武汉大学药学院
School of Pharmaceutical Sciences

2022

GalNAc-siRNA

2022.05.12　　王浩

Tai Lab

siRNA

未修饰的siRNA易被核酸酶降解等 → 化学修饰

siRNA的亲水性、带负电等使其不能够进入细胞发挥作用 → 递送系统

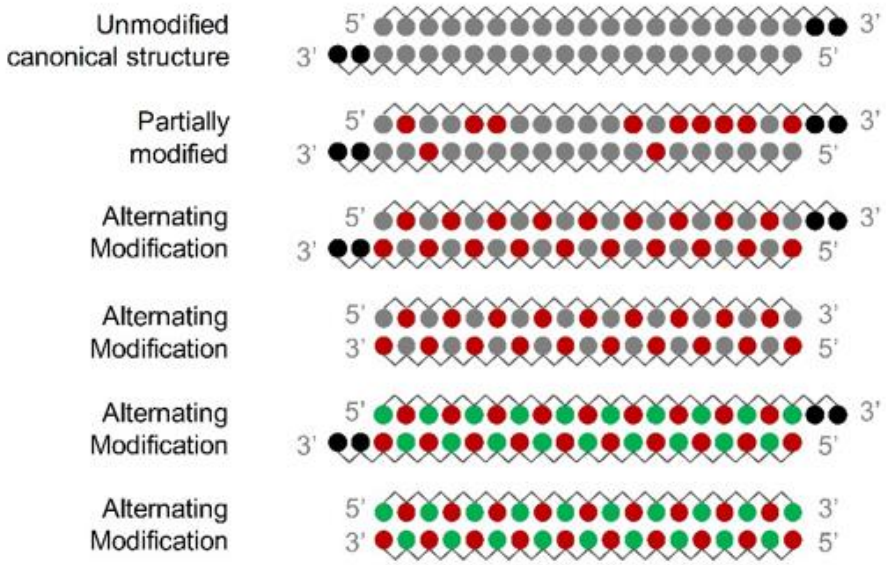
×不具备成药性

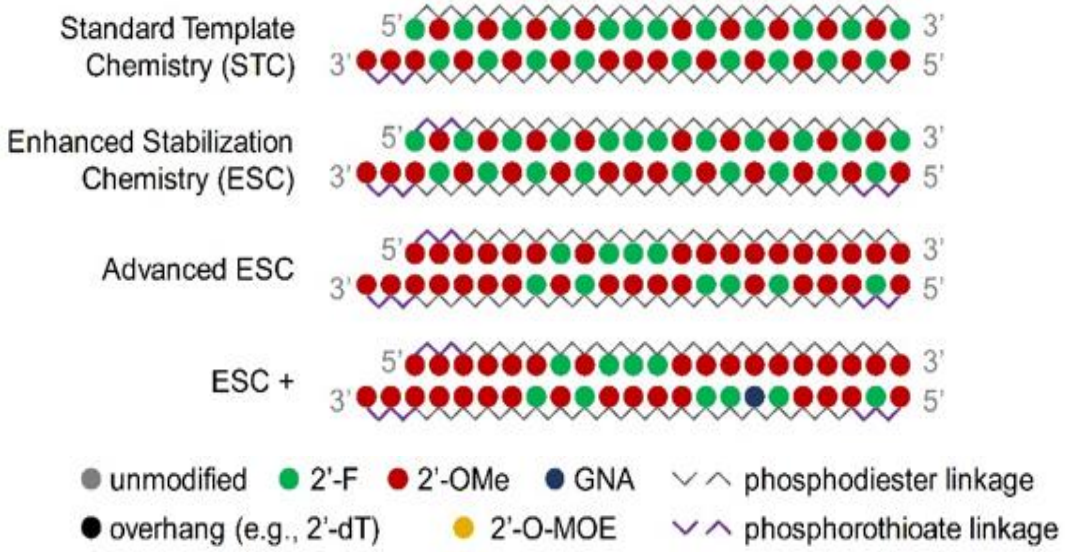
Marketed siRNA drugs and in clinical trials

