1. Supplementary material and methods: Identification of packaged RNA

To confirm that the desired RNA was packaged in corresponding VLPs, 8 μL of the VLP was digested with DNase I (Thermo Fisher, USA) at 37°C for 30 minutes to eliminate residual DNA fragments, and then 1 μL of 50 mM EDTA was added to the system and heated at 80°C for 5 minutes to inactive DNase I and release packaged RNA. One microliter of the released RNA was reverse transcribed to cDNA using PrimeScript RT reagent Kit (Takara, Japan) with hexa-random primers at 37°C for 15 minutes and 85°C for 5 seconds. Then 1 μL of cDNA was tested by real-time PCR using specific primers as shown in Table S2. The real-time PCR was performed using TB Green Premix Ex Taq kits(Takara, Japan) in Abi 7500 real-time PCR system according to the instructions.

2. Supplementary material and methods: Identification of the capsid protein and confirmation of crosslinking

Sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) was performed to identify the capsid protein and to confirm crosslinking. Ten micrograms of the VLP or the GE11-VLP was mixed with 5×loading buffer (CWBIO, China) and boiled in water bath for 5 minutes. The sample was run by SDS-PAGE in 5% gel at 80 V for 25 minutes and in 12% gel at 120V for 30 minutes. The gel was stained with Coomassie Blue Fast Staining Solution (Tiangen, China) according to the instructions to visualize proteins.

Table S1. The sequence wrapped in virus-like particles

Name	Sequence (5'-3')	Remarks
miR-21 sponge	ACATGAGGATCACCCATGTTCAACATC AGTCTGATAAGCTATATACTCAACATC AGTCTGATAAGCTAACATCTCAACATC AGTCTGATAAGCTATCTTCATCAACAT CAGTCTGATAAGCTAACATGGGTGATC CTCATGT	The sequence in shadow is the pac site, and the underlined one is the spacer between complementary sequence.
mir-122-miR-21 sponge	ACATGAGGATCACCCATGT*CCTTAGCA GAGCTGTGGAGTGTGACAATGGTGTTTG TGTCTAAACTATCAAACGCCATTATCACA CTAAATAGCTACTGCTAGGC***GTGCTCG*** ***CTTCGGCAGCACATATACTA***TCAACA TCAGTCTGATAAGCTATATACTCAACA TCAGTCTGATAAGCTAACATCTCAACA TCAGTCTGATAAGCTATCTTCATCAAC ATCAGTCTGATAAGCTA**AGAGCGGAC TTCGGTCCGCTATT**ACATGGGTGATC CTCATGT	The sequence in shadow is the pac site, and the sequence in *Italic* is the sequence of pre-miR-122, and it in **bold** is the cassettes, and the sequence underlined is the sponge.
Negative Control (NC)	ACATGAGGATCACCCATGTTGAACAG TGTATATCCGTACGAACCTATACTGAA CAGTGTATATCCGTACGAACCACATCT GAACAGTGTATATCCGTACGAACCTCT TCATGAACAGTGTATATCCGTACGAAC CACATGGGTGATCCTCATGT	The sequence in shadow is the pac site, and the underlined one is the spacer between complementary sequence.

The Sequences of miR-21 and miR-122 are searched from mirbase database, that is Human>hsa-miR-21-5p (MIMAT0000076) UAGCUUAUCAGACUGAUGUUGA, Human> hsa-miR-122-5p(MIMAT0000421) UGGAGUGUGACAAUGGUGUUUG.

