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Supplemental information

Direct cardiac reprogramming via combined CRISPRa-mediated endogenous Gata4 activation and exogenous Mef2c and Tbx5 expression

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Table S1. Sequence, location and activation efficiency of Gata4 sgRNA in MEF and FCF

| | sgRNA sequence | Location | Gata4 endo in MEF | | Gata4 total in MEF | | Gata4 endo in FCF | | Gata4 total in FCF | |
|-----|----------------------|----------------|-------------------|---------|--------------------|---------|-------------------|--------|--------------------|--------|
| G1 | GGATCTCAGGAAAATCCCAG | chr14:63246528 | 2.14 | ± 0.30 | 1.69 | ± 0.03 | 1.94 | ± 0.07 | 1.75 | ± 0.20 |
| G2 | GGAGTGGGAAGAAGTGTCGG | chr14:63245877 | 129.21 | ± 33.39 | 174.25 | ± 8.74 | 1.40 | ± 0.10 | 1.65 | ± 0.10 |
| G3 | GTGGACCACTGAGAGTAGGG | chr14:63245551 | 132.10 | ± 15.62 | 191.68 | ± 20.51 | 1.49 | ± 0.19 | 1.76 | ± 0.40 |
| G4 | GTCGGTCAGAGAGATTACAC | chr14:63244811 | 2.14 | ± 0.30 | 1.69 | ± 0.03 | 0.10 | ± 0.02 | 0.09 | ± 0.02 |
| G5 | TTGCTAGCCTCAGATCTACG | chr14:63245674 | 1.94 | ± 0.07 | 1.75 | ± 0.20 | 1.40 | ± 0.10 | 1.65 | ± 0.10 |
| G6 | GGGCTGCACTGAGGGCAGAA | chr14:63245473 | 226.72 | ± 18.97 | 302.77 | ± 33.00 | 0.90 | ± 0.08 | 2.50 | ± 0.09 |
| G7 | GGGGCGGGGAGCCCGGACC | chr14:63245339 | 31.58 | ± 2.48 | 43.15 | ± 9.42 | 1.44 | ± 0.15 | 1.73 | ± 0.04 |
| G8 | GCCTAAGGGAGTCACGTGCA | chr14:63245313 | 3.16 | ± 0.33 | 2.12 | ± 0.39 | 0.93 | ± 0.11 | 0.78 | ± 0.04 |
| G9 | GGGGCCCGGGGAACCGCGCC | chr14:63245264 | 37.30 | ± 2.55 | 30.64 | ± 2.59 | 1.14 | ± 0.15 | 1.32 | ± 0.09 |
| G10 | CGCCGGGCGGAGGTGCTGCC | chr14:63245357 | 284.69 | ± 18.10 | 311.04 | ± 5.91 | 1.82 | ± 0.13 | 1.72 | ± 0.04 |
| G11 | GCATGGACTTTGCCTGTTGG | chr14:63245407 | 0.93 | ± 0.05 | 1.21 | ± 0.05 | 0.10 | ± 0.02 | 0.09 | ± 0.02 |
| G12 | TTGGGAAGAGTCCTGCGGGC | chr14:63245380 | 23.25 | ± 1.90 | 30.66 | ± 1.15 | 1.29 | ± 0.07 | 1.57 | ± 0.13 |
| G13 | AGCGCAGGCGATCGCTACGC | chr14:63245285 | 20.13 | ± 1.46 | 25.72 | ± 1.40 | 1.44 | ± 0.15 | 1.73 | ± 0.04 |
| G14 | GAGTCCTGCGGGCGGGCGCC | chr14:63245373 | 14.07 | ± 2.19 | 14.92 | ± 1.20 | 0.82 | ± 0.04 | 0.89 | ± 0.10 |
| G15 | CGCAGGCGATCGCTACGCGG | chr14:63245283 | 20.81 | ± 2.20 | 14.04 | ± 2.57 | 0.95 | ± 0.17 | 0.81 | ± 0.05 |

Table S2. Sequence, location and activation efficiency of Mef2c sgRNA in MEF and FCF

| | sgRNA sequence | Location | Mef2c endo in MEF | Mef2c total in MEF | Mef2c endo in FCF | Mef2c total in FCF |
|-----|-----------------------|----------------|-------------------|--------------------|-------------------|--------------------|
| M1 | AAATGAGCTGCGGCAAAGAA | chr13:83503732 | 0.62 ± 0.05 | 0.65 ± 0.04 | 0.48 ± 0.02 | 0.46 ± 0.03 |
| M2 | AAGAGACTCGGTGTCAAAC | chr13:83503618 | 0.60 ± 0.07 | 0.55 ± 0.06 | 0.44 ± 0.01 | 0.35 ± 0.02 |
| M4 | TCCAATGGAAAATATCCAAT | chr13:83503980 | 0.51 ± 0.05 | 0.40 ± 0.02 | 0.64 ± 0.05 | 0.46 ± 0.05 |
| M5 | TACATTTCCAAGAATAATCT | chr13:83503868 | 0.39 ± 0.04 | 0.40 ± 0.06 | 0.42 ± 0.01 | 0.31 ± 0.09 |
| M6 | GTGGCTGGAACTTTTTAA | chr13:83503818 | 0.56 ± 0.04 | 0.50 ± 0.03 | 0.70 ± 0.03 | 0.55 ± 0.05 |
| M7 | GAAAAAAGCAAATGAGCTG | chr13:83503722 | 0.68 ± 0.01 | 0.61 ± 0.21 | 1.03 ± 0.05 | 0.95 ± 0.25 |
| M8 | GCTACTGTACCATTTAAAA | chr13:83503560 | 0.42 ± 0.00 | 0.39 ± 0.03 | 0.57 ± 0.05 | 0.41 ± 0.06 |
| M9 | CCGATTGGATATTTTCCAT | chr13:83503979 | 0.53 ± 0.03 | 0.53 ± 0.06 | 4.68 ± 0.22 | 2.56 ± 0.12 |
| M10 | AGTTACAAGCTTTCTAATT | chr13:83503643 | 0.75 ± 0.00 | 0.55 ± 0.03 | 0.62 ± 0.03 | 0.46 ± 0.03 |
| M11 | TGAAAAAAGCAAATGAGCTG | chr13:83503722 | 0.85 ± 0.11 | 0.89 ± 0.13 | 0.66 ± 0.00 | 0.71 ± 0.04 |
| M12 | AAAATGGACACTCACGTCTG | chr13:83503544 | 0.98 ± 0.05 | 0.96 ± 0.14 | 0.80 ± 0.10 | 0.78 ± 0.08 |
| M13 | GACTCGGTGTCAAACCTGGA | chr13:83503614 | 1.81 ± 0.09 | 1.88 ± 0.16 | 0.70 ± 0.01 | 0.76 ± 0.09 |
| M14 | ACTAACAGTGTAGAGGCTTG | chr13:83504003 | 0.97 ± 0.32 | 1.05 ± 0.31 | 0.68 ± 0.04 | 0.79 ± 0.03 |
| M15 | TAAATGGTACAGTAGCATTG | chr13:83503566 | 0.80 ± 0.02 | 0.85 ± 0.10 | 0.84 ± 0.11 | 0.91 ± 0.18 |
| M16 | GTAAAACTTATCACATAGG | chr13:83503679 | 1.27 ± 0.09 | 1.36 ± 0.10 | 0.98 ± 0.04 | 0.95 ± 0.06 |
| M17 | TTTAAAGCCTGTGTGAAATG | chr13:83503893 | 0.59 ± 0.03 | 0.64 ± 0.11 | 1.07 ± 0.01 | 1.00 ± 0.21 |
| M18 | AGTTTTTGTTC AATTAATTG | chr13:83503836 | 1.12 ± 0.12 | 1.12 ± 0.23 | 0.75 ± 0.05 | 0.88 ± 0.07 |
| M21 | GGTCATGGCACTTAAACGAT | chr13:83503593 | 0.69 ± 0.01 | 0.71 ± 0.04 | 0.89 ± 0.10 | 1.00 ± 0.10 |

