

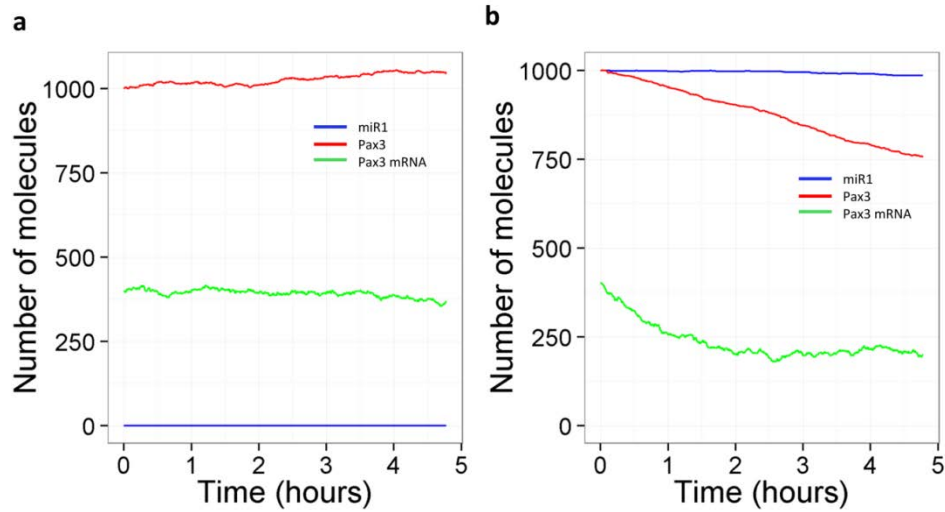
# **Supplementary Information**

## **Using computer simulation models to investigate the most promising microRNAs to improve muscle regeneration during ageing**

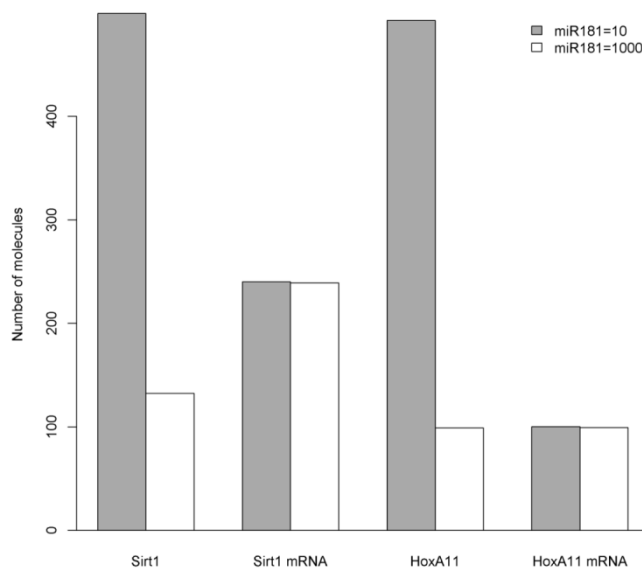
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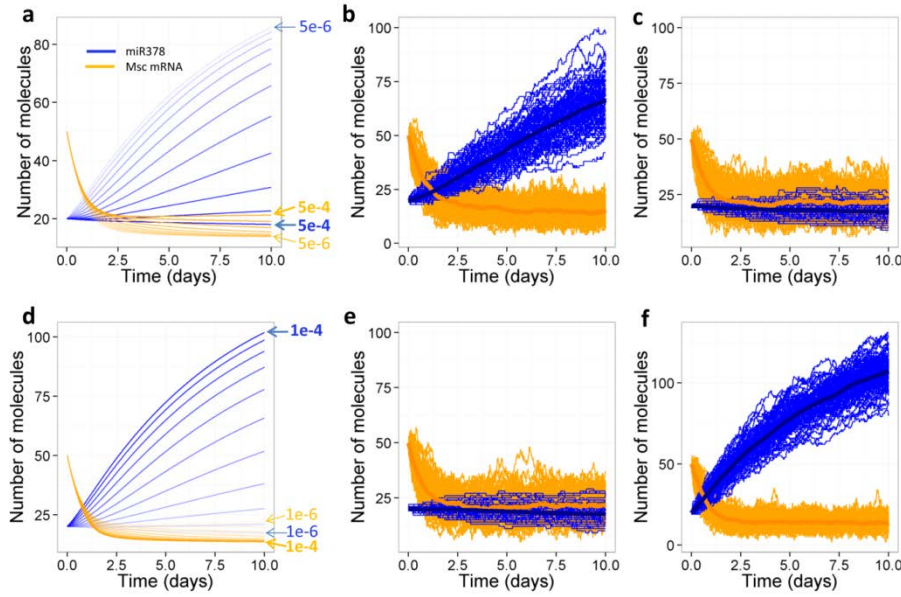
**Figure S1. Validating the miR-1 model against data for Rugli cells.** The Rugli cell line does not express miR-1 but expresses high levels of Pax3<sup>1</sup>. Parameters were set for high Pax3 (Pax3=1000, Pax3mRNA=400,  $k_{\text{synPax3}}=6\text{e-}5 \text{ mol s}^{-1}$ ,  $k_{\text{synPax3mRNA}}=0.08 \text{ s}^{-1}$ ). (a) No miR-1 (miR1=0,  $k_{\text{synmiR1}}=0 \text{ s}^{-1}$ ,  $k_{\text{synmiR1MyoD}}=0 \text{ s}^{-1}$ ); (b) Addition of miR1 (miR1=1000,  $k_{\text{synmiR1}}=1\text{e-}4 \text{ s}^{-1}$ ,  $k_{\text{synmiR1MyoD}}=5\text{e-}4 \text{ s}^{-1}$ ). Two individual stochastic simulations are shown.



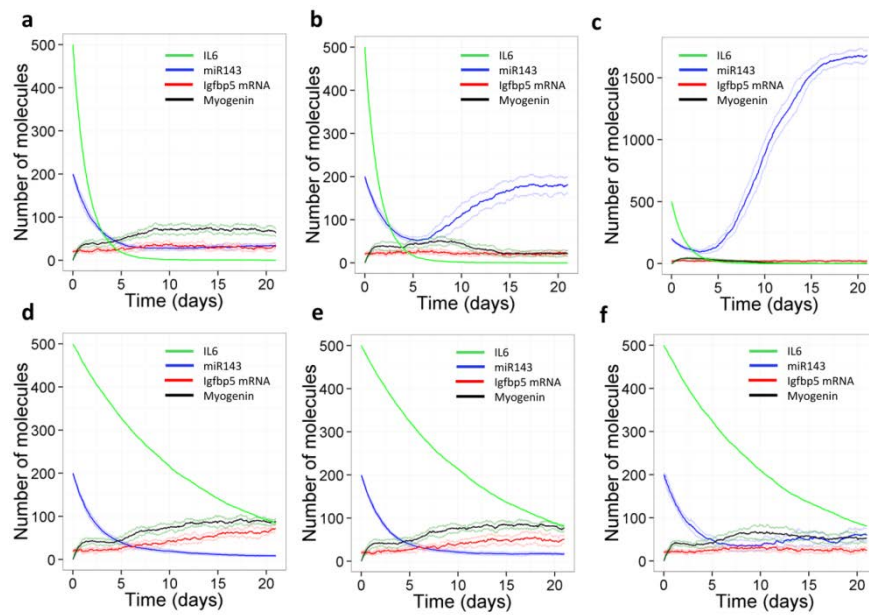
**Figure S2. Validating the miR-181 model against experimental data.** Experimental data shows that miR-181 affects HoxA11 and Sirt1 protein levels but not mRNA levels<sup>2,3</sup>. The model was simulated over a ten day time period with low levels of miR-181 (miR181=10,  $k_{\text{synmiR181}}=6\text{e-}6 \text{ s}^{-1}$ ) or high levels of miR-181 (miR181=1000,  $k_{\text{synmiR181}}=6\text{e-}4 \text{ s}^{-1}$ ) and the mean levels of Sirt1 and HoxA11 protein and mRNA from 1000 time-points were calculated. Stochastic simulation was used and the mean of 10 runs are shown.



