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Direct Epigenetic Reprogramming of Human Somatic Cells into Insulin-Producing Cell

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ABSTRACT

Restoring insulin production through replacement of pancreatic β-cells presents a promising strategy for treating individuals with type 1 diabetes. However, current methods involving induced pluripotent stem cell differentiation are often time-consuming, multi-stage, and limited by safety and efficiency concerns. To overcome these challenges, we developed a simplified and direct strategy to convert human somatic cells into insulin-producing cells using an epigenetic activation system. This system combines a multiplex epigenetic engineering vector composed of dCas9.P300core and guide RNAs targeting five key β-cell genes: PDX1, NKX6.1, MAFA, Insulin, and glucose transporter type 2 (Glut2). The resulting Glut2^{+} cells exhibited glucose-responsive insulin secretion and expressed essential β-cell transcription factors including NKX2.2, along with insulin-processing and secretory machinery genes (Cav1.3, GSK3β, KCNJ11, SLC30A8). Absence of α-cell markers (aristaless-related homeobox or glucagon) confirmed lineage specificity and functional fidelity. This reprogramming approach eliminates the need for pluripotent intermediates and significantly reduces the time required to generate functional β-like cells. Our platform offers a rapid, non-integrative, and scalable method for producing insulin-secreting cells, with potential applications in personalized cell therapy, disease modeling, and high-throughput drug screening for diabetes research.

Introduction

Restoration of insulin-producing pancreatic β-cells holds transformative potential for treating type 1 diabetes (T1D), a condition characterized by autoimmune destruction of native β-cells. While allogeneic islet transplantation has demonstrated clinical success in reestablishing glycemic control without exogenous insulin, this approach remains constrained by severe donor shortages and lifelong immunosuppression requirements[1-3]. Xenotransplantation using porcine islets has shown promise in non-human primate models[4-9], yet safety concerns related to porcine endogenous retroviruses (PERVs) and zoonotic transmission continue to limit clinical translation[10]. To circumvent donor limitations, efforts have turned toward generating insulin-producing cells from induced pluripotent stem cells (iPSCs)[11-13]. However, these methods are technically complex, involve multi-stage differentiation spanning 4–6 weeks, require precisely timed cytokine and small molecule exposure, and carry risks of teratoma formation or off-target lineage differentiation[14-16]. These limitations underscore the urgent need for simpler, scalable, and safer approaches to generate β-like cells directly from accessible human somatic sources.

Recent advances in CRISPR-based epigenetic engineering have enabled direct gene activation without introducing double-strand breaks or integrating foreign DNA[17-19]. In particular, the use of a catalytically inactive Cas9 (dCas9) fused to the P300core histone acetyltransferase domain has demonstrated potent transcriptional activation of silent genes by remodeling local chromatin[20-22]. Unlike traditional trans activators, the P300core domain enhances acetylation of H3K27, allowing for robust transcription even in the absence of endogenous transcription factors[23] A landmark study demonstrated that dCas9.P300core can activate target genes—even in the absence of their native transcription factors—by guiding histone acetylation at promoter regions[20].

Building on this foundation, we hypothesized that targeted activation of multiple β-cell lineage regulators—pancreatic and duodenal homeobox 1 (PDX), NK6 homeobox 1 (NKX6.1), musculoaponeurotic fibrosarcoma oncogene homolog A (MAFA), Insulin, and Glut2—could convert somatic cells into glucose-responsive insulin-producing cells. We therefore engineered a Multiplex Epigenetic Engineering Vector-β (MEEV-β) that integrates all necessary guide RNAs with the dCas9.P300core fusion in a single delivery platform. This approach bypasses pluripotent intermediates, eliminates the need for staged cytokine cues, and achieves lineage-specific β-cell gene expression in just seven days. Importantly, the absence of α-cell lineages marker such as aristaless-related homeobox (ARX) or glucagon (GCG), expression supports the specificity of conversion. This proof-of-concept lays the foundation for a new class of programmable, non-integrative β-cell engineering tools with translational potential in autologous therapy, disease modeling, and drug screening for T1D.

Methods

Cell Culture: Human somatic cells used in this study included lung endothelial cells ($CD31^+$), aortic endothelial cells ($CD31^+$), lung fibroblasts, and peripheral blood mononuclear cells (PBMCs). Endothelial cells were cultured in EGM-2 or EGM-2 MV medium (Lonza) on collagen-coated dishes. Lung fibroblasts were maintained in DMEM supplemented with 10% FBS, 1% Penicillin-Streptomycin, and 1% antimycotic agent. PBMCs were isolated using Ficoll-Paque Plus and stimulated with PHA (5 µg/mL) for 48 hours prior to transfection.

Cloning and assembly of the MEEV-β guide RNA design and cloning: gRNAs targeting DNase I hypersensitive promoter regions of PDX1, NKX6.1, MAFA, Insulin, and Glut2 (**Supplementary Table 1**) were designed using the CRISPR direct tool (http://crispr.dbcls.jp). The most effective gRNAs (determined via RT-qPCR) were cloned into Addgene vectors: PDX1 into pX330A-1x5, NKX6.1, MAFA, Insulin, and Glut2 into pX330S-2, -3, -4, -5. To generate a single multiplex construct, gRNA-expressing plasmids were assembled using Golden Gate cloning. Following the manufacturer's instructions for Golden Gate assembly, the reaction mixture was prepared using: 1.5 µL each of 100 ng/µL plasmids pX330S-2 (NKX6.1), pX330S-3 (MAFA), pX330S-4 (Insulin), and pX330S-5 (Glut2); 1.5 µL of 50 ng/µL pX330A-1x6 (PDX1); 2 µL of 10× T4 DNA Ligase Buffer (Cat #B0202S, NEB); 1 µL of BsaI (Cat #R0535S, NEB); 1 µL of Quick Ligase (Cat #E6047, NEB); and 8.5 µL of nuclease-free water (Ambion), bringing the total reaction volume to 20 µL. The mixture was subjected to thermal cycling at 37°C for 5 min and 16°C for 10 min, repeated for 25 cycles, to facilitate assembly. Assembled plasmids were transformed into TOP10 competent *E. coli* (Catalog # C737303) and verified by colony PCR and sequencing. Purified plasmid was screen for golden gate assembly by PCR using CRISPR-step2 (**Supplementary Table 2**).

Fusion of P300core into dCas9 vector: To enable epigenetic activation, the P300core domain was cloned in-frame into the pX330A-dCas9 1x6 backbone (Addgene #63600) using HiFi DNA assembly. The NLS was removed from dCas9 by EcoRI and FseI digestion. P300core was PCR-amplified from pcDNA-dCas9. P300core. The assembled product was transformed into Stbl3 *E. coli* cell (Catalog # C737303) to prevent recombination and confirmed by sequencing. The final construct, named MEEV-β, contained dCas9.P300core and five gRNAs targeting β-cell genes.

In-frame Cloning of P300core into the Multiplex dCas9 Vector: To construct the MEEV-β vector, the P300core domain was cloned in-frame into the dCas9 region of the pX330A-dCas9 1x6 plasmid containing gRNAs for PDX1, NKX6.1, MAFA, Insulin, and Glut2. First, the nuclear localization signal (NLS) was removed from the dCas9 cassette using EcoRI (Cat #R0101, NEB) and FseI (Cat

#R0588, NEB) restriction digestion. Simultaneously, the P300core domain (including its NLS signal) was PCR-amplified from the pcDNA-dCas9.P300core vector using Q5 High-Fidelity 2X Master Mix (Cat #M0492S, NEB). Primer sequences are listed in **Supplementary Table 3**. Each 50 µL PCR reaction contained: 25 µL Q5 Master Mix, 5 µL 10 µM forward primer, 5 µL 10 µM reverse primer, 200 ng template DNA (pcDNA-dCas9.P300core) and nuclease-free water to 50 µL. The thermal cycling conditions were: Initial denaturation: 98°C for 30 sec, 35 cycles of 98°C for 10 sec, 72°C for 30 sec, final extension: 72°C for 15 min and hold at 4°C. The PCR product was purified using a gel extraction kit (Qiagen).

For vector assembly, 50 ng of linearized vector and 100 ng of purified P300core PCR product were mixed with NEBuilder HiFi DNA assembly master mix (Cat #E2623, NEB) and incubated at 50°C for 1 hour. The assembled vector was transformed into One Shot® Stbl3™ Chemically Competent *E. coli* (Cat #C737303, ThermoFisher) to minimize recombination within the repetitive P300core sequence. Correct in-frame cloning was confirmed by PCR and sequencing using primers flanking the left and right junctions (listed in **Supplementary Table 2**). The verified MEEV-β plasmid was then used to transfect lung endothelial cells, lung fibroblasts, aortic endothelial cells, and human PBMCs. After 14 days, Glut2$^+$ cells were enriched via flow cytometry using anti-Glut2-PE (Cat #NBP2-22218SS, Novus Biologicals).

Quantitative RT-PCR: Total RNA was extracted from transfected and flow-sorted Glut2$^+$ cells using the RNeasy Plus Micro Kit (Cat #74136, Qiagen). cDNA was synthesized using the iScript™ cDNA Synthesis Kit (Cat #1708891, Bio-Rad) in a 20 µL reaction. Thermal cycling for cDNA synthesis: 25°C for 5 min (priming), 46°C for 20 min (reverse transcription), 90°C for 1 min (enzyme inactivation) and hold at 4°C. Real time PCR was performed using SsoAdvanced™ Universal SYBR Green Supermix (Cat #1725271, Bio-Rad) on a CFX96 Real-Time PCR System (Bio-Rad).

Glucose stimulated Insulin secretion. Flow sorted Glut2+ cells were plated in collagen coated 96 well plates (1000 cells each well). After 48h cells showed the signs of attachment and the cells were carefully washed in Krebs buffer containing 2mM glucose. Following are the components of the stock solution of Krebs buffer: 128 mM NaCl (Cat #S65886; Sigma), 5 mM KCl (Cat #6858-03; Sigma), 2.7 mM $CaCl_2$ dihydrate (Cat# 223506; Sigma-Aldrich), 1.2 mM $MgCl_2$ (Cat #7791-16-6; J.T. Baker), 1 mM Na_2HPO4 (Cat # S9763), 1.2 mM KH_2PO4, 5 mM NaHCO3 (Cat #S6296; Sigma), 10 mM HEPES (Cat # 15630080; Life Technologies;), and 0.1% BSA (Proliant; 68700) in deionized water. After washing, the cells were incubated for 2hr in 2 mM glucose (Cat#G7528; Sigma) prepared in Krebs buffered. The cells were then washed again and incubated sequentially under following conditions: 30 min each with 2.8 mM, 28 mM, 2 mM, 28 mM, 2 mM, and 20 mM glucose in Krebs buffer. The insulin secretion was from these supernatants was detected as per instructions of Human Ultrasensitive Insulin ELISA (ALPCO Diagnostics; 80-INSHUU-E01.1).

