Leveraging Adverse Outcome Pathways to develop New Approach Methodologies for reproductive toxicology

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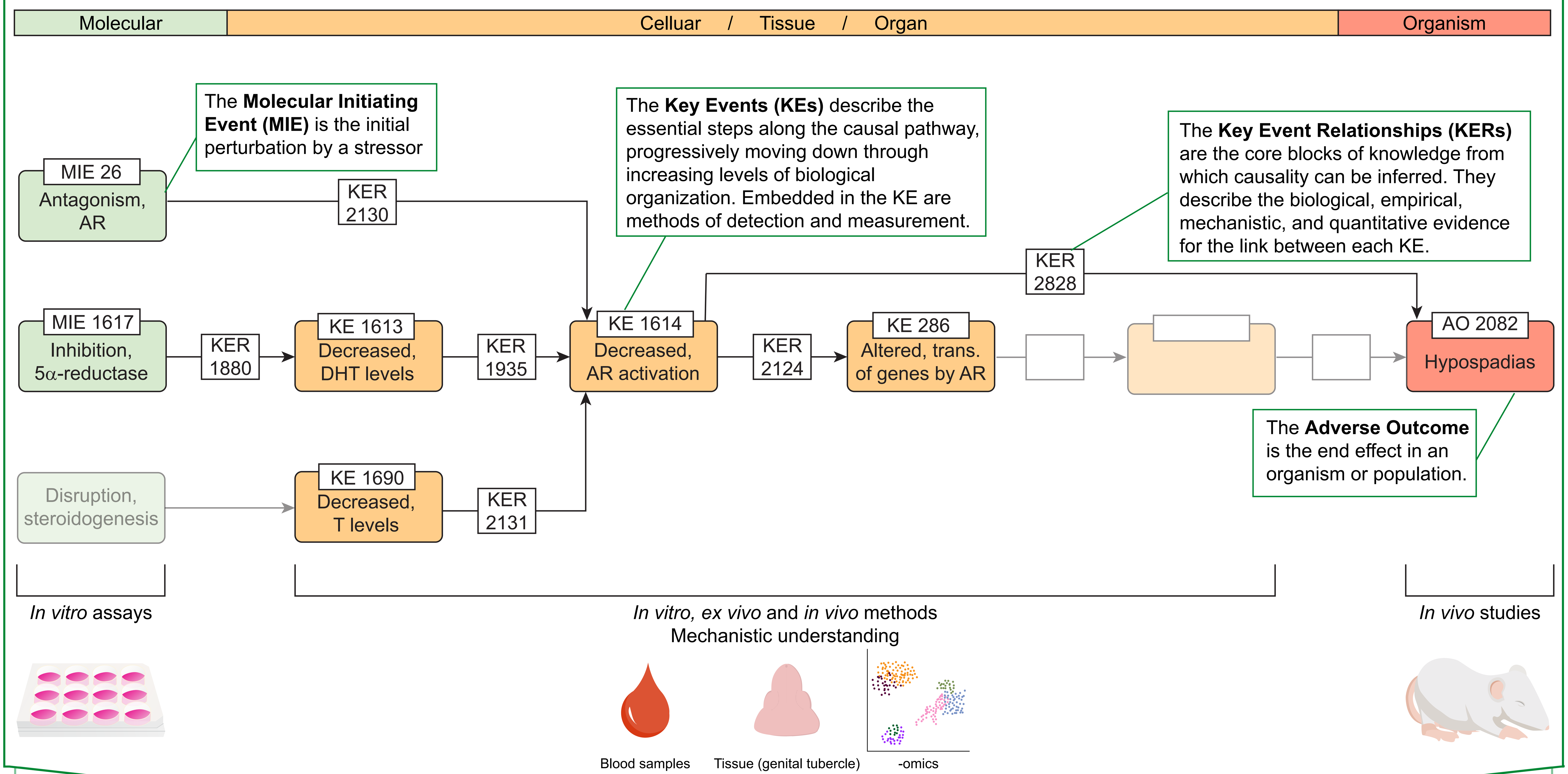
Introduction

Animal studies remain extensively used in chemical testing and risk assessment. Endocrine disruptive properties are tested in rodents to assess potential harmful effects of chemicals resulting in adverse outcomes such as genital malformations. While *in vitro* tests for endocrine disrupting activity exist, their predictive capacities are currently not sufficient to replace *in vivo* assesment. For this, we need detailed understanding of causal pathways from molecular stressor events to adverse outcome to allow development of New Approach Methodologies (NAMs) to replace animals.
We are developing Adverse Outcome Pathways (AOPs), an OECD endorsed framework for organizing empirical data linking molecular stressor events to an adverse outcome. Here, we describe AOPs for anti-androgenic modes-of-action causing the genital malformation hypospadias in males. With this we demonstrate the utility of AOPs in methodology development for predictive toxicology aligned with a Next Generation Risk Assessment paradigm.

Adverse Outcome Pathways
Organization of knowledge and test methods



Development of New Approach Methodologies
New test methods relying less on animals

Improvement of predictive toxicology
Better prediction and identification of harmful chemicals

T= testosterone, DHT=dihydrotestosterone, AR= androgen receptor

The AOPs for hypospadias

Our AOPs for hypospadias outline the main events by which anti-androgenic stressors can cause hypospadias. Within this network, the KERs capture the current knowledge on how the genital tubercle differentiation is disrupted and provides a framework for expansion of this information. For example, within Key Event 286, Altered transcription of genes by AR, the delineation of the transcriptional and spatial pattern changes caused by anti-androgenic actions may feed into development of -omics-based NAMs for this human-relevant endpoint.

Perspectives

The organization of knowledge and available test methods in the AOP framework enables interdisciplinary usage for chemical risk assessors, toxicologists, developmental scientists and method developers. From a 3R perspective, AOPs can facilitate the development of new test methods and refining current test methods to better predict *in vivo* outcomes from *in vitro* or *ex vivo* experiments.

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