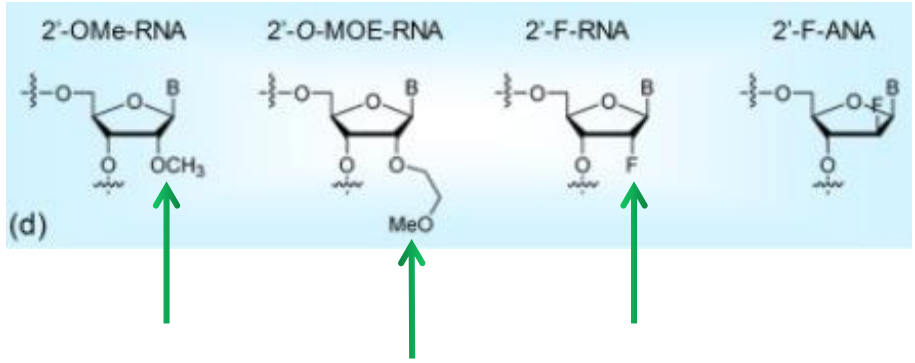
Therapeutic name	Condition(s)	Modification chemistry	Delivery system	Target(s)	Sponsor	Phase	NCT ID
ONPATTRO® (patisiran, ALN-TTR02)	TTR-mediated amyloidosis	2′-OMe, 2′-F	LNP (DLin-MC3-DMA)	TTR	Alnylam Pharmaceuticals		
GIVLAARI™ (givosiran, ALN-AS1)	Acute hepatic porphyrias	PS, 2′-OMe, 2′-F	GalNAc–siRNA conjugate	ALAS1	Alnylam Pharmaceuticals		
Lumasiran (ALN-GO1)	Primary hyperoxaluria type 1	PS, 2′-OMe, 2′-F	GalNAc–siRNA conjugate	HAO1	Alnylam Pharmaceuticals		
Inclisiran (ALN-PCSsc)	Hypercholesterolemia	PS, 2′-OMe, 2′-F	GalNAc–siRNA conjugate	PCSK9	Alnylam Pharmaceuticals		
Vutrisiran (ALN-TTRSC02)	Amyloidosis	PS, 2′-OMe, 2′-F	GalNAc–siRNA conjugate	TTR	Alnylam Pharmaceuticals	3	NCT03759379
Fitusiran (ALN-AT3SC)	Hemophilia	PS, 2′-OMe, 2′-F	GalNAc–siRNA conjugate	AT	Alnylam Pharmaceuticals partnered with Genzyme	3	NCT03549871 NCT03974113 NCT03754790 NCT03417102 NCT03417245
Cemdisiran (ALN-CC5)	Complement-mediated diseases	PS, 2′-OMe, 2′-F	GalNAc–siRNA conjugate	C5	Alnylam Pharmaceuticals	2	NCT03999840 NCT03841448
ALN-AAT02	Alpha-1 liver disease	PS, 2′-OMe, 2′-F	GalNAc–siRNA conjugate	AAT	Alnylam Pharmaceuticals	1/2	NCT03767829
ALN-AGT	Hypertension	PS, 2′-OMe, 2′-F, GNA	GalNAc–siRNA conjugate	AGT	Alnylam Pharmaceuticals	1	NCT03934307
ARO-AAT	Alpha-1 antitrypsin deficiency	PS, 2′-OMe, 2′-F, inverted base	GalNAc–siRNA conjugate	AAT	Arrowhead Pharmaceuticals	2/3	NCT03946449 NCT03362242 NCT03945292
ARO-HBV	Hepatitis B	PS, 2′-OMe, 2′-F, inverted base	GalNAc–siRNA conjugate	HBV gene	Arrowhead partnered with Janssen	1/2	NCT03365947
ARO-APOC3	Hypertriglyceridemia, familial chylomicronemia	PS, 2′-OMe, 2′-F, inverted base	GalNAc–siRNA conjugate	ApoC3	Arrowhead Pharmaceuticals	1	NCT03783377
ARO-ANG3	Hypertriglyceridemia	PS, 2′-OMe, 2′-F, inverted base	GalNAc–siRNA conjugate	ANGPTL3	Arrowhead Pharmaceuticals	1	NCT03747224
AMG 890	Cardiovascular disease	Undisclosed	GalNAc–siRNA conjugate	Lp(a)	Arrowhead Pharmaceuticals partnered with Amgen	2	NCT03626662

