

MRC National Programme for Training and Capacity Building in Integrative Toxicology

OPINION GATHERING WORKSHOP

5th November, 2007, Royal Society of Medicine, London, UK

EXECUTIVE SUMMARY

The Workshop was convened to gather views and input on the MRC Training and Capacity Building Programme in Integrative Toxicology for PhD students and Career Development Fellows (CDFs) to explain the background of the initiative to strengthen research and training in a strategically important aspect of health sciences. Starting 2008 the initiative would fund both 4y PhDs and 3y CDFs with both integrative research topics and taught courses. Funding would be distributed in an open and transparent way based on scientific quality and integrative merit. Three eminent scientists Professor Sten Orrenius (Karolinska Institute, Stockholm), Professor Paul Matthews (GSK/Imperial College) and Professor Marcello Lotti (Padua) emphasized the importance of fundamental and integrative studies in the development of drugs and in understanding the hazards and risks of exposure to toxic chemicals. Views on the content and processes for training young scientists in integrative toxicology in the MRC initiative were led by perspectives from Professor Kevin Park (Liverpool) representing academia, Professor Tim Hammond (AstraZeneca) giving a pharmaceutical industry view and Professor Kevin Chipman (Birmingham) on behalf of the British Toxicology Society. Other members of the Workshop provided complementary and additional advice on the content and organisation of the Programme if it was to serve the future needs of academic, industrial and regulatory organisations.

- Toxicology is a well recognised discipline that needs to be retained and its profile strengthened but there is a shortage of young, highly motivated scientists attracted into toxicology research into the UK.
- Toxicologists in drug safety are expected to support the discovery and development of novel therapeutics from target identification right through to post-marketing. This requires a broad range of integrative practical and knowledge based skills from

understanding current concepts in molecular medicine to appreciation of regulatory procedures.

- Toxicologists in chemical, plant protection and food industries, together with those in environmental health, food and drug regulatory authorities, must be trained similarly but with specialised knowledge of risk assessment.
- Training will need to be multi-stranded but could incorporate many elements of those relevant MRes courses that are conducted by various universities in the UK.
- General aspects of modern research common to most PhD programmes could be covered by standard practices of host universities.
- Core curriculum subjects specific for the Programme should be decided by the Steering Committee. More specialised subjects could be selected depending on the students and their PhD supervisor pertinent to their research project and future career.
- Although PhD studentships were to be for 4 years the first year need not necessarily be spent on the taught aspects with the remainder spent on a PhD research topic. It might be better to start in the normal 3 year manner but include focused toxicological modules throughout the next 2 years.
- All students should spend some time in other laboratories or establishments that had a direct toxicological role with strong input from industry, government health protection organisations and regulatory agencies.
- A sense of identity amongst the students and CDFs on the programme should be fostered by holding away meetings for taught courses and presentation of their projects.
- The courses should be accredited perhaps through the BTS/IOB UK/EUROTOX Register of Toxicologists or other professional body although co-ordinated via the MRC Toxicology Unit.
- It would be vital to attract high quality students and CDFs and employability advantages of the Programme should be evident.

REPORT

Background and Initiation of the Programme

The Chair of the Workshop and the Programme, Professor Nicotera, the Director of the MRC Toxicology Unit, illustrated how the face of fundamental and medical science had changed greatly since the introduction of many of the common toxicology tests in practice for the regulation of drugs and chemicals. Many professional bodies and government organisations agreed that a new generation of toxicologists should be encouraged, especially with wide integrative skills in molecular, immunological and imaging techniques, *in vivo* expertise, knowledge of risk assessment including drug design, environmental and occupational health, and product safety. There was a great need to predict more precisely the toxicity of drugs and chemicals, especially sporadic adverse reactions. Regulators needed to be trained to appreciate and understand new scientific advances for efficient decision making. Unveiling new, common mechanisms in injury response and comparison with other disease pathogenesis could help derive more reliable biomarkers for risk assessment, clinical trials and design of new therapies. Some of the techniques were available in the MRC Toxicology Unit, e.g. imaging of neuronal death processes, gene array of micro RNAs and software for comparing biological connectivity networks. The aim of the new MRC initiative was to integrate classic toxicology with advanced molecular science with a 4 year rolling PhD programme and some CDFs. It could be envisaged as a virtual high school with competitive research projects and it was hoped to encourage partnership between academia, industry and regulatory agencies.

