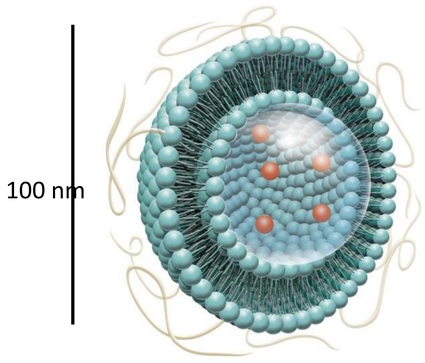
Liposome for small molecule delivery

FUJIFILM
Value from Innovation

Basic Liposome Structure



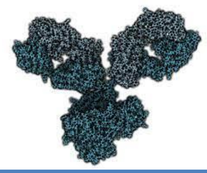
Lipid bilayer
- Internal aqueous phase

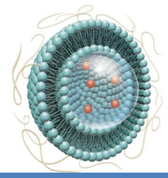
DDS carrier
- Water-soluble drug in inner aqueous phase

PEG hydration layer
- Liposome stabilization in circulation

Containing small molecule: API in stable carriers
✓ Prolongs plasma half-life
✓ Improves biodistribution in tumor

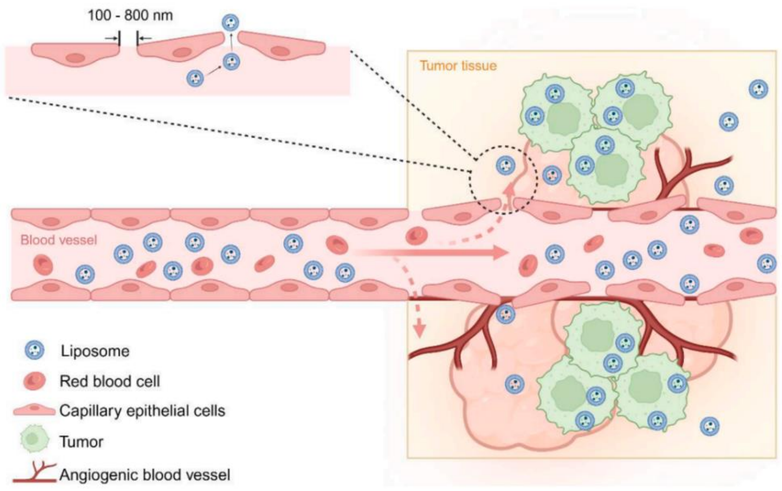
Features of Liposome in Comparison to ADC





	ADC	Liposome
Distribution mode	Accumulating in tumor by EPR effect Specific bind to antigen expression cell	Accumulating in tumor by EPR effect
Linker modification on API	Required for chemical connecting to antibody via linker	Not required Physically encapsulating into internal volume
Payload capacity	Limited Less than 8 per antibody	Large capacity Approx. 10,000 per particle
Selected launched product	Enhertu® (trastuzumab deruxtecan) Kadcyla® (trasuzumab emtansine) Trodelvy® (Sacituzumab govitecan)	Doxil® (doxorubicin) Vyxeos® (daunorubicin and cytarabine) Onivyde® (irinotecan)

Passive Targeting to Tumor by Enhanced Permeability and Retention (EPR) effect



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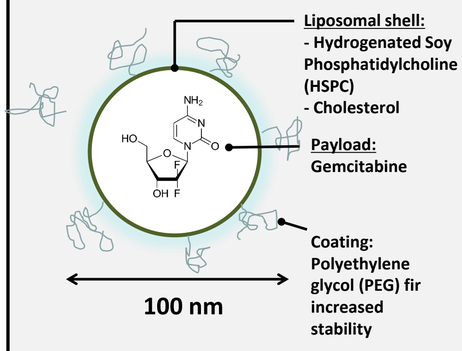
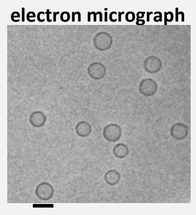
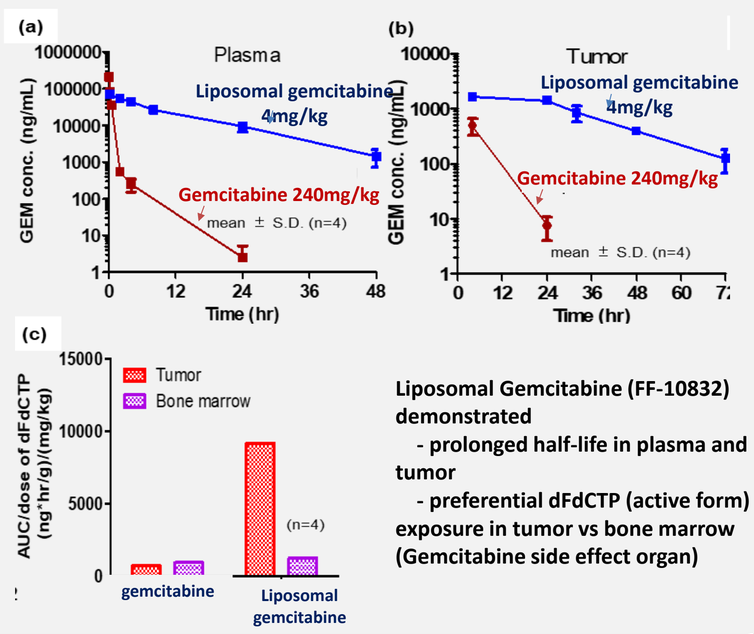
- Liposome (Φ100 nm) cannot leak out from normal blood vessels (blood vessels retain particles larger than 6 nm)
- Immature blood vessels in tumors have large pores and liposomes leak out of them.

