

Supplemental Table S1, List of antibodies.

| | | |
|---|---------------------------|----------------|
| Mouse anti- β -ACTIN | Sigma-Aldrich | Cat# A5316 |
| Rabbit anti-NRF2 | Abcam | Cat# Ab62352 |
| Rabbit anti-NRF2 | Santa Cruz Biotechnology | Cat# SC-13032x |
| Rabbit anti-GCLC | Abcam | Cat# Ab41463 |
| Rabbit anti-NQO1 | Abcam | Cat# Ab80588 |
| Rabbit anti-HMOX1 | Abcam | Cat# Ab68477 |
| Rabbit anti-NQO1 | Abcam | Cat# Ab80588 |
| Rabbit anti-Catalase | Santa Cruz Biotechnology | Cat# SC-50508 |
| Rabbit anti-GCLC | Abcam | Cat# Ab41463 |
| Rabbit anti-GCLM | Abclonal | Cat# A5314 |
| Rabbit anti-SLC7A11 | Cell Signaling Technology | Cat# 12691 |
| Rabbit anti-EZH2 | Sigma-Aldrich | Cat# 07-689 |
| Mouse anti-adult hemoglobin (HbA) | Santa Cruz Biotechnology | Cat# SC-21757 |
| Mouse anti-fetal hemoglobin (HbF) | Santa Cruz Biotechnology | Cat# SC-21756 |
| Sheep IgG isotype FITC control antibody | MyBioSource | Cat# MBS524511 |
| FITC conjugated mouse anti-HbF | BD biosciences | Cat# 552829 |
| Donkey anti-Mouse IgG, secondary, HRP | Santa Cruz Biotechnology | Cat# SC-2096 |
| Donkey anti-Rabbit IgG, secondary, HRP | Santa Cruz Biotechnology | Cat# SC-2077 |

Supplemental Table S2, List of DNA oligoes.

| cDNA analysis | Forward primer | Reverse primer |
|--|---------------------------|-------------------------|
| β -ACTB (both human NM_001101 and mouse NM_007393) | GACGAGGCCCCAGAGCAAGAGAG G | TCTCAAACATGATCTGGGTCATC |
| CAT (both human NM_001752 and mouse NM_009804) | GGTTTGGCCTCACAAGGACTACC | CGGTAGGGACAGTTCACAGGTAT |
| GCLC (both human NM_001498 and mouse NM_010295) | GAGTATGGGAGTTACATGAT | TCTGGAAAGAAGAGGGGACTT |
| NQO1 (both human NM_000903 and mouse NM_008706) | ATCCTGGAAGGATGGAAGAAAC | TCTAGCTTTGATCTGGTTGTCAG |
| GCLM (both human NM_002061 and mouse NM_008129) | AAGTGCCCGTCCACGCACAG | CTTCTAGTTGATGATGAAGA |
| SLC7A11 (both human NM_014331 and mouse NM_011990) | CTCCAGAACACGGGCAGCGT | CAAATGCCAGGGATATCACA |
| KDM6a (human NM_001291415) | TCACTTCAACCTCTTATTGGAAG | CTTTGAACATAAGCCCAAGTCGT |
| KDM6b (human NM_001080424) | TCCTCCTGCCACCAAATACCTC | CCAGCCCATCAGGTAGGATCTTG |

