Cell-Based Therapy of Myocardial Infarction

Stefanie Dimmeler, Jana Burchfield, Andreas M. Zeiher

Abstract—Cell-based therapy is a promising option for treatment of ischemic diseases. Several cell types have experimentally been shown to increase the functional recovery of the heart after ischemia by physically forming new blood vessels, differentiating to cardiac myocytes and—additionally or alternatively—by providing proangiogenic and antiapoptotic factors promoting tissue repair in a paracrine manner. Clinical studies preferentially used adult bone marrow–derived cells for the treatment of patients with acute myocardial infarction. Most of the studies suggested that cell therapy reduced the infarct size and improved cardiac contractile function. However, cell therapy is in its early stages, and various questions remain. For example, the identification of those patients who benefit most from cell therapy, the optimal cell type and number for patient with acute and chronic diseases, the best time and way of cell delivery, and the mechanisms of action by which cells exhibit beneficial effects, need to be further evaluated. Although no major safety concerns were raised during the initial clinical trials, several potential side effects need to be carefully monitored. The present review article summarizes the results of the clinical studies and discusses the open issues.

Key Words: cell therapy ■ neovascularization ■ stem cells ■ acute myocardial infarction

Ischemic diseases remain one of the major causes of morbidity and mortality in the industrialized world despite the development of several new therapeutic modalities, such as improved pharmacological therapies and improved interventional strategies (eg, catheter-based reopening of vessels). Peripheral ischemic vascular disease is still associated with a high morbidity and impairment of quality of life, whereas cardiac ischemia leading to postinfarction heart failure particularly in patients with large myocardial infarction is associated with a high mortality. Over the last decade, it has become apparent that the heart possesses regenerating capacities with respect to cardiomyocytes and new blood vessel formation (for review see1,2). Specifically, it has been shown that a sizeable fraction of cardiac myocytes “refreshes” the heart after injury insults like ischemia or pressure overload.3 Based on experimental data demonstrating that infusion or
injection of stem/progenitor cells improves heart function after myocardial infarction and enhances blood flow in models of peripheral ischemia, clinical trials were initiated in 2001 to treat patients with peripheral or cardiac ischemia with circulating blood or bone marrow–derived cells. The present review article will summarize the experimental data and the clinical application of cell-based therapies focusing on patients with acute myocardial infarction, where most clinical data are available at present.

Types of Stem Cells
Numerous studies have experimentally addressed the potential of different types of stem cells to augment neovascularization and cardiac repair or regeneration. In general, two types of stem cells should be discussed separately: embryonic stem cells and adult stem cells. Whereas embryonic stem cells clearly have the capacity to differentiate into a variety of cell types and give rise to tissues and organs, most adult stem cells are more specified (more lineage committed) and the use of adult stem cells for organogenesis appears to be rather limited. This review will focus on the different types of adult stem cells and their therapeutic role in the salvage of ischemic tissue and in treatment of heart disease. Adult stem cells comprise at least 3 different groups: bone marrow–derived stem cells, the circulating pool of stem or progenitor cells, which, at least in part, are derived from the bone marrow, and tissue-resident stem cells.

Bone marrow–derived stem cells are the best characterized and have been used in the majority of clinical trials performed to date. Bone marrow contains a complex assortment of progenitor cells, including hematopoietic stem cells (HSCs); so-called “side population cells” (SP cells, defined by the expression of the Abcg2 transporter allowing to export a Hoechst dye),4 mesenchymal stem cells (MSCs) or stromal cells,5 and multipotent adult progenitor cells (MAPCs), a subset of MSCs.6 Several studies have shown the incorporation of these different bone marrow–derived cells into ischemic tissue, and it appears that these cells play a distinct role in the salvage of damaged tissue.

