JOHNS HOPKINS
BLOOMBERG
SCHOOL of PUBLIC HEALTH

CAAT Scholars Program

Translational Toxicology Research and Training: Translating Discovery into Practice

A new post-doctoral research program offered by:

Johns Hopkins Center for Alternatives to Animal Testing (CAAT)
Department of Environmental Health Sciences
Bloomberg School of Public Health
Johns Hopkins University
111 Market Place / Suite 840
Baltimore, Maryland 21202-6709
Tel: (410) 223-1692 / Fax (410) 223-1603
http://caat.jhsph.edu

CONTENT

1. BACKGROUND

1.1 The pressing need for translational toxicology

Toxicology now stands at a cross roads. Introduction and development of new medicines, chemicals and consumer products is escalating, and applying toxicology to assess their hazards and benefits is an urgent public health issue. The push for additional toxicological tests is rising, driven by the public's desire to know more about exposure and possible effects of compounds and products. At the same time, the use of animals in toxicology is being challenged by a public that is increasingly concerned with animal welfare, humane science, and ethics.

Legislation in Europe and the US now requires the testing of tens of thousands of chemical compounds. The cost has been estimated at billions of dollars. It takes many years to complete a testing program. Millions of animals will have to be used. The pressure is on to identify low-cost, efficient and humane testing methods, by both understanding the basic mechanisms of toxicity, AND converting them into practical solutions for industry and government programs, that will result in a safer public health environment.

In the US, the NIH spends billions of dollars on understanding mechanisms of action of chemicals and on rate-limiting steps in biological processes. However, there is currently no money spent by the US government on translating these mechanisms into methods for product development and safety evaluation.

In the future, toxicologists will need to be more multidisciplinary in their training, and will need to embrace and incorporate the newest technologies and methods into their hazard identification and risk assessment research. Regulators will have to evaluate in vitro data to determine safety, hazard and risk.

1.2 Building a 21st Century Translational Toxicology Research Program

In order to meet the needs of industry and government agencies, CAAT has developed a new academic research training program here at Johns Hopkins University. It is called CAAT Scholars. The CAAT Scholars program is unique in that post-doctoral fellows will work in selected laboratories throughout the University and will focus on developing methods that are mechanistically based – translational toxicology..

A key strategy of government agencies, such as the NIEHS, is to identify examples of translational research that will contribute to the public health solutions for the future. That is, moving beyond the basic research and discovery and towards the practical application of identified mechanisms and methods in order to alleviate public health concerns. We believe that the CAAT Scholars program will train a new breed of toxicologist to be skilled in translating basic research and discovery into practice, thus contributing to the public health solutions of tomorrow.

CAAT has a hugely successful track record of facilitating in vitro research programs on behalf of sponsoring organizations (e.g. Avon, Gillette). CAAT is situated as an academic

center within the Johns Hopkins University Bloomberg School of Public Health, an institution recognized worldwide for its teaching and research programs.

Established in 1981, CAAT is dedicated to the advancement of humane science and is recognized internationally for its efforts to promote the development, validation and use of alternatives to animals in research, product safety testing, and education. It is the leading alternatives center in the United States and has an unparalleled record for bringing together and achieving consensus among diverse groups with often divergent interests regarding the use of animals in research and testing. These groups, both in the US and throughout Europe, include government departments, industry, research scientists, animal protection groups, academia, and the interested public.

Industry's sponsorship and participation in the CAAT Scholars Program is critical to provide the deeper understanding of the utilization of the data, to identify areas of need, and to contribute to the general discussion and interaction that will be an integral part of the CAAT Scholars program.

2. CAAT SCHOLARS PROGRAM IN TRANSLATIONAL TOXICOLOGY

2.1 How will translational toxicology improve public health?

It is our objective to provide a program that not only identifies the basic mechanisms of toxicity but converts these mechanisms into new methods, information and tools that can be applied by government agencies and industry partners to solve issues in hazard identification, safety evaluation, and risk assessment.

For our CAAT Scholars, translation will mean using an understanding of mechanisms of toxicity to develop in vitro methods that can be translated to the needs of stakeholders (government and industry partners). The methods developed will use a spectrum of different systems: from cell and organotypic cultures, to the use of non-mammalian systems.

The CAAT Scholars program will train scientists to develop the mechanistic basic methods that will permit the evaluation of risk, and extrapolation of in vitro data into health consequences that will have a beneficial impact on public health overall.

2.2 What does the CAAT Scholars program offer?

The program offers industry and government an opportunity to partner in training the toxicologists of the future. These will be toxicologists who have learned to work in multidisciplinary teams – a critical and necessary skill for success in translational toxicology research.

Initially, the proposed research and training program will consist primarily of post-doctoral fellows to be identified as CAAT Scholars. CAAT Scholars will work in a laboratory where the mechanistic studies are focused on problem areas related to sponsors' interests, or as identified by program mentors (Drs Michael A. Trush and Alan M. Goldberg).

Additional mentor researchers will be drawn from faculty members at Johns Hopkins University involved in toxicology, cell and molecular biology, bio-engineering and modeling, and computational biology.

Some initial mechanisms of potential interest are mitochondrial function, transport mechanisms, and hypersensitivity, among others, but CAAT anticipates discussions with our industrial sponsors to identify their areas of need and to pursue these areas, provided the necessary expertise is available. The following list highlights other potental target mechanisms and models (as identified in ECVAM's report #50) that may be common to many cell types and responsible for cellular failure:

Cell communication – intracellular or cell–cell – botulinum toxin
Gene regulation – dioxin
Protein turnover – cycloheximide
Membrane structure and function – peptide toxins
Glycolysis – n-hexane
Mitochondrial function – cyanide
Energy production and metabolism – 3-acetylpyridine
Reactive oxygen species - paraquat

Potential model assay systems for quantifying susceptible functional endpoints also have been identified. Examples of organ specific functions which might be examined are:

Lung / respiratory – membrane integrity
Cardiovascular – contraction
Central nervous system – neurotransmission
Liver – metabolic transformation, protein regulation
Kidney – transport, filtration
Skin – barrier function, hypersensitivity

Our goal is to see mechanistic-based research translated into methods that can be used for risk assessment, safety evaluation, and hazard identification. The process for doing this will involve all of our scholars participating in meetings with sponsors (and invited others) at six-month intervals to discuss progress of the research projects and technology transfer. A unique aspect of the program is that the CAAT Scholars will not work in isolation but will be coordinated as a team by Dr Michael Trush. He will hold bi-weekly mentoring sessions that will focus on the translational aspect of the program. These meetings will allow researchers

i) to meet to understand how to make decisions using in vitro methods;
ii) to interact with people from government and industry (speakers or sponsor representatives);
iii) to understand industry's needs and regulatory requirements (currently a serious weakness in academia).

Fellows will also have access to classes at Johns Hopkins in fields appropriate for their career development. They all will participate in the Certificate Program in Humane Sciences and Toxicology Policy (see course description attached at Appendix II).

The aim is to recruit 6-10 post-doctoral scholars initially, with the intention of adding 4-6 more each year. The program will be funded through government and corporate sponsorship. Government support will be by supplementary post-doctoral support applications by faculty interested in this program who are already supported by NIH funding.

3. SPONSORING TRANSLATIONAL RESEARCH AT CAAT

3.1 The opportunity

An opportunity exists for your organization to sponsor the CAAT Scholars Program in Translational Toxicology Research and Training at Johns Hopkins University.

3.2 The benefits

For your organization:

- access to new technology, knowledge and strategies in areas of interest to you, that will enable you to make decisions in risk assessment and safety evaluation
- access to potential employees
- several leading scientists from different laboratories focusing on the translation of mechanism to method
- leading world-class researchers solving issues of importance to you
- membership on CAAT's Advisory Board for the duration of the sponsorship agreement
- opportunity to train employees in translational toxicology

For the CAAT scholar:

- unique, high-level training in translational toxicology
- obtain Certificate in Humane Sciences and Toxicology Policy
- first of new breed of toxicologists
- career development / career path – possibility of internship with sponsoring organization
- learn to work in a multi-disciplinary environment
- focus on issues of relevance to government and industry

For public health:

- more highly trained scientists mean better public health solutions
- new methods, information and tools that can be applied to solve issues in hazard identification, safety evaluation, and risk assessment.
- defines a new toxicology
- meets the demand from post-doctoral candidates for this type of program and training

3.3 The cost

Each scholar will cost $100,000 per year.

A minimum 3 year commitment is required by a sponsor

Payment will be in three annual installments at the start of the academic year

Total cost for the three year program is $300,000 per CAAT Scholar.

APPENDIX - I

Dr. Michael A. Trush – background information

This CAAT program will be coordinated by Dr. Michael A. Trush.

Dr. Trush was originally trained at the baccalaureate and at Masters level in plant physiology/toxicology. He holds a doctorate degree in pharmacology/toxicology and did his post-doctorate training in the target organ toxicity of anti-neoplastic agents as a PRAT Fellow at NCI.

Dr. Trush joined Johns Hopkins in 1983 and he currently holds a number of positions:

Professor of Toxicological Sciences
Deputy Director of the Johns Hopkins NIEHS Center in Urban Environmental Health
Director of the Center's Community Outreach and Education Program
Associate Director of the NIEHS Training Grant
Director of the Short-term Minority Training Program, and
Co-Director of the Principles of Toxicology course

Dr. Trush's research interests are diverse and include mechanistic research in the toxicology of the following systems: blood and immune cells, bone marrow, cardiovascular, renal, pulmonary, hepatic, central nervous system, and skin. He has also investigated many different environmental and pharmaceutical agents with these systems. Mechanistically, he is interested in the role of reactive oxygen (ROS) in mechanisms of toxicity and, more recently, in normal cell biology and cell signaling. He is a pioneer in the use of ROS-based chemiluminescence in assessing cell function and mechanisms of toxicity. His laboratory developed and validated a lucigenin–based method for assessing intramitochondrial superoxide. Currently the laboratory has translated this method to applications in cell differentiation, cellular aging and mechanisms of mitochondrial toxicity.

Dr. Alan M. Goldberg – background information

Alan M. Goldberg received his Bachelor's degree from Long Island University, Brooklyn College of Pharmacy, and his Ph.D. in Pharmacology from the University of Minnesota. After doing postdoctoral work at the University of Indiana, he joined the faculty at Indiana University and then moved to The Johns Hopkins School of Hygiene and Public Health in the Department of Environmental Health Sciences. His research areas included cholinergic biology, neurotoxicology, and during the last 25 years has focused on the development of in vitro methodology in risk evaluation, safety assessment. He is the author of over 100 scientific articles, the editor of the book series Alternative Methods in Toxicology, and the co-editor of books dealing with cholinergic mechanisms and in vitro toxicology.

Dr. Goldberg has served on numerous government and non-government panels, including the U.S. Congressional Office of Technology Assessment (OTA) and the Institute for Laboratory Animal Research of the National Academy of Sciences, and the National Advisory Committee

for the Interagency Coordinating Committee for Validation of Alternative Methods (ICCVAM). He worked with the Organization for Economic Cooperation and Development (OECD) as a consultant on animal welfare issues. Currently, he is a commissioner of the Pew Foundation for a study of industrial animal production, and a member of the Woodrow Wilson Center program on nanotechnology.

He is the first recipient of the Russell and Burch Award of the Humane Society of the United States, and was awarded the 1998 Society of Toxicology's Ambassador of Toxicology, and in 2001 received the Society of Toxicology's Enhancement of Animal Welfare Award.

Dr. Goldberg served in the Dean's Office at the Johns Hopkins University School of Hygiene and Public Health for 15 years. Dr. Goldberg is a Professor of Toxicology at The Johns Hopkins University, and the Director and Chairman of the Board of the Johns Hopkins Center for Alternatives to Animal Testing at the Johns Hopkins Bloomberg School of Public Health.

Appendix - II

Draft details of new certificate program to be taken by CAAT Scholars

HUMANE SCIENCES AND TOXICOLOGY POLICY CERTIFICATE

Educational Objectives: The educational objective of this certificate program is to provide students with an understanding of the principles that govern the relationship between biomedical researchers and laboratory animals and illustrate the role that transgenic, in-vitro, computational, non-mammalian or non-animal research plays in biomedical research. The program will introduce, and explain the application of, the "3Rs," (reduction, replacement and refinement) which are the guiding principles of humane science as well as demonstrate how the use of humane science principles in biomedical research can lead to more robust scientific methodology and knowledge. The certificate program courses cover the scientific principles needed to appreciate humane science and identify and evaluate its implications in biomedical research and public health policy. Persons completing the course of study leading to the certificate will be well equipped to translate new toxicological knowledge into scientifically credible product safety evaluations and hazard assessments.

Intended Audience: The certificate program is open to persons who hold undergraduate or graduate degrees in public health (e.g., B.S., B.A., M.P.H. or M.H.S) or the biomedical sciences. It is also open to any person in a degree-granting program at the University, although it is anticipated that most enrollees will be students at the Bloomberg School of Public Health. Persons who are members of IACUCs and/or involved in animal welfare issues who have completed the prerequisite course of study (as outlined below) are also eligible for admission to this certificate program.

Admissions Criteria:

Students not enrolled in a degree program at the Johns Hopkins Bloomberg School of Public Health: If you are not a student enrolled in a degree program in the School but want to apply for this certificate, you must have an undergraduate degree from an accredited college or university. This will enable you to be admitted to the School as a special student regular through the Department of Environmental Health Sciences. When a student becomes a special student regular, the Department will assign an advisor from a list of interested faculty members.

If you have experience in toxicology and biostatistics, then you can seek permission to waive the pre-requisite course requirements (see below), thereby enrolling as a special student-limited.

You should formally apply for the Certificate no later than the first week of the term in which the final course is offered. Your application must include a recent copy of your transcript and a general information form provided by the Institute.

Degree-seeking students at the Johns Hopkins Bloomberg School of Public Health: If you are in a masters or doctoral program at the School, you are welcome to enroll in the Certificate Program as part of your training. You should formally apply for the Certificate no later than the first week of the term in which the final course in the Certificate Program is offered. Your application must include a general information form provided by the Institute.

Pre-requisite courses: The following courses are required pre-requisites:

180.601.01 or .81	Environmental Health
187.610.01 or .81	Principles of Toxicology
140.615.01	Statistics for Laboratory Scientists I

Course of Study: The core curriculum consists of the successful completion of four courses that will address critical issues in humane sciences, examine the 3Rs in biomedical research, enhance knowledge about experimental design and analysis, and study the translational and policy implications of humane sciences. These courses are:

- 180.890.01 Animals in Research: Law, Policy and Humane Sciences (2 credits)
- 180.XXX.01 Journal Club – In vitro Toxicology or Seminar in In vitro toxiclogy (2 credits)
- 306.665.01 Research Ethics And Integrity: US and International Issues (3 credits)
- 187.632.01 Molecular Toxicology (4 credits)

Requirements for Successful Completion: 1. All courses must be taken for academic credit to count toward the certificate. 2. The student must receive a passing letter grade of A or B. The student must complete the pre-requisite courses, or hold an approved waiver from the certificate program directors.

Faculty Sponsors: Paul A. Locke and Alan M. Goldberg (410-502-2525 (Locke); 223-1692 (Goldberg); plocke@jhpsh.edu and agoldber@jhsph.edu)

Administrative Contact: Pamela Derrick (410-502-5918 or pderrick@jhsph.edu)

Department of Environmental Health Sciences
111 Market Place / Suite 840
Baltimore, Maryland 21202-6709
(410) 223-1692 / Fax (410) 223-1603
E-mail: caat@jhsph.edu
Websites: http://caat.jhsph.edu / http://altweb.jhsph.edu

Center for Alternatives to Animal Testing

Alan M. Goldberg, PhD
Professor of Toxicology
Director, Center for Alternatives to Animal Testing

2006 CAAT ADVISORY BOARD MEMBERS

Larry Andrews, PhD
Rohm and Haas Company

Frank W. Baker, PhD
Consultant

Rebecca Bascom, MD, MPH
Penn State Hershey

Marilyn Brown, DVM, MS
Charles River

John L. Butenhoff. PhD
3M

James J. Freeman, PhD
ExxonMobil Biomedical Sciences Inc.

Clifford Gabriel, PhD*
US Environmental Protection Agency

A. Jay Gandolfi, PhD
The University of Arizona

Alan M. Goldberg, PhD
Johns Hopkins University

A. Wallace Hayes, PhD, DABT, FATS, FIBiol
Harvard University at Amherst

Brian Jones, PhD
Mary Kay, Inc.

Herman B.W.M. Koëter, DrTox
European Food Safety Authority

Rick Main, MS MPH
Alberto Culver Company

Steven W. Mann, PhD, DABT
Johnson & Johnson

Daniel S. Marsman, DVM, PhD
Procter & Gamble Company

David E. Owen, PhD
Royal Dutch/Shell Group of Companies

Bernard Robaire, PhD
McGill University

Noel R. Rose, MD, PhD
Johns Hopkins University

Andrew N. Rowan, DPhil
Humane Society of the United States

Leonard Schechtman, PhD*
US Food and Drug Administration

Ladd W. Smith, PhD, DABT
Research Institute for Fragrance Materials, Inc. (RIFM)

William S. Stokes, DVM*
National Institute of Environmental Health Sciences

Gihan I. Tennekoon, MBBS, LRCP, MRCS
University of Pennsylvania

Eve Lloyd Thompson
Bernice Barbour Foundation, Inc.

Marilyn L. Wind, PhD
US Consumer Product Safety Commission

James D. Yager, PhD
Johns Hopkins University

* US Government observers