| | | |
|--------------------------------------|--|---------------------------|
| <i>EZH1</i> (human NM_001991) | TGGTTCCCATCATGTATTCCTGG | GATCCAGGGATCATCTCTTCTTC |
| <i>EZH2</i> (human NM_004456) | ATGGGCCAGACTGGGAAGAAATC | GCGCAATGAGCTCACAGAAGTCA |
| <i>HBG1</i> (human NM_000559) | GTGGATCCTGAGAACTTCA | GCTTGCAGAATAAAGCCTATCCTTG |
| <i>HBB</i> (human NM_000518) | GTGGATCCTGAGAACTTCA | TTAGGCAGAATCCAGATGCTCAAGG |
| <i>Tgfb</i> (mouse NM_011577) | GGTGCTCGCTTTGTACAACA | ACTGCTTCCCGAATGTCTGA |
| <i>Tgfa</i> (mouse NM_031199) | CATTGAGCCCACCCTTGTTT | ATGAGGAACAGGCAGCTTCT |
| <i>Il1b</i> (mouse NM_008361) | ACTCATTGTGGCTGTGGAGA | TGTTGTTTCATCTCGGAGCCT |
| <i>Il6</i> (mouse NM_031168) | CTGGGGATGTCTGTAGCTCA | CAGGTCTGTTGGGAGTGGTA |
| <i>Ccl2</i> (mouse NM_011333) | AGGTGTCCCAAAGAAGCTGT | ACAGAAGTGCTTGAGGTGGT |
| <i>Ccl3</i> (mouse NM_011337) | GATCTGCGCTGACTCCAAAG | GTCCCTCGATGTGGCTACTT |
| <i>Ccl4</i> (mouse NM_013652) | CCTCTCTCTCCTCTTGCTCG | CTCTCCTGAAGTGGCTCCTC |
| <i>Ccl5</i> (mouse NM_013653) | TGCCCACGTCAAGGAGTATT | AGATGCCCATTTTCCCAGGA |
| <i>Ccl7</i> (mouse NM_013654) | TGAAGCCAGCTCTCTCACTC | TATAGCCTCCTCGACCCACT |
| <i>Ccl11</i> (mouse NM_011330) | CACAAAGCACCTGGACCAAA | TCGTCCCATTGTGTTCTCA |
| <i>Ccl17</i> (mouse NM_011332) | GCTTCTGGGGACTTTTCTGC | TTGAAACCATGGACAGCAGC |
| <i>Cxcl1</i> (mouse NM_008176) | AGTTCCAGCACTCCAGACTC | CTCGCGACCATTCTTGAGTG |
| <i>Cxcl10</i> (mouse NM_021274) | ACATCAGCTGCTACTCCTCC | CTGAGCTAGGGAGGACAAGG |
| ChIP analysis | Forward primer | Reverse primer |
| <i>HBG1</i> (human NM_000559) | CTGAAACGGTCCCTGGCTA | CTGTGAAATGACCCATGGCG |
| <i>HBB</i> (human NM_000518) | CACTTAGACCTCACCTGTGGAGCCACACCCTAGGGTTGGC | CTTGTAACCTTGATACCAACCTG |
| <i>HMOX1</i> ARE (human NM_002133) | CACGGTCCCGAGGTCTATT | AAGGGTGGAGGAGCTGCTAT |
| <i>NQO1</i> ARE (human NM_000903) | ATTACCTGCCTTGAGGAGCA | CAGAGGCCTCAAAAATCTGG |
| <i>SLC7A11</i> ARE (human NM_014331) | TGCATGAGGAAAATGATCCA | GCATGGAAAAGGTCAGAACC |
| <i>Nqo1</i> ARE (mouse NM_008706) | TTTCTAAGAGCAGAACGCAGCAC | AGACCTCCTGGGTACAAAATGGA |
| <i>Cat</i> ARE (mouse NM_009804) | GTAGGGAGAGACACGGTTTCCA | AGAAAAGACAAATCAAGAACCAG |
| <i>Hmox1</i> ARE (mouse NM_010442) | AGTCACGGTCCCGAGGTCT | TCGAGTTGATCTTCTTACAGTG |

| | | |
|--|--|--|
| <i>Gcl</i> c ARE (mouse NM_010295) | CTCTTAACCGCTGAGCCATC | TATTGGGAGATGGGGAGAGA |
| <i>Slc7a11</i> ARE (mouse NM_011990) | AAATTTCCGGCTTTGAGCTA | CTTGTGAGCACAGCGTGATT |
| shRNA constructs | Forward primer | Reverse primer |
| shControl | CCGGCCTAAGGTTAAGTCGCCCT CGCTCGAGCGAGGGCGACTTAA CCTTAGGTTTTTG | AATTCAAAAACCTAAGGTTAAGTCGC CCTCGCTCGAGCGAGGGCGACTTAA CCTTAGG |
| sh <i>EZH2</i> construct 1 (targeting human <i>EZH2</i> NM_004456) | CCGGTGACTTCTGTGAGCTCATT GCCTCGAGGCAATGAGCTCACA GAAGTCATTTTTG | AATTCAAAAATGACTTCTGTGAGCTC ATTGCCTCGAGGCAATGAGCTCACA GAAGTCA |
| sh <i>EZH2</i> construct 2 (targeting human <i>EZH2</i> NM_004456) | CCGGGTTTGTGCGGGAAGCGT GTACTCGAGTACACGCTTCCGCC AACAACTTTTTG | AATTCAAAAAGTTTGTGCGGGAAGC GTGTACTCGAGTACACGCTTCCGCC AACAAAC |

Supplemental Figures

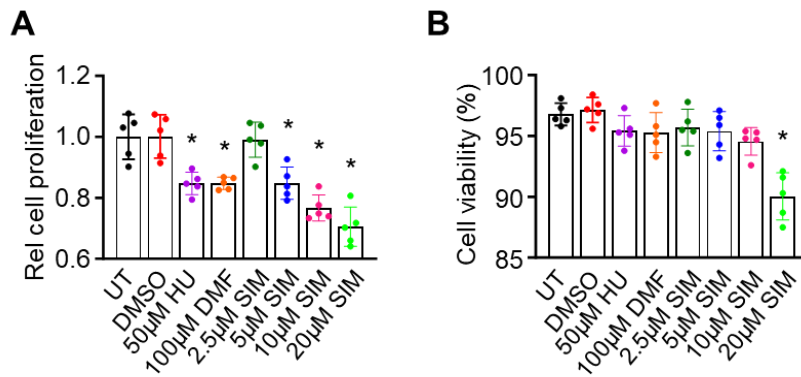


Figure S1, Effect of HbF inducers on cellular proliferation and viability of SCD erythroblasts. Cellular proliferation (A) and viability (B) of SCD erythroblasts at day 12 after 48 h of treatments with 0.1% DMSO, 50 μ M hydroxyurea (HU), 100 μ M dimethyl fumarate (DMF), 2.5-20 μ M simvastatin (SIM), or untreated control (UT). Data represents mean \pm SD of three biological replicates. *, $p < 0.05$.