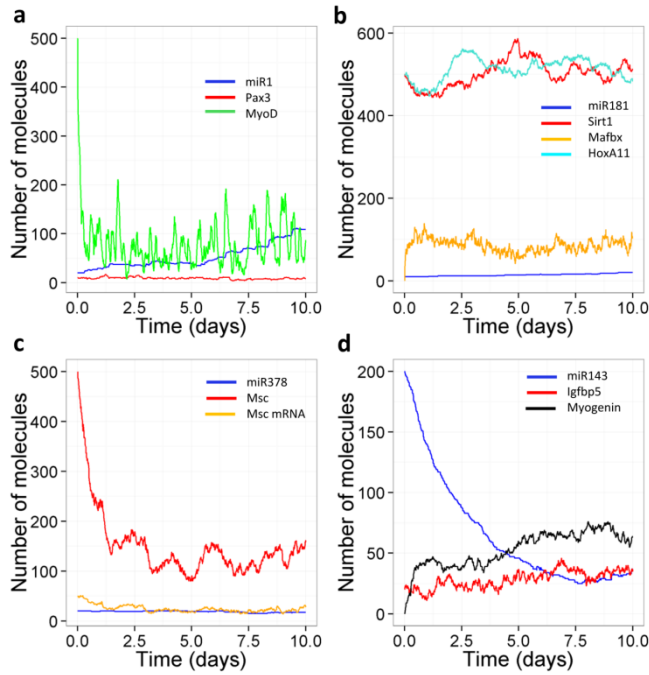
**Figure S3. Simulating the effect of increasing/inhibiting miR-378 in the miR-378 model.** (a) Deterministic model with  $k_{binmiR378geneMsc}$  varying from  $1e-6$  to  $1e-4 \text{ mol}^{-1}\text{s}^{-1}$  using logarithmic scale (default value  $=1e-5 \text{ mol}^{-1}\text{s}^{-1}$ ) indicated by increasing thickness of the lines in the plot. (b-c) stochastic model with  $k_{binmiR378geneMsc}=1e-6$  or  $1e-4 \text{ mol}^{-1}\text{s}^{-1}$  respectively, output from 100 simulation, thick lines show mean values. (d) Deterministic model with  $k_{binmiR378geneMyoD}$  varying from  $1e-6$  to  $1e-4$  using logarithmic scale (default value  $=1e-5 \text{ mol}^{-1}\text{s}^{-1}$ ) indicated by increasing thickness of the lines in the plot. b-c Stochastic model with  $k_{binmiR378geneMyoD}=1e-6$  or  $1e-4 \text{ mol}^{-1}\text{s}^{-1}$  respectively, output from 100 simulations, thick lines show mean values. Range of values of  $k_{binmiR378geneMsc}$  and  $k_{binmiR378geneMyoD}$  are indicated at side of deterministic plots in (a) and (d) respectively. (mol = number of molecules).



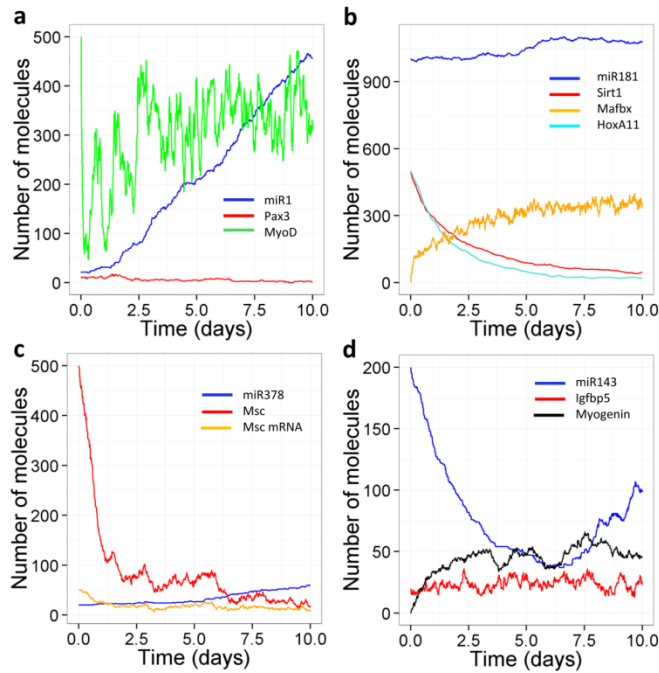
**Figure S4. The effect of varying miR-143 synthesis rate when IL-6 signalling is transient or sustained in the miR-143 model.** (a-c) Transient IL-6 signalling ( $k_{degIL6}=8e-6 \text{ s}^{-1}$ ). (d-f) Sustained IL-6 signalling ( $k_{degIL6}=1e-6 \text{ s}^{-1}$ ). (a,d)  $k_{synmiR143}=5e-5 \text{ s}^{-1}$ . (b,e)  $k_{synmiR143}=5e-4 \text{ s}^{-1}$  (default value). (c,f)  $k_{synmiR143}=5e-3 \text{ s}^{-1}$ . Ten individual stochastic simulations are shown.



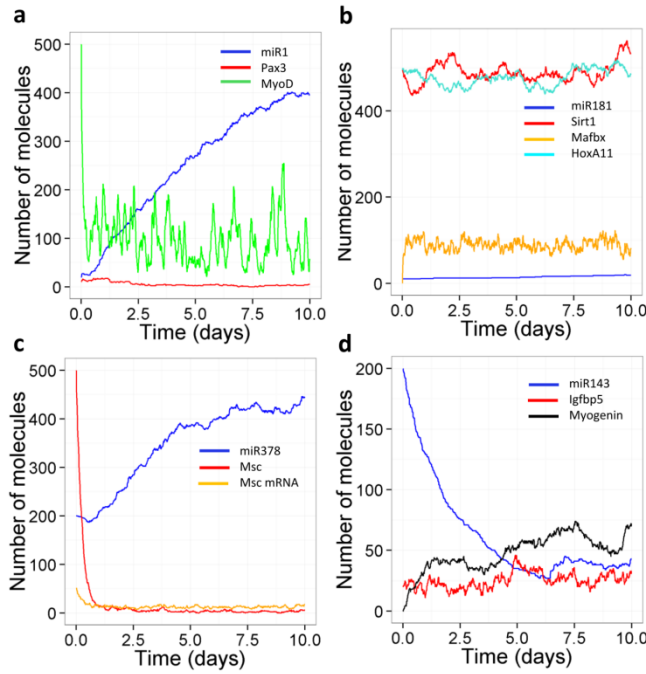
**Figure S5. Simulation output from integrated model with default parameters.** (a-b) MyoD is low, despite low Pax3 due to high levels of HoxA11. (c) miR-378 is low due to low levels of MyoD. (d) miR-143 starts to recover at day 10 and is back to basal by 21 days (not shown).



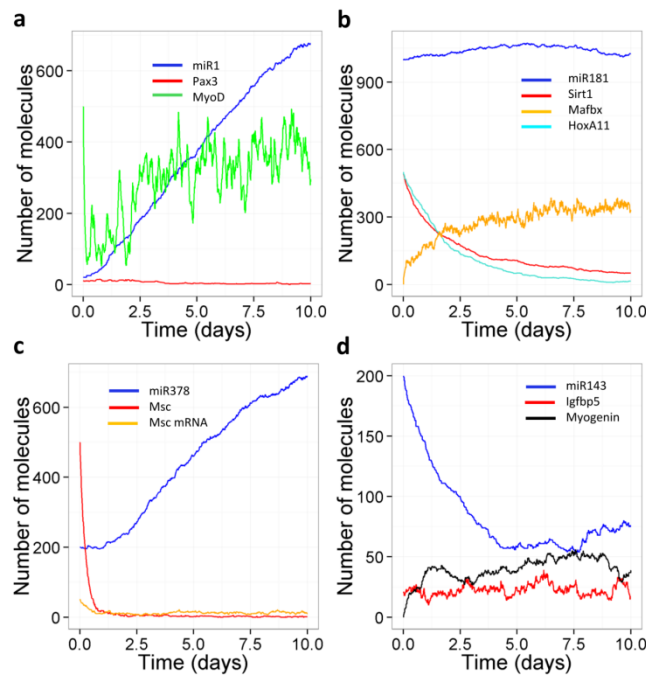
**Figure S6. Simulation output from integrated model with high levels of miR-181.** (a-b) MyoD and Mafbx is high as Sirt1 and HoxA11 protein decline. (c) miR-378 starts to increase due to higher levels of MyoD. (d) miR-143 starts to recover at day 10 and is back to basal by 21 days (not shown). (a-d)  $\text{miR181}=1000$ ,  $k_{\text{synmiR181}}=6\text{e-}4 \text{ s}^{-1}$ .



