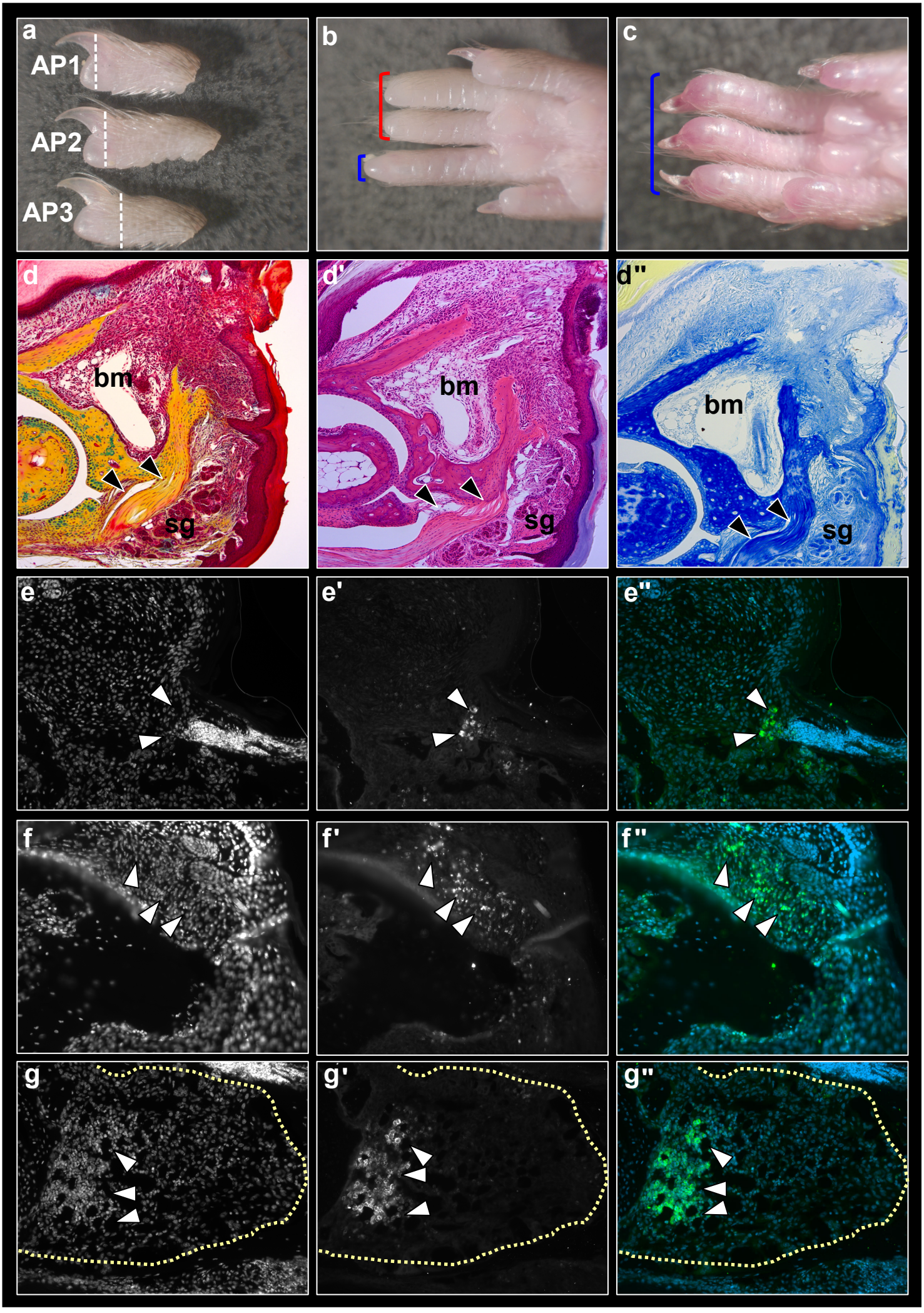
