DMPK AND TOXICOLOGY

CHEMPARTNER

DEDICATED TO LIFESCIENCE

A SCIENCE-BASED CULTURE OF EXCELLENCE

15+ YEARS OF EXPERIENCE IN DRUG DISCOVERY AND DEVELOPMENT

At ChemPartner, our team draws on their experience at world-renowned pharmaceutical companies, emphasizes a science-based culture and executes quality drug metabolism pharmacokinetic (DMPK) and exploratory toxicology studies and integrates DMPK/toxicology data into our biopharmaceutical clients' discovery programs as well as support of their regulatory filings.

IN VITRO ADME

- Discovery ADME
- Metabolite profiling

PHARMACOKINETICS AND TOXICOLOGY

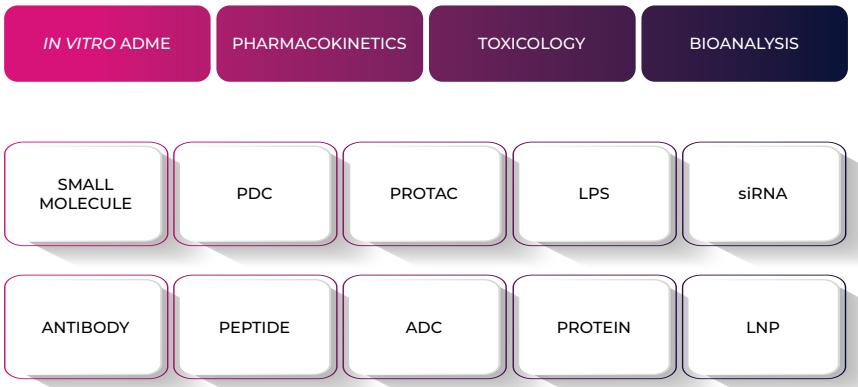
- Large animal and rodents
- Varies surgical models

BIOANALYSIS

- Discovery and development (regulated)
- LCMS and ELISA/MSD-based
- Biomarker

FORMULATION

HISTO- AND CLINICAL PATHOLOGY



300+
SCIENTISTS

200+
IND PROJECTS

200+
ENDOGENOUS BIOMARKERS

1000m²
LAB SPACE

CNAS
Office of Laboratory Animal Welfare
OLAW
aaalac INTERNATIONAL

1000+
CLIENTS GLOBALLY

9000m²
ANIMAL FACILITY

SUPPORT FDA/NMPA/EMA IND FILING

HELPED 11 COMPOUNDS MOVE TO THE MARKET

7K+ and **10K+**
PK/TOX AND ADME STUDIES PER YEAR

IN VITRO ADME

GAIN CRITICAL INSIGHT INTO METABOLISM AND POTENTIAL DRUG INTERACTIONS

In-vitro ADME assays are critical for gaining insight into metabolism and potential drug interactions. Moving quickly through drug discovery and development saves you time and money. ChemPartner has industry-leading turnaround times for data to help our clients make risk-based decisions on the drug-like properties of hits and lead molecules quickly.

HIGHLIGHTS

- Comprehensive *in vitro* ADME platform and advanced instruments
- Experienced team with very low turnover rate
- Strong scientific background and good communication skills
- Streamlined processes and fast-turnaround times
- High-quality and traceable data with good compliance
- Support both early discovery and IND filing

IN VITRO ASSAYS

ABSORPTION

- Caco-2
- MDCK-MDR1
- MDCK-BCRP
- MDCK-MDR1-BCRP
- OATP1B1 AND 1B3

DISTRIBUTION

- Protein binding
- Kbb
- RBC

METABOLISM

- Stability
- Phenotyping
- IC50
- IC50 shift
- Ki/Kinact
- CYP induction

PHYSI-CHEM

- Solubility
- Stability
- LogD, LogP, pKa
- PLM, DSC, TGA, XRPD
- Particle size distribution
- Dissolution Test

CUSTOMIZED ASSAYS

- Develop new or customized methods based on client requirements

CASE STUDIES

CYP INDUCTION STUDY IN IND PACKAGE

STEP 1

PROVIDE DOSING CONCENTRATION SUGGESTIONS

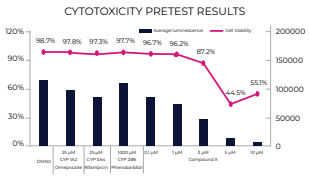
Propose concentration based on TK/PK exposure data and protein binding data, then expansion at least 30 fold*

*Species difference, variability, liver to blood ratio, et al. exist, also considering induction is a toxicity related study, 30 fold is reasonable for safe side.

STEP 2

CONDUCT PRE-TEST, INCLUDING:

- Solubility in incubation medium
- Hepatocyte toxicity



STEP 3

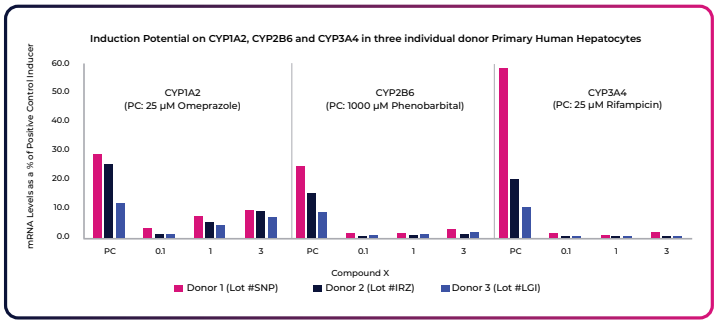
DISCUSS DOSING CONCENTRATION WITH CLIENT

Proposed Conc. in Step 1 must be compromised with solubility and cytotoxicity results in Step 2

STEP 4

CONDUCT EXPERIMENT

Follow standard procedure and evaluate the results according to FDA 2020 guidance



LEARN MORE

METABOLITE IDENTIFICATION

GENERATE ACTIONABLE INSIGHTS WITH EFFICIENT, ACCURATE SOLUTIONS

HIGHLIGHTS

- Tenured and stable team
- High-accuracy data and fast-turnaround times
- Experienced metabolite identification (met ID) expert with over 10 years met ID experience and background in organic chemistry
- Standardized lab and advanced equipment

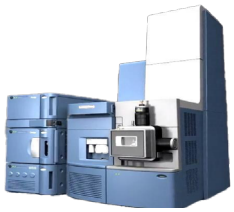
METABOLITE IDENTIFICATION ASSAYS

- Met ID in liver microsomes, S9, hepatocytes, lysosomes, plasma, tumor cells, and tissues
- Met ID for *in vivo* samples such as plasma, urine, bile, feces, and tissues (et al.)
- GSH trapping study in liver microsomes or S9

