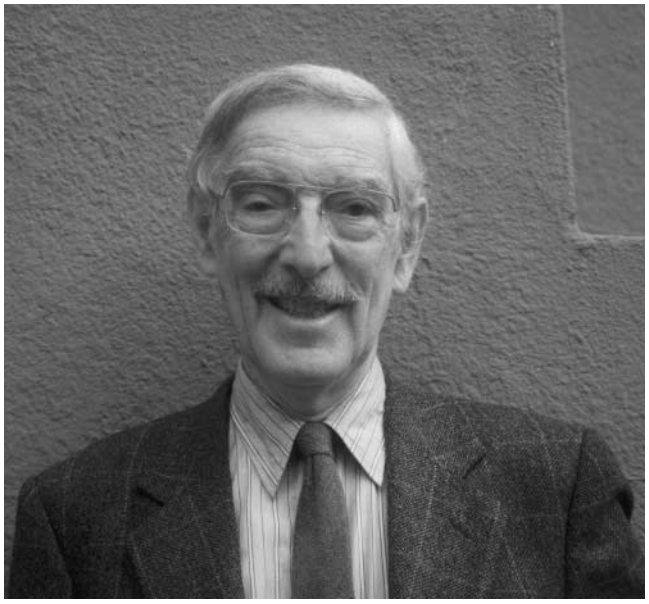
The 2004 GSA Honors and Awards

The Genetics Society of America annually honors members who have made outstanding contributions to genetics. The Thomas Hunt Morgan Medal recognizes a lifetime contribution to the science of genetics. The Genetics Society of America Medal recognizes particularly outstanding contributions to the science of genetics within the past 15 years. The George W. Beadle Medal recognizes distinguished service to the field of genetics and the community of geneticists. We are pleased to announce the 2004 awards.



Bruce Ames

The 2004 Thomas Hunt Morgan Medal

Bruce Ames

DURING a research career sparked by vision and enthusiasm and spanning more than 50 years, Bruce Ames has used microbes to solve basic genetic problems that have direct implications for human well-being. In this research he has imaginatively combined genetics with biochemistry to elucidate mechanisms underlying gene expression, mutagenesis, and carcinogenesis. Capitalizing on mutants from his early work on the genetics of histidine biosynthesis, he developed the Salmonella "Ames test," one of the simplest and most widely used assays for mutagens and potential carcinogens. A current Google search reveals $>10^4$ website references to the Salmonella Ames test, attesting to the extensive influence of Bruce's work. In addition, he has assessed the relative contributions to human carcinogenesis of synthetic and natural chemicals in our environment and has recently investigated the roles of deficiency of vitamins and antioxidants in DNA damage and aging.

Aside from his research projects at Bronx High School of Science, Bruce began his research as a graduate student with Herschel Mitchell at Caltech in 1950. He completed his Ph.D. degree in just three years with research on histidine biosynthesis, one of the most complex pathways for synthesis of an amino acid. During this time he developed a simple chromatographic assay for imidazole compounds accumulating in histidine-requiring Neurospora mutants, which allowed him to deduce much of the histidine biosynthetic pathway.

During his postdoctoral research with B. L. Horeker at the National Institutes of Health, Ames initiated a long-term collaboration with bacterial geneticist Phil Hartman, who had an extensive collection of histidine-requiring (*his*) mutants of *Salmonella typhimurium*. These mutants became the basis of Ames' next 20 years of varied research, beginning with elucidation of the rest of the histidine biosynthetic pathway. With Hartman he showed that a group of nine contiguous genes, now known as the *his* operon, is coordinately regulated by a mechanism acting at the promoter-proximal end of the operon. Starvation for histidine derepresses the entire operon, the longest then known. These observations had an important influence on the formulation of the operon concept by Francois Jacob and Jacques Monod. Analysis of constitutively derepressed *his* operon mutants led Ames to the discovery that alterations in histidine transfer RNA, such as reducing its level or eliminating some of its modified bases, derepress the operon. This observation was important to the subsequent elucidation by others of the mechanism of transcriptional attenuation that regulates expression of many genes in bacteria.

In the mid-1960s, Ames began to think about a possible connection between mutagenesis and carcinogensis, a link that is widely accepted today but was controversial at the time because many people thought viruses were the prime suspects for carcinogenesis. After moving to the University of California at Berkeley in 1967, Ames developed a test for mutagenesis based on reversion of carefully selected Salmonella *his* mutants. A key feature of this test was Bruce's finding of a set of strains with mutations that are particularly sensitive to mutagen-induced reversion, which proved to be more informative than forward mutagenesis. An additional critical feature is the inclusion of liver extract, stemming from Bruce's recognition that certain compounds become mutagenic only after metabolism by an animal. During the development of this test, undergraduates in a UC Berkeley lab were asked to bring items from home to test for mutagenicity—one brought a commonly used hair dye, which proved remarkably potent. Subsequent tests by Ames and the students showed that 89% of hair dyes then commercially available were mutagenic, a result that led to the reformulation of hair dyes.

