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| **Key Resources Table** |
| **Reagent type****(species) or****resource** | **Designation** | **Source or Reference** | **Identifiers** | **Additional information** |
| experimental model, mouse strain | Mouse*: Apcfl/fl*  | (Kuraguchi et al. 2006) | Kucherlapati Lab  |  |
| experimental model, mouse strain | Mouse*: Axin2-LacZ*  | The Jackson Laboratory; (Lustig et al. 2002) |  |  |
| experimental model, mouse strain | Mouse: CD1/ICR | Charles River | Fuchs Lab |  |
| experimental model, mouse strain | Mouse: Fucci | *595, Riken*(Sakaue-Sawano et al. 2008) |  |  |
| experimental model, mouse strain | Mouse: *Krt14-rtTA*  | (Nguyen, Rendl, and Fuchs 2006) | Fuchs Lab |  |
| experimental model, mouse strain | Mouse: *Lhx2-EGFP* | The Gene Expression Nervous System Atlas (GENSAT) Project, NINDS Contracts N01NS02331 & HHSN271200723701C to The Rockefeller University, New York, NY, USA |  |  |
| experimental model, mouse strain | Mouse*: Notum KO* and*Notum fl/fl*  | (Canal et al. 2016) | Jean Paul-Vincent Lab |  |
| experimental model, mouse strain | Mouse*: Rosa26Flox-Stop-Flox-tdTom*  | The Jackson Laboratory |  |  |
| experimental model, mouse strain | Mouse: *Wif1-KO*  | Igor Dawid (NIH)  |  |  |
| antibody | anti-human APC(rabbit polyclonal) | Sigma-Aldrich | Cat#:HPA013349RRID:AB\_1844913 | IHC(1:500) |
| antibody | anti-human, canine, bovine, chicken β-catenin (15B8)(mouse monoclonal) | Sigma-Aldrich | Cat#:C7207RRID:AB\_476865 | IHC(1:1000) |

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| antibody | anti-mouse β-catenin (mouse monoclonal) | BD Biosciences | Cat#:610154RRID:AB\_397555 | IF (1:200) |
| antibody | anti-human and mouse CD49f-PE/Cy7 (Integrin-α6)(rat monoclonal) | BioLegend | Cat#:313622RRID: AB\_2561705 | FACS(1:200) |
| antibody | anti-mouse CD31-APC(rat monoclonal) | BioLegend | Cat#:102410 RRID: AB\_312905 | FACS (1:200) |
| antibody | anti-mouse CD140a-APC(rat monoclonal) | BioLegend | Cat#:135908 RRID:AB\_2043970  | FACS (1:200) |
| antibody | anti-human, mouse E-Cadherin (24E10)(rabbit monoclonal) | Cell Signaling | Cat#:3195SRRID:AB\_2291471 | IF(1:500) |
| antibody | anti-human, mouse FZD10(rabbit polyclonal) | MyBioSource  | Cat#:MBS9606335 | IF(1:200) |
| antibody | all species anti-GFP/YFP(chicken polyclonal) | Abcam | Cat#:Ab13970RRID:AB\_300798 | IF (1:2000)  |
| antibody | anti-human, mouse, rat, monkey, Phospho-Histone H2A.X (Ser139) (20E3)(rabbit monoclonal) | Cell Signaling | Cat#:9718SRRID:AB\_2118009 | IF (1:200)  |
| antibody | anti-mouse Integrin-β4 (346-11A) (CD104)(rat monoclonal) | BD Biosciences | Cat#:553745RRID:AB\_395027 | IF (1:500) |
| antibody | anti-human, mouse, rat LEF1 (C12A5)(rabbit monoclonal) | Cell Signaling | Cat#:2230RRID:AB\_823558 | IF(1:300) |
| antibody | anti-mouse LEF1 (rabbit polyclonal) | Fuchs Lab |  | IF (1:300) |
| antibody | anti-mouse LEF1 (guinea pig polyclonal) | Fuchs Lab |  | IF (1:500) |
| antibody | anti-mouse LHX2(rabbit polyclonal) | Fuchs Lab |  | IF (1:2000) |
| antibody | all species anti-MYC (71D10)(rabbit monoclonal) | Cell Signaling | Cat#:2278RRID:AB\_490778 | IF (1:500) |

