SUPPLEMENTARY METHODS

1. Polymer synthesis.

The polymers were synthesized in the BioADD facility at Stanford University. The sequences of polymers were as follows: (i) **PEI-Arg;** (ii) **PEI-His;** (iii) **GHK-PEI;** (iv) **(t-Boc)2-GHK-PEI;** (v) **L-Carnosine-PEI;** (vi) **t-Boc-Carnosine-PEI;** (vii) **Beta-Ala-His-GHK-PEI**, which is a combined peptide of L-Carnosine and GHK; and (viii) **t-Boc-TAT-PEI**, whereby TAT (GRKKRRQRRRPQK) is a cell permeable peptide. All Fmoc protected natural amino acids, Fmoc resins, HCTU, 20% piperidine in DMF, and 0.4 M *N*-methylmorpholine (NMM) in DMF were purchased from Anaspec (Fremont, CA). Solvents were purchased from VWR (West Chester, PA) and used without further purification. Anisole, ethanedithiol (EDT) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were purchased from Sigma-Aldrich (St. Louis, MO) and trifluoroacetic acid (TFA) was purchased from Spectrum (Gardena, CA). Synthesis was carried out on a *Prelude* peptide synthesizer at 100 μmol scale using five-fold excess of Fmoc-amino acids (500 mM) relative to the Fmoc- resin (0.47 mmol/g). Deprotection was performed using 20% piperidine/DMF. Coupling was performed using 1:1:2 amino acid:HCTU:NMM in DMF.

Crude peptide (1.0 mmol) was dissolved in milli Q water (6.8 mL) and NaOH (240 mg, 6.0 mmol) and *tert*-butyl phenyl carbonate (388 mg, 2.0 mmol) was added to the peptide solution. The reaction mixture was stirred for 3.5 h and was monitored by ninhydrin test. First, the mixture was acidified using saturated ammonium chloride solution until pH = 6 followed by addition of HCl (5 mL, 1.0 M) until a pH of 3 was attained. The mixture was divided into two equal volume solutions, and they were lyophilized overnight to obtain a white solid. The above solids were dissolved in DMF (7.0 mL each). To this solution, N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide (145 mg, 0.75 mmol), N-hydroxysuccinimide (87 mg, 0.75 mmol), and

disopropylethylamine (0.14 mL, 0.75 mmol) were added. The reaction mixture was stirred for 10 min, and polyethyleneimine (200 mg, 8 mmol) was added, followed by borate buffer (5.0 mL, 77 mM, pH = 8.4). This reaction mix was subjected to overnight stirring and was purified by dialysis with MES buffer (50 mM, pH = 6). The aqueous solution so obtained was lyophilized to obtain a pale yellow solid.

2. Proton NMR.

Peptide-PEI sample (5 mg) was dissolved in 0.75 mL of DMSO-d6 (from Acros Organic, 0.75 mL ampules, 99.9 atom % D), and protons ratio in the sample was analyzed using 400 MHz NMR spectrometer by Varian Mercury.

3. Atomic Force Microscopy (AFM).

AFM (Multimode, Veeco Metrology) topography images were acquired in the light tapping mode regime with scan rates of 1Hz. Samples for AFM analysis being prepared as follows: Glass substrates were cleaned with piranha solution and rinsed with water. Next, 20 µl of each solution were dispensed onto the glass substrates. The samples were then rinsed with deionized water, dried under light N_2 gas flow, and then imaged. Two different samples of each type were analyzed, with a representative image displayed.

2.6. Isolation of fibroblasts from human skin.

Punch biopsies of 4-6 mm in diameter were obtained from the skin of a healthy adult volunteer. Skin samples were collected in Hanks' Balanced Salt Solution (HBSS; Gibco) and rinsed three times in Dulbecco's Phosphate buffered saline (DPBS; Gibco) containing antibiotics: penicillin

(100 IU/ml), streptomycin (100 µg/ml) and amphotericin B (0.25 µg/ml). The biopsy was subjected to enzymatic digestion with 0.25% trypsin for 30 min at room temperature (RT). Dermis was then separated from the epidermis using sterile forceps and cut into small pieces. To these pieces, 10 ml of dissociation solution was added, comprising of collagenase I and hyaluronidase in RPMI medium (Gibco). The pieces were incubated at RT for 3 hours. Following this, the suspension was mechanically dissociated by pipetting multiple times and the slurry was filtered through a 70 µm strainer to remove the tissue fragments. The cell suspension was centrifuged at 400 g for 10 min and the cell pellet so obtained was seeded in a 10 cm culture dish in DMEM supplemented with 10% serum (Gibco). Media was replaced 24 hours later to remove the non adherent cells.