PROFESSIONAL METHODOLOGY

- Hydrogen-deuterium exchange technology can be used to distinguish between nitrogen oxidation and hydroxylation metabolites
- Synthesize the major metabolites in microsomes and purify it to get pure metabolites and get the exact structure by NMR and 2D-NMR

AB SCIEX
X500B Q-TOF

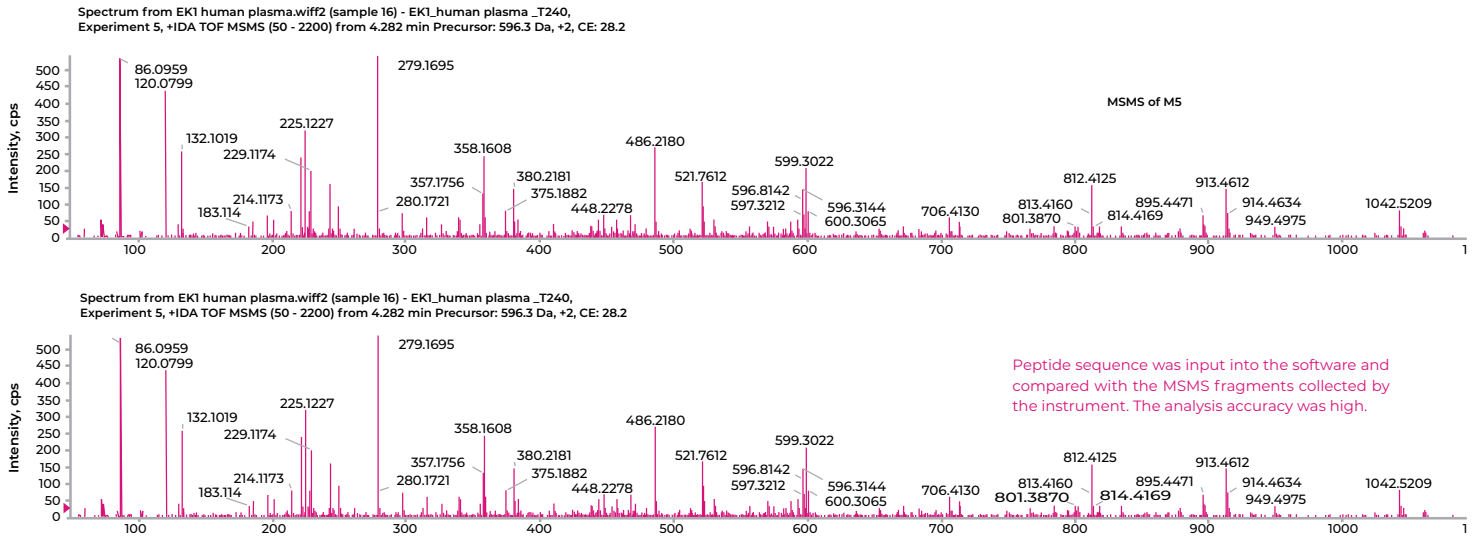


Waters G2-XS Q-TOF
UPLC-MS System

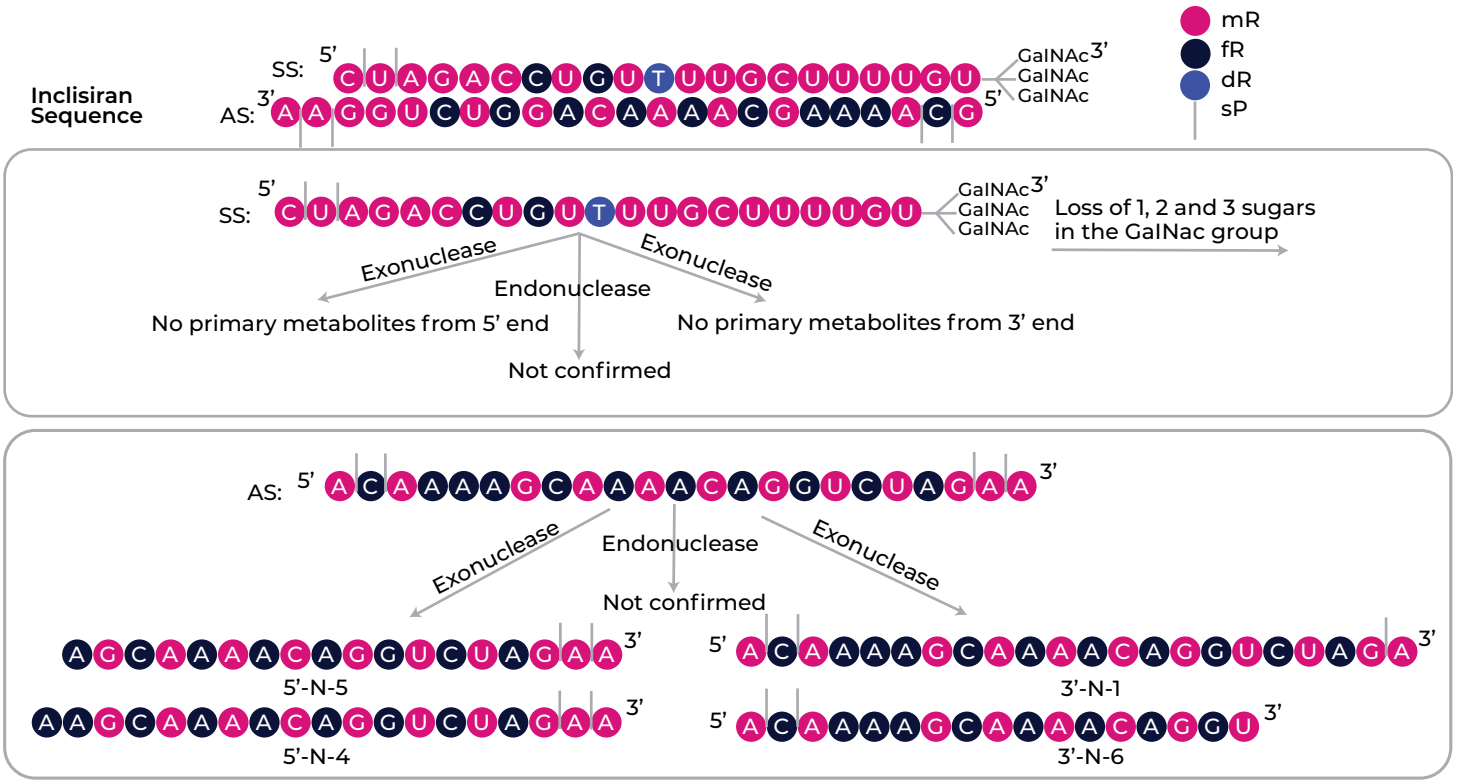
SCOPE OF SERVICE

FROM SMALL MOLECULE TO ADC

PEPTIDE MET ID IN PLASMA *IN VITRO*

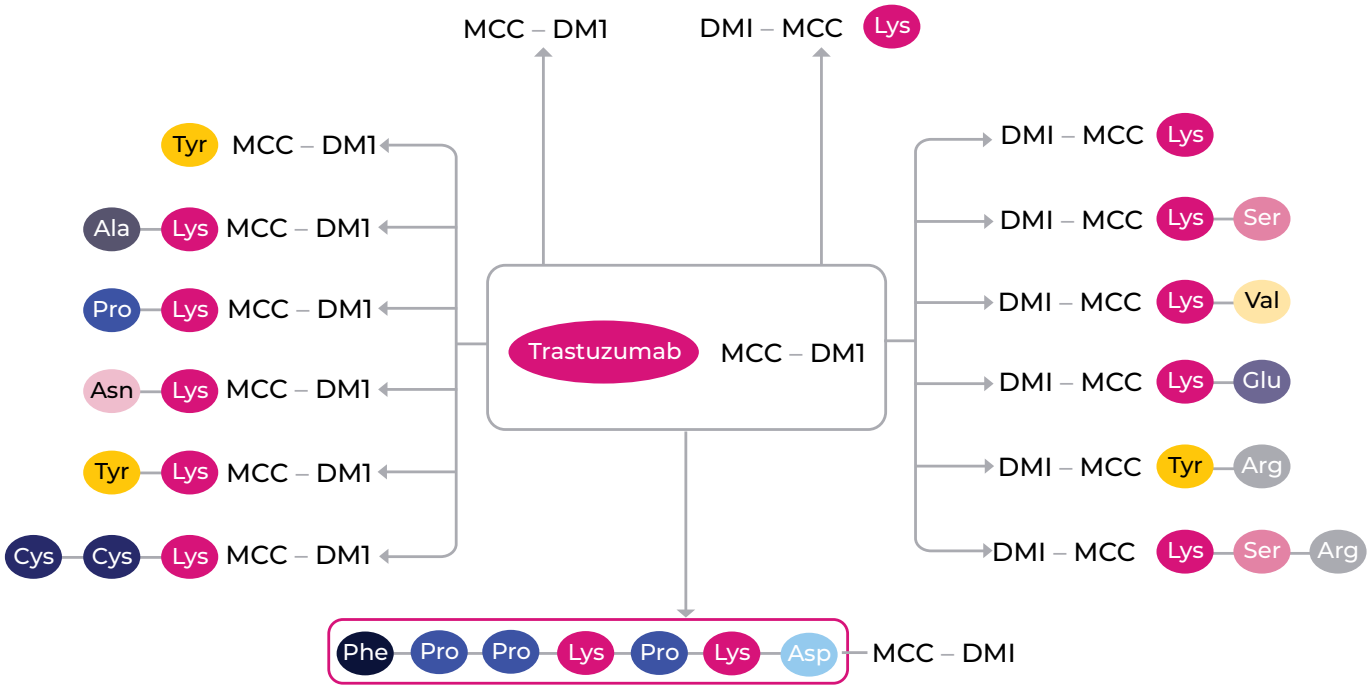


SiRNA DRUG METABOLISM *IN VITRO*



Pathway of Inclisiran in C57 mouse liver tissues, human, rat, mouse, monkey live S9

ADC DRUG METABOLISM *IN VITRO*



Proposed catabolic pathways of T-DM1 after incubation in human and monkey live S9

FORMULATION

THINKING A STEP AHEAD TO DELIVER HIGH-QUALITY INTERPRETATION AND DATA

PREFORMULATION SERVICES

- Physicochemical characterization
  - Polarized light microscopy
  - DSC &TGA
  - XRPD
  - DVS
  - log D, log P, pKa
  - Thermodynamic solubility
