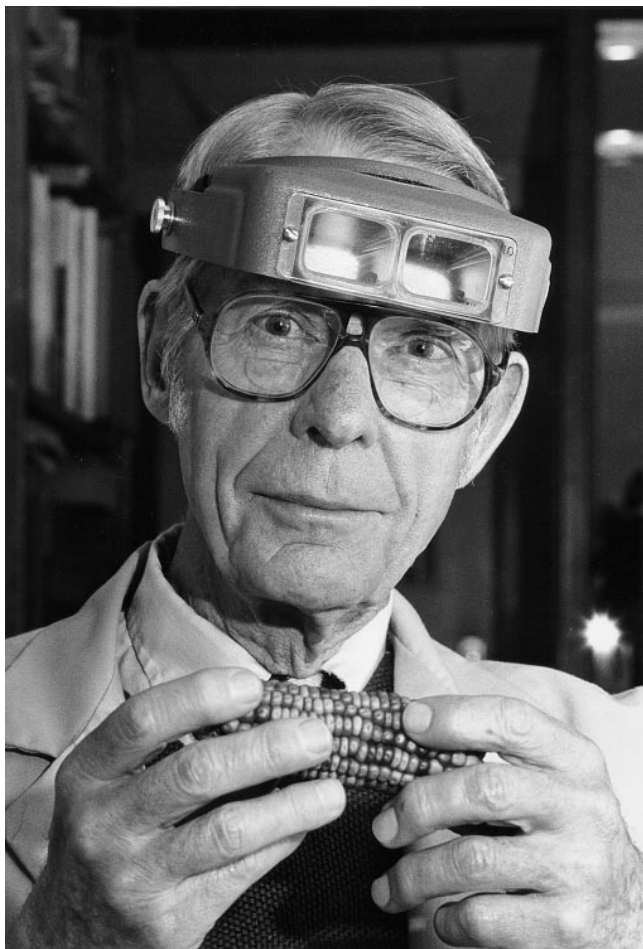# The 1997 GSA Honors and Awards

The Genetics Society of America makes two awards annually to honor members who have made outstanding contributions to the science of genetics. The Thomas Hunt Morgan Medal recognizes a lifetime contribution to genetics. The Genetics Society of America Medal recognizes particularly outstanding contributions to genetics within the past fifteen years. We are pleased to announce the 1997 awards.



Oliver Evans Nelson, Jr. in the lab. Photo by
B. Wolfgang Hoffmann.

## The 1997 Thomas Hunt Morgan Medal

## Oliver Evans Nelson, Jr.

OLIVER EVANS NELSON, JR. exemplifies a "lifetime contribution to genetics." His published work spans a 50-year period and includes seminal contributions in several different areas of investigation. Although focused on maize, the results of his research have had profound and broad impact on agronomic genetics, physiological genetics of plants, and eukaryotic gene structure and function.

Oliver was born in Seattle in 1920. After receiving his early education in the New Haven area, he was introduced to genetics before starting college during a summer working as an assistant in the Department of Genetics, Connecticut Agricultural Experiment Sta-

tion. Here he worked with D. F. Jones, a well-known corn breeder and geneticist. His early interest in genetics was further developed by training he received under E. W. Sinnott. Oliver completed his doctoral research under D. F. Jones at Yale in 1947 and thereupon assumed a faculty position at Purdue University where he remained until 1969. During these years, he initiated a successful popcorn breeding program—some of the lines he developed are still in commercial use.

In the 1950's Oliver realized that the expression of the *waxy* gene in pollen grains afforded a unique opportunity to screen very large numbers of gametes for rare recombinants. Utilizing this system, he carried out

the first fine structure analysis of a gene in higher plants. This was one of the first and most detailed studies of its kind in any eukaryote. One of the important discoveries from this investigation was the demonstration that transposable elements mapped throughout the gene long before such ideas were part of the accepted wisdom. Oliver's fine structure work on *waxy* was undoubtedly stimulated by the analysis of the rII locus being conducted by his Purdue colleague, Seymour Benzer. In turn, on a trip through the cornfields with Seymour, Oliver drew Seymour's attention to a nongeotropic mutant cornstalk crawling along the ground. This experience helped convince Seymour to choose Drosophila when he decided to work on behavioral genetics.

