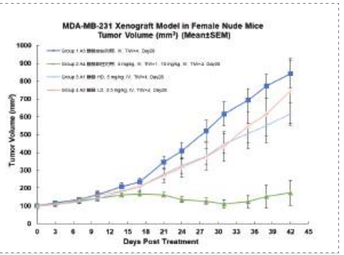
Pharmacology evaluation

- Contrast of different drug delivery methods.
- Relevance analysis between pharmacology and target mRNA/protein degradation & nucleic acid drug PK

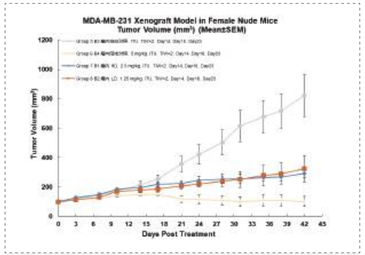


Animals: Female BALB/c Nude mice

Cells: MDA-MB-231, 5*10⁶/mouse

Model Establishment: Right flank SC injection

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



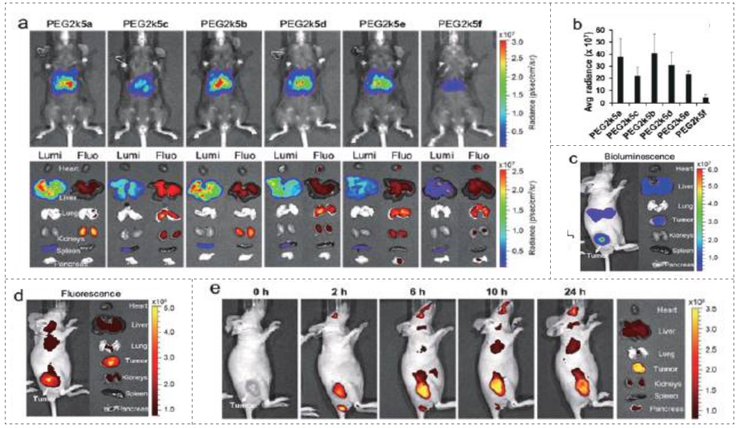
Animals: Female BALB/c Nude mice

Cells: MDA-MB-231, 5*10⁶/mouse

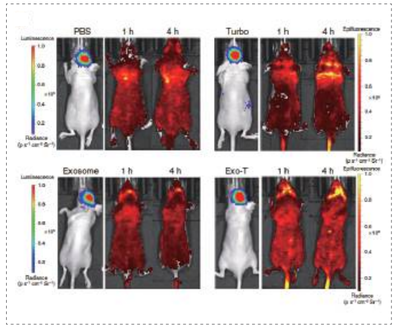
Model Establishment: Right flank SC injection

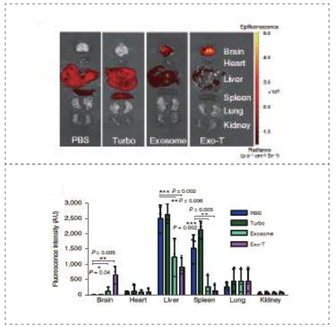
Treatment: Intratumor injection; TIW (three times a week); Group 7, 8: mRNA (LNP) group.

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



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





Syngeneic mouse models

Cancer Type	Cell Line
Bladder Cancer	MB49
Brain Cancer	G261
Breast Cancer	4T1, EMT6, JC, EO771
Colon Cancer	CT26.WT, MC-38, Colon26
Leukemia	C1498, L1210, WEHI-3
Liver Cancer	H22, Hepa 1-6
Lung Cancer	LLC1, KLN205
Lymphoma	A20, EL4, L5178-R, E.G7-OVA
Mastocytoma	P815
Melanoma	B16-F10, Clone-M3
Pancreas Cancer	Panc 02
Renal Cance	RENCA
Luciferase Cell Line	
G261-luc, 4T1-luc, MC38-luc, H22-luc, B16-F10-luc, LLC1-luc	

