection.

In conclusion, the combination of brentuximab vedotin and lenalidomide is impressive in this phase 1 trial, and a confirmatory randomized phase 3 trial is now ongoing. The results of this and other similar trials highlight a large and increasingly urgent need: let's prepare for success.

**Conflict-of-interest disclosure:** The author has received research funding from Kite/Gilead, BMS, Novartis, Genetech/Roche, Morphosys, AstraZeneca, Janssen, ADC Therapeutics, Merck, and Precision Biosciences, and has served on advisory boards for Kite/Gilead, BMS, Novartis, Genetech/Roche, Morphosys, AstraZeneca, Janssen, ADC Therapeutics, Merck, Iksuda, and Umoja. ■

## REFERENCES

1. Ward JP, Berrien-Elliott MM, Gomez F, et al. Phase 1/dose expansion trial of brentuximab vedotin and lenalidomide in relapsed or refractory diffuse large B-cell lymphoma. *Blood*. 2022;139(13):1999-2010.
2. Jacobsen ED, Shaman JP, Oki Y, et al. Brentuximab vedotin demonstrates objective responses in a phase 2 study of relapsed/refractory DLBCL with variable CD30 expression. *Blood*. 2015;125(9):1394-1402.
3. Hernandez-Ilizaliturri FJ, Deeb G, Zinzani PL, et al. Higher response to lenalidomide in relapsed/refractory diffuse large B-cell lymphoma in nongerminal center B-cell-like than in germinal center B-cell-like phenotype. *Cancer*. 2011;117(22):5058-5066.
4. Bartlett NL, Yasenchak CA, Ashraf KK, Harwin WN, Sims RB, Nowakowski GS. Brentuximab vedotin in combination with lenalidomide and rituximab in subjects with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) (trials in progress). *J Clin Oncol*. 2021;39(15 suppl):TPS7571.
5. Duell J, Maddocks KJ, González-Barca E, et al. Long-term outcomes from the Phase II L-MIND study of tafasitamab (MOR208) plus lenalidomide in patients with relapsed or refractory diffuse large B-cell lymphoma. *Haematologica*. 2021;106(9):2417-2426.
6. Goy A, Ramchandren R, Ghosh N, et al. Ibrutinib plus lenalidomide and rituximab has promising activity in relapsed/refractory non-germinal center B-cell-like DLBCL. *Blood*. 2019;134(13):1024-1036.
7. Sehn LH, Hertzberg M, Opat SS, et al. Polatuzumab vedotin plus bendamustine and rituximab in relapsed/refractory DLBCL: survival update and new extension cohort [published online ahead of print 8 November 2021]. *Blood Adv*. 2021; bloodadvances.2021005794.
8. Caimi PF, Ai W, Alderuccio JP, et al. Loncastuximab tesirine in relapsed or refractory diffuse large B-cell lymphoma (LOTIS-2): a

multicentre, open-label, single-arm, phase 2 trial. *Lancet Oncol*. 2021;22(6):790-800.

9. Benjamin RS. Freireich's laws in the treatment of sarcomas. *Clin Cancer Res*. 1997;3(12 Pt 2):2648-2654.
10. Cavallo J. 2021. <https://ascopost.com/issues/february-25-2021/oncology-community-mourms->

the-death-of-chemotherapy-pioneer-emil-j-freireich/. Accessed on 12/2/2021

DOI 10.1182/blood.2021014678

© 2022 by The American Society of Hematology

## HEMATOPOIESIS AND STEM CELLS

Comment on Loeffler et al, page 2011

# Asymmetric division: the choice of fate for huHSCs

Marie-Dominique Filippi | Cincinnati Children's Hospital Research Foundation and University of Cincinnati College of Medicine

