



小核酸偶联递送专利技术分析

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目 录

01 背景

02 组织递送相关技术和专利概述

03 肝脏递送及GalNAc专利布局

04 肝外递送技术

05 总结

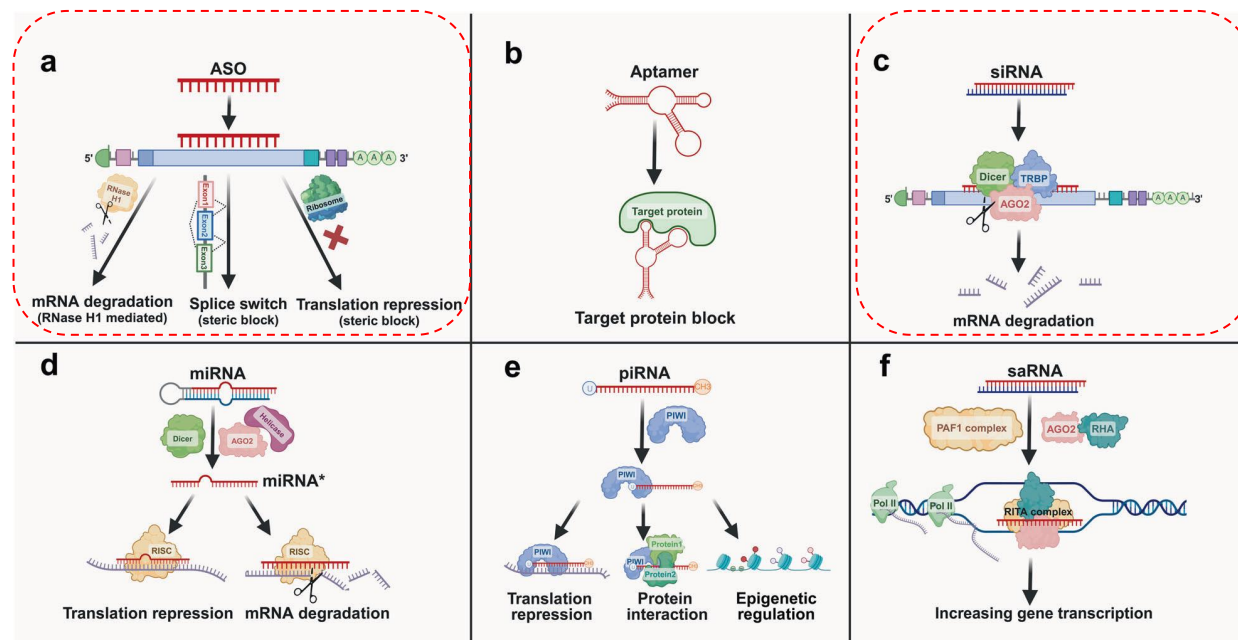
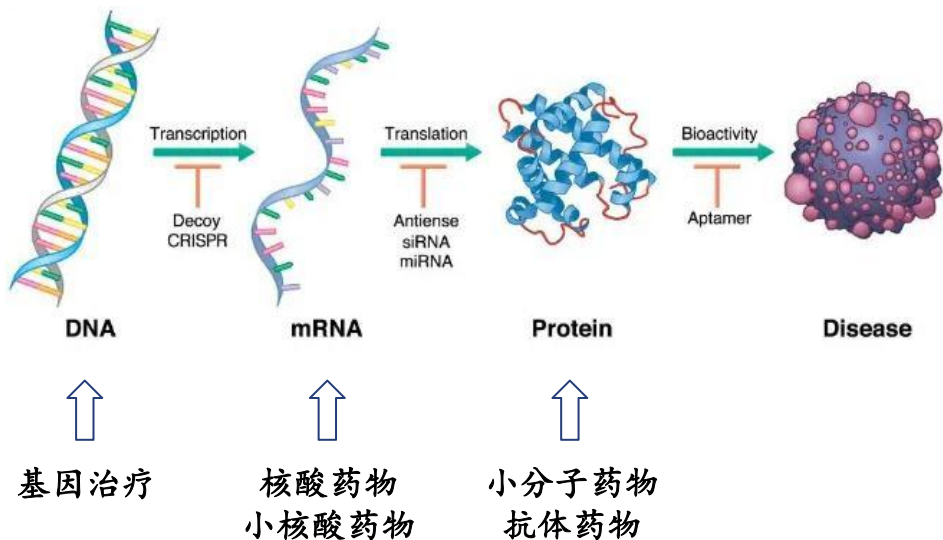


01 小核酸偶联递送技术背景

核酸药物：作用于上游的创新机制药物

- **核酸药物**：传统小分子和抗体药物，大多直接作用于已经生成的蛋白质；而核酸药物把干预环节前移到了蛋白质翻译之前，通过调控RNA来影响蛋白质表达，其药物成分由序列经过特定设计的核苷酸构成，分为小核酸药物和mRNA药物/疫苗等。
- **小核酸药物**是由十几个到几十个核苷酸组成的单链或双链寡核苷酸序列。广义的小核酸药物按作用机制可分为两类：
 - ✓ 以RNA为靶点、通过促进或抑制翻译来调节蛋白质表达，包括**反义核酸(ASO)**、**小干扰核酸(siRNA)**、**微小RNA(miRNA)**、**小激活RNA(saRNA)**和**PIWI-interacting RNA(piRNA)**，目前上市药物主要集中在siRNA和ASO；
 - ✓ 以蛋白质为靶点的**Aptamer (适配体)**，可特异性结合靶蛋白，起到类似抗体的功能。

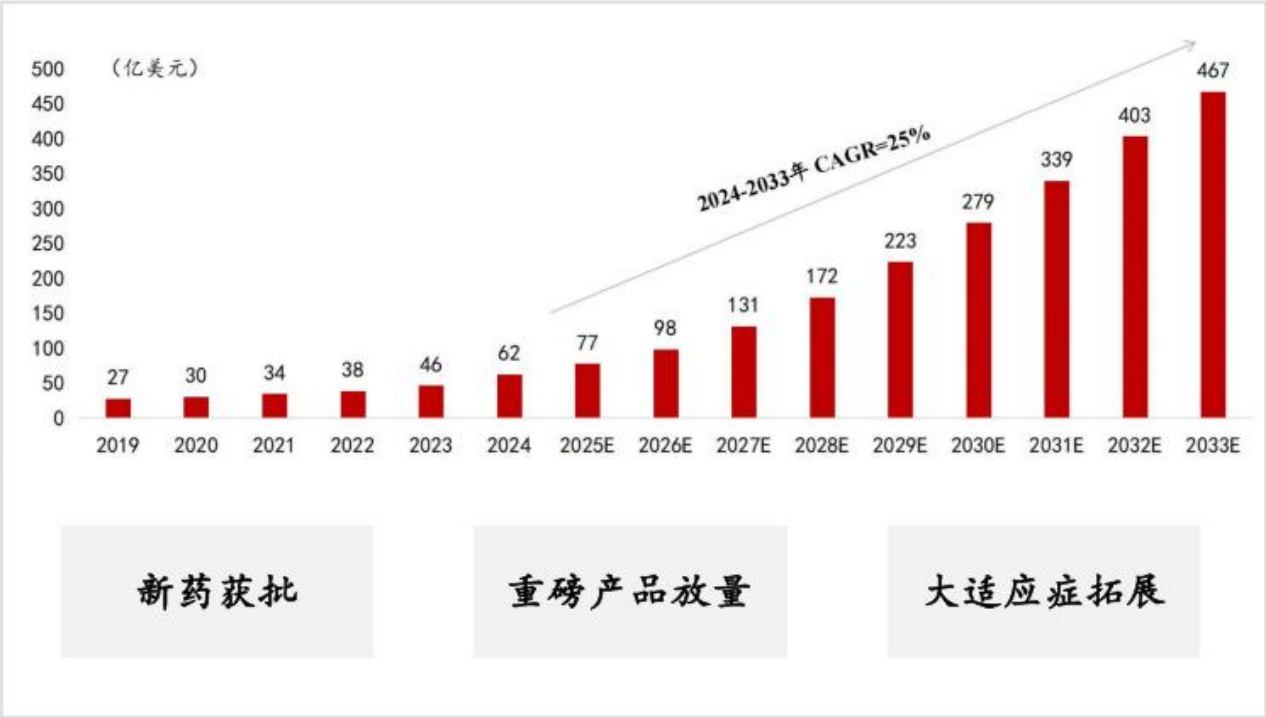
药物作用目标



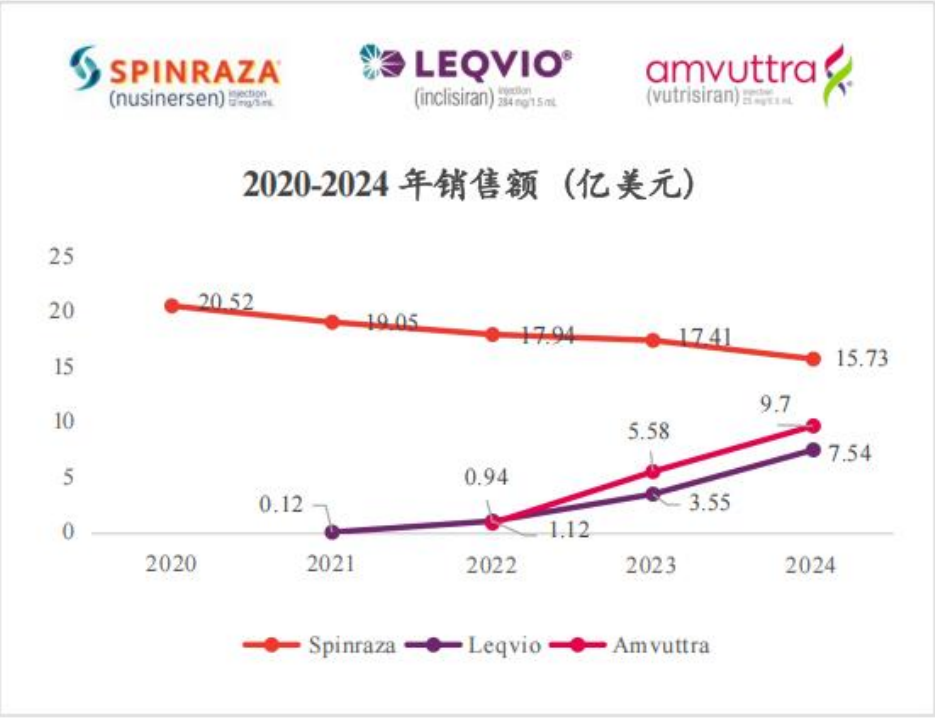
全球核酸市场快速增长

➤ 全球小核酸药物市场增长强劲，市场规模从2019年的27亿美元增长至2024年的**62亿美元**，2033年有望达到467亿美元，2024-2033年市场将保持高速增长，复合年增长率达**25%**。尤其值得关注的是，未来市场增长未必主要来自更多罕见病产品，而可能来自给药频率低、患者基数大的**慢病产品**。

全球小核酸药物市场规模（2019-2033年）



潜在销售额破\$1B 的重磅炸弹



重大交易与并购事件（部分）

时间	买方-标的	金额	涉及平台
2019	诺华-The Medicines Co.	97亿美元	Inclisiran(GalNAc)
2021	诺和诺德-Dicerna	~33亿美元	GalXC平台
2023.07	罗氏-Alnylam zilebesiran	28亿美元	AGT siRNA高血压
2023.11	BMS-Avidity心血管	最高23亿美元	AOC心血管≤5靶点
2024.01	诺华-船望心血管siRNA	1.85亿首付+41.65亿潜在	siRNA心血管组合
2024.11	Sarepta-Arrowhead	首期8.25亿+最高100亿	罕见病siRNA 4+3款
2025.06	AbbVie-Capstan收购	21亿美元	CellSeeker tLNP
2025.10	诺华-Avidity收购	120亿美元(溢价46%)	AOC平台+3项III期
2025.11	礼来-圣因RNAi平台	12亿美元	LEAD平台代谢病
2026.02	罗氏-圣因单药许可	2亿首付+15亿	RNAi肥胖/CVM
2026.05	GSK-时安SA030	10.05亿美元	ALK7 siRNA脂肪靶向