Another population of progenitor cells that has also been shown to have therapeutic potential is the pool of progenitor cells circulating within the blood. Circulating progenitor cells were initially discovered, when searching for proangiogenic cells for therapeutic vasculogenesis. Asahara and Isner isolated the so-called “endothelial progenitor cells” defined by their function to form new blood vessels and enhance neovascularization after ischemia (for review see7,8). According to the assumption that these cells may represent adult hemangioblasts, these cells were characterized by the expression of at least 2 hematopoietic stem cell markers (CD133+ or CD34+) and the endothelial marker VEGF-receptor 2 (also known as KDR or flk-1). The use of the marker combination CD34+CD133+KDR+ to identify clonally expandable circulating progenitor cells with a high capacity to acquire an endothelial phenotype has recently been challenged, and in vitro studies suggested that CD34+/CD45− cells have a higher capacity to acquire an endothelial phenotype, whereas CD34+CD133+KDR+ do not differentiate to endothelial cells.9 Although it is not entirely clear to what extent these data can be translated into the in vivo situation, where ischemic/necrotic tissue may provide an entirely different environment to dictate cell fate, it is evident from various studies that circulating progenitor cells, particularly when cultured in vitro, comprise several different cell populations. Whereas individual cells may indeed have clonal potential and stem cell characteristics, other cells may provide proangiogenic factors or promote vessel maturation or may act as pericytes together leading to neovascularization. For example, one subpopulation within these cultured or endogenously circulating cells consists of myeloid and myeloid precursor cells, which may preferentially act as proangiogenic cells,10,11 in addition (or alternatively) to their capacity to differentiate to endothelial cells.7,12 Alternatively, myeloid cells have been shown to fuse with skeletal muscle myotubes13,14 indicating that myeloid subpopulations may not only act to mediate neovascularization, but may also aid in muscle regeneration. Therefore, the so-called “endothelial progenitor cells” most likely consist of several cell types that together may mediate salvage of ischemic tissue. As such the term “endothelial progenitor cells” refers to one functional aspect of a heterogeneous cell population, which is capable to induce neovascularization.

Other populations of stem cells that have been shown to have therapeutic potential in the setting of ischemia are derived from tissue and include mesoangioblasts, both mesenchymal and endothelial progenitor cells derived from adipose tissue, and tissue-resident cardiac stem cells. Mesoangioblasts are vessel-associated multipotent progenitors that express the key marker of angiopoietic progenitors, VEGF-receptor 2, but are distinct from hematopoietic endothelial progenitor cells. In vitro mesoangioblasts differentiate into many mesoderm cell types, such as smooth, cardiac and striated muscle, bone and endothelium, and have been shown in vivo to improve skeletal muscle function in a muscular dystrophy model as well as to improve heart function.15,16 Adipose tissue is a rich source of distinct subsets of stem/progenitor cells potentially useful for cardiac repair and neovascularization improvement.17,18 Both, mesenchymal stem cells and endothelial progenitor cells were isolated after enzymatic digestion of adipose tissue and showed beneficial effects in experimental studies.

The discovery of tissue-resident stem cells in the heart, the “cardiac stem” cells, offers the potential for in vivo induction of proliferation and differentiation of these cells, which are primed to acquire a cardiac phenotype and, therefore, might be optimally suited for cardiac repair. Several different populations have been identified and characterized including c-Kit+ cells,19 Sca-1+ cells,20 side population cells (SP),21 and cells expressing the protein Islet-1.22 Whereas c-Kit+ cells, Sca-1+ cells, and cardiac SP cells have been isolated from adult hearts, cells expressing Islet-1 so far only have been detected in neonatal hearts. Whether c-Kit+, Sca-1+, and cardiac SP cells comprise 3 different cell populations is not entirely clear. Another type of cardiac stem cell has been identified by growing self-adherent clusters (termed “cardiospheres”) from subcultures of murine or human biopsy specimens.23,24 Others have generated cardiac SP-cell derived cardiospheres by adapting a method used for creating neuro-
Islet-1 unclear. Two recent studies suggest that c-Kit mechanisms maintaining the cardiac stem cell pool are subpopulations such as a fraction of hematopoietic and without further ex vivo expansion. In a few studies, specific isolated bone marrow–derived cells are injected into the heart mesenchymal stem cells, and side population cells. So far, hematopoietic stem cells, endothelial progenitor cells, and peripheral blood mononuclear cells were compared in another study. This study suggested that single clonally subpopulation, unpurified MSC, bone marrow mononuclear cells, and peripheral blood mononuclear cells were compared in another study. This study suggested that single clonally purified MSC are most efficient for cardiac repair. Interestingly, unpurified MSC had similar beneficial effects on adverse remodeling of infarcted hearts compared with freshly isolated bone marrow mononuclear cells. However, because the rats were treated with cyclosporin A, one cannot exclude that the immunosuppression itself modulated the effects of the different stem cell populations. Clearly, a ranking of cells used for cell therapy will not only be based on the assessment of the functional capacities of the cells, but also on the safety and feasibility of the treatment in the clinical setting.