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| antibody | anti-human NOTUM(rabbit polyclonal) | Sigma-Aldrich | Cat# HPA023041 RRID: AB\_1854569 | IF (1:100) |
| antibody | anti-mouse P-CADHERIN(goat polyclonal) | R&D | Cat#:AF761RRID:AB\_355581 | IF (1:300) |
| antibody | all species anti-RFP (5F8)(rat monoclonal) | Chromotek | Cat#:5f8-100RRID:AB\_2336064 | IF (1:1000) |
| antibody | anti-human, mouse, rat Phospho-Smad1 (Ser463/465)/ Smad5 (Ser463/465)/ Smad9 (Ser465/467) (D5B10) (rabbit monoclonal)  | Cell signaling | Cat#:13820RRID:AB\_2493181 | IF (1:200) |
| antibody | anti-mouse SHH(goat polyclonal) | R&D | Cat#:AF445 | IF (1:50) |
| antibody | anti-human SOX2 (EPR3131)(rabbit monoclonal) | Abcam | Cat#:ab92494RRID:AB\_10585428 | IF (1:200) |
| antibody | anti-mouse SOX9(guinea pig polyclonal) | Fuchs Lab |  | IF(1:1000) |
| antibody | anti-human, mouse TCF1/TCF7 (C63D9)(rabbit monoclonal) | Cell signaling | Cat#:2203 | IF(1:200) |
| antibody | anti-mouse, rat, chinese hamster TGN46 (rabbit polyclonal) | Abcam | Cat#:ab16059RRID:AB\_443307 | IF(1:200) |
| antibody | anti-mouse WIF1(goat polyclonal) | R&D | Cat#:AF135RRID:AB\_354748 | IF (1:100) |
| antibody | anti-chicken AF488 conjugated antibody(donkey polyclonal) | Jackson ImmunoResearch | Cat#:703-545-155RRID:AB\_2340375 | IF (1:1000) |
| antibody | anti-goat AF488 conjugated antibody(donkey polyclonal) | Jackson ImmunoResearch  | Cat#:705-545-003RRID:AB\_2340428 | IF (1:1000) |
| antibody | anti-goat RRX conjugated antibody(donkey polyclonal) | Jackson ImmunoResearch  | Cat#:705-295-147RRID:AB\_2340423 | IF (1:1000) |

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| antibody | anti-goat AF647 conjugated antibody(donkey polyclonal) | Jackson ImmunoResearch  | Cat#:705-605-003RRID:AB\_2340436 | IF (1:1000) |
| antibody | anti-guinea pig AF488 conjugated antibody(donkey polyclonal) | Jackson ImmunoResearch | Cat#:706-545-148RRID:AB\_2340472 | IF (1:1000) |
| antibody | anti-guinea pig RRX conjugated antibody(donkey polyclonal) | Jackson ImmunoResearch | Cat#:706-295-148RRID:AB\_2340468 | IF (1:1000) |
| antibody | anti-guinea pig AF647 conjugated antibody(donkey polyclonal) | Jackson ImmunoResearch | Cat#:706-605-148RRID:AB\_2340476 | IF (1:1000) |
| antibody | anti-rabbit AF488 conjugated secondary(donkey polyclonal) | Jackson ImmunoResearch | Cat#:711-545-152RRID:AB\_2313584 | IF (1:1000) |
| antibody | anti-rabbit RRX conjugated secondary(donkey polyclonal) | Jackson ImmunoResearch | Cat#:711-295-152RRID:AB\_2340613 | IF (1:1000) |
| antibody | anti-rabbit AF647 conjugated secondary(donkey polyclonal) | Jackson ImmunoResearch | Cat#:711-605-152RRID:AB\_2492288 | IF (1:1000) |
| antibody | anti-rat AF488 conjugated antibody(donkey polyclonal) | Jackson ImmunoResearch | Cat#:712-546-153RRID:AB\_2340686 | IF (1:1000) |
| antibody | anti-rat RRX conjugated antibody(donkey polyclonal) | Jackson ImmunoReserach | Cat#:712-295-153RRID:AB\_2340676 | IF (1:1000) |
| antibody | anti-rat AF647 conjugated antibody(donkey polyclonal) | Jackson ImmunoResearch | Cat#:712-605-153RRID:AB\_2340694 | IF (1:1000) |
| sequenced-based reagent | pCR4-*mApcdd1* | Angela Cristiano Lab |  |  |
| sequenced-based reagent | pGEMT-*mDkk4* | David Schlessinger Lab |  |  |
| sequenced-based reagent | pCRII-*mWif1\_3* | Fuchs Lab |  |  |
| sequenced-based reagent | PCRII-*Wnt10b* | Fuchs Lab |  |  |