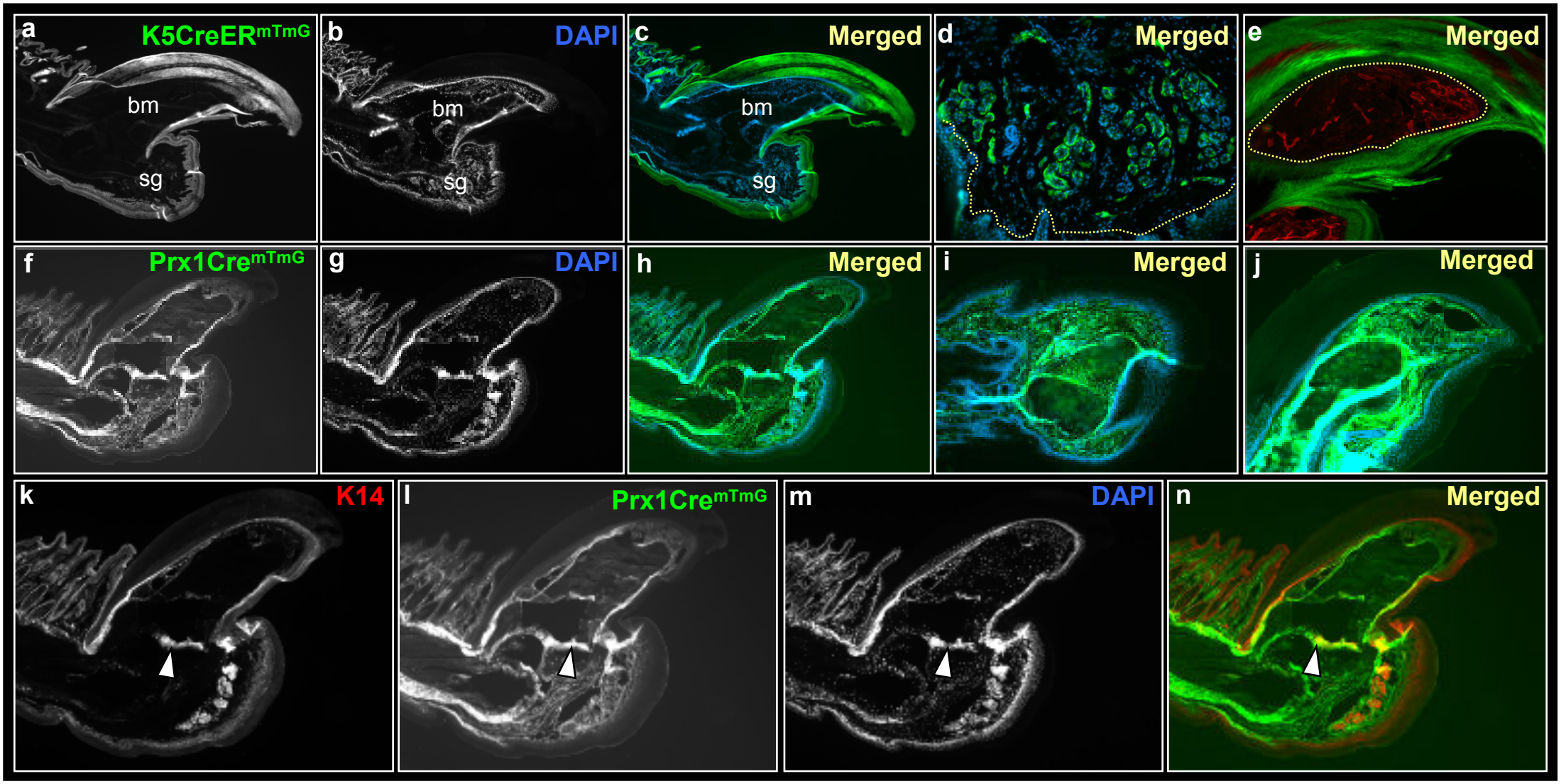
Supplementary Fig. 1