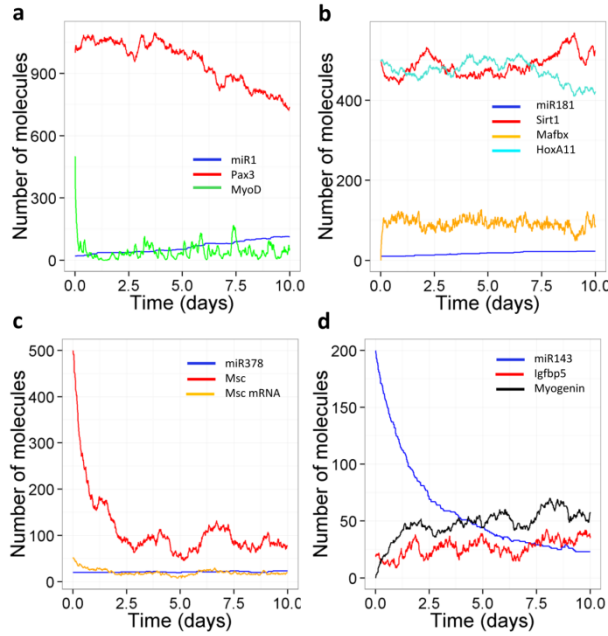
**Figure S7. Simulation output from integrated model with high levels of miR-378.** (a-b) MyoD and Mafbx are low as Sirt1 and HoxA11 protein levels are high when miR-181 is low. (c) Higher levels of miR-378 leads to lower levels of Msc. (d) Output of miR-143 components is not affected. (a-d)  $\text{miR181}=10$ ,  $k_{\text{synmiR181}}=6\text{e-}6 \text{ s}^{-1}$ ,  $\text{miR378}=200$ ,  $k_{\text{synmiR378}}=0.001 \text{ s}^{-1}$ .



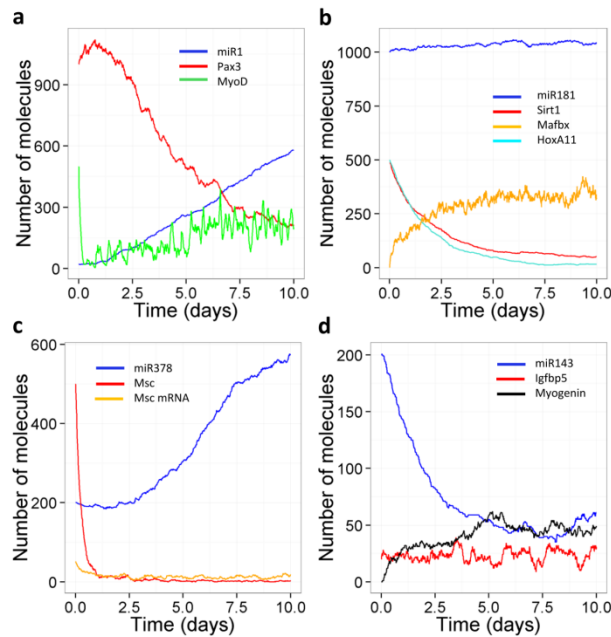
**Figure S8. Simulation output from integrated model with high levels of miR-181 and miR-378.** (a-b) MyoD and Mafbx are high as Sirt1 and HoxA11 protein levels are low when miR-181 is high. (c) Higher levels of MyoD lead to a further increase in miR-378 and lower levels of Msc. (d) Output of miR-143 components is not affected. (a-d)  $\text{miR181}=1000$ ,  $k_{\text{synmiR181}}=6\text{e-}4 \text{ s}^{-1}$ ,  $\text{miR378}=200$ ,  $k_{\text{synmiR378}}=0.001 \text{ s}^{-1}$ .



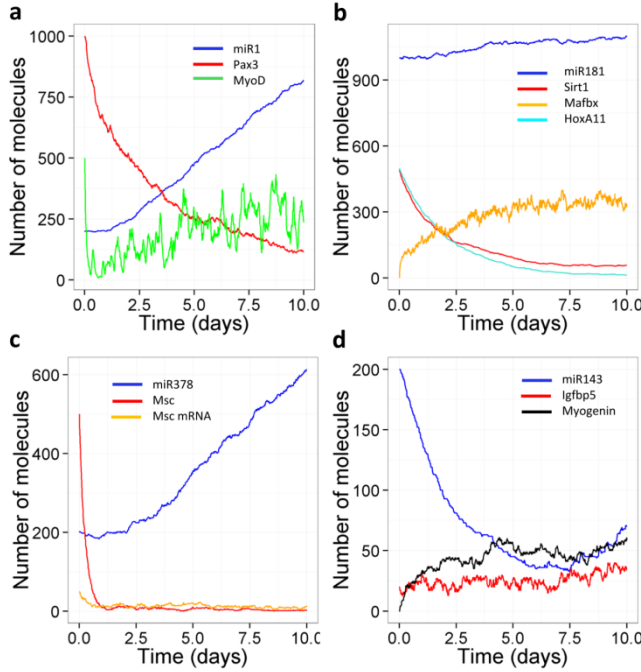
**Figure S9. Simulation output from integrated model with high levels of Pax3 and low miR-181 and miR-378.** (a-b) MyoD and Mafbx are low as Pax3, Sirt1 and HoxA11 protein levels are high. (c) Msc levels are high due to low levels of miR-378. (d) Output of miR-143 components is not affected. (a-d) Pax3= 1000, Pax3mRNA=400,  $k_{synPax3}=6.0e-5 s^{-1}$ ,  $k_{synPax3mRNA}=0.08 molecules s^{-1}$ , miR181=10,  $k_{synmiR181}=6e-6 s^{-1}$ , miR378=20,  $k_{synmiR378}=1e-4 s^{-1}$ .



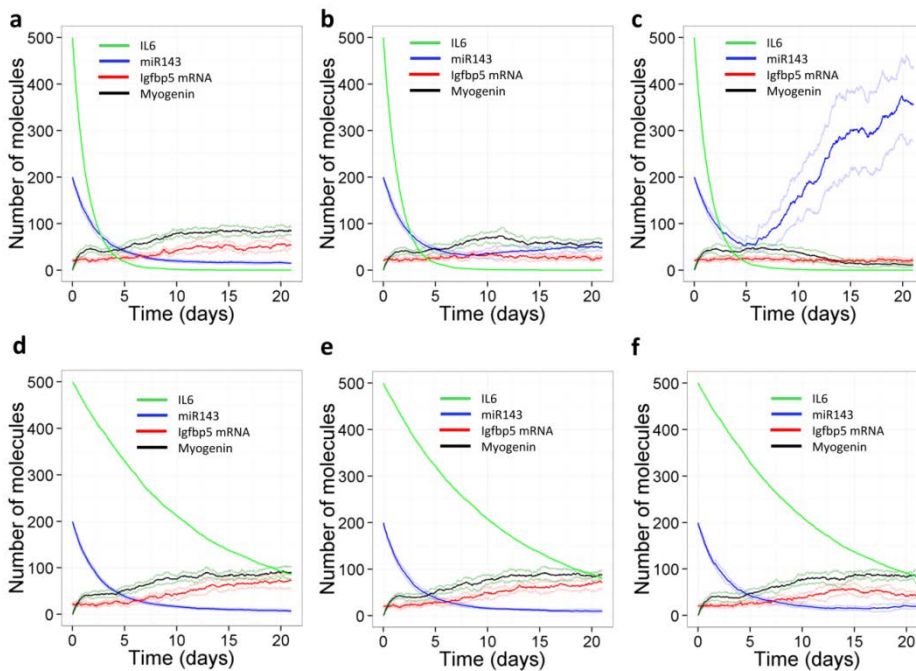
**Figure S10. Simulation output from integrated model with high levels of Pax3 and high levels of miR-181 and miR-378.** (a) miR-1 levels increase leading to inhibition of Pax3 so that MyoD levels start to increase. (b) Mafbx increases as high levels of miR-181 leads to decrease in Sirt1 and HoxA11 protein. (c) Msc levels are low due to high levels of miR-378. (d) Output of miR-143 components is not affected. (a-d) Pax3= 1000, Pax3mRNA=400,  $k_{synPax3}=6.0e-5 s^{-1}$ ,  $k_{synPax3mRNA}=0.08 molecules s^{-1}$ , miR181=1000,  $k_{synmiR181}=6e-4 s^{-1}$ , miR378=200,  $k_{synmiR378}=0.001 s^{-1}$ .