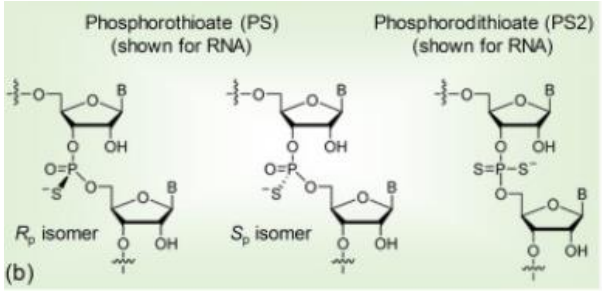
1 siRNA的化学修饰

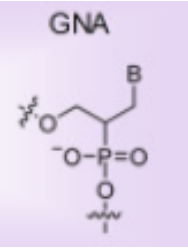
siRNA的化学修饰

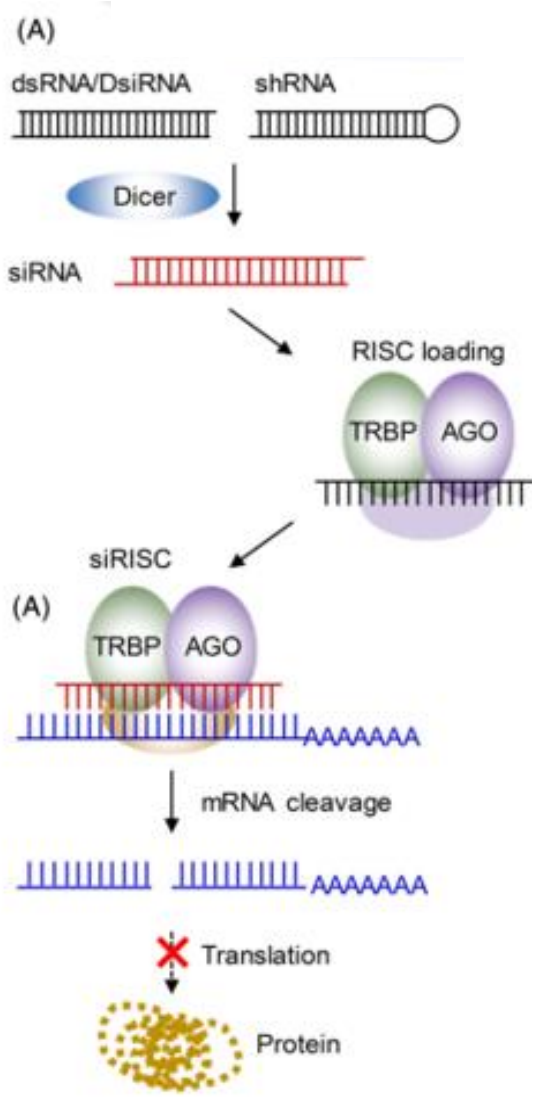










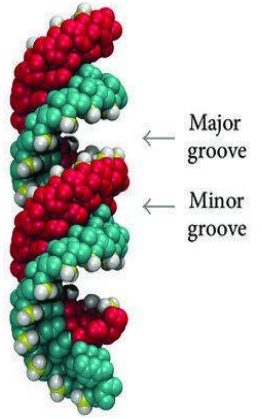


siRNA沉默机制

对siRNA的化学修饰规则：

1、保持或模拟双链A型RNA的特性，该双链A型RNA具有带电荷的磷酸二酯键骨架和至少19个核苷酸的sense链；

2、2‘-F和2-OMe与2‘-OH基团的特性非常相似，并对TRBP蛋白和Ago2具有高度耐受性。