Supplementary Figure 1

Regeneration of the mouse digit tip following distal amputations. Three amputation planes (AP) were examined along the distal digit (**a**), removing the distal one third (AP1), half (AP2) or two thirds to the entire distal digit (AP3). Partial to complete regrowth was observed in distal planes only (AP1/2). Regrowth of the distal digit after 70 days following amputations through plane 1 or 2 (**b**, **c**, blue bracket) but not through plane 3 (**b**, red bracket). Amputation of the distal digit following 10 days showing a histological undifferentiated zone at the distal digit apex. Pentachrome staining shows collagen and bone in yellow and green, epidermis in red, and dermis/mesenchyme in purple (**d**). Hematoxylin and eosin staining showing mesenchyme at the digit apex (**d**'). Aniline blue staining shows bone in dark blue and connective tissue/mesenchyme in light blue (**d**''). Black arrowheads point to ventral tendon (**d-d**''). A single pulse of BrdU after 7 days, shows local proliferations in the hair follicle (**e-e**'', white arrowheads), nail organ (**f-f**'', white arrowheads) and bone marrow (**g-g**'', white arrowheads). Dashed line outlines the marrow cavity within the distal digit (**g-g**''). bm, bone marrow; sg, sweat glands.

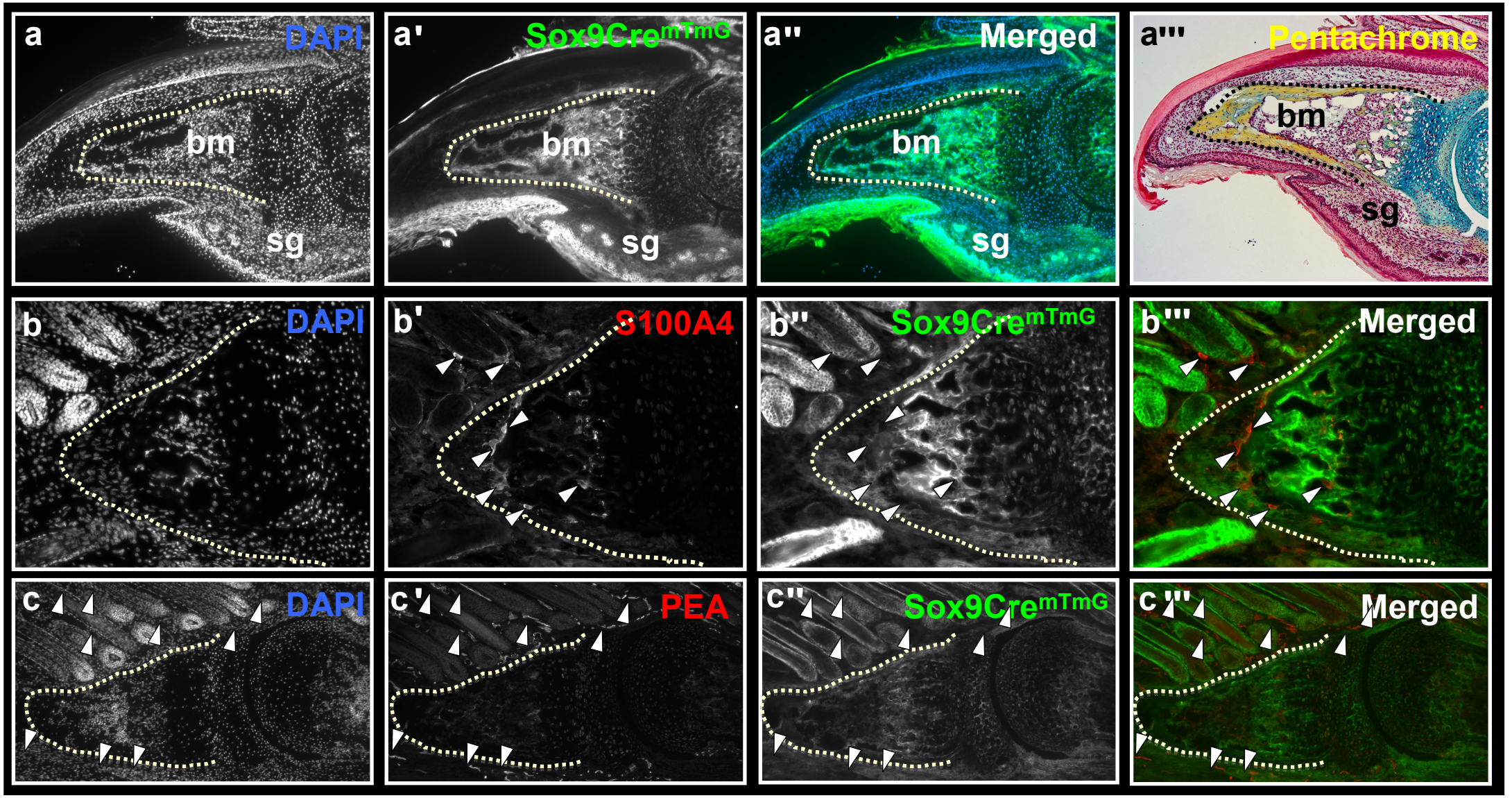
Supplementary Fig. 2



Supplementary Figure 2

Germ layer restriction of ectoderm and mesoderm during digit tip regeneration. Sections through a distal digit of K5CreER^{mTmG} (**a-e**) and Prx1Cre^{mTmG} (**f-n**) transgenic mice, following three months post-amputation. Ectoderm contributes to epidermis, nail and sweat glands and fails to contribute to mesoderm tissues (**a-e**). Dashed line outlines the border between epidermis/dermis (**d**) and nail plate/matrix (**e**). Lineage tracing of Prx1-expressing limb mesenchyme shows restriction of GFP expression to bone, tendon and mesenchyme, with no contribution to ectoderm derivatives (**f-j**). In regenerated digits from Prx1Cre^{mTmG}, Keratin 14 (K14) expression is mutually exclusive from GFP expression (**k-n**). Staining of K14 within the bone (**k-n**, white arrowhead) is an outcome of tissue artifact and is not seen in high magnification images of same or other tissue sites. bm, bone marrow; sg, sweat glands.

