

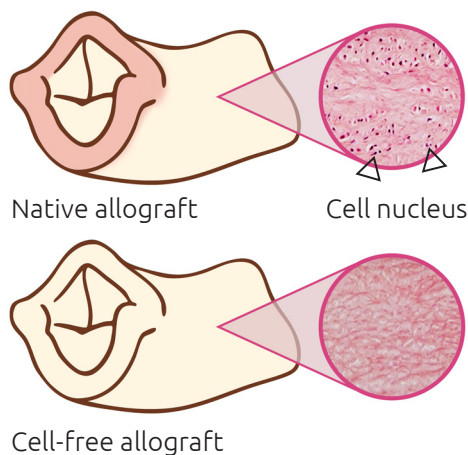
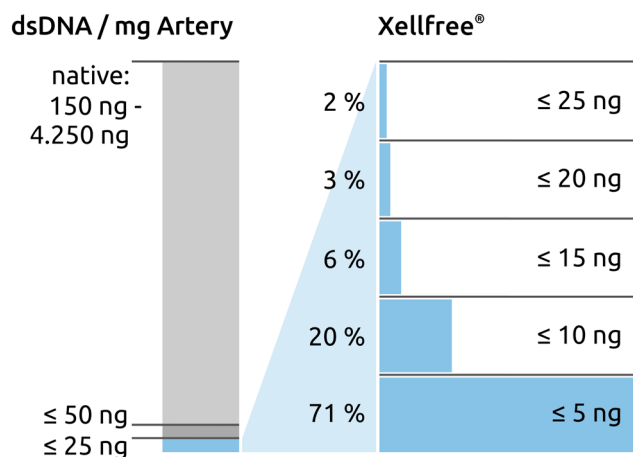
Xellfree®

Almost thirty processing steps are needed to make a tissue cell-free. In this Newsletter we describe what “cell-free” means and how the decellularization of an allograft affects its immunogenicity.



Allografts, such as human heart valves are anatomically perfectly suited to their task. Consequently, allografts, also known as homografts, represent excellent haemodynamics. As with all transplants, conventional homografts may be rejected by the recipient. While cells carry HL-antigens, the connective tissue is not immunologically individualised. In the Xellfree®

procedure the donor cells are removed from the tissue. The resulting cell-free allograft retains its original form and full functionality, and has a less immunogenic effect than a conventional homograft. It is technically impossible to fully confirm “freedom from cells” without destroying the allograft. Consequently at the end of the process, samples are taken from the edges and examined.



Freedom from dsDNA:

Double-stranded DNA (dsDNA) is a component of the cell nucleus. It is possible to stain dsDNA specifically and efficiently which makes it suitable as a surrogate parameter for cell density in the tissue. In the literature, “cell-free” is defined as ≤50 ng dsDNA per mg tissue (Crapo 2011). Xellfree®-Technology goes further: after processing, only ≤25 ng dsDNA per mg tissue is acceptable. The vestigial content in >90% of all cell-free allografts is in fact only ≤10 ng/mg.

No intact nuclei, but intact extracellular Matrix:

Every individual cell-free allograft is histologically examined by independent specialists for pathology. No intact nuclei are permitted (H&E-staining). The extracellular matrix must demonstrate a fibre structure that proves the donor’s good health. For instance, allografts with damaged fibre structure are discarded.

Less immunogenicity

The longevity of cell-free allografts is also dependent on a low level of immunogenicity. Cell-free allografts induce only a low level of HLA-specific antibodies, as Coti et al. (2020) have recently demonstrated.¹

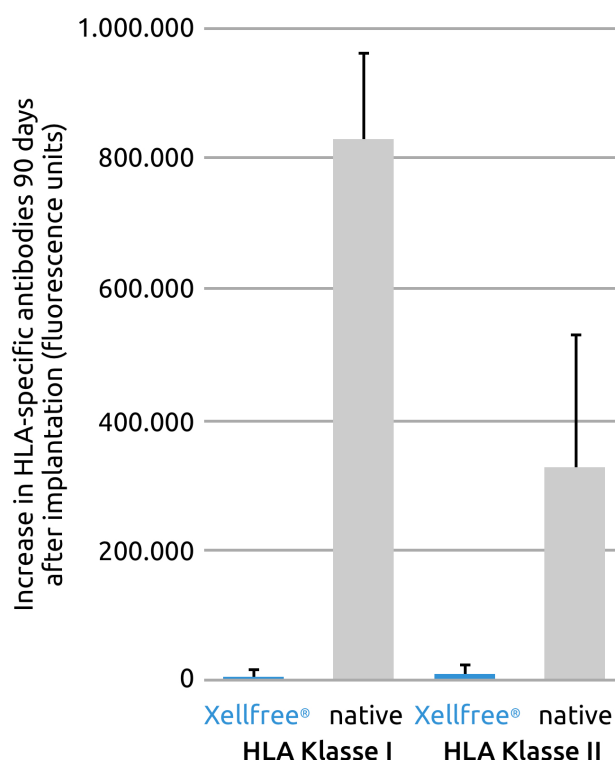
Neuman et al. (2014) quantified cellular immune responses following cell-free pulmonary valve replacement in 47 patients. After 2.5 ± 1.0 years, no significant changes in cell count could be detected in comparison with baseline values.²

In spite of mild humoral and cellular immune reaction, early immune system-induced failure was observed in a few patients. Ebken et al. (2020) demonstrated preformed antibodies to cell-free allografts in treatment-naïve patients in very different concentrations.³ Whether and how individual risks may be detected in time in order to stabilise intervention success is currently under scientific investigation and discussion.

Conclusion

A markedly milder humoral or cellular immune response following cell-free heart valve replacement supports the concept that cell-free allografts offer a basis for autologous regeneration.

PS: Would you like to report on cell-free allografts? We will support your report with graphics. Contact us on: hello@corlife.eu



Cell-free allografts do not induce formation of HLA-specific antibodies (from Coti et al. 2020)

Cell-free human heart valves are also called “Hannover valves”, because they were introduced clinically in the Hannover Medical Institute. Other synonym denominations are “TE-valves” and “Growing heart valve”. The scientific literature and German OPS-code use the process-related term “decellularized”, which many find a tongue-twister. Alternatively there is the teleological “cell-free”, which is short, and describes in fact the essential property of the tissue preparation.

- 1 Coti I, Wenda S, Andreeva A, Kocher A, Laufer G, Fischer G, Andreas M. Donor-specific HLA antibodies after fresh decellularized vs cryopreserved native allograft implantation. *HLA*. 2020 Nov; 96(5):580-588.
- 2 Neumann A, Sarikouch S, Breymann T, Cebotari S, Boethig D, Horke A, Beerbaum P, Westhoff-Bleck M, Bertram H, Ono M, Tudorache I, Haverich A, Beutel G. Early systemic cellular immune response in children and young adults receiving decellularized fresh allografts for pulmonary valve replacement. *Tissue Eng Part A*. 2014 Mar;20(5-6):1003-11.
- 3 Ebken J, Mester N, Smart I, Ramm R, Goecke T, Jashari R, Boethig D, Horke A, Cebotarib S, Tudorache I, Avsar M, Bobylev D, Haverich A, Sarikouch S, Hilfiker R. Residual immune response towards decellularized homografts may be highly individual. *Eur J Cardiothorac Surg* 2020; doi:10.1093/ejcts/ezaa393.