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MEDIA RELEASE

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INTERNATIONAL COLLABORATION TO ADVANCE RESEARCH ON NON-ANIMAL APPROACHES TO CHEMICAL SAFETY TESTING

*A*STAR and the US EPA to co-develop innovative methods to assess and predict the safety of chemicals, without relying on animal testing*

Singapore – Singapore's Agency for Science, Technology and Research (A*STAR) and the United States Environmental Protection Agency (EPA) are partnering to develop new approaches to identify chemicals that could pose a risk to human health.

Tens of thousands of chemicals are currently in use, and many are essential to modern life. For example, preservatives protect food from harmful microbial contamination; sunscreen filters protect against skin cancer; surfactants in soaps, shower gels, shampoos and washing detergents help to remove dirt and grease.

For almost a century, chemical safety testing has been performed mainly on laboratory animals. However, there is growing scientific agreement that animal testing, besides being costly and time consuming, may result in poor prediction of human toxicity due to inter-species differences. Furthermore, animal testing for cosmetics products and ingredients has been banned in regions such as the European Union (EU) due to ethical concerns.

It could therefore prove valuable for companies in the consumer care, food and nutrition, chemicals and pharmaceutical industries to develop innovative methods for assessing large numbers of chemicals, and their effects on human health, more accurately and efficiently.

With an integrated research and innovation ecosystem, which pulls together both biomedical sciences and engineering capabilities into multidisciplinary teams, Singapore is well-positioned to contribute to new approaches to chemical safety prediction. Scientists from A*STAR's Institute of Bioengineering and Nanotechnology (IBN), Bioinformatics Institute (BII), and Singapore Immunology

Network (SIgN), and researchers from the EPA's National Center for Computational Toxicology are interested in collaborating on three areas of research:

- Kidney toxicity – This project will use the first and only predictive kidney technologies that were developed by IBN and BII to predict the effects of environmental toxicants on the human kidney efficiently and accurately. Their innovative technologies include stem cell-based models and a powerful high-throughput platform.

- Liver toxicity – This project will use 3D liver models developed at IBN and computational tools at the NCCT to identify novel predictive biomarkers of human liver toxicity to overcome limitations in existing 2D model tests, which limit their sensitivity, especially over extended periods. Machine learning approaches will be used to analyse and improve existing predictive models of acute and sub-acute liver toxicity.

- Developmental toxicity – This project aims to investigate the potential of certain chemicals to disrupt the development of blood vessels and the blood-brain-barrier during prenatal development – a key process during one of the most important life stages.

Dr Kenneth Lee, Senior Director of A*STAR's Biomedical Research Council (BMRC) said, "Chemicals are essential to modern life. If we can identify reliably and efficiently specific chemicals that pose a risk to human health, this should enable industry to predict the safety of their products in development, and ultimately benefit consumers and society. We look forward to working with the EPA, an international leader in safety science research, and being part of the global effort to advance chemical safety assessment."

Dr Russell Thomas, Director of the EPA National Center for Computational Toxicology, said, "We are excited to combine our computational and toxicological expertise with the world-class biomedical research capabilities of A*STAR. Through this collaboration, we hope to develop more efficient and economical ways to evaluate the potential health effects of chemicals that can be used by both industry and governmental agencies."

In all of the projects, A*STAR will draw on its multidisciplinary capabilities in stem cell research and tissue models, genomics, high throughput bioimaging, and computational sciences. The collaboration will build on EPA's ToxCast program which has generated high-throughput screening data on over 1,800 chemicals.

More information on the relevant A*STAR technologies can be found in Annex A.

Enclosed:

ANNEX A – A*STAR SAFETY SCIENCES TECHNOLOGIES

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About the Agency for Science, Technology and Research (A*STAR)
The Agency for Science, Technology and Research (A*STAR) is Singapore's lead public sector agency that spearheads economic oriented research to advance scientific discovery and develop innovative technology. Through open innovation, we collaborate with our partners in both the public and private sectors to benefit society.

As a Science and Technology Organisation, A*STAR bridges the gap between academia and industry. Our research creates economic growth and jobs for Singapore, and enhances lives by contributing to societal benefits such as improving outcomes in healthcare, urban living, and sustainability.