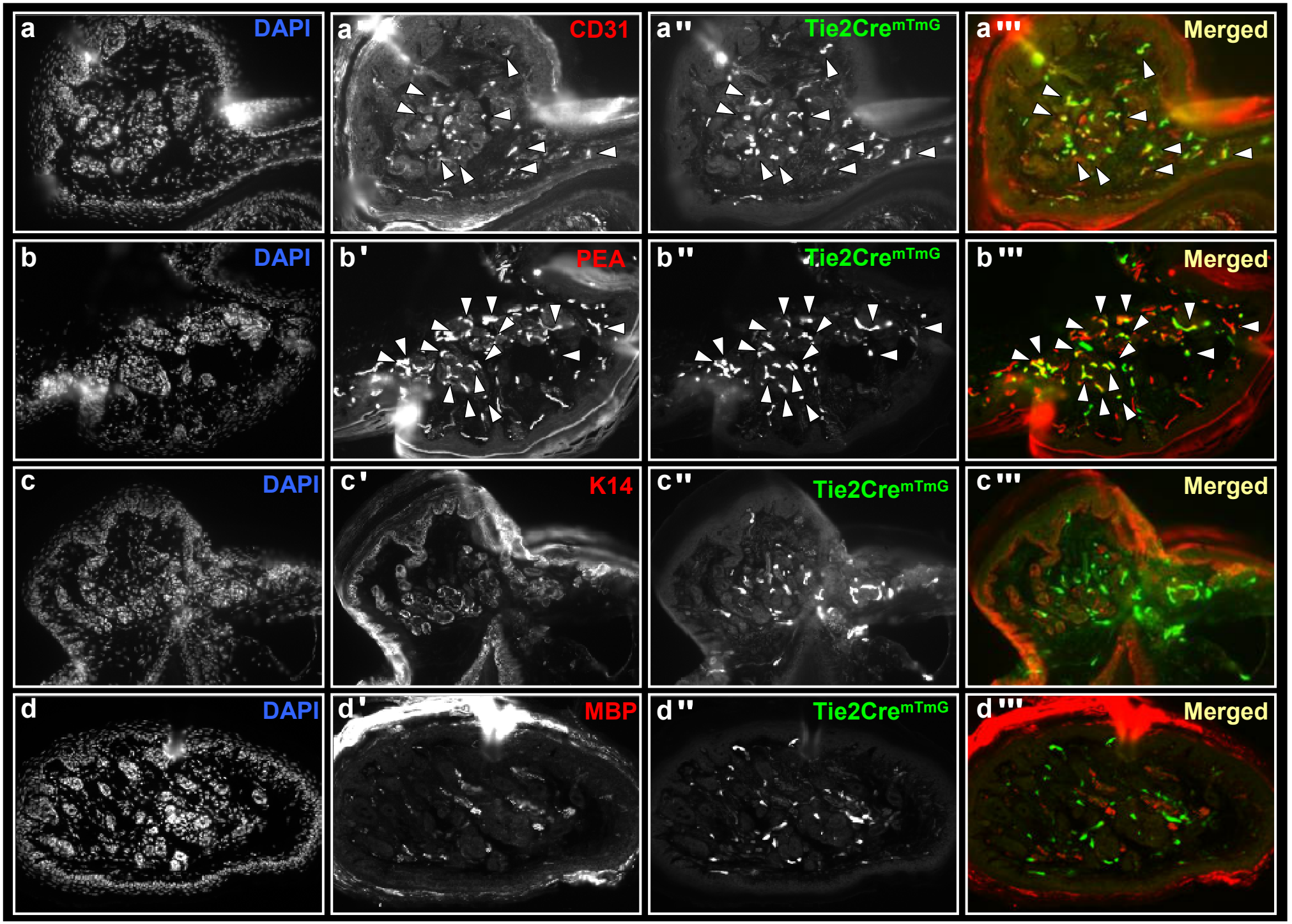
Supplementary Fig. 3



Supplementary Figure 3

Lineage restriction of osteoblasts to the distal digit bone. Sections through a regenerated distal digit from Sox9Cre^{mTmG} mice. Within the mesoderm, GFP expression is restricted to the distal digit bone (**a**-**a**''). Pentachrome staining of the same section as in **a**'' shows the regenerated reticular bone of the distal digit stained in yellow (**a**'''). High magnification images of the distal digit from Sox9Cre^{mTmG} mice (**b**-**c**'''). GFP expression does not co-localize with the fibroblast marker S100A4 (**b**-**b**''', white arrowheads) or the endothelial marker PEA (**c**-**c**''', white arrowheads). Dashed lines outline the distal digit bone. bm, bone marrow; sg, sweat glands.

