**SUPPLEMENTARY FIGURE LEGENDS**

**Supplementary Figure S1**: Tracing of BC cell derivatives in the adult PNS and efficiency of targeted *Nf1* deletion in *Prss56Cre,R26tdTom,Nf1flox/flox* mice

(A) RT-PCR analysis of *Prss56* and *Nf1* expression in *Nf1*-KO mutant skin. FACS-sorted, TOM+ and TOM- fractions isolated from newborn (P0) *Nf1*-KO mutant skin, unsorted cells isolated from adult *Nf1*-KO mutant skin and E12.5 neural tube with attached BCs from *Prss56Cre,R26tdTom* animals (Ctrl+) were used for RNA preparation and RT-PCR analysis with *Prss56*-, *Nf1*- and *ß-actin*-specific primers. The negative control (Ctrl-) is a no-template reaction. (B) Transverse section through adult *Prss56Cre,R26tdTom* sciatic nerve immunolabelled for TOM, TUJ1 (axons) and S100 (Schwann cells). TOM staining corresponds to a subset of axons and is absent from S100+ Schwann cells. (C-E) Transverse and longitudinal sections through adult *Prss56Cre,R26tdTom* dorsal nerve root, immunolabelled for TOM and fibroblast markers CD34 (C), PDGFRα (D) and PDGFRβ (E). Inset in E shows a higher magnification of the indicated area. Note that CD34+/PDGFRα+ endoneurial cells and PDGFRβ+ perineurial cells (arrowheads in E) do not express TOM. (F) Skin section of adult *Prss56Cre,R26tdTom* mouse immunolabelled for TOM, S100 and MBP. Traced (TOM+) mSCs are co-labelled with S100 and MBP (open arrowheads and small insets) and traced nmSCs are only S100-positive (full arrowheads). Large inset shows high magnification of traced arrector pili glia. (G) Ultrastructure of subepidermal glia (arrowheads) surrounding bundles of small-diameter axons in the subepidermal nerve plexus. Dotted line separates epidermis (epi) and dermis (der). (H, H’) Longitudinal section through a hair follicle immunolabelled for TOM and the melanocyte marker KIT. TOM+/KIT+ cells correspond to follicular melanocytes (arrowhead). Scale bar: 50 µm (B-F, H, H’), 500 nm (G).

**Supplementary Figure S2:** Characterisation ofplexiform neurofibromas

(A-B’) Longitudinal sections through a 10-month-old control (CTRL) (A, A’) and *Nf1*-KO (B, B’) spinal nerve roots immunolabelled for TOM and SOX2. (A’, B’) show single labelling for SOX2 with the nuclear (Nu) stain. (C-F’) Transverse sections through control nerve root (C, C’, E and E’) and a paraspinal plexiform neurofibroma from a *Nf1*-KO animal (D, D’, F and F’) immunolabelled for KIT (mastocytes) or IBA1 (macrophages). Insets show co-labelling with TOM to identify traced cells. (C’, D’, E’ and F’) Higher magnifications of the areas indicated in (C-F). Note that in the control, mastocytes and macrophages are found predominantly in the nerve sheath (arrowheads in C’ and E’), while the endoneurial fraction is scarce. Spc, spinal cord; DR, dorsal root; DRG, dorsal root ganglia. Dotted lines in (A, A’, C’ and E’) denote nerve root boundaries. (G) Electron micrograph depicting perineurial fibroblasts in subcutaneous plexiform neurofibroma (spNF). Note the presence of basal lamina and pinocytic vesicles (arrowheads). (H, H’) Transverse sections through spNF from a *Nf1*-KO mouse immunolabeled for TOM (H), KIT and IBA1 (H’). Scale bar: 50 µm (A-F’, H, H’), 1µm (G).

**Supplementary Figure S3:** Characterisation ofdiffuse cutaneous neurofibromas

(A-F) Transverse sections through diffuse cNFs from 16-month-old *Nf1*-KO animals immunolabelled for TOM and markers of nmSCs/immature SCs (p75NTR; A, NCAM; B, L1; C), dedifferentiated SCs (SOX2; D), ERK1/2 (E), and a vascular marker (PECAM; F). Keratin 15 (K15) labelling in (F) corresponds to the basal layer of epidermis and hair follicles. Most TOM-positive cells express markers of dedifferentiated/immature SC. Note that TOM-negative, Vimentin (VIM)-positive SCs and/or fibroblasts (both populations express VIM) do not co-express SOX2 (D). (E) Most traced SCs express high levels of the phosphorylated form of ERK. Inset shows high magnification of cells positive for both TOM and ERK1/2 (arrows); lack of ERK1/2 expression in neighbouring non-traced cells (arrowheads). Cell nuclei are shown in white. (F) Tumours are highly vascularised as indicated by intense PECAM staining of endothelial cells in comparison to control (CTRL) skin. (G-J) Ultrastructure analysis of a tumour reveals the presence of numerous dermal fibroblasts with a dense network of endoplasmic reticulum (a sign of active protein synthesis) (G, H, arrows) and cytoplasm enclosing collagen fibres (G, I), and frequent polymorphonuclear neutrophils (J, arrows). V, lumen of a blood vessel. (K) Transverse sections through cNFs immunolabelled for TOM and a proliferation marker (PHH3). Only ~~a small fraction of traced cells undergo mitosis (arrows and insets).~~ (L-N) Transverse sections through cNF from 20-month-old *Nf1*-KO animal immunolabelled for TOM, S100 (SCs; M), KIT (mastocytes) and IBA1 (macrophages) (N). Scale bar: 50 µm (A-F, K-N) and 1 µm (G-J).