Another of Oliver's seminal contributions during the Purdue years was the discovery, with biochemist Edwin T. Mertz, of mutants with a high content of lysine and tryptophan, thereby greatly enhancing the food value of corn. This was no accidental discovery but the outcome of a deliberate search based on Oliver's deep knowledge of the corn kernel and the properties of the available mutants. Feeding studies with rats were remarkable. Laboratory rats grown on *opaque-2* grew more than three times faster than rats fed on ordinary corn. This pioneering achievement led to further work in other plants, such as sorghum, and in making plant breeders aware of the fact that nutritional quality could be improved through selection. The agricultural impact of this pioneering achievement continues to be felt today.

Early on, Oliver recognized the importance of being able to characterize the enzymatic defect in various maize mutants to address problems of basic genetic significance, particularly those concerned with gene structure, function, and regulation. He worked toward this aim beginning with a sabbatical in 1954 at the Biochemical Institute at the University of Stockholm. He continued this pursuit with another sabbatical leave in 1961 at the California Institute of Technology. His subsequent biochemical studies on the biosynthesis of starch, lignin, protein, and anthocyanin in seeds were one outcome of these sabbaticals. Another was his marriage to Gerda in 1963 after making her acquaintance first in Stockholm and then crossing paths with her again later in California. Perhaps unsurprisingly, Oliver has not been permitted another sabbatical since.

In 1969, Oliver moved to the Laboratory of Genetics at the University of Wisconsin, to fill the vacancy created upon the retirement of R. A. Brink. Fortunately, Brink's retirement was an active one and the interactions between Nelson and Brink provided a fertile and stimulating environment for the training of new generations of corn geneticists. Beginning in the late 1960s, Oliver focused on developing a system in which the effect of transposable elements on the function of a gene could be assayed at the protein level. In collaboration with Nina Fedoroff, Oliver's laboratory cloned the *bronze* gene. This represented the first successful application of transposon tagging in plants and established the *bronze* locus, with its many interesting alleles, as a model system for investigation of gene regulation in plants and the effect of transposable elements at the molecular level.

Oliver also continued to pursue a long-standing interest in the biosynthesis of starch. His earlier discovery that the *waxy* locus encoded a starch-bound ADP-glucose glucosyl transferase was one of the first to relate a phenotypically identified plant gene with the underlying enzymatic defect. Although for many years the topic received little attention, the importance of starch in cereals, roots, and tubers as a major food source for humans and domesticated animals as well its importance as an industrial commodity have contributed to renewed interest in starch synthesis and its modification through genetics and biotechnology. Most of what is currently known about the biochemical lesions responsible for quantitative or qualitative alterations in starch biosynthesis is based on mutations first identified in maize. Oliver and his students have been major contributors to these studies. After his retirement in 1991, work on the *bronze* gene and on starch biosynthesis continued to occupy Oliver's attention.

Oliver has received numerous prestigious awards and honors for his achievements including election to the National Academy of Sciences in 1972. Among his most lasting contributions are the numerous students and postdoctoral associates that he trained. In 1990 his former students and colleagues dedicated a commemorative issue of *Maydica*, the specialty journal of maize genetics, to Oliver upon the occasion of his seventieth birthday. Oliver joins other luminaries, including R. A. Brink, Edward Coe, Marcus Rhoades, and Barbara McClintock (all of whom were themselves recipients of the Thomas Hunt Morgan Medal), in being honored with such a commemorative issue. The respect, admiration, and affection with which Oliver is regarded by his students and associates is quite apparent in this commemorative issue.

