**Supplemental Methods – Text S1:**

**Reagents**

All cell culture reagents were purchased from Sigma Aldrich (St. Louis, MO, USA). PLGA was purchased from Lakeshore Biomaterials (Birmingham, AL, USA) as a 50:50 monomer ratio with a molecular weight of 58 kDa and inherent viscosity of 0.43 dl/g.

**Cell culture**

Human pancreatic cancer AsPC-1 and BxPC-3 cells were obtained from the American Type Culture Collection and propagated in Dulbecco’s modified Eagle medium supplemented with 10% fetal bovine serum and 1% penicillin-streptomycin in a humidified chamber at 37°C and 5% CO2.

**Immunohistochemical analysis**

Heat-induced epitope retrieval was performed on 4-μm formalin-fixed, paraffin-embedded sections utilizing a pressurized Decloaking Chamber (Biocare Medical LLC, Concord, CA) in citrate buffer (pH 6.0) at 99°C for 18 minutes. **Brightfield:** Slides were incubated in 3% hydrogen peroxide at room temperature for 10 minutes. After incubation with primary antibody [Nanog and KLF4 (Abcam Inc., Cambridge, MA), c-Myc (Santa Cruz Biotechnologies Inc., Santa Cruz, CA) or Notch-1 (Santa Cruz Biotechnologies)] overnight at 4°C, slides were incubated in Promark peroxidase-conjugated polymer detection system (Biocare Medical LLC) for 30min at room temperature. After washing, slides were devolved with Diaminobenzidine (Sigma–Aldrich). **Fluorescence:** Slides were incubated in a normal serum and BSA blocking step at room temperature for 20 minutes. After incubation with primary antibody [VEGFR1 and VEGFR2 (Santa Cruz Biotechnologies Inc., Santa Cruz, CA)] overnight at 4°C, slides were labeled with Alexa Fluor dye-conjugated secondary antibody and mounted with ProLong Gold (Invitrogen). **Microscopic Examination:** Slides were examined utilizing a Nikon 80i microscope and DXM1200C camera for brightfield analysis. Fluorescent images were taken with PlanFluoro objectives, utilizing CoolSnap ES2 camera (Photometrics). Images were captured utilizing NIS-Elements software (Nikon).

**Real-time Reverse Transcription-Polymerase Chain Reaction analyses**

Total RNA isolated from tumor xenografts and cancer cells was subjected to reverse transcription using Superscript™ II RNase H-Reverse Transcriptase and random hexanucleotide primers (Invitrogen, Carlsbad, CA). The complementary DNA (cDNA) was subsequently used to perform real-time polymerase chain reaction (PCR) by SYBR™ chemistry (SYBR Green I, Molecular Probes, Eugene, OR) for specific transcripts using gene-specific primers and JumpStart™ Taq DNA polymerase (Sigma-Aldrich). The crossing threshold value assessed by real-time PCR was noted for the transcripts and normalized with β-actin messenger RNA (mRNA). The quantitative changes in mRNA were expressed as fold-change relative to control with ± SEM value.

The following primers were used:

-actin: forward: 5'-GGTGATCCACATCTGCTGGAA-3',

reverse: 5'-ATCATTGCTCCTCCTCAGGG-3';

DCLK1: forward: 5'- CAGCAACCAGGAATGTATTGGA -3',

reverse: 5'- ctcaactcggaatcggaagact-3';

c-Myc: forward: 5'-CACACATCAGCACAACTACGCA-3',

reverse: 5'-TTGACCCTCTTGGCAGCAG-3';

Notch-1: forward: 5'-CGGGTCCACCAGTTTGAATG-3',

reverse: 5'-GTTGTATTGGTTCGGCACCAT-3'.

KRAS: forward: 5'- -3',

reverse: 5'-GTTGTATTGGTTCGGCACCAT-3'.

ZEB1: forward: 5'-AAGAATTCACAGTGGAGAGAAGCCA-3',

reverse: 5'-CGTTTCTTGCAGTTTGGGCATT-3';

ZEB2: forward: 5'-AGCCGATCATGGCGGATGGC-3',

reverse: 5'-TTCCTCCTGCTGGGATTGGCTTG-3';

Snail: forward: 5'-AAGGCCTTCTCTAGGCCCT-3',

reverse: 5'-CGCAGGTTGGAGCGGTCAG-3';

Slug: forward: 5'-TGCTTCAAGGACACATTA-3',

reverse: 5'-CAGTGGTATTTCTTTAC-3';

Nanog: forward: 5'-ACCAGAACTGTGTTCTCTTCCACC-3',

reverse: 5'-CCATTGCTATTCTTCGGCCAGTTG-3';

KLF4: forward: 5'-CCAATTACCCATCCTTCCTG-3',

reverse: 5'-CGATCGTCTTCCCCTCTTTG-3';

OCT4: forward: 5'-AAGCGATCAAGCAGCGACTAT-3',

reverse: 5'-GGAAAGGGACCGAGGAGTACA-3';

SOX2: forward: 5'-CGAGATAAACATGGCAATCAAAAT-3',

reverse: 5'-AATTCGCAAGAAGCCTCTCCTT-3';

RREB1: forward: 5'-CTGGCGAGAGGCCTTACAAG-3',

reverse: 5'-CTACGTTTCAGAGGAGATGGA-3';

LIN28B: forward: 5’-GATGTATTTGTACACCAA-3’

reverse: 5’-TACCCGTATTGACTCAAGGCC-5’

**miRNA Analysis**

Total RNA isolated from tumor xenografts and cancer cells was subjected to reverse transcription with Superscript II RNase H-Reverse Transcriptase and random hexanucleotide primers (Invitrogen). The cDNA was subsequently used to perform real-time PCR by SYBR chemistry for *pri-let-7a, pri-miR-144, pri-miR-200a* and *pri-miR-145* transcripts using specific primers and JumpStart Taq DNA polymerase. The crossing threshold value assessed by real-time PCR was noted for *pri-let-7a, pri-miR-144,* and *pri-miR-200a* miRNAs and normalized with *U6* pri-miRNA. The changes in pri-miRNAs were expressed as fold-change relative to control with ± SEM values [1](#_ENREF_1).

