Molecular Static and Dynamic Analyses Reveal Flaw in Murine Model used by US FDA to Detect Drug Carcinogenicity

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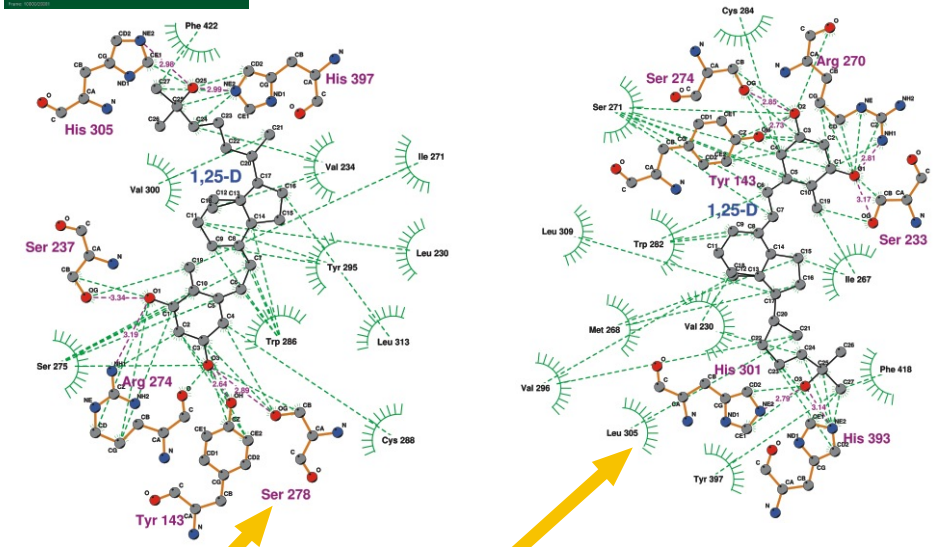
The US FDA currently accepts carcinogenicity studies of pharmaceutical drugs based on murine models. In addition to 6 month studies with p53(+/-) and ras.H2 transgenic mice, lifetime studies (typically 2 years) in WT mice or rats are also considered as evidence that a drug lacks carcinogenic activity. This model is not always exhaustive. For example, during the acceptance testing of the ARB Olmesartan[1], possible carcinogenicity observed in hamsters was not able to be duplicated in rats, or in transgenic mice. We have previously used the static molecular modeling of AutoDock to demonstrate that Olmesartan has agonostic activity in the PDB:1DB1 model of the human VDR Nuclear Receptor[2], while it has antagonistic activity in the PDB:1RK3 model of the rat VDR. This agonism has now been confirmed with Molecular Dynamics, using GROMACS. The murine VDR indeed lost its ability to bind the DRIP 205 co activator when Olmesartan was the ligand, while the human VDR was activated by Olmesartan similarly to its native ligand (1,25-dihydroxyvitamin-D). Since the VDR is believed to express 913 genes[3], many of which are known to be associated with cancer pathogenesis, good homology between human VDR, and the animal model VDR, is exceedingly important.

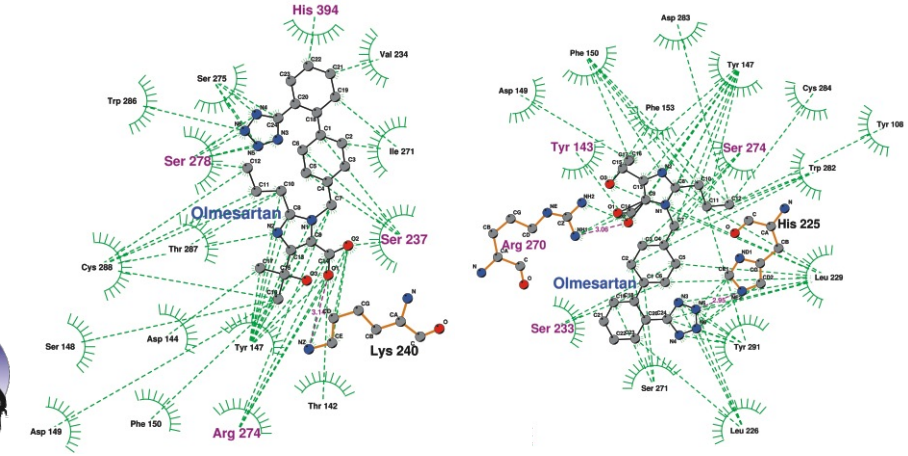
CONCLUSION: The murine environment is inadequate to accurately model drug carcinogenic activity in humans. A species should be chosen which has a VDR LBP homology closer to that of man. AutoDock and GROMACS molecular analyses are useful in resolving any remaining anomalies in the observed data.