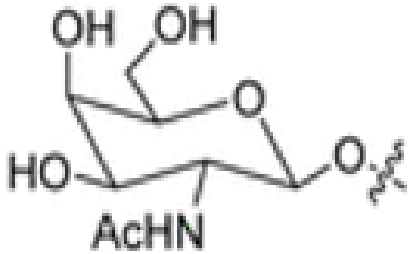
A-form siRNA

2

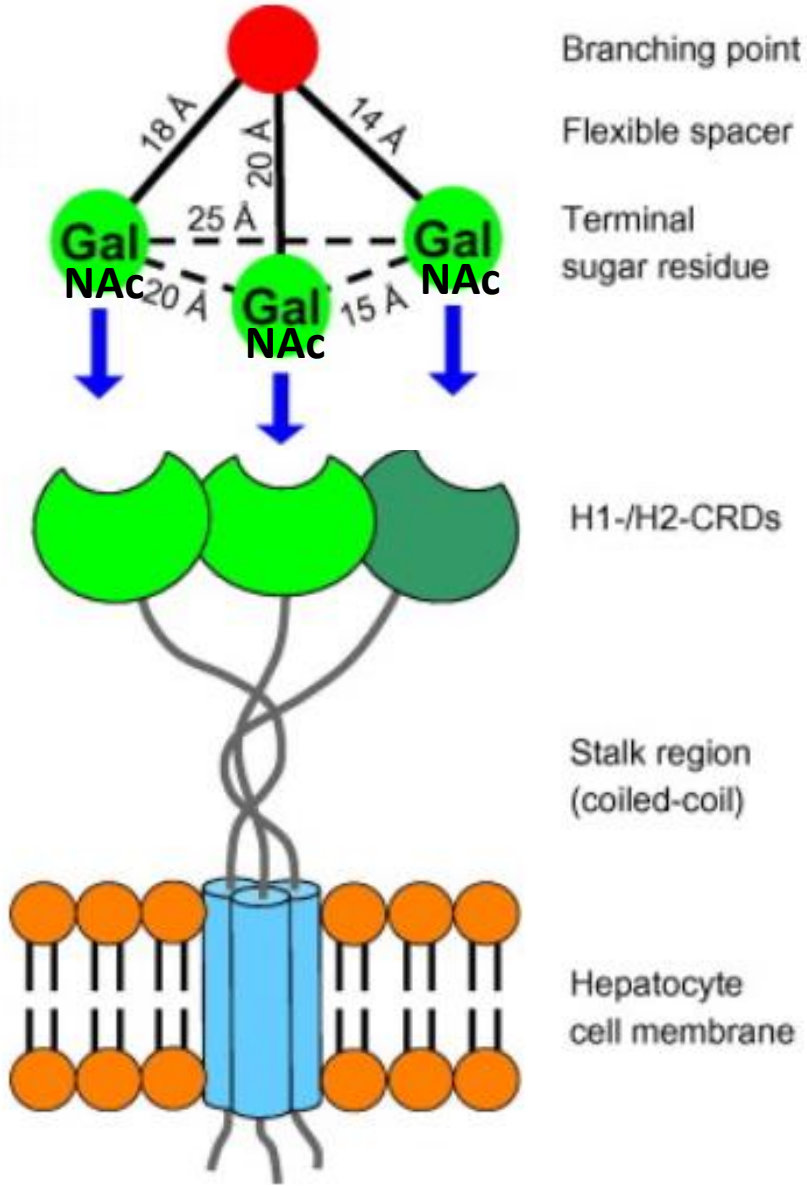
GalNAc递送系统

GalNAc对ASGPR的特异性结合

GalNAc



ASGPR



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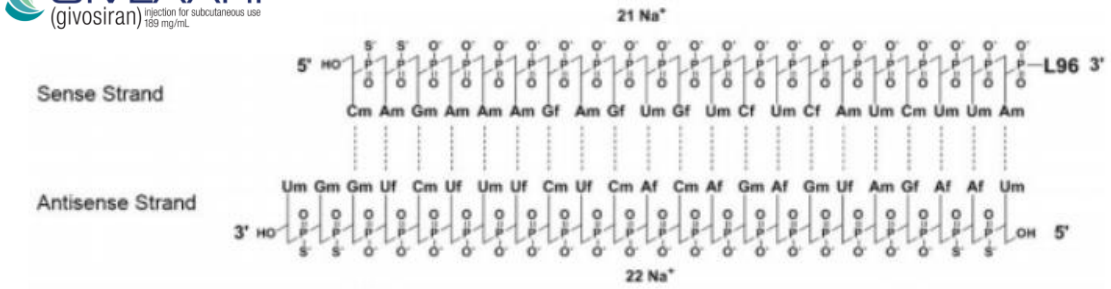
The first and only FDA-approved medicine for the treatment of adults with acute hepatic porphyria (AHP)

