Fujifilm has built a new facility to manufacture liposome drugs at the pharmaceutical production site of the Fujifilm group company Toyama Chemical Co., Ltd. Operations at the plant started in February 2020.

Liposomes are artificially constructed vesicles made from organic phospholipids similar to those that make up cell and bio membranes. Liposomes are produced by harnessing nano-dispersion technologies.

Advanced nano-dispersion and process technology was first cultivated by Fujifilm as it innovated the photographic film business. That technical history proved a marked advantage as Fujifilm moved into methods of drug manufacturing and testing which are now central to ground-breaking, headline-making advances in CRISPR, CAR-T immuno-oncology and gene therapies.

Fujifilm's pharma division will be expanding its clinical trials for cancer drugs and will use the new plant to produce liposomes designed to be the efficient delivery vehicles for such highly-advanced drug candidates.

Breakthroughs in these latest new drug therapies have been nothing short of revolutionary, bringing amazing therapeutic options and renewed hope for patients and their families all over the world. But getting newer drugs affordably to market remains a global challenge.

Only 14 percent of all drugs in clinical trials will eventually receive approval by the US Food and Drug Administration (FDA), the most powerful regulatory agency in the global pharmaceutical industry. A drug candidate that looks successful in vitro often fails to demonstrate its expected performance in vivo due to the lack of instability in the blood, poor targeting delivery and consequent side effects.

FUJIFILM Pharmaceuticals U.S.A., Inc. is determined to address these newer challenges head on. It will use its new facility with its liposome-manufacturing capabilities to significantly improve the population of available and approved therapies.

The facility will be one of the most advanced in the world, providing new and transparent manufacturing processes producing the elements of enduring cancer cures in ways likely to increase regulatory approvals, delivery success, and disease abatement.
Liposomes as an agent for drug delivery can enhance today’s therapeutics

Developed by harnessing nano-dispersion technologies, liposomes are artificially constructed vesicles made from organic phospholipids similar to those that make up cell and bio membranes. These small particles provide a type of drug delivery system (DDS) technology that can deliver the required amount of a drug to the specific area of the body on a predetermined schedule.

One of the biggest challenges we face in cancer treatments is that in some cases, anti-cancer agents can act on healthy tissues and cells instead of the cancerous tumor, leading to adverse side effects. By encapsulating a drug in a liposome, it is expected that the drug will be preferentially delivered to the tumor, suppressing side effects, and enhancing the pharmacological efficacy of the drug.

By harnessing its advanced nano-dispersion technology, analysis technology, and process technology cultivated through its wide range of product development, Fujifilm conducts research and development on the potential use of encapsulating drugs in liposomes.

Fujifilm is developing new drug delivery systems — including liposomal formulations — to advance therapeutic progress to meet unmet medical needs, such as cancer.

The advantage of Fujifilm’s liposomal particles is evident in its physical characteristics. Unique emulsification methods were optimized to yield liposomes that are uniform in size and shape, which enables a controllable release rate, and makes the technology applicable to various lipid formulations. The uniform shape in nano size allows the encapsulated drug to be delivered to the targeted area of concern.
**Progress in the clinic — FF-10850**

FF-10850 is a liposome-based agent encapsulating the anti-cancer agent topotecan (Hycamtin®) developed by GlaxoSmithKline plc. and distributed by Novartis for the treatment of ovarian cancer, small-cell lung cancer, and cervical cancer.

As topotecan has an extremely short half-life in the blood, and has been found to cause bone marrow suppression as a side effect in more than 80 percent of patients, the hope is that a liposomal formulation can resolve the drug delivery challenges while minimizing harmful side effects of the therapy. Fujifilm has succeeded in stabilizing topotecan encapsulated in a liposome membrane (FF-10850) composed of dihydro sphingomyelin (DHSM), and has obtained encouraging results in preclinical studies.

The pharmacokinetics of topocan significantly improved with the FF-10850 formulation, as the drug was detected in mice plasma three days post-injection (Figure 1A). The post-injection plasma concentration of FF-10850 was also higher than that of an HSPC-encapsulated topotecan (Figure 1B), demonstrating the potential of Fujifilm’s liposome technology in comparison with conventional liposome formulations.

Preclinical studies in mice utilizing FF-10850 suggests tumor-regression effects, improved pharmacological efficacy when administered in combination with an immune checkpoint inhibitor (anti-PD-1 antibody), and prolonged survival compared to the monotherapy (see our technical bulletin for combination of liposome and immuno check point inhibitors).

![Figure 1. Pharmacokinetics improvement in mice.](image)

1HSPC (hydrogenated soy phosphatidylcholine) is a conventional liposomal lipid used in an FDA-approved liposomal doxorubicin
**FF-10850 — High tumor regression effects confirmed with monotherapy**

In a preclinical study, mice transplanted with human-derived ovarian cancer cells (ES-2) were administered either topotecan and FF-10850, and the efficacy and tolerability were confirmed for each dosage. The period of administration was five consecutive days for topotecan and two cycles of one administration per week for FF-10850.