2.7. Isolation of cardiac progenitor cells (CPCs) from heart samples.

The source of cardiac tissue was from a human fetal heart provided by Advanced Bioscience Research (Alameda, CA). The tissue was thoroughly washed with PBS containing antibiotics (as described for fibroblast isolation), cut into small pieces, and subjected to digestion with 1 mg/ml collagenase A (Sigma) at 37^{o}C for 2 hours. This was followed by pipetting the suspension multiple times to release the cells, and the slurry was filtered through a 70 µm strainer to remove the tissue debris. After multiple washes of the strainer with cold PBS buffer, the cell suspension was centrifuged at 300g for 5 mins at RT. The pellet was resuspended in the growth media at a cell density of 5 cells/ml. 100 µl of cell suspension was seeded per well of a 96-well plate coated with 0.1% gelatin. The cells were passaged using 0.25% trypsin on reaching 80% confluency and allowed to expand.

2.8. Isolation of adipose stromal cells (ASCs) from liposuction.

Adipose stromal cells (ASCs) were isolated from an adult patient undergoing lipoaspiration. The cell pellet was given multiple washes with antibiotic-containing PBS and then seeded in Dulbecco's modified Eagle's Medium (DMEM) with 10% FBS, Glutamax-I, 4.5 g/L glucose, 110 mg/L sodium pyruvate, 50 U/ml penicillin, and 50 μg/ml streptomycin. These cells were maintained at 37^{o}C in a humidified incubator maintained at 5% CO_2. Media was changed every two days.

SUPPLEMENTAL FIGURE & TABLE LEGEND

Supplementary Fig. 1. Representative proton NMR spectra of peptide-PEI recorded in DMSO-d_6. Spectra for the polymers, namely **(A)** GHK-PEI, **(B)** L-Carnosine, **(C)** TAT-PEI, and **(D)** β-Ala-His-GHK-PEI have been shown with the Boc-containing polymers on the left panel and de-proteceted polymers on the right panel. Protons from Boc protecting group are singlet at ~1.35 ppm. The Boc group has been shown as an insert for each polymer. This group was not observed after deprotection. Protons from PEI are multiplet at ~ 2.49 ppm (DMSO impurity, if present, is a singlet at 2.54 ppm).

Supplementary Fig. 2. Atomic force microscopic (AFM) images of polymer alone **(A and C)** and polymer-DNA complex **(B and D)**. Left panel represents the topography image and right panel is the corresponding phase image. All images are 2x2 μm resolution. At far right is a cross section image of the topography scan. In Boc-2-GHK-PEI and L-Carnosine-PEI, fibril like structures can be observed. In L-Carnosine-PEI DNA, a nearly complete film is observed as opposed to aggregate particles.

Supplementary Fig. 3. Phase contrast microscopic image of **(A)** ASCs **(B)** dermal fibroblasts and **(C)** cardiac progenitor cells, 48 hours post transfection with the peptide-PEI hybrid polymers.

