Janus kinase inhibitors, based on the unique molecular features of DS-ALL, is an avenue that may eventually enable safe reductions in conventional chemotherapy.[10]

As survival has improved in pediatric ALL, the need for efforts to reduce IRM is clear. This work by O'Connor and colleagues is a valuable contribution to the field, demonstrating the importance of capturing well-defined toxicity data on large cooperative group trials and identifying important aspects of IRM that will guide future efforts to more effectively prevent and treat infections during the treatment of ALL.

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REFERENCES

1. O'Connor D, Bate J, Wade R, et al. Infection-related mortality in children with acute lymphoblastic leukemia: a retrospective analysis of infectious deaths on UKALL 2003. *Blood.* 2014;124(7):1056-1061.

2. Vora A, Goulden N, Wade R, et al. Treatment reduction for children and young adults with low-risk acute lymphoblastic leukaemia defined by minimal residual disease (UKALL 2003): a randomised controlled trial. *Lancet Oncol.* 2013;14(3):199-209.

3. Pui CH, Pei D, Sandlund JT, et al. Long-term results of St Jude Total Therapy Studies 11, 12, 13A, 13B, and 14 for childhood acute lymphoblastic leukemia. *Leukemia.* 2010;24(2):371-382.

4. Hunger SP, Lu X, Devidas M, et al. Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the children's oncology group. *J Clin Oncol.* 2012;30(14):1663-1669.

5. Sung L, Aplenc R, Alonzo TA, Gerbing RB, Lehrnbecher T, Gamis AS. Effectiveness of supportive care measures to reduce infections in pediatric AML: a report from the Children's Oncology Group. *Blood.* 2013;121(18):3573-3577.

6. Buitenkamp TD, Izraeli S, Zimmermann M, et al. Acute lymphoblastic leukemia in children with Down syndrome: a retrospective analysis from the Ponte di Legno study group. *Blood.* 2014;123(1):70-77.

7. Patrick K, Wade R, Goulden N, et al. Outcome of Down syndrome associated acute lymphoblastic leukaemia treated on a contemporary protocol. *Br J Haematol.* 2014; 165(4):552-555.

8. Maloney KW, Larsen E, Mattano LA, et al. Improvement in the Infection-Related Mortality for Children with Down Syndrome in Contemporary Children's Oncology Group Acute Lymphoblastic Leukemia Clinical Trials. Plenary Session Presented at American Society of Pediatric Hematology/Oncology 21st Annual Meeting. May 15-16, 2008. Cincinnati, Ohio.

9. Maloney KW, Carroll WL, Carroll AJ, et al. Down syndrome childhood acute lymphoblastic leukemia has a unique spectrum of sentinel cytogenetic lesions that influences treatment outcome: a report from the Children's Oncology Group. *Blood.* 2010;116(7):1045-1050.

10. Maude SL, Tasian SK, Vincent T, et al. Targeting JAK1/2 and mTOR in murine xenograft models of Ph-like acute lymphoblastic leukemia. *Blood.* 2012;120(17): 3510-3518.

Comment on Wang et al, page 1089

Old and new news in CLL: "It's the pathway, stupid!"

