TRIESTE SCIENCE PRIZE

THE 2012 ERNESTO ILLY TRIESTE SCIENCE PRIZE, AWARDED IN THE FIELD OF HUMAN HEALTH, WAS PRESENTED TO YUK MING DENNIS LO (LI KA SHING INSTITUTE OF HEALTH SCIENCES OF THE CHINESE UNIVERSITY OF HONG KONG, CHINA) FOR HIS WORK ON NON-INVASIVE PRENATAL DIAGNOSIS.

The winner of the eighth edition of the Ernesto Illy Trieste Science Prize was announced at the TWAS 12th General Conference and 23rd General Meeting in Tianjin. The prestigious prize, worth USD100,000, rewards scientists living and working in developing countries whose research has had a significant impact on sustainable development. In previous years, the Ernesto Illy Trieste Science Prize has been awarded for research on climate change, renewable energy, and materials science. This year's Prize was awarded in the area of human health. The Prize is sponsored by the world-renowned coffee maker illycaffè (also based in Trieste), supported by the Ernesto Illy Foundation and administered by TWAS.

During the Opening Ceremony of the TWAS 12th General Conference, President Hu of China announced Lo as the winner and presented the specially-commissioned trophy. Later in the week, Lo received the prize money from TWAS president Jacob Palis, and subsequently presented his research to an audience of more than 400 scientists, ministers of science and presidents of science academies from around the globe.

Yuk Ming Dennis Lo is currently director of the Li Ka Shing Institute of Health Sciences and professor of chemical pathology at the Chinese University of Hong Kong (CUHK). He received the award for developing, with his team of researchers, a ground-breaking technology for the genetic analysis of a foetus based on a blood sample obtained from its pregnant mother.

Lo's path to this groundbreaking technology began in 1997 when he demonstrated the presence of high concentrations of cell-free foetal DNA in the plasma of pregnant women, which could then be sampled and tested. This discovery opened up new possibilities for non-invasive prenatal diagnosis, and has effectively reduced our reliance on previous invasive and potentially risky, methods.

ERNESTO ILLY TRIESTE SCIENCE PRIZE

Instituted in 2004 by TWAS and illycaffè*, the Prize is designed to bring recognition and distinction to the developing world's most eminent scientists. The award is jointly named: after Ernesto Illy, the late chairman of* illycaffè*; and after the city of Trieste. Ernesto Illy's passion for the sciences has made the award possible. Trieste, home to TWAS's headquarters, is known for its significant role in promoting science in the developing world.*

Lo commented: "The common procedures for prenatal diagnosis based on amniocentesis (the removal of amniotic fluid from the womb) and chorionic villus sampling (taking a piece of tissue from the placenta) are not entirely risk-free due to their invasiveness. To have a non-invasive test that can give accurate answers is a concrete help in obstetrics and brings tangible benefits to both the mother and the foetus, increasing the safety of prenatal genetic tests during pregnancy and reducing the stress due to invasive procedures. In the long-term, this technology will bring positive healthcare benefits to both developed and developing countries, reducing the suffering and healthcare burden caused by genetic diseases."

Lo graduated from Cambridge University and obtained his DPhil from the University of Oxford in 1994, but his heart remained in Hong Kong, the city where he was born, and he decided to return home in 1997. His move back to Asia was an opportunity to start a new research programme on a hitherto 'high risk' research area, namely, the investigation of extracellular DNA in plasma. Lo and colleagues had already noted previous work describing the presence of tumour-derived DNA in the plasma and serum of cancer patients, an observation that led Lo to wonder if he could also observe foetal DNA in the blood of pregnant women. At the same time, molecular biology techniques that are now widely used were just catching on.

