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.
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.

“This technology will bring positive healthcare benefits to both developed and developing countries.”

“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
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.

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 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

• 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.

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.
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!”

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.