Delivery has moved from exposure to productive biology

Industry progress, remaining engineering gaps, and the differentiated potential of PSK SGRL-Exo™

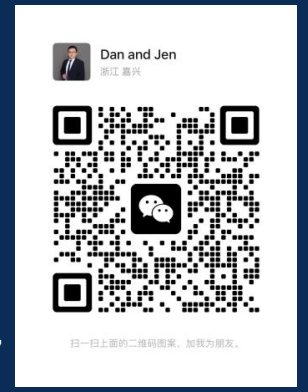
TARGET

CARGO

PRODUCTIVE RELEASE

PSK Biosciences | ICNS 2026

Tinghe Wu: 180-6702-9687



INVESTMENT THESIS

MNCs pay when delivery data remove a specific development risk

1	2	3	4	5
Tissue exposure	**Target-cell access**	**Productive release**	**Human PD**	**Clinical path**
Where did the payload go?	Which cells received it?	Did cargo reach cytosol / nucleus?	Did the target move in patients?	Can PD translate to benefit?

The commercial inflection

Preclinical platform deal	Magnitude + cross-species translation + reusable platform
Clinical asset / acquisition	Human tissue PD + tolerability + registration path
Engineered exosome deal	Target-cell access + productive cargo + repeatability + CMC

BBB DELIVERY LANDSCAPE

Four modalities now compete on different definitions of ‘brain delivery’

RMT shuttles

Human validated

Antibody / enzyme

Validated strength

Large cargo; receptor-mediated

Remaining gap

Receptor saturation; peripheral sink

Ligand–oligo

NHP → Phase I

ASO / siRNA

Validated strength

Systemic, repeatable RNA

Remaining gap

Human CNS PD still pending

Engineered AAV

NHP → clinical

Gene payload

Validated strength

High transduction; durability

Remaining gap

Redosing, immunity, dose ceiling

LNP / exosome

Preclinical → Phase I

mRNA / RNAi

Validated strength

Programmable; multi-cargo

Remaining gap

Cell specificity, escape, CMC

The winning platform is not the one with the highest brain signal—it is the one that converts systemic dose into reproducible target-cell pharmacology.

BBB DEAL MAP

Five transactions show what buyers acquired—and what they did not

Partner / seller	Timing	Scope	Upfront / equity	Headline potential
Sanofi / ABL Bio	Jan 2022	ABL301 asset license	$75M upfront	$1.06B total
BMS / BioArctic	Dec 2024	BAN1503/2803 assets	$100M upfront	$1.35B total
GSK / ABL Bio	Apr 2025	Multi-program Grabody-B	£77.1M upfront + near-term	£2.14B potential
Lilly / ABL Bio	Nov 2025	Multi-modality platform	$40M + $15M equity	$2.602B total
Lilly / BioArctic	Jun 2026	One undisclosed candidate	$30M upfront	Other platform rights retained

Interpretation: asset deals buy a program; platform deals buy option value. Headline milestones are contingent—not cash paid at signing.

Human CNS pharmacology has now validated BBB shuttling as a drug strategy

AVLAYAH™ / Denali ETV

ACCELERATED

91%
Mean CSF heparan sulfate reduction
Week 24; n=44

93%
Reached non-Hunter range
41 of 44 patients

CSF HS reduction — 91%

Why it matters

Direct CNS PD plus a regulatory path converted a delivery platform into an approved medicine.

Trontinemab / Roche Brainshuttle™

PHASE Ib/IIa → PHASE III

91%
Amyloid PET-negative
Week 28; 49 of 54

<5%
ARIA-E incidence
Blinded pooled data

PET-negative — 91%

Why it matters

Rapid plaque clearance with low ARIA-E supports efficient parenchymal exposure and repeat systemic dosing.

Remaining question: biomarker success must still translate into durable clinical benefit.