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| recombinant DNA reagent | *pLKO.1-Pgk-Cre-mRFP* (plasmid) | Fuchs Lab |  |  |
| recombinant DNA reagent | *pLKO.1-Pgk-Cre-EGFP* (plasmid) | This paper |  | *See Materials and Methods section: mouse strains, lentiviral transduction and constructs*  |
| recombinant DNA reagent | *pLKO-TK-12xTOP-EGFP-Pgk-Cre*(plasmid) | This paper |  | *See Materials and Methods section: mouse strains, lentiviral transduction and constructs*  |
| recombinant DNA reagent | *LV-TRE-Gene-Pgk-H2BGFP*(plasmid) | Fuchs Lab |  |  |
| recombinant DNA reagent | *pGEM-Apcdd-Myctag* (plasmid) | Origene | Cat#:MR225129 |  |
| recombinant DNA reagent | *pGEM-mBmp4*(plasmid) | Sino Biological Inc. | Cat#:MG50439-G |  |
| recombinant DNA reagent | *pCMV6-Dkk4-Myctag* (plasmid) | Origene | Cat#:MR202533 |  |
| recombinant DNA reagent | *pCMV6-Notum-Myctag* (plasmid) | Origene | Cat#:MR217230 |  |
| recombinant DNA reagent | *pCMV6-Wif1-Myctag* (plasmid) | Origene | Cat#:MR202510 |  |
| recombinant DNA reagent | *pCMV6-Wnt3-Myctag* (plasmid) | Origene | Cat#:MR222492 |  |
| recombinant DNA reagent | *pCMV6-Wnt10b-Myctag* (plasmid) | Origene | Cat#:MR224739 |  |
| recombinant DNA reagent | *LV-TRE-Apcdd-M-Pgk-H2BGFP* (plasmid) | This paper |  | *See Materials and Methods section: mouse strains, lentiviral transduction and constructs*  |
| recombinant DNA reagent | *LV-TRE-Bmp4-Pgk-H2BGFP*(plasmid) | Fuchs Lab |  |  |
| recombinant DNA reagent | *LV-TRE-Dkk4-M-Pgk-H2BGFP*(plasmid) | This paper |  | *See Materials and Methods section: mouse strains, lentiviral transduction and constructs*  |
| recombinant DNA reagent | *LV-TRE-Notum-M-Pgk-H2BGFP*(plasmid) | This paper |  | *See Materials and Methods section: mouse strains, lentiviral transduction and constructs*  |

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| recombinant DNA reagent | *LV-TRE-Notum-Aqp4-M-Pgk-H2BGFP*(plasmid) | This paper |  | *See Materials and Methods section: mouse strains, lentiviral transduction and constructs*  |
| recombinant DNA reagent | *LV-TRE-Wif1-M-Pgk-H2BGFP*(plasmid) | This paper |  | *See Materials and Methods section: mouse strains, lentiviral transduction and constructs*  |
| recombinant DNA reagent | *LV-TRE-Wif1-Aqp4-M-Pgk-H2BGFP*(plasmid) | This paper |  | *See Materials and Methods section: mouse strains, lentiviral transduction and constructs*  |
| recombinant DNA reagent | *LV-TRE-Wnt3-M-Pgk-H2BGFP*(plasmid) | This paper |  | *See Materials and Methods section: mouse strains, lentiviral transduction and constructs*  |
| recombinant DNA reagent | *LV-TRE-Wnt10b-M-Pgk-H2BGFP*(plasmid) | This paper |  | *See Materials and Methods section: mouse strains, lentiviral transduction and constructs*  |
| chemical compound, drug | Doxycycline | Sigma | Cat#:D9891 |  |
| chemical compound, drug | LGK974 | Cayman Chemical | Cat#:14072 |  |
| chemical compound, drug | Tunicamycin | Milipore Sigma | Cat#:504570 |  |
| chemical compound, drug | 16% Paraformaldehyde Solution | Electron Microscopy Science | Cat#:15700 |  |
| commercial assay or kit | Click-it Edu Alexa Fluor 647 Imaging kit | Life Technologies | Cat#:C10340 |  |
| commercial assay or kit | Direct-zol RNA MiniPrep kit  | Zymo Research | Cat#:R2050 |  |
| commercial assay or kit | ImmPRESS® Universal PLUS Polymer Kit, Peroxidase (Horse Anti-Mouse/Rabbit IgG) | Vector Laboratories | Cat#:MP-7800 |  |
| commercial assay or kit | ImmPACT® DAB Peroxidase (HRP) Substrate  | Vector Laboratories | Cat#:SK-4105 |  |
| commercial assay or kit | M.O.M.® (Mouse on Mouse) Basic Kit  | Vector Laboratories | Cat#:BMK-2202 |  |

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| software, algorithm | Adobe Illustrator CS5 | Adobe.com | RRID:SCR\_010279 |  |
| software, algorithm | FACS DiVa software | BD Biosciences | RRID:SCR\_001456 |  |
| software, algorithm | Fiji (Image J) | (<https://fiji.sc/>) | RRID:SCR\_003070 |  |
| software, algorithm | FlowJo Software | BD Biosciences | RRID:SCR\_008520 |  |
| software, algorithm | Graphpad Prism 8 | Graphpad.com | RRID:SCR\_002798  |  |
| software, algorithm | Gene Set Enrichment Analysis (GSEA) | (Subramanian et al. 2005) | RRID:SCR\_003199 |  |
| software, algorithm | PANTHER Classification System | GENEONTOLOGY | RRID:SCR\_015893 |  |
| software, algorithm | R studio | Rstudio.com | RRID:SCR\_000432 |  |
| other | SlowFade™ Diamond Antifade Mountant (Invitrogen) | TermoFisher | Cat#:S36963 |  |
| other | Dispase | Gibco | Cat#:17105-041 |  |
| other | Trypsin-EDTA 0.25% | Gibco | Cat#:25200056 |  |
| other | Trizol LS (Invitrogen) | TermoFisher | Cat#:10296010 |  |