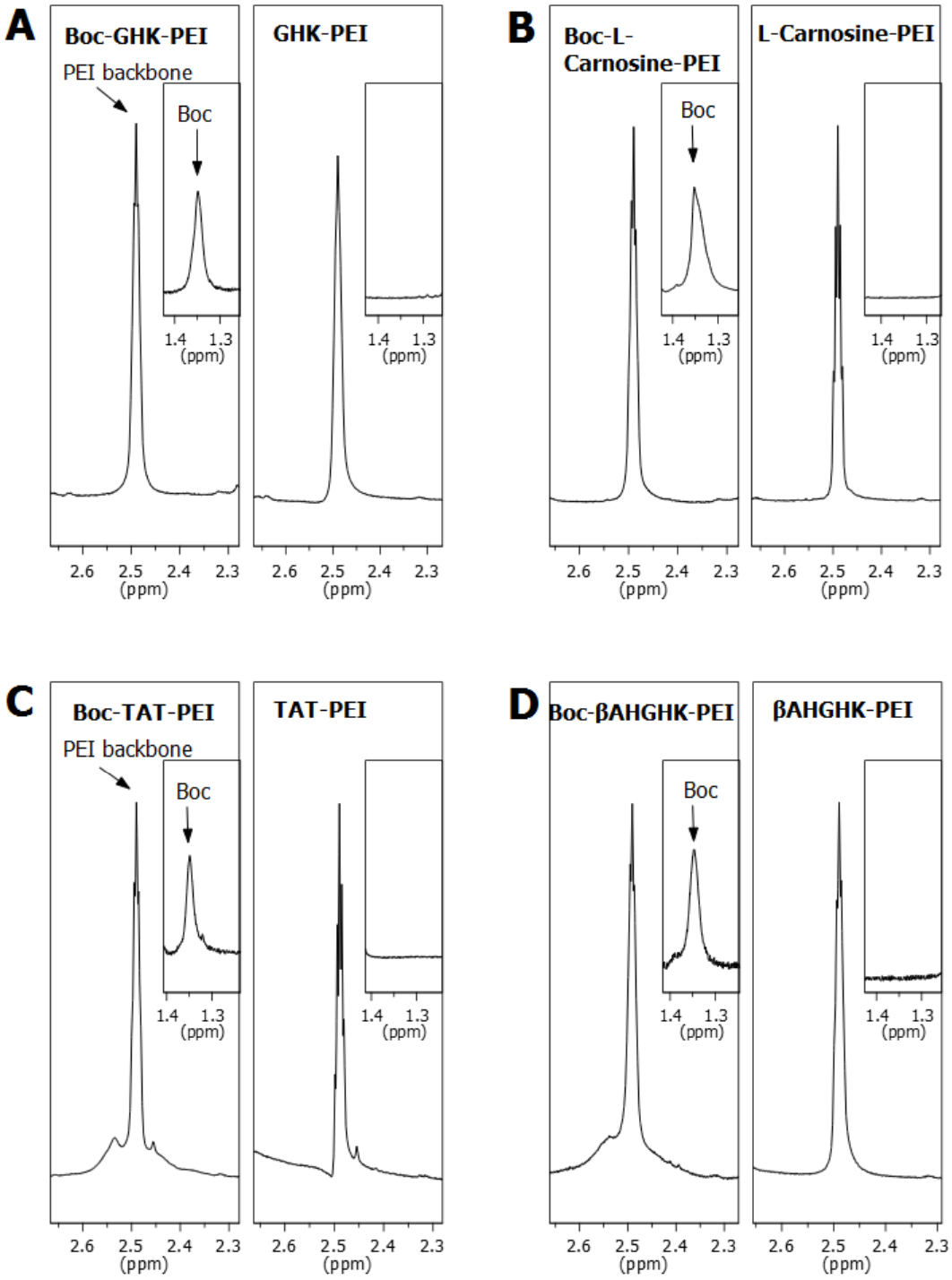
Supplementary Fig. 4. Validation of the superior transfection efficiency of Carnosine-based polymers on two cell types using a GFP-encoding vector, pMAX-GFP. Phase contrast microscopic image of **(A)** ASCs and **(D)** CPCs 24 hours post transfection with L-Carnosine and

Boc-L-Carnosine. Blank is the negative control. Lipofectamine is the positive control. Transfection efficiency was assessed by flow cytomtery based quantification of the GFP signal in **(B)** ASCs and **(E)** CPCs (* $p<0.05$; ** $p<0.005$; *** $p<0.0005$). Cell death was assessed by trypan blue staining and represented as % cell survival in **(C)** ASCs and **(F)** CPCs. Error bars represent triplicates with standard deviation.

