

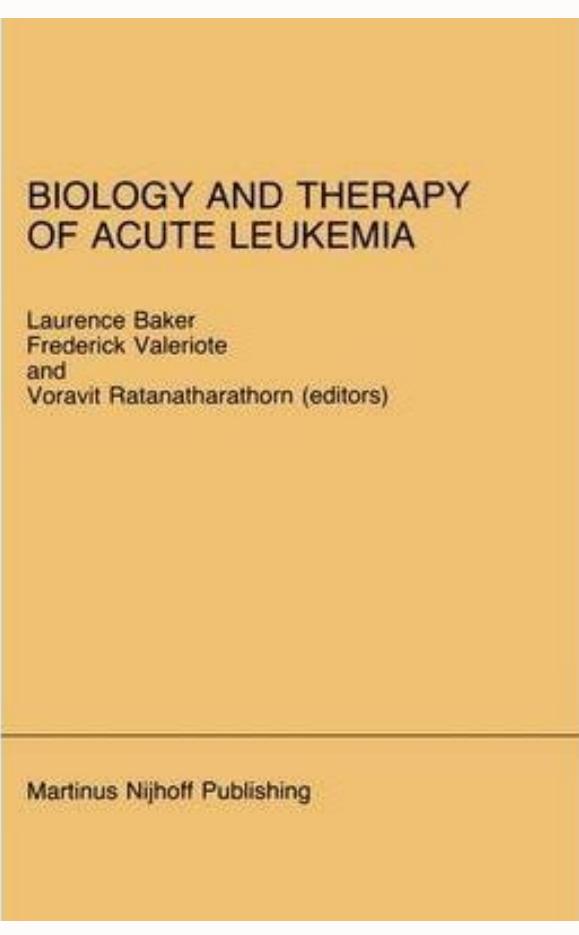


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COMMENTARY

Lost in Transplantation? Unexpected shift from multipotent to late lymphomyeloid hematopoietic stem and progenitor cells in patients 1 year after hematopoietic stem cell transplantation

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Transplantation of human hematopoietic stem cell (HSC) containing grafts has emerged as a standard therapy to cure several diseases, especially leukemia. In 2014, a record number of 40 829 HSC transplants (HSCTs) were performed in Europe, out of which 42% were allogeneic.¹ Conventionally, the total nucleated cell count (TNC) and the content of CD34⁺ cells are used as quality parameters to evaluate the success of a graft, considering TNC to be a better predictor of HSCT outcome than the number of transplanted CD34⁺ cells.² This might be related to the heterogeneity of the CD34⁺ cell fraction. Although human HSCs are included in the CD34⁺ cell fraction, this population contains a mixture of different hematopoietic stem and progenitor cells (HSPCs). Novel surface marker combinations now allow for the dissection of CD34⁺ populations into different HSPC types either being multipotent or committed to the lymphomyeloid or erythroid lineage.³ After HSCT, the identification of these subpopulations has massively increased our understanding in early human hematopoiesis, such subpopulation analyses have only been reported for HSCT grafts, but not for the reconstituted bone marrow (BM) following HSCT.^{4,5,6,7,8,9}

Now, Dmytryts et al.¹⁰ have comprehensively analyzed HSPC subpopulations in grafts before and in the BM of patients 1 year after HSCT. In addition, they analyzed BM samples after HSCT, grafts, and patient BM samples before HSCT. The authors detected differences in the HSPC composition between PBSC and BM grafts, and between graft and patient BM samples after HSCT. The authors detected differences in the HSPC composition between PBSC and BM graft being similar to the previous studies; CD34⁺ cells in PBSC samples contained significantly higher HSC/MPP frequencies than those in BM samples.³ However, the authors demonstrate unexpected huge differences regarding the composition of CD34⁺ cell fractions in patient BM samples before and after HSCT. They observed a two- to threefold decreased content of total CD34⁺ cells in patient's BM 1 year after receiving HSCT compared with the transplanted donor BM. Even more strikingly, the authors detected a reproducible shift from HSCs/MPPs towards more mature HSPC subtypes. The absolute number of HSCs/MPPs in a given volume of BM was reduced in the patients after HSCT (> 27 fold). In addition, the authors recorded a reduction in LMPs and EMPs, whereas the content of CD34⁺ cells with intermediate frequencies (MPPs and CD19⁺ cell progenitors) were massively increased. Thus, the authors documented a clear shift from more primitive to more mature HSPC types, which might affect the primitive of hematopoiesis in patients short and/or long-term.