Oliver has never avoided taking on extra responsibilities. He served as Chair of the Laboratory of Genetics from 1986 to 1989 and for many years was the local organizer of the annual maize genetics conference. In his free time, Oliver enjoyed life in the country and outdoor activities. Over the years, he has been an avid golfer, gardener, and companion to golden retrievers.

As a scientist, Oliver's enormous contributions to agriculture and to basic genetics, his clarity of vision, and his deep knowledge and insights have been an inspiration and an example for others to follow. As a person, in his modest demeanor and in his comportment always as a gentleman, Oliver is also worthy of respect and emulation. This year's Thomas Hunt Morgan Medal honors the remarkable achievements of a remarkable man.

Barry Ganetzky

Christine Guthrie in 1991. Photo by Bill Santos.

## The 1997 Genetics Society of America Medal

## Christine Guthrie

CHRISTINE GUTHRIE's outstanding contributions to the understanding of nuclear premessenger RNA splicing have been recognized with the awarding of the 1997 Genetics Society of America Medal. In the 20 years since the unanticipated presence of introns in eukaryotic genes was revealed, no one else has applied "the awesome power of yeast genetics" more consistently and successfully to the how and why of splicing.

Confronted with the challenge to identify the machinery and mechanisms of intron removal, and charged by the provocative hypothesis that small nuclear RNAs (snRNAs) might be involved in splicing, Christine and her colleagues set out in the early '80s to discover whether yeast might have snRNAs. Using antibodies against the unusual vertebrate snRNA cap structure and a clever labeling strategy that got around the presence of contaminating degradation products, Christine showed that yeast has a diverse family of snRNAs (Riedel *et al.* 1986; Wise *et al.* 1983). Christine's lab cloned and sequenced the genes for most of the snRNAs they could detect (the *SNR* genes) in what can only be described as a macromolecular tour de force. Although many questions about the relevance of yeast snRNAs to events in mammalian cells remained, future events would reveal Christine's pioneering work in this area to be foundational to the understanding of both premessenger RNA splicing and eukaryotic preribosomal RNA processing.

In addition to leading the chase for cellular factors that might carry out splicing, Christine and her colleagues created intron-containing reporter genes whose expression depended on splicing. The yeast actin intron served as a model, and tests of mutations in the conserved splice sites and branchpoint sequences within the intron revealed a complex set of molecular phenotypes: some mutations blocked splicing completely, others allowed only the first steps of splicing, still others shifted the splicing reactions to alternate sites (Cellini *et al.* 1986; Parker and Guthrie 1985; Vijayraghavan *et al.* 1986). These complex patterns had to mean that recognition of splice sites in yeast must occur multiple times during splicing. But recognition by what?

As work on mammalian splicing progressed, it be-

came clear that the vertebrate snRNAs U1, U2, U4, U5, and U6 snRNA worked together in a large ribonucleoprotein complex called the spliceosome. During the years of 1987 and 1988, Christine's laboratory demonstrated that yeast U1 is encoded by *SNR19*, U4 by *SNR14*, U5 by *SNR7*, and U6 by *SNR6*, and showed that each is essential (Brow and Guthrie 1988; Patterson and Guthrie 1987; Siliciano *et al.* 1987a,b). All the spliceosomal snRNAs, including U2 (*SNR20*), had been identified and cloned in their comprehensive study of yeast snRNAs (Riedel *et al.* 1986). With these ingredients, Christine and her colleagues set out to examine the hypothesis that RNA-RNA base pairing between snRNAs and conserved intron sequences contributes to splice site recognition.

Christine chose to answer this question with genetics, by testing the ability of snRNA genes with compensatory base changes to suppress defects in reporter splicing and expression. First to be exposed by this effort was the interaction between the intron branchpoint sequence and U2 snRNA (Parker *et al.* 1987). Christine's lab also showed in yeast that, as in mammalian cells, 5′ splice site mutations could be suppressed by compensatory U1 mutations (Siliciano and Guthrie 1988), but here was a new mystery: suppression was not uniform, and it appeared that although U1 was responsible for identifying the 5′ splice site region, something else recognized the 5′ splice site when it was cutting time.

