1. **Translation of OATP1B1 and BCRP Inhibition on the Systemic Exposure of Rosuvastatin: Linking Drug Interaction Mechanism to Derived Pharmacokinetic Translation of Parameters**

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Transporters play a critical role in the absorption, distribution and elimination of drugs, and they determine plasma and tissue concentrations of a broad variety of drugs. Inhibition or induction of transporters by co-administered drugs can alter the pharmacokinetics and pharmacodynamics of the victim drug. This study investigated the clinically observed drug-drug interactions (DDIs) for rosuvastatin attributable to inhibition of intestinal efflux transporter breast cancer resistance protein (BCRP) and hepatic uptake transporter organic anion transporting polypeptide iB1 (OATP1B1). Our hypothesis is that changes in rosuvastatin pharmacokinetic parameters AUC and Cmax are correlated with three mechanisms of transporter inhibition: (1) mainly BCRP, (2) mainly OATP1B1, and (3) inhibition of both BCRP and OATP1B1. Rifampicin, cyclosporine, asunaprevir, fostamatinib and velpatasvir were selected as representative perpetrator drugs, and their IC50 values of BCRP and OATP1B1 were generated using the BCRP vesicular transport assay and OATP1B1 (HEK293-MSRII Frozen cells) imaging assay, respectively. Based on data analysis, we concluded that (1) BCRP interactions in the gastrointestinal tract can increase the systemic exposure of rosuvastatin with no marked difference between the increases in AUC and Cmax (2) hepatic OATP1B1 drug interactions usually cause significant increases of rosuvastatin systemic exposure with a more marked effect on Cmax relative to AUC (3) Inhibition of both BCRP and OATP1B1 usually results in significant exposure increase of rosuvastatin, and there is marked difference between AUC and Cmax increases.

2. **Enhancing Accumulation and Penetration of Semifluorinated Nanoassemblies with iRGD for Targeted Drug Delivery to Solid Tumors**

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Limited tumor penetration is one of major hurdles for achieving high therapeutic efficiency in nanoscale drug delivery system due to heterogeneity of tumor environments. Most of nanoparticles, at the same time, encounter a limited accumulation through the enhanced permeability and retention (EPR) effect where they passively extravasate to the tumor site via a leaky vasculature, leading to a lower nanoparticle efficiency. iRGD, an internalizing RGD, is a cyclic tumor- penetrating peptide that possesses RGD and CendR motifs that are responsible for improving tumor accumulation and penetration, respectively. iRGD actively targets tumors by binding to cancerous cells overexpressing αv integrins through RGD motif. The exposed CendR motif, after proteolytic cleavage, specifically binds to neuropilin-1 receptors initiating transcytosis
pathway, thus allowing tumor penetration. Herein, we have developed iRGD functionalized tri-perfluoro-tert-butyl (PFFTTRI)-containing semifluorinated triblock copolymer. Our previous studies have demonstrated that the fluorous segment in the triblock copolymer improved the stability of the corresponding self-assembled nanoparticles, resulting in a longer \textit{in vivo} blood circulation time. The iRGD ligand was successfully conjugated to the semifluorinated triblock copolymer. Our semifluorinated polymer showed a low critical micelle concentration (CMC) of 11.5 µM with an aggregation number of 57 ± 1. The self-assembled micelles prepared from iRGD functionalized semifluorinated polymer maintained a small size similar to that of the non-functionalized micelles. Our results show a negligible cytotoxicity of the synthesized polymer to breast cancer cell line even at a high concentration (1 mM). A high encapsulation efficiency of various hydrophobic drugs was achieved. Moreover, the cellular uptake of iRGD conjugated micelles was significantly higher compared to non-functionalized micelles. Results on the efficacy of this delivery system will be presented.

3. \textbf{In-vitro pH responsive drug release kinetics of alkali extracted carrageenan crosslinked genipin/chitosan matrices}

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In this study, carrageenan, a sulphated polysaccharide was extracted using KOH treatment of different concentrations (0, 0.1, 0.3 M) from the red marine algae, Kappaphycus alvarezi. The alkali played a vital role in the transformation of carrageenan to its Kappa (κ) form thus improving the gelling properties. The membranes were prepared by blending varying amounts of κ-carrageenan (20-40 v/v % of the prepared solution) with the cross linked chitosan and genipin solutions. The model drug was loaded onto the films by “encapsulating” it between two layers of the pre-gel blend solution and vacuum dried. Drug release from the membranes was investigated in three different pH media (1.2, 4.5, and 6.8) and was measured by UV/Vis spectrophotometer. Carrageenan treated with different concentrations of KOH had an impact on the sulphate content and molecular weight. With increasing KOH concentration, the sulphate recovered was 17.13, 15.72 & 8.71 % and the molecular weight was determined to be 64.2, 49.5, 8.2 ( x 10^5 g/mol ) respectively. This affected the gelling behaviour and as a result had an effect on the drug release profile. Membranes containing κ-carrageenan treated with 0.3 M KOH showed faster release of the drug than the carrageenan treated with 0.1 M KOH. However, there was little difference seen at a higher pH (6.8). This confirms that the release is responsive to pH changes. The release kinetics has been analyzed using the Zero order, First Order kinetic model, Higuchi plot and the Korsmeyer-Peppas model.
4. Fc receptor immunoreactivity at brain-cerebrospinal fluid interfaces: implications for antibody delivery & distribution in the rat central nervous system (CNS)

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Characterizing antibody distribution in the brain microenvironment is critical for successful translation of antibody therapies for treatment of central nervous system (CNS) disorders and is dependent on factors such as antibody binding to Fc receptors in the CNS. Surprisingly, the expression of these receptors in the CNS has not been well described. Here, we describe new studies using immunohistochemistry to investigate the distribution of two Fc receptors in the brain - the inhibitory, low affinity-binding (Kd ~ 10^-6 M) Fc gamma receptor (FcγRIIb) and the neonatal Fc receptor (FcRn) known to be involved in recycling/transport at peripheral interfaces. The expression of these receptors was studied at the nasal epithelia (olfactory and respiratory), trigeminal nerve, and lymph nodes in addition to the brain, dura and spinal cord. Our findings suggest that FcRn and FcγRIIb immunoreactivity is relatively high at the brain-cerebrospinal fluid (CSF) interfaces. We postulate that reversible binding of FcγRIIb with circulating IgG molecules at these interfaces may be limiting their distribution in the CNS. FcRn expression profiles were largely associated with immune cells, astrocytes, and cells at the brain-CSF interfaces; some relatively low expression may also be present in the vascular endothelial cells. We hypothesize that such an expression pattern for FcRn may have an important influence on the uptake and transport of administered IgG within the CSF and brain. Overall, our findings may inform the engineering of antibody therapeutics for more efficient distribution within the CNS as well as provide a better perspective on physiological factors influencing endogenous IgG distribution.