**Clinical Application**

**Clinically Used Cell Types**

Currently, a variety of autologous adult progenitor cells are undergoing preclinical evaluation. Bone marrow is, at present, the most frequent source used clinically for cardiac repair. The rapid transition from bench to bedside was facilitated by the more than 30 years of clinical experience and the excellent safety profile of infused bone marrow–derived mononuclear cells (BMCs) used for bone marrow reconstitution. After bone marrow aspiration the mononuclear cell fraction is obtained by density gradient centrifugation in most of the studies (only the BOOST trial used a sedimentation protocol). The mononuclear fraction includes a heterogeneous mixture of cells with varying percentages of hematopoietic stem cells, endothelial progenitor cells, mesenchymal stem cells, and side population cells. So far, isolated bone marrow–derived cells are injected into the heart without further ex vivo expansion. In a few studies, specific subpopulations such as a fraction of hematopoietic and endothelial progenitor cells expressing the marker protein CD133 are purified. Lastly, peripheral blood–derived progenitor cells are clinically used both for cardiac repair and peripheral ischemia. Circulating blood–derived cells have been isolated from mononuclear blood cells and selected ex vivo by culturing in “endothelium-specific” medium for 3 days, or a specific subfraction, the hematopoietic progenitor cells CD34+, is enriched from whole blood after G colony–stimulating factor (CSF) mediated mobilization from the bone marrow into the blood.

**Clinical Results**

The results of clinical trials published to date, aiming at progenitor cell-based myocardial repair in patients with acute myocardial infarction, are summarized in the Table. Overall, the published studies demonstrate that the intracoronary infusion of autologous BMC is safe and feasible in patients with acute myocardial infarction. The initial pilot studies by Strauer, the TOPCARE-AMI, the BOOST-trial, and the study performed by Fernandez-Aviles reported nearly identical results—an improvement in global LV ejection fraction by an absolute 6 to 9 percentage point, reduced end-systolic LV volumes, and improved perfusion in the infarcted area 4 to 6 months after cell transplantation. A randomized controlled trial by Janssens did not reveal a significant effect on global ejection fraction, but showed an improvement in regional ejection fraction and a reduction of the infarct size in the BMC group. Only one larger study, the ASTAMI trial, did not show any benefit on left ventricular functional parameters. The reason for the failure of the ASTAMI trial to show a benefit of cell therapy may have been because of the different cell isolation and storage protocol, which significantly affected the functional capacity of the cells. Because, however, no preclinical functional testing of the cells used for the ASTAMI trial was reported, it is essentially impossible to judge the negative outcome of this trial.

The beneficial effects observed in most of the pilot phase I/II studies were confirmed in the so far largest double-blind, randomized, multicenter REPAIR-AMI trial. This study used BMCs and demonstrated a significant improvement of global and regional ejection fraction in the BMC group (+5.5 percentage points) compared with placebo (+3 percentage points) 4 months after follow-up. End systolic volumes significantly increased in the placebo group but remained unchanged in the BMC group. Interestingly, although the study was not powered to address a potential benefit on clinical end points, the incidence of the cumulative end point death, recurrence of myocardial infarction, and rehospitalization for heart failure was significantly lower in the BMC-treated patients compared with placebo after 1 year follow-up.

What variables might influence outcome? The larger number of patients enrolled in the REPAIR-AMI trial allowed to test several predefined secondary end points to generate hypothesis for the next generation trials. There was a significant interaction between the baseline ejection fraction and the improvement seen after BMC therapy. Patients with a lower baseline ejection fraction (≤48.9%) showed a signifi-
cant 3-fold higher recovery in global ejection fraction indicating that patients with more severe myocardial infarction profit most from BMC therapy. Indeed, the beneficial effect on clinical end points was also preferentially observed in those patients with a lower baseline ejection fraction after myocardial infarction. These results confirmed the previous observation of the TOPCARE-AMI pilot trial. A second predefined end point addressed the question, whether the timing of BMC delivery affects the outcome. Surprisingly, patients being treated up to 4 days after the myocardial infarction showed no benefit, whereas later treatment (day 4 to 8) provided an enhanced improvement of ejection fraction during follow-up. Given that several experimental studies demonstrated that the cells provide cytoprotection coinciding with a reduction of cardiomyocyte apoptosis one would have expected that early timing of cell infusion would be most efficient. With the data of the REPAIR-AMI trial, one may speculate that the microenvironment after acute myocardial infarction changes during the first week after reperfusion, thereby modulating the homing or the subsequent functional activity of the infused cells.

