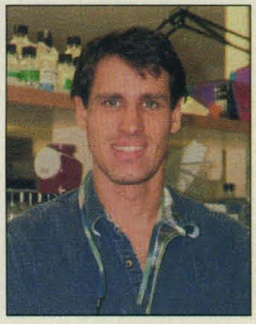
1996 Grand Prize Winner

Pharmacia Biotech and *Science* are pleased to announce the 1996 grand prize winner of the Pharmacia Biotech & *Science* Prize for Young Scientists. The winner of the 1996 grand prize in molecular biology was chosen from among the regional winners from four geographical areas: North America, Europe, Japan, and all other countries. The grand prize has been awarded to a regional winner from North America, Scott Seiwert, for his essay on RNA editing in trypanosomes. This essay, reprinted below, describes his doctoral research at Yale University.



Scott Seiwert

Dr. Seiwert was born and spent the early part of his life in Cincinnati, Ohio. As a teenager he lived in southern California. His interest in RNA arose as an undergraduate at the University of California, Santa Cruz, where he performed research on yeast pre-mRNA splicing in the laboratory of Manuel Ares. He received his graduate training in the Department of Molecular Biophysics and Biochemistry at Yale University in the laboratory of Joan A. Steitz and concluded his studies in absentia at Seattle Biomedical Research Institute in the laboratory of Kenneth Stuart. Early in the coming year, Dr. Seiwert will join the laboratory of Olke Uhlenbeck at the University of Colorado, Boulder, as a postdoctoral fellow.

Regional Winners

Europe. **Yen Choo** for his essay "Grasping the Double Helix: The Design of Sequence Specific DNA Binding Proteins," which is based on work performed at the University of Cambridge, Cambridge, UK.

North America. **Hwai-Jung Cheng**, for his essay "The EPH Ligand Family and Neuronal Topographic Mapping," describing work performed at Harvard University, Cambridge, MA, USA, and **Maria A. Schumacher** for the essay "Crystallographic Studies on the Purine Repressor: A Paradigm, Allostery, and a Novel Binding Motif," which reports work done at the Oregon Health Sciences Center, Portland, OR, USA.

Japan. **Tohru Mizushima**, for the essay "Molecular Mechanisms of Cellular Stress Recognition—Relaxation of DNA in *Escherichia coli* Cells and Induction of Heat Shock Protein," reporting work done at Kyushu University, Fukuoka, Japan.

All other countries. **Hilary Anne Vaughan** for "From Pig to Human: The Definition of the Major Pig Xenoantigen and the Development of Strategies to Prevent Hyperacute Rejection in Pig-to-Human Xenografts" on work performed at the University of Melbourne, Australia.

The other finalists were as follows: from North America, **Yong Liu**, **Hiten Madhani**, **Kornelia Polyak**, and **Hongtao Yu**; from Europe, **Oliver Sorgenfrei**; from Japan, **Masashi Kato**; and from all other countries, **Peter Revill**.

The full text of the essays written by the regional winners can be seen in *Science* Online in the Special Features/Beyond the Printed Page section: http://www.aaas.org/science or http://www.aaas.org/science/prize.htm.

RNA Editing Hints of a Remarkable Diversity in Gene Expression Pathways

Scott D. Seiwert

In *The Rescue: A Romance in the Shallows*, Joseph Conrad stoically proclaims "there is no rest for the messenger till the message is delivered." Although he could not have known, Conrad's statement serves as an apt metaphor for the dramatic remodeling of precursor mRNAs (pre-mRNAs) by the now familiar RNA processing reactions of higher eukaryotes. Although less explored, reactions required for gene expression in early diverging eukaryotes have demonstrated the generality of this metaphor within the eukaryotic kingdom.

Trypanosomatid protozoa represent a lineage of organisms that diverged close to the origin of eukaryotes, soon after the bacterial ancestors of mitochondria were engulfed (*1*). These organisms have received considerable attention because they pose significant threats to world health (*2*). Consequently, they provide an excellent means to examine the possible characteristics of gene expression in ancient eukaryotes. Studies of nuclear genes in trypanosomes have uncovered RNA trans-splicing, a process that may be a molecular fossil representing an intermediate step in the evolution from autoexcising introns to ribonucleoprotein particle–catalyzed intron removal (*3*). Examination of the expression of mitochondrial genes has identified a novel RNA processing reaction, termed RNA editing, that involves the transfer of genetic information between RNAs.

Mitochondrial DNA in trypanosomes is unusual in that it comprises two classes of circular molecules. The primary transcripts derived from the larger class of DNAs, maxicircles, have their coding information remodeled by the site-specific insertion and deletion of uridylate (U) residues (*4*). This sequence remodeling creates mRNAs homologous to those encoded by the mitochondrial DNA in other organisms and often produces more than 50% of a transcript's coding information.

