EDITORIAL

RNA interference: Perspectives and caveats

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RNA interference (RNAi) can still be regarded as a recently discovered phenomenon, but it has already made its way as a widely used method in molecular biology. In 1998, Andrew Fire and Craig Mello were the first to describe the mechanism of RNAi in the nematode *C. elegans* (Fire et al, 1998). Long double-stranded RNA molecules were found to mediate posttranscriptional silencing of genes with a homologous sequence. However, such long double-stranded RNAs were found to induce the interferon response in mammalian cells, and it took another few years before Thomas Tuschl and colleagues found a way to use this method in mammalian cells by discovering that small interfering RNAs (siRNAs) – being 21 nucleotides in length – could be employed to induce RNAi without activating the interferon response (Elbashir et al, 2001). This landmark publication has been cited nearly 2000 times according to the ISI Web of Knowledge (August 2005) and initiated a boost of studies employing this novel, powerful technique. In fact, the annual number of papers on RNAi has the highest rate of growth in the biotech literature (Lawrence, 2005). Furthermore, this newly discovered universe of small RNA molecules was elected to be the breakthrough of the year in 2002 (Couzin, 2002) and since it has been in the Top 10 in the preceding and succeeding years. Many scientists consider RNAi to be the most important revolution in molecular biology since the discovery of polymerase chain reaction (PCR). It is anticipated that, just like PCR, the method of RNAi is to become a standard procedure in almost any life science laboratory around the world.

RNAi is now being used at various levels: Academic researchers are usually interested in the function of a single gene and try to understand its function by studying a loss-of-function phenotype. In contrast, big centres and companies have set up libraries for large scale screens employing thousands of siRNAs or short hairpin RNA (shRNA) encoding vectors to identify new factors involved in certain pathways. Pharmaceutical companies make use of RNAi as a rapid approach for target validation before screening large libraries for small molecular drugs. Medical researchers have new opportunities to study disease models *in vivo* without the need to generate expensive and time consuming knock-out animals. It is mainly biotech companies that try to develop siRNAs into a new class of therapeutics. For a long-term perspective the vision has been brought up that RNAi might drastically accelerate the process of drug development. New targets can be identified by genome-wide screens with siRNA libraries; the siRNA can immediately be used for target validation and only minor modifications of the same siRNA according to a standard pattern will be necessary to use it in clinical settings.

Only just over three years after the initial demonstration that siRNAs can be used to silence genes in mammalian cells, the first clinical trials based on RNAi were initiated in late 2004. Acuity Pharmaceutical and Sirna Therapeutics commenced studies to treat patients with age-related macular degeneration (AMD) with intravitreally injected siRNAs targeting VEGF and its receptor, respectively. First data from these trials demonstrate that the drug is safe and well tolerated, and even some promising indications on the visual acuity of the patients have been reported (Whelan, 2005), although the effectiveness of a new drug is not in the focus of a phase I trial.

Despite this enthusiasm about the new tools available now, some problems will have to be dealt with openly. Off-target effects and the induction of the interferon response even by the short double-stranded RNA molecules have intensively been discussed in the scientific community. These caveats make clear that data obtained in RNAi experiments have to be interpreted with great care and that proper controls are indispensable. The future will show whether the unspecific effects of RNAi will prohibit the extended use of this method for systemic application of siRNAs in humans. One must, however, keep in mind that almost every drug has its unwanted side-effects and we will have to find out whether the benefits of an RNAi treatment outweigh its

adverse effects. In some cases, e.g. treatment of viral infections, a moderate induction of the interferon response might even be a beneficial aid for the specific treatment by siRNAs.

The field of RNAi is highly dynamic with dozens of publications added to the database every week. Researchers in the field do not only profit from the great interest in RNAi, but also have to cope with hard competition. We, therefore, see a need for a journal specialized on this topic. Authors will profit from rapid handling of their manuscripts and open access to all accepted papers which guarantees wide recognition of their work. The *Journal of RNAi and Gene Silencing* will not only deal with RNAi, but also welcomes studies with traditional antisense and ribozyme applications. These techniques are still extremely valuable as a complementary approach and researchers in the RNAi field will definitively benefit from lessens learned with antisense oligonucleotides and ribozymes in the last 25 years. We are therefore excited to receive numerous interesting manuscripts on new developments in gene silencing.

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