Risk and Benefit of CD133+ Progenitors
To the Editor:
In their commentary to our recent article published in Circulation Research, Chen et al analyze possible additional mechanisms that could amplify or negate the therapeutic action of CD133+ cells. They also pinpoint the important finding that CD133+ cells can be successfully substituted by application of their conditioned medium, since both treatments produce a similar therapeutic effect. One important aspect of our study not mentioned in the commentary is that for the first time stem cells were applied to diabetic ulcer model with superimposed ischemia, a harmful and common association in diabetic patients. This novel model appears the most appropriate to define the true curative action of stem cells as well as secreted morphogens.

Chen et al are concerned about the use of fetal CD133+ cells because of problematic accessibility and risk of cancer induction. Although the use of fetal stem cells may raise ethical and practical arguments, adult CD133+ cells can be sorted in sufficient number from bone marrow for autologous transplantation and are being used in translational research. The ongoing TRANSact I trial at our institution (R.A.; http://www.controlled-trials.com/ISRCTN65630838/TransACT), with its double-blind placebo control design in patients with recent large anterior myocardial infarct undergoing coronary surgery, will ascertain the safety and efficacy of autologous bone marrow derived CD133+ cell transplantation. From feasibility clinical studies, the risk of spreading cancer by intramyocardial injection of autologous CD133+ cells appears remote. The application of CD133+ cells to ischemic ulcers offers the additional advantage that unwanted consequences can be easily monitored through direct examination of wounds.

Another relevant issue regards the possibility that stimulation of Wnt signaling in the wound of the recipient may produce an immature neovascularization. This possibility cannot be discarded, because although increased in number, wound neovascularization appeared leaky and prone to bleed. We suspect that these characteristics are typical of the diabetic condition rather than attributable to activation of Wnt signaling by transplanted cells, because fetal CD133+ cell transplantation stimulates mature neovascularization in nondiabetic mice. Wound healing is a complex phenomenon, with angiogenesis playing an important but not exclusive role in cicatrization. Wnt signaling was shown to be fundamental for wound cicatrization by activation of local epithelial stem cells. Therefore, the activation of Wnt by CD133+ cells might favor cicatrization by vascular and nonvascular means. Rapid cicatrization is of paramount importance because an open diabetic wound is highly susceptible of infection and chronicization.

It is known that wounds heal so well in fetuses that no scar can be visible at birth. It is therefore possible that, when fetal stem cells are transplanted onto diabetic ulcers, they reactivate a fetal program in the recipient to allow those adult ulcers to repair as efficiently as fetal wounds do. Standardization of the curative components of conditioned medium is essential to make this strategy clinically exploitable. Finally, it would be of paramount importance to determine whether the conditioned medium of adult CD133+ cells can promote healing of ischemic ulcers similar to the conditioned medium of fetal CD133+ cells.

Disclosures
None.

Raimondo Ascione
Paolo Madeddu
Bristol Heart Institute
Bristol, United Kingdom
E-mail madeddu@yahoo.com

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Raimondo Ascione and Paolo Madeddu

doi: 10.1161/CIRCRESAHA.109.201814
_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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