Denali OTV demonstrates systemic ASO delivery beyond CSF exposure

IV ASO | NHP

54%

MALAT1 knockdown in frontal cortex

Single 30 mpk dose; RNA remaining ≈46% of control

Broad

Neuronal and glial distribution

More uniform than intrathecal naked ASO

What the data de-risk

- ✓ Systemic exposure across cortical and deep regions
- ✓ Cellular uptake beyond vascular signal
- ✓ Target knockdown after IV administration

Next value gate: human CNS pharmacodynamics and a practical chronic dosing regimen.

CNS-TRiM achieves 70–80% NHP MAPT knockdown after SC dosing

SC siRNA | NHP

70–80%

MAPT mRNA knockdown

Across 17 CNS regions; up to ~85% in cortex

0.5–1.5

µg siRNA per g brain

Broad tissue exposure after SC dosing

Why this matters

A simple systemic route can generate deep regional RNAi in NHP—an important translational bridge for chronic CNS disease.

Still unproven

Public human CNS target-engagement data have not yet been disclosed; Phase 1/2a is the decisive next step.

Platform value will rise sharply if human CSF or imaging biomarkers track predicted brain knockdown.

Engineered AAV reaches high CNS transduction—but redosing remains hard

Capsida CAP-003 | NHP

IV AAV | CLINICAL

70–90%

Neuronal transduction in several regions

Company-reported NHP data

+415%

GCase protein

With 59–79% GluSph reduction

Critical interpretation

CAP-003 fold comparisons used historical AAV9 controls with different dose/route; treat magnitude as directional, not head-to-head.

Dyno-yp2 | humanized mice + NHP

PRECLINICA

113×

Brain transduction vs AAV9

hTfR1-humanized mice

up to 50%

Premotor-cortex neurons

NHP at 3×10^{13} vg/kg

Critical interpretation

Mouse TfR biology and NHP transduction do not eliminate immunogenicity, manufacturing, or repeat-dose barriers.

AAV maximizes durable expression; non-viral platforms may win where dose titration, reversibility, or repeat dosing matters.

BBB entry is advancing faster than cell-selective, repeatable delivery

Risk	Why it persists	What closes it
Translation	Receptor density and trafficking vary by species	**Cross-species receptor biology + NHP benchmark**
Specificity	Brain exposure can coexist with liver / endothelial trapping	**Cell-level co-localization + organ-normalized dose**
Productive release	Uptake does not prove cytosolic or nuclear access	**Subcellular localization + functional rescue**
Repeat dosing	AAV and some biologics face immunity / dose constraints	**Chronic dosing, reversibility, anti-drug response**
CMC	Particle heterogeneity weakens dose–potency linkage	**Release assay tied to in vivo pharmacology**

This unresolved intersection—targeting × cargo loading × intracellular release × redosing—is where engineered exosomes can differentiate.

Extrahepatic RNA delivery

Human tissue pharmacology—not plasma exposure—has become the decisive value inflection.

Muscle **Adipose** **Lung** **Immune cells**

Avidity converted biopsy PD and late-stage readiness into a $12B acquisition

HUMAN MUSCLE BIOPSY

100%

Participants with DMPK reduction

Active participants with evaluable biopsies

45%

Mean DMPK mRNA reduction

After 1–2 doses

31%

Muscle-specific splicing improvement

Mechanistic downstream readout

$12B

Novartis acquisition

Completed Feb 2026

Why buyers paid

01 **Target tissue biopsy**

02 **Root-cause mechanism**

03 **Downstream functional biology**

04 **Phase III / launch path**

Commercial lesson: intracellular mechanism in the target tissue is more persuasive than total tissue concentration or plasma PK.

Arrowhead delivers human RNAi pharmacology in adipose and lung

ARO-ALK7 — adipose

SC siRNA | PHASE I/IIa

−88%

Mean adipose ALK7 mRNA

200 mg; week 8; n=4

−94%

Maximum ALK7 mRNA

Human adipose biopsy

Additional signal

−14.1% placebo-adjusted visceral fat at week 8 after a single ARO-ALK7 dose.

ARO-RAGE — pulmonary epithelium

INHALED RNAi | PHASE I/II

−77%

Mean maximum serum sRAGE

Asthma patients after two doses

−88%

Maximum serum sRAGE

Long-lasting PD

Remaining question

Biomarker knockdown must translate into durable clinical outcomes and acceptable chronic safety.

