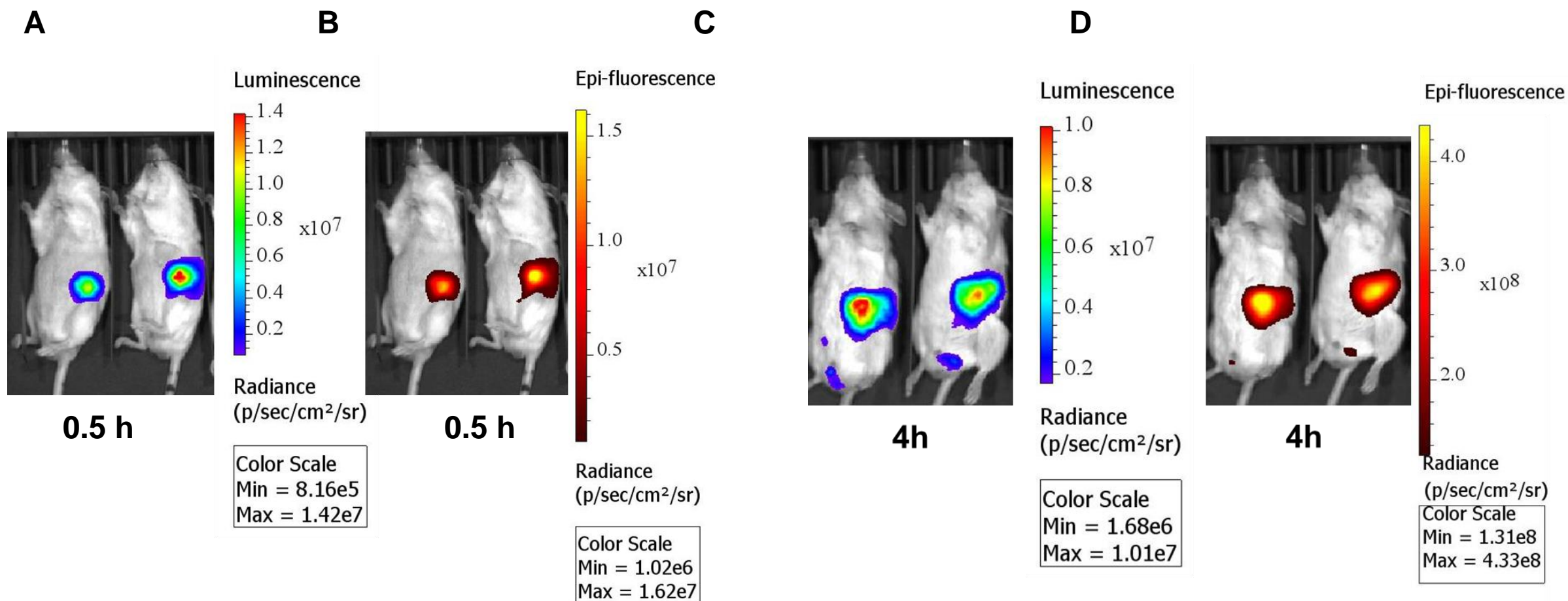
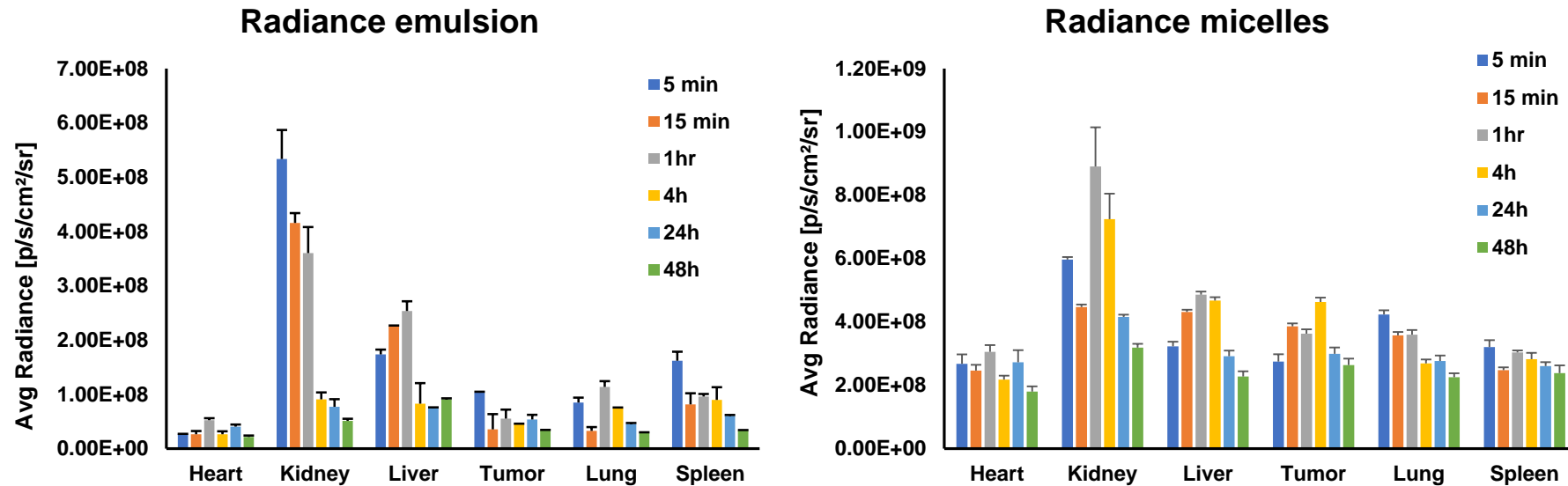