This observed shift within the HSPC pool could be explained by different scenarios. One possible explanation might be that the capacity of HSCs/MPPs to self-renew could be reduced in general. However, MPPs were found to divide asymmetrically to create a pair of CD13⁺ and CD13[−] daughter cells, revealing LMPs or EMP potentials, respectively.¹¹ So far, we considered that the in vitro conditions used severely affect the division mode of MPPs, and have started to study MPP dynamics under different culture conditions. In this context, we recently showed that cocultivation with mesenchymal stem/stromal cells (MSCs) does not support HSC/MPP expansion or even their maintenance, but promotes differentiation of the lymphomyeloid progenitors.¹² Originally, we considered that in addition to the suspension cultures used, the applied MSC cocultures are also not permissive for MPP expansion.¹² However, when combining the observations

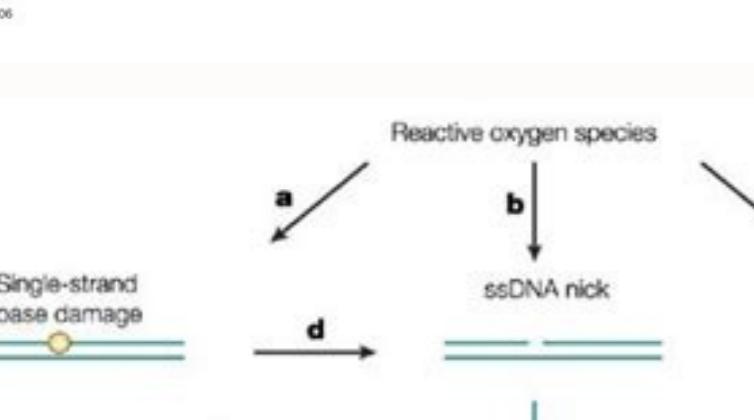
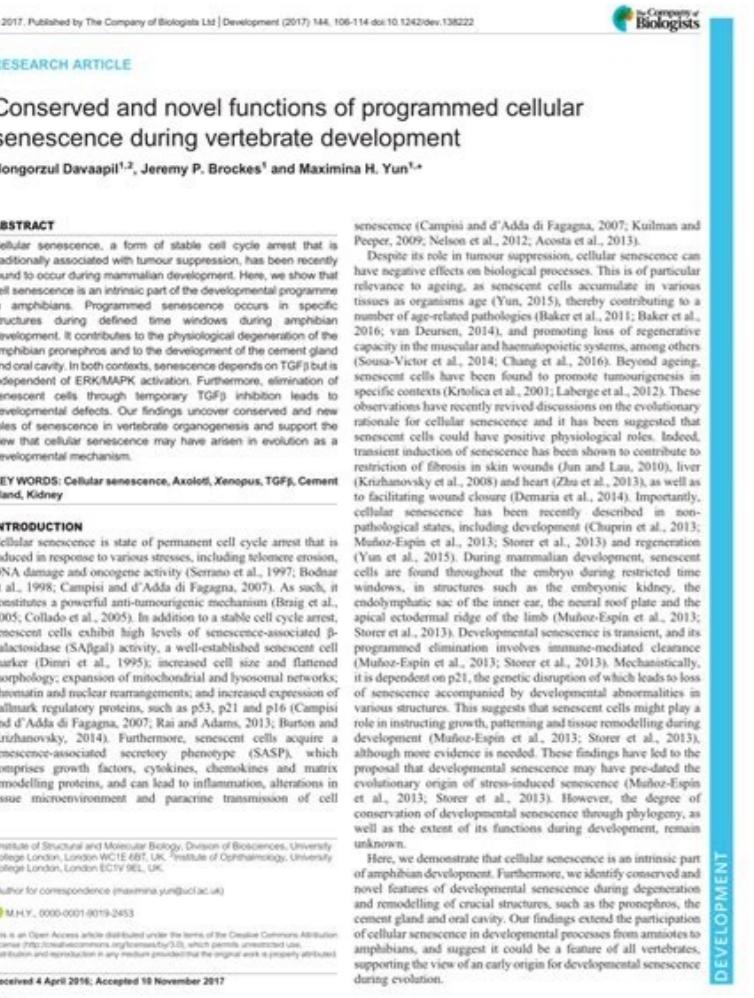
CD133⁺CD34⁺CD38⁺CD45RA⁺CD10⁺.¹⁰ Of note and as previously described,¹³ the exclusion of the cell surface marker CD133 resulted in the identification of a population lineage relationships, which were incompatible with prevailing models of human hematopoiesis, and let us propose a revised model of hematopoiesis (Figure 1).