Results

Rational design for β-cell programming via epigenetic activation

Previous studies have established that the transcription factors PDX1, NKX6.1, and MAFA serve as master regulators of pancreatic β-cell development and function. These factors are essential for activating downstream gene networks involved in insulin biosynthesis, storage, and glucose responsiveness[12,13,24-26]. To harness this biology for direct somatic cell reprogramming, we prioritized these genes as primary epigenetic targets for activation in non-β cells. (**Supplementary Fig. 1**). Under physiological conditions, PDX1, NKX6.1, and MAFA loci remain epigenetically repressed in non-β cells, typically residing in heterochromatin regions[26]. To enable transcriptional activation, we mapped DNase I hypersensitive sites (DHSs) near the promoters of each gene—particularly within 100 bp upstream of the transcription start site and enriched for H3K4me1 histone marks—regions known to favor chromatin remodeling[27]. These DHS regions were selected to design multiple guide RNAs (gRNAs) targeting the transcriptional regulatory elements (TATA and BRE motifs)[28]. as shown in **Supplementary Fig. 2A–E and Supplementary Table 1.** Each gRNA was cloned into the pSPgRNA backbone (**Fig. 1A–C**) and co-transfected with the pcDNA-dCas9.P300core vector into human somatic cells **(Supplementary Fig. 3 A, B).** After 4 days, qRT-PCR revealed robust transcriptional activation of the targeted genes[29]. The top-performing gRNAs—gRNA2 (PDX1), gRNA3 (NKX6.1), and gRNA3 (MAFA)—were selected for subsequent experiments (**Fig. 1F–H**).

Development of Multiplex Epigenetic Engineering Vector (MEEV-β)

To efficiently co-deliver all five gRNAs and the dCas9.P300core activator in a single construct, we created a custom multiplex epigenetic engineering vector, termed MEEV-β. While multiplex CRISPR systems have been widely implemented for gene editing, their adaptation for epigenetic modulation—particularly using dCas9.P300core—had not been demonstrated.

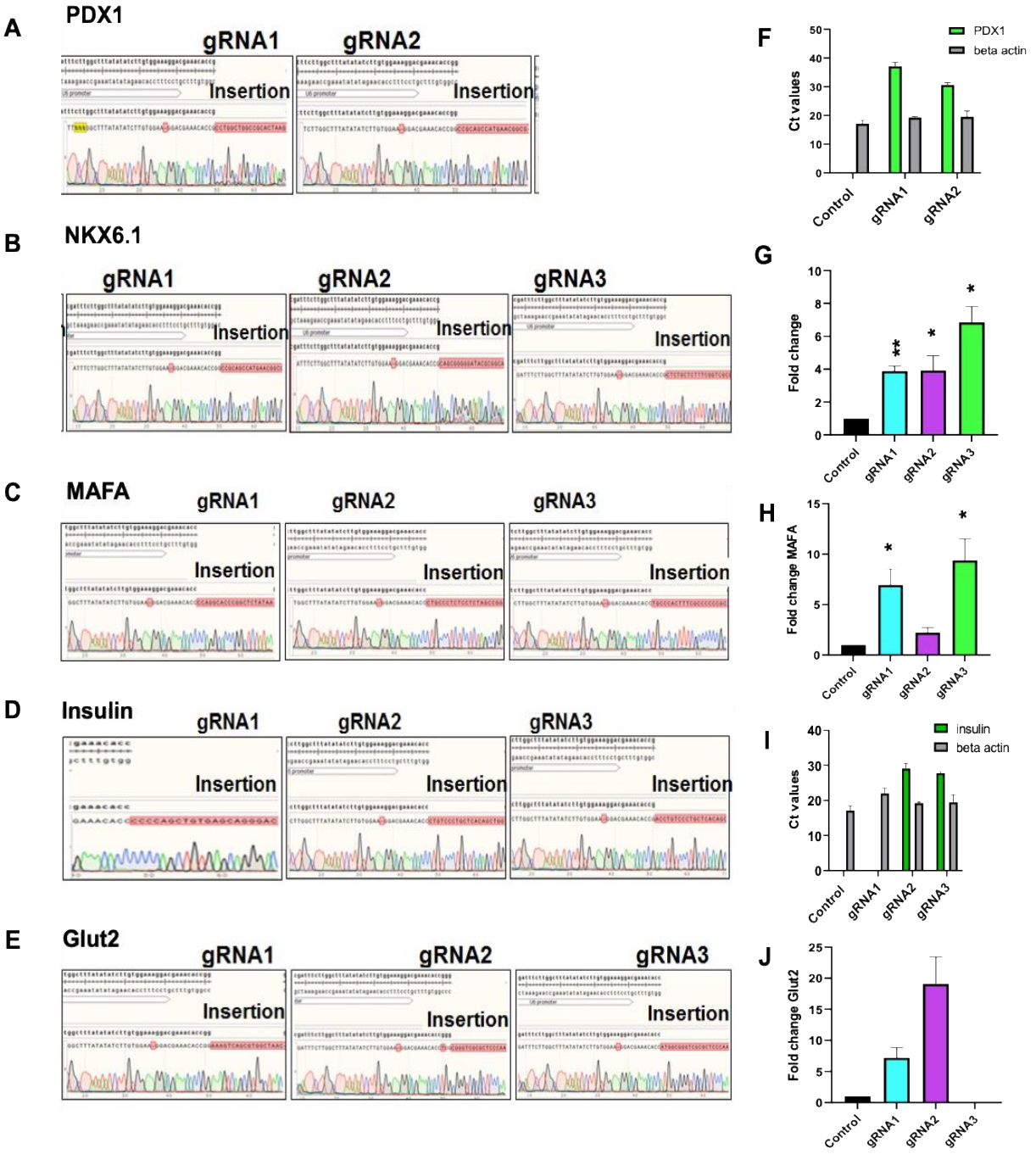

Figure 1: Elucidation of targeted epigenetic engineering and activation of beta cells genes in human lung fibroblasts using dCas9.P300^{core}. (A-E) Cloning confirmation of annealed oligonucleotides targeting 5' DNase I hypersensitive sites of PDX1, NKX6.1, MAFA, Insulin, Glut2 genes in pSPgRNA vector at BbsI sites **(F-J)** qRT-PCR of PDX1, NKX6.1, MAFA, Insulin, Glut2 driven by different gRNAs because of epigenetic engineering by dCas9.P300^{core}.

We began by modifying the pX330A-dCas9 1x5 vector backbone to accommodate in-frame insertion of the P300core domain. This involved: 1) Removing the nuclear localization signal (NLS) from dCas9 via restriction digestion. 2) PCR amplification of P300core (with an NLS) from the pcDNA-dCas9.P300core plasmid, using primers overlapping the N- and C-termini of dCas9 and the vector backbone. 3) Assembly of the P300core insert into the linearized vector using HiFi DNA assembly, confirmed by junctional sequencing (**Fig. 2A**). After verifying the correct in-frame fusion, we proceeded to clone the five optimal gRNAs into pX330A-dCas9.P300core (1x5) and accompanying vectors (pX330S2–S4) using Golden Gate assembly (**Fig. 2B–F, Supplementary Fig. 4**). The final construct—MEEV-β—thus comprised one vector delivering the dCas9.P300core fusion protein and all five gRNAs targeting PDX1, NKX6.1, MAFA, insulin, and Glut2.

Functional validation: Glucose-responsive insulin secretion

Human somatic cells from our in-house cell bank were transfected with the MEEV-β construct. After 7 days, Glut2^{+} cells were enriched by flow sorting (**Fig. 3A, Supplementary Fig. 5**), as Glut2 expression is a reliable surrogate for β-cell glucose sensitivity. Sorted cells were then challenged with low (2.8 mM) and high (28 mM) glucose concentrations in Krebs buffer to assess glucose-stimulated insulin secretion (GSIS). The Glut2^{+} cells exhibited a 1.5-fold increase in insulin secretion at high

glucose levels compared to low glucose conditions, confirming their functional β-cell-like phenotype (**Fig. 3B**).

Molecular characterization of Glut2⁺ β-like cells

To further validate the β-cell identity of MEEV-β-derived Glut2⁺ cells, we performed RT-qPCR analysis of genes involved in insulin processing, vesicle trafficking, and glucose-stimulated insulin secretion. These included NKX2.2 (a downstream transcription factor of PDX1 and MAFA), as well as β-cell functional genes such as SLC30A8, KCNJ11, GSK3β, and Cav1.3 (**Supplementary Fig. 6**). These markers are essential for β-cell maturation, KATP channel function, and insulin granule exocytosis. Importantly, Glut2⁺ cells lacked expression of α-cell markers, such as ARX (alpha cell-specific transcription factor) and GCG (glucagon), confirming lineage specificity and eliminating concerns about off-target endocrine fate (**Fig. 3C**). The expression profile was most consistent and robust in fibroblast-derived cells, suggesting that fibroblasts represent an optimal somatic source for β-cell reprogramming using this platform.