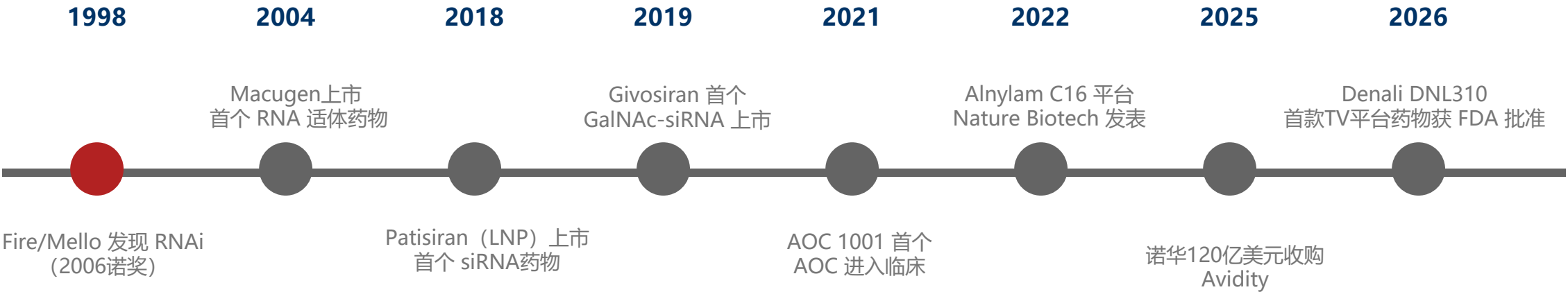
全球已上市**小核酸偶联药物**——均为GalNAc偶联（截至2026-09）

药物（商品名）	公司	靶点	递送方式	获批年	适应症
Givosiran(Givlaari)	Alnylam	ALAS1	GalNAc-siRNA	2019	急性肝卟啉病
Lumasiran(Oxlumo)	Alnylam	HAO1	GalNAc-siRNA	2020	PH1
Inclisiran(Leqvio)	诺华/Alnylam	PCSK9	GalNAc-siRNA	2020/21	高胆固醇血症
Vutrisiran(Amvuttra)	Alnylam	TTR	GalNAc-siRNA	2022	hATTR-PN+ATTR-CM
Nedosiran(Rivfloza)	Dicerna/诺和诺德	LDH	GalXC-siRNA	2023	PH1
Fitusiran(Qfitlia)	Sanofi/Alnylam	AT	GalNAc-siRNA	2025	血友病A/B
Plozasiran(Redempto)	Arrowhead	ApoC-III	GalNAc(TRiM)-siRNA	2025	FCS/高甘油三酯
Eplontersen(Wainua)	Ionis/AZ	TTR	GalNAc-ASO	2023	hATTR-PN
Olezarsen(Tryngolza)	Ionis	ApoC-III	GalNAc-ASO	2024	FCS
Donidalorsen	Ionis/大冢	PKK	GalNAc-ASO	2025	预防12岁及以上患者的遗传性血管性水肿发作

偶联递送平台分类（按缀合基团）

平台类型	代表靶头/配体	可递送组织	代表公司
GalNAc 偶联	ASGPR（三/四价 GalNAc）	肝	Alnylam/Ionis/Dicerna/瑞博/舶望
抗体偶联 AOC	TfR1/CD22/Nectin-4/SIRPα	肌肉/心肌/CNS/免疫/肿瘤	Avidity/Dyne/Tallac/Denali/迦进
脂质偶联	C16/C22/DCA/胆固醇	CNS/肺/眼/心/肌/脂肪/肾	Alnylam/McGill
多肽偶联 PAC	细胞穿透肽	肌肉/皮肤/肿瘤	PepGen/圣诺
小分子配体偶联	整合素/GLP1R/AdipoLigand	肺/心/脂肪/肿瘤	Arrowhead/Alnylam
适体偶联	PEG-RNA 适体	眼	Eyetechnology/Iveric
自递送 SCAD	辅助寡核苷酸 ACO	CNS/眼/肺/关节	中美瑞康

小核酸偶联递送技术重要里程碑事件



02 组织递送相关技术概览

组织递送技术总览

组织	主导平台	主导受体/靶点	最高临床进度	已上市产品
肝	GalNAc	ASGPR	上市	8 siRNA+多ASO
骨骼肌	AOC	TfR1	III期+BLA	无
CNS	C16/TV/SCAD	TfR1/CD98hc/ACO	I-II期	无
心脏	AOC/TRiM	TfR1/GLP1R	IND前	无
脂肪	TRiM双脂质	ALK7/INHBE	I/IIa期	无
肾脏	STRIKE	Megalin	I/II期	无
肺	TRiM/C16	$\alpha v\beta 6$ /亲脂	I/II期	无

肝脏靶向技术高度成熟，肝外靶向尚处于早期探索阶段

公司	肝脏	CNS	脂肪	骨骼肌	肺	心脏	肾脏
Alnylam	上市	Ph2 (ALN-APP)	Ph1	Pre	Pre	Pre	Pre
Arrowhead	上市	Ph1 (ARO-MAPT)	Ph1	Ph1	Ph2 (ARO-RAGE)	Pre	Pre
Ionis	上市	Pre		Pre		Ph1 (ION826)	Pre
Avidity				注册临床 (AOC-1044)			
Dyne				注册临床 (DNYE-251)			
中国企业	Ph3	Pre	Ph1	Pre	Pre	Pre	Pre

肝脏靶向—性价比与速度

技术特征：

GalNAc平台高度成熟，底层技术在国内已具备广泛验证基础。

交易核心：

合作对价相对较低，Pharma更看重管线推进速度与末端商业化成本控制。

肝外靶向—概念验证与平台溢价

技术特征：

处于早期探索阶段，跨组织递送构成极高的核心技术护城河。

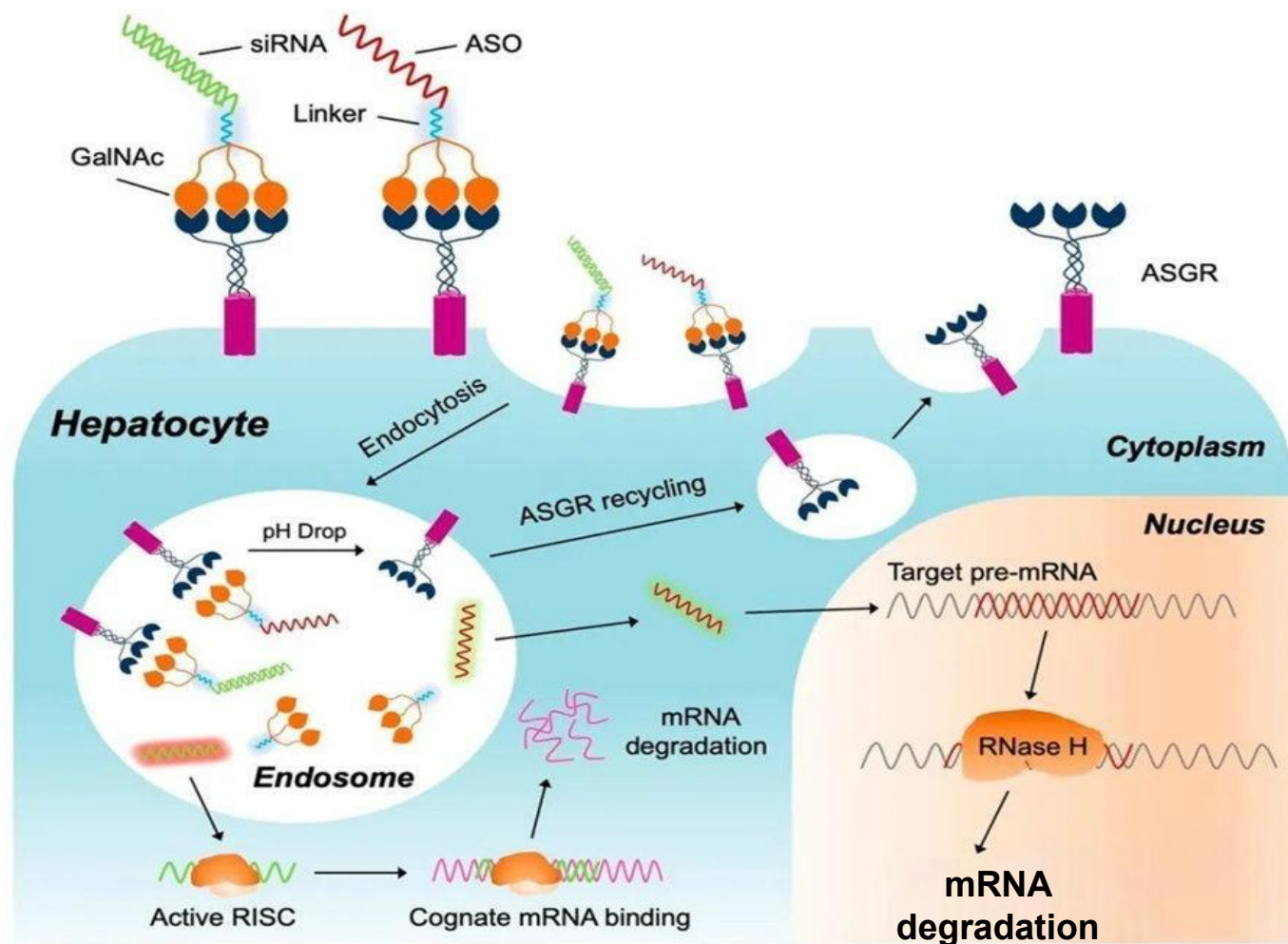
交易核心：

率先实现CNS/肌肉等肝外组织突破的企业，享有极高平台溢价和交易对价。

03 肝脏递送技术 · GalNAc专利布局

GaINAc-ASGPR 肝靶向偶联

三价 GaINAc 经 ASGPR 受体介导内吞，肝内摄取占比高

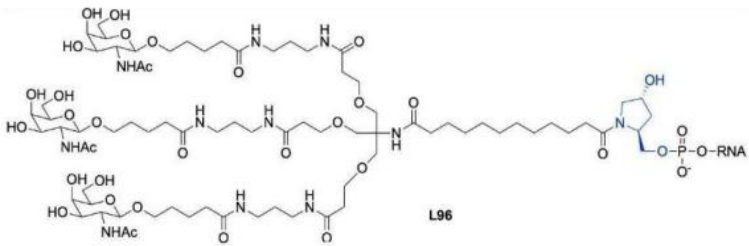


技术要点

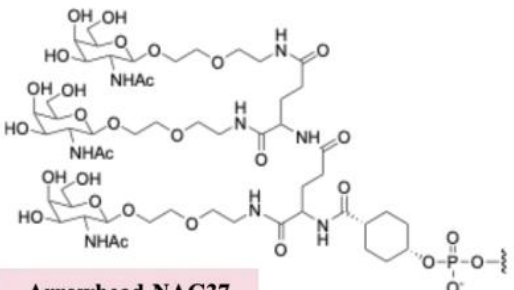
- ASGPR 在肝细胞表面高表达并快速循环，对三价 GaINAc 的亲和力达纳摩尔级
- 皮下给药后肝内摄取占全身清除的大部分（文献报道 >90%）；靶蛋白降幅因靶点而异，多在 50%–90%
- 获批产品的给药间隔从每月一次（givosiran）到每年两次（inclisiran）不等

肝脏代表平台与公司

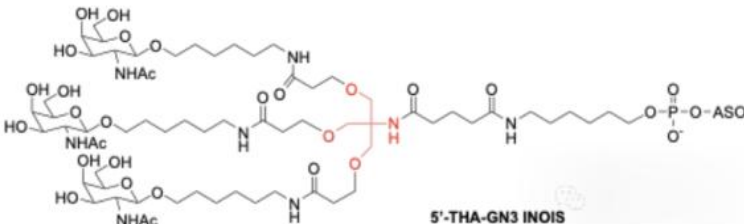
公司/平台	配体架构	阶段
Alnylam GalNAc	三叉戟 GalNAc	6款上市
Ionis LICA	三叉戟 GalNAc	Eplontersen/Olezarsen上市
Arrowhead	三触 NAG25/NAG37	Divesiran/Zerlasiran II/III期
Dicerna GalXC	四触GalNAc(tetraloop)	Nedosiran上市；诺和诺德33亿收购