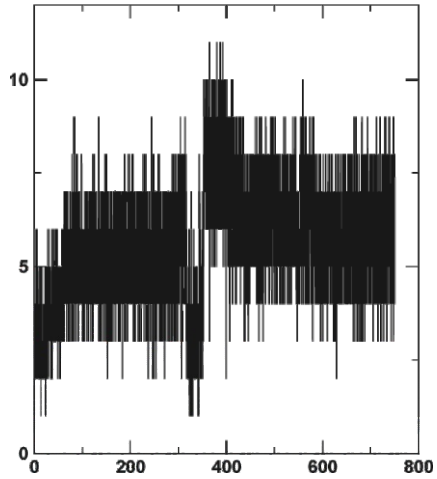
References:
1. FDA CDER: NDA-21-286, Sankyo Pharma Inc Available from URL http://www.fda.gov/cder/foi/nda/2002/21-286_Benicar.htm
2. Marshall TG: VDR Nuclear Receptor Competence is the Key to Recovery from Chronic Inflammatory and Autoimmune Disease. Abstract presentation, DMM2006.
3. Wang TT, et al: Large-scale in silico and microarray-based identification of direct 1,25-dihydroxyvitamin-D3 target genes. Mol Endocrinol. 2005 Nov;19(11):2685-95.

This video was created using the GROMACS Molecular Dynamics software on a small computing cluster assembled from PCs based on Core-2-duo CPU technologies. The difference in steady-state ligand conformation between human and rat VDR can clearly be seen at http://autoimmunityresearch.org/dmm2007/dmm2007.ram

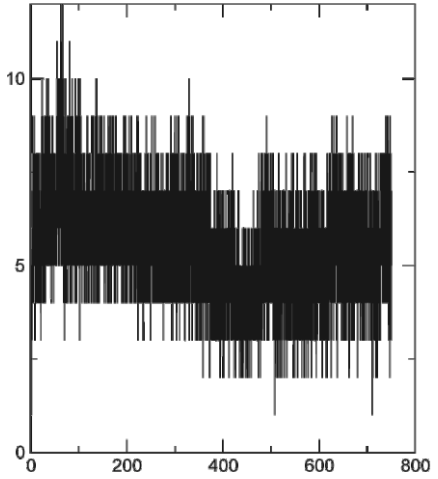


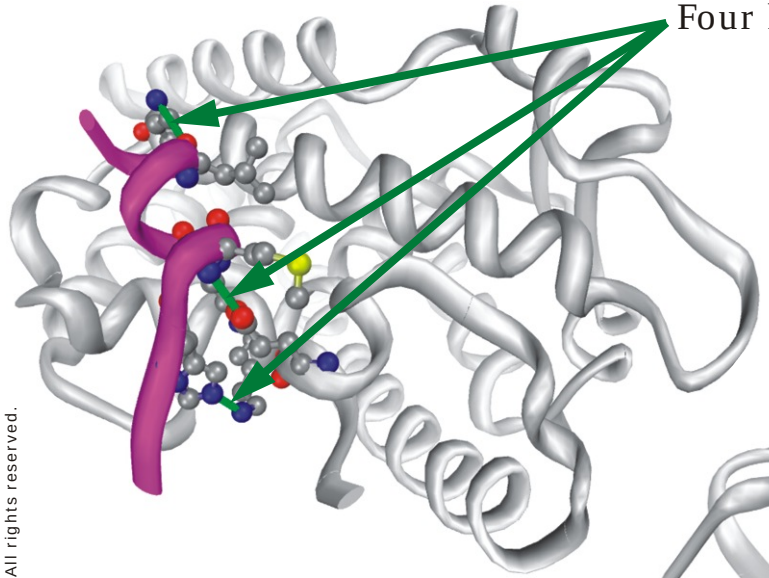
Plots of inter-molecular atomic contacts make it easy to see that 1,25-dihydroxyvitamin-D binds symmetrically into the VDR from both Homo sapiens and Rattus norvegicus, yet the conformation of chemical ligands is different, due to lack of VDR homology.





Plots of the instantaneous number of hydrogen bonds compiled during the molecular dynamics simulations show surprising similarities, and differences, between the behavior of the Olmesartan-VDR complexes.





Analysis of the rat VDR and DRIP205 model (PDB:1RK3) show that the activation of the VDR is only partly due to the AF-2 domain. There are hbonds from GLU416 to DRIP MET629/LEU630, but there are also hbonds from LYS260 to HIS627, and LYS242 to LEU633.