  - Solution/suspension stability
  - Solid state property
- Salt screening and polymorph screening
- Solid dispersion screening and spray drying

DSC

TGA

XRPD

FORMULATION SERVICES

- Formulation preparation and screening for PK, toxicology, and pharmacology study of small molecules, peptide, and protac compounds
  - For various administration routes (IV, PO, IP, SC, IV infusion)
  - Evaluate proper pharmaceutical formulation for tox study
- Solubility and stability in selected formulation
- Dilution study to predict precipitation and super-saturation of test article *in vivo*
- Formulation evaluation for oral exposure
  - Solution
  - Suspension
  - Nano-suspension
  - Emulsion/micro-emulsion/nano-emulsion
  - Solid dispersion

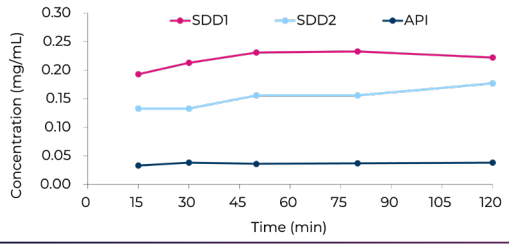
Focused-ultrasonicator

SPRAY DRIED DISPERSION (SDD)

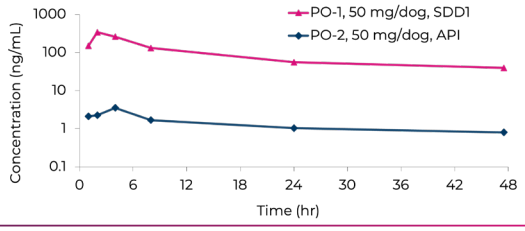
COMPOUND → SOLID DISPERSION SCREENING → SDD PREPARATION → PK, NON-GLP TOX, AND PHARMACOLOGY

SDD1 VS. API: 68-FOLD INCREASE IN EXPOSURE (AUC)

