### Major Resources Table

In order to allow validation and replication of experiments, all essential research materials listed in the Methods should be included in the Major Resources Table below. Authors are encouraged to use public repositories for protocols, data, code, and other materials and provide persistent identifiers and/or links to repositories when available. Authors may add or delete rows as needed.

#### Animals (in vivo studies)

| Species | Vendor or Source | Background Strain | Sex | Persistent ID / URL |
|---------|-----------------|-------------------|-----|---------------------|
| Mouse   | Jackson         | C57BL/6J          |     | https://www.jax.org/strain/000664 |

#### Genetically Modified Animals

| Parent  | Species         | Vendor or Source       | Background Strain | Other Information | Persistent ID / URL |
|---------|-----------------|------------------------|-------------------|-------------------|---------------------|
|         | Cdh5-CreER<sup>72</sup> | Keio University (Yoshiaki Kubota) | C57BL/6J |                     | http://www.keiovascular.com/ |
|         | Dll4<sup>fl/fl</sup> | University College London (David Shima) | C57BL/6J |                     | Not applicable |
|         | Notch1<sup>fl/fl</sup> | KAIST (Dae-Sik Lim) | C57BL/6J |                     | Not applicable |
|         | Sox17<sup>fl/fl</sup> | Morrison Lab, UT Southwestern | C57BL/6J |                     | https://cri.utsw.edu/scientists/sean-morrison-laboratory/ |
|         | Gt(ROSA)26Sor<sup>tm1(Notch1)Dam/J</sup> | Jackson | C57BL/6J |                     | https://www.jax.org/strain/008159 |
|         | RPL22<sup>tm1.Psam</sup> | Jackson | C57BL/6J |                     | https://www.jax.org/strain/008159 |

#### Antibodies

| Target antigen | Vendor or Source | Catalog # | Working concentration | Persistent ID / URL |
|----------------|-----------------|-----------|-----------------------|---------------------|
| anti-CD31      | Millipore       | MAB1398Z  | 1:200                 | https://www.sigmaaldrich.com/KR/ko/product/mm/mab1398z?gclid=Cj0KCQjw_7KXBhCoARIsAPdTfhimMeWQyLaapQkAsBkCDkJaI857sLfKrZ3eiTSjpCuZINKmmf42VYaAga8EALw_wC8B |
| anti-CD31      | BD Bioscience   | 550274    | 1:200                 | https://wwwbdbiosciences.com/en-ca/products/reagents/flow-cytometry-reagents/research-reagents/single-color-antibodies-ruo/purified-rat-anti-mouse-cd31.550274 |
| anti-Sox17     | R&D             | AF1924    | 1:200                 | https://www.rndsystems.com/products/human-sox17-antibody_af1924 |
| anti-CD11b     | BD Bioscience   | 553308    | 1:200                 | https://wwwbdbiosciences.com/ja-jp/products/reagents/flow-cytometry-reagents/research-reagents-single-color-antibodies-ruo/Purified-Rat-Anti-CD11b.553308 |
| anti-Ki67      | Abcam           | ab16667   | 1:200                 | https://www.abcam.com/ki67-antibody-sp6-ab16667.html |
| anti-S100A4    | Abcam           | ab41532   | 1:200                 | https://www.abcam.com/s100a4-antibody-ab41532.html |
| anti-HGF       | Abcam           | ab83760   | 1:200                 | https://www.abcam.com/hgf-antibody-ab83760.html |
| FITC-conjugated anti-SMA | Sigma-Aldrich | F3777 | 1:2000               | https://www.sigmaaldrich.com/KR/ko/product/sigma/f3777?gclid=Cj0KCQjw_7KXBhCoARIsAPdTfhRN9dUfugqZxZ6o |
| Description | Source | Persistent ID / URL |
|-------------|--------|---------------------|
| Sildenafil | selleckchem | S4684 |
| Macitentan | selleckchem | S8051 |

**DNA/cDNA Clones**

| Clone Name | Sequence | Source / Repository | Persistent ID / URL |
|------------|----------|---------------------|---------------------|
| Not applicable | Not applicable | Not applicable | Not applicable |

**Cultured Cells**

| Name | Vendor or Source | Sex (F, M, or unknown) | Persistent ID / URL |
|------|-----------------|------------------------|---------------------|
| Human Umbilical Vein Endothelial Cell (HUVEC) | Biotherapeutics Translational Research Center, Korea Research Institute of Bioscience and Biotechnology | unknown | Not applicable |

**Data & Code Availability**

| Description | Source / Repository | Persistent ID / URL |
|-------------|---------------------|---------------------|
| Transcriptomic profiles of pulmonary endothelial cells of control/normoxic mice and Sox17<sup>ΔEC</sup>/hypoxic mice | NCBI Gene ExpressionOmnibus | GSE210505 |

**Other**

| Description | Source | Persistent ID / URL |
|-------------|--------|---------------------|
| Sildenafil | selleckchem | S4684 |
| Macitentan | selleckchem | S8051 |

DOI [to be added]
| Compound    | Supplier     | ID   |
|-------------|--------------|------|
| Crizotinib  | selleckchem  | S1068|
| Capmatinib  | selleckchem  | S1068|
ARRIVE GUIDELINES

The ARRIVE guidelines (https://arriveguidelines.org/) are a checklist of recommendations to improve the reporting of research involving animals. Key elements of the study design should be included below to better enable readers to scrutinize the research adequately, evaluate its methodological rigor, and reproduce the methods or findings.

Study Design

| Groups                                      | Sex | Age  | Number (prior to experiment) | Number (after termination) | Littermates (Yes/No) | Other description |
|---------------------------------------------|-----|------|------------------------------|-----------------------------|----------------------|-------------------|
| Group 1 (Control/normoxic)                  | M&F | 13 weeks | Many                        | No deaths during procedure | Yes                  |                   |
| Group 2 (Sox17^{ΔEC}/normoxic)              | M&F | 13 weeks | Many                        | No deaths during procedure | Yes                  |                   |
| Group 3 (control/hypoxic)                   | M&F | 13 weeks | Many                        | No deaths during procedure | Yes                  |                   |
| Group 4 (Sox17^{ΔEC}/hypoxic)               | M&F | 13 weeks | Many                        | No deaths during procedure | Yes                  |                   |
| Group 5 (control/hypoxic->normoxic)         | M&F | 16 weeks | Many                        | No deaths during procedure | Yes                  |                   |
| Group 6 (Sox17^{ΔEC}/hypoxic-> normoxic)    | M&F | 16 weeks | Many                        | No deaths during procedure | Yes                  |                   |

Sample Size: Sample size was determined based on previous reports using PAH animal models and no statistical method was used to predetermine the sample size.

Inclusion Criteria

Mice were included in this study according to experimental schedule.

Exclusion Criteria

There were no exclusion criteria

Randomization

Both male and female mice were randomly assigned to each experiment.

Blinding

To minimize the possibility of biases, investigators were blinded to group allocation during data collection.