If the intron could be recognized by U1 and U2, then what did the other snRNAs do? Mammalian U4 and U6 were known to be associated. Rigorous phylogenetic analysis made possible by the availability of the yeast U4 and U6 sequences revealed much more (Brow and Guthrie 1988): the two RNAs are extensively base paired to each other in a striking Y-shaped arrangement. Paradoxically the variation in sequence is asymmetric, with U4 adrift, and U6 remaining conserved. Since evolutionary conservation is the footprint of functional constraints, this result only deepened the mystery of U6. It must be doing something else, quite possibly something that did not involve U4.

Biochemical studies had shown that U4 is destabilized from the assembling spliceosome before the splicing reactions begin. If U6 became separated from U4, where would it go? Mutations in U6 revealed which bases were important for function, but their phenotypes were not consistent with a "lone U6" structure within the spliceosome (Madhani *et al.* 1990). A bold investigation into the possibility that invariant residues in U6 would pair with another spliceosomal RNA exposed the double life of U6: as it leaves U4, it runs straight into the arms of U2 (Madhani and Guthrie 1992).

The structure formed by their embrace remains a most compelling image for those of us who believe that a heart of RNA beats in the breast of the spliceosome.

Christine's most recent application of the compensatory base suppression approach identified U6 as the second snRNA to pair with the 5′ splice site, displacing U1 (Lesser and Guthrie 1993). This final interaction completes our current picture of snRNA interactions with the intron during splicing, and brings two reactive parts of the pre-mRNA together with a highly conserved spliceosomal snRNA secondary structure that can only be generated during spliceosome assembly (Guthrie 1991; Guthrie and Patterson 1988; Madhani and Guthrie 1994).

But the spliceosome is mostly protein, and even the most riboptimistic among us must account for this. How to find the proteins that are most critical to splicing? Nothing beats genetics in the game of truth or consequences, and Christine's efforts in the search for key splicing proteins paralleled her work on snRNA. One of the first and most revealing studies began with the identification of a suppressor of an intron branchpoint mutation. If the branchpoint A is changed to C, splicing is halted midstream, and reporter expression is reduced (Vijayraghavan *et al.* 1986). A suppressor hunt uncovered *prp16*, which allowed splicing to continue when the branched nucleotide is a C (Couto *et al.* 1987; Burgess *et al.* 1990). The *PRP16* protein turned out to be the first of several splicing factors with homology to an emerging family of proteins resembling the ATP-dependent helicases, and acts by mediating ATP-dependent RNA-RNA or RNA-protein rearrangements precisely at the time when the identity of the branched nucleotide is critical (Burgess *et al.* 1990; Schwer and Guthrie 1991; Schwer and Guthrie 1992). Christine has folded these observations into a model for proofreading during splicing, in which the reduced rate of ATP hydrolysis by the mutant protein spares spliceosomes containing incorrect branched nucleotides from a discard pathway and allows them to continue on the splicing pathway (Burgess and Guthrie 1993). Thus, Christine's studies with Prp16p have provided a clear view of the way in which proteins may help shepherd RNA throughout the splicing pathway and why they may be necessary.

Christine has had a justified affection for cold-sensitive splicing mutations, no doubt tracing back to her studies of the ribosome (Guthrie *et al.* 1969). She uncovered Prp24p as a suppressor of a cold-sensitive U4 snRNA mutation (Shannon and Guthrie 1991), and through biochemical characterization has revealed a role for this protein in the dynamic interaction between U4 and U6 (Jandrositz and Guthrie 1995; Shannon and Guthrie 1991). A cold-sensitive splicing mutation showed that the ATP-dependent helicase family member Prp28p is also involved in these interactions as the *prp28* mutation is synthetically lethal with *prp24* (Strauss and Guthrie 1991). Recently, another cold-sensitive mutation, *brr2*, affecting yet another member of this family has also been shown to influence the asso-

ciation between U4 and U6 (Noble and Guthrie 1996). The finding of two such proteins was not unexpected: For U4 and U6 to be recycled after splicing, their unusual association must be regenerated. Thus, the most recent findings from Christine and her colleagues are serving to close the circle of the splicing pathway.

