Inducible gene expression systems can be used to control the expression of a gene of interest by means of a small-molecule. One of the most common designs involves engineering a small-molecule responsive transcription factor (TF) and its cognate promoter, which often results in a compromise between minimal uninduced background expression (leakiness) and maximal induced expression. Here, we focussed on an alternative strategy using quantitative synthetic biology to mitigate leakiness while maintaining high expression, without modifying neither the TF nor the promoter. Through mathematical modelling and experimental validations, we designed the CASwitch, a mammalian synthetic gene circuit based on combining two well-known network motifs: the Coherent Feed-Forward Loop (CFFL) and the Mutual Inhibition (MI). The CASwitch combines the CRISPR-Cas endoribonuclease CasRx with the state-of-the-art Tet-On3G inducible gene system to achieve high performances. To demonstrate the potentialities of the CASwitch, we applied it to three different scenarios: enhancing a whole-cell biosensor, controlling expression of a toxic gene and inducible production of Adeno-Associated Virus (AAV) vectors.