# Excelling in analytical and **environmental toxicology**



**Distinguished Professor X Chris Le** heads a multidisciplinary team researching the chemistry and toxicology of environmental contaminants and the implications for human health

**What are the key aims and objectives of your research?**

Our research aims to develop new analytical technologies and novel applications through the study of human health in relation to the environment. We design and develop ultrasensitive and highly specific techniques and assays for proteins, DNA and environmental contaminants. We are also identifying and detecting environmental contaminants, such as arsenic compounds, and researching how they interact with biological molecules to exert health effects.

**You have studied arsenic for many years. Why have you focused on this element?**

The main reasons for our continued efforts in studying arsenic are threefold: its environmental health impact; interesting and complex chemistry; and the potential for therapeutic effects. More than 50 arsenic compounds have very different toxic effects. How these arsenic compounds cause various toxicities is not well understood. Studying arsenic chemistry and toxicology will lead to fundamental knowledge and practical measures that could contribute to protecting public health and developing improved therapeutics.

**What is the relationship between your research on arsenic and your interest in DNA and proteins?**

Arsenic is now recognised as one of the most important environmental agents causing cancers of the skin, bladder and lungs. However, how arsenic causes various cancers remains to be fully elucidated. Many carcinogens act by causing damage to our DNA. But arsenic alone has been repeatedly demonstrated to be non-mutagenic. We are currently studying how arsenic species affect the cellular machinery to repair the genetic damage and how they influence proteins, including anti-tumour molecules. Within the scope of this research, we measure trace levels of specific DNA damage; monitor the cellular repair of the damage; examine the proteins involved in the repair process; and determine the interaction of arsenic species with these proteins as well as with cells and experimental animals.

**How are DNA-protein binding, nano-material assembly and signal amplification advantageous to biomedical research?**

Proteins carry out many essential biological functions. Detection of proteins is critical to understanding biological processes and to the diagnosis of diseases. Although many techniques are available for the detection of proteins that are present at high concentrations, few can detect important and rare proteins that are often present at trace levels. While tiny amounts of DNA can be amplified by polymerase chain reaction (PCR), there is no comparable technique to chemically amplify proteins. Thus, detection of low-abundance proteins is a tremendous challenge. To address this problem, we make use of DNA-protein binding, nano-material assembly and signal amplification. This approach achieves ultrasensitive detection of proteins.

**Do you collaborate with others on this diverse range of research topics?**

We collaborate extensively with researchers in biology, chemistry, environmental sciences, engineering, epidemiology, public health, pharmacology and toxicology. Our collaborations with more than 20 research groups around the world have resulted in 120 peer-reviewed publications. I am particularly interested in bridging the development of novel analytical technology and its applications to environmental and health sciences.

**Do you attach any importance to international links?**

I have helped many research groups and institutions to initiate collaborative research, facilitate exchange and secure joint funding. Working with the Canadian and Chinese academic sectors, our collaborators and I initiated the Canada-China Analytical Chemistry Conference series in 2007. These conferences have been held every two years, alternating between Canada and China. Most recently we held the 10th International Symposium on Persistent Toxic Substances. These provide platforms for scientists to highlight the most recent advances in the pertinent topics, explore international collaboration opportunities and facilitate joint training of the next generation of analytical and environmental scientists.