**Supplementary Figure S4**: Impact of *Nf1* inactivation on the proliferation of embryonic and early postnatal BC cell-derived melanocyte and glial lineages

(A, B) Whole-mount preparations of E13.5 control (CTRL, (A)) and *Nf1*-KO (B) skin immunolabelled for TOM and TUJ1. (C) Quantification of TOM+/TRP2- cells (SC precursors) along the axons. (D, E) Whole-mount preparations of E15.5 control (CTRL, (D)) and *Nf1*-KO (E) skin immunolabelled for TOM and TUJ1. (F) Quantification of TOM+/TRP2- cells (immature SCs) along the axons. (G-H) Whole-mount preparations of E15.5 control (CTRL, (G)) and *Nf1*-KO (H) skin immunolabelled for TOM and TUJ1. (I) Quantification of TOM+ /TRP2+ cells not associated with axons (melanoblasts). (J-L) Whole-mount preparations of E15.5 *Nf1*-KO skin immunolabelled for TOM and TUJ1, and melanocyte lineage markers MITF (J), KIT (K) or TRP2 (L). Arrowheads indicate melanoblasts. Immature TOM+ SCs, lacking MITF, KIT and TRP2 expression, are associated with axons. (M-N) Quantification of TOM+ extrafollicular and follicular melanocytes (M), and of TOM+ SCs (N) in P9 control (CTRL) and *Nf1*-KO mutant skin. Traced melanocytes were identified based on TOM and TRP2 expression and lack of axonal contact, while TOM+ cells were considered SCs based on lack of TRP2 expression and association with axons. Quantification data are represented as mean values ± SD. Fold change (FC) differences are given for each quantification. (O, P) Transverse sections through 3-month-old control (O) and *Nf1*-KO (P) dorsal skin immunolabeled for macrophage marker IBA1. Dotted lines indicate epidermis/dermis boundaries. Scale bar: 50 µm.

**Supplementary Figure S5**: Schwann cell hypertrophy and increased density of innervation in the *Nf1*-KO dermis

(A-D) Dorsal view of clarified 3-month-old skin from control (CTRL) (A, C) and *Nf1*-KO (B, D) animals immunolabelled for TOM and TUJ1. Abnormal morphology of *Nf1*-KO Schwann cells is apparent in the upper dermis (B), whereas mutant SCs in the lower dermis do not show obvious morphological atypia and are tightly associated with axons (D). Positions of the lanceolate nerve endings were used for anatomical orientation, and portions of the skin present above or below these structures were considered as upper and lower dermis, respectively. Insets represent TOM labelling of the corresponding images. (E-G) Dorsal view of the clarified 3-month-old control (E) and *Nf1*-KO (F, G) upper dermis (containing or devoid of traced cells) immunolabelled for the pan-axonal marker TUJ1. The figures show maximum intensity projections of 35 µm thick z-stacks acquired from the skin surface. Insets represent TOM labelling of the corresponding images. (H) Quantification of TOM+ sensory neurons in whole-mount preparations of control and *Nf1*-KO newborn DRGs at the cervical level. Each data point corresponds to the number of TOM+ neurons per DRG. Data are represented as mean value ± SD. (I-L) Transverse sections of control skin (CTRL, (I, K)) and of a micro-NF from a 6-month-old *Nf1*-KO mutant (J, L) immunolabelled for TOM and the peptidergic neuronal marker CGRP. (K, L) Single CGRP channels. Dotted lines indicate tissue limits in the control (outside of the field of view in the mutant). Scale bar: 50 µm.

**Supplementary Figure S6:** Schematic of the four successive steps of development of diffuse cNFs in *Prss56Cre,Nf1fl/-* mutant animals

See the discussion for description of this figure.

**SUPPLEMENTARY TABLE LEGENDS**

**Supplementary Table 1:** Tumour phenotypes in *Prss56Cre, R26tdTom, Nf1flox/flox* and *Prss56Cre, R26tdTom, Nf1flox/-* mice.

The table summarises characteristics of *Nf1*-KO mice that had to be sacrificed to avoid suffering or those that were found dead.

**Supplementary Table 2:** Overview of the top 6 overrepresented KEGG pathways among upregulated transcripts in injured vs uninjured skin of *Nf1*-KO and control mice.The table shows the lists of genes belonging to each category, with the corresponding fold change values