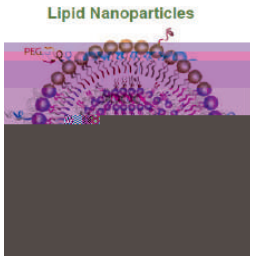
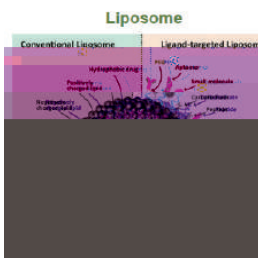




Ball milling, high-pressure homogenization, ultrasound, extruding

Solvent volatilization, precipitation, T-tube, microfluidics

Easily modified, easily synthesized, easily produced.The on-target and off-target ratio of delivery should be within an acceptable range.The effective dose must be significantly lower than the toxic dose.The bioactivity of the nucleic acid should be consistent from batch to batch.In most clinical cases, repeated administration does not result in loss of efficacy or safety.

Spray dryer

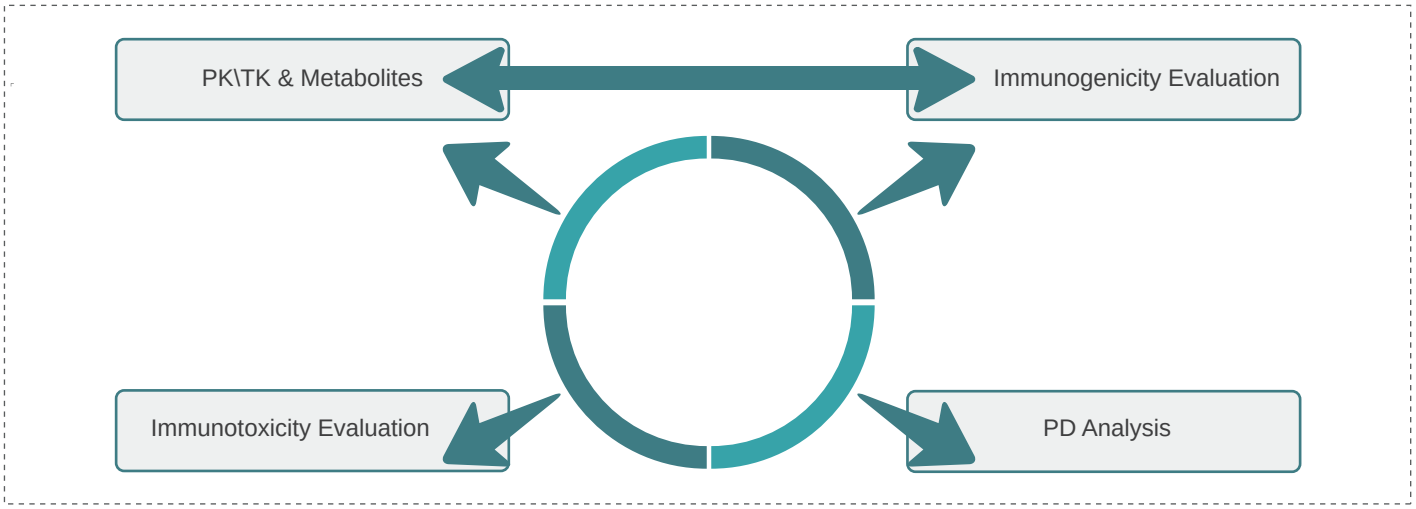
Agilent InfinityLab Bio LC

Thermo U3000+CAD detector Thermo

Agilent biological analyze

ZETA nanoparticle Potentiostat

- Formulation: drug to lipid ratio, solvent screening, aqueous to organic solvent ratio
- Process: Preparation methods
- Stability
- Dosage form screening



	• Molecular hybridization-enzyme assay (H-ELISA) • Molecular hybridization-electrochemiluminescence analysis (H-ECL) • Reverse transcription fluorescence quantitative PCR (RT-qPCR) • Quantitative PCR (qPCR) • Digital Microdrop (ddPCR) • LC-MS/MS Platform
	• Total Anti-Drug Antibody (ADA) Assay: MSD • Neutralizing antibody (Nab) analysis: CLBA or Cell-based Assay
	• Singleplex (based on various LBA technologies) • Multiplex (Luminex, MSD, FACS CBA technologies) • FACS