Table S2. Primers used in the RT-qPCR test

Target	Primer name	Sequence (5'-3')
miR-21 sponge	21sp-qF	CAGTCTGATAAGCTAACATCTCA
	21sp-qR	GCTTATCAGACTGATGTTGATGA
NC	NCsp-qF	TGTATATCCGTACGAACCACATCT
	NCsp-qR	TTCGTACGGATATACACTGTTCATGAAG
pre-miR-122-miR-21-sponge	122-21-qF	GGGGTACCACATGAGGATCACCCATGTCCTTAGCAGAGCTGTGGA
	122-21-qR	CCTTAATTAAACATGGGTGATCCTCATGTAATAGCGGACCGAAGTCCGCTCT
U6	U6-F	CTCGCTTCGGCAGCACATATACTAAAAT
	U6-R	AACGCTTCACGAATTTGCGTGTCAT
GAPDH	GAPDH-F	ATGATGACATCAAGAAGGTGGTGA
	GAPDH-R	GTCATACCAGGAAATGAGCTTGACA
miR-122	122RT-Primer	GTCGTATCCAGTGCAGGGTCCGAGGTATTCGCACTGGATACGACCAAACA
	miR122-F	GGCTGGAGTGTGACAATGGT
	miR122-R	GTGCAGGGTCCGAGGT
PTEN	PTEN-F	ACCCCTTCATTGACCTCAACTA
	PTEN-R	TCTCGCTCCTGGAAGATGGTGA
PDCD4	PDCD4-F	TGGATGTCCCACATTCATACTCTG
	PDCD4-R	TCTGGTTTAAGACGACCTCCATCT
RECK	RECK-F	CCTCAGTGAGCACAGTTCAGA
	RECK-R	GCAGCACACACACTGCTGTA

Table S3. The Ct values of GAPDH and Tm for miR-21 sponge in RT-qPCR

Sample name	Ct of GAPDH	Tm for miR-21 sponge
Hep3B-NC [a]	21.3	75.5
Hep3B-NC	22.1754	75.5
Hep3B-NC	22.0475	75.5
Hep3B-21 [b]	21.2812	80.3
Hep3B-21	21.8877	80.6
Hep3B-21	21.4378	80.6
Hep3B-122 [c]	20.6743	80.0
Hep3B-122	20.5266	80.0
Hep3B-122	20.7439	80.0
HEPG2-NC	18.1199	72.3
HEPG2-NC	17.2788	72.3
HEPG2-NC	17.2582	72.3
HEPG2-21	17.362	80.7
HEPG2-21	17.3475	81.1
HEPG2-21	17.166	81.1
HEPG2-122	15.7808	81.1
HEPG2-122	16.055	81.1
HEPG2-122	15.7391	81.1
HUH7-NC	17.0697	75.1
HUH7-NC	16.804	75.1
HUH7-NC	17.3686	77.6
HUH7-21	17.5042	80.3
HUH7-21	17.2422	80.3
HUH7-21	17.0103	80.7
HUH7-122	16.9391	80.7
HUH7-122	17.3479	80.7
HUH7-122	17.009	80.7

SMMC-7721-NC	17.9022	75.2
SMMC-7721-NC	18.2702	75.2
SMMC-7721-21	17.4738	79.6
SMMC-7721-21	17.8195	79.6
SMMC-7721-21	17.4558	79.6
SMMC-7721-122	18.1667	80.3
SMMC-7721-122	19.9229	80.6
SKHEP1-NC	16.9734	75.6
SKHEP1-NC	17.2289	75.2
SKHEP1-21	17.5399	80.3
SKHEP1-21	16.8751	80.3
SKHEP1-21	19.6232	80.3
SKHEP1-21	17.6948	80.3
SKHEP1-122	18.0581	80.3
SKHEP1-122	17.1371	79.9

The treatment presented in the sample name is abbreviated. a: NC is negative control; b: 21 is miR-21 sponge; c: 122 is mir-122-miR-21 sponge.