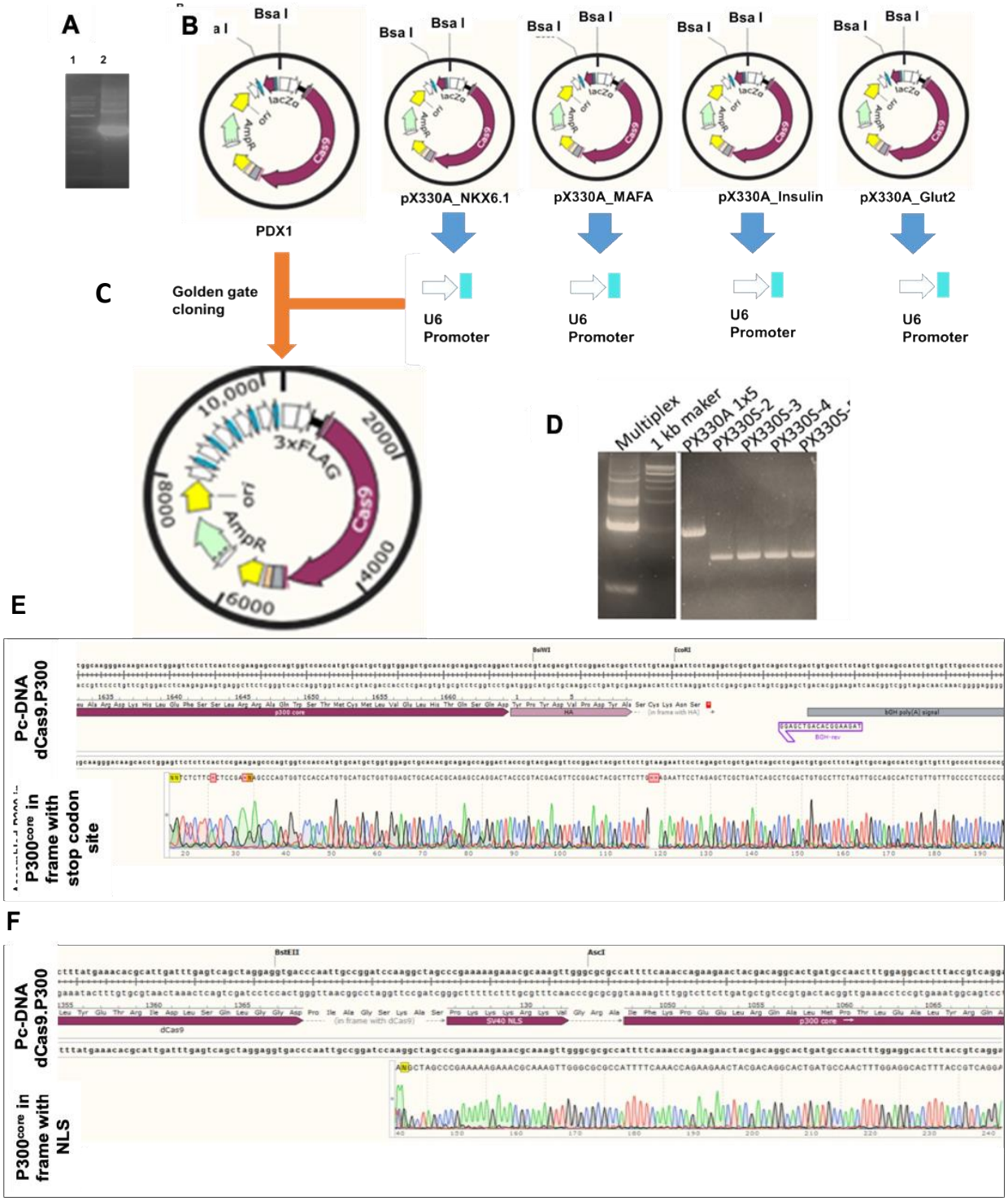

Figure 2: Multiplex Epigenetic Engineering Vector Assembly.

(**A**) Amplification of P300core fragment for insertion into pX330 vector. (**B–C**) Schematic of cloning five β-cell gene–targeting gRNAs into the dCas9.P300core backbone via Golden Gate assembly. (**D**) PCR confirmation of gRNA insertion. (**E–F**) Sequencing validation of in-frame P300core cloning and gRNA integration using SnapGene. Schematics of cloning and assembly in (**B**) and (**C**) was generated in SnapGene.

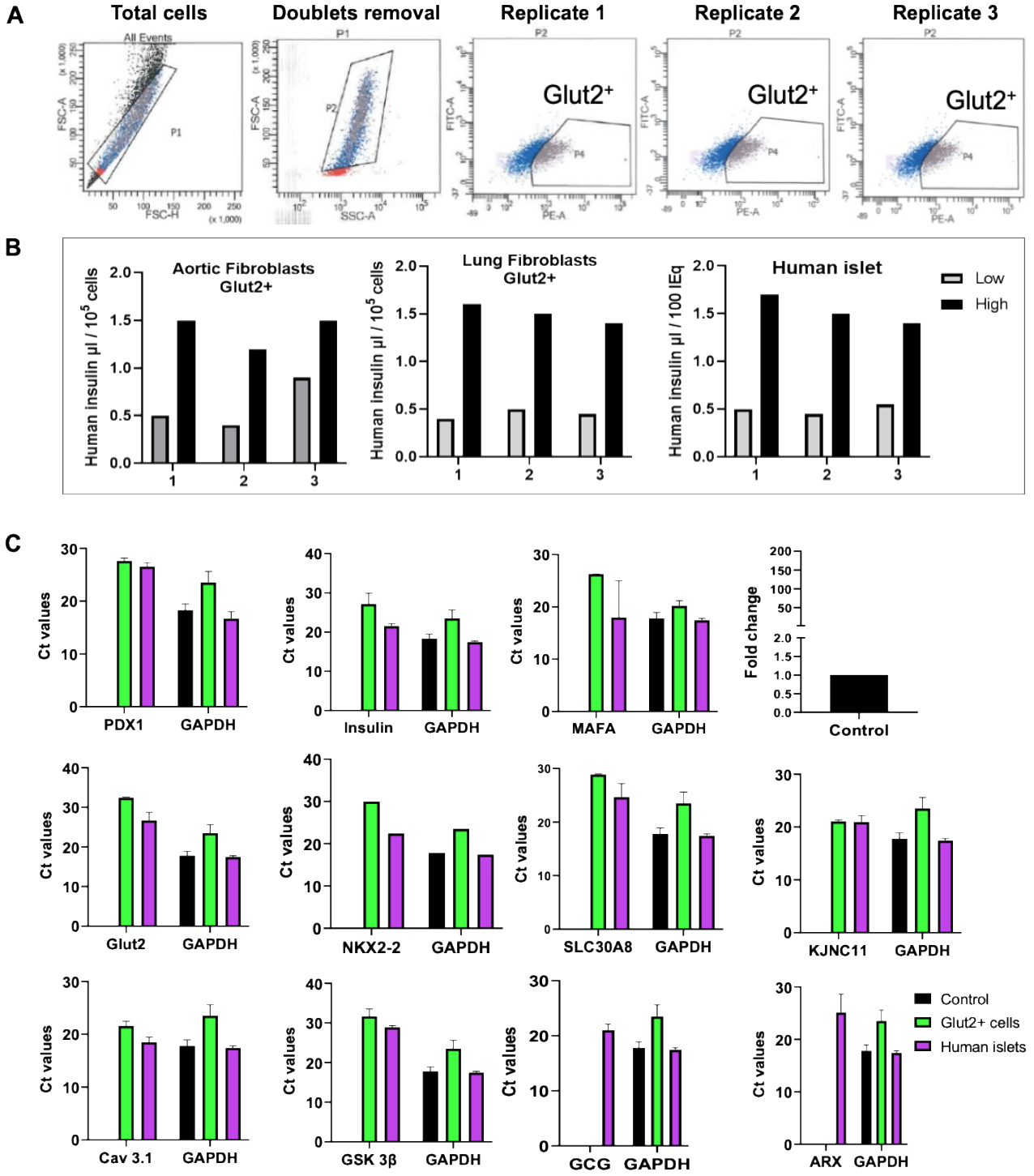

Figure 3: Sorting and functional validation of Glut2$^+$ insulin-producing cells. (**A**) FACS sorting of Glut2$^+$ cells from MEEV-β–transfected fibroblasts across three replicates. (**B**) Glucose-stimulated insulin secretion assay shows dose-dependent response of Glut2$^+$ cells. (**C**) qRT-PCR confirms β-cell gene expression; human islets served as positive control, and α-cell markers (ARX, GCG) as negative controls.

Discussion

Conventional strategies for generating insulin-producing β-like cells typically involve multi-step differentiation protocols starting from iPSCs or human embryonic stem cells (hESCs). These methods often require 4 to 6 weeks of tightly timed culture conditions, sequential exposure to stage-specific cytokines and growth factors and specialized extracellular matrices to mimic developmental cues[11-13,30]. While powerful, these approaches have limitations: they are labor-intensive, require multiple cytokines and developmental cues[31], and carry risks linked to any residual pluripotent cells, such as tumorigenicity and teratoma formation[15,16]. In contrast, our MEEV-β platform introduces a streamlined, 7-day single-step conversion from primary somatic cells directly into Glut2$^+$ insulin-producing cells. By targeting five essential β-cell lineage-defining genes (PDX1, NKX6.1, MAFA, Insulin, GLUT2) via a dCas9.P300core-based multiplexed epigenetic editing strategy, we eliminate the need for pluripotency induction, transgene integration, or exogenous cytokine supplementation. This dramatically reduces time, cost, and safety risks, while maintaining high efficiency of conversion. Notably, we observed a complete absence of α-cell markers such as ARX and

GCG, underscoring the specificity of our conversion process. By contrast, prior reprogramming efforts—like those described in earlier several studies[32-34]—often produced mixed endocrine populations, including both β- and α-like cells, due to the shared developmental origins and plasticity among islet cell types[35]. Ensuring such specificity is critical in therapeutic contexts, as inadvertent generation of glucagon-secreting cells may counteract insulin-producing functions. Furthermore, our approach is cell-type agnostic, functioning effectively in human lung endothelial cells, fibroblasts, and PBMCs—making it adaptable for autologous therapies from accessible tissue sources. Overall, this study sets the groundwork for a next-generation, epigenetics-driven platform for efficient, safe, and scalable generation of functional β-cells.

Collectively, these results demonstrate that our in-house developed MEEV-β system enables simultaneous activation of multiple β-cell-specific genes in a single step. This combinatorial epigenetic programming effectively launches a developmental and functional β-cell transcriptional network, culminating in the production of insulin in response to glucose. By activating both early developmental regulators (PDX1, NKX6.1, MAFA) and late-stage functional effectors (insulin and Glut2) synchronously, the system eliminates the timing lag observed in sequential reprogramming strategies. This acceleration of the β-cell conversion process—from weeks to just seven days—represents a significant technical and translational advancement. Furthermore, the use of Glut2-based cell sorting ensures that only glucose-sensing, insulin-secreting cells are enriched—an aspect often missing from current stem cell-derived β-cell transplantation protocols. As only ~25% of native pancreatic β-cells are Glut2$^+$, selecting this subtype could reduce the number of transplanted cells needed to achieve normoglycemia.