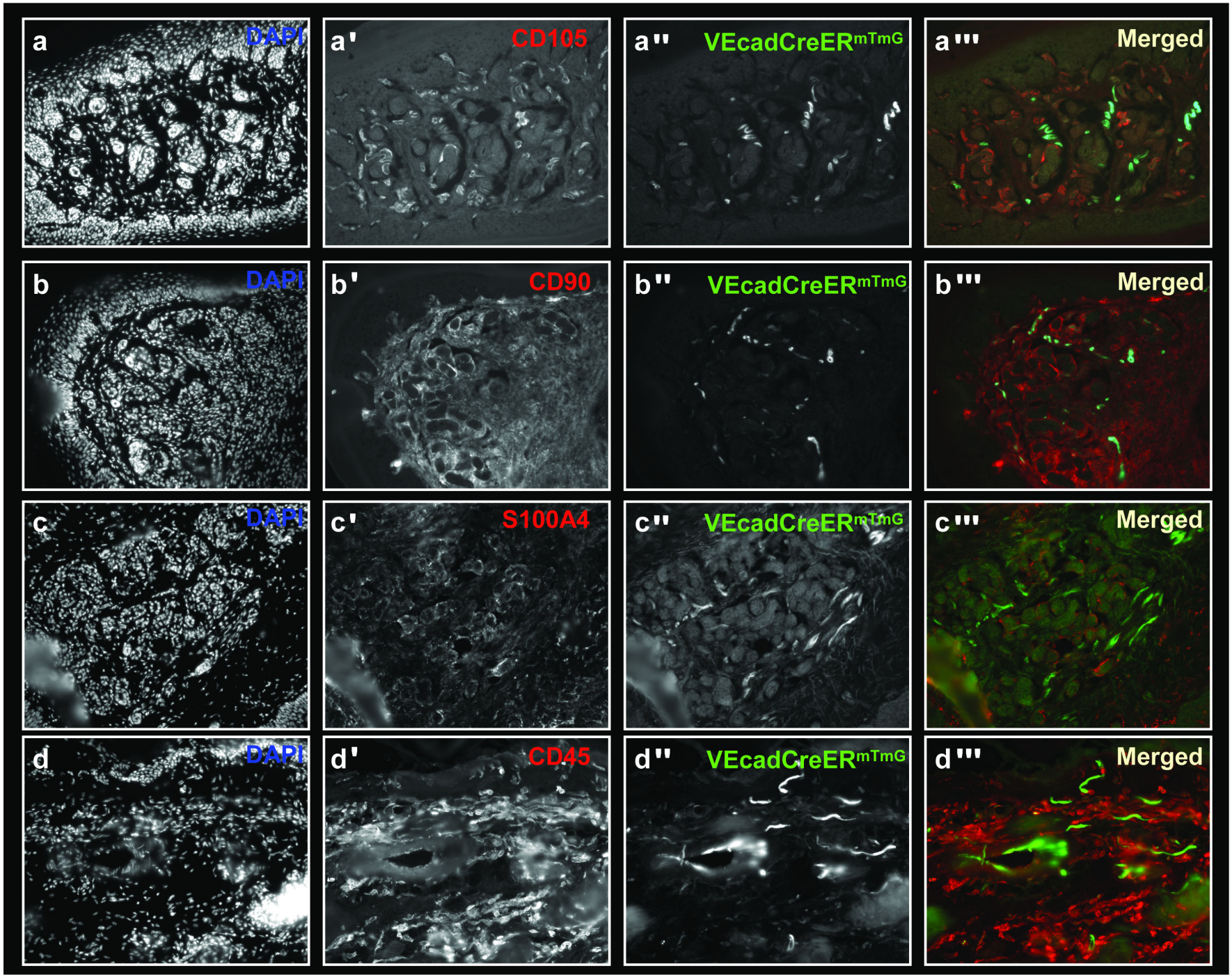
Supplementary Fig. 4



Supplementary Figure 4

Lineage restriction of endothelium to blood vessels within the regenerated digit. Co-localization of Tie2Cre with the endothelial markers CD31 (**a-a**’’’, white arrowheads) and PEA (**b-b**’’’, white arrowheads), but not keratin 14 (K5, **c-c**’’’) or myelin basic protein (MBP, **d-d**’’’).

