AXLR8 Strategic Directions for Development of Alternatives in the EU

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Summary

Conventional approaches to toxicity testing and risk assessment often are decades old, costly, low-throughput, and of dubious relevance to humans. The call for a transition to a 21st century toxicity testing paradigm will require a robust understanding of the cellular response/toxicity pathways that can lead to adverse effects when perturbed, appropriate in vitro systems to study chemical interactions at key targets along a pathway, and computational systems biology models to describe the underlying pathways as a basis for creating biologically realistic dose-response models.

The EU FP7 coordination support action project AXLR8 (= accelerate) aims to support the transition to a toxicity pathway-based paradigm for quantitative risk assessment and will: 1) organize a series of annual workshops to map research progress, gaps, and needs in the FP6/FP7 program on alternative testing strategies. 2) Provide a range of tools and opportunities for enhanced interdisciplinary and international communication, coordination, and collaboration in order to maximize the impact of available resources. 3) Work to streamline regulatory acceptance procedures to provide for the uptake of validated 3Rs methods, including a smooth transition to 21st century systems as they become available. 4) Produce annual progress reports on the state of the science, including recommendations on priority research and funding targets to ensure a prominent role for European science in this rapidly developing global research area.

The first AXLR8 workshops (AXLR8-1 & AXLR8-2), held in 2010 and 2011, focused on progress made in the EU FP6/FP7 projects funded by the Health theme of the DG RTD, “Alternative Testing Strategies: Replacing, reducing and refining use of animals in research.” The results of the discussions and recommendations of the AXLR8 Scientific Panel at the AXLR8-1 workshop have been published (AXLR8 Progress Report 2010). These results are presented, along with the recommendations of the AXLR8-2 2011 workshop on a “Roadmap to innovative toxicity testing (ITT).”

Keywords: AXLR8, toxicology in the 21st century, molecular toxicology, toxicity pathways, roadmap to innovative toxicology

1 Introduction

AXLR8 is a coordination and support action funded by the European Commission Directorate General for Research & Innovation under the Health theme of the 7th Framework Program (FP7) within the funding framework on Alternative Testing Strategies: Replacing, reducing and refining use of animals in research. AXLR8 is aimed specifically at accelerating a transition in Europe toward a more sophisticated approach to chemical and product safety assessment, with the common goals of improved health and environmental protection, positioning the EU on the leading-edge of a rapidly developing global research area, and working toward replacement of animal testing. An essential element of the AXLR8 project is the organization of annual workshops to provide a scientific platform for high-level information exchange and critical discourse among coordinators of EU-funded projects and independent European and international scientists on progress achieved in developing alternative testing strategies, as well as challenges, needs, and priorities for future EU research.

The second annual AXLR8 workshop (AXLR8-2), held in Berlin, Germany on May 22-25, 2011, focused on developing a “roadmap to innovative toxicity testing.” The 50-some invited participants included representatives of projects funded by the FP6/7 Health and Environment programs, the heads of Member State centers on alternatives to animal testing, the leaders of international efforts to establish advanced molecular toxicology from the United States and Japan, and members of the AXLR8 Scientific Panel and Consortium. The workshop began with a public satellite meeting that provided an overview of current EU and global research efforts, such as the joint initiative between DG Research & Innovation and the European Cosmetics Industry Association (COLIPA), aimed at “replacement of in vivo repeated dose systemic toxicity testing” with the long-
The general view within and among breakout groups was that limitations intrinsic to conventional high-dose in vivo studies limit their relevance and utility as tools for modern safety assessments aimed at protecting and improving human health (e.g., in relation to nanomaterials, endocrine disrupters, and environmental chemicals), and that the way forward requires a shift towards a pathway-based paradigm for safety assessment. In particular, assessment of a substance’s toxic “mode of action,” is considered by the AXLR8 Scientific Panel and other authorities to be a cornerstone of 21st century safety assessment (NRC, 2007; Berg et al., 2008; ePA, 2009). Development of a robust understanding of the networks of biological pathways – many of which are not yet described in full – and key events associated with chemical toxicity (Fig. 1) can feed back into the innovation cycle to support greener, “biocompatible” chemistries and can contribute to the study and treatment of human diseases (Gohlke et al., 2009), guiding research on fundamental biology and feeding into the product innovation cycle. By focusing on priority diseases with integration of hu-
man patient data, biomonitoring of healthy and diseased populations, and other modern exposure assessment tools, it should be possible to better understand population diversity and susceptibility, and perhaps to achieve a closer alignment between human health and environmental risk assessments. Opportunities were noted for synergistic partnerships between EU projects with high-impact initiatives, such as Germany’s Virtual Liver project, the Japanese METI-NEDO High Throughput Assay Systems project, and the US Virtual Embryo, tox21, and NexGen programs.

