Health is our natural state of being. With rare exceptions, we are born healthy and we live much of our lives in a state of virtually perfect health. We are maintained in that naturally healthy state by the normal functioning of all of our tissues and organs and their component cells.

Recently, the power of cells to restore health is being widely recognized. Autologous T cells are being programmed to target specific antigens expressed by previously lethal leukemias, achieving unprecedented apparent cures.\(^1\) Conversely, regulatory T cells are being tested in type 1 diabetes mellitus in an attempt to re-establish immune tolerance in this condition.\(^2,3\) with some earlier examples of resultant insulin independence.\(^4\) In the cardiovascular (CV) arena, the use of a variety of cell types to treat heart failure\(^5,6\) and ischemic heart disease\(^7\) is being widely tested. This generation of cellular medicine, targeting the reversal of disease, may fundamentally change how medicine is practiced.

Prevention of disease is certainly more attractive than disease treatment to both healthcare payers and patients. A next step for cellular medicine would be to target the maintenance of health, rather than treat clinically evident disease, which presents itself after years, if not decades, of subclinical injury, and represents a state of exhaustion of reparative capacity. Critical for this mission is an understanding of the mechanisms by which we are maintained in a state of health; implicit in this is a deeper understanding of cellular reparative capacity. The discovery of resident tissue stem cells in adult tissues and circulating stem cells capable of incorporating into areas of ischemia or injury has sparked interest in the role of these cells in reparative processes.\(^8\)

Traditionally, CV risk has been identified by measurement of factors, which predict rates of adverse events; however, these factors do not provide the biological mechanisms that ultimately lead to the decline in CV health. Because of the increased attention to the role played by reparative processes in maintaining health, interest in measuring capacity for repair has focused on determination of the numbers of circulating progenitor cells (CPCs).\(^9-12\)

As pointed out in the work of Rigato et al,\(^13\) CPCs, purportedly of bone marrow origin, are associated with angiogenic capability in ischemic animal models. Although these cells have been identified using different techniques and markers, and do not represent a uniform population, each cell type has been associated with the presence of vascular disease: the numbers of risk factors for vascular injury,\(^8,10\) the degree of vascular disease present,\(^14\) and aerobic physical capacity.\(^15,16\)

A series of reasonably sized studies has evaluated the association of CPCs with CV outcomes, and demonstrated an association of the vascular markers of repair with a risk of myocardial infarction and mortality.\(^11,12\) The size of these experiences is limited by difficulties inherent in measuring rare populations of cells in nonmobilized blood samples, where CPCs represent from <0.1% to 1% of mononuclear cells. In addition, identification of rare cells types is not readily done from frozen or processed samples.

The work of Rigato et al\(^13\) is a stimulating and valuable addition to the literature. These authors analyze 21 studies encompassing 4155 patients, demonstrating that in general, there is an association of a variety of CPCs, most notably those expressing CD34 or both CD34 and CD133, with CV events and overall mortality. The analysis is hampered by significant variability between studies in CPC and end point definitions; thus, the number of trials incorporated in individual analyses is variable and sometimes small. It is important to question whether the conclusions drawn are driven by the underlying biology, or merely by the numbers (or lack thereof) of patients that contribute to individual analyses.

Where does this work lead us? CV medicine is now replete with novel cardiac biomarkers, which to varying degree allow for a better assessment of risk. Do we need another CV biomarker? By offering a unique assessment of reparative capacity, CPCs might offer significant prognostic information independent of conventional markers, which predominantly reflect propensity for vascular injury. However, there are significant limitations to CPC measurement; notably, such analyses are best done on fresh blood samples, necessitating immediate assessment, and requiring specialized culture or flow cytometric techniques, which are not easily available. Our own experience is that this has been difficult to implement into larger scale clinical trials using a local cell cryopreservation technique.\(^17\) Although flow cytometric analysis has been performed at central laboratories for other indications, this is usually done on populations that are more prevalent than CPCs. In this regard, an analysis using a single biomarker,
such as CD34, which is typically expressed at high levels, offers a high level of discrimination between expressing and nonexpressing cells, and identifies a more prevalent CPC population than cells expressing combinations of multiple markers, might offer the best opportunity to develop a biomarker that could be easily implemented in the clinical setting.

It should be recognized, however, that biomarkers are helpful for other reasons; for instance, they may lead to new inferences concerning mechanisms of disease. The discovery of an association between Proprotein convertase subtilisin–kexin type 9 genetic variants, hyperlipidemia, and propensity to CV disease led to the development of antagonists of this pathway that have proven highly effective at lowering cholesterol and preventing CV events in select patients. Might the identification of CPCs as markers of CV risk serve a similar purpose?

To cardiologists, regenerative medicine has not captured a significant piece of our lexicon because of the long held belief that adult cardiac tissue is unchanging and incapable of regeneration. Several recent lines of evidence question this dogma, including the demonstration of myocytes expressing host chromosomes in donor-transplanted tissue and the definitive demonstration of turnover in human adult cardiac myocytes using natural radiological labeling experiments. Nonetheless, as clinical practitioners of acute infarction patients recognize, cardiac regeneration does not occur to the degree required to make a clinically meaningful impact.

Might the synthesis of work as accomplished by Rigato and colleagues add impetus to research in cell-mediated CV repair? In this regard, it is of interest that the most studied cells express CD34 alone or in combination with other markers. Correspondingly, on the therapeutic side, selection of CD34+ cells was found to improve the efficacy of the cell product in preclinical studies.

Randomized double-blinded trials have demonstrated that CD34+ cell administration is associated with improvements in symptoms of angina and exercise capacity, a finding confirmed in observational studies.

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Randomized double-blinded trials have demonstrated that CD34+ cell administration is associated with improvements in symptoms of angina and exercise capacity, a finding confirmed in meta-analyses. In heart failure, administration of CD34+ cells may be associated with improvements in mortality.

The findings presented here further establish the importance of regenerative pathways in the pathophysiology of CV disease, adding further credence to the paradigm that disease is a balance between injury and repair. Results like this should not only motivate researchers to further our understanding of the effectiveness of stem cell-mediated repair as a treatment for CV disease but also stimulate the development of novel approaches to harnessing and enhancing native reparative mechanisms to impede development of overt disease. Important in this regard will be further investigations of whether the associations observed in this study are because of stem cell depletion with time, reflecting a loss of reparative capacity after years of injury, or whether patients are born with inherently impaired altered reparative capacity. Answering such questions will require assessment of CPCs in younger healthier patients and temporal assessment of changes in CPCs with aging.

As we face an ever-increasing economic burden in the healthcare system, we are forced to confront our inability to manage disease, particularly on a global scale. Health is relatively inexpensive to manage. Accordingly, we must now divert ever-increasing attention to the maintenance of health. By understanding the cellular mechanisms of CV repair and regeneration, we open the door to perpetuating the natural state of health.

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