DISSOLUTION CURVE FOR SDDS VS. API

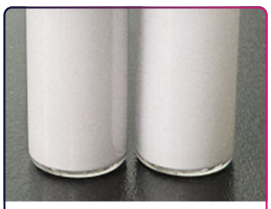


DOG PK PROFILE FOR SDD1 VS. API

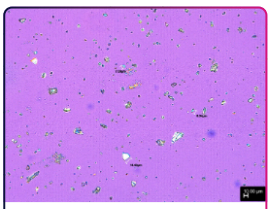


Mini Spray Dryer S-300

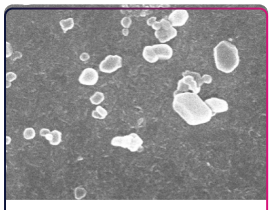
NANO-SUSPENSION FORMULATION FOR IV INFUSION



APPEARANCE



PLM (BEFORE MILL)



SEM (AFTER MILL)

Particle size (D50) decreased after mill
- from 8000 to 300 nm

Ball Mill

PHARMACOKINETICS

AAALAC AND OLAW ACCREDITED FACILITIES

OUR STRENGTHS

- Quality data
  - Well established process and QC system to ensure data quality and integrity
- Fast turnaround time
  - 5 working days from compound receipt to data delivery for most small molecule PK
- Flexibility
  - Last minute change allowed to accommodate R&D needs
- Extensive experience
  - Over 10,000 PK studies and 1,000 clients globally

STUDY TYPES

- Screening single or cassette PK study
- Tissue distribution study
- Excretion and mass balance study
- BE, DDI, ocular PK, etc.

ANIMAL SPECIES

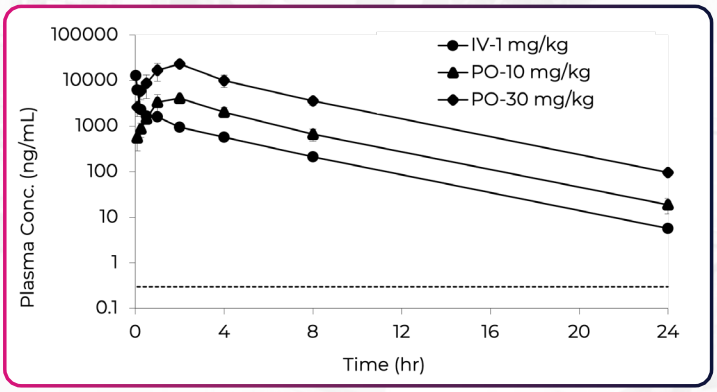
- Small animal
  - Mouse, rat, guinea pig, hamster, and rabbit
- Large animal
  - Beagle dog, cyno monkey, and mini-pig

COMPREHENSIVE *IN VIVO* TECHNIQUES

- Various dosing routes
  - IV, PO, SC, IM, intrathecal, intra-tracheal, ICV, AZ pump, programmable infusion pump, nasal drop, buccal, and capsule dosing in rats
- Sampling
  - Micro-sampling, facial vein, tail vein, jugular vein, CSF, sublingual, tear, lymph
- Surgical model (Cannulation)
  - Jugular vein, carotid, femoral vein, portal vein, duodenum, bile duct, lymph duct
- Tissue collection
  - Spinal cord, sciatic nerve, specific brain regions, cornea

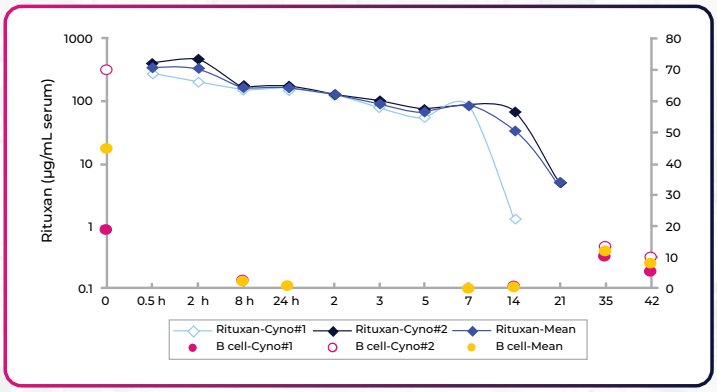
REGULAR MOUSE PK STUDY

- Serial bleeding for 9 time points from single mouse
- BA analysis using diluted whole blood or plasma



PK/PD STUDY IN NHP

- Animals were dosed at 10mg/kg, IV bolus (N=2).
- Blood samples were collected until 42 days post dosing
- ELISA measurement for Rituxan concentration; FACS analysis for B cell counting



ADVANTAGE

- Reduce the number of animals from 27 to 9
- Reduce the amount of compound usage
- Minimize PK data variability

B cell depleted immediately after IV dosing and maintained at low level until 21 days when starting to recover

LEARN MORE

EXPLORATORY TOXICOLOGY

MITIGATE THE RISK OF UNEXPECTED CHALLENGES

GENERAL NON-GLP TOXICOLOGY

STUDY TYPES

- MTD and DRF study
- Single dose study with 4-7 days observation
- Repeated dose study: 4-day, 7-day, 14-day or 28-day

ENDPOINT READOUT

- Mortality, clinical observation, body weight, body temperature, and food consumption
- Clinical pathology
  - Hematology, serum chemistry, coagulation, and urine routines)
- Necropsy and histopathology
- Ophthalmology, ECG, PD biomarkers, immunophenotyping, etc.

ANIMAL SPECIES

- Small animal
  - Mouse, rat, guinea pig, hamster, and rabbit
- Large animal
  - Beagle dog, cyno monkey, and mini-pig

IN VITRO EXPLORATORY TOXICOLOGY ASSAYS

HEPATOTOXICITY

- Hepatocyte cell viability (LDH, ALT)
- Mitochondrial toxicity
- Steatosis and phospholipidosis

CARDIAC TOXICITY

- hERG and Nav1.5 Screening (Qpatch-48)

