Dennis Lo (1963-) [1]

By: Abboud, Alexis Keywords: noninvasive genetic diagnosis [2] fetal DNA [3] maternal plasma [4]

Dennis Lo, also called Yuk Ming Dennis Lo, is a professor at the Chinese University of Hong Kong [5] in Hong Kong, China. In 1997, Lo discovered fetal DNA in maternal plasma, which is the liquid component of a pregnant woman's blood. By 2002, Lo distinguished the DNA differences between pregnant women and their fetuses, enabling scientists to identify fetal DNA in pregnant women's blood. Lo used his discoveries to develop several non-invasive and prenatal genetic tests, including tests for blood group status and Trisomy 21, also called Down's Syndrome. Lo's discovery of fetal DNA in maternal plasma lessened the risks to pregnant women and fetuses during prenatal testing, and it enabled early identification of potential genetic mutations in developing fetuses.

Lo was born in 1963 in the Kowloon region of Hong Kong, then part of the British Commonwealth. Lo's father was former head of Qingsham Hospital, the oldest psychiatric hospital in Hong Kong. Lo's mother sang and taught music, instructing Lo and his brother Eric in piano, while their psychiatrist father encouraged the boys to cultivate talents that would help them with medical careers. Lo recalled spending his childhood reading *National Geographic* and developing his interests in photography and drawing.

Lo began school in the British school system in Hong Kong, but in his fifth year he passed an examination and transfered to St. Joseph's College, Hong Kong. After his time at St. Joseph's, Lo earned his undergraduate degree in preclinical medical training at the University of Cambridge in Cambridge, England, finishing the degree in 1986. He then spent a year studying cloning [6] before moving to Oxford University in Oxford, England. At Oxford, Lo finished his PhD with Kenneth Fleming in 1994 and eventually became doctor of medicine in 2001. He worked in several jobs at Oxford for the next seven years. In 1997, Lo left Oxford to return to Hong Kong, which by that time had reverted to Chinese control.

While in England, Lo met fellow graduate student Alice Siu Ling Wong. Originally from Hong Kong, Alice was at Oxford University completing her doctorate in semi-conductor physics. Lo and Wong married while at Oxford.

During his time at Oxford in 1987, Lo hypothesized that polymerase chain reaction (PCR), a technique to amplify and discern small amounts of DNA, could be used to find fetal cells in maternal plasma. Lo spent ten years searching for these fetal cells before concluding that there were not enough fetal cells within the pregnant women's blood to detect differences between maternal and fetal DNA. However, Lo assumed that fetal DNA would only appear in fetal cells. Usually, DNA is only within a cell's nucleus [7], but it can sometimes leave the cell.

In 1996, the article "Microsatellite alterations in plasma DNA of small cell lung cancer patients," reported that Xu Qi Chen's research team at the University of Geneva [8] in Geneva, Switzerland, found tumor DNA in the plasma of patients with small cell lung cancer, a type of aggressive malignant lung cancer often associated with smoking. After reading the article, Lo hypothesized that if free-floating DNA from a small tumor could be detected in plasma, then perhaps free-floating DNA from a fetus [9] could also be detected in plasma. Lo noted that one of the largest differences between maternal DNA and fetal DNA is when the fetus [9] is male and has a Y-chromosome, Lo used PCR to detect Y-chromosomes from male fetuses in maternal blood. In his 1997 article "Presence of fetal DNA in maternal serum and plasma," Lo reported that he found male fetal DNA in maternal plasma outside of the confines of an intact fetal cell.

At first, Lo's discovery allowed only for prenatal sex type determination [10]. Doctors could take a sample of the pregnant woman's blood and test it to determine the sex of her fetus [9]. In 1998, Lo developed a test for the rhesus (Rh) blood group status of the fetus [9]. The Rh blood group status, named after the rhesus monkey [11] (*Macaca mulatta* [12]) in which the blood type was first identified, refers to antibodies found in blood. When a pregnant woman and her fetus [9] have incompatible antibodies, often the woman's immune system perceives the pregnancy [13] as foreign and harms the developing fetus [9]. If doctors can determine whether the Rh blood group status of the pregnant woman and the fetus [9] are compatible early in the pregnancy [13], then they can help to lessen that risk. In the article "Prenatal Diagnosis of Fetal RhD Status by Molecular Analysis of Maternal Plasma," Lo and his research team presented a method for determining blood group status through a non-invasive blood test.

Those first tests relied on genetic abnormalities passed from the sire to the fetus [9], because the sire's portion of the fetus [9]'s DNA was easier to distinguish from the pregnant woman's DNA. Even though fetal DNA comprises almost ten percent of maternal plasma during the first and second trimesters, it is still a small portion of an overall blood sample, often lost in the

background of maternal DNA. For this reason, doctors more easily isolated the paternal part of fetal DNA from the overall maternal blood sample. Therefore, the first non-invasive prenatal genetic tests could only detect those genetic abnormalities inherited from the sire.

However, the differences in DNA methylation [14] between pregnant women and fetuses offered researchers another way to differentiate fetal from maternal DNA. DNA methylation [14] is a process in which a methyl group is added to some parts of a DNA sequence, affecting how that sequence produces proteins or other products. In a fetus [9], a large portion of DNA is methylated, as DNA methylation [14] plays a large role in fetal development. In 2002, Leo Poon, Lo's associate at the University of Hong Kong, along with Lo and several other researchers, used the DNA methylation [14] differences between a pregnant woman and her fetus [9] to isolate fetal DNA within the woman's blood. This technique for non-invasive prenatal genetic diagnosis is called maternal plasma fetal DNA recovery.

In 2003, the outbreak of severe acute respiratory syndrome (SARS) in Hong Kong interrupted Lo's work on non-invasive prenatal genetic testing. His laboratory, along with several others in Hong Kong, sequenced the SARS virus to use this sequence to develop and treat the disease. In 2007, Lo and his team designed a non-invasive maternal blood test to determine whether or not a fetus [9] has Down's syndrome, a genetic defect caused by the presence of an extra copy of chromosome 21 in the nuclei of the fetus [9]'s cells.

Compared to Lo's non-invasive testing techniques, amniocentesis and chorionic villus sampling are both invasive prenatal genetic testing techniques, which require a breach of the womb [15] that can expose the fetus [9] to potential harms and, in some scenarios, result in spontaneous abortions. Amniocentesis [16] requires doctors to test the amniotic fluid from inside the placenta [17]. The breakage of the placental barrier causes spontaneous abortion [18] in two to three of every 1,000 pregnancies, a 0.3 percent increase in risk compared to women who do not undergo amniocentesis. Chorionic villus sampling, the sampling of the tissue surrounding the fetus [9], causes spontaneous abortion [18] approximately 3.6 percent of the time, an increase in risk of 0.8 percent compared to mothers who undergo non-invasive testing. With Lo's discovery, pregnant women could learn about potential genetic mutation of their fetuses in a way that lessened the risk of spontaneous abortion [18].

In 2005, in recognition of his scientific work, the State Council of China awarded Lo the State Natural Science Award. A year later, Lo received the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) Abbott Award for Outstanding Contribution to Molecular Diagnostics, and the US National Academy of Clinical Biochemistry Distinguished Scientist Award. In 2009, Lo received a Fulbright Distinguished Scholar Award. In 2011, he was elected Fellow of the Royal Society and named Foreign Associate of the US National Academy of Sciences [19] in 2013.

As of 2014, Lo teaches medicine and chemical pathology at the Chinese University of Hong Kong [5], where he develops more prenatal genetic tests.

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