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|-----|----------------------|----------------|-------------|-------------|-------------|-------------|
| M22 | CAATCCAAAGAAATATTAGA | chr13:83503701 | 0.77 ± 0.06 | 0.79 ± 0.08 | 0.84 ± 0.03 | 0.99 ± 0.25 |
| M23 | GTTGGCTTCAGTCTTGGTCG | chr13:83502595 | 0.38 ± 0.05 | 0.34 ± 0.05 | 0.58 ± 0.04 | 0.65 ± 0.01 |
| M24 | TACATAAGAATGAGACCTGA | chr13:83502807 | 0.44 ± 0.02 | 0.37 ± 0.05 | 0.35 ± 0.05 | 0.36 ± 0.05 |
| M25 | AGAGAAGTACACAGTGAGAG | chr13:83503012 | 0.81 ± 0.04 | 0.72 ± 0.06 | 0.41 ± 0.06 | 0.41 ± 0.02 |
| M26 | GTCTATGTTTTATCTGAAAG | chr13:83503076 | 0.43 ± 0.14 | 0.40 ± 0.12 | 0.50 ± 0.09 | 0.64 ± 0.17 |
| M27 | TTAAAACTGAGAAAAGTTTA | chr13:83502652 | 0.35 ± 0.01 | 0.33 ± 0.04 | 0.30 ± 0.00 | 0.54 ± 0.06 |
| M28 | AAGAATGAGACCTGATGGAG | chr13:83502812 | 0.56 ± 0.04 | 0.52 ± 0.04 | 0.31 ± 0.06 | 0.38 ± 0.07 |
| M29 | TATTTAATAATTATACGGGT | chr13:83502942 | 0.26 ± 0.01 | 0.25 ± 0.04 | 0.41 ± 0.08 | 0.42 ± 0.10 |
| M30 | CAGTGAGAGAGGTGCTTGCA | chr13:83503023 | 0.50 ± 0.05 | 0.43 ± 0.09 | 0.58 ± 0.17 | 0.46 ± 0.10 |
| M31 | GACACAAGGCCTTTGAAAAG | chr13:83502714 | 0.31 ± 0.00 | 0.27 ± 0.02 | 0.22 ± 0.01 | 0.19 ± 0.04 |
| M32 | ATGAGACCTGATGGAGAGGT | chr13:83502816 | 0.34 ± 0.03 | 0.30 ± 0.03 | 0.45 ± 0.04 | 0.35 ± 0.11 |
| M33 | GGAGCTTGCTAAAAAGAAAC | chr13:83502911 | 0.29 ± 0.00 | 0.27 ± 0.02 | 0.31 ± 0.03 | 0.29 ± 0.05 |
| M34 | ATGGCATCACCCAGTATCCA | chr13:83503049 | 0.36 ± 0.04 | 0.30 ± 0.03 | 0.20 ± 0.02 | 0.18 ± 0.03 |
| M35 | TTTGTTAGGCCACTTTTCAA | chr13:83502723 | 0.31 ± 0.01 | 0.29 ± 0.04 | 0.29 ± 0.02 | 0.28 ± 0.04 |
| M36 | ATGAAATATGAGGAAACCTA | chr13:83502857 | 0.30 ± 0.02 | 0.30 ± 0.01 | 0.30 ± 0.06 | 0.32 ± 0.08 |
| M37 | AATGGCATCACCCAGTATCC | chr13:83503050 | 0.38 ± 0.05 | 0.35 ± 0.07 | 0.44 ± 0.02 | 0.39 ± 0.16 |
| M38 | TCTGAAAGTGGAGCCCTGCA | chr13:83503088 | 0.43 ± 0.02 | 0.36 ± 0.02 | 0.29 ± 0.01 | 0.31 ± 0.04 |
| M39 | AAAAGTGGCCTAACAAATAT | chr13:83502729 | 0.47 ± 0.00 | 0.38 ± 0.08 | 0.29 ± 0.01 | 0.28 ± 0.01 |
| M40 | TGAAATATGAGGAAACCTAA | chr13:83502858 | 0.33 ± 0.02 | 0.34 ± 0.03 | 0.26 ± 0.02 | 0.22 ± 0.07 |
| M41 | GATACTGGGTGATGCCATTC | chr13:83503054 | 0.39 ± 0.05 | 0.38 ± 0.04 | 0.40 ± 0.09 | 0.34 ± 0.09 |
| M42 | TGGAGCCCTGCAGGGAAATG | chr13:83503096 | 0.37 ± 0.02 | 0.38 ± 0.10 | 0.18 ± 0.02 | 0.15 ± 0.02 |