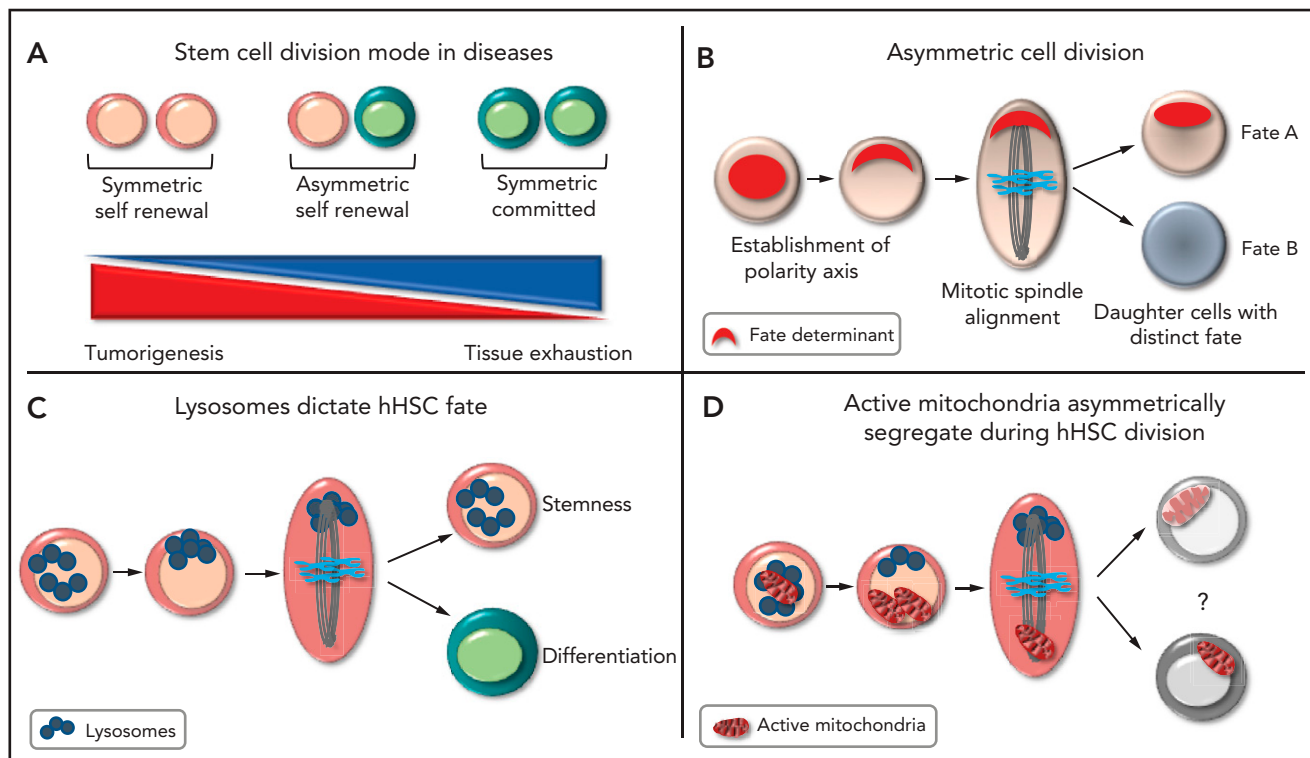
**In this issue of *Blood*, Loeffler et al<sup>1</sup> provide evidence that human hematopoietic stem cells (hHSCs) can undergo asymmetric cell division (ACD) to generate 2 cells with distinct functional fates, and that lysosome asymmetric inheritance determines these fates. These findings answer the long-standing question of ACD in HSC biology and uncover unexpected factors that determine cell fate that may be used for developing new protocols for HSC expansion.**

Remaining a stem cell or committing to differentiation is the most important fate-determining event in the lifetime of the HSC. This process maintains the balance between the pool of HSCs and progenitors and ensures homeostasis of the hematopoietic system. During development, stem cells use ACD to create cellular diversity and maintain adequate numbers of both stem cells and differentiated cells. Stem cells can adapt their mode of division and divide symmetrically (generating 2 stem cells or 2 progenitors) or asymmetrically, to meet the regenerative need of tissues,<sup>2</sup> the failure of which can cause long-term tissue exhaustion or tumor development (see figure panel A). Although hHSC are believed to divide asymmetrically, definite evidence has been lacking.

