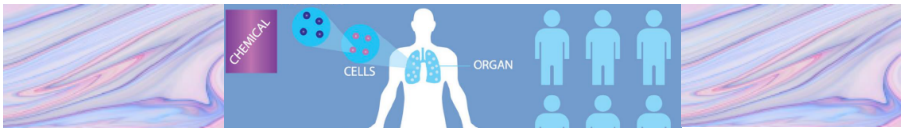
Adverse outcome pathways at early stages of the design of antiparasitic drugs

17th October 2024 - 9:00am-10:30am AND 3:30pm – 4:30 pm CET (VIRTUAL)

COST Action OneHealth*drugs*



Abstract

Adverse Outcome Pathways (AOPs) provide a framework for curating and organising toxicological & ecotoxicological knowledge with associated measurements of key events and the dose & temporal concordance of relationships between these events. AOPs have been the topic of many conferences and workshops since the concept was first proposed in 2012 when the Organisation for Economic Co-operation and Development (OECD) launched a new programme on the development of adverse outcome pathways. A guidance document that describes in detail how AOPs are to be developed, reviewed, agreed is published at the OECD level. To date these qualitative AOPs have made little impact in regulatory toxicology beyond chemical reactivity-driven endpoints. However, quantitative AOPs are likely to be significantly more impactful in next generation risk assessments using new approach methods without the need to conduct animal studies. There is, though little guidance on best practices for quantitative AOP generation. AOPs are important for expanding the use of mechanistic toxicological data for risk assessment and regulatory applications with recent applications in further disciplines such as climate science.

Our workshop has the objective to introduce to these concepts

Definition: An **adverse outcome pathway** (**AOP**) is structured representation of biological events leading to adverse effects and is considered relevant to risk assessment. The AOP links in a linear way existing knowledge along one or more series of causally connected **key events** (**KE**) between two points — a **molecular initiating event** (**MIE**) and an **adverse outcome** (**AO**) that occur at a level of biological organization relevant to risk assessment. The linkage between the events is described by **key event relationships** (**KER**) that describe the causal relationships between the key events.

To participate, register at the following link:

https://docs.google.com/forms/d/e/1FAIpQLSf4UlOIRg6YysU-J7QILUz-lEpD4oquRszJ20fJM3P8SHg_Og/viewform?usp=sharing

9:00 – 9:05
Introduction to the workshop
Maria Paola Costi

9:05 – 9:50
Thomas Hartung (Johns Hopkins Bloomberg School of Public Health, US, and University of Konstanz, Germany)

Biosketch

Thomas Hartung, MD PhD, is professor at Johns Hopkins Bloomberg School of Public Health and the Whiting School of Engineering, Georgetown University, Washington D.C., and University of Konstanz, Germany; he also is Director of Centers for Alternatives to Animal Testing (CAAT) in the US and Europe and Field Chief Editor of Frontiers in AI. He authored 690+ scientific publications with 49,000+ citations (h-index 119) and his COURSERA toxicology classes had 20,000+ active learners.

Title: Adverse Outcome Pathways at Early Stages of the Design of (Antiparasitic) Drugs

The development of drugs is traditionally reliant on empirical methods and animal models, which can be resource-intensive and may not accurately predict efficacy and safety in humans. Integrating the Adverse Outcome Pathway (AOP) framework early in the drug design process offers a novel approach to enhance predictability and reduce reliance on animal testing. AOPs, which organize mechanistic knowledge from molecular initiating events to adverse outcomes at different biological levels, provide a structured method for assessing the impact of chemical interventions on biological pathways. By incorporating AOPs into drug design, researchers can identify potential toxicological hazards, optimize pharmacological targets, and prioritize lead candidates with higher human relevance. This presentation will discuss the application of AOPs in the context of drug discovery, highlighting the potential of this approach to streamline safety assessments, reduce development costs, and improve translational success rates. Key examples include the use of AOP-based methodologies to predict organ-specific toxicities and adverse systemic effects in early-stage screening of drug candidates. Moreover, integration of emerging technologies such as metabolomics, computational toxicology and Microphysiological Systems (MPS) further enhances the utility of AOPs in understanding and mitigating off-target effects. This strategy holds promise for the development of safer, more effective drugs, ultimately contributing to a reduction in attrition rates during the clinical development phase.