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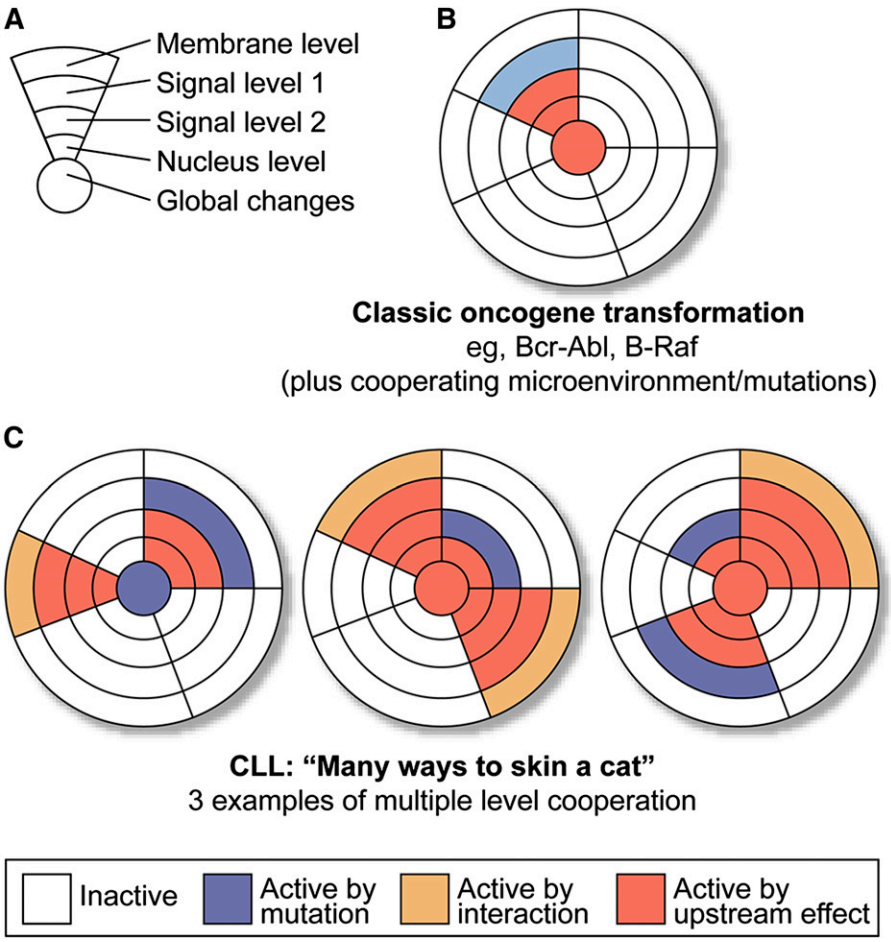
In this issue of *Blood*, Wang et al demonstrate how mutations in the Wnt/β-catenin pathway in chronic lymphocytic leukemia (CLL) lead to activation of this pathway.[1] The work presented demonstrates that this pathway is likely to contribute to CLL pathogenesis, at least in a subset of patients, and suggests that it may contain potential therapeutic targets. These observations are following the authors' groundbreaking work on the genetic landscape in CLL[2,3] and by using exciting, novel transfection technology (ie, silicon nanowires).[4] Thus, the notoriously difficult-to-transfect CLL cells could be modified to be able to target a pathway that has been identified by indirect evidence from next generation sequencing, demonstrating that attacking the mutated proteins by genetic modification is feasible. Indeed, at least for some proteins tested, modification of the pathway on a number of levels led to changes in CLL behavior consistent with a role of the Wnt/β-catenin pathway in CLL pathogenesis. The paper must be read to fully appreciate the elegance of the approaches taken, as well as understand the potential limitations of the approach.

The paper has impact beyond CLL that is worth exploring. First, the authors attack a recurrent problem, observed during the recent explosion of genetic knowledge on tumorigenesis. Massively parallel sequencing approaches suggest that certain mutations in tumors act as so-called "drivers" largely using a "guilt-by-association" approach. The logic is that recurrent mutations selected by independent tumor evolution pathways must be important. If the mutation can be also placed into the context of a plausible oncogenic pathway, then we tend to believe that we have, indeed, found the culprits. We commend Wang et al[1] for taking their own observations from genetics to a cell biology platform and their attempts to move a step closer to elucidating not just the association, but the action of the mutations they described earlier.

Of course, such approaches have been taken in the past, but mainly for a limited type of lesion, leading to the second point. We, as hematologists (I cannot speak for all hematologists, but as a figure of speech, allow me to say) have been raised on simple tumor biology models, not the least because it was in hematology, where some of the first insights into molecular oncogenesis were developed. Single and highly recurrent lesions, such as the Bcr-Abl or PML-RARA translocations (or more recently B-Raf mutations) were identified, validated in cell biology and animal models to the point where it was possible to stringently identify culprits, fulfilling Koch's postulates, and targeted treatment could be initiated effectively. This enormous success story may have biased our views and expectations in many malignancies, until the arrival of next-generation sequencing and the confusing complexity we have "endured" since then. Enter CLL! CLL seems a very particular beast in that is a prototypically odd malignancy for a number of reasons. First, it shows an intricate interaction and dependency on multiple microenvironmental cues (see the review by Burger[5]), suggesting that not all transforming "events" need to be hardwired by mutations in the leukemic clone itself. Indeed, CLL induces signaling in its microenvironment that seems essential for its survival.[6] Second, with the possible exception of deletion 13q, no real high frequency transforming events have been defined yet. Indeed, the genetic landscape, as previously demonstrated by the authors of this paper in discussion, looks extraordinarily "colorful."[2,3] The important achievement of the Dana Farber group was to use a bioinformatic pattern