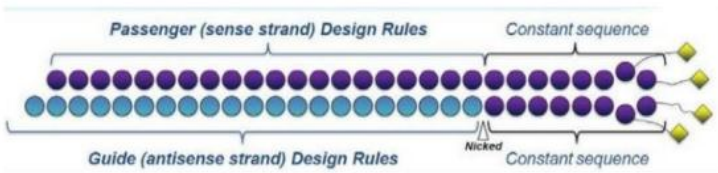
Alnylam-L96



Arrowhead-NAG37



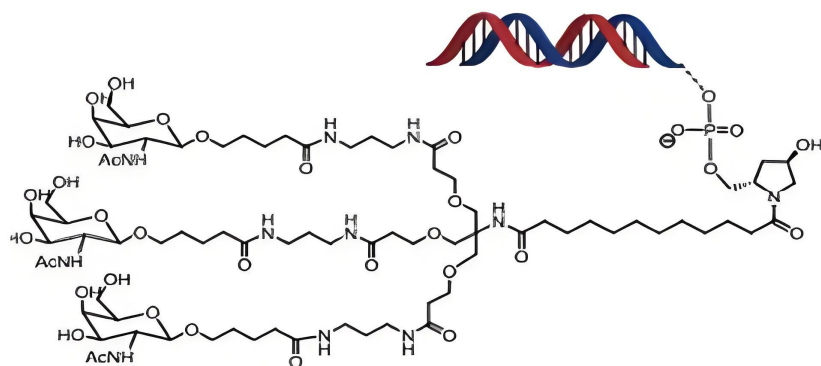
Ionis-5'THA-GN3



Dicerna-GalXC

L96的布局策略：一个分子被拆分成两部分——“五元环连接子”与“三叉戟”

L96 分子结构



三价 GalNAc 通过“三叉戟 + 连接子”偶联于 siRNA 有义链 3' 末端，以高亲和力结合肝细胞表面 ASGPR，实现肝靶向摄取。L96 是 Alnylam 众多候选中的代表分子，也是其基础专利体系的“载体”。

Alnylam 的 GalNAc 专利布局策略

GalNAc 单糖不可独占：属已公开糖类，无法对“三价 GalNAc 本身”主张通式。

链状连接子属常规：线性 PEG 等链状连接设计不被视为显著创新点。

把创新拆分：①五元环连接子；②三叉戟骨架。分别布局专利族。

策略意义：拆分后的每族独立可执行，给竞争对手规避造成更大阻碍。

Alnylam的GalNAc专利布局

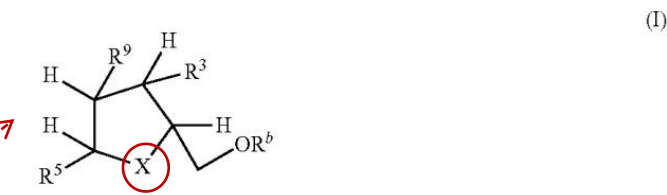
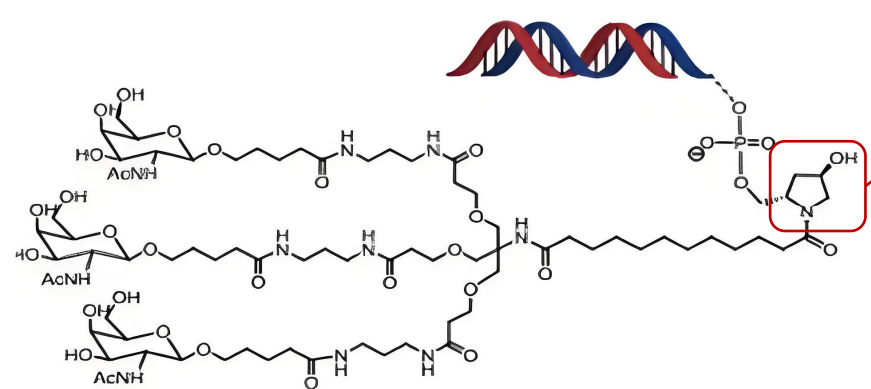
专利族	代表专利	权利要求要点	(预估) 到期
五元环连接子族	WO2004094595A2 族 (Alnylam 2004)	限定含五元环连接子的 GalNAc 偶联物结构	2025年已过期
三叉戟族	WO2009073809 族 (US8106022B2/ US8828956B2)	三个 GalNAc 经同一碳原子三叉戟与核酸偶联 (“三叉戟专利”)	2028-08 / 2028-12

2028 年前后，GalNAc 偶联家族专利陆续到期

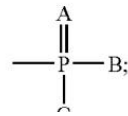
Alnylam的GalNAc专利布局

五元环连接子家族WO2004094595A2 代表专利US8344125B2 (到期时间2029-12-12, 无中国同族)

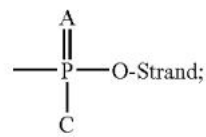
1. An iRNA agent comprising a first strand and a second strand, wherein at least one subunit having a formula (I) is incorporated into at least one of said strands:



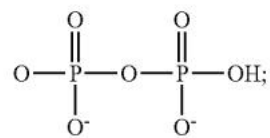
wherein:
X is N(CO)R⁷, or NR⁷;
Each of R³ and R⁹ is, independently, H, OR^a, or OR^b,
provided that only one of R³ or R⁹ is OH, OR^a, or OR^b;
R⁵ is H, or C₁-C₆ alkyl;
R⁷ is C₁-C₂₀ alkyl substituted with NR^cR^d or NHC(O)R^d;
R^a is H or:



R^b is H or:



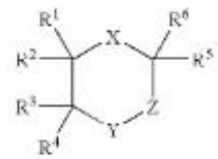
Each of A and C is, independently, O or S;
B is OH, O⁻, or



R^c is H or C₁-C₆ alkyl; and

R^d is a carbohydrate radical.

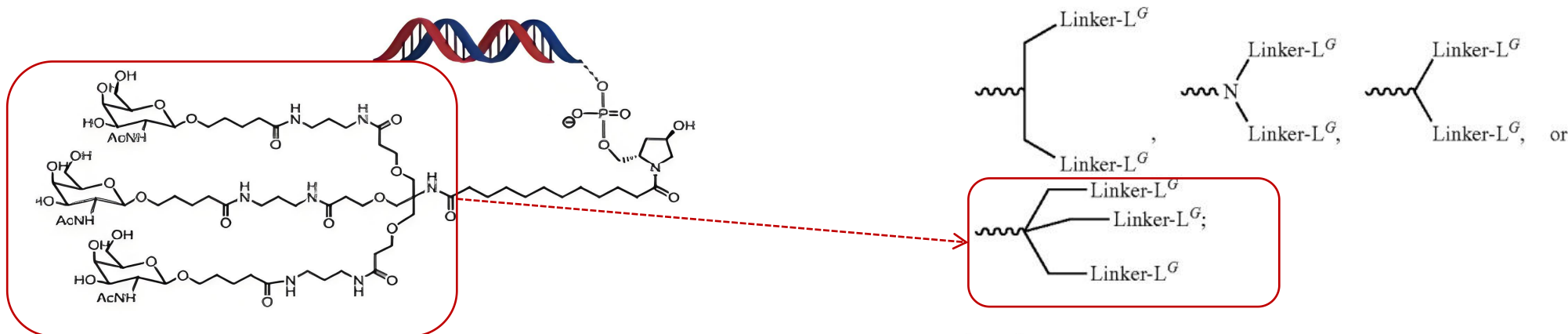
保护范围：涵盖了五元环连接子。美国同族专利US8507661B2保护了六元环



Alnylam的GalNAc专利布局

三叉戟家族WO2009073809A2（无中国同族）_代表专利1: US8828956B2（到期时间2028年12月4日）

1. A modified RNA agent comprising a structure shown below:



wherein:

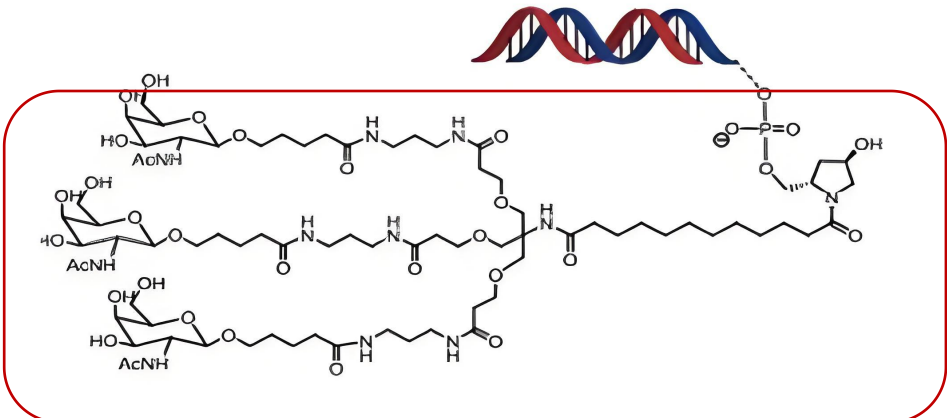
L^G is independently for each occurrence a ligand; and all of the nucleotide sugars of the modified RNA agent are modified.

保护范围: 1) 多种双分叉结构, 以及三叉戟结构, 2) 未限定与RNA试剂的连接方式 (例如五元环)

限制：三叉戟结构的分支点为C原子

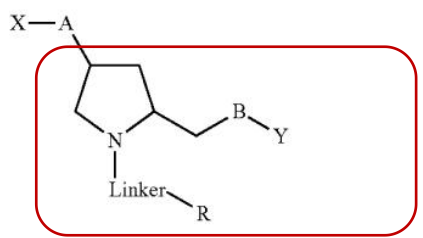
Alnylam的GalNAc专利布局

三叉戟家族WO2009073809A2 (无中国同族) _代表专利2: US8106022B2



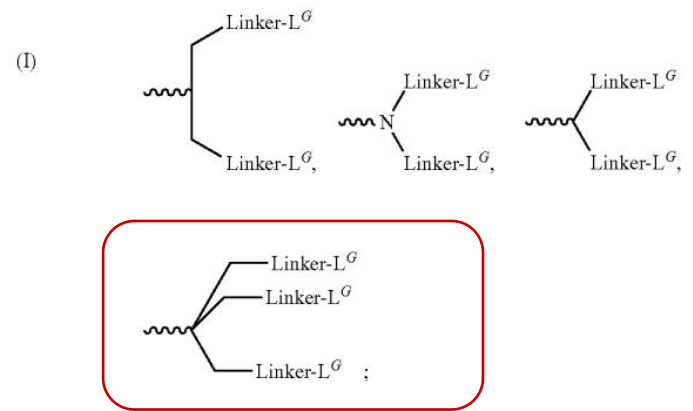
保护范围：五元环+三叉戟结构的组合

1. An iRNA agent comprising a compound having the structure shown in formula (I)

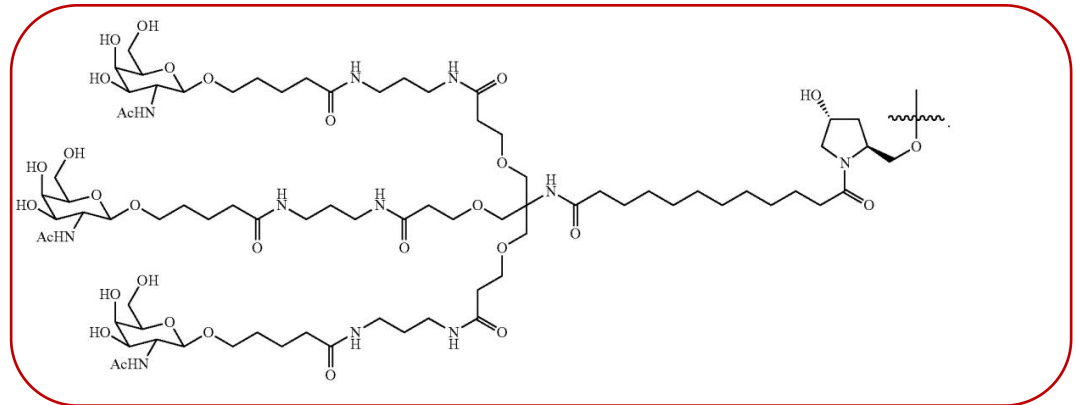


wherein:

R is L^G or has the structure shown below:



15. The iRNA agent of claim 2, wherein said compound has the structure

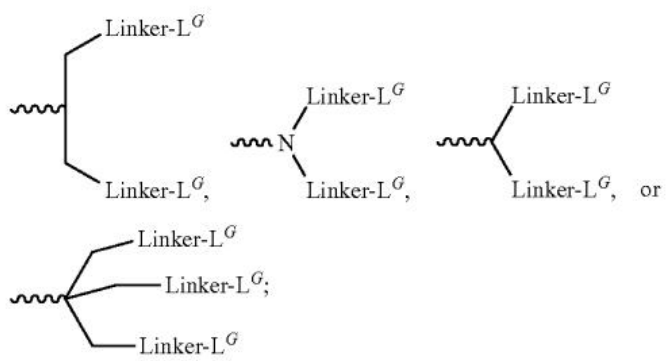


Alnylam的GalNAc专利布局

三叉戟WO2009073809A2族——基于三叉戟的靶点专利（部分）

US9370581B2

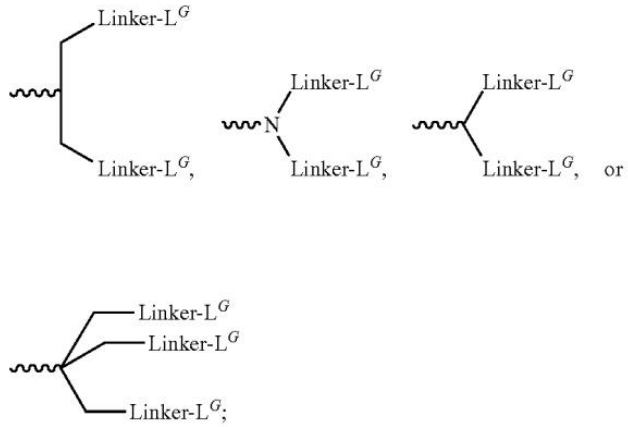
1. A modified TTR-targeting oligonucleotide comprising a structure shown below:



wherein L^G is independently for each occurrence a ligand;
and
wherein the oligonucleotide targets the TTR gene.