During the two decades since introns and splicing were discovered, many labs contributed key findings; often nearly identical results came from different labs simultaneously. Extensive crosstalk between workers using yeast and mammalian systems contributed to the high rate and quality of discovery. But even among the handful of groups that have made original, sustained, and consistent contributions to our understanding of splicing, Christine's record of accomplishment stands out and is the one most skillfully seasoned with the flavors of genetics. Congratulations Christine!

<div align="right">Manuel Ares, Jr.</div>

## SELECTED PAPERS BY CHRISTINE GUTHRIE

Brow, D. A., and C. Guthrie, 1988   Spliceosomal RNA U6 is remarkably conserved from yeast to mammals. Nature **334:** 213–218.

Burgess, S., J. R. Couto and C. Guthrie, 1990   A putative ATP binding protein influences the fidelity of branchpoint recognition in yeast splicing. Cell **60:** 705–717.

Burgess, S. M., and C. Guthrie, 1993   A mechanism to enhance mRNA splicing fidelity: the RNA-dependent ATPase Prp16 governs usage of a discard pathway for aberrant lariat intermediates. Cell **73:** 1377–1391.

Cellini, A., R. Parker, J. McMahon, C. Guthrie and J. Rossi, 1986   Activation of a cryptic TACTAAC box in the Saccharomyces cerevisiae actin intron. Mol. Cell Biol. **6:** 1571–1578.

Couto, J. R., J. Tamm, R. Parker and C. Guthrie, 1987   A trans-acting suppressor restores splicing of a yeast intron with a branch point mutation. Genes Dev. **1:** 445–455.

Guthrie, C., 1991   Messenger RNA splicing in yeast: clues to why the spliceosome is a ribonucleoprotein. Science **253:** 157–163.

Guthrie, C., H. Nashimoto and M. Nomura, 1969   Structure and function of *E. coli* ribosomes. 8. Cold-sensitive mutants defective in ribosome assembly. Proc. Natl. Acad. Sci. USA **63:** 384–391.

Guthrie, C., and B. Patterson, 1988   Spliceosomal snRNAs. Annu. Rev. Genet. **22:** 387–419.

Jandrositz, A., and C. Guthrie, 1995   Evidence for a Prp24 binding site in U6 snRNA and in a putative intermediate in the annealing of U6 and U4 snRNAs. EMBO J. **14:** 820–832.

Lesser, C. F., and C. Guthrie, 1993   Mutations in U6 snRNA that alter splice site specificity: Implications for the active site. Science **262:** 1982–1988.

Madhani, H. D., R. Bordonne and C. Guthrie, 1990   Multiple roles for U6 snRNA in the splicing pathway. Genes Dev. **4:** 2264–2277.

Madhani, H. D., and C. Guthrie, 1992   A novel base-pairing interaction between U2 and U6 snRNAs suggests a mechanism for the catalytic activation of the spliceosome. Cell **71:** 803–817.

Madhani, H. D., and C. Guthrie, 1994   Dynamic RNA-RNA interactions in the spliceosome. Annu. Rev. Genet. **28:** 1–26.

Noble, S. M., and C. Guthrie, 1996   Identification of novel genes required for yeast pre-mRNA splicing by means of cold-sensitive mutations. Genetics **143:** 67–80.

Parker, R., and C. Guthrie, 1985   A point mutation in the conserved hexanucleotide at a yeast 5′ splice junction uncouples recognition, cleavage, and ligation. Cell **41:** 107–118.