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|-----|-----------------------|----------------|-------------|-------------|-------------|-------------|
| M43 | ATCACACACCAATATTTGTT | chr13:83502737 | 0.26 ± 0.02 | 0.25 ± 0.00 | 0.32 ± 0.09 | 0.36 ± 0.09 |
| M44 | TGCGTCATAACAAAACCCCTT | chr13:83502873 | 0.23 ± 0.01 | 0.18 ± 0.03 | 0.81 ± 0.19 | 0.96 ± 0.24 |
| M45 | TTATTTAATAATTATACGGG | chr13:83502943 | 0.27 ± 0.03 | 0.24 ± 0.01 | 0.31 ± 0.11 | 3.57 ± 0.18 |
| M46 | AGATAAAACATAGACCTGAA | chr13:83503068 | 0.20 ± 0.00 | 0.16 ± 0.02 | 0.62 ± 0.09 | 1.88 ± 0.49 |
| M47 | ACAAGCCTCATTTCCCTGCA | chr13:83503101 | 0.52 ± 0.02 | 0.47 ± 0.07 | 0.60 ± 0.06 | 0.61 ± 0.04 |
| M49 | TCTTGTTCCAAGATTATTCT | chr13:83503861 | 0.85 ± 0.17 | 0.64 ± 0.10 | 1.88 ± 0.25 | 1.73 ± 0.11 |
| M50 | CAGTGTAGAGGCTTGGGGTG | chr13:83504008 | 0.87 ± 0.19 | 0.84 ± 0.08 | 1.40 ± 0.10 | 1.14 ± 0.23 |
| M51 | TCTTTTGCCAGCACTGACAA | chr13:83504048 | 0.59 ± 0.05 | 0.48 ± 0.05 | 0.16 ± 0.02 | 0.19 ± 0.01 |
| M52 | CGGTGTTTCATAGAAAAGGAG | chr13:83504202 | 0.74 ± 0.04 | 0.64 ± 0.11 | 0.85 ± 0.06 | 0.58 ± 0.02 |
| M53 | TGCACCTGTTTCATGTCACTC | chr13:83504108 | 0.50 ± 0.08 | 5.04 ± 0.36 | 0.23 ± 0.04 | 0.22 ± 0.03 |
| M54 | AATAGCACATGGAATTTTTG | chr13:83504798 | 0.86 ± 0.14 | 0.77 ± 0.14 | 0.77 ± 0.02 | 0.54 ± 0.01 |
| M55 | TGCCAGCACTGACAAAGGTC | chr13:83504053 | 0.54 ± 0.04 | 0.57 ± 0.10 | 0.21 ± 0.01 | 0.18 ± 0.03 |
| M56 | TACTCCAGAGTGACATGAAC | chr13:83504104 | 1.18 ± 0.03 | 1.03 ± 0.02 | 1.29 ± 0.05 | 1.25 ± 0.09 |
| M57 | GTTCCCGTCAGCACCTGCTG | chr13:83504326 | 0.55 ± 0.01 | 0.57 ± 0.10 | 0.30 ± 0.01 | 0.29 ± 0.01 |
| M58 | AAGGAAGCAGCTCAAAGCTA | chr13:83505263 | 1.05 ± 0.14 | 1.00 ± 0.14 | 1.17 ± 0.12 | 1.07 ± 0.05 |
| M60 | GGCGAGCGCAGCCCAAAGT | chr13:83504226 | 0.74 ± 0.16 | 0.83 ± 0.11 | 0.13 ± 0.00 | 0.21 ± 0.02 |
| M61 | TGCTGACGGGAACAACCTCC | chr13:83504336 | 0.40 ± 0.05 | 0.52 ± 0.06 | 0.23 ± 0.02 | 0.22 ± 0.02 |
| M62 | ATGGAATTTACTTATTAATA | chr13:83505310 | 0.79 ± 0.10 | 0.43 ± 0.04 | 1.12 ± 0.07 | 1.07 ± 0.09 |
| M64 | TGAAGAGAAACCCCCAGTT | chr13:83504238 | 0.68 ± 0.05 | 0.63 ± 0.08 | 0.24 ± 0.02 | 0.19 ± 0.03 |
| M65 | ATCATCAGCCTTGTGAACAG | chr13:83504463 | 0.61 ± 0.07 | 0.56 ± 0.05 | 0.56 ± 0.04 | 0.52 ± 0.03 |
| M66 | TTCCATATTCACAAGCAACA | chr13:83505327 | 0.66 ± 0.01 | 0.63 ± 0.15 | 0.23 ± 0.02 | 0.22 ± 0.02 |