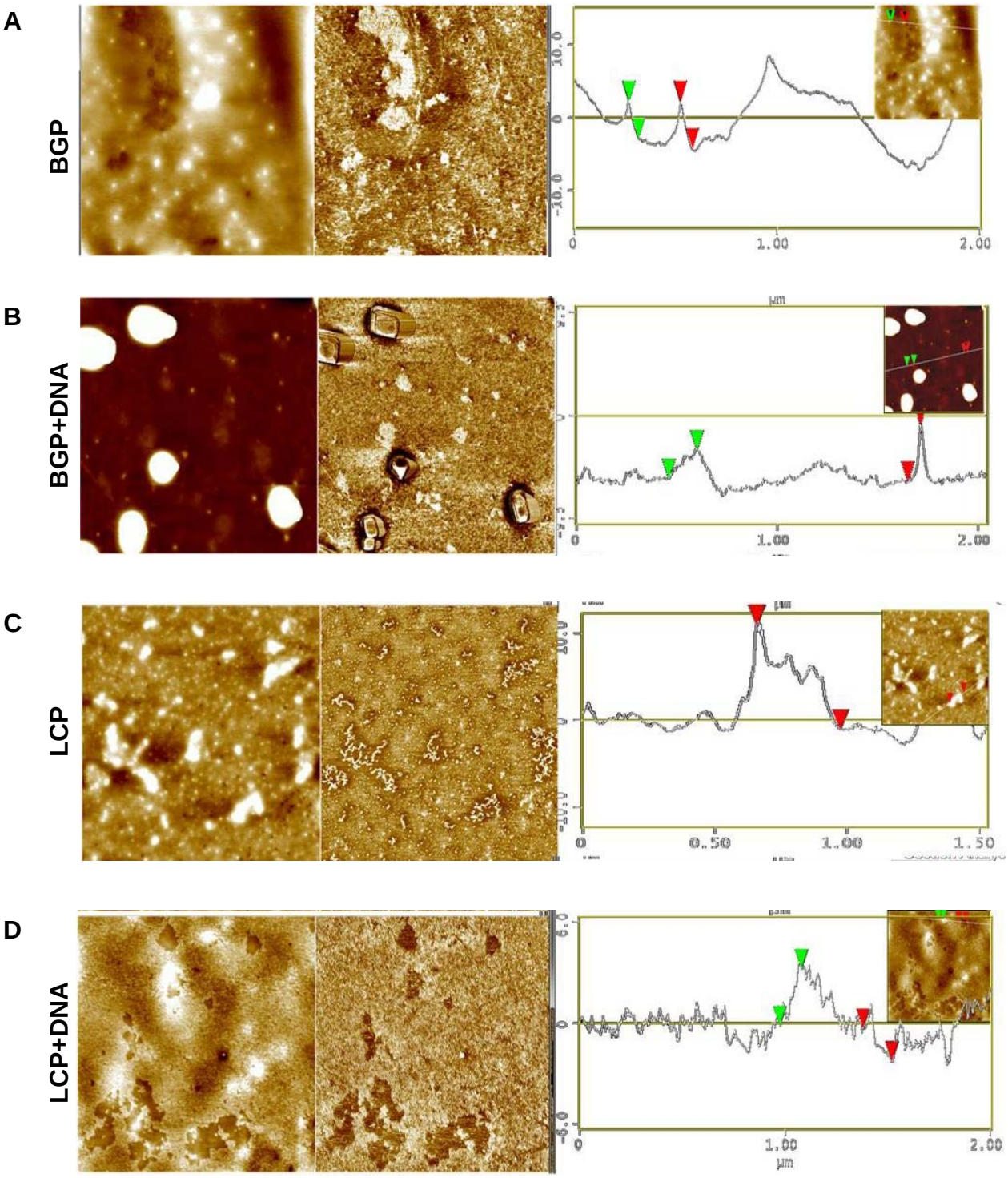
Supplementary Fig. 5. Validation of the transfection efficiency of L-Carnosine and Boc-L-Carnosine on the human cervical cancer cell line (HeLa) using luciferase encoding vector. **(A)** Phase contrast microscopic image of HeLa 24 hours post transfection with the selected polymers. **(B)** Transfection efficiency was assessed by quantitative luciferase assay, with the signal intensity normalized to the total protein. **(C)** Cell death was assessed by trypan blue staining and represented as % cell survival. Error bars represent triplicates with standard deviation.

Supplementary Table 1. List of significant pathways and corresponding genes, as determined by Ingenuity Pathway Analysis, which are commonly activated in cardiac progenitor cells transfected with both L-Carnosine-PEI and Boc-L-Carnosine-PEI.

Supplementary Table 2. List of significant pathways and corresponding genes, as determined by Ingenuity Pathway Analysis, which are activated only in L-Carnosine-PEI transfected cardiac progenitor cells.