Parker, R., P. G. Siliciano and C. Guthrie, 1987   Recognition of the TACTAAC box during mRNA splicing in yeast involves base pairing to the U2-like snRNA. Cell **49:** 229–239.

Patterson, B., and C. Guthrie, 1987   An essential yeast snRNA with a U5-like domain is required for splicing in vivo. Cell **49:** 613–624.

Riedel, N., J. A. Wise, H. Swerdlow, A. Mak and C. Guthrie, 1986   Small nuclear RNAs from Saccharomyces cerevisiae: unexpected diversity in abundance, size, and molecular complexity. Proc Natl. Acad. Sci. USA **83:** 8097–8101.

Schwer, B., and C. Guthrie, 1991   PRP16 is an RNA-dependent ATPase that interacts transiently with the spliceosome. Nature **349:** 494–499.

Schwer, B., and C. Guthrie, 1992   A conformational rearrangement in the spliceosome is dependent on PRP16 and ATP hydrolysis. EMBO J. **11:** 5033–5039.

Shannon, K. W., and C. Guthrie, 1991   Suppressors of a U4 snRNA mutation define a novel U6 snRNP protein with RNA-binding motifs. Genes Dev. **5:** 773–785.

Siliciano, P. G., D. A. Brow, H. Roiha and C. Guthrie, 1987a   An essential snRNA from S. cerevisiae has properties predicted for U4, including interaction with a U6-like snRNA. Cell **50:** 585–592.

Siliciano, P. G., M. H. Jones and C. Guthrie, 1987b   Saccharomyces cerevisiae has a U1-like small nuclear RNA with unexpected properties. Science **237:** 1484–1487.

Siliciano, P. G., and C. Guthrie, 1988   5′ splice site selection in yeast: genetic alterations in base-pairing with U1 reveal additional requirements. Genes Dev. **2:** 1258–1267.

Strauss, E. J., and C. Guthrie, 1991   A cold-sensitive mRNA splicing mutant is a member of the RNA helicase gene family. Genes Dev. **5:** 629–641.

Vijayraghavan, U., R. Parker, J. Tamm, Y. Iimura, J. Rossi *et al.,* 1986 Mutations in conserved intron sequences affect multiple steps in the yeast splicing pathway, particularly assembly of the spliceosome. EMBO J. **5:** 1683–1695.

Wise, J. A., D. Tollervey, D. Maloney, H. Swerdlow, E. J. Dunn *et al.,* 1983   Yeast contains small nuclear RNAs encoded by single copy genes. Cell **35:** 743–751.

# Previous Recipients of These Awards

| Thomas Hunt Morgan Medal | | Genetics Society of America Medal |
|---:|:---:|:---|
| Barbara McClintock and Marcus M. Rhoades | 1981 | Beatrice Mintz |
| Sewall Wright | 1982 | Gerald R. Fink |
| Edward B. Lewis | 1983 | Charles Yanofsky |
| George W. Beadle and R. Alexander Brink | 1984 | David S. Hogness |
| Herschel L. Roman | 1985 | Philip Leder |
| Seymour Benzer | 1986 | Gerald M. Rubin |
| James F. Crow | 1987 | Sydney Brenner |
| Norman H. Giles | 1988 | David Boststein and Ira Herskowitz |
| Dan L. Lindsley | 1989 | Allan C. Spradling |
| Charles Yanofsky | 1990 | Nancy Kleckner |
| Armin Dale Kaiser | 1991 | Bruce S. Baker |
| Edward H. Coe, Jr. | 1992 | Maynard V. Olson |
| Ray D. Owen | 1993 | Jonathan R. Beckwith |
| David D. Perkins | 1994 | Leland H. Hartwell |
| Matthew Meselson | 1995 | Eric Wieschaus |
| Franklin W. Stahl | 1996 | Elliot Meyerowitz |