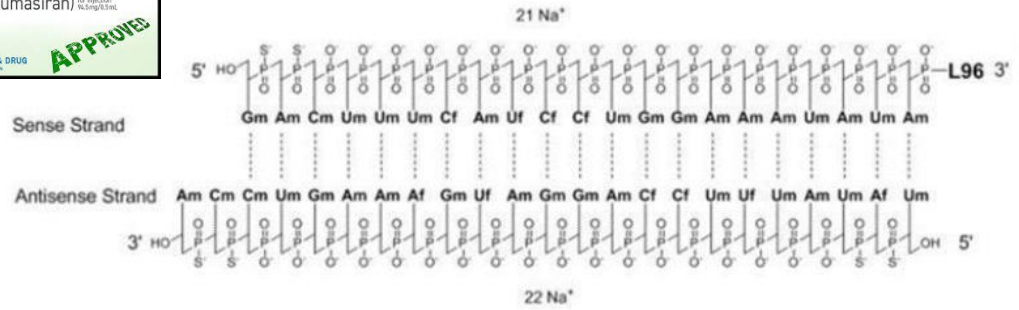
GIVLAARI™ (givosiran) injection for subcutaneous use 189 mg/mL



Alnylam

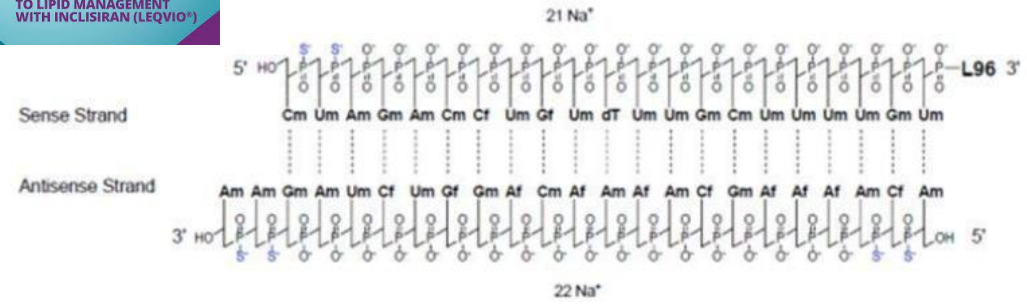
OXLUMO (lumasiran) for injection 94.5mg/0.5mL

U.S. FOOD & DRUG ADMINISTRATION APPROVED



LEQVIO® inclisiran

INTRODUCING AN INNOVATIVE APPROACH TO LIPID MANAGEMENT WITH INCLISIRAN (LEQVIO®)