This is the first report to leverage a multiplexed epigenetic editing strategy for direct reprogramming into insulin-producing cells without passing through a pluripotent or progenitor state. Previous studies have shown single-gene activation (e.g., globin gene via dCas9.P300)[20], but our work builds upon this by demonstrating simultaneous, synergistic activation of five genes critical for β-cell identity and function. Moreover, our Glut2$^+$ sorted cells express β-cell-specific markers (NKX2.2, Cav1.3, GSK3β, KCNJ11, SLC30A8) and exhibit glucose-responsive insulin secretion, strongly supporting their functional competence.

This study establishes a proof-of-concept for the rapid and direct conversion of human somatic cells into functional insulin-producing β-cells using a targeted, multiplexed epigenetic activation strategy. The core of this platform, termed MEEV-β, integrates dCas9.P300core with a multi-guide RNA cassette designed to simultaneously activate five pivotal β-cell genes, enabling coordinated initiation of a comprehensive β-cell transcriptional program. To our knowledge, this is the first demonstration of a multiplexed epigenetic programming system capable of driving such conversion within a single vector, bypassing the need for pluripotency, viral transgenes, or prolonged multistage culture. The process completes within just seven days, offering a non-integrative, single-step, and time-efficient alternative to conventional iPSC-based protocols. Notably, the resulting Glut2$^+$ cells exhibit expression of key β-cell markers and demonstrate glucose-responsive insulin secretion, underscoring their functional competence. (**Fig. 4: Graphical abstract**). Beyond basic proof-of-concept, the MEEV-β platform offers broad translational potential. It could enable personalized autologous cell therapy for individuals with type 1 diabetes, disease modeling using patient-derived somatic cells, and high-throughput drug screening for β-cell–targeted therapeutics. The simplicity and scalability of the system make it an attractive tool for both experimental and therapeutic applications. Nonetheless, important limitations remain. In vivo engraftment studies are needed to evaluate the functionality, integration, and safety of these cells within physiologic environments. The long-term stability and epigenetic fidelity of reprogrammed cells must be rigorously assessed under extended culture or transplantation settings. Moreover, issues of immune compatibility and potential immunogenicity—particularly in autoimmune contexts such as type 1 diabetes—must be carefully investigated before advancing toward clinical translation.

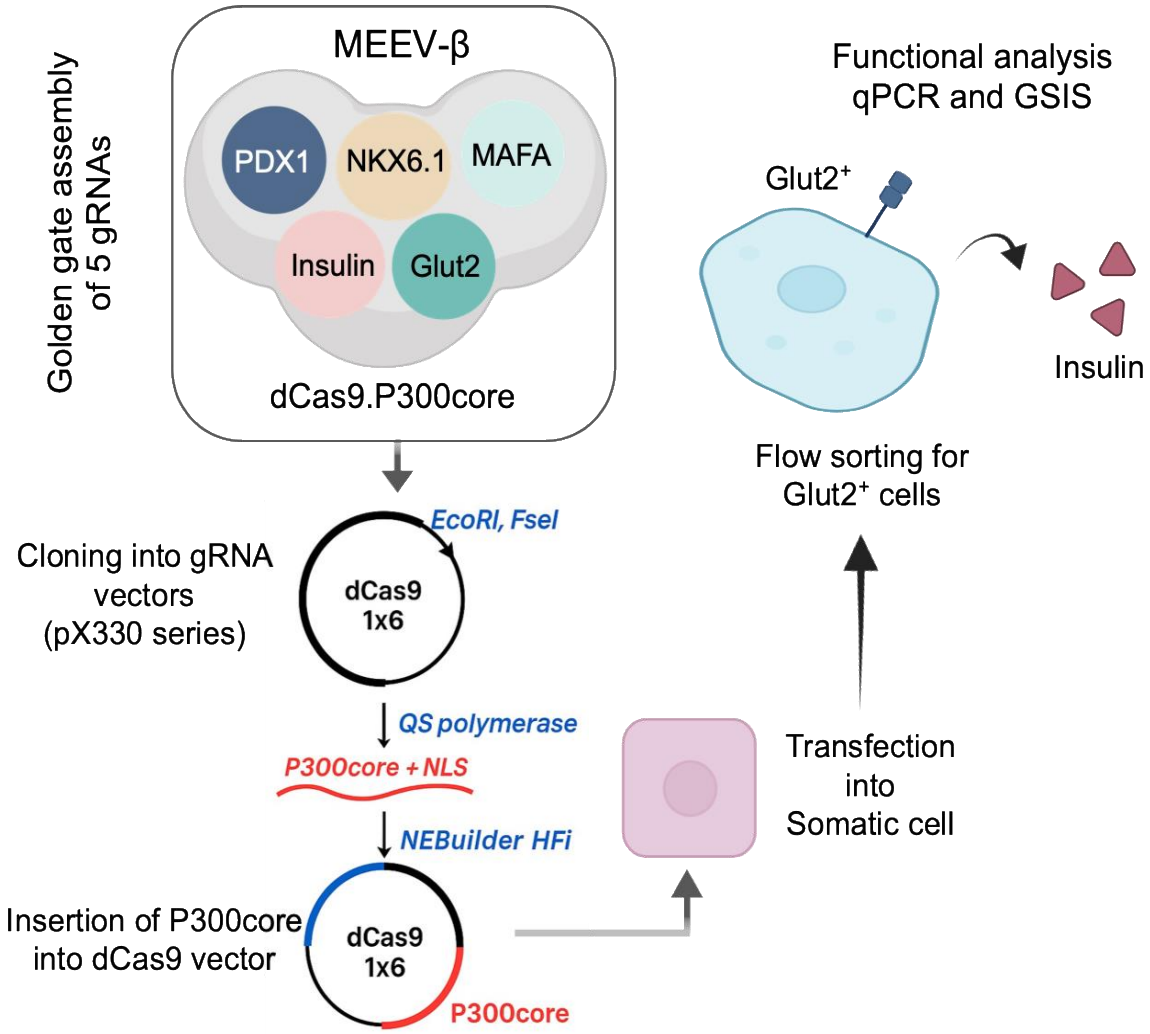

Figure 4: Graphical summary of MEEV-β–mediated β-cell conversion. Schematic illustrating how the MEEV-β system, carrying dCas9.P300core and multiplex gRNAs targeting β-cell genes, activates transcriptional networks to reprogram somatic cells into insulin-producing β-like cells capable of glucose-stimulated insulin secretion.

Conclusions

While these findings are promising, in vivo validation is essential to assess the durability, safety, and functional integration of MEEV-β-derived cells post-transplantation. Additionally, studies on immune compatibility, off-target epigenetic effects, and long-term expression stability will be critical for translational application. Future optimization of delivery methods—e.g., non-viral nanoparticles or mRNA-based systems—may further enhance the clinical feasibility of this platform. Overall, MEEV-β sets the stage for a new generation of **precision cell engineering technologies**, bridging the gap between synthetic biology and regenerative medicine.

Declaration of competing interest:

The authors have no conflict of interest.

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Authorship contribution statement

Raza Ali Naqvi: Conceptualized, written and corrected the manuscript.
Amar Singh: Conceptualized, written, edited, and revised the manuscript
Afsar Raza Naqvi: Conceptualized and corrected the final draft.
Medha Priyadarshini: Corrected the final draft.
Sujata Prasad: Significantly contributed to revision, edited the final draft