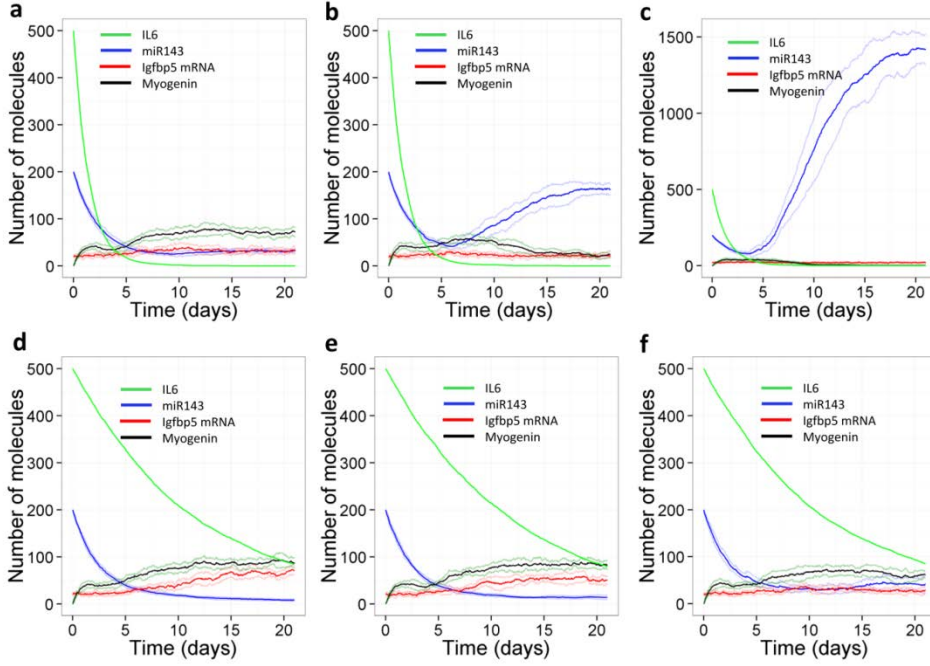
**Figure S11. Simulation output from integrated model with high levels of Pax3 and high levels of miR-1, miR-181 and miR-378.** (a) Higher miR-1 levels at the start leads to faster inhibition of Pax3 and an earlier increase in MyoD. (b) Components of the miR181 network are not affected by increase in miR-1. (c) Components of the miR378 network are not affected by increase in miR-1. (d) Output of miR-143 components is not affected. (a-d) Pax3= 1000, Pax3mRNA=400,  $k_{synPax3}=6.0e-5 s^{-1}$ ,  $k_{synPax3mRNA}=0.08 molecules s^{-1}$ , miR1=1000,  $k_{synmiR1}=1e-4 s^{-1}$ , miR181=1000,  $k_{synmiR181}=6e-4 s^{-1}$ , miR378=200,  $k_{synmiR378}=0.001 s^{-1}$ .



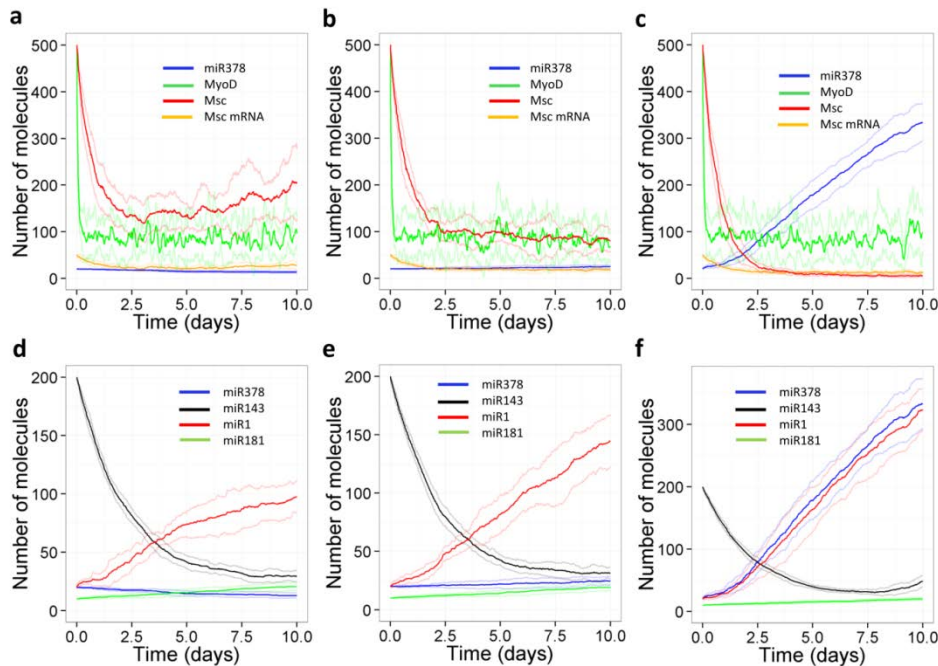
**Figure S12. The effect of varying miR-143 synthesis rate when IL-6 signalling is transient or sustained in the integrated model.** (a-c) Transient IL-6 signalling ( $k_{degIL6}=8e-6 s^{-1}$ ). (d-f) Sustained IL-6 signalling ( $k_{degIL6}=1e-6 s^{-1}$ ). (a,d)  $k_{synmiR143}=5e-5 s^{-1}$ . (b,e)  $k_{synmiR143}=5e-4 s^{-1}$  (default value). (c,f)  $k_{synmiR143}=5e-3 s^{-1}$ . The mean and standard deviation of ten individual stochastic simulations are shown.



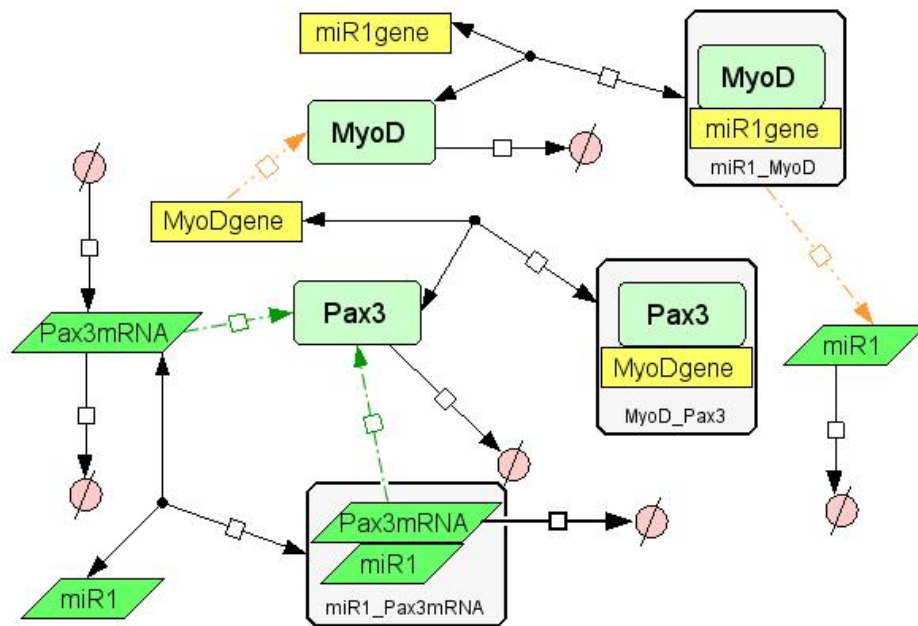
**Figure S13. The effect of varying miR-143 synthesis rate when IL-6 signalling is transient or sustained with high levels of miR-181 and miR378 in the integrated model. (a-c) Transient IL-6 signalling ( $k_{degIL6}=8e-6 s^{-1}$ ). (d-f) Sustained IL-6 signalling ( $k_{degIL6}=1e-6 s^{-1}$ ). (a,d)  $k_{synmiR143}=5e-5 s^{-1}$ . (b,e)  $k_{synmiR143}=5e-4 s^{-1}$  (default value). (c,f)  $k_{synmiR143}=5e-3 s^{-1}$ . The mean and standard deviation of ten individual stochastic simulations are shown. (a-f) miR-181=1000,  $k_{synmiR181}=6e-4 s^{-1}$ , miR378=200,  $k_{synmiR378}=0.001 s^{-1}$ .**