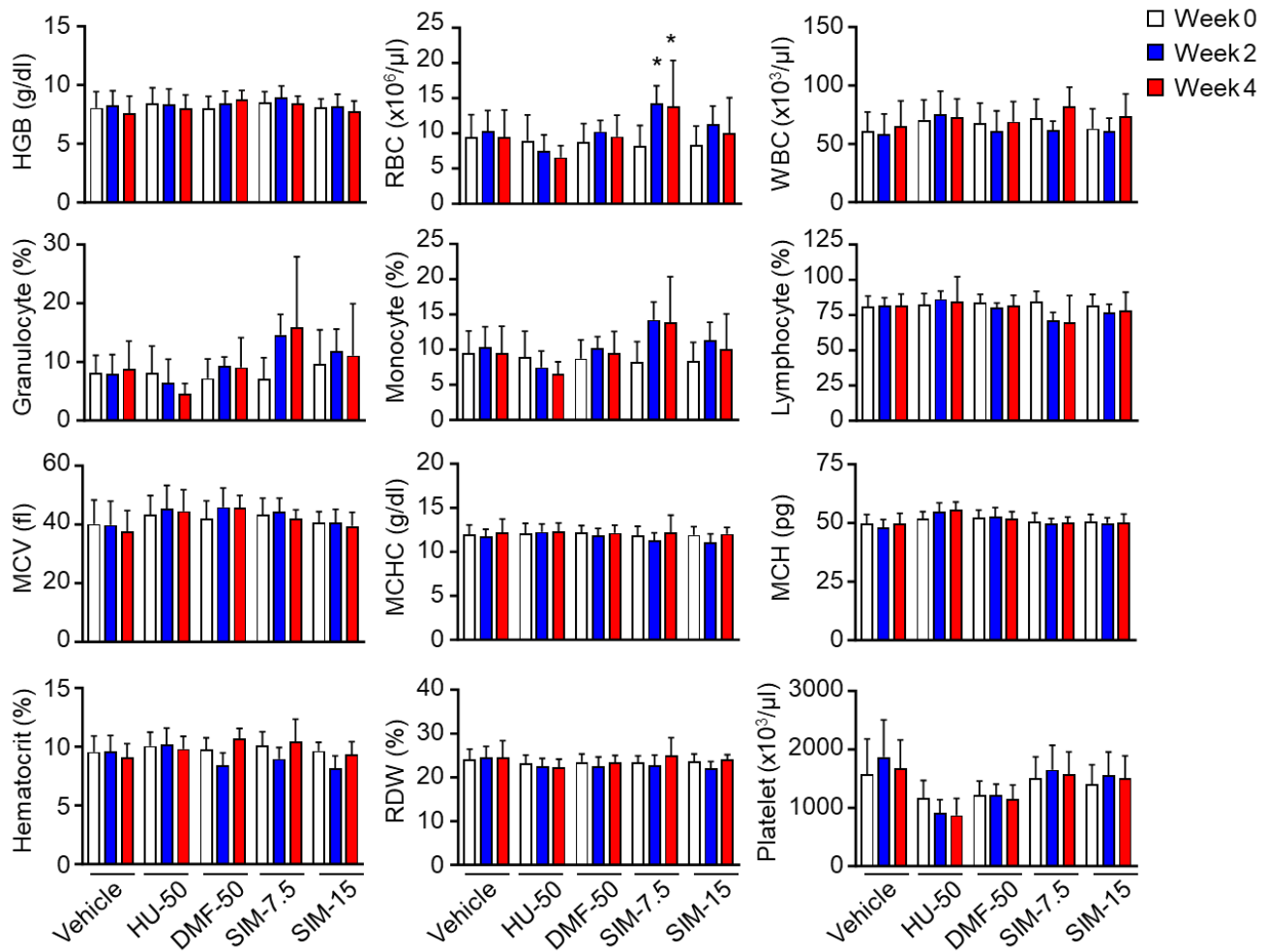


Figure S2, Hematological indices of SCD mice treated with simvastatin. Complete blood count and differentials for peripheral blood of the SCD mice, at week 0, week 2, and week 4 of treatment of simvastatin (SIM, 7.5-15 mg/kg), hydroxyurea (HU, 50 mg/kg) or dimethyl fumarate (DMF, 50 mg/kg) daily, 5 days a week. One-way ANOVA with Bonferroni's multiple comparison test was used for statistical analysis (n=5 mice). *, $p < 0.05$.