Linker

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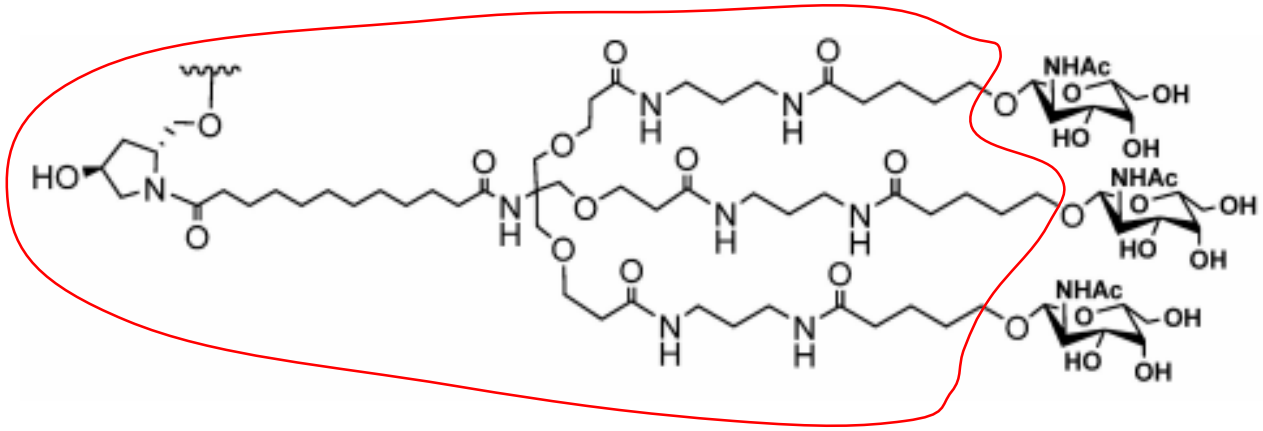
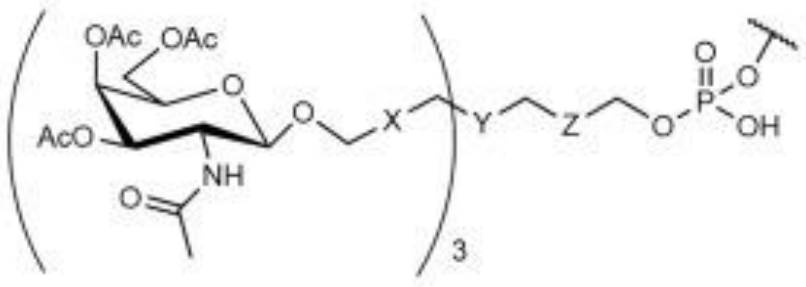
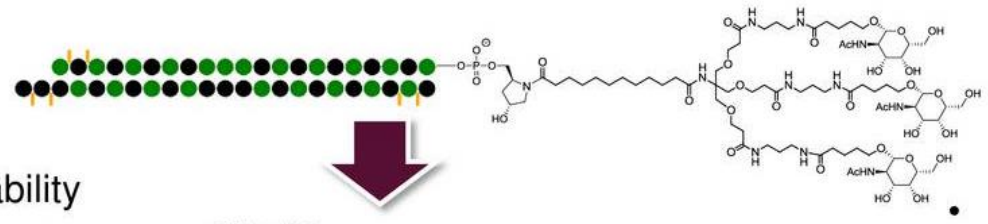