An exemplification: liposomal gemcitabine (FF-10832)



Transmission electron micrograph



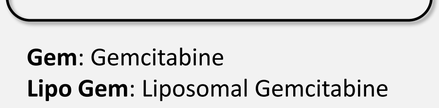


Liposomal Gemcitabine (FF-10832) demonstrated
- prolonged half-life in plasma and tumor
- preferential dFdCTP (active form) exposure in tumor vs bone marrow (Gemcitabine side effect organ)

Liposomal gemcitabine combination with Immune Check point Inhibitor (ICI)

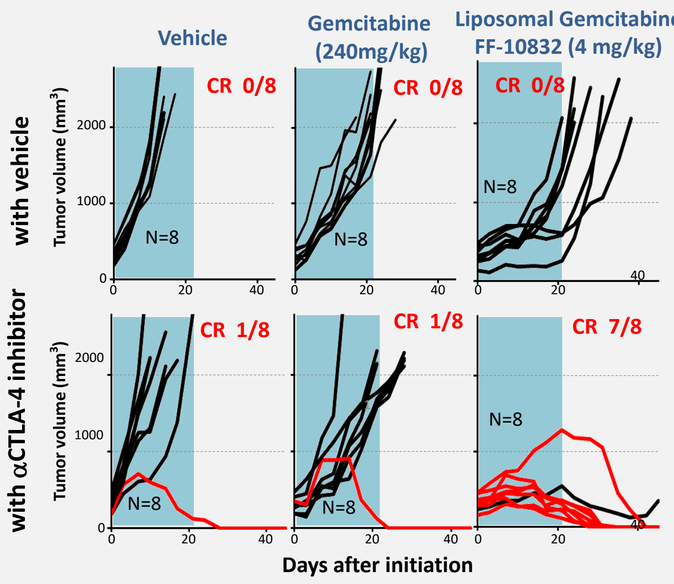
Anti-tumor Effects of FF-10832 in Combination with ICI (CTLA-4 inhibitor)

Study protocol Mouse model



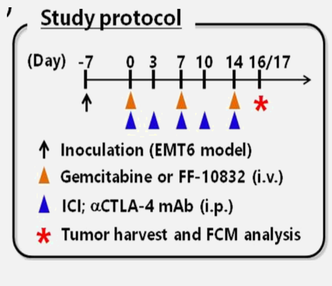
Gem: Gemcitabine
Lipo Gem: Liposomal Gemcitabine

Treatment period
CR: Complete remission

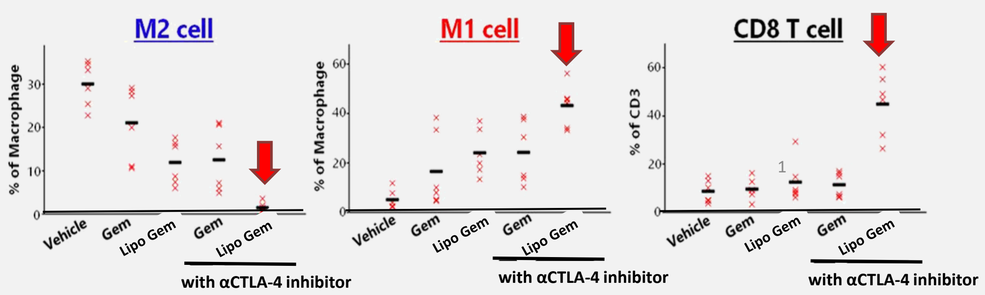


FCM Analysis of Tumor Microenvironment

Mouse model



:ICI (αCTLA-4) combination with Liposomal Gemcitabine

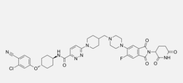


In the ICI plus gemcitabine group, 1 of 8 animals experienced complete response; in the ICI plus Liposomal gemcitabine group, this number increased to 7 of 8 animals.