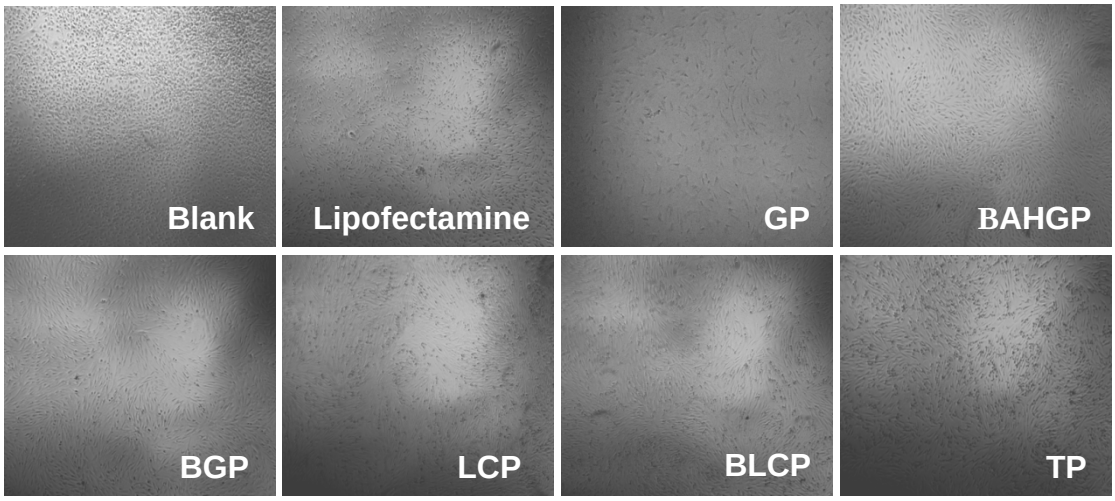


Supplementary Figure 1



Supplementary Figure 2

A



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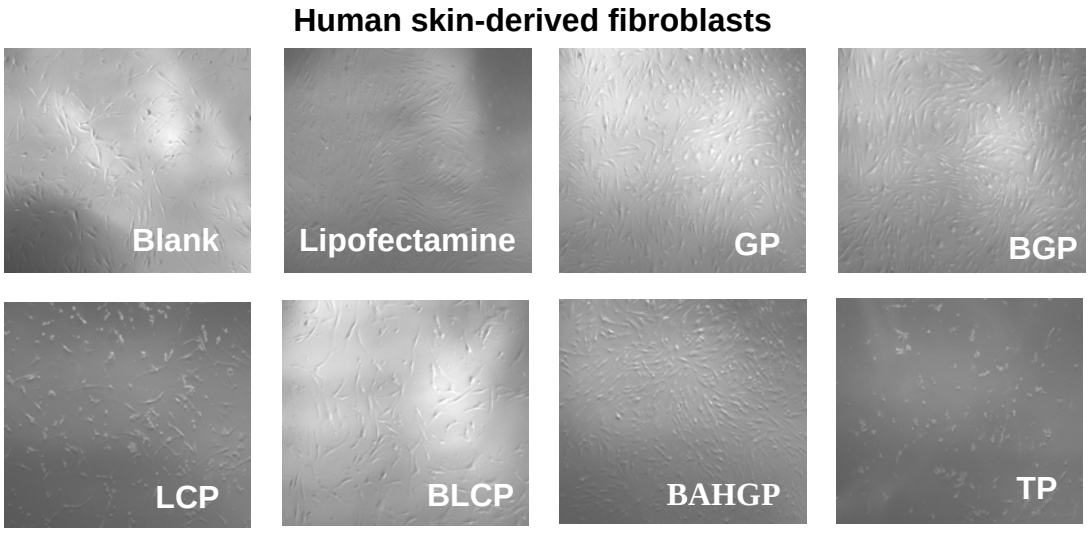