GalNAc

GalNAc递送系统作用特点

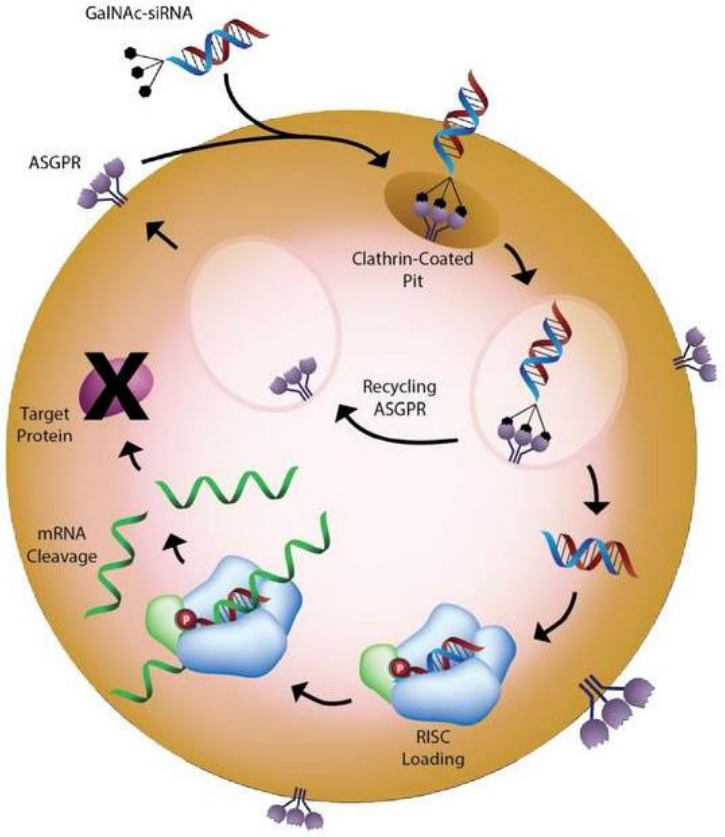


siRNA

- Metabolic stability
- Intrinsic potency

Ligand

- Trivalent GalNAc
- High affinity and specificity



Asialoglycoprotein Receptor (ASGPR)

- Highly expressed in hepatocytes
- High capacity receptor
- Conserved across species