The background and proposed operation of the MRC Training and Capacity Building Programme in Integrative Toxicology was introduced by Professor Stephen Holgate in his capacity as present chairman of the MRC Physiological Systems and Clinical Sciences Board. An MRC strategic review of toxicology, was conducted in 2006 in the context of the scientific review of the MRC Toxicology Unit. It was felt that there should be more synergy and integration of different disciplines relevant to toxicology from fundamental mechanisms to risk assessment. At the same time, consultations with stakeholders had illustrated that there was an increasing shortage of original thinking research scientists well-trained in the multi-

disciplines pertinent to toxicology. In the light of these recommendations, the MRC allocated to the Toxicology Unit a total of £2.25M to co-ordinate and lead a national programme of training and capacity building in integrative toxicology. It is hoped that this allocation will act as pump priming funding to attract further support. The aim was to integrate research into fundamental mechanisms of toxicity with taught and interactive exposure to drug safety, environmental research and regulatory toxicology by using a 4 year rolling PhD programme and some career Development Fellows. The Programme would be overseen and facilitated by the Steering Committee with a broad membership drawn from academia, industry, and environmental and regulatory backgrounds. A Scientific Sub-Committee would select projects and monitor progress of students. The first round of funding opportunities would be advertised in December with a deadline for applications by the end of January 2008. It was hoped first awards would be made in March. Due to limited funds some initial focus of projects on particulate fields may be required.

Vital Role of Innovative and Integrative Research

To stimulate thought-provoking discussion, Professor Sten Orrenius (Karolinska Institute, Stockholm), Professor Paul Matthews (GSK/ Imperial College) and Professor Marcello Lotti (Padua) described findings in research on cell death, brain imaging and pulmonary exposure respectively. Concepts of malfunctions of fundamental cell biology and physiology are as applicable to toxicological mechanisms and in hazard assessment as they are to any other disease processes. Fundamental cross talk between cell-death pathways was no different in pathological circumstances than in toxic scenarios, both often involving disturbances of mitochondrial function. Pharmacological use of MRI is now able to follow and elucidate central mechanisms and functional connectivity in brain plasticity in the course of seeking new targets for therapy of injury. This should enable more rationale-based therapeutic development rather than a serendipitous approach. An open minded dissection of the true importance of inflammation in acute cardiopulmonary diseases associated with particulates requires multidisciplinary studies, from cellular to epidemiological. Understanding the real mechanism has important consequences in predicting thresholds of exposure.

In summary, science is rapidly advancing and is of a multidisciplinary nature. Past concepts are outmoded and often in need of replacement. New concepts and integrative

approaches evolving in biomedical research are as relevant to toxicology as any other aspect of health safety and need to be incorporated in to hazard and risk assessments.

Discussion of the Programme for Training and Capacity Building

In discussing the way forward for the MRC Programme, generation of opinions and concerns from the Workshop members on the future needs, training and professional standing of a new generation of toxicologists were led by presentations from Professors Tim Hammond (AstraZeneca), Kevin Park (Liverpool) and Kevin Chipman (Birmingham) representing industry, academia and the BTS/IUTOX viewpoints. What are the needs and how could the MRC initiative be organised to start fulfilling the diverse toxicological requirements of the UK scientific community given limited funding? What sort of young scientists needed to be recruited? What other opportunities might be available to give added value? What were the views and help that the professional toxicology community could contribute?

Needs of the toxicological using community

- A majority view was that toxicology is a well recognised discipline with a long history that needs to be retained, strengthened and its profile elevated in the UK, both at the fundamental and applied levels. In the UK and the EU there was a lot of good will for an initiative in training future scientists in this discipline in a new way.
- As far as the pharmaceutical industry is concerned, toxicologists are expected to support the discovery and development of novel therapeutics from target identification right through to post marketing. This requires a broad range of skills from understanding current concepts in molecular medicine and an appreciation of chemistry, physiology, pharmacology, pathology, statistics, experimental design, legislation of the use of animals in research, and national and international regulations in drug safety. In addition to these, specialist skills in immunology, reproductive toxicology, systems biology etc are vital and lack of one can lead to severe impediment of drug evaluation and registration. Much better understanding of modern concepts and approaches is desperately needed in the light of costly failure of drugs in regulatory agencies.
- Although drug companies are funding PhD studentships in universities, recruiting of well trained staff is very difficult so that 25% are obtained from abroad. Many of the

current skilled staff are approaching retirement. Traditionally, companies have stayed in the UK because of access to a high skill base but there is increasing competition from outside the EU, especially China and India. Consensus opinion was that the situation is even worse in the rest of the EU, such as Sweden and Germany, and that there are now few veterinary or medically qualified recruits into toxicology.