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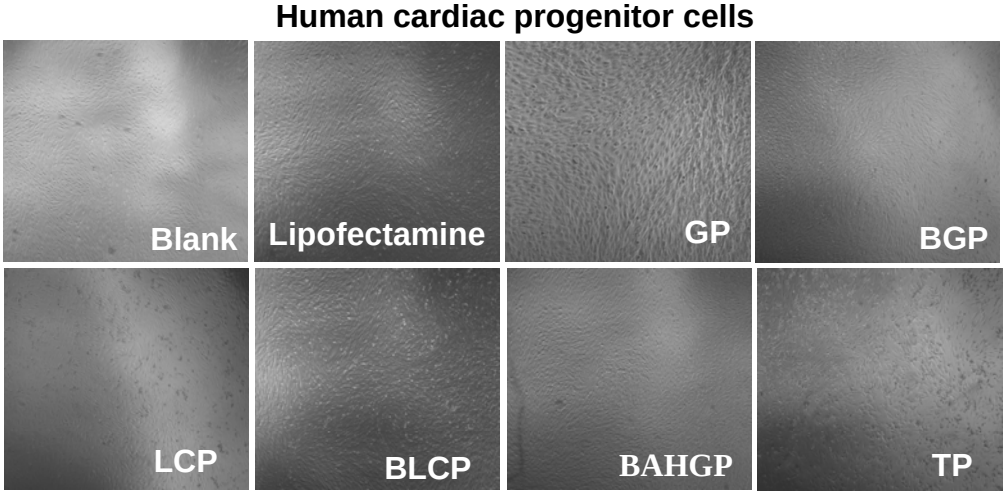
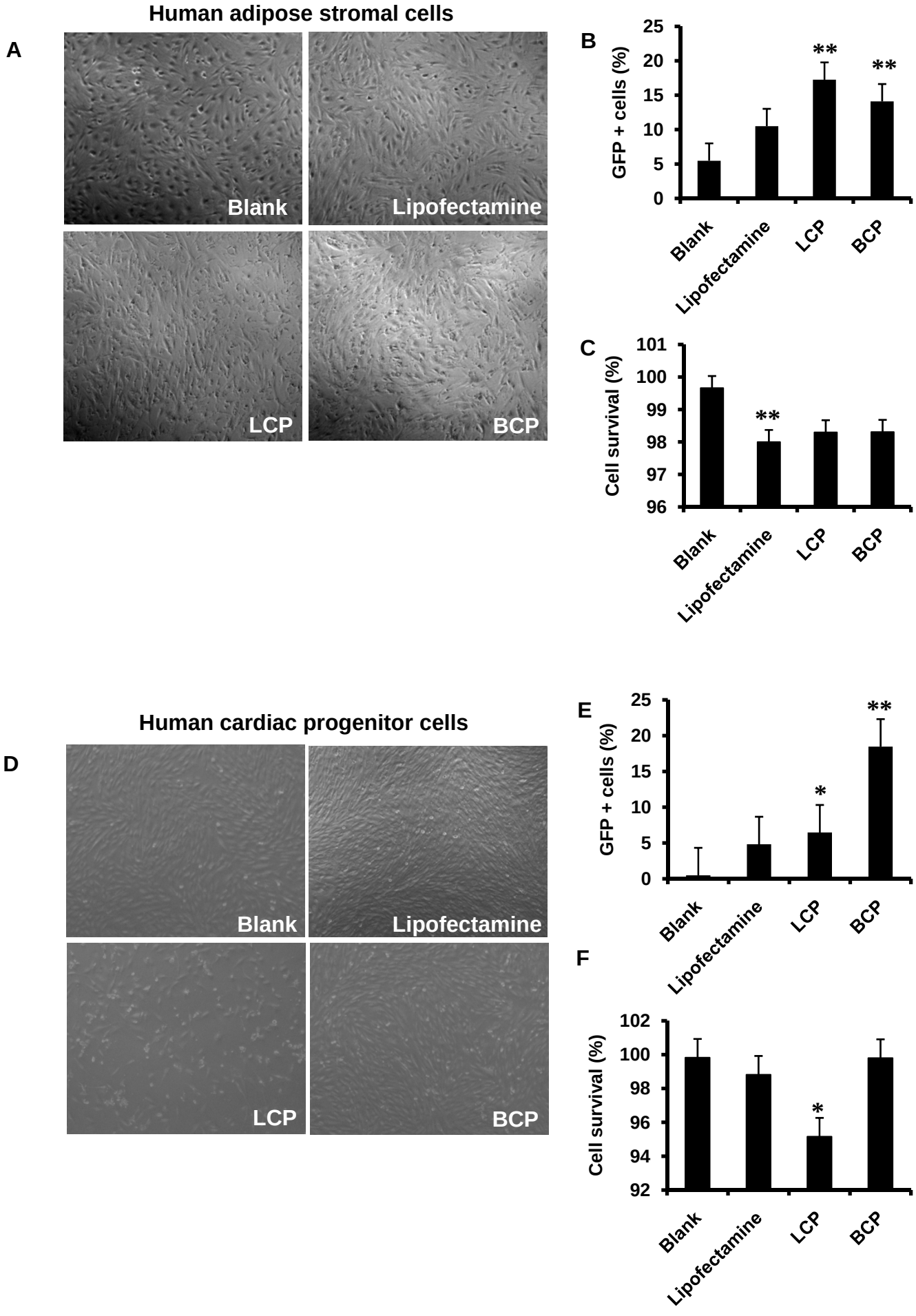
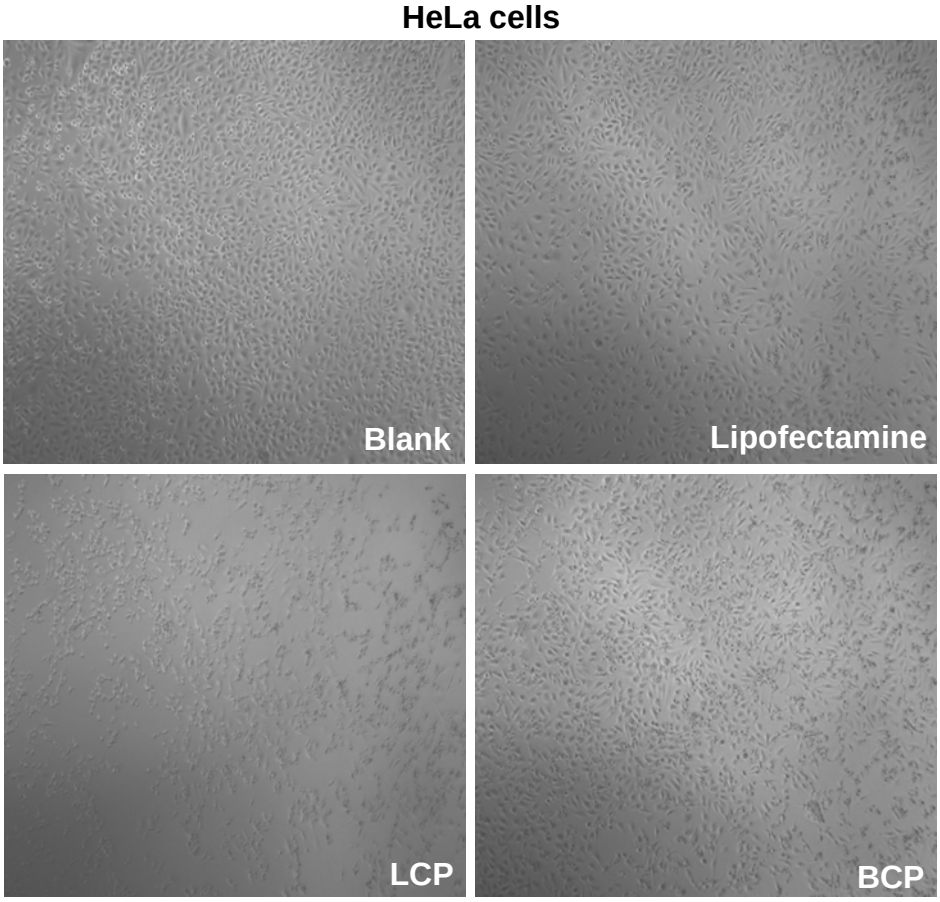