ACD is the unequal partitioning of cellular components during cell division that enables daughter cells to have distinct fates. ACD is controlled by the asymmetric reorganization of the cytoskeleton, which results in cellular polarity, with an asymmetric accumulation of factors that determine the fate of the cell. The orientation of the mitotic spindle along the polarity axis ensures unequal partitioning of these factors between daughter cells, with the level of fate-determining factors received deciding the future identity of each daughter cell (see figure panel B).<sup>2</sup>

Demonstrating ACD requires the linking of factors that alter cell fate to their asymmetric distribution. Identifying these linking factors has been a challenging task in HSCs because of the limited knowledge of the factors that determine HSC identity. HSCs are retrospectively defined by their ability to generate mature cells, making assessment of HSC fate dependent on the behavior of the progeny. ACD was first suggested in HSCs when paired daughter cells generated clones of distinct size and myeloid lineage potential *in vitro*.<sup>3</sup> In murine HSCs, cellular factors, including lysosomes, can asymmetrically segregate and alter HSC fate.<sup>4,5</sup> In hHSCs, studies have shown that the surface markers CD53 and CD62L are unequally partitioned, which can correlate with the potential lineage of daughter cells.<sup>6</sup> The endosomal protein Ap2a2<sup>7</sup> and myosin II<sup>8</sup> can both alter hHSC fate and may be asymmetrically inherited. None of the aforementioned studies linked asymmetric inheritance of these components to hHSC fate.

In a tour de force, Loeffler et al were able to link asymmetric lysosomal inheritance to hHSC fate *ex vivo*, demonstrating that hHSCs can use ACD to generate daughter cells with distinct fates. They used a long-term quantitative single-cell imaging technique to quantify factors inherited by paired daughter cells during



The principles of asymmetric cell division. (A) Different modes of cell division. (B) Steps leading to the asymmetric partitioning of fate-determining factors. (C) Asymmetric inheritance of lysosomes is linked to asymmetric hHSC fate. (D) Daughter cells receiving more lysosomes inherit fewer active mitochondria in hHSCs, the function of which is unknown.

hHSC division and to trace the offspring of each daughter cell until the potential lineage was revealed. In a highly purified CD49f<sup>+</sup> hHSC population, they first showed that lysosomes are asymmetrically inherited during hHSC division. Importantly, asymmetric lysosomal inheritance correlates with asymmetric segregation of different stem cell markers. The group created real-time differentiation landscapes of different cellular states during culture, by using surface markers enriched for stem cell potential (CD201 and CD49c). Cells receiving more lysosomes preferentially produced cells expressing high levels of CD49c that divided slower, an indicator of stem cell potential. Daughter cells receiving fewer lysosomes were prone to give rise to CD33-expressing cells, indicative of myeloid differentiation. Hence, the absolute quantity of inherited lysosomes correlated with daughter cell fate, predicting the cell cycle length and differentiation potential of the daughter cells *in vitro* (see figure panel C). It will be interesting to confirm that hHSCs receiving more lysosomes retain long-term repopulating activity *in vivo*. Loeffler et al observed other types of hHSC division, implying

that ACD is regulated and can be modulated to meet the demand. ACD is most likely not limited to lysosome distribution. They showed that endosomes, active mitochondria, and mitophagosomes can all be asymmetrically partitioned. Interestingly, daughter cells receiving more lysosomes inherited fewer active mitochondria during hHSC division, although the impact on hHSC fate was less clear (see figure panel D), perhaps because mitochondria are known to permanently remodel during and after HSC division.<sup>9</sup> These findings imply that lysosomes are bona fide hHSC fate-determining factors and that organelles and metabolic functions are integral parts of ACD in hHSCs.