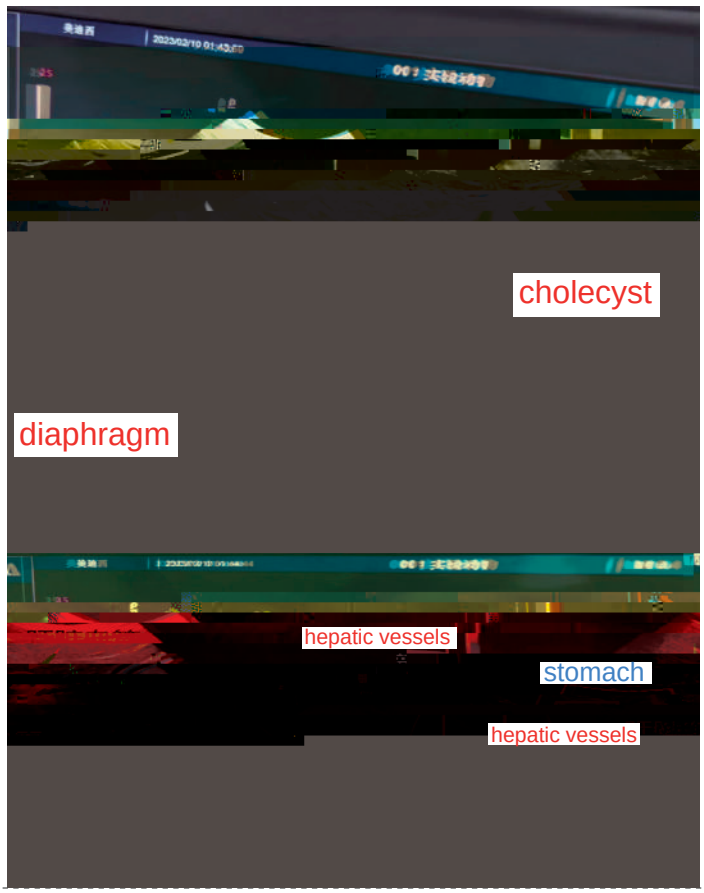
- High specificity
- High sensitivity: ng level
- Advantages: end product detectable

- High specificity
- Sensitivity: Detectable within 1 log copy
- Advantage： More Sensitive

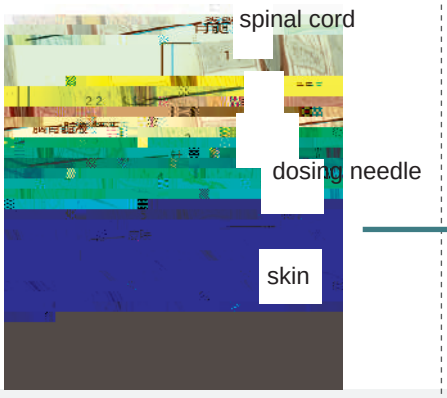
- Sensitivity: pM level
- Advantages: variable marking strategy; personalized reaction strategy.

The development of gene therapy and nucleic acid drugs has made the establishment of monkey models and related research a hot topic. Due to the high similarity of genetic, morphological, physiological and biochemical characteristics with humans, non-human primates, especially cynomolgus monkeys, are closest to humans in terms of evolution, and have outstanding advantages in model construction, disease mechanism research, and drug development. Many disease models have been established so far.

In the long-term dynamic experimental observation of the changes in the liver disease model of cynomolgus monkeys, due to the limitations of animal disease models and experimental objective conditions, researchers mostly obtain liver



siRNA IV infusion	Plasma Muscle biopsy Liver biopsy	N=2	▪ Cytokine study ▪ Complement study ▪ Lipid study ▪ Cir-luc mRNA	▪ IHC slide ▪ hELISA study ▪ MSTN Protein
	Plasma Muscle biopsy	N=2	▪ hELISA study ▪ NHP mRNA ▪ NHP MSTN Protein	▪ IHC slide ▪ Cytokine study ▪ Complement study