Workshop participants emphasized the importance of the higher level of human-relevant biological understanding that can be achieved by means of an integrated pathway and modeling approach to safety assessment but noted that a substantial investment in targeted interdisciplinary research and related infrastructure will be required to fully develop each of the key building blocks (illustrated in Fig. 1) and demonstrate their functional integration before such benefits can be fully realized. It also was noted that early and active interactions with regulatory authorities, regulated industry, and civil society stakeholders will be necessary to achieve timely acceptance and integration of new testing tools and strategies as part of an evolutionary shift in the safety testing and assessment paradigm.

During its in camera session aimed at developing an innovative toxicity testing roadmap for consideration under the forthcoming Common Strategic Framework for Future EU Research and Innovation Funding, the AXLR8 Scientific Panel appreciated the substantial progress that has been made in Europe in the development of alternative testing strategies as a product of funding by DG Research & Innovation under FP6 and FP7 (Fig. 2). The SEURAT-1 initiative was recognized as another important step towards a new experimental approach to safety testing and, as a public-private partnership between the Com-

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1 A major national initiative funded by the German Federal Ministry for Education and Research, http://www.virtual-liver.de
2 Virtual Embryo Project – A computational framework for developmental toxicity, http://www.epa.gov/ncct/v-Embryo
3 Memorandum of Understanding, research, develop, validate and translate innovative chemical testing methods that characterize toxicity pathways, http://www.epa.gov/ncct/tox21
4 Advancing the Next Generation of Risk Assessment, http://www.epa.gov/risk/nexgen
mission and regulated industry, it represents a promising new funding model. Indeed, COLIPA’s direct financial support for this initiative was extremely welcome and is preferred over, e.g., in-kind contributions from the private sector.

Structurally, the Scientific Panel welcomed the “cluster-type” design of SEURAT-1, i.e., multiple project-level “building blocks” organized around a central coordinating action (Fig. 3). This approach facilitates intense scientific exchange and supervision of the research projects/areas and governance of the cluster. Procedurally, it was recommended that up-front coordination and development of project plans and consortia around a central unifying vision – including clear scientific objectives and tangible milestones and deliverables at both project and cluster levels – is essential to ensure strategic alignment within and across projects and cohesion at cluster-level. Procedurally, it was recommended that the existing Scientific Experts Panels should start now with the development of a detailed roadmap to innovative toxicity testing. It also was recognized that project co-ordination at cluster-level requires a permanent secretariat run by a group of experts with a multitude of skills at administrative, organizational, and scientific levels. Additional administrative instruments to support and enforce cluster-level interactions, e.g., exchange of data and standard operating procedures, should be explored in future programs.

The AXLR8 Scientific Panel felt that the fields of systems toxicology and medicine are primed to advance by a quantum leap, and the EU – as a leading innovator in the area of health

Fig. 3: Illustration of the proposed SEURAT-2 structure
Six large-scale clusters encompassing five human health effect areas together with cross-cutting infrastructure would be developed under the direction of a central co-ordination action. There should be a strong focus in all clusters on core “building blocks”, illustrated here as four distinct projects/research areas; however, the exact number of projects per cluster should be determined on a case-by-case basis.
research funding aimed at advancing the science of safety testing – is well positioned to play a major role in this dynamic and rapidly evolving research area. Not since the Human Genome Project has the EU been presented with such a tremendous opportunity to contribute to world-class scientific breakthroughs. Indeed, mapping the human “toxome” is directly analogous to the human genome mapping of the 1990s, and it has the potential to be a “game changer,” with substantial benefits foreseen in the areas of public health and environmental protection, economic growth and competitiveness, and animal welfare. Thus, to build on the momentum of successful FP6/7 projects (e.g., ReProTect and Sens-it-iv) and to cover the full spectrum of health and toxicity concerns, the experts concluded that it would be essential to extend SEURAT-1 to its next phase, with integration of all relevant aspects of systems medicine into the core research strategy.

