Liposome for anti-cancer drug development

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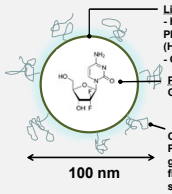
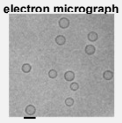
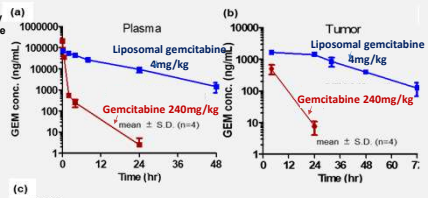
FUJIFILM Value from Innovation

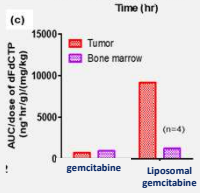
An exemplification of Fujifilm liposome



Transmission electron micrograph



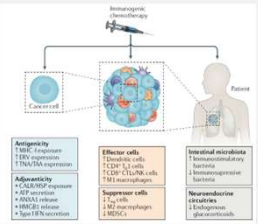




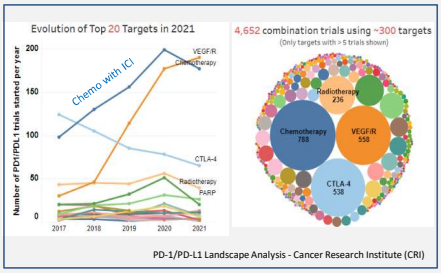
Liposomal Gemcitabine (FF-10832) demonstrated
- **prolonged half-life in plasma and tumor**
- **preferential dFdCTP (active form) exposure in tumor vs bone marrow (Gemcitabine side effect organ)**

Field of ICI combination chemotherapies

Increasing number of ICI combination chemotherapies in development



Calluzzi et al, Nature Review, Clinical Oncology 2020



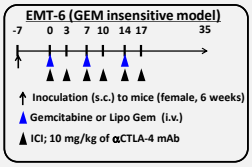
PD-1/PD-L1 Landscape Analysis - Cancer Research Institute (CRI)

ICI-combined chemotherapies convert the tumor immune environment from COLD to HOT

Liposome formulation enhanced synergistic effect of chemotherapy in combination with ICI (animal model)

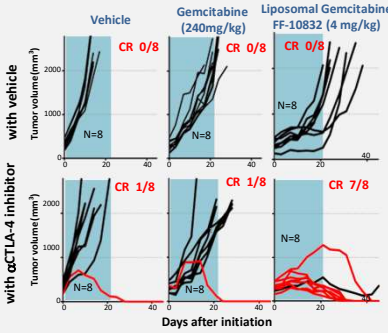
Anti-tumor Effects of FF-10832 in Combination with ICI (CTLA-4 inhibitor)

Study protocol Mouse model



Gem: Gemcitabine
Lipo Gem: Liposomal Gemcitabine

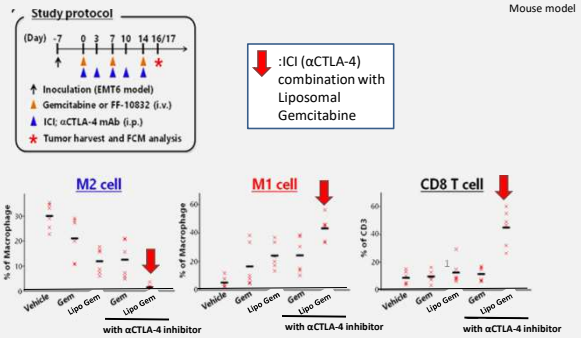
Treatment period
CR: Complete remission



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.