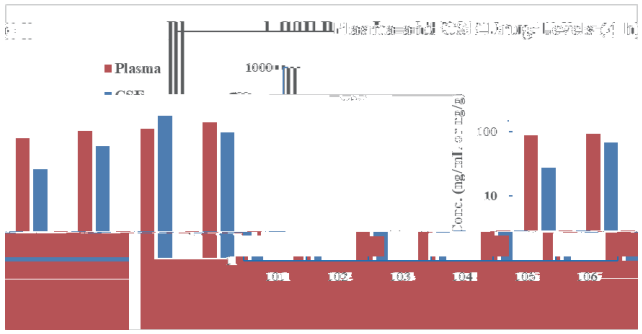


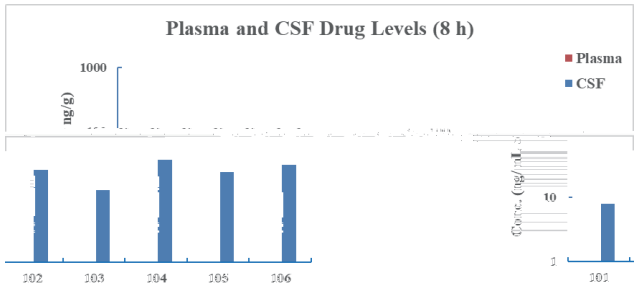
monkey IT dosing schematic lumbar

monkey dose location: lumbar
X-ray imaging monitoring

monkey CSF collection schematic

1	MED-002	6 mg/Monkey	IT on Day 1 6 monkeys	2 mL (Infusion, 3 min) Location: Lumbar	Post-dose at 4 h and 8 h

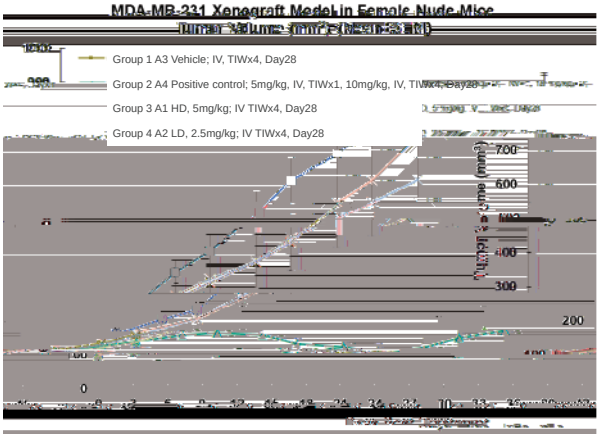




The coefficient of variation (CV%)

1	MED-002	6 mg/Monkey	IT on Day 1 6 monkeys	2 mL (Infusion, 3 min) Location: Lumbar	Post-dose at 4 h and 8 h

- **Animals:**
  Female NOG mice
- **Tumor Cells:**
  HCT15, 2x10^6/mouse
- **PBMC:**
  5x10^6/mouse
- **Treatment:**
  Intracutaneous injection

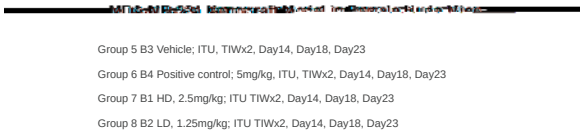


Animals: Female BALB/c Nude mice

Cells: MDA-MB-231, 5x10^6/mouse

Model Establishment: Right flank SC injection

Treatment: injection; TIW (three times a week); Group3, 4: mRNA (LNP) group.