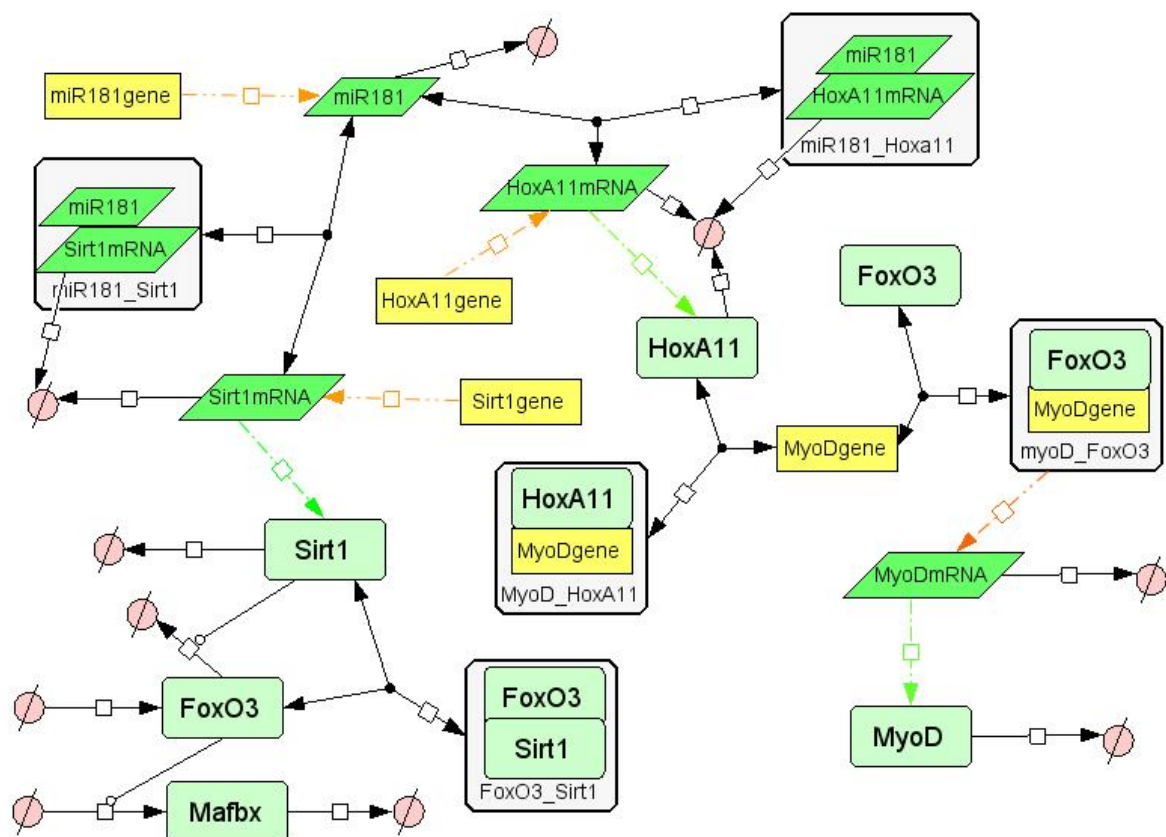
**Figure S14. The effect of varying miR-378 synthesis rate on MyoD, Msc and other miRs. (a,d) Decreased miR-378 synthesis ( $k_{synmiR378}=1e-5 s^{-1}$ ). (b,e) Default value ( $k_{synmiR378}=1e-4 s^{-1}$ ). (c,f) Increased miR-378 synthesis ( $k_{synmiR378}=0.001 s^{-1}$ ). The mean and standard deviation of ten individual stochastic simulations are shown.**



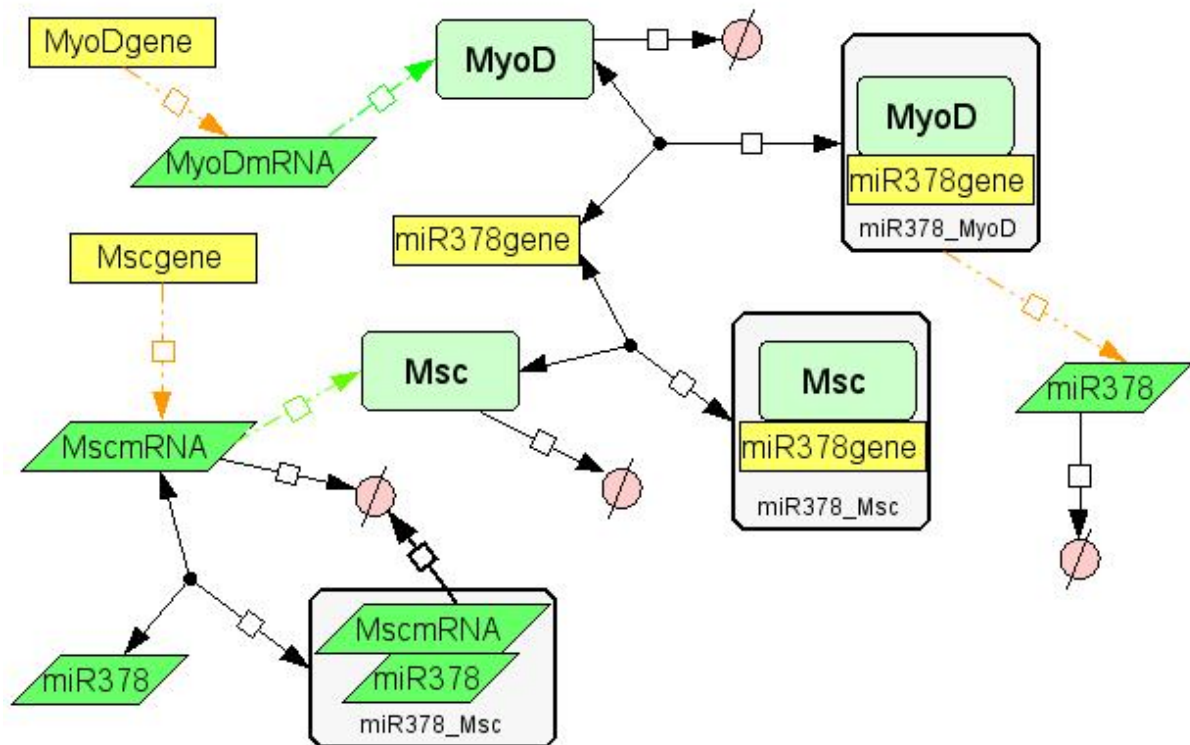
**Figure S15 Network diagram of miR-1 model**



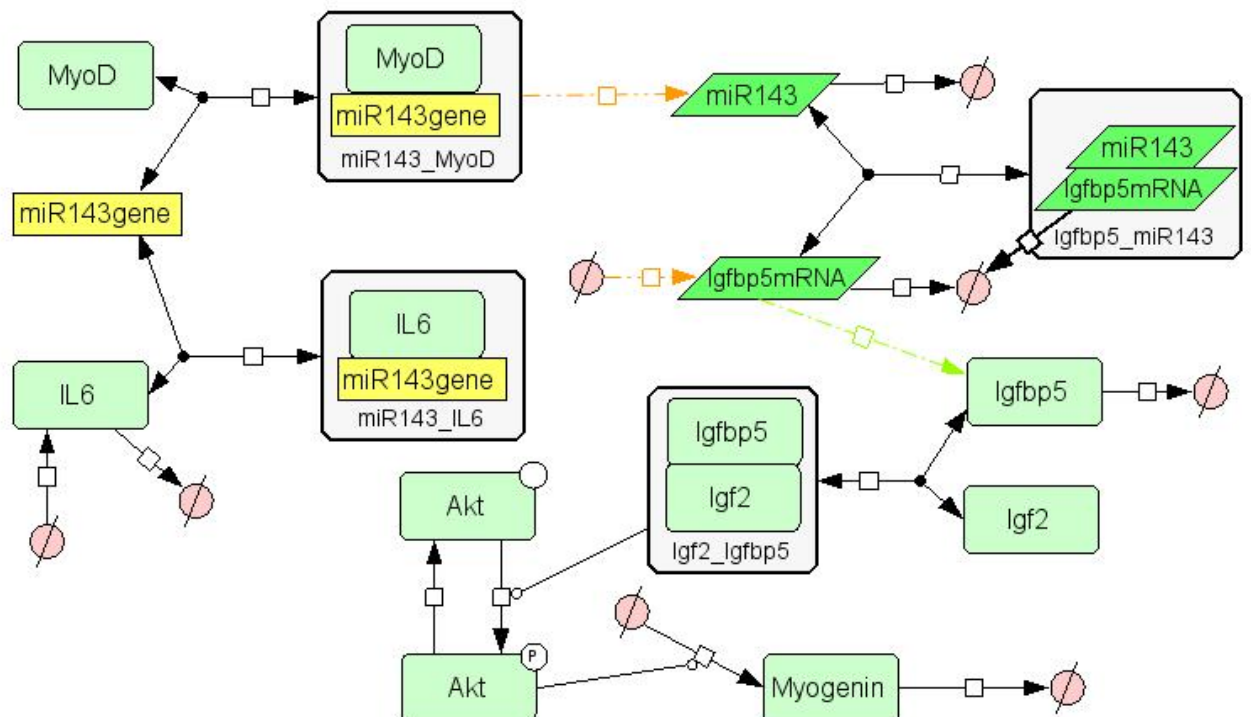
**Figure S16 Network diagram of miR-181 model**