Capstan shows MNCs may buy pre-human PD when the treatment model changes

up to 80%

NHP CD8+ T cells CAR-engineered

Transient, in vivo cell programming

Deep

B-cell depletion

Blood and lymphoid tissues

$2.1B

AbbVie acquisition

Completed Aug 2025

PHASE I AT ACQUISITION

Why AbbVie could underwrite pre-human PD risk

01	**Targeted modality**	Replaces ex vivo manufacturing	02	**Cell-selective delivery**	Preferential CD8 engineering
03	**Transient payload**	mRNA expression avoids permanent integration	04	**Functional large-animal PD**	CAR expression translated into tissue B-cell depletion

Risk retained by the buyer: public human PD was not available at acquisition; clinical selectivity and repeat dosing still required proof.

EXTRAHEPATIC RNA MATURITY

No platform yet combines reach, selectivity, payload breadth and redosing

Tissue	Best public evidence	Commercial signal	Key unresolved space
Muscle	Human biopsy PD; late-stage programs	$12B Avidity acquisition	Broad muscle subtype coverage; chronic safety
Adipose	Human biopsy gene knockdown	First-in-human adipocyte RNAi	Distribution across depots; metabolic outcomes
Lung	Human local biomarker PD	Multiple clinical RNAi programs	Airway heterogeneity; durability
Immune cells	NHP functional cell engineering	$2.1B Capstan acquisition	Human selectivity; cytokines; repeat dosing
CNS	Strong NHP PD; first human programs	Large platform / asset deals	Human brain PD; cell specificity; release

Engineered exosomes are most differentiated if they close several gaps simultaneously—not merely if they reach another organ.

EXTRAHEPATIC RNA BD SIGNALS

MNCs are paying for reusable tissue-selective delivery, not only targets

Deal	Delivery logic	Maturity / economics	Why paid / open space
Sanegene Genentech	LEAD tissue-selective RNAi	$200M upfront / $1.5B total	Reusable platform; CNS validation undisclosed
SiranBio GSK	Adipocyte-directed ALK7 siRNA	Phase I; up to $1.005B	Obesity/CVR option; needs human depot proof
Frontier GSK	Kidney-disease siRNA assets	IND + preclinical; $963M total	Renal option; delivery details remain opaque
CSPC AZ	Extrahepatic targeted siRNA discovery	PCC stage; $1.77B total	AI/HTS + renal targets; early translation risk
PSK angle	CNS RNA delivery remains under-served	Few public CNS RNA delivery BD cases	Exosomes can combine BBB reach, RNA loading and redosing

Takeaway: China RNAi BD validates extrahepatic delivery as a platform asset; CNS delivery remains the white space for engineered exosomes.

Why engineered exosomes

A differentiated platform must co-engineer targeting, cargo loading, intracellular release and manufacturability.

TARGET

LOAD

RELEASE

REPEAT

ENGINEERED-EXOSOME THESIS

Exosome differentiation should be measured as a system—not as particle uptake

Value claim	Quantitative endpoint	Minimum convincing experiment
1. Target-cell advantage	% target cells positive; cargo/cell	Head-to-head vs route-matched benchmark
2. Productive release	RISC / translation / editing readout	Subcellular localization + functional assay
3. Dose efficiency	PD per mg cargo and per particle	Dose–exposure–effect across rodent and NHP
4. Repeat-dose window	Durable PD without cumulative immunity	≥3–6 doses; cytokines, complement, ADA
5. CMC–potency linkage	Cargo/particle, empty fraction, integrity	Release assay that predicts in vivo PD

The investable claim: a programmable, repeat-dosable delivery system that puts functional cargo in the right cell at a competitive dose.

PSK SGRL-Exo™

A structure-guided, biologically manufactured platform designed for systemic, functional CNS RNA delivery.

INTERNAL MOUSE DATA

NHP VALIDATION ONGOING

Internal validated PLATFORM STAGE

Claims below are separated into demonstrated results, current interpretation, and the next value-defining experiment.

