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The Use of D2-40 for Blood Vessels is Inappropriate

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This study was performed to observe development of the venous system in fetuses because anatomical studies are scare on embryological development of the vascularization process during the fetal stage. However, it was a serious mistake to use D2-40 as a marker to observe blood vessels. D2-40 is a marker specific to lymphatic endothelial cells (LECs), not to blood vessels. The lymphatic vessels are located in close proximity to the venous system. Nevertheless, the lymphatic system is a discrete anatomical entity, different from the venous system, and thus, markers for lymphatic vessels can not be used as substitute markers for venous vessels.

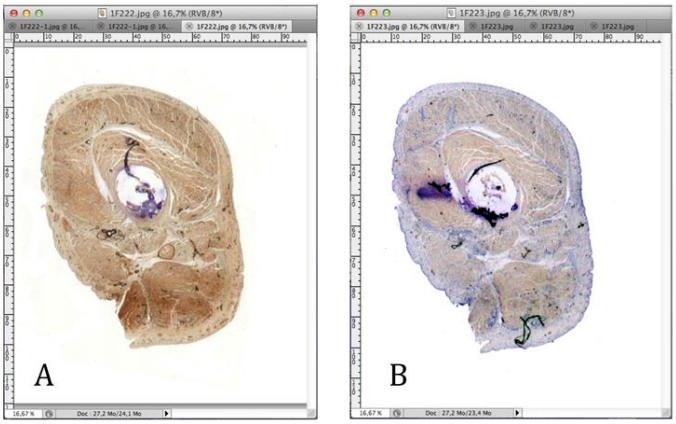

Figure 1 (A, B): serial Section stained by IHC: SMA, D2-40: W14 right femoral position of a normal human male fetus (FFPE).

A: 1F222 SMA

B: 1F223 D2-40

Bond Refine DAB direction Kit (Leica, Aistralia) However, in the first experiment in this study (W14 right femoral speciment of a normal human male fetus), αSMA (SMA, M0851, Dako, Denmark) at pH6, a dilution of 1:300 was used.

After Immunohistochemistry (IHC), the tissue slides were processed by the computer. Since

the digitalized images were reffered to by their corresponding ID numbers thereafter (Figure 1), Uhl.J.F 3D reconstructor, should have confirmed the names of markers on the original slides.

From the viewpoint of developmental biology, and the role of the D2-40 marker; an anti-Podoplanin (PDPN) antibody, Lymphangiogenesis starts with the expression of lymphatic vessel endothelial hyaluronan receptor (LYVE)-1 in the venous endothelial cells (VECs). Platelet activation is mediated by binding of PDPN to C-type lectin-like receptor 2 (CLEC-2) expressed on the platelets in the venous vessels, from which lymphatic vessels arise, so the vasculature totally differs from the venous vessels. Lymphangiogenesis completes at this point. This means PDPN is expressed by endothelial cells (ECs) on vessels destined to become lymphatic vessels, not by regular VECs. Therefore, it is impossible to detect normal blood vessels using D2-40. Furthermore, there are reports claiming that PDPN-positive cells do not overlap with cells positive to α-smooth muscle actin (αSMA), a marker used to detect smooth muscle cells in blood vessels [6]. Therefore, vascular structures expressing PDPN, a LEC-specific marker, are lymphatic vessels, and PDPN should not be used as a detection marker for blood vessels. From the above, it is concluded that the 3D models reconstructed based on D2-40 staining represented lymphatic vessels, except for the W14 right femoral model. Study results obtained using inappropriate markers have been presented in various countries, and negative influence on vascular research is of concern. If one still insists that the 3D models in this study represented venous vessels, it should be required to use correct markers such as Ephrin type-B receptor 4 (EphB4), apelin receptor (APJ) and endomucin, in experiments to accurately identify the venous system. Correction of the text: the specimen mentioned in Figure 2 and 3 should be W14, and that in Figure 4 should be W15.

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