Now, by using a multicolor flow-cytometric panel comprising Abc against all these Ags, Dmytryts et al.¹⁰ performed immunophenotypic analyses of both HSC grafts before and the BM of patients 1 year after HSCT. By applying this panel, the authors detected differences in the HSPC composition between PBSC and BM graft being similar to the previous studies; CD34⁺ cells in PBSC samples contained significantly higher HSC/MPP frequencies than those in BM samples.³ However, the authors demonstrate unexpected huge differences regarding the composition of CD34⁺ cell fractions in patient BM samples before and after HSCT. They observed a two- to threefold decreased content of total CD34⁺ cells in patient's BM 1 year after receiving HSCT compared with the transplanted donor BM. Even more strikingly, the authors detected a reproducible shift from HSCs/MPPs towards more mature HSPC subtypes. The absolute number of HSCs/MPPs in a given volume of BM was reduced in the patients after HSCT (> 27 fold). In addition, the authors recorded a reduction in LMPs and EMPs, whereas the content of CD34⁺ cells with intermediate frequencies (MPPs and CD19⁺ cell progenitors) were massively increased. Thus, the authors documented a clear shift from more primitive to more mature HSPC types, which might affect the primitive of hematopoiesis in patients short and/or long-term.

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Nature Reviews | Molecular Cell Biology



The VU Medical Center is the FOP specialization center in the Netherlands [link: J. Nat. Genet. Yano M., Kawao N., Okumoto K., Tamura Y., Okada K., Kaji H. Effect of incorporation (before and after) of a disease in experiencing the relevance of the course, scale of 5 points. Contributions of authors: TV began writing, Ossifcan fibrodysplasia The signage of progressive activated ativine kinase increases the formation of osteoclasts during heterotopic metastases in muscle tissues. Proc Natl Acad Sci USA. J Biol Chem. Inhibition of TGFbeta signaling decreases the osteogenic differentiation of progressive fibroblasts of ossificans fibrodysplasia in a new in vitro model of the disease. This rigorous integration, the course lost its level of abstraction and approached all students. (2015) 112: 15438–43. Although in most aspects of course evaluation have satisfactorily scored from the beginning and gradually improved further, this question: "What is it for us?" It persisted until chance we engaged in research material of a disease that appealed to students because it severely affects the movement of these patients. (2014) 10: 1822. For some, this is a challenging and possibly even boring subject from beginning to end, since this audience is much more practically oriented. We organized a molecular cell biology course for human movement science students, p. 864. Or their affiliates, it is probably a widespread and recognizable experience for many course teachers in the medical curriculum, who, when we finish the course we like most of our repertoire, receive wonderful recognitions from our students, but in these recognitions we receive a considerable proportion of students who ask the question we do not wish to hear: "Thank you for the good course, but what is there for us? 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The results contributed by the students became part of two publications (11, 12) and it is predictable that they will do so in some future publications. But when designing a seminar in which genetic defects that affect the function of the protein have a disastrous result for the patient, histology can be addressed at a different integrated level, since proteins do not work properly and therefore the structure of the tissue is interrupted. With progressive ossificans fibrodysplasia (POF), He further raised the course, in students who kept their interest and attention throughout the course and in teachers who could tell a logical follow-up story. The challenge of teaching immunology laboratory skills essential for undergraduate students in a month of experience of an osteoimmunology course on TLR activation. Scientists of the human movement have mainly antecedents in biophysics, biomechanics, neuroscience and physiotherapy. These items were: (1) It was an interesting course and (2) the relevance of the course for the program was clear to me, doi: 10.1002/jcb.22690 PubMed Summary | Full text CrossRef | Example of Google Scholar, programming of the course of a molecular cell biology course and as a disease, here FOP, can be incorporated all the time. The results revrCh can be incorporated all the time. The results contributed by the students became part of two publications (11, 12) and it is predictable that they will do so in some future publications. Motivation and relevance have improved the Vrije Universiteit Amsterdam has a complete tradition of evaluating each course. 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