PSK PLATFORM DESIGN

PSK co-engineers BBB targeting, anchor enrichment and RNA loading

8×
Brain signal vs internal TfR-ligand benchmark
Ago2 peptide screen

200×
Anchor enrichment after truncation
Producer-cell engineering

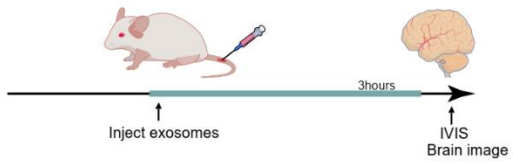
>10^5×
RNA-loading efficiency improvement
Structure-guided RBP–RNA design

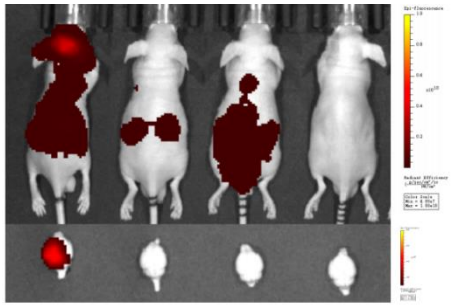
~200
RNA copies per vesicle
Assay-based batch estimate

What this could solve	Targeting	Loading	Function	CMC
	more brain access	predictable cargo dose	reproducible knockdown	batch control

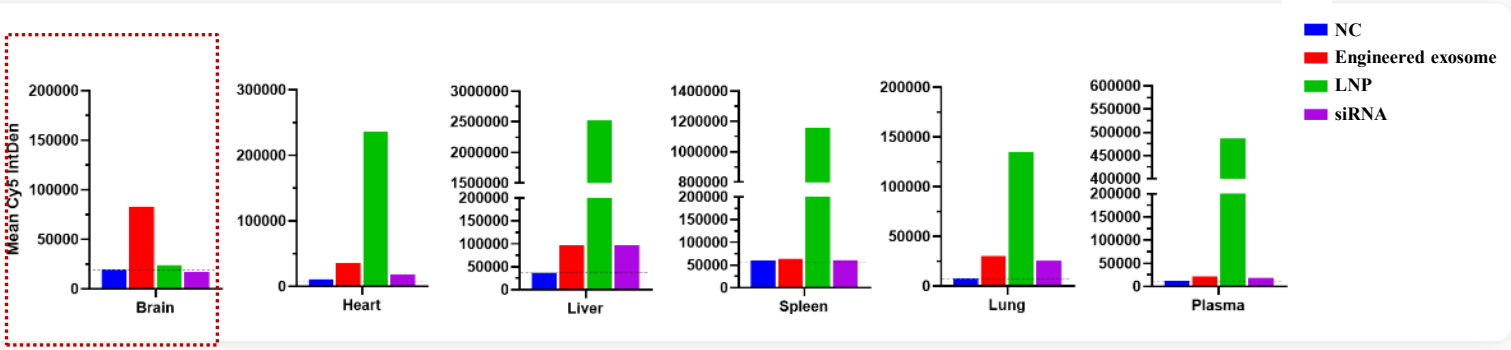
Diligence need: lock assay definitions, normalization and denominators before using cross-platform magnitude claims externally.

Perfused-brain fluorescence supports exposure—BP ratio 2.0





Cy5-labeled siRNA-loaded exosomes, LNPs, and naked siRNA were intravenously administered at an equivalent dose (20 μg/mouse). In vivo fluorescence imaging (IVIS) was performed at 3 h post-injection.