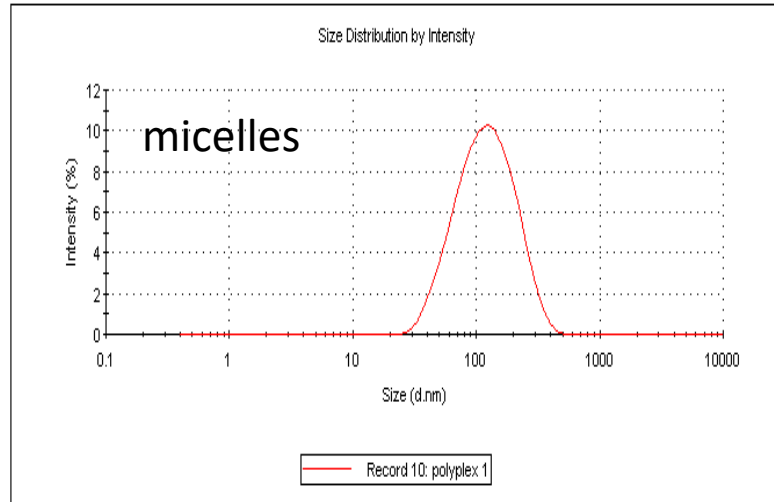
**Figure S1.** Luciferase expression from orthotopic pancreatic tumors after imaging of pancreas in NSG mice. Each mouse received  $\sim 1 \times 10^6$  MIA PaCa-2 cells.



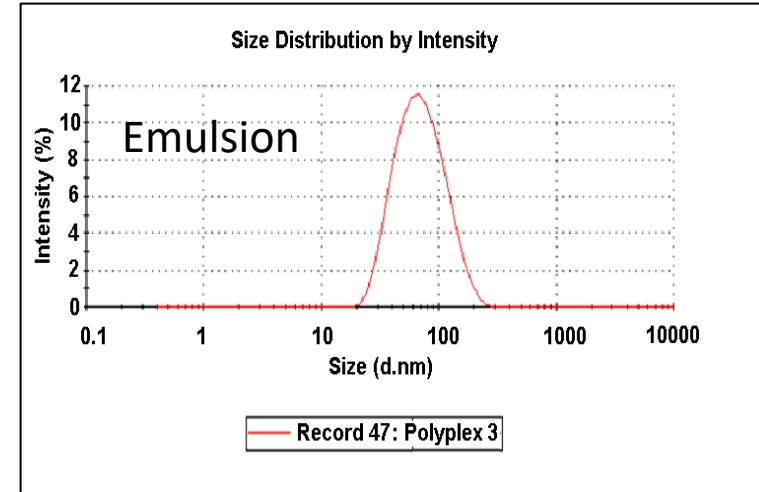
**Figure S2.** After 0.5 h and 4h of injecting micelles carrying GDC-0449 and Cy5.5-let-7b, Epi-fluorescence signal from Cy5.5-let-7 and bioluminescence signal from tumor cells were co-localized at 30 min and 4h post injection.



