Novel SN-38 Derivatives

~ A Nano Carrier-free Prodrug for High Anti-Tumor Activity and Safety ~

KEY INVENTION

- A prodrug utilizing SS bond reduction by glutathione (GSH) localized in tumors
- A nano carrier-free DDS designed by making the drug itself into nanoparticles

For development of a novel drug showing a high anti-tumor activity and safety!

(A medical doctor-led clinical trial is expected to be carried out.)

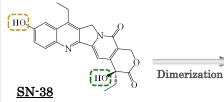
[Disadvantage of Current Nano Carriers and Prodrugs] [Advantage of SN-38 Derivatives]

- Nano Carriers (LNP, etc.)
 - High Liver Accumulation (>90%)
 - Low API Loading (<10%)
 - Side Effects by Carriers (other than API)
- - · Low efficacy and side effect by metabolism before delivery to the target cells

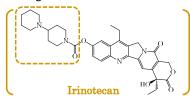


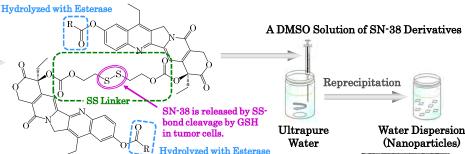
- **High Target Cell Accumulation**
- **High API Loading**
- Nanoparticles by Drug Itself (No Carrier)
- - Poorly metabolized before delivery to the target cell (metabolized by GSH)

SUMMARY of INVENTION



- · Topoisomerase Inhibitor
- · Low Water Solubility (<5 ppm)
- · Prodrug (Irinotecan) is commercialized.





SN-38 Derivatives (SN-38 SS Linker Dimers)

- · SN-38 Dimers through SS Linker including an SS Bond
- · Prodrug utilizing SS Bond Cleavage (Reduction) by GSH
- · Less impact on normal cells due to less GSH in the cells

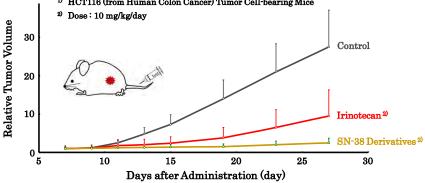
High Dispersion Stability

COMPARISON with and ADVANTAGE over CURRENT TECHNOLOGY

[Efficacy and Safety Comparisons of this Technology with Current Technology]

a. *in vivo* Trial (Mice 1), i.v.)

b. Safety (SN-38 vs. SN-38 Derivatives) 1) HCT116 (from Human Colon Cancer) Tumor Cell-bearing Mice



The anti-tumor activity of SN-38 derivatives is higher than that of Irinotecan.

 ${
m Inhibitory\,Activity:IC_{50}\,(\mu M)}$ 10 Normal Cells (HMEC) High Safety

> SN-38 **SN-38 Derivatives**

Cancer Cells

(KPL-4)

The safety of SN-38 derivatives is higher than that of SN-38.

Low

Safety

APPLICATION expected

Development of Novel Anti-Cancer Drugs such as for Lung, Breast, Colorectal, Cervical or Stomach Cancers

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