RNA editing was initially thought to represent a challenge to the dogma that genetic information is encoded in nucleic acids because it adds sequence information after transcription. However, it was soon suggested that the sequence information required for this process is supplied by small RNAs transcribed from the second component of the mitochondrial DNA (*5*). These small RNAs, termed guide RNAs (gRNAs), have a sequence of approximately 10 nucleotides at their 5′ end that allows them to hybridize to a specific pre-mRNA at a defined location. Bulged purine nucleotides in the adjacent sequence of the gRNA are capable of directing the appropriate insertion of U's into the pre-mRNA, and U's bulged in the pre-mRNA could be deleted. Both of these events would extend the complementarity of the initial intermolecular duplex to produce a pre-mRNA containing the mature sequence. Thus, RNA editing could involve the transfer of genetic information from one RNA to another.

This model for RNA editing solved the dilemma for the central dogma, but raised the question of how sequence information is transferred between two RNAs. Several proposals were made for the mechanism of this reaction (that is, U insertion or deletion at a single site) (*5*–*8*). One popular model suggested that RNA editing is mechanistically

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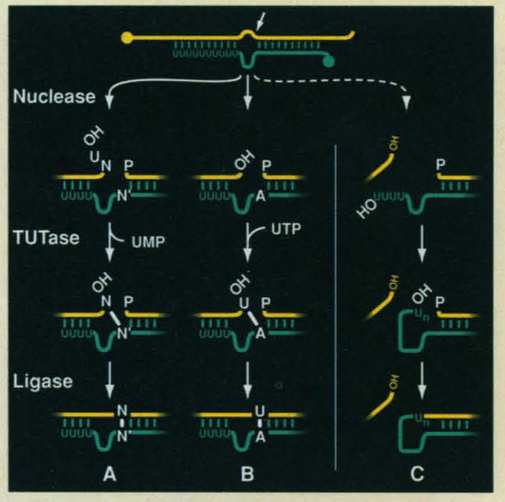
related to the self-splicing reactions of introns (*7*, *8*). In this model, non-encoded U residues at the 3′ end of gRNAs serve as a repository for those inserted and deleted within pre-mRNAs during two coupled transesterification reactions. Excitement grew for this proposal after the discovery of chimeric molecules consisting of 5′ gRNA sequences linked to the 3′ portion of their cognate pre-mRNAs, the intermediates predicted by this model (*8*).

Formal proof of the reaction mechanism required biochemical probing of the RNA editing reaction, studies that were made possible in part by my thesis work. Using an assay system that indirectly monitored processing, I was able to demonstrate the transfer of genetic information from gRNA to pre-mRNA in vitro (*9*), thus confirming that gRNAs are the source of genetic information during the RNA editing reaction. In subsequent studies, I established the reaction mechanism by directly visualizing the processing of a synthetic pre-mRNA (*10*). I found that catalysis is performed not by the RNAs themselves, but by a familiar set of protein enzymes (RNA endonuclease, terminal nucleotidyl transferase, and RNA ligase) that are found in a macromolecular complex (*10*, *11*).

The editing reaction is initiated by endonucleolytic cleavage of the pre-mRNA at a site programmed by gRNA–pre-mRNA mismatch (see figure). During the deletion reaction (A), U residues are removed as uridine 5′-monophosphate from the 3′ end of the 5′ cleavage product (*10*). During the addition reaction, U's are donated from free uridine triphosphate to this same terminus of the 5′ cleavage product (B) (*12*). In both types of reaction, gRNA specifies the edited sequence found at the processing site by aligning the 3′ end of a 5′ cleavage product containing the correct number of U's with the 5′ end of the 3′ cleavage product during RNA ligation. The gRNA–pre-mRNA chimeric molecules found in vivo (*8*) and previously taken as intermediates (*7*, *8*) are also produced in vitro (*10*, *12*). However, it seems that these molecules are nonproductive end products of an aberrant reaction and are not intermediates (C) (*10*). Thus, unlike trans-splicing, RNA-directed RNA remodeling likely represents a genetic phenomenon without analogy in other organisms.



A mechanism for RNA editing. Uridylate (**A**) deletion, (**B**) insertion, and (**C**) chimera formation occur through similar mechanisms. Chimeras are formed when an interaction between the 3′-oligo(U) tail of the gRNA and the 5′-cleavage product is weakened. For clarity, the portions of the pre-mRNA (yellow) and the gRNA (green) not adjacent to the processing site are omitted.

From an evolutionary perspective, the question remains as to why such a baroque method of gene expression arose and why it has been maintained. In modern trypanosomes, RNA editing regulates the expression of mitochondrial genes (*13*). I have suggested that this type of RNA remodeling could have originally promoted the rapid evolution of protein coding sequences through the combinatorial use of divergent gRNAs (*14*). However, until the origin of RNA editing is placed in a paleohistorical context, one can only guess the selective pressures that led to its development. No matter what its origin, RNA editing in trypanosomes and unrelated forms of RNA editing in other organisms (*15*) indicate that the gene expression pathways in more familiar organisms are probably the result of chance occurrences and are not necessary eventualities. In this sense these processes can be viewed as the molecular equivalent to fossils of the Burgess shale, fossils which show that the familiar body plans of present-day animals most likely result from the good fortune of certain clades of ancient organisms.

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