

Linking Liver X Receptor Modulation To Effects In Vivo

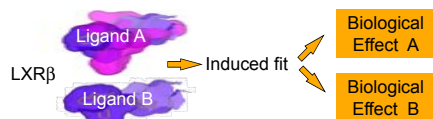
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Aim

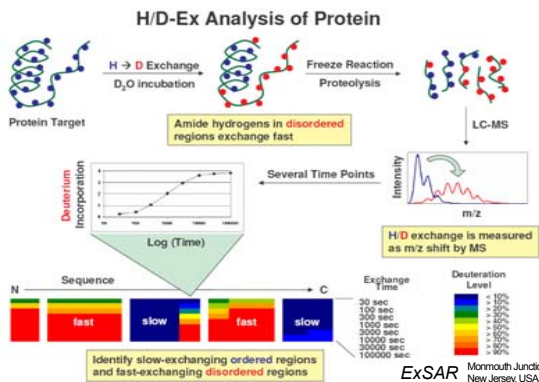
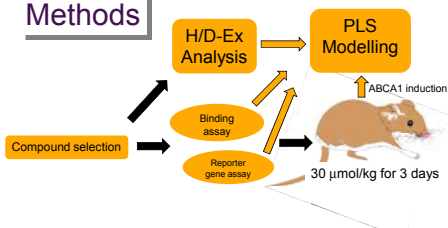
Explore if H/D-Exchange can be used to better predict in vivo effects of LXR ligands

Introduction

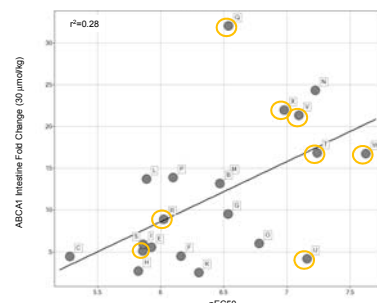
Liver X receptors (LXR) α and β are ligand activated transcription factors, which are potential targets for development of anti-atherosclerotic drugs via effects on cholesterol metabolism and inflammation. The therapeutic potential of LXR ligands has been questioned due to unfavourable side effects including increased plasma triglyceride levels and hepatic steatosis. With the aim of developing synthetic LXR modulators with a more favourable profile lacking lipogenesis, a novel class of LXR modulators were identified using a combination of in vitro and in vivo assays. Binding and reporter gene assays did only give a limited amount of information that was not suitable for predicting a favourable profile in vivo, which probably demonstrates increased complexity of receptor modulation in vivo. To identify and optimize LXR modulators with an advantageous profile, we applied an unbiased in vivo screen in golden Syrian hamsters that have a more human-like lipoprotein profile compared to mice. Compounds with an encouraging profile in hamsters were then subjected to further testing in progression and regression models of atherosclerosis in mice to validate effects on disease. To better understand the relationship between receptor dynamics of human LXR β and in vivo profiles we investigated a number of LXR modulators originating from the same structural class, with similar in vitro profiles but different in vivo profiles (favourable and unfavourable) using a hydrogen/deuterium exchange (H/D-Ex) assay developed by ExSAR.



Methods

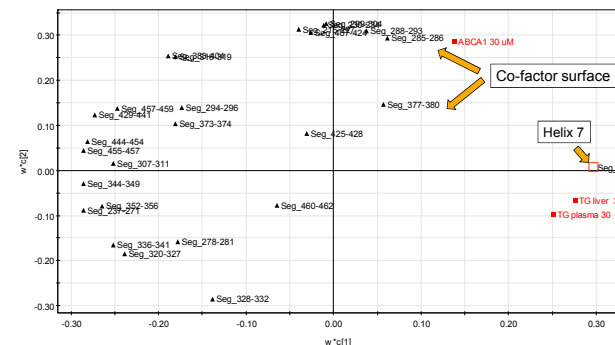


Weak correlation between in vitro and in vivo data



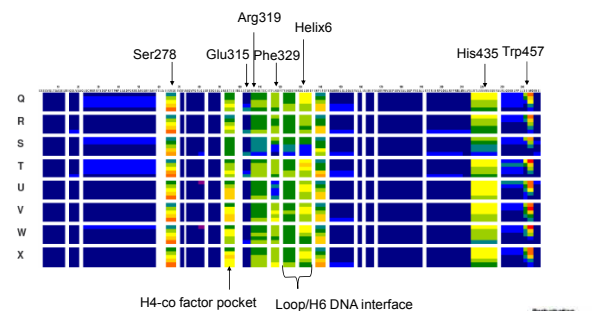
Correlating hLXR β ligand binding domain reporter gene (pEC50) data with ABCA1 mRNA upregulation in mice treated orally with 30 μ mol/kg LXR agonist for 3 days (4 doses)

H/D-Ex data links ABCA1 induction and lipogenic effects to different parts of LXR β

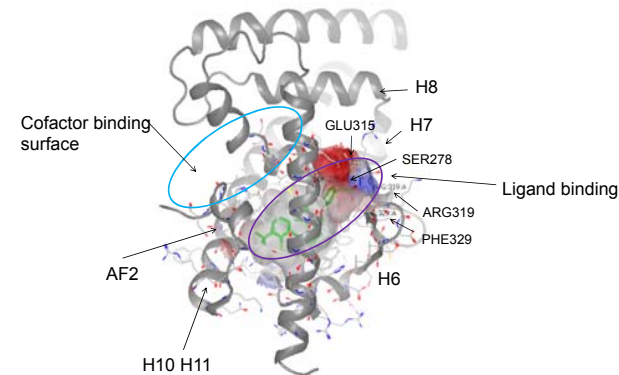


PLS regression modelling using H/D-Ex data to test if H/D-Ex can be used to distinguish compounds with positive (intestinal ABCA1 mRNA induction) and negative (plasma and liver triglyceride increase) effects.

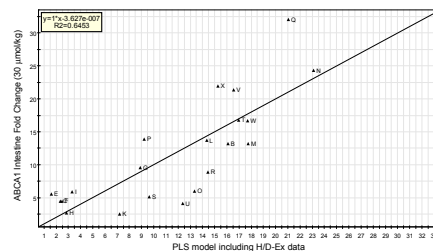
H/D-Ex data from 8 different LXR agonists



H/D-Ex perturbations of human LXR β ligand binding domain. Dark blue indicates no change in deuterium level upon ligand binding. Other colors indicate changes upon ligand binding shown in the insert



H/D-Ex data improves in vivo - in vitro correlation



PLS (Partial Least Square) regression modelling that includes H/D-Ex data to test if H/D-Ex can be used to predict in vivo effects.

Conclusions

- H/D-Ex - A method to predict in vivo effects of LXR agonists
- H/D-Ex - A way to optimize selective LXR agonists
- H/D-Ex - New opportunities to enhance structure based design