Humanized mouse models

Cancer Type	Cell Lines in PBMC or HSC CD34⁺ Humanized Mice
Brain Cancer	U-87 MG
Breast Cancer	HCC1954, MDA-MB-231, JIMT-1
Colon Cancer	HT29, LoVo, Ls174T, HT-15
Gastric Cancer	NCI-N87, NUGC-4
Leukemia	THP-1
Lung Cancer	HCC827, NCI-H1975, NCI-H292, A549
Lymphoma	Raji, TMD8, MOLM-13
Melanoma	A375
Myeloma	RPMI-8226, NCI-H929, MM.1S
Ovarian Cancer	OVCAR-3
Pancreatic Cancer	Capan-2
Renal Cancer	786-O
Skin Cancer	A431

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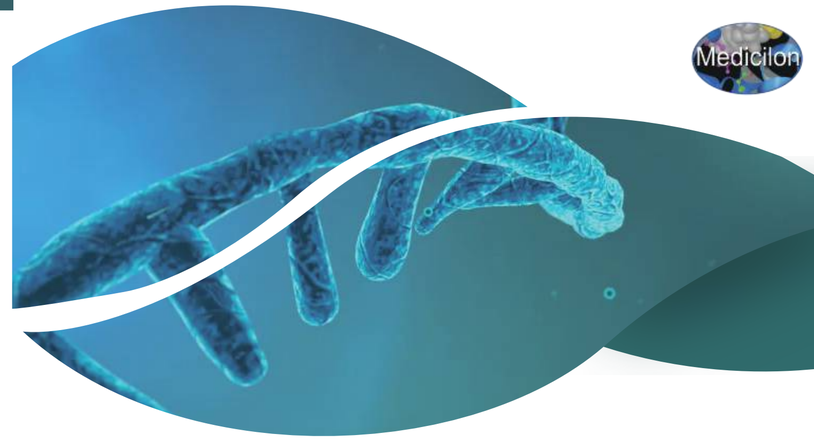


Medicilon Nucleic Acid Drug R&D Platform

Medicilon nucleic acid drug R&D platform is an integrated and comprehensive solution that covers drug discovery, CMC and preclinical research services. Based on a rigorous scientific attitude, an open-minded scientific spirit and advanced equipment, our integrated solution can meet the industry's research and development needs for cutting-edge innovative nucleic acid drugs, and undertake research programs like nucleic acid drug discovery, screening and preclinical research services for pharmaceutical companies and scientific research institutions.

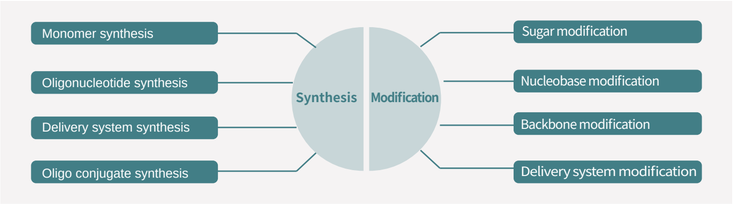
Popular types

ASO | siRNA | mRNA | Aptamer

Advantages

For its fast and intuitive design of base sequences, the development of nucleic acid drugs applies simple materials, convenient preparation processes and affordable production costs, which greatly shorten the drug development cycle, making it possible to customize individualized treatment plans. Hence, it offers a feasible solution for rare diseases and other problems currently plagued.

Nucleic Acid Synthesis and Chemical Modifications



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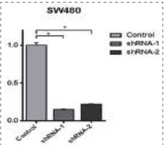
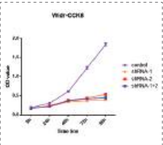
Bioactivity Screening

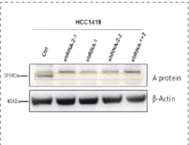
- Evaluation of binding between siRNA-GALNAc and targeted liver cells (ELISA, SPR, FP, FACS, MSD, Confocal microscope)
- Evaluation of decrease in target mRNA/protein level.
- Evaluation of cell phenotypes and functional interfere.



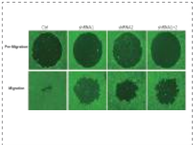
Q-PCR



Cell proliferation



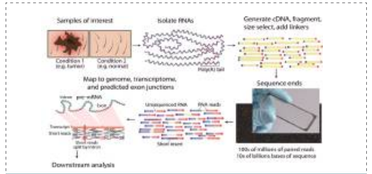
Western Blot



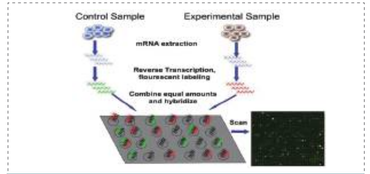
Cell migration

- Evaluation of off-target effect

  - Searching for potential off-target mRNA/protein in the database, such as NCBI, nucleotide BLAST.
  - Overall analysis applying RNAseq or RNA Microarray.