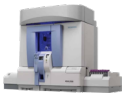
CYTOTOXICITY

- ATP depletion, LDH, and MTT

GENOTOXICITY

- Ames test
- *In vivo* MNT

ACL TOP 350 CTS
Coagulation Analyzer

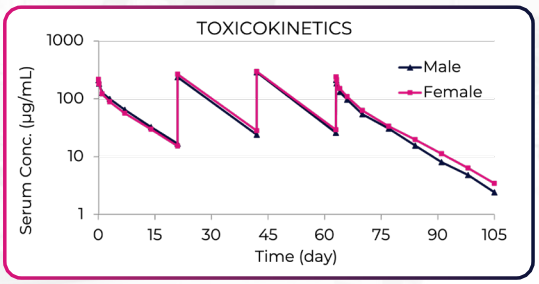


ADVIA® 2120i
Hematology System

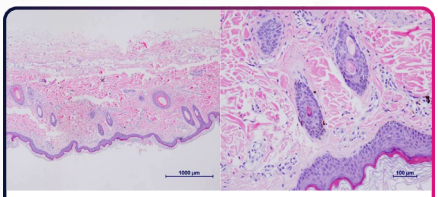
ADVIA® Chemistry
XPT System

CASE STUDY

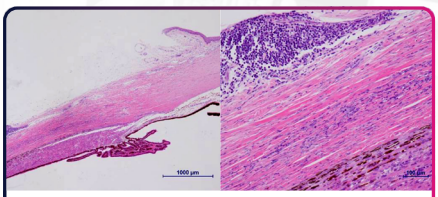
REPEAT IV INFUSION TOLERABILITY IN MONKEY



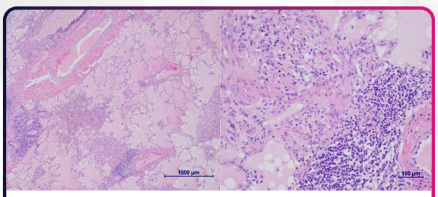
- Body weight: Steady
- Food consumption: Reduced
- Clinical abnormality: Corneal edema; corneal ulcer; squama in the face
- Clinical pathology: Reduced neutrophil#; elevated creatine kinase



- Hyperplasia, epidermal, mild
- Hyperkeratosis, mild



- Chronic inflammation, sclera, slight
- Atrophy, retina, slight
- Neovascularization, corneal stroma, slight



- Inflammation, chronic-active, moderate, multifocal
- Edema, alveolar, moderate
- Inflammation, chronic, pleura, moderate

LEARN MORE

PATHOLOGY

AN INTEGRATED SUITE OF SERVICES IN A VARIETY OF ANIMAL SPECIES

HIGHLIGHTS

- The mature and stable team member (5-10 years pathology working experience)
- Experienced pathologist
  - 1 board-certified veterinary pathologist (more than 10 years of diagnosis experience; Member of Society of Toxicology Pathology (USA)).
  - 1 clinical pathologist (more than 13 years of diagnosis experience of clinical samples in 3A hospital)
- Established protocol for IHC/IF staining: 100+ antibodies
- Standardized lab and advanced equipment

EXPERTISE

HISTOLOGY

- Tissues processing and embedding (FFPE/Frozen)
- Paraffin sectioning / cryosectioning / vibratome sectioning
- Cytospin preparation
- H&E staining / Special staining (Sirius Red, PAS, Oil red O, Masson's, LFB, Safranin O, Wright-Giemsa, etc.)

Thermo
AutoWorkstation-Stainer

BOND RX^{m} AutoStainer

Digital Pathology
Aperio ScanScope AT2

MOLECULAR PATHOLOGY

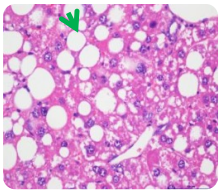
- Immunohistochemical staining (IHC)
- Immunofluorescent staining (IF)
- IHC double and IF triple staining
- Digital image analysis
- New antibody validation and new assay development

LEARN MORE

REPRESENTATIVE IMAGES

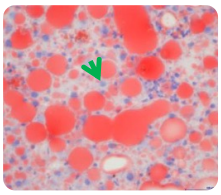
H&E AND SPECIAL STAINING

NASH MODEL, HFD+LMCD-INDUCED



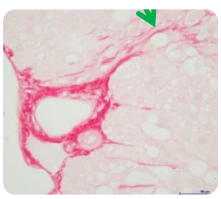
H&E

GREEN ARROW:
FAT DROPLET



OIL RED O

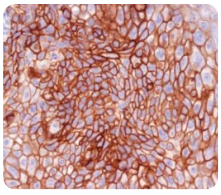
GREEN ARROW:
FAT DROPLET



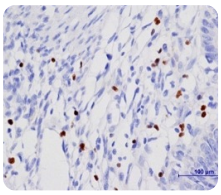
PICROSIRIUS
RED

GREEN ARROW:
FIBROSIS

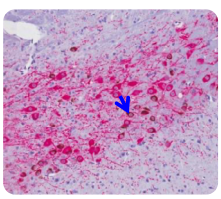
IMMUNOHISTOCHEMICAL (IHC) STAINING



P-EGFR
PDX TUMOR

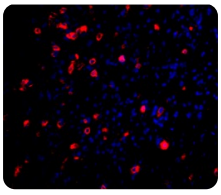


FOXP3 HUMAN
COLON CANCER

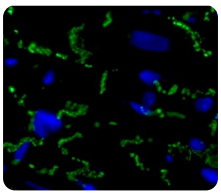


TH/α-SYNUCLEIN
PHOSPHO
(SER129)
MOUSE BRAIN

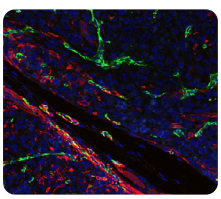
IMMUNOFLUORESCENT (IF) STAINING



NKP-46/DAPI
PDX TUMOR



CONNEXIN43/
DAPI
MOUSE HEART



CD31/αSMA/DAPI
CDX TUMOR

BIOANALYSIS

COMPREHENSIVE DISCOVERY, PRE-CLINICAL, AND CLINICAL BIOANALYSIS

HIGHLIGHTS AND SPECIALTIES

- 50+ LC/MS/MS instruments
  - SCIEX Triple Quad 6500/7500 coupled with ADDA/UPLC, HRMS API 5600, Waters Synapt G2-S Q-TOF, SCIEX X500B and Thermo Q Exactive, Micro-LC, Nano-LC, Elisa, MSD, PCR
- Experienced BA experts, mature and stable team member
- Comprehensive bioanalysis platform
  - Small molecular and large molecular compounds
  - Discovery assays to clinical trials