US9370582B2

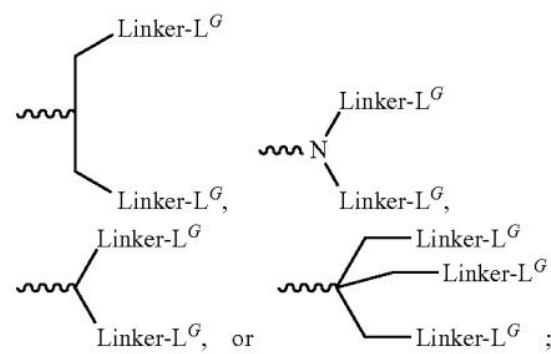
1. A modified PCSK9-targeting oligonucleotide comprising a structure shown below:



wherein L^G is independently for each occurrence a ligand;
and
wherein the oligonucleotide targets the PCSK9 gene.

US9252048B2

1. A modified HBV-targeting oligonucleotide comprising a structure shown below:



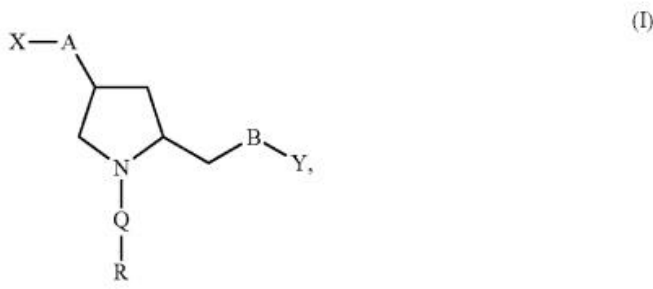
wherein L^G is independently for each occurrence a ligand,
and all of the nucleotide sugars of the oligonucleotide
are modified; and
wherein the oligonucleotide targets the HBV gene.

保护范围：靶向目的基因的寡核苷酸+三叉戟结构
价值：利用递送平台布局相关药物的结构性专利，范围大。

Alnylam的GalNAc专利布局

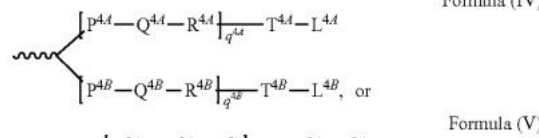
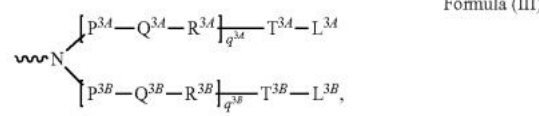
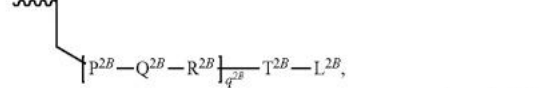
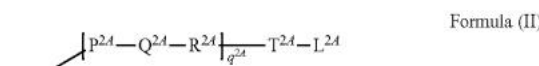
三叉戟WO2009073809A2族（无中国同族）_代表专利3: US11110174B2

1. A ligand-containing conjugate having the structure shown in formula (I):



wherein:
A and B are each independently for each occurrence O, N(R^N), or S;
one of X and Y is a solid support optionally linked via a linker group, or a phosphoramidite, and the other of X and Y is a protecting group;
R is L¹ or has the structure shown in formula (II)-(V)

R is L¹ or has the structure shown in formula (II)-(V)



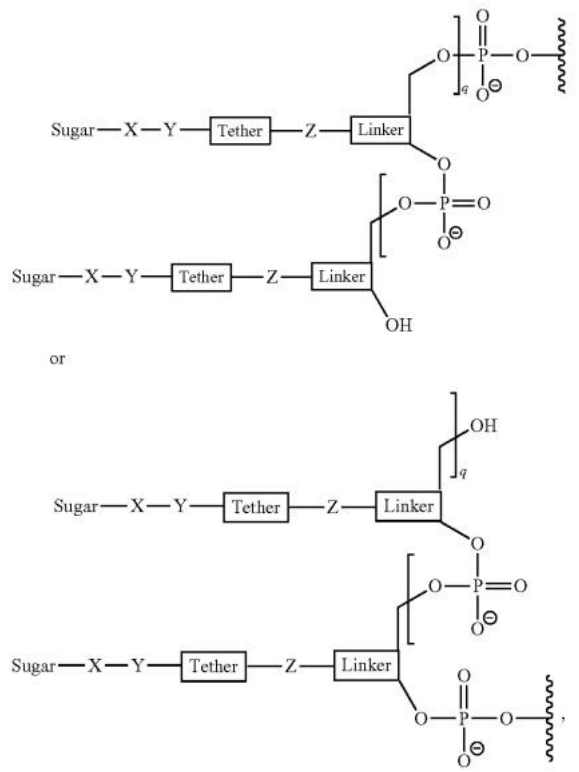
q^{2A}, q^{2B}, q^{3A}, q^{3B}, q^{4A}, q^{4B}, q^{5A}, q^{5B} and q^{5C} represent independently for each occurrence 0-20 and wherein the repeating unit can be the same or different;

保护范围：非最终产品，不包含小核酸；保护了固相合成时的结构

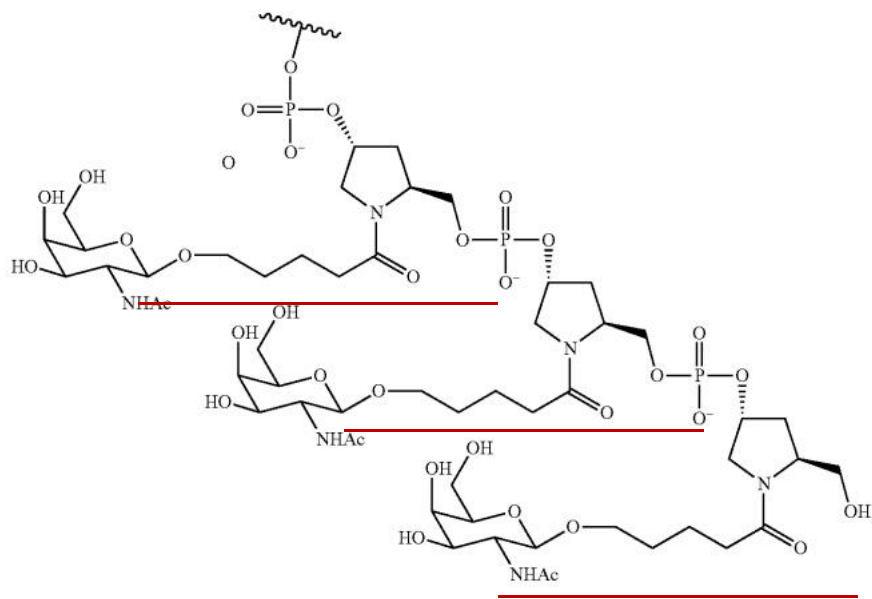
Alnylam的GalNAc专利布局

1+1+1族——US9867882B2

1. An oligonucleotide comprising one or more conjugate structures shown below:



29. The oligonucleotide of claim 5, wherein the conjugate structure is:



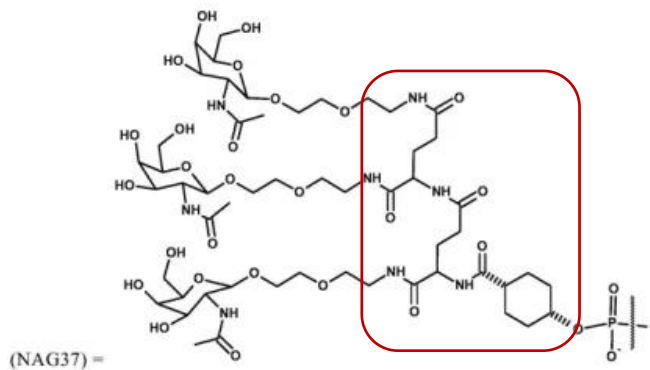
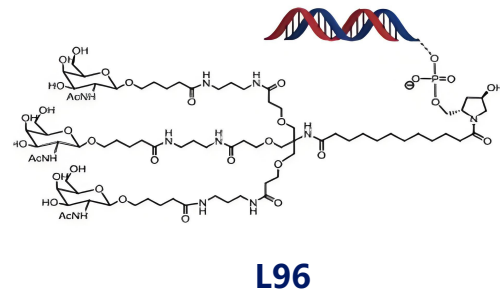
保护范围：三组并行的五元环+GalNAc的结构

专利规避思路之一：Arrowhead 两次“换骨”：NAG37 → NAG25

NAG37（第一代）

规避策略：

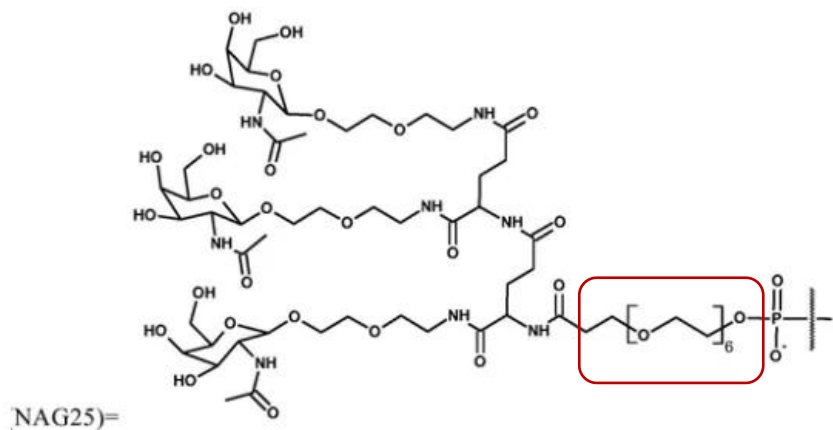
- (1) 双谷氨酸（天然氨基酸）构建三叉戟支架，避免连接到同一个碳原子；
- (2) 考虑到五元环linker的作用是作为一个中枢结构向外伸出三个基团，分别连接siRNA、GalNAc和固相载体，可将GalNAc 移至 5' 端；用环己烷 / 苯环（六元环）替代四氢吡咯（五元环连接子）——去掉五元环中与固相载体连接的基团。