Although these findings provide remarkable insights into one of the biggest mysteries of stem cell biology, much remains to be learned about the regulatory pathways that determine how stemness is inherited by daughter cells. How are lysosomes asymmetrically partitioned? How do lysosomes dictate HSC fate? Lysosomes are major components of the cellular degradative machinery, but they also serve as signaling hubs for anabolic

processes and thus have both progrowth and antigrowth functions. HSCs possess large lysosomes that degrade slowly and act as reservoirs of cargo, including mitochondria, to maintain HSC quiescence.<sup>10</sup> It is possible that lysosomes terminate the activity of HSCs to enable daughter cells to return to quiescence. Conversely, do lysosomes provide building blocks for biomass and progrowth signals for HSC activation? If so, how is lysosomal activity regulated throughout HSC division? Likewise, the exact role of active mitochondria in hHSC fate requires further investigation.

In general, there is a need to examine HSC behavior and understand organelle biology and metabolic requirements during active HSC division when fate is determined. The development of the metabolomics of a small number of cells integrated with sophisticated RNA sequencing and assay for transposase-accessible chromatin sequencing at the single-cell level will help in dissecting the regulatory pathways of ACD in HSCs. Influencing HSC division modes can be a powerful way to amplify HSCs, as it would enable doing so in only a few

Comment on Wu et al, page 2024

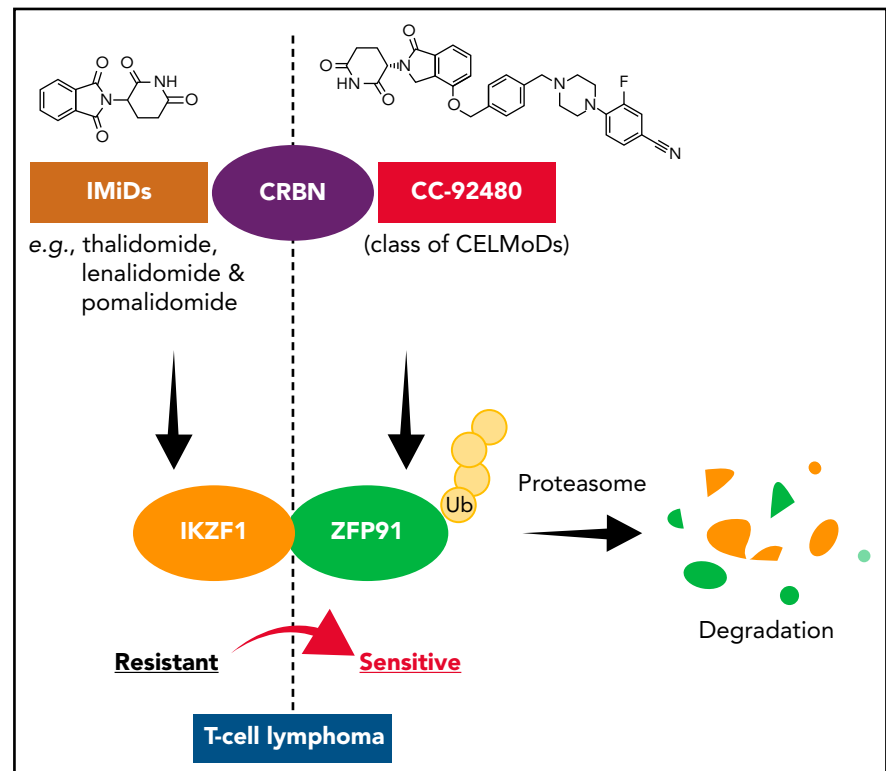
# Targeting IMiD-resistant T-cell lymphoma

Huan-Chang Liang and Kojo S. J. Elenitoba-Johnson | University of Pennsylvania

**In this issue of *Blood*, Wu et al<sup>1</sup> describe a novel yet critical transcriptional factor network that confers resistance to immunomodulatory imide drugs (IMiDs) in T-cell lymphomas (TCLs). They identify a pivotal codependence of Ikaros (IKZF1) and zinc finger protein 91 (ZFP91) in IMiD-resistant TCLs, thereby revealing an acquired mechanism of resistance to IMiD treatment. Furthermore, their study provides an attractive therapeutic strategy that uses more potent next-generation degraders targeting IKZF1 and ZFP91 for treating patients with TCL.**