RNA Seq



RNA Microarray

Nucleic Acid Process R&D

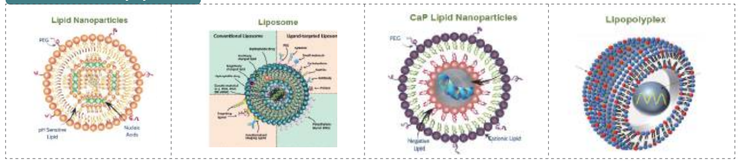
Select starting materials	We aim to choose starting materials with traits like easy to purchase, mild toxicity, good quality stability;
Process R&D of nucleic acid	We aim to develop stable and green synthesis routes with low cost and high security.
Quality Control	Up-to-date quality control system with complete technical standard.
Select starting materials	End to end service ensuring smooth transfer.

Nucleic acid drugs preparation

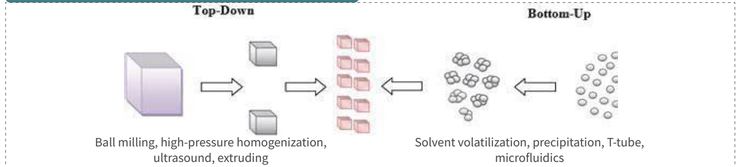
Due to their low immunogenicity, biocompatibility, and high encapsulation efficiency for oligonucleotide molecules, lipids and their derivatives have become the go-to delivery systems for nucleic acid drugs that have attracted much attention in recent years. The system is positively charged in the physiological environment. The negatively charged nucleic acid molecules are encapsulated by electrostatic action, and the positively charged surface can also help the entire carrier system to combine with the cell membrane of the target cell, thereby playing a delivery role.


Picture Source：Science China Life Sciences volume 62,pages333-348(2019)

Common delivery systems



Medicilon' s preparation methods of nanoparticles



Traits of successful delivery systems

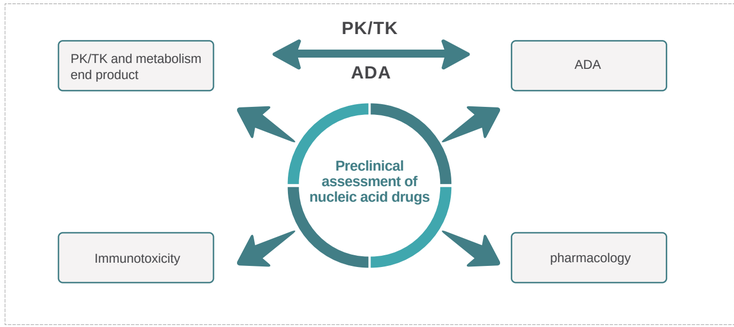
Easily modified, easily synthesized, easily produced.The on-target and off-target ratio of delivery should be within an acceptable range.The effective dose must be significantly lower than the toxic dose.The bioactivity of the nucleic acid should be consistent from batch to batch.In most clinical cases,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

Medicilon' s nanoparticle R&D lab


Spray dryer | Agilent InfinityLab Bio LC | Thermo U3000+CAD detector Thermo | Agilent biological analyze | ZETA nanoparticle Potentiostat

Nucleic acid-lipid system R&D	• Formulation: drug to lipid ratio, solvent screening, aqueous to organic solvent ratio • Process: Preparation methods • Stability • Dosage form screening

寡核苷酸生物分析



PK/TK analysis	• H-ELISA LC-MS/MS • H-ECL • RT-qPCR	• qPCR • ddPCR
ADA analysis	• Total ADA • MSD • Nab analysis: CLBA or cell-based assay	
PD or TOX related cytokines & biomarkers	Cytokine&Biomarker • Singleplex • Multiplex (Luminex, MSD, FACS CBA) • FACS	

Solutions for Nucleic acid bioanalysis

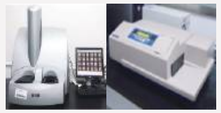
LC-MS/MS/HRMS Platform

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

qPCR/ddPCR Platform

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

Hybridization-EIA/ECL Platform



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