The Dr H.P. Heineken Prize for Biochemistry and Biophysics

The work of Dr Andrew Z. Fire presented by Professor R. Kaptein, chair of the Jury of the Dr H.P. Heineken Prize for Biochemistry and Biophysics

Prize citation: for 'his discovery of RNA interference'.

Your Royal Highness,
Your Excellencies,
Members of the Board of the Heineken Foundation
and the Alfred Heineken Fondsen Foundation, in particular their Chair, Ms De Carvalho,
Distinguished laureates,
Ladies and gentlemen,

Dr. Fire,

The way in which proteins are synthesized in living cells was well understood by the nineteen nineties. As proteins are coded for by genes, segments of DNA, this process is often called gene expression. Its basic principle and the way it is controlled were already well known. It therefore came as a surprise when a novel regulatory mechanism called RNA interference or RNAi was discovered in 1998. Double-stranded RNA (or ribonucleic acid) inhibits gene expression when its sequence corresponds with that of the gene. First discovered in the roundworm, *C.elegans*, it was soon found to be a universal mechanism in eukaryotic organisms. It plays an important role in the organism's defense against viral infection. It also turned out to be an extremely useful tool in the hands of molecular biologists. And potentially, it provides a new way to cure disease.

Andrew Fire was instrumental in the discovery of RNA interference and it is for this reason that he has been awarded the H.P. Heineken Prize for Biochemistry and Biophysics. At the age of 45, he is actually the youngest recipient of the H.P. Heineken Prize.

Scientists had noted as early as the mid-nineteen eighties that anti-sense RNA could affect gene expression, but the results were sometimes erratic. For instance, it was observed that both anti-sense and sense RNA were able to silence genes in *C.elegans*. Andrew Fire, in collaboration with Craig Mello, then came up with the brilliant notion that the actor was in fact double-stranded RNA, and it was soon confirmed that dsRNA indeed produced a much stronger gene-silencing effect. His discovery led to the famous *Nature* article of 1998, which is generally regarded as the birth announcement of RNA interference.

Based on a natural process, RNAi soon developed into a powerful new technology for knocking out genes. Previously this had to be done by means of mutation, but injecting dsRNA is obviously much simpler. By making use of RNA libraries and high-throughput screening techniques, the method can now be used to analyze gene function on a genome-wide scale. It has become a major technology for the identification and validation of drug targets.

The discovery of RNAi, and the subsequent discovery of small interfering RNAs, or siRNAs, provided the basis for discovering a novel class of regulatory RNA molecules, the micro-RNAs or miRNAs. These are found in all plants and animals and play a crucial role in development. Their mechanism of action shares many components with the RNAi machinery.

It is truly amazing how quickly both the concept of RNAi as a novel regulatory mechanism and its use as a tool in molecular genetics were adopted by the scientific community. In 1998, only fifteen papers on RNAi were published; by 2003, that number had leaped to 1000. In 2002, the journal *Science* named RNAi "the technology of the year". A year later, *Fortune* dubbed it "the next billion dollar

breakthrough" in biotechnology. Whether RNAi can be used directly to cure disease remains to be seen, but as a biomedical technology it is already extremely important.

Singling out a person by awarding them a prestigious prize does not do full justice to the way science actually works: scientific breakthroughs are normally the result of the efforts of many different scientists. David Baulcombe, who conducted careful research on gene silencing in plants and Craig Mello with his anti-sense RNA work in *C.elegans* both made major contributions. Many other research groups helped to establish RNAi as a universal mechanism. Nevertheless, the real breakthrough came when Andrew Fire suggested that it was dsRNA that caused the effect. This was a huge mental leap at the time, and it is for this reason that the jury has awarded this year's H.P. Heineken Prize to Dr. Fire.

Today, the Academy is honoring a highly creative scientist who laid the foundations of a new and important field of research. We are convinced that Dr. Fire will go on vigorously pursuing his work on the gene expression and developmental biology of the *C.elegans* worm. Dr. Fire, on behalf of the jury I would like to congratulate you warmly on your H.P. Heineken Prize for Biochemistry and Biophysics, which I hope will prove to be major incentive for your further scientific research.