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|-----|-----------------------|----------------|-------------|-------------|-------------|-------------|
| M67 | GCACAAGTGTCTGGCAGGCC | chr13:83504132 | 0.58 ± 0.02 | 0.53 ± 0.10 | 0.19 ± 0.01 | 0.17 ± 0.01 |
| M68 | TAGAATAAAGCCAGACCAGC | chr13:83504264 | 0.42 ± 0.03 | 0.56 ± 0.05 | 0.23 ± 0.01 | 0.27 ± 0.01 |
| M69 | AAGGCTGATGATGAGTGAGC | chr13:83504474 | 0.45 ± 0.05 | 0.52 ± 0.05 | 0.23 ± 0.01 | 0.27 ± 0.01 |
| M70 | AATGAATGTAAAAGACACAA | chr13:83505353 | 0.55 ± 0.02 | 0.46 ± 0.07 | 0.77 ± 0.03 | 0.79 ± 0.03 |
| M71 | CTGCCAGACACTTGTGCAGA | chr13:83504138 | 0.48 ± 0.02 | 0.39 ± 0.06 | 0.68 ± 0.11 | 0.75 ± 0.03 |
| M72 | GAGGCGAGCGCAGCCCAAAC | chr13:83504224 | 0.28 ± 0.01 | 0.49 ± 0.04 | 0.20 ± 0.01 | 0.19 ± 0.02 |
| M73 | GCACCTAGCAACCCCACTGT | chr13:83504514 | 0.71 ± 0.07 | 0.51 ± 0.11 | 0.31 ± 0.00 | 0.34 ± 0.03 |
| M74 | TCAATTTTCTGGGCTGTGGG | chr13:83505418 | 0.88 ± 0.02 | 0.23 ± 0.01 | 0.88 ± 0.02 | 0.78 ± 0.07 |
| M76 | CGAGCGCAGCCCAAACCTGGG | chr13:83504228 | 0.94 ± 0.15 | 0.60 ± 0.13 | 0.23 ± 0.02 | 0.22 ± 0.01 |
| M77 | TTTCTTAGAGGAGACAGTGC | chr13:83504436 | 0.82 ± 0.04 | 0.78 ± 0.07 | 0.30 ± 0.03 | 0.30 ± 0.04 |
| M78 | TGGGCTGTGGGGGGTAGGAT | chr13:83505427 | 0.62 ± 0.05 | 0.93 ± 0.08 | 0.63 ± 0.07 | 0.59 ± 0.08 |
| M80 | TTTGTTGTCCAAACTCTGAC | chr13:83504301 | 0.59 ± 0.08 | 0.84 ± 0.14 | 0.21 ± 0.04 | 0.20 ± 0.03 |
| M81 | GATGATGAGTGAGCTGGAAA | chr13:83504480 | 0.60 ± 0.02 | 0.78 ± 0.07 | 0.28 ± 0.01 | 0.26 ± 0.01 |
| M82 | TACTGTTTATTATAAAGGA | chr13:83505820 | 0.60 ± 0.07 | 0.58 ± 0.07 | 0.60 ± 0.07 | 0.52 ± 0.03 |
| M84 | TGGACAACAAAGCCCTCAGC | chr13:83504313 | 0.77 ± 0.03 | 0.67 ± 0.07 | 0.22 ± 0.00 | 0.22 ± 0.03 |
| M85 | GGAGCCAACCTCCCAACAG | chr13:83504501 | 0.96 ± 0.12 | 0.55 ± 0.07 | 0.29 ± 0.01 | 0.29 ± 0.03 |
| M86 | CTTTACTTAAGGCTTCGCAT | chr13:83505874 | 1.50 ± 0.03 | 0.56 ± 0.05 | 1.50 ± 0.03 | 1.32 ± 0.18 |
| M88 | AAGCCCTCAGCAGGTGCTGA | chr13:83504322 | 0.79 ± 0.03 | 0.52 ± 0.03 | 0.23 ± 0.01 | 0.21 ± 0.01 |
| M89 | ACAACGCCAACAACATTTGA | chr13:83504542 | 0.74 ± 0.01 | 0.72 ± 0.06 | 0.72 ± 0.10 | 0.53 ± 0.05 |
| M90 | ACTTATTGCTGATTCTGAGA | chr13:83505930 | 0.81 ± 0.04 | 0.72 ± 0.06 | 0.81 ± 0.04 | 0.78 ± 0.07 |
| M91 | TGGAGTAAATTTAGCTGTAA | chr13:83504088 | 0.46 ± 0.07 | 0.99 ± 0.20 | 0.46 ± 0.07 | 0.53 ± 0.05 |

| | | | | | | | |
|------|-----------------------|----------------|-----|-------------|-------------|-------------|---------------|
| M92 | CTCACCGCTTGACGATCAAG | chr13:83504170 | ME | 0.46 ± 0.06 | 0.42 ± 0.04 | 1.02 ± 0.03 | 1.09 ± 0.06 |
| M93 | GATCCCTCTGCACAAGTGTC | chr13:83504141 | ME | 0.58 ± 0.02 | 0.53 ± 0.06 | 1.12 ± 0.03 | 1.12 ± 0.17 |
| M94 | CTCCCCTGACCGATAGATAG | chr13:83523356 | HFE | 1.41 ± 0.07 | 1.27 ± 0.08 | 2.48 ± 0.16 | 91.44 ± 12.36 |
| M95 | AGTAAGGTGTGGAGGGAAGG | chr13:83523436 | HFE | 0.66 ± 0.08 | 0.56 ± 0.06 | 1.40 ± 0.05 | 1.51 ± 0.07 |
| M96 | TCACCGCTTGACGATCAAGG | chr13:83504171 | ME | 0.62 ± 0.02 | 0.52 ± 0.04 | 1.01 ± 0.03 | 1.12 ± 0.06 |
| M97 | TAAGTTTCCTCATTTACAC | chr13:83503900 | ME | 0.74 ± 0.02 | 0.64 ± 0.05 | 0.80 ± 0.07 | 0.78 ± 0.06 |
| M98 | TGGTTTACTTGCTAATGACC | chr13:83523404 | HFE | 0.38 ± 0.01 | 0.34 ± 0.01 | 1.20 ± 0.00 | 1.25 ± 0.08 |
| M99 | TACACTGTGGAGCAGTTTA | chr13:83572135 | ESE | 0.46 ± 0.06 | 0.43 ± 0.03 | 1.30 ± 0.09 | 1.35 ± 0.08 |
| M100 | ATTTTGGATAGACTTCCGAT | chr13:83503965 | ME | 0.48 ± 0.02 | 0.41 ± 0.05 | 1.08 ± 0.02 | 1.16 ± 0.11 |
| M101 | CATTGGAACAAACAGTGTAG | chr13:83503996 | ME | 0.92 ± 0.05 | 0.85 ± 0.10 | 0.83 ± 0.02 | 0.86 ± 0.04 |
| M102 | TCAGGGGAGCCTAATGCATT | chr13:83523370 | HFE | 1.60 ± 0.09 | 1.43 ± 0.31 | 2.99 ± 0.06 | 3.32 ± 0.20 |
| M103 | CAGCAACCGCGAACAATAAA | chr13:83572175 | ESE | 0.50 ± 0.04 | 0.46 ± 0.04 | 1.11 ± 0.03 | 1.12 ± 0.02 |
| M104 | TTGCCCCCTTGATCGTCAAG | chr13:83504174 | ME | 0.49 ± 0.01 | 0.43 ± 0.05 | 1.23 ± 0.18 | 38.58 ± 9.25 |
| M105 | TGTGGCTGGAACTTTTTAA | chr13:83503818 | ME | 0.51 ± 0.03 | 0.47 ± 0.05 | 1.05 ± 0.03 | 1.03 ± 0.09 |
| M106 | GAAATCTCGACTTTATCCCC | chr13:83523522 | HFE | 0.35 ± 0.04 | 0.34 ± 0.07 | 1.21 ± 0.08 | 1.29 ± 0.08 |
| M107 | GAAACACGCACAGACTGGCC | chr13:83572212 | ESE | 0.51 ± 0.01 | 0.42 ± 0.01 | 0.91 ± 0.01 | 0.94 ± 0.05 |
| M108 | CGATCAAGGGGGCAAAGCTT | chr13:83504182 | ME | 0.66 ± 0.06 | 0.63 ± 0.03 | 1.03 ± 0.02 | 1.05 ± 0.07 |
| M109 | ACCCGCTATCTATCGGTCAG | chr13:83523354 | HFE | 0.87 ± 0.09 | 0.77 ± 0.02 | 1.85 ± 0.02 | 2.14 ± 0.10 |
| M110 | ATCTGGACAAATTTACTGAG | chr13:83523481 | HFE | 0.61 ± 0.09 | 0.50 ± 0.08 | 1.20 ± 0.02 | 1.23 ± 0.08 |
| M111 | AGATTCTTCTGTTACTAGGA | chr13:83572249 | ESE | 0.54 ± 0.05 | 0.49 ± 0.02 | 1.33 ± 0.05 | 1.27 ± 0.04 |
| M112 | AACCAGACCTTTGTCAAGTGC | chr13:83504055 | ME | 0.60 ± 0.08 | 0.50 ± 0.01 | 0.93 ± 0.02 | 1.15 ± 0.11 |