Liposome formulation enhanced conversion of the tumor immune environment from COLD to HOT

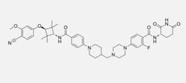
Liposomal Targeted Protein Degraders (TPD)

ARV-110



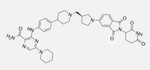
Molecular weight: 812.3g/mol
Solubility: poor solubility in water

ARV-766



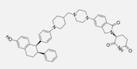
Molecular weight: 808.0 g/mol
Solubility: poor solubility in water

NX-2127



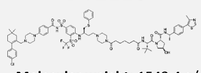
Molecular weight: 719.8 g/mol
Solubility: poor solubility in water

ARV-471



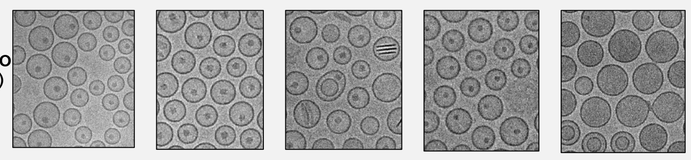
Molecular weight: 723.9 g/mol
Solubility: poor solubility in water

DT2216



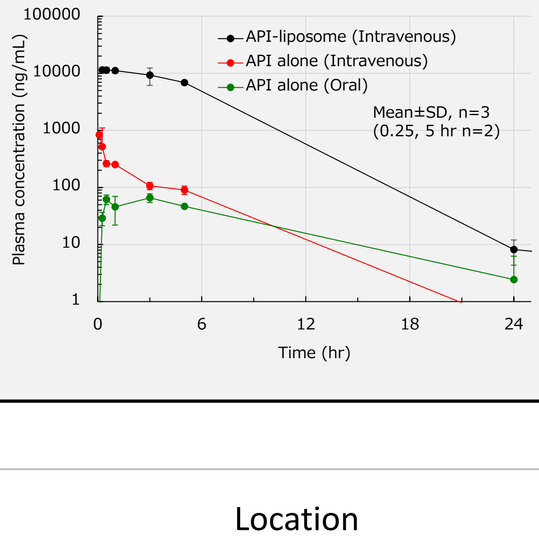
Molecular weight: 1542.4 g/mol
Solubility: poor solubility in water

TPDs encapsulated in liposome

	ARV-110	ARV-471	ARV-766	NX-2127	DT2216
Yield	98%	96%	99%	>99%	46%
Encapsulation ratio	>99%	99%	99%	91%	88%
Particle size	108 nm	99 nm	105 nm	110 nm	118 nm
Morpholo (TEM)					

PK study of liposomal TPD

LiposomalARV-471 Mice PK



Pharmacokinetic parameters of ARV-471 after IV and PO administration to mice

Parameter	API-liposome	API alone	
	Intravenous	Intravenous	Oral
Cmax (ng/mL)	11,450	841	65.9
$T_{1/2}$ (hr)	3.65	2.51	4.43
$AUC_{0\text{-}24hr}$ (ng·hr/mL)	113,474	1,841	731
AUC_{inf} (ng·hr/mL)	113,662	1,842	746
CL (mL/hr/kg)	17.6	1,086	–
MRT (hr)	3.91	3.22	5.28
V_{ss} (mL/kg)	68.6	3,491	–
Bioavailability (%)	–	–	40.5

Animal：Mouse（SIc:ICR、6 weeks, male）
Dose：2mg/kg ,i.v or o.p.

ARV-471 liposome
Particle size: 99 nm
API concentration: 0.50 mg/mL
Encapsulation efficiency: 99%
Yield: 96.1%

Fujifilm as a Liposome CRDMO

Manufacturing facility

- ✓ GMP production of LNPs and liposomes
- ✓ Fujifilm preparatory liposome manufacturing equipment
- ✓ LNP / Liposome NxGen™ Microfluidic mixer (0.2 – 100L)
- ✓ Highly potent APIs handling area
- ✓ KrosFlo® KMPi and Mobius Flex Ready® from mL scale to ~100 L
- ✓ Vial filling system 3000 vials/hour

Analytical method and Spec Devs.

- ✓ *In vitro release test method development*
- ✓ *Assay encapsulated and unencapsulated API*
- ✓ *HPLC method development for lipids and API with quantification and validation of ICH guidelines*
- ✓ *Size and distribution by DLS*
- ✓ *Zeta potential, pH, osmolality, Particle matter*
- ✓ *Residual solvent analysis by GC (FID)*
- ✓ *Sterility*
- ✓ *Spectroscopy (UV, IR) and others*

Location