**Figure S17 Network diagram of miR-378 model**



**Figure S18 Network diagram of miR-143 model**



**Table S1 Details of species in miR-1 model**

| Species ID     | Description                                      | Initial Amount |
|----------------|--------------------------------------------------|----------------|
| miR1           | microRNA-1                                       | 20             |
| miR1_gene      | miR-1 gene                                       | 2              |
| miR1_gene_MyoD | miR gene bound by MyoD                           | 0              |
| miR1_Pax3_mRNA | Pax3 mRNA bound by miR-1                         | 0              |
| MyoD           | MyoD protein                                     | 100            |
| MyoD_gene      | MyoD gene (MYOD1)                                | 2              |
| MyoD_gene_Pax3 | MyoD_gene bound by Pax3 to inhibit transcription | 0              |
| Pax3           | Pax3 protein (PAX3)                              | 10             |
| Pax3_mRNA      | Messenger RNA of Pax3                            | 10             |

**Table S2 Details of reactions in miR-1 model**

| Reaction ID                   | Reactants and products                 | Kinetic rate law                                        | Parameter Value <sup>a</sup>                  |
|-------------------------------|----------------------------------------|---------------------------------------------------------|-----------------------------------------------|
| miR1_gene_MyoD_binding        | miR1_gene + MyoD → miR1_gene_MyoD      | $k_{binmiR1geneMyoD} * \text{miR1\_gene} * \text{MyoD}$ | $1\text{e-}5 \text{ mol}^{-1} \text{ s}^{-1}$ |
| miR1_gene_MyoD_release        | miR1_gene_MyoD → miR1_gene + MyoD      | $k_{relmiR1geneMyoD} * \text{miR1\_gene\_MyoD}$         | $0.001 \text{ s}^{-1}$                        |
| miR1_synthesis_by_MyoD        | miR1_gene_MyoD → miR1_gene_MyoD + miR1 | $k_{synmiR1MyoD} * \text{miR1\_gene\_MyoD}$             | $5\text{e-}4 \text{ s}^{-1}$                  |
| miR1_synthesis                | miR1_gene → miR1_gene + miR1           | $k_{synmiR1} * \text{miR1\_gene}$                       | $1\text{e-}8 \text{ s}^{-1}$                  |
| miR1_degradation              | miR1 → Sink                            | $k_{degmiR1} * \text{miR1}$                             | $1.6\text{e-}6 \text{ s}^{-1}$                |
| Pax3_transcription            | Source → Pax3_mRNA                     | $k_{synPax3mRNA} * \text{Source}$                       | $0.002 \text{ mol s}^{-1}$                    |
| Pax3_mRNA_degradation         | Pax3_mRNA → Sink                       | $k_{degPax3mRNA} * \text{Pax3\_mRNA}$                   | $2\text{e-}4 \text{ s}^{-1}$                  |
| miR1_Pax3mRNA_binding         | miR1 + Pax3_mRNA → miR1_Pax3_mRNA      | $k_{binmiR1Pax3} * \text{miR1} * \text{Pax3\_mRNA}$     | $1\text{e-}5 \text{ mol}^{-1} \text{ s}^{-1}$ |
| miR1_Pax3mRNA_release         | miR1_Pax3_mRNA → miR1 + Pax3_mRNA      | $k_{relmiR1Pax3} * \text{miR1\_Pax3\_mRNA}$             | $0.001\text{ s}^{-1}$                         |
| Pax3_mRNA_degradation_by_miR1 | miR1_Pax3_mRNA → miR1                  | $k_{degPax3mRNAmiR1} * \text{miR1\_Pax3\_mRNA}$         | $4\text{e-}4 \text{ s}^{-1}$                  |
| Pax3_translation              | Pax3_mRNA → Pax3_mRNA + Pax3           | $k_{synPax3} * \text{Pax3\_mRNA}$                       | $3\text{e-}5 \text{ s}^{-1}$                  |
| Pax3_translation2             | miR1_Pax3_mRNA → miR1_Pax3_mRNA + Pax3 | $k_{synPax3miR1} * \text{miR1\_Pax3\_mRNA}$             | $5\text{e-}7 \text{ s}^{-1}$                  |
| Pax3_degradation              | Pax3 → Sink                            | $k_{degPax3} * \text{Pax3}$                             | $2\text{e-}5 \text{ s}^{-1}$                  |
| MyoD_gene_Pax3_binding        | Pax3 + MyoD_gene → MyoD_gene_Pax3      | $k_{binMyoDgenePax3} * \text{Pax3} * \text{MyoD\_gene}$ | $1\text{e-}5 \text{ mol}^{-1} \text{ s}^{-1}$ |
| MyoD_gene_Pax3_release        | MyoD_gene_Pax3 → Pax3 + MyoD_gene      | $k_{relMyoDgenePax3} * \text{MyoD\_gene\_Pax3}$         | $5\text{e-}4 \text{ s}^{-1}$                  |
| MyoD_synthesis                | MyoD_gene → MyoD_gene + MyoD           | $k_{synMyoD} * \text{MyoD\_gene}$                       | $0.1 \text{ s}^{-1}$                          |
| MyoD_degradation              | MyoD → Sink                            | $k_{degMyoD} * \text{MyoD}$                             | $2.6\text{e-}4 \text{ s}^{-1}$                |

<sup>a</sup>mol=number of molecules

**Table S3 Details of species in miR-181 model**

| <b>Species ID</b>  | <b>Description</b>                    | <b>Initial Amount</b> |
|--------------------|---------------------------------------|-----------------------|
| FoxO3              | FOXO3 protein                         | 400                   |
| FoxO3_Sirt1        | FOXO3 bound by SIRT1                  | 100                   |
| HoxA11             | HOXA11 protein                        | 500                   |
| HoxA11_mRNA        | HOXA11 mRNA                           | 100                   |
| Mafbx              | Mafbx protein                         | 0                     |
| miR181             | microRNA-181                          | 10                    |
| miR181_HoxA11_mRNA | HOXA11 mRNA bound by miR-181          | 0                     |
| miR181_Sirt1_mRNA  | SIRT1 mRNA bound by miR-181           | 0                     |
| miR181_gene        | miR-181 gene                          | 2                     |
| MyoD               | MyoD protein                          | 0                     |
| MyoD_gene          | MyoD gene                             | 2                     |
| MyoD_gene_FoxO3    | MyoD_gene bound by FoxO3 (activator)  | 0                     |
| MyoD_gene_HoxA11   | MyoD gene bound by HOXA11 (inhibitor) | 0                     |
| Sirt1              | SIRT1 protein                         | 400                   |
| Sirt1_mRNA         | SIRT1 mRNA                            | 100                   |