代价：骨架合成复杂、成本高，携带与体内稳定性需重新优化。

NAG25（第二代）

去掉环状连接子，进一步降低成本



Alnylam v. Dicerna商业秘密诉讼

2015

起诉：Alnylam 在马萨诸塞州法院起诉 Dicerna，指控其盗用与 GalNAc 偶联技术相关的商业秘密。

2016–2017

互诉升级：Dicerna 提反诉，并在联邦法院指控 Alnylam 反竞争行为；双方就商业秘密与竞争行为展开多线交锋。

2018-04-20

庭前和解：陪审团开庭前数日达成和解；Alnylam 撤诉、Dicerna 撤反诉，双方均不承认过错。

和解条款：2500 万+靶点限制+不含任何 GaINAc IP 许可

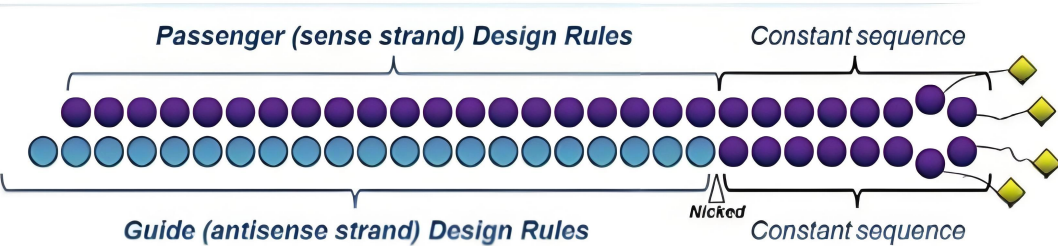
和解条款	具体内容
赔偿金额	总计 2500 万美元：首付 200 万现金 + 983,208 股普通股（作价约 1000 万）+ 另 1300 万分四年支付
靶点限制	Dicerna 在 “指定的 Alnylam 靶点” 上，18 个月至 4 年内不得推进寡核苷酸治疗药物开发
撤诉安排	Alnylam 撤销商业秘密盗用全部指控；Dicerna 撤销反诉及联邦法院的反竞争行为指控
IP 许可	不含任何 GaINAc 偶联 IP 许可，亦无其他 IP 授权——双方知识产权各自保留

解读：和解未授权 GaINAc 专利——Dicerna 以自有 GalXC 结构继续，这正是后来 Nedosiran 落地的专利背景。

专利规避思路之二：Dicerna的规避路径

GalXC / tetraloop 通过增加核苷酸形成tetraloop提供GalNAc偶联的基础

GalXC 设计原理



单一前体链折叠成双链，顶端 tetraloop 稳定结构；模拟体内RNA干扰机制（shRNA），进入细胞后由 **Dicer 酶加工** 为成熟 siRNA。
以“延伸双链 + 四环”代替“五元环连接子 + 三叉戟”，结构层不落入 Alnylam 基础族字面范围。

核心差异、代价与专利

规避逻辑：不以“三价 + 单一碳原子三叉戟”为必由路径，重构骨架本身。

代价：每分子多用约 16 个核苷酸，物料成本约 +36%；依赖 Dicer 内源加工路径。

专利：GalXC 平台族 WO2016100401A1，约至 2034 年；Nedosiran（2023 上市）为该平台代表性产品。

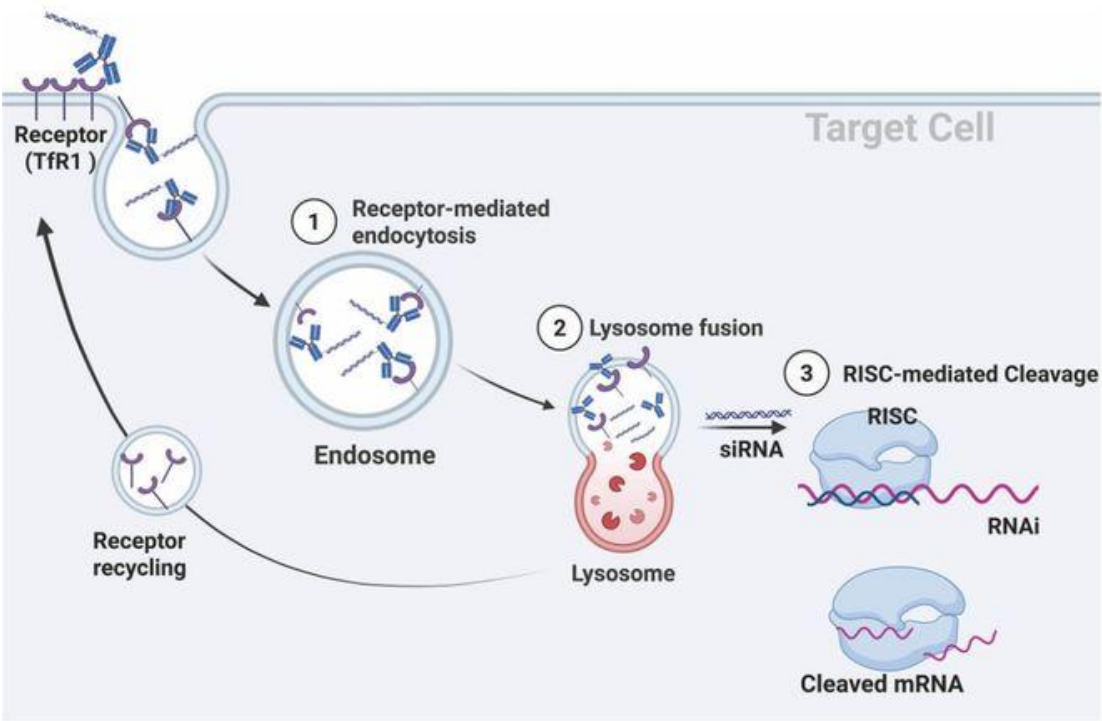
04-1 骨骼肌・AOC/POC 平台

骨骼肌递送的代表性平台

公司	平台	偶联策略	代表项目	阶段
Avidity(诺华)	AOC	全长抗TfR1 mAb+siRNA/PMO (AOC)	Del-zota (DMD)/ Del-desiran (DM1)/ Del-brax(FSHD)	III期+BLA
Dyne	FORCE™	TfR1 Fab+ASO/PMO(可 断裂linker) (AOC)	DYNE-101/251/302	III期+BLA (DYNE-251)
Sarepta/Arrowhead	TRiM™	α v β 6整合素靶向肽+siRNA (POC)	SRP-1001 (FSHD) / SRP-1003 (DM1)	I期
PepGen	EDO™	线性细胞穿透肽+PMO (POC)	PGN-EDO51/53(DM1)	II期
Entrada	EEV	环状细胞穿透肽 (POC)	VX-670 (DM1)	I/2期

AOC（抗体偶联寡核苷酸）：爆发前夜

Avidity TfR1 AOC原理



- TfR1 在骨骼肌、心肌高表达，并可介导血脑屏障跨越；TfR1 抗体/Fab 内吞后经溶酶体释放载荷
- 载荷类型覆盖 siRNA、ASO、PMO 等（Avidity/Dyne）
- 优势：特异性高，适配性强，半衰期长，工艺稳定

临床阶段的AOC绝大多数为TfR1靶向

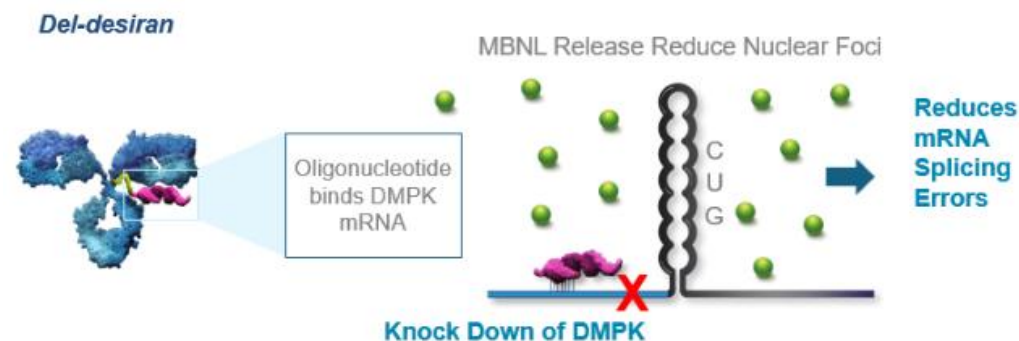
Drug	Company	Target	Linker	Antibody	Oligonucleotide	Indications	Phase
AOC-1001	Avidity	DMPK	SMCC	TfR1-targeted mAb	DMPK-siRNA	DM1	Phase III
AOC-1020	Avidity	DUX4	SMCC	TfR1-targeted mAb	DUX4-siRNA	FSHD	Phase III
AOC-1044	Avidity	Exon-44	SMCC	TfR1-targeted mAb	Exon-44-skipping PMO	DMD	Phase III
DYNE-101	Dyne	DMPK	Val-cit	TfR1-targeted Fab	DMPK-ASO	DM1	Phase I/II
DYNE-251	Dyne	Exon-51	Val-cit	TfR1-targeted Fab	Exon-51-skipping PMO	DMD	Phase I/II
TAC-001	Dyne	TLR9	PEG ₂₄ Phosphate bond	CD22-targeted mAb	CpG(TLR9 agonist)	Cancer	Phase I/II

TfR1 transferrin receptor 1, CD22 Siglec-2, DMPK dystrophin myotonia protein kinase, siRNA small interfering RNA, PMO phosphorodiamidate morpholino oligomer, DUX4 double homeobox protein 4, ASO antisense oligonucleotide, CpG cytosine phosphoric acid guanine, TLR9 toll-like receptor 9, DM1 myotonic dystrophy type 1, DMD Duchenne muscular dystrophy, FSHD facioscapulohumeral muscular dystrophy, SMCC succinimidyl 4-N-maleimidomethylsyclohexane-1-carboxylate.

Avidity TfR1-AOC的核心专利举例

WO2019113393A1, 申请日2019.6.7/ 美国同族**US10881743B2**, 授权日2021年1月5日——DM1适应症

1. A siRNA molecule conjugate comprising an anti-transferrin receptor antibody conjugated to a sense strand of a siRNA molecule that hybridizes to a target sequence of human DMPK mRNA and mediates RNA interference against the human DMPK mRNA preferentially in muscle cells in a human subject, wherein the anti-transferrin receptor antibody comprises two light chain variable domains and two heavy chain variable domains.



保护范围：转铁蛋白受体的**全长抗体**+靶向DMPK的siRNA组成的AOC。未限定抗体序列或者siRNA序列。

中国同族CN111902148B限定了几条具体siRNA序列：“其中所述siRNA包含指导链，所述指导链包含选自SEQ ID NO:13463、14048、14047、14049、14146、14072、13478、14147、12234和14199的核酸序列”

DYNE FORTE™平台的核心专利举例

Subramanian专利族，申请日2018年8月2日，包括可用于DM1、FSHD治疗的多个范围各异的AOC专利

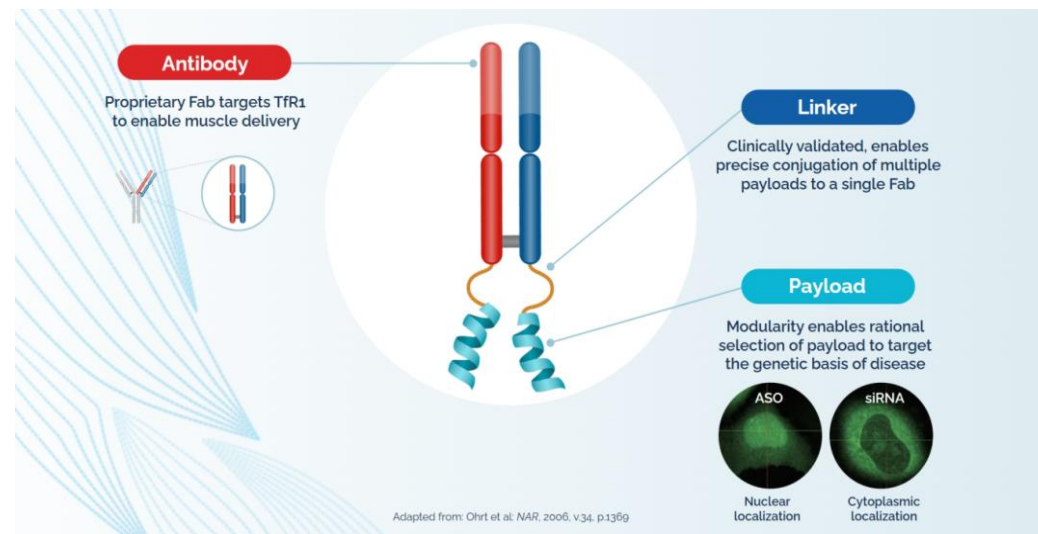
1. A complex comprising an anti-transferrin receptor antibody covalently linked to a 5' end or a 3' end of an oligonucleotide,

wherein the anti-transferrin receptor antibody binds in the range of C89 to F760 of human transferrin receptor protein 1 (TfR1) having an amino acid sequence as set forth in SEQ ID NO: 1 and wherein the anti-transferrin receptor antibody does not specifically bind to the transferrin binding site of TfR1;

wherein the oligonucleotide comprises one or more modifications and comprises a region of complementarity of at least 15 nucleotides in length to the nucleotide sequence as set forth in SEQ ID NO: 199, wherein the oligonucleotide is in the range of 15-30 nucleotides in length;

wherein the one or more modifications comprise a 2'-modified nucleoside selected from the group consisting of: a 2'-O-methyl nucleoside, a 2'-fluoro nucleoside, a 2'-O-methoxyethyl nucleoside, 2',4'-bridged nucleosides, and combinations thereof, and/or comprise a modified backbone comprising one or more phosphorothioate linkages.

