Drug Distribution of $[^{14}C]$Gemcitabine Using Quantitative Whole-Body Autoradiography after a Single Oral and Intravenous Bolus Doses Administration to Male Nu/Nu Mice

W. Hao, L. Yang, J. Wang, S. Hsueh, C. Hsu
Innopharmax Inc.

Purpose
To evaluate the drug distribution after a single dose of oral OralPAS® gemcitabine formulation (D07001-F4) or intravenous gemcitabine-HCl administration to male Nu/Nu mice.

Methods
Sixteen male Nu/Nu mice were allocated into two groups. Each group were received a single oral dose of $[^{14}C]$Gemcitabine in D07001-F4 or intravenous dose of $[^{14}C]$Gemcitabine in gemcitabine-HCl, respectively. The target dose was 3 mg/kg which included both non-radiolabeled Gemcitabine and $[^{14}C]$Gemcitabine. One mouse per time point per group was euthanized at 0.25, 0.5, 1, 2, 4, 8, 24 and 48 hours post-dose. For quantitative whole-body autoradiography (QWBA) analysis, mice carcasses were frozen and embedded into blocks, which blocks were cut into sagittal sections and expressed to phosphor image screens. The concentrations of radioactivity in whole-blood and tissues were then quantified.

Results
The distribution of drug-related radioactivity in tissues has no significant difference after oral and intravenous dosing. The C$_{max}$ of blood was similar and observed at 0.25 hour post-dose; on the other hand, the C$_{max}$ were observed at 0.25 to 1 hour post-dose in other tissues. The highest concentrations of radioactivity that was observed in tissues were found in the following order: urinary bladder > lymph node > spleen > kidney > stomach > lung, liver, large intestine and pancreas > blood > testis > prostate gland. Nonetheless, the concentrations in stomach contents and small intestine contents from a single oral dose were higher than intravenously dose at 0.25 and 0.5 hour, respectively. High concentrations were seen in alimentary canal contents, bile and urine, which reflected the routes of elimination after oral administration.

Conclusion
Following a single oral administration of $[^{14}C]$ Gemcitabine in D07001-F4, the drug-derived radioactivity was well absorbed and widely distributed to tissues. The distribution of drug-related radioactivity in tissues was almost similar after oral and intravenous dosing; nonetheless, higher concentrations in stomach and small intestines were found following a single oral dose. It suggests that gemcitabine in D07001-F4 might effectively distribute through the alimentary canal via oral route and its application in new indication will be further explored.