The AXLR8 project

New tools for chemical safety assessment…

Chemicals are essential to modern life, yet we lack innovative, efficient and human-relevant testing tools to inform regulatory safety decisions that protect against adverse health and environmental impacts of chemicals, replace animal use, and support economic growth and greener chemistries. Accelerated development and integration of advanced molecular and computational biology tools into health research and safety testing has been identified by the European Commission as an important societal challenge to be addressed under the new EU research and innovation framework programme Horizon 2020.

The European Commission-funded coordination project AXLR8 (pronounced 'accelerate') is working to lay the scientific groundwork for exactly this objective. A collaboration between the Freie Universität Berlin, Humane Society International and the Flemish Institute for Technological Research, AXLR8 acts as a focal point for dialogue and coordination among leading European and global research teams working to develop advanced tools for safety testing and risk assessment by organising annual scientific workshops and publishing an annual 'state of the science' report (available online at axlr8.eu/publications). AXLR8 also serves as a bridge between test method developers and end-users to ensure that the needs of industry and regulators are understood in order to support efficient uptake of novel testing and assessment tools as they become available.

Paradigm shift in safety testing

The past two decades have seen unprecedented scientific and technological advances. These include sequencing of the human genome, the birth of functional genomics, the fast growth of computing power and computational biology, and robot-automated high-speed chemical screening systems. Together, these advances have triggered a revolution in biology and have made available a wide range of new tools for studying the effects of chemicals on cells, tissues and organisms in a rapid and cost-efficient manner.

'A not-so-distant future in which virtually all routine toxicity testing would be conducted in human cells or cell lines,' is the way one eminent scientific panel has described its vision of toxicity testing in the 21st Century, or Tox21. The approach involves uncovering exactly how chemicals disrupt normal processes in the human body at the level of cells and molecules. Then with the help of

Tool	How it's used
Biomarkers	Predictive markers of biological change that can be detected before a toxic effect is seen in people
Computational systems biology	Computer simulation of the human body to describe and predict complex interactions among cells, tissues, organs and organ systems
High-throughput platforms	Ultrahigh-speed robotic automation of human cell-based tests
Human biomonitoring	Measurement of toxic chemicals in human blood, urine or other tissues that can be used to identify biomarkers of exposure and toxicity
Human cell-based tests	Model critical 'circuits' in human toxicity pathways and test for chemically induced perturbations
Human genomic tests	Examine how chemical exposures affect the activity and interactions of genes, proteins and metabolites
Human pathway discovery	Studying chemicals' mode(s) of toxic action to identify critical cellular targets which, when perturbed by chemicals, lead to toxicity. These 'targets' can then be modelled in human cell tests
Pharmacokinetic modelling	Mathematical approach to predicting how a chemical will be absorbed, transported within, metabolised, and excreted from the body
Structure-activity relationship modelling	Predict a chemical's biological properties based on its molecular structure on the basis that similar molecules often have similar activities