The Ames test is still in use today, more than 30 years after its development. In fact, it has become a workhorse of high school biology labs, because it is simple, cheap, and so fast that results appear while you sleep. In many cases it has saved much time and money by enabling industry to weed out mutagenic chemicals early in the pipeline.

Ames' determination of the mutagenicity of thousands of compounds and complex mixtures, such as cigarette smoke, made it clear that there is a strong correlation between mutagenicity in the Ames test and carcinogenicity in rodents and humans. Animal cancer tests and the Ames test led to much public concern about the contribution to human cancer of synthetic chemicals, including pesticides, in food and the environment. Ames, however, came to believe that naturally occurring chemicals, such as the pesticides that plants produce in self-defense, probably account for most of our exposure to exogenous carcinogens. For example, he estimates that by weight, 99.99% of human dietary pesticides are natural. These considerations led him to devise the human exposure dose/rodent potency dose (HERP) index, which relates the potency of a particular compound and the daily exposure to it to other exposures such as the carcinogenic aflatoxins in peanut butter. This test has injected the voice of reason into the debate over the risks in our environment by putting synthetic exposures in the context of the much greater exposure of natural chemicals.

The realization that natural compounds can be carcinogenic led Bruce to turn his attention to the role of diet in human health. In the early 1990s he and his students showed that folic-acid deficiency leads to chromosomal breaks, apparently via reduced synthesis of thymidylate, increased incorporation of uracil into DNA, and its subsequent excision. Prompted by these results, he has investigated inadequate vitamin and mineral intake as a major source of DNA damage and multivitamin-mineral supplements for the prevention of DNA damage.

Ames is currently focusing on understanding oxidative damage to mitochondria and its contribution to aging. He has found that feeding normal mitochondrial metabolites such as lipoic acid and acetylcarnitine to old rats can reverse some mitochondrial dysfunction. This research grew in part out of his earlier work on the genetic control of the oxygen stress response in Salmonella, which established the key role of OxyR as a sensor of oxygen stress. Today, Ames continues his research on aging unabated, saying "aging has not damaged my enthusiasm genes."

Throughout his career Bruce has emphasized the importance of developing new, simple methods to analyze complex problems, amply illustrated by the Ames test. His chromatographic assay for imidazole compounds was key to his early work on histidine biosynthesis. One of his articles in 1961 described a convenient method for determining the molecular mass of a protein by sucrose-gradient centrifugation. This article was one of the most frequently cited publications for many years, a record that has since been eclipsed by the Salmonella Ames test, with more than 2500 PubMed citations in the past 25 years.

In his career at the NIH, UC Berkeley, and currently at the Children's Hospital Oakland Research Institute, Ames has trained approximately 150 undergraduate and 50 graduate students and 100 postdoctoral fellows, many of whom are now scientific leaders training others in the art and science of genetics and biochemistry.

For most of this time Bruce's wife Giovanna Ferro-Luzzi Ames has been studying in a neighboring lab, the genetics and biochemistry of histidine permeation in Salmonella. Their combined labs have nurtured a productive environment, filled with humor. When chided by her that he was not exercising enough, he retorted, "What do you mean I don't exercise enough? I exercise every day. I run my experiments, skip controls, and jump to conclusions."

Bruce Ames has received numerous other awards recognizing his achievements. Among these are the Eli Lilly Award (1964), election to the National Academy of Sciences (1972), the Charles S. Mott Prize from the General Motors Cancer Research Foundation (1983), election to the Royal Swedish Academy of Sciences (1989), the Japan Prize (1997), and the National Medal of Science (1998).

Gerald R. Smith
Mark Johnston

Trudy F. C. Mackay

The 2004 Genetics Society of America Medal

Trudy F. C. Mackay

THE 2004 GSA Medal is awarded to Trudy F. C. Mackay for her substantial contributions to quantitative genetics. Much of what we now know about the genetic basis of variation in quantitative traits follows from Trudy's meticulous experiments on bristle number in *Drosophila melanogaster*, and our future understanding of the molecular mechanisms affecting life span and olfactory behavior will be shaped by Trudy's current genetic dissection of these traits in Drosophila.