**Figure S3: Radiance measurement** Values of fluorescence signal for the IVIS images in of dissected organs after 0.08, 0.25, 1, 4, 24 h and 48 h of administration of micelles or micellar formulations.

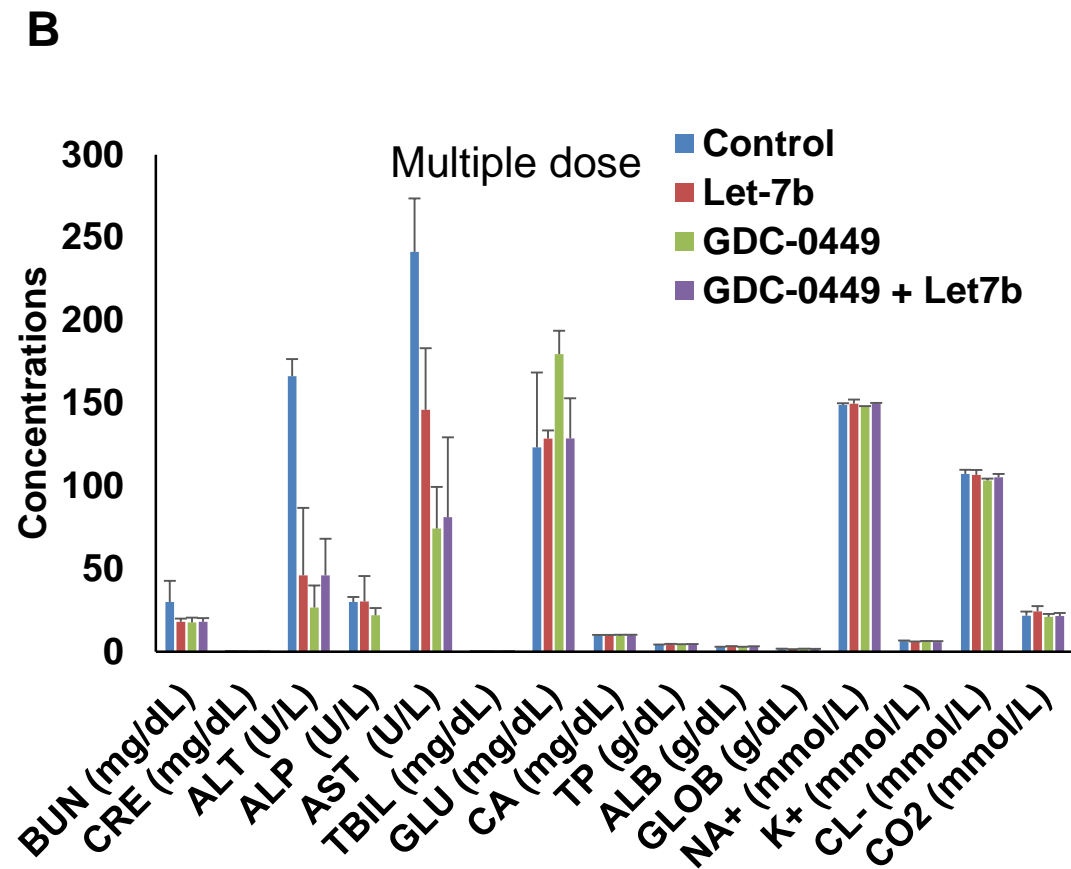
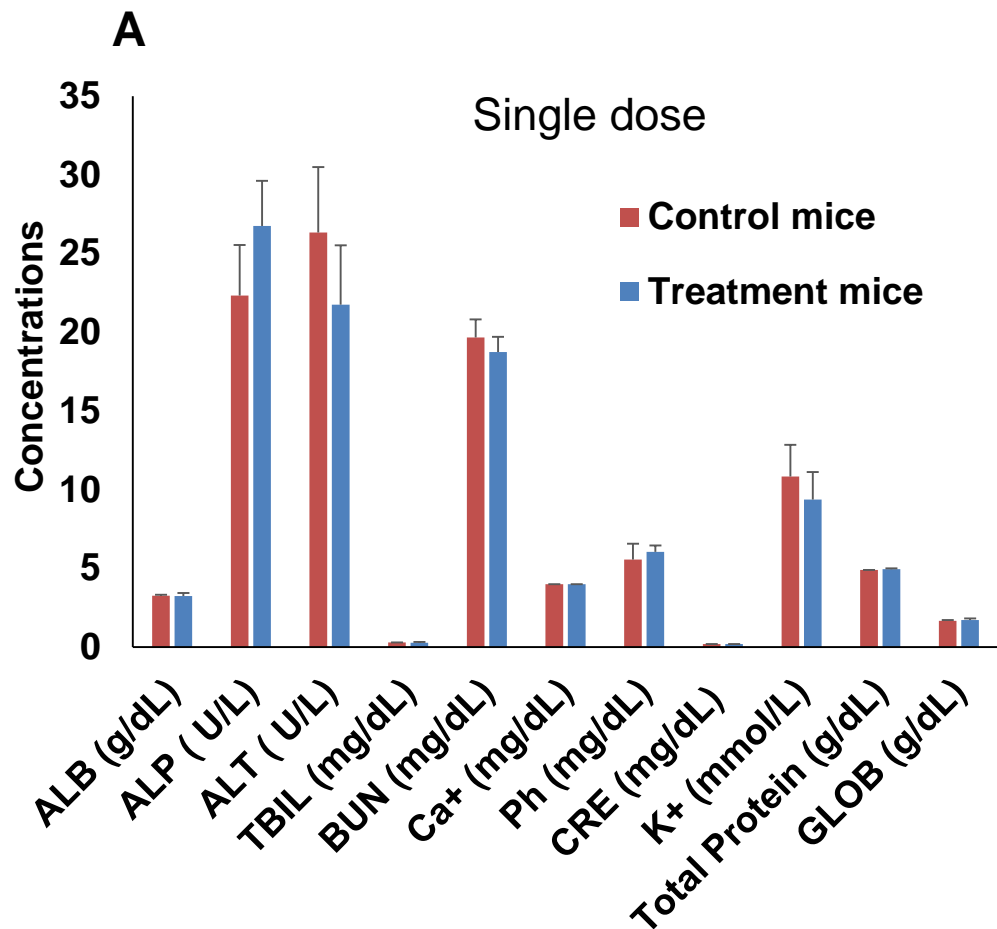
**A**