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“waves” of cells. Therefore, it is conceivable that cell homing might be best after a few days rather than immediately after reperfusion. Further studies are warranted to prospectively address this question.

Safety and Long Term Benefit of Cell Therapy

Although the initial experimental studies confirmed that infusion of bone marrow–derived mononuclear cells or CD34+ does not cause major side effects, several potential issues were raised during the last years including a potential effect of cell therapy on electrical stability, increased restenosis, or progression of atherosclerotic disease. However, none of the clinical studies with BMCs so far reported an increased incidence of arrhythmias (as have been seen in some of the myoblast trials). Moreover, restenosis, which was considered as potential side effect by progenitor cell–mediated plaque angiogenesis or plaque inflammation,42 was only increased in one study using CD133+ cells.43 This is surprising, because the isolation of selected progenitor cells excluding contaminating proinflammatory cells would have been assumed to reduce rather than increase the risk of restenosis and atherosclerotic disease progression. Because CD133+ cells were isolated by using a mouse antibody, one may speculate that the remaining antibody might have elicited a local proinflammatory reaction despite the failure to detect systemic anti-mouse antibodies in the patients. All other studies did not observe an augmented risk for restenosis44-46; if anything, there was a decreased necessity for revascularization procedures in the REPAIR-AMI trial.19

Intramyocardial calcification was reported to occur in murine models of myocardial infarction after direct injection of unpurified bone marrow cells or mesenchymal stem cells.45,46 In the various clinical trials, none of the investigators reported the occurrence of calcifications by MRI imaging. This may be explained by the enrichment of mononuclear cells by density gradient centrifugation used in the majority of the clinical studies. Indeed, in a side-by-side comparison, only unfractionated bone marrow cells and MSC, but not purified hematopoietic progenitor cell injection did induce pathological abnormalities and calcification in experimental models.46

Overall, the clinical data available at present indicate that cell therapy with bone marrow–derived cells is feasible and safe at least for the duration of follow-up presently available (up to 5 years for the initial studies). It had been discussed that the proangiogenic capacity particularly of EPC might relate to an increased tumor vascularization. Although it is unclear whether a single application of EPC is sufficient to promote tumor growth, most of the clinical trials did exclude patients with known tumors. During follow-up of the available studies, no increased incidence of cancer was seen in BMC-treated patient. However, because of the low incidence of such events, this needs to be carefully monitored in the future.

An important issue is whether the improvement seen during the initial 6 months after cell therapy is maintained for a prolonged time. Careful evaluation of the 18 months follow-up data of the BOOST trial indicates that the ejection fraction of the cell therapy group is maintained from 6 to 18 months follow-up, however the difference between the cell therapy and the control group was no longer statistically significant. The small number of patients (30 per group) may preclude detecting a statistical difference between the 2 groups. The long term 5 years follow-up MRI-derived data of the TOPCARE-AMI trial showed that the ejection fraction is maintained and even further augmented in the treated patients, in parallel with a sustained reduction in NT-proBNP serum levels suggesting a sustained beneficial effect on long term left ventricular remodeling (S.D. and A.M.Z., unpublished data). However, longer term follow up in larger scale randomized trials will finally address this important question. In addition, repetitive treatment might be an option in case cell therapy provides only a transient benefit. Finally, preliminary as yet unpublished results suggested that the intravenous infusion of nonautologous mesenchymal bone-marrow derived cells may have some effects in patients with anterior myocardial infarction. Such an off-the-shelf strategy for cell therapy would potentially make the procedural logistics easier.