TCLs are a group of heterogeneous lymphoid malignancies of T-cell origin with diverse clinical presentations and therapeutic responses. Many TCLs have a poor prognosis with a <30% 5-year overall survival in some subtypes.<sup>2</sup> To date, 29 different subtypes have been recognized by the World Health Organization on the basis of their histological and molecular features.<sup>3</sup>

Therapy for TCLs, however, has generally been extrapolated from trials of B-cell lymphomas that use multiagent chemotherapy such as cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). Given the poor outcomes with standard therapy, there remains a dire need to identify novel vulnerabilities for effective treatment strategies in patients with TCL.



CC-92480, a cereblon (CRBN) E3 ligase-modulating drug (CELMoD), overcomes IMiD resistance in T-cell lymphomas. IMiD-resistant T-cell lymphomas show crucial co-dependence of IKZF1 and ZFP91 transcription factors. Binding of CC-92480 to CRBN leads to selective and potent degradation of IKZF1 and ZFP91, overcoming IMiD resistance in multiple subtypes of T-cell lymphoma. Ub, ubiquitin.

divisions. This knowledge will guide the development of culture protocols for HSC-based therapies. Future research should examine how HSCs use ACD, whether ACD contributes to HSC heterogeneity, and how ACD is modulated in response to stress or contributes to clonal hematopoiesis and hematopoietic neoplasms if deregulated. Answering these questions is critical to exploiting the regenerative potential of HSCs for clinical purposes or for antitumor therapies.

*Conflict-of-interest disclosure:* The author declares no competing financial interests. ■

## REFERENCES

- Loeffler D, Schneiter F, Wang W, et al. Asymmetric organelle inheritance predicts human blood stem cell fate. *Blood*. 2022; 139(13):2011-2023.
- Knoblich JA. Asymmetric cell division: recent developments and their implications for tumour biology. *Nat Rev Mol Cell Biol*. 2010;11(12):849-860.
- Suda T, Suda J, Ogawa M. Disparate differentiation in mouse hemopoietic colonies derived from paired progenitors. *Proc Natl Acad Sci USA*. 1984;81(8): 2520-2524.
- Ito K, Ito K. Hematopoietic stem cell fate through metabolic control. *Exp Hematol*. 2018;64:1-11.
- Loeffler D, Wehling A, Schneiter F, et al. Asymmetric lysosome inheritance predicts activation of haematopoietic stem cells [published correction appears in *Nature*. 2019;573(7775):E5]. *Nature*. 2019; 573(7774):426-429.
- Beckmann J, Scheitza S, Wernet P, Fischer JC, Giebel B. Asymmetric cell division within the human hematopoietic stem and progenitor cell compartment: identification of asymmetrically segregating proteins. *Blood*. 2007;109(12):5494-5501.
- Ting SB, Deneault E, Hope K, et al. Asymmetric segregation and self-renewal of hematopoietic stem and progenitor cells with endocytic Ap2a2. *Blood*. 2012;119(11): 2510-2522.
- Shin JW, Buxboim A, Spinler KR, et al. Contractile forces sustain and polarize hematopoiesis from stem and progenitor cells. *Cell Stem Cell*. 2014;14(1):81-93.
- Hinge A, He J, Bartram J, et al. Asymmetrically Segregated Mitochondria Provide Cellular Memory of Hematopoietic Stem Cell Replicative History and Drive HSC Attrition. *Cell Stem Cell*. 2020;26(3):420-430.e6.
- Liang R, Arif T, Kalmykova S, et al. Restraining Lysosomal Activity Preserves Hematopoietic Stem Cell Quiescence and Potency. *Cell Stem Cell*. 2020;26(3):359-376.e7.

DOI 10.1182/blood.2021012726

© 2022 by The American Society of Hematology