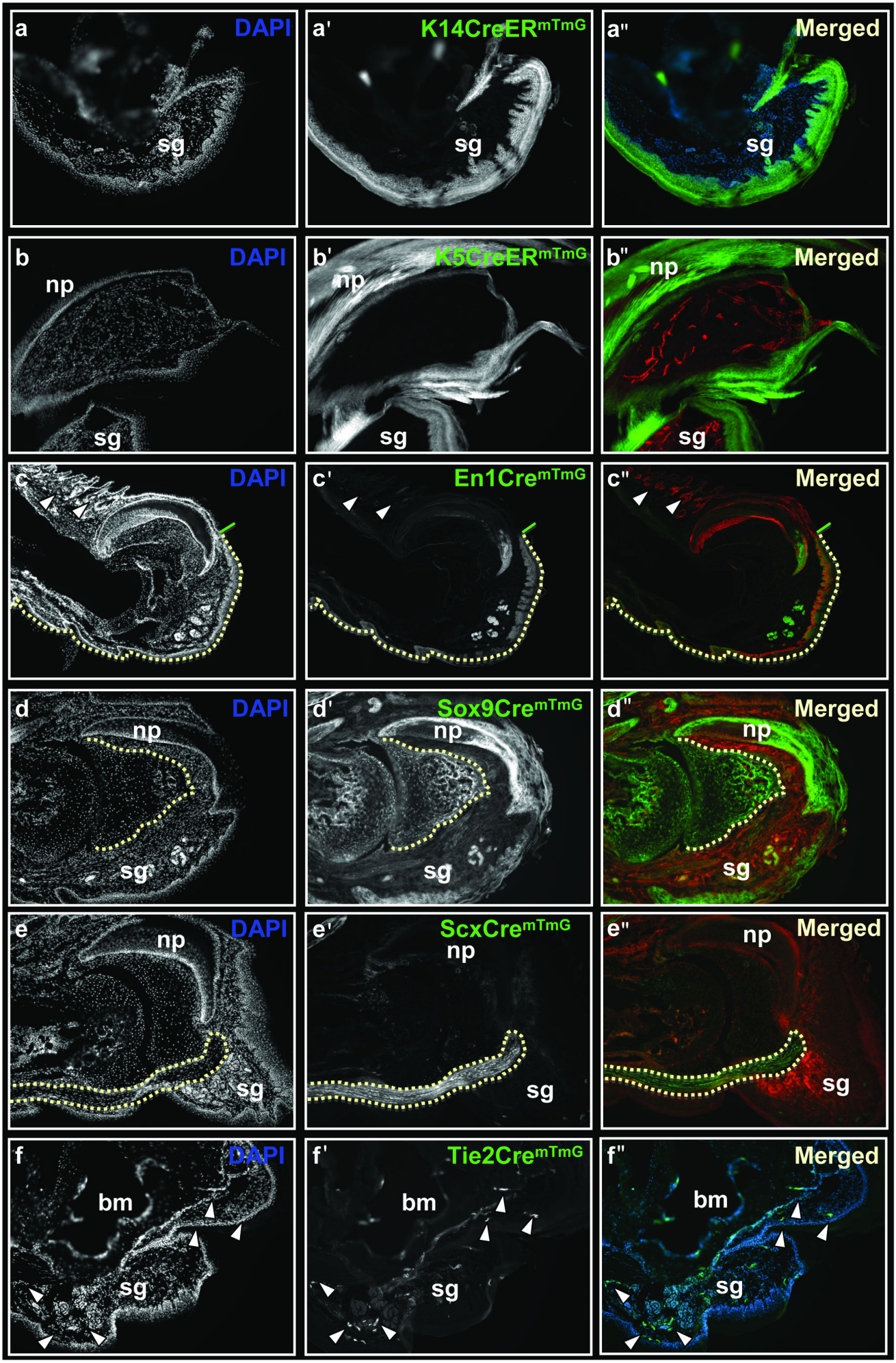
Supplementary Fig. 5



Supplementary Figure 5

Lineage restriction of endothelium to blood vessels within the regenerated digit. GFP positive cells from VEcadCreER^{mTmG} regenerated distal digit do not co-localize with fibroblast markers CD105 (**a-a**’’’), CD90 (**b-b**’’’), S100A4 (**c-c**’’’) or the hematopoietic marker CD45 (**d-d**’’’).