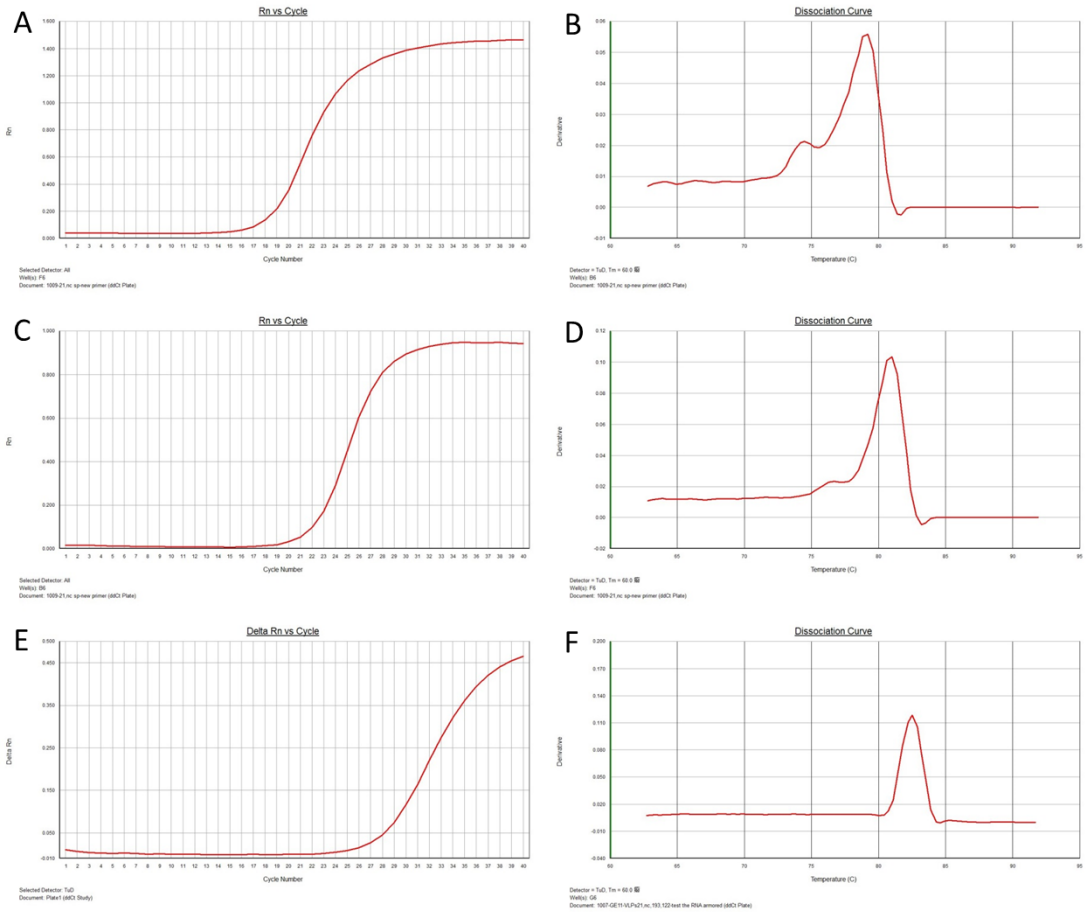

Figure S1. The RNA packaged in the VLP was identified by rRT-PCR. A: Amplification curve of VLP containing miR-21 sponge; B: Melt curve of VLP containing miR-21 sponge; C: Amplification curve of VLP containing NC sponge; D: Melt curve of VLP containing NC sponge; E: Amplification curve of VLP containing pre-miR-122-miR-21 sponge; F: Melt curve of VLP containing pre-miR-122-miR-21 sponge.