**Z Average (d.nm):  $95 \pm 10$**

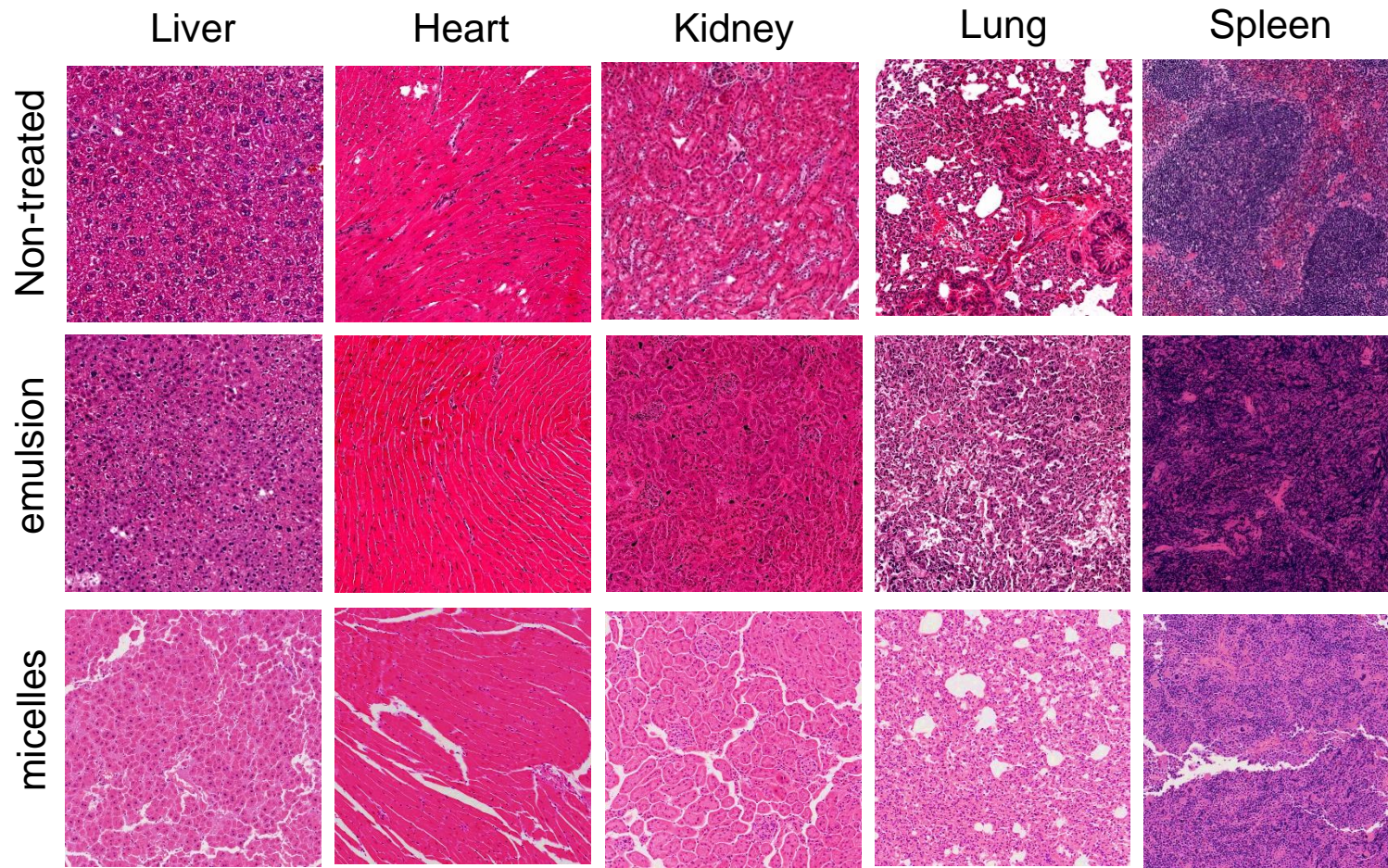
**B**

**Z Average (d.nm):  $80 \pm 10$**