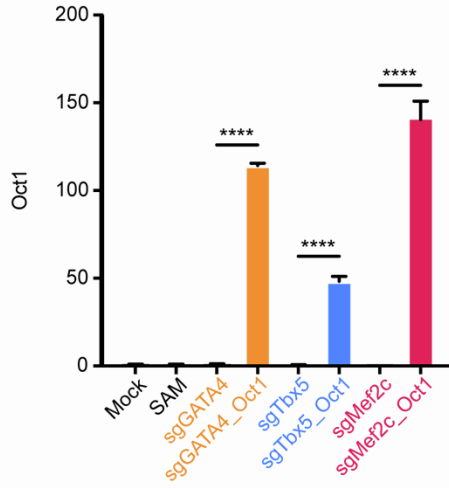
| | | | | | | | | | | | | | | | |
|------|-----------------------|----------------|-----|------|---|------|------|---|------|------|---|------|------|---|------|
| M113 | CACCCGCTATCTATCGGTCA | chr13:83523353 | HFE | 1.36 | ± | 0.15 | 1.18 | ± | 0.17 | 2.65 | ± | 0.15 | 2.75 | ± | 0.04 |
| M114 | GGATAAAGTCCAGTAAGGTG | chr13:83523425 | HFE | 0.64 | ± | 0.07 | 0.62 | ± | 0.05 | 1.20 | ± | 0.02 | 1.30 | ± | 0.12 |
| M115 | ACTGCTCCACAAGTGTA AAA | chr13:83572129 | ESE | 0.52 | ± | 0.04 | 0.46 | ± | 0.02 | 0.98 | ± | 0.03 | 1.02 | ± | 0.04 |
| M116 | AGCTTCGGTGTTTCATAGAAA | chr13:83504197 | ME | 0.48 | ± | 0.05 | 0.46 | ± | 0.03 | 0.94 | ± | 0.11 | 0.78 | ± | 0.10 |
| M117 | ATTCGAAAGTTAATGGCCCG | chr13:83523506 | HFE | 0.78 | ± | 0.08 | 0.71 | ± | 0.13 | 0.86 | ± | 0.05 | 0.73 | ± | 0.09 |
| M118 | GACCTGGATAAAGTCCAGTA | chr13:83523420 | HFE | 0.49 | ± | 0.01 | 0.46 | ± | 0.06 | 0.72 | ± | 0.04 | 0.60 | ± | 0.04 |
| M120 | TGACATGAACAGGTGCACCC | chr13:83504114 | ME | 1.34 | ± | 0.03 | 1.25 | ± | 0.06 | 0.85 | ± | 0.07 | 7.47 | ± | 1.06 |
| M121 | TGAAGTCACCCGCTATCTAT | chr13:83523347 | HFE | 0.68 | ± | 0.09 | 0.63 | ± | 0.03 | 1.68 | ± | 0.04 | 1.31 | ± | 0.16 |
| M122 | GTTTCAGCTGCACAGGAAGC | chr13:83523311 | HFE | 0.23 | ± | 0.01 | 0.22 | ± | 0.01 | 1.08 | ± | 0.06 | 0.90 | ± | 0.08 |
| M123 | ACGCACAGACTGGCCAGGGA | chr13:83572207 | ESE | 0.56 | ± | 0.00 | 0.54 | ± | 0.02 | 0.79 | ± | 0.03 | 0.71 | ± | 0.04 |
| M124 | GAGAAGGAAGTGGAGAGTTT | chr13:83572103 | ESE | 1.24 | ± | 0.02 | 1.15 | ± | 0.09 | 1.00 | ± | 0.07 | 1.08 | ± | 0.13 |

ME, Muscle enhancer; HFE, Heart field enhancer; ESE, Endothelial cell-specific enhancer