Mechanisms of Action

One of the most urgent questions in basic science, to elucidate the mechanism by which stem/progenitor cells achieve a functional improvement, is difficult to be tested in the clinical scenario. Although clinicians can measure flow reserve and heart function, the underlying detailed mechanism cannot be determined with an ethically applicable technology in the near future. The demonstration of improvement of neovascularization by bone marrow–derived mononuclear cells and endothelial progenitor cells is, historically, the inception of virtually all cell-based therapies using bone marrow or its circulating derivatives for myocardial ischemia. It has been shown, using a variety of progenitor/stem cell populations, that these cells contribute to neovascularization. Neovascularization can be mediated by the physical incorporation of progenitor cells into new capillaries47 or by perivascular accumulation of cells. Furthermore, incorporated progenitor cells, of most, if not all types, may release growth factors that promote angiogenesis by acting on mature endothelial cells.10,48 The extent to which progenitor cells contribute to vasculogenesis by becoming physical elements of newly formed vessels versus acting through secreted factors may plausibly depend on the environment to which the cells are exposed, and may in part depend on the applied cell type. This may explain the large difference in endothelial incorporation detected in different experimental studies. However, human bone marrow–derived endothelial progenitor cells were shown to exert both classes of effects and most experimental studies, which applied cells for therapeutic neovascularization, demonstrated a rate of incorporated cells in capillaries between 2% to 29% after cell therapy.7 The Doppler substudy of the REPAIR-AMI trial provided convincing clinical evidence that intracoronary BMC administration in patients with acute myocardial infarction is associated with profound improvements in vascular conductance capacity and microvascular function in the cell-treated coronary territory.49 It will be important to determine whether increased coronary vascular conductance capacity ultimately
translates into improved clinical outcome to establish a cause-and-effect relationship between cell therapy–based improvements in neovascularization and functional cardiac regeneration.

In addition to enhanced neovascularization, activating cytoprotection must be considered as among the most important possible consequences of cell-based therapies. Paracrine factors may beneficially influence cardiac repair by protecting cardiac myocytes from apoptotic stimuli or activate cardiac-resident stem cells to enhance the endogenous repair capacity.48,50,51 In a porcine model of myocardial infarction, transplantation of allogeneic mesenchymal stem cells, in the absence of definitive cardiac myocyte differentiation, led to cardiac myocyte cell cycle entry and decreased apoptosis suggesting the stem cell transplantation may activate cardiac-resident stem cells to enhance endogenous repair.52 Indeed, soluble factors released by ex vivo cultured human EPCs stimulated migration of cardiac stem cells in vitro.48

Dysregulated inflammation in the heart after myocardial infarction is considered to be a normal part of the healing process after ischemic injury, which might be modulated by administered cell therapy. Indeed, analysis of gene expression profiles revealed that genes, which are involved in the inflammatory response under hypoxic conditions are highly expressed in BMCs. An antiinflammatory role for administered MSCs was demonstrated at 4 weeks after myocardial infarction with the downregulation of tumor necrosis factor (TNF)-alpha, interleukin (IL)-1beta, and IL-6, cytokines known to be involved in adverse LV remodeling.53 Thus suppression of inflammation during remodelling most likely will contribute to the improvement in LV function and the attenuation of adverse LV remodeling. In fact, several reports have shown that myocardial transplantation of progenitor/stem cells leads to a decrease in myocardial fibrosis after myocardial infarction.47,54 However, it is unclear whether the stem cell–mediated decrease in fibrosis is a secondary effect to limited cardiac myocyte apoptosis thereby negating the need for synthesis of a provisional extracellular matrix, or whether stem cells have a direct effect on extracellular matrix remodelling. At least MSCs were shown to directly attenuate cardiac fibroblast proliferation and collagen synthesis via the release of paracrine factors in vitro.55 Whether other progenitor/stem cell populations or their secreted factors modulate other extracellular matrix proteins or modulate the differentiation of fibroblasts into myofibroblasts, the cell responsible for collagen deposition, has not been investigated so far.

Experimental studies addressing the capacity of transplanted bone marrow–derived stem cells to differentiate into the cardiomyogenic lineage yielded conflicting results.1,56,57 In contrast to ES cells, most adult stem or progenitor cells do not spontaneously differentiate into cardiomyocytes but rather require an adequate stimulus to do so. The local microenvironment plays an important role to induce cell fate changes by physical cell-to-cell interaction or by providing paracrine factors. A recent study supports this notion by demonstrating that endogenous replacement of cardiomyocytes only occurs after injury.3 The identification of subsets of adult stem cells with a higher capacity to differentiate into cardiac myocytes and the enhancement of cardiac differentiation by interacting with the pathways controlling differentiation are currently under investigation.