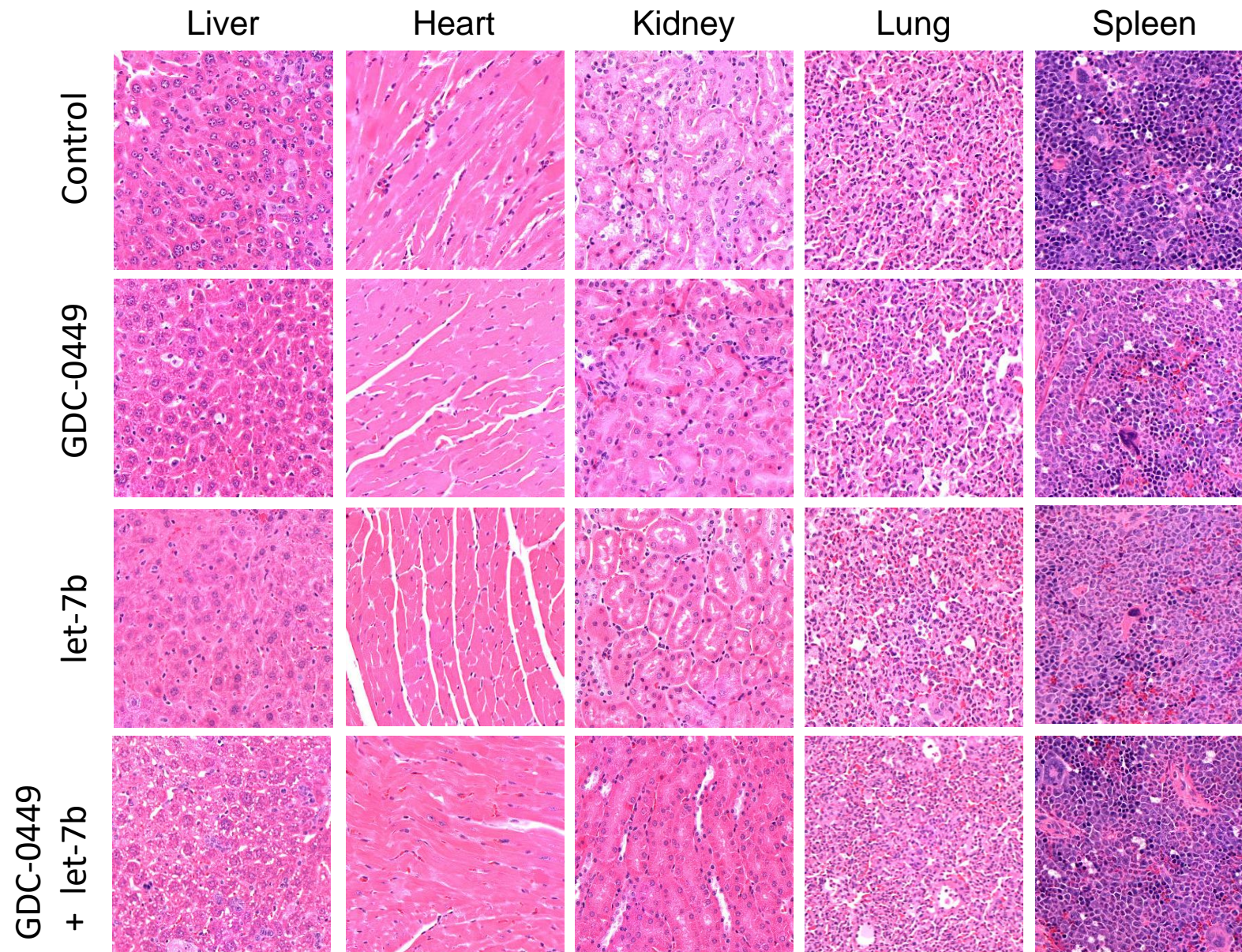
**Figure S4.** Particle size distribution of GDC-0449 and Let7b loaded (A) micelles and (B) emulsion formulations.