- The chemical, pesticide and food industries, together with environmental health, food and drug regulatory authorities, are as important sectors for employing toxicologists as the pharmaceutical industry. All have need of scientists trained in modern core concepts of disease and toxicology but with specialised experience such as risk assessment and regulatory affairs.
- Most importantly, there was a need to attract young, talented graduates into toxicology research at the fundamental level. These young scientists need to be aware of the breadth of knowledge required for toxicology but at the same time be able to drive original multidisciplinary approaches in order to fundamental research to generate new concepts of cell and tissue injury that could be used in the development of new drugs and assessment of risk from toxic chemicals.

Implementation and training

- The future of toxicology requires integration between cutting-edge and applied science and is an opportunity to be proactive as well as reactive.
- Training in the Toxicology programme will need to be multi-stranded but could incorporate many elements of those few relevant MRes courses that are conducted by various universities in the UK. A number of UK universities would be keen to participate in this.
- PhD training at most universities includes general aspects of modern research such as statistics, ethics, basic practical skills, biomedical procedures, radiation, basic bioinformatics, writing and discussing papers etc and these could be covered locally if agreed in advance.
- What aspects of scientific knowledge must be Core curriculum subjects specific for the Programme should be decided by the Steering Committee with perhaps advice from a working party.

- More specialised subjects could be selected depending on the students and the inclinations of their PhD supervisor inclinations and pertinence to their research project and future career.
- Although the PhD studentships were to be designed for 4 years this should not imply that the first year need necessarily be spent on the taught aspects with the remainder spent on a PhD research topic. It might be better to start in the normal 3 year manner but include focussed toxicological modules throughout the next 2 years. In fact, this might be vital in attracting and holding high quality students keen to be involved in research from the beginning.
- To gain additional practical experience and knowledge of issues in the applied world, all students should spend some time in other laboratories or establishments that had a direct toxicological role. In fact, it would be central to the initiative to have strong input from industry, government health protection organisations and regulatory agencies.
- A sense of identity amongst the students and CDFs on the programme should be fostered. This could be achieved by holding meetings away together (perhaps summer schools) for taught courses and presentation and discussion of their projects.
- It was recognised that organisation of taught courses to meet the aspirations of the programme would be a challenging endeavour to avoid unacceptable disruption of personal lives of students.
- A taxing problem to be overcome would be accreditation of the overall course and the taught modules. This would take time to achieve and also had to be centred on the MRC Toxicology Unit which had the responsibility to co-ordinate the programme delegated from the MRC Council. As is customary, it was envisaged that the award of the PhD would remain, , with the host universities for the supervisor and student.
- One way for accreditation might be through the UK/EUROTOX Register of Toxicologists. The Royal College of Pathologists also have an accreditation scheme as might other professional bodies.
- In particular, the British Toxicology Society (BTS) sees this programme as an important initiative to attract top quality recruits, especially as the BTS has had similar concerns in recruiting new toxicologists. BTS would be keen to work with the MRC and has experience in trying to address some of the issues. Around the world toxicology as a subject and as an image is declining, despite benefiting almost every

aspect of our life,. Similar concerns have been raised by IUTOX and ASIATOX. It is important that new blood funding support is given for academic appointments and that this is a key element of the RAE and seen as a long term commitment, possibly by a higher profile in medical training.

- To attract good students and postdoctoral fellows, employability advantages of the Programme would need to be evident.

Interactions and Development

Given the wide multidisciplinary nature of toxicology and due to the limitations on funds, in the first instance the ambitions of the programme might have to be focussed on specific research areas such as adverse drug reactions. On the other hand, food and environmental exposure and the associated reconsideration of risk assessment and regulation are extremely important toxicological aspects of health protection requiring input of modern molecular concepts. Other organisations such as OSCHR and NERC might be receptive to requests for additional resources to help cover a wider remit. BBRC had also raised concern about the issue and efforts are being made to liaise with them. A wider European dimension could also give access to more funding to contribute and broaden the scheme.

Conclusions

Clearly, there is a consensus that the profile of toxicology needs to be increased and new toxicologists trained in state of the art multidisciplinary approaches not restricted to traditional toxicological methods. The Steering Committee will have to formulate how this challenging task can be accomplished based on the advice and comments of the workshop. Toxicology is not a dead subject and maintaining and developing the integrative skills for stimulating drug development and assessing true risks from chemicals in our environment is vital for the future economic and individual health of the UK and EU.