20. The complex of claim 1, wherein the anti-transferrin receptor antibody is in the form of a Fab fragment.



TfR1抗体Fab片段的优势：

- ▶ 降低免疫原性：Fab分子量小，缺乏抗体的Fc段，可能减少不必要的免疫反应。
- ▶ 改善组织渗透：较小的尺寸有利于在目标组织间质中更有效地扩散。

保护范围：结合TfR1胞外区的抗体+靶向DUX4的带修饰的寡核苷酸，未限定抗体序列和核苷酸序列，从权限定是Fab片段。

Sarepta/Arrowhead $\alpha v \beta 6$ 整联蛋白靶向肽肌肉递送专利

WO2018085415 申请日2017.11.01/
中国同族CN109952376B, 授权日2021年1月5日

1. 一种 $\alpha v \beta 6$ 整联蛋白配体, 其包含:

$RG^1DLXaa^1Xaa^2L-Xaa^3Xaa^4L-R^1$ (SEQ ID NO:96) (式VIII)

其中

R是L-精氨酸;

G^1 是L-甘氨酸或N-甲基甘氨酸;

D是L-天冬氨酸或L-天冬氨酸盐或酯;

L是L-亮氨酸;

Xaa^1 是L-丙氨酸;

Xaa^2 是L- α -丁酸 (Abu);

Xaa^3 是L-瓜氨酸;

Xaa^4 是L- α -氨基异丁酸 (Aib);

R^1 是任选的, 存在时, 其包含PEG和/或连接基团。

16. 如权利要求14所述的组合物, 其中所述 $\alpha v \beta 6$ 整联蛋白配体与RNAi试剂偶联, 所述RNAi试剂能够抑制 **上皮细胞中靶基因** 的表达。

19. 如权利要求18所述的用途, 其中, 所述细胞选自下述: I型和II型肺泡上皮细胞, 杯状细胞, 分泌性上皮细胞, 纤毛上皮细胞, 角膜和结膜上皮细胞, 真皮上皮细胞, 胆管上皮细胞, 肠上皮细胞, 导管上皮细胞, 腺上皮细胞, 肾小管和上皮肿瘤或上皮癌。

保护范围: $\alpha v \beta 6$ 整联素结合多肽序列, 权利要求保护的具体用途并未涉及肌肉, 主要是各类**上皮细胞**

WO2022056277A1 申请日2021.09.10 (肌肉平台核心专利, 大部分同族在审)

1. A delivery vehicle for inhibiting expression of a gene expressed in skeletal muscle cells comprising:

(a) **an RNAi agent** comprising:

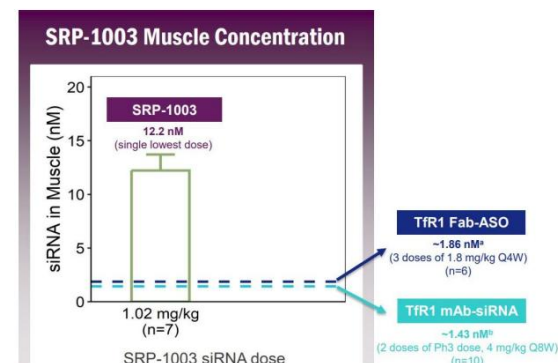
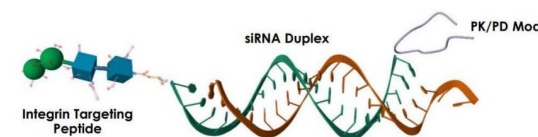
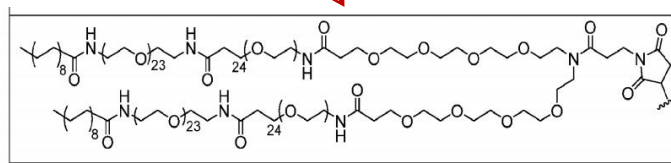
(i) an antisense strand comprising 17-49 nucleotides wherein at least 15 nucleotides are complementary to the mRNA sequence of a gene that is expressed in skeletal muscle cells

(ii) a sense strand that is 16-49 nucleotides in length that is at least partially complementary to the antisense strand;

(b) **a targeting ligand** with affinity for a receptor present on the surface of a skeletal muscle cell, wherein the targeting ligand is a polypeptide; and

(c) **a PK/PD modulator**;
wherein the RNAi agent is covalently linked to the targeting ligand and to the PK/PD modulator.

示例



要求保护范围: $\alpha v \beta 6$ 靶向肽 (Pep1为主力配体) + siRNA 载荷 (实施例测试了靶向MSTN、SOD1等基因) + 脂质PK/PD调节剂 (脂质链+PEG) (PK/PD增加了创造性高度)

04-2 CNS • 穿越 BBB

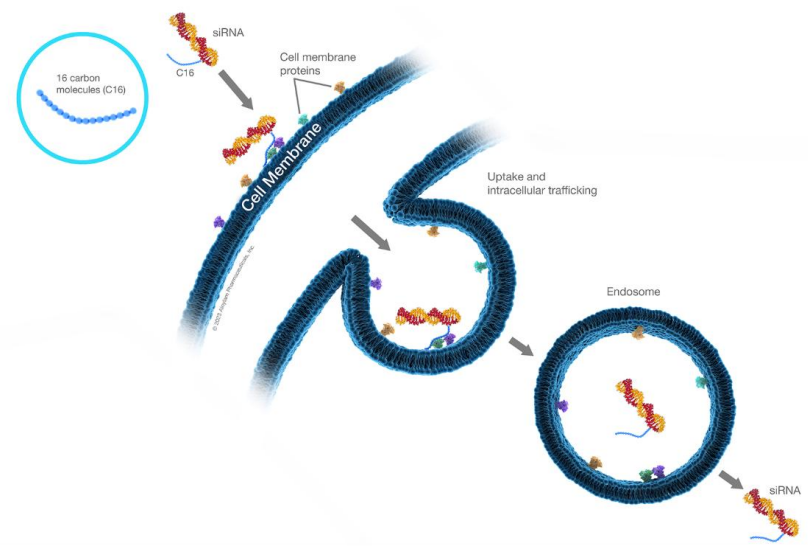
CNS递送代表技术平台

公司/平台	递送机制	给药途径	关键管线	阶段
Alnylam C16	2'-O-十六烷基亲脂链，增强（脑脊液）CSF半衰期+膜亲和	鞘内	Mivelsiran/ALN-APP(AD)	I期完成，II期启动
Denali TV/OTV	工程化Fc段结合TfR1/CD98hc，脑暴露>1000倍	静脉	DNL310(MPS II,已FDA批准AVLAYAH)、DNL628(MAPT)	DNL310上市；MAPT OTV I期
Arrowhead TRiM-BBB	小分子TfR1配体+共价连接+siRNA	皮下	ARO-MAPT(AD)、ARO-SNCA(PD)	I期
中美瑞康 SCAD	siRNA+辅助寡核苷酸(ACO)模块化偶联，自递送	鞘内/ICV	RAG-17(SOD1-ALS)	I期完成(Nature Medicine 2026.7)

Alnylam——C16亲脂偶联专利族

WO2019217459A1 申请日2019.05.07/US12397013B2, 中国同族处于驳回后复审状态

1. A double-stranded iRNA agent comprising:
an antisense strand which is complementary to a target gene;
a sense strand which is complementary to said antisense strand; and
one or more lipophilic moieties conjugated only to one or more internal positions on at least one strand, optionally via a linker or carrier;
wherein the one or more lipophilic moieties comprise a saturated or unsaturated C₄-C₁₈ hydrocarbon chain, and an optional functional group selected from the group consisting of hydroxyl, amine, carboxylic acid, sulfonate, phosphate, thiol, azide, and alkyne;
wherein the one or more internal positions are selected from the positions consisting of: positions 4-8 and 13-18 on the sense strand, and positions 6-10 and 15-18 on the antisense strand, counting from the 5' end of each strand; and
wherein the double-stranded iRNA agent does not comprise a N-acetylgalactosamine (GalNAc) conjugate.



★C16能够增加siRNA的疏水性，使得药物更容易与脑脊液中的内源性脂质或蛋白质结合，**提高半衰期**。
★改善siRNA与细胞膜及相关膜蛋白的相互作用，促进了细胞的**主动摄取**，同时亲脂链的物理特性亦有助于破坏内体囊泡，提升**内体逃逸效率**。

保护范围：双链核酸与C4-18（另一个美国同族专利限定为C16）烃链缀合，缀合至核酸链内部的选定位置。

Arrowhead——TRiM BBB皮下给药核心专利

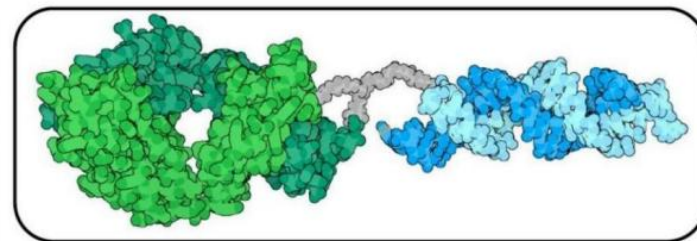
WO2025160275A1 申请日2025.01.23 美国同族 US12527877B2, 授权日2026年1月20日

1. An antibody that binds a transferrin receptor (TfR1), the antibody comprising a heavy chain that comprises a heavy chain variable region (VH) and a light chain that comprises a light chain variable region (VL);

wherein the VH comprises:

8. A conjugate comprising an antibody that binds a transferrin receptor (TfR1) (anti-TfR1 antibody) and an oligonucleotide-based agent, wherein the anti-TfR1 antibody is set forth in claim 1.

5 14. The conjugate of claim 11, wherein the sense strand is conjugated to the anti-TfR1 antibody, wherein the anti-TfR1 antibody is a Fab molecule.



- ❖ Subcutaneous (SC) administration for crossing blood-brain barrier (BBB)
- ❖ siRNA conjugated to a TfR-targeting ligand through a stable, non-reversible covalent linkage
- ❖ Stable in circulation

★使用Fab片段，分子量小，粘稠度相对低，适合制备成注射体积；循环半衰期可控，皮下注射后形成低峰值、相对平缓且持续的系统暴露，降低外周组织负担。

保护范围：权利要求1限定了TfR1抗体的可变区序列，权利要求8保护了基于该抗体的寡核苷酸缀合物，从权限定了**抗体为Fab**。

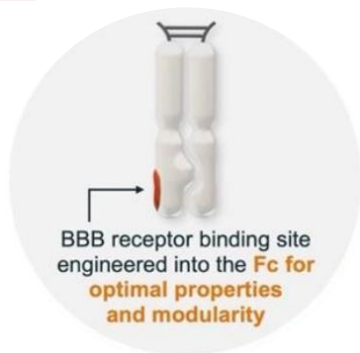
基于该平台性技术，Arrowhead布局了WO2025212467A1（保护了MAPT siRNA+AOC），以及WO2026060370A1（保护SCNA的siRNA+AOC——2025年9月以22亿美元许可给诺华，帕金森+其它突触核蛋白病）

Denali TV (Transport Vehicle) 专利族

WO2018152326A1 申请日2018.02.15/

US11795232B2/中国同族在审

1. A polypeptide comprising a CH3 domain that specifically binds to a transferrin receptor, wherein the CH3 domain comprises five, six, seven, or eight substitutions in a set of amino acid positions comprising 118, 119, 120, 122, 210, 211, 212, and 213; and (i) wherein the substitutions and the positions are determined with reference to amino acids 114-220 of SEQ ID NO:1 and (ii) the CH3 domain has at least 80% identity to amino acids 114-220 of any one of SEQ ID NOS:30-46.