9:50-10:20 Discussion on the topic

10:30 – 3:30 Break

3:30 – 4:00

Luigi Margiotta-Casaluci (King's College London)

The evolving role of Adverse Outcome Pathways: from qualitative biological models to quantitative prediction tools**.**

Biosketch

Dr Luigi Margiotta-Casaluci is an Associate Professor of Mechanistic & Integrative Toxicology at King's College London. His research focuses on understanding the multi-scale mechanisms underlying chemical-induced toxicity and developing high-precision predictive toxicology methods for chemical safety assessment. Since 2022, he has served as an appointed Member of the UK Government Defra Hazardous Substances Advisory Committee (HSAC), where he contributes to safeguarding environmental health by advising on policy and regulatory frameworks related to hazardous substances.

Title: The evolving role of Adverse Outcome Pathways: from qualitative biological models to quantitative prediction tools

The Adverse Outcome Pathway (AOP) is a conceptual framework that facilitates the synthesis, organisation, and interpretation of toxicological data from a mechanistic perspective. AOPs are playing an increasingly important role in the chemical safety assessment paradigm, offering a transparent, hypothesis-driven rationale for the design of tailored toxicity testing strategies. However, the direct application of AOPs in hazard and risk assessment remains limited by their qualitative nature, leading to growing calls for the development of quantitative AOPs (qAOPs). The ambition for a rapid transition

toward qAOPs is justified by the expanding availability of digital resources, large data repositories, and Artificial Intelligence (AI)-powered mathematical modelling tools for toxicology applications. This presentation will discuss the application of pharmacodynamic (PD) and pharmacokinetic (PK) considerations in the development of qAOPs for drug safety assessment. Through practical examples and original data, this presentation will highlight emerging trends in predicting drug-target interactions across species (Molecular Initiating Events) and emphasise the importance of internal exposure dynamics, polypharmacology, disease state, and target engagement duration in determining the ultimate predictive value of qAOP models. Given the increasing ethical, scientific, and political demand to reduce animal testing, we will also discuss the critical role of New Approach Methodologies (NAMs) in advancing the development of qAOPs across species, ultimately transforming the landscape of safety assessment.

4:00-4:30
Francesco Angelucci (University of Aquila – IT)
Biosketch
Francesco Angelucci completed his Ph.D. in Biochemistry in 2005 at Sapienza, University of Rome. In 2001, he got a permanent position as assistant professor in Molecular Biology at the University of L'Aquila. Since 2021, he holds the position of full Professor in Biochemistry at the University of L'Aquila, leading the structural biology laboratory. His research mainly focuses on investigating the structure-function relationship of thiol-dependent redox active proteins of biomedical relevance.

Title: Bypassing Nucleophilic Active Sites of Thioredoxin Reductases for Selective Inhibition: The Role of the Doorstop Pocket
Understanding the structure-function relationships of drug targets can significantly enhance preclinical studies, potentially reducing the need for extensive in vivo experiments. This talk aims to present a narrative on applying this approach to a challenging drug target for parasitic infections.
High-molecular-weight thioredoxin reductases (TrxRs) and glutathione reductases (GRs) belong to the pyridine nucleotide-disulfide oxidoreductase family and play a key role in vertebrate redox pathways, regulating essential cellular functions. TrxRs, in particular, are considered crucial drug targets for a variety of human diseases, including parasitic infections. Despite over 25 years of research, no selective TrxR inhibitors have yet advanced through the drug development pipeline. This challenge arises primarily from two factors: the research community's heavy reliance on electrophilic and redox-active compounds, which frequently induce off-target effects in vivo, and the scarcity of structural data on protein-inhibitor complexes, hindering effective compound optimization.
Recently, using a fragment-based approach, we and others have identified a novel regulatory and druggable site on TrxRs and GR-like enzymes, which we have termed the "doorstop pocket." This site, located distantly from the nucleophilic active site, plays a critical role in facilitating the entry of NADPH and the exit of $NADP^+$ during enzyme turnover. Targeting this pocket presents a novel and promising strategy for selective inhibition for both TrxRs and GRs.
Our approach has shown particularly encouraging results in the context of *Schistosoma mansoni* Thioredoxin Glutathione Reductase (TGR), a validated drug target for schistosomiasis. Some of the initial compounds identified exhibit superior efficacy compared to current treatments for this debilitating disease in animal models.

- Renaud JP et al., Biophysics in drug discovery: impact, challenges and opportunities. Nat Rev Drug Discov. 2016 15, 679-98.
- Petukhova VZ, Aboagye SY, Ardini M et al. Non-covalent inhibitors of thioredoxin glutathione reductase with schistosomicidal activity in vivo. Nat Commun. 2023, 14, 3737.
- Ardini M. The "Doorstop Pocket" In Thioredoxin Reductases–An Unexpected Druggable Regulator of the Catalytic Machinery. J Med Chem. 2024, 67,15947-15967.
-

4:30-4:35 Closure