QUANTIFICATION AND SEPARATION OF VARIOUS TYPES OF MOLECULES

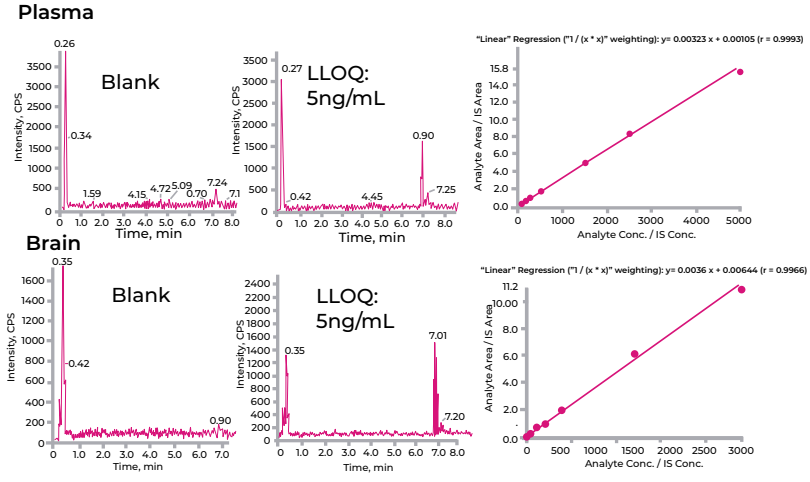
Peptide, ASO, siRNA, LNP, LPS, ADC, PDC, Protac	Endogenous biomarker assay, polar compounds	Prodrug and parent drug, unstable compounds	Chiral compounds

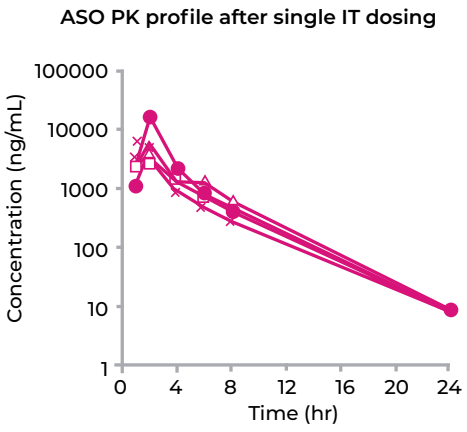
APPLICATION IN DIFFERENT TYPES OF STUDIES

Plasma, urine, heart, liver, kidney, CSF, PBMC, skin, bone marrow, and more	Cassette PK sample analysis, microdialysis sample assay	Protein assay by bottom up/down	Semi-quantification of metabolites

CASE STUDY

ASO ANALYSIS IN MALE SD RAT PK STUDY





Determined IT PK profile of antisense oligonucleotide 10 Da in male SD rats

CLINICAL BIOMARKER (URIC ACID) ANALYSIS

OBJECTIVE

- Develop and validate a method to quantify uric acid in human plasma and urine

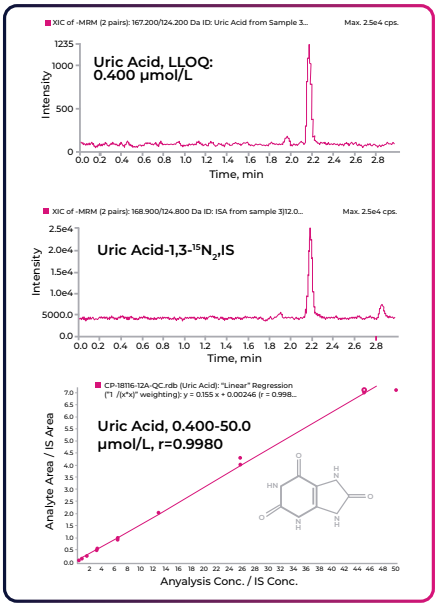
CHALLENGE

- Uric acid is an endogenous compound.
- The endogenous concentrations of uric acid in human plasma and human urine need to be accurately valuated by replicate analysis.

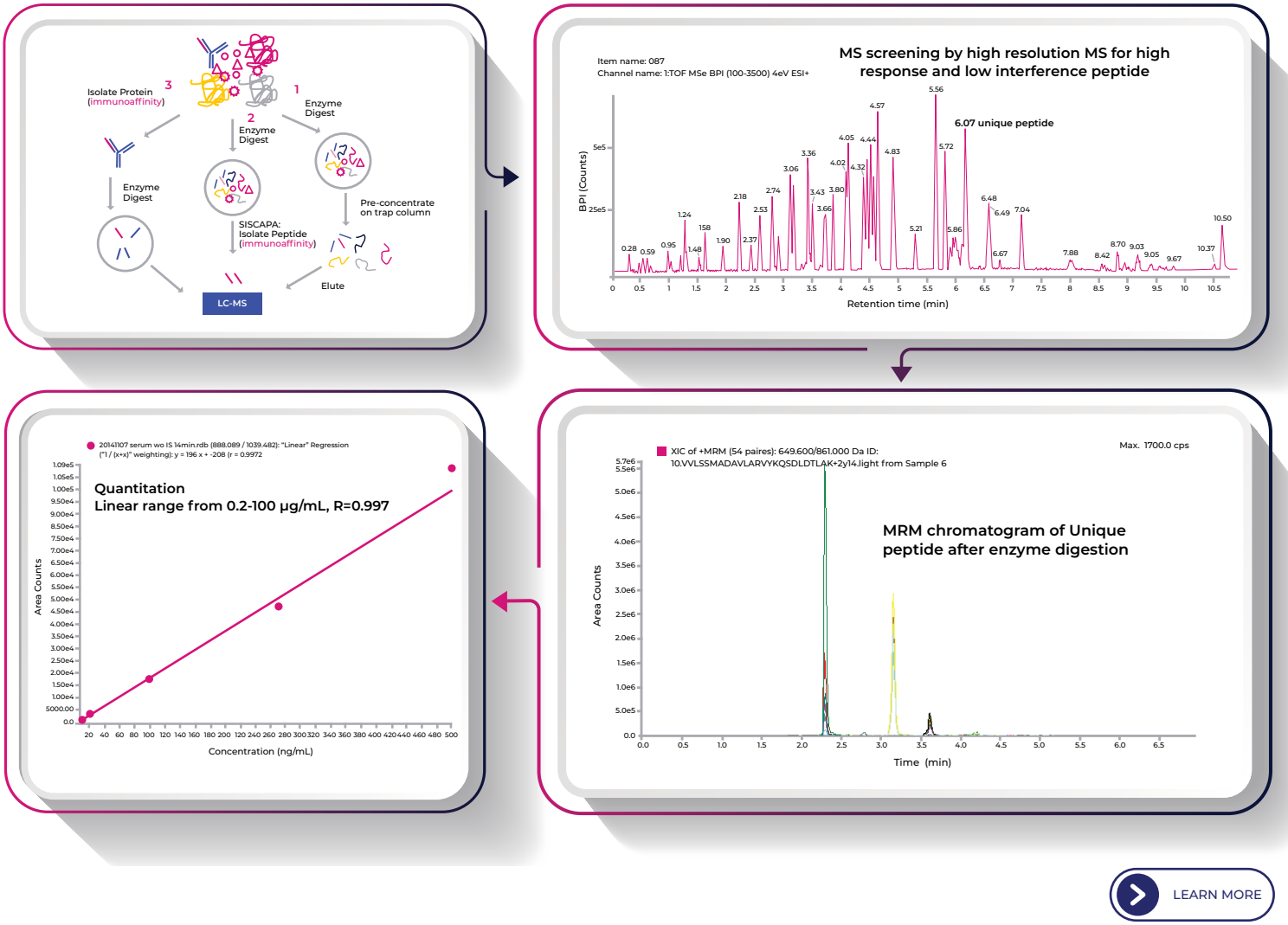
INSTRUMENT

- API 6500+, ESI, Negative Column
  - Halo LILIC (4.6x150 mm, 2.7 µm)

