Over the last decades, umbilical cord blood (UCB) has emerged as a novel stem cell source. Already as early as 1974 researchers had shown that UCB contains functional hematopoietic progenitor cells, that multi-lineage colony-forming units were present and that cryopreservation was possible. This set the stage for cord blood as a source for clinical applications in hematological diseases. In 1989, the successful engraftment of UCB in a young patient with Fanconi’s Anemia demonstrated the feasibility of transplanting UCB instead of bone marrow.

Since then, hematopoietic stem cells (HSCs) from UCB are transplanted for hematologic reconstitution, and cord blood is now a widely accepted treatment for blood cancer, bone marrow failure and inherited hematologic deficiencies. As babies delivered represent the general population, a much larger pool of matched donors can be attained than for bone marrow, for which only a small fraction of the population is registered as donors. Umbilical cord is thus a good source of stem cells for ethnic minorities which are usually underrepresented in transplant registries and have difficulties in finding a compatible donor. Additional advantages of UCB over bone marrow are that the collection is risk-free and painless to the donor and that UCB can be frozen and stored in banks and thus offers the advantages of an 'off-the-shelf' treatment.

Over the years it has emerged that beyond HSCs, cord blood and the tissue lining the cord itself contain other types of stem cells. Other than HSCs, cord blood contains endothelial progenitor cells (EPC), a low number of multipotent stromal cells (MSCs) and a rare population of unrestricted
somatic stem cells (USSCs). The loose connective tissue surrounding the umbilical cord, called Wharton’s jelly cell (WJC), is rich in MSCs with properties similar to bone marrow MSCs. 3

As umbilical cord and blood are considered fetal tissue, it is not surprising that the stem cells therein are ‘younger’ than in the grown adult. It has been shown that HSC, MSCs and EPCs lose their potential with increasing age or with disease. For example, it was observed that the number of circulating endothelial precursor cells (EPC) and their functionality are reduced in smokers and patients with certain pathological conditions such as diabetes and coronary artery disease. 4 MSCs and HSCs also lose their regenerative capacity with increasing age. Thus, using autologous cells to transplant into older patients, that is, using their own stem cells mostly from the bone marrow, will likely not be very beneficial. Umbilical cord stem cells thus may provide better transplantation material than their adult counterpart.

In pre-clinical disease and developmental models, umbilical cord stem cells have been transplanted successfully and demonstrated regenerative potential. Accordingly, umbilical cord stem cells are under investigation as potential cell source for non-hematologic regeneration as for example cardio-vascular disease, spinal cord injury, Alzheimer's and Parkinson's disease, and as a potential source for immunotherapy and gene therapy. 3

### Hematopoietic Stem Cells (HSCs)

Umbilical cord blood is richer in HSCs than adult bone marrow. Thanks to its easy procurement UCB has become a mainstay for researchers investigating human HSCs. HSCs in cord blood are more primitive than their counterpart in bone marrow, with longer telomeres and a higher proliferation and differentiation potential. Expression of CD34 on human HSCs has been shown to correlate with human engraftment. Cord blood also contains very primitive HSC, lacking the expression of CD34 but capable of engrafting mice. Additional markers have been identified over the years. One such marker is the detoxifying enzyme aldehyde dehydrogenase (ALDH). In mouse studies, all regenerative capacity seems to be contained within cells expressing ALDH. However, the relevance of CD34 negative and/or ALDH positive cells in the clinical setting remains to be evaluated. One marker that is already being used to purify HSCs for clinical transplantation is CD133. 5 Interestingly, CD133 is also expressed by the hemangioblast, the common precursor of the HSC and the EPC.

### Endothelial Progenitor Cells (EPCs)

Since their first successful use in therapeutic angiogenesis over 10 years ago, endothelial progenitor cells (EPCs) have been the focus of intensive investigation, as millions of cardiac patients could benefit from cellular therapies to improve blood flow. 6 EPCs reside in the bone marrow and home to sites of neovascularization where they differentiate into endothelial cells. Normally, circulating EPCs in our blood contribute to regenerative angiogenesis during ischemia, wound healing, and a variety of other pathological conditions in the adult. It was shown that vascular trauma and myocardial infarction induced a rapid mobilization of EPC into the peripheral blood. 7 Unfortunately, the numbers and capacity of these cells decline with age in diseases such as coronary artery disease and diabetes, there is a decreased capacity for repair in the aged and increased risk for cardiovascular events. This suggests that transplantation of younger EPCs could improve conditions caused by declining neo-angiogenesis.