Supplementary Figure 3



Supplementary Figure 4

A



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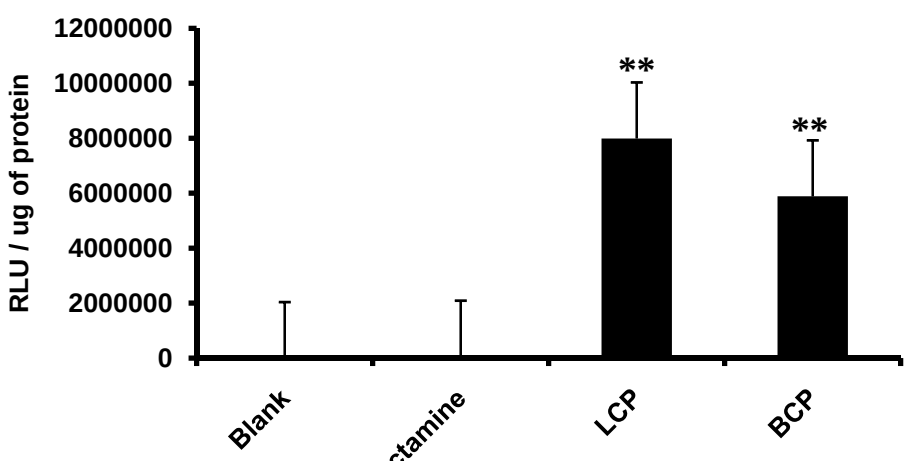