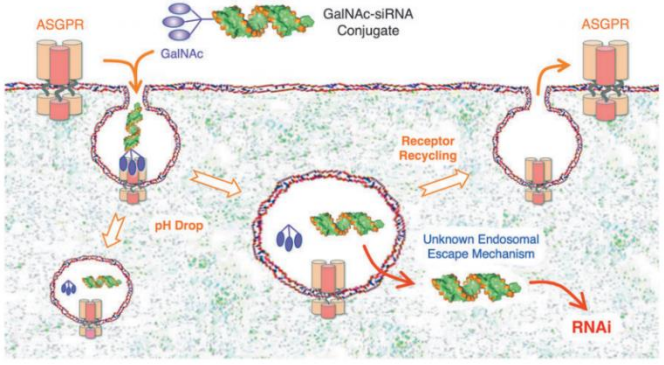
Alnylam PHARMACEUTICALS

受体为ASGPR,仅在肝脏实质细胞特异性高表达

细胞表面ASGPR数量级为10^6 **优势1**

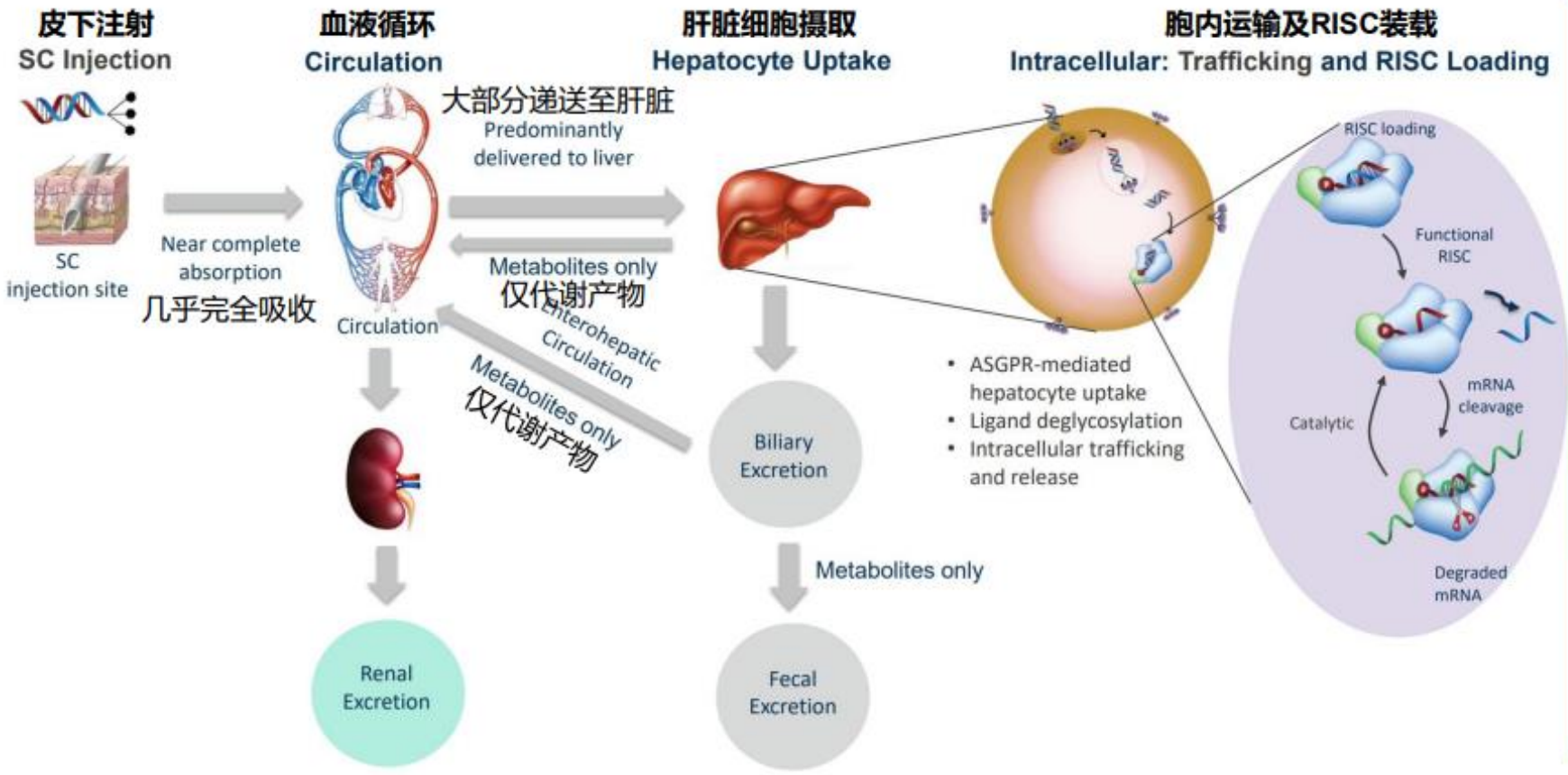
内吞循环速度快，仅需15min **优势2**

内吞体逃逸速度低于0.01%



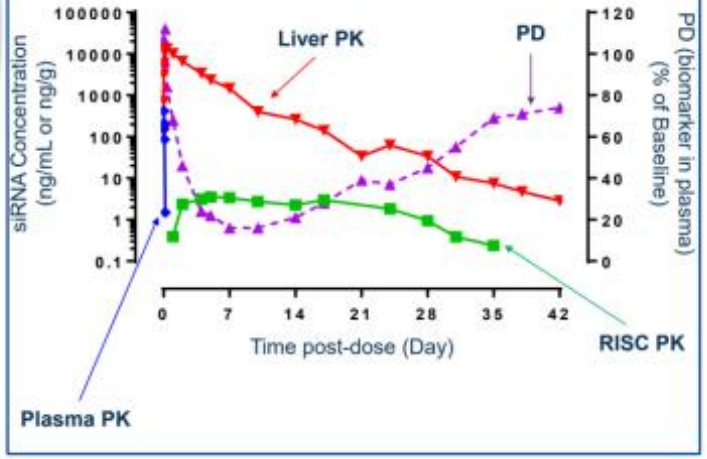
GalNAc-siRNA代谢过程及作用机制

优势3



GalNAc-siRNA:

- 迅速被肝脏细胞内吞
- 在溶酶体中累积（对siRNA稳定性要求高）
- siRNA能够持续不断从溶酶体中释放，相比LNP递送有更持久的RISC装载过程
- 完成装载后RISC半衰期变化不大



劣势： 1、仅靶向肝脏，限定了应用器官
2、肝癌中，ASGPR在肝脏的非实质细胞中不表达，限制了治疗