EPC can also be isolated from umbilical vein and cord blood and have a similar phenotype as their adult counterpart. They are however more prolific than adult EPCs, generating more endothelial cells in culture, and forming capillaries faster. In pre-clinical animal models of therapeutic neovascularization for limb ischemia, cardiac regeneration and diabetic neuropathy, EPCs from cord blood performed better. 7 While vessels formed by EPCs derived from adult peripheral blood regressed within 3 weeks after transplantation, cord blood-derived EPCs formed stable blood vessels lasting for more than 4 months. 8

### Multipotent Stromal Cells (MSCs)

MSCs are cells residing in the bone marrow and adipose tissue that can generate bone, stroma, tendon, cartilage, muscle, fat tissue and neurons. Bone marrow-derived MSCs are starting to be used on a larger scale in the clinical setting where they are used to support ex vivo expansion of HSCs, engraftment of HSCs in leukemia patients, improvement of graft versus host disease and bone fractures. MSCs have one very interesting property: they can modulate the immune system and are not rejected by allogeneic immune cells, potentially being universal donor cells. In animal models they have also been shown the regenerate heart tissue. However, similar to other stem cells in the body they also age with their ‘host’. As human bone marrow is not an abundant source and collection is not risk-free to the donor, it was disappointing to realize that cord blood, similar to peripheral blood, did not seem to contain any MSCs. But improvements in culture techniques has enabled isolation of MSCs from cord blood that are very similar to bone marrow-derived MSCs. Similar to bone marrow or adipose tissue-derived MSCs, cord blood MSCs could be shown to generate bone, cartilage, tendon, muscle, fat tissue, stromal cells and neurons. Nevertheless, cord blood is a poor source of MSC, and much more MSC-like cells can be isolated from the surrounding connective tissue of the umbilical cord - Wharton’s jelly. These cells can be easily expanded in culture to large amounts. Again, as with other umbilical cord cells, they have a greater proliferation and expansion potential, compared to adult MSCs. WJCs have been used successfully to regenerate animal models of Parkinson’s disease, retinal degeneration and stroke. They have been used to derive tissue-engineered heart valves, pulmonary conduits, cartilage and bone constructs, making WJCs an exciting cell source for future tissue engineering work and regenerative medicine. 4
The Unrestricted Somatic Stem Cell (USSC)

UCB also contains a pluripotent stem cell capable of generating tissue of endodermal, mesodermal and ectodermal origin. This cell was named unrestricted somatic stem cell, (USSC), and is a rare cell that can be isolated from roughly only every third cord blood collection. This cell has been shown to be able to generate blood cells and to engraft in animal models. The USSC can also generate neurons, glial cells, liver cells, cardiac cells, as well as the cell repertoire generated by MSCs. It appears that the USSC may be a precursor cell of MSCs. USSCs share overlapping features with MSCs isolated from fetuses, can contribute to both injured and developing tissue, and support engraftment of HSCs. USSCs can be isolated and grown in culture to significant amounts and when transplanted into animal models these cells persist for months, making them very attractive cells for cellular therapies.

Conclusions

The last years have shown that umbilical cord and its surrounding tissue are rich in human stem cells. The abundance of umbilical cord and ease of procurement make it a very attractive source of human stem and progenitor cells for clinical applications, raising the hope that umbilical cord stem cells could one day be used on a large scale in regenerative medicine for cardiac disease, diabetes, neurodegenerative diseases, orthopaedic reconstruction, tissue and biomedical engineering.

As umbilical cord reflects the population surrounding the maternity which collected the cord, it provides a large pool of matched donor cells for that population. This provides hope for all patients that are not represented in organ donor registries, and waiting on transplant lists to benefit from life-saving therapies.