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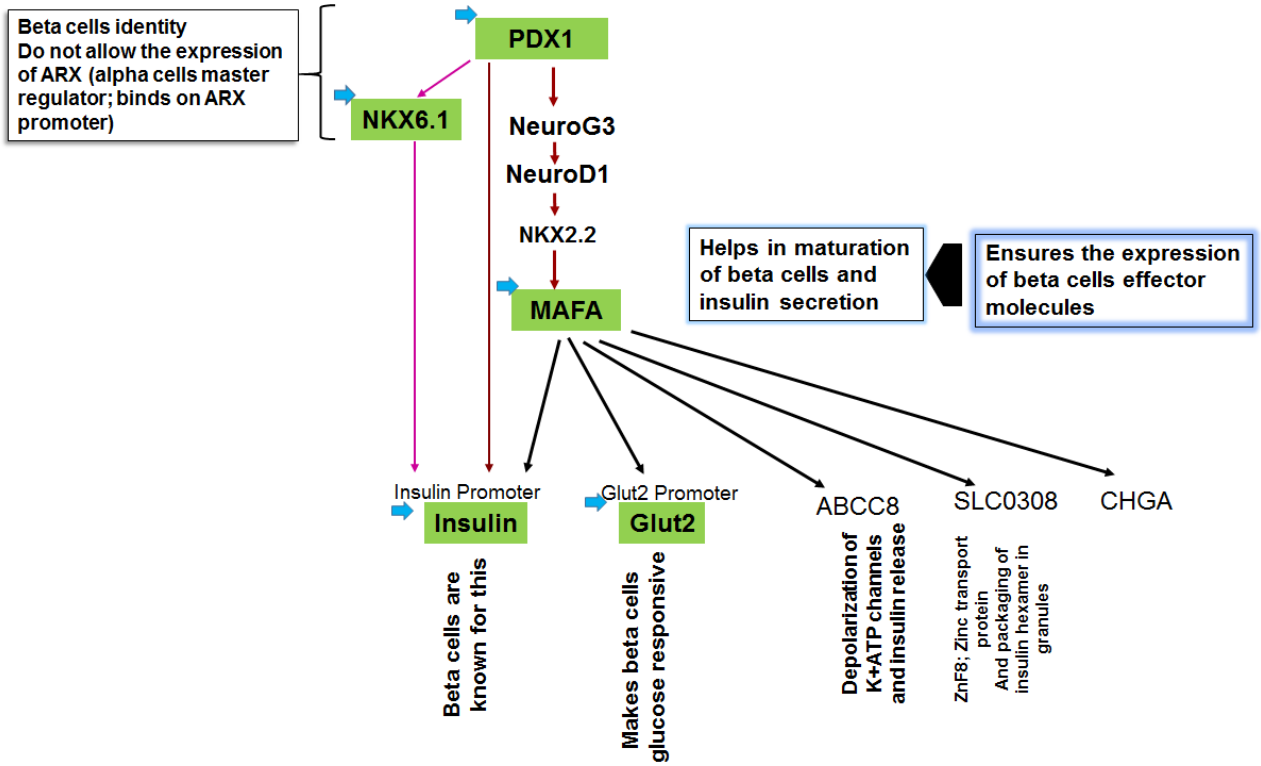
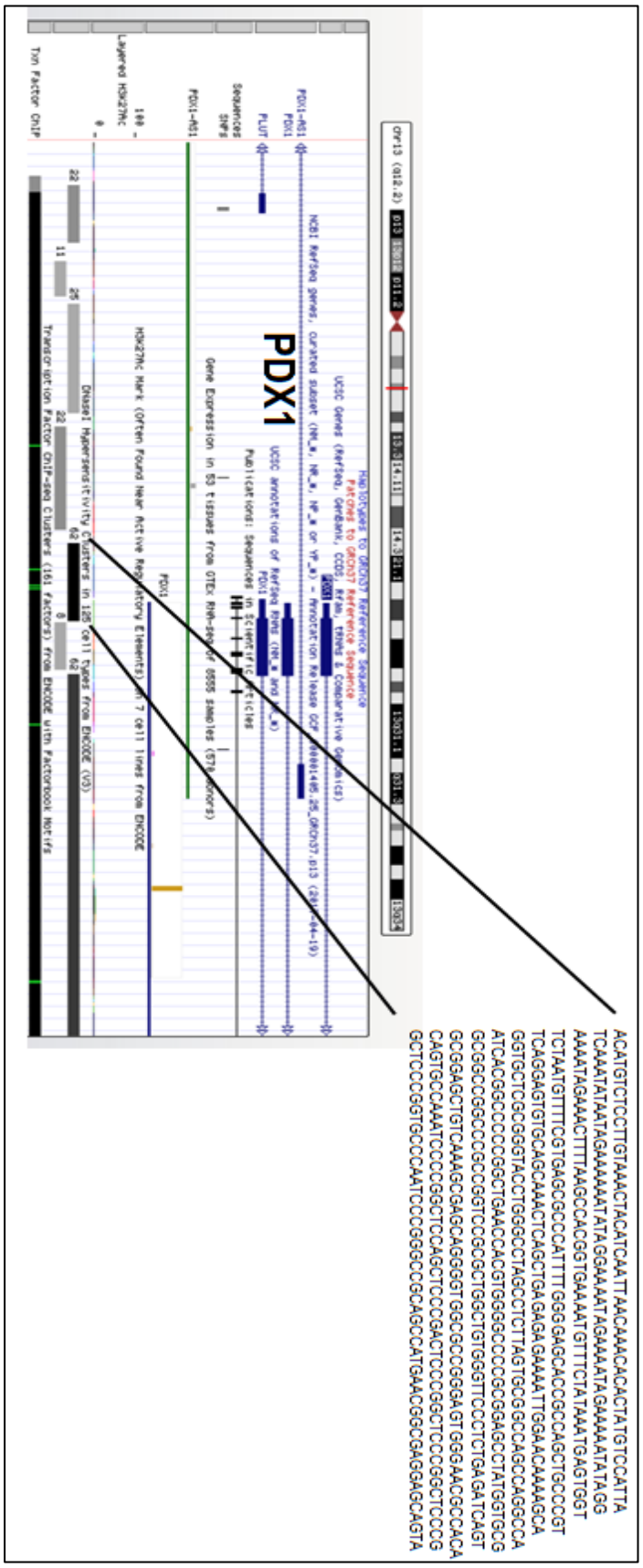


Supplementary Fig. 1: Rationale of choosing PDX1, NKX6.1, insulin, Glut2 and MAFA to induce beta cells. PDX1 expresses in all endocrine cells initially and later on it's only restricted in beta cells of endocrine pancreas[1-3]. PDX1 importantly induces the expression of NKX6.1- a transcription factor that restricts the development of beta cells[4]. NKX6.1 reported to bind at the promoter of ARX1 – a master regulator of alpha cells and also suppresses the glucagon expression[5]. On other hand NKX6.1 also binds at insulin promoter and facilitates the expression of insulin[6]. Thus, NKX6.1 can function as both transcriptional activator as well as transcriptional repressor. Initially, we have thought of taking NKX6.1 to induce the beta cells genetic program, but insulin promoter- the major effector molecule of beta cells not only has NKX6.1 binding site but also PDX1 binding site[1-3]. Therefore, even though NKX6.1 can be expressed by dCas9.P300^{core} even in the absence of its transcription factor PDX1 but to get the adequate and sustained expression of insulin gene we need to have PDX1 along with NKX6.1. Also, PDX1, induces the genetic program leading to another transcription factor of insulin gene-MAFA[1], which in turn leads Glut2 gene expression- a glucose transporter[9,10]. Learning the lessons from stem cells derived beta cells, we came to know the expression of MAFA only possible when PDX1 would induce NKX2.2 via NEUROG3 and NEUROD1[1-3]. Therefore, to reduce the time from PDX1 to MAFA, we have already targeted MAFA, so that it could provide positive feed-back for its own expression. Targeting of insulin and Glut2 simultaneously can only enforce the somatic cells to move towards the conversion of beta cells with no further decision-making process related to the beta cells specific genetic network. Blue arrow indicates the activation of these loci by gRNA driven dCas9.P300^{core}.

2A


PDX1
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ATCACGGCCCCCGGCTGAACCACGTGGGGCCCCGCGGAGCCTATGGTGCG
GCGGCCGGCCCGCCGGTCCGCGCTGGCTGTGGGTTCCCTCTGAGATCAGT
GCGGAGCTGTCAAAGCGAGCAGGGGTGGCGCCGGGAGTGGGAACGCCACA
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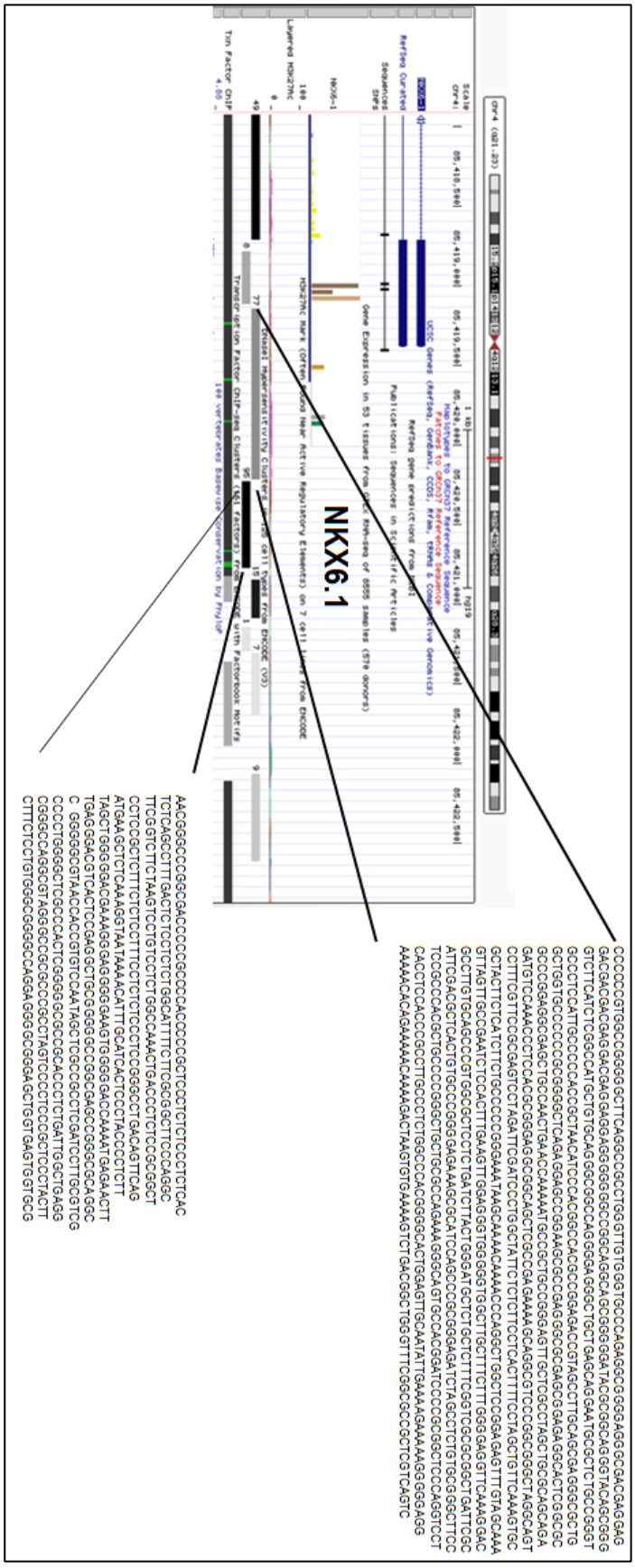
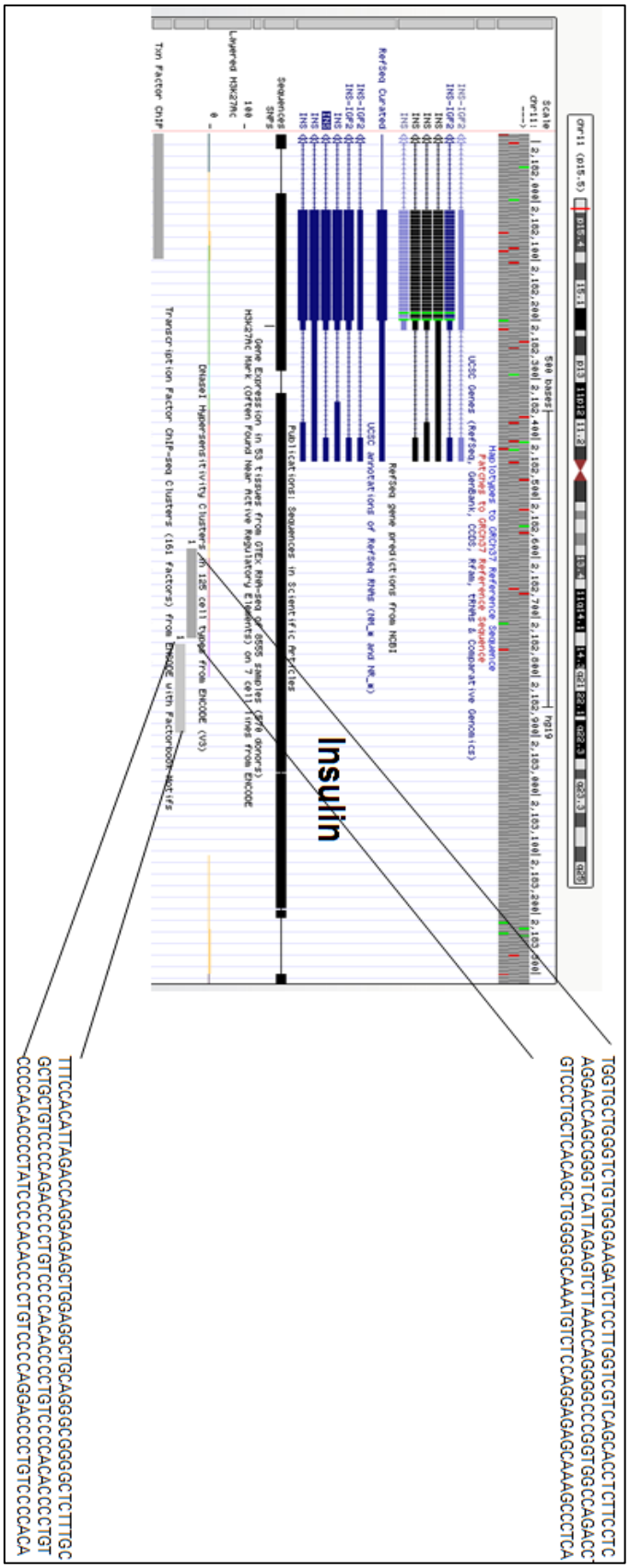
GCTCCCGGTGCCCAATCCCGGGCGCAGCCATGAACGGCGAGGAGCAGTA