3 Recommendations for future EU research and innovation funding

The AXLR8 Scientific Panel recommends swift and decisive action to develop a flagship-level interdisciplinary research effort that builds upon the results of European FP6/7 projects and the emerging results of SEURAT-1 but on a much larger scale, given the magnitude of work that is still needed to achieve a full paradigm shift in toxicological safety assessment. The general concept, illustrated in Figures 2 and 3, is denoted here as SEURAT-2. Taking into account the positive experience of SEURAT-1, SEURAT-2 should be established as a public-private partnership (PPP) that includes the Commission, Member States, and regulated industry.

As successfully introduced in SEURAT-1, the key element of SEURAT-2 should be the “cluster,” comprising a group of typically four to six individual research projects focused on a particular area. A total of six clusters should be funded, organized around five priority health concerns, i.e., cancer/carcinogenicity, fertility and developmental health/toxicity, specific target organ toxicities, and immune disorders/toxicity (including sensitization), all of which have been identified elsewhere as requiring additional research resources (Adler et al., 2011). An additional cluster is envisaged to address infrastructure and servicing needs, including knowledge management, high-throughput screening platforms, bioengineering, communications, training, and outreach. Overall management of the six clusters should be handled by a central coordination action. Based on the SEURAT-1 model, a funding level of 50 million € per cluster could be envisioned. Taken together with a coordination action with three to four full-time personnel, a total budget of 325 million € would seem appropriate.

In contrast to previous research, there should be a strong focus in all clusters on the following cross-cutting themes and development of the core “building blocks” of technical capabilities and models for a common toolbox:

- Identification and understanding of toxicological modes-of-action associated with adverse health effects and disease, including elucidation of critical perturbations/pathways at the molecular and cellular levels.
- Development of experimental, theoretical, and computational models that capture specific mode-of-action events at different scales (molecular, cell, tissue, organ, organism), underpinned by a systems biology approach to integrate models and make quantitative predictions.
- Expansion and refinement of physiologically-based biokinetic (PBBK) modeling and computational chemistry methods to predict in vivo bioavailability, biotransformation, and bioactivity of exogenous chemicals.
- Translation research and proof-of-concept activities to realize fit-for-purpose methods and tools for toxicological hazard prediction, as well as the demonstration and evaluation of these in a safety assessment context.

It is recommended that the SEURAT-2 central coordination action should be responsible for articulating initial scientific objectives, milestones, and deliverables at both cluster and project levels. As projects are established, contract agreements should be put in place to clearly define responsibilities and relationships within and among projects, including at the cluster level. Consideration should be given to the use of contracts as opposed to grant agreements, in some cases, for specific research or service needs. The coordination action also should establish a scientific panel to monitor progress continually, at both project and cluster levels, to stimulate communication between projects and clusters, and to define and coordinate future tasks and long-range planning of the cluster, as well as to ensure accountability of all partners toward the common goals. The scientific panel should include the coordinators of all projects and additional external experts. The day-to-day running of the coordination action should be managed by permanent administrative and scientific secretariats. It is recommended that the role of the coordination action be reinforced with effective tools to ensure alignment among projects and enforcement of milestones and deliverables. Sufficient flexibility must be provided to make midstream course corrections as needed, for example by bringing in new projects.

“Value added” collaborations among established research teams (e.g., the US Tox21 collaboration, Japanese institutes, etc.) in key areas should be encouraged to share the workload, create synergies without duplication, and together reach for an ambitious, global objective that would be impractical to pursue on a regional basis. This should allow for recruitment of international partners as appropriate, as well as joint funding calls with Member States, international agencies, and funding bodies. Targeted multidisciplinary partnerships also should be encouraged, given that a solution for more predictive and animal-free safety assessment needs the mobilization of the best scientists in their fields, many of whom would not traditionally apply their work to toxicology. Funding for SEURAT-2 should, as a matter of principle, be used to support research that does not involve the use of living animals.
References

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