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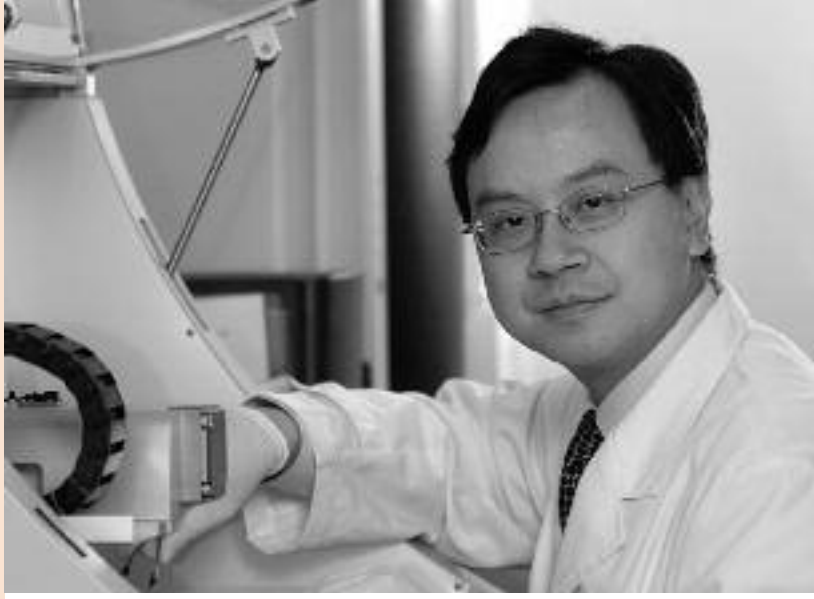
"Biology textbooks used to teach that the mother and baby's blood are separate but our research challenged this. You can take blood from a pregnant woman and you can detect male DNA in it. In fact, approximately 50% of pregnant women have male DNA in their blood plasma. We followed this up and found that those pregnant women with circulating male DNA go on to have a baby boy. So in this way we had shown that foetal DNA is present in the blood



LO'S GROUNDBREAKING CONTRIBUTIONS TO HUMAN HEALTH RESEARCH

Lo has published over 300 scientific papers. His main scientific achievements include:

1997

- *Discovered the presence of cell-free foetal DNA in maternal plasma, opening up a new field of research and new possibilities for non-invasive prenatal diagnosis.*

1998

- *Developed a new non-invasive prenatal test of foetal RhD blood group status, especially valuable for Caucasian subjects, in whom 15% of individuals are RhD-negative.*
- *Discovered the presence of the DNA from a transplanted organ in the plasma of a recipient's plasma. This discovery opened up the possibility of using plasma DNA to monitor graft rejection following transplantation.*

1999

- *Discovered the presence of cancer-derived DNA methylation changes in plasma, which has opened up a new class of tumour markers.*
- *Demonstrated that the quantitative measurement of Epstein-Barr virus DNA in the plasma of patients suffering from nasopharyngeal cancer is a powerful diagnostic and prognostic marker.*

2000

- *Demonstrated that plasma DNA measurement can be used to monitor patients suffering from trauma, stroke and cardiac disorders. This work has opened up the future use of plasma DNA analysis for emergency medicine.*

2002

- *First use of DNA methylation differences between mother and foetus to develop a new generation of molecular markers for prenatal diagnosis.*

2003

- *During the SARS epidemic, Lo's research team was the first group in Asia to publicly announce the complete sequence of the SARS-coronavirus. The group was also the first to report the molecular epidemiology, tracing the transmission of the SARS-coronavirus across Hong Kong, mainland China and Taiwan.*

plasma of pregnant women. We could thus use plasma DNA analysis for non-invasive prenatal diagnosis, including the prediction of the sex and blood type of the baby."

Knowing the blood type of the foetus can be crucial in preventing or managing potentially serious disorders that can affect the foetus because of the incompatibility of the blood types. If a woman is rhesus negative, for example, and carrying a baby whose blood type is rhesus positive, the mother's immune system might treat her baby as an intruder. The risk of the mother attacking the baby immunologically can be reduced by injecting the mother with antibodies. It would thus be beneficial for the woman to have this compatibility information. Lo's non-invasive prenatal testing technology allows this to be done safely and has already been adopted in many countries, including Denmark, the United Kingdom and the USA.

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There have been many positive outcomes of this technology, and Lo is not short of examples: "Another intervention we can do now that we have this information is a test which identifies the sex of a baby at risk of congenital adrenal hyperplasia (CAH). In CAH, the baby produces excess male hormones. If the baby is female, such excess male hormones leads to masculinization of the foetus. If we know the sex of the baby early and intervene by treating the mother with steroids, this can be avoided."