QUALIFICATION ELEMENT		RESULTS
Calibration curve (n=9)	0.400 - 50.0 µm	3.8%~3.0%
Intra-assay (n=6)	Endogenous conc. + LLOQ QC conc.	~4.4%
	Endogenous conc. + low QC conc.	~6.1%
	Endogenous conc. + medium QC conc.	~6.7%
	Endogenous conc. + high QC conc.	~10.9%
Inter-assay (n=18)	Endogenous conc. + LLOQ QC conc.	2.7%
	Endogenous conc. + low QC conc.	5.3%
	Endogenous conc. + medium QC conc.	3.8%
	Endogenous conc. + high QC conc.	2.5%



THERAPEUTIC PROTEIN ANALYSIS



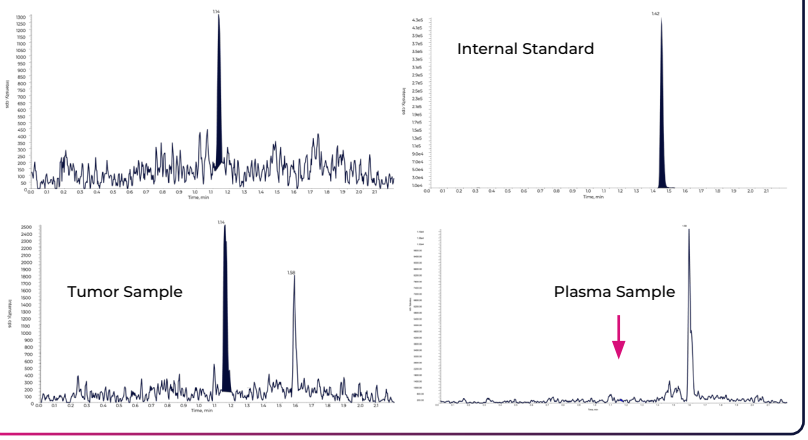
LEARN MORE

ADC/XDC ANALYSIS

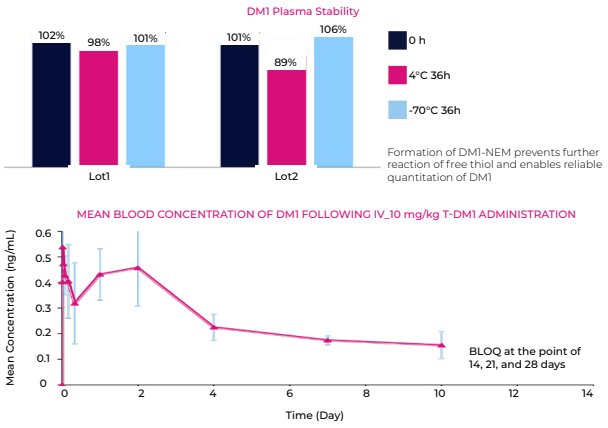
HIGH-QUALITY SERVICES FOR QUALITATIVE AND QUANTITATIVE DRUG ANALYSIS

FREE PAYLOAD ANALYSIS

ADC-PAYLOAD EXATECAN

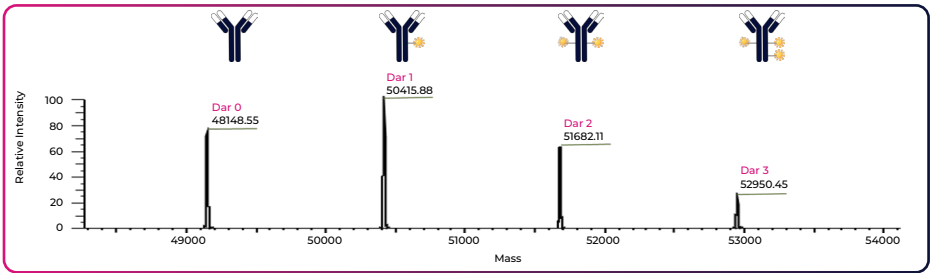


QUANTIFICATION OF DM1 WITH BLOCKING/ STABILIZING REAGENTS

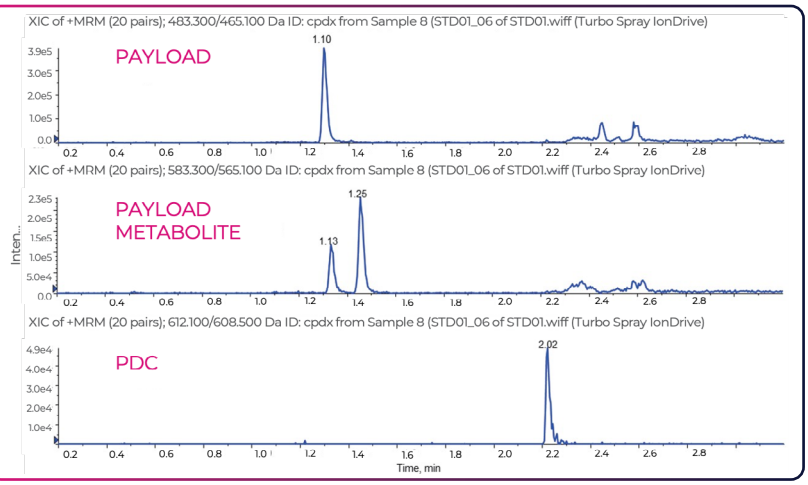


DAR VALUE DETERMINATION

- **IMMUNE ENRICHMENT**
  - *In vitro* stability samples
  - *In vivo* pk samples
  - .....
- **DEGLYCOSYLATION REDUCTION**
  - For Cysteine-conjugated ADC
  - If needed
- **LC SEPARATION**
- **HRMS ANALYSIS**
  - Deconvolution
  - Data analysis