**Table S4 Details of reactions in miR-181 model**

| Reaction ID                       | Reactants and products                        | Kinetic rate law                                           | Parameter Value <sup>a</sup>   |
|-----------------------------------|-----------------------------------------------|------------------------------------------------------------|--------------------------------|
| miR181_synthesis                  | miR181_gene → miR181_gene + miR181            | $k_{synmiR181} * \text{miR181gene}$                        | $6e-6s^{-1}$                   |
| miR181_degradation                | miR181 → Sink                                 | $k_{degmiR181} * \text{miR181}$                            | $1.6e-6 s^{-1}$                |
| Sirt1_transcription               | Source → Sirt1_mRNA                           | $k_{synSirt1mRNA} * \text{Source}$                         | $0.005 \text{ mol s}^{-1}$     |
| Sirt1_mRNA_degradation            | Sirt1_mRNA → Sink                             | $k_{degSirt1mRNA} * \text{Sirt1_mRNA}$                     | $2e-5s^{-1}$                   |
| Sirt1_translation                 | Sirt1_mRNA → Sirt1_mRNA + Sirt1               | $k_{synSirt1} * \text{Sirt1_mRNA}$                         | $2e-5s^{-1}$                   |
| Sirt1_degradation                 | Sirt1 → Sink                                  | $k_{degSirt1} * \text{Sirt1}$                              | $2.4e-5s^{-1}$                 |
| miR181_Sirt1mRNA_binding          | miR181 + Sirt1_mRNA → miR181_Sirt1_mRNA       | $k_{binmiR181Sirt1} * \text{miR181} * \text{Sirt1_mRNA}$   | $5e-5 \text{ mol}^{-1} s^{-1}$ |
| miR181_Sirt1mRNA_release          | miR181_Sirt1_mRNA → miR181 + Sirt1_mRNA       | $k_{relmiR181Sirt1} * \text{miR181_Sirt1_mRNA}$            | $0.001 s^{-1}$                 |
| Sirt1_mRNA_degradation_by_miR181  | miR181_Sirt1_mRNA → miR181                    | $k_{degSirt1mRNAmiR181} * \text{miR181_Sirt1_mRNA}$        | $2e-5 s^{-1}$                  |
| HoxA11_transcription              | Source → HoxA11_mRNA                          | $k_{synHoxA11mRNA} * \text{Source}$                        | $0.002 \text{ mol s}^{-1}$     |
| HoxA11_mRNA_degradation           | HoxA11_mRNA → Sink                            | $k_{degHoxA11mRNA} * \text{HoxA11_mRNA}$                   | $2e-5 s^{-1}$                  |
| miR181_HoxA11mRNA_binding         | miR181 + HoxA11_mRNA → miR181_HoxA11_mRNA     | $k_{binmiR181HoxA11} * \text{miR181} * \text{HoxA11_mRNA}$ | $5e-5 \text{ mol}^{-1}s^{-1}$  |
| miR181_HoxA11mRNA_release         | miR181_HoxA11_mRNA → miR181 + HoxA11_mRNA     | $k_{relmiR181HoxA11} * \text{miR181_HoxA11_mRNA}$          | $0.001 s^{-1}$                 |
| HoxA11_mRNA_degradation_by_miR181 | miR181_HoxA11_mRNA → miR181                   | $k_{degHoxA11mRNAmiR181} * \text{miR181_HoxA11_mRNA}$      | $2e-5 s^{-1}$                  |
| HoxA11_translation                | HoxA11_mRNA → HoxA11_mRNA + HoxA11            | $k_{synHoxA11} * \text{HoxA11_mRNA}$                       | $3.2e-5 s^{-1}$                |
| HoxA11_degradation                | HoxA11 → Sink                                 | $k_{degHoxA11} * \text{HoxA11}$                            | $6.4e-6 s^{-1}$                |
| MyoD_gene_FoxO3_binding           | MyoD_gene + FoxO3 → MyoD_gene_FoxO3           | $k_{binMyoDgeneFoxO3} * \text{MyoD_gene} * \text{FoxO3}$   | $1e-5 \text{ mol}^{-1}s^{-1}$  |
| MyoD_gene_FoxO3_release           | MyoD_gene_FoxO3 → MyoD_gene + FoxO3           | $k_{relMyoDgeneFoxO3} * \text{MyoD_gene_FoxO3}$            | $0.001 s^{-1}$                 |
| MyoD_transcription                | MyoD_gene_FoxO3 → MyoD_gene_FoxO3 + MyoD_mRNA | $k_{synMyoDmRNA} * \text{MyoD_gene_FoxO3}$                 | $0.005 s^{-1}$                 |
| MyoD_gene_HoxA11_binding          | HoxA11 + MyoD_gene → MyoD_gene_HoxA11         | $k_{binMyoDgeneHoxA11} * \text{HoxA11} * \text{MyoD_gene}$ | $1e-5 \text{ mol}^{-1}s^{-1}$  |
| MyoD_gene_HoxA11_release          | MyoD_gene_HoxA11 → HoxA11 + MyoD_gene         | $k_{relMyoDgeneHoxA11} * \text{MyoD_gene_HoxA11}$          | $5e-4 s^{-1}$                  |
| MyoD_translation                  | MyoD_mRNA → MyoD_mRNA + MyoD                  | $k_{synMyoD} * \text{MyoD_mRNA}$                           | $0.002 s^{-1}$                 |
| MyoD_mRNA_degradation             | MyoD_mRNA → Sink                              | $k_{degMyoDmRNA} * \text{MyoD_mRNA}$                       | $2e-4 s^{-1}$                  |
| MyoD_degradation                  | MyoD → Sink                                   | $k_{degMyoD} * \text{MyoD}$                                | $2.6e-4 s^{-1}$                |
| FoxO3_Sirt1_binding               | FoxO3 + Sirt1 → FoxO3_Sirt1                   | $k_{binFoxO3Sirt1} * \text{FoxO3} * \text{Sirt1}$          | $1e-5 \text{ mol}^{-1} s^{-1}$ |
| FoxO3_Sirt1_release               | FoxO3_Sirt1 → FoxO3 + Sirt1                   | $k_{relFoxO3Sirt1} * \text{FoxO3_Sirt1}$                   | $0.001 s^{-1}$                 |
| Fox3_degradation_via_Sirt1        | FoxO3_Sirt1 → Sirt1                           | $k_{degFoxO3Sirt1} * \text{FoxO3_Sirt1}$                   | $9.6e-5 s^{-1}$                |
| Fox3_degradation                  | FoxO3 → Sink                                  | $k_{degFoxO3} * \text{FoxO3}$                              | $4.8e-5 s^{-1}$                |
| Fox3_synthesis                    | Source → FoxO3                                | $k_{synFoxO3} * \text{Source}$                             | $0.038 \text{ mol s}^{-1}$     |
| Mafbx_synthesis                   | FoxO3 → FoxO3 + Mafbx                         | $k_{synMafbx} * \text{FoxO3}$                              | $1e-4 s^{-1}$                  |
| Mafbx_degradation                 | Mafbx → Sink                                  | $k_{degMafbx} * \text{Mafbx}$                              | $2e-4 s^{-1}$                  |

<sup>a</sup>mol=number of molecules

**Table S5 Details of species in miR-378 model**

| Species ID       | Description                            | Initial Amount |
|------------------|----------------------------------------|----------------|
| miR378           | microRNA-378                           | 20             |
| miR378_gene      | miR-378 gene                           | 2              |
| miR378_gene_MyoD | miR-378 gene bound by MyoD (activator) | 0              |
| miR378_gene_Msc  | miR-378 gene bound by Msc (inhibitor)  | 0              |
| miR378_Msc_mRNA  | Msc mRNA bound by miR378               | 0              |
| MyoD             | MyoD protein                           | 500            |
| MyoD_gene        | MyoD gene                              | 2              |
| MyoD_mRNA        | MyoD mRNA                              | 20             |
| Msc              | Musculin protein (also known as MyoR)  | 500            |
| Msc_gene         | Msc gene                               | 2              |
| Msc_mRNA         | Msc mRNA                               | 50             |

**Table S6 Details of reactions in miR-378 model**

| Reaction ID                    | Reactants and products                             | Kinetic rate law                                            | Parameter Value <sup>a</sup>                  |
|--------------------------------|----------------------------------------------------|-------------------------------------------------------------|-----------------------------------------------|
| miR378_gene_MyoD_binding       | miR378_gene + MyoD<br>→ miR378_gene_MyoD           | $k_{binmiR378geneMyoD} * \text{miR378\_gene} * \text{MyoD}$ | $1\text{e-}5 \text{ mol}^{-1} \text{ s}^{-1}$ |
| miR_gene_MyoD_release          | miR378_gene_MyoD →<br>miR378_gene + MyoD           | $k_{relmiR378geneMyoD} * \text{miR378\_gene\_MyoD}$         | $0.001 \text{ s}^{-1}$                        |
| miR378_synthesis               | miR378_gene_MyoD →<br>miR378_gene_MyoD +<br>miR378 | $k_{synmiR378} * \text{miR378\_gene\_MyoD}$                 | $1\text{e-}4 \text{ s}^{-1}$                  |
| miR378_degradation             | miR378 → Sink                                      | $k_{degmiR378} * \text{miR378}$                             | $1.6\text{e-}6 \text{ s}^{-1}$                |
| MyoD_transcription             | MyoD_gene →<br>MyoD_gene +<br>MyoD_mRNA            | $k_{synMyoDmRNA} * \text{MyoD\_gene}$                       | $0.005 \text{ s}^{-1}$                        |
| MyoD_mRNA_degradation          | MyoD_mRNA → Sink                                   | $k_{degMyoDmRNA} * \text{MyoD\_mRNA}$                       | $2\text{e-}4 \text{ s}^{-1}$                  |
| MyoD_translation               | MyoD_mRNA →<br>MyoD_mRNA + MyoD                    | $k_{synMyoD} * \text{MyoD\_mRNA}$                           | $0.002 \text{ s}^{-1}$                        |
| MyoD_degradation               | MyoD → Sink                                        | $k_{degMyoD} * \text{MyoD}$                                 | $2.6\text{e-}4 \text{ s}^{-1}$                |
| Msc_transcription              | Msc_gene → Msc_gene<br>+ Msc_mRNA                  | $k_{synMscmRNA} * \text{Msc\_gene}$                         | $2.5\text{e-}4 \text{ s}^{-1}$                |
| Msc_translation                | Msc_mRNA →<br>Msc_mRNA + Msc                       | $k_{synMsc} * \text{Msc\_mRNA}$                             | $5\text{e-}4 \text{ s}^{-1}$                  |
| Msc_mRNA_degradation           | Msc_mRNA → Sink                                    | $k_{degMscmRNA} * \text{Msc\_mRNA}$                         | $1\text{e-}5 \text{ s}^{-1}$                  |
| miR378_Msc_binding             | miR378 + Msc_mRNA<br>→ miR378_Msc_mRNA             | $k_{binmiR378MscmRNA} * \text{miR378} * \text{Msc\_mRNA}$   | $1\text{e-}4 \text{ mol}^{-1} \text{ s}^{-1}$ |
| miR378_Msc_release             | miR378_Msc_mRNA →<br>miR378 + Msc_mRNA             | $k_{relmiR378MscmRNA} * \text{miR378\_Msc\_mRNA}$           | $0.001 \text{ s}^{-1}$                        |
| Msc_mRNA_degradation_by_miR378 | miR378_Msc_mRNA →<br>miR378                        | $k_{degMscmRNAmiR378} * \text{miR378\_Msc\_mRNA}$           | $4\text{e-}5 \text{ s}^{-1}$                  |
| miR378_gene_Msc_binding        | miR378_gene + Msc →<br>miR378_gene_Msc             | $k_{binmiR378geneMsc} * \text{miR378\_gene} * \text{Msc}$   | $5\text{e-}5 \text{ mol}^{-1} \text{ s}^{-1}$ |
| miR378_gene_Msc_release        | miR378_gene_Msc →<br>miR378_gene + Msc             | $k_{relmiR378geneMsc} * \text{miR378\_gene\_Msc}$           | $0.001 \text{ s}^{-1}$                        |
| Msc_degradation                | Msc → Sink                                         | $k_{degMsc} * \text{Msc}$                                   | $5\text{e-}5 \text{ s}^{-1}$                  |