Trudy began her education in biology at Dalhousie University and in 1976 she went to the University of Edinburgh on an 1851 Exhibition Scholarship. There she began a partnership with Douglas Falconer and Bill Hill that has ensured the continuation of excellence of the Edinburgh school of quantitative genetics. A very visible symbol of this continuation was Trudy's joining with Falconer in 1996 as a coauthor of *Principles of Quantitative Genetics*, the bible of quantitative genetics since it first appeared in 1960. Trudy is also North American editor of that other Edinburgh beacon, Genetical Research. After a postdoctoral period back in Dalhousie, Trudy returned to Edinburgh in 1980 and began her work with transposable elements. We were fortunate to be able to attract her to North Carolina State in 1987.

Quantitative, or measured, traits are of central importance for human health and agricultural production and so our health and welfare will benefit from an understanding of their genetic basis. Trudy has used the number of sensory hairs of *Drosophila melanogaster* as a model quantitative trait, and she used transposable elements to study the effects of mutation on such traits. In a series of experiments she constructed lines that differed in the numbers and locations of *P* elements and quantified their effects on bristle number and viability. Trudy's training in classical quantitative genetics allowed her to provide statistically sound estimates of pleiotropic and epistatic effects, and she demonstrated the asymmetric and highly leptokurtic nature of *P*-ele-

ment effect on bristle number (*e.g.*, Genetics 130: 315–332, 1992). Most of the increase in mutational variation was due to a few lines with large effects, contradicting conventional wisdom that quantitative variation is caused by many genes of small effect. This finding offers hope for the ability to manipulate genes affecting quantitative traits of economic importance or those affecting human health. The *P*-element studies were accompanied by an investigation, with long-term collaborator Chuck Langley, of naturally occuring variation and a demonstration that this is correlated with variation at the DNA sequence level (Science **266:** 1697–1702, 1994).

Although bristle number has proved to be a trait with considerable genetic complexity, Trudy has more recently taken up the challenge of investigating longevity (*e.g.,* Proc. Natl. Acad. Sci. USA **94:** 9734–9739, 1997). She has mapped quantitative trait loci (QTL) with effects on life span, survivorship, and mortality in *Drosophila melanogaster*. Her finding of late age-of-onset QTL effects is consistent with the mutation accumulation hypothesis of senescence, whereas her demonstration of sex-specific QTL effects suggests a novel mechanism for maintaining genetic variation for life span, depending on the existence of QTL genotype by sex interaction for fitness.

Together with husband Robert Anholt, Trudy has been extending her genetic studies to behavioral traits, with an emphasis on odor-guided behavior (*e.g.*, Behav. Genet. **31:** 17–27, 2001). In a recent Nature Genetics article (**35:** 180–184, 2003) Robert, Trudy, and their colleagues reported on a genome-wide expression analysis of smell-impaired and control lines of *Drosophila melanogaster*. They were able to identify new candidate genes for regulating olfactory behavior.

Trudy's work on characterizing the genetic basis of quantitative genetic variation follows a tradition of using Drosophila as a model organism that distinguished the work of her mentor Robertson and provided the first QTL interval mapping study of J. M. Thoday in 1961. In her Nature Reviews Genetics article (**2:** 11–20, 2001), Trudy made an eloquent case for the continued use of Drosophila as a model for human disease studies. This very nice review makes it abundantly clear that these studies will owe much to her very careful experiments and interpretations.

Trudy's research has made her an international figure and a worthy recipient of the GSA Medal, and her service to her profession demonstrates a generosity of spirit. She has served on the GSA Board of Directors and was a member of the Genetics Editorial Board 1991–2002. Few volumes of Genetics in recent years have *not* carried several of Trudy's articles. Trudy has been a voice of support for excellent research in population and quantitative genetics at study sections and review panels. She directs a training grant at North Carolina State and guides a large team of graduate and postdoctoral students. I am fortunate to have her as a colleague—our Society and our profession are fortunate to have her scientific leadership.

Bruce S. Weir

Norbert Perrimon

The 2004 George W. Beadle Medal

Norbert Perrimon

THE 2004 George W. Beadle Medal is awarded to Norbert Perrimon in recognition of his outstanding contributions to the Drosophila genetics community. His continuous development of new genetic and molecular tools have allowed Drosophila laboratories to make rapid progress in many different fields of research. Norbert Perrimon has been a key figure in the genetic analysis of many signaling pathways in Drosophila. He not only has developed tools for these analyses, but also has made them readily available to the whole Drosophila community. It is for these achievements that the GSA honors Norbert Perrimon with this prize.