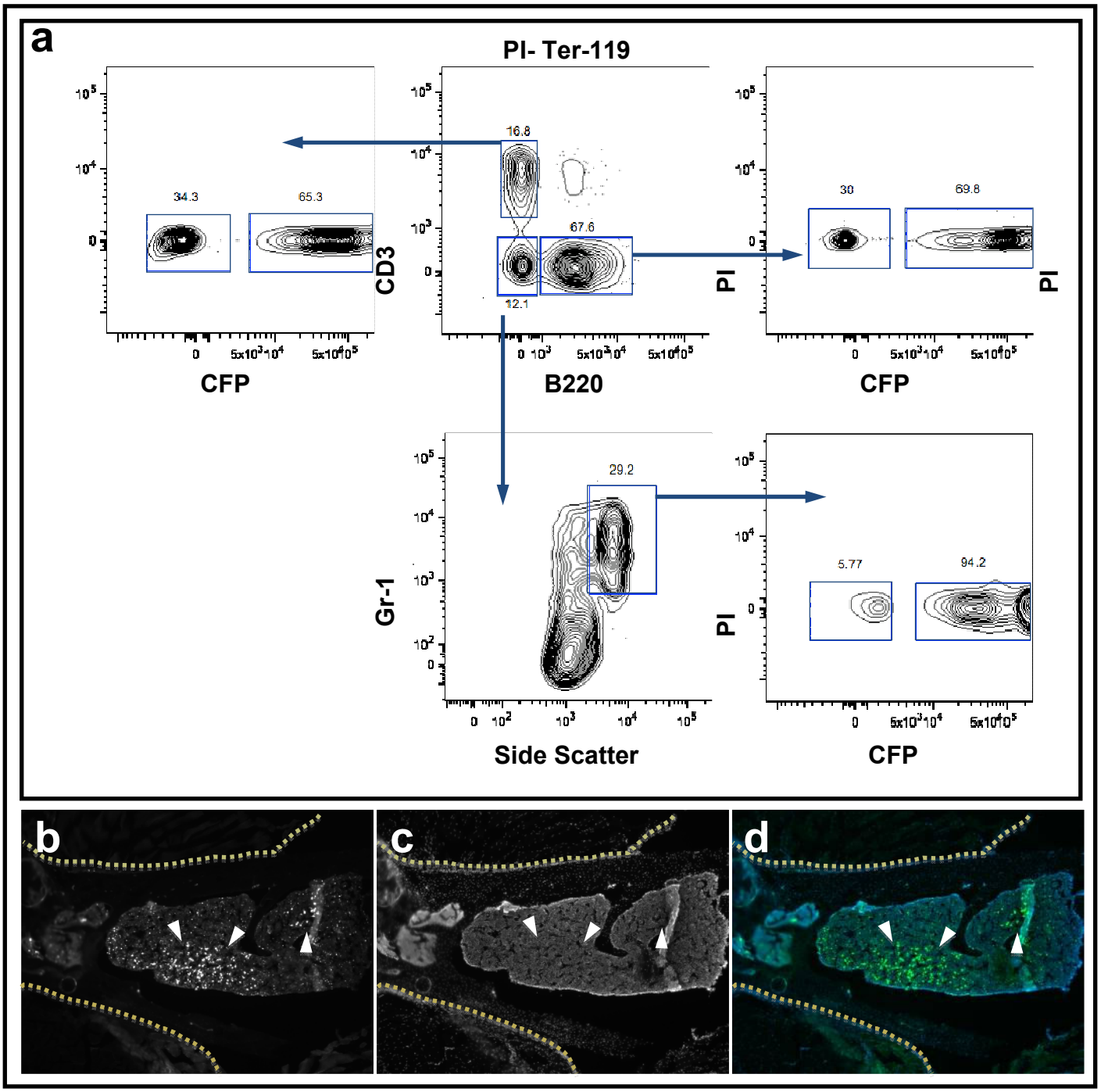
Supplementary Fig. 6



Supplementary Figure 6

Lineage restriction of stem/progenitors at 10 days post amputation of the distal digit. Digits from K14CreER^{mTmG} (**a-a**''), K5CreER^{mTmG} (**b-b**'') and En1Cre^{mTmG} (**c-c**'') mice show GFP expression is restricted to epidermis (**a-a**''), nail plate (**b-b**'') and ventral sweat glands (**c-c**''). In En1Cre^{mTmG} mice, GFP expression is restricted to ventral epidermis (white dashed line) but not dorsal epidermis or associated hair follicles (white arrowheads). Merged image showing co-localization of GFP (green) and keratin 14 protein (red) expressions in ventral ecotoderm (**c**'', white dashed line). In Sox9Cre^{mTmG} mice, GFP expression within the mesoderm is restricted to the distal digit bone (**d-d**'', outlined by a dashed white line). In ScxCre^{mTmG} mice, GFP expression is apparent in the ventral tendons (**e-e**'', outlined by a dashed white line). In Tie2Cre^{mTmG} mice, GFP expression is apparent in blood vessels surrounding the ventral sweat glands and beneath the nail plate (**f-f**'', white arrowheads). bm, bone marrow; np, nail plate; sg, sweat glands.

Supplementary Fig. 7



Supplementary Figure 7

Flow chart showing blood chimerism after transplantation of genetically marked HSCs (**a**). Section through the tibia of host mice showing donor derived CFP blood cells occupying the marrow cavity (**b**-**d**, white arrowheads). Dotted lines outline the borders of the tibia.

Supplementary table 1

amputation plane (AP)	no regrowth	partial regrowth	complete regrowth
AP-1	1/56	17/56	38/56
AP-2	24/54	18/54	12/54
AP-3	15/15	0/15	0/15

Planes of amputation included the distal one third of the digit (AP-1), distal half (AP-2) or distal two-thirds to entire digit (AP-3). Regrowth of tissues was examined after 3 months from operations.