<sup>a</sup>mol=number of molecules

**Table S7 Details of species in miR-143 model**

| Species ID         | Description                           | Initial Amount |
|--------------------|---------------------------------------|----------------|
| Akt                | Akt protein                           | 100            |
| Akt_P              | Phosphorylated Akt                    | 0              |
| Igf2               | Igf2 protein                          | 500            |
| Igf2_Igfbp5        | Igf2 bound by Igfbp5                  | 0              |
| Igfbp5             | Igfbp5 protein                        | 100            |
| Igfbp5_mRNA        | Igfbp5 mRNA                           | 20             |
| Igfbp5_mRNA_miR143 | Igfbp5 mRNA bound by miR143           | 0              |
| IL6                | IL6 protein                           | 500            |
| miR143             | microRNA-143                          | 200            |
| miR143_gene        | miR-143 gene                          | 2              |
| miR143_gene_IL6    | miR143 bound by a TF activated by IL6 | 0              |
| miR143_gene_MyoD   | miR-143 gene bound by MyoD            | 0              |
| MyoD               | MyoD protein                          | 500            |
| Myogenin           | Myogenin protein                      | 0              |

**Table S8 Details of reactions in miR-143 model**

| Reaction ID                       | Reactants and products                       | Kinetic rate law                                  | Parameter Value <sup>a</sup>            |
|-----------------------------------|----------------------------------------------|---------------------------------------------------|-----------------------------------------|
| miR143_gene_MyoD_binding          | miR143_gene + MyoD → miR143_gene_MyoD        | $k_{binmiR143geneMyoD} * miR143\_gene * MyoD$     | $1e-5 \text{ mol}^{-1} \text{ s}^{-1}$  |
| miR143_gene_MyoD_release          | miR143_gene_MyoD → miR143_gene + MyoD        | $k_{relmiR143geneMyoD} * miR143\_gene\_MyoD$      | $0.001 \text{ s}^{-1}$                  |
| miR143_synthesis                  | miR143_gene_MyoD → miR143_gene_MyoD + miR143 | $k_{synmiR143} * miR143\_gene\_MyoD$              | $5e-4 \text{ s}^{-1}$                   |
| miR143_degradation                | miR143 → Sink                                | $k_{degmiR143} * miR143$                          | $5e-6 \text{ s}^{-1}$                   |
| IL6_degradation                   | IL6 → Sink                                   | $k_{degIL6} * IL6$                                | $8e-6 \text{ s}^{-1}$                   |
| miR143_gene_IL6_binding           | miR143_gene + IL6 → miR143_gene_IL6          | $k_{binmiR143geneIL6} * miR143\_gene * IL6$       | $0.001 \text{ mol}^{-1} \text{ s}^{-1}$ |
| miR143_gene_IL6_release           | miR143_gene_IL6 → miR143_gene + IL6          | $k_{relmiR143geneIL6} * miR143\_gene\_IL6$        | $5e-4 \text{ s}^{-1}$                   |
| Igfbp5_transcription              | Source → Igfbp5_mRNA                         | $k_{synIgfbp5mRNA} * \text{Source}$               | $0.001 \text{ mol s}^{-1}$              |
| Igfbp5_mRNA_degradation           | Igfbp5_mRNA → Sink                           | $k_{degIgfbp5mRNA} * Igfbp5\_mRNA$                | $1e-5 \text{ s}^{-1}$                   |
| Igfbp5_mRNA_miR143_binding        | Igfbp5_mRNA + miR143 → Igfbp5_mRNA_miR143    | $k_{binmiR143Igfbp5mRNA} * Igfbp5\_mRNA * miR143$ | $1e-4 \text{ mol}^{-1} \text{ s}^{-1}$  |
| Igfbp5_mRNA_miR143_release        | Igfbp5_mRNA_miR143 → Igfbp5_mRNA + miR143    | $k_{relmiR143Igfbp5mRNA} * Igfbp5\_mRNA\_miR143$  | $0.001 \text{ s}^{-1}$                  |
| Igfbp5_mRNA_degradation_by_miR143 | Igfbp5_mRNA_miR143 → miR143                  | $k_{degIgfbp5mRNAmiR143} * Igfbp5\_mRNA\_miR143$  | $5e-5 \text{ s}^{-1}$                   |
| Igfbp5_translation                | Igfbp5_mRNA → Igfbp5_mRNA + Igfbp5           | $k_{synIgfbp5} * Igfbp5\_mRNA$                    | $8e-5 \text{ s}^{-1}$                   |
| Igfbp5_degradation                | Igfbp5 → Sink                                | $k_{degIgfbp5} * Igfbp5$                          | $5e-5 \text{ s}^{-1}$                   |
| Igf2_Igfbp5_binding               | Igf2 + Igfbp5 → Igf2_Igfbp5                  | $k_{binIgf2Igfbp5} * Igf2 * Igfbp5$               | $5e-6 \text{ mol}^{-1} \text{ s}^{-1}$  |
| Igf2_Igfbp5_release               | Igf2_Igfbp5 → Igf2 + Igfbp5                  | $k_{relIgf2Igfbp5} * Igf2\_Igf2\_Igfbp5$          | $0.001 \text{ s}^{-1}$                  |
| Akt_phosphorylation               | Igf2_Igfbp5 + Akt → Igf2_Igfbp5 + Akt_P      | $k_{phosAkt} * Igf2\_Igf2\_Igfbp5 * Akt$          | $5e-4 \text{ mol}^{-1} \text{ s}^{-1}$  |
| Akt_dephosphorylation             | Akt_P → Akt                                  | $k_{dephosAkt} * Akt\_P$                          | $0.01 \text{ s}^{-1}$                   |
| Myogenin_synthesis                | Akt_P → Akt_P + Myogenin                     | $k_{synMyogenin} * Akt\_P$                        | $1e-5 \text{ s}^{-1}$                   |
| Myogenin_degradation              | Myogenin → Sink                              | $k_{degMyogenin} * Myogenin$                      | $1e-5 \text{ s}^{-1}$                   |

<sup>a</sup>mol=number of molecules

**Table S9 Database Terms of Model Species**

| Model name | Approved gene name | Database term              |
|------------|--------------------|----------------------------|
| Akt        | AKT1               | <a href="#">HGNC:391</a>   |
| FoxO3      | FOXO3              | <a href="#">HGNC:3821</a>  |
| HoxA11     | HOXA11             | <a href="#">HGNC:5101</a>  |
| Igf2       | IGF2               | <a href="#">HGNC:5466</a>  |
| Igfbp5     | IGFBP5             | <a href="#">HGNC:5474</a>  |
| IL6        | IL6                | <a href="#">HGNC:6018</a>  |
| Mafbx      | FBX032             | <a href="#">HGNC:16731</a> |
| miR1       | MIR1-1             | <a href="#">HGNC:31499</a> |
| miR143     | MIR143             | <a href="#">HGNC:31530</a> |
| miR181     | MIR181A1           | <a href="#">HGNC:31590</a> |
| mir378     | MIR378A            | <a href="#">HGNC:31871</a> |
| MyoD       | MYOD1              | <a href="#">HGNC:7611</a>  |
| Myogenin   | MYOG               | <a href="#">HGNC:7612</a>  |
| Msc        | MSC                | <a href="#">HGNC:7321</a>  |
| Pax3       | PAX3               | <a href="#">HGNC:8617</a>  |
| Sirt1      | SIRT1              | <a href="#">HGNC:14929</a> |

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