Animals: Female BALB/c Nude mice

Cells: MDA-MB-231, 5x10^6/mouse

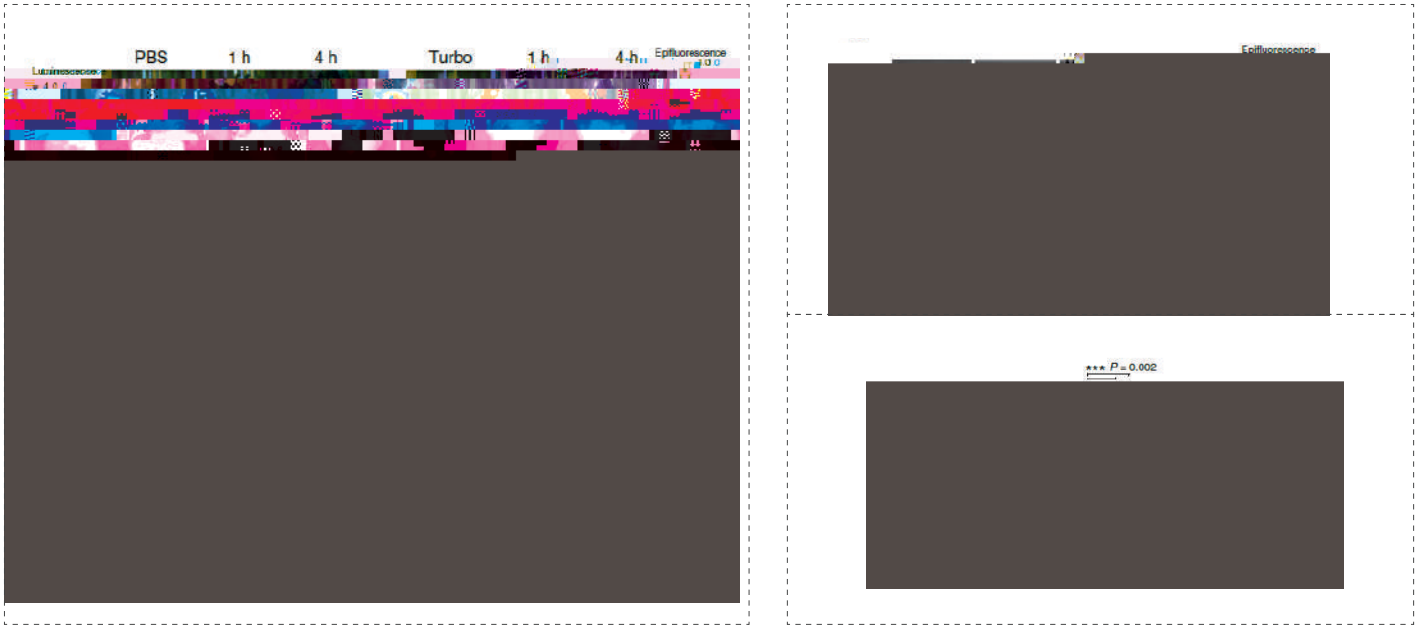
Model Establishment: Right flank SC injection

Treatment: injection; TIW (three times a week); Group 7, 8: mRNA (LNP) group.

In vivo *in vivo*

- Dendrimer LNP
- Luc mRNA; IV and intra-tumoral

- CNP-generated exosome
- Delivery of PTEN mRNA by Glioma-directed Exosome EXO-T,IV



Brain cancer	CHP-212, LN-229, U-87 MG, U-251 MG
Breast cancer	BT474, HCC70, HCC1569, HCC1806, HCC1954, JIMT-1, MCF7, MDA-MB-231, MDA-MB-436, MDA-MB-468, MX-1, SUM 149PT, ZR-75-1
Cervix	Hela, SiHa
Colon cancer	COLO 205, DLD-1, HCT-8, HCT-15, HCT-116, HT-29, LIM-1215, LoVo, Ls174T, NCI-H508, RKO, SW48, SW480, SW620, SW837
Endometrium	AN3 CA, HEC-1-A, HEC-1-B, RL95-2
Esophageal	KYSE-520
Fibrosarcoma/Soft tissue	HT-1080
Gastric cancer	Hs 746T, MKN-45, NCI-N87, NUGC-4, SNU-16
Head and neck cancer	CAL-27, Detroit562, FaDu, TT
Leukemia	CCRF-CEM, HEL, HL-60, Jurkat E6.1, JVM-3,K-562, MOLM-13, MOLM-16, MOLT-3, MOLT-4, MV-4-11, OCI-AML-3, TF-1a, THP-1, U-937
Liver cancer	HCCLM3, Hep G2, HuH-7
Lung cancer	A427, A549, Calu-1, Calu-3, Calu-6, DMS114, EBC-1, HCC827, MOTO-211H, NCI-H69, NCI-H292, NCI-H358, NCI-H460, NCI-H520, NCI-H522, NCI-H526, NCI-H727, NCI-H820, NCI-H1299, NCI-H1373, NCI-H1568, NCI-H1581, NCI-H1650, NCI-H1703,NCI-H1975, NCI-H2122, NCI-H2228, NCI-H3122, NCI-H3255, PC9
Lymphoma	Daudi, DB, DOHH2, HH, JeKo-1, Karpas299, MAVER-1, Mino, OCI-LY10, OCI-LY19, Raji, RL, SR, SU-DHL-1, SU-DHL-2, SU-DHL-4, SU-DHL-6, TMD-8, WSU DLCL2
Melanoma	A375, C32
Myeloma	MM.1R, MM.1S, NCI-H929, OPM-2, RPMI-8226
Osteosarcoma	SJSA-1
Ovary	A2780, OVCAR-3, OVCAR-8, PA-1, SK-OV-3
Pancreatic cancer	
Prostate	
Renal cancer	
Skin cancer	
Urinary bladder cancer	