It is essential to distinguish between the target patient populations, eg, acute versus chronic ischemia, when discussing mechanisms considered to improve functional recovery, because fundamentally different pathophysiological processes are targeted. In patients with acute myocardial infarction, progenitor cell transplantation aims to prevent or ameliorate postinfarction left ventricular remodeling, thereby reducing postinfarction heart failure. Such an effect might even be achieved by enhanced neovascularization and reduced cardiomyocyte apoptosis, irrespective of long-term engraftment and transdifferentiation. Conversely, the former 2 mechanisms acting alone may have limited benefit in patients with long-established scars, absent hibernating myocytes and end-stage heart failure, where cardiomyogenesis in its pure sense would be desirable. Thus, the putative mechanisms underlying cell therapy–mediated functional recovery of the heart illustrated in the Figure may differ with respect to the clinical relevance in different entities of cardiac failure.

Outlook: Open Questions

In acute myocardial infarction, the established safety and proof-of-concept studies provide a cogent rationale for larger, randomized trials addressing the question whether cellular therapy aimed at cardiac repair not only improves pump function, but also reduces mortality and morbidity. In planning such clinical outcome trials, one should take into account that aggressive reperfusion strategies in acute myocardial infarction have dramatically improved prognosis for those patients, in which reperfusion is associated with recovery of contractile function. In contrast, for patients with failure of contractile recovery despite successful reperfusion, which constitute approximately 20% of the entire cohort of patients with STEMI, mortality and morbidity are still markedly increased, and this has not changed over the last 15 years.58,59 Thus, this patient population will be the primary target to establish a potential clinical relevance of cell-based therapies in patients with acute myocardial infarction. Moreover, several open-ended questions are likely to be answered in the future: (1) What is the optimal time of cell delivery after acute myocardial infarction? (2) Is there a dose response relationship? and (3) How do different cell types compare? Clearly, bone marrow–derived cells have set the stage and have provided beneficial effects in various studies. However, the extent to which ejection fraction is improved, particularly in patients with chronic heart failure, is limited.60 Therefore, additional cell types will enter the clinical arena: adipose tissue–derived stem cells, multipotent cells from bone marrow or skeletal muscle (minuscule subpopulations, distinct from the unfraccionated bone marrow and the myoblasts in current trials), somatic stem cells from placental cord blood, and cardiac-resident progenitor cells that have a heightened predisposition to adopt the cardiac muscle fate. However, whether the experimentally suggested promise of augmented cardiac myogenesis will translate into enhanced
contractile function, when applying these cells in patients with chronic heart failure, is currently unknown.

More complex and challenging are a series of pathobiological concerns, sending the scientific community from bedside to bench and back again. As long as patients’ own cells are used in the autologous setting, certain patients’ cells may be unsatisfactory, in their naïve and unmanipulated state, prompting systematic dissection of each step in progenitor cell function. Cell enhancement strategies to improve patient-derived cells by pretreatment with small molecules or genetic modification may contribute to an augmented recruitment as well as in the future may enhance differentiation or other beneficial functions.

Clearly, the use of stem/progenitor cells for cardiac repair is currently not at a stage to be used in routine clinical practice. Despite a wealth of experimental and clinical data suggesting feasibility, safety, and even early clinical efficacy in patients with acute myocardial infarction, progression to widespread clinical application of progenitor cell administration to promote functional cardiac regeneration must be balanced against the inherent risk of testing a novel therapy. As such, attempts of regenerative therapeutic interventions in patients with significant cardiac dysfunction should proceed in controlled trials with the utmost rigorous scientific and ethical standards, paralleled by further extensive in vitro and animal studies. Such a strategy will not only maximize patient safety, which is of paramount interest, but will also generate reciprocal insights into mechanisms and potential shortcomings of cell-based therapies aiming at functional cardiac regeneration. Specific attention should be given to the processing of the cells and to ascertain their functionality for regenerative purposes before initiating their clinical application. The promise of functional cardiac regeneration by cell-based therapies offers novel opportunities to address the large unmet clinical need of treating patients with severe cardiac dysfunction.

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Disclosures

S.D. and A.M.Z. are founders and advisors of t2cure GmbH.

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