Fig. 1: The Tox21 Toolbox

Infrastructure of research funding in toxicology

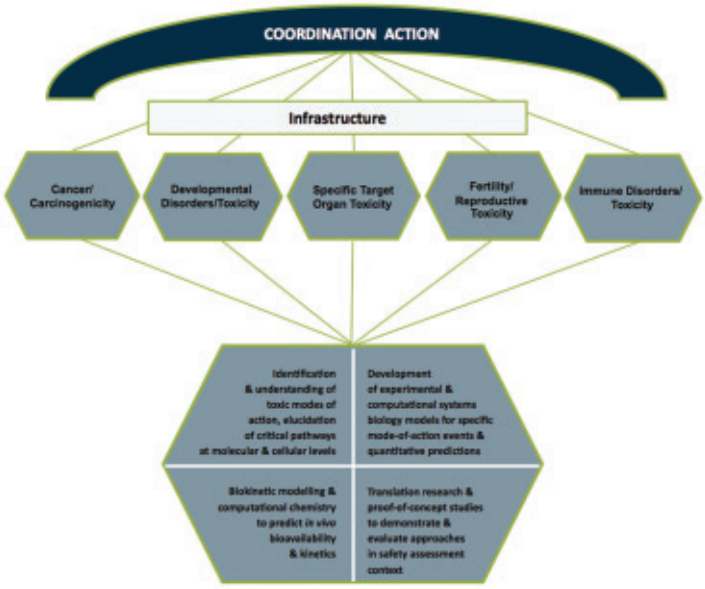

Fig. 2: Illustration of the proposed structure of research in toxicology funded by the DG Research and Innovation of the European Commission. Six large-scale clusters encompassing five human health effect areas together with cross-cutting infrastructure would be developed under the direction of a central coordination action. There should be a strong focus in all clusters on core 'building blocks', illustrated here as four distinct projects/research areas. The exact number of projects per cluster should be determined on a case-by-case basis

state-of-the-art test tube, computer, and robotic tools, scientists can test for these disruptions and make predictions regarding real-world chemical risks to people.

The ultimate goals are to assess safety:

- Of a much larger number of substances and mixtures than is currently possible;
- More rapidly, efficiently, and cost-effectively than at present;
- In systems that may be more relevant to toxicity in humans, as well as capable of identifying the cellular mechanisms at the root of toxicity and disease;
- Using fewer or no animals.

Toward a European Tox21 research programme

The EU has long been a leader in supporting research to advance the development and validation of 'alternative', non-animal testing strategies for regulatory purposes, including nearly €150m in funding under the 6th and 7th Research and Innovation Framework Programmes alone. But in the past number of years, similarly large-scale research initiatives have been launched in the United States, Japan and elsewhere. Whereas EU research has traditionally been 'policy-driven' (ie, responsive to legislative mandates to replace the use of animals cosmetics and chemicals testing) and 'bottom-up' (ie, where research proposals are considered on their own scientific merit without regard to a wider strategy), programmes in other regions are increasingly 'science-driven' and strategic 'top-down' in nature. Thus, while opportunities for synergistic collaboration clearly exist, it is first necessary to reconcile the divergent research approaches.

The 'roadmap' recommended by the AXLR8 Scientific Panel for future EU research in this area is a hybrid of European and international models. As shown in Fig. 2, It maintains a focus on key areas of health policy concern (ie, cancer, reproduction, development, immune system and allergies, and organ toxicity), while incorporating Tox21 tools as core 'building blocks' of any research strategy. It recognises that classical 'integrated projects' need to evolve into larger-scale research 'clusters', with each health concern cluster warranting funding at a level of €50m over at least five years. The need for dedicated funding to support world-class research infrastructure was also strongly underlined. But most important is the need for effective and up-front coordination – even before calls for proposals are issued and research consortia come together – to maximise potential synergies within and between projects and clusters; clearly define responsibilities, relationships, milestones and deliverables; lead long-range planning; and be empowered to ensure general accountability of all participants. 'Value added' collaborations among established research teams in other parts of the world should be encouraged to share the workload, develop synergies without duplication, and together reach for an ambitious, global objective that would be impractical to pursue on a regional basis.

Prioritising Tox21 research in Europe

AXLR8's Scientific Panel considers that the fields of toxicology and human biomedicine could advance by a quantum leap through the refocusing of research resources to understand the root causes of human toxicity and disease, coupled with development of innovative and more human-relevant research and testing tools as described above. Will the EU rise to embrace this opportunity through Horizon 2020?

AXLR8

Professor Dr med Horst Spielmann
Scientific Coordinator of the EU FP7 project AXLR8

Faculty of Biology, Chemistry, Pharmacy
Freie Universität Berlin
Königin-Luise-Str. 2-4
14195 Berlin
Germany

Tel: +49 30 7118661
Fax: +49 30 71581672

horst.spielmann@fu-berlin.de
www.AXLR8.eu