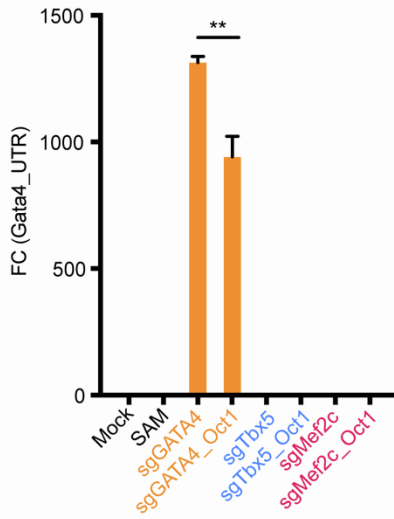
Table S3. Sequence, location and activation efficiency of Tbx5 sgRNA in MEF and FCF

| | sgRNA sequence | Location | Tbx5 endo in MEF | | Tbx5 total in MEF | | Tbx5 endo in FCF | | Tbx5 total in FCF | |
|-----|----------------------|----------------|------------------|--------|-------------------|--------|------------------|---------|-------------------|--------|
| T1 | CTGAGCCAGTGGTTGCAGGG | chr5:119834446 | 2.58 | ± 1.10 | 2.45 | ± 1.12 | 0.35 | ± 0.03 | 0.71 | ± 0.04 |
| T2 | AAGTCCTAGAGAGCTTGGAG | chr5:119834094 | 3.05 | ± 0.77 | 2.31 | ± 0.29 | 3.67 | ± 2.95 | 1.06 | ± 0.09 |
| T5 | GGACAATGAGTCTGAAGTGG | chr5:119834128 | 5.56 | ± 1.75 | 4.07 | ± 0.86 | 37.07 | ± 1.65 | 11.22 | ± 1.41 |
| T6 | GAAATCGGGTGAGGCTGCAG | chr5:119834236 | 1.93 | ± 0.42 | 0.71 | ± 0.03 | 7.04 | ± 2.15 | 1.33 | ± 0.09 |
| T7 | AGGAAGGAAGGAAAGAAGGA | chr5:119834374 | 2.39 | ± 0.89 | 1.21 | ± 0.32 | 38.13 | ± 7.87 | 10.26 | ± 1.16 |
| T9 | TATAGTGGTTCAAGAGTTTG | chr5:119834546 | 0.49 | ± 0.40 | 1.04 | ± 0.03 | 0.92 | ± 0.13 | 0.95 | ± 0.03 |
| T10 | GCCCTGCAGAGAACCAAGAC | chr5:119834289 | 1.01 | ± 0.22 | 1.59 | ± 0.16 | 6.04 | ± 0.56 | 2.29 | ± 0.32 |
| T11 | TAGGCGTGTGCACACACCCA | chr5:119834260 | 0.78 | ± 0.09 | 0.61 | ± 0.09 | 3.23 | ± 0.62 | 1.02 | ± 0.07 |
| T12 | GCTAGTCCTGGCTCTGCAAG | chr5:119834166 | 5.10 | ± 0.54 | 3.45 | ± 0.48 | 8.53 | ± 0.99 | 2.28 | ± 0.28 |
| T13 | AGTGGGGGTGGGAATCAGC | chr5:119834520 | 1.60 | ± 0.67 | 0.85 | ± 0.05 | 0.28 | ± 0.09 | 0.50 | ± 0.08 |
| T14 | AAGAGGATGGGAAGTGGAAA | chr5:119834497 | 1.11 | ± 0.36 | 0.86 | ± 0.02 | 8.17 | ± 8.83 | 0.70 | ± 0.04 |
| T15 | AAAGTGGGAAAGGTGGTGGG | chr5:119834582 | 1.55 | ± 0.37 | 3.01 | ± 0.08 | 16.20 | ± 15.07 | 0.66 | ± 0.06 |
| T16 | AGTCAACAGAGATGGAAGGA | chr5:119834472 | 34.74 | ± 4.50 | 15.05 | ± 2.30 | 29.63 | ± 33.36 | 1.00 | ± 0.22 |
| T17 | GGGAAGTGGAAAGGGAGTGG | chr5:119834505 | 1.55 | ± 0.21 | 1.23 | ± 0.01 | 0.32 | ± 0.04 | 0.64 | ± 0.16 |
| T18 | ATCTAGTGAGAAAGTGGGAA | chr5:119834572 | 0.72 | ± 0.05 | 2.17 | ± 0.37 | 2.30 | ± 0.44 | 0.99 | ± 0.20 |

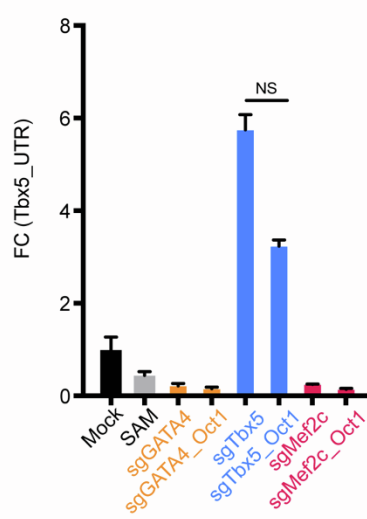
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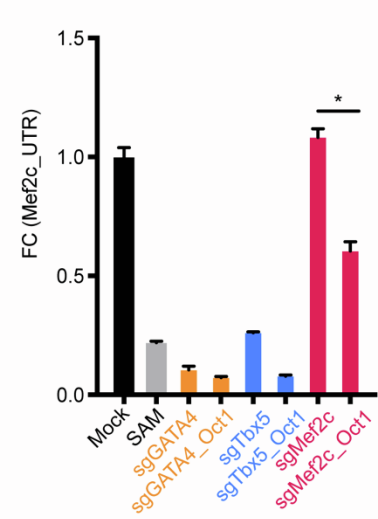
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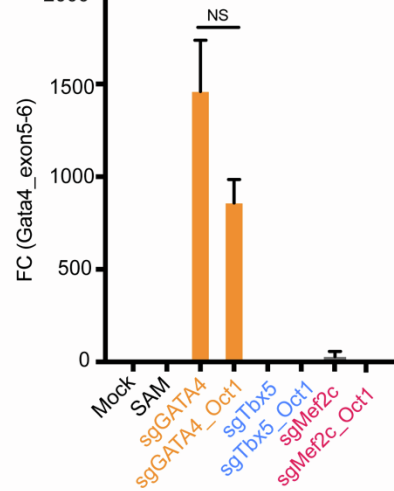
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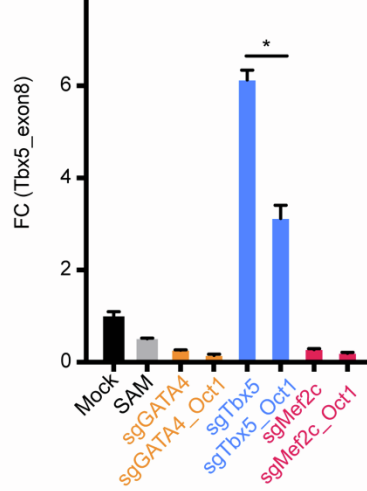
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C



