HOT TOPIC

RNAi's rapid elevation to Nobel fame: Drs Andrew Fire and Craig Mello win nobel prize for their discovery of RNAi

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Although some are barely old enough to remember where they were when US president Kennedy was shot, most RNA researchers remember when they first read about double stranded RNA silencing. *Science* declared RNAi the "breakthrough of the year" in 2002, following multiple observations that exogenously applied chemically synthesised small RNAs directed specific knockdown of target mRNA expression in mammalian cells. This week, the Nobel prize committee jointly awarded Andrew Fire and Craig Mello the 2006 Nobel prize for Medicine for their 1998 publication of RNA interference in *C. elegans* - acknowledging that this key paper allowed the translation of RNA-directed silencing from a confusing phenomenon to a widespread technique for gene silencing in animal models (Fire et al, 1998).

The rapid recognition by the Nobel committee reflects the exponential growth in the application of this technology, and the tremendous rate at which the method has been taken up for therapeutic applications. In some ways RNAi has been uniquely benefited in the timing of its emergence in that many related fields have converged to spur its growth. Plant research has educated understanding of the mechanism underlying RNAi, and techniques developed to deliver gene therapy and antisense reagents have proved well suited for RNAi agent delivery. The ability to simply silence genes by RNAi in so many systems has ensured the wide spread use of the technique amongst researchers in varied fields. As a discovery, RNAi has both borne out the dictum that "what is true for petunias is true for people", and also debunked the notion that all classical molecular biology problems have been solved. An increasing number of observations that new non-coding RNAs exist in mammals, plants and viruses suggest that the RNA interference may just be the tip of the RNA iceberg, and that researchers still have further opportunities for Nobel recognition for their work on RNA.

Andrew Fire began a PhD under Nobel Laureate Phillip Sharp (1993, RNA Splicing) as a 19 year old maths graduate at MIT, and after publishing work understanding transcriptional processing publishing work understanding transcriptional processing moved to the laboratory of Syndey Brenner (Nobel Prize 2002, Cambridge, UK) learning techniques to introduce DNA into *C.elegans*. Craig Mello received his PhD from Harvard University in 1990, and trained with Victor Ambros (*lin-4* small RNA) and James Priess before moving to the University of Massachusetts Medical School in 1994, where he is now Professor of Molecular Medicine. Thomas Tushcl and Philip Zamore, whose discovered that RNAi could be stimulated in *Drosophila* embryo lysate (Tuschl et al, 1999), also trace their exposure to RNAi to Massachusetts, and New England has provided an unusually large input into the development of this field. The rapid rise of RNAi owes much to the timing of its discovery, the facilitating work that came before, and the subsequent invention of researchers in the field who have rapidly established its role at the forefront of molecular biology research. Recognition of the extraordinary potential of this field has not, as is often for the Nobel, come after this potential has been realised. The Nobel Assembly at the Karolinska Institute in Stockholm commented: "Although it was evident RNA played a key role in gene silencing, the phenomenon remained enigmatic until the discovery of RNA interference provided a most unexpected explanation with many profound consequences. It was evident from the very beginning that the significance of the discovery of RNAi would be exceptional."

The historical context of Fire and Mello's 1998 discovery of double-stranded RNA mediated gene silencing is of some interest. Inhibition of viral replication by antisense RNA had been described in the late 1980s, and "co-suppression" of protein synthesis by RNA was known in plants by1990. By 1998, a review by Wassenegger and Pelissier had proposed a model for transcriptional gene silencing (discovered in *C. elegans* in 2005: Wassenegger and Pelissier, 1998; Grishok et al, 2005) but the importance and widespread eukaryotic relevance of the mechanism

behind these observations only became clear after the demonstration of the phenomenon by Fire and Mello in their nematode system. Their collaborative work published later in 1998 provided a mechanistic basis for silencing that brought into focus the role of other small non-coding RNAs such as *lin-4* and *let-7*, and paved the way for the discovery of the roles of miRNAs in development. It also re-invigorated research into antisense therapeutics, capitalizing upon much research into *in vivo* stability and delivery, and has allowed the rapid progress of RNAi agents to clinical trials for Macular degeneration, hepatitis B and Respiratory Syncytial Virus (Bradbury, 2005; Morrisey et al 2005) – just 8 years after their initial observation.

Although the importance of RNAi both as a research tool and an endogenous mechanism is clear, there remain many facets of the RNAi pathway to be understood. In particular, the roles of non-coding RNAs in the regulation of transcription, cell development and plasticity, and even fertilization are of great interest and expanding research. A recently published brain-expressed ncRNA appears to have evolved more rapidly since the separation of chimp and human lineages than in the previous 140 million years, suggesting a human specific role in brain development (Tuschl et al, 1999). Prospects for a future in ncRNA research continue to excite.

The Journal of RNAi and Gene Silencing warmly congratulates Andrew Fire and Craig Mello for their exceptional research and deserved recognition. It is worth noting that Nobel Laureates James Watson and Francis Crick, won their prize nine years after discovering the structure of DNA – to most the fundamental building block of life. Some might consider that RNA has just been realised more important.

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