We play a key role in nurturing and developing a diversity of talent and leaders in our Agency and Research Institutes, the wider research community and industry. A*STAR oversees 18 biomedical sciences and physical sciences and engineering research entities primarily located in Biopolis and Fusionopolis.

For more information on A*STAR, please visit www.a-star.edu.sg.

ANNEX A

ANNEX – A*STAR SAFETY SCIENCES TECHNOLOGIES

1) **Liver Toxicity: Improved liver models for the screening of chemicals**
Institute of Bioengineering and Nanotechnology (IBN)

a) 3D CelluSponge Platform

3D liver spheroids are often used for drug testing as they strongly resemble liver tissue. However, such spheroids are often hard to control, with high variability during chemical safety testing. IBN Group Leader Prof Hanry Yu and co-workers have developed a novel biocompatible porous scaffold, which constrains many spheroids separately in multi-well plates more effectively, thus allowing greater control while maintaining the cell polarity and metabolic functions over weeks for sub-acute toxicity testing. The platform also has similar mechanical properties as the human liver.

b) HepatoCue Platform

Prof Hanry Yu's team at IBN has also developed a novel, robust system for high-throughput 3D cell culture that facilitates acute liver toxicity testing. Using this technology, cells are maintained as 3D *in vivo*-like configuration while preserving the advantages of 2D multi-well chemical screening platforms commonly used in industry. This allows 3D cells or liver constructs to be anchored in high-throughput acute liver toxicity testing of chemicals for up to a week. The scalability in terms of low cost, ease of automatic function, robustness and high-level metabolic functions with minimal chemical absorption makes this an ideal high-throughput platform for large-scale evaluation of chemical safety with improved metabolic activities over 2D models.

2) **Kidney Toxicity: Unique high-throughput imaging platform for predicting kidney toxicity**
Institute of Bioengineering and Nanotechnology (IBN), Bioinformatics Institute (BII)

IBN and BII have developed the world's first high-throughput platform for kidney toxicity prediction. In 2013, researchers from IBN, led by Dr Daniele Zink, Team Leader and Principal Research Scientist, developed a novel cell-based platform for the accurate prediction of kidney toxicity in humans, using proximal tubular (PT) cells, which are key targets for many toxic chemical compounds. This model used PT cells that had been directly harvested from the body. Subsequently, IBN developed a new protocol for producing PT cells from human pluripotent stem cells, and then found an effective way of producing PT cells from human induced pluripotent stem cells (iPSCs). Such cells were used to establish the world's first iPSC-based platform for kidney toxicity prediction. In collaboration with Dr Lit-Hsin Loo, Principal Investigator from BII, the platform also used machine learning methods developed by BII

to make more accurate predictions. Further improving on this, IBN and BII have jointly developed an innovative method based on automated imaging of kidney cells, phenotypic profiling and machine learning that could be used to test much larger numbers of compounds at much lower costs, making it the first high-throughput imaging platform for kidney toxicity prediction. This automated platform is capable of accurately predicting the human renal toxicity of compounds with diverse chemical structures, such as drugs, industrial chemicals, environmental toxicants and natural compounds. It would help companies to develop safer products without using animal tests.

3) **Developmental Toxicity: Expertise to develop generation of human foetal macrophages from induced pluripotent stem cells**
Singapore Immunology Network (SIgN)
Macrophages are a type of white blood cells essential for the immune system to protect the body against foreign substances such as viruses and bacteria. They also play a crucial role in tissue development and homeostasis. Notably, macrophages are involved in the early development of the brain from blood vessel development (angiogenesis) to the maturation of the blood-brain-barrier (BBB). The BBB is a crucial selective permeability barrier that separates circulating blood from the brain extracellular fluid in the central nervous, to block harmful substances from entering the brain. Its formation, maintenance, and function in the embryo-foetus are important considerations for developmental neurotoxicity. Dr Florent Ginhoux and his team from A*STAR's Singapore Immunology Network (SIgN) have developed an experimental model that generates human foetal macrophages from induced pluripotent stem cells, which can be used to examine the specific mechanisms by which macrophages modulate BBB establishment and predict how toxic molecules may affect brain development.