2 B



2 C


Insulin
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AGGACCAGCGGGTCATTAGAGTCTTAACCAGGGGCCCGGTGGCCAGACC
GTCCCTGCTCACAGCTGGGGGCAAATGTCTCCAGGAGAGCAAAGCCCTCA
TTTCCACATTAGACCAGGAGAGCTGGAGGCTGCAGGGCGGGGCTCTTTGC
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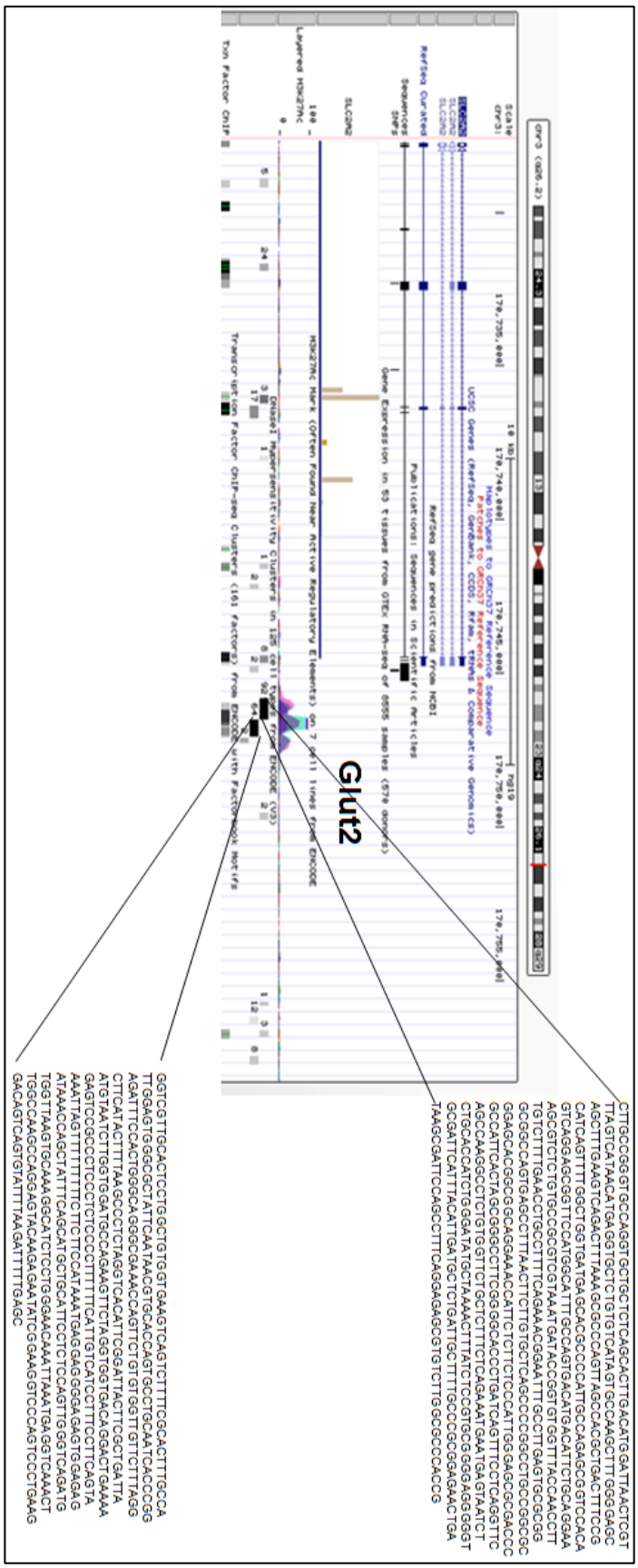
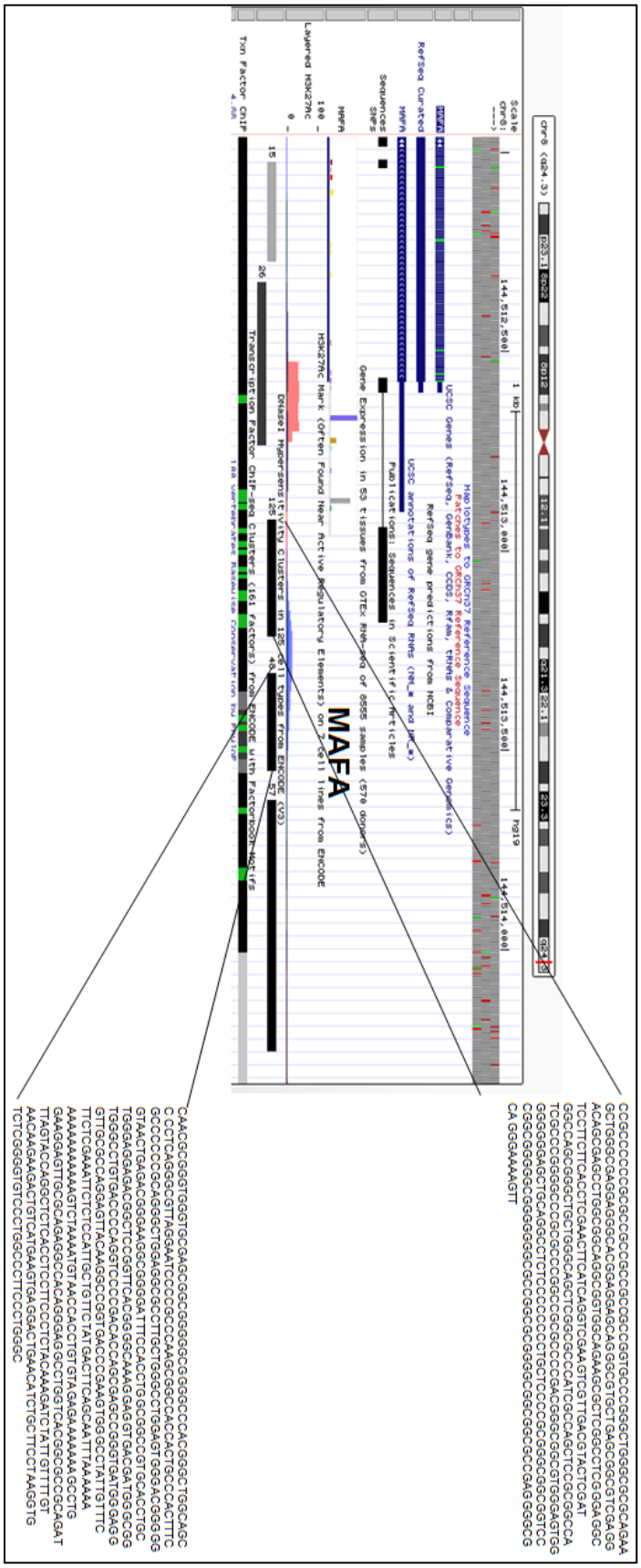
2 D