Norbert Perrimon began his scientific career in the laboratory of Madeleine Gans at the University of Paris. Madeleine Gans was one of the outstanding geneticists of her time, and when Norbert joined her group, her laboratory was involved in screens for female sterile and maternal effect mutations on the X chromosome of Drosophila. A deep appreciation for the power of genetic screens and the realization that unhindered sharing of tools and mutations allows rapid progress remained characteristic of Norbert's own research throughout the years. It was also in the Gans laboratory that Norbert first started to use a dominant female sterile mutation as a tool for clonal analysis in the germline. After he moved to the laboratory of Anthony Mahowald, then at Case Western University for his postdoctoral work, he perfected the dominant female sterile approach for the X chromosome. This allowed him to test a large number of mutations that are homozygous lethal, but yield interesting phenotypes when made homozygous in the germline after induction of mitotic recombination. Among the mutations that Norbert and his colleagues analyzed in these first large-scale experiments were mutations in *pole hole*, the Drosophila *Raf* homolog, as well as mutations in *hopscotch* (the Drosophila JAK homolog) and *disc large* (which is involved in determining epithelial cell polarity). After establishing his own laboratory at Harvard Medical School, Norbert Perrimon continued the study of several of the maternal genes involved in embryonic patterning, in particular genes involved in signaling pathways such as *Raf* and *corkscrew*, which led

to further studies of the Torso and Egfr pathways; *dishevelled*, *zeste white 3* (*sgg*), and *porcupine*, which initiated important work on Wingless signaling; and *hopscotch* and *marelle* (*Stat92E*), which established the analysis of JAK/STAT signaling in Drosophila. These experiments led to many new insights in the signal transduction area and influenced cell biological thinking about signal production, transport, and reception in general.

However, while pursuing these important scientific questions, Norbert Perrimon, in a unique manner, also spent considerable time and effort making effective tools for developmental analyses in Drosophila. While the *ovoD* technique to induce homozygous germline clones by X-ray-induced mitotic recombination worked reasonably efficiently for the X chromosome, the available dominant female sterile mutations on other chromosome arms were tedious and much less useful to employ. Norbert decided that it would therefore be worth transforming the dominant *ovoD* mutation on to the other chromosome arms, and he also realized that the newly introduced FLP-FRT system in flies would be extremely useful for the induction of germline clones. In a heroic effort, Tze-Bin Chou and Norbert succeeded in combining the two systems into a useful tool that allows Drosophila laboratories a relatively easy approach to studying the effects of their favorite mutations in germline clones. At the same time, Andrea Brand and Norbert undertook another risky experiment, transforming the yeast *GAL4* gene, a powerful transcriptional regulator, into flies and inserting the GAL4 UAS target sites in front of test genes such as *Raf* and *lacZ*. The outcome of their efforts transformed the way Drosophila laboratories have been designing mis- and overexpression experiments, and countless screens and investigations into gene function have derived from this original set of experiments.

Very notably, Norbert Perrimon not only generated useful stocks and constructs that he used in his own research, but also very generously gave out those tools to the scientific community as soon as they were available. His inventiveness in developing the tools and immediate sharing of the stocks have impacted the way all Drosophila laboratories perform experiments and have led to numerous new insights that have affected the Genetics community as a whole.

Trudi Schüpbach

Previous Recipients of These Awards

	Thomas Hunt Morgan Medal	Genetics Society of America Medal	George W. Beadle Medal
1981	Barbara McClintock and Marcus M. Rhoades	Beatrice Mintz	
1982	Sewall Wright	Gerald R. Fink	
1983	Edward B. Lewis	Charles Yanofsky	
1984	George W. Beadle and R. Alexander Brink	David S. Hogness	
1985	Herschel L. Roman	Philip Leder	
1986	Seymour Benzer	Gerald M. Rubin	
1987	James F. Crow	Sydney Brenner	
1988	Norman H. Giles	David Botstein and Ira Herskowitz	
1989	Dan L. Lindsley	Allan C. Spradling	
1990	Charles Yanofsky	Nancy Kleckner	
1991	Armin Dale Kaiser	Bruce S. Baker	
1992	Edward H. Coe, Jr.	Maynard V. Olson	
1993	Ray D. Owen	Jonathan R. Beckwith	
1994	David D. Perkins	Leland H. Hartwell	
1995	Matthew Meselson	Eric Wieschaus	
1996	Franklin W. Stahl	Elliot Meyerowitz	
1997	Oliver Evans Nelson, Jr.	Christine Guthrie	
1998	Norman H. Horowitz	Ronald W. Davis	
1999	Salome G. Waelsch	Charles H. Langley	Michael Ashburner
2000	Evelyn M. Witkin	Jack W. Szostak	John Sulston and Robert Waterston
2001	Yasuji Oshima	H. Robert Horvitz	Gerald R. Fink
2002	Ira Herskowitz	Andrew Fire	Robert Mortimer and André Goffeau
2003	David S. Hogness	Jeffrey C. Hall	Gerald M. Rubin and Allan C. Spradling