With FF-10850, tumor regression effects were seen with 2.67 mg/kg (1.33 mg/kg, twice). Furthermore, the relative body weight change, which is an indicator of tolerability, was less than that observed with topotecan treatment. FF-10850 is expected to show pharmacological efficacy that exceeds that of topotecan and DOXIL®1, while maintaining tolerability even when dosage is increased (Figure 2).

With topotecan, efficacy was observed with 10 mg/kg (2 mg/kg, five times), whereas with FF-10850, efficacy was confirmed with 1 mg/kg (0.5 mg/kg, twice). When the two drugs were compared, FF-10850 demonstrated efficacy that was greater than, or equal to topotecan, but with only 1/10 of the total dose of the latter. Consequently, FF-10850 treatment resulted in longer median survival rates compared to topotecan (Figure 3).

![Figure 2. Efficacy in subcutaneous ES-2 tumor model. A) Tumor volume, and B) relative body weight change upon administration of topotecan and FF-10580.](image)

1DOXIL® is a doxorubicin liposomal drug indicated for ovarian cancer, AIDS-related Kaposi’s sarcoma and multiple myeloma.
In a separate study, 5 mg/kg (1mg/kg, five times) and 0.25 or 1 mg/kg (one dose each) were administered to rats in order to analyze and compare the hematotoxicity of FF-10850 and topotecan. Blood cell count was conducted every two days for two consecutive weeks, and the results demonstrated that the hematotoxicity post-drug administration was lower in rats treated with FF-10850 (Figure 4).

**Figure 3. Efficacy in peritoneal tumor model.** Survival rate of mice treated with topotecan and FF-10850 at three different concentrations.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median survival (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>10</td>
</tr>
<tr>
<td>Topotecan</td>
<td>20</td>
</tr>
<tr>
<td>FF-10850 (1 mg/kg)</td>
<td>24</td>
</tr>
<tr>
<td>FF-10850 (2 mg/kg)</td>
<td>31.5</td>
</tr>
<tr>
<td>FF-10850 (4 mg/kg)</td>
<td>35.5</td>
</tr>
</tbody>
</table>

**Figure 4. Hematotoxicity in rats.** Blood count change upon administration of topotecan and FF-10850.
Finally, mice treated with FF-10850 and DOXIL® at maximum tolerable doses (MTD) were observed for the development of hand-foot syndrome (HFS), a common adverse effect of a liposomal doxorubicin approved by the FDA for the treatment of ovarian cancer, AIDS-related Kaposi’s sarcoma, and multiple myeloma. HFS is characterized by skin eruptions and swelling, pain, erythema and desquamation. Although HFS is experienced by 51% of patients treated with a liposomal doxorubicin, mice treated with FF-10850 never developed any HFS-like symptoms (Figure 5).

![Figure 5. Skin toxicity in mice. HFS-like skin toxicity in mice treated with DOXIL® and FF-10850 at MTD.](image)

**The promise of liposomal technologies**

Fujifilm’s biggest strength is its wide range of advanced technologies, such as chemical synthesis, analysis, nanotechnologies and manufacturing know-how.

Currently, the company is also undertaking initiatives with the aim of applying these technologies not only to existing drugs, but expanding to next-generation therapeutics, such as nucleic acid drugs and gene therapy drugs.

The opening of the new liposome plant will advance production of the latest new therapies and DDS technologies, address unmet needs, save innumerable lives, and improve the quality of life for patients now at risk in every corner of our world.
About Fujifilm

Established in 2010, FUJIFILM Pharmaceuticals U.S.A., Inc. is based in Boston, Massachusetts, and specializes in clinical research and development of pharmaceutical products. FUJIFILM Pharmaceuticals U.S.A., Inc. strives to contribute to the further development of global health care through new drug development of unique therapeutic compounds, to combat illnesses such as influenza, Alzheimer’s and cancer.

FUJIFILM Holdings Corporation, Tokyo, Japan, brings cutting edge solutions to a broad range of global industries by leveraging its depth of knowledge and fundamental technologies developed in its relentless pursuit of innovation. Its proprietary core technologies contribute to the various fields including healthcare, graphic systems, highly functional materials, optical devices, digital imaging and document products. These products and services are based on its extensive portfolio of chemical, mechanical, optical, electronic and imaging technologies. For the year ended March 31, 2019, the company had global revenues of $22 billion, at an exchange rate of 111 yen to the dollar. Fujifilm is committed to responsible environmental stewardship and good corporate citizenship.

For more information, please visit: www.fujifilmpharma.com

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