★**TfR靶向模块的核心专利**：将Fc改造用于结合TfR，从而穿透血脑屏障

WO2019070577A1 申请日2018.10.01

US10870837B2/中国同族在审

1. A protein comprising:
a. a fusion polypeptide comprising a first Fc polypeptide linked to an iduronate 2-sulfatase (IDS) amino acid sequence, wherein the IDS amino acid sequence comprises a sequence having at least 90% identity to SEQ ID NO: 92, and wherein the IDS amino acid sequence is linked to the N-terminus of the first Fc polypeptide; and
b. a second Fc polypeptide comprising a sequence having at least 90% identity to SEQ ID NO: 151 that is capable of specifically binding to a transferrin receptor.

Enzyme TV
(ETV)



Enzyme replacement therapy for the body and brain

WO2024263852A2 申请日2023.06.22

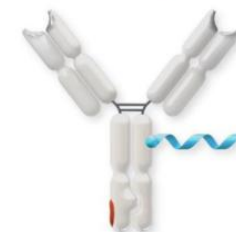
CN121729493A, 在审

1. 一种长度为17-19个核苷酸并且包含SEQ ID NO: 4-9、19-37和38-56中任一个的核苷酸序列的MAPT反义寡核苷酸 (MAPT ASO), 其中所述MAPT ASO包含至少一个经修饰的核苷间连接和/或至少一个经修饰的糖。

24. 如权利要求1-23中任一项所述的MAPT ASO, 其中所述MAPT ASO与靶向配体或递送媒介物缀合。

25. 如权利要求24所述的MAPT ASO, 其中所述靶向配体特异性结合转铁蛋白受体 (TfR) 或在血脑屏障腔表面上表达的分子。

Oligonucleotide TV
(OTV)



Genetic medicines for the brain, delivered systemically

04-3 心脏・心肌靶向

心脏递送代表性平台

公司/平台	递送机制	给药	关键管线	阶段
Atrium AOC(继承Avidity)	TfR1 mAb-siRNA心肌靶向	静脉	ATR1072(PRKAG2)、 ATR1086(PLN)	IND 2026H2/2027
Arrowhead TRiM-心肌	GLP1R配体心肌靶向	/	未公开	临床前

Arrowhead——GLP1R小分子配体递送核心专利

WO2026030210A1 申请日2025.07.28 (还有一件同日PCT申请**WO2026030212A1**, 请求保护GLP1R+RNAi试剂, 无PK/PD modulator)

1. A compound, or a pharmaceutically acceptable salt thereof, of Formula (I):



wherein:

the targeting ligand has affinity for a receptor present on the surface of a cardiomyocyte;

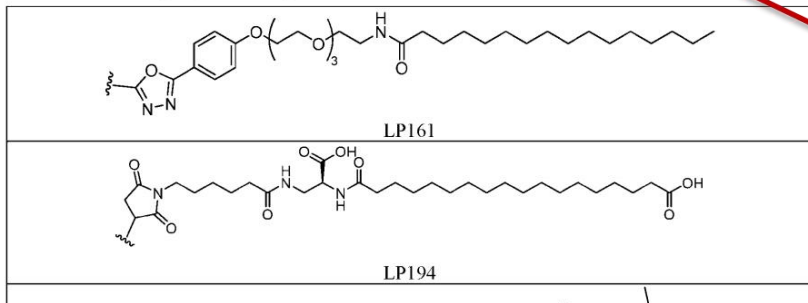
the RNAi agent comprises:

(iii) an antisense strand comprising 17-49 nucleotides wherein at least 15 nucleotides are complementary to the mRNA sequence of a gene that is expressed in cardiomyocytes;

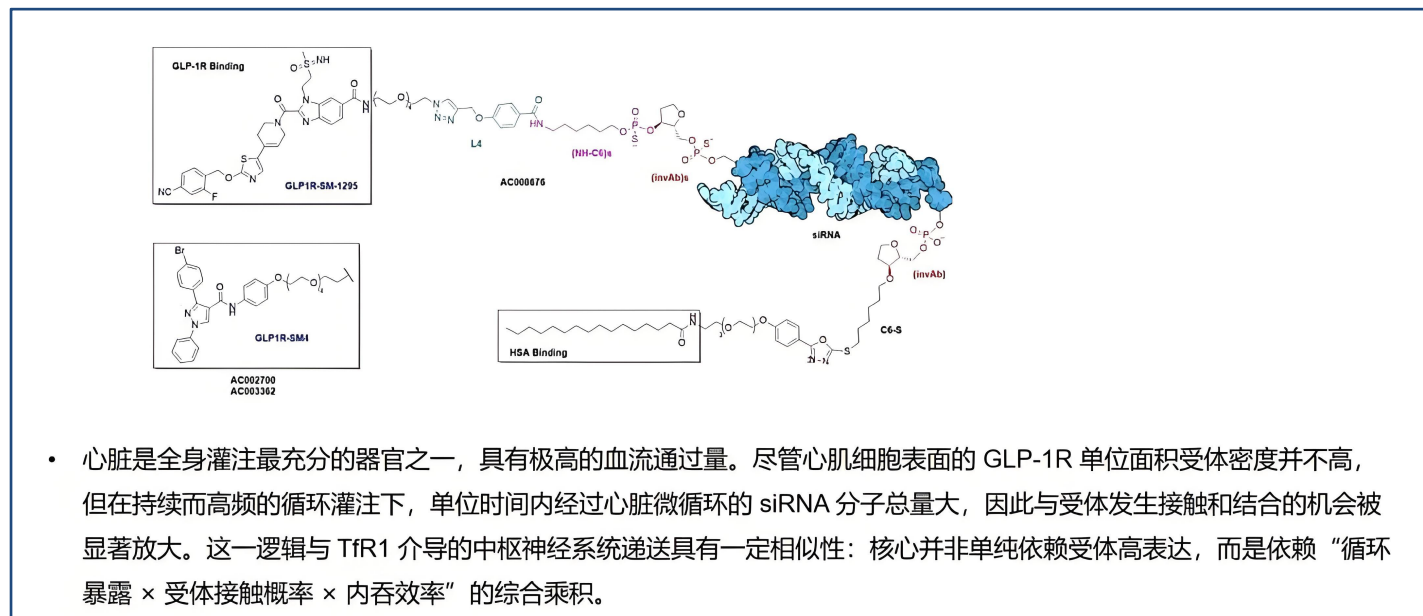
(iv) a sense strand that is 16-49 nucleotides in length that is at least partially complementary to the antisense strand; and

m is 1, 2, 3, 4, or 5.

18. The compound of any one of claims 1-17, wherein the PK/PD modulator is selected from the group consisting of:



59. The compound of any one of claims 1-58, wherein the targeting ligand has affinity for the GLP receptor 1 (GLP1R).



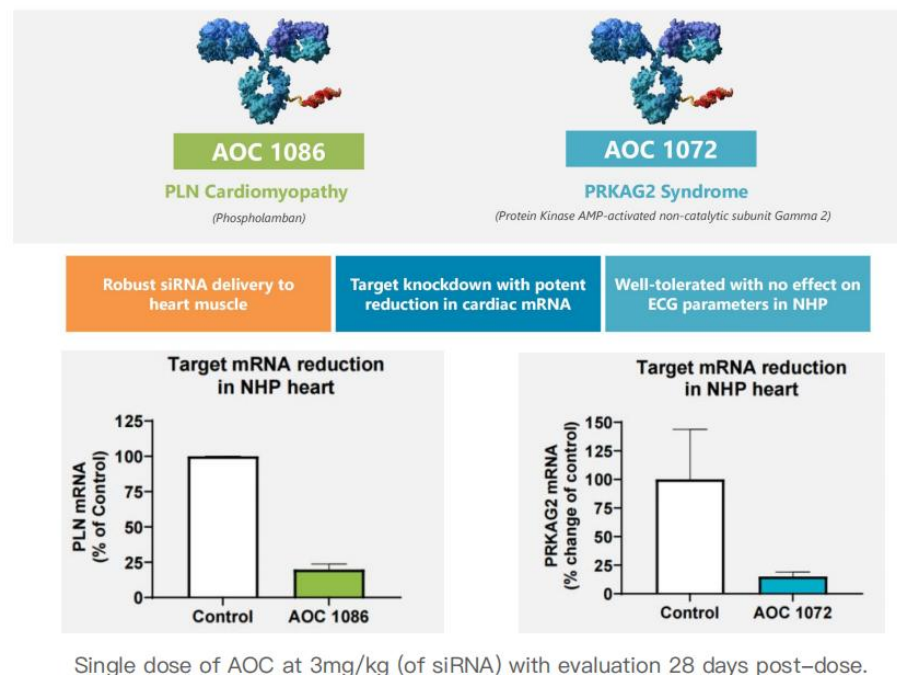
关键设计：Arrowhead在分子设计中引入了PK/PD Enhancer (白蛋白结合脂质)，通过与血浆白蛋白高亲和结合，降低肾清除率并显著延长循环半衰期。

保护范围： GLP1R结合小分子+RNAi试剂+PK/PD modulator, 覆盖 TRiM 平台第7类细胞（心肌细胞）。

Atrium——沿用Avidity TfR1抗体进行心脏递送

WO2025007063A1 申请日2024.06.28 美国同族 US12409230B2, 授权日2025年09月09日

1. A polynucleotide conjugate comprising an anti-transferrin receptor antibody or antigen-binding fragment thereof conjugated to a polynucleotide that hybridizes to a target sequence of PLN mRNA and mediates downregulation of the PLN mRNA in a cardiac muscle cell, wherein the polynucleotide hybridizes to a nucleic acid sequence at positions 195-213, 242-379, 449-546, 780-811, 967-1002, 1072-1099, 1119-1138, and 1234-1253 of the PLN mRNA (NM 002667.5).



保护范围：转铁蛋白受体的**抗体**+靶向PLN的siRNA组成的AOC，限定了siRNA序列的多段靶向位置——AOC1086的核心专利。

04-4 脂肪・肺・肾脏靶向

脂肪/肾脏/肺代表平台与临床数据

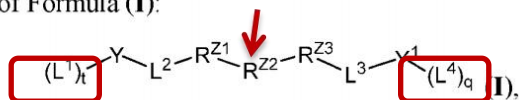
公司	平台/项目	递送机制	给药途径	靶向组织	阶段
Arrowhead	TRiM Adipose platform (ARO-ALK7)	双脂质偶联物	SC	脂肪	I期, 8周脂肪ALK7 mRNA -88%(最大-94%)、内脏脂肪-14.1%
Alnylam	ALN-2232 (ACVR1C,ALK7)	AdipoLigand 1	SC	脂肪	I期, 2026H2数据读出
Arrowhead	TRIM	α v β 6整合素小分子配体	雾化吸入	肺部	I期
Judo Bio	STRIKE+Megalin-STRIKERs	Megalin配体+siRNA	SC	肾脏	临床前, NHP单次SC 70%肾靶基因敲低+2月持续

Arrowhead脂肪递送——双脂质偶联

平台专利 WO2024148329A1 申请日2024.01.05

US12442002B2, ARO-ALK7核心专利, 申请日2024.12.19

1. A compound of Formula (I):



or a pharmaceutically acceptable salt thereof, wherein:

R^{Z1} and R^{Z3} each independently a bond or a capping residue;

R^{Z2} comprises an oligonucleotide containing about 8 to about 50 nucleotides, each of

which may be independently modified or unmodified;

Y is a bond or a linker connecting at least one L^1 to L^2 when present, or to R^{Z1} ;

Y^1 is a bond or a linker connecting at least one L^3 to L^4 when present, or to R^{Z3} ;

L^2 and L^3 are each independently a linker;

q is 1, 2, or 3, as valency permits;

t is 1, 2, or 3, as valency permits; and

L^1 and L^4 are each independently a lipid comprising from about 10 to about 50 carbon

atoms.