**Figure S5.** Plasma toxicity profile after treatment with (A) single dose of miRNA and GDC-0449 loaded micelles (48 h) and (B) multiple dose of different micelles formulations.



**Figure S6. Organ toxicity after single dose.** H&E staining of vital organ slices after single intravenous injection of emulsion or micellar formulations of GDC-0449 and Cy5.5-let-7b in orthotopic pancreatic tumor-bearing NSG mice at the equivalent dose of 10 and 2 mg/kg, respectively.



**Figure S7. Organ toxicity after multiple dose.** H&E staining of vital organ slices after single intravenous injection of micellar formulations of GDC-0449 and let-7b into orthotopic pancreatic tumor-bearing NSG mice at the equivalent dose of 10 and 2 mg/kg, respectively.

**Supplementary Table 1.** Percent of injected dose (ID) of Cy5-let-7b after intravenous injection of emulsion and mPEG-b-PCC-g-DC-g-TEPA micellar formulations in orthotopic pancreatic tumor-bearing NSG mice. Results are presented as the mean  $\pm$  S.D. (n=4).

| <b>% ID emulsion</b> |                 |                 |                  |                  |                 |                 |
|----------------------|-----------------|-----------------|------------------|------------------|-----------------|-----------------|
| <b>Time</b>          | <b>Kidney</b>   | <b>Lung</b>     | <b>Liver</b>     | <b>Tumor</b>     | <b>Heart</b>    | <b>Spleen</b>   |
| <b>0.08 h</b>        | 8.20 $\pm$ 1.49 | 4.82 $\pm$ 0.44 | 41.20 $\pm$ 5.55 | 9.38 $\pm$ 3.32  | 1.14 $\pm$ 0.13 | 2.25 $\pm$ 0.44 |
| <b>0.25 h</b>        | 7.7 $\pm$ 99    | 2.42 $\pm$ 0.74 | 42.39 $\pm$ 8.98 | 6.23 $\pm$ 1.26  | 0.91 $\pm$ 0.17 | 2.93 $\pm$ 0.32 |
| <b>1 h</b>           | 3.38 $\pm$ 0.25 | 2.89 $\pm$ 0.31 | 17.13 $\pm$ 4.97 | 6.80 $\pm$ 1.04  | 1.75 $\pm$ 0.59 | 3.06 $\pm$ 0.1  |
| <b>4 h</b>           | 2.54 $\pm$ 0.74 | 2.17 $\pm$ 1.15 | 13.76 $\pm$ 1.12 | 4.92 $\pm$ 2.39  | 0.96 $\pm$ 0.45 | 2.13 $\pm$ 1.23 |
| <b>24 h</b>          | 0.35 $\pm$ 0.02 | 0.42 $\pm$ 0.2  | 3.78 $\pm$ 1.14  | 0.62 $\pm$ 0.37  | 0.12 $\pm$ 0.02 | 0.18 $\pm$ 0.03 |
| <b>% ID micelles</b> |                 |                 |                  |                  |                 |                 |
| <b>0.08 h</b>        | 3.33 $\pm$ 0.23 | 2.84 $\pm$ 0.34 | 34.51 $\pm$ 4.55 | 9.30 $\pm$ 1.63  | 1.81 $\pm$ 0.22 | 1.30 $\pm$ 0.45 |
| <b>0.25 h</b>        | 6.87 $\pm$ 2.40 | 2.61 $\pm$ 0.19 | 38.26 $\pm$ 6.42 | 10.73 $\pm$ 2.97 | 1.92 $\pm$ 0.06 | 2.26 $\pm$ 0.15 |