E



G

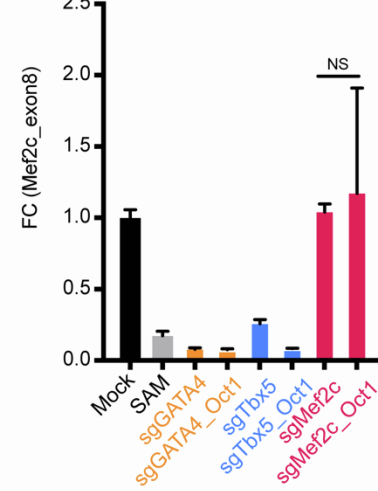


Figure S1. Gata4, Tbx5 and Mef2c activation level by adding Oct1 in MEF. (A) Transcriptional activation of Oct1 in MEFs with SAM system among mock, M/G/T sgRNA alone or Oct1 combination groups. (B) and (C) Transcriptional activation of endogenous Gata4 (B) and total Gata4 (C) with SAM activators. (D) and (E) Transcriptional activation of endogenous Tbx5 (D) and total Tbx5 (E) with SAM activators. (F) and (G) Transcriptional activation of endogenous Mef2c (F) and total Mef2c (G) with SAM activators.

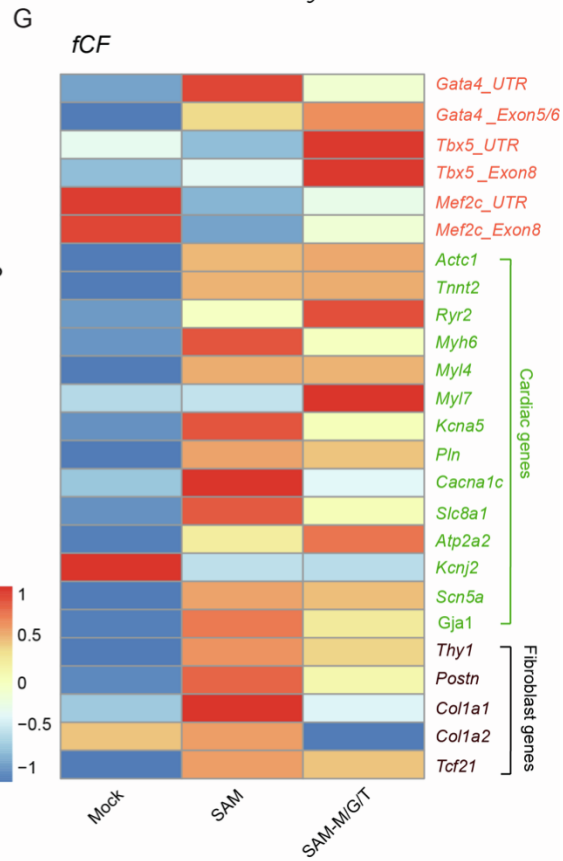
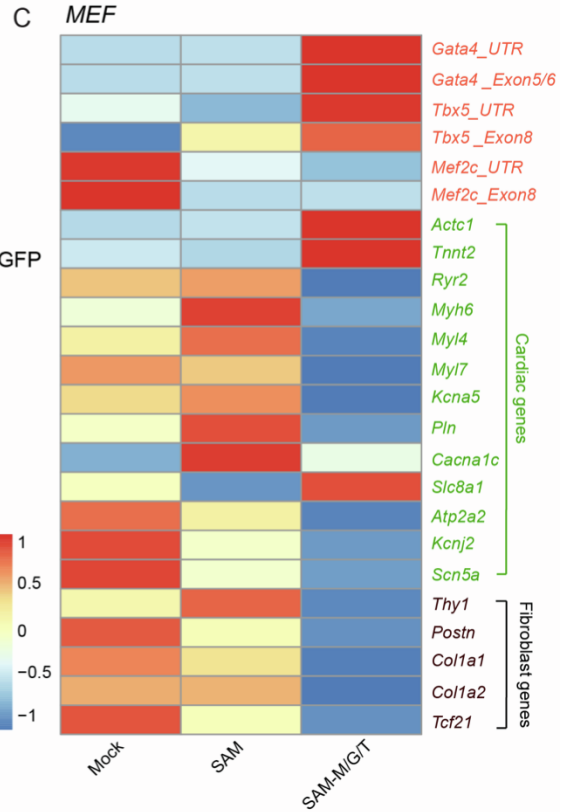
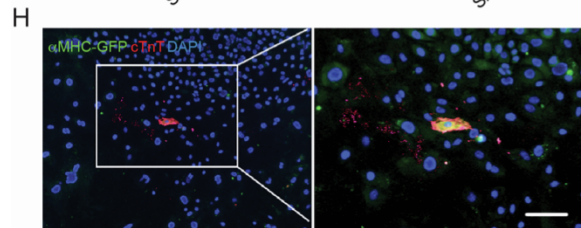
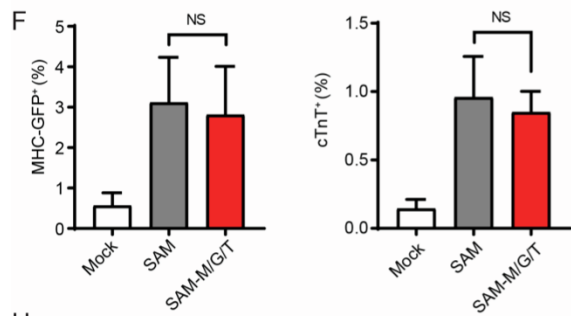
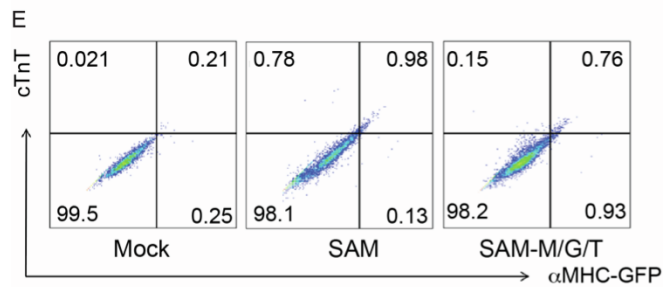
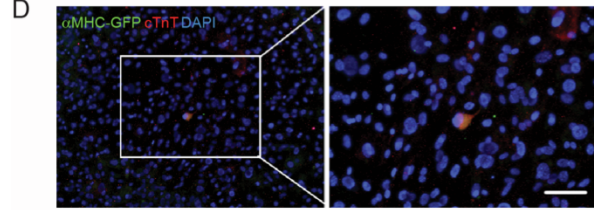
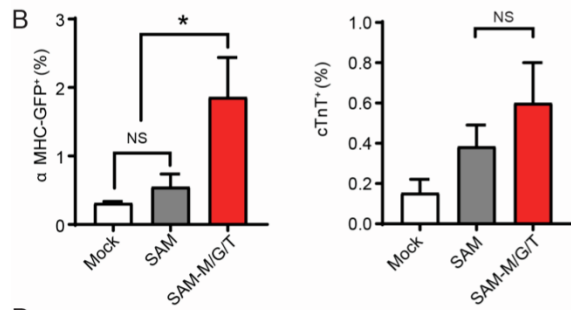
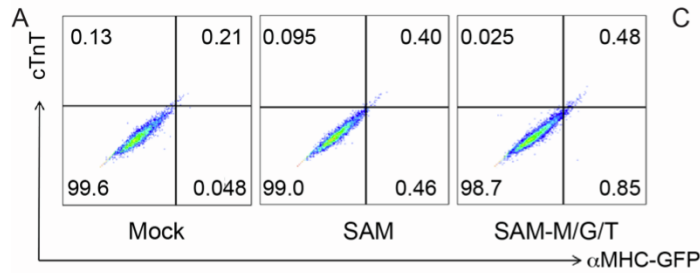