Lo also developed a methodology that allows scientists to amplify and quantify the DNA present in trace

amounts in a plasma sample (such as foetal DNA circulating in maternal plasma that, on average, accounts for 10% of the total DNA in maternal plasma). Applying this technique to an analysis of the plasma of pregnant women, Lo was not only able to determine the sex of the foetus, but also whether the foetus has inherited mutations, such as those causing beta-thalassaemia, from the father.

In a further refinement of the analysis, Lo and his team showed that it was possible to follow the natural

- *Discovered the presence of placenta-derived RNA in the plasma of a pregnant woman. This finding has opened up hundreds of new markers for non-invasive prenatal diagnosis.*

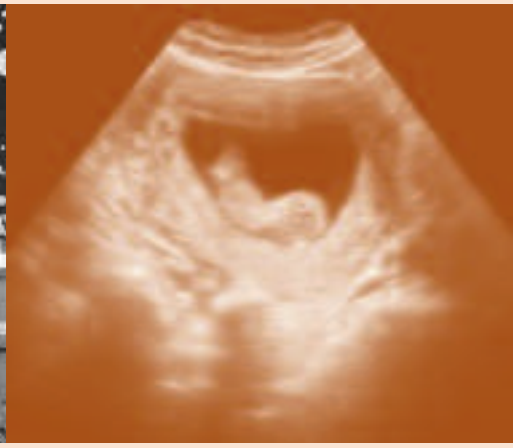
2005

- *Developed a universal DNA methylation for non-invasive prenatal diagnosis. This marker can be used irrespective of the gender and genetic makeup of the foetus.*

2007

- *First report of a method for the prenatal diagnosis of Down's syndrome by using foetal RNA in the plasma of a pregnant woman. The accuracy of this test is over 90%, the most accurate single marker for Down's syndrome up to this date.*


Flickr/David Jones



fluctuating levels of foetal DNA in maternal blood during pregnancy, and that virtually all traces of this DNA disappear within a few hours after birth. An important application of this study concerns some of the most common ailments associated with pregnancy, such as pre-eclampsia (characterized by oedema, proteinuria and hypertension) and pre-term delivery (which occurs before the 37th completed week of gestation). In both cases, as Lo discovered, the detection of abnormal amounts of foetal DNA in maternal blood can be used as a marker of such conditions. In the future, these markers might allow scientists to predict the risk of a pregnant woman developing such conditions.

Down's syndrome (or trisomy 21) is perhaps the most important reason why many pregnant women go for prenatal testing. The syndrome is characterized by the presence of three copies of chromosome 21 instead of the usual two, and causes a general slowing of psychomotor and intellectual development. In 1999, Lo showed that Down's syndrome pregnancies were associated with increased levels of foetal DNA in

2008

- *Demonstrated that through the sequencing of millions of DNA molecules in maternal plasma, one can work out a proportional representation of each chromosome in plasma and hence detect Down's syndrome with high accuracy.*

2010

- *Developed a technology for scanning the entire genome of a foetus from a blood sample obtained from its pregnant mother.*

2011

- *Following the publication of the first large-scale study by Lo's group for Down's syndrome detection and replication by other groups, in October 2011 this approach was introduced into clinical practice. It is now available in China, the USA, and in parts of Europe.*

YUK MING DENNIS LO COMMENTS ON THE CHALLENGES OF DOING EXCELLENT SCIENTIFIC RESEARCH IN A DEVELOPING COUNTRY

The Ernesto Illy Trieste Science Prize is very special and receiving it from the President of China made it even more memorable. TWAS is international, and the prize highlights the fact that scientists in developing countries can achieve the highest standards of scientific excellence despite great difficulties.

It's not impossible to do good research with few resources, but it's certainly a challenge. When I began doing this research, I asked myself what was the cheapest way to extract DNA from the mother's blood plasma. The answer was to get a sample of plasma and boil it. This shows that researchers do not always have to be well funded to do original work.

But of course there is a huge difference in what you can achieve if you have the facilities and back up. In developing countries you simply have to work much harder to have your work accepted by prestigious journals – and to be awarded patents.