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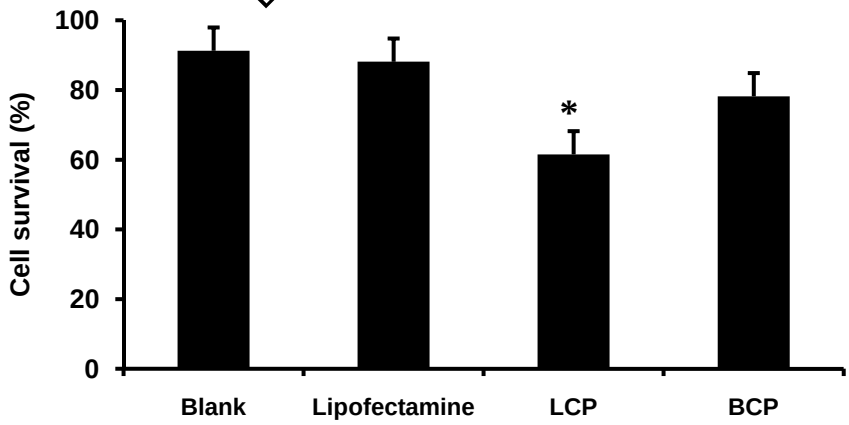

Supplementary Figure 5

Supplementary Table 1. Selected common pathways and genes affected by transfection with L-Carnosine-PEI and Boc-L-Carnosine-PEI.

Pathways	**Genes**
PPAR Signaling	PPARG,FOS,IL1A,NFKBIA,IL1RL1,PDGFRA,IL1B,PTGS2,INSR,NFKB2,PDGFRB
TNFR2 signaling	FOS,NFKBIA,TNFAIP3,NFKB2,BIRC3,TRAF1
Interferon Signaling	IFIT3,IFIT1,OAS1,IFITM1,MX1,IFI35,STAT2,IRF9,PSMB8,STAT1,TAP1,IRF1
NF-κB Signaling	PIK3C2B,IL1A,BMP4,MYD88,RELB,BMP2,TNFAIP3,IRAK3,NFKB2,TLR2,NFKBIA,TLR6,PDGFRA,IL1B,MAP3K8,INSR,EIF2AK2,TLR3,TNFSF13B,PDGFRB
IL-6 Signaling	COL1A1,IL8,FOS,IL1A,NFKBIA,IL1RL1,CD14,IL1B,CEBPB,NFKB2,IL6,TNFAIP6
p38 MAPK Signaling	IL1A,H3F3A,DDIT3,DUSP1,IL1RL1,DUSP10,PLA2G5,TGFB2,IL1B,IRAK3,STAT1,IRAK2
Toll-like Receptor Signaling	TLR2,FOS,NFKBIA,MYD88,TLR6,CD14,NFKB2,IRAK3,EIF2AK2,TLR3,IRAK2

Supplementary Table 2. Selected pathways and genes additionally affected only in L-Carnosine-PEI transfected cells.

Pathways	**Genes**
Hypoxia Signaling in the Cardiovascular System	VEGFA,TP53,JUN,NFKBIA,CSNK1D,CREB5,NFKBIB,UBE2L6,ATM
Growth Hormone Signaling	PIK3C2B,FOS,GHR,PRKCH,JAK2,RPS6KA2,STAT1,PRKCA,ATM
p53 Signaling	TP53,PRKDC,CASP6,PIK3C2B,TP53INP1,JUN,CCND2,CSNK1D,PML,PMAIP1,DRAM1,ATM
ATM Signaling	TP53,JUN,NFKBIA,RAD9A,CREB5,CDK1,CDC25A,ATM
CD40 Signaling	PIK3C2B,FOS,ICAM1,JUN,NFKBIA,TNFAIP3,NFKB2,NFKBIB,NFKB1,ATM,TRAF1
Production of Nitric Oxide and Reactive Oxygen Species in Macrophages	PIK3C2B,MAP3K13,JAK2,NFKB2,NFKB1,IRF1,TLR2,FOS,MAP3K12,NFKBIA,JUN,RND3,NCF2,MAP3K8,PRKCH,NFKBIB,STAT1,ATM,PRKCA
PDGF Signaling	PIK3C2B,FOS,JUN,ABL2,PDGFRA,JAK2,EIF2AK2,STAT1,PDGFRB,PRKCA,ATM
Acute Phase Response Signaling	SERPING1,IL1A,MYD88,C1S,SERPINA3,IL6,NFKB2,CEBPB,JAK2,NFKB1,RBP1,C1R,FOS,JUN,SOD2,NFKBIA,CFB,IL1B,SERPINA1,NFKBIB
DNA Double-Strand Break Repair by Non-Homologous End Joining	PRKDC,DCLRE1C,PARP1,ATM
EGF Signaling	PIK3C2B,FOS,JUN,ITPR2,ITPR3,STAT1,PRKCA,ATM

Supplementary Table 2