Figure S2. CRISPRa-mediated activation of endogenous *Mef2c*, *Gata4*, and *Tbx5* promotes cardiac gene expression and suppresses the fibroblast gene program in embryonic fibroblasts and fresh cardiac fibroblasts. (A) Flow cytometry analysis of GFP and cTnT in MEFs after reprogramming and the statistics graph of *A* (B). (C) Heat map of transcriptional activators, cardiac progenitor markers and fibrosis markers on day 10 post infection by M/G/T-sgRNA in MEFs. (D) Immunofluorescence labeling of GFP and cTnT on day 14 of reprogramming in MEFs. (E) Flow cytometry analysis of GFP and cTnT in fCFs after reprogramming and the statistics graph of *E* (F). (G) Heat map of transcriptional activators, cardiac progenitor markers and fibrosis markers on day 10 post infection by M/G/T-sgRNA in fCFs. (H) Immunofluorescence labeling of GFP and cTnT on day 14 of reprogramming in fCFs. Scale bars, 100 μm (D and H). * $p < 0.05$.

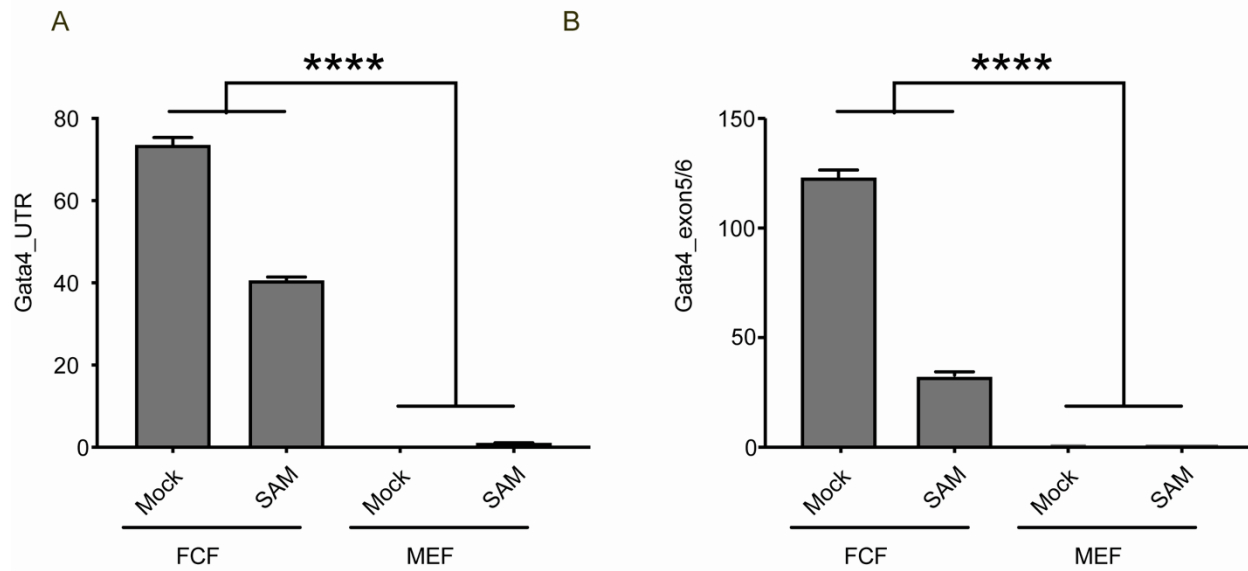


Figure S3. Basic expression level of endogenous and total Gata4 in fCFs and MEFs. (A) Expression level of endogenous Gata4 (Gata4_UTR) in fCFs vs. MEFs. (B) Expression level of total Gata4 (Gata4_exon5/6) in fCFs vs. MEFs. **** $p < 0.0001$.