INTERNAL MOUSE DATA

Observed

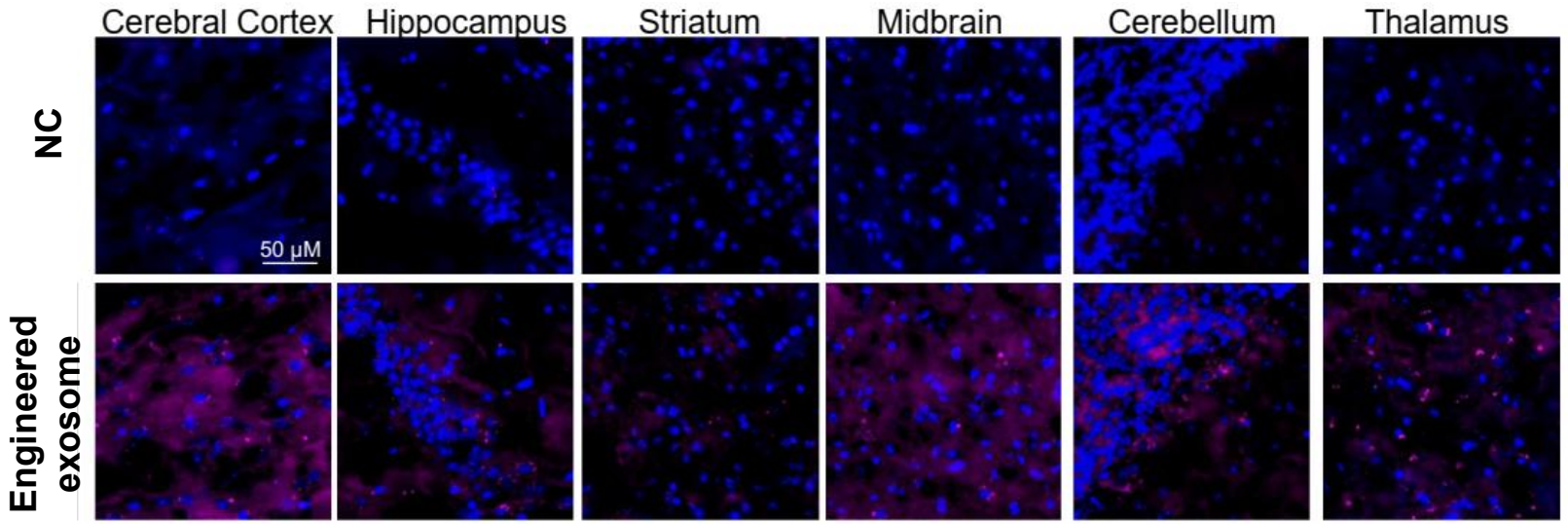
- IV administration
- 20 μg siRNA/mouse
- Perfused brain signal at 3–6 h
- Broad regional fluorescence

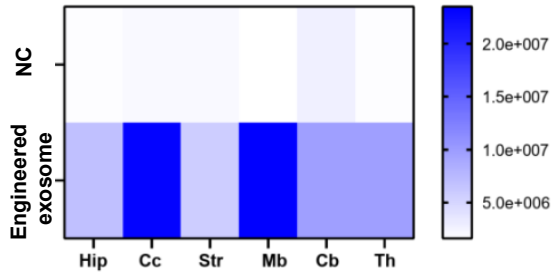
Not yet resolved

Intact cargo vs free dye; capillary depletion; absolute ng/g; dose-normalized brain/plasma PK.

Next experiment: radiolabeled or LC–MS cargo quantification with capillary depletion and matched LNP / naked-RNA controls.