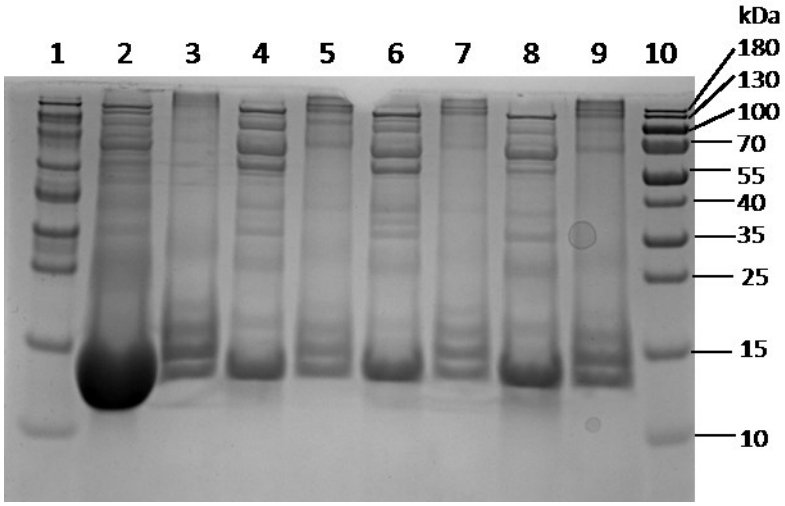

Figure S2. The SDS-PAGE electrophoresis was performed to confirm that the cross linker was connected to the VLP. Lane 1 and lane 10, protein marker; lane 2, MS2 VLPs containing pre-miR-122; lane 3, GE11 cross linked VLPs containing pre-miR-122; lane 4, MS2 VLPs containing miR21 sponge; lane 5, GE11 cross linked VLPs containing miR21 sponge; lane 6, MS2 VLPs containing pre-miR122-miR21 sponge; lane 7, GE11 cross linked VLPs containing pre-miR122-miR21 sponge; lane 8, MS2 VLPs containing NC sequence; lane 9, GE11 cross linked VLPs containing NC sequence. The MS2 monomer is around 14 kilo Dalton, which is consistent with the SDS-PAGE result. As a GE11 peptide is 1.6 kilo Dalton, four bands in Lane 3, 5, and lane 7 indicated that each monomer was cross linked with 0~3 GE11 peptides

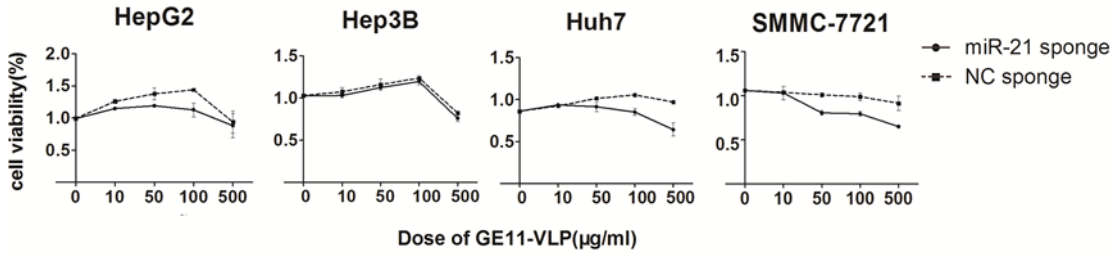

Figure S3. The cytotoxicity of GE11-VLPs.

Four cell lines were dosed with different concentration of GE11-VLPs containing miR-21 sponge or NC. The dosed cells were cultured 48 hours for Hep3B and 72 hours for the other three cell lines. Then the cell viability was tested by the CCK-8 assay. The cell viability is calculated as a ratio between a dosed group and corresponding blank group without any treatment. compared with NC group, a concentration dependent effect was observed in all HepG2, Huh7 AND SMMC-7721 cell lines when treated with miR-21 sponge up to the concentration of 100 μg/mL. It indicated that miR-21 had adverse effects on proliferation of HCC cells. As for HepG2 and Hep3B, a significant reduce of cell viability was found in both miR-21 sponge or NC groups at a concentration of 500 μg/mL, which indicated that 500 μg/mL of the GE11-VLP could inhibit the proliferation of HCC cells itself. So the effects of RNA delivered by GE11-VLP are supposed to be studied at a concentration of 100 μg/mL.

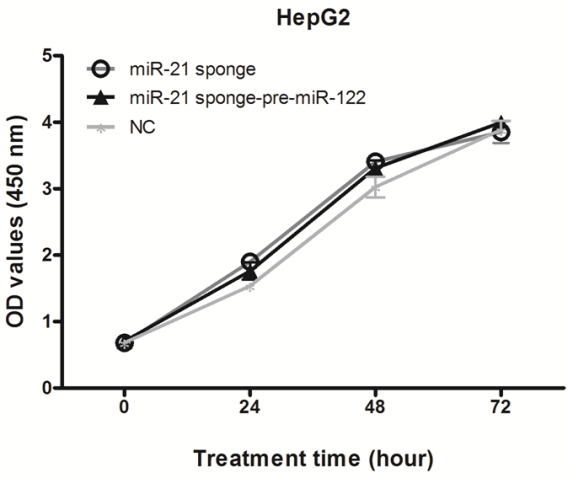

Figure S4. The OD values detected by CCK-8 assay represents HepG2 cell number. No difference was observed between treatment and control groups.