The following primers were used:

*pri-U6*: forward: 5'-CTCGCTTCGGCAGCACA-3',

reverse: 5'-AACGCTTCACGAATTTGCGT-3';

*pri-let-7a*: forward: 5'-GAGGTAGTAGGTTGTATAGTTTAGAA-3',

reverse: 5'-AAAGCTAGGAGGCTGTACA-3';

*pri-miR-144*: forward: 5'-GCTGGGATATCATCATATACTG-3',

reverse: 5'-CGGACTAGTACATCATCTATACTG-3';

*pri-miR-200a*: forward: 5'-TTCCACAGCAGCCCCTG-3',

reverse: 5'-GATGTGCCTCGGTGGTGT-3'.

*pri-miR-143/145*: forward: 5'-AGGGCCAGCAGCAGGC-3',

reverse: 5'-TCAGGAAATGTCTCTGGCTGTG-3'.

*pri-miR-145*: forward: 5'-GGATGCAGAAGAGAACTCCA-3',

reverse: 5'-CCTCATCCTGTGAGCCAG-3'.

**Western blot analysis**

Tumor xenograft samples treated with siRNA-NPs were lysed and the concentration of protein was determined by the BCA protein assay kit (Pierce Biotechnology Inc., Rockford, IL). Forty g of the protein was size separated in a 7.5-15% SDS polyacrylamide gel and transferred onto a nitrocellulose membrane with a semidry transfer apparatus (Amersham-Pharmacia, Piscataway, NJ). The membrane was blocked in 5% non-fat dry milk for 1 h and probed overnight with rabbit anti-c-Myc (Cell Signaling Danvers, MA) or rabbit anti-VEGFR1 (Santa Cruz Biotechnologies Inc., Santa Cruz, CA). Actin, used as a loading control was identified using a goat polyclonal IgG (Santa Cruz Biotechnology Inc). Subsequently, the membrane was incubated with anti-rabbit or anti-goat IgG horseradish peroxidase-conjugated antibodies (Amersham-Pharmacia) for 1 h at room temperature. The proteins were detected using ECLTM Western Blotting detection reagents (Amersham-Pharmacia).

**Cell Invasion Assay**

AsPC-1 cells were treated with NPsiSCR or NPsiDCLK1 for 48h and subjected to invasion assay using the BD BioCoatTM Tumor Invasion Assay System (BD Biosciences, Bedford, MA). 5000 cells were seeded with serum-free medium (containing NPsiRNA) into the upper chamber of the system. Bottom wells in the system were filled with growth media containing 10% FBS. After 24 h of incubation, the cells in the upper chamber were removed, and the cells that had invaded through Matrigel matrix membrane was fixed with methanol and stained with 1% toluidine blue and 1% borax for 2 min. This was destained with distilled water and mounted on slide and counted for invading cells (stained blue). 5 fields were counted on each insert (a total of 3 inserts per treatment) at 10X magnification.

**Luciferase reporter gene assay**

AsPC-1 cells were transfected with a plasmid containing the firefly luciferase (*Photinus pyralis*) gene with a complementary *miR-145* and *let-7a* (separate plasmids) binding site at its’ 3’ UTR obtained from Signosis Inc. (Sunnyvale, CA). The cells were also co-transfected with the *Renilla* luciferase expressing plasmid pRL-TK (Promega) as an internal control. Following transfection, the cells were treated with NPs alone, NP-siSCR, or NP-siDCLK1 and subjected to luciferase activity measurement. Luciferase activity was determined as per the manufacturer’s instructions (Dual-Luciferase Reporter Assay System; Promega) using a Biotek Synergy HT multi plate reader (BioTek, Winooski, VT) as described previously [1](#_ENREF_1), [2](#_ENREF_2).

Plasmids containing binding sites for *miR-200a, miR-200b, miR-200c* at the 3’UTR of firefly luciferase gene and plasmids with luciferase gene under the control of VEGFR1 and VEGFR2 3’UTR were obtained from Switchgear genomics (Menlo Park, CA). AsPC-1 cells were transfected with the above said plasmids along with pRL-TK. Following transfection, the cells were treated with NPs, NP-siSCR or NP-siDCLK1 and subjected to luciferase activity measurement (according to manufacturer’s instructions) using Bioteck Synergy HT multi plate reader.

The activity, normalized to *Renilla* luciferase activity, is presented as relative luciferase units relative to control with ± SEM values. Assays were performed in triplicate wells and experiments were repeated three times.

**Statistical analysis**

All experiments were performed in triplicates. Results are reported as average ± SEM unless otherwise indicated. Data were analyzed using the Student’s *t*-test. Results were considered statistically significant when *p* < 0.01.

**References:**

1. Sureban SM, May R, Ramalingam S, et al. Selective blockade of DCAMKL-1 results in tumor growth arrest by a *Let-7a* MicroRNA-dependent mechanism. Gastroenterology 2009;137:649-59, 659 e1-2.

2. Sureban SM, May R, Lightfoot SA, et al. DCAMKL-1 regulates epithelial-mesenchymal transition in human pancreatic cells through a *miR-200a*-dependent mechanism. Cancer Res 2011;71:2328-38.