Microscopy supports parenchymal distribution and neuronal uptake





Blue: DAPI

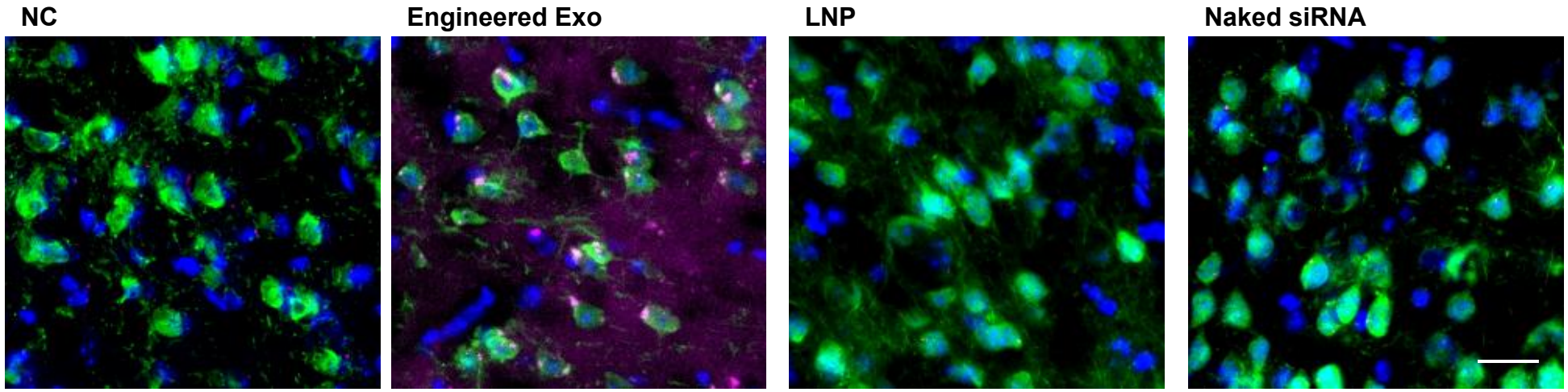
Magenta: Cy5

Scale bar: 50 μm

Parenchyma across six regions

Next experiment: 3D orthogonal imaging + endothelial marker + RNase protection / FISH to distinguish internalized intact cargo.

Microscopy supports parenchymal distribution and neuronal uptake

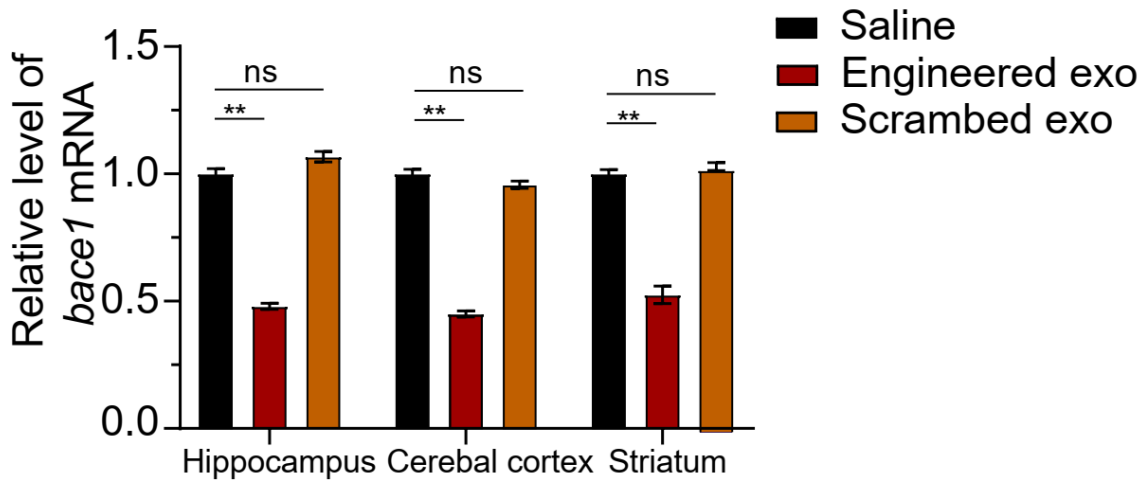


Green: **NeuN（neuron）**
Blue: DAPI
Magenta: Cy5
Scale bar: 20 μm

Cy5-labeled siRNA-loaded exosomes were prepared and compared with LNP-encapsulated siRNA and naked siRNA. All formulations were intravenously administered at an equivalent dose (20 μg siRNA/mouse). Brains were collected 6 h post-injection following perfusion, sectioned, and stained for IBA1 (microglia). Whole-slide fluorescence imaging was performed (DAPI, Alexa Fluor 488, Cy5) under consistent acquisition settings.

Next experiment: 3D orthogonal imaging + endothelial marker + RNase protection / FISH to distinguish internalized intact cargo.