Even so, my heart is in Hong Kong and that is where I have chosen to live and work. The students I teach, I think of them as my successors, I am especially attached to them. But I think researchers in Hong Kong in general have better opportunities than they used to. Young researchers need to share their thoughts, their questions, their results. Ideally, as a scientist you need to discuss a lot with people from all over the world working in your field. Now, using Skype and emails, such networking is getting easier. This is the democratization of science.

But still, scientists from developing countries need to pay more attention to science communication. If you are having difficulty publishing in high impact journals – part of that is communication. You need to convince others of the value of your research. Such 'salesmanship' is important when communicating science to your colleagues, to journal editors, to industry, and maybe even the government.

I think it would be highly beneficial for researchers from developing countries to have specific training in, for example, intellectual property rights. Scientists can be quite naïve, they talk about work that's not yet published or patented. Such intellectual property rights are often important for catalyzing the commercial adoption of inventions. Without such protection, very few companies are willing to invest to develop inventions into products. Inventions, if properly protected, would ultimately benefit the researchers' own universities and economies.

maternal plasma. However, the levels in Down's and normal pregnancies overlap to a significant extent. For the next 9 years, Lo and his team explored many approaches to enhance the distinction between Down's and normal pregnancies. In 2008, they demonstrated that by sequencing millions of DNA molecules amplified from maternal plasma, it was possible to work out the proportions of each chromosome and hence detect Down's syndrome with unprecedented accuracy. The technique has now been validated in many large scale studies and shown to be over 99% accurate and is widely used to detect Down's syndrome and a number of other chromosomal aneuploidies (abnormalities in chromosome number) in China, Europe and the United States.

As ever, there are ethical and cultural issues surrounding this test, but in general it is seen as a very welcome advance for expectant parents who would normally take the amniocentesis test, which is invasive and carries the risk that a percentage of babies will abort.

Lo's development of prenatal diagnoses does not stop there. Two years ago, in 2010, it was the turn of

the 'foetal genomic map', obtained by sequencing foetal DNA present in maternal plasma and comparing it with the maternal and paternal genomes.

Describing the complexity of the matter, Lo ventures, "Imagine you have one of those difficult, sophisticated jigsaw puzzles – many, many tiny pieces that all fit together. Well, trying to sequence the human genome is like solving a jigsaw puzzle – it's fragmented in many pieces – but it's a jigsaw puzzle times ten!"

Flickr/Merryly

With over 20 patents filed, Lo is ensuring that his research efforts are being applied where it matters.

Lo found the inspiration for solving this puzzle in, of all places, the cinema, watching *Harry Potter and the Half Blood Prince* with his wife (also a scientist). He explains: "It was one of the first *IMAX* movies to be shown in Hong Kong. When the title appeared in 3D, the words seemed to come straight at me. They got nearer and nearer and then the 'H' in 'Harry' seemed to jump out and I could see in the shape of that 'H', the two members of a chromosome pair, one half from the father, one from the mother. Then, like everything in science, the answer suddenly became obvious." Lo turned to his wife and said, "I think I have the answer! I need to solve the problem in two halves."

And indeed Lo then went on to tackle the problem of the foetal genome by thinking separately about the father and the mother. "I started by looking for DNA sequences that the foetus had inherited from the father, and which were absent in the mother's DNA. Such DNA sequences, as a whole, represented the half-genome that the foetus had inherited from the father."

"Then I turned my attention to the half of the foetal genome that had come from the mother. Such sequences would have an increased concentration in maternal plasma as their concentrations represented a summation of the mother's and the baby's contributions."

The excitement of doing research has clearly never left Lo. "Doing research is like going on holiday every day – but with no guidebook. Research is my hobby." His eyes light up when he is asked about his current research interests and his enthusiasm is infectious.

"Right now I'm pondering the biological meaning of what we are detecting. It's extraordinary that the mother clears the foetus's DNA within two hours of giving birth. This is a message from the foetus that will take another 10 years to decode."

With over 20 patents filed based on his work, Lo is ensuring that his research efforts are being applied where it matters and continue to have a major impact on obstetrics care. In recognition of these achievements, Lo was made a Fellow of the Royal Society (UK) in 2011. ■