responsible organ in the distribution of this drug. The slope of the integration polt was linear up to 5 min after its iv administration. The CLuptake value for IH-901 was thus calculated as 0.262 ml/min/g liver. Furthermore, we determined the CLbiliary by measuring the plasma concentration, bile concentration and liver concnetration, after its iv infusion at the infusion rate of 40-400 ug/min/kg. Both the plasma and the bile concentration of IH-901 were reached at steady-state at 45 min (5 times of t1/2) after its iv infusion. The CLbiliary value for IH-901 was 0.85 ml/min/g liver. The liver concentration of IH-901 was higher by 23 times than that of plasma at steady-state. In conclusion, IH-901 was mainly distributed in the liver, followed by being excreted into the bile as a intact form. The mechanism by which IH-901 uptakes into hepatocytes requires further in vitro studies such as isolated hepatocytes and cultured hepatocytes.

[PE2-11] [ 10/18/2002 (Fri) 13:30 - 16:30 / Hall C ]

## New Analytical Method of Cyclosporine A in Human Serum by High -performance Liquid Chromatography/Diode Array Detector and Its Application to Pharmacokinetics of Cyclosporine A in Human Volunteers

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A simple, specific and sensitive method for the determination of cyclosporine A (CsA) in human serum has been developed by a high performance liquid chromatography/diode array detector (DAD) and applied to pharmacokinetic study of CsA. This method involves the use of solid phase extraction procedure following rapid protein precipitation with zinc sulphate from 1 ml of human serum, using a disposable $C_{18}$ extraction cartridge. Two diffenent kinds of HPLC column (XTerra $RP_{18}$ (2.1 x 150 mm, 5μm) vs. Symmetry 300 (3.9 x 150 mm, 5 μm)) and mobile phases (acetonitrile:$H_2O$ (65: 35, v/v%) vs. actonitrile: methanol:$H_2O$ (50:15:35, v/v/v%)) were used for comparison of peak areas and linearity of CsA and CsD. Effects of pressure setting of a vacuum manifold on cumulative peak areas of CsA and CsD were compared. As a result, XTerra $RP_{18}$ column, low pressure (-4~-9 inch Hg), and acetonitrile/$H_2O$ (62/38, v/v%) as mobile phase were selected for the assay. CsA and CsD showed good resolutions in this conditions and no significant interfering peaks were observed. The detection limit is less than 50 ng/ml. A good linearity (r >0.9986) was obtained in the range of 50-500 ng/ml CsA. Intra-day accuracy and precision (CV%) were 94.3-113.3% and 4.3-10.1% and inter-day accuracy and precision were 85.9-110.8% and 6.5-15.5%, respectively. The developed method was applied on the pharmacokinetic study of CsA after oral administration of CsA (200 mg) to 8 healthy human volunteers. The principal pharmacokinetic parameters resulted in 602.5 ± 250.9 ng·hr/ml of $AUC_{0\rightarrow 8hr}$, 270.0 ± 82.7 ng/ml of Cmax, 1.69 ± 0.26 hr of Tmax, 0.4627 ± 0.2331 $hr^{-1}$ of Ke, and 1.88 ± 0.99 hr of $t_{1/2}$.

[PE2-12] [ 10/18/2002 (Fri) 13:30 - 16:30 / Hall C ]

## In vivo kinetics and biodistribution of a HIV-1 DNA vaccine after administration in mice

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The present study evaluates the pharmacokinetics and tissue distribution of GX-12, a multiple plasmid DNA vaccine for the treatment of HIV-1 infection. PCR analysis after i.v. injection in mice showed that plasmid DNA was rapidly degraded in blood with a half-life of 1.34 min and was no longer detectable at 90 min post-injection. Plasmid DNA concentration also rapidly declined at the injection site after i.m. injection, with less than 1% of the initial concentration remaining at 90 min post-injection. However, sub-picogram levels (per mg tissue) were occasionally detected until 14 days post-injection. The ratios of the individual plasmids remained approximately constant at the injection site until 90 min post-injection. Plasmid DNA levels in various organs other than the injection site peaked at 90 min post-injection but was not detected after 8 h. The rapid in vivo degradation of GX-12 and low persistence in nontarget tissues suggest that the risks of potential gene-related toxicities by GX-

12 administration, such as insertional mutagenesis or germline transmission, are minimal.

[PE2-13] [ 10/18/2002 (Fri) 13:30 - 16:30 / Hall C ]

## Pharmacokinetics of DA-3021 (mono-PEGylated recombinant human interferon α-2a) after Subcutaneous Administrations to Experimental Animals

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Interferon has therapeutic potential for a wide range of infectious and proliferative disorders such as chronic hepatitis C and malignant melanoma. However, it has some therapeutic problems as other protein therapeutics do. A variety of approaches have been developed to circumvent these problems. Among them, the attachment of a polyethylene glycol (PEG) moiety to interferon is considered as one of the most promising solutions for its ability of extending the plasma residence time. Mono-PEGylated recombinant human interferon α-2a was prepared by conjugating reaction and then appropriate separation and purification steps. Its pharmacokinetic parameters were estimated after subcutaneous administration into SD rats, beagle dogs, and cynomolgus monkeys. Area under the plasma concentration-time curve (AUC) and the peak plasma concentration (Cmax) increased in a dose-related manner in SD rats. The time to reach the plasma peak (Tmax) was 47.8hr in rats and 72hr in both dogs and monkeys. The elimination half-life (t1/2) was 31.7hr in rats, 157.2hr in dogs, and 93.6hr in monkeys, respectively. These results indicate that DA-3021 has sustained absorption and a longer half-life than unmodified interferon yielding longer periods in the circulation. Considering these pharmacokinetic studies, we can expect that enhanced pharmacological profiles for DA-3021 would come out in clinical trials.

[PE2-14] [ 10/18/2002 (Fri) 13:30 - 16:30 / Hall C ]

## In vivo Characterization of Sustained-Release Formulation of Recombinant Human Growth Hormone in Immunosuppressed Rats and Dogs

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The in vivo release characteristics of rhGH-loaded PLGA microsphere prepared using a double emulsion process from hydrophilic 50:50 poly(D,L-lactide-co-glycolide) (PLGA) polymers were analyzed. This formulation showed particle size of ca 53.1㎛ with high drug incorporation efficiency. To investigate in vivo release kinetics without the interference of formation of antibodies to rhGH in the experimental animals, the animals were immunosuppressed by treatment with Cyclosporin. When this formulation was subcutaneously administrated in immunosuppressed rats, it showed an initial burst of 4-8 hrs followed by a sustained release phase and produced serum levels above 1-5 ng/ml rhGH for 14 days and followed by a diminished release which terminated after 4 weeks. And it showed dose-dependent patterns in serum rhGH levels. When dosed every 2 weeks, this formulation showed slightly different release patterns and no accumulative effects were observed. These results suggested that this formulation would be efficacious for sustained delivery of rhGH over 14 days. In case of dogs, results obtained after administration of this formulation were similar with those of rats. This formulation showed elevation in serum rhGH levels with dose-dependent patterns for 10 days. As in case of rats, no accumulative effects were observed after consecutive administration of this formulation in dogs. These studies demonstrated the potential for a sustained release, 14-day formulation for rhGH.

## Poster Presentations - Field E3. Physical Pharmacy