FEDERATION OF EUROPEAN TOXICOLOGISTS & EUROPEAN SOCIETIES OF TOXICOLOGY

EARLY CAREER AWARDS

Presented during the annual EUROTOX congress to early career scientists judged to have made the best oral or poster presentation. The first and presenting author must be under 35 years of age as of 31 December of the year of the EUROTOX congress.

EUROTOX Gerhard-Zbinden Early Career Award for drug-oriented toxicological research presented to Dr. Timothy Allen during the EUROTOX Brussels congress, September 2-5, 2018

P05-13 Computational approaches for predicting Molecular Initiating Events

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The Adverse Outcome Pathway (AOP) provides a framework to encapsulate the chemical and biological processes that can lead to toxicological outcomes. The Molecular Initiating Event (MIE) is the first key event in an AOP, and an MIE can be thought of as a chemical interaction between a toxicant molecule and a biological system. If we can understand the chemistry behind these processes we can link the chemistry of molecules to their biological activity at specific targets.

We have attempted to do this in several ways. Firstly, 2D chem- ical structure encodes much of the information about the shape and interaction potential of molecules. We have utilized chemical informatics approaches to computationally construct structure- activity relationships for over 100 human MIEs. Open source data from ChEMBL is used and maximal common substructure searches performed to return structural features associated with biological activity at each MIE. These structural alerts are coded in SMILES to allow for the rapid in silico processing of large numbers of chemicals to identify their potential MIEs.

Secondly, we have utilised quantum mechanical density func- tional theory calculations to probe covalent bond forming reactions that are associated with the MIE for DNA binding. DNA is able to directly react with an electrophilic chemical, modifying its structure and causing damage that can lead to genotoxic adverse outcomes. By computationally modelling the transition state of these reactions and calculating the activation energy we can estab- lish why some molecules are able to react with DNA and return a positive Ames test, and why some chemically similar molecules cannot.

Finally, we have begun to investigate the use of chemical and biological similarity through machine learning and artificial intel- ligence algorithms to predict MIEs. Neural networks and deep learning provide a strong platform for MIE prediction due to their high rates of predictivity. By incorporating large amounts of ChEMBL and ToxCast data and a variety of chemical descriptors we aim to use these powerful approaches to predict MIEs.