PDC BIOANALYSIS



TARGET PEPTIDE

- Target specific
- Cell penetration

LINKER

- Non-cleavable
- Cleavable

PAYLOAD

- Cytotoxic agent
- Radionucleotides
- Imaging agents

EXPERIENCE WITH PDC PAYLOADS

- Doxorubicin
- Paclitaxel
- Daunorubicin
- Gemcitabine
- and more

BIOANALYSIS INSTRUMENTS

MESO QuickPlex® SQ 120MM

Luminex™ FLEXMAP 3D™

BD FACSCanto™ II

BD LSRFortessa-4 Laser

Triple Quadruple API 7500

HRMS Q Exactive HF-X

Attune™ NxT Flow Cytometer

BIOLOGICS BIOANALYSIS

TRADITIONAL AND INNOVATIVE APPROACHES FOR LARGE MOLECULE ANALYSIS

CAPABILITIES OVERVIEW

- Generic assay for mAb, bi-specific antibody, tribody, ADCs, or XDCs
- Specific assay: LBA or anti-idiotype mAb-based assays
- ADA assay: screening, confirmatory, titer, and neutralization assay
- Regulatory BA (GLP): GLP TK and clinical PK analysis
- Biomarker analysis (method development, method validation, and sample analysis)

PROJECT EXPERIENCE FOR EXPLORATORY BIOMARKERS

MULTIPLEX CYTOKINE BY ELISA/MSD/LUMINEX METHOD

MOUSE	RAT	DOG	CYNO	HUMAN
TNFα, IL-2, Adiponectin, CXCL12, Chemerin, Human Total PSA, Albumin, CYPA/ CYPB, EPO, GDF-15, Total STAT4, p-STAT4, PSA, Resistin	TNFα; Luteinizing Hormone (LH); C-Peptide; cAMP; PGE2; cGMP; EPO; C-peptide; Bile Acid; Lactate; LH; Osteocalcin; Akt/ pAkt; Erk/ pErk; Osteocalcin	CRP, IL-6, IL-10, CCL-2, TNFα, CCL-5, CXCL10	Activin A, IFN-γ, TNFα, IL-2, IL-6, IGF-1, Human P1NP, Osteocalcin, Inhibin A, Aβ peptides, Aβ38/40/42, GDF-15, CTX-I, p-STAT4, Total FGF23/ Free FGF23, IgG, IgA, IgM, C-peptide, Insulin, FLT3L	IL-8, IL-6, TNFα, IL-17, IL-2, IL-10, IL-1β, CCL2, IL-17

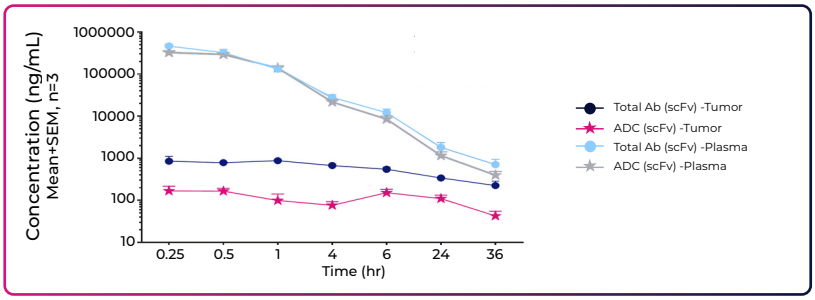
CASE STUDY

PK STUDY OF ADC IN SCID MICE WITH NCI-N87 XENOGRAFT MODEL

PURPOSE: Evaluate PK property of ADC via IV administration into SCID mice bearing NCI-N87 tumors

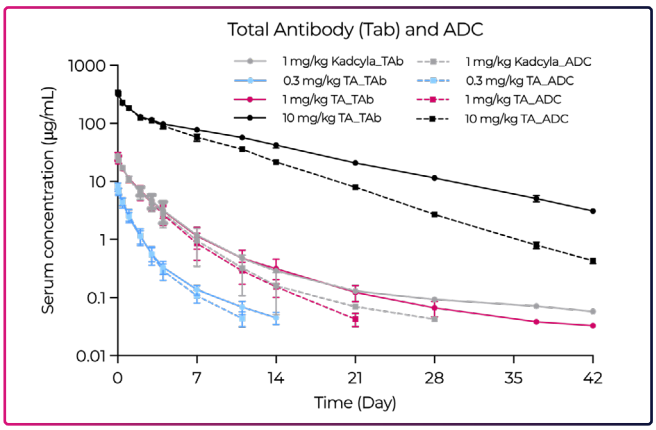
STUDY DESIGN

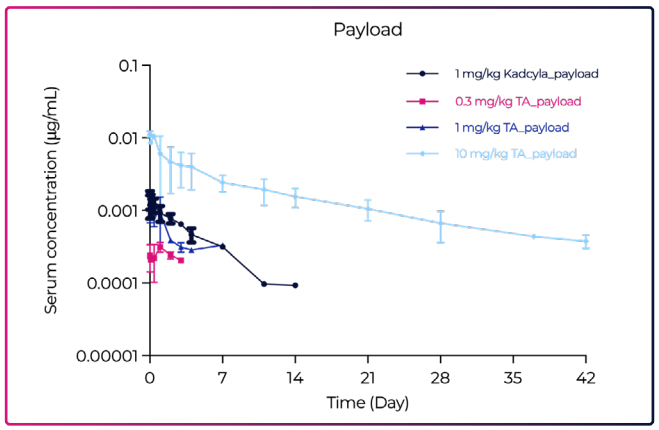
- ADC drug administration in the NCI-N87 xenograft tumor model
- Plasma/tumor collection at indicated time points
- Total antibody and ADC analysis in plasma/tumor



CASE STUDY

TARGET-MEDIATED CLEARANCE IN CYNOMOLGUS MONKEY





Shanghai Global Headquarters
1F & 3F, Block A, 2829 JinKe Road,
Zhangjiang Hi-Tech Park
PuDong New Area, Shanghai, China 201203
+86 21 5132 0088

South San Francisco Innovation Center
280 Utah Avenue, Suite 100
South San Francisco, CA 94080
+1 650 419 9974

Copenhagen Field Office
Ole Maaloees Vej 3, 2200
Copenhagen, Denmark
+45 4586 9000

✉ Contact@ChemPartner.com
🌐 ChemPartner.com

CHEMPARTNER

DEDICATED TO LIFESCIENCE