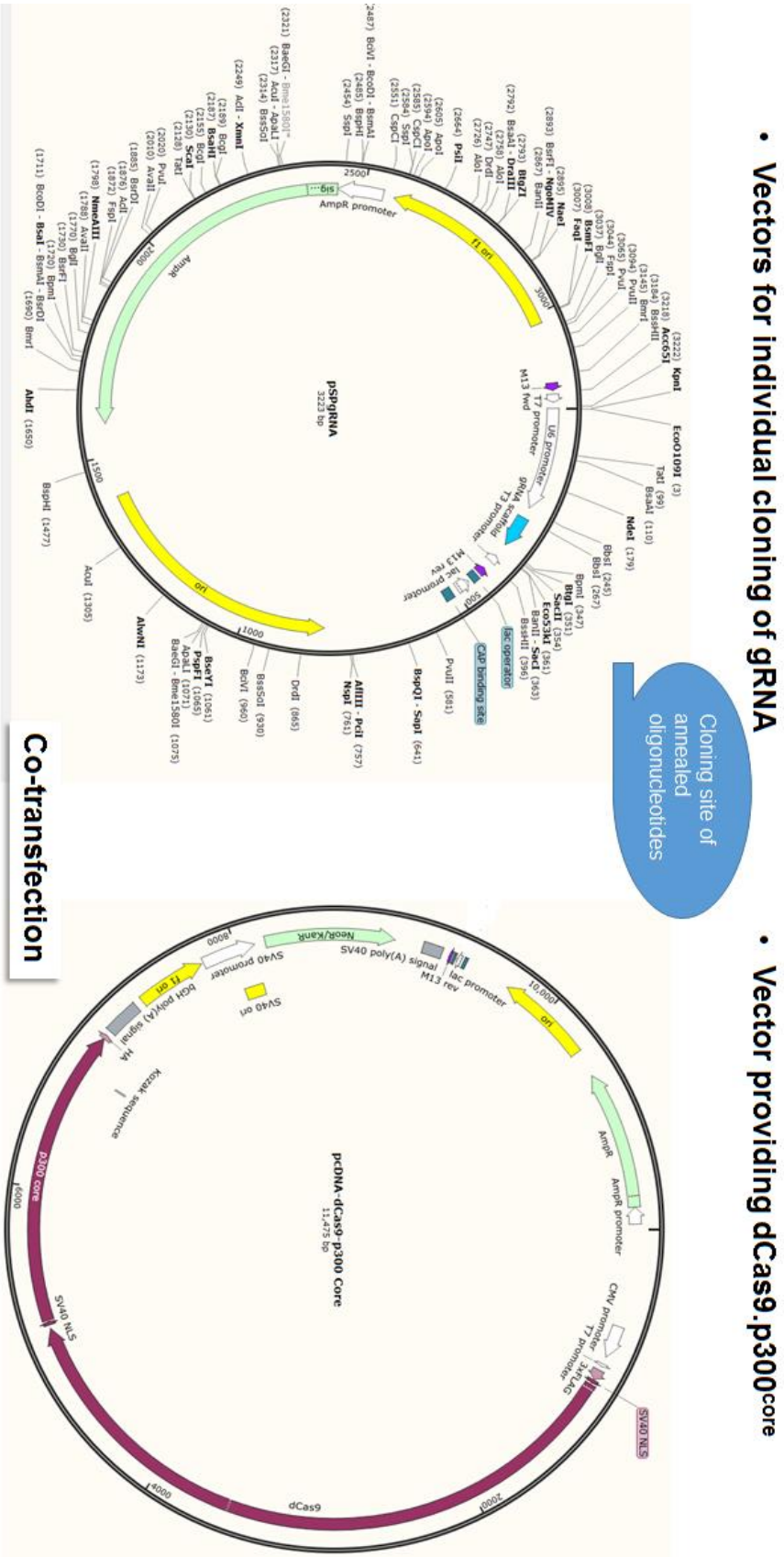


2 E



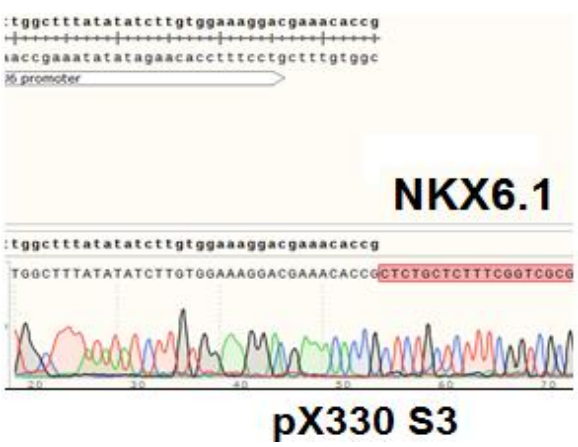
Supplementary Fig. 2: Mapping of DNase 1 hypersensitive region 5' to transcription start site (TSS) of β-cells genes using UCSC genome browser. DNA sequence extraction at (**A**) PDX1, (**B**) NKX6.1, (**C**) Insulin, (**D**) Glut2, (**E**) MAFA genes for designing of gRNAs. Source: https://genome.ucsc.edu/cgi-bin/hgGateway?hgsid=782633553_HLISFvwgjA1juVNq9lmKBHMn9gx3. Number given along with DNase I hypersensitive site indicate the number of cell line showing this DNase I hypersensitive site.

A



B

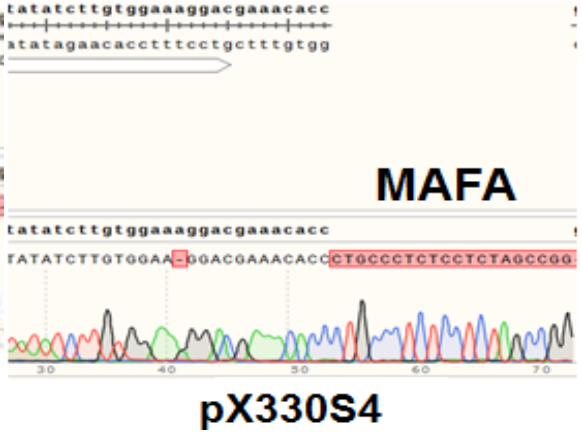
Supplementary Fig. 3: Snap gene generated maps of (**A**) pSPgRNA vector (Addgene # 47108) with restriction sites (**B**) pcDNA-dCas9.P300^{core} **(**Addgene # 61357**).** Individual annealed oligonucleotides of each gene were cloned separately in Bbs I site of pSPgRNA vector. All the oligonucleotides (obtained from IDT) were dissolved in nuclease free water to get 100 uM concentration. ~1ul of both 100 uM of forward and reverse oligonucleotides were mixed in 1ul of 10x polynucleotide kinase (PNK) buffer (NEB), 1 ul PNK (NEB) and 4ul nuclease free water. This mixture was kept in thermal cycler with following temperature cycle: 95◦ C for 5 min, slow cooling till 25◦ C by reducing 1 C per cycle. Cloning was done as per instructed in step1; Multiplex CRISPR/Cas9 Assembly System Kit protocol (Addgene #). Cut Smart Buffer and Bsb I was obtained from NEB. Each vector containing oligonucleotide sequence was co-transfected in lung endothelial cells along with pc-gRNA-dCads9.p300 (Addgene # 61357). These cells were in culture over a period of 14 days and then RNA was isolated by Rneasy mini kit and SYBR green based qRT-PCR was done to test the best guide



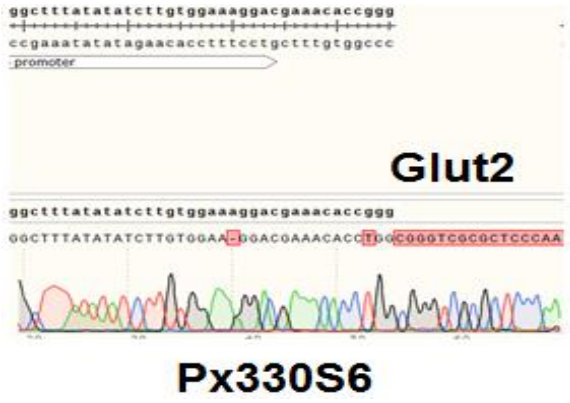
A

B

C

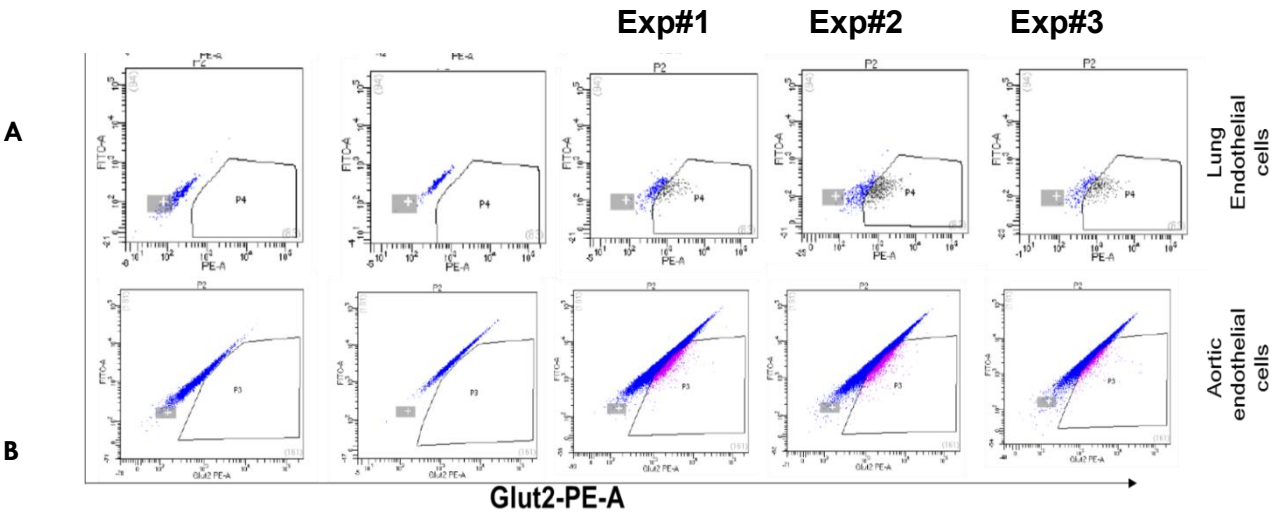


D

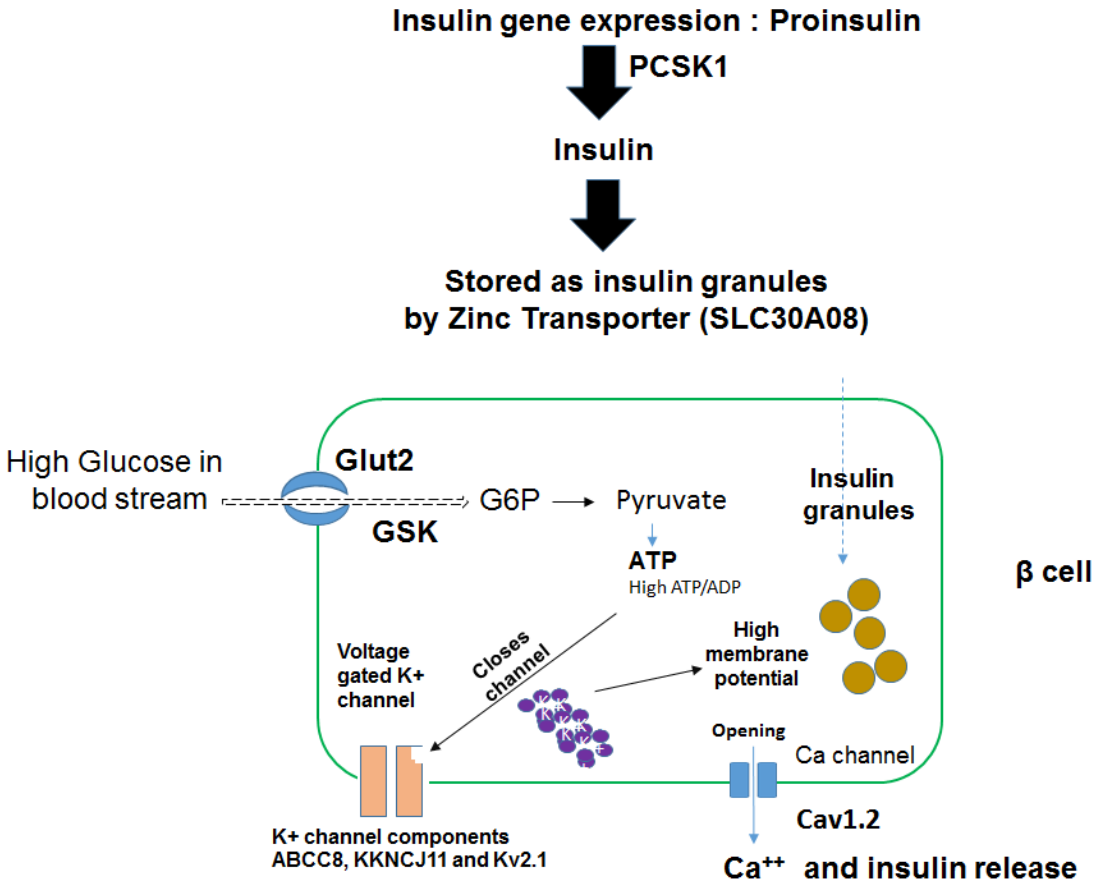


E

Supplementary Fig. 4: Cloning of annealed oligonucleotide showed comparatively better expression in donor vectors. (**A**) PDX1 (gRNA2) in pX330S2, (**B**) NKX6.1 (gRNA3) in px330S3, (**C**) MAFA (gRNA3) in pX330S4, (**D**) Insulin (gRNA3) in pX330S5, (**E**) Glut2 (gRNA3) in pX330S6. All the sequencing data was analyzed in Snapgene.