FCM Analysis of Tumor Microenvironment (CTLA-4 inhibitor combo)

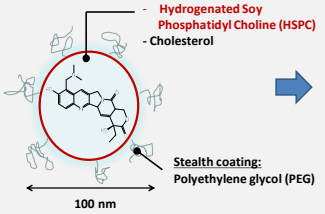
Mouse model



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

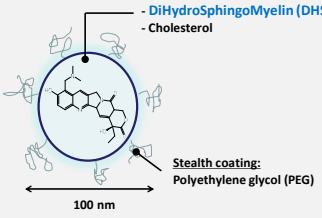
The DHSM based high stable liposome formulation: Fujifilm offers for customers

➢ Conventional Liposome

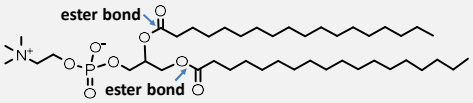


*HSPC (Hydrogenated Soy Phosphatidylcholine): Conventional lipid used in the marketed liposomal drug

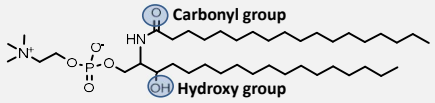
➢ DHSM Liposome



➢ HSPC (Hydrogenated Soy Phosphatidyl Choline)



➢ DHSM (DiHydroSphingoMyelin)

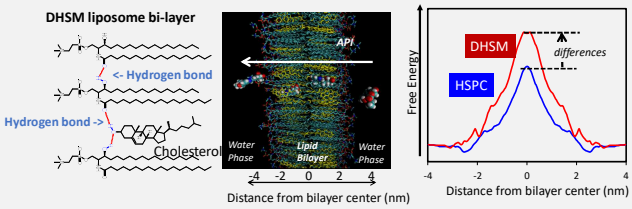


- ✓ **No hydrolysis site(ester bond):** High stability during long-term storage of liposomes in liquid suspension
- ✓ **Carbonyl group and hydroxyl group:** Formation of tight lipid bilayer membranes by intermolecular hydrogen bonding

❑ Computational analysis on lipid bi-layer of DHSM liposome

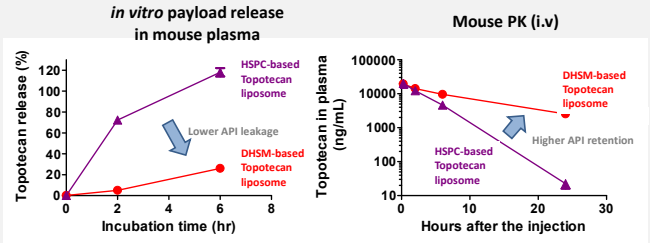
Estimation of free energy barriers for API to penetrate DHSM or HSPC bi-layer using Molecular Dynamics simulation

DHSM liposome bi-layer



Hydrogen bonds formed between DHSM-DHSM and DHSM-cholesterol molecules stabilize the liposome bilayer, reducing drug leakage in plasma *in vivo* , and extending storage stability

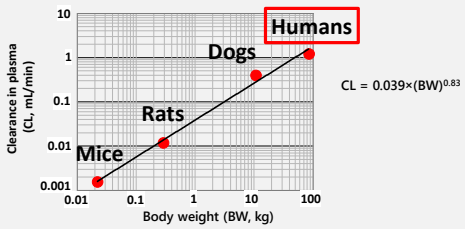
❑ Exemplification DHSM Liposome (Payload topotecan)



DHSM-based liposomal formulation allowed stable encapsulation and prolonged plasma circulation

❑ Species differences in PK profile DHSM Liposome

Allometric Association between clearance and body weight



❑ Track record of Fujifilm DHSM Liposome in human Clinical trial

DHSM Liposome encapsulating topotecan

Fujifilm Starts a U.S. Phase I Clinical Trial of Anti-Cancer Agent "FF-10850" on Advanced Solid Tumors

Clinical Development of a Novel Liposome Drug with Mechanism of Selective Delivery of Anti-Cancer Agent to Tumors

INVESTIGATIONAL USE ONLY: NOT FOR SALE IN THE US

- ✓ Formulation designed of the DHSM Liposome, preclinical tox, PK, efficacy studies, CTM manufacturing, and Phase1 clinical trials in the U.S. were fully conducted by Fujifilm.
- ✓ **Fujifilm is the CDMO possesses the hands-on knowledge of liposome formulation development**

The DHSM-based liposomal Topotecan Liposome shows robust PK extrapolation from preclinical animal studies to human clinical trials.