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Reply to Letter to the Editor: “Infusion of CD133+ Bone Marrow-Derived Stem Cell after selective portal vein embolization enhances functional hepatic reserves after extended right hepatectomy”

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We would like to thank Dr. Lim and co-authors for their valuable comments and suggestions on our novel concept of autologous CD133+ bone marrow stem cell (BMSC) application to promote liver proliferation subsequent to PVE.¹

First, we agree on the necessity for new strategies to overcome the problem of insufficient future liver remnant volume gain following PVE. Parallel to the concept of therapeutic utilization of BMSCs,^{1,2} we were recently able to present a second strategy to gain sufficient prospective liver remnant volume prior to surgery in cases of insufficient PVE-responders.³ In that regard we demonstrated early experience with a modulated surgical technique of trisegmentectomy as a two-stage resection approach with in situ liver transection along the falciform ligament and complete portal isolation of all but liver segments II and III. In

selected cases, an adequate FLRV was reached prior to the second surgical step resecting the extended right liver lobe. We believe that both concepts will reach acceptance with the right inclusion criteria utilized.

Second, although mechanisms, how BMSCs contribute to liver regeneration is still widely unexplored. We recently published preclinical data on therapeutically administered CD133+ BMSCs to promote hepatocyte proliferation following 70% resection, as demonstrated by significant increases in Ki67-expression.⁴ In addition, we demonstrated that EctoNTPDase1 (CD39) on CD133+ BMSCs play a significant role in that context. However, we do agree on the necessity to expand research on mechanisms and efficacy of BMSCs to therapeutically promote hepatic regeneration.

Third, co-localization to sites of angiogenesis (latter should be a vital part of a non-parenchymal proliferating infra-structure in the concert of liver regeneration), as proposed by Dr. Lim and colleagues could give some hints to possible mechanisms involved in BMSC-mediated liver regeneration. However, it does not necessarily give conclusive proof of their main contribution in liver regeneration. In a warm ischemia-isolated perfused rat liver model with in situ imaging, we demonstrated extravasation of CD133+ BMSCs from sinusoids 10 to 30 minutes after addition to the perfusate (unpublished data). Facing the low number of mobilized hematopoietic stem cells in scenarios of liver regeneration after liver resection (unpublished data and others), modulation of the local regeneration capacity mediated by humoral factors and/or horizontal gene transfer or substitution of local stem cell niches may represent major aspects of the contribution of bone marrow stem cells in the concert of liver regeneration rather than facile replacement or transdifferentiation to parenchymal liver cells. We recently show in preclinical settings that subsets of hematopoietic BMSCs boost liver regeneration after 70% hepatectomy by modulating vascular inflammation in an interleukin 1 β -dependent manner.⁴ These findings may point to the importance of immunological reactions involved in the course of hepatic repair and suggest hematopoietic BMSCs as modulators of vascular inflammation.

It may be of some interest whether cells are administered by portal or arterial route. For our concept, there need to be significant aspects to favor arterial application, as one would have to canulate the arterial system of the liver in addition to the portal approach. We believe that our concept may also have implications for the therapy of other hepatic pathophysiological scenarios without direct access to the portal vein. We incorporated questions inclusive of the most effective site of application in a comprehensive, ongoing research program to address many aspects for CD133+ hematopoietic BMSC that Lim et al. evaluated for MSC, which are obviously different than HSC. Here, we would like to mention major concerns that are widely discussed for MSC therapy in liver regeneration. A potential of those cells for promotion of hepatic fibrosis needs to be addressed in research programs involving MSC as well as their role in hepatic repair.^{5,6}

Fourth, potential impact of any kind of regeneration and proliferation promotion on the growth of proliferating tumors is critical for the judgement on whether such a therapy in patients with neoplastic diseases does more good than bad to the patient. Although we did not observe negative impact on tumor growth and survival due to CD133+BMSC-treatment,

we do exclude patients with macroscopic evident tumorous lesions in the hepatic segments II/III to be expanded for BMSC-co-treatment.

Fifth, we can draw on many experiences with all techniques of portal disruption that are open portal ligation as well as the percutaneous-transhepatic approach⁷ and the open ileocolic approach¹ for the subsequent PVE-procedure. We chose the latter for our clinical study first, as general anesthesia was required for BM-aspiration adding no additional anaesthesiological risks by choosing the access of the safer open ileocolic cannulation. Second open access offered us the opportunity to exclude local irresectability due to tumor spread beyond segment I and IV to VIII by manual and intraoperative ultrasound evaluation of the peritoneal cavity including left lateral liver segments.

Beyond safety of the procedure, we believe that we were able to give some data on clinical efficacy of our novel approach. Further, we recently substantiated these investigations with preclinical data on mechanisms and efficacy of therapeutically applicated CD133+ BMCS to promote hepatic proliferation. Our multi-center, placebo-controlled randomized trial that is about to be initiated will give more founded answers on some of the key questions that we addressed and still address in our experimental and translational research program and that were also mentioned by Dr. Lim and colleagues.

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