Transformation via "canonical hits" vs "pathway tweaking." (A) Schematic depiction of a generic pathway and possible levels of "oncogenic" lesions: "membrane level" includes extracellular signals, both from the microenvironment (including BCR signaling) or via autocrine stimulation, as well as mutations in receptors; "signaling levels 1 and 2" simplify different levels of action in a single pathway; "nuclear controls" mean transcription factor changes; and "global controls" mean changes in micro RNA, epigenetics, splicing machinery, or DNA damage response. (B) Model of classic oncogene transformation (1 strong and highly recurrent driver leads to clonal expansion). Of course, this is a gross simplification, whereas in reality, there are collaborating lesions in all these instances. (C) Multiple ways of transformation in CLL by activation with or without mutation, and on multiple levels of a defined set of collaborating pathways. Professional illustration by XavierStudio.

recognition approach (potentially flawed by biases) to align the mutations with core pathways, seemingly mutated in CLL recurrently, with a higher frequency than the individual mutations suggested. The importance of this paper is to create a dataset that corroborates the idea that the genetic activation or silencing of a pathway can (and will) occur on multiple levels, with a relatively consistent effect on the output of the overall pathway. To phrase this on a more general level, as opposed to the classic paradigm of a recurrent mutation in a defined oncogene or tumor suppressor as a hallmark event in transformation (panels A and B) a picture of a much more promiscuous pattern of transformation emerges for CLL (and as a paradigm for a number of other malignancies). There seems to be a set of defined evolutionary "tasks" that a CLL clone has to "take care of" (ie, a combination of activated pathways that needs to be present in the cell for effective transformation). In contrast to the simpler classical model, it seems that CLL is not very restricted regarding the type of "solutions" emerging in its evolution. An extracellular (microenvironmental or autocrine) signal may be substituted by a pathway mutation that can happen on multiple levels along the pathway (panel C). Ultimately, the combination of multiple events leads to a progressive CLL clone with the clinical consequences we observe. I would like to stress that these do not necessarily need to be strong biological drivers, individually. Thus, an enormous plethora of solutions may exist for the question: "What is necessary to program a CLL cell?" Although this is not particularly new (ie, Hanahan and Weinberg's[7] seminal Hallmarks of Cancer Perspective), it seems that CLL is particularly "creative" regarding its solutions and Wang et al[1] have provided important work on the path to recognizing this.[2,3] Finally, although the creativity of a malignancy is generally not our friend, if we are clinicians aiming to treat a disease, the paradigm of activated, and maybe critical, pathways can be exploited to our benefit. Understanding the pathway map that is important to a disease and identifying important nodules (even if, or specifically when, they are not mutated) will lead to successful targets, as can be witnessed currently in the clinical development of BCR signaling inhibitors. Importantly, as Wang et al[1] demonstrate that the mutations observed in CLL may be used to "paint" the pathways, we need to target the best effects. Also, the mutations "painted" some really novel scenery. It is exciting times!

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REFERENCES

1. Wang L, Shalek AK, Lawrence M, et al. Somatic mutation as a mechanism of Wnt/β-catenin pathway activation in CLL. *Blood.* 2014;124(7):1089-1098.

2. Landau DA, Carter SL, Stojanov P, et al. Evolution and impact of subclonal mutations in chronic lymphocytic leukemia. *Cell.* 2013;152(4):714-726.

3. Wang L, Lawrence MS, Wan Y, et al. SF3B1 and other novel cancer genes in chronic lymphocytic leukemia. *N Engl J Med.* 2011;365(26):2497-2506.

4. Shalek AK, Gaublomme JT, Wang L, et al. Nanowire-mediated delivery enables functional interrogation of primary immune cells: application to the analysis of chronic lymphocytic leukemia. *Nano Lett.* 2012;12(12):6498-6504.

5. Burger JA. Nurture versus nature: the microenvironment in chronic lymphocytic leukemia. Hematology Am Soc Hematol Educ Program. 2011;2011: 96-103.

6. Lutzny G, Kocher T, Schmidt-Supprian M, et al. Protein kinase c-β-dependent activation of NF-κB in stromal cells is indispensable for the survival of chronic lymphocytic leukemia B cells in vivo. *Cancer Cell.* 2013; 23(1):77-92.

7. Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell.* 2000;100(1):57-70.