Supplementary
Fig. 5: Sorting of various Glut2⁺ cells upon transfection with multiplex epigenetic vector in 14 days. Three experiments were performed per cells, Exp#1, Exp#2, and Exp #3. ~1x 10^6 cells per transfection were taken into consideration. Gate P3 in (a) and Gate P4 in (**B**) and (**C**) depicts the Glut2⁺ cells.



Supplementary Fig. 6: Schematics of genes involved in insulin secretion. The concerted actions of PDX1, NKX6.1, MAFA, NKX2-2, NEUROG1 orchestrates the glucose responsive (Glut2⁺) β cells in the pancreas to produce insulin[1-10]. Under the effect of these transcriptional factors, insulin gene transcribes and translates into pro-insulin. PCSK1 converts pro-insulin into mature insulin molecules[11]. SLC30A8 – is Zinc transporter 8 protein, mainly expressed in pancreatic islet cells and mediates zinc (Zn^{2+}) uptake into secretory granules for the storage of insulin molecules[12]. The glucose independent transporter molecule SLC2A2 (also known as GLUT2) transports glucose inside beta cells[13], which is immediately phosphorylated in glucose 6 phosphate (G6P) by glucokinase (GCK)[14,15]. This reaction is called glycolysis- results in the 1) synthesis of 2 ATP molecules, 2) and results in increased ATP/ADP ratio inside the beta cells[13]. ATP molecule binding with ATP-sensitive K+ (K_{ATP}) channels in the beta cell membrane triggers the K+ channel closure. Increase in intracellular K+ ions leads to generation of bursts of action potentials and exocytosis of insulin granules via opening of voltage gated [Ca^{2+}] channels. ABCC8, KKNCJ11 and Kv2.1 are the key components of K_{ATP} channels[14-18].

Supplementary Table 1: List of oligonucleotides DNase I hypersensitive region targeting 5' to exon 1

	Location	+/- strand	DNase I hypersensitive site score	Chromosomal location of DNase hypersensitive site
PDX1				
gRNA 1	-276 to – 298 bp	+	62	chr13:28493746-28494295
gRNA2	-521 to – 543 bp	-	62	
NKX6.1				
gRNA1	-107 to -129 bp	+	77	chr4:85419146-85420215
gRNA2	-492 to - 514 bp	-	77	
gRNA3	-755 to -777 bp	+	77	
gRNA4	-349 to -371 bp	-	95	chr4:85420226-85420775
Glut2				
gRNA1	-127 to - 149 bp	-	92	chr3:170745821-170746515
gRNA2	-433 to - 455 bp	-	92	
gRNA3	-432 to - 454 bp	-	92	
gRNA4	-1 to - 23 bp	+	64	chr3:170746526-170747055
Insulin				
gRNA1	-9 to - 31bp	+	1	chr11:2184006-2184155
gRNA2	-98 to - 120 bp	-	1	
gRNA3	-96 to - 118 bp	+	1	
gRNA4	-93 to – 115 bp	-	1	
MAFA				
gRNA1	-4 to -26 bp	-	125	chr8:144512921-144513215
gRNA2	-170 to - 192 bp	+	125	
gRNA3	-90 to - 112 bp	+	57	chr8:144513626-144514255
gRNA4	-204 to - 226	+	57	

DNase I hypersensitive site score = number of cell types showed this site as a DNA hypersensitive site. 1(a) and 1(b): these two sites are only reported in pancreas.

Supplementary Table 2: List of primers for qRT-PCR primers

Gene	Forward Primer (5' to 3')	Reverse Primer (5' to 3')	Accession Number	Specificity
PDX1	CCCATGGATGAAGTCTACCAAAGC	AAGTTCAACATGACAGCCAGCT	NM_000209.4	β-cells
NKX6.1	ACACGAGACCCACTTTTTCCGGA	CTTCTTCCTCCACTTGGTCCGG	NM_006168.2	β-cells
MAFA	CTTCAGCAAGGAGGAGGTCATCC	TCTCCTTGTACAGGTCCCGCT	NM_201589.4	β-cells
Insulin	AGCCTTTGTGAACCAACACCTG	CACGCTTCTGCAGGGACC	NM_001185098.1	β-cells
Glut2	GCTACCGACAGCCTATTCTAGTGG	TCGCCCTGCCTTCTCCACA	AH002747.2	β-cells
CHGA	CTCTGAACACAGGCAGCTTTCT	ATGTTACAGTCAGGAGTTCTCAGCTTTC	NM_001275.4	β-cells
NeuroD1	TTGCACCAGCCCTTCCTTTGATG	TCGCTGCAGGATAGTGCATGGTAA	AK313799.1	β-cells
NKX2-2	TGAACTCTACGCCGTGTTTACAGAATG	GACATTAACGCTGGGACGGTTT	NM_002509.4	β-cells
ABCC8	ACCACAGCACATGGCTTCATTTC	TGTACAGGTGCAGATGGTGGGATT	NM_001287174.2	β-cells
NEUROG3	TAAGAGCGAGTTGGCACTGAGCAA	TTTGAGTCAGCGCCCAGATGTAGT	NM_020999.4	β-cells
SLC30A8	ACAGCCAAGTGGTTCGGAGAGAAA	TTGGGAAACTGACGGTGTGACTGA	NM_173851.3	β-cells
KCNJ11	GCGCTTTGTGCCCATTGTA	TTGATGGTGTTGCCAAACTTG	NM_000525.3	β-cells
PCSK1	AGCTGGACCTTCATGTGATACC	GCTAGCCTCTGGATCATAGTTGG	NM_000439.5	β-cells
GAD65	TTCCTCCAAGCTTGCGTACT	ACCATGCGGAAGAAATTGAC	NM_000818.2	β-cells
CACNA1D	GGTGATCCCCTTCCCCATTC	ATAGTTTGCCTCGTTCGCGT	NM_001128840.3	β-cells
Kv2.2	AGGGCAGTGTGGGCTCTTC	ATGGTAAATGTCTTGCCTACAGTTGT	NM_004770.2	β-cells
GCK	CTTCCCTCAGTTTTTCGGTGG	TTGATTCCAGCGAGAAAGGTG	NM_001354800.1	β-cells
GCG	AGGCAGACCCACTCAGTGAT	TCGCCCTGCCTTCTCCACA	NM_002054.5	α-cells
GAPDH	CACCAGGGCTGCTTTTAACTCT	GAGGGATCTCGCTCCTGGAAGA	NM_002046.5	q-RT-PCR control

**Amplicons obtained from all these primers are ≤ 200 bp.*

**PDX1 (pancreatic and duodenal homebox 1), NKX6.1 (NK6 homeobox 1), MAFA (v-maf musculoaponeurotic fibrosarcoma oncogene homolog A), Glut2 (carrier family 2 : facilitated glucose transporter, member 2), CHGA (chromogranin A), NEUROD1(neuronal differentiation 1), NKX2.2 (NK2 homeobox 2), ABCC8 (ATP-binding cassette, sub-family C : CFTR/MRP), NEUROG3 (neurogenin 3), SLA30A8 (solute carrier family 30 : zinc transporter), GCG (glucagon), GAPDH*

(glyceraldehyde-3-phosphate dehydrogenase), KCNJ11 (Potassium Inwardly Rectifying Channel Subfamily J Member 11), PCSK1 (Proprotein Convertase Subtilisin/Kexin Type 1), GAD65 (glutamic acid decarboxylase), *CACNA1D encodes Cav1.3 (voltage-gated calcium channel), Kv2.2 (Voltage-gated potassium channels), GCK (Glucokinase), MAFb (v-maf musculoaponeurotic fibrosarcoma oncogene homolog b), GCG (glucagon).*

Supplementary Table 3: List of primers for PCR

Name of gene	Forward primer (5' to 3')	Reverse Primer (5' to 3')	Purpose
P300 with 50p overlap	TCACCGGCCTGTACGAGACACGG ATCGACCTGTCTCAGCTGGGAGG CGACCCAATTGCCGGATCCAAGG CTAGCC	CTGGCAACTAGAAGGCACAGTCGAGG CTGATCAGCGAGCTCTAGGAATTCTCAA GAAGCGTAGTCCGGAACGTCGTAC	For amplification of P300
Left junction primers	ATCTGGGAGCCCCTGCCG	AGCTGAGGGTCCACAGGTTGACG	For orientation of P300 at left side
Right junction primer	GTCGGGATGCGTTTCTCACGCTGG	ATTCTCTTCCCAATCCTCCCCCTTGCTG	For orientation of P300 at right side
U6 F	---------- ---	CTAGAGCCATTTGTCTGCAGAATT	To confirm oligonucleotide insertion
CRISPR-step2	GCCTTTTGCTGGCCTTTTGCTC	CGGGCCATTTACCGTAAGTTATGTAACG	Multiplex assembly

**Underlined nucleotides indicating the 50 bp overlap with pX330A 1x6 dCas9 vector*

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