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Response

To force the expression of CCR4 and/or of CCR5 chemokine receptor in T cells for immunotherapy of Hodgkin lymphoma: that is the question

We have recently shown that forced expression of CCR4 by effector T cells enhances their migration to Hodgkin tumor, so that coexpression of both CCR4 and a chimeric antigen receptor directed to the Hodgkin lymphoma (HL)–associated antigen CD30 produces better tumor control when these cells are infused intravenously in mice engrafted with human $CD30^+$/thymus and activation-regulated chemokine–secreting HL.[1]

In their letter to the editor, Aldinucci and colleagues point out that Hodgkin Reed-Sternberg cells also produce CCL5/Rantes in addition to other, previously reported chemokines, such as thymus and activation-regulated chemokine and macrophage-derived chemokine.

Although we agree with the suggestion by Aldinucci et al that it is therefore appropriate to consider overexpressing CCR5 (the receptor for CCL5/Rantes) in T cells to maximize tumoral migration, we chose not to do this for two reasons. First, CCL5/Rantes is constitutively expressed in normal lung,[2,3] where it mediates T-cell transmigration from the pulmonary vasculature compartment into the interstitium.[4] Expression is increased during infection or inflammation. Hence, T cells overexpressing CCR5 could well be diverted to normal lung tissue. Because pulmonary vascular trapping of infused T lymphocytes undoubtedly occurs even with unmodified cells, we were anxious not to further increase this process.

Our second reason relates to receptor desensitization.[5] As previously described,[6] many activated T cells themselves secrete CCL5/Rantes and this secretion may block or down-regulate receptor expression and interfere with migration in response to paracrine production of CCL5/Rantes by tumor cells.

Hence, we agree that migration of T cells may, in principle, benefit from the expression of multiple chemokine receptors, but we suggest that addition of CCR5 may be problematic, and that for the present, CCR4 may be the most suitable single-receptor option for increasing T-cell migration to the HL microenvironment.

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To the editor:

WHO classification of myeloid neoplasms and leukemia

Vardiman et al have focused their paper[1] on major changes in the 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and leukemia compared with the 2001 edition and have provided the rationale for those changes. Many of these changes and new definitions follow biologic features and include important information for prognosis. They pave the way not only to a better understanding of acute myeloid leukemia (AML) but also will advance outcome for patients. However, we cannot agree with the rationale for maintaining the category of "acute myeloid leukemia with multilineage dysplasia" (MLD), first established in the third edition in 2001, that is now subgrouped in the group of "AML with myelodysplasia-related changes."

We have shown in 2 large AML studies[2,3] of 2 different study groups (Study Alliance Leukemia and German AML Cooperative Group) in 2380 patients that MLD has no independent prognostic relevance if compared for patients when cytogenetics are also available (a must in WHO classification). Even more, MLD per se has absolutely no prognostic significance in patients 60 years of age or younger with de novo AML and, additionally, in the important subgroup of patients with normal karyotype.

We could show that it is of prognostic relevance to include now "MDS [myelodysplastic syndrome]–related cytogenetic changes"[1p945] in the definition of this new WHO subgroup. However, to define only by morphology AML that "exhibit dysplasia in 50% or more of the cells in 2 or more myeloid lineages"[1p946] cannot be justified based on published data. Thus, MLD as a marker of an AML subgroup should be omitted because it is prognostically and clinically misleading.

Vardiman et al further stated that there is no data concerning the correlation of "morphologic dysplasia" and the molecular mutations *NPM1* and *FLT3*-ITD. As published in our paper in *Blood*,[2] we could show in more than 1200 patients with AML that *NPM1* was mutated in 30% of patients with AML and MLD, which was

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