Multi-region BACE1 knockdown closes the uptake-to-function gap



40–60%

BACE1 mRNA knockdown

Hippocampus, cortex, striatum

2

Targets demonstrated

BACE1 and SOD1

Cross-batch result

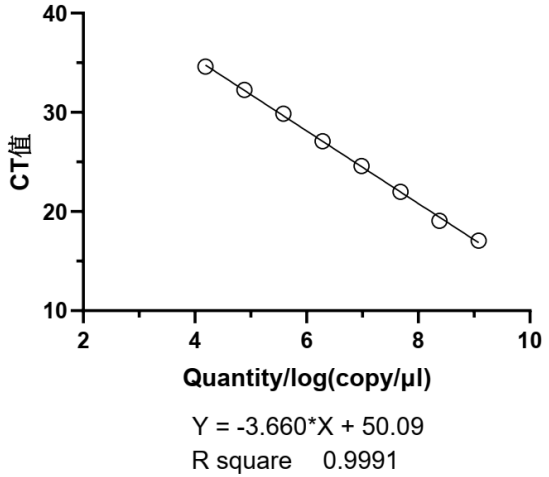
Source data report comparable cortical knockdown across three production batches, with no statistical difference.

Study design Multiple IV doses: 1.5×10^{11} particles/mouse/dose; total 7.5×10^{11}; tissue collected 48 h after final dose; n≥5/group.

This closes the uptake→function gap in mice. The major value leap is route-matched NHP knockdown with exposure–response and cell-type resolution.

Loading, repeat-dose and formulation data support an early CMC story

siRNA Standard Curve



Known Sample Test Results

Known Sample	Theoretical Copies (copies/μl)	Measured Copies (copies/μl)	%Bias
2nM-siRNA	1.20E+09	1.06E+09	-11.8
80pM-siRNA	4.82E+07	4.77E+07	-1.0
3.2pM-siRNA	1.93E+06	1.94E+06	0.5

LOQ: 1.54e+4 copies/μl

The CV of the RNA loading efficiency assay can be controlled within 10%, demonstrating consistent RNA loading.

Exosome Batch Test Results

Batch	Test Date	CT	Copies/pcs
Batch-1	20250417	21.80	188
	20250516	21.95	205
	20250616	22.10	222
	20250716	21.88	198
	20250815	21.92	207
CV% copies=6.7%			

Batch	Test Date	CT	Copies/pcs
Batch-1	20250417	21.75	182
Batch-2	20250620	21.40	235
Batch-3	20250909	21.95	195
Batch-4	20251010	21.60	218
Batch-5	20251114	22.05	175
CV% copies=9.3%			

brain knockdown across scale-up batches.

CMC is already operating at engineering-batch scale

PSK has moved from feasibility work to repeat engineering batches with defined upstream scale, producer-cell control and release-relevant analytics.

3
engineering batches
Completed process runs

~30 L
per batch scale
Bioreactor-scale production

MCB/WCB
producer-cell logic
Biologics-like starting material

20–50 L
platform range
~6 × 10^{13} particles/L reference

Stable producer cells

Carrier + payload constructs; MCB/WCB control

Endogenous RNA loading

Payload expressed and loaded during exosome biogenesis

Scalable production

~30 L engineering batches; 20–50 L platform window

Release analytics

Particle, RNA cargo, potency and stability readouts

CMC implication: engineered exosomes can be presented as a controllable biologic product candidate, not only as an exploratory delivery concept.

Source: PSK CMC development deck and internal ICNS data package.

RNA loading, potency and stability are linked in one CMC story

The stronger claim is a coupled evidence chain: cargo is measurable, the unit product is functionally active, and formulation attributes are retained over storage.