Breast cancer	201B, 203B
Cervix	371Ce
Colon cancer	002C, 008C, 011C, 013C, 015C, 016C, 020C, 021C, 057C, 058C, 059C, 060C, 061C, 062C, 064C, 065C, 069C, 070C, 072C, 075C, 076C, 084C, 087C, 088C, 095C, 102C, 104C, 110C, 116cC, 117C, 128C, 143C
Endometrium	361En
Esophagus cancer	341Es
Gastric cancer	091Ga, 092Ga, 122Ga, 126Ga, 142Ga, 145Ga, 254Ga, 256Ga, 258Ga, 259Ga, 381Ga
Head and neck cancer	281T, 285HN, 284HN, 286HN
Leukemia	291Le, 292Le, 293Le, 294Le, 295Le
Liver cancer	212Li, 213Li, 214Li, 216Li
Lung cancer	028Lu, 047Lu, 050Lu, 053Lu, 054Lu, 263Lu, 264Lu, 265Lu, 267Lu
Lymphoma	244Ly, 245Ly
Myeloma	321Bm
Ovary	271O, 272O, 273O, 274O
Pancreatic cancer	221Pa, 222Pa, 223Pa, 224Pa, 225Pa, 226Pa, 228Pa
Prostate	351Pr, 353Pr, 354Pr, 355Pr
Renal cancer	301R, 303R, 304R
Sarcoma	332Sa, 333Sa, 334Sa
Urinary bladder cancer	232U, 234U, 235U, 236U

Brain cancer	Neuro-2a
Breast cancer	4T1, EMT6, EO771, JC
Colon cancer	Colon26, CT26.WT, MC-38
Leukemia	C1498, L1210, WEHI-3
Liver cancer	H22
Lung cancer	KLN205, LLC1, M109
Lymphoma	A20, E.G7-OVA, EL4, L5178-R
Mastocytoma	P815
Melanoma	B16, B16-F0, B16-F10, Clone-M3, YUMM1.7
Myeloma	J558
Pancreas cancer	KPC, Panc 02
Prostate	RM-1
Renal cancer	RENCA
Sarcoma	S180, WEHI-164
Urinary bladder cancer	MB49

Brain cancer	U-87 MG
Breast cancer	HCC70, HCC1954, JIMT-1, MDA-MB-231, MDA-MB-468
Colon cancer	HT-15, HT29, LoVo, Ls174T
Gastric cancer	NCI-N87, NUGC-4
Leukemia	MOLM-13, THP-1
Liver cancer	Hep G2, HuH-7
Lung cancer	A549, HCC827, NCI-H292, NCI-H838, NCI-H1975
Lymphoma	Raji, TMD8
Melanoma	A375
Myeloma	MM.1S, NCI-H929, RPMI-8226
Ovarian cancer	OVCAR-3
Pancreatic cancer	Capan-2
Renal cancer	786-O, A498
Skin cancer	A431
Urinary bladder cancer	UM-UC-3

Brain cancer	LN299-luc, U87-MG-luc, U251-luc	G261-luc
Breast cancer	BT-474-luc, MCF-7-luc,MDA-MB-231-luc	4T1-luc
Colon cancer	HCT-116-luc, HT29-luc	MC38-luc
Gastric cancer	NCI-N87-luc	/
Leukemia	K562-luc, MOLM-13-luc, MV-4-11-luc, Nalm-6-luc, THP-1-luc	/
Liver cancer	HuH-7-luc, Hep G2-luc	H22-luc
Lung cancer	A549-luc, NCI-H460, NCI-H1650-luc, NCI-H1975-luc	LLC1-luc
Lymphoma	Raji-luc, JeKo-1-luc	/
Melanoma	A375-luc	B16-F10-luc
Myeloma	NCI-H929-luc, MM.1S-luc, OPM-2-luc	/
Ovary	OVCAR-3-luc, SK-OV-3-luc	/
Pancreatic cancer	Mia-Paca 2-luc, PANC-1-luc	Panc 02-luc
Prostate	PC-3-luc	/
Renal cancer	A498-luc	/
Sarcoma	HT1080-luc, SJSA-1-luc	/
Urinary bladder cancer	UM-UC-3-luc	MB49-luc

	G261-luc, 4T1-luc, MC38-luc, H22-luc, B16-F10-luc, LLC1-luc

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