Molecular modelling of LXR binding in relation to the MoA/AOP framework for liver steatosis

E. Fioravanzo\(^a\), A. Bassan\(^b\), S. Kovarich\(^c\), I. Tsakovska\(^d\), A. Worth\(^e\), C. Yang\(^f\), M.T.D. Cronin\(^g\)

\(^a\) S-IN Solutions Informatici srl, Vicenza, Italy; \(^b\) Institute of Biophysics and Biomedical Engineering, Sofia, Bulgaria; \(^c\) European Commission Joint Research Centre, Institute for Health and Consumer Protection, Systems Toxicology Unit, Ispra, Italy; \(^d\) Altamira, LLC, Columbus OH43235-1623, United States; \(^e\) School of Pharmacy and Chemistry, Liverpool John Moores University, Liverpool, England.

Introduction and Aims

Within the COSMOS Project innovative in silico approaches are being explored to study the molecular initiating events involved in liver steatosis MoA (mode-of-action), e.g., the binding and activation of the nuclear receptor LXR (liver X receptor). To this aim, different molecular modelling (MM) methods are investigated and applied to predict the binding of small molecules to LXR.

The challenging objective is to lay the foundations for the application of MM in predictive toxicology as a part of an integrated strategy which combines multiple methods and approaches (e.g., in silico, in vitro, mechanistic information) to support toxicity prediction and risk assessment in the MoA/AOP framework.

DRUG DISCOVERY

<table>
<thead>
<tr>
<th>GOALS</th>
<th>Evaluate the effects/risks of a specific molecule on human health and environment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHEMICAL SPACE</td>
<td>Drugs have specific ADMET profiles and prescribed chemical properties; strong interactions with a specific target.</td>
</tr>
<tr>
<td>PURPOSES OF MM METHODS</td>
<td>- HT Identification/Lead Identification/Optimization; - ADMET Optimisation; - Screening for drug candidates: identification of most potent chemicals: minimise false positive (FP)</td>
</tr>
</tbody>
</table>

RISK ASSESSMENT

<table>
<thead>
<tr>
<th>ACTIVE compounds (i.e., LXR potential binders)</th>
</tr>
</thead>
</table>

From Drug Discovery to Risk Assessment

Molecular modelling has been widely used in pharmaceutical discovery for more than 50 years.

Applying tools developed for drug discovery to the problem of predicting the potential toxicity of chemicals requires that the MM methods are tuned taking into account the differences between the two frameworks.

LXR is among the nuclear receptors that could play a role in the development of liver steatosis. The MoA from LXR activation to liver steatosis has been elaborated and described by the SEURAT-1 MoA WG as a first step in building a "prototype" safety assessment framework\(^c\). The definition of the AOP for liver steatosis is still on-going.

The research leading to these results has received funding from the European Community’s 7th Framework Program (FP7/2007-2013) COSMOS Project under grant agreement n° 266835 and from Cosmetics Europe.

www.cosmostox.eu

Acknowledgements

3. RCSB Protein Data Bank. http://www.rcsb.org
8. COSMOS Database v.1.0. http://www.cosmostox.eu/what/COSMOSdb/