1. RNA cargo loading is quantitative

RNA copies/vesicle assay established

Assay/batch CV controlled within 10%

Observed CV range: 6.7–9.3%

2. Unit exosome potency is measurable

BACE1 mRNA knockdown: ~40–60%

Dose: 1.5 × 10^{11} particles/mouse/dose

Comparable cortical knockdown across 3 batches

3. Formulation stability is demonstrated

Lyophilized product stable at 4°C

6-month stability window observed

Particle, RNA and in vitro activity retained

Product attribute	Current PSK evidence	Why it matters
Carrier scale	3 × ~30 L engineering batches	Scale-up is already being tested
Cargo loading	RNA copies/vesicle CV 6.7–9.3%	Defines dose and batch comparability
Functional potency	~40–60% BACE1 knockdown at particle-defined dose	Connects exosome unit dose to PD
Repeat dosing	5 IV doses; no significant TNF-α / IL-6 rise reported	Supports chronic-use direction
Stability	6 months at 4°C after lyophilization	Enables practical formulation development

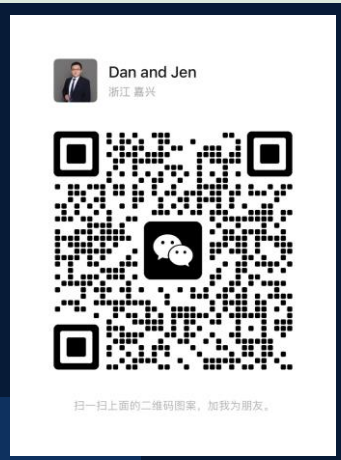
Investor-facing message: PSK is building a release-ready package around carrier + RNA + function; the next gate is NHP-linked potency release.

Source: PSK ICNS data package; Exosome CMC Development deck. Internal/preclinical data; present as platform-readiness evidence.

Four experiments can make PSK partner-ready

01	**NHP translation**	Quantitative brain PK + capillary depletion + cell distribution	**Receptor and species relevance**
02	**NHP functional PD**	Route-matched knockdown across regions and cell types	**Productive delivery at competitive dose**
03	**Repeat-dose window**	≥3–6 systemic doses; cytokines, complement, ADA, pathology	**Chronic CNS treatment feasibility**
04	**CMC–potency bridge**	Scale-up batches linked to cargo integrity and in vivo PD	**Partnerable manufacturing package**

Best BD entry point: after NHP functional PD and before IND-enabling scale-up—when platform risk is materially reduced but option value remains broad.



A programmable, repeat-dosable CNS RNA delivery infrastructure

PSK has generated an early but coherent chain of evidence:

1. **Controlled cargo loading**
2. **Perfused brain exposure**
3. **Parenchymal and cell uptake**
4. **Multi-region functional knockdown**
5. **Batch and formulation consistency**

Value-defining next proof

NHP functional knockdown
+ dose efficiency
+ repeat-dose safety
+ CMC–potency linkage

If achieved, exosomes can compete on flexibility and chronic usability—not merely on BBB crossing.

APPENDIX — DATA INTERPRETATION

Comparisons are credible only when species, route, dose and endpoint are aligned

Readout	What it does not prove	Preferred confirmatory test
Brain/plasma ratio	Can rise because plasma falls; does not quantify cells reached	Absolute ng/g + AUC + capillary depletion
Fluorescent signal	May reflect dye, fragments or endosomal cargo	Intact-cargo assay + RNase protection + FISH
Fold vs comparator	Can be inflated by different dose, route or time point	Prospective head-to-head, dose-normalized study
Bulk-tissue knockdown	Strong function signal, but cell identity remains uncertain	Sorted cells / spatial transcriptomics
Cytokines after dosing	Useful early safety signal, not chronic tolerability	Pathology, complement, ADA, recovery phase

Use the evidence ladder consistently: exposure → cell access → productive release → PD → benefit.

Asset rights and platform rights must be attributed separately

Technology / asset	Counterparty	What changed hands	Timing
ABL301	Sanofi	Exclusive worldwide asset rights; Grabody-B platform remained with ABL Bio	2022
Grabody-B programs	GSK	Multi-program research / license collaboration	2025
Grabody platform	Lilly	Multiple therapeutics across modalities and therapeutic areas	2025
BAN1503 / BAN2803	BMS	Worldwide asset rights; BAN2803 uses BrainTransporter	2024
One Lilly candidate	Lilly + BioArctic	Research collaboration; BioArctic retained other BrainTransporter rights	2026

Key distinction: Lilly did not 'buy BioArctic'; it selected one candidate collaboration while BioArctic retained other platform rights.