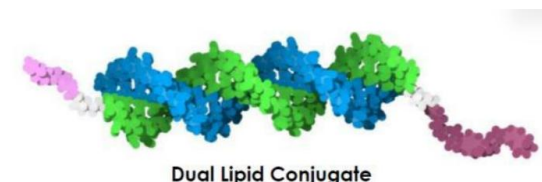
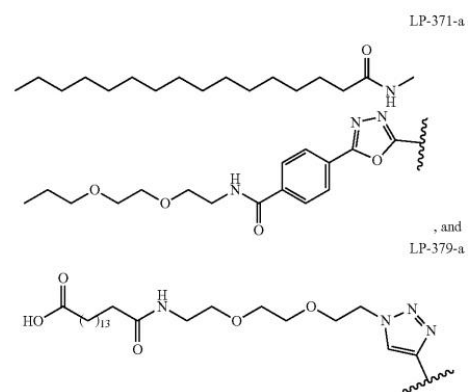
保护范围：寡核苷酸通过linker在两侧与脂质连接的结构——不限定寡核苷酸靶点和序列，脂质链长度10-50个碳原子。

1. An RNAi agent for inhibiting expression of a Activin Receptor-Like Kinase 7 (ALK7) gene, comprising:

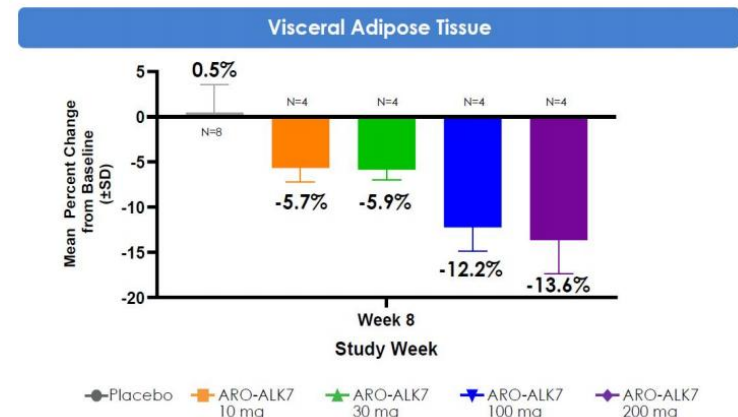
an antisense strand wherein nucleotides 1-21 of the anti-sense strand (5'→3') comprise the nucleotide sequence (5'→3'): AUUGUUGGAACUAUGACAGAC (SEQ ID NO: 558); and

a sense strand that comprises a nucleotide sequence that differs by 0 or 1 nucleotides from the nucleotide sequence (5'→3'): GUCUGUCAUAGUCCAACAAU (SEQ ID NO: 599);

wherein all of the nucleotides of the antisense strand and all of the nucleotides of the sense strand are modified nucleotides, wherein the modified nucleotides are selected from the group consisting of 2'-fluoro modified nucleotides, 2'-O-methyl modified nucleotides, and cyclopropyl phosphonate-containing nucleotides, wherein the sense strand is linked to one or more lipid moieties, and wherein each of the one or more lipid moieties is independently selected from the group consisting of:



Arrowhead ARO-ALK7 临床I期结果



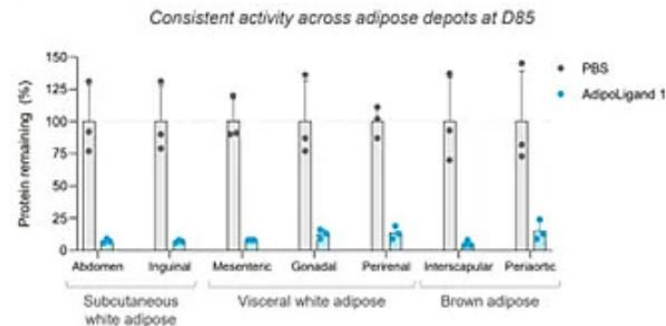
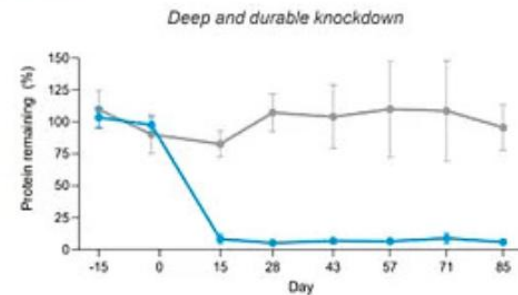
Alnylam 脂肪递送——Adipoligand 1

脂肪酸转运蛋白结合的小分子配体AdipoLigand1，专利未公开

Adipose: Small Molecule Conjugate Elicits Robust Knockdown in NHP After SC Injection



NHP Data from ACVR1C
Single dose · SC · 3 mg/kg



AdipoLigand 1



- SC dosing ✓
- ≤ 3 mg/kg dose ✓
- Efficient manufacturing ✓

Alnylam

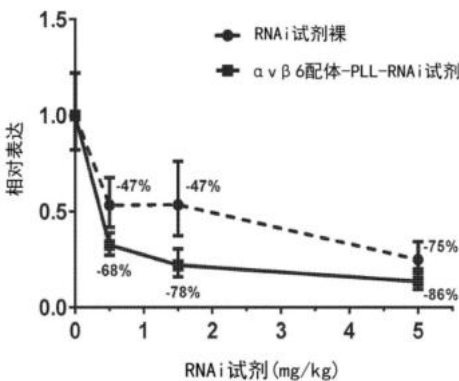
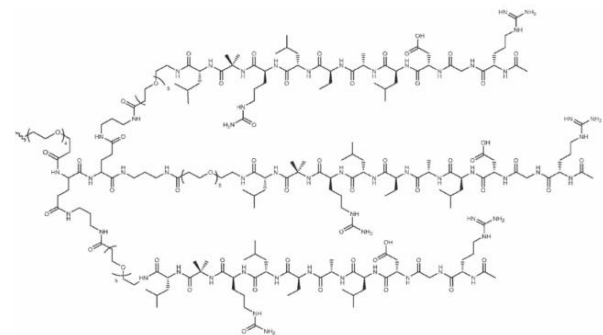
Arrowhead肺部递送—— $\alpha v \beta 6$ 整合素小分子配体

CN109952376B，多数实施例均展示肺部递送

1. 一种 $\alpha v \beta 6$ 整联蛋白配体，其包含：
RG¹DLXaa¹Xaa²L-Xaa³Xaa⁴L-R¹ (SEQ ID NO:96) (式VIII)
其中
R是L-精氨酸；
G¹是L-甘氨酸或N-甲基甘氨酸；
D是L-天冬氨酸或L-天冬氨酸盐或酯；
L是L-亮氨酸；
Xaa¹是L-丙氨酸；
Xaa²是L- α -丁酸 (Abu)；
Xaa³是L-瓜氨酸；
Xaa⁴是L- α -氨基异丁酸 (Aib)；
R¹是任选的，存在时，其包含PEG和/或连接基团。

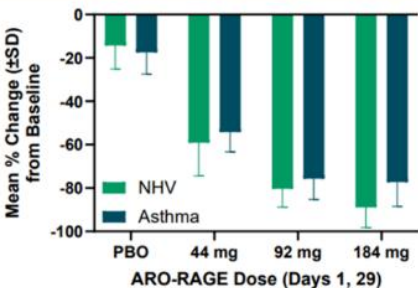
16. 如权利要求14所述的组合物，其中所述 $\alpha v \beta 6$ 整联蛋白配体与RNAi试剂偶联，所述RNAi试剂能够抑制上皮细胞中靶基因的表达。

示例性 $\alpha v \beta 6$ 配体——TAI4 三齿结构



ARO-RAGE 临床I期结果

Mean Maximum Serum sRAGE Reduction Following 2 Doses of ARO-RAGE



Serum sRAGE Modeling Supports Q2 Month Dosing in Subsequent Studies

Arrowhead在研肺部疾病管线

	ARO-RAGE	ARO-MMP7*
靶点	RAGE	MMP7
临床阶段	Phase 2	Phase 1
适应症	黏液阻塞性和炎症性肺部疾病	IPF
给药方式	吸入给药	吸入给药

Judo Bio肾脏递送STRIKE平台——Megalin (LRP2) 靶向

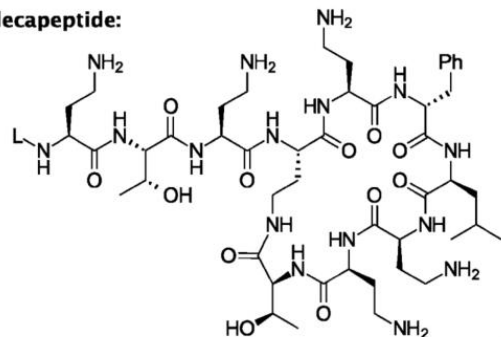
WO2025072713A1, 申请日2024年

多粘菌素

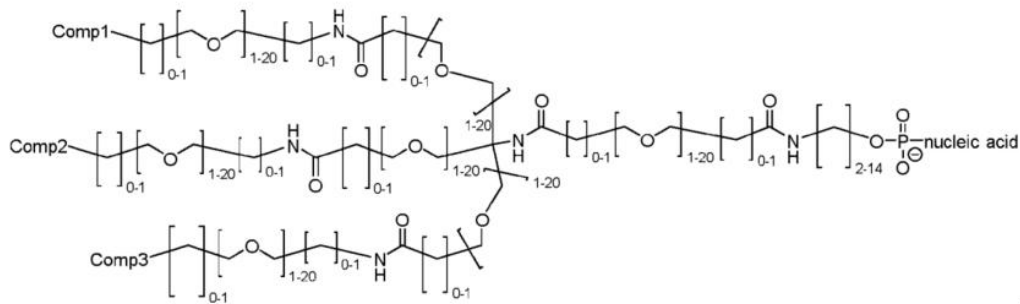
1. A nucleic acid conjugate agent comprising a nucleic acid conjugated to a polymyxin moiety or analog thereof, wherein the nucleic acid is conjugated to the polymyxin moiety or analog by a linker.

示例性多粘菌素B

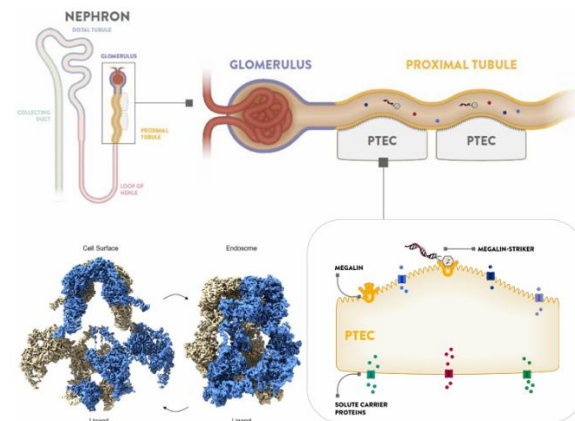
PMB decapeptide:



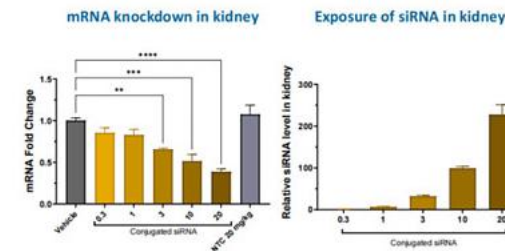
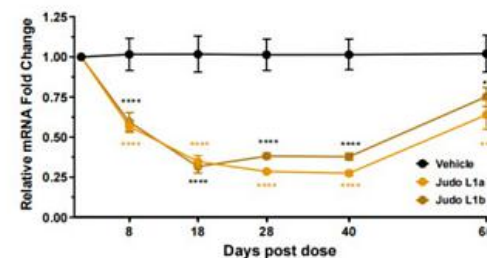
示例性连接子



Megalin是肾脏中表达最丰富的受体之一，生理功能是介导多种配体（维生素结合蛋白、载脂蛋白等）的内吞和溶酶体降解回收，这一高效的分子转运机制被Judo Bio改造用于核酸递送。



小鼠体内数据：长达4-6周持续敲低+剂量依赖性药效与暴露量成比例增加



总结

01

技术趋势

小核酸偶联递送正从“肝靶向GalNAc一家独大”迈向“**肝外多组织精准递送**”阶段。

02

专利布局

技术平台价值最高，也是专利布局的核心。重点是AOC、靶向多肽、偶联脂质等“**靶头**”**相关**的专利布局。

03

申请策略

专利申请时，**基于递送机制，结合通式和功能限定**，力求获得更大的保护范围，彰显平台专利的价值。



YOUNGEN
尧景基因

感谢聆听!