conditioning. As low as 1% of initial allogeneic chimerism was enough to reverse the diabetogenic process in pancreatic islets of prediabetic mice and the restoration of endogenous β-cell function to physiologically sufficient levels was achievable even if the BM transplantation (BMT) was performed after the clinical onset of diabetes [8]. More generally, BM has been shown to harbor cells that possess the capacity to enter extramedullary tissues and to differentiate into functional parenchymal cells of the respective tissue, such as the liver, intestinal, skin and bronchial epithelia, skeletal, heart muscle, and cells of the central nervous system [9–12]. These observations are not limited to experimental mouse models but are also made in biopsy material of human recipients of BMT [13]. This suggests that BM stem cells may be attracted at distant extramedullary peripheral sites after intense injuries and can participate in the tissue repair of damaged areas through remodeling and regeneration processes [14].

Several different types of adult stem cells can be found in the hematopoietic system. The most extensively characterized stem cell of mesodermal origin is the HSC, which can be isolated from peripheral blood (PB), BM, or cord blood (CB). The definition of HSC is the following: 1) a self-renewing ability, which can maintain the total pool of HSC at a constant level throughout life, and 2) a multiple differentiating capability, which can produce hematopoietic progenitor cells (HPCs) that differentiate into every type of mature blood cell in a well-defined hierarchy. These HSC/HPC are characterized by their surface expression of various kinds of antigens (CD34, CD33, CD38, HLA-DR, LFA-1, Thy-1, CD133, Bcrp-1), adhesion molecules/chemokine receptors (CXCR4, CD49d, CD49e, CD31, CD54, CD62L, CD106), cytokine receptors (IL-6R, IL-3R, IL-11R, G-CSF-R, LIF-R, c-Mpl, gp130), and receptor-type tyrosine kinases (c-kit, flt3, c-fms).

Among these markers, the cell surface glycoprotein CD34 antigen is considered a particularly reliable marker for murine and human HSC/HPC. BM, PB, and CB stem cell transplantation studies indicate that the CD34+ subpopulation in the BM, PB, or CB can provide durable long-term donor-derived lymphohematopoietic reconstitution. Recent data also have suggested that CD34+ HSC exist, challenging the concept that HSCs necessarily and exclusively express the CD34 antigen. In addition to HSCs, mesenchymal stem cells (MSCs) can also be isolated from BM or CB and contribute to the formation of mesenchymal tissues, such as bone, cartilage, muscle, ligament, tendon, adipose tissue, and stroma. Moreover, various progenitors with specific differentiation potential have been described within the hematopoietic system. These include multipotent adult progenitor cells, marrow-isolated adult multilineage inducible (MIA MI) cells and tissue-committed stem cells from BM [15–17], and unrestricted somatic stem cells [18] and multilineage progenitor cells [19] from CB. The relationship between these stem cells remains uncertain.

**HSC Differentiation to Insulin-producing Cells**

Diverse groups investigated the contribution of HSCs to β-cell replacement as direct differentiation into insulin-producing cells, and attempts to transdifferentiate HSCs into insulin-producing cells have produced conflicting results. Initial experiments focused on the transplantation of unpurified BM cells from a green fluorescent protein (GFP) mouse. The observation of GFP-marked cells expressing pancreatic markers was interpreted as confirming transdifferentiation. Ianus et al. [20] used a CRE-LoxP cell tracking system and BM from male mice with GFP replacing insulin expression for transplantation into lethally irradiated recipient female mice. After 4 to 6 weeks, recipient mice revealed Y chromosome and GFP positivity in 1.7% to 3% of cells in pancreatic islets [20]. The BM-derived β cells expressed Insulin, Glut2, Pdx1, and Pax6 and secreted insulin in response to a glucose challenge.

Other teams did not confirm these data, and additional studies reported much lower frequencies (0.004%) or even a total absence of regeneration phenomena in β cells of BM origin. Using GFP transgenic mice as donors, Choi et al. [21] evaluated the distribution of HSC in the pancreas after BMT and found that none of GFP-positive cells localized in islet expressed insulin. Even after pancreatic injury, obtained with low doses of streptozotocin, no GFP-positive cells expressing insulin were found in the islets or around the ducts of the pancreas. In other pancreatic injury models, Lechner et al. [22] confirmed the same results: mice were transplanted with GFP-positive sex-mismatched BM after partial pancreatectomy and streptozotocin administration. BM engrafted successfully, but 3 months after transplantation only a few β cells (2/100,000 screened) were of BM origin.

Further BMT studies in normal and diabetic mice were performed using a transgenic mouse expressing GFP under the control of insulin promoter as a donor. Even in this model, all the BM-derived cells engrafted in pancreas expressed hematopoietic markers and not insulin or Pdx1 [23]. In humans, a recent study by Butler et al. [24] analyzed 31 human pancreata obtained at autopsy from HSC transplant recipients who had received their transplant from a donor of the opposite sex; no contribution of HSC to endocrine pancreas was observed.

These studies support the hypothesis that transdifferentiation of BM cells is not a significant mechanism for adult pancreatic β-cell renewal. In addition, evidence that cell fusion rather than differentiation lies at the root of many processes of apparent BM differentiation into ectodermal or endodermal tissues makes all the studies that investigate the in vivo transdifferentiation of BM cells based on the existence of donor-specific genes, such as Y chromosome or GFP markers, controversial [25].