| <b>1 h</b>           | 9.77 $\pm$ 0.63 | 2.32 $\pm$ 0.32 | 35.54 $\pm$ 3.15 | 10.52 $\pm$ 1.04 | 2.85 $\pm$ 0.31 | 3.30 $\pm$ 0.58 |
| <b>4 h</b>           | 9.03 $\pm$ 0.23 | 2.12 $\pm$ 0.10 | 34.69 $\pm$ 4.53 | 17.08 $\pm$ 1.11 | 1.09 $\pm$ 0.19 | 2.72 $\pm$ 0.95 |
| <b>24 h</b>          | 7.48 $\pm$ 0.94 | 1.69 $\pm$ 0.15 | 15.80 $\pm$ 0.41 | 5.32 $\pm$ 1.69  | 1.02 $\pm$ 0.13 | 1.52 $\pm$ 0.27 |



**Supplementary Table 2.** Percent of injected dose (ID) of GDC-0449 in major tissues from tumor-bearing NSG mice intravenously administering Cy5.5-let-7b and GDC-0449 emulsion or micelles at a dose of 2 mg/kg of miRNA and 10 mg/kg GDC-0449, respectively. Results are presented as the mean  $\pm$  S.D. (n=4).

| <b>%ID emulsion</b> |                 |                 |                 |                 |                 |                 |
|---------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| <b>Time</b>         | <b>Kidney</b>   | <b>Lung</b>     | <b>Liver</b>    | <b>Tumor</b>    | <b>Heart</b>    | <b>Spleen</b>   |
| <b>0.08 h</b>       | 2.06 $\pm$ 0.15 | 0.89 $\pm$ 0.12 | 9.14 $\pm$ 1.36 | 1.1 $\pm$ 0.4   | 0.73 $\pm$ 0.11 | 0.05 $\pm$ 0.02 |
| <b>0.25 h</b>       | 2.05 $\pm$ 0.27 | 0.76 $\pm$ 0.07 | 10.9 $\pm$ 1.29 | 1.53 $\pm$ 0.26 | 0.62 $\pm$ 0.04 | 0.76 $\pm$ 0.04 |
| <b>1 h</b>          | 0.83 $\pm$ 0.11 | 0.55 $\pm$ 0.1  | 5.8 $\pm$ 0.55  | 1.41 $\pm$ 0.36 | 0.44 $\pm$ 0.02 | 0.92 $\pm$ 0.03 |
| <b>4 h</b>          | 0.15 $\pm$ 0.03 | 0.06 $\pm$ 0.03 | 0.89 $\pm$ 0.13 | 0.25 $\pm$ 0.02 | 0.05 $\pm$ 0.02 | 0.05 $\pm$ 0.01 |
| <b>24 h</b>         | -               | -               | 0.07 $\pm$ 0.02 | -               | -               | -               |
| <b>%ID micelles</b> |                 |                 |                 |                 |                 |                 |
| <b>0.08 h</b>       | 0.81 $\pm$ 0.05 | 0.75 $\pm$ 0.04 | 4.79 $\pm$ 0.39 | 1.06 $\pm$ 0.12 | 0.54 $\pm$ 0.04 | 0.18 $\pm$ 0.01 |
| <b>0.25 h</b>       | 1.60 $\pm$ 0.37 | 0.74 $\pm$ 0.14 | 7.16 $\pm$ 0.86 | 1.52 $\pm$ 0.25 | 0.88 $\pm$ 0.18 | 0.17 $\pm$ 0.03 |
| <b>1 h</b>          | 1.20 $\pm$ 0.14 | 0.52 $\pm$ 0.18 | 7.84 $\pm$ 0.79 | 1.69 $\pm$ 0.23 | 0.46 $\pm$ 0.04 | 0.37 $\pm$ 0.06 |
| <b>4 h</b>          | 1.08 $\pm$ 0.11 | 0.37 $\pm$ 0.16 | 4.28 $\pm$ 0.19 | 1.35 $\pm$ 0.27 | 0.14 $\pm$ 0.07 | 0.09 $\pm$ 0.01 |
| <b>24 h</b>         | 0.09 $\pm$ 0.02 | -               | 0.85 $\pm$ 0.08 | 0.27 $\pm$ 0.10 | -               | 0.05 $\pm$ 0.01 |

**Supplementary Table 3.** Quantitative determination of liver, kidney, and pancreas profile markers in lithium-heparinized whole blood from NSG mice (n=4).

| Marker       | Single dose study |                       |                       | Multiple dose study |                                |                              |   |
|--------------|-------------------|-----------------------|-----------------------|---------------------|--------------------------------|------------------------------|---|
|              | Untreated mice    | Emulsion treated mice | Micelles treated mice | Control mice        | GDC-0449 micelles treated mice | let-7b micelles treated mice | GDC-0449 + let-7b micelles treated mice |
| ALB (g/dL)   | 3.27              | 2.77                  | 3.25                  | 2.6                 | 3.0                            | 2.8                          | 2.6                                     |
| ALP (U/L)    | 22.33             | 21.0                  | 26.75                 | 30.0                | 30.3                           | 22.0                         | 25.6                                    |
| ALT (U/L)    | 36.33             | 28.25                 | 21.75                 | 66.3                | 46.0                           | 26.7                         | 38.4                                    |
| AMY (U/L)    | 740.6             | 979.7                 | 762.2                 | -                   | -                              | -                            | -                                       |
| TBIL (mg/dL) | 0.30              | 0.25                  | 0.27                  | 0.30                | 0.30                           | 0.30                         | 0.28                                    |
| BUN (mg/dL)  | 19.67             | 19.25                 | 18.75                 | 20.0                | 18.0                           | 17.7                         | 19.61                                   |
| Ca+ (mg/dL)  | 4.00              | 9.87                  | 4.00                  | 9.9                 | 9.9                            | 9.8                          | 9.7                                     |
| PHOS mg/dL   | 5.57              | 10.15                 | 6.05                  | -                   | -                              | -                            | -                                       |
| CRE (mg/dL)  | 0.20              | 0.25                  | 0.20                  | 0.3                 | 0.2                            | 0.2                          | 0.2                                     |
| GLU (mg/dL)  | 196.33            | 159.5                 | 187.5                 | 123.3               | 128.7                          | 179.7                        | 167.2                                   |
| Na+ (mmol/L) | 160.33            | 147.75                | 151.75                | 149.0               | 149.7                          | 147.7                        | 158.3                                   |
| K+ (mmol/L)  | 10.83             | 5.77                  | 9.37                  | 3.6                 | 5.8                            | 6.0                          | 5.9                                     |
| TP (g/dL)    | 4.90              | 4.45                  | 4.95                  | 4.1                 | 4.4                            | 4.5                          | 4.3                                     |
| GLOB (g/dL)  | 1.6               | 1.7                   | 1.7                   | 1.4                 | 1.4                            | 1.7                          | 1.6                                     |

**Markers:** Albumin (ALB), Alkaline Phosphatase (ALP), Alanine Aminotransferase (ALT), Amylase (AMY), Total Bilirubin(TBIL), Urea Nitrogen (BUN), Calcium (CA), Phosphorus (PHOS), Creatinine (CRE), Glucose (GLU), Sodium (Na+), Potassium (K+), Total Protein (TP), Globulin (GLOB)