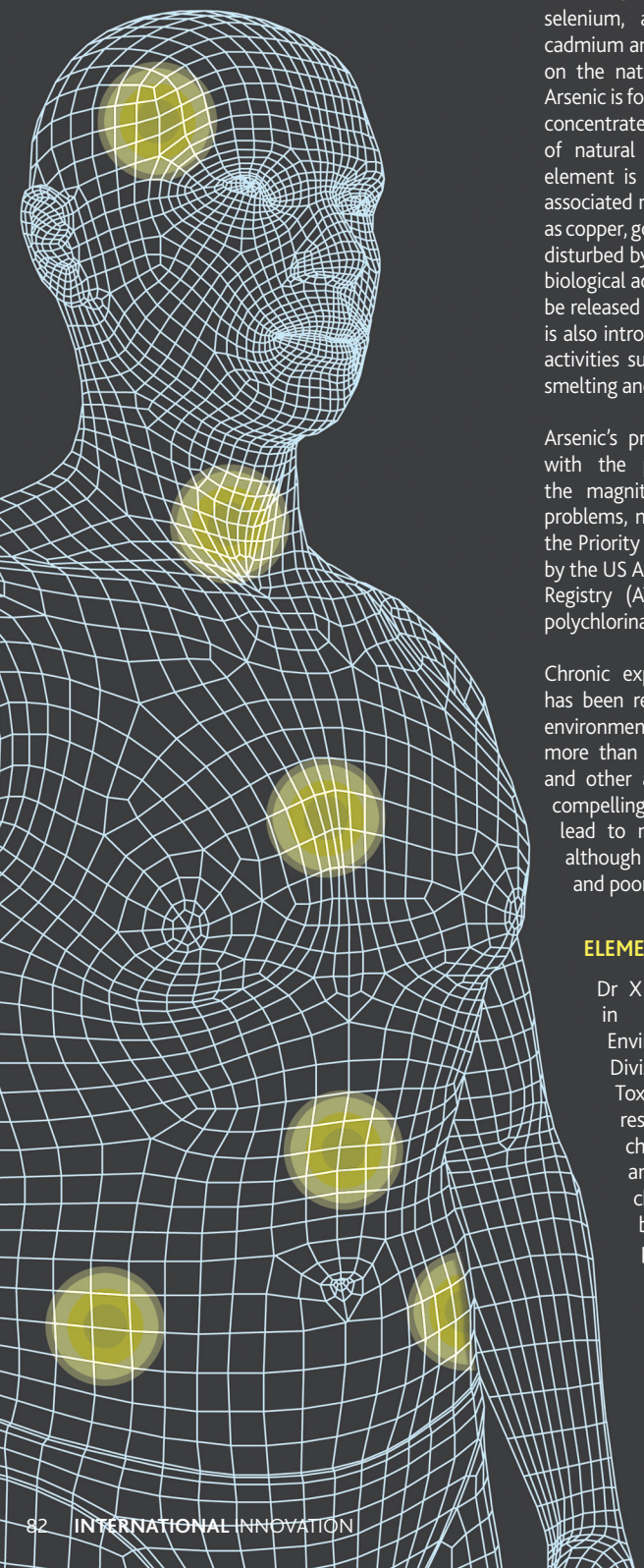
**What approach do you take towards students and postdoctoral researchers?**

I am very proud of my students and postdoctoral researchers, and I consider them as my junior colleagues. They motivate me and elevate my energy levels. Recognising their individual strengths and attributes, I give them complete freedom to learn, discover and innovate. Through international conferences and seminar series, we create opportunities for our trainees to organise and chair scientific sessions, thereby interacting with leading scientists and practising their communication skills.

Our students and researchers in the Division of Analytical and Environmental Toxicology arrive with previous training in various areas of basic sciences: chemistry, biology, microbiology, pharmacology, etc. Students benefit from cross-disciplinary collaboration, joint supervision and access to advanced research facilities. Many of our trainees have been recognised for their academic achievements and have received competitive scholarships and academic awards. In state-of-the-art laboratories, we carry out cutting-edge research into the development of analytical and bioanalytical technology, water and food safety, the effects of environmental contaminants on human health, and molecular mechanisms responsible for the health effects. Working as a team, members in our Division contribute to academic excellence in analytical and environmental toxicology.

# An element of **risk**

The Bio-Analytical Technology and Environmental Health programme at the **University of Alberta**, Canada, brings together researchers from various disciplines to study the implications of human exposure to arsenic and consequent effects on DNA repair



**METALLOIDS SUCH AS** arsenic, antimony and selenium, and metals such as mercury, lead, cadmium and vanadium have an important impact on the natural environment and human health. Arsenic is found in the Earth's crust and can become concentrated in some parts of the world because of natural mineralisation. This ubiquitous trace element is a component of 245 minerals and is associated most frequently with other metals such as copper, gold, lead and zinc in sulphidic ores. When disturbed by natural processes such as weathering, biological activity or volcanic eruption, arsenic may be released into the surrounding area. The element is also introduced into the environment by human activities such as burning fossil fuels, mining, ore smelting and well drilling.

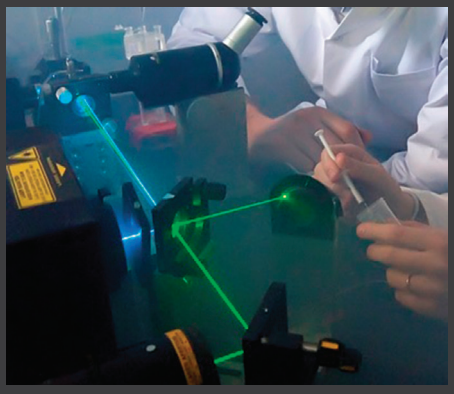
Arsenic's prevalence in the natural world, along with the potential for human exposure and the magnitude and severity of related health problems, means the element ranks at the top of the Priority List of Hazardous Substances compiled by the US Agency for Toxic Substances and Disease Registry (ATSDR), ahead of lead, mercury and polychlorinated biphenyls (PCBs).

Chronic exposure to arsenic from groundwater has been recognised as the cause of the largest environmental health disaster in the world, putting more than 100 million people at risk of cancer and other arsenic-related diseases. There is also compelling evidence that exposure to arsenic can lead to numerous other adverse side effects, although the exact mechanisms are complicated and poorly understood.

## ELEMENT SPECIATION

Dr X Chris Le is Canada Research Chair in Bio-Analytical Technology and Environmental Health and Director of the Division of Analytical and Environmental Toxicology at the University of Alberta. His research programme is a collaboration of chemists, toxicologists and clinicians, and has three major themes: arsenic chemistry and toxicology; DNA damage biomarkers; and novel techniques for protein detection.

In view of the significant impact of metals and metalloids on the natural environment and human health, the chemical speciation of trace elements plays a major role in the work of Le's team, which has developed chromatography and mass spectrometry techniques to analyse trace element species in environmental, biochemical and toxicological studies. Le explains: "The toxicity of arsenic depends on its chemical forms (species). The relative toxicities of arsenicals vary by more than a million times between the most toxic arsenic species to the least toxic arsenic species." As a result, Le believes that rather than measure the total amount of arsenic, it is more toxicologically important to measure individual species of the element.



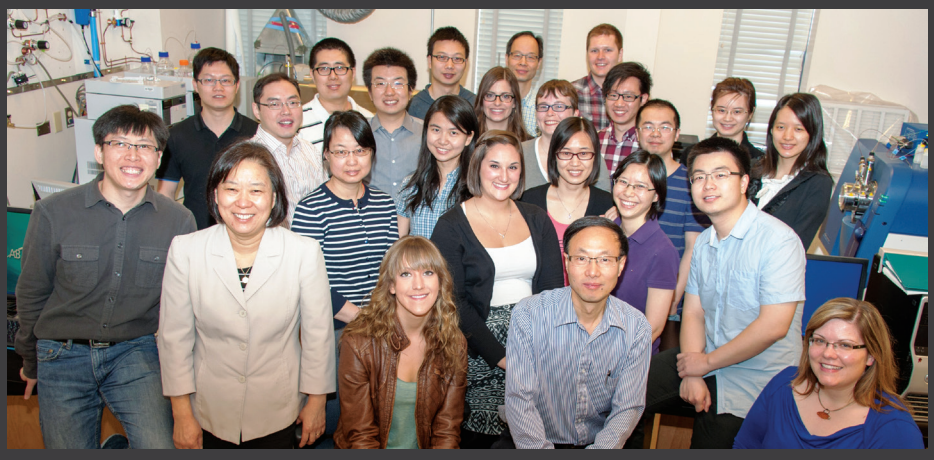
A LASER-INDUCED FLUORESCENCE POLARISATION SYSTEM BUILT IN THE LE LAB

The researchers' speciation techniques have enabled the identification of arsenic metabolites and their interaction with proteins, which is essential to the understanding of arsenic metabolic pathways and arsenic resistance mechanisms in microorganisms. According to Le, "a mechanistic understanding of arsenic's health effects is necessary for establishing scientifically sound regulatory guidelines that protect public health and also for developing arsenic-based therapeutics".

## DNA DAMAGE BIOMARKERS

The second area of the group's research involves the development of highly sensitive bioanalytical techniques for studying DNA damage, which represents a common link between many environmental contaminants that may contribute to human cancer. DNA damage and cellular repair are key determinants in the early stages of carcinogenesis, ageing and cancer therapy.

Le and collaborators have developed a novel assay for measuring DNA damage, with a detection limit of $3 \times 10^{-21}$ moles. This ultrasensitive assay, which has received both US and Canadian patents, allows the measurement of DNA damage caused by environmentally and clinically relevant exposures, and has paved the way for studies into DNA repair and enhanced biomarker development.



THE LE GROUP CONSISTS OF STUDENTS AND RESEARCHERS FROM DIVERSE ACADEMIC BACKGROUNDS

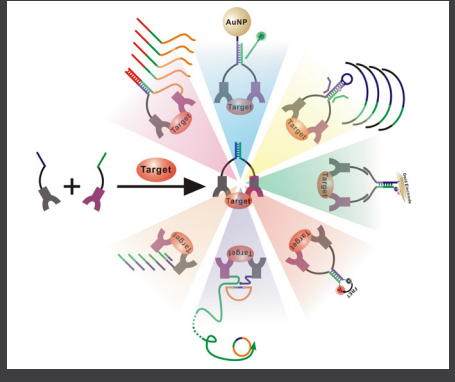
"Our research team and others have shown that trivalent arsenic species interfere with the repair of DNA damage caused by other agents, such as ultraviolet light and chemicals present in cigarette smoke," elaborates Le, who sees these findings as consistent with population surveys, which show synergies between arsenic exposure and cigarette smoking in lung cancer risk.

## PROTEIN DETECTION

The third area of Le's research involves the development of novel techniques for protein detection, taking advantage of DNA-protein binding, nano-material assembly and polymerase amplification. These techniques are applied to studies of protein biomarkers, natural toxins, therapeutic drugs, environmental contaminants and DNA-protein interactions. Often, just a few protein molecules are sufficient to control biological functions, hence the importance of developing an ultrasensitive detection method for minuscule amounts of proteins.

Very small amounts of DNA can be amplified by the polymerase chain reaction (PCR), but there is no comparable technique to chemically amplify proteins. As a result, the detection of low-abundance proteins represents an enormous challenge for researchers. To resolve this issue, Le and his colleagues developed innovative techniques to detect trace levels of proteins.

First, the team binds specific DNA aptamers that have unique and high affinity binding to target proteins. The aptamer-protein complex is then separated from the unbound aptamer by using capillary electrophoresis. The fractions containing the aptamer-protein complexes are collected, the aptamer is dissociated from the complexes, and the dissociated aptamer is amplified by PCR.




SEVERAL DNA-PROTEIN BINDING ASSAYS INCORPORATING SIGNAL AMPLIFICATION STRATEGIES

The amplification of the aptamer to which the protein binds dramatically improves the sensitivity of the detection of proteins. The group is able to detect as few as 180 molecules of a viral protein. As Le describes, "this concept and approach have diverse potential applications, ranging from bio-sensing to personalised and point-of-care diagnostics to the study of molecular interactions".

## ULTRASENSITIVE ASSAYS

Looking ahead, the team would like to expand their research to cover antimony and vanadium, as these chemical elements carry similar environmental and health risks to arsenic. Further research will also target a mechanistic understanding of the effect of toxic elements on the induction and repair of DNA damage caused by common carcinogens in the environment such as cigarette smoke.

Meanwhile, the progress made by the researchers in detecting remarkably low levels of proteins has opened up new horizons in biomedical and environmental health research, and Le intends to further develop ultrasensitive assays for other targets and extend the methodology to point-of-care diagnostics.

The University of Alberta group's studies into the effects of arsenic on DNA repair are improving our understanding of how arsenic causes cancer. All of the knowledge gained will also have implications for cancer research in general, as DNA repair is an essential process in protecting against cancer. In addition, fellow scientists will be able to apply Le's research approach to their own studies into other environmental carcinogens.

In advancing analytical and toxicological sciences, Le and his collaborators hope their work will help regulatory bodies to develop rational guidelines on arsenic as well as measures to prevent and reduce health problems caused by the element, as Le concludes: "We seek novel approaches to assess and prevent adverse health effects in humans and our environment".

## INTELLIGENCE

### CANADA RESEARCH CHAIR IN BIO-ANALYTICAL TECHNOLOGY AND ENVIRONMENTAL HEALTH

#### OBJECTIVES

To develop new analytical technology for the study of the impact of environmental contaminants, such as arsenic compounds, on human health. Linking chemistry, toxicology, clinical medicine and public health, the group designs ultrasensitive and highly specific techniques and assays for proteins, DNA and environmental contaminants.

#### KEY COLLABORATORS

USA: **Dr K Cantor**, National Cancer Institute; **Dr S Cohen**, Nebraska University School of Medicine; **Dr D Thomas**, National Health and Environmental Exposure Research Laboratory

Canada: **Dr W R Cullen**, University of British Columbia; **Dr K J Reimer**, Royal Military College; **Dr M Weinfeld**, Cross Cancer Institute

China: **Dr G B Jiang**, Chinese Academy of Sciences; **Dr M D Lai,** Zhejiang University; **Dr Q K Zhuang**, National Natural Sciences Foundation of China; **Dr H F Zou**, Chinese Academy of Sciences

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#### CONTACT

**Professor X Chris Le, PhD FCIC FRSC**
Canada Research Chair in Bio-Analytical Technology and Environmental Health;
Director, Division of Analytical and Environmental Toxicology

University of Alberta
Department of Laboratory Medicine and Pathology
Faculty of Medicine and Dentistry,
10-102 Clinical Sciences Building
Edmonton, Alberta T6G 2G3
Canada

**T** +1 780 492 6416
**E** xc.le@ualberta.ca

**www.ualberta.ca/~xcle/contact.html**

**PROFESSOR X CHRIS LE** holds an inaugural Canada Research Chair in Bio-Analytical Technology and Environmental Health. He is Distinguished University Professor in the Departments of Laboratory Medicine and Pathology, Chemistry, and Public Health Sciences, and is the Director of Analytical and Environmental Toxicology Division. In 2010, Le was elected Fellow of the Royal Society of Canada, Academy of Science. As well as receiving numerous awards and distinctions for his